PHOTOCHEMICAL PREPARATION OF SALICYLATE/RESORCYLATE ESTERS/AMIDES: ASYMMETRIC SYNTHESIS OF SCH 351448

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In memory of my father Ali,

and for my mother Zohreh.

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by

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Omid Soltani Ph.D.

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Supervising Professor: Jef K. De Brabander Ph.D.

This body of work is divided into two parts. The first part describes the development and general application of a photochemical based methodology for the preparation of substituted salicylate/resorcylate esters and amides. Substitued salicylate/resorcylate esters and amides are found in a variety of biologically active natural products. Naturally occurring molecules with these structural moieties are of interest to both the chemistry and biology communities due to their unique structures and biological activities. Preparation of these esters and amides is often a non-trivial task due to a combination of electronic and steric effects. To date, a variety of methods have been developed to access salicylate/resorcylate esters and amides, however many of these methods suffer from limitations such as poor substrate scope or they require the use of harsh conditions. The photochemical based method described herein addresses some of these issues and provides a general method for the efficient preparation of these structural units.

The second portion of this thesis is concerned with the asymmetric synthesis of the natural product SCH 351448. This synthesis utilizes a highly convergent approach that takes advantage of the dimeric nature of the natural product. A key step in the sequence involves the photochemical coupling of two analogous fragments to provide the complete carbon skeleton of SCH 351448. Also, an optimized and shortened route to the natural product is presented. Finally, preliminary experiments provide insight into the biological function of the natural product.

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PRIOR PUBLICATIONS

- Ashoke Bhattacharjee, Omid Soltani, Jef K. De Brabander: "Synthesis of the C1-C21 (C1'-C21') Fragment of the Dimeric Polyketide Natural Product SCH 351448", *Organic Letters*, **2002**, 4, 481-484.

- Omid Soltani, Jef K. De Brabander: "Synthesis of Functionalized Salicylate Esters and Amides by Photochemical Acylation", *Angewandte Chemie International Edition*, **2005**, 44, 1696-1699.

- Omid Soltani, Jef K. De Brabander: "A Concise Synthesis of SCH 351448", *Organic Letters*, **2005**, 7, 2791-2793.

- Omid Soltani, Ashoke Bhattacharjee, Xiao-Song Xie, Jef K. De Brabander, "Synthesis and Initial Functional Evaluation of the Natural Product SCH 351448", Manuscript in Preparation.

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LIST OF ABBREVIATIONS

Ac – Acetyl

AIBN – Azobis(isobutyronitrile)

aq – Aqueous

9-BBN – 9-Borobicyclo[3.3.1]nonane

Bn – Benzyl

BRSM – Based on Recovered Starting Material

n-Bu – butyl

cat – Catalytic

d – Day

DCC – Dicyclohexyl Carbodiimide

DCM – Dichloromethane

DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DIAD – Diisopropylazodidicarboxylate

DIPEA – Diisopropyl ethylamine

DMAP – 4-Dimethylaminopyridine

DME – Dimethoxyethane

DMF – Dimethylformamide

DMSO – Dimethylsulfoxide

EtOAc – Ethyl acetate

Hex – Hexane

hGH – Human Growth Hormone

hr – Hour

hν – Light

i-Pr – Iospropyl

IR – Infrared

$LiAlH_4$ – Lithium Aluminum Hydride

min – Minute

MOM – Methoxymethylether

NaHMDS – Sodium Hexamethyldisilazide

NMM – *N*-methylmorpholine

NMO – *N*-methylmorpholine-*N*-oxide

NMP – *N*-methylpyrrolidinone

Ph – Phenyl

PMB – Paramethoxybenzyl

TBAF – Tetra-*n*-butylammonium fluoride

TBS – *tert*-Butyldimethylsilyl

t-Bu – *tert*-Butyl

TES – Triethylsilyl

Tf – Trifuoromethanesulfonyl

TMS – Trimethylsilyl

TMSE – Trimethylsilyl Ethyl

UV – Ultraviolet

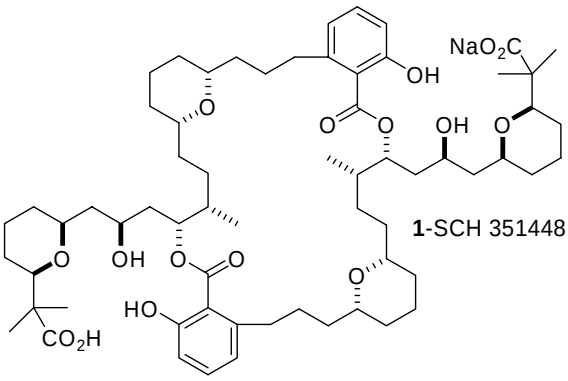
CHAPTER ONE

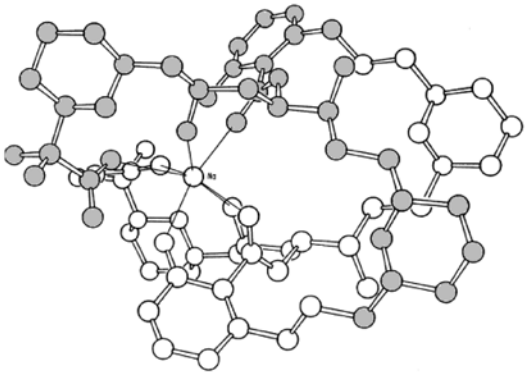
SALICYLATE/RESORCYLATE NATURAL PRODUCTS AND METHODS FOR THEIR PREPARATION

1.1 Salicylate Ester Formation for the Natural Product SCH 351448

SCH 351448 is a macrocyclic salicylate containing natural product derived from a *Micromonospora* microorganism[1] (Fig. 1.1). Bioassay guided fractionation aided the isolation of this compound which displayed moderate activity in a low density lipoprotein receptor (LDL-R) transcription translation assay (EC_{50} = 25 μM). Extensive spectroscopic and x-ray crystallographic analysis unambiguously established SCH 351448 as a C_2 symmetrical dimer composed of two identical diacids. Intrigued by SCH 351448's novel ionophoric structure and promising biological activity, we initiated a synthetic program to access ample quantities of the natural product for further structural and biochemical studies.

Fig. 1.1 SCH 351448 (Reproduced from Ref. 1)

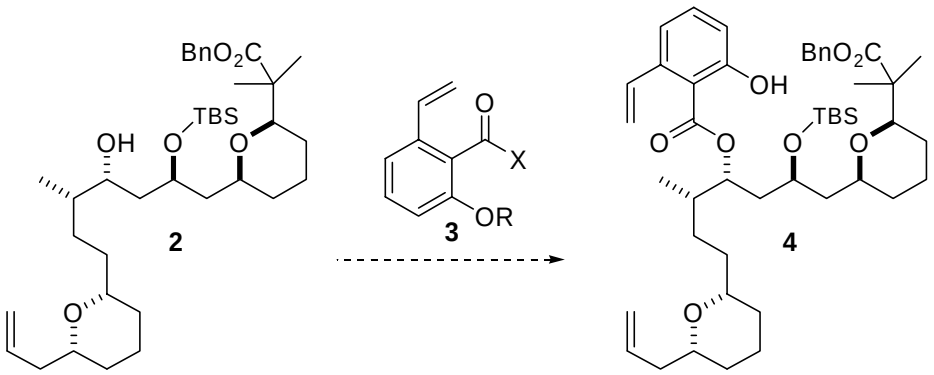




Crystal Structure of **1**

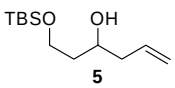
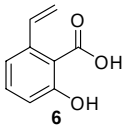
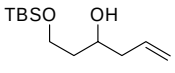
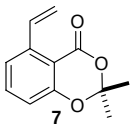
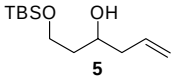
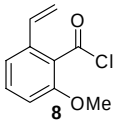
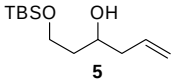
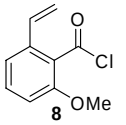
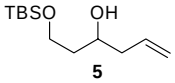
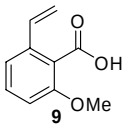
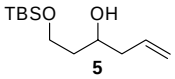
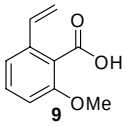
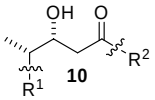
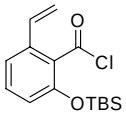
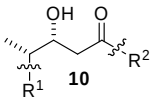
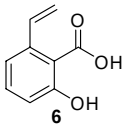
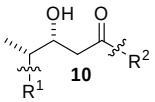
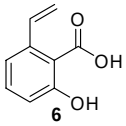
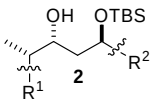
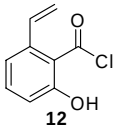
A major obstacle encountered during the synthesis of SCH 351448 was the acylation of alcohol **2** to provide vinyl substituted salicylate ester **4** (Eq. 1).

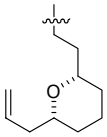
Eq. 1

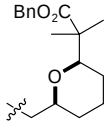


This pivotal transformation was explored under a variety of conditions with model substrates and fully elaborated intermediates such as alcohol **2** (Table 1.1). Many of the conditions attempted are well established protocols for ester formation (e.g. Mitsunobo inversion, Yamaguchi acylation, esterification with acid-chlorides). A majority of these methods rely upon activation of the carbonyl to provide a highly electrophilic center. Unfortunately, we were unable to exploit any of these contemporary acylation methods.

Table 1.1 Attempted Salicylate Ester Formation

Entry	Substrates		Conditions	Results
1	 **5**	 **6**	HATU, DIPEA, 95 °C, DMF	No Rxn.
2	 **5**	 **7**	EtMgBr, THF	Decomposition
3	 **5**	 **8**	Et_3N, DMAP, CH_2Cl_2	No Rxn.
4	 **5**	 **8**	NaH, THF	Decomposition
5	 **5**	 **9**	Yamaguchi Acylation	No Rxn.
6	 **5**	 **9**	2,2-dipyridyl disulfide, $AgClO_4$, PPh_3, THF	No Rxn.
7	 **10**	 **11**	Et_3N, DMAP, CH_2Cl_2	No Rxn.
8	 **10**	 **6**	Yamaguchi Acylation	No Rxn.
9	 **10**	 **6**	DCC, DMAP, CH_2Cl_2	No Rxn.
10	 **2**	 **12**	Pyridine, DMAP, Ph-Me, 65 °C	No Rxn.

R^1 = 

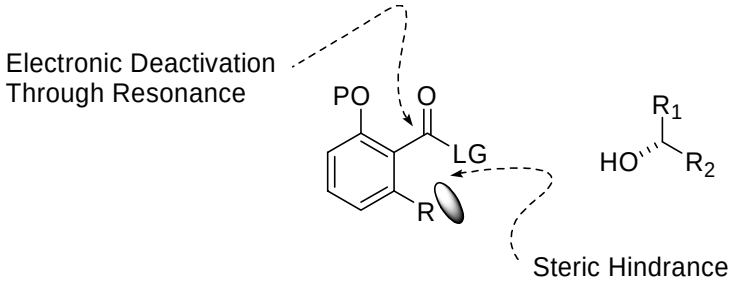
R^2 = 

For example, coupling of acylchloride **12** with alcohol **2** at 65 ˚C resulted in complete recovery of the alcohol (Table 1.1, entry 10). In another experiment, attempted ester formation of model alcohol **5** under strong basic conditions resulted in decomposition of the starting materials (Table 1.1, entries 2 and 4).

1.2 Synthesis of Salicylate Containing Natural Products

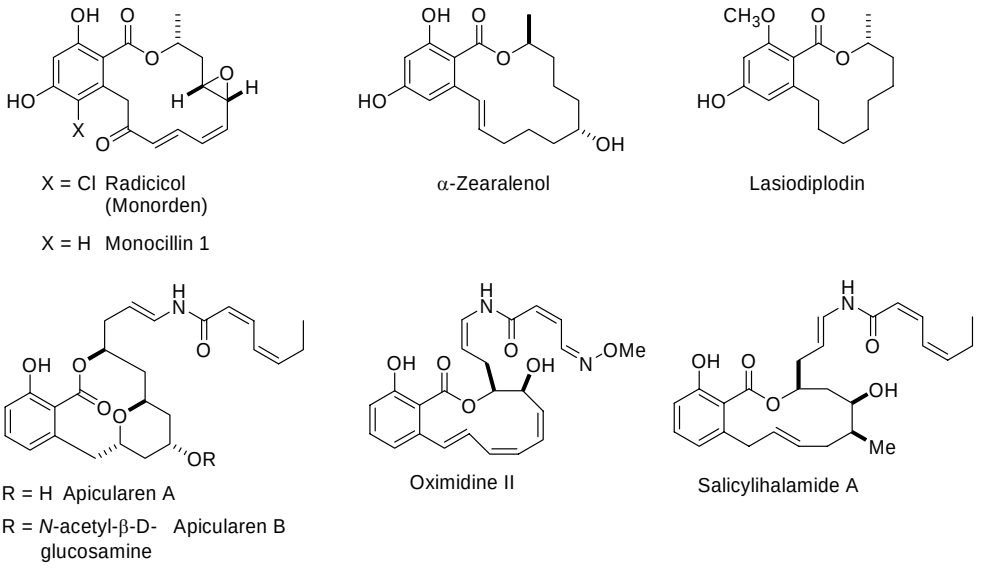
The difficulties encountered when preparing benzoate esters is two-fold in nature. First, the aromatic ring can donate electron density through resonance to the acyl carbon, thus diminishing the electrophilicity of the carbonyl group (Fig. 1.2). Secondly, steric hindrance associated with the ortho-substituents of the aromatic component obstructs the path of the incoming nucleophile (Fig. 1.2). This effect is exacerbated in cases where the coupling partner is also sterically encumbered.

Fig. 1.2 Acylation of Salicylate acid Derivatives



Despite the inherent problems associated with salicylate ester formation, numerous solutions have been formulated in the context of several biologically active natural products that contain this structural moiety[2] (Fig. 1.3).

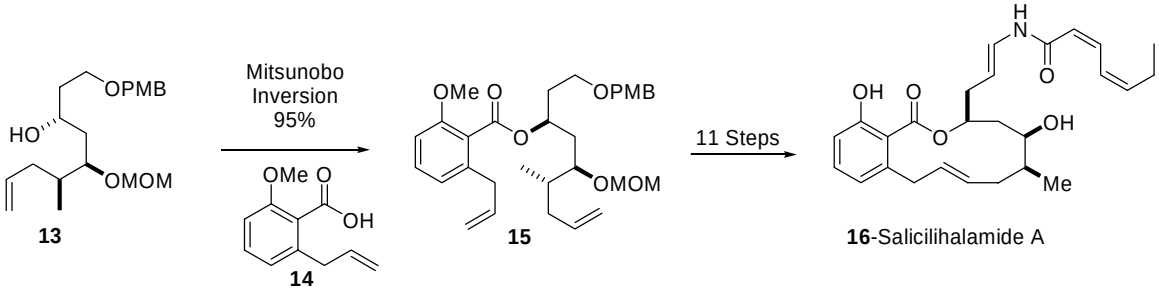
Fig. 1.3 Salicylate/Resorcylate Natural Products



Reactivity umpolung via the Mitsunobo esterification has provided one solution for the synthesis of several salicylate and resorcylate containing natural products (e.g. salicylihalamide and radicicol). This reaction is particularly well suited for the preparation of benzoate esters because the electron rich aromatic acid can now serve as an effective nucleophile in a Sn2 type process.

Salicylihalamide A, a potent inhibitor of the mammalian vacuolar type (H^+) ATPase (V-ATPase)[3], has been synthesized by several groups who utilized the Mitsunobo inversion for ester bond formation[2]. An example of this approach is outlined in scheme 1.1 with De Brabander's synthesis of Salicylihalamde A[4].

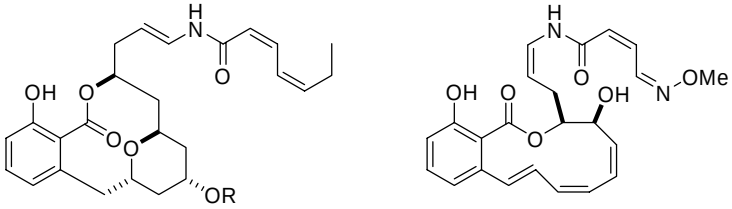
Scheme 1.1



De Brabander and colleagues noted that numerous protocols for ester bond formation were examined unsuccessfully prior to establishing the Mitsunobo reaction as the method of choice. De Brabander's synthesis of salicylihalamide A established an efficient approach to this class of natural products that would be adopted by other groups[5]. To illustrate how essential this reaction has been for the preparation of salicylate ester containing natural products one need only to look at the various syntheses of salicylihalamide A[2]. To date there are more than half a dozen published syntheses of salicylihalamide A, an overwhelming majority of which utilized the Mitsunobo inversion for ester bond formation. Despite this fact, this reaction has a number of limitations that cannot be overlooked. For example, certain scenarios may arise where inversion at a stereogenic center may not be desired, thus requiring hydrolysis of the initial ester formed followed by a subsequent invertive acylation. Also, substrates such as β-hydroxyketones are prone to undergo elimination processes under the basic conditions employed in the Mitsunobo reaction. Also worth noting, hindered secondary and tertiary alcohols are inert under Mitsunobo conditions. Finally, a major by-product of this reaction, triphenylphosphine oxide, often impedes the purification process.

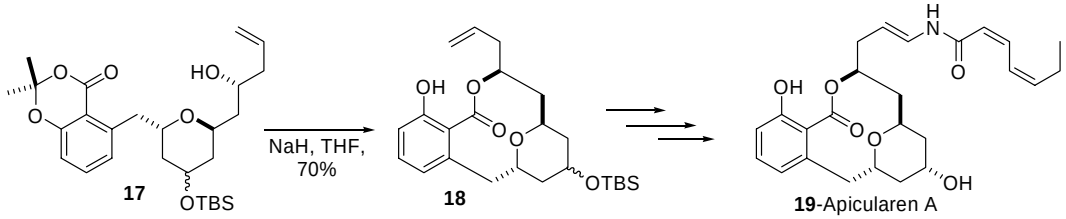
Alkoxide mediated acylation of benzodioxinones is another method used to prepare substituted benzoate esters. Benzodioxinones are quite susceptible to alkaline transesterification even with highly hindered nucleophiles. A variety of natural products such as apicularen A[6,7] and oximidine II[8] have been accessed via this methodology (Fig. 1.4).

Fig. 1.4 Apicularen A and B and Oximidine II



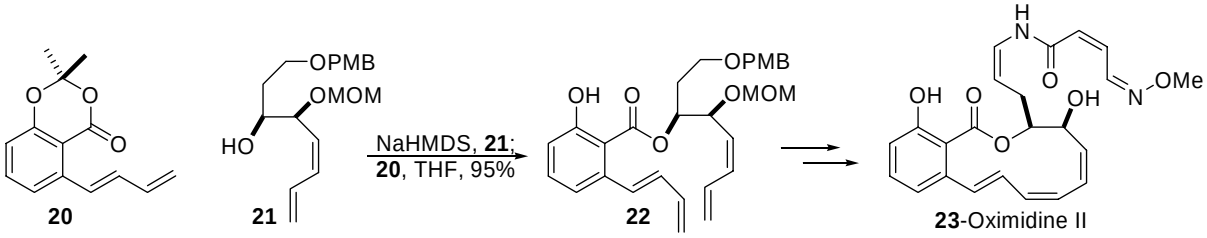
Perhaps one of the first and most elegant applications of this approach comes from De Brabander and coworkers' synthesis of the cytotoxin apicularen A (Scheme 1.2)[9,10]. In this example, the sodium alcoholate derived from alcohol **17** underwent smooth intramolecular macrolactonization to afford lactone **18**.

Scheme 1.2



An ensuing synthesis of apicularen A by Nicolaou[11,12] et al also relied on this strategy for ester formation. Porco and coworkers used this method in a bimolecular sense in their oximidine II synthesis[13] (Scheme 1.3). Also worth noting, Molander and coworkers utilized alkoxide mediated esterification en route to an intermediate in Porco's synthesis of oximidine II, thus achieving a formal total synthesis of this natural product[14].

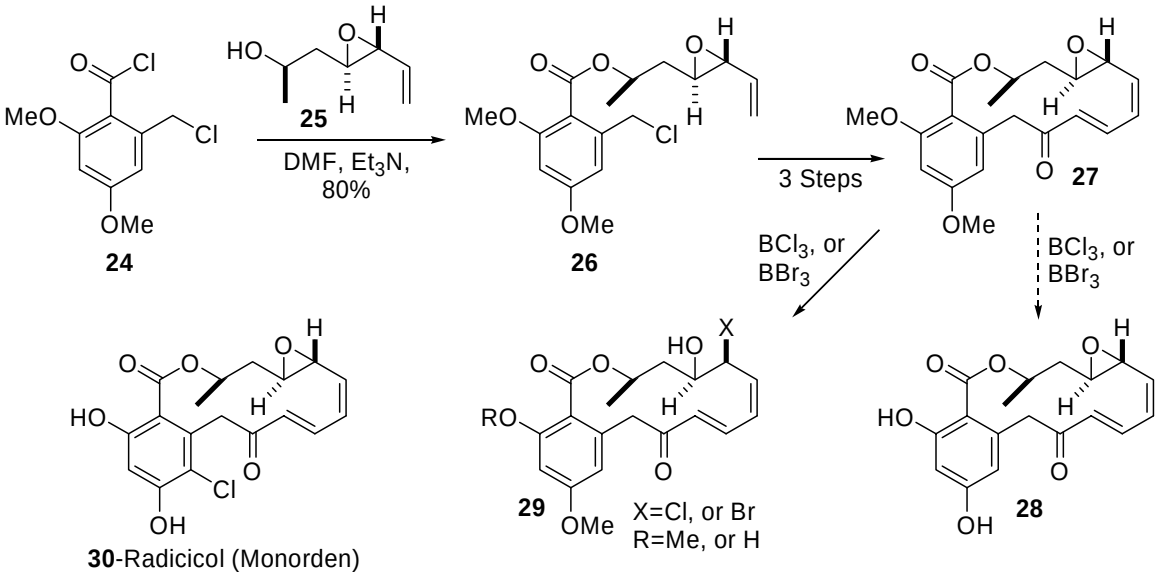
Scheme 1.3



Alkoxide mediated transesterification of benzodioxinones is an effective strategy for both inter and intramolecular acylation, however, a significant disadvantage is the strong basic conditions employed. Substrates susceptible to elimination, olefin isomerization, or other base mediated process are obviously poor candidates for this method of esterification.

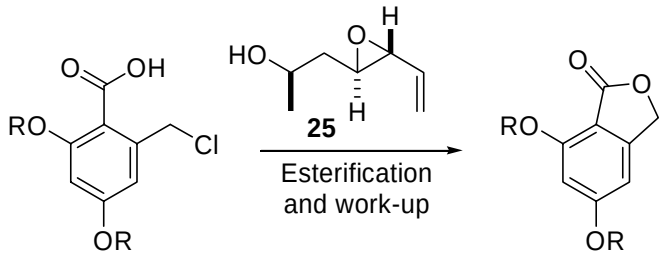
Another strategy for the synthesis of this class of natural products is de-novo aryl synthesis. Notably, Danishefsky and Rychnovsky have taken advantage of this chemistry in their syntheses of functional radicicol analogues[15,16] and apicularen A[17] respectively. Danishefsky's first generation approach to radicicol called for acylation of acid chloride **24** with the relatively non-hindered alcohol **25** (Scheme 1.4). This strategy led to bis-methoxy ether **27**, a compound that could not be liberated to the free phenol without degradation of the labile epoxide.

Scheme 1.4



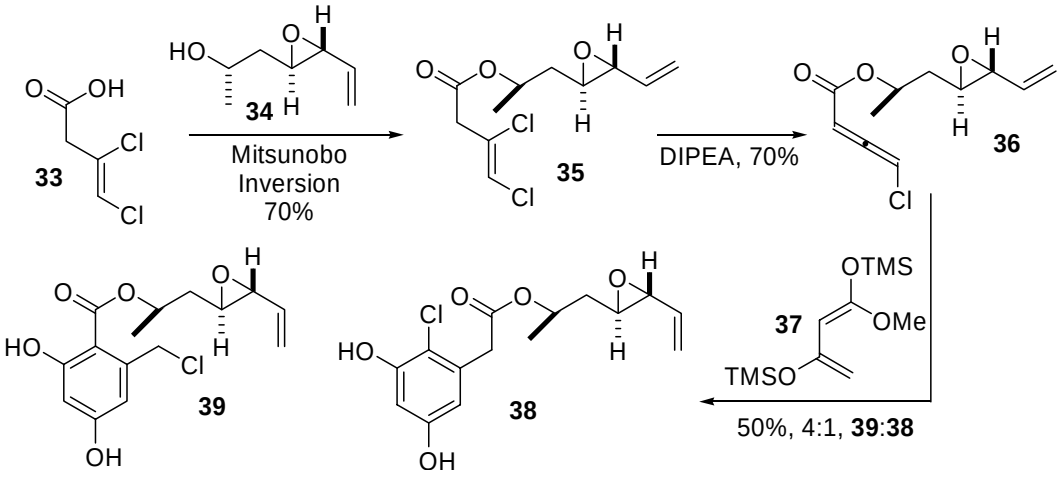
Screening of various protecting groups at the phenol position led to substrates that underwent competing phthalide formation (**31**→**32**) rather than acylation (Scheme 1.5).

Scheme 1.5



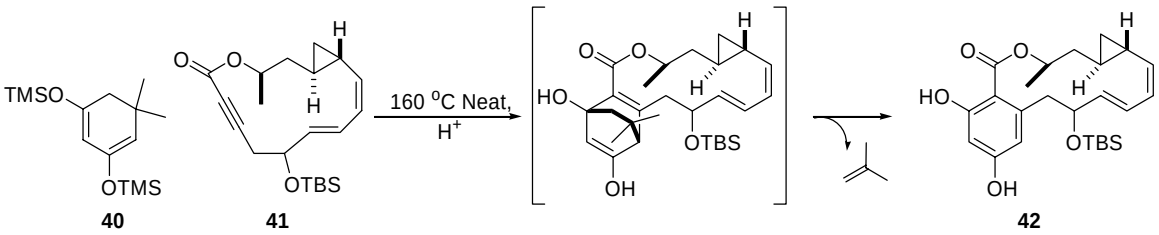
To circumvent phthalide formation, Diels-Alder chemistry was employed to construct the aromatic portion of the molecule following esterification (Scheme 1.6). Briefly, heating of electron rich diene **37** in the presence of chloroallene **36** led to the regioisomeric cycloadducts **38** and **39**. Although this cycloaddition proved successful, the poor regioselectivity was less than desirable.

Scheme 1.6



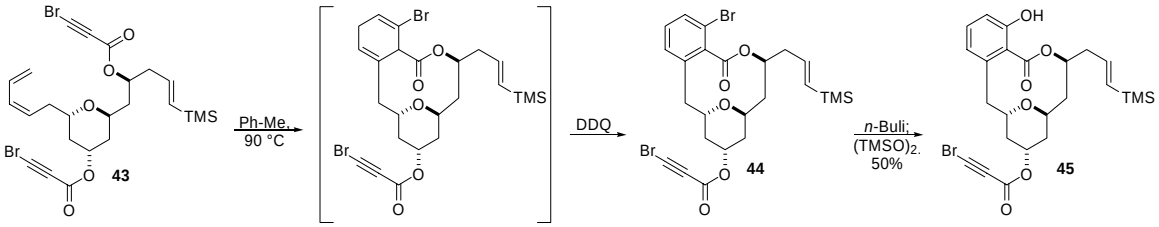
Subsequent to this result, Danishefsky and colleagues developed ynolide based cycloaddition methodology for the preparation of various resorcylate containing natural products and analogues[16] (Scheme 1.7). After substantial experimentation, they found that cycloaddition of cyclic diene **40** with ynoate **41** provided resorcylate **42** via a Diels-Alder retro Diels-Alder sequence.

Scheme 1.7



In a conceptually similar approach, Rychnovsky and coworkers prepared the macrocyclic benzoate **44** via intramolecular Diels-Alder of ynoate **43**, followed by aromatization of the resultant 1,4-cyclohexadiene with DDQ (Scheme 1.8). An additional oxidation of bromide **44** to phenol **45** was required (50%). In this example, the unimolecular nature of the reaction helped overcome the high entropic barrier associated with cycloaddition reactions of acyclic dienes.

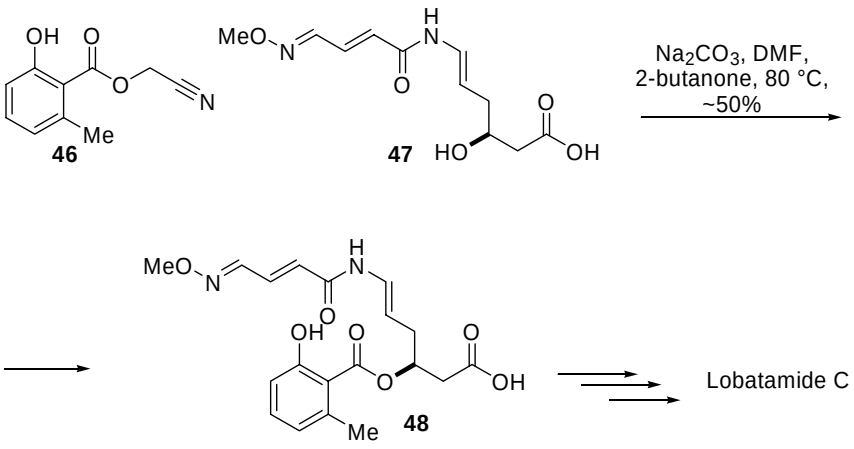
Scheme 1.8



De-novo aryl ester synthesis is a refreshing solution to aromatic ester formation. One drawback to this approach however, is the utilization of high temperatures for successful cycloaddition (90 ˚C-160 ˚C).

Finally, Porco and co-workers have developed chemistry, based on precedent described in a South African patent[18], which utilizes cyanomethyl esters for the synthesis of salicylate esters[19]. Application of this chemistry led to a synthesis of the *N*-acyl enamine containing natural product lobatamide C[19] (Scheme 1.9).

Scheme 1.9



Experimentation in this arena has shown that free phenolic cyanomethyl esters such as **46** undergo efficient acylation upon heating in the presence of sodium or potassium carbonate (Scheme 1.9). Substrates with protected phenols or without substitution at the ortho-position were shown to be significantly less reactive. Additionally, molecular modeling studies indicate that the free phenol may play a role as a general base in this acylation. It is postulated that acylation is aided by rotation of the ester carbonyl out of the plane of the aromatic ring thus enhancing its electrophilicity[19].

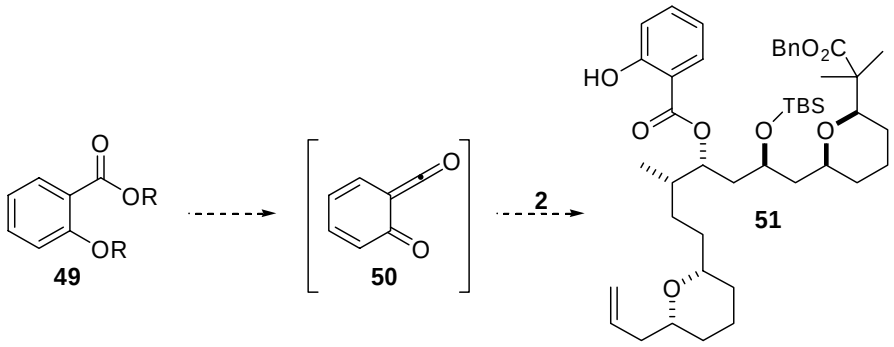
Broad application of this chemistry has yet to be realized, however, successful implementation of this approach with acid sensitive substrates such as *N*-acyl enamine **47** is impressive (Scheme 1.9). The use of carbonate bases at high temperatures probably precludes the use of base sensitive materials under these conditions. Finally, the scope of compatible nucleophiles for this reaction remains largely unknown.

1.3 Summary and Conclusions

The variety of methods available for the synthesis of substituted salicylate and resorcylate ester and amides continues to grow and highlights the problems associated with more conventional approaches. Many of the approaches discussed above provided

an adequate solution to the synthesis of this structural unit, however successful implementation of these methods is often case dependent. As mentioned in the introduction, our synthesis of the natural product SCH 351448 was impeded by a surprisingly difficult salicylate ester bond formation (Fig. 1.1, pg. 1). This was unexpected considering the number of synthetic tools available, including those discussed above. This roadblock prompted efforts to uncover potentially new reaction manifolds to these molecules. One potential solution we envisioned was the formation of an electrophilic salicylate congener in the form of quinoketene **50** (Scheme 1.10). We inferred that a quinoketene such as **50**, if generated in a synthetically useful manner, would be electrophilic enough to couple with hindered nucleophiles such as alcohol **2** – a process that would benefit from gaining aromatic stabilization. Examination of the literature on quinoketenes revealed several studies that showed promise regarding the desired transformation (Scheme 1.10, **48**→**51**). These reports will be discussed thoroughly in the following chapter.

Scheme 1.10



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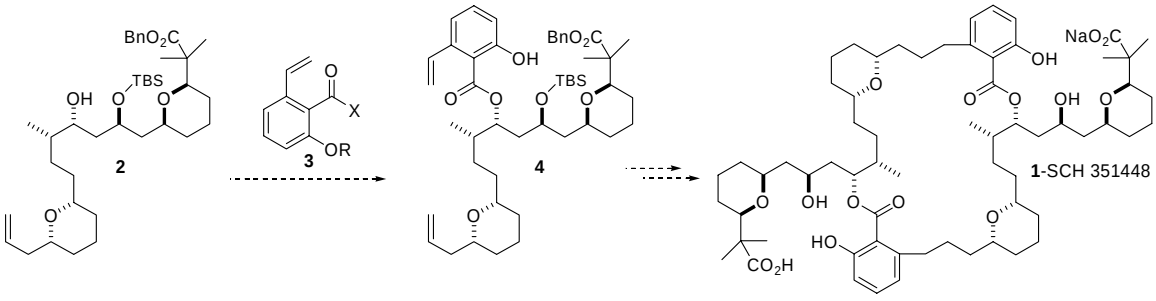
CHAPTER TWO

PHOTOCHEMICAL PREPARATION OF SALICYLATE/RESORCYLATE ESTERS AND AMIDES

2.1 Synthesis of SCH 351448

As mentioned in the introduction, our initial efforts towards the synthesis of the natural product SCH 351448 called for the acylation of alcohol **2** with *o*-vinyl substituted salicylate **3**. Bis terminal olefin **4** would then serve as a precursor for a head-to-tail dimerization (vide infra). As discussed in chapter 1, numerous efforts to promote coupling of hindered aliphatic alcohol **2** with an activated aromatic fragment resulted in either recovered starting materials or decomposition (see Chapter 1, Table 1.1). Methods employed to promote this reaction included the Mitsunobo inversion, Yamaguchi esterification, acylation with acid-chlorides, and several peptide coupling protocols.

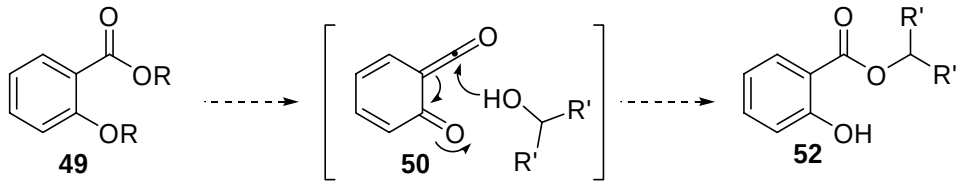
Scheme 2.1



The high degree of steric hindrance associated with the alcohol **2** coupled with the relatively inert nature of salicylic acid derivatives towards acylation are factors that contributed to this difficult transformation.

One approach considered for the formation of benzoate ester **4** was *in-situ* generation and addition of quinoketenes such as **50** (Scheme 2.2).

Scheme 2.2

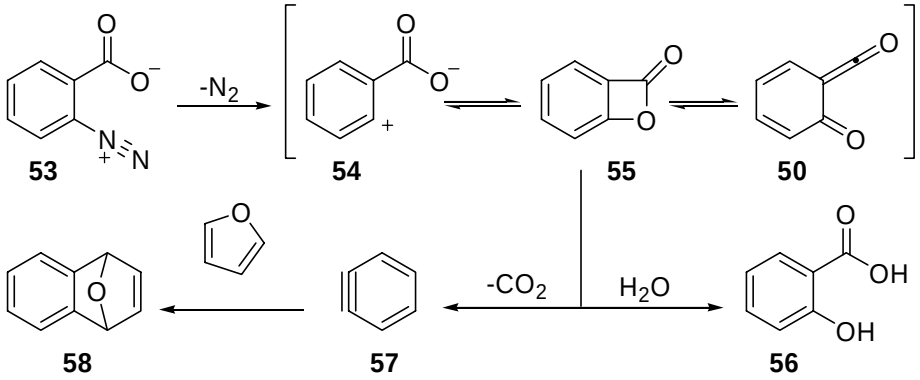


Examination of the literature regarding these reactive intermediates revealed numerous studies which ranged from the late 1960's to the 1990's. Many of these reports focused on these reactive species in terms of spectral characterization. Few, if any of these studies concerned the utilization of these ketenes as useful intermediates in synthesis. A likely source of discouragement in this regard was the fact that access to this reactive species required high energy input in the form of ultraviolet light or extreme temperatures (See Section 2.3).

2.2 Identification of Quinoketene Intermediates

In an the late 1960's Gompper and co-workers studied the decomposition of *o*-benzenediazonium carboxylates[1] (e.g. **53**, Scheme 2.3). These reactive precursors decomposed to the reactive intermediate of interest, benzyne **57**, via loss of nitrogen and carbon dioxide (Scheme 2.3). Indirect evidence for the formation of **57** was obtained via trapping with furan to afford the corresponding dihydroepoxynaphthalene **58**. An unexpected outcome of these experiments was the formation of salicylic acid **56**. It was conjectured that formation of this acid was the result of hydration of the reactive lactone species **55**. The authors of this study went on to propose the equilibrium between lactone **55**, ketene **50**, and carboxylate **53**.

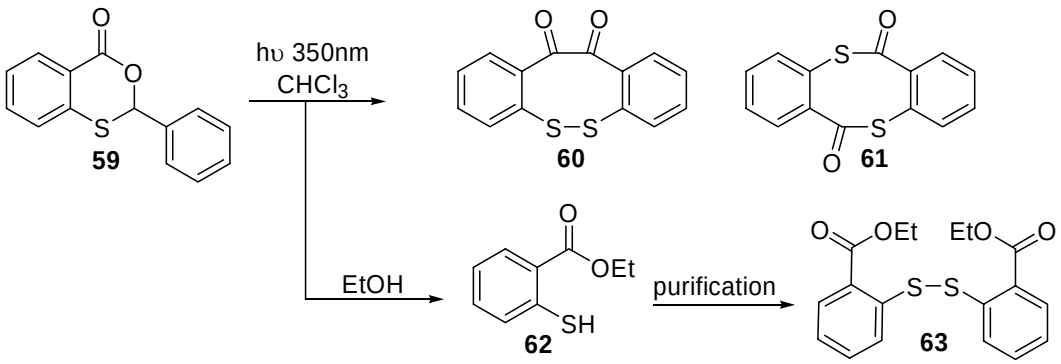
Scheme 2.3



Direct evidence corroborating existence of either of intermediates **55** or **50** was not obtained, however formation of salicylic acid provided some indirect evidence for the existence of these intermediates. A potential mechanism of decomposition initiates with loss of nitrogen followed by decarboxylation to provide **57**, which then undergoes Diels-Alder chemistry with furan (Scheme 2.3). Alternatively, hydration of **50** or **55** may occur prior to decarboxylation to provide acid **56**. Interestingly, varying the concentration of water, furan, or carboxylate **53** did not affect product ratio. This initial finding provided an impetus for more detailed studies of these reactive intermediates.

In 1970 Kolc published studies concerning photochemical properties of benzoxathiones[2]. In this report, benzoxathione related compounds were found to undergo photochemical fragmentation to produce a variety of products depending on the nature of the reaction conditions (Scheme 2.4). More specifically, photolysis of 2-phenyl-3,1-benzoxathian-4-one **59** in non-polar solvents such as chloroform led to the formation of a solid that was later identified as either head-to-head dimer **60** or head-to-tail dimer **61**. Comparison of this material by TLC, and melting point with the known thioester **61** apparently revealed dramatic differences in these properties, thereby revealing **60** as the correct structure.

Scheme 2.4



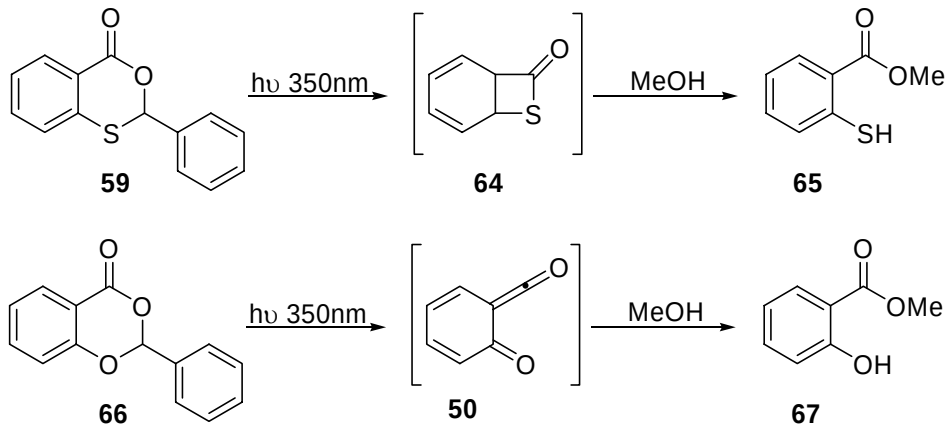
Compound **60** was treated with Raney nickel resulting in disulfide bond cleavage and formation of benzoin and benzil. In contrast to this previous result, photolysis of **59** in ethyl alcohol resulted in formation of benzaldehyde and ethyl ester **62** (Scheme 2.4). Also, a product resulting from dimerization of **62** via disulfide bond formation was isolated. This product was attributed to the purification step since **63** was not observed in the crude reaction mixture.

To gain insights into this reaction, low temperature photolysis experiments were carried out in hydrocarbon glass to allow for direct observation of short lived intermediates by UV spectroscopy. In this experiment, benzoxathione **59** was photolyzed (350 nm) for one half hour at 77 K. After the initial photolysis, UV spectra revealed the depletion of the starting material. The sample was then shielded from any source of light and allowed to warm to room temperature. Kolc and coworkers noted that formation of benzaldehyde was clearly observed only when the sample was allowed to warm. Also, an absorption band with similar spectral properties as the starting material was observed during the warming process. Quantum yield studies of benzoxathione substrates with varied substituents at the acetal position revealed a dramatic enhancement of photolytic

efficiency in the presence of aryl substituents at the 2-position. This finding pointed to a mechanism involving homolytic bond cleavage at the acetal position.

Soon after this study by Kolc, Chapman and co-workers conducted flash photolysis experiments with benzoxathione **59**[3]. Chapman found that photolysis of this substrate did indeed produce a dimeric compound as reported by Kolc, however Chapman concluded this dimer was in fact the head to tail bis-thioester **61** (Scheme 2.4, vide supra). This study utilized flash photolysis as a technique to identify reactive intermediates by IR spectroscopy. Photolysis of **59** at 77 ˚K revealed IR bands corresponding to benzaldehyde (1699 cm^{-1}) and an unknown species (1803 cm^{-1}). At this temperature, IR bands corresponding to the previously isolated disulfide **60** were not identified. After the irradiation period, the sample was brought to -40 ˚C. This resulted in formation of an IR absorption band corresponding to thioester **61**. Also during the warming period, disappearance of the IR band corresponding to the unknown intermediate at 1803 cm^{-1} was observed. This pointed to an intermediate that is a potential precursor to thioester **61** (Scheme 2.4). When the reaction was conducted in the presence of methanol the intermediate IR absorption at 1803 cm^{-1} was once again observed at 77 ˚K, however, warming of the reaction resulted in disappearance of that band and concomitant formation of an IR absorption corresponding to methyl ester **65** (Scheme 2.5).

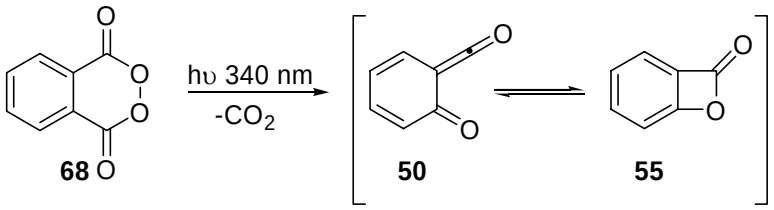
Scheme 2.5



These results led the authors to conclude that the unknown intermediate band (1803 cm^{-1}) is likely 2-thiobenzpropiolactone **64** (Scheme 2.5). They extended their study to benzodioxinone **66**. Flash photolysis of **66** in methanol led to the formation of methyl salicylate **67**. This result confirmed a similar reactivity pattern for **66** to that of **59**. In this particular example, however, IR absorption indicative of a lactone intermediate analogous to **64** was not observed. An absorption band at 2118 cm^{-1} was identified and assumed to be that of quinoketene **50**.

Similar studies on the photolysis of pthaloyl peroxide by Chapman and coworkers identified the formation of both the keto-ketene **50** reported earlier, in addition to benzpropiolactone **55**[4] (Scheme 2.6**)**. In these experiments, the products of photolysis were trapped at 8 ˚K which allowed for the observation of the short lived intermediate benzpropiolactone **55**. Chapman also pointed out that the intermediate keto-ketene **50** and the benzpropiolactone **55** were interconverable at 8 ˚K via irradiation at different wavelengths. He noted that wavelengths >340 nm favored conversion to the presumed lactone species, while those above 315 nm favored the keto-ketene.

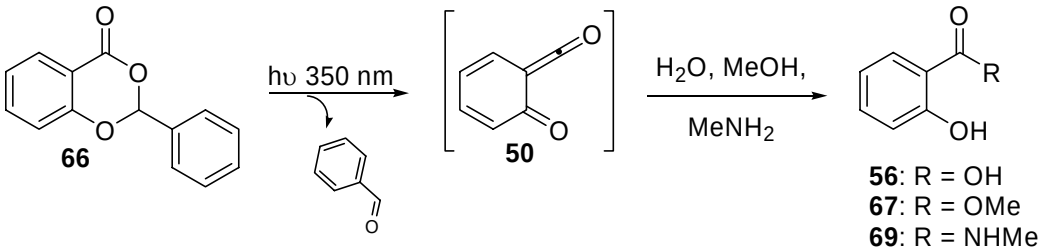
Scheme 2.6



More recently, extensive studies by Tidwell and co workers regarding the formation and reactivity of quinoketene **50** in solution were conducted[5]. In these studies time resolved laser flash photolysis was employed to characterize short-lived intermediates, and permitted the observation of quinoketene **50** in solution and at room temperature.

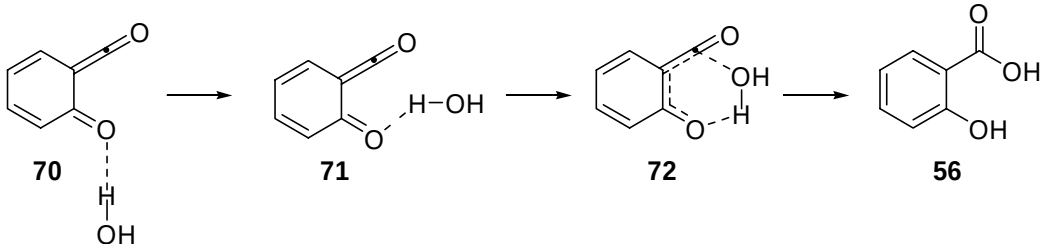
Once again the appearance of IR bands corresponding to benzaldehyde (1703 cm^{-1}) and ketene **50** (2135 cm^{-1}) were initially observed, followed by those corresponding to salicylic acid (1693 cm^{-1}) resulting from hydration of ketene **50**. The disappearance of benzodioxinone **66** was shown to be irreversible in nature. Also, the reaction order of **50** with water, methanol, and diethylamine was shown to be first order in nucleophile with rate constants of $(1.5 \pm 0.3) \times 10^7$, $(3.0 \pm 0.6) \times 10^7$, and $(1.1 \pm 0.2) \times 10^9$ M^{-1} s^{-1} respectively (Scheme 2.7).

Scheme 2.7



Computational studies were also carried out which pointed to a stepwise mechanism for the hydration of α-oxoketenes (Scheme 2.8).

Scheme 2.8



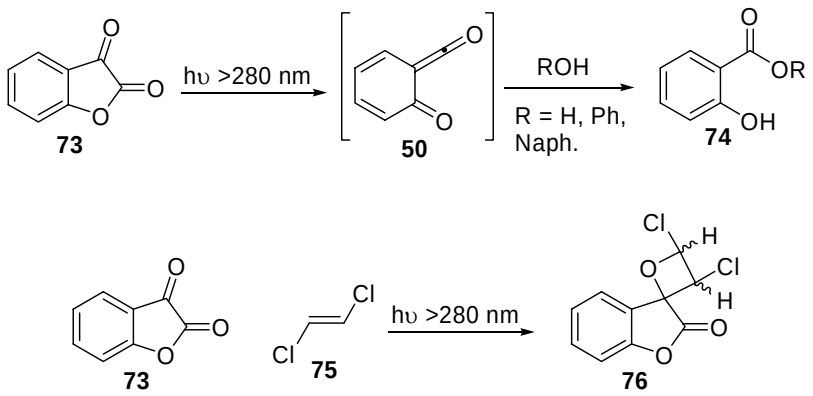
The mechanism described is reminiscient to that proposed for various acyclic α-oxoketenes. Following formation of hydrogen bonded complex **70**; rearrangement of the nucleophile forms a highly structured pseuodopericyclic transition state **72**, which leads to the aromatized product **56**. Despite the unfavorable entropic barrier associated with this highly ordered transition state, the overall process is thermodynamically favorable due to the resonance stabilization gained upon rearomatization. A series of calculations by Tidwell and co-workers estimated this process to be thermodynamically favorable by 39-40 kcal/mol.

2.3 Alternative Access to Quinoketenes

Although a majority of investigations related to the generation and study of quinoketenes focused on benzodioxinone **66** as a suitable precursor, these reactive intermediates are accessible from a variety of materials.

For example, Horspool and coworkers have shown that coumarandiones provide quinoketenes upon irradiation[6] (Scheme 2.9). In this brief report, coumarandione **73** was shown to efficiently decarbonylate to the reactive ketene intermediate **50** ($\Phi = 0.11$), which trapped a variety of nucleophiles including carboxylic acids, phenols, and water. Yields for these reactions ranged from 70 to 100%. Horspool went on to discuss the nature of the excited state and provided evidence for an $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition.

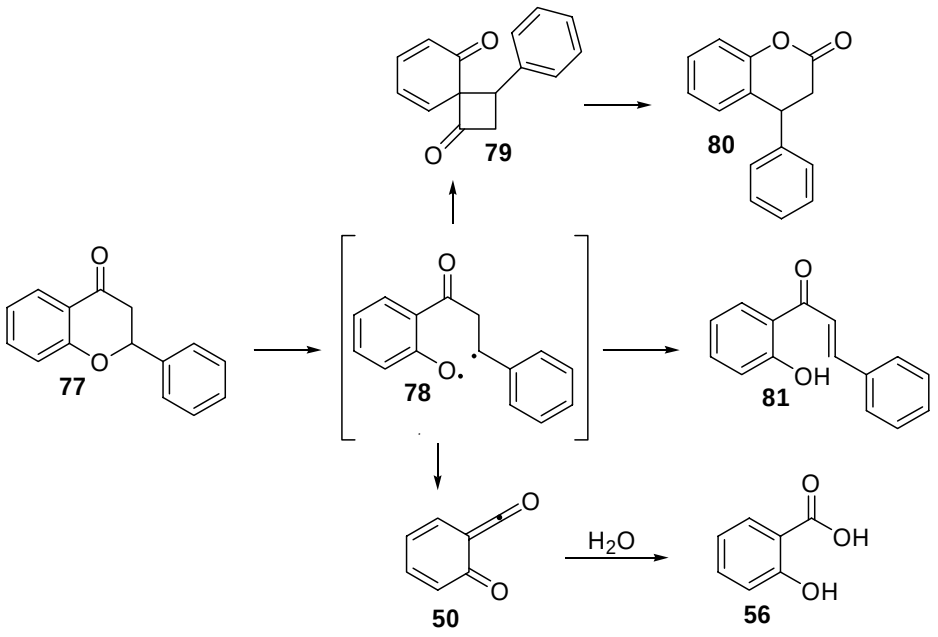
Scheme 2.9



Perhaps the most conclusive evidence for an n → π* transition maybe from the reaction of the coumarandione with cis-1,2-dichloroethylene to provide the corresponding [2+2] cycloadduct. This result is in agreement with previous reports by Hammond and coworkers who established that photochemical oxetane formation occurs from an n → π* excited state[7]. Finally, the slight hypsochromic shift (200 cm^{-1}, cyclohexane to benzene) further supports an n → π* excited state.

Pinhey et al revealed that flavanones undergo photochemical fragmentation to give a number of products[8]. Irradiation of flavanone **77** at 254 nm in benzene provides three products (Scheme 2.10).

Scheme 2.10

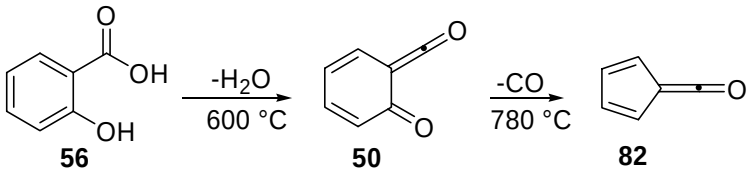


The major product of the reaction is 2-hydroxychalcone **81** (20%), pointing to a mechanism of fragmentation involving initial homolytic cleavage of the benzylic ether bond to give bis-radical **78**, followed by 1,5 hydrogen atom abstraction to provide chalcone **81**. Formation of the second major product, 4-phenyldihydrocoumarine **80** (13%), is rationalized by initial formation of spirocyclobutanone **79,** followed by a second photochemical induced rearrangement to give lactone **80**. Finally, salicylic acid was formed in low quantities (4%) via hydration of quinoketene **50**.

Although a majority of studies dealing with the generation of quinoketene **50** utilize photochemical means to access this reactive intermediate, thermal activation is also a viable pathway. Schweig and colleagues conducted a study aimed at identifying several high energy intermediates by photoelectron spectroscopy, which included **50** (Scheme 2.11)[9]. Exposure of coumarandione and salicylic acid to high temperatures (600 ˚C) lead to dehydration of salicylic acid and decarbonylation of coumarandione to give

ketoketene **50**. Additionally, a further increase in temperature (780 ˚C) resulted in decarbonylation of **50** to provide a ring contracted ketene **82** (Scheme 2.11).

Scheme 2.11

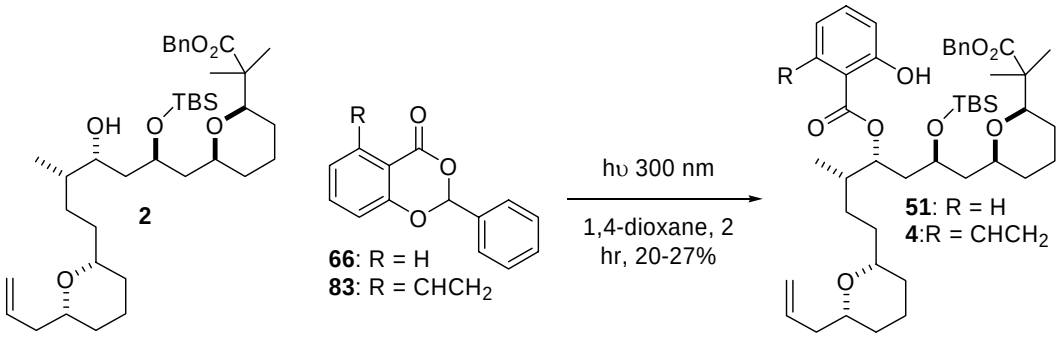


Also, unpublished work by Wentrup and co-workers noted that methyl salicylate eliminates methanol at high temperatures to obtain **50**[10].

2.4 Synthetic Applications of Quinoketenes

Despite the lack of precedence for utilizing quinoketenes in complex molecule synthesis, exploration of this chemistry was initiated. Our preliminary experiments were encouraging and showed that photolysis of 2-phenyl-1,3-benzodioxinone **66**[11] in the presence of alcohol **2** afforded the desired ester in 20-27% yield (Scheme 2.12). Despite this modest yield, it was encouraging to see that quinoketenes such as **50** could be trapped with alcohols as sterically hindered as **2**. More so, photochemical coupling with *o*-vinyl substituted benzodioxinone **83** provided the corresponding ester **4** in comparable yields.

Scheme 2.12

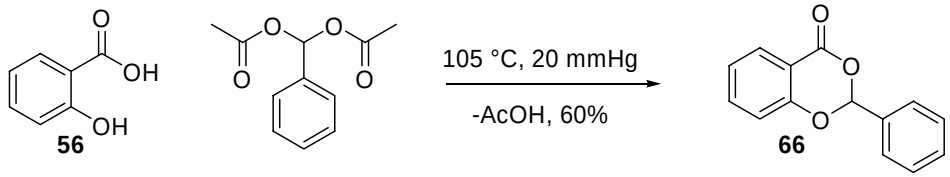


Not only was it apparent that this photochemical reaction could provide an entry into salicylic acid esters of **2**, but other ortho salicylate substituents would be tolerated as well. With these positive initial results we took this opportunity to explore the photochemical esterification further.

2.5 Synthesis of Ortho Substituted Benzodioxinones

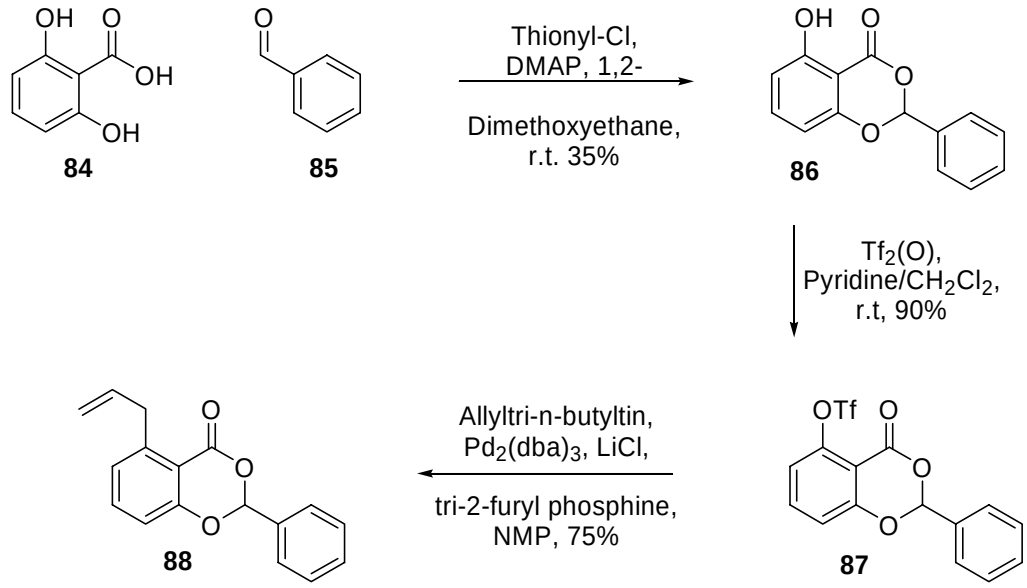
Prior to exploring the photochemistry, a short, scalable, and flexible route to various benzodioxinones was required. Preparation of ortho hydroxyl-substituted benzodioxinones was first attempted in the manner described for constructing unsubstituted benzodioxinone **66**[11] (Scheme 2.13).

Scheme 2.13



Application of this procedure for the preparation of dioxinone **86** from 2,6-dihydroxybenzoic acid **84** was unsuccessful (Scheme 2.14). Finally, exploiting a procedure reported for acetalization of 2,6-dihydroxybenzoic acid with thionyl chloride and acetone was adequate for the preparation of aryl acetals as well[12] (Scheme 2.14). Following this initial acetalization step, a variety of modified substrates can be accessed in an efficient and rapid manner. For example, phenol **86** can be alkylated with a variety of alkyl halides or converted in nearly quantitative yield to triflate **87** with trifluoromethanesulfonic anhydride and pyridine. With the triflate in hand, a wealth of ortho substituted benzodioxinones is accessible via palladium catalyzed cross coupling methodology[13] (e.g. **87**→**88**).

Scheme 2.14

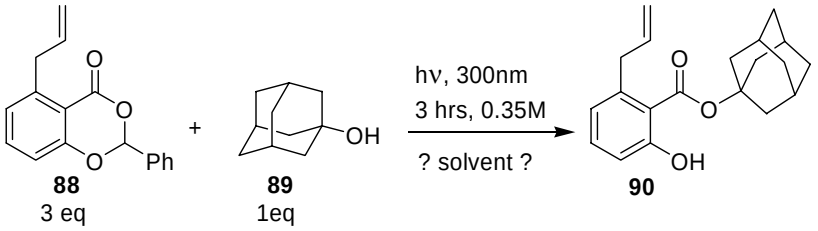


2.6 Optimization Studies

With a viable route to numerous benzodioxinones, the photochemical acylation of 1-adamantanol with benzodioxinone **88** was chosen as a test reaction to determine optimal reaction parameters.

The first parameter examined was the effect of solvent on the reaction. Previous experiments were conducted in commercially available anhydrous 1,4-dioxane. This solvent was chosen because it lacks a chromophore in the UV region, and its high freezing point allows for facile degassing via freeze, pump, thaw cycles. A range of commonly used solvents were screened under anhydrous conditions. The general trend observed was that reactions conducted in relatively non-polar solvents such as dichloromethane or benzene showed moderate but significant improvements in yield relative to 1,4-dioxane (Table 2.1).

Table 2.1 Solvent Effects

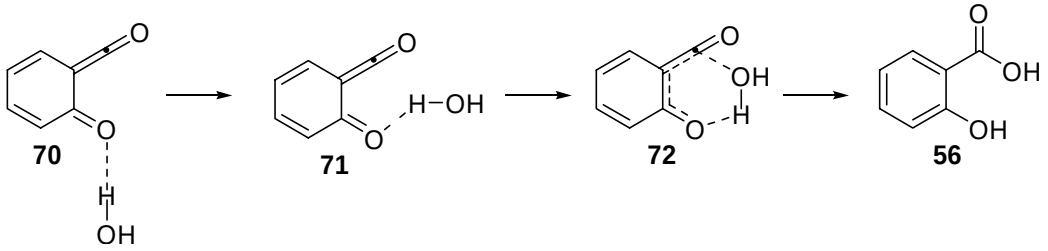


Solvent	Yield %
Benzene	73
Degassed Benzene	73
Degassed Dichloromethane	73
Degassed THF	55
1,4-Dioxane	59
*Acetonitrile	60
Acetone	60
DMF	25

* 0.2M Due to Insolubility

Relatively polar solvents such as acetone, acetonitrile, and tetrahydrofuran gave products with slightly lower yields than when run in apolar solvents. Also, *N*,*N*-dimethylformamide did not fare well as a solvent, which was attributed to the nucleophilicity of the solvent. From a practical standpoint it is noteworthy that reactions run in solvents that were not degassed performed equally well to those in vigorously degassed systems. The mild solvent polarity effect can be rationalized if one considers the hypothesized mechanism of hydration of α-oxoketenes depicted earlier (Scheme 2.15). For example, computational studies by Tidwell and co-workers identified the hydrogen bonded intermediate **70** as an essential intermediate during quinoketene hydration (Scheme 2.15).

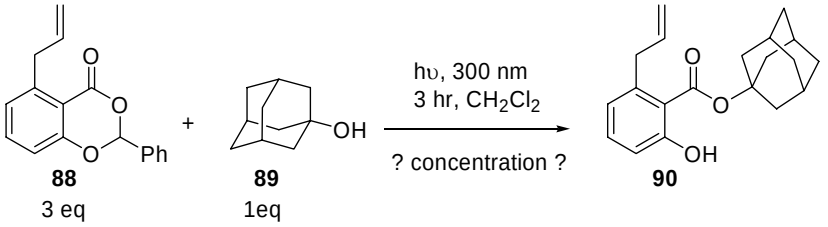
Scheme 2.15



Polar solvents such as acetone or THF could interfere with this mechanism by disrupting this key hydrogen bond.

Upon establishing a general trend for optimal photoacylation with respect to solvent, the effect of overall concentration on reaction efficiency was examined. In this series of experiments, solutions of 1-adamantanol **89** and benzodioxinone **88** at varying concentrations were irradiated with 300 nm UV-light for 4.5 hours at room temperature (Table 2.2).

Table 2.2 Concentration Effects



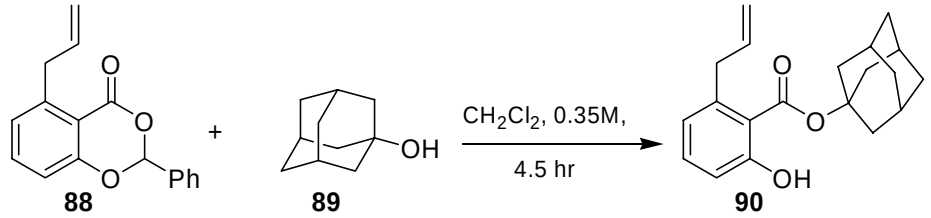
Concentration (M)	Yield %
0.05	60
0.1	73
0.35	73
0.7	58

Not surprisingly for a bimolecular reaction, concentrations below 0.1M compromised reaction yields. A bit unexpected was the finding that reactions conducted at concentrations above 0.35M also produced diminished yields. Although only product formation was quantified in these reactions, it was observed that at higher concentrations a greater abundance of unreacted benzodioxinone was present. At these higher

concentrations, increased excited state quenching could potentially compete with quinoketene formation.

Using the same model reaction, optimal reagent stoichiometry was examined next by varying the benzodioxinone to adamantanol ratio from 1:2 to 3:1. These experiments revealed that a 1.5-2.0 fold excess of either reaction parter provided optimal yields (Table 2.3).

Table 2.3 Stoichiometry Effects



88 **89** **90**

3 Equivalents	1 Equivalent	80% Yield
2 Equivalents	1 Equivalent	81% Yield
2 Equivalents	1.5 Equivalents	68% Yield
1 Equivalent	1 Equivalent	55% Yield
1 Equivalent	2 Equivalents	71% Yield

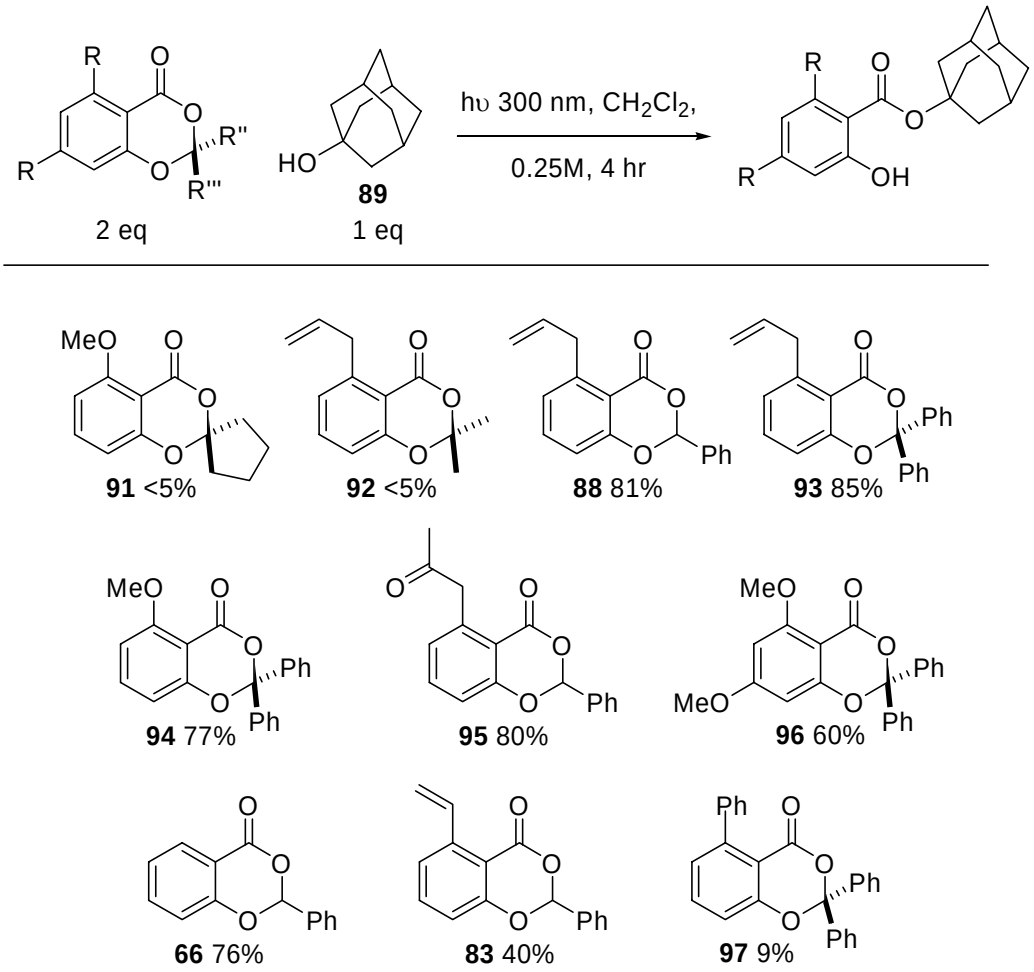
Therefore, selection of the alcohol or benzodioxinone as the limiting reagent can be guided by accessibility without compromising reaction efficiency.

With the emergence of a numerous and diverse collection of salicylate and resorcylate natural products, it was imperative to establish the scope of benzodioxinone substitution in the photochemical acylation. Examination of benzodioxinone scope revealed several interesting findings (Fig. 2.1).

A brief study examining the influence of substitution at the acetal position was undertaken. Despite having virtually indistinguishable UV-spectra from their 2-phenyl substituted counterparts (Fig. 2.2), substrates such as **91** and **92** displayed dramatically

diminished activity. This orthogonal reactivity can provide a means for chemoselective activation of an aryl-substituted benzodioxinone in the presence of an alkyl-substituted one. The striking influence of alkyl versus phenyl substitution at the benzodioxinone 2-position led to a number of questions regarding the mechanism of fragmentation which leads to the reactive quinoketene, as will be discussed in section 2.7.

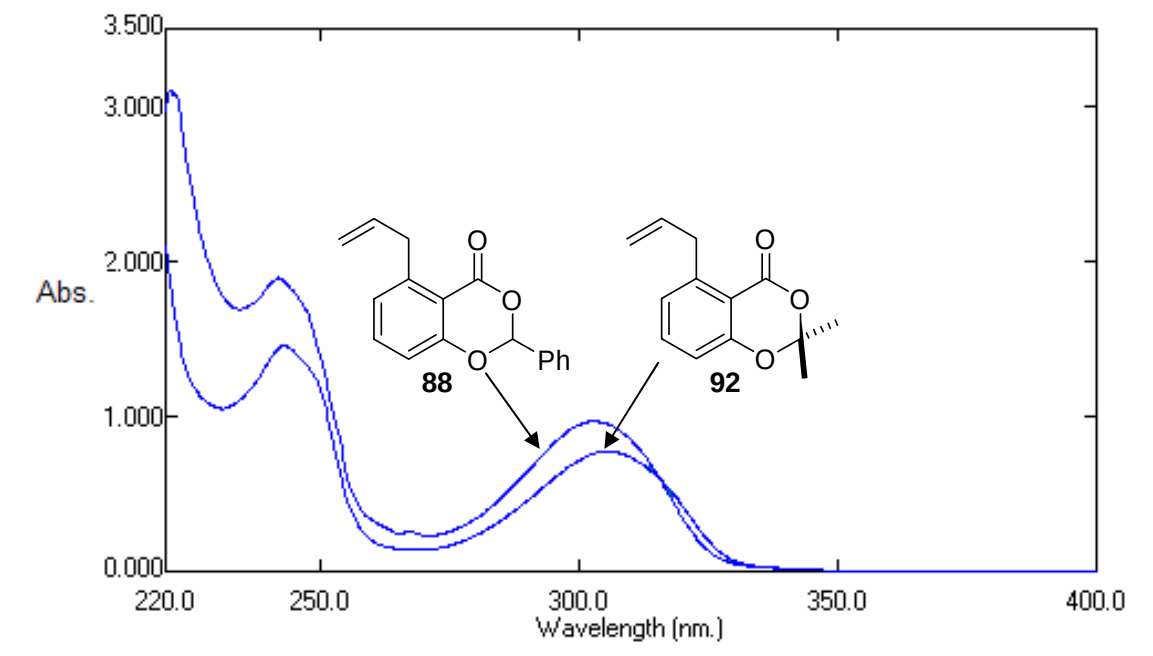
Fig. 2.1 Benzodioxinone Scope



Not surprisingly, the parent benzodioxinone **66** underwent photoacylation uneventfully, as did the *o*-allyl substituted substrate **88** utilized in the optimization studies. Electron rich methoxy substituted benzodioxinone **94** and **95** also underwent successful photoacylation with 1-adamantanol. Benzodioxinone **96** represents an

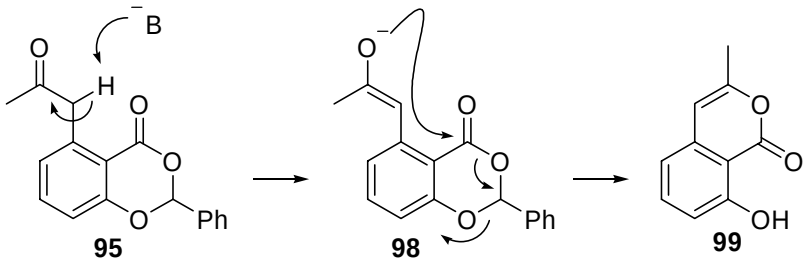
important class of quinoketene precursors because it provides a means to access the resorcylic class of natural products that include radicicol.

Fig. 2.2 UV Spectrum of 88 and 92



In another important example, homobenzylic ketone **95** also underwent efficient photochemical acylation. Benzoate esters with ketones at the homobenzylic position are difficult to synthesize under both basic and acidic conditions. These ketones readily enolize and undergo facile intramolecular cyclization to form the corresponding isocoumarins (Scheme 2.16). This undesired side reaction was taken into account during Danishefsky's synthesis of radicicol, via protection of the ketone as an acetal[14].

Scheme 2.16

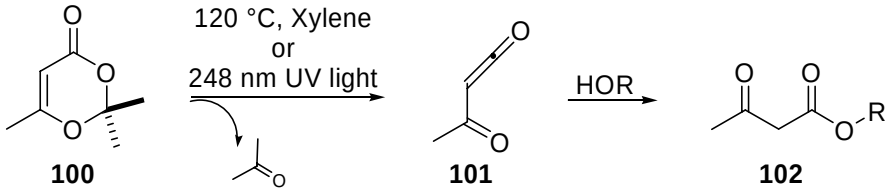


Benzodioxinones with conjugating functionality in the ortho-position such as *o*-vinyl and *o*-phenyl substituted compounds **83** and **97** were consistently poor quinoketene precursors. The inefficient acylation in these two cases was attributed to minimal quinoketene formation since significant quantities of these two reagents were recovered after irradiation. Compounds **83** and **97** exhibit some degree of fluorescence under UV-light, therefore it was surmised that energy from the excitation is dissipated via alternative processes such as fluorescence emission (see section 2.7).

2.7 Potential Mechanisms of Photolysis

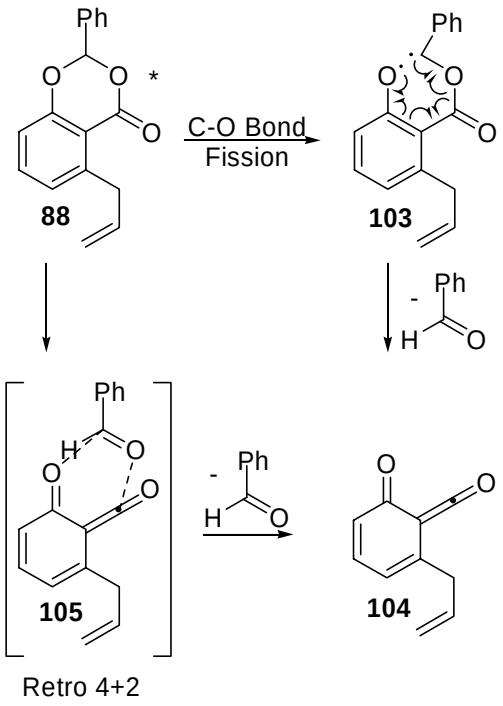
The mechanism involved in the photochemical fragmentation of 2-arylbenzodioxinones to quinoketenes has yet to be determined. One potential mechanism is a photochemically induced [4+2] cycloreversion. In this scenario, a molecule of benzaldehyde is expelled directly upon excitation to provide quinoketene **104** (Scheme 2.18). This mechanism is similar to the one involved during the thermal and photochemical extrusion of acetone from 2,2,6-trimethyl-1,3-dioxin-4-one **100** ("diketene-acetone adduct")[15-17] (Scheme 2.17).

Scheme 2.17



A second possibility is that homolytic cleavage of the benzylic C-O bond occurs from a triplet excited state to provide resonance stabilized diradical **103** (Scheme 2.18). This diradical may then undergo thermal fragmentation and expulsion of benzaldehyde, leading to quinoketene **104**.

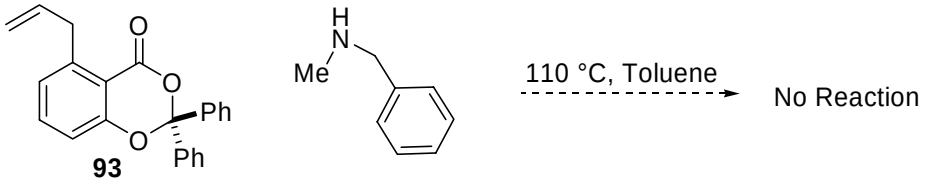
Scheme 2.18



The latter mechanism is corroborated by structure-reactivity studies of differentially substituted benzodioxinones that clearly show the necessity of aryl substitution for efficient photoacylation. For example, benzodioxinones lacking aryl substitution at the acetal position (Fig. 2.4, **91**, **92)** were poor photolysis substrates despite displaying nearly identical ultraviolet spectra (Fig. 2.5) as compounds such as **88**. These results are best explained by invoking biradical **103** – an intermediate that is better stabilized by aryl rather than alkyl substitution. Attempts to indirectly detect diradical **103** via reduction with 1,4-cyclohexadiene were unsuccessful.

In a control experiment performed to exclude the possibility of thermal quinoketene formation, a solution of benzodioxinone **66** or **93** was heated to 110 ˚C in the presence of an amine or alcohol in the dark (Scheme 2.19).

Scheme 2.19

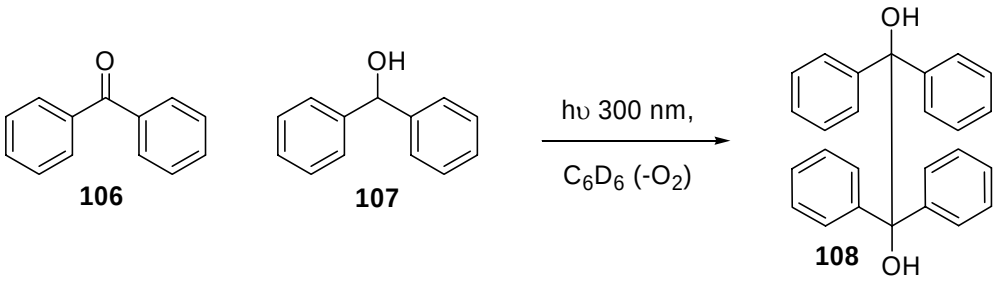


After 3 hours, the starting materials were fully recovered, establishing that 1) the photochemical induced acylation does in fact require ultraviolet irradiation and 2) 2-phenyl-1,3-benzodioxinones are thermally stable to temperatures sufficient to generate acyl ketenes from 2,2,6-trimethyl-1,3-dioxin-4-one **100** (Scheme 2.17).

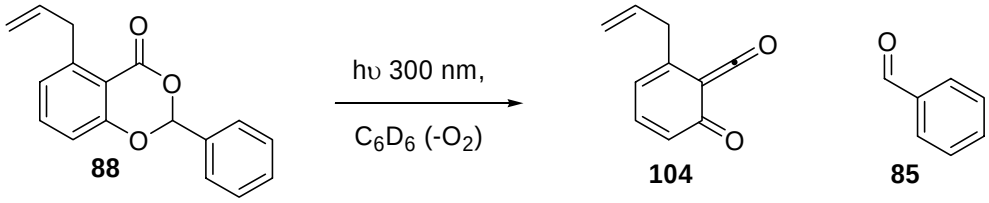
2.8 Quantum Yield Determination

To gain an understanding of the efficiency with which the initial photochemical induced fragmentation takes place, quantum yield determination of quinoketene formation was undertaken. After several unsuccessful attempts at determining the absolute quantum yield with the commonly used ferrioxalate actinometer[18], a method was employed to elucidate the relative quantum yield. Specifically, photodegradation of benzodioxinone **88** was measured and compared to the benzophenone-benzhydrol actinometer[19] (Eq.1, Eq.2, vide infra). Photolysis reactions of the benzhydrol-benzophenone actinometer (Eq. 1) and benzodioxinone **88** (Eq. 2) in deuterated benzene were monitored over time by proton NMR. In the benzhydrol-benzophenone system (Eq. 1), the reaction was quantified by measuring benzpinacol product formation (by integration of proton NMR peaks). Photolysis efficiency for the reaction of choice (Eq. 2) was determined by measuring the loss of benzodioxinone **88** by proton NMR. Benzaldehyde formation was also measured as a means to estimate quinoketene formation. In these experiments benzodioxinone consumption is assumed to be irreversible and equivalent to quinoketene formation[5].

Eq. 1

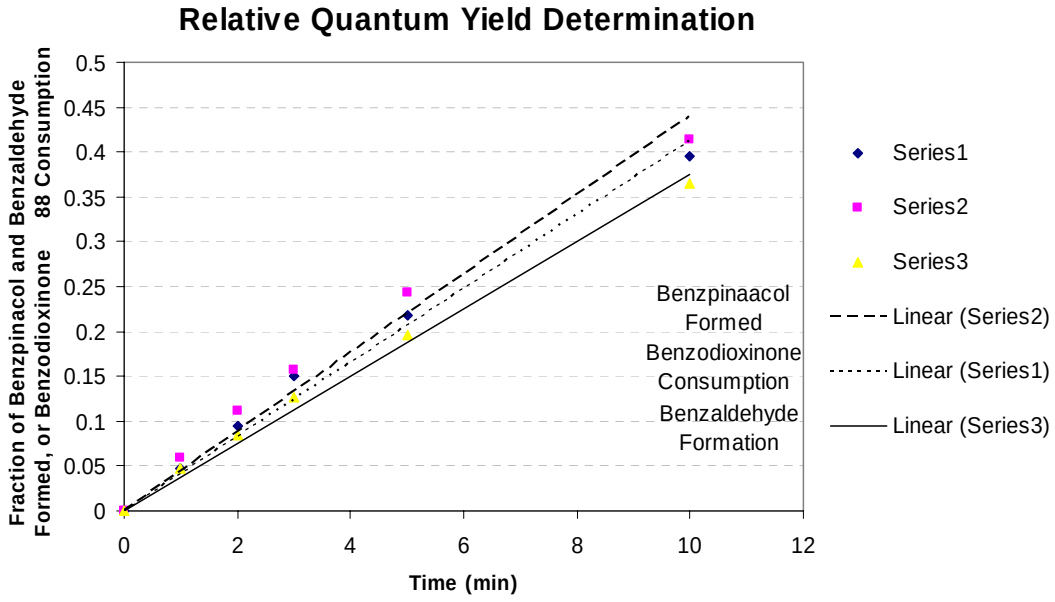


Eq. 2



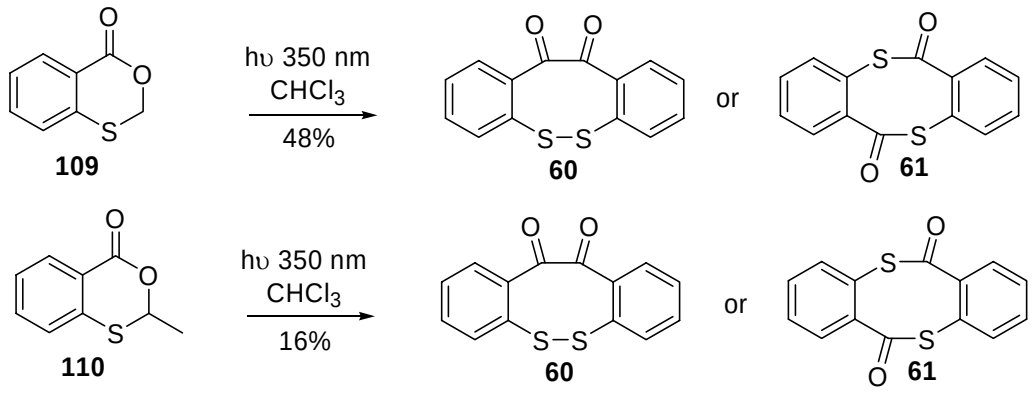
Data analysis revealed photochemical consumption of benzodioxinone **88** was quite efficient (Fig. 2.3). The quantum yield of benzodioxinone consumption and benzaldehyde formation was determined to be $\Phi = 0.64$ and $\Phi = 0.58$ respectively (assuming $\Phi = 0.68$ for the benzophenone-benzhydrol system[19]).

Fig. 2.3 Quantum Yield Determination



Although there are no previously published quantum yield values for benzodioxinones such as **88**, the quantum yield of related benzothioxanone **59** was reported; in the specific case of 2-phenyl-3,1-benzoxathian-4-one $\Phi = 0.05$[2]. Although this value is significantly lower than what was determined for substrate **88**, Kolc's data for several benzoxathiones agreed with our findings related to the beneficial effect of aryl substituted at the 2-position. It is worth noting, however, that benzoxathiones **109** and **110** did photolyze with modest efficiency (48% and 16% respectively) to provide disulfide **60** or thioester **61** (Scheme 2.20).

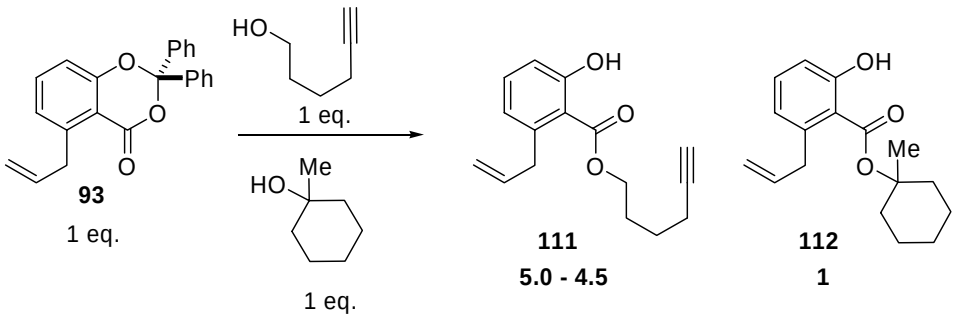
Scheme 2.20



2.9 Steric Competition Experiment

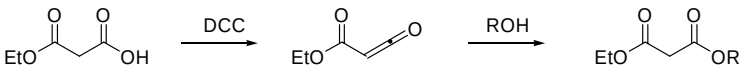
To obtain a sense of how strongly the steric bulk of incoming nucleophiles is felt by quinoketenes, a competition experiment was conducted. Equimolar quantities of a primary and tertiary alcohol were photolyzed in the presence of quinoketene precursor **93** (Scheme 2.21). Examination of the crude mixture by proton NMR revealed a ratio of 4.5-5:1 of primary versus tertiary esterification product respectively.

Scheme 2.21



The modest degree to which the primary alcohol is favored clearly illustrates the extent of insensitivity quinoketenes have towards nucleophilic steric bulk. These findings bode well for the prospective acylation of tertiary alcohols and other highly hindered nucleophiles. In this context, kinetic studies by Shelkov and colleagues examining hydration of acyclic alpha oxo-ketenes with simple alcohols demonstrated that nucleophilic addition to the acyl-ketene is not dramatically affected by alcohol steric bulk[16,20] (Fig. 2.4, reproduced from ref. 19). Kinetic studies on the acylation of MeOH, *i*-PrOH, and *t*-BuOH with phenylacetyl-chloride in CH_2CH_2 showed that relative rates of addition were highly dependent on steric bulk (relative rates: MeOH = 1; *i*-PrOH = 0.04; *t*-BuOH = <0.01).

Fig. 2.4 Acylation of α-Oxo-ketenes



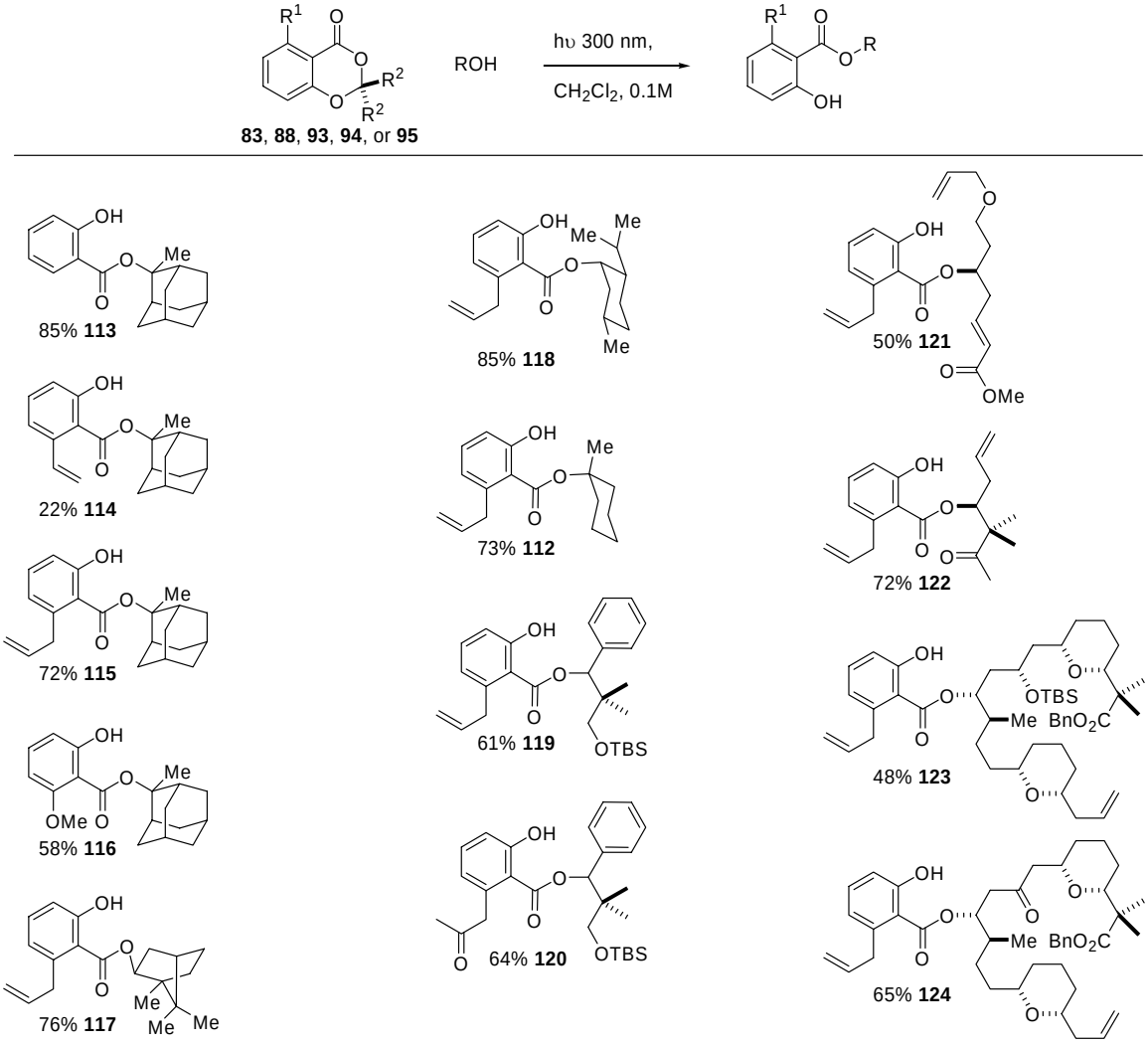
R	Relative Rates in CH_2Cl_2
Me	1
Et	1
i-Pr	1
t-Bu	0.07
Ph	0.01

2.10 Nucleophile Scope

To test the scope of the photoacylation, a series of hindered aliphatic alcohols were subjected to the optimized photoacylation conditions. As shown in figure 2.5, a

wide array of substrates with varying functional groups underwent successful acylation. Both cyclic and acyclic alcohols showed good reactivity, although cyclic substrates consistently provided higher yields. Two noteworthy entries are β-acyloxyketone **124** and enone **121**, which were isolated without any sign of elimination products. Several commonly utilized protecting groups (TBS ether, benzyl ester, allyl ether) were tolerance to the reaction conditions.

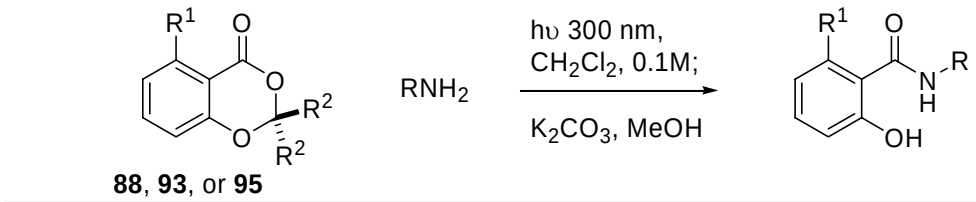
Fig. 2.5 Scope of Aliphatic Alcohols



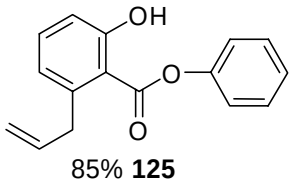
Photoacylation of aromatic nucleophiles proved highly fruitful. A series of phenols and anilines with varying degrees of steric hindrance was studied, and all these

substrates underwent successful acylation in high yields (Fig. 2.6). Interestingly, yields did not diminish as the level of steric hindrance associated with the phenol or aniline increased. This is dramaticaly illustrated with the formation of ester **127** and amides **131** and **128**, compounds with considerable steric bulk that are inaccessible via standard acylation methodology. Also worth noting, photoacylation of ketone substituted benzodioxinone **95** with 2,6-diisopropylaniline led to formation of imidate **133b** in addition to the desired amide **133a**. In this example, imidate formation is the result of cyclodehydration of the parent amide **133a** – an explanation for this outcome has yet to be formulated. In several cases examined, more pronounced with the amides, products resulting from secondary photoacylation at the phenol were formed (Scheme 2.22). Fortunately, the desired materials were readily accessed after brief treatment with a mild base (K_2CO_3, MeOH).

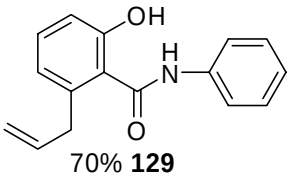
Fig. 2.6 Photoacylation of Phenols and Amines



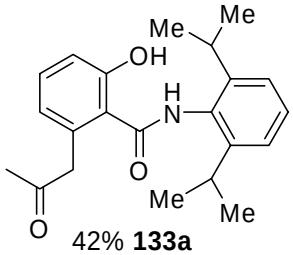
88, **93**, or **95**



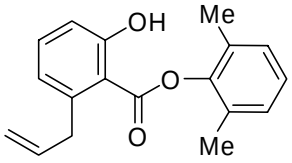
85% **125**



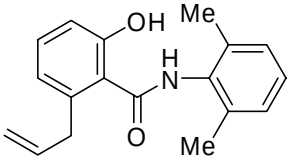
70% **129**



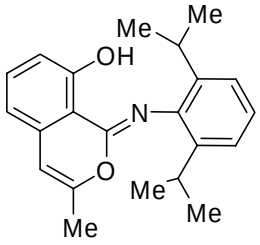
42% **133a**



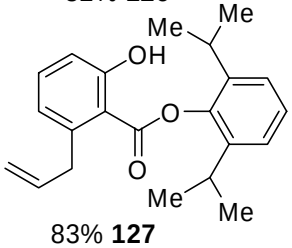
82% **126**



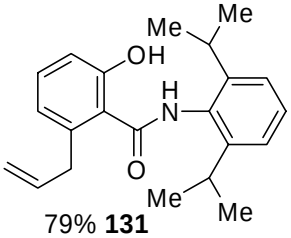
73% **130**



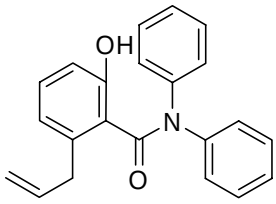
27% **133b**



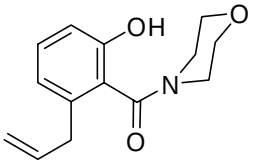
83% **127**



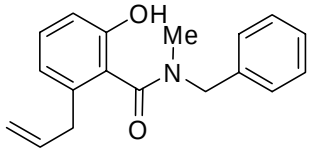
79% **131**



78% **128**



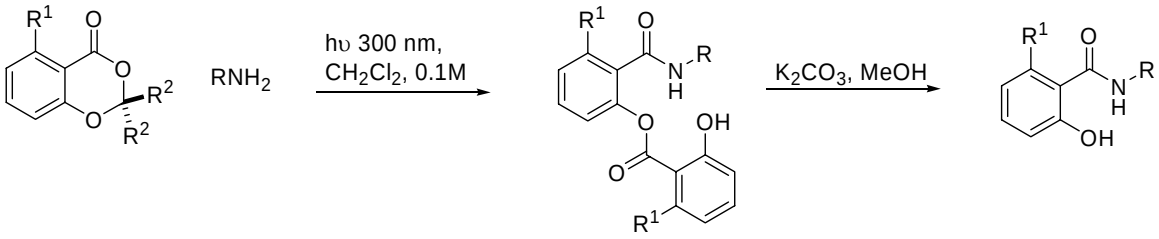
64% **132**



73% **134**

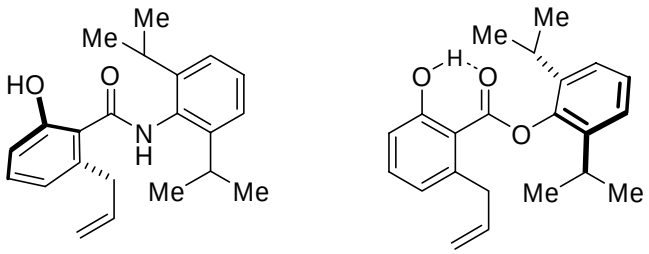
The secondary acylation observed with amine and aniline nucleophiles might result from base-catalysis by these substrates (Scheme 2.22).

Scheme 2.22



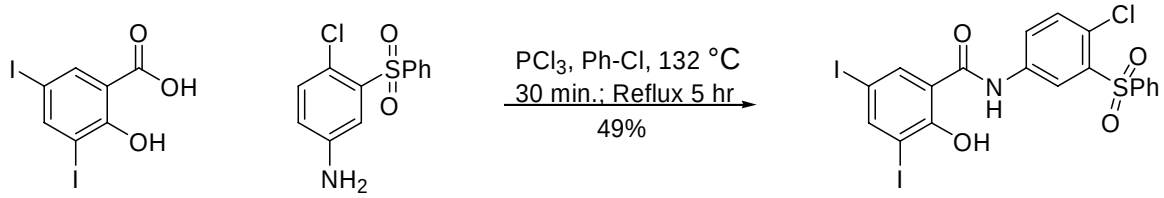
In addition, conformational preferences for the salicylamide products could favor rotation of the carbonyl group out of conjugation, thereby disrupting the hydrogen bond to the carbonyl and increasing the nucleophilicity of the phenol (Fig. 2.7).

Fig. 2.7



In conclusion, the photochemical acylation of phenols and anilines is remarkably efficient. It is noteworthy that few successful examples of amidation of hindered anilines with salicylic esters have been reported[21] (Scheme 2.23).

Scheme 2.23

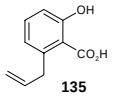
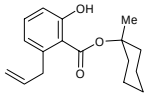
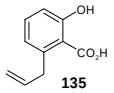
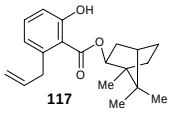
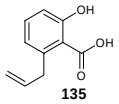
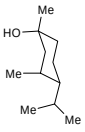
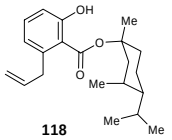
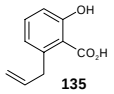
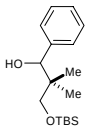
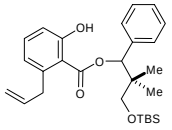
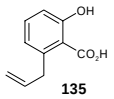
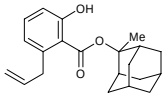
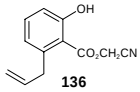
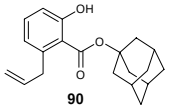
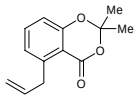
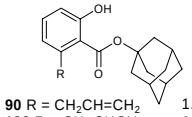
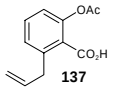
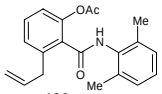


2.11 Comparison with Alternative Acylation Methods

In order to fully evaluate the utility of the photoesterification methodology, several common esterification procedures were examined and compared to the photoacylation. The reactants used under photochemical conditions were also used in these studies. As evidenced in table 2.4, many contemporary acylation methods were completely ineffective. Alkoxide mediated acylation of acetonide derivative **92** occurred in 25% yield, however, the strong basic conditions employed resulted in significant isomerization (1.5:1 ratio of isomerized to non-isomerized) of the terminal olefin (Table 2.4, entry 9). Although Mitsunobo esterification produced products in a number of cases,

overall yields never exceeded 36% (Table 2.4, entries 2-5). Interestingly, Mitsunobo esterification of borneol (Table 2.4, entry 3) generated a product identical to that obtained under photochemical conditions, indicating that this reaction occurred with retention of configuration at the carbinol center. Retentive Mitsunobo type reactions have been reported previously, and have been rationalized by case specific steric, electronic, and conformational attributes[22]. Also worth noting, acylation with the cyanomethyl esters (Table. 2.4, entry 8) developed by Porco and colleagues failed to provide any coupling product. Finally, attempted amide formation via carbonyl di-imidazole mediated coupling was completely unsuccessful (entry 10).

Table 2.4 Examination of Alternative Acylation Methods

Entry	Substrate a	Substrate b	Conditions	Product	Yield (%)
1	 **135**		**A**	 **112**	0
2	 **135**		**B**	 **117**	30
3	 **135**		**C**	 **118**	36
4	 **135**		**C**	 **119**	7
5			**D**		30
6			**E**		0
7	 **135**		**E**	 **115**	0
8	 **136**		**F**	 **90**	0
9	 **92**		**G**	 **90** R = $CH_2CH{=}CH_2$ 1.5:1 **138** R = $CH{=}CHCH_3$ **138**:**90**	25
10	 **137**		**H**	 **139**	0

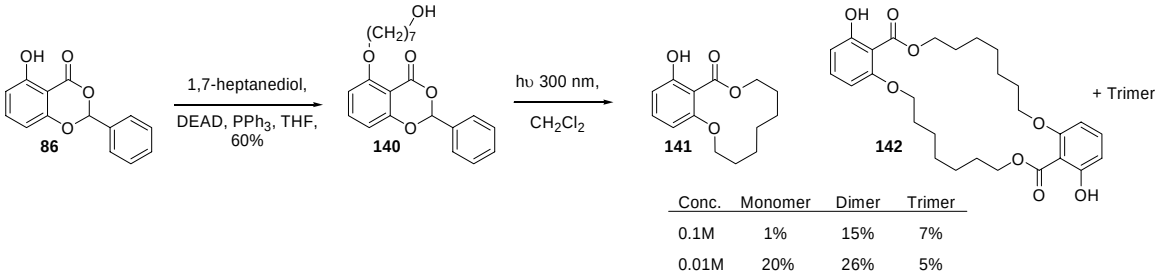
Conditions: (**A**): acid **135** (5 eq), $(COCl)_2$ (10 eq), DMF cat., CH_2Cl_2, 2 hr then N_2 flush; add CH_2Cl_2/pyridine (3/1), 10 mol% DMAP, alcohol (1 eq), 0 ˚C→ rt, 2 hr (**B**): acid **135** (3 eq), alcohol (1 eq), DEAD (3 eq), PPh_3 (3 eq), Et_2O, 5 hr, rt. (**C**): acid **135** (1.2 eq), alcohol (1 eq), DEAD (1.2 eq), PPh_3 (1.2 eq), Et_2O, 24 hr, rt. (**D**): acid **135** (5 eq), alcohol (1 eq), DEAD (5 eq), PPh_3 (5 eq), Et_2O, 48 hr, rt. (**E**): acid **135** (5 eq), alcohol (1 eq), 2,4,6-trichloro-BzCl (5 eq), Et_3N (7 eq), DMAP (2 eq), THF / toluene, 100 ˚C, 2 hr. (**F**): cyanomethyl ester **136** (1.5 eq), alcohol (1 eq), 5 mol% K_2CO_3, N,N-dimethylacetamide, 90 ˚C, 3 hr (**G**): dioxinone **92** (1.5 eq), alcohol (1 eq), NaHMDS (1.05 eq), THF, rt, 2 hr. (**H**): acid **137** (1.5 eq), 2,6-dimethylaniline (1 eq), CDI (1.5 eq), THF, 80 ˚C, 12 hr. DMF = dimethylformamide, DMAP = 4-dimethylaminopyridine, DEAD = diethylazodicarboxylate, BzCl = benzoyl, NaHMDS: sodium bis(trimethylsilyl) amide, CDI = carbonyl diimidazole.

2.12 Intramolecular Photoacylations

Thus far, all the photoacylations studied were conducted in a bimolecular sense. Simple derivatization/photoesterification of substrates such as **86** would allow rapid

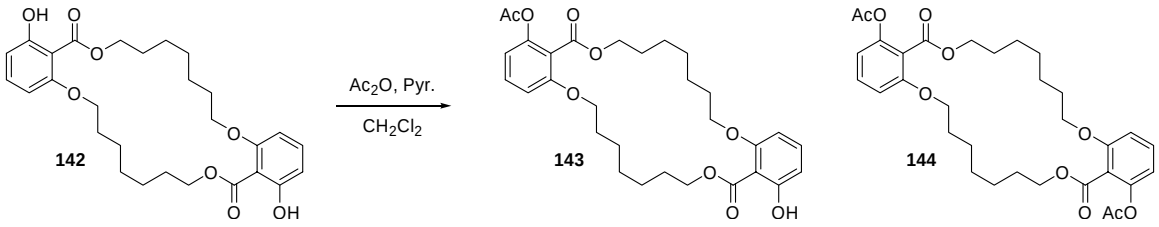
access to the macrocyclic structures found in numerous benzolactone natural products. With this in mind, a bifunctional benzodioxinone **140** was prepared in two steps from commercially available starting materials (Scheme 2.24). Photolysis of a diluted solution (0.01M) of benzodioxinone **140** did result in formation of macrocycle **141**, however this was not the major product of the reaction. Careful purification and evaluation of the crude reaction mixture revealed the major product to be the dimeric macrocycle **142**. In addition, a small portion of the trimeric adduct was also isolated.

Scheme 2.24



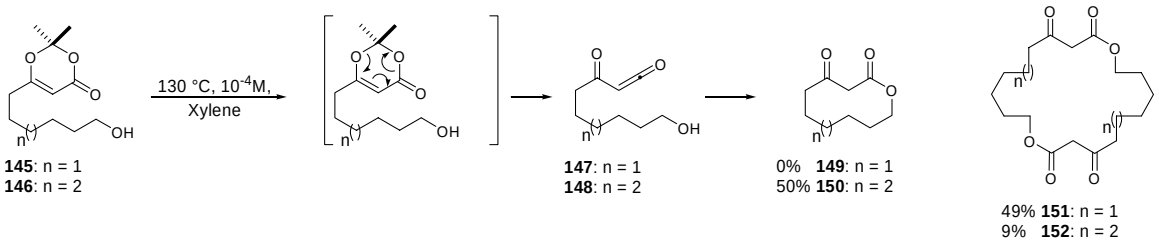
Because these macrocycles were virtually identical by proton NMR, electrospray mass spectrometry was employed to clearly identify the dimeric and trimeric compounds. To further characterize the formation of these oligomers, diester **142** was subjected to acetylation with a minimal amount of acetic anhydride such that a distribution of sm, mono-acylation, and bis-acylation products (**143** and **144**) could be obtained (Scheme 2.25). Once again mass spectral analysis of this crude reaction mixture revealed the presence of these three compounds verifying the formation of the dimeric macrocycle **142**.

Scheme 2.25



The propensity for the formation of polymeric acylation products seemed unusual, however this result is not without precedence. Previous studies on the thermal generation and intramolecular trapping of acylketenes from 2,2-dimethyldioxinone resulted in exclusive formation of dimeric and trimeric macrocycles[23] (Scheme 2.26). The same report by Kurth and coworkers detailed a number of fruitless efforts to obtain monomeric esterification products under high dilution (10^{-4}M). For example, the acylation of α-oxo-ketene **147** resulted in a 49% yield of dilactone **151**, and no sign of the intramolecular acylation product **149**.

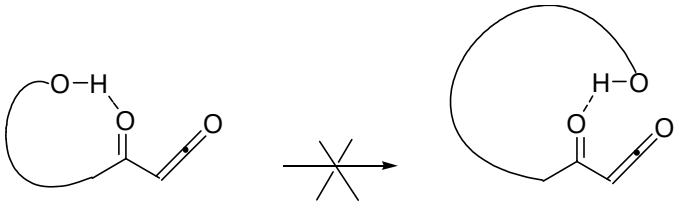
Scheme 2.26



Of the various substrates Kurth and co-workers examined, only alcohol **146** led to the formation of an intramolecular macrocyclization product (12 membered lactone **150**). The authors concluded that subtle transition state conformational effects, which are ring size dependent, influence the formation of either monomeric or oligomeric macrolactonization products. This result may be explained by invoking the mechanism of addition to α-oxo-ketenes proposed by Tidwell and coworkers (Scheme 2.15). In the

case of a short chain alcohol, the tether is too short to adopt the proper alignment for hydrogen bonding and assisted delivery to the ketene (such as in **153**, Fig. 2.8). This situation is in contrast to extended alcohols that have the conformational flexibility to undergo assisted delivery following hydrogen bond formation (such as in **154**, Fig. 2.8).

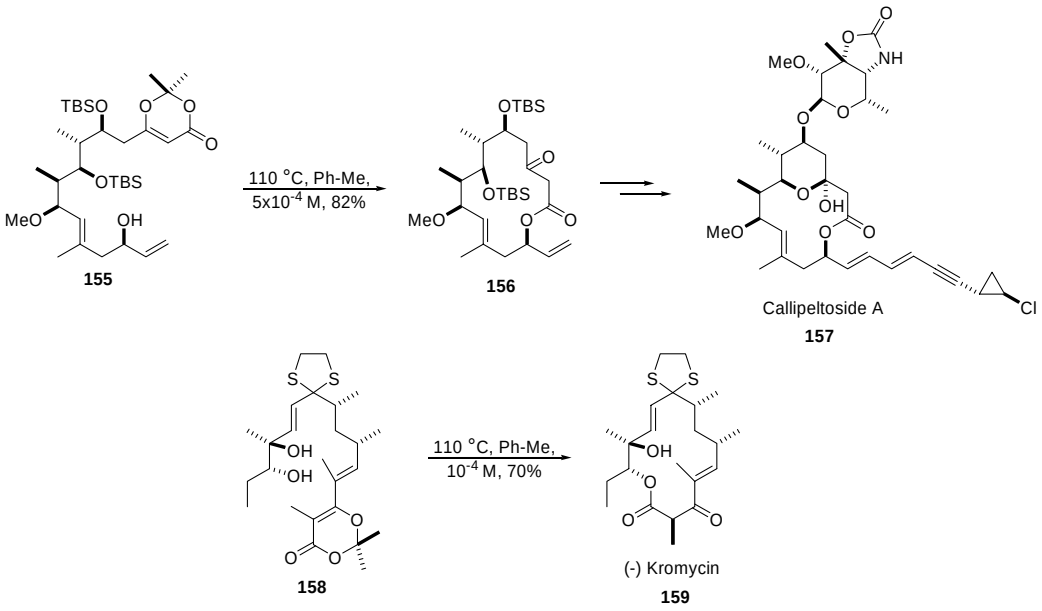
Fig. 2.8



153 **154**

Utilization of α-oxo-ketenes in the context of natural product synthesis has been extensive. In 2002 Trost, and colleagues utilized this reactive intermediate in the complex natural product callipeltoside A[24] (Scheme 2.27). As delineated in scheme 2.27, a key transformation in route to the natural product involved acylation of the ketene derived from dioxinone **155** to afford lactone **156** in 82% yield. In another example, Boeckman and co-workers synthesized the natural product (-) Kromycin via thermal activation of a dilute solution of dioxinone **158**[25] (Scheme 2.27).

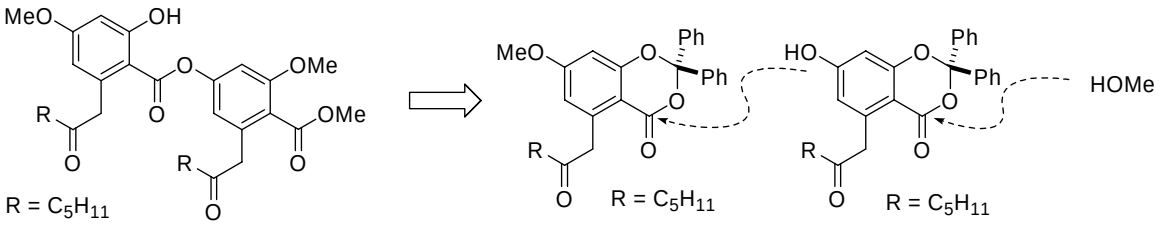
Scheme 2.27



2.13 An Entry to Depside Natural Products

Gustastatin (**160**) is representative of a class of resorcinylic natural products, orcinol-type depsides, which are composed of two resorcinylic acid derivatives that contain alkyl or 2-oxo-alkyl chains (Scheme 2.28). The synthesis of this natural product was accomplished by Jorge Garcia-Fortanet and Robb De Bergh in the De Brabander group, in 9 steps from commercially available starting materials[26]. As shown in scheme 2.27, they took advantage of the photochemical esterification of 2,2-diphenyl benzodioxinones **161** and **162** to methanolyze and dimerize these fragment under mild photochemical conditions. Worth noting, both photoacylation of **162** with methanol (hν 300 nm, MeOH) and dimerization of 2,2-diphenyl benzodioxinone **161** with the methyl ester derived from **162** resulted in smooth esterification with no sign of competing isocoumarin formation – a result that underscores the mild nature of the photoesterification.

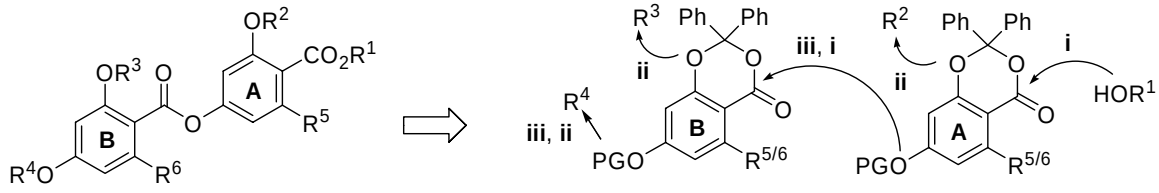
Scheme 2.28



160 Gustastatin **161** **162**

The elegant and concise synthesis of gustastatin clearly demonstrates the power of the photochemical acylation methodology, and exemplifies a modular and general approach to the orcinol-type depside system that allows access to natural as well as designed members for further exploration (Scheme 2.29). The general strategy outlined in scheme 2.28 is as follows, (1) irradiation of a protected *p*-hydroxybenzodiozinone (ring A) in the presence of an alcohol (step i); (2) optional functionalization of the liberated *o*-phenol (step ii); (3) deprotection of the *p*-phenol (step iii); (4) repeating this sequence with a liberated *p*-phenol A-ring donor and benzodioxinone B-ring acceptor (steps i, iii, ii).

Scheme 2.29



orcinol-type depsides

i: hυ; **ii**: functionalization (optional); **iii**: deprotection

2.14 Summary and Future Experiments

The development, scope, limitations, and mechanistic studies of a photochemical based method for the formation of salicylate/resorcylate esters and amides are described. A number of sterically hindered salicylate esters and amides were prepared in good yields under mild conditions. Experiments with 2-alkyl (photosilent) and 2-phenyl (photoactive) benzodioxinones revealed a way to conduct chemoselective acylation with

these orthogonally reactive substrates. Also, head to tail dimerization products were formed while attempting to access benzolactones photochemically. This observation may serve as a model for the synthesis of the dimeric macrocyclic salicylate SCH 351448.

