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A Toolbox for Divergolide and Hygrocin Ansamycin Assembly: Total Synthesis of Divergolide I

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Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Dirk Trauner betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, den 15.03.2018

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Daniel W. Terwilliger

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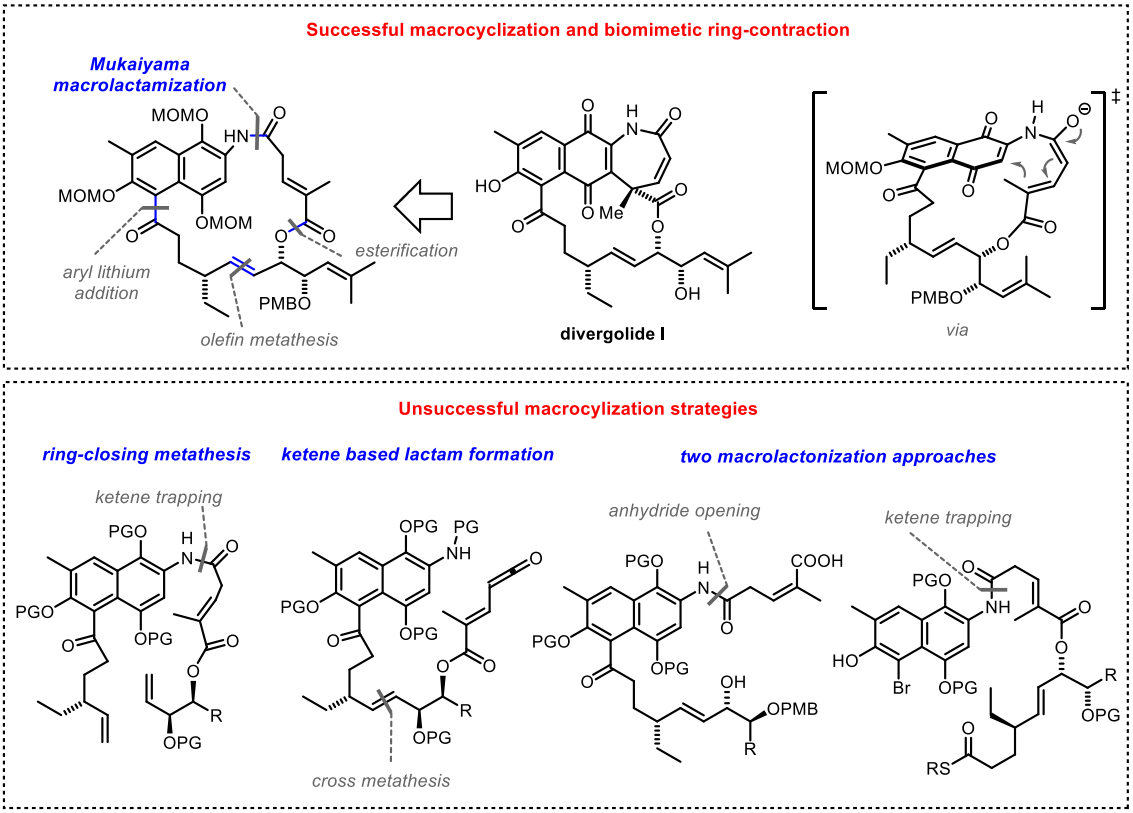
For my late grandmothers Marianne and Gloria

Abstract

The result s described in this thesis detail the efforts towards the chemical synthesis of members of the divergolide and hygrocin class of ansamycins. These related macrocyclic polyketides comprise a continually growing class of structurally diverse compounds that exhibit broad antibacterial activity. Their thoroughly researched biosynthesis hinges on different modes of ring-contraction of a macrocyclic progenitor, giving rise to many structurally distinct natural products. In the course of our campaign, we pursued diverse tactics to construct a precursor molecule that would allow us to study aforementioned ring-contractions. After evaluation of several unsuccessful strategies we eventually devised a pathway that allowed for atroposelective construction of a macrocycle that underwent a surprisingly selective biomimetic cyclization, culminating in the enantioselective total synthesis of the azepinone divergolide I. Our synthetic material could secure the absolute and relative configurations of the ansamycin families and revealed interesting stereochemical properties of the macrocyclic progenitor molecule. The established convergent route could then also be adopted for the synthesis of an *epi*-hygrocin, highlighting the power of our fragment-based approach.



Acknowledgements

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Last but not least, I have to thank my family and my partner in crime Angélique for their patience with the crazy scientist. I could not have done it without you! To countless good souls from various corners of this earth who supported me sustaining a life outside chemistry – thanks for providing the balance I needed. Y'all know who you are.

Abbreviations

AHBA	3-Amino-5-hydroxybenzoic acid
4-AMP	4-(Aminomethyl)piperidine
Ac	Acetyl
ACP	Acyl carrier protein
Alloc	Allyloxycarbonyl
AT	Acetyl transferase
Aux	Auxiliary
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BOPCl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
brsm	By recovered starting material
Bu	Butyl
CAN	Ceric ammonium nitrate
CM	Cross metathesis
CoA	Coenzyme A
CSA	Camphorsulfonic acid
cyHex	Cyclohexyl
dba	Dibenzylidieneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Δ	Heat
DH	Dehydratase
DIBAL-H	Diisobutylaluminium hydride
DIC	*N*,*N*-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridin
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide

DPPA	Diphenylphosphoryl azide
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
ER	Enoylreductase
ESI-HRMS	Electrospray ionization high resolution mass spectrometry
FDPP	Pentafluorophenyl Diphenylphosphinate
Fmoc	Fluorenylmethyloxycarbonyl chloride
HATU	Uronium salt developed for peptide couplings
HG II	Hoveyda-Grubbs 2nd generation catalyst
HMTA	Hexamethylenetetramine
HPLC	High-performance liquid chromatography
Hsp90	Heat shock protein 90
HSQC	Heteronuclear single quantum coherence spectroscopy
HWE	Horner–Wadsworth–Emmons reaction
Ipc	Diisopinocampheylborane
KHMDS	Potassium bis(trimethylsilyl)amide
KR	Ketoreductase
KS	Ketosynthase
LAH	Lithium aluminium hydride
MABR	Methylaluminium bis(4-bromo-2,6-di-tert-butyl-phen-oxide)
Me	Methyl
Mes	Mesityl
MNBA	2-Methyl-6-nitrobenzoic anhydride
MOM	Methoxymethyl
NADPH	Nicotinamide adenine dinucleotide phosphate
NBS	N-Bromosuccinimide
NHK	Nozaki–Hiyama–Kishi reaction
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
OBt	Hydroxybenzotriazolyl
OTf	Triflate
p	Pressure

PCC	Pyridinium chlorochromate
Ph	Phenyl
Piv	Pivalate
PKS	Polyketide synthase
PMB	*para*-Methoxybenzyl
Pr	Propyl
RCM	Ring closing metathesis
SEM	2-(Trimethylsilyl)ethoxymethyl
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetra-n-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TE	Thioesterase
TEA	Triethylamine
Teoc	Trimethylsilylethoxycarbonyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Trt	Trityl

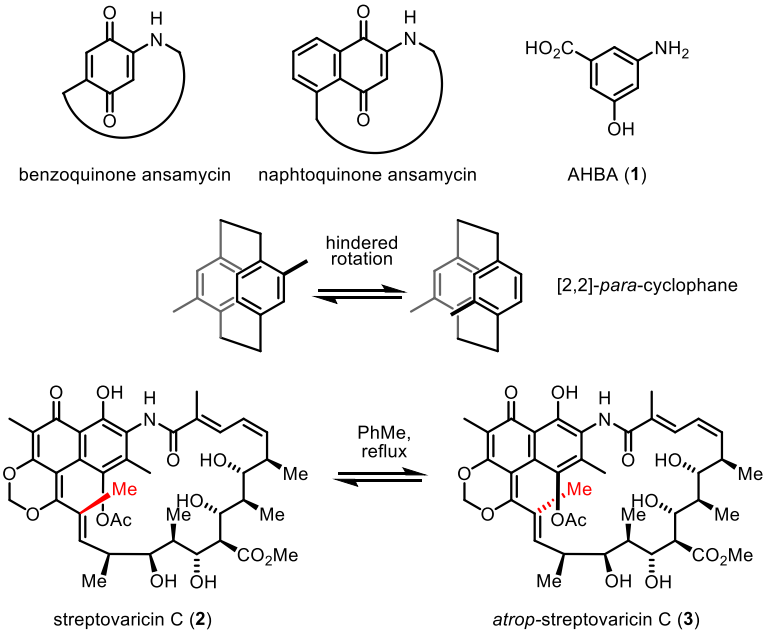
Table of Contents

1 Introduction

1.1 Biosynthetic origin of ansamycin polyketides

1.1.1 Classification and stereochemical properties of ansamycins

Ansamycins encompass a continually growing family of biologically active macrolide antibiotics of polyketide origin, sharing 3-amino-5-hydroxy benzoic acid (AHBA, **1**) as a structural element. Their descriptive name (*ansa* is Latin for "handle") coined by Prelog and Oppolzer,[1] groups natural products in which an aminoquinone or aminonaphthoquinone serves as the base for a chain that connects the nitrogen *via* an amide bond to a non-adjacent position on the chromophore (Scheme 1). As was first recognized in a class of molecules now commonly called cyclophanes, conformational restriction of the aromatic unit's perpendicular orientation relative to the so called *ansa* chain results in a special case of atropisomery, referred to as planar chirality.[2] This phenomenon can also be observed in some ansamycins,[3] and has proved to be key to explaining some results described in this thesis.



Scheme 1 Ansamycin definition, planar chirality of *ansa*-compounds.

Ansamycins can be further grouped into two classes according to their chromophore, which can either be a benzoquinone (Hsp90 inhibitor geldanamycin[4] being the most famous example) or a naphthoquinone, featured in the clinically relevant class of the rifamycins.[5] Reports on the isolation of novel naphthoquinone ansamycins are plentiful, especially in the last decade.[6] Figure 1 shows a selection of some naphthoquinone ansamycins, to display their

molecular intricacy. This introduction omits in-depth discussions of chemical ansamycin synthesis in favor of discussing briefly the biosynthetic origin of polyketides in general and a more detailed discussion of divergolide and hygrocin biosynthesis, the two naphthoquinone families that concern this thesis. To cover the impressive successes in ansamycin synthesis the reader is referred to appendix 5.1, which comprises a comprehensive overview of chemical ansamycin studies predating 2014, prepared by the author of this dissertation in course of the Trauner literature seminar series.

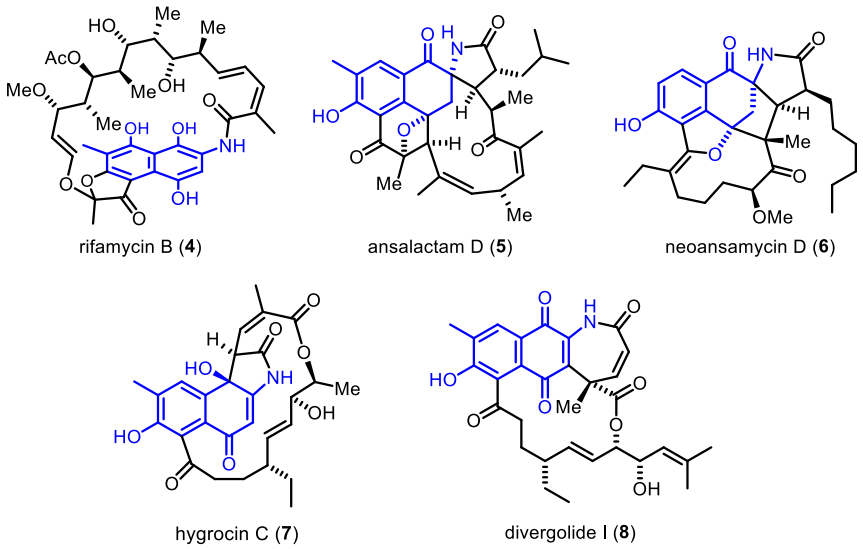
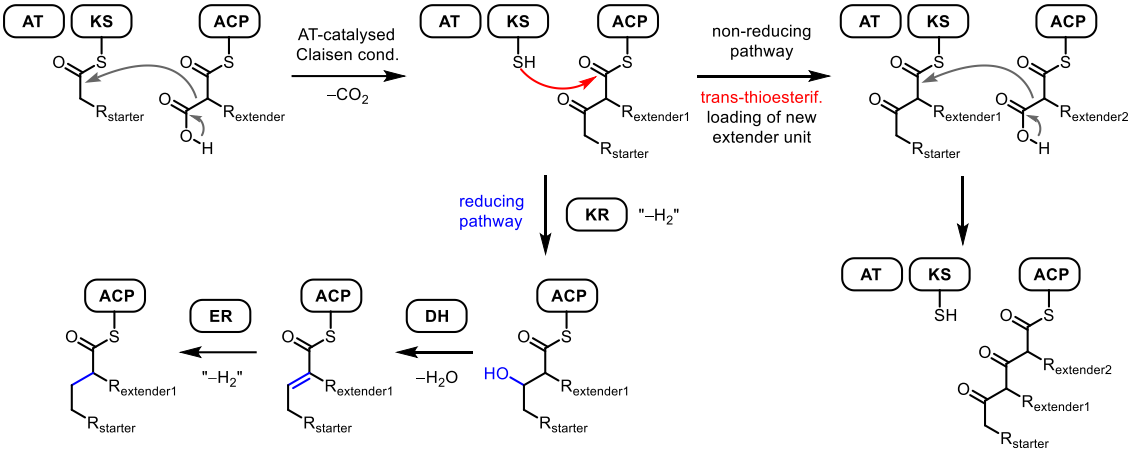


Figure 1 Structures of representative naphthoquinone ansamycins.

1.1.2 The biosynthetic logic of polyketide construction

The biosynthesis of every polyketide synthase begins with the loading of an acetyl-CoA activated starter unit onto the ketosynthase (KS) domain of the respective polyketide synthase (PKS), a multi-enzyme complex capable of merging and processing of small carbon fragments.[7] Scheme 2 illustrates the basic logic of such biotransformations. An acetyl transferase (AT) catalyzes a Claisen thioester condensation of the starter unit with a malonic acid-derived extender unit that was loaded onto an acetyl carrier protein domain (ACP), giving rise to a β–keto thioester intermediate. The diversity of polyketide natural products stems from further optional processing of this intermediate, since further elongation with different extender units can follow either immediately, or after reductive modification of the intermediate. Typical processing usually involves three NADPH/H$^+$-dependent reduction processes catalyzed by ketoreductase (KR), dehydratase (DH) and enoylreductase (ER) domains of the PKS. By varying the degree of reductive processing, different structural motifs can be incorporated.



Scheme 2 Polyketide construction and β-keto-processing.

Once elongation and initial processing of the chain is finished, most PKS incorporate a thioesterase (TE) domain which can either cyclize or release the nascent polyketide. After release by the TE, the PKS can further influence the structure of the polyketide by providing a specific cavity in which the precursor may orient in a specific manner to favor spontaneous intramolecular cyclization, *e.g.* by condensation reactions between the 1,3-diketone motifs. The starter units which are initially loaded onto the PKS are introduced as acetyl coenzyme A thioesters and can vary greatly. While simple acetyl- and propionyl-CoA units are commonly employed, many more elaborate CoA-thioesters have been reported in the literature. For example, branched *iso*-valeryl-CoA **9** is incorporated during the biosynthesis of the antibiotics of the avermectin class,[8] and cyclohexene diol thioester **10** is used for rapamycin[9]and AHBA-CoA (**11**) for rifamycin production.[10]

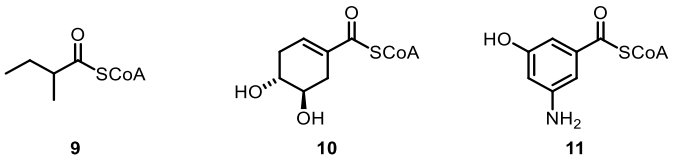
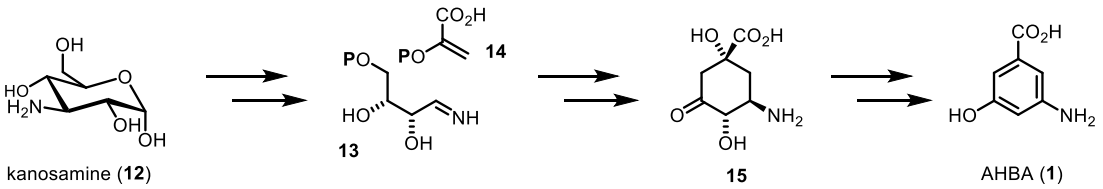


Figure 2 Different starter units initiating polyketide biosynthesis.

A brief overview of the proposed AHBA (**1**) biosynthesis[11] is described in Scheme 3, as AHBA is the common starter unit of all ansamycins.



Scheme 3 AHBA (**1**) biosynthesis.

Analogous to the shikimic acid biogenesis, aminosugar kanosamine (**12**) is cleaved after phosphorylation and isomerization to yield amino-erythrose-4-phosphate (**13**). Combination with phosphoenol pyruvate (**14**) yields amino dehydroquinic acid **15**, which after elimination of two equivalents water yields AHBA (**1**).

Most PKS extender units are malonyl-derived ACP-thioesters (see Figure 3).

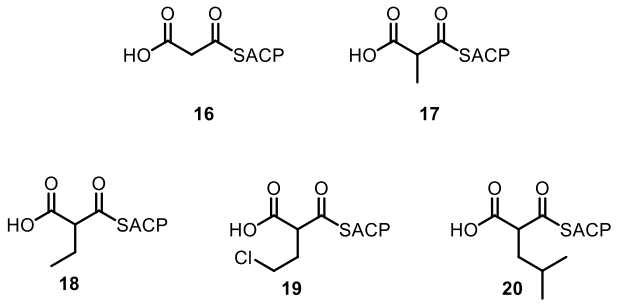


Figure 3 Some extender units employed in polyketide biogenesis.

While the majority of utilized extender unit are of the malonyl- and methyl malonyl- type (**16** and **17**),[7] the erythromycins incorporate ethyl malonyl units (**18**).[9] A chloro-*S*-adenosyl methionine-derived chloro-ethyl malonyl unit (**19**) is involved in the biosynthesis of salinosporamide A[12], while crotyl-CoA has been shown to be the precursor of the *iso*-butyrylmalonyl unit (**20**), incorporated in the ansalactams.[6]

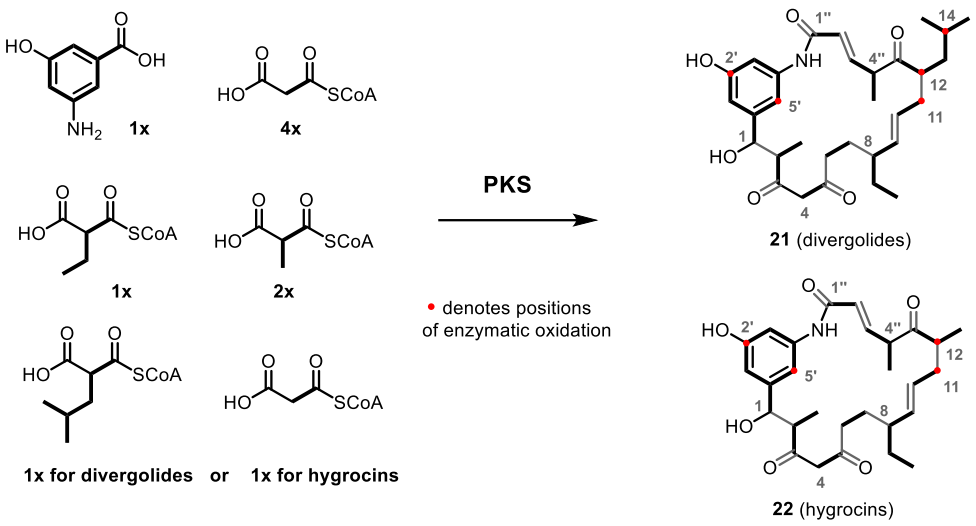
Having discussed the primary assembly of polyketide carbon skeletons and the standard 1,3-oxidation pattern, we now move on to discuss further oxidative tailoring, structural rearrangements, particularly in an intramolecular fashion to reach further layers of diversity. Hence, the intriguing biosyntheses of the divergolides and hygrocins will be discussed in the following section to introduce the two ansamycin families that concern this thesis.

1.2 The divergolide and hygrocin families of ansamycins

1.2.1 Polyketide assembly and processing of the nascent ansamycin

The divergolides and hygrocins constitute a bioactive family of structurally related tetracyclic ansamycins, whose biosynthetic origin has been the subject to intense study.[13a-e,14a-e] The two natural product families differ by only one extender unit used by the respective PKS. To date, a total of 29 divergolide and hygrocin natural products and biosynthetic intermediates have been isolated and the ansamycin-producing clusters have been analyzed on the genetic level. The first report on the hygrocins was disclosed by Parker and coworkers in 2005,[14a] followed by Hertweck and coworkers' account of the divergolides from 2011.[13d] These reports already allowed for biosynthetic conclusions just based on the structure of the natural products and guided a first hypothesis, that was later consolidated and refined by the sequencing of the respective biosynthetic clusters. The overview given here will represent the current state of knowledge and not follow a chronological listing of the findings to give a clearer picture of the state of the art as the current literature is still missing a comprehensive analysis.

The primary source for divergolides are a *Streptomyces sp.* strain (HKI 0595), an endophyte collected by Hertweck's team from the mangrove *Bruguiera guimnorrhiza* or *Streptomyces sp.* strain W112, an endophyte collected from the Chinese medicinal herb *Camphotacea accuminata* by Shen. Most hygrocins were isolated from either *Streptomyces hygroscopicus* strain ATCC25293 (Carter and coworkers) or a *Streptomyces sp.* strain (LZ35) that was genetically modified to suppress geldanamycin production to favor the production of low abundance ansamycins (Shen and coworkers). Scheme 4 shows the starter unit AHBA as well as the individual extender units. Macrocyclic species **21** ad **22** are believed to be the intermediates that the thioesterase domain of the type I PKS releases. Note that in the hygrocin series (**22**), the rare *iso*-butyl-malonyl-CoA unit[15] is switched to a methyl malonyl CoA unit. Otherwise, the two families appear to be structurally completely analogous.



Scheme 4 Assembly of macrocycles **21** and **22**.

Macrocyclic precursors **21** and **22** are subsequently subject to several enzyme-catalyzed oxidations. P450-dependent oxygenases promote allylic oxidation of position 11 (Scheme 4), and in the case of the divergolides the tertiary carbon 14. The resultant alcohol allows for dehydration, installing the characteristic *iso*-butenyl unit of the divergolides. An enzyme resembling a Bayer-Villigerase[13d] was identified to be responsible for oxygen insertion to ketone 5'' to form the ester, while no specific enzymes responsible for subsequent olefin isomerization of the thus created glutaconic acid (**24**) unit from the 2'' to the 3'' position could be identified. The configuration of the 3''-glutaconic olefin is not known. It is important to note that the (*S*,*S*)-1,2-diol motif created (carbons11 and 12) allows for facile 1,2-shifts of the glutaconic ester (see Figure 4). No enzymes that catalyze this isomerization were characterized, but many divergolides and hygrocins resemble acyl shifted isomers. Several structural features of **23** (and the analogous hygrocin species **24**) can also be found in the final natural products: the C9-C10 (*E*)-configured olefin and the C8 (*R*)-ethyl moiety are ubiquitous for every member of the families, while the C1-(*S*)-configured benzylic alcohol is only retained in some congeners.

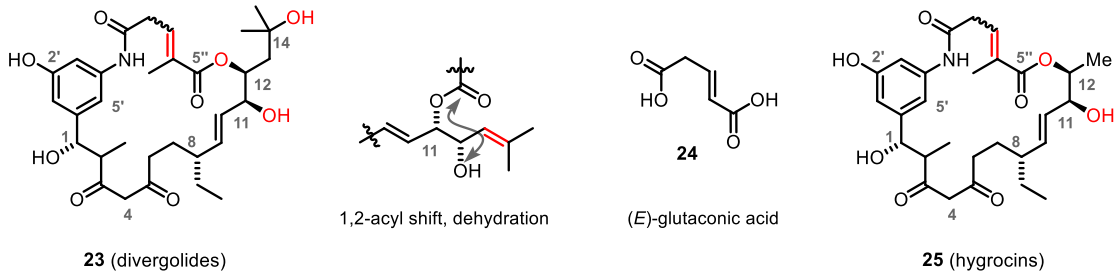
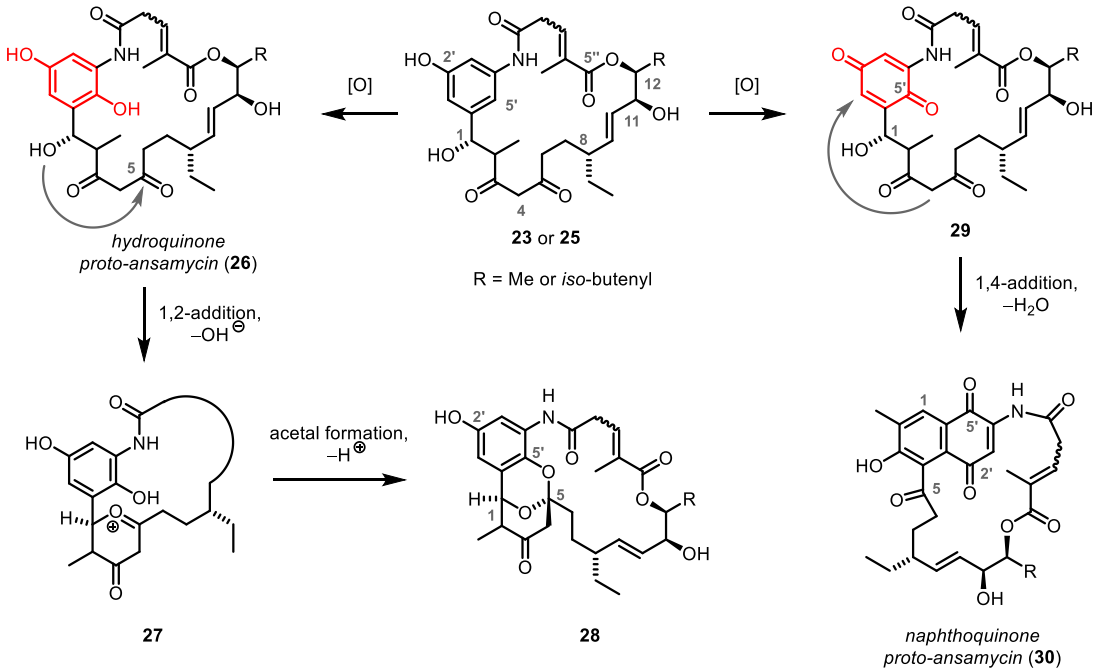


Figure 4 Oxidative tailoring, acyl shifts.

A first branching point to two structurally very distinct core structures is offered by the action of redox enzymes that promote oxidation of the aromatic amino phenol to the amino hydroquinone (**26**) or amino benzoquinone (**29**). Quinone **29** is able to form amino naphthoquinone of type **30** by a condensation reaction, while hydroquinone **26** can undergo transketalization reactions with the C5-ketone to create spiroacetals of type **28**. To stress the importance of intermediates **26** and **30**, we refer to them as *proto*-ansamycins.



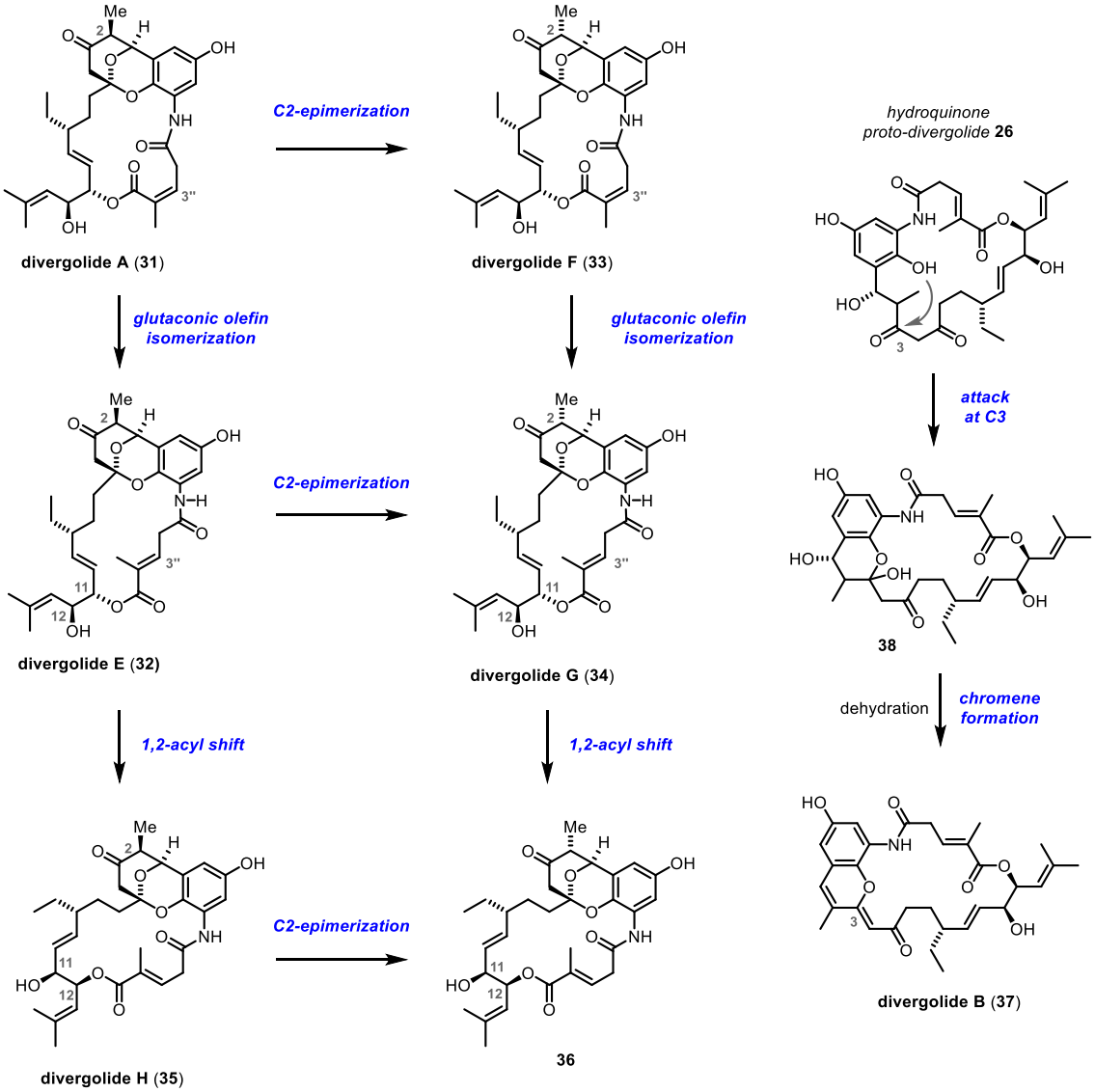
Scheme 5 *proto*-Ansamycins and their diversification.

1.2.2 Amino hydroquinone *proto*-ansamycin diversification

It is noteworthy that only in the divergolide series natural products resembling acetals of type **28** were observed. Interestingly, during their genetic analyses of hygrocin biosynthesis, Shen proposed that naphthoquinone formation (**30**) occurs already during polyketide assembly,[14d] while Hertweck proposes that in the case of the divergolides,[13b] this occurs after release from the PKS. The isolation and characterization of divergolides A (**31**), E (**32**),[I] F (**33**), G (**34**) and H (**35**, Scheme 6) by Hertweck is in accord with their hypothesis, while Shen's suggestion is reflected in the fact, that no hygrocin with structures related to **28** were isolated to date. Upon closer examination of the relationship of ansamycins **31**–**35**, it is clear that not

[I] **32**'s description in the literature coincided with another communication reporting novel divergolides, hence the name „divergolide E" appears in the literature describing two compounds, **32** and **43**.

only the C2 position can epimerize during the transketalization processes, but also both glutaconic olefin isomers ((*Z*)-configuration in A and F, (*E*)-configuration in E, G and H) and 1,2-acyl shifted isomers are occurring, with structure **36** being the only isomer that was not

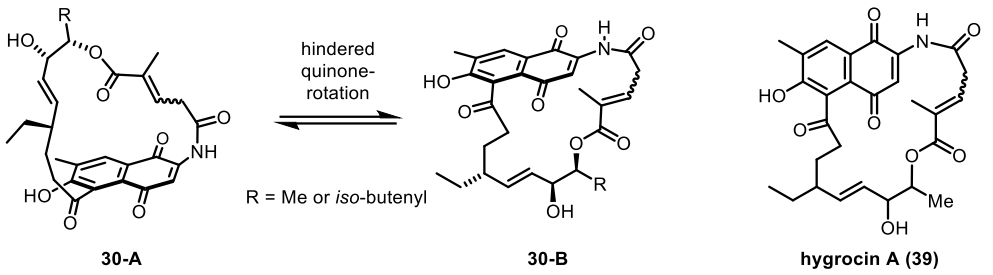


Scheme 6 Spiroketal and chromene type divergolides.

isolated. Another congener that was isolated is divergolide B (**37**). The formation of the chromene core of **37** is induced by attack of the C5′ hydroxyl onto the C3 ketone yielding intermediate **38** and subsequent dehydration. Divergolide B is the only known natural product with this core structure in the ansamycin families.

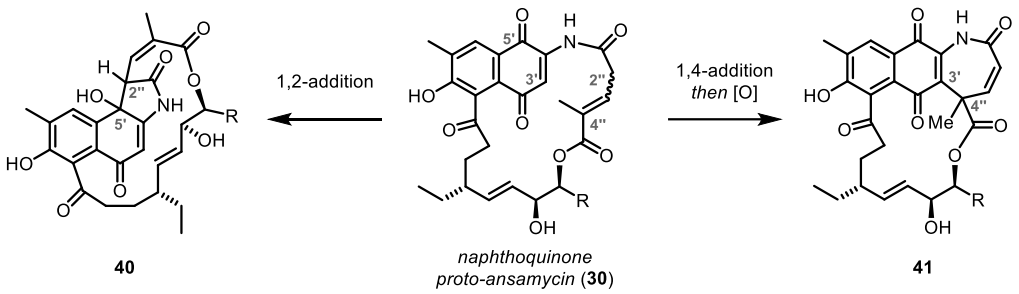
1.2.3 Aminonaphthoquinone *proto*-ansamycin diversification

Having covered the reactivity of the amino hydroquinone *proto*-ansamycin (**26**), the next section will discuss the diversification of aminonaphthoquinone *proto*-divergolide **30**. An important aspect when examining the diversification of this intermediate is the occurrence of planar chirality as an inherent element of stereochemistry in **30**. Scheme 7 shows two different diastereomers of the 20-membered macrocycle, a consideration that was so far omitted in the literature published on divergolides and hygrocins.



Scheme 7 Suspected occurrence of planar chirality in **30**, hygrocin A (**39**).

It is not known if a specific atropisomer, or both diastereomers are formed in Nature. However, one can speculate by analyzing the stereochemistry of the isolated pyrrolidinone natural products, that it is not unlikely that *only one atropisomer* is a biosynthetic intermediate. We will revisit this hypothesis later in this section once the different modes of ring-contraction of **30** and the remaining divergolides and hygrocins are introduced. In the hygrocin series, an unstable isomer of **30** was isolated (hygrocin A, **39**). **39**'s relative stereochemistry could not be fully elucidated,[14a] as it converted into a pyrrolidinone isomer (see below) upon acquisition of NMR data. The possibility of atropisomery was not discussed, but the isolation of the strained macrocycle is a remarkable achievement of the Carter group. This elusive macrolide, or derivatives thereof, never reappeared as an isolated species in any of the plentiful subsequent reports on hygrocins or divergolides, but the existence of a *proto*-ansamycin of this type was canon in all biosynthetic models. Scheme 8 displays how an aldol type 1,2-addition of the glutaconic methylene (C2'') of **30** to the C5' carbonyl effects the formation of a chiral pyrrolidinone (**40**), as opposed to a 1,4-addition resulting in azepinone formation (**41**, vinylogous attack of C4'' to C3'). In the case of the latter, a quarternary stereocenter at C4'' is generated adjacent to an electron-rich benzohydroquinone, that spontaneously oxidizes to the naphthoquinone. No enzymes which catalyze these ring-contractions to yield tetracyclic compounds were identified in either the hygrocin or divergolide biosynthetic clusters.

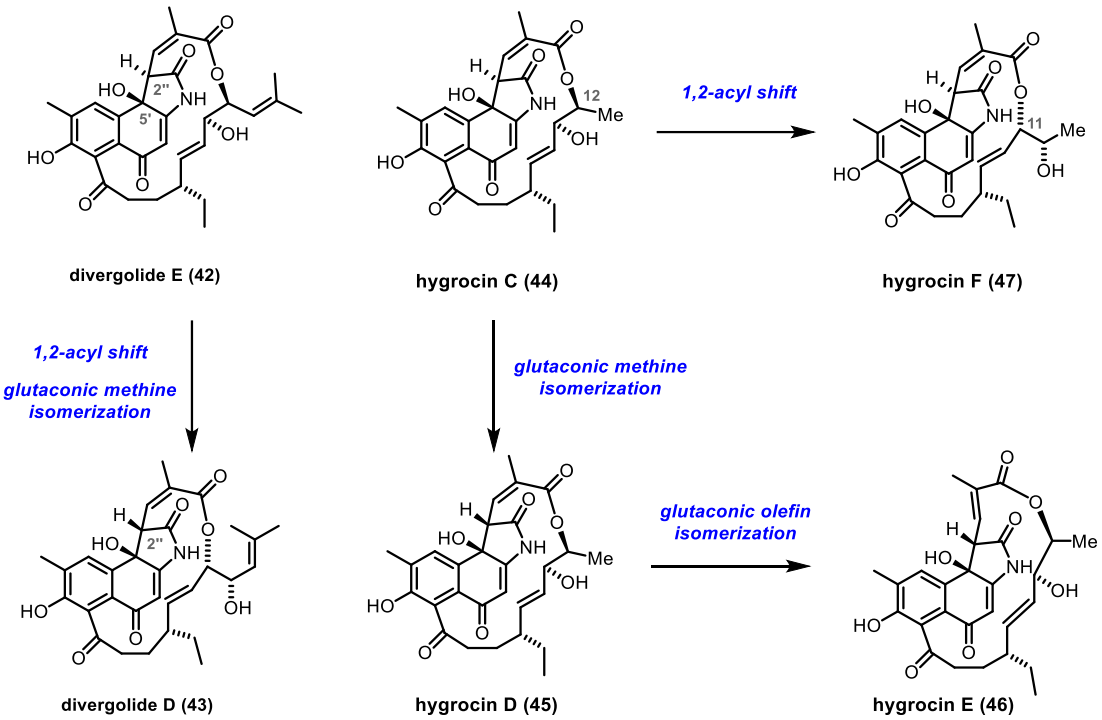


Scheme 8 Pyrrolidinone (**40**) and azepinone (**41**) formation.

These reactivities are the consequence of two factors:

(A) Space filling molecular models of the *proto*-ansamycin **30** show that the *ansa* chain, untypically short in comparison to classic ansamycins, stretches closely over the quinoid core. The chromophore cannot freely rotate relative to the *ansa* chain, hence preorganizing the framework for selective intramolecular addition events. Molecular modeling (see chapter 2.4) supports the hypothesis that planar chirality is likely in molecules resembling the *proto*-ansamycin structure **30**.

(B) The methyl glutaconic acid tethered by both an amide and an ester functionality features fairly acidic methylene protons, making enolate formation conceivable without enzymatic catalysis. By interpreting the glutaconic acid functionality as vinylogous malonic diester, one can estimate the pK_a of the corresponding species to have a value of approximately 13.[16] The reactivity of glutaconic acid derivatives is separately discussed in chapter 1.2.6 as it is the capriciousness of this very unit that dictates some of the most unique features of hygrocin and divergolide diversity.

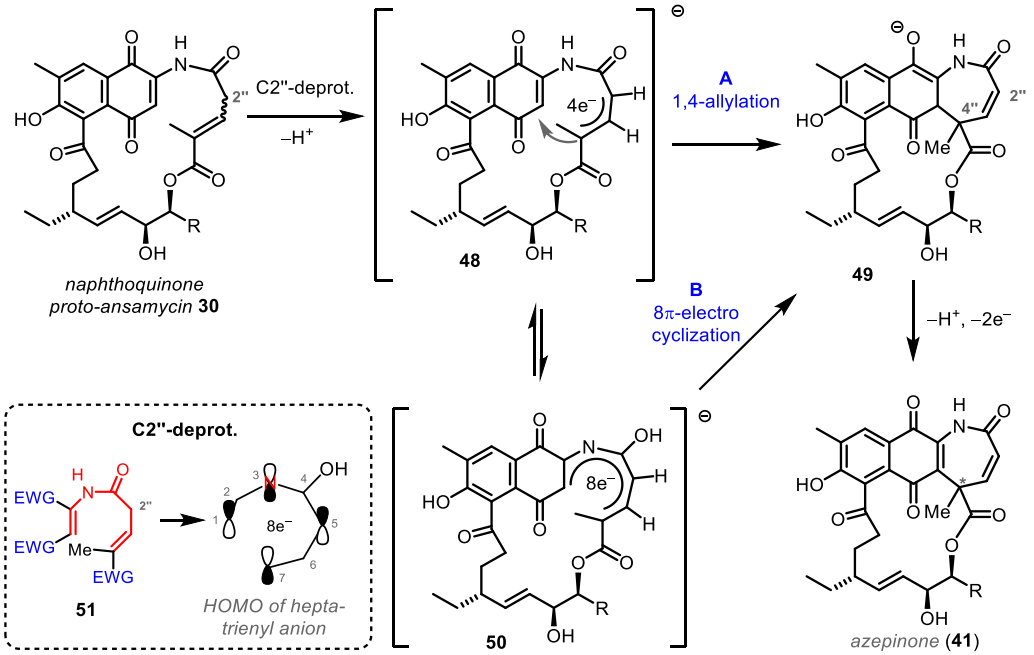


Scheme 9 Pyrrolidinone divergolides and hygrocins.

Scheme 9 displays the two pyrrolidinone divergolides, D (**42**) and E[1] (**43**) and the four analogous hygrocins C (**44**), D (**45**), E (**46**) and F (**47**). Within the respective families, all structures are isomers of each other, stemming from three inherent chemical reactivities that could not be connected to any enzymatic control. When comparing divergolides D (**42**) and E (**43**), the 1,2-acyl shifted nature of the respective products is reminiscent of the isomerism already encountered in the spiroketal type divergolides (see above). Moreover, the acidity of the alkylated glutaconic acid, now incorporated into the pyrrolidinone, is reflected by the epimeric nature of the glutaconic methine (C2'') in **42** and **43**. When moving on to the four hygrocin pyrrolidinone isomers (**44**–**47**), the allegedly facile C2''-epimersation as well as 1,2-acyl shifts (C11 and C12 diol) can again be observed. Moreover, hygrocin E (**46**) features additional (*Z*) to (*E*) isomerization of the glutaconic acid's olefin, adding an additional layer of stereochemical complexity. This accentuates the diverse reactivity of glutaconic acid derivatives but also bears imminent pitfalls: isomerization events as artifacts of natural product isolation cannot be excluded.

[1] **43**'s description in the literature coincided with another communication reporting novel divergolides, hence the name „divergolide E" appears in the literature describing two compounds, **43** and **32**.

One stereochemical feature, that *all pyrrolidinone divergolides and hygrocins share*, however, is the configuration of the tertiary hydroxyl resulting from 1,2-addition to the C5′ carbonyl. Even though this reaction is presumably reversible, the glutaconic acid seems to only add to one of two diastereotopic faces of the carbonyl. A plausible explanation for this selectivity might be given by the following argument: if one assumes that *proto*-divergolide **30** exists as *only one* of two possible atropisomers (see Scheme 7, **30-A** and **30-B**), facial selectivity is easily explained by the fixed conformation of the chromophore that cannot freely rotate. A supposed 1:1 equilibrium mixture of both stereoisomers can be assumed to yield an equal distribution of pyrrolidinones epimeric with respect to the tertiary hydroxyl at C5′. The sample size of six ansamycins is small, but sufficient for a hypothesis.



Scheme 10 Plausible mechanisms of azepinone formation.

We will now move on to inspect the other reactivity of *proto*-ansamycin**30**, yielding azepinones (**41**) in an irreversible reaction since it involves subsequent reoxidation of the adduct to the naphthoquinone after formal 1,4-addition of the glutaconic acid (Scheme 10). Note, that during this reaction pathway, the glutaconic acid displays nucleophilicity at the trisubstituted C4′′-position, as opposed to the C2′′-position during 1,2-additions and the stereochemical information of the glutaconic olefin is lost as only the *cis*-configuration can be realized in the resultant azepinone. Two mechanisms for this reaction can be conceived (Scheme 10). Pathway A shows an allylation pathway (**48** to **49**), while the alternative mechanism (B, **50** to **49**) follows an electrocyclization. 1,7-8π-electrocyclizations[17] are rare, but have interestingly been used for construction of *N*-heterocycles, specifically azepine derivatives.[18] Taking into account that the

quinone michael system is not part of the aromatic phenol, the highlighted system (**51**)represents a very electron-poor precursor to a heptatrienyl anion competent to undergo conrotatory ring closure. Generally, 3-aza-heptatrienyl anions react slower than the much more thoroughly studied 2- and 4-aza derivatives[19], but as mentioned above, a strong degree of preorganization is to be expected in the *proto*-ansamycin. The electrocyclizations are believed to occur *via* a helical transition state,[20] hence the 3-aza-heptatrienyl anion generated from **30** by simple deprotonation has to either reorganize or already display a favorable orientation towards the michael system if an electrocyclization indeed takes place in Nature.

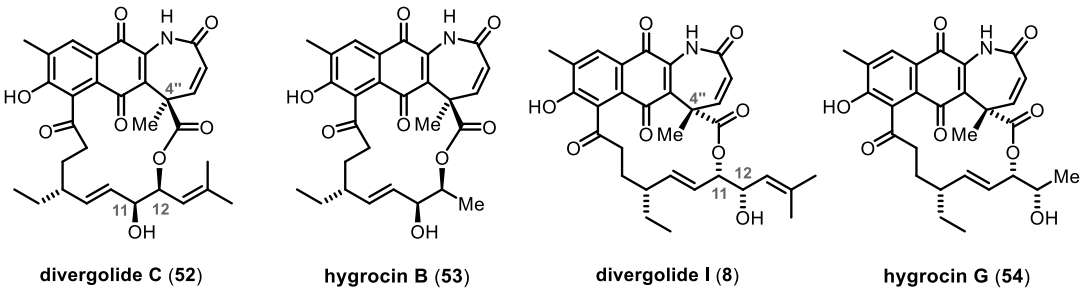


Figure 5 Azepinone type divergolides and hygrocins.

During structural elucidation of divergolides C (**52**)[I] and I (**8**) isolated by Hertweck, circular dichroism spectroscopy revealed the epimeric nature of the quarternary C4'' carbon in between the two azepinones, that represent 1,2-acyl shifted isomers (Figure 5). The structures of hygrocins B (**53**, Carter) and G (**54**, Shen) were reported without showing relative stereo-chemistry and the configurations shown here are based on our synthesis of *epi*-hygrocin G (see chapter 2.4.2) and the studies conducted by Sun *et al*. published in 2017.[21] Note that in this important communication that secures the configuration of the azepinone divergolides and hygrocins, unfortunately unnecessary jargon is created by renaming divergolide C (**52**) to olimycin B while stating in the manuscript that the spectral data matched that of **52**.It is interesting that the configuration of the quarternary stereocenter is the same for the respective acyl shifted isomers. However, since it cannot be excluded that these four natural products **52**-**54**and **8**have the same amount of C4'' epimeric analogues in Nature, we refrain from speculating on a possible influence of diol connectivity on transannular selectivity in the absence of supporting data. This finalizes the overview of the known divergolide and hygrocin natural products.

[I]Divergolide C's structure was initially wrongly described as the hydroquinone.

1.2.4 Crystal structures of hygrocins and divergolides

The intricate molecular structures of the hygrocins and divergolides were elucidated mostly by thorough NMR analyses, but this task could have not been accomplished without securing the relative stereochemistry by single crystal X-ray analysis of some representative members of the ansamycins. For each of the three basic core structures (spiroketals, pyrrolidinones and azepinones) a crystal structure could be obtained. The following section will briefly discuss the structural features of the individual natural products.

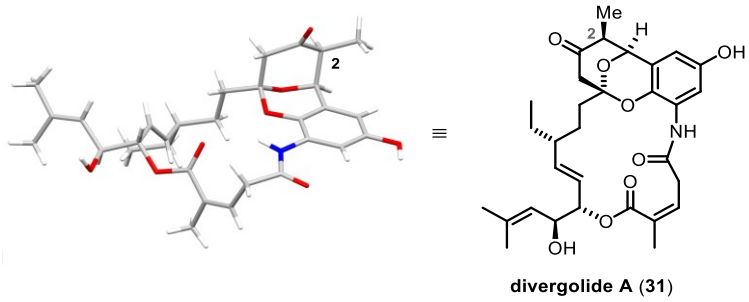


Figure 6 X-ray structure of divergolide A (**31**).

The solid state structure of spiroketal type divergolide A (**31**) was disclosed by Hertweck.[13d] The overall structure can be described, when comparing it to the other two basic types in the families, as rather flat, since the 17-membered macrocycle can be viewed as being approximately in the same plane as the aromatic portion. This makes the spiroketal type ansamycins the species which can cover the biggest horizontal surface area. The pyranone portion of **31** stands perpendicular to the rest of the framework, making the acidic C2 position easily accessible for epimerization, as can be seen in several congeners of divergolide A (see Scheme 6). Also, the (*Z*)-glutaconic acid, which has not undergone intramolecular reactions, is accessible for isomerization reactions, as exemplified in divergolide the congeners that show the (*E*)-configured glutaconic acid.

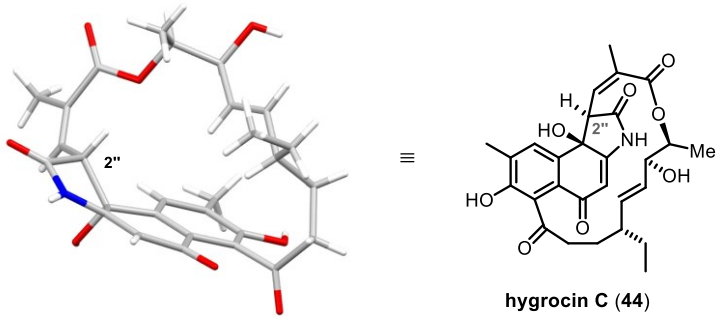


Figure 7 X-ray structure of hygrocin C (**44**).

An X-ray structure of pyrrolidinone hygrocin C (**44**) was reported by Shen.[14b]**44** displays a basket-like structure typical of classic ansamycins. It makes the pyrrolidinone type ansamycins more compact then the spiroketals, with the *ansa* chain stretching over the aromatic core giving it a T-shape when projecting along the handle. The prerequisite pyrrolidinone lies slightly tilted the naphthoquinone, leaving the glutaconic methine (C2'') relatively accessible for the isomerization reactions that lead to the congeners that show opposite configurations at this center and/or isomerization to the (*E*)-glutaconic acid (see Scheme 9)

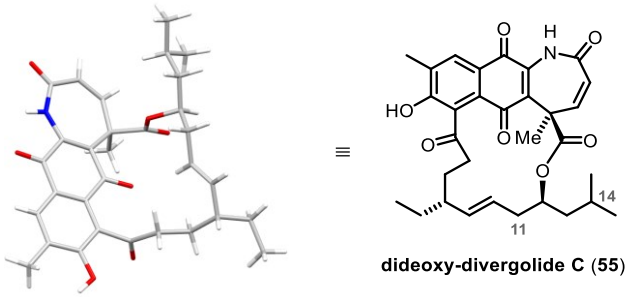


Figure 8 X-ray structure of a dideoxy-divergolide C (**55**).

The latest contribution to divergolide solid state structures by Sun *et al*.[21] is the crystal structure of biosynthetic intermediate**55** towards divergolide C (**52**). This azepinone, confusingly named olimycin A by the authors of the study, lacks two degrees of oxygenation, namely at the allylic position C11and the tertiary position C14 (see section 1.2.1). For the overall structure, however, it can be assumed to be of minor relevance. The shape of **55** resembles an L-from, since the azepinone structure lies almost perfectly in the same plane as the annealed naphthoquinone. Thus, it is easily deduced why the CD-spectra of divergolide C (**52**) and I (**8**), that show opposite configurations at the quarternary stereocenter, differ so greatly.[13e]

1.2.5 Shunt and degradation products of divergolides and hygrocins

Having covered the biosynthesis and structural diversity of the divergolides and hygrocins this section will cover the shunt products and biosynthetic intermediates that were isolated. In some cases, the isolation of these intermediates was helpful in substantiating the biosynthetic model.

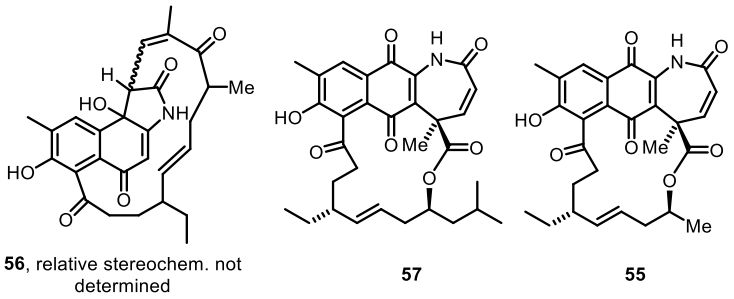


Figure 9 Biosynthetic intermediates lacking oxygenation.

An interesting case are the isolations of a dideoxy-hygrocin C (**56**), hydro-deoxy-divergolide C (**57**) and a dideoxy-hygrocin C (**55**). In these molecules, the naphthoquinone *proto*-ansamycin **30** underwent both available modes of ring-contraction *before* the oxidative tailoring was finished, paying homage to the high reactivity of the glutaconic acid. Also, this might be a hint that naphthoquinone formation can occur *during* chain elongation, as proposed by Shen (see chapter 1.2.2).

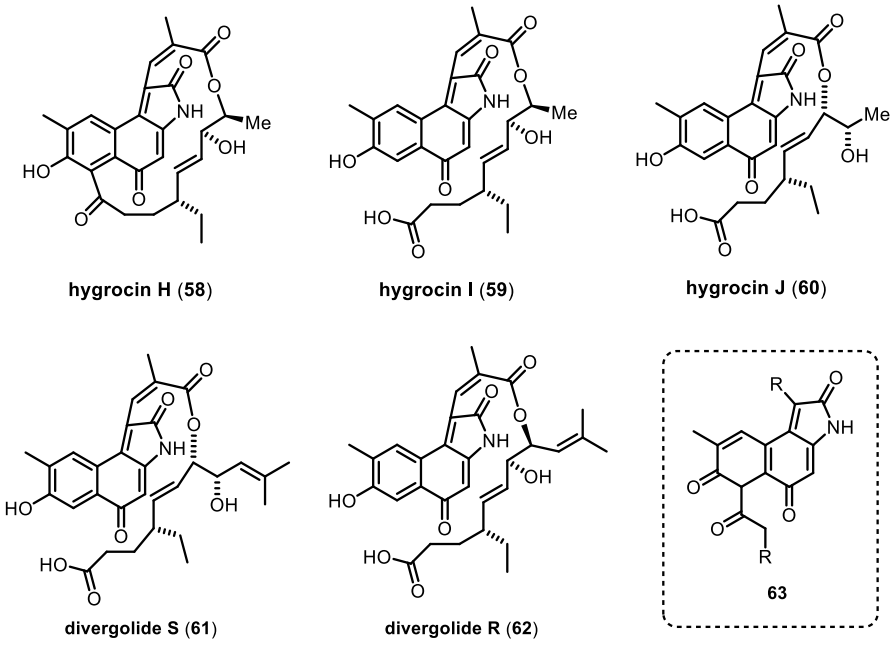


Figure 10 Dehydrated and *seco*-variants of pyrrolidinone ansamycins.

Hygrocins H (**58**), I (**59**) and J (**60**), as well as the divergolide analogues R (**61**) and S (**62**), feature a dehydrated pyrrolidinone (Figure 10). The extended π-system gives *seco* ansamycins **59**–**62** a

red color, as opposed to the usually yellow naphthoquinone derivatives.[13a] Since the tetracyclic derivative **58** exists as well, it can be speculated that the pyrrolidinone dehydration precedes the ring-opening to the *seco* variants, possibly by additional ring-strain arising from further planarization of the initially basket-shaped compound. The mechanism through which ring-opening proceeds was suggested to occur *via* a *retro*-Claisen reaction of tautomer **63**.

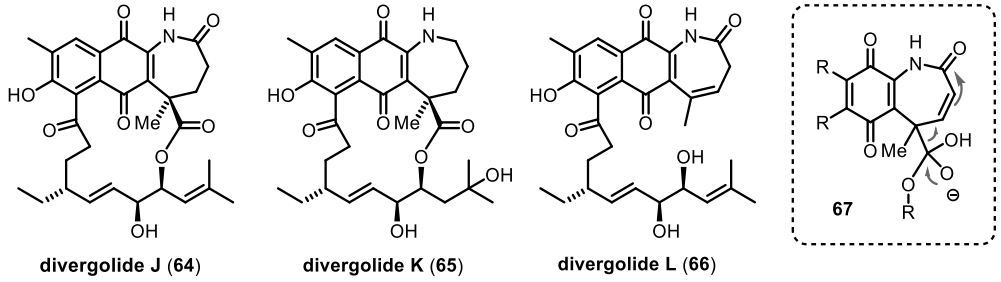
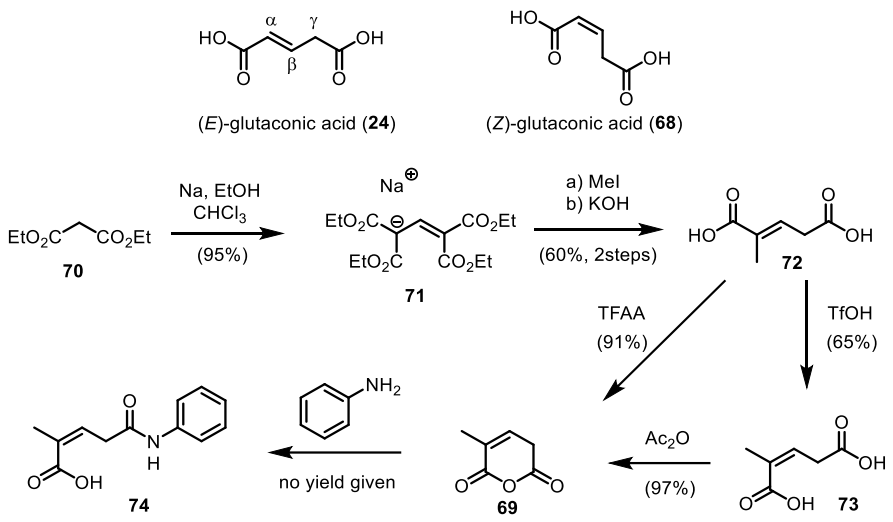


Figure 11 Reduced and decarboxylated derivatives.

The azepinone derivatives divergolide J (**64)**, K (**65**) and L (**66**) seem to resemble congeners of natural products that underwent further reduction processes, as **64** and **65**show two additional degrees of reduction of the *N*-heterocycle. Interestingly, divergolide K (**65**) still bears the tertiary alcohol on its *iso*-butyl side chain and can be seen as an intermediate towards *iso*-butenyl formation. The tricyclic species divergolide L (**66**) could arise either by base-mediated decarboxylation from of divergolide C (**52**) or I (**8**), or by decarboxylation of the reduced derivative divergolide J (**64**), followed by hydroquinone reoxidation (Figure 11).

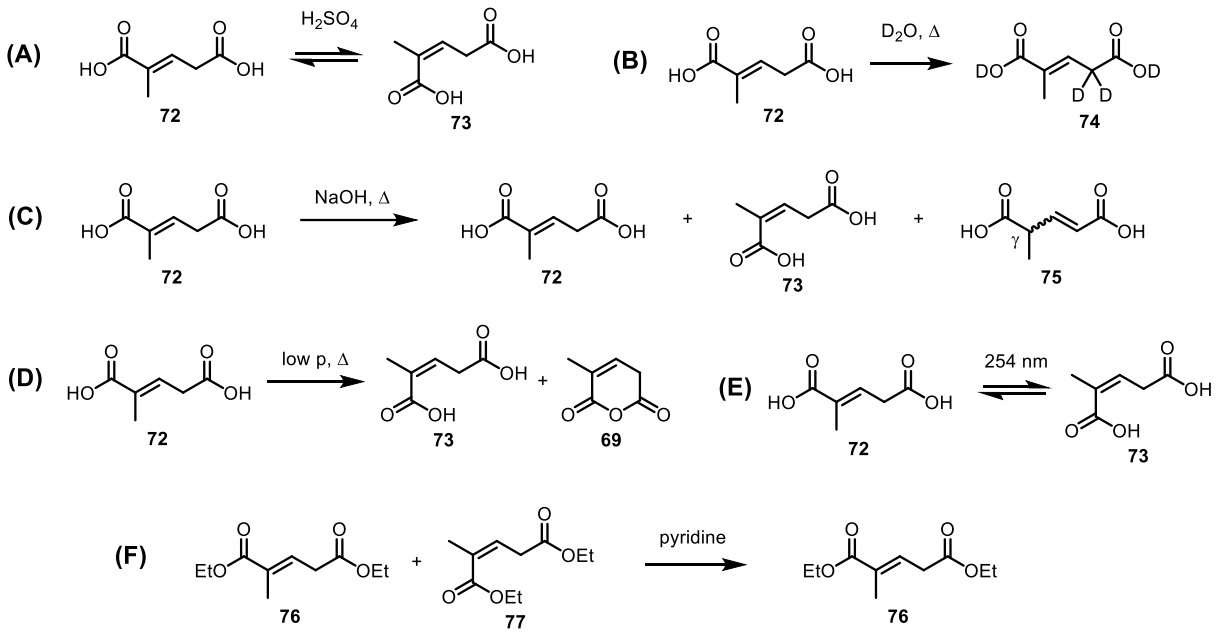
1.2.6 Glutaconic acid chemistry

The glutaconic acids**24** and **68**(Scheme 11) are a fascinating structural unit, whose isomerism and structure have generated much debate since the first reports of the synthesis of related isomers and substituted derivatives. To cite the most comprehensive study finally clarifying the ongoing debate, "heated polemics were associated with the progress toward understanding the tautomerism and isomerism of glutaconic acids". In their communication released in 1975, Kagan and coworkers[22] systematically synthesized α- and γ-methylglutaconic acids to study their spectral properties and the influence of a variety of conditions with respect to isomerism and conformation of the glutaconic olefin. As the *proto*-divergolides and hygrocins are very likely to contain an either (*Z*)- or (*E*)-configured methylglutaconic acid embedded between an amide and an ester linkage, it is instructional to carefully review Kagan's study.



Scheme 11 α-Methylglutaconic acid synthesis.

In 1883, Conrad and Guthzeit[23] were the first to report a synthesis of γ-methylglutaconic anhydride (**69**) and in 1909, Feist and Pomme successfully realized the regioselective thermal amidation of anilines (Scheme 11).[24] The synthesis began by a double displacement/elimination of malonic ethyl ester **70** and chloroform, yielding an allyl anion sodium salt (**71**). Following methylation, a one-pot saponification/decarboxylation yields (*E*) glutaconate **72**, which can be directly isomerized and dehydrated by the action of trifluoroacetic anhydride using Zhao's modification,[25] or isomerized with triflic acid and subsequently dehydrated with acetic anhydride as reported initially. Anhydride **69**'s structure was indeed only secured by NMR spectroscopic data obtained by Kagan in 1975. The hydroxy pyrone tautomer of **69** was previously suggested as the predominant species, which was demonstrated to form only under strongly acidic conditions.



Scheme 12 Reactivity of α-methyl glutaconic acid derivates.

Scheme 12 summarizes the findings:

(A) Under strongly acidic conditions, acids **72** and **73** are interconverting and upon prolonged heating, the species equilibrate to a 1:1 mixture of the (*E*) isomer and the (*Z*) acid as the anhydride (**69)**.

(B) Complete deuterium exchange of the methylene protons of **72** occurs within 20 minutes in heated D_2O solution.

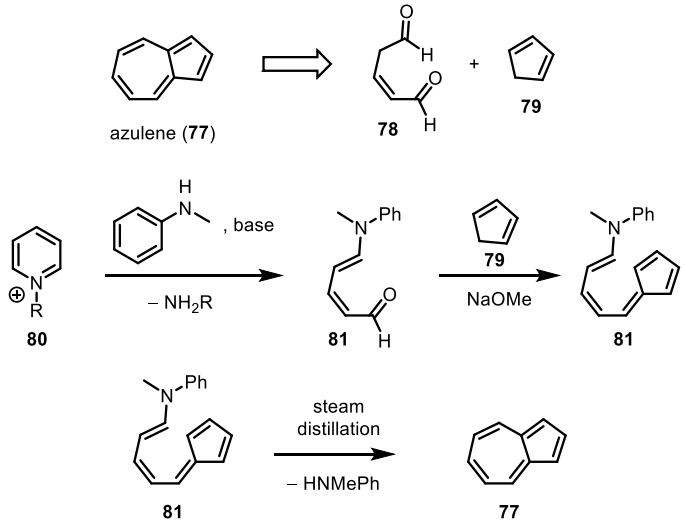
(C) Refluxing an alkaline solution of **72**for 6 days results not only in partial isomerization of the double bond but forms detectable amounts of a single γ–methylglutaconic acid (**75**) isomer as well.

(D) Prolonged sublimation at 160 °C under vacuum of (*E*) isomer **72** produced, depending on the surface temperature of the condensation site, either the (*Z*) isomer **73** or its anhydride **69**. No isomerization to γ–methylglutaconic isomers (**75**) was detected during this process.

(E) Photochemical isomerization (2 h, 254 nm) of cold diethyl ether solutions of either pure **72** or **73** produced equimolar mixtures of **72** and **73**, again without formation of γ-methylglutaconic isomers.

(F) The probably most useful insight from Kagan's study for the synthetic endeavors described in this thesis, was the finding that the equilibrium of diethyl ester derivatives **76** and **77**when treated with pyridine proved to be nearly completely in favor of the (*E*)-isomer **76**.

To conclude this section concerning the reactivity of glutaconic acid derivatives, the Hafner-Ziegler azulene synthesis will be discussed. In 1957, Hafner[26]and Ziegler reported a very straight forward synthesis of the dark blue hydrocarbon (**77**), which is an isomer of the colorless naphthalene. Hafner's insight was that azulene can be seen as the double condensation product of glutacon-dialdehyde**78** and cyclopentadiene (**79**). As the reactivity of glutaconic dialdehydes complicates their isolation, the use of Zincke aldehydes as surrogates traced the starting materials for azulene synthesis back to **79** and an activated pyridine of the type**80**. The three-step synthesis generates masked aldehyde **81** through methyl aniline promoted ring-opening of pyridinium **80** followed by subsequent condensation with **79** to give the dark red, crystalline fulvene**81**. Azulene(**77**) can be produced from **81** by steam distillation from high boiling hydrocarbons at temperatures above 150 °C.



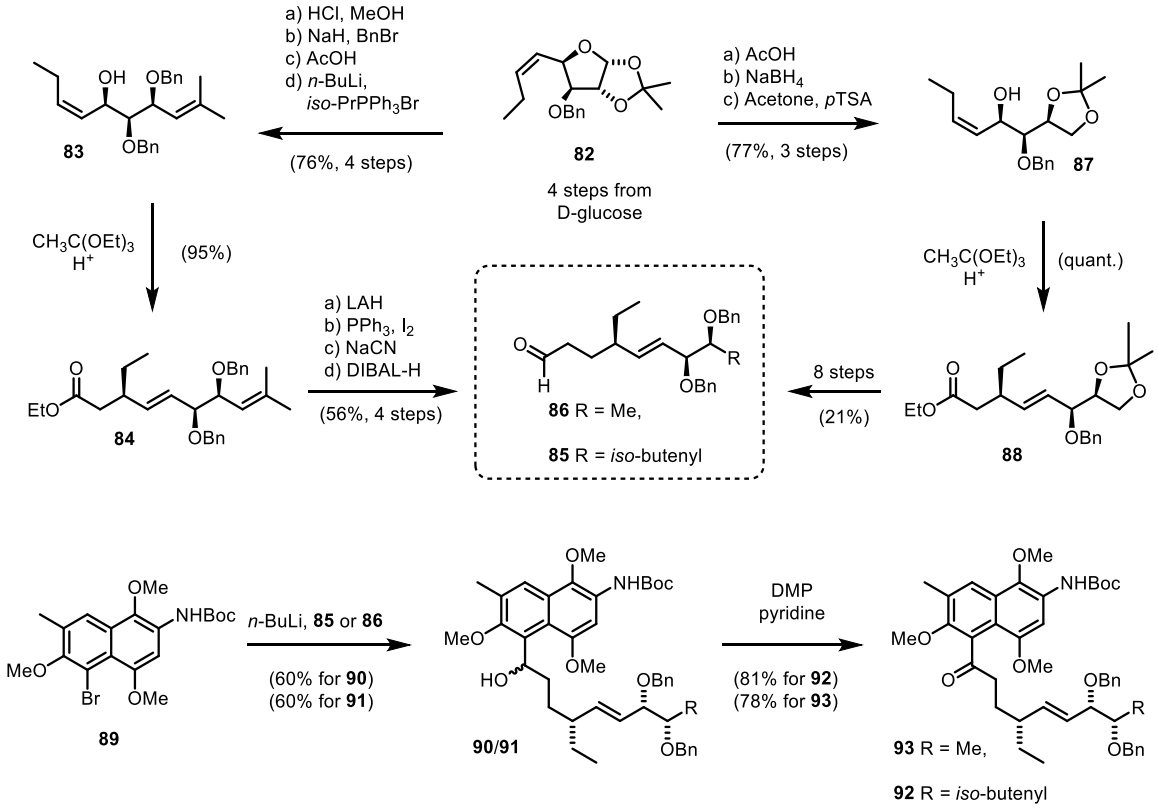
Scheme13 Originally reported Hafner-Ziegler azulene synthesis.

1.3 Published synthetic studies towards divergolides and hygrocins

From 2012 until the last report in 2015, four research groups, including the Trauner group, have released communications detailing their efforts towards the synthesis of various divergolides and hygrocins. While the published results offer some insights into different strategies to access various members of the ansamycin families, no completed synthesis was reported. Notably, construction of a macrocyclic compound remained elusive, with the Trauner approach published in 2013 being the only one providing an entry into a linear congener that constitutes the entire carbon skeleton. In the following sections, these approaches will be discussed, with the Trauner approach from 2013 serving as a starting point for the work undertaken by the author of this thesis.

1.3.1 Rasapalli's approach

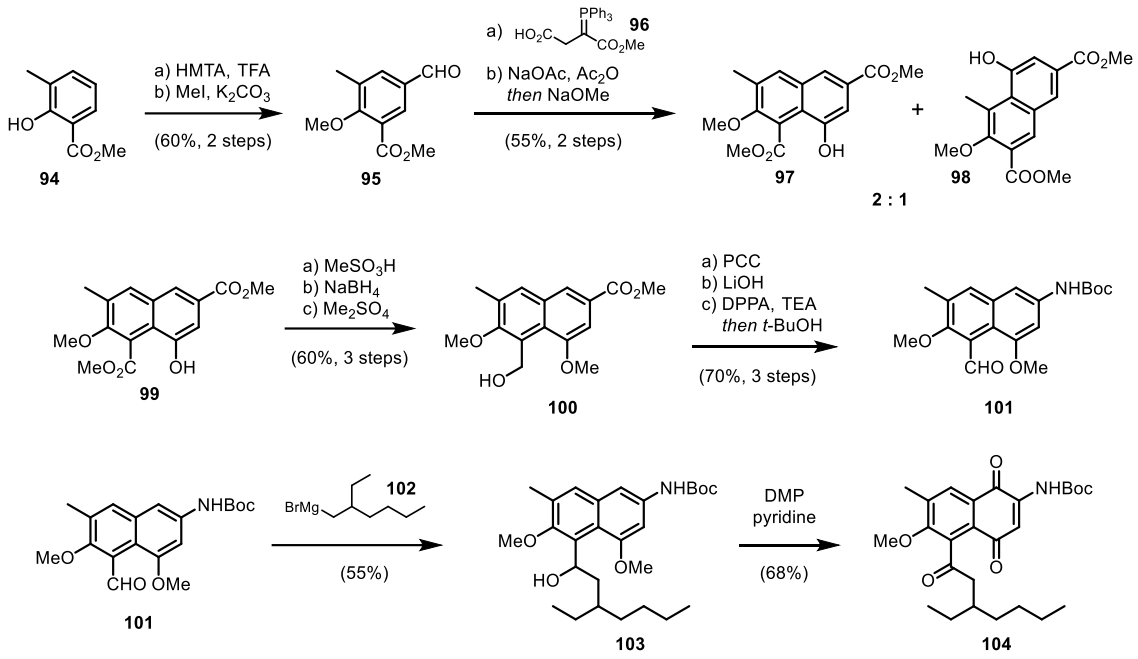
The Rasapalli group released three communications dedicated to studies towards azepinone- and pyrrolidinone-type divergolides and hygrocins.[27]Rasapalli and coworkers realized the structural similarities between the two families make a unifying approach feasible and devised syntheses for the chiral fragments of the *ansa* chains of both families. The overall strategy hinges on the biomimetic ring-contraction of a macrocyclic quinoid precursor, though a macrocyclization strategy was not disclosed. Scheme 14 gives an overview of exploiting the chiral pool to not only excise the (*S*,*S*)-1,2-diol motif from a sugar derivative, but also use the sugar's defined hydroxyl stereochemistry to set the (*R*)-configuration of the ethyl side branch.



Scheme 14 Rasapalli's syntheses of divergolide and hygrocin *ansa*-fragments.

D-Glucose diacetonide **was** transformed to (*Z*)-configured olefin **82** *via* Wittig reaction following oxidative diol cleavage. After further elaboration that leads to the *iso*-butenyl group representative of the divergolide *ansa* chain (**83**), a Johnson-Claisen rearrangement furnished (*E*) olefin **84**. Ester reduction, homologation and reduction of the resultant nitrile provided access to aldehyde **85**. Conveniently, the synthesis could be easily adopted to yield hygrocin fragment **86** as well. Both aldehydes could be coupled to naphthoquinone **89**, a compound whose preparation was adopted from a recently published PhD thesis from the Trauner group.[28]In a

third communication by Rasapalli and coworkers, a report on their studies towards the aminonaphthoquinone core was presented.



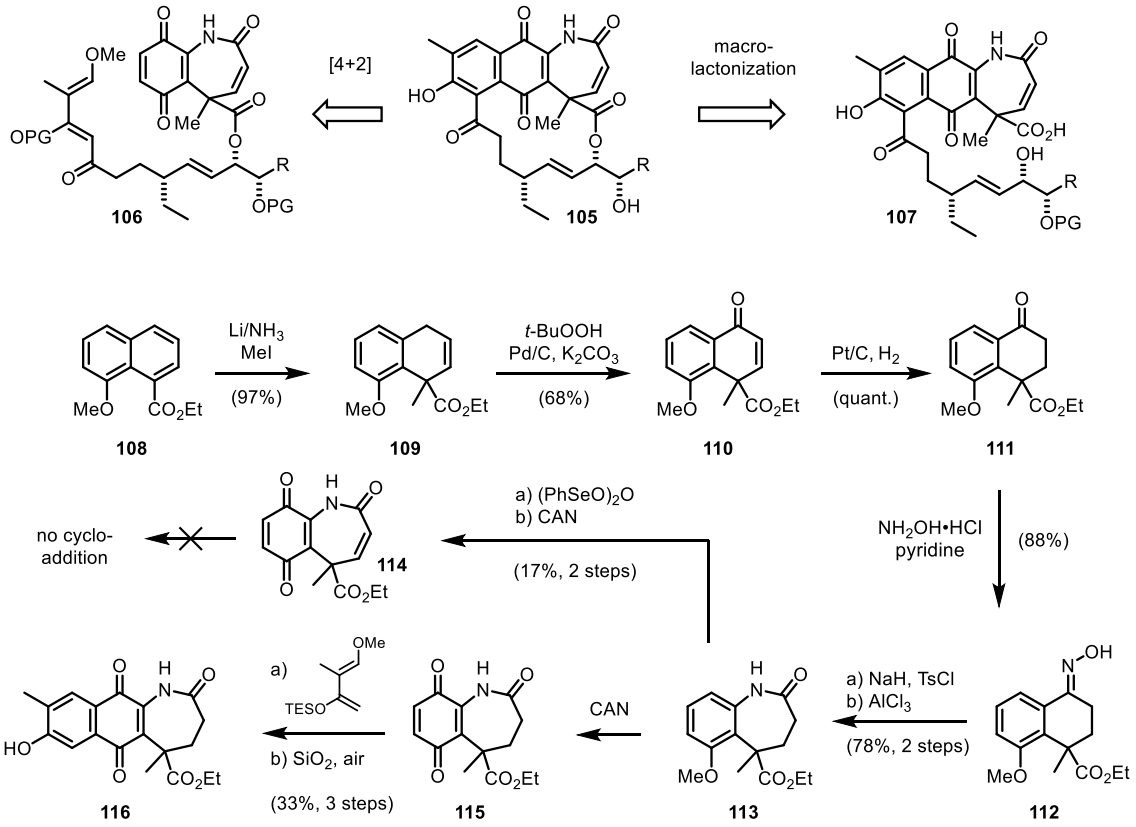
Scheme 15 Rasapalli's studies on naphthoquinone synthesis.

Scheme 15 details how the naphthalenic system was constructed. Duff's formylation of phenol **94** was followed by methylation and Wittig olefination. The intramolecular Friedel-Crafts reaction towards**97**suffered from poor yield and regioselectivity but granted enough material to allow for further elaboration to naphthyl alcohol **100**.Oxidation and methyl ester saponification were followed by installation of the nitrogen *via* Curtius rearrangement giving **101**. An interesting finding, that concludes the study, was that after coupling to an organomagnesium reagent (**102**), Dess-Martin oxidation not only affected naphthyl alcohol oxidation, but also oxidized the electron rich naphthalene **103** to the corresponding naphthoquinone (**104**). Unfortunately, this reactivity could not be reproduced with substrates bearing an *ansa* chain containing useful γ-ethyl functionality for divergolide or hygrocin synthesis, but only on the β-ethyl model compound **103**.

While the rapid chiral pool based installation of the entire *ansa* chain stereoinformation by Rasapalli and coworkers can only be commended, differentiation of the 1,2-diol hydroxyl groups was not realized. More importantly, coupling of *ansa* fragments to the aromatic core of the molecule was not optimized and the sequence was lengthy, rendering it impractical to reach the end game of the synthesis.

1.3.2 Moody's approach

The strategy towards azepinone type divergolides and hygrocins disclosed by Moody and coworkers in 2014[29] is conceptually distinct, as it aims to construct the azepinone (**105**) not using a biomimetic ring-contraction. Instead, the strategy offers a racemic entry to establish the azepinone core annealed to a benzoquinone and outlines the competency of some related bicycles to undergo Diels-Alder reactions (Scheme 16). The macrocyclization strategy called for either cyclization through an intramolecular cycloaddition (**106**), or by intermolecular cycloaddition followed by macrolactonization (**107**).



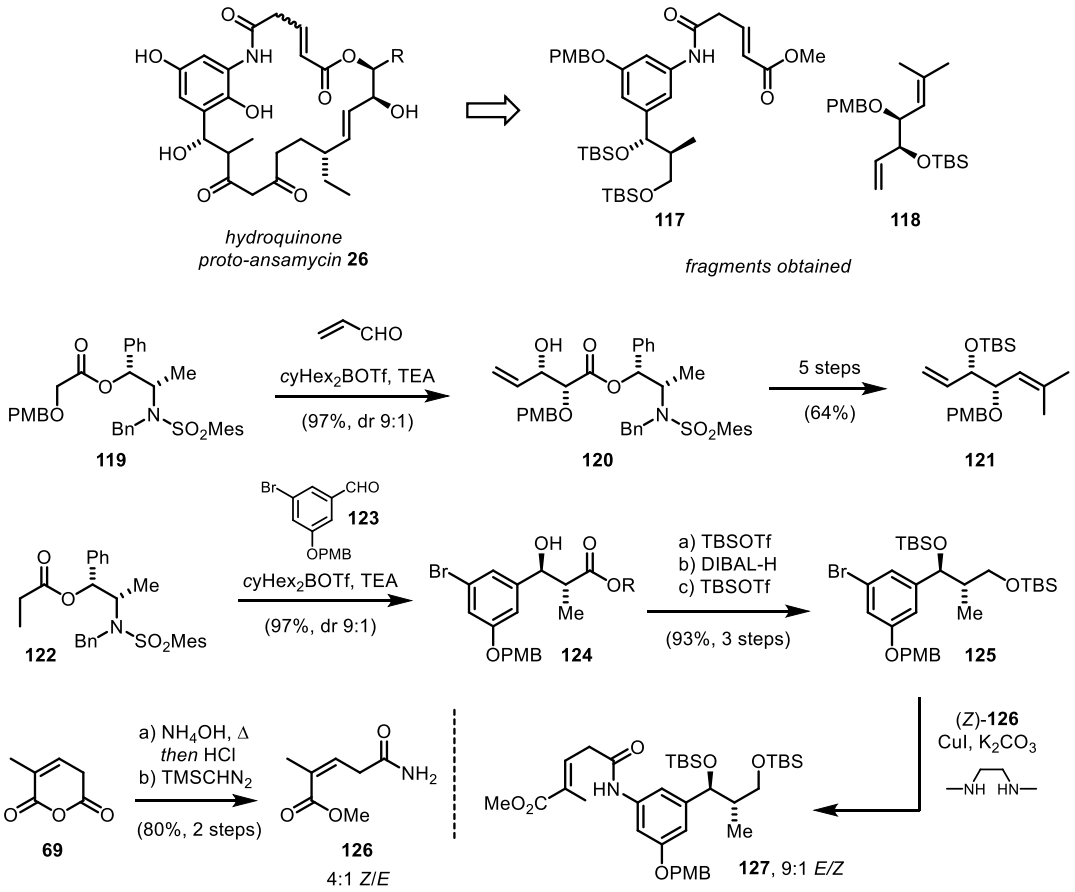
Scheme 16 Moody's strategy towards azepinone synthesis.

As outlined above, the azepinone was constructed *via* Beckmann rearrangement of a tetralone, prepared by Birch alkylation of naphthalene **108**. Beckmann rearrangement of an α,β-unsaturated oxime derived from**110** proved unfruitful but proceeded smoothly using reduced derivative **111**. Reintroduction of the unsaturation and quinone formation however was hampered by issues of low yield and scalability (**114**), attributed to sensitivity of intermediates. Ultimately, Diels-Alder reaction with suitable dienophiles only proved viable with the saturated azepinones **115**, adding a further complication to the strategy.

In summary, Moody's approach towards azepinone divergolides and hygrocins creatively circumvents the challenging 19- or 20-membered macrocycle formation by successful installation of the azepinone-benzoquinone in a non-biomimetic fashion. Nonetheless, low yields and scalability denied completion of the synthesis and also only produced racemic material. Results detailing the construction of *ansa* chain components were not described. It should be noted that a PhD thesis entitled "Approaches to the Synthesis of Hygrocin A" was submitted by L. Pennington in fulfillment of a PhD degree conducted under the guidance of C. Moody in 2010 as well. The access to the thesis is still restricted, hinting at some experimental data concerning hygrocin ansamycin synthesis that is still awaiting publication.[30]

1.3.3 Zhao's approach

The Zhao group was the first to publish synthetic strategies towards divergolide synthesis in 2012,[31] followed by another report in 2015.[25] Zhao and coworkers aimed at the synthesis of divergolides bearing the complex spiroketal bicycle of divergolides A (**31**), and provided insights into the synthesis of some of the prerequisite precursors, albeit without successfully assembling the unique ring system. Nevertheless, Zhao's findings concerning glutaconic acid synthesis and installation provide insight into the capricious nature of this highly reactive unit. Scheme 17 outlines the results of their studies.



Scheme 17 Zhao's studies towards spiroketal divergolides.

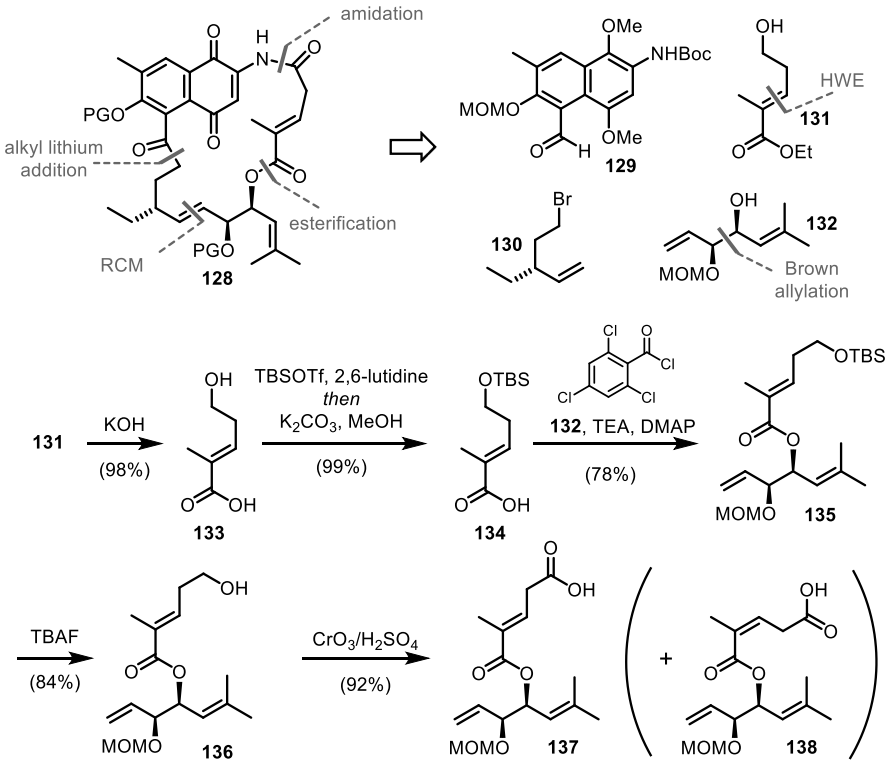
The ability of norephedrine derivatives to control diastereoselectivity of aldol reactions[32] was elegantly demonstrated, as both the synthesis of the (*S*,*S*)-1,2-diol motif and the chiral spiroacetal components could be realized in good yields. A challenging glycolate aldol reaction of chiral ester **119** with acrolein gave *syn*-product **120**, which was carried on to yield differentially protected diol **121** after five additional steps. Interestingly, reaction of propionic ester **122** and benzaldehyde **123** gave the *anti*-aldol **124**. Reductive auxiliary removal and silyl-protection furnished aryl bromide **125**. Studies on the copper catalyzed arene amidation using (*Z*)-configured glutaconamide species **126** showed that the couplings can be realized in high yields but invoked near complete glutaconamide isomerization to the (*E*)-configuration (**127**). Also, an improved procedure to obtain the valuable methyl glutaconic anhydride **69** was disclosed (see chapter 1.2.6).

Overall, Zhao's approach demonstrated the usefulness of auxiliary-based stereoinduction for construction of some of the *ansa* chain's fragments and provided valuable insight into the synthesis and reactivity of glutaconic acid derivatives. However, none of the ultimate challenges for ketal type divergolide synthesis, namely spiroacetal formation or macrocyclization were addressed.

1.3.4 Trauner's1st generation approach

The last approach towards the biomimetic construction of azepinone and pyrrolidinone divergolides to be discussed is the report by Trauner and coworkers published in 2013.[33] The chemistry will be discussed in more detail, as it served as a starting point of the work described in this thesis. The author of this thesis was involved in the preparation of the late-stage intermediates as an undergraduate worker and carried on the work in fulfillment of his Master and PhD studies. In course of the project, the synthesis outlined below was repeated several times before an alternative strategy was chosen.

Following the proposed biosynthesis, the strategy aims towards construction of a macrocyclic naphthoquinone (**128**) to study the diversification of this macrolactam/macrolactone in subsequent biomimetic ring-contractions. The divergent approach dissects a protected variant of a *proto*-divergolide into four fragments (Scheme 18). Macrocyclization was to be realized by ring-closing olefin metathesis (RCM).

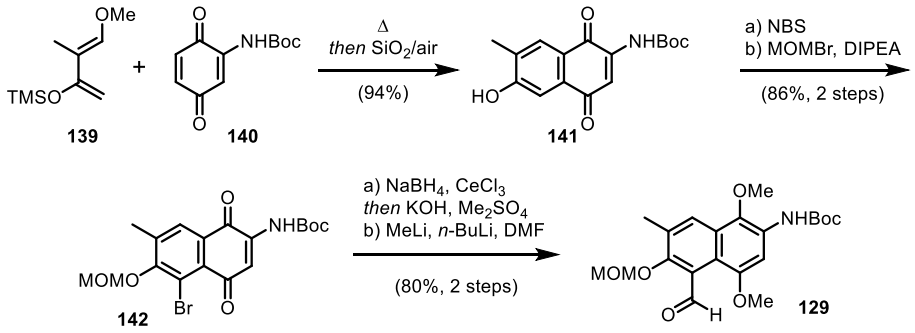


Scheme 18 Retrosynthesis of *proto*-divergolide, synthesis of ester **137**.

The Western fragment of the *proto*-divergolide was assembled from diol **132** and carboxylic acid **134**. The former was obtained by Brown allylation[34]of prenal and the latter by Horner-Wadsworth-Emmonds (HWE) olefination,[35] followed by protecting group manipulations. The Yamaguchi protocol[36] furnished ester **135**, while a Jones oxidation after TBAF-mediated

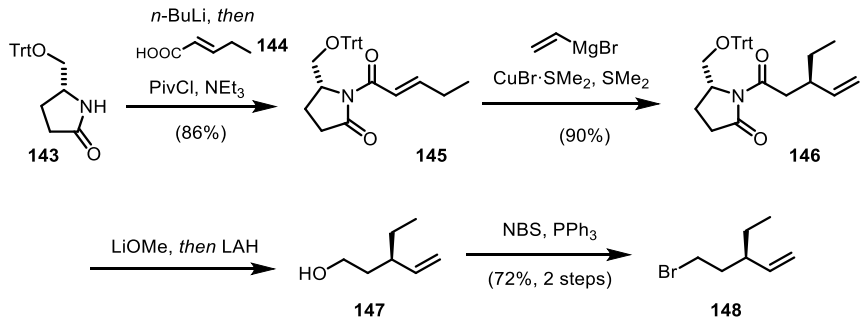
desilation provided carboxylic acid **137**, albeit with minimal isomerization of the glutaconic olefin (**138**).

The synthesis of the aromatic core was slightly improved after publication and robustly produced gram quantities hexa-substituted naphthaldehyde **129**. The optimized procedure is detailed below (Scheme 19).



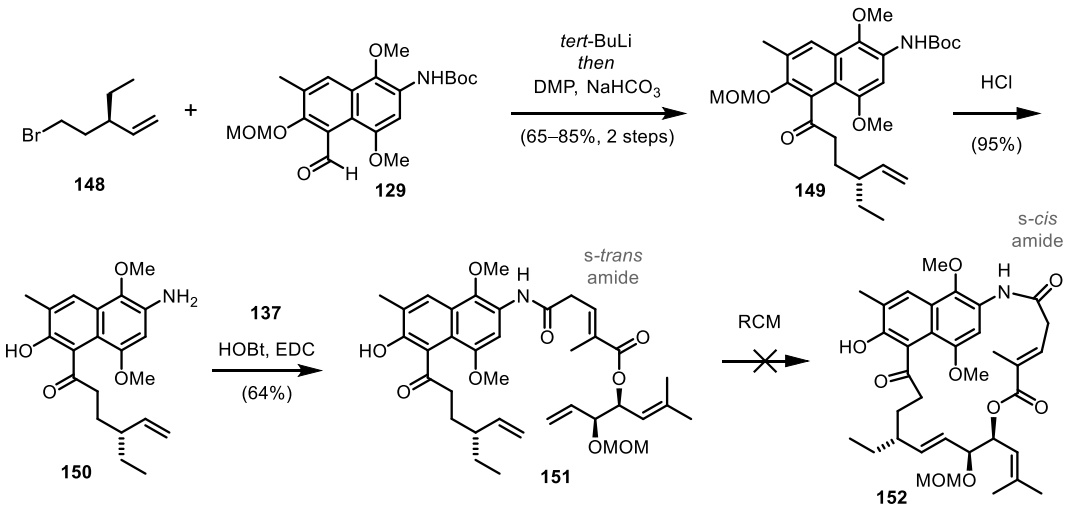
Scheme 19 Construction of naphthaldehyde **129**.

The yield of the Diels-Alder reaction of modified Danishefsky diene **139**[37] and aminoquinone **140**,[38] followed by methanol elimination and oxygen mediated aromatization was found to be improved by ensuring complete conversion to naphthoquinone **141**. Typically, three days of vigorous stirring under air were required, also due to the poor solubility of the product, resulting in suspensions of reaction intermediates. A clean bromination reaction required recrystallized NBS on scale and crystallization furnished material of high purity to enable a higher yielding MOM protection of the phenol. The reduction of **142** and subsequent trapping of the resulting hydroquinone as methyl ethers required strict degassing of all reaction solvents and careful use of Schlenk-technique to ensure that the air-sensitive hydroquinone intermediate is not reoxidized, a process otherwise rapidly outcompeting methylation. Formylation could be achieved in good yield on 1 g scale, if the carbamate was deprotonated by action of MeLi prior to halogen-metal exchange.



Scheme 20 Koga-auxiliary based synthesis of alkyl bromide **148**.

To obtain chiral alkyl bromide **148**, we performed a diastereoselective 1,4-addition of a vinyl cuprate to Koga auxiliary (**143**) based imide **145**[39]that furnished olefin **147** with no detectable amounts of the other diastereomer (Scheme 20). This reaction was performed on a 20 g scale and purified by crystallization in 90% yield but required stoichiometric amounts of costly CuI·SMe_2. The subsequent methanolysis/reduction/bromination sequence reproducibly provided bromide **148** in up to 72% yield over two steps, but the volatility of both **147** and **148** called for time consuming distillation of the reaction intermediates after both extractive workup and the necessary chromatography steps. On multigram scale, procuring the material took up to seven days.



Scheme 21 Fragment coupling towards RCM precursor **151**.

Halogen-metal exchange of alkyl bromide**148** could be achieved using *tert*-butyl lithium, but 4 to 5 equivalents of the precious olefin was needed to give reasonable yields of the naphthylic alcohol, that was typically immediately oxidized with Dess-Martin periodinane (DMP) (Scheme 21). This can surely be attributed to the acidity of the carbamate proton of **129**, a complication that was addressed later on in the project. It has to be noted that the reaction suffered from low reproducibility and more often than not contained by-products that could only be separated by preparative HPLC. Switching the solvent from THF to diethyl ether allowed for a cleaner coupling but could not completely eliminate side reactions to intractable byproducts. Even after careful titration of the *tert*-butyl lithium solution and determination of alkyl bromide concentration by high field NMR, the stoichiometry of reactants could not be optimized to allow for a robust and scalable reaction. Nevertheless, sufficient amounts of valuable naphthyl ketone **149** could be produced to allow for initial studies towards the construction of a macrocyclization precursor. Boc-deprotection of **149** was achieved with concomitant MOM ether cleavage to yield air sensitive naphthyl amine **150**. Carbodiimide-mediated coupling of

carboxylic acid **137** then furnished amide **151**, the first published compound to contain the entire carbon skeleton of a divergolide. Initial studies on the competency of **151** to undergo ring-closing metathesis were unsuccessful and attributed to unfavorable amide geometry, as **151** was assumed to reside in the depicted s-*trans* amide configuration, making it conformationally challenging to make the intramolecular reaction happen.

This concludes the introductory part of this thesis. Chapter 2 will concern the synthetic efforts undertaken to build upon the lessons learned from the 1st generation approach by Trauner and resolve the challenge of accessing synthetic *proto*-divergolides and *proto*-hygrocins.

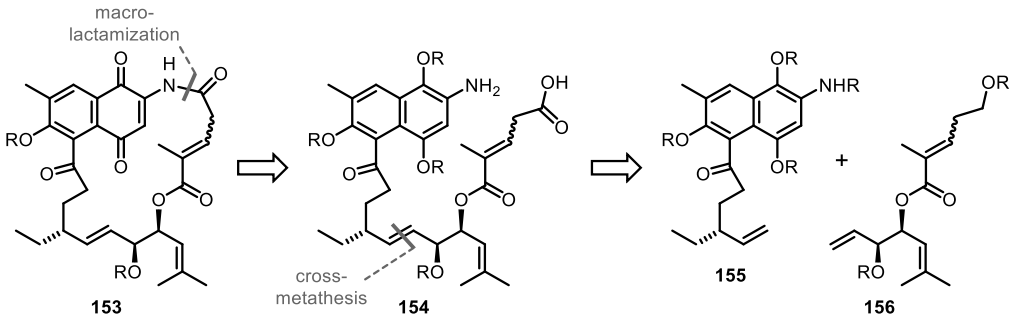
2 Synthetic studies towards divergolides and hygrocins

The results in this thesis are presented chronologically. In some cases, insights gained at earlier stages of the project were helpful to carry on with the current endeavors, but the final optimization of a particular transformation was realized at a later point. In these cases, a footnote was added that will point the reader to the respective later chapter revealing the optimized conditions.

2.1 Attempted macrocyclization *via* macrolactamization I

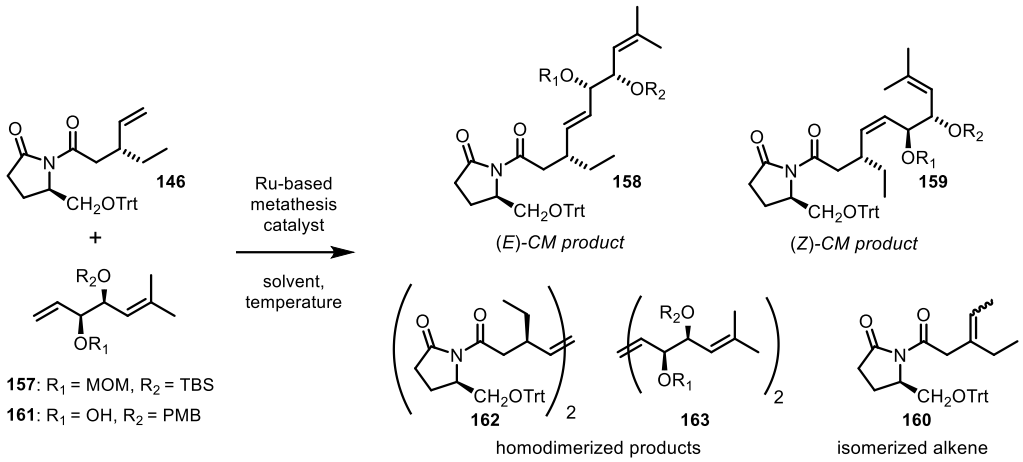
2.1.1 Development of an olefin cross metathesis

Building on the lessons learnt from our 1st generation approach towards naphthoquinone divergolides (chapter 1.3.4), it was established that the ring-closing metathesis strategy pursued was unlikely to be successful. Instead, we opted to explore an olefin cross metathesis (CM) to circumvent the challenging RCM (**154**, Scheme 22), which was first probed using olefins derived from precursors whose synthesis we had established before.



Scheme 22 Retrosynthesis based on a late-stage cross metathesis.

We sought to first explore the CM on model substrates to preserve precious material. After realizing that protection of the homoallylic alcohol of the diol was necessary to obtain significant amounts of CM products, the initial studies explored the competency of a TBS derivative (**157**) of *syn*-diol **132** to undergo CM with the chiral olefin **146**. A PMB protected variant bearing a free allylic alcohol was investigated as well. Scheme 23 shows all observed products that arose by reaction of our test substrates using ruthenium-based metathesis catalysts.



Scheme 23 Possible cross metathesis products.

The effects of different reaction parameters on the CM were explored (see experimental for screening table). The results that guided the further development of the reaction with more elaborate substrates are summarized below:[I]

1) The reaction appears to be completely (*E*) selective (**158**), as no (*Z*)-product (**159**) could be isolated and characterized.

2) A variety of second generation metathesis catalysts in aromatic solvents can affect the reaction, so the catalyst can be exchanged if a simple purification of the reaction product was hampered by side products resulting from catalyst decomposition.

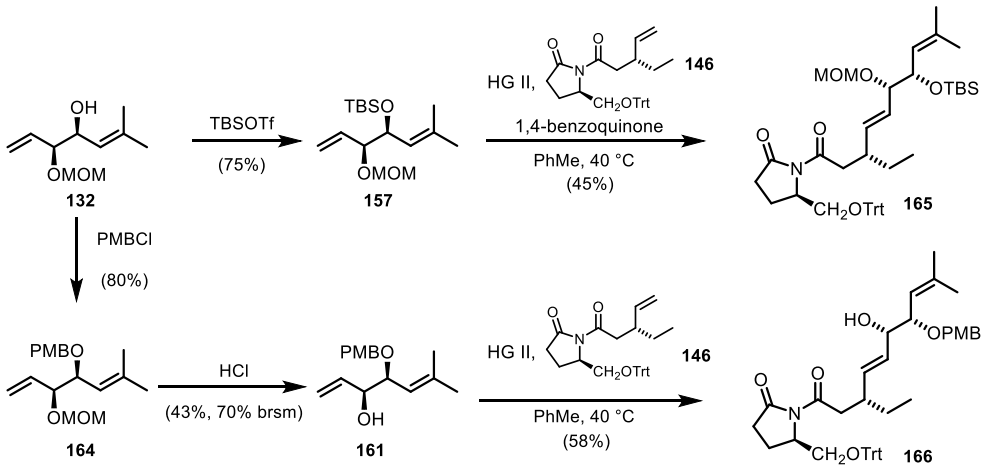
3) At temperatures higher than 45 °C, isomerization of olefin **146** to the internal alkene (**160**) was observed as a substantial side reaction, so heating above 40 °C was avoided.[40]

4) A free allylic alcohol on the reactant (**161**) results in higher yields[41] of the cross metathesis product, and the allylic alcohol should be used in slight excess (1.5–2 eq).

5) While olefin **146** is slow to form dimers (**162**), especially the free allylic alcohol **161** dimerizes rapidly (**163**), supposedly before any cross metathesis occurs.

Scheme 24 shows the best results obtained by the initial screening efforts.

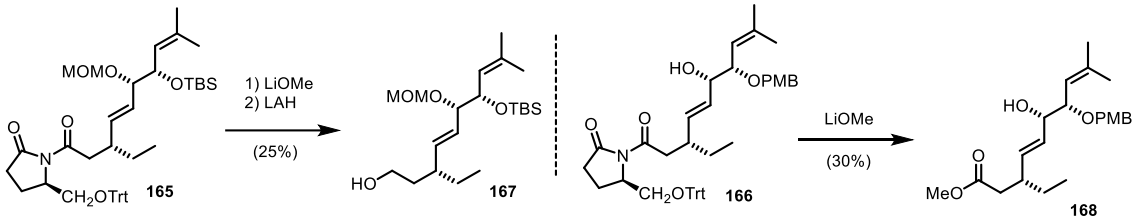
[I] See chapter 2.2.3 for the insights that ultimately lead to yields in the range of 80%.



Scheme 24 Optimized cross metatheses.

It becomes apparent that if a CM was to be included in the synthetic plan, an olefin derivative bearing a free allylic alcohol was to be preferred. However, MOM ether removal in presence of the TBS group (**157**) could not be achieved and yields for MOM removal in presence of the PMB ether proved to not exceed 50%, but yielded sufficient material (**161**) for preliminary evaluation of the CM. It should be noted, that only Brønsted acidic conditions (HCl in cold dioxanes) were successful in removing the MOM ether from **164**, but the reaction had to be quenched at ca 60% conversion as the PMB group was affected as well. The usual alternatives (Lewis acids in combination with thiols or use of *B*-bromo catecholborane at low temperatures) lead to intractable mixtures.[I]

In an attempt to make use of the obtained CM products **165** and **166**, we explored Koga-auxiliary cleavage on these substrates, hoping for easier isolation of non-volatile products (see chapter 1.3.4).



Scheme 25 Cleavage of Koga's auxiliary

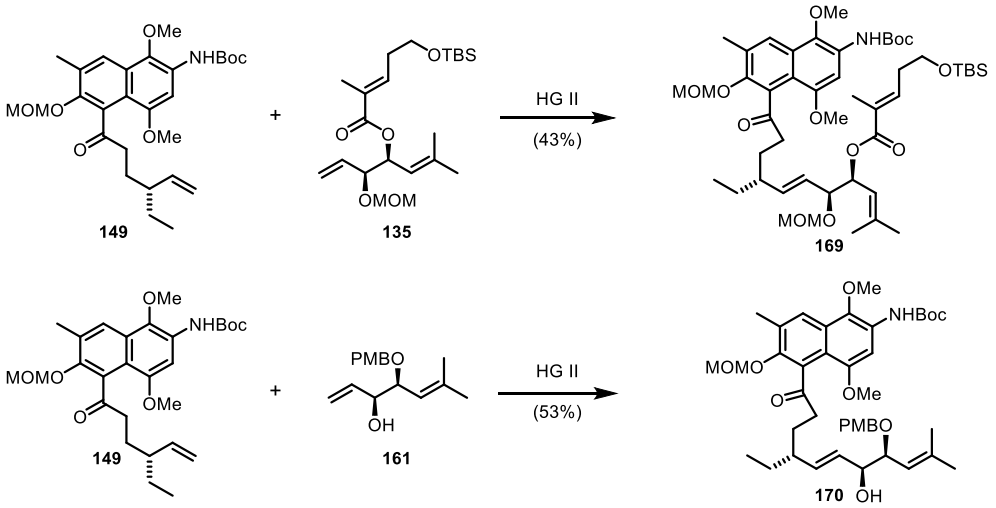
Disappointingly, only the previously established conditions using lithium methoxide (3 eq) were able to cleave the auxiliary in low yields on both **165** and **166**. Boron-based hydrides ($LiBHEt_3$, $LiNH_2BH_3$) or increasing the lithium methoxide concentration lead to even lower

[I] See chapter 2.2.3 for a combination of protecting groups that proved to be orthogonal.

yields or cleaved the imide at the wrong carbonyl. It became clear that an alternative to the Koga auxiliary-based installation of the chiral ethyl branch had to developed at some point, but the exploration of the CM strategy's viability was undertaken with the 1st generation fragments nonetheless.

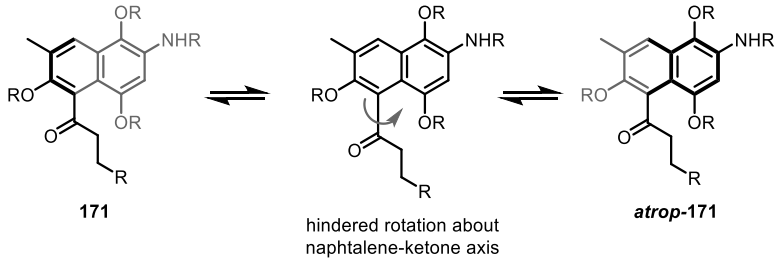
2.1.2 Elaboration of divergolide cyclization precursors

Having established cross metathesis conditions on model substrates, we were able to successfully merge olefins **149** and **135** in 43% yield using Hoveyda-Grubbs 2nd generation catalyst (HG II) at 40 °C (Scheme 26). The reaction towards (*E*)-alkene **169** suffered from low conversion, but the starting materials could be largely recovered. As observed on the model studies, a higher yield of the CM could be obtained by using allylic alcohol **161** as coupling partner for olefin **149**.



Scheme 26 Cross metatheses of larger fragments.

At this point it is instructional to briefly discuss the phenomenon of atropisomery that was observed in virtually all substrates bearing the naphthyl ketone moiety (Scheme 27).



Scheme 27 Atropisomery of naphthyl ketones.

The naphthalene-ketone axis flanked by two alkoxyl moieties in *ortho*- and *peri*-position has to overcome a substantial energetic barrier, if rotated. This is reflected by the room temperature

NMR spectra of compounds of this type; as many protons and carbons in the spectra show two sets of resonances, each representing one atropisomer of the naphthyl ketone. This phenomenon is well documented for similar compounds.[42] Heating solutions to over 60 °C provides enough energy to overcome this rotational barrier, as is exemplified in Figure 12. A DMSO-d_6 solution of ketone **169** was subjected to variable temperature NMR and proton spectra were recorded in 10 °C increments, revealing that most signals of the two atropisomers converge at 60 °C.

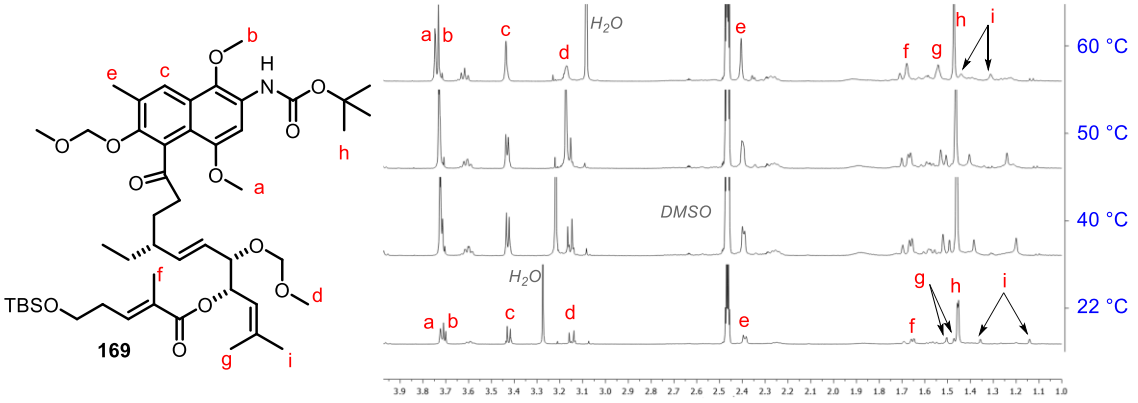
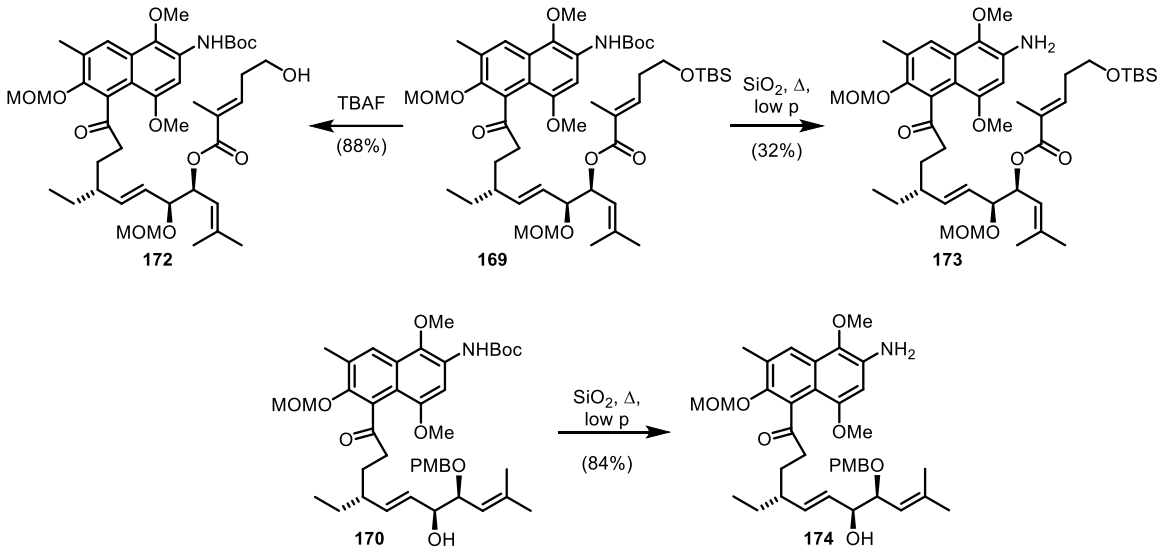


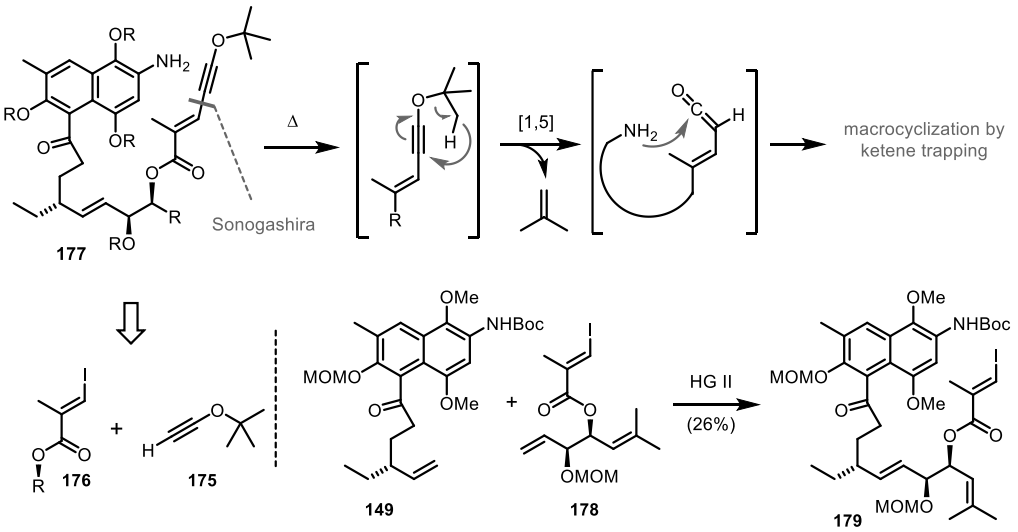
Figure 12 Variable temperature NMR studies of a representative naphthyl ketone.

We moved on to explore further elaboration of CM product **169** that comprises the entire naphthoquinone divergolide carbon skeleton. The goal was to obtain an amino acid, a precursor to macrolactamization (Scheme 28). While deprotection of the silyl ether to yield alcohol **172** proceeded in good yields, a Jones oxidation, that had proven to be the only viable oxidation strategy to yield the glutaconic acid (see 1st generation approach chapter 1.3.4), was not successful. Only traces of a product that seemed to bear a quinone could be isolated, a result that in hindsight was not too surprising. HCl-mediated Boc-deprotection of alcohol **172** failed, but alternative deprotection conditions were realized on silyl ether **169**, albeit in low yields: Adsorbing the substrate on silica and heating under low pressure furnished amine **173**. While this low yielding reaction could not be implemented in a sustainable reaction sequence, the realization of selective *N*-deprotection in presence of the phenolic MOM ether was an important discovery. The much higher yield of the thermal Boc-deprotection of allylic alcohol **170** giving naphthyl amine **174** was a hint that the presence of the α,β-unsaturated ester might be the culprit of the low yields.



Scheme 28 Elaboration of CM products, selective *N*-deprotection.

These results were instructive, but scarcity of material prevented excessive evaluation of conditions to a) obtain a glutaconic acid by oxidation and b) find a sequence that enabled sustainable *N*-deprotection of the all-carbon precursor. Keeping these unsolved problems in mind, we set out to explore a new strategy to install the glutaconic acid and evaluate different *N*-protecting groups using a new batch of material. The revised plan to construct the sensitive glutaconic acid motif was motivated by a contemporaneous publication released by the Ready group that describes the installation of essentially an acetate synthon that can be converted to a ketene under mild conditions.[43]



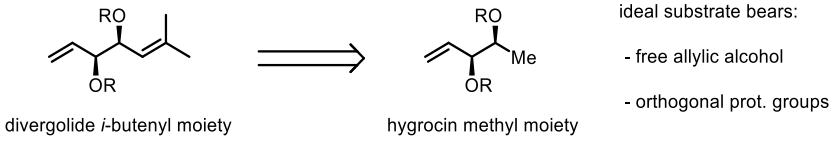
Scheme 29 Macrocyclization strategy based on thermal ketene generation.

Scheme 29 describes the strategy we sought to pursue to generate an alkynyl ether *via* Sonogashira coupling of *t*-butoxy acetylene **175** and esters of vinyl iodides (**176**). After generation of

a peculiar poly-unsaturated ether (**177**), *N*-deprotection should be followed by a thermally induced 1,5-H-shift that generates a ketene. This ketene should be intramolecularly intercepted by the naphthyl amine, generating the macrolactam without the need of coupling reagents. An unoptimized preliminary result that showed the competency of vinyl iodide **178** to participate in cross metathesis reactions was somewhat promising, as the yields with derivatives of **178** bearing a free allylic alcohol were expected to be higher. Thermal Boc-deprotection in presence of the vinyl iodide failed, making a reevaluation of the *N*-protecting group a necessity.

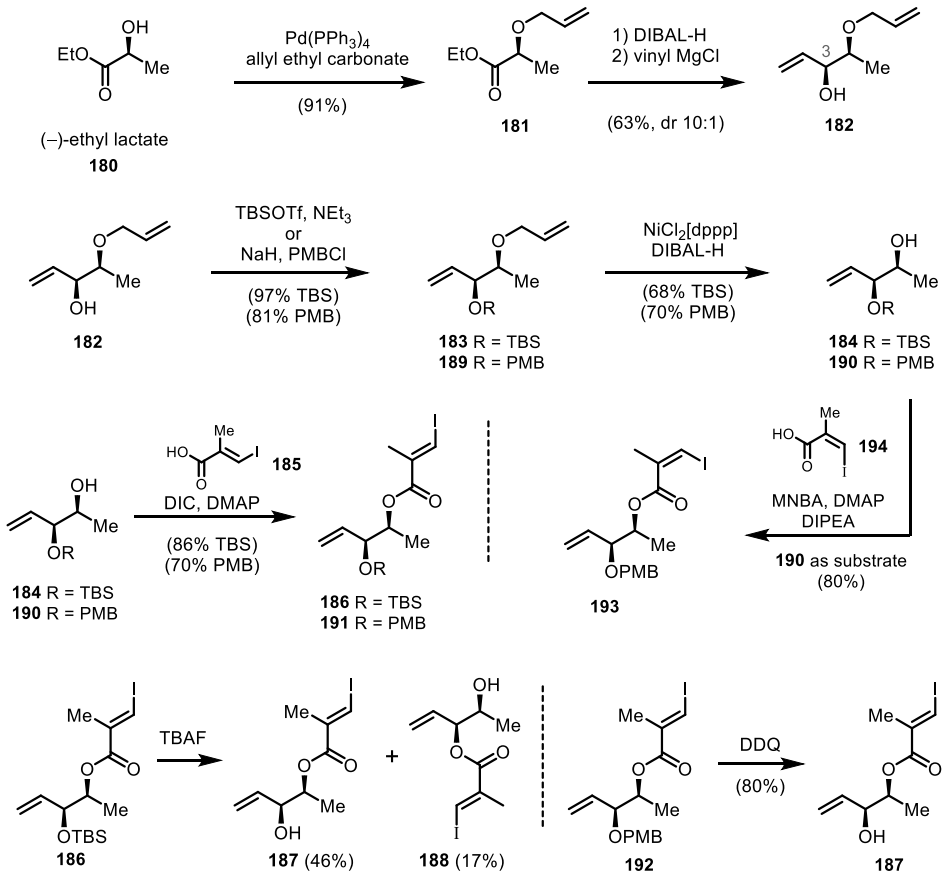
2.1.3 Synthesis of hygrocin 1,2-diol fragments

To evaluate the viability of the ketene based strategy (Scheme 29) we chose to switch the 1,2-diol fragment to one bearing the methyl group present in the hygrocin family, as the resilient MOM-ether in our divergolide building block (Scheme 24) complicated generation of a fragment bearing an allylic alcohol needed for efficient cross metathesis.



Scheme 30 Hygrocin 1,2-diol vs. divergolide 1,2-diol.

A literature survey showed that the (*S*,*S*)-1,2-diol motif could be generated by an aluminum-chelate controlled addition of a vinyl Grignard reagent to allyl-lactaldehyde.[44] Conveniently, cheap commercially available (−)-ethyl lactate (**180**) showed the desired configuration of the hydroxy group, making the expensive reagents employed for installation of the allyl ether by a Tsuji-Trost reaction[45] bearable. The reason for employing this rather sophisticated chemistry for a simple protecting group installation was to ensure that no racemization of **181** took place. Scheme 31 outlines the synthesis.



Scheme 31 Hygrocin diol synthesis, 1,2-acyl shift during silyl ether deprotection

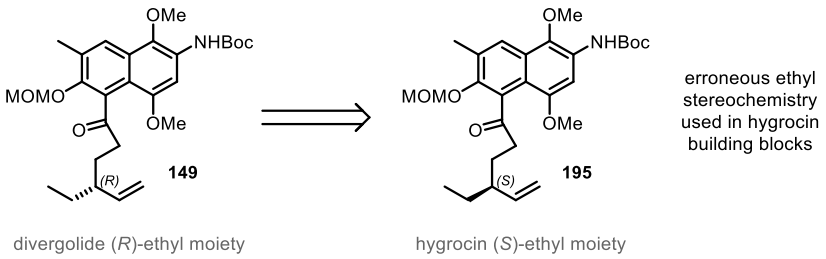
Known allyl ether **182** could be prepared according to literature procedure,[44] but although the reported dr of 10:1 (C3) could be achieved on smaller scale (580 mg) the selectivity dropped when procuring more than one gram. We then proceeded to protect the C3-hydroxyl as TBS ether (**183**) and moved on to remove the allyl group. To this end, we resorted to use Ogasawara's nickel catalyzed deallylation methodology to access homoallylic alcohol **184**,[46] a mild reaction that offers an alternative to the commonly employed two-step procedure involving first base- or transition metal-mediated isomerization to the vinyl ether followed by acidic hydrolysis. Upon esterification of the resultant alcohol with carboxylic acid **185** (prepared in three steps according to the literature)[47] with carbodiimide DIC we went on to cleave the silyl ether of vinyl iodide **186**. Interestingly, we observed the formation of significant amounts of 1,2-acyl shifted isomer **188** apart from the desired ester **187** when using TBAF, TBAF in buffered solutions, or TASF as a desilating reagents. This is reminiscent of the 1,2-acyl shifts observed in the divergolide and hygrocin congeners in Nature, but nevertheless prompted us to repeat the synthesis using a PMB ether instead of the silyl ether. The PMB ether of **192** could be cleaved in good yields and without concomitant acyl shift using DDQ to give desired allylic alcohol **187**. Having proven the viability of the PMB ether as a protecting group, we also went forth to

prepare (*Z*)-configured vinyl iodide **193** in addition to the (*E*)-isomer. The carboxylic acid **194** (prepared according to the literature in three steps)[48] was coupled to homoallylic alcohol **190** using the Shiina-protocol,[49] as carbodiimide based reagents, that worked well for the (*E*)-isomer, proved to be less effective in this transformation.

2.1.4 Elaboration of hygrocin cyclization precursors

Having established robust entries to hygrocin fragments bearing an allylic alcohol and the vinyl iodide we moved on to explore the cross metathesis and subsequently the Sonogashira coupling with *t*-butoxy acetylene **175**.

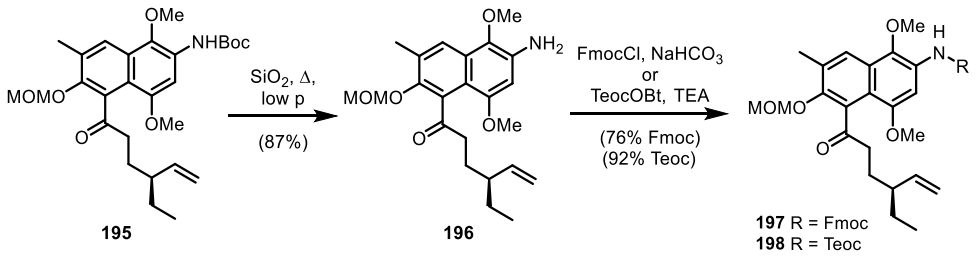
A **disclaimer** has to be made though, before moving on: At this point, the literature regarding hygrocin natural products was not very developed and a misinterpretation of the crystal structure of hygrocin C (see chapter 1.2.4) labeled the hygrocins to have an (*S)*-configured ethyl branch. The author of this thesis failed to notice the mishap and carried on to synthesize *all hygrocin-based compounds* with the (*S*)-configured ethyl branch (see Scheme 32). This error was not noticed until the synthesis of *epi*-ethyl hygrocin G (chapter 2.4.2). Nevertheless, the chemistry explored with the *epi*-ethyl building block **195**[I] was key to advance the project.



Scheme 32 Switch of ethyl stereochemistry for fragments used in hygrocin syntheses

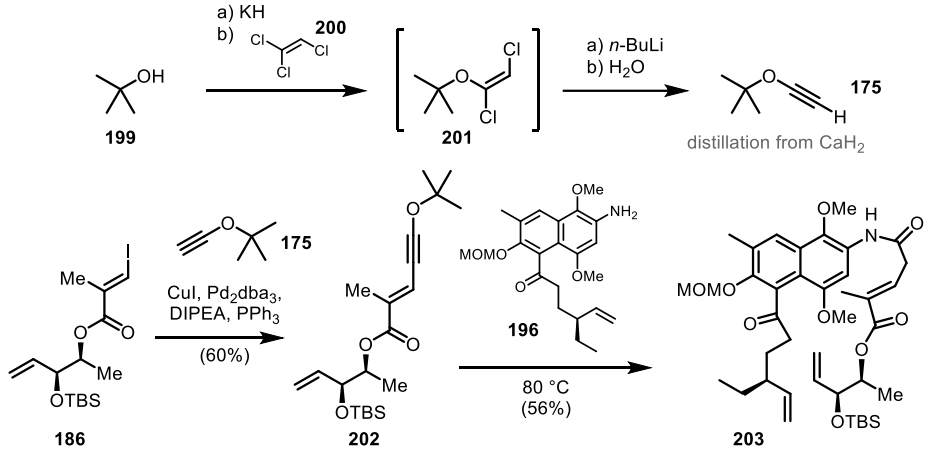
In order to switch the *N*-Boc protecting group whose late-stage removal proved troublesome, derivatives bearing the base-labile Fmoc group as well as the fluoride-sensitive Teoc group were prepared. Thermal Boc removal gave rise to naphthyl amine **196**. The free amine proved to decompose when exposed to air, making it a necessity to connect rotary evaporators to a nitrogen stream. This enabled to achieve good isolated yields of the amine, that was typically immediately *N*-protected to avoid decomposition (Scheme 33).

[I] obtained by using the other enantiomer of the Koga auxiliary (prepared according to the literature[39] in three steps from (S)-pyroglutamate) for the synthesis of **195** (see chapter 1.3.4)



Scheme 33 Nitrogen protecting group manipulations.

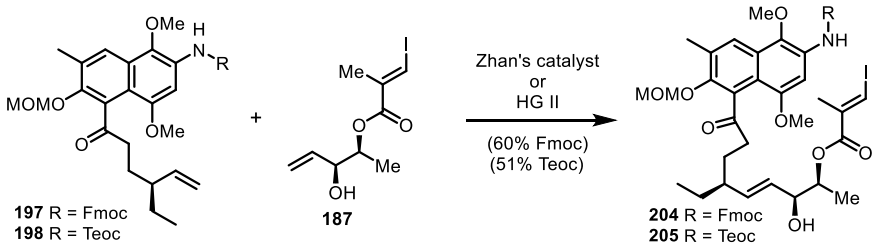
Sufficient buffering with $NaHCO_3$ during protection with FmocCl allowed for carbamate installation without loss of the phenolic MOM ether (**197**), while a hydroxy benzotriazole based carbamoylation reagent proved to give the best yields for Teoc installation (**198**).



Scheme 34 Verification of the viability of the Sonogashira/ketene strategy for amidation.

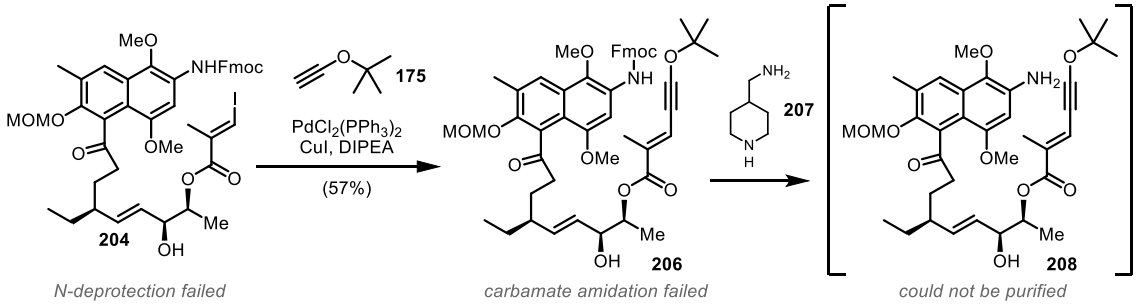
Before exploring cross metatheses with the hygrocin fragments, we wanted to verify that the envisioned Sonogashira coupling and subsequent ketene trapping were viable. Preparation of alkynyl ether **175** was performed according to the procedure given by Pericàs and Ready.[43] The author is indebted to Wenhan Zhang (Ready group), who upon request provided spectral data of **175** to verify the successful procedure. *t*-Butoxy acetylene (**175**) was thus obtained on gram-scale as a solution in hexanes and butyl ethers. This solution was employed as reaction solvent for the Sonogashira couplings. We were please to find that electron-poor vinyl iodide **186** was a good substrate for the coupling of **175** using the conditions described by Ready, as full conversion of **186** could be achieved at room temperature in less than three hours. When the structurally intriguing ether **202** was heated with stoichiometric amounts of naphthyl amine **196** in toluene, amide **203** was formed within minutes, demonstrating the viability of the strategy for the envisioned macrocyclization (see Scheme 29). It should be noted that this amidation

reaction was also performed with the PMB-protected variant of **186** that could be deprotected without 1,2-acyl shifts after amidation (not shown[I]). The thus obtained allylic alcohol was briefly evaluated for ring closing metathesis, but as described above (chapter 1.3.4), RCM could not be realized. Instead, clean formation of a dimer occurred, reflecting the high reactivity of allylic alcohols in olefin metatheses, as well as the unfavorable amide geometry.



Scheme 35 Cross metatheses with Fmoc and Teoc derivatives.

Gratifyingly, cross metatheses employing allylic alcohol **187** proved possible in acceptable yields using either the Teoc- or Fmoc-protected naphthalene. The use of Zhan's catalyst[50], a slightly modified variant of Hoveyda-Grubbs 2nd generation catalyst, was solely based on the easier purification of CM product **204**.



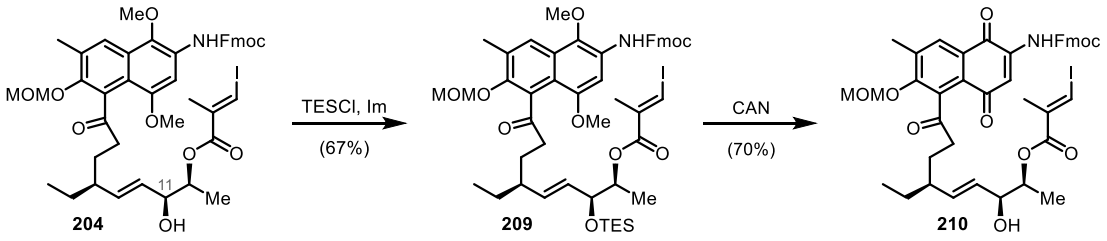
Scheme 36 Sonogashira coupling and Fmoc-deprotection.

Scheme 36 describes the initially promising results of the elaboration of the Fmoc-variant **204**. Sonogashira coupling of *t*-butoxy acetylene **175** was possible in moderate yields by switching the catalyst from Pd_2dba_3/PPh_3 to $PdCl_2(PPh_3)_2$. Alkynyl ether **206** could be isolated and fully characterized but proved to easily decompose upon storage, even when kept frozen in a benzene matrix under argon. Hoping that a quick Fmoc-deprotection/cyclization would generate a more stable macrocycle we set out to remove the carbamate (heating **206** in toluene in an attempt to directly acylate the carbamate failed).

[I] The identity of these compounds was only verified by ^{1}H-NMR and HRMS and are not part of the experimental section.

Before, we had screened the effect of four amine bases (piperidine, pyrrolidine, cyclohexylamine and dicyclohexylamine) in cold DCM and DMF on Fmoc naphthalene **197** as a model substrate. Interestingly only pyrrolidine in DMF yielded free amine **196** in a clean reaction. Unfortunately, these conditions lead to decomposition when vinyl iodide **204** was used as a substrate, leaving us with the challenge to remove the Fmoc group on the sensitive alkynyl ether **206**.

Treatment of **206** with pyrrolidine in DMF lead to full conversion of the starting material, but isolation of clean amine **208** was not possible with aqueous workups and chromatography. Dilution of the crude material with toluene and heating (60 °C) to achieve macrocyclization also did not lead to a desirable outcome; in this case HRMS indicated that the ketene was trapped by residual pyrrolidine instead of the naphthyl amine. Keeping in mind that amine **208** proved not stable to chromatography, but a macrolactamization presumably required a clean precursor, we resorted to using 4-methylamino piperidine (4-AMP, **207**). This reagent was developed to not only cleave Fmoc protecting groups, but to also scavenge the fulvene byproducts by converting them to water soluble adducts.[51] Using 4-AMP, full conversion to the putative amine ((+)ESI-HRMS: 640.34811, $M+H^+$) could seemingly be achieved, but aqueous workups or chromatography could not deliver a clean product, and heating of the material in toluene did not result in macrocyclic products.



Scheme 37 Protection of allylic alcohol, quinone oxidation.

In an effort to rule out a negative effect of the C11 allylic alcohol (Scheme 37), it was protected as a TES ether (**209**). Sonogashira coupling to give the alkynyl ether was successful (not shown), but *N*-deprotection could again not be achieved. In an effort to alter the amine substitution, we oxidized the hydroquinone ether to the naphthoquinone which was accompanied by TES deprotection when using Lewis acidic CAN as an oxidant. Quinone **210** did not undergo Sonogashira coupling, nor could the Fmoc group be removed by pyrrolidine or 4-AMP. Briefly, we studied the transformations illustrated in Scheme 36 with the Teoc derivative **205** only to run

into the same problems when attempting to remove the *N*-protecting group.[I] It was possible to obtain the corresponding alkynyl ether through Sonogashira coupling, but attempts at subsequent Teoc removal with TBAF or TASF were met with failure to isolate a clean amine.

2.1.5 Lessons from the failed cross metathesis/ketene route

At this point the decision was made to change the strategy and redesign our synthetic route. While there were arguably still a variety of possibilities to potentially achieve successful *N*-deprotection of the advanced precursors (Scheme 36 and Scheme 37), it ultimately was the inability of the current route to reliably provide enough material[II] to overcome the challenges of the endgame: naphthyl amine deprotection, glutaconic acid synthesis and of course a macrocyclization that can yield two different atropisomers (see chapter 1.2.3). The most important insights from chapter 2.1 were the following:

- (*E*)-selective **olefin cross metathesis** can be achieved best with a free allylic alcohol as substrate and conditions to generally achieve yields exceeding 50% could be identified.

- A novel **(*E*)-glutaconic acid synthesis**[III] could be achieved *via* Sonogashira coupling of *t*-butoxy acetylene and subsequent trapping of a thermally generated ketene.

- A new route should carefully select an ***N*-protecting group** that can be removed late stage under conditions compatible with the glutaconic acid/ the glutaconic acid precursor. **Thermal Boc-deprotection** proceeds without naphthylic MOM cleavage.

- The straightforward synthesis of a (*S*,*S*)-1,2-diol useful for **hygrocin synthesis** was realized. Studies on the removal of hydroxyl protecting groups neighboring an ester revealed that a **PMB group** can be removed without inducing 1,2 acyl shifts.

- The 1st generation route's biggest complication was connecting the naphthalenic fragment to the *ansa* chain fragment *via* alkyl lithium addition generated from a volatile alkyl bromide. A new strategy should **re-evaluate the coupling of the *ansa* chain** to the aromatic core.

[I] These intermediates were not fully characterized and are not part of the experimental section.
[II] See the critical discussion of the 1st generation approach in chapter 1.3.4.
[III] We were unable to convert (*Z*)-vinyl iodides (Scheme 31) to alkynyl ethers (not discussed)

2.2 Redesigning the *ansa* chain synthesis

Building on the pitfalls encountered in our previous strategy (see chapter 2.1.5), we set out to redesign our route (Figure 13).

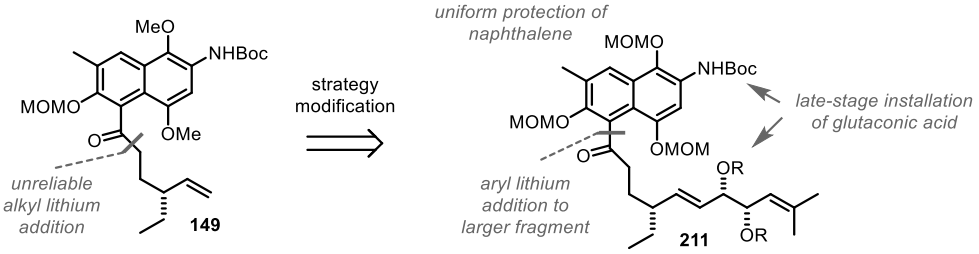
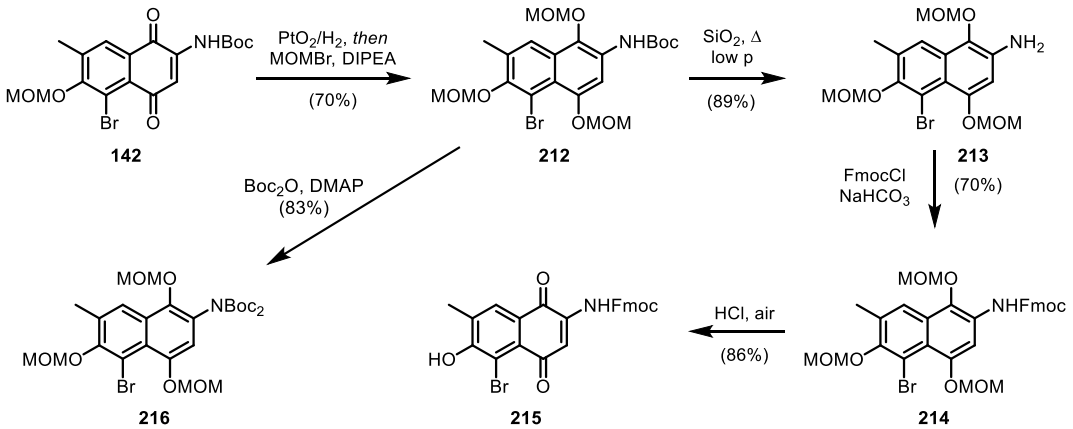


Figure 13 Revised plan for key intermediate **211**.

Our revised approach aimed at coupling an aryl lithium to a ketonic electrophile, which required one carbon homologation of the previous chiral alkyl fragment. Moreover, we wanted to make use of the developed cross metathesis to attach the diol portion before coupling to the aromatic core. The naphthalenic fragment should display a uniform O-protection pattern, making a one-pot triple MOM-deprotection/hydroquinone air-oxidation achievable if needed.

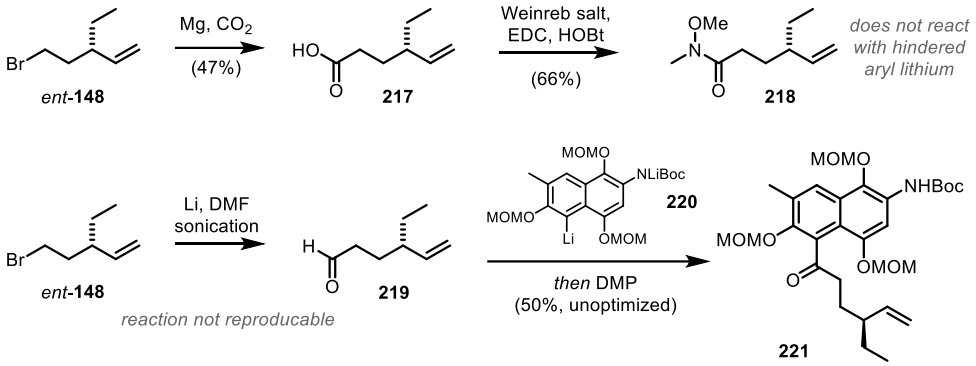
2.2.1 Modification of naphthalenic portion and coupling studies

We first set out to modify the benzohydroquinone protecting groups, aiming at installation of MOM ethers by reduction/trapping of the previously prepared quinone **142** (Scheme 38). Developing this reaction was not trivial, as the intermediate hydroquinone is readily oxidized on air and the aryl bromide can be reduced by the reaction conditions.



Scheme 38 Elaboration of the aromatic core.

Indeed, aryl bromide reduction was the major product when **142** was treated with Adam's catalyst/H_2 in methanol. Switching the solvent to degassed THF however, allowed for exclusive reduction of the naphthoquinone. Conveniently, complete conversion to the hydroquinone could be assessed by discoloration of the bright yellow reaction mixture. After solvent exchange by blowing off THF with argon to avoid reoxidation, the use of several equivalents of MOM-bromide and DIPEA granted good yields of the triple MOM-protected naphthalene **212**. We briefly verified the ability to induce a one-pot ether deprotection / air oxidation to the quinone and were pleased to find that (after switching to an acid-stable *N*-protecting group) **214** can be converted to the deprotected and oxidized naphthoquinone **215** in good yields. Lastly, we found that *N*,*N*-dicarbamoylated variant **216** could be accessed by the action of DMAP/Boc_2O to mask all acidic protons for efficient halogen-metal exchange.