2.15 EXPERIMENTAL SECTION

2.15.1 Materials and Methods

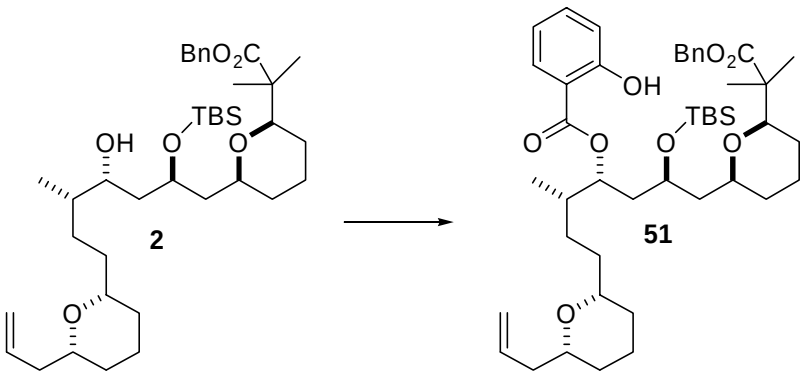
Unless otherwise noted, commercially available materials were used without further purification. All solvents were of HPLC or ACS grade. Solvents used for moisture sensitive operations were distilled from drying reagents under a nitrogen atmosphere: Et_2O and THF from sodium benzophenone ketyl; benzene and toluene from sodium; CH_2Cl_2 from CaH_2, acetone over 4Å m.s., N,N-dimethylformamide, 1,4-dioxane and CH_3CN were from commercially available anhydrous sources. Reactions were performed under an atmosphere of nitrogen with magnetic stirring unless noted otherwise. All photochemical reactions were performed with a Rayonett RPR-100 reactor fitted with a test tube carousel and 300 nm bulbs unless noted otherwise. Flash chromatography (FC) was performed using *E Merck* silicagel 60 (240–400 mesh) according to the protocol of Still, Kahn, and Mitra (*J. Org. Chem.* **1978**, *43*, 2923). Thin layer chromatography was performed performed using precoated plates purchased from *E. Merck* (silicagel 60 PF254, 0.25 mm) that were visualized using a $KMnO_4$ or Ce (IV) stain.

Nuclear magnetic resonance (NMR) spectra were recorded on either a *Varian Inova*-400 or *Mercury*-300 spectrometer at operating frequencies of 400/300 MHz (^{1}H NMR) or 100 / 75 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to

residual solvent (usually chloroform δ 7.26 for H^1 NMR or δ 77.23 for proton decoupled C^{13} NMR), and coupling constants (*J)* in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet, whereby the prefix app is applied in cases where the true multiplicity is unresolved, and *br* when the signal in question is broadened.

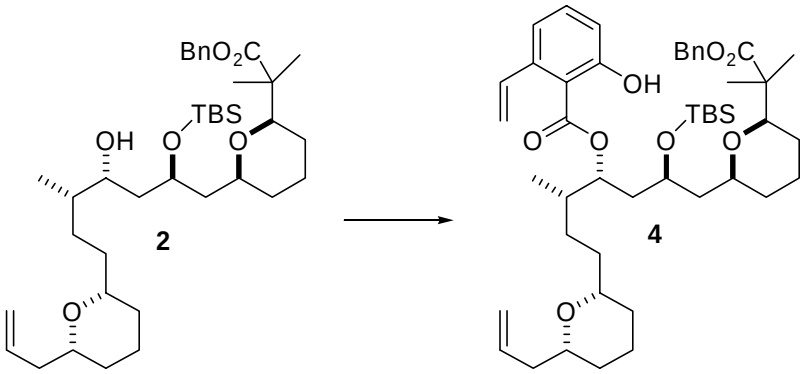
Infrared spectra were recorded on a *Perkin-ElmerI* 1000 series FTIR with wavenumbers expressed in cm^{-1} using samples prepared as thin films between salt plates. UV-VIS spectra were taken in anhydrous diethyl ether and recorded with a Shimadzu UV-1601 spectrometer. Low-resolution mass spectra (LRMS) were recorded on either a Shimadzu 2010-LCMS, or at the NIH regional mass spectrometry facility at the Washington University, St. Louis, MO. High-resolution mass spectra (HRMS) were recorded at the NIH regional mass spectrometry facility at the Washington University, St. Louis, MO. Optical rotations were measured at 23˚C on a *Perkin-Elmer 241 MC* polarimeter.

2.15.2 PREPARATIVE PROCEDURES



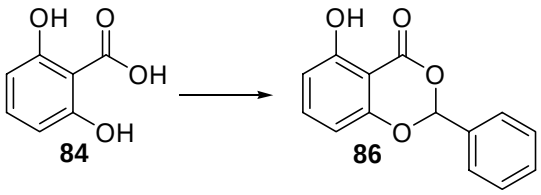
Compound 50. To an ovendried quartz test tube under nitrogen inlet was added dioxinone **66** (16.5 mg, 0.11 mmol) followed by a solution of alcohol **2** (4.0 mg, 0.0062

mmol) in 1,4-dioxane (0.3 mL). This solution was then degassed (freeze, pump, thaw, 3X). The degassed solution was then photolyzed for 4 hr at 350 nm. TLC analysis showed minimal product conversion with a majority of starting material having gone unreacted. The reaction solution was photolyzed for an additional 2 hr at 300 nm. TLC showed a significant improvement in product formation at 300 nm. The solvent was removed under vacuo and the crude material was purified by FC (5% EtOAc in hexanes) to afford 1 mg (21%) of **51**. $[\alpha]_D$ = -14.4 ($CHCl_3$, c 0.05). IR (film) 3369, 2928, 2855, 1734, 1670, 1458, 1375, 1252, 1121, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.00 (1H, s), 7.83 (1H, dd, *J* = 2.0, 8.0 Hz), 7.69–7.73 (1H, m), 7.51–7.55 (1H, m), 7.28–7.42 (4H, m), 6.95 (1H, d, *J* = 8.0 Hz), 6.81 (app t, *J* = 8.4 Hz), 5.83 (1H, dddd, *J* = 6.4, 6.4, 10.0, 16.8 Hz), 5.25–5.31 (1H, m), 5.06 (2H, s), 5.01–5.05 (1H, m), 4.97 (1H, d, *J* = 6.4 Hz), 4.27–4.35 (1H, m), 3.91–3.97 (1H, m), 3.43 (1H, app d, *J* = 10.0 Hz), 3.34–3.39 (1H, app t, *J* = 10.0 Hz), 3.23–3.31 (1H, m), 2.22–2.36 (1H, m), 2.09–2.18 (1H, m), 1.68–1.84 (6H, m), 1.13–1.62 (15H, m), 1.12 (3H, s), 1.10 (3H, s), 0.91 (3H, d, *J* = 6.8 Hz), 0.88 (9H, s), -0.01 (3H, s), -0.02 (3H, s).



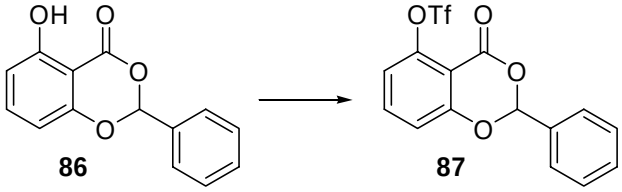
Compound 4. Benzodioxinone **83** (27 mg, 0.11 mmol) and alcohol **2** (7.6 mg, 0.012 mmol) were combined and dried via azeotropic removal of water with benzene under

nitrogen inlet flushing. The dried materials were then dissolved in anhydrous 1,4-dioxane (0.4 mL) and transferred to an ovendried quartz test tube followed by degassing (freeze, pump, thaw 3X). The sealed test tube was then photolyzed for 4 hr at 300 nm. The solvent was removed under vacuo and the crude material was purified by FC (5/95, EtOAc/Hex) to afford 2 mg (20%) of **4**. $[\alpha]_D$ = -48.8 ($CHCl_3$, c 0.025). IR (film) 3380, 2930, 2857, 1736, 1657, 1451, 1372, 1252, 1217, 1086 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.52 (1H, s), 7.28–7.37 (7H, m), 6.89 (1H, d, *J* = 8.0 Hz), 6.83 (1H, d, *J* = 7.6 Hz), 5.83 (1H, dddd, *J* = 6.8, 6.8, 10.4, 17.2 Hz), 5.39 (1H, d, *J* = 17.2 Hz), 5.31–5.36 (1H, m), 5.19 (1H, d, *J* = 10.8 Hz), 5.05 (2H, s), 5.01–5.04 (1H, m), 4.97 (1H, d, *J* = 6.4 Hz), 3.88 (1H, app t, *J* = 8.0 Hz), 3.39 (1H, d, *J* = 10.4 Hz), 3.21–3.34 (3H, m), 2.23–2.33 (1H, m), 2.09–2.17 (1H, m), 1.89–1.94 (1H, m), 1.78–1.86 (2H, m), 1.39–1.72 (12H, m), 1.09–1.37 (6H, m), 1.06 (3H, s), 1.01 (3H, s), 0.92 (3H, d, *J* = 6.8 Hz), 0.87 (9H, s), -0.01 (3H, s), -0.02 (3H, s).



Benzodioxinone 86. [Hadfield, A; Schweitzer, H; Trova, M. P.; Green, K. Syn. Commun. 1994, *24*, 1025-1028] To a flask containing 2,6-dihydroxybenzoic acid **84** (11.6 g, 75 mmol) and DMAP (916 mg, 7.5 mmol) was added benzene (100 mL), followed by removal of the solvent *in vacuo*. This sequence was repeated followed by the addition of ethylene glycol dimethyl ether (45 mL) and benzaldehyde (11.4 mL, 113 mmol). This solution was cooled to 0 ˚C under N_2 followed by the dropwise addition of

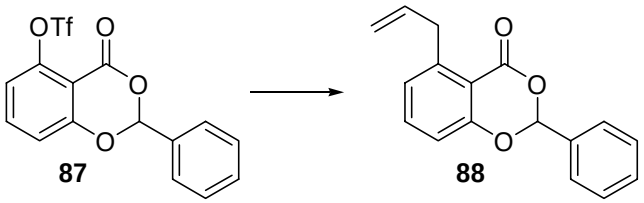
thionyl chloride (8.2 mL, 113 mmol). The reaction was brought to rt and stirred for 18 hr after which the volatiles were removed via nitrogen inlet flushing while under vacuum. When the volume was reduced by approximately 50%, the remaining solution was rapidly chromatographed to minimize acetal hydrolysis (5/95, EtOAc/Hex), and afforded 5.5 g (30%) of **86**. IR (film) 3264, 1715, 1391, 1200, 967, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.20 (1H, s), 7.61–7.68 (2H, m), 7.44–7.52 (4H, m), 6.73 (1H, d, *J* = 8.8 Hz), 6.60 (1H, dd, *J* = 8.0 Hz), 6.57 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 162.0, 157.8, 138.2, 133.7, 130.8, 128.9, 126.8, 111.8, 107.1, 101.2, 100.7. HRMS (FAB, MNBA, added LiI) Calcd for $C_{14}H_{10}O_4Li$ $[MLi]^+$: 249.0739. Found: 249.0744.



86 **87**

Triflate 87. To a solution of phenol **86** (2.04 g, 8.4 mmol), and pyridine (3.4 mL, 42 mmol) in CH_2Cl_2 (40 mL) was added trifluoromethanesulfonic anhydride (1.85 mL, 11 mmol) dropwise at 0 ˚C. After stirring for 1.5 hr at rt, the reaction was quenched at 0 ˚C with sat. $NaHCO_3$ (20 mL), and extracted with Et_2O (3 × 150 mL). The organic phase was washed with aqueous saturated $CuSO_4$ (200 mL), dried over $MgSO_4$, and concentrated. After purification by FC (20/80, EtOAc/Hex), 3.0 g (95%) of pure triflate **87** was obtained. IR (film) 1755, 1622, 1429, 1210, 1140, 849; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.70 (3H, m), 7.47–7.55 (3H, m), 7.22 (1H, d, *J* = 8.4 Hz), 7.12 (1H, d, *J* = 8.4 Hz), 6.58 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 158.0, 149.2, 136.6, 133.2,

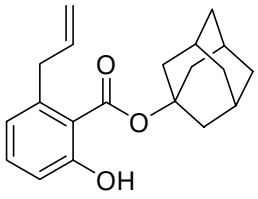
131.0, 129.0, 126.9, 121.0, 117.9, 117.7, 116.8, 109.2, 100.8. HRMS (ESI) Calcd for $C_{15}H_{19}F_3O_6SNa$ $[MNa]^+$: 396.9970. Found: 396.9982.



Compound 88. To a solution of triflate **87** (2.3 g, 6.1 mmol), tri-2-furylphosphine (300 mg, 1.28 mmol) and LiCl (775 mg, 18.3 mmol) in N-methyl pyrrolidinone (20 mL) at ambient temperature was added solid Pd_2dba_3 (391mg, 0.427 mmol). After stirring for 15 min, tributyl allyltin (2.64 mL, 8.54 mmol) was added dropwise. After stirring for 14 hr the reaction was quenched by addition of a solution of KF (1.77 g, 30.5 mmol in 30 mL H_2O). This suspension was allowed to stir for 2 hr, followed by filtration through a pad of celite. The filtrate was diluted with H_2O (50 mL), extracted with Et_2O (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated. After purification by FC (3/97 → 10/90, EtOAc/Hex gradient), 1.0 g (62%) of **88** was obtained. IR (film) 1741, 1605, 1582, 1478, 1291, 1095, 977, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.69 (2H, m), 7.46-7.51 (4H, m), 7.08 (1H, d, J = 7.6 Hz), 7.01 (1H, d, J = 8.0 Hz), 6.45 (1H, s), 6.06 (1H, ddt, J = 6.4, 10.4, 19.2 Hz), 5.10–5.15 (1H, m), 4.03 (1H, dd, J = 6.8, 15.4 Hz), 3.86 (1H, dd, J = 6.6, 15.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 159.5, 146.1, 136.5, 135.5, 134.3, 130.5, 128.8, 126.8, 125.9, 116.6, 115.3, 113.1, 100.0, 38.2. HRMS (ESI) Calcd for $C_{17}H_{14}O_3Na$ $[MNa]^+$: 289.0841. Found: 289.0834.

General Procedure for Solvent Study (Table 2.1)

To an ovendried borosilicate test tube was added 1-adamantanol **89** (15 mg, 0.098 mmol) and **88** (78 mg, 0.294 mmol). The test tube was then sealed with a rubber septum and solvent was added (300 μL, 0.35M) under nitrogen. The reaction vessel was then sealed with parafilm and the solution was photolyzed for 3 hr at 300 nm. The solvent was removed under vacuo and the crude residue was purified by FC (5/95, EtOAc/Hex) to afford **90** with the yield indicated in table 2.1.



90

Ester 90. IR (film) 2912, 1654, 1605, 1450, 1349, 1296, 1248, 1222, 1124, 1046, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, t, *J* = 8.0 Hz), 6.85 (1H, d, *J* = 7.6 Hz), 6.71 (1H, d, *J* = 6.8 Hz), 6.02 (1H, ddt, *J* = 6.2, 10.4, 17.2 Hz), 5.02 (1H, dd, *J* = 1.6, 10.0 Hz), 4.95 (1H, dd, *J* = 1.6, 17.2 Hz), 3.70 (2H, d, *J* = 6.4 Hz), 3.69 (1H, s), 2.27–2.32 (6H, m), 2.21–2.27 (3H, m), 1.66–1.78 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 162.8, 142.7, 138.2, 134.0, 122.5, 116.3, 115.3, 113.7, 84.5, 41.7, 40.5, 36.3, 31.2. HRMS (ESI) Calcd for $C_{17}H_{30}O_2Na$ $[MNa]^+$: 313.1804. Found: 313.1800.

General Procedure for Concentration Study (Table 2.2)

To an ovendried borosilicate test tube was added 1-adamantanol **89** (15 mg, 0.098 mmol) and **88** (78 mg, 0.294 mmol). The test tube was then sealed with a rubber septum and CH_2Cl_2 was added under nitrogen. The reaction vessel was then sealed with parafilm and the solution was photolyzed for 3 hr at 300 nm. The solvent was removed under

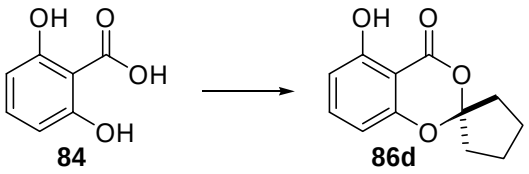
vacuo and the crude residue was purified by FC (5/95, EtOAc/Hex) to afford **90** with the yield indicated in table 2.2.

General Procedure for Stoichiometry Study (Table 2.3)

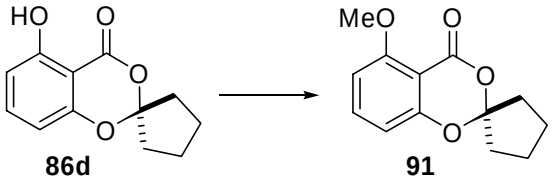
To an ovendried borosilicate test tube was added the indicated portions of 1-adamantanol **89** and benzodioxinone **88**. The test tube was then sealed with a rubber septum and CH_2Cl_2 was added (0.25M) under nitrogen. The reaction vessel was then sealed with parafilm and the solution was photolyzed for 4.5 hr at 300 nm. The solvent was removed under vacuo and the crude residue was purified by FC (5/95, EtOAc/Hex) to afford **90** with the yield indicated in table 2.3.

Study of Benzodioxinone Scope (Fig. 2.1)

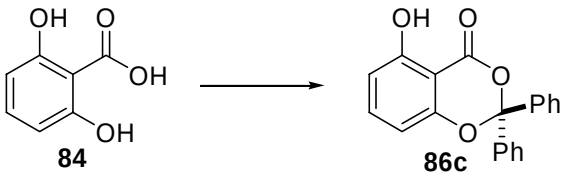
Part 1: Synthesis of Benzodioxinones



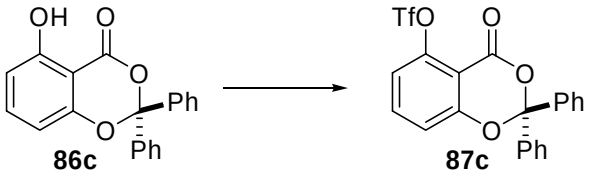
Spiroacetal 86d. Prepared according to the procedure for compound **86**, (57%). IR (film) 3208, 2968, 1704, 1634, 1588, 1487, 1360, 1229, 1101, 968, 809, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.28 (1H, s), 7.39 (1H, t, *J* = 8.2 Hz), 6.63 (1H, d, *J* = 8.0 Hz), 6.46 (1H, d, *J* = 8.0 Hz), 2.12–2.22 (4H, m), 1.76–1.92 (4H, m); ^{13}C NMR (75MHz, $CDCl_3$) δ 156.9, 161.3, 156.2, 137.6, 116.8, 110.7, 107.1, 99.8, 36.8, 23.0. MS (ES) m/z (%): 221.05 ($[MH]^+$, 100).



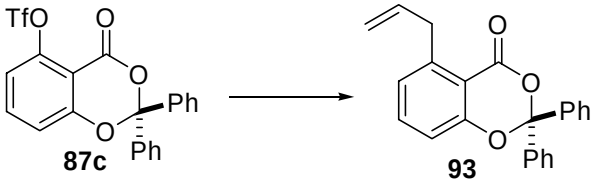
Spiroacetal 91 Prepared according to the procedure for compound **96**, (80%). IR (film) 2965, 1743, 1607, 1585, 1484, 1343, 1260, 1108, 976 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, t, *J* = 8.4 Hz), 6.63 (1H, d, *J* = 8.4 Hz), 6.58 (1H, dd, *J* = 0.8, 8.0 Hz), 3.95 (3H, s), 2.06–2.22 (4H, m), 1.72–1.92 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 159.2, 158.7, 136.4, 115.3, 109.4, 105.7, 103.9, 56.5, 36.9, 23.3. MS (ES) m/z (%): 235.05 ($[MH]^+$, 80).



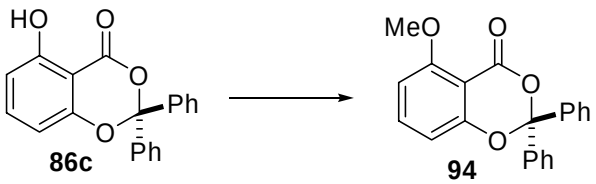
Benzodioxinone 86c. Prepared according to the procedure for compound **86** (34%). IR (film) 3240, 1694, 1633, 1587, 1471, 1342, 1225, 1110, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (1H, d, *J* = 4.8 Hz), 7.53–7.62 (4H, m), 7.29–7.41 (7H, m), 6.64 (1H, d, *J* = 8.4 Hz), 6.54 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 161.5, 156.0, 139.2, 138.2 129.5, 128.7, 126.5, 111.2, 108.3, 107.6, 101.0. HRMS (ESI) Calcd for $C_{20}H_{14}O_4Na$ $[MNa]^+$: 341.0790. Found: 341.0787.



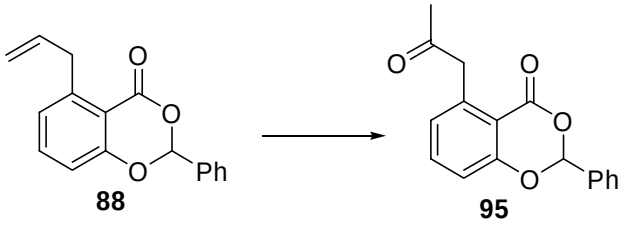
Triflate 87c. Prepared according to the procedure for compound **87** (85%). IR (film) 3068, 1756, 1621, 1473, 1430, 1211, 750, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52–7.64 (5H, m), 7.33–7.41 (6H, m), 7.23 (1H, dd, *J* = 1.05, 8.6 Hz), 6.94 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 157.3, 148.8, 138.7, 136.8, 129.7, 128.8, 126.7, 120.9, 118.4, 117.2, 116.6, 109.5, 107.6. HRMS (FAB, MNBA, added LiI) Calcd for $C_{21}H_{13}F_3O_6SNa$ $[MLi]^+$: 457.0547. Found: 457.0544.



Benzodioxinone 93. Prepared according to the procedure for compound **88** (65%). IR (film) 3065, 1738, 1606, 1582, 1476, 1448, 1289, 1266, 1205, 1098, 1065, 991, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.61 (4H, m), 7.41 (1H, t, *J* = 8.0 Hz), 7.27–7.37 (6H, m), 7.03 (1H, dd, *J* = 1.1, 8.3 Hz), 6.86 (1H, app d, *J* = 7.8 Hz), 5.89 (1H, ddt, *J* = 6.1, 10.1, 17.3 Hz), 4.91 (1H, ddd, *J* = 1.5, 1.5, 10.2 Hz), 4.70 (1H, ddd, *J* = 1.5, 1.7, 17.1 Hz), 3.79 (2H, app d, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 157.6, 145.3, 139.9, 136.4, 135.6, 130.2, 129.3, 128.6, 126.7, 125.5, 116.1, 115.9, 113.7, 106.2, 38.2. MS (ES) m/z (%): 365.00 ($[MNa]^+$, 40). HRMS (ESI) Calcd for $C_{23}H_{18}O_3Na$ $[MNa]^+$: 365.115. Found: 365.1167.

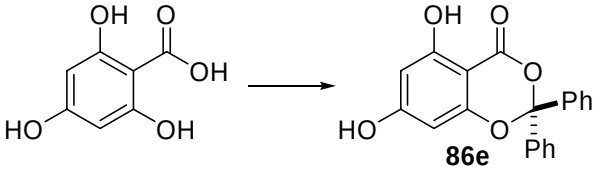


Compound 94. To a stirred solution of phenol **86c** (421 mg, 1.34 mmol) and K_2CO_3 (6.5 g, 47.1 mmol) in acetone (15 mL) at ambient temperature was added MeI (2.0 mL, 31.4 mmol). After stirring for 16 hr the reaction was diluted with Et_2O (100 mL), filtered through a pad of celite, and concentrated. Purification by FC (30/70, EtOAc/Hex) provided 390 mg (87%) of **94**. IR (film) 1748, 1608, 1584, 1483, 1257, 1094, 978, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.61 (4H, m), 7.42 (1H, t, *J* = 8.4 Hz), 7.25–7.36 (6H, m), 6.75 (1H, d, *J* = 8.0 Hz), 6.50 (1H, d, *J* = 8.8 Hz), 3.84 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 158.4, 158.2, 139.8, 136.8, 129.2, 128.6, 126.6, 109.6, 105.9, 56.4. MS (ES) m/z (%): 355.05 ($[MNa]^+$, 60). HRMS (ESI) Calcd for $C_{21}H_{16}O_4Na$ $[MNa]^+$: 355.0946. Found: 355.0956.



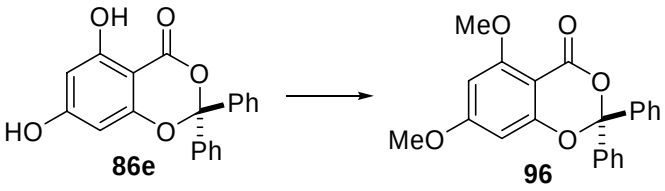
Ketone 95. A suspension of CuCl (2 mg, 0.018 mmol) and $PdCl_2$ (6.4 mg, 0.036 mmol) in DMF:H_2O (10:1, 1 mL) was allowed to stir under an oxygen balloon for 2 hr at rt. To this suspension was then added a solution of alkene **88** (50 mg, 0.18 mmol) in DMF:H_2O (10:1, 0.5 mL). After stirring for 48 hr at ambient temperature, the reaction was filtered through a pad of celite and washed with Et_2O (50 mL). The ethereal phase was washed with $NaHCO_3$, H_2O, and brine. The organic phase was dried over $MgSO_4$, concentrated, and purified by FC (40/60, EtOAc/Hexanes) to afford 25 mg (49%) of ketone **95**. IR (film) 1738, 1607, 1293, 1099, 1069, 975, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.70 (2H, m), 7.52 (1H, t, *J* = 8.0 Hz), 7.44–7.51 (3H, m), 7.07 (1H, d, *J* = 8.0 Hz), 6.96

(1H, d, *J* = 7.6 Hz), 6.52 (1H, s), 4.41 (1H, d, *J* = 17.2 Hz), 4.49 (1H, d, *J* = 17.2 Hz), 2.34 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 162.0, 159.5, 139.7, 135.7, 134.1, 130.6, 128.9, 127.5, 126.9, 116.5, 100.3, 49.2, 30.4. HRMS (ESI) Calcd for $C_{17}H_{14}O_4Na$ $[MNa]^+$: 305.0790. Found: 305.0780.

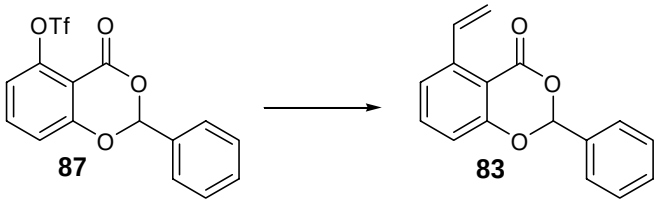


86e

Benzodioxinone 86e. Prepared according to the procedure described in Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc*., **1992**, *114*, 655-659. To a roundbottom flask containing 2,4,6-trihydroxybenzoic acid monohydrate (15 g, 71.6 mmol) was added under nitrogen inlet at 0 ˚C trifluoroacetic acid (118 mL) and trifluoroacetic anhydride (92 mL). The reaction was warmed to ambient temperature and then stirred for 24 hr. The slightly yellow homogenous mixture was concentrated and the residue was dissolved in toluene (40 mL) and concentrated again. This operation was repeated (3X). The crude residue was purified by FC in a rapid fashion to minimize acetal hydrolysis (5/95, EtOAc/Hex) to yield 7.6 g (32%) of **86e**. IR (film) 3260, 1667, 1640, 1597, 1480, 1269, 1161, 1094, 695 cm^{-1}: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (1H, s), 7.53-7.55 (4H, m), 7.33-7.36 (6H, m), 6.27 (1H, s), 6.16 (1H, d, *J* = 2.0 Hz), 6.00 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.1, 163.1, 157.6, 139.0, 129.4, 128.6, 126.3, 107.3, 98.1, 96.2, 94.5; HRMS (ESI, added NaO_2CCF_3) Calcd for $C_{20}H_{14}O_5Na$ $[MNa]^+$: 357.0739. Found: 357.0727.

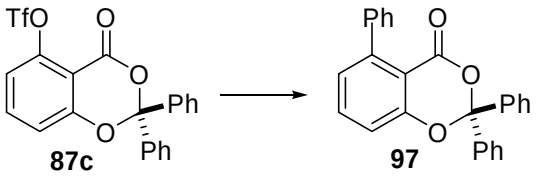


Compound 96. To a stirred solution of phenol **86e** (0.70 g, 2.10 mmol) in acetone (6.6 mL) was added anhydrous K_2CO_3 (1.38 g, 9.95 mmol) followed by MeI (1.24 mL, 19.9 mmol). The reaction was then allowed to stir at ambient temperature for 45 min. The reaction was then poured into H_2O (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (40/60, EtOAc/Hex) to afford 340 mg (44%) of **96**. IR (film) 1739, 1617, 1579, 1494, 1470, 1453, 1427, 1266, 1220, 1161, 1120, 979, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.59 (4H, m), 7.26–7.33 (6H, m), 6.27 (1H, d, J = 2.4 Hz), 6.02 (1H, d, J = 2.1 Hz), 3.81 (3H, s), 3.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 163.0, 159.8, 158.5, 139.9, 129.1, 128.6, 126.5, 106.1, 98.2, 94.0, 56.3, 55.9. MS (ES) m/z (%): 363.10 ($[MH]^+$, 100).



Compound 83. To a solution of triflate **87** (2.25g, 6.01mmol), tri-2-furyl phosphine (278mg, 1.2mmol), and LiCl (763mg, 18mmol), in N-methyl pyrrolidinone (40 mL) at room temp was added solid Pd_2dba_3 (275 mg, 0.3 mmol). After stirring for 15 min. tri-n-butyl vinyl tin (2.3 ml, 7.82 mmol) was added dropwise. After stirring for 3 hr at ambient temperature the reaction was quenched by addition of a solution of KF (8.82 g,

152 mmol in 100 mL H_2O). This suspension was allowed to stir for 2 hr followed by filtration through a pad of celite. The filtrate was diluted with H_2O (50 mL), extracted with Et_2O (3 x 100 mL), dried over $MgSO_4$, filtered and concentrated. After purification by FC (3/97→10/90, EtOAc/Hex gradient) 1.13 g (74%) of **83** was obtained. IR (film) 1732, 1598, 1458, 1319, 976, 909, 814, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.76 (3H, m), 7.47–7.60 (4H, m), 7.38 (1H, d, *J* = 8 Hz), 7.05 (1H, d, *J* = 8.4 Hz), 5.77 (1H, dd, *J* = 0.8, 17.2 Hz), 5.48 (1H, dd, *J* = 0.8, 11 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 159.1, 143.0, 135.5, 135.1, 134.1, 130.5, 128.8, 126.8, 122.2, 118.3, 116.2, 112.0, 100.1. MS (ES) m/z (%) : 307.00 ($[MNaMeOH]^+$, 100), 274.95 ($[MNa]^+$, 30).

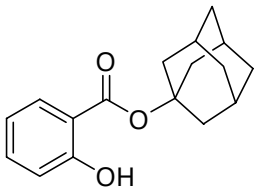


Biaryl 97. DMF (10 mL) was added to a roundbottom flask charged with triflate **87c** (500 mg, 1.11 mmol), LiCl (141 mg, 3.33 mmol), and $PdCl_2(PPh_3)_2$ (77 mg, 0.11 mmol). After stirring for 10 min at ambient temperature Bu_3SnPh (0.54 mL, 1.66 mmol) was added dropwise. The reaction was allowed to stir at ambient temperature for 12 hr. The reaction was then poured into H_2O (100 mL) and extracted with Et_2O (2 x 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (7/93, EtOAc/Hex). The chromatographed material contained significant amounts of stannane by-product which was removed by washing with EtOH (10 mL) to obtain 271 mg (65%) of biaryl **97** as a white solid. IR (film)1752, 1574, 1471, 1311, 1260, 1206, 1111, 1062, 757, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.65 (4H, m), 7.49 (1H, t, *J* = 8.0 Hz), 7.33–7.41 (9H, m), 7.14 (1H, dd, *J* = 1.0, 8.0 Hz), 7.08–7.11 (2H, m), 6.90

(1H, dd, *J* = 1.0, 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 157.6, 146.1, 140.1, 139.8, 135.3, 129.4, 128.7, 128.5, 128.1, 127.8, 126.8, 126.1, 116.7, 113.7. MS (ES) m/z (%): 401.10 ($[MNa]^+$, 100).

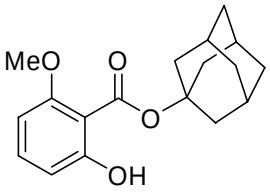
Part 2: General Procedure for Benzodioxinone Study (Fig. 2.1)

To an ovendried borosilicate test tube was added 1-adamantanol **89** and benzodioxinone. The test tube was then sealed with a rubber septum and CH_2Cl_2 (0.25 M) was added under nitrogen. The reaction vessel was then sealed with parafilm and the solution was photolyzed for 4 hr at 300 nm. The solvent was removed *in-vacuo* and the crude residue was purified by FC (EtOAc/Hex) to afford the benzoate ester product with the yield indicated in fig. 2.1.



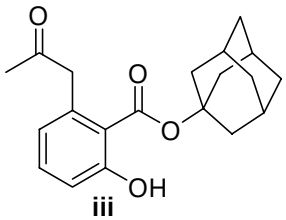
i

Ester i. IR (film) 2917, 1661, 1485, 1344, 1215, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (1H, s), 7.78 (1H, app t, *J* = 7.8 Hz), 7.40 (1H, td, *J* = 1.6, 7.8 Hz), 6.94 (1H, d, *J* = 8.4 Hz), 6.84 (1H, td, *J* = app t, 7.6 Hz), 2.26 (6H, m), 2.24 (3H, s), 1.66–1.78 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 161.9, 135.3, 130.3, 119.0, 117.7, 114.1, 83.1, 41.6, 36.3, 31.1. HRMS (FAB, MNBA, added LiI) Calcd for $C_{17}H_{20}O_3$ $[MLi]^+$: 279.1572. Found: 279.1578.



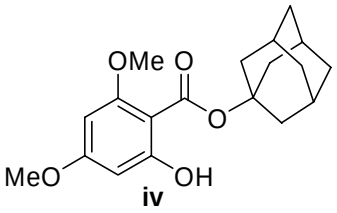
ii

Ester ii. IR (film) 2916, 1653, 1608, 1463, 1367, 1233, 1096, 814, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.52 (1H, s), 7.28 (1H, t, *J* = 8.0 Hz), 6.56 (1H, d, *J* = 8.4 Hz), 6.38 (1H, d, *J* = 8.4 Hz), 3.82 (3H, s), 2.28 (6H, s), 2.22 (3H, s), 1.64–1.78 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 163.5, 161.2, 134.6, 132.6, 130.3, 128.5, 110.2, 102.9, 83.2, 56.3, 41.8, 36.4, 31.2. HRMS (FAB, MNBA, added LiI) Calcd for $C_{18}H_{22}O_4$ $[MLi]^+$: 309.1678. Found: 309.1670.



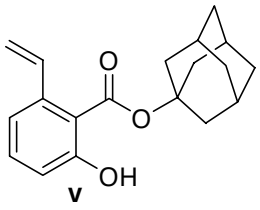
iii

Ester iii. IR (film) 2913, 1723, 1655, 1451, 1352, 1221, 1044 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (1H, s), 7.31 (1H, t, *J* = 8.0 Hz), 6.92 (1H, d, *J* = 8.4 Hz), 6.62 (1H, d, *J* = 7.6 Hz), 4.05 (2H, s), 2.23 (9H, s), 2.16 (3H, s), 1.70 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 169.8, 162.7, 136.9, 134.0, 123.6, 117.6, 85.1, 51.7, 41.6, 36.2, 31.2, 29.8. MS (ES) m/z (%): 351.10 ($[M+Na]^+$, 100). HRMS (ESI) Calcd for $C_{17}H_{30}O_2Na$ $[MNa]^+$: 351.1573. Found: 351.1561.



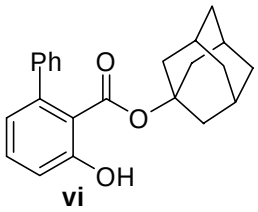
iv

Ester iv. IR (film) 2913, 2853, 1614, 1336, 1266, 1217, 1160, 1116, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (1H, s), 6.08 (1H, d, *J* = 2.0 Hz), 5.94 (1H, d, *J* = 2.0 Hz), 3.79 (3H, s), 3.78 (3H, s), 2.26–2.27 (6H, m), 2.21–2.22 (3H, m), 1.69–1.73 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 166.0, 164.9, 162.5, 132.6, 130.3, 128.5, 98.3, 93.6, 91.9, 82.7, 56.1, 55.6, 41.8, 36.4, 31.2. MS (ES) m/z (%): 355.05 ($[MNa]^+$, 100).



v

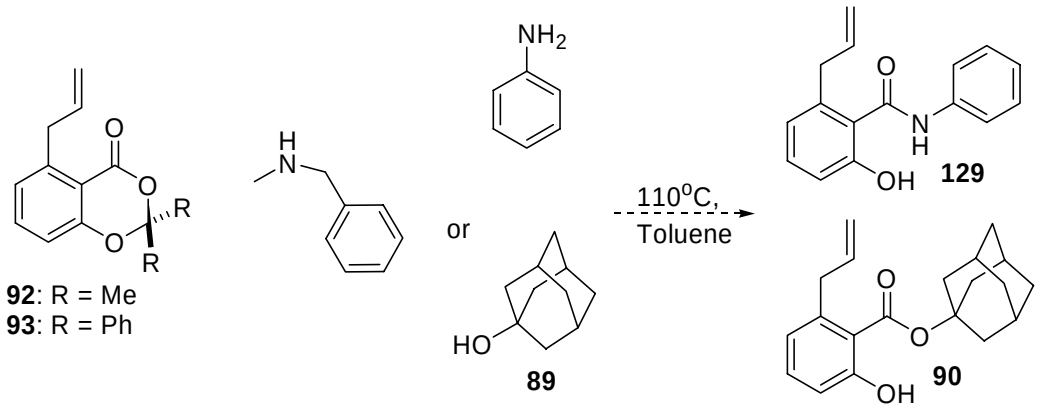
Ester v. IR (film) 2912, 2854, 1655, 1601, 1449, 1350, 1252, 1217, 1047, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (1H, s), 7.33 (1H, t, *J* = 8.0 Hz), 7.28 (1H, dd, *J* = 10.8, 17.2 Hz), 6.92 (1H, d, *J* = 4.4 Hz), 6.90 (1H, d, *J* = 4.4 Hz), 5.42 (1H, dd, *J* = 1.6, 17.2 Hz), 5.20 (1H, dd, *J* = 1.6, 10.8 Hz), 2.28–2.30 (6H, m), 2.22–2.26 (3H, m), 1.68–1.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 162.3, 142.1, 139.0, 134.0, 120.0, 117.3, 115.1, 112.3, 84.6, 41.8, 36.3, 31.2.



vi

Biaryl vi. IR (film) 3060, 2913, 2852, 1756, 1658, 1600, 1453, 1439, 1351, 1272, 1221, 1174, 1049, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.86 (1H, s), 7.61–7.64 (1H, m), 7.32–7.41 (3H, m), 7.22–7.26 (2H, m), 6.92 (1H, d, *J* = 8.0 Hz), 6.74 (1H, d, *J* = 7.6 Hz), 2.01–2.05 (3H, m), 1.72–1.73 (6H, m), 1.50–1.58 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 161.6, 135.3, 133.2, 129.4, 128.7, 128.6, 128.2, 126.9, 122.7, 116.7, 83.2, 40.7, 36.2, 30.9.

General Procedure for Thermal Control Experiment (Scheme 2.19)

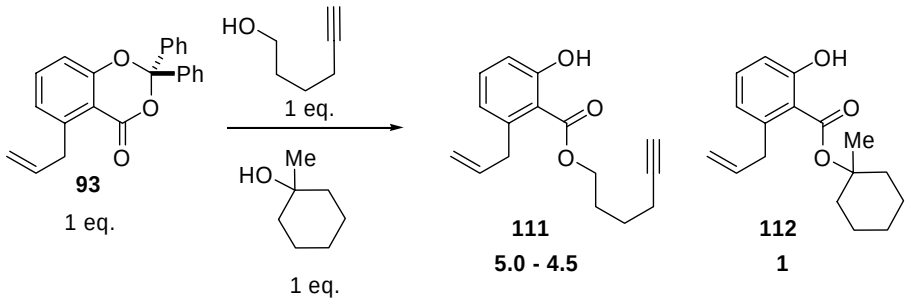


To a glass vial was added benzodioxinone **92** (1 eq) or **93** (1 eq) and *N*-methyl-benzylamine (2 eq), aniline (2 eq), or alcohol **89** (2 eq) and toluene (0.3 M). The vial was sealed and the reaction was allowed to stir at 110 ˚C for 3 hr. Examination of the reaction after this period revealed neither product formation nor decomposition of the starting materials. The solvent was removed *in-vacuo* and substrates **92** and **93** were recovered in >97% yield after purification by FC (EtOAc/Hex).

General Procedure for Quantum Yield Determination (Fig. 2.3)

To an ovendried NMR tube containing 7 μL of tert-butyl methyl ether as an internal standard (δ 1.05 and 3.01ppm) was added 0.8 mL of a 0.1 M solution of benzophenone (18.2 mg, 0.1 mmol) and benzhydrol (18.4 mg, 0.1 mmol) in C_6D_6 (1 ml, degassed 3X via freeze, pump, thaw). In the same manner 0.8 mL of a 0.1 M solution of benzodioxinone **88** in degassed C_6D_6 was transferred to an ovendried NMR tube. These samples were photolyzed together in a Rayonett reactor (turned on for ½ hr to warm lamps prior to submission of samples) at 300 nm and the reaction progress was monitored by ^{1}H NMR (400MHz). Both the fraction of benzodioxinone consumed (acetal proton at δ 5.85 ppm) and benzaldehyde formed (aldehyde proton at δ 9.63 ppm) versus the actinometer (alcohol proton δ 2.92ppm) were plotted as shown in fig. 2.6. Comparison of the reaction rates shows a relative quantum yield of 0.64 for benzodioxinone consumption and 0.56 for benzaldehyde formation, assuming a quantum yield of 0.68 for the actinometer. This procedure provided reproducible reaction rates when repeated.

General Procedure for Steric Competition Experiment (Scheme 2.20)



To an oven-dried borosilicate test tube was added 1-methylcyclohexanol (28 mg, 0.244 mmol), 5-hexyn-1-ol (24 mg, 0.244 mmol) and **93** (84 mg, 0.244 mmol). The test tube was then sealed with a rubber septum and the starting materials were dissolved in freshly distilled CH_2Cl_2 (1 mL) under nitrogen inlet. The nitrogen inlet was removed and the reaction vessel was sealed with parafilm. This solution was then photolyzed for 4 hr

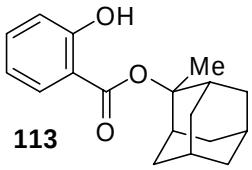
at 300 nm in the Rayonett reactor. The solvent was removed and crude proton NMR was taken to determine ratio of esters **111** and **112** formed. Proton NMR revealed a ratio of ~4.5–5:1 of **111**:**112** respectively.

General Procedure for Nucleophile Study (Fig. 2.5-2.6)

Procedure A: To an ovendried borosilicate test tube was added the benzodioxinone (2–3 eq) and nucleophile (1 eq) indicated in figures 2.5 and 2.6. The test tube was then sealed with a rubber septum and freshly distilled CH_2Cl_2 was added (0.25–0.35 M/nucleophile concentration) under nitrogen. The reaction vessel was then sealed with parafilm and the solution was photolyzed for 3–4 hr at 300 nm. The solvent was removed *in-vacuo* and the crude residue was purified by FC (EtOAc/Hex) to afford benzoate ester or amide with the yield indicated in figures 2.5 and 2.6.

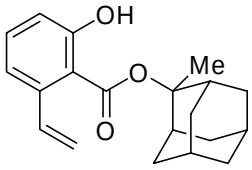
Procedure B: To an ovendried borosilicate test tube was added the benzodioxinone (2–3 eq) and nucleophile (1 eq) indicated in figure 2.6. The test tube was then sealed with a rubber septum and freshly distilled degassed (15 min N_2 purge) CH_2Cl_2 was added (0.25–0.35 M/nucleophile concentration) under nitrogen. The reaction vessel was then sealed with parafilm and the solution was photolyzed for 3–4 hr at 300 nm. The solvent was removed *in-vacuo* and transferred to a roundbottom flask. The crude residue was then dissolved in anhydrous MeOH and treated with K_2CO_3 (1.5 eq relative to nucleophile added) and the reaction was stirred at ambient temperature for 2 hr. The solvent was then removed and the crude residue was then poured into H_2O and extracted with EtOAc (3X). The organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC

(EtOAc/Hex) to afford the desired benzoate ester or amide with the yield indicated in figure 2.6.



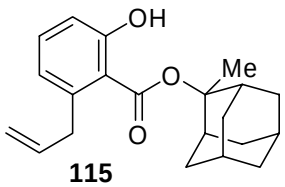
113

Ester 113. IR (film) 3140, 2915, 2862, 1662, 1613, 1587, 1485, 1340, 1250, 1215, 1103, 1089, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (1H, s), 7.85 (1H, dd, *J* = 1.6, 8.0 Hz), 7.43 (1H, ddd, *J* = 1.6, 7.2, 8.4 Hz), 6.96 (1H, dd, *J* = 0.8, 8.4 Hz), 6.86 (1H, ddd, *J* = 1.2, 7.6, 7.6 Hz), 2.44–2.50 (2H, m), 2.08–2.16 (2H, m), 1.92–1.98 (2H, m), 1.72–1.88 (9H, m), 1.63–1.68 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 162.1, 135.3, 130.3, 119.1, 117.8, 114.1, 89.9, 38.3, 36.7, 33.4, 27.5, 26.8, 22.7. HRMS (FAB, MNBA, added LiI) Calcd for $C_{18}H_{22}O_3Li$ $[MLi]^+$: 293.1729. Found: 293.1727.



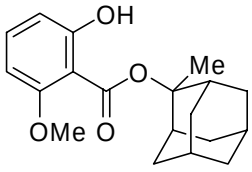
114

Ester 114. IR (film) 2913, 2861, 1654, 1601, 1573, 1450, 1351, 1252, 1214, 1092, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (1H, s), 7.33 (1H, t, *J* = 8.0 Hz), 7.29 (1H, dd, *J* = 6.8, 17.6 Hz), 6.92 (2H, app t, *J* = 7.2 Hz), 5.45 (1H, dd, *J* = 1.6, 17.2 Hz), 5.18 (1H, dd, *J* = 1.4, 10.8 Hz), 2.49-2.51 (2H, m), 2.07-2.10 (2H, m), 1.93-1.97 (2H, m), 1.76-1.85 (6H, m), 1.72-1.73 (2H, m), 1.57-1.61 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 138.7, 134.0, 92.2, 38.4, 36.8, 34.9, 33.3, 29.9, 27.5, 26.8, 23.1. MS (ES) m/z (%): 355.10 ($[MNa]^+$, 100).



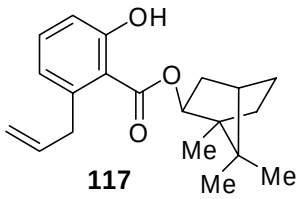
115

Ester 115. IR (film) 2916, 1654, 1606, 1450, 1351, 1250, 1217, 1102, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.10 (1H, s), 7.29 (1H, t, *J* = 8.0 Hz), 6.86 (1H, dd, *J* = 1.0, 8.2 Hz), 6.72 (1H, d, *J* = 7.2 Hz), 5.98 (1H, ddt, *J* = 6.0, 10.2, 17.2 Hz), 5.03 (1H, app dd, *J* = 1.6, 10.0 Hz), 4.93 (1H, app ddd, *J* = 1.4, 1.8, 17.0 Hz), 3.75 (2H, app d, *J* = 6.4 Hz), 2.52 (2H, s), 2.07 (2H, br. m), 1.96 (2H, br. m), 1.75-1.88 (7H, m), 1.74 (2H, br. m), 1.64 (2H, br. m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 162.4, 142.3, 138.0, 133.8, 122.4, 116.3, 115.7, 114.2, 92.1, 39.9, 38.3, 36.8, 34.9, 33.4, 27.5, 26.7, 22.6. HRMS (FAB, MNBA, added LiI) Calcd for $C_{21}H_{26}O_3$ $[MLi]^+$: 333.2042. Found: 333.2043.



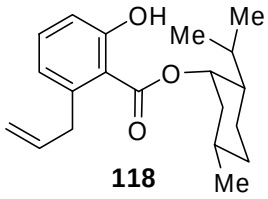
116

Ester 116. IR (film) 2910, 1650, 1607, 1458, 1365, 1236, 1094, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, t, *J* = 8.4 Hz), 6.57 (1H, d, *J* = 8.4 Hz), 6.39 (1H, d, *J* = 8.4 Hz), 3.82 (3H, s), 2.41–2.43 (2H, m), 2.24–2.29 (2H, m), 1.91–1.97 (9H, m), 1.57–1.63 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 163.9, 161.0, 134.6, 110.2, 102.3, 90.6, 56.0, 38.5, 36.8, 34.9, 33.0, 27.6, 27.0, 22.8 HRMS (ESI) Calcd for $C_{19}H_{24}O_4Na$ $[MNa]^+$: 339.1572. Found: 339.1560.



117

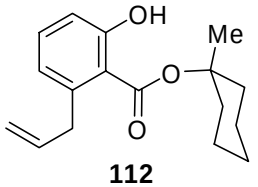
Ester 117. $[\alpha]_D$ = -3.4 ($CHCl_3$, c 0.92). IR (film) 2956, 1656, 1606, 1450, 1315, 1250, 1220, 1118, 974, 817, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.22 (1H, s), 7.32 (1H, t, *J* = 8.0 Hz), 6.88 (1H, d, 8.0 Hz), 6.75 (1H, d, *J* = 6.8), 6.02 (1H, ddt, *J* = 6.0, 10.4, 17.2 Hz), 5.17–5.23 (1H, m), 5.05 (1H, dd, *J* = 1.2, 10.0 Hz), 4.94 (1H, dd, *J* = 1.4, 17.0 Hz), 3.82 (1H, dd, *J* = 6.2, 15.8 Hz), 3.74 (1H, d, 6.2, 15.8 Hz), 2.50 (1H, m), 1.98, (1H, m), 1.72–1.86 (2H, m), 1.42–1.47 (1H, m), 1.22–1.32 (1H, m), 1.16 (1H, dd, *J* = 3.7, 13.8 Hz), 0.97 (3H, s), 0.93 (3H, s), 0.91 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 162.7, 142.5, 137.8, 134.3, 122.4, 116.4, 115.8, 113.0, 83.5, 49.1, 48.2, 44.8, 40.2, 37.0, 28.3, 28.1 19.9, 19.1, 14.0. HRMS (ESI) Calcd for $C_{20}H_{26}O_3Na$ $[MNa]^+$: 337.1780. Found: 337.1779.



118

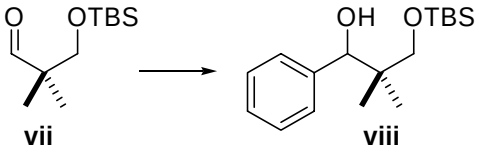
Ester 118. $[\alpha]_D$ = +5.1 ($CHCl_3$, c 0.90). IR (film) 2958, 2928, 1654, 1606, 1450, 1221, 1121, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, t, *J* = 8.0 Hz), 6.88 (1H, d, *J* = 8 Hz), 6.74 (1H, d, *J* = 7.2 Hz), 6.00 (1H, ddt, *J* = 6.0, 10.2, 17.2 Hz), 5.08 (1H, ddd, *J* = 4.4, 10.8, 10.8 Hz), 5.03 (1H, dd, *J* = 1.4, 6.2 Hz), 4.95 (1H, dd, *J* = 1.6, 17.2 Hz), 3.74 (1H, dd, *J* = 5.8, 15.4), 3.64 (1H, dd, *J* = 6.0, 15.6 Hz), 2.13 (1H, m), 1.92 (1H, dq, *J* = 2.4, 7.2 Hz), 1.69–1.75 (2H, m), 1.49–1.62 (2H, m), 1.04–1.30 (2H, m), 0.95 (3H, d, *J* =

6.4 Hz), 0.91 (3H, d, *J* = 7.2 Hz), 0.79 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 163.0, 142.9, 138.0, 134.4, 122.7, 116.4, 115.5, 112.6, 76.3, 47.3, 41.1, 40.4, 34.3, 31.8, 29.9, 26.3, 23.3, 22.2, 21.1, 16.2. HRMS (ESI) Calcd for $C_{20}H_{28}O_3Na$ $[MNa]^+$: 339.1936. Found: 339.1946.



112

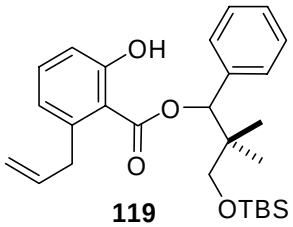
Ester 112. IR (film) 2935, 1655, 1606, 1450, 1355, 1318, 1246, 1222, 1150, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, t, *J* = 8.0 Hz), 6.86 (1H, d, *J* = 7.6 Hz), 6.72 (1H, d, *J* = 7.6 Hz), 6.01 (1H, ddt, *J* = 6.0, 10.2, 17.2 Hz), 5.03 (1H, dd, *J* = 1.4, 10.2 Hz), 4.94 (1H, dd, *J* = 1.8, 17.0 Hz), 3.74 (2H, d, *J* = 6.4 Hz), 2.26 (2H, m), 1.63 (3H, s), 1.48–1.74 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 162.7, 142.5, 138.1, 133.9, 122.4, 116.4, 115.6, 114.0, 86.6, 40.3, 37.2, 25.5, 25.2, 22.6. HRMS (FAB, MNBA, added LiI) Calcd for $C_{17}H_{22}O_3$ $[MLi]^+$: 281.1729. Found: 281.1731.



vii **viii**

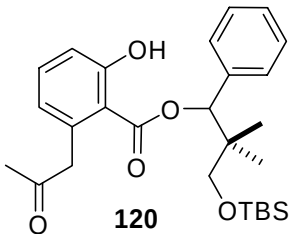
Alcohol viii. To a stirred solution of aldehyde **vii** [Wender, P. A; Baryza, J. L.; Bennett, C. E.; Bi, F. C.; Brenner, S. E.; Clarke, M. O.; Horan, J. C.; Kan, C.; Lacôte, E.; Lippa, B.; Nell, P. G.; Turner, T. M. J. Am. Chem. Soc. **2002**, *124*, 13648–13649] (2.78 g, 12.8 mmol) in THF (50 mL) at -78 ˚C was added phenyllithium (10.7 mL, 19.3 mmol, 1.8 M in THF). After stirring for 2 hr at -60 ˚C, the reaction was quenched by addition of EtOH

(50 mL). The mixture was diluted with H_2O (50 mL), extracted with Et_2O (3 × 100 mL), dried over $MgSO_4$, filtered, concentrated, and purified by FC (3/97, EtOAc/Hex) to afford 2.3 g (62%) of **viii**. IR (film) 3467, 2956, 2930, 2858, 1473, 1254, 1087, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17–7.30 (5H, m), 4.56 (1H, d, *J* = 3.6 Hz), 4.31 (1H, d, *J* = 3.6 Hz), 3.48 (1H, d, *J* = 10.0 Hz), 3.43 (1H, d, *J* = 10.0 Hz), 0.91 (9H, s), 0.80 (3H, s), 0.78 (3H, s), 0.07 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 127.9, 127.6, 127.2, 82.0, 72.9, 39.1, 26.0, 22.8, 19.4, 18.3. HRMS (ESI) Calcd for $C_{17}H_{30}O_2SiNa$ $[MNa]^+$: 317.1913. Found: 317.1902.



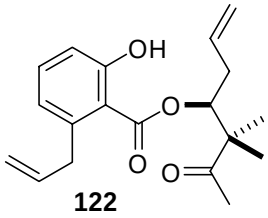
119

Ester 119. IR (film) 2956, 2930, 2858, 1659, 1607, 1450, 1251, 1218, 1099, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.40 (6H, m), 6.85 (1H, d, *J* = 7.6 Hz), 6.77 (1H, d, *J* = 7.2 Hz), 6.16 (1H, s), 6.06–6.18 (1H, app ddt, *J* = 6.0, 10.4, 17.2 Hz), 5.15 (1H, dd, *J* = 1.4, 10.2 Hz), 5.01 (1H, dd, *J* = 1.6, 17.2 Hz), 3.98 (1H, dd, *J* = 5.8, 16.2 Hz), 3.91 (1H, dd, *J* = 6.0, 16.0 Hz), 3.44 (1H, d, *J* = 9.6 Hz), 3.24 (1H, d, *J* = 9.6 Hz), 1.06 (3H, s), 0.92 (9H, s), 0.88 (3H, s), 0.03 (3H, s), -0.10 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 163.2, 142.3, 137.7, 134.4, 128.2, 128.1, 125.8, 122.3, 116.5, 116.4, 112.7, 82.2, 69.5, 40.1, 40.0, 30.5, 26.1, 21.3, 21.0, 18.5. HRMS (ESI) Calcd for $C_{27}H_{38}O_4SiNa$ $[MNa]^+$: 477.2437. Found: 477.2420.



120

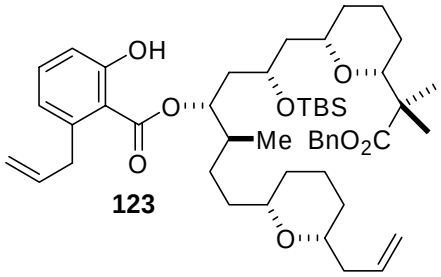
Ester 120. IR (film) 2956, 2857, 1724, 1659, 1609, 1451, 1360, 1253, 1216, 1166, 1110, 838, 777, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.69 (1H, s), 7.27–7.37 (6H, s), 6.93 (1H, d, *J* = 8.4 Hz), 6.66 (1H, d, *J* = 7.6 Hz), 6.15 (1H, s), 4.28 (1H, d, *J* = 17.6 Hz), 4.11 (1H, d, *J* = 17.2 Hz), 3.38 (1H, d, *J* = 9.6 Hz), 3.22 (1H, d, *J* = 10.0 Hz), 2.15 (3H, s), 1.03 (3H, s), 0.92 (9H, s), 0.89 (3H, s), 0.04 (3H, s), 0.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 162.3, 137.4, 137.3, 134.4, 128.1, 123.8, 117.8, 82.4, 69.5, 50.9, 40.0, 30.1, 26.1, 21.3, 18.3 HRMS (FAB, MNBA, added LiI) Calcd for $C_{27}H_{38}O_5SiLi$ $[MLi]^+$: 477.2649. Found: 477.2651.



122

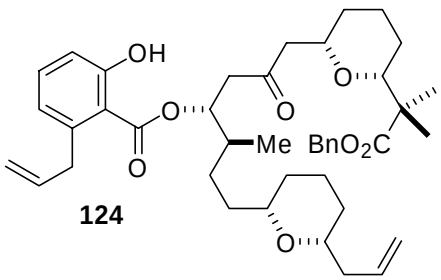
Ester 122. $[\alpha]_D$ = +1.2 ($CHCl_3$, c 1.1). IR (film) 2979, 1707, 1655, 1607, 1450, 1356, 1248, 1217, 1116, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.1 (1H, s), 7.32 (1H, t, *J* = 8.0 Hz), 6.87 (1H, app d, *J* = 7.6 Hz), 6.74 (1H, d, *J* = 8.0 Hz), 5.99 (1H, ddt, *J* = 6.0, 10.4, 17.0 Hz), 5.78–5.83 (1H, m), 5.76 (1H, app ddt, *J* = 6.6, 10.4, 17.2 Hz), 5.08 (1H, dd, J = 1.6, 17.2 Hz), 5.03–5.06 (2H, m), 4.93 (1H, dd, *J* = 1.4, 17.0 Hz), 3.74 (1H, dd, *J* = 5.8, 15.8 Hz), 3.63 (1H, dd, *J* = 6.0, 16.0 Hz), 2.27–2.42 (2H, m), 2.19 (3H, s), 1.24 (3H, s), 1.21 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 162.9, 142.7, 137.7, 134.6,

134.0, 122.6, 118.5, 116.5, 116.0, 112.3, 78.3, 51.7, 40.0, 35.5, 26.0, 21.4, 20.8. HRMS (ESI) Calcd for $C_{19}H_{24}O_4Na$ $[MNa]^+$: 339.1572. Found: 339.1560.



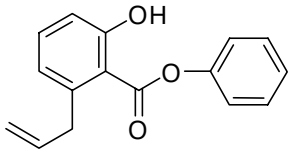
123

Ester 123. $[\alpha]_D$ = -0.2 ($CHCl_3$, c 1.0). IR (film) 2933, 1733, 1656, 1606, 1451, 1252, 1222, 1087, 1049, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.4 (1H, s), 7.24–7.39 (6H, m), 6.85 (1H, d, *J* = 8.4 Hz), 6.68 (1H, d, *J* = 7.2 Hz), 6.00 (1H, ddt, *J* = 6.2, 10.2, 17.0 Hz), 5.83 (1H, ddt, *J* = 7.2, 9.8, 17.0 Hz), 5.37 (1H, m), 4.92–5.12 (7H, m), 3.89 (1H, m), 3.71 (2H, d, *J* = 5.2 Hz), 3.14–3.50 (4H, m), 2.28 (1H, m), 2.13 (1H, m), 1.91 (1H, m), 1.82 (2H, m), 1.00–1.74 (21H, m), 1.08 (3H, s), 1.05 (3H, s), 0.95 (3H, d, *J* = 6.4 Hz), 0.89 (9H, s), 0.02 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 171.3, 163.0, 142.6, 138.0, 136.6, 135.6, 134.1, 128.6, 128.2, 128.0, 122.4, 116.3, 115.8, 112.8, 81.9, 78.1, 74.9, 66.5, 66.1, 46.9, 45.5, 41.2, 40.3, 37.6, 36.6, 34.3, 32.3, 31.8, 31.5, 29.9, 28.9, 26.2, 25.9, 23.9, 22.5, 19.8, 18.2, 15.0, -3.9, -4.7. HRMS (ESI) Calcd for $C_{48}H_{72}O_8SiNa$ $[MNa]^+$: 827.4894 Found: 827.4905.



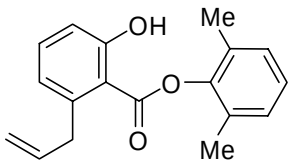
124

Ester 114. $[\alpha]_D$ = -1.1 ($CHCl_3$, c 1.0). IR (film) 2935, 1729, 1656, 1606, 1480, 1221, 1085, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.17 (1H, s), 7.24–7.39 (6H, m), 6.86 (1H, d, *J* = 8.4 Hz), 6.70 (1H, d, *J* = 7.2 Hz), 5.93 (1H, ddt, *J* = 5.6, 10.8, 16.4 Hz), 5.80 (1H, ddt, *J* = 7.0, 10.0, 17.0 Hz), 5.57–5.65 (1H, m), 4.87–5.16 (7H, m), 3.48–3.78 (4H, m), 3.14–3.35 (2H, m), 2.62–2.88 (2H, m), 2.53 (1H, dd, *J* = 8.0, 14.8 Hz), 2.20–2.44 (2H, m), 2.06–2.18 (1H, m), 1.93 (1H, m), 1.81 (2H, br), 1.38–1.68 (10H, m), 1.04–1.29 (4H, m), 1.15 (3H, s), 1.11 (3H, s), 0.94 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 170.7, 162.8, 142.5, 137.9, 136.7, 135.6, 134.3, 132.3, 129.1, 128.7, 128.2, 128.2, 122.5, 119.6, 118.2, 116.4, 115.7, 112.8, 82.6, 78.1, 75.4, 75.1, 49.8, 46.8, 45.5, 44.7, 41.2, 40.1, 36.4, 34.2, 31.7, 31.4, 28.6, 25.0, 23.8, 23.5, 21.4, 20.6, 15.3. HRMS (ESI) Calcd for $C_{42}H_{56}O_8Na$ $[MNa]^+$: 711.3867 Found: 711.3845.



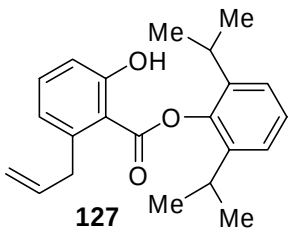
125

Ester 125. IR (film) 3077, 1673, 1450, 1293, 1188, 1163, 915, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.91 (1H, d, *J* = 1.2 Hz), 7.97 (1H, t, *J* = 7.8 Hz), 7.42 (1H, t, *J* = 8.0 Hz), 7.33 (1H, t, *J* = 7.6 Hz), 7.20 (2H, d, *J* = 8.8 Hz), 6.95 (1H, d, *J* = 8.4 Hz), 6.85 (1H, d, *J* = 7.6 Hz), 6.09 (1H, ddt, *J* = 6.0, 10.4, 17.2 Hz), 5.09 (1H, dt, *J* = 1.4, 10.4 Hz), 4.99 (1H, dt, *J* = 1.5, 17.2 Hz), 3.85 (2H, d, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 163.5, 150.0, 143.2, 137.8, 135.4, 129.9, 126.7, 123.1, 121.9, 116.7, 115.9, 111.7, 40.7. HRMS (ESI) Calcd for $C_{16}H_{14}O_3Na$ $[MNa]^+$: 277.0841. Found: 277.0832.



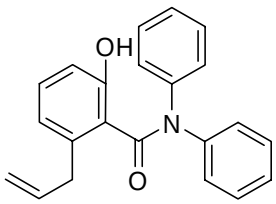
126

Ester 126. IR (film) 3077, 1668, 1609, 1449, 1156, 1106, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, t, *J* = 7.8 Hz), 7.15 (3H, s), 6.97 (1H, d, *J* = 8.0 Hz), 6.88 (1H, d, *J* = 7.6 Hz), 6.11 (1H, ddt, *J* = 6.2, 10.4, 17.2 Hz), 5.09 (1H, dd, *J* = 1.2, 10.0 Hz), 4.99 (1H, dd, *J* = 1.2, 17.2 Hz), 3.91 (2H, d, *J* = 6.0 Hz), 2.22 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 164.1, 147.8, 143.6, 137.6, 135.4, 130.3, 129.1, 126.6, 123.1, 116.7, 116.1, 111.1, 40.7, 16.9. HRMS (ESI) Calcd for $C_{18}H_{18}O_3Na$ $[MNa]^+$: 305.1154. Found: 305.1158.



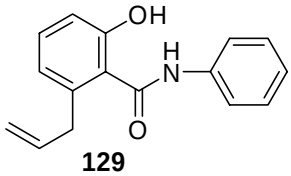
127

Ester 127. IR (film) 2965, 1670, 1609, 1449, 1293, 1246, 1215, 1160, 1097, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, t, *J* = 7.8 Hz), 7.21–7.38 (3H, m), 6.97 (1H, d, *J* = 8.4 Hz), 6.88 (1H, d, *J* = 7.6 Hz), 6.10 (1H, ddt, *J* = 6.0, 10.4, 16.8 Hz), 5.08 (1H, dd, *J* = 1.2, 10.0 Hz), 4.98 (1H, dd, *J* = 1.2, 17.2 Hz), 3.90 (2H, d, *J* = 5.6 Hz), 2.96 (2H, heptet, *J* = 6.8 Hz), 1.17–1.30 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 143.5, 140.6, 137.5, 135.4, 127.3, 124.5, 123.1, 116.8, 116.0, 40.4, 27.7, 24.4, 23.1. HRMS (ESI) Calcd for $C_{22}H_{26}O_3Na$ $[MH]^+$: 339.1960. Found: 339.1949.



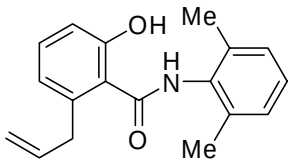
128

Amide 128. IR (film) 3253, 1634, 1586, 1492, 1466, 1362, 1285, 911 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90–7.44 (10H, m), 7.09 (1H, t, *J* = 7.8 Hz), 6.72 (1H, d, *J* = 8.4 Hz), 6.68 (1H, s), 6.53 (1H, d, *J* = 8.0 Hz), 5.70 (1H, ddt, *J* = 6.8, 10.0, 16.8 Hz), 4.99–5.09 (2H, m), 3.31 (1H, *br* s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 154.2, 142.6, 137.2, 136.6, 130.7, 129.1, 127.3, 127.1, 123.9, 121.0, 116.8, 114.8, 37.6. HRMS (ESI) Calcd for $C_{22}H_{19}NO_2Na$ $[MNa]^+$: 352.1313 Found: 352.1315.



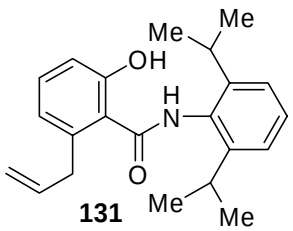
129

Amide 129. IR (film) 3285, 1647, 1596, 1534, 1441, 1325, 1287, 991, 916, 753, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (1H, s), 8.32 (1H, s), 7.54 (2H, d, *J* = 7.6 Hz), 7.28–7.42 (3H, m), 7.18 (1H, t, *J* = 7.4 Hz), 6.92 (1H, dd, *J* = 1.0, 8.2 Hz), 6.76 (1H, dd, *J* = 0.8, 7.6 Hz), 6.33 (1H, ddt, *J* = 5.0, 10.4, 17.6 Hz), 5.43 (1H, dd, *J* = 1.2, 10.4 Hz), 5.09 (1H, dd, *J* = 1.2, 17.2 Hz), 3.61–3.66 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 159.9, 138.8, 137.2, 136.2, 132.8, 129.4, 125.3, 123.5, 120.6, 119.2, 118.5, 116.4, 39.0. HRMS (ESI) Calcd for $C_{16}H_{15}NO_2Na$ $[MNa]^+$: 276.1000 Found: 276.1001.



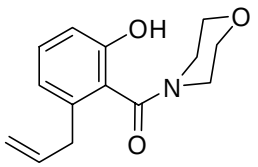
130

Amide 130. IR (film) 3075, 1628, 1587, 1520, 1463, 1309, 992, 911, 784, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (1H, s), 7.92 (1H, s), 7.35 (1H, t, *J* = 8.0 Hz), 7.11–7.20 (3H, m), 6.94 (1H, dd, *J* = 0.8, 8.0 Hz), 6.78 (1H, d, *J* = 7.6 Hz), 6.28 (1H, ddt, *J* = 5.0, 10.4, 17.6 Hz), 5.33 (1H, dd, J = 1.6, 10.4 Hz), 5.04 (1H, dd, *J* = 1.2, 17.6 Hz), 3.74–3.78 (2H, m), 2.12 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 160.8, 139.0, 136.8, 135.2, 133.4, 132.9, 128.6, 127.9, 123.4, 118.4, 117.9, 116.6, 39.3, 19.0. HRMS (ESI) Calcd for $C_{18}H_{19}NO_2H$ $[MH]^+$: 282.1572 Found: 282.1488.



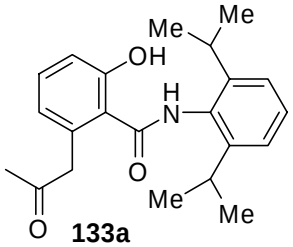
131

Amide 131. IR (film) 3231, 2965, 1636, 1510, 1463, 1304, 991, 911, 737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (1H, s), 7.87 (1H, s), 7.36 (2H, t, *J* = 7.8 Hz), 7.24 (2H, d, *J* = 8.0 Hz), 6.95 (1H, dd, *J* = 0.8, 8.4 Hz), 6.79 (1H, dd, *J* = 1.0, 7.8 Hz), 6.28 (1H, ddt, *J* = 5.0, 10.2, 17.2 Hz), 5.32 (1H, dd, *J* = 1.6, 10.4 Hz), 5.05 (1H, dd, *J* = 1.4, 17.4 Hz), 3.74–3.81 (2H, m), 3.02 (2H, heptet, *J* = 6.8 Hz), 3.75–3.80 (2H, m), 1.10–1.35 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 160.9, 146.0, 138.8, 136.5, 133.0, 130.4, 129.0, 123.9, 123.4, 118.4, 117.7, 116.7, 39.2, 29.3, 24.6, 23.2. HRMS (ESI) Calcd for $C_{22}H_{27}NO_2H$ $[MH]^+$: 338.2120 Found: 338.2107.



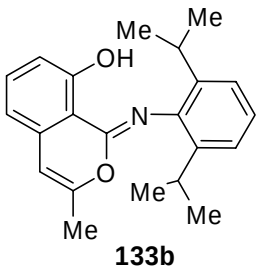
132

Amide 132. IR (film) 3176, 1586, 1463, 1279, 1114, 1022, 916 cm^{-1}; ^{1}H NMR$^{55\ ^{\circ}C}$ (400 MHz, $CDCl_3$) δ 7.38–7.54 (1H, *br* s), 7.06 (1H, t, *J* = 8.0 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 6.61 (1H, d, *J* = 8.4 Hz), 5.88 (1H, ddt, *J* = ddt, 6.8, 9.8, 17.6 Hz), 5.04 (2H, app d, *J* = 13.6 Hz), 3.28–3.72 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 153.4, 138.1, 136.8, 130.2, 122.6, 121.1, 116.3, 114.3, 66.9, 47.3, 42.2, 37.5. (ES) m/z (%): 246.10 ($[MH]^+$, 30), 270.05 ($[MNa]^+$, 80).



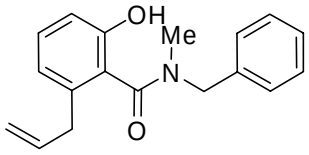
133a

Amide 133a. IR (film) 3436, 2963, 1655, 1599, 1465, 1394, 1241, 913 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.43 (1H, s), 7.41 (1H,l d, *J* = 7.6 Hz), 7.37 (1H, d, *J* = 7.6 Hz), 7.30 (1H, d, *J* = 8.0 Hz), 7.23 (1H, d, *J* = 7.6 Hz), 6.91 (1H, d, *J* = 8.4 Hz), 6.78 (1H, d, *J* = 7.2 Hz), 3.55 (1H, d, *J* = 15.6 Hz), 3.25–3.31 (1H, m), 3.22 (1H, d, *J* = 16.0 Hz), 2.94 (1H, s), 2.86–2.93 (1H, m), 1.28–1.29 (6H, m), 1.24 (3H, d, *J* = 7.2 Hz), 1.18 (3H, d, *J* = 6.8 Hz), 1.08 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 162.0, 145.7, 139.5, 138.5, 135.2, 130.1, 124.7, 115.1, 112.5, 107.6, 28.8, 24.9, 23.5, 21.0. MS (ES) m/z (%): 354.15 ($[MH]^+$, 60).



133b

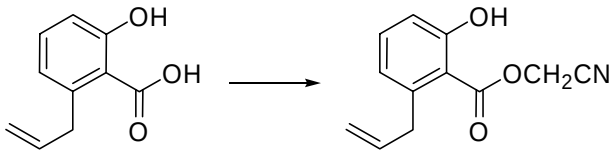
Imidate 133b. IR (film) 2935, 1734, 1458, 1243, 1087, 1040, 917 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, t, *J* = 8.0 Hz), 7.48 (1H, t, *J* = 8.0 Hz), 7.32 (2H, d, *J* = 8.4 Hz), 6.94 (1H, d, *J* = 8.4 Hz), 6.86 (1H, d, *J* = 8.0 Hz), 6.53 (1H, s), 2.55 (2H, heptet, *J* = 7.2 Hz), 1.92 (3H, s), 1.20 (6H, d, *J* = 7.2 Hz), 1.16 (6H, d, *J* = 6.8 Hz), -2.16 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 171.0, 135.6, 128.7, 128.2, 128.0, 116.4, 96.6, 82.3, 78.2, 77.4, 75.0, 74.6, 72.4, 66.3, 56.0, 46.9, 42.3, 41.3, 36.8, 34.3, 32.1, 31.7, 31.4, 28.6, 25.7, 23.8, 22.2, 21.4, 20.4, 14.8. MS (ES) m/z (%): 336.15 ($[MH]^+$, 100).



134

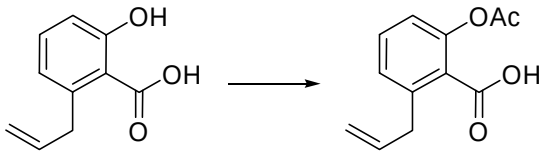
Amide 134. IR (film) 3172, 1614, 1465, 1287, 993, 914, 734 cm^{-1}; ^{1}H NMR$^{55\ °C}$ (400 MHz, $CDCl_3$) δ 7.22–7.38 (4H, m), 7.02–7.12 (2H, m), 6.76 (1H, d, *J* = 7.6 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 5.91 (1H, ddt, *J* = 6.8, 9.6, 17.2 Hz), 5.04 (2H, d, *J* = 12.4 Hz), 4.40–4.80 (2H, *br* s), 3.34 (2H, m), 2.83 (3H, *br* s), 1.70 (1H, *br* s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 153.4, 138.0, 136.8, 130.1, 128.9, 128.4, 127.7, 123.9, 121.3, 116.3, 115.0, 37.5. MS (ES) m/z (%): 282.10 ($[MH]^+$, 30), 304.10 ($[MNa]^+$, 100).

Examination of Alternative Acylation Methods (Table 2.4)



135 **136**

Cyanomethyl ester 136. To a stirred solution of acid **135** [Fürstner, A; Dierkes, T.; Thiel, O. R.; Blanda, G. Chem. Eur. J. 2001, 7, 5286–5298] (0.25 g, 2.4 mmol) and Et_3N (1.7 mL, 8.4 mmol) in acetone (5 mL) was added chloroacetonitrile (0.25 mL, 4.2 mmol) dropwise at ambient temperature. After stirring at 65 ˚C for 5 hr the reaction was poured into phosphate buffer (pH = 7.0, 20 mL), extracted with Et_2O (3 × 50 mL), dried over $MgSO_4$, filtered, concentrated, and purified by FC (33/67, EtOAc/Hex) to afford 196 mg (64%) of **136**. IR (film) 3080, 1671, 1609, 1449, 1293, 1247, 1212, 1114, 915, 814, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.50 (1H, s), 7.40 (1H, t, *J* = 8.0 Hz), 6.92 (1H, d, *J* = 8.0 Hz), 6.80 (1H, d, *J* = 7.2 Hz), 5.97 (1H, ddt, *J* = 6.0, 10.2, 17.0 Hz), 5.07 (1H, app dd, *J* = 1.6, 10.0 Hz), 4.97 (2H, s), 4.91–5.00 (1H, m), 3.69 (2H, app d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 163.1, 143.0, 137.1, 123.1, 116.6, 116.0, 114.0, 110.6, 49.0, 40.4. HRMS (ESI) Calcd for $C_{12}H_{11}NO_3Na$ $[MNa]^+$: 240.0637. Found: 240.0629.



135 **137**

Acid 137. To a stirred solution of acid **135** (500 mg, 2.82 mmol) in pyridine at 0 ˚C was added acetic anhydride (0.53 mL, 5.62 mmol). The reaction was warmed to ambient temperature and allowed to stir for 1 hr. The reaction was then poured into H_2O (50 mL) and extracted with EtOAc (3 x 100 mL). The organic phase was then washed with 10%

HCl (3 x 50 mL). The organic phase was then dried with $MgSO_4$, filtered, and concentrated to afford 525 mg (85%) of **137**. IR (film) 3076, 1771, 1606, 1460, 1372, 1208, 1020, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, t, *J* = 8.0Hz), 7.18 (1H, d, *J* = 8.0Hz), 7.03 (1H, t, *J* = 8.4Hz), 5.96 (1H, ddt, *J* = 6.6, 10.2, 16.8Hz), 5.05–5.12 (2H, m), 3.60 (2H, d, *J* = 6.4Hz), 2.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 169.6, 148.9, 140.8, 136.2, 131.7, 127.9, 125.0, 121.3, 116.7, 38.0, 20.9. MS (ES) m/z (%) : 219.10 ($[M-H]^-$, 100).

Referenced Procedures from Comparative Acylation Study (Table 2.4)

Condition **B**-**D**: (a) Mitsunobu, O. Synthesis 1981, 1–28. (b) Snider, B.; Song, F. Org. Lett. 2001, 3, 1817–1820.

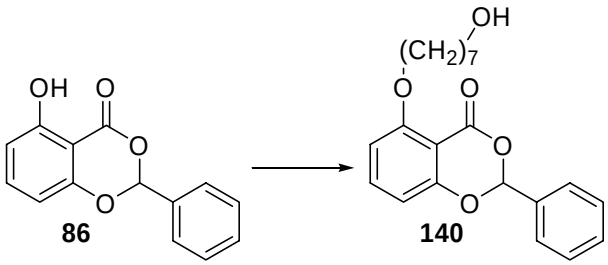
Condition **E**: (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. Bull. Chem. Soc. Jpn. 1979, 52, 1989–1993. (b) Runge, M.; Haufe, G. J. Org. Chem. 2000, 65, 8737–8742.

Condition **F**: Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. J. Am. Chem. Soc. 2003, 125, 7889–7901.

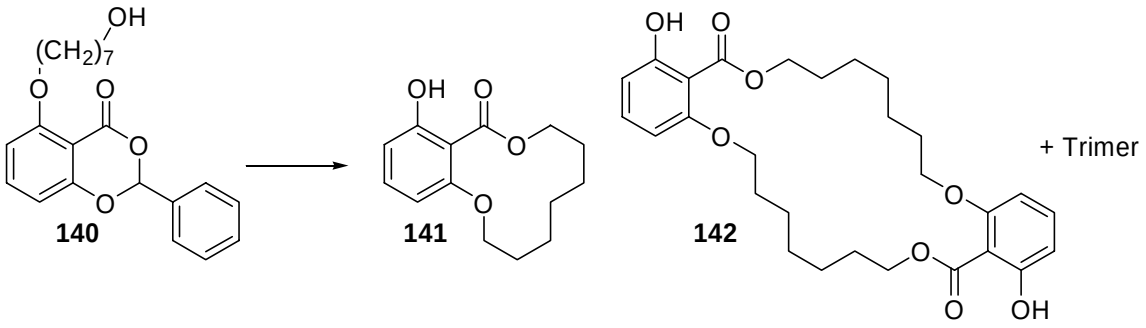
Condition **G**: Wang, X.; Porco, J. A. J. Am. Chem. Soc. 2003, 125, 6040–6041.

Condition **H**: Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. Bioorg. Med. Chem. 2002, 10, 3997–4004.

General Procedure for Intramolecular Photoacylations (Scheme 2.23)



Alcohol 140 To a stirred solution of phenol **86** (0.7 g, 2.89 mmol), 1,7-heptanediol (0.8 mL, 5.78 mmol), and PPh_3 (1.3 g, 5.2 mmol), in THF (30 mL) at 0 ˚C was added DIAD (1.0 mL, 5.2 mmol). After stirring at rt for 12 hr the solvent was removed *in-vacuo*, and the crude material was purified by FC (40/60, EtOAc/Hex gradient) to afford 600 mg (60%) of **140**. IR (film) 3421, 2933, 2858, 1748, 1607, 1582, 1484, 1463, 1385, 1258, 1089, 971, 803 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62–7.70 (2H, m), 7.24–7.52 (4H, m), 6.68 (1H, d, J = 8.7 Hz), 6.68 (2H, d, J = 8.7 Hz), 6.44 (1H, s), 4.04–4.18 (2H, m), 3.60–3.70 (2H, m), 1.85–1.97 (2H, m), 1.52–1.64 (3H, m), 1.38–1.48 (3H, m), 1.30–1.38 (1H, m), 1.22–1.29 (2H, m); ^{13}C NMR (75MHz, $CDCl_3$) δ 161.6, 161.0, 159.2, 136.6, 134.2, 130.4, 128.7, 126.8, 108.4, 107.2, 104.4, 99.8, 69.4, 62.9, 32.6, 29.1, 28.9, 25.8, 25.6, 22.0. MS (ES) m/z (%) : 379.10 ($[MNa]^+$, 100).



Photoacylation of 140. Benzodioxinone **140** (50 mg, 0.15 mmol) was weighed out in an ovendried borosilicate test tube and sealed with a rubber septum and parafilm. The starting material was then dissolved with freshly distilled CH_2Cl_2 (1.47 mL, 0.1 M) under

nitrogen inlet. This solution was photolyzed for 4 hr at 300 nm. The solvent was then removed *in-vacuo* and the crude residue was purified by FC (10/90, EtOAc/Hex) to afford 0.4 mg (1%) of lactone **141**, 5.5 mg (15%) of dimer **142**, 2.5 mg (7%) of trimer. The same procedure at 0.01 M afforded 7.5 mg (20%) of lactone **141**, 9.5 mg (26%) of dimer **142**, and 1.7 mg (5%) of trimer.

141: IR (film) 2925, 2856, 1652, 1610, 1580, 1456, 1394, 1302, 1229, 1130, 1077, 811 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.26 (1H, s), 7.29 (1H, t, *J* = 8.4 Hz), 6.56 (1H, dd, *J* = 0.8, 8.4 Hz), 6.39 (1H, d, *J* = 8.4 Hz), 4.34 (2H, t, *J* = 5.6 Hz), 4.01 (2H, t, *J* = 5.6 Hz), 1.78–1.88 (4H, m), 1.58–1.69 (6H, m); ^{13}C NMR (75MHz, $CDCl_3$) δ 171.4, 163.3, 160.7, 135.1, 110.0, 103.8, 69.9, 67.0, 28.3, 26.8, 25.7, 25.4, 25.0

142: IR (film) 2935, 2858, 1652, 1608, 1455, 1396, 1354, 1301, 1229, 1123, 813 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.66 (2H, s), 7.28 (2H, t, *J* = 8.4 Hz), 6.55 (2H, dd, *J* = 0.4, 8.4 Hz), 6.37 (2H, d, *J* = 8.0 Hz), 4.37 (4H, t, *J* = 6.4 Hz), 3.98 (4H, t, *J* = 6.0 Hz), 1.75–1.85 (8H, m), 1.48–1.59 (8H, m), 1.40–1.47 (4H, m); ^{13}C NMR (75MHz, $CDCl_3$) δ 171.8, 164.0, 160.7, 135.2, 109.9, 103.1, 69.2, 66.0, 29.7, 29.1, 26.9, 26.8. MS (ES) m/z (%): 523.25 ($[MNa]^+$, 100), 501.20 ($[MH]^+$, 40).

Trimer: IR (film) 3800, 2932, 2859, 1653, 1608, 1456, 1400, 1358, 1301, 1269, 1234, 1130, 1089, 812 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (3H, s), 7.29 (3H, t, *J* = 8.4 Hz), 6.55 (3H, d, *J* = 8.0 Hz), 6.36 (3H, d, *J* = 8.4 Hz), 4.33 (6H, t, *J* = 6.8 Hz), 3.96 (6H, t, *J* = 6.0 Hz), 1.75–1.85 (12H, m), 1.41–1.57 (18H, m); ^{13}C NMR (75MHz, $CDCl_3$) δ

171.8, 164.0, 160.7, 135.3, 110.0, 103.0, 68.9, 65.6, 29.6, 29.4, 28.8, 26.4, 26.3. MS (ES) m/z (%): 773.35 ($[MNa]^+$, 100), 751.30 ($[MH]^+$, 20).

2.18 Notes and References

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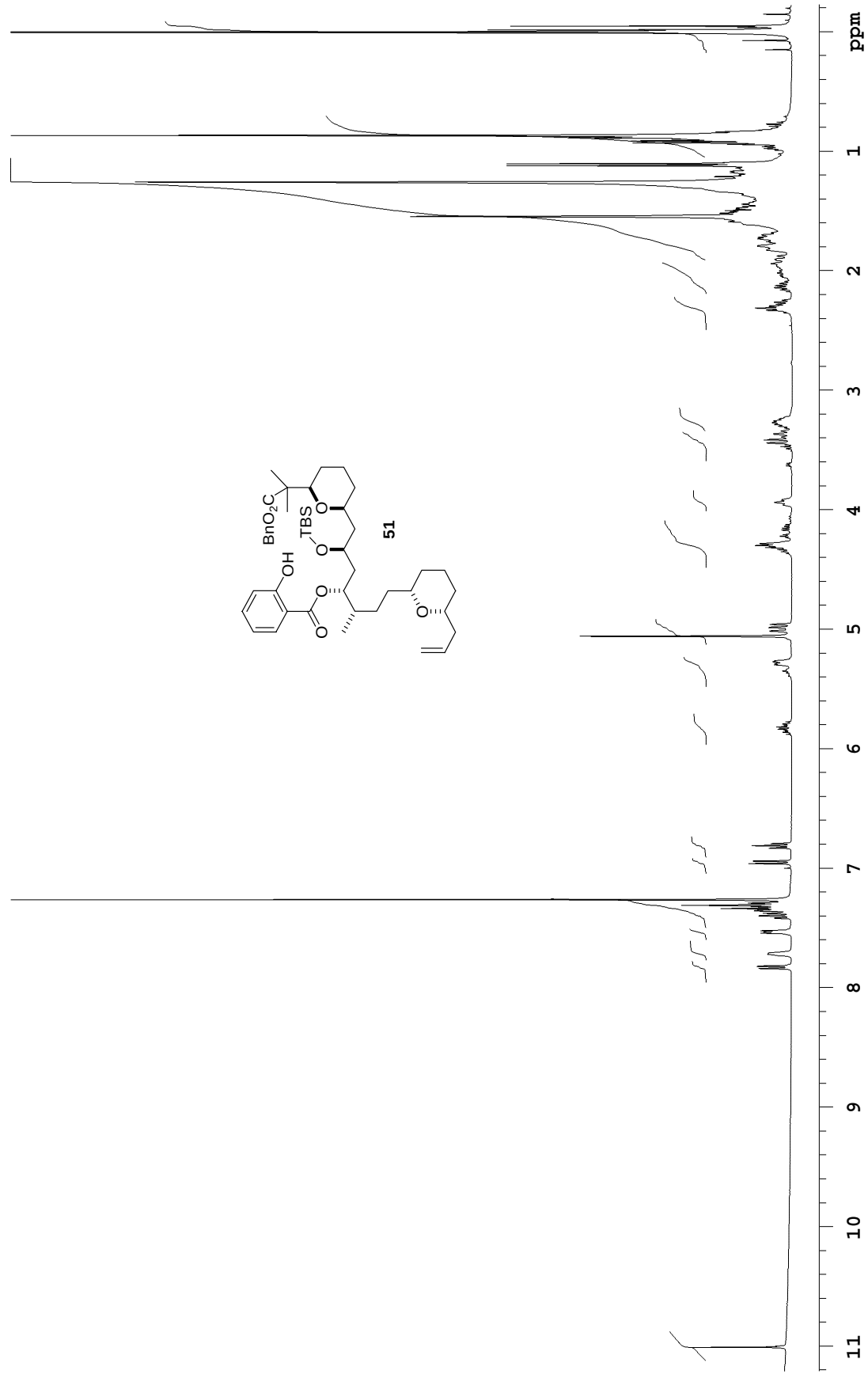
Appendix One: Spectra of Compounds Appearing In Chapter 2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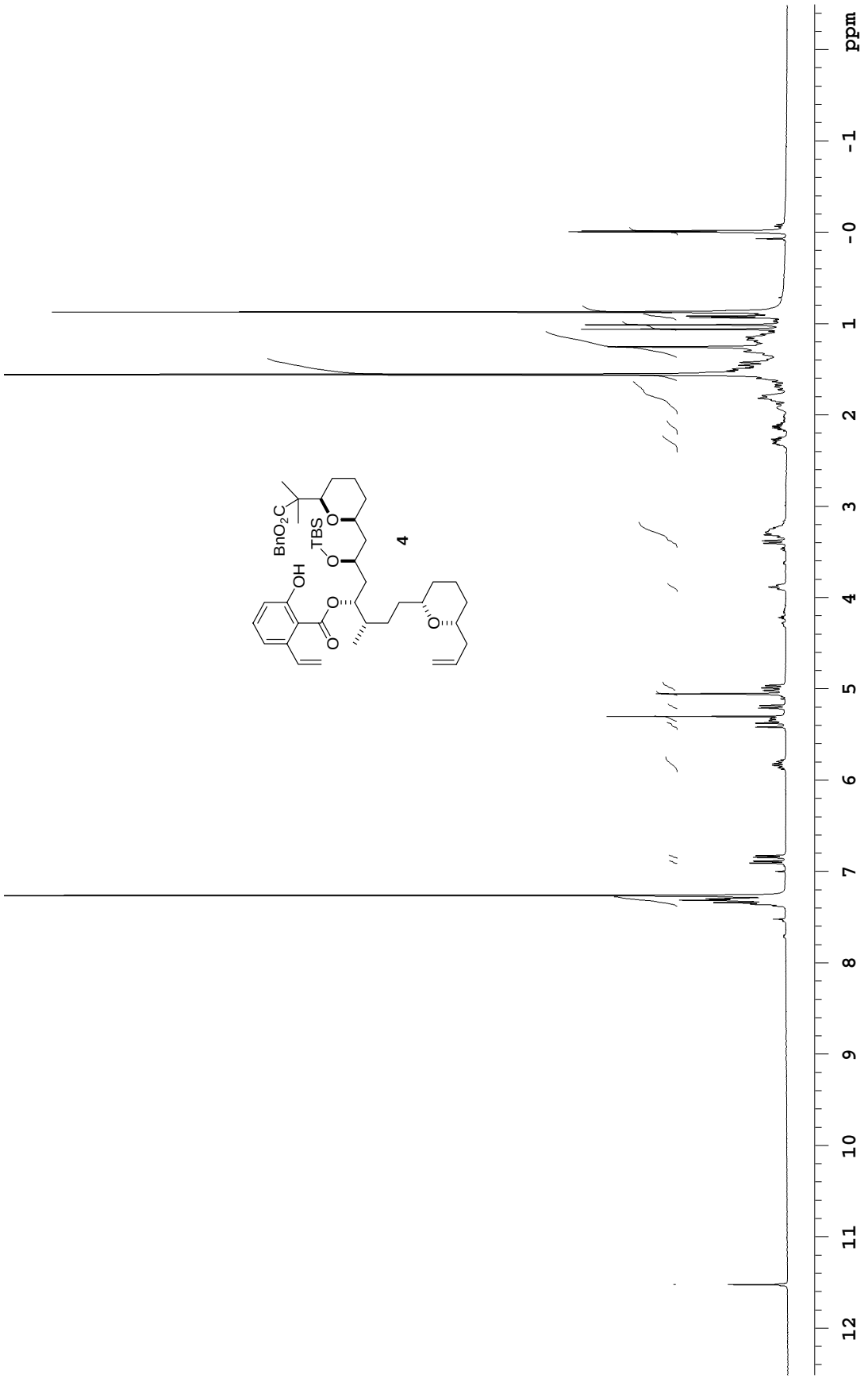
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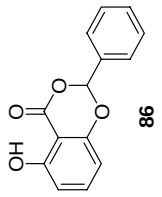

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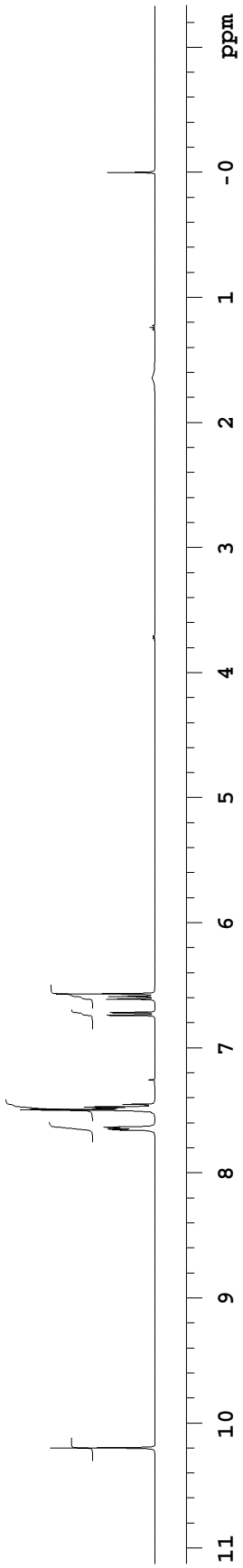

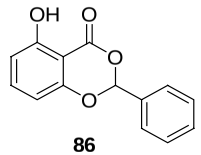

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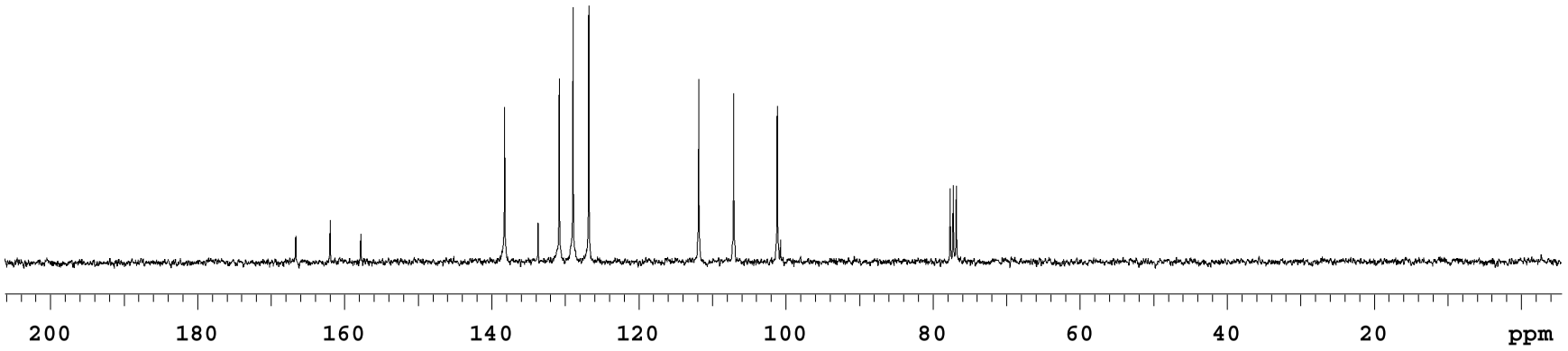

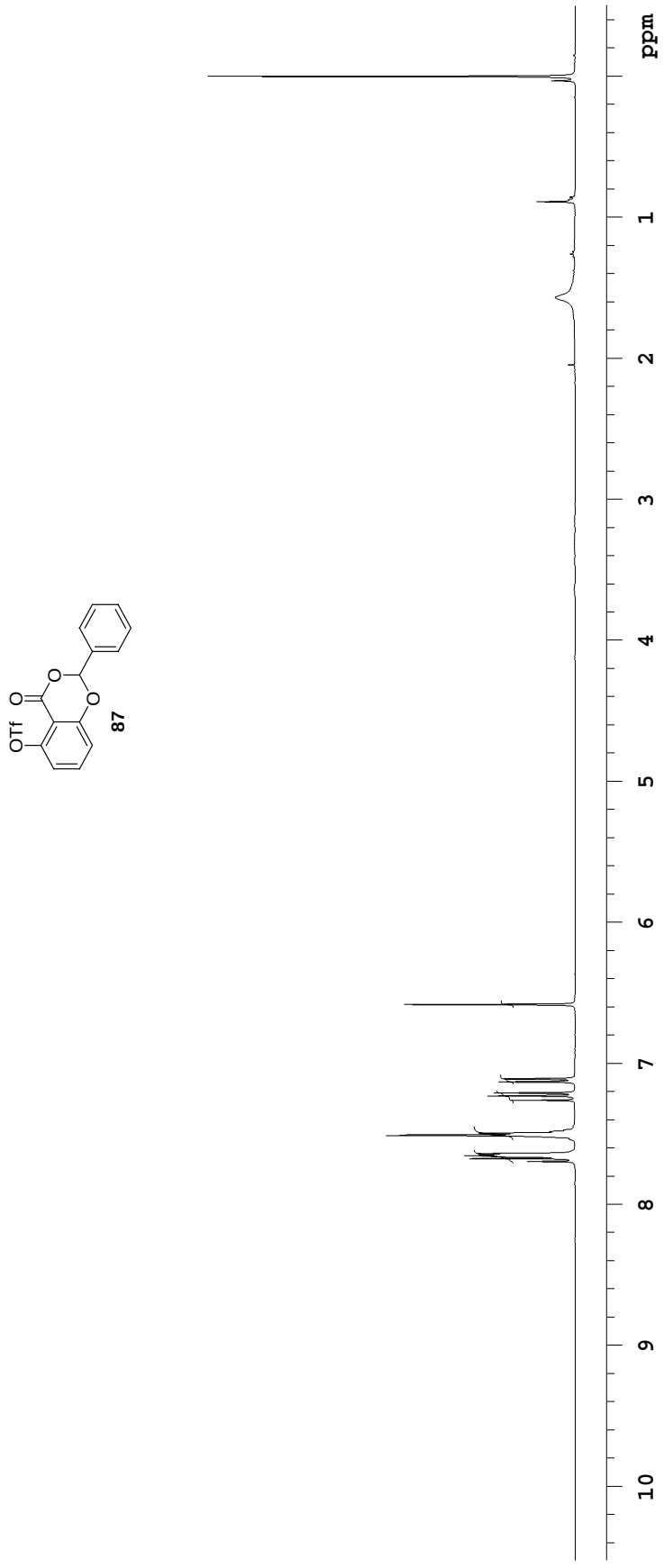
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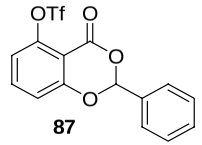

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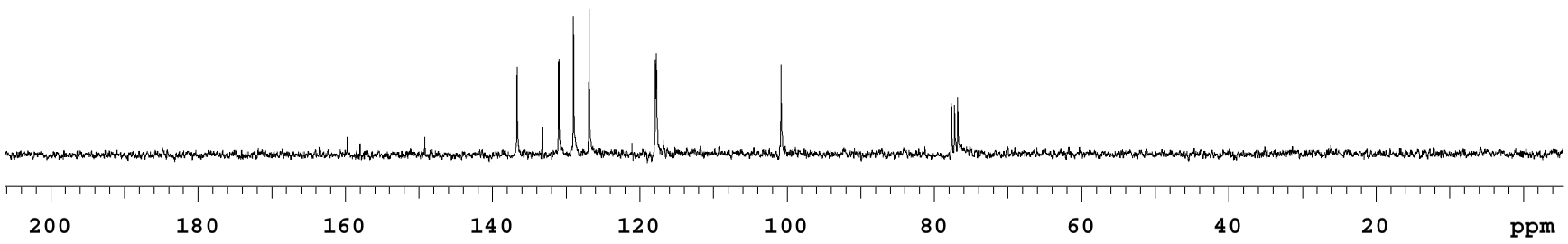

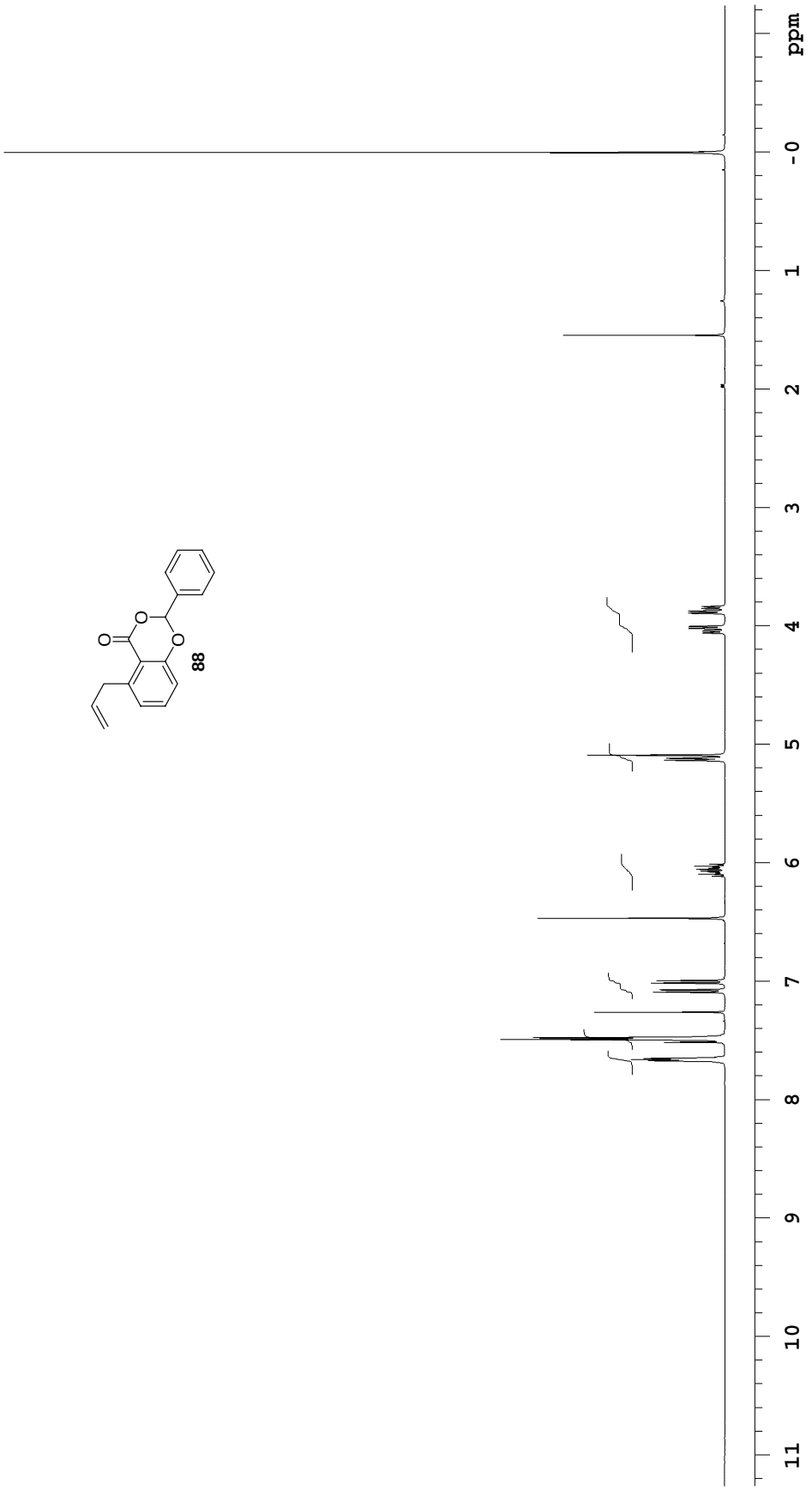
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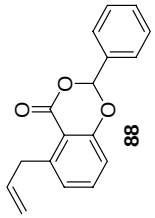

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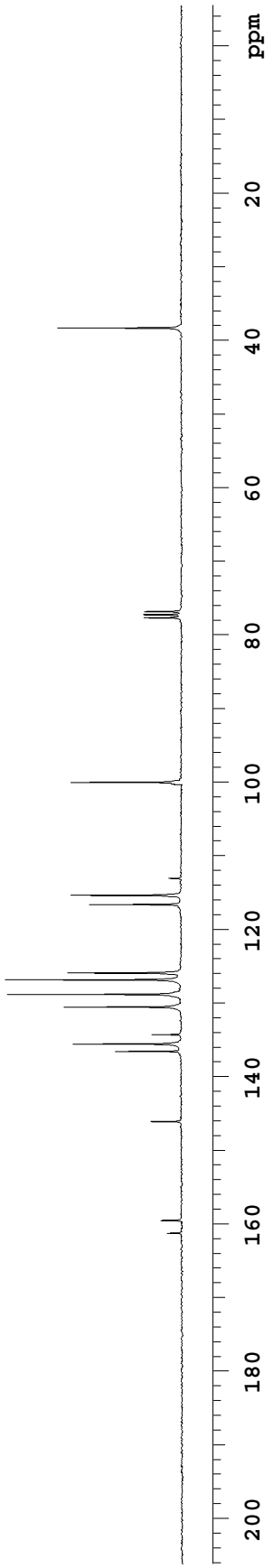

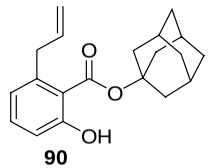

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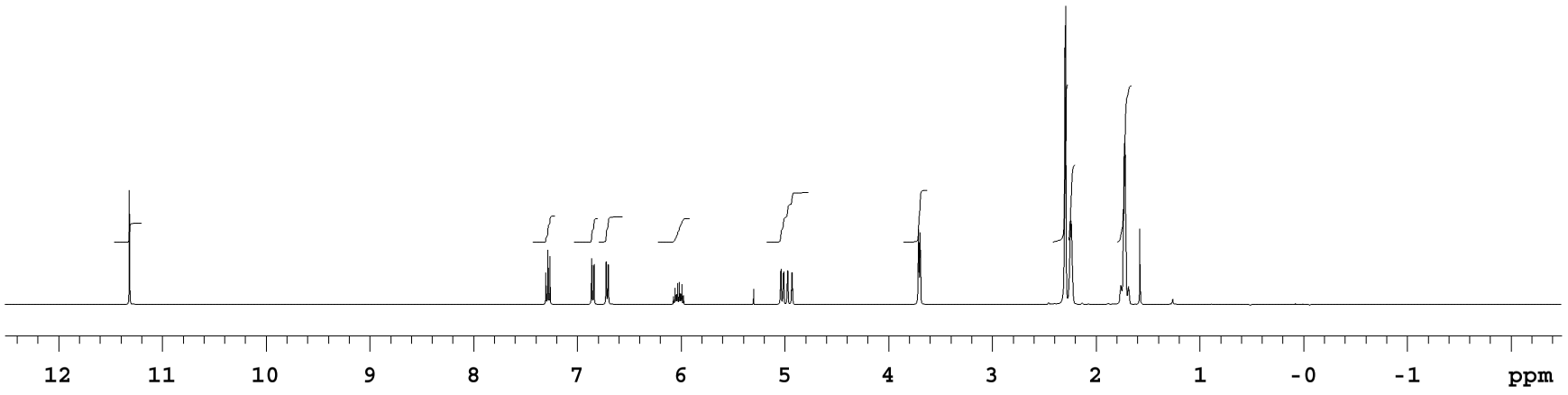

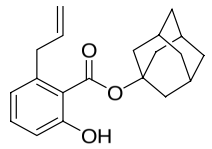

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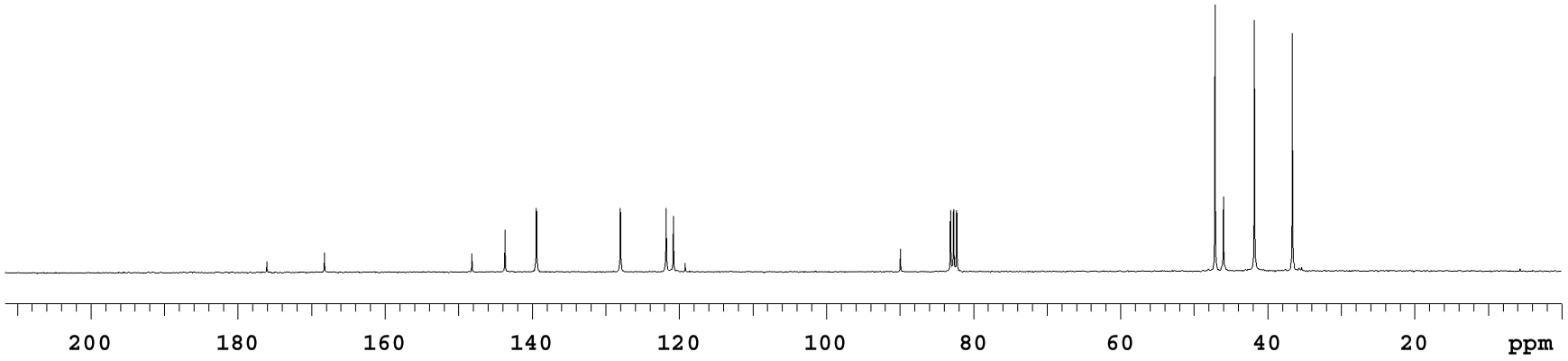