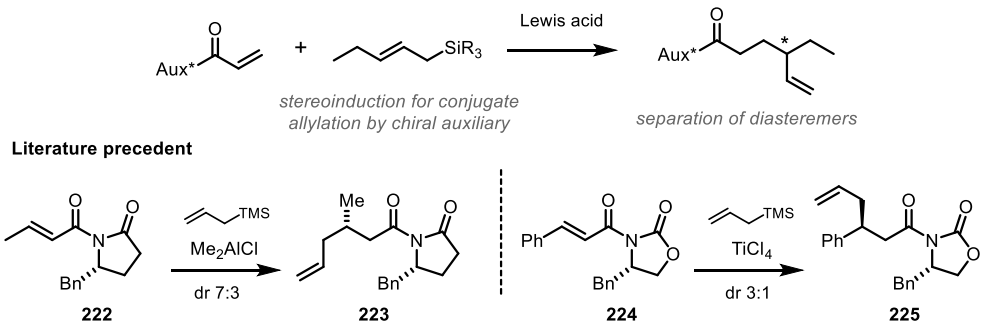


Scheme 39 Investigation of homologation and aryl lithium coupling.

To investigate the feasibility of coupling a homologated variant of the *ansa* chain, we made use of the existing fragments from the 1st generation route (Scheme 39). Thus, (*S*)-alkyl bromide *ent*-**148** was transformed into the corresponding Grignard reagent and reacted with CO_2. Elaboration of **217** to the Weinreb amide **218** revealed that no reaction with aryl lithium **220** took place, hinting at the hindered nature of the nucleophile with MOM groups in *ortho* and *peri* position. Using a modified Bouveault reaction[52] to access aldehyde **219** proved difficult to reproduce but with some quantities of **219** at hand, we demonstrated the ability of γ-substituted aldehydes to react with hindered aryl lithium **220** in a clean reaction allowing for isolation of pure ketone **221**.

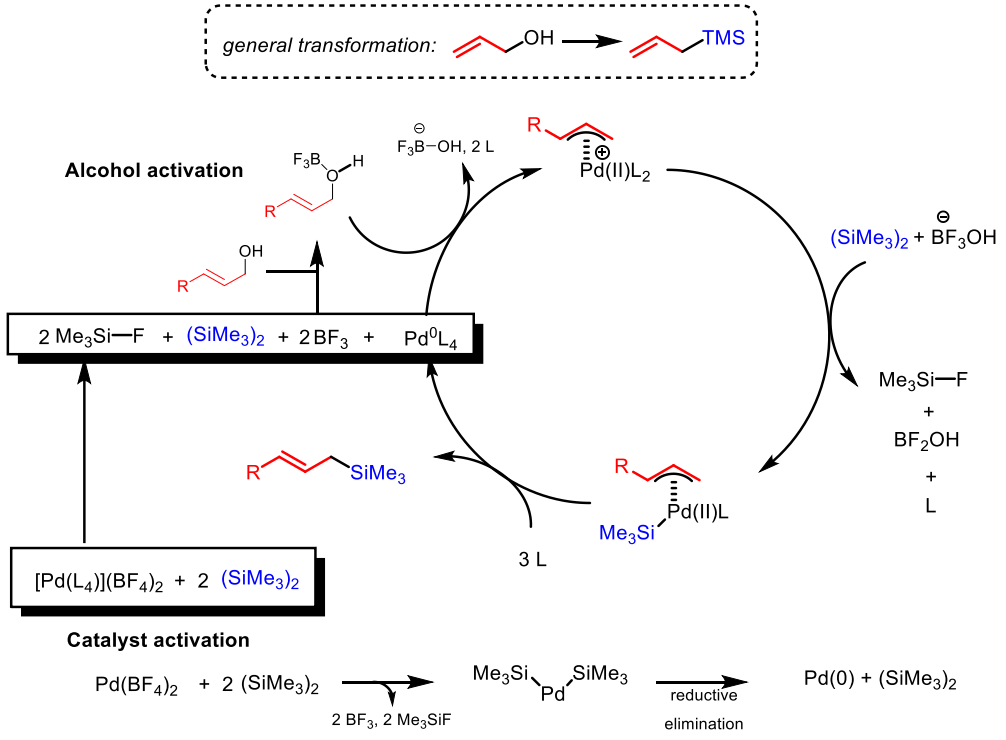
2.2.2 Investigation of a diastereoselective Hosomi-Sakurai reaction

Moving on to develop a quick access to chiral γ-ethyl functionalized ketones with an olefinic handle for cross metathesis, we sought out to investigate the ability of acrylated chiral auxiliaries to stereochemically bias 1,4-allylations.



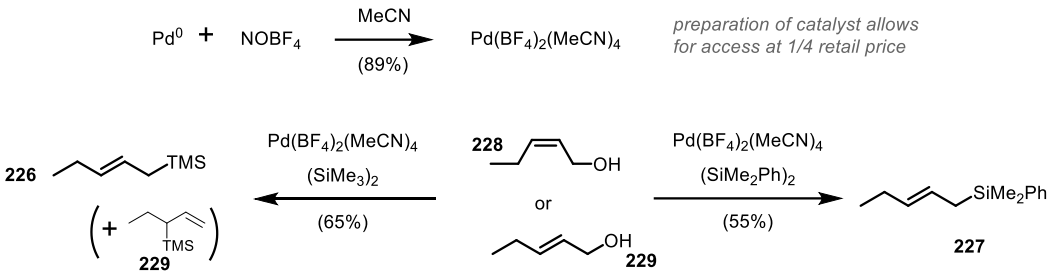
Scheme 40 Straightforward access to γ-functionalized fragment

A literature survey revealed that diastereoselectivity in 1,4-additions can be achieved by the Lewis acid-mediated Hosomi-Sakurai allylation of chiral pyrrolidinones (**222**) and oxazolidinones (**224**).[53] Further reading showed that multistep procedures of the desired silanes were reported, but aiming for a short reaction sequence we identified Szabó's palladium catalyzed C-OH functionalization methodology[54] to potentially deliver the silanes in a one-pot reaction from commercially available materials. The Szabó allyl silane synthesis effectively transforms an (*E*)- or (Z)-allylic alcohol into the corresponding (*E*)-allylic silane under a combination of palladium catalysis and boron-mediated alcohol activation. Scheme 41 shows the putative mechanism.[55]



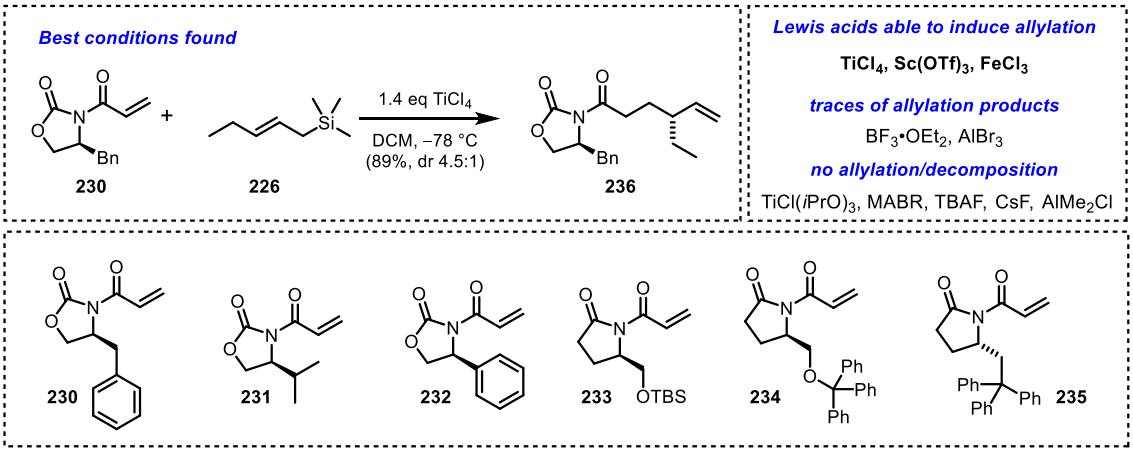
Scheme 41 Mechanism of allyl silane formation according to Szabó.

We were pleased to find that this modern silane synthesis proved to robustly yield silanes **226** and **227**, as the reaction could be conducted at a 50 mmol scale (Scheme 42).



Scheme 42 Catalyst and allyl silane synthesis.

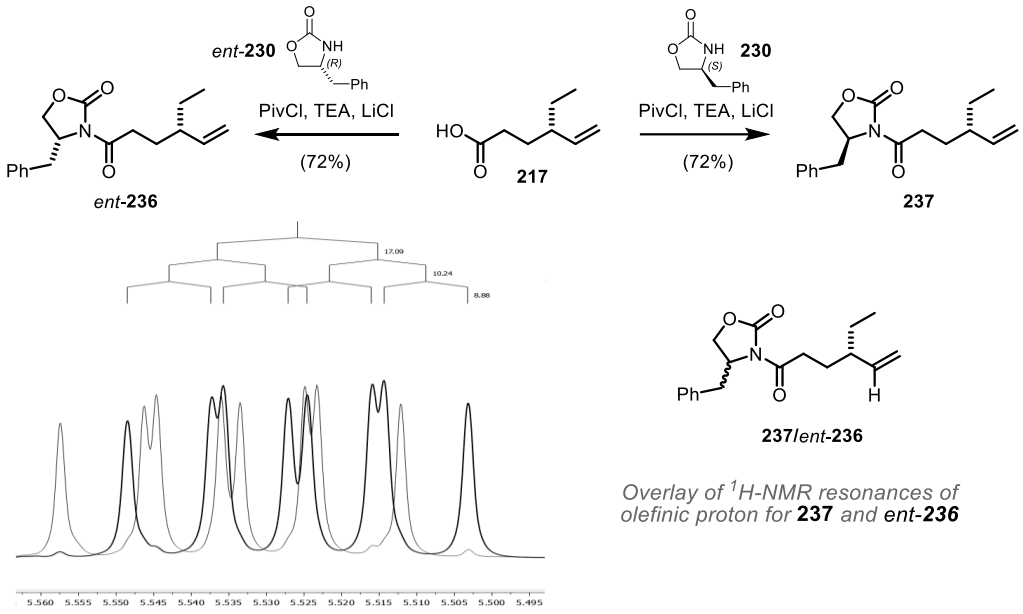
The palladium catalyst could be prepared according to the literature[56] in one step from palladium sponge in high yields, enabling the preparation of larger silane batches. The reaction worked with either (*Z*)- or (*E*)-3-pentenol (**228** or **229**), but the cheaper (*Z*) isomer was preferred. Purification of the very apolar allyl silanes could be easily achieved by pouring the crude reaction mixture on a large silica plug and eluting with *n*-pentane. Bulkier silane **227** could then simply be concentrated to give the pure compound, while the TMS derivative **226** was volatile. Hence, **226** was typically only concentrated to a 50 weight % solution in *n*-pentane. It should be added that during formation of **226**, the isomeric secondary silane **229** was formed in minor amounts as well. We did not observe any undesired side reactions attributed to this species when using the mixture in allylations.



Scheme 43 Development of the Hosomi-Sakurai reaction.

Scheme 43 summarizes the results obtained for a quick evaluation of readily available chiral auxiliaries. Known Evans-type oxazolidinones **230**–**232** could be prepared by reaction of the deprotonated cyclic carbamates with acryloyl chloride, while pyroglutamate-based imides **233**–**235** were prepared by carbodiimide mediated installation of the acrylic acid moiety. The unreported trityl species **235** could be accessed by reaction of a copper-trityl species with the

known corresponding iodide. All acrylated variants were evaluated in the Hosomi-Sakurai reaction (see Scheme 43), with only the benzyl-Evans derivate **230** giving diastereoselectivities exceeding a 2:1 ratio. Typically, TMS silane **226** gave a cleaner reaction than the dimethylphenyl derivative **227**. When exploring the effect of different Lewis acids, we found $Sc(OTf)_3$ and $FeCl_3$ to be competent to induce allylation but yields and diastereomeric ratios were higher using excess $TiCl_4$. We established that when a vigorously stirred (suspensions may form) DCM solution of oxazolidinone **230** at −78 °C is treated first with fresh $TiCl_4$ (1.4 equivalents, 1 M in DCM) and then with a pre-cooled solution of allyl silane **226** (2 equivalents), clean 1,4-addition takes place within one hour with a diastereomeric ratio of 4.5:1 on gram scale.



Scheme 44 Independent synthesis of diastereomeric oxazolidinones *ent*-**236** and **237**.

To verify the identity of the diastereomeric products of the allylation, we set out to independently prepare the diastereomers to obtain reference spectra (Scheme 44). Thus, carboxylic acid **217** (preparation see Scheme 39) was coupled to both enantiomers of the benzyl-Evans auxiliary to give the enantiomers of both diastereomers of the Hosomi-Sakurai reaction (note that **217** shows the (*S*)-ethyl configuration). By overlaying the 800 MHz ^{1}H-NMR resonances of the highlighted olefinic proton, distinguishing between the diastereomers and thus determination of diastereomeric ratios was realized.

Not too unsurprisingly, the diastereomeric olefins were not separable by column chromatography. Undeterred, we set out to use the 4.5:1 mixtures obtained from the optimized allylation conditions (Scheme 43) in cross metatheses with a chiral diol in the hope of separating the unwanted species at a later point.

2.2.3 Synthesis and coupling of the chiral *ansa* chain portion

Having established a robust route to gain access to the desired chiral olefin bearing the chiral ethyl moiety, we set out to synthesize a (*S*,*S*)-1,2-diol competent for cross metathesis and identify conditions for the sustainable elaboration of a fragment that can be cleanly coupled to a suitable aryl lithium species.

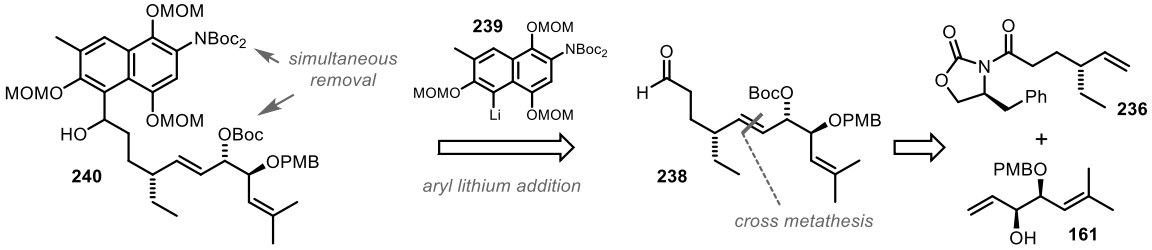
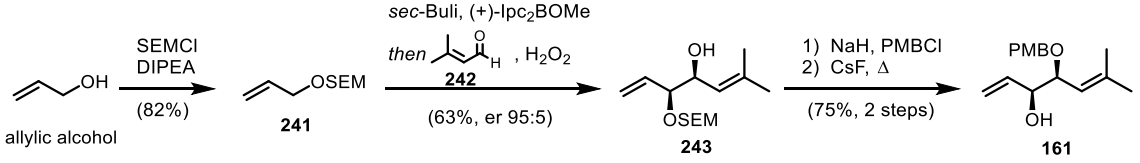


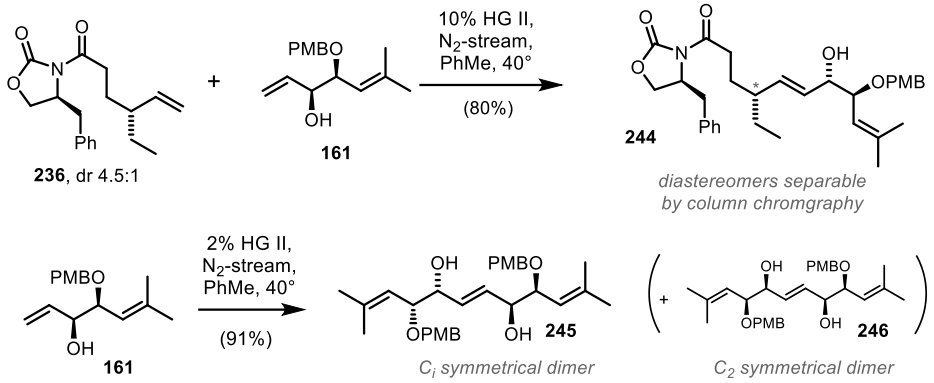
Figure 14 Synthetic strategy for fragment coupling.

Figure 14 outlines the strategy for coupling and the requirements for the coupling partners **138** and **139**. With benzylic alcohol **240** as the target, we aimed for Boc-protecting groups on the nitrogen and one of the diol's hydroxyls, since we assumed that we could cleave them all under established conditions and further selectively manipulate the nitrogen for *N*-functionalization. Di-Boc aryl lithium **239** was envisioned to be a more competent coupling partner than the dilithiated mono-Boc variant used in earlier experiments. A cross metathesis followed by a short series of transformations consisting of carbonate installation and oxazolidinone reduction to give desired aldehyde **238** should traced back the starting materials to olefins **161** and **236**, whose synthesis was already established (see chapters 2.1.1 and 2.2.2). However, a straightforward synthesis of allylic alcohol **161** still needed to be developed as the previously prepared MOM protected precursors (see Scheme 24) proved to be a poor choice in regard to orthogonality with the PMB ether. Hence, we mined the literature for alternative Brown-allylation substrates with a different protecting group. Luckily, Overman and coworkers had established[57] that enantioselective allylations can be realized in good yields and high enantiomeric excess using SEM-protected allylic alcohol **241** (Scheme 45).



Scheme 45 Brown allylation employing SEM-protected allylic alcohol **241**.

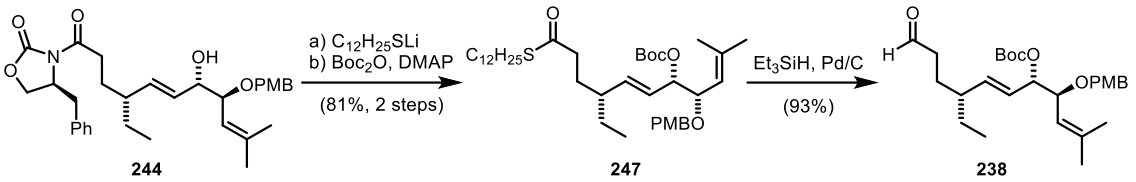
SEM allyl alcohol **241** could be purified by distillation, ensuring the high purity of reagents that Brown allylations typically require.[58] By using fresh bottles of *sec*-BuLi and the *iso*-pinocamphenylborane, reaction with prenal (**242**) could be realized in 63% yield and good enantioselectivity (enantiomeric ratio by Mosher ester[59] 95:5) on 11 mmol scale. After PMB protection, the SEM ether could be selectively cleaved by excess CsF and high temperatures to give desired allylic alcohol **161**.



Scheme 46 Cross metathesis of **236** and **161** and dimerization of allylic alcohol.

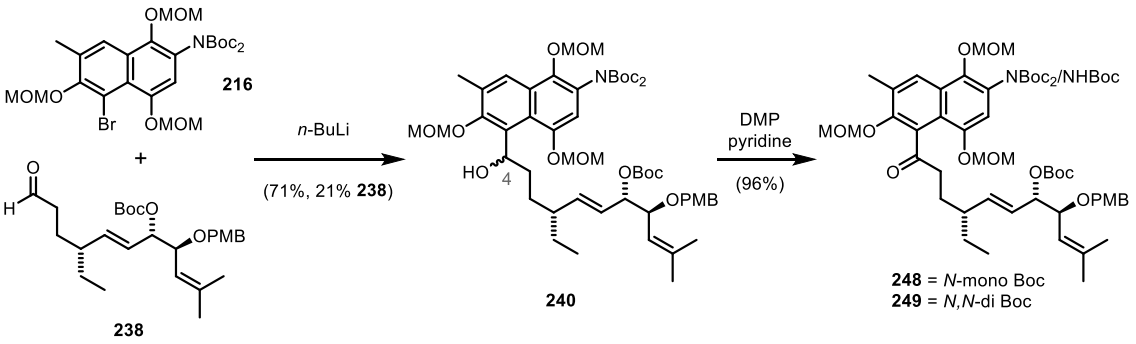
Investigation of the cross metathesis reaction of **236** and **161** finally revealed conditions that ensured full conversion of the reactants. By running a constant stream of nitrogen over a 40 °C toluene solution of Hoveyda-Grubbs 2nd generation catalyst, oxazolidinone **236** and allylic alcohol **161** (1.7 equivalents), the mixture was concentrated close to dryness over the course of two hours. This gave **244** as a mixture of diastereomers (Scheme 46), arising from the dr of starting olefin **236**. Gratifyingly, the desired diastereomer could be separated by careful chromatography, giving rise to diastereomerically pure oxazolidinone **244** in high yields. Upon realizing that a dimer of **161** could be separated from the crude reaction mixture as well, we subjected the allylic alcohol to the established metathesis conditions individually. Rapid and high yielding dimerization to **245** occurred at low catalyst loadings, and even traces of the C_2-symmetric dimer (**246**) could be isolated. This results from metathesis of enantiomers when low *ee* batches of **161** were used. The dimers (inseparable) could be used as substrates for the preparation of **244**, giving essentially the same yields when 0.7 equivalents of the dimer were subjected to cross metathesis with olefin **236**.[I]

[I] not included in experimental section.



Scheme 47 Auxiliary cleavage, carbonate formation and Fukuyama aldehyde synthesis.

With access to pure oxazolidinone **244** established, we chose to cleave the Evans auxiliary by action of odorless *n*-dodecane lithium thiolate. Subsequent hydroxyl protection as Boc-carbonate gave thioester **247** in good yield over two steps. Fukuyama's palladium catalyzed aldehyde synthesis[60] gave desired aldehyde **238** in excellent yields on 280 mg scale. It has to be noted though that diminished yields were sometimes encountered using different batches of Pd/C, but isolated yields never dropped below 80%.



Scheme 48 Coupling of aldehyde **238** to the aryl lithium generated from **216**, naphthyl ketone synthesis.

The stage was now set to explore the coupling of the aromatic core to the novel aldehyde. We were able to achieve good yields of naphthyl alcohol **240** (dr approximately 1:1) when using lithiated *N*,*N*-di-Boc variant **216** (1.7 equivalents). We reasoned that halogen-metal exchange with *n*-BuLi was more efficient as with the *N*-mono-Boc variant that quickly protodemetalates the intermediary lithium species *via* its acidic carbamate proton. Unreacted aldehyde could be almost completely recovered, making the crucial coupling a viable pathway towards the endgame of the synthesis. The inconsequential mixture of C4 diastereomers was oxidized with DMP in combination with pyridine. Excess $NaHCO_3$ or *t*-BuOH as additives were unable to effect full conversion of alcohol **240** to the naphthyl ketone. Upon oxidation however, approximately 25% of material showed that one Boc group was hydrolyzed (**248**), presumably during the reductive workup ($Na_2S_2O_3$) used to quench residual DMP. This, however, was without consequence as the next step in the synthesis would call for global Boc deprotection. Nevertheless, the species could be separated and individually characterized, which was omitted upon scale up. The *N*-mono-Boc species **241** was also subjected to variable temperature NMR

experiments (DMSO-d_6) to verify the existence of two atropisomers as we already expected from our experience with similar naphthyl ketones (see *e.g.* Figure 12). The distinct NMR-resonances of the two atropisomers of **248** were shown to interconvert at 80 °C (Figure 15).

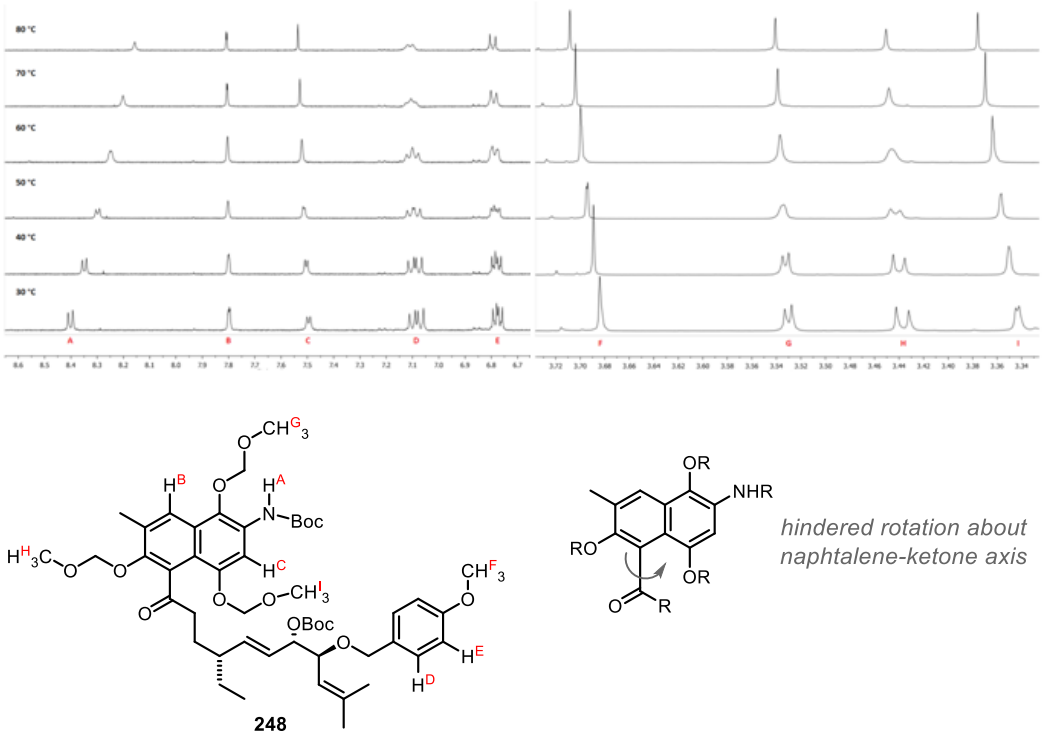
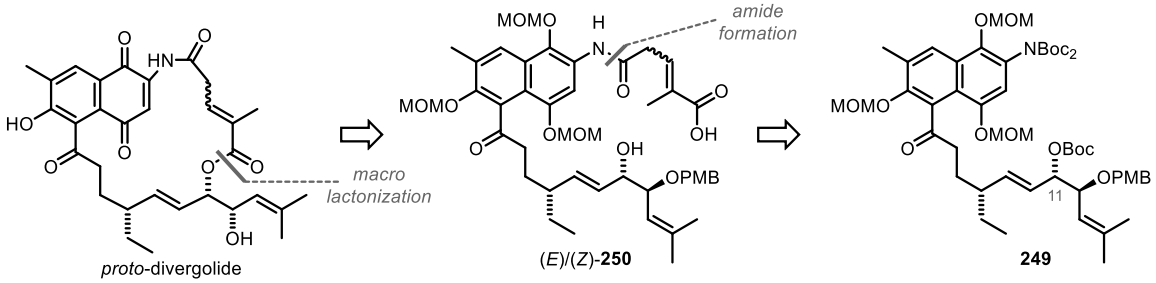


Figure 15 Variable temperature NMR verifies existence of atropisomers of **248**.

With a reproducible and high yielding coupling method to merge the aromatic core and a significant portion of the *ansa* chain in a longest linear sequence of 10 linear steps (22 individual steps) we had a stable entry into a divergolide precursor that lacked only the glutaconic acid moiety. Having solved some of the challenges revealed by the first-generation route (see chapter 2.1.5), we could now focus on the remaining obstacles for *proto*-divergolide construction: installation of the glutaconic acid, macrocyclization and biomimetic ring-contraction. The endgame strategies to solve these problems will be discussed in chapter 2.3.

2.3 Attempted macrocyclization *via* macrolactonization

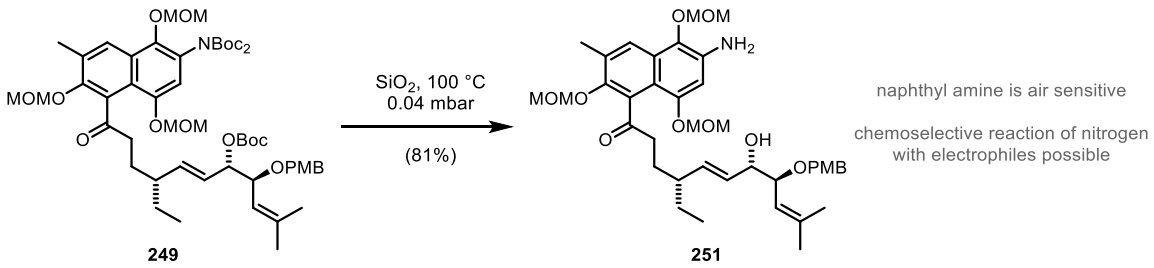
With robust access to Boc-protected naphthalene **249** (prepared routinely in batches >100 mg), we set out to explore the end game. We needed to install the glutaconic acid moiety, invoke formation of the 19-membered macrocycle and then explore the biomimetic ring-contractions (Scheme 8). The first strategy we pursued was hinging on a macrolactonization as ring closing event. Scheme 49 outlines the plan that relies on acylation of the nitrogen to give cyclization precursors of type **250**, with an either (*E*) or (*Z*) configured glutaconic amide.



Scheme 49 Strategy for ring closure by macrolactonization.

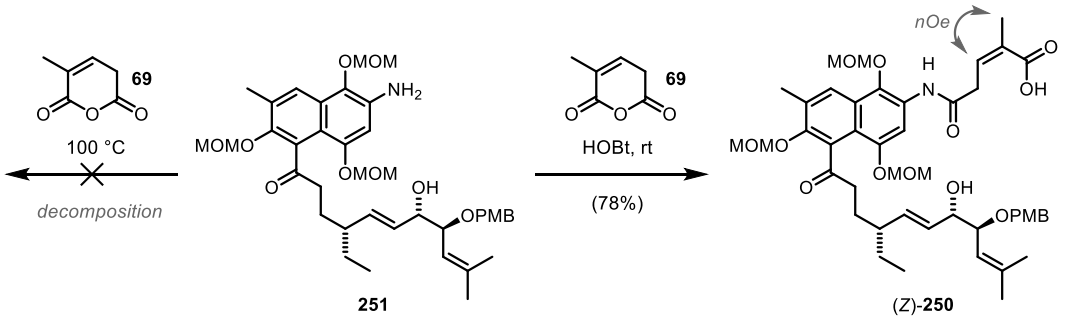
2.3.1 Late-stage installation of a (*Z*)-glutaconic amide

The first challenge to overcome was the global Boc deprotection of *N*- and *O*-11 protected naphthalene **249**. Having already established that thermal *N*-Boc removal can be achieved in presence of the sensitive MOM ethers (Scheme 38), we set out to test the trusted conditions. Further literature precedence[61] that Boc-carbonates are readily removed thermally encouraged us. Hence, we adsorbed **249** on dry silica, applied vacuum (ideally below 0.1 mbar) and immersed the reaction vessel in a pre-heated oil bath. After experimenting with different temperatures, we found that to ensure complete conversion the reaction should be held at >90 °C for 15 h. At lower temperatures or reaction times, the mono-*N*-Boc species (two-fold Boc deprotection) can be isolated. It can then be resubjected to the reaction conditions to yield air sensitive naphthyl amine **251**.



Scheme 50 Global *N*- and *O*-Boc deprotection.

When purifying amine **251** it was critical to expose the crude product on silica to as little air as possible. This is achieved by backfilling the flask with argon after cooling to ambient temperature and pouring the silica *directly* onto an equilibrated silica column. In solution, **251** is rather stable but when concentrating the amine, backfilling the rotary evaporator with inert gas is necessary.

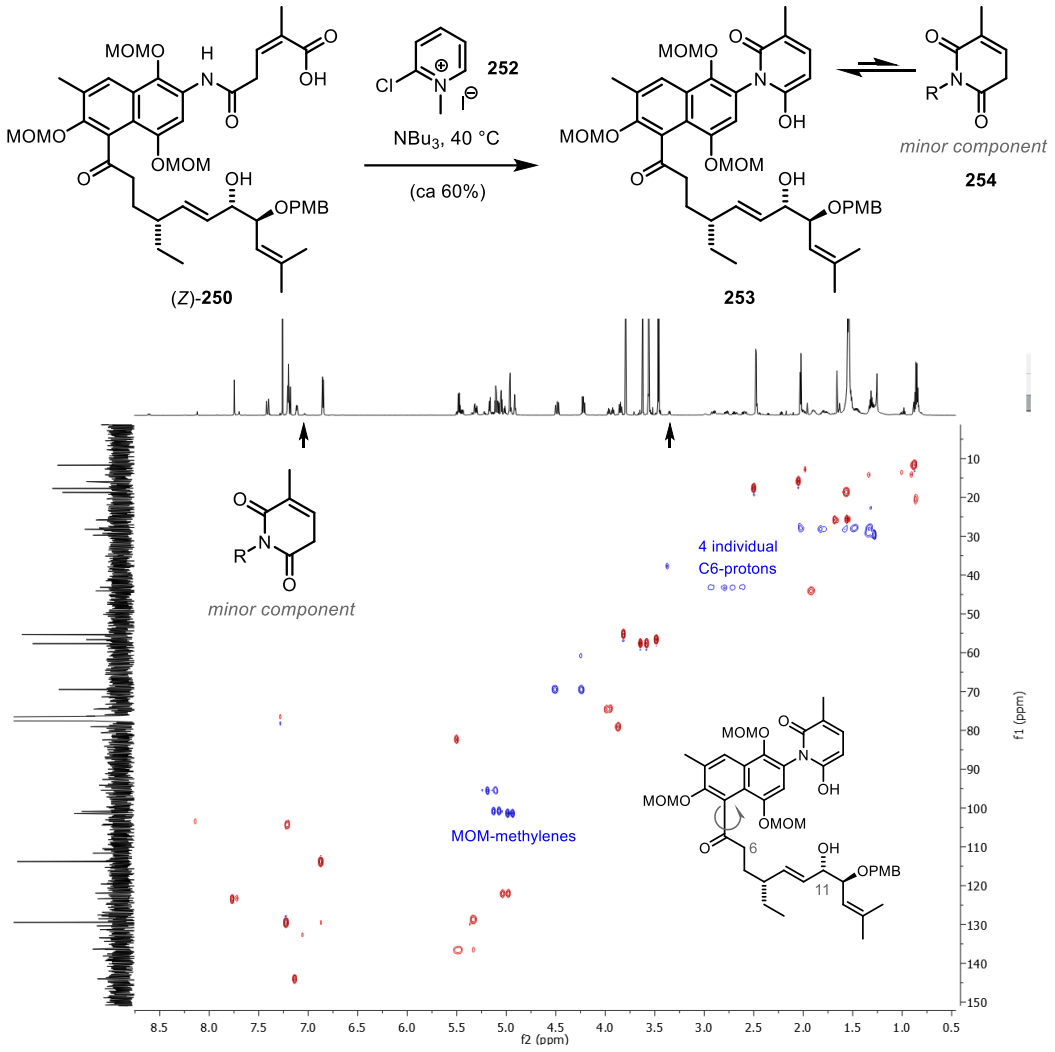


Scheme 51 N-Acylation to give (*Z*)-glutaconic acid derivatives.

We identified the most straightforward way to introduce a methylglutaconic acid was to expand on the findings of Feist and Pomme from the early 20th century.[24] In their communication, the thermal acylation of aniline was reported to be feasible using methylglutaconic anhydride **69** (for the preparation see Scheme 11) and heat. Mimicking the reported conditions (excess **69**, 100 °C in toluene) lead to decomposition when using naphthyl amine **251** as a substrate (Scheme 51). Undeterred, we sought to find milder conditions and were pleased to discover that HOBt opens anhydride **69** at the more reactive ketone and delivers the activated glutaconic acid selectively to the amine (no *O*-acylation observed). The glutaconic olefin remained in the (*Z*)-configuration as was demonstrated by nOe measurements of **250** and the relatively downfield shift of the glutaconic methyl group (δ = 20.7 ppm).[13d]

The successful synthesis of a cyclization precursor in 12 linear steps (28 individual steps) was exhilarating, but when high dilution conditions for the elusive macrolactonizations were investigated we encountered an interesting, but dismaying result. Employing the macrocyclization methodologies developed by Shiina[49] or Yamaguchi[36] lead to intractable

mixtures but using the original Mukaiyama protocol[62](**252**, NBu_3) lead to a sensitive compound that showed the correct mass ((−)-ESI: 802.38014; $M-H^-$) for a condensation product. Isolation of this isomer of the desired macrocycle proved challenging, as the product decomposed under basic and neutral workup conditions but proved somewhat stable when using a slightly acidic (aq. NH_4Cl) workup, followed by quick filtration over silica.



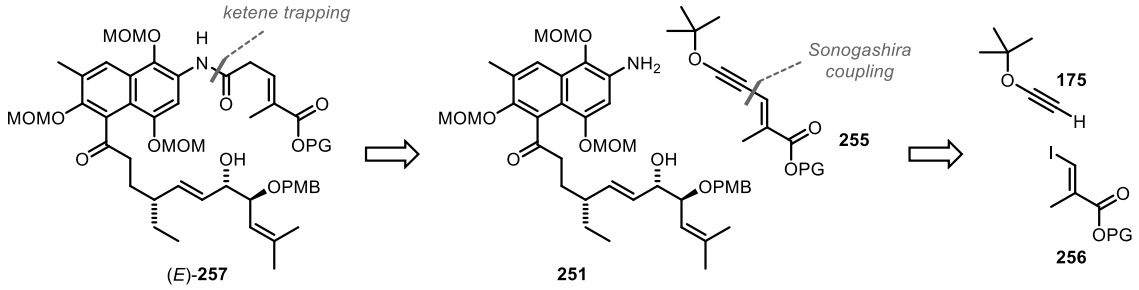
Scheme 52 Putative formation of pyridone species.

Scheme 52 shows the proton, carbon and HSQC spectrum of the isolated species, which we tentatively assigned to pyridone structure **253**. When comparing the spectral data to the starting acid (*E*)-**250**, it can clearly be deduced that the glutaconic acid reacted, but not with the intended C11 hydroxyl. This is also demonstrated by the atropisomerism still exhibited by the product: A telltale sign of the hindered naphthyl ketone rotation in any compound we encountered were the beautifully separated resonances of the two sets of two diastereotopic C6 protons, as well as two signals for all homotopic MOM methylenes, representing the two atropisomers. Approximately 10% of material the material showed resonances that could

correspond to the diketo tautomer **254**. Realizing that a (*Z*)-configured glutaconic acid in **250** might generally prefer 6-membered ring formation over the desired closure to a 19-memeberd macrocycle, we decided to abandon examination of more cyclization conditions and construct a macrolactonization precursor bearing an (*E*)-glutaconic acid.

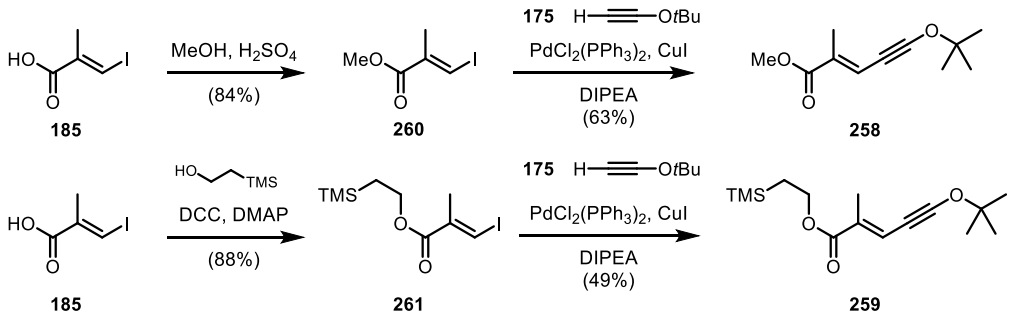
2.3.2 Late-stage installation of an (*E*)-glutaconic amide

Luckily, we already had developed chemistry capable of delivering an (*E*)-glutaconic acid fragment to a naphthyl amine related to **251** (see Scheme 34). We expected the construction of carboxyl-protected latent ketene **255** to be quickly achieved by Sonogashira couplings of *t*-butoxy acetylene **175** and (*E*)-vinyl iodides (**256**). In contrast to our anhydride-based *N*-acylation strategy for the construction of (*Z*) configured glutaconic amides, we did not expect complete *N*-selectivity during the ketene trapping, as the highly active intermediates might also *O*-acylate. This selectivity issue was expected to be ameliorated by using a 1:1 stoichiometry of reactants **251** and **255** in amidation experiments.



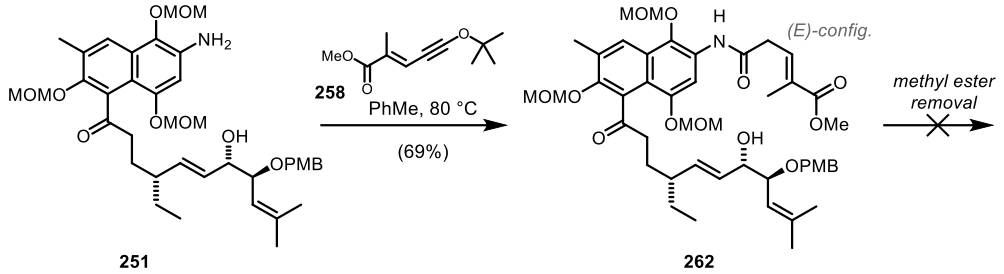
Scheme 53 Installation of (*E*)-glutaconic amides (**257**)*via* ketene trapping.

Preparation of two alkynyl ethers **258** and **259**, bearing a methyl or SEM-ester respectively, was achieved in a straightforward sense as illustrated in Scheme 54. Fischer and Steglich esterifications of carboxylic acid **185** gave good yields of vinyl iodides **260** and **261**. The subsequent Sonogashira couplings to alkyne **175** proceeded in moderate yield under the established conditions (see Scheme 36).



Scheme 54 Preparation of alkynyl ethers for (*E*)-glutaconic amide formation.

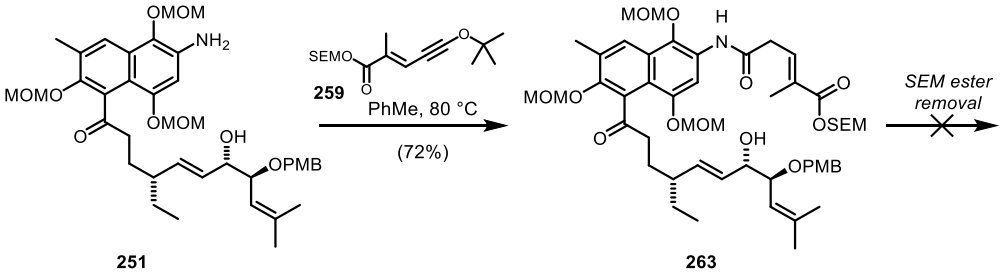
Generation of a ketene from **258** and subsequent trapping with naphthyl amine **251** proceeded in 69% yield (Scheme 55), partially attributed to double acylation as was indicated by an uncharacterized side product that showed the expected mass ((−)-ESI: 974.45436; $M-H^+$).



Scheme 55 (*E*)-glutaconic amide synthesis, failed methyl ester removal.

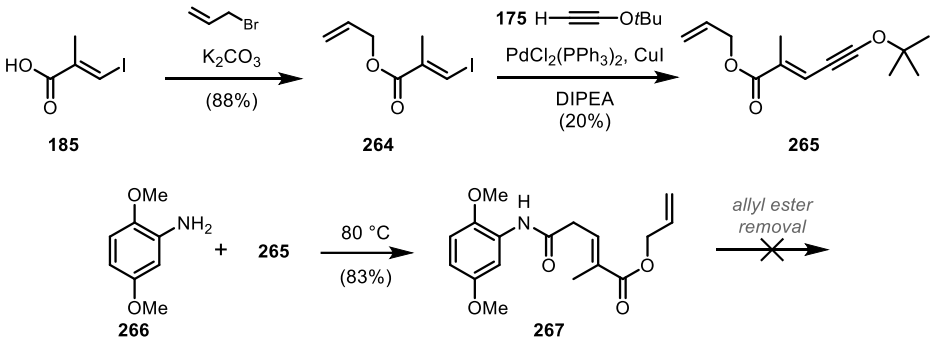
Unfortunately, we could not effect clean removal of the methyl ether. After direct cyclization of **262** could not be induced by action of Na or NaH, we found that exposure to LiOH, KOH or TMSOK[63] lead to decomposition. The only reagents that could partially cleave the methyl ester were tin-based: Me_3SnOH, a reagent repopularized by Nicolaou,[64] gave a product with the right mass and a reasonable proton NMR spectrum, but even prolonged reaction times and superstoichiometric use of the reagent (>40 equivalents) could not achieve full conversion of **262**, that was inseparable from the reaction product. Using Mascaretti's[65] $(Bu_3Sn)_2O$ (2 eq) at high temperatures (PhMe, 120 °C) allowed for full conversion of **262** and most of the side products could be removed by extraction into pentane after mildly acidic workup, but still not provided material we deemed clean enough for the macrolactonization. Consequently, slow addition of the putative acid to solutions containing the reagents for Shiina, Yamaguchi or Mukaiyama macrocyclization resulted in intractable mixtures. Nevertheless, no pyridone formation (see Scheme 52) was observed under Mukaiyama conditions, raising the hopes that if the right protecting group for the α,β-unsaturated ester is found, macrolactonization was still a viable option.

We moved on to test the resilience of the SEM ester derivative and could synthesize the required (*E*)-glutaconamide **263** by ketene trapping, again also isolating traces of a double



Scheme 56 Synthesis of SEM-ester **263**.

acylation product. Unfortunately, the use of TBAF or TASF were ineffective to remove the SEM ester but lead to decomposition. $MgBr_2 \cdot OEt_2$ showed some traces of the desired carboxylic acid, but the reaction conditions could not be optimized. In a last attempt to find a right protecting group for our strategy we set out to synthesize an allyl ester (Scheme 57).

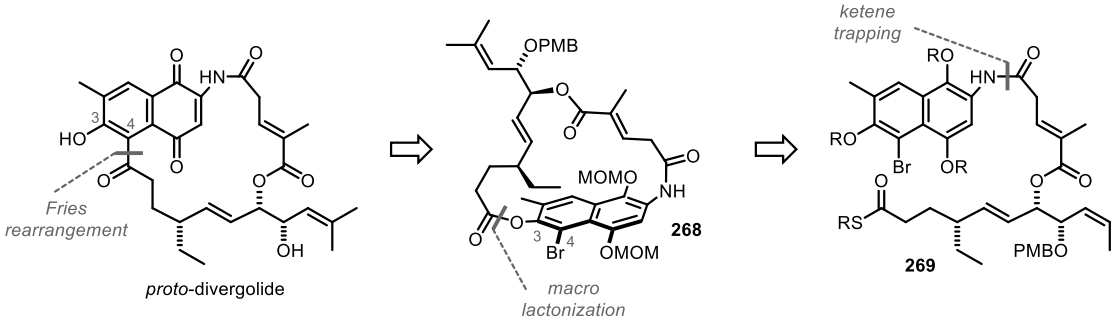


Scheme 57 Synthesis of model allyl ester **267**.

After allyl ester formation to give vinyl iodide **264**, it was not too unexpected that Sonogashira coupling with **175** gave a low yield of ynol ether **265**. To have a model system for allyl ester removal, we synthesized amide **267**. After not being able to obtain any of the desired carboxylic acid probing palladium catalyzed deallylations,[66] we abandoned this macrolactonization approach entirely. There was some reactivity to the glutaconic acid tethered between an amide and an ester that we could not pinpoint but was almost certainly attributed to the acidity of the glutaconic methylene, making hydrolysis of the already deactivated α,β-unsaturated ester non-trivial.

2.3.3 Studies towards construction of precursors for a Fries-rearrangement

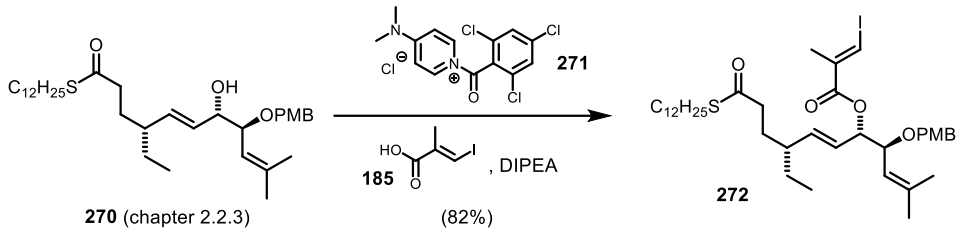
A last effort for a different macrolactonization was briefly pursued before abandoning ester formation for ring-closure overall. Scheme 58 describes our strategy:



Scheme 58 Macrolactonization onto the phenolic hydroxyl, followed by Fries-rearrangement.

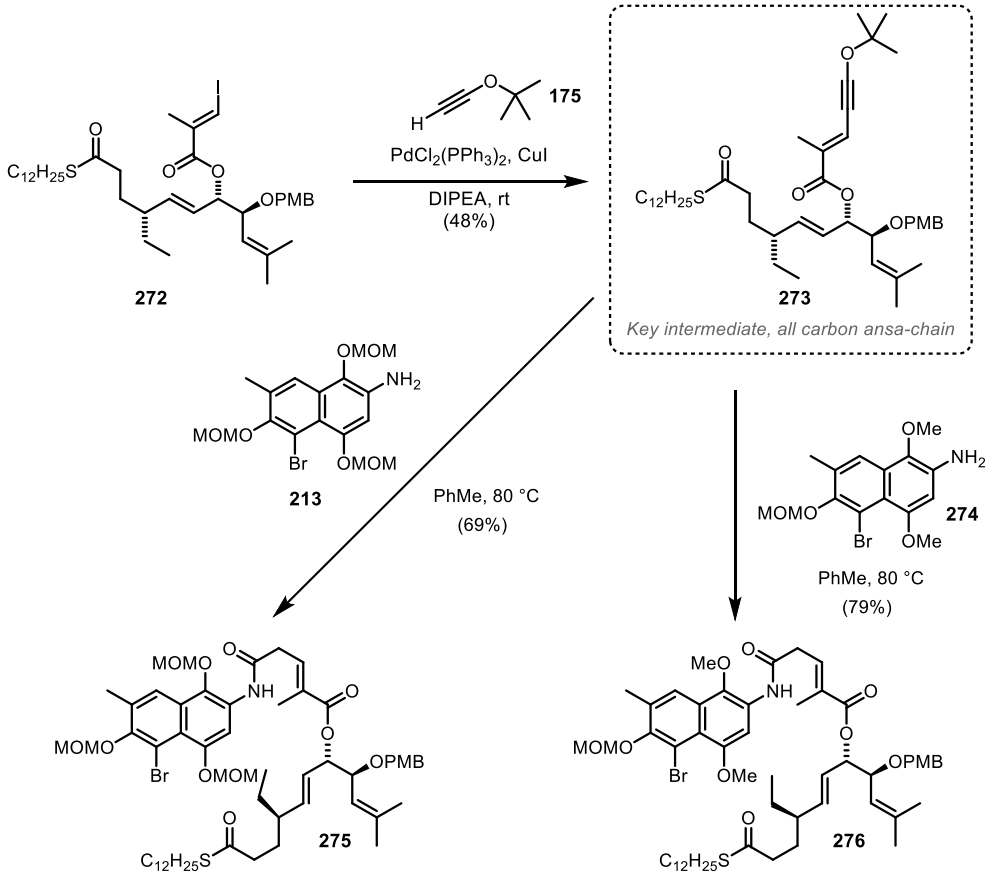
After installing the entire *ansa* chain in one ketene mediated *N*-acylation, ring closure was to take place with the C3-naphthol as a nucleophile to give macrolide **268** (for clarity of

representation, we chose to draw **268** as one atropisomer in the scheme), containing two lactones and a lactam. The resultant acyl moiety was to be transferred to the C4 position by some form of Fries-rearrangement.[67]



Scheme 59 Modified Yamaguchi esterification to access vinyl iodide **272**.

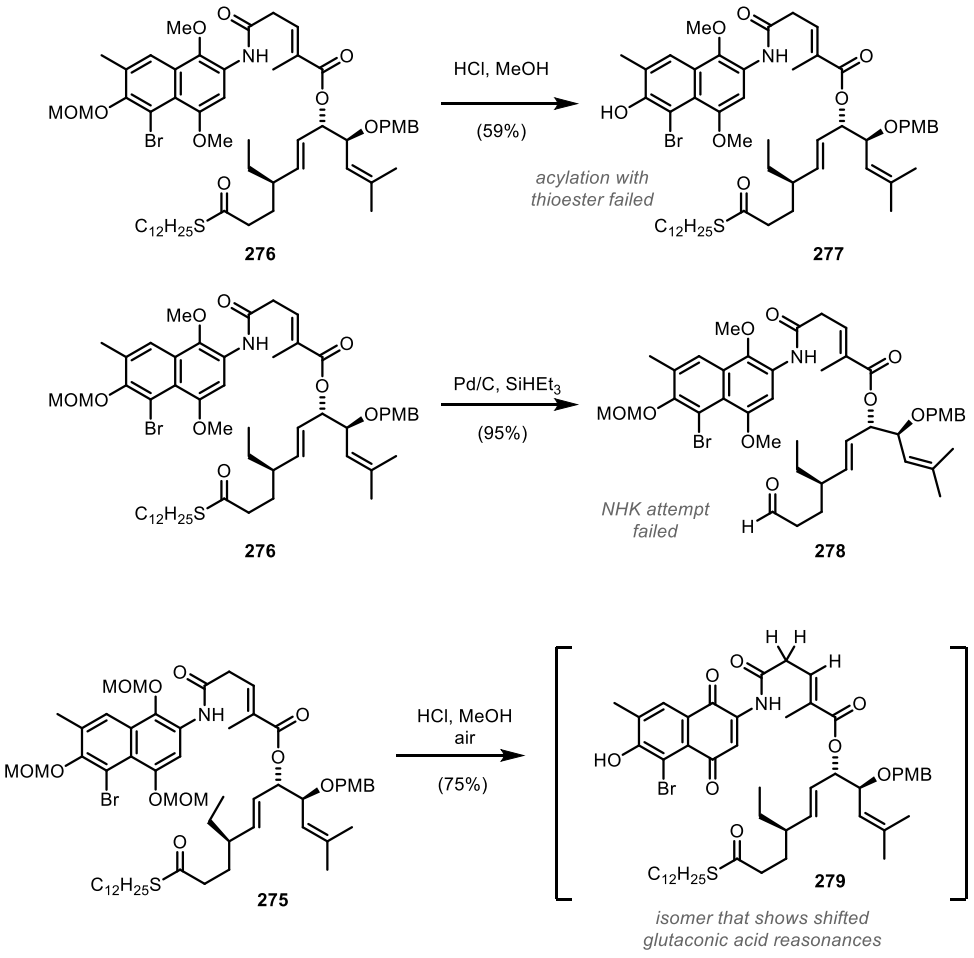
A modified Yamaguchi reagent[68] (**271**) enabled coupling to vinyl iodide **185** giving unsaturated ester **272** in good yields. Although not the most atom economic reagent, acyl pyridinium salt **271** is a stable solid easily prepared from the acid chloride and DMAP. The preparation of **271** represents a convenient method to make use of old bottles of the somewhat more sensitive acid chloride.



Scheme 60 Preparation of differentially protected amides **275** and **276**.

Sonogashira coupling of vinyl iodide **272** and alkyne **175** proceeded with moderate yield but provided the first compound that constitutes all carbon atoms of the *ansa* chain in the right

oxidation pattern. Subsequent trapping of the latent ketene was performed with both naphthalenes **213** and **274**, that could be either globally MOM deprotected and oxidized to the quinone by air (**275**) or transformed into the free naphthol in the hydroquinone oxidation state (**276**).[I] In comparison to the previously prepared naphthyl ketones, the NMR spectra of **275** and **276** were clearly resolved and showed no signs of atropisomerism. This was in stark contrast to all previously described compounds that comprised all divergolide carbon atoms.



Scheme 61 Brief evaluation of alternative cyclization precursors **275** and **276**.

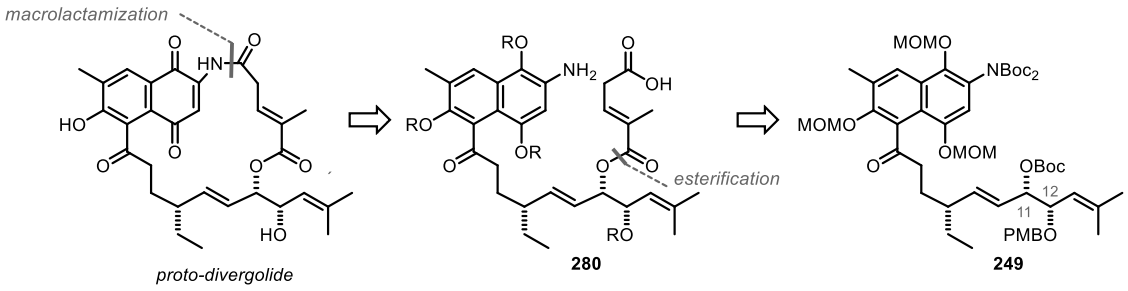
Scheme 61 depicts our brief endeavors (see footnote) of achieving the alternative macrolactonization. Bis-methyl ether **276** could be MOM deprotected under acidic conditions in moderate yields. In four test experiments, we subjected naphthol **277** to heat, DIPEA, KHMDS and a combination of DMAP, silver(I)trifluoroacetate and TEA but could not observe formation of any macrocyclic species. Fukuyama reduction of **276** worked well, but aldehyde **278** was

[I] As opposed to **276**, triple MOM ether **275**'s formation was only verified by HRMS and ^{1}H-NMR and is not part of the experimental section as are the results depicted in Scheme 61.

unreactive to Nozaki-Hiyama-Kishi conditions when heated up to 100 °C in DMF (4 equivalents $CrCl_2$, 1 equivalent $NiCl_2$). When subjecting triple MOM protected naphthalene **275** to acidic conditions, however, we obtained an interesting result. A single isomer of quinone **279** ((−)-ESI: 948.37211 + 950.37012; $M-H^+$) could be isolated, but we failed to deduce the structure. The characteristic glutaconic acid (downfield triplet coupling to an upfield doublet, $J \approx 7$ Hz) resonances were missing, indicating an acid catalyzed transformation. The small amount of solid did not give crystals suitable for X-ray analysis and investigation of this enticing result was abandoned in favor of a different strategy, which should finally reveal conditions for construction of a macrocyclic species. The successful development of a pathway once again relying on macrolactamization will be discussed in the following chapter.

2.4 Macrocyclization *via* macrolactamization II

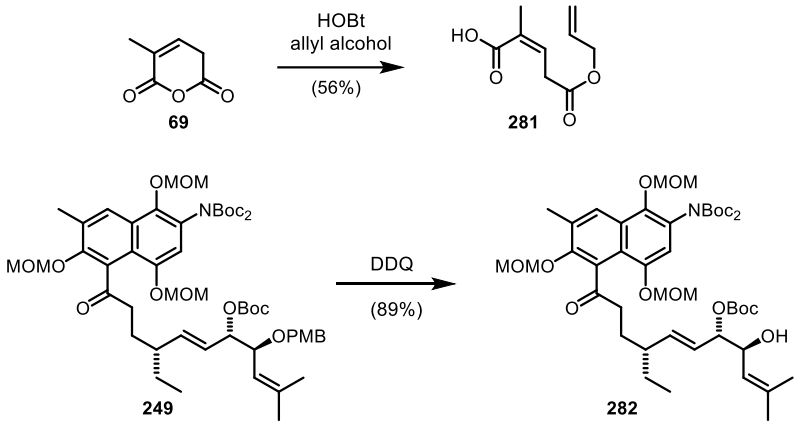
The strategy that should finally solve the outstanding problem of macrocyclization was based on late-stage installation of the glutaconic acid, just as the macrolactonization attempts discussed in chapters 2.3.1 and 2.3.2.; now though, we decided to install the glutaconic acid on either the C11 or C12 hydroxyl group. After deprotection of the glutaconic acid and the nitrogen, an amino acid of type **280** should be generated, giving a new entry into a macrolactamization precursor.



Scheme 62 Macrolactamization after late-stage installation of glutaconic acid.

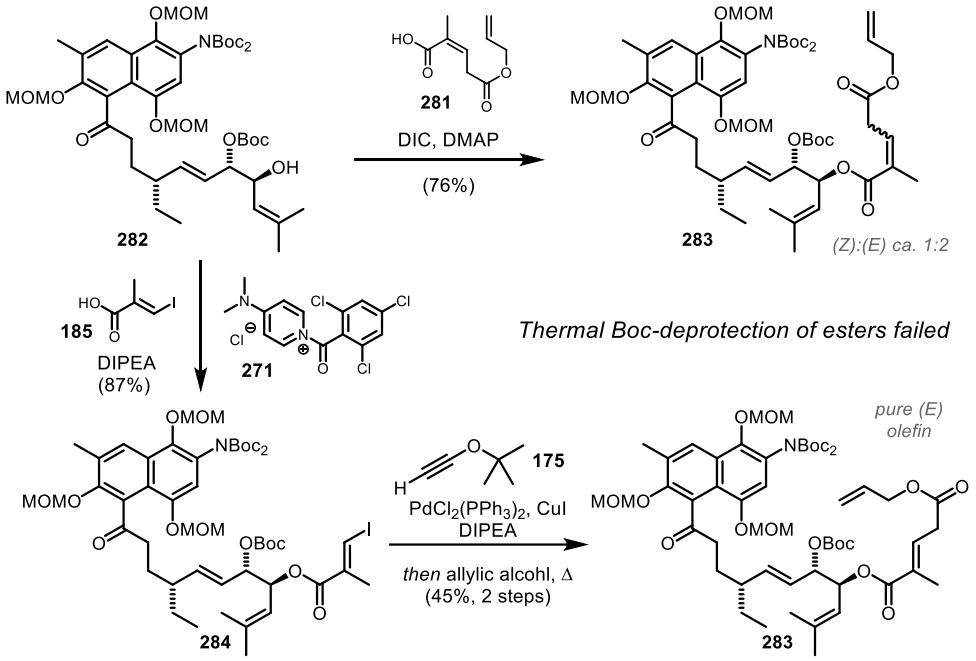
2.4.1 Total synthesis of divergolide I

In search of a mono-protected methylglutaconic acid we made use of our discovery that anhydride **69** can be regioselectively opened by HOBt at the less deactivated ketone. Thus, addition of allylic alcohol gave rise to crystalline allyl (*Z*)-methylglutaconic acid **281**. Having access to a carboxylic acid suitable to our macrolactamization strategy, we went forth to oxidatively deprotect the C12 PMB ether of **249** using DDQ granting allylic alcohol **282**.



Scheme 63 Synthesis of a methylglutaconic allyl ester, DDQ deprotection of PMB ether **249**.

EDC (HCl salt) or the modified Yamaguchi reagent **271**[68] gave very low yields in attempts to couple allylic alcohol **282** with carboxylic acid **281**. We discovered that carbodiimide DIC in combination with DMAP was able to deliver ester **283** in good yields, but the NMR spectra suggested a scrambling of the glutaconic olefin geometry in favor of the (*E*) isomer (Scheme 64).[I] This effect was attributed to DMAP, as pyridine was shown to isomerize (*Z*)-methylglutaconic diesters to the (*E*) isomer (see Scheme 12 in the introduction).

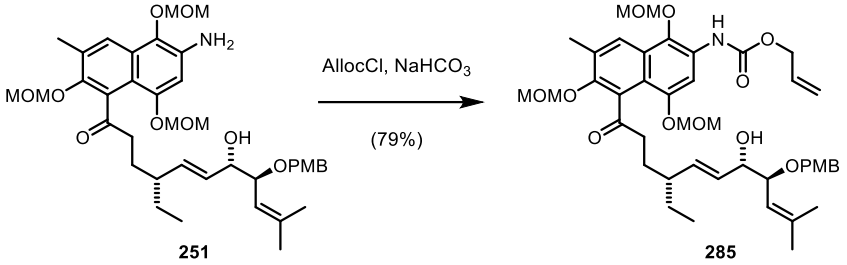


Scheme 64 Glutaconic olefin isomerization during esterification.

We verified the olefin scrambling by independent synthesis of the pure (*E*) glutaconic ester to make sure we did not confuse alkene diastereomers with atropisomers. Based off of the experience we had with (*E*)-glutaconic acid synthesis as latent ketenes, vinyl iodide **185** was installed under the previously developed conditions in good yield. After Sonogashira coupling to alkyne **175**, the ynol ether was filtered over a plug of silica, followed by heating the crude product in allylic alcohol. Trapping of the ketene produced pure (*E*)-methylglutaconic diester **283**, confirming our hypothesis that an olefin isomerization takes place under the ester coupling conditions. However, the required thermal global Boc deprotection lead only to decomposition of the esters. Nevertheless, our strategy could easily be modified by removing the Boc groups first and reprotecting the nitrogen with a strategically more useful protecting group.

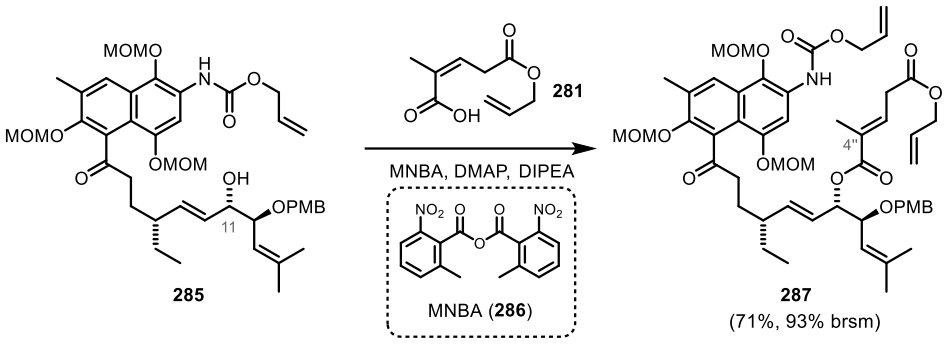
[I] The identity of all compounds shown in Scheme 64 were verified by HRMS and proton NMR and are not included in the experimental section.

Having already established that global deprotection works on naphthalene **249** (see Scheme 50), we chose to reprotect amine **251** as Alloc-carbamate in hopes of cleaving it later on simultaneously with the allyl ester on the glutaconic acid.[69]



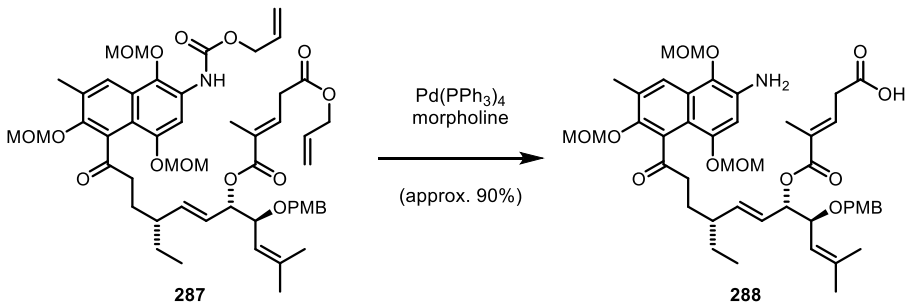
Scheme 65 Alloc-carbamate installation on the nitrogen.

To achieve high yields in the nitrogen protection it was key to immediately subject sensitive naphthyl amine **251** to the carbamoylation conditions after Boc removal. Moreover, we found that freshly distilling the chloroformate from calcium hydride before addition ensured clean conversion to allylic alcohol **285** (Scheme 65). The stage was now set to investigate the glutaconic acid installation.



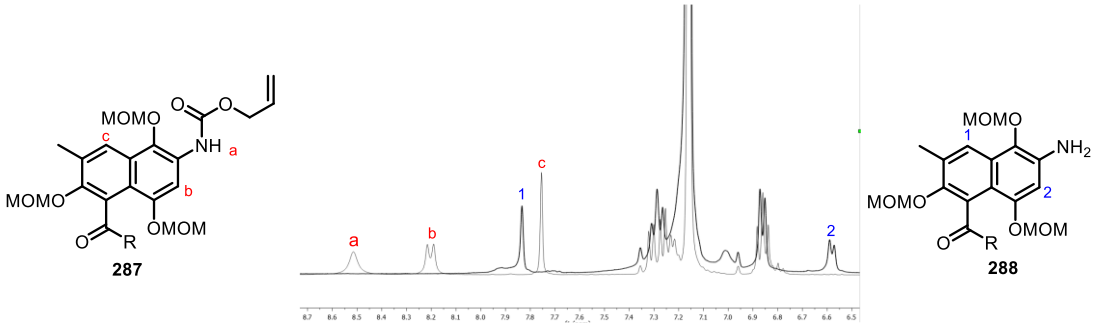
Scheme 66 Glutaconic acid installation.

Unfortunately, DIC mediated installation of the glutaconic acid on the supposedly more hindered C11 alcohol was not met with the good yields encountered in the C12 esterification. EDC (freebase or HCl salt) or the Yamaguchi[36] reagent also lead to low yields and incomplete olefin isomerization. Shiina's reagent[49] (**286**) however, delivered better yields and we could invoke *complete* olefin isomerization if all reagents were added in excess (3 equivalents each). The configurational purity of the (*E*)-methylglutaconic diester (chemical shift of C4'' methyl carbon 12.6 ppm) simplified NMR analysis of the atropisomeric mixture and additionally, unreacted allylic alcohol **285** could be reisolated, adding further value to the transformation. We went forth to test if the elusive amino acid could be generated by cleavage of both the carboxyl and the nitrogen protecting groups at the same time.



Scheme 67 Synthesis of amino acid **288**.

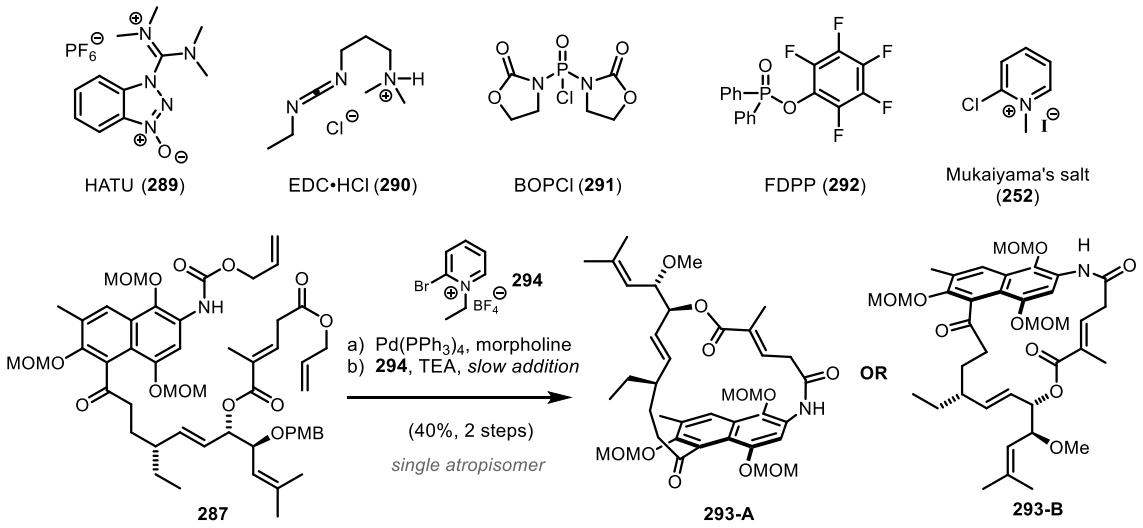
We anticipated that amino acid **288** would be highly sensitive; as discussed previously, all synthesized naphthyl amines proved to be sensitive to air and unprotected terminal glutaconic acids have largely remained elusive. Gratifyingly, the removal of both protecting groups proceeded rapidly in degassed THF (0 °C) in the presence of $Pd(PPh_3)_4$ and excess morpholine as allyl cation scavenger within 15 minutes. A quick workup with phosphate buffer (pH 5.5) removed the amine and careful chromatography over Davisil® afforded amino acid **288** after concentration on a rotary evaporator under a nitrogen atmosphere ((−)-ESI: 820.39129; $M-H^-$).



Scheme 68 Proton NMR resonances of naphthyl amine

While the acquisition of a clean carbon NMR spectrum of amino acid **288** was hampered by the sensitivity of the species, we could easily asses naphthyl amine formation by the dramatically different chemical shift of the aromatic proton adjacent to the amine, apart from HRMS. Scheme 68 shows the substantial upfield shift of proton 2 of amine **288** to approximately 6.6 ppm when compared to the same proton in carbamate **287** ($\delta \approx 8.2$ ppm). The respective signals appear as doublets, as the atropisomerism of **287** and **288** alters the chemical environment of protons b and 2 in a more pronounced manner than *e.g.* that of protons c and 1. As we observed this upfield shift in all naphthyl amines prepared so far, we were confident to have finally established a robust synthetic access to a macrolactamization precursor.

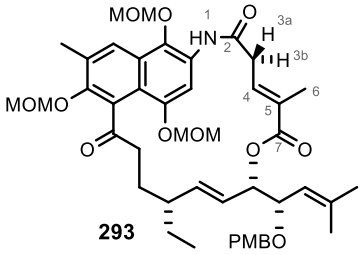
Cyclization attempts of freshly prepared **288** were performed by slow addition of solutions of the amino acid to a mixture containing the coupling reagents by syringe pump over the course of several hours. We first examined uronium salt HATU (**289**), carbodiimides EDC·HCl/EDC freebase (**290**), phorphoramide BOPCl (**291**) and penta-fluorophenyl diphenylphosphinate FDPP (**292**) and could not isolate any macrocyclic species. Gratifyingly, using a mixture of Mukaiyama's pyridinium salt **252** and TEA we could isolate a single condensation product that could be assigned to the desired macrocyclic structure **293**. We could also deduce that the macrolactam was formed as a single diastereomer since the absence atropisomerism was indicated by the brilliantly resolved 800 MHz NMR spectra (Scheme 69).



Scheme 69 Mukaiyama macrolactamization gives only *one* of the two atropisomers **293-A** and **293-B**.

Optimizing the low yielding macrolactamization proved arduous. Carefully controlled addition of high-purity amino acid in degassed DCM over eight hours (final concentration approximately 0.2 mM) was necessary to prioritize intramolecular reaction, as dimers (which in contrast to the 19-membered macrolide**293** exhibited heavy atropisomerism) were otherwise the main product. Cooling (0 °C, −20 °C) lead to more dimer formation and heating (45 °C) caused decomposition. We discovered that the modified Mukaiyama reagent **294**[70] results in fewer side products, but still the best yield achieved did not exceed 40% over two steps (Scheme 69). Possibly, only one of the two atropisomers of amino acid **288** can undergo cyclization, but heating to supply energy for the isomer-interconversion to occur more facile was not possible. Nevertheless, we had finally established a stable route to a progenitor of the venerable *proto*-divergolide as a single atropisomer. Efforts to elucidate which of the two possible atropisomers **293-A** or **293-B** was isolated by 2D-NMR alone proved futile, as no convincing nOe couplings could be identified. Nevertheless, especially the glutaconic acid unit's proton NMR revealed

that the *ansa* chain must be residing in a relatively rigid conformation above the naphthalenic core, whose rotation was restricted. Figure 16 shows the glutaconic acid ^{1}H- and ^{13}C-NMR chemical shifts and couplings.

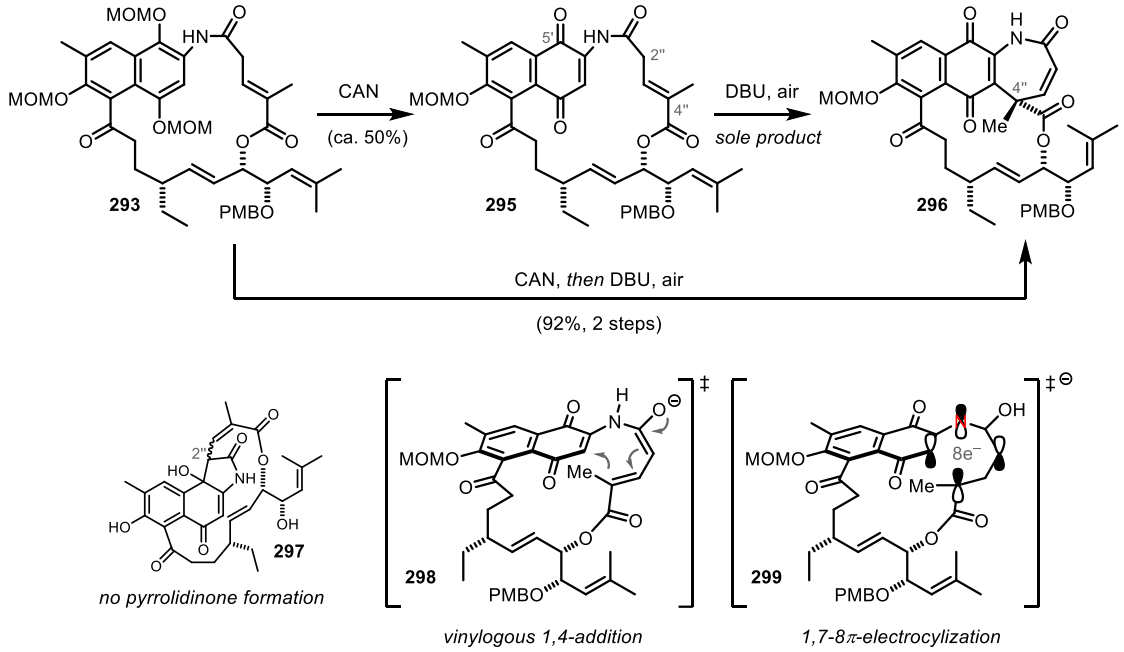


Pos.	δ ^{1}H	δ ^{13}C
1	6.46 (s)	-
2	-	170.8
3a	3.57 (dd, 16.0, 10.8 Hz)	36.5
3b	2.97 (ddq, 16.0, 3.6, 1.7 Hz)	
4	6.71 (ddq, 10.8, 3,6, 1.6 Hz)	134.6
5	-	129.7
6	1.17 (dd, 1.7, 1.6 Hz)	11.8
7	-	165.8

Figure 16 ^{1}H-NMR resonances of the macrocycle's glutaconic acid unit.

Especially the substantially different chemical shifts of protons 3a and 3b ($\Delta\delta$ = 0.60 ppm) reflect the distinct conformation of the ansa chain relative to the aromatic chromophore, as well as the homoallylic coupling observed only between methyl group 6 and proton 3b. Also, the upfield carbon shift of the C6 methyl (δ = 11.8 ppm) reveals the (*E*) configuration of the double bond. We came to the conclusion that while the data does support the notion that **293** was isolated as a single atropisomer, it is however not possible to make assumptions about which stereochemistry or amide geometry **293** shows in solution. Nevertheless, we believe that the macrolide exhibits a "basket-structure", typical of ansamycins. To investigate the interconversion and structure of the possible atropisomers of the macrocycle, we performed a macrocyclic conformational sampling on a simplified model system (all MOM and PMB protecting groups were replaced with methyl substituents) with the OPLS3 molecular force field and the program Macromodel of the Schrodinger Suite.[71] The author of this thesis is indebted to Martin S. Maier (Trauner group) for performing the calculations. It was found that a conformer search starting from either of the possible atropisomers did not return structures with the *ansa* bridge on the opposing side of the aromatic plane. As the method used for the conformer search employed a combination of low-mode sampling and simulated annealing, this finding strongly suggests a high energy barrier preventing the interconversion of both atropisomers. The lowest energy conformers of both atropisomers are energetically similar with a difference of less than 5 kJ/mol with a preference for the atropisomer structure corresponding to **293-B**. For both atropisomers there is a clear energetic preference for the *cis*-amide conformation over the *trans*-amide conformation of more than 30 kJ/mol.

Moving on to investigate oxidation of the naphthalenic macrocycle **293** to the naphthoquinone **295**, we found that ceric ammonium nitrate (CAN) induced the desired reaction, but yields were not exceeding 50%.[I] Nevertheless, we could finally study the biomimetic ring-contractions on a protected *proto*-divergolide in the right oxidation states. We got very lucky when we treated **295** with DBU in a flask open to air as our first attempt at C2'' deprotonation and were able to identify reoxidized azepinone **296** as the sole reaction product in the crude reaction mixture. Upon realizing that the low yields of the CAN oxidation were due to concomitant ring-contraction during the course of the reaction, we subjected the crude products of the oxidation after aqueous workup directly to DBU and obtained the azepinone in good overall yield as the only reaction product.

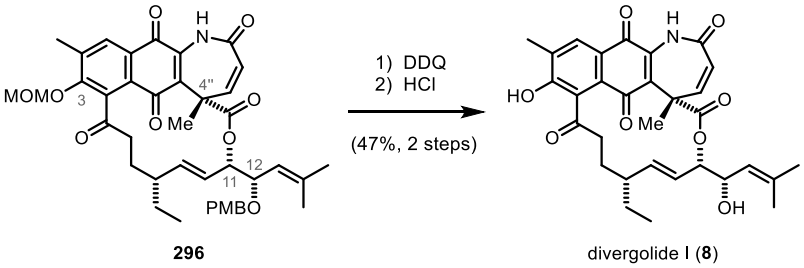


Scheme 70 Selective biomimetic ring-contraction of protected *proto*-divergolide **295** gives azepinone **296**.

This ring-contraction to give the core structure of the natural product divergolide I (**8**) is remarkable in several respects. Even though hypothesized to occur in Nature, the facile transformation of the tricyclic 6-6-19 ring system to the oxidized tetracyclic 6-6-7-14 array of **296** in the laboratory was not expected to occur so selectively. Firstly, no aldol-type additions (C2'' to quinone carbonyl C5') to give the naturally occurring pyrrolidinones (**297**) was detected – not even traces of this adduct could be detected by highly sensitive ESI-HRMS of the crude reaction product. Secondly, the degree of selectivity when forming the quarternary C4'' stereocenter is

[I] Quinone **295** was only characterized by proton NMR and HRMS and is not part of the experimental section.

very intriguing as no quantifiable amounts of the C4'' diastereomer could be isolated. On the other hand, this most likely results from the fact that we only subjected a single atropisomer to the ring-contraction conditions. We concluded that the selectivity arises from the planer chirality of the macrocycle guiding the transannular selectivity in the formal 1,4-addition. Moreover, the rapidly occurring oxidation of the electron-rich hydroquinone renders this process irreversible, making a Curtin-Hammet scenario in which the intermediate 1,4-addition product gets swiftly removed from potentially competing equilibria by oxidation also possible. Concerning the mechanism of the ring-contraction (for a detailed discussing see chapter 1.2.3, Scheme 10), both a 1,4-addition of a vinylogous *cis*-amide enolate (**298**) or a conrotatory 1,7-8π-electrocyclization (*via* **299**) are chemically sound pathways.

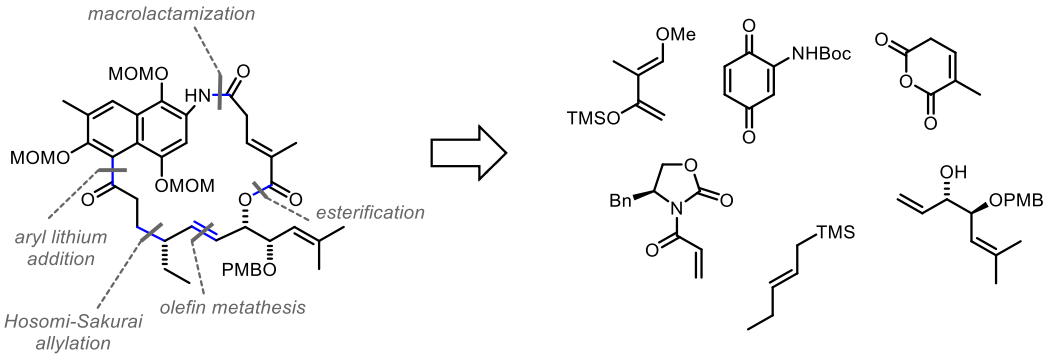


296 divergolide I (**8**)

Scheme 71 Hydroxyl deprotection of azepinone **296** completes the synthesis of divergolide I (**8**).

We then moved on to the last task, namely C3 hydroxyl deprotection of the phenolic MOM ether and C12 hydroxyl PMB removal to convert **296** into divergolide I. This would reveal if the natural C4'' configuration was generated in the ring-contraction. DDQ (freshly sublimed) mediated PMB ether deprotection proceeded smoothly without any hints of concomitant 1,2-acyl shifts. This result was expected from our previous studies (see chapter 2.1.3, Scheme 31) and we were delighted that our hypothesis held true for the cyclic substrate **296** as well. Careful hydrolysis of the phenolic MOM ether was performed by treating the PMB deprotected product with HCl in methanol (0 °C). The HCl solution was freshly prepared by saturating methanol with HCl generated from drop wise addition of concentrated H_2SO_4 onto NaCl for 20 minutes and drop wise addition of this solution (1 part) to the azepinone dissolved in cold methanol (9 parts). We realized that the free phenol renders divergolide I (**8**) soluble in the saturated aqueous $NaHCO_3$ solution used for quenching the reaction after complete conversion, demonstrated by the purple color of the aqueous phase during workup. By addition of saturated aqueous NH_4Cl solution to the biphasic mixture, divergolide I was protonated and soluble in the organic layer, as could be observed by the yellow color of the DCM extracts. The acidity of the phenol also had to be taken into account for further chromatography, as divergolide I (**8**) only could be eluted with mixtures containing acetic acid.

Rigorous characterization of the natural product confirmed its identity and relative configuration, as the 1D- and 2D-NMR spectra (see experimental section for a table comparing the chemical shifts) were in very good agreement with the data provided by Hertweck,[13e] who reported the natural product in 2015. Furthermore, the optical rotation we measured ($[\alpha]_D^{20} = -174$ ($c = 0.24$ in MeOH) matched very well ($[\alpha]_D^{20} = -179$ (c = 0.4 in MeOH reported by Hertweck), hence also securing the absolute configuration of the divergolide and hygrocin natural product families. In antimicrobial assays conducted by the Hertweck group,[13e] divergolide I showed the broadest antimicrobial activity of any divergolide or hygrocin reported to date, as 50 µg samples of **8** significantly inhibited growth of *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis*, *Escherichia coli* and *Sporobolomyces salmonicolor*.

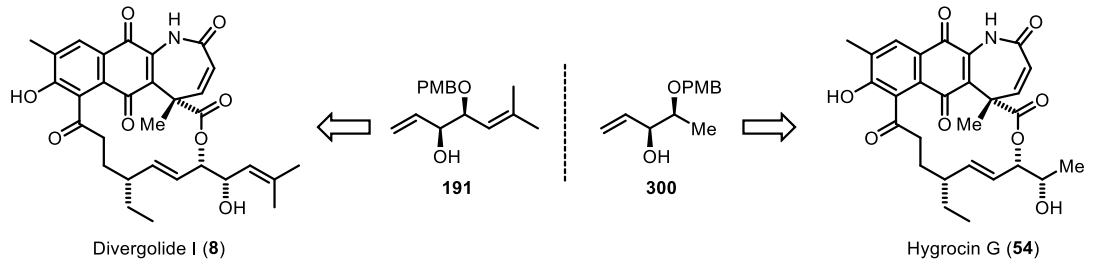


Scheme 72 Dissection of divergolide I into the fragments used to successfully build the natural product.

The enantioselective synthesis of divergolide I concludes our studies towards naphthoquinone divergolides. The successful route selectively gave the azepinone natural product in a longest linear sequence of 19 steps. Considering that 36 individual steps were needed to complete the synthesis, our final pathway distinguishes the usefulness of a convergent, fragment-based approach. Hence, the strategy could continually be modified to meet our endeavors, oftentimes making use of abandoned tactics and building blocks to quickly explore novel chemistry. The highlights of the successful synthesis were the unusual use of a Hosomi-Sakurai reaction to generate the (*R*)-ethyl stereocenter, a high-yielding (*E*)-selective cross metathesis of an allylic alcohol, late-stage installation of a sensitive, isomerically pure, glutaconic acid, a highly challenging atroposelective macrolactamization and a ring-contraction whose transannular selectivity was controlled by planar chirality. The strategic orchestration of protecting groups for the reactive functionalities evolved continuously throughout the project and proved key to enable the fragment coupling and cyclization up to the very last steps of the synthesis.

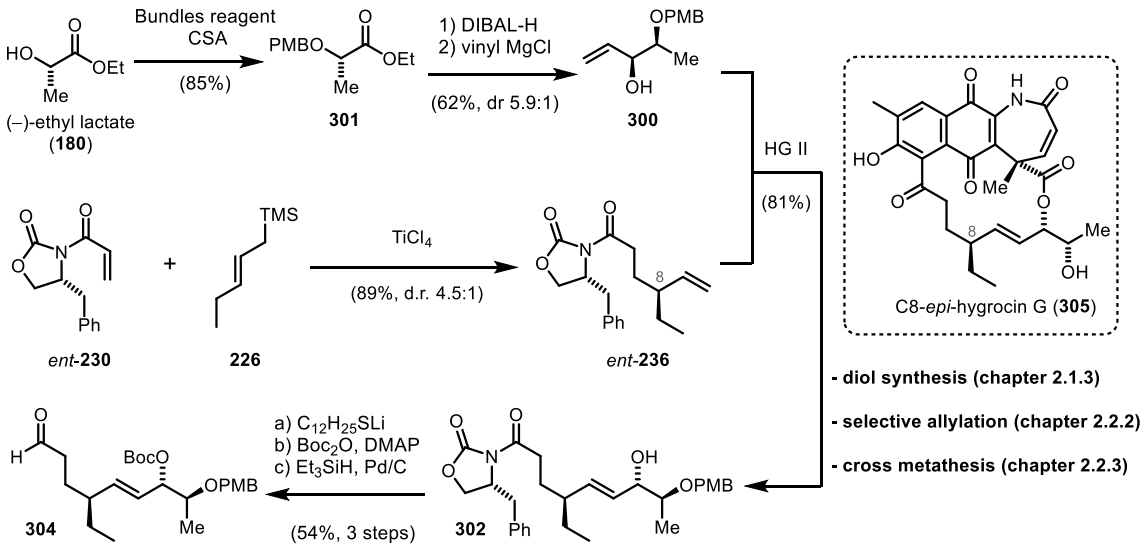
2.4.2 Total synthesis of *epi*-hygrocin G

Having established a route to reach azepinone type divergolides, we sought to adapt the synthesis to also provide an entry into hygrocin ansamycins. Since our fragment-based approach allows for introduction of the diol as a separate unit and cross metatheses with hygrocin diols were already investigated (see chapter 2.1.3), we saw a chance to prove our pathway is also competent to reach the closely related natural product family.



Scheme 73 Access to hygrocin G by changing the diol fragment to **300**.

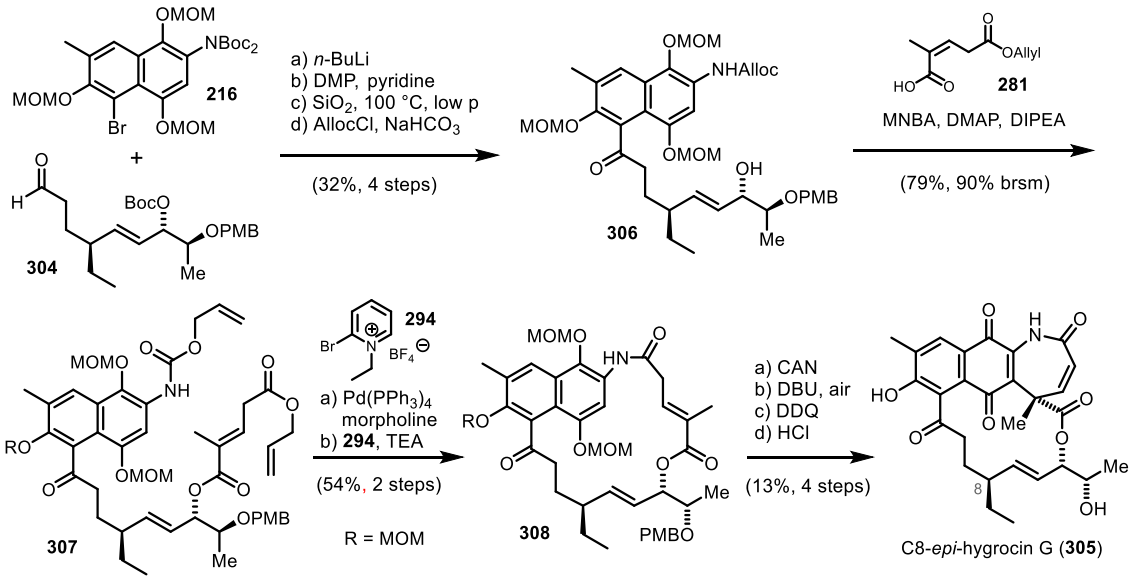
The synthesis was mostly carried out by Julian Feilner, a former Master student in the Trauner group. The author of this thesis devised the strategy, supplied some intermediates and helped in scale up experiments. Julian's tireless efforts to run through the established synthesis during the course of his Master's thesis have to be highly commended.



Scheme 74 Synthesis of aldehyde **304** using the established strategy.

Scheme 74 shows how the divergolide route could be followed in essentially the same reaction pathway, by only changing the PMB protecting group based off of the synthesis of previously prepared diols. The key cross metathesis worked in similar yield, giving rise to (*E*)-alkene **302**.

As already discussed in the disclaimer at the beginning of chapter 2.1.4, we failed to recognize that the hygrocins have the same (*R*)-ethyl configurations as the divergolides. Hence, the result of the synthesis depicted in Scheme 75 lead to total synthesis of the C8 epimer of hygrocin G (**305**).

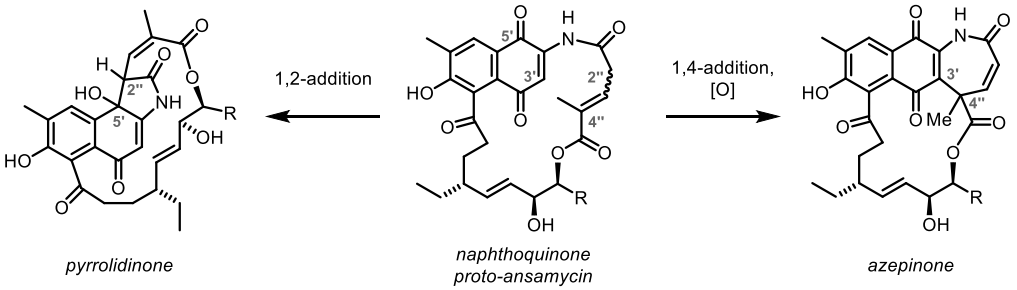


Scheme 75 Total synthesis of C8-*epi*-hygrocin G (**305**) verifies the synthetic access to hygrocin derivatives.

The yields of the endgame are not optimized, but gratifyingly all reaction conditions developed in course of the divergolide I synthesis proved to work on the C8-*epi*-hygrocin fragments as well. Coupling of aldehyde **304** to aryl bromide **216** was achieved in 72% yield and the key esterification of allylic alcohol **306** provided facile entry to the precursor to the 2-step cyclization procedure. The deprotection/macrolactamization reaction towards **308** could be reproducibly carried out, in the hygrocin case with an optimized yield of 54% over two steps. The endgame, starting with oxidation to the quinone and ring-contraction were at this point not completely developed but the same selectivity for only a single azepinone product was once again observed. Upon deprotection of the PMB and MOM ethers we discovered upon rigorous NMR analysis that we had synthesized C8-*epi*-hygrocin G (see experimental section for the comparison of the spectra by Shen and our C8-*epi*-hygrocin G). The azepinone-naphthoquinone NMR resonances matched very well and can be assumed to have the natural C4'' configuration, but the signals from protons in proximity to the C8-ethyl group were in accordance with those expected from an C8-epimer. While these results were rather anticlimactic, we still had proved that our pathway can be easily adopted to reach hygrocin congeners in addition to divergolides.

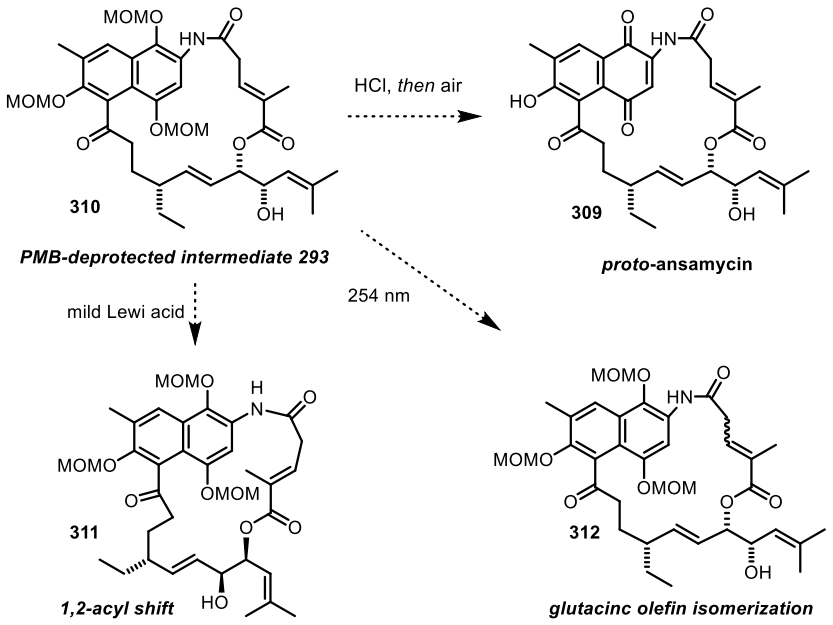
3 Outlook

The chemo- and diastereoselectivity of the biomimetic azepinone formation serendipitously provided us with synthetic access to divergolide I, but also stimulated interest in finding alternative reaction conditions to induce the pyrrolidinone formation that also takes place in Nature (Scheme 76).



Scheme 76 Pyrrolidinone and azepinone formation of the *proto*-ansamycin.

In attempts to isolate the 19-membered quinone **295** (Scheme 70) that had not undergone ring-contraction yet, we were always met with yields below 50%, which turned out to be because the azepinone formation already happens under the not only oxidative but also Lewis acidic conditions during CAN oxidation. If trying to isolate the "true" naphthoquinone *proto*-ansamycin **309**, a reasonable start of an investigation would be to use the established Brønsted acidic conditions to remove all three MOM ethers (Scheme 38, Scheme 61), *after* the PMB group was removed from our macrolactonization product **293**, to yield allylic alcohol **310**.

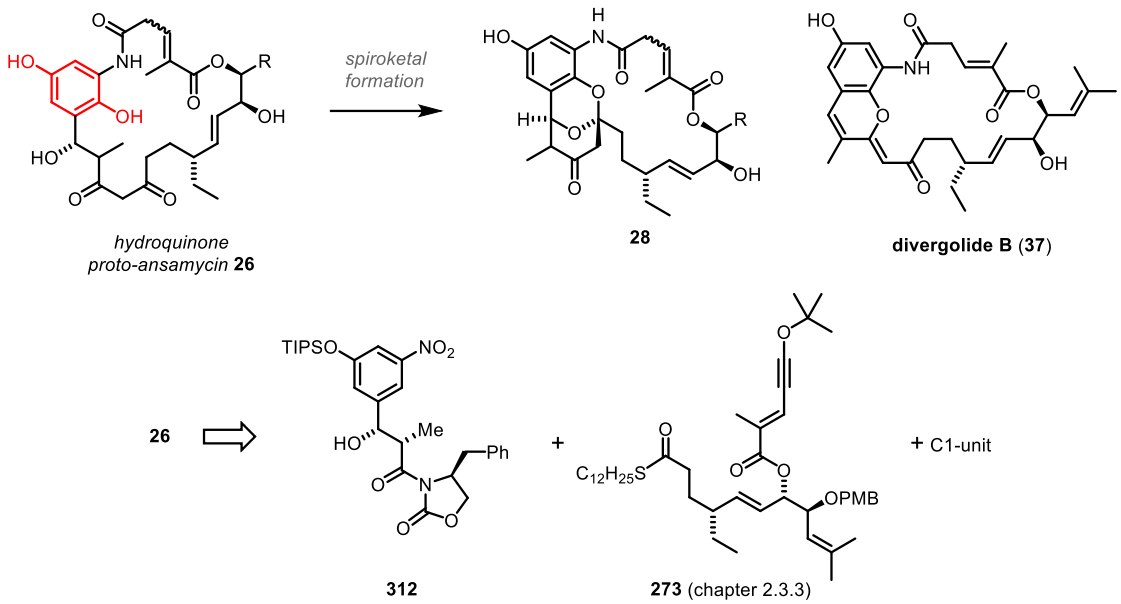


Scheme 77 Potential access to the *proto*-ansamycin and diversification of the macrocycle.

Moreover, the 1,2-acyl shift can be studied with this intermediate. Provided that conditions are found to induce complete ester migration, or at least scrambling, the resultant 20-membered macrocycle **311** might show a different diastereoselectivity when contracting to an azepinone. If this holds true, a selective synthesis of divergolide C (Figure 5) will be achieved.

Apart from the ester positioning, the glutaconic olefin's geometry might very well be an important factor governing the chemoselectivity of the ring-contraction. When examining the six known pyrrolidinone divergolides and hygrocins (Scheme 9), it is eye-catching that five of the congeners show (*Z*)-configuration of the glutaconic acid unit. Since our precursor was (*E*)-configured, we have perhaps biased the alternative reactivity by configurational preference. In their studies of glutaconic acid derivatives, Kagan[22] showed that scrambling of the olefin can be easily induced photochemically (Scheme 12), so it would be intriguing to see how naphthalenes **310** or **293** behave under the described conditions. Since pyridine and DMAP completely isomerize from (*Z*) to (*E*), perhaps a nitrogen base can be found or designed that makes use of this affinity of the glutaconic acid and the base to invert the selectivity.

Lastly, we regret not having acquired CD spectra of the 19-membered macrocycle resulting from Mukaiyama lactamization (**293**). It should be easy to calculate the CD spectra of the two atropisomers that can result from the cyclization. Perhaps the differences in the respective calculated spectra would be pronounced enough to match the data collected from our own measurements of the atropisomer we synthesized (Scheme 69). This could shed light onto the diastereoselectivity of the amide bond formation. If **293**'s identity is revealed, perhaps Rinehart's studies[3] on the atropisomer interconversion of streptovaricin C can be mimicked, potentially giving access to *atrop*-**293**. This would open up a whole new avenue to study this isomer's selectivity in ring-contractions.



Scheme 78 Potential synthesis of spiroketal-type divergolides.

While this thesis only discussed endeavors towards the synthesis of naphthoquinone divergolides and hygrocins, the alkynyl ether **273** could act as an entry towards the hydroquinone *proto*-ansamycin **26** as well. Oxazolidinone **312**'s synthesis was carried out by Dr. Julien Lefranc in course of his postdoctoral studies in the Trauner group and might be a good entry towards a methyl ketone that could undergo *e.g.* a cross-Claisen reaction with **273**'s thioester to merge the fragments. Macrocyclization could then be achieved *via N*-ketene trapping. It would be interesting to study if oxidation to the hydroquinone of a macrocyclic compound would trigger cyclizations leading to some spiroacetals (**28**) or the chromene structure of divergolide B (**37**).

4 Experimental section

4.1 Methods and equipment

Unless noted otherwise, all reactions were performed in oven-dried (200 °C) or heat-gun dried (650 °C) glassware and stirred magnetically under inert gas atmosphere (N_2) using standard Schlenk techniques. The reaction temperature was controlled by using the external bath temperature. Reactions were heated using silicon oil baths and cooled using the following mixtures: acetone/liq. N_2 (−98 °C), acetone/dry ice (−78 °C), distilled water/ice (0 °C). Otherwise, low temperatures were achieved using a cryostat.

Solvents were purchased from Acros Organics as 'extra dry' reagent over molecular sieves and handled under inert gas atmosphere. If an experimental procedure indicates use of degassed solvents, this was done by either three consecutive freeze-pump-thaw cycles or sparging with argon for 30 min. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium and benzophenone, dichloromethane (DCM), triethylamine (TEA), diisopropylamine (DIPEA), morpholine and allyl chloroformate (AllocCl) from calcium hydride. Solvents for column chromatography were purchased in technical grade and distilled on a rotary evaporator. Unless otherwise mentioned, all other **reagents** were purchased from commercial sources and used without further purification except DDQ, which was sublimed before use. Generally, **stock solutions of reagents** in the respective reaction solvent were prepared to achieve greater precision when appropriately small amounts needed to be added.

Flash column chromatography was carried out using Merck silica gel 60 (40-63 μm particle size) or Grace Discovery Sciences synthetic Silica Davisil LC60Å (40.63 μm particle size). Analytical thin-layer chromatography (TLC) was realized using pre-coated glass plates (Merck TLC Silica gel 60 F_{254}) and visualized by ultraviolet light (254 and 366 nm) together with aqueous acidic ceric ammonium molybdate(IV) stain or potassium permanganate stain.

Nuclear magnetic resonance spectroscopy was realized on a 400 MHz Bruker Biospin AVIII HD (cryoprobe), a Varian AMX 600 MHz or a Bruker Avance III HD (cryoprobe) 800 MHz spectrometer at room temperature. Deuterated chloroform ($CDCl_3$), benzene (C_6D_6) and methanol (D_3COD) was used as solvent and the residual protic solvent served as an internal reference ($CHCl_3$: $\delta = 7.26$ ppm, C_6H_6:$\delta = 7.16$ ppm, H_3COH: $\delta = 3.31$ ppm).Chemical shifts (δ scale) of ^1H NMR are expressed in parts per million (ppm) and reported as follows: chemical shift (δ/ppm) (multiplicity, coupling constant(s)[Hz], integration). Couplings are expressed as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentett, h = heptett, m = multiplet or

combinations thereof. Carbon nuclear magnetic resonance spectroscopy was realized on the same spectrometers at 100, 150 and 200 MHz respectively. The central carbon resonance of $CDCl_3$ (δ = 77.16 ppm) or C_6D_6(δ = 128.06 ppm) and D_3COD (δ = 49.00 ppm) served as internal reference.Chemical shifts (δ scale) of ^{13}C NMR are also expressed in parts per million (ppm) and reported analogously. In order to assign the ^{1}H and ^{13}C NMR spectra various 2D NMR experiments (COSY, HSQC, HMBC, NOESY) were recorded and evaluated.

High resolution mass spectrometry (HRMS) data was measured on a Varian MAT CH7A mass spectrometer to obtain high resolution electron impact (EI) mass. Electrospray ionization mass spectrometry (ESI) data was obtained using a Varian MAT 711 MS instrument.

A Perkin Elmer Spectrum BX II (FTIR System) with an attenuated total reflection (ATR) measuring unit was used to record **infrared spectra** (IR). The data is reported as in frequency of absorption (cm^{-1}) and the IR bands are characterised as: w = weak, m = medium, s = strong, br = broad, or combinations thereof.

Melting points (mp in °C). Melting points were measured on a Büchi Melting Point B-540 or SRS MPA120 EZ-Melt apparatus and are uncorrected.

Optical rotations were determined on an Anton Paar MCP200 polarimeter using a sodium lamp (λ = 589 nm, D-line) at 20 °C or a Krüss P8000-T polarimeter at the reported temperature X [°C]. Path length (l) of the measurement cell was 0.5 dm. Concentrations (c) are expressed in g/100 mL. The specific rotations were calculated by:

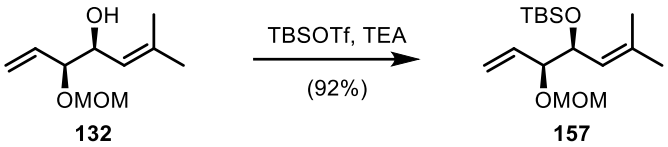
$$[\alpha]_D^X = \frac{100\alpha}{cl}$$

with [10^{-1}deg cm^2 g^{-1}] as unit and α representing the measured optical rotation.

Flash column chromatography of samples of less than 10 mg was performed using columns made from standard Pasteur pipettes:

4.2 Experimental procedures

Synthesis of silyl ether **157**



Silyl ether 157. To a solution of allylic alcohol **132**[I] (764 mg, 4.10 mmol, 1 eq) in dichloromethane (30 mL) was added triethylamine (910 µL, 6.56 mmol, 1.6 eq) at room temperature, then TBS triflate (1.41 mL, 6.15 mmol, 1.5 eq) was added dropwise. After 10 min of stirring at room temperature, the reaction was quenched by adding aqueous saturated ammonium chloride solution and the resulting mixture was extracted three times with ethyl acetate, the combined organic phases washed with brine and dried over Na_2SO_4. Concentration of the organic extract on a rotary evaporator afforded the crude product, which was purified by flash column chromatography (8:1 hexanes:EtOAc) to yield silyl ether **157** (1.12 g, 3.77 mmol, 92%) as a colorless liquid.

Physical state: colorless liquid

$\mathbf{R_f}$ = 0.72 (9:1 hexanes:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +16.5 (*c* = 1.42 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ =δ = 5.75 (ddd, *J* = 17.3, 10.5, 6.7 Hz, 1H), 5.25 (ddd, *J* = 17.4, 2.0, 1.2 Hz, 1H, 5.19 (ddd, *J* = 10.5, 2.0, 1.1 Hz, 1H), 5.13 (ddt, *J* = 9.2, 2.8, 1.4 Hz, 1H), 4.67 (d, *J* = 0.6 Hz, 2H), 4.35 (dd, *J* = 9.2, 6.1 Hz, 1H), 4.00 – 3.91 (m, 1H), 3.37 (s, 3H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.64 (d, *J* = 1.4 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 135.39, 133.82, 125.51, 117.52, 95.02, 81.08, 72.40, 55.56, 26.02, 25.99, 18.77, 18.39, −4.23,−4.57ppm.

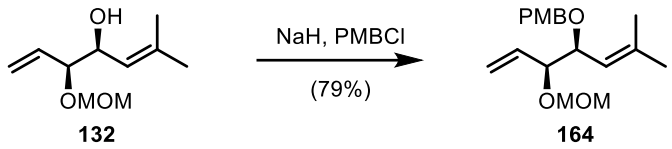
IR (ATR): $\tilde{\nu}$ = 2928 (w), 2856 (w), 1676 (w), 1472 (w), 1361 (w), 1249 (m), 1101 (m), 1038 (s), 921 (m), 832 (s), 775 (m), 668 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{16}H_{32}SiO_3Na^+$: 323.2013 $[M+Na]^+$

found: 323.2016 $[M+Na]^+$

[I] prepared according to *Synlett* **2013**, *24*, 1945–1920

Synthesis of PMB-ether **164**



PMB-ether 164. Sodium hydride (60% suspension in mineral oil, 113 mg, 2.83 mmol, 1.3 eq) was dissolved in DMF (6.6 mL) and the stirred solution cooled to 0 °C. Then, a solution of allylic alcohol **132** (405 mg, 2.18 mmol, 1 eq) in DMF (2.7 mL) was added dropwise and after further stirring at 0 °C for 10 min, *para*-methoxy benzyl chloride (380 µL, 2.82 mmol, 1.3 eq) was added. Cooling was removed after 5 min and the yellow slurry was stirred for 1.5 h at room temperature. The reaction was quenched by adding water and after stirring for 30 min at room temperature the reaction mixture was extracted three times with diethyl ether. The organic extracts were then washed three times with aqueous 10% LiCl solution, the combined aqueous phases were back extracted once with diethyl ether and the combined ether phases dried over Na_2SO_4 and concentrated on a rotary evaporator. The thus obtained crude product was subjected to flash column chromatography (10:1 *n*-Pentane:EtOAc) to yield double protected bisallylic alcohol **164** (527 mg, 1.72 mmol, 79%) as a pale yellow oil.

Physical state: pale yellow oil

$\mathbf{R_f}$ = 0.55 (5:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +70.0 (*c* = 0.33 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 – 7.22 (m, 2H), 6.87 – 6.83 (m, 2H), 5.79 (ddd, *J* = 17.3, 10.5, 6.8 Hz, 1H), 5.29 – 5.17 (m, 3H), 4.70 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 4.13 – 4.06 (m, 2H, H-3), 3.80 (s, 3H), 3.36 (s, 3H), 1.78 (d, *J* = 1.3 Hz, 3H), 1.62 (d, *J* = 1.3 Hz, 3H) ppm.

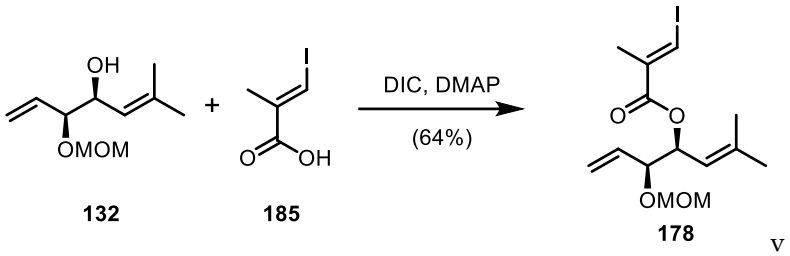
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.07, 137.71), 135.23, 131.13, 129.28, 122.61, 117.89, 113.72, 94.58, 79.52, 77.16, 69.69, 55.59, 55.39, 26.17, 18.74 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3012 (w), 2934 (w), 1613 (w), 1514 (m), 1442 (w), 1302 (w), 1248 (m), 1216 (m), 1036 (m), 922 (w), 823 (w), 751 (s), 668 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{18}H_{26}O_4Na^+$: 329.1723 $[M+Na]^+$

found: 329.1724 $[M+Na]^+$

Ester coupling of alcohol **132**and carboxylic acid**185**



132 **185** **178** v

Ester 178. Allylic alcohol **132** (143 mg, 768 μmol, 1 eq) was dissolved in DCM (6.5 mL) under argon and the solution cooled to 0 °C. Then, carboxylic acid**185**[I] (195 mg, 921 μmol, 1.2 eq),*N*,*N*'-diisopropylcarbodiimide (178 μL, 1.15 mmol, 1.5 eq) and DMAP (19 mg, 154 μmol, 0.2 eq) were added and the cooling removed. After 21 h of stirring at room temperature, the reaction was filtered over celite and concentrated on a rotary evaporator. The thus obtained crude product was subjected to flash column chromatography (75:1 → 50:1*n*-pentane:acetone) to yield ester **178** (186 mg, 489 μmol, 64%) as a pale yellow oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.36 (9:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = −4.3 (*c* = 1.24 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 1.4 Hz, 1H), 5.70 – 5.58 (m, 2H), 5.33 – 5.24 (m, 2H), 5.14 (dq, *J* = 9.6, 1.5 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.15 (t, *J* = 6.9 Hz, 1H), 3.33 (s, 3H), 2.04 (d, *J* = 1.2 Hz, 3H), 1.75 (d, *J* = 1.3 Hz, 3H), 1.72 (d, *J* = 1.4 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.01, 140.08, 140.00, 133.80, 119.57, 119.49, 98.73, 94.15, 78.26, 73.59, 55.68, 26.07, 20.51, 18.90 ppm.

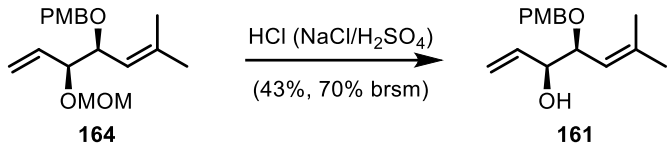
IR (ATR, film): $\tilde{\nu}$ = 2931 (w), 1712 (s), 1601 (w), 1442 (w), 1379 (w), 1288 (s), 1212 (s), 1151 (m), 1098 (s), 1027 (s), 996 (m), 937 (m), 922 (m), 837 (w), 726 (w), 683 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{14}H_{21}INaO_4^+$: 403.0377 $[M+Na]^+$

found: 403.0375 $[M+Na]^+$

[I] prepared in three steps according to *J. Chem. Soc., Perkin Trans. 1*, **1990**, 47–65

Synthesis of allylic alcohol **161**



164 **161**

(3*S*,4*S*)-4-((4-methoxybenzyl)oxy)-6-methylhepta-1,5-dien-3-ol(161). MOM ether **164** (230 mg, 0.75 mmol) was dissolved in 1,4-dioxane (6.5 mL) and cooled to approximately 15 °C using an ice bath. 1,4-Dioxanes saturated with HCl (4.3 mL) was added dropwise, cooling removed and the solution let stir at room temperature for 20 min. Then, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution after TLC indicated concomitant PMB ether cleavage. The mixture was extracted three times with diethyl ether, the combined organic extracts washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography of the crude product (25:1 →15:1 *n*-pentane:EtOAc) afforded unreacted starting material **164** (90 mg, 0.30 mmol, 39%) as well as allylic alcohol **161** (85 mg, 0.32 mmol, 43%, 70% brsm) as a pale yellow oil.

Physical state: colorless oil

R_f = 0.55 (3:1 hexane:EtOAc)

$[\alpha]_D^{24}$ = +26.2 (*c* = 0.48 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 – 7.21 (m, 2H), 6.92 – 6.85 (m, 2H), 5.78 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.35 (dt, *J* = 17.2, 1.7 Hz, 1H), 5.15 (dt, *J* = 10.6, 1.7 Hz, 1H), 5.09 (dh, *J* = 9.5, 1.4 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 4.04 (ddt, *J* = 8.2, 5.4, 1.5 Hz, 1H), 3.91 (dd, *J* = 9.5, 7.9 Hz, 1H), 3.80 (s, 3H), 2.92 (s, 1H), 1.80 (d, *J* = 1.4 Hz, 3H), 1.65 (d, *J* = 1.4 Hz, 3H) ppm.

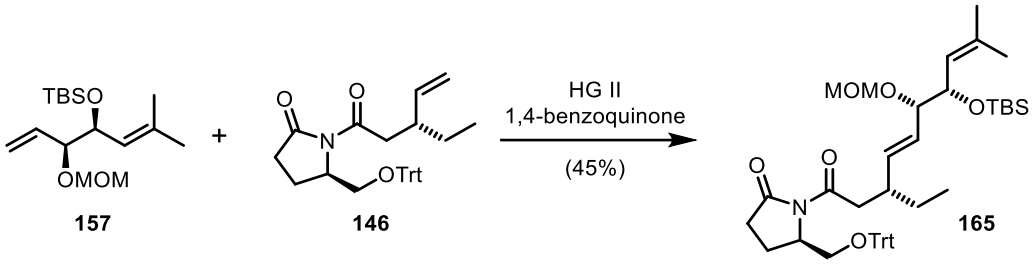
^{13}C-NMR(100 MHz, $CDCl_3$): δ = 159.37, 139.55, 136.30, 130.55, 129.62, 121.89, 116.45, 113.98, 78.84, 74.88, 69.65, 55.44, 26.20, 18.99 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3488 (w), 2913 (w), 1612 (w), 1514 (s), 1443 (m), 1377 (w), 1301 (w), 1248 (s), 1075 (w), 1036 (s), 821 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{16}H_{22}NaO_3^+$: 285.1461 $[M+Na]^+$

found: 285.1464 $[M+Na]^+$

Olefin cross metathesis of alkenes **157**and **146**



Imide 165. In a solution of protected bisallylic alcohol **157** (42 mg, 0.14 mmol, 2 eq) in toluene (0.1 mL),alkene**146** (33 mg, 70 μmol, 1 eq) was dissolved. Hoveyda-Grubbs 2nd generation catalyst (4.4 mg, 7 μmol, 0.1 eq) and 1,4-benzoquinone (0.8 mg, 7 μmol, 0.1 eq) was added, the reaction mixture diluted with toluene (0.2 mL), flushed with argon and a reflux condenser was installed. The mixture was stirred at 40 °C for 43 h, then concentrated on a rotary evaporator. The crude product was subjected to flash column chromatography (15:1 →10:1 hexanes:EtOAc) to yield imide**165** (23 mg, 32 μmol, 45%) as a colorless oil along with unreacted starting material (alkene**146**: 16 mg, 35 μmol, 50%; bisallylic alcohol **157**: 29 mg, 97 μmol, 66%).

Physical state: colorless oil

$\mathbf{R_f}$ = 0.74 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_D^{22}$ = +5.5 (*c* = 0.33 in $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.35 (dd, *J* = 8.3, 1.2 Hz,6H), 7.31 – 7.26 (m, 6H, 7.25 – 7.21 (m, 3H), 5.55 (ddd, *J* = 15.5, 8.4, 0.7 Hz, 1H), 5.37 (ddd, *J* = 15.6, 7.2, 0.7 Hz, 1H), 5.11 (d, *J* = 9.2 Hz, 1H), 4.67 (d, *J* = 6.6 Hz, 1H), 4.62 (d, *J* = 6.6 Hz, 1H), 4.46 – 4.42 (m, 1H), 4.33 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.91(t,*J* = 6.8 Hz, 1H, 3.50 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.35 (s, 2H), 3.19 (dd, *J* = 9.7, 2.6 Hz, 1H), 3.08 (dd, *J* = 16.4, 8.5 Hz, 1H), 2.90 (ddd, *J* = 17.8, 11.2, 9.8 Hz, 1H), 2.75 (dd, *J* = 16.4, 5.3 Hz, 1H), 2.51 (ddd, *J* = 12.8, 8.5, 4.1 Hz, 1H), 2.45 (ddd, *J* = 17.8, 9.8, 1.5 Hz, 1H), 2.06 (dtd, *J* = 12.5, 11.2, 9.9 Hz, 1H), 1.93 (dd, *J* = 12.0, 10.5 Hz, 1H), 1.68 (d,*J* = 1.1 Hz, 3H), 1.62 (d, *J* = 1.1 Hz, 3H), 1.49 (ddd, *J* = 13.3, 7.5, 4.3, Hz, 1H), 1.27–1.24 (m, 1H), 0.87 (s, 9H), 0.83 (t, *J* = 7.4 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 3H) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 176.21, 172.65, 143.80, 137.08, 133.58, 128.68, 128.07, 128.03, 127.28, 125.80, 94.63, 87.15, 80.62, 72.57, 63.96, 56.82, 55.49, 42.33, 39.79, 33.28, 27.33, 26.03, 21.44, 11.74, −4.23, −4.51 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3466 (br w), 2928 (m), 1737 (s), 1693 (m), 1448 (m), 1372 (m), 1249 (m), 1195 (m), 1084 (s), 1035 (s), 917 (m), 832 (s), 773 (m), 704 (s) cm^{-1}.

HRMS (+ESI): calc. for $C_{45}H_{61}NKSiO_6^+$: 778.3900 $[M+K]^+$

found: 778.3897$[M+K]^+$

Koga auxiliary cleavage and reduction of imide **165**

Alcohol 167. Methanol (13 μL, 324 μmol, 9 eq) was added to THF (100 μL) and the solution was cooledto 0 °C. Then, a solution of *n*-BuLi (2.5 M in hexanes, 86 μL, 216 μmol, 6 eq), was added dropwise and the solution let come to room temperature over the course of 15 min. Imide **164** (26.8 mg, 36 μmol, 1 eq) in THF (300 μL) was added *via* syringe and the mixture was stirred at room temperature for 19 h. Then, lithium aluminum hydride (27 mg, 72 μmol, 2 eq) was added in small portions and the mixture was stirred at room temperature for 4 h. After cooling with an ice bath, the reaction was carefully quenched by dropwise addition of saturated aqueous Rochelle's salt solution, then diluted with water and the mixturewas stirred at room temperature for 2 h. The mixture was then extracted three times with ethyl acetate, the combined organic extracts washed with brine and dried over $MgSO_4$. Concentration under reduced pressure afforded the crude product which was subjected to flash column chromatography (9:1 → 4:1 hexanes:EtOAc) to yield alcohol **167** (3.3 mg, 9 μmol, 25%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.44 (2:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +45 (*c* = 0.20 in $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.41 (dd, *J* = 15.5, 9.1 Hz, 1H), 5.30 (dd, *J* = 15.5, 8.0 Hz, 1H), 5.09 (ddt, *J* = 9.3, 2.7, 1.3 Hz, 1H), 4.70 (d, *J* = 6.5 Hz, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.36 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.92 (dd, *J* = 7.8, 6.5 Hz, 1H), 3.65 – 3.54 (m, 2H), 3.36 (s, 3H), 2.03 (ddt, *J* = 18.6, 9.2, 4.6 Hz, 1H), 1.71 (d, *J* = 1.3 Hz, 3H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.49 – 1.38 (m, 2H), 1.33 – 1.24 (m, 2H), 0.87 (d, *J* = 5.0 Hz, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.05 (s, 3H), 0.02 (s, 3H)ppm.

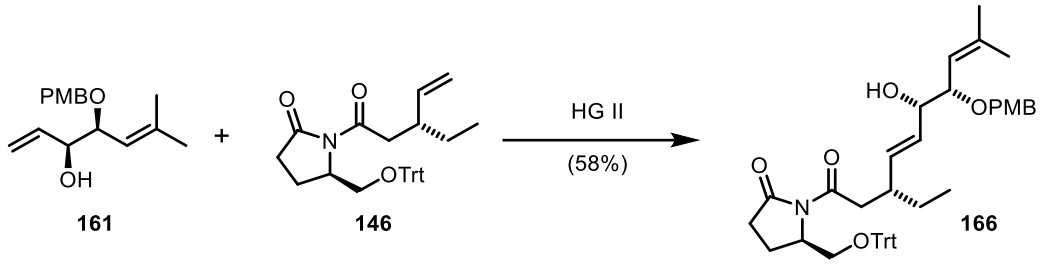
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 139.27, 133.96, 127.49, 125.66, 94.35, 80.94, 72.38, 61.49, 55.45, 42.28, 38.03, 28.45, 26.05, 26.03, 18.84, 18.42, 11.94, −4.28, −4.56 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3420 (br w), 2956 (m), 2927 (m), 2855 (m), 1678 (w), 1463 (w), 1376 (w), 1250 (m), 1149 (m), 1101 (m), 1039 (s), 973 (w), 876 (w), 833, 776 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{21}H_{42}SiNaO_4^+$: 409.2745 $[M+Na]^+$

found: 409.2748 $[M+Na]^+$

Olefin cross metathesis of alkenes **161**and **146**



Imide 165. In a solution of allylic alcohol **161** (89 mg, 0.34 mmol, 2 eq) in toluene (0.5 mL), imide **146** (79 mg, 0.17 mmol, 1 eq) was dissolved at room temperature. Then, Hoveyda-Grubbs 2nd generation catalyst (10.6 mg, 17 μmol, 0.1 eq) was added and the reaction mixture diluted with toluene (0.5 mL). A reflux condenser was installed and the reaction mixture was heated to 40 °C for 27 h. Then, the reaction mixture was concentrated under reduced pressure and the thus obtained crude product purified by flash column chromatography (3:2 →1:1 *n*-pentane:diethyl ether) to yield olefin **166** (69.6 mg, 98 μmol, 58%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.18 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = +60.7 (*c* = 0.49 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.34 (m, 6H), 7.29 – 7.20 (m, 11H), 6.89 – 6.86 (m, 2H), 5.64 (ddd, *J* = 15.6, 8.5, 1.3 Hz, 1H), 5.43 (ddd, *J* = 15.5, 5.6, 0.9 Hz, 1H), 5.06 (dt, *J* = 9.6, 1.4 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.46 – 4.42 (m, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 4.01 – 3.97 (m, 1H), 3.89 (dd, *J* = 9.5, 8.0 Hz, 1H), 3.79 (s, 3H), 3.51 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.18 (dd, *J* = 9.7, 2.7 Hz, 1H), 3.03 (dd, *J* = 16.6, 8.0 Hz, 1H), 2.90 – 2.80 (m, 2H), 2.54 –2.46(m, 1H), 2.44 (ddd, *J* = 17.8, 8.9, 2.3 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.95 – 1.89 (m, 1H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.63 (d, *J* = 1.4 Hz, 3H), 1.53 – 1.46 (m, 1H), 1.33 – 1.24 (m, 1H), 0.83 (t, *J* = 7.4 Hz, 3H) ppm.

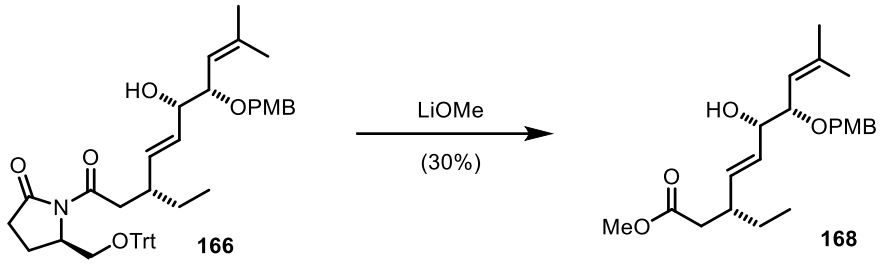
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.26, 172.73, 159.34, 143.80, 139.21, 135.49, 130.64, 129.61, 128.67, 128.52, 128.03, 127.28, 122.17, 113.97, 87.13, 79.30, 74.53, 69.65, 63.93, 56.79, 55.42, 42.33, 39.73, 33.27, 27.28, 26.16, 21.43, 18.99, 11.70 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3542 (br w), 2961 (m), 2933 (m), 1737 (s), 1693 (s), 1616 (w), 1513 (m), 1449 (m), 1374 (m), 1280 (s), 1082 (m), 1034 (s), 821 (w), 706 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{45}H_{51}NNaO_6^+$: 724.3609 $[M+Na]^+$

found: 724.3612 $[M+Na]^+$

Koga auxiliary cleavage of imide **166**



Ester 168. Allylic alcohol **166** (16.3 mg, 23 μmol, 1 eq) was dissolved in methanol (200 μL) and the solution stirred at room temperature. Then, a solution of lithium methoxide (1 M in methanol, 69 μL, 69 μmol, 3 eq), was added dropwise and the solution stirred for 10 min at room temperature. The reaction was then quenched by addition of saturated aqueous ammonium chloride solutionand was then extracted three times with diethyl ether, the combined organic extracts washed with brine and dried over Na_2SO_4. Concentration under reduced pressure afforded the crude product which was subjected to flash column chromatography (5:1 →3:1 →1:1 *n*-pentane:EtOAc) to yield ester **168** (2.5 mg, 7 μmol, 30%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.44 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +30.0 (*c* = 0.10 in $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.3 Hz, 2H), 6.87 (d,*J* = 8.3 Hz, 2H), 5.57 (dd, *J* = 15.5, 8.1 Hz, 1H), 5.39 (dd, *J* = 15.5, 5.7 Hz, 1H), 5.05 (d, *J* = 9.4 Hz, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.26 (d, *J* = 11.1 Hz, 1H), 3.98 (t, *J* = 6.6 Hz, 1H), 3.87 (t, *J* = 8.8 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 2.86 (brs, 1H), 2.49 –2.40 (m, 1H), 2.38 – 2.23 (m, 2H), 1.78 (s, 3H), 1.64 (s, 3H), 1.50 – 1.38 (m, 1H), 1.36 – 1.23 (m, 1H), 0.84 (t, *J* = 7.4 Hz, 3H) ppm.

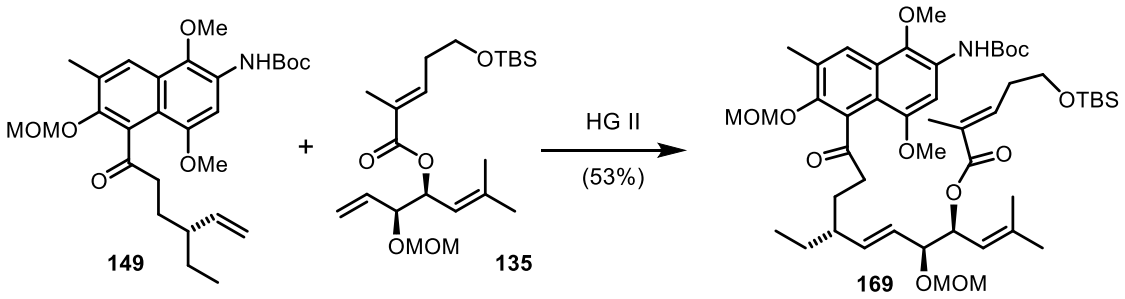
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 173.15, 159.37, 139.28, 134.96, 130.57, 129.62, 128.79, 122.09, 113.99, 79.18, 74.52, 69.66, 55.44, 51.55, 40.56, 39.68, 27.44, 26.18, 18.98, 11.53 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3520 (br w), 2959 (m), 2932 (m), 2364 (w), 1738 (s), 1679 (w), 1613 (m), 1587 (m), 1514 (s), 1439 (m), 1376 (m), 1308 (m), 1249 (s), 1173 (m), 1113 (m), 1035 (w), 977 (m), 822 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{22}H_{32}NaO_5^+$: 399.2142 $[M+Na]^+$

found: 399.2148 $[M+Na]^+$

Olefin cross metathesis of alkenes **149**and **135**



Olefin 169. Olefins **149** (17.2 mg, 34.3 µmol, 1 eq), **135** (28.3 mg, 68.6 µmol, 2 eq) and Hoveyda-Grubbs 2nd genearation catalyst (6.4 mg, 10.3 µmol, 0.3 eq) were dissolved in hexafluorobenzene (0.3 mL) and the mixture was stirred at 40 °C for 40 h. Then, the mixture was allowed to come to room temperature and was poured onto a column. Gradient elution (20:1 → 10:1 → 5:1 *n*-pentane:EtOAc) afforded starting materials **149** (7.0 mg, 41% recovered) and **135** (15.2 mg, 54% recovered) as well as the cross metathesis product **169** (13.0 mg, 14.7 µmol, 43%) as a pale yellow oil

Physical state: pale yellow oil

$\mathbf{R_f}$ = 0.49 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_D^{\mathbf{23}}$ = +14.9 (*c* = 0.48 in $CHCl_3$)

*Note: At room temperature compounds **196** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.77 (s, 1H), 7.72 – 7.69 (m, 1H), 7.12 (s, 1H), 6.85 – 6.66 (m, 1H), 5.62 – 5.53 (m, 1H), 5.43 (ddd, *J* = 15.5, 11.1, 8.7 Hz, 1H), 5.19 (ddd, *J* = 15.4, 8.0, 4.7 Hz, 1H), 5.07 – 5.00 (m, 0.5H), 4.98 – 4.88 (m, 2.5H), 4.73 – 4.64 (m, 1H), 4.56 – 4.47 (m, 1H), 4.14 – 4.06 (m, 1H), 3.87 – 3.84 (m, 3H), 3.84 – 3.82 (m, 3H), 3.71 – 3.60 (m, 2H), 3.57 – 3.54 (m, 3H), 3.32 – 3.27 (m, 3H), 2.83 – 2.49 (m, 2H), 2.49 – 2.46 (m, 3H), 2.43 – 2.31 (m, 2H), 1.99 – 1.86 (m, 1.5H), 1.83 – 1.80 (m, 1.5H), 1.81 – 1.79 (m, 1.5H), 1.78 – 1.73 (m, 1H), 1.65 (d, *J* = 1.1 Hz, 1.5H), 1.62 (d, *J* = 1.1 Hz, 1.5H), 1.57 (s, 9H), 1.53 – 1.50 (m, 1H), 1.47 (d, *J* = 1.4 Hz, 1.5H), 1.30 (d, *J* = 1.4 Hz, 1.5H), 1.27 – 1.24 (m, 1H), 0.90 – 0.86 (m, 9H), 0.87 – 0.82 (m, 3H), 0.04 (s, 3H), 0.03 (s, 3H)ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 206.65, 167.22, 152.90, 151.25, 149.20, 149.13, 140.38, 140.22, 139.12, 138.48, 135.67, 135.63, 132.97, 132.90, 131.54, 131.43, 129.60, 128.25, 128.09, 126.34, 126.22, 125.73, 123.05, 120.42, 120.37, 118.17, 101.72, 99.09, 93.57, 93.51, 80.98, 78.07, 78.04, 72.87, 72.81,

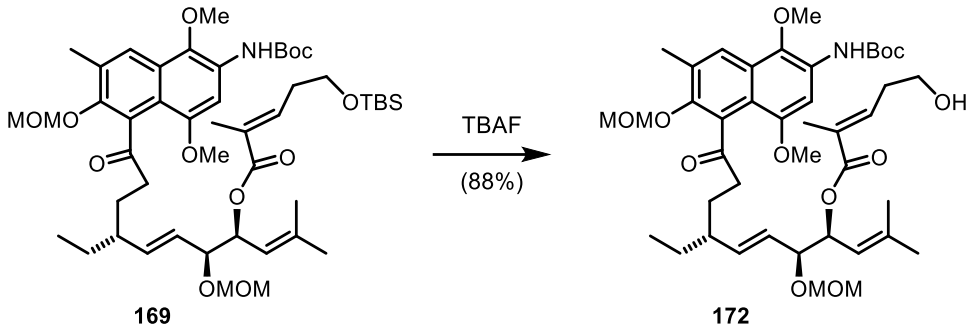
61.89, 61.56, 57.76, 57.71, 56.50, 55.44, 55.41, 44.36, 44.32, 43.28, 42.97, 32.64, 29.86, 28.55, 28.14, 28.03, 26.05, 25.66, 25.51, 18.79, 18.46, 17.79, 12.76, 11.88, 11.83, −5.17 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3435 (w), 2955 (m), 2933 (m), 2362 (w), 1782 (m), 1710 (s), 1627 (m), 1606 (w), 1493 (m), 1458 (m), 1405 (m), 1368 (m), 1249 (m), 1231 (s), 1158 (s), 1100 (m), 1048 (m), 1034 (m), 988 (m), 935 (m), 878 (w), 837 (m), 778 (w), 744 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{48}H_{75}NNaO_{12}^{+}$: 908.4951 $[M+Na]^+$

found: 908.4961 $[M+Na]^+$

Deprotection of silyl ether **169**



Alcohol 172. Silyl ether **169** (5.9 mg, 6.66 μmol, 1 eq.) was dissolved in THF (9.3 mL) and cooled with an ice bath. A solution of *N*-tetrabutylammonium fluoride (1 M in THF, 15 μL, 15 μmol, 2.2 eq.) was added dropwise, upon which the yellow solution turned purple. The ice bath was removed and the solution stirred for 60 min at room temperature, then pH 7 phosphate buffer was added and the purple color dissipated. The reaction mixture was then extracted three times with ethyl acetate, the combined organic phases washed with brine and dried over Na_2SO_4. Concentration under reduced pressure afforded the crude product, which was subjected to flash column chromatography (2:1 *n*-pentane:EtOAc) to obtain alcohol **172** (4.5 mg, 5.8 μmol, 88%) as a pale yellow oil.

Physical state: pale yellow oil

$\mathbf{R_f}$ = 0.40 (1:1 hexane:EtOAc)

$[\alpha]_D^{20}$ = +15.5 (*c* = 0.23 in $CHCl_3$)

Note: At room temperature compounds ***172*** *exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.77 (s, 1H), 7.75 – 7.69 (m, 1H), 7.13 (s, 1H), 6.83 – 6.70 (m, 1H), 5.67 – 5.54 (m, 1H), 5.50 – 5.38 (m, 1H), 5.27 – 5.17 (m, 1H), 5.10 – 5.05 (m, 0.5H), 5.00 – 4.97 (m, 0.5H), 4.97 – 4.87 (m, 2 H), 4.76 – 4.60 (m, 1H), 4.59 – 4.47 (m, 1H), 4.14 – 4.09 (m, 1H), 3.90 – 3.83 (m, 3H), 3.85 – 3.79 (m, 3H), 3.77 – 3.68 (m, 2H), 3.57 (s, 1.5H), 3.56 – 3.48 (m, 1.5H), 3.32 (s, 1.5H), 3.31 (s, 1.5H), 2.86 – 2.50 (m, 2H), 2.53 – 2.45 (m, 3H), 2.45 – 2.34 (m, 2H), 2.05 – 1.86 (m, 2H), 1.85 – 1.82 (m, 1.5H), 1.82 – 1.78 (m, 1.5H), 1.78 – 1.72 (m, 1H), 1.67 (d, *J* = 1.3 Hz, 1.5H), 1.65 (d, *J* = 1.3 Hz, 1.5H), 1.56 (s, 9H), 1.51 (d, *J* = 1.4 Hz, 1.5H), 1.49 – 1.42 (m, 1H), 1.34 (d, *J* = 1.4 Hz, 1.5H), 1.30 – 1.26 (m, 1H), 0.89 – 0.82 (m, 3H) ppm.

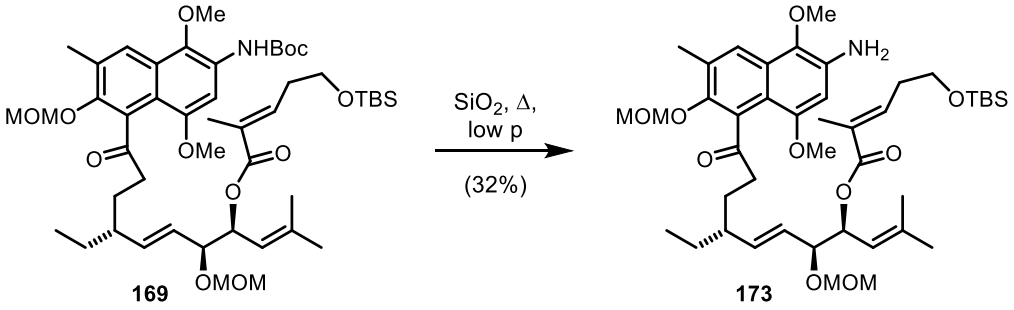
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 206.84 (from HMBC), 167.08, 152.95, 151.23, 149.21, 140.64, 139.33, 138.03, 135.70, 131.51, 131.40, 130.38, 129.29, 128.25, 126.28, 126.19, 125.74, 123.08, 120.37, 120.22, 120.18, 118.19, 101.72, 101.61, 99.10, 93.54, 93.45, 81.05, 78.00, 72.99, 72.91, 61.57, 57.79, 57.72, 56.52, 55.47, 44.48, 44.33, 43.07, 32.32, 28.55, 28.55, 28.25, 28.07, 27.95, 25.76, 25.60, 18.81, 17.80, 12.82, 11.90, 11.84 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3427 (w), 2930 (m), 2361 (w), 2338 (w), 2153 (w), 1708 (s), 1626 (m), 1606 (w), 1497 (s), 1458 (m), 1368 (m), 1231 (s), 1159 (s), 1098 (m), 1049 (s), 1034 (s), 989 (m), 931 (m), 800 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{42}H_{61}NNaO_{12}^+$: 794.4086 $[M+Na]^+$

found: 794.4105$[M+Na]^+$

Deprotection of carbamate **169**



Naphthyl amine 173. Carbamate **169** (28 mg, 31.6 μmol) was dissolved in DCM (3 mL). Silica (200 °C oven dried overnight, 570 mg) was added and the mixture carefully concentrated under reduced pressure. Then, the flask was flushed with argon, immersed in an oil bath and heated to 80 °C. Then, vacuum (0.1 mbar) was applied and the reaction left at 75 °C for 18 h. Then, heating was removed , the flask carefully filled with argon and the silica poured onto a column (equilibrated with 4:1 *n*-pentane:EtOAc with 1% TEA). Gradient elution (4:1 → 3:1 *n*-pentane:EtOAc) furnished air sensitive naphthyl amine **173** (7.10 mg, 10.1 μmol, 32%).

Physical state: orange oil

$\mathbf{R_f}$ = 0.22 (2:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +6.5 (*c* = 0.49 in $CHCl_3$)

*Note: At room temperature compounds **173** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.66 – 7.62 (m, 1H), 6.79 – 6.71 (m, 1H), 6.35 – 6.29 (m, 1H), 5.63 – 5.53 (m, 1H), 5.48 – 5.37 (m, 1H), 5.24 – 5.14 (m, 1H), 4.96 – 4.88 (m, 2H), 4.71 – 4.62 (m, 1H), 4.56 – 4.48 (m, 1H), 4.14 – 4.07 (m, 1H), 3.83 – 3.79 (m, 3H), 3.79 – 3.76 (m, 3H), 3.69 – 3.63 (m, 2H), 3.58 – 3.54 (m, 3H), 3.36 – 3.27 (m, 3H), 2.84 – 2.50 (m, 2H), 2.47 – 2.44 (m, 3H), 2.41 – 2.32 (m, 2H), 2.03 – 1.86 (m, 2H), 1.84 – 1.78 (m, 4H), 1.69 (d, *J* = 4.8 Hz, 1H), 1.65 (d, *J* = 1.3 Hz, 1H), 1.59 (d, *J* = 1.3 Hz, 1H), 1.46 (d, *J* = 1.4 Hz, 2H), 1.31 (d, *J* = 1.4 Hz, 1H), 1.28 – 1.24 (m, 1H), 0.89 – 0.87 (m, 9H), 0.86 – 0.79 (m, 3H), 0.06 – 0.02 (m, 6H) ppm.

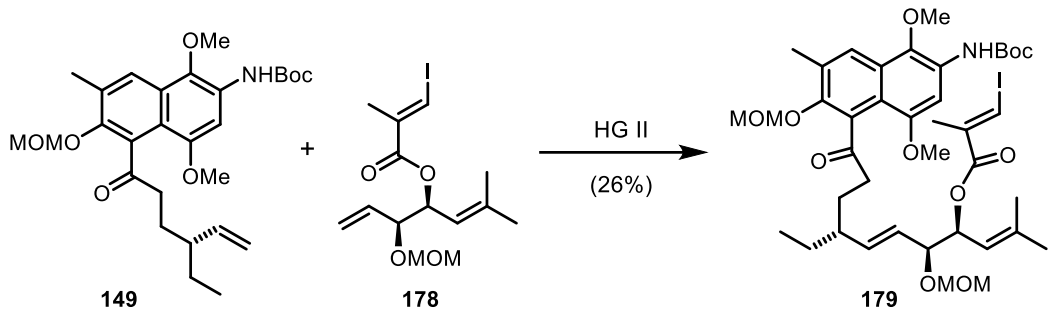
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 207.11, 167.24, 151.60, 147.58, 147.53, 140.47, 140.32, 139.26, 139.19, 138.53, 138.50, 135.32, 133.47, 132.72, 132.66, 131.49, 131.41, 129.57, 127.10, 126.24, 126.15, 122.12, 120.37, 120.28, 116.12, 101.61, 101.57, 98.98, 98.88, 93.50, 93.44, 78.06, 78.02, 72.80, 61.87, 60.14, 57.73, 57.67, 56.39, 55.44, 55.42, 44.31, 44.27, 43.12, 43.02, 32.62, 28.42, 28.34, 28.20, 27.99, 26.04, 25.65, 25.49, 18.81, 18.74, 18.46, 17.75, 17.73, 12.77, 12.75, 11.87, −5.18 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3362 (br w), 2931 (s), 2359 (w), 1706 (s), 1627 (m), 1462 (m), 1386 (m), 1232 (m), 1156 (m), 1098 (s), 1029 (s), 931 (m), 836 (m), 776 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{43}H_{67}NSiNaO_{10}^+$: 808.4426 $[M+Na]^+$

found: 808.4429 $[M+Na]^+$

Olefin cross metathesis of alkenes **149** and **178**



Vinyl iodide 178. To a solution of olefin **149** (30.4 mg, 60.6 μmol, 1 eq) and olefin **178** (46.8 mg, 123 μmol, 2 eq) in degassed toluene (0.6 mL), Hoveyda-Grubbs 2nd genearation catalyst (7.8 mg,12.1 μmol, 0.2 eq) was added and the mixture heated to 40 °C for 3 days. Then, the reaction mixture was loaded on a column (equilibrated with 10:1 *n*-pentane:EtOAc). Gradient elution (10:1 → 5:1 *n*-pentane:EtOAc) furnished unreacted olefin **149** (21.8 mg, 43.6 μmol, 72%) and vinyl iodide **179** (13.7 mg, 15.8 μmol, 26%) as a pale yellow oil.

Physical state: pale yellow oil

$\mathbf{R_f}$ = 0.21 (5:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +5.2 (*c* = 0.76 in $CHCl_3$)

*Note: At room temperature compounds **179** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.81 – 7.73 (m, 2H), 7.70 – 7.68 (m, 1H), 7.11 (s, 1H), 5.56 – 5.51 (m, 1H), 5.46 – 5.38 (m, 1H), 5.18 – 5.13 (m, 1H), 5.04 – 5.01 (m, 0.5H), 4.96 – 4.90 (m, 2.5H), 4.69 – 4.64 (m, 1H), 4.51 – 4.47 (m, 1H), 4.10 – 4.06 (m, 1H), 3.86 – 3.83 (m, 3H), 3.83 – 3.80 (m, 3H), 3.57 – 3.51 (m, 3H), 3.32 – 3.25 (m, 3H), 2.82 – 2.66 (m, 1.5H), 2.58 – 2.53 (m, 0.5H), 2.48 – 2.44 (m, 3H), 2.01 – 1.97 (m, 3H), 1.96 – 1.87 (m, 2H), 1.83 – 1.71 (m, 2H), 1.63 (d, *J* = 1.4 Hz, 1.5H), 1.62 – 1.59 (m, 1.5H), 1.54 (s, 9H), 1.47 (d, *J* = 1.4 Hz, 1.5H), 1.28 (d, *J* = 1.6 Hz, 1.5H), 1.26 (s, 1H), 0.87 – 0.81 (m, 3H) ppm.

^{13}C-NMR (150 MHz, $CDCl_3$): δ = 206.54, 162.99, 152.90, 151.22, 149.19, 149.11, 140.86, 140.66, 140.07, 139.87, 135.63, 132.95, 132.88, 131.50, 131.39, 128.25, 126.03, 125.89, 125.72, 123.06, 119.84, 119.79, 118.16, 101.73, 101.69, 99.11, 98.48, 93.62, 93.53, 93.44, 80.99, 77.99, 77.37, 73.86, 73.79,

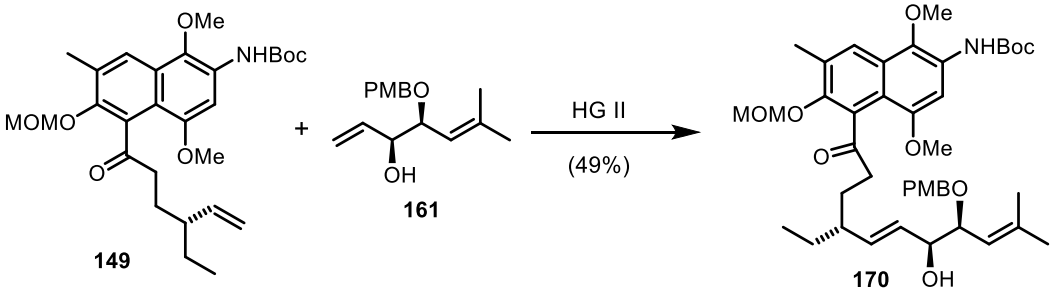
61.56, 57.76, 57.71, 56.52, 55.51, 55.48, 44.36, 44.29, 43.23, 42.92, 28.53, 28.36, 28.23, 28.14, 27.97, 25.65, 25.46, 20.46, 18.77, 17.79, 11.87, 11.80 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2930 (br w), 1713 (s), 1626 (m), 1497 (m), 1457 (m), 1368 (m), 1230 (s), 1215 (s), 1158 (m), 1100 (m), 1048 (m), 934 (m), 870 (w), 727 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{40}H_{56}NINaO_{11}^{+}$: 876.2790 $[M+Na]^{+}$

found: 876.2782 $[M+Na]^{+}$

Olefin cross metathesis of alkene **149** and allylic alcohol **161**



Olefin 170. To a solution of olefin **149** (65.0 mg, 130 μmol, 1 eq) and allylic alcohol**191** (97.0 mg, 370 μmol, 2.8 eq) in degassed toluene (1.5 mL), Hoveyda-Grubbs 2nd genearation catalyst (16.3 mg,26.0 μmol, 0.2 eq) was added and the mixture heated to 40 °C for 2 days. Then, the reaction mixture was loaded on a column (equilibrated with 5:1 *n*-pentane:EtOAc). Gradient elution (5:1 → 3:1 *n*-pentane:EtOAc) furnished olefin **170** (46.0 mg, 63.0 μmol, 49%) as a pale yellow oil.

Physical state: pale yellow oil

$\mathbf{R}_f$ = 0.34 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −5.3 (*c* = 0.15 in $CHCl_3$)

*Note: At room temperature compounds **170** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.77 (s, 1H), 7.72 – 7.67 (m, 1H), 7.22 – 7.19 (m, 2H), 7.16 – 7.09 (m, 1H), 6.87 – 6.83 (m, 2H), 5.49 – 5.42 (m, 1H), 5.31 – 5.27 (m, 1H), 5.02 – 4.98 (m, 0.5H), 4.98 – 4.96 (m, 1H), 4.95 – 4.91 (m, 1.5H), 4.51 – 4.45 (m, 1H), 4.23 – 4.19 (m, 1H), 3.97 – 3.92 (m, 1H), 3.86 – 3.85 (m, 3H), 3.83 (s, 1.5H), 3.82 (s, 1.5H), 3.80 – 3.79 (m, 3H), 3.57 – 3.55 (m, 3H), 2.92 – 2.49 (m, 2H), 2.48 – 2.46 (m, 3H), 1.99 – 1.94 (m, 0.5H), 1.93 – 1.84 (m, 1H), 1.83 – 1.74 (m, 1H),

1.74 – 1.70 (m, 0.5H), 1.63 (d, *J* = 1.4 Hz, 1.5H), 1.56 (s, 9H), 1.53 (d, *J* = 1.4 Hz, 1.5H), 1.49 (d, *J* = 1.3 Hz, 1.5H), 1.48 (d, *J* = 1.4 Hz, 1.5H), 1.46 – 1.41 (m, 1H), 1.32 – 1.26 (m, 1H), 0.87 – 0.83 (m, 3H) ppm.

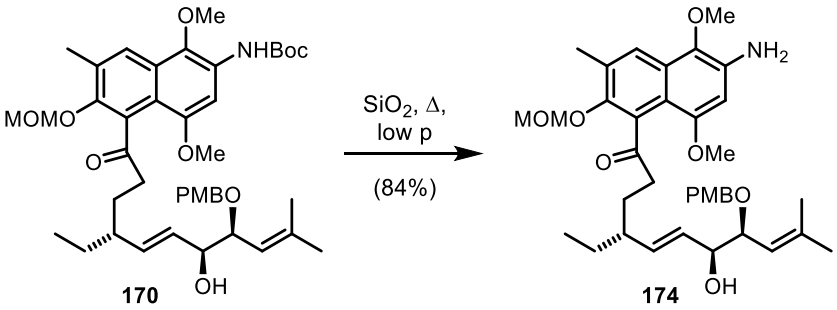
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 206.85, 206.81, 159.31, 152.94, 152.90, 151.31, 151.27, 149.18, 149.08, 139.17, 139.16, 137.43, 137.13, 137.09, 135.63, 135.55, 132.98, 132.90, 132.87, 131.62, 131.52, 130.61, 130.58, 129.65, 129.63, 129.58, 128.81, 128.78, 128.66, 128.56, 128.25, 128.21, 125.72, 125.71, 123.01, 122.99, 122.20, 122.18, 122.11, 122.05, 118.20, 118.18, 114.11, 113.94, 101.71, 101.70, 101.68, 101.56, 98.96, 80.98, 79.17, 79.01, 74.86, 74.84, 69.61, 69.58, 61.57, 61.55, 57.76, 57.73, 56.47, 56.46, 56.44, 55.42, 44.26, 44.13, 43.33, 42.99, 28.54, 28.48, 28.30, 28.25, 28.04, 27.95, 25.90, 25.76, 18.81, 18.78, 17.80, 11.79, 11.76, 11.65 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2931 (br w), 2360 (s), 2340 (m), 1717 (m), 1507 (m), 1457 (m), 1367 (m), 1247 (m), 1231 (s), 1158 (s), 1048 (m), 987 (m), 933 (m), 820 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{42}H_{61}N_2O_{10}^+$: 753.4321 $[M+NH_4]^+$

found: 753.4329$[M+NH_4]^+$

Deprotection of carbamate **170**



Naphthyl amine 174. Carbamate **170** (25.4 mg, 29.9 μmol) was dissolved in DCM (8.5 mL). Silica (200 °C oven dried overnight, 1.50 g) was added and the mixture carefully concentrated under reduced pressure. Then, the flask was flushed with argon, after which vacuum was applied (0.03 mbar). The flask was then immersed in an oil bath and heated to 80 °C for 21 h. Then, heating was removed, the flask carefully filled with argon and the silica poured onto a column (equilibrated with 2:1 *n*-pentane:EtOAc with 1% TEA). Gradient elution (2:1 →1:1 *n*-pentane:EtOAc) furnished air sensitive naphthyl amine **174** (16.0 mg, 25.2 μmol, 84%).

Physical state: colorless oil

R_f = 0.64 (1:1 hexane:EtOAc)

$[\alpha]_D^{25}$ = +14.4 (*c* = 0.50 in $CHCl_3$)

*Note: At room temperature compounds **174** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.62 – 7.49 (m, 1H), 7.19 – 7.09 (m, 2H), 6.85 – 6.76 (m, 2H), 6.27 – 6.17 (m, 1H), 5.47 – 5.32 (m, 1H), 5.24 – 5.14 (m, 1H), 4.98 – 4.78 (m, 3H), 4.49 – 4.33 (m, 1H), 4.23 – 4.12 (m, 1H), 3.93 – 3.84 (m, 1H), 3.82 – 3.75 (m, 1H), 3.75 – 3.71 (m, 6H), 3.71 – 3.66 (m, 3H), 3.50 – 3.46 (m, 3H), 2.82 – 2.41 (m, 1H), 2.40 – 2.36 (m, 3H), 1.93 – 1.85 (m, 0.5H), 1.85 – 1.77 (m, 1H), 1.77 – 1.64 (m, 1H), 1.64 – 1.60 (m, 0.5H), 1.55 (d, *J* = 1.4 Hz, 1.5H), 1.46 (d, *J* = 1.1 Hz, 1.5H), 1.41 – 1.37 (m, 3H), 1.28 – 1.17 (m, 2H), 0.84 – 0.76 (m, 3H). ppm.

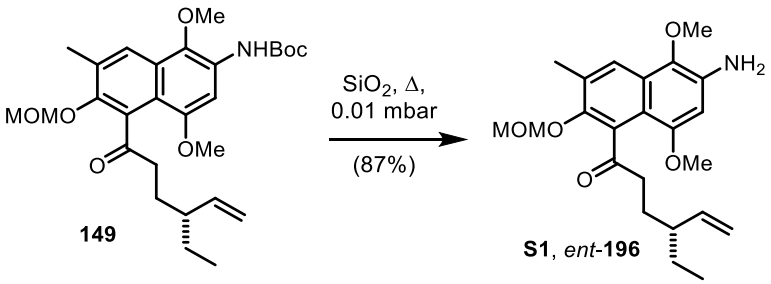
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 207.14, 207.09, 159.17, 159.15, 151.51, 151.49, 147.34, 139.15, 139.11, 137.04, 137.00, 135.15, 135.11, 132.49, 130.43, 130.40, 129.47, 129.46, 128.46, 128.36, 126.95, 121.92, 121.82, 116.03, 113.80, 101.45, 98.69, 98.60, 79.03, 78.97, 74.75, 74.67, 69.44, 60.01, 57.59, 57.56, 56.18, 55.28, 44.07, 44.01, 43.05, 42.93, 28.15, 28.10, 28.02, 27.77, 25.77, 25.60, 18.68, 18.60, 17.62, 11.67, 11.66 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3360 (br w), 2930 (m), 1700 (m), 1628 (s), 1513 (m), 1456 (m), 1386 (m), 1230 (s), 1157 (s), 1062 (s), 1030 (s), 971 (s), 929 (s), 821 (m) 731 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{37}H_{53}N_2O_8^+$: 653.3796 $[M+Na]^+$

found: 653.3812$[M+Na]^+$

Thermal Boc-deprotection of carbamate **149**



Naphthyl amine S1 (*ent*-**196**). Carbamate**149**[I] (60 mg, 120 µmol) was dissolved in DCM (6 mL).Silica(200 °C oven dried overnight, 1.00 g) was added and the mixture carefully concentrated under reduced pressure. Then, the flask was flushed with argon, immersed in an

[I] prepared according to S*ynlett***2013**, *24*, 1945–1920

oil bath and heated to 75 °C. Then, vacuum (0.02 mbar) was applied and the reaction left at 75 °C for 18 h. Then, heating was removed, the flask carefully filled with argon and the silica poured onto a column (equilibrated with 3:1 *n*-pentane:EtOAc). Gradient elution (3:1 → 2:1 → 1:1 *n*-pentane:EtOAc) furnished air sensitive naphthyl amine **S1** (*ent*-**196**)(41.8 mg, 104 µmol, 87%), which was concentrated on a rotary evaporator with a nitrogen inlet.

*Note: The reaction was also performed with ent-**149** (**195**), thus leading to the enantiomeric naphthyl amine.*

Physical state: orange oil

$\mathbf{R_f}$ = 0.10 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +6.9 (*c* = 0.72 in $CHCl_3$)

*Note: At room temperature compounds **S1** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (s, 1H), 6.34 – 6.28(m, 1H), 5.59 – 5.44 (m, 1H), 4.98 – 4.87 (m, 4H), 4.06 – 3.82 (br s, 2H), 3.80 (s, 3H), 3.79 – 3.75 (m, 3H), 3.58 – 3.55 (m, 3H), 2.94 – 2.55 (m, 2H), 2.46 (s, 3H), 2.00 – 1.95 (m, 0.5H), 1.93 – 1.84 (m, 1H), 1.84 – 1.74 (m, 1H), 1.61 – 1.56 (m, 0.5H), 1.51 – 1.42 (m, 1H), 1.35 – 1.27 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H)ppm.

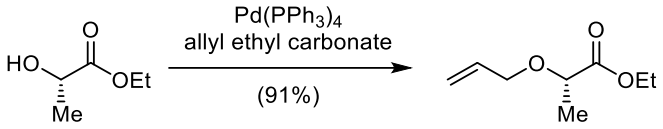
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 207.49, 207.43, 151.62, 147.46, 147.38, 142.65, 142.58, 135.33, 133.31, 132.68, 131.60, 127.08, 122.09, 116.10, 115.07, 114.98, 101.55, 101.45, 98.76, 98.63, 60.13, 57.72, 56.30, 56.22, 45.44, 45.42, 43.21, 43.14, 28.25, 28.22, 27.93, 27.73, 17.75, 17.74, 11.78, 11.77 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3365 (br w), 2956 (m), 1702 (m), 1627 (s), 1501 (w), 1449 (m), 1386 (s), 1231 (s), 1157 (s), 1063 (m), 926 (s), 755 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{23}H_{32}NO_5^+$: 402.2278 $[M+H]^+$

found: 402.2276 $[M+H]^+$

Allyl-protection of (−)-ethyl lactate **180**



180 **181**

Ethyl (S)-2-(allyloxy)propanoate (181). Allyl ethyl carbonate (2.63 mL, 20.0 mmol, 2 eq) and tetrakis(triphenylphosphine)palladium(0) (290 mg, 0.25 mmol, 0.025 eq) were dissolved in THF (50 mL) and the resulting mixture was added to a solution of (−)-ethyl lactate (**180**) (1.14 mL, 10 mmol, 1 eq) in THF (50 mL) *via* cannula. The reaction mixture turned orange and was heated to reflux for 3 h. After cooling to ambient temperature the mixture was filtered through a short silica pad which was washed with MTBE. The combined organic phases were concentrated under reduced pressure yielding the crude product which was purified by flash column chromatography (20:1 →10:1 *n*-Pentane>Et_2O) to afford volatile ester **181** (1.44 g, 9.10 mmol, 91%) as a light yellow oil.

Physical state: light yellow liquid

$\mathbf{R_f}$ = 0.40 (9:1 hexanes:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = −68.9 (*c* = 0.94 in $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.89 (ddt, *J* = 17.0, 10.3, 5.8 Hz, 1H), 5.26 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.18 (qd, *J* = 7.1, 3.0 Hz, 2H), 4.12 (ddt, *J* = 12.7, 5.5, 1.7 Hz, 1H), 3.98 (q, *J* = 6.8 Hz, 1H), 3.91 (ddt, *J* = 12.6, 6.1, 1.4 Hz, 1H,), 1.39 (d, *J* = 6.8 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm.

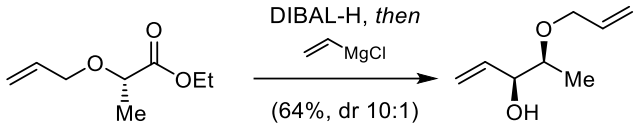
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.37, 134.19, 117.79, 74.09, 71.14, 60.90, 18.70. 14.32 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3362 (br w), 753 (s) cm^{-1}. IR (ATR): $\tilde{\nu}$ = 2986 (m), 1747 (s), 1448 (m), 1373 (m), 1264(m), 1197 (s), 1136(s), 1114 (s), 1021 (m), 922 (m) cm^{-1}

HRMS (+EI): calc. for $C_8H_{15}O_3^+$: 159.1016 $[M+H]^+$

found: 159.1013 $[M+H]^+$

Grignard-addition to ester **181**



181 **182**

(3S,4S)-4-(allyloxy)pent-1-en-3-ol (182). A solution of ester **181** (580 mg, 3.67 mmol, 1 eq) in DCM (30 mL) was cooled to −92 °C and DIBAL-H (1 M in DCM, 5.02 mL, 5.02 mmol, 1.37 eq) was added *via* syringe pump (1 mL/min). After 10 min TLC indicated complete consumption of the starting material and a solution of vinyl magnesium chloride (1.6 M in THF, 4.50 mL, 7.19 mmol, 1.96 eq) was added *via* syringe pump (1 mL/min). After complete addition the reaction mixture was allowed to come to ambient temperature and was stirred for one additional hour. The reaction was quenched by addition of saturated aqueous Rochelle's salt solution (100 mL) under ice cooling. After an additional hour of stirring at room temperature the reaction was extracted three times with Et_2O, the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product, which was subjected to flash column chromatography (15:1 →15:2 *n*-Pentane:Et_2O) yielding volatile alcohol **182** (331 mg, 2.33 mmol, 64%, dr10:1) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.47 (5:1 *n*-pentane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +38.4 (*c* = 3.7 in $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.91 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.81 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H), 5.35 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.21 (dt, *J* = 10.5, 1.4 Hz, 1H), 5.17 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.13 (ddt, *J* = 12.6, 5.5, 1.5 Hz, 1H), 3.95 (ddt, *J* = 12.6, 5.8, 1.4 Hz, 1H), 3.90 (ddt, *J* = 7.5, 6.5, 1.2 Hz, 1H), 3.34 (dq, *J* = 7.2, 6.2 Hz, 1H), 2.66 (br s, 1H), 1.12 (d, *J* = 6.3 Hz, 3H) ppm.

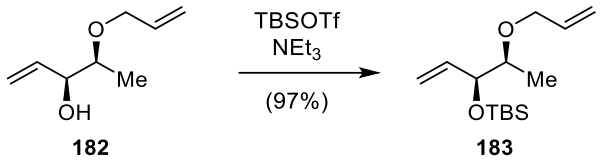
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 136.89, 134.86, 117.66, 117.24, 78.16, 76.72, 70.19, 15.61 ppm.

IR (ATR): $\tilde{\nu}$ = 3444 (br m), 2980 (m), 2872 (m), 2361 (m), 1647 (w), 1424 (w), 1377 (m), 1261 (br w), 1132 (m), 1079 (s), 994 (s), 924 (s) cm^{-1}.

HRMS (EI): calc. for $C_8H_{13}O$: 125.0966 [M−OH]

found: 125.0960 [M−OH]

TBS-protection of allylic alcohol **182**



182 **183**

(((3S,4S)-4-(allyloxy)pent-1-en-3-yl)oxy)(tert-butyl)dimethylsilane (183). To a solution of allylic alcohol **182** (590 mg, 4.15 mmol, 1 eq, d.r.10:1) in DCM (20 mL) was added triethylamine (920 µL, 6.64 mmol, 1.6 eq) and the reaction mixture was cooled to 0 °C. *tert*-Butyldimethylsilyltrifluoromethanesulfonate (1.43 mL, 6.22 mmol, 1.5 eq) was added dropwise at this temperature. After complete addition the mixture was allowed to warm to room temperature and was quenched after 15 min by addition of saturated aqueous NH_4Cl solution). The mixture was extracted three times with Et_2O), the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure affording the crude product which was subjected to flash column chromatography (50:1 *n*-pentane:Et_2O) to yield silyl ether **183** (1.03 g, 4.03 mmol, 97%, d.r.10:1) as a colorless oil.

Physical state: colorless oil

R_f = 0.65 (10:1 *n*-Pentane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ = −37.1 (*c* = 0.57 in $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.00 – 5.82 (m, 2H), 5.26 (m,2H), 5.15 (m, 2H), 4.18 (tt, *J* = 5.4, 1.5 Hz, 1H), 4.10 – 4.01 (m, 2H), 3.41 (dt, *J* = 11.9, 6.2 Hz, 1H), 1.05 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 1H) ppm.

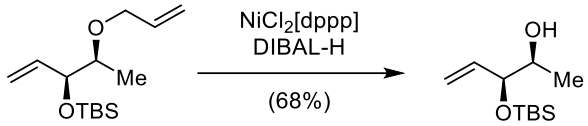
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 137.48, 135.57, 116.64, 115.67, 78.16, 75.33, 70.68, 25.98, 18.38, 14.93, −4.54, −4.73 ppm.

IR (ATR): $\tilde{\nu}$ = 3746 (w), 2956 (m), 2930 (m), 2858 (m), 2361 (m), 1473 (w), 1458(w), 1362 (w), 1252 (m), 1074 (m), 1058 (m), 1026 (m), 923 (m), 833 (s), 774 (s), 669 (m) cm^{-1}.

HRMS (ESI): calc. for $C_{14}H_{28}O_2SiNa^+$: 279.17508 $[M+Na]^+$

found: 279.17506 $[M+Na]^+$

Deallylation of diol **183**



183 **184**

(2S,3S)-3-((tert-butyldimethylsilyl)oxy)pent-4-en-2-ol (184). To a solution of allyl ether **183** (d.r. 10:1, 486 mg, 1.90 mmol, 1 eq) in diethyl ether (6.3 mL) was added dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (10.3mg, 19.0 µmol, 0.01 eq). The mixture was cooled to 0 °C and a solution of DIBAL-H (1 M in toluene, 2.84 mL, 2.84 mmol, 1.5 eq) was added dropwise. After 5 min the reaction mixture was warmed to room temperature and was quenched after an additional 20 min under ice cooling by diluting the mixture with Et_2O and the subsequent addition of water. After 1 h of stirring at ambient temperature the mixture was dried over $MgSO_4$, filtered over celite and concentrated under reduced pressure to afford the crude product which was subjected to flash column chromatography (20:1 *n*-pentane:Et_2O), yielding homoallylic alcohol **184** (single diastereomer, 280 mg, 1.30 mmol, 68%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.27 (20:1 *n*-Pentane:EtOAc)

$[\boldsymbol{\alpha}]_D^{\mathbf{23}}$ = +11.3 (*c* = 0.55 in $CHCl_3$)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.78 (ddd, *J* = 17.4, 10.4, 7.1 Hz, 1H), 5.24 (ddd, *J* = 17.3, 1.7, 1.1 Hz, 1H), 5.18 (ddd, *J* = 10.4, 1.7, 0.9 Hz, 1H), 3.82 (ddt, *J* = 7.4, 6.5, 1.0 Hz, 1H), 3.56 (p, *J* = 6.3 Hz, 1H), 2.49 (br s, 1H), 1.12 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H) ppm.

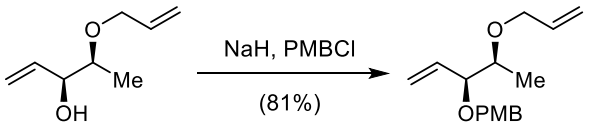
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 138.37, 117.27, 79.56, 70.89, 25.99, 18.44, 18.31, −3.88, −4.75 ppm.

IR (ATR): $\tilde{\nu}$ = 3746 (w), 2956 (m), 2930 (m), 2858 (m), 2361 (m), 1717 (br, m), 1473 (w), 1362 (m), 1252 (m), 1074 (br, m), 1026 (m), 923 (m), 834 (s), 775 (s), 669 (m) cm^{-1}.

HRMS (EI): calc. for $C_{10}H_{21}O_2Si^+$: 201.1306 $[M-CH_3]^+$

found: 201.1306 $[M-CH_3]^+$

PMB-protection of allylic alcohol **182**



182 **189**

PMB-ether 189. NaH (60% dispersion in mineral oil, 77 mg, 1.93 mmol, 1.1 eq) was suspended in DMF (5.5 mL) and cooled to 0 °C. A solution of allylic alcohol **182** (250 mg, 1.76 mmol, 1 eq) in DMF (1.5 mL) was added and the mixture stirred for 15 min at 0 °C, after which *para*-methoxy benzylchloride (310 µL, 2.29 mmol, 1.3 eq) was added and the cooling removed. After 30 min of stirring at room temperature the reaction was quenched by addition of water. The mixture was then extracted three times with Et_2O, the combined organic extracts washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography (15:1 n-pentane:Et_2O) yieldedPMB ether**189** (367 mg, 1.43 mmol, 81%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.50 (9:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +9.8 (*c* = 0.53 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 – 7.21 (m, 2H), 6.88 – 6.82 (m, 2H), 5.89 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.77 (ddd, *J* = 17.1, 10.6, 7.5 Hz, 1H), 5.33 – 5.19 (m, 3H), 5.11 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.05 (dt, *J* = 5.7, 1.5 Hz, 2H), 3.77 (s, 3H), 3.75 (ddt, *J* = 6.6, 5.6, 1.0 Hz, 1H), 3.58 – 3.46 (m, 1H), 1.09 (d, *J* = 6.4 Hz, 3H) ppm.

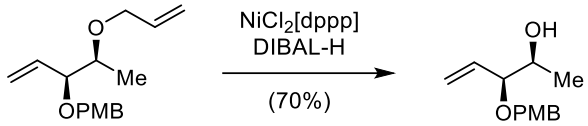
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.12, 135.56, 135.47, 130.82, 129.39, 118.64, 116.55, 113.77, 83.02, 76.81, 70.91, 70.30, 55.37, 16.25 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2865 (br m), 1613 (m), 1513 (s), 1463 (w), 1301 (w), 1247 (s), 1172 (m), 1081 (s), 1036 (s), 995 (m), 925 (m), 820 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{16}H_{26}NO_3^+$: 280.1907 $[M+NH_4]^+$

found: 280.1907$[M+NH_4]^+$

Deallylation of diol **189**



189 **190**

(2*S*,3*S*)-3-((4-methoxybenzyl)oxy)pent-4-en-2-ol 190. To a solution of allyl ether **189** (508 mg, 1.93 mmol, 1 eq) in diethyl ether (6.0 mL) was added dichloro[1,3-bis(diphenyl-phosphino)propane]nickel(II) (10.5mg, 19.0 µmol, 0.01 eq). The mixture was cooled to 0 °C and a solution of DIBAL-H (1 M in toluene, 2.13 mL, 2.84 mmol, 1.1 eq) was added dropwise and the cooling removed. After 1 h and 20 min the reaction mixture was quenched under ice cooling by diluting the mixture with Et_2O and the subsequent addition of water. After 30 min of stirring at ambient temperature the mixture was dried over $MgSO_4$, filtered over celite and concentrated under reduced pressure to afford the crude product which was subjected to flash column chromatography (4:1 *n*-pentane:Et_2O), yielding homoallylic alcohol **190** (299 mg, 1.35 mmol, 70%) as a colorless oil.

Physical state: colorless oil

R_f = 0.55 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ = +39.6 (*c* = 0.57 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.14 (m, 2H), 6.89 – 6.71 (m, 2H), 5.64 (ddd, *J* = 17.1, 10.4, 8.1 Hz, 1H), 5.41 – 5.23 (m, 2H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.22 (d, *J* = 11.1 Hz, 1H), 3.75 (s, 3H), 3.62 (dq, *J* = 7.8, 6.3 Hz, 1H), 3.45 (tt, *J* = 7.8, 0.7 Hz, 1H), 2.72 (s, 1H), 1.06 (d, *J* = 6.3 Hz, 3H) ppm.

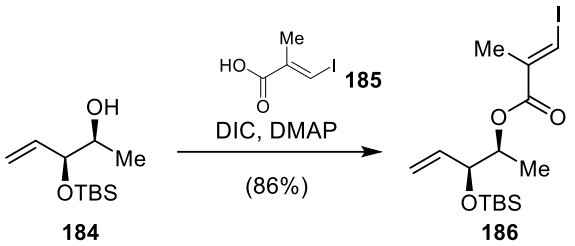
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.41, 135.41, 130.20, 129.74, 120.38, 114.02, 85.94, 70.25, 69.68, 55.43, 18.32 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2917 (br w), 1613 (m), 1513 (s), 1463 (w), 1367 (w), 1301 (w), 1248 (s), 1173 (m), 1067 (m), 1035 (m), 931 (w), 820 (m), 759 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{13}H_{22}NO_3^+$: 240.1594 $[M+NH_4]^+$

found: 240.1595 $[M+NH_4]^+$

Esterification of alcohol **184**



(2S,3S)-3-((tert-butyldimethylsilyl)oxy)pent-4-en-2-yl (E)-3-iodo-2-methylacrylate (186). To a solution of alcohol **184** (277 mg, 1.28 mmol, 1.0 eq) in DCM (13.4 mL) was added acid **185**[I] (326 mg, 1.54 mmol, 1.2 eq), *N*,*N*′-diisopropylcarbodiimide (297 µL, 1.92 mmol, 1.5 eq) and DMAP (31.8 mg, 0.26 mmol, 0.2 eq) at 0 °C. The resulting mixture was warmed to ambient temperature and was stirred for 1 h. The reaction mixture was filtered through a pad of celitewhich was washed with DCM. Subsequent concentration under reduced pressure afforded the crude product which was subjected to flash column chromatography (40:1 *n*-Pentane/Et O) to yield the ester **186** (453 mg, 1.10 mmol, 86%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R}_f$ = 0.40 (15:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +4.8 (*c* = 1.48 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 (q, *J* = 1.3 Hz, 1H), 5.80 (ddd, *J* = 17.1, 10.5, 5.8 Hz, 1H), 5.29 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.20 (ddd, *J* = 10.5, 1.9, 1.3 Hz, 1H), 4.93 (qd, *J* = 6.5, 5.5 Hz, 1H), 4.18 (tt, *J* = 5.7, 1.3 Hz, 1H), 2.05 (d, *J* = 1.3 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.20, 140.10, 136.81, 117.04, 98.54, 74.59, 74.00, 25.85, 20.44, 18.25, 14.96, −4.39, −4.86 ppm.

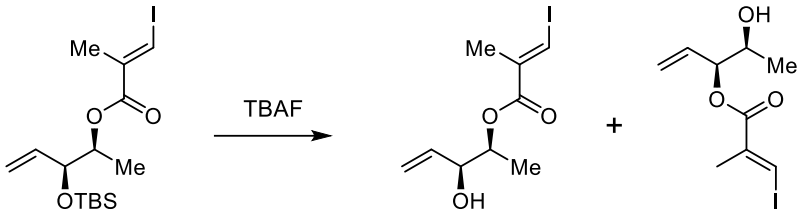
IR (ATR, neat): $\tilde{\nu}$ = 2955 (m), 2929 (m), 2857(m), 2361 (w), 1713 (s), 1601 (m), 1472 (w), 1380 (w), 1288 (s), 1252 (m), 1213 (s), 1142 (m), 1099 (s), 1061 (s), 993 (m), 926 (m), 834 (s), 776 (s), 727 (m), 681 (m) cm^{-1}.

HRMS (EI): calc. for $C_{13}H_{24}ISiO_3^+$: 383.0539 [M−vinyl]

found: 383.0531 [M−vinyl]

[I] prepared in three steps according to *J. Chem. Soc., Perkin Trans. 1*, **1990**, 47–65

Deprotection of silyl ether **186**



186 **187**, 46% **188**, 17%

Alcohols 187 and 188. A solution of silyl ether **186**(81.5 mg, 199 μmol, 1 eq) in THF (3.8 mL) was cooled to 0 °C before a solution of TBAF (1 M in THF, 219 μL, 219 μmol, 1.1 eq) was added drop wise. The mixture was stirred at 0 °C for 1.5 h, then at room temperature for another hour. Then, pH 7 phosphate buffer was added and the mixture extracted three times with EtOAc, the combined organic extracts dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (9:1 *n*-pentane:Et_2O) provided allylic alcohol **187** (27.3 mg, 92.0 μmol, 46%) as well as the 1,2-acyl shifted isomer **188** (9.70 mg, 34.0 mmol, 17%).

Allylic alcohol 187:

Physical state: colorless oil

$\mathbf{R_f}$ = 0.68 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = −0.8 (*c* = 1.38 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81 (t, *J* = 1.2 Hz, 1H), 5.85 (ddd, *J* = 16.9, 10.5, 6.0 Hz, 1H), 5.37 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.26 (dt, *J* = 10.5, 1.2 Hz, 1H), 4.96 (p, *J* = 6.3 Hz, 1H), 4.15 (t, *J* = 6.0 Hz, 1H), 2.06 (d, *J* = 1.2 Hz, 3H), 1.99 (br s, 1H), 1.27 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.48, 139.79, 136.45, 117.84, 99.22, 75.26, 74.24, 20.51, 16.20 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3460 (br, m), 3081 (w), 2983 (m), 1711 (s), 1600 (m), 1380 (w), 1293 (s), 1218 (s), 1102 (s), 1051 (m), 992 (m), 929 (m), 729 (m), 684 (w) cm^{-1}.

HRMS (EI): calc. for $C_9H_{13}IO_3^+$: 295.9909 [M]

found: 295.9901[M]

Homoallylic alcohol 188:

Physical state: colorless oil

$\mathbf{R_f}$ = 0.46 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = −36.8 (*c* = 0.28 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H), 5.82 (ddd, *J* = 17.2, 10.6, 6.6 Hz, 1H), 5.37 (d, *J* = 17.7 Hz, 1H), 5.33 (d, *J* = 10.8 Hz, 1H), 5.17 (t, *J* = 6.3 Hz, 1H), 3.92 (p, *J* = 6.3 Hz, 1H), 2.08 (s, 3H), 1.85 (br s, 1H), 1.22 (d, *J* = 6.4 Hz, 3H) ppm.

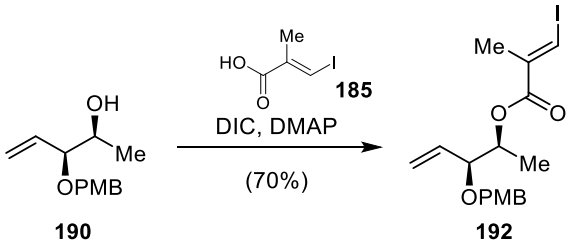
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.06, 139.68, 132.85, 119.71, 99.48, 79.82, 68.97, 20.54, 18.98 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3435 (br, m), 3080 (w), 2929 (m), 2358 (w), 1715 (s), 1600 (m), 1379 (w), 1289 (s), 1214 (s), 1102 (s), 992 (m), 729 (m), 683 (w) cm^{-1}.

HRMS (EI): calc. for $C_{13}H_{13}IO_3^+$: 295.9909 [M]

found: 295.9909[M]

Esterification of alcohol **190** with carboxylic acid **185**



Ester 192. A solution of alcohol **190** (500 mg, 2.25 mmol, 1.0 eq) in DCM (26.5 mL) was added to carboxylic acid **185** (572 mg, 2.70 mmol, 1.2 eq) and DMAP (82.4 mg, 675 µmol, 0.3 eq). *N*,*N*′-Diisopropylcarbodiimide (523 µL, 3.38 mmol, 1.5 eq) was added and the reaction mixture stirred for 18 h at room temperature. Then, the mixture was filtered over a pad of celite, silica was added to the filtrate and the mixture carefully concentrated on a rotary evaporator. Flash column chromatography (dry load, 10:1 *n*-pentane:Et_2O) afforded ester **192** (654 mg, 1.58 mmol, 70%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.57 (5:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +38.0 (*c* = 0.36 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.72 (q, *J* = 1.2 Hz, 1H), 7.25 – 7.18 (m, 2H), 6.93 – 6.84 (m, 2H), 5.73 (ddd, *J* = 17.3, 10.4, 7.7 Hz, 1H), 5.41 – 5.28 (m, 2H), 5.04 (p, *J* = 6.4 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.30 (d, *J* = 11.9 Hz, 1H), 3.82 (s, 3H), 3.77 (ddt, *J* = 7.3, 6.2, 0.9 Hz, 1H), 2.04 (d, *J* = 1.2 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H) ppm.

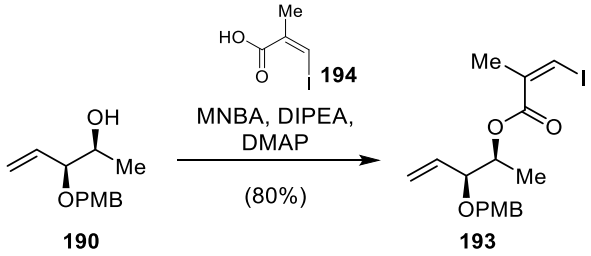
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.25, 159.30, 140.03, 134.45, 130.26, 129.59, 120.11, 113.87, 98.83, 81.12, 72.75, 69.93, 55.44, 20.48, 16.12 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3079 (w), 2935 (br, w), 1712 (s), 1601 (m), 1513 (s), 1455 (w), 1380 (w), 1292 (s), 1247 (s), 1217 (s), 1173 (w), 1100(s), 1071 (m), 996 (w), 821 (w), 728 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{17}H_{25}NIO_4^+$: 434.0823 $[M+NH_4]^+$

found: 434.0824 $[M+NH_4]^+$

Esterification of alcohol **190** with carboxylic acid **185**



Ester 193. A solution of alcohol **190** (200 mg, 900 µmol, 1.0 eq) and DIPEA (346 µL, 1.98 mmol, 2.2 eq) in DCM (12 mL) was added to carboxylic acid **194**[1] (229 mg, 1.08 mmol, 1.2 eq), DMAP (33.0 mg, 270 µmol,0.3 eq) and 2-methyl-6-nitrobenzoic acid (465 mg, 4.35 mmol, 1.5 eq) under argon. The mixture was stirred for 14 h at room temperature after which EtOAc and aqueous $NaHCO_3$ was added. The biphasic mixture was extracted three times with EtOAc, the combined organic phases washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (5:1 *n*-pentane:EtOAc) afforded ester **193** (301 mg, 724 µmol, 80%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.65 (5:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +2.9 (*c* = 1.04 in $CHCl_3$)

[1] prepared in three steps according to *J. Org. Chem.***1997**, *62*, 8591–8594

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 – 7.21 (m, 2H), 6.90 – 6.83 (m, 2H), 6.79 (q, *J* = 1.5 Hz, 1H), 5.78 (ddd, *J* = 17.0, 10.6, 7.4 Hz, 1H), 5.39 – 5.31 (m, 2H), 5.14 (p, *J* = 6.4 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.34 (d, *J* = 11.6 Hz, 1H), 3.87 (ddt, *J* = 7.1, 6.0, 1.0 Hz, 1H), 3.80 (s, 3H), 2.03 (d, *J* = 1.6 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 3H) ppm.

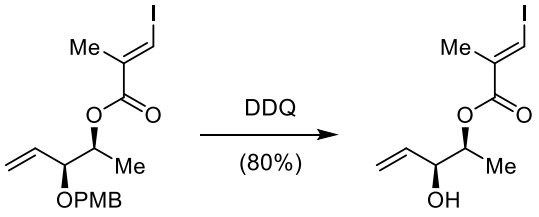
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.26, 159.23, 139.31, 134.48, 130.43, 129.41, 119.90, 113.85, 82.40, 81.21, 72.67, 70.25, 55.42, 22.69, 15.99 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2983 (w), 2934 (br, w), 2866 (w), 2836 (w), 1720 (s), 1612 (m), 1512 (s), 1442 (m), 1378 (w), 1299 (s), 1245 (s), 1194 (s), 1108 (s), 1068 (s), 1034 (s), 932 (m), 819 (s), 756 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{17}H_{25}NIO_4^+$: 434.0823 $[M+NH_4]^+$

found: 434.0821 $[M+NH_4]^+$

Deprotection of PMB ether **192**



192 **187**

Allylic alcohol 187. A solution of PMB ether **192** (108 mg, 259 μmol, 1.0 eq) in DCM (2.5 mL) and water (130 μL) was cooled to 0 °C. Then, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (82.4 mg, 363 μmol, 1.4 eq) was added and the mixture stirred for 3 h at 0 °C. The reaction mixture was then filtered through a plug of celite and $MgSO_4$ and concentrated under reduced pressure.Flash column chromatography (7:1 n-pentane/Et_2O) afforded allylic alcohol**187** (61.6 mg, 208 μmol, 80%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.68 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = −0.8 (*c* = 1.38 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81 (t, *J* = 1.2 Hz, 1H), 5.85 (ddd, *J* = 16.9, 10.5, 6.0 Hz, 1H), 5.37 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.26 (dt, *J* = 10.5, 1.2 Hz, 1H), 4.96 (p, *J* = 6.3 Hz, 1H), 4.15 (t, *J* = 6.0 Hz, 1H), 2.06 (d, *J* = 1.2 Hz, 3H), 1.99 (br s, 1H), 1.27 (d, *J* = 6.4 Hz, 3H) ppm.

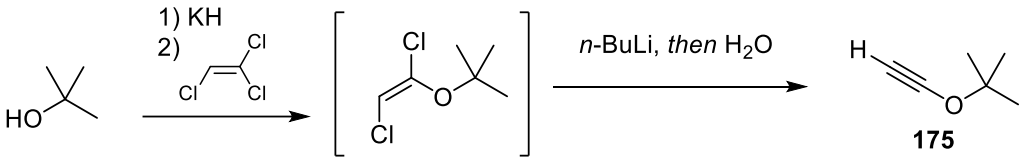
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.48, 139.79, 136.45, 117.84, 99.22, 75.26, 74.24, 20.51, 16.20 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3460 (br, m), 3081 (w), 2983 (m), 1711 (s), 1600 (m), 1380 (w), 1293 (s), 1218 (s), 1102 (s), 1051 (m), 992 (m), 929 (m), 729 (m), 684 (w) cm^{-1}.

HRMS (EI): calc. for $C_9H_{13}IO_3^+$: 295.9909 [M]

found: 295.9901[M]

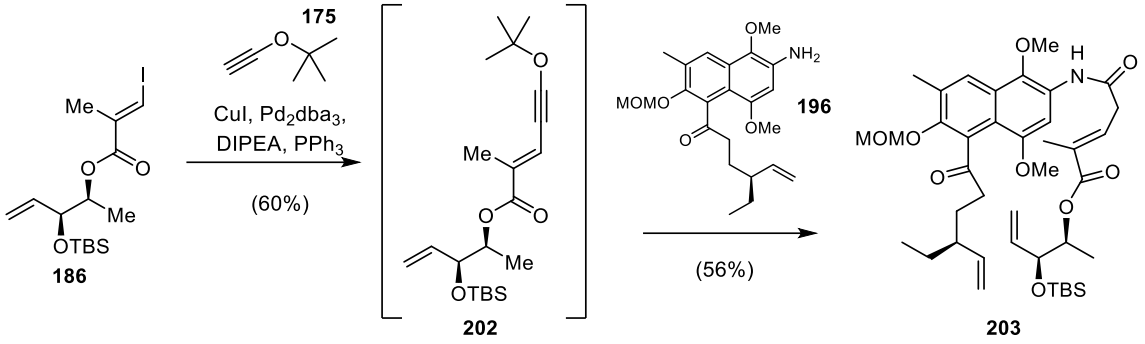
Preparation of *tert*-butoxyacetylene **175**



2-(Ethynyloxy)-2-methylpropane (175). Potassium hydride in mineral oil (5.71 g, 142 mmol, 2.04 eq) was washed with hexanes (3×20 mL) in a Schlenk flask and dried overnight on a vacuum line. The next day it was suspended in diethyl ether (36 mL), a gas bubbler was installed and *tert*-butyl alcohol (6.68 mL, 71.2 mmol, 1.02 eq) in diethyl ether (74 mL) was added dropwise *via* syringe pump (2 mL/min). After approximately 1 h, hydrogen evolution ceased and the mixture was cooled to −40 °C using a cryostat. Trichloroethylene (6.28 mL, 69.8 mmol, 1 eq) in diethyl ether (58 mL) was added dropwise to the reaction mixture at this temperature via syringe pump (2 mL/min) and the mixture was allowed to warm to room temperature. After 1.5 h of stirring at ambient temperature the brown slurry was cooled to −78 °C and *n*-butyl lithium (2.5 M, 71 mL, 178 mmol, 2.55 eq) was added via syringe pump (2 mL/min). After complete addition the reaction mixture was warmed to −50 C in the course of 30min and was stirred for an additional hour before quenching with water (40mL). The mixture was warmed to ambient temperature, extracted with diethyl ether (3×50 mL) and the organic extracts were dried over Na_2SO_4. Concentration was achieved on a rotary evaporator, equipped with a room temperature water bath and dry ice cooling, by firstly removing volatiles at 300 mbar. Then, the fraction from 300–50 mbar was collected and redistilled from CaH_2, yielding volatile alkyne **175** (7.42 g) as a colorless solution in hexanes, ethyl ether and butyl ethers. This solution was stored under Argon at −20 °C and was used as is in subsequent reactions. If the reagent goes bad over time, the solution will turn yellow and develop an unpleasant, characteristic odor.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.53 (s, 1H), 1.40 (s, 9H) ppm.

Sonogashira coupling and ketene generation



Amide 203. To vinyl iodide **186** (108 mg, 262 μmol, 1 eq) was added Pd_2dba_3 (48.0 mg, 53 μmol, 0.2 eq), PPh_3 (108 mg, 262 μmol, 0.8 eq) and CuI (6.5 mg, 34 μmol, 0.13 eq). DIPEA (1.0 mL), *t*-butoxy acetylene **175**(1 mL of the solution obtained following the procedure of Ready[1]) and molecular sieves (4 Å) were added and the mixture stirred at room temperature. After 5 h, more CuI (0.13 eq), Pd_2dba_3 and **175** (1 mL) were added. After another 4 h of stirring at room temperature, the reaction mixture was filtered through Al_2O_3 (Brockmann V grade) and concentrated. Flash column chromatography (40:1 *n*-pentane:Et_2O) yielded sensitive alkynyl ether **202** (59.2 mg, 156 μmol, 60%) that was immediately used in the next step.

Naphthyl amine**196** (30.6 mg, 76.2 μmol, 1 eq) and alkynyl ether **202** (30.7 mg, 80.7 μmol, 1.1 eq) were dissolved in toluene (3.0 mL) and heated to 80 °C for 3 h. Then, the mixture was concentrated and the crude material subjected to flash column chromatography to afford amide **203** (31 mg, 42.7 μmol, 56%) as a light yellow oil

Physical state: light yellow oil

$\mathbf{R_f}$ = 0.44 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = −6.8 (*c* = 0.49 in $CHCl_3$)

*Note: At room temperature compounds **203** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

[1] *Angew. Chem.***2014**, *126*, 9126–9130

^{1}H-NMR (800 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 5.6 Hz, 1H), 7.90 (s, 1H), 7.72 (s, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 5.84 (ddd, *J* = 16.6, 10.5, 5.6 Hz, 1Hz), 5.56 – 5.47 (m, 1H), 5.34 – 5.28 (m, 1H), 5.23 – 5.18 (m, 1H), 5.02 – 4.88 (m, 6H), 4.23 (t, *J* = 5.5 Hz, 1H), 3.87 – 3.85 (m, 3H), 3.82 – 3.80 (m, 3H), 3.58 – 3.56 (m, 3H), 3.44 – 3.37 (m, 2H), 2.91 (ddd, *J* = 17.6, 10.8, 4.0 Hz, 0.5H), 2.79 (ddd, *J* = 18.2, 10.9, 5.0 Hz, 0.5H), 2.68 (ddd, *J* = 18.0, 10.6, 5.1 Hz, 0.5H), 2.57 (ddd, *J* = 18.2, 10.7, 5.1 Hz, 0.5H), 2.49 (s, 3H), 1.99 (s, 3H), 1.91 – 1.87 (m, 1H), 1.81 (s, 1H), 1.63 – 1.57 (m, 1H), 1.47 – 1.43 (m, 1H), 1.33 – 1.30 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.89 – 0.87 (m, 12H), 0.07 (s, 3H), 0.04 (s, 3H). ppm.

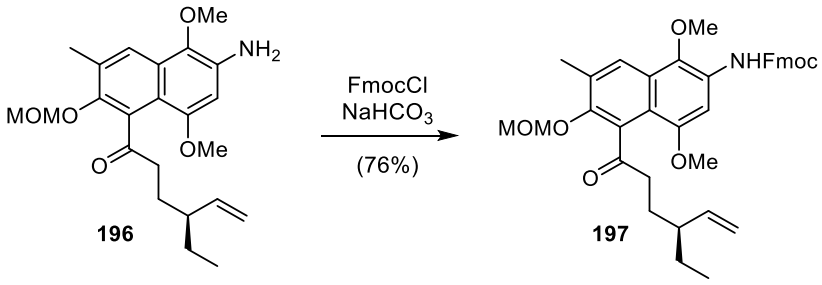
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.90, 206.85, 167.54, 166.63, 151.20, 149.74, 149.66, 142.56, 142.52, 136.80, 136.61, 133.21, 132.85, 132.52, 131.73, 131.69, 127.51, 125.41, 123.24, 119.12, 116.83, 115.17, 115.06, 101.70, 101.60, 99.69, 99.56, 77.36, 74.31, 73.50, 61.72, 57.78, 56.46, 56.40, 45.45, 45.43, 43.26, 43.16, 37.90, 28.22, 28.19, 27.95, 27.75, 25.85, 18.24, 17.83, 17.82, 14.82, 13.07, 11.79, 11.77, −4.47, −4.85.ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2956 (m), 2931 (s), 2857 (m), 1708 (s), 1625 (m), 1606 (m), 1495 (s), 1461 (m), 1362 (m), 1252 (s), 1197 (m), 1160 (s), 1067 (s), 990 (m), 777 (w)cm^{-1}.

HRMS (+ESI): calc. for $C_{40}H_{63}N_2SiO_9^+$: 743.4297 $[M+NH_4]^+$

found: 743.4303 $[M+NH_4]^+$

Fmoc-protection of naphthyl amine **197**



Carbamate 197. To a solution of naphthyl amine **196** (25.9 mg, 64.5 μmol, 1 eq) in DCM (2 mL), $NaHCO_3$ (16.2 mg, 194 μmol, 3 eq) was added, then FmocCl (25.0 mg, 96.8 μmol, 1.5 eq). After 17 h of stirring at room temperature, the mixture was diluted with EtOAc and aqueous NH_4Cl solution. The biphasic mixture was extracted three times with EtOAc, the combined organic phases washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography (6:1 *n*-pentane:EtOAc) afforded carbamate **197** (30.7 mg, 49.2 μmol, 76%) as a yellow foam.

Physical state: yellow foam

R_f = 0.53 (3:1 hexane:EtOAc)

$[\alpha]_D^{21}$ = −10.9 (*c* = 0.15 in $CHCl_3$)

*Note: At room temperature compounds **197** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (800 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.5 Hz, 2H), 7.78 – 7.70 (m, 2H), 7.67 – 7.64 (m, 2H), 7.44 – 7.41 (m, 2H), 7.38 – 7.31 (m, 3H), 5.59 – 5.47 (m, 1H), 5.00 – 4.92 (m, 4H), 4.59 – 4.53 (m, 2H), 4.34 (t, *J* = 7.1 Hz, 1H), 3.87 – 3.83 (m, 6H), 3.58 (s, 1.5H), 3.57 (s, 1.5H), 2.93 (ddd, *J* = 18.4, 11.1, 4.5 Hz, 0.5H), 2.81 (ddd, *J* = 18.3, 10.8, 5.1 Hz, 0.5H), 2.70 (ddd, *J* = 18.3, 10.6, 5.3 Hz, 0.5H), 2.59 (ddd, *J* = 18.4, 10.8, 5.2 Hz, 0.5H), 2.53 – 2.48 (m, 3H), 2.01 – 1.96 (m, 0.5H), 1.94 – 1.88 (m, 1H), 1.85 – 1.76 (m, 1H), 1.64 – 1.58 (m, 0.5H), 1.50 – 1.43 (m, 1H), 1.35 – 1.29 (m, 1H), 0.89 – 0.86 (m, 3H) ppm.

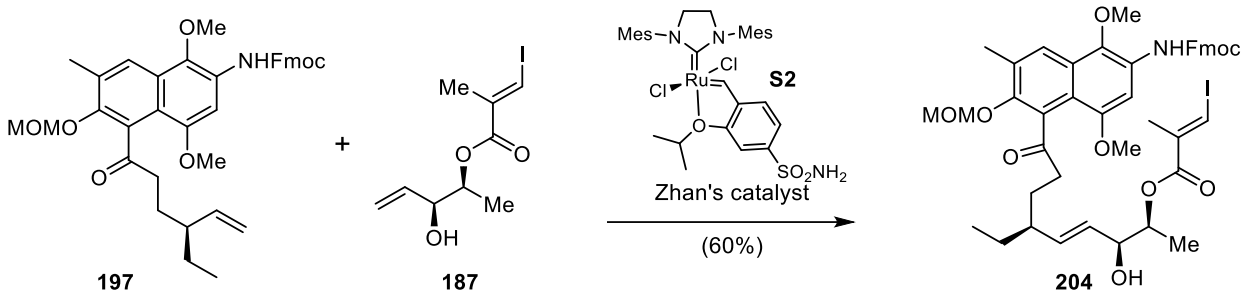
^{13}C-NMR (200 MHz, $CDCl_3$): δ = 206.91, 206.86, 153.61, 151.41, 149.46, 149.39, 143.80, 142.62, 142.57, 141.53, 136.22, 133.18, 131.74, 131.70, 128.01, 127.45, 127.30, 125.74, 125.15, 123.13, 120.27, 118.67, 118.64, 115.13, 115.02, 101.72, 101.63, 67.32, 61.67, 57.78, 56.46, 56.40, 47.30, 45.46, 45.43, 43.26, 43.17, 28.26, 28.22, 27.95, 27.76, 17.83, 11.78, 11.77. ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3312 (br w), 2959 (m), 2932 (m), 2361 (w), 1734 (m), 1717 (m), 1717 (m), 1627 (m), 1508 (s), 1498 (s),1228 (s), 1204 (s), 1049 (m), 989 (m) 927 (m) 759 (m) 741 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{38}H_{42}NO_7^+$: 624.2956 $[M+H]^+$

found: 624.2962 $[M+H]^+$

Olefin cross metathesis of alkenes **197** and **187**



Alkene 204. A solution of allylic alcohol **187** (50.0 mg, 169 µmol, 2 eq) in DCM (1.0 mL) was added to naphthalene **197** (53.0 mg, 84.5 µmol, 1 eq) and Zhan's catalyst (**S2**)(12.4 mg, 16.9 µmol, 0.2 eq) in a pressure tube. The tube was flushed with argon, sealed and heated to 40 °C for 25 h. Then, the mixture was concentrated under reduced pressure and subjected to flash column chromatography (4:1 → 2:1 *n*-pentane:EtOAc) to afford alkene **204**(45.6 mg, 51.2 µmol, 60%) as a light yellow oil.

Physical state: light yellow oil

$\mathbf{R_f}$ = 0.48 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −4.5 (*c* = 0.22 in $CHCl_3$)

*Note: At room temperature compounds **204** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (800 MHz, $CDCl_3$): δ = 7.80 – 7.78 (m, 3H), 7.77 – 7.73 (m, 2H), 7.66 – 7.64 (m, 2H), 7.44 – 7.42 (m, 2H), 7.35 – 7.33 (m, 3H), 5.48 (ddd, *J* = 17.5, 15.5, 8.6 Hz, 1H), 5.41 (ddd, *J* = 15.6, 8.6, 7.2 Hz, 1H), 4.97 – 4.95 (m, 2H), 4.94 – 4.88 (m, 1H), 4.57 – 4.54 (m, 2H), 4.34 (t, *J* = 7.0 Hz, 1H), 4.10 – 4.05 (m, 1H), 3.86 – 3.83 (m, 6H), 3.58 (s, 1.5H), 3.57 (s, 1.5H), 2.89 (ddd, *J* = 18.3, 9.6, 4.7 Hz, 0.5H), 2.83 (ddd, *J* = 18.4, 9.6, 6.3 Hz, 0.5H), 2.71 (ddd, *J* = 18.3, 9.3, 5.9 Hz, 0.5H), 2.61 (ddd, *J* = 18.3, 9.7, 5.7 Hz, 0.5H), 2.50 (d, *J* = 1.0 Hz, 1.5H), 2.48 (d, *J* = 1.0 Hz, 1.5H), 2.03 – 2.00 (m, 4H), 1.95 – 1.90 (m, 1H), 1.84 – 1.80 (m, 1H), 1.60 – 1.55 (m, 1H), 1.50 – 1.47 (m, 1H), 1.23 – 1.21 (m, 3H), 0.87 – 0.85 (m, 3H) ppm.

^{13}C-NMR (200 MHz, $CDCl_3$): δ = 206.57, 206.38, 163.47, 153.60, 151.35, 151.32, 149.48, 149.34, 143.78, 141.51, 139.91, 139.88, 139.03, 138.95, 136.27, 133.12, 132.95, 131.54, 131.37, 129.26, 129.13, 128.14, 128.06, 128.00, 127.49, 127.29, 125.75, 125.73, 125.14, 123.31, 123.23, 120.34, 120.26, 118.61,

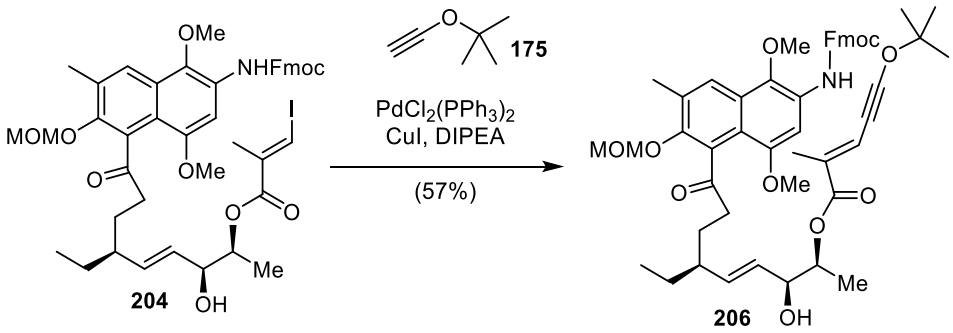
101.71, 101.33, 99.22, 99.01, 98.97, 77.36, 75.39, 75.32, 74.62, 74.42, 67.31, 61.68, 57.88, 57.74, 56.54, 56.53, 47.26, 44.19, 43.94, 43.35, 42.82, 29.84, 28.41, 28.22, 28.04, 27.98, 20.45, 20.43, 17.90, 17.85, 16.22, 11.89 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3425 (br w), 2958 (m), 2926 (m), 2360 (w), 1708 (s), 1627 (m), 1603 (m), 1498 (m), 1378 (m), 1292 (s), 1206 (s), 1158 (m), 1101 (m), 1047 (s) 985 (m) 928 (m), 801 (w), 758 (m), 741 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{45}H_{54}N_2IO_{10}^+$: 909.2818 $[M+NH_4]^+$

found: 909.2821 $[M+NH_4]^+$

Sonogashira coupling of **204** and **175**



Alkylnyl ether 206. To vinyl iodide**204** (20.0 mg, 22.4 µmol, 1 eq),$PdCl_2(PPh_3)_2$ (5.0 mg, 7.12 µmol, 0.3 eq), CuI (1.0 mg, 5.3 µmol, 0.24 eq) and molecular sieves (3 Å) was added DIPEA (160 µmL) and *t*-butoxy-acetylene**175** (600 µL the solution obtained following the procedure of Ready[I]) upon which the mixture turned dark red. After 2.5 h of stirring at room temperature the reaction mixture was filtered through Al_2O_3 (Brockmann V grade) and concentrated. Flash column chromatography (3:1 → 2:1 *n*-pentane:EtOAc) yielded sensitive alkynyl ether **206** (11.0 mg, 12.8 µmol, 57%) as a light yellow oil.

Physical state: light yellow oil

$\mathbf{R_f}$ = 0.67 (3:2 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +4.8 (*c* = 0.17 in $CHCl_3$)

*Note: At room temperature compounds **206** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets*

[I] *Angew. Chem.***2014**, *126*, 9126–9130

representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.

^{1}H-NMR (800 MHz, C_6D_6): δ = 8.17 (br s, 1H), 7.87 – 7.85 (m, 1H), 7.69 – 7.66 (m, 2H), 7.60 – 7.55 (m, 2H), 7.36 – 7.31 (m, 3H), 5.53 – 5.48 (m, 1H), 5.48 – 5.41 (m, 1H), 5.26 – 5.12 (m, 3H), 4.61 – 4.56 (m, 2H), 4.19 (t, *J* = 6.7 Hz, 1H), 4.08 (t, *J* = 6.5 Hz, 1H), 3.62 (s, 1.5H), 3.60 (s, 1.5H), 3.49 (s, 1.5H), 3.46 (s, 1.5H), 3.43 – 3.41 (m, 3H), 3.10 (ddd, *J* = 18.1, 9.4, 4.7 Hz, 0.5H), 3.01 (ddd, *J* = 18.1, 10.4, 5.6 Hz, 0.5H), 2.94 (ddd, *J* = 18.0, 10.2, 4.8 Hz, 0.5H), 2.84 (ddd, *J* = 18.2, 9.2, 6.5 Hz, 0.5H), 2.50 (d, *J* = 1.0 Hz, 1.5H), 2.46 (d, *J* = 1.0 Hz, 1.5H), 2.30 (d, *J* = 1.3 Hz, 1.5H), 2.28 (d, *J* = 1.3 Hz, 1.5H), 2.18 – 2.12 (m, 0.5H), 2.06 – 1.98 (m, 1H), 1.95 – 1.89 (m, 0.5H), 1.85 – 1.76 (m, 1H), 1.46 – 1.39 (m, 2H), 1.29 (d, *J* = 6.4 Hz, 1.5H), 1.26 (d, *J* = 6.4 Hz, 1.5H), 1.20 – 1.15 (m, 9H), 0.97 – 0.92 (m, 3H) ppm.

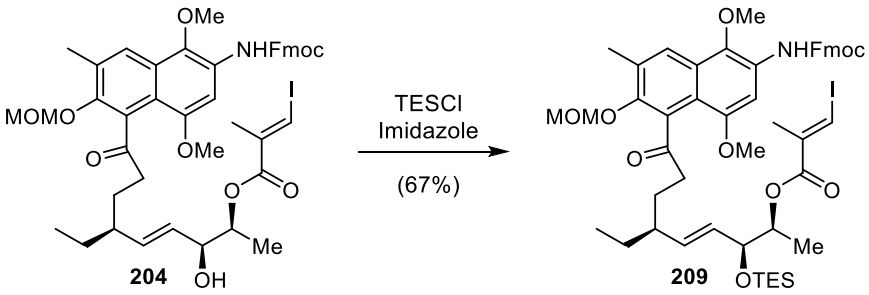
^{13}C-NMR (200 MHz, C_6D_6): δ = 204.91, 204.70, 167.06, 153.55, 151.96, 151.90, 150.23, 150.13, 144.26, 141.98, 141.87, 141.51, 137.83, 137.77, 136.70, 134.61, 134.56, 133.60, 133.53, 132.74, 130.25, 128.59, 128.35, 128.29, 127.99, 126.23, 125.31, 123.23, 122.10, 122.07, 120.39, 119.37, 111.12, 109.19, 109.17, 102.46, 102.18, 99.94, 87.97, 87.95, 75.10, 75.04, 73.91, 73.77, 67.11, 60.87, 57.46, 57.34, 56.29, 56.27, 47.68, 44.26, 44.14, 43.32, 42.94, 42.54, 29.12, 28.88, 28.37, 28.20, 26.88, 26.86, 17.85, 16.07, 15.36, 15.34, 12.08 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3428 (br w), 2958 (m), 2930 (m), 2232 (m), 1731 (s), 1705 (s), 1627 (m), 1606 (m), 1498 (m), 1451 (m), 1370 (m), 1248 (s), 1229 (s), 1204 (s) 1157 (m) 1119 (m), 985 (m), 929 (m), 803 (w) 759 (m), 741 (m), 680 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{51}H_{63}N_2O_{11}^+$: 879.4426 $[M+NH_4]^+$

found: 879.4437 $[M+NH_4]^+$

TES-protection of allylic alcohol **204**



Silyl ether 209. To allylic alcohol **204** (22.0 mg, 24.7 μmol, 1 eq) and imidazole (3.40 mg, 49.4 μmol, 2 eq) in DMF (0.3 mL), TESCl (4.7 μL, 32.1 μmol, 1.3 eq) was added. The mixture was stirred at room temperature for 20 h. Then, EtOAc was added and the mixture washed three times with 10% aqueous LiCl solution, the organic phase dried (Na_2SO_4) and concentrated

under reduced pressure. Flash column chromatography (7:1 *n*-pentane/EtOAc) yielded silyl ether**209** (15.0 mg, 16.5 μmol, 67%) as a light yellow oil.

Physical state: light yellow oil

$\mathbf{R}_f$ = 0.89 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ = −5.6 (*c* = 0.50 in $CHCl_3$)

*Note: At room temperature compounds **209** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.81 – 7.78 (m, 2H), 7.77 – 7.69 (m, 3H), 7.67 – 7.63 (m, 2H), 7.45 – 7.41 (m, 2H), 7.37 – 7.30 (m, 3H), 5.42 – 5.36 (m, 2H), 5.00 – 4.96 (m, 1H), 4.96 – 4.91 (m, 1H), 4.90 – 4.83 (m, 1H), 4.55 (d, *J* = 6.6 Hz, 2H), 4.34 (t, *J* = 7.0 Hz, 1H), 4.14 – 4.10 (m, 1H), 3.90 – 3.80 (m, 6H), 3.59 – 3.57 (m, 1.5H), 3.57 – 3.55 (m, 1.5H), 2.90 (ddd, *J* = 18.0, 10.9, 4.6 Hz, 0.5H), 2.80 (ddd, *J* = 17.8, 10.2, 5.7 Hz, 0.5H), 2.69 (ddd, *J* = 17.9, 10.0, 6.0 Hz, 0.5H), 2.59 (ddd, *J* = 18.0, 10.6, 5.0 Hz, 0.5H), 2.52 – 2.48 (m, 3H), 2.03 – 1.98 (m, 3H), 1.97 – 1.90 (m, 1H), 1.85 – 1.77 (m, 1H), 1.66 – 1.58 (m, 1H), 1.54 – 1.45 (m, 1H), 1.31 – 1.27 (m, 1H), 1.15 (d, *J* = 6.6 Hz, 1.5H), 1.11 (d, *J* = 6.4 Hz, 1,5H), 0.88 – 0.83 (m, 6H), 0.80 (t, *J* = 7.9 Hz, 3H), 0.58 – 0.48 (m, 4H), 0.48 – 0.44 (m, 2H) ppm.

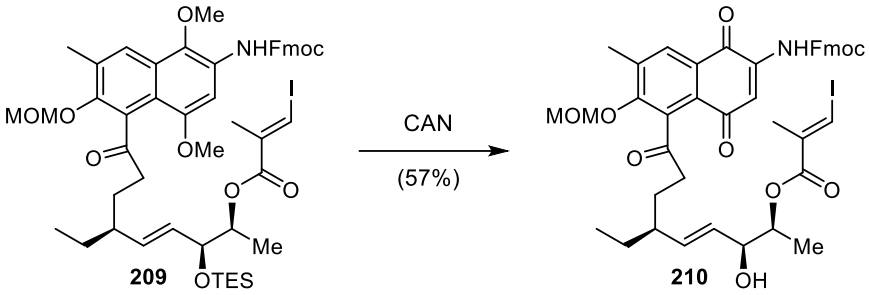
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 206.67, 206.62, 163.19, 153.53, 151.34, 149.57, 149.46, 143.79, 141.51, 140.11, 137.33, 136.50, 136.18, 133.19, 133.14, 131.59, 131.55, 129.48, 129.33, 128.00, 127.46, 127.28, 125.72, 125.14, 123.12, 120.26, 118.61, 118.56, 117.81, 101.77, 101.72, 99.08, 98.41, 74.41, 67.31, 61.67, 57.78, 57.71, 56.48, 56.43, 47.29, 44.26, 44.16, 43.53, 43.34, 28.63, 28.59, 28.08, 28.05, 20.39, 17.83, 14.92, 11.83, 11.79, 6.93, 6.87, 6.82, 5.02, 4.97. ppm.

IR (ATR, film): $\tilde{\nu}$ = 2955 (m), 1735 (m), 1710 (s), 1627 (m), 1603 (w), 1498 (m), 1459 (m), 1407 (w), 1378 (w), 1290 (m), 1158 (m), 1050 (m), 982 (m), 929 (m) 741 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{51}H_{68}N_2ISiO_{10}^+$: 1023.3682 $[M+NH_4]^+$

found: 1023.3679 $[M+NH_4]^+$

Oxidation of benzohydroquinone**209**



Naphthoquinone 210. Methyl ether**209** (4.20 mg, 4.17 μmol, 2 eq) was dissolved in wet MeCN (0.4 mL, 5% H_2O), cooled to 0 °C and a solution of CAN (4.80 mg, 8.77 μmol, 2.1 eq) in 1:1 MeCN:H_2O(50 μL) was added. After 30 min at 0 °C, the mixture was diluted with EtOAc, washed successively with water, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure.Flash column chromatography (3:1 n-pentane:EtOAc) afforded naphthoquinone**210** (2.00 mg, 2.32 μmol, 56%) as a yellow oil.

Physical state: yellow oil

R_f = 0.82 (2:1 hexane:EtOAc)

*Note: At room temperature compounds **210** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

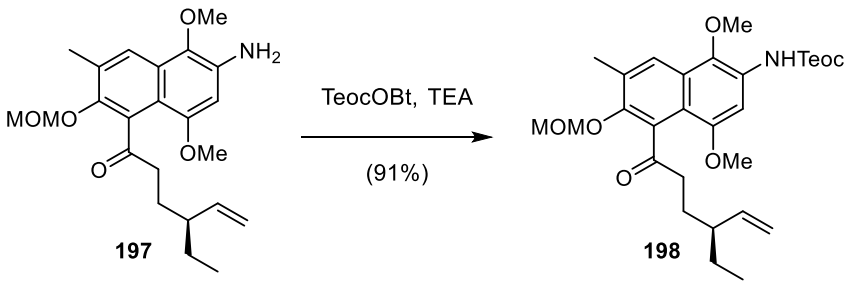
^{1}H-NMR (800 MHz, $CDCl_3$): δ = 7.99 (s, 1H), 7.89 – 7.87 (m, 1H), 7.81 – 7.78 (m, 2H), 7.78 – 7.76 (m, 1H), 7.62 – 7.59 (m, 2H), 7.45 – 7.42 (m, 2H), 7.42 – 7.38 (m, 1H), 7.36 – 7.33 (m, 2H), 5.54 – 5.41 (m, 2H), 5.00 – 4.96 (m, 2H), 4.93 – 4.89 (m, 1H), 4.59 – 4.56 (m, 2H), 4.28 (t, *J* = 6.8 Hz, 1H), 4.12 – 4.08 (m, 1H), 3.57 – 3.54 (m, 3H), 2.81 (ddd, *J* = 17.8, 8.9, 4.5 Hz, 0.5H), 2.73 (ddd, *J* = 16.6, 9.5, 5.8 Hz, 0.5H), 2.61 (ddd, *J* = 18.1, 9.1, 4.6 Hz, 0.5H), 2.54 (ddd, *J* = 16.4, 7.0 Hz, 7.0 Hz, 0.5H), 2.47 – 2.43 (m, 3H), 2.08 – 2.05 (m, 0.5H), 2.02 (d, *J* = 2.6 Hz, 3H), 2.01 – 1.96 (m, 0.5H), 1.81 – 1.75 (m, 0.5H), 1.73 – 1.67 (m, 0.5H), 1.51 (dt, *J* = 13.2, 6.6 Hz, 1.5H), 1.35 – 1.26 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 0.88 – 0.85 (m, 3H) ppm.

^{13}C-NMR (200 MHz, $CDCl_3$): δ = 204.96, 179.56, 163.48, 152.18, 143.95, 143.33, 141.51, 140.68, 139.92, 139.08, 138.78, 130.84, 129.57, 129.23, 128.99, 128.15, 127.87, 127.38, 127.20, 126.48, 125.16, 125.02, 120.36, 120.15, 115.53, 101.53, 101.27, 98.99, 75.39, 74.60, 74.52, 68.19, 67.08, 47.25, 46.94, 44.20, 43.83, 41.86, 41.70, 33.38, 32.08, 29.85, 28.22, 22.85, 20.46, 17.58, 16.29, 14.28, 11.93 ppm.

HRMS (+ESI): calc. for $C_{43}H_{48}N_2IO_{10}^+$: 879.2348 $[M+NH_4]^+$

found: 879.2340 $[M+NH_4]^+$

Teoc-protection of naphthyl amine **196**



Carbamate 198. To a solution of naphthyl amine**197** (70.5 mg, 176 µmol, 1 eq) in DCM (3.0 mL), TEA (48.6 µL, 351 µmol, 2 eq) and TeocOBt (98.1 mg, 351 µmol, 2 eq)were added. The reaction vessel was sealed and heated in a 50 °C oil bath for 48 h. Then, the reaction was diluted with DCM and aqueous NH_4Cl solution. The biphasic mixture was extracted three times with DCM, the combined organic phases washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (15:1 →1:1 *n*-pentane:EtOAc) afforded carbamate **198** (88.0 mg, 161 µmol, 91%) as a light yellow oil.

Physical state: light yellow oil

$\mathbf{R_f}$ = 0.61 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ =–3.7 (*c* = 0.70 in $CHCl_3$)

*Note: At room temperature compounds **198** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.78 (s, 1H), 7.72 (s, 1H), 7.24 (s, 1H), 5.62 – 5.42 (m, 1H), 5.02 – 4.89 (m, 4H), 4.34 – 4.25 (m, 2H), 3.91 – 3.84 (m, 3H), 3.83 (s, 3H), 3.61 – 3.54 (m, 3H), 2.92 (ddd, *J* = 18.3, 11.0, 4.5 Hz, 0.5H), 2.81 (ddd, *J* = 18.0, 10.1, 5.8 Hz, 0.5H), 2.68 (ddd, *J* = 17.9, 9.8, 6.0 Hz, 0.5H), 2.57 (ddd, *J* = 18.2, 10.7, 5.1 Hz, 0.5H), 2.49 (s, 3H), 2.01 – 1.94 (m, 0.5H), 1.93 – 1.84 (m, 1H), 1.84 – 1.74 (m, 1H), 1.62 – 1.57 (m, 0.5H), 1.51 – 1.42 (m, 1H), 1.33 – 1.27 (m, 1H), 1.13 – 1.05 (m, 2H), 0.89 – 0.84 (m, 3H), 0.08 (s, 9H) ppm.

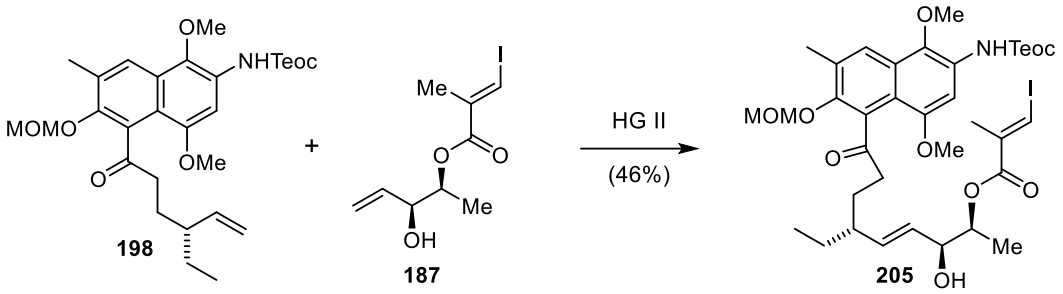
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 207.05, 206.99, 153.94, 151.32, 149.23, 149.14, 142.60, 142.55, 135.74, 133.04, 131.66, 131.61, 127.82, 125.70, 123.06, 118.32, 115.15, 115.04, 101.68, 101.58, 63.91, 61.59, 57.78, 56.39, 56.33, 45.46, 45.44, 43.26, 43.17, 29.41, 28.24, 28.21, 27.95, 27.76, 17.87, 17.81, 11.80, 11.78, −1.32 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3432 (br w), 2956 (m), 1731 (s), 1709 (m), 1606 (m), 1498 (s), 1407 (m), 1368 (w), 1249 (m), 1228 (s), 1204 (s), 1049 (s), 990 (m), 928 (m), 839 (m), 766 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{29}H_{44}NSiO_7^+$: 546.2882 $[M+H]^+$

found: 546.2882 $[M+H]^+$

Olefin cross metathesis of alkenes **198** and **187**



Olefin 205. To a solution of alkene **198** (24.4 mg, 44.7 μmol, 1 eq) and allylic alcohol **187** (26.0 mg, 87.8 μmol, 2 eq) in degassed toluene (0.3 mL) Hoveyda-Grubbs 2nd genearation catalyst (5.60 mg, 8.7 μmol, 0.2 eq) was added and the reaction was heated to 40 °C for 40 h. Concentration under reduced pressure followed by flash column chromatography (2:1 *n*-pentane:Et_2O) afforded alkene **205** (16.9 mg, 20.8 μmol, 46%) as a light yellow oil.

Physical state: light yellow oil

$\mathbf{R_f}$ = 0.30 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +4.6 (*c* = 0.78 in $CHCl_3$)

*Note: At room temperature compounds **205** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.78 (br s, 2H), 7.72 (s, 1H), 7.24 (s, 1H), 5.53 – 5.36 (m, 2H), 4.96 (s, 2H) 4.93 – 4.86 (m, 1H), 4.34 – 4.27 (m, 2H), 4.11 – 4.03 (m, 1H), 3.89 – 3.84 (m, 3H), 3.83 (s, 3H), 3.58– 3.57 (m, 1.5H), 3.56 – 3.53 (m, 1.5H), 2.92 – 2.56 (m, 2H), 2.48 –2.46 (m, 3H), 2.17 (br s, 0.5H) 2.04 – 1.94 (m, 4H), 1.84 – 1.77 (m, 1H), 1.63 (s, 1H), 1.53 – 1.43 (m, 1H), 1.30 – 1.20 (m, 4H), 1.12 – 1.06 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.08 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.66, 206.45, 163.45, 153.92, 151.27, 149.27, 149.10, 139.88, 139.85, 139.05, 138.96, 135.79, 132.98, 132.80, 131.48, 131.28, 129.27, 129.11, 127.87, 125.70, 123.23, 123.14, 118.29, 101.67, 101.27, 99.06, 99.02, 75.40, 75.31, 74.60, 74.38, 63.91, 61.60, 57.87, 57.71,

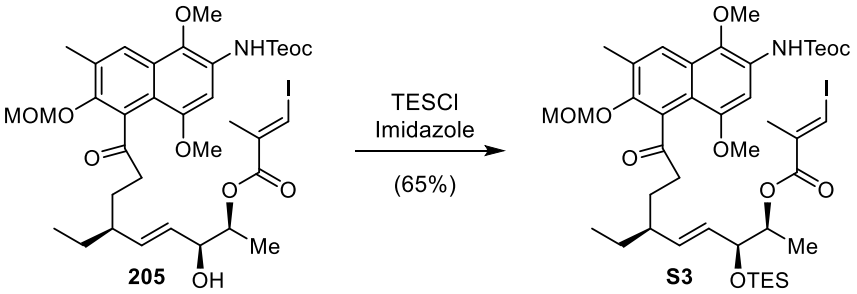
56.48, 56.46, 44.19, 43.93, 43.36, 28.40, 28.21, 28.04, 27.99, 20.45, 17.89, 17.85, 16.22, 11.91, −1.32 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3429 (br w), 2955 (m), 1709 (s), 1627 (m), 1498 (m), 1406 (w), 1292 (m), 1215 (s), 1101 (m), 1047 (s), 987 (m), 838 (m), 757 (w), 692 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{36}H_{56}N_2ISiO_{10}^+$: 831.2743 $[M+NH_4]^+$

found: 831.2751 $[M+NH_4]^+$

TES-protection of allylic alcohol **205**



Silyl ether S3. To allylic alcohol **205** (6.2 mg, 7.6 µmol, 1 eq) and imidazole (1.0 mg, 15.2 µmol, 2 eq) in DMF (0.1 mL), TESCl (1.4 µL, 8.40 µmol, 1.1 eq) was added. The mixture was stirred at room temperature for 16 h. Then, Et_2O was added and the mixture washed three times with 10% aqueous LiCl solution, the organic phase dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (2:1 *n*-pentane/Et_2O) yielded silyl ether**S3** (4.2 mg, 4.9 µmol, 65%) as a colorless yellow oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.74 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = −3.8 (*c* = 0.26 in $CHCl_3$)

*Note: At room temperature compounds **S3** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1H), 7.74 – 7.68 (m, 2H), 7.24 (s, 1H), 5.42 – 5.32 (m, 2H), 4.99 – 4.89 (m, 2H), 4.89 – 4.81 (m, 1H), 4.33 – 4.26 (m, 2H), 4.15 – 4.07 (m, 1H), 3.89 – 3.84 (m, 3H), 3.84 – 3.79 (m, 3H), 3.58 – 3.54 (m, 3H), 2.97 – 2.53 (m, 2H), 2.50 – 2.46 (m, 3H), 2.03 – 1.99 (m, 3H), 1.99 – 1.95 (m, 0.5H), 1.95 – 1.88 (m, 1H), 1.82 – 1.77 (m, 0.5H), 1.65 – 1.59 (m, 1H), 1.52 –

1.45 (m, 1H), 1.32 – 1.27 (m, 1H), 1.15 (d, *J* = 6.5 Hz, 1.5H), 1.12 – 1.07 (m, 3.5H), 0.93 – 0.83 (m, 9H), 0.81 – 0.77 (m, 3H), 0.56 – 0.40 (m, 6H), 0.09 – 0.06 (m, 9H) ppm.

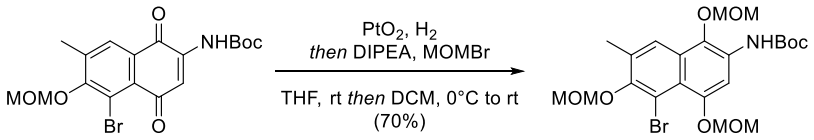
^{13}C-NMR (200 MHz, $CDCl_3$): δ = 206.73, 206.68, 163.21, 163.19, 153.92, 153.87, 151.32, 151.29, 149.39, 149.27, 140.12, 137.37, 137.34, 135.85, 133.07, 133.02, 131.55, 131.51, 129.48, 129.32, 127.87, 127.84, 125.73, 123.05, 118.36, 118.31, 101.75, 101.70, 98.98, 98.40, 74.43, 74.41, 63.89, 61.58, 61.56, 57.77, 57.69, 56.43, 56.38, 44.26, 44.15, 43.52, 43.34, 29.85, 28.64, 28.59, 28.08, 28.03, 20.38, 17.90, 17.81, 17.79, 14.92, 11.82, 11.78, 6.92, 6.90, 6.86, 6.80, 5.05, 5.02, 4.96, −1.31 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3425 (br w), 2954 (m), 1712 (s), 1627 (w), 1604 (w), 1498 (m), 1459 (m), 1407 (w), 1291 (w), 1249 (m), 1227 (s), 1175 (m), 1051 (s), 929 (m), 838 (m), 744 (w), 727 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{52}H_{70}N_2ISi_2O_{10}^+$: 945.3608 $[M+NH_4]^+$

found: 945.3612 $[M+NH_4]^+$

Reduction and MOM-protection of quinone **142**



142 **212**

***tert*-butyl 5-bromo-1,4,6-tris(methoxymethoxy)-7-methylnaphthalen-2-yl)carbamate (212)**.

Quinone **142**[1] (500 mg, 1.18 mmol. 1 eq) and PtO_2(40.0 mg, 176 μmol) were dissolved in degassed THF (30 mL) under argon, resulting in a bright yellow solution. Then, the solution was purged with H_2 until it appeared colorless (40 min). The flask was then purged with argon, DCM (100 mL) was added and the solution cooled to 0 °C. DIPEA (2.00 mL, 11.8 mmol, 10 eq) was added drop wise and the solution was stirred at room temperature for 30 min. Then, after cooling to 0 °C, MOMBr (554 μL, 7.05 mmol, 6 eq) was added drop wise and the mixture stirred at room temperature for 19 h. Then, while cooling with an ice bath, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The biphasic mixture was extracted three times with EtOAc, the combined organic extracts washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 15:1 →10:1 *n*-pentane:EtOAc) afforded MOM ether **212** (428 mg, 0.829 mmol, 70%) as a pale yellow solid.

[1] **142** prepared according to Hager, A.; Kuttruff, C. A.; Hager, D.; Terwilliger, D. W.; Trauner, D. *Synlett*, **2013**, *24*, 1915–1920

Physical state: pale yellow solid

R_f = 0.41 (5:1 hexane:EtOAc)

Melting point: 82–83 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1H), 7.68 (q, *J* = 1.0 Hz, 1H), 7.68 (s, 1H), 5.32 (s, 2H), 5.16 (s, 2H), 5.07 (s, 2H), 3.68 (s, 3H), 3.66 (s, 3H), 3.61 (s, 3H), 2.51 (d, *J* = 1.0 Hz, 3H), 1.54 (s, 9H) ppm.

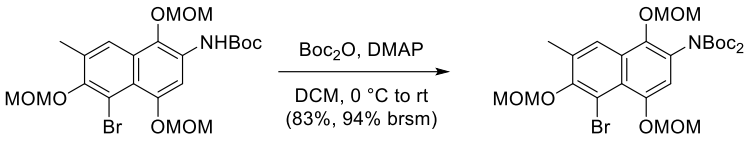
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 152.8, 152.7, 149.8, 134.7, 133.2, 129.1, 128.1, 122.3, 120.5, 111.8, 105.2, 100.9, 100.3, 95.7, 80.7, 58.0, 57.9, 57.1, 28.5, 18.7 ppm.

IR (ATR, solid): $\tilde{\nu}$ = 3337 (w), 2928 (br, w), 1727 (m), 1626 (m), 1504 (m), 1426 (w), 1391 (w), 1368 (m), 1306 (m), 1227 (m), 1144 (s), 1062 (s), 1017 (s), 984 (w), 948 (s), 876 (m), 822 (w), 758 (m), 712 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{22}H_{34}BrN_2O_8^+$: 553.1493 [^{79}Br, M+NH_4]$^+$

found: 553.1493 [^{79}Br, M+NH_4]$^+$

Boc-protection of carbamate**212**



212 **216**

***N,N*-di-Boc protected naphthalene (216)**. Carbamate **212** (465 mg, 900 µmol, 1 eq) and DMAP (165 mg, 1.35 mmol, 1.5 eq) were dissolved in DCM (28 mL). Di-*tert*-butyl dicarbonate (983 mg, 4.50 mmol, 5 eq) was added as a solution in DCM (9.5 mL). After 16 h of stirring at room temperature, an additional amount of di-*tert*-butyl dicarbonate (197 mg, 900 µmol, 1 eq) and DMAP (55.0 mg, 450 µmol, 0.5 eq) was added. After five more hours of stirring at room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl. The biphasic mixture was extracted three times with DCM, the combined organic layers washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Two consecutive rounds of flash column chromatography (silica, 10:1 → 5:1 *n*-pentane:EtOAc) afforded reisolated carbamate **212** (54 mg, 105 µmol, 12%) as well as the di-Boc protected title compound **216** (461 mg, 748 µmol, 83%, 94% brsm) as a colorless oil.

Physical state: colorless oil

R_f = 0.54 (3:1 hexane:EtOAc)

^{1}H-NMR (400 MHz, $CDCl_3$): δ =7.95 (q, *J* = 0.9 Hz, 1H), 6.94 (s, 1H), 5.23 (s, 2H), 5.18 (s, 2H), 5.03 (s, 2H), 3.69 (s, 3H), 3.60 (s, 3H), 3.57 (s, 3H), 2.53 (d, *J* = 1.0 Hz, 3H), 1.40 (s, 18H) ppm.

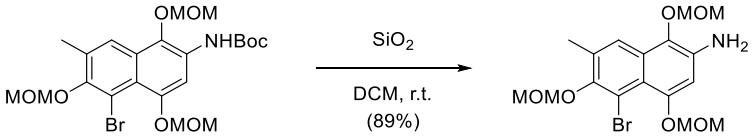
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.4, 151.3, 149.3, 142.9, 133.0, 128.7, 128. 5, 124.4, 124.3, 113.5, 111.5, 100.3, 100.2, 100.1, 96.1, 82.9, 58.03, 57.98, 56.5, 28.0, 18.6 ppm.

IR (ATR, film): $\tilde{\nu}$ = 2979 (w), 1790 (m), 1752 (m), 1717 (m), 1606 (w), 1570 (w), 1457 (w), 1369 (m), 1317 (m), 1275 (s), 1252 (m), 1152 (vs), 1099 (s), 1022 (m), 949 (s), 890 (w), 854 (w), 779 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{27}H_{39}BrNO_{10}^+$: 616.1752 [^{79}Br, M+H]$^+$

found: 616.1779 [^{79}Br, M+H]$^+$

Boc-deprotection of hydroquinone **212**



212 **213**

2-amino-5-bromo-1,4,6-tri(methoxymethoxy)-7-methyl-naphthalene (213).

SiO_2 (680 mg, 11.3 mmol, 117 eq) was added to a stirred solution of MOM-protected hydroquinone **6** (50.0 mg, 96.8 μmol, 1 eq) in 5 mL DCM at room temperature. Subsequently the solvent was removed on a a rotary evaporator and the residue was heated to 80 °C and vacuum applied (0.05 mbar). The reaction was stopped 19 h later by transferring the adsorbed crude product as a dry load to gradient flash column chromatography (5:1⟶2:1 *n*-pentane/EtOAc) yielding free amine **213** (36 mg, 86.5 μmol, 89%).

Physical state: red oil

R_f = 0.26 (1:1 hexanes/EtOAc)

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.87 (d, *J* = 1.1 Hz, 1H), 6.72 (s, 1H), 5.15 (s, 2H), 5.05 (s, 2H), 4.85 (s, 2H), 3.65 (br, d, *J* = 33.3 Hz, 2H), 3.43 (s, 3H), 3.35 (s, 3H), 3.30 (s, 3H), 2.49 (d, *J* = 1.0 Hz, 3H) ppm.

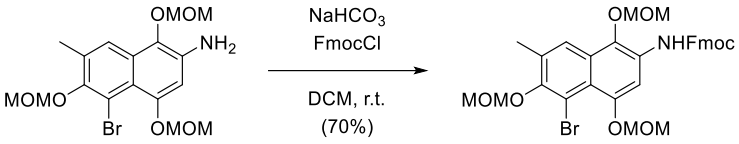
^{13}C-NMR (100 MHz, C_6D_6) δ = 151.76, 151.00, 136.77, 133.14, 131.96, 130.07, 128.59, 121.92, 118.51, 112.39, 104.95, 100.39, 99.96, 95.62, 57.33, 55.97, 18.71ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3454 (br, w), 3365 (w), 2938 (br, w), 2360 (w), 1629 (s), 1432 (w), 1374 (m), 1213 (m), 1236 (m), 1152 (s), 1070 (m), 1016 (m), 961 (s), 779 (w) cm^{-1}.

HRMS ((+)-ESI): calc. for $[C_{17}H_{23}O_6N^{79}Br]^+$: 416.0703 $[M+H]^+$

found: 416.0707 $[M+H]^+$

Fmoc-protection to free amine **213**



213 **214**

Fmoc naphthalene 214. Free amine **213** (36.0 mg, 86.5 μmol, 1 eq) was dissolved in 2.8 mL DCM at room temperature. After addition of $NaHCO_3$ (21.8 mg, 25.9 μmol, 3 eq) and FmocCl (33.6 mg, 130 μmol, 1.5 eq) the mixture was stirred for 15 h at room temperature, followed by quenching the reaction with 10 mL EtOAc and 10 mL aqueous sat. NH_4Cl solution. Thereafter the mixture was extracted with EtOAc (3× 10 mL) and the combined organic layers were dried over $MgSO_4$ to obtain after concentration under reduced pressure the crude product. Purification through flash column chromatography (3:1 *n*-pentane/EtOAc) yielded Fmoc-protected hydroquinone **214** (38.9 mg, 60.9 μmol, 70%).

Physical state: yellow oil

R_f= 0.50 (3:1 hexanes/EtOAc)

^{1}H-NMR (400 MHz, $CDCl_3$): δ =8.09 (br, s, 2H), 7.78 (dt, *J* = 7.5, 0.9 Hz, 2H), 7.70 (d, *J* = 1.1 Hz, 1H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.42 (tt, *J* = 7.4, 0.9 Hz, 2H), 7.33 (td, *J* = 7.4, 1.2 Hz), 5.32 (s, 2H), 5.17 (s, 2H), 5.09 (s, 2H), 4.55 (d, *J* = 6.9 Hz, 2H), 4.32 (t, *J* = 6.9 Hz, 1H), 3.69 (s, 3H), 3.60 (d, *J* = 1.6 Hz, 6H), 2.53 (d, *J* = 0.9 Hz, 3H) ppm.

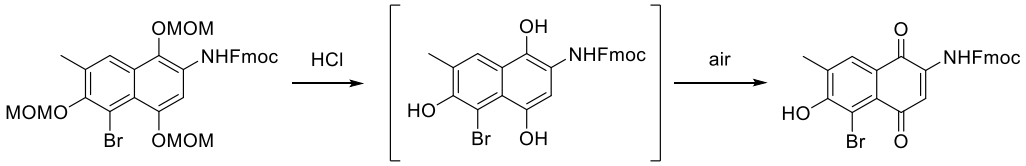
^{13}C-NMR (100 MHz, $CDCl_3$) δ = 153.31, 152.84, 149.85, 143.79, 141.37, 135.11, 133.24, 128.19, 128.03, 127.77, 127.11, 125.03, 122.22, 120.70 120.02, 111.72, 104.93, 101.07, 95.70, 66.93, 57.87, 57.64, 56.82, 47.08, 18.54 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2950 (m), 2360 (w), 1734 (s), 1626 (s), 1575 (w), 1513 (s), 1480 (m), 1450 (m), 1427 (w), 1393 (w), 1359 (w), 1315 (m), 1242 (m), 1206 (s), 1154 (s), 1070 (m), 1031 (s), 958 (s), 924 (s), 758 (m), 741 (m), 621 (w) cm^{-1}.

HRMS ((+)-ESI): calc. for $[C_{30}H_{17}O_5N_2{}^{79}Br]^+$: 655.1650 $[M-NH_4]^+$

found: 655.1654 $[M-NH_4]^+$

MOM-deprotection and oxidation of the hydroquinone**214**



214 **215**

Quinone 215.HCl (sat. in MeOH, 100 μL) was added to a stirred solution of Fmoc-protected hydroquinone **214** (5.0 mg, 7.83 μmol, 1 eq) in a mixture of MeOH and EtOAc (1.5 mL, 2:1) at room temperature on air. The reaction was quenched 70 min later by addition of aqueous $NaHCO_3$ solution (10 mL, sat.) and subsequently extracted with EtOAc (3× 10 mL), followed by washing the combined organic layers with 10 mL brine. Through drying over Na_2SO_4 and concentration under reduced pressure crude product was obtained, which was subjected to flash column chromatography (3:1 *n*-pentane/EtOAc) yielding Fmoc-protected naphthoquinone**215** (2.7 mg, 5.35 μmol, 86%).

Physical state: yellow oil

R_f= 0.37 (3:1 hexanes/EtOAc)

^{1}H-NMR (400 MHz, DMSO-d_6): 10.43 (s, 1H), 9.63 (d, *J* = 2.2 Hz, 1H), 7.94– 7.77 (m, 5H, H-6), 7.43 (td, *J*= 7.5, 1.1 Hz, 2H), 7.34 (td, *J*= 7.5, 1.2 Hz, 2H), 7.22 (s, 1H), 4.43 (d, *J* = 7.2 Hz, 2H), 4.30 (t, *J*= 7.1 Hz, 1H), 2.36 (s, 3H) ppm.

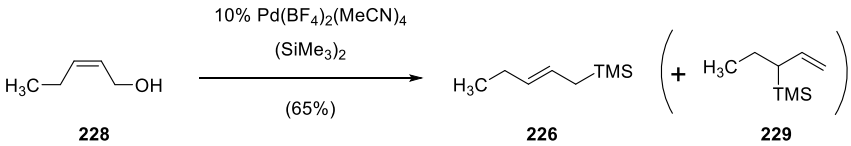
^{13}C-NMR (101 MHz, DMSO-d_6) δ = 183.89, 178.92, 159.18, 153.48, 143.94, 141.17, 141.10, 131.24, 129.57, 128.44, 128.26, 127.61, 125.99, 125.10, 120.61, 116.94, 109.95, 67.68, 46.68, 17.88 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3410 (br, w), 2923 (m), 2361 (m), 1741 (m), 1662 (m), 1586 (w), 1511 (s), 1450 (w), 1329 (s), 1197 (s), 1026 (m), 802 (w), 741 (m), 667 (w) cm^{-1}.

HRMS ((+)-ESI): calc. for $[C_{26}H_{17}O_5NBr]^-$: 502.0296 $[M-H]^-$

found: 502.0296 $[M-H]^-$

C-OH functionalization of allylic alcohol **228**



228 **226** **229**

(*E*)-trimethyl(pent-2-en-1-yl)silane(226). To a solution of allylic alcohol **228** (5.15 mL, 51.0 mmol, 1.0 eq) in DMSO (60 mL) and MeOH (60 mL), $Pd(BF_4)_2(MeCN)_4$[I] (2.27 g, 5.10 mmol, 0.1 eq) and Me_6Si_2 (11.0 mL, 53.5 mmol, 1.05 eq) were added. The mixture was heated to 50 °C for 10 h, let come to room temperature and was poured on a silica gel column (equilibrated with 98:2 *n*-pentane:Et_2O) and eluted with *n*-pentane. Volatile allyl silane **226** (4.69 g, 33.0 mmol, 65%, 5–10% secondary silane **229**) was carefully concentrated on a rotary evaporator to give a 50 wt% colorless solution in *n*-pentane.

Physical state: colorless liquid

$\mathbf{R_f}$ = 0.95 (*n*-pentane)

*Note: To obtain an analytical sample of **20**, a small amount was briefly concentrated under high vacuum.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.43 – 5.23 (m, 2H), 1.98 (m, 2H), 1.41 – 1.35 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H), −0.02 (s, 9H) ppm.

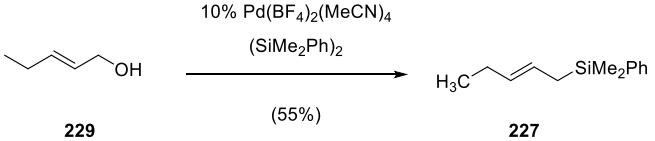
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 130.8, 125.1, 26.0, 22.6, 14.6, −1.9 ppm.

IR (ATR): $\tilde{\nu}$ = 2956 (w), 2896 (w), 1461 (w), 1404 (w), 1291 (w), 1246 (m), 1156 (w), 1091 (w), 1049 (w), 986 (w), 962 (w), 897 (w), 833 (s), 747 (w), 721 (w), 690 (m) cm^{-1}.

HRMS (+EI): calc. for $C_8H_{18}Si^+$: 142.1178 $[M]^+$

found: 142.1178 $[M]^+$

C-OH functionalization of allylic alcohol **229**



229 **227**

Allyl silane 227..To a solution of allylic alcohol **229** (894 µL, 8.80 mmol, 1.0 eq) in DMSO (6.1 mL) and MeOH (6.2 mL), $Pd(BF_4)_2(MeCN)_4$ (196 mg, 441µmol, 0.05 eq) and

[I] $Pd(BF_4)_2(MeCN)_4$ prepared according to Bigi, M. A.; White, C. M. *J. Am. Chem. Soc.*, **2013**, *135*, 7831–7834

$Ph_2Me_4Si_2$(2.86 g, 10.6 mmol, 1.2 eq) were added over the course of two hours. The mixture was heated to 50 °C for 16 h, let come to room temperature and was poured on a silica gel column (equilibrated with 98:2 *n*-pentane:Et_2O) and eluted with *n*-pentane.Allyl silane **227** (991 mg, 4.85 mmol, 55%) was obtained as a colorless liquid.

Physical state: colorless liquid

$\mathbf{R_f}$ = 0.56 (*n*-pentane)

^{1}H-NMR (400 MHz, $CDCl_3$): δ =7.43 – 7.39 (m, 1H), 7.26 – 7.24 (m, 2H), 5.33 – 5.16 (m, 1H), 1.92 – 1.82 (m, 1H), 1.58 – 1.52 (m, 1H), 0.83 (t, *J* = 7.4 Hz, 2H), 0.16 (s, 3H).ppm.

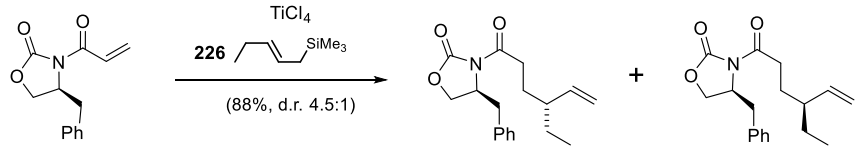
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 139.21, 133.79, 131.60, 129.01, 127.84, 127.81, 124.41, 26.00, 21.64, 14.54, −3.28 ppm.

IR (ATR): $\tilde{\nu}$ = 3069 (w), 3050 (w), 3016 (w), 2958 (m), 2930 (w), 1460 (w), 1297 (w), 1156 (w), 1047 (w), 984 (w), 900 (w), 830 (s), 787(w), 729 (m), 709 (w), 698 (m) cm^{-1}.

HRMS (+EI): calc. for $C_{13}H_{20}Si^+$: 204.1334 $[M]^+$

found: 204.1326 $[M]^+$

Hosomi-Sakurai reaction of enone**230**and allyl silane **226**



230 **236** ***ent*-237**

(*S*)-4-benzyl-3-((*R*)-4-ethylhex-5-enoyl)oxazolidin-2-one (236). Acrylated Evans auxiliary **230**[I](1.28 g, 5.56 mmol, 1 eq) was dissolved in DCM (52 mL) and cooled to −78 °C. A solution of $TiCl_4$ (7.75 mL, 1 M in DCM, 7.75 mmol, 1.4 eq) was added drop wise under vigorous stirring and the mixture was stirred for 10 min at −78 °C. Then a solution of allyl silane **226** (1.57 g, 50wt% in *n*-pentane, 11.1 mmol, 2 eq) in DCM (12 mL), cooled to −78 °C, was added rapidly *via* cannula. Upon addition of the silane, the orange suspension turned deep purple. After one hour and 20 min at −78 °C, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ until the purple color faded. Then, more saturated aqueous $NaHCO_3$ and EtOAc were added and the mixture was warmed to room temperature over the course of one hour. The biphasic

[I]**230** prepared according to Evans, D. A.; Chapman, K. T.; Bisha, J. *J. Am. Chem. Soc.*, **1998**, *110*, 1238–1256

mixture was then extracted three times with EtOAc, the combined organic extracts washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 8:1 *n*-pentane:EtOAc) afforded olefins **236** and *ent*-**237** (1.48 g, 4.89 mmol, 88%) as a 4.5:1 mixture of diastereomers.

Olefin 236 (major diastereomer):

Physical state: colorless oil

$\mathbf{R_f}$ = 0.59 (4:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +102 (*c* = 0.69 in $CHCl_3$)

^{1}H-NMR (800 MHz, $CDCl_3$): δ = 7.34 – 7.31 (m, 2H), 7.29 – 7.26 (m, 1H), 7.22 – 7.19 (m, 2H), 5.53 (ddd, *J* = 17.1, 10.2, 8.9 Hz, 1H), 5.04 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.01 (ddd, *J* = 17.1, 2.0, 0.8 Hz, 1H), 4.66 (ddt, *J* = 9.6, 7.7, 3.1 Hz, 1H), 4.18 (dd, *J* = 8.8, 8.0 Hz, 1H), 4.15 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.29 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.95 – 2.90 (m, 2H), 2.77 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.00 – 1.95 (m, 1H), 1.83 (dddd, *J* = 13.5, 8.9, 7.0, 4.6 Hz, 1H), 1.62 – 1.56 (m, 2H), 1.50 – 1.44 (m, 1H), 1.35 – 1.28 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C-NMR (200 MHz, $CDCl_3$): δ = 173.7, 153.5, 142.1, 135.5, 129.6, 129.1, 127.5, 115.6, 66.3, 55.3, 45.5, 38.1, 33.6, 29.0, 27.9, 11.7 ppm.

IR (ATR, film): $\tilde{\nu}$ = 2960 (w), 2925 (w), 2874 (w), 2361 (w), 1776 (s), 1696 (s), 1454 (w), 1383 (m), 1351 (m), 1290 (w), 1249 (m), 1210 (s), 1195 (s), 1154 (w), 1099 (m), 1076 (m), 1051 (m), 997 (m), 913 (m), 842 (w), 760 (m), 743 (m), 700 (s),674 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{18}H_{24}NO_3^+$: 302.1751 $[M+H]^+$

found: 302.1758 $[M+H]^+$

Olefin *ent*-237 (minor diastereomer):

Physical state: colorless oil

$\mathbf{R_f}$ = 0.58 (4:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = −62 (*c* = 0.45 in $CHCl_3$)

^{1}H-NMR (800 MHz, $CDCl_3$): 7.35 – 7.31 (m, 2H), 7.29 – 7.26 (m, 1H), 7.22 – 7.19 (m, 2H), 5.53 (ddd, *J* = 17.1, 10.2, 8.8 Hz, 1H), 5.04 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.01 (ddd, *J* = 17.1, 2.0, 0.8 Hz, 1H), 4.66 (ddt, *J* = 9.9, 7.7, 3.1 Hz, 1H), 4.19 (dd, *J* = 8.7, 7.8 Hz, 1H), 4.15 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.30 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.97 (ddd, *J* = 17.1, 9.3, 5.4 Hz, 1H), 2.88 (ddd, *J* = 17.1, 9.3, 6.4 Hz, 1H), 2.75 (dd, *J* = 13.4, 9.7 Hz, 1H), 1.99 – 1.93 (m, 1H), 1.80 (dddd, *J* = 13.8, 9.3, 6.4, 4.6 Hz, 1H), 1.63

(dddd, *J* = 13.6, 9.4, 9.4, 5.5 Hz, 1H), 1.50 – 1.44 (m, 1H), 1.31 (ddq, *J* = 13.5, 8.7, 7.4 Hz, 1H), 0.88 (t, *J* = 7.4 Hz, 3H)ppm.

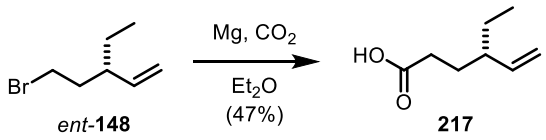
^{13}C-NMR (200 MHz, $CDCl_3$): δ = 173.7, 153.5, 142.1, 135.5, 129.6, 129.1, 127.5, 115.6, 66.3, 55.3, 45.6, 38.1, 33.6, 29.0, 27.9, 11.7 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3067 (w), 3030 (w), 2962 (w), 2926 (w), 2874 (w), 1781 (s), 1698 (m), 1641 (w), 1498 (w), 1481 (w), 1454 (w), 1385 (m), 1352 (m), 1324 (w), 1290 (w), 1251 (w), 1211 (m), 1196 (m), 1154 (w), 1100 (w), 1077 (w), 1053 (w), 998 (w), 915 (w), 915 (w), 762 (w), 743 (w), 702 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{18}H_{24}NO_3^+$: 302.1751 $[M+H]^+$

found: 302.1758 $[M+H]^+$

Carboxylation of bromide ent-**148**



ent-**148** **217**

Carboxylic acid 217. Mg turnings (26.0 mg) were dried in a pressure tube (650 °C), and the tube backfilled with argon. Then, Et_2O (1 mL) and 1,2-dibromoethane (1 drop) were added and the mixture briefly heated to reflux. Then, bromide *ent*-**148** (116 mg, 657 μmol, ca. 60% solution in *n*-pentane) was added as a solution in Et_2O(1 mL) and after stirring at room temperature for 25 min, the sealed tube was heated in a 60 °C oil bath and after stirred an additional 30 min at room temperature. Then, CO_2(sublimation of dry ice) was bubbled through the mixture (2 mL Et2O were added to replace evaporated solvent)and the solution was stirred an additional 30 min. Then, HCl (2 M) was added under ice cooling, and after the remaining magnesium was dissolved, the mixture was extracted three times with diethyl ether, the organic extracts dried ($MgSO_4$) and concentrated on a rotary evaporator. Flash column chromatography (3:1 *n*-pentane/Et_2O) yielding carboxylic acid **217** (44.0 mg, 309 μmol, 47%) as a colorless oil.

Physical state: colorless oil

R_f = 0.15 (5:1 hexanes:EtOAc)

$[\alpha]_D^{21}$ = −3.0 (*c* = 0.27 in DCM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.47 (ddd, *J* = 17.1, 10.3, 8.9 Hz, 1H), 5.03 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.98 (ddd, *J* = 17.1, 2.0, 0.8 Hz, 1H), 2.43 – 2.25 (m, 2H), 1.88 (dp, *J* = 13.7, 4.6 Hz, 1H), 1.77

(dddd, *J* = 13.7, 9.3, 6.8, 4.4 Hz, 1H), 1.57 – 1.47 (m, 1H), 1.47 – 1.37 (m, 1H), 1.29 (dtdd, *J* = 14.8, 7.3, 6.2, 1.9 Hz, 1H), 0.86 (t, *J* = 7.4 Hz, 3H)ppm.

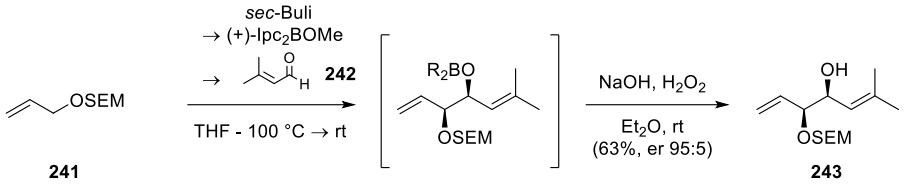
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 180.37, 141.80, 115.86, 45.57, 32.08, 29.32, 27.87, 11.72 ppm.

IR (ATR): $\tilde{\nu}$ = 3077 (w),2964 (m), 2927 (m), 2360 (w), 1710 (s), 1420 (m), 1215 (w), 997(w), 914 (m), 668 (w) cm^{-1}.

HRMS (EI): calc. for $C_8H_{13}O_2^-$: 141.0911 $[M-H^+]^+$

found: 141.0921$[M-H^+]^+$

Brown allylation of SEM-protected allylic alcohol **241**



(3S,4*S*)-6-methyl-3-((2-(trimethylsilyl)ethoxy)methoxy)hepta-1,5-dien-4-ol (18). SEM allyl alcohol **241**[I] (2.10 g, 11.2 mmol, 1 eq) was dissolved in THF (23 mL) and cooled to −78 °C. A solution of *s*-BuLi (1.4 M in cyclohexane, 7.97 mL, 11.2 mmol, 1 eq) was added *via* syringe pump (0.5 mL/min) and the mixture stirred for 15 min at −78 °C. Then, a solution of (+)-B-methoxydiisopinocampheylborane (3.53 g, 11.2 mmol, 1 eq) in THF (11 mL) was added *via* syringe pump (0.5 mL/min) and the mixture stirred for one hour at −78 °C. Then, the mixture was cooled to −100 °C and 3-methylbut-2-enal**242**(2.74 mL, 29.0 mmol, 2.9 eq) was added drop wise and the mixture stirred for 3 h at−100 °C after which the cooling was removed. After 30 min of stirring at room temperature, the mixture was concentrated on a rotary evaporator, the residue dissolved in Et_2O (42 mL) and cooled to 0 °C. NaOH (350 mg) was added followed by drop wise addition of 30% aqueous H_2O_2(8.0 mL). The biphasic mixture was then stirred for 15 h at room temperature. Then, the phases were separated and the aqueous phase extracted twice with Et_2O. The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 5:1 *n*-pentane:EtOAc) afforded diol **18** (1.93 g, 7.08 mmol, 63%, er 95:5 by Mosher ester) as a colorless oil.

[I]**241** prepared according to Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.*, **1995**, *117*, 5958−5966

Physical state: colorless oil

$\mathbf{R_f}$ = 0.17 (8:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +123 (*c* = 0.91 in $CHCl_3$)

^{1}H-NMR(400 MHz, $CDCl_3$): δ = 5.67 (ddd, *J* = 17.5, 10.4, 7.2 Hz, 1H), 5.28 (d, *J* = 17.5 Hz, 1H),5.28 (d, *J* = 10.3 Hz, 1H), 5.16 (dt, *J* = 9.1, 1.6 Hz, 1H), 4.73 (dd, *J* = 18.1, 6.9 Hz, 2H), 4.27 (dd, *J* = 8.9, 7.3 Hz, 1H), 3.91 (t, *J* = 7.3 Hz, 1H), 3.77 (dd, *J* = 9.2, 8.8 Hz, 1H), 3.56 (dd, *J* = 9.6, 9.1 Hz, 1H), 2.61 (br s, 1H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 0.95 (dd, *J* = 9.2, 7.7 Hz, 2H) ppm.

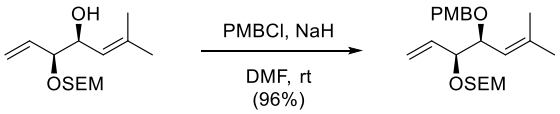
^{13}C-NMR(100 MHz, $CDCl_3$): δ = 138.1, 134.7, 123.1, 119.1, 93.0, 81.9, 70.8, 65.8, 26.1, 18.8, 18.2, −1.3 ppm.

IR (ATR): $\tilde{\nu}$ = 2929 (w), 1668 (s), 1386 (m), 1251 (m), 1090 (m), 922 (w), 861 (w), 836 (m), 658 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{14}H_{28}NaO_3^+$: 295.1700[M+Na]$^+$

found: 295.1699 [M+Na]$^+$

PMB protection of bisallylic diol **243**



243 **S4**

Bisallylic diol S4. NaH (60% dispersion in mineral oil, 97.4 mg, 2.43 mmol, 1.3 eq) was suspended in DMF (6.0 mL) and cooled to 0 °C. Then, a solution of allylic alcohol **243** (510 mg, 1.87 mmol, 1 eq) in DMF (3.7 mL) was added drop wise and the mixture stirred for 20 min at 0 °C. Then, PMBCl (329 µmL, 2.43 mmol, 1.3 eq) was added drop wise and cooling was stopped after further 15 min. After 3 h of stirring at room temperature, the reaction was quenched by the addition of water. The mixture was extracted three times with Et_2O and the combined organic extracts were washed three times with 10% aqueous LiCl solution, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (15:1 *n*-pentane:EtOAc) afforded PMB ether **S4** (707 mg, 1.80 mmol, 96%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.73 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +87 (*c* = 0.28 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 – 7.21 (m, 2H), 6.87 – 6.82 (m, 2H), 5.81 (ddd, *J* = 17.2, 10.5, 6.5 Hz, 1H), 5.25 (d, *J* = 17.3 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.72 (s, 2H), 4.55 (d, *J* = 11.8 Hz,

1H), 4.32 (d, *J* = 11.8 Hz, 1H), 4.13 – 4.05 (m, 2H), 3.79 (s, 3H), 3.77 – 3.67 (m, 1H), 3.60 – 3.51 (m, 1H), 1.78 (s, 3H), 1.60 (s, 3H), 0.93 – 0.87 (m, 2H), −0.01 (s, 9H) ppm.

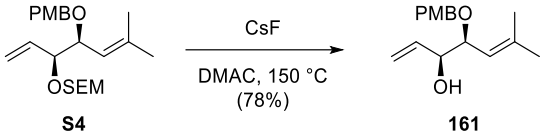
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.0, 137.7, 135.3, 131.1, 129.3, 122.6, 117.8, 113.7, 92.7, 79.3, 69.5, 65.2, 55.4, 26.2, 18.7, 18.1, −1.3 ppm.

IR (ATR): $\tilde{\nu}$ = 2953 (m), 1613 (w), 1514 (m), 1457 (w), 1377 (w), 1302 (w), 1248 (s), 1172 (w), 1001 (m), 1038 (s), 123 (w), 860 (m), 835 (s), 760 (w), 694 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{22}H_{40}NO_4Si^+$: 410.2721 $[M+NH_4]^+$

found: 410.2725 $[M+NH_4]^+$

SEM-deprotection of bisallylic diol **S4**



(3*S*,4*S*)-4-((4-methoxybenzyl)oxy)-6-methylhepta-1,5-dien-3-ol (161). SEM ether **S4** (760 mg, 1.94 mmol, 1 eq) was dissolved in *N*,*N*-dimethylacetamide (34 mL). CsF was added (2.94 g, 19.4 mmol, 10 eq) and the mixture was heated to 150 °C for 5.5 h. After letting the mixture come to room temperature, saturatedaqueous $NaHCO_3$ was added and the biphasic mixture extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 10:1 *n*-pentane:EtOAc) afforded allylic alcohol **161** (398 mg, 1.52 mmol, 78%) as a colorless oil.

Physical state: colorless oil

R_f = 0.55 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +26 (*c* = 0.48 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 – 7.21 (m, 2H), 6.92 – 6.85 (m, 2H), 5.78 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.35 (dt, *J* = 17.2, 1.7 Hz, 1H), 5.15 (dt, *J* = 10.6, 1.7 Hz, 1H), 5.09 (dh, *J* = 9.5, 1.4 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.27 (d, *J* = 11.2 Hz, 1H), 4.04 (ddt, *J* = 8.2, 5.4, 1.5 Hz, 1H), 3.91 (dd, *J* = 9.5, 7.9 Hz, 1H), 3.80 (s, 3H), 2.92 (s, 1H), 1.80 (d, *J* = 1.4 Hz, 3H), 1.65 (d, *J* = 1.4 Hz, 3H) ppm.

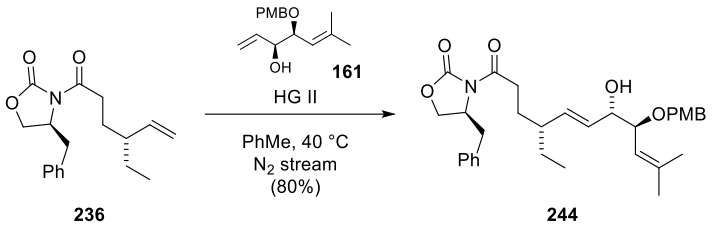
^{13}C-NMR(100 MHz, $CDCl_3$): δ = 159.4, 139.6, 136.3, 130.6, 129.6, 121.9, 116.5, 114.0, 78.8, 74.9, 69.7, 55.5, 26.2, 19.0 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3488 (w), 2913 (w), 1612 (w), 1514 (s), 1443 (m), 1377 (w), 1301 (w), 1248 (s), 1075 (w), 1036 (s), 821 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{16}H_{22}NaO_3^+$: 285.1461 $[M+Na]^+$

found: 285.1464 [M+Na]$^+$

Cross metathesis of olefin **236** and allylic alcohol **161**



236 **244**

Olefin 244. Oxazolidinone **236** (d.r., 4.5:1, 683 mg, 2.26 mmol, 1 eq) and allylic alcohol **13** (889 mg, 3.39 mmol, 1.5 eq) were dissolved in degassed toluene (26 mL) and Hoveyda-Grubbs 2nd generation catalyst (142 mg, 226 µmol, 0.1 eq) was added. The mixture was heated to 40 °C and the septum was pierced in a way that enabled a constant flow of nitrogen through the flask's atmosphere, concentrating the reaction to dryness within 2 h. Flash column chromatography (silica, 4:1 →3:1 →2:1 →1:1 *n*-pentane:Et$_2$O) afforded diasteromerically impure **244** (1.02 g, 1.90 mmol, 84%), which was further chromatographed (silica, 2:1 →1:1 *n*-pentane:Et$_2$O) to yield olefin **244** (756 mg, 1.41 mmol, 62%, 80% based on dr of **326**) as a single diastereomer.

Physical state: colorless oil

R$_f$ = 0.37 (2:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +15 (*c* = 0.30 in CHCl$_3$)

^{1}H-NMR (400 MHz, CDCl$_3$): δ = 7.33 (m, 2H), 7.30 – 7.26 (m, 1H), 7.25 – 7.22 (m, 2H), 7.21 – 7.17 (m, 2H), 6.90 – 6.84 (m, 2H), 5.49 (ddd, *J* = 15.6, 8.8, 1.1 Hz, 1H), 5.37 (dd, *J* = 15.5, 5.7 Hz, 1H), 5.07 (dh, *J* = 9.6, 1.4 Hz, 1H), 4.65 (ddt, *J* = 10.3, 6.9, 3.3 Hz, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.26 (d, *J* = 11.1 Hz, 1H), 4.21 – 4.13 (m, 2H), 4.01 (ddd, *J* = 6.9, 5.7, 1.1 Hz, 1H), 3.90 (dd, *J* = 9.5, 8.1 Hz, 1H), 3.80 (s, 3H), 3.28 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.97 – 2.79 (m, 3H), 2.74 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.77 (s, 3H), 1.65 (d, *J* = 1.3 Hz, 3H), 1.64 – 1.55 (m, 1H), 1.52 – 1.40 (m, 1H), 1.36 – 1.27 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H) ppm.

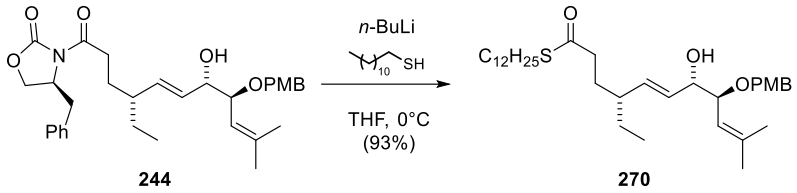
^{13}C-NMR (100 MHz, CDCl$_3$): δ = 173.7, 159.3, 153.5, 139.3, 136.2, 135.5, 130.6, 129.6, 129.6, 129.1, 129.1, 127.5, 122.2, 114.0, 79.2, 74.6, 69.6, 66.3, 55.4, 55.3, 44.1, 38.1, 33.7, 29.4, 28.0, 26.2, 19.0, 11.8 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3534 (w), 2925 (m), 1782 (s), 1697 (m), 1612 (w), 1513 (m), 1452 (w), 1384 (m), 1352 (m), 1301 (w), 1248 (s), 1212 (m), 1033 (m), 823 (w), 761 (w), 703 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{32}H_{45}N_2O_6^+$: 553.3272 $[M+NH_4]^+$

found: 553.3284 $[M+NH_4]^+$

Thioesterification of oxazolidinone **244**



244 **270**

Thioester (270). *n*-Dodecane thiol (445 µL, 1.87 mmol, 2.5 eq) was dissolved in THF (10 mL) and cooled to 0 °C. A solution of *n*-BuLi (627 µL, 2.5 M in hexanes, 1.57 mmol, 2.1 eq) was added drop wise and after 5 min oxazolidinone **244** (400 mg, 746 µmol, 1 eq) was added drop wise as a solution in THF (8.0 mL). After 10 min at 0 °C, the reaction was quenched by adding saturated aqueous NH_4Cl. The mixture was extracted three times with EtOAc, the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 10:1 → 5:1 *n*-pentane:EtOAc) afforded thioester **270** (391 mg, 697 µmol, 93%) as a colorless oil.

Physical state: colorless oil

R_f = 0.30 (5:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +18 (*c* = 0.43 in $CHCl_3$)

^{1}H-NMR (800 MHz, $CDCl_3$): δ = 7.26 – 7.21 (m, 2H), 6.91 – 6.84 (m, 2H), 5.40 (ddd, *J* = 15.4, 8.9, 1.0 Hz, 1H), 5.32 (dd, *J* = 15.4, 6.5 Hz, 1H), 5.05 (dh, *J* = 9.7, 1.4 Hz, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 3.98 (ddd, *J* = 7.8, 6.5, 1.1 Hz, 1H), 3.90 (dd, *J* = 9.6, 8.2 Hz, 1H), 3.81 (s, 3H), 2.91 (br s, 1H), 2.84 (td, *J* = 7.3, 2.4 Hz, 3H), 2.47 (ddd, *J* = 15.3, 9.8, 5.4 Hz, 1H), 2.38 (ddd, *J* = 15.3, 9.7, 6.4 Hz, 1H), 1.85 (m, 1H), 1.80 (d, *J* = 1.4 Hz, 3H), 1.78 – 1.74 (m, 1H), 1.67 (s, 3H), 1.54 (p, *J* = 7.4 Hz, 2H), 1.52 – 1.47 (m, 1H), 1.42 – 1.37 (m, 1H), 1.37 – 1.31 (m, 2H), 1.31 – 1.22 (m, 17H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H)ppm.

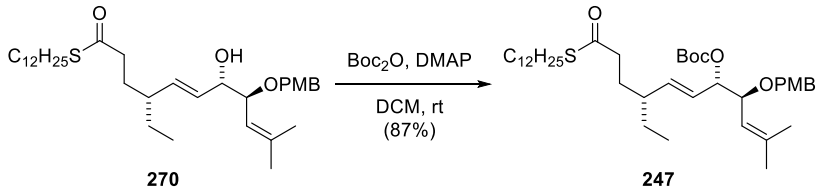
^{13}C-NMR (200 MHz, $CDCl_3$): δ = 199.9, 159.4 139.4, 136.8, 130.6, 129.6, 129.4, 122.2, 114.0, 79.1, 75.1, 69.6, 55.4, 44.2, 42.2, 32.1, 30.4, 29.79, 29.78, 29.75, 29.73, 29.65, 29.5, 29.3, 29.00, 28.97, 28.1, 26.2, 22.8, 19.0, 14.3, 11.8 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3541 (w), 2924 (s), 2854 (m), 1690 (m), 1612 (w), 1548 (w), 1514 (m), 1462 (w), 1377 (w), 1301 (w), 1248 (m), 1173 (w), 1036 (m), 971 (w), 822 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{34}H_{60}NO_4^+$: 578.4238 $[M+NH_4]^+$

found: 578.4250 $[M+NH_4]^+$

Boc-protection of allylic alcohol **270**



270 247

Allylic carbonate 247. To allylic alcohol **270** (391 mg, 697 µmol, 1 eq) in THF (8.0 mL) was added DMAP (85.2 mg, 697 µmol, 1 eq) and di-*tert*-butyl dicarbonate (456 mg, 2.09 mmol, 3 eq) as a solution in THF (4.0 mL) at room temperature. After 20 h of stirring at room temperature the reaction was quenched by addition of water. The mixture was extracted three times with EtOAc, the combined organic extracts washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 40:1 → 30:1 *n*-pentane:EtOAc) afforded carbonate **247** (399 mg, 604 µmol, 87%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.61 (6:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +17 (*c* = 0.29 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 – 7.21 (m, 2H), 6.87 – 6.81 (m, 2H), 5.41 (dd, *J* = 15.4, 8.6 Hz, 1H), 5.33 (dd, *J* = 15.4, 7.2 Hz, 1H), 5.11 – 5.02 (m, 2H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.17 (dd, *J* = 9.8, 7.5 Hz, 1H), 3.79 (s, 3H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.43 – 2.24(m, 2H), 1.89– 1.79 (m, 1H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.76 – 1.69 (m, 1H), 1.62 (d, *J* = 1.3 Hz, 3H), 1.58 – 1.50 (m, 2H), 1.45 (s, 9H), 1.43 – 1.16 (m, 21H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H) ppm.

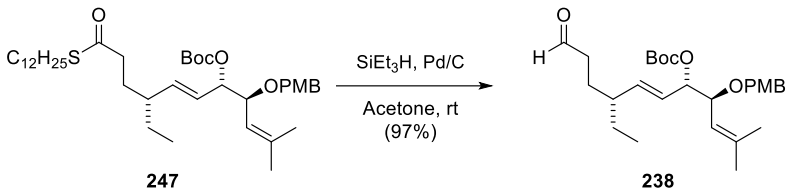
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.9, 159.1, 153.1, 139.0, 138.9, 131.0, 129.2, 126.3, 121.8, 113.7, 81.9, 79.6, 76.0, 69.6, 55.4, 44.3, 42.1, 32.1, 30.5, 29.8, 29.8, 29.7, 29.6, 29.5, 29.3, 29.99, 28.95, 27.99, 27.96, 26.2, 22.8, 18.9, 14.3, 11.8 ppm.

IR (ATR, film): $\tilde{\nu}$ = 2924 (s), 2854 (m), (s), 1742 (m), 1691 (m), 1513 (w), 1250 (s), 1171 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{39}H_{68}NO_6^+$: 678.4762 $[M+NH_4]^+$

found: 678.4775 $[M+NH_4]^+$

Fukuyama reduction of thioester **247**



247 **238**

Aldehyde 238. To thioester **247** (280 mg, 425 μmol, 1 eq) and palladium on charcoal (10%, 108 mg, 101 μmol, 0.24 eq) was added $SiEt_3H$ (337 μL, 2.12 mmol, 5 eq) as a solution in acetone (21.2 mL). After stirring at room temperature for 35 min, the reaction mixture was filtered through celite and concentrated. Flash column chromatography (silica, 10:1*n*-pentane:EtOAc) afforded aldehyde **238** (189 mg, 410 μmol, 97%) as a colorless oil.

Physical state: colorless oil

R_f = 0.24 (6:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +28 (*c* = 0.47 in $CHCl_3$)

^{1}H-NMR (800 MHz, $CDCl_3$): δ = 9.69 (t, *J* = 1.6 Hz, 1H), 7.25 – 7.22 (m, 2H), 6.86 – 6.83 (m, 2H), 5.40 (ddd, *J* =15.4, 9.1, 0.8 Hz, 1H), 5.33 (dd, *J* = 15.5, 7.4 Hz, 1H), 5.08 – 5.04 (m, 2H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 4.17 (dd, *J* = 9.7, 7.2 Hz, 1H), 3.79 (s, 3H), 2.34 (dddd, *J* = 17.6, 9.2, 5.4, 1.4 Hz, 1H), 2.27 (dddd, *J* = 17.6, 8.8, 6.7, 1.8 Hz, 1H), 1.84 (tp, *J* = 9.2, 4.5 Hz, 1H), 1.77 (d, *J* = 1.4 Hz, 3H), 1.72 (dddd, *J* = 13.6, 9.2, 6.7, 4.3 Hz, 1H), 1.61 (d, *J* = 1.4 Hz, 3H), 1.47 (s, 9H), 1.45 – 1.38 (m, 2H), 1.26 (ddq, *J* = 13.5, 9.0, 7.4 Hz, 1H), 0.81 (t, *J* = 7.4 Hz, 3H) ppm.

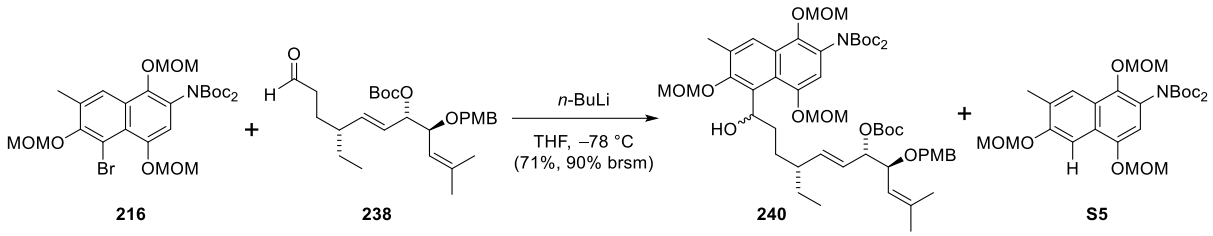
^{13}C-NMR (200 MHz, $CDCl_3$): δ = 202.6, 159.1, 153.1, 138.9, 138.8, 130.9, 129.3, 126.3, 121.9, 113.8, 81.9, 79.4, 76.0, 69.7, 55.4, 44.3, 42.0, 28.1, 28.0, 27.0, 26.2, 18.8, 11.8 ppm.

IR (ATR, film): $\tilde{\nu}$ = 2931 (w), 1738 (s), 1612 (w), 1513 (m), 1452 (w), 1368 (m), 1274 (s), 1250 (s), 1162 (s), 1076 (m), 1036 (m), 974 (w), 822 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{27}H_{44}NO_6^+$: 478.3163 $[M+NH_4]^+$

found: 478.3174 $[M+NH_4]^+$

Coupling of aryl bromide**216**and aldehyde **238**



Naphthylalcohol 240. Aryl bromide **216** (194 mg, 315 μmol, 1.7 eq) was concentrated from benzene in a Schlenk flask, dried under high vacuum and redissolved in THF (17 mL) under Argon. The solution was cooled to −78 °C and a solution of *n*-BuLi (146 μL, 2.47 M in hexanes, 361 μmol, 1.95 eq) was added drop wise at −78 °C. After 30 min, aldehyde **238** (85.3 mg, 185 μmol, 1 eq) was added drop wise as a solution in THF (1.0 mL) and the reaction mixture was stirred for an additional 30 min at −78 °C. Then, the reaction was quenched by adding saturated aqueous NH_4Cl solution and the mixture was allowed to warm to room temperature over the course of one hour. The biphasic solution was then extracted three times with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 7:1 → 5:1 → 2:1 *n*-pentane:EtOAc) afforded aldehyde **238** (17.4 mg, 38 μmol, 21% reisolated), protodemetalated naphthalene **S5** (80.7 mg, 150 μmol, 48% based on aryl bromide **216**) and naphthyl alcohol **240** (d.r. 1:1.5, 132 mg, 132 μmol, 71 %, 90% brsm based on aldehyde **238**). As **240** exists as a 1:1 mixture of atropisomers of each diastereomer at room temperature, the naphthyl alcohols were immediately oxidized for ease of characterization.

Protodemetalated napthalene S5:

Physical state: colorless oil

R_f = 0.43 (3:1 hexane:EtOAc)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.87 (s, 1H), 7.66 (s, 1H), 6.81 (s, 1H), 5.37 (s, 2H), 5.30 (s, 2H), 5.05 (s, 2H), 3.61 (s, 3H), 3.54 (s, 3H), 3.52 (s, 3H), 2.42 (s, 3H), 1.39 (s, 18H) ppm.

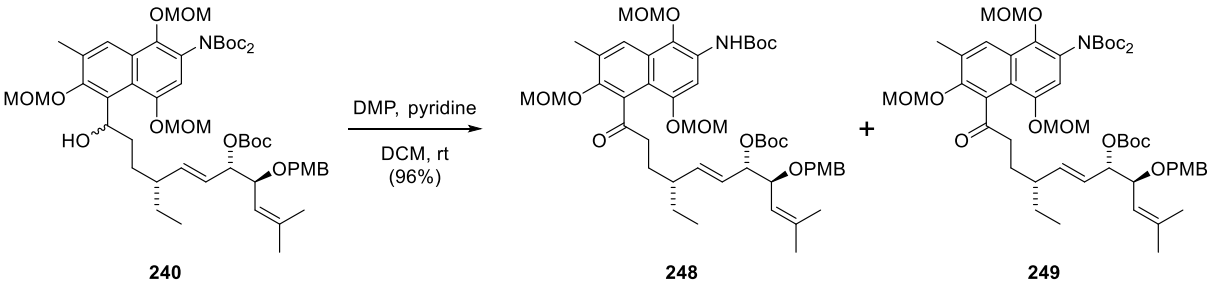
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.6, 151.7, 148.5, 142.8, 129.5, 126.7, 126.2, 124.6, 124.1, 109.4, 102.9, 100.0, 95.4, 94.4, 82.5, 57.8, 56.4, 56.2, 28.0, 17.4 ppm.

IR (ATR, film): $\tilde{\nu}$ = 2976 (w), 2826 (w), 1786 (m), 1748 (m), 1607 (w), 1504 (w), 1454 (w), 1431 (w), 1392 (w), 1367 (m), 1331 (m), 1274 (m), 1250 (m), 1219 (w), 1146 (s), 1096 (s), 1076 (s), 1060 (m), 1025 (m), 985 (m), 945 (m),924 (m), 888 (w), 854 (m), 803 (w) ,779 (m), 753 (w), 666 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{27}H_{40}NO_{10}^+$: 538.2647 $[M+NH_4]^+$

found: 538.2665 $[M+NH_4]^+$

Oxidation of naphthyl alcohol**240**



240 **248** **249**

Ketones248 and 249. To naphthyl alcohol **240** (139 mg, 139 μmol, 1 eq) in DCM (15 mL) was added pyridine (150 μL) and DMP (62.0 mg, 146 μmol, 1.05 eq) and the mixture was stirred at room temperature. After 30 min, an additional amount of DMP (12.0 mg, 28 μmol, 0.2 eq) was added. After 50 min a 1:1 solution of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$(20 mL) was added and the biphasic mixture was stirred for 10 min at room temperature. The mixture was then extracted three times with EtOAc, the combined organic layers washed with brine and dried over Na_2SO_4. Flash column chromatography (silica, 7:1 → 2:1 *n*-pentane:EtOAc) afforded **248** (31.3 mg, 34.9 μmol) and**249** (97.4 mg, 97.8 μmol) in a combined yield of 96%.