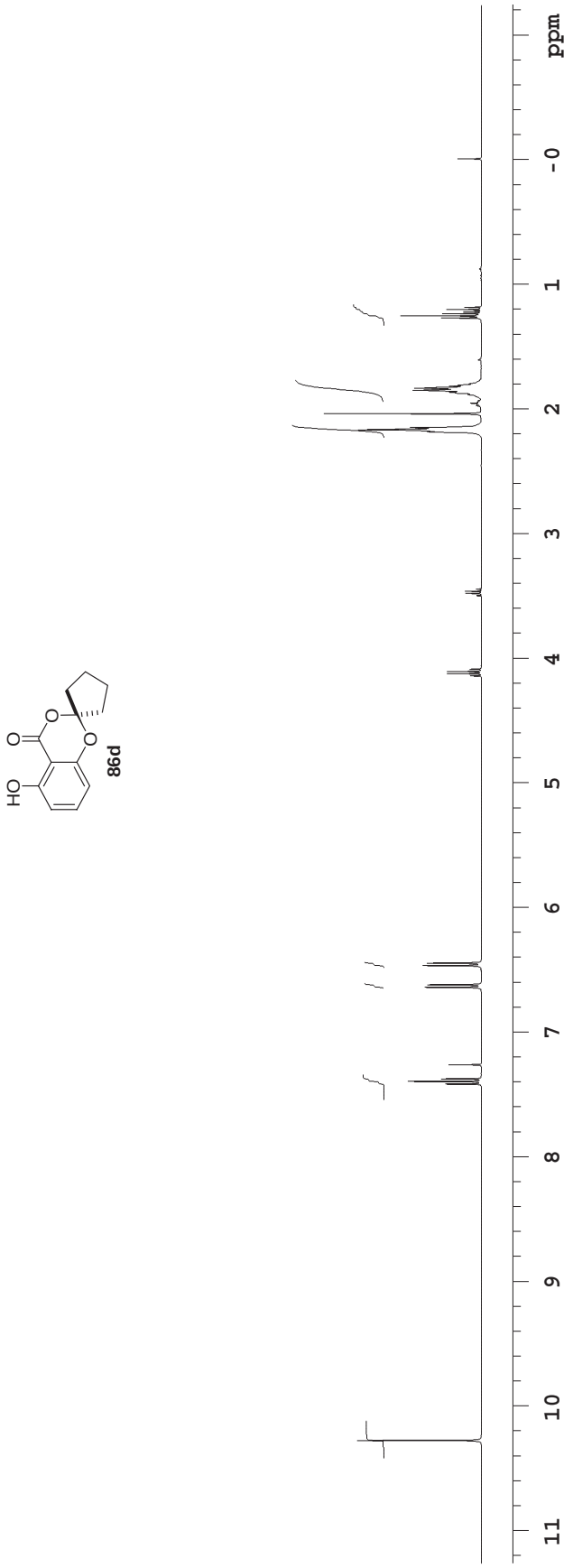
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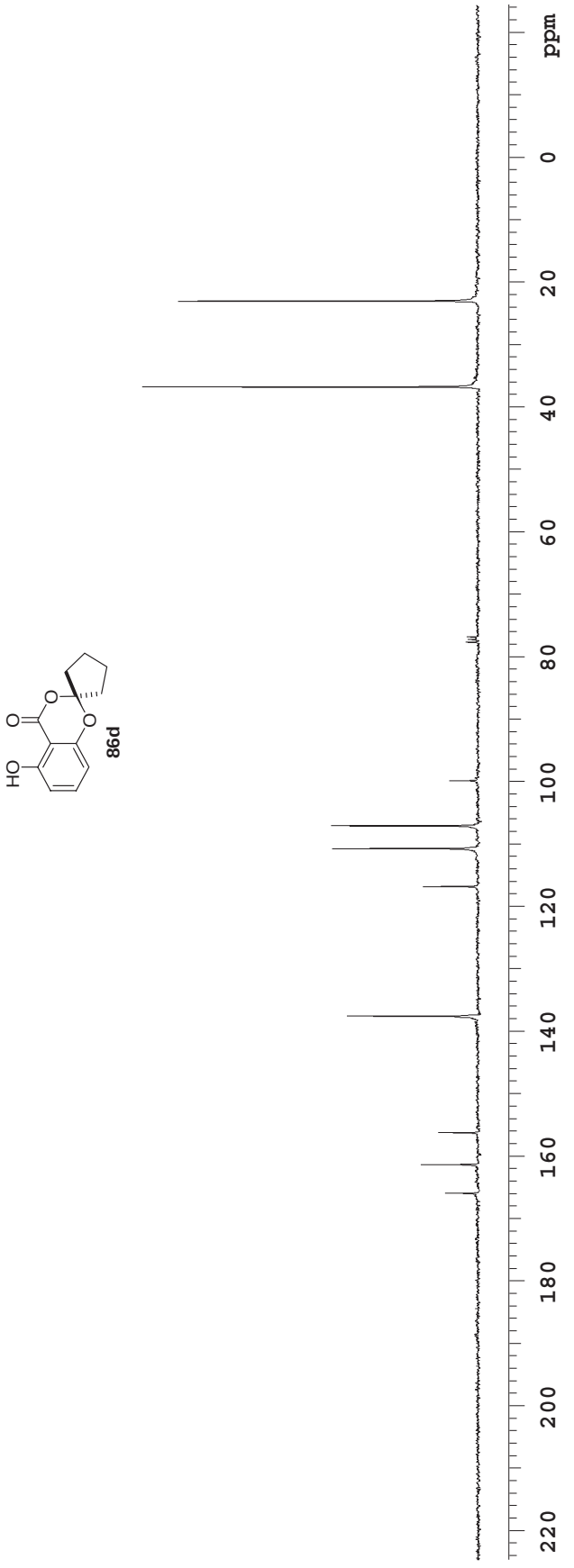
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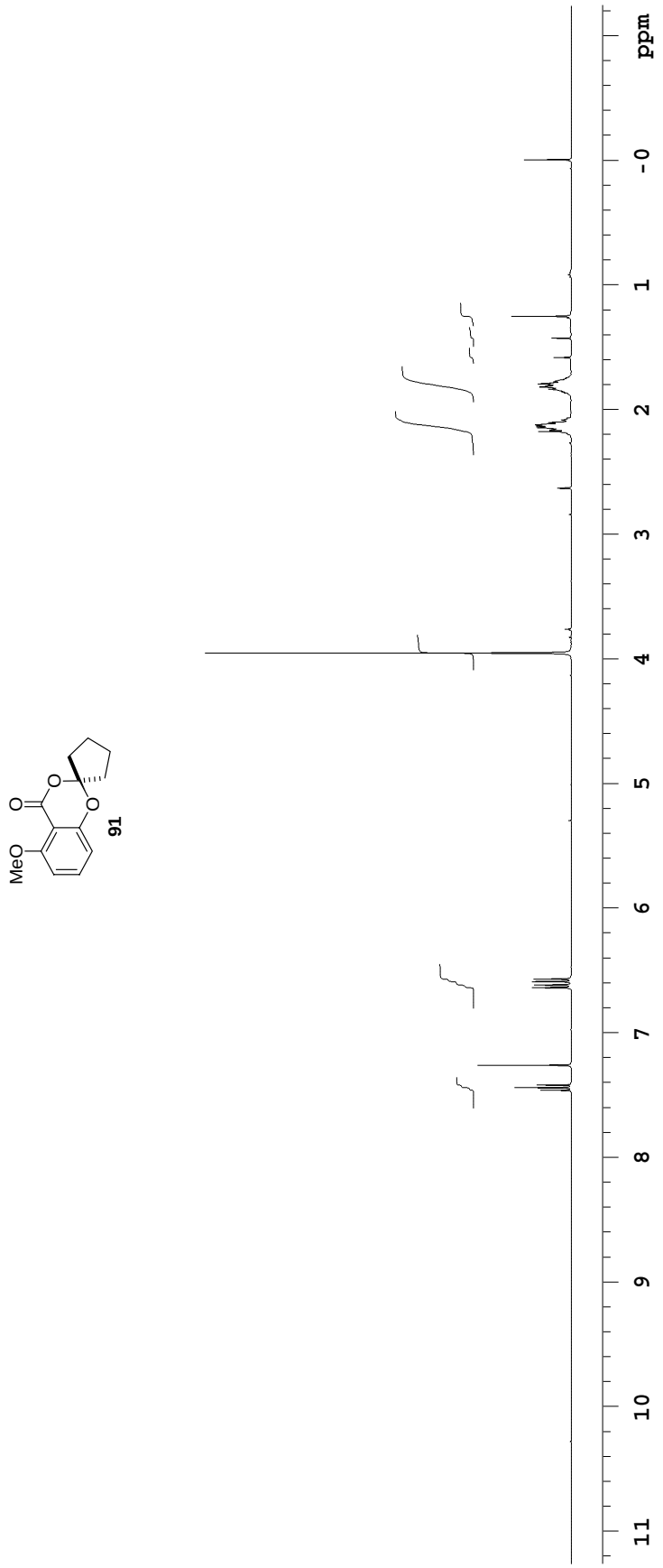
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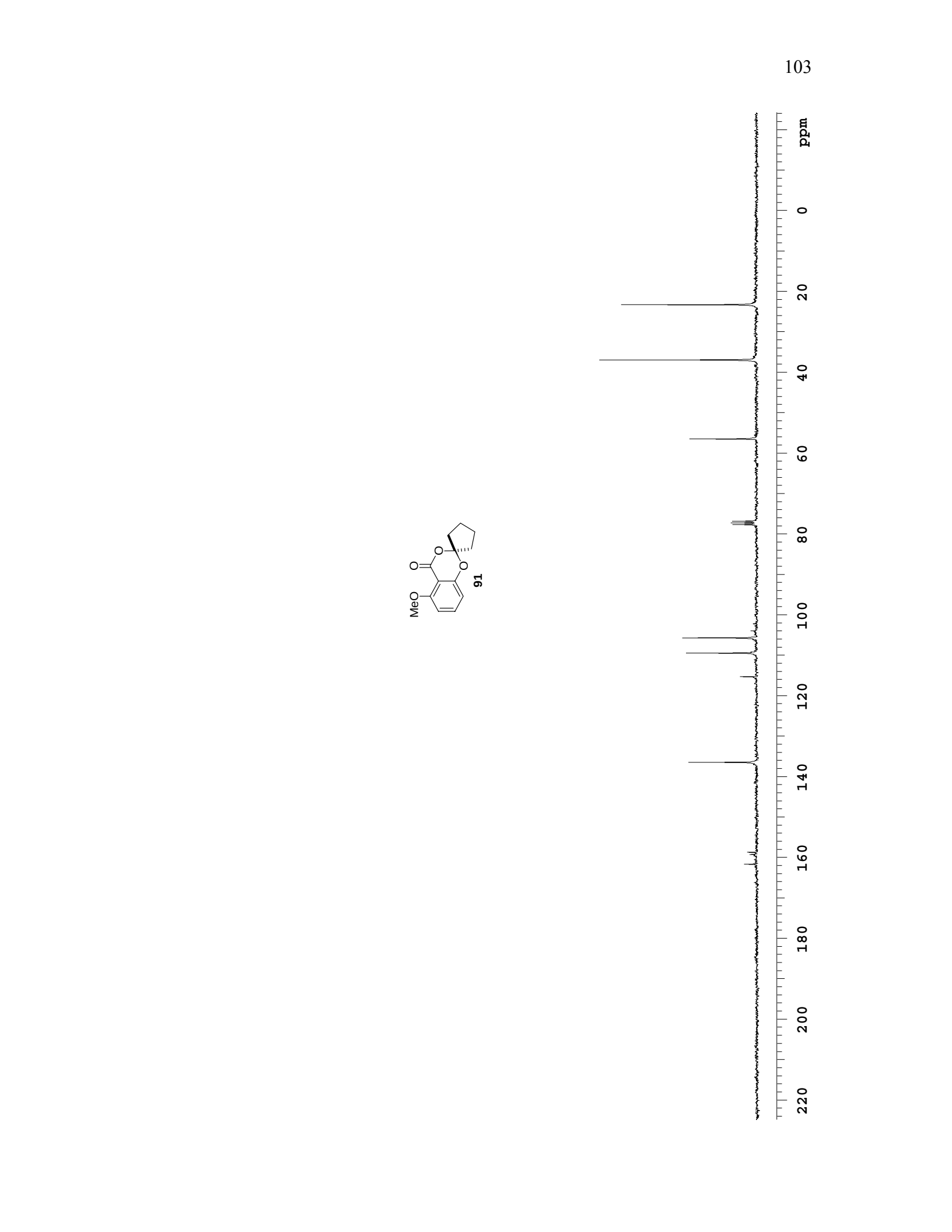
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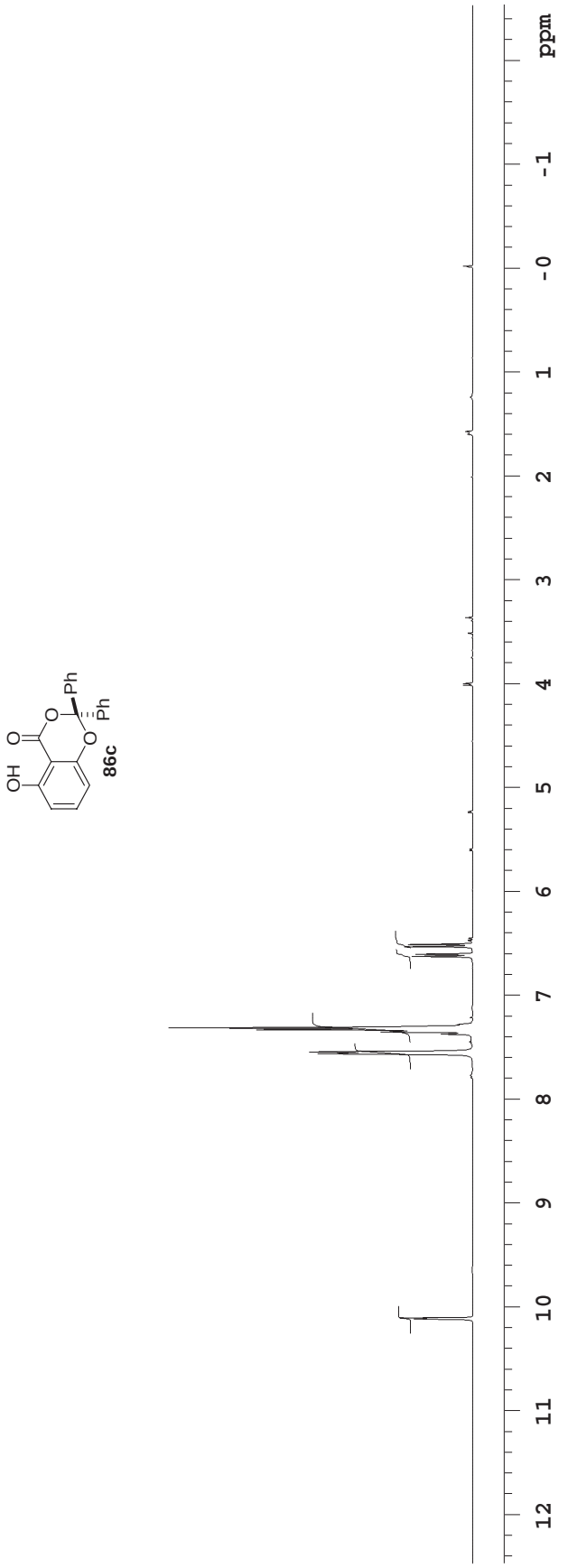
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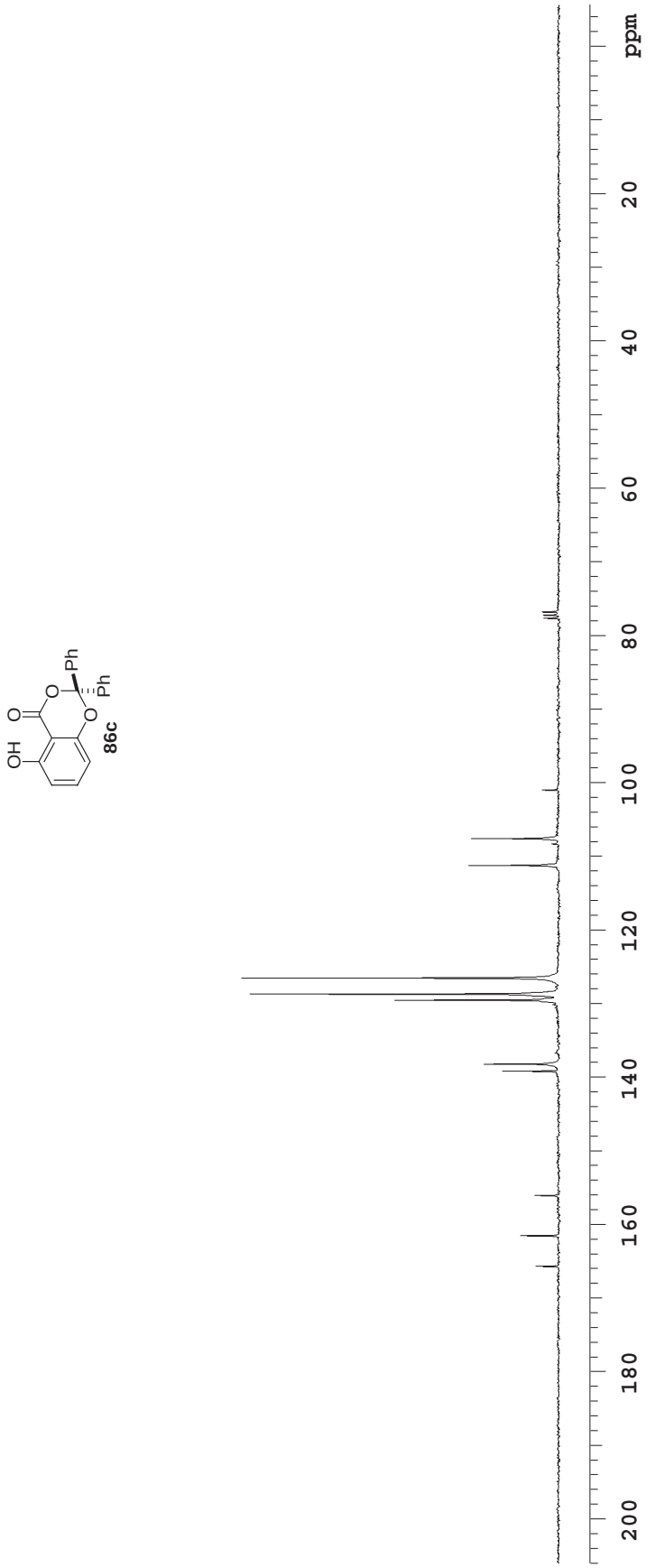
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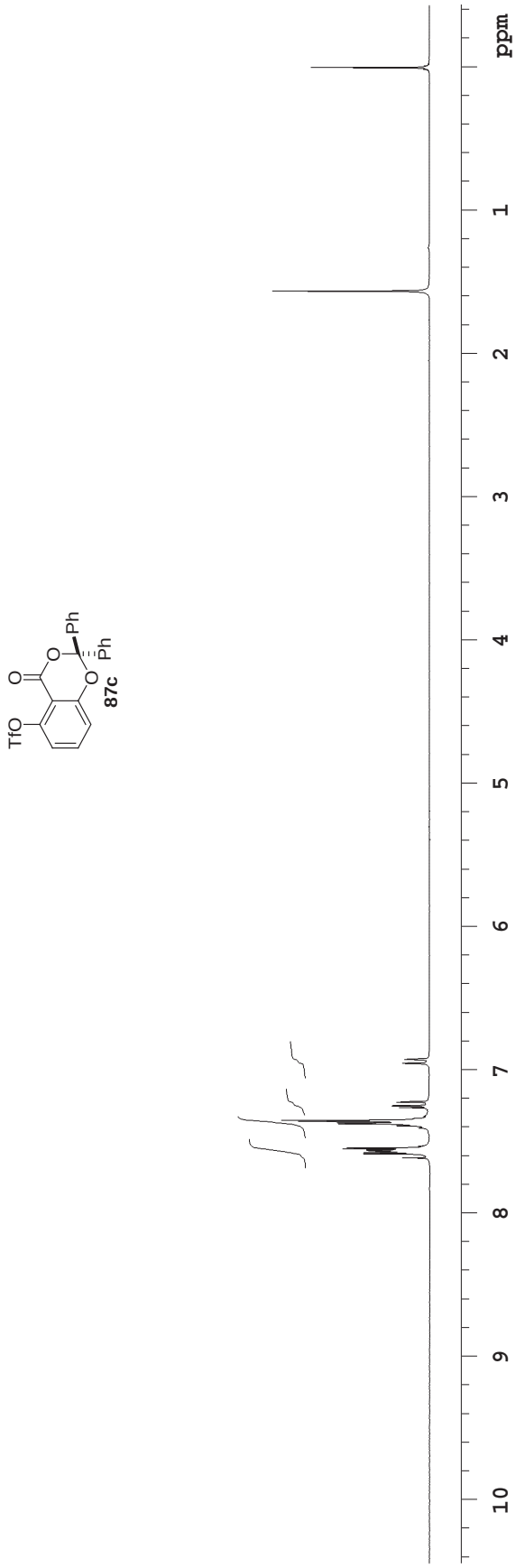
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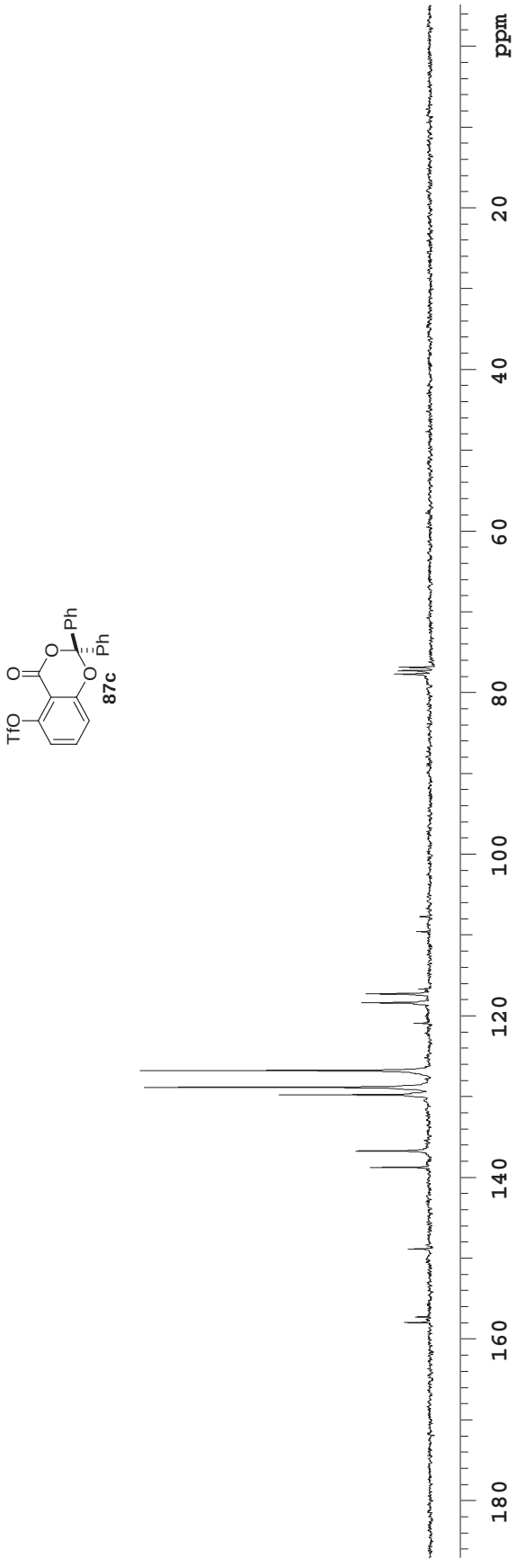
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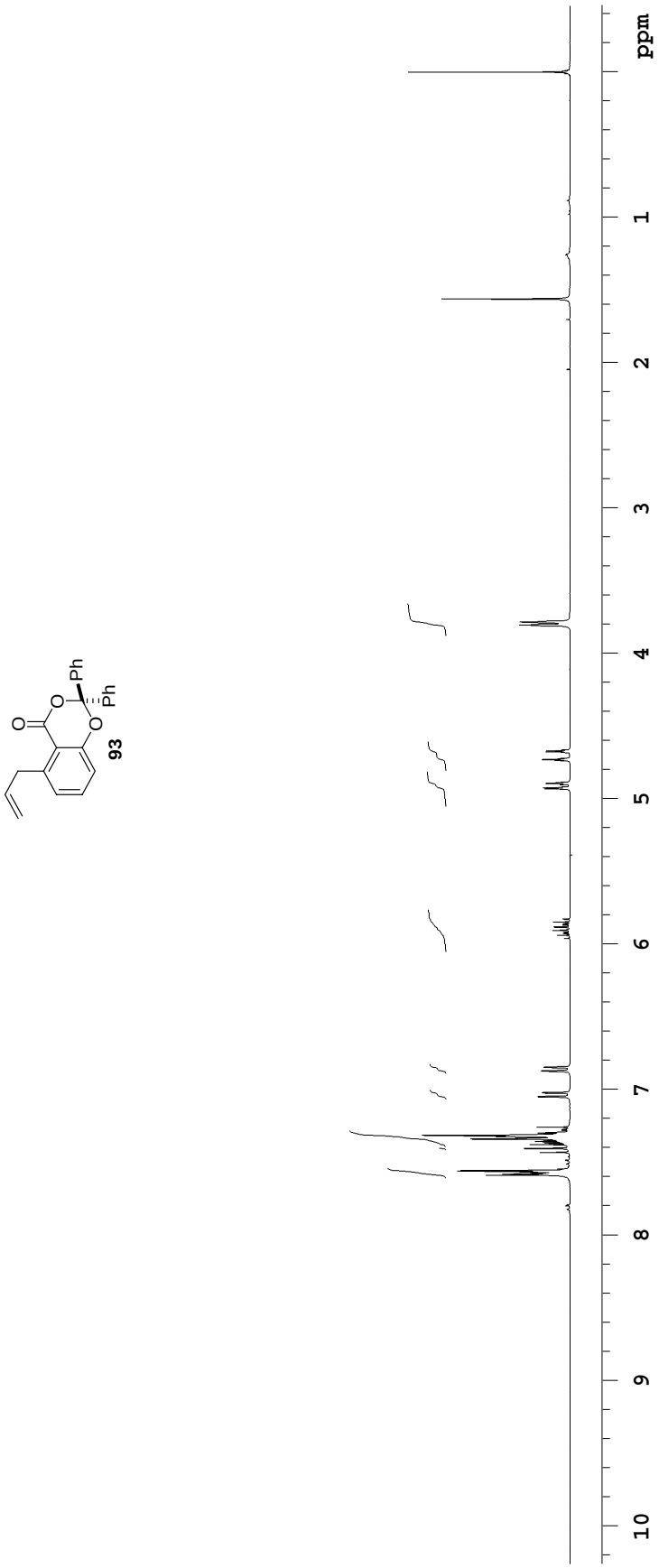
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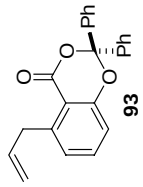

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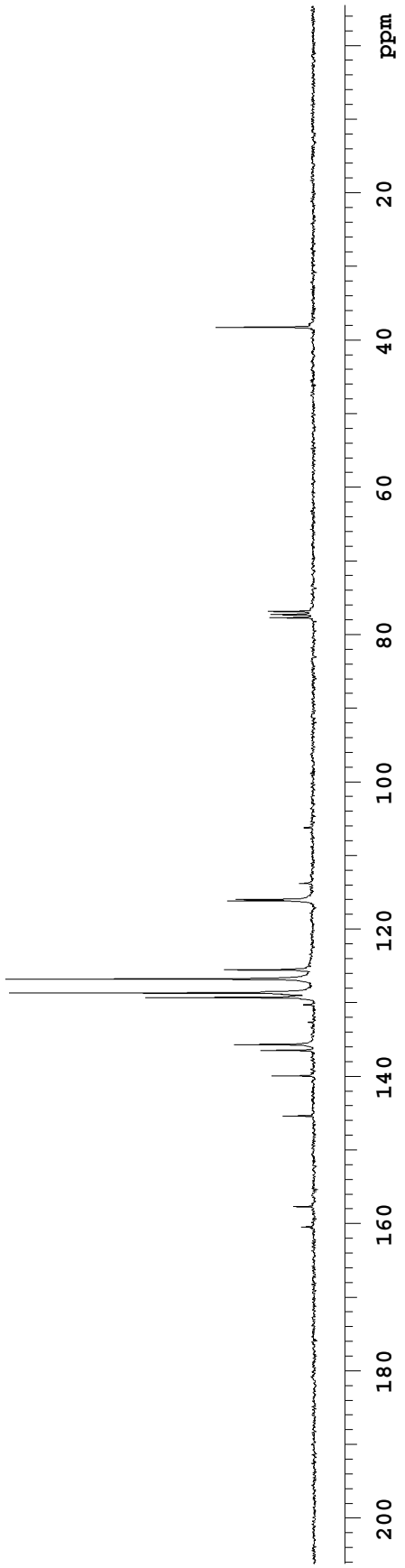

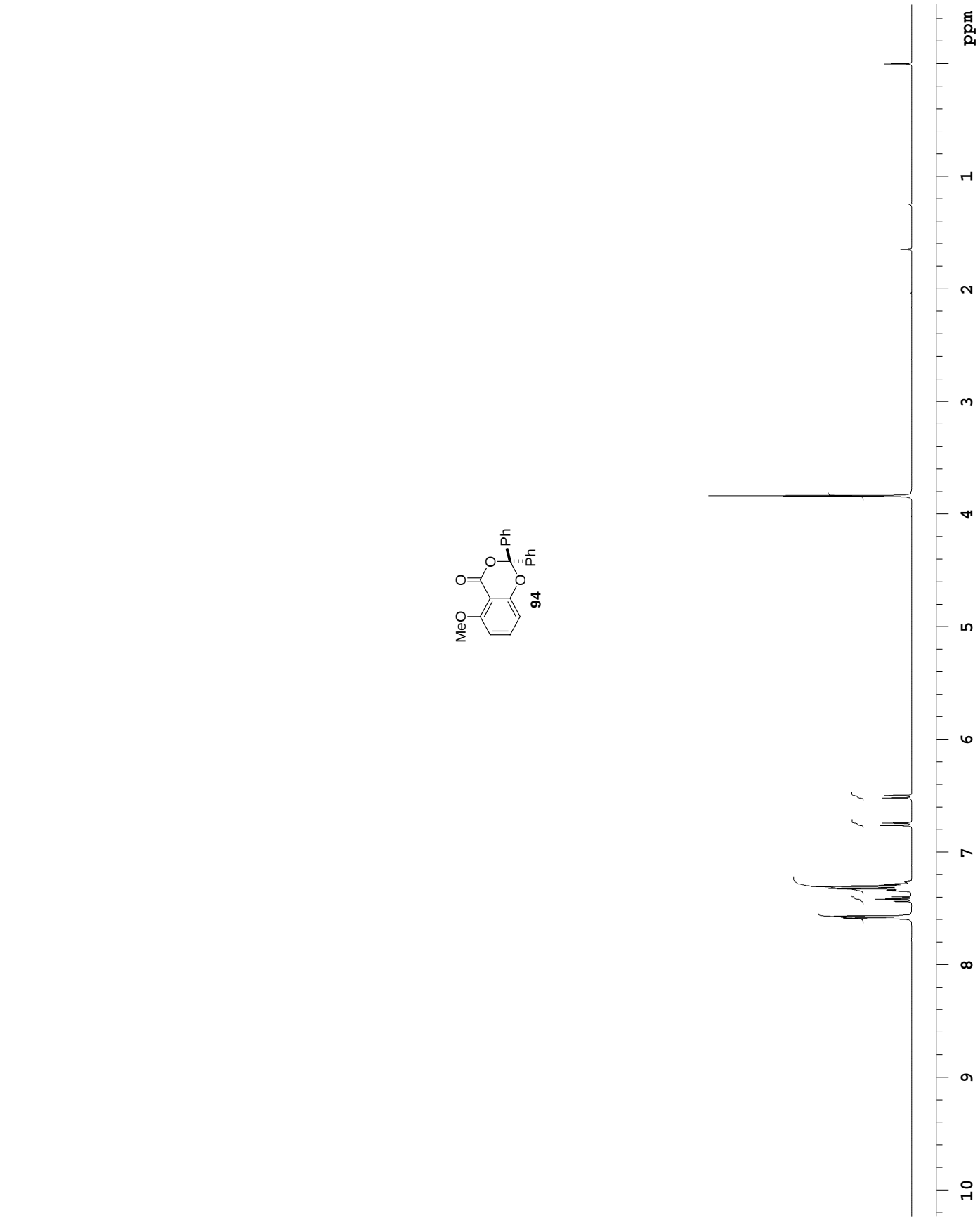
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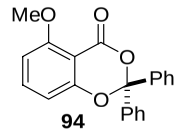

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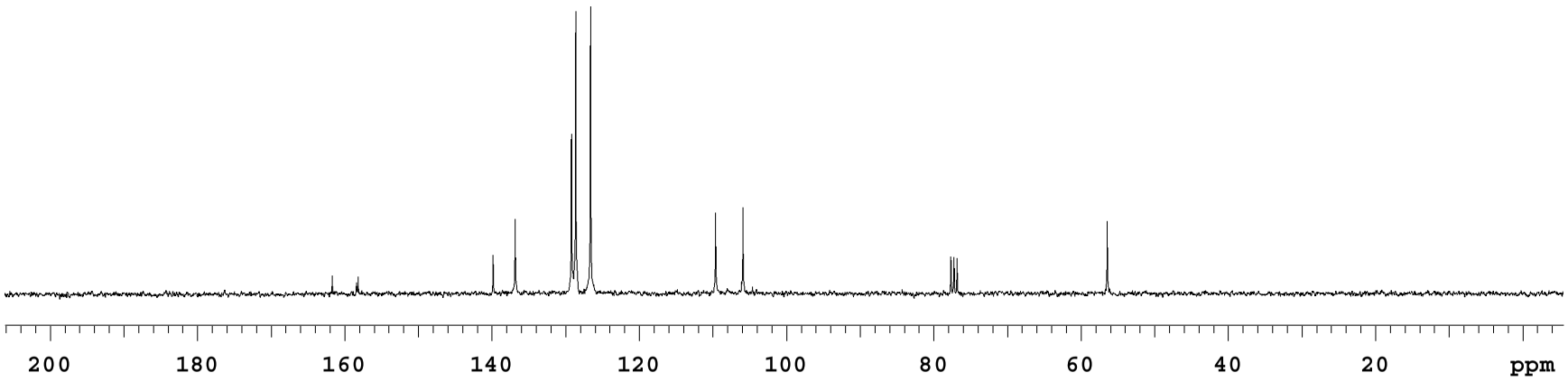

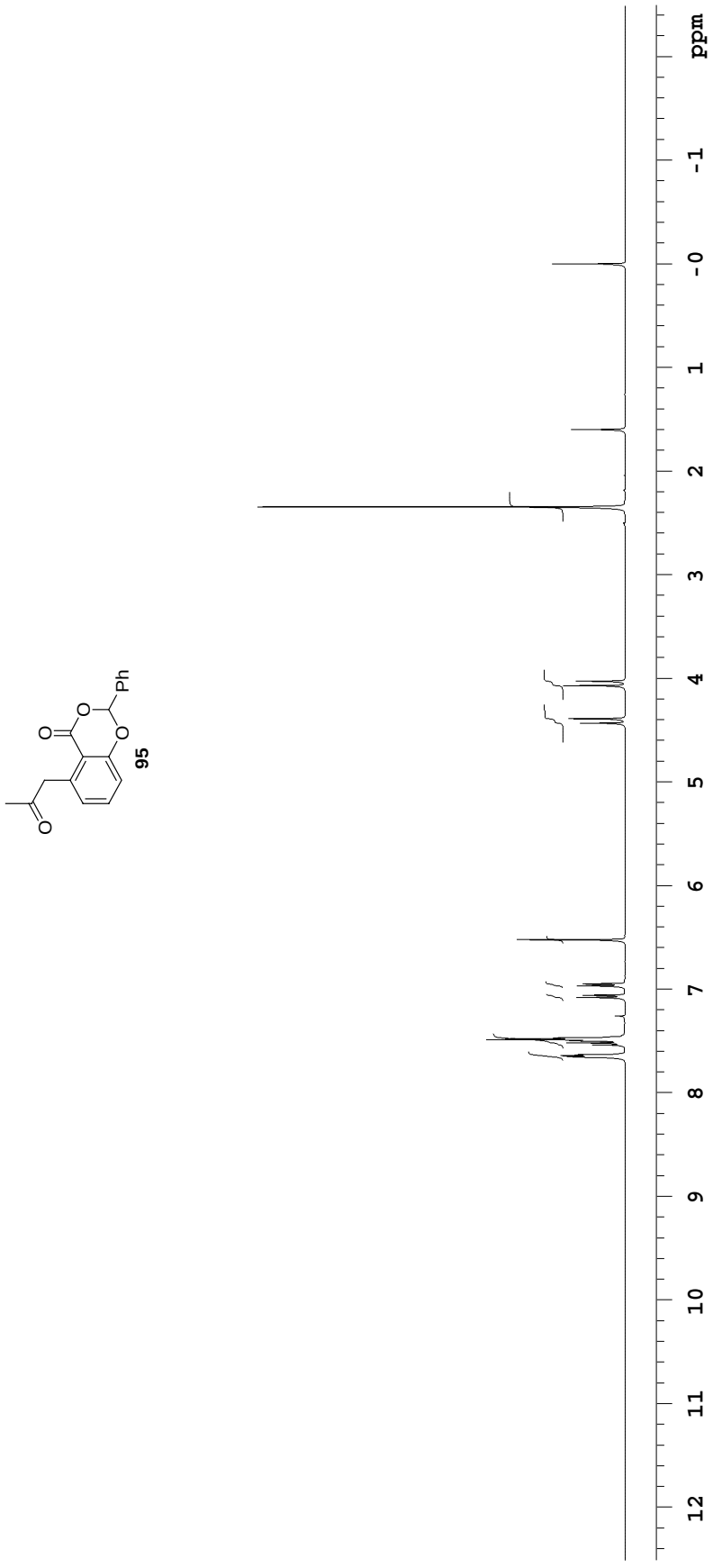
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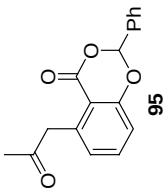

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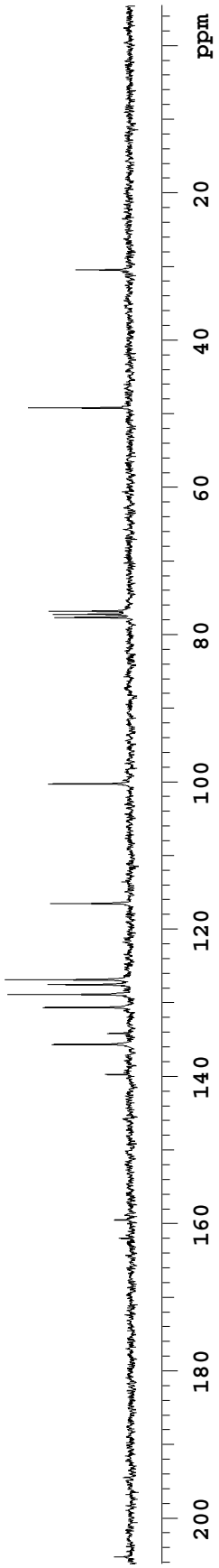

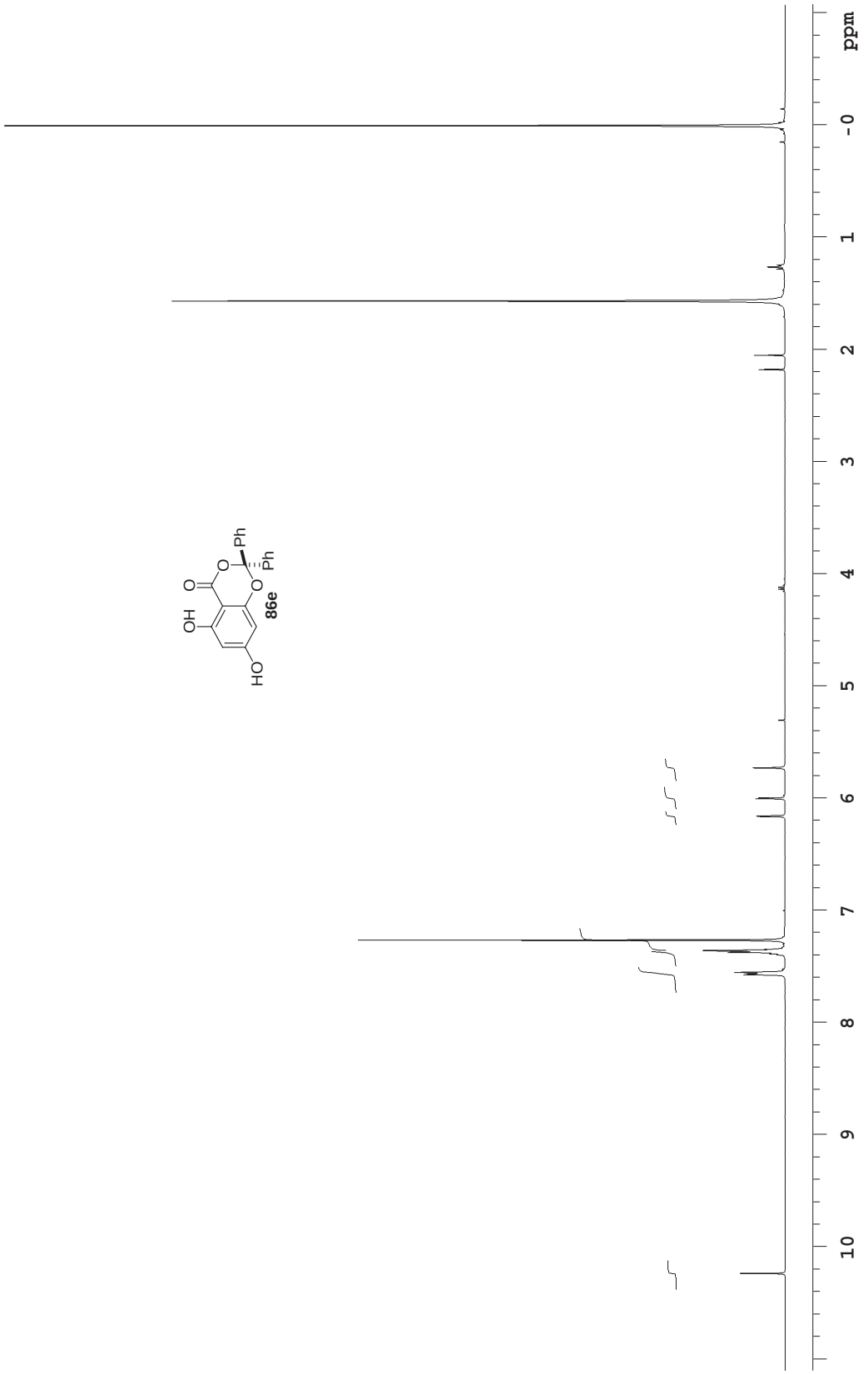
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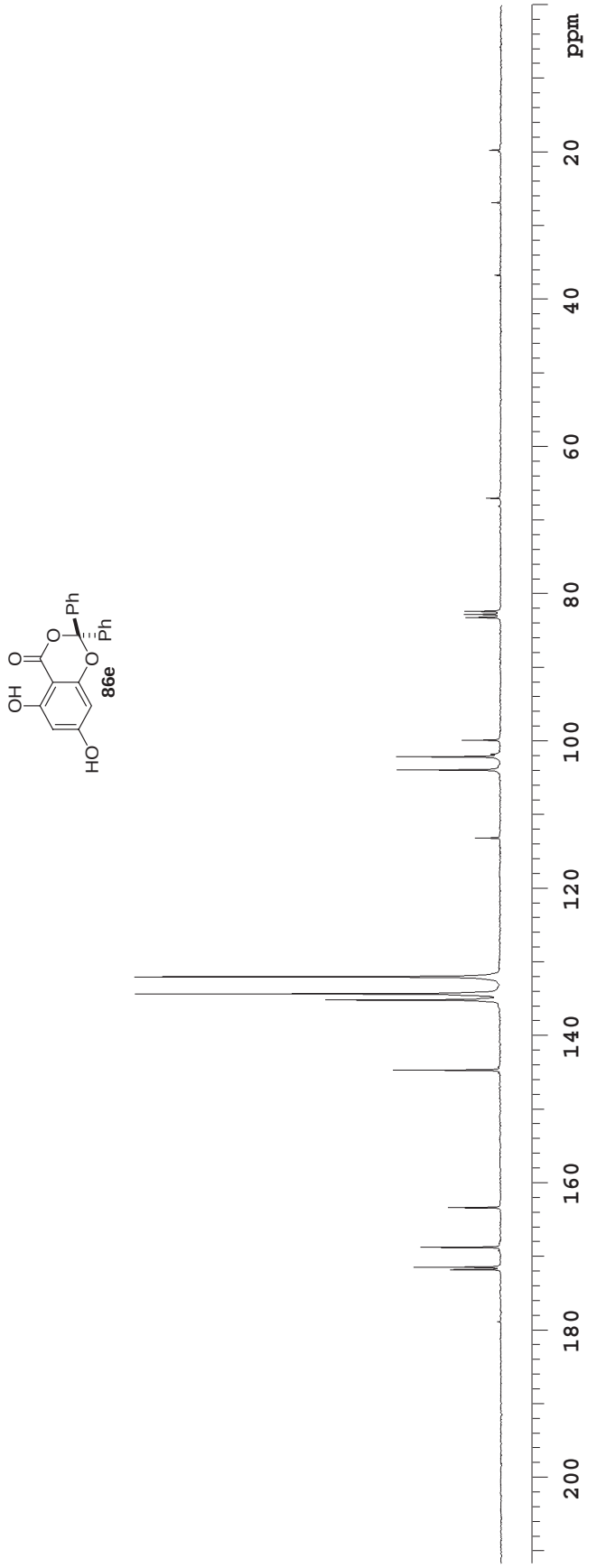
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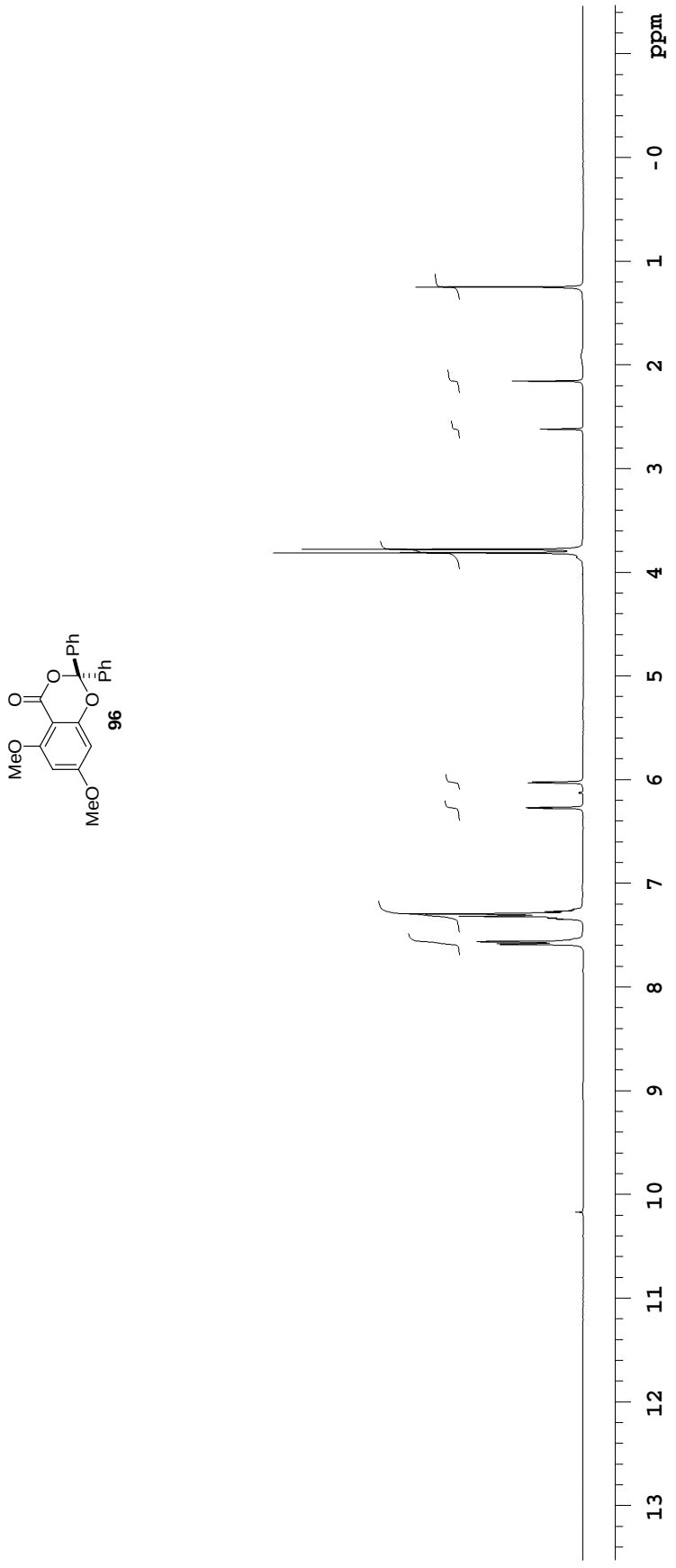
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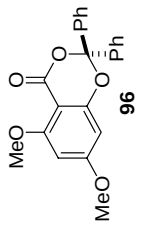

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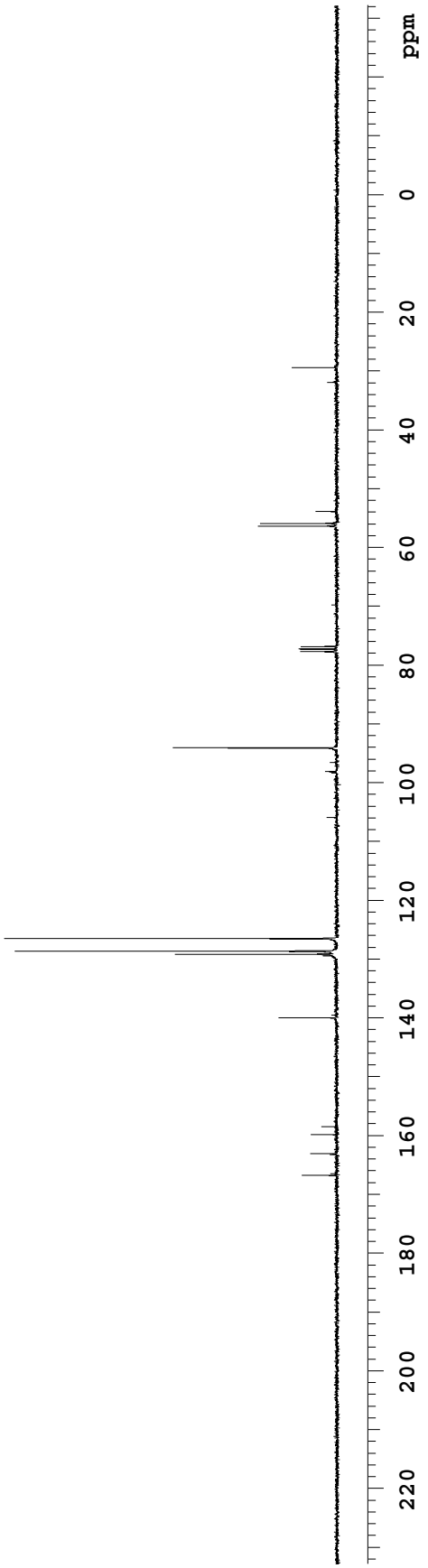

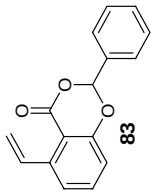
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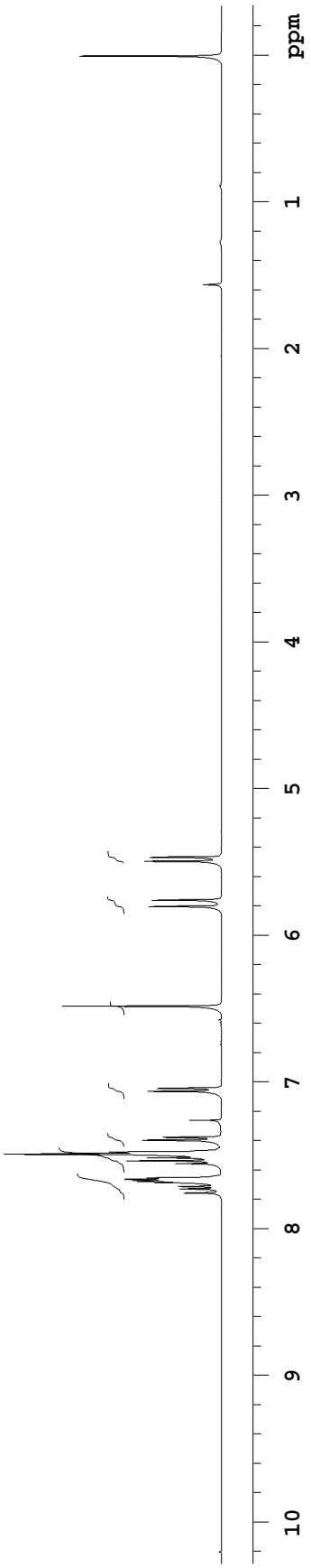
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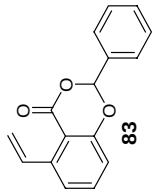
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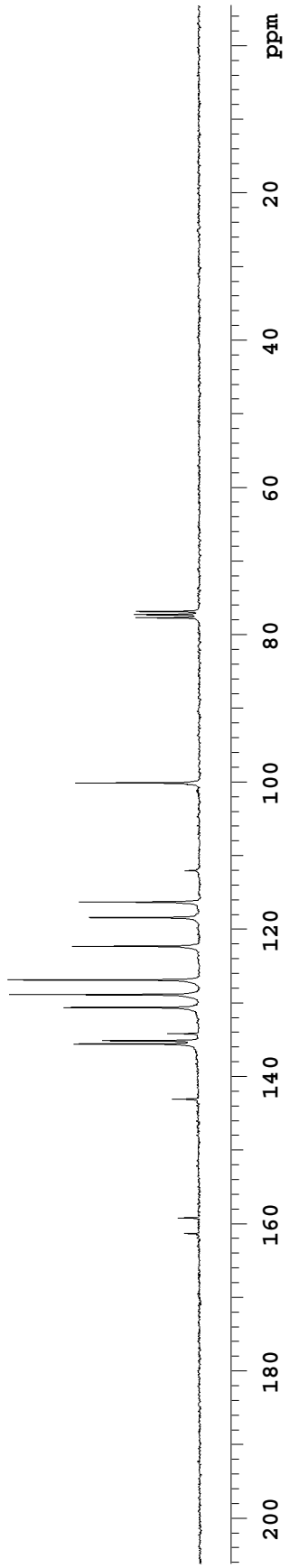
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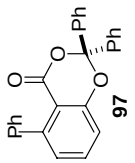

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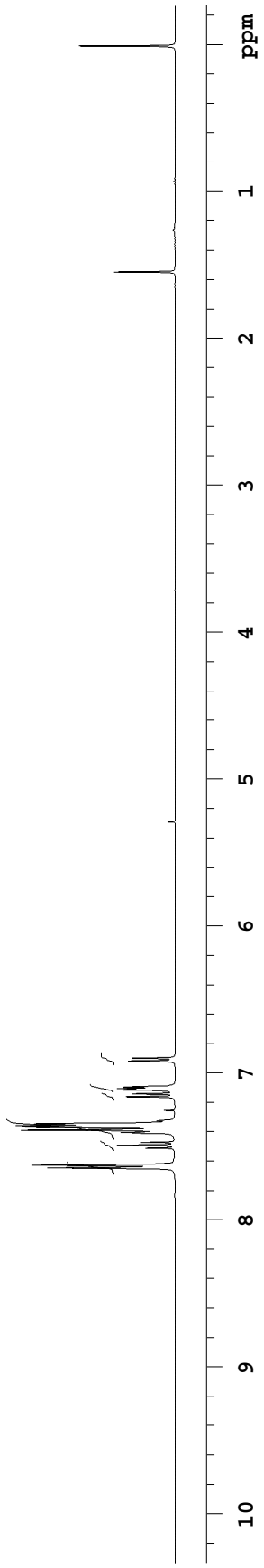

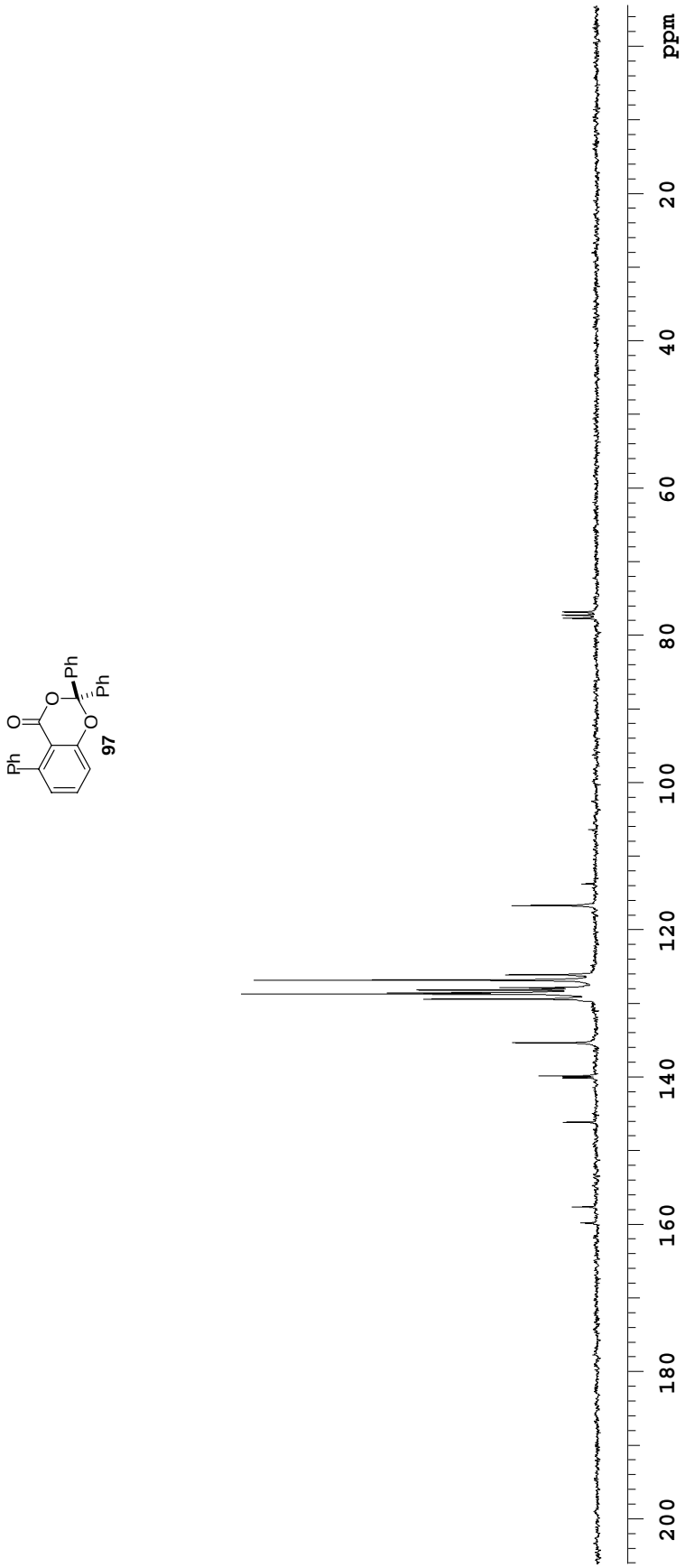
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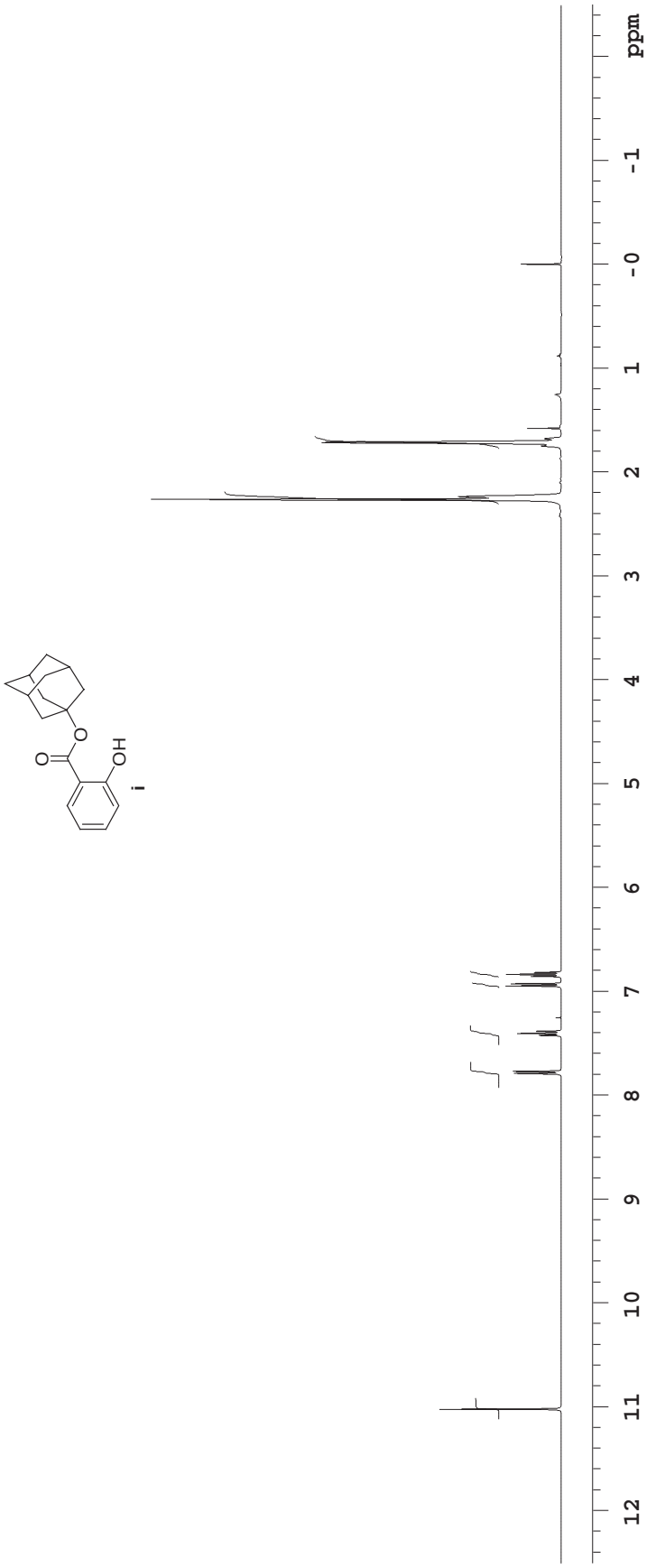
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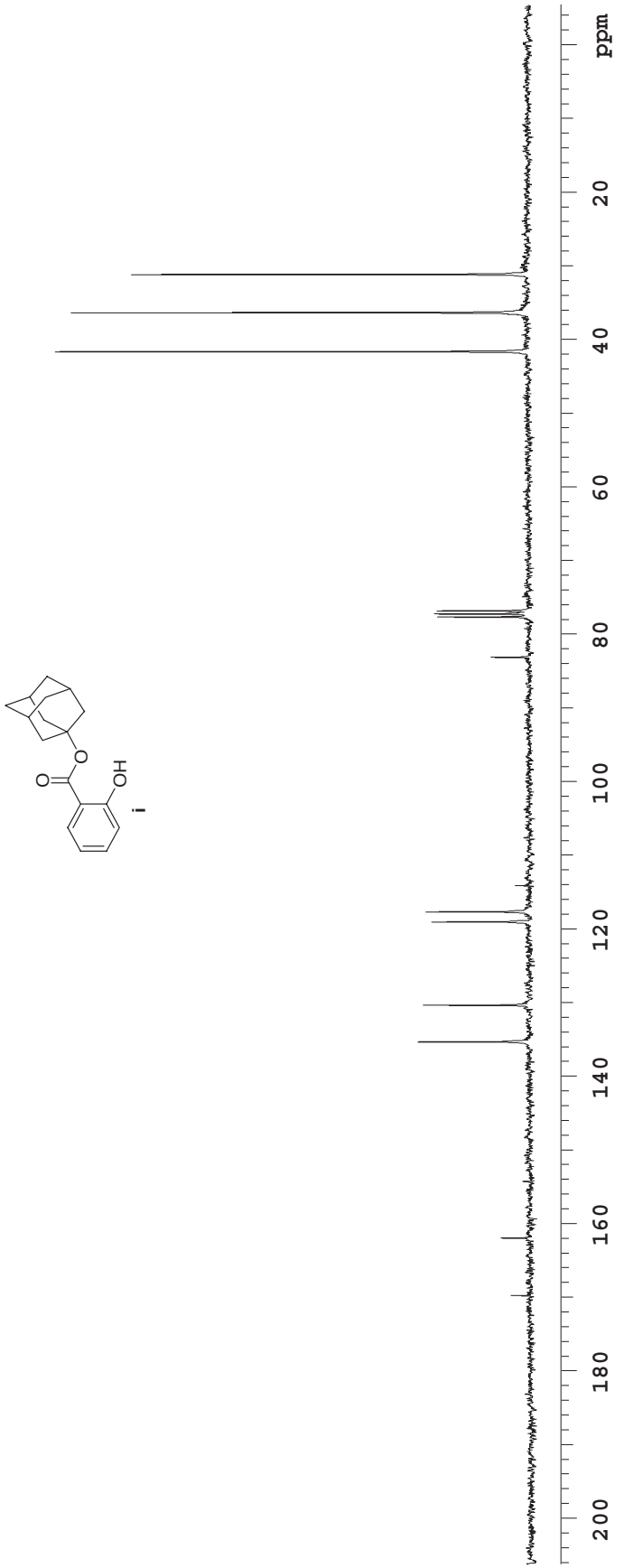
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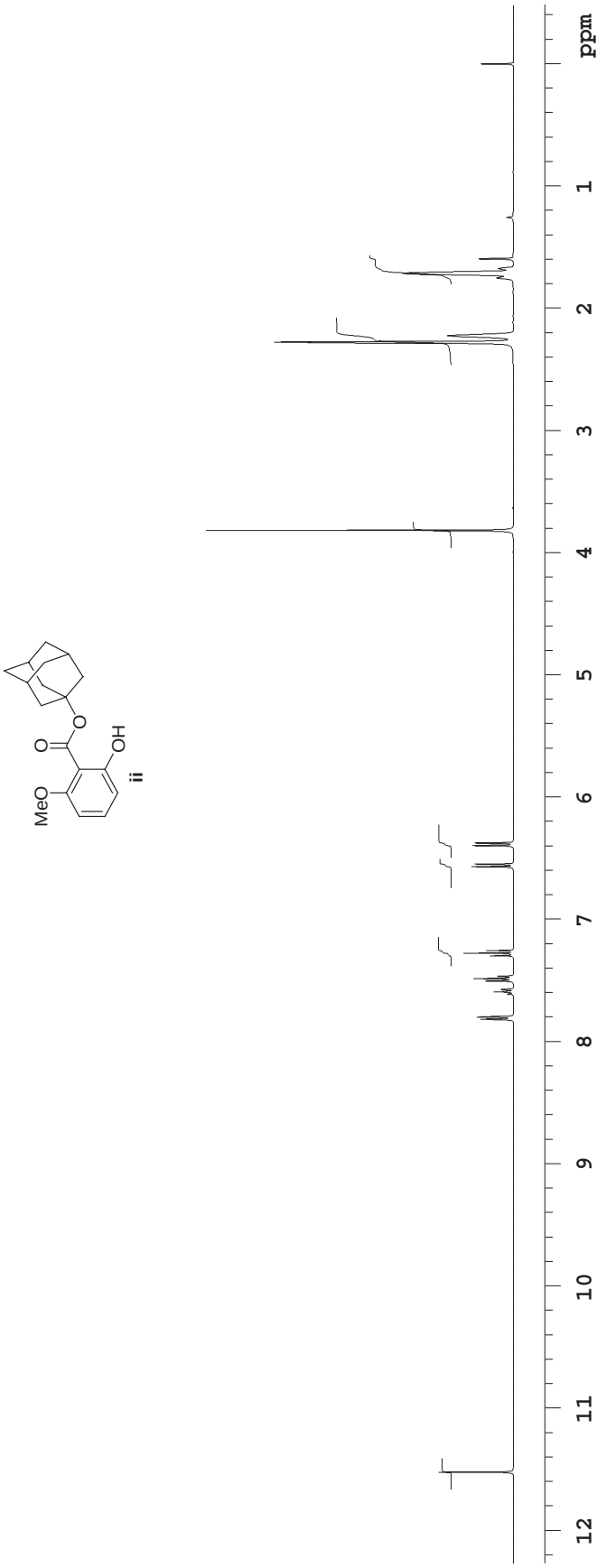
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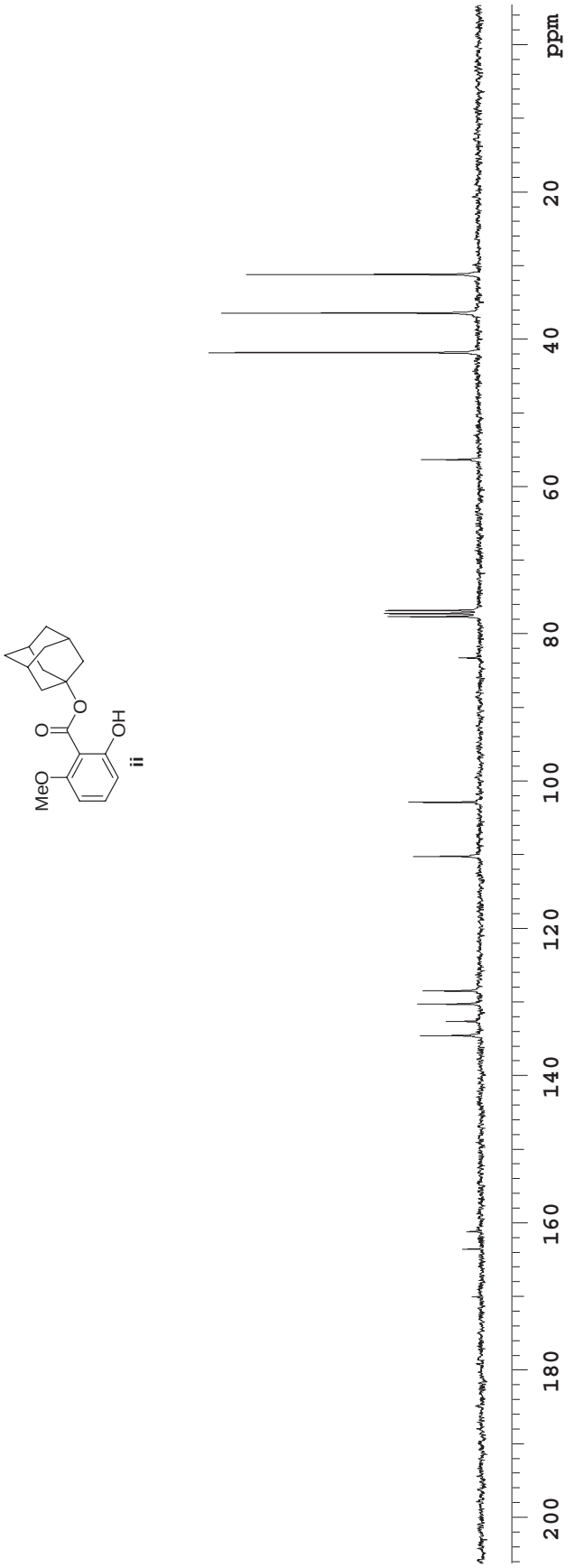
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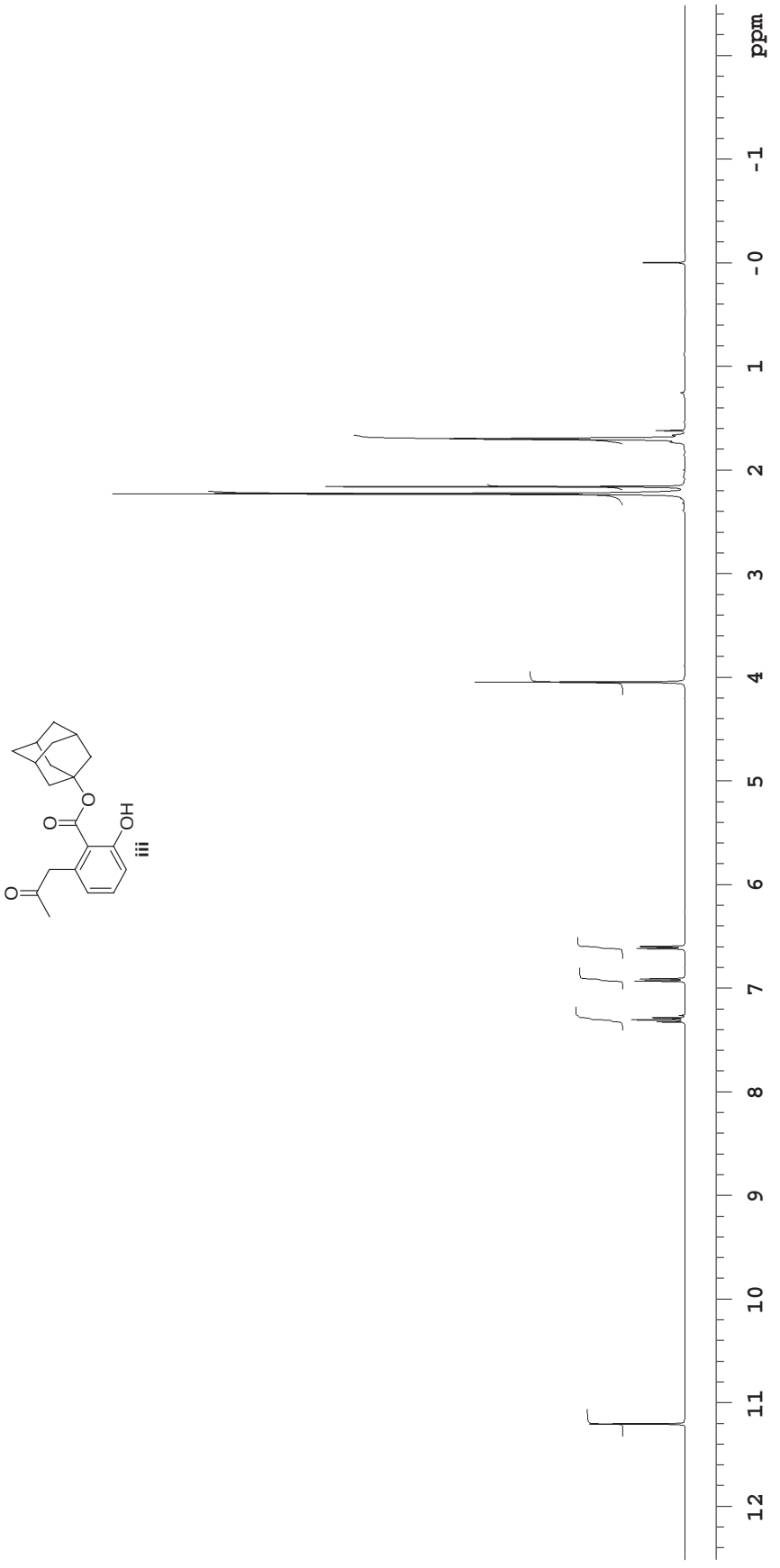
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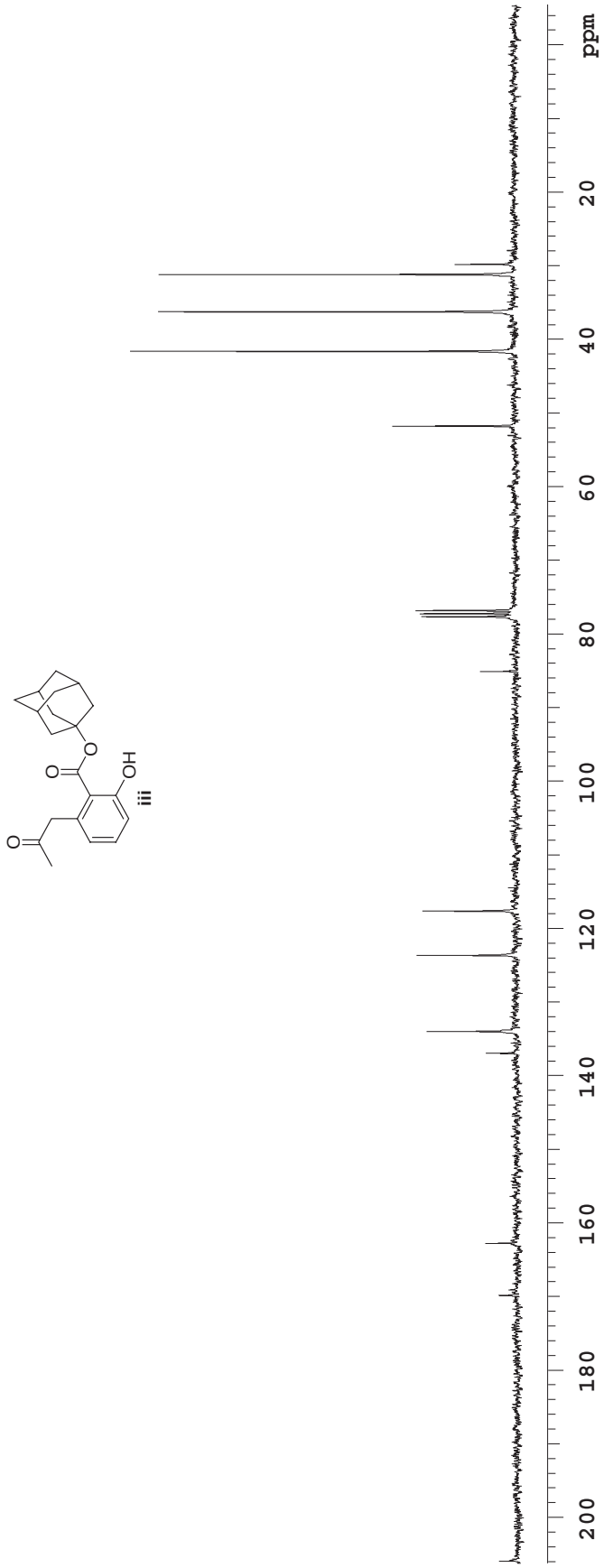
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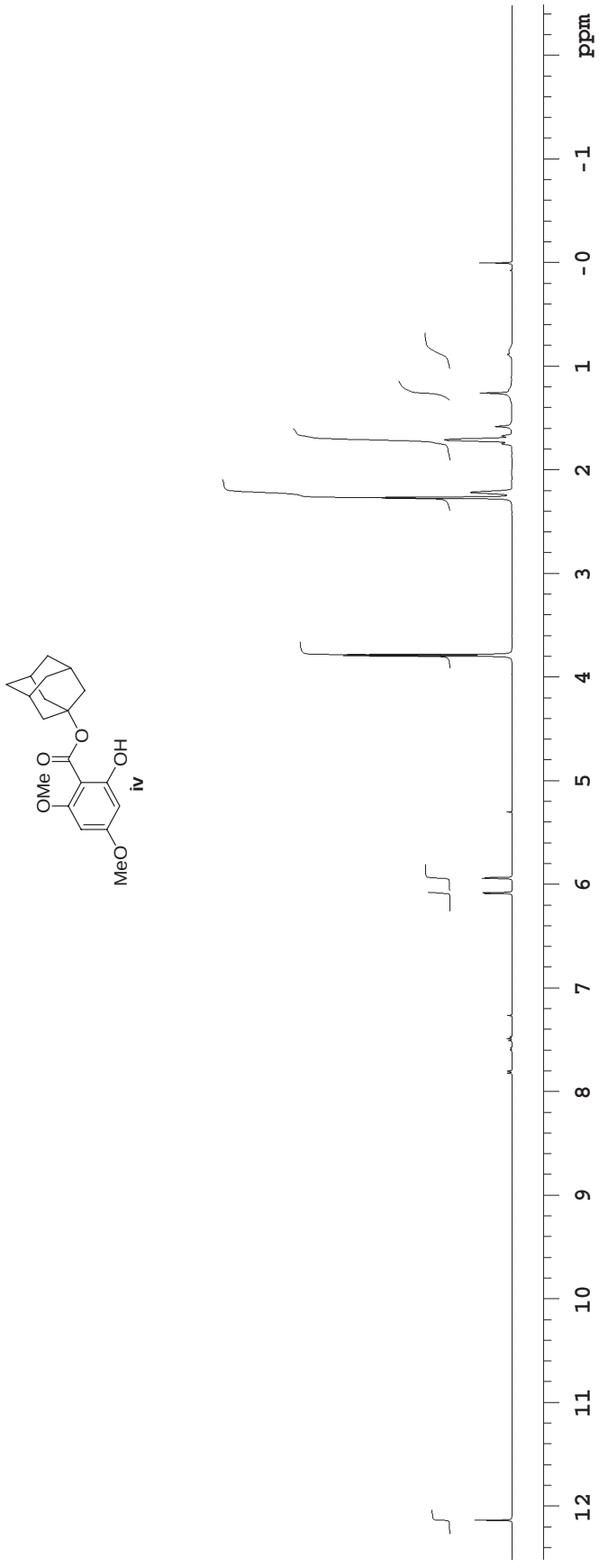
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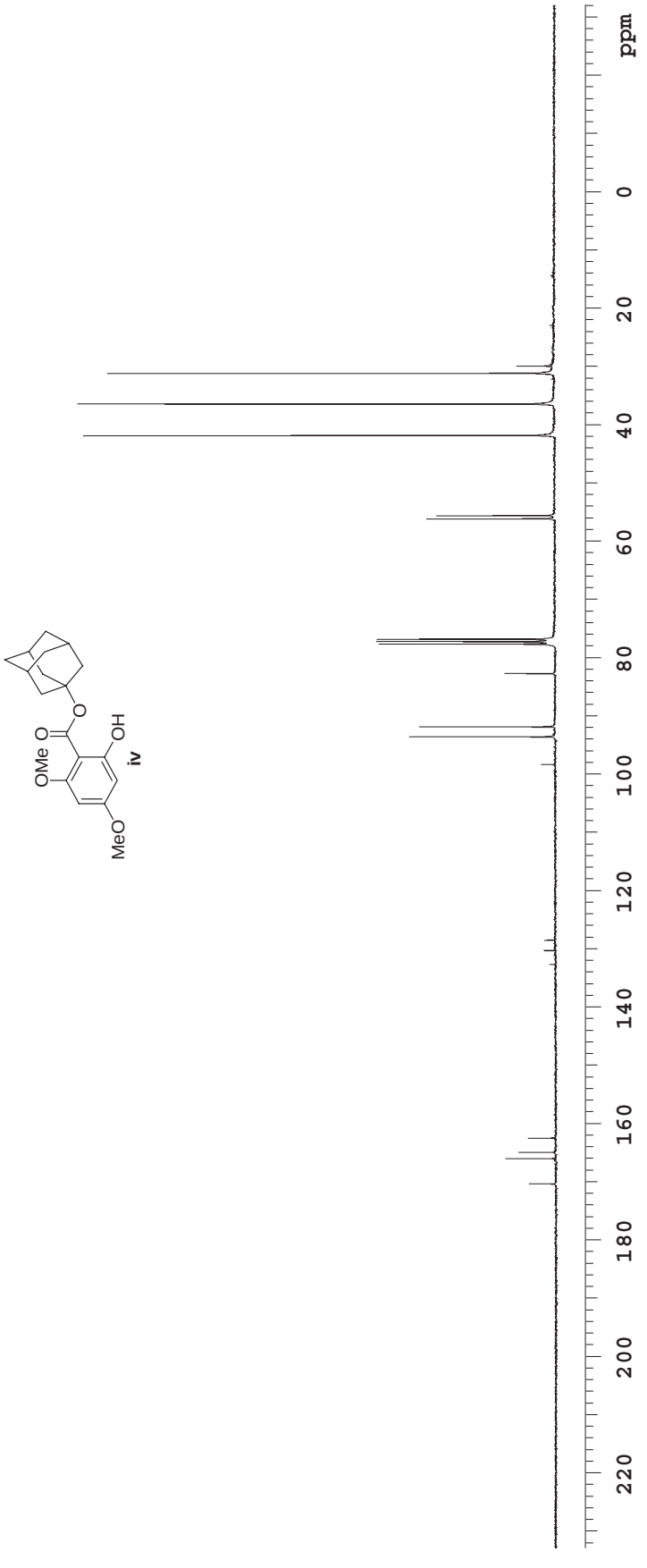
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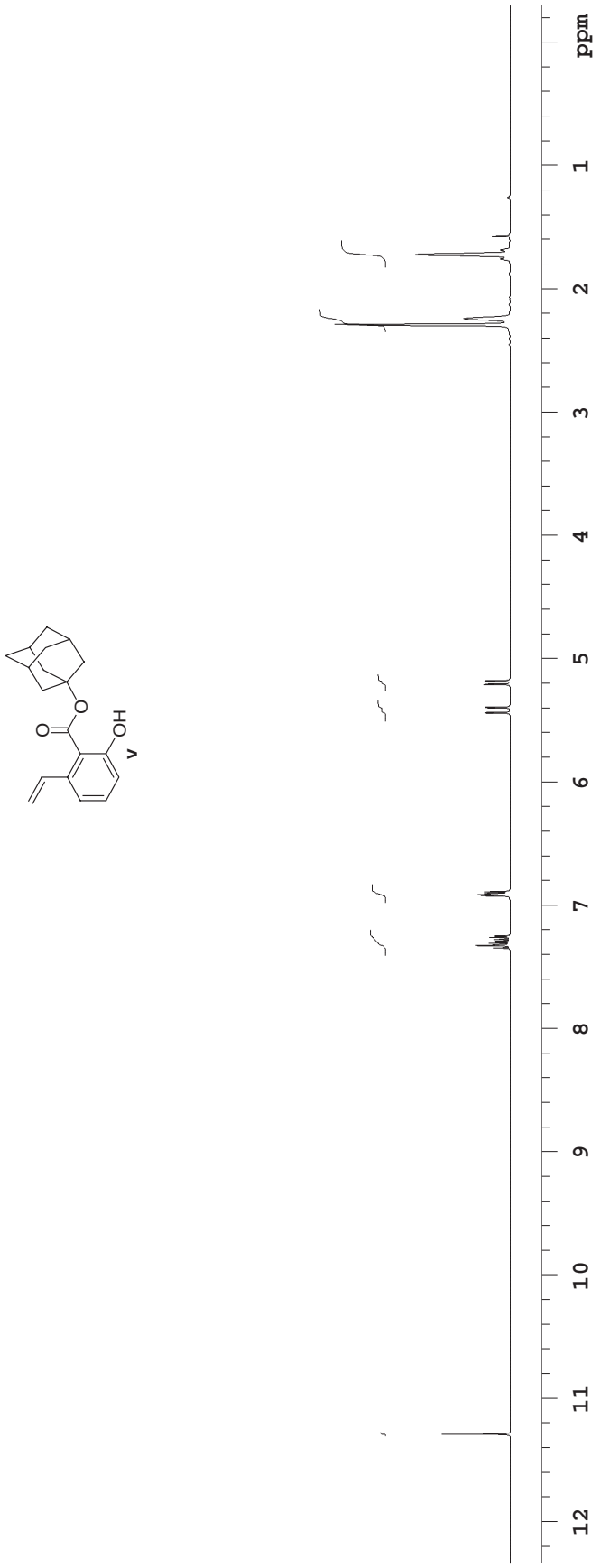
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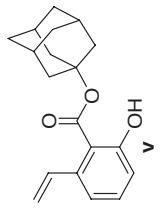

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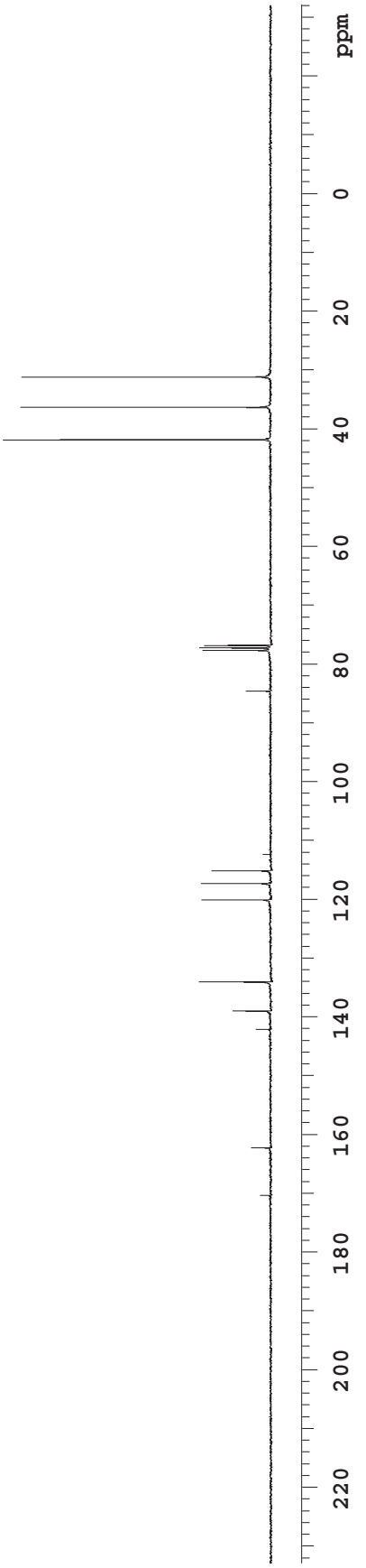

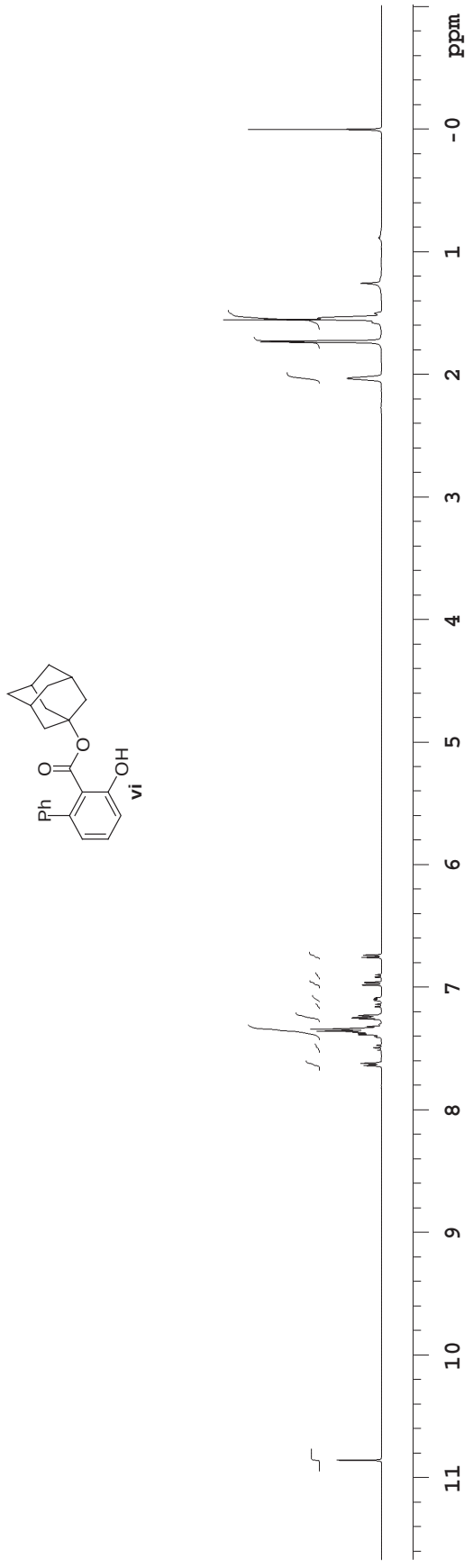
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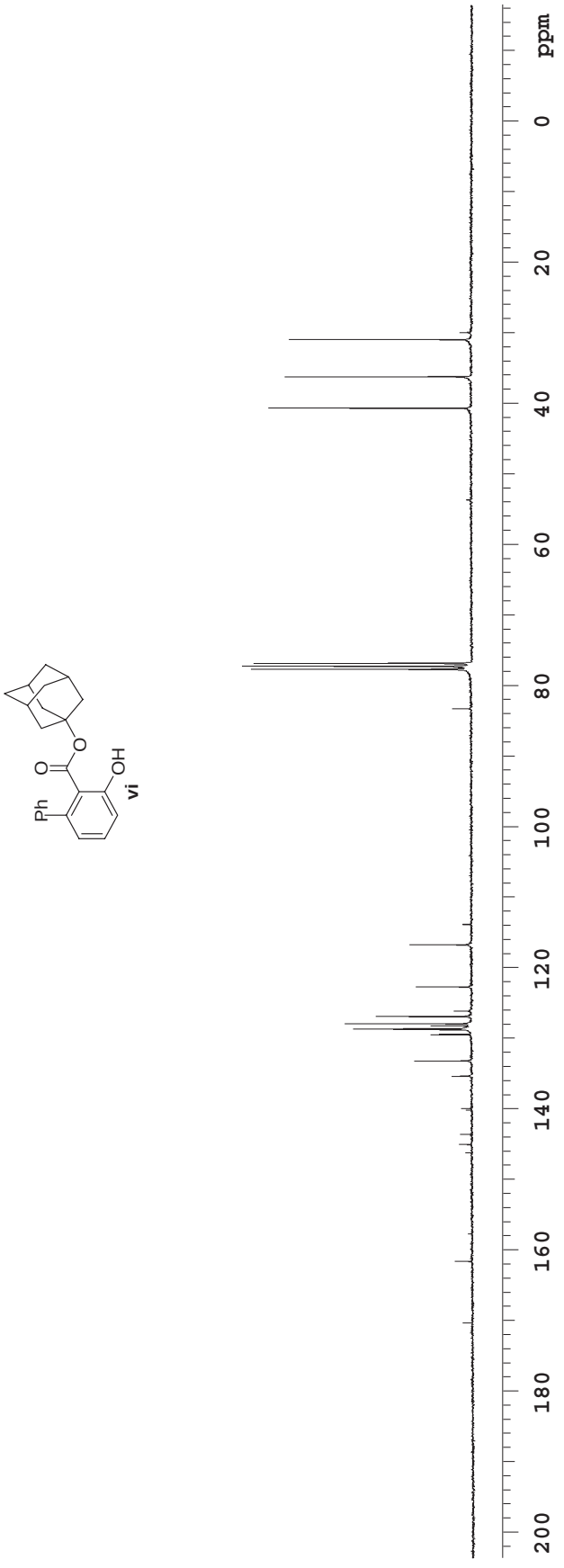
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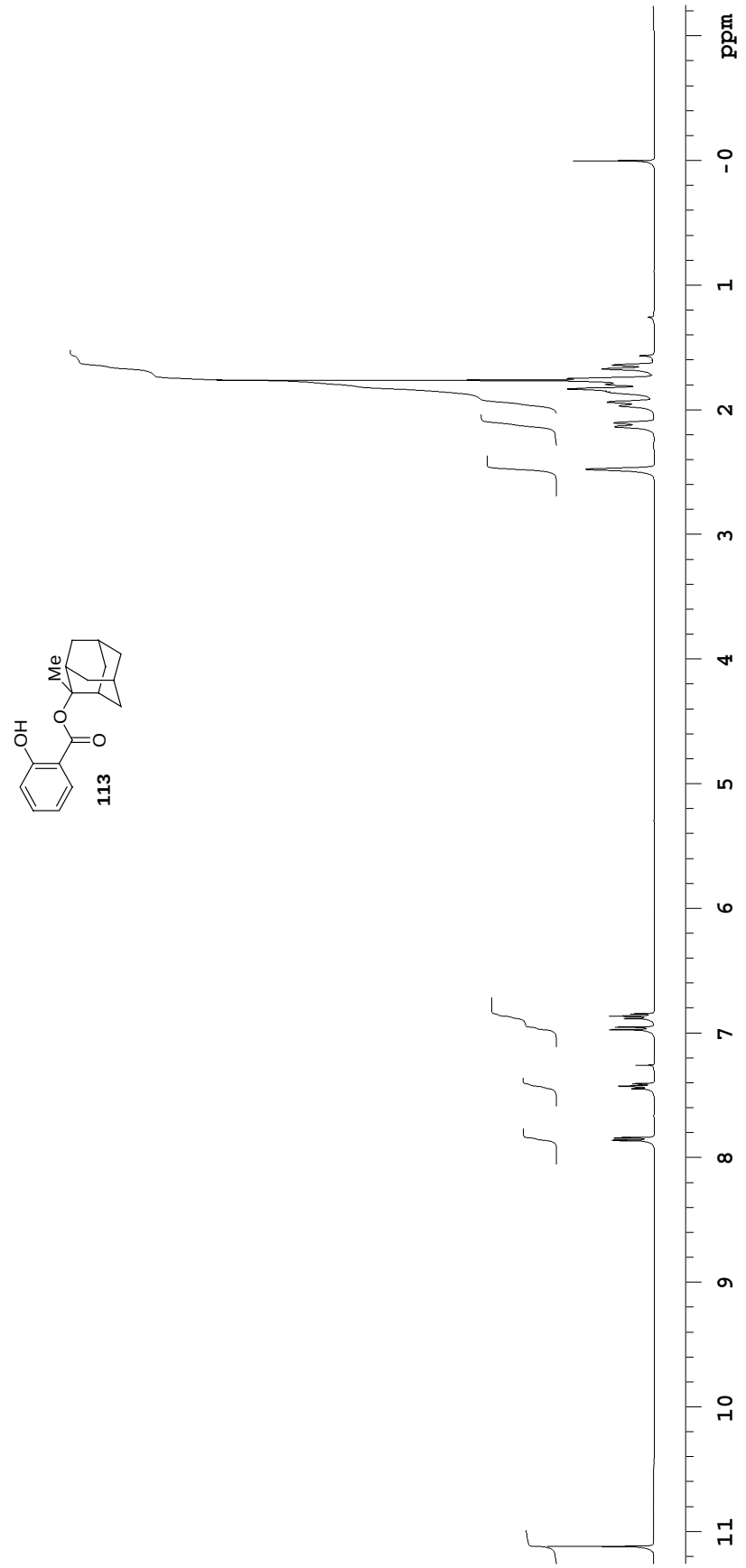
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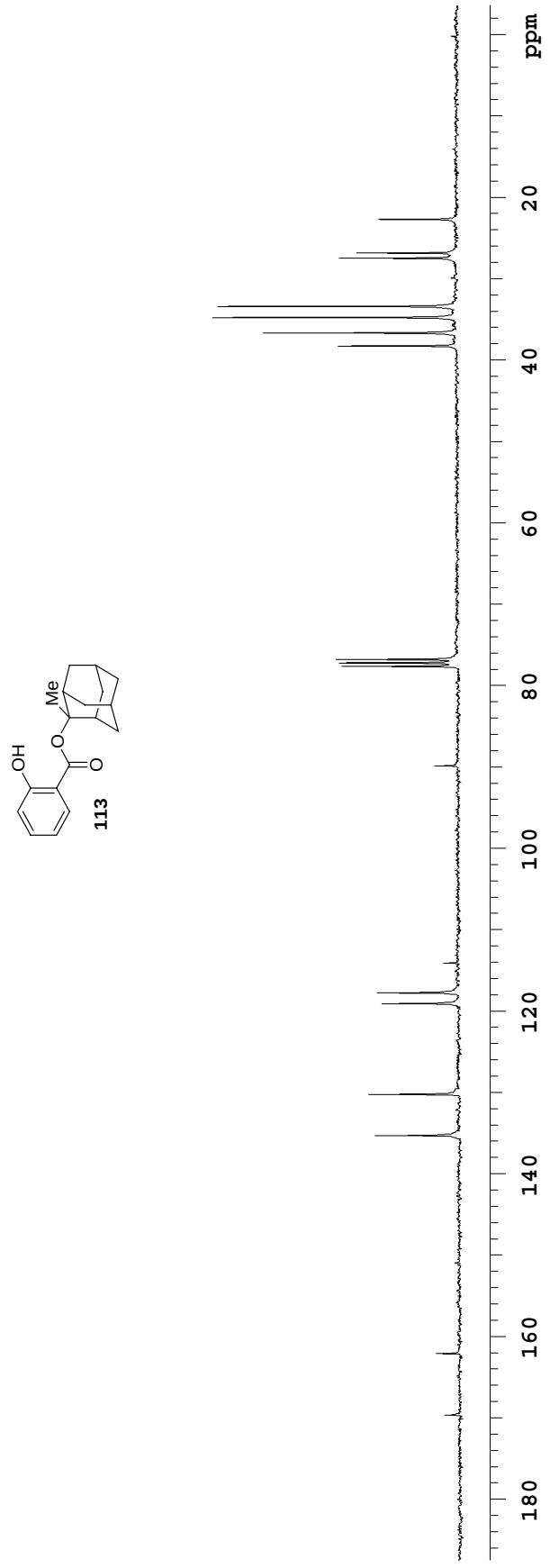
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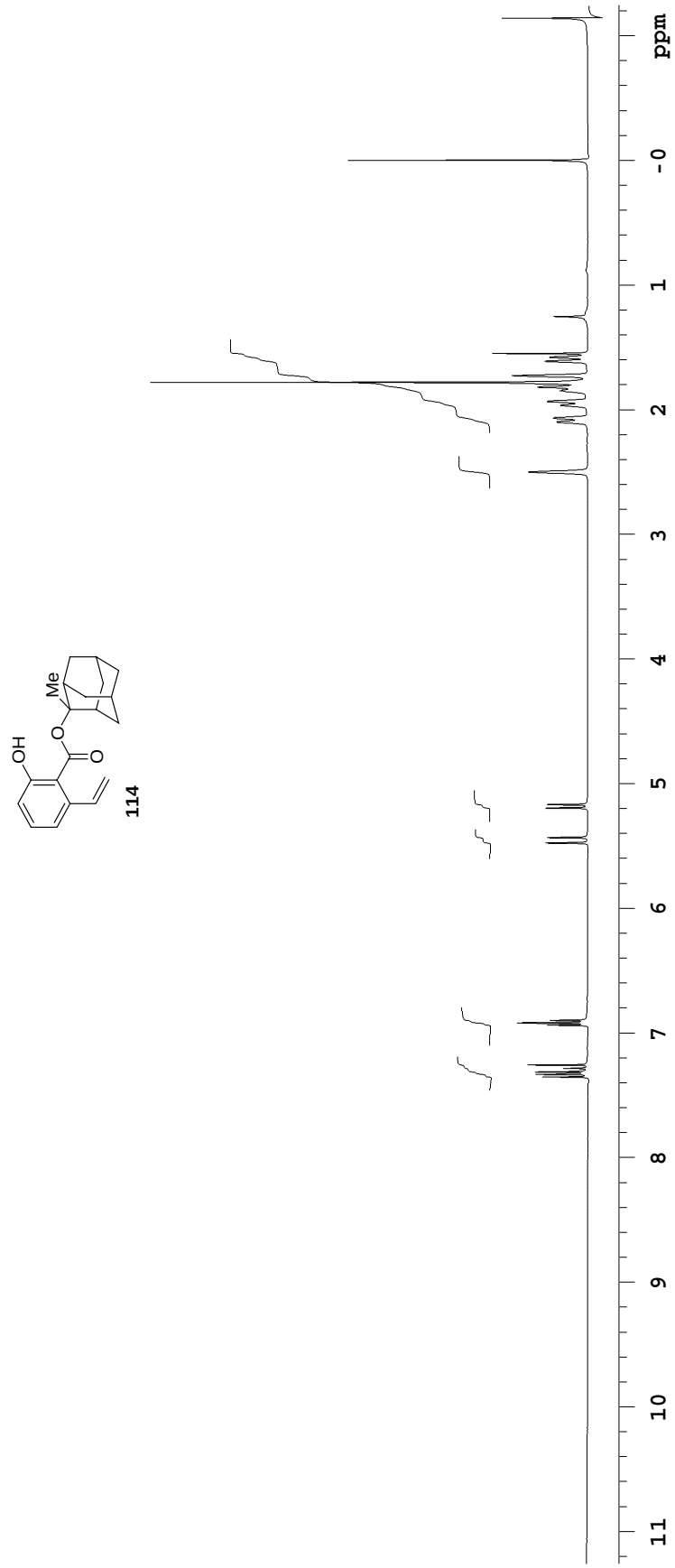
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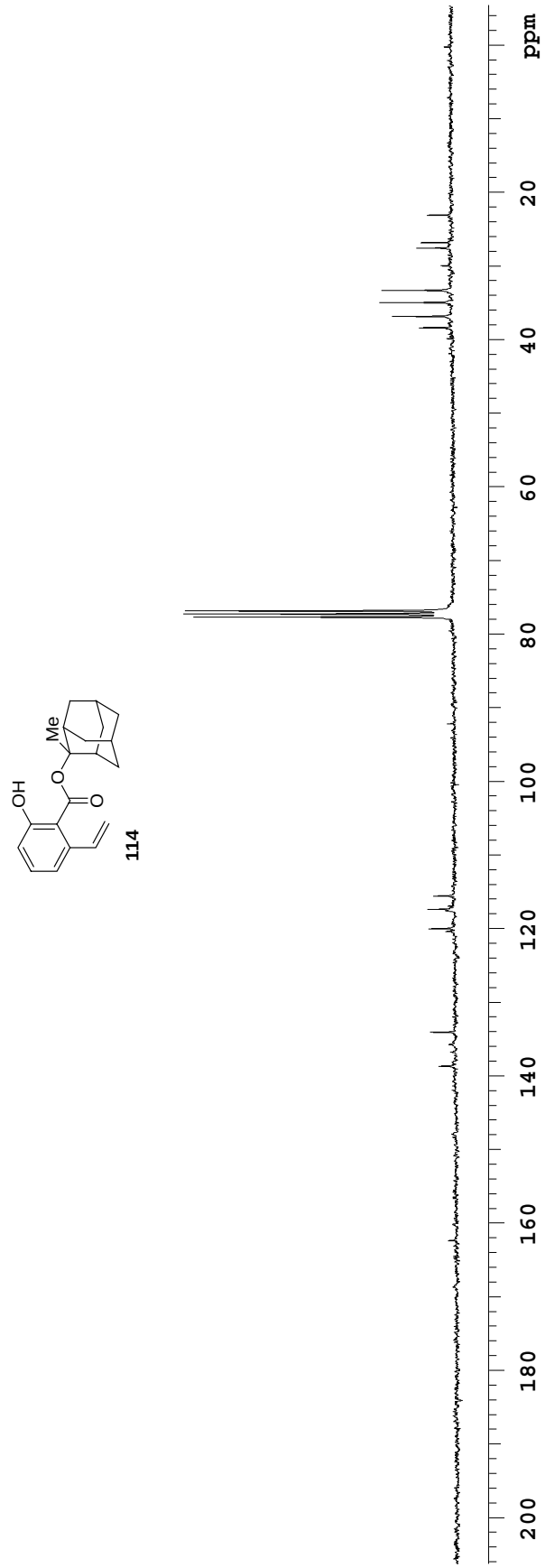

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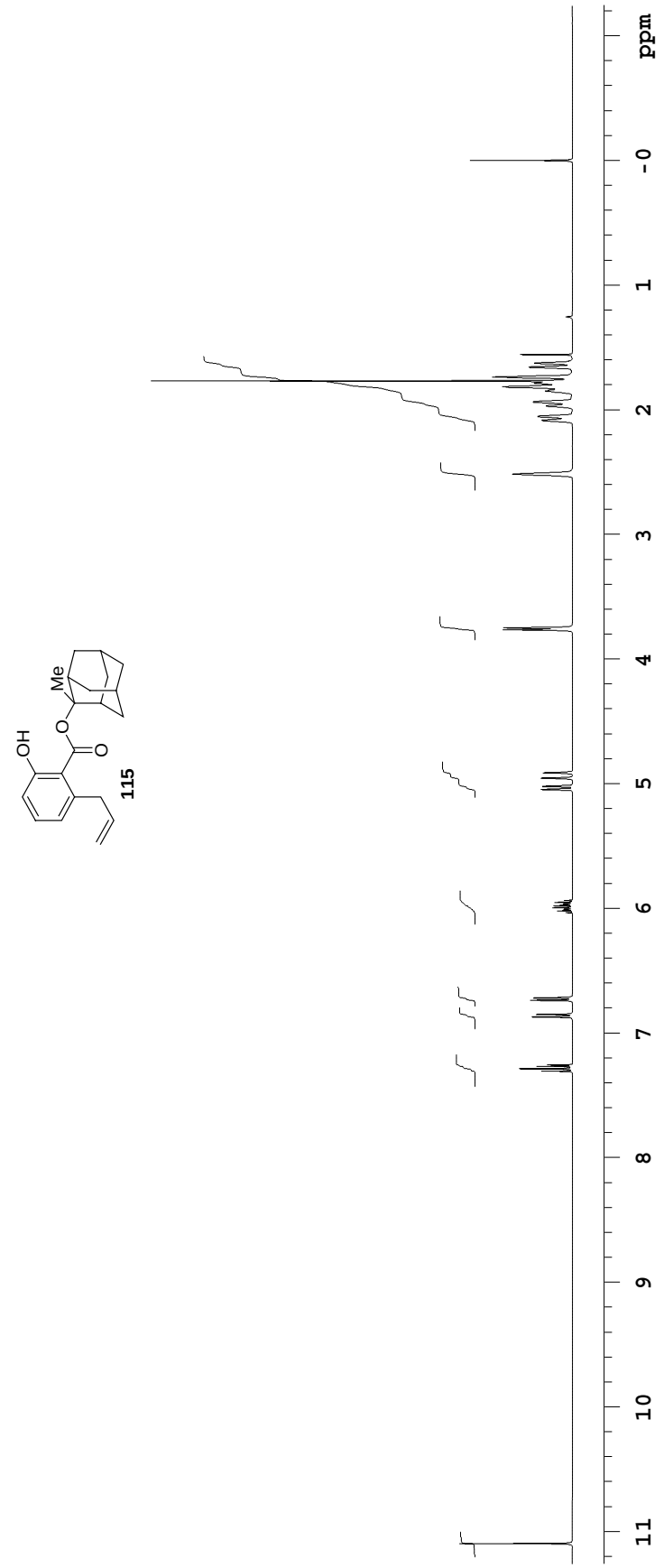
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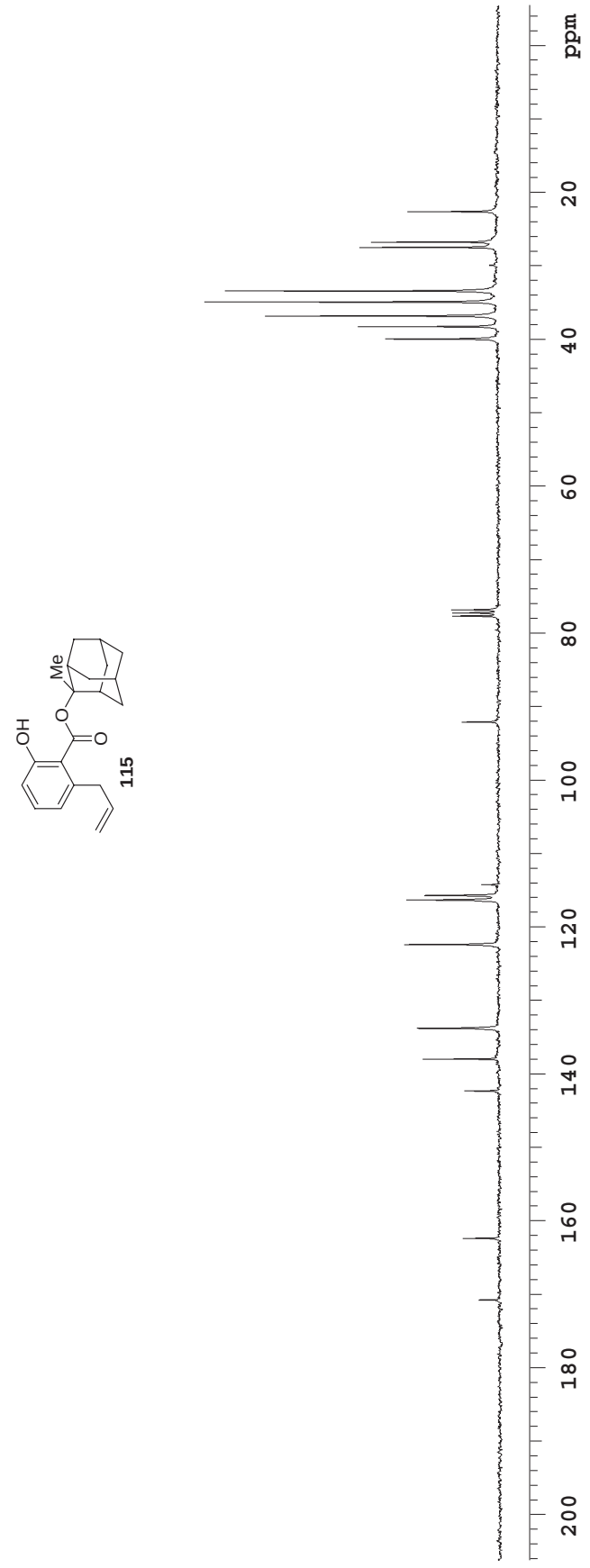
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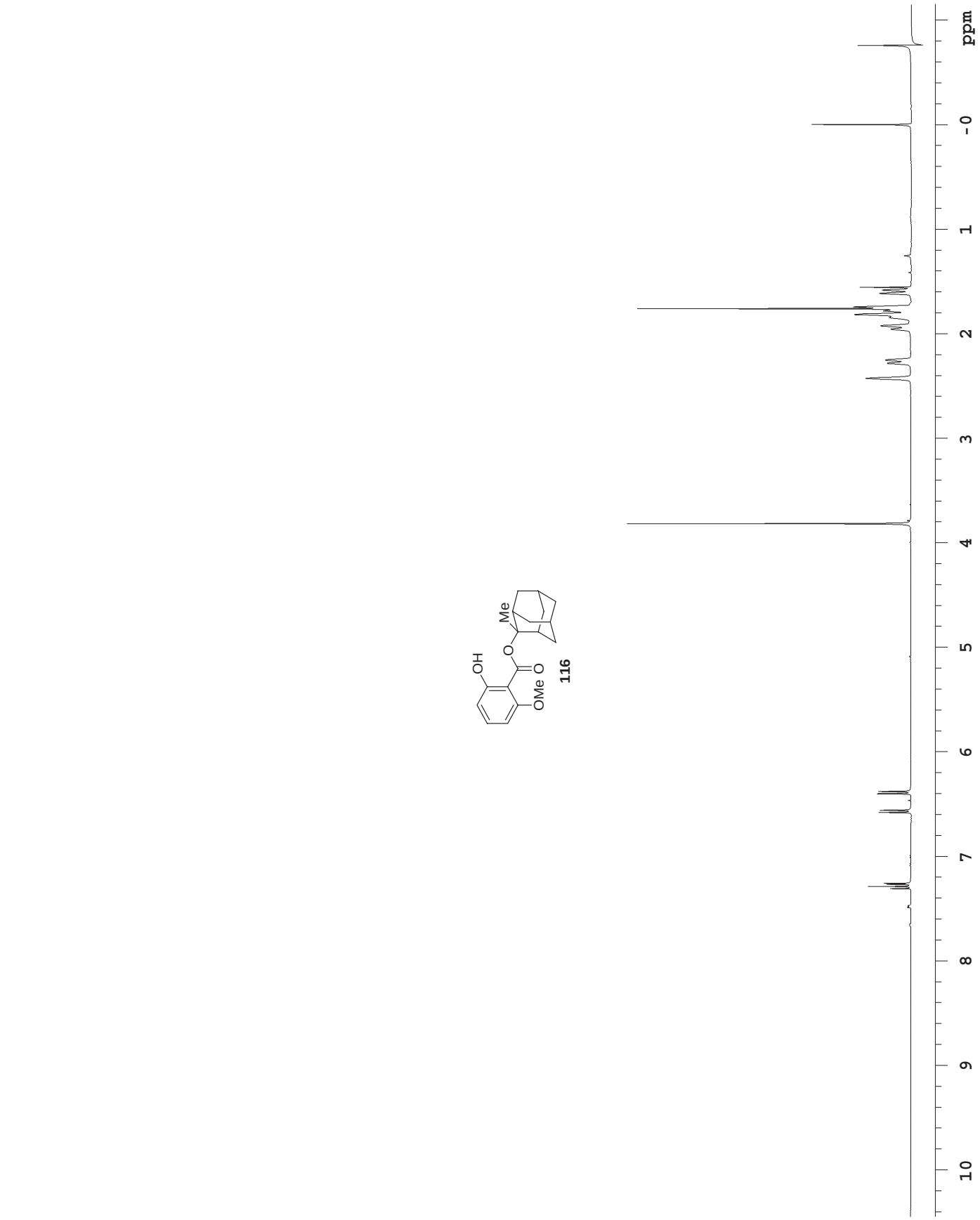
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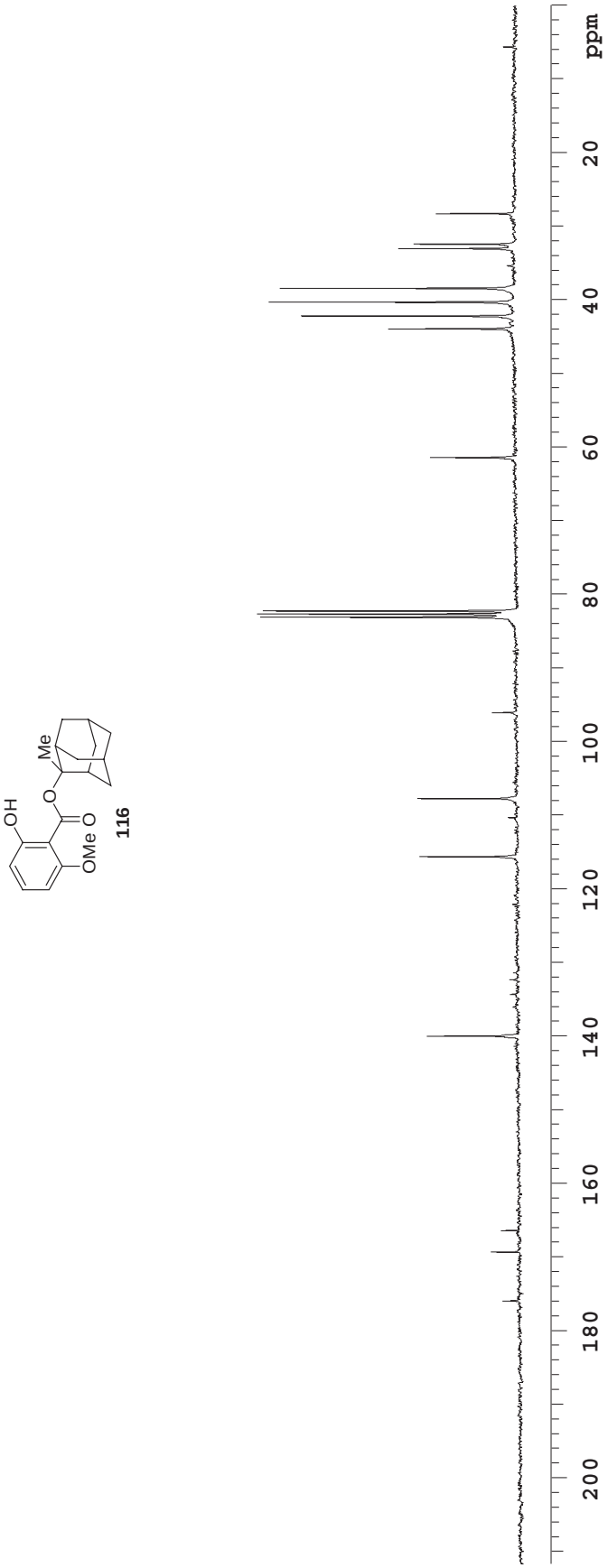