Mono-*N*-Boc naphthylic ketone248:

Physical state: light yellow oil

$\mathbf{R_f}$ = 0.59 (2:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = −53 (*c* = 0.25 in $CHCl_3$)

*Note: At room temperature compound **248** exists as a mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers and the carbon NMR signals as they appear at 25 °C, even though some signals overlap.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85 (m, 1H), 7.70 – 7.64 (m, 2H), 7.22 – 7.14 (m, 2H), 6.84 – 6.76 (m, 2H), 5.52 – 5.41 (m, 1H), 5.33 – 5.25 (m, 1H), 5.25 – 5.20 (m, 1H), 5.16 – 5.07 (m, 2H), 5.08 – 5.00 (m, 2H), 5.00 – 4.87 (m, 3H), 4.51 – 4.40 (m, 1H), 4.29 – 4.20 (m, 1H), 4.14 – 4.07 (m, 1H), 3.77 (s, 3H), 3.66 – 3.63 (m, 3H), 3.56 – 3.53 (m, 3H), 3.48 – 3.45 (m, 3H), 2.91 – 2.49 (m, 2H), 2.47 – 2.43 (m, 3H), 2.03 – 1.65 (m, 3H), 1.53 (s, 9H), 1.52 (d, *J* = 1.4 Hz, 2H), 1.49 (d, *J* = 1.3 Hz, 1H), 1.48 (d, *J* = 1.4 Hz, 1H), 1.46 – 1.41 (m, 9H), 1.39 (d, *J* = 1.4 Hz, 2H), 0.85 – 0.76 (m, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.8, 206.7, 159.0, 153.12, 153.10, 152.9, 152.8, 149.4, 149.3, 148.72, 148.69, 139.7, 139.5, 138.71, 138.68, 135.1, 135.0, 133.0, 132.9, 131.3, 131.2, 131.0, 130.9, 129.2, 129.04, 128.97, 126.38, 126.36, 125.53, 125.49, 123.1, 121.7, 121.6, 118.5, 118.4, 113.67, 113.65, 101.6, 101.5, 100.9, 95.5, 95.4, 81.83, 81.82, 80.7, 79.5, 76.2, 76.1, 69.60, 69.55, 57.9, 57.8, 57.7, 57.0, 55.4, 44.5, 44.4, 43.4, 43.1, 28.5, 28.4, 28.3, 28.2, 28.0, 27.9, 25.8, 25.7, 18.70, 18.67, 17.81, 17.80, 11.8 ppm.

IR (ATR, film): $\tilde{\nu}$ = 2930 (m), 2360 (w), 1734 (m), 1626 (w), 1513 (m), 1497 (m), 1456 (m), 1393 (w), 1367 (m), 1273 (m), 1250 (s), 1233 (m), 1158 (s), 1072 (m), 1024 (m), 957 (m), 933 (m), 866 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{49}H_{73}N_2O_{14}^+$: 913.5056 $[M+NH_4]^+$

found: 913.5069 $[M+NH_4]^+$

***N,N*-di-Boc naphthylic ketone 249:**

Physical state: light yellow oil

R_f = 0.25 (3:1 hexane:EtOAc)

$[\alpha]_D^{25}$ = +14.1 (*c* = 1.01 in $CHCl_3$)

*Note: At room temperature compound **249** exists as a mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers and the carbon NMR signals as they appear at 25 °C, even though some signals overlap.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 1H), 7.24 – 7.14 (m, 2H), 6.82 – 6.76 (m, 2H), 5.53 – 5.40 (m, 1H), 5.33 – 5.23 (m, 1H), 5.15 – 4.86 (m, 8H), 4.52 – 4.39 (m, 1H), 4.30 – 4.19 (m, 1H), 4.16 – 4.06 (m, 1H), 3.77 (s, 3H), 3.60 (s, 3H), 3.58 – 3.53 (m, 3H), 3.47 – 3.41 (m, 3H), 2.93 – 2.52 (m, 2H), 2.50 – 2.42 (m, 3H), 2.06 – 1.94 (m, 1H), 1.94 – 1.73 (m, 2H), 1.67 – 1.56 (m, 1H), 1.51 (s, 1.5H), 1.48 (s, 1.5H), 1.47 (s, 1.5H), 1.44 (s, 9H), 1.43 – 1.35 (m, 18H), 1.33 – 1.29 (m, 1.5H), 0.86 – 0.79 (m, 3H)ppm.

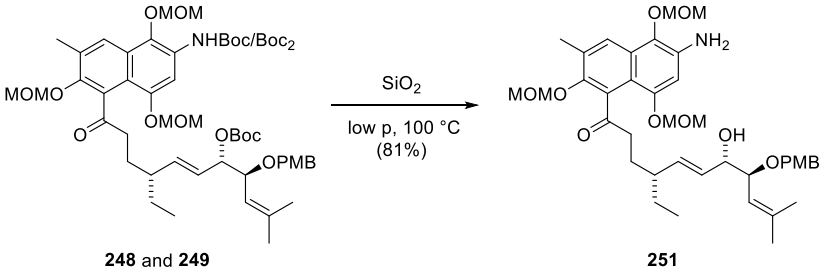
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 207.1, 207.0, 159.4, 153.42, 153.40, 151.74, 151.66, 151.5, 151.3, 148.6, 148.4, 143.5, 143.4, 140.0, 139.8, 138.99, 138.97, 133.0, 132.9, 131.5, 131.4, 131.23, 131.18, 129.49, 129.47, 128.7, 128.6, 127.28, 127.27, 125.9, 125.8, 125.51, 125.49, 122.61, 122.56, 122.03, 121.95, 114.0, 111.0, 110.8, 101.7, 101.6, 100.5, 96.2, 96.0, 83.2, 83.1, 82.17, 82.16, 79.83, 79.76, 76.5, 76.4, 69.9, 69.8, 58.3, 58.1, 58.0, 56.82, 56.80, 55.7, 44.9, 44.8, 43.8, 43.5, 28.8, 28.7, 28.4, 28.3, 28.3, 28.1, 26.1, 25.9, 19.0, 18.0, 12.13, 12.11 ppm.

IR (ATR, film): $\tilde{\nu}$ = 2976 (w), 2933 (w), 1788 (m), 1741 (m), 1709 (m), 1613 (w), 1514 (m), 1499 (w), 1456 (w), 1422 (w), 1392 (m), 1344 (m), 1274 (s), 1250 (s), 1154 (s), 1099 (s), 1024 (m), 950 (s), 854 (m), 822 (w), 779 (w), 159 (m), 666 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{54}H_{81}N_2O_{16}^+$: 1013.5581 $[M+NH_4]^+$

found: 1013.5588 $[M+NH_4]^+$

Global Boc-deprotection of naphthylamines **248**and **249**



248 and **249** **251**

Naphthylamine 251. To a mixture of **248**and **249** (157 mg, 113 µmol **249**, 50.0 µmol **248**) in DCM (18 mL) was added silica (7.50 g, dried overnight in an oven at 200 °C). The mixture was carefully concentrated on a rotary evaporator before vacuum (0.04 mbar) was applied and the flask immersed in a 100 °C oil bath. After 15 h the flask was flushed with argon, cooled to room temperature and the silica was poured on a packed silica column. Elution with 1:1 *n*-pentane:EtOAcand concentration of the product containing fractions on a rotary evaporator with a nitrogen inlet provided air sensitive naphthylamine **251** (92 mg, 132 µmol, 81%) as a yellow oil. To avoid decomposition, **251** was typically immediately *N*-protected as described below.

Physical state: yellow oil

$\mathbf{R_f}$ = 0.68 (1:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +15 (*c* = 0.45 in benzene)

*Note: At room temperature compound **251** exists as a mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers and the carbon NMR signals as they appear at 25 °C, even though some signals overlap.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (s, 1H), 7.24 – 7.16 (m, 2H), 6.88 – 6.81 (m, 2H), 6.71 – 6.66 (m, 1H), 5.52 – 5.39 (m, 1H), 5.34 – 5.25 (m, 1H), 5.13 – 4.85 (m, 7H), 4.52 – 4.42 (m, 1H), 4.25 – 4.18 (m, 1H), 3.98 – 3.88 (m, 1H), 3.86 – 3.81 (m, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.57 – 3.53 (m, 3H), 3.46 – 3.40 (m, 3H), 2.94 – 2.83 (m, 0.5H), 2.80 – 2.65 (m, 1H), 2.62 – 2.53 (m, 0.5H), 2.48 – 2.40 (m,

3H), 2.03 – 1.95 (m, 1H), 1.91 – 1.82 (m, 1H), 1.82 – 1.71 (m, 1H), 1.63 (s, 1.5H), 1.53 (s, 1.5H), 1.50 – 1.47 (m, 3H), 1.46 – 1.40 (m, 1H), 1.34 – 1.26 (m, 1H), 0.87 – 0.82 (m, 3H)ppm.

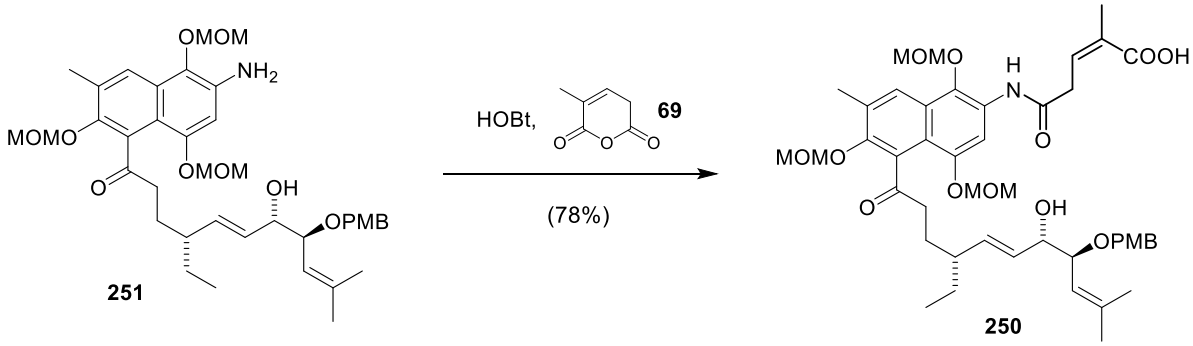
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 207.2, 207.1, 159.3, 149.4, 147.8, 147.8, 139.3, 139.2, 136.9, 136.8, 132.7, 132.6, 131.3, 131.2, 130.52, 130.50, 129.6, 128.7, 128.6, 127.6, 125.6, 122.4, 122.3, 122.03, 121.95, 113.9, 102.6, 102.4, 101.4, 100.3, 95.7, 95.5, 79.2, 79.1, 74.7, 74.6, 69.6, 57.9, 57.71, 57.68, 56.6, 55.4, 50.9, 45.4, 44.3, 43.3, 43.2, 33.7, 28.5, 28.3, 28.2, 28.0, 25.9, 25.8, 24.7, 18.79, 18.76, 17.8, 11.8 ppm.

IR (ATR, film): $\tilde{\nu}$ =3356 (w), 2956 (m), 2363 (w), 2140 (m), 1703 (m), 1631 (s), 1514 (m), 1450 (m), 1384 (m), 1302 (m), 1247 (s), 1156 (s), 1067 (s), 1016 (s), 966 (s), 929 (s), 822 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{39}H_{54}NO_{10}^+$: 696.3742 $[M+H]^+$

found: 696.3751 $[M+H]^+$

Acylation of naphthyl amine **251** with anhydride **250**



Amide 250. To naphthyl amine **251** (14.0 mg, 20.1 μmol, 1 eq), anhydride**69** (5.10 mg, 40.2 μmol, 2 eq) and HOBt (ca 12% H_2O, 3.70 mg, 24.1 μmol, 1.2 eq) was added DCM (2.0 mL). After 48 h of stirring at room temperature. Then, the mixture was concentrated and the residue subjected to flash column chromatography (Davisil, 1% → 2% MeOH in DCM). Amide **250** (12.9 mg, 15.7 μmol, 78%) was obtained as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.40 (9:1 DCM:MeOH)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +15.9 (*c* = 0.16 in $CHCl_3$)

*Note: At room temperature compounds **250** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets*

representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.95 – 8.81 (m, 1H), 8.10 (s, 1H), 7.72 (s, 1H), 7.25 – 7.15 (m, 2H), 6.89 – 6.81 (m, 2H), 6.44 – 6.34 (m, 1H), 5.51 – 5.40 (m, 1H), 5.33 – 5.25 (m, 1H), 5.25 – 5.19 (m, 1H), 5.17 – 5.08 (m, 2H), 5.06 – 4.87 (m, 4H), 4.53 – 4.44 (m, 1H), 4.25 – 4.17 (m, 1H), 4.00 – 3.89 (m, 1H), 3.89 – 3.81 (m, 1H), 3.81 – 3.76 (m, 3H), 3.64 (d, *J* = 7.7 Hz, 2H), 3.60 (s, 3H), 3.58 – 3.53 (m, 3H), 3.50 – 3.42 (m, 3H), 2.94 – 2.51 (m, 3H), 2.50 – 2.42 (m, 3H), 2.07 – 2.01 (m, 3H), 1.96 – 1.70 (m, 3H), 1.63 (d, *J* = 1.4 Hz, 1.5H), 1.53 (d, *J* = 1.3 Hz, 1.5H), 1.52 – 1.49 (m, 3H), 1.49 – 1.39 (m, 2H), 0.86 – 0.83 (m, 3H). ppm.

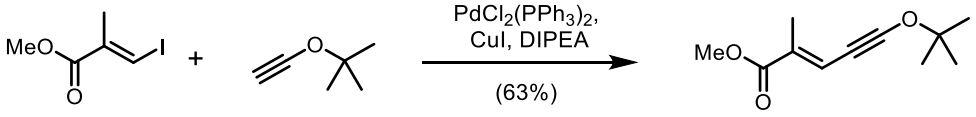
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.75, 170.57, 169.20, 159.31, 150.08, 149.98, 148.65, 139.20, 136.81, 136.03, 135.92, 135.10, 133.24, 133.12, 131.46, 131.34, 131.03, 130.52, 129.61, 128.71, 128.62, 128.14, 126.15, 123.46, 122.08, 122.04, 119.48, 113.93, 103.67, 103.47, 101.57, 101.01, 95.62, 95.50, 79.16, 74.71, 74.67, 69.61, 69.57, 58.06, 57.78, 57.76, 57.04, 55.41, 44.25, 44.20, 43.47, 43.16, 38.81, 29.85, 28.30, 28.22, 28.14, 28.03, 25.93, 25.82, 20.70, 18.81, 17.83, 11.80 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3374 (br w), 2926 (s), 2359 (m), 2340 (m), 1700 (s), 1624 (m), 1514 (s), 1496 (m), 1456 (m),1377 (m), 1302 (w), 1248 (s), 1157 (s),1069 (s), 1016 (m), 954 (s), 931 (s), 820 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{45}H_{63}N_2O_{13}^+$: 839.4325 $[M+NH_4]^+$

found: 839.4330 $[M+NH_4]^+$

Sonogashira coupling of vinyl iodide **260** and alkyne **175**



260 **175** **158**

Methyl-(*E*)-5-(*tert*-butoxy)-2-methylpent-2-en-4-ynoate 158. To ester **260**[I] (132 mg, 580 µmol, 1.0 eq), $PdCl_2(PPh_3)_2$ (20.4 mg, 29.1 µmol, 0.05 eq), CuI (11.1 mg, 58.2 µmol, 0.1 eq) and molecular sieves (4 Å) was added DCM (4.0 mL) under argon at room temperature. To the stirred suspension DIPEA (810 µL, 4.76 mmol, 8.18 eq) followed *t*-butoxy acetylene**175** (1.5 mL of the solution obtained following the procedure of Ready[II]) was added dropwise and the reaction turned dark red. The reaction mixture stirred for 2 h 45 min until TLC indicated the consumption of the starting material. Then, Davisil was added and the solvent was removed

[I] prepared according to *Org. Lett.***2010**, *12*, 340

[II] *Angew. Chem.***2014**, *126*, 9126–9130

under reduced pressure.The crude product was subjected to column chromatography (dry load, Davisil, 30:1 *n*-pentane:EtOAc) affordingalkynyl ether **158** (72.2 mg, 368 µmol, 63%) as a light yellow oil.

Physical state: light yellow oil

R$_f$ = 0.74 (9:1 hexane:EtOAc)

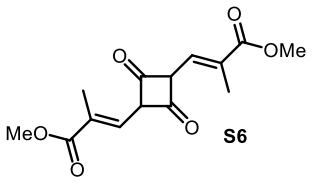
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.73 (q, *J* = 1.3 Hz, 1H), 3.74 (s, 3H), 2.00 (d, *J* = 1.3 Hz, 3H), 1.46 (s, 9H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.40, 133.40, 122.11, 108.96, 88.63, 51.93, 42.05, 27.32, 15.07 ppm.

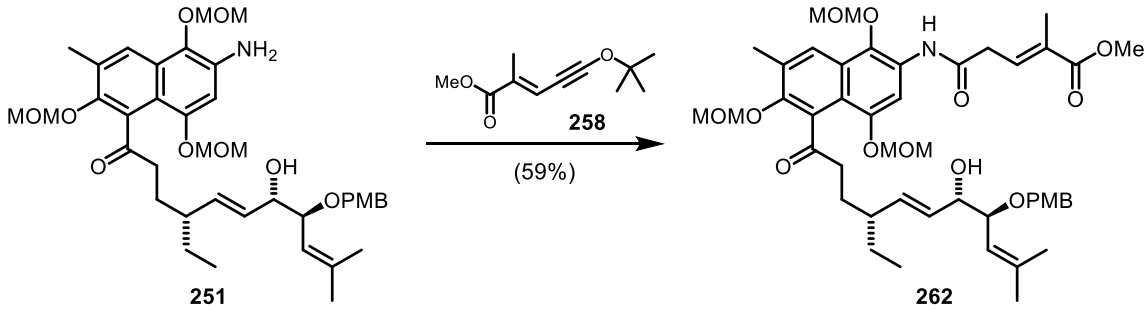
IR (ATR, neat): $\tilde{\nu}$ = 3854 (w), 3838 (w), 3802 (w), 3745 (m), 3735 (w), 3712 (w), 3689 (w), 3675 (w), 3649 (w), 3629 (w), 2955 (w), 2360 (s), 2341 (s), 2233 (w), 1733 (s), 1717 (s), 1684 (m), 1653 (m), 1558 (m), 1540 (m), 1457 (w), 1258 (s), 1180 (m), 1124 (m), 1032 (w), 747 (w), 668 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{14}H_{17}O_6^+$: 281.1020 $[Ms_6+H]^+$

found: 281.1017 $[Ms_6+H]^+$



Ketene amidation of naphthyl amine **251** with alkynyl ether **258**



Amide 262. A solution of naphthyl amine**251** (10.6 mg, 15.2 µmol, 1.0 eq) and alkynyl ether **258** (4.20 mg, 21.3 µmol, 1.4 eq) in toluene (2.0 mL) was heated to 80 °C for 30 min. Then, the mixture was concentrated under reduced pressure and purified by flash column chromatography (1.2:1*n*-pentane:EtOAc) to yield amide**262** (7.40 mg, 8.90 µmol, 59%) as a pale yellow oil.

Physical state: pale yellow oil

R$_f$ = 0.28 (1:1 hexane:EtOAc)

$[\alpha]_D^{21}$ = +11.4 (*c* = 0.21 in $CHCl_3$)

Note: At room temperature compounds ***262*** *exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}**H-NMR** (400 MHz, $CDCl_3$): δ = 8.65 – 8.54 (m, 1H), 8.11 (s, 1H), 7.69 (s, 1H), 7.23 – 7.17 (m, 2H), 7.09 – 7.01 (m, 1H), 6.81 – 6.75 (m, 2H), 5.51 – 5.39 (m, 1H), 5.34 – 5.25 (m, 1H), 5.25 – 5.18 (m, 1H), 5.17 – 5.07 (m, 2H), 5.05 – 4.85 (m, 4H), 4.52 – 4.44 (m, 1H), 4.24 – 4.18 (m, 1H), 3.99 – 3.89 (m, 1H), 3.84 (t, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.56 (s, 3H), 3.56 (s, 3H), 3.48 – 3.44 (m, 3H), 3.35 (d, *J* = 7.5 Hz, 2H), 2.96 – 2.50 (m, 3H), 2.49 – 2.42 (m, 3H), 1.96 (s, 3H), 1.91 – 1.70 (m, 3H), 1.63 (s, 1.5H), 1.60 – 1.54 (m, 1H), 1.53 (s, 1.5H), 1.51 (s, 1.5H), 1.50 (s, 1.5H), 1.47 – 1.40 (m, 1H), 1.33 – 1.27 (m, 1H), 0.88 – 0.81 (m, 3H) ppm.

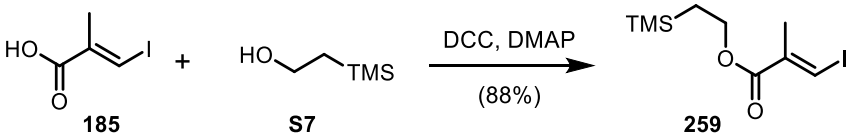
^{13}**C-NMR** (100 MHz, $CDCl_3$): δ = 206.72, 206.68, 167.98, 167.71, 167.66, 159.30, 150.04, 149.93, 148.65, 148.62, 139.17, 136.82, 136.79, 136.07, 135.94, 133.27, 133.14, 133.11, 131.66, 131.64, 131.51, 131.40, 130.54, 129.59, 128.73, 128.64, 128.24, 128.18, 126.07, 123.30, 122.10, 122.06, 119.42, 119.34, 113.93, 113.71, 103.63, 103.42, 101.57, 101.20, 95.61, 95.49, 79.17, 79.14, 74.69, 69.61, 69.56, 57.86, 57.85, 57.79, 57.76, 57.06, 55.41, 52.12, 44.27, 44.21, 43.48, 43.15, 37.79, 28.31, 28.22, 28.14, 28.05, 25.92, 25.81, 18.81, 17.83, 13.03, 11.81 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2953 (m), 2913 (s), 2848 (m), 1723 (s), 1624 (m), 1513 (m), 1471 (m), 1390 (m), 1272 (m), 1252 (s), 1110 (m), 1172 (s), 1113 (m), 958 (m), 815 (w), 716 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{46}H_{65}N_2O_{13}^+$: 853.4481 $[M+NH_4]^+$

found: 853.4501$[M+NH_4]^+$

SEM ester formation between carboxylic acid **185** and alcohol **S7**



2-(trimethylsilyl)ethyl (E)-3-iodo-2-methylacrylate **259**. To carboxylic acid **185**[I] (907 mg, 4.29 mmol, 1.0 eq), DCC (1.06 g, 5.13 mmol, 1.2 eq) and DMAP (131 mg, 1.07 mmol, 0.25 eq) was added DCM (14.0 mL) and the reaction mixture was cooled to 0 °C.After dropwise addition of

[I] prepared in three steps according to *J. Chem. Soc., Perkin Trans. 1*,**1990**, 47–65

2-(trimethylsilyl)ethan-1-ol **S7** (800 µL, 5.58 mmol, 1.3 eq) the cooling was removed and the reaction for 15 h. Then, the suspension was filtered over celite and the filtrate concentrated under reduced pressure. The crude product was subjected to flash column chromatography (dry load, 30:1 *n*-pentane:EtOAc) to yield ester**259** (1.18 g, 3.78 mmol, 88%) as a pale yellow liquid.

Physical state: pale yellow liquid

$\mathbf{R_f}$ = 0.53 (9:1 hexane:EtOAc)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 (t, *J* = 1.2 Hz, 1H), 4.28 – 4.20 (m, 2H), 2.05 (d, *J* = 1.2 Hz, 3H), 1.08 – 1.00 (m, 2H), 0.05 (s, 9H) ppm.

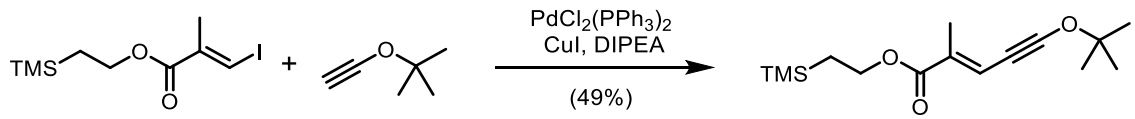
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.15, 140.11, 98.32, 63.83, 20.45, 17.49, −1.34 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2954 (w), 2924 (w), 1711 (s), 1601 (w), 1380 (w), 1286 (s), 1250 (m), 1209 (s), 1178 (m), 1095 (s), 1062 (w), 1041 (w), 933 (m), 834 (s), 761 (m), 726 (m), 694 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_8H_{14}ISiO_2^+$: 296.9808 $[M-CH_3]^+$

found: 296.9799 $[M-CH_3]^+$

Sonogashira coupling of vinyl iodide **259** and alkyne **175**



259 **175** **259**

2-(Trimethylsilyl)ethyl (*E*)-5-(tert-butoxy)-2-methylpent-2-en-4-ynoate 259. To vinyl iodide**259** (110 mg, 352 µmol, 1.0 eq), $PdCl_2(PPh_3)_2$ (12.3 mg, 17.6 µmol, 0.05 eq), CuI (6.70 mg, 35.2 µmol, 0.1 eq) and molecular sieves (4 Å) was added DCM (2.4 mL) under argon at room temperature. To the stirred suspension DIPEA (450 µL) followed *t*-butoxy acetylene**175** (1.0 mL of the solution obtained following the procedure of Ready[1]) was added drop wise and the reaction turned dark red. The reaction mixture stirred for 2 h 30 min until TLC indicated the consumption of the starting material. Then, Davisil was added and the solvent was removed under reduced pressure. The crude product was subjected to column chromatography (dry load, Davisil, 40:1 *n*-pentane:Et_2O) affording alkynyl ether **259** (49.2 mg, 174 µmol, 49%) as a light yellow oil.

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[1] *Angew. Chem.***2014**, *126*, 9126–9130

Physical state: light yellow oil

R$_f$ = 0.40 (25:1 hexane:EtOAc)

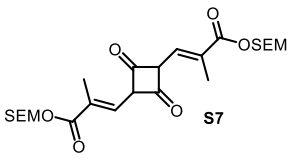
^{1}H-NMR (400 MHz, C_6D_6): δ = 7.21 (d, *J* = 1.4 Hz, 1H), 4.29 – 4.18 (m, 2H), 2.27 (d, *J* = 1.3 Hz, 3H), 1.08 (s, 9H), 0.92 – 0.82 (m, 2H), −0.10 (s, 9H) ppm.

^{13}C-NMR (100 MHz, C_6D_6): δ = 167.42, 134.81, 121.66, 108.91, 87.88, 62.66, 42.56, 26.87, 17.51, 15.46, −1.55. ppm.

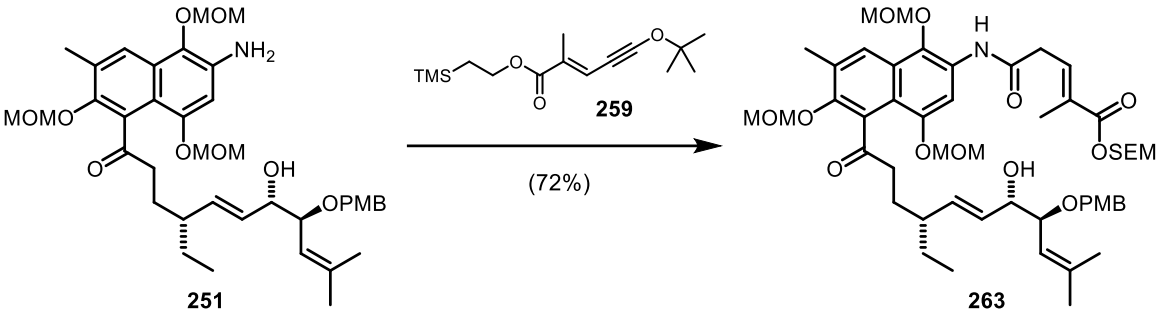
IR (ATR, film): $\tilde{\nu}$ = 2954 (w), 2233 (s), 1703 (s), 1614 (w), 1372 (m), 1295 (s), 1250 (s), 1152 (m), 1118 (s), 939 (m), 858 (s), 837 (s), 747 (m), 717 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{22}H_{37}O_6Si_2^+$: 453.2123 [M_{S7}+H]$^+$

found: 453.2123 [M_{S7}+H]$^+$



Ketene mediated amidation of naphthyl amine **251**



Amide 263. A solution of naphthyl amine **251** (12.7 mg, 18.3 μmol, 1.0 eq) and alkynyl ether **259** (6.20 mg, 21.9 μmol, 1.2 eq) in toluene (2.4 mL) was heated to 80 °C for 17 min. Then, the mixture was concentrated under reduced pressure and purified by flash column chromatography (1.1:1 *n*-pentane:Et$_2$O) to yield amide**263** (12.1 mg, 13.1 μmol, 72%) as a pale yellow oil.

Physical state: pale yellow oil

R$_f$ = 0.61 (9:1 DCM:MeOH)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +15.8 (*c* = 0.13 in $CHCl_3$)

*Note: At room temperature compounds **263** exists as approx. 1:1 mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers when appropriate and the carbon NMR signals as they appear at room temperature, even though some signals overlap.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.64 – 8.57 (m, 1H), 8.11 (s, 1H), 7.70 (s, 1H), 7.22 – 7.17 (m, 2H), 7.05 – 6.98 (m, 1H), 6.88 – 6.82 (m, 2H), 5.50 – 5.40 (m, 1H), 5.34 – 5.25 (m, 1H), 5.24 – 5.20 (m, 1H), 5.17 – 5.10 (m, 2H), 5.04 – 4.88 (m, 4H), 4.51 – 4.45 (m, 1H), 4.28 – 4.18 (m, 3H), 4.00 – 3.90 (m, 1H), 3.84 (t, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 3.59 – 3.52 (m, 6H), 3.48 – 3.44 (m, 3H), 3.35 (d, *J* = 7.5 Hz, 2H), 2.94 – 2.55 (m, 3H), 2.49 – 2.45 (m, 3H), 1.95 (s, 3H), 1.90 – 1.69 (m, 3H), 1.63 (s, 1.5H), 1.53 (s, 1.5H), 1.50 (s, 3H), 1.33 – 1.27 (m, 1H), 1.08 – 1.02 (m, 2H), 0.89 – 0.81 (m, 3H), 0.05 (s, 9H).ppm.

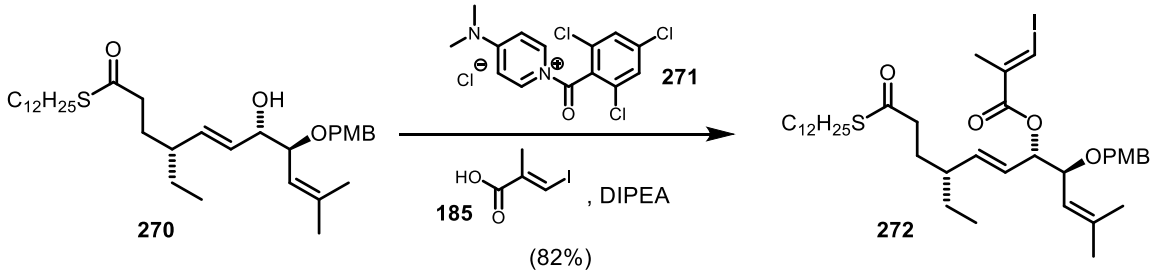
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 206.73, 206.68, 167.76, 167.70, 159.31, 150.04, 149.93, 148.61, 139.18, 136.83, 136.80, 136.09, 135.97, 133.25, 133.13, 132.60, 132.17, 131.51, 131.39, 130.54, 129.60, 128.73, 128.64, 128.26, 128.20, 126.09, 123.32, 122.10, 122.06, 119.42, 113.93, 103.67, 103.46, 101.58, 101.20, 95.62, 95.49, 79.18, 79.13, 74.72, 74.69, 69.61, 69.56, 63.24, 57.89, 57.79, 57.76, 57.06, 57.03, 55.42, 44.27, 44.21, 43.49, 43.15, 37.88, 28.31, 28.22, 28.14, 28.05, 25.93, 25.81, 18.82, 17.83, 17.54, 13.02, 11.81, −1.34 ppm.

IR (ATR, film): $\tilde{\nu}$ = 2955 (m), 2358 (w), 1706 (s), 1625 (m), 1514 (m), 1495 (m), 1450 (m), 1377 (m), 1249 (s), 1158 (s), 1069 (m), 954 (s), 839 (m) cm^{-1}.

HRMS (−ESI): calc. for $C_{50}H_{70}NSiO_{13}^+$: 920.4622 $[M-H]^-$

found: 920.4624 $[M-H]^-$

Esterification of allylic alcohol **270**



Ester 272. Vinyl iodide **185**[I] (34.4 mg, 162 µmol, 1.3 eq) was dissolved in toluene (3.1 mL) at room temperature. DIPEA (32.7 µL, 187 µmol, 1.5 eq) and modified Yamaguchi reagent **271**[II] (68.5 mg, 187 µmol, 1.5 eq) were added and the mixture stirred for 15 min at room temperature. Then, a solution of allylic alcohol **270** (70.0 mg, 125 µmol, 1 eq) in toluene (0.5 mL) was added and the mixture stirred for 4 h at room temperature before quenching by addition of water and

[I] prepared according to *J. Chem. Soc., Perkin Trans. 1*, **1990**, 47–65
[II] prepared according to *Synth. Commun.***2014**, *44*, 2854–2860

EtOAc. The biphasic mixture was extracted three times with EtOAc, the combined organic extracts washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was redissolved in DCM, silica was added and the mixture again concentrated under reduced pressure.Flash column chromatography (dry load, 20:1 *n*-pentane:EtOAc) yieldedester**272** (77.2 mg, 102 μmol, 82%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.78 (6:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +11.9 (*c* = 0.52 in $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1H), 7.24 – 7.14 (m, 2H), 6.90 – 6.80 (m, 2H), 5.43 – 5.27 (m, 3H), 5.06 (d, *J* = 9.7 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.25 (d, *J* = 12.0 Hz, 1H), 4.17 – 4.08 (m, 1H), 3.82 (s, 3H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.50 – 2.34 (m, 2H), 2.05 (s, 3H), 1.86 – 1.72 (m, 5H), 1.63 (s, 3H), 1.58 – 1.47 (m, 3H), 1.25 (s, 20H), 0.88 (t, *J* = 6.7 Hz, 4H), 0.77 (t, *J* = 7.4 Hz, 3H) ppm.

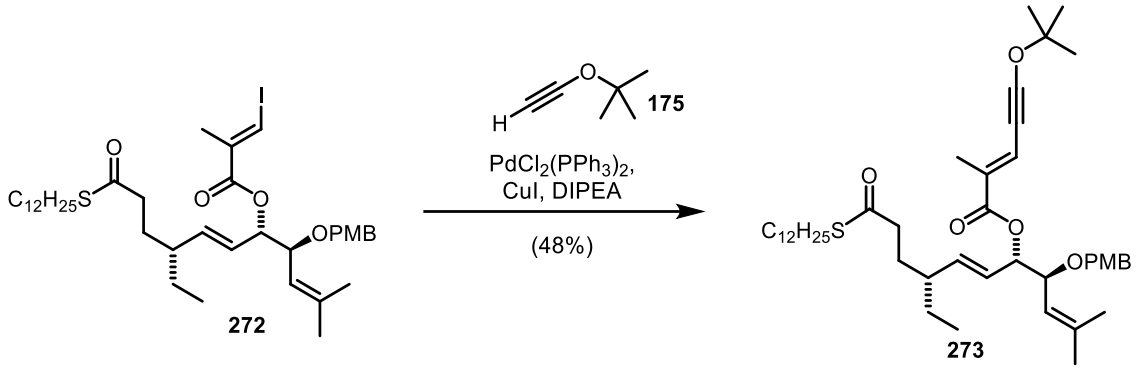
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.86, 162.93, 159.19, 140.18, 139.29, 139.07, 130.74, 129.45, 126.02, 121.75, 113.78, 98.60, 77.53, 75.28, 69.17, 55.43, 44.17, 42.04, 32.06, 30.36, 29.79, 29.78, 29.73, 29.65, 29.50, 29.28, 29.00, 28.97, 27.91, 26.25, 22.84, 20.53, 18.95, 14.29, 11.72 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2925 (s), 2854 (m), 1715 (s), 1690 (m), 1612 (w), 1513 (m), 1455 (w), 1378 (w), 1291 (m), 1248 (m), 1212 (s), 1172 (w), 1098 (m), 1038 (m), 972 (w), 820 (w), 726 (w), 685 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{38}H_{63}NISO_5^+$: 772.3466 $[M+NH_4]^+$

found: 772.3486 $[M+NH_4]^+$

Sonogashira coupling of vinyl iodide **272** and alkynyl ether **175**



Alkynyl ether 273. To vinyl iodide **272** (38.6 mg, 51.1 μmol, 1.0 eq), $PdCl_2(PPh_3)_2$ (5.00 mg, 7.12 μmol, 0.14 eq), CuI (4.00 mg, 21.0 μmol, 0.41 eq) and molecular sieves (4 Å) was added DCM (1.0 mL) under argon at room temperature. To the stirred suspension DIPEA (100 μL) followed *t*-butoxy acetylene**175** (2.0 mL of the solution obtained following the procedure of Ready[1]) was added drop wise and the reaction turned dark red. The reaction mixture stirred for 4 h 30 min until TLC indicated the consumption of the starting material. Then, Davisil was added and the solvent was removed under reduced pressure. The crude product was subjected to column chromatography (dry load, Davisil, 17:1 *n*-pentane:EtOAc) affording ynol ether **273** (17.8 mg, 24.6 μmol, 48%) as a light yellow oil.

Physical state: light yellow oil

$\mathbf{R_f}$ = 0.49 (6:1 hexane:EtOAc)

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.35 – 7.31 (m, 2H), 7.26 (s, 1H), 6.90 – 6.85 (m, 2H), 5.83 (t, *J* = 7.2 Hz, 1H), 5.50 (dd, *J* = 15.4, 7.4 Hz, 1H), 5.39 (dd, *J* = 15.4, 8.7 Hz, 1H), 5.26 (d, *J* = 9.7 Hz, 1H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.41 – 4.32 (m, 2H), 3.33 (s, 3H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.51 – 2.32 (m, 2H), 2.28 (d, *J* = 1.2 Hz, 3H), 1.77 – 1.67 (m, 5H), 1.56 (s, 3H), 1.53 – 1.41 (m, 3H), 1.32 – 1.19 (m, 20H), 1.06 (s, 9H), 0.92 (t, *J* = 6.7 Hz, 3H), 0.75 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, C_6D_6): δ = 198.42, 166.55, 159.68, 138.79, 138.16, 134.97, 131.46, 129.55, 127.29, 123.05, 121.80, 114.06, 108.98, 87.85, 76.86, 75.78, 69.57, 54.78, 44.47, 42.58, 42.35, 32.37, 30.71, 30.27, 30.13, 30.06, 29.97, 29.85, 29.56, 29.22, 29.04, 28.86, 28.17, 26.86, 26.17, 23.16, 18.76, 15.51, 14.42, 11.89 ppm.

HRMS (+ESI): calc. for $C_{44}H_{72}NSO_6^+$: 742.5075 $[M+NH_4]^+$

found: 742.5094 $[M+NH_4]^+$

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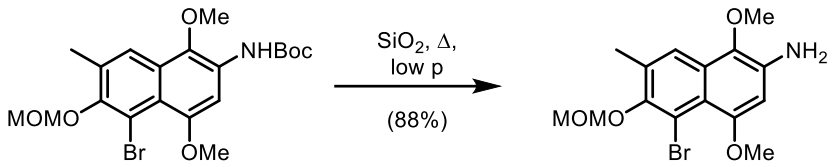
[1] *Angew. Chem.***2014**, *126*, 9126–9130

Boc-deprotection of carbamate **S9**



S9 **274**

Naphthyl amine 274. Carbamate **S9** (54.0 mg, 119 μmol) was dissolved in DCM (5.0 mL). Silica (200 °C oven dried overnight, 900 mg) was added and the mixture carefully concentrated under reduced pressure. Then, the flask was flushed with argon, after which vacuum was applied (0.03 mbar). The flask was then immersed in an oil bath and heated to 75 °C for 17 h. Then, heating was stopped, the flask carefully filled with argon and the silica poured onto a column (equilibrated with 1:1 *n*-pentane:EtOAc). Elution (1:1 *n*-pentane:EtOAc) furnished air sensitive naphthyl amine **274** (37.5 mg, 105 μmol, 88%) as a red oil.

Physical state: red oil

$\mathbf{R_f}$ = 0.52 (3:1 hexane:EtOAc)

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.82 (s, 1H), 5.95 (s, 1H), 5.09 (s, 2H), 3.51 (s, 3H), 3.46 (s, 3H), 3.37 (s, 3H), 3.28 (br s, 2H), 2.43 (d, *J* = 1.0 Hz, 3H). ppm.

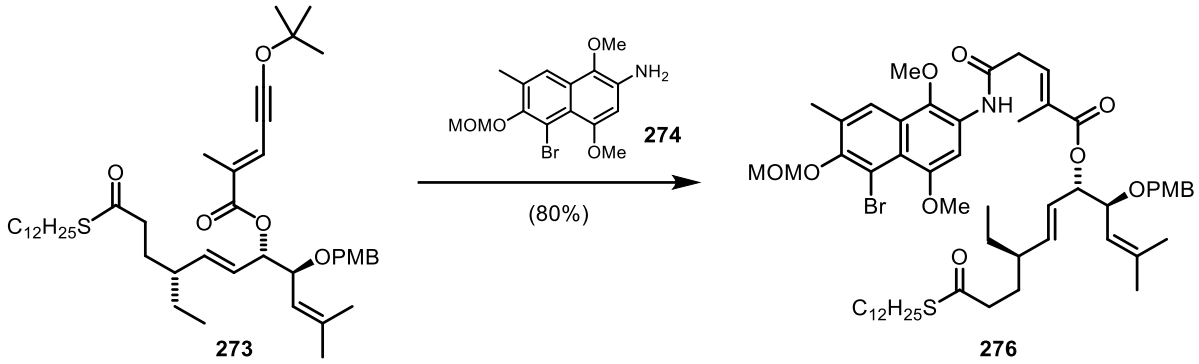
^{13}C-NMR (100 MHz, C_6D_6): δ = 153.29, 151.61, 135.91, 133.32, 133.11, 129.40, 121.53, 118.51, 112.69, 100.68, 100.34, 59.27, 57.31, 55.71, 18.64 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3368 (m), 2935 (m), 1627 (s), 1571 (w), 1460 (m), 1416 (m), 1378 (s), 1312 (s), 1235 (s), 1149 (s), 1064 (m), 1031 (s), 980 (s), 923 (s), 823 (w), 780 (m) cm^{-1}.

HRMS (+ESI): calc. for $C_{15}H_{19}N\,O_6Br^{79+}$: 356.0492 $[M+H]^+$

found: 356.0493 $[M+H]^+$

Ketene coupling of alkynyl ether **273** and naphthyl amine **274**



Amide 276. A solution of naphthyl amine **274** (7.80 mg, 21.9 µmol, 1.0 eq) and ynol ether **273** (17.4 mg, 24.0 µmol, 1.1 eq) in toluene (1.5 mL) was heated to 80 °C for 50 min. Then, the mixture was concentrated under reduced pressure and purified by flash column chromatography (4:1 *n*-pentane:Et_2O) to yield amide**276** (17.9 mg, 17.5 µmol, 80%) as a pale yellow oil.

Physical state: pale yellow oil

$\mathbf{R_f}$ = 0.57 (2:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_D^{16}$ = +17.7 (*c* = 0.37 in $CHCl_3$)

^{1}H-NMR (600 MHz, C_6D_6): δ = 8.51 (s, 1H), 7.79 (d, *J* = 1.1 Hz, 1H), 7.65 (s, 1H), 7.37 – 7.32 (m, 2H), 7.23 (td, *J* = 7.5, 1.6 Hz, 1H), 6.91 – 6.86 (m, 2H), 5.79 (t, *J* = 7.0 Hz, 1H), 5.49 – 5.40 (m, 2H), 5.22 (dp, *J* = 9.7, 1.4 Hz, 1H), 5.08 (s, 2H), 4.66 (d, *J* = 11.9 Hz, 1H), 4.39 (dd, *J* = 9.7, 7.4 Hz, 1H), 4.36 (d, *J* = 11.8 Hz, 1H), 3.67 (s, 3H), 3.44 (s, 3H), 3.35 (s, 3H), 3.33 (s, 3H), 2.86 (td, *J* = 7.3, 1.4 Hz, 2H), 2.82 – 2.76 (m, 2H), 2.49 – 2.42 (m, 4H), 2.37 (ddd, *J* = 15.3, 9.1, 6.4 Hz, 1H), 1.83 (d, *J* = 1.4 Hz, 3H), 1.75 (d, *J* = 1.5 Hz, 3H), 1.74 – 1.68 (m, 2H), 1.58 (d, *J* = 1.3 Hz, 3H), 1.50 (p, *J* = 7.4 Hz, 2H), 1.46 – 1.41 (m, 1H), 1.34 – 1.16 (m, 19H), 1.09 (ddd, *J* = 13.6, 8.6, 7.3 Hz, 1H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.77 (t, *J* = 7.4 Hz, 3H)ppm.

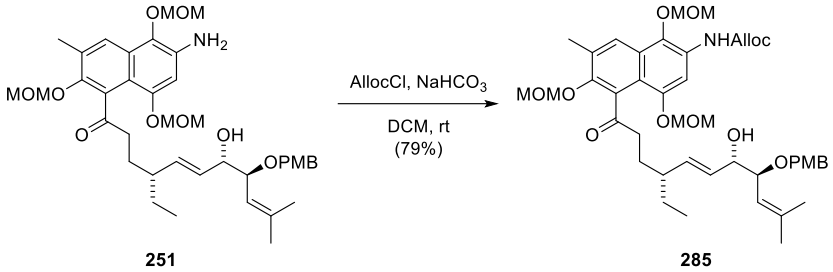
^{13}C-NMR (150 MHz, C_6D_6): δ = 198.37, 166.95, 166.39, 159.77, 153.74, 153.20, 139.27, 138.56, 135.98, 133.72, 133.17, 132.69, 131.33, 129.54, 128.59, 122.89, 122.46, 121.50, 114.17, 112.90, 101.47, 100.46, 77.41, 75.87, 69.60, 61.03, 57.34, 55.61, 54.82, 44.42, 42.35, 37.54, 32.36, 30.70, 30.26, 30.12, 30.11, 30.05, 29.95, 29.83, 29.55, 29.23, 29.08, 28.14, 26.16, 23.14, 18.83, 18.62, 14.39, 13.09, 11.85 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3336 (br w), 2925 (s), 2854 (m), 1692 (s), 1623 (m), 1612 (m), 1574 (w), 1513 (m), 1482 (m), 1456 (m), 1366 (m), 1316 (m), 1246 (s), 1160 (m), 1070 (m), 1033 (m), 980 (m), 927 (m), 824 (w), 732 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{54}H_{77}NSBr^{79}O_{10}^{+}$: 1024.4437 $[M+NH_4]^+$

found: 1024.4436 $[M+NH_4]^+$

Alloc-protection of naphthylamine **251**



251 **285**

Carbamate (285). To naphthylamine**251** (92.0 mg, 132 µmol, 1.0 eq) under argon was added DCM (1.7 mL) and $NaHCO_3$ (33.3 mg, 396 µmol, 3 eq). Then, allyl chloroformate (16.8 µL, 159 µmol, 1.2 eq) in DCM (1.7 mL) was added and the reaction mixture stirred for 15 h at ambient temperature. The mixture was then poured onto H_2O, extracted three times with EtOAc and the combined organic phases dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 3:1 → 2:1 *n*-pentane:EtOAc) afforded carbamate **285** (81.0 mg, 104 µmol, 79%) as a light yellow oil.

Physical state: light yellow oil

$\mathbf{R_f}$ = 0.55 (2:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = −26 (*c* = 0.19 in $CHCl_3$)

*Note: At room temperature compound **285** exists as a mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers and the carbon NMR signals as they appear at 25 °C, even though some signals overlap.*

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.03 – 7.86 (m, 2H), 7.69 (s, 1H), 7.24 – 7.17 (m, 2H), 6.88 – 6.82 (m, 2H), 6.04 – 5.94 (m, 1H), 5.50 – 5.20 (m, 5H), 5.17 – 5.11 (m, 2H), 5.06 – 4.89 (m, 4H), 4.72 – 4.66 (m, 2H), 4.51 – 4.44 (m, 1H), 4.25 – 4.18 (m, 1H), 3.98 – 3.89 (m, 1H), 3.87 – 3.81 (m, 1H), 3.81 – 3.77 (m, 3H), 3.67 – 3.62 (m, 3H), 3.57 – 3.53 (m, 3H), 3.49 – 3.44 (m, 3H), 2.95 – 2.51 (m, 3H), 2.49 – 2.42 (m, 3H), 2.02 – 1.93 (m, 1H), 1.91 – 1.73 (m, 2H), 1.64 – 1.60 (m, 1.5H), 1.54 –1.51 (m,

1.5H), 1.49 – 1.47(m, 1.5H), 1.48 (m, 1.5H), 1.46 – 1.42 (m, 1H), 1.34 – 1.27 (m, 1H), 0.87 – 0.82 (m, 3H) ppm.

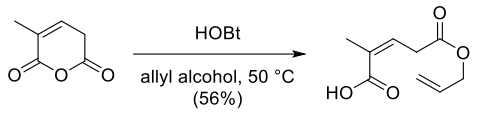
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 206.81, 206.77, 159.3, 153.4, 149.6, 149.5, 148.87, 148.85, 139.2, 136.9, 136.8, 135.44, 135.35, 133.1, 133.0, 132.6, 131.4, 131.3, 130.5, 129.6, 128.7, 128.6, 128.4, 126.3, 123.2, 122.1, 122.0, 118. 8, 118.7, 118.1, 113.9, 102.7, 102.6, 101.6, 101.1, 95.7, 95.5, 79.2, 79.1, 74.73, 74.69, 69.60, 69.55, 66.0, 57.9, 57.78, 57.75, 57.0, 55.4, 44.3, 44.2, 43.5, 43.2, 28.3, 28.23, 28.17, 28.0, 25.9, 25.8, 18.8, 17.8, 11.8 ppm.

IR (ATR, film): $\tilde{\nu}$ = 2930 (m), 1736 (m), 1706 (m), 1627 (m), 1514 (m), 1499 (m), 1453 (w), 1377 (w), 1247 (s), 1207 (s), 1157 (s), 1070 (s), 1035 (s), 954 (s), 930 (s), 821 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{43}H_{61}N_2O_{12}^+$: 797.4219 $[M+NH_4]^+$

found: 797.4220 $[M+NH_4]^+$

Opening of anhydride **281**



69 **281**

(*Z*)-5-(allyloxy)-2-methyl-5-oxopent-2-enoic acid (281). To anhydride **69**[I] (100 mg, 793 μmol, 1 eq) and HOBt (84%, 24.3 mg, 151 μmol, 0.2 eq) was added allyl alcohol (3.8 mL). The mixture was heated to 50 °C for 15 h and then concentrated on a rotary evaporator. Flash column chromatography (silica, 2:1 *n*-pentane:EtOAc) afforded allyl ester **281** (81.0 mg, 440 μmol, 56%) as a white solid.

Physical state: waxy white solid

R_f = 0.20 (2:1 hexane:EtOAc)

Melting point: 48–50 °C

^{1}H-NMR (400 MHz, CD_3OD):δ = 6.21 (tq, *J* = 7.1, 1.6 Hz, 1H), 5.94 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.31 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.60 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.60 (dq, *J* = 7.1, 1.5 Hz, 2H), 1.94 (q, *J* = 1.5 Hz, 3H)ppm.

^{13}C-NMR (100 MHz, CD_3OD): δ = 172.9, 170.5, 134.3, 133.6, 131.7, 118.3, 66.4, 35.5, 20.8 ppm.

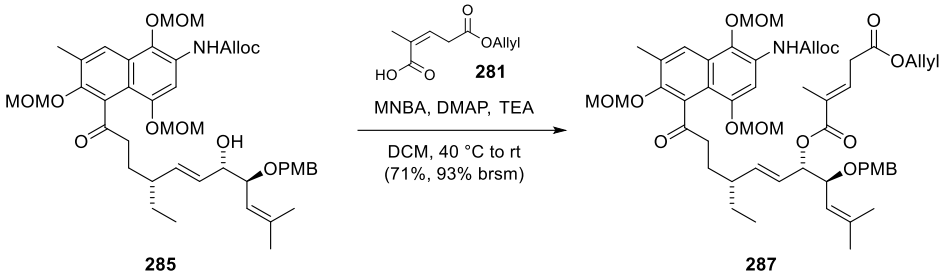
[I]preparation of **69** seeZhao, G.; Wu, J.; Dai, W.-M.*Tetrahedron*, **2015**, *71*, 4779–4787

IR (ATR, solid): $\tilde{\nu}$ = 2929 (m), 1739 (s), 1693 (s), 1647 (m), 1458 (m), 1317 (m), 1264 (m), 1175 (s), 987 (m), 932 (m) cm^{-1}.

HRMS (−ESI): calc. for $C_9H_{11}O_4^-$: 183.0663 $[M-H]^-$

found: 183.0662 $[M-H]^-$

Esterification of allylic alcohol **285** with carboxylic acid **281**



Ester 287. To glutaconic acid derivate **281** (57.4 mg, 312 µmol, 3.0 eq), 2-methyl-6-nitrobenzoic anhydride (107 mg, 312 µmol, 3.0 eq) and DMAP (38.1 mg, 312 µmol, 3.0 eq) was added DCM (6.2 mL) in a Schlenk flask under argon. Triethylamine (59.0 µL, 426 µmol, 4.1 eq) was added and the yellow solution turned dark red. Allylic alcohol **285** (81.0 mg, 104 µmol, 1.0 eq) in DCM (6.2 mL) was added and the mixture heated to 40 °C for 30 min and then stirred at room temperature for 16 h. Then reaction mixture was poured onto pH 7 phosphate buffer and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 3.5:1 → 3:1 → 2.5:1 *n*-pentane:EtOAc) afforded starting material **285** (19 mg, 24 µmol, 23%) as well as ester **287** (70.0 mg, 74 µmol, 71%, 93% brsm) as a pale yellow oil.

Physical state: pale yellow oil

$\mathbf{R_f}$ = 0.76 (1:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +19 (*c* = 0.11 in $CHCl_3$)

*Note: At room temperature compound **287** exists as a mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers and the carbon NMR signals as they appear at 25 °C, even though some signals overlap.*

^{1}H-NMR (400 MHz, C_6D_6): δ = 8.50 (br s, 1H), 8.26 – 8.15 (m, 1H), 7.81 – 7.71 (m, 1H), 7.33 – 7.24 (m, 2H), 7.24 – 7.18 (m, 1H), 6.91 – 6.80 (m, 2H), 5.84 – 5.52 (m, 5H), 5.29 – 5.16 (m, 1H), 5.16 – 4.92 (m, 8H), 4.73 – 4.67 (m, 1H), 4.65 – 4.48 (m, 4H), 4.40 – 4.24 (m, 4H), 3.42 – 3.37 (m, 3H), 3.37 – 3.33 (m, 3H), 3.31 – 3.24 (m, 3H), 3.22 – 3.14 (m, 3H), 3.11 – 2.69 (m, 4H), 2.50 – 2.40 (m, 3H),

2.31 – 2.18 (m, 1H), 2.03 – 1.84 (m, 2H), 1.76 – 1.69 (m, 3H), 1.62 – 1.55 (m, 1.5H), 1.54 – 1.46 (m, 4.5H), 1.30 – 1.20 (m, 2H), 0.91 – 0.82 (m, 3H) ppm.

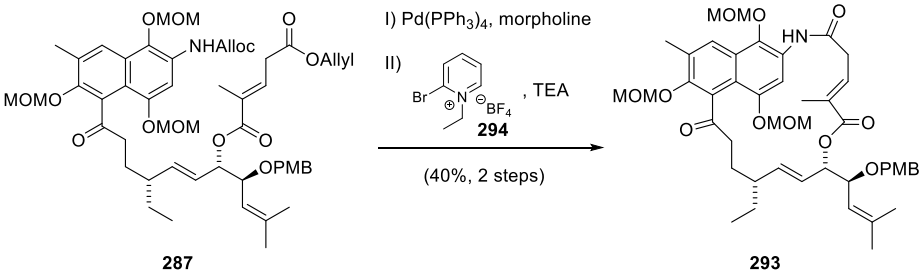
^{13}C-NMR (100 MHz, C_6D_6): δ = 205.3, 166.39, 166.36, 159.64, 159.62, 153.34, 153.30, 150.4, 150.3, 149.48, 149.45, 139.5, 139.4, 138.30, 138.25, 135.9, 133.54, 133.47, 133.1, 132.9, 132.6, 132.5, 132.4, 131.44, 131.38, 129.5, 129.2, 129.1, 126.9, 126.6, 126.5, 123.3, 122.84, 122.76, 119.5, 118.0, 117.7, 114.1, 114.0, 102.4, 102.3, 101.0, 95.8, 95.7, 77.0, 75.9, 75.8, 69.6, 69.5, 65.9, 65.4, 57.4, 57.3, 57.1, 56.6, 54.8, 44.6, 44.5, 43.5, 43.3, 34.03, 34.01, 28.8, 28.4, 28.1, 25.9, 25.8, 18.7, 17.93, 17.90, 13.0, 12.02, 12.00ppm.

IR (ATR, film): $\tilde{\nu}$ = 2926 (m), 1738 (s), 1711 (s), 1628 (w), 1514 (m), 1501 (m), 1366 (w), 1248 (s), 1206 (s), 1158 (s), 1073 (m), 1036 (m), 931 (m), 820 (w)cm^{-1}.

HRMS (−ESI): calc. for $C_{52}H_{66}NO_{15}^-$: 944.4438 [M−H]$^-$

found: 944.4437 [M−H]$^-$

Deprotection and macrolactamization of amino acid **29**



Macrolactam 293. In an argon filled Schlenk flask Alloc/Allyl protected amino acid **287** (10.0 mg, 10.6 μmol, 1.0 eq) was dissolved in THF (3.20 mL, freshly degassed) containing morpholine (18.4 mg, 212 μmol, 20 eq). The mixture was cooled with an ice bath and $Pd(PPh_3)_4$ (3.10 mg, 2.60 μmol, 0.25 eq) was added. After 12 min at 0 °C the mixture was poured onto pH 7 phosphate buffer. The mixture was extracted three times with EtOAc, dried over $NaSO_4$ and concentrated on a rotary evaporator with a nitrogen inlet (the amino acid is sensitive to oxygen). The crude material was purified by flash column chromatography (DAVISIL, 1% → 2% → 5% MeOH in DCM) and concentrated on a rotary evaporator with a nitrogen inlet. The thus obtained amino acid was either used directly in a cyclization reaction or stored overnight under argon in a matrix of degassed benzene at −20 °C for a maximum of one day.

To a solution of 2-bromo-1-ethylpyridinium tetrafluoroborate (**294**) (4.30 mg, 15.9 μmol, 1.5 eq) in DCM (20 mL) under argon was added triethylamine (4.4 μL, 3.2 μmol, 3.0 eq). A solution of the amino acid in DCM (30 mL) was added to the mixture *via* a Teflon hose over 8 h. After 9 more hours of stirring at room temperature, the reaction mixture was poured onto pH 7

phosphate buffer and extracted three times with EtOAc, washed with brine, dried over $Na_2SO_4$and concentrated on a rotary evaporator. Flash column chromatography (DAVISIL, 5% →10% →15% acetone in DCM) afforded macrolactam **293** (3.40 mg, 4.24 μmol, 40% over 2 steps) as a single atropisomer.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.38 (15% acetone in DCM)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +15 (*c* = 0.23 in $CHCl_3$)

^{1}H-NMR (800 MHz, C_6D_6): δ = 7.97 (q, *J* = 1.0 Hz, 1H), 7.21 – 7.19 (m, 2H), 6.80 – 6.75 (m, 2H), 6.71 (ddq, *J* = 10.8, 3.6, 1.6 Hz, 1H), 6.69 (s, 1H), 6.46 (s, 1H), 5.70 (td, *J* = 7.1, 1.0 Hz, 1H), 5.51 (dd, *J*= 16.1, 6.3 Hz, 1H), 5.28 (ddd,*J* = 16.1, 7.3, 1.1 Hz, 1H), 5.21 (d, *J* = 6.7 Hz, 1H), 5.19 (d, *J* = 5.8 Hz, 1H),5.13 – 5.11 (m, 1H), 5.11 (d,*J*= 5.9 Hz,1H), 4.88 (d, *J* = 6.7 Hz, 1H), 4.84 (d, *J* = 5.9 Hz, 1H), 4.80 (d, *J* = 5.9 Hz, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.23 (d, *J* = 12.1 Hz, 1H), 4.16 (dd, *J* = 9.6, 6.9 Hz, 1H), 3.57 (dd, *J* = 16.0, 10.8 Hz, 1H), 3.39 (s, 3H), 3.32 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 2.97 (ddq, *J* = 16.0, 3.6, 1.7 Hz, 1H), 2.76 (ddd, *J* = 16.1, 9.0, 7.1 Hz, 1H), 2.69 (ddd, *J* = 16.1, 9.5, 6.6 Hz, 1H), 2.39 (d, *J* = 1.0 Hz, 3H), 2.14 – 2.08 (m, 2H), 1.99 – 1.93 (m, 1H), 1.55 (d, *J* = 1.4 Hz, 3H), 1.39 (d, *J* = 1.4 Hz, 3H), 1.17 (dd, *J* = 1.7, 1.6 Hz, 3H), 1.14 – 1.11 (m, 2H), 0.74 (t, *J* = 7.4 Hz, 3H)ppm.

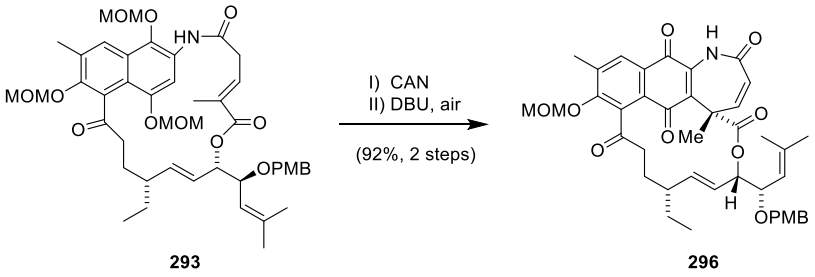
^{13}C-NMR (200 MHz, $CDCl_3$): δ = 204.7, 171.2, 166.2, 159.7, 152.0, 148.5, 143.4, 138.0, 137.7, 134.9, 133.8, 131.6, 131.2, 130.1, 129.4, 126.3, 124.8, 122.8, 122.6, 114.0, 111.4, 108.0, 103.1, 100.2, 95.6, 75.74 (2C), 69.4, 57.8, 57.3, 56.5, 54.8, 42.3, 41.9, 36.9, 28.2, 26.0, 25.7, 18.6, 17.9, 12.2, 12.0ppm.*(one aromatic C buried under solvent signal)*

IR (ATR, film): $\tilde{\nu}$ = 3358 (m), 3198 (w), 2923 (s), 2852 (m), 1707 (m), 1660 (m), 1633 (s), 1513 (w), 1468 (w), 1246 (m), 1158 (m), 1071 (m), 1017 (m), 935 (m), 810 (w), 723 (w) cm^{-1}.

HRMS (−ESI): calc. for $C_{45}H_{56}NO_{12}^-$: 802.3808 $[M-H]^-$

found: 802.3808 $[M-H]^-$

Oxidation and ring-contraction of macrolactam **293**



293 **296**

Azepinone 296. Macrolactam **293** (2.20 mg, 2.74 μmol, 1.0 eq) in MeCN (860 μL) and H_2O (150 μL) was cooled to 0 °C under argon. Ceric ammonium nitrate (4.50 mg, 8.21 μmol, 3.0 eq) was added and the reaction was stirred for 15 min at 0 °C. Then, the reaction mixture was poured onto H_2O and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The obtained material was redissolved in benzene (4.5 mL) and MeOH (2.25 mL), DBU (0.42 mg, 2.74 μmol, 1 eq) was added and the mixture was left stirring for 20 h under air. Then, the reaction mixture was poured onto pH 7 phosphate buffer and extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude material was purified by flash column chromatography (DAVISIL, 3% acetone in DCM) affording azepinone **296** (1.80 mg, 2.51 μmol, 92% over 2 steps) as a yellow oil.

Physical state: yellow oil

$\mathbf{R_f}$ = 0.83 (5% acetone in DCM)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = −9 (*c* = 0.05 in DCM)

^{1}H-NMR (400 MHz, C_6D_6): δ = 8.68 (d, *J* = 2.4 Hz, 1H), 7.55 (d, *J* = 0.7 Hz, 1H), 7.28 – 7.21 (m, 2H), 6.90 – 6.81 (m, 2H), 6.27 (d, *J* = 12.5 Hz, 1H), 6.16 (dd, *J* = 16.0, 6.0 Hz, 1H), 6.06 (t, *J* = 8.6 Hz, 1H), 5.95 (dd, *J* = 12.5, 2.3 Hz, 1H), 5.20 (dd, *J* = 16.2, 8.7 Hz, 1H), 5.03 (dh, *J* = 9.7, 1.3 Hz, 1H), 4.97 (d, *J* = 6.0 Hz, 1H), 4.91 (d, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.29 (dd, *J* = 9.7, 8.5 Hz, 1H), 4.17 (d, *J* = 11.5 Hz, 1H), 3.35 (s, 3H), 3.21 (s, 3H), 2.81 – 2.66 (m, 1H), 2.45 – 2.27 (m, 2H), 2.09 – 2.03 (m, 1H), 2.01 (s, 3H), 1.93 – 1.83 (m, 1H), 1.52 (d, *J* = 1.4 Hz, 3Hz), 1.47 (s, 3H), 1.37 (d, *J* = 1.3 Hz, 3H), 1.23 – 1.13 (m, 1H), 1.06 – 0.97 (m, 1H), 0.64 (t, *J* = 7.3 Hz, 3H) ppm.

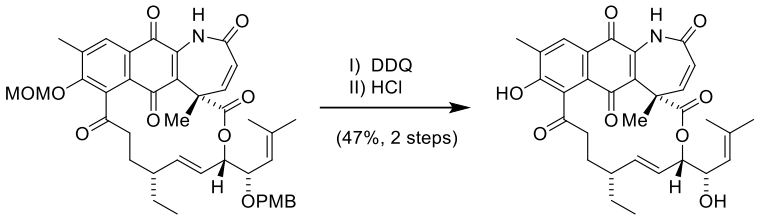
^{13}C-NMR (100 MHz, C_6D_6): δ = 202.6, 189.2, 182.0, 178.8, 172.2, 164.0, 159.9, 158.4, 146.4, 141.8, 139.3, 138.7, 138.0, 135.8, 130.9, 130.8, 129.7, 126.0, 124.8, 124.1, 122.59 (2C), 114.2, 102.4, 76.8, 76.3, 69.6, 57.4, 54.9, 50.8, 39.9, 37.8, 25.9, 24.9, 24.6, 22.7, 18.7, 17.0, 11.9 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3360 (w), 3300 (w), 2924 (vs), 2853 (m), 2361 (w), 1743 (m), 1697 (m), ,1670 (s), 1652 (m), 1631 (s), 1577 (w), 1514 (m), 1467 (m), 1413 (w), 1374 (w), 1331 (s), 1298 (m), 1224 (s), 1159 (m), 1096 (m), 1044 (m), 972 (w), (m), 923 (m), 820 (w), 750 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{41}H_{49}N_2O_{10}^+$: 729.3382 $[M+NH_4]^+$

found: 729.3394 $[M+NH_4]^+$

Deprotection of azepinone**296**



Divergolide I (8). To azepinone **296** (3.30 mg, 4.64 μmol, 1 eq) under argon was added DCM (1.8 mL) and H_2O (180 μL) and the solution cooled to 0 °C. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.90 mg, 8.35 μmol, 1.8 eq) was added and the cooling bath removed. After 8.5 h, the solution was filtered first through a plug of celite/Na_2SO_4(DCM elution) and then through a plug of DAVISIL (elution with 5% acetone in DCM). The material was concentrated and redissolved in MeOH (1.8 mL) and cooled to 0 °C. MeOH saturated with HCl (0.2 mL) was added drop wise and the cooling removed after 20 min at 0 °C. After 7 h of stirring at room temperature, the mixture was cooled to 0 °C and saturated aqueous $NaHCO_3$ was added drop wise until the mixture turned purple. The mixture was then poured onto saturated aqueous NH_4Cl and extracted six times with DCM (the organic phase turned yellow), the combined organic phases dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (DAVISIL, 5% acetone in DCM, 1 drop conc. acetic acid per 50 mL eluent) afforded divergolide I (**8**) (1.20 mg, 2.20 μmol, 47% over 2 steps) as a yellow solid.

Divergolide I (8):[I]

Physical state: yellow solid

R$_f$ = 0.18 (10% acetone in DCM)

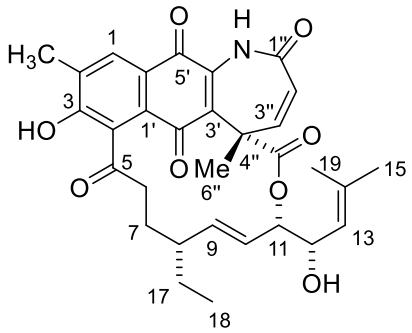
$[\alpha]_D^{20}$ = −174 (*c* = 0.24in MeOH) *Optical rotation Hertweck: −179 (c = 0.4 in MeOH)*

I**R** (ATR, film): $\tilde{\nu}$ = 3290 (w), 2960 (m), 2925 (s), 2854 (m), 1742 (m), 1692 (m), 1662 (m), 1223 (m), 1577 (m), 1453 (w), 1414 (w), 1373 (w), 1338 (s), 1259 (vs), 1223 (s), 1096 (vs), 1053 (s), 1028 (s), 975 (w), 926 (w), 801 (vs), 744 (w), 673 (w) cm^{-1}.

IR Hertweck: $\tilde{\nu}$ = 3284, 2932, 1693, 1622, 1575, 1452, 1340, 1258, 1227, 1100, 976, 906, 673, 631 cm^{-1}.

HRMS (−ESI): calc. for $C_{31}H_{32}NO_8^-$: 546.2133 [M−H]$^-$

found: 546.2141 [M−H]$^-$



divergolide I (**1**)

NMR data are given in the table below. Atom numbering refers to the numbering originally suggested by Hertweck.

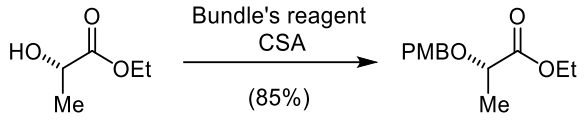
[I]**Isolation divergolide I**: Ding, L.; Franke, J.; Hertweck, C.*Org.Biomol. Chem.***2015**, *13*, 1618−1623.

C-4'' reassignment: Sun, C.; Zhang, C.; Qin, X.; Wei, X.; Liu, Q.; Li, Q.; Ju, J. *Tetrahedron***2018**, *74*, 199−203

Comparison of NMR data of the isolated material (Hertweck) and fully synthetic material (Trauner)

	Hertweck	**Trauner**	**Hertweck**	**Trauner**
Position	**^{1}H-spectrum**	**^{1}H-spectrum**	**^{13}C-spectrum**	**^{13}C-spectrum**
1	7.95 (d, *J* = 0.4 Hz)	7.97 (d, *J* = 0.9 Hz)	131.3	131.3
2	-	-	133.5	133.5
3	-	-	158.1	158.1
4	-	-	122.2	122.1
5	-	-	208.5	208.6
6	2.73 (m), 2.11 (m)	2.76 (dt, *J* = 18.2, 6.6 Hz), 2.09 (dt, 18.0, 8.6 Hz)	38.3	38.2
7	1.89 (m)	1.93-1.85 (m)	24.8	24.8
8	2.33 (m)	2.37-2.30 (m)	39.6	39.5
9	6.01 (dd, *J* = 16.0, 6.0 Hz)	6.02 (dd, *J* = 16.0, 6.1 Hz)	141.9	141.9
10	5.18 (dd, 15.8, 8.8 Hz)	5.19 (dd, 16.2, 8.7 Hz)	123.5	123.5
11	5.48 (dd, 8.2, 8.2 Hz)	5.49 (dd, *J* = 8.2 8.2 Hz)	78.7	78.6
12	4.42 (dd, 8.2, 8.2 Hz)	4.42 (dd, *J* = 8.2, 8.2 Hz)	70.0	69.9
13	5.06 (d, *J* = 9.0 Hz)	5.06 (dt, *J* = 9.0, 1.5 Hz)	122.8	122.7
14	-	-	138.6	138.7
15	1.69 (d, 0.9 Hz)	1.70 (d, 1.3 Hz)	25.9	25.8
16	2.32 (d, *J* = 0.4 Hz)	2.33 (d, *J* = 0.8 Hz)	16.5	16.4
17	1.25 (m)	1.28-1.24 (m)	22.6	22.5
18	0.79 (t, *J* = 7.3 Hz)	0.80 (t, *J* = 7.3 Hz)	11.7	11.7
19	1.66 (d, 0.9 Hz)	1.68 (d, 1.3 Hz)	18.7	18.6
1'	-	-	131.3	131.4
2'	-	-	182.6	182.5
3'	-	-	124.3	124.3
4'	-	-	135.6	135.5
5'	-	-	178.4	178.3
6'	-	-	124.8	124.6
1''	-	-	164.5	164.4
2''	6.08 (dd, *J* = 12.5, 2.2 Hz)	6.08 (dd, *J* = 12.5, 2.4 Hz)	122.8	122.7
3''	6.40 (d, *J* = 12.4 Hz)	6.40 (d, *J* = 12.5 Hz)	145.7	145.6
4''	-	-	50.2	50.2
5''	-	-	172.3	172.2
6''	1.58 (s)	1.56 (s)	24.4	24.4
NH	8.83 (d, *J* = 1.7 Hz)	8.81 (d, *J* = 1.3 Hz)	-	-
Ar-OH	not reported	8.08 (br s), visible when H_2O present	-	-

PMB-protection of (−)-ethyl lactate **180**



180 **301**

Ethyl (*S*)-2-((4-methoxybenzyl)oxy)propanoate(301). A solution of (−)-ethyl lactate**180** (967 µl, 8.46 mmol, 1.0 eq) and PMB-trichloroacetimidate (2.28 mL, 11.0 mmol, 1.3 eq) in DCM (12 mL) was cooled to 0 °C before CSA (197 mg, 846 µmol, 0.1 eq) was added. The mixture was allowed to warm to room temperature. After 14 h hexane was added (60 mL) and the mixture was cooled to −25 °C (30 min). The suspension was filtered through a pad of celite, concentrated on a rotary evaporator, dissolved in hexane (100 mL), cooled to −25 °C (2 h), filtered through a pad of celite and concentrated on a rotary evaporator. Flash column chromatography (silica, 98:2 ~~→97~~:3 ~~→9~~5:5 hexanes:EtOAc) afforded PMB ether **301** (1.71 g, 7.19 mmol, 85%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.42 (5:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −63.3 (*c* = 0.3 in DCM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ =7.33 – 7.27 (m, 2H), 6.91 – 6.84 (m, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.21 (qd, *J* = 7.2, 2.6 Hz, 2H), 4.02 (q, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm.

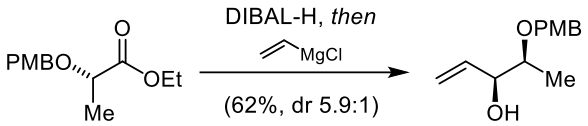
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.50, 159.46, 129.78, 113.92, 73.83, 71.75, 60.93, 55.39, 18.87, 14.38 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2921.6 (m), 1745.1 (s), 1613.2 (m), 1514.0 (s), 1465.7 (w), 1371.8 (w), 1371.8 (w), 1301.9 (m), 1248.8 (s), 1198.4 (m), 1142.4 (s), 1064.5 (m), 1033.5 (m), 821.7 (m) cm^{-1}.

HRMS (+EI): calc. for $C_{13}H_{18}O_4^+$: 238.1205 $[M]^+$

found: 238.1199 $[M]^+$

Grignard-addition to ester **301**



301 **300**

(3*S*,4*S*)-4-((4-methoxybenzyl)oxy)pent-1-en-3-ol (300). A solution of ester **301** (2.20 g, 9.23 mmol, 1.0 eq) in DCM (110 mL) was cooled to –98 °C before a solution of DIBAL-H (1.0 M in DCM, 13.9 mL, 13.8 mmol, 1.5 eq) was added *via* syringe pump (70 µL/min). After the addition, a solution of vinyl magnesium chloride (1.6 M in THF, 20.2 mL, 32.3 mmol, 3.5 eq) was added *via* syringe pump (900 µL/min). The mixture was allowed to warm to room temperature slowly in the cooling bath before saturated aqueous Rochelle's salt (200 mL) was added. After stirring for 30 min at room temperature, the suspension was extracted two times with DCM, the combined organic layers were dried over $MgSO_4$, concentrated on a rotary evaporator and purified by flash column chromatography [99.2:0.8 $CHCl_3$:acetone]. Allylic alcohol **300** (1.27 g, 5.73 mmol, 62%) was obtained as 5.9:1 mixture of diastereomers. **300** could be enriched to a dr. of 20:1 via flash column chromatography (silica, 99.2:0.8 $CHCl_3$:acetone).

Physical state: colorless oil

$\mathbf{R_f}$ = 0.42 (3:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ = +39.2 (*c* = 0.50 in DCM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = =7.21 – 7.18 (m, 2H), 6.87 – 6.78 (m, 2H), 5.75 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.30 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.16 (dt, *J* = 10.5, 1.3 Hz, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.33 (d, *J* = 11.1 Hz, 1H), 3.85 (t, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 3.34 (p, *J* = 6.4 Hz, 1H), 2.51 (br s, 1H), 1.11 (d, *J* = 6.2 Hz, 3H) ppm.

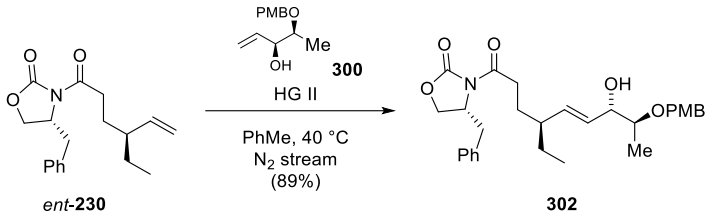
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.45, 136.98, 130.36, 129.59, 117.70, 114.04, 78.09, 76.81, 70.98, 55.44, 15.67 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3442.0 (w), 2975.0 (w), 2933.6 (w), 2870.1 (w), 2837.4 (w), 1612.6 (m), 1586.4 (w), 1513.5 (s), 1464.5 (w), 1376.0 (w), 1301.9 (w), 1247.6 (s), 1174.1 (w), 1078.2 (m), 1034.4 (s), 994.1 (m), 926.6 (w), 821.2 (m), 756.7 (w) cm^{-1}.

HRMS (+EI): calc. for $C_{13}H_{18}O_3^+$: 222.1256 $[M+2H]^+$

found: 222.1247 $[M+2H]^+$

Cross metathesis of olefin *ent*-**230** and allylic alcohol **300**



Olefin 302.Oxazolidinone*ent*-**230** (dr, 4.5:1, 500 mg, 1.66 mmol, 1 eq) and allylic alcohol **300** (553 mg, 2.49 mmol, 1.5 eq) were dissolved in degassed toluene (20 mL) and Hoveyda-Grubbs 2nd generation catalyst (104 mg, 166 µmol, 0.1 eq) was added. The mixture was heated to 40 °C and the septum was pierced in a way that enabled a constant flow of nitrogen through the flask's atmosphere, concentrating the reaction to dryness within 4 h. Flash column chromatography (silica, 4:1 → 3:1 *n*-pentane:Et_2O) afforded diastereomerically impure **302** (753 mg, 1.52 mmol, 92%), which was further chromatographed (silica, 6:1 *n*-pentane:EtOAc) to yield olefin **302** (542 mg, 1.09 mmol, 61%, 89% based on dr of *ent*-**230**) as a single diastereomer.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.53 (1:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = -11.3 (*c* = 0.3 in DCM)

^{1}H-NMR(400 MHz, $CDCl_3$): δ =7.37 – 7.29 (m, 2H), 7.28 – 7.25 (m, 3H), 7.23 – 7.16 (m, 2H), 6.92 – 6.85 (m, 2H), 5.48 (dd, *J* = 15.5, 8.4 Hz, 1H), 5.40 (dd, *J* = 15.4, 6.8 Hz, 1H), 4.72 – 4.53 (m, 2H), 4.38 (d, *J* = 11.1 Hz, 1H), 4.19 (t, *J* = 8.4 Hz, 1H), 4.12 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.87 (t, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 3.38 (p, *J* = 6.4 Hz, 1H), 3.28 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.03 – 2.83 (m, 2H), 2.74 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.13 (s, 1H), 1.97 (qt, *J* = 9.2, 4.8 Hz, 1H), 1.86 – 1.76 (m, 1H), 1.73 – 1.62 (m, 1H), 1.53 – 1.42 (m, 1H), 1.35 – 1.27 (m, 1H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H) ppm.

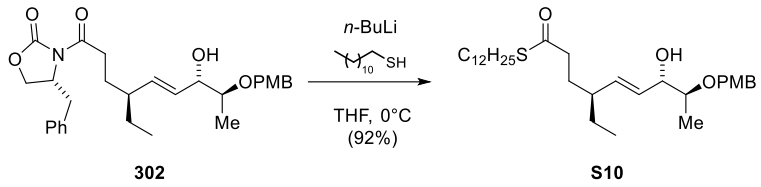
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.63, 159.40, 153.61, 137.93, 135.57, 130.46, 129.99, 129.58, 129.08, 127.43, 114.03, 78.46, 76.72, 70.95, 66.30, 55.43, 55.37, 44.57, 38.09, 33.55, 29.14, 28.04, 15.80, 12.01 ppm.

IR (ATR): $\tilde{\nu}$ = 3531 (w), 2961 (w), 2926 (m), 2872 (w), 1781 (s), 1698 (m), 1613 (w), 1514 (m), 1454 (w), 1387 (m), 1352 (m), 1302 (w), 1248 (s), 1212 (m), 1179 (m), 1079 (m), 1032 (m), 978 (w), 823 (w), 762 (w), 704 (w) cm^{-1}.

HRMS (+EI): calc. for $C_{29}H_{38}NO_6^+$: 496.2694 $[M+H]^+$

found: 496.2694 $[M+H]^+$

Thioesterification of oxazolidinone **302**



302 **S10**

***n*-Dodecyl (4*R*,7*S*,8*S*,*E*)-4-ethyl-7-hydroxy-8-((4-methoxybenzyl)oxy)non-5-enethioate (S10).**

n-Dodecane thiol (436 µL, 1.82 mmol, 2.5 eq) was dissolved in THF (10 mL) and cooled to 0 °C. A solution of *n*-BuLi (695 µL, 2.20 M in hexanes, 1.53 mmol, 2.1 eq) was added drop wise and after 5 min oxazolidinone **302** (361 mg, 728 µmol, 1 eq) was added drop wise as a solution in THF (10 mL). After 20 min at 0 °C, the reaction was quenched by adding saturated aqueous NH_4Cl. The mixture was extracted three times with EtOAc, the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 93:7 hexanes:EtOAc) afforded thioester **S10** (349 mg, 670 µmol, 92%) as a colorless oil.

Physical state: colorless oil

R_f = 0.21 (9:1 hexane:EtOAc)

$[\alpha]_D^{20}$ = +27.6 (*c* = 0.5 in DCM)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.28 – 7.26 (m, 2H), 6.91 – 6.86 (m, 2H), 5.44 (dd, *J* = 15.4, 8.3 Hz, 1H), 5.40 (dd, *J* = 15.4, 6.5 Hz, 1H), 4.61 (d, *J* = 11.1 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 3.88 (dd, *J* = 7.6, 6.4 Hz, 1H), 3.81 (s, 3H), 3.38 (dq, *J* = 7.6, 6.2 Hz, 1H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.58 – 2.45 (m, 2H), 1.94 – 1.86 (m, 2H), 1.83 – 1.76 (m, 1H), 1.61 – 1.51 (m, 3H), 1.47 – 1.38 (m, 1H), 1.35 – 1.33 (m, 1H), 1.31 – 1.24 (m, 18H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H) ppm.

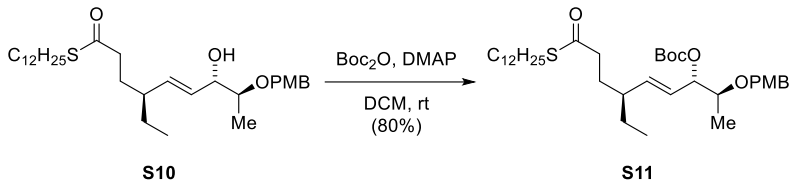
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 199.96, 159.45, 137.46, 130.40, 130.19, 129.59, 114.05, 78.44, 76.62, 70.97, 55.42, 44.10, 42.23, 32.06, 30.49, 29.79, 29.77, 29.73, 29.64, 29.49, 29.28, 29.00, 28.99, 28.00, 22.84, 15.79, 14.27, 11.89 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 3467 (w), 1925 (s), 2854 (m), 1690 (m), 1613 (w), 1514 (m), 1464 (w), 1377 (w), 1302 (w), 1248 (m), 1173 (w), 1084 (m), 1038 (m), 973 (w), 822 (w) cm^{-1}.

HRMS (+EI): calc. for $C_{31}H_{52}SO_4$: 520.3586 [M]

found: 520.3578 [M]

Boc protection of thioester **S10**



S10 **S11**

Allylic carbonate (S11).To allylic alcohol **S10** (847 mg, 1.63 mmol, 1 eq) in THF (8.7 mL) was added DMAP (199 mg, 1.63 mmol, 1 eq) and di-*tert*-butyl dicarbonate (1.06 g, 4.88 mmol, 3 eq) as a solution in THF (9.5 mL) at room temperature. After 1.5 h of stirring at room temperature the reaction was quenched by addition of water. The mixture was extracted three times with EtOAc, the combined organic extracts washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 19:1 → 10:1 *n*-pentane:EtOAc) afforded carbonate **S11** (807 mg, 1.30 mmol, 80%) as a colorless oil.

Physical state: colorless oil

R_f = 0.46 (9:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$ = +14.0 (*c* = 1.0 in DCM)

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.27 – 7.25 (m, 2H), 6.88 – 6.83 (m, 2H), 5.46 (dd, *J* = 15.4, 8.3 Hz, 1H), 5.42 (dd, *J* = 15.4, 6.9 Hz, 1H), 5.02 (t, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 3.79 (s, 3H), 3.62 (p, *J* = 6.3 Hz, 1H), 2.86 – 2.80 (m, 2H), 2.54 – 2.40 (m, 2H), 1.93 – 1.86 (m, 1H), 1.83 – 1.76 (m, 1H), 1.56 – 1.51 (m, 3H), 1.48 (s, 9H), 1.44 – 1.38 (m, 1H), 1.34 – 1.24 (m, 19H), 1.14 (d, *J* = 6.4 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H) ppm.

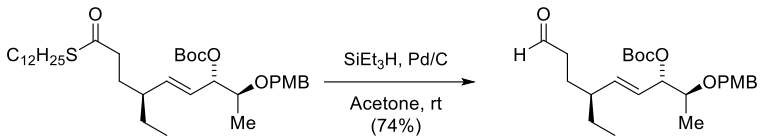
^{13}C-NMR (150 MHz, $CDCl_3$): δ = 199.79, 159.21, 153.07, 139.34, 130.83, 129.36, 126.30, 113.79, 82.00, 80.24, 75.56, 71.34, 55.37, 44.19, 42.12, 32.04, 30.39, 29.77, 29.76, 29.72, 29.71, 29.63, 29.48, 29.26, 28.97, 28.93, 28.00, 27.97, 22.82, 16.33, 14.25, 11.82 ppm

IR (ATR, neat): $\tilde{\nu}$ = 3356 (br, w), 2958 (w), 2924 (m), 2854 (m), 1739 (m), 1690 (m), 1613 (w), 1587 (w), 1517 (m), 1457 (w), 1393 (w), 1368 (m), 1339 (m), 1302 (m), 1273 (s), 1248 (s), 1162 (s), 1095 (m), 1036 (m), 972 (m), 856 (m), 821 (m), 792 (m), 764 (w), 721 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{36}H_{64}NO_6S^+$: 638.4449 $[M+NH_4]^+$

found: 683.4438 $[M+NH_4]^+$

Fukuyama reduction of thioester **S11**



S11 **304**

***t*-Butyl ((2*S*, 3*S*, 6*S*, *E*)-6-ethyl-2-((4-methoxybenzyl)oxy)-9-oxonon-4-en-3 yl) carbonate (304)**.

To thioester **S11** (100 mg, 161 µmol, 1 eq) and palladium on charcoal (10%, 16.7 mg, 16.1 µmol, 0.1 eq) was added $SiEt_3H$ (129 µL, 805 µmol, 5 eq) as a solution in acetone (8.0 mL). After stirring at room temperature for 30 min, the reaction mixture was filtered through celite and concentrated on a rotary evaporator. Flash column chromatography (silica, 9:1 *n*-pentane:EtOAc) afforded aldehyde **304** (50.3 mg, 120 µmol, 74%) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.19 (9:1 hexane:EtOAc)

$[\alpha]_D^{20}$ = +8.4 (*c* = 0.5 in DCM)

^{1}H-NMR (400 MHz, $CDCl_3$): δ =9.71 (t, *J* = 1.5 Hz, 1H), 7.27 – 7.25 (m, 2H), 6.90 – 6.80 (m, 2H), 5.49 – 5.36 (m, 2H), 5.02 (t, *J* = 6.5 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.62 (p, *J* = 6.4 Hz, 1H), 2.47 – 2.29 (m, 2H), 1.95 – 1.84 (m, 1H), 1.82 – 1.71 (m, 1H), 1.53 – 1.40 (m, 11H), 1.30 – 1.23 (m, 1H), 1.14 (d, *J* = 6.4 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H) ppm.

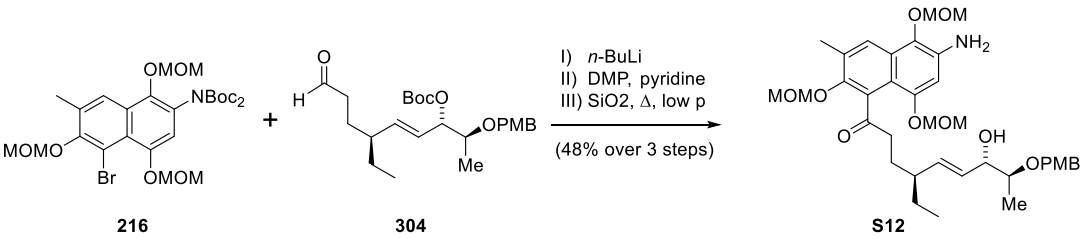
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 202.64, 159.23, 153.10, 139.55, 130.77, 129.43, 129.40, 126.33, 113.81, 82.07, 80.24, 77.48, 77.36, 77.16, 76.84, 75.46, 75.36, 71.34, 55.41, 44.32, 42.05, 28.11, 27.94, 26.92, 16.31, 11.91, 1.18 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2968 (w), 2933 (w), 2360 (w), 1738 (s), 1613 (w), 1514 (m), 1457 (w), 1369 (m), 1275 (s), 1251 (s), 1164 (m), 1098 (m), 1036 (m), 976 (w), 820 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{24}H_{40}NO_6^+$: 438.2850 $[M+NH_4]^+$

found: 438.2843 $[M+NH_4]^+$

Coupling of **304** and subsequent oxidation and deprotection



216 **304** **S12**

Amino alcohol S12. Naphthalene **216** (293 mg, 476 μmol, 2.0 eq) was dissolved in THF (20 mL) and cooled to –78 °C. A solution of *n*-BuLi (294 μl, 1.62 M in hexane, 476 μmol, 2.0 eq) was added dropwise at –78 °C. After 17 min aldehyde **304** (100 mg, 238 μmol, 1.0 eq) was added dropwise as solution in THF (3.0 mL). After 30 min, a sat. aq. solution of NH_4Cl (20 mL) was added, the reaction let come to room temperature and the mixture was extracted with three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 9:1 →7:3hexane:EtOAc) gave an inseparable mixture of mono- and di-*N*-Boc protected naphthyl alcohols as 1:1 mixture of diastereomers,each diastereomer existing as 1:1 mixture of atropisomers (148 mg) along with protodemetalated naphthalene**S5**(101 mg, 189 μmol, 40%, see above) as well as reisolated aldehyde **304** (26.3 mg, 62.5 μmol, 26%)

The obtained naphthyl alcohols (assuming 166 μmol, 1.0 eq) were dissolved in DCM (19.4 mL).Pyridine (196 μl) was added and the suspension treated with DMP (105 mg, 249 mmol, 1.5 eq) at r.t. After 20 min, a sat. aq. solution of $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) was added and the biphasic mixturestirred until the organic layer became a clear solution. The aqueous layer was extracted three times with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (silica, 9:1 →7:3 →3:1*n*-pentane:EtOAc) afforded the oxidation products (147 mg) as inseparable mixture of mono- and di-*N*-Boc protected products, each as a mixture of atropisomers.

A part of the mixture (136.1 mg, 160 μmol, 1.0 eq) was dissolved in DCM (40 mL) before silica (200 °C oven dried, 9.55 g) was added. The mixture was concentrated on a rotary evaporator and heated to 100 °C under high vacuum (<10^{-1} mbar). After 14 h the silica heating was removed and the reaction let come to room temperature. The silica was poured on a packed silica column. Elution with EtOAc and concentration of the product containing fractions on a rotary evaporator with a nitrogen inlet provided air sensitive naphthylamine **S12** (69.4 mg, 106 μmol, 66% over three steps) as a yellow oil. To avoid decomposition, **S12** was typically immediately *N*-protected as described below.

Physical state: yellow oil

$\mathbf{R_f}$ = 0.30 (1:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +16.5 (*c* = 1.33 in DCM)

*Note: At room temperature compound **S12** exists as a mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers (when signals overlap) and the carbon NMR signals as they appear at 25 °C, even though some signals overlap.*

^{1}H-NMR (600 MHz, C_6D_6): δ =7.84 (m, 1H), 7.17 – 7.15 (m, 1H), 7.14 – 7.11 (m, 1H), 6.81 – 6.76 (m, 2H), 6.55 – 6.51 (m, 1H), 5.54 – 5.44 (m, 2H), 5.11 – 5.04 (m, 2H), 4.98 – 4.93 (m, 1H), 4.92 – 4.83 (m, 3H), 4.44 (d, *J* = 11.4 Hz, 0.5H), 4.39 (d, *J* = 11.4 Hz, 0.5H), 4.23 (d, *J* = 11.4 Hz, 0.5H), 4.18 (d, *J* = 11.4 Hz, 0.5H), 3.99 – 3.95 (m, 1H), 3.64 (br s, 2H), 3.40 – 3.38 (m, 3H), 3.32 – 3.30 (m, 4H), 3.29 – 3.28 (m, 3H), 3.16 – 3.10 (m, 0.5H), 3.01 – 2.97 (m, 1H), 2.90 – 2.83 (m, 0.5H), 2.69 (br s, 0.5H), 2.66 (br s, 0.5H), 2.44 (d, *J* = 1.0 Hz, 1.5H), 2.41 (d, *J* = 1.0 Hz, 1.5H), 2.28 – 2.21 (m, 0.5H), 2.15 – 2.09 (m, 0.5H), 2.05 – 1.99 (m, 0.5H), 1.99 – 1.91 (m, 1H), 1.87 – 1.79 (m, 0.5H), 1.48 – 1.39 (m, 1H), 1.33 – 1.23 (m, 1H), 1.08 (d, *J* = 6.2 Hz, 1.5H), 1.05 (d, *J* = 6.1 Hz, 1.5iH), 0.90 – 0.86 (m, 3H) ppm.

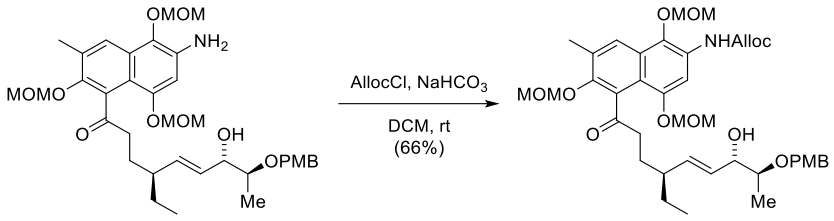
^{13}C-NMR (150 MHz, C_6D_6): δ = 205.83, 205.77, 159.80, 159.79, 149.90, 149.88, 148.34, 148.33, 137.33, 137.24, 136.81, 132.99, 132.98, 132.45, 132.42, 132.37, 132.28, 131.14, 131.07, 130.86, 129.58, 129.58, 128.46, 122.58, 122.54, 116.70, 116.63, 114.16, 114.15, 102.88, 102.66, 102.30, 102.12, 100.04, 100.02, 95.82, 95.75, 78.54, 78.48, 76.53, 76.48, 70.94, 70.88, 57.37, 57.32, 57.29, 56.39, 56.34, 54.81, 44.53, 44.29, 43.46, 43.27, 29.39, 29.21, 28.57, 28.14, 17.92, 17.91, 15.82, 15.74, 12.20 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 2933 (w), 1727 (m), 1613 (m), 1502 (m), 1465 (w), 1427 (w), 1368 (w), 1329 (w), 1255 (w), 1221 (w) (1150 (s), 1074 (m), 1026 (m), 973 (m), 924 (w), 877 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{36}H_{50}NO_{10}^+$: 656.3429 $[M+H]^+$

found: 656.3428 $[M+H]^+$

Alloc-protection of naphthylamine **S12**



S12 **306**

Carbamate 306. To naphthylamine**S12** (82.7 mg, 126 μmol, 1.0 eq) under argon was added DCM (1.7 mL) and $NaHCO_3$ (31.8 mg, 378 μmol, 3 eq). Then, allyl chloroformate (17.4 μL, 164 μmol, 1.3 eq) was added and the reaction mixture stirred for 18 h at ambient temperature. The mixture was then poured onto H_2O, extracted three times with EtOAc and the combined organic phases dried over Na_2SO_4 and concentrated on a rotary evaporator.Flash column chromatography (silica, 17:3 → 4:1 → 3:1 *n*-pentane:EtOAc) afforded carbamate **306** (61.7 mg, 83.4 μmol, 66%) as a light yellow oil.

Physical state: light yellow oil

$\mathbf{R}_f$ = 0.54 (1:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_D^{\mathbf{20}}$ = +15.0 (*c* = 1.0 in DCM)

*Note: At room temperature compound **306** exists as a mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing both atropisomers and the carbon NMR signals as they appear at 25 °C, even though some signals overlap.*

^{1}H-NMR (600 MHz, C_6D_6): δ = 8.51 (s, 1H), 8.24 – 8.15 (m, 1H), 7.77 – 7.73 (m, 1H), 7.16 – 7.12 (m, 2H), 6.82 – 6.75 (m, 2H), 5.78 – 5.69 (m, 1H), 5.55 – 5.44 (m, 2H), 5.16 – 5.07 (m, 3.5H), 5.06 – 5.01 (m, 1.5H), 4.98 – 4.93 (m, 1H), 4.71 – 4.67 (m, 1H), 4.64 – 4.60 (m, 1H), 4.53 – 4.49 (m, 2H), 4.44 (d, *J* = 11.4 Hz, 0.5H), 4.41 (d, *J* = 11.4 Hz, 0.5H), 4.23 (d, *J* = 11.4 Hz, 0.5H), 4.20 (d, *J* = 11.4 Hz, 0.5H), 3.99 – 3.95 (m, 1H), 3.39 (s, 1.5H), 3.38 (s, 1.5H), 3.34 – 3.26 (m, 7H), 3.18 – 3.15 (m, 3H), 3.07 – 2.94 (m, 1.5H), 2.87 – 2.82 (m, 0.5H), 2.64 (br s, 1H), 2.45 (d, *J* = 0.9 Hz, 1.5H), 2.41 (d, *J* = 0.9 Hz, 1.5H), 2.25 – 2.20 (m, 0.5H), 2.12 – 2.08 (m, 0.5H), 2.05 – 2.00 (m, 0.5H), 1.97 – 1.92 (m, 1H), 1.85 – 1.79 (m, 0.5H), 1.45 – 1.39 (m, 1H), 1.30 – 1.25 (m, 1H), 1.09 (d, *J* = 6.2 Hz, 1.5H), 1.05 (d, *J* = 6.2 Hz, 1.5H), 0.91 – 0.88 (t, *J* = 7.4 Hz, 1.5H), 0.88 – 0.85 (t, *J* = 7.4 Hz, 1.5H) ppm.

^{13}C-NMR (150 MHz, C_6D_6): δ = 205.32, 205.24, 159.79, 159.79, 153.36, 153.33, 150.39, 149.53, 149.51, 137.17, 137.13, 135.97, 135.86, 133.49, 133.48, 133.10, 132.59, 132.46, 131.15, 131.13, 130.93,

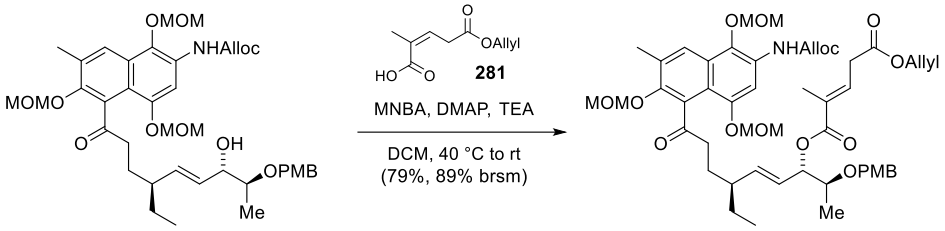
130.90, 129.57, 129.16, 126.97, 123.36, 123.33, 119.56, 119.48, 117.64, 117.63, 114.15, 114.14, 103.53, 103.27, 102.48, 102.28, 100.99, 100.97, 95.86, 95.81, 78.61, 78.47, 76.48, 76.38, 70.93, 70.90, 65.84, 57.41, 57.36, 57.11, 56.74, 56.68, 54.80, 44.45, 44.32, 43.41, 29.23, 29.10, 28.59, 28.23, 17.94, 17.92, 15.81, 15.73, 12.19, 12.18 ppm.

IR (ATR, neat): $\tilde{\nu}$ = 34632 (w), 3364 (w), 2929 (w), 1703 (m), 1630 (m), 1513 (m), 1465 (w), 1416 (w), 1245 (s), 1191 (m), 1153 (s), 1068 (s), 1035 (m), 1014 (s), 961 (s), 928 (s), 879 (w), 822 (m), 756 (w) cm^{-1}.

HRMS (+ESI): calc. for $C_{40}H_{52}NO_{12}^-$: 738.3495 $[M-H]^-$

found: 738.3527 $[M-H]^-$

Esterification of allylic alcohol **306**



306 **307**

Ester 307. To glutaconic acid derivate **281** (20.8 mg, 113 µmol, 3.0 eq) 2-methyl-6-nitrobenzoic anhydride (38.9 mg, 113 µmol, 3.0 eq) and DMAP (13.8 mg, 312 µmol, 3.0 eq) was added DCM (2.1 mL) in a Schlenk flask under argon. Triethylamine (21.3 µL, 159 µmol, 4.1 eq) was added and the yellow solution turned dark red. Allylic alcohol **306** (27.8 mg, 37.6 µmol, 1.0 eq) in DCM (2.0 mL) was added and the mixture heated to 40 °C for 30 min and then stirred at room temperature for 20 h. Then reaction mixture was poured onto brine and extracted threetimes with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (Davisil, 17:1 → 4:1 *n*-pentane:EtOAc) afforded starting material **306** (19 mg, 24 µmol, 23%) as well as ester **307** (70.0 mg, 74 µmol, 71%, 93% brsm) as a pale yellow oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.35 (2:1 hexane:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +1.9 (*c* = 0.83 in $CHCl_3$)

*Note: At room temperature compound **307** exists as a mixture of atropisomers due to hindered rotation around the bond connecting the aromatic core to the ketone. Due to this, the proton and carbon spectra NMR spectra become fairly complex. We here report the proton NMR signals as multiplets representing*

both atropisomers and the carbon NMR signals as they appear at 25 °C, even though some signals overlap.

^{1}H-NMR (600 MHz, C_6D_6): δ = 8.52 (br s, 1H), 8.21 (s, 1H), 7.75 (q, *J* = 1.1 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.21 – 7.18 (m, 0.5H), 7.13 – 7.08 (m, 0.5H), 6.85 – 6.81 (m, 2H), 5.77 – 5.50 (m, 5H), 5.27 – 5.24 (m, 0.5H), 5.14 – 4.96 (m, 6.5H), 4.75 – 4.68 (m, 1H), 4.65 – 4.60 (m, 1H), 4.54 – 4.33 (m, 7H), 3.68 – 3.57 (m, 1H), 3.43 – 3.38 (m, 3H), 3.35 – 3.29 (m, 6H), 3.19 – 3.16 (m, 3H), 3.15 – 3.10 (m, 0.5H), 3.01 – 2.86 (m, 1H), 2.84 – 2.76 (m, 2.5H), 2.48 – 2.41 (m, 3H), 2.27 – 2.21 (m, 0.5H), 2.12 – 2.00 (m, 1H), 1.95 – 1.87 (m, 1H), 1.85 – 1.77 (m, 0.5H), 1.73 – 1.71 (m, 1.5H), 1.65 – 1.61 (m, 1.5H), 1.28 – 1.23 (m, 2H), 1.17 – 1.13 (m, 1.5H), 1.12 – 1.09 (m, 1.5H), 0.89 – 0.84 (m, 3H) ppm.

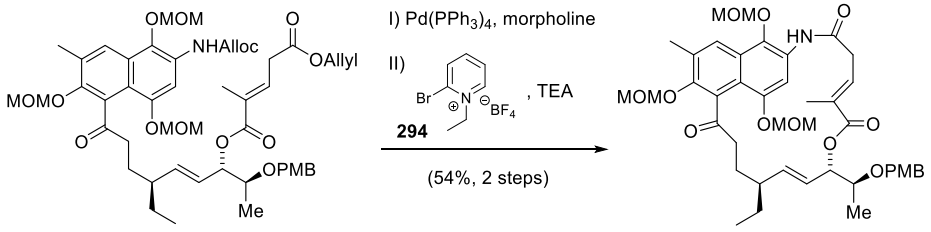
^{13}C-NMR (150 MHz, C_6D_6): δ = 205.25, 205.24, 169.60, 169.58, 166.26, 159.70, 159.69, 153.34, 153.32, 150.36, 149.57, 149.50, 139.71, 139.44, 135.95, 135.79, 133.50, 133.45, 133.11, 133.10, 133.01, 132.93, 132.63, 132.54, 132.51, 132.49, 131.42, 131.41, 131.31, 131.28, 130.29, 130.20, 129.46, 129.16, 129.13, 126.93, 126.91, 126.49, 126.29, 123.29, 123.23, 119.55, 119.47, 117.96, 117.93, 117.65, 117.64, 114.08, 114.06, 102.52, 102.43, 102.36, 102.29, 100.99, 95.80, 95.76, 77.32, 77.13, 75.50, 75.48, 71.17, 65.85, 65.37, 65.36, 57.39, 57.12, 57.11, 56.70, 56.62, 54.79, 44.62, 44.32, 43.50, 43.38, 34.04, 33.96, 29.21, 29.09, 28.50, 28.09, 17.93, 17.91, 16.13, 16.12, 12.89, 12.79, 12.14, 12.10 ppm.

IR (ATR): $\tilde{\nu}$ = 3367 (w), 2926 (w), 2855 (w), 1735 (m), 1708 (m), 1627 (m), 1610 (w), 1513 (m), 1498 (m), 1456 (m), 1427 (w), 1395 (w), 1364 (m), 1302 (w), 12456 (s), 1230 (s), 1204 (s), 1155 (s), 1071 (s), 1033 (s), 925 (s), 821 (m), 764 (m), 729 (m) cm^{-1}.

HRMS (−ESI): calc. for $C_{49}H_{62}NO_{15}^-$: 904.4125 $[M-H]^-$

found: 904.4148 $[M-H]^-$

Deprotection and macrolactamization of **307**



307 **308**

Macrolactam 308. In an argon filled Schlenk flask Alloc/Allyl protected amino acid **307** (5.70 mg, 6.30 μmol, 1.0 eq) was dissolved in THF (0.9 mL, freshly degassed) containing morpholine (11.5 μL, 132 μmol, 20 eq). The mixture was cooled with an ice bath and $Pd(PPh_3)_4$ (1.82 mg, 1.58 μmol, 0.25 eq) was added. After 12 min at 0 °C the mixture was poured onto pH 7

phosphate buffer. The mixture was extracted 3 times with EtOAc, dried over $NaSO_4$ and concentrated on a rotary evaporator with a nitrogen inlet (the amino acid is sensitive to oxygen). The crude material was purified by flash column chromatography (Davisil, 1% → 2% → 4% MeOH in DCM) and concentrated on a rotary evaporator with a nitrogen inlet. The thus obtained amino acid was either used directly in the cyclization reaction or stored overnight in a matrix of degassed benzene under argon in the freezer for a maximum of one day.

To a solution of 2-bromo-1-ethylpyridinium tetrafluoroborate (2.59 mg, 9.45 μmol, 1.5 eq) in DCM (10 mL, freshly degassed) under argon was added triethylamine (1.74 μL, 12.6 μmol, 2.0 eq). A solution of the amino acid in DCM (9.0 mL) was added to the mixture *via* a teflon hose over 9 h. After 9 more hours stirring at room temperature, the reaction mixture was poured onto brine and extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (DAVISIL, 5% → 7.5% → 10% acetone in DCM) afforded macrolactam **308** (single atropisomer, 2.60 mg, 3.40 μmol, 54% over 2 steps, single diastereomer) as a colorless oil.

Physical state: colorless oil

$\mathbf{R_f}$ = 0.22 (9:1 hexanes:EtOAc)

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +1.1 (*c* = 0.18 in DCM)

^{1}H-NMR (400 MHz, C_6D_6): δ = 7.96 (d, *J* = 1.2 Hz, 1H), 7.20 – 7.17 (m, 2H), 6.80 – 6.74 (m, 2H), 6.68 (s, 1H), 6.68 – 6.63 (m, 1H), 6.36 (s, 1H), 5.52 (dd, *J* = 9.4, 6.4 Hz, 1H), 5.32 – 5.23 (m, 2H), 5.20 – 5.11 (m, 3H), 4.93 (d, *J* = 6.5 Hz, 1H), 4.85 (d, *J* = 5.8 Hz, 1H), 4.81 (d, *J* = 5.8 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.27 (d, *J* = 11.9 Hz, 1H), 3.54 (dd, *J* = 16.0, 11.0 Hz, 1H), 3.41 (s, 3H), 3.32 (s, 3H), 3.31 (s, 3H), 3.27 (s, 3H), 3.02 – 2.89 (m, 2H), 2.47 – 2.40 (m, 1H), 2.39 (d, *J* = 1.0 Hz, 3H), 2.32 – 2.19 (m, 1H), 1.62 – 1.52 (m, 2H), 1.38 – 1.35 (m, 2H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.98 (t, *J* = 1.7 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H)ppm.

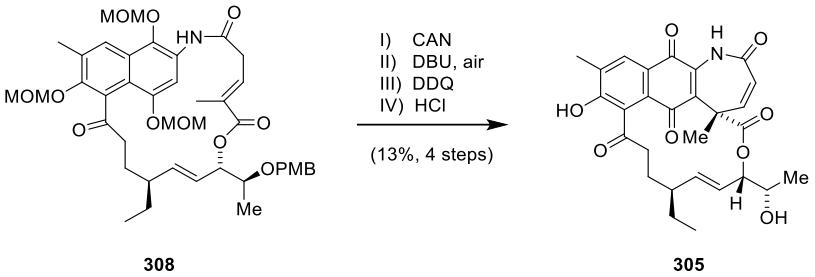
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 204.05, 171.67, 166.32, 159.70, 151.83, 148.38, 143.61, 141.69, 134.85, 133.81, 132.17, 131.19, 130.11, 129.41, 126.23, 124.67, 122.88, 113.99, 111.48, 103.07, 100.19, 95.78, 77.51, 75.00, 70.95, 57.84, 57.30, 56.53, 54.76, 45.30, 44.59, 36.89, 30.24, 28.96, 17.89, 16.12, 12.31, 12.06 ppm. *(2 aromatic signals buried under solvent signal)*

IR (ATR, film): $\tilde{\nu}$ = 3344 (br, w), 2926 (m), 2855 (w), 1709 (m), 1672.7 (s), 1620 (m), 1514 (m), 1498 (w), 1454 (m), 1378 (m), 1342 (m), 1304 (w), 1245 (s), 1190 (m), 1156 (s), 1068 (s), 1037 (m), 1016 (w), 990 (m), 950 (s), 932 (s), 823 (m), 737 (m) cm^{-1}.

HRMS (−ESI): calc. for $C_{42}H_{52}NO_{12}^-$: 762.3495 $[M-H]^-$

found: 762.3524 $[M-H]^-$

Oxidation, ring contraction and deprotection of macrolactam **308**



308 **305**

C8 *epi*-Hygrocin G (305). To a solution of macrolactam**308** (7.00 mg, 9.16 μmol, 1.0 eq) in MeCN (2.5 mL) and H_2O (420 μl) was added CAN (12.6 mg, 22.9 μmol, 2.5 eq) at 0 °C. After 15 min the reaction mixture was poured into a half-saturated aqueous solution of NaCl (4 mL). The mixture was extracted three times with EtOAc, the combined organic layers washed with a saturated aqueous solution of NaCl, dried over Na_2SO_4 and concentrated on a rotary evaporator. The crude product was dissolved in benzene (4.5 mL) and MeOH (2.3 mL) before DBU (0.3 M in MeOH, 22.2 μl, 6.66 μmol, 1.6 eq) was added. After 7 h of stirring under air at room temperature, phosphate buffer (pH = 7.0, 5.0 mL) was added and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated on a rotary evaporator. Flash column chromatography (3% acetone in DCM) followed by preparative TLC (5% DCM in acetone) gave protected *epi*-hygrocin G (2.00 mg, 2.98 μmol, 33% over 2 steps) as yellow oil.

To a solution of protected *epi*-hygrocin G (2.00 mg, 2.98 μmol, 1.0 eq) in DCM (600 μl) was added H_2O (60 μl), and DDQ (0.95 mg, 4.17 μmol, 1.4 eq). After 3 h the reaction mixture was filtered through a pad of celite and $MgSO_4$ and concentrated on a rotary evaporator. Preparative TLC (9:1 DCM:acetone) gave MOM-protected *epi*-hygrocin G which was dissolved in MeOH (900 μl) before MeOH saturated with HCl (100 μl) was added drop wise at 0 °C. The yellow solution was allowed to warm to room temperature. and after 1.25 h DCM (10 mL) and saturated aqueous $NaHCO_3$ (1 mL) was added. Then a saturated aqueous solution of NH_4Cl was added dropwise until the purple color in the aqueous layer disappeared and the organic layer turned yellow. The aqueous layer was separated and extracted twice with DCM. The combined organic layers were dried (Na_2SO_4) and concentrated on a rotary evaporator. Flash column chromatography (5% →10% →20% →30% acetone in DCM) affordedC8-*epi*-hygrocin G(**305**) (0.6 mg, 1.18 μmol, 13% over 4 steps) as yellow solid.

C8-*epi*-Hygrocin G (305):

Physical state: yellow solid

R_f = 0.21 (10% acetone in DCM)

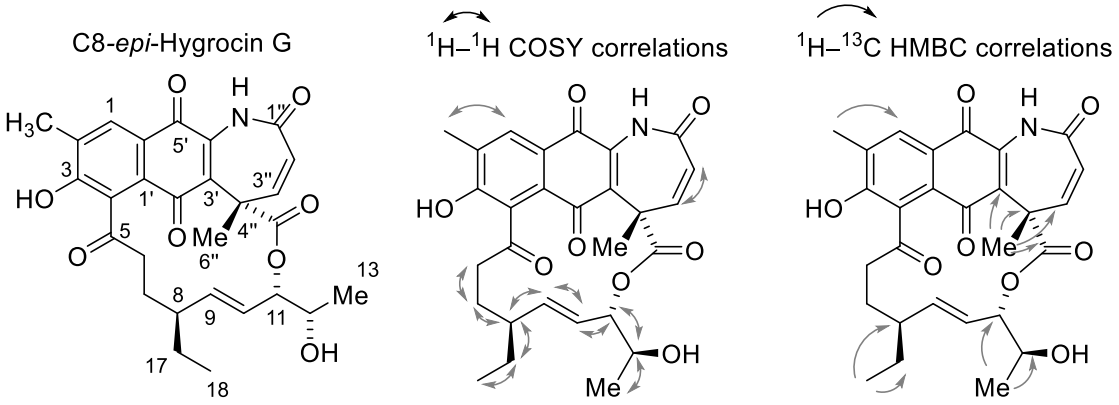
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.83 (s, 1H, H-17), 8.00 (d, *J* = 0.9 Hz, 1H, H-26), 6.37 (d, *J* = 12.5 Hz, 1H, H-14), 6.08 (dd, *J* = 12.5, 2.3 Hz, 1H, H-15), 5.74 (dd, *J* = 15.3, 9.3 Hz, 1H, H-5), 5.44 – 5.33 (m, 1H, H-7), 5.25 (dd, *J* = 15.3, 9.3 Hz, 1H, H-6), 3.85 (p, *J* = 6.4 Hz, 1H, H-8), 2.96 (ddd, *J* = 18.6, 11.4, 1.8 Hz, 1H, H-2a), 2.36 (d, *J* = 0.9 Hz, 3H, 3 x H-30), 2.14 (ddd, *J* = 18.1, 10.7, 6.8 Hz, 1H, H-2b), 2.00 – 1.91 (m, 2H, 2 x H-3), 1.70 – 1.59 (m, 1H, H-4), 1.59 (s, 3H, 3 x H-18), 1.53 – 1.40 (m, 2H, 2 x H-10), 1.18 (d, *J* = 6.4 Hz, 3H, 3 x H-9), 0.92 – 0.83 (m, 3H, 3 x H-11) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 208.35, 183.07, 178.52, 172.28, 164.40, 158.48, 145.35, 144.78, 135.60 133.82, 131.67, 130.17, 126.03, 124.36, 124.19, 122.38, 122.85, 80.23, 69.20, 50.85, 44.34, 42.18, 28.30, 27.32, 24.99, 19.66, 16.70, 12.21 ppm.

IR (ATR, film): $\tilde{\nu}$ = 3357 (w), 2908 (s), 2851 (s), 1738 (w), 1698 (w), 1659 (m), 1633 (s), ,1580 (w), 1468 (m), 1412 (s), 1343 (w), 1260 (m), 1096 (m), 1020 (m), 767 (m), 722 (w) cm^{-1}.

HRMS (−ESI): calc. for $C_{28}H_{28}NO_8^-$: 506.1820 $[M-H]^-$

found: 506.1832 $[M-H]^-$



	C8-*epi*-Hygrocin G	Hygrocin G (Shen)	C8-*epi*-Hygrocin G	Hygrocin G (Shen)
Pos.	**^{1}H-NMR**	**^{1}H-NMR**	**^{13}C-NMR**	**^{13}C-NMR**
1	8.00 (d, *J* = 0.9 Hz, 1H)	8.00 (s, 1H)	131.67	131.4
2			133.82	133.7
3			158.48	158.2
4			122.38	122.2
5			208.35	208.5
6	2.96 (ddd, *J* = 18.6, 11.4, 1.8 Hz, 1H) 2.14 (ddd, *J* = 18.1, 10.7, 6.8 Hz, 1H)	2.78 (m, 1H) 2.17 (dt, *J* = 17.4, 8.5 Hz 1H)	42.18	38.4
7	2.00 – 1.91 (m, 2H)	1.93 (s, br, 2H)	27.23	24.8
8	1.70 – 1.59 (m, 1H)	2.39 – 2.38 (m, 1H)	44.34	39.7
9	5.74 (dd, *J* = 15.3, 9.3 Hz, 1H)	6.12–6.08 (m, 1H)	144.78	142.6
10	5.25 (dd, *J* = 15.3, 9.3 Hz, 1H)	5.30 (s, br, 1H)	126.03	123.8
11	5.44 – 5.33 (m, 1H)	5.39 (s, br, 1H)	80.23	79.8
12	3.85 (p, *J* = 6.4 Hz, 1H)	3.89 (s, br, 1H)	69.20	69.1
13	1.18 (d, *J* = 6.4 Hz, 3H)	1.19 (d, *J* = 6.4 Hz, 3H)	19.66	19.6
16	2.32 (d, *J* = 0.4 Hz)	2.33 (d, *J* = 0.8 Hz)	16.5	16.4
17	1.53 – 1.40 (m, 2H)	1.39– 1.30 (m, 2H)	28.30	22.8
18	0.92 – 0.83 (m, 3H)	0.87 (t, *J* = 7.2 Hz, 3H)	12.21	12.0
1'	-	-	124.36	124.5
2'	-	-	183.07	182.4
3'	-	-	124.19	128.7
4'	-	-	135.60	135.6
5'	-	-	178.52	178.4
6'	-	-	130.17	130.45
1''	-	-	164.40	164.3
2''	6.08 (dd, *J* = 12.5, 2.3 Hz, 1H)	6.10 (d, *J* = 12.5, 1H)	122.85	122.8
3''	6.37 (d, *J* = 12.5 Hz, 1H)	6.37 (d, *J* = 12.5 Hz, 1H)	145.35	145.3
4''	-	-	50.85	50.5
5''	-	-	172.28	172.2
6''	1.59 (s, 3H)	1.58 (s, 3H)	24.99	24.7

5 Appendices

5.1 Handout of a literature seminar about ansamycin syntheses

In course of the Trauner group's literature seminar a presentation concerning ansamycin syntheses was given by the author of this thesis in May 2014. The handout for this meeting was prepared to accompany the seminar and contains a comprehensive overview of benzo- and naphthoquinone ansamycin syntheses until the date of the seminar. Since the introduction of this thesis focused on how Nature produces ansamycins, reprinting the handout of the seminar should complement the discussion with the impressive knowledge synthetic chemists have gathered during their campaigns to access many ansamycins by chemical synthesis.

What is an Ansamycin?

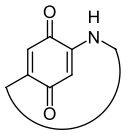
ANTIBIOTICS WITH ANSA RINGS

Antibiotics with Ansa Rings

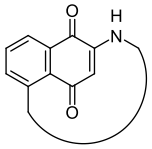
KENNETH L. RINEHART, JR.

Often when an antibiotic of a new structural type appears on the chemotherapeutic scene it is soon joined by additional representatives of the same type, so that one can begin to speak of a class of antibiotics. This is the case with a new class of antibiotics containing an aliphatic ansa bridge,[1] a bridge connecting two nonadjacent positions of an aromatic nucleus, for which the term "ansamycins" has been suggested by Prelog.

(1) The term *ansa* compounds was originally proposed by Lüttringhaus [A. Lüttringhause and H. Gralheer, *Justus Liebigs Ann. Chem.*, 550, 67 (1942)] for compounds of this general structural type, usually meta- and para-bridged benzenes.



Benzoquinone ansamycin



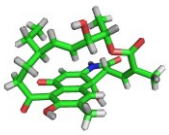
Naphtoquinone ansamycin

Ansamycins consist of an aromatic chromophore and a macrolactam ring that connects two non-adjacent carbons on the chromophore

Basket-like structure, with the aliphatic chain being the handle (*lat.* ansa = handle)

Many show potent anitbiotic activity, a Rifamycin derivative is known to have eradicated widespread tuberculosis and leprosy

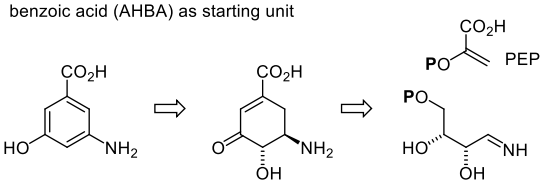
K. L. Rinehart, *Acc. Chem. Res.*, **1972**, *5*, 57-65; H. G. Floss, T.-W. Yu, *Chem. Rev.* **2005**, *105*, 621-632



Representative X-Ray displaying the basket structure of Hygrocin C

Biosynthesis

Ansamycins are polyketide natural products using 3-amino-5-hydroxy benzoic acid (AHBA) as starting unit



AHBA
Amino-DHS
Imino-E4P

CoA-activated extender units: malonate, methylmalonate, ethylmalonate, *i*-butyrate

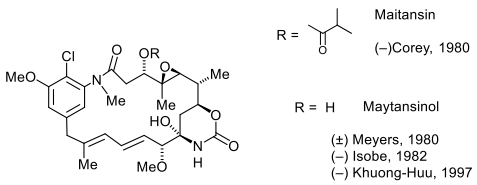
For "off pattern" hydroxy groups: glycolate-derived building blocks

Carbamates: citrulline; O-Methylation: SAM

Post-assembly processing: Dehydrogenases, Baeyer-Villigerases, etc

C. Lu, Y. Li, J. Deng, S. Li, Y. Shen, H. Wang, Y. Shen, *J. Nat. Prod.* **2013**, *76*, 2175-217; J. Kibby, I. McDonald R. W. Rickards, *J. Chem. Soc., Chem. Commun.* **1980**, 768-769; Q. Kang, Y. Shen, L. Bai, *Nat. Prod. Rep.* **2012**, *29*, 243

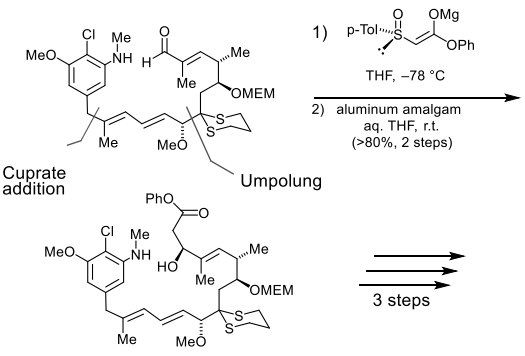
Maytansinoid ansamycins



R = Maitansin (–)Corey, 1980

R = H Maytansinol (±) Meyers, 1980 (–) Isobe, 1982 (–) Khuong-Huu, 1997

Corey (1980)

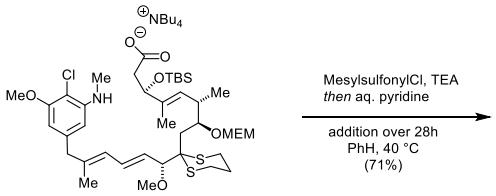


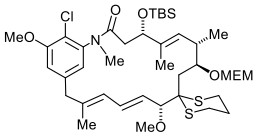
Cuprate addition

Umpolung

3 steps

E. J. Corey, L. Weigel, A. R. Chamberlin, H. Cho, D. H. Hua, *J. Am. Chem. Soc.* **1980**, *102*, 6613-6615

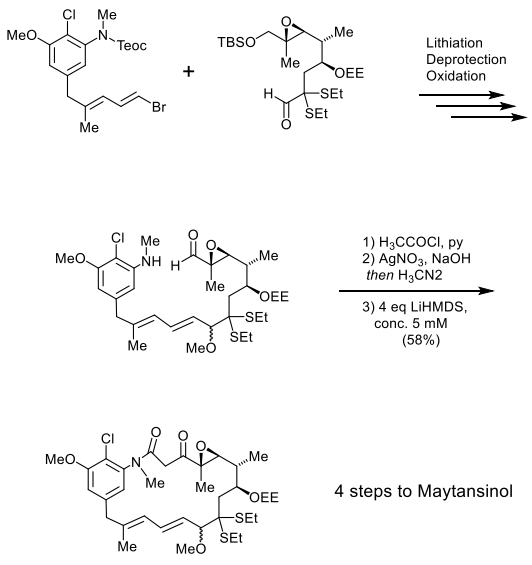




eight steps to Maitansin

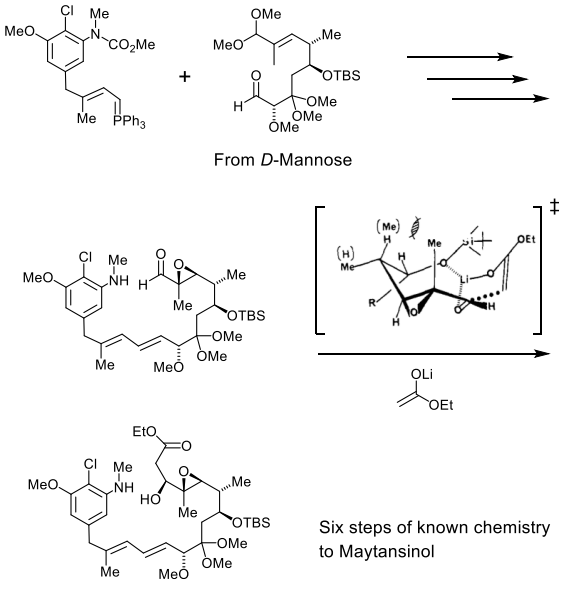
Corey was the first to synthetically make an ansamycin; it used a chiral pool approach for the eastern half of the molecule (glucose) and gallic acid for setting the aromatic of the molecule. The 30+ step synthesis was covered in several papers from 1977 until 1980. It relies on the (not diastereoselctive) coupling of two advanced precursors, macrolactamization of an NEt_4 salt and several substrate controlled stereoselective transformations.

Meyers (1980)



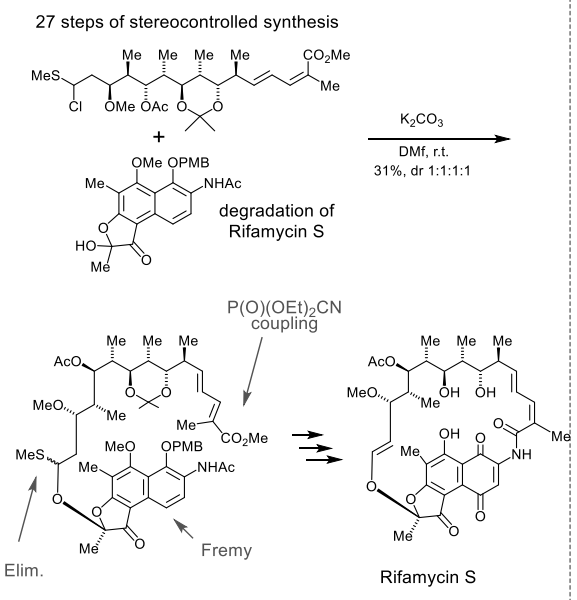
A. I. Meyers, P. J. Reider, A. L. Campbel *J. Am. Chem. Soc.* **1980**, *102*, 6597-6598

Isobe (1982)



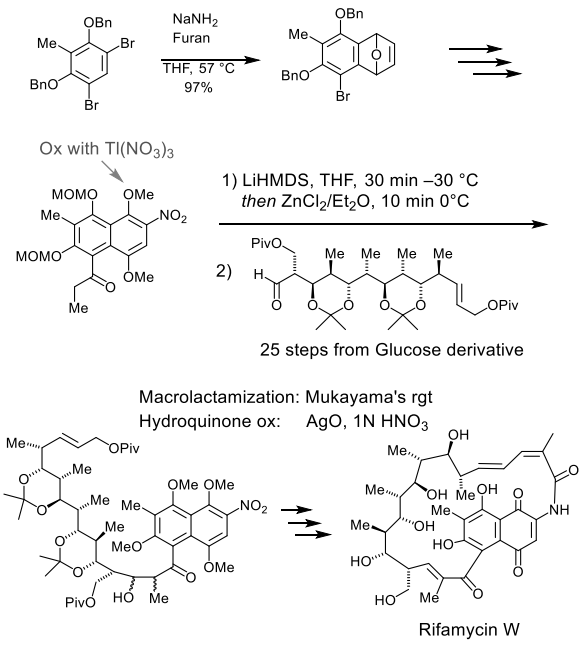
M. Kitamura, M. Isobe, Y. Ichikawa, T. Goto, *J. Am. Chem. Soc.* **1984**, *106*, 3252-3257

Rifamycin S, Kishi (1980)



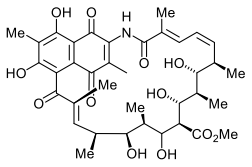
H. Iio, H. Nagaoka, Y. Kishi, *J. Am. Chem. Soc.* **1980**, *102*, 7965-796

Rifamycin W, Nakata (1990)

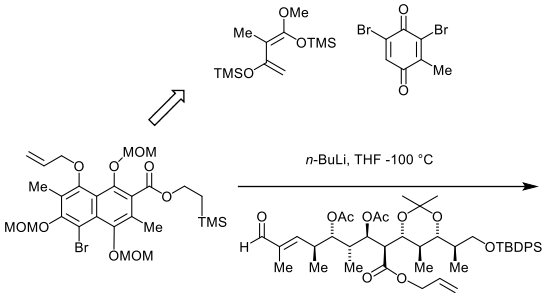


M. Nakata, N. Akiyama, J. Kamata, K. Kojima, H. Masuda, M. Kinoshita, K. Tatsuta, *Tetrahedron*, **1990**, *13(14)*, 4629-4652

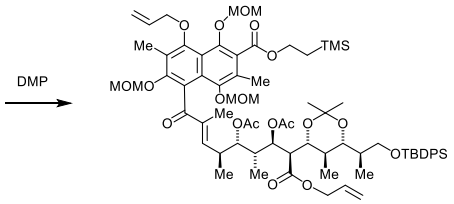
Damavaricin D, Roush (1997)



- last naphtoquinone ansamycin synthesized!
- precursor to closley related Streptovaricins
- lots of publications towards to Streptovaricins

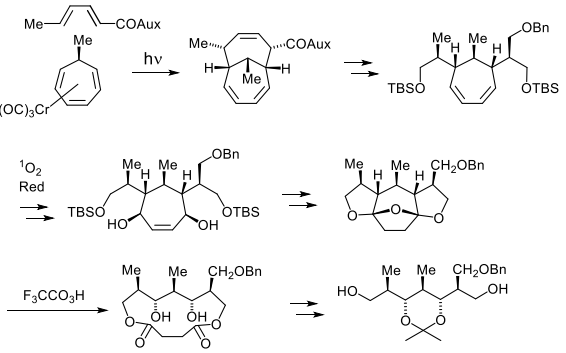


W. R. Roush, D. S. Coffey, D. J. Madar, *J. Am. Chem. Soc.* **1997**, *119(46)*, 11331-11332



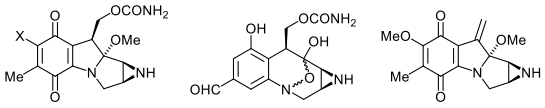
- Amine *via* Curtius, *ansa* chain extension *via* Wittig
- Macrolactamization *via* Mukayama's salt
- Quinone via acidic MOM removal and air oxidation

Most creative approach towards ansa chain by Rigby (1998)



J. H. Rigby, K. R. Fales, *Tet. Lett.*, **1998**, *39*, 5717-5720

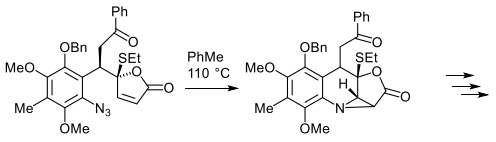
Mitomycin-type Antitumor antibiotics



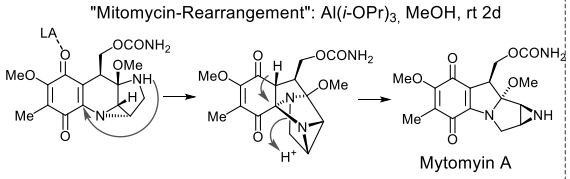
Fukuyama, 1987 Fukuyama, 1991 Danishefsky, 1993

(AHBA-derived, but technically not real ansamycins)

Fukuyama (1987)

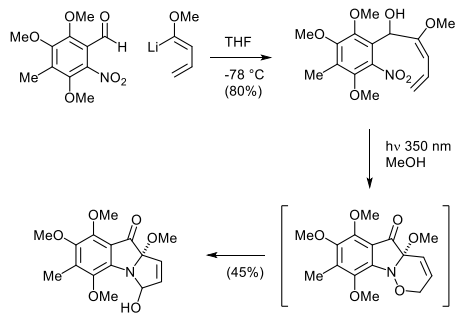


"Mitomycin-Rearrangement": Al(*i*-OPr)$_3$, MeOH, rt 2d



T. Fukuyama, L. Yang, *J. Am. Chem. Soc.*, **1987**, *109*, 7882-7884; M. Kono, Y. Saitoh, K. Shirahata, *J. Am. Chem. Soc.*, **1987**, *109*, 7224-7225

Danishefsky (1993)

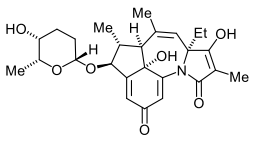


nine steps to Mitomycin K

Key step: Photo-induced intramolecular redox reaction followed by Nitroso-Diene Diels-alder and subsequent rearrangement

J. W. Benbow, K. F. McClure, S. J. Danishefsky, *J. Am. Chem. Soc.* **1993**, *115*, 12305-12314

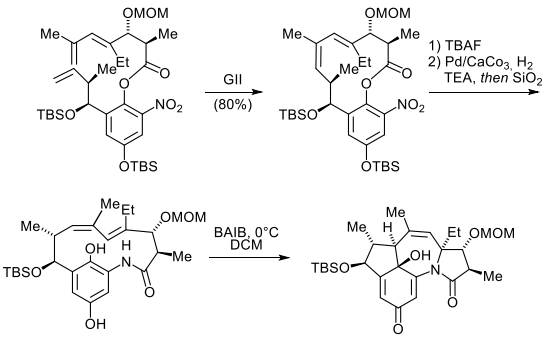
Studies towards Tetrapetalone ansa-mycins



Tetrapetalone A

- potent lipooxygenase inhibitor
- possibly derived from macrocyclic ansmycin

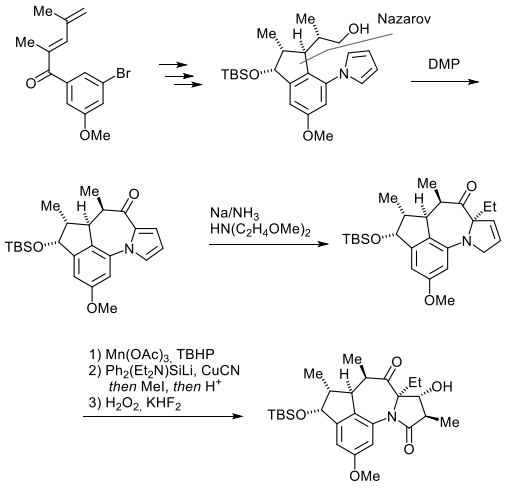
Porco (2005)



Oxidative [4+3] cycloaddition after acylshift to construct core

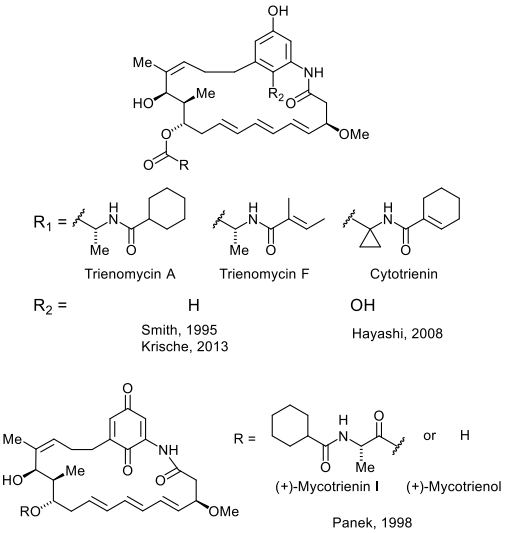
X. Wang, J. A. Porco Jr., *Angew. Chem. Int. Ed.* **2005**, *44*, 3067 –3071

Sarpong (2010)



A. P. Marcus, R. Sarpong, *Org. Lett.* **2010**, *12(20)*, 4560-4563

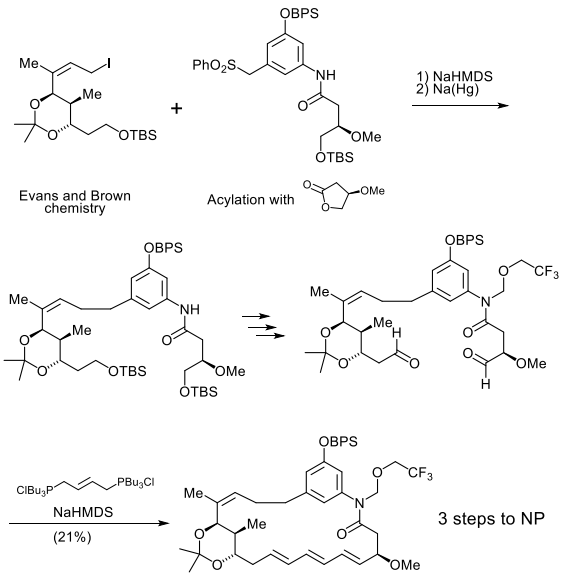
Ansatrienin Benzoquinone ansamycins



C17-benze ansamycins with triene motif and anti cancer activity

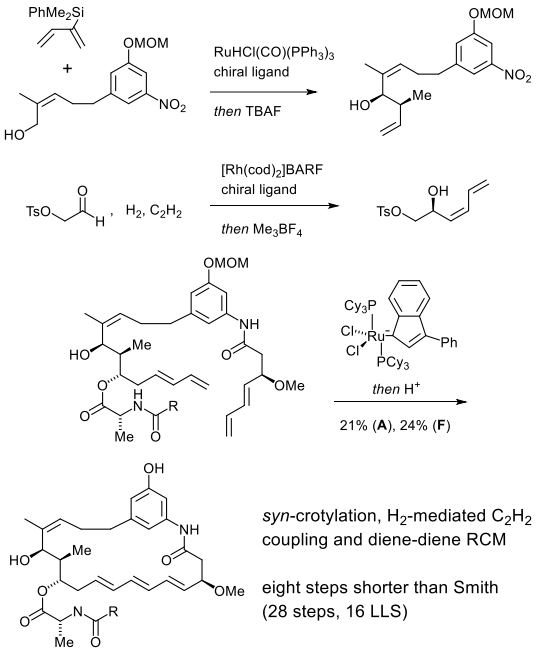
I. W. Wrona, V. Agouridas, J. S. Panek, *C. R. Chimie*, **2008**, *11,* 1483-1522

Trienomycin A +F (Smith 1995)



A. B. Smith III, J. Barbosa, W. Wong, J. L. Wood, *J. Am. Chem. Soc.* **1995**, *117*, 10777-10778

Trienomycin A + F, Krische (2013)

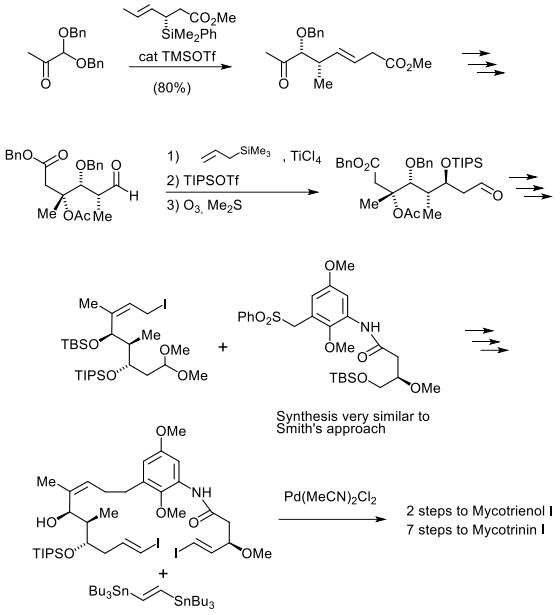


syn-crotylation, H_2-mediated C_2H_2 coupling and diene-diene RCM

eight steps shorter than Smith (28 steps, 16 LLS)

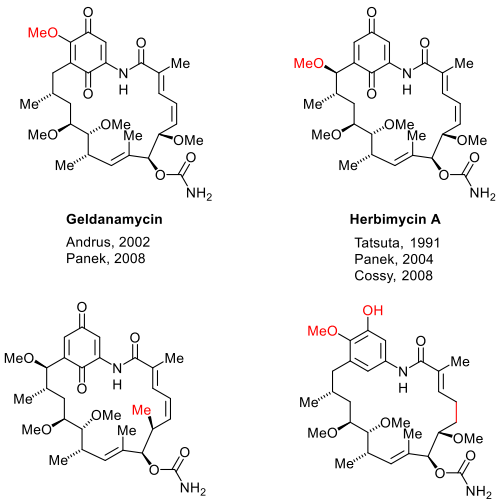
D.J. Del Valle, M. J. Krische, *J. Am. Chem. Soc.* **2013**, *135*, 10986-10989

Mycotrienin I + Mycotrienol I, Panek (1998)



C. E. Masse, M. Yang, J. Solomon, J. S. Panek, *J. Am. Chem. Soc.* **1998**, *120*, 4123-4134

C15-benzoquinone ansamycins



Geldanamycin
Andrus, 2002
Panek, 2008

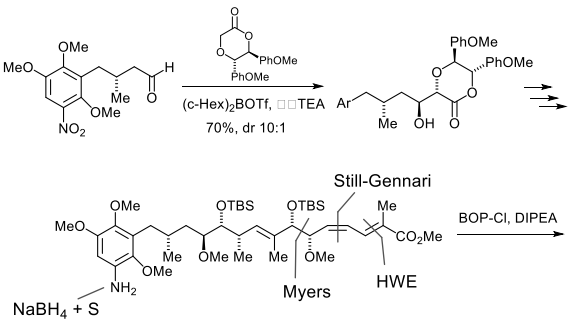
Herbimycin A
Tatsuta, 1991
Panek, 2004
Cossy, 2008

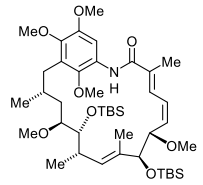
Macbecin I
Baker, 1992
Martin, 1993 (formal)
Evans, 1993
Panek, 1995
Micalizio, 2008

Reblastin
Panek 2005

prominent targets for synthesis, all show potent bioactivity (Hsp90)

Geldanamycin, Andrus 2002





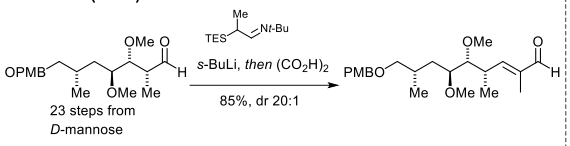
Unfortunately only trace amounts (ca. 5%) of Geldanamycin could be synthesized from this precursor (*ortho*-quinone major product)

Panek 2008: 20 steps to Geldanamycin (2% overall yield). Synthesis uses his silane crotylation methodology to great effect and closes the macrocycle via Cu(I) mediated aryl amidation. He also wisely chose a differet protecting group pattern on the aromatic core.