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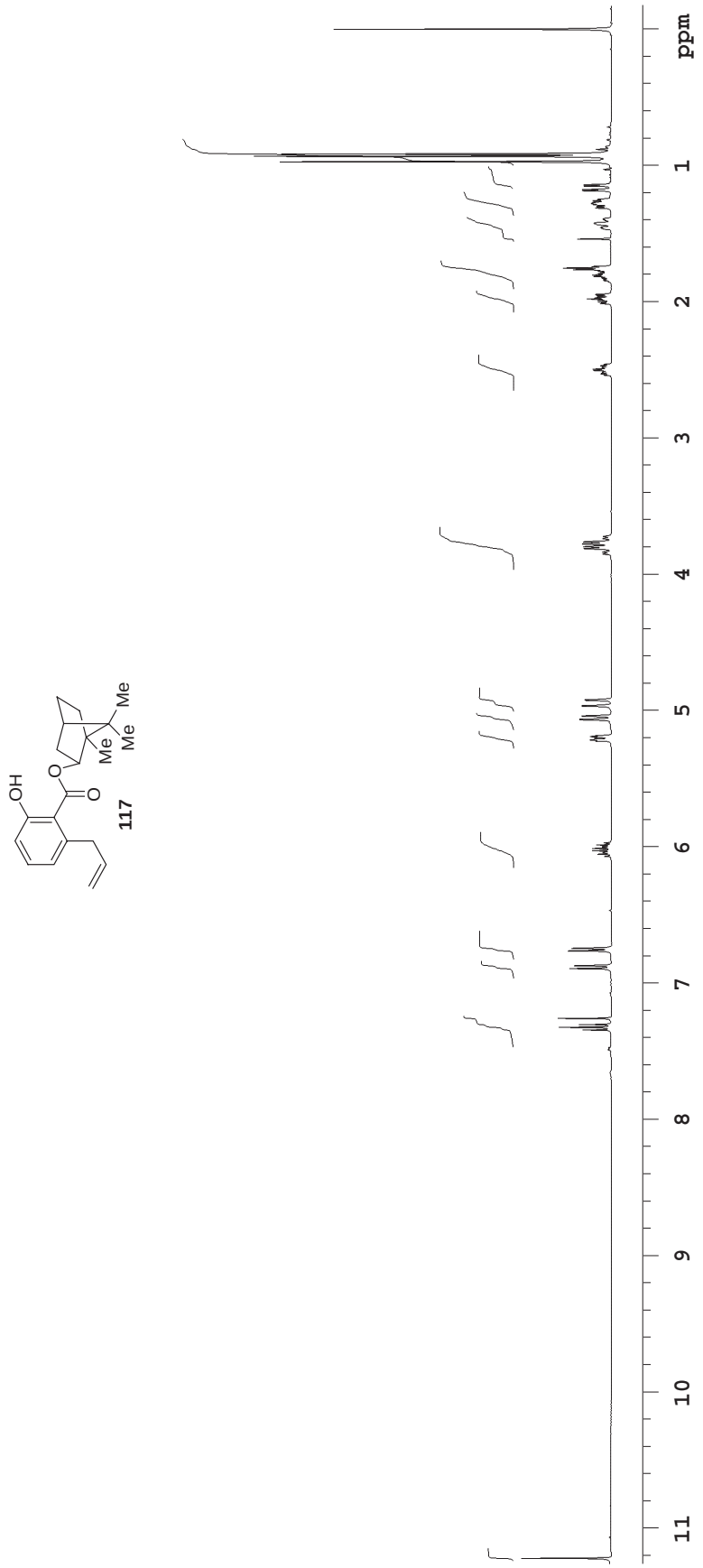
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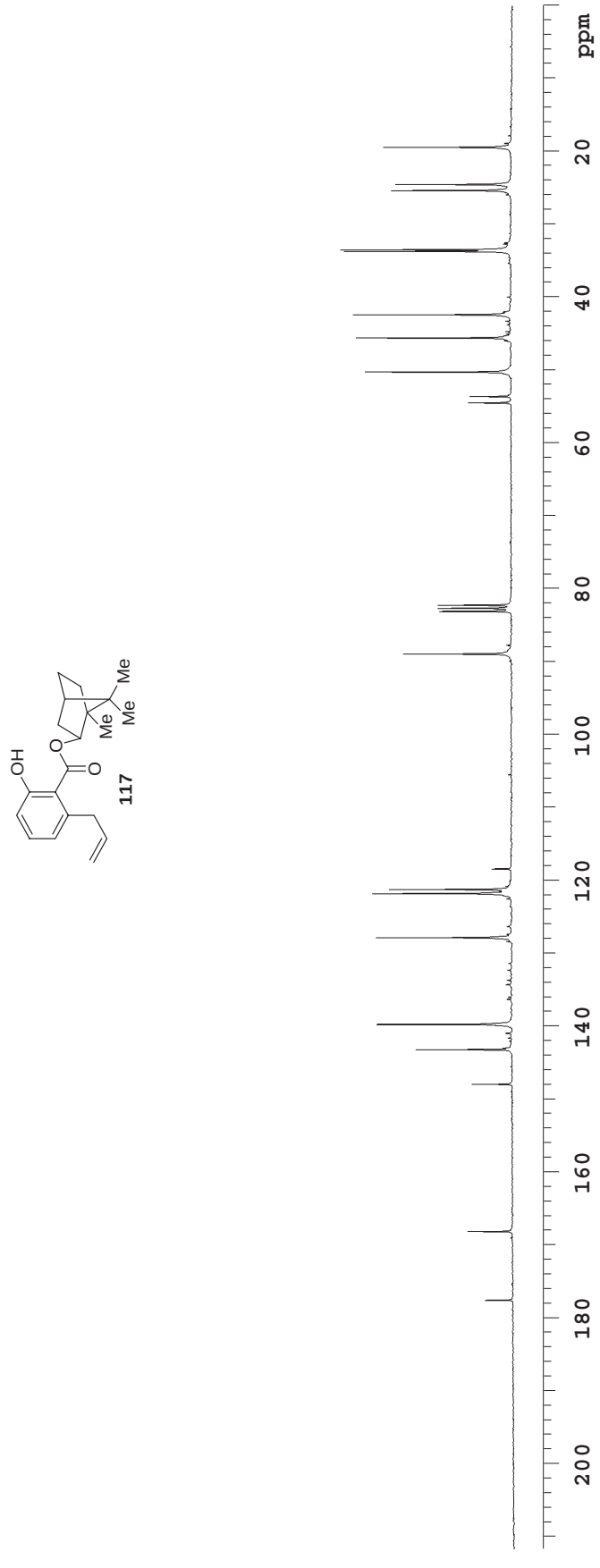
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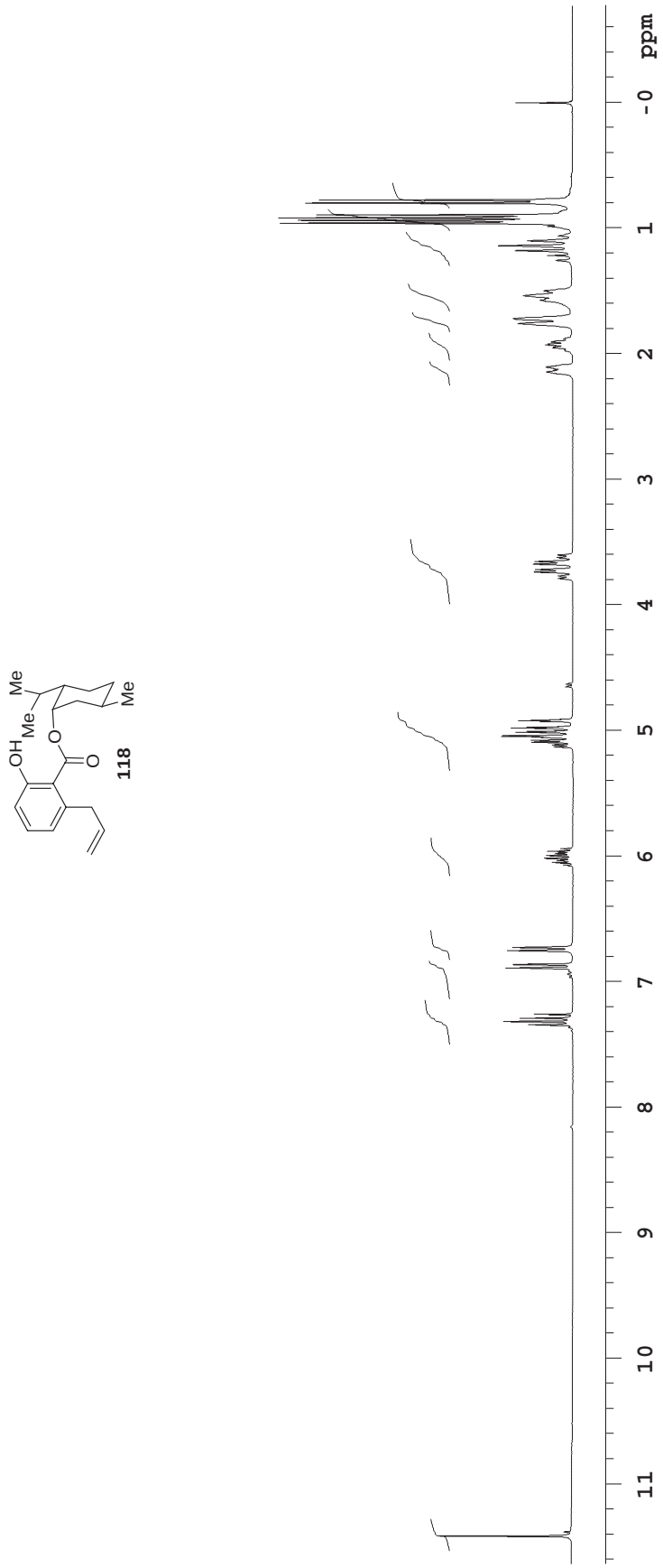
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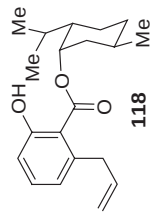

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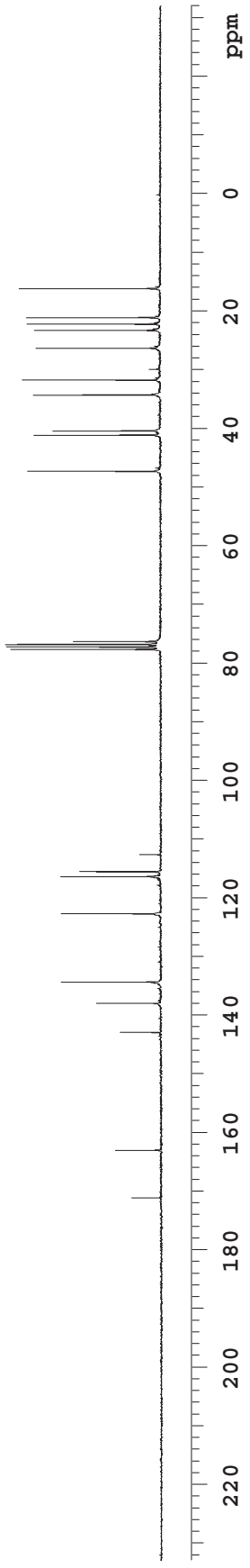

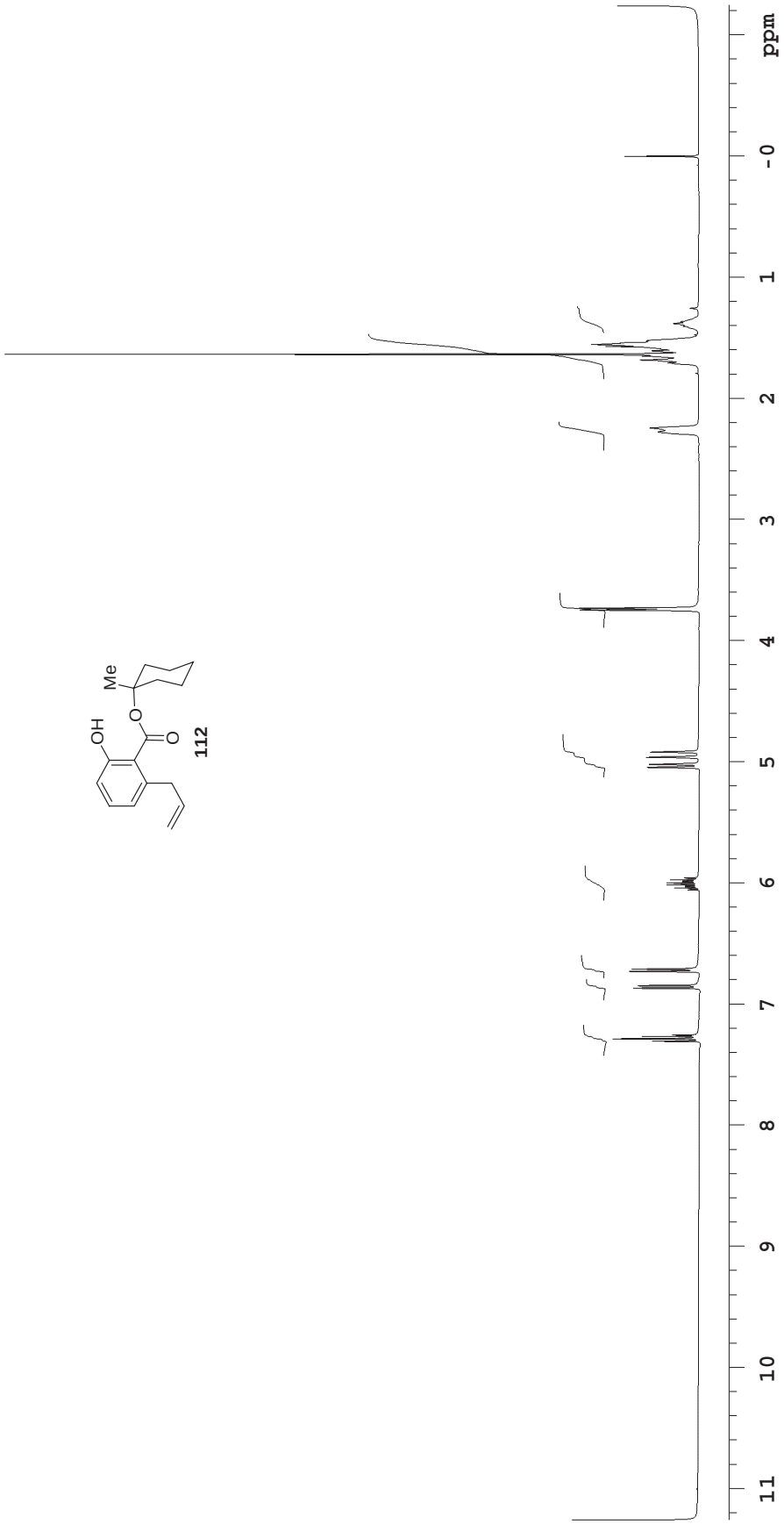
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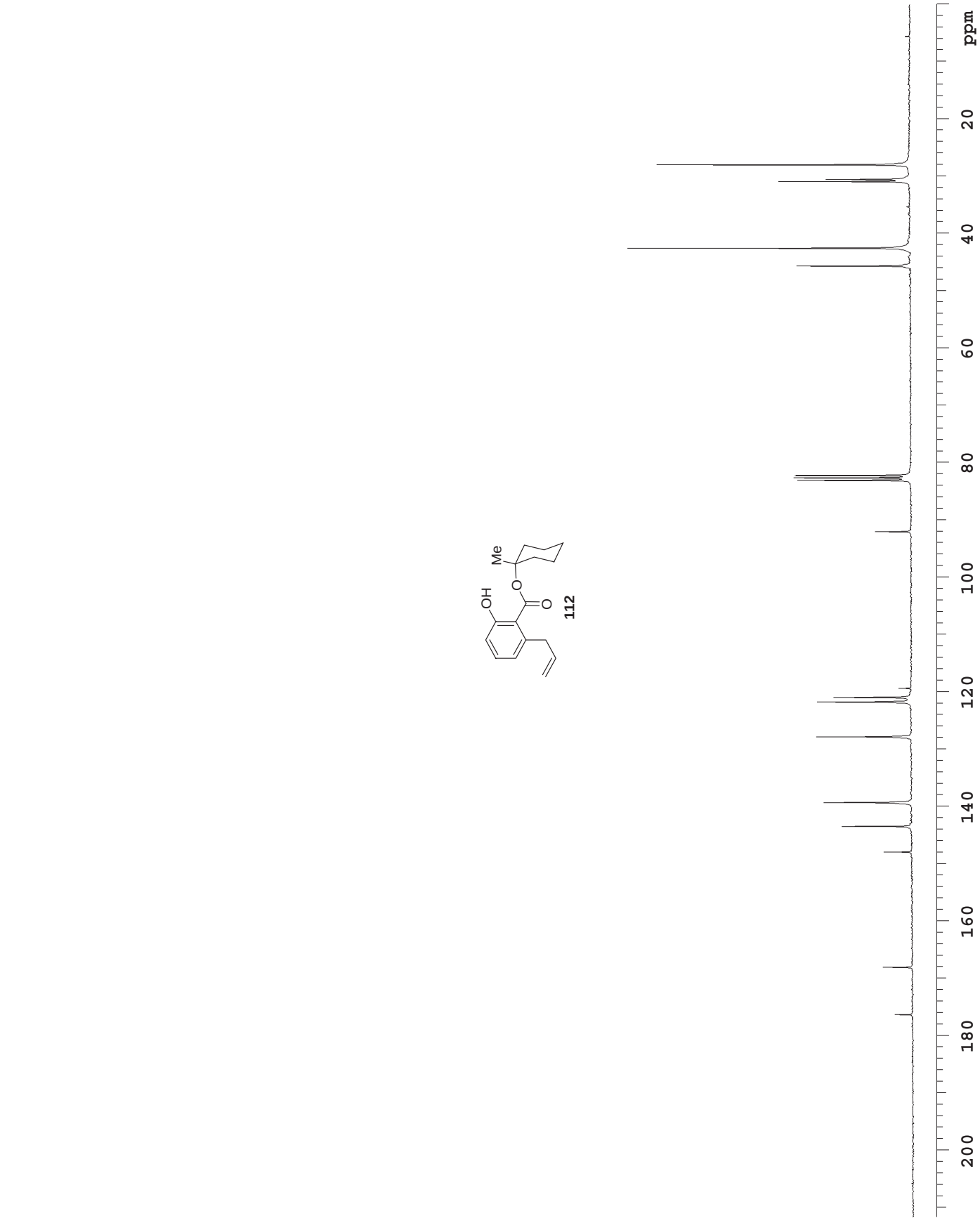
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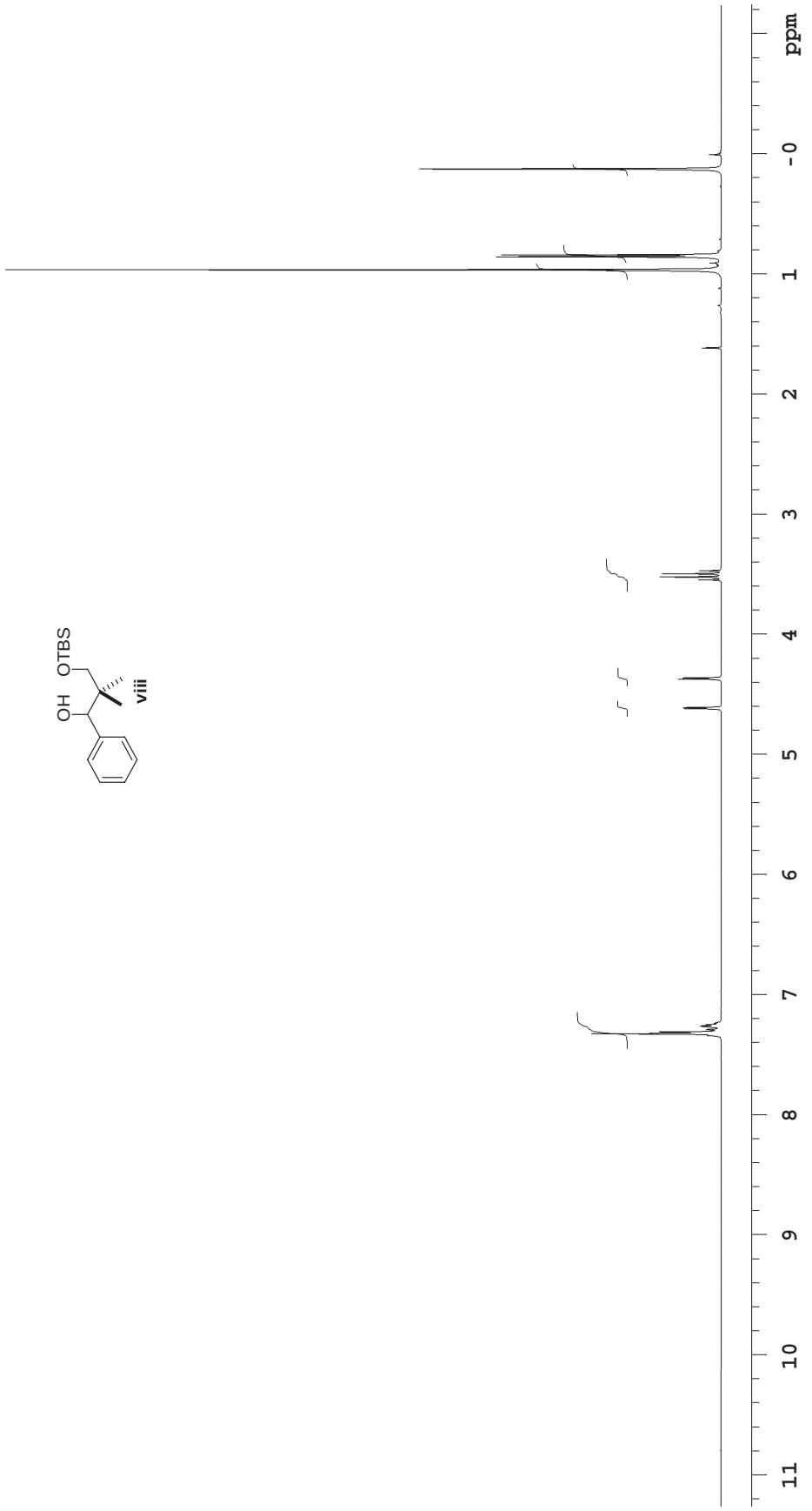
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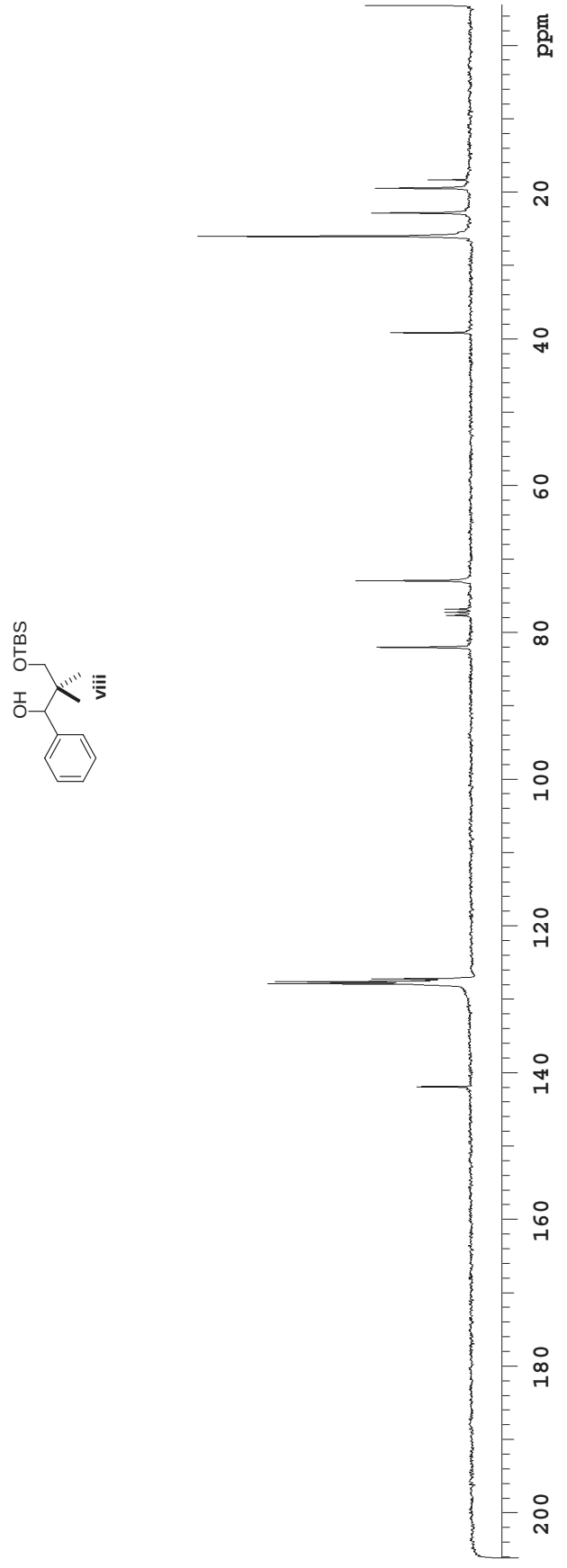
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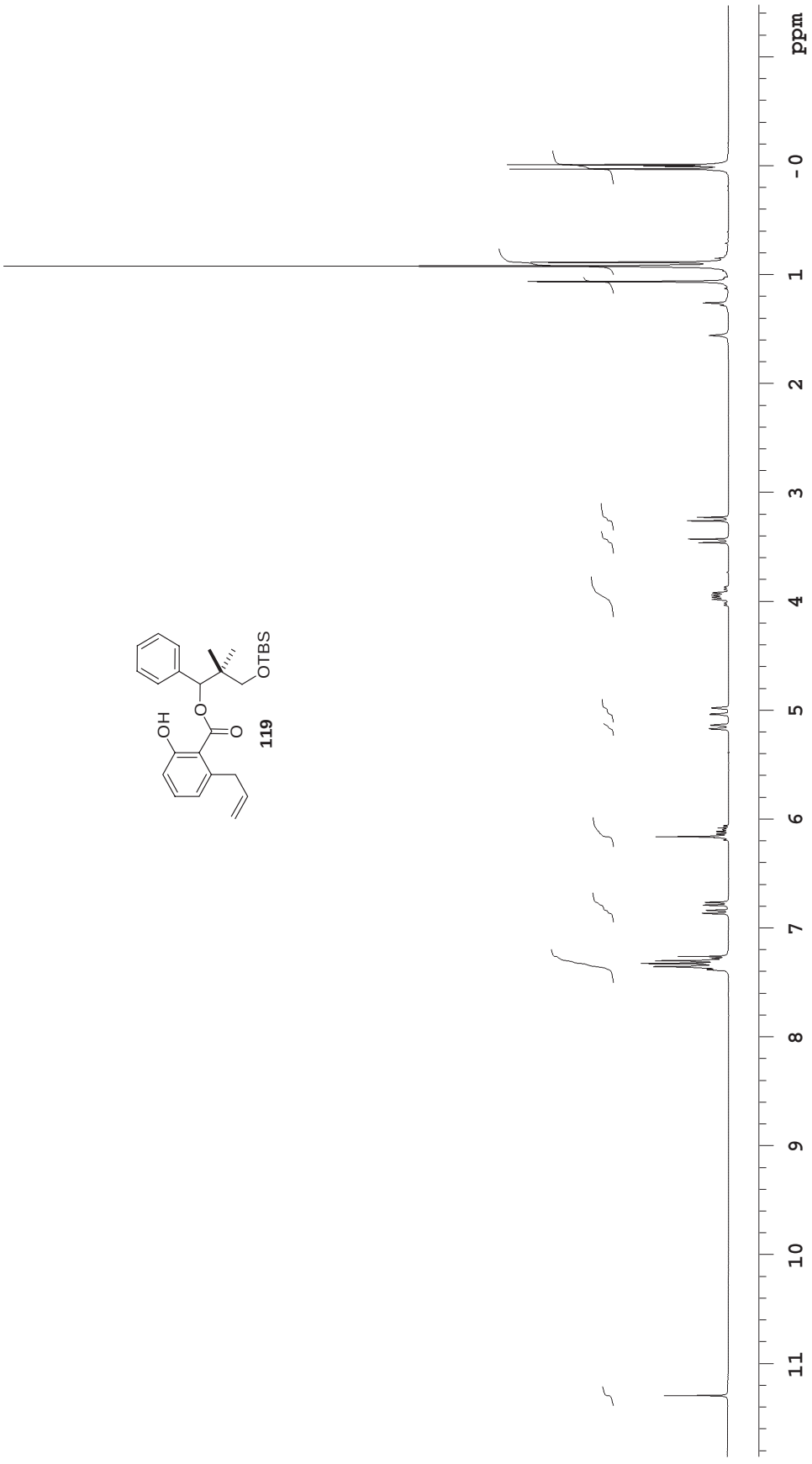
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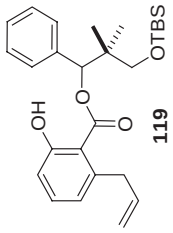

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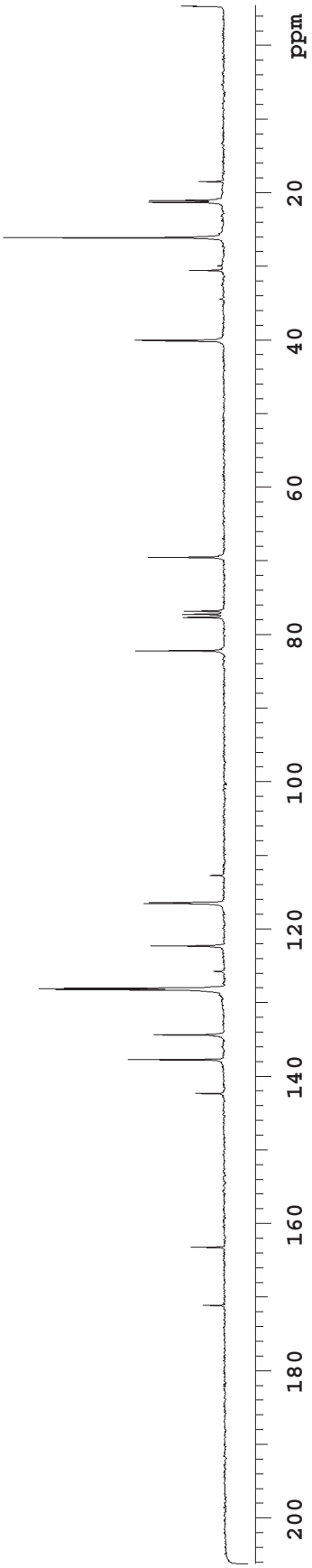

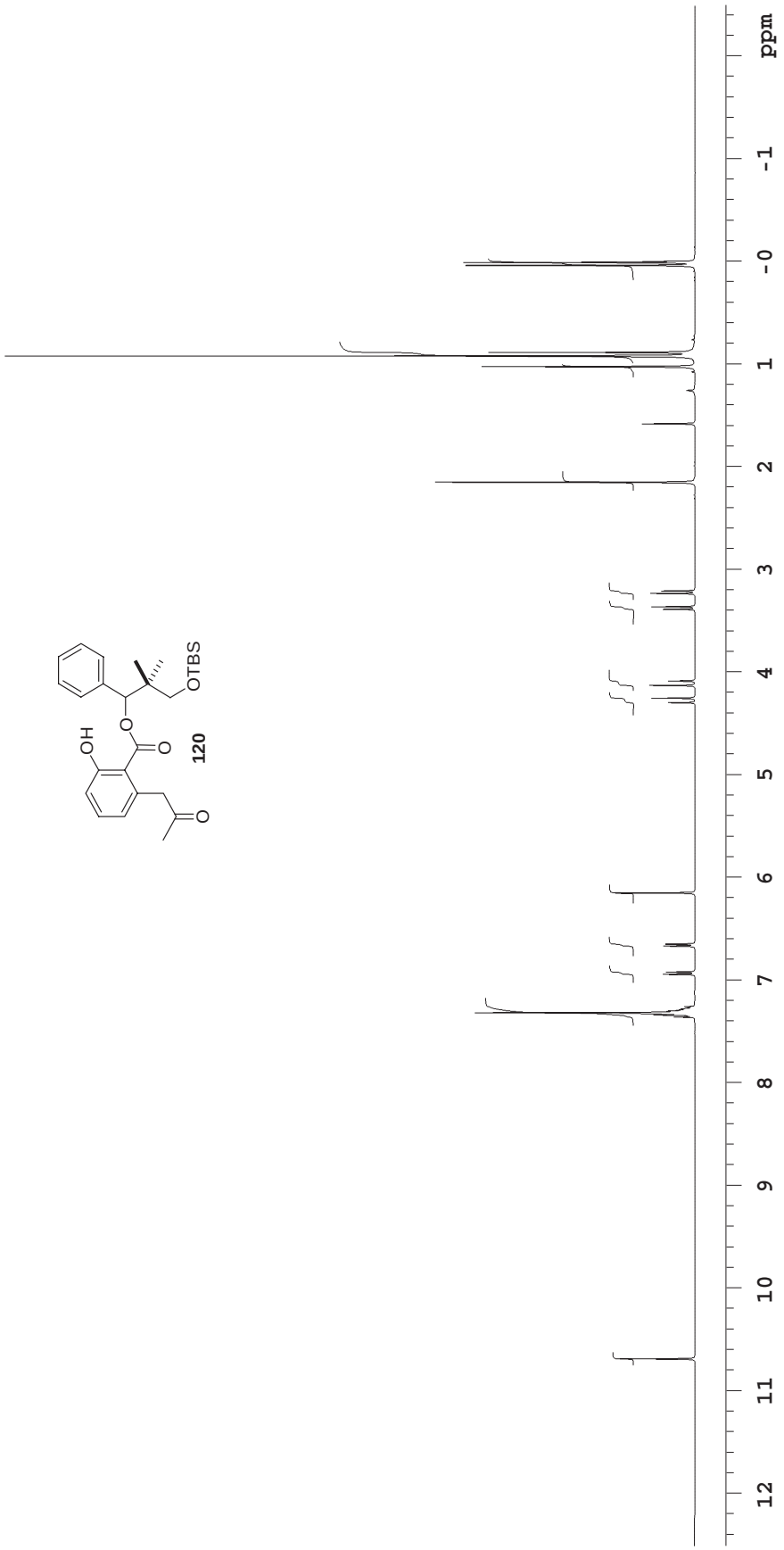
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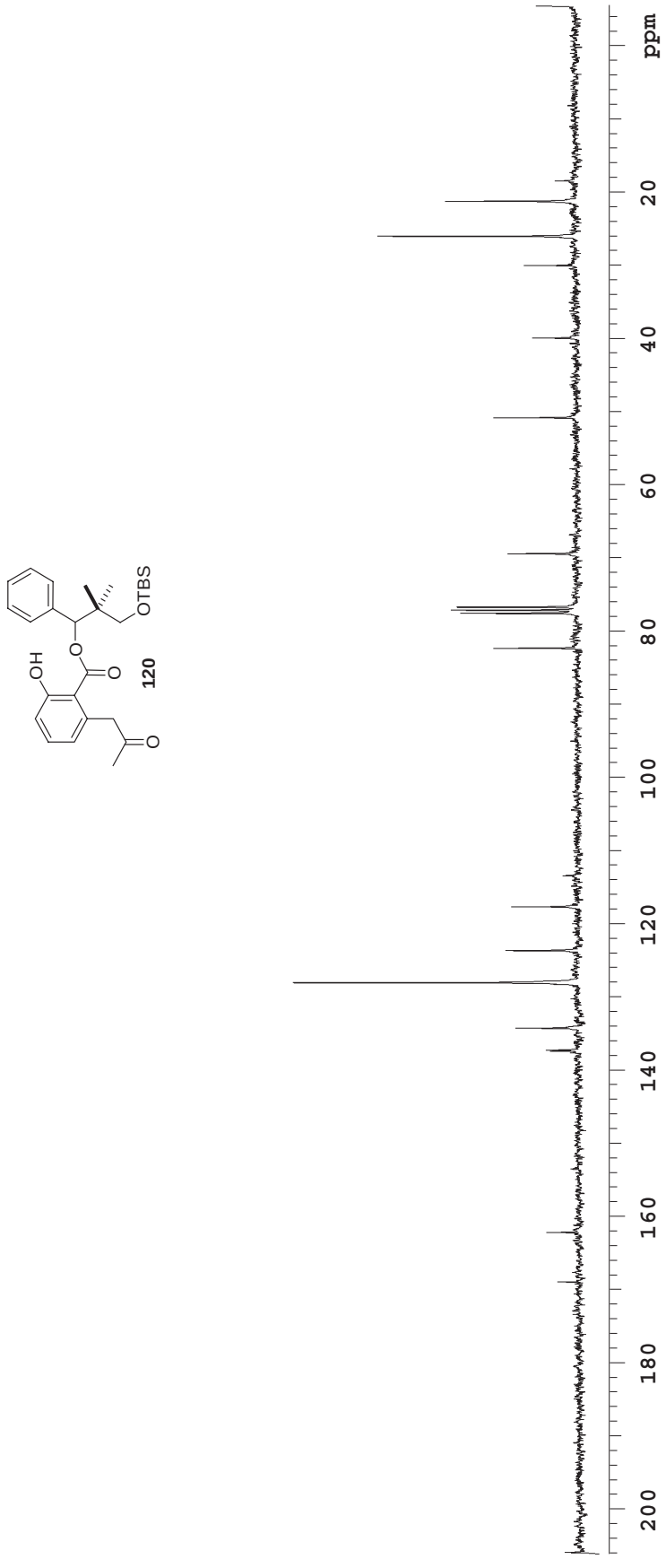
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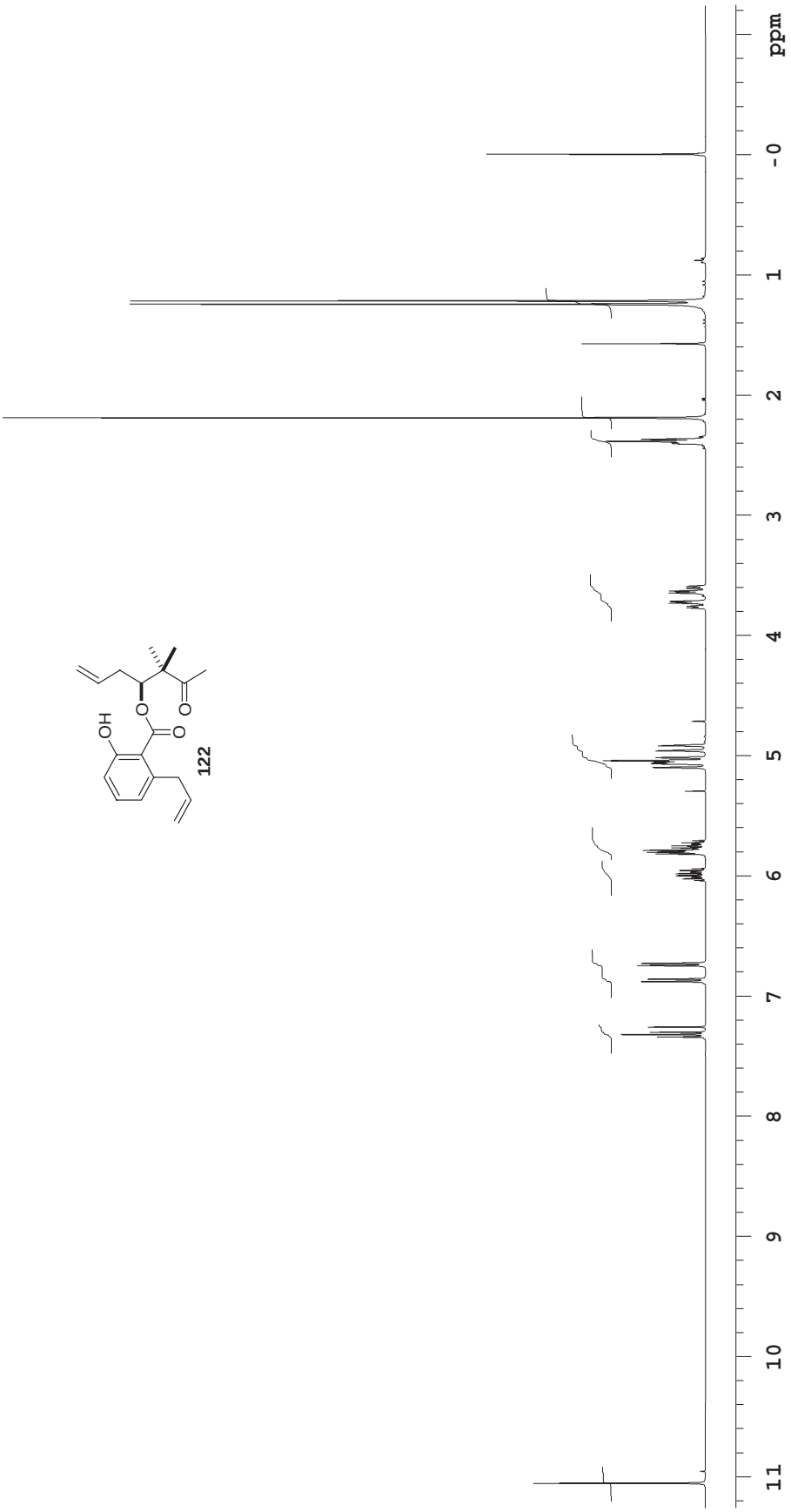
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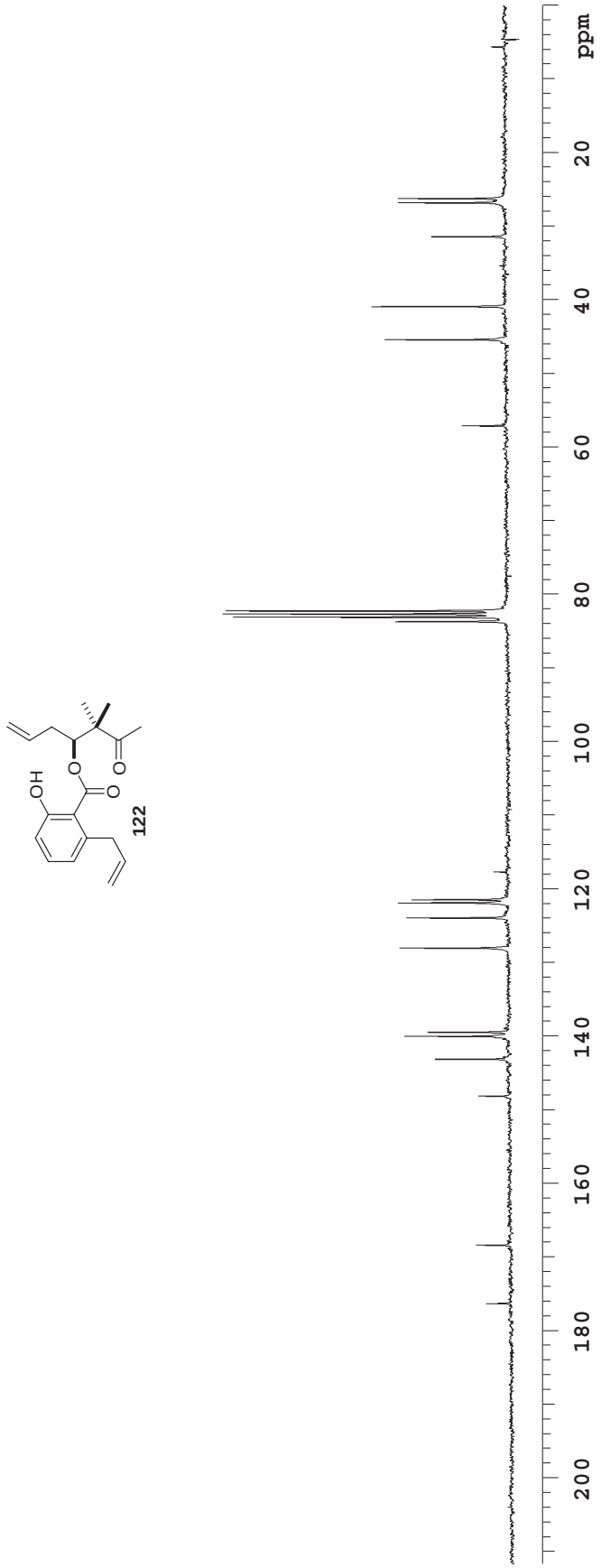
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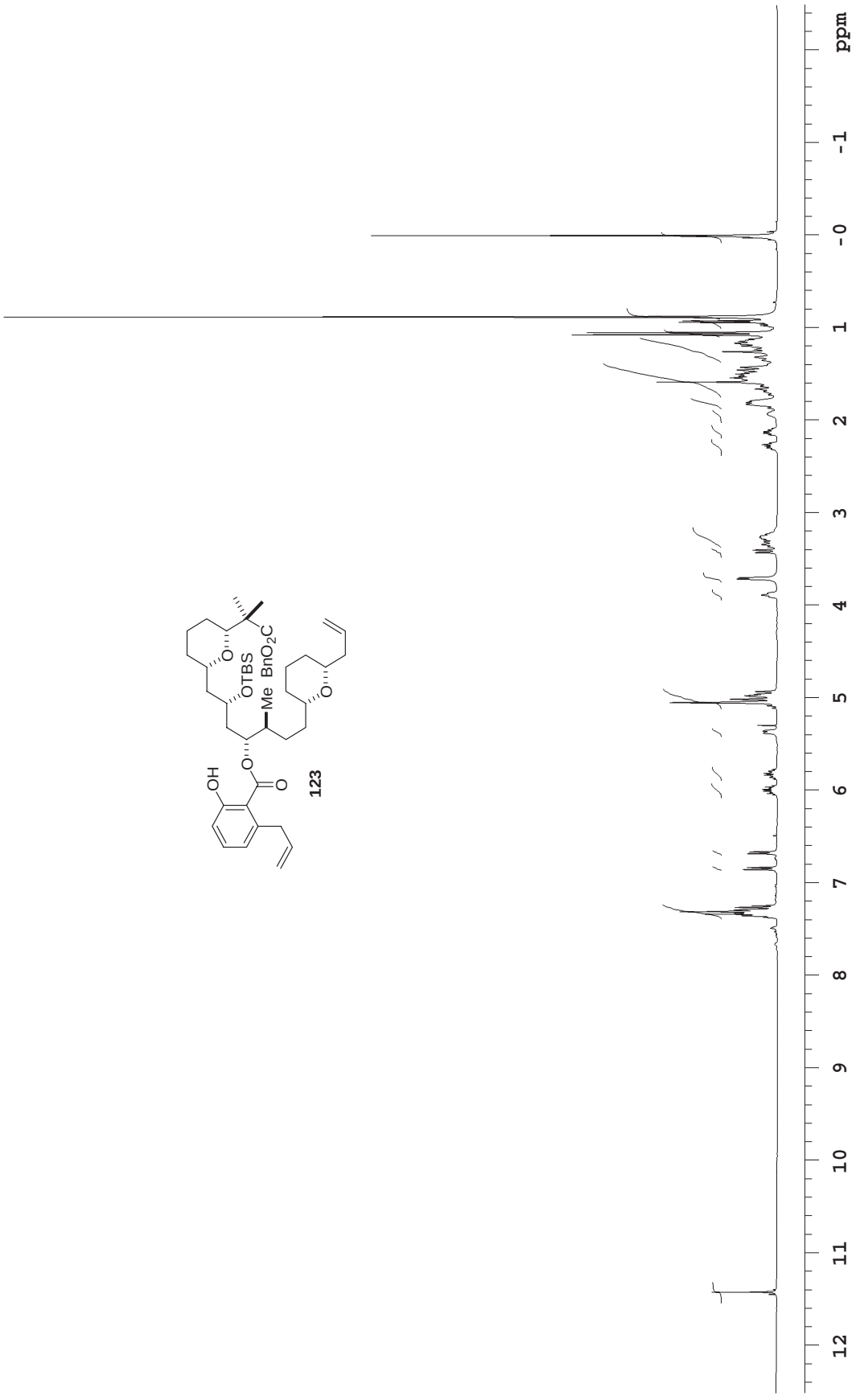
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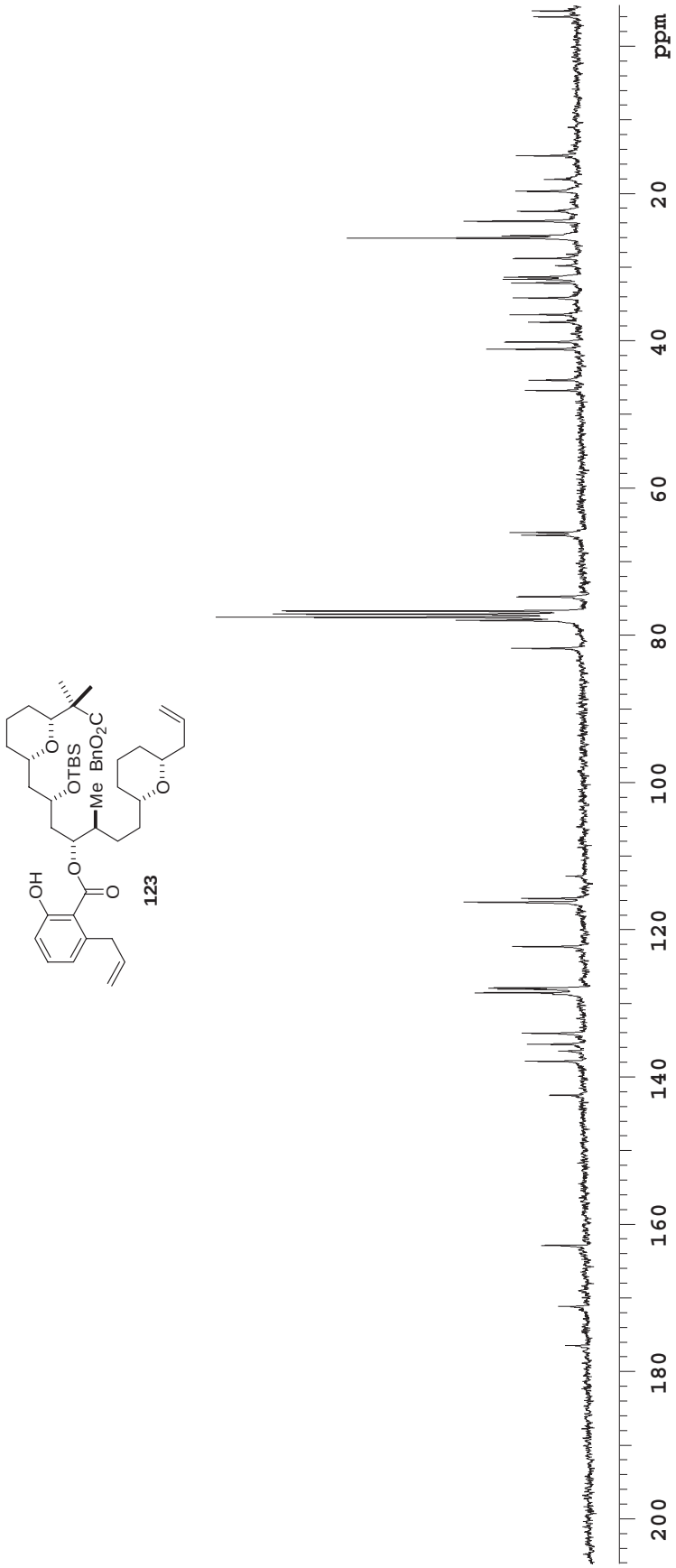
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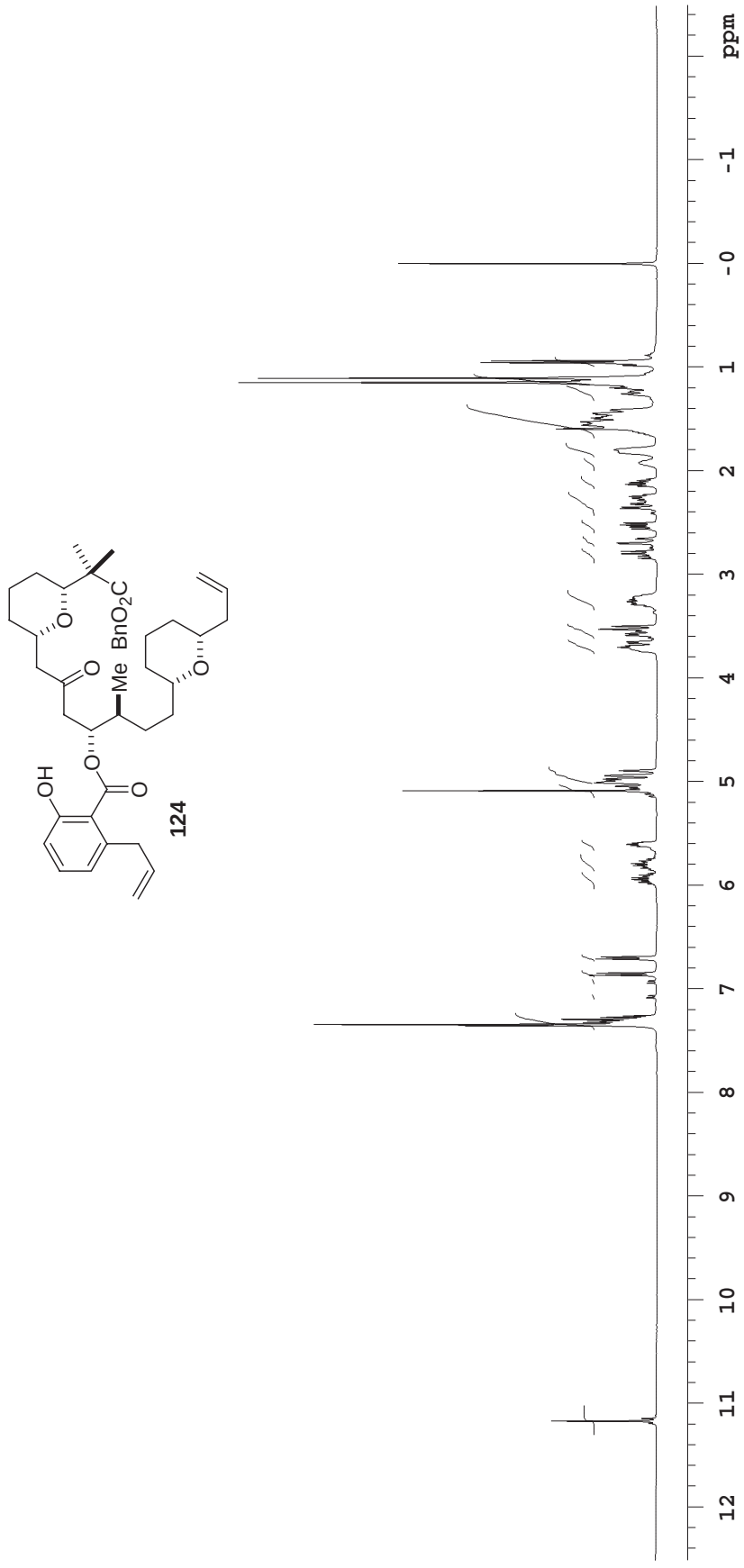
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BnO2C
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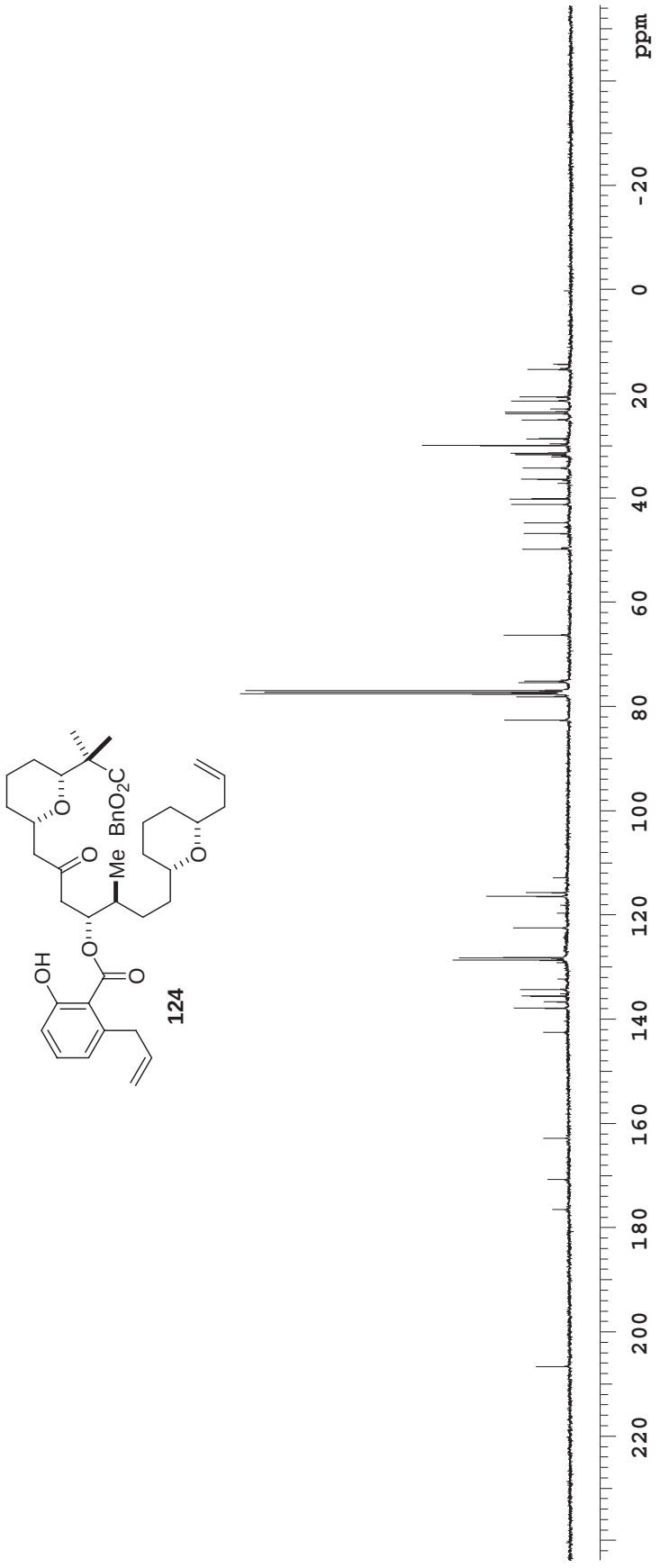
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O
O
O
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BnO2C
O
124
ppm
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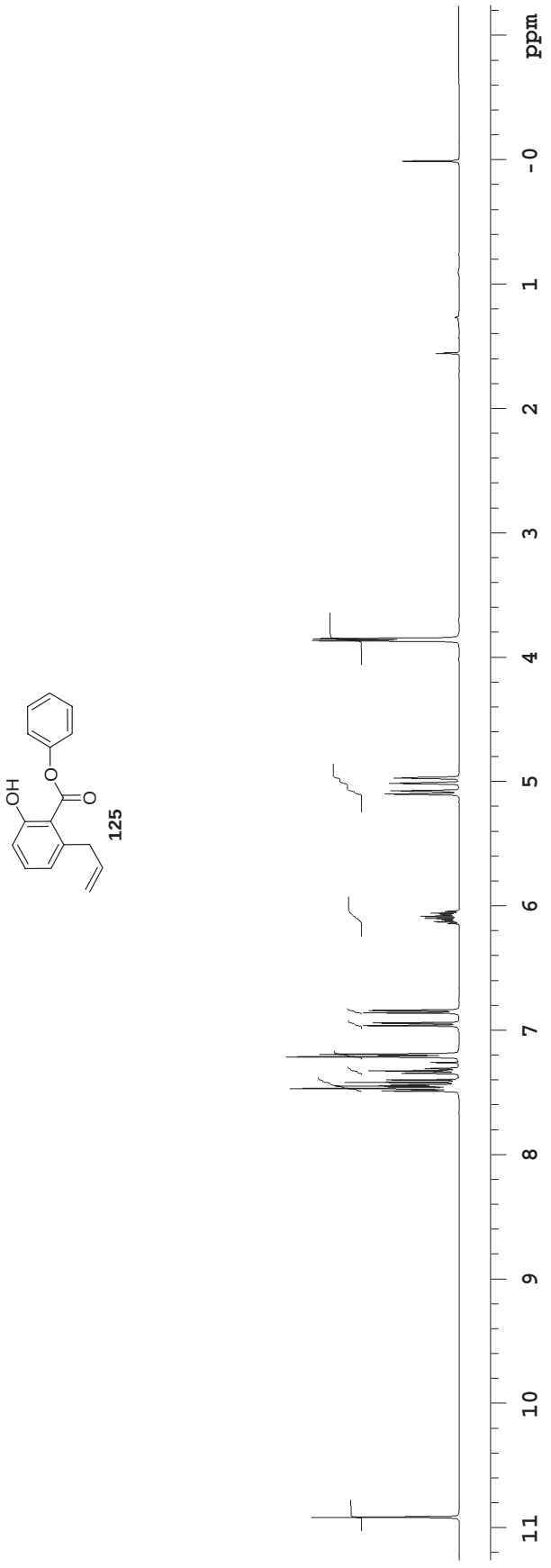
-20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ppm
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10
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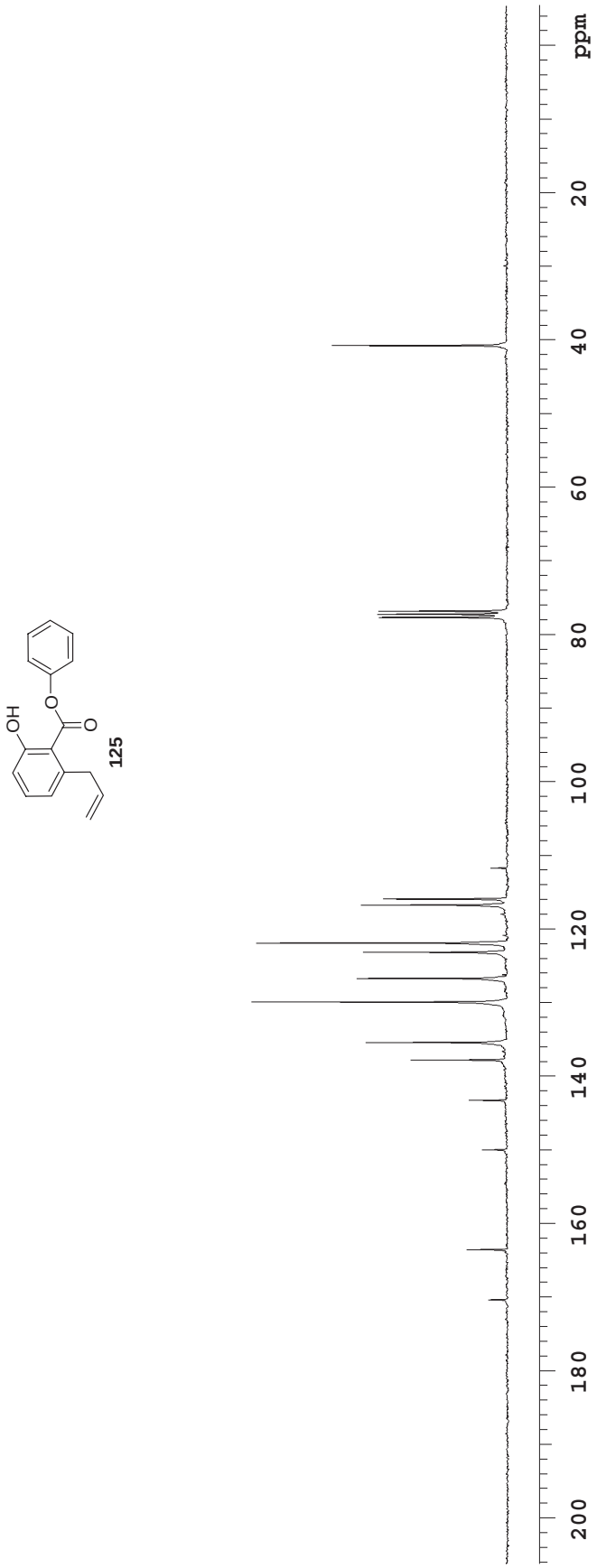
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O
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ppm
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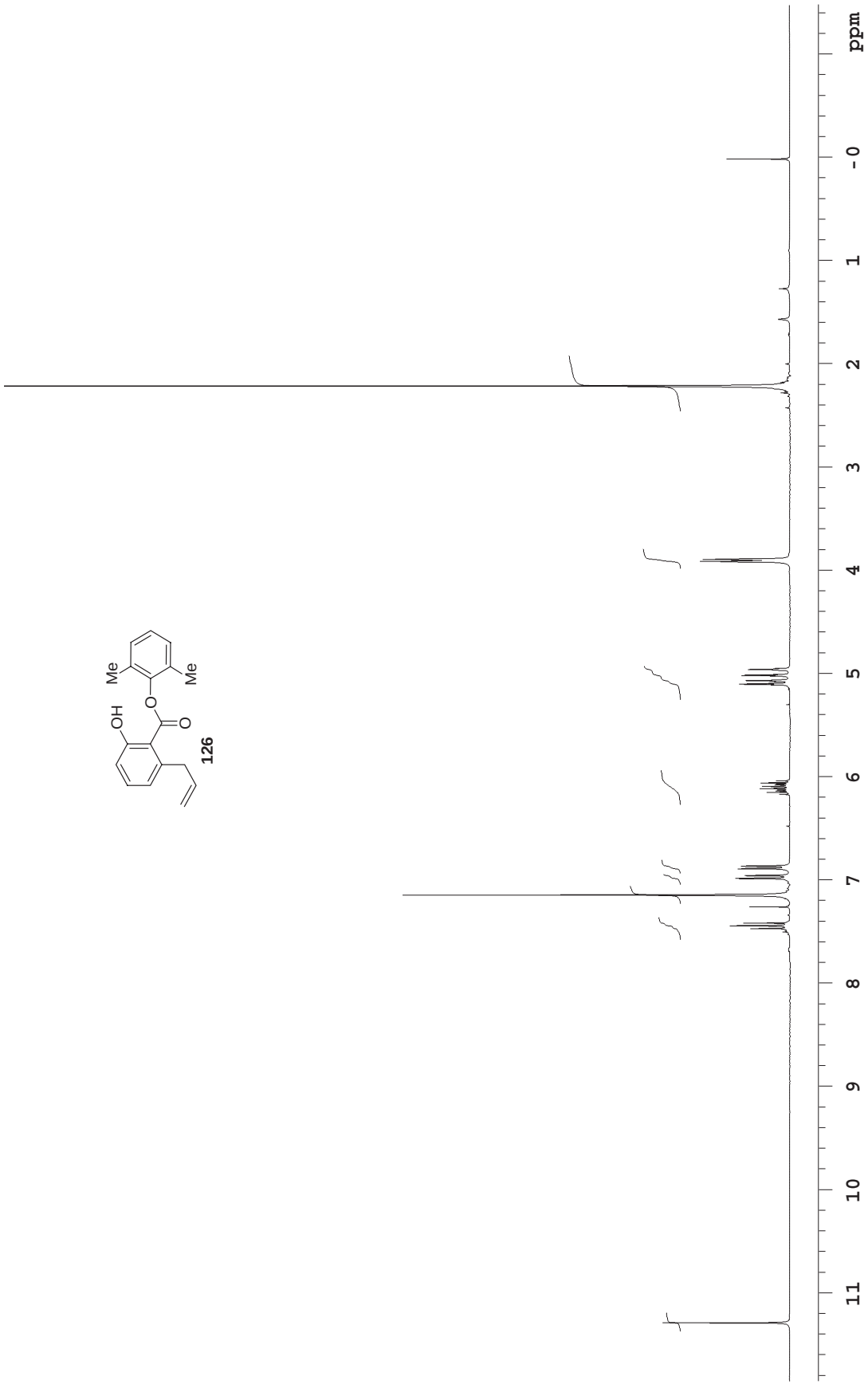
Me
Me
OH
O
O
126
ppm
-0
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2
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4
5
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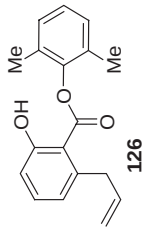
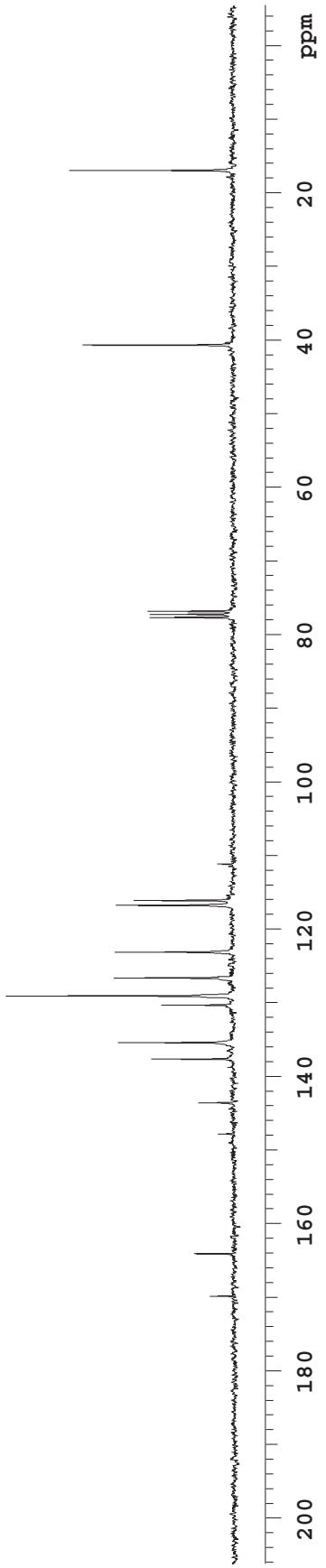
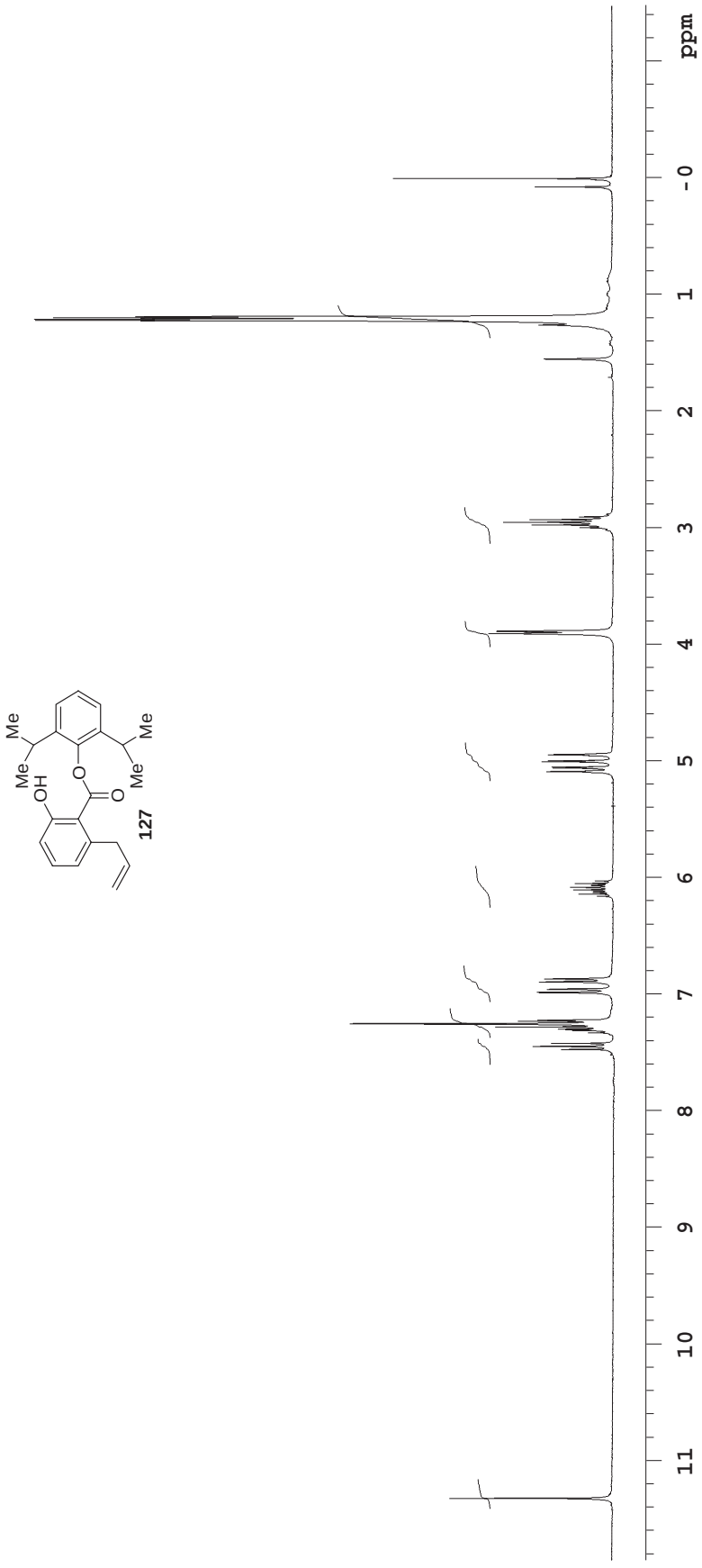
8
9
10
11



126




Me
Me
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O
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Me
Me
127
ppm
-0
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2
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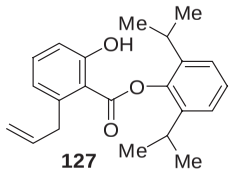
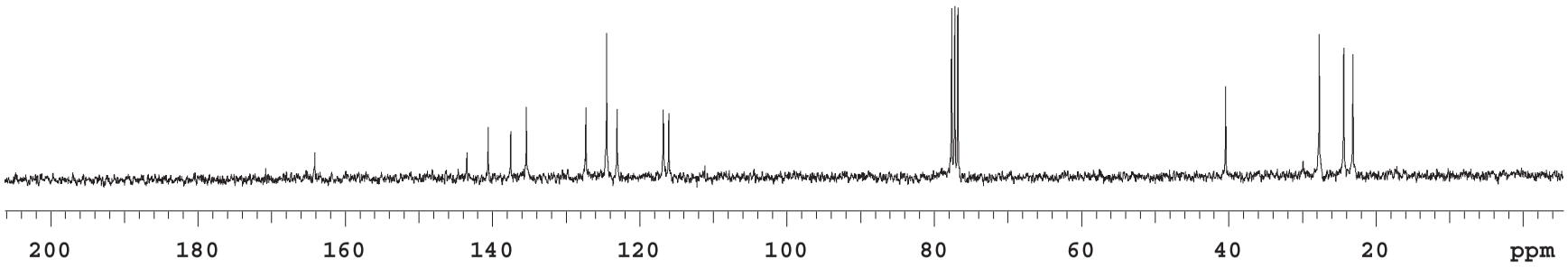
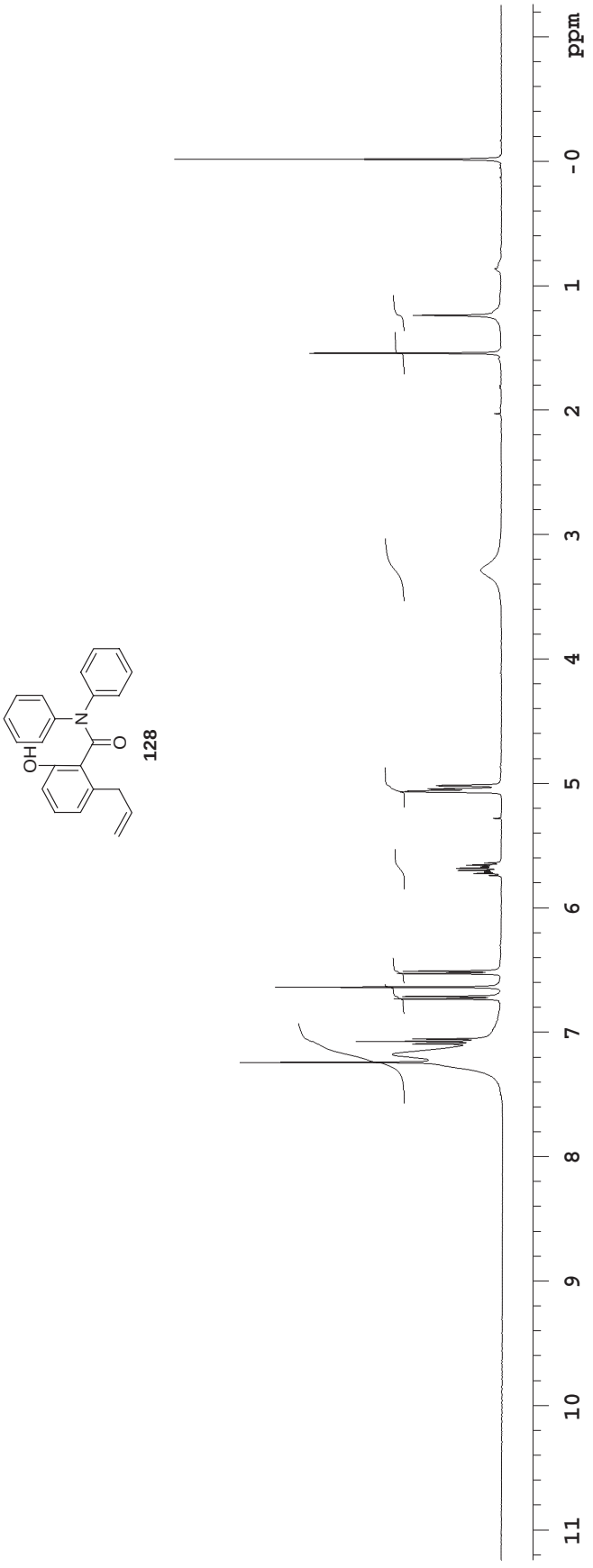
8
9
10
11



127

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128
ppm
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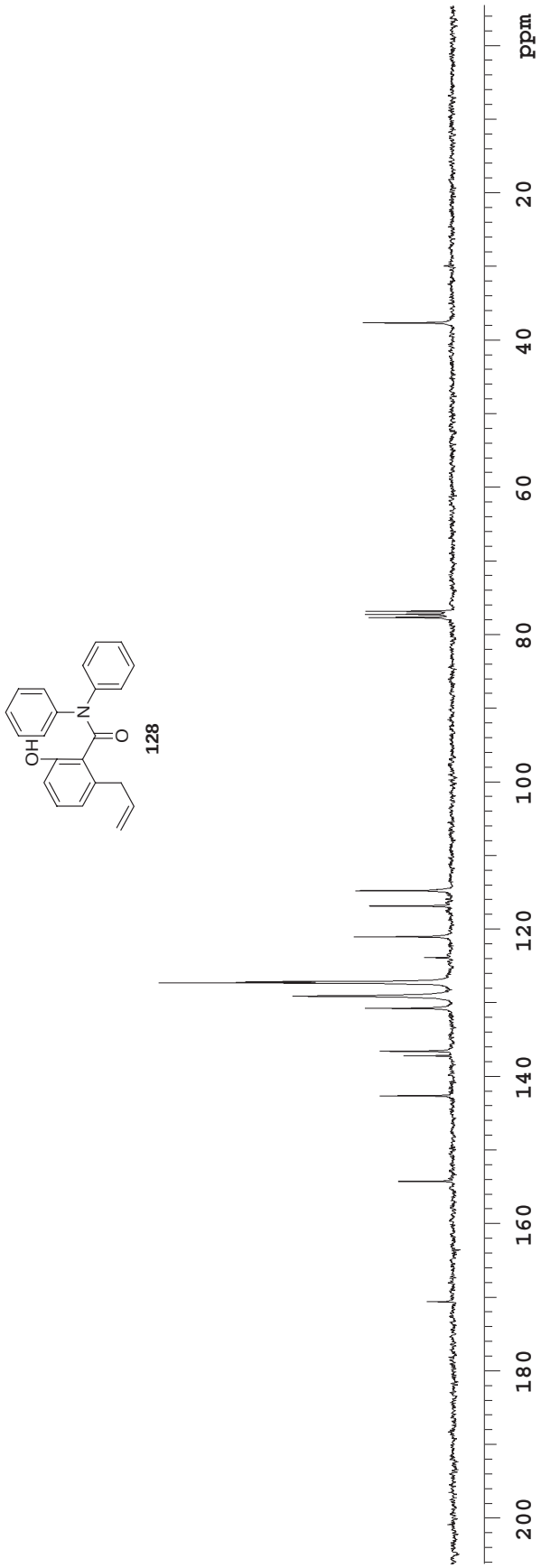
10
11


ppm
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200
OH
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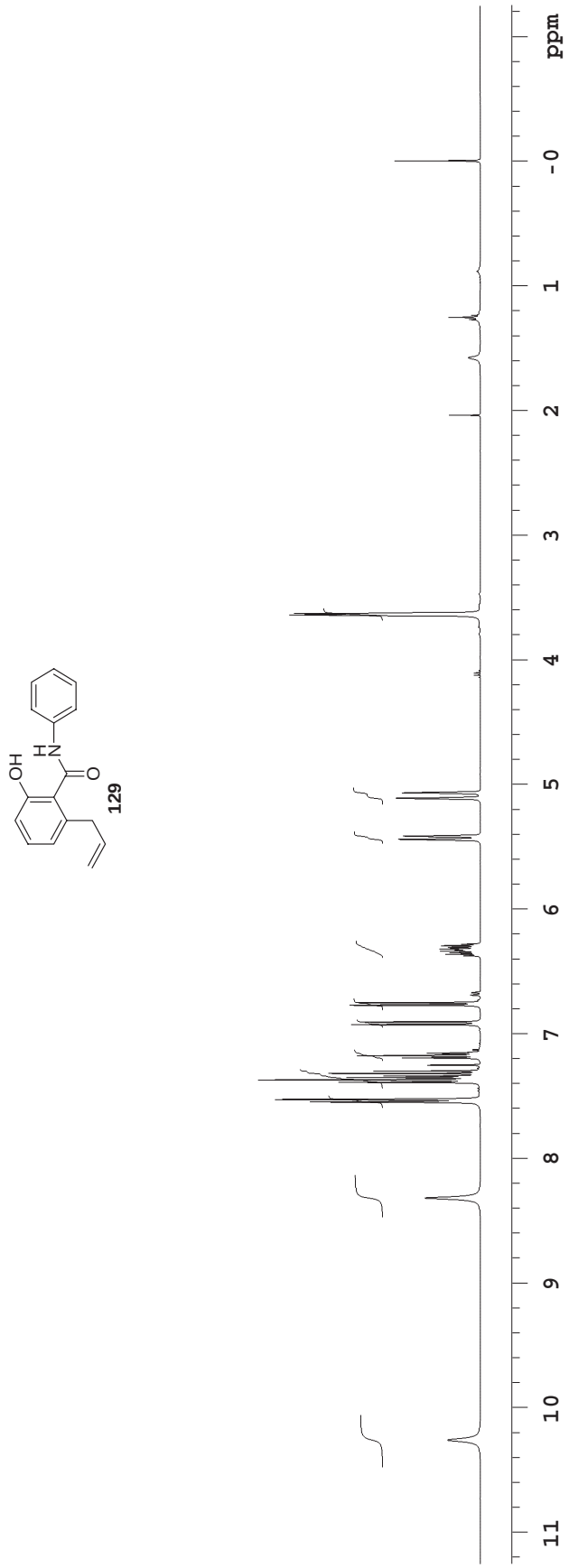
O
128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10
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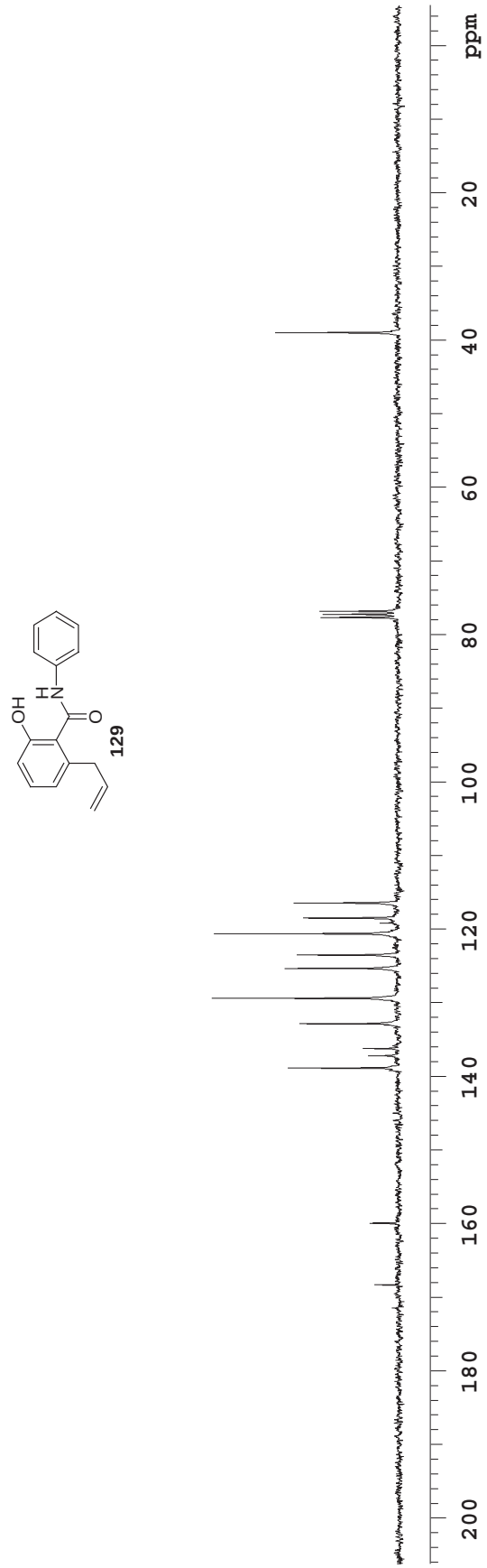
OH
H
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O
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ppm
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40
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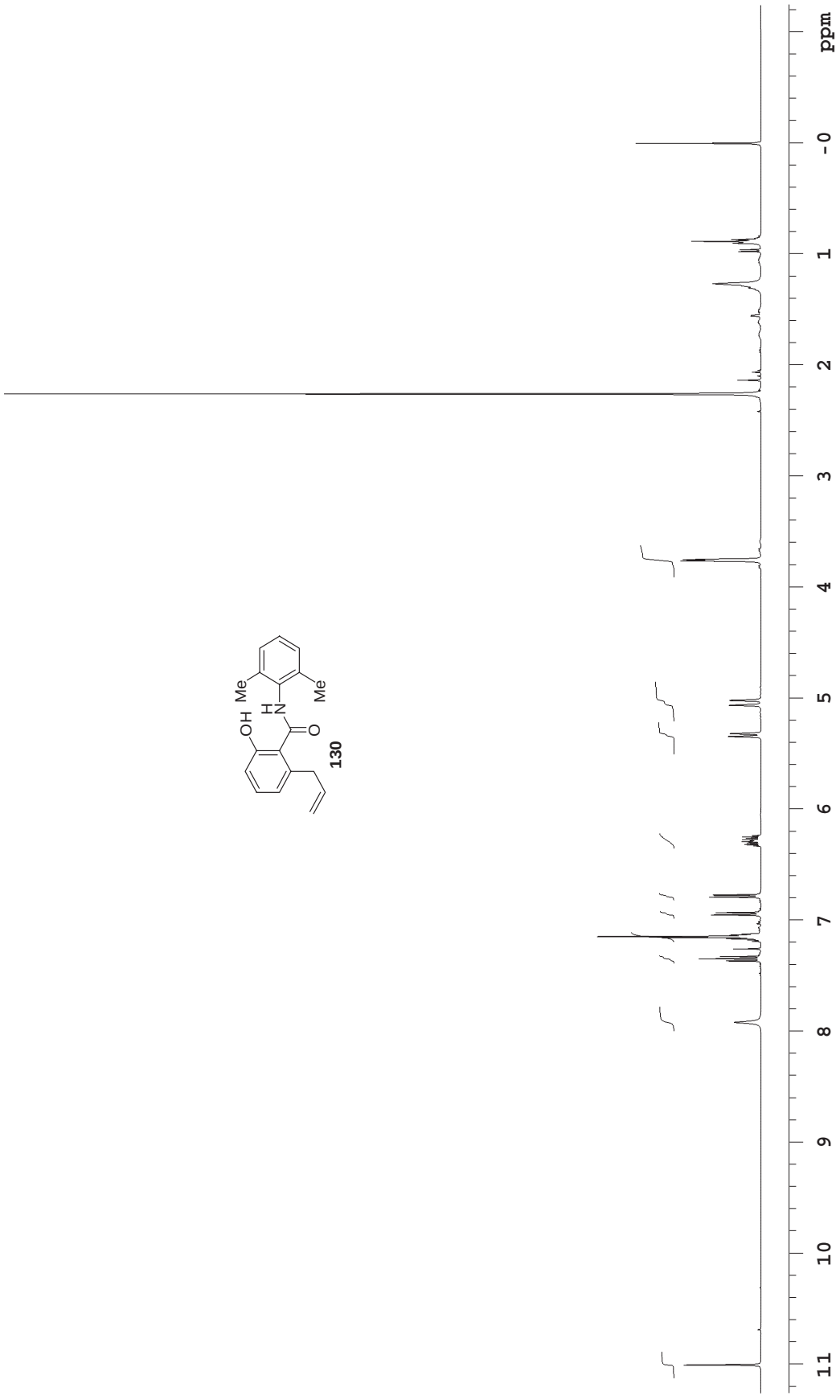
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10
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8
7
6
5
4
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2
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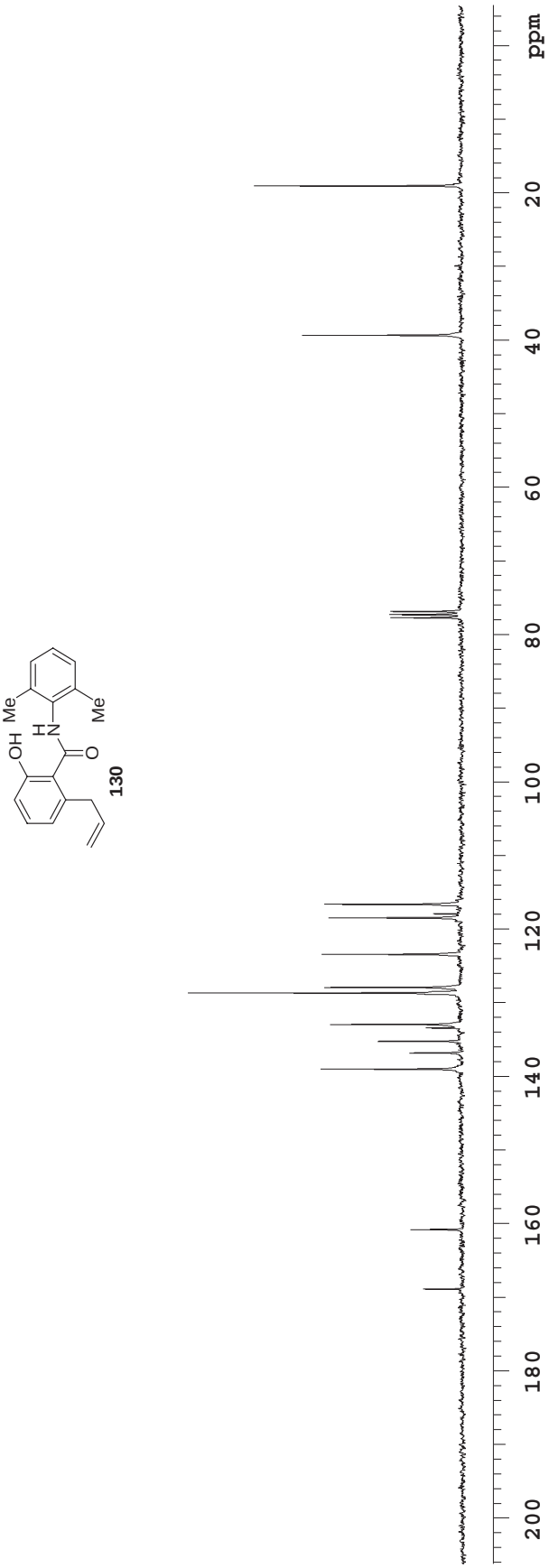
-0
Me
H
N
OH
O
Me
130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OH
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Me
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ppm
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60
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100
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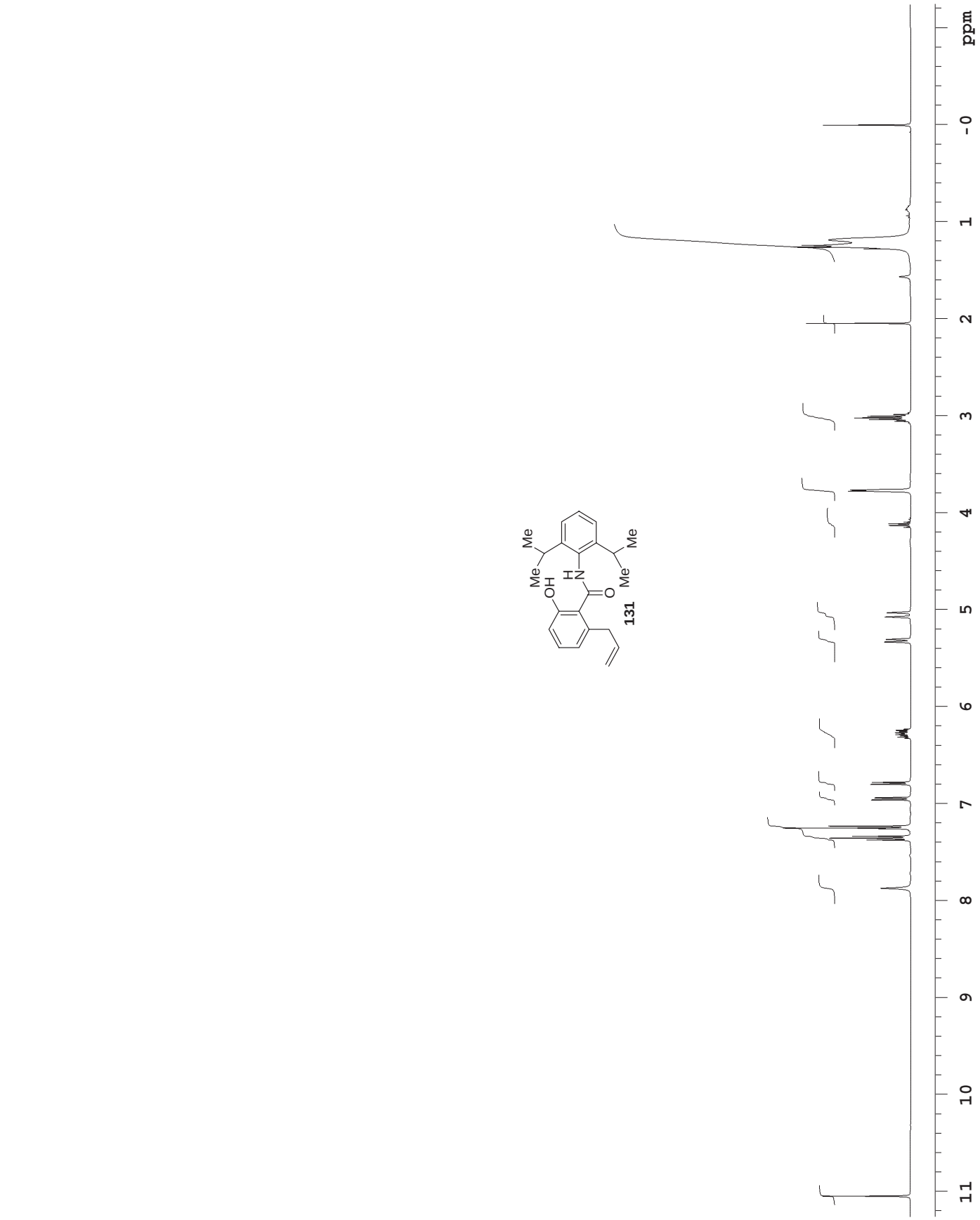
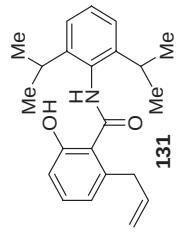
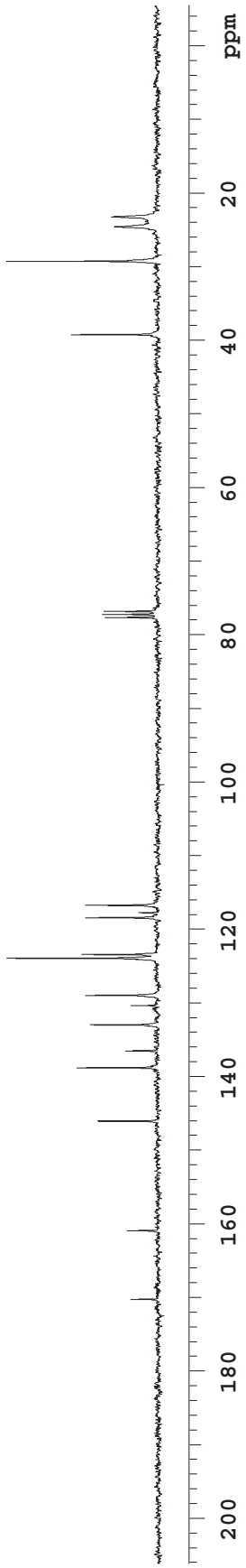
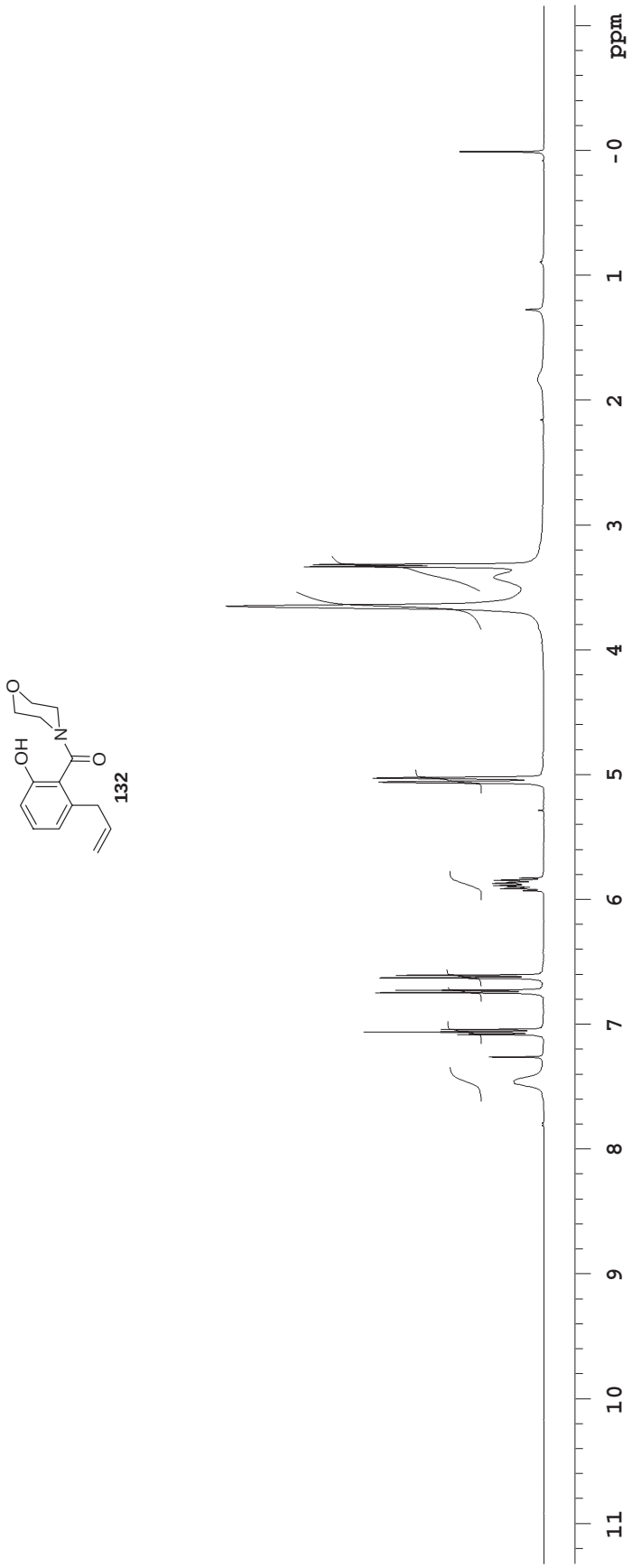
180
200


Me
Me
OH
H
N
O
Me
Me
131
ppm
-0
1
2
3
4
5
6
7
8
9
10
11



131

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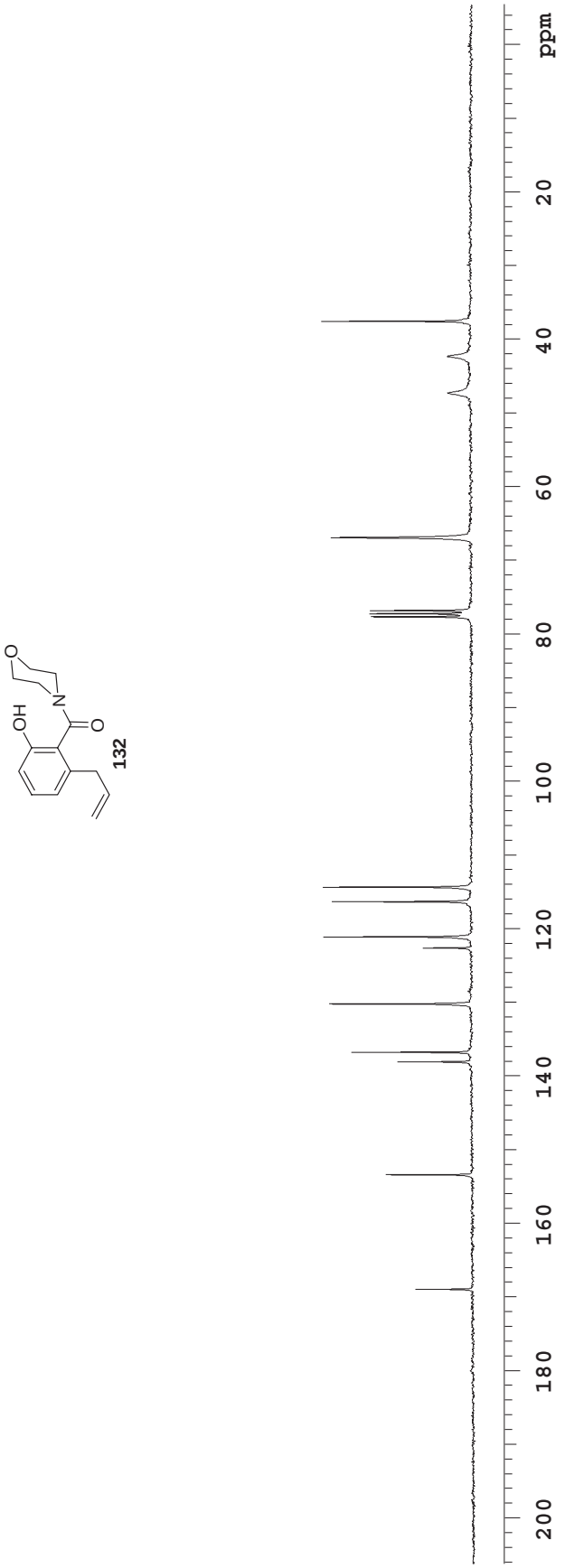
8
9
10
11
OH
O
N
O
132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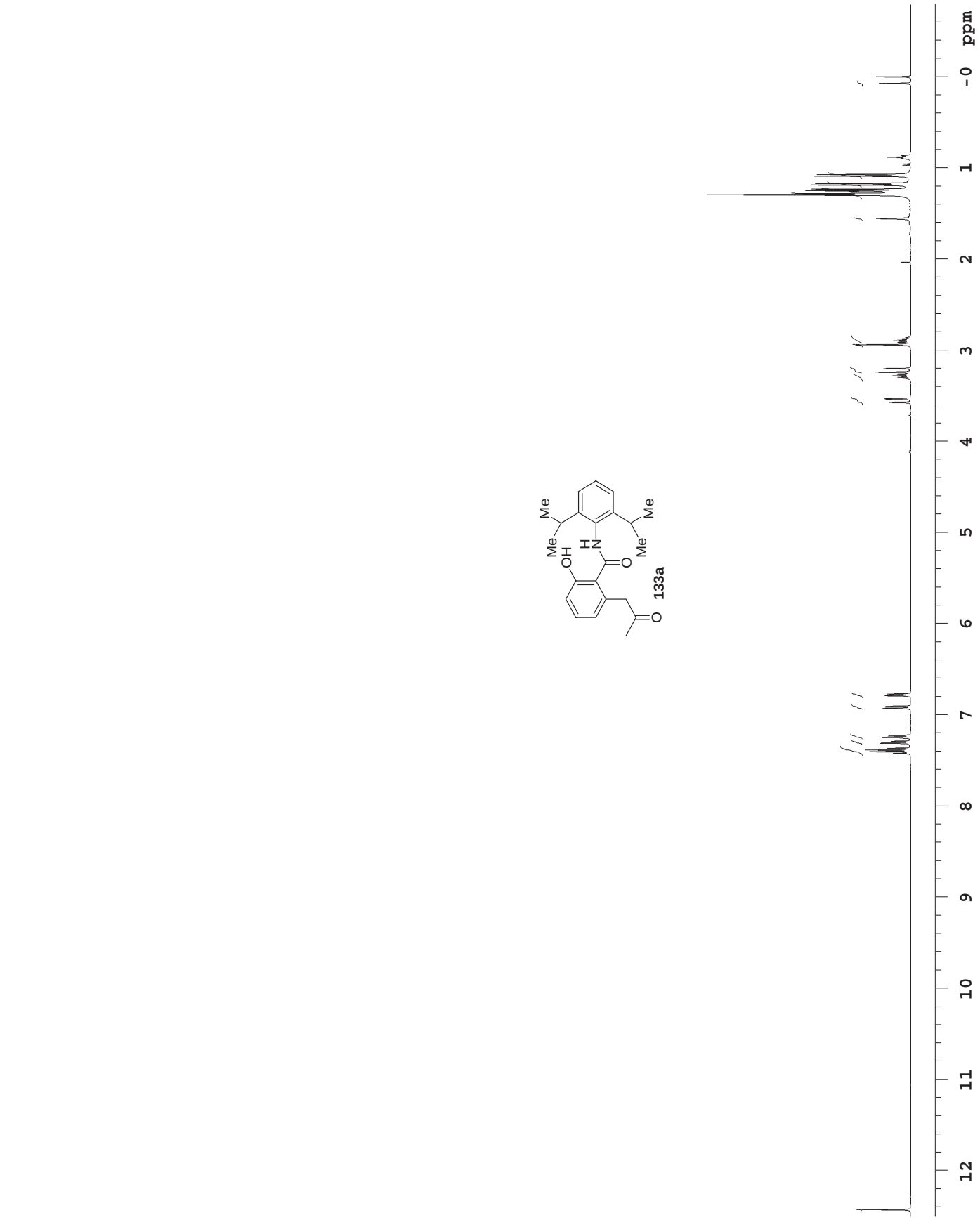
Me
Me
OH
H
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O
Me
Me
O
133a
ppm
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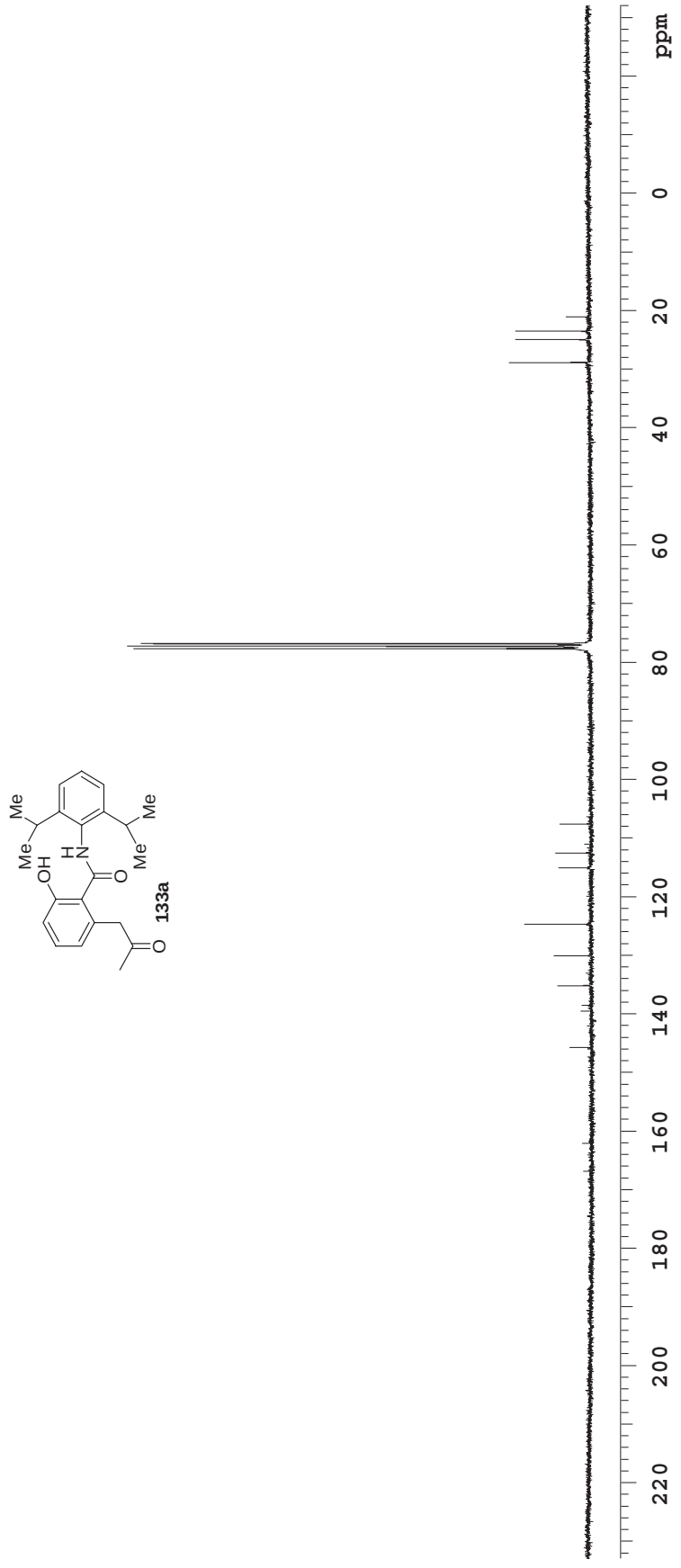
1
2
3
4
5
6
7
8
9
10
11
12


Me
Me
OH
H
N
O
Me
Me
O
133a
ppm
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200
180
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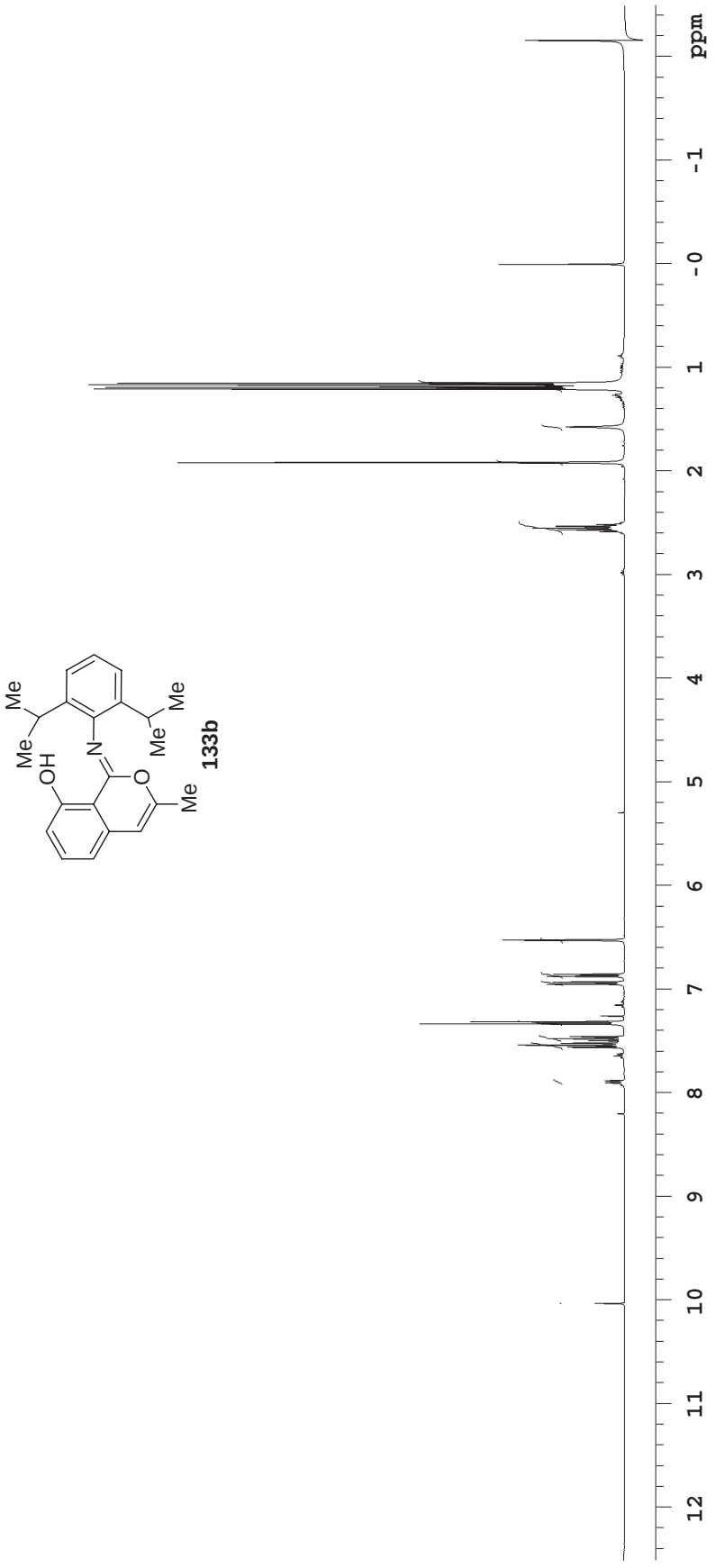
140
120
100
80
60
40
20
0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Me
Me
Me
N
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Me
133b
ppm
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10
9
8
7
6
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4
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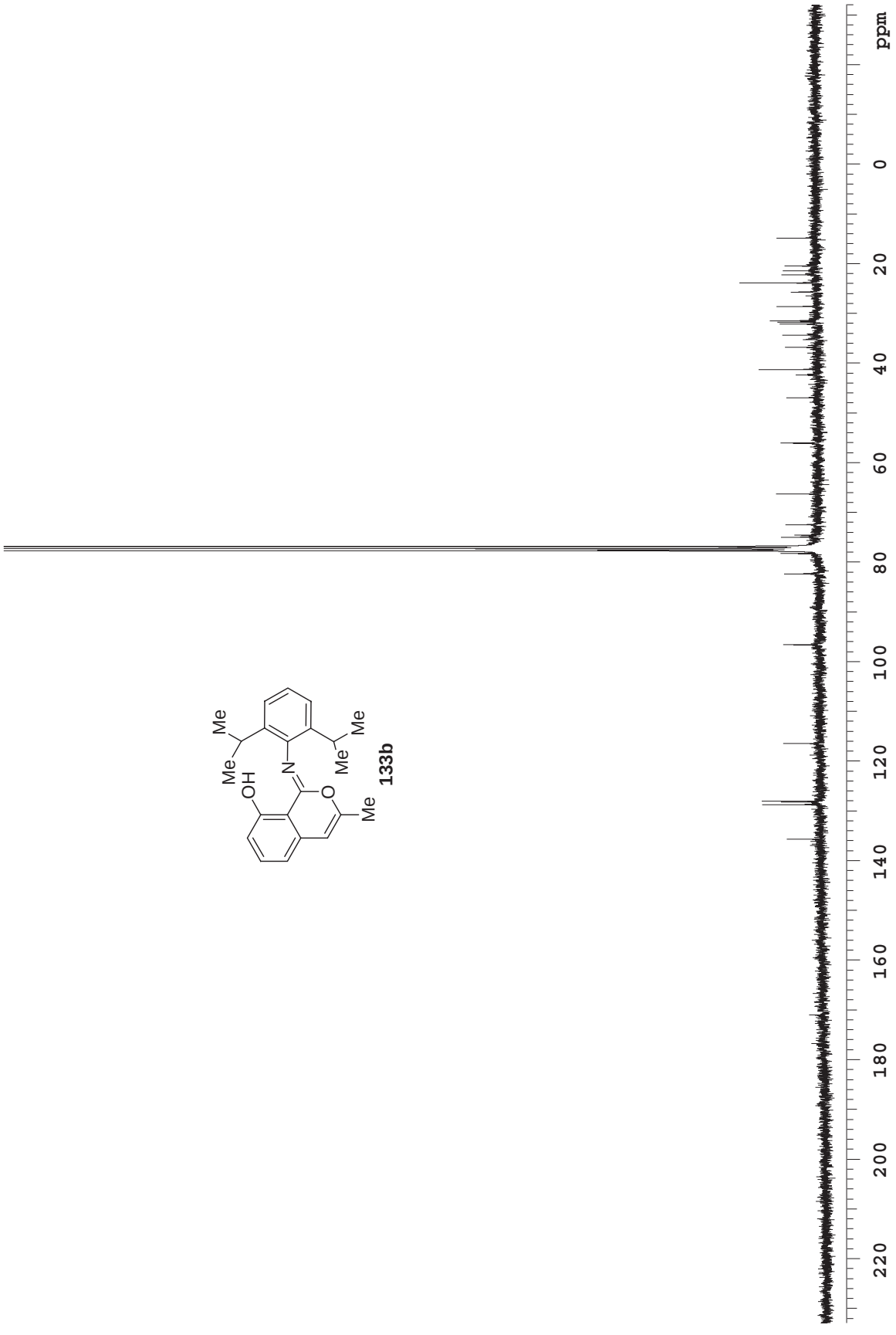
2
1
-0
-1


Me
Me
Me
Me
OH
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O
Me
133b
ppm
0
20
40
60
80
100
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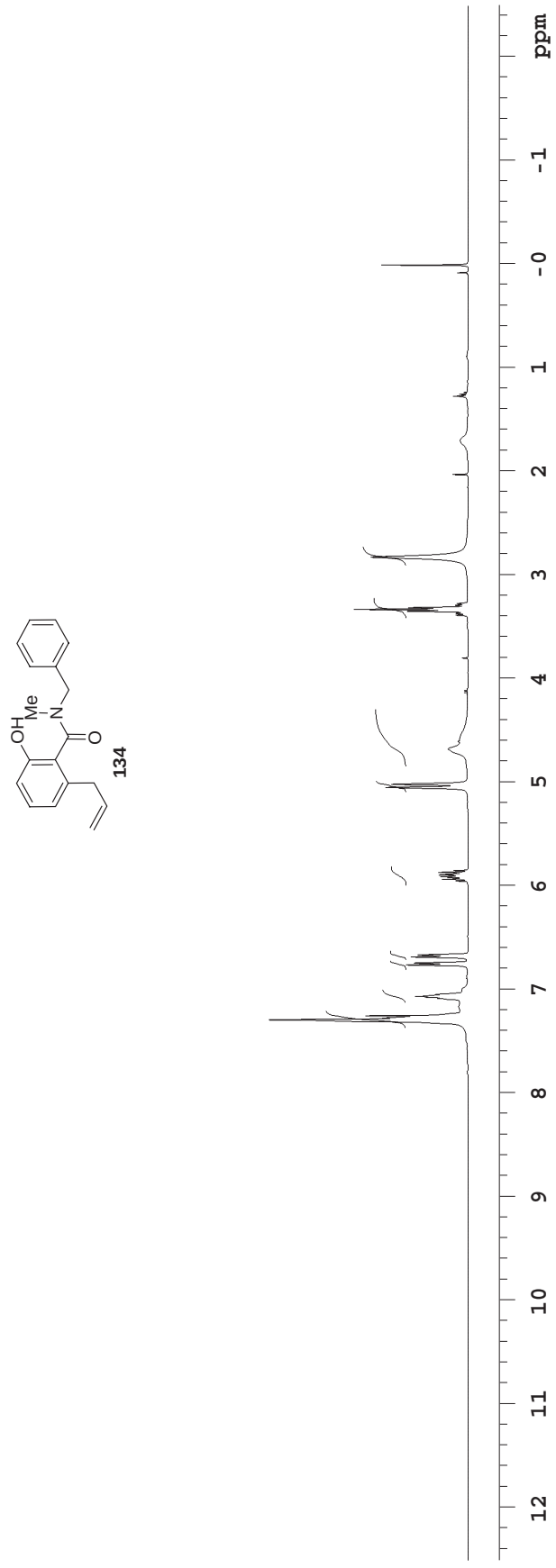
140
160
180
200
220


OH
Me
N
O
134
ppm
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11
10
9
8
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6
5
4
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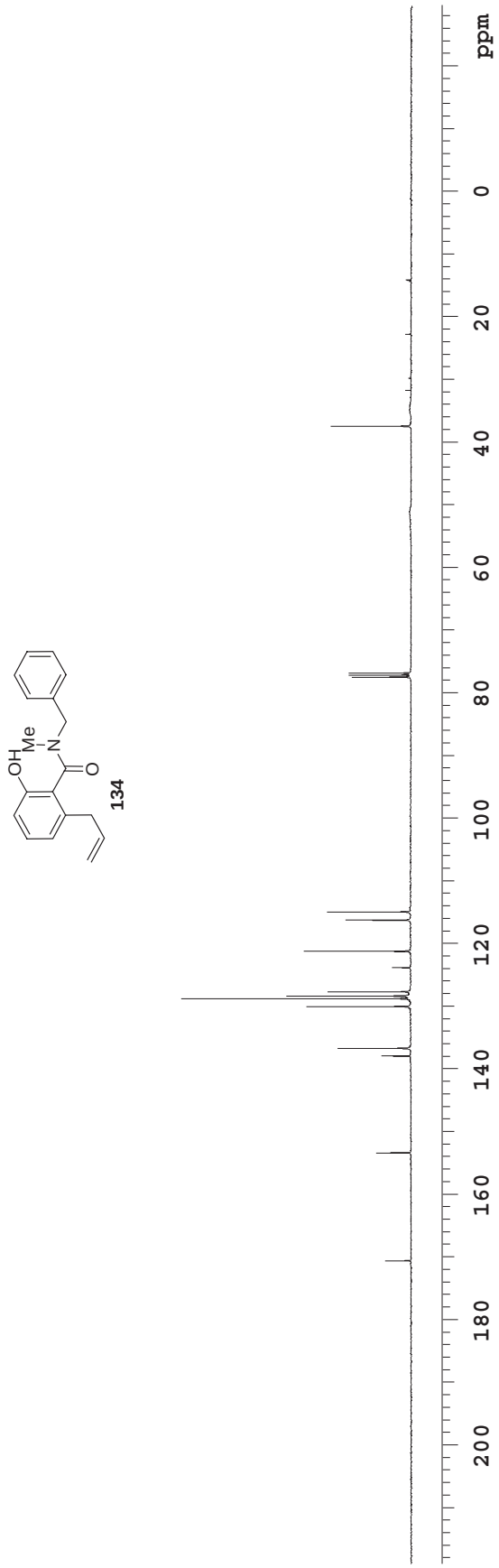
2
1
-0
-1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Me
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O
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ppm
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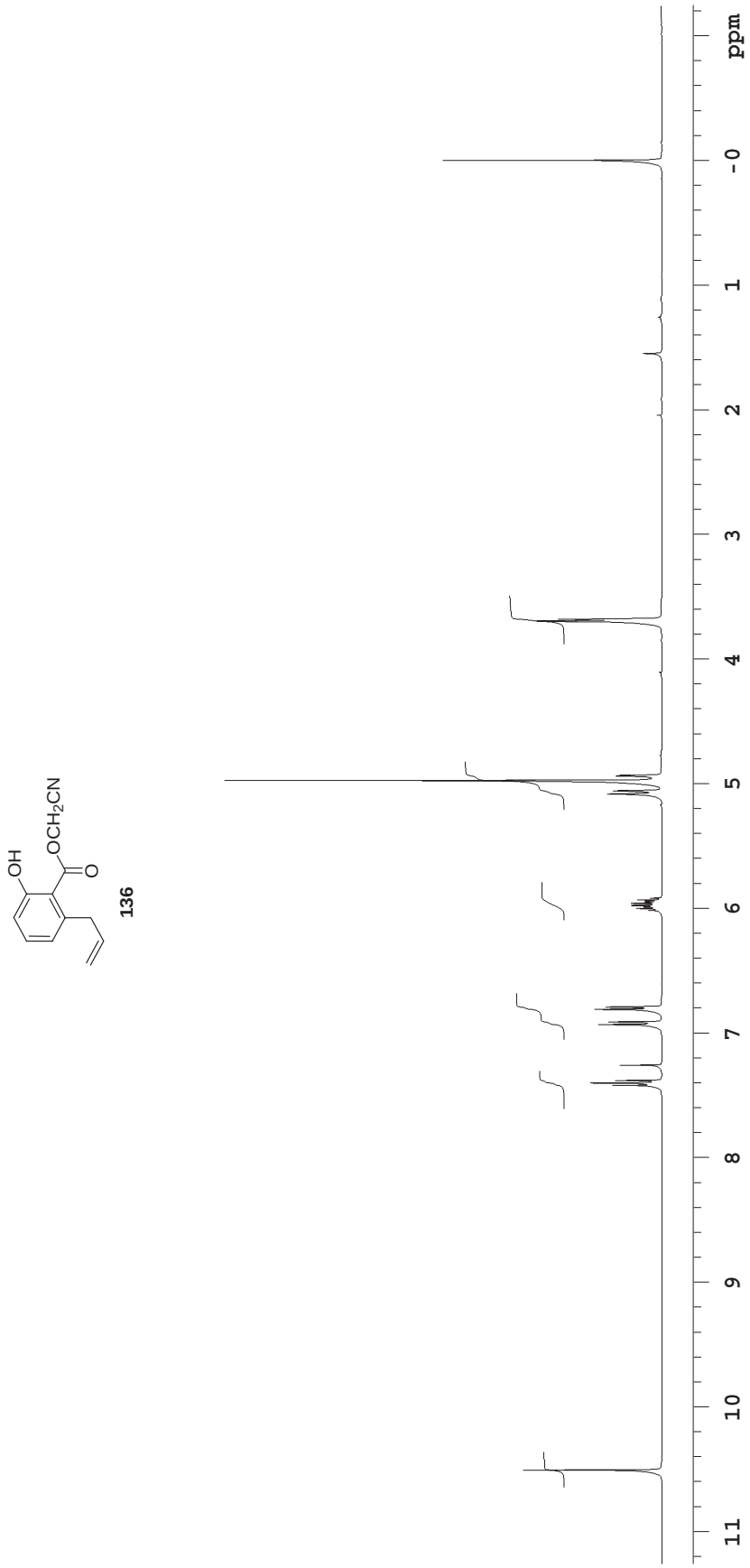
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136
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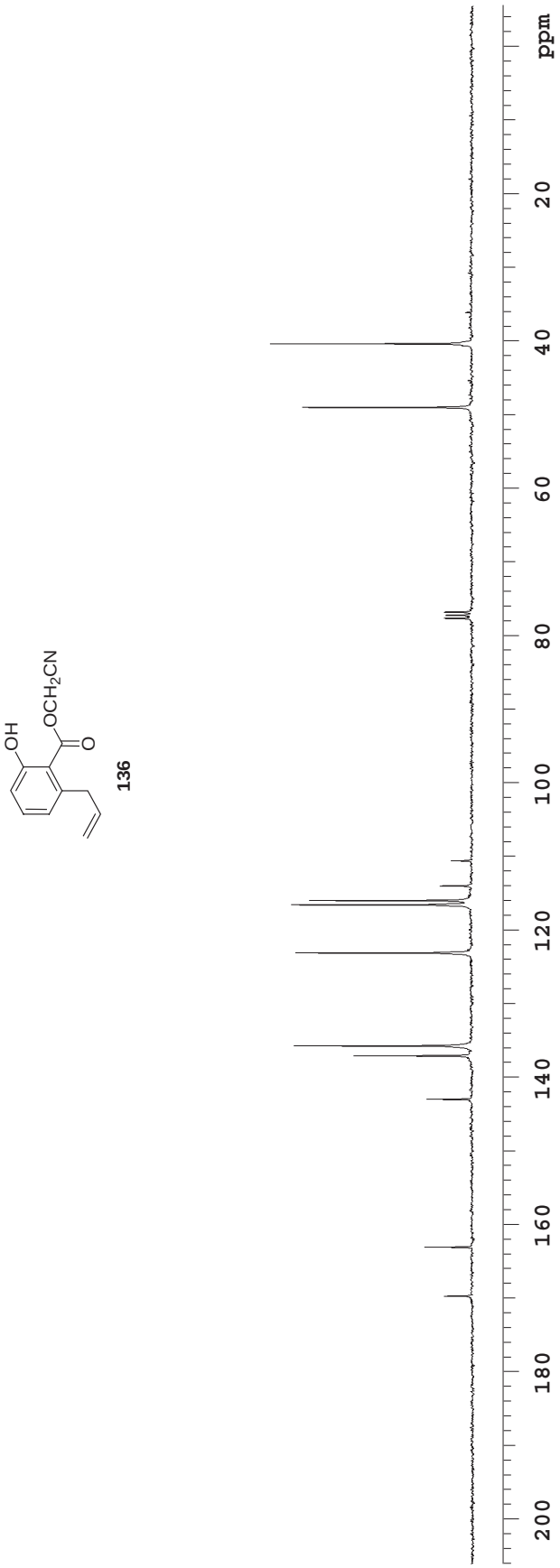
8
9
10
11


OH
OCH2CN
O
136
ppm
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140
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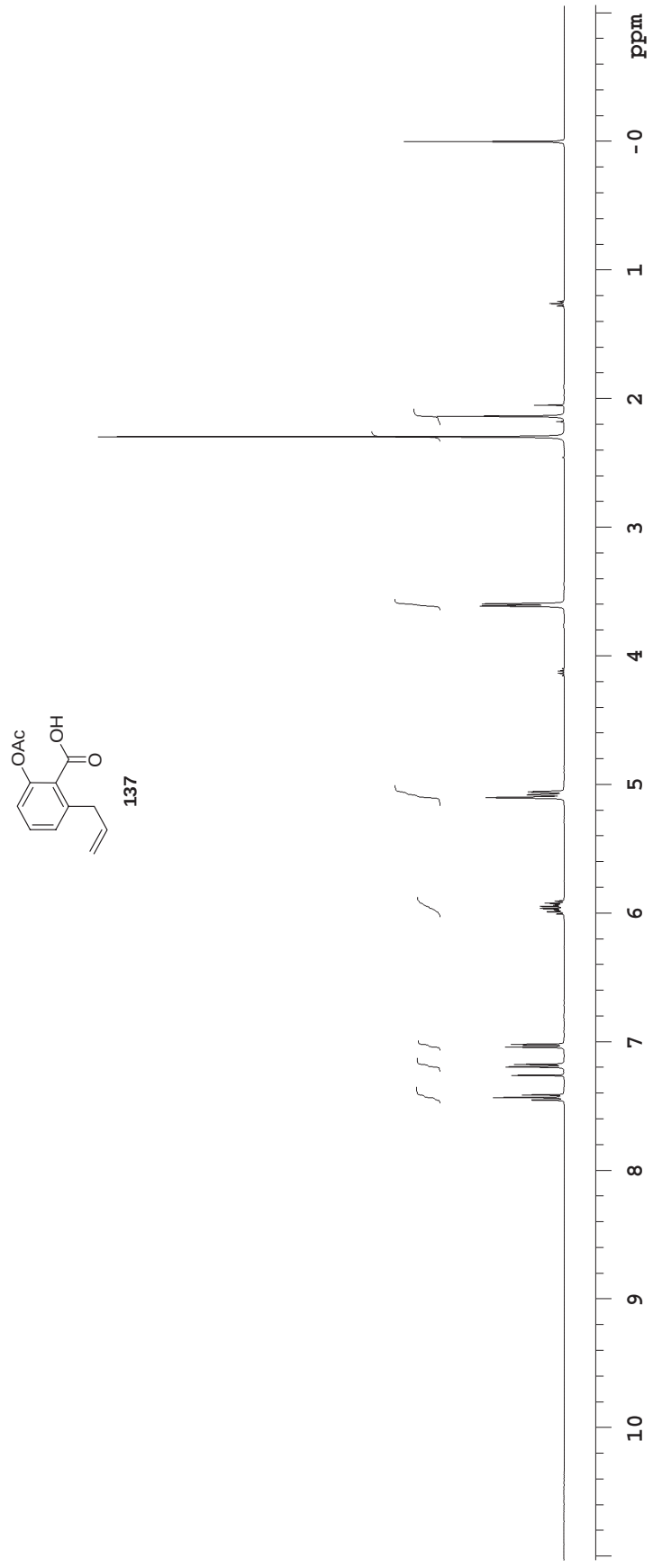
80
60
40
20


OAc
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ppm
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3
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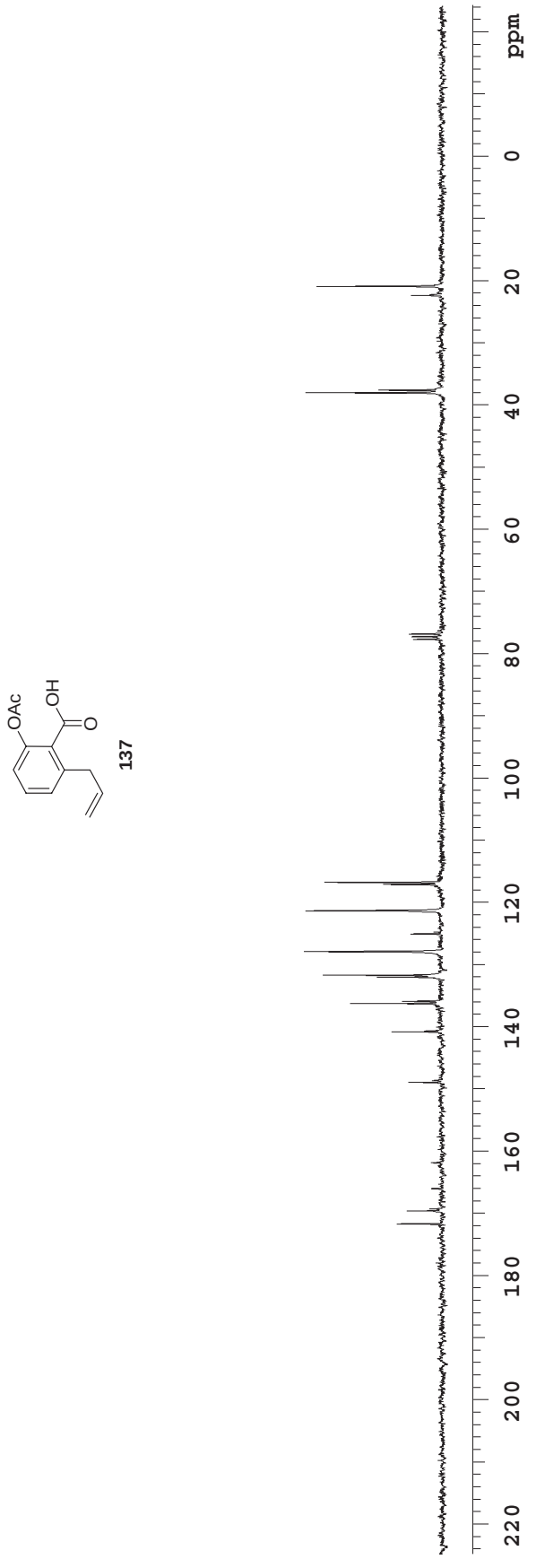
1
0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OH
O
137
ppm
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140
120
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60
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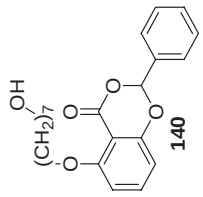
20
0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(CH2)7
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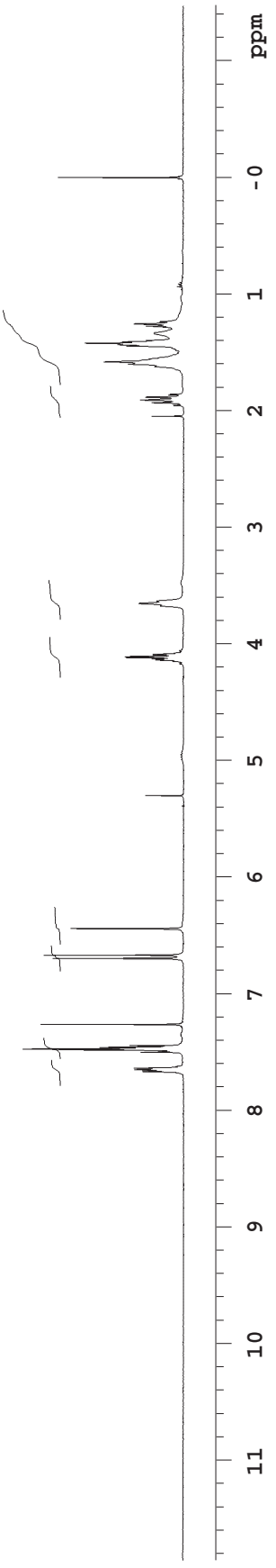
O
O
O
-
140


ppm
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2
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4
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8
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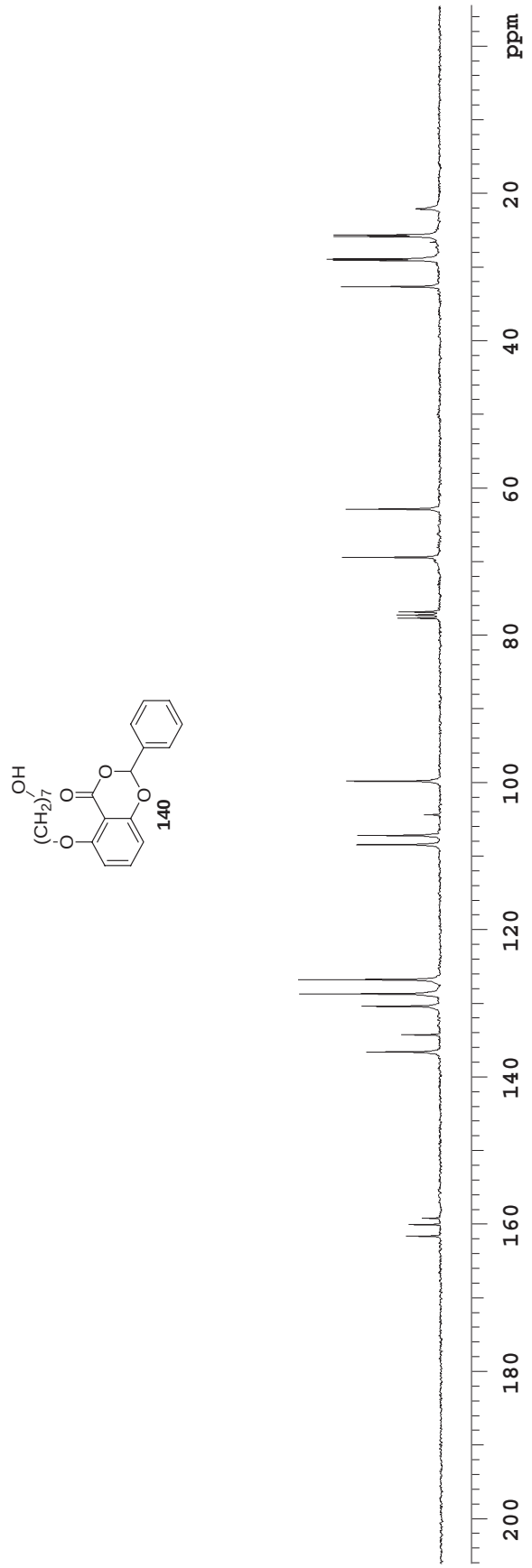
10
11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(CH2)7
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O
O
O
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ppm
200
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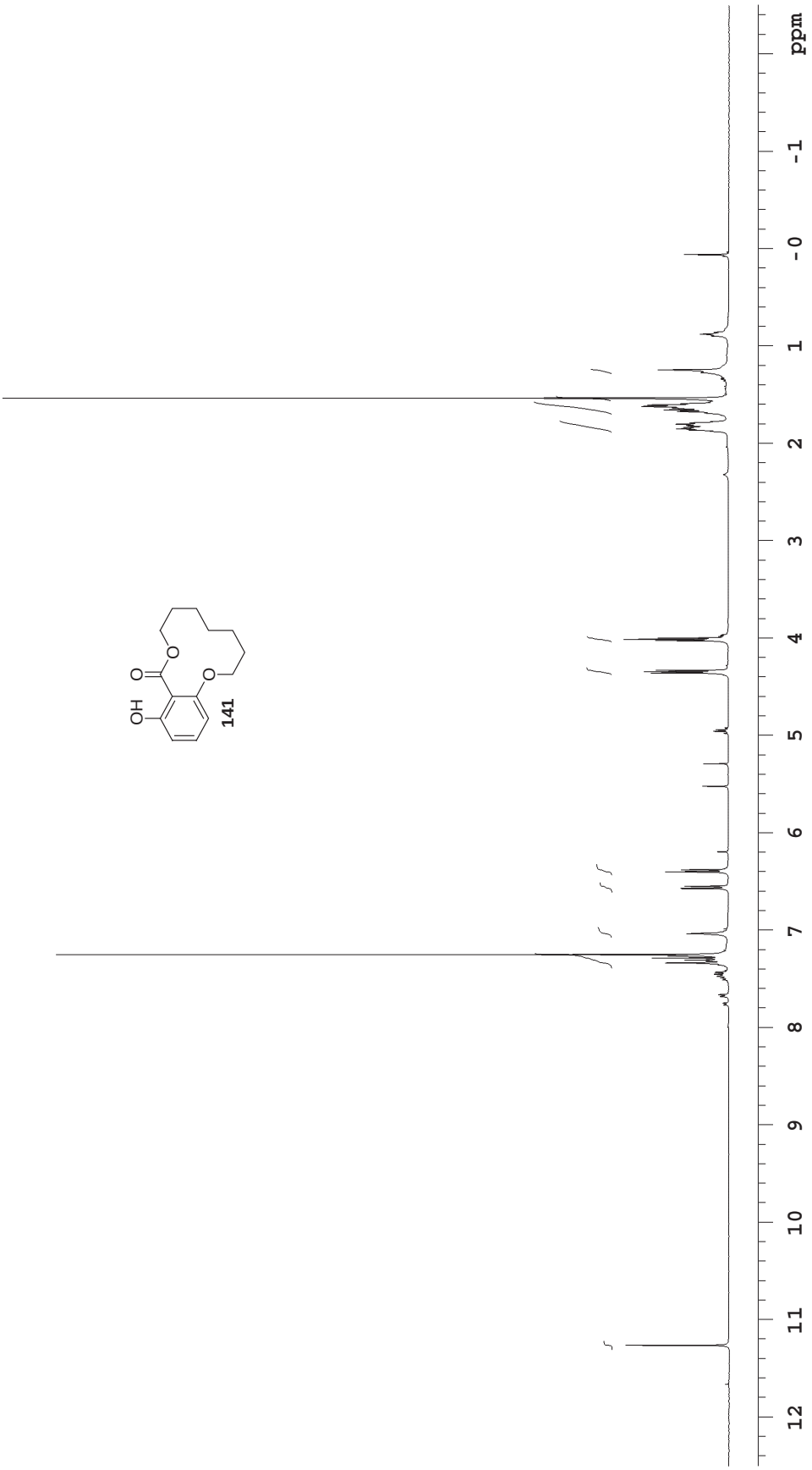
140
120
100
80
60
40
20


ppm
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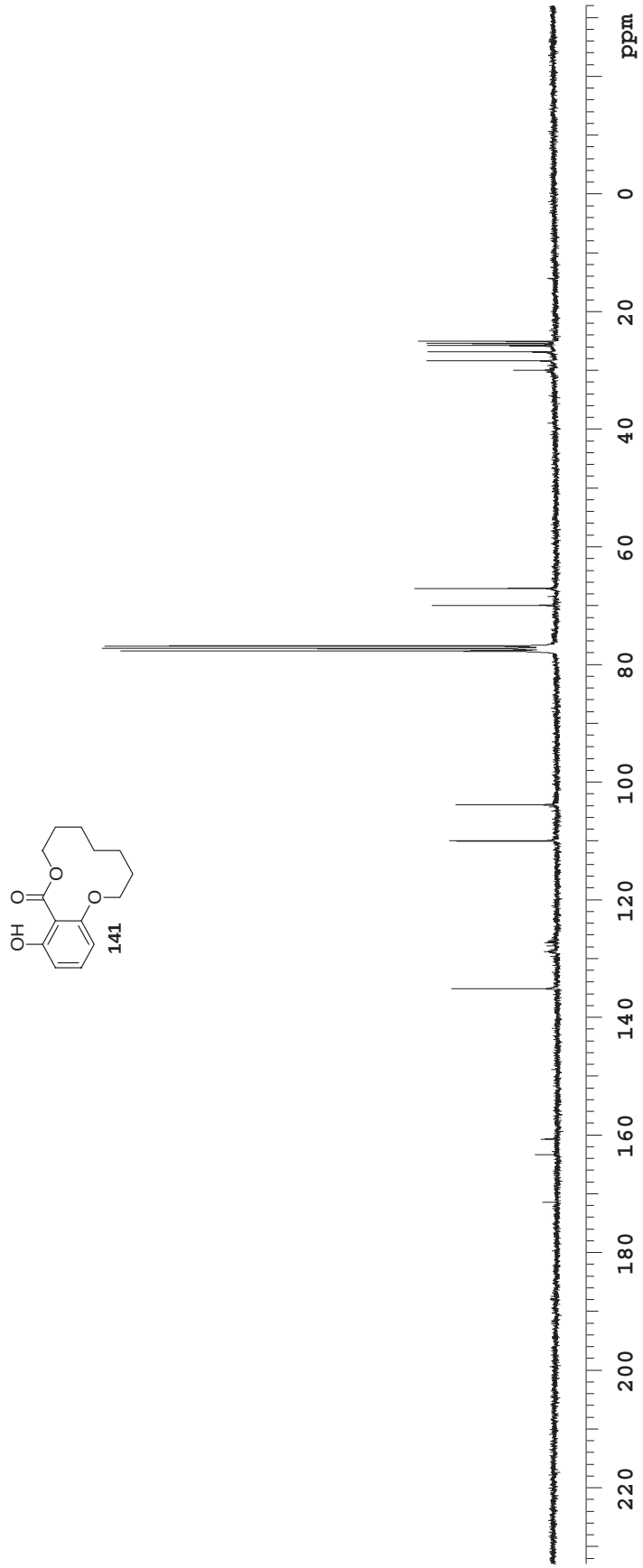
-0
-1
O
O
O
OH
141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O
O
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ppm
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140
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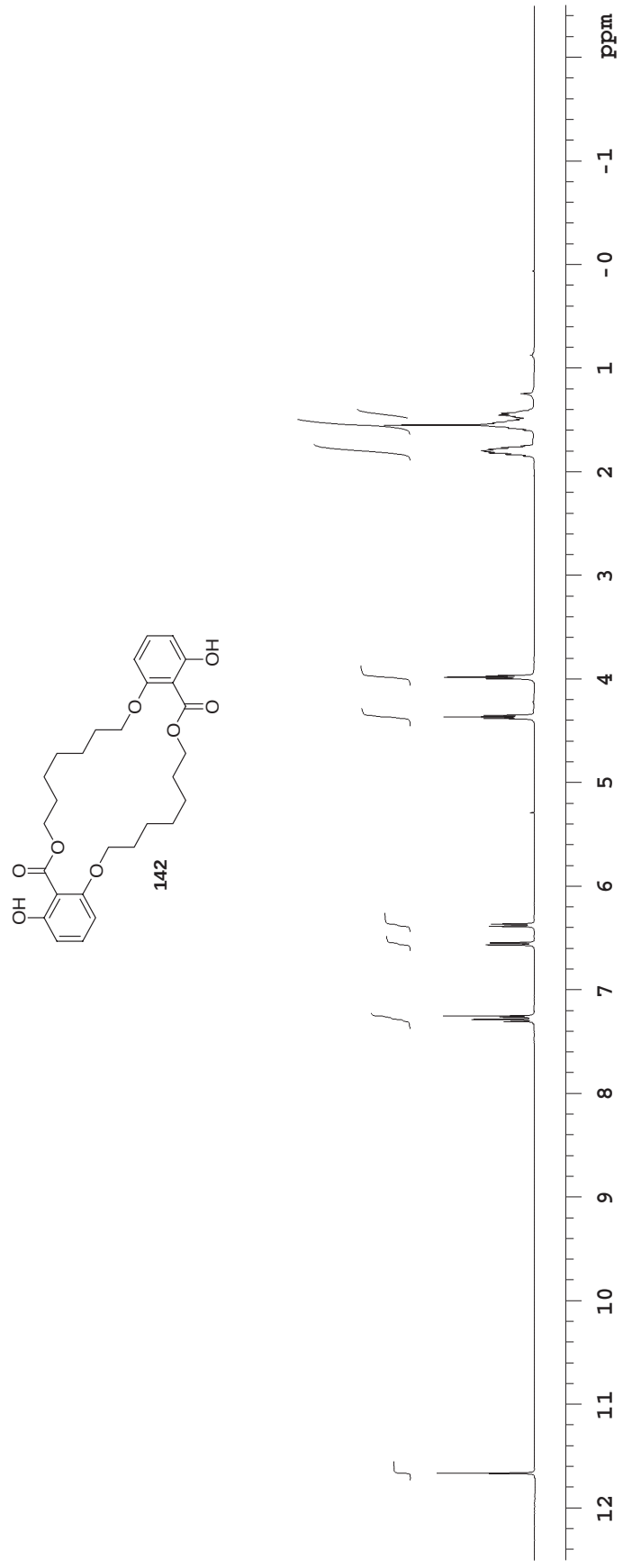
20
0


OH
O
O
O
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O
O
OH
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ppm
12
11
10
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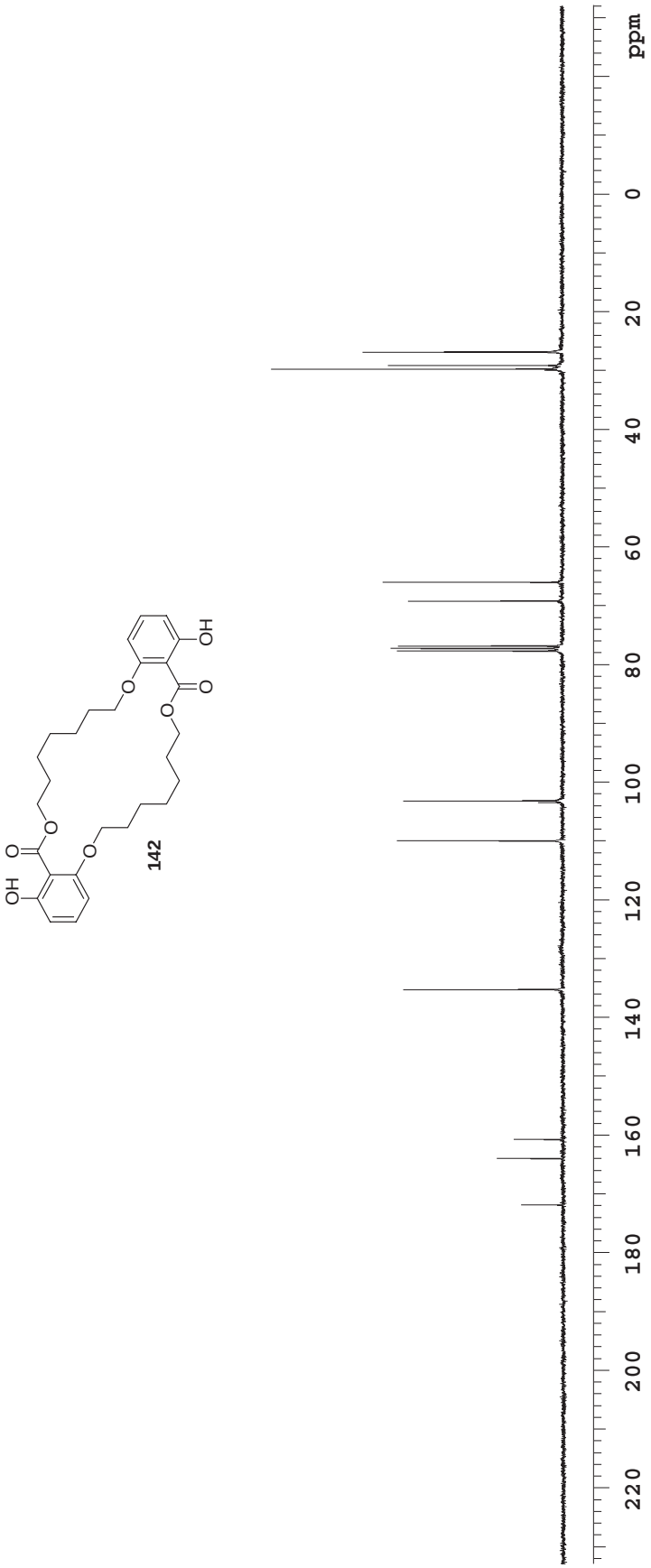
8
7
6
5
4
3
2
1
-0
-1


OH
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O
O
O
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O
OH
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ppm
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200
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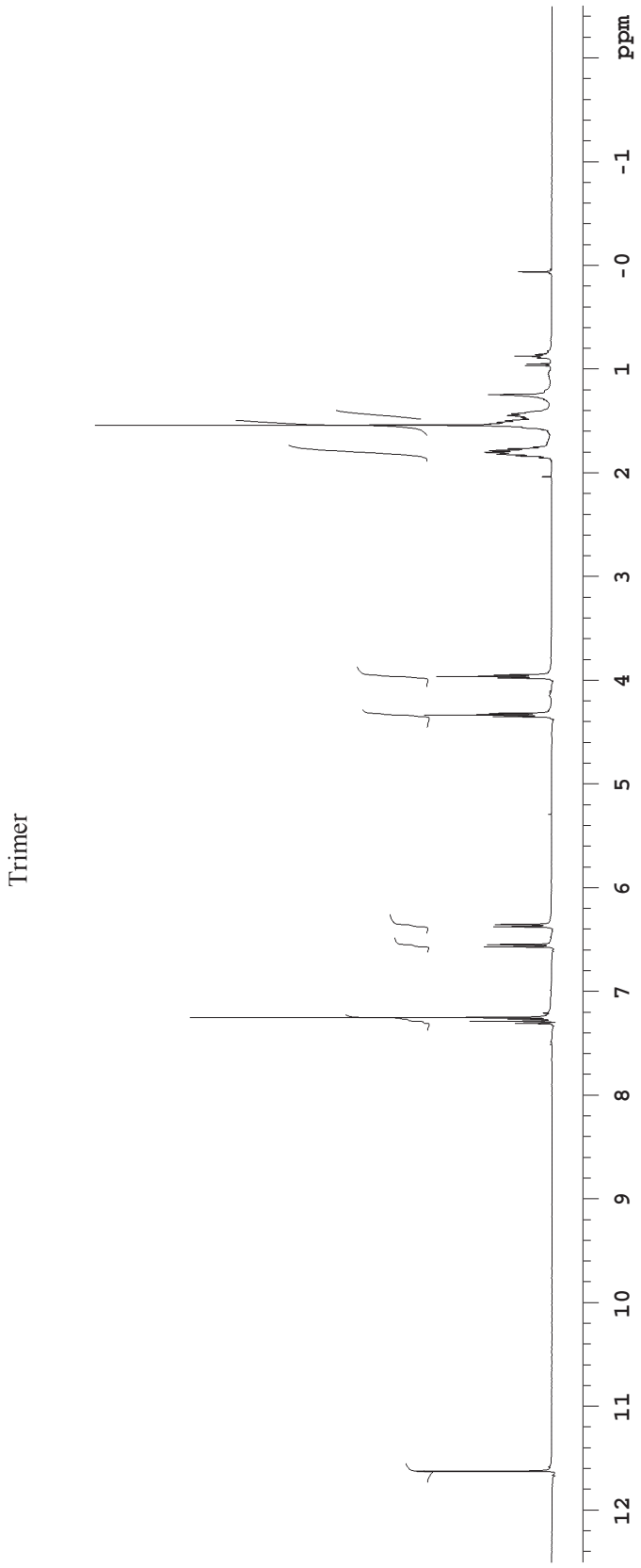
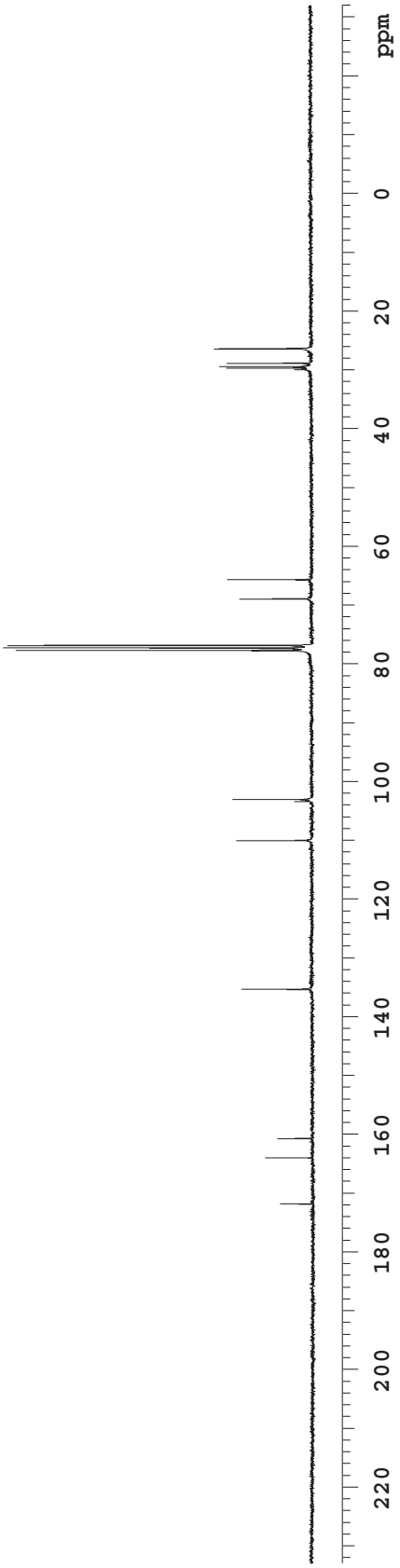
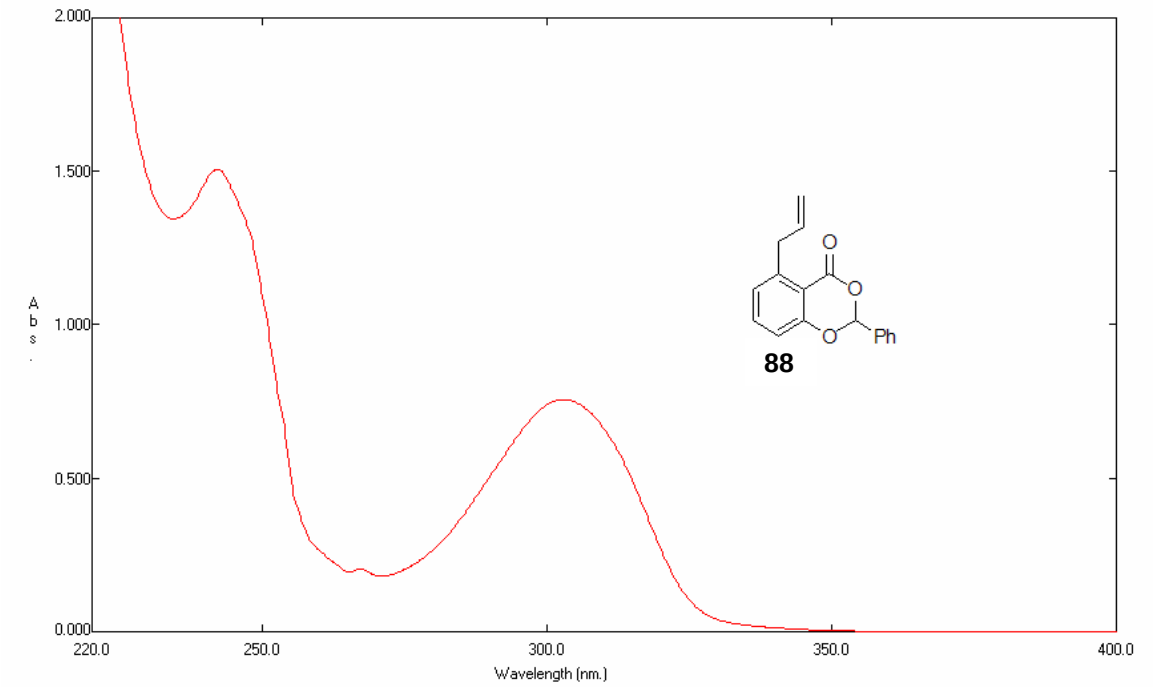
160
140
120
100
80
60
40
20
0

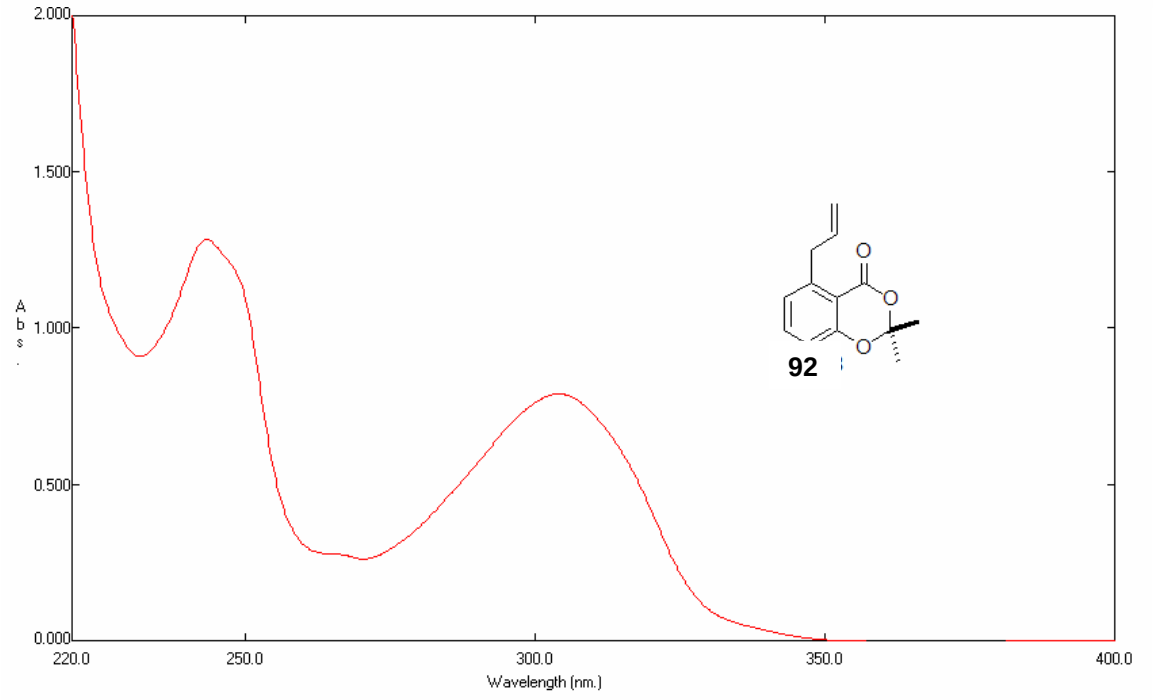

Trimer
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1

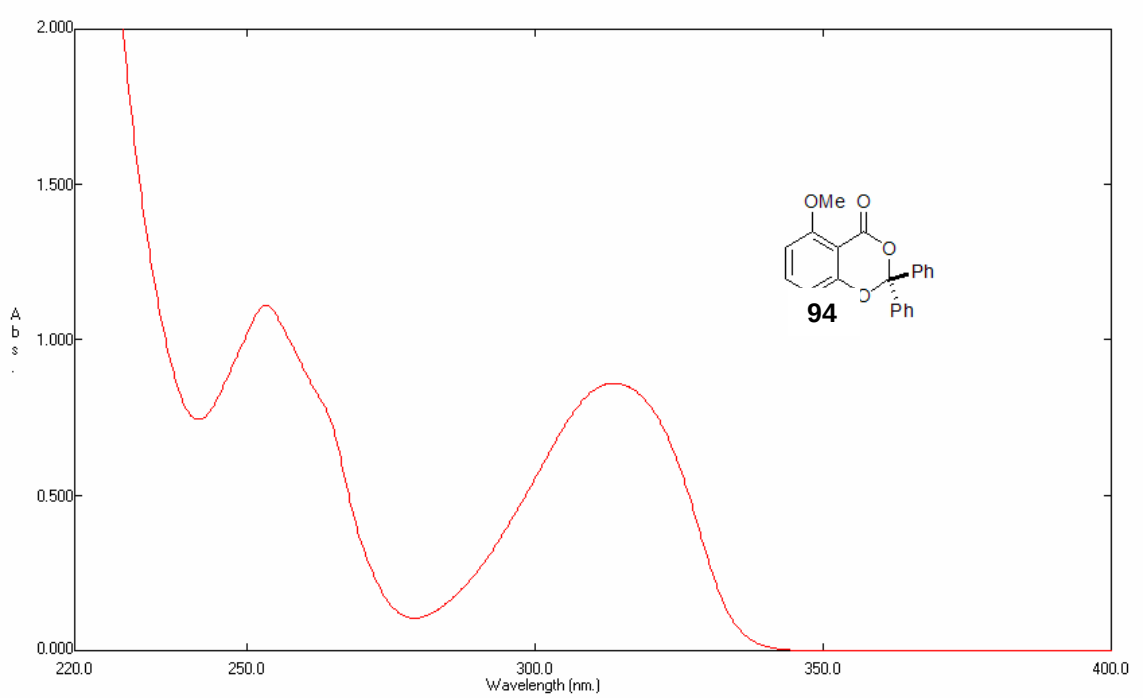
Trimer

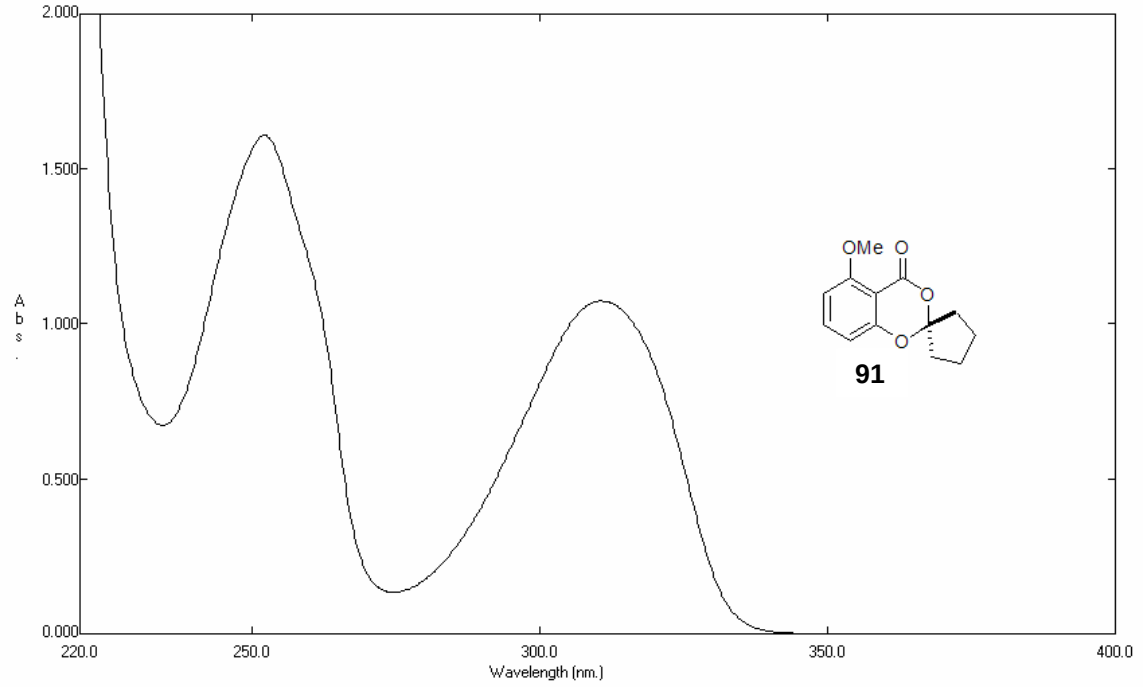


UV Spectrum of Various Benzodioxinones






2.000
1.500
1.000
0.500
0.000
Abs.
220.0
250.0
300.0
350.0
400.0
Wavelength (nm.)
OMe
O
O
O
Ph
Ph
94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Wavelength (nm.)
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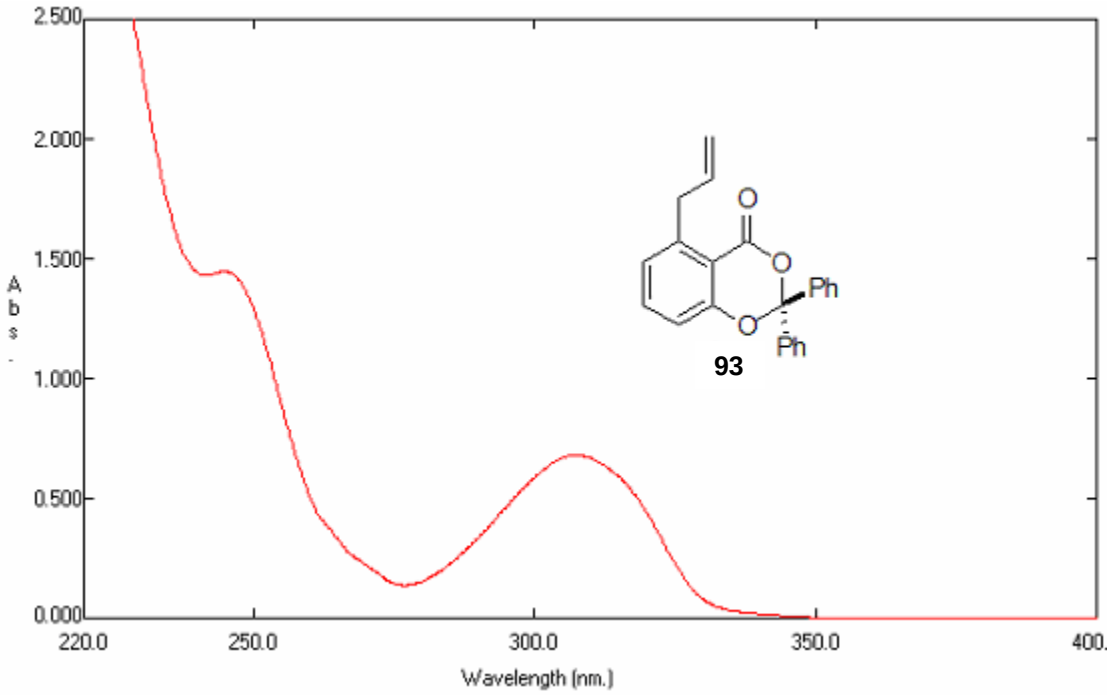
91


2.500
2.000
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Wavelength (nm.)
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Ph

93

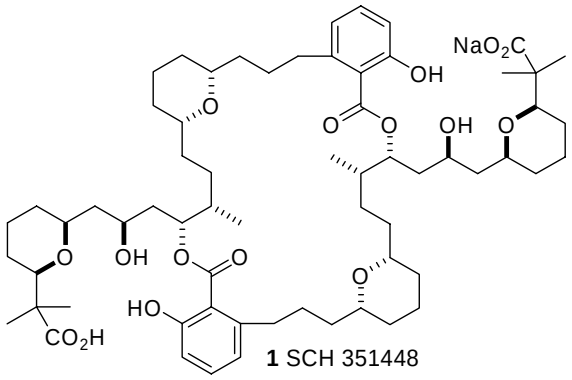
PART II
CHAPTER THREE

SCH 351448: BACKGROUND AND SIGNIFICANCE

3.1 Isolation and Structure Determination

In 2000 a team of researches at Schering-Plough Research Institute and Duke University published the isolation and structural elucidation of the natural product SCH 351448 (Fig. 3.1)[1]. In this report, crude organic extracts from a fermentation broth of a *Micromonospora* microorganism displayed significant upregulatory activity in a low density lipoprotein receptor (LDL-R) transcription translation assay. Bioassay guided fractionation and HPLC purification of the hexane soluble extracts led to the isolation of pure SCH 351448 (Fig. 3.1).

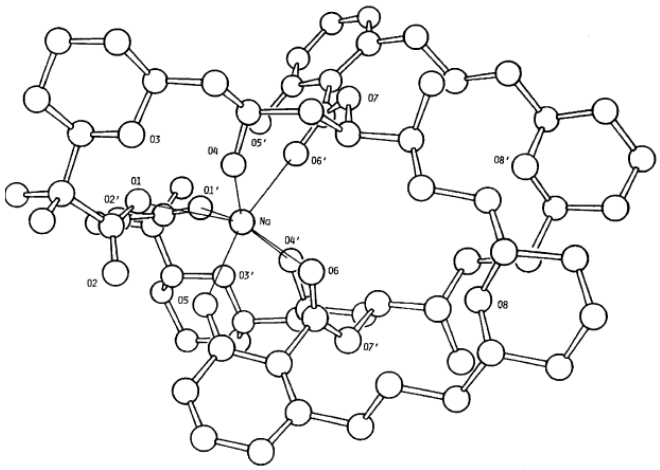
Fig. 3.1 SCH 351448



1 SCH 351448

Single crystal X-ray analysis of SCH 351448 revealed a C_2 symmetrical mono-sodium salt of a bis-carboxylate (Fig. 3.2). The ionized and un-ionized carboxy groups are intramolecularly hydrogen bonded and together with the phenol and hydroxyl groups accommodate the heptacoordinate sodium ion in the interior cavity of a hydrophobic globular structure. It remains to be seen whether the role of the chelated sodium ion is simply structural, or whether SCH 351448 functions as an ion transporter.

Fig. 3.2 Crystal Structure of SCH 351448 (Reproduced from ref. 1)



SCH 351448 is a natural product with a number of structural features indicative of polyketide biosynthesis. The core of the molecule is composed of a 28 member macrocyclic bis-lactone that is essentially a head to tail dimer of two identical fragments. This macrocyclic region contains two salicylate esters, two cis fused tetrahydropyranyl rings, and 10 of the 14 stereogenic centers. Outside of the macrolactone core are two additional cis fused tetrahydropyranyl rings flanked to a geminal dimethyl and free carboxylate.

3.2 Biological Profile of SCH 351448

Isolation of **1** was aided by its ability to elicit specific upregulation of the low density lipoprotein receptor (LDL-R) [1]; a cellular component intimately involved in maintaining homeostatic levels of cholesterol[2]. More specifically, **1** displayed modest activity in an assay aimed at identifying small molecules that specifically upregulate LDL-R expression. Briefly, JEG-3 cells were transiently transfected with vectors containing either the LDL-R promoter or the SRα promoter upstream of the human growth hormone (hGH) gene. Incubation of these tranfected cells with either **1** or 25-hydroxycholesterol overnight led to production of hGH which was quantified with an

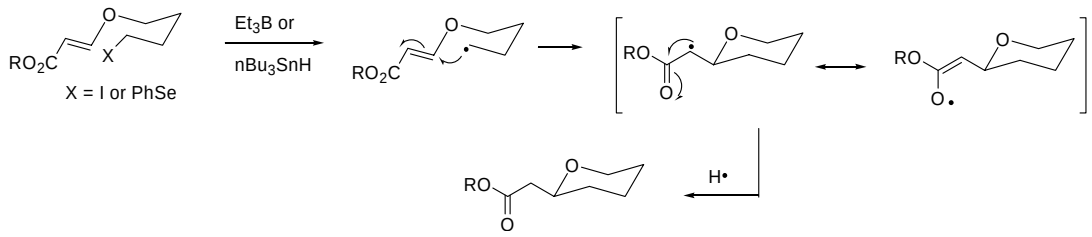
ELISA binding assay. Pure **1** showed activity in this assay with an EC_{50} of 25 μM. Also, cells transfected with vectors containing the SRα promoter as a control showed no hGH formation indicating **1** does not act as a general transcriptional activator. Although these results indicate that SCH 351448 is capable of inducing transcription in this reporter assay, the mechanism by which it is doing so remains unclear.

3.3 Previous Syntheses of SCH 351448

3.3.1 Lee Synthesis

In 2004 Eun Lee and co-workers disclosed the first stereoselective total synthesis of (+)-SCH 351448[3]. This synthesis, albeit lengthy considering the total number of synthetic operations (47), is relatively efficient and provided >13 mg of the natural product.

This route to the natural product highlights methodology concerning radical mediated stereoselective tetrahydropyran formation developed by Lee and co-workers[4] (Eq. 1).



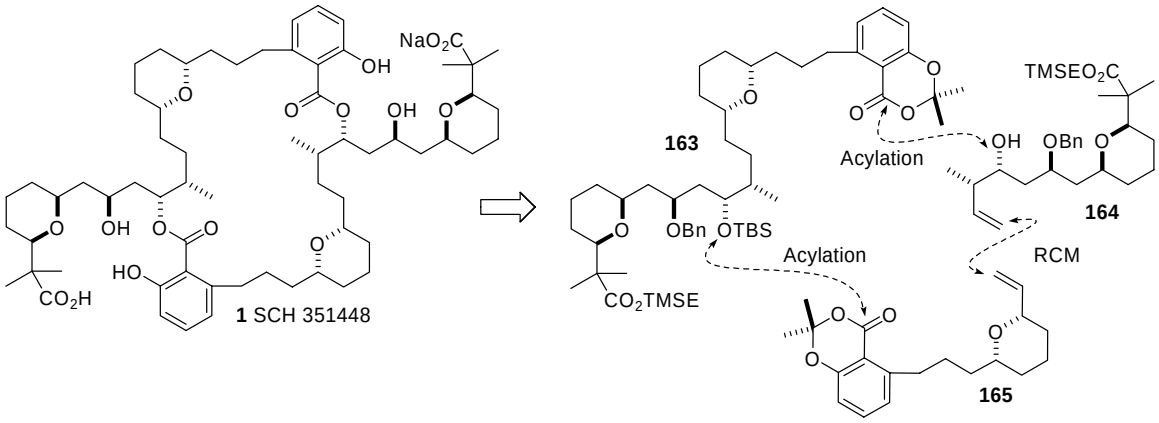
Eq. 1

Other key steps include sodium alkoxide promoted salicylate ester formation and macrocyclization via ring closing olefin metathesis. Worth noting is that Lee's synthesis does not take full advantage of the dimeric nature of **1**.

The retrosynthesis of SCH 351448 by Lee and co-workers divided the natural product into three advanced fragments (**163-165**) (Scheme 3.1). The most advanced intermediate, **163**, is in turn derived from fragments **164** and **165** in **7** additional steps.

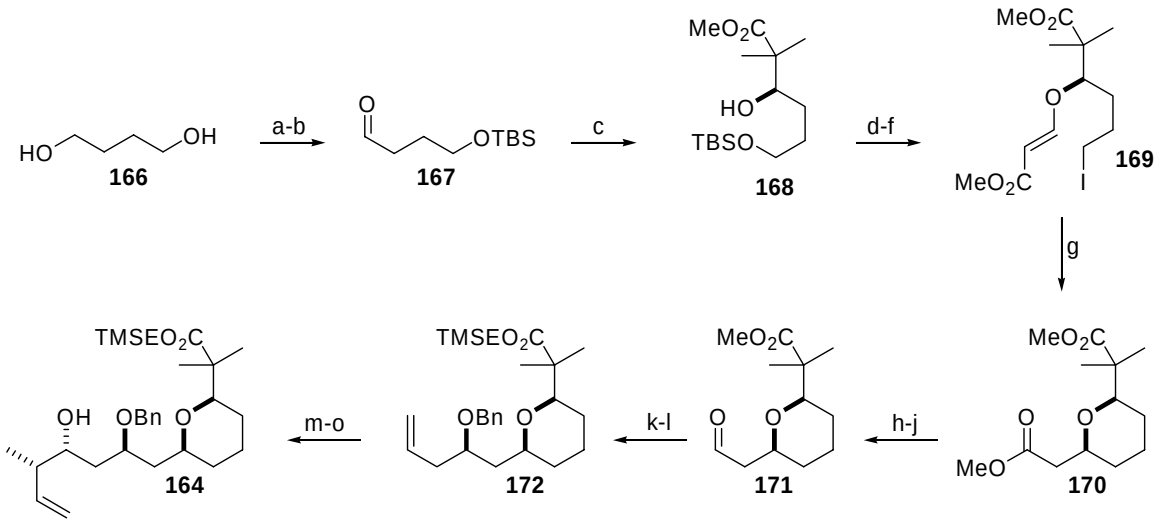
Connecting these three intermediates via base induced salicylate ester formation followed by ring closing metathesis provided the head to tail dimer.

Scheme 3.1



The synthesis of fragment **164** begins with protection and oxidation of commercially available 1,4-butanediol (Scheme 3.2). Enatioselective aldol addition of a silyl ketene acetal to aldehyde **167** using conditions described by Kiyooka[5] provided alcohol **168** (>95% ee). Following O-alkylation, deprotection, and iodination, triethylborane catalyzed radical cyclization of iodide **169** afforded *syn*-pyran **170** in nearly quantitative yield. Next, chemoselective hydrolysis of the less hindered methyl ester and oxidation state adjustment provided aldehyde **171**. Finally, allylation, benzyl protection, oxidative cleavage, and crotylation provided alcohol **164**. This sequence provided fragment **164** in 15 steps from commercially available starting materials. Stereoselective tetrahydropyran formation was accomplished with radical cyclization methodology developed by Lee and colleagues. The final two stereocenters were set with an asymmetric allylboration/ oxidative cleavage/crotylboration sequence.

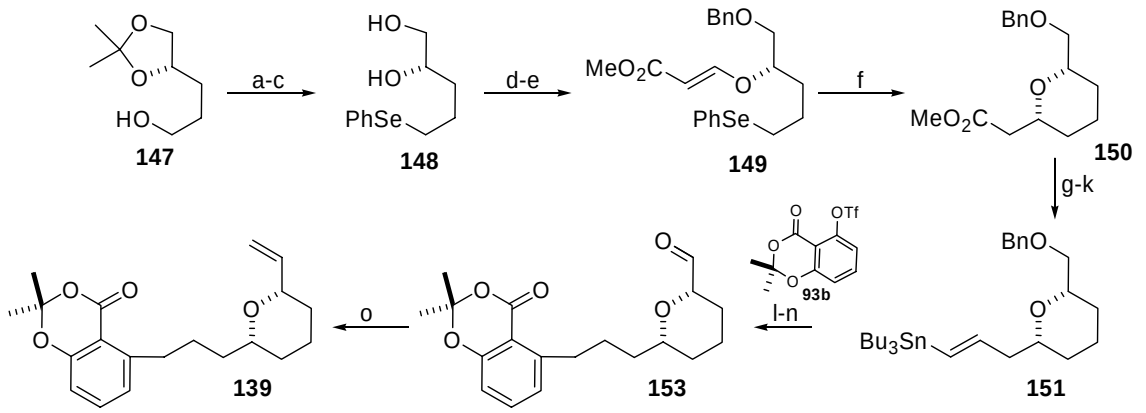
Scheme 3.2



Reagents and Conditions: a) NaH, TBSCl, THF 0 ˚C; b) SO_3·Pyr, Et_3N, DMSO:CH_2Cl_2 (1:1), 0 ˚C, 95% 2 steps; c) *N*-tosyl-l-valine, 1.0 equiv BH_3·THF, CH_2Cl_2, r.t. 30 min; 1.0 equiv. **167**, 1.1 equiv. $Me_2CC(OMe)(OTMS)$, -78 ˚C 4 hr, 94% 2 steps; d) 1.5 equiv $HCCCO_2Me$, 0.2 equiv NMM, MeCN, r.t. 48 hr; e) conc. HCl, MeOH, r.t., 30 min; f) 1.5 equiv. I_2, 1.5 equiv. Ph_3P, 3 equiv. imidazole, THF, 0 ˚C, 2 hr, 71% 3 steps; g) H_3PO_2, 1-ethylpiperidine, Et_3B, EtOH 99%; h) KOH, THF-H_2O-MeOH (3:1:1); i) BH_3·DMS, $B(OMe)_3$, THF, 0 ˚C; j) SO_3·Pyr, TEA, DMSO– CH_2Cl_2 (1:1); k) $CH_2CHCH_2B(^{l}IPC)_2$, ether, -78 ˚C; NaOH, H_2O_2, reflux; l) NaHMDS, BnBr, THF-DMF (4:1), 0 ˚C to r.t.; m) $Ti(Oi\text{-}Pr)_4$, $TMSCH_2$ CH_2OH, DME, 120 ˚C 55% 6 steps; n) OsO_4, NMO, acetone-H_2O (3:1); $NaIO_4$; o) (E)-$CH_3CHCHCH_2B(^{d}Ipc)_2$, THF, -78 ˚C to r.t. 66% two steps.

The synthesis of fragment **165** is similar to that of **164** in that it exploits radical mediated tetrahydropyran formation developed by Lee and co-workers (Scheme 3.3). In this instance, organoselenide **175** served as a precursor for the stereoselective radical cyclization (**175→176**). After oxidation state adjustment and transformation to vinyl stannane **177**, the stage was set for a Stille coupling with aryl triflate **87b**. Finally, single carbon homologation via Wittig olefination afforded **165**.

Scheme 3.3



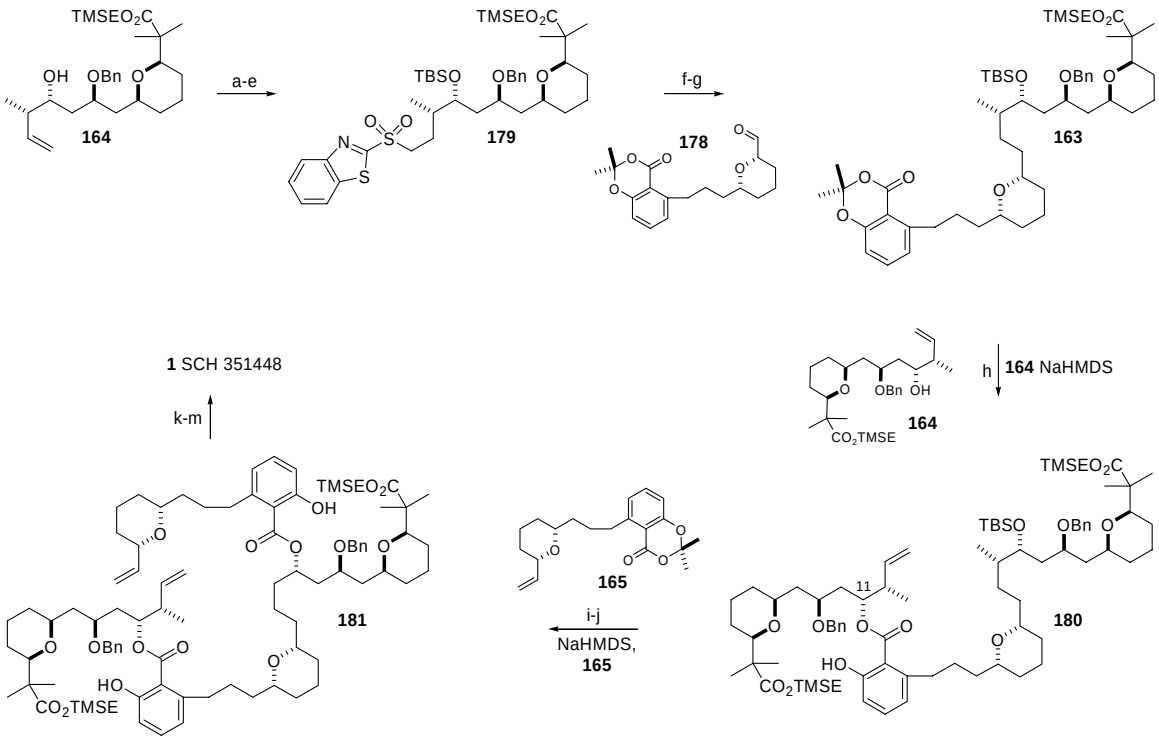
Reagents and Conditions: a) TsCl, Et_3N, CH_2Cl, 0 ˚C; b) PhSePh, $NaBH_4$, EtOH; c) conc. HCl, MeOH 81% three steps; d) Bu_2SnO, benzene, reflux, (-H_2O); BnBr, TBAI, benzene, reflux; e) $CHCCO_2Me$, NMM, MeCN 61% two steps; f) Bu_3SnH, AIBN, benzene (0.01 M), reflux 98%; g) LAH, THF, 0 ˚C; h) SO_3·Pyr, Et_3N, DMSO- CH_2Cl (1:1); i) CBr_4, HMPT, THF, -30 ˚C; j) *n*-BuLi, THF, -78 ˚C; k) Bu_3SnH, AIBN, benzene (0.02 M), reflux 75% five steps; l) $PdCl_2(PPh_3)_2$, **87b**, LiCl, Ph_3P, DMF (0.1 M), 120 ˚C; m) H_2, Pd/C, MeOH; n) SO_3·Pyr, Et_3N, DMSO- CH_2Cl (1:1) 96% three steps; o) $Ph_3PCH_3^+Br^-$, *n*-BuLi, THF, 0 ˚C; -78 ˚C→r.t. 60%.

Preparation of fragment **165** utilized stereoselective radical mediated tetrahydropyran formation in a similar fashion to alcohol **164**, and a Stille coupling which incorporated the salicylate unit. This sequence required a total of 19 steps from commercially available D-mannitol.

Julia olefination of sulfone **179** (5 steps from **164**) and aldehyde **178** followed by diimide reduction provided a fully elaborated C1-C29 fragment **163** (Scheme 3.4). This material would serve as a template for late stage fragment coupling leading to the natural product. Acylation of acetonide **163** with the sodium alkoxide derived from **164** proved to be a powerful method for combining these fragments in an efficient manner. Following C11 silyl deprotection, the second salicylate ester was formed once again via alcoholysis of acetonide **165**. Ring-closing metathesis of diene **181** proceeded uneventfully to give the desired macrocycle in 82% yield. Finally, hydrogenolysis of the benzyl ethers and fluoride mediated deprotection of the carboxylate groups provided (+)-

SCH 351448. Interestingly, Lee and co workers noted that SCH 351448 was obtained only after treatment with a highly acidic (4N HCl) saturated sodium chloride solution.

Scheme 3.4



Reagents and Conditions: a) TBSOTF, 2,6-lutidine, CH_2Cl_2, 0 ˚C; b) OsO_4, acetone:H_2O (3:1); $NaIO_4$; c) $NaBH_4$, EtOH; d) Benzothiazole-2-thiol, DIAD, Ph_3P, THF, 0 ˚C; e) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, 0 ˚C to r.t. 84% five steps; f) NaHMDS, Et_2O, **178**, -78 ˚C to r.t.; g) $TsNNH_2$, NaOAc, DME:H_2O (1:1), reflux 79% two steps; h) **164**, NaHMDS, THF, 0 ˚C; **163**, 0 ˚C; i) conc. HCl, MeOH; j) NaHMDS, THF, 0 ˚C; **165**, 0 ˚C 77% three steps; k) 10 mol % Grubbs' 2nd Gen. Catalyst, CH_2Cl_2, (3 mM), 80 ˚C; l) H_2, Pd/C MeOH:EtOAc (3:1) 70% two steps; m) TBAF, THF; 4 N HCl (sat. NaCl) 91%.

3.3.2 Leighton Synthesis

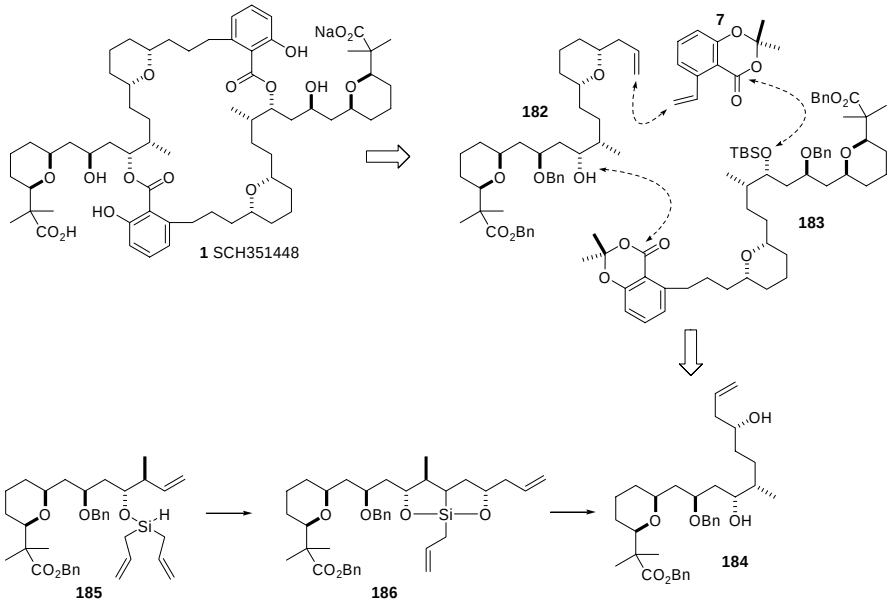
Shortly after our total synthesis, Leighton and co-workers published the third reported total synthesis of (+)-SCH 351448[6]. Upon cursory examination, Leighton's retrosynthetic analysis of the natural product closely resembles that of the Lee synthesis, namely the final steps of the synthesis involve alkoxide mediated salicylate ester formation followed by ring closing metathesis (Scheme 3.5). Leighton's preparation of

these fragments however, is quite novel with a number of key steps involving methodologies developed by his group.

The first retrosynthetic step involves dissection of the symmetrical dimer along the salicylate ester bonds. This leaves two large fragments (**182** and **183**) of near equal complexity in addition to an *o*-vinyl substituted benzodioxinone **7**. Fragments **182** and **183** are obtained from diol **184**, an intermediate that contains much of the stereochemical elements present in the natural product. Finally, alcohol **184** was derived from a sequential allylation/hydrosilylformylation reaction developed by Leighton and co-workers (**185→186→184**).

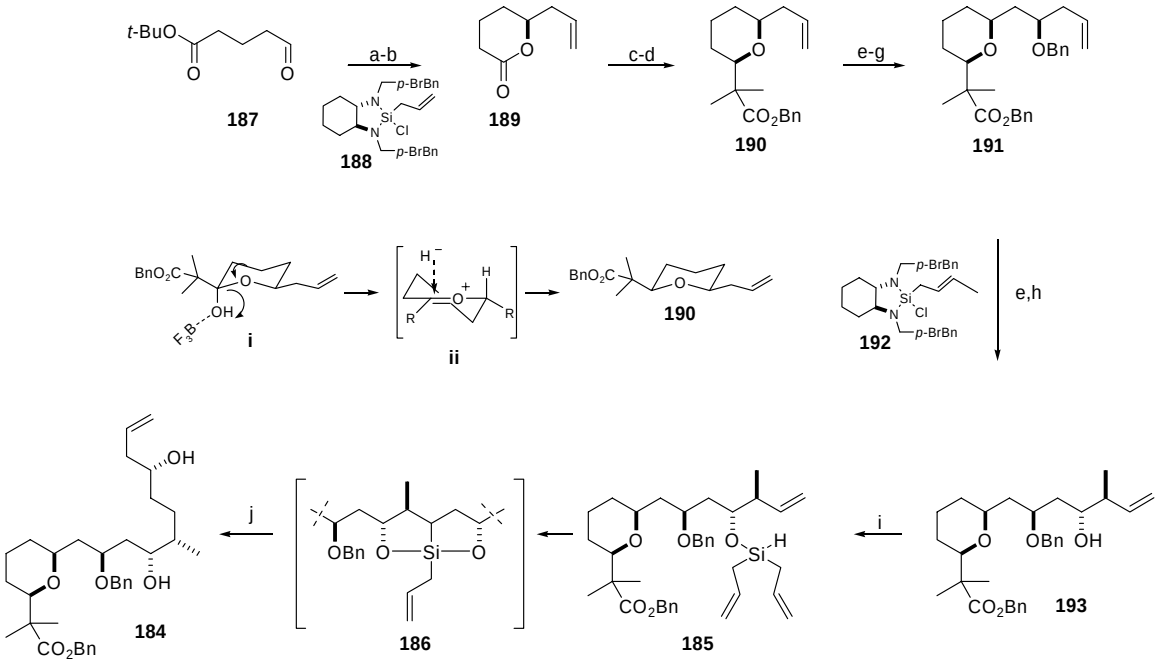
Coupling of advanced fragments **182** and **183** was envisaged to proceed via sequential sodium alcoholate mediated transesterifcation of acetonides **183** and **7**, similar to the strategy employed by Lee and coworkers (see section 3.3.1). Like Lee's synthesis, Leighton's route to SCH 351448 does not take full advantage of the symmetry of the dimeric nature of the natural product.

Scheme 3.5



Synthesis of compound **184** begins with asymmetric allylation of aldehyde **187**, utilizing the allylsilane reagent **188** developed in their lab, followed by acid catalyzed dehydration to form lactone **189** (Scheme 3.6). Following enolate addition to lactone **189**, Lewis acid catalyzed reduction of the hemiacetal **i** with triethylsilane (via oxonium intermediate **ii**) afforded cis tetrahydropyran **190**. Following oxidative cleavage of the terminal olefin, asymmetric allylation and deprotection provided homoallylic alcohol **191**. Leighton and coworkers noted that the highest level of 1,3 *syn* selectivity was achieved with Brown's allyborane (10:1 *dr*), in contrast to allylsilane **188** (2.5:1 *dr*). A second oxidative cleavage of the terminal olefin preceded asymmetric crotylation with Leighton's diaminocyclohexane derived crotylsilane reagent **192**. Conversion of this material to the bis-allylsilane **185** set the stage for the rhodium catalyzed tandem silylformylation-allylsilation reaction developed by Leighton and coworkers.

Scheme 3.6

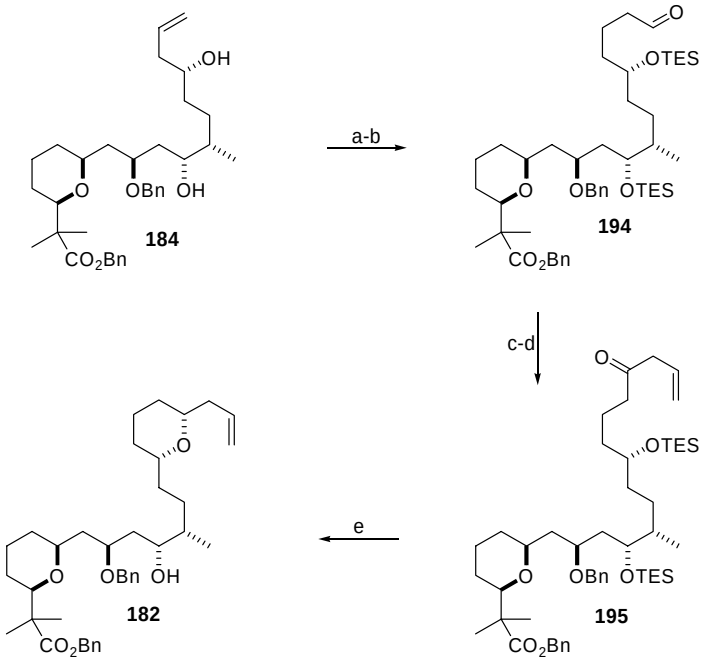


Reagents and Conditions: a) **188**, CH_2Cl_2, -10 ˚C; b) *p*-TsOH, benzene 72% two steps; c) $BnO_2CCH(Me)_2$, LDA, THF, 0 ˚C; d) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, -78 ˚C 68% two steps; e) OsO_4, NMO, acetone, H_2O; $NaIO_4$, THF, H_2O; f) (+)-*B*-

methoxydiisopinocampheylborane, AllylMgBr, Et_2O, -100 ˚C; g) NaH, BnBr, DMF, 0 ˚C 74% three steps; h) **192**, DCM, 0 ˚C 80%; i) Diallyldiethylaminosilane, CH_2Cl_2; j) 5 mol % $Rh(acac)(CO)_2$, 900 psi CO, benzene, 65 ˚C; TBAF, THF, reflux 69% two steps.

Bis-triethylsilyl protection and subsequent hydroformylation of fragment **184**, a common intermediate for the preparation of **183** and **182**, gave aldehyde **194** in 79% yield (Scheme 3.7). Addition of allylzinc bromide to the aldehyde, followed by oxidation of the epimeric alcohols provided ketone **195**. Finally, Lewis acid catalyzed tetrahydropyran formation yielded alcohol **182**.

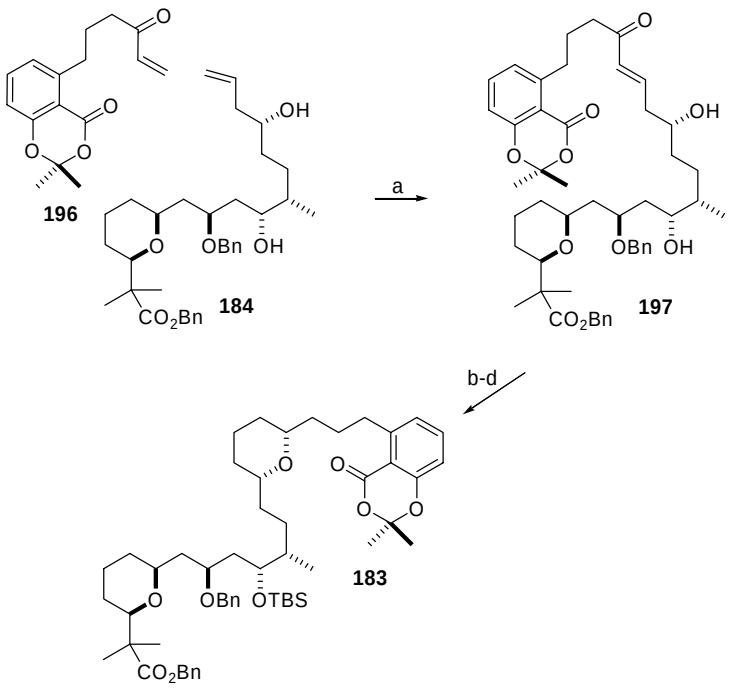
Scheme 3.7



Reagents and Conditions: a) TESOTf, Et_3N, CH_2Cl_2, -78 ˚C 99%; b) 5 mol % $Rh(acac)(CO)_2$, 12 mol % Nixantphos, 600 psi 1/1 H_2/CO, THF, 60 ˚C 79%; c) AllylMgBr, Zn, NH_4Cl, H_2O, THF; d) Dess-Martin Periodinane, CH_2Cl_2 86% two steps; e) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, -78 ˚C 67%.

Synthesis of acetonide **183** initiated from cross metathesis of terminal olefins **184** and **196** to give conjugated enone **197** in 85% yield. Reduction of the cross metathesis product was followed by *cis*-pyran formation as before to yield the fully elaborated C1-C29 fragment **183** (>20:1 *dr*) (Scheme 3.7, **195→182**).

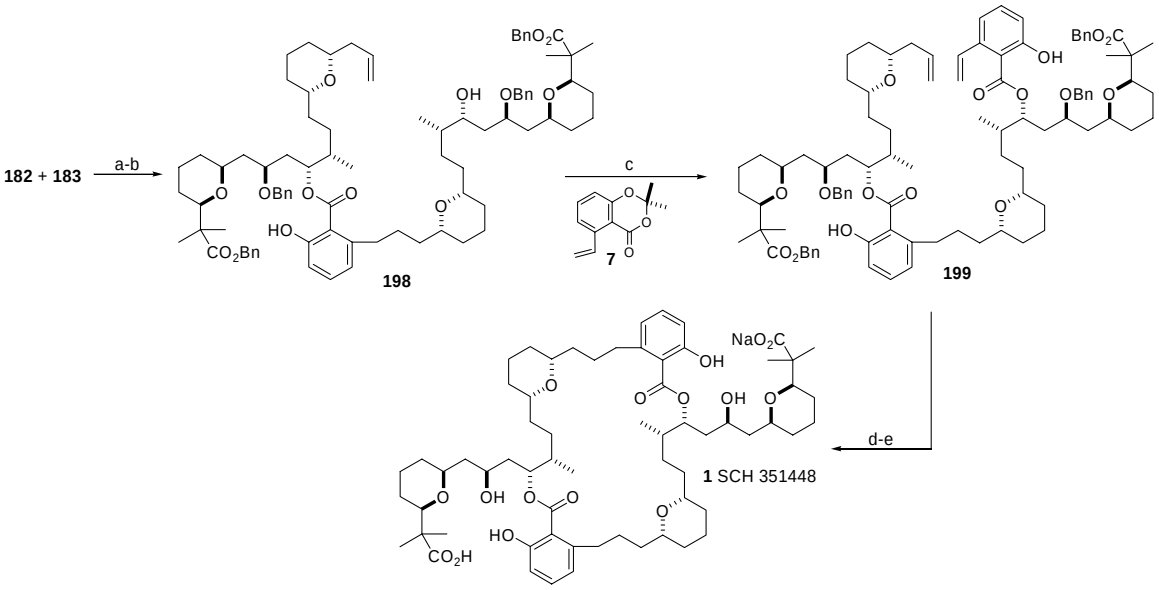
Scheme 3.8



Reagents and Conditions: a) 10 mol % Grubbs 2nd Gen. Catalyst, CH_2Cl_2, reflux 85%; b) Lindlar catalyst, H_2, MeOH; c) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, -78 ˚C 91% two steps; d) TBSOTf, Et_3N, CH_2Cl_2, -78 ˚C 99%.

With advanced intermediates **182** and **183** in hand, the stage was now set for the completion of the synthesis (Scheme 3.9). Deprotonation of **182** followed by treatment with acetonide **183** led to smooth formation of ester **198** (66%). Subsequent base mediated coupling of this material with benzodioxinone **7** provided RCM precursor **199** (63%). In the event, treatment of the bis-olefin with Grubbs' second generation catalyst yielded the unsaturated macrocycle in high yield (82%). Finally, hydrogenation and concomitant hydrogenolysis of the benzyl ethers and esters provided the natural product after equilibration with a 4N HCl solution saturated with NaCl.

Scheme 3.9



Reagents and Conditions: a) **182**, NaHMDS, THF, 0 ˚C, then **183**; b) HCl, Et_2O, MeOH 66% two steps; c) NaHMDS, THF, 0 ˚C then **7** 63%; d) 10 mol % Grubbs' 2nd Gen. catalyst, CH_2Cl_2, reflux; e) Pd/C, H_2, MeOH, EtOAc 57% two steps.

Leighton's approach to SCH 351448 provides a relatively short and efficient route to the natural product. Utilization of methodologies for asymmetric additions to aldehydes and silylformylation/allylsilylation of homoallylic alcohols provided a clever approach for the synthesis of advanced fragments. Despite a similar end game as the Lee synthesis, Leighton's route has significant advantages in terms of number of total steps (34 vs. 47 total steps).

3.4 Ion Exchange Studies

In 2005 Lee and colleagues published a full paper of their work on SCH 351448[7]. Experiments in this report detailed SCH 351448's ability to exchange various metal cations under equilibrating conditions. Starting with either a sodium or calcium bound molecule, equilibration in a biphasic solution of dichloromethane and a saturated metal solution provided new metal bound substrates. These materials were confirmed by NMR

and mass spectrometry (MALDI-TOF). A survey of various metals showed that SCH 351448 preferred to coordinate divalent metals (Ca^{2+}, Mg^{2+}, Cu^{2+}) under neutral conditions, while monvalent metals (Na^{+}, K^{+}, Rb^{+}) complexed to the natural product at acidic pH. Further experiments extending these studies to a possible role for SCH 351448 in a biological setting were not conducted.

3.5 Notes and References

(1) Hegde, V. R.; Puar, M. S.; Dai, P.; Patel, M.; Gullo, V. P.; Das, P. R.; Bond, R. W.; McPhail, A. T. *Tet Lett* **2000**, *41*, 1351-1354.

(2) Brown, M. S.; Goldstein, J. L. *Science* **1986**, *232*, 34-47.

(3) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J Am Chem Soc* **2004**, *126*, 2680-2681.

(4) Lee, E., Han, H. O. *Tet Lett* **2002**, *43*, 7295-7296.

(5) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *Journal of Organic Chemistry* **1991**, *56*, 2276-2278.

(6) Bolshakov, S.; Leighton, J. L. *Org Lett* **2005**, *7*, 3809-3812.

(7) Kang, E. J.; Cho, E. J.; Ji, M. K.; Lee, Y. E.; Shin, D. M.; Choi, S. Y.; Chung, Y. K.; Kim, J. S.; Kim, H. J.; Lee, S. G.; Lah, M. S.; Lee, E. *J Org Chem* **2005**, *70*, 6321-6329.

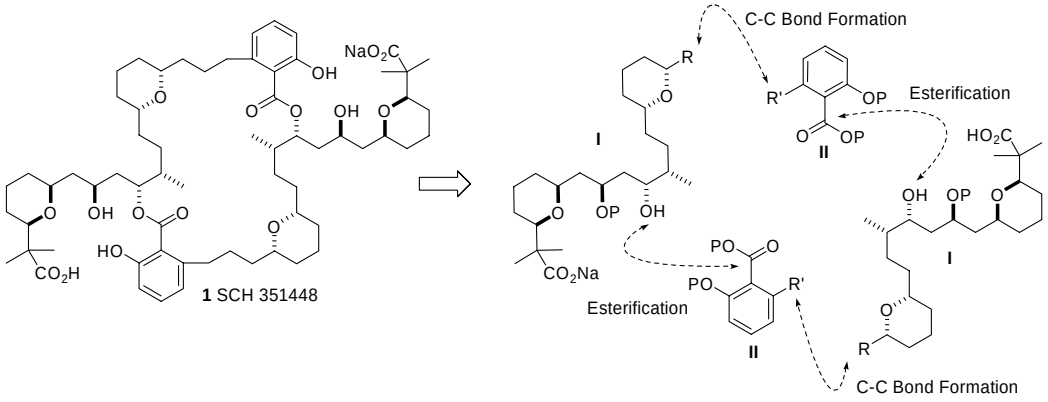
CHAPTER FOUR

METATHESIS BASED APPROACHES FOR THE SYNTHESIS OF SCH 351448

4.1 Synthetic Strategy

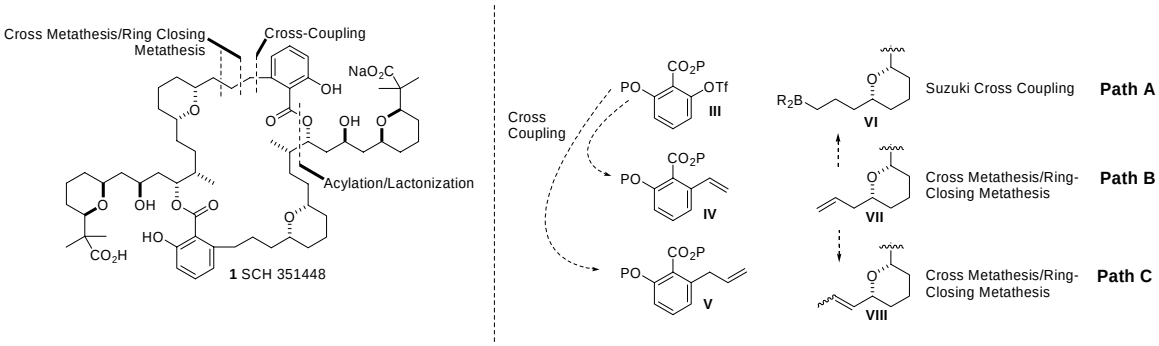
Evaluation of SCH 351448's structure led us to consider a general strategy that would take full advantage of the natural product's dimeric nature (Fig. 4.1). As delineated in figure 4.1, our approach looked to dimerize identical acyclic fragments **I** with aromatic fragment **II**.

Fig. 4.1



Coupling and cyclization could proceed through initial carbon-carbon bond formation, followed by esterification/lactonization, or via initial esterification followed by cross metathesis/ring closing metathesis.

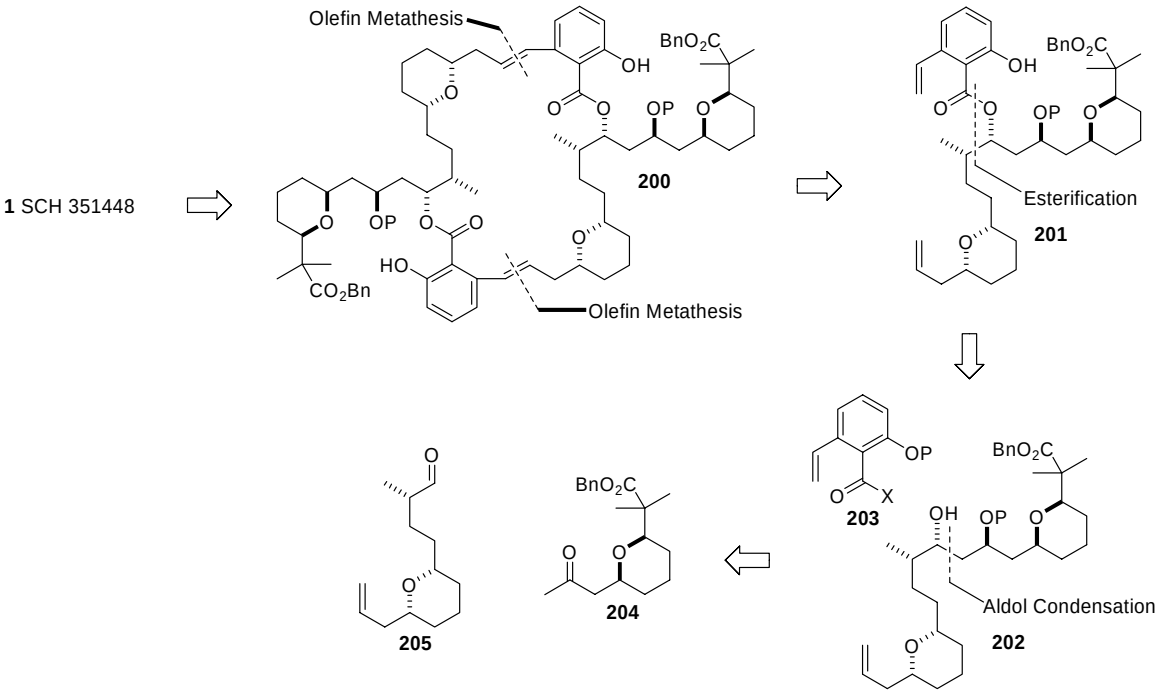
Fig.4.2



A fundamental advantage we hope to convey with the metathesis based approach is that a fully functionalized dimer is potentially accessed in one step from a single intermediate. Also worth noting, several modes of dimerization can be explored upon brief transformation of advanced intermediates such as terminal olefin **VII** (Fig. 4.2, Path B) and aryl-triflate **III** (Fig. 4.2, Path A). For example, **VII** would be a precursor for a Suzuki cross-coupling (via **VI**) with triflate **III**. Also, transposition of the olefin to (**VII→VIII**), would produce a precursor for an alternative metathesis with allyl-substituted salicylate **V** (from **III**).

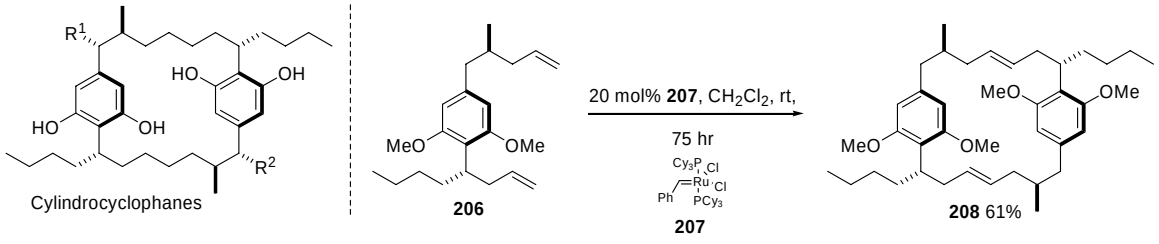
With this dimerization strategy in mind, formation of macrocycle **200** was envisioned to proceed via a tandem head-to-tail olefin cross metathesis/ring closing metathesis of diene **201** (Scheme 4.1) – a material accessible from alcohol **202** via salicylate ester formation with fragment **203**. Finally, 1,3-diol **202** is to be derived from a stereoselective aldol reaction of methyl ketone **204** and aldehyde **205**, followed by a 1,3-anti-reduction of the resulting β-hydroxyketone.

Scheme 4.1



This approach takes full advantage of the dimeric nature of the natural product, and could potentially access the 28 membered macrocycle in a single synthetic operation. In similar fashion, Smith and co-workers exploited the reversible nature of the metathesis reaction to construction various cylindrocyclophane natural products[1] (Scheme 4.2).

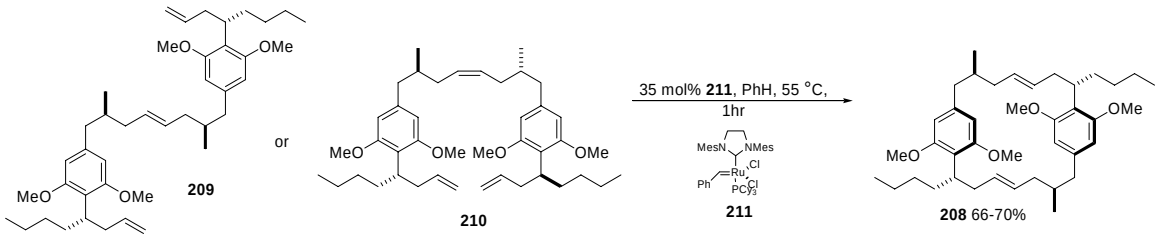
Scheme 4.2



In this example, diene **206** exclusively formed the head-to-tail dimerization product in the presence of Grubbs' 1st generation catalyst **207**. Additional experiments demonstrated the preference for head-to-tail dimer formation. For example, when either linear head-to-

head dimers **209** or **210** were subjected to Grubbs 2nd generation catalyst **211**, the product of head-to-tail dimerization was once again realized (Scheme 4.3).

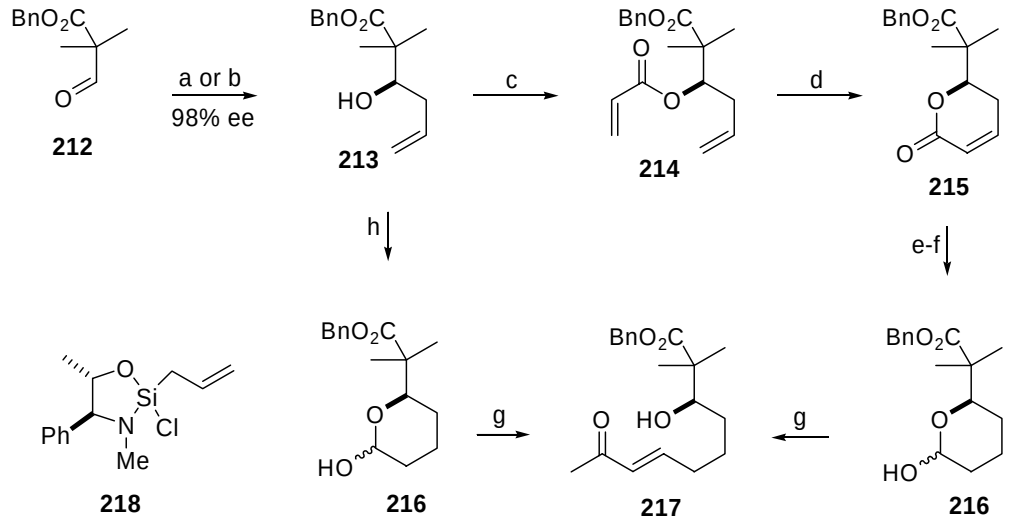
Scheme 4.3



4.2 Fragment Preparation

Synthesis of methylketone **204** commences with the asymmetric allylation of known aldehyde **212**[2] (Scheme 4.4). Brown's allyldiisopinocampheylborane reagent[3] and Leighton's allylsilane[4] **218** (98% ee) both provided homoallylic alcohol **213** in good yield and selectivity, however, utilization of Leighton's allylsilane was found to be more convenient. Acylation of alcohol **213** with acrolyl chloride proceeded best with Hünig's base to furnish diene **214** in 83% yield. Next, treatment of acrylate **214** with Grubbs' 2nd generation catalyst[5] yielded valerolactone **215**. After extensive experimentation by Dr. Bhattacharjee, reduction of the olefin and ester functionalities with $CoCl_2/NaBH_4$ in THF provided lactol **216**, however this protocol was not reproducible on a large scale. Instead a two step sequence initiating with olefin reduction ($NaBH_4$/ $NiCl_2 \cdot 6H_2O$ in THF[6]), followed by DIBAL-H reduction of the saturated lactone yielded lactol **216**.

Scheme 4.4

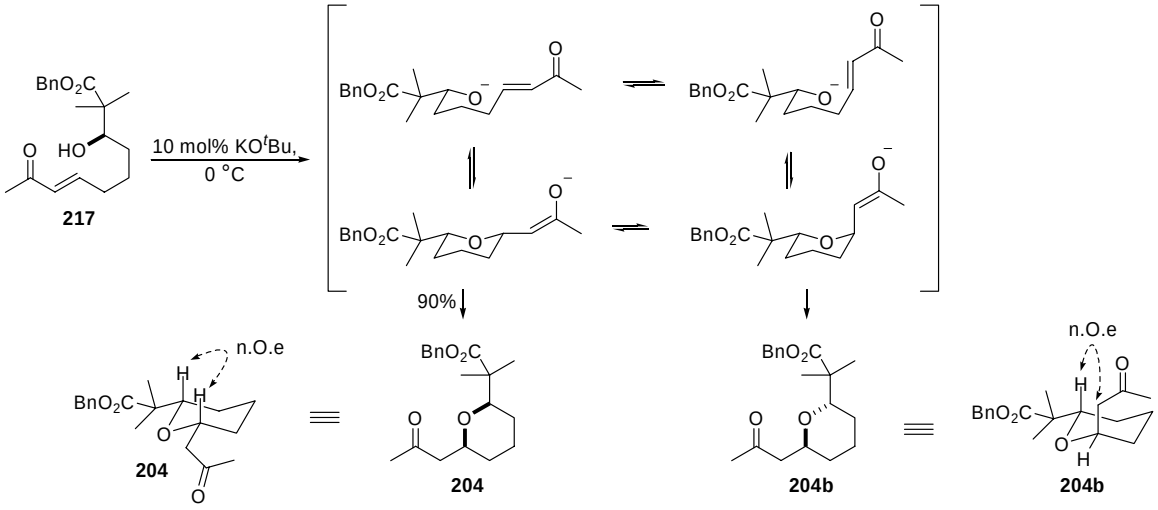


Reagents and conditions: (a) (+)-Ipc$_2$BOMe, allylMgBr, Et_2O, -78 ˚C (80%, 94% ee) or (b) **218**, PhMe, -10 ˚C (67%, 95% BRSM, 98% ee); (c) Acrolyl-Cl, DIPEA, DMAP, CH_2Cl_2, 0 ˚C (83%); (d) 5 mol% Grubbs 2nd Gen. Cat., CH_2Cl_2, rt (76%); (e) $NiCl_2{\cdot}6H_20$, $NaBH_4$, THF, 0 ˚C (87%); (f) DIBAL-H, CH_2Cl_2, -78 ˚C, (96%); (g) 1-triphenylphosphoranilydene-2-propanone, CH_3CN, 90 ˚C (70%); (h) 500 psi H_2/CO, 20% Nixantphos, 5% $Rh(CO)_2$acac, 50 ˚C (77%).

Wittig olefination of hemiacetal **216** afforded enone **217** (70%), which was primed to undergo hetero-Michael addition. In the event, treatment of alcohol **217** with catalytic potassium tertiary butoxide at 0 ˚C resulted in exclusive formation of the cis-pyran **204** (Scheme 4.5, 90%, cis configuration determined by coupling constants and n.O.e). Conjugate addition at lower temperatures (-78 ˚C) favored kinetic formation of the trans-pyran (9:1 trans:cis).

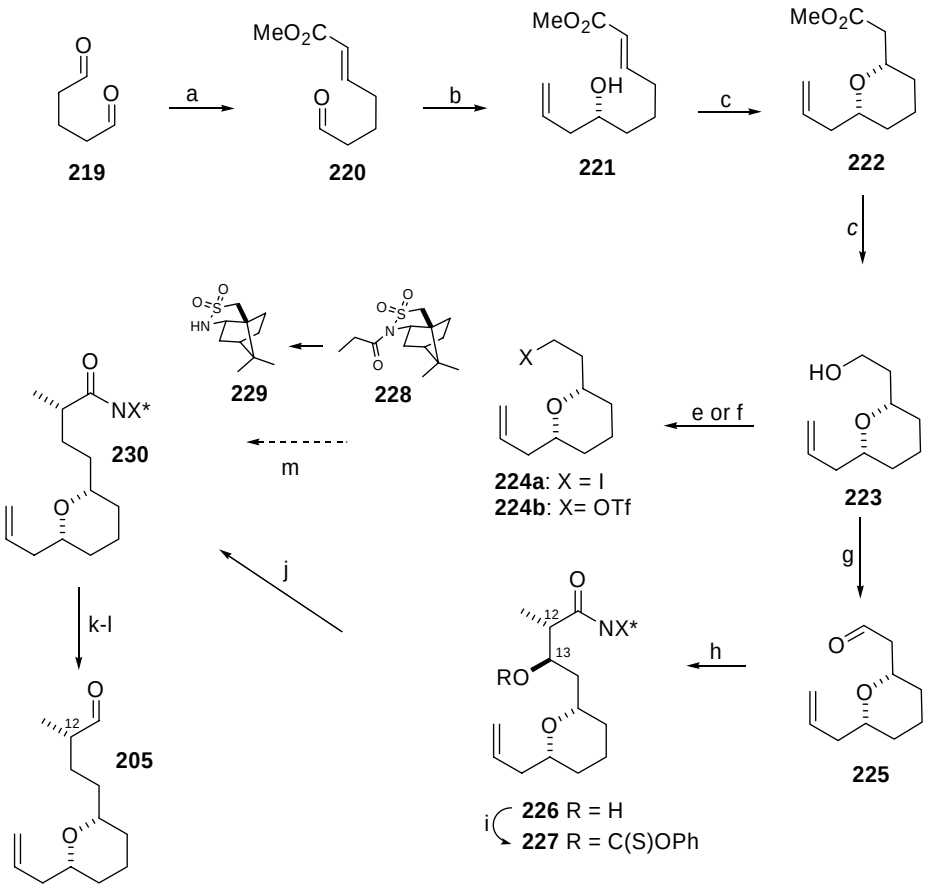
An alternative and shorter sequence to methyl ketone **204** was realized when hydroformylation[7,8] (500 psi 1:1 H_2/CO, Nixanthpos, 50 ˚C, THF) of terminal olefin **213** provided direct access to lactol **217** (75%). Under these conditions no sign of branched product formation was observed, however formation of a by-product (~15-20%) resulting from saturation of the terminal olefin did occur. Nonetheless, this reaction eliminated three steps in the sequence to methylketone **204** (4 total steps from **212**), which can be prepared in multi-gram quantitites.

Scheme 4.5



Construction of pyran **205** initiates with the asymmetric allylation of known aldehyde **220**[9] (1 step from $) with *B*-allylbis-(4-isocaranyl)borane to afforded homoallylic alcohol **221** in good yield (70%) and acceptable ee (88-92% ee)[3] (Scheme 4.6). As seen before (Scheme 4.4, **217→204**), hetero-Michael addition catalyzed by potassium tertiary butoxide (80%, -50 ˚C) led to *cis*-pyran (confirmed by n.O.e.) formation (**221→222**). In contrast to enone **217**, acrylate **221** required nearly equimolar portions of base (60 mol%) for smooth conversion to the *cis*-pyran. Next, reduction of the methyl ester was followed by conversion of the primary alcohol **223** to iodide **224a**.

Scheme 4.6



Reagents and Conditions: (a) **219**, carbomethoxymethylenetriphenylphosphorane, CH_2Cl_2 (77%); (b) *B*-allyl bis(4-isocarenyl)borane, -78 ˚C (70%, 94% ee); (c) KO^{t}Bu, THF, -78→-50 ˚C (80%); (d) $LiAlH_4$, Et_2O, 0 ˚C (99%); (e) I_2, PPh_3, imidazole, 1:1 CH_3CN:Et_2O, rt (65%); (f) $Tf_2(O)$, pyridine, CH_2Cl_2, -78 ˚C (70% crude); (g) DMSO, $(COCl)_2$, Et_3N, -78→0 ˚C (75%); (h) **228**, $TiCl_4$, DIPEA, CH_2Cl_2, -78 ˚C; then add **225**, (71%); (i) PhOC(S)Cl, pyridine, CH_2Cl_2, rt (81%); (j) Bu_3SnH, cat. AIBN, PhH, reflux (87%); (k) $LiAlH_4$, Et_2O, 0 ˚C (90%); (l) DMSO, $(COCl)_2$, Et_3N, -78→0 ˚C (95%); (m) **228**, LDA, THF -78 ˚C; **224a** or **224b**.

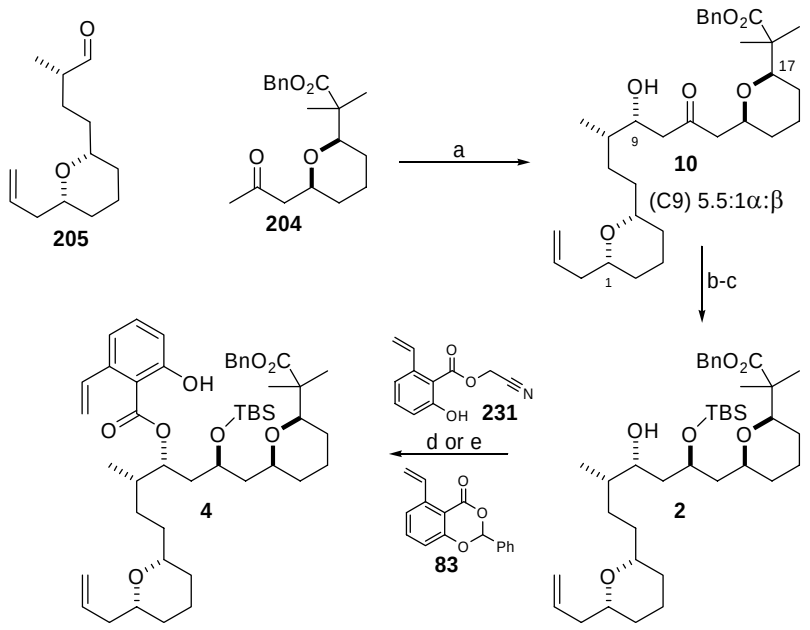
Surprisingly, alkylation of iodide **224a** or triflate **224b** with the lithium enolate derived from sulfonamide **228** was unsuccessful. Alkylation at elevated temperatures (23 ˚C) resulted in elimination to the free sulfonamide **229**. Asymmetric carbon-carbon bond formation was also attempted with Myers' pseudoephedrine based auxiliary[10]. Metal enolates derived from these reagents are noted to be quite stable at elevated temperatures, however, iodide **224a** failed to react under these conditions. This difficult transformation prompted investigation of an alternative approach for incorporation of the three carbon propionyl fragment. It was surmised that an aldol reaction of the enolate derived from

228 with aldehyde **225** would set the α-methyl stereocenter at C12. To this end, asymmetric aldol reaction of aldehyde **225** with the Z(O)-titanium enolate derived from sultam **228** resulted in formation of a single *syn*-diastereomer (as determined by ^{1}H NMR) of the β-hydroxysulfonamide **226**[11]. Removal of the unwanted C13 hydroxy group was achieved through a modified Barton-McCombie prodedure[12]. Briefly, acylation of alcohol **226** with chlorothionocarbonate provided xanthate **227**, which was then cleaved under radical generating conditions (AIBN/Bu_3SnH) to provide sulfonamide **230**. Finally, reductive cleavage of the sulfonamide auxiliary with $LiAlH_4$ and Swern oxidation of the primary alcohol afforded target aldehyde **205** in 95% yield (10 total steps from **220**).

4.3 Fragment Coupling and Salicylate Ester Formation

With fragments **204** and **205** in hand, the stage was set to investigate their coupling (Scheme 4.7). Optimization and investigation of this reaction was conducted entirely by Dr. Ashoke Bhattacharjee and is detailed elsewhere[13]. Screening of several boron enolates in this aldol reaction showed that the desired 1,5-*anti* selectivity improved as the size of the boron substituents decreased. The highest level of 1,5-induction was achieved with the diethylboron enolate derived from methyl-ketone **204** (5.5:1 α:β C9-OH). Further experimentation showed that the induced stereoselectivity was independent of aldehyde structure, thus establishing the enolborinate as the stereocontrolling element. Stereoselective reduction of the β-hydroxyketone with $Me_4N(OAc)_3BH$ yielded the desired trans-diol as the major product (82% yield) along with two minor diastereomers that were conveniently removed upon purification by flash chromatography[14].

Scheme 4.7



Reagents and Conditions: (a) **204**, Et_2BOTf, Et_3N, Et_2O, -78→0 ˚C, then add **205**, -78 ˚C (80%); (b) $Me_4N(OAc)_3BH$, AcOH, CH_3CN, rt (70%); (c) TBSCl, imidazole, cat. DMAP, DMF, -10 ˚C (80%); (d) **83**, hν 300 nm, 1,4-dioxane, rt (20%, 50% BRSM); (e) **230**, K_2CO_3, DMA, microwave 200 ˚C (25%, 46% BRSM).

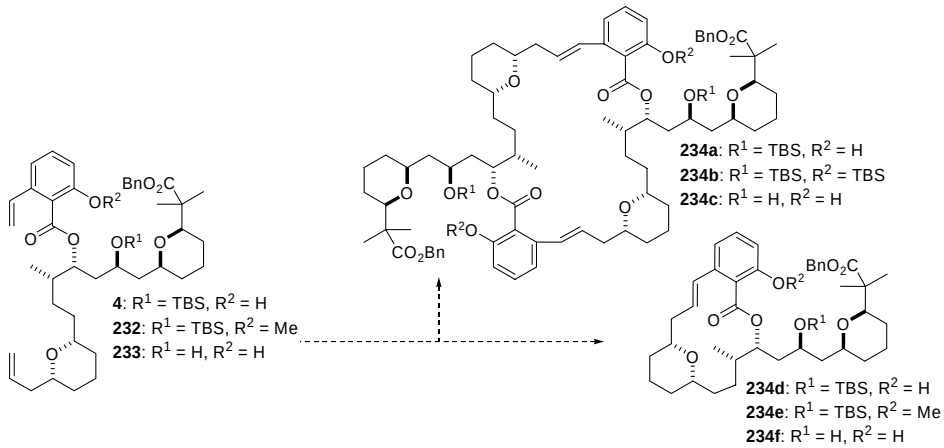
Regioselective protection of the less hindered C9 hydroxyl was accomplished in 80% yield with imidazole, DMAP, and a modest excess of TBSCl at -10 ˚C. Incorportation of the salicylate moiety was now required to access dimerization precursor **4**. As discussed previously (see chapter 2), synthesis of the salicylate ester in this context was challenging. Utilization of cyanomethyl ester **231** under microwave conditions provided the desired material in 25% yield, however considerable decomposition also took place in this reaction. Finally, we discovered that photolysis of quinoketenes precursors such as benzodioxinone **83**, provided a means to acylate alcohol **2**. Successful acylation now allowed for the examination of the metathesis based dimerization of **4**.