M. B. Andrus, E. L. Meredith, B. L. Simmons, B. B. V. S. Sekhar, E. J. Hicken, *Org. Lett.* **2002**, *4(20)*, 3549-3552; H.-L. Qin, J. S. Panek, *Org. Lett.* **2008**, *10(12)*, 2477-2479

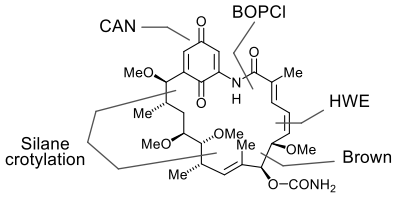
Herbimycin A syntheses

Tatsuta (1991)



Brown allylation, Li-mediated coupling to the aromatic core, BOPCl macrolactamization AgO oxidation to the quinone finish the lengthy, but first synthesis of a Herbimycin.

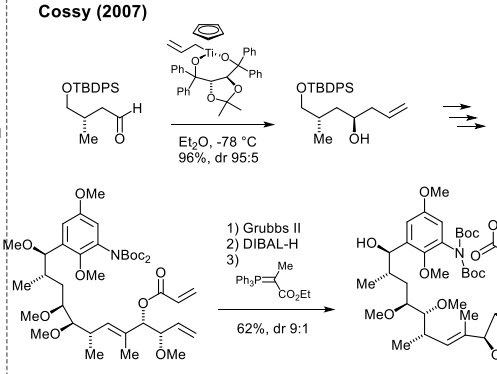
Panek (2004)



Nothing "new", but the synthesis highlights the effectivness of Panek's methodology; generally the yields of the 27 step linear are excellent (1.09% overall).

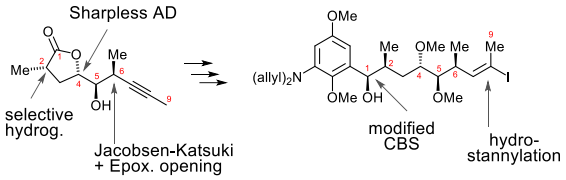
M. Nakata, T. Osumi, A. Ueno, T. Kimura, T. Tamai, K. Tatsuta, *Tet. Lett.* **1991**, *32(42)*, 6015-6018; K. D. Carter, J. S. Panek, *Org. Lett.* **2004**, *1*, 55-57

Cossy (2007)



- Ringclosure: BOP-Cl, hydroquinone oxidation: CAN
- 30 steps, 1.5% overall yield

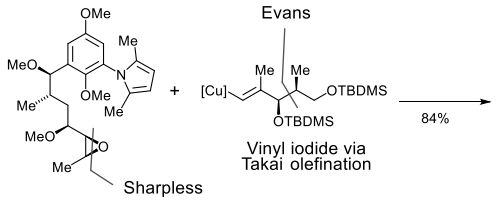
Yu (2014)

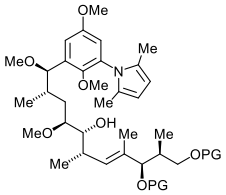


S. Canova, V. Bellosta, A. Bigot, P. Mailliet, S. Mignani, J. Cossy, *Org. Lett.* **2007**, *1*, 145-148; R. Yan, C. Bian, X. Yu, *Org. Lett.* **2014,** dx.doi.org/10.1021/ol5012899

Macbecin I syntheses

Baker (1991)

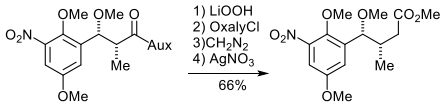




Macrolactamization: Mukayama

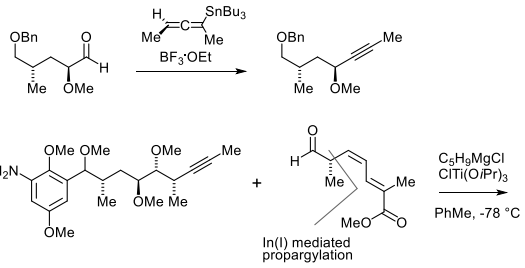
Hydroquinone oxidation: CAN

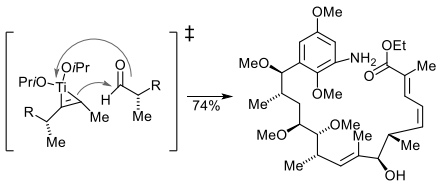
Evans (1993)



R. Baker, J. L. Castro, *J. Chem. Soc. Perkin Trans. 1*, **1990**, 47-65; D. A. Evans, S. J. Miller, M. D. Ennis, *J. Org. Chem.*, **1993**, *58*, 471-485

Micalizio (2008)



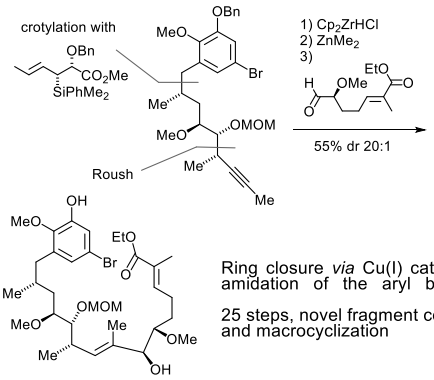


Panek (1995)

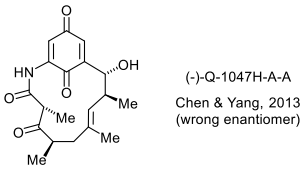
Macbecin in 25 steps relying soley on his organosilicon crotylation methodology and the established macrocyclization strategies

J. K. Belardi, G. C. Micalizio, *Angew. Chem. Int. Ed.* **2008**, *47*, 4005-4008; J. S. Panek, F. Xu, *J. Am. Chem. Soc.* **1995**, *117*, 10587-10588

Reblastin, Panek (1995)

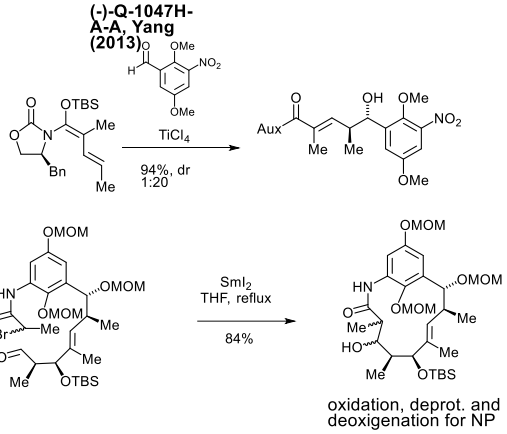


Medium-sized 13-membered macrolactam ansamycin

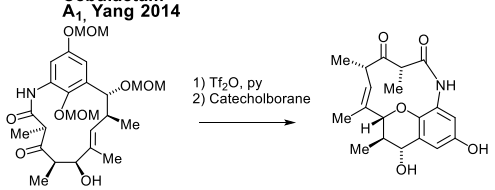


I. E. Wrona, A. E. Gabarda, G. Evano, J. S. Panek, *J. Am. Chem. Soc.* **2005**, *127*, 15026-15027

(-)-Q-1047H-A-A, Yang (2013)

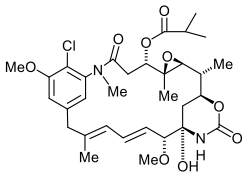


Cebulactam A_1, Yang 2014



S. Yang, Y. Xi, R. Zhu, L. Wang, J. Chen, Z. Yang, *Org. Lett.* **2013**, *15(4)*, 812-815; S. Yang, Y. Xi, J.-H. Chen, Z. Yang, *Org. Chem. Front.* **2014**, *1*, 91-99

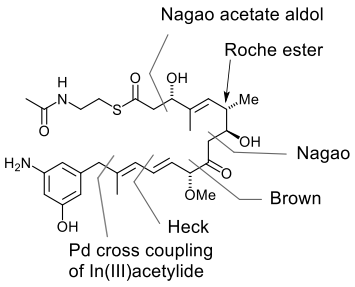
Ansamitocin P3, Kirschning (2010)



Plant derived analogue of Maytansionids

Tubulin binding, but shot in clinical trials after promising toxicity studies

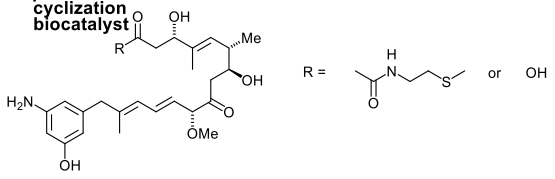
Preparation of SNAC couples *seco*-ansamycin in 2006



Cyclization of *seco*-anamycin never worked

T. Frenzel, M. Brünjes, M. Quitschalle, A. Kirschning, *Org. Lett.* **2006**, *8(1)*, 135-138

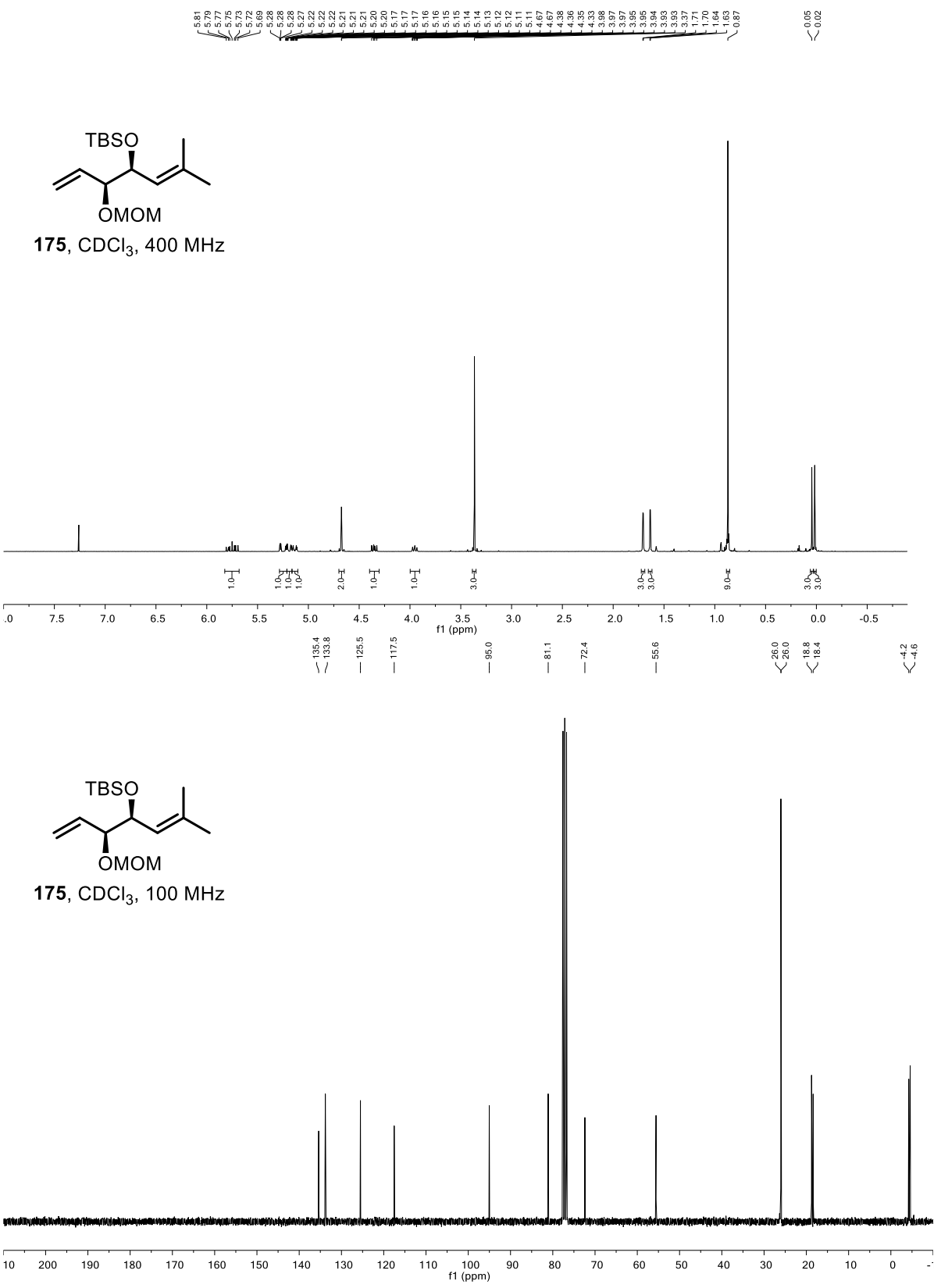
***Actinosynnema pretiosum* as cyclization biocatalyst**

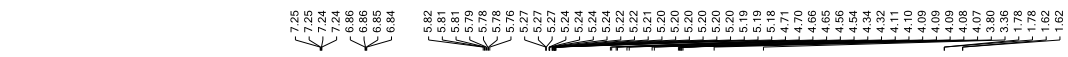


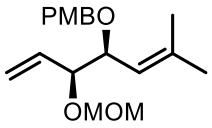
Supplementation of *seco*-derivatives to a culture of AHBA-blocked mutant strain gave 0.2% (SNAC ester) and 0.15% (*seco*-acid) of cyclized and derivatized Ansamitocin P3 after 7 days!

K. Harmrolfs, M. Brünjes, G. Dräger, H. G. Floss, F. Sasse, F. Taft, A. Kirschning, *Chem. Bio. Chem.* **2010**, *11*, 2517-2520

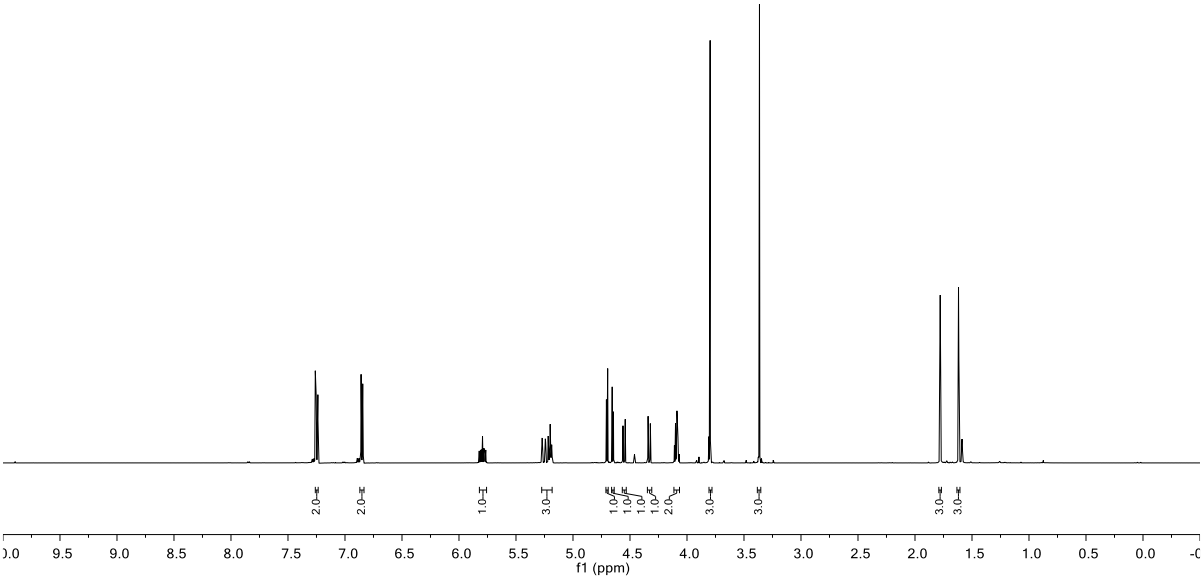
5.2 NMR spectra

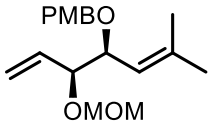




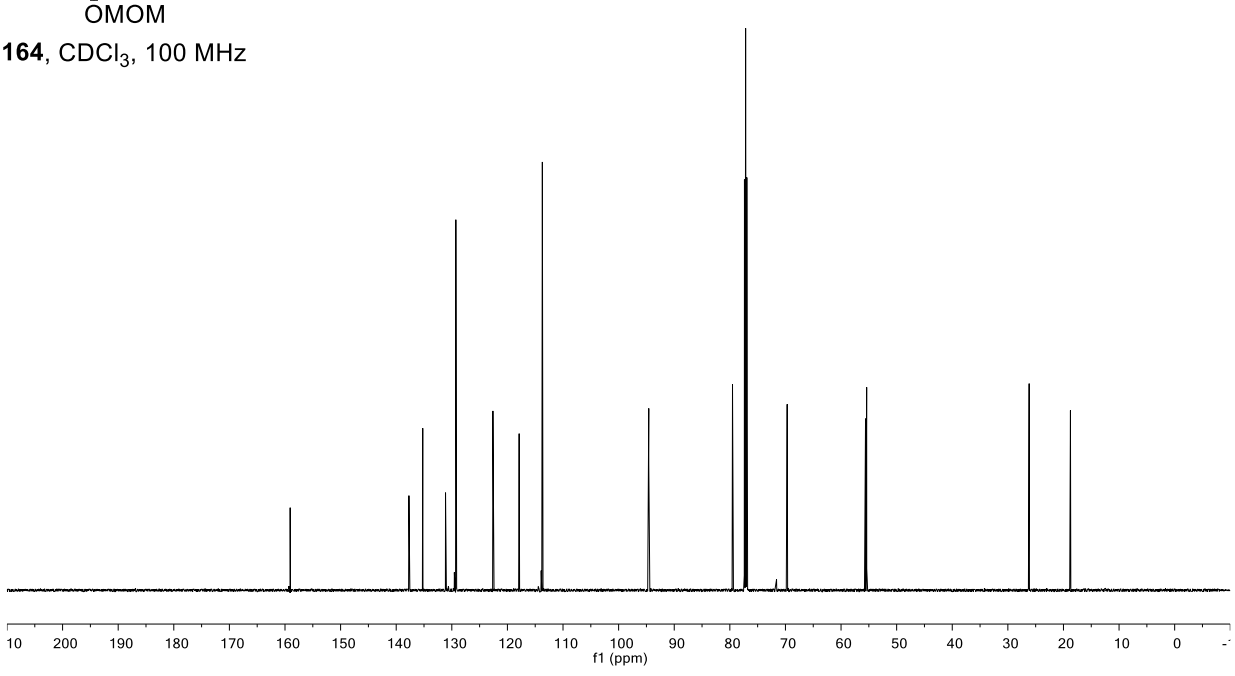


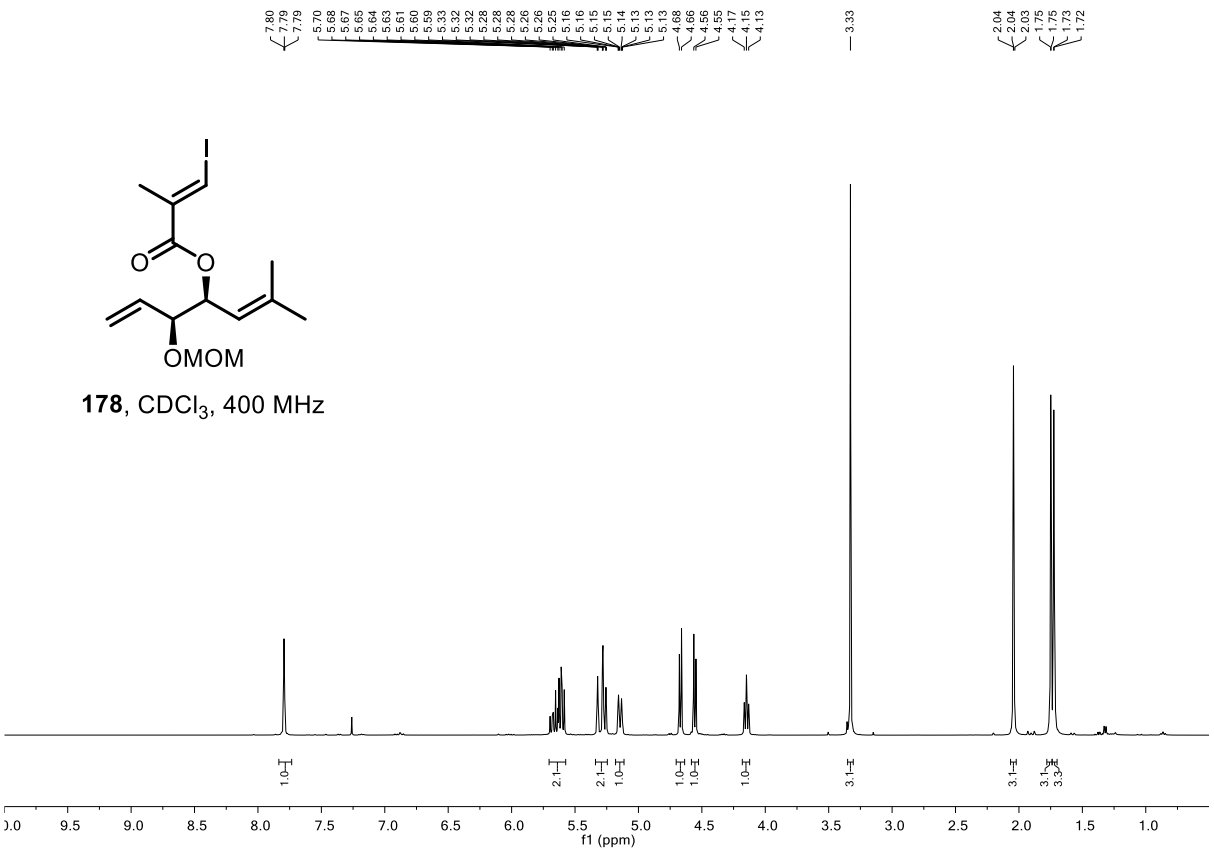
164, $CDCl_3$, 400 MHz



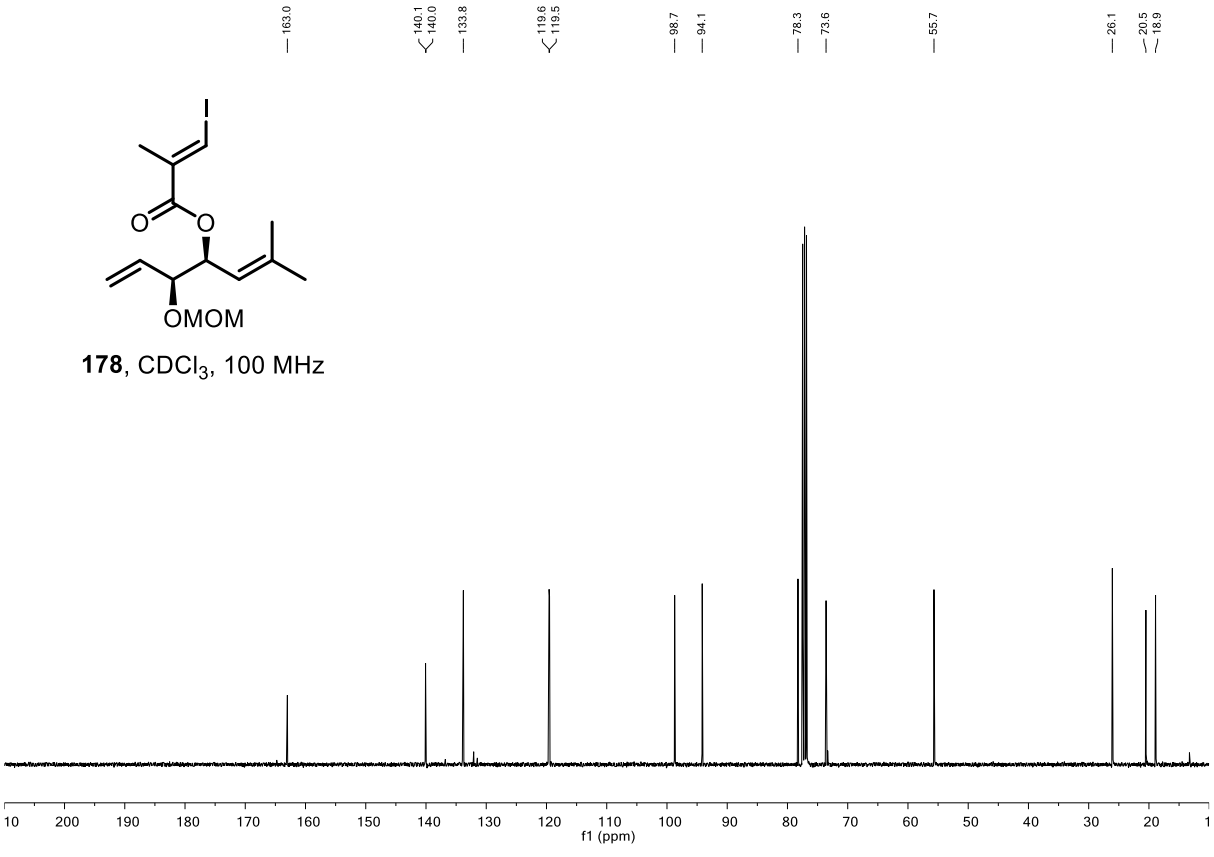


164, $CDCl_3$, 100 MHz

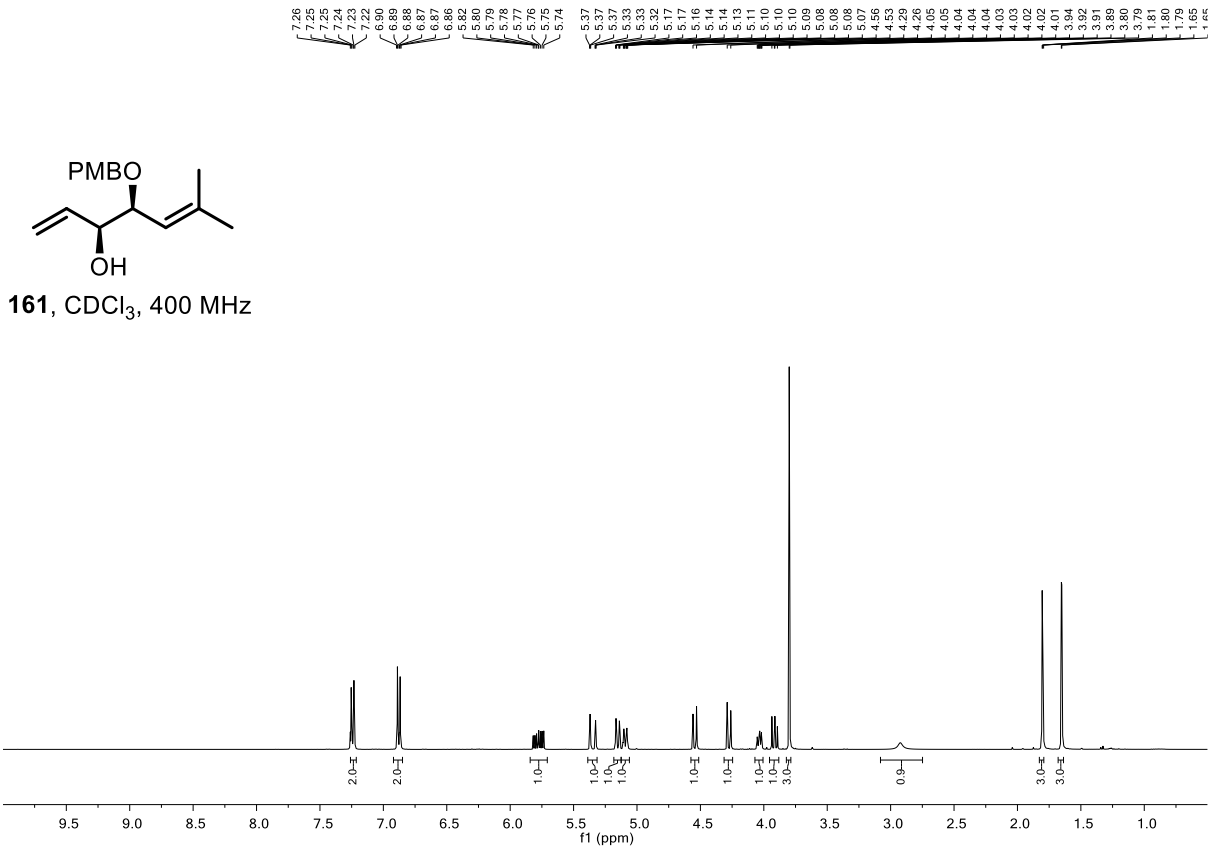




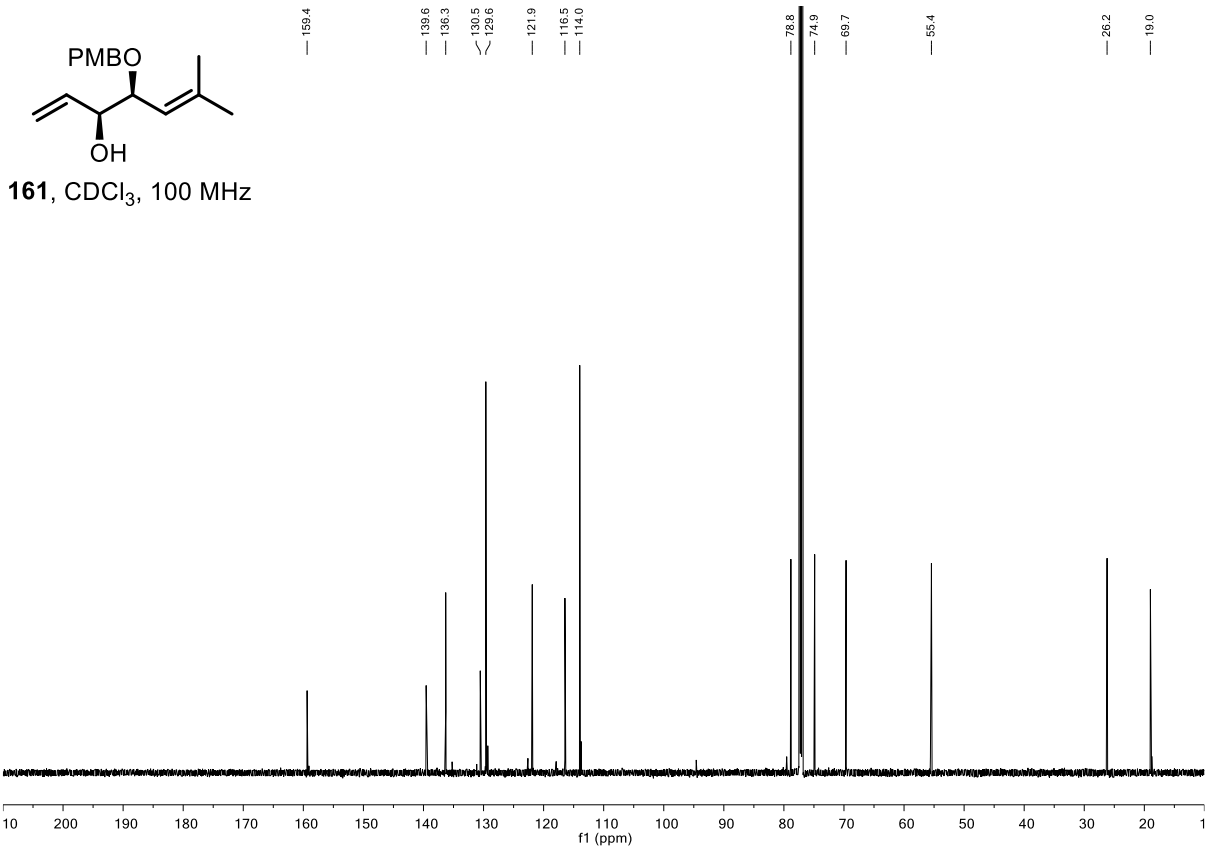
178, $CDCl_3$, 400 MHz



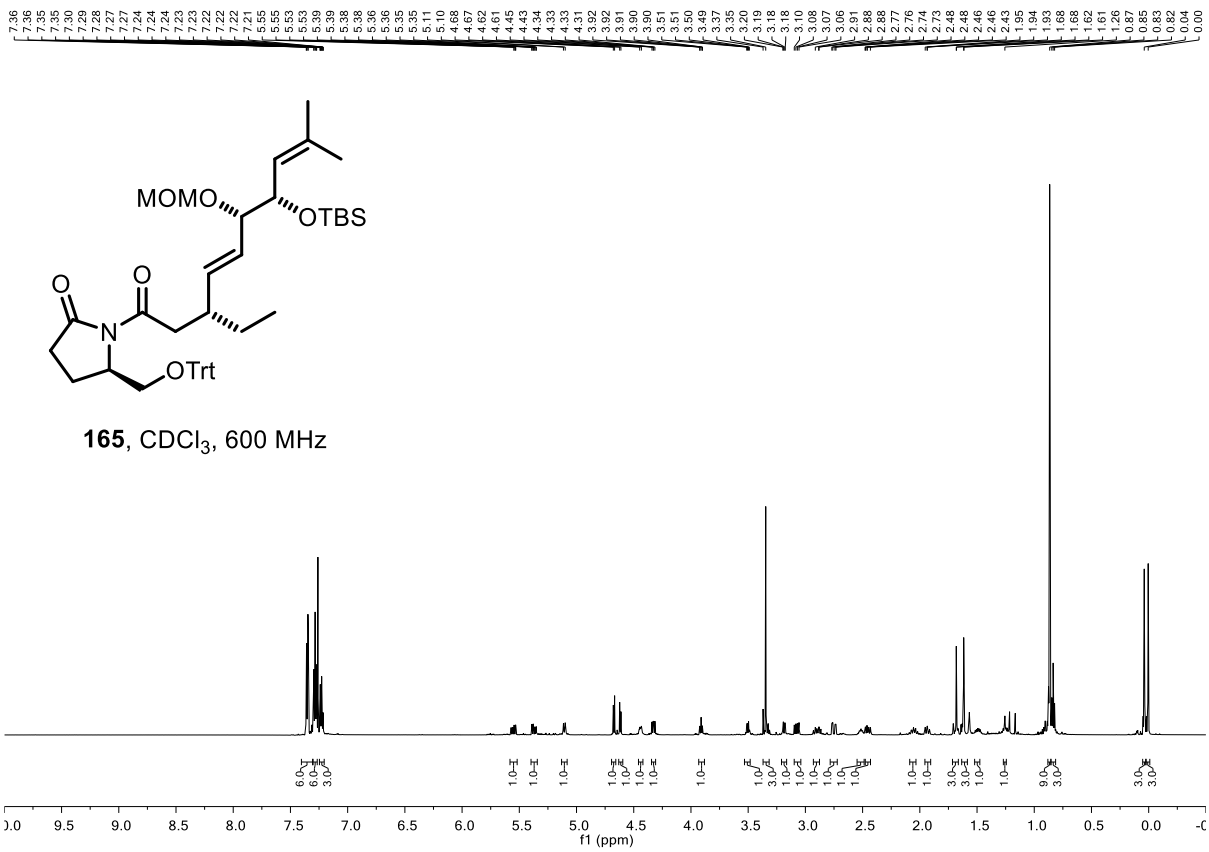
178, $CDCl_3$, 100 MHz



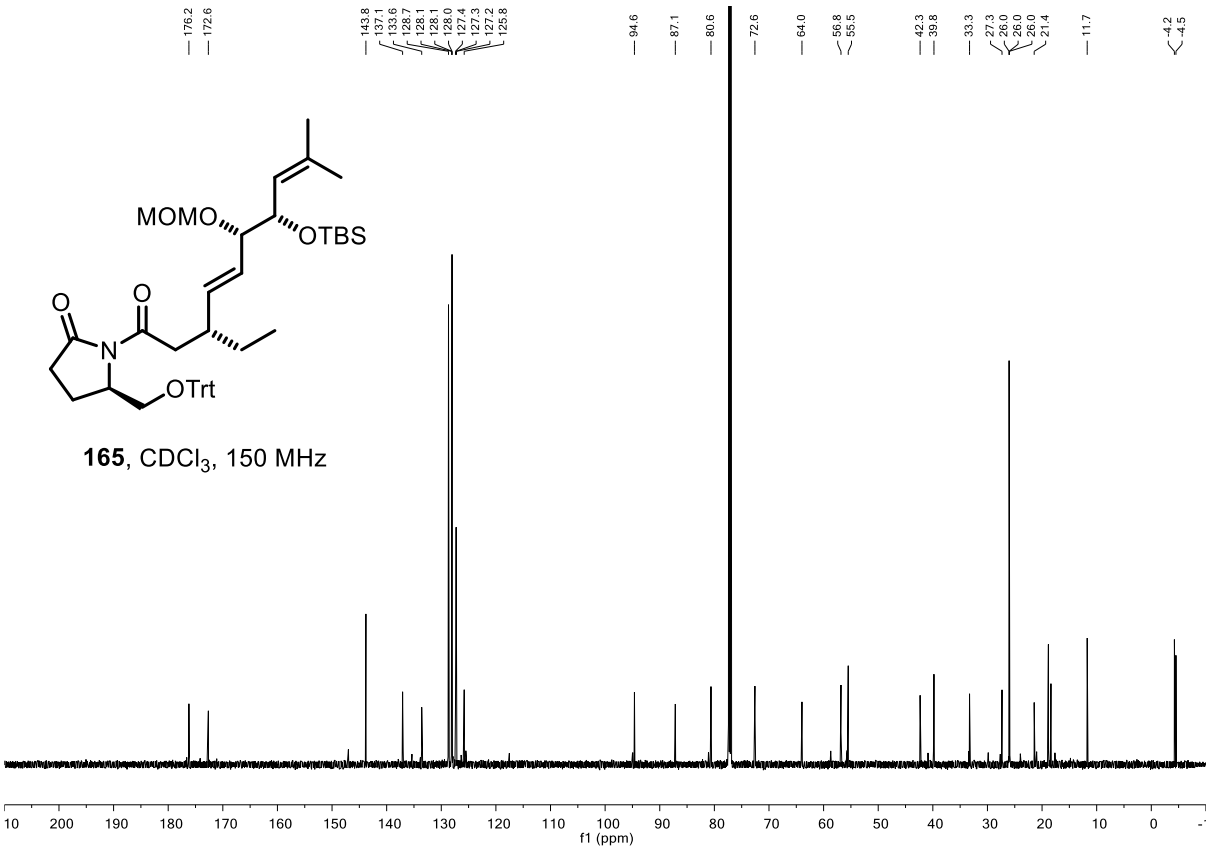
161, $CDCl_3$, 400 MHz



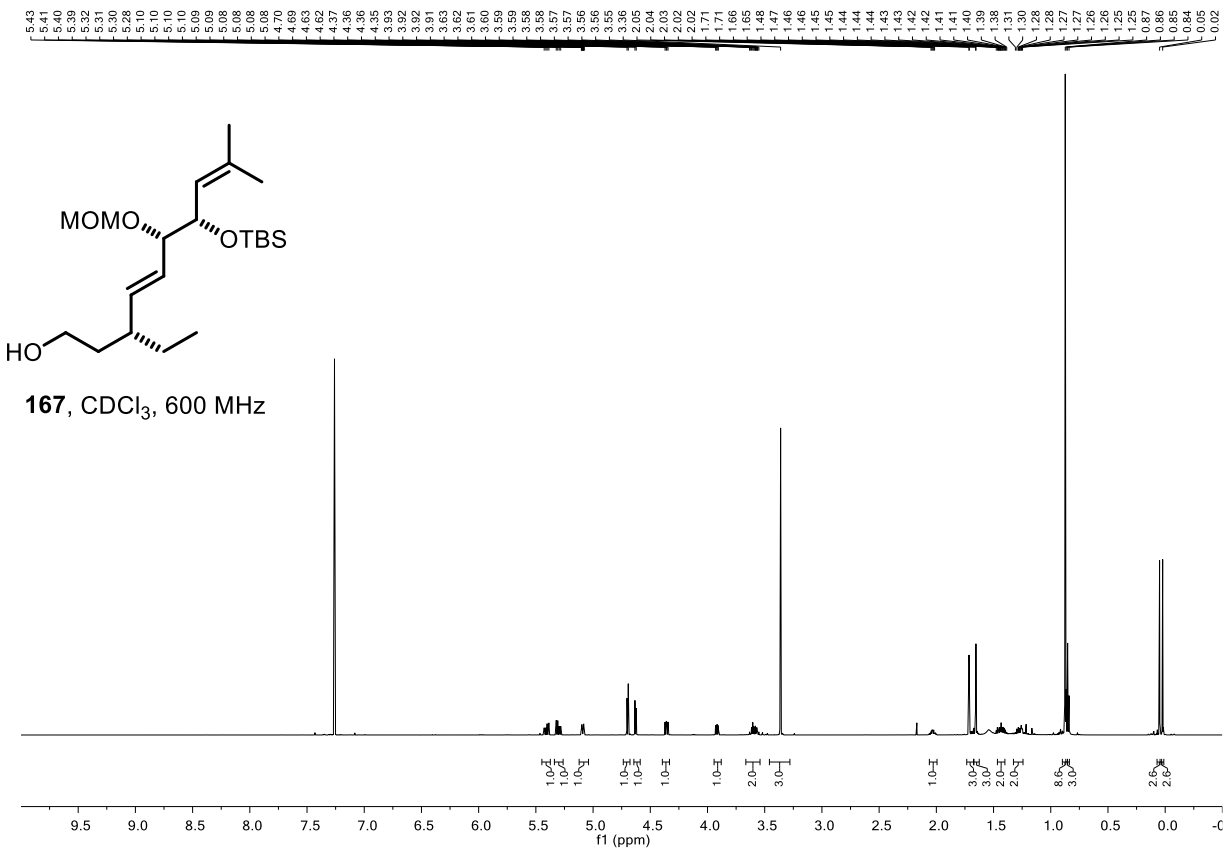
161, $CDCl_3$, 100 MHz



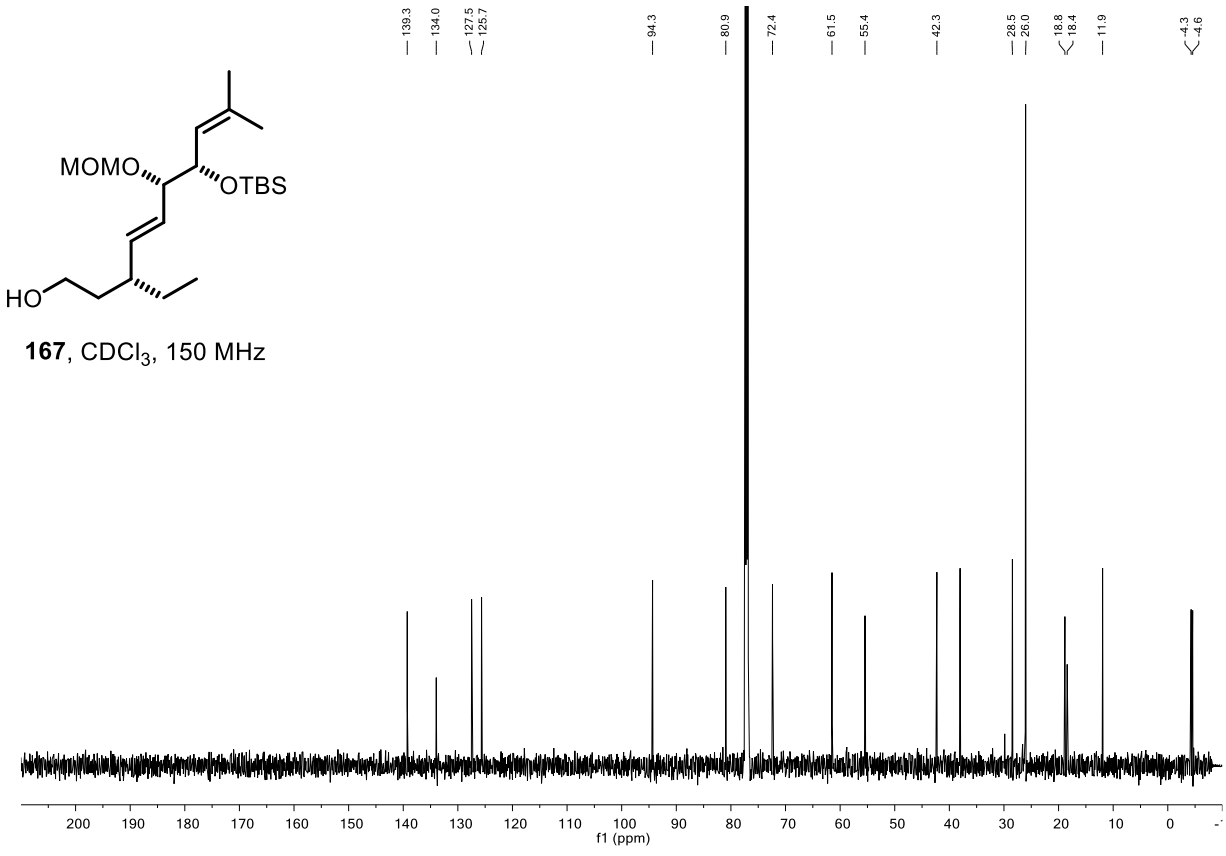
165, $CDCl_3$, 600 MHz



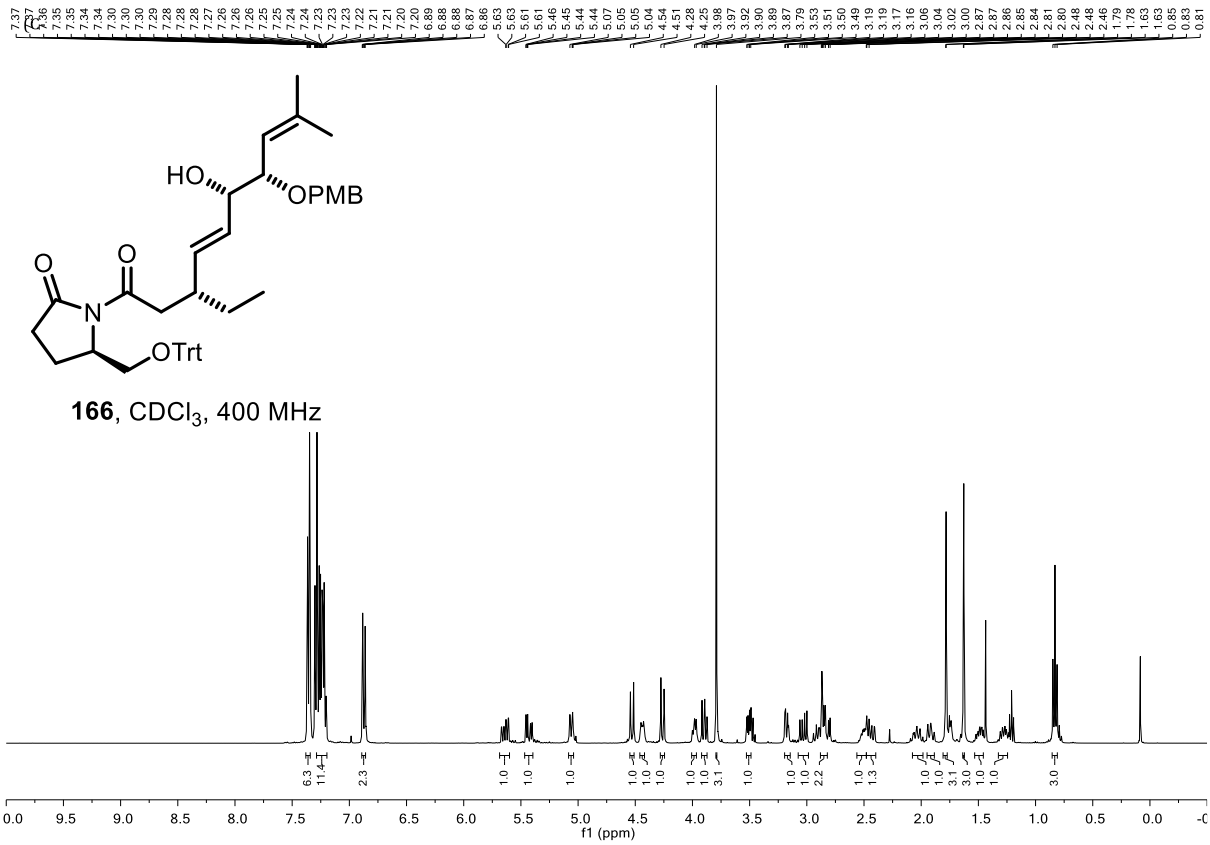
165, $CDCl_3$, 150 MHz



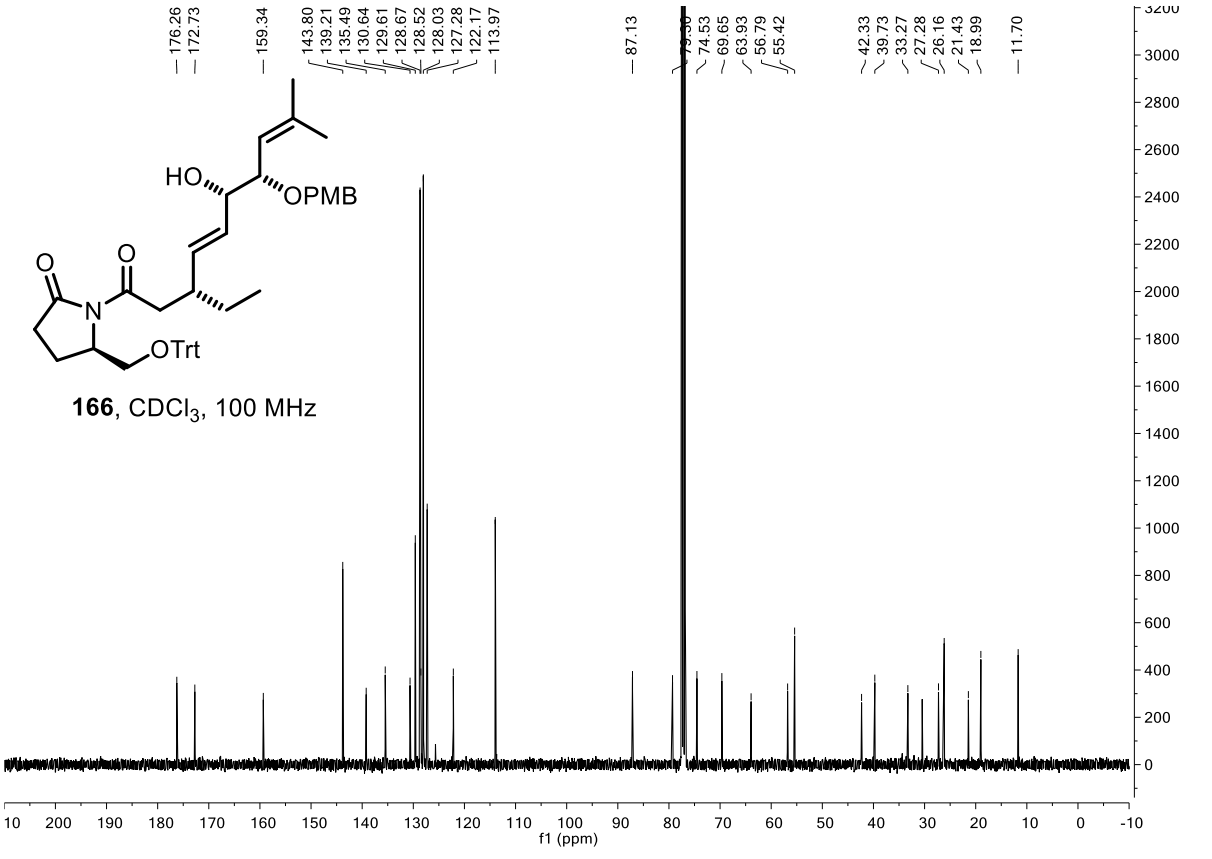
167, $CDCl_3$, 600 MHz



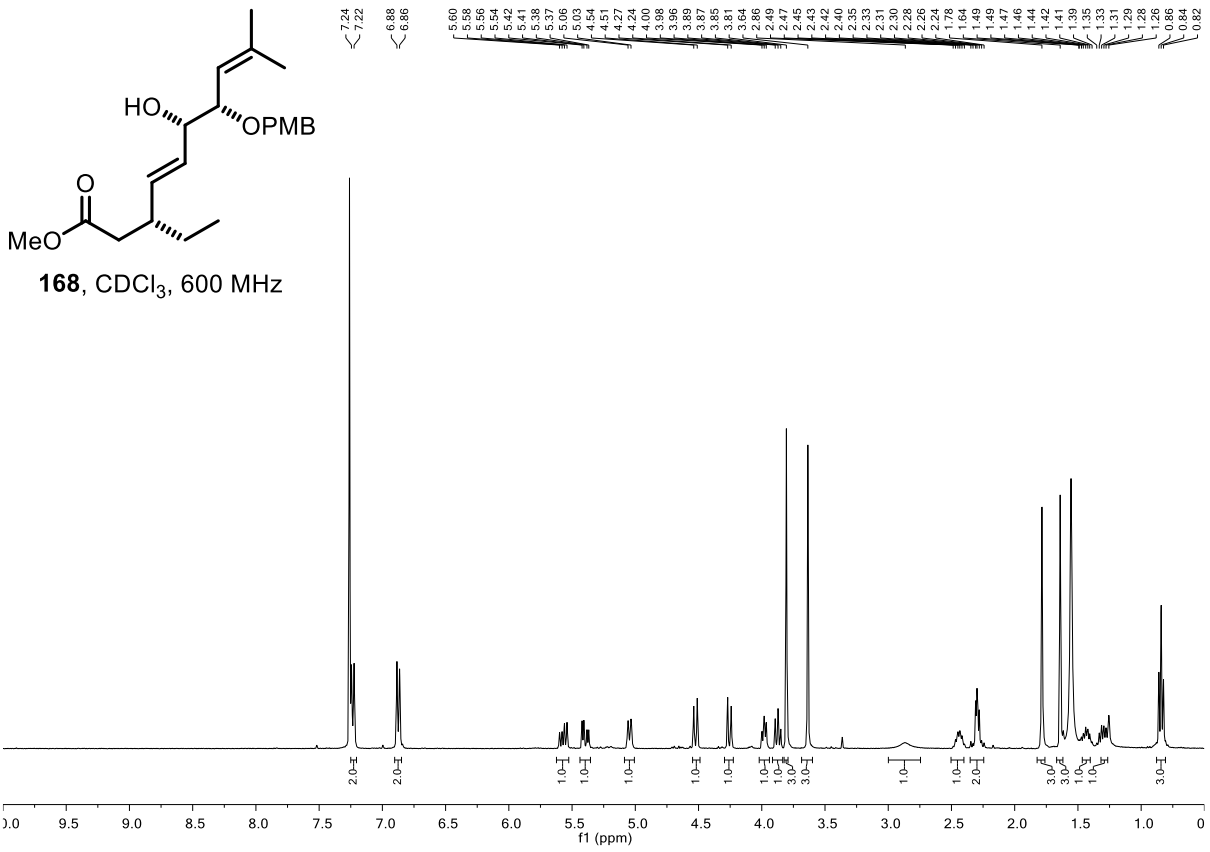
167, $CDCl_3$, 150 MHz

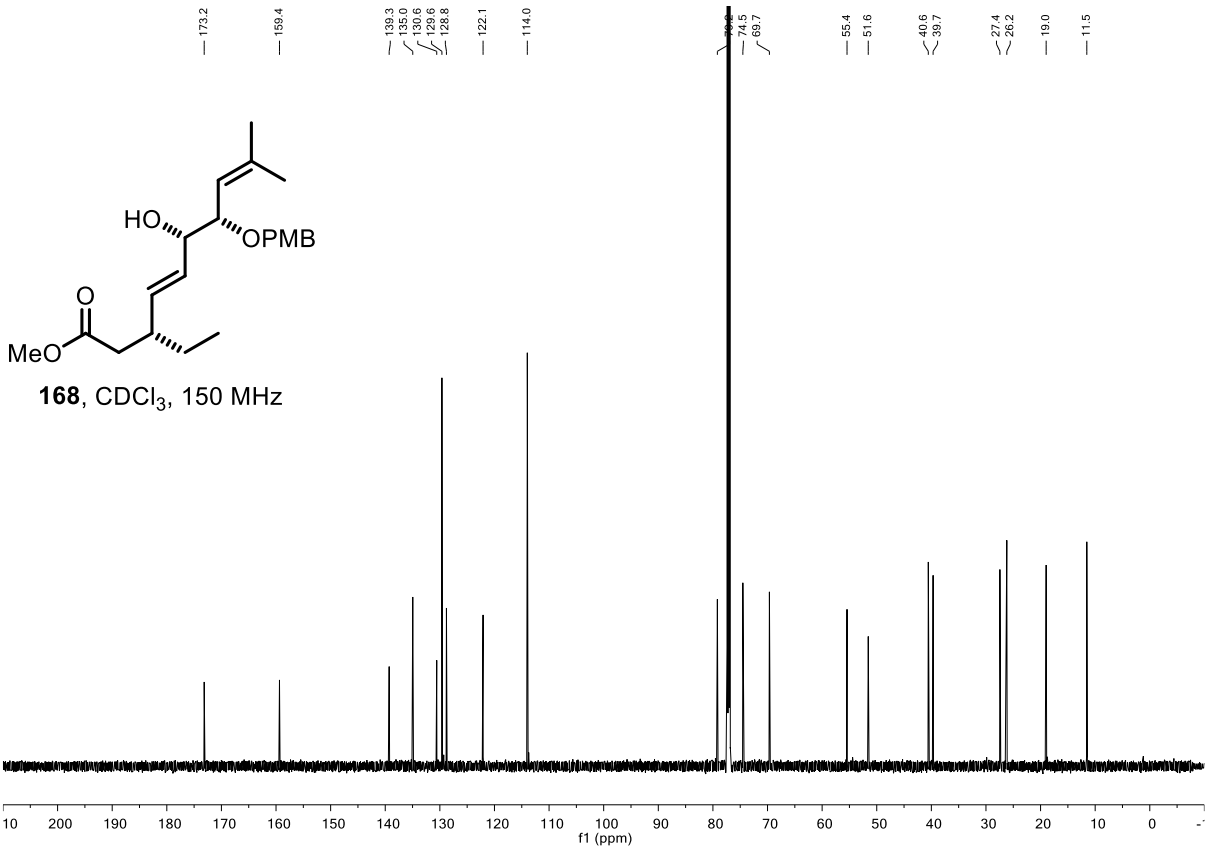


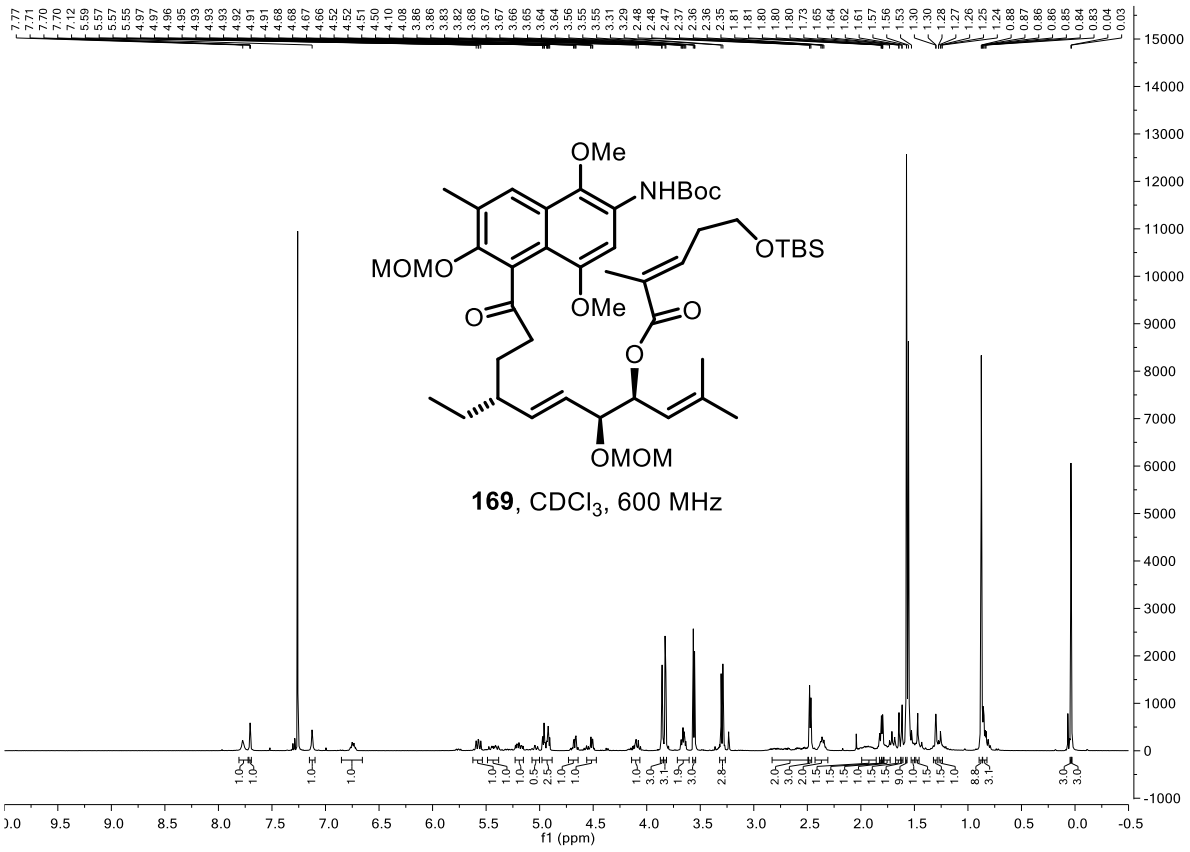
166, $CDCl_3$, 400 MHz



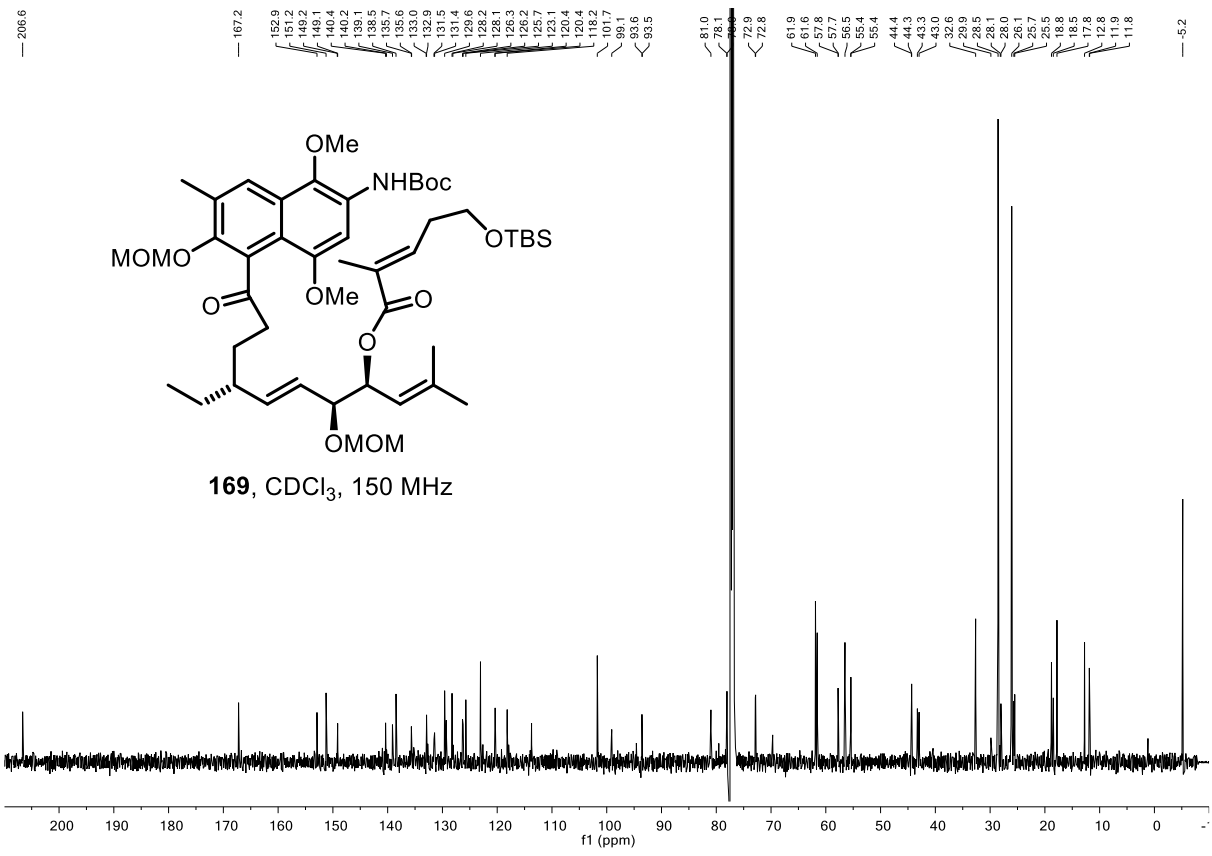
166, $CDCl_3$, 100 MHz


HO
OPMB
O
MeO
168, CDCl3, 600 MHz
f1 (ppm)

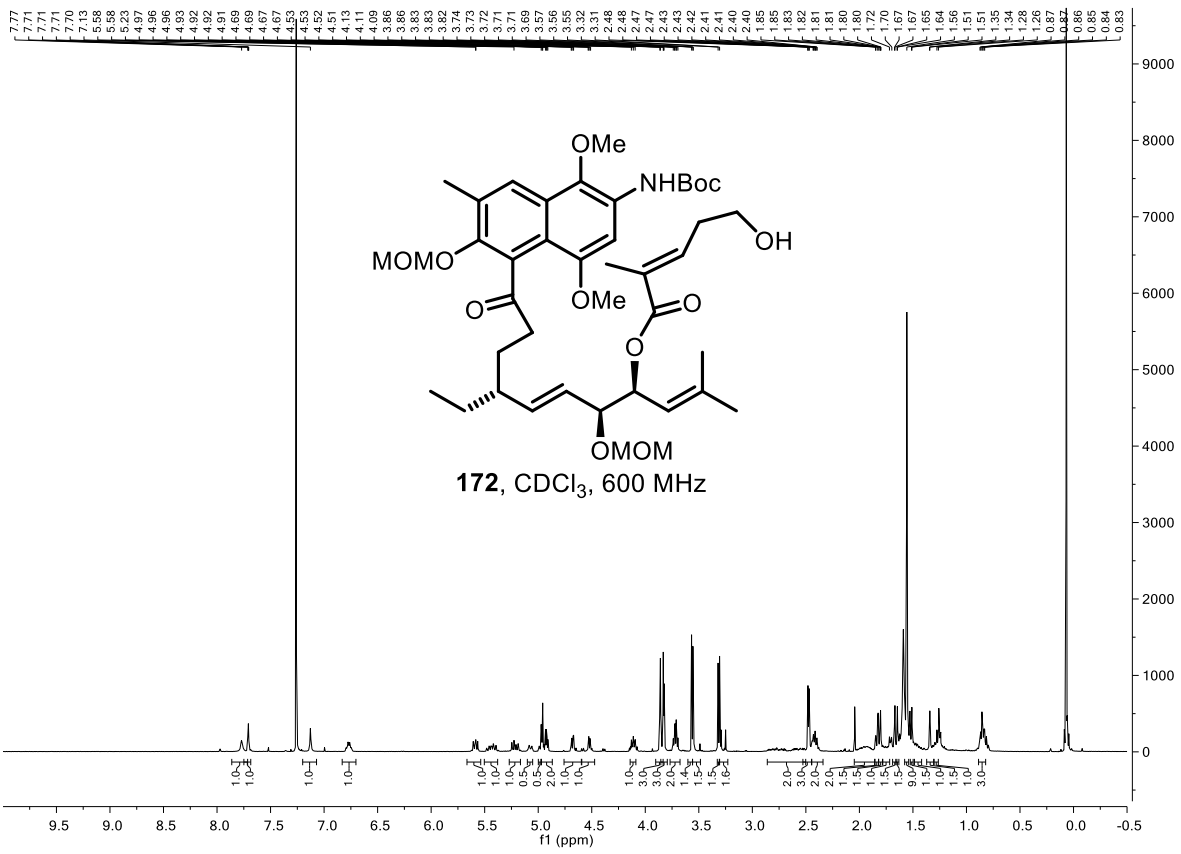

HO
OPMB
O
MeO
168, CDCl3, 150 MHz
f1 (ppm)



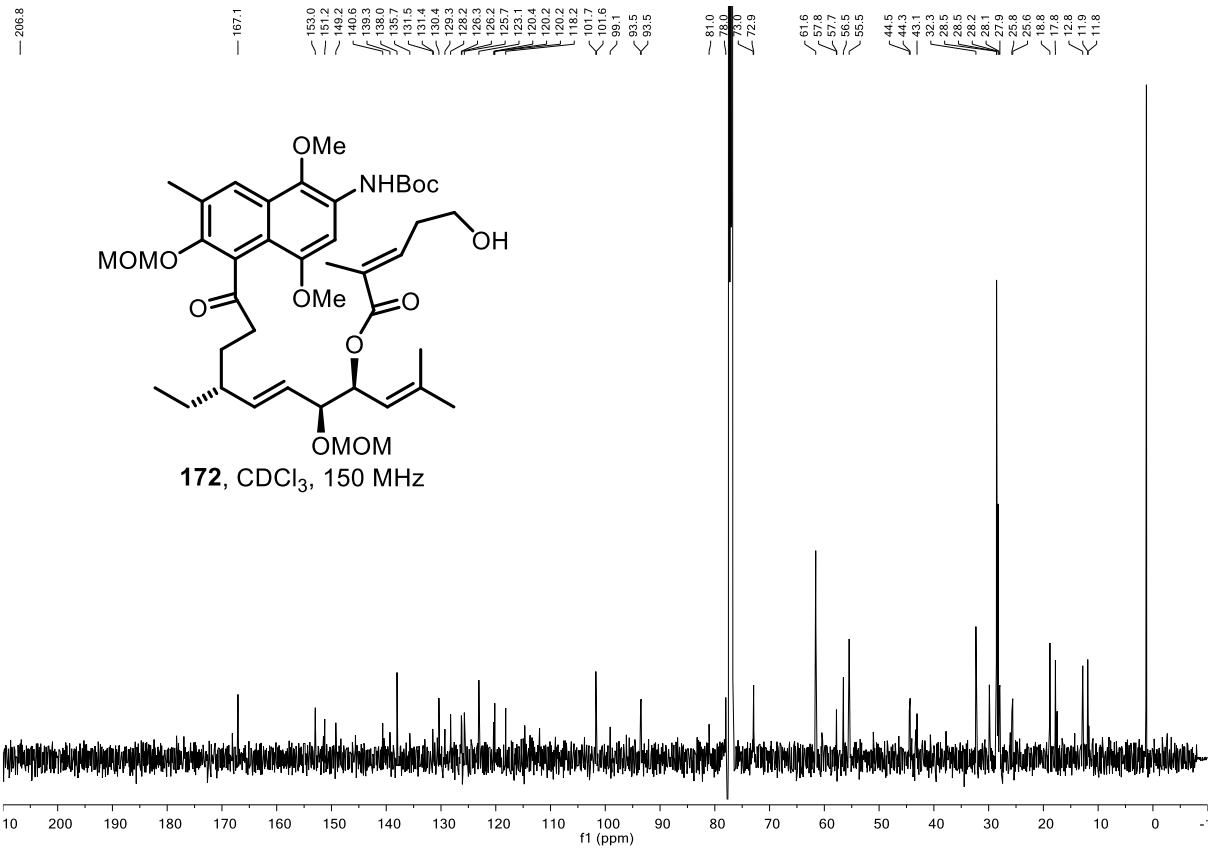
169, $CDCl_3$, 600 MHz



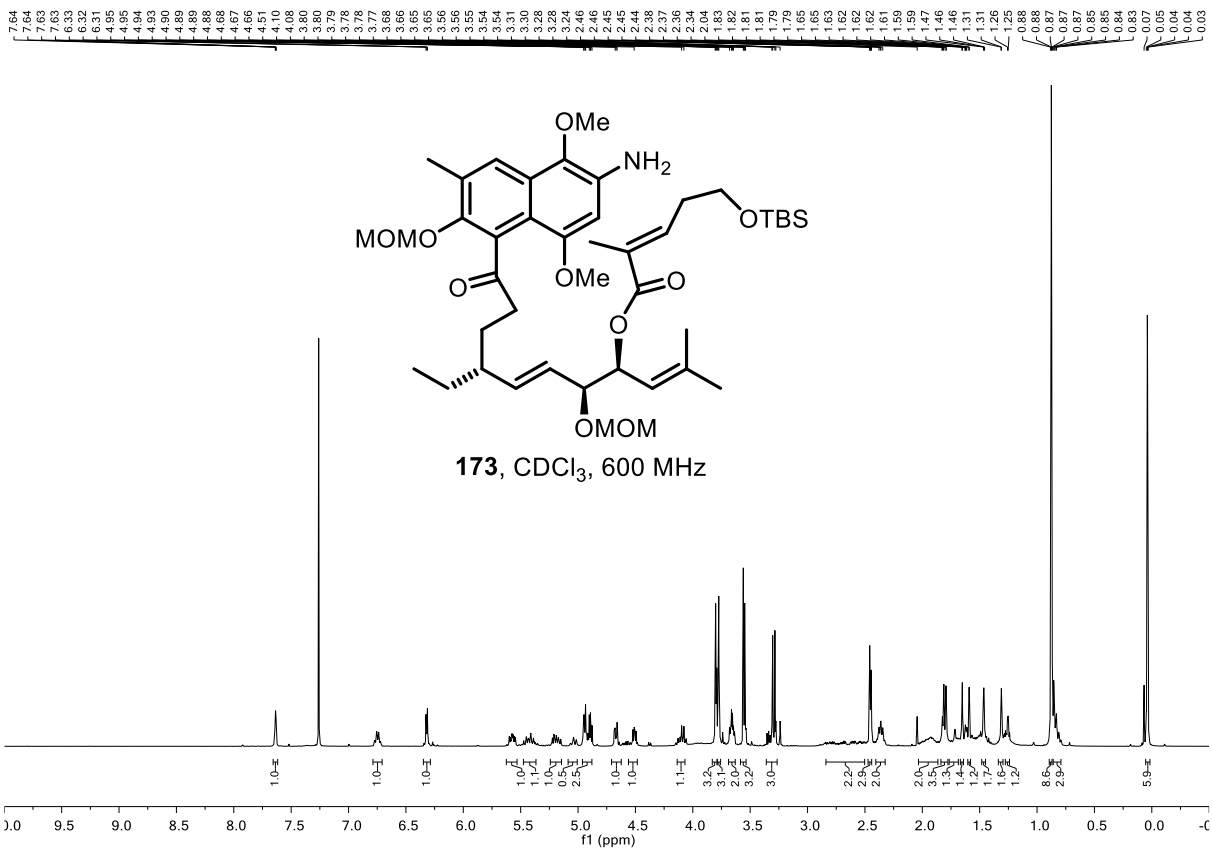
169, $CDCl_3$, 150 MHz



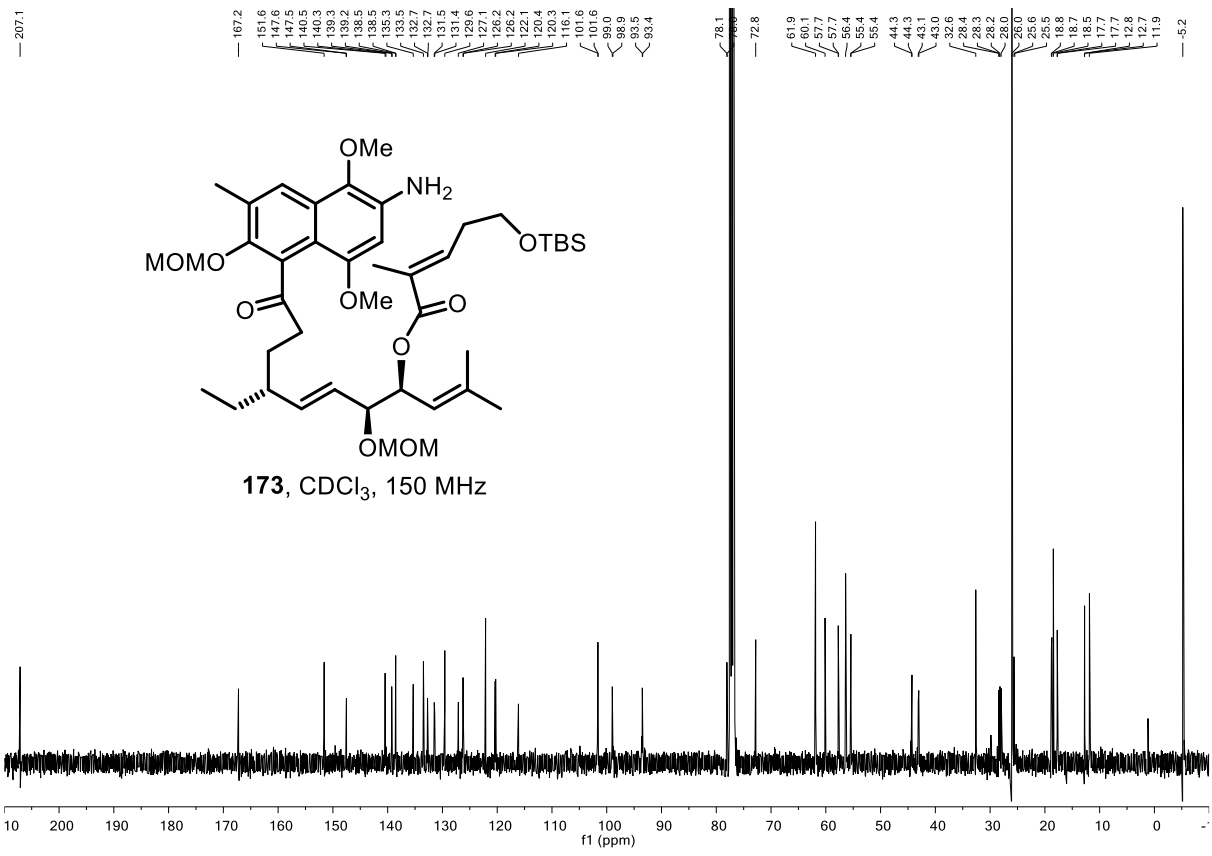
172, $CDCl_3$, 600 MHz



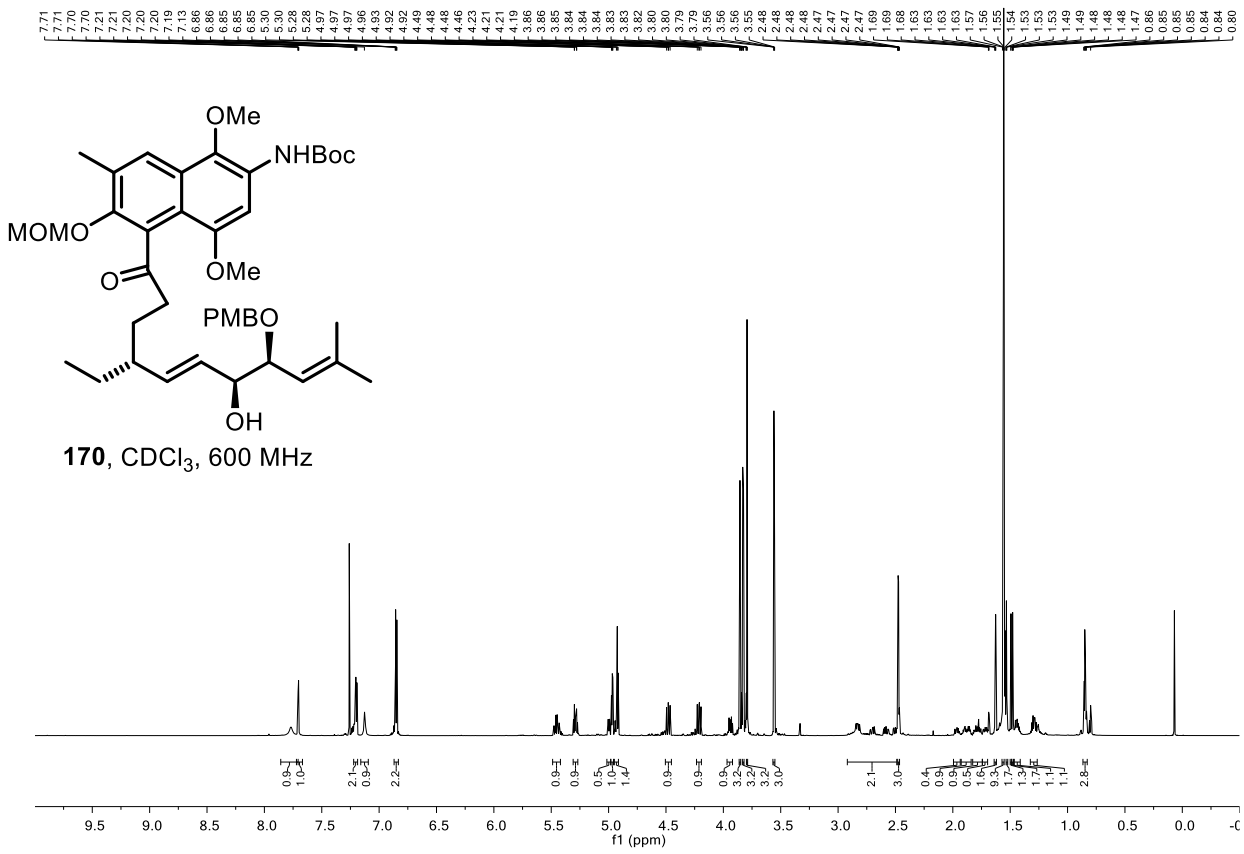
172, $CDCl_3$, 150 MHz



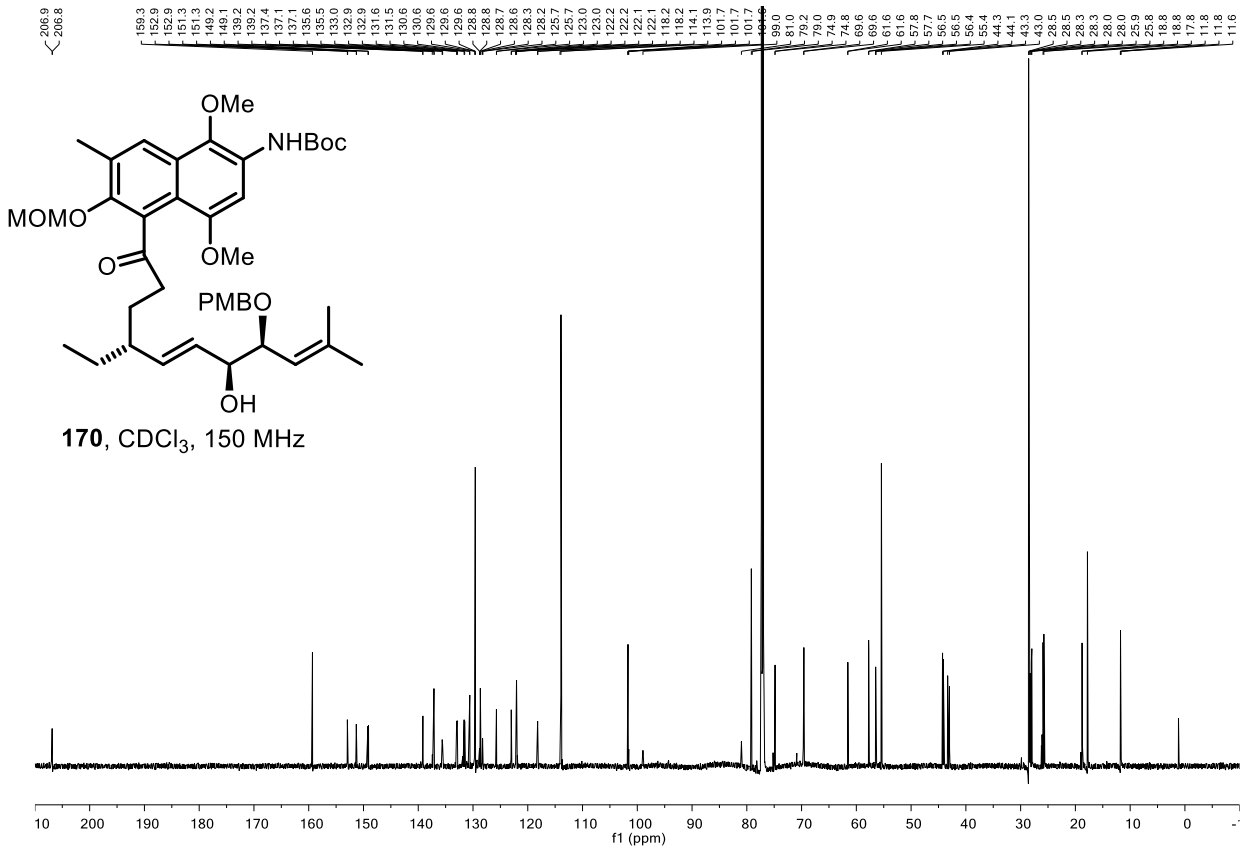
173, $CDCl_3$, 600 MHz



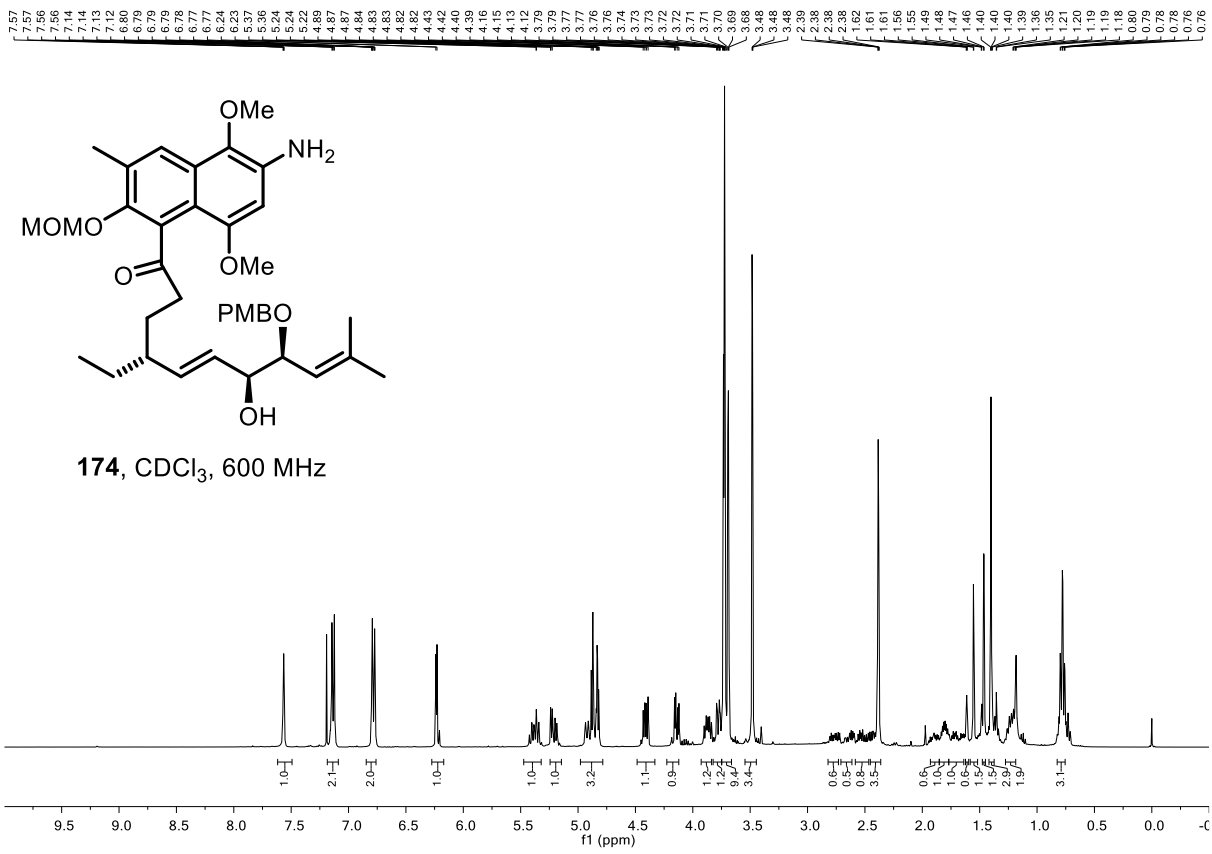
173, $CDCl_3$, 150 MHz



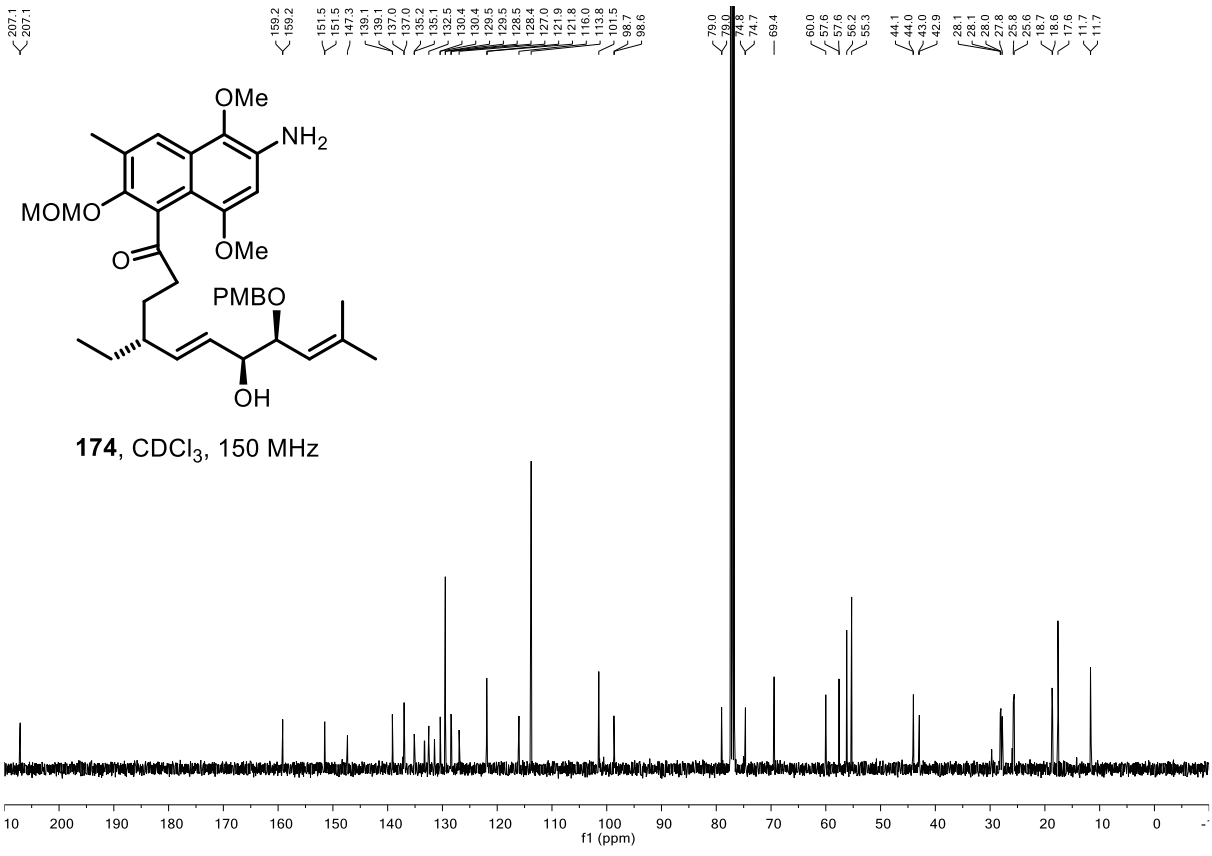
170, $CDCl_3$, 600 MHz



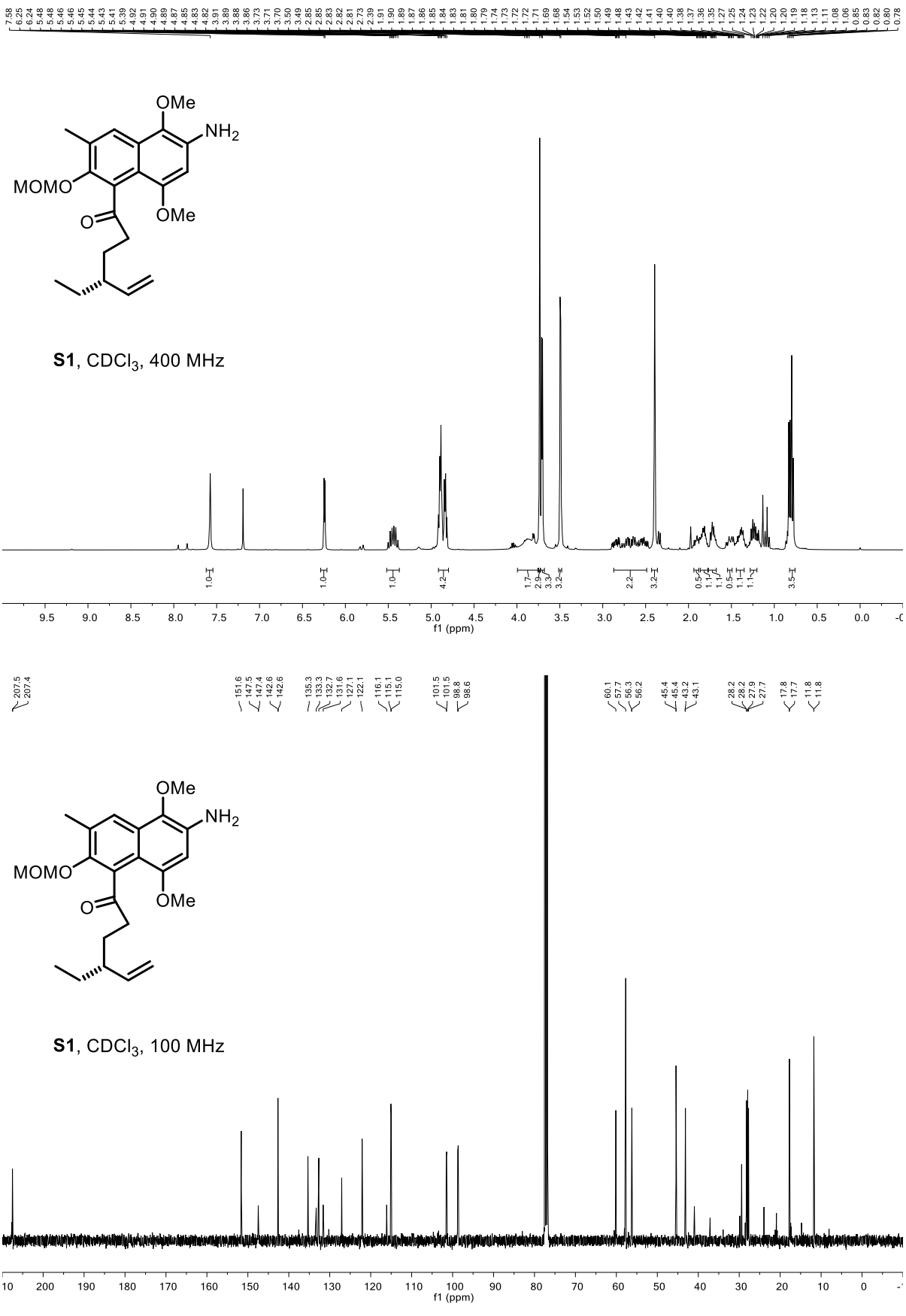
170, $CDCl_3$, 150 MHz

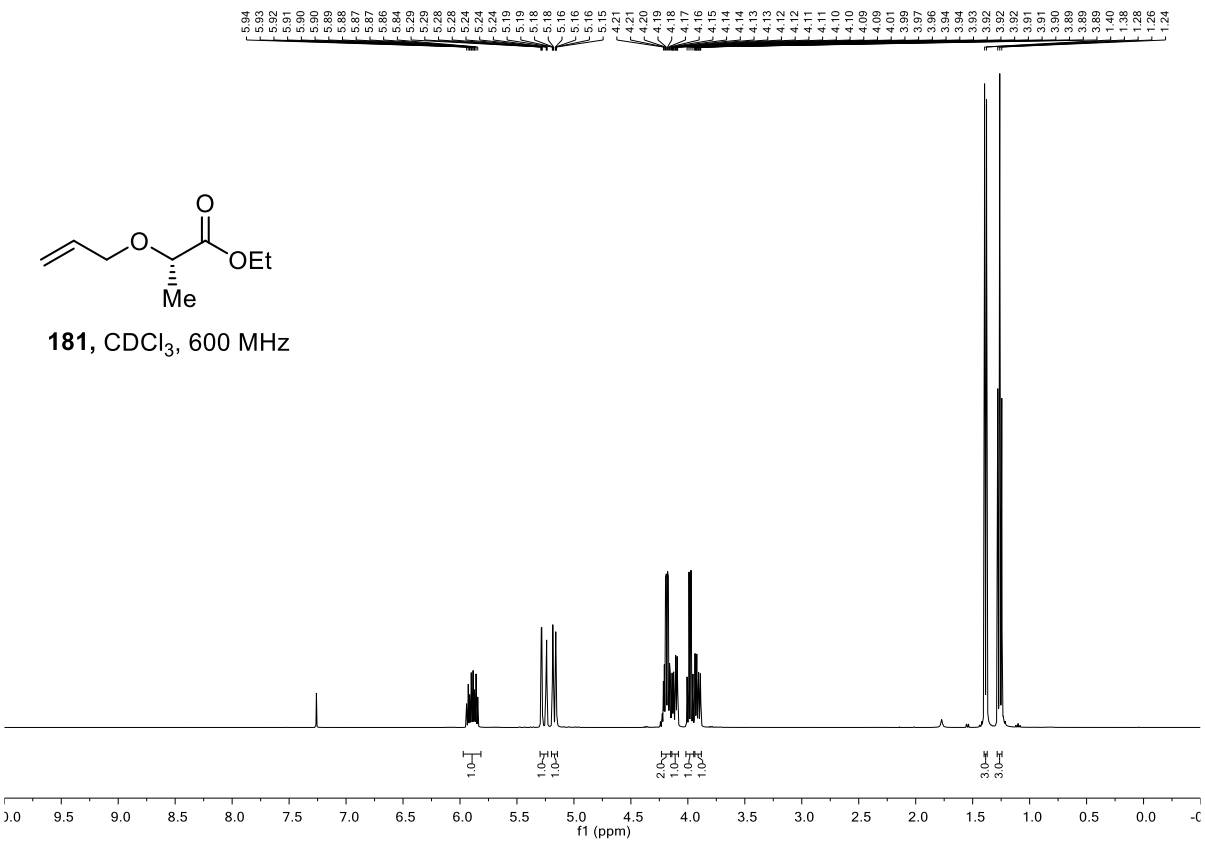


174, $CDCl_3$, 600 MHz

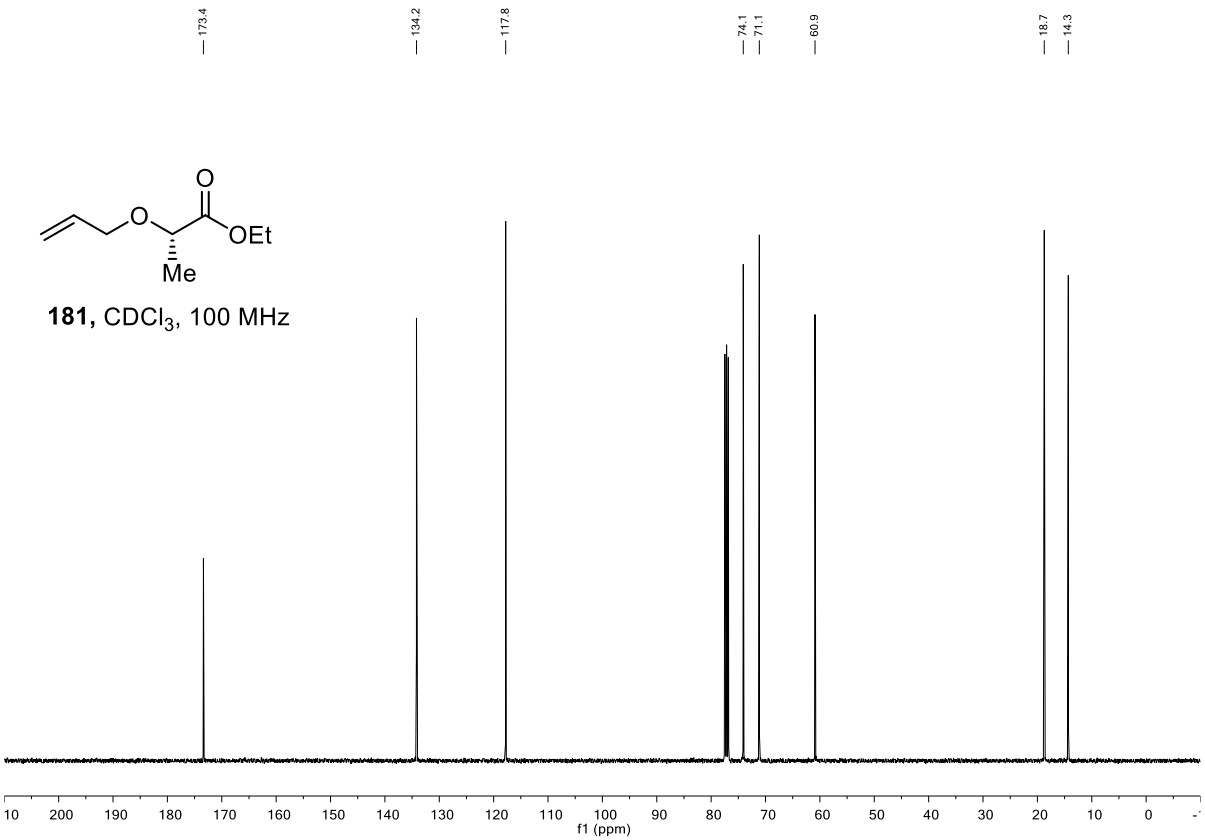


174, $CDCl_3$, 150 MHz

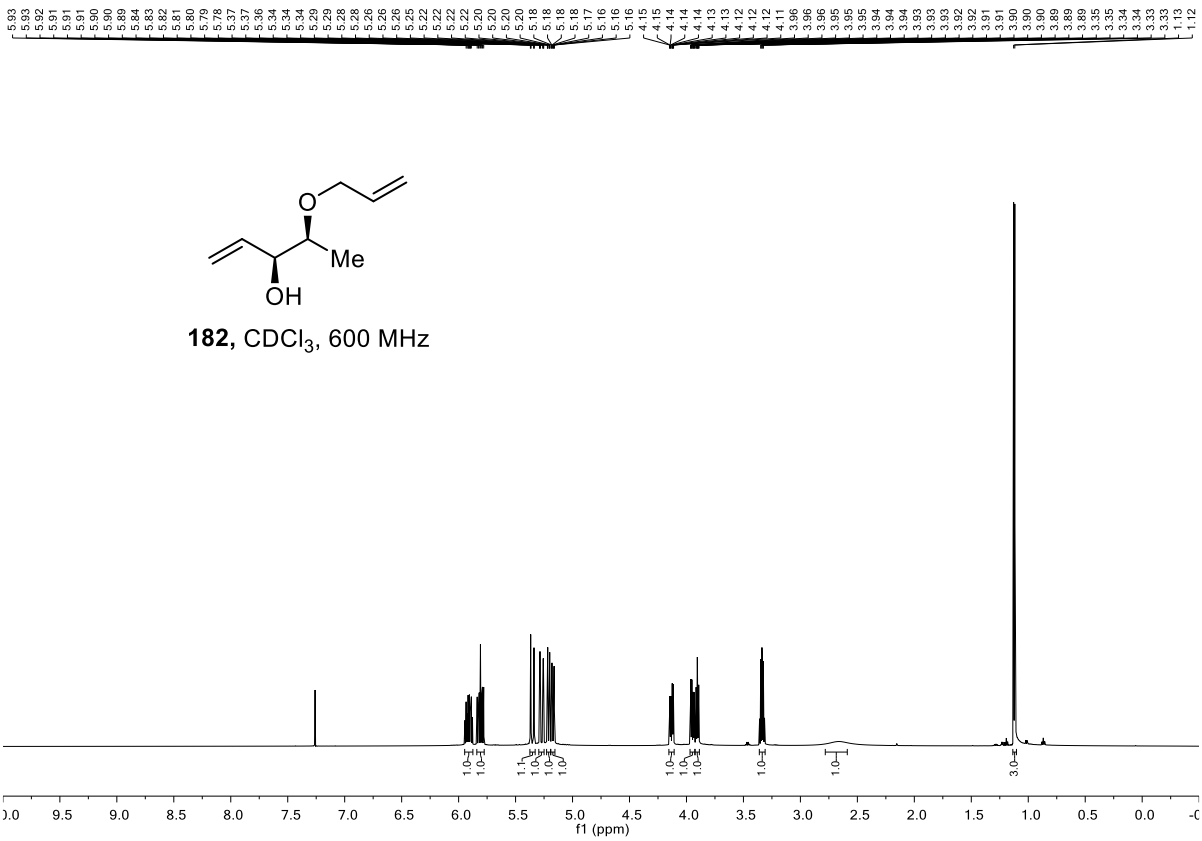

OMe
NH2
MOMO
O
OMe
S1, CDCl3, 400 MHz
f1 (ppm)
OMe
NH2
MOMO
O
OMe
S1, CDCl3, 100 MHz
f1 (ppm)