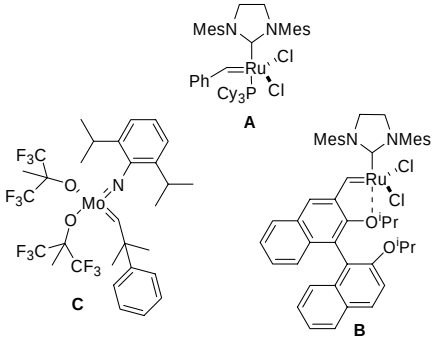
4.4 Metathesis Based Dimerization

As shown in table 4.1, attempted tandem cross metathesis/ring closing metathesis of several bis olefins (**4**, **232**, **233**) with ruthenium and molybdenum based catalysts **A**, **B**,

and **C** failed to produce the desired dimer. The corresponding cyclomonomer was obtained with catalyst **A** and **B**. As noted in table 4.2 (entry 4), using an excess of catalyst **A** was required to obtain the ring closing metathesis product **234** (30%) in respectable yields

Table 4.1 Metathesis Dimerization





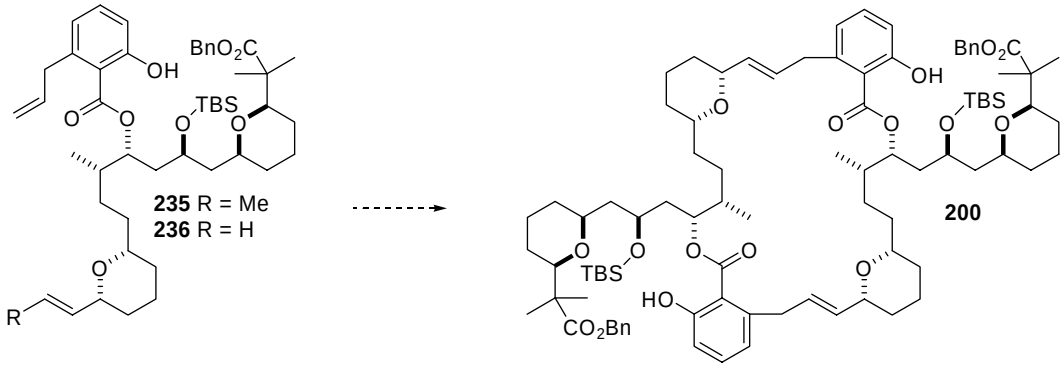
Entry	Substrate	Catalyst (mol%)	Conditions	Results
1	**4**	**A** (30)	CH_2Cl_2, r.t. 17 hr	S.M. Recovered
2	**232**	**A** (15)	Toluene, 55 °C, 2 d	Decomposition
3	**4**	**C** (55)	Ph-H, r.t. 6 hr	S.M. Recovered
4	**4**	**A** (125)	Ph-H, r.t., 12 hr	30% **234d** + Decomposition
5	**233**	**B** (30)	CH_2Cl_2, r.t. 24 hr	25% **234f** + Decompositon
6	**4**	**B** (30)	CH_2Cl_2, r.t. 24 hr	15% **234d** + Decompositon

Schrock's molybdenum based catalyst **C**[15] failed to react with olefin **4** completely, perhaps due to decomposition or poisoning of the catalyst (entry 3). Another dimerization attempt with 20 mol% air-stable catalyst **B**[16] (Table 4.1, entry 6) yielded intramolecular macrocycle **234d** once again. The apparent preference for the intramolecular metathesis product was disappointing, and the substrates examined in

table 4.1 were clearly predisposed to undergo intramolecular ring closing metathesis. The lack of dimer formation in these reactions indicates that either 1) a thermodynamic system was not established to funnel the reactive intermediates to the most stable head-to-tail dimer, or 2) the intramolecular ring closing metathesis products are the thermodynamic products.

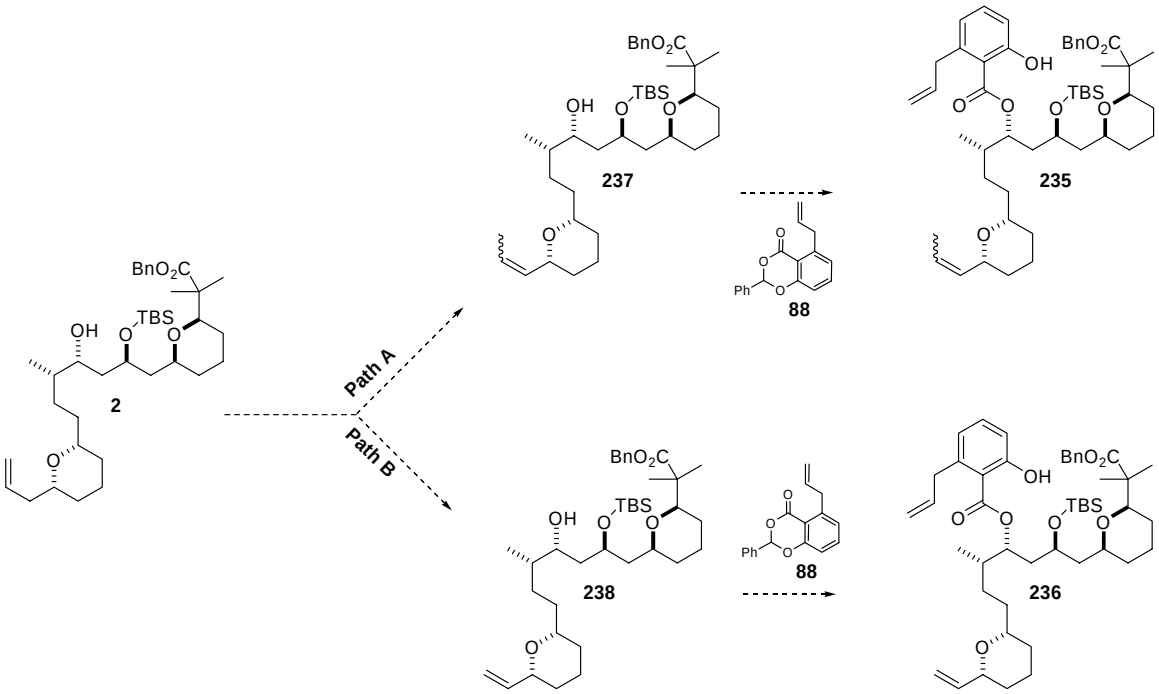
Despite these disappointing results, further experimention in this area with deconjugated olefins was persued (Fig. 4.2, Path C). Few examples of metathesis reactions conducted with substituted styryl derivatives exist in the literature, perhaps due to their poor reactivity in olefin metathesis reactions[17]. In this context, we decided to explore the metathesis based dimerization with olefin transposed substrates **235** and **236** (Scheme 4.8).

Scheme 4.8



Utilization of this *o*-allyl benzoate ester requires truncation of the pyran containing olefin to obtain the desired 28 membered macrocycle (Scheme 4.5). Our general strategy provided for this eventuality (Fig. 4.2), and as discussed previously, olefin transposition of alcohol **2** to **235** would quickly provide a precursor en route to a dimerization precursor (Scheme 4.9, Path A).

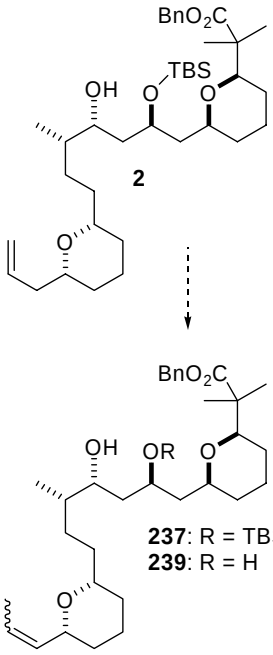
Scheme 4.9



An alternative approach involves excision of a methylene unit to yield truncated olefin **238** (Path B), followed by photochemical esterification with **88** to provide the desired bis-olefin **236**.

In an attempt to conduct the shortest possible sequence to a new diene, we chose to pursue path A first. As shown in table 4.2, several conditions were attempted to effect the isomerization of terminal olefin **2**.

Table 4.2 Olefin Isomerization



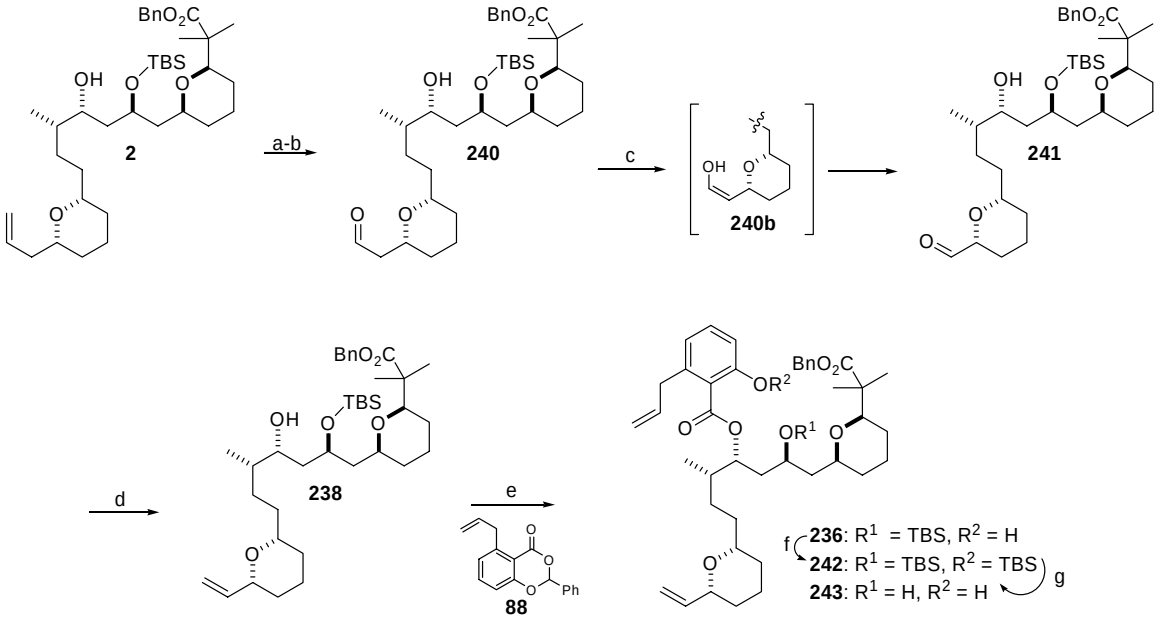
Entry	Substrate	Conditions	Result
1	**2**	10 mol% $RhCl(PPh_3)_3$,3:1 EtOH: H_2O, 70 ^oC 12 hr	16% Yield of 1:1 mixture of **2** and **237**
2	**2**	50 mol% $CoCl_2$, 1.5eq. PPh_3, 50 mol% $NaBH_4$, THF,-20 ^oC	SM Recovered
3	**2**	10eq. $CH_2CHSi(OMe)_3$, 5 mol% Grubbs 2nd Gen. cat., CH_2Cl_2, 45 ^oC 3 hr.	Decomposition + 30% **2**
4	**2**	10eq. ethylvinylether, 5 mol% Grubbs 2nd Gen. cat., CH_2Cl_2, r.t. 12 hr, 50 ^oC 14 hr.	SM Recovered
5	**2**	5 mol% $RhCl_3$, 5:1 EtOH:H_2O, 65 ^oC 19 hr	9% Yield of **237**
6	**2**	10 mol% $PdCl_2(PhCN)_2$, PhH, 80 ^oC 3 hr, r.t 24 hr	Traces of **239** + decomposition

Our efforts in this area focused on transition metal mediated olefin isomerization[18]. Unfortunately, many of the conditions attempted resulted in either extensive decomposition to unidentified by-products or were completely unproductive. For example, olefin **2** with either Wilkinson's catalyst[19] (Table 4.2, entry 1) or rhodium trichloride[20] (Table 4.2, entry 5) provided small quantities of a transposed product in addition to an intractable mixture of polar by-products. Also, a mild procedure which utilizes *in situ* prepared cobalt hydride was surprisingly unproductive[21] (Table 4.2, entry 2). Finally, a recently disclosed method for the catalytic isomerization of olefins with Grubbs' 2nd generation catalyst[22] was employed and resulted in recovered starting material on two occasions (Table 4.2, Entries 3-4).

After these preliminary findings, synthesis of truncated olefin **238** was examined (Path B, Scheme 4.9). Following a standard dihydroxylation/oxidative cleavage of the terminal olefin **2**, a second oxidative cleavage of aldehyde **240** (via the corresponding

enol **240b**), as described by Cossy and co-workers[23], provided shortened aldehyde **241** (40%, 3 Steps). Wittig olefination of this sensitive aldehyde provided terminal olefin **238** (20%) (Scheme 4.10).

Scheme 4.10

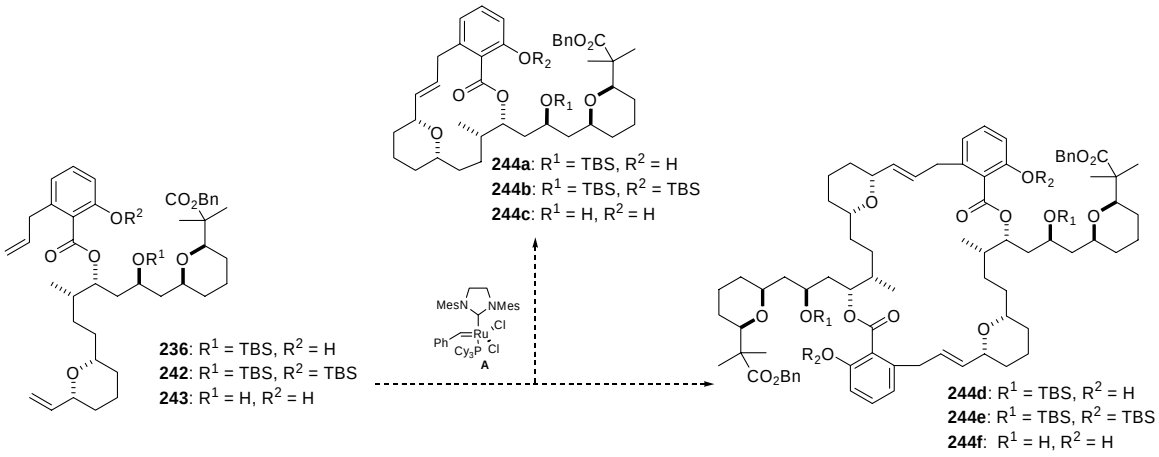


Reagents and Conditions: (a) 5% OsO_4, NMO, acetone, rt; (b) $NaIO_4$·silicagel, CH_2Cl_2, rt; (c) 10% OsO_4, NMO, NMM, 9:1 acetone:H_2O, rt (40% 3 steps); (d) PPh_3MeBr, n-BuLi, 0 ˚C; then add **241**, 0 ˚C (20%); (e) **88**, hν 300 nm, 1,4-dioxane, (22%); (f) TBSCl, imidazole, cat. DMAP, DMF, rt (95%); (*g*) TBAF, THF, rt (67%).

Although the sequence to olefin **238** provided the desired product, substantial quantities of advanced material was sacrificed due to several low yielding steps. Despite this, enough material was available for the photochemical acylation.

Photoacylation of alcohol **238** with benzodioxinone **88** led to the desired ester **236**. Once again, substrates with various protecting group combinations were prepared to thoroughly explore the metathesis dimerization.

Table 4.3 Metathesis Dimerization of Truncated Substrate



Entry	Substrate	Catalyst (mol%)	Conditions	Results
1	**242**	**A** (20)	CH_2Cl_2, 40 ^oC, 3 hr	**244b** by Mass Spec
2	**236**	**A** (20)	CH_2Cl_2, r.t., 6 hr	S. M. Recovered
3	**236**	**A** (15)	1,2-dichloroethane, 40 ^oC 2 hr	S. M. Recovered
4	**242**	**A** (30)	1,2-dichloroethane, 3 hr 45 ^oC, 14 hr r.t.	**244b** by Mass Spec
5	**242**	**A** (30)	CH_2Cl_2, 1 hr r.t,. 4 hr 45 ^oC	Decompositon
6	**243**	**A** (20)	CH_2Cl_2, 12 hr r.t., 4 hr 40 ^oC	Decompositon

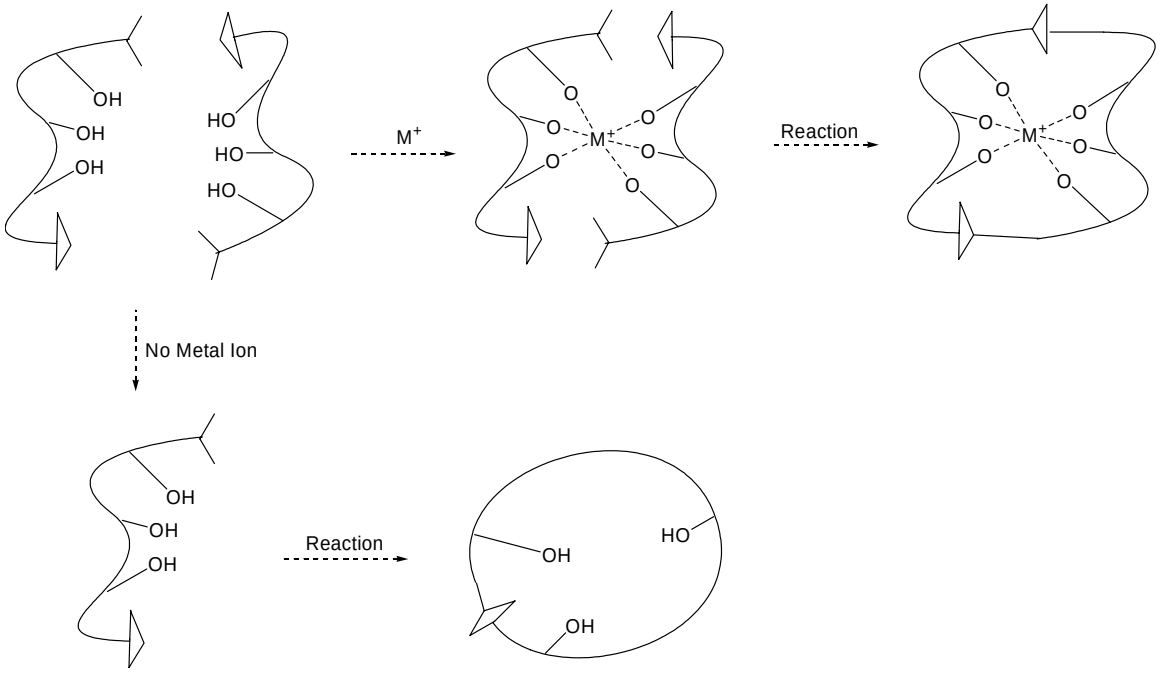
As before (see table 4.2), bis olefins **236**, **242**, and **243** were treated with Grubbs' ruthenium alkylidene catalyst **A** in dichloromethane or 1,2-dichloroethane. Surprisingly, we found these substrates to be unreactive at ambient temperature. In addition, attempted dimerization at elevated temperatures (40 to 45 ˚C) led to rapid decomposition of the starting materials; perhaps via oligomerization. At this stage, it was clear to us that dimerization via olefin metathesis was not an ideal approach to the natural product, and that alternative dimerization strategies should be examined.

4.5 Summary and Future Experiments

In this chapter we described an efficient synthesis of a monomeric fragment that contains all of the carbon atoms found in the dimeric natural product SCH 351448.

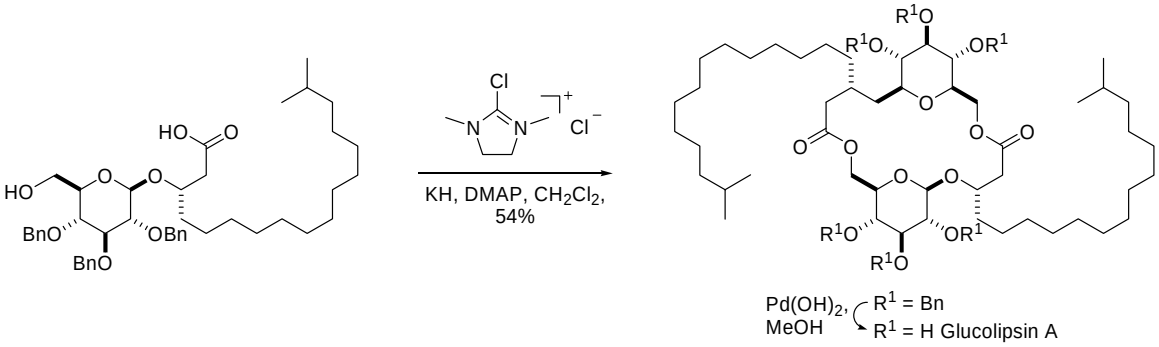
Several attempts to induce a tandem cross metathesis/ring closing metathesis were unsuccessful. Further experimentation in this area may include a metal templated metathesis dimerization of a fully deprotected bis olefin (Scheme 4.11). The x-ray crystal structure of SCH 351448 shows a central hepta-coordinated sodium cation that complexes polar functional groups from several regions of the molecule. The preference for this coordination sphere may be exploited to affect a head-to-tail dimerization en-route to the natural product. As shown in scheme 4.11, metal complexation may induce pre-organization of two identical monomeric units that can then undergo facile head-to-tail dimer formation.

Scheme 4.11



Metal complexation as a means to access macrocyclic dimers has been successfully applied for natural products synthesis such as glucolipsin A by Fürstner and coworkers[24] (Scheme 4.12), and may be a means to avoid intramolecular macrocyclization in the context of an SCH 351448 synthesis.

Scheme 4.12



4.6 Experimental Section

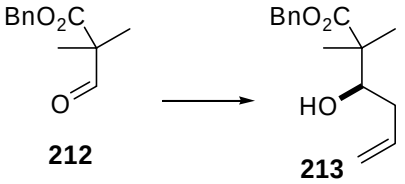
4.6.1 Materials and Methods

Unless otherwise noted, commercially available materials were used without further purification. All solvents were of HPLC or ACS grade. Solvents used for moisture sensitive operations were distilled from drying reagents under a nitrogen atmosphere: Et_2O and THF from sodium benzophenone ketyl; benzene and toluene from sodium; CH_2Cl_2 from CaH_2, pyridine over solid KOH, anhydrous N,N-dimethylformamide, and CH_3CN were purchased from commercial sources. Reactions were performed under an atmosphere of nitrogen with magnetic stirring unless noted otherwise. All photochemical reactions were performed with a Rayonett RPR-100 reactor fitted with a test tube carousel and 300 nm bulbs. Flash chromatography (FC) was performed using *E Merck* silicagel 60 (240–400 mesh) according to the protocol of Still, Kahn, and Mitra (*J. Org. Chem.* **1978**, *43*, 2923). Thin layer chromatography was performed performed using precoated plates purchased from *E. Merck* (silicagel 60 PF254, 0.25 mm) that were visualized using a $KMnO_4$ or Ce (IV) stain.

Nuclear magnetic resonance (NMR) spectra were recorded on a *Varian Inova*-400 or *Mercury*-300 spectrometer at operating frequencies of 400/300 MHz (^{1}H NMR) or 100 / 75 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform δ 7.26 for ^{1}H NMR or δ 77.23 for proton decoupled ^{13}C NMR), and coupling constants (*J)* in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet, whereby the prefix app is applied in cases where the true multiplicity is unresolved, and *br* when the signal in question is broadened.

Infrared spectra were recorded on a *Perkin-ElmerI* 1000 series FTIR with wavenumbers expressed in cm^{-1} using samples prepared as thin films between salt plates. Electrospray ionization mass spectra (ESI-MS) were recorded on a Shimadzu 2010-LCMS. Optical rotations were measured at 20 ˚C on a Rudolph Research Analytical Autopol® IV polarimeter.

4.6.2 Preparative Procedures



212 **213**

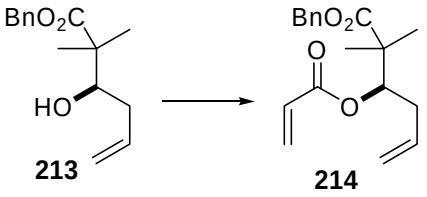
Alcohol 213 (*Procedure A*). Allylmagnesium bromide (1 M in Et_2O, 32.3 mL, 32.3 mmol) was added dropwise to a stirred solution of (+)-*B*-methoxy diisopinocampheylborane (10.8 g, 34 mmol) in Et_2O (50 mL) at -78 ˚C. The mixture was then stirred for 1 hr at -78 ˚C, allowed to warm to rt, and stirred for 2 hr, filtered under nitrogen and re-cooled to -78 ˚C. A solution of aldehyde **212** (3.5 g, 17 mmol) in Et_2O (20

mL) was added dropwise and the reaction mixture was stirred for 4 hr. The reaction was quenched with EtOH:THF (1:1, 34 mL), phosphate buffer (pH = 7, 34 mL) and 30% aq. H_2O_2 (34 mL) and stirred at rt for 24 hr. Extraction (EtOAc, 3 × 100 mL), washing (brine), drying and concentration afforded 3.3 g (79%) pure alcohol **213** after purification by FC (10/90, EtOAc/Hex).

Alcohol 213 (*Procedure B*). To a roundbottom flask charged with allylsilane **218** (8.8 g, 32.6 mmol) and toluene (50 mL) at 0 ˚C was added a solution of aldehyde **212** (5.18 g, 25.0 mmol) in toluene (10 mL). The reaction was then stored in a freezer at -10 ˚C overnight. The reaction was then poured into 1M HCl (100 mL), and extracted with Et_2O (2 x 250 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (10/90, EtOAc/Hex) to afford 4.16 g (67%) of alcohol **213**, and 1.3 g of recovered aldehyde **212** (25%). $[\alpha]_D$ = +4 ($CHCl_3$, *c* 1.0). IR (film) 3508, 2978, 1724, 1640, 1456, 1261, 1136, 1069, 991, 914, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.39 (5H, m), 5.85 (1H, dddd, *J* = 6.4, 7.6, 9.6, 17.4 Hz), 5.14 (2H, s), 5.06–5.13 (2H, m), 3.75 (1H, ddd, *J* = 2.0, 5.6, 10.0 Hz), 2.34 (1H, d, *J* = 5.6 Hz), 2.22–2.28 (1H, m), 2.04 (1H, *br* ddd, *J* = 8.8, 10.0, 14.0 Hz), 1.23 (3H, s), 1.22 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 136.1, 135.7, 128.6, 128.3, 128.0, 117.6, 75.6, 66.4, 47.1, 36.6, 21.7, 20.7. HRMS (FAB, MNBA, added LiI) Calcd for $C_{15}H_{20}O_3Li$ (MLi^+): 255.1573. Found: 255.1588.

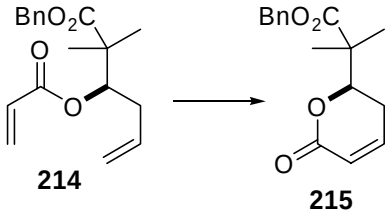
(*S*)-Mosher ester of homoallylic alcohol **213**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 7.0 Hz), 7.30–7.42 (8H, m), 5.21 (1H, dddd, *J* = 6.8, 6.8, 10.0, 17.6 Hz), 5.57 (1H, *app*.t, *J* = 6.4 Hz), 5.10 (1H, d, *J* = 12.0 Hz), 5.02 (1H, d, *J* = 12.0 Hz), 4.98–5.05 (2H,

m), 3.51 (3H, s), 2.31–2.37 (2H, m), 1.17 (3H, s), 1.16 (3H, s). Integration of H_3CO- at 3.51 (major) and 3.47 ppm (minor) indicated 94% ee.

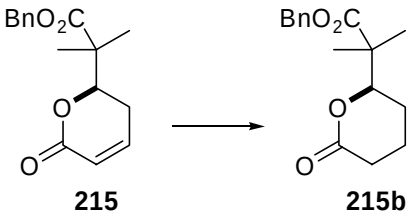


213 **214**

Diene 214. To a solution of homoallylic alcohol **213** (1.2 g, 4.8 mmol), *i*-Pr_2NEt (2 mL, 12 mmol) and DMAP (59 mg, 0.48 mmol) in CH_2Cl_2 (15 mL) was added acryloyl chloride (1 mL, 9.6 mmol) at 0 ˚C. After stirring for 1 hr, the reaction mixture was diluted with EtOAc (50 mL) and aq. NH_4Cl (50 mL), extracted (EtOAc, 2 × 50 mL), washed with 1N aq. HCl (3 × 50 mL) and saturated aq. $NaHCO_3$ (3 × 50 mL), dried and concentrated. After purification by FC (4/96, EtOAc/Hex), 1.2 g (83%) of pure ester **214** was obtained. $[\alpha]_D$ = -25 ($CHCl_3$, *c* 1.5). IR (film) 1732, 1637, 1456, 1405, 1265, 1189, 1143, 986, 806, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.40 (5H, m), 6.37 (1H, dd, *J* = 0.8, 17.2 Hz), 6.05 (1H, dd, *J* = 10.4, 17.2 Hz), 5.82 (1H, dd, *J* = 0.8, 10.4 Hz), 5.67 (1H, dddd, *J* = 6.8, 6.8, 10.0, 17.2 Hz), 5.38 (1H, app t, *J* = 6.4 Hz), 5.14 (1H, d, *J* = 12.0 Hz), 5.07 (1H, d, *J* = 12.0 Hz), 4.99 (1H, *br* dd, *J* = 17.2 Hz), 4.98 (1H, *br* d, *J* = 10.0 Hz), 2.24 (2H, app t, *J* = 6.8 Hz), 1.23 (3H, s), 1.227 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 165.5, 135.9, 134.1, 130.9, 128.6, 128.4, 128.3, 117.7, 76.3, 66.6, 46.6, 35.3, 22.2, 20.5. HRMS (FAB, MNBA, added LiI) Calcd for $C_{18}H_{22}O_4Li$ (MLi^+): 309.1678. Found: 308.1671.

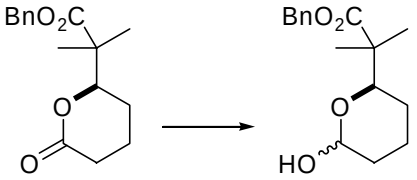


Acrylate 192. To a solution of Grubb's 2nd generation catalyst (170 mg, 5 mol%) in CH_2Cl_2 (400 mL) was added acryloyl ester **214** (1 g, 3.3 mmol) over 30 min at rt. After stirring for 4 hr, the solvent was evaporated and the crude mixture was purified by FC (20/80, EtOAc/Hex) to give 880 mg (76%) of pure lactone **215**. $[\alpha]_D$ = +72 ($CHCl_3$, *c* 1.0). IR (film) 1738, 1732, 1455, 1383, 1257, 1132, 1078, 1039, 815, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.40 (5H, m), 6.86 (1H, ddd, *J* = 2.0, 6.4, 10.0 Hz), 6.02 (1H, dd, *J* = 2.4, 10.0 Hz), 5.16 (2H, s), 4.66 (1H, dd, *J* = 3.6, 12.8 Hz), 2.41 (1H, dddd, *J* = 2.0, 2.4, 12.8, 18.2 Hz), 2.21 (1H, ddd, *J* = 3.6, 6.4, 18.2 Hz), 1.36 (3H, s), 1.26 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 164.0, 145.2, 135.8, 128.7, 128.4, 128.1, 121.3, 81.4, 66.8, 45.9, 24.7, 21.4, 20.4. HRMS (FAB, MNBA, added LiI) Calcd for $C_{16}H_{18}O_4Li$ (MLi^+): 281.1365. Found: 281.1376.



Lactone 215b. To a mixture of unsaturated lactone **215** (507 mg, 1.8 mmol) and $NiCl_2 \cdot 6H_20$ (650 mg, 2.7 mmol) in THF (25 mL) was added $NaBH_4$ (205 mg, 5.4 mmol) in portions at 0 ˚C. Within 5 min gas evolution started and the solution turned black. Stirring was continued for 2 hr at the same temperature after which the reaction was

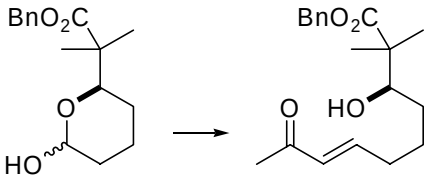
diluted with Et_2O (100 mL) and quenched with 1N aq. HCl (50 mL). An extraction was performed (Et_2O, 2 × 50 mL) and the combined organic layers were washed with aq. $NaHCO_3$ (2 × 100 mL), dried and concentrated. After purification of the crude mixture by FC (20/80, EtOAc/Hex), 420 mg (82%) of pure lactone **215b** and 33 mg (6%) of lactol **216** were obtained. $[\alpha]_D$ = -11 ($CHCl_3$, *c* 1.0). IR (film) 1735, 1500, 1455, 1244, 1130, 1050, 1003, 738, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.38 (5H, m), 5.14 (2H, s), 4.52 (1H, dd, *J* = 2.8, 11.6 Hz), 2.58 (1H, ddd, *J* = 4.8, 6.4, 17.3 Hz), 2.37 (1H, ddd, *J* = 8.4, 8.4, 17.3 Hz), 1.84–1.94 (1H, m), 1.71–1.84 (2H, m), 1.46–1.59 (1H, m), 1.30 (3H, s), 1.21 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 171.1, 135.8, 128.5, 128.2, 127.9, 83.8, 66.5, 46.3, 29.3, 22.7, 20.8, 20.2, 18.4. HRMS (FAB, MNBA, added LiI) Calcd for $C_{16}H_{20}O_4Li$ (MLi^+): 283.1522. Found: 283.1523.



215b **216**

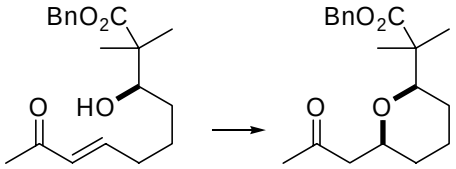
Lactol 216 (*Procedure A*). DIBAL-H (1.0 mL, 5.6 mmol) was added dropwise to a solution of lactone **215b** (1.54 g, 5.6 mmol) in THF (50 mL) at -78 ˚C and stirred for 1 hr. The reaction was quenched with 2N aq. Na-K tartrate (10 mL) and stirred at rt for ½ hr. After extraction with ether (3 × 100 mL), washing with aq. $NaHCO_3$ (3 × 100 mL) and brine (3 × 100 mL), drying and concentration, the crude residue was purified by FC (15/85, EtOAc/Hex) to afford 1.48 g (96%) of pure lactol **216** as a 1:1 mixture of anomers.

Lactol 193 (*Procedure B*). A Parr bomb reaction vessel was charged with alcohol **213** (1.5 g, 6.04 mmol) NIXANTPHOSligand (400 mg, 0.72 mmol), $Rh(CO)_2acac$ (78 mg, 0.30 mmol), and THF (10 mL). The starting materials were mixed thoroughly so as to obtain a homogenous solution prior to addition to the high pressure reactor. The reactor was then sealed and flushed with 250 psi H_2 (3X). Then the reactor was pressured with 225 psi H_2 and 225 psi CO. The reactor was then placed in a 50 ˚C oil bath and stirred for 20 hr. The reaction was then brought to room temperature and the pressure was released. The cude material was then collected and the reaction was repeated on the same scale (4X). The crude material from all five reactions was combined and concentrated *in-vacuo*. The crude residue was purified directly by FC (10/90, EtOAc/Hex) to afford 6.4 g (77%) of lactol **216**. $[\alpha]_D$ = -36 ($CHCl_3$, *c* 1.6). IR (film) 3450, 1729, 1500, 1456, 1267, 1139, 1035, 979, 916, 736, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.41 (5H, m), 5.38 (0.5H, d, *J* = 12.0 Hz), 5.22 (0.5H, d, *J* = 12.4 Hz), 5.08 (0.5H, *br* s), 5.05 (0.5H, d, *J* = 12.4 Hz), 4.93 (0.5H, d, *J* = 12.0 Hz), 4.53–4.58 (0.5H, m), 4.16 (0.5H, dd, *J* = 1.6, 11.6 Hz), 3.65 (0.5H, dd, *J* = 1.6, 11.2 Hz), 2.63–2.72 (0.5H, m), 1.72–1.88 (2H, m), 1.24–1.63 (4H, m), 1.23 (1.5H, s), 1.17 (1.5H, s), 1.16 (1.5H, s), 1.13 (1.5H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 176.6, 136.7, 156.6, 128.71, 128.7, 128.6, 128.5, 128.3, 96.9, 92.2, 80.7, 73.3, 66.2, 65.9, 46.5, 46.3, 32.6, 29.6, 24.8, 24.2, 22.1, 22.0, 21.6, 20.1, 19.2, 17.7. HRMS (FAB, MNBA, added LiI) Calcd for $C_{16}H_{22}O_4Li$ (MLi^+): 285.1678. Found: 285.1675.



216 **217**

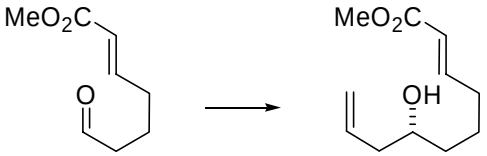
Enone 217. A mixture of lactol **216** (505 mg, 1.8 mmol) and 1-triphenylphosphoranylidene-2-propanone (700 mg, 2.2 mmol) was refluxed in acetonitrile (20 mL) for 30 hr. After removal of the solvent, the residue was dissolved in EtOAc (50 mL) and filtered. The filtrate was washed with brine (3 × 50 mL), dried, concentrated and purified by FC (30/70, EtOAc/Hex) to yield 400 mg (70%) of unsaturated ketone **217**. $[\alpha]_D$ = +15 ($CHCl_3$, *c* 0.35). IR (film) 3453, 1727, 1700, 1672, 1626, 1456, 1363, 1258, 1129, 980, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.40 (5H, m), 6.77 (1H, ddd, *J* = 6.8, 6.8, 16.0 Hz), 6.06 (1H, d, *J* = 16.0 Hz), 5.14 (2H, s), 3.63 (1H, ddd, *J* = 2.0, 6.8, 6.8 Hz), 2.47 (1H, d, *J* = 6.8 Hz), 2.23 (3H, s), 2.14–2.27 (2H, m), 1.71–1.82 (1H, m), 1.36–1.55 (2H, m), 1.20–1.36 (1H, m), 1.21 (3H, s), 1.20 (3H, s); ^{13}C NMR (75MHz, $CDCl_3$) δ 198.9, 177.6, 148.2, 136.0, 131.6, 128.8, 128.5, 128.1, 76.5, 66.6, 47.4, 32.5, 31.2, 27.1, 25.4, 22.4, 20.5. HRMS (FAB, MNBA, added LiI) Calcd for $C_{19}H_{26}O_4Li$ (MLi^+): 325.1991. Found: 325.2008.



217 **204**

Pyran 204. KO^{t}Bu (4.16 mg, 0.037 mmol) was added to a solution of unsaturated ketone **217** (118 mg, 0.37 mmol) in THF (5 mL) at 0 ˚C and stirred for 10 min. The reaction was quenched with sat. aq. NH_4Cl (1 mL), extracted with ether (3 × 30 mL), washed with brine, dried, concentrated and purified by FC (10/90, EtOAc/Hex) to provide 105 mg (90%) pure *cis*-tetrahydropyran derivative **204**. $[\alpha]_D$ = +4 ($CHCl_3$, *c* 0.6). IR (film) 1732,

1716, 1500, 1456, 1357, 1262, 1155, 1129, 1086, 1047, 913, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.38 (5H, m), 5.08 (2H, s), 3.73 (1H, dddd, *J* = 1.6, 4.4, 8.0, 10.8 Hz), 3.56 (1H, dd, *J* = 1.6, 11.2 Hz), 2.52 (1H, dd, *J* = 8.0, 14.8 Hz), 2.32 (1H, dd, *J* = 4.4, 14.8 Hz), 2.12 (3H, s), 1.80–1.89 (1H, m), 1.42–1.63 (3H, m), 1.09–1.30 (2H, m), 1.17 (3H, s), 1.12 (3H, s); ^{13}C NMR (75MHz, $CDCl_3$) δ 208.3, 176.7, 136.6, 128.6, 128.2, 128.1, 82.5, 75.3, 66.3, 50.3, 46.8, 31.5, 31.4, 24.9, 23.5, 21.5, 20.2. HRMS (FAB, MNBA, added LiI) Calcd for $C_{19}H_{26}O_4Li$ (MLi^+): 325.1991. Found: 325.1989. Cis configuration of the pyran was confirmed by n.O.e experiment.

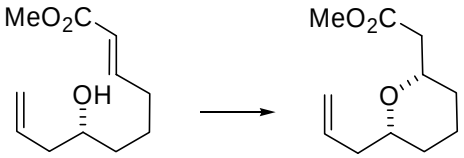


220 **221**

Alcohol 221. To a solution of *B*-allyl bis-(4-isocaranyl)borane (prepared from 3-carene, 2.4 g, 5.2 mmol) in Et_2O:pentane (1:1, 40 mL) was added aldehyde **220** (0.6 g, 4 mmol) at -78 °C. After stirring at -78 °C for 4 hr, the reaction mixture was quenched with EtOH (10 mL). Phosphate buffer (pH = 7, 10 mL) and 30% aq. H_2O_2 (10 mL) were added and the mixture was stirred at rt for 24 hr, extracted with EtOAc (3 × 50 mL), washed, dried, concentrated and purified by FC (20/80, EtOAc/Hex) to yield 530 mg of homoallyl alcohol **221** (70%). $[\alpha]_D$ = +8 ($CHCl_3$, *c* 0.3). IR (film) 3441, 1726, 1658, 1624, 1437, 1274, 1203, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (1H, ddd, *J* = 7.2, 7.2, 15.6 Hz), 5.82 (1H, *br* d, *J* = 15.6 Hz), 5.75–5.85 (1H, m), 5.13 (1H, *br* d, *J* = 11.6 Hz), 5.12 (1H, *br* d, *J* = 15.6 Hz), 3.71 (3H, s), 2.28 (1H, ddd, *J* = 4.8, 6.4, 14.0 Hz), 2.22 (1H, app dt, *J* = 7.2, 7.2 Hz), 2.13 (1H, ddd, *J* = 8.0, 8.0, 14.0 Hz), 1.57–1.73 (2H, m), 1.40–1.57

(3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 149.4, 134.8, 121.3, 118.5, 70.5, 51.6, 42.2, 36.3, 32.3, 24.3. MS (CI) *m/z* 199 ([MH^+], 16), 121 (100).

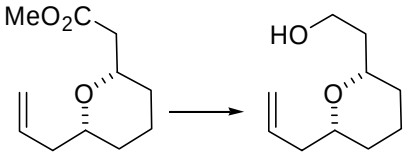
(*R*)-Mosher ester of homoallylic alcohol **221**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.57 (2H, m), 7.36–7.43 (3H, m), 6.83 (1H, ddd, *J* = 6.4, 6.4, 15.6 Hz), 5.75 (1H, *br* d, *J* = 15.6 Hz), 5.74 (1H, dddd, *J* = 6.8, 6.8, 9.6, 16.8 Hz), 5.15 (1H, app tt, *J* = 5.6 Hz), 5.12 (1H, *br* d, *J* = 16.8 Hz), 5.11 (1H, *br* d, *J* = 9.6 Hz), 3.73 (3H, s), 3.56 (3H, s), 2.34–2.47 (2H, m), 2.03–2.17 (2H, m), 1.55–1.64 (2H, m), 1.25–1.38 (2H, m). Integration of the peaks at 6.83 ppm (major) and 6.92 ppm (minor) indicated 92% ee.



221 **222**

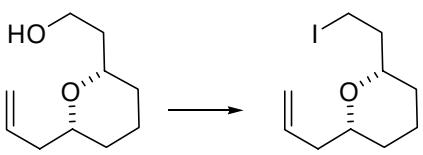
Pyran 222. A solution of KO^{t}Bu (760 mg, 6.35 mmol) in THF (7 mL) was added to a solution of homoallyl alcohol **221** (2.16 mg, 10.9 mmol) in THF (5 mL) at -78 °C and slowly warmed to -50 °C. After stirring for 30 min at -50 °C, the reaction was quenched with saturated aq. NH_4Cl (1 mL) and extracted with ether (3 × 30 mL), washed, dried, concentrated. The residue was purified by FC (5/95, EtOAc/Hex) to give 1.74 g (80%) of pure *cis*-tetrahydropyran derivative **222** as the only diastereomer. $[\alpha]_D$ = -5 ($CHCl_3$, *c* 1.8). IR (film) 1744, 1643, 1437, 1198, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, dddd, *J* = 7.2, 7.2, 10.4, 17.2 Hz), 5.04 (1H, *br* d, *J* = 17.2 Hz), 4.99 (1H, *br* d, *J* = 10.4 Hz), 3.75 (1H, dddd, *J* = 1.6, 5.6, 8.0, 10.8 Hz), 3.67 (3H, s), 3.36 (1H, dddd, *J* = 1.6, 6.4, 6.8, 10.8 Hz), 2.54 (1H, dd, *J* = 8.0, 15.2 Hz), 2.39 (1H, dd, *J* = 5.6, 15.2 Hz), 2.27 (1H, *br* ddd, *J* = 6.8, 6.8, 14.0 Hz), 2.12 (1H, *br* ddd, *J* = 6.4, 7.2, 14.0 Hz), 1.79–

1.86 (1H, m), 1.55–1.66 (2H, m), 1.46–1.57 (1H, m), 1.11–1.27 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 135.2, 116.5, 77.8, 74.6, 51.7, 41.7, 40.9, 31.3, 30.8, 23.5. MS (CI) *m/z* 199 ([MH^+], 44), 125 (100). Cis configuration was confirmed by n.O.e.



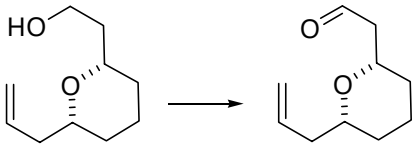
222 **223**

Alcohol 223. To a suspension of $LiAlH_4$ (288 mg, 7.6 mmol) in ether (15 mL) was added methyl ester **222** (380 mg, 1.9 mmol) at 0 °C and the mixture was stirred for 30 min before quenching with $Na_2SO_4 \cdot 10H_2O$ (2.4 g, 7.6 mmol). The white suspended materials were filtered and repeatedly washed with Et_2O, concentrated, and purified by FC (20% EtOAc in hexanes) to provide 326 mg (100%) of alcohol **223**. $[\alpha]_D$ = +18 ($CHCl_3$, *c* 2.0). IR (film) 3400, 1642, 1439, 1373, 1197, 1083, 1046, 913 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, dddd *J* = 6.8, 7.2, 10.4, 16.8 Hz), 5.07 (1H, *br* d, *J* = 16.8 Hz), 5.05 (1H, *br* d, *J* = 10.4 Hz), 3.71–3.82 (2H, m), 3.56 (1H, dddd, *J* = 2.0, 2.8, 9.6, 7.2 Hz), 3.40 (1H, dddd, *J* = 2.2, 5.8, 7.4, 13.0 Hz), 3.16 (1H, dd, *J* = 3.6, 7.2 Hz), 2.15–2.26 (2H, m), 1.70–1.85 (2H, m), 1.45–1.67 (4H, m), 1.17–1.36 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2, 117.2, 79.7, 77.5, 62.4, 41.2, 37.9, 31.7, 31.2, 23.5. MS (CI) *m/z* 171 ([MH^+], 100).



223 **224a**

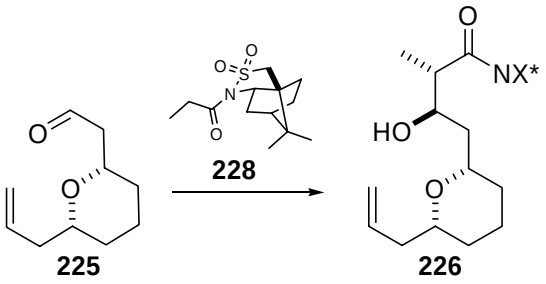
Iodide 224a. To a solution of alcohol **223** (70 mg, 0.41 mmol), PPh_3 (322 mg, 1.23 mmol), and imidazole (62 mg, 0.91 mmol) in Et_2O:CH_3CN (2:1, 4.5 mL) was added I_2 (312 mg, 1.23 mmol). The reaction was allowed to stir at room temperature 2 hr then diluted with Et_2O (30 mL) and washed with H_2O (30 mL) and extracted with Et_2O (2 x 20 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (5/95, EtOAc/Hex) to afford 72.3 mg (62%) of iodide **224a**. $[\alpha]_D$ = -32.2 ($CHCl_3$, *c* 3.6). IR (film) 3076, 2934, 2845, 1642, 1439, 1373, 1334, 1191, 1085, 1045, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77–5.88 (1H, ddt, *J* = 7.2, 10.4, 17.2), 5.00–5.08 (2H, m), 3.26–3.41 (4H, m), 2.23–2.31 (1H, m), 2.11–2.17 (1H, m), 1.88–2.00 (2H, m), 1.78–1.86 (1H, m), 1.48–1.62 (2H, m), 1.13–1.31 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 116.2, 77.1, 76.5, 40.8, 40.0, 31.0, 30.9, 23.4, 3.2.



223 **225**

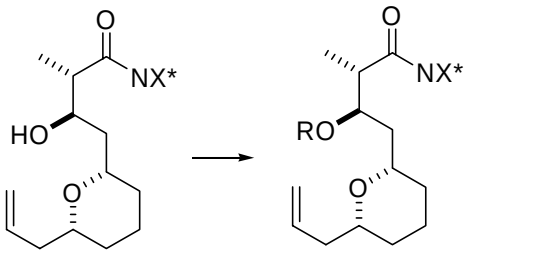
Aldehyde 225. To a stirred solution of oxalyl chloride (21.2 mL, 243.0 mmol) in CH_2Cl_2 (450 mL) at -78 ˚C was added anhydrous DMSO (28.8 mL, 405.0 mmol). After 45 min a solution of alcohol **223** (27.6 g, 162.0 mmol) in CH_2Cl_2 (50 mL) was added dropwise. After 1.5 hr the reaction was warmed to 0 ˚C for 10 min, then back to -78 ˚C. Then Et_3N (79.0 mL, 576.0 mmol) was added dropwise, and the reaction was allowed to warm slowly to 0 ˚C over 3 hr. The reaction was then quenched by addition of sat. NH_4Cl (200 mL), and extracted with pentane (3 x 250 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (10/90, Et_2O/Pentane) to provide

21.8 g (80%) of aldehyde **225**. $[\alpha]_D$ = +6.5 ($CHCl_3$, *c* 1.0); IR (film) 1727, 1643, 1373, 1199, 1081, 1050, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, app t, *J* = 2.4 Hz), 5.80 (1H, dddd, *J* = 6.8, 7.6, 10.4, 17.4 Hz), 5.04 (1H, *br* d, *J* = 17.4 Hz), 5.00 (1H, *br* d, *J* = 10.4 Hz), 3.84 (1H, dddd, *J* = 2.0, 4.6, 8.0, 11.2 Hz), 3.37 (1H, dddd, *J* = 2.0, 6.8, 6.8, 11.2 Hz), 2.58 (1H, ddd, *J* = 2.4, 8.0, 16.4), 2.44 (1H, ddd, *J* = 2.4, 4.6, 16.4 Hz), 2.26 (1H, ddddd, *J* = 1.2, 1.6, 6.8, 6.8, 13.6 Hz), 2.14 (1H, ddddd, *J* = 1.2, 1.2, 6.4, 7.2, 13.6 Hz), 1.81–1.88 (1H, m), 1.47–1.63 (3H, m), 1.13–1.31 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 135.1, 116.7, 77.8, 73.3, 50.2, 40.9, 31.5, 30.8, 23.5. MS (CI) *m/z* 169 ($[MH^+]$, 68), 81 (100).



Aldol 226. $TiCl_4$ (0.115 mL, 1.05 mmol) was added to a solution of *N*-propionyl bornanesultam **228** (298 mg, 1.1 mmol) at -78 °C. After 15 min, *i*-Pr_2NEt (0.192 mL, 1.1 mmol) was added to this light yellow mixture, which changed color to dark red. After stirring for 1 hr at -78 °C, aldehyde **225** (170 mg) was added and stirred for 1 hr before quenching with phosphate buffer (pH = 7, 1 mL) and saturated aq. $NaHCO_3$ (1 mL). After extraction with EtOAc (3 × 50 mL), the combined organic layers were washed, dried, concentrated, and purified by FC (15/85, EtOAc/Hex) to afford 264 mg (70%) of β-hydroxy amide **226**. M.p. = 93 °C (recrystallized from Et_2O/Hex); $[\alpha]_D$ = +67.5

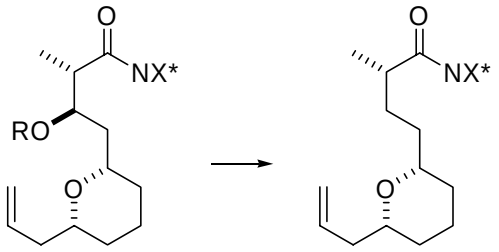
($CHCl_3$, *c* 1.8). IR (film) 3487, 2936, 1690, 1643, 1457, 1384, 1333, 1134 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, dddd, *J* = 7.2, 7.2, 10.4, 17.6 Hz), 5.05 (1H, *br* d, *J* = 17.6 Hz), 5.02 (1H, *br* d, *J* = 10.4 Hz), 4.10–4.15 (1H, m), 3.88 (1H, app t, *J* = 6.0 Hz), 3.68 (1H, dddd, *J* = 2.4, 3.2, 8.4, 11.2 Hz), 3.66 (1H, d, *J* = 4.4 Hz), 3.50 (1H, d, *J* = 13.6 Hz), 3.42 (1H, d, *J* = 13.6 Hz), 3.37–3.45 (1H, m), 3.14 (1H, dq, *J* = 7.2, 7.2 Hz), 2.25 (1H, *br* ddd, *J* = 7.2, 7.6, 14.0 Hz), 2.17 (1H, *br* ddd, *J* = 5.6, 6.8, 14.0 Hz), 2.02–2.06 (2H, m), 1.71 (1H, ddd, *J* = 3.2, 7.2, 14.4 Hz), 1.66 (1H, ddd, *J* = 3.6, 8.4, 14.4 Hz), 1.16–1.95 (11H, m), 1.33 (3H, d, *J* = 7.2), 1.15 (3H, s), 0.97 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 135.3, 116.9, 77.29, 75.5, 69.5, 65.1, 53.3, 48.5, 47.9, 45.1, 44.7, 41.1, 39.3, 38.5, 32.9, 31.5, 31.1, 26.6, 23.6, 20.9, 20.1, 14.4. HRMS (FAB, MNBA, added LiI) Calcd for $C_{23}H_{37}NO_5SLi$ (MLi+): 446.2553. Found: 446.2713.



226 **227** R = C(S)OPh

Thionocarbonate 227. To a solution of alcohol **226** (900 mg, 2 mmol) in CH_2Cl_2 (15 mL) was added pyridine (0.750 mL, 9 mmol) at 0 ˚C followed by phenyl chlorothionocarbonate (0.415 mL, 3 mmol). After stirring at rt for 4 hr, the reaction mixture was diluted with EtOAc (100 mL) and saturated aq. NH_4Cl (100 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with 1N aq. HCl (3 × 100 mL), saturated aq. $NaHCO_3$ (3 × 100 mL), dried, concentrated and purified by FC (10/90, EtOAc/Hex) to give 950 mg (81%) of

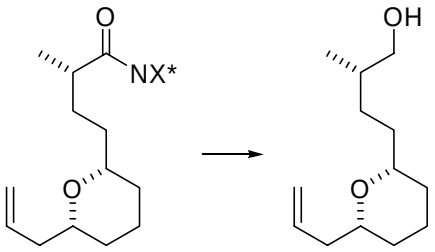
thionocarbonate **227**. $[\alpha]_D$ = +82 ($CHCl_3$, *c* 1.2). IR (film) 1693, 1640, 1593, 1491, 1333, 1286, 1198; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, app t, *J* = 7.6 Hz), 7.27 (1H, t, *J* = 7.6 Hz), 7.14 (2H, d, *J* = 7.2 Hz), 5.99 (1H, ddd, *J* = 3.6, 6.0, 9.2 Hz), 5.87 (1H, dddd, *J* = 6.8, 7.2, 10.0, 17.2 Hz), 5.00 (1H, *br* d, *J* = 17.2 Hz), 4.95 (1H, *br* d, *J* = 10.0 Hz), 3.93 (1H, app t, *J* = 6.4 Hz), 3.65 (1H, dq, *J* = 6.0, 7.6 Hz), 3.51 (1H, d, *J* = 13.6 Hz), 3.45 (1H, d, *J* = 13.6 Hz), 3.38 (1H, *br* t, *J* = 9.6 Hz), 3.29 (1H, dddd, *J* = 1.2, 6.4, 7.2, 13.0 Hz), 2.33 (1H, *br* ddd, *J* = 6.4, 6.8, 14.0 Hz), 2.14 (1H, *br* ddd, *J* = 7.2, 7.2, 14.0 Hz), 2.05 (1H, ddd, *J* = 2.4, 9.2, 14.0 Hz), 2.05–2.09 (2H, m), 1.75–1.95 (5H, m), 1.17–1.64 (7H, m), 1.33 (3H, d, *J* = 7.6 Hz), 1.16 (3H, s), 0.97 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 173.1, 153.8, 135.8, 135.4, 129.6, 126.5, 122.3, 122.2, 116.3, 82.2, 77.5, 73.9, 65.3, 53.4, 48.6, 48.0, 44.8, 44.3, 43.4, 41.2, 39.3, 38.5, 38.3, 33.0, 31.8, 31.3, 31.0, 30.8, 26.6, 23.8, 23.6, 21.0, 20.1, 14.9, 14.6. HRMS (FAB, MNBA, added LiI) Calcd for $C_{30}H_{41}NO_6S_2Li$ (MLi+): 582.2535. Found: 582.2534.



227 R = C(S)OPh **230**

Sulfonamide 230. A mixture of thionocarbonate **227** (130 mg, 0.23 mmol), Bu_3SnH (0.124 mL, 0.46 mmol) and AIBN (7.5 mg, 0.046 mmol) in benzene (20 mL, degassed) was refluxed for 7 hr. After cooling to rt, the solvent was removed and the residue purified by FC (10/90, EtOAc/Hex) to afford 73 mg (76%) of pure deoxygenated product **230**. $[\alpha]_D$ = +68 ($CHCl_3$, *c* 1). IR (film) 1694, 1640, 1460, 1331, 1268, 1133, 1060 cm^{-1};

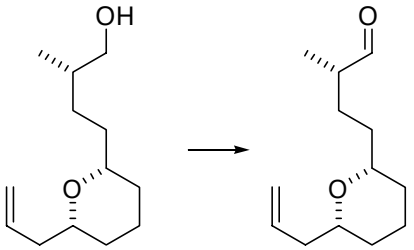
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, dddd, *J* = 6.4, 7.2, 10.0, 16.8 Hz), 5.03 (1H, *br* d, *J* = 16.8 Hz), 4.98 (1H, *br* d, *J* = 10.0 Hz), 3.88 (1H, app t, *J* = 6.4 Hz), 3.48 (1H, d, *J* = 13.6 Hz), 3.41 (1H, d, *J* = 13.6 Hz), 3.20–3.32 (2H, m), 3.00–3.11 (1H, m), 2.28 (1H, *br* ddd, *J* = 6.8, 7.2, 14.0 Hz), 2.11 (1H, *br* ddd, *J* = 6.4, 7.2, 14.0 Hz), 2.01–2.05 (2H, m), 1.80–1.94 (4H, m), 1.74–1.80 (1H, m), 1.29–1.57 (9H, m), 1.19 (3H, d, *J* = 6.4 Hz), 1.07–1.18 (1H, m), 1.14 (3H, s), 0.95 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 135.7, 116.3, 77.44, 77.40, 65.2, 53.3, 48.4, 48.0, 44.8, 41.2, 40.0, 38.6, 33.8, 33.0, 31.5, 31.3, 28.4, 26.6, 23.8, 21.0, 21.0, 19.2. HRMS (FAB, MNBA, added LiI) Calcd for $C_{23}H_{38}NO_4S$ (MH+): 424.2522. Found: 424.2544.



230 **230b**

Alcohol 230b. To a suspension of $LiAlH_4$ (65 mg, 1.7 mmol) in ether (15 mL) was added amide **230** (600 mg, 1.4 mmol) at 0 ˚C. After stirring for 1 hr, the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ (2.3 g, 7.1 mmol). The white suspended materials were filtered and repeatedly washed with ether, followed by concentration of the filtrate. Purification of the residue by FC (10/90, EtOAc/Hex) provided 291 mg (97%) of alcohol **230b**. $[\alpha]_D$ = -14 ($CHCl_3$, *c* 1.0); IR (film) 3384, 1642, 1456, 1439, 1197, 1083, 1046, 911 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, dddd, *J* = 6.8, 7.2, 10.4, 17.2 Hz), 5.05 (1H, *br* d, *J* = 17.2 Hz), 5.01 (1H, *br* d, *J* = 10.4 Hz), 3.49 (1H, dd, *J* = 5.2, 10.4 Hz), 3.44 (1H, dd, *J* = 6.0, 10.4 Hz), 3.30 (1H, dddd, *J* = 1.6, 6.4, 6.4, 10.8 Hz), 3.24 (1H, dddd, *J* = 2.0, 6.4, 6.4,

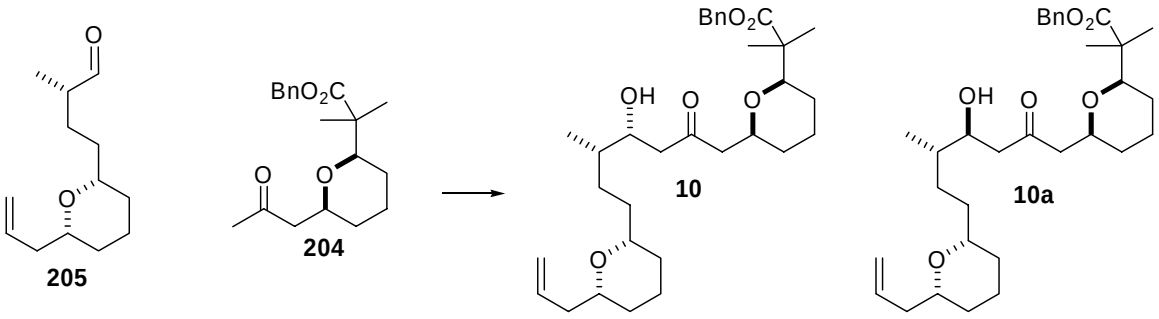
10.8 Hz), 2.30 (1H, *br* ddd, *J* = 6.4, 6.8, 14.0 Hz), 2.14 (1H, *br* ddd, *J* = 6.4, 7.2, 14.0 Hz), 1.77–1.84 (1H, m), 1.70 (1H, *br* s), 1.40–1.70 (7H, m), 1.10–1.21 (3H, m), 0.91 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 116.5, 78.6, 77.7, 68.3, 41.2, 35.9, 33.8, 31.7, 31.4, 29.2, 23.8, 16.9. HRMS (FAB, MNBA, added LiI) Calcd for $C_{13}H_{24}O_2Li$ (MLi+): 219.1936. Found: 219.1932.



230b **205**

Aldehyde 205. To a stirred solution of oxalyl chloride (1.23 mL, 14.2 mmol) in CH_2Cl_2 (35 mL) at -78 ˚C was added anhydrous DMSO (1.67 mL, 23.5 mmol). After 45 min a solution of alcohol **230b** in CH_2Cl_2 (5 mL) was added dropwise. After 1.5 hr the reaction was warmed to 0 ˚C for 10 min, then back to -78 ˚C. Then Et_3N (4.58 mL, 32.9 mmol) was added dropwise, and the reaction was allowed to warm slowly to 0 ˚C over 3 hr. The reaction was then quenched by addition of H_2O (50 mL) and extracted with pentane (3 x 100 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (10/90, Et_2O/Pentane) to provide 1.83 g (93%) of aldehyde **205**. $[\alpha]_D$ = +10 ($CHCl_3$, *c* 0.2). IR (film) 1727, 1646, 1456, 1376, 1196, 1084, 912; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (1H, d, *J* = 2.0 Hz), 5.83 (1H, dddd, *J* = 6.8, 7.2, 10.4, 17.6 Hz), 5.05 (1H, *br* d, *J* = 17.6 Hz), 5.01 (1H, *br* d, *J* = 10.4 Hz), 3.20–3.34 (2H, m), 2.36 (1H, dddq, *J* = 2.0, 6.8, 6.8, 7.2 Hz), 2.29 (1H, *br* ddd, *J* = 6.8, 6.8, 14.0 Hz), 2.14 (1H, *br* ddd, *J* = 6.0, 7.2, 14.0 Hz), 1.85-1.95 (1H, m), 1.78-1.85 (1H, m), 1.35-1.62 (6H, m), 1.10-

1.26 (2H, m), 1.09 (3H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 135.5, 116.5, 77.8, 77.6, 46.4, 41.2, 33.8, 31.8, 31.4, 26.7, 23.8, 13.5. MS (CI) *m/z* 211 ([MH^+], 84), 81 (100).



β-Hydroxyketone 10. Et_3N (0.302 mL, 2.169 mmol) was added to a solution of methylketone **204** (230 mg, 0.723 mmol) in Et_2O (5 mL) at -78 ˚C followed by the addition of freshly prepared Et_2BOTf (2.17 mL, 1M in hexane). The solution was allowed to reach 0 ˚C and re-cooled to -78 ˚C followed by the addition of a solution of aldehyde **205** (182 mg, 0.87 mmol) in Et_2O (1 mL). After stirring for 3 hr at -78 ˚C, the mixture was warmed to -30 ˚C and stirred for an additional hour. The reaction was quenched by the addition of MeOH / pH = 7 phosphate buffer (5 mL, 6/1), warmed to rt and treated with MeOH / 30% aq. H_2O_2 (5 mL, 2/1) and stirred for 3 hr. The reaction mixture was extracted with EtOAc (3 × 50 mL), washed with saturated aq. $NaHCO_3$ (3 × 50 mL), dried, concentrated and purified by FC (15/85, EtOAc/Hex) to provide 325 mg (85%) of β-hydroxyketone **10** as the major diastereomer. ^{1}H NMR of the crude reaction mixture indicated a 5:1 diastereomeric ratio. The diastereomers were separated by HPLC (column 25 cm × 10 mm, silicagel 5 μm, 15 % EtOAc in hexanes, flow rate 3 mL/ min): R_t (minor) 22.3 min, R_t (major) 23.7 min. Major isomer **10**: $[\alpha]_D$ = +19 ($CHCl_3$, *c* 0.2). ^{1}H

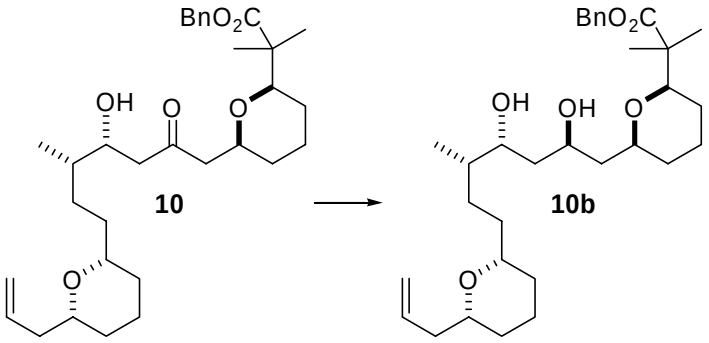
NMR (400 MHz, $CDCl_3$) δ 7.27–7.37 (5H, m), 5.83 (1H, dddd, *J* = 6.8, 7.2, 10.4, 17.2 Hz), 5.09 (2H, s), 5.05 (1H, *br* d, *J* = 17.2 Hz), 5.00 (1H, *br* d, *J* = 10.4 Hz), 3.87 (1H, *br* dddd, *J* = 2.0, 2.4, 4.0, 10.0 Hz), 3.76 (1H, *br* dddd, *J* = 2.0, 4.4, 8.4, 10.8 Hz), 3.54 (1H, dd, *J* = 1.2, 11.2 Hz), 3.30 (1H, *br* dddd, *J* = 1.2, 6.4, 6.4, 10.8 Hz), 3.23 (1H, *br* dddd, J = 1.6, 5.6, 5.6, 10.8 Hz), 3.07 (1H, d, *J* = 2.4 Hz), 2.57 (1H, dd, *J* = 2.0, 17.6 Hz), 2.54 (1H, dd, *J* = 8.4, 14.8 Hz), 2.48 (1H, dd, *J* = 10.0, 17.6 Hz), 2.34 (1H, dd, *J* = 4.4, 14.8 Hz), 2.30 (1H, *br* ddd, *J* = 6.4, 6.4, 13.6 Hz), 2.13 (1H, *br* ddd, *J* = 6.4, 6.8, 13.6 Hz), 1.77–1.88 (2H, m), 1.39–1.65 (11H, m), 1.09–1.36 (4H, m), 1.16 (3H, s), 1.11 (3H, s), 0.88 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 176.6, 136.6, 128.6, 128.24, 128.2, 116.5, 82.6, 78.5, 77.4, 75.1, 71.3, 66.4, 50.1, 47.6, 46.8, 41.3, 38.3, 34.2, 31.7, 31.5, 31.4, 28.2, 24.5, 23.8, 23.5, 21.4, 20.4, 15.3. MS (ES) *m/z* 529 ($[MH^+]$).

Minor isomer **10a**: $[\alpha]_D$ = -17 ($CHCl_3$, *c* 0.24). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.38 (5H, m), 5.83 (1H, dddd, *J* = 6.8, 6.8, 10.0, 17.2 Hz), 5.12 (1H, d, *J* = 12.4 Hz), 5.07 (1H, d, *J* = 12.4 Hz), 5.05 (1H, *br* d, *J* = 17.2 Hz), 5.00 (1H, *br* d, *J* = 10.0 Hz), 3.94 (1H, *br* dddd, *J* = 2.8, 3.6, 4.0, 9.6 Hz), 3.77 (1H, *br* dddd, *J* = 1.6, 4.0, 8.4, 12.0 Hz), 3.54 (1H, dd, *J* = 1.6, 11.6 Hz), 3.29 (1H, *br* dddd, *J* = 1.6, 6.8, 6.8, 10.8 Hz), 3.22 (1H, *br* dddd, *J* = 1.6, 6.4, 6.8, 10.8 Hz), 2.87 (1H, d, *J* = 3.6 Hz), 2.58 (1H, dd, *J* = 9.6, 17.2 Hz), 2.57 (1H, dd, *J* = 8.4, 15.2 Hz), 2.49 (1H, dd, *J* = 2.8, 17.2 Hz), 2.36 (1H, dd, *J* = 4.0, 15.2 Hz), 2.30 (1H, *br* ddd, *J* = 6.8, 6.8, 14.0 Hz), 2.13 (1H, *br* ddd, *J* = 6.8, 6.8, 14.0 Hz), 1.76–1.88 (2H, m), 1.30–1.64 (11H, m), 1.09–1.28 (4H, m), 1.16 (3H, s), 1.11 (3H, s), 0.89 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 176.7, 136.6, 135.6, 128.7, 128.22, 128.20, 116.5, 82.6, 78.5, 77.4, 75.2, 70.9, 66.4, 50.2, 48.4, 46.8, 41.3, 38.3, 34.4, 31.7, 31.4, 29.1, 24.9, 23.8, 21.4, 20.5, 14.3. MS (ES) *m/z* 529 ($[MH^+]$).

(*R*)-MTPA ester of **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.52 (2H, m), 7.28-7.38 (8H, m), 5.81 (1H, dddd, *J* = 6.8, 6.8, 10.0, 17.2 Hz), 5.54 (1H, *br* ddd, *J* = 2.0, 4.0, 9.2 Hz), 5.08 (2H, s), 5.04 (1H, *br* d, *J* = 17.2 Hz), 4.99 (1H, *br* d, *J* = 10.0 Hz), 3.60–3.67 (1H, m), 3.52 (3H, s), 3.48–3.52 (1H, mixed with singlet at 3.52), 3.17-3.31 (2H, m), 2.75 (1H, dd, *J* = 9.2, 17.2 Hz), 2.48 (1H, dd, *J* = 2.0, 17.2 Hz), 2.40 (1H, dd, *J* = 7.6, 14.8 Hz), 2.27 (1H, *br*.ddd, *J* = 6.4, 6.4, 14.0 Hz), 2.17 (1H, dd, *J* = 4.0, 14.8 Hz), 2.11 (1H, *br* dd, 6.8, 6.8, 14.0 Hz), 1.83–1.93 (1H, m), 1.75-1.83 (2H, m), 1.37–1.60 (10H, m), 1.09–1.26 (4H, m), 1.14 (3H, s), 1.10 (3H, s), 0.92 (3H, d, *J* = 6.8 Hz).

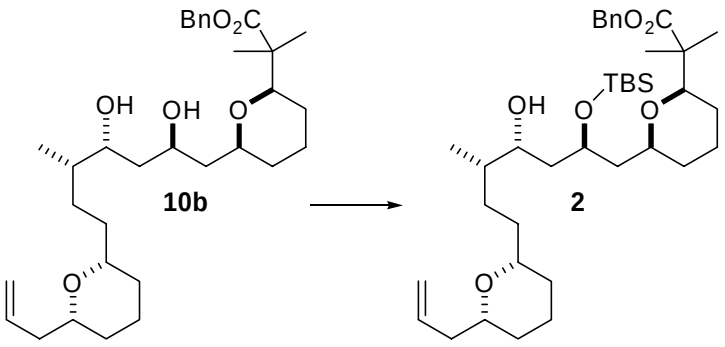
(*S*)-MTPA ester of **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.51 (2H, m), 7.27–7.37 (8H, m), 5.82 (1H, dddd, *J* = 6.8, 7.2, 10.4, 17.2 Hz), 5.51 (1H, ddd, *J* = 2.4, 4.0, 10.0 Hz), 5.09 (2H, s), 5.04 (1H, *br* d, *J* = 17.2 Hz), 5.00 (1H, *br* d, *J* = 10.4 Hz), 3.65–3.73 (1H, m), 3.51 (1H, dd, *J* = 1.6, 11.2 Hz), 3.49 (3H, s), 3.24–3.33 (1H, m), 3.15–3.24 (1H, m), 2.77 (1H, dd, *J* = 10.0, 18.0 Hz), 2.52 (1H, dd, *J* = 2.4, 18.0 Hz), 2.47 (1H, dd, *J* = 7.6, 14.4 Hz), 2.28 (1H, dd, *J* = 4.8, 14.4 Hz), 2.24–2.30 (1H, m), 2.12 (1H, *br* ddd, *J* = 6.8, 7.2, 14.0 Hz), 1.76–1.92 (3H, m), 1.37–1.60 (10H, m), 1.04–1.37 (4H, m), 1.13 (3H, s), 1.10 (3H, s), 0.75 (3H, d, *J* = 6.4 Hz).

	H-15	H-12	H-23	H-10A	H-10B	H-8A	H-8B	H-7
R-MTPA ester	3.212	1.882	0.915	2.752	2.4745	2.4025	2.167	3.635
S-MTPA ester	3.199	1.870	0.751	2.773	2.5255	2.4685	2.2835	3.686
$\delta_S - \delta_R$	-0.011	-0.012	-0.164	+0.021	+0.051	+0.066	0.1165	0.051



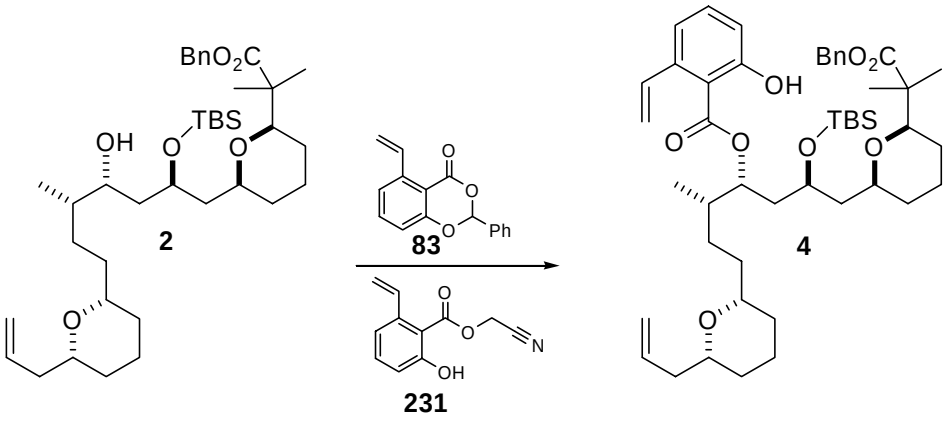
Diol 10b. To a solution of $Me_4N(OAc)_3BH$ (526 mg, 1.9 mmol) in CH_3CN (2 mL) and glacial acetic acid (2 mL) was added β-hydroxyketone **10** (200 mg, 0.38 mmol, ~5:1 mixture with **10a**) in CH_3CN (2 mL) at -20 ˚C. The reaction mixture was slowly warmed to rt, stirred for 4 hr and transferred to a stirred biphasic mixture of CH_2Cl_2 (50 mL) and saturated aq. $NaHCO_3$ (50 mL). After stirring for 10 min, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried, concentrated, and purified by FC (20/80, EtOAc/Hex) to give a less polar syn-diol (10 mg, 5%), the desired trans-diol **10b** (165 mg, 82%) and a more polar minor trans-diol (15 mg, 7%). $[\alpha]_D$ = -13 ($CHCl_3$, *c* 0.75). IR (film) 3500, 1732, 1647, 1456, 1265, 1085, 1047, 910, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.38 (5H, m), 5.83 (1H, dddd, *J* = 6.8, 7.2, 10.4, 17.2 Hz), 5.16 (1H, d, *J* = 12.4 Hz), 5.08 (1H, d, *J* = 12.4 Hz), 5.05 (1H, *br* d, *J* = 17.2 Hz), 5.00 (1H, *br* d, *J* = 10.4 Hz), 4.03–4.13 (1H, m), 3.83 (1H, s), 3.68–3.76 (1H, m), 3.61 (1H, dd, *J* = 1.6, 11.0 Hz), 3.54–3.62 (1H, m), 3.17–3.33 (3H, m), 2.30 (1H, *br* ddd, *J* = 6.4, 7.2, 13.6 Hz), 2.13 (1H, *br* ddd, *J* = 6.4, 7.2, 13.6 Hz), 1.38–1.89 (17H, m), 1.08–1.38 (4H, m), 1.19 (3H, s), 0.85 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 136.4, 135.6, 128.7, 128.2, 116.4, 83.1, 80.4, 78.6, 77.6, 72.5, 70.7, 66.7, 46.8, 42.6, 41.3, 39.1, 38.9,

34.2, 32.2, 31.6, 31.4, 28.3, 24.9, 23.8, 23.4, 21.9, 20.0, 15.4; MS (ES) *m/z* 553.38 ([MNa^+], 100), 531.36 ([MH^+], 70).



Alcohol 2. To a stirred solution of diol **10b** (1.11 g, 2.10 mmol), imidazole (873 mg, 12.84 mmol), and DMAP (26 mg, 0.214 mmol) in anhydrous DMF (15 mL) at 0 ˚C was added TBSCl (969 mg, 6.43 mmol). The reaction was allowed to stir for 2 hr at 0 ˚C before addition of water (150 mL). The solution was extracted with Et_2O (3 × 200 mL), dried over $MgSO_4$, concentrated, and purified by FC (5/95, EtOAC/Hex) to afford 1.10 g (80%) of **2**. $[\alpha]_D$ = -11.0 ($CHCl_3$, *c* 0.15). IR (film) 3511, 2935, 2858, 1737, 1462, 1389, 1258, 1087, 1051, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.38 (5H, m), 5.84 (1H, dddd, *J* = 6.8, 6.8, 10.0, 16.4 Hz), 5.14 (1H, d, *J* = 12.8 Hz), 5.06 (1H, d, *J* = 12.8 Hz), 5.03 (1H, app d, *J* = 6.8 Hz), 5.00 (1H, app d, *J* = 16.4 Hz), 4.18–4.26 (1H, m), 3.68–3.76 (1H, m), 3.50 (1H, d, *J* = 10.8 Hz), 3.19–3.34 (3H, m), 2.26–2.36 (1H, m), 2.09–2.18 (1H, m), 1.77–1.88 (2H, m), 1.71 (2H, t, *J* = 6.8 Hz), 1.39–1.63 (12H, m), 1.08–1.29 (5H, m), 1.20 (3H, s), 1.12 (3H, s), 0.88 (9H, s), 0.84 (3H, d, *J* = 6.8 Hz), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 136.5, 135.6, 128.7, 128.2, 127.8, 116.4, 82.2, 78.6, 77.6, 75.3, 72.0, 68.7, 66.3, 46.9, 42.6, 41.3, 39.1, 36.3, 34.3,

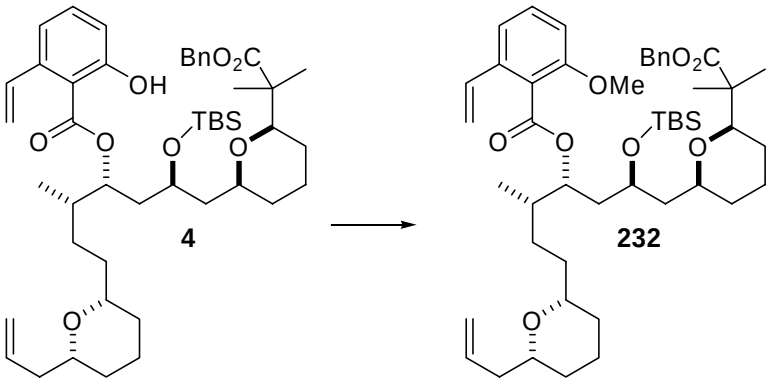
32.3, 31.6, 31.5, 28.2, 26.0, 25.2, 23.8, 21.4, 20.5, 18.1, 15.2, -4.5, -4.8. MS (ES) *m/z* (%): 667.52 ([MNa]$^+$, 100).



Photoacylation of Alcohol 2. To an ovendried quartz test tube was added and solution of **2** (7.6 mg, 0.012 mmol) and **83** (27 mg, 0.11 mmol) in anhydrous 1,4-dioxane (0.4 mL). This solution was then degassed (freeze, pump, thaw, 3X). The solution was then photolyzed for 4 hr (300 nm). The solvent was then removed and purified by FC (5/95, EtOAc/Hex) to yield 2.5 mg (27%) of **4**.

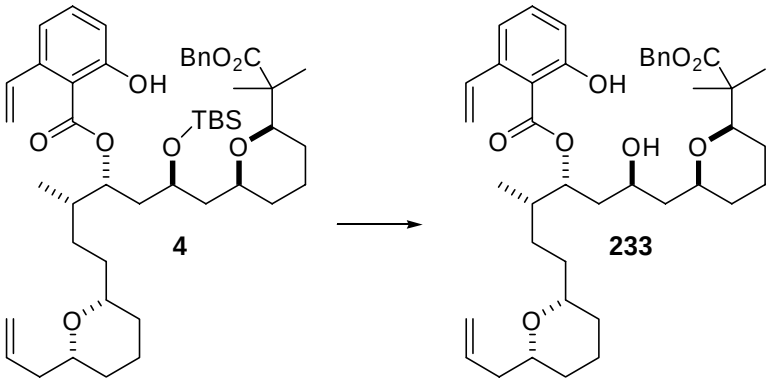
Transesterification of Alcohol 2. To an ovendried microwave reaction vial was combined K_2CO_3 (43 mg, 0.31 mmol), and a solution of **2** (400 mg, 0.62 mmol) and **231** (380 mg, 1.86 mmol) in anhydrous *N,N*-dimethylacetamide (0.8 mL). The reaction vessel was then sealed while flushing with N_2 and reacted in the microwave for 13 min at 210 ˚C. The crude reaction was diluted with Et_2O (50 mL), washed with H_2O (30 mL), and extracted with Et_2O (2 x 50 mL). The combined organic phase was dried over Na_2SO_4, filtered, concentrated, and purified by FC (4/96, EtOAc/Hex) to afford 122 mg (25%) of ester **4** and 187 mg (47%) of recovered alcohol **2**. $[\alpha]_D$ = -48.8 ($CHCl_3$, *c* 0.025). IR (film) 3380, 2930, 257, 1736, 1657, 1451, 1372, 1252, 1217, 1086 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 11.52 (1H, s), 7.28–7.37 (7H, m), 6.89 (1H, d, *J* = 8.0 Hz), 6.83 (1H, d, *J* = 7.6 Hz), 5.83 (1H, dddd, *J* = 6.8, 6.8, 10.4, 17.2 Hz), 5.39 (1H, d, *J* = 17.2 Hz), 5.31–5.36 (1H, m), 5.19 (1H, d, *J* = 10.8 Hz), 5.05 (2H, s), 5.01–5.04 (1H, m), 4.97 (1H, d, *J* = 6.4 Hz), 3.88 (1H, app t, *J* = 8.0 Hz), 3.39 (1H, d, *J* = 10.4 Hz), 3.21–3.34 (3H, m), 2.23–2.33 (1H, m), 2.09–2.17 (1H, m), 1.89–1.94 (1H, m), 1.78–1.86 (2H, m), 1.39–1.77 (12H, m), 1.09–1.37 (6H, m), 1.06 (3H, s), 1.01 (3H, s), 0.92 (3H, d, *J* = 6.8 Hz), 0.87 (9H, s), -0.01 (3H, s), -0.02 (3H, s). MS (ES) *m/z* (%): 814.00 ($[MNa]^+$, 30).

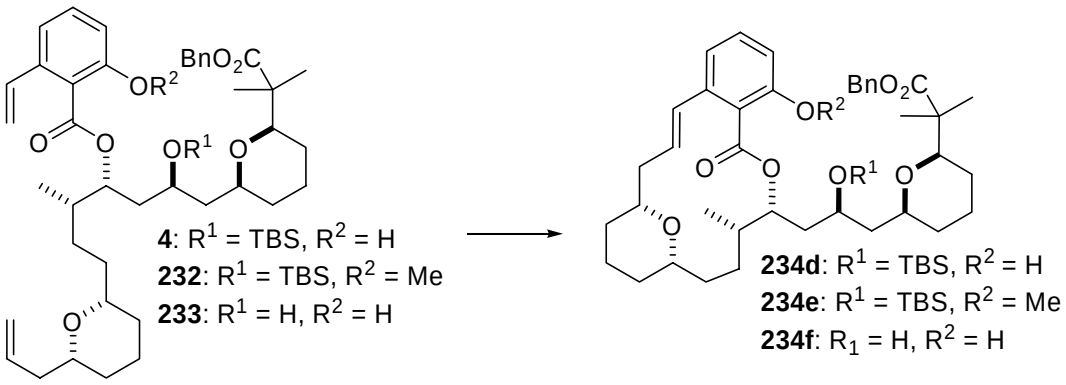


Diene 232. To a stirred solution of phenol **4** (8.6 mg, 0.011 mmol) in anhydrous acetone (0.3 mL) was added K_2CO_3 (2.2 mg, 0.016 mmol) and methyl iodide (3.3 μL, 0.054 mmol). The reaction was allowed to stir at ambient temperature for 72 hr. The reaction was diluted with Et_2O (5 mL), filtered through a sintered funnel, and concentrated. The crude was then purified by FC (10/90, EtOAc/Hex) to afford 6.4 mg (73%) of **232**. $[\alpha]_D$ = +7.7 ($CHCl_3$, *c* 1.5). IR (film) 2934, 1728, 1472, 1270, 1071, 914, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.34 (7H, m), 7.12 (1H, d, *J* = 7.6 Hz), 6.77 (1H, d, *J* = 8.4 Hz), 5.80–5.91 (1H, m), 5.71 (1H, d, *J* = 17.6 Hz), 5.23–5.30 (2H, m), 4.98–5.08 (4H, m), 3.93–3.99 (1H, m), 3.77 (3H, s), 3.38–3.44 (2H, m), 3.22–3.32 (2H, m), 2.25–2.34

(1H, m), 2.11–2.18 (1H, m), 1.37–1.82 (15H, m), 1.02–1.32 (12H, m), 0.90–0.92 (12H, m), 0.15 (3H, s), 0.08, 3H, s). MS (ES) *m/z* (%): 827.60 ($[MNa]^+$, 100)

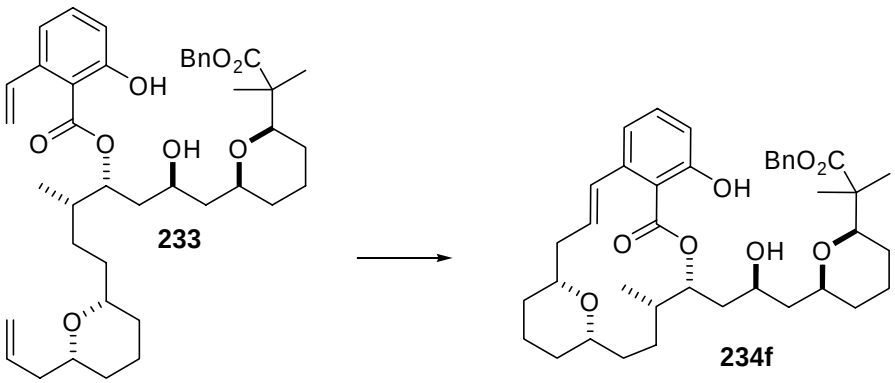


Diene 233. To a stirred solution of **4** (31.5 mg, 0.04 mmol) in THF (0.2 mL) was added TBAF (1.0 mL, 1.0 mmol). The reaction was allowed to stir at room temperature for 96 hr. The reaction was concentrated and purified by FC (20/80, EtOAc/Hex) to afford 17 mg (64%) of **233**. $[\alpha]_D$ = +0.89 ($CHCl_3$, *c* 0.45). IR (film) 3524, 2936, 1732, 1658, 1451, 1252, 1084, 1046, 913, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.34 (1H, s), 7.23–7.35 (7H, m), 6.87–6.91 (2H, m), 5.81 (1H, dddd, *J* = 7.2, 7.2, 10.4, 17.2 Hz), 5.46–5.50 (1H, m), 5.42 (1H, dd, *J* = 1.6, 17.2 Hz), 5.18 (1H, dd, *J* = 1.6, 10.8 Hz), 5.06 (2H, s), 4.96–5.05 (2H, m), 3.77–3.83 (1H, m), 3.50–3.57 (2H, m), 3.19–3.31 (2H, m), 2.25–2.32 (1H, m), 2.09–2.15 (1H, m), 1.41–1.88 (19H, m), 1.10–1.22 (8H, m), 0.93 (3H, d, *J* = 6.8 Hz). MS (ES) *m/z* (%): 699.35 ($[MNa]^+$,100).

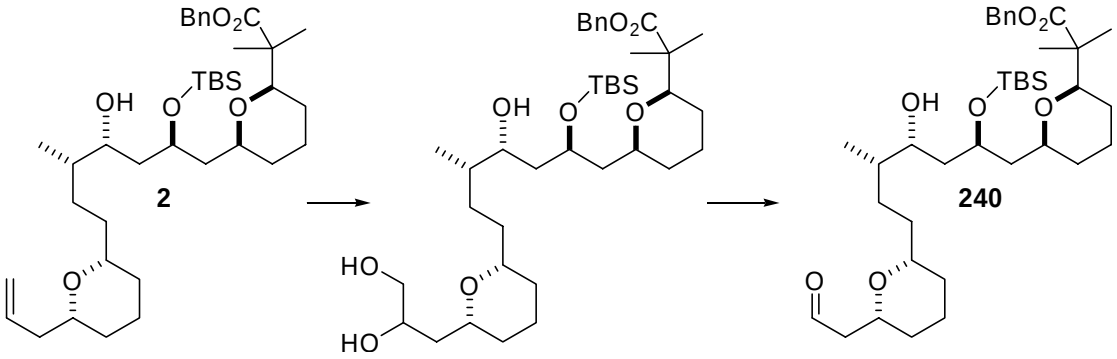


Represenative procedure for attempted metathesis dimerization (Table 4.1, Entry 6)

Macrocycle 234d. To an ovendried vial was added metathesis catalyst **B** (1.4 mg, 0.0012 mmol) (Table 4.1), diene **4** (19.5 mg, 0.025 mmol), and CH_2Cl_2 (0.04 mL). After ½ hr the solvent evaporated so additional CH_2Cl_2 (0.1 mL) was added. After 4 hr additional catalyst was added (1.4 mg, 0.0012 mmol) and the reaction was allowed to stir overnight (12 hr) at ambient temperature. At this stage significant starting material was present so additional catalyst was added (5 mg, 0.0044 mmol) and allowed to stir for an additional 2 hr. The solvent was removed and the crude material purified by preperative thin layer chromatography (10/90, EtOAc/Hex) to afford 5.7 mg (15%) of **234d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (1H, s), 7.22–7.32 (6H, m), 7.12 (1H, d, *J* = 15.6 Hz), 6.81–6.84 (2H, m), 5.84 (1H, dt, *J* = 6.0, 15.6 Hz), 5.15–5.21 (1H, m), 5.06 (2H, s), 3.90–3.94 (1H, m), 3.26–3.42 (3H, m), 3.20 (1H, t, *J* = 10.8 Hz), 2.27–2.36 (1H, m), 2.08–2.16 (1H, m), 0.80–2.04 (40H, m), 0.00–0.03 (6H, m). MS (ES) *m/z* (%): 763.35 ($[MH]^+$, 100).

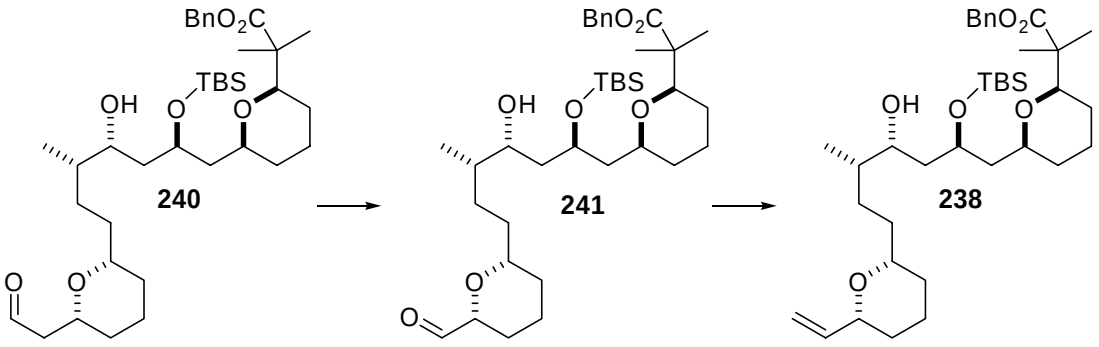


Macrocycle 234f. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.79 (1H, s), 7.25–7.33 (6H, m), 7.09 (1H, d, *J* = 16.0 Hz), 6.93 (2H, app t, *J* = 6.0, 11.6 Hz), 5.16–5.22 (1H, m), 5.09 (2H, s), 3.73–3.78 (1H, m), 3.35–3.52 (3H, m), 3.20–3.26 (1H, m), 2.26–2.28 (1H, m), 2.08–2.16 (1H, m), 1.02–1.98 (27H, m), 0.89 (3H, d, *J* = 6.8 Hz). MS (ES) *m/z* (%): 649.57 ($[MH]^+$, 100).



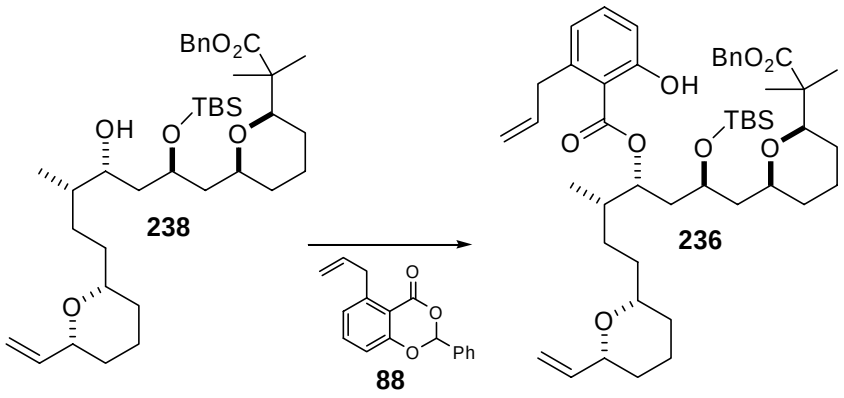
Aldehyde 240. A roundbottom flask was charged with acetone (10 mL), **2** (621 mg, 0.96 mmol), OsO_4 (0.48 mL, 0.048 mmol, 1 M in ^{t}BuOH) and NMO (5.99 mL, 28.9 mmol, 50% by weight in H_2O). The flask was sealed and allowed to stir overnight (12 hr) at ambient temperature. TLC analysis showed unreacted starting material so additional OsO_4 (0.24 mL, 0.024 mmol) and NMO (5.99 mL, 28.9 mmol) was added. After 9 hr the reaction was quenched by addition of $Na_2S_2O_3$ (40 mL, sat. soln.) and the reaction was allowed to stir for an additional 2 hr. The mixture was then poured into brine (30 mL),

and extracted with EtOAc (3 x 150 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford 654 mg of crude diol. This crude material was then dissolved in CH_2Cl_2 (20 mL) and treated with $NaIO_4$ supported on silica gel (1.83 g, 1.25 mmol). After 10 min the reaction was filtered through a pad of celite and concentrated to afford 555 mg of crude aldehyde **240**. $[\alpha]_D$ = -8.4 ($CHCl_3$, *c* 2.8). IR (film) 3509, 2935, 1729, 1462, 1390, 1258, 1086, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, *J* = 2.0 Hz), 7.30–7.35 (5H, m), 5.13 (1H, d, *J* = 12.8 Hz), 5.50 (1H, d, *J* = 12.4 Hz), 4.19–4.23 (1H, m), 3.78–3.84 (1H, m), 3.67–3.71 (1H, m), 3.50 (1H, d, *J* = 10.4 Hz), 3.18–3.31 (2H, m), 2.55 (1H, ddd, *J* = 2.8, 8.4, 16.4 Hz), 1.81–1.85 (1H, m), 1.70 (1H, app t, *J* = 6.8 Hz), 1.40–1.62 (14H, m), 1.12–1.29 (11H, m), 0.87 (9H, s), 0.82 (3H, d, *J* = 6.8 Hz), 0.06 (3H, s), 0.05 (3H, s). MS (ES) *m/z* (%): 701.45 ($[MMeOHNa]^+$, 100).



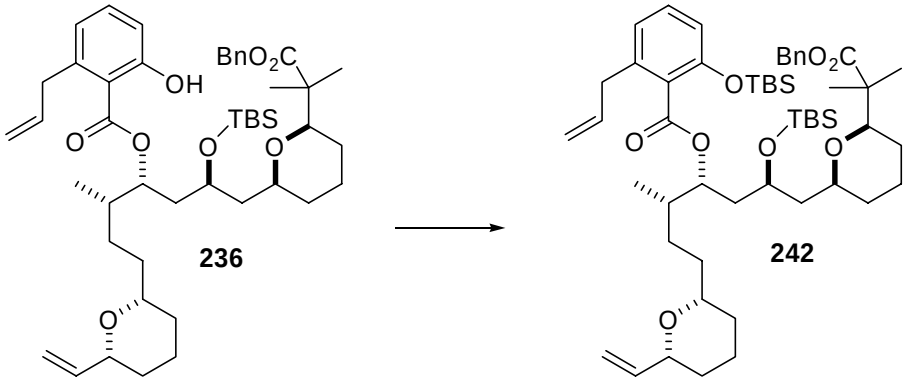
Olefin 238. To a solution of crude aldehyde **240** (555 mg) in acetone:H_2O 3:1 (20 mL) was added OsO_4 (0.43 mL, 0.043 mmol, 0.1 M in ^{t}BuOH), NMO (0.35 mL, 1.72 mmol, 50% by weight in H_2O), NMM (0.122 mL, 1.11 mmol), and $NaIO_4$ (735 mg, 3.44 mmol). The reaction was allowed to stir for 36 hr at ambient temperature. The reaction was then filtered through a pad of celite, diluted with EtOAc (100 mL) and washed with H_2O (40

mL). The organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (2/8, EtOAc/Hex) to afford 382 mg (72%) of aldehyde **241** with some impurities present by ^{1}H-NMR. To a stirred solution of crude aldehyde **241** (378 mg, 0.59 mmol) in anhydrous THF (5 mL) at 0 ˚C was added a solution of ylide derived from methyltriphenylphosphoniumylide (3.73 mL, 1.79 mmol). The reaction was allowed to stir at 0 ˚C for 2 hr. The reaction was then quenched by addition of excess sat. $NH_4^+Cl^-$ (30 mL), and extracted with Et_2O (3 x 100 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated and purified by FC (7/93, EtOAc/Hex) to afford 70 mg (19%) or **238**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.38 (5H, m), 5.86 (1H, ddd, *J* = 5.2, 10.4, 16.0 Hz), 5.04–5.24 (4H, m), 4.19–4.23 (1H, m), 3.77–3.82 (1H, m), 3.68–3.73 (1H, m), 3.49–3.51 (2H, m), 3.20–3.33 (2H, m), 1.81–1.88 (1.40–1.64 (14H, m), 1.11–1.34 (11H, m), 0.88 (9H, s), 0.84 (3H, d, *J* = 6.8 Hz), 0.07 (3H, s), 0.06 (3H, s).



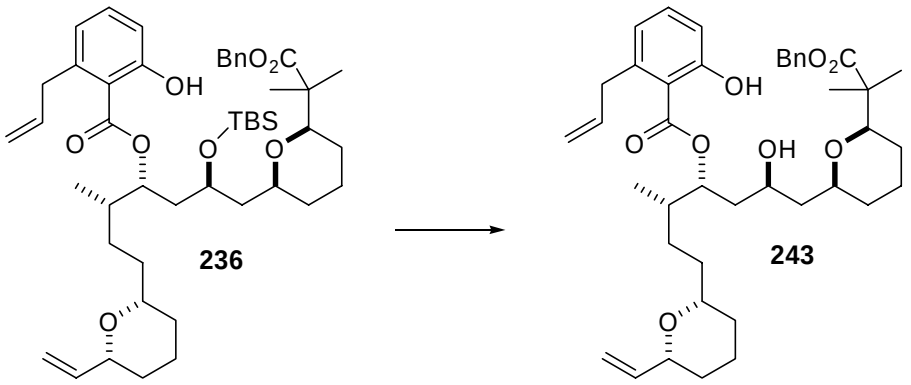
Diene 236. To an ovendried borosilicate test tube was added alcohol **238** (39 mg, 0.062 mmol) and **88** (50 mg, 0.186 mmol). These starting materials were dissolved in anhydrous CH_2Cl_2 (0.2 mL) and the reaction vessel was flushed with N_2 prior to capping with a rubber septum. This solution was photolyzed (300 nm) for 2 hr in the Rayonett reactor. The solvent was then removed and the crude was purified directly by FC (3/97,

EtOAc/Hex) to afford 11 mg (22%) of **236** and 15 mg (37%) of recovered **238**. $[\alpha]_D$ = +7.6 ($CHCl_3$, *c* 1.0). IR (film) 3432, 2934, 1732, 1657, 1606, 1452, 1371, 1257, 1221, 1088, 1049, 916, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.42 (1H, s), 7.29–7.37 (5H, s), 7.26 (1H, t, *J* = 8.0 Hz), 6.84 (1H, d, *J* = 8.4 Hz), 6.67 (1H, d, *J* = 7.6 Hz), 5.99 (1H, dddd, *J* = 6.0, 6.0, 10.0, 16.0 Hz), 5.84 (1H, ddd, *J* = 5.2, 10.8, 16.0 Hz), 5.35–5.38 (1H, m), 5.18–5.23 (1H, m), 5.01–5.08 (3H, m), 4.95 (1H, dd, *J* = 1.6, 17.2 Hz), 3.86–3.92 (1H, m), 3.75–3.81 (1H, m), 3.68–3.72 (2H, m), 3.41 (1H, d, *J* = 9.6 Hz), 3.29–3.36 (2H, m), 1.11–1.98 (22H, m), 1.07 (3H, s), 1.05 (3H, s), 0.93 (3H, d, *J* = 7.2 Hz), 0.88 (9H, s), 0.03 (6H,s). MS (ES) *m/z* (%): 813.65 ($[MNa]^+$, 100).



Diene 242. To a stirred solution of phenol **236** (8 mg, 0.01 mmol) in DMF (1 mL) was added DMAP (2 mg, 0.016 mmol), imidazole (68 mg, 1.0 mmol), and TBSCl (76 mg, 0.5 mmol). The reaction was allowed to stir at rt for 14 hr. Water (10 mL) was then added and the crude material was extracted with Et_2O (2 x 50 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (4/96, EtOAc/Hex) to afford 7.3 mg (81%) of bis-silyl ether **242**. $[\alpha]_D$ = -0.47 ($CHCl_3$, *c* 1.35). IR (film) 2933, 1727, 1464, 1260, 1086, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.34 (5H, m), 7.13 (1H, t, *J* = 8.0 Hz), 6.77 (1H, d, *J* = 7.6 Hz), 6.68 (1H, d, *J* = 8.4 Hz), 5.81–5.98

(2H, m), 5.25 (1H, d, *J* = 17.6 Hz), 5.13–5.18 (1H, m), 5.02–5.09 (5H, m), 3.96–4.02 (1H, m), 3.76–3.83 (1H, m), 3.39–3.48 (3H, m), 3.33 (2H, d, *J* = 6.4 Hz), 1.98–2.06 (1H, m), 1.08–1.88 (26H, m), 0.96 (9H, s), 0.86–0.91 (12H, m), 0.22 (3H, s), 0.20 (3H, s), 0.12 (3H, s), 0.06 (3H, s). MS (ES) *m/z* (%): 928.45 ($[MNa]^+$, 100).



Diene 243. To a round bottom flask charged with diene **236** (8.5 mg, 0.0094 mmol) was added TBAF (0.7 mL, 1M soln. in THF). The reaction was allowed to stir overnight. The solvent was removed and the crude was purified directly to afford 4.0 mg (67%) of ester **243**. $[\alpha]_D$ = -0.03 ($CHCl_3$, *c* 0.6). IR (film) 3520, 2936, 1731, 1654, 1451, 1251, 1084, 1045, 1251, 1084, 1045, 914, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.23 (1H, s), 7.27–7.33 (6H, m), 6.83 (1H, d, *J* = 8.4 Hz), 6.72 (1H, d, *J* = 7.2 Hz), 5.97 (1H, dddd, *J* = 5.6, 5.6, 10.4, 16.0 Hz), 5.84 (1H, ddd, *J* = 5.2, 10.0, 16.0 Hz), 5.48–5.53 (1H, m), 5.20 (1H, d, *J* = 17.6 Hz), 3.73–3.82 (3H, m), 3.50–3.64 (4H, m), 3.27–3.33 (1H, m), 1.80–1.91 (4H, m), 1.46–1.72 (17H, m), 1.10–1.34 (10H, m), 0.94 (3H, d, *J* = 7.2Hz). MS (ES) *m/z* (%): 699.45 ($[MNa]^+$, 90).