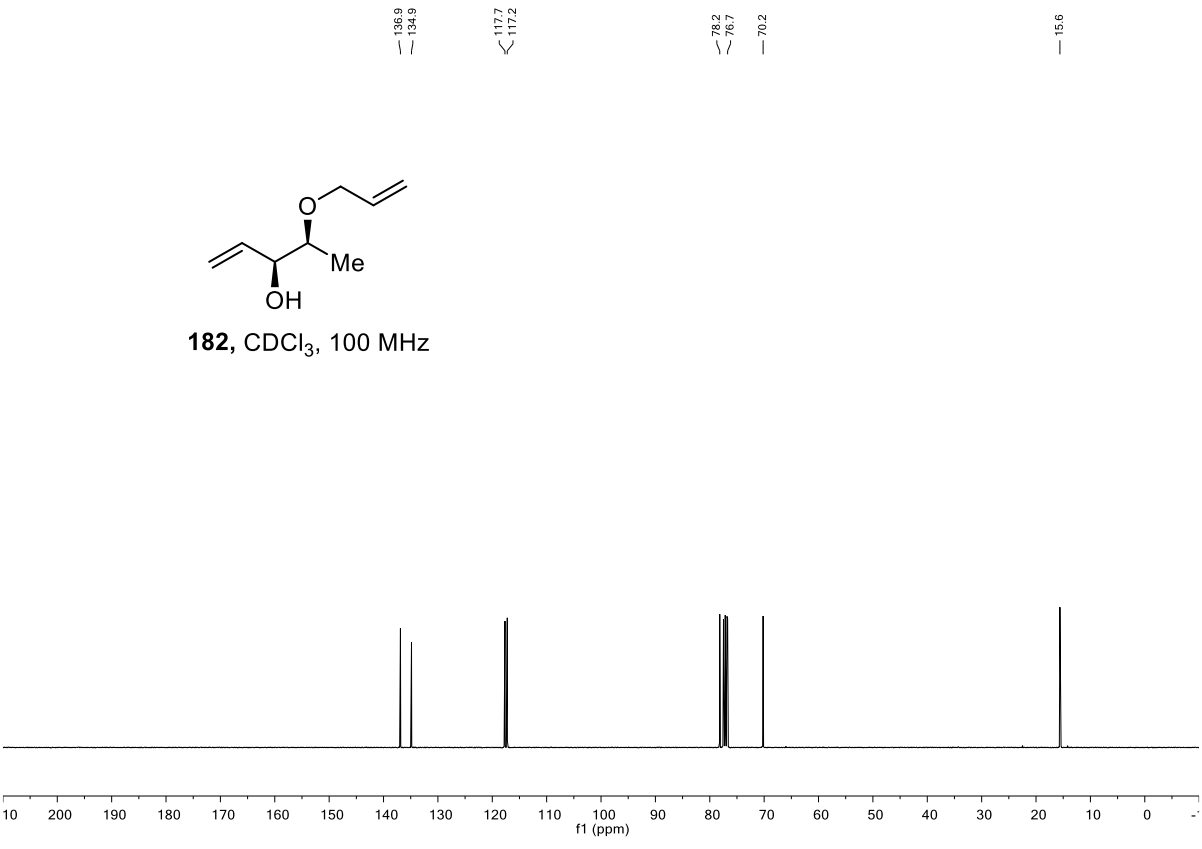
181, $CDCl_3$, 600 MHz



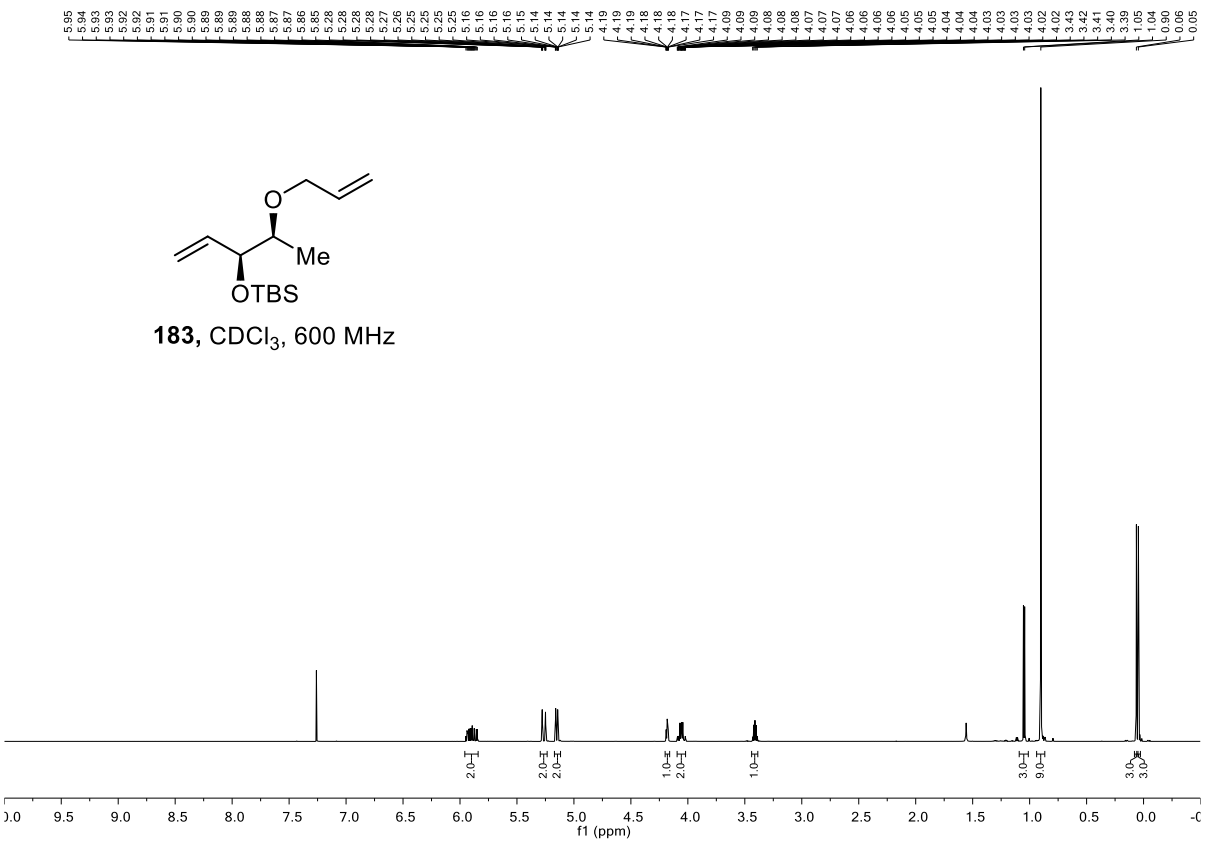
181, $CDCl_3$, 100 MHz



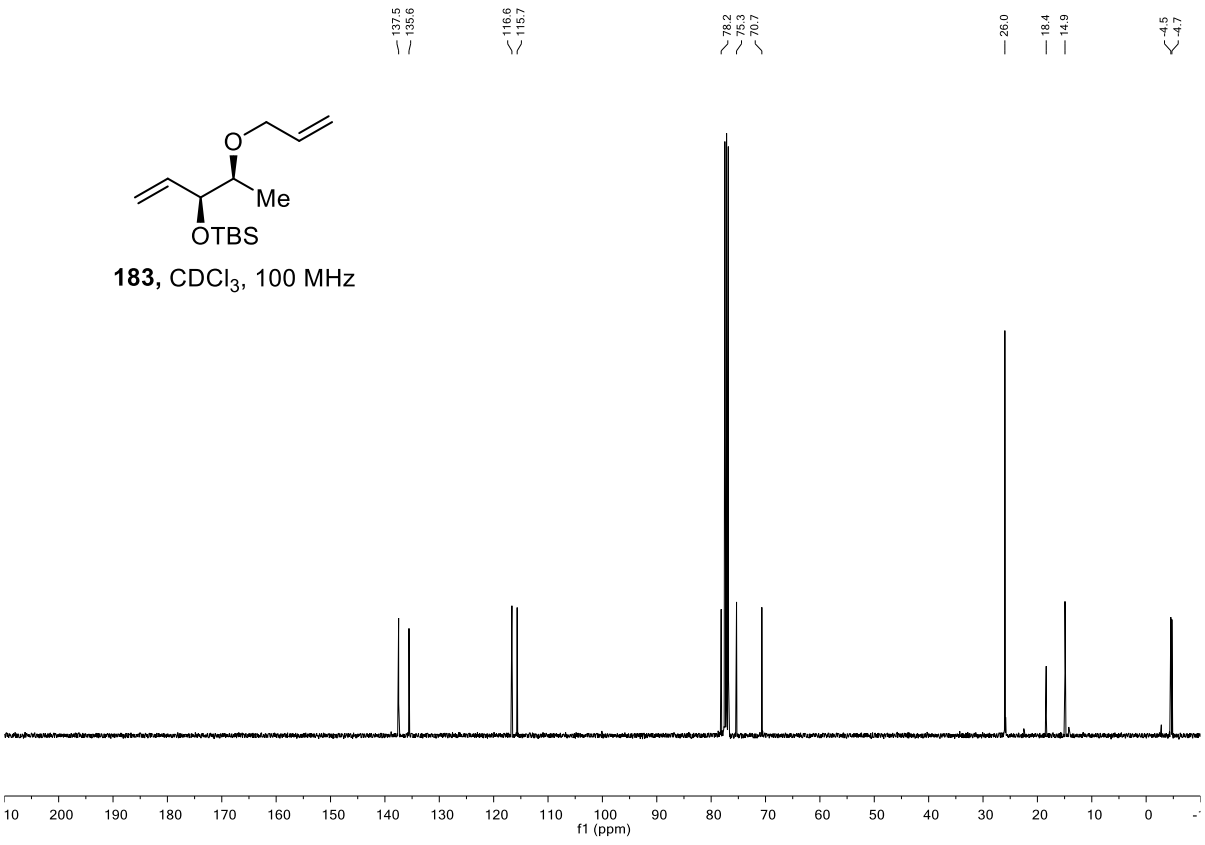
182, $CDCl_3$, 600 MHz



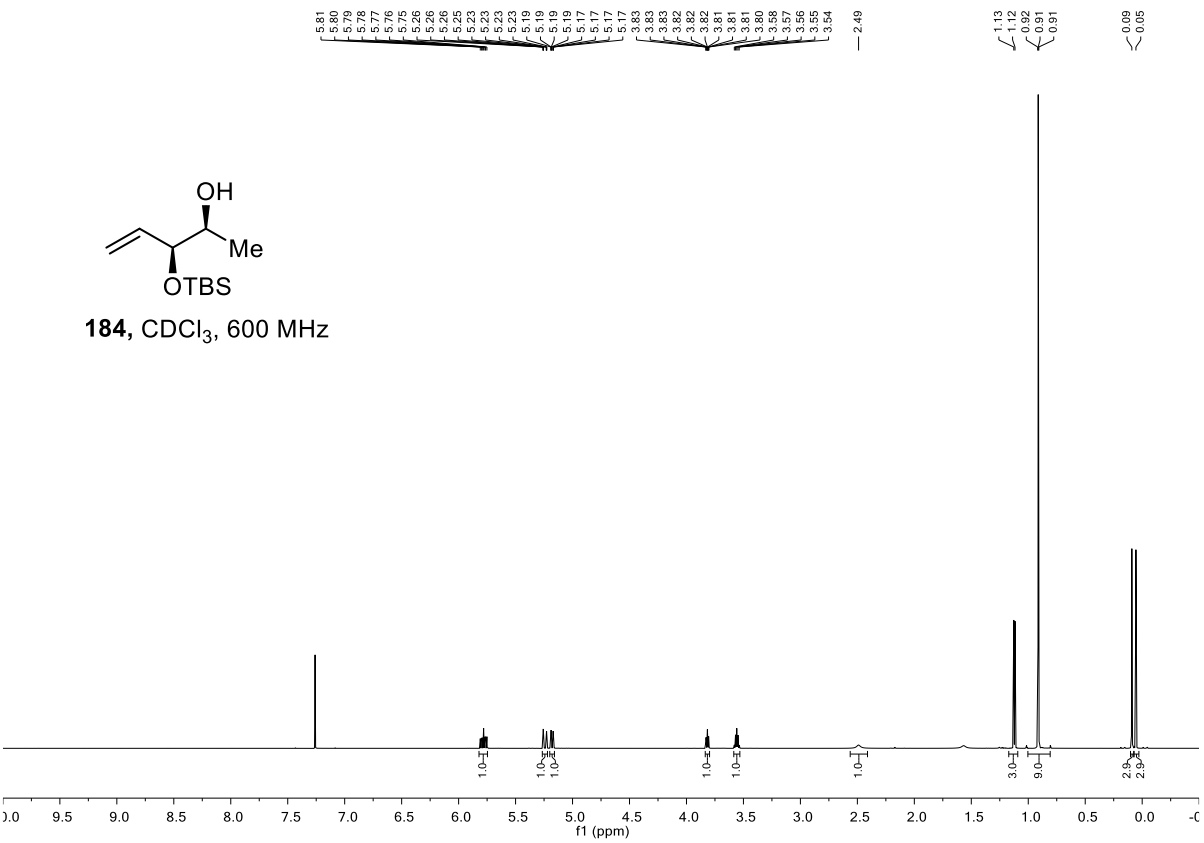
182, $CDCl_3$, 100 MHz



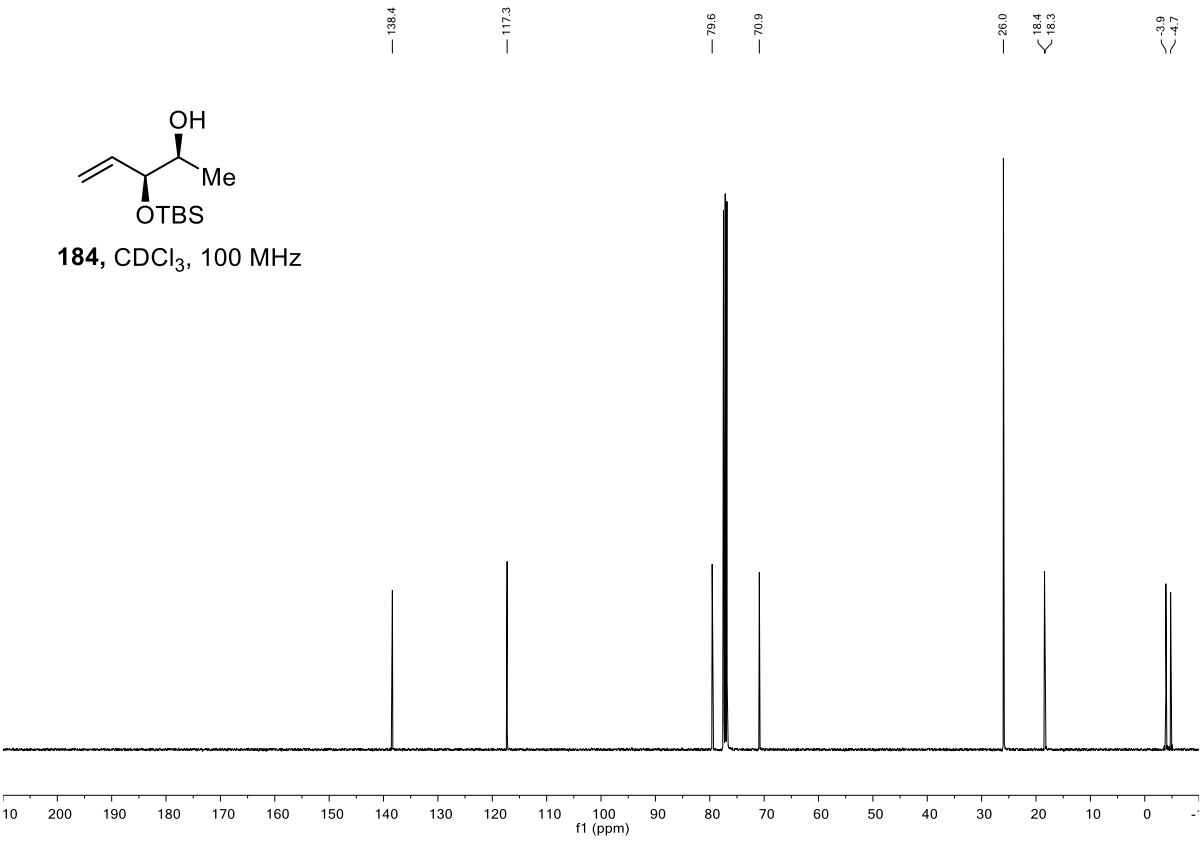
183, $CDCl_3$, 600 MHz



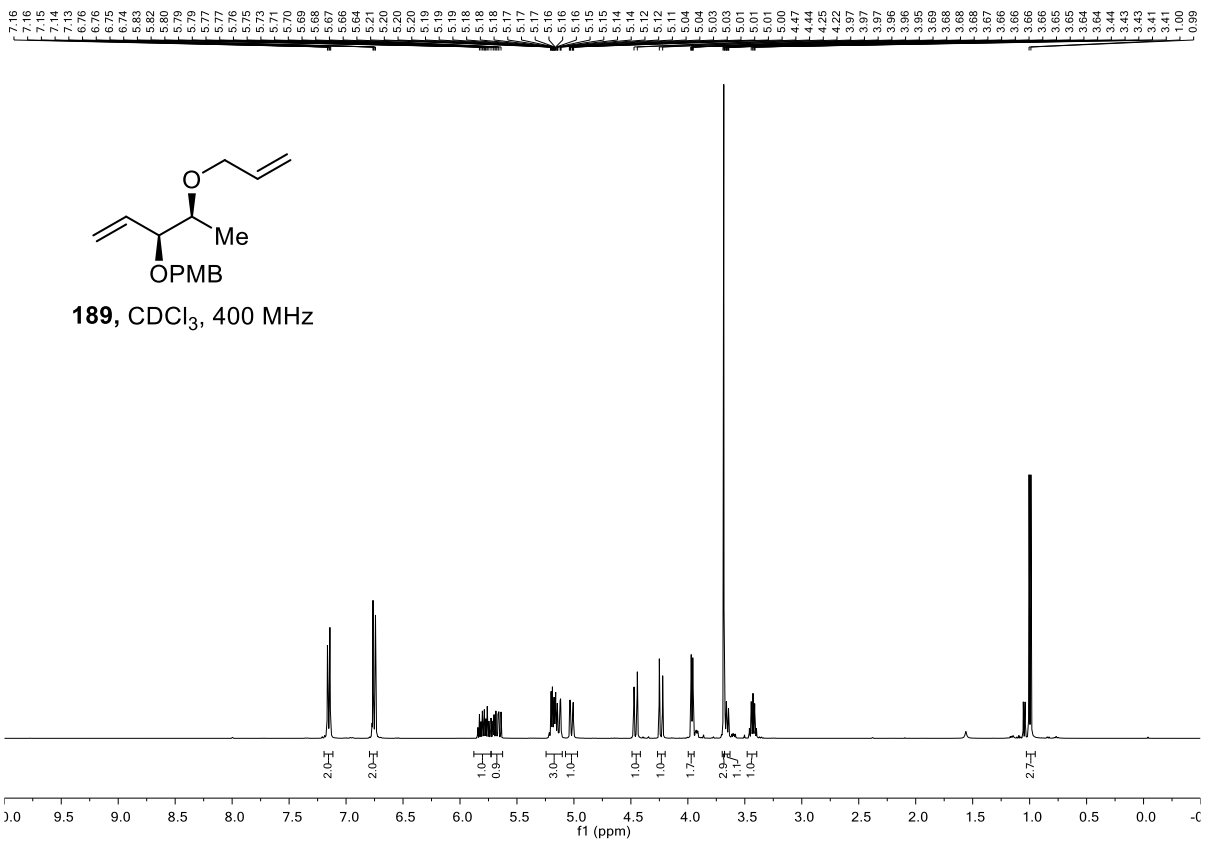
183, $CDCl_3$, 100 MHz



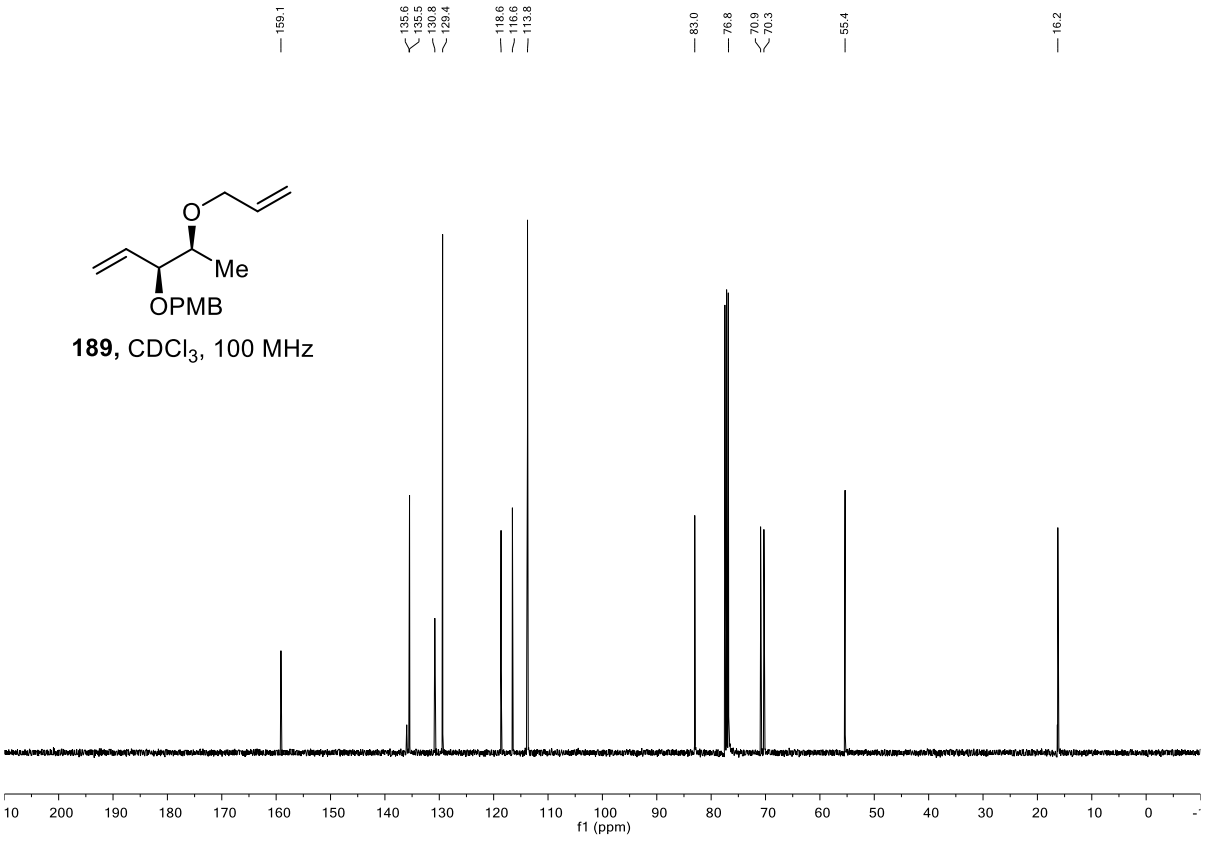
184, $CDCl_3$, 600 MHz



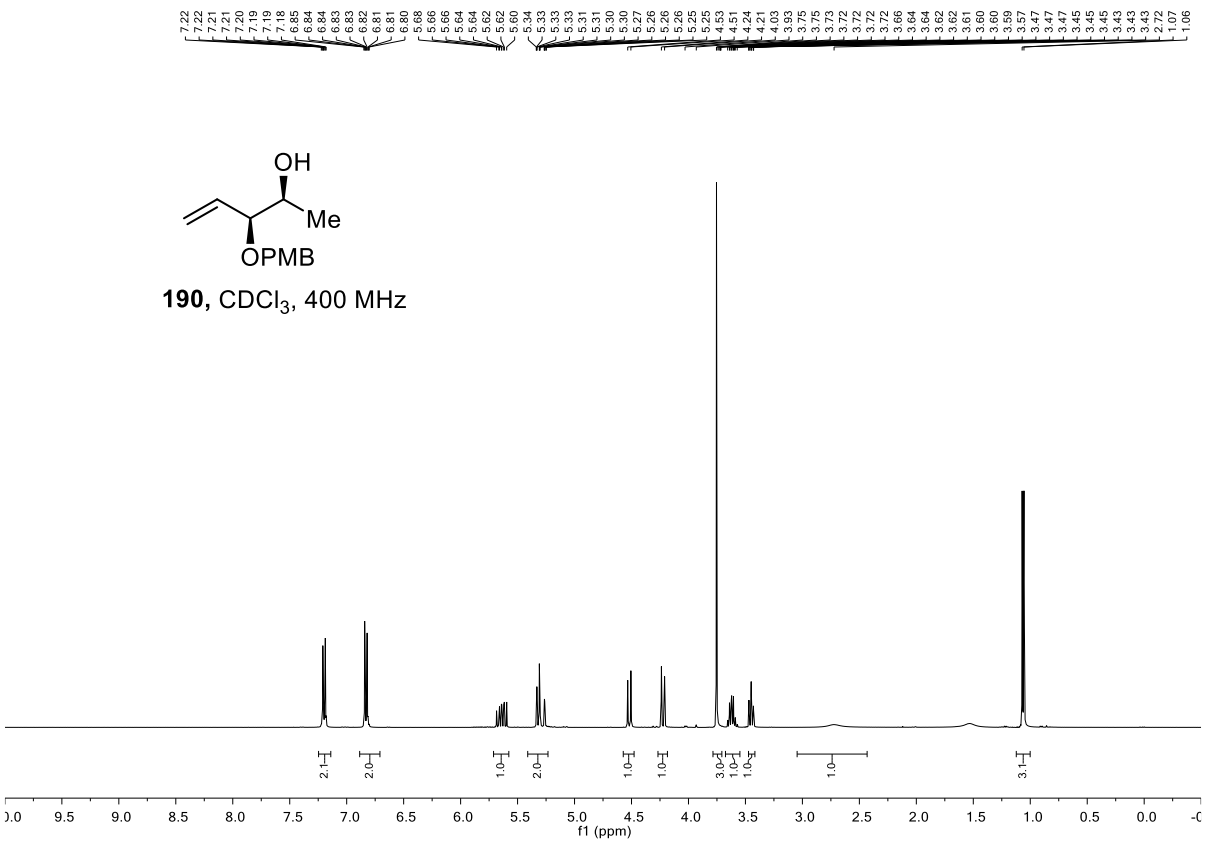
184, $CDCl_3$, 100 MHz



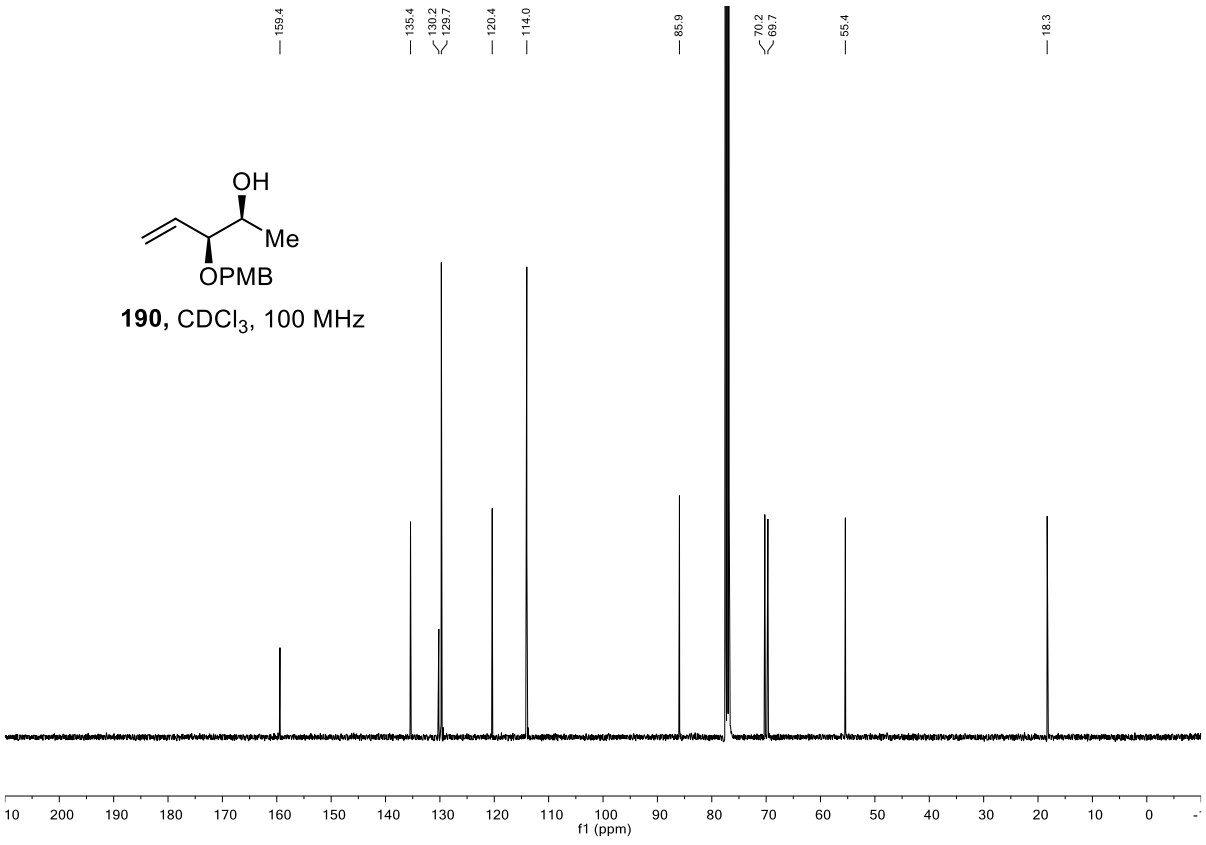
189, $CDCl_3$, 400 MHz



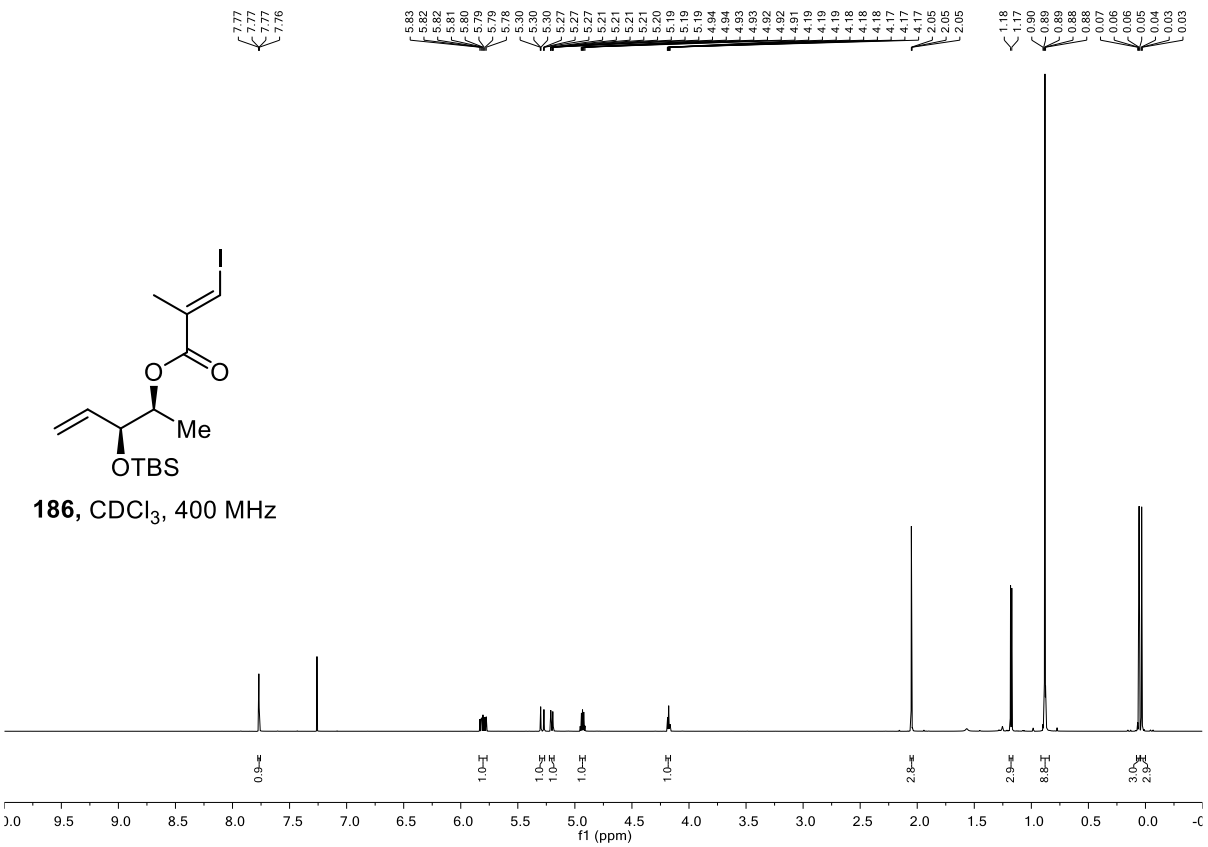
189, $CDCl_3$, 100 MHz



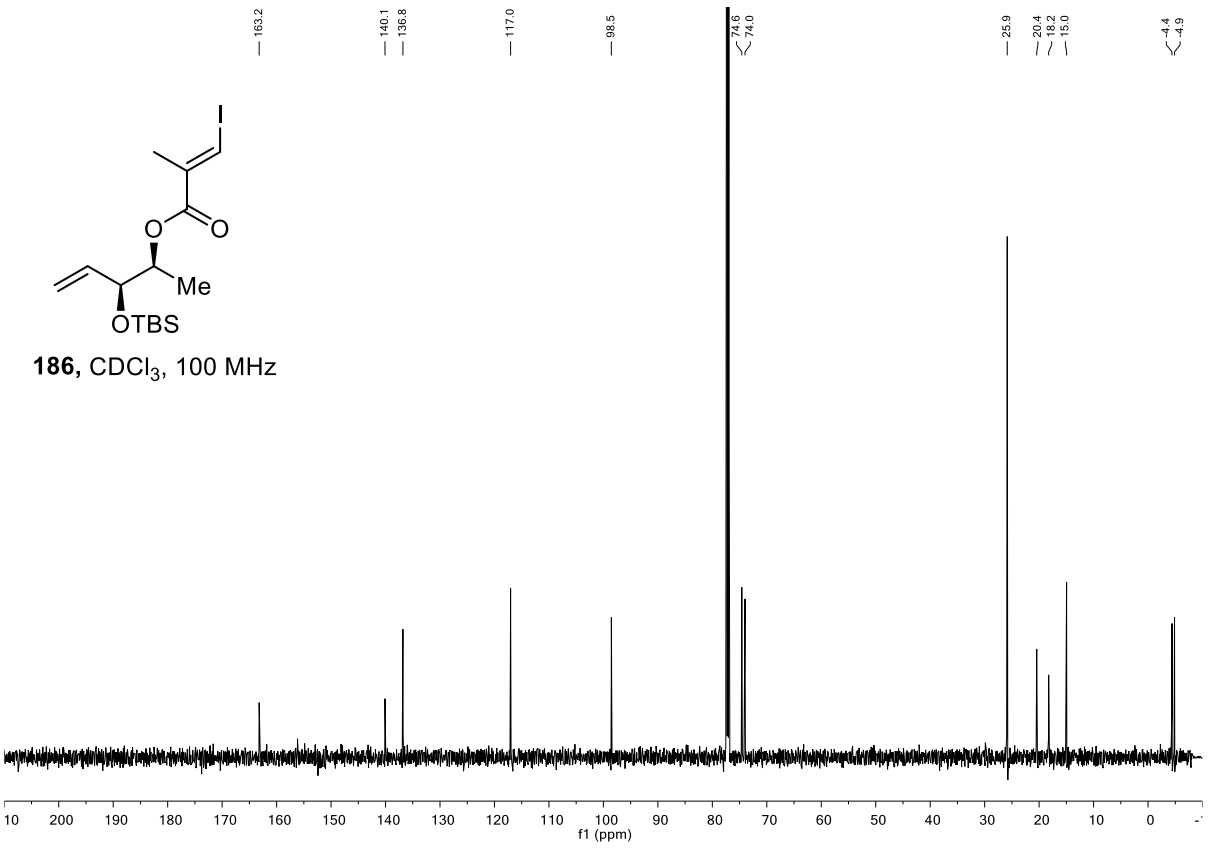
190, $CDCl_3$, 400 MHz



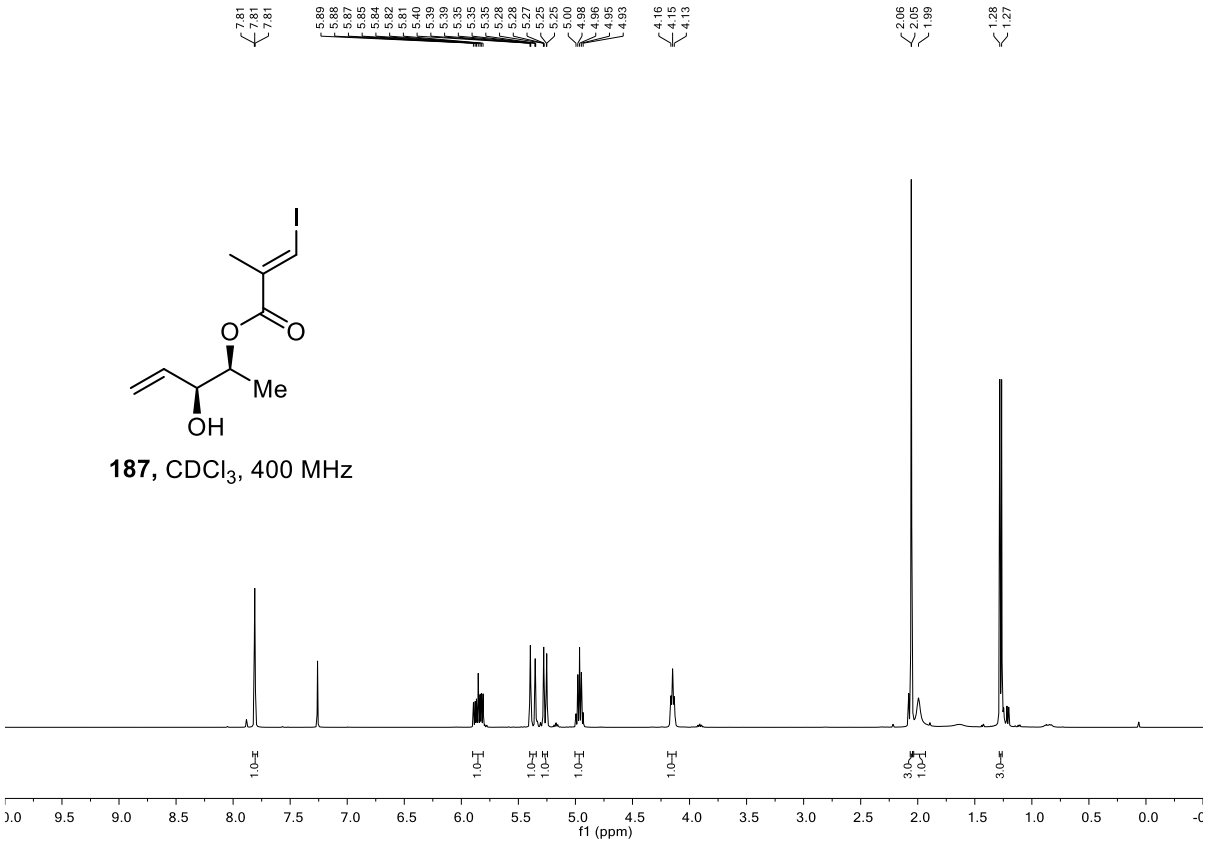
190, $CDCl_3$, 100 MHz



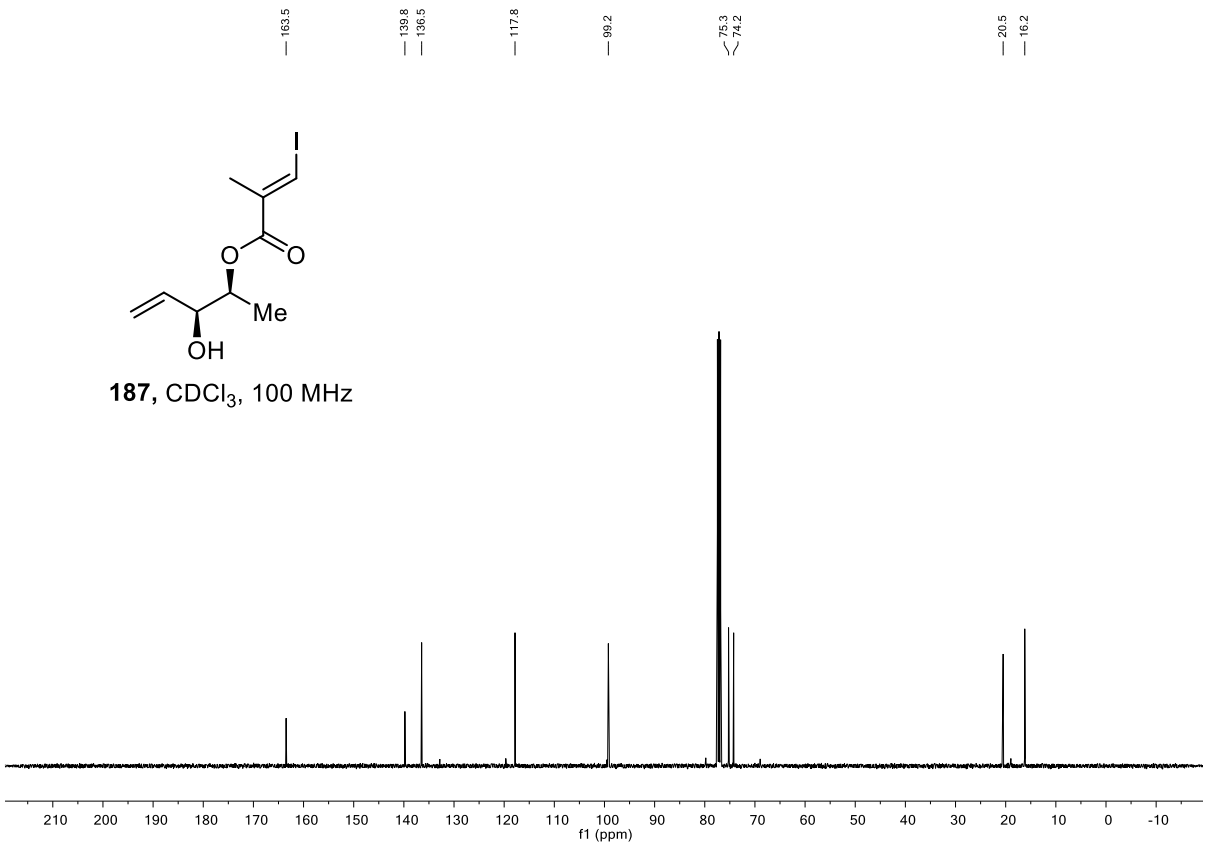
186, $CDCl_3$, 400 MHz



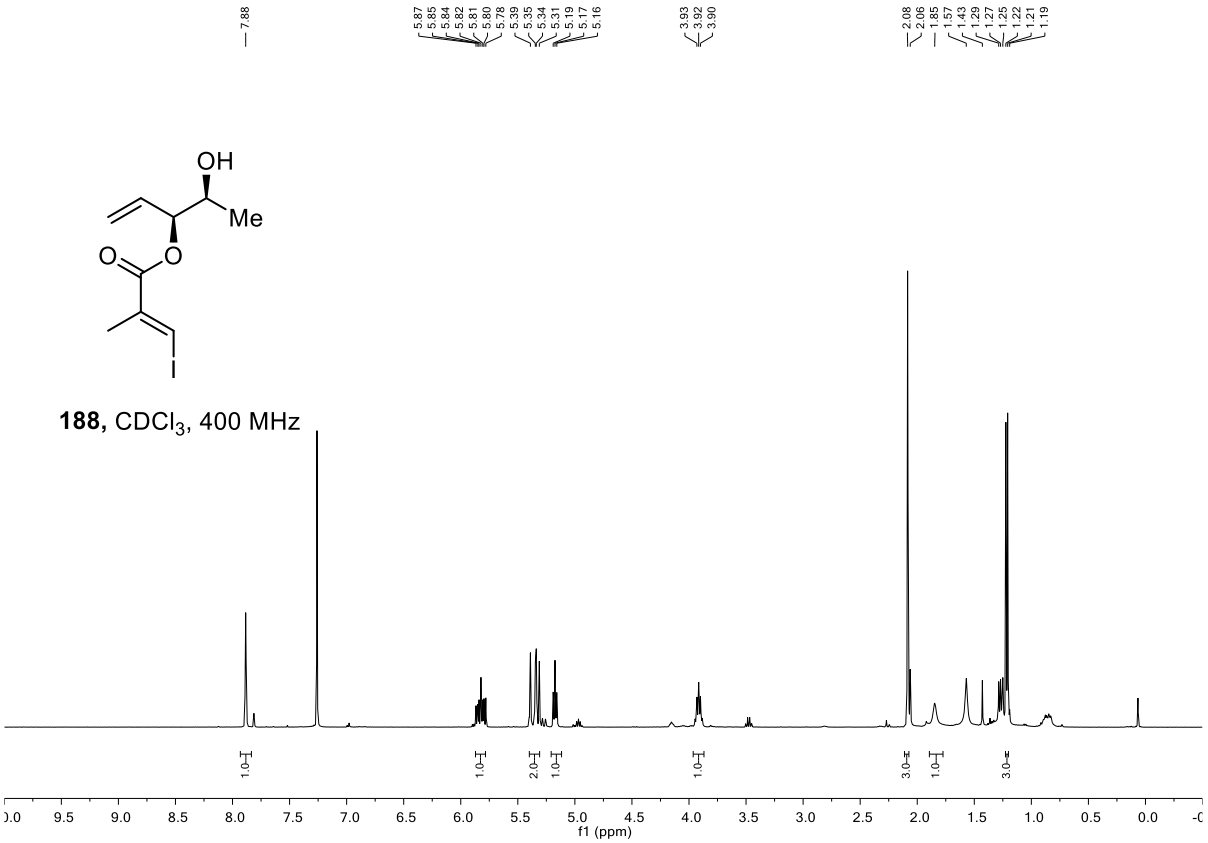
186, $CDCl_3$, 100 MHz



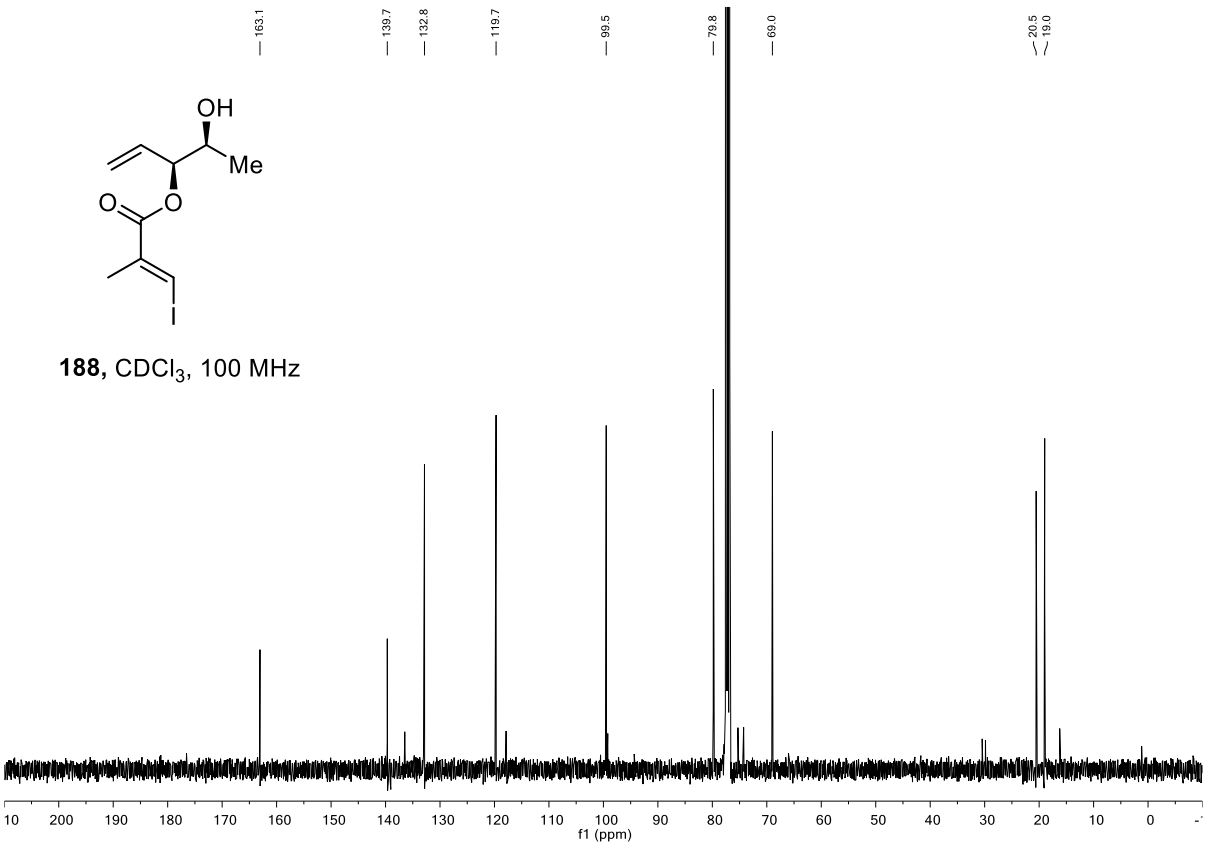
187, $CDCl_3$, 400 MHz



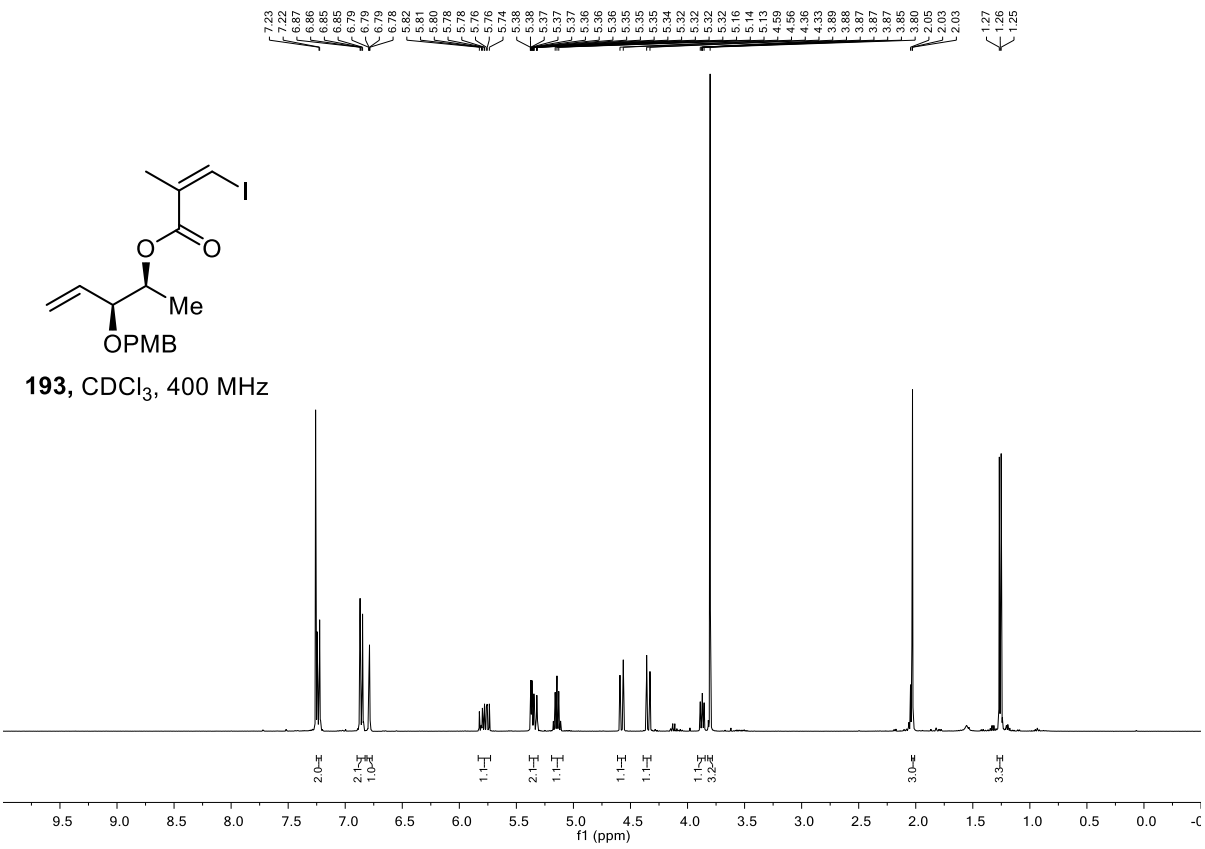
187, $CDCl_3$, 100 MHz



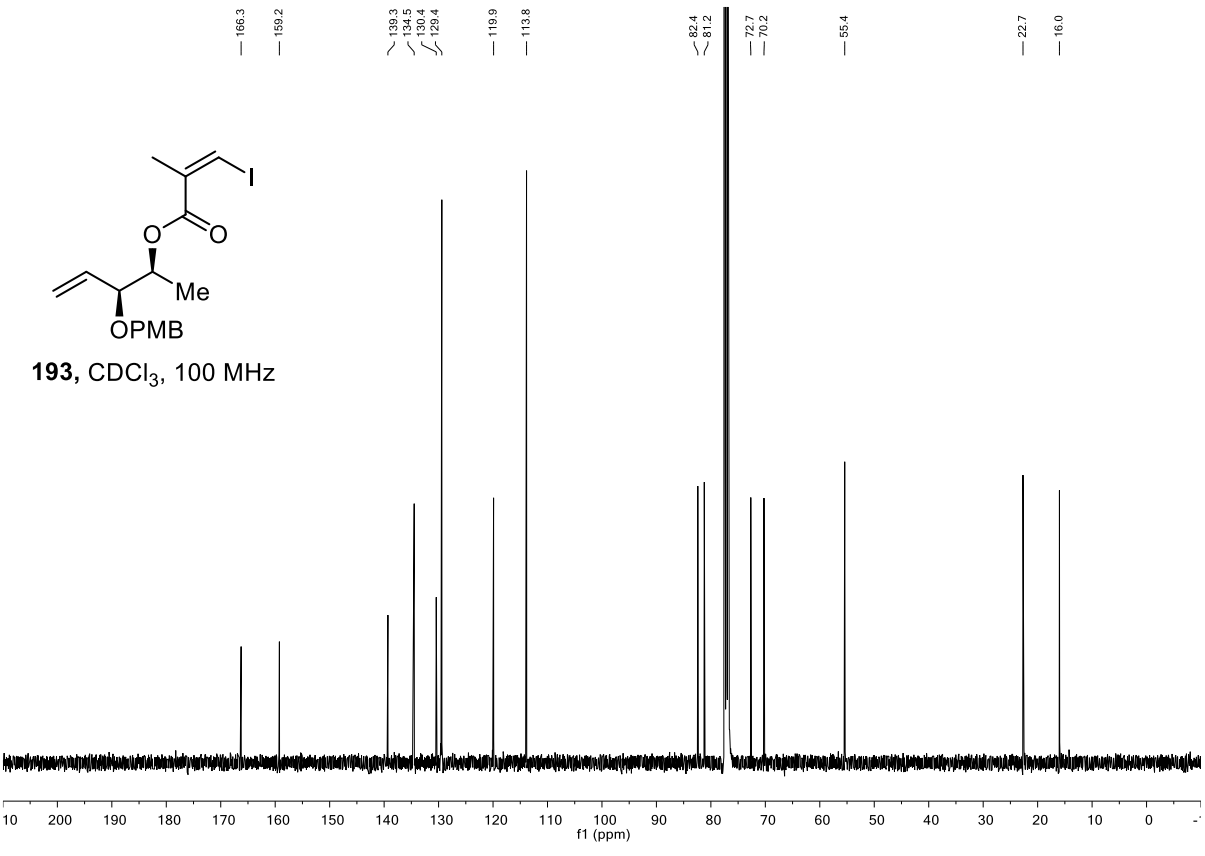
188, $CDCl_3$, 400 MHz



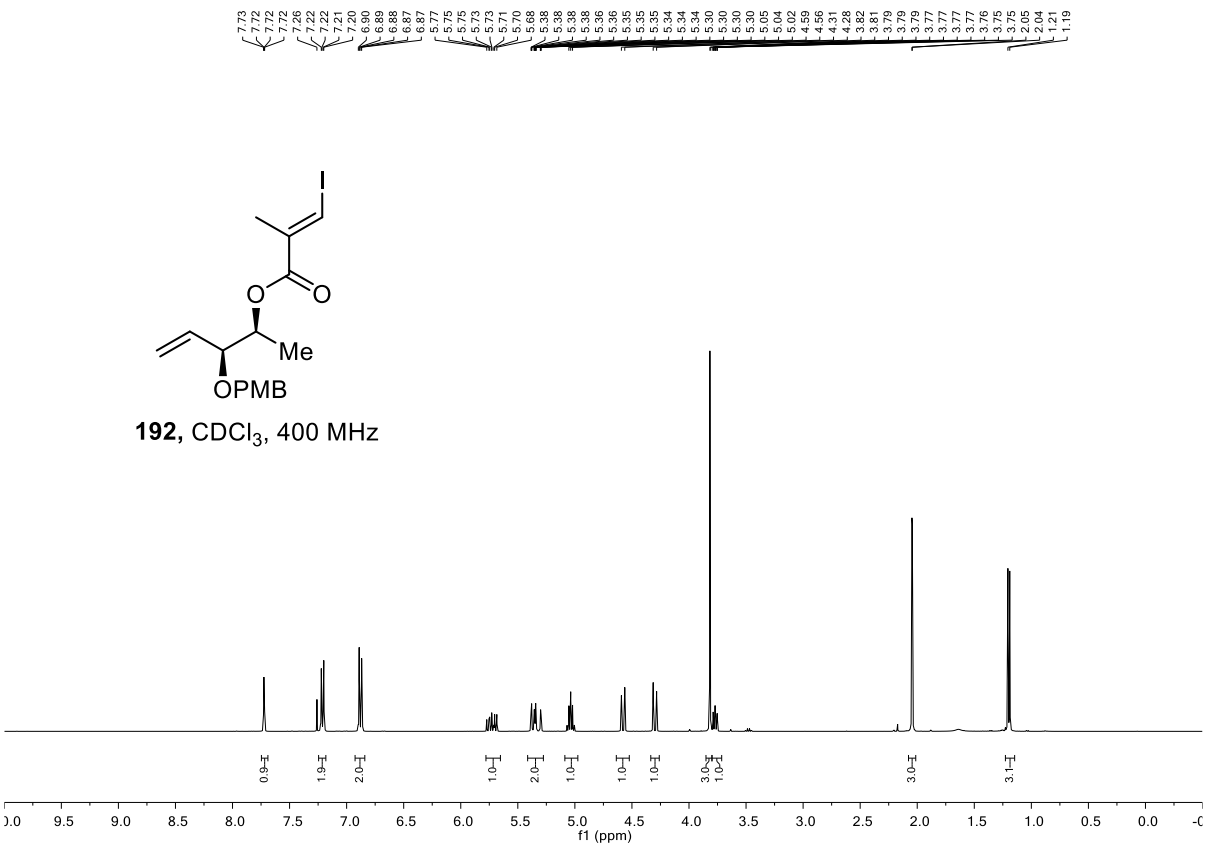
188, $CDCl_3$, 100 MHz

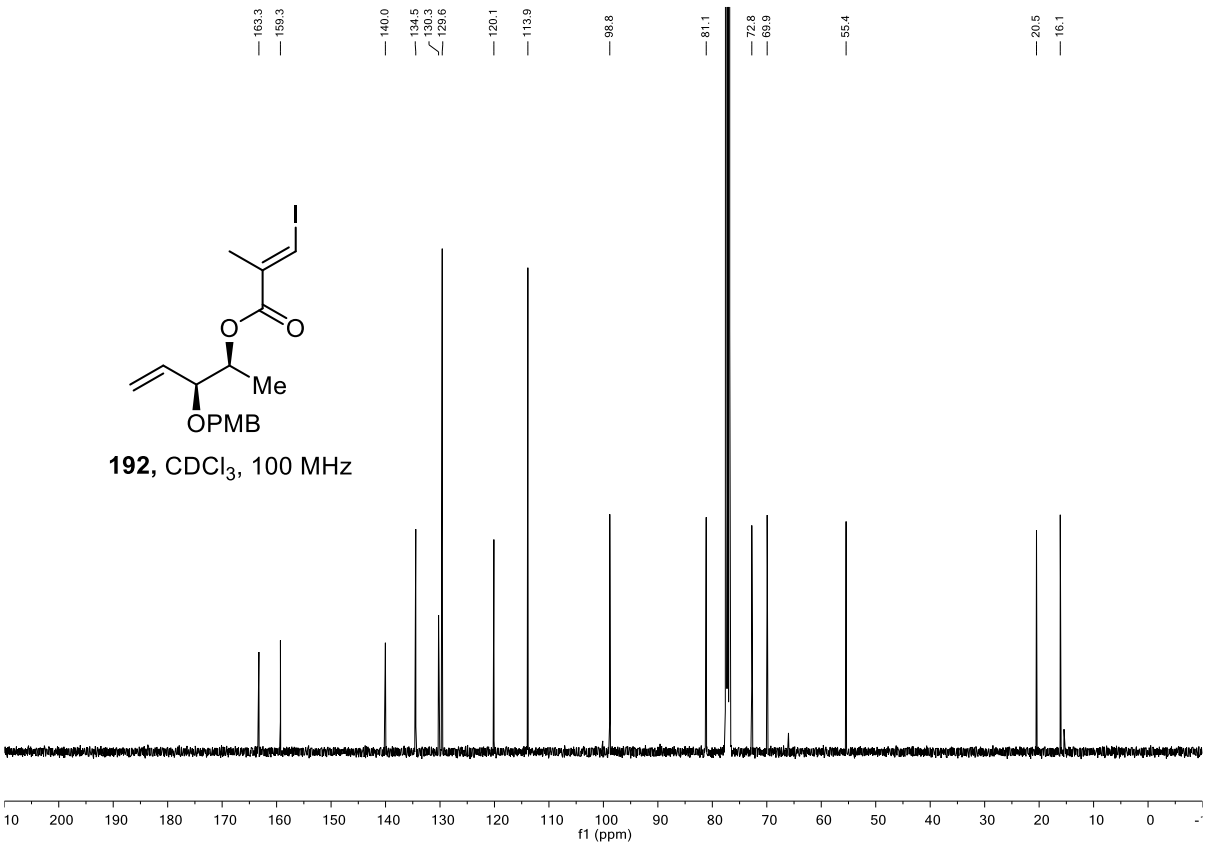


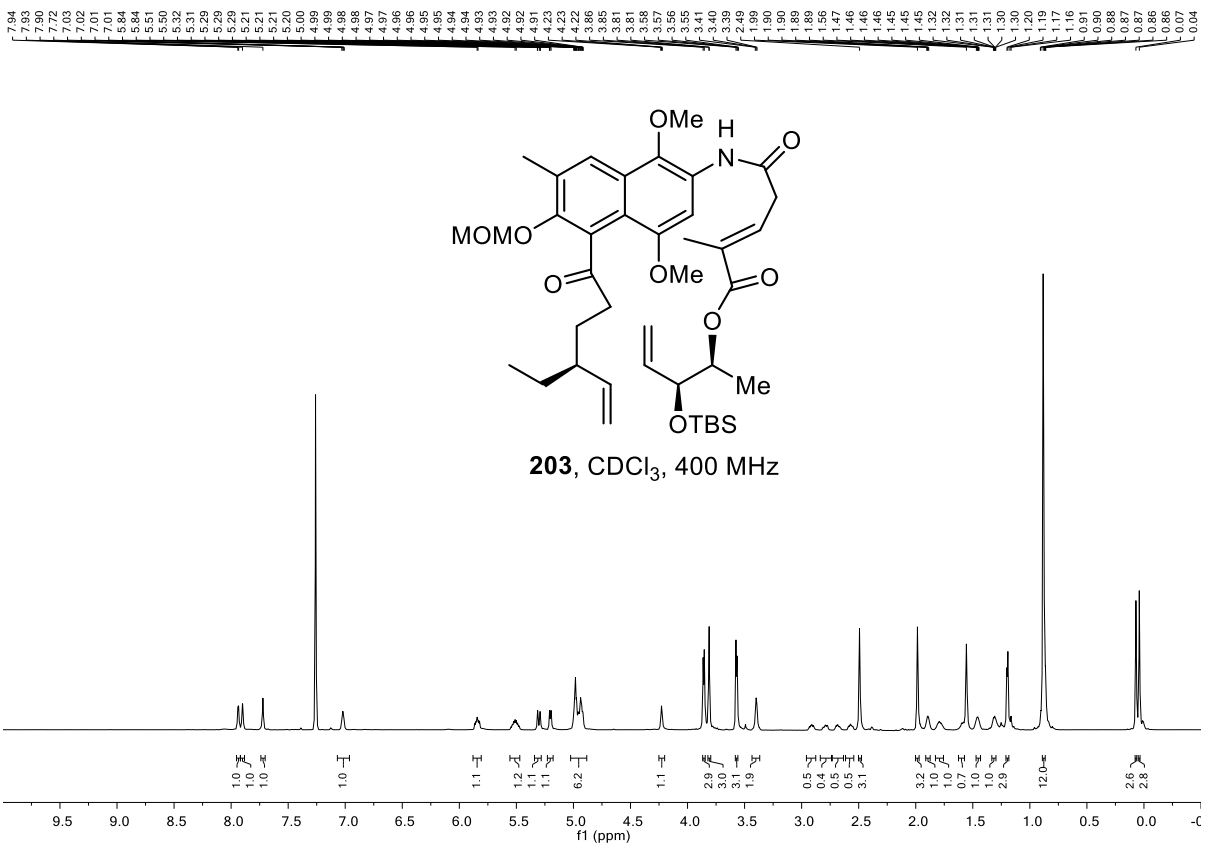
193, $CDCl_3$, 400 MHz



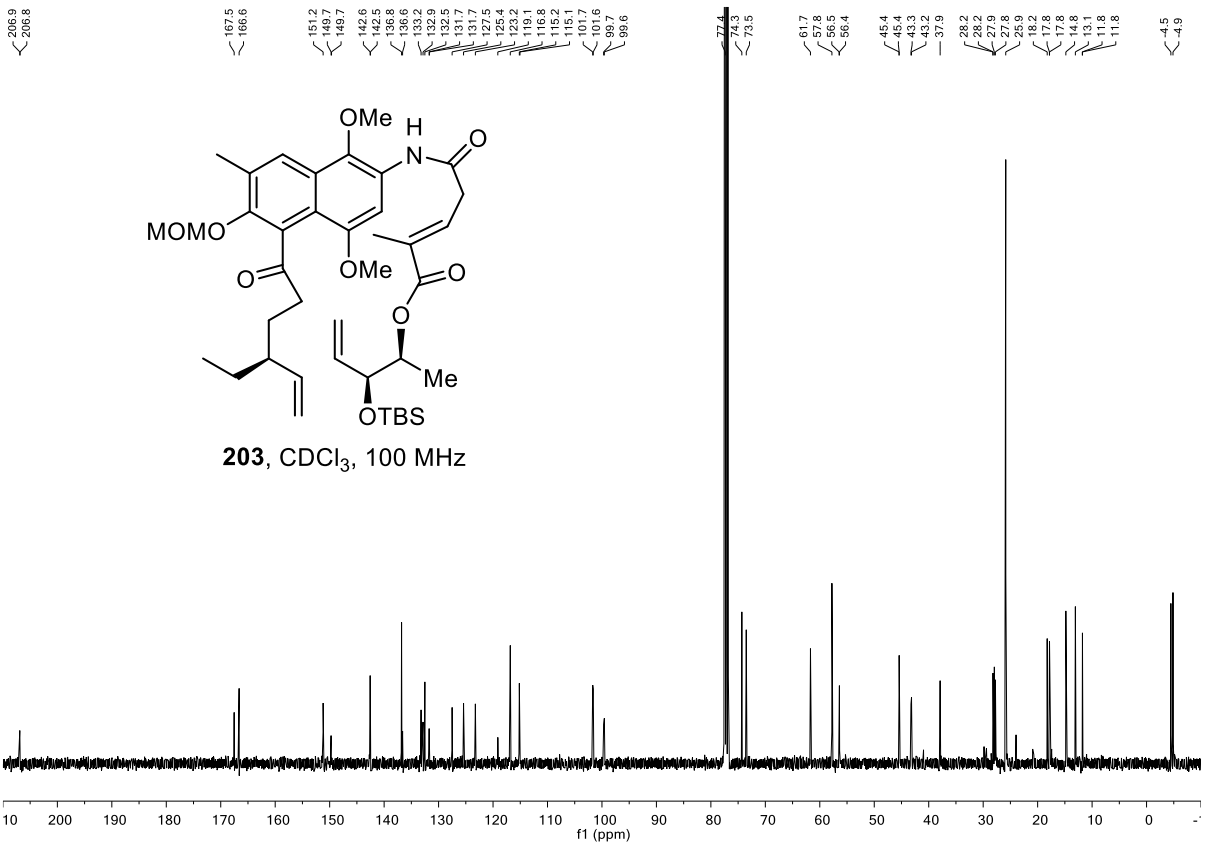
193, $CDCl_3$, 100 MHz


7.73 7.72 7.72 7.72 7.26 7.22 7.22 7.21 7.20 6.90 6.89 6.88 6.87 6.87 5.77 5.75 5.75 5.73 5.73 5.71 5.70 5.68 5.38 5.38 5.38 5.38 5.36 5.36 5.35 5.35 5.34 5.34 5.30 5.30 5.30 5.30 5.05 5.04 5.02 4.59 4.56 4.31 4.28 3.82 3.81 3.79 3.79 3.79 3.77 3.77 3.77 3.77 3.76 3.75 3.75 2.05 2.04 1.21 1.19
I
O
O
Me
OPMB
192, CDCl3, 400 MHz
0.9 1.9 2.0 1.0 2.0 1.0 1.0 1.0 3.0 1.0 3.0 3.1
f1 (ppm)

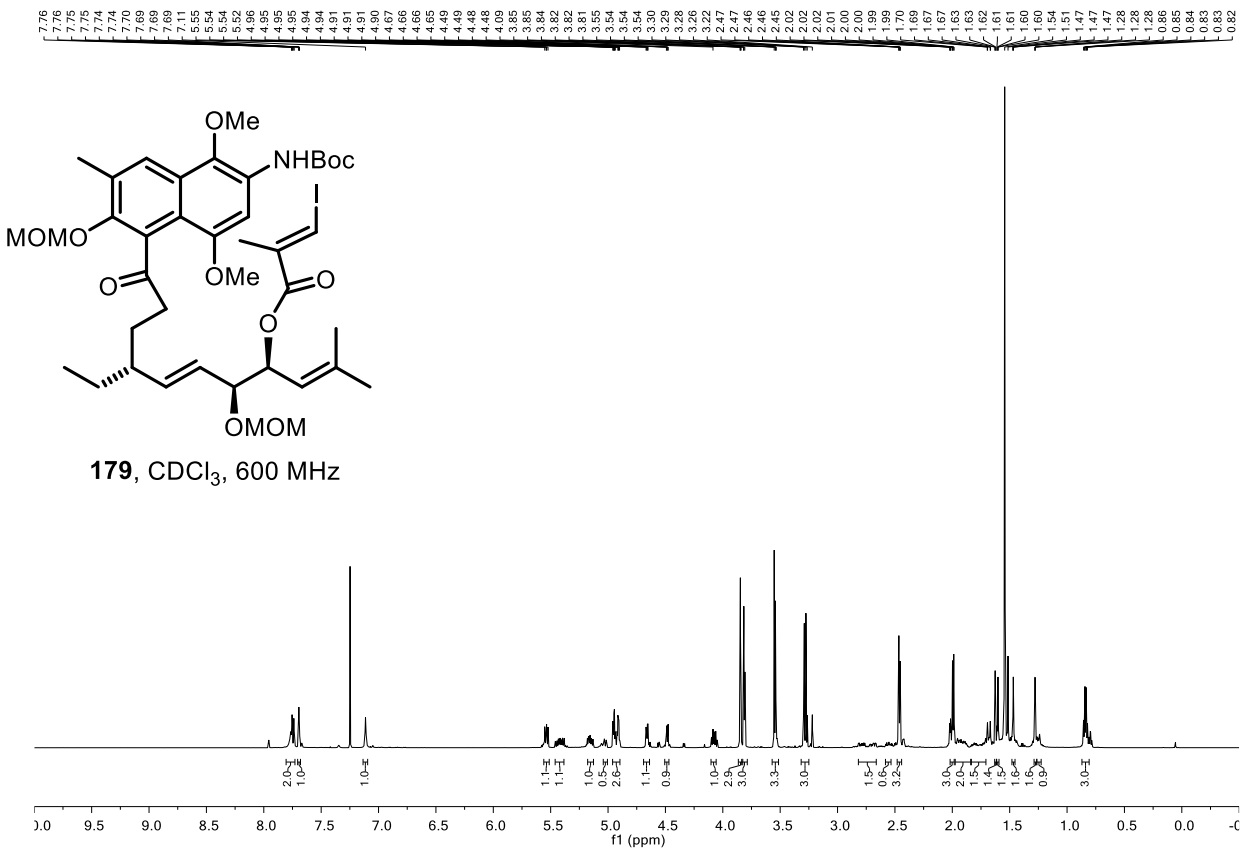

163.3 159.3 140.0 134.5 130.3 129.6 120.1 113.9 98.8 81.1 72.8 69.9 55.4 20.5 16.1
I
O
O
Me
OPMB
192, CDCl3, 100 MHz
f1 (ppm)



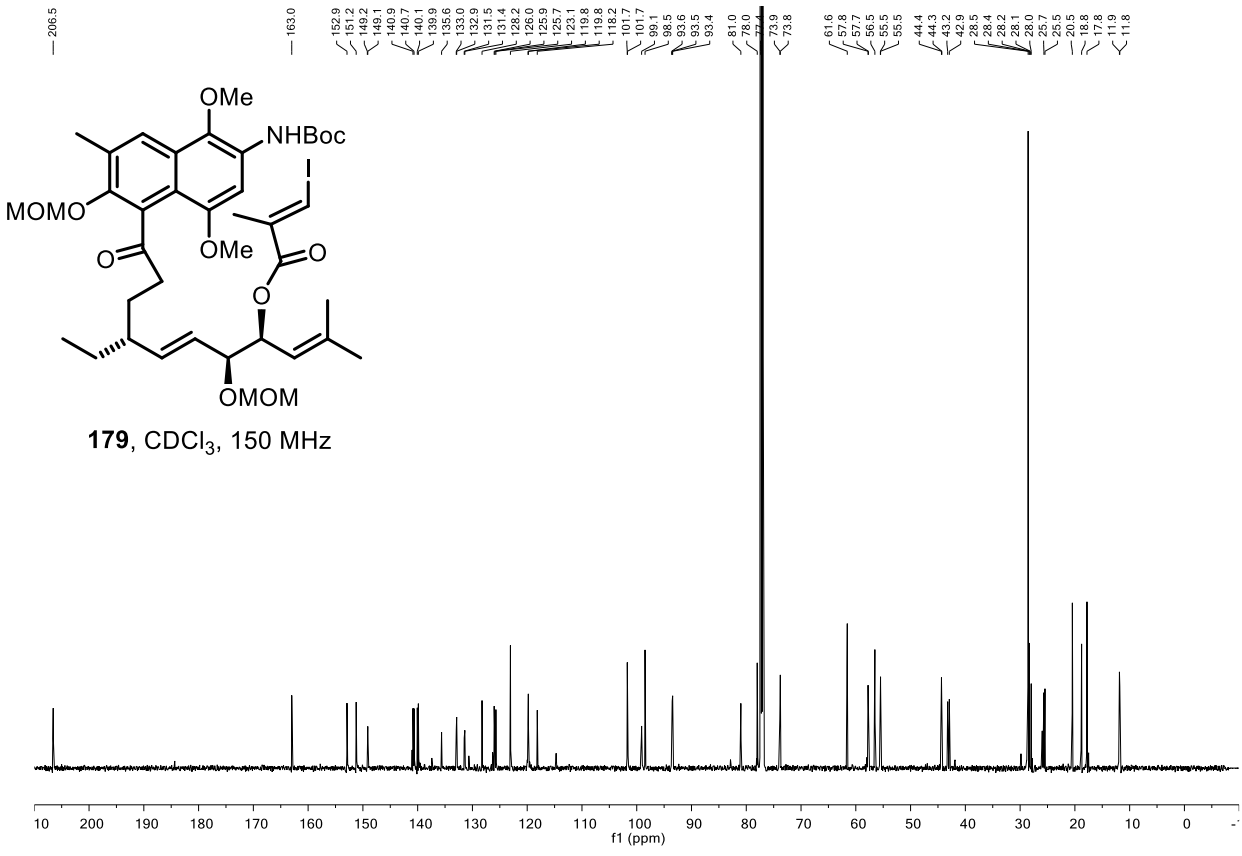
203, $CDCl_3$, 400 MHz



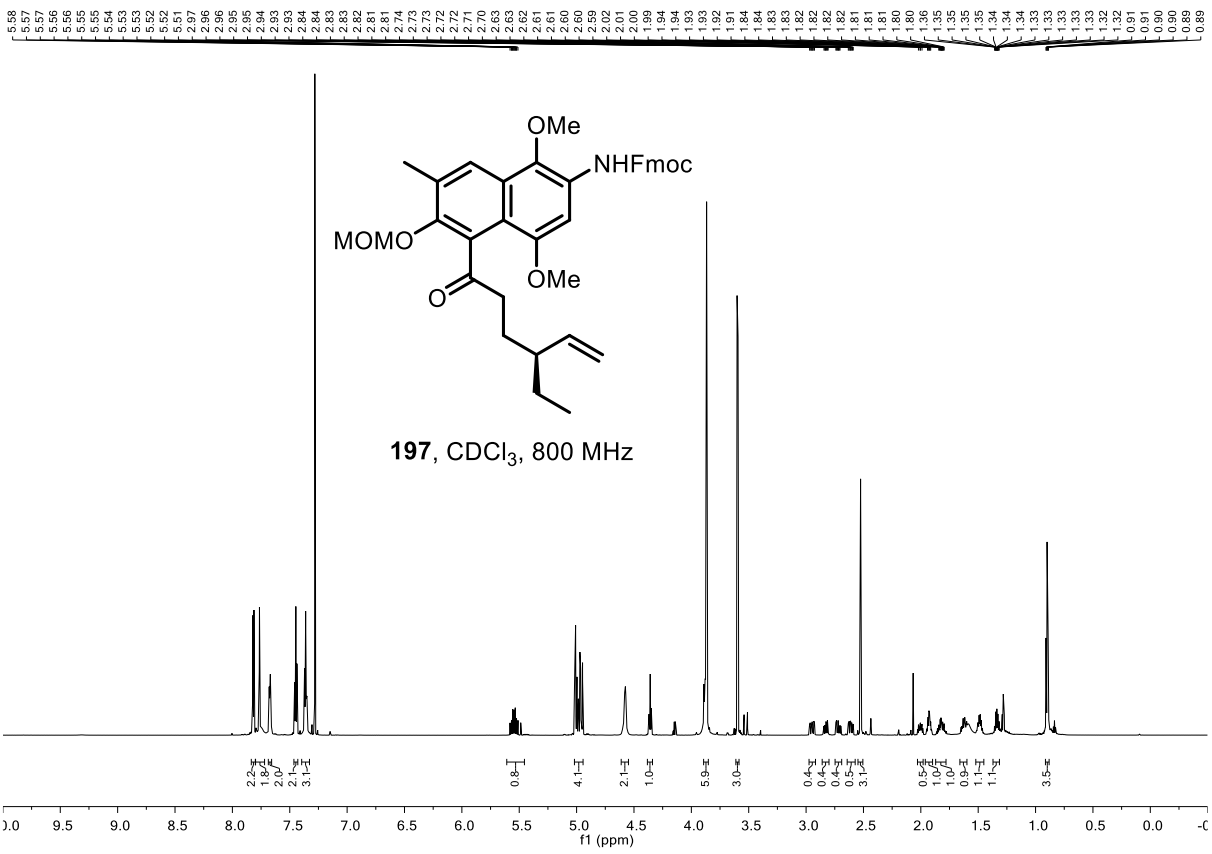
203, $CDCl_3$, 100 MHz



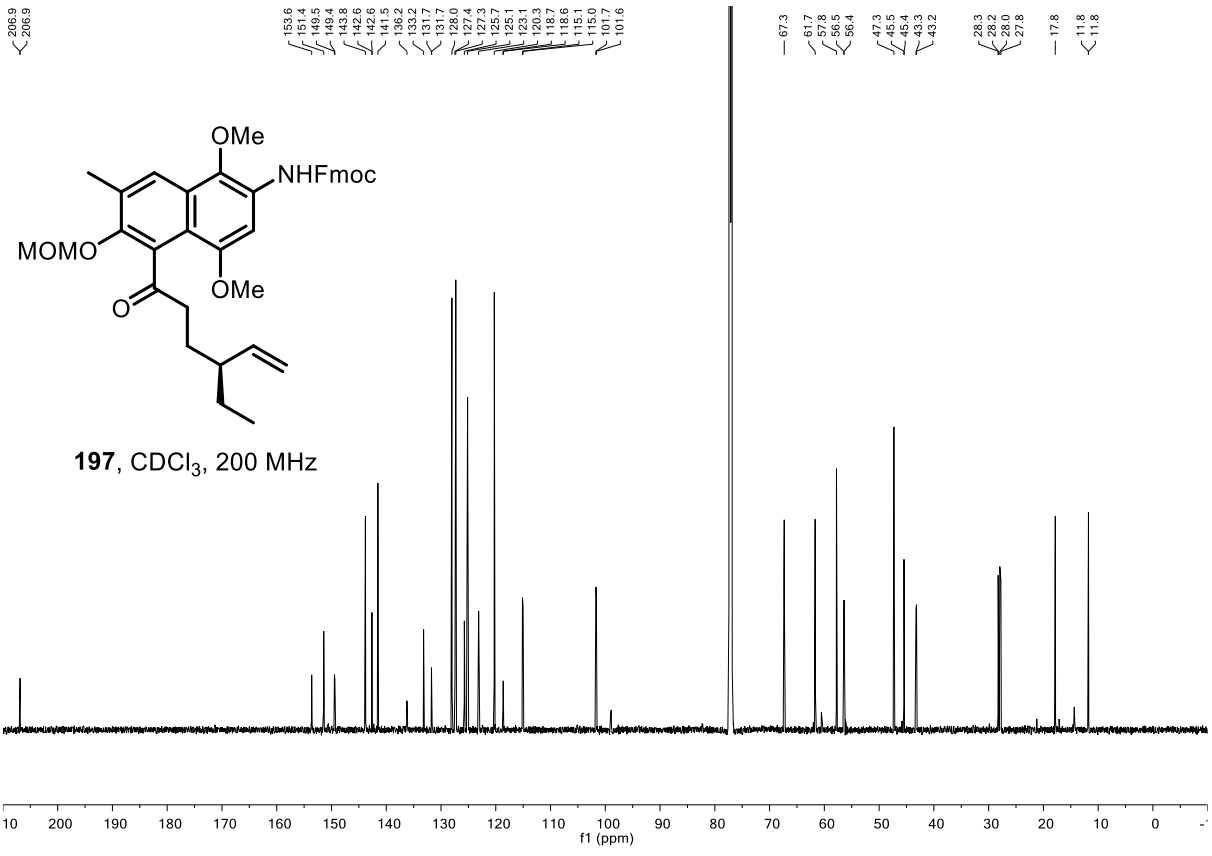
179, $CDCl_3$, 600 MHz



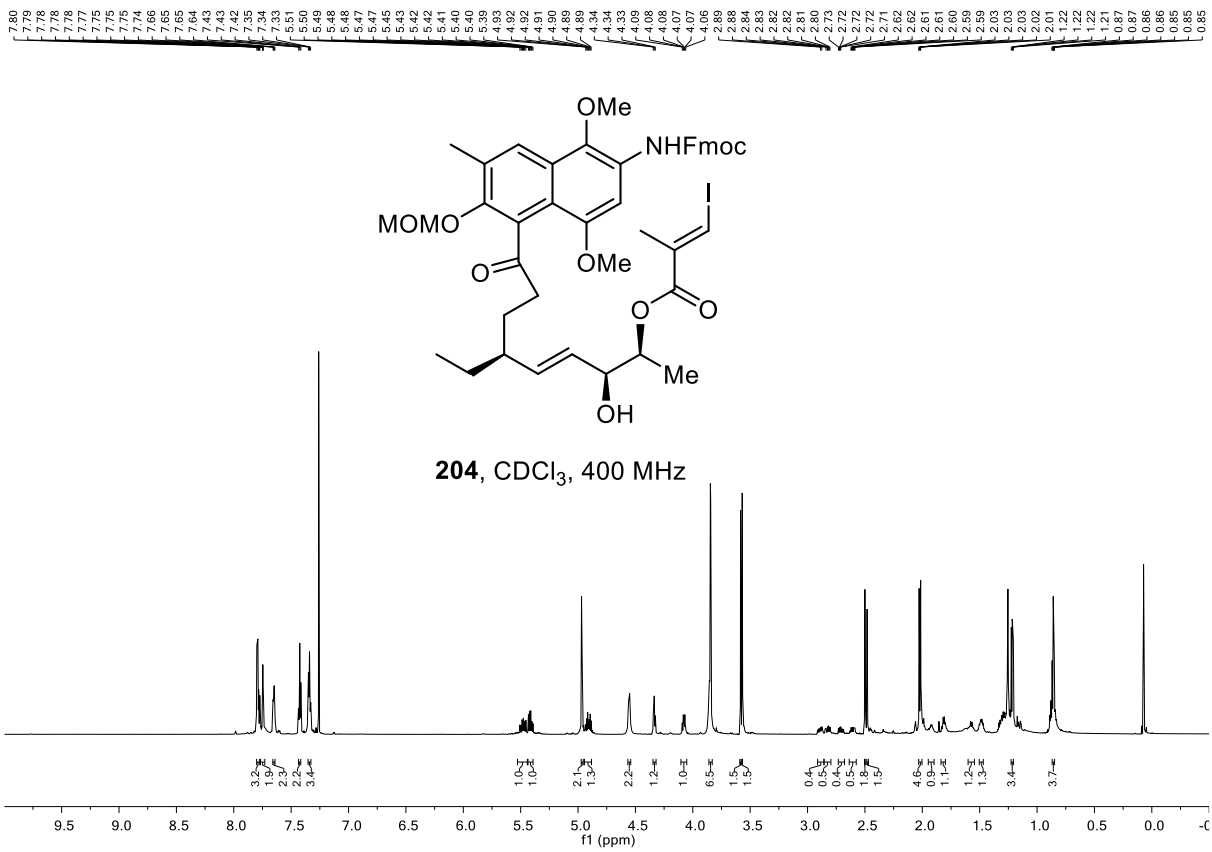
179, $CDCl_3$, 150 MHz



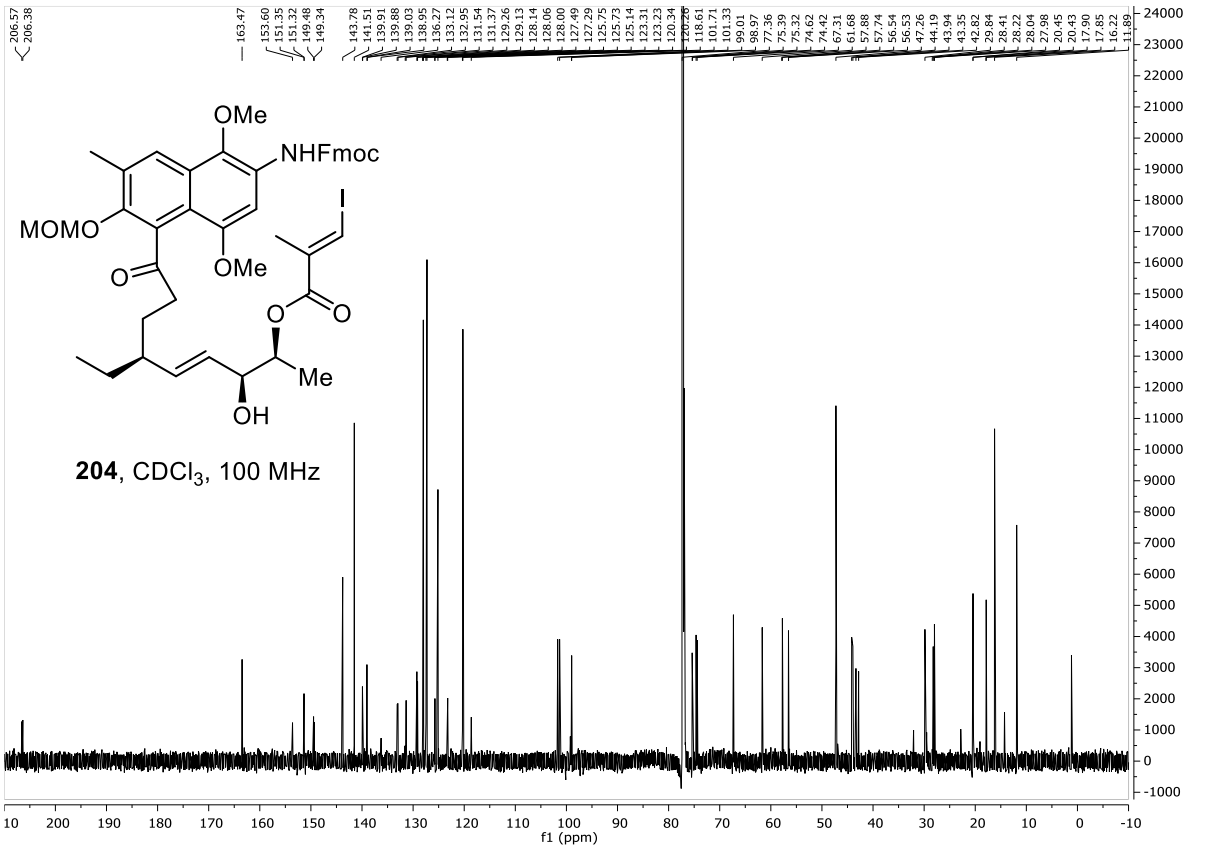
197, $CDCl_3$, 800 MHz



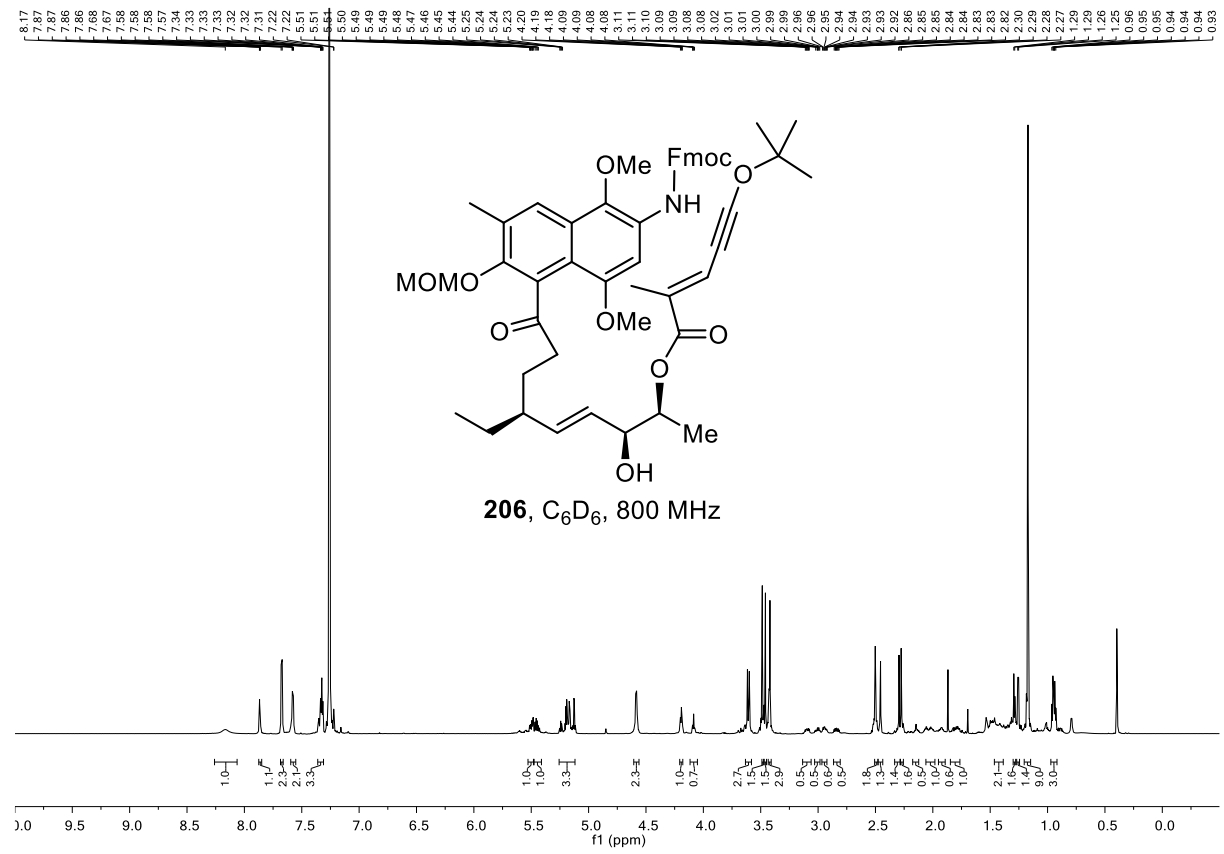
197, $CDCl_3$, 200 MHz



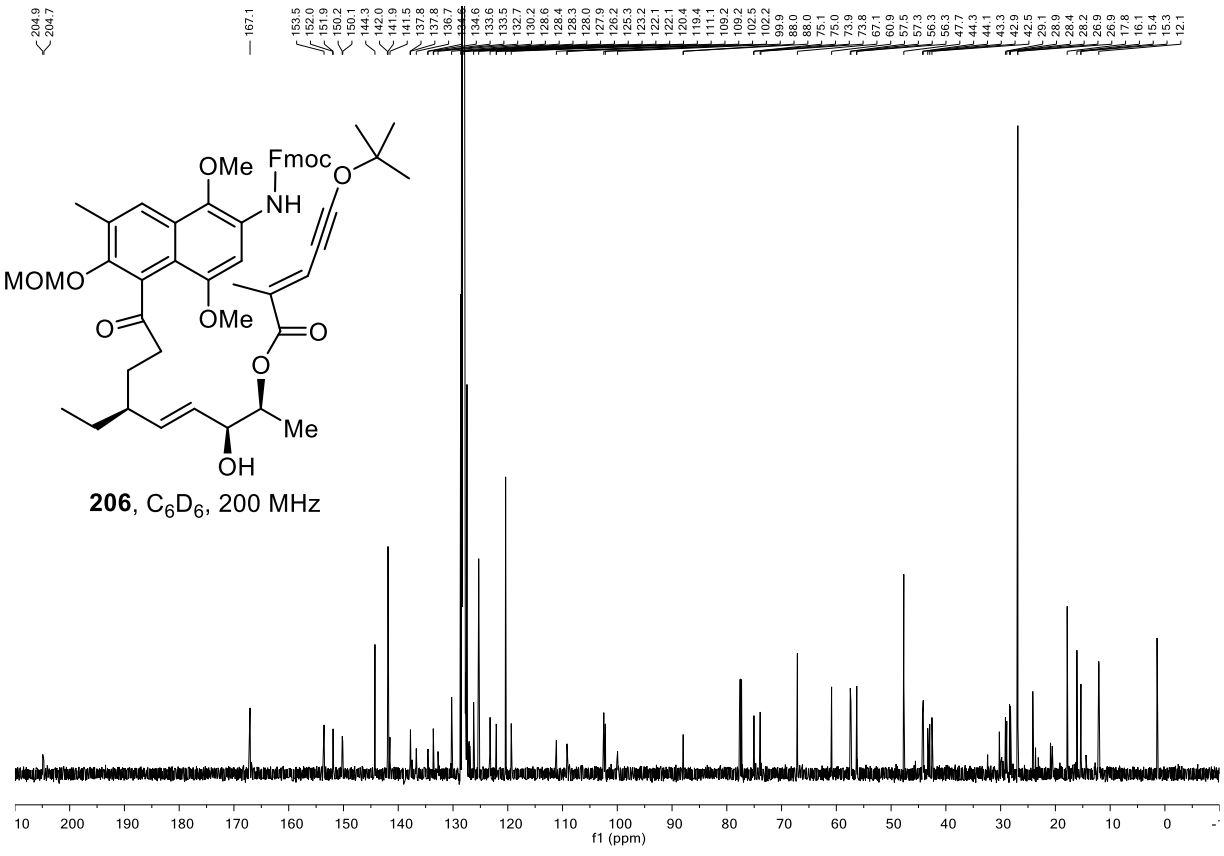
204, $CDCl_3$, 400 MHz



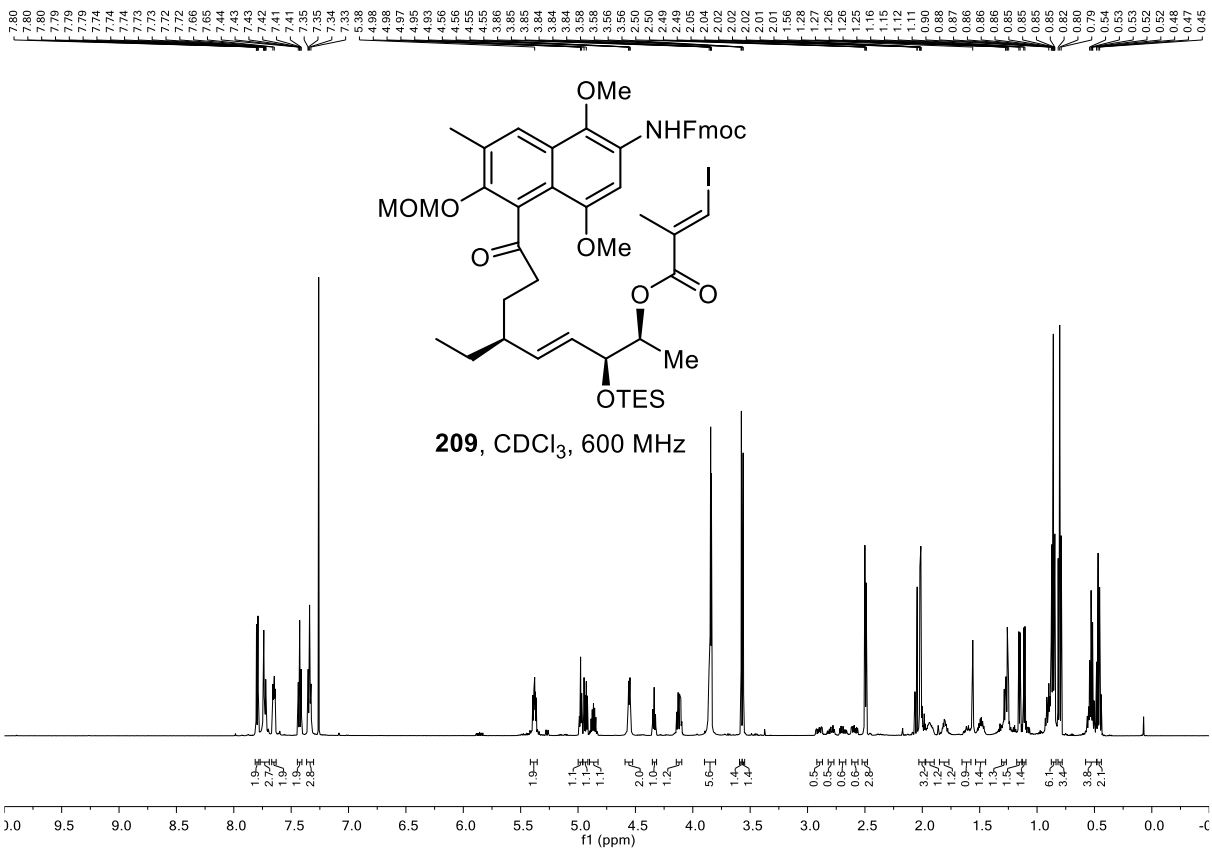
204, $CDCl_3$, 100 MHz

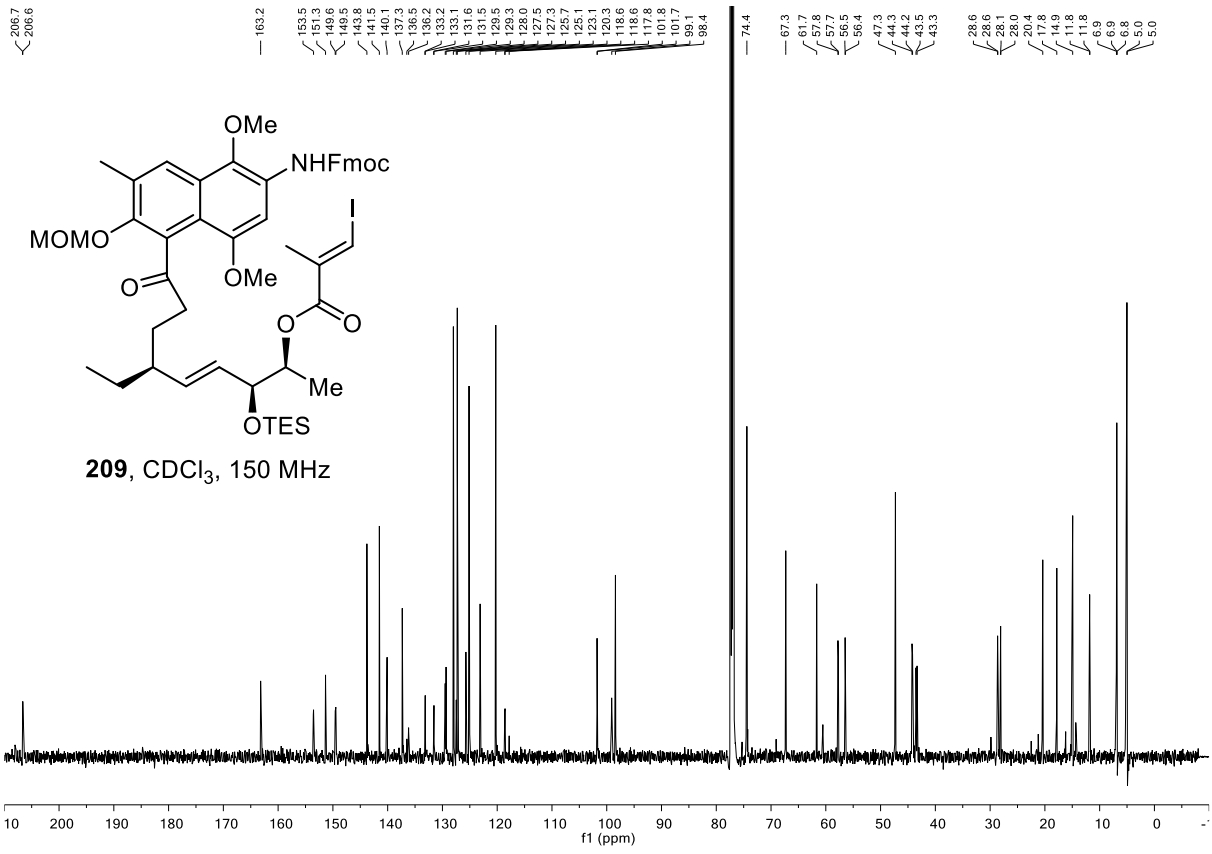


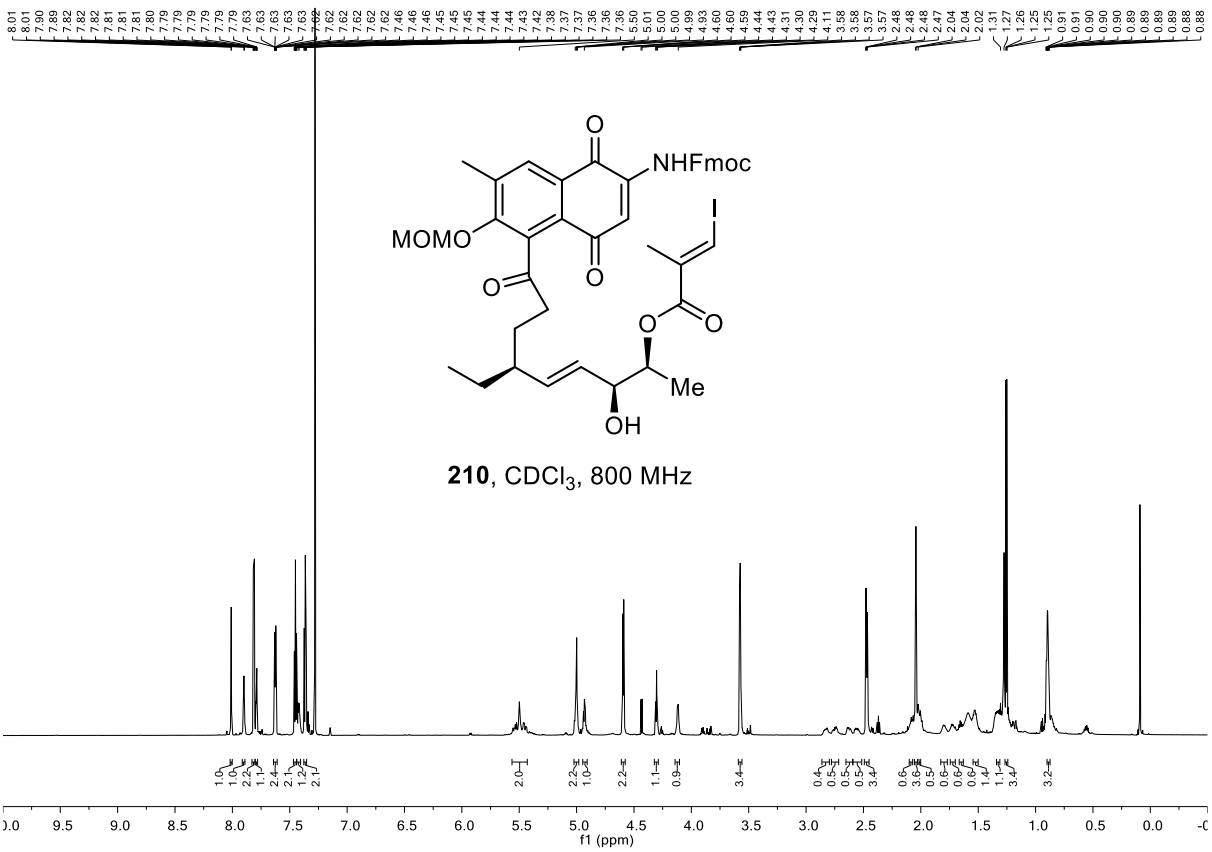
206, C_6D_6, 800 MHz



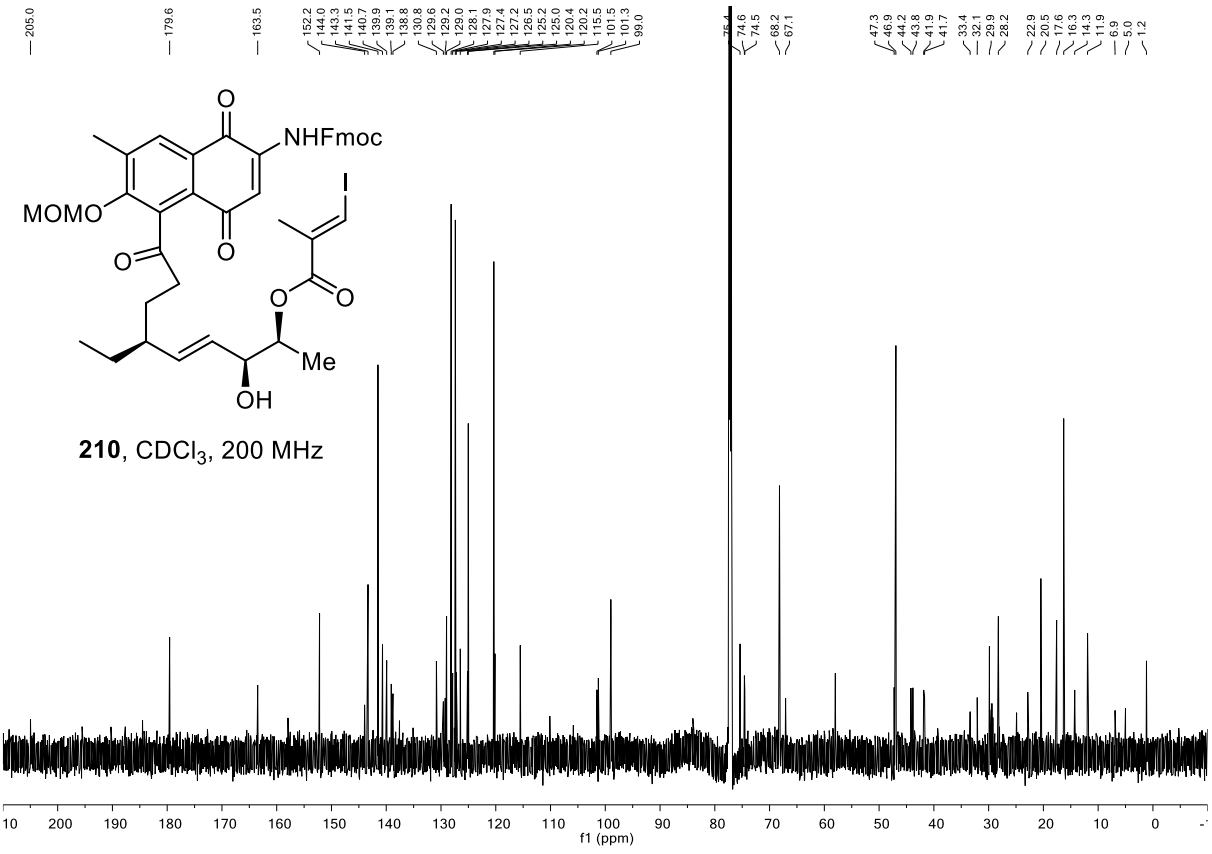
206, C_6D_6, 200 MHz


OMe
NHFmoc
MOMO
OMe
O
O
O
I
Me
OTES
209, CDCl3, 600 MHz
f1 (ppm)

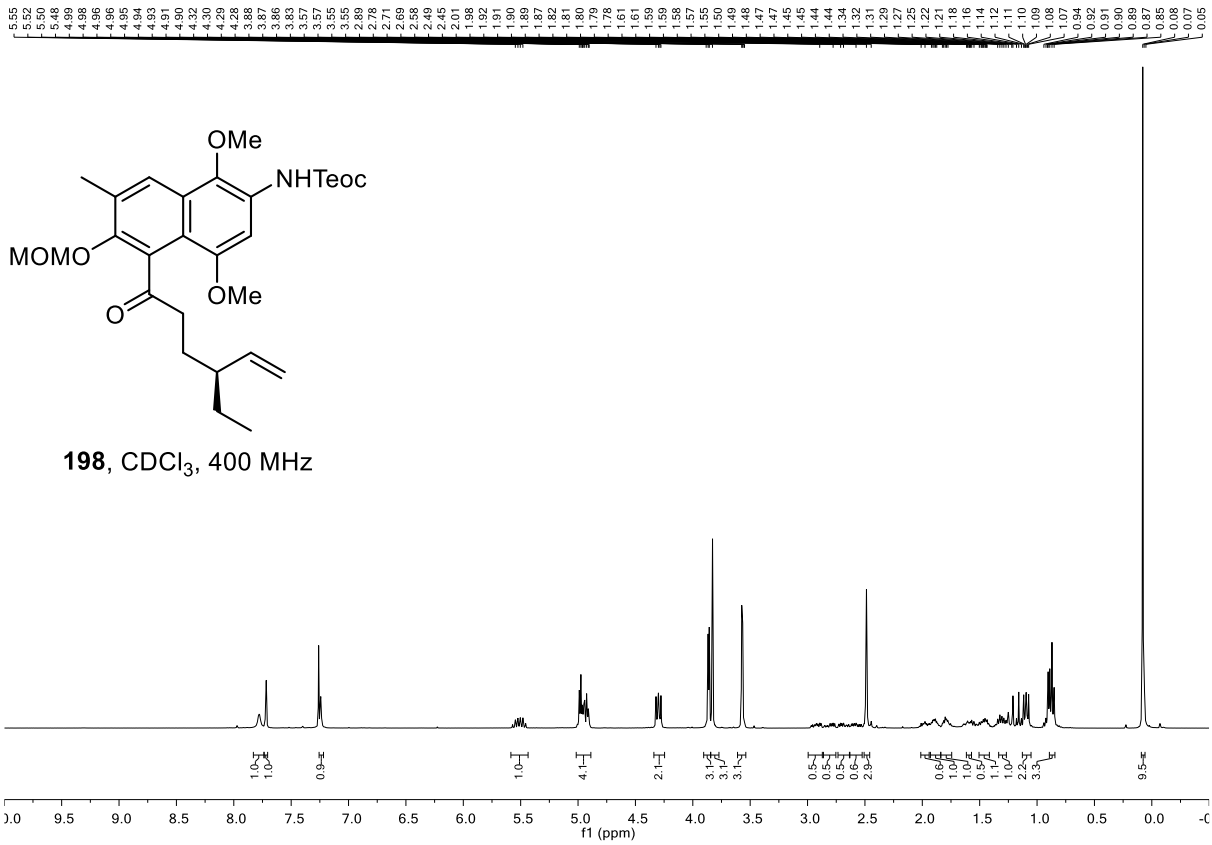

OMe
NHFmoc
MOMO
OMe
O
O
O
I
Me
OTES
209, CDCl3, 150 MHz
f1 (ppm)



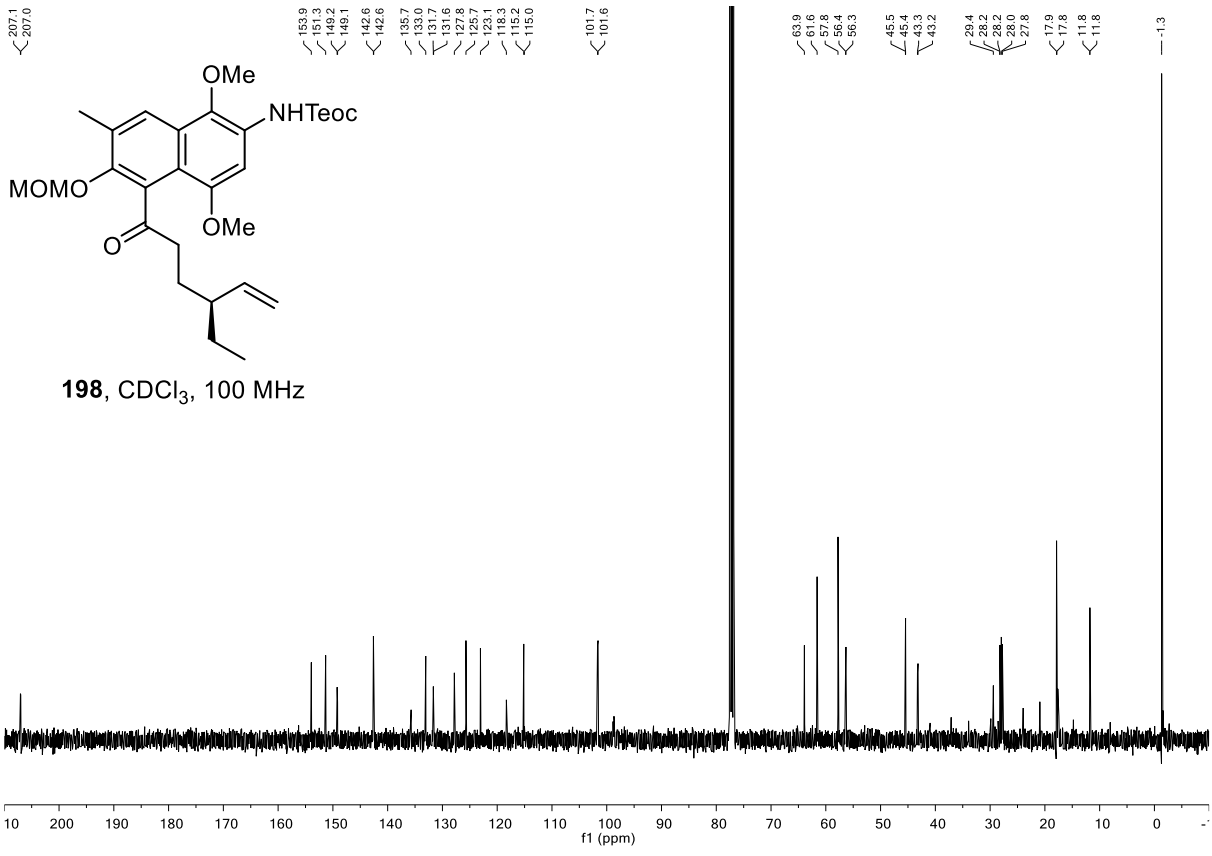
210, $CDCl_3$, 800 MHz



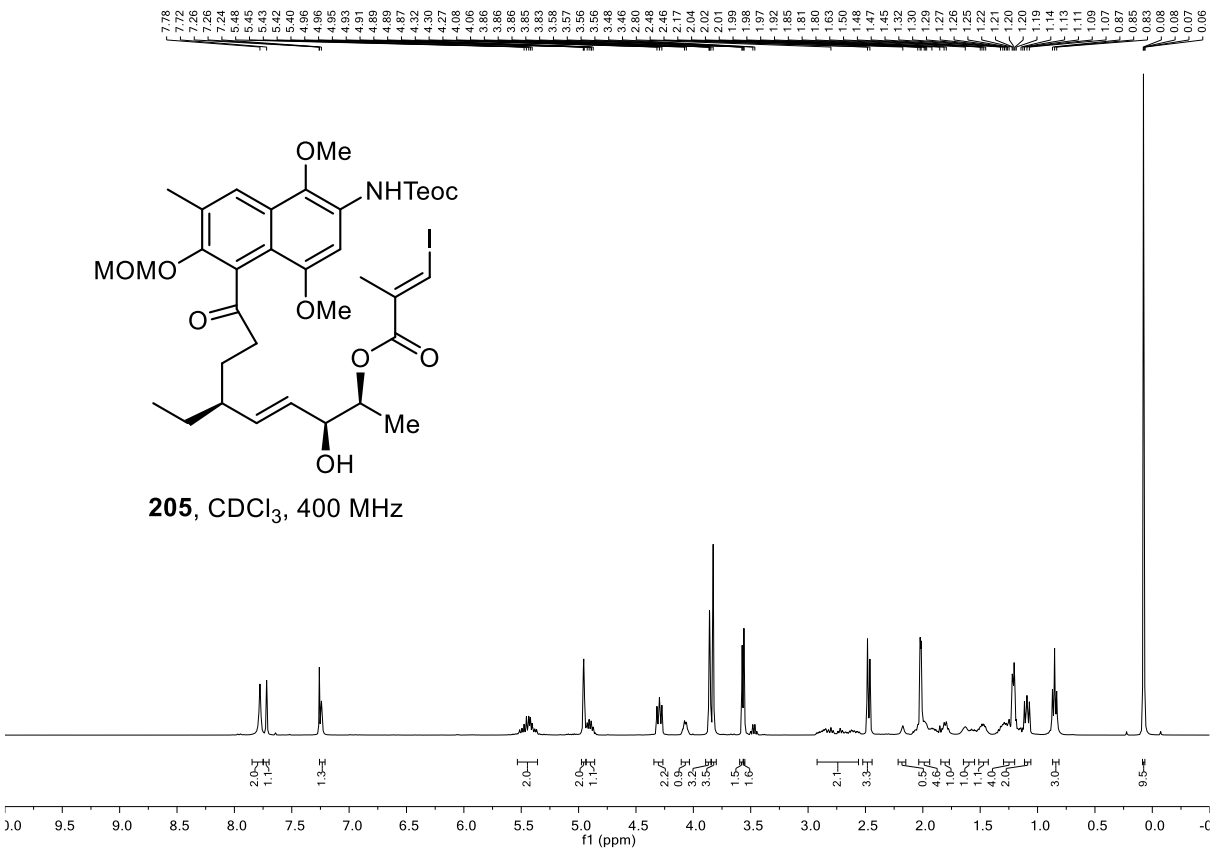
210, $CDCl_3$, 200 MHz



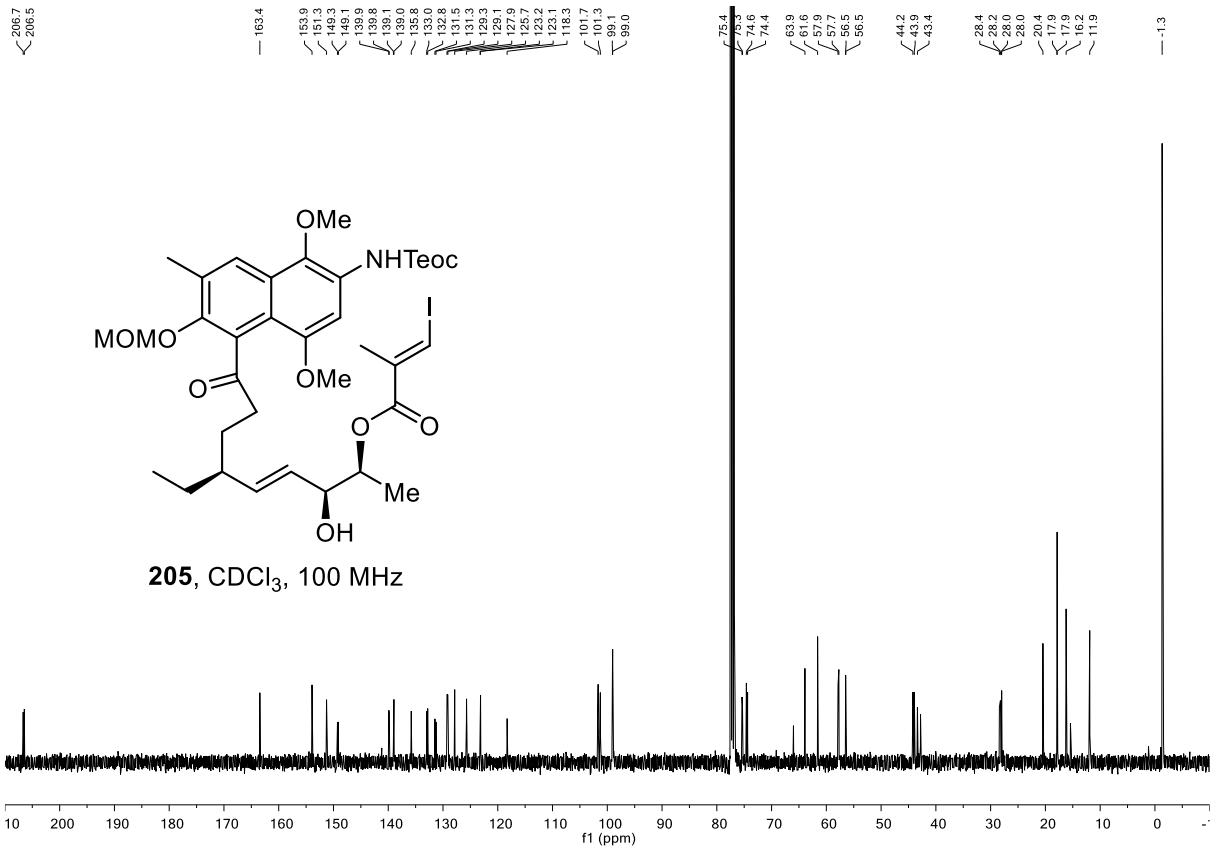
198, $CDCl_3$, 400 MHz



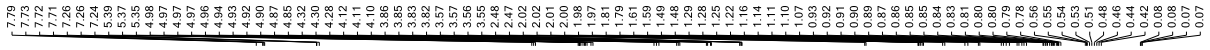
198, $CDCl_3$, 100 MHz

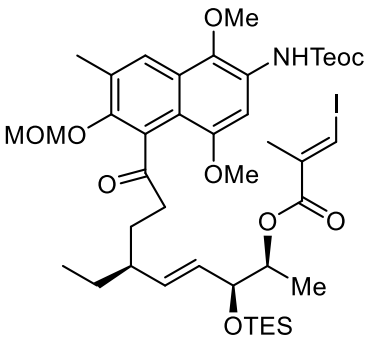


205, $CDCl_3$, 400 MHz

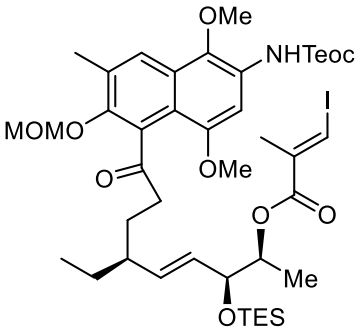


205, $CDCl_3$, 100 MHz

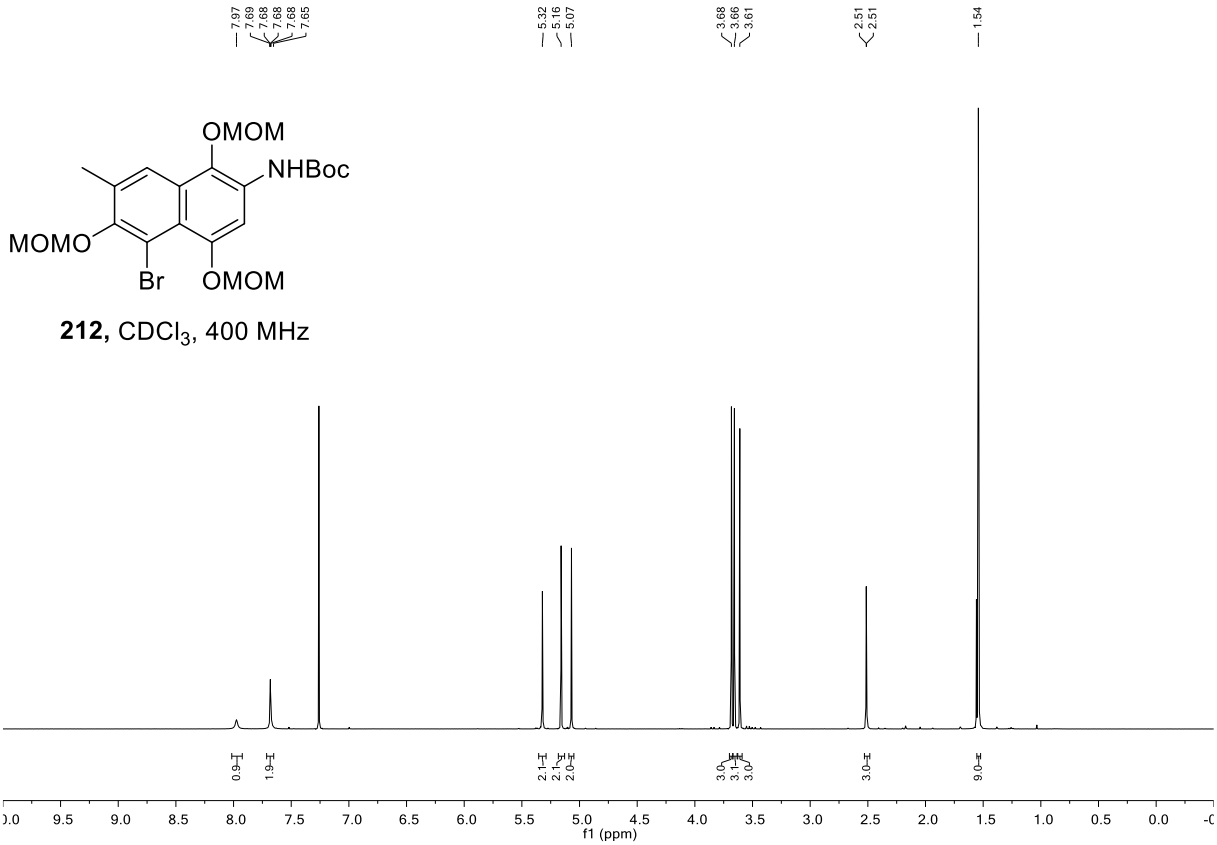




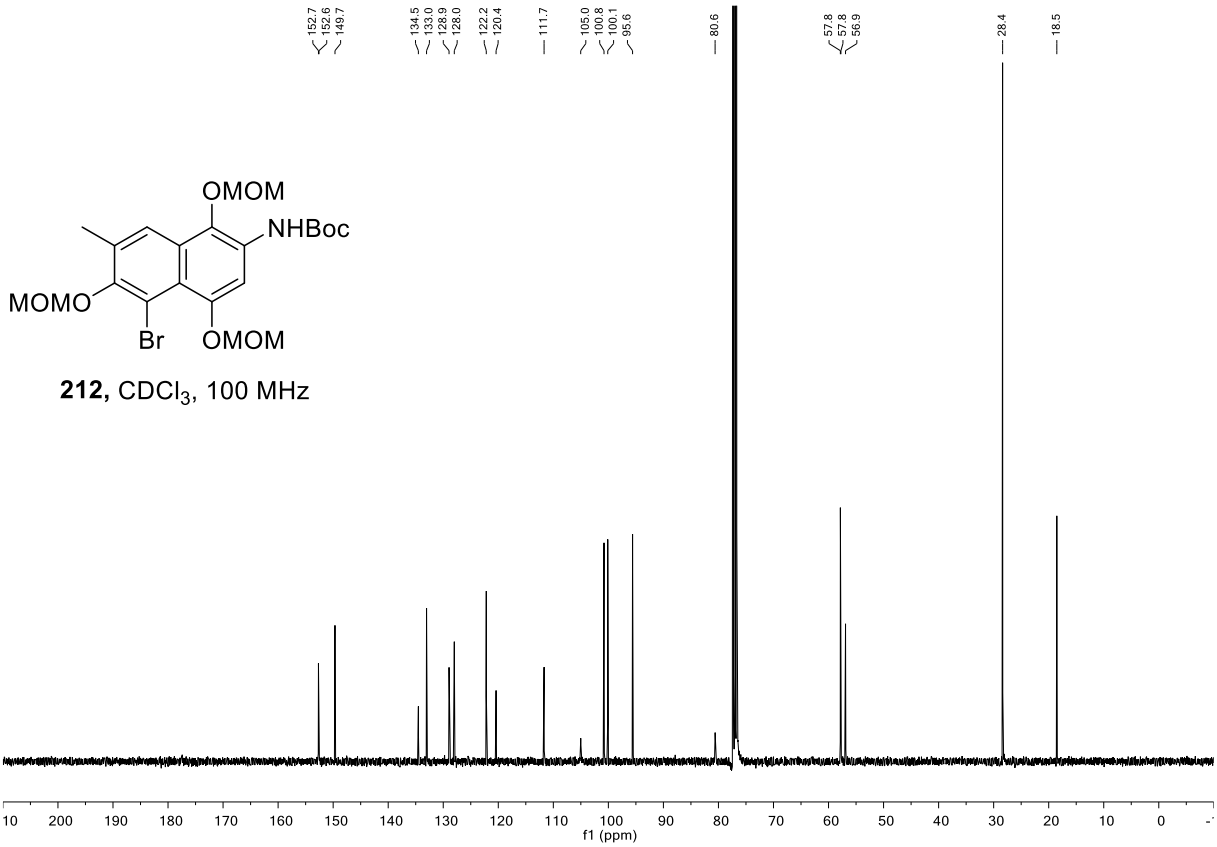
205, $CDCl_3$, 400 MHz



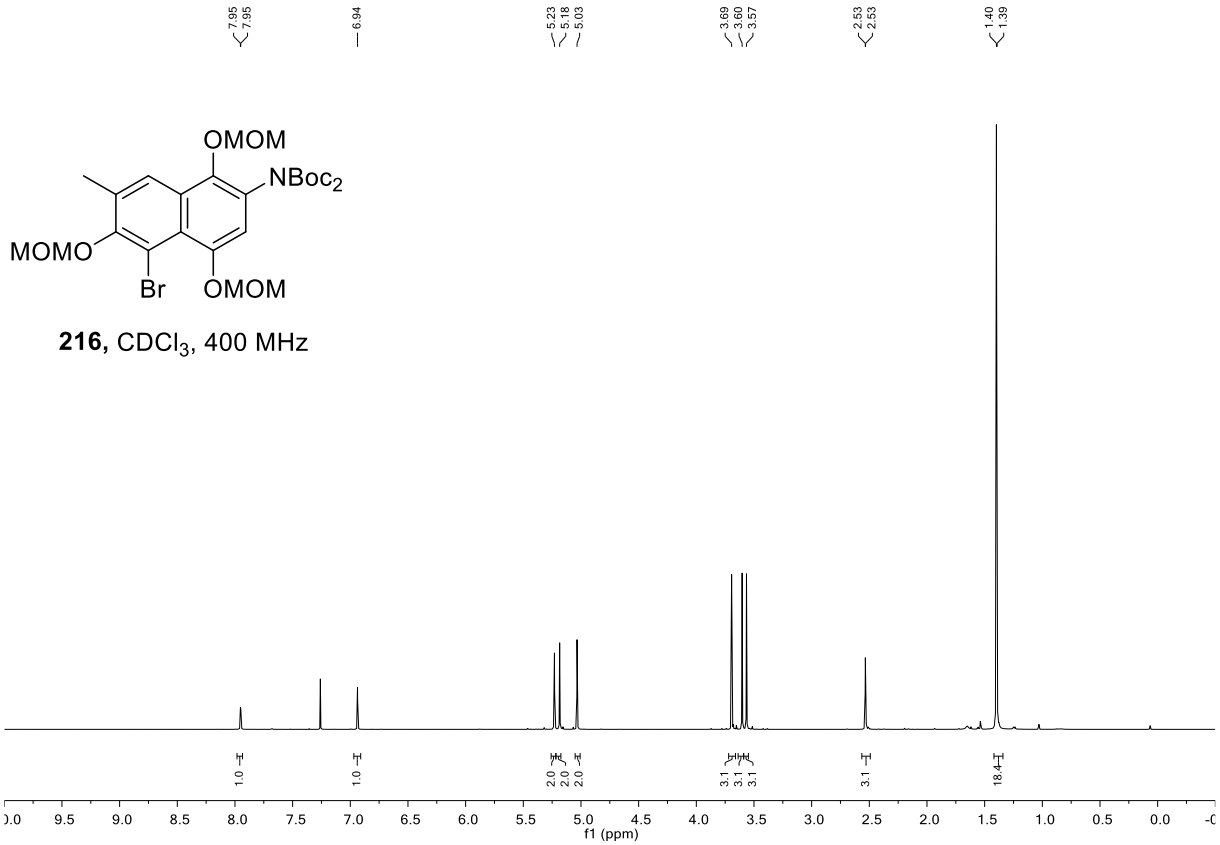
205, $CDCl_3$, 100 MHz



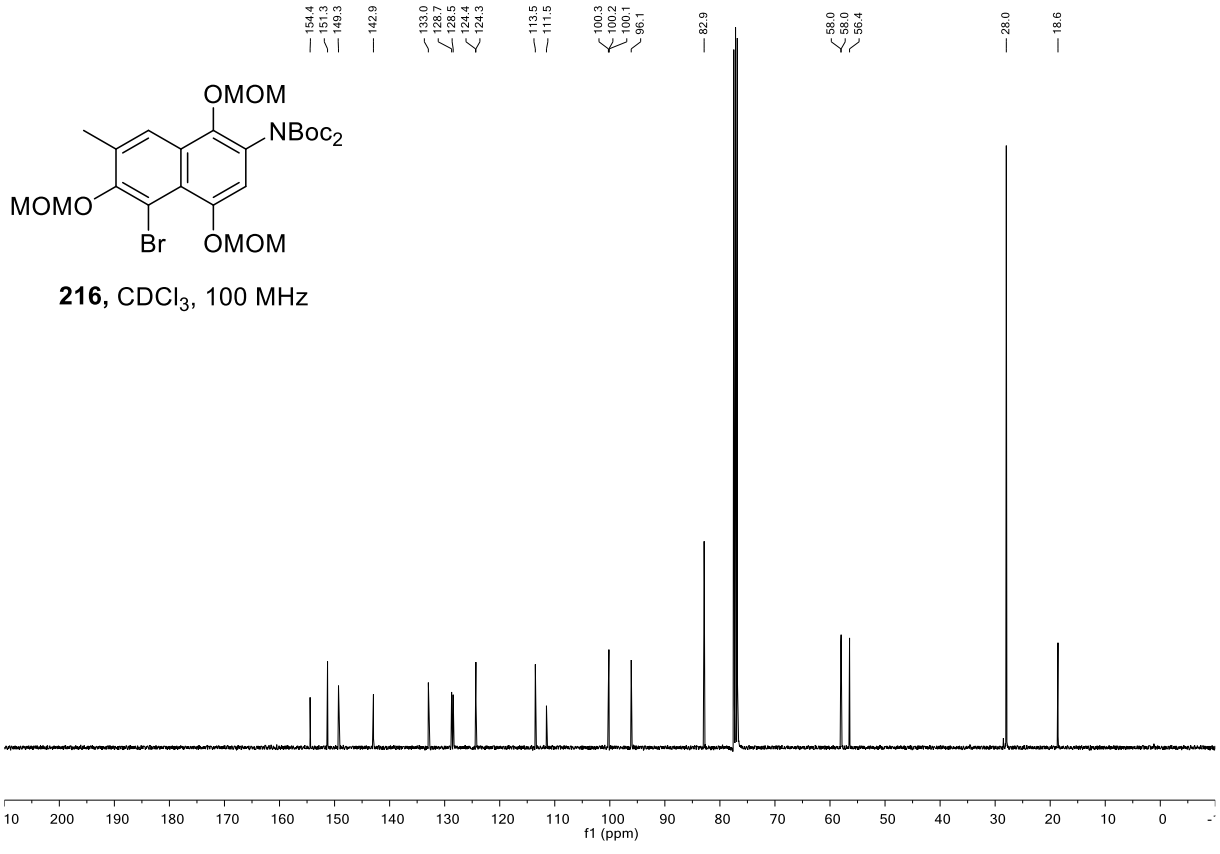
212, $CDCl_3$, 400 MHz



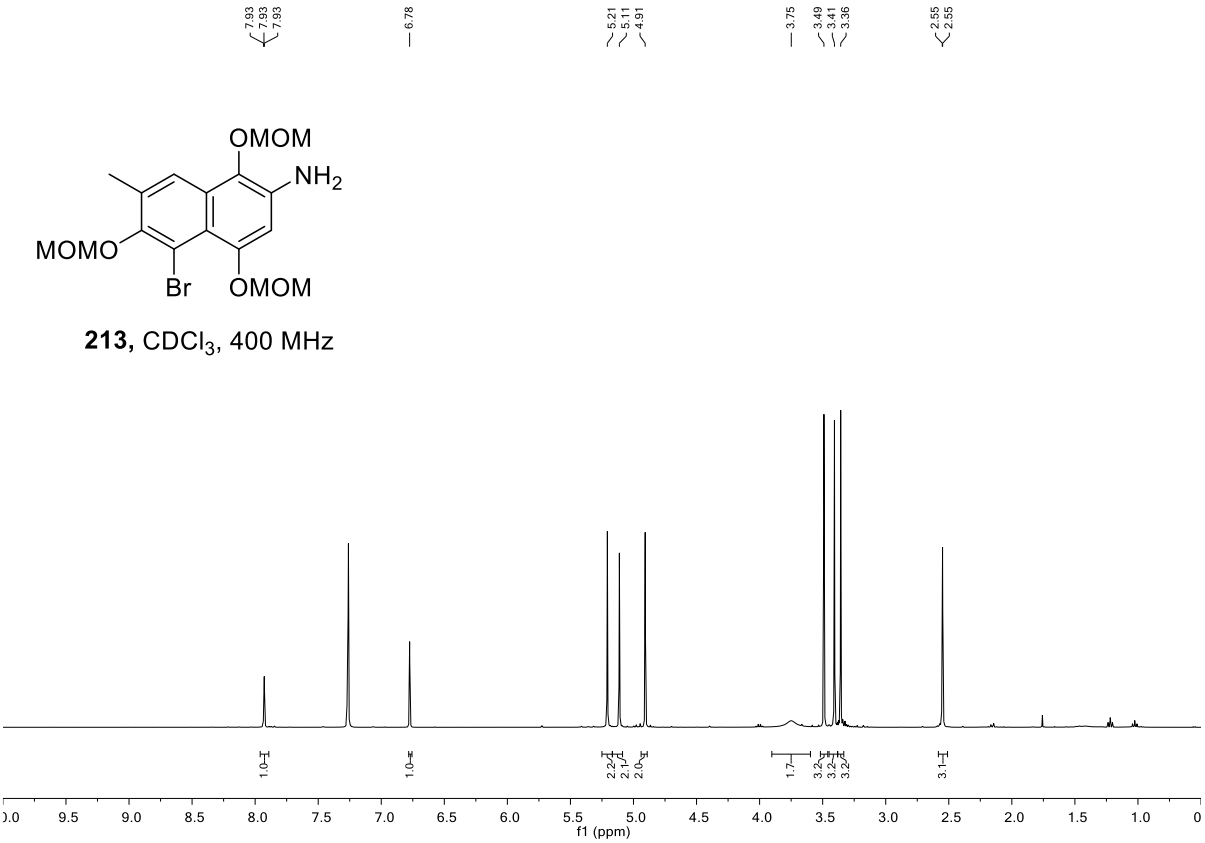
212, $CDCl_3$, 100 MHz



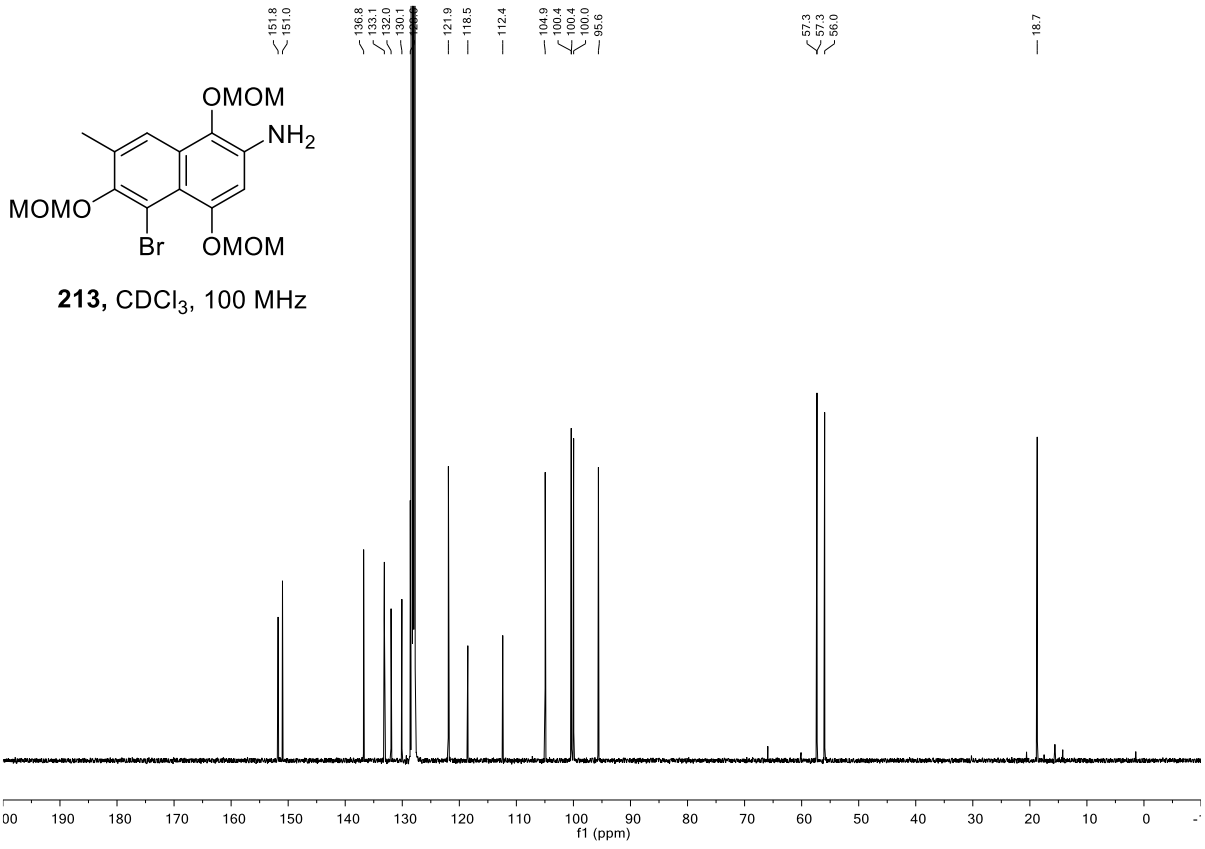
216, $CDCl_3$, 400 MHz



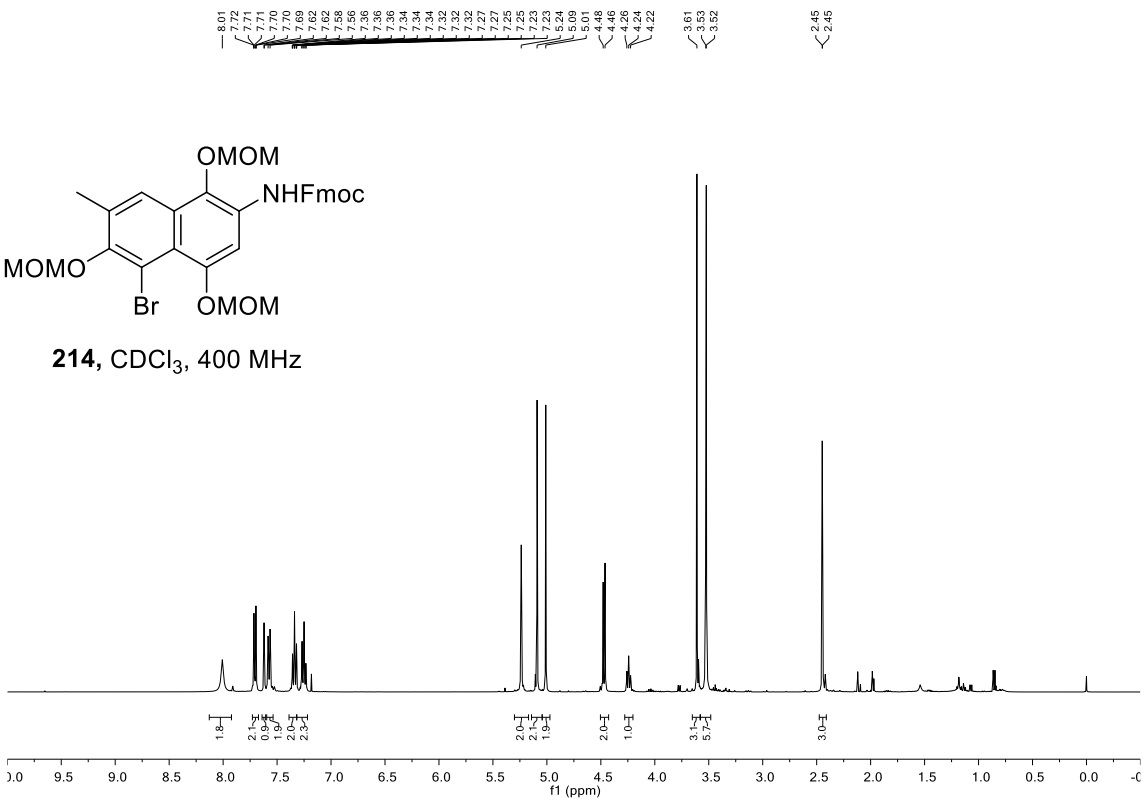
216, $CDCl_3$, 100 MHz

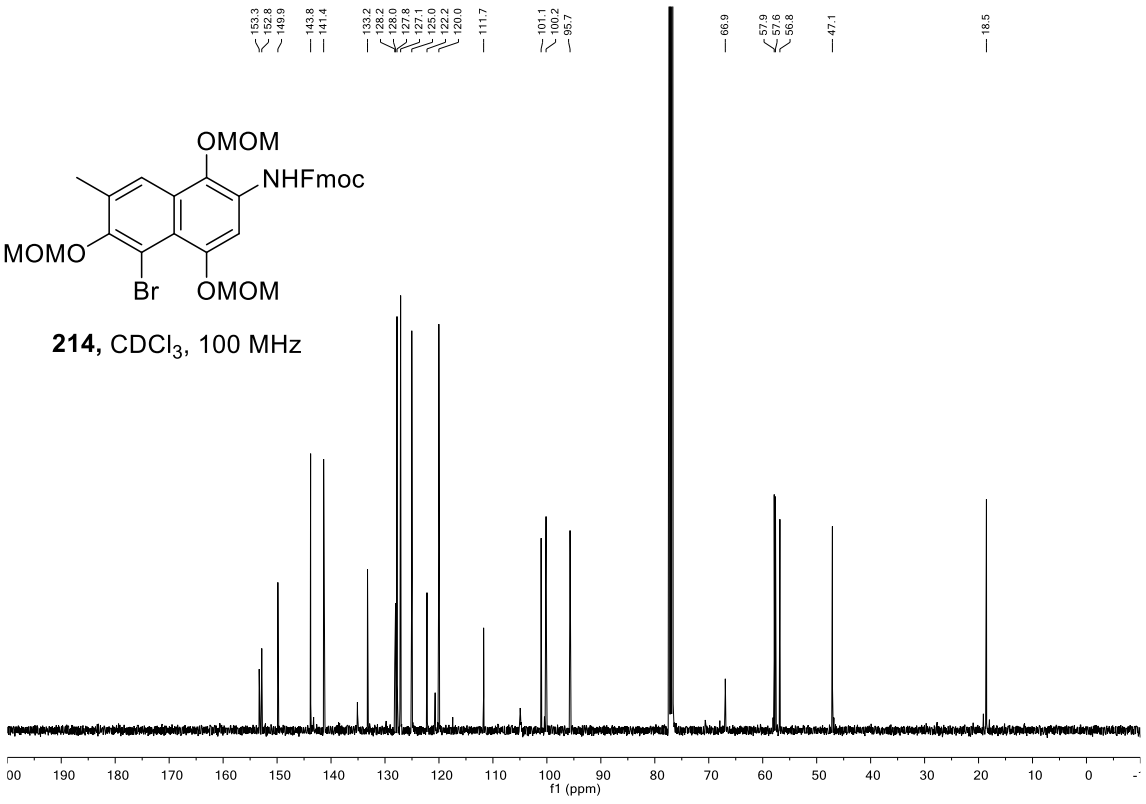


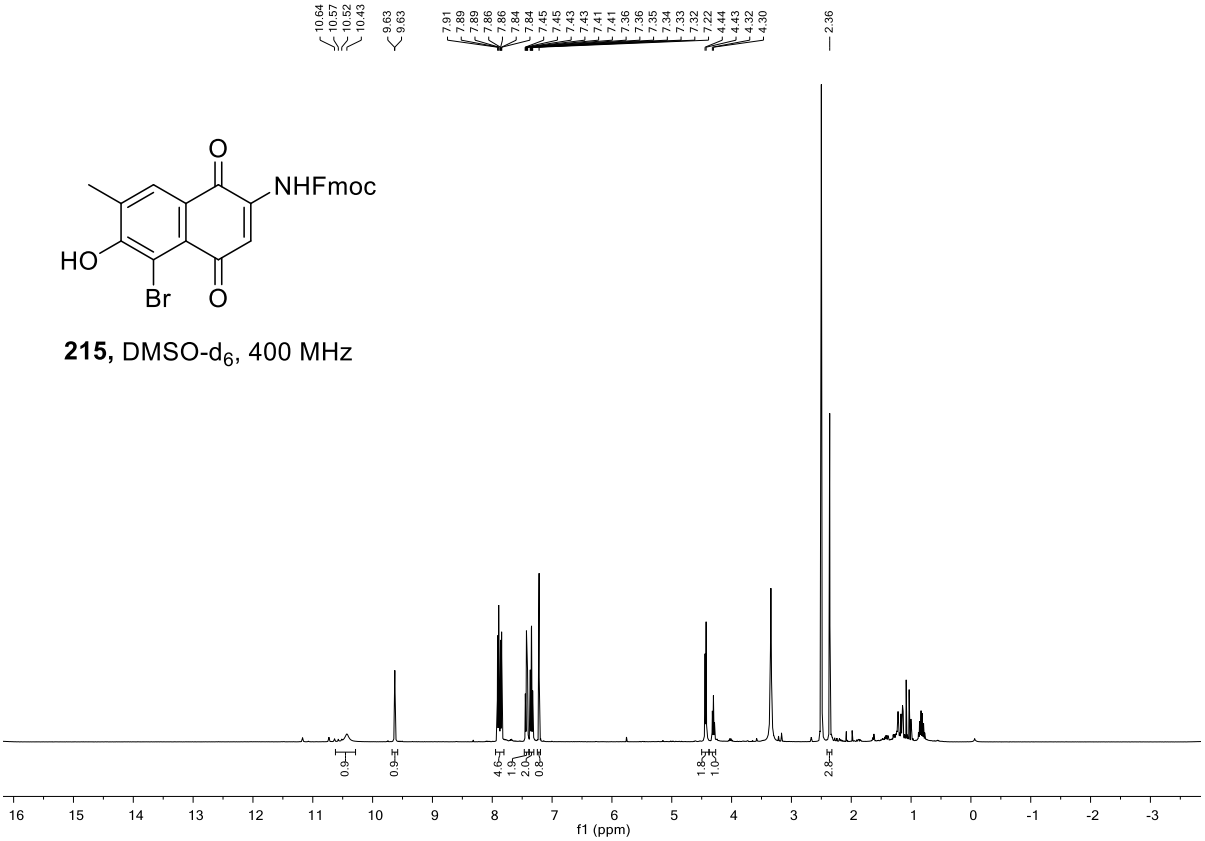
213, $CDCl_3$, 400 MHz



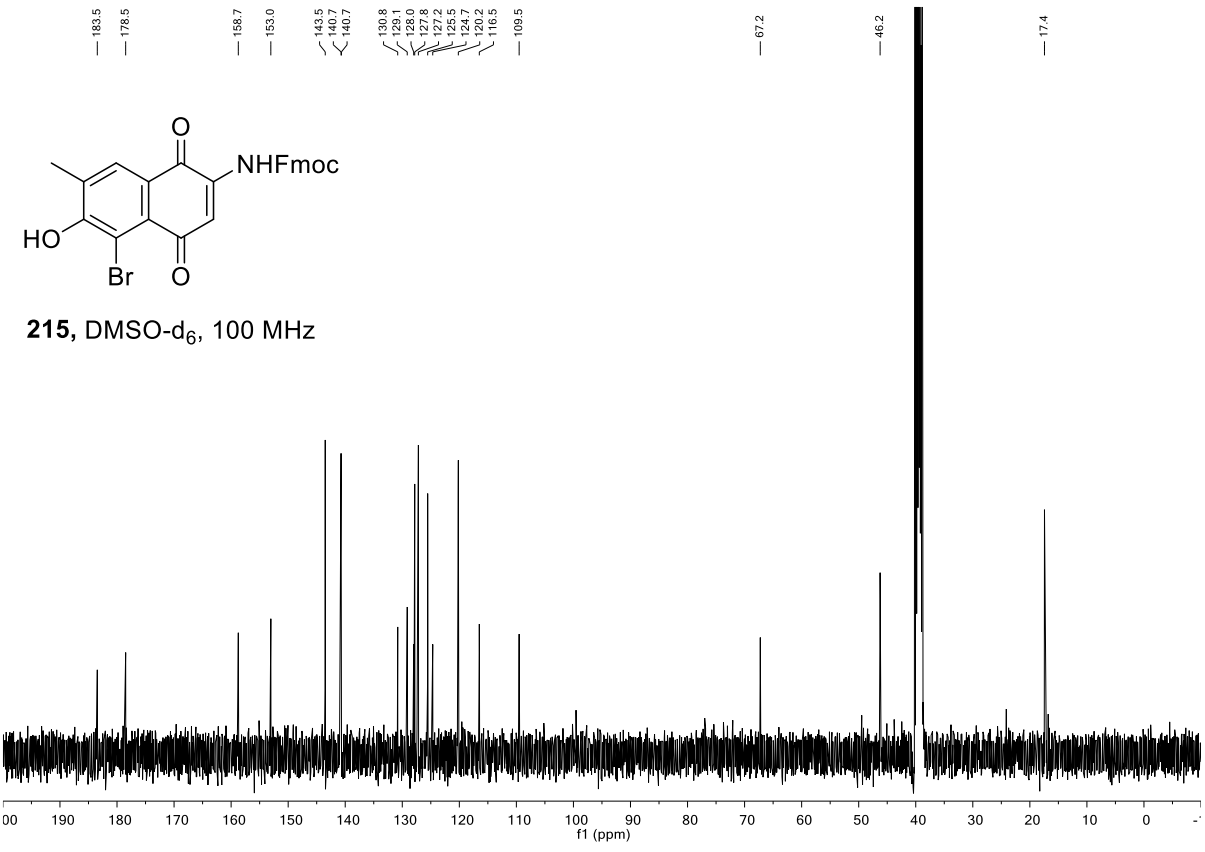
213, $CDCl_3$, 100 MHz


8.01
7.72
7.71
7.71
7.70
7.70
7.69
7.62
7.62
7.58
7.56
7.36
7.36
7.36
7.34
7.34
7.34
7.32
7.32
7.32
7.27
7.27
7.25
7.25
7.23
7.23
5.24
5.09
5.01
4.48
4.46
4.26
4.24
4.22
3.61
3.53
3.52
2.45
2.45
OMOM
NHFmoc
MOMO
Br
OMOM
214, CDCl3, 400 MHz
1.8
2.1
0.9
1.9
2.0
2.3
2.0
2.1
1.9
2.0
1.0
3.1
5.7
3.0
f1 (ppm)

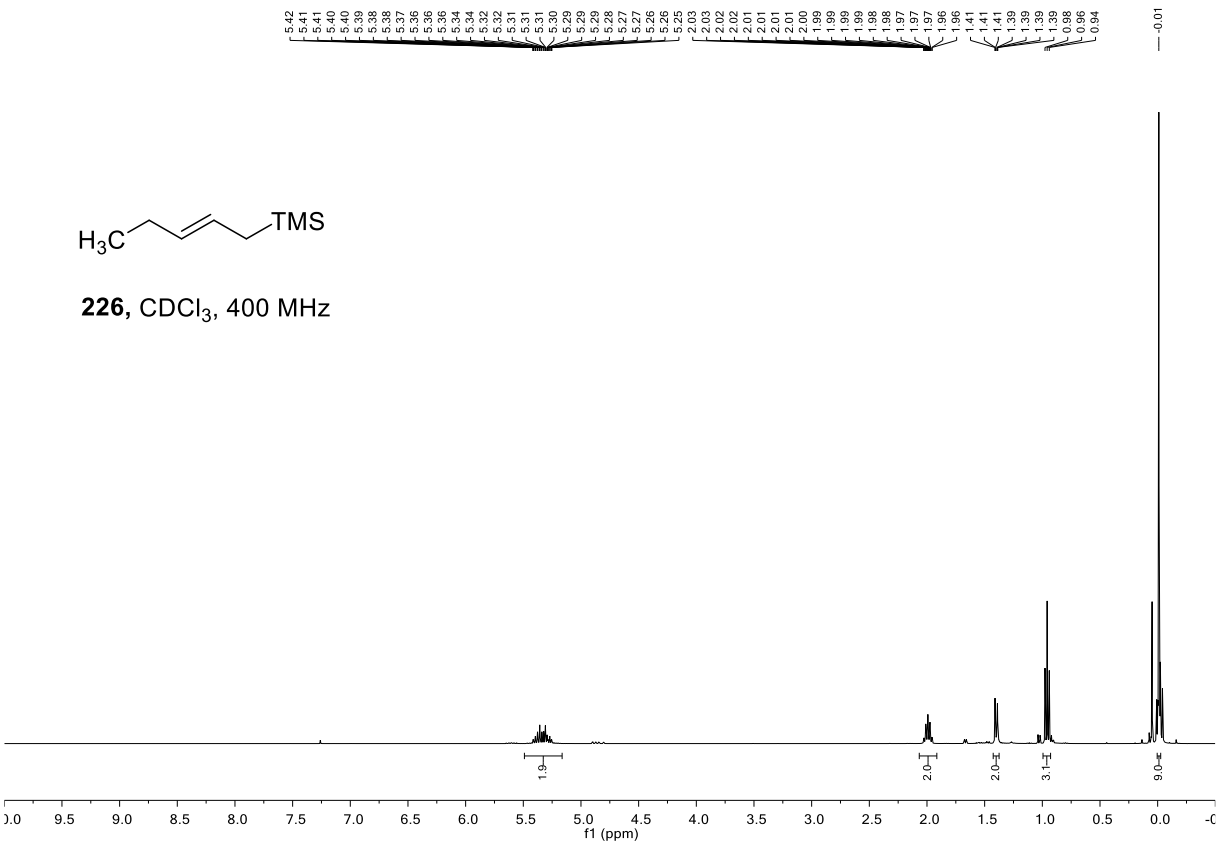

153.3
152.8
149.9
143.8
141.4
133.2
128.2
128.0
127.8
127.1
125.0
122.2
120.0
111.7
101.1
100.2
95.7
66.9
57.9
57.6
56.8
47.1
18.5
OMOM
NHFmoc
MOMO
Br
OMOM
214, CDCl3, 100 MHz
f1 (ppm)

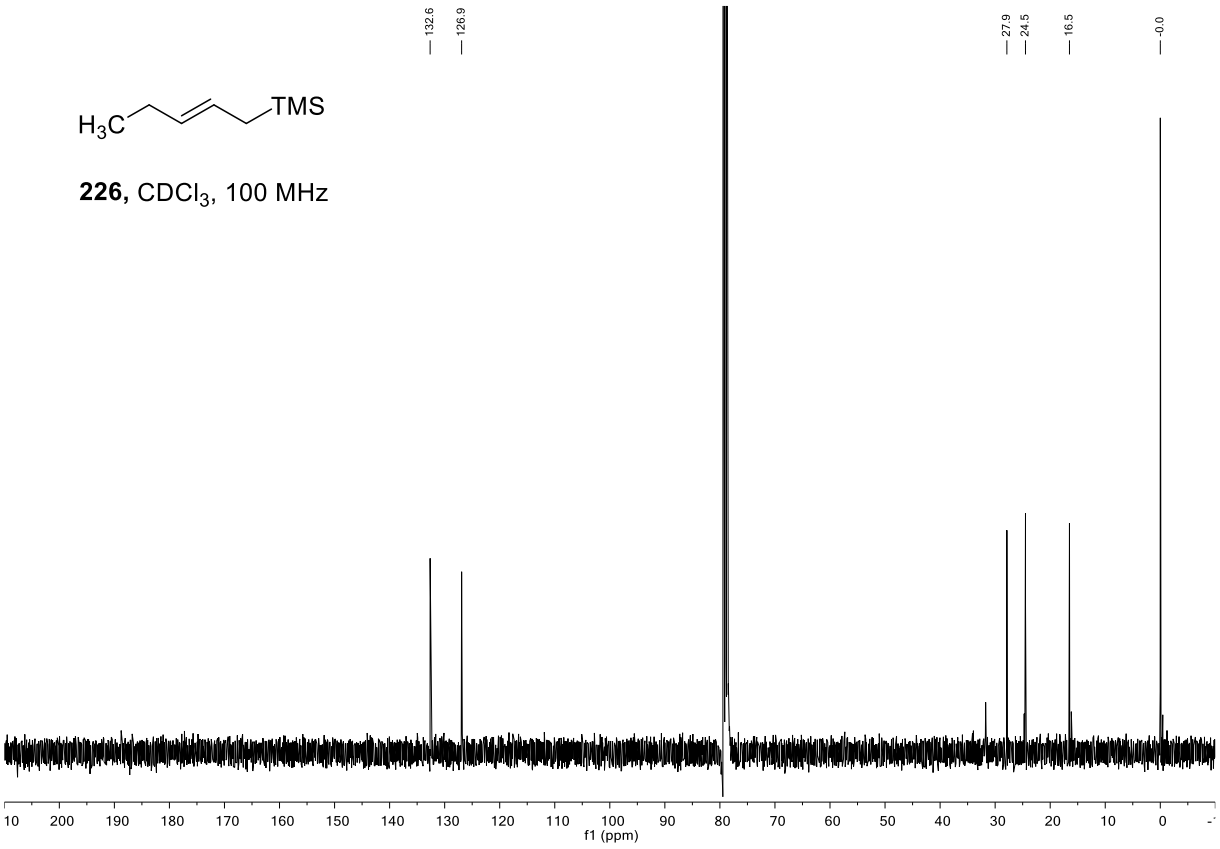


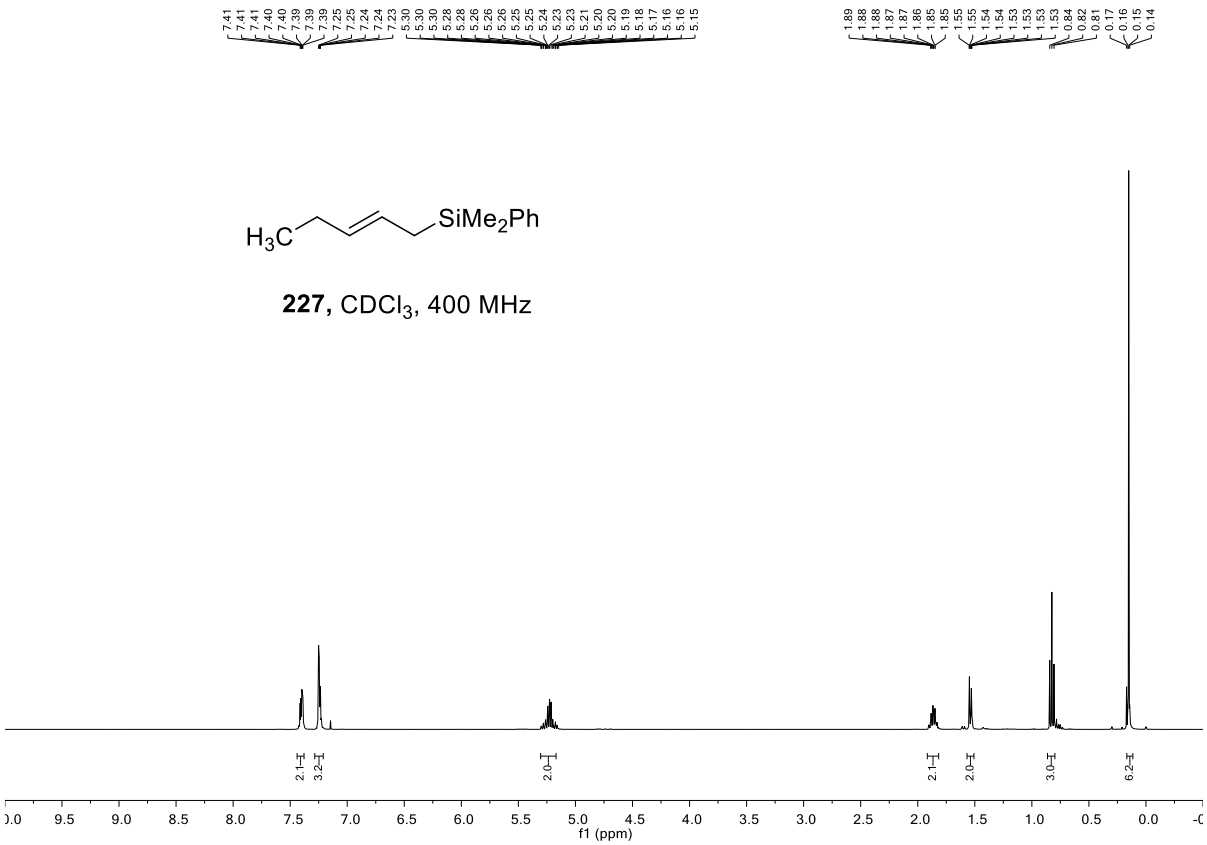
215, DMSO-d_6, 400 MHz



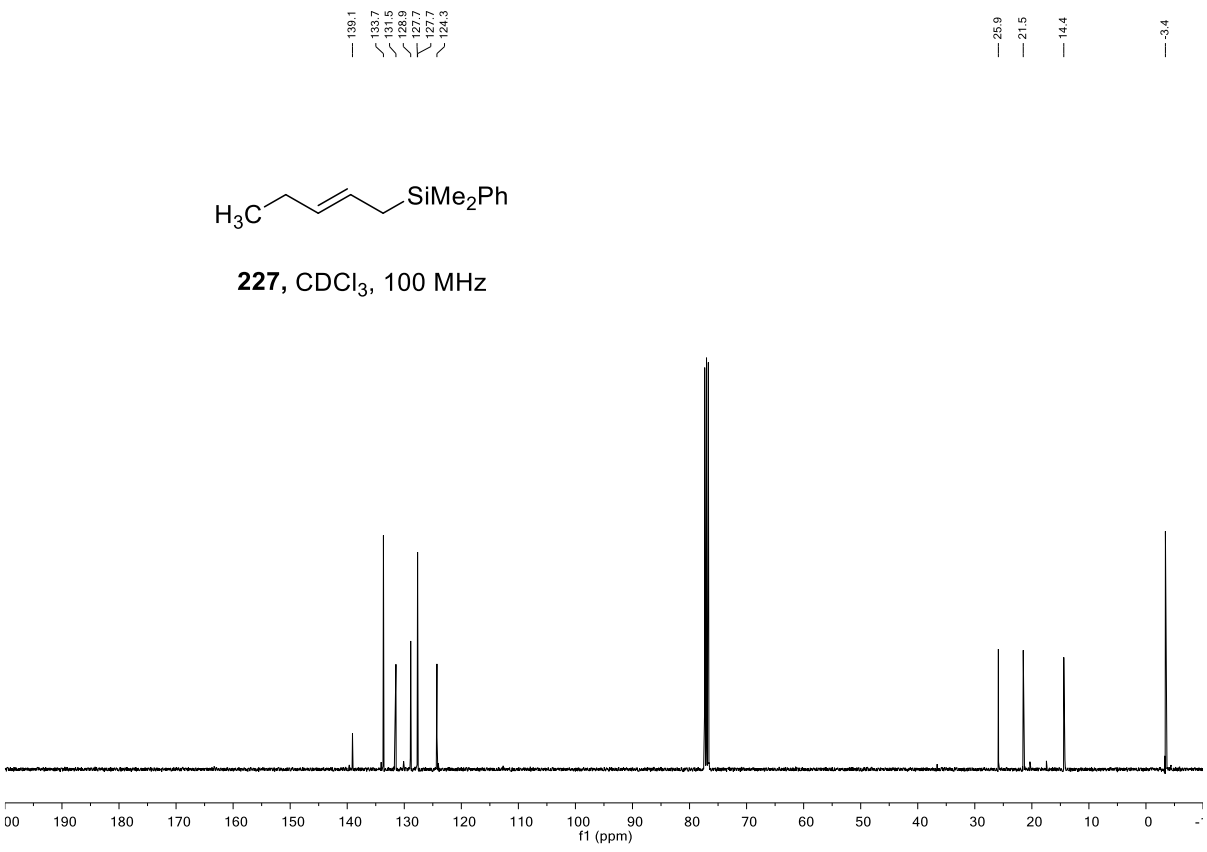
215, DMSO-d_6, 100 MHz


TMS
H3C
226, CDCl3, 400 MHz
f1 (ppm)

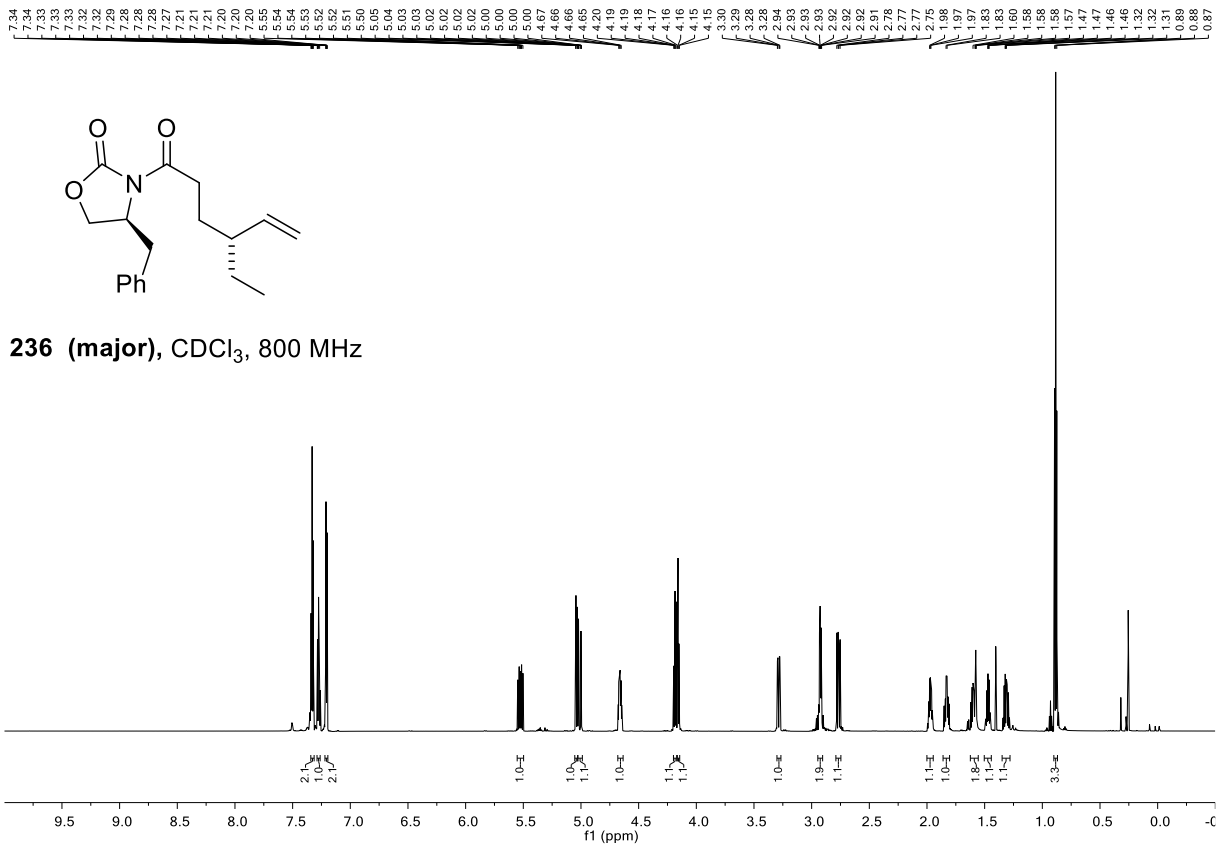

TMS
H3C
226, CDCl3, 100 MHz
f1 (ppm)



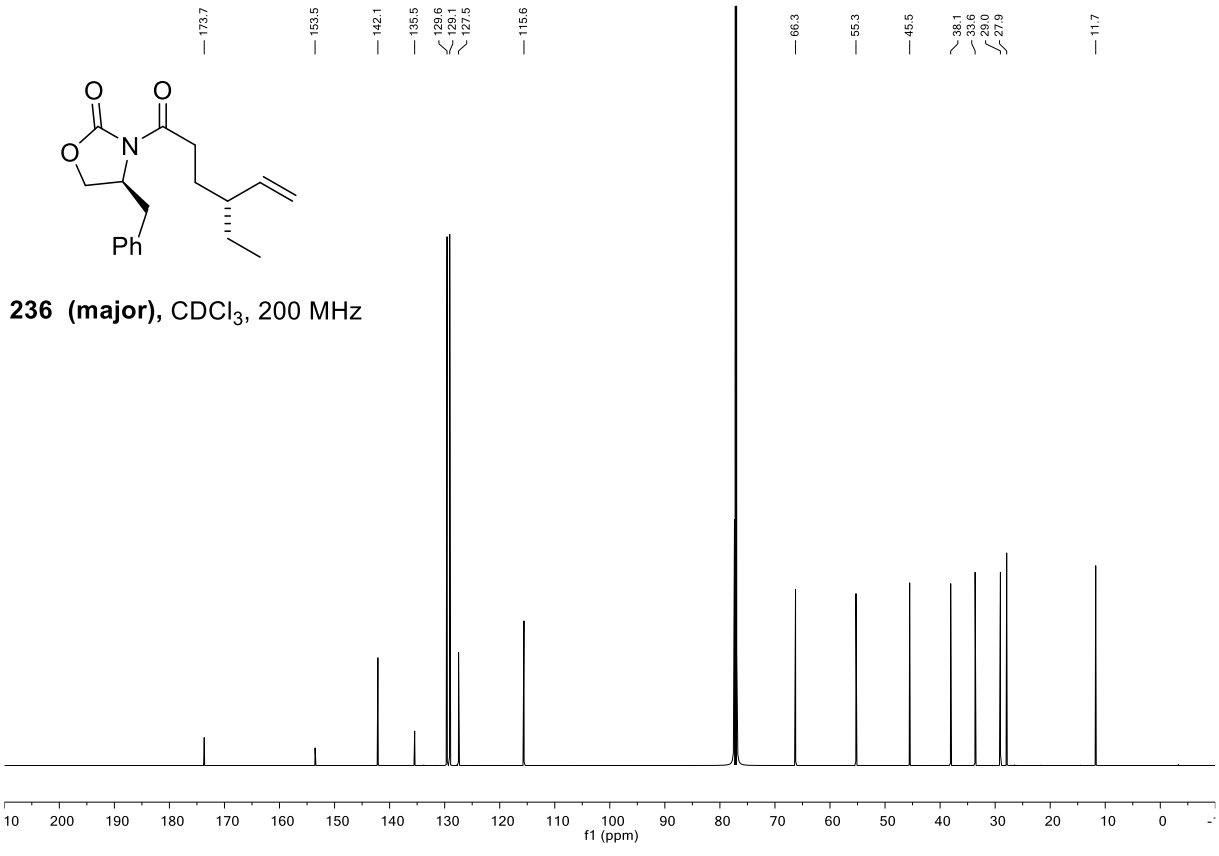
227, $CDCl_3$, 400 MHz



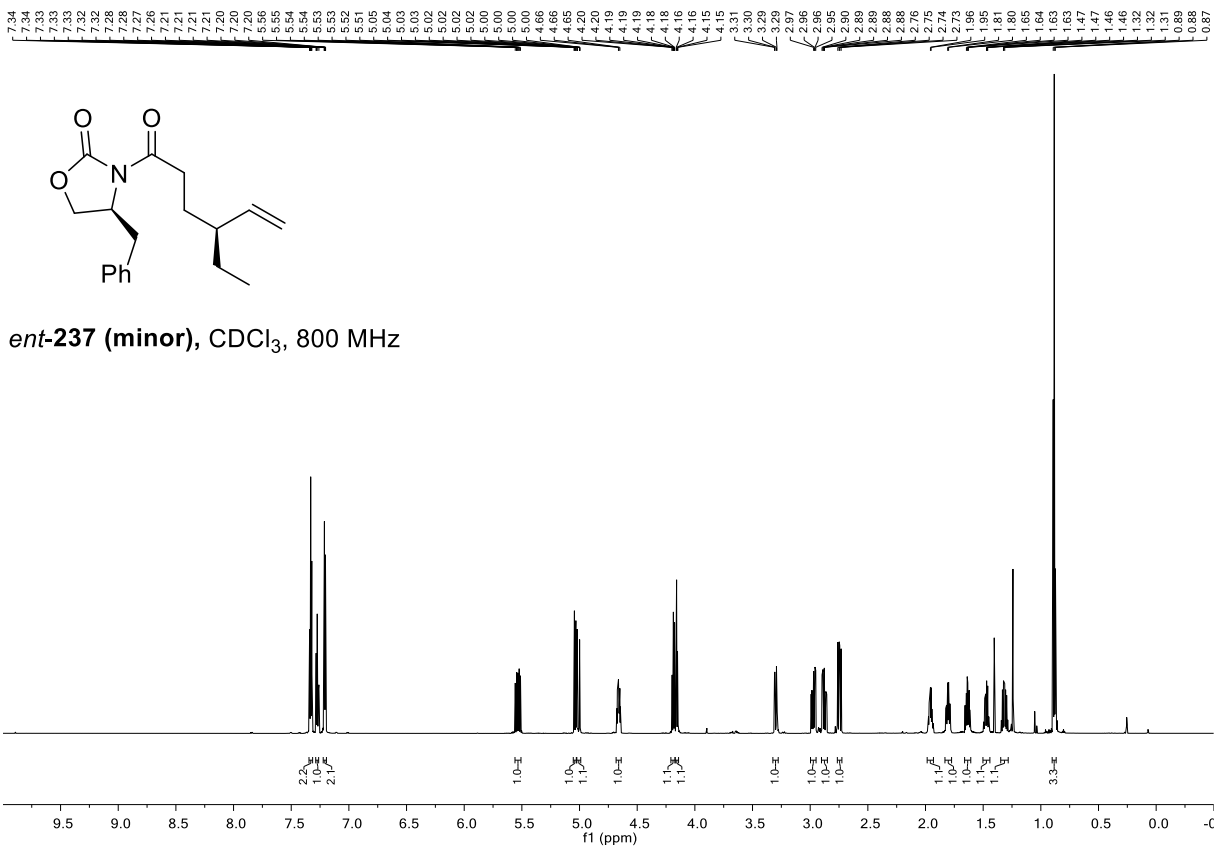
227, $CDCl_3$, 100 MHz



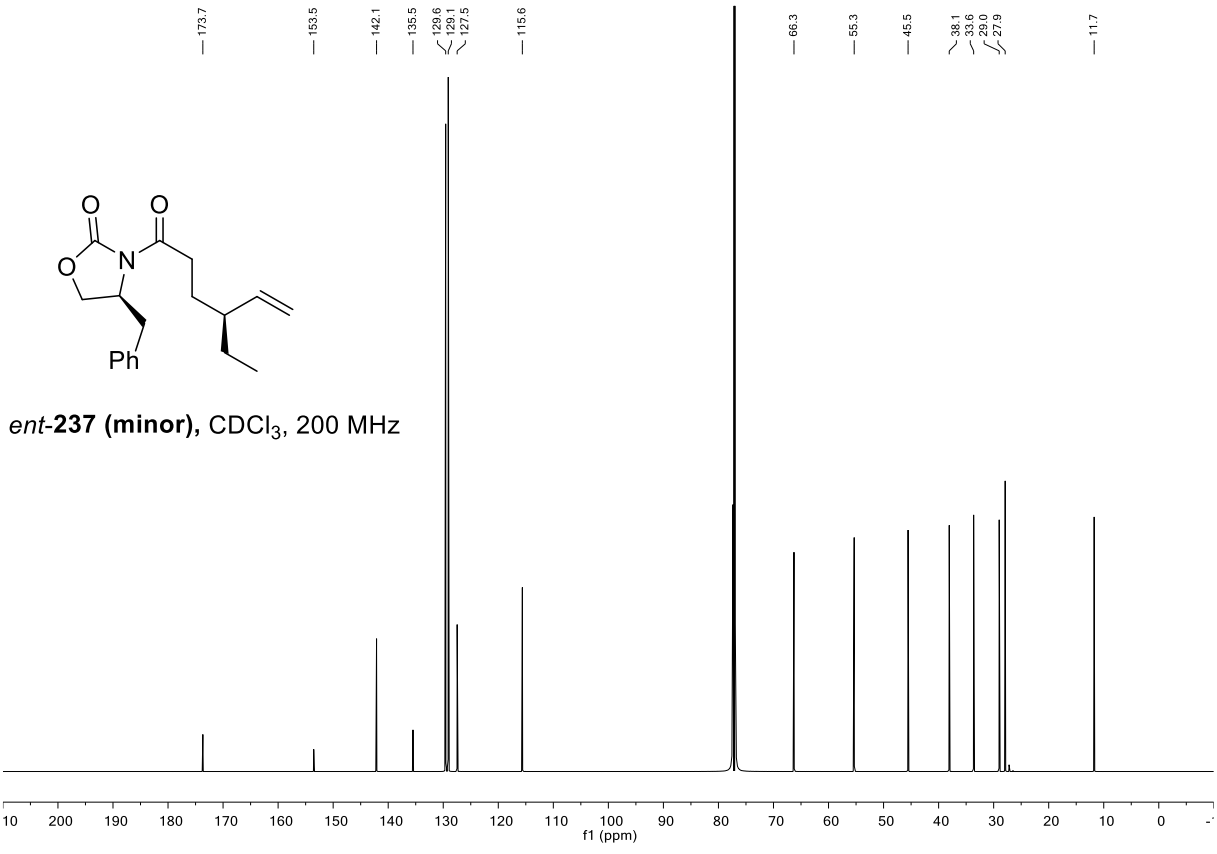
236 (major), $CDCl_3$, 800 MHz



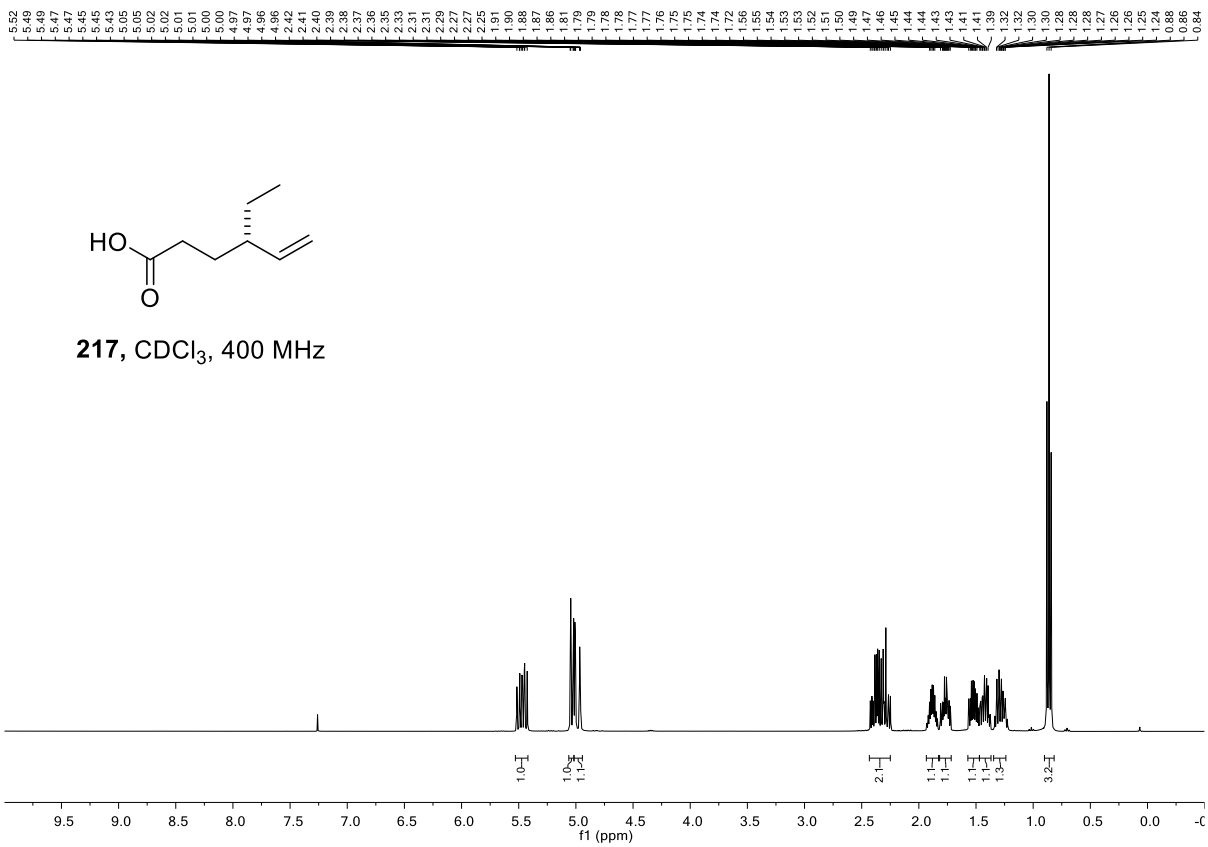
236 (major), $CDCl_3$, 200 MHz



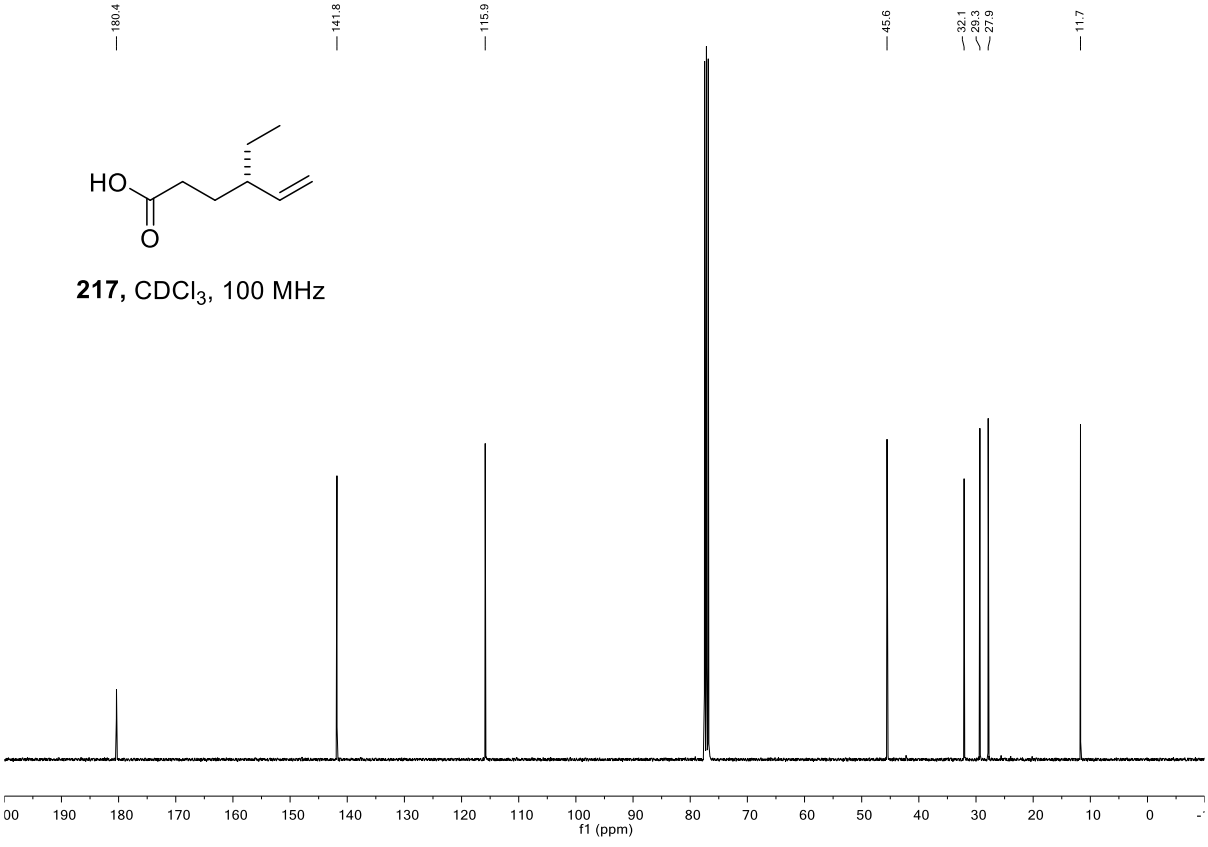
ent-**237 (minor),** $CDCl_3$, 800 MHz



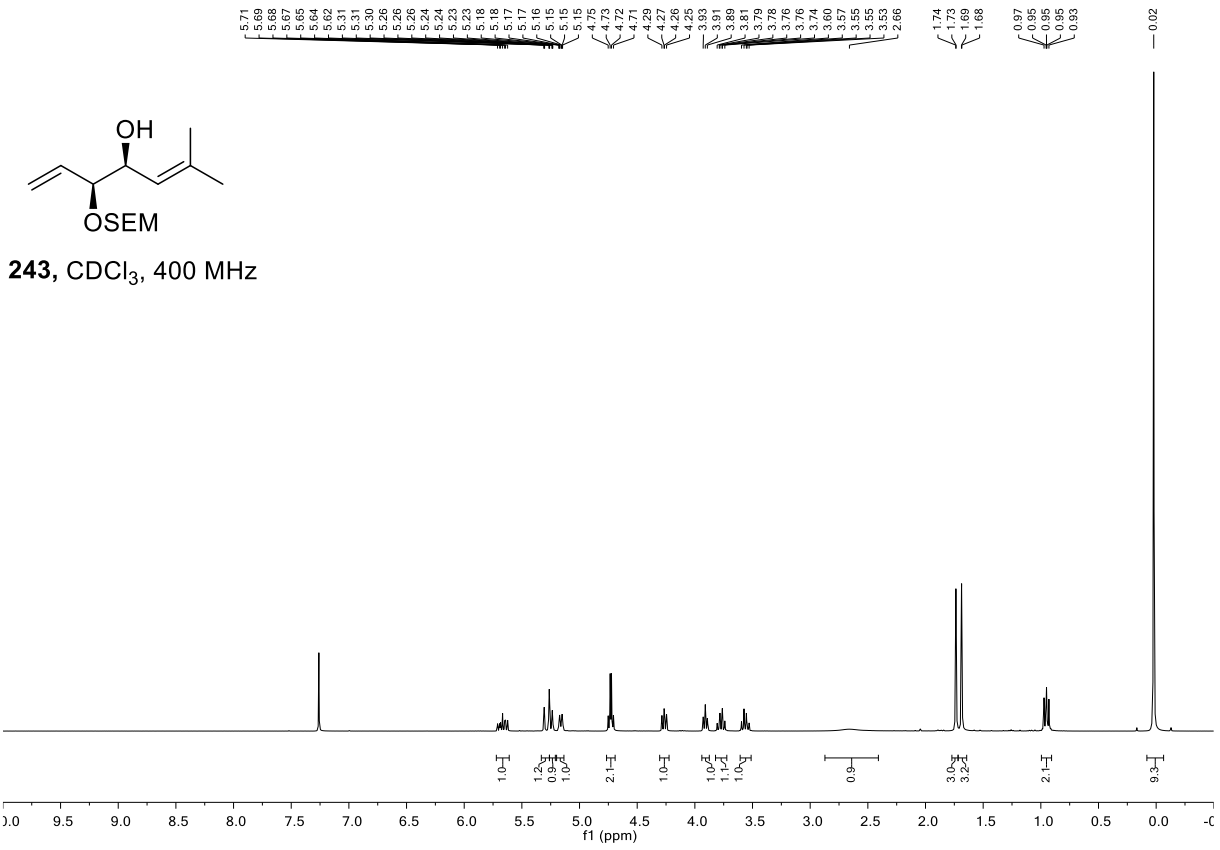
ent-**237 (minor),** $CDCl_3$, 200 MHz



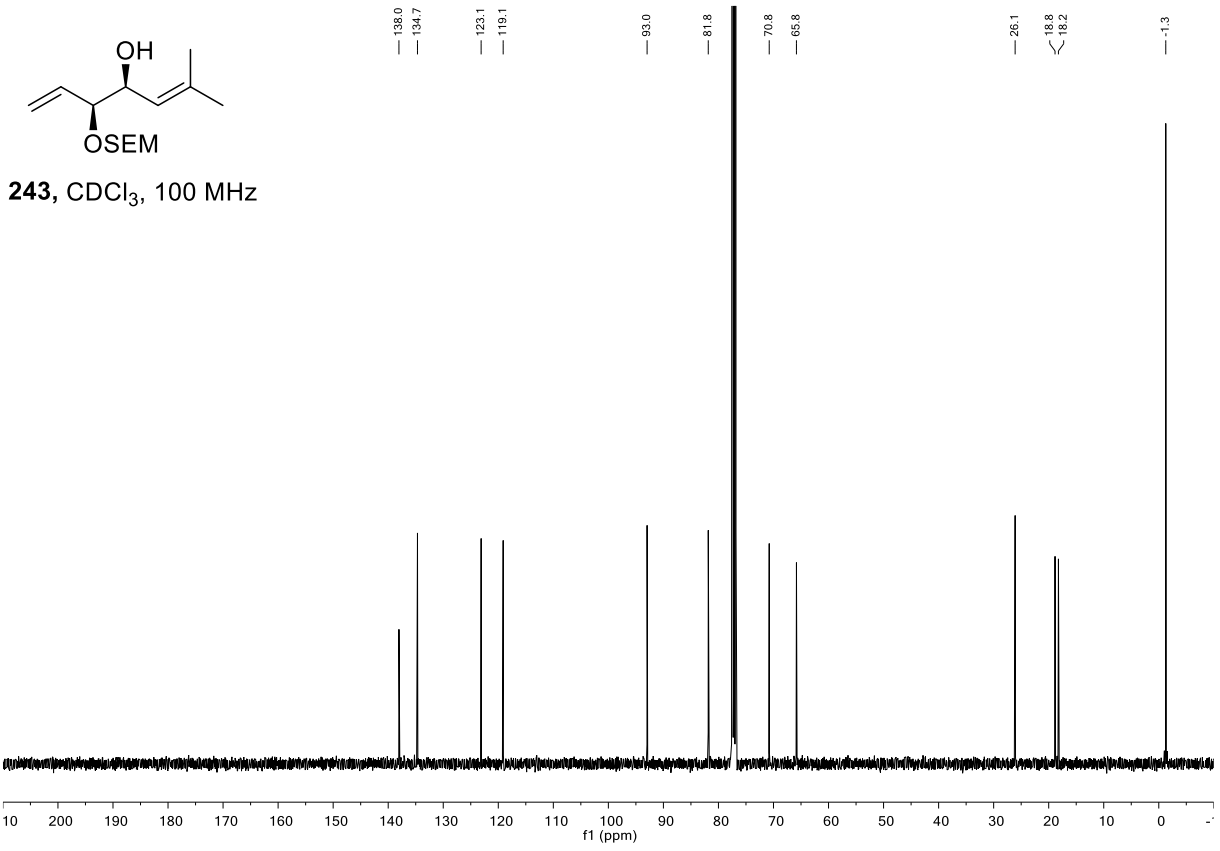
217, $CDCl_3$, 400 MHz



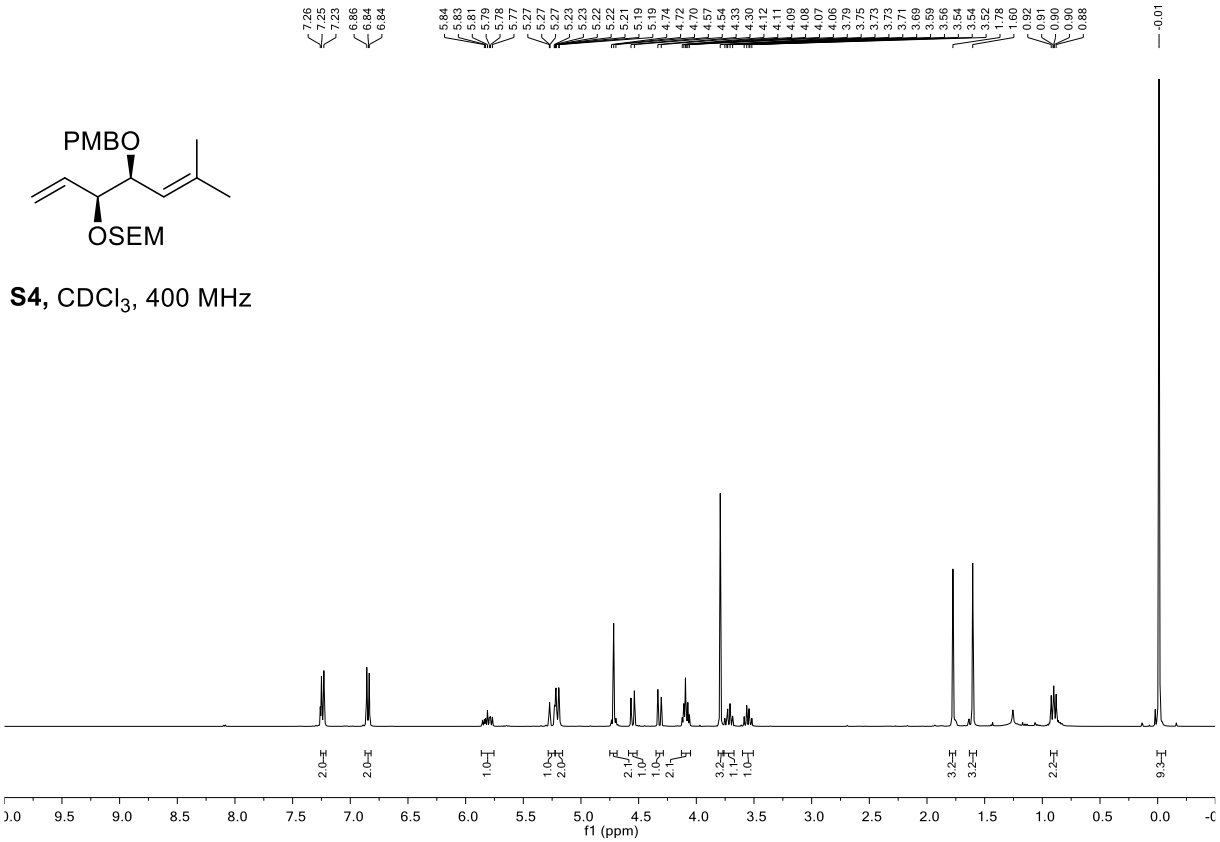
217, $CDCl_3$, 100 MHz



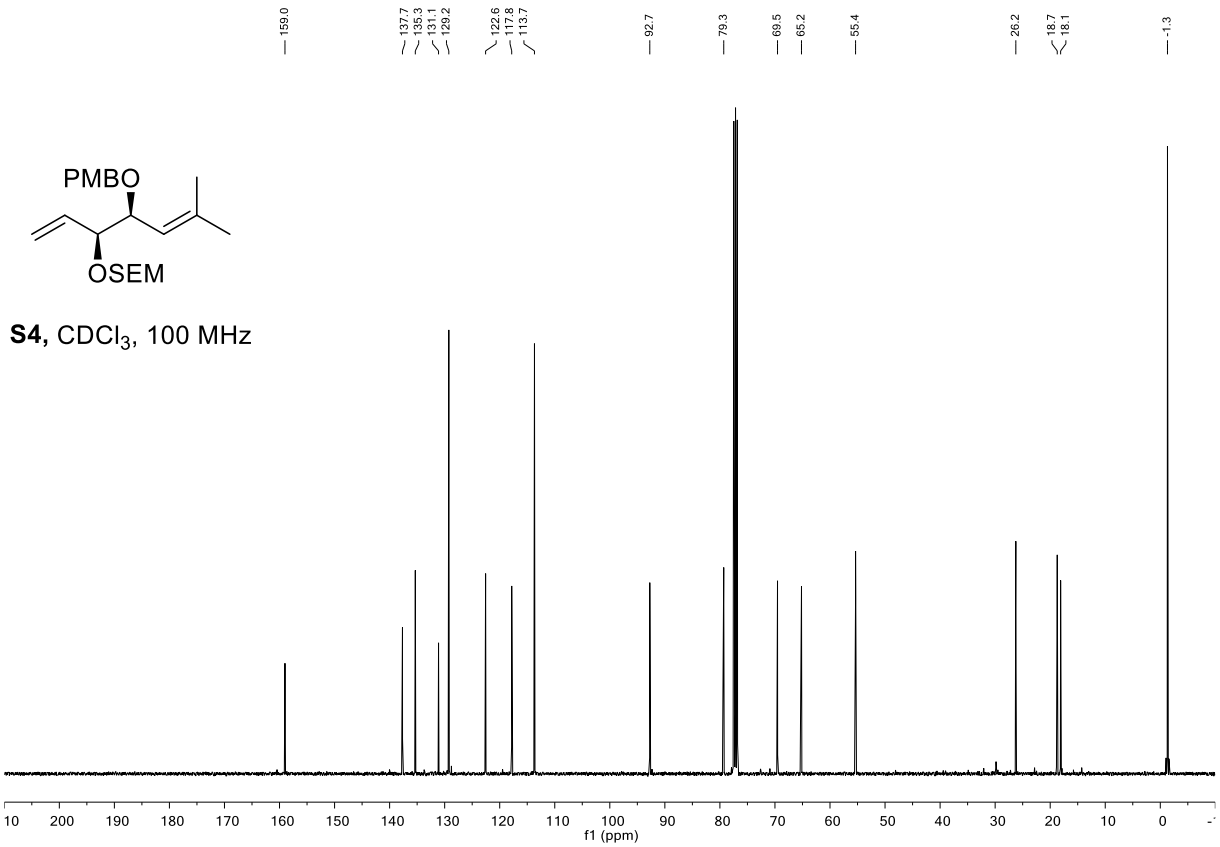
243, $CDCl_3$, 400 MHz



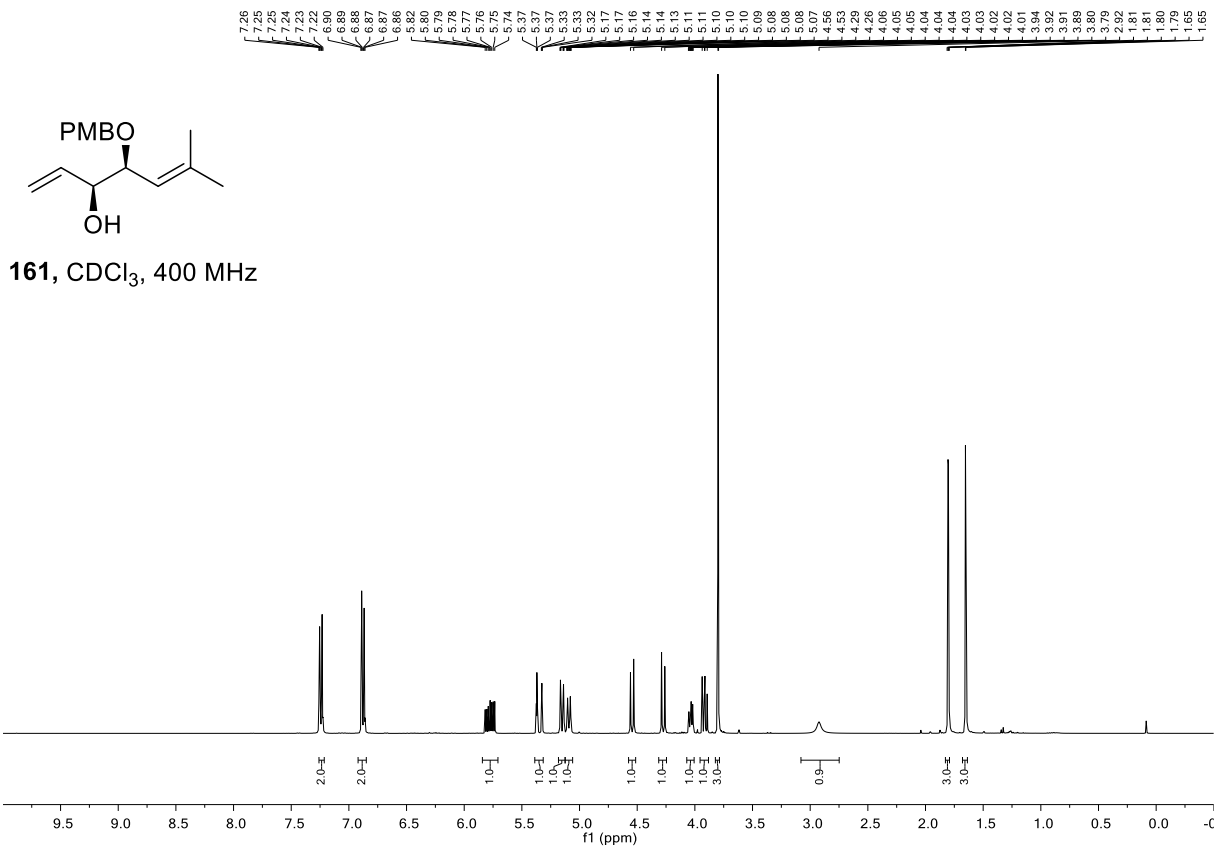
243, $CDCl_3$, 100 MHz



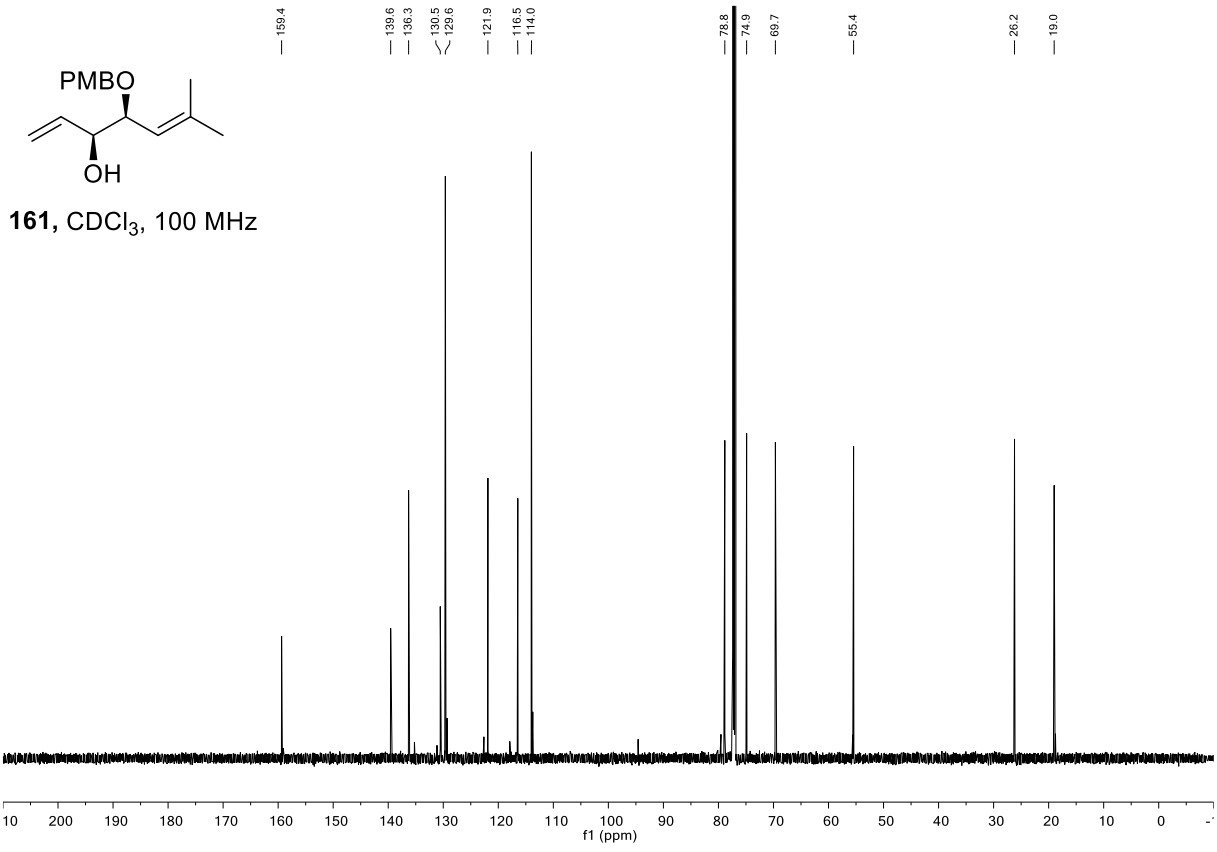
S4, $CDCl_3$, 400 MHz



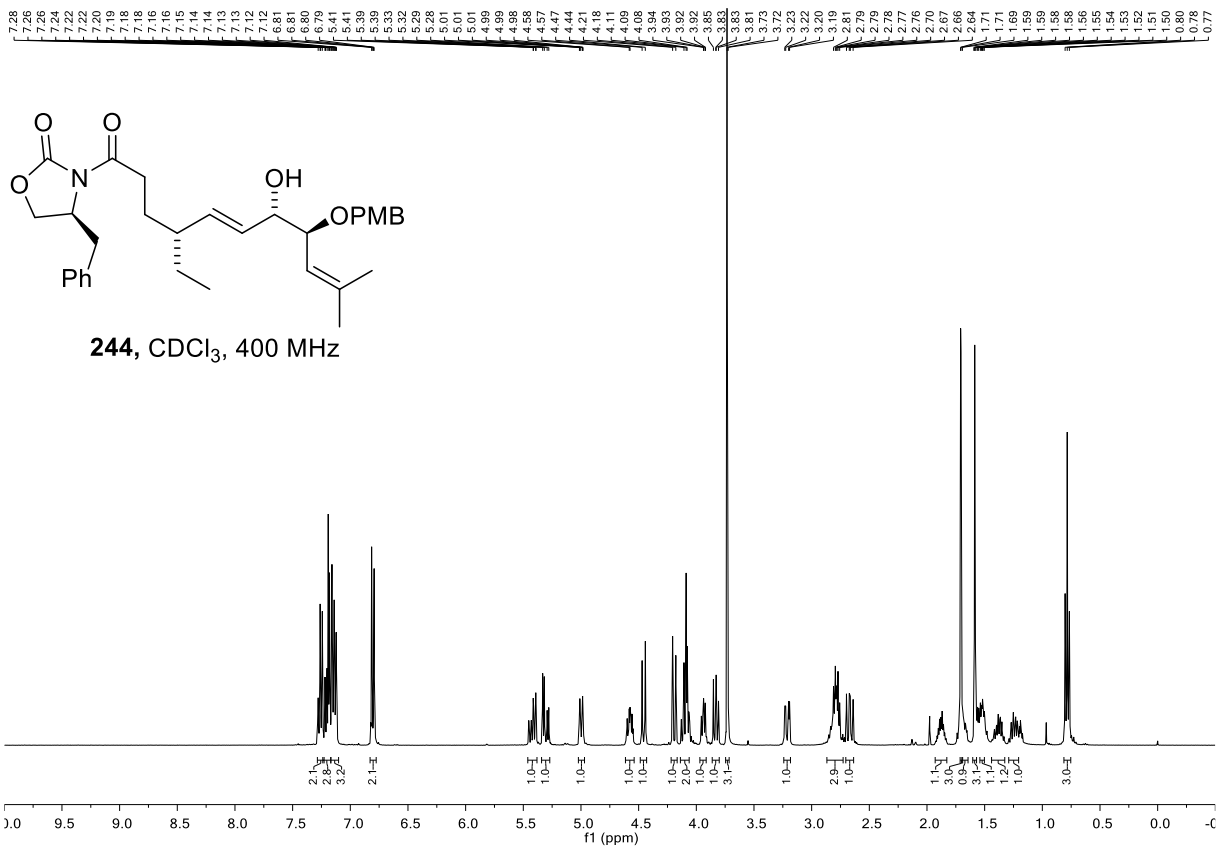
S4, $CDCl_3$, 100 MHz



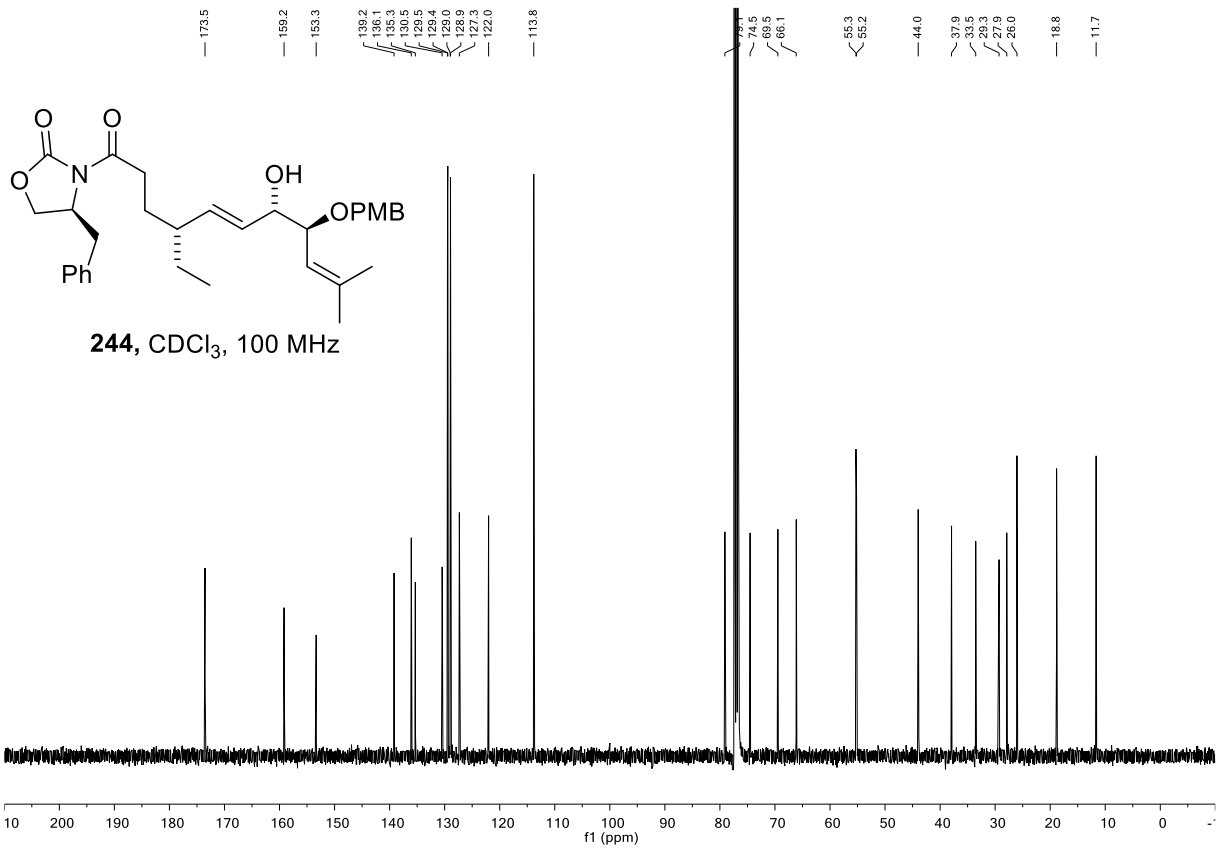
161, $CDCl_3$, 400 MHz



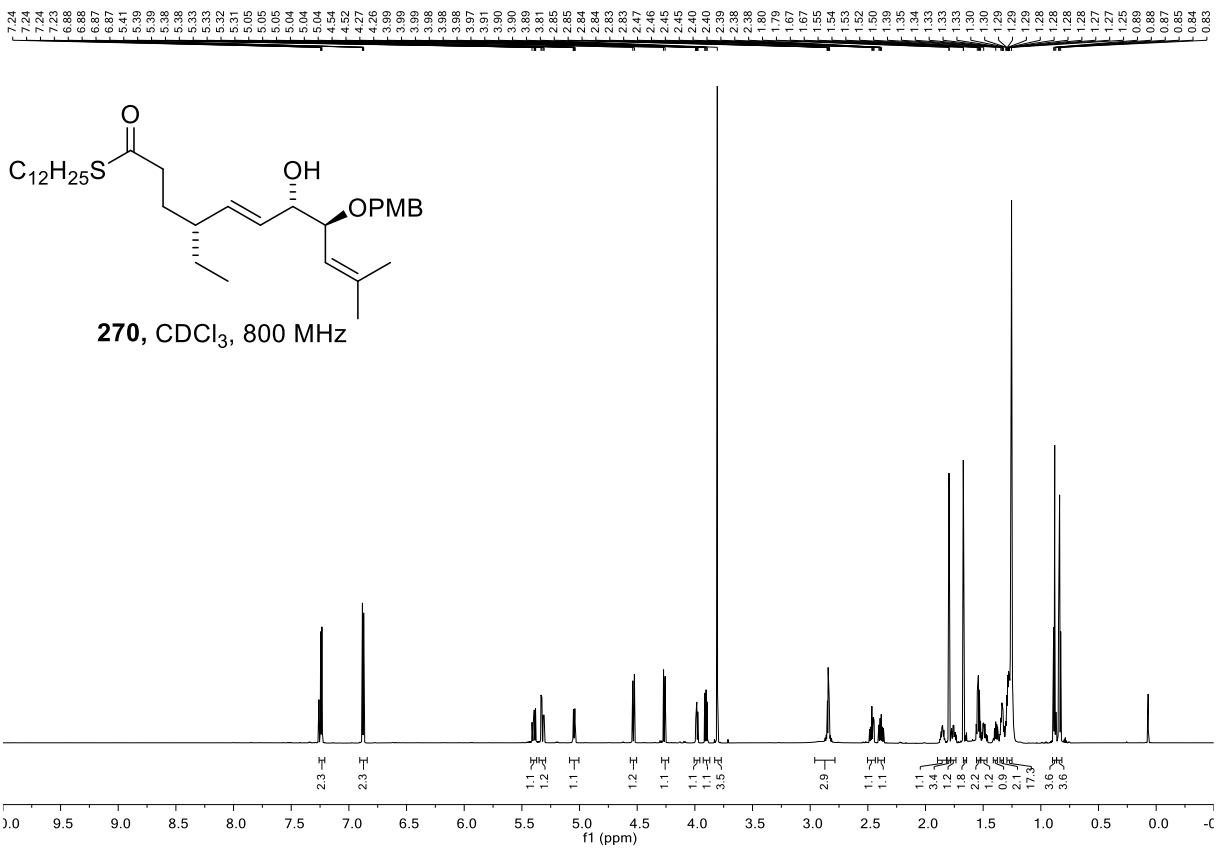
161, $CDCl_3$, 100 MHz



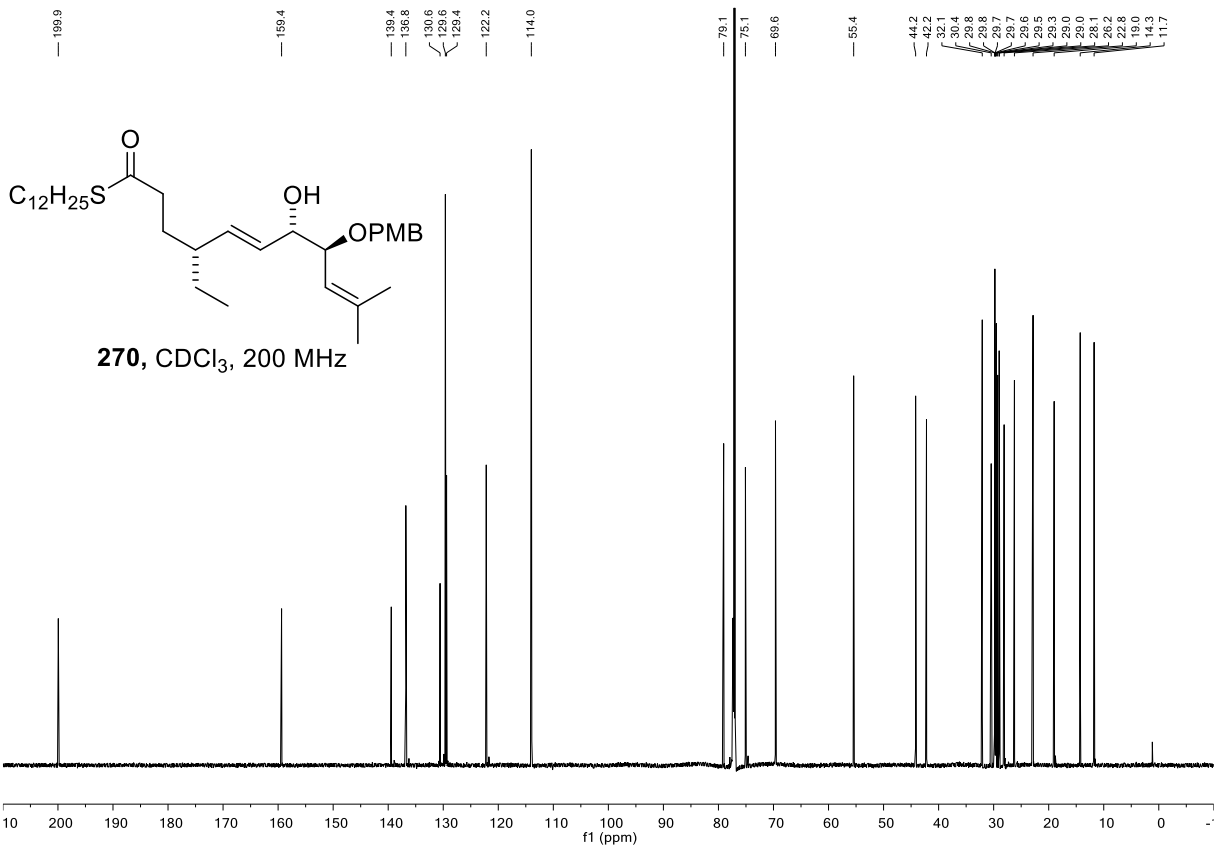
244, $CDCl_3$, 400 MHz



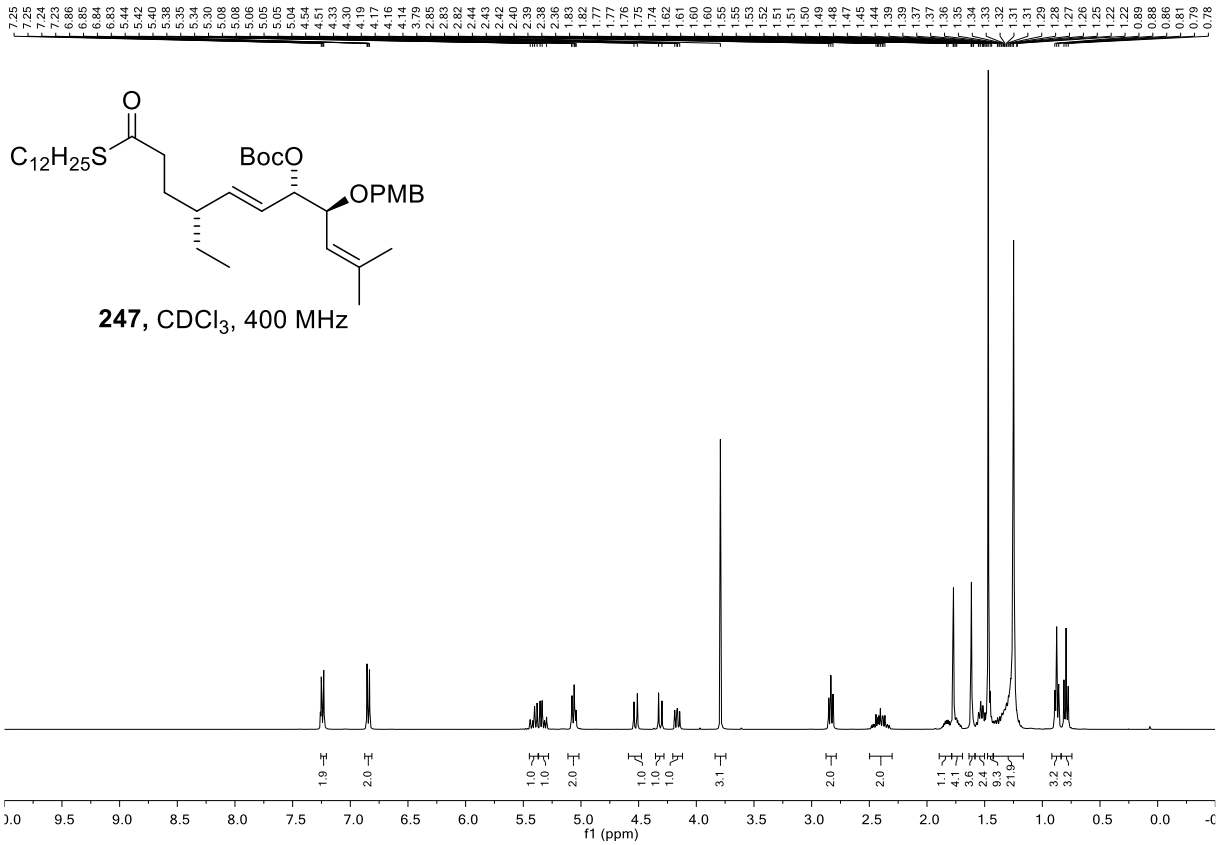
244, $CDCl_3$, 100 MHz



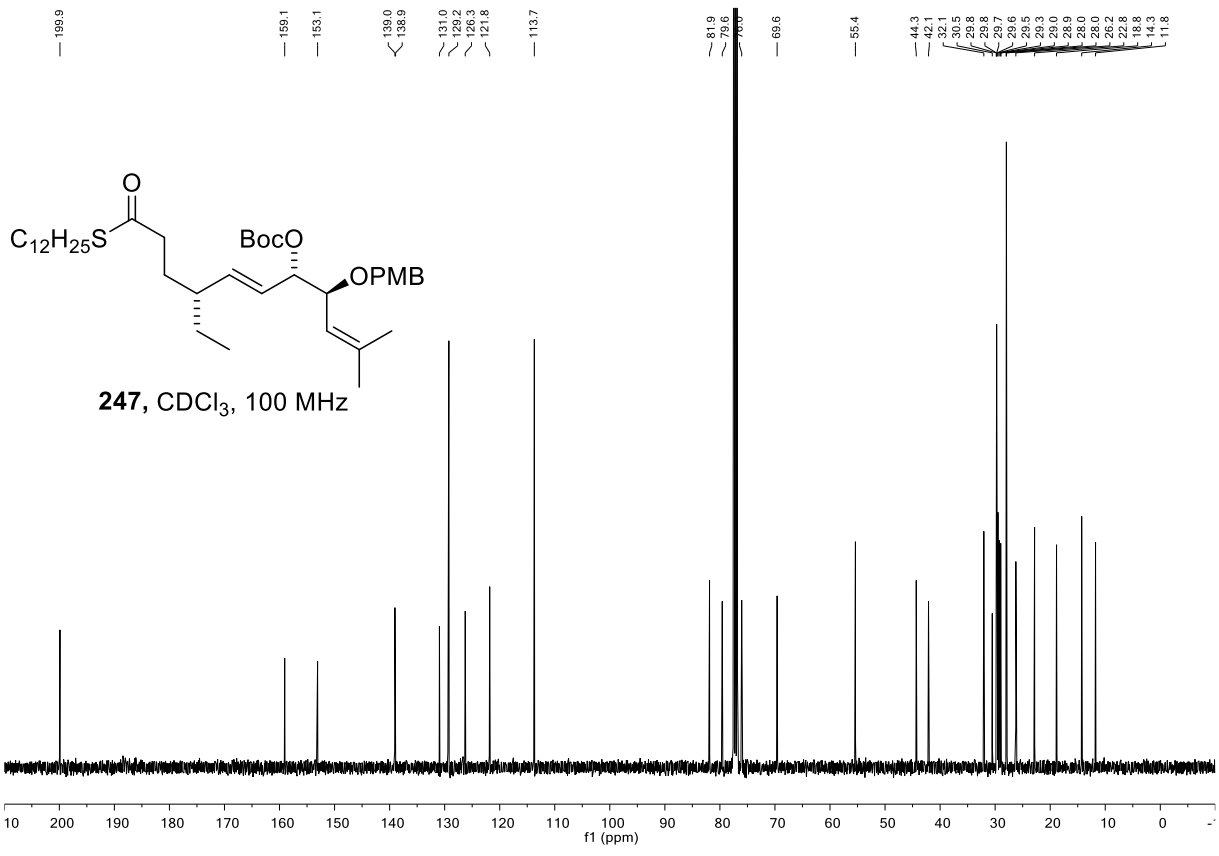
270, $CDCl_3$, 800 MHz



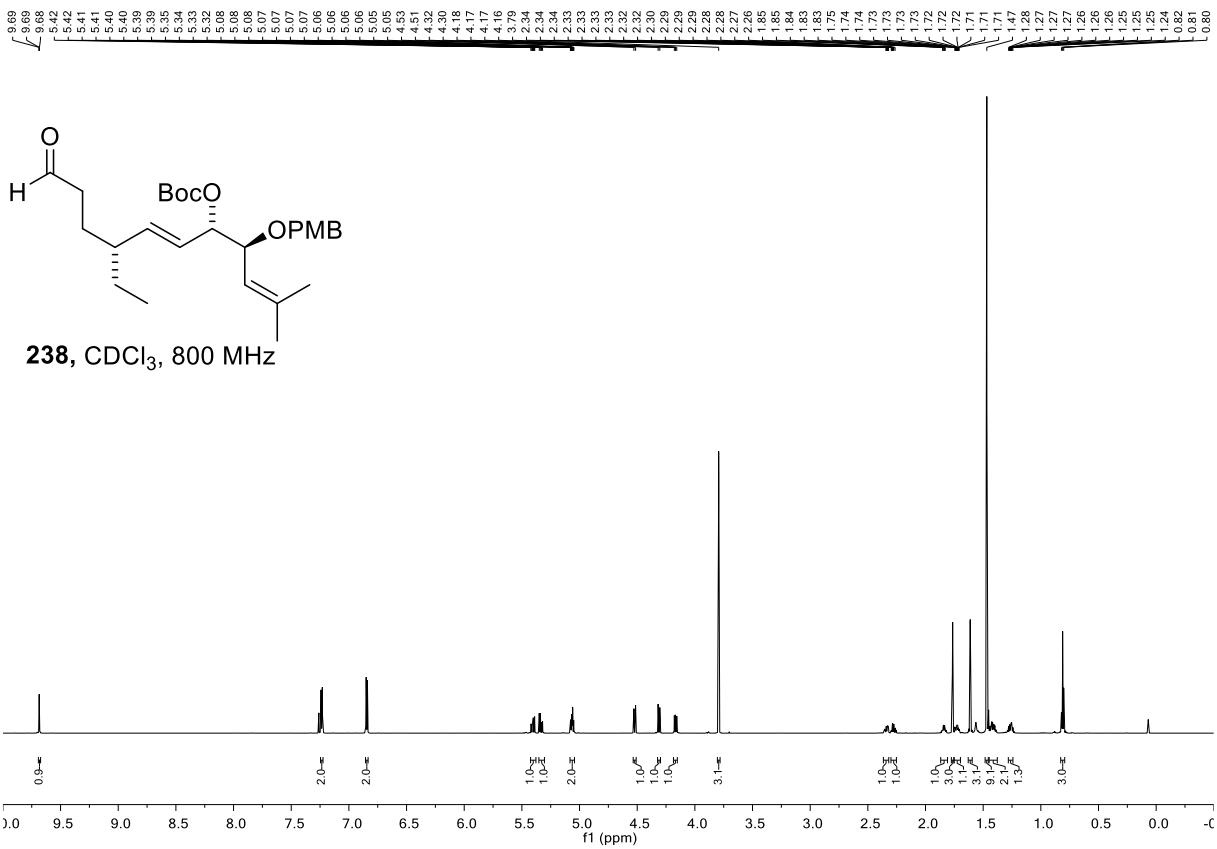
270, $CDCl_3$, 200 MHz



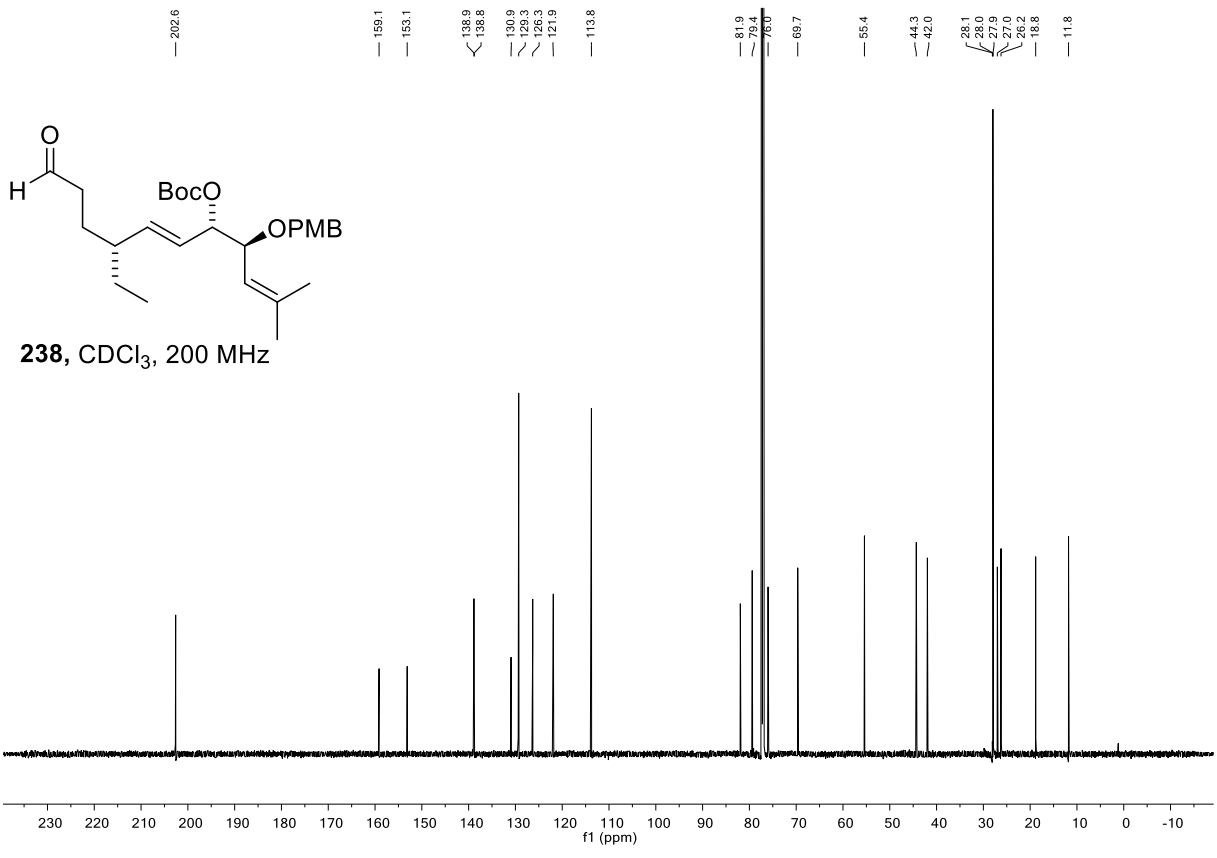
247, $CDCl_3$, 400 MHz



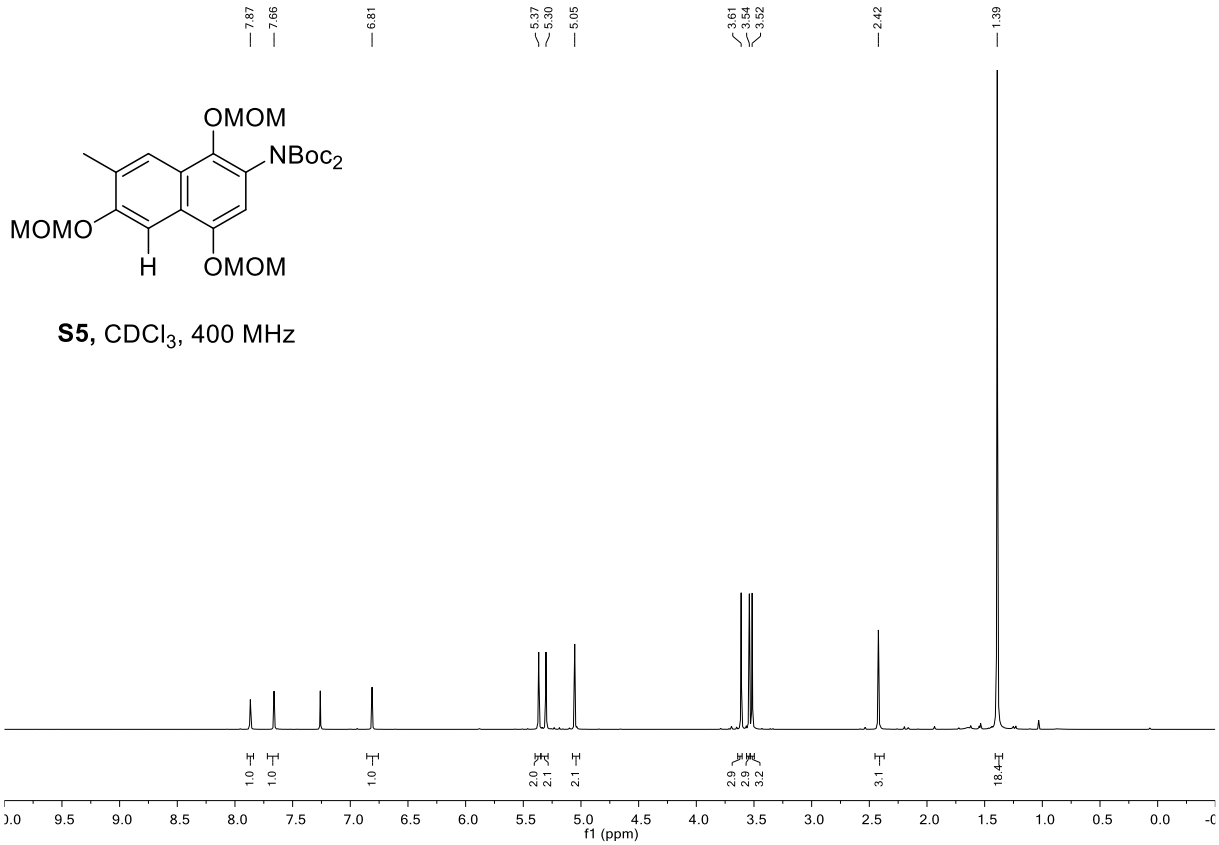
247, $CDCl_3$, 100 MHz



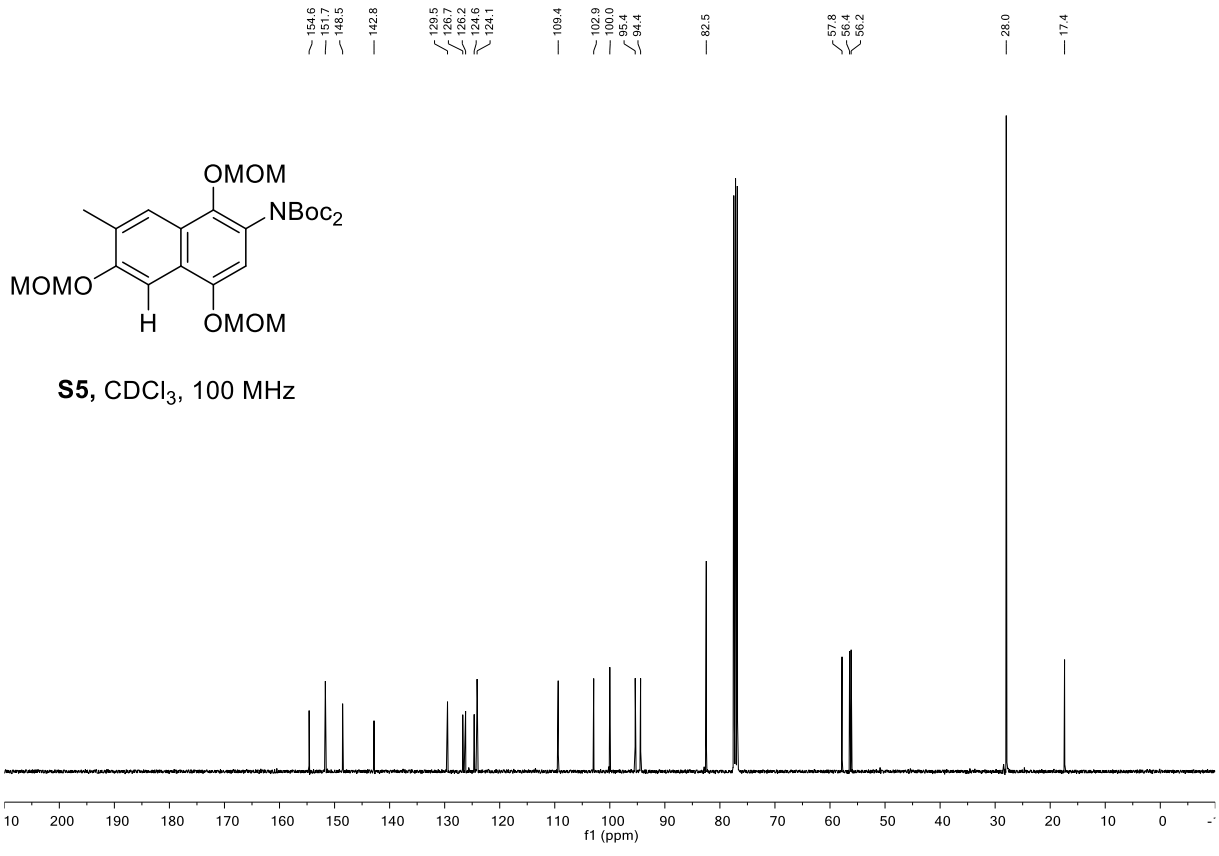
238, $CDCl_3$, 800 MHz



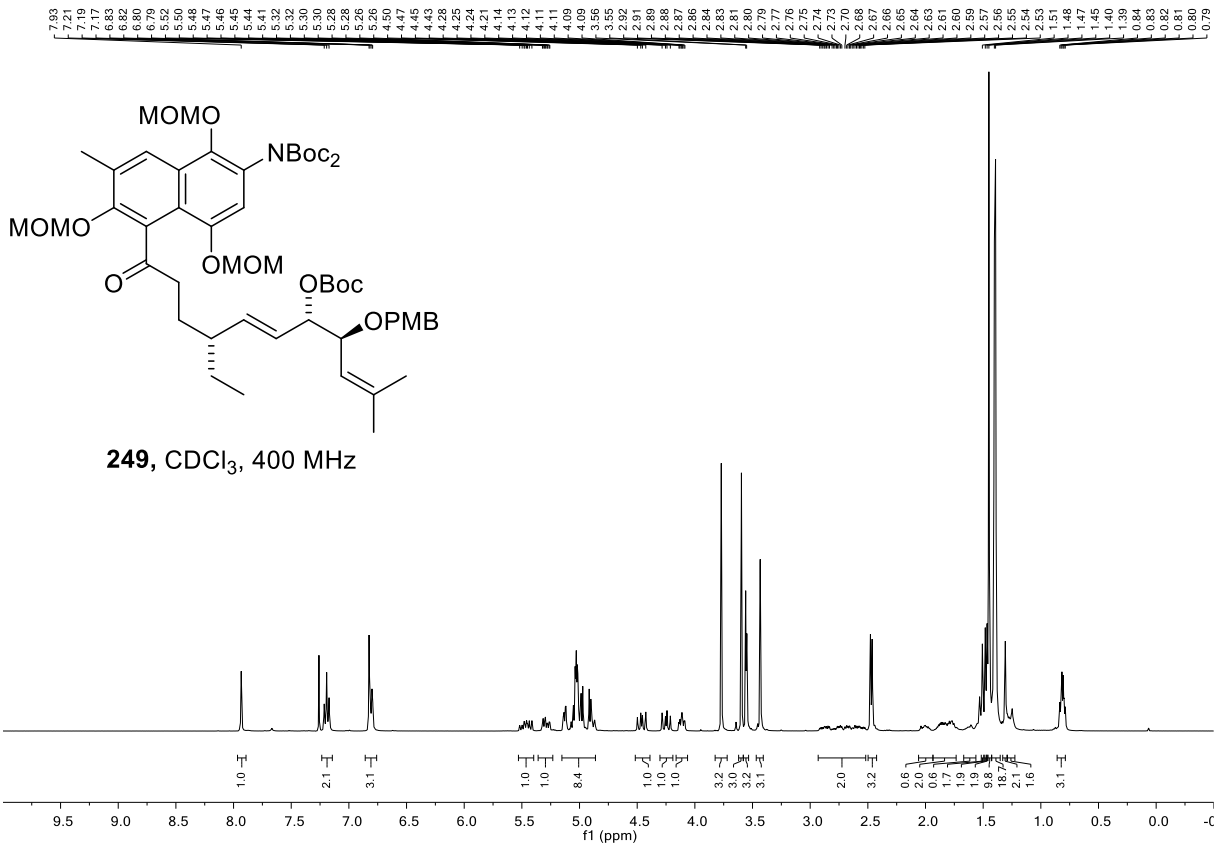
238, $CDCl_3$, 200 MHz



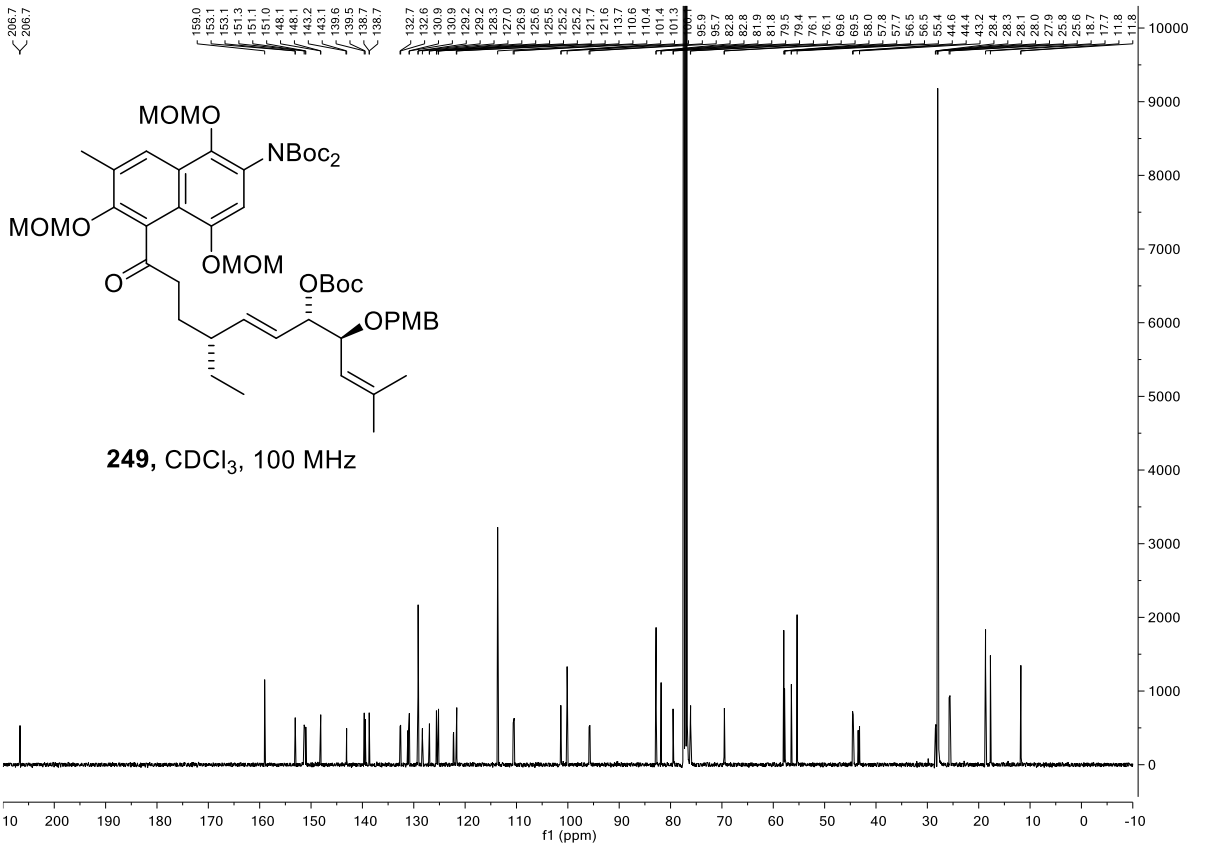
S5, $CDCl_3$, 400 MHz



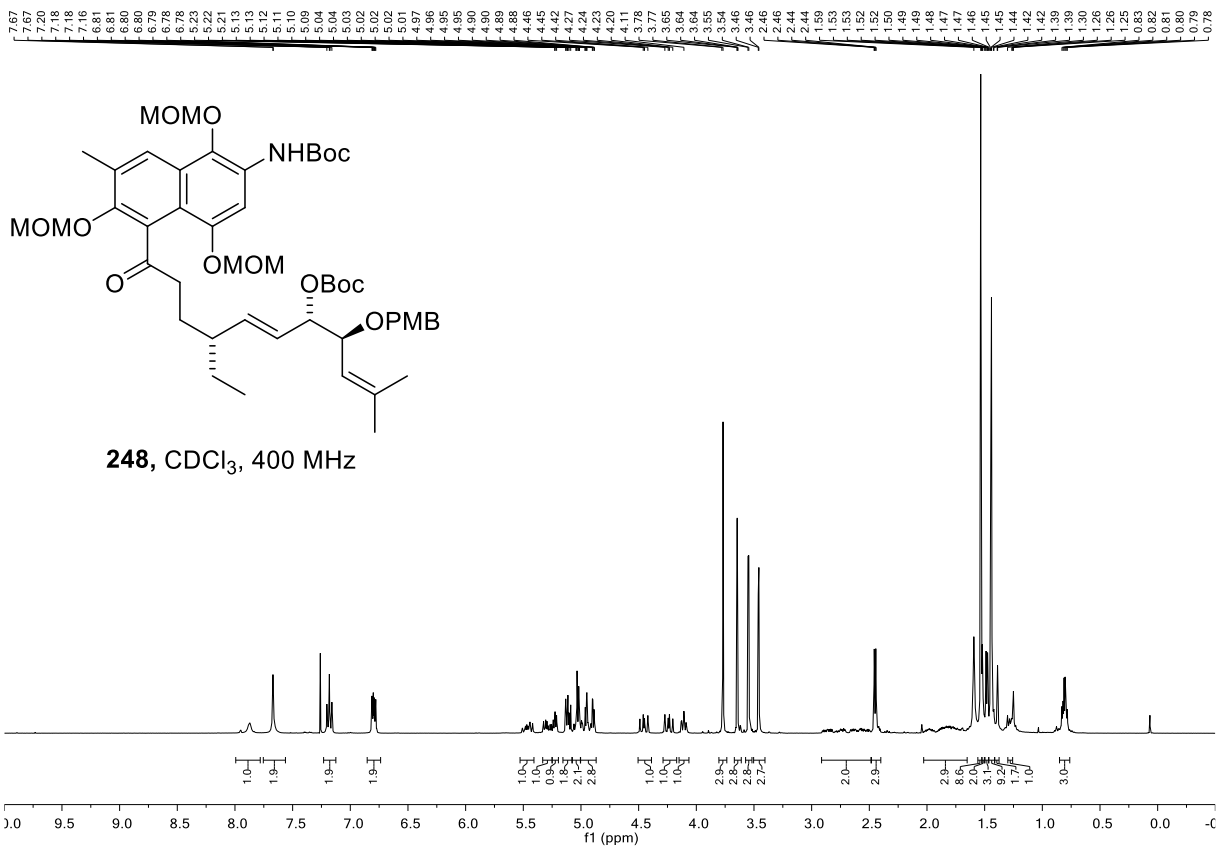
S5, $CDCl_3$, 100 MHz



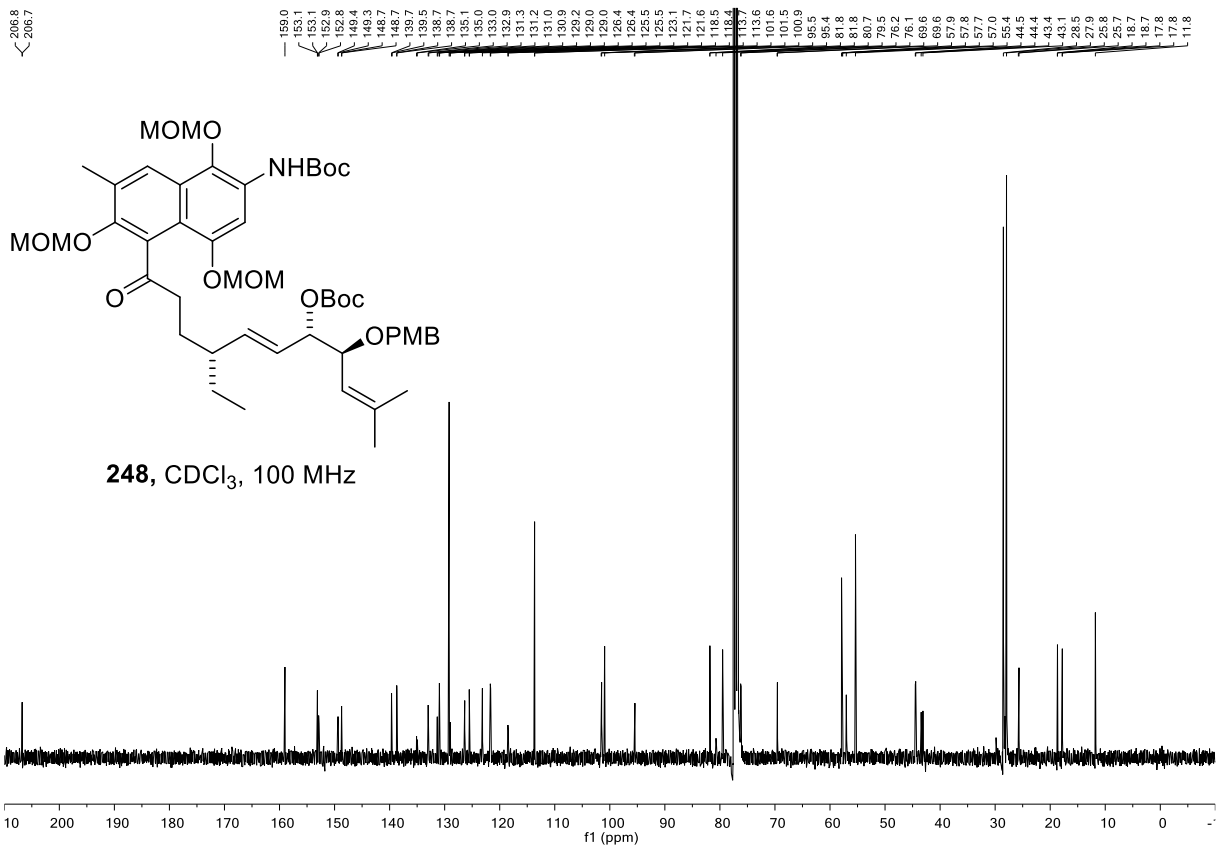
249, $CDCl_3$, 400 MHz



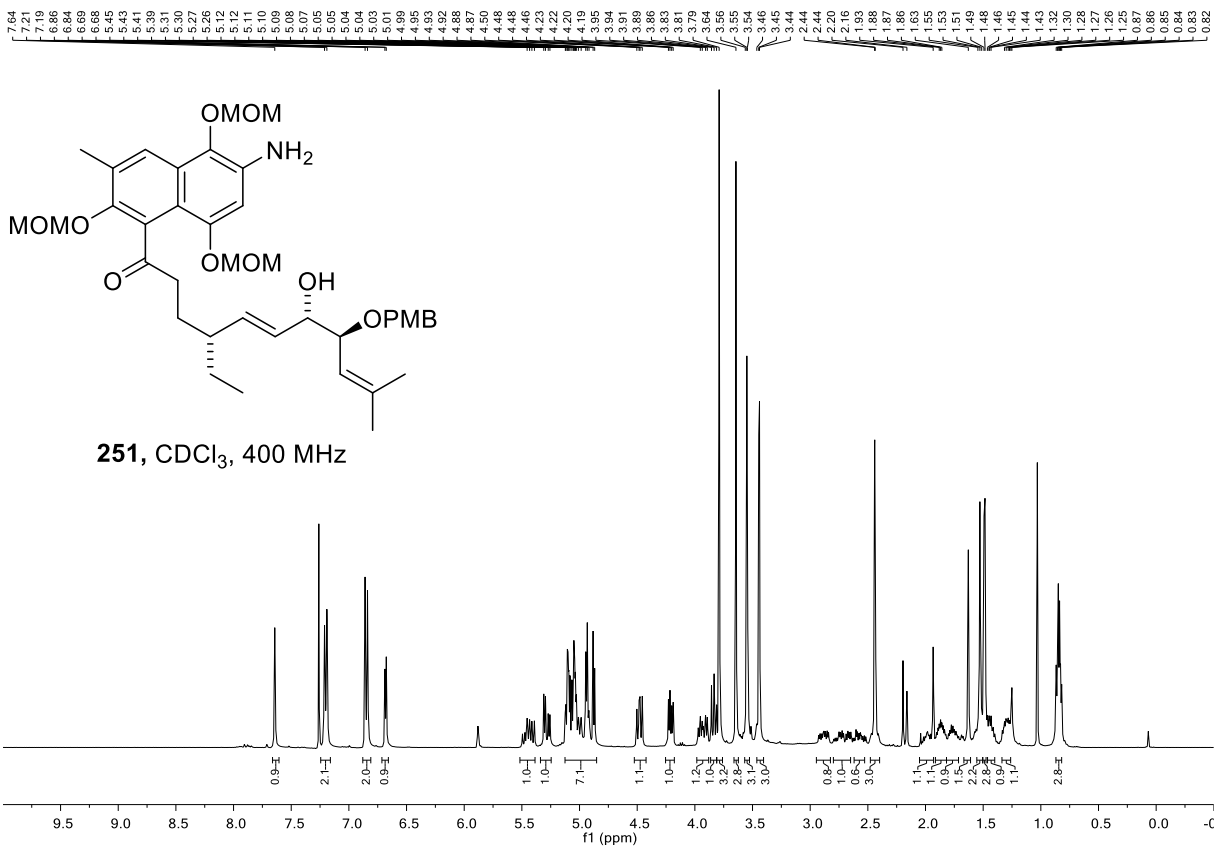
249, $CDCl_3$, 100 MHz



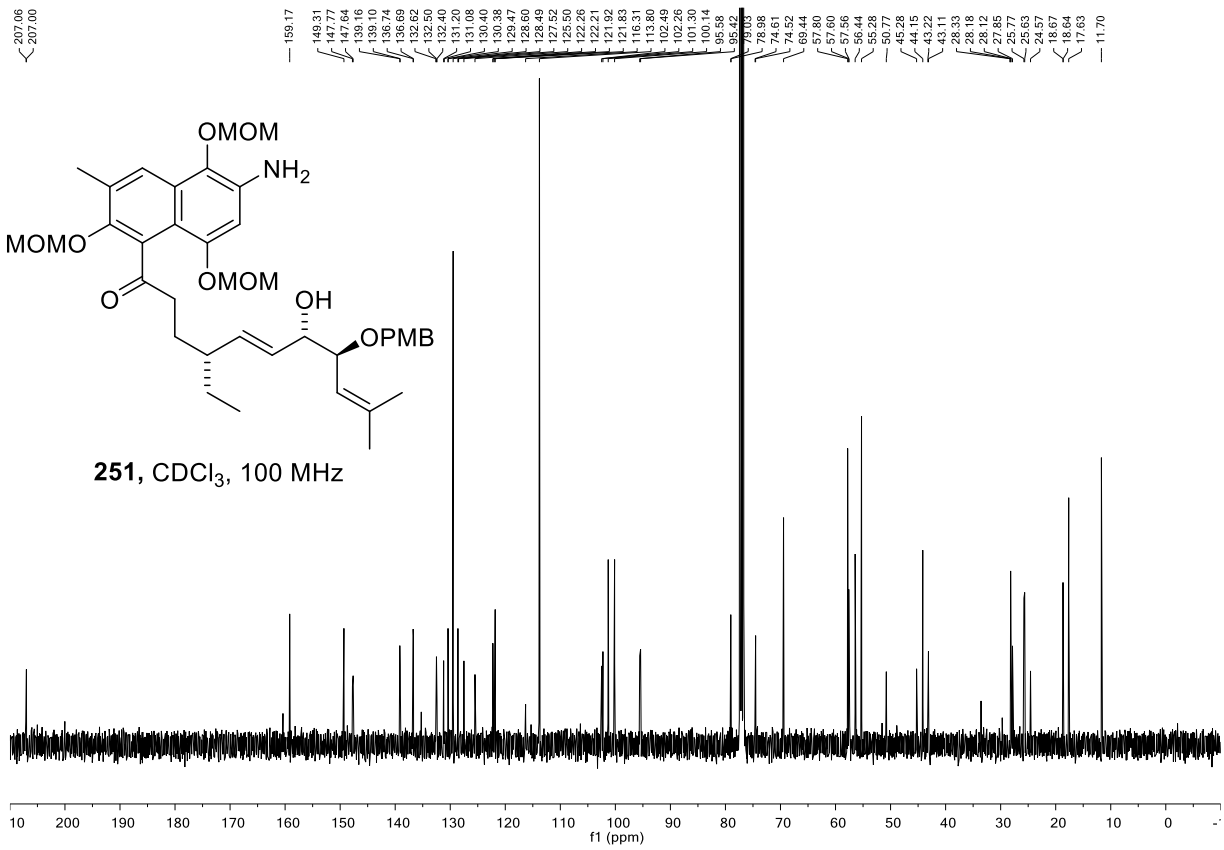
248, $CDCl_3$, 400 MHz



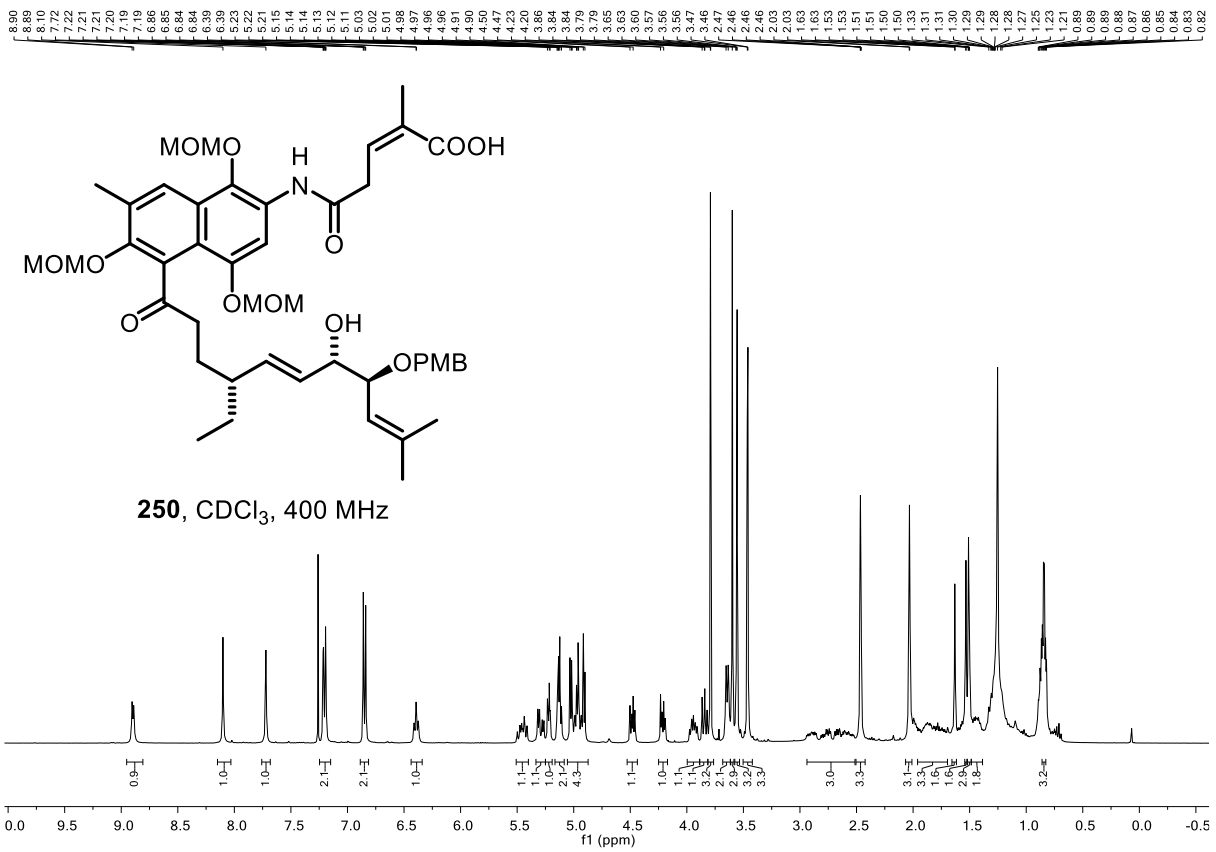
248, $CDCl_3$, 100 MHz



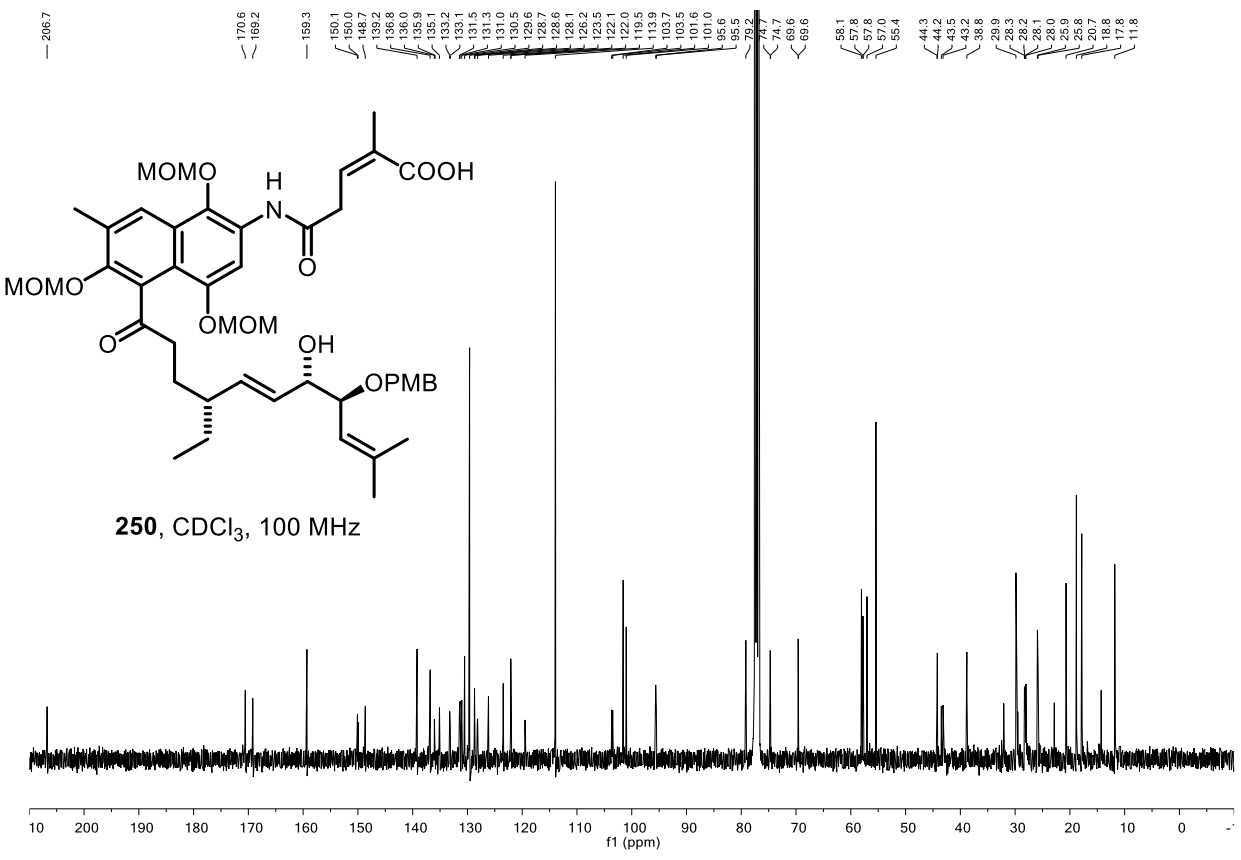
251, $CDCl_3$, 400 MHz



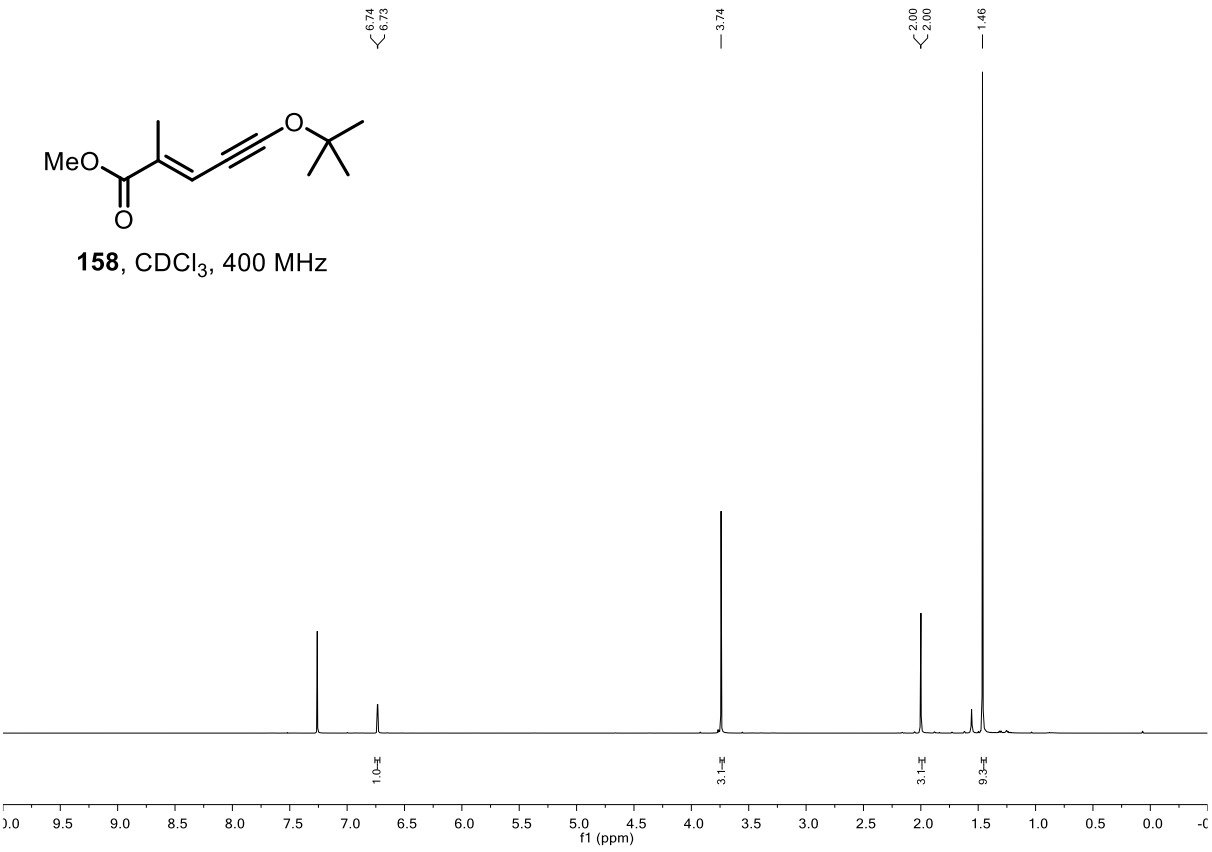
251, $CDCl_3$, 100 MHz



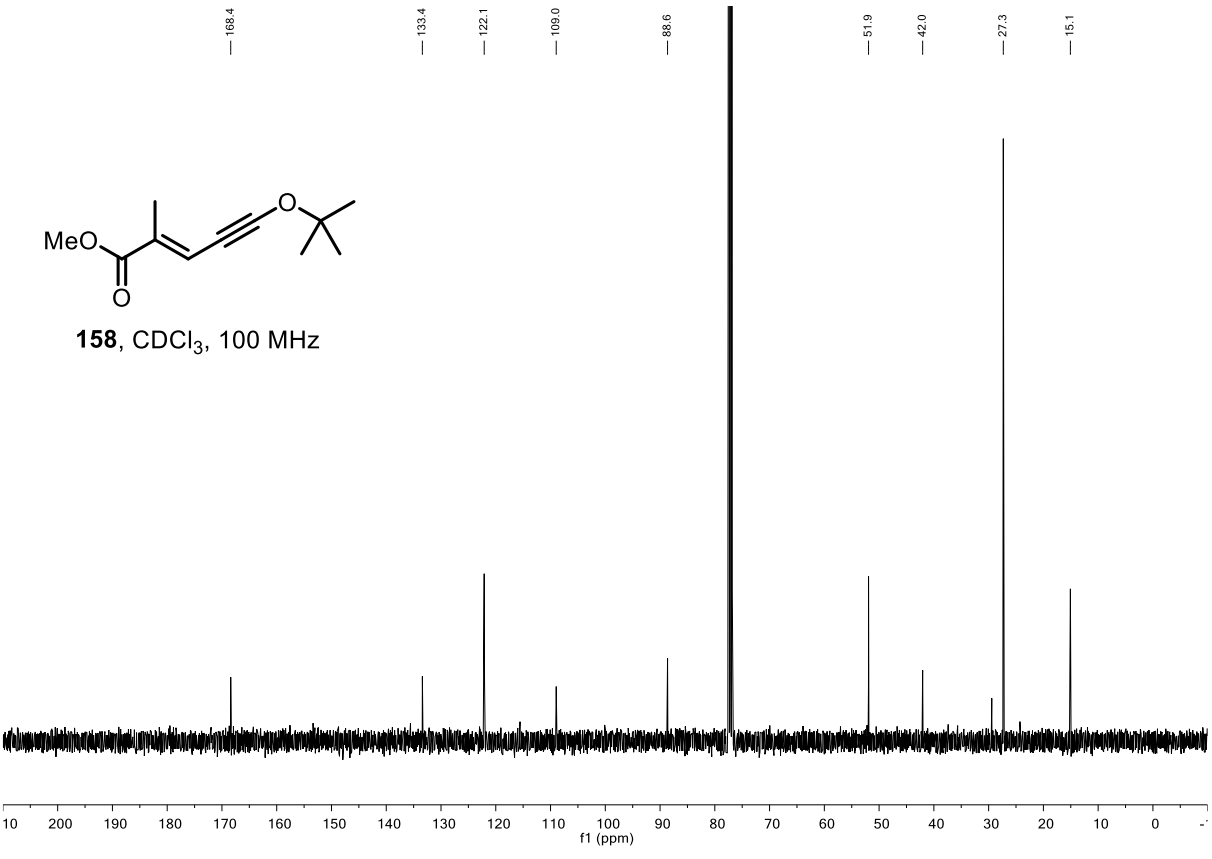
250, $CDCl_3$, 400 MHz



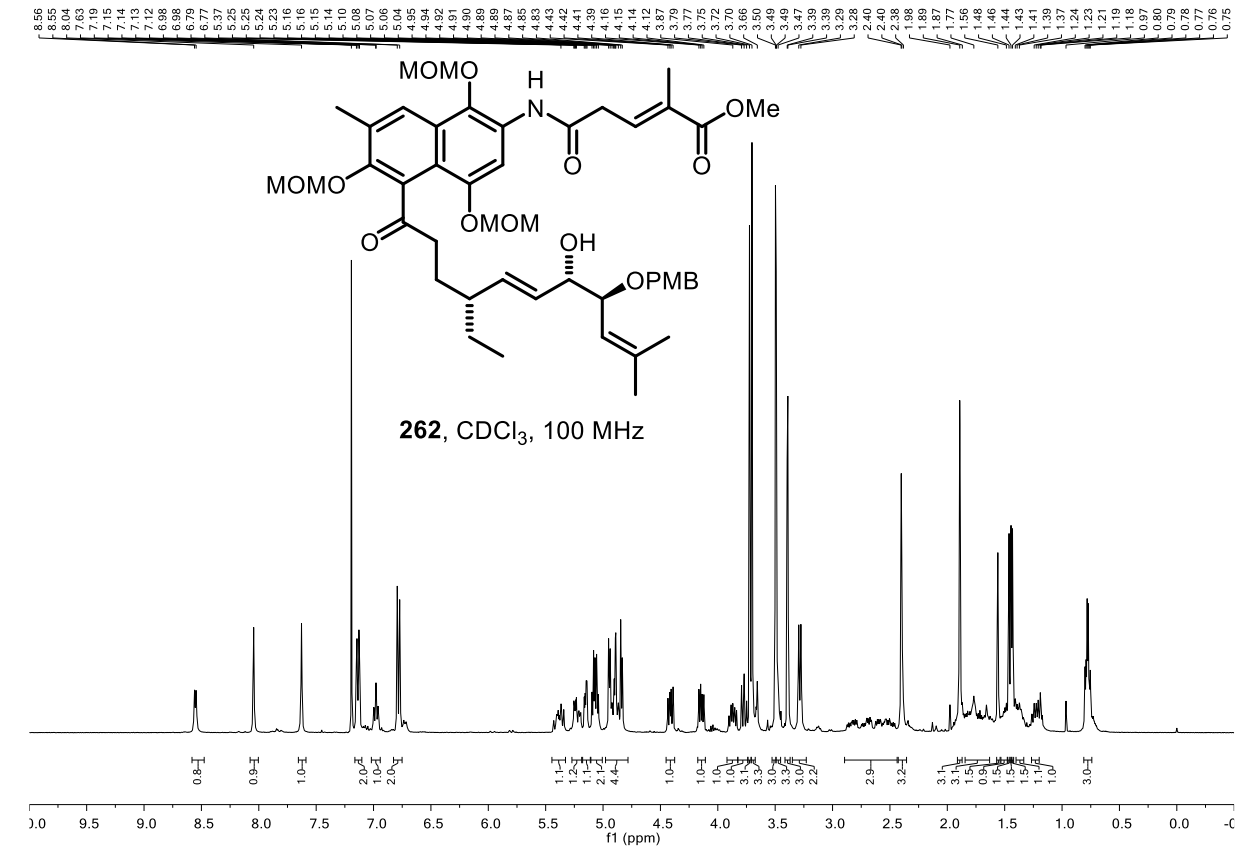
250, $CDCl_3$, 100 MHz



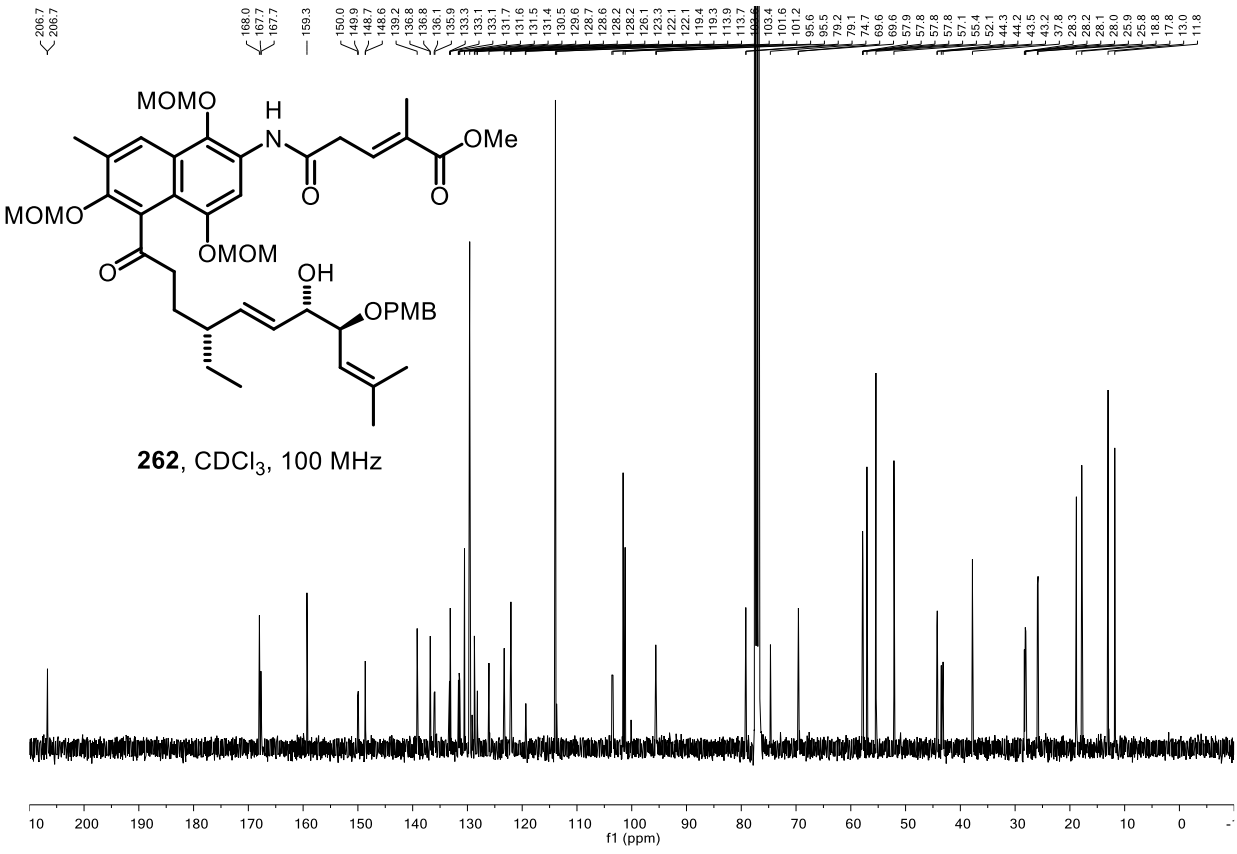
158, $CDCl_3$, 400 MHz



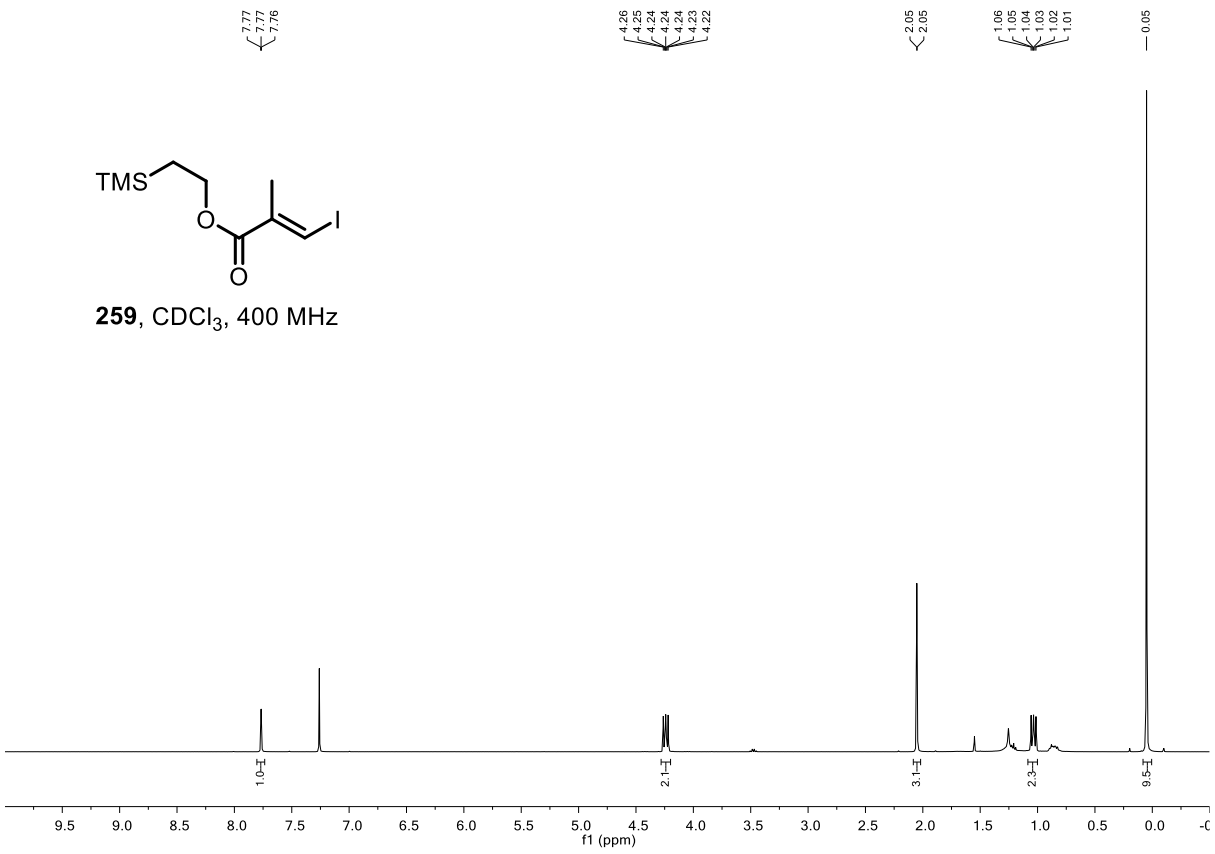
158, $CDCl_3$, 100 MHz



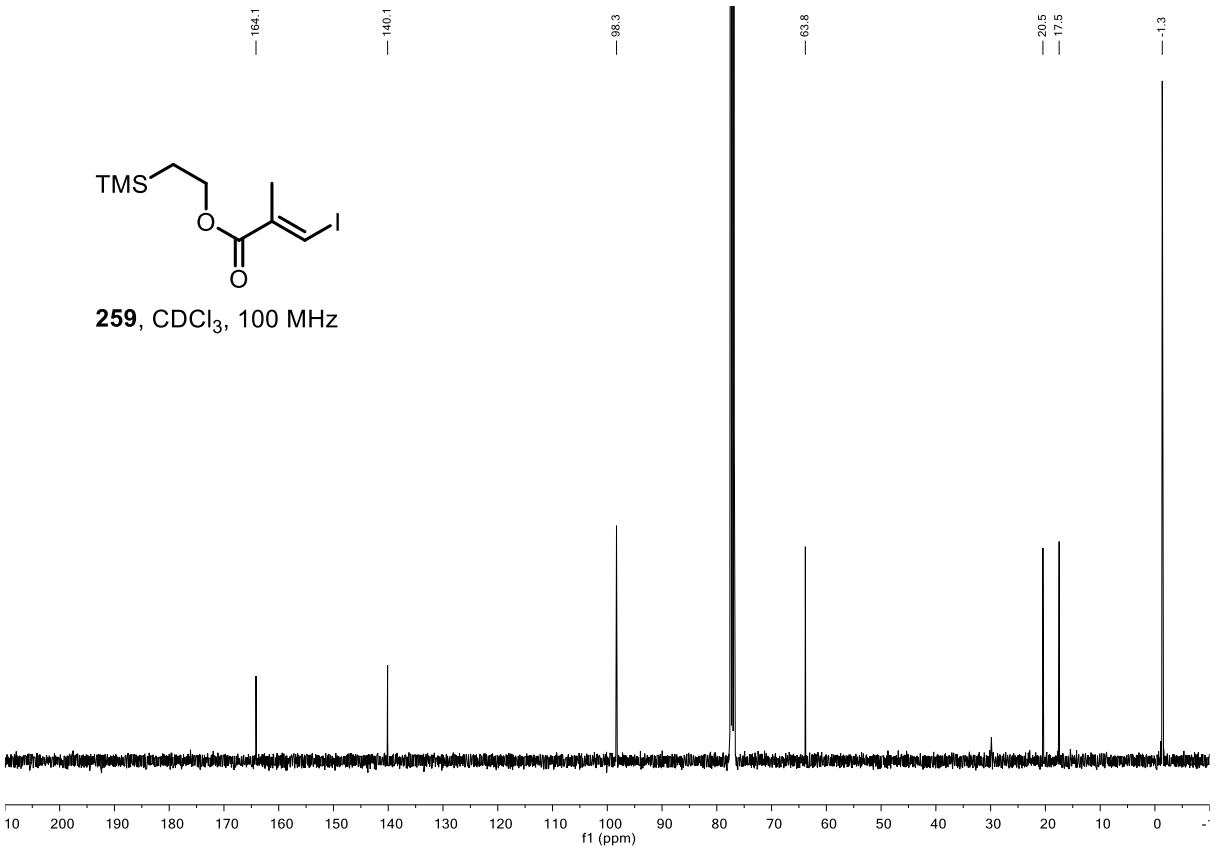
262, $CDCl_3$, 100 MHz



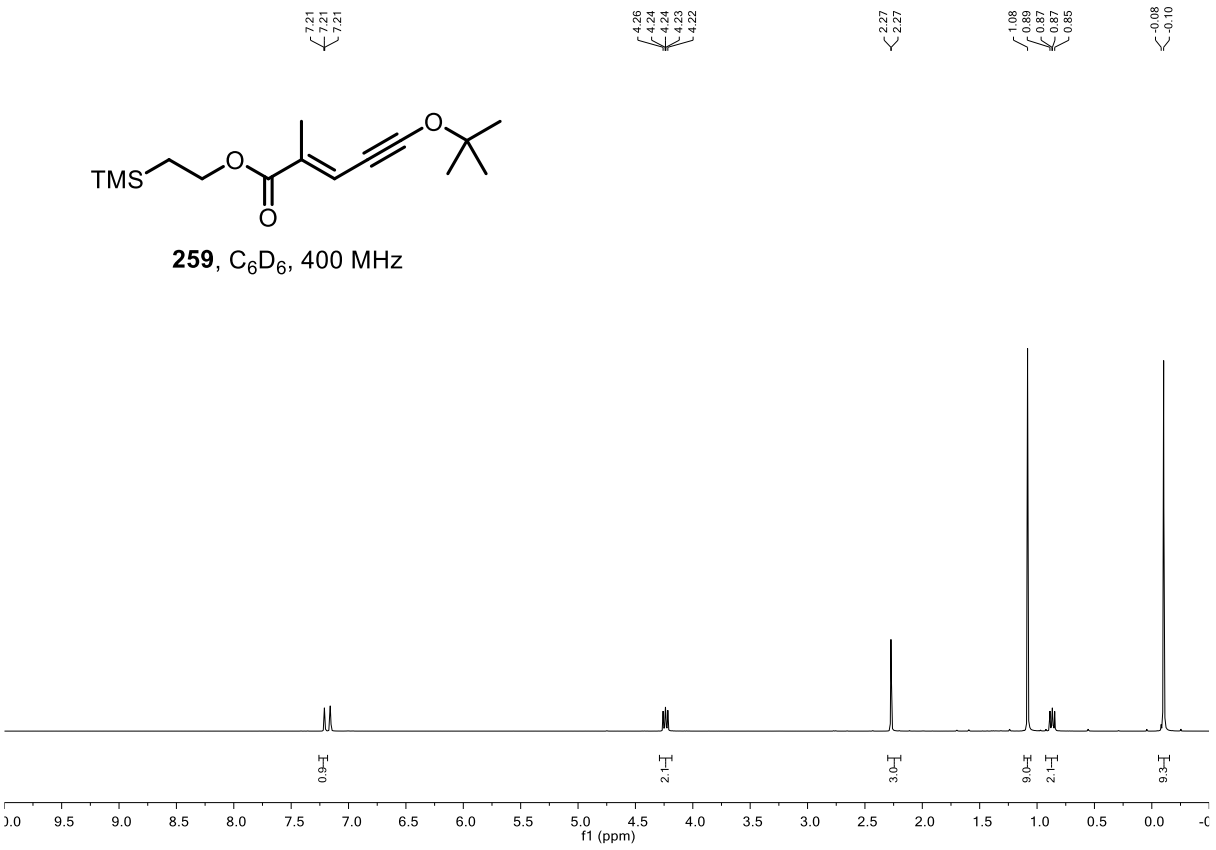
262, $CDCl_3$, 100 MHz



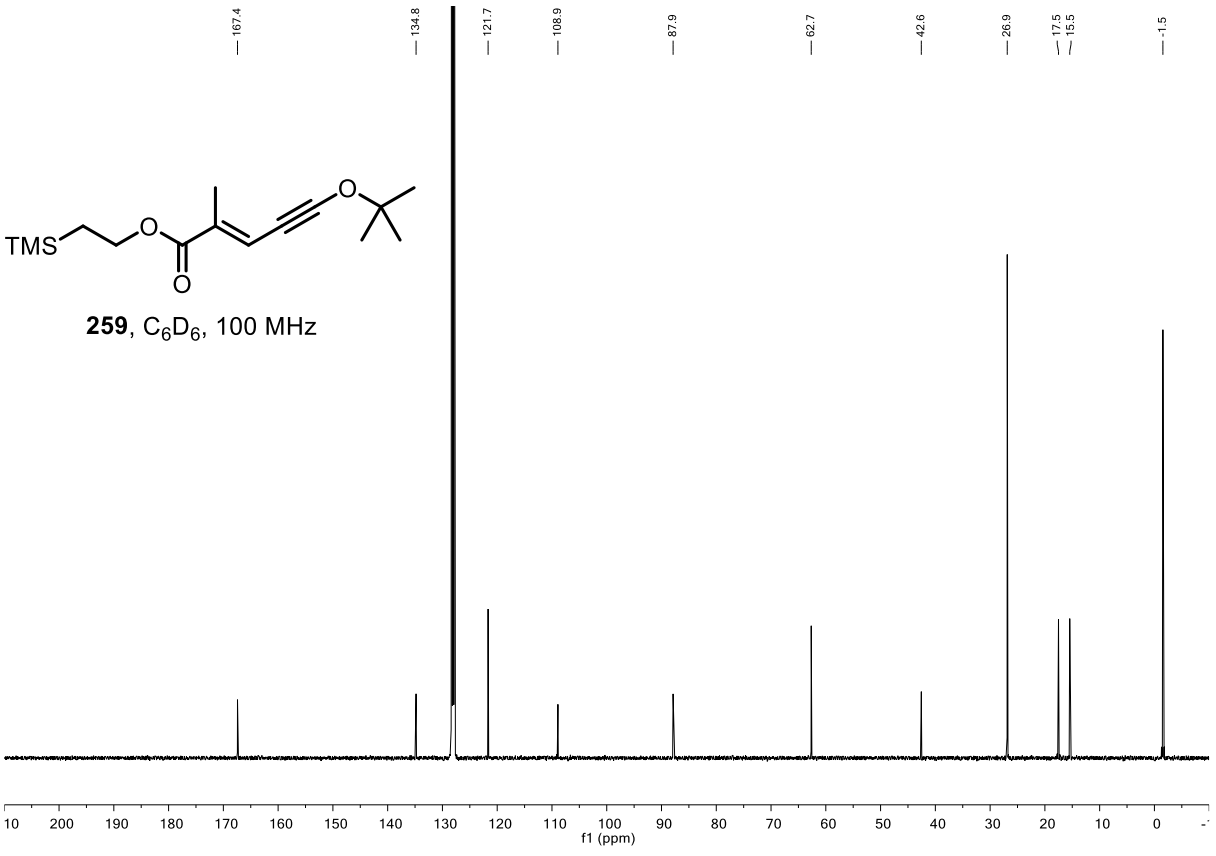
259, $CDCl_3$, 400 MHz



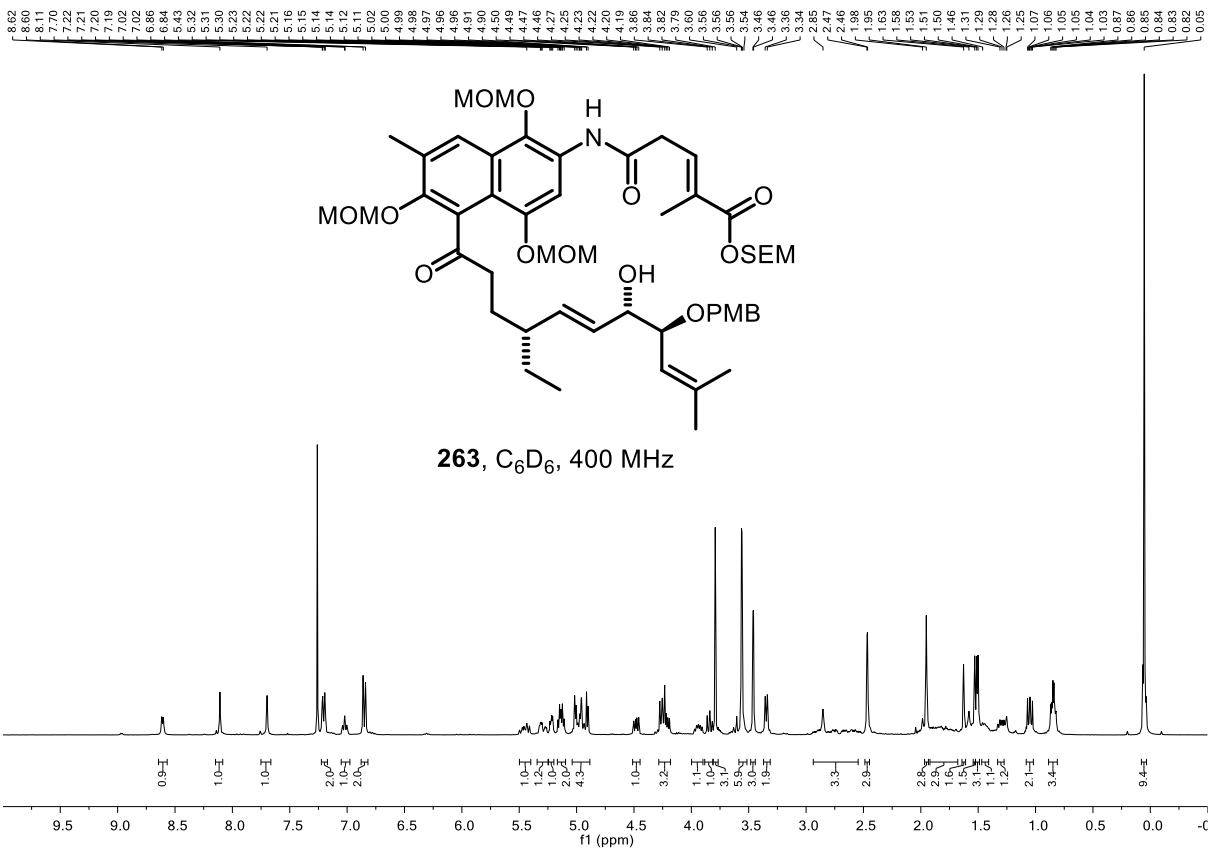
259, $CDCl_3$, 100 MHz



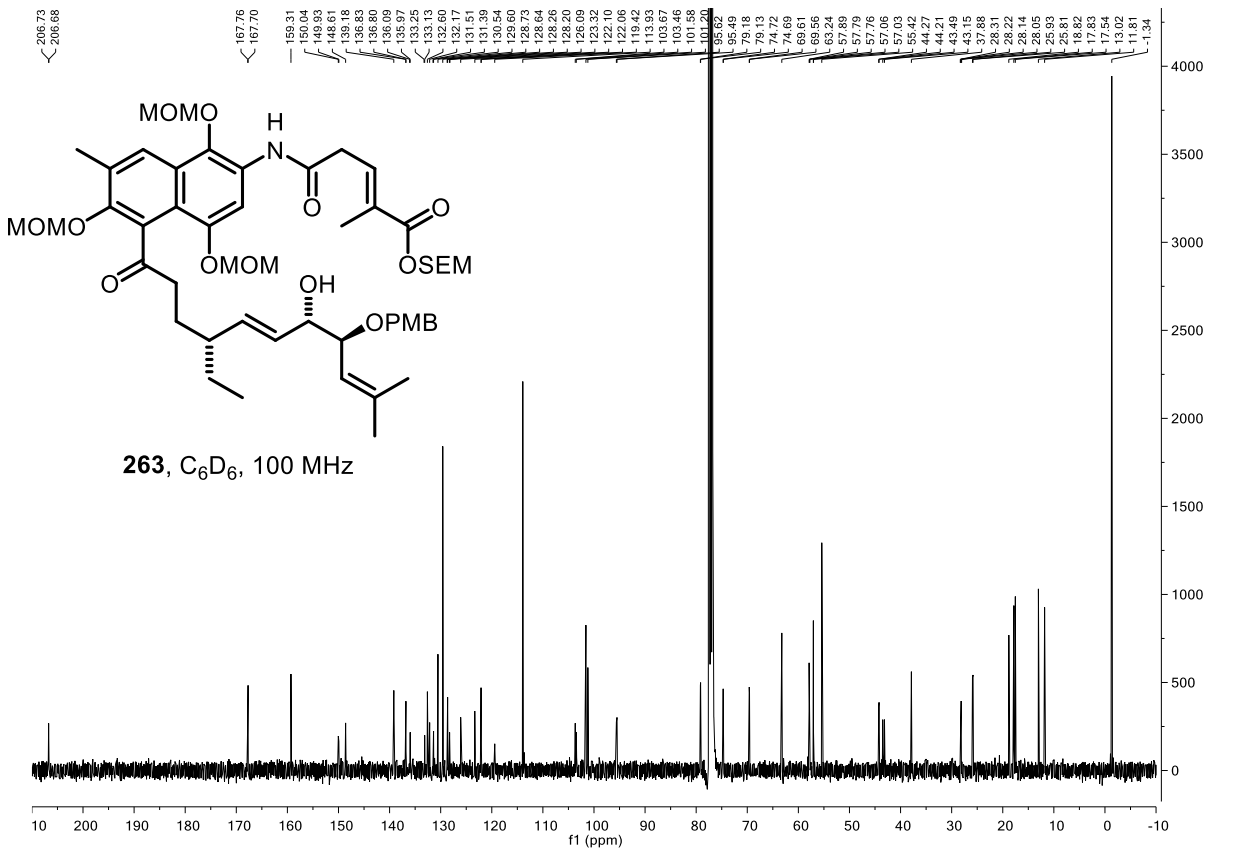
259, C_6D_6, 400 MHz



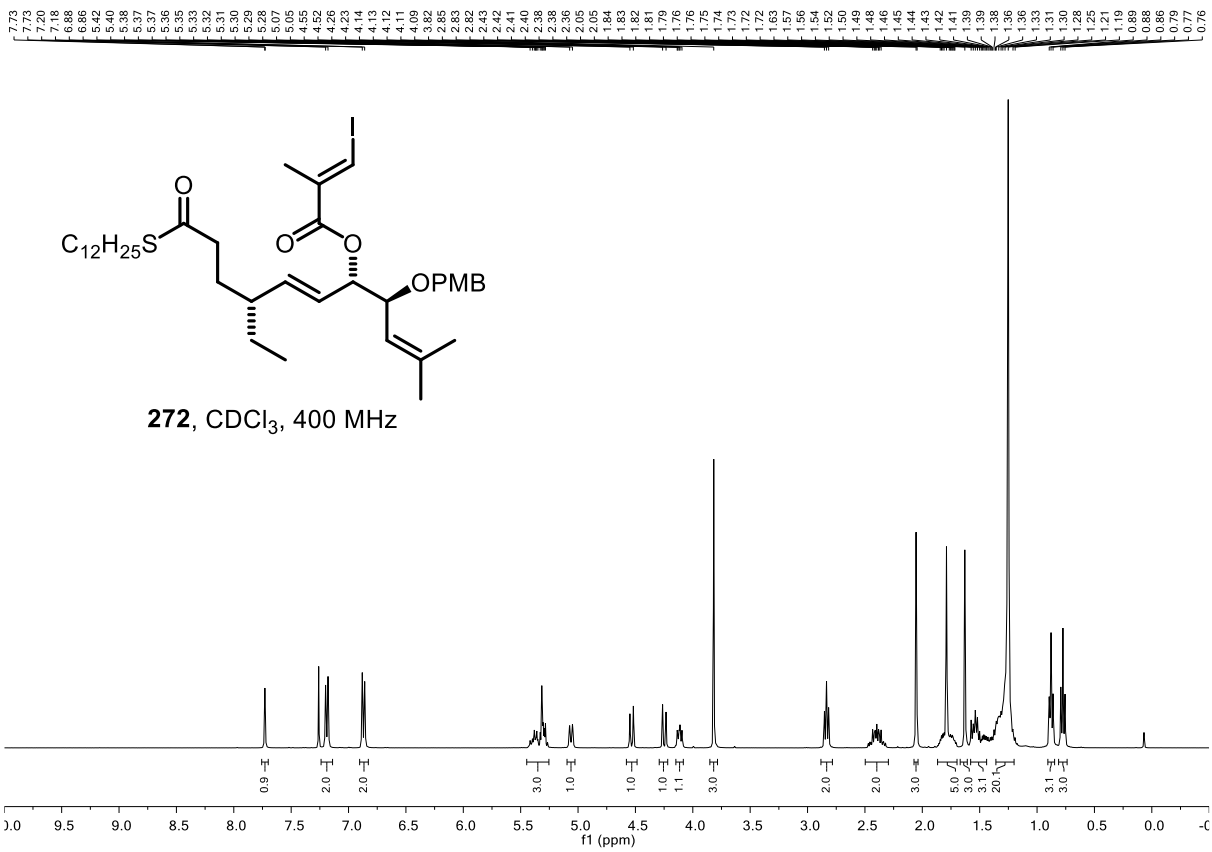
259, C_6D_6, 100 MHz



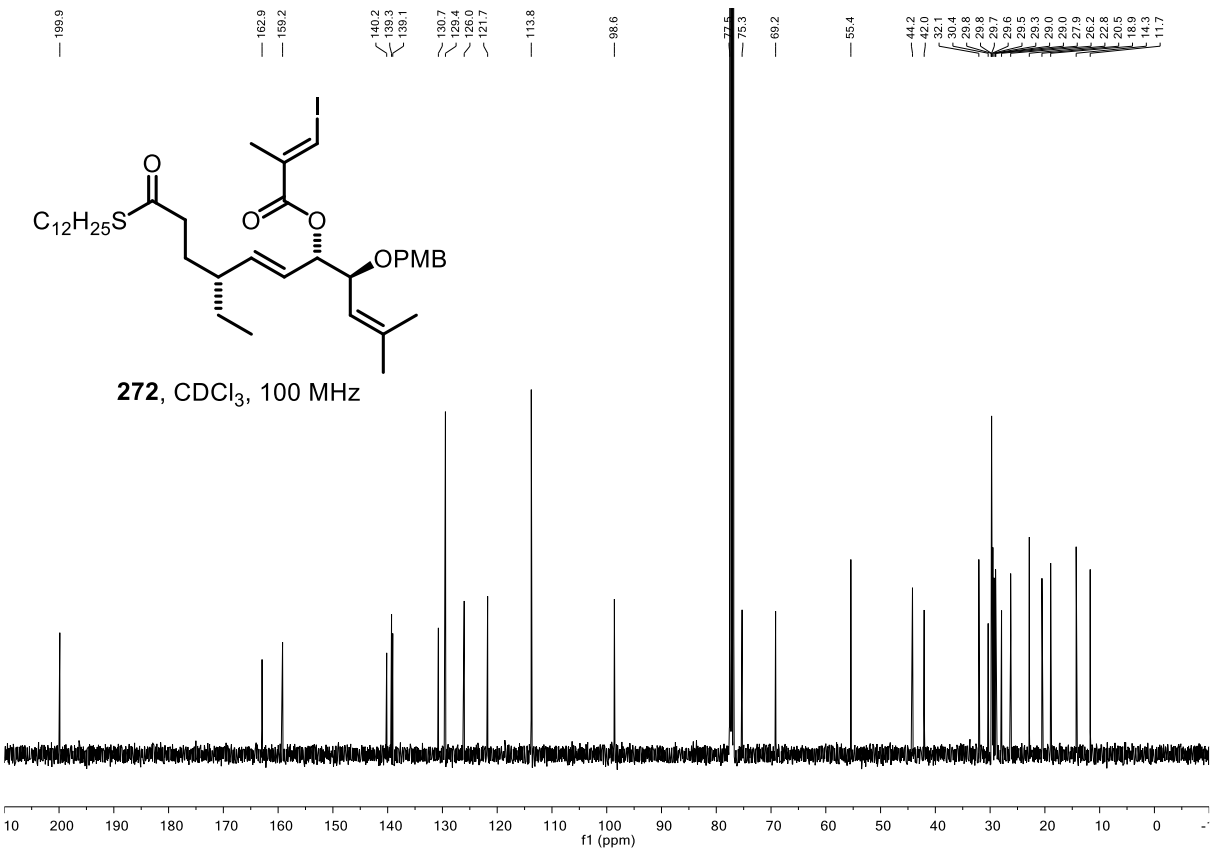
263, C_6D_6, 400 MHz



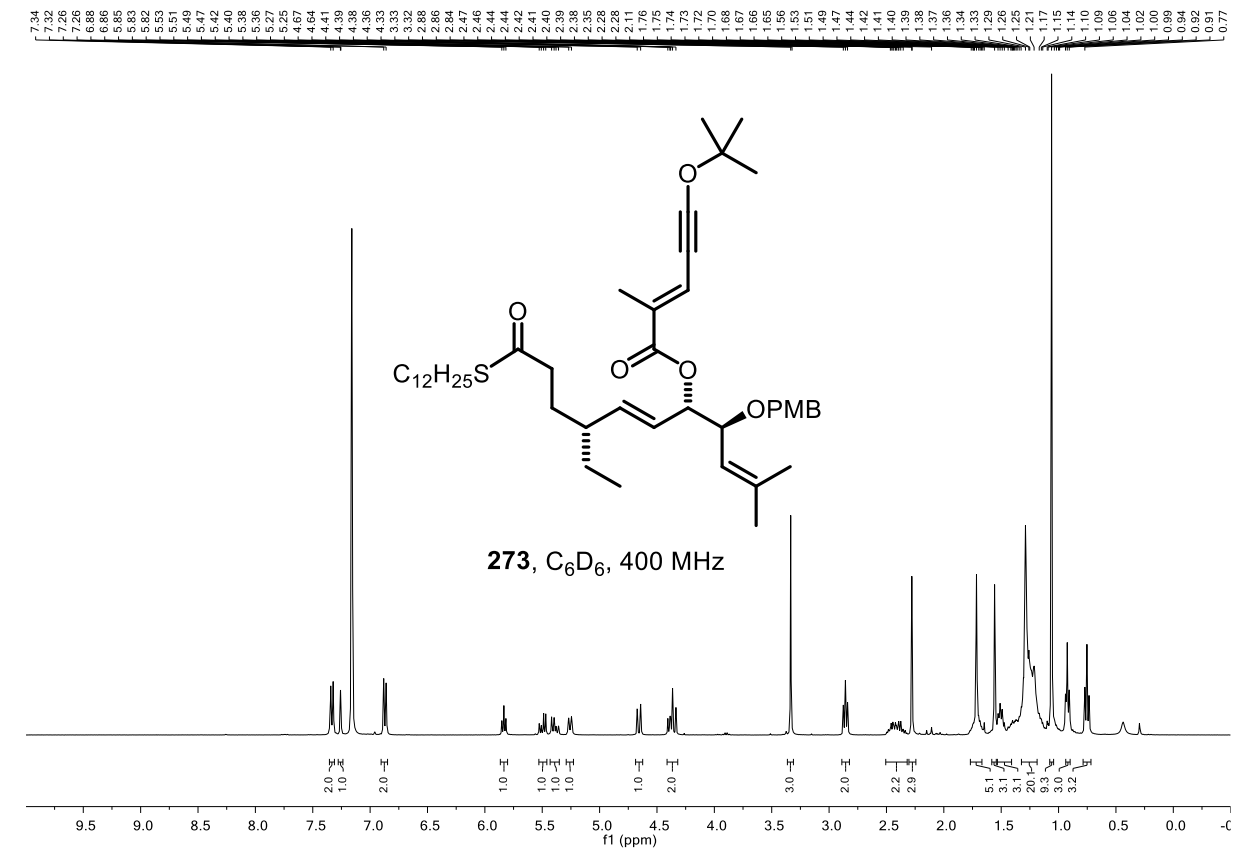
263, C_6D_6, 100 MHz

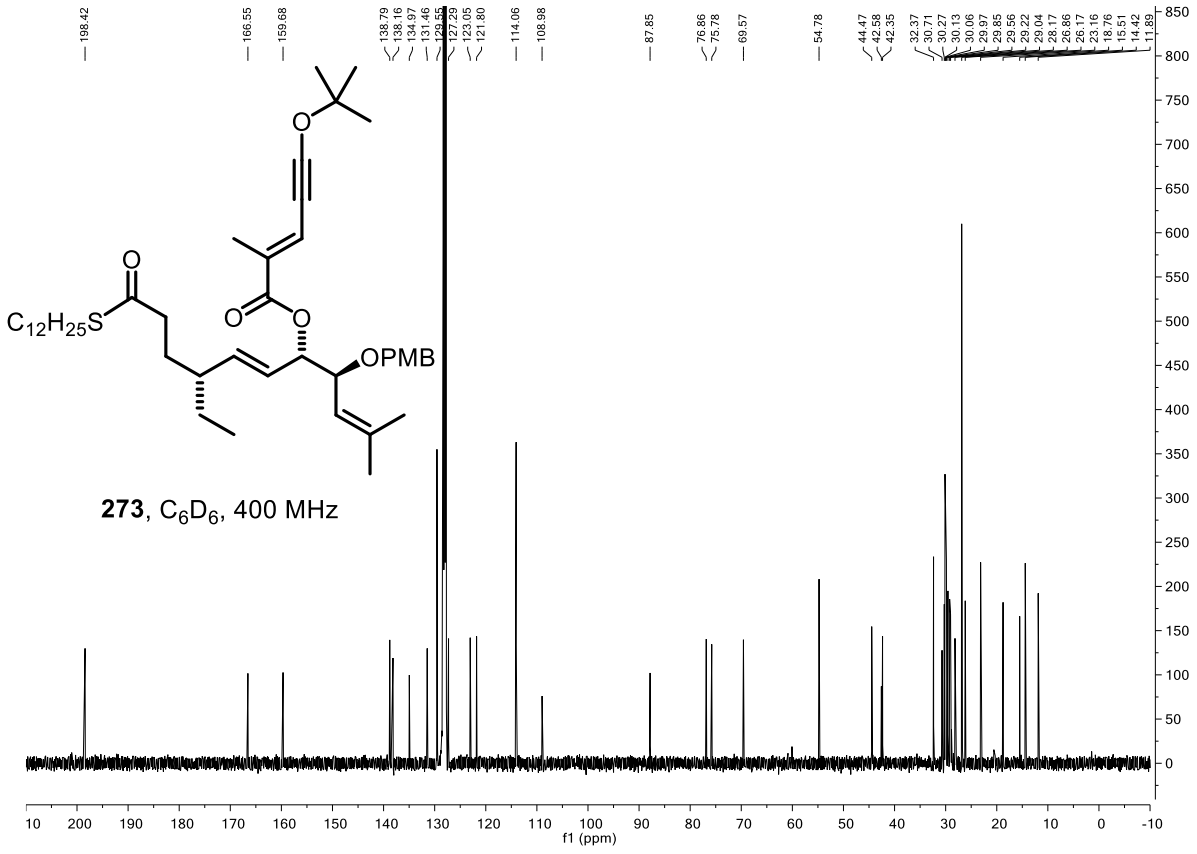


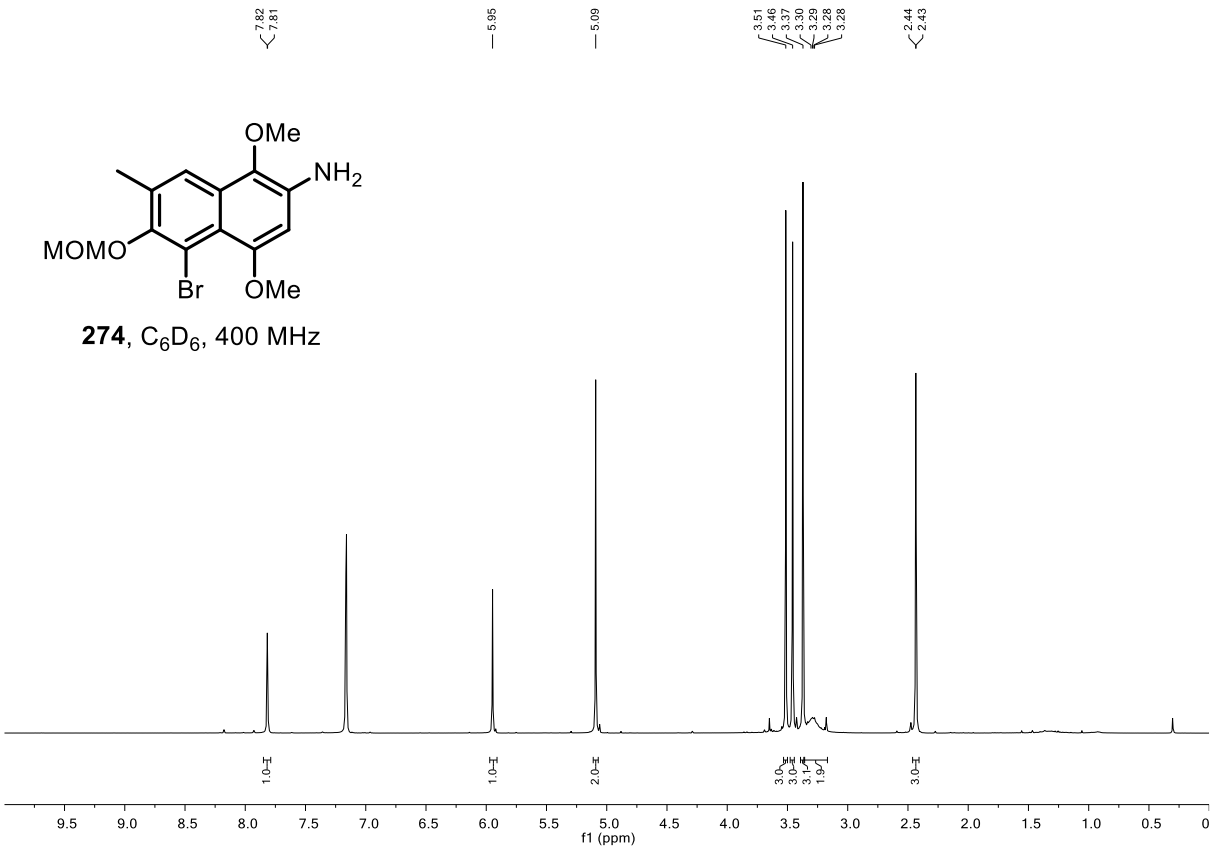
272, $CDCl_3$, 400 MHz



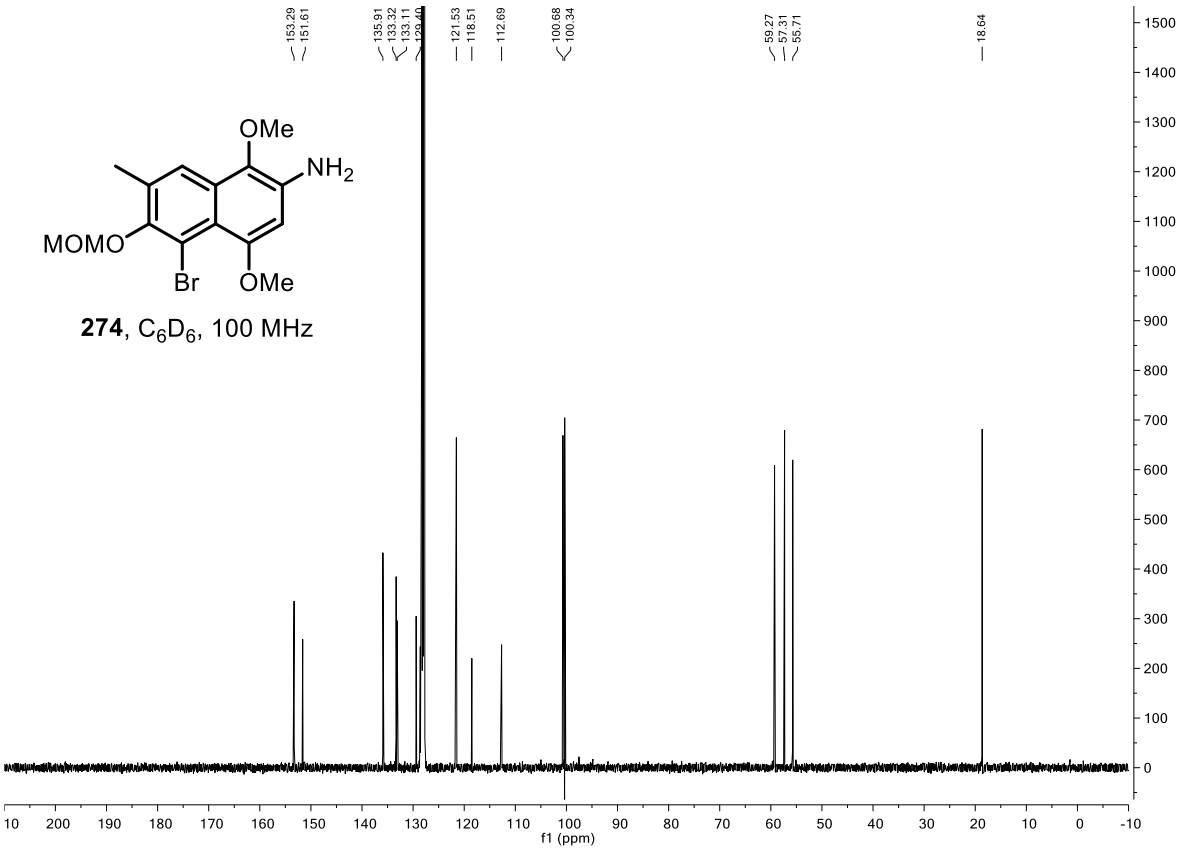
272, $CDCl_3$, 100 MHz


OPMB
273, C_6D_6, 400 MHz
f1 (ppm)