4.7 Notes and References

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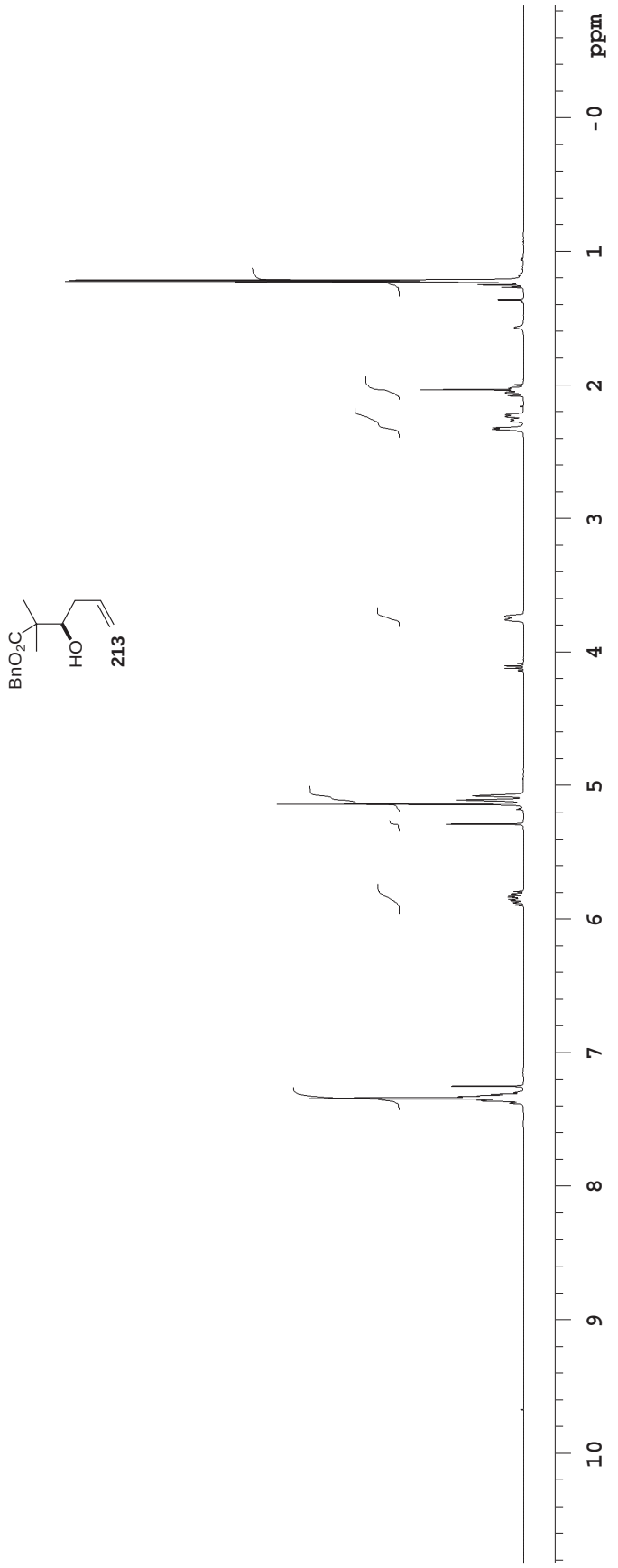
Appendix Two: Spectra of Compounds Appearing In Chapter 4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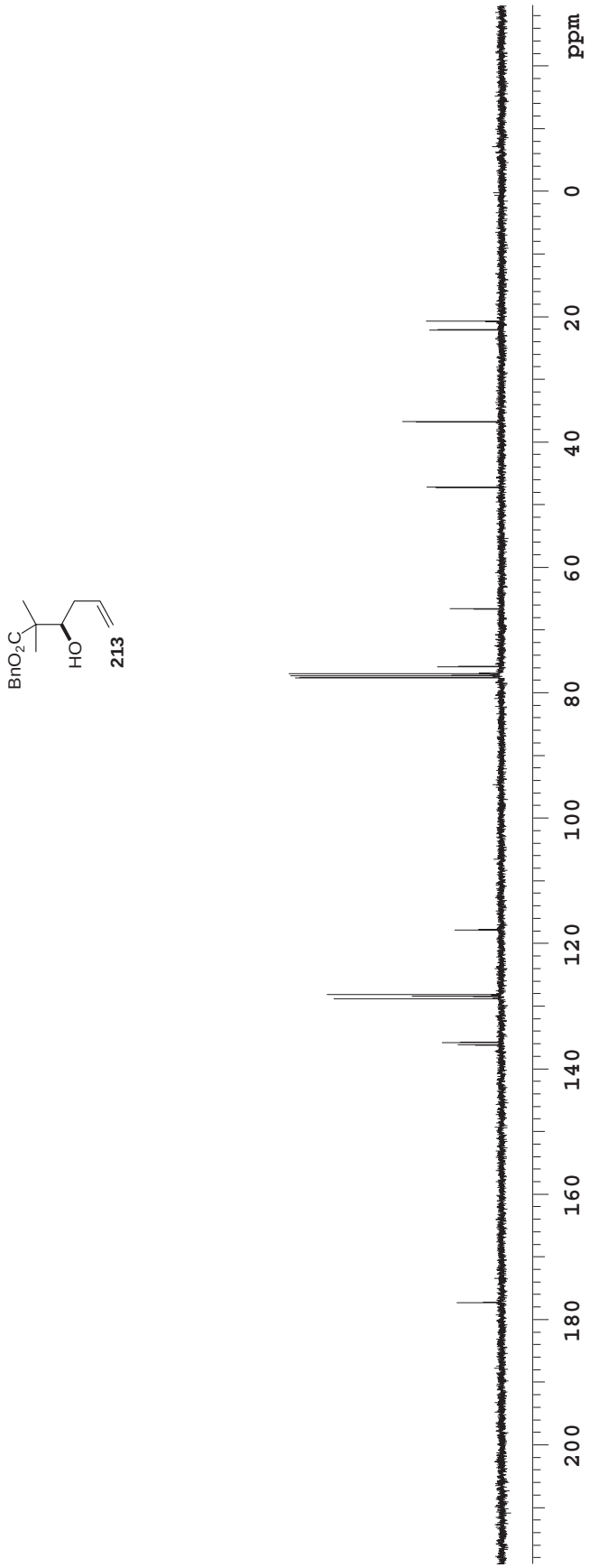
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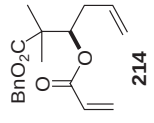

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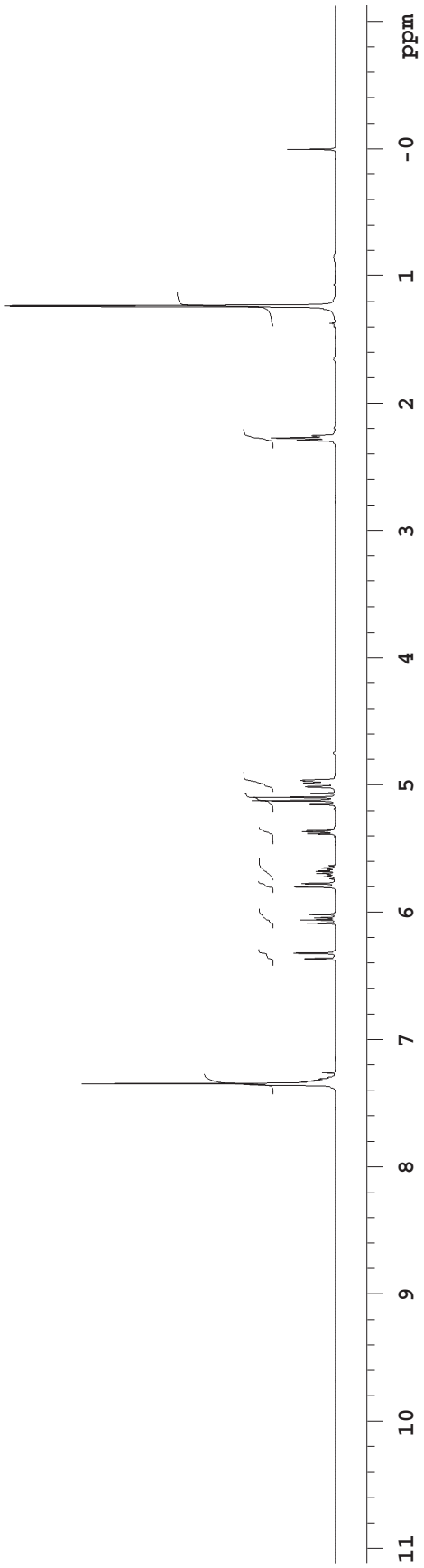

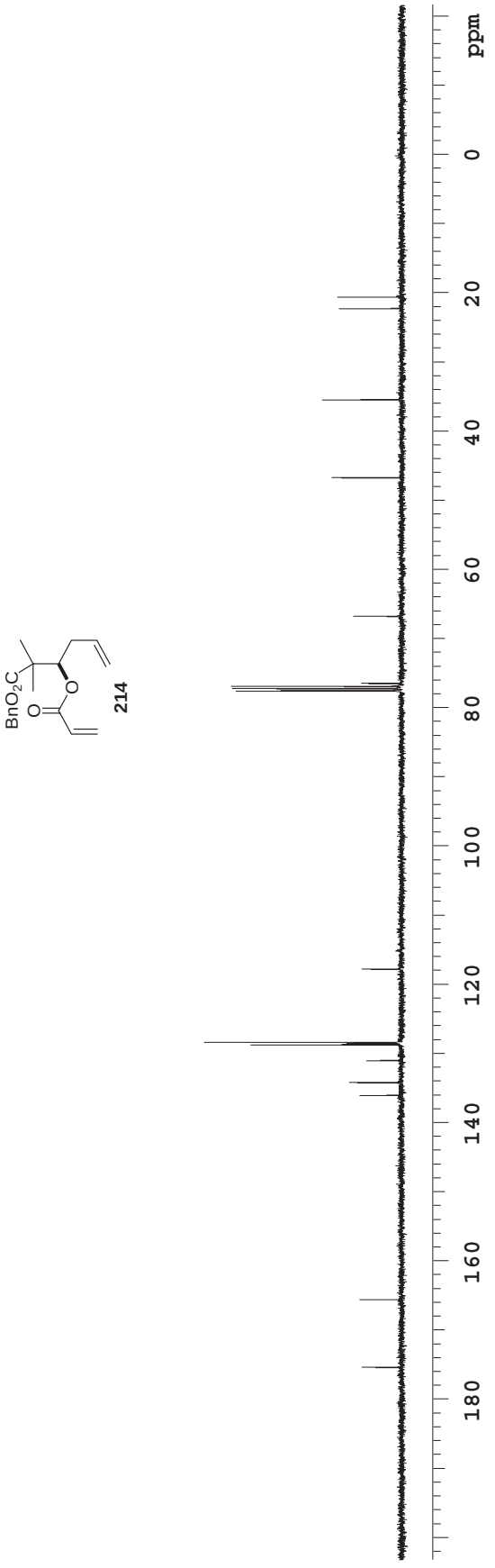
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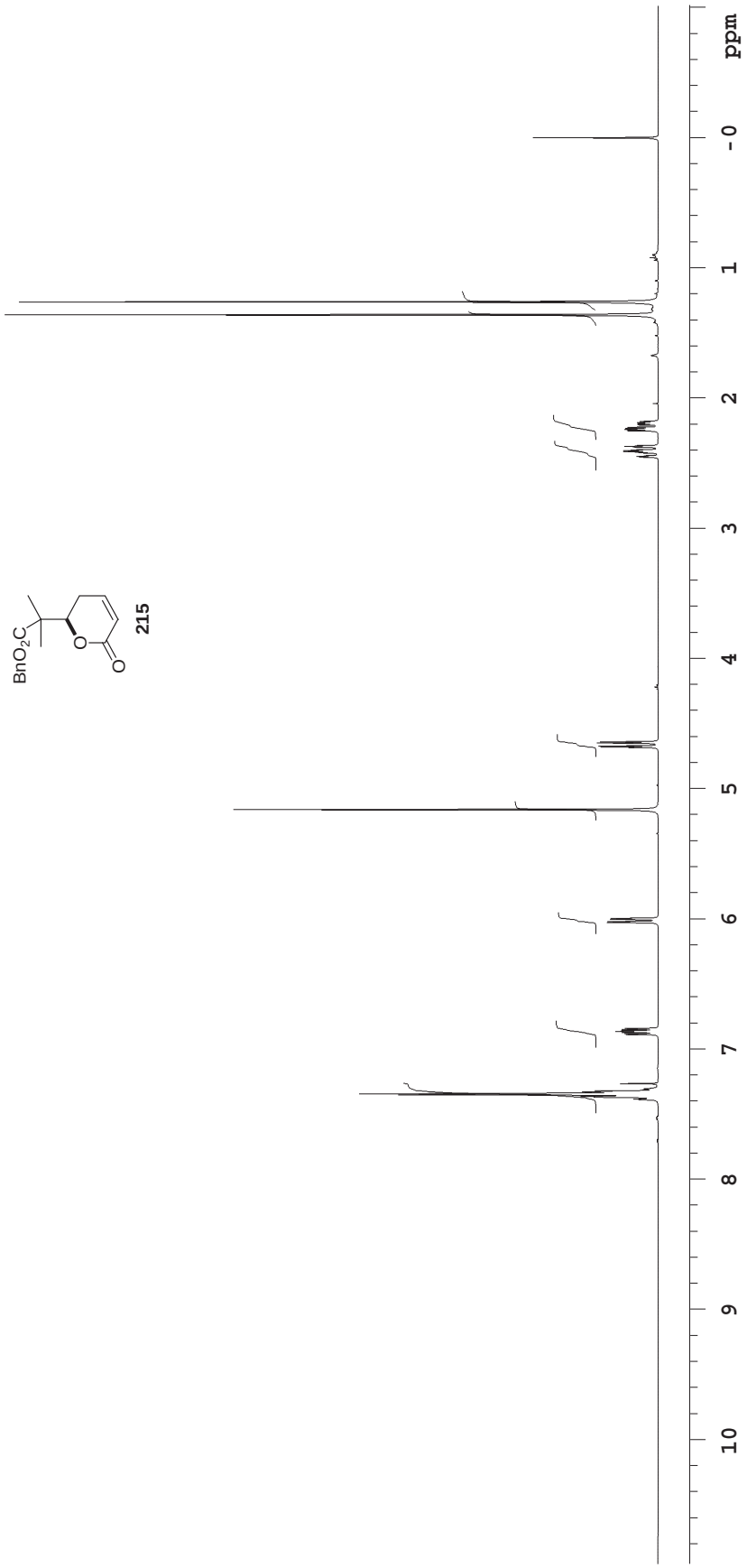
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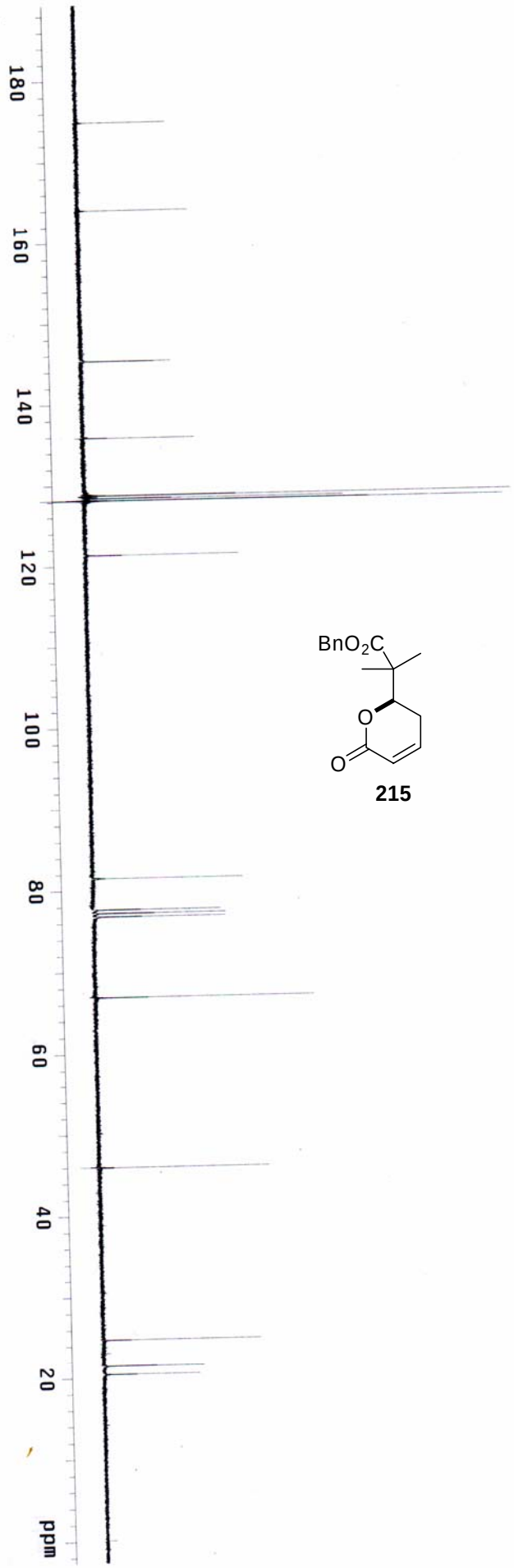

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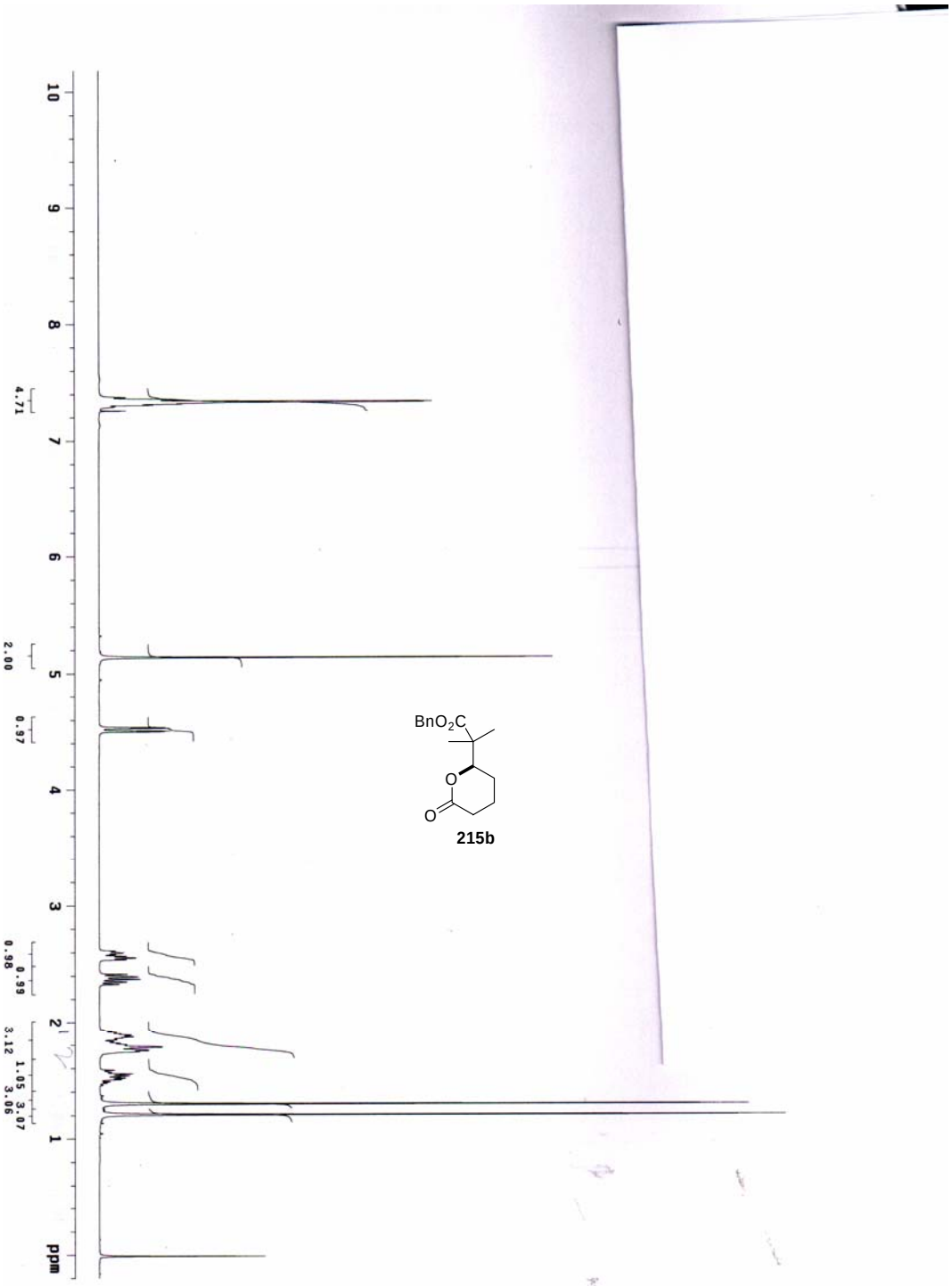
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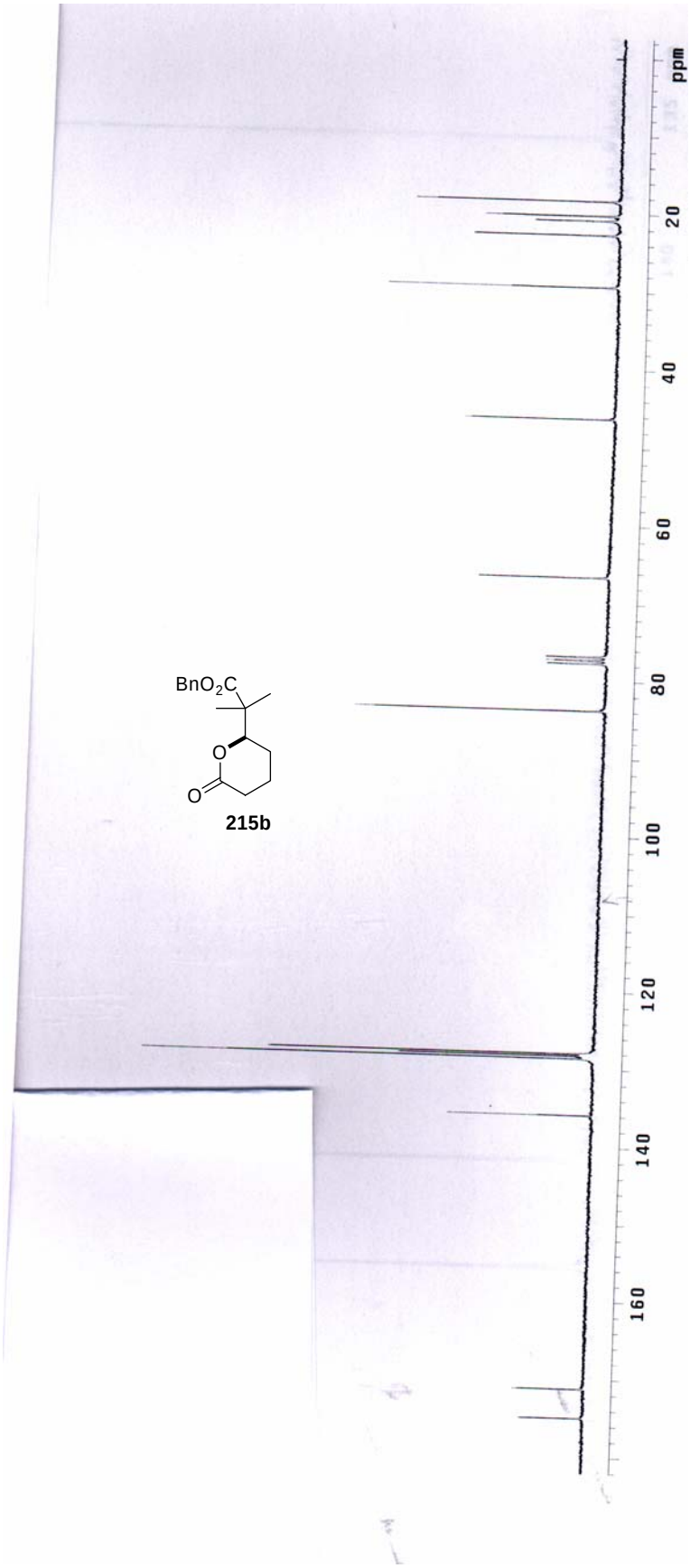

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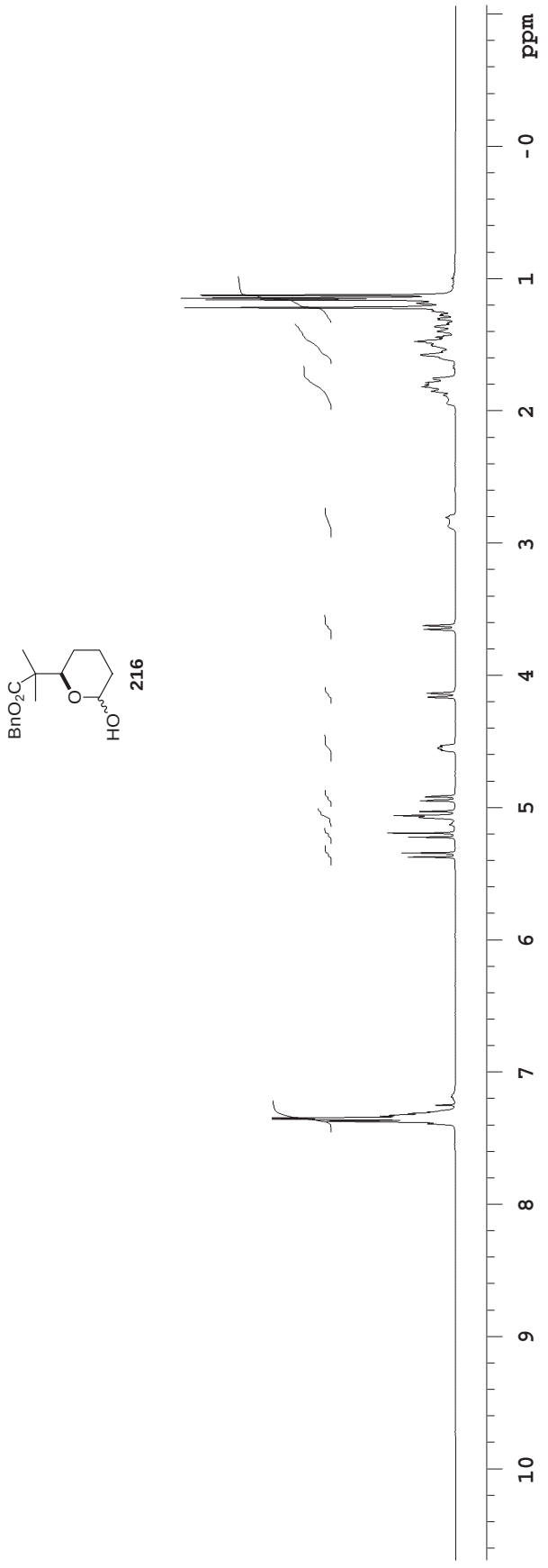
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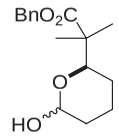

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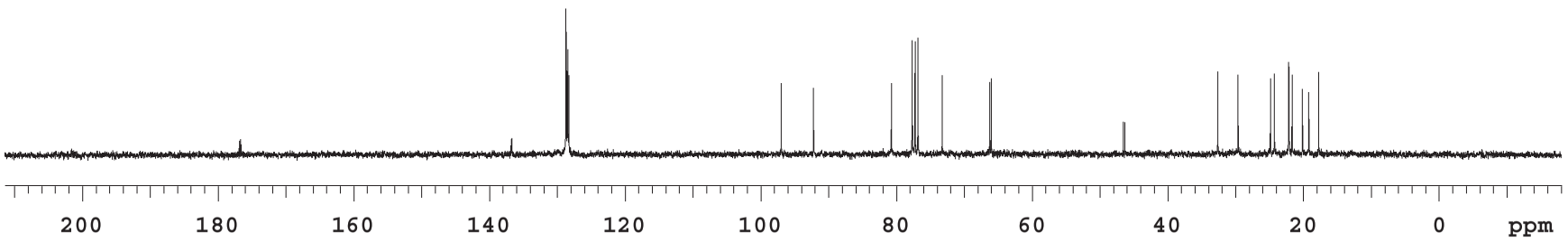

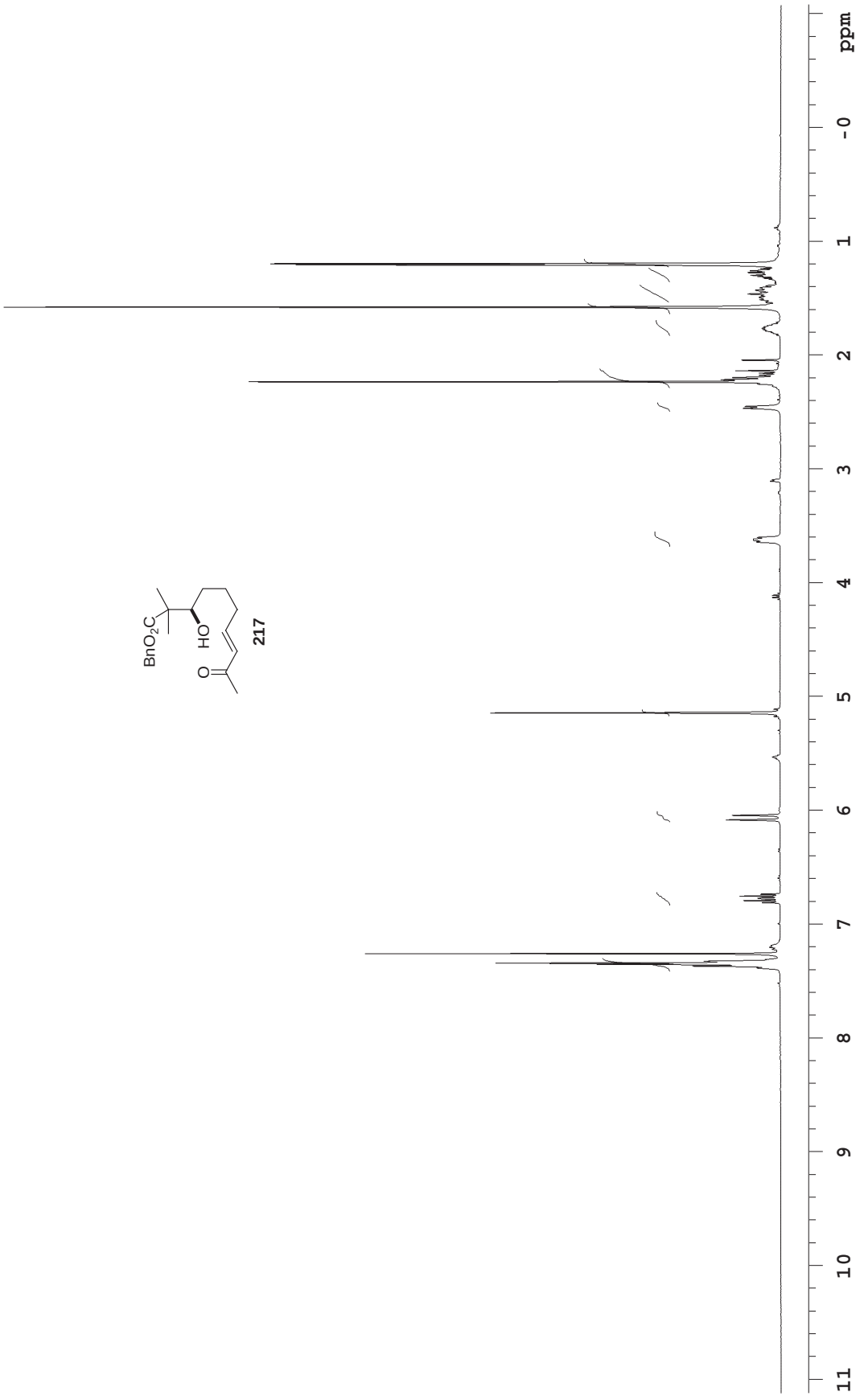
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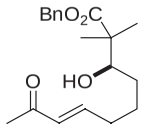

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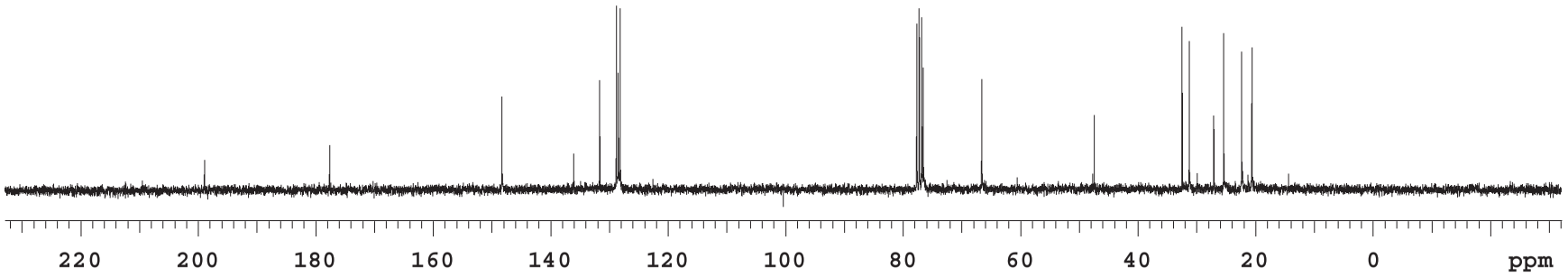

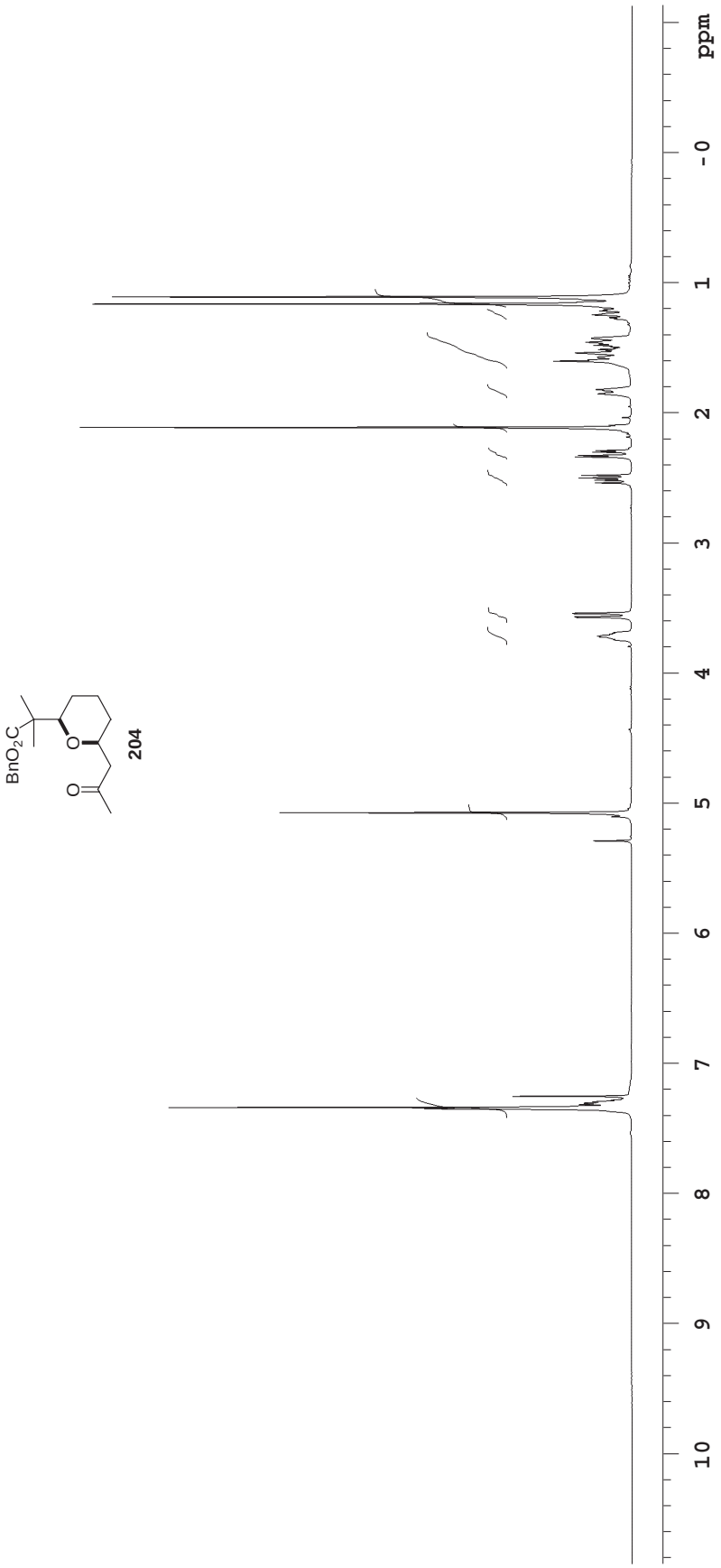
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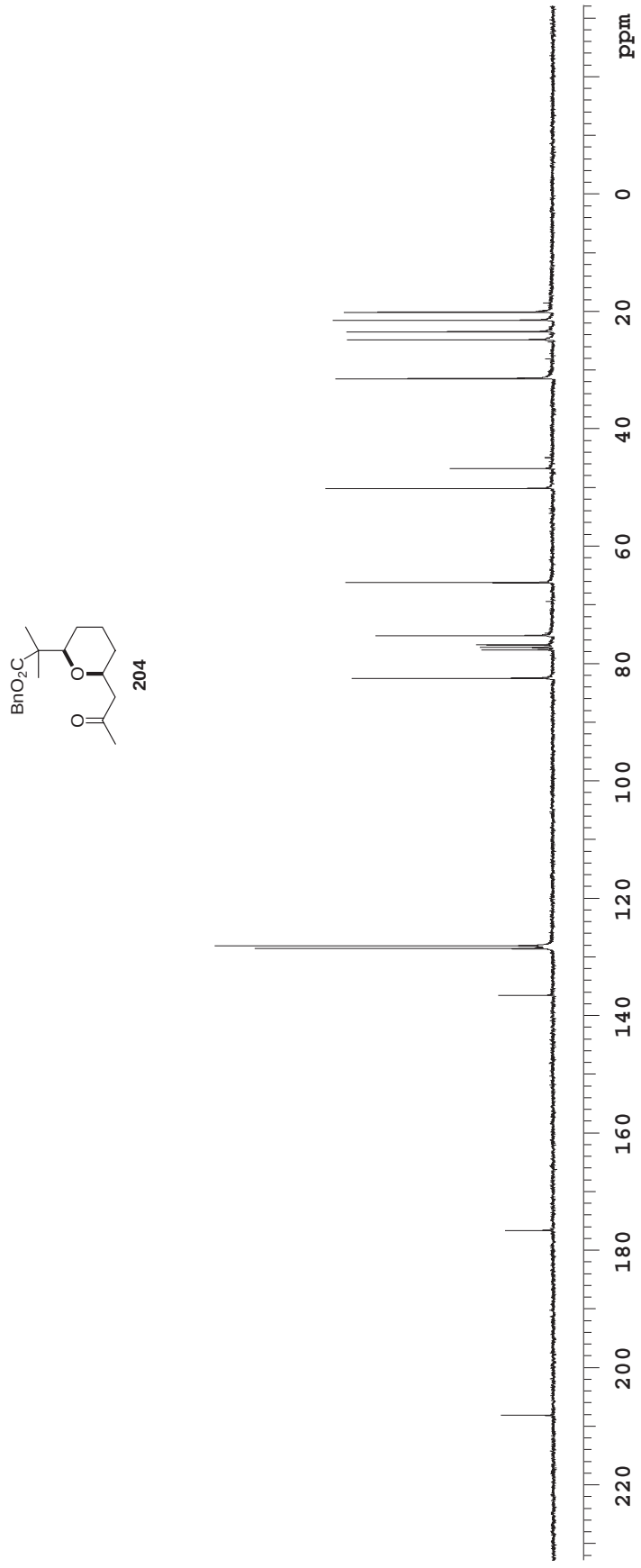
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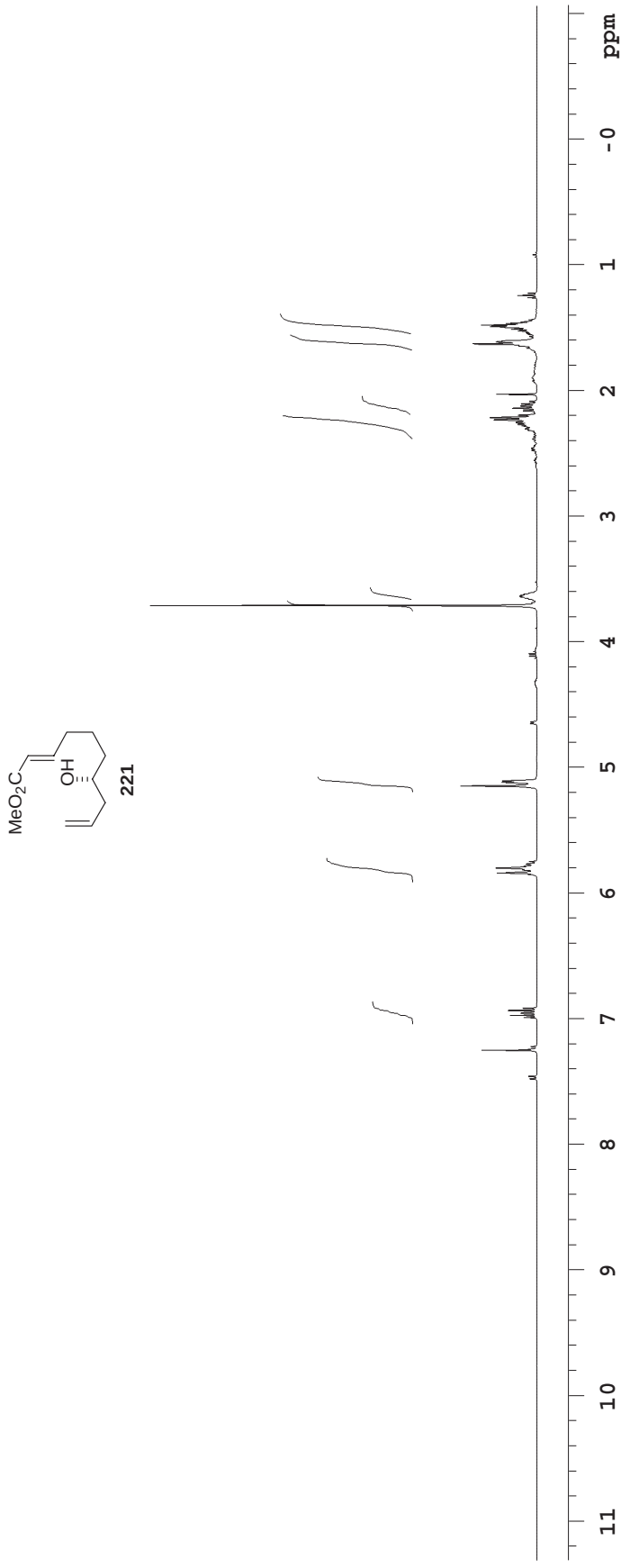
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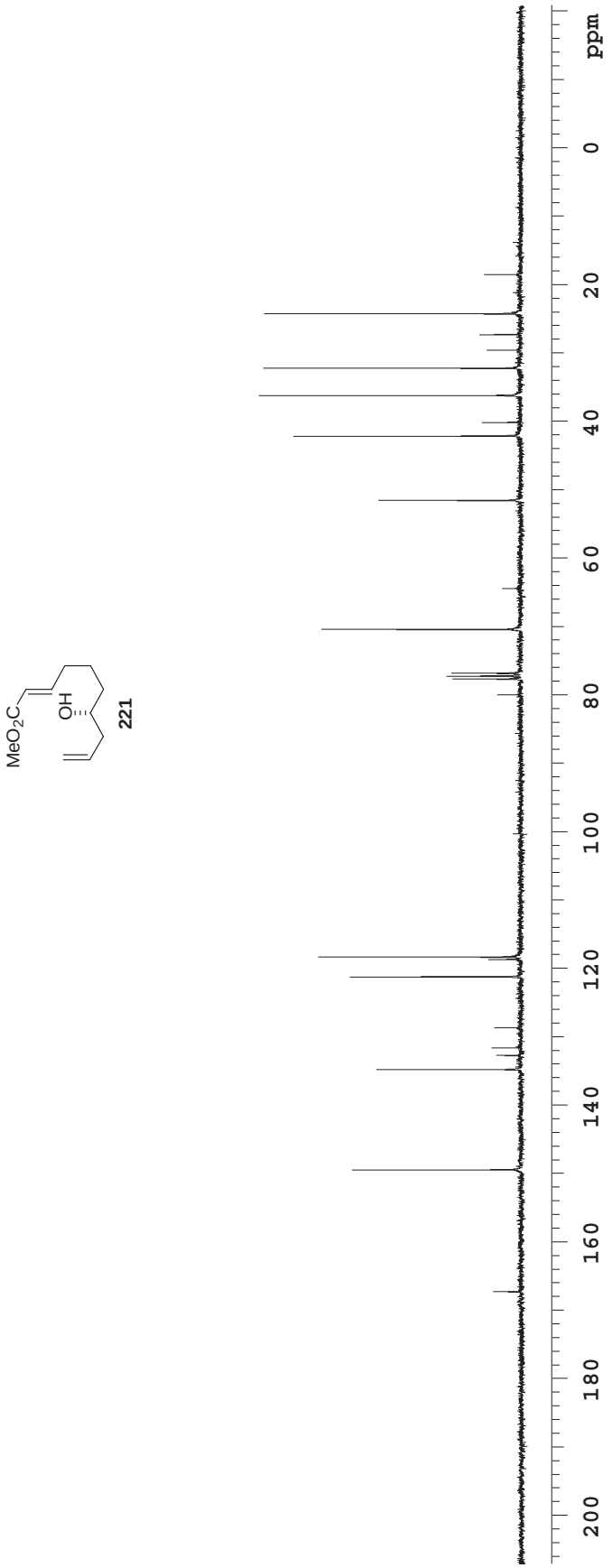
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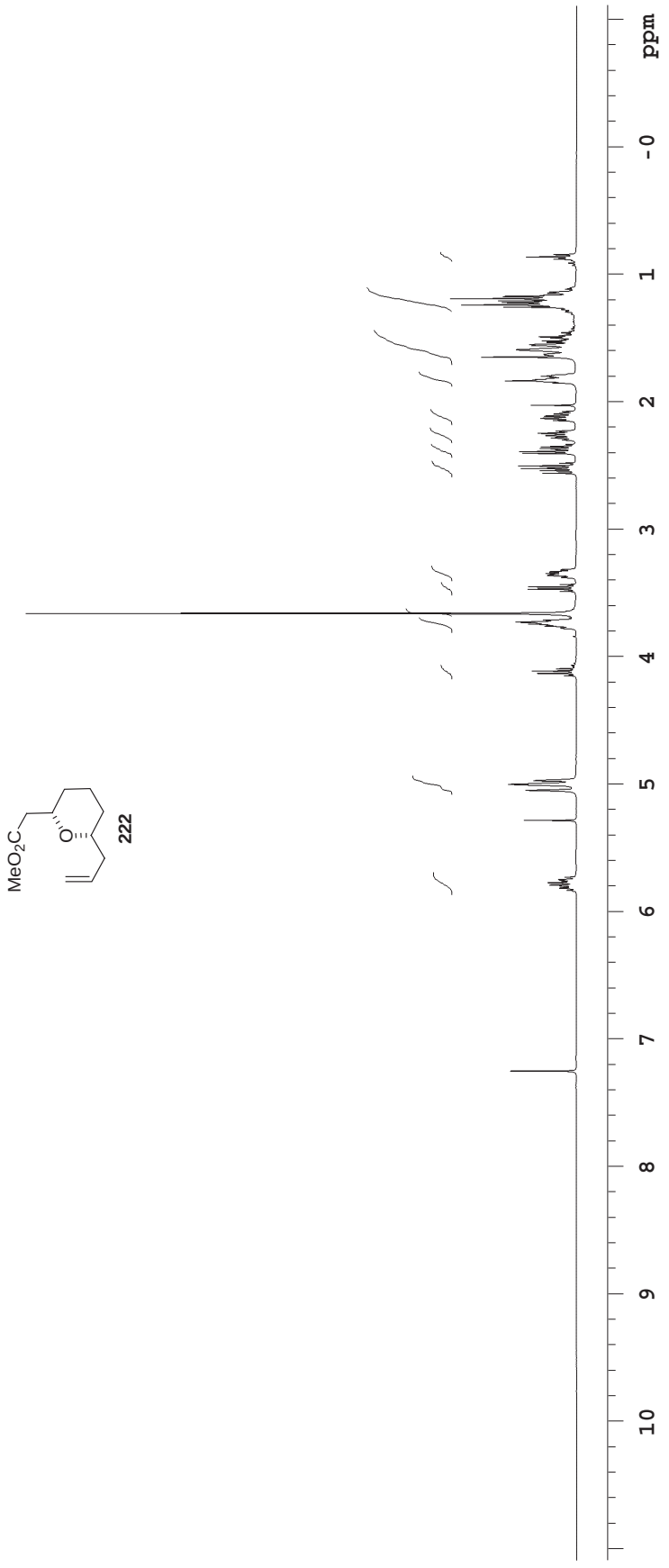
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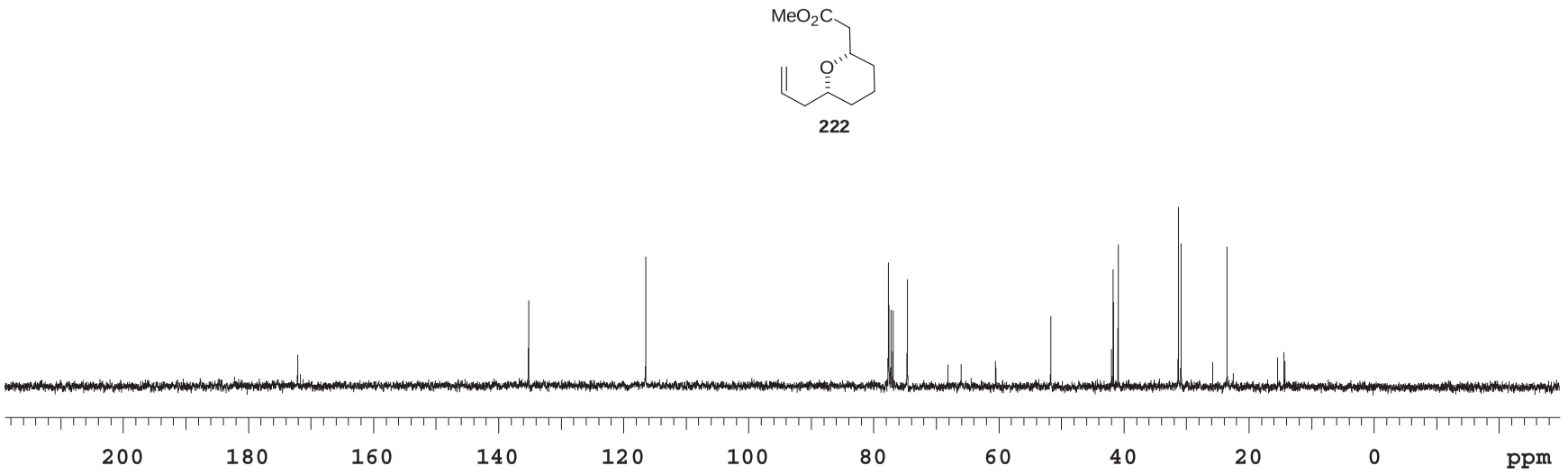
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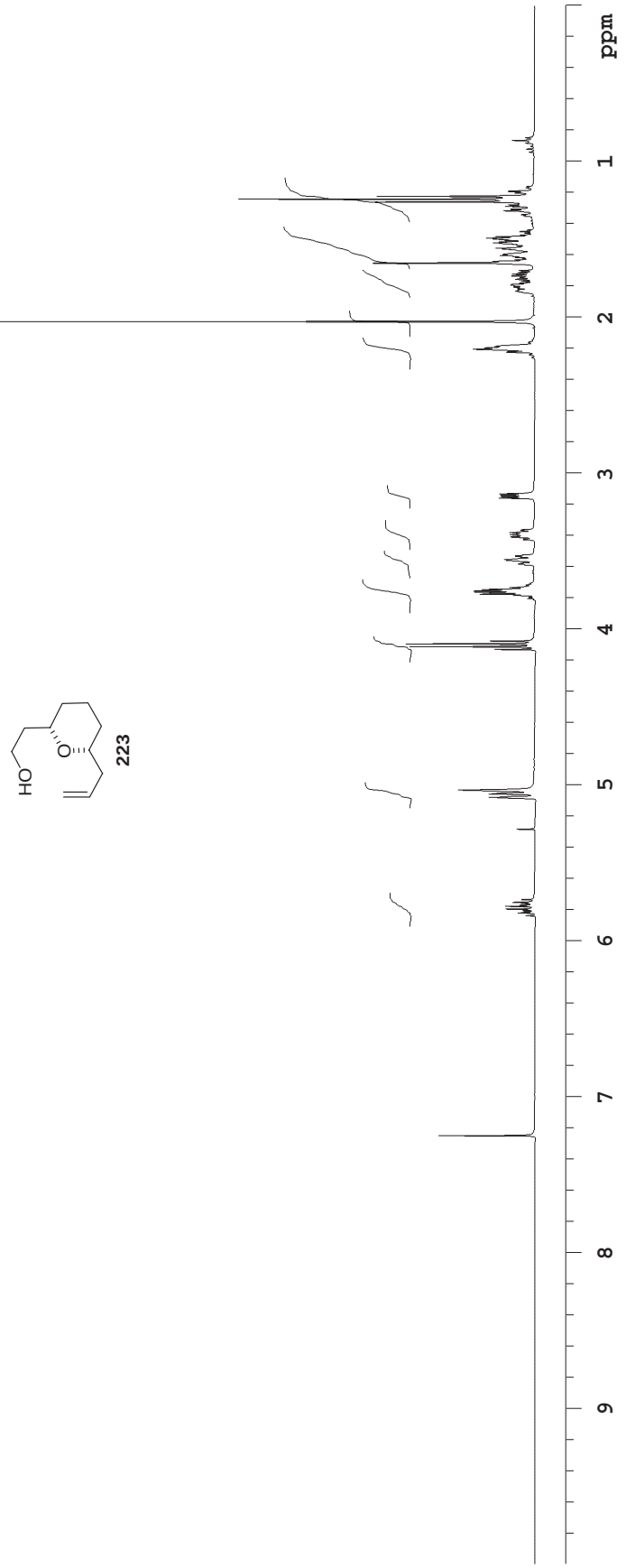
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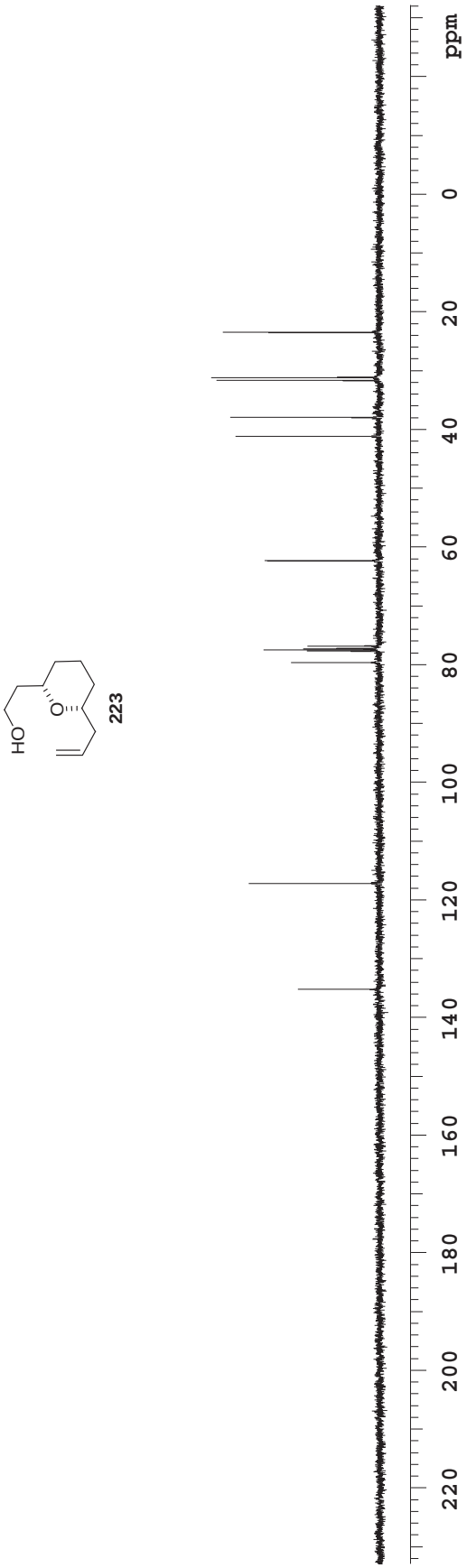
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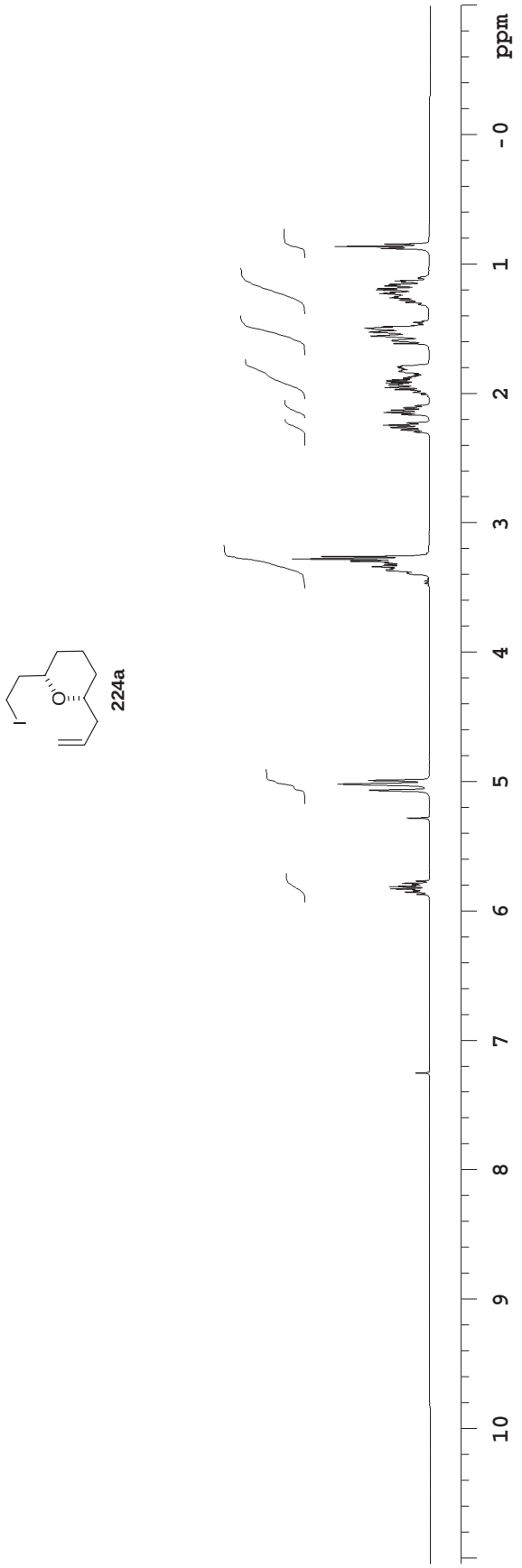
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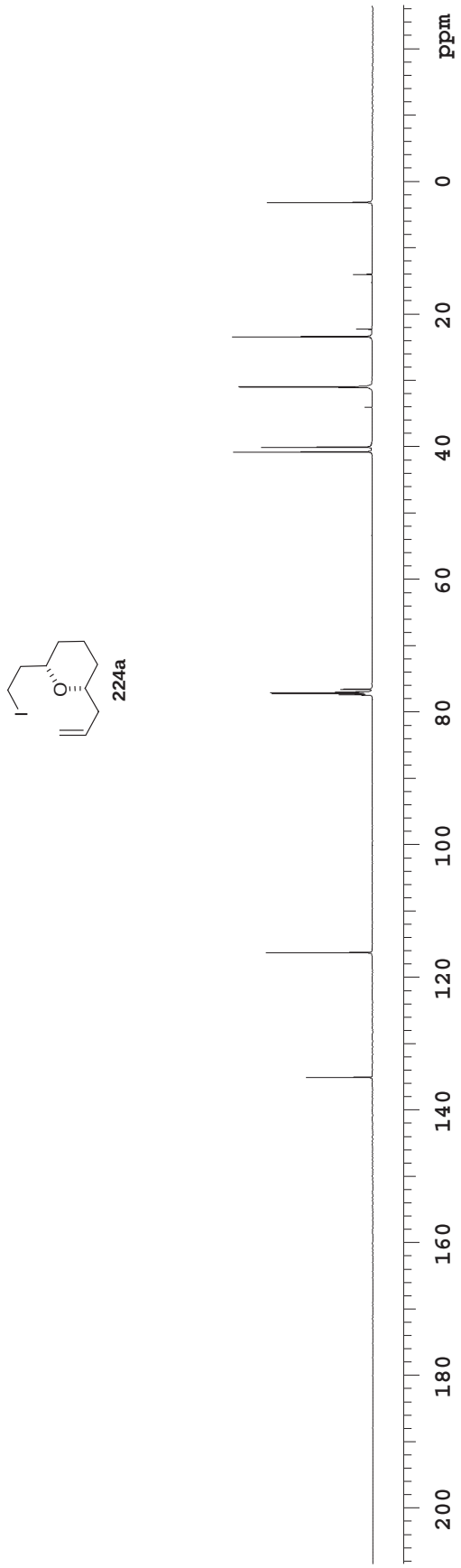
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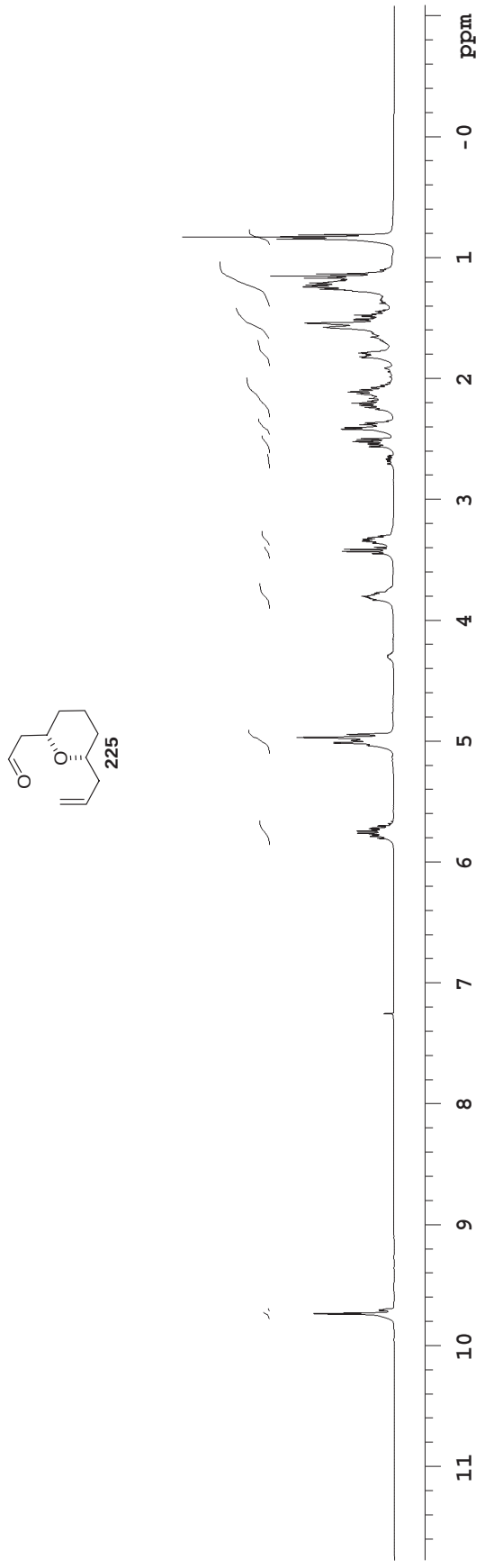
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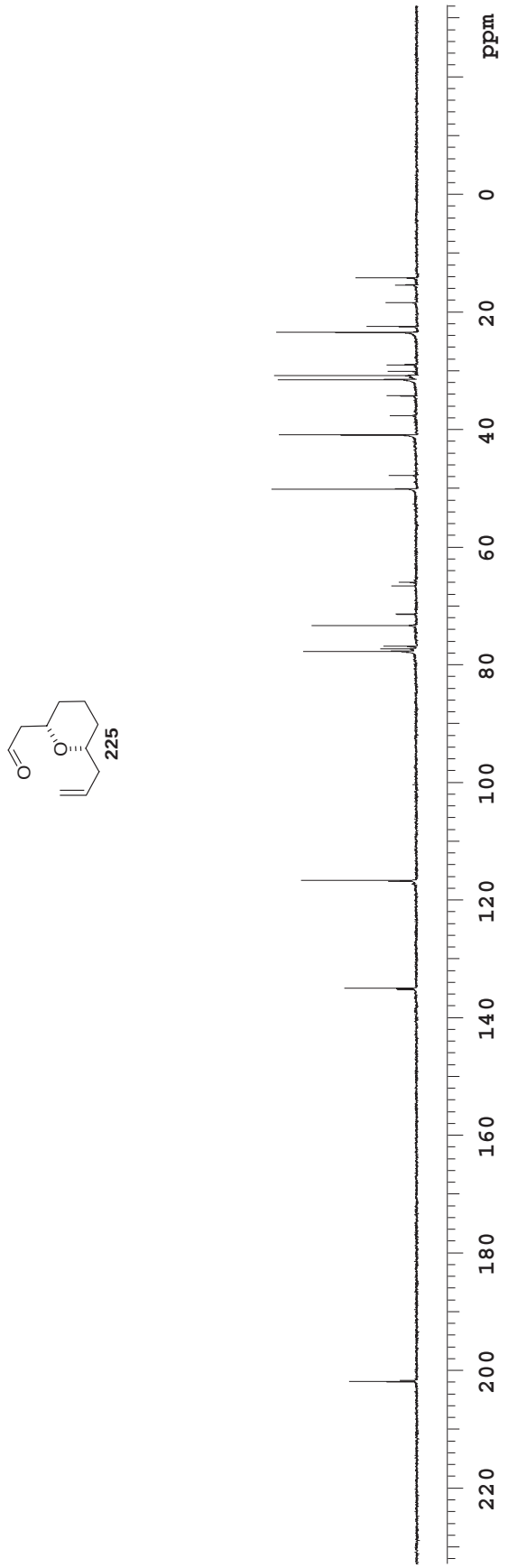
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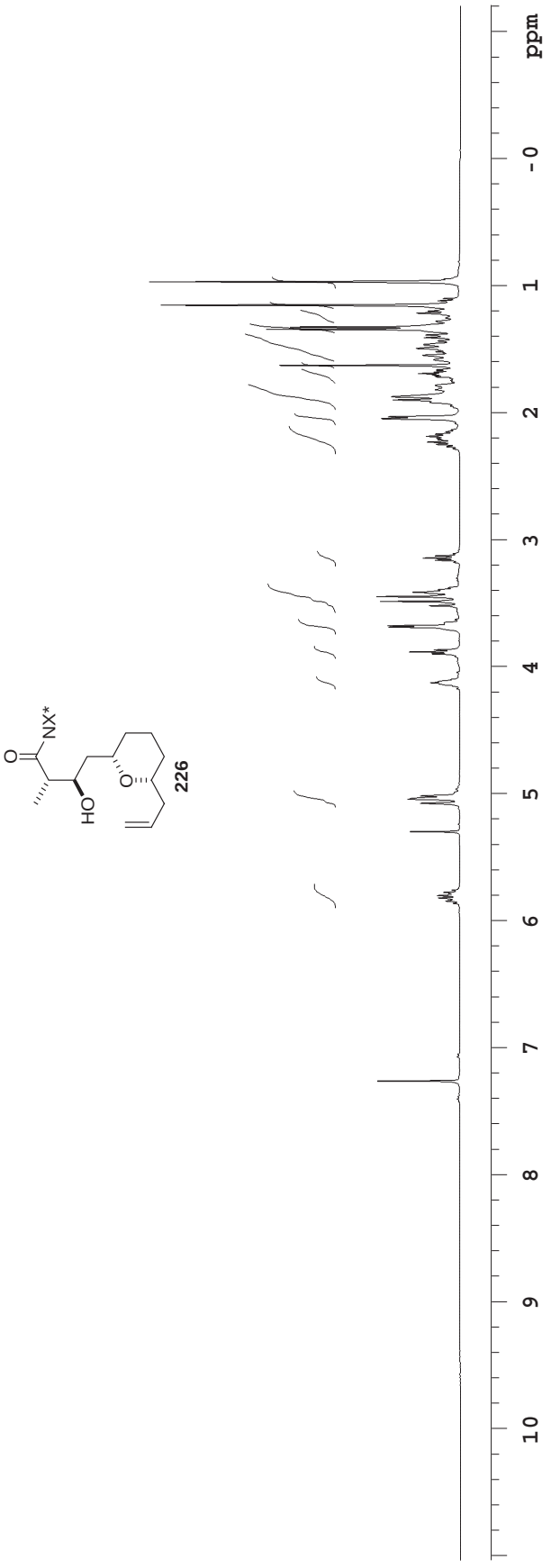
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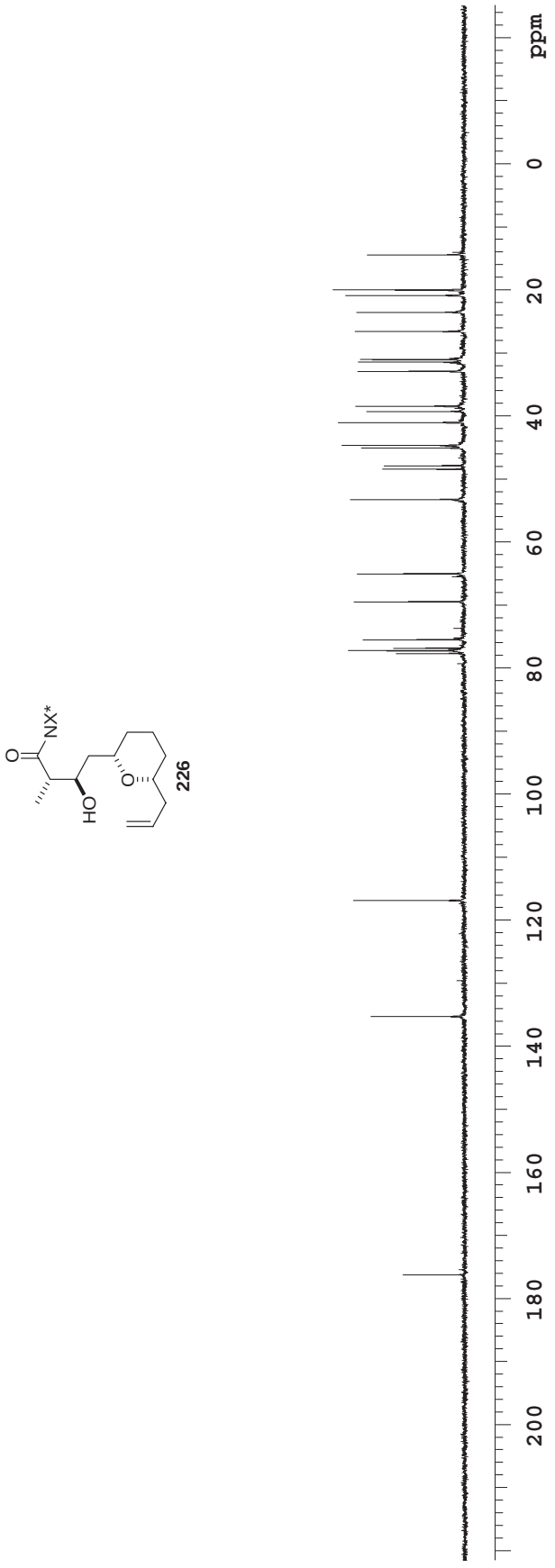
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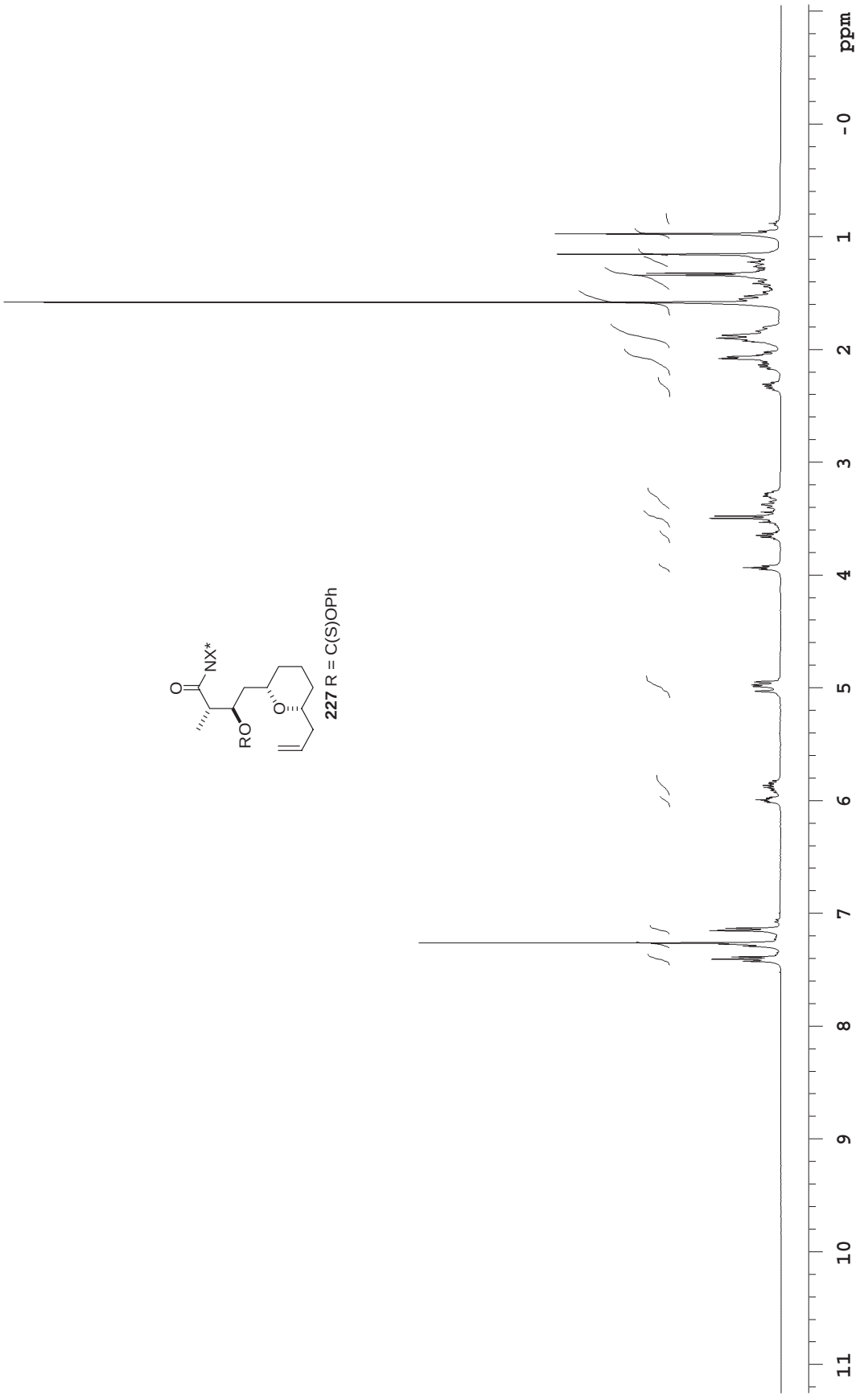
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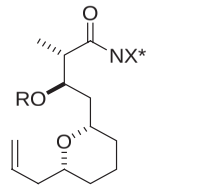

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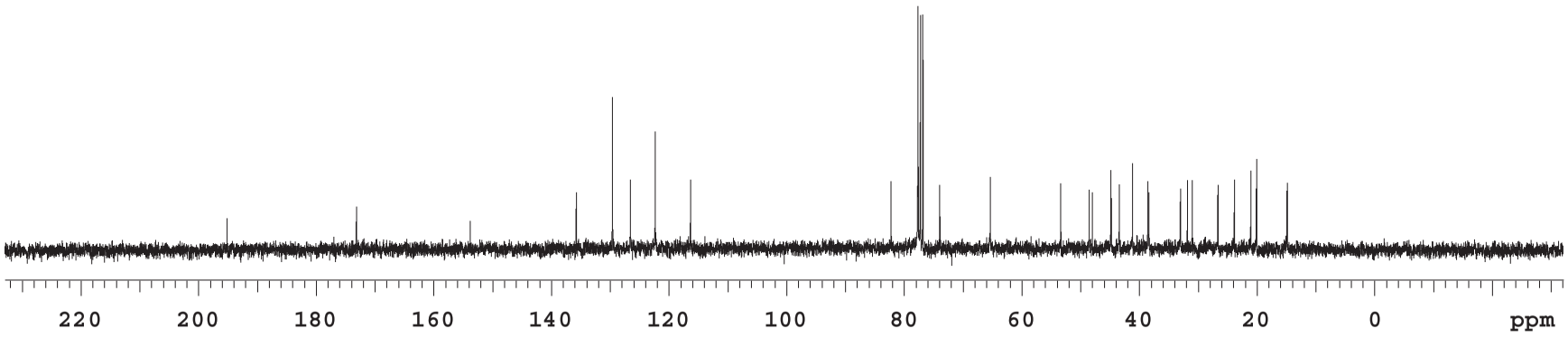

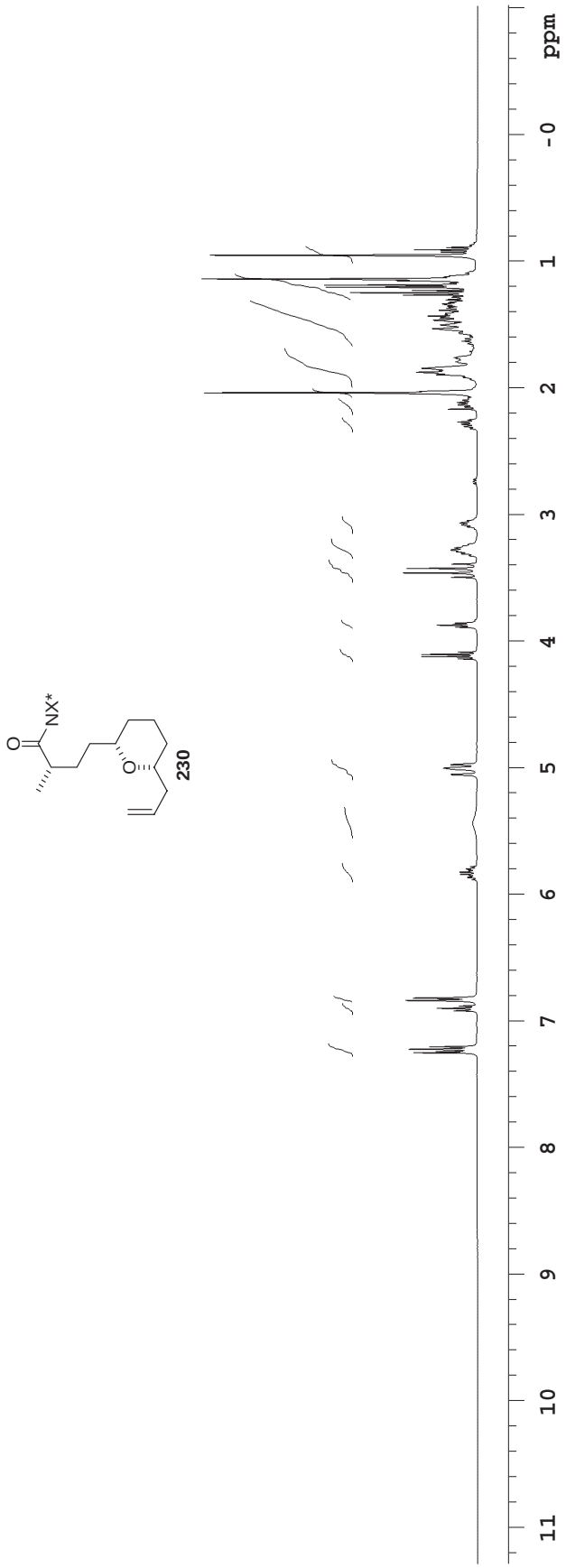
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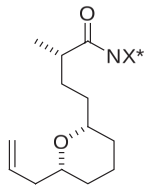

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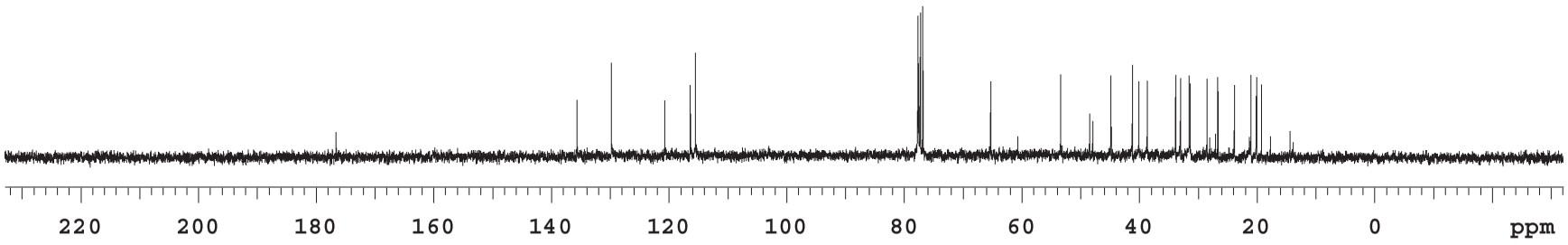

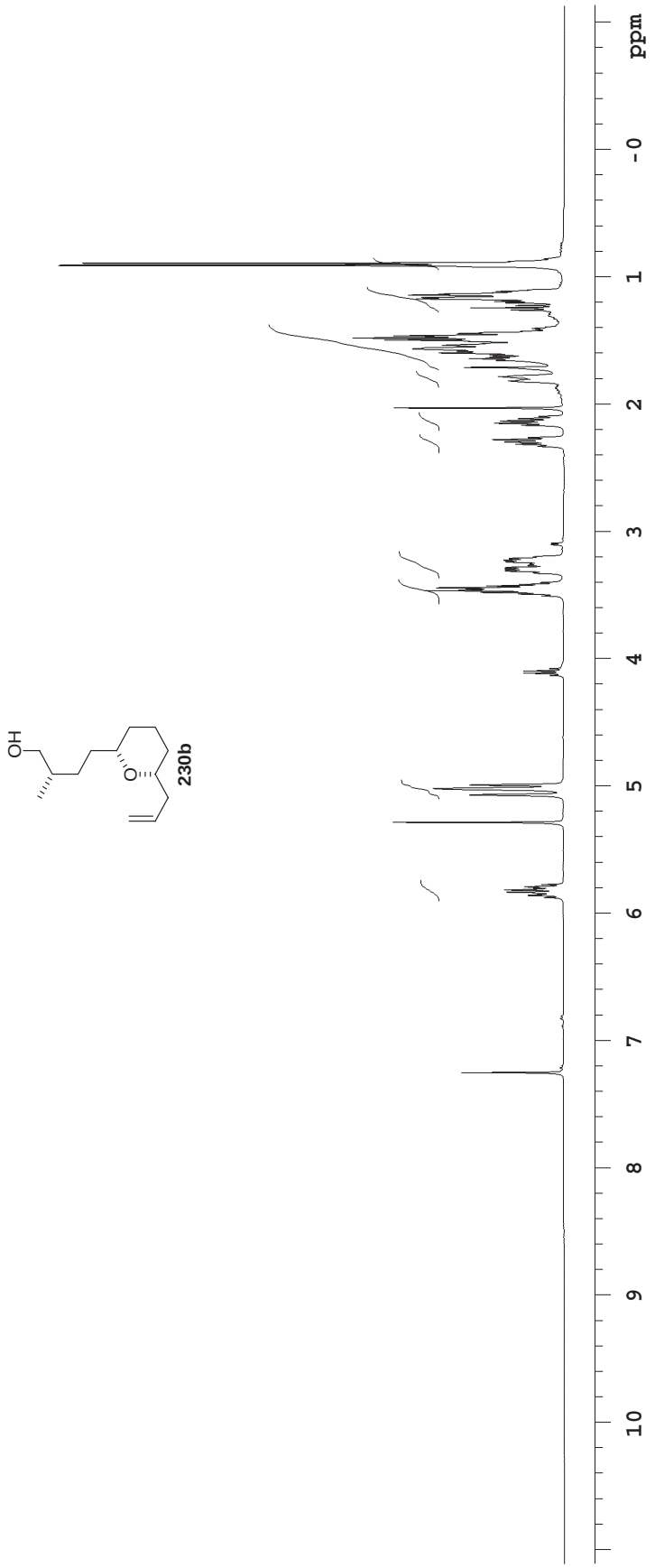
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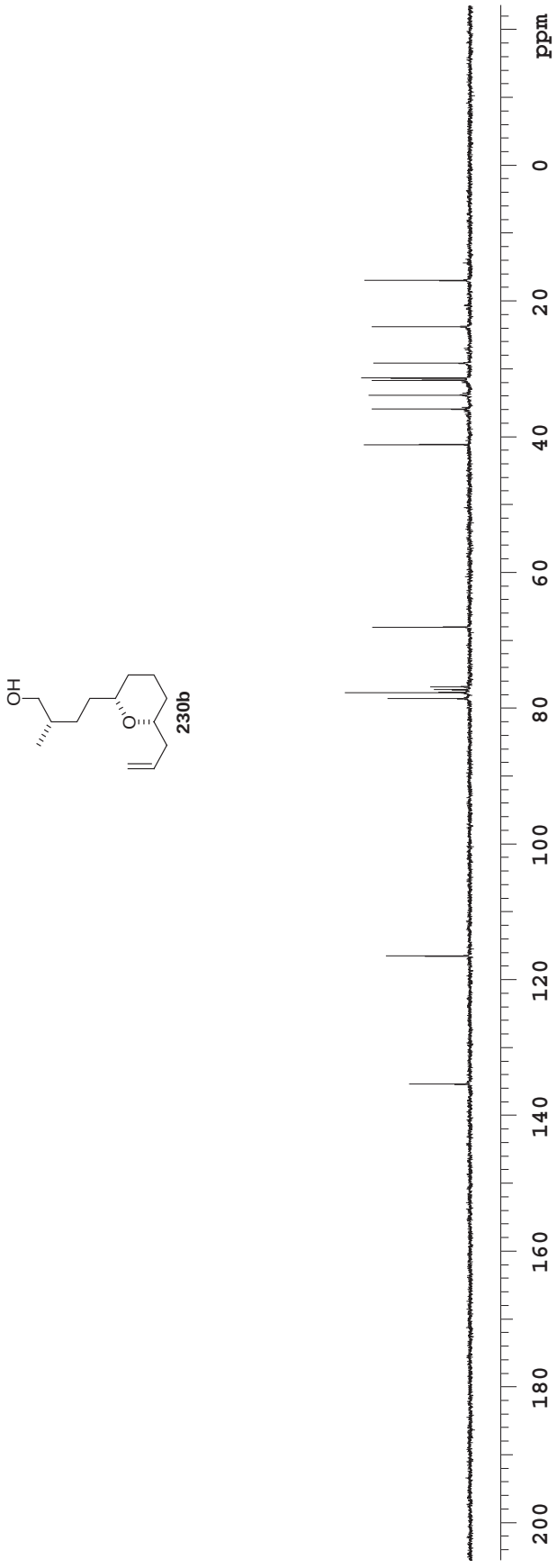
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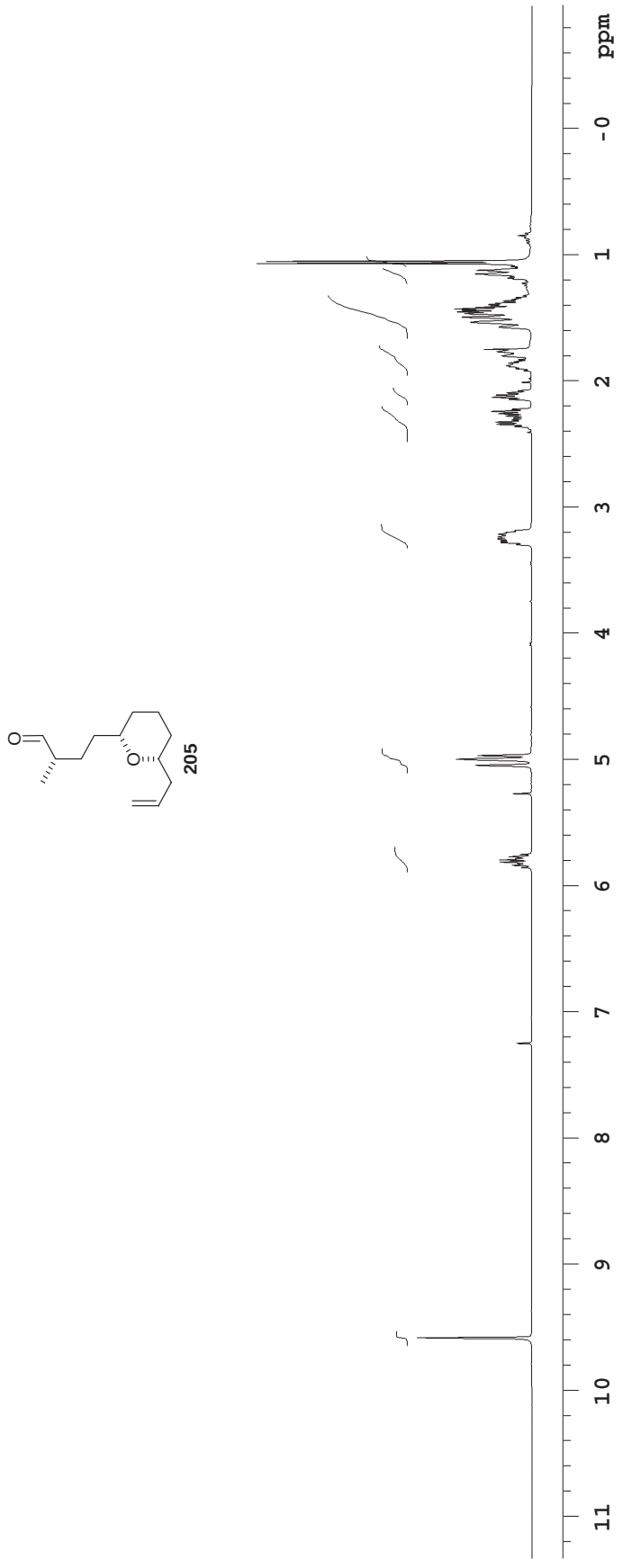
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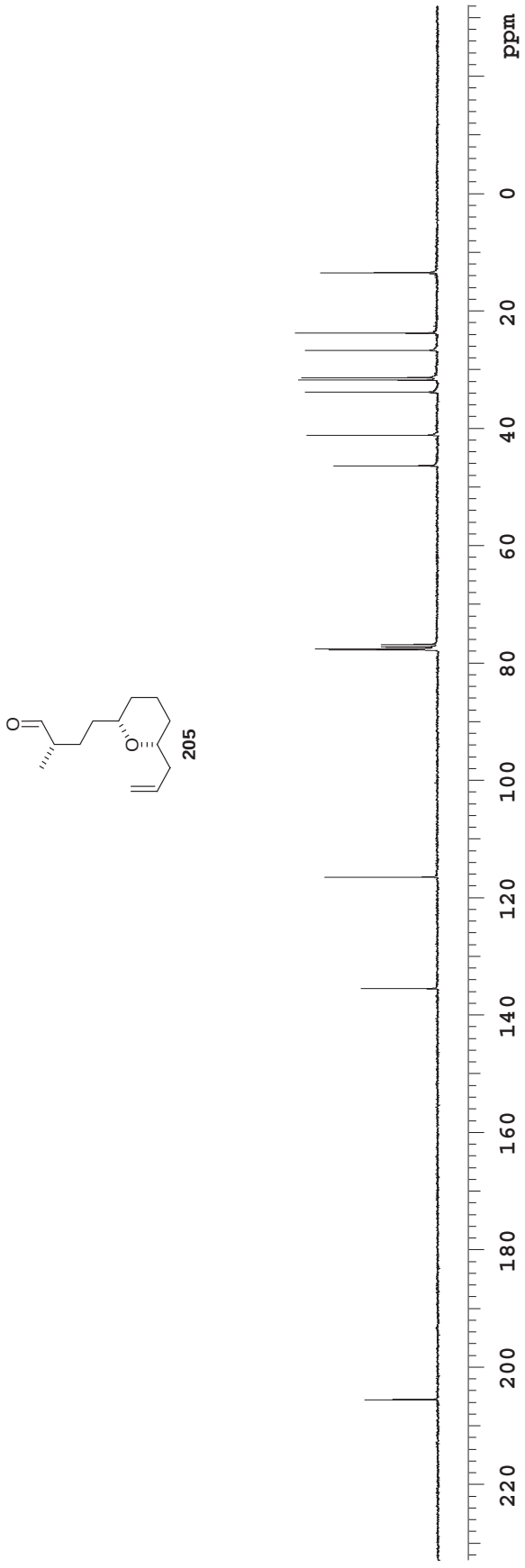
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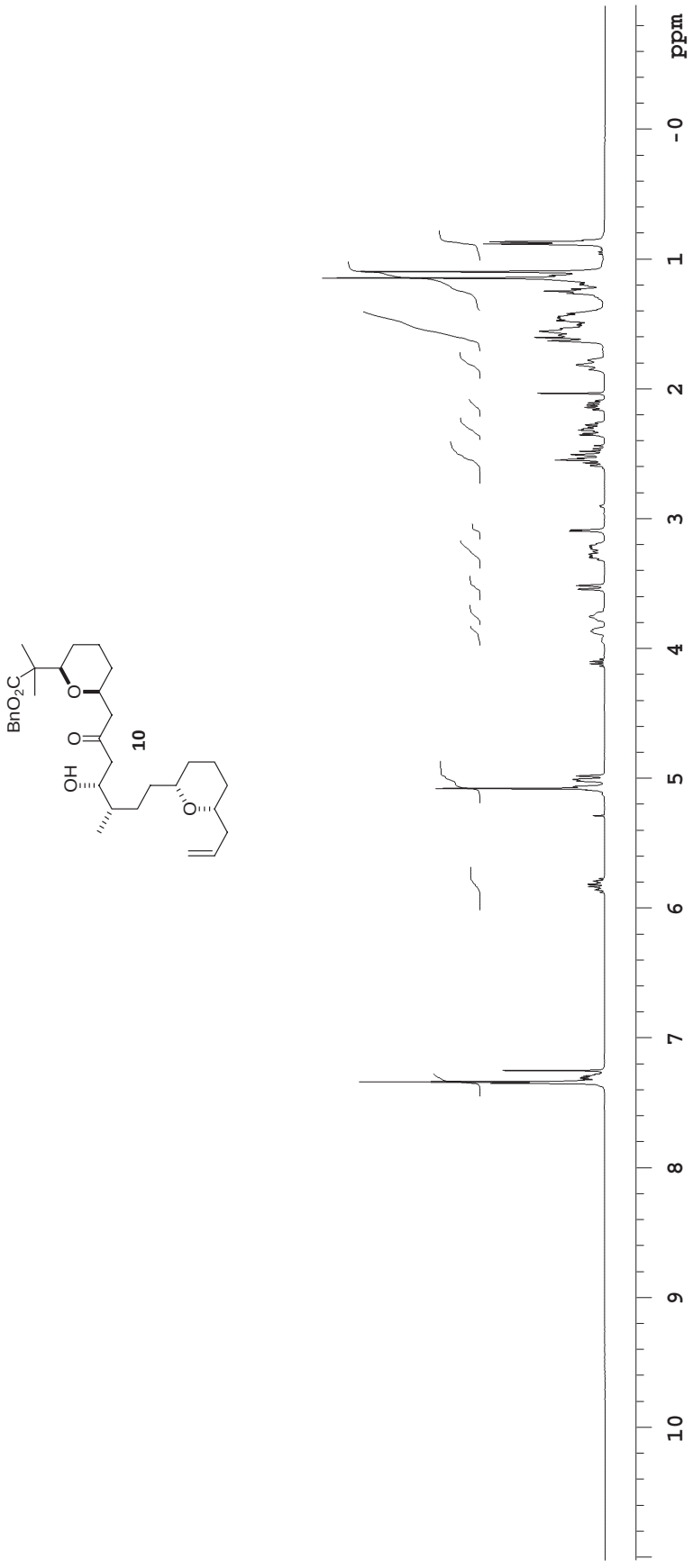
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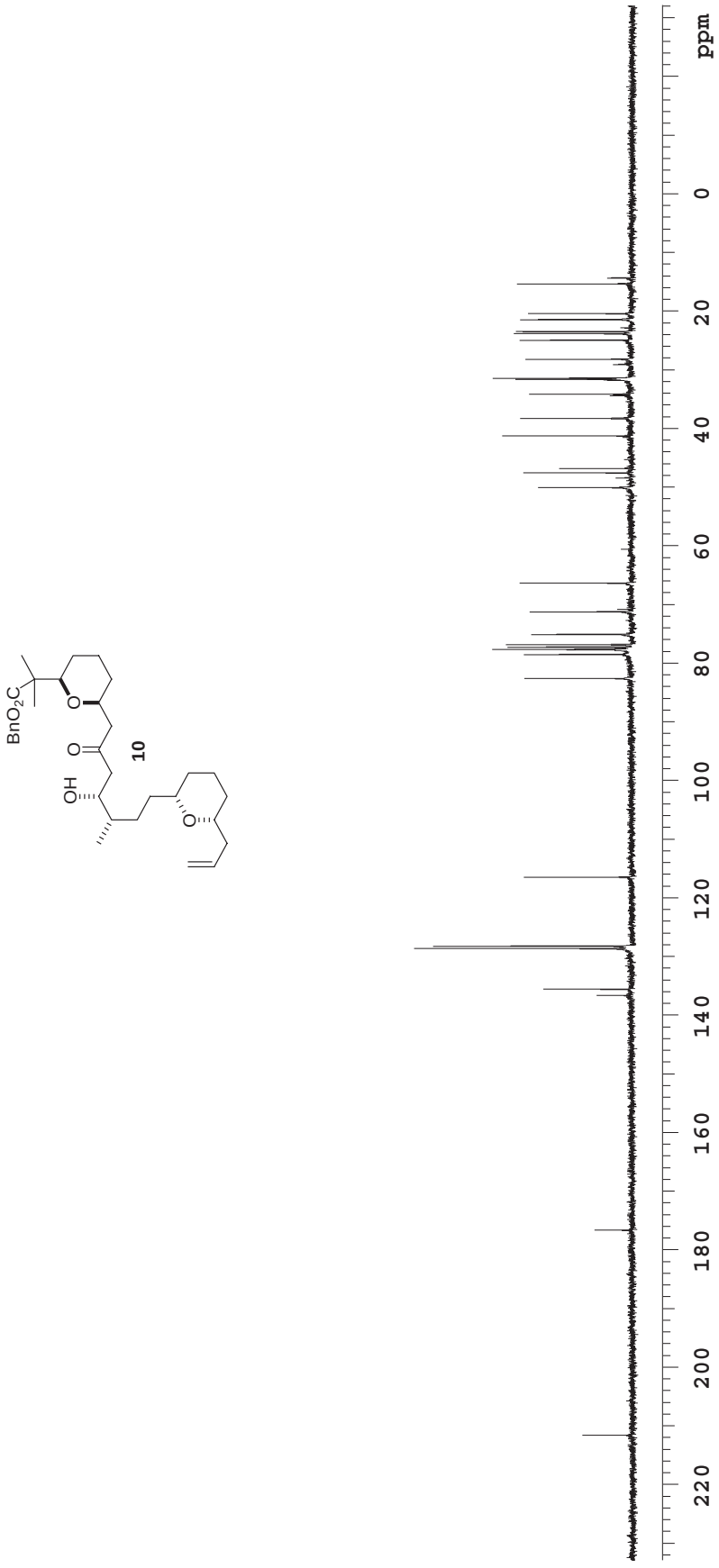
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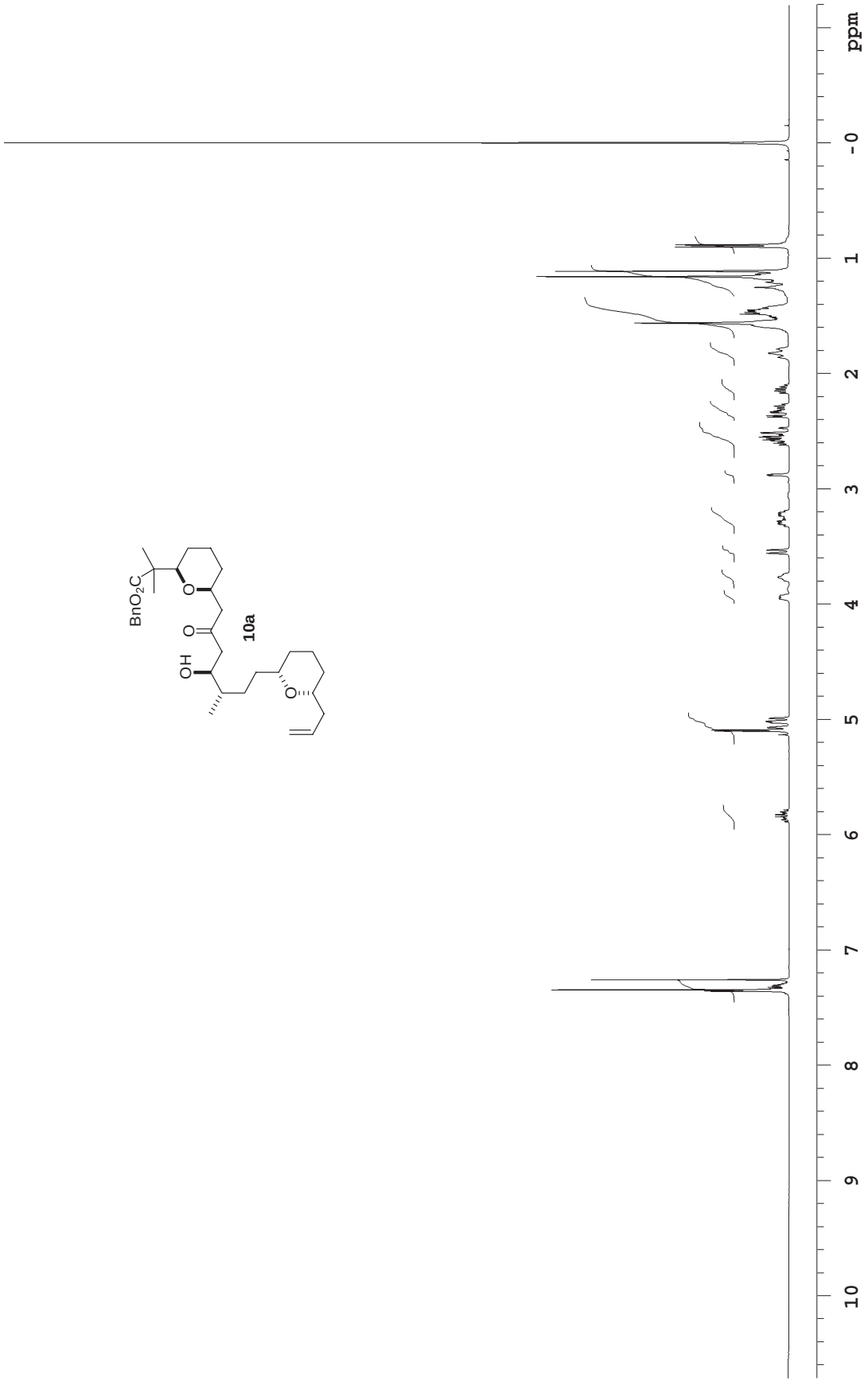
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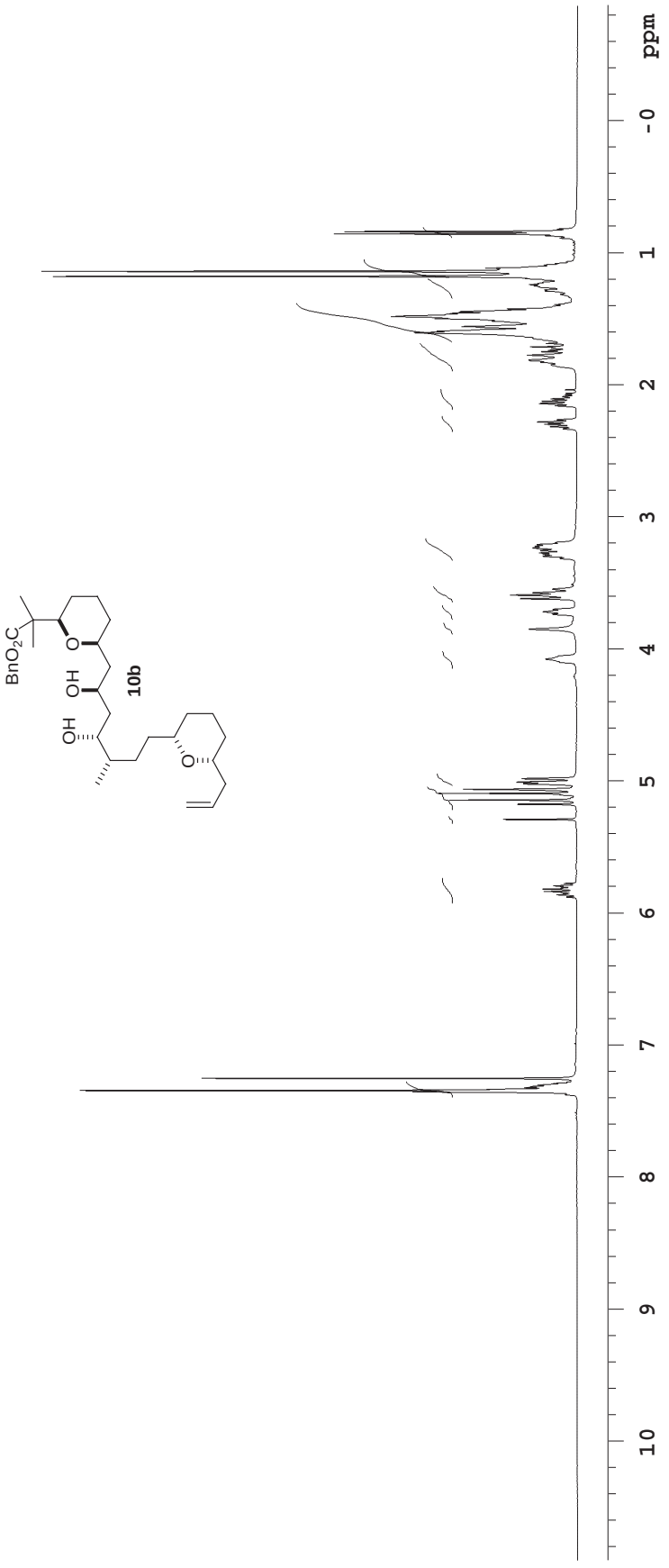
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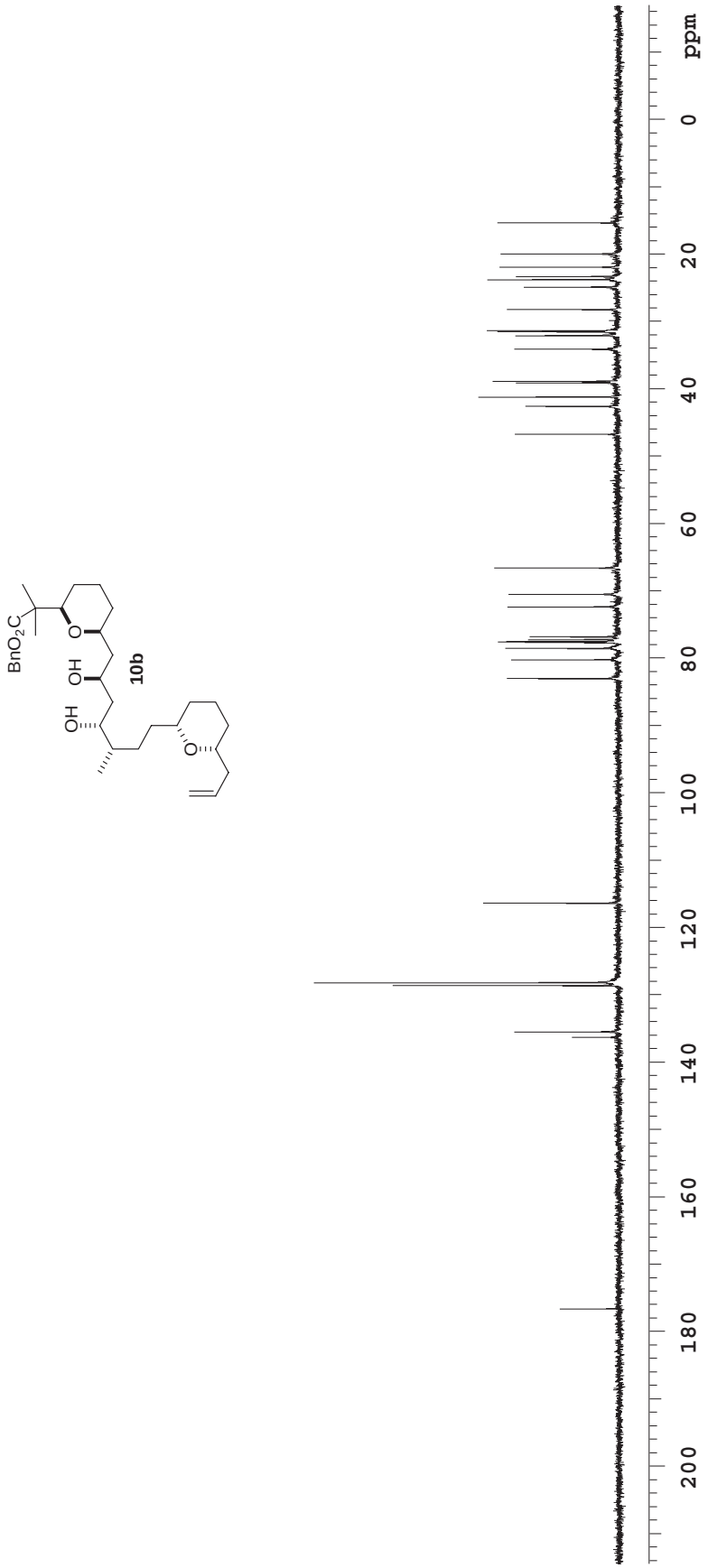
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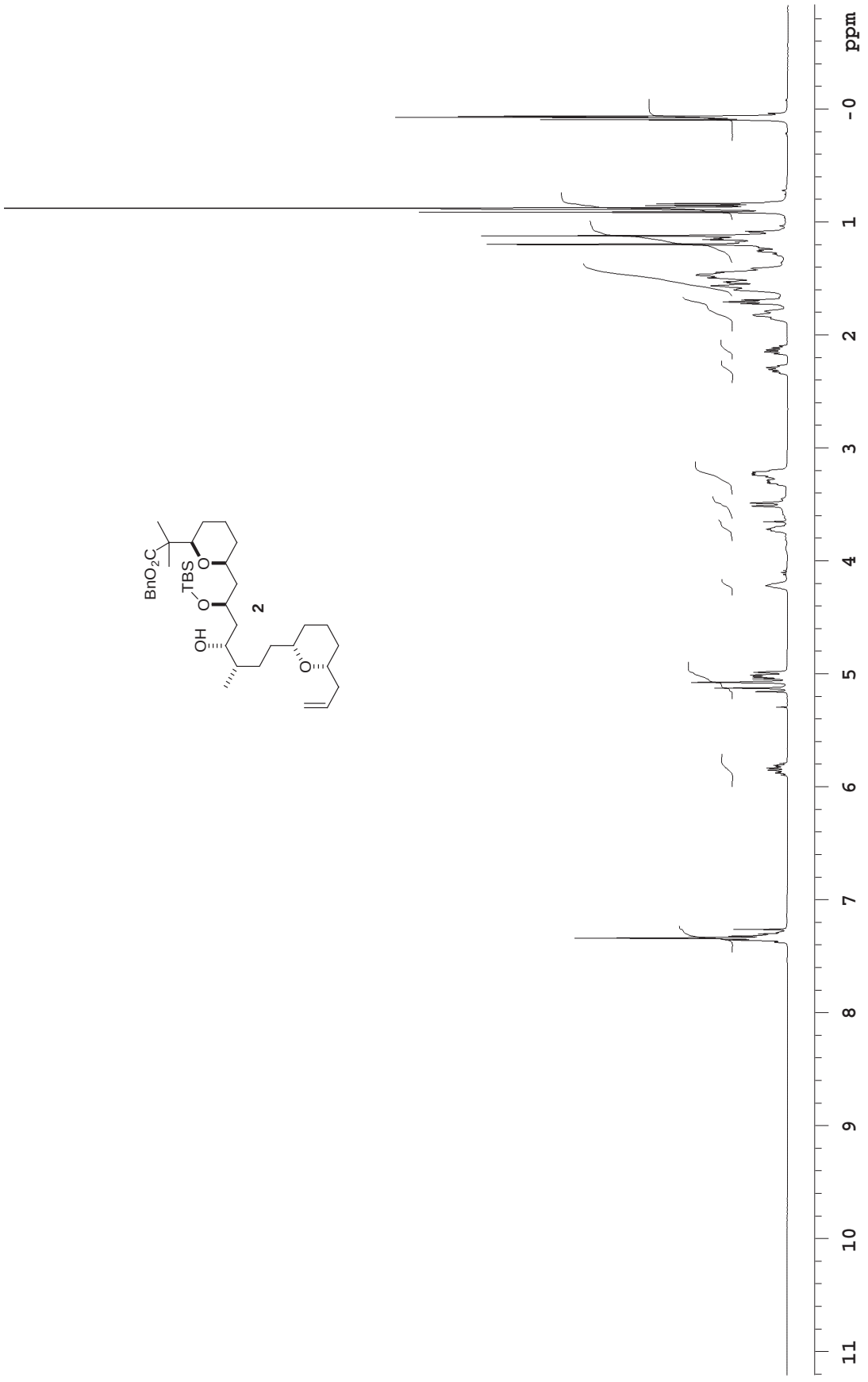
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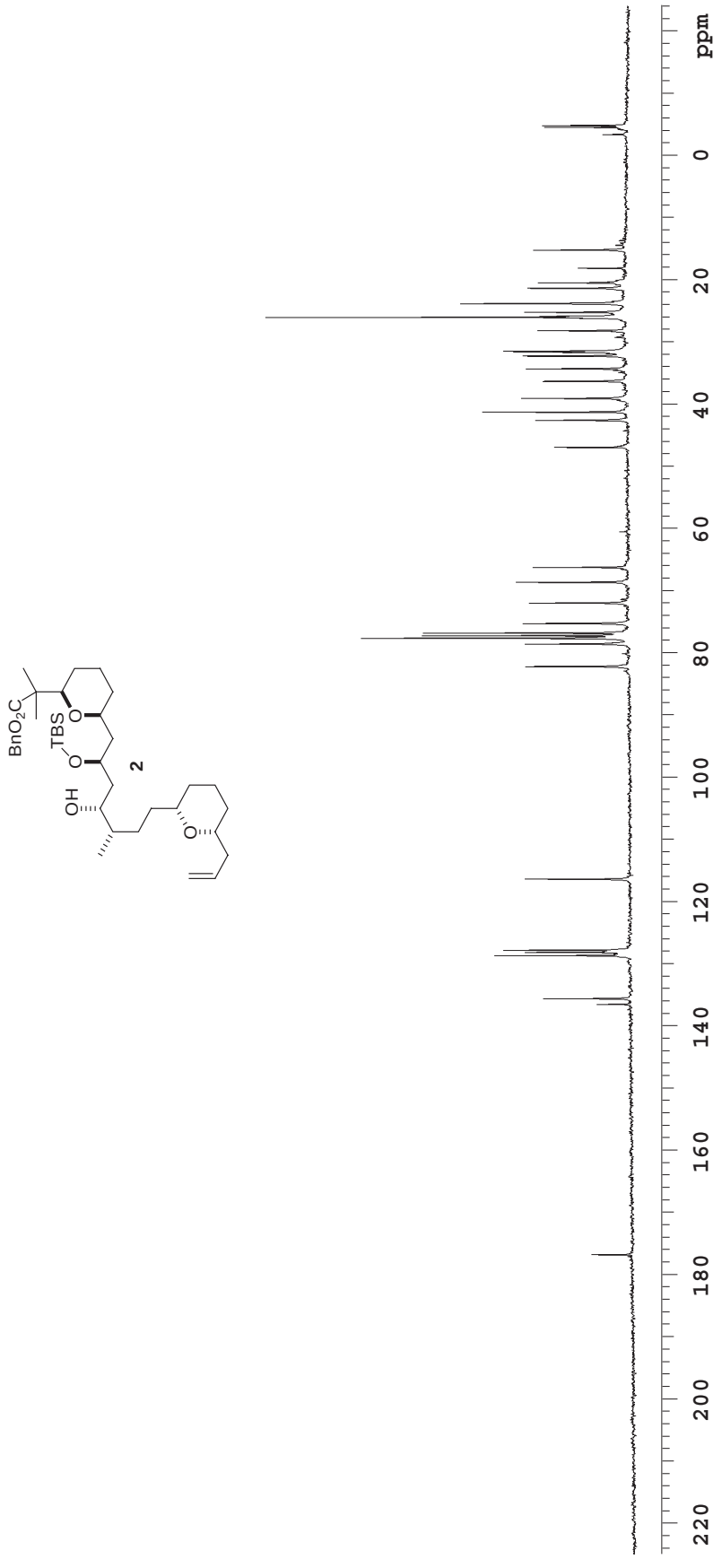
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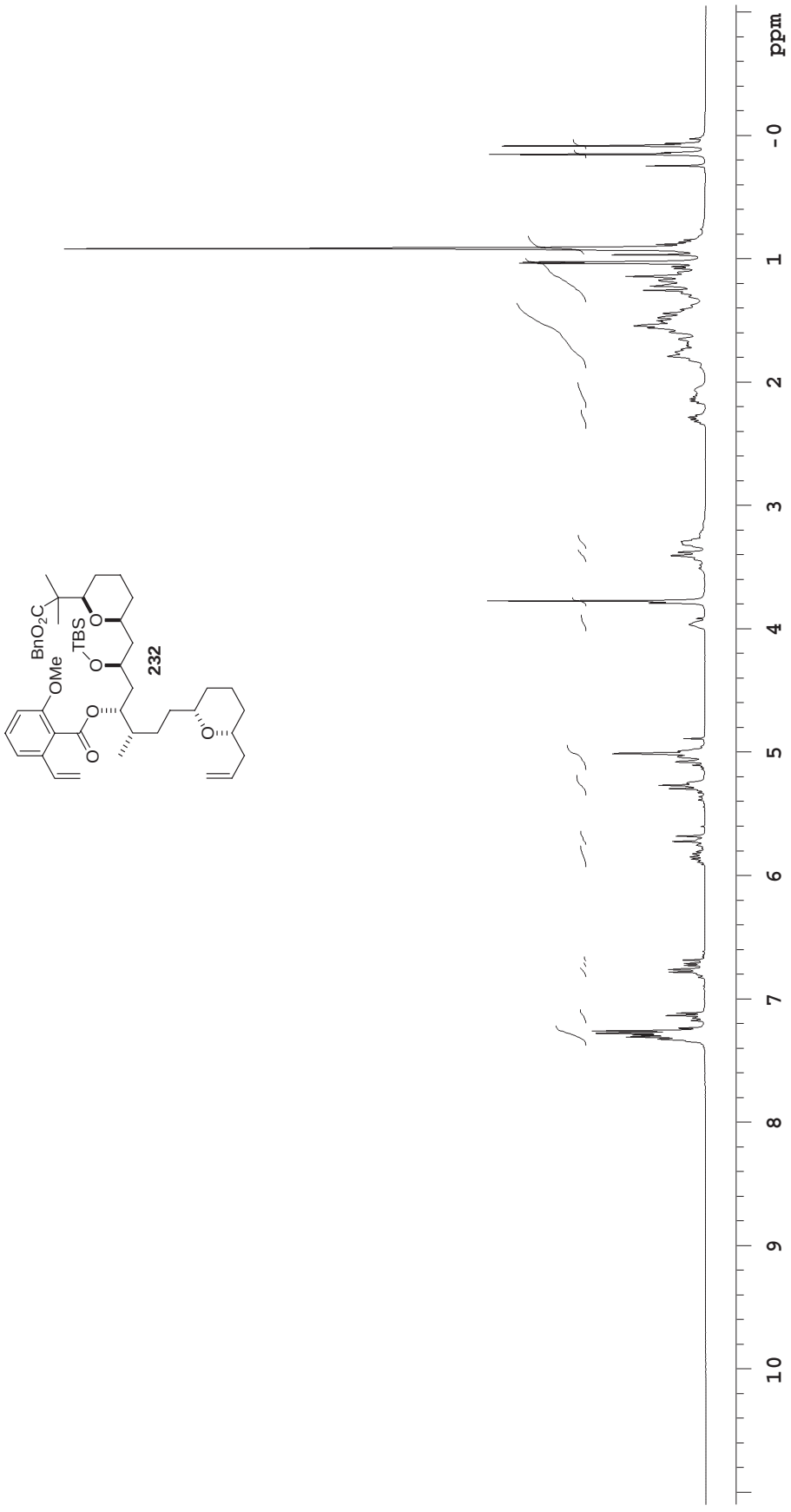
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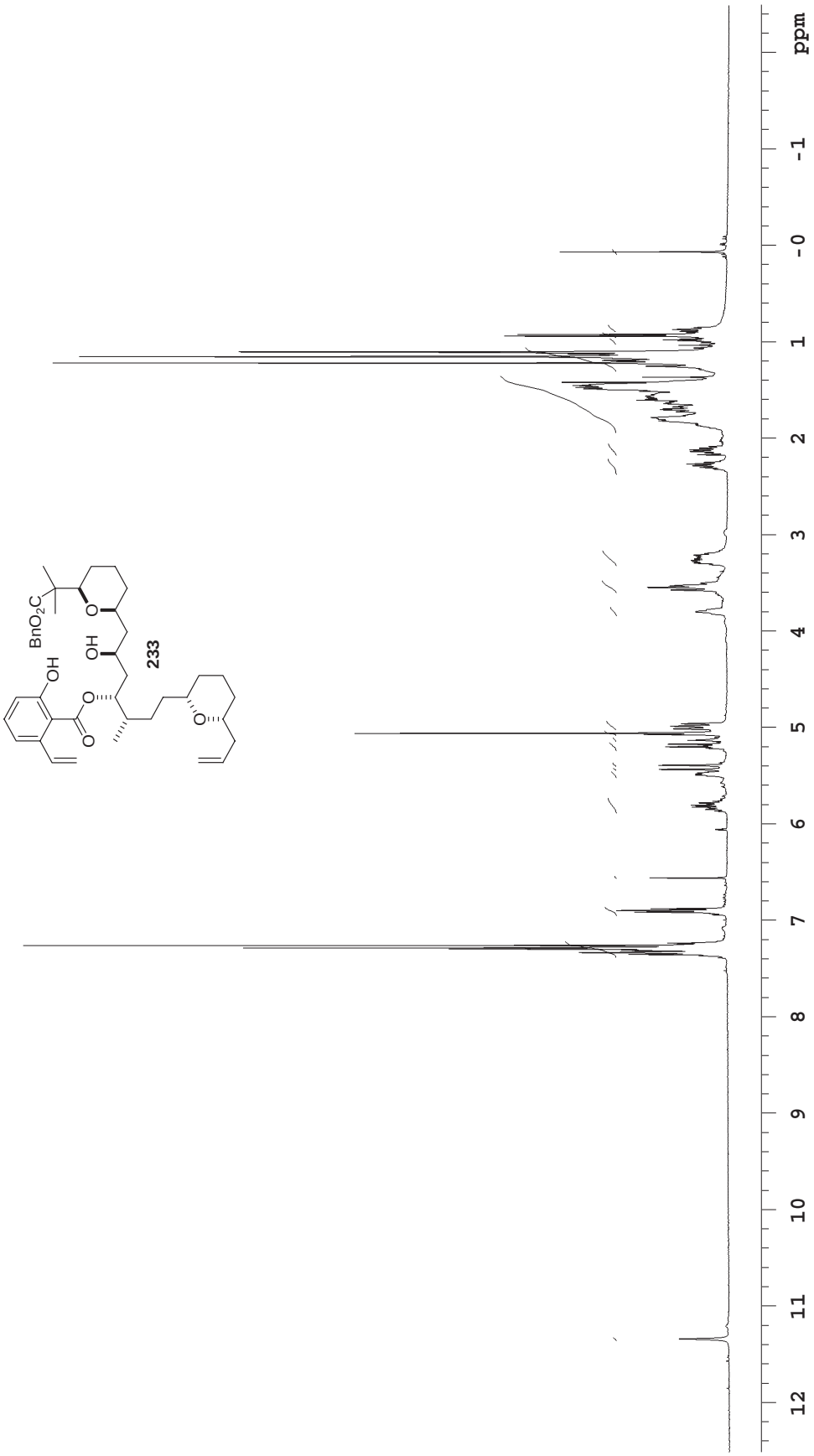
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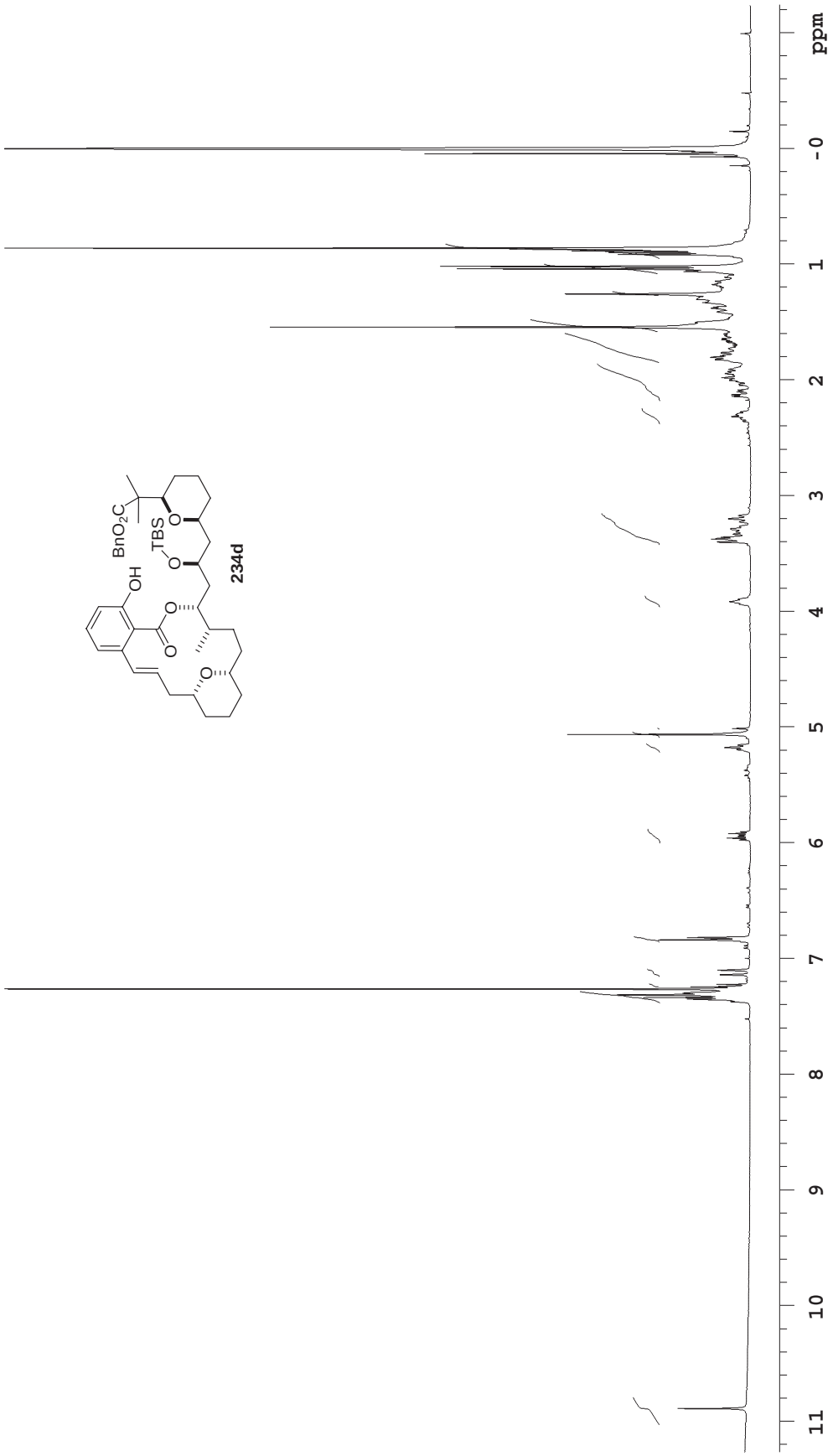
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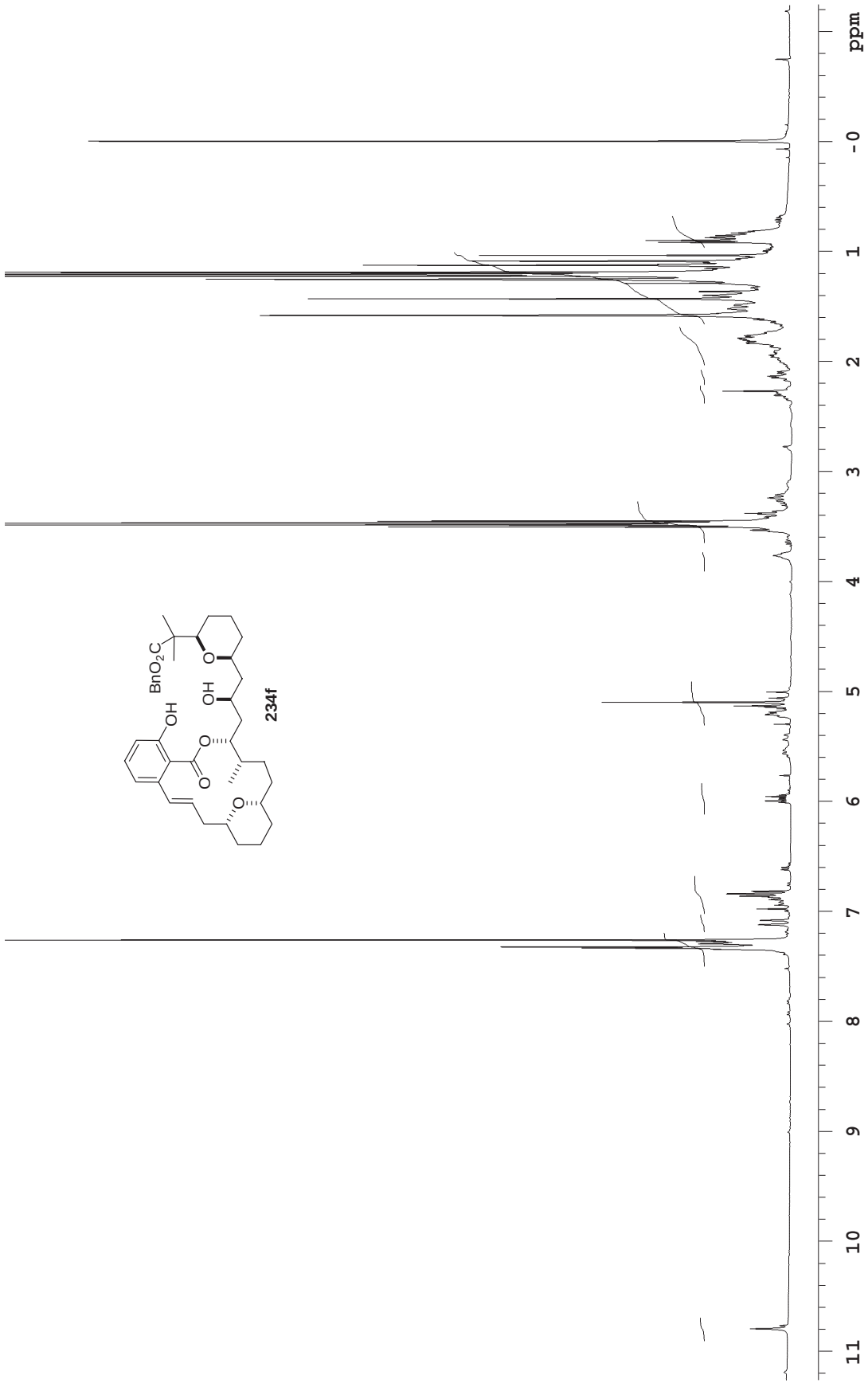
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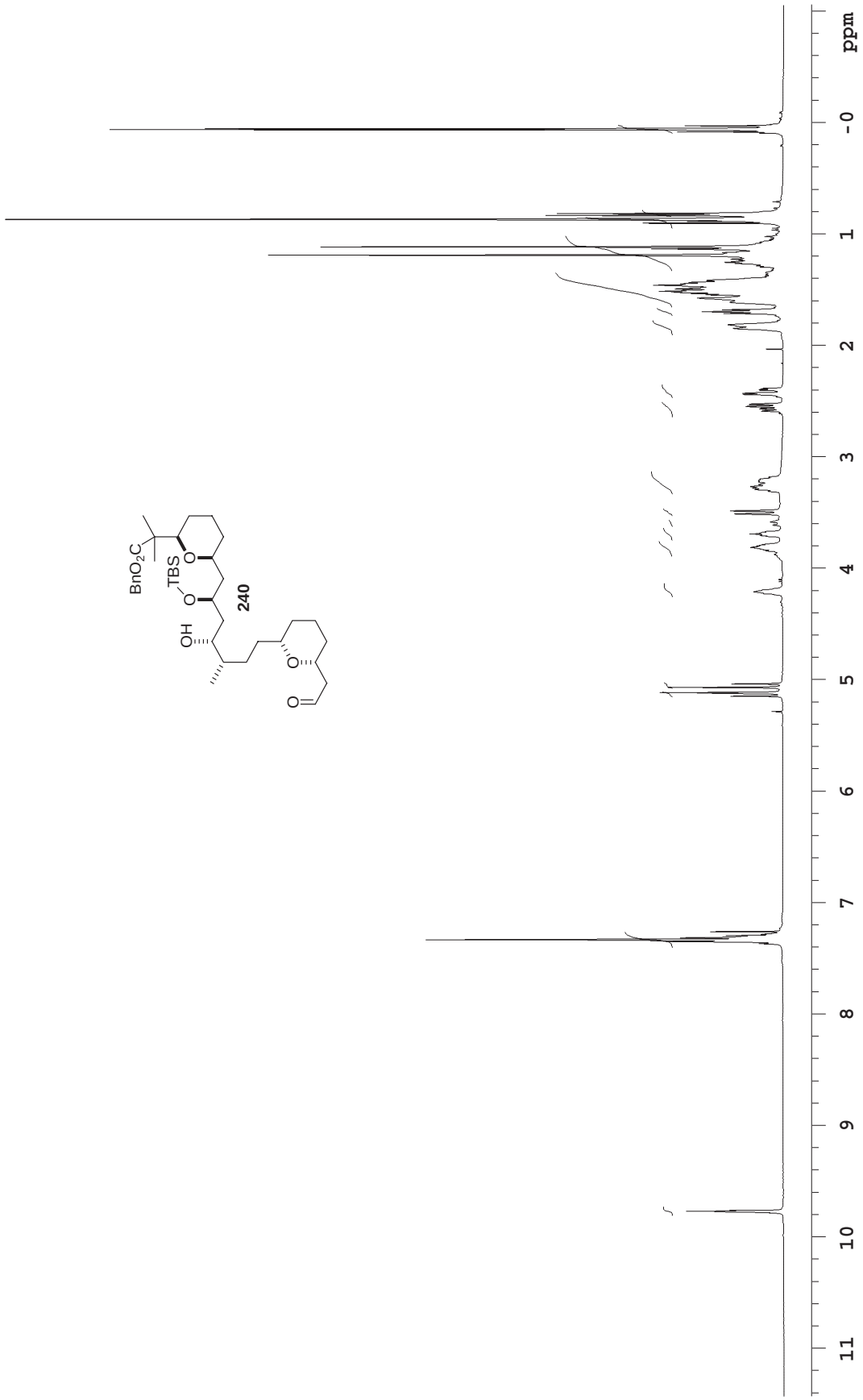
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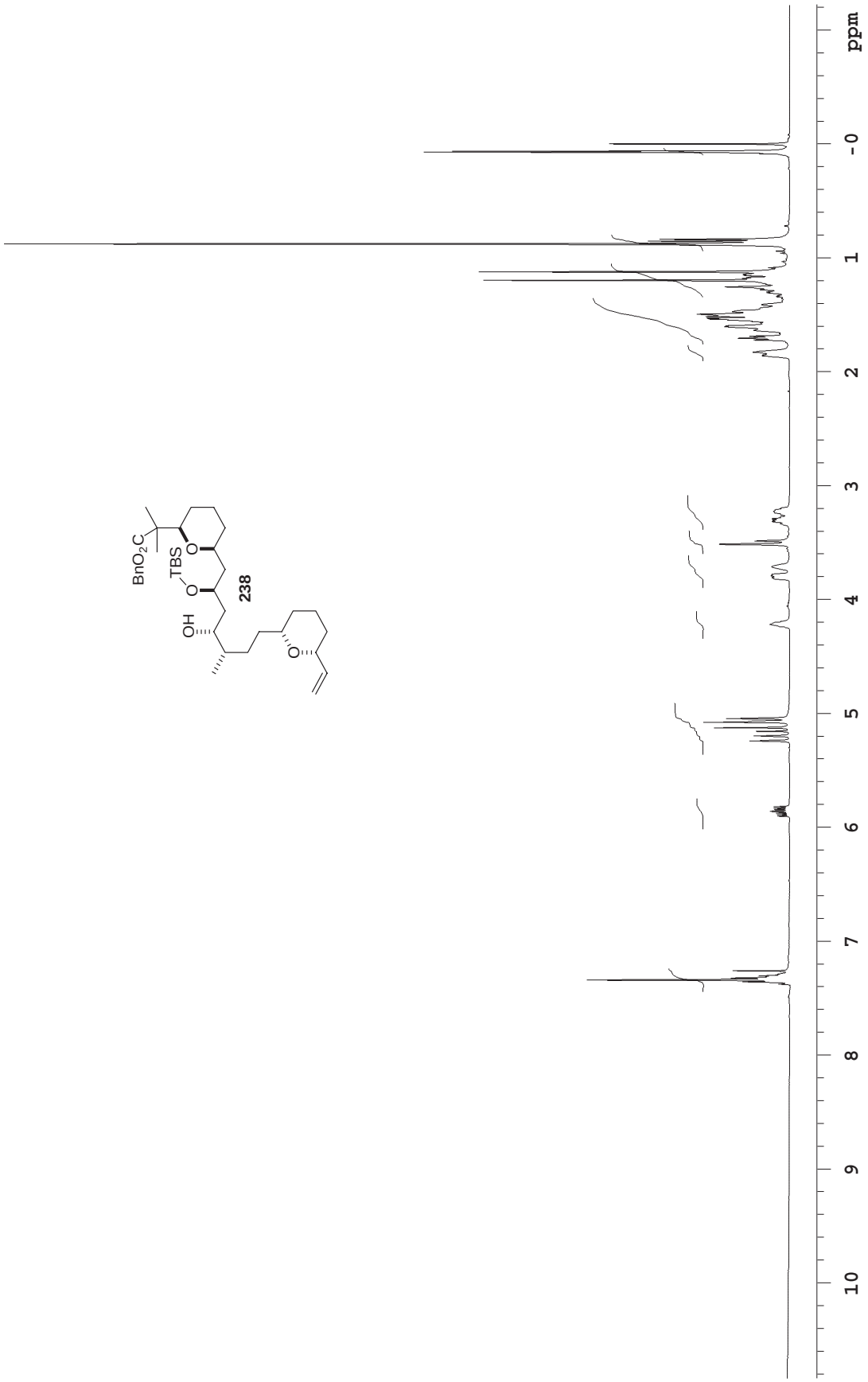
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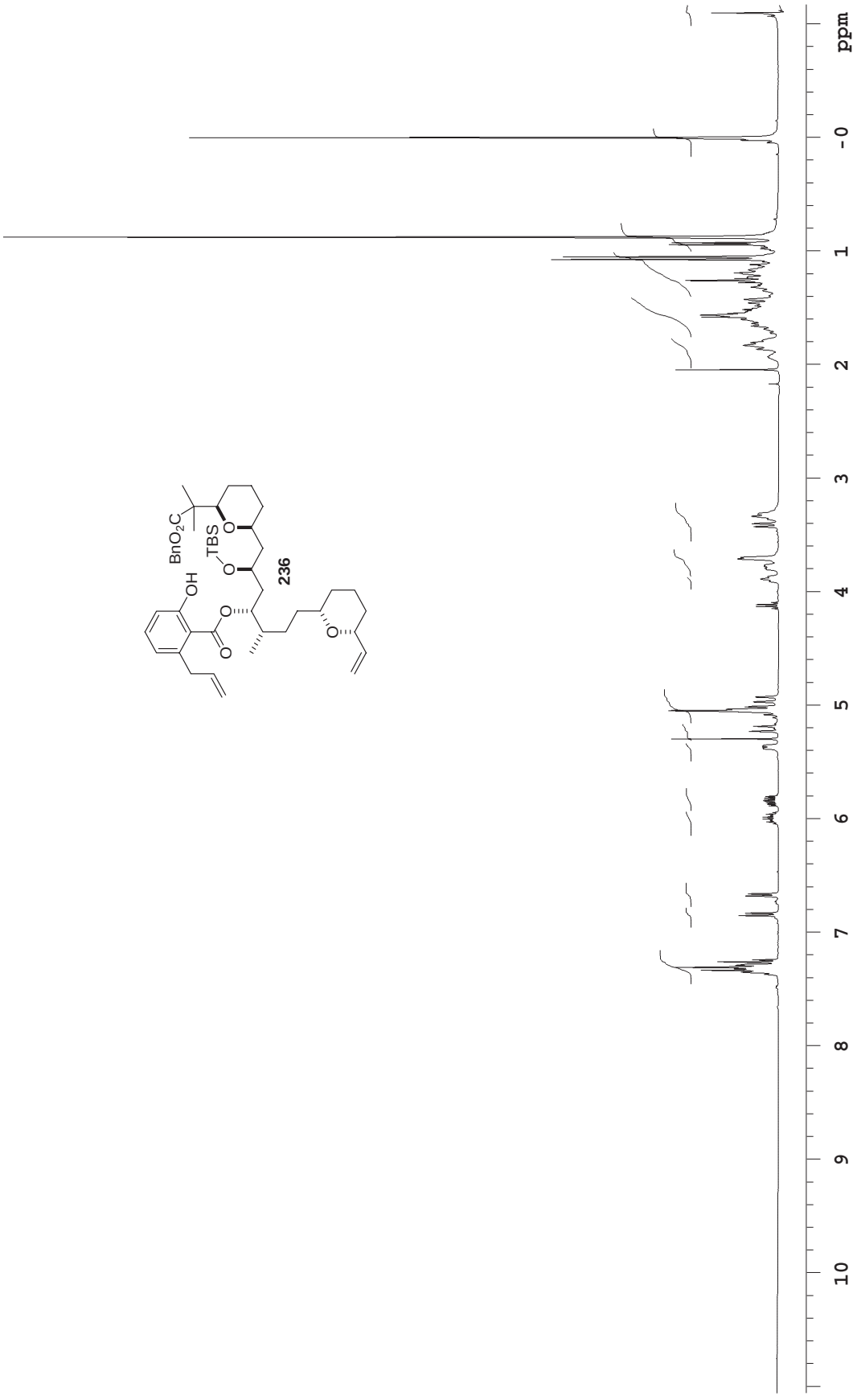
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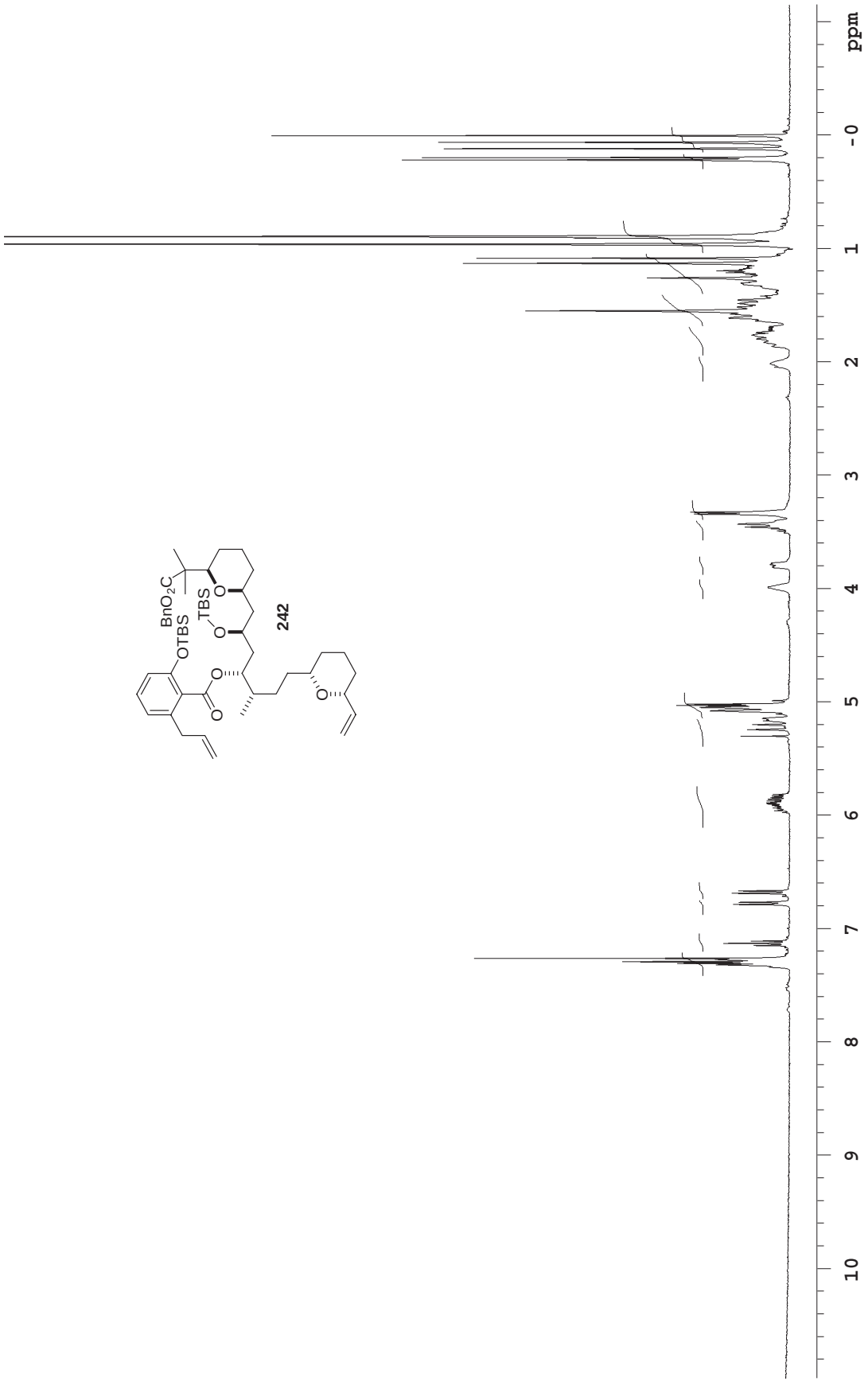
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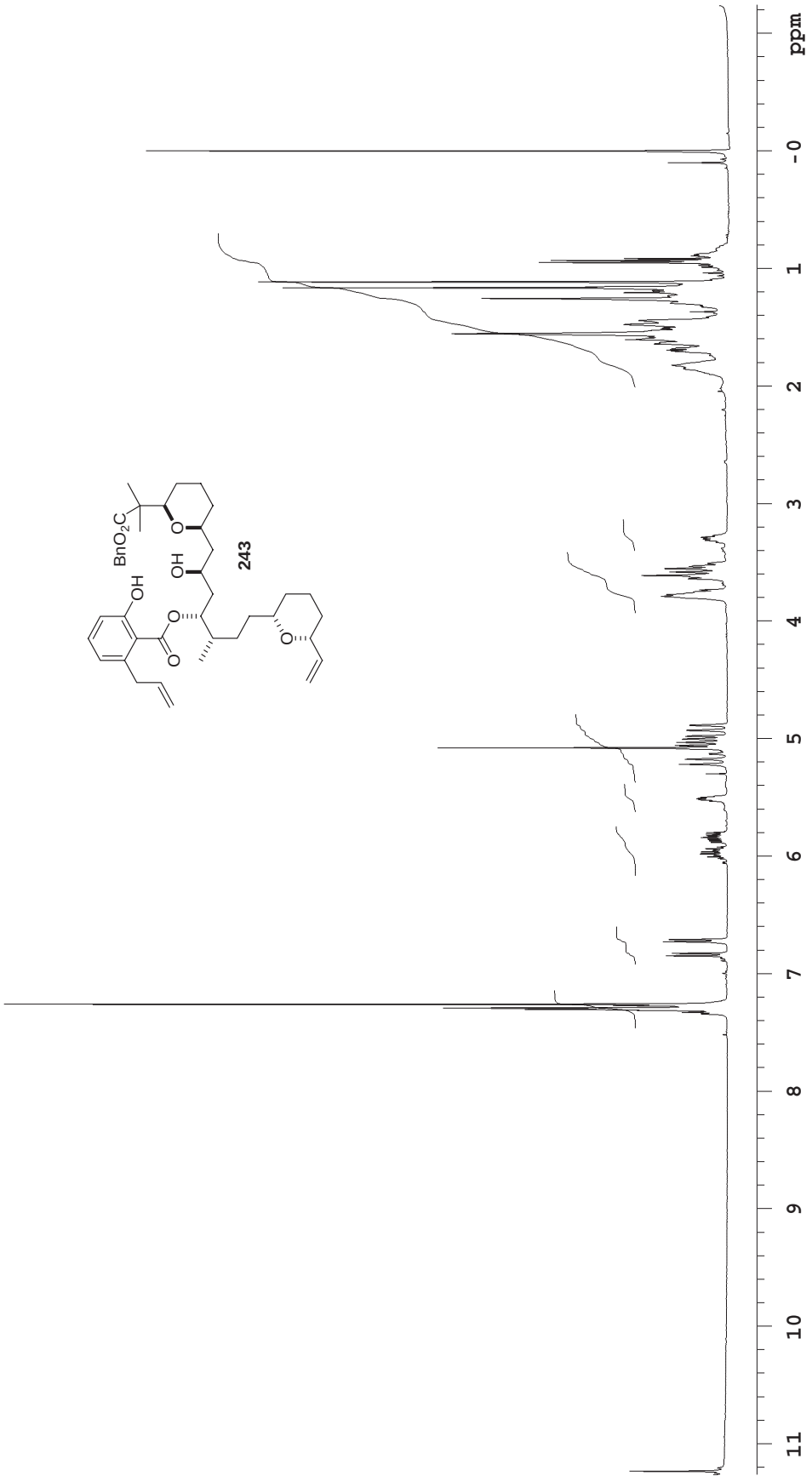
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243