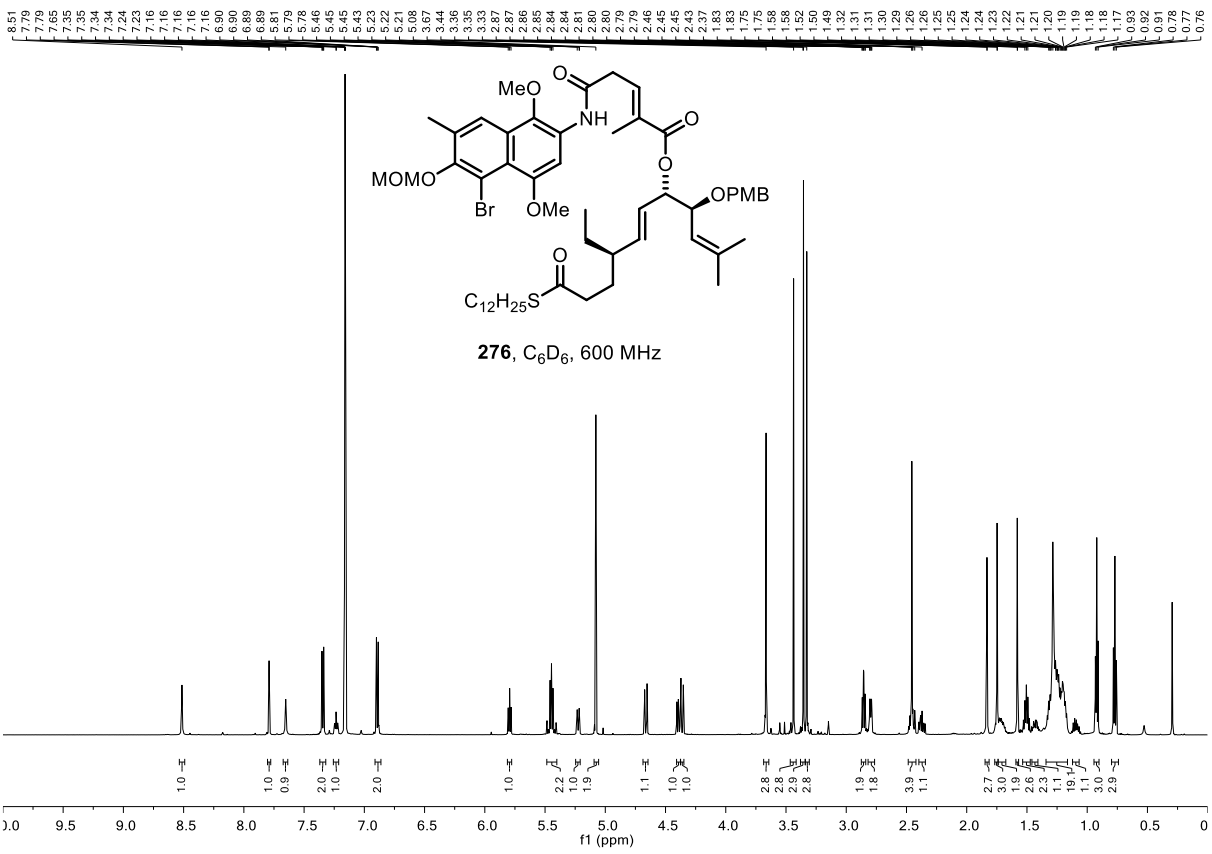

OPMB
273, C_6D_6, 400 MHz
f1 (ppm)

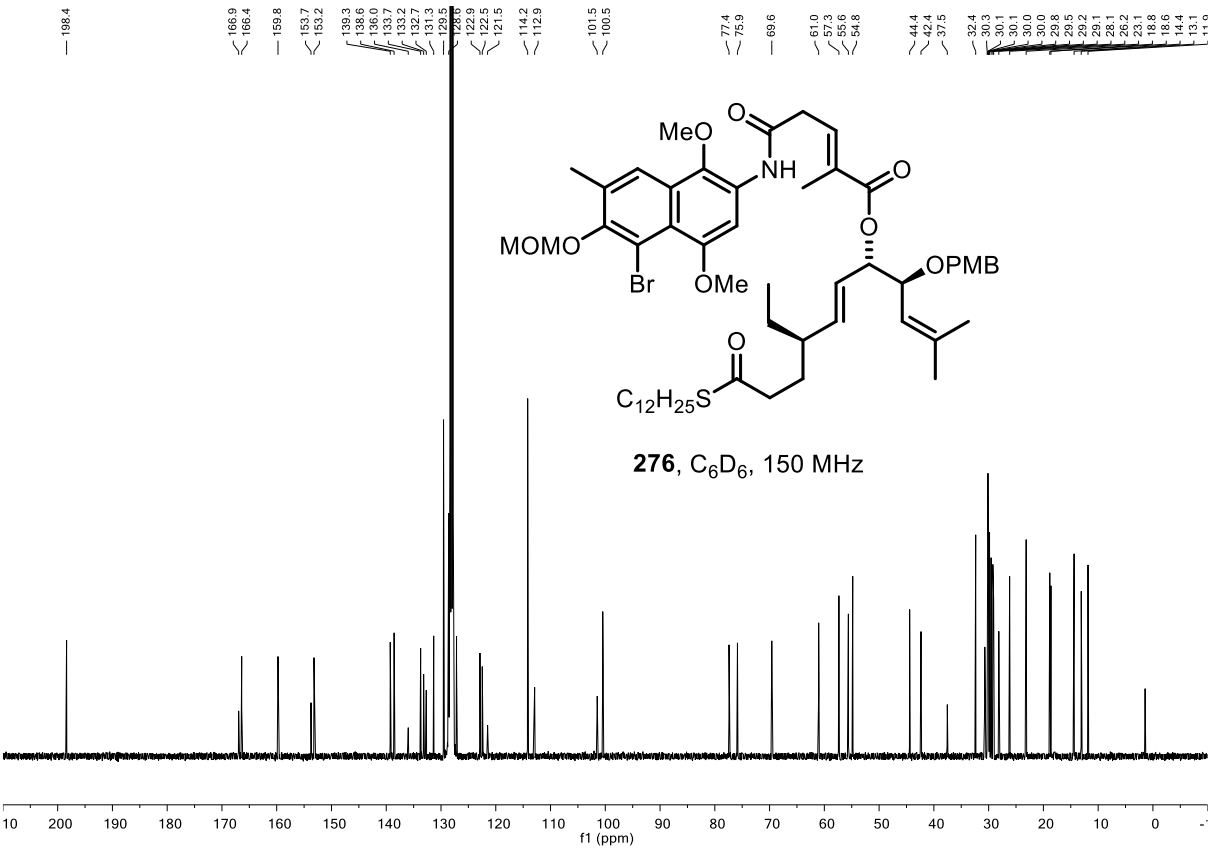


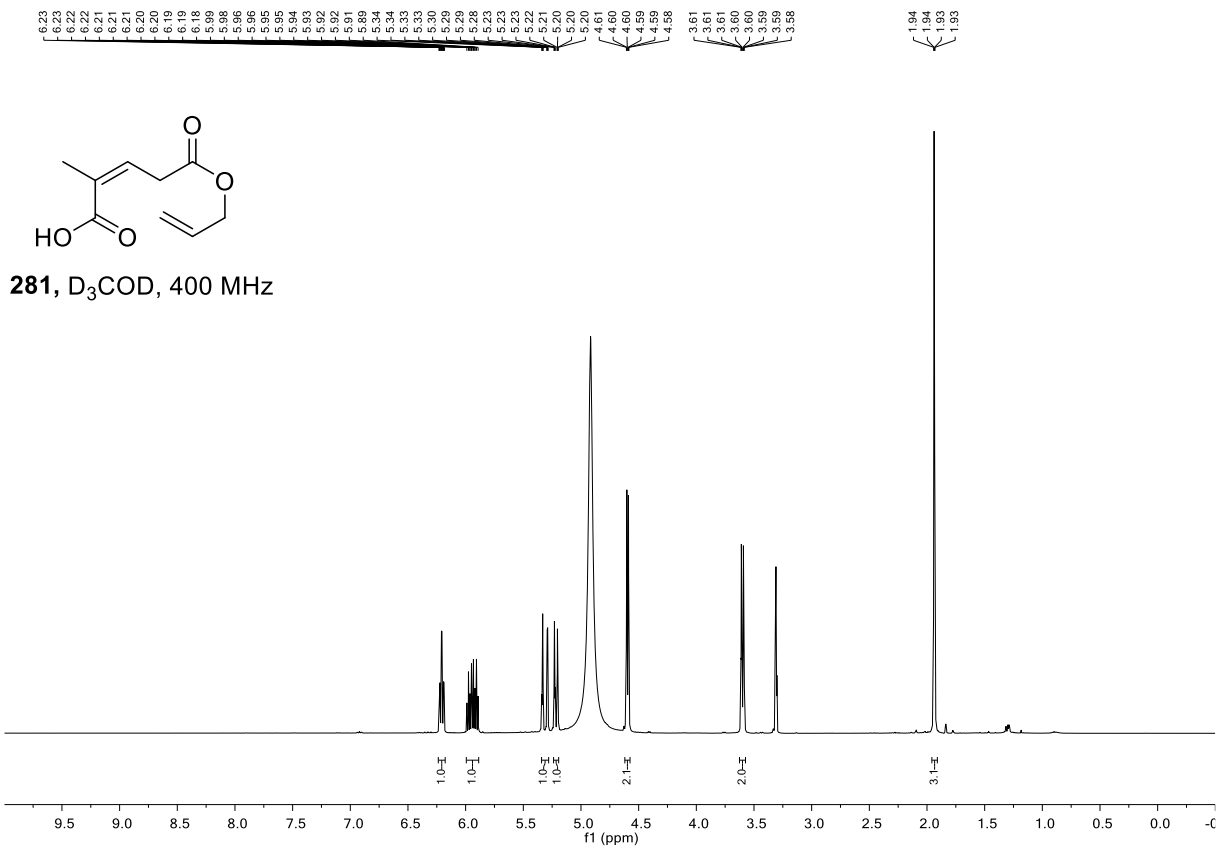
274, C_6D_6, 400 MHz



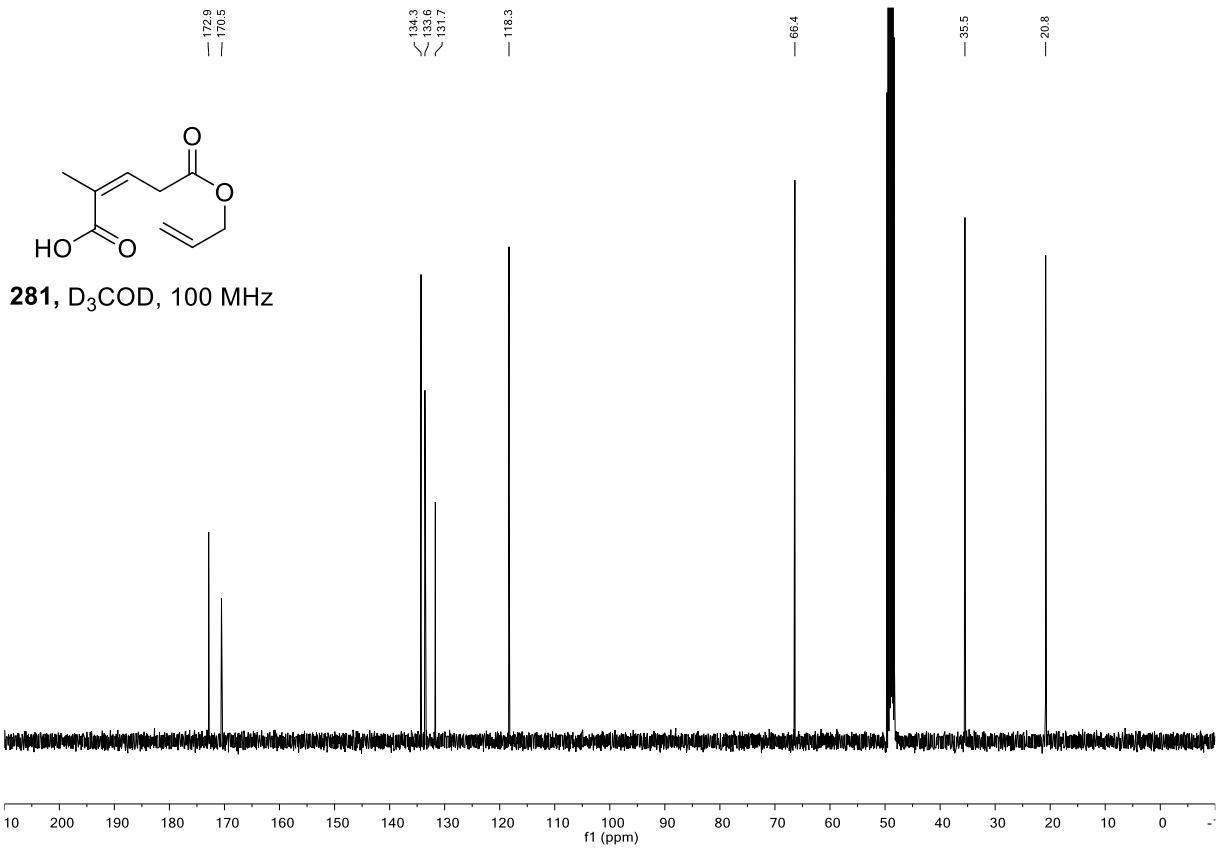
274, C_6D_6, 100 MHz


MeO
NH
MOMO
Br
OMe
OPMB
C12H25S
276, C6D6, 600 MHz
f1 (ppm)

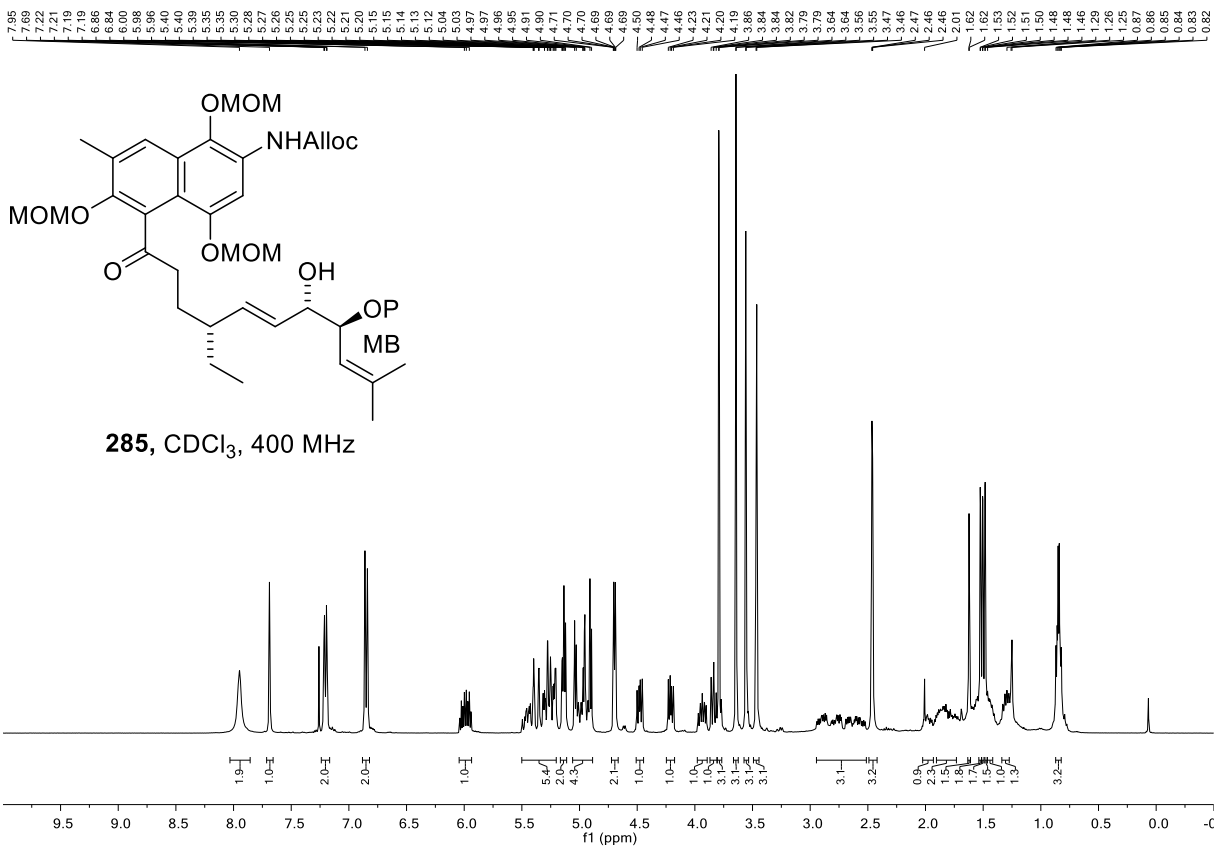

MeO
NH
MOMO
Br
OMe
OPMB
C12H25S
276, C6D6, 150 MHz
f1 (ppm)



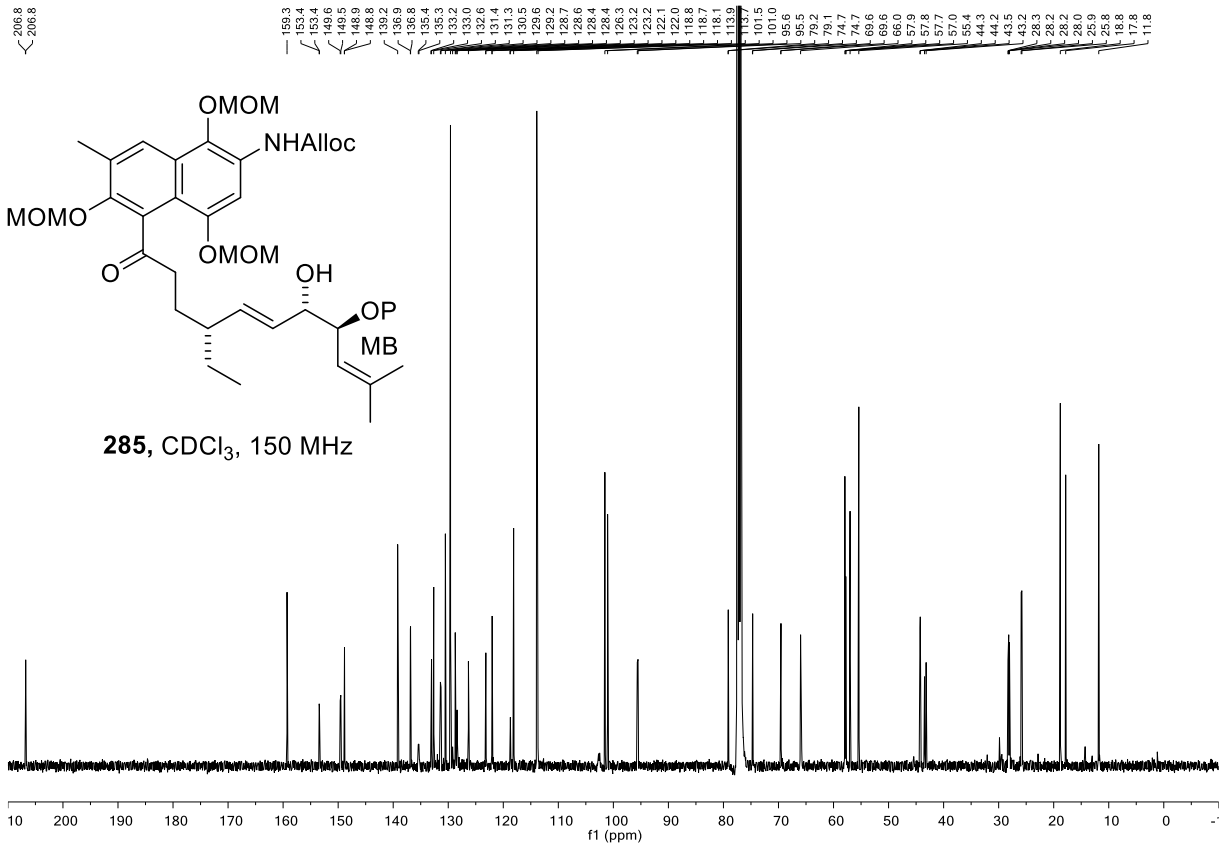
281, D_3COD, 400 MHz



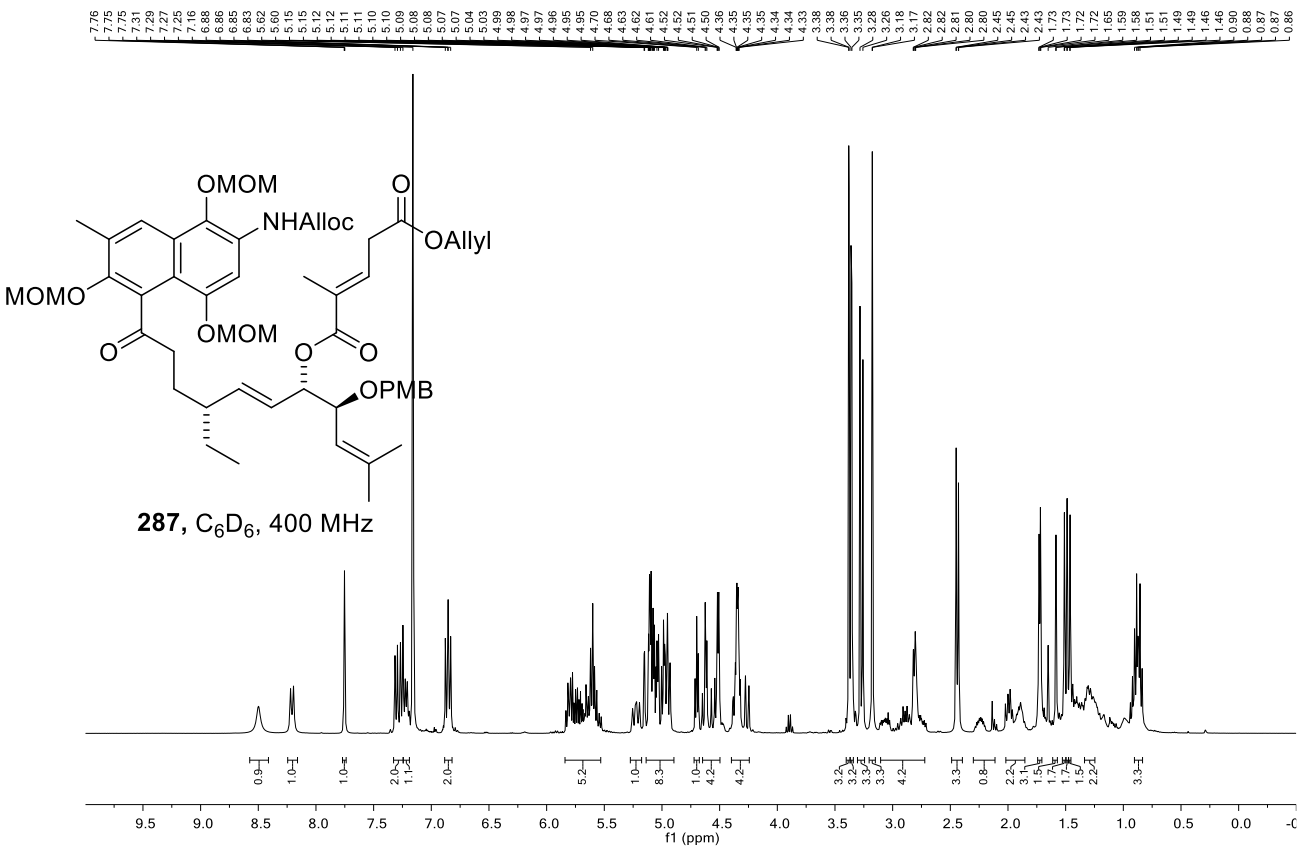
281, D_3COD, 100 MHz



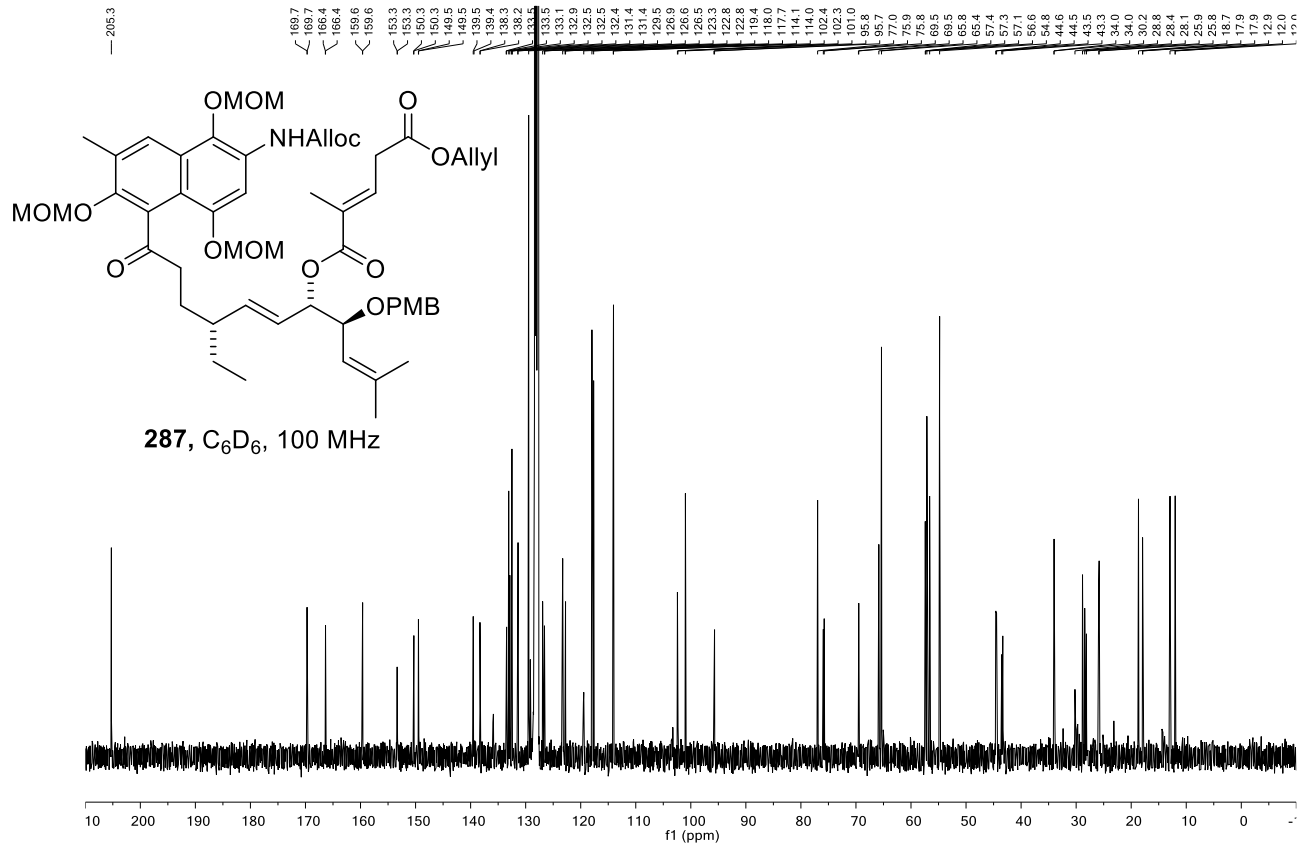
285, $CDCl_3$, 400 MHz



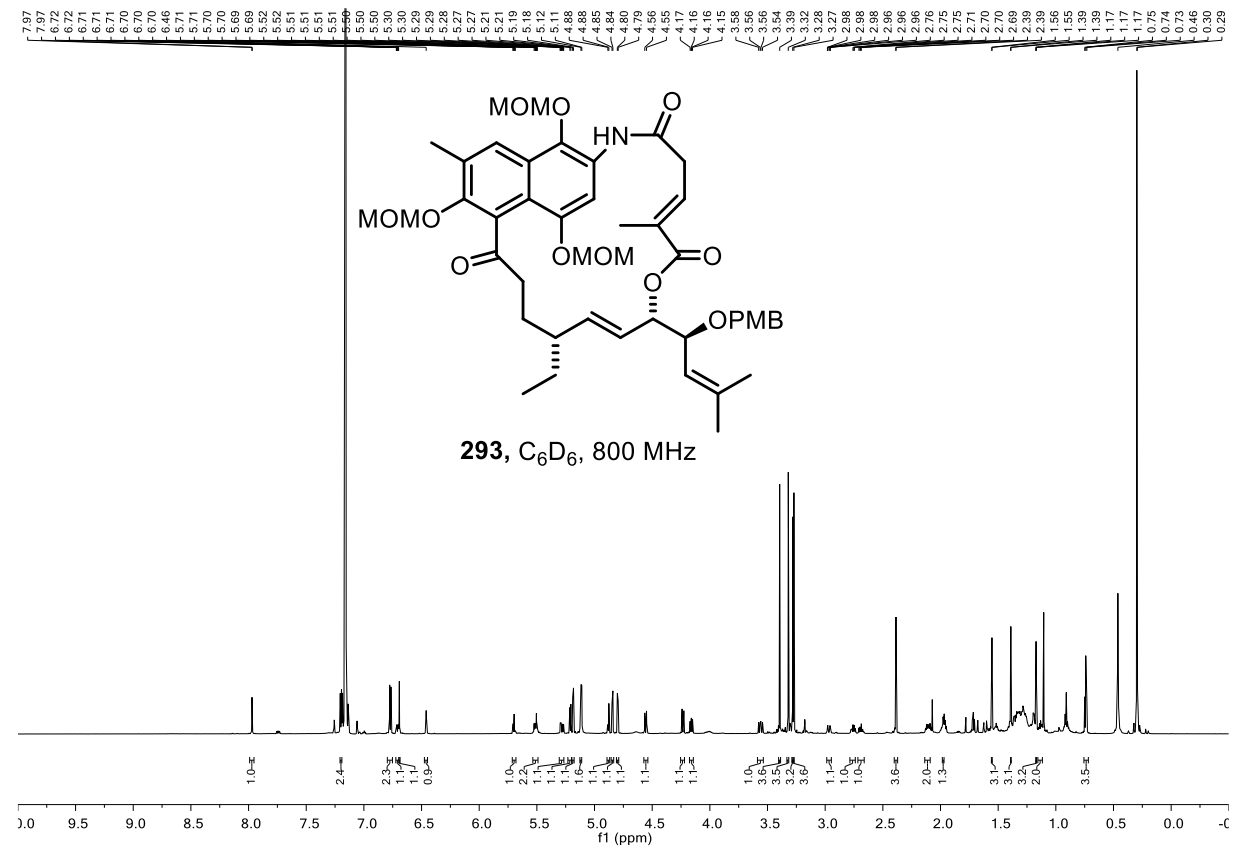
285, $CDCl_3$, 150 MHz



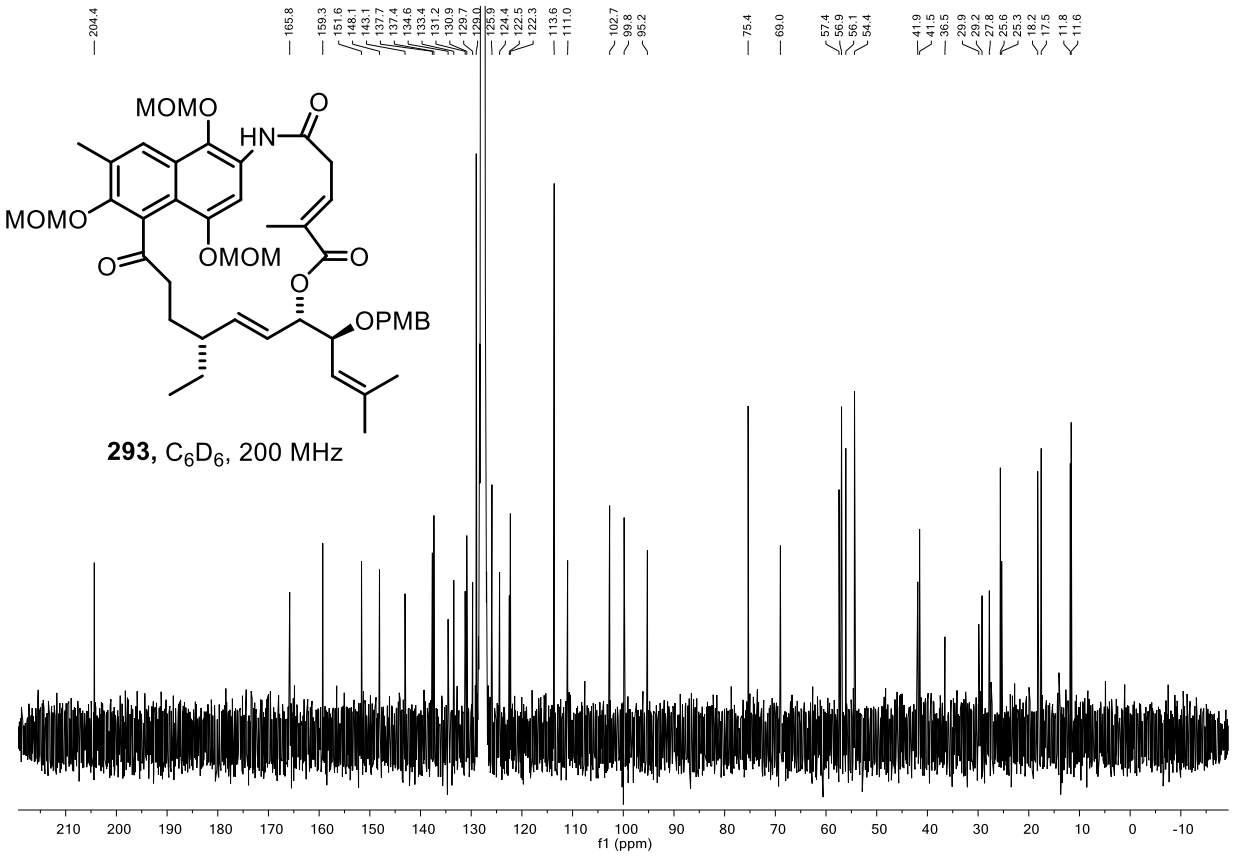
287, C_6D_6, 400 MHz



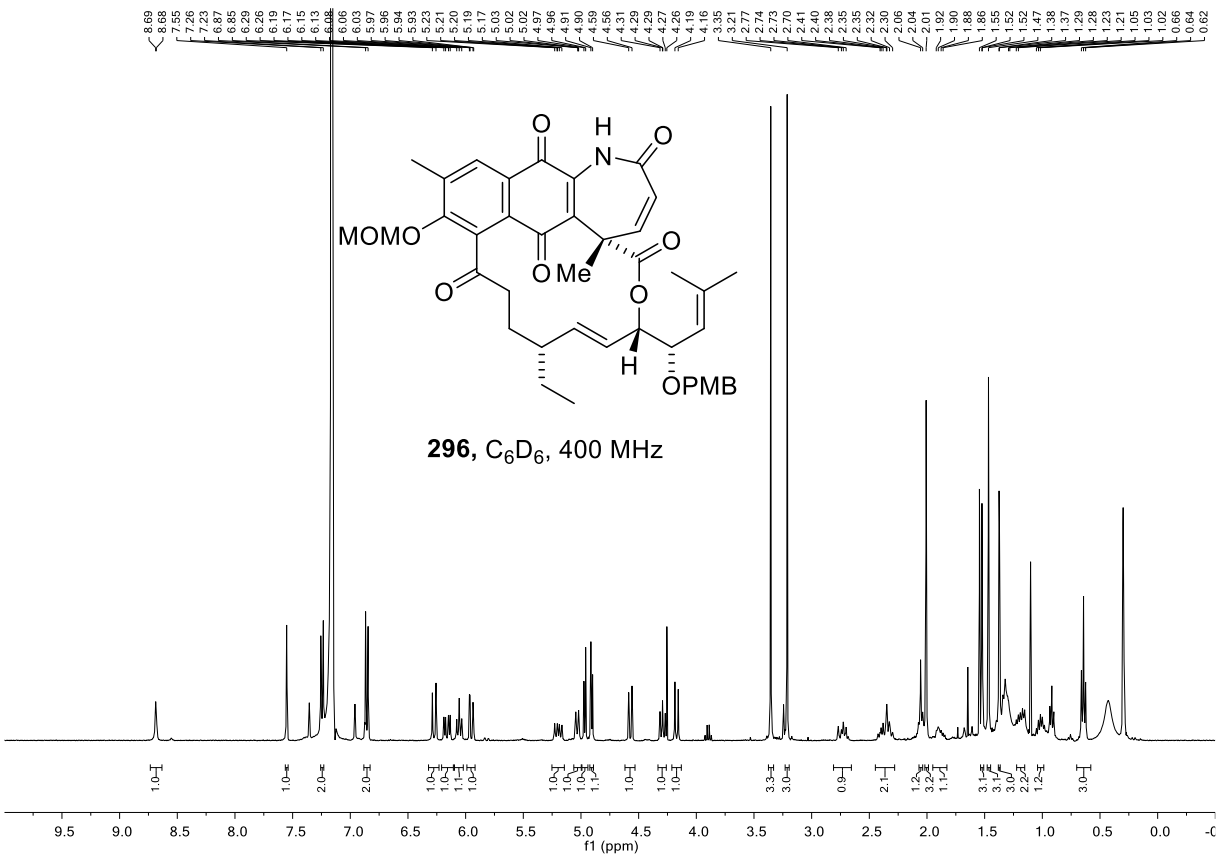
287, C_6D_6, 100 MHz



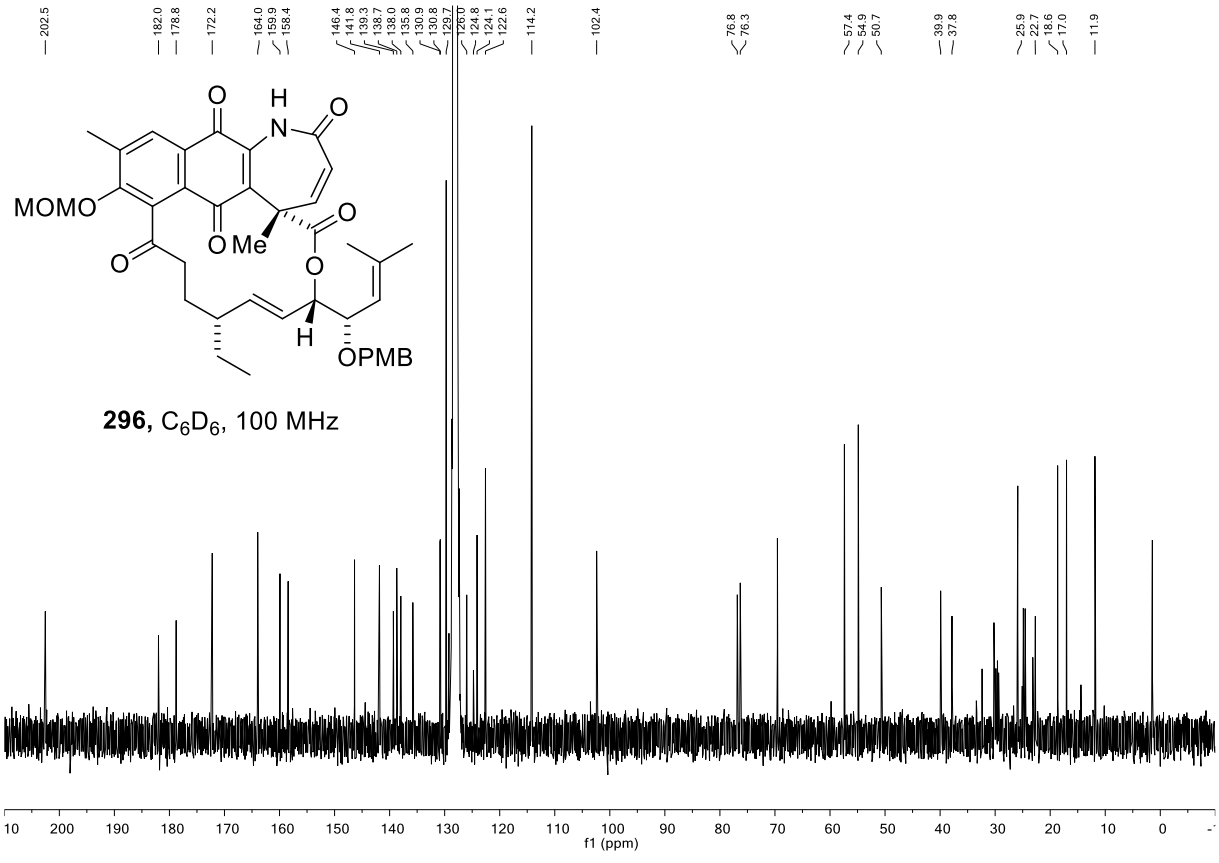
293, C_6D_6, 800 MHz



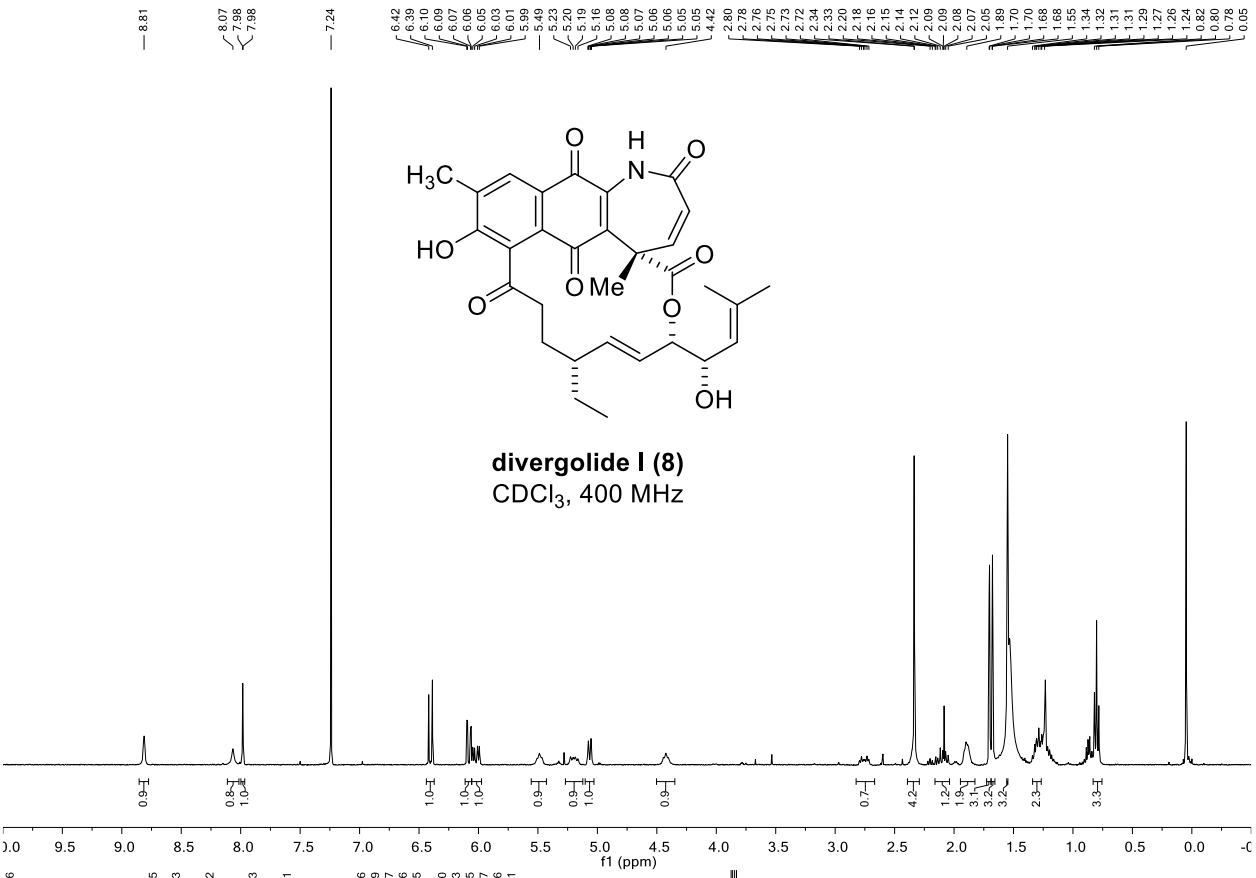
293, C_6D_6, 200 MHz

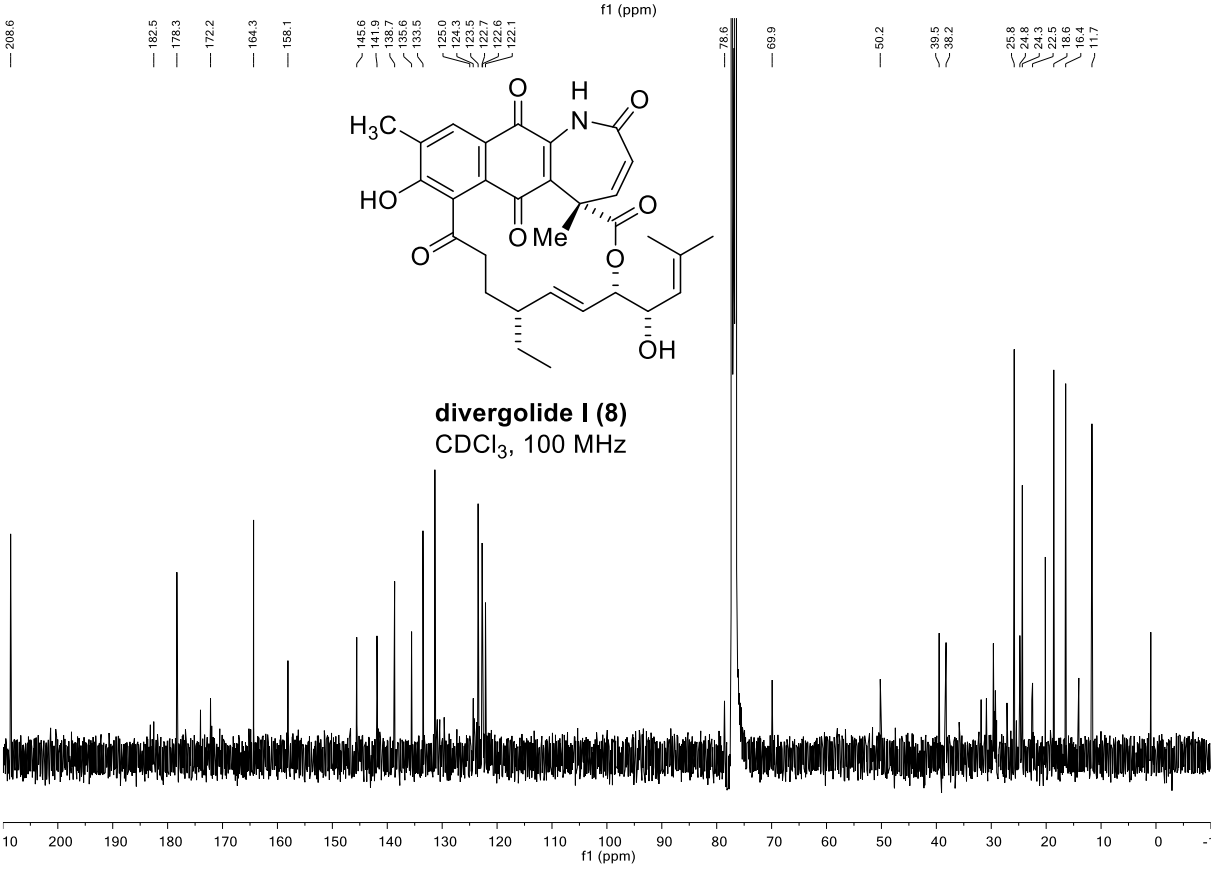


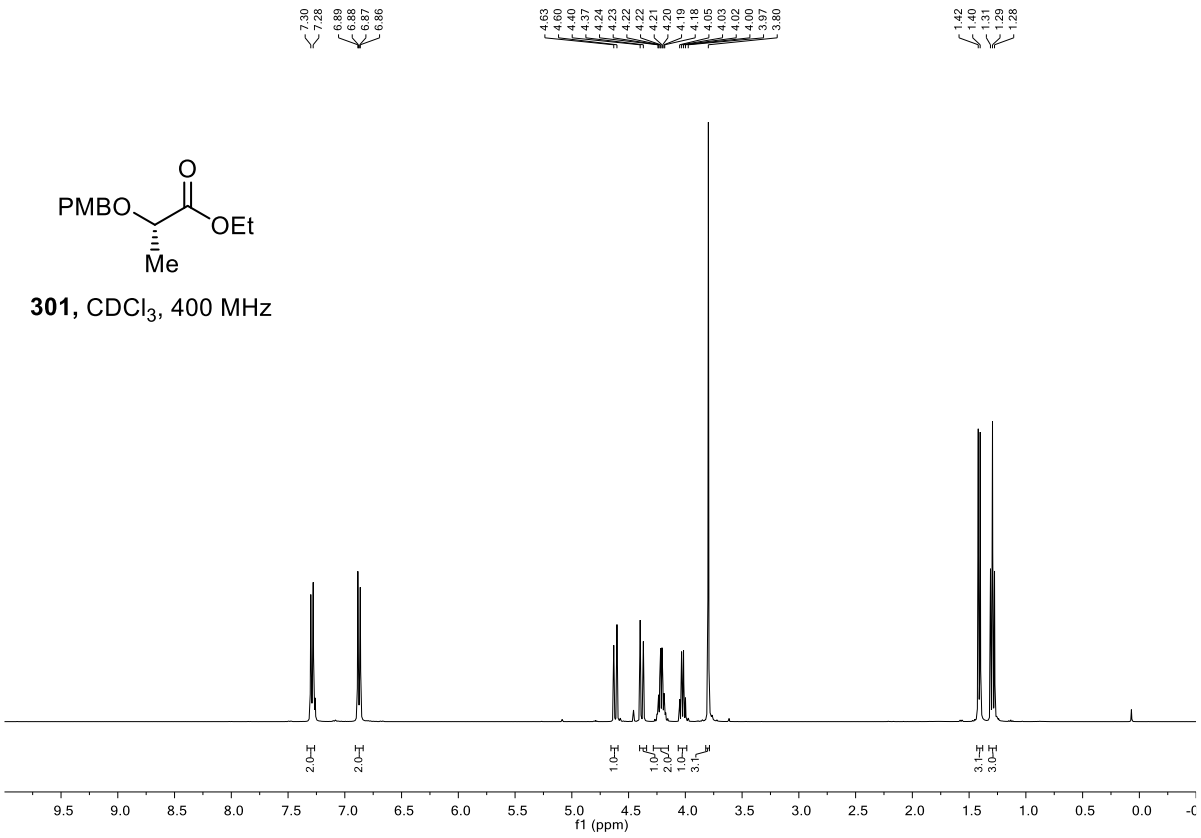
296, C_6D_6, 400 MHz



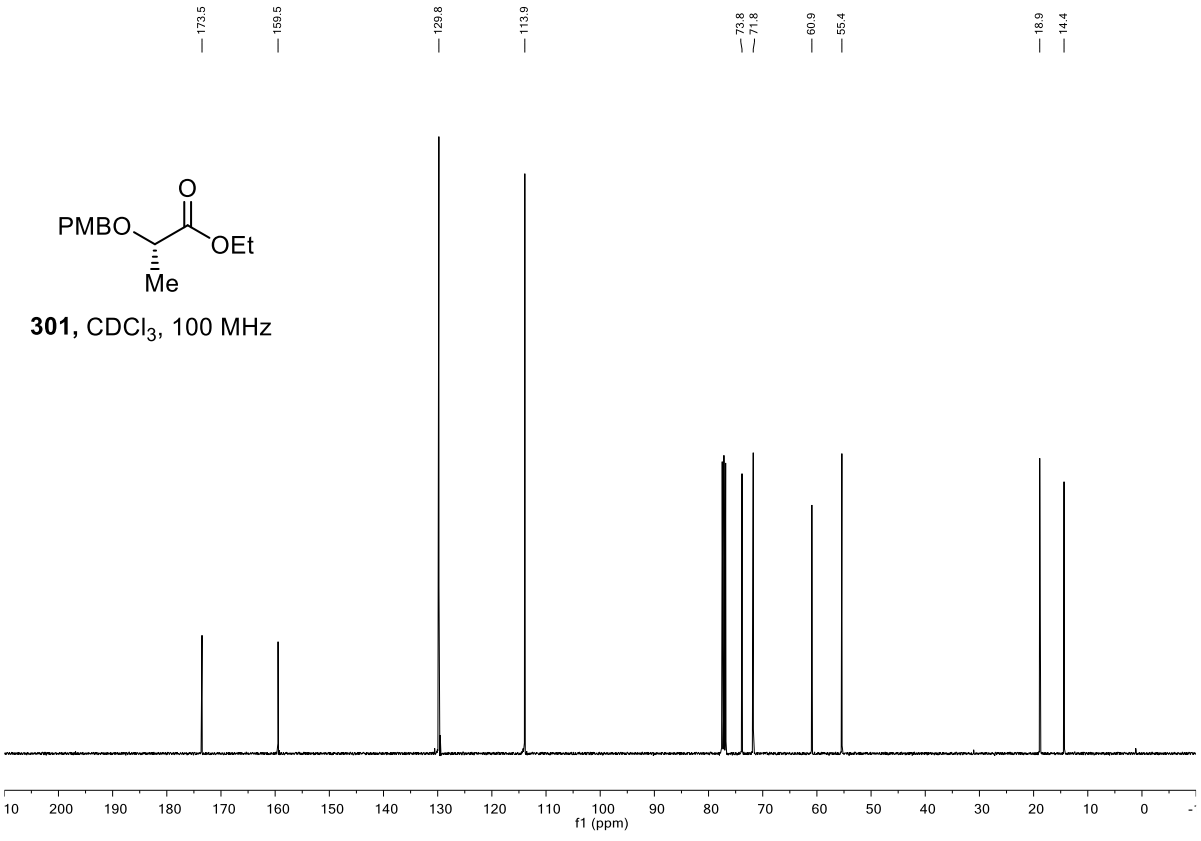
296, C_6D_6, 100 MHz


divergolide I (8)
CDCl3, 400 MHz
f1 (ppm)

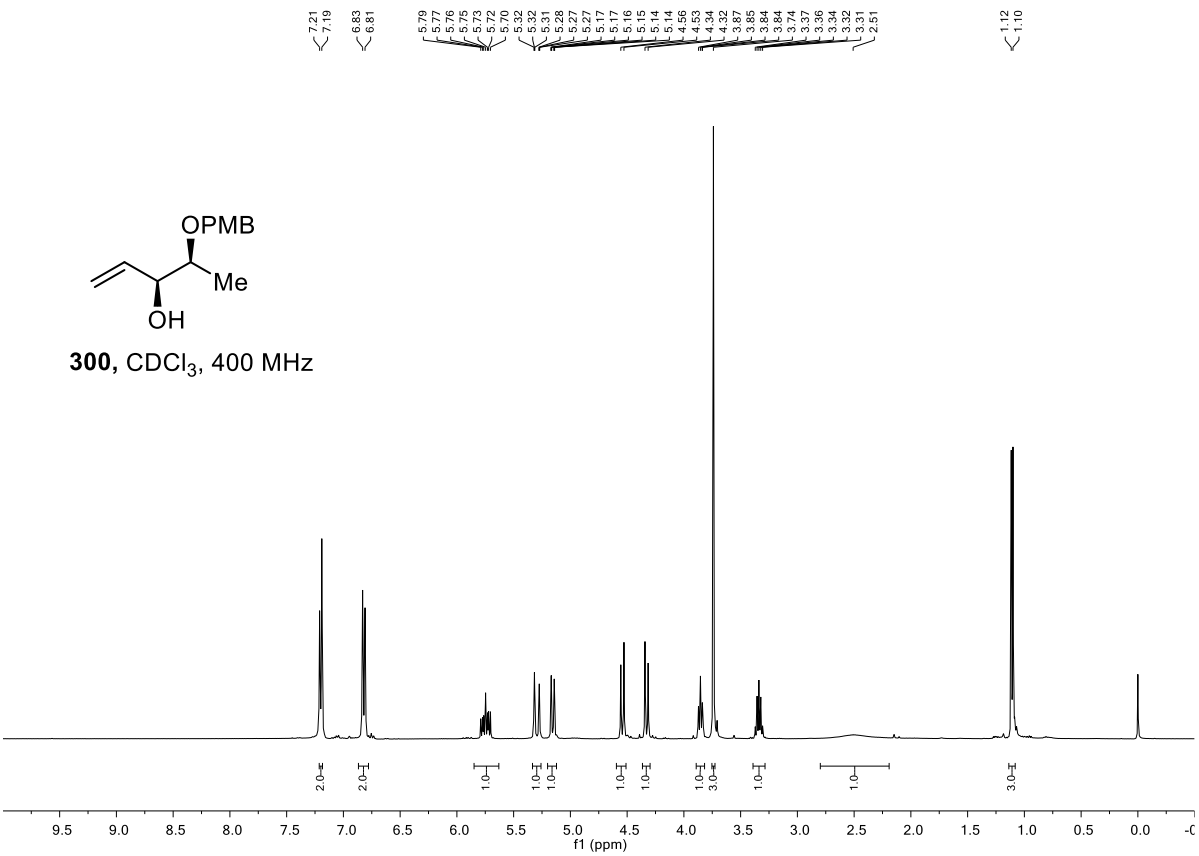

divergolide I (8)
CDCl3, 100 MHz
f1 (ppm)

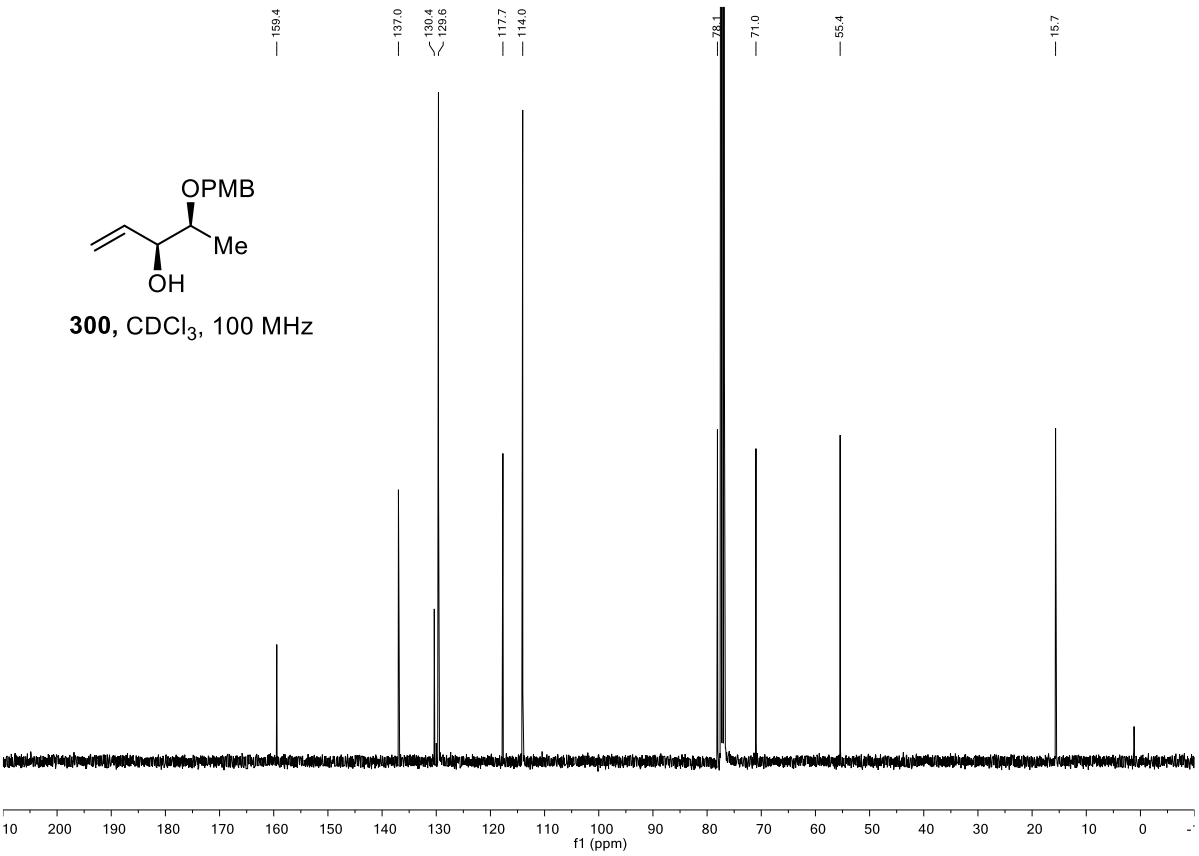


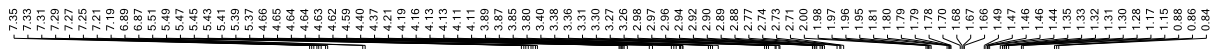
301, $CDCl_3$, 400 MHz

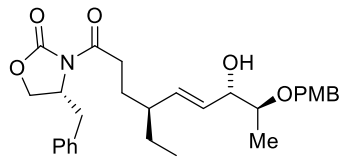


301, $CDCl_3$, 100 MHz

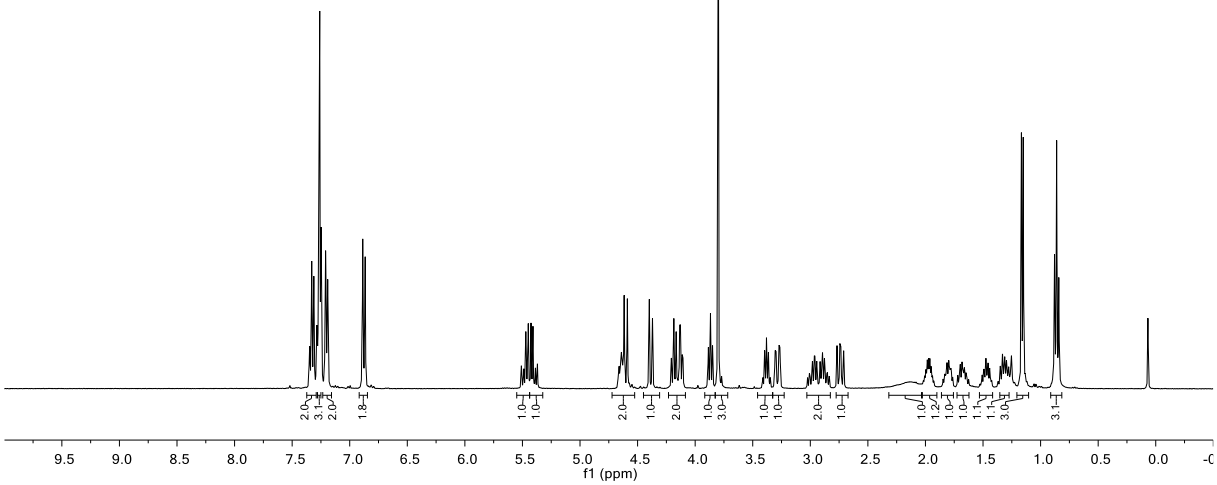

OPMB
Me
OH
300, CDCl3, 400 MHz
f1 (ppm)

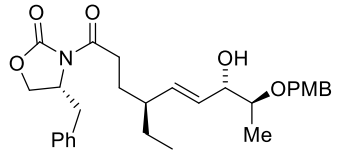

OPMB
Me
OH
300, CDCl3, 100 MHz
f1 (ppm)



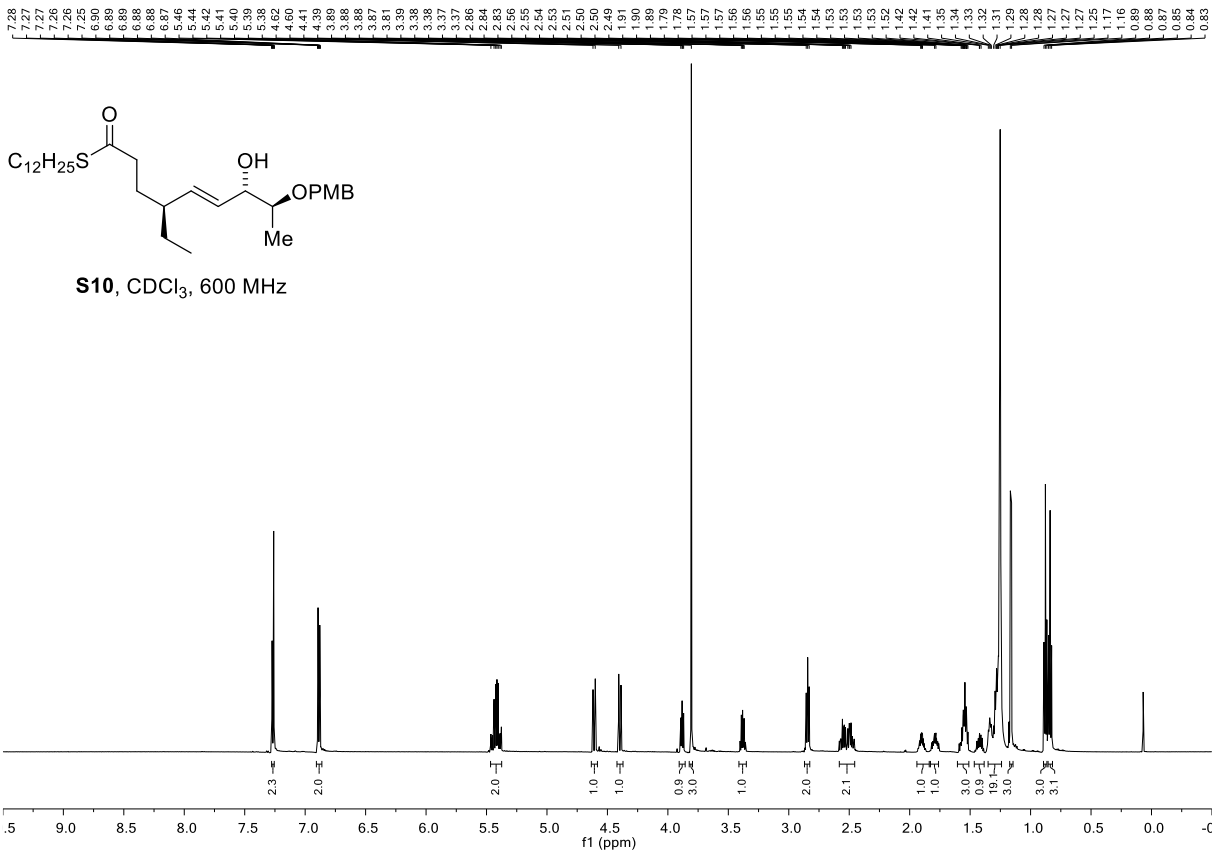


302, $CDCl_3$, 400 MHz

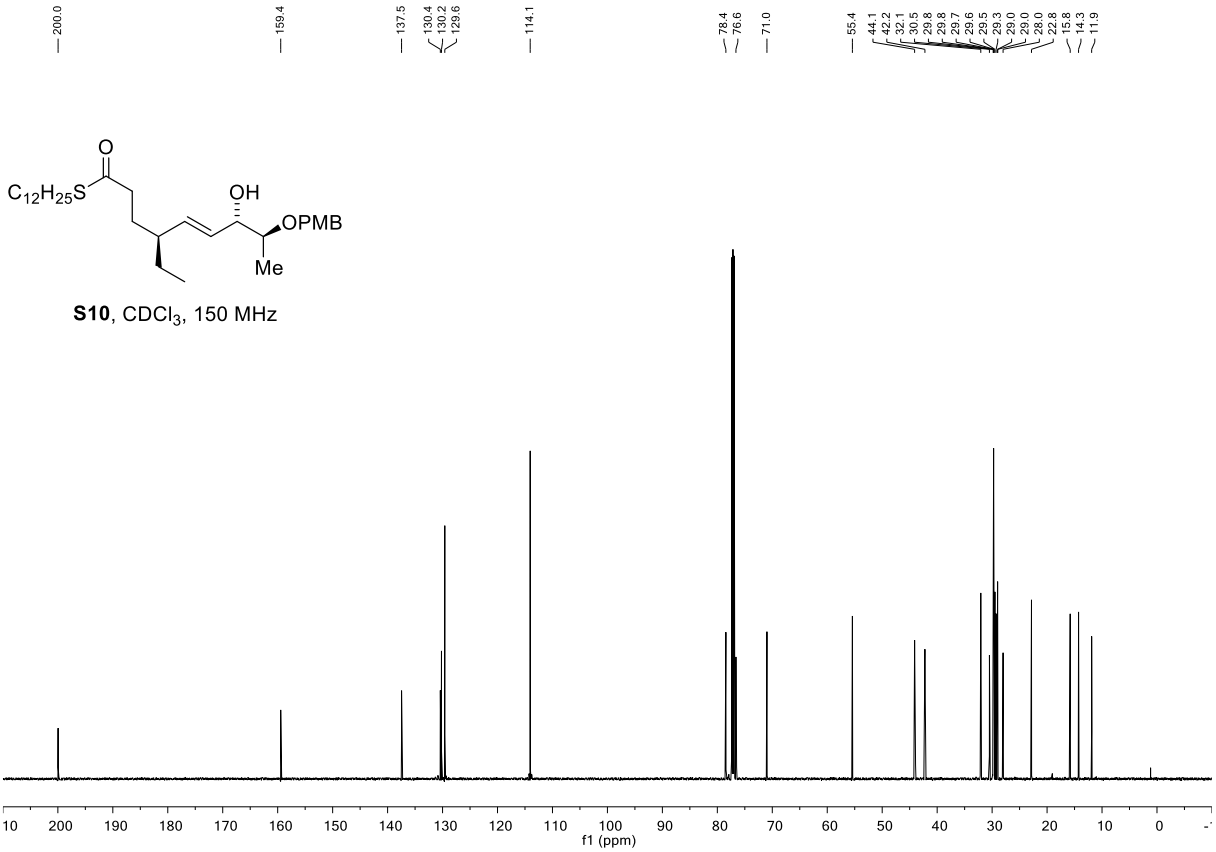




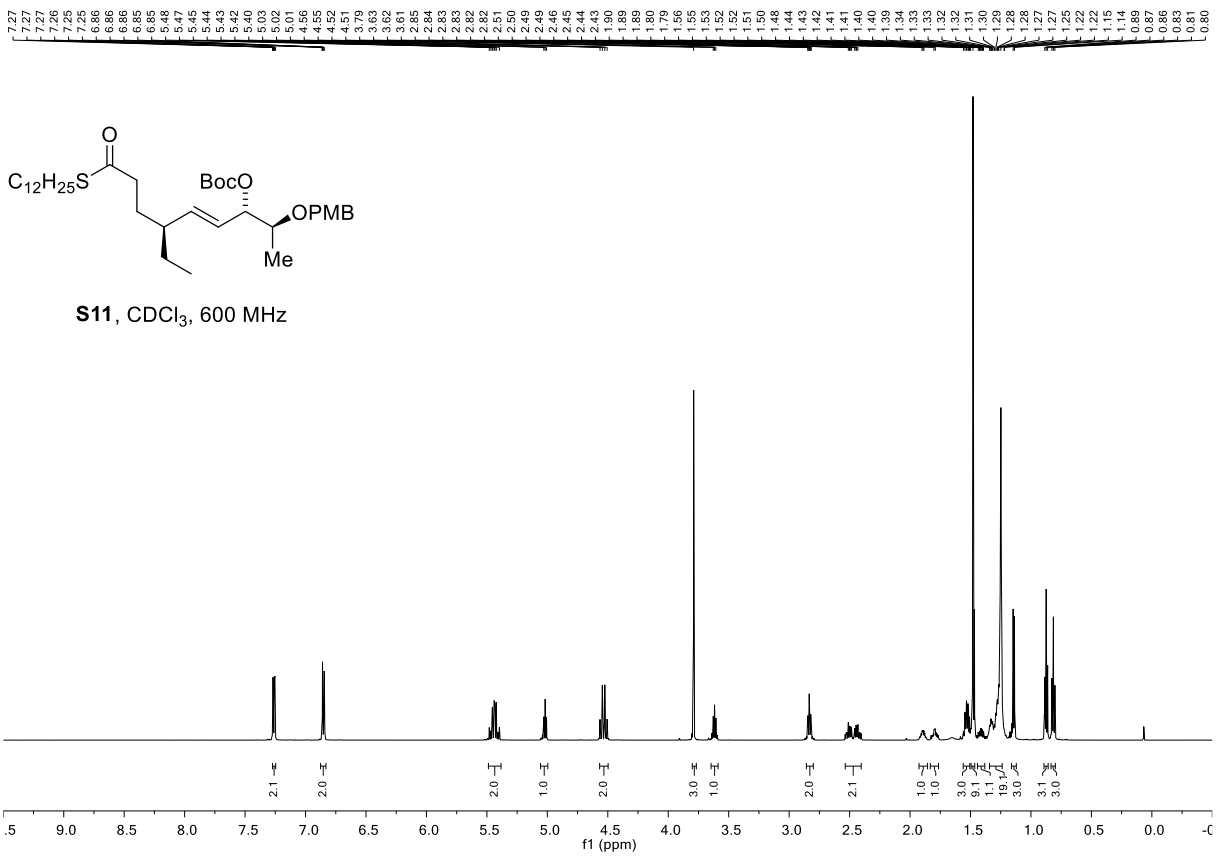
302, $CDCl_3$, 100 MHz



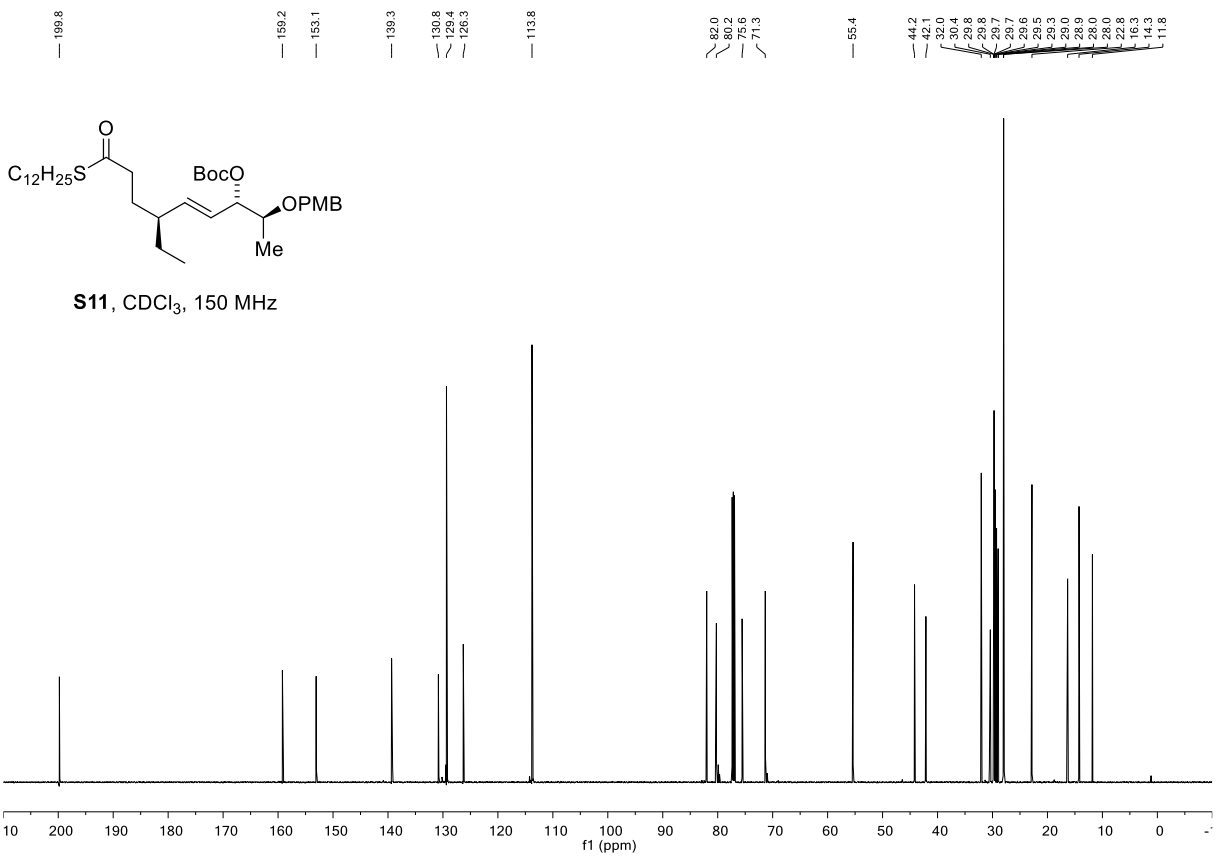
S10, $CDCl_3$, 600 MHz



S10, $CDCl_3$, 150 MHz



S11, $CDCl_3$, 600 MHz



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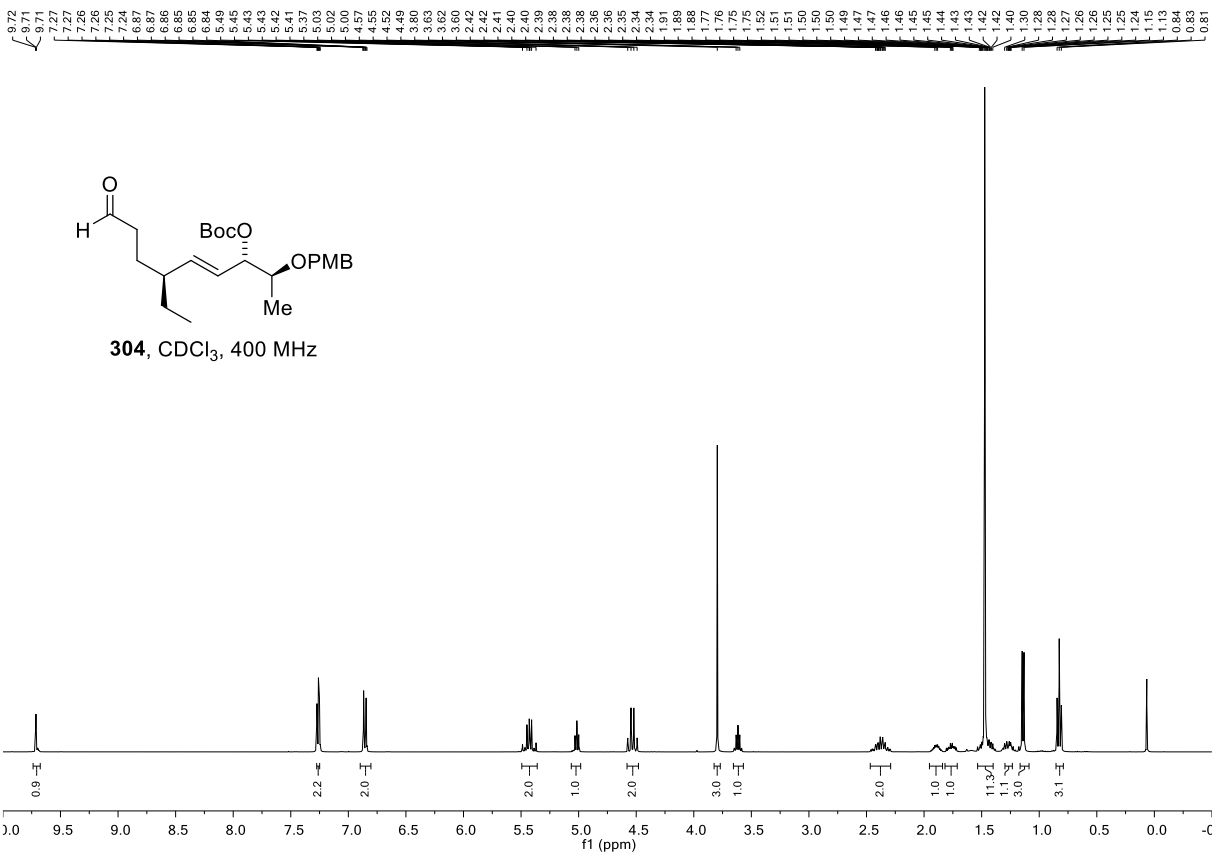

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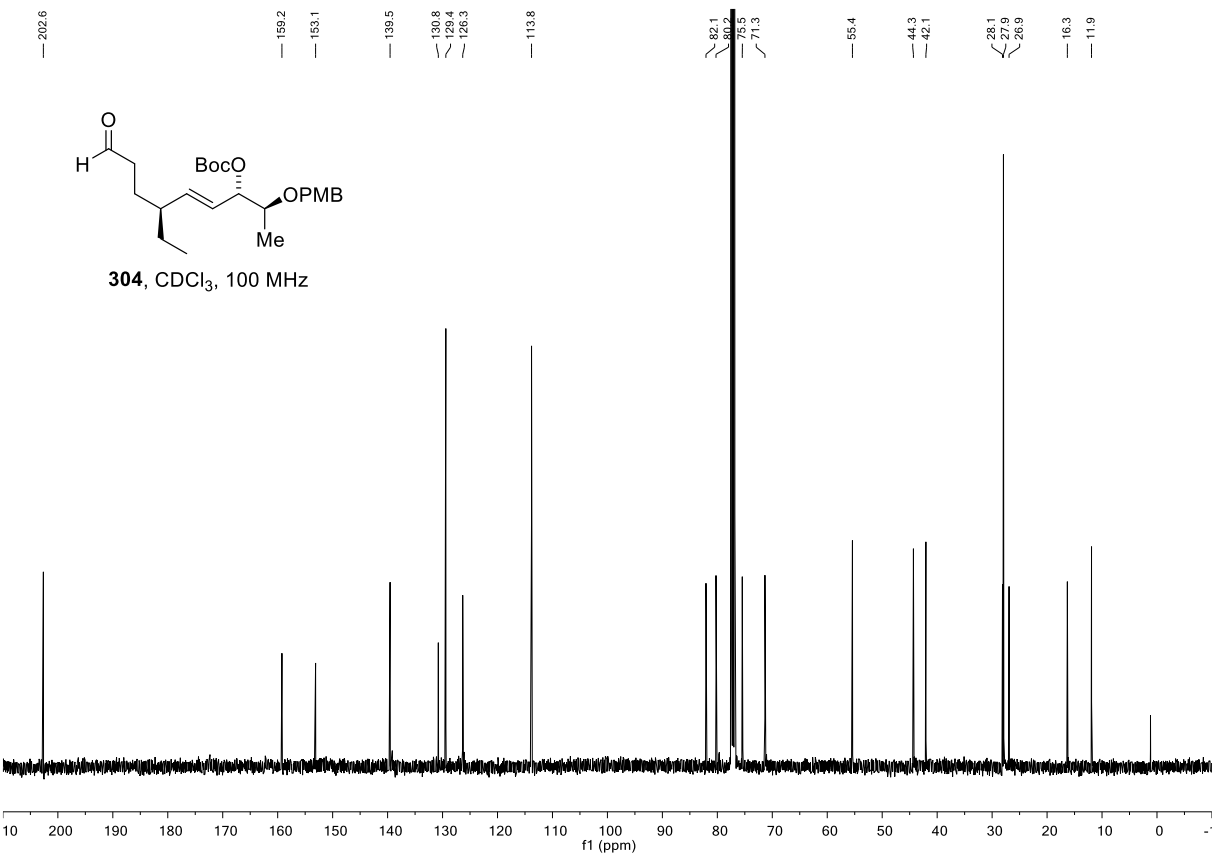
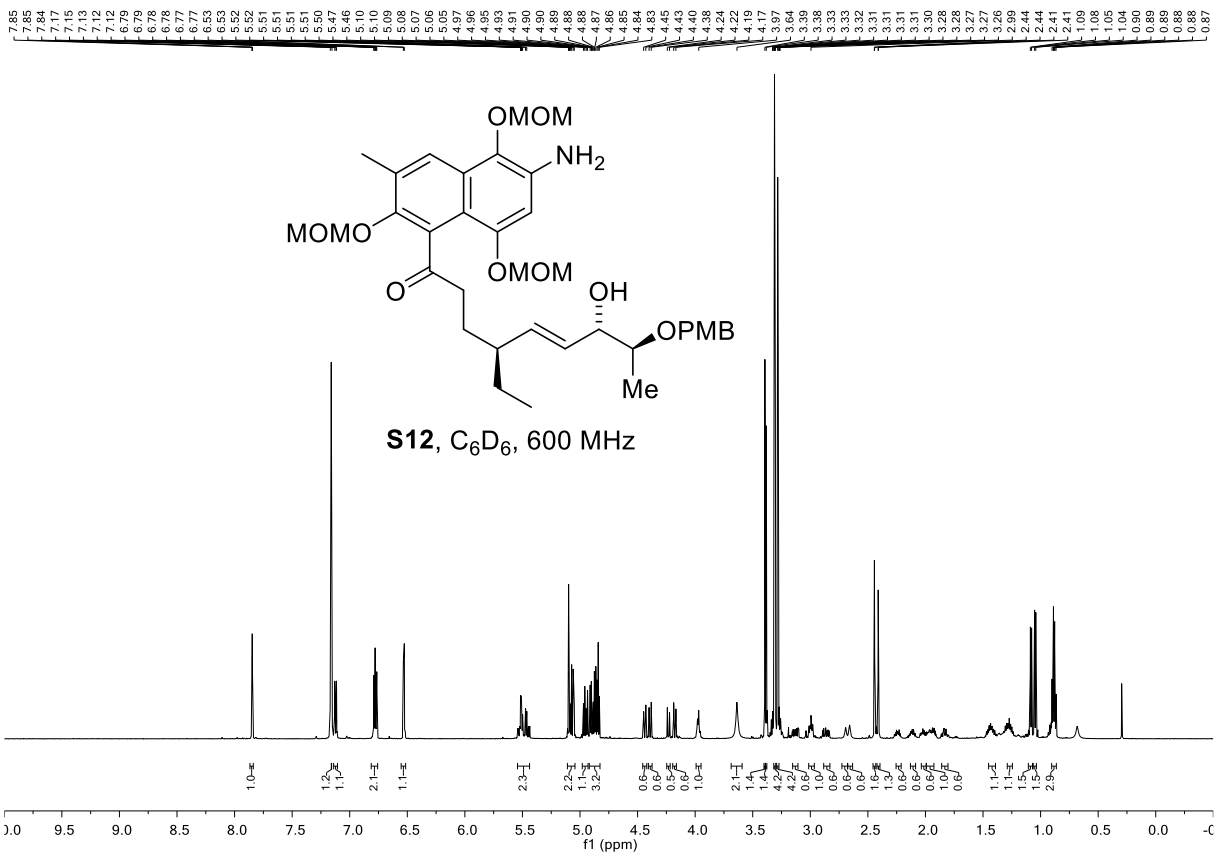
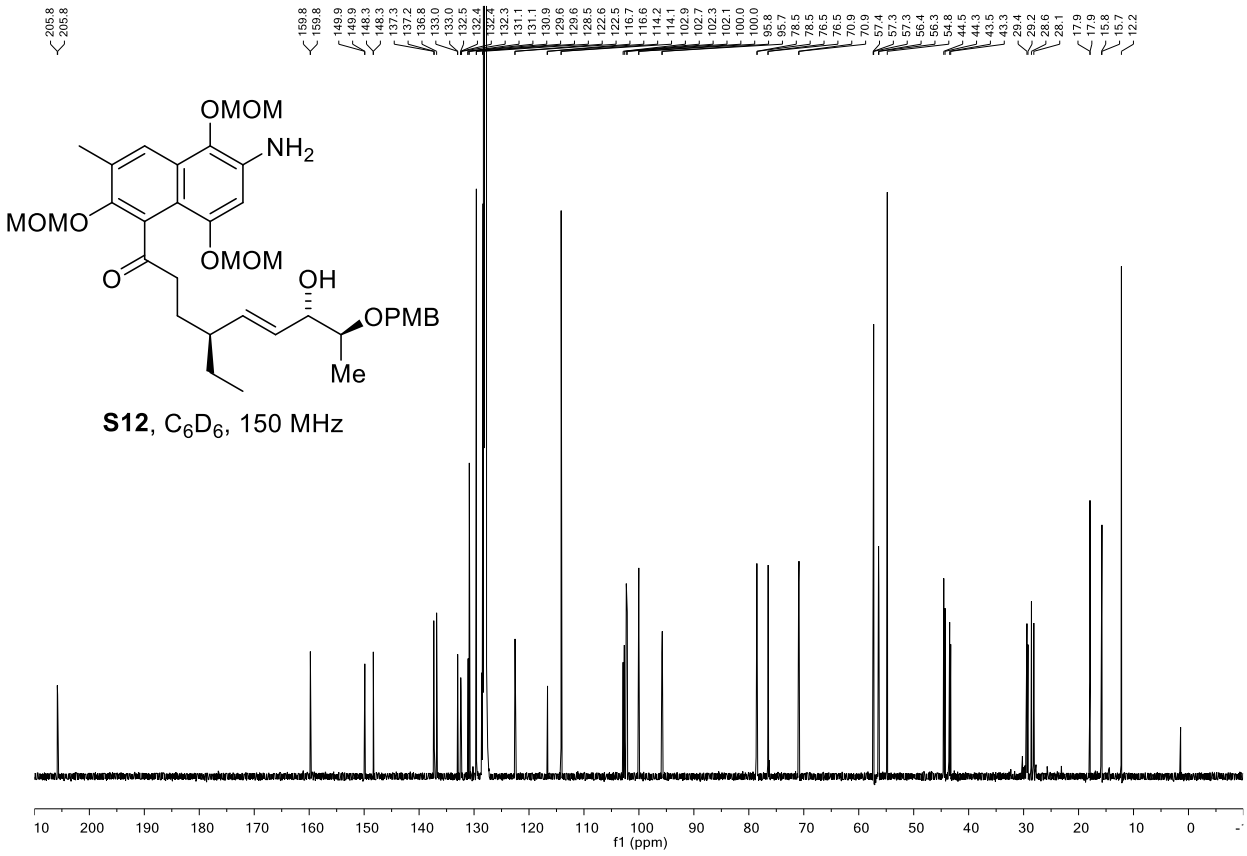


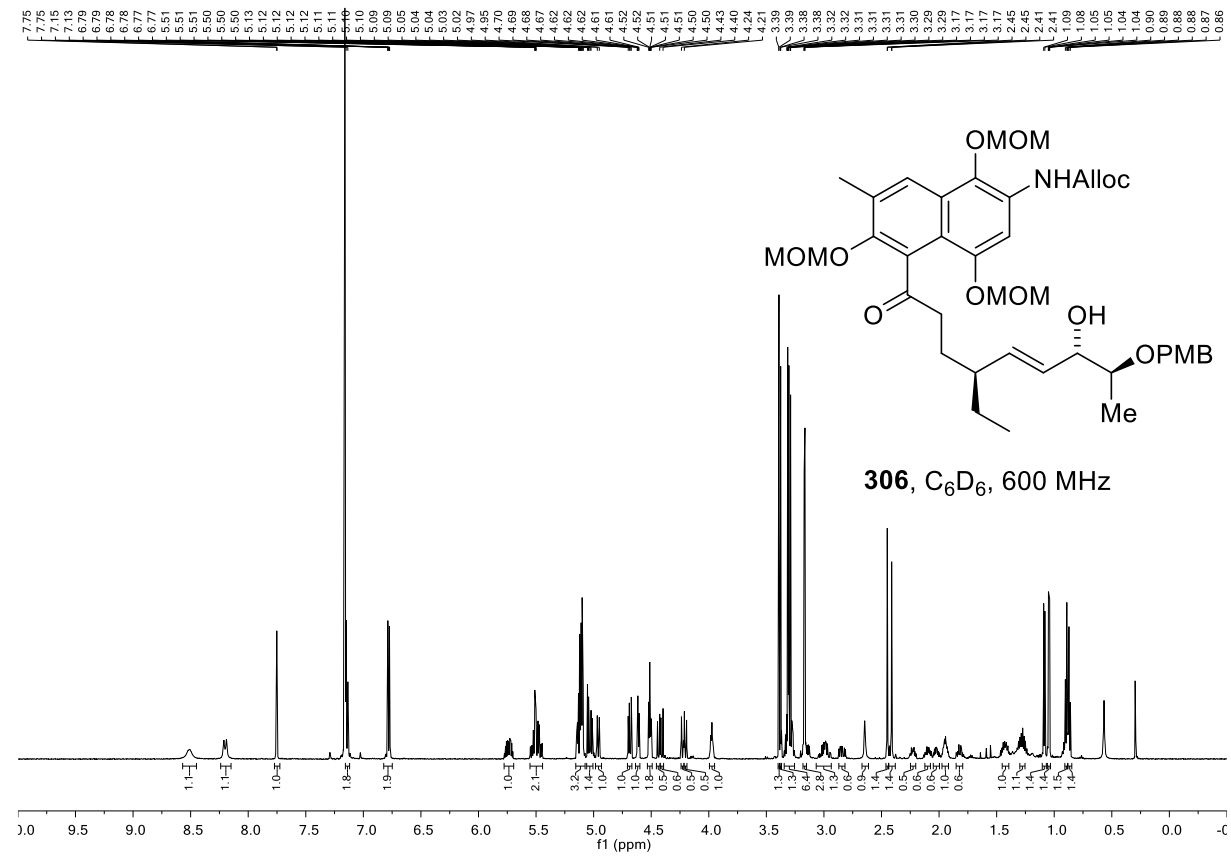
304, $CDCl_3$, 100 MHz

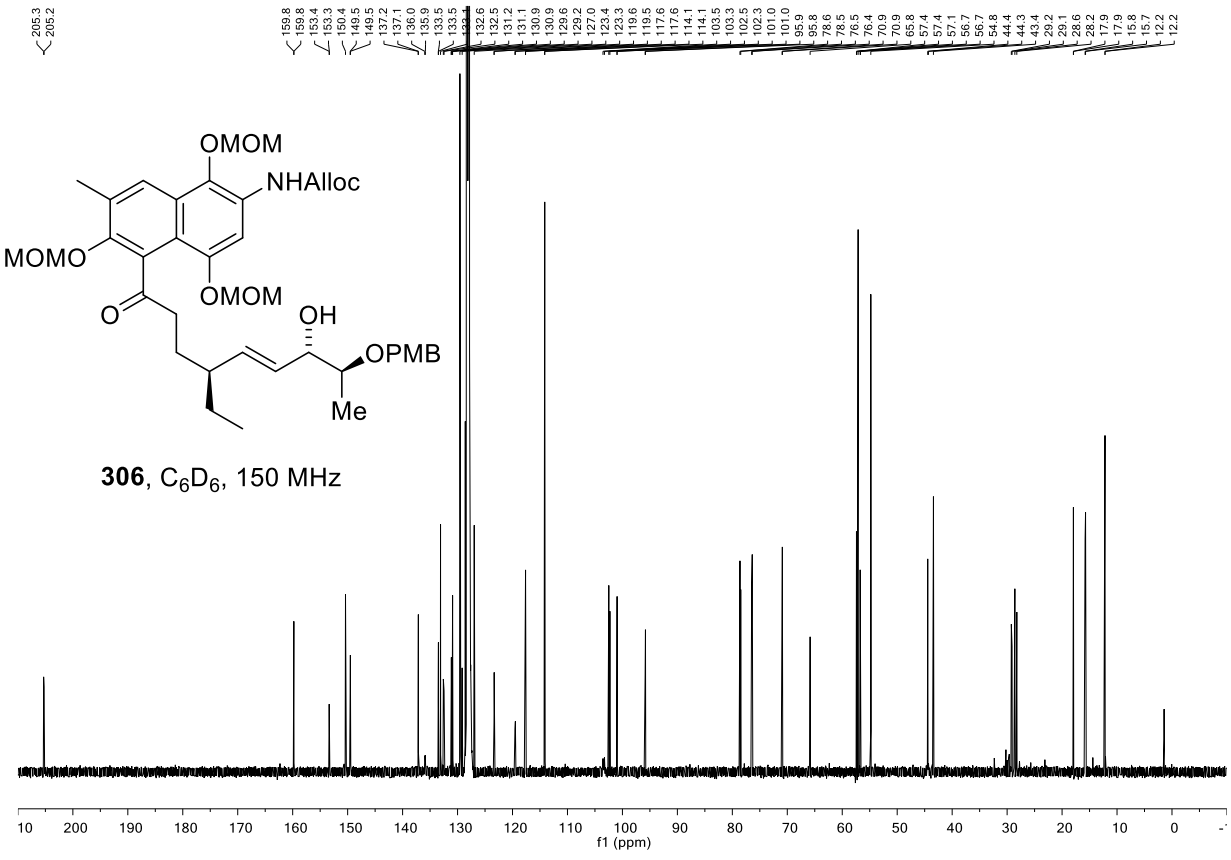


S12, C_6D_6, 600 MHz



S12, C_6D_6, 150 MHz


OMOM
NHAlloc
MOMO
OMOM
O
OH
OPMB
Me
306, C6D6, 600 MHz
f1 (ppm)


OMOM
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MOMO
OMOM
O
OH
OPMB
Me
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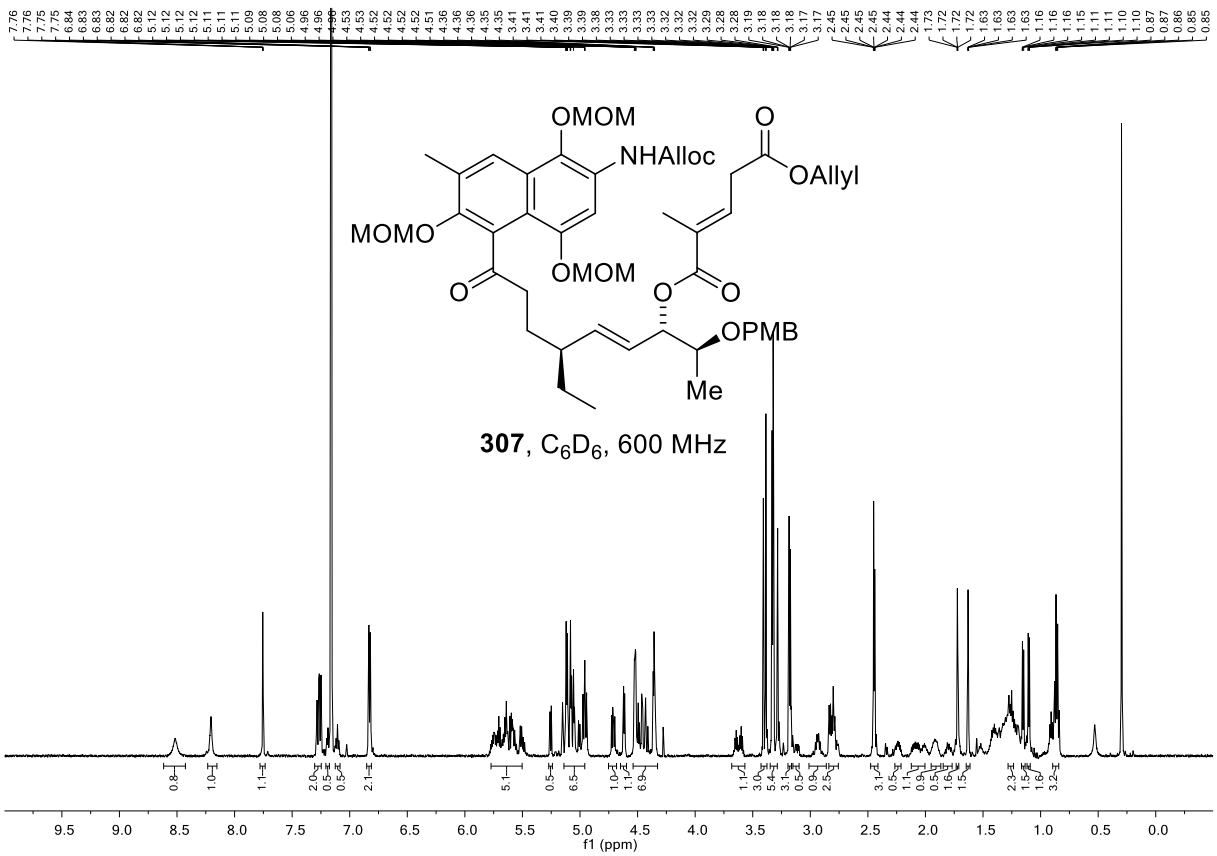
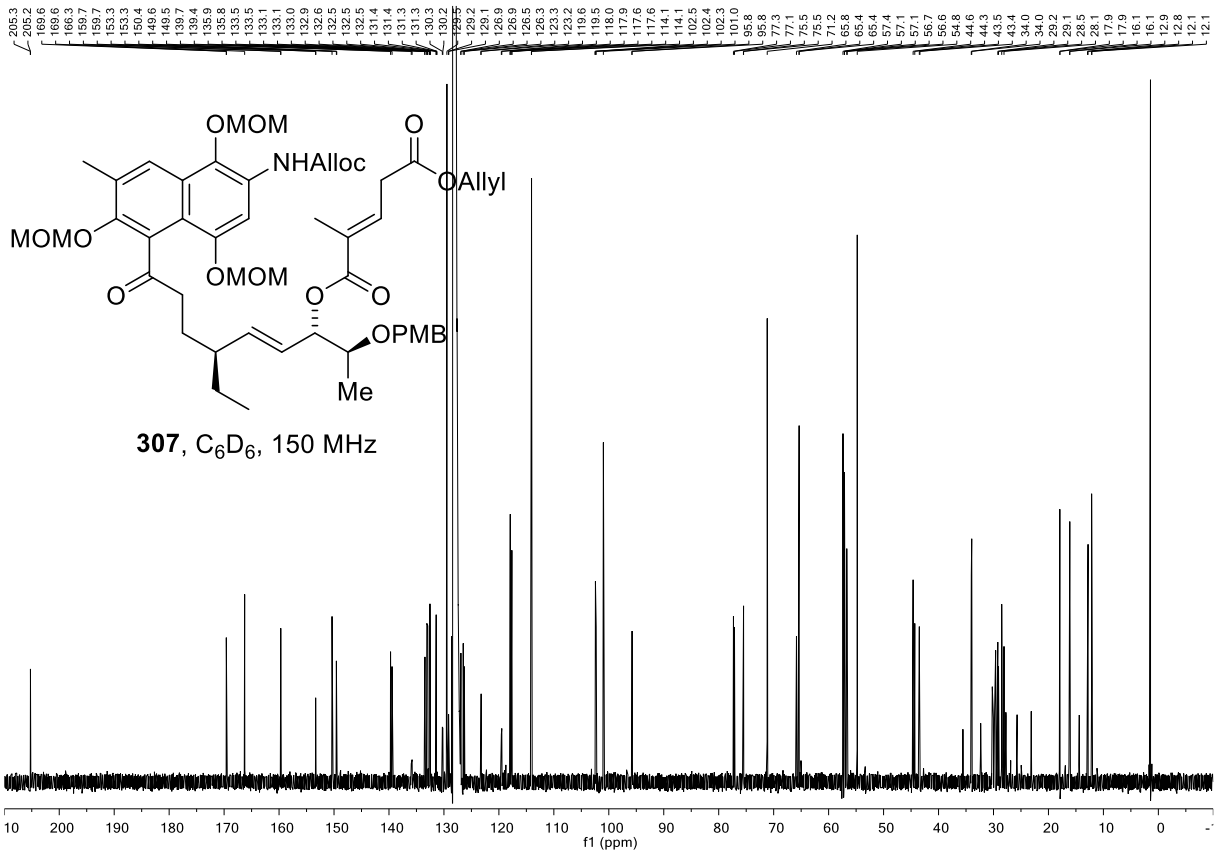
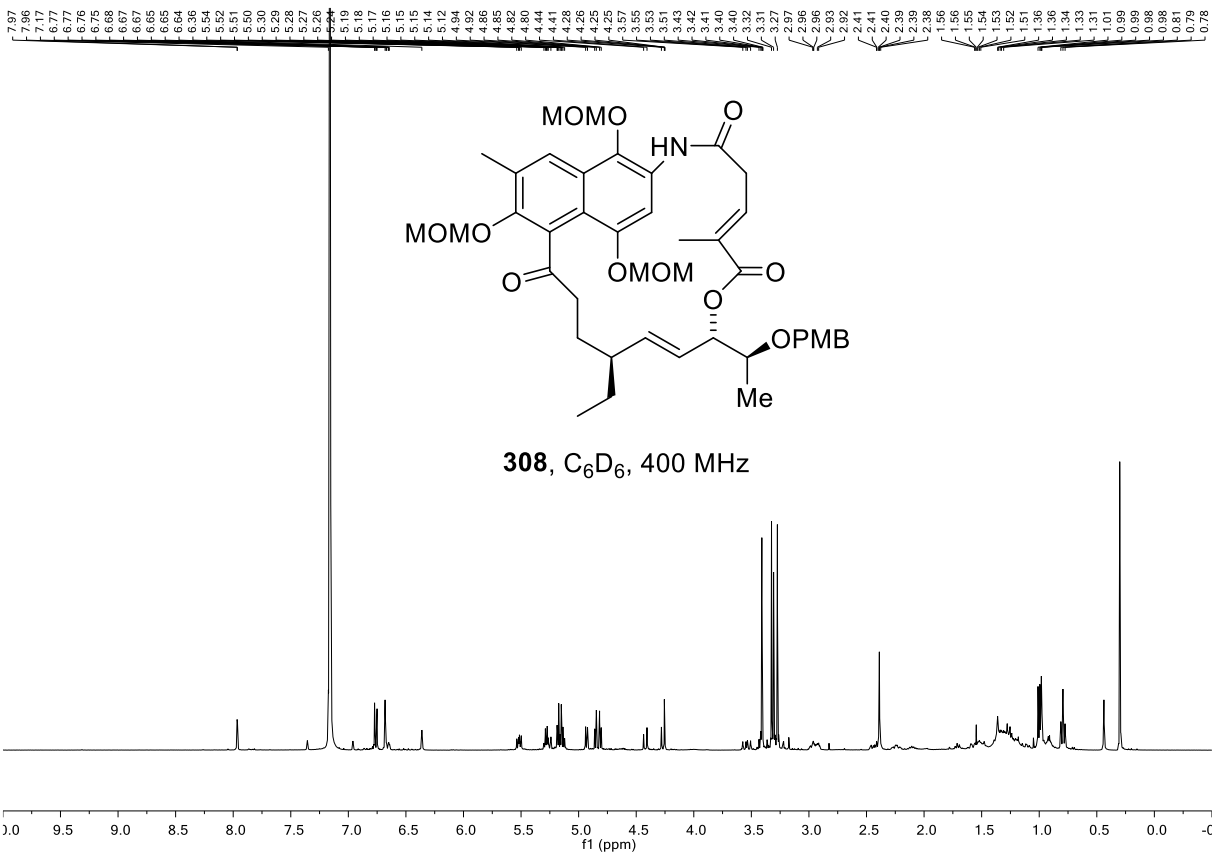
f1 (ppm)



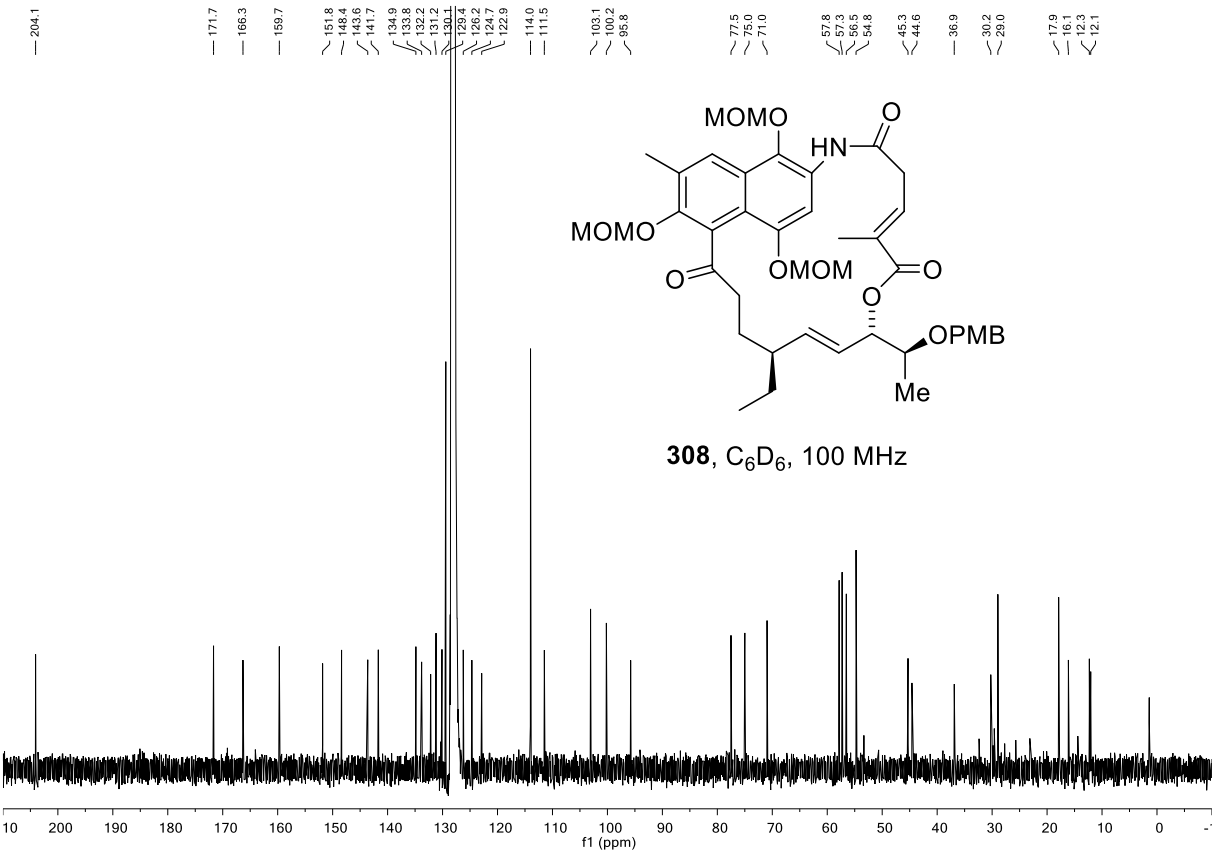
307, C_6D_6, 600 MHz



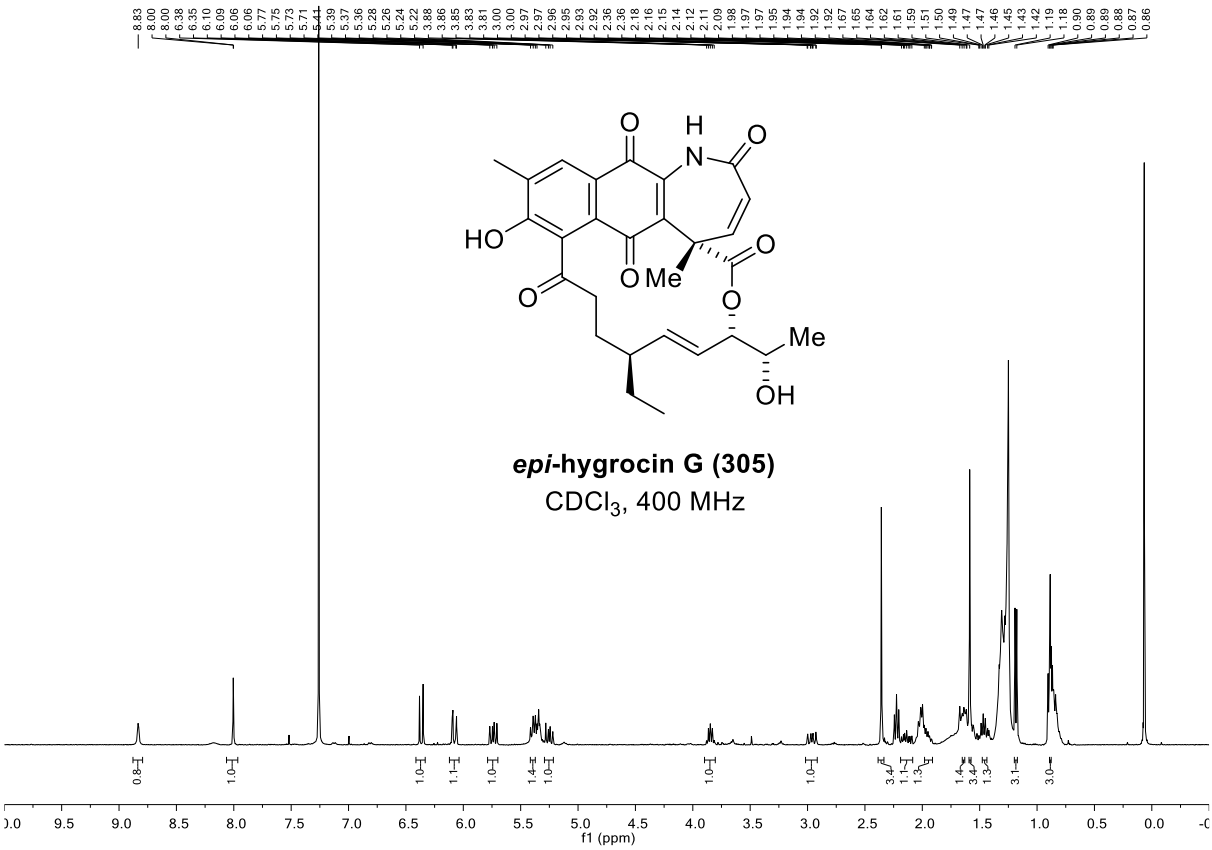
307, C_6D_6, 150 MHz



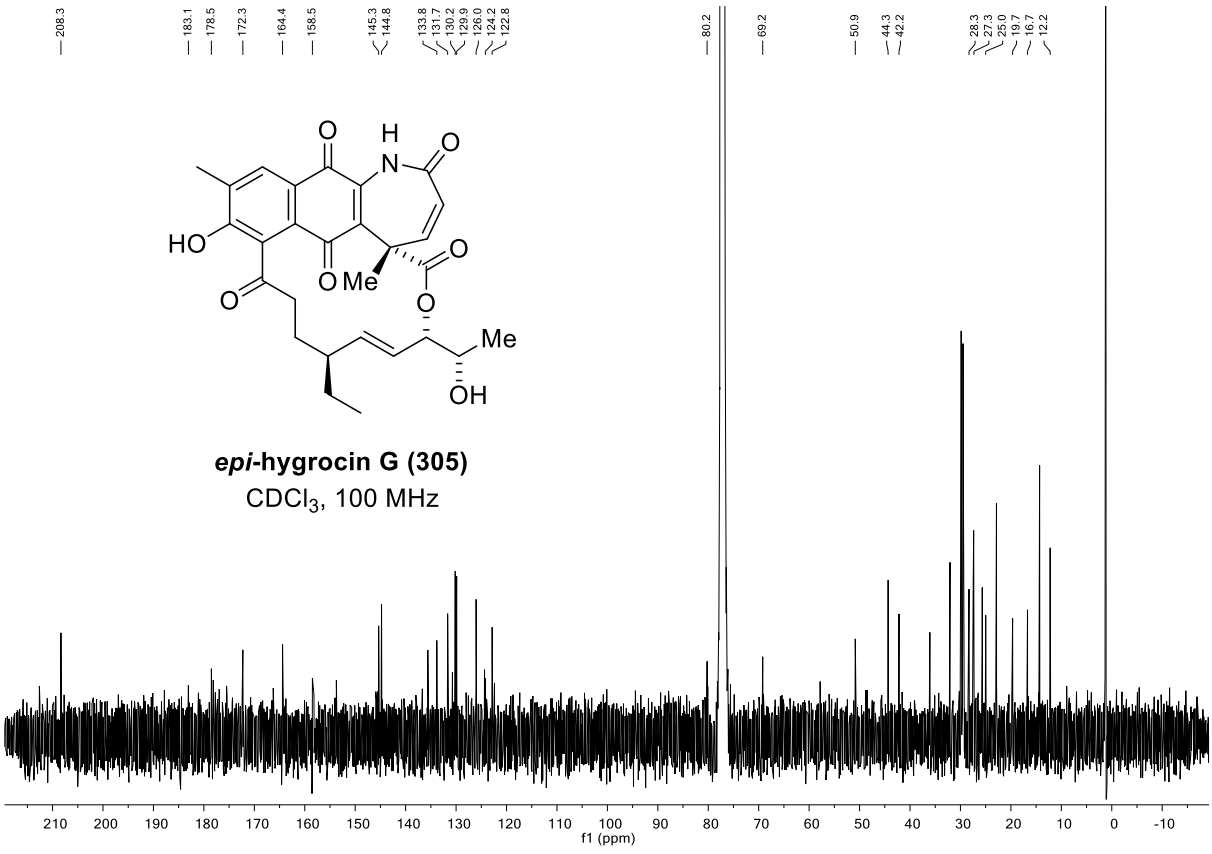
308, C_6D_6, 400 MHz



308, C_6D_6, 100 MHz



***epi*-hygrocin G (305)**
$CDCl_3$, 400 MHz



***epi*-hygrocin G (305)**
$CDCl_3$, 100 MHz

5.3 Selective Synthesis of Divergolide I (published communication)

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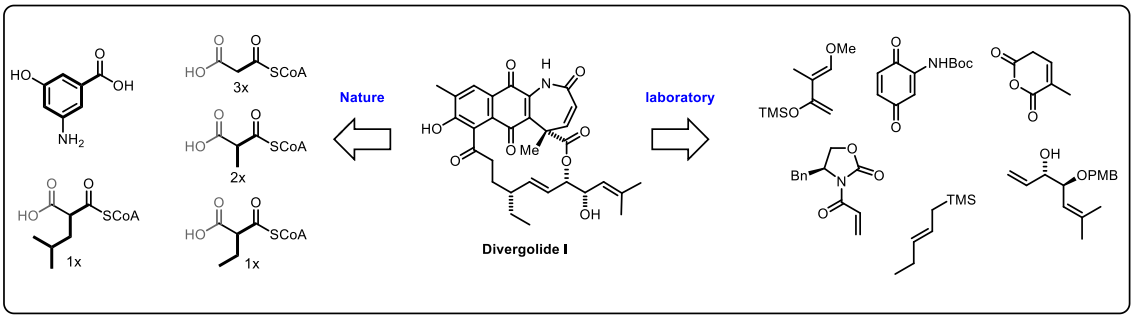

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Selective Synthesis of Divergolide I

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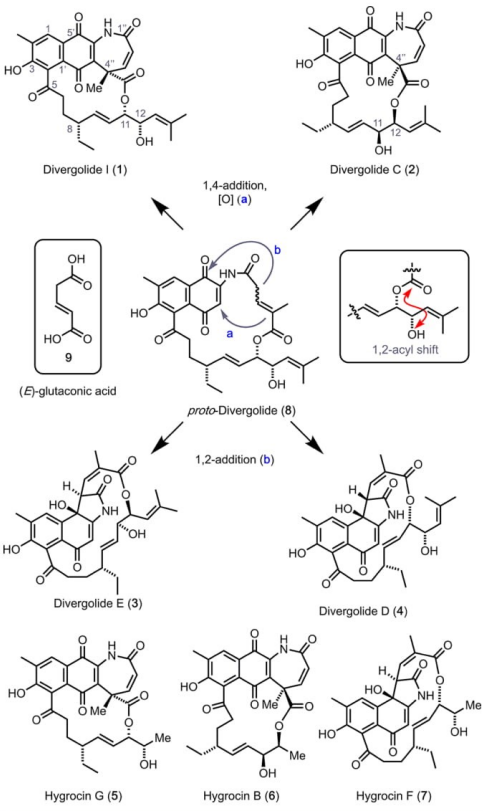
Supporting Information

ABSTRACT: Divergolide I (**1**) is a naphthoquinone ansamycin that exhibits broad antibacterial activity. Its tetracyclic ring system is believed to be biosynthetically assembled via ring contraction of a macrocyclic precursor (*proto*-divergolide) that is both a macrolactone and a macrolactam. We here report a convergent and enantioselective synthesis that delivers the target molecule in less than 20 linear steps. Our work establishes the absolute configuration of divergolide I, confirms its relative configuration, and demonstrates that the biomimetic cyclization of a *proto*-divergolide can be surprisingly selective.

The divergolides and hygrocins constitute a recently established and still growing family of ansamycins that combine structural diversity with interesting biological activities.[1a−d] Over a dozen members have been isolated to date, represented by divergolide I (**1**), C (**2**), E (**3**), and D (**4**) as well as hygrocin G (**5**), B (**6**), and F (**7**) (Scheme 1). Biosynthetically,[1b] the divergolides have been traced back to a single precursor, the hypothetical *proto*-divergolide (**8**), whose 19-membered macrolactam and macrolactone incorporate a glutaconic acid (**9**) moiety. Deprotonation of the most acidic C−H bond, followed by 1,4-addition to the naphthoquinone and reoxidation, would result in the formation of azepinones **1** and **2** (path a). Note that these molecules are not simply C4″-diastereomers but also constitutional isomers due to a concomitant 1,2-acyl shift. Conversely, deprotonation of **8** and intramolecular 1,2-addition to the C5′-carbonyl would yield the pyrrolidinones **3** and **4** (path b). Again, the lactone linkage is shifted in the two isomers. This diversity can be further increased through modification of the cyclization precursor, as it is the case in the hygrocins.[1e−g] These tetracyclic ansamycins share their ring systems with the divergolides but incorporate one different extender unit in their biosynthesis,[2] which results in a methyl group instead of an isobutenyl side chain.

Ansamycins have been popular objects of study due to their potent bioactivities, interesting biosyntheses, molecular complexity, and unusual stereochemical features.[3] Compared with classic ansamycins, the divergolides and hygrocins feature additional heterocycles and lactone linkages as well as highly strained *ansa* chains. Their structural diversity and unusual features have led to extensive investigations into their biosynthesis. Furthermore, the question arises whether they are formed more or less spontaneously and unselectively once the hypothetical precursor **8** is assembled or whether the cyclizations and acyl shifts require enzymatic catalysis, which could result in the selective formation of certain congeners. In combination with their bioactivities, this has promoted us, and others, to investigate the divergolides and hygrocins and explore their origin through biomimetic synthesis.[4]

Scheme 1. Divergolides, Their Biosynthetic Origin, and Their Relation to the Hygrocins



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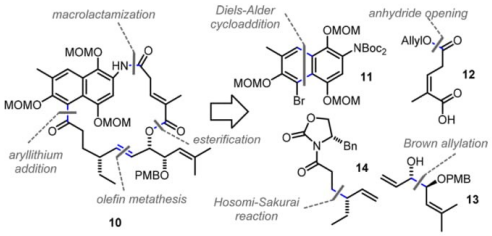
We now report a concise synthesis of divergolide I (**1**) that proceeds through a *proto*-divergolide of type **8** and sheds light on the conditions needed for its cyclization. Divergolide I was reported by Hertweck in 2015 from *Strepromyces* sp. HKI0595 and showed the broadest antibacterial activity of all members of the family examined to date.[1c] The configuration of its quaternary C4″-carbon was very recently assigned to be (*S*) using a comparison of X-ray and CD spectra.[5]

From the outset, we aimed at a synthesis of *proto*-divergolide (**8**), or a protected derivative thereof, to study the proposed biosynthetic diversification. A *proto*-divergolide, which has never been isolated, is a challenging target in itself due to the presence of a lactam and a lactone linkage held together by a sensitive and reactive glutaconic acid moiety. After extensive evaluation of different assembly strategies using different *ansa* fragments and protecting groups strategies, we arrived at the synthetic strategy depicted in Scheme 2. It dissects a protected

Scheme 2. Retrosynthetis of a *proto*-Divergolide Precursor (10)

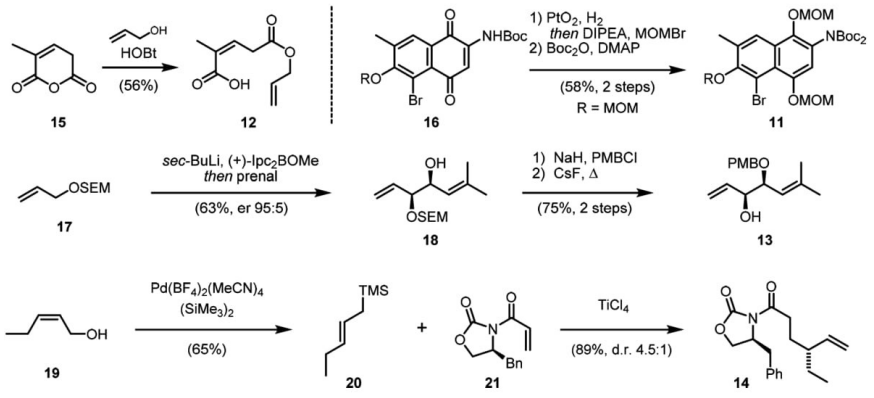


precursor to the *proto*-divergolide (**8**) into four fragments that represent the naphthoquinone moiety (**11**), the glutaconic acid unit (**12**), and the stereochemically complex portions of the *ansa* chain (**13** and **14**). A linear macrolactamization precursor could be assembled from these via olefin cross metathesis and aryl lithium addition to an aldehyde followed by esterification of an allylic alcohol. Cyclization would furnish 19-membered macrolide **10**, which was to be further elaborated via a biomimetic ring contraction to arrive at **1**.

The assembly of these fragments is shown in Scheme 3. Treatment of the readily available anhydride **15**[6] with HOBt in allyl alcohol afforded monoester **12** as the sole product. Naphthalene **11** could be accessed by reducing the previously prepared naphthoquinone **16**[4c] with H_2 in the presence of Adam's catalyst and trapping of the hydroquinone as a *bis*-MOM ether. A second carbamoylation of the Boc-carbamate masked its acidic functionalities to allow for an efficient halogen−metal exchange. The (*S*,*S*)-1,2-diol portion of the *ansa* chain was installed via Brown allylation.[7] Deprotonation of the SEM-protected allyl alcohol **17**[8] followed addition of (+)-Ipc_2BOMe, and then prenal gave allylic alcohol **18** with high enantiomeric excess. PMB-protection and desilylation then afforded allylic alcohol **13** as a suitable substrate for olefin cross-metathesis.[9] The choice of a PMB ether as a protecting group in **13** was based on the expectation that this group could be removed at a late stage of the synthesis without inducing a concomitant 1,2-acyl shift. The last fragment of the *ansa* chain was assembled via Hosomi−Sakurai reaction. To this end, Szabó's method[10] was used to directly convert (*Z*)-pent-2-enol (**19**) into allyl silane **20**. Lewis acid promoted addition of **20** to the chiral acryl oxazolidinone **21**[11] afforded alkene **14** in good yield and with acceptable diastereoselectivity (4.5:1).[12] An extensive screening of different Lewis acids and acrylated chiral auxiliaries was carried out, but the d.r. of the reaction could not be improved.

With olefin **14** in hand, the stage was set to explore the cross metathesis with allylic alcohol **13** (Scheme 4). After thorough examination of reaction conditions, we established that concentrating a solution of **13** and **14** at 40 °C in the presence of a Hoveyda−Grubbs second generation catalyst resulted in high yields of (*E*)-alkene **22**. A subsequent three-step sequence consisting of oxazolidinone cleavage with a thiol, protection of the allylic hydroxy group as a carbonate, and Fukuyama reduction of the thioester[13] afforded desired aldehyde **23**. Having developed robust routes for all carbon fragments, the assembly of divergolide I (**1**) commenced by addition of the aryllithium species generated from aryl bromide **11** to aldehyde **23** to afford alcohol **24** as an inconsequential mixture of diastereomers. Dess-Martin oxidation then yielded ketone **25** as a 1:1 mixture of atropisomers, which is well documented for naphthyl ketones of this type.[3d,4c] Thermal Boc-deprotection of

Scheme 3. Fragment Assembly: Synthesis of Glutaconic Acid 12, Naphthalene 11, (*S*,*S*)-Diol 13, and Olefin 14



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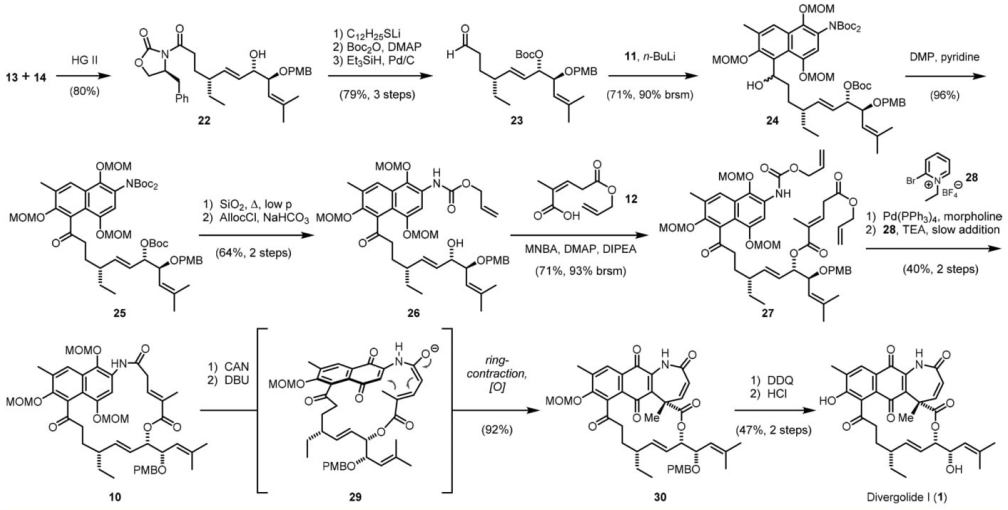
Scheme 4. Total Synthesis of Divergolide I (1): Cross Metathesis, Macrolactamization, and Biomimetic Ring Contraction



the naphthyl amine and the secondary hydroxy group and selective reprotection of the free amine as an allyl carbamate yielded alcohol **26**. Our endgame strategy called for the formation of an ester bond between hindered secondary alcohol **26** and glutaconate **12**, followed by macrolactamization. Other attempts at closing the 19-membered heterocycle of **10**, e.g. via olefin metathesis or macrolactonizations, had failed. Screening of several coupling methodologies revealed that only the Shiina protocol[14] delivered ester **27** in good yields. Interestingly, the esterification was accompanied by complete (*Z*) to (*E*) isomerization of the glutaconic diester.

With the carbon skeleton assembled, we proceeded to simultaneously cleave the nitrogen and carboxyl protecting groups. Using palladium catalysis,[15] we were able to isolate an air-sensitive amino acid, which was immediately subjected to macrolactamization. After evaluating the Yamaguchi reagent and carbodiimide, uronium, and phosphonic acid based reagents to no avail, we found that Mukaiyama type salts[16] could deliver macrolide **10** in an acceptable yield under high-dilution conditions. We isolated a single atropisomer of **10**, which means that the macrolactamization proceeds with high diastereoselectivity.[17] Unfortunately, we were unable to fully elucidate the stereochemistry of this atropisomer since NOE measurements were inconclusive and **10** failed to yield suitable crystals for X-ray analysis. Molecular models, literature precedence,[4c,18] and our NMR spectra suggest, however, that the naphthalene moiety cannot rotate freely relative to the *ansa* chain and that atropisomery should indeed be possible.

In the final stage of our synthesis, we investigated the oxidation of the highly electron-rich naphthalene **10** to the corresponding naphthoquinone. This compound would presumably be highly unstable.[1e] Our hope was that addition of a base would trigger one or several of the biomimetic cyclization modes shown in Scheme 1 and would lead to isolable products. Thus, we subjected **10** to CAN, followed by treatment of the resulting crude material with DBU in the presence of air. We were pleasantly surprised that this yielded azepinone **30**, which bears the C4″ quarternary stereocenter, *as the sole product and in very high yield*. Removal of the remaining allylic PMB group and the naphthalenic MOM ether then furnished divergolide I (**1**). NMR, HRMS, IR, and optical rotation data of synthetic **1** were in good agreement to those published by Hertweck.[1c] This confirms the relative configuration of divergolide I and establishes the absolute configuration of the divergolide and hygrocin series.[1]

In summary, we have reported the first synthesis of a divergolide class ansamycin, which provided insights into the formation of these molecules in Nature. Our synthesis is highly convergent, relatively short (19 steps longest linear sequence), and enantioselective. It provides access to a *proto*-divergolide in a protected form, and we believe it could be adapted to reach other divergolides and hygrocins. It features the strategic use of a cross metathesis and the application of advanced methods for ester and amide bond formations. Several protecting group manipulations were required to install the sensitive and reactive glutaconic acid moiety at a late stage of the synthesis. We believe that their orchestration is an intellectual achievement in itself. The final cyclization and ring contraction are noteworthy in several respects. The glutaconic enolate formed from **30** must undergo bond rotation, and the amide has to reside in the *s-cis* conformation for the cyclization to occur (cf. compound **29**, Scheme 4). The ring contraction could be seen as an intramolecular conjugate addition of a vinylogous enolate onto the napththoquinone or as an 8π-electrocyclization.[19] Under our conditions, the cyclization was surprisingly selective yielding only **1** and not **2**, **3**, or **4**, as 1,2-additions during ring contraction and 1,2-acyl shifts during PMB removal were not observed. It is interesting to speculate whether the other divergolides could be formed from an atropisomer of *proto*-divergolide **8** and whether a 1,2-acyl shift or glutaconic olefin isomerization prior to cyclization would lead to a different regio- and stereochemical outcome. Although no evidence from the sequencing of the biosynthetic clusters has been provided,[1b,2] it cannot be excluded that the final cyclizations

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and/or the 1,2-acyl shifts in the divergolide and hygrocin biosyntheses are catalyzed by enzymes. As our program on the divergolides and hygrocins unfolds, we hope to provide additional answers to some of the questions posed by these fascinating molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b13092.

Experimental procedures and spectral data (PDF)
Crystallographic data for compound **12** (CIF)
Crystallographic data for compound **16** (CIF)

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Notes

The authors declare no competing financial interest.

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(17) A more in-depth discussion of the available data can be found in the Supporting Information.

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