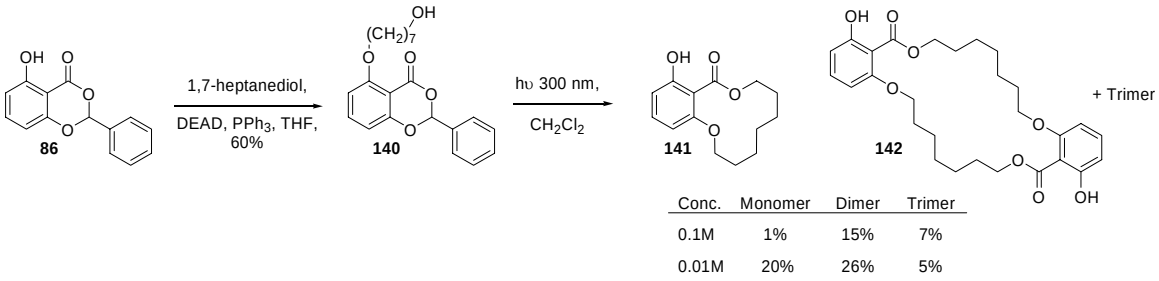
CHAPTER FIVE

PHOTOCHEMICAL BASED APPROACHES FOR SCH 351448, AND INITIAL BIOCHEMICAL CHARACTERIZATION

5.1 Photochemical Dimerization

Experiments utilizing the photochemical mediated acylation of quinoketenes for the preparation of macrocyclic salicylates (see chapter 2) led to the surprising finding that cyclodimer **142** was produced as the major product (Scheme 5.1).

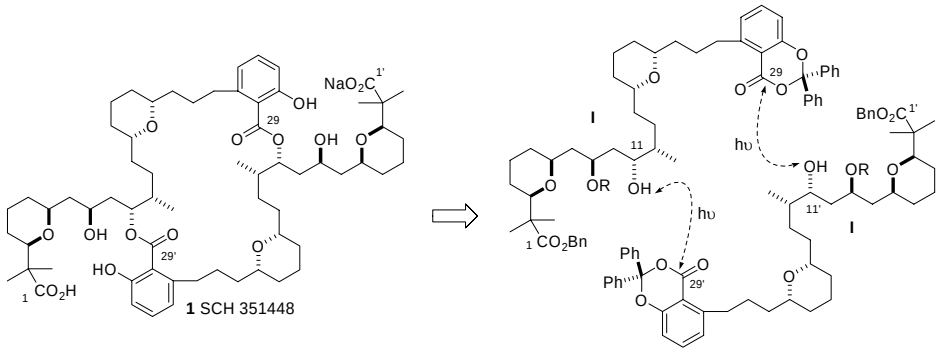
Scheme 5.1



Conc.	Monomer	Dimer	Trimer
0.1M	1%	15%	7%
0.01M	20%	26%	5%

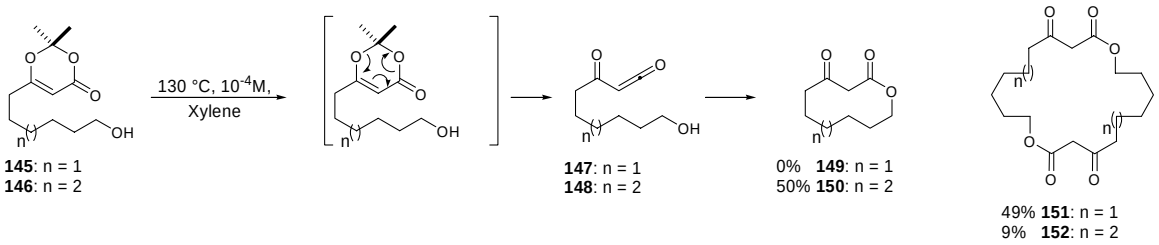
This fortuitous result spurred an effort to apply the photoacylation methodology in the context of the SCH 351448 synthesis. It was envisaged that photolysis of a photochemically active monomeric fragment **I** with a free C11 hydroxy could provide the head-to-tail bis-acylation product (Fig. 5.1).

Fig. 5.1 Photochemical Dimerization



As mentioned in chapter 2, ω-hydroxy-acyl-ketenes such as **147** favor formation of cyclodimers depending on the choice of tether length (Scheme 5.2). However, exploitation of this phenomenon in the context of a natural product synthesis is unprecedented.

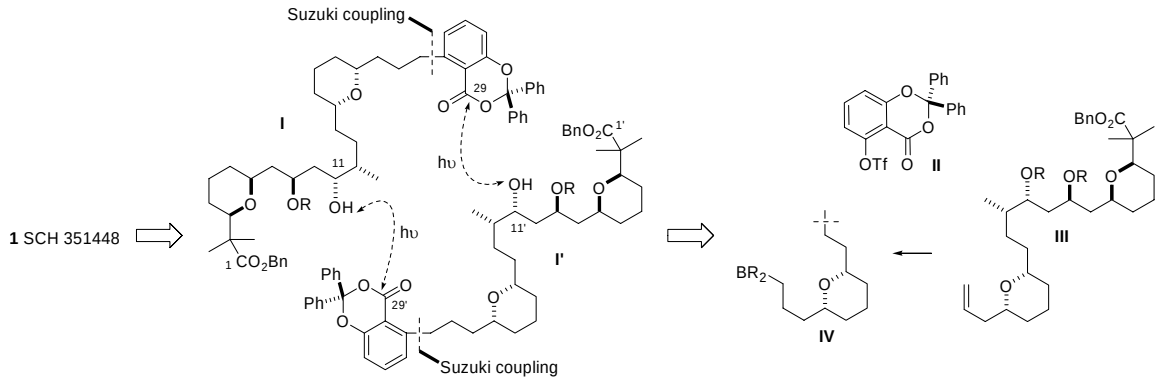
Scheme 5.2



5.2 Synthesis of Photosubstrates

To fully explore the photochemical cyclodimerization, a fully functional C1-C29 (C1'-C29') had to be prepared. As discussed in chapter 4 (Fig. 4.2), such a fragment was anticipated to be synthesized via the coupling of aryl triflate **II** and terminal olefin **III** via a hydroboration/Suzuki cross-coupling sequence (Fig. 5.2).

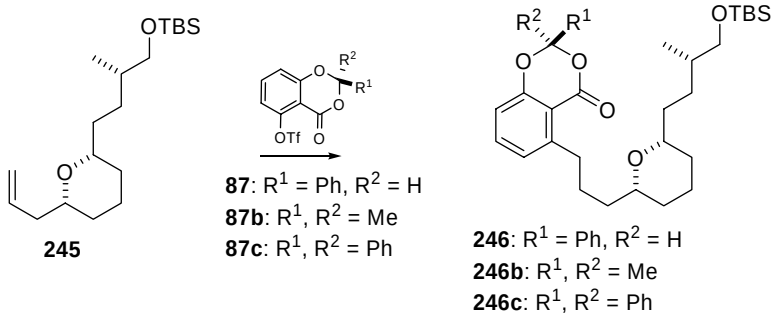
Fig. 5.2



As shown in table 5.1 terminal olefin **245** was identified as a viable starting point for the synthesis of a model photoactive monomer. Synthesis of such a substrate would aid in identifying a viable route to the fully functionalized dimerization precursor (Fig. 5.2, **I**) in

addition to providing material for model photochemical dimerizations. A straight-forward approach to the target molecule called for a B-alkyl Suzuki coupling[2] of terminal olefin **245** with aryl-triflate **87** (Table 5.1).

Table 5.1



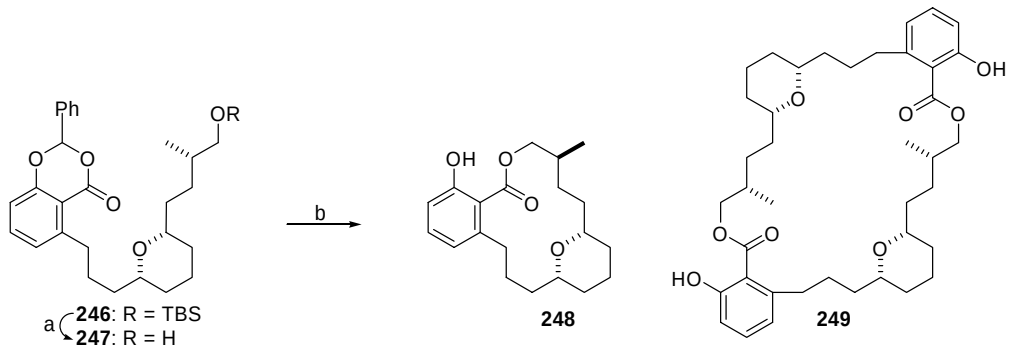
Entry	Substrates	Conditions	Results
1	**245** - **87**	9-BBN soln., $PdCl_2dppf$, K_3PO_4, KBr, THF: 30% H_2O_2	SM Recovered
2	**245** - **87**	9-BBN soln., $PdCl_2dppf$, Cs_2CO_3, Ph_3As, KBr, THF: 30% H_2O_2	Decomposition
3	**245** - **87b**	9-BBN solid., $PdCl_2dppf$, Tl_2CO_3, KBr, THF:H_2O	32%
4	**245** - **87b**	9-BBN soln., $PdCl_2dppf$, NaOMe, KBr, THF: 30% H_2O_2	43%
5	**245** - **87c**	9-BBN soln., $PdCl_2dppf$, NaOMe, KBr, THF: 30% H_2O_2	28%
6	**245** - **87**	9-BBN solid., $PdCl_2dppf$, K_3PO_4, KBr, THF: 30% H_2O_2	30-58%
8	**245** - **87c**	9-BBN solid., $PdCl_2dppf$, K_3PO_4, KBr, THF:DMF	65%

As shown in table 5.1, formation of the required carbon-carbon bond turned out to be a major undertaking. In one of the first reactions conducted (Table 5.1, entry 1), the terminal olefin failed to undergo hydroboration with commercially available 9-BBN (0.5M soln. in THF). Soon afterward, successful hydroboration was consistently achieved with the more stable crystalline form of 9-BBN. After brief screening of several base additives (Table 5.1, entries 3-6), potassium phosphate was chosen for further studies since a moderate yield (Table 5.1, entry 6, 58%) of product was obtained

in an early attempt[3]. We were disapointed however, by the inconsistent yields of these reactions which ranged from 30% to nearly 60% (Table 5.1, entry 6). The inconsistent nature of this reaction was traced to the addition of 30% aqueous hydrogen peroxide in the work-up step. On a number of occasions, these cross-couplings appeared to be high yielding based on TLC analysis, however after the work-up, the amount of coupling product diminished and the formation of benzaldehyde was observed. This indicated that benzodioxinone hydrolysis was taking place in the presence of hydrogen peroxide. Once this reagent was excluded from the work-up step, this reaction was reproducible with yields in excess of 60% (Table. 5.1, entry 8)

Following successful cross-coupling, protodesilylation provided free alcohol **247**, which was primed to undergo photochemical mediated dimerization (Scheme 5.3). Photolysis of alcohol **247** (300 nm, 30 min) resulted in nearly exclusive formation of the macrocyclic lactone **248**. A small quantity (<3%) of the symmetrical dimer **249** was isolated and characterized by electrospray mass spectrometry and proton NMR.

Scheme 5.3

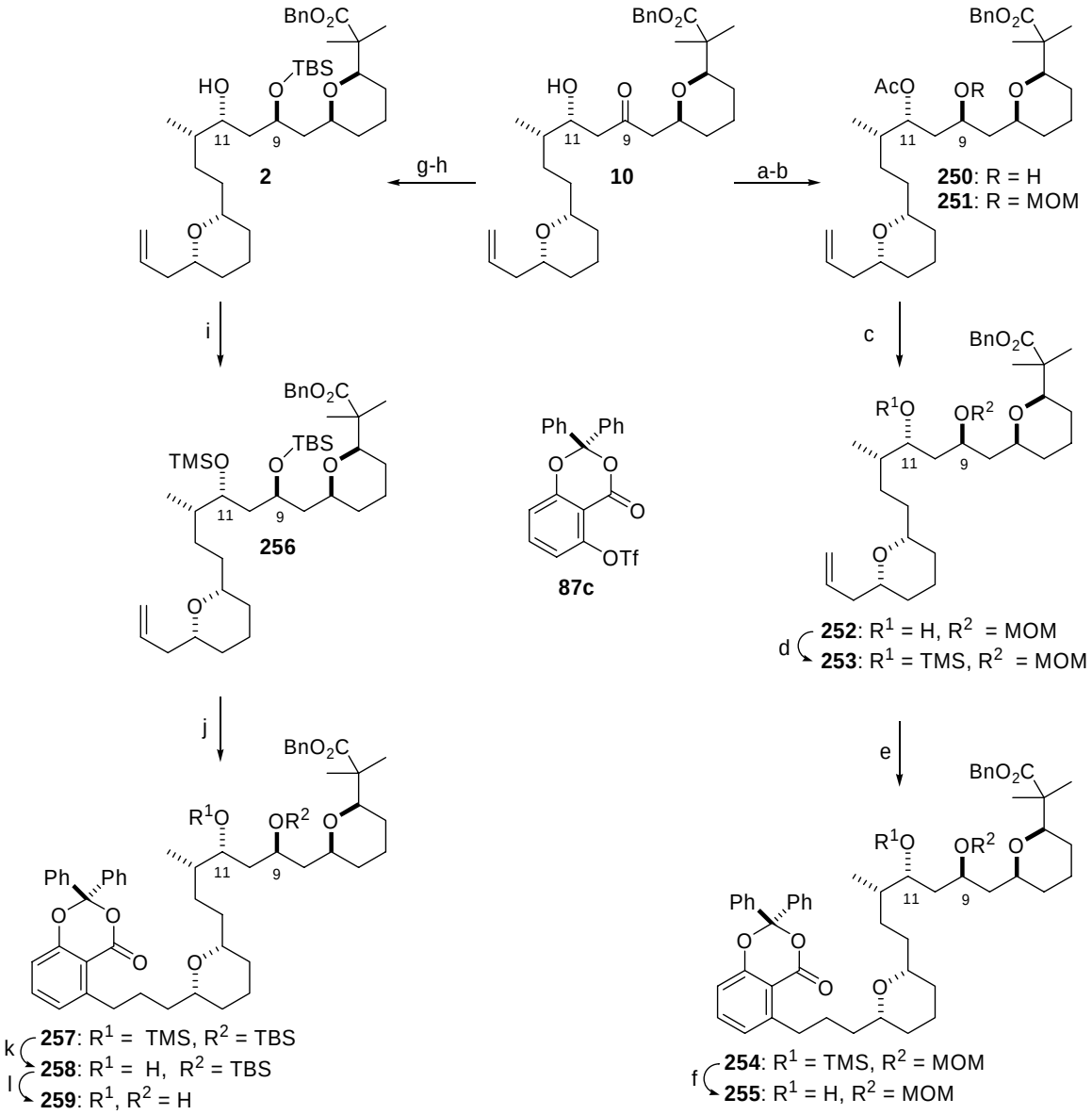


Reagents and Conditions: (a) HF·Pyr, Pyr, THF, rt 12 hr, 88%; (b) hν (300 nm), CH_2Cl_2, rt 1/2 hr, 35% **248**, <3% **249**.

Despite the poor selectivity for dimer formation in our model study (Scheme 5.3), this approach to the natural product was pursued further. In contrast to model alcohol

247, full length precursors would contain all the functionality of the natural product and may therefore have an inherent preference for dimerization over intramolecular acylation. Thus, a series of differentially protected fully functionalized substrates were prepared using the B-alkyl Suzuki coupling protocol developed for olefin **246**. Synthesis of these substrates initiates with β-hydroxyketone **10** (Scheme 5.4), which can be stereoselectively reduced to the 1,3-anti-diol under conditions previously noted (see chapter 4). Regioselective silyl protection of the less hindered C9 hydroxy group was followed by trimethylsilyl protection of the C11 alcohol. Suzuki-Miyaura coupling of the bis-silyl ether **256** proceeded smoothly under conditions determined for model substrate **246**. Facile removal of the trimethylsilyl ether with a buffered solution of HF·Pyridine provided dimerization precursor **258**. In addition, the free diol **259** was also prepared via fluoride mediated silyl deprotection. A second series of substrates based on MOM protection at the C9 position was then prepared. Regioselective incorporation of the MOM group required a slightly different approach than that utilized for the C11 TBS protected substrates. This sequence begins with a SmI_2 catalyzed Evans-Tishchenko acylation/reduction of β-hydroxyketone **10**.

Scheme 5.4



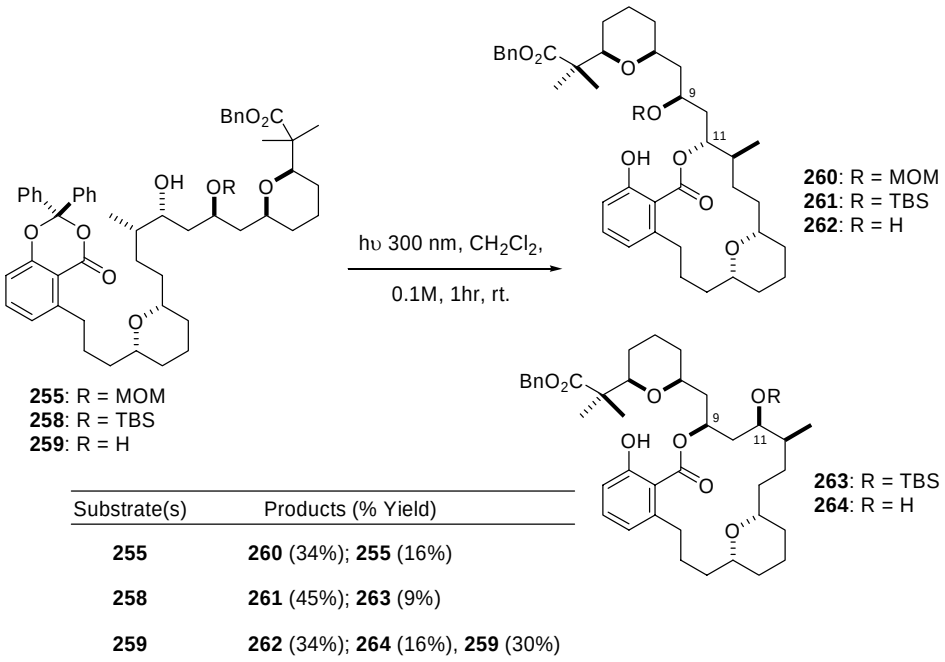
Reagents and Conditions: (a) CH_3CHO, cat. SmI_2, THF, -10 ˚C→0 ˚C 8 hr, 82%; (b) *i*-Pr_2EtN, MOMCl, CH_2Cl_2, 12 hr rt, 3 hr 50 ˚C, 95%; (c) K_2CO_3, MeOH, 60 hr rt, 70%; (d) Et_3N, TMSCl, CH_2Cl_2, 1 hr 0 ˚C, 96%; (e) 9-BBN, THF, rt 12 hr, 3M K_3PO_4, $PdCl_2$dppf, **87c**, DMF, rt 20 hr; (f) HF·Pyr, Pyr, THF, rt 20 hr, 80% 2 steps; (g) $Me_4N(OAc)_3BH$, CH_3CN:HOAc (1:1), 0 ˚C→rt 5 hr, 82%; (h) Imidazole, cat. DMAP, TBSCl, 0 ˚C 2 hr, 80%; (i) TMSCl, Et_3N, CH_2Cl_2, 0 ˚C→rt 12 hr, 84%; (j) 9-BBN, THF, rt 17 hr, 3M K_3PO_4, $PdCl_2$dppf, **87c**, DMF, rt 3 hr; (k) HF·Pyr, Pyr, THF, rt 1 hr, 65% 2 steps; (l) HF·Pyr, 10 hr rt, 66%.

This reaction was pivotal for allowing both a regioselective protection of the C9 hydroxyl with a small stable protecting group, and for setting the correct stereochemistry at that center. MOM protection of the C9 hydroxy proceeded uneventfully to provide a fully

protected intermediate **251**. Next, methanolysis of the acetate group (K_2CO_3, MeOH, rt) provided the free alcohol **252**, in addition to a by-product resulting from methanolysis of the C1 benzyl ester (**252b**, ca. 15-20%). The free alcohol was then reprotected (→**253**) with trimethylsilylchloride. Exchange of the acetate for a silyl ether protecting group was crucial for the subsequent cross-coupling with aryl-triflate **87c** – a reaction that proceeded to yield benzodioxinone **254** in 70-80% yield. As will be discussed later in table 5.2, C11-TMS protection was crucial to all cross-couplings studied thus far. Finally, silyl deprotection proceeded uneventfully to provide the dimerization substrate **255.**

Unfortunately, as for substrate **247**, photolysis of compounds **255**, **258**, or **259** gave only monomeric cycloadducts **260**-**264** (Scheme 5.5). Interestingly, in the case of TBS protected intermediate **258**, a regioisomeric acylation product **263** resulted in which silyl migration preceded photoacylation.

Scheme 5.5



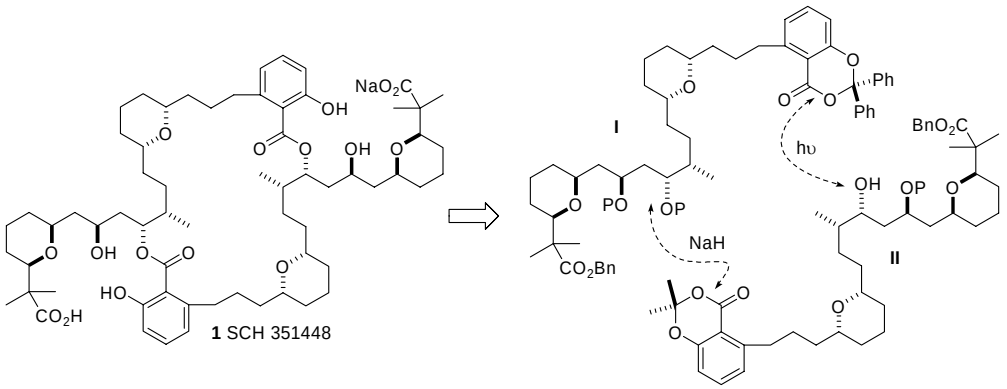
Substrate(s)	Products (% Yield)
255	**260** (34%); **255** (16%)
258	**261** (45%); **263** (9%)
259	**262** (34%); **264** (16%), **259** (30%)

Not surprisingly, photoacylation of diol **259** resulted in a 1:2 mixture of C9 and C11 lactones (**262** and **264**) respectively, in addition to recovered starting material (30%). Products resulting resulting from photoacylation in a bimolecular sense were not detected. Photolysis of MOM ether **254** provided lactone **260** and recoverd starting material **255** (16%). Exploration of various reaction parameters including concentration and solvent did not change the course of this reaction. With these results in hand, it was clear that dimerization was an unfavorable pathway in every system investigated thus far, therefore the coupling of monomeric substrates in a stepwise fashion was required.

5.3 Orthogonal Dimerization

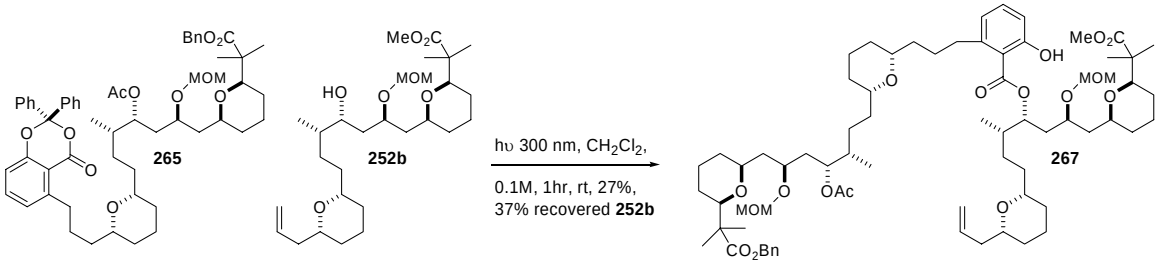
In order to circumvent the issue of competing intramolecular lactonization, an approach that would exploit the orthogonal reactivity exhibited by phenyl versus alkyl substituted benzodioxinones was initiated (Fig. 5.3). This strategy calls for initial intermolecular photoacylation of a fully protected photoactive monomer **I** with an unprotected (C11-OH) photosilent fragment **II** (Fig. 5.3). This acylation step avoids the potential for intramolecular lactonization while maintaining a symmetry based strategy. Following photochemical esterification, liberation of the C11 hydroxyl group and base induced macrocyclization would provide the desired 28 membered macrolactone. Finally, simple cleavage of the remaining protecting groups would yield the natural product.

Fig. 5.3 Orthogonal Dimerization



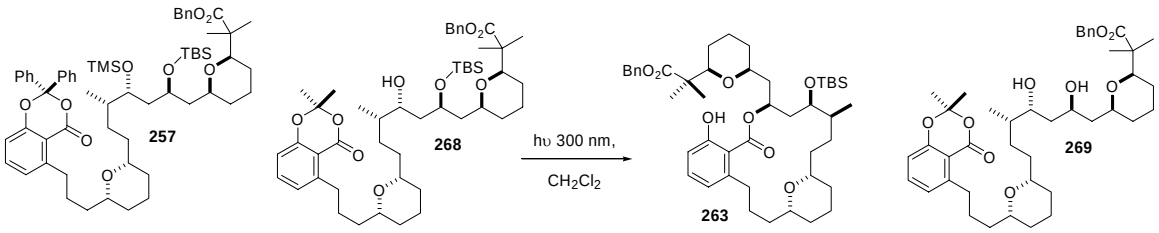
A model study was conducted to establish the feasibility of this approach. Irradiation of photoactive benzodioxinone **265** and alcohol **252** resulted in successful bimolecular photoacylation, thus establishing a pathway by which two advanced monomeric units could be coupled (Scheme 5.6). This experiment prompted further investigation of the orthogonal photoacylation/lactonization strategy.

Scheme 5.6



Our first attempted orthogonal acylation with full length fragments utilized bis-silyl protected diphenyl benzodioxinone **257** and alcohol **268**, which was derived from the Suzuki coupling of **256** and **87b** (Scheme 5.4). Irradiation of these substrates resulted in intramolecular acylation of **257** to give macrolactone **263** (10%), in addition to recovered alcohol **268** (10%) and diol **269** (65%) (Scheme 5.7).

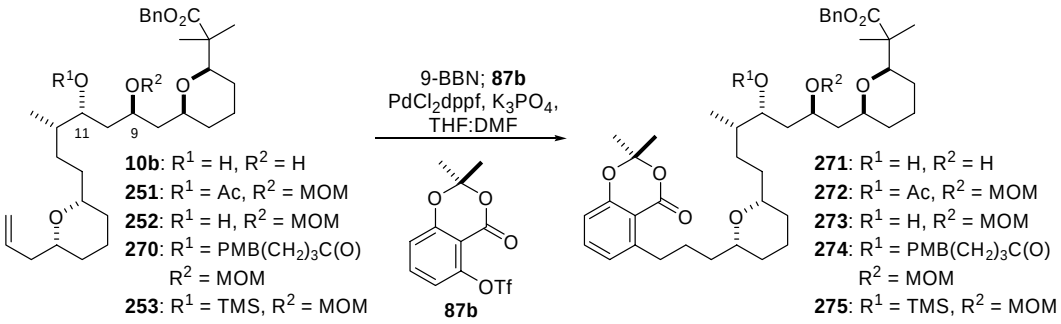
Scheme 5.7



Based on this result, it was clear that C9/C11 protecting groups with greater stability under photochemical conditions (300 nm UV light) were required for successful acylation.

Synthesis of a series of photoactive/inactive coupling partners was initiated utilizing chemistry established for the preparation of the homo-dimerization substrates (See Scheme 5.4). Attempts to synthesize photoinactive monomers directly from substrates such as acetate **251**, alcohol **252**, or diol **10b** resulted in either inconsistent or incomplete cross-coupling reactions (Table 5.2). These results led us to an alternative sequence to these monomers that called for trimethylsilyl protection at C11 prior to cross-coupling (Table 5.2, Entry 5). Simple exchange of protecting groups at the C11 position (C11-TMS→C11-OH→C11-OR) would allow us to access monomeric fragments with a variety of substitution patterns (See Scheme 5.4).

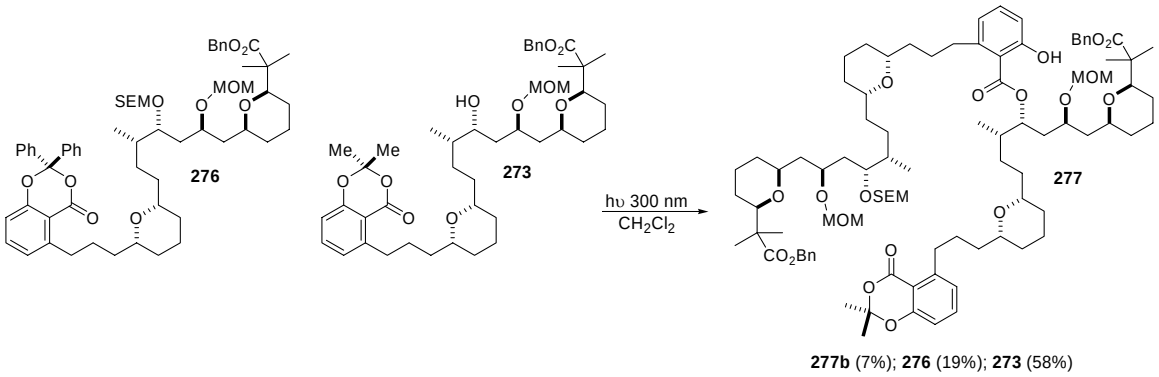
Table 5.2



Entry	Substrate	Product	Yield
1	**10b**	**271**	0%
2	**251**	**272**	21-68%
3	**252**	**273**	0%
4	**270**	**274**	14%
5	**253**	**275**	85%

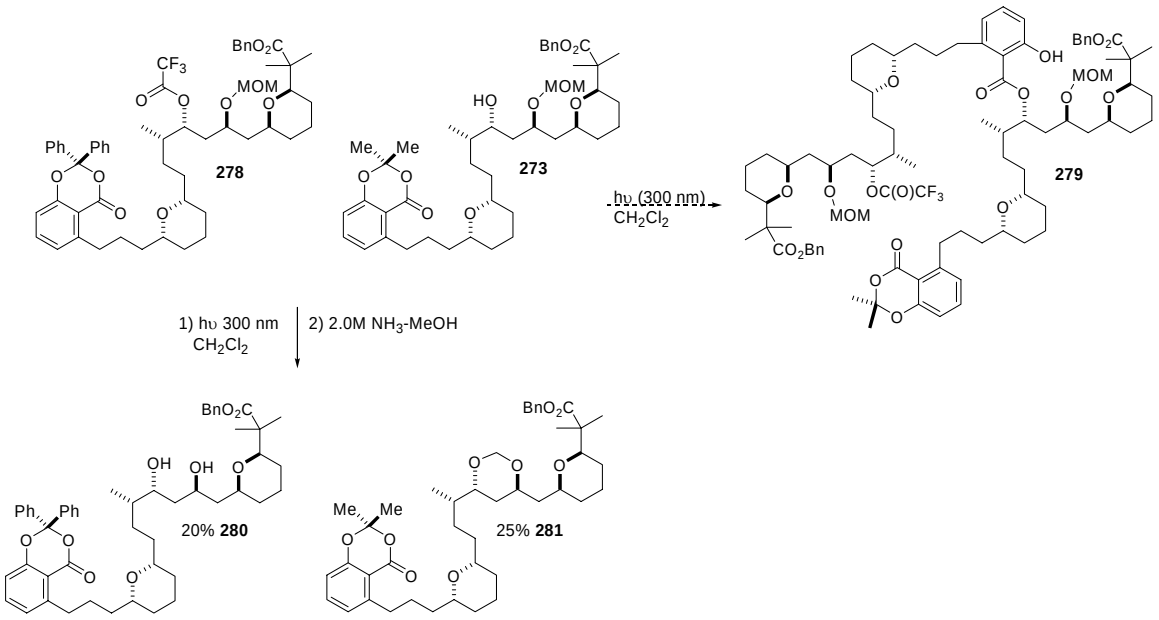
Several substrates were prepared according to the optimized cross-coupling conditions. When considering which protecting groups to install at the C11 position prior to the orthogonal acylation, two potential problems were considered: 1) the stability of this protecting group during irradiation and 2) ease of deprotection after acylation. With these issues in mind, we proceeded to investigate the orthogonal acylation strategy (Scheme 5.8). A nucleophilic monomer with a C9 methoxymethyl ether (**273**) was envisioned to be a more stable substrate. Also, the C9-MOM ether would be sterically less encumbered than a C9-TBS ether. In the event, photolysis of a photoactive monomer with a silyl protecting group (**276**, C11-SEM) and alcohol **273** resulted in successful photoacylation to provide ester **277**, albeit in low yield (7%). Moreover, attempted removal of the SEM group with 70% HF·Pyr resulted in decomposition of the starting material.

Scheme 5.8



We then switched to a more labile group at the C11 position. Photolysis of trifluoroacetate ester **278** with alcohol **273** yielded a complex mixture of compounds that did not include the desired benzoate ester **277** (Scheme 5.9). Partial purification of this mixture, followed by treatment with methanolic ammonia provided two compounds with vastly different polarities identified as diol **280** and methylene acetal **281**.

Scheme 5.9

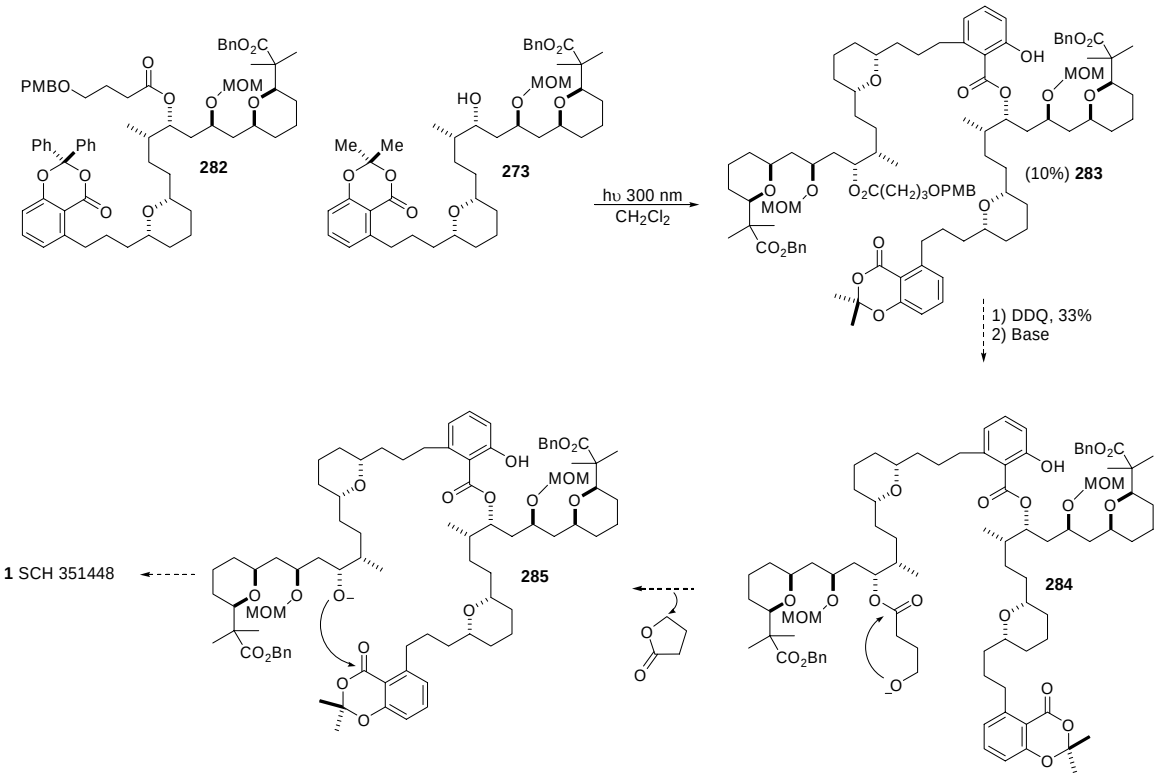


To account for this unexpected result, we postulated that adventitious water caused hydrolysis of the trifluoroacetate group resulting in the formation of catalytic quantities

of trifluoroacetic acid. This strong acid could facilitate deprotection of the MOM group (**278**), in addition to catalyzing the acetal formation reminiscent of **281**. This scenario also accounts for the methyl salicylate ester products observed in the crude mass spectrum, presumably derived from photoacylation with methanol obtained upon MOM deprotection of **273** and **278**.

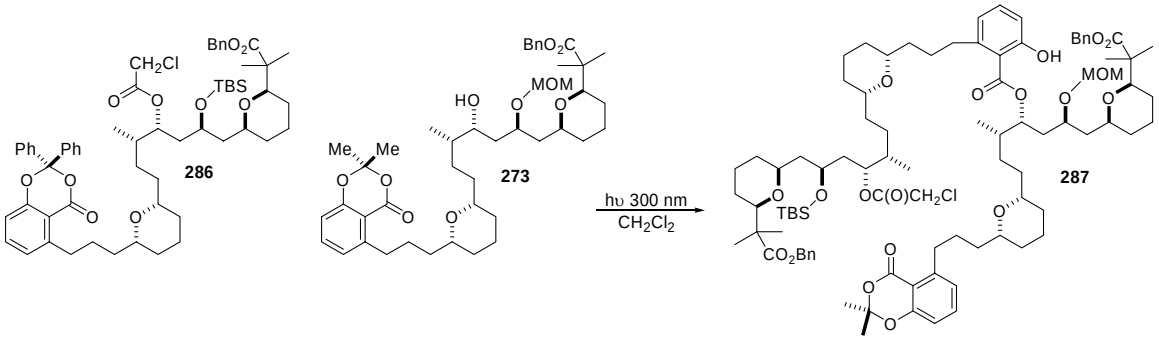
These results indicated that trifluoroacetate **278** is too unstable for the photochemical step. Previous studies with **272** (Table 5.2) revealed that chemoselective acetate cleavage (See Table 5.2) in the presence of the benzodioxinone was difficult. Finding a compromise between stability and ease of removal, we prepared masked γ-hydroxyester **282** (Scheme 5.10). This ester was predicted to have a similar stability as acetate **272**, but could be activated (DDQ deprotection) for a mild intramolecular transesterification of γ-hydroxyester **284** – a process driven by the release of butyrolactone. A potential spin-off would be a concomitant macrocyclization of alkoxide **285** following cyclodeprotection. Unfortunately, this attractive proposal produced a low yield (10%) in both the photoacylation step (→**283**), and the subsequent DDQ deprotection (33%), although cyclodeprotection did proceed as planned.

Scheme 5.10



Moving on, we were pleased to find that photolysis of chloroacetate **286** in the presence of alcohol **273** did provide a modest yield of salicylate ester **287** (31%), in addition to recovered starting materials (Scheme 5.11). Attempts to remove the chloroacetate group (2.0M NH_3·MeOH, K_2CO_3-MeOH, NaCN-MeOH), however, resulted in either recovered starting material or competing methanolysis of the benzodioxinone.

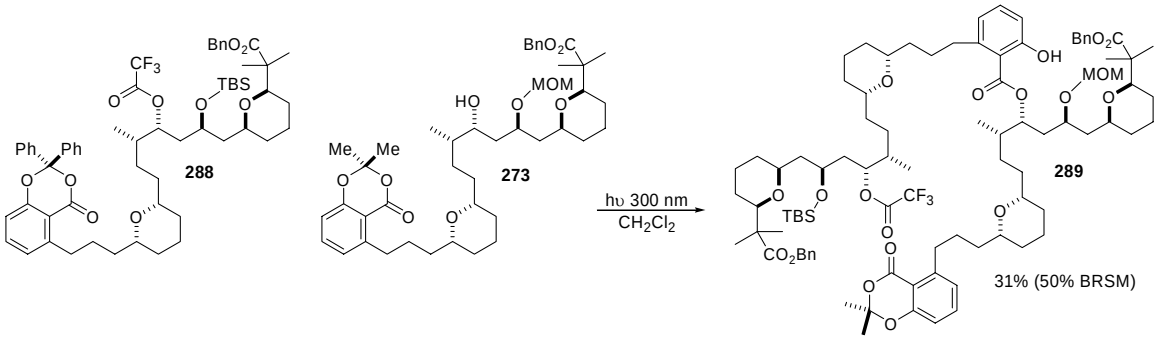
Scheme 5.11



287 (31%); **273** (65%); **286** (27%)

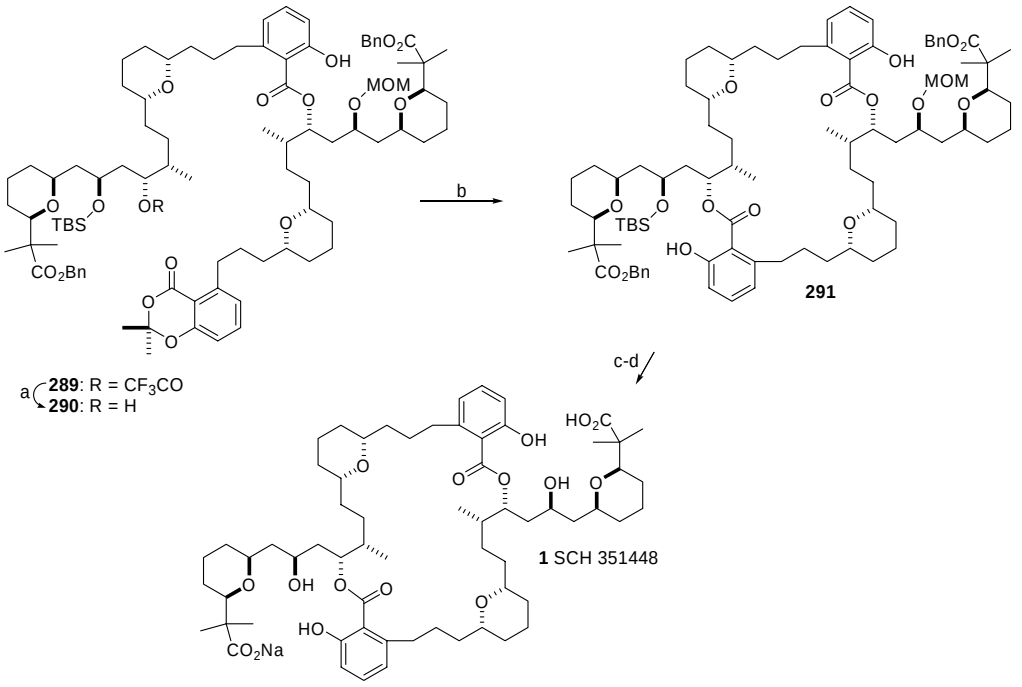
Since competing benzodioxinone methanolysis was an issue in this case, we decided to test a photoactive monomer with a C11 trifluoroacetate and C9 TBS ether. We reasoned that the adjacent bulky silyl group may subdue hydrolysis of the trifluoroacetate group during photoacylation. Also, removal of the trifluoroacetate would likely proceed under mild basic conditions (2.0M NH_3·MeOH) that would not result in methanolysis of the benzodioxinone. Gratifyingly, irradiation of trifluoroacetate **288** in the presence of alcohol **273** produced a modest yield of the acylation product **289** (27%, 50% BRSM) in addition to unreacted starting materials which were readily recovered and recycled (Scheme 5.12). In contrast to C11 MOM protected trifluoroacetate **278**, compound **288** showed no signs of trifluoroacetate hydrolysis.

Scheme 5.12



Following successful photochemical coupling, trifluoroacetate removal was readily achieved upon treatment with 2.0 M ammonia in methanol to afford alcohol **290** in 94% yield (Scheme 5.13). Next, macrocyclization of alcohol **290** was investigated with non-nucleophilic bases such as sodium and potassium hydride. Surprisingly, utilization of these bases consistently resulted in decomposition of the macrocyclization precursors. Proton NMR and mass spectral analysis of the crude mixture from one reaction revealed extensive formation of the benzodioxinone hydrolysis product.

Scheme 5.13



Reagents and Conditions: (a) 2.0M NH_3 in MeOH, rt 12 hr, 94%; (b) NaHMDS, -78→-20 ˚C 1 hr, -20 ˚C ½ hr, THF, 50%; (c) 10% Pd/C, H_2, MeOH, rt 3.5 hr, 93%; (d) 48% aqHF, CH_3CN, 48 hr rt, 77%.

Successful lactonization was realized when treatment of alcohol **290** with sodium hexamethyldisilazide provided macrocycle **291** in 50% yield. Some decomposition was also observed with this amide base. Proton NMR and mass spectral data of the crude reaction mixture indicated that aminolysis of the benzodioxinone took place. Finally, hydrogenolysis of the benzyl esters revealed the bis-carboxylate (93%), which was filtered and treated with 70% aqueous hydrofluoric acid in acetonitrile to remove the MOM and TBS groups (77%) (**291→1**). Surprisingly, TLC analysis of this reaction revealed the product to be considerably less-polar than the reactant. Extraction of the natural product with hexane from a 4N HCl, sat. NaCl solution[4] provided a pure sample of the natural product. To obtain an analytically pure sample of the natural product for

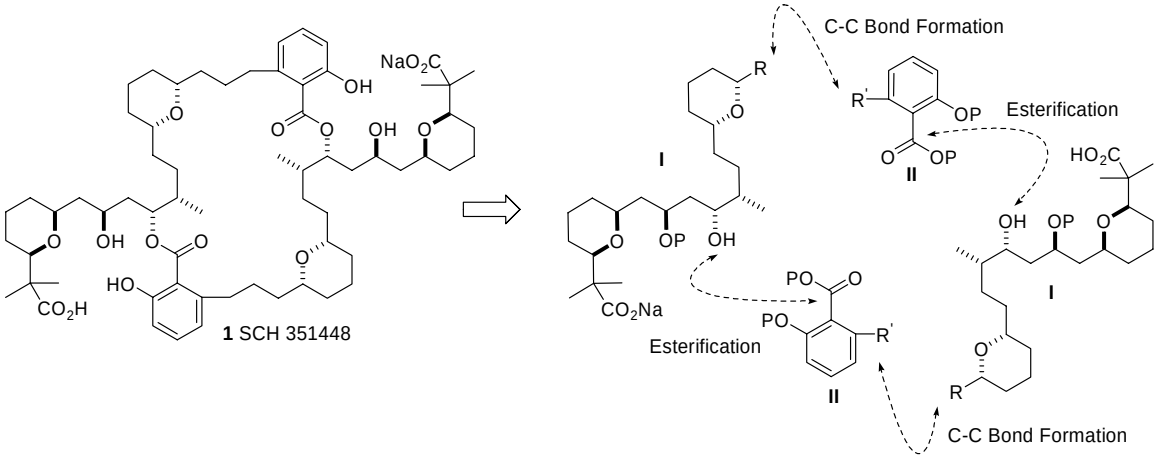
spectral characterization, reverse phase HPLC was employed (C18 column, 8:92 H_2O:MeOH).

Interestingly, purification of SCH 351448 by silicagel chromatography yielded a compound displaying NMR data similar, but not identical to that reported for SCH 351448[5]. A comparable observation was noted in Eun Lee's full account of his SCH 351448 synthesis[1]. These investigators went on to conduct mass spectral analysis (MALDI-TOF) of this sample of SCH 351448, and confirmed that formation of a calcium bound molecule resulted upon purification with calcium enriched Merck silica gel[6].

5.4 An Alternative Route

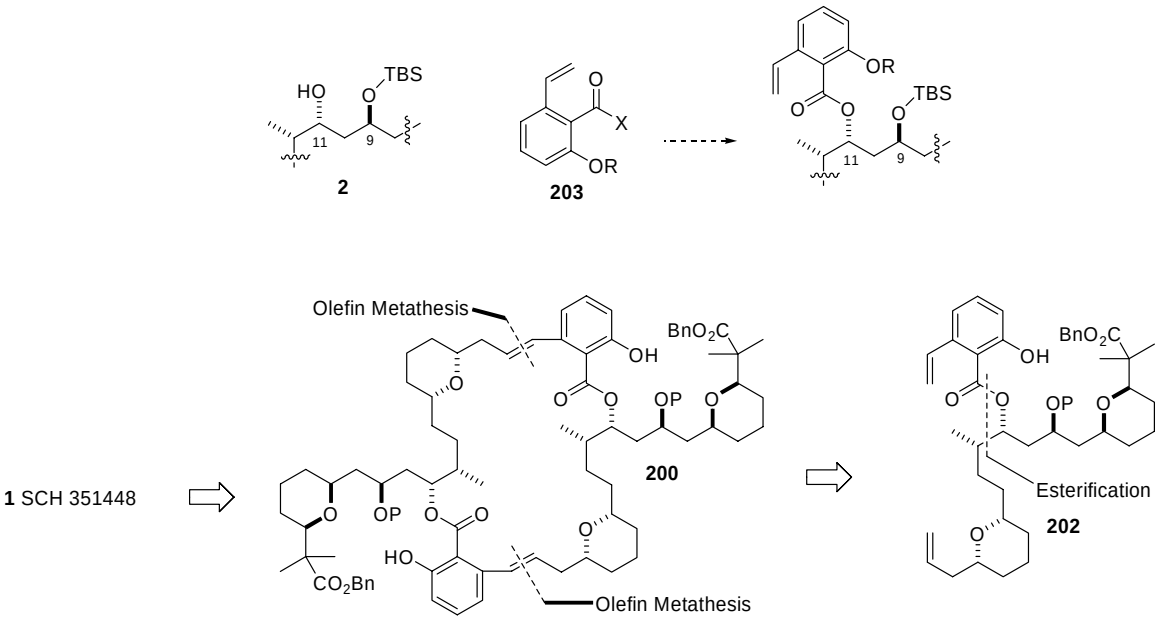
Our general strategy towards the natural product SCH 351448 (Fig. 5.4) provided the flexibility to explore various pathways based on the dimerization of identical units **I** and **II** (Fig. 5.4).

Fig. 5.4



As discussed previously (See Chapter 2 and 4), initial attempts to apply this strategy via esterification of **I** and **II**, followed by a cross metathesis/ring closing metathesis sequence was stalled by our inability to efficiently acylate hindered alcohols at the C11 position (Scheme 5.14).

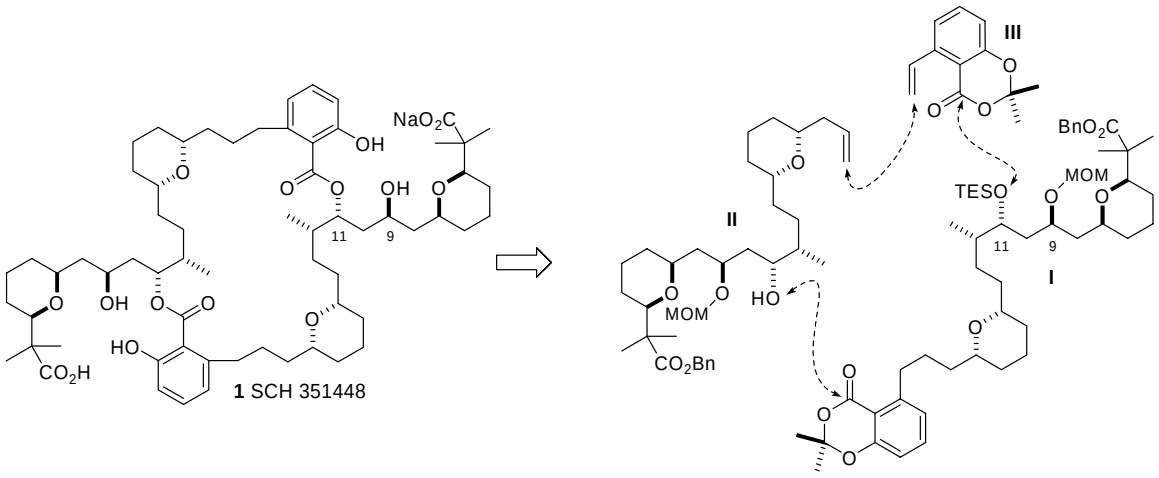
Scheme 5.14



Many of the popular acylation methods explored (Mitsunobo, Yamaguchi, DCC, etc) were completely ineffective, and procedures that utilize strong bases such as alkoxide mediated acylation and transesterification of cyanomethylesters resulted in poor yields and extensive decomposition stemming from TBS deprotection and migration.

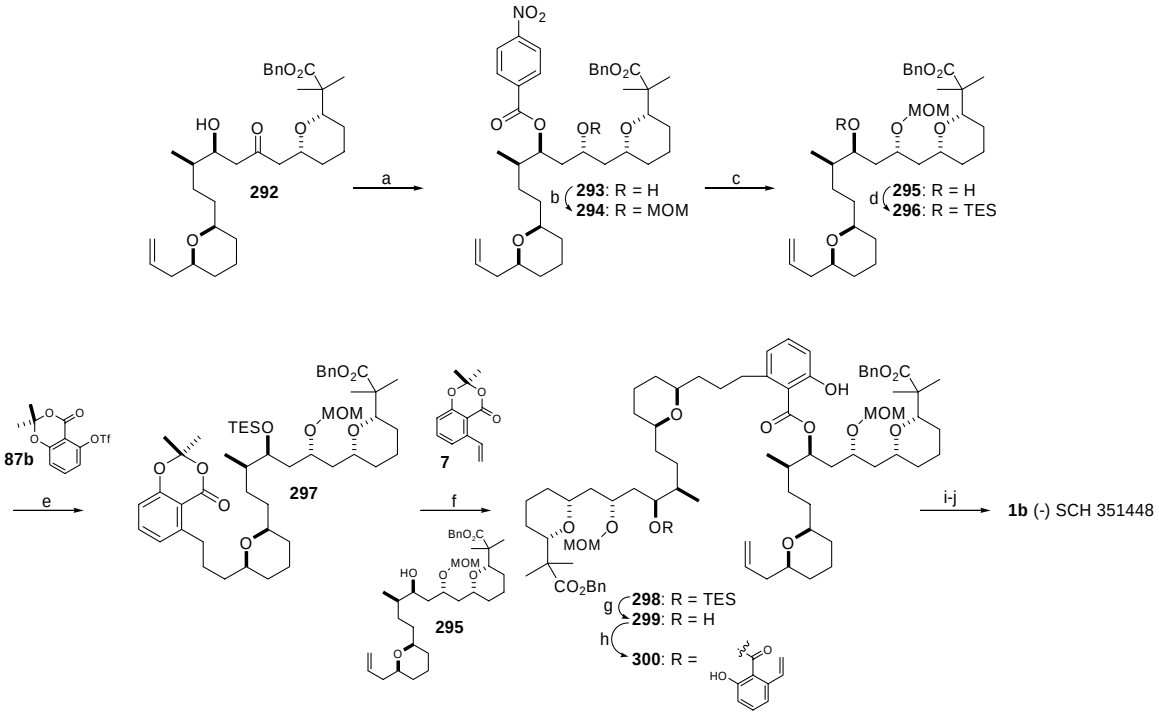
Since establishing the Evans-Tishchenko reaction as a robust procedure to incorporate small/stable protecting groups such as MOM ethers at the C9 position, we proceeded to develop an alternative path to the natural product that would utilize alkoxide mediated acylation and ring closing olefin metathesis to prepare the natural product (Scheme 5.16). This strategy would benefit from our experience in preparing monomeric benzodioxinones such as **I** and alcohol **II** (Scheme 5.15).

Scheme 5.15



This effort commences with an Evans-Tishchenko reduction of β-hydroxyketone **292** with *p*-nitrobenzaldehyde. Subsequent MOM protection and methanolysis of the benzoate proceeded smoothly to provide the MOM protected alcohol **295**. Utilization of *p*-nitrobenzaldehyde rather than acetaldehyde allowed for clean removal of the benzoate, and avoided competing methanolysis of the C1 benzyl ester which was observed previously (See Scheme 5.4). Divergence of the two fragments begins at this stage with the triethylsilyl protection of alcohol **295** (→**296**), followed by Suzuki coupling with triflate **87b** to provide acetonide **297** in excellent yield (81%). Experience with the previous route was evident here since silyl protection provided for an efficient coupling in addition to facile deprotection under mild conditions.

Scheme 5.16



Reagents and Conditions: (a) 4-$NO_2C_6H_4CHO$, cat. SmI_2, THF, 0 ˚C 1.5 hr, 71%; (b) *i*-Pr_2EtN, MOM-Cl, CH_2Cl_2, 8 hr rt, 12 hr 50 ˚C; (*c*) K_2CO_3, MeOH, 12 hr rt, 84% 2 steps; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, -78 ˚C 1 hr, 78%; (e) 9-BBN, THF, rt, 3M K_3PO_4, $PdCl_2$dppf, **87b**, DMF, rt, 81%; (f) **295**, NaHMDS, 0 ˚C ½ hr, THF, then **297**, THF, 0 ˚C 1.5 hr, 45%; (g) HF·Pyr, Pyr, THF, rt 5 hr, 96%; (h) NaHMDS, 0 ˚C ½ hr, then **7**, THF, 0 ˚C 1.5 hr, 57%; (i) 10% Grubbs' 2nd Gen. Cat., CH_2Cl_2, 50 ˚C 8 hr, 38%; (j) 10% Pd/C, H_2, MeOH, rt 3.5 hr, then 48% aqHF, CH_3CN, 48 hr rt.

Next, deprotonation of alcohol **295** with NaHMDS followed by addition of acetonide **297** allowed for construction of the first salicylate ester. Incorporation of the second salicylate ester was achieved after removal of the TES group, deprotonation of the resulting alcohol, and treatment of the sodium alkoxide with 2 equivalents of *o*-vinyl salicylate **7**. Ring closing metathesis of bis-olefin **300** with Grubbs' 2nd generation catalyst at elevated temperature afforded the 28 membered macrocycle. Hydrogenolysis of the benzyl ester protecting groups with concomitant saturation of the disubstituted olefin was followed by deprotection of the MOM groups with aqueous HF and work up with an acidic NaCl solution as before. This sequence exploits the alkoxide mediated acylation methodology developed initially by De Brabander for the synthesis of

apicularen A[7], and used by both Lee and Leighton in their syntheses of SCH 351448[4,8]. This route also takes advantage of the information gathered in our previous synthesis in regards to the substitution pattern tolerated in the Suzuki coupling step. The number of steps from β-hydroxyketone **292** was reduced from 17 to 11, and greater efficiency in the fragment coupling steps was also achieved. This optimized route is 27 steps from commercially available starting materials (Longest Linear Sequence = 21 steps), which compares well with both the photochemical based route (34 Total Steps, Longest Linear Sequence = 28 steps), and the Leighton and Lee syntheses (Leighton: 34 Total, Longest Linear Sequence = 24, Lee: 47 Total Steps, Longest Linear Sequence = 28).

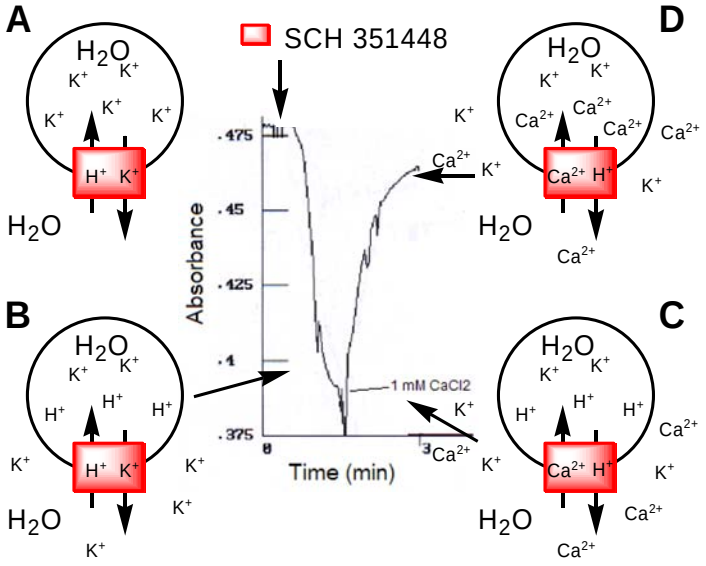
5.5 Ion Transport Studies

The study of natural and non-natural ion-binding small molecules has been an area of interest for the last several decades[9]. Ionophores have been used to study various biological processes such as metabolism and energy-linked transport[10,11]. More recently, naturally occurring ionophores such as the Na^+/H^+ transporter monensin have found use as a feeding additive for diary cattle. There is evidence that this ionophore inhibits growth of certain gram-positive bacteria found in ruminants thereby increasing energy capture from feeds. In addition to SCH's crystal structure and non-polar nature, its intimately complexed sodium ion led us to question whether this molecule has the capability of transporting ions across cell-membranes.

Recently, we have initiated experiments (in collaboration with Professor Xiao-Song Xie, UT Southwestern Departments of Physiology and Internal Medicine) to elucidate a possible physiological role for SCH 351448 as a transporter of ions across lipid bilayers. In brief K^+-loaded vesicles (in NaCl containing buffer) were treated with a

potassium selective ionophore (valinomycin) and a proton ionophore (1799) (Fig. 5.5). K^+/H^+ exchange results in acidification of the vesicle – a process which is measured by quenching of acridine orange absorbance[12]. Subsequent addition of SCH 351448 results in neutralization of the vesicle via Na^+/H^+ exchange. In this setting, SCH alone (i.e. in the absence of valinomycin and/or 1799) could not acidify the vesicles because of K^+/Na^+ exchange. To gain a more comprehensive understanding of SCH's ion-transport properties another experiment was conducted in which K^+ loaded vesicles were treated with SCH 351448 in a low-ion content buffer (Fig. 5.5, A). Under these conditions, SCH 351448 effected vesicle acidification via H^+/K^+ exchange (Fig. 5.5, A→B)). The resulting proton gradient was collapsed upon addition of various mono and divalent metals (Ca^{2+}, Mg^{2+}, Li^+) (Fig. 5.5, C), indicating SCH 351448 can readily exchange these metal cations with protons (Fig. 5.5, C→D). In these assays, SCH 351448 is effective at mid to low nanomolar concentrations. The uv absorbance diagram depicted in figure 5.5 represents an experimental graph of vesicle acidification upon addition of SCH 351448. These experiments identify a biologically relevant function for SCH 351448, a compound that can efficiently collapse various proton and ion gradients.

Fig. 5.5 Ion Transport by SCH 351448



Recently, preliminary experiments with Dr. Richard Anderson and Dr. Peter Michaely (UT Southwestern Department of Cell Biology) have shown that (+)-SCH 351448 disrupts low density lipoprotein receptor recycling in a fashion not unlike the Na^+/H^+ ionophore monensin[13]. Based on these preliminary results, we can conclude that SCH 351448's effect on the low density lipoprotein receptor is likely mediated by its ion-exchange properties. Experiments to further evaluate SCH 351448's biological profile are ongoing.

5.6 Experimental Section

5.6.1 Materials and Methods

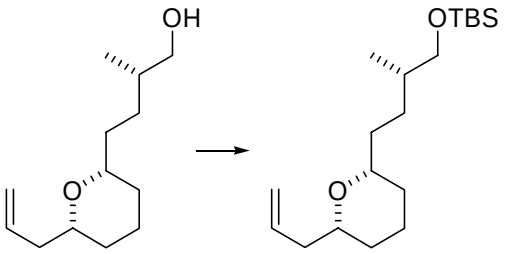
Unless otherwise noted, commercially available materials were used without further purification. All solvents were of HPLC or ACS grade. Solvents used for moisture sensitive operations were distilled from drying reagents under a nitrogen atmosphere: Et_2O and THF from sodium benzophenone ketyl; benzene and toluene from sodium;

CH_2Cl_2 from CaH_2, pyridine over solid KOH, anhydrous N,N-dimethylformamide, and CH_3CN were purchased from commercial sources. Reactions were performed under an atmosphere of nitrogen with magnetic stirring unless noted otherwise. All photochemical reactions were performed with a Rayonett RPR-100 reactor fitted with a test tube carousel and 300 nm bulbs. Flash chromatography (FC) was performed using *E Merck* silica gel 60 (240–400 mesh) according to the protocol of Still, Kahn, and Mitra (*J. Org. Chem.* **1978**, *43*, 2923). Thin layer chromatography was performed performed using precoated plates purchased from *E. Merck* (silicagel 60 PF254, 0.25 mm) that were visualized using a $KMnO_4$ or Ce (IV) stain.

Nuclear magnetic resonance (NMR) spectra were recorded on a *Varian Inova*-400 or *Mercury*-300 spectrometer at operating frequencies of 400/300 MHz (^{1}H NMR) or 100 / 75 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform δ 7.26 for ^{1}H NMR or δ 77.23 for proton decoupled ^{13}C NMR), and coupling constants (*J)* in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet, whereby the prefix app is applied in cases where the true multiplicity is unresolved, and *br* when the signal in question is broadened.

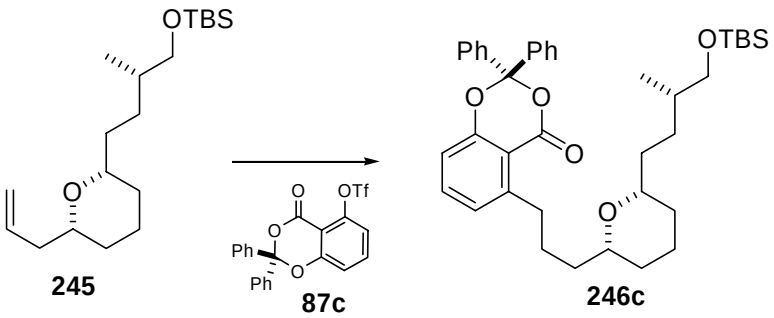
Infrared spectra were recorded on a *Perkin-ElmerI* 1000 series FTIR with wavenumbers expressed in cm^{-1} using samples prepared as thin films between salt plates. Electrospray ionization mass spectra (ESI-MS) were recorded on a Shimadzu 2010-LCMS. Optical rotations were measured at 20 ˚C on a Rudolph Research Analytical Autopol® IV polarimeter.

5.6.2 Experimental Procedures



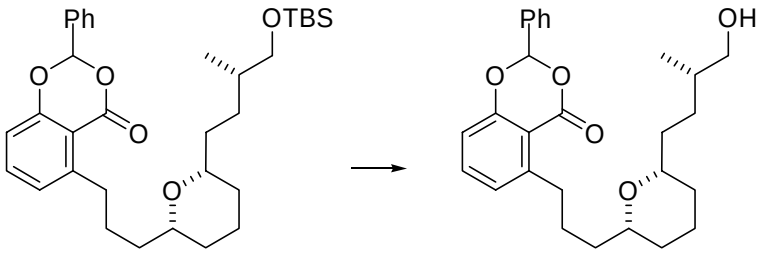
230b **245**

Pyran 245. To a stirred solution of alcohol **230b** (684 mg, 3.23 mmol) in THF (20 mL) at 0 ˚C was added imidazole (2.2 g, 32.3 mmol), DMAP (394 mg, 3.23 mmol), and TBSCl (2.4 g, 16.2 mmol). The reaction was allowed to stir at ambient temperature for 1 hr. The reaction was then poured into H_2O (50 mL) and extracted with Et_2O (2 x 75 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (5/95, EtOAc/Hex) to afford 800 mg (76%) of **245**. $[\alpha]_D$ = -15.8 ($CHCl_3$, *c* 0.85). IR (film) 2933, 1472, 1257, 1087, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (1H, dddd, *J* = 6.8, 6.8, 10.4, 17.2 Hz), 5.03–5.08 (1H, m), 5.00–5.02 (1H, m), 3.18–3.46 (4H, m), 2.27–2.34 (1H, m), 2.10–2.17 (1H, m), 1.78–1.83 (1H, m), 1.41–1.61 (7H, m), 1.02–1.22 (3H, m), 0.03 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 116.4, 78.6, 77.7, 68.6, 41.3, 36.0, 34.2, 31.7, 31.5, 29.3, 26.2, 23.9, 16.9, -5.1. MS (ES) *m/z* (%): 327.10 ($[MH]^+$, 100).



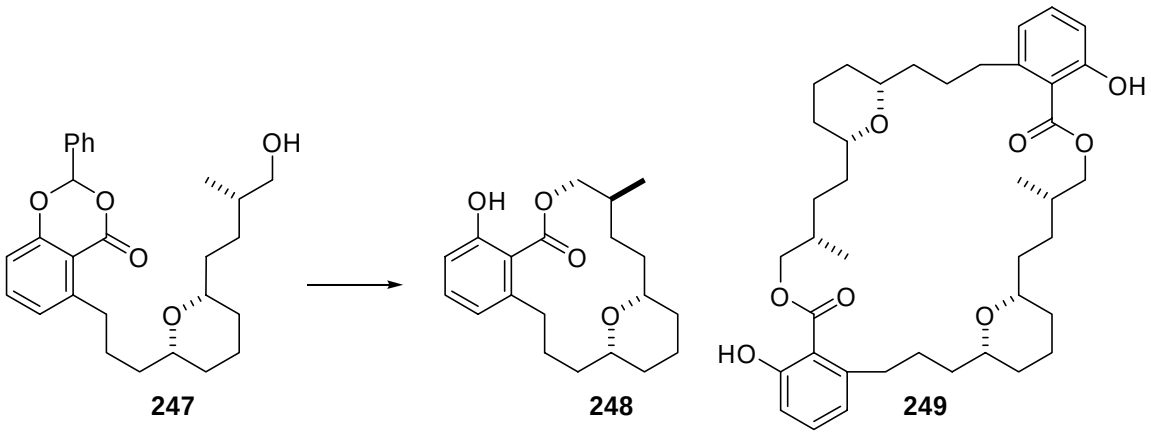
245 **87c** **246c**

Silyl Ether 246c. To a roundbottom flask containing **245** (30 mg, 0.092 mmol) was added solid 9-BBN (13 mg, 0.11 mmol), followed by THF (1 mL). This reaction was allowed to stir at ambient temperature for 16 hr. Then a solution of K_3PO_4 (0.052 mL, 0.156 mmol, 3 M soln.) was added followed by a solution of $PdCl_2$dppf (4 mg, 0.0046 mmol) and aryltriflate **87c** (62 mg, 0.14 mmol) in THF (1 mL). The reaction was allowed to stir at ambient temperature for 18 hr. The reaction solution was then poured into H_2O (30 mL) and extracted with Et_2O (2 x 40 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (5/95, EtOAc/Hex) to afford 37 mg (65%) of **246c**. $[\alpha]_D$ = -1.4 ($CHCl_3$, *c* 0.7). IR (film) 2930, 1745, 1607, 1580, 1475, 1453, 1266, 1093, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.58 (4H, m), 7.28–7.35 (7H, m), 6.98 (1H, d, *J* = 8.0 Hz), 6.82 (1H, d, *J* = 8.0 Hz), 3.44 (1H, dd, *J* = 5.6, 9.6 Hz), 3.32 (1H, dd, *J* = 6.8, 9.6 Hz), 3.14–3.20 (2H, m), 2.92–3.08 (2H, m), 1.75–1.80 (1H, m), 1.38–1.62 (9H, m), 1.20–1.26 (2H, m), 1.01–1.14 (3H, m), 0.88 (9H, s), 0.86 (3H, d, *J* = 6.8 Hz), 0.02 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 157.7, 148.5, 140.0, 135.4, 129.2, 129.1, 128.6, 126.7, 125.7, 115.6, 113.6, 78.4, 77.8, 68.6, 36.3, 34.3, 31.8, 29.3, 26.9, 26.2, 24.0, 18.5, -5.1. MS (ES) *m/z* (%): 651.30 ($[MNa]^+$, 100).



246 **247**

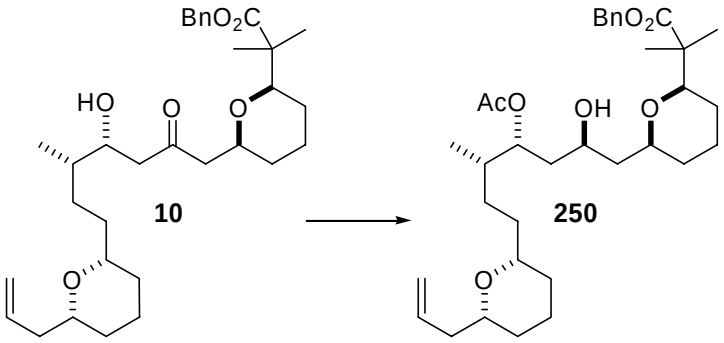
Alcohol 247. To a stirred solution of **246** (15 mg, 0.027 mmol) in THF (0.2 mL) was added HF·Pyridine buffered with additional pyridine (0.3 mL). The reaction was allowed to stir for 14 hr at ambient temperature. The reaction was then poured into H_2O (20 mL) and extracted with EtOAc (2 x 70 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated, purified by PTLC (40/60, EtOAc/Hex) to afford 11.7 mg (99%) of **247**. $[\alpha]_D$ = -12.0 ($CHCl_3$, *c* 0.35). IR (film) 3300, 2933, 1744, 1605, 1303, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.67 (2H, m), 7.43–7.49 (4H, m), 7.05 (1H, dd, *J* = 4.0, 7.2 Hz), 6.96 (1H, d, *J* = 8.0 Hz), 6.46 (1H, d, *J* = 6.8 Hz), 3.41–3.50 (2H, m), 3.20–3.34 (2H, m), 2.94–3.13 (2H, m), 1.12–1.83 (15H, m), 0.90 (3H, app dd, *J* = 2.0, 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 159.6, 149.0, 135.4, 134.4, 130.5, 128.8, 126.9, 126.1, 114.9, 113.0, 99.9, 78.5, 77.9, 77.8, 68.2, 36.5, 36.0, 34.4, 33.9, 31.9, 29.3, 27.3, 23.9, 16.9. MS (ES) *m/z* (%): 461.15 ($[MNa]^+$, 100).



Photoacylation of 247. To an ovendried roundbottom glass test tube was added **247** (5.6 mg, 0.0128 mmol) followed by CH_2Cl_2 (1.2 mL). The test tube was sealed with a rubber septum while flushing with N_2 and the reaction solution was then photolyzed (300 nm) for 1/2 hr at ambient temperature. The solvent was then removed the crude residue was

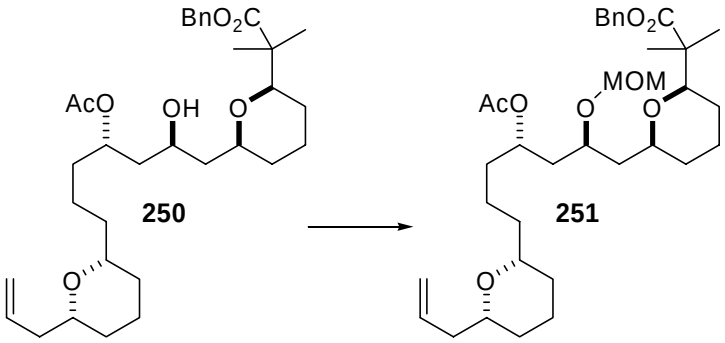
purified by PTLC (5/95, EtOAc/Hex) to afford 1.5 mg (35%) of **248** and <1 mg of **249**. **248**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.73 (1H, s), 7.30 (1H, t, *J* = 8.0 Hz), 6.83 (1H, dd, *J* = 1.0, 8.0 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 4.24 (1H, dd, *J* = 3.0, 10.8 Hz), 3..99 (1H, t, *J* = 10.8 Hz), 3.24–3.38 (3H, m), 2.77 (1H, dt, *J* = 2.8, 12.8 Hz), 2.22–2.31 (1H, m), 2.10–2.20 (1H, m), 1.79–1.86 (2H, m), 1.16–1.66 (11H, m), 0.93 (3H, d, *J* = 7.2 Hz). MS (ES) *m/z* (%): 333.21, $[MH]^+$, 100).

249: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (2H, s), 7.23 (2H, t, *J* = 8.0 Hz), 6.80 (2H, d, *J* = 8.0 Hz), 6.65 (2H, d, *J* = 7.2 Hz), 4.24 (2H, dd, *J* = 6.0, 10.8 Hz), 4.11 (2H, dd, *J* = 7.2, 10.4 Hz), 3.15–3.22 (4H, m), 3.03–3.11 (2H, m), 2.69–2.77 (2H, m), 1.98–2.06 (2H, m), 1.70–1.90 (6H, m), 1.10–1.59 (18H, m), 1.03 (6H, d, *J* = 6.4 Hz), 0.86–0.89 (4H, m). MS (ES) *m/z* (%): 687.35, $[MNa]^+$, 100).



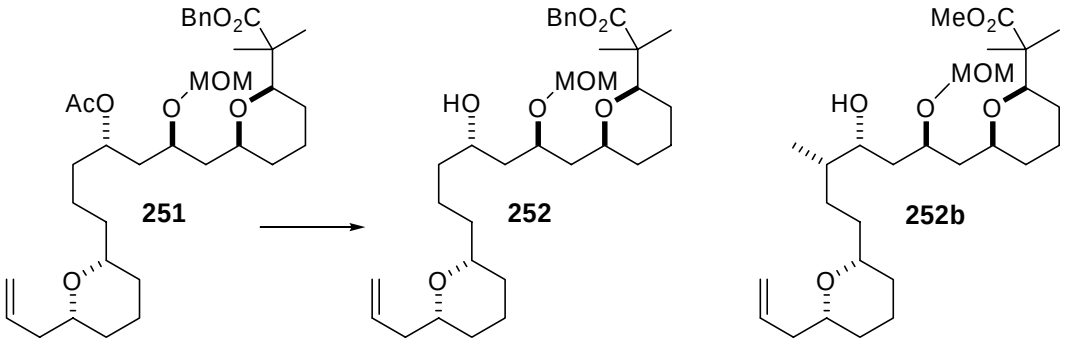
Acetate 250. To a stirred solution of β-hydroxyketone **10** (1.95 g, 3.7 mmol) and acetaldehyde (1.59 mL, 28.4 mmol) in THF (20 mL) at –10 ˚C was added a freshly prepared solution of SmI_2 (0.1 M in THF, 11 mL, 1.1mmol) dropwise. The reaction was allowed to warm to 0 ˚C and stirred at that temperature for 8 hr. Saturated aq NH_4Cl (5 mL) was added, followed by water (50 mL) and extraction with Et_2O (3 × 100 mL). The organic phase was dried over $MgSO_4$, concentrated, and purified by FC (1/4, EtOAc/Hex)

to afford 1.73 g (82%) of **250**. $[\alpha]_D$ = +6.5 ($CHCl_3$, *c* 3.0). IR (film) 3527, 2936, 2860, 1732, 1373, 1247, 1085, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.38 (5H, m), 5.83 (1H, dddd, *J* = 7.6, 7.6, 10.4, 17.2 Hz), 5.15 (1H, d, *J* = 12.4 Hz), 5.10 (1H, d, *J* = 12.8 Hz), 4.89–5.09 (3H, m), 3.66–3.74 (1H, m), 3.57 (1H, d, *J* = 10.8 Hz), 3.49–3.56 (1H, m), 3.47 (1H, s), 3.25–3.32 (1H, m), 3.15–3.24 (1H, m), 2.23–2.34 (1H, m), 2.08–2.18 (1H, m), 2.01 (3H, s), 1.76–1.87 (2H, m), 1.40–1.73 (14H, m), 1.02–1.33 (5H, m), 1.19 (3H, s), 1.14 (3H, s), 0.86 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 171.3, 136.5, 135.5, 128.6, 128.1, 116.4, 82.8, 78.8, 78.2, 77.5, 75.0, 67.4, 66.5, 46.8, 43.5, 41.2, 38.4, 36.9, 34.2, 32.0, 31.6, 31.4, 28.3, 25.0, 23.8, 23.5, 21.5, 21.3, 20.3, 15.1. MS (ES) *m/z* (%): 595.40 ($[MNa]^+$, 100).



MOM Ether 251. To a stirred solution of free alcohol **250** (1.67 g, 2.92 mmol), and *i*-Pr_2NEt (7.60 mL, 43.8 mmol) in CH_2Cl_2 (25 mL) at ambient temperature was added MOMCl (1.55 mL, 20.4 mmol). The reaction was stirred for 12 hr at ambient temperature and 3 hr at 50 ˚C. The reaction solution was poured into water (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic phase was dried over $MgSO_4$, concentrated, and purified by FC (1/9, EtOAc/Hex) to afford 1.71 g (95%) of **251**. $[\alpha]_D$ = -0.8 ($CHCl_3$, *c* 1.0). IR (film) 2935, 1732, 1455, 1372, 1243, 1087, 1041, 918 cm^{-1}; ^1H

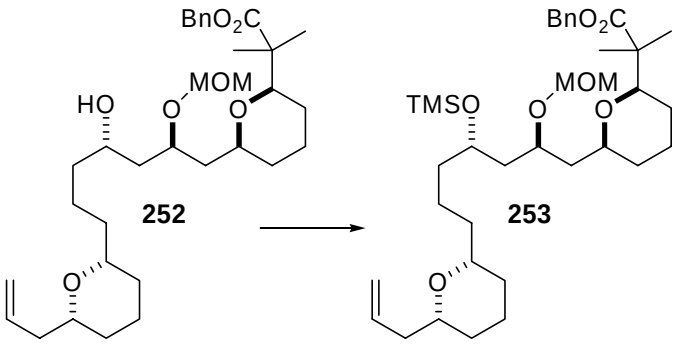
NMR (400 MHz, $CDCl_3$) δ 7.28–7.38 (5H, m), 5.83 (1H, dddd, *J* = 7.2, 7.2, 10.4, 17.2 Hz), 5.12 (2H, s), 5.06–5.08 (1H, m), 4.97–5.04 (2H, m), 4.61 (1H, d, *J* = 6.8 Hz), 4.53 (1H, d, *J* = 6.8 Hz), 3.62–3.71 (1H, m), 3.47 (1H, dd, *J* = 1.6, 11.2 Hz), 3.17–3.42 (3H, m), 3.34 (3H, s), 2.25–2.34 (1H, m), 2.09–2.18 (1H, m), 2.01 (3H, s), 1.76–1.89 (2H, m), 1.68–1.76 (1H, m), 1.36–1.62 (12H, m), 1.02–1.31 (6H, m), 1.23 (3H, s), 1.15 (3H, s), 0.85 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 170.6, 136.4, 135.4, 128.5, 127.9, 127.8, 116.2, 96.3, 82.1, 78.0, 77.3, 74.8, 74.3, 72.2, 66.0, 55.8, 46.7, 42.1, 41.0, 36.6, 35.0, 34.1, 31.9, 31.5, 31.2, 28.4, 25.5, 23.6, 21.8, 21.2, 20.4, 14.7. MS (ES) *m/z* (%): 639.35 ($[MNa]^+$, 100).



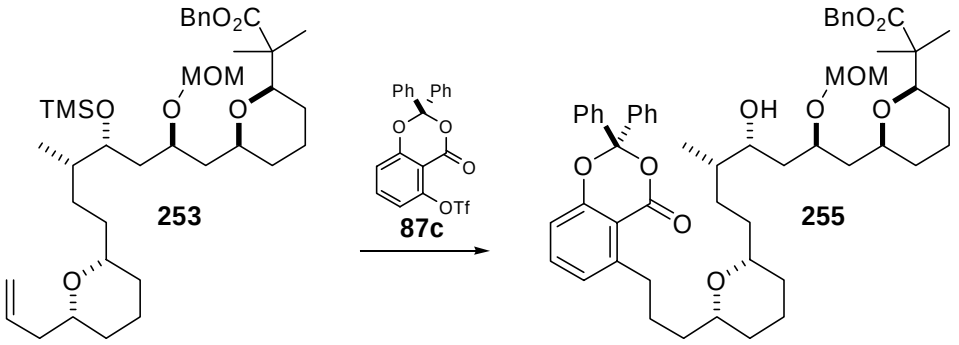
Acetate hydrolysis. To a stirred solution of acetate **251** (400 mg, 0.65 mmol) in anhydrous methanol (7 mL) was added anhydrous K_2CO_3 (358 mg, 2.59 mmol). The reaction was allowed to stir for 48 h at ambient temperature before additional K_2CO_3 (1.0 g, 7.24 mmol) was added. After 60 hr total reaction time, the reaction was poured into water (100 mL) and extracted with Et_2O (3 × 50 mL). The organic phase was dried over $MgSO_4$, concentrated, and purified by FC (15/85, EtOAc/Hex) to afford 261 mg (70%) alcohol **252**.

252: $[\alpha]_D$ = -15.8 ($CHCl_3$, *c* 0.7). IR (film) 3512, 2934, 1730, 1457, 1374, 1268, 1149, 1088, 1039, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.40 (5H, m), 5.84 (1H, dddd, *J* = 6.8, 6.8, 9.6, 16.4 Hz), 5.13 (2H, s), 5.05 (1H, d, *J* = 17.6 Hz), 5.01 (1H, d, *J* = 10.4 Hz), 4.63 (1H, d, *J* = 6.8 Hz), 4.59 (1H, d, *J* = 6.8 Hz), 3.92–4.00 (1H, m), 3.64–3.71 (1H, m), 3.52 (1H, d, *J* = 10.8 Hz), 3.19–3.42 (3H, m), 3.37 (3H, s), 2.95 (1H, br s), 2.27–2.35 (1H, m), 2.09–2.18 (1H, m), 1.77–1.89 (2H, m), 1.41–1.68 (12H, m), 1.12–1.29 (7H, m), 1.21 (3H, s), 1.13 (3H, s), 0.88 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 136.5, 135.4, 128.5, 128.0, 127.8, 116.3, 96.1, 82.3, 78.5, 77.5, 75.0, 73.5, 71.6, 66.2, 55.8, 46.8, 41.2, 41.1, 39.0, 37.1, 34.2, 32.0, 31.5, 31.3, 28.2, 25.2, 23.7, 21.4, 20.5, 15.3. MS (ES) *m/z* (%): 597.45 ($[MNa]^+$, 100).

252b: $[\alpha]_D$ = +88.6 ($CHCl_3$, *c* 0.93). IR (film) 3519, 2936, 1732, 1440, 1375, 1270, 1150, 1088, 1040, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (1H, dddd, *J* = 7.2, 7.2, 10.4, 16.8 Hz), 5.05 (1H, d, *J* = 17.2 Hz), 5.00 (1H, d, *J* = 1.2, 10.0 Hz), 4.64 (1H, d, *J* = 6.8 Hz), 4.61 (1H, d, *J* = 6.8 Hz), 3.91–3.98 (1H, m), 3.69–3.78 (1H, m), 3.67 (3H, s), 3.48 (1H, d, *J* = 6.8 Hz), 3.38 (3H, s), 3.22–3.33 (3H, m), 2.28–2.34 (1H, m), 2.10–2.17 (1H, m), 1.79–1.88 (3H, m), 1.42–1.65 (14H, m), 1.05–1.29 (10H, m), 0.89 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 135.6, 116.5, 96.2, 82.4, 78.6, 75.1, 73.6, 71.7, 56.0, 52.1, 46.8, 41.3, 39.1, 36.9, 34.3, 32.1, 31.6, 31.4, 28.3, 25.2, 23.8, 21.6, 20.3, 15.4. MS (ES) *m/z* (%): 521.35 ($[MNa]^+$, 70).

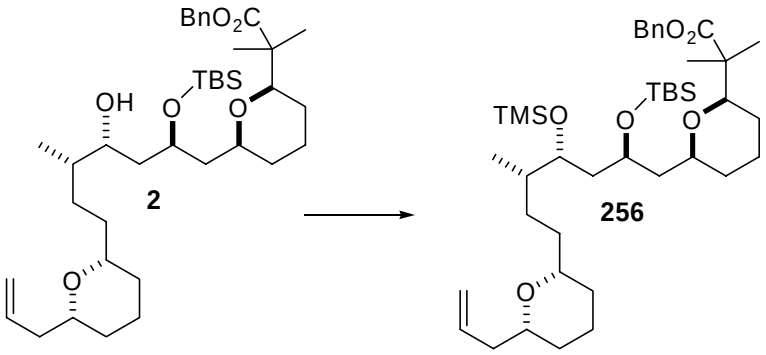


Silyl Ether 253. To a stirred solution of alcohol **252** (140 mg, 0.244 mmol) in CH_2Cl_2 (5 mL) at 0 ˚C was added Et_3N (0.68 mL, 4.88 mmol) followed by TMSCl (0.31 mL, 2.44 mmol). After 1 hr, the reaction was quenched by addition of water (30 mL) and extracted with Et_2O (2 × 50 mL). The organic phase was then dried over $MgSO_4$, concentrated, and purified by FC (1/9, EtOAc/Hex) to afford 150 mg (96%) of silyl ether **253**. $[\alpha]_D$ = -2.8 ($CHCl_3$, *c* 0.3). IR (film) 2936, 1736, 1456, 1375, 1250, 1087, 1042, 918, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.38 (5H, m), 5.83 (1H, dddd, *J* = 6.4, 6.4, 10.4, 16.8 Hz), 5.11 (2H, s), 5.05 (1H, app d, *J* = 17.2 Hz), 5.00 (1H, app d, *J* = 10.0 Hz), 4.63 (2H, s), 3.70–3.84 (2H, m), 3.46 (1H, d, *J* = 7.2 Hz), 3.38–3.44 (1H, m), 3.36 (3H, s), 3.25–3.34 (1H, m), 3.16–3.24 (1H, m), 2.26–2.35 (1H, m), 2.09–2.18 (1H, m), 1.77–1.86 (3H, m), 1.30–1.62 (12H, m), 0.94–1.29 (6H, s), 1.23 (3H, s), 1.14 (3H, s), 0.84 (3H, d, *J* = 6.8 Hz), 0.09 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 136.6, 135.4, 128.5, 127.9, 127.8, 116.3, 96.3, 82.0, 78.3, 77.5, 75.0, 73.7, 73.0, 66.0, 55.6, 46.8, 42.7, 41.1, 39.5, 37.7, 34.8, 31.9, 31.6, 31.3, 29.0, 25.7, 23.7, 22.3, 20.2, 13.8, 0.76. MS (ES) *m/z* (%): 669.40 ($[MNa]^+$, 100).



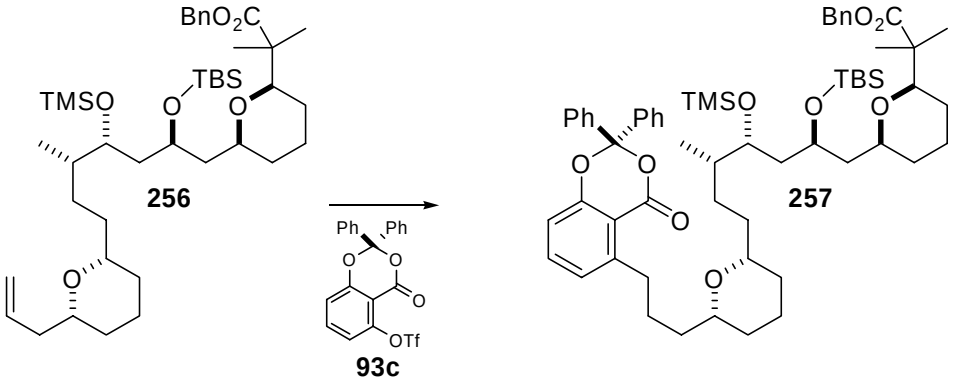
Compound 255. To a round bottom flask containing olefin **253** (281 mg, 0.43 mmol) and solid 9-BBN dimer (160 mg, 1.3 mmol) was added freshly distilled THF (2 mL). The reaction was allowed to stir for 12 hr at ambient temperature. Then a degassed aqueous solution of 3 M K_3PO_4 (0.43 mL, 1.29 mmol) was added dropwise, followed by a solution of **87c** (290 mg, 0.65 mmol), and $PdCl_2$dppf (17.5 mg, 0.022 mmol) in degassed DMF (2 mL). The reaction was allowed to stir for 20 hr at ambient temperature, followed by the addition of water (40 mL) and extraction with Et_2O (3 × 30 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and filtered through a short pad of silica (8/92, EtOAc/Hex). The crude filtrate was concentrated, taken up in THF (20 mL), and treated with HF·pyridine [3 mL from a stock solution composed of 70% HF·pyridine (2.15 mL), pyridine (10.75 mL), and THF (29 mL]. The reaction was allowed to stir at ambient temperature for 2 h at which time the mixture was diluted with water (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (1/4 EtOAc/Hex) to afford 301 mg (80% for 2 steps) of alcohol **255**. $[\alpha]_D$ = -2.3 ($CHCl_3$, *c* 0.18). IR (film) 3520, 2934, 2860, 1739, 1607, 1580, 1476, 1454, 1267, 1093, 1039, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.58 (4H, m), 7.26–7.37 (12H, m), 6.70 (1H, d, *J* = 8.0 Hz), 6.81 (1H, d, *J* = 7.6 Hz), 5.11 (2H, s), 4.60 (1H, d, *J* = 6.8 Hz), 4.57 (1H, d, *J* = 6.4 Hz), 3.91–

3.98 (1H, m), 3.61–3.68 (1H, m), 3.50 (1H, d, *J* = 11.2 Hz), 3.28–3.38 (1H, m), 3.36 (1H, s), 3.34 (3H, s), 3.12–3.22 (2H, m), 3.00–3.07 (1H, m), 2.91–2.97 (1H, m), 1.74–1.87 (3H, m), 1.37–1.64 (16H, m), 0.98–1.28 (7H, m), 1.19 (3H, s), 1.12 (3H, s), 0.86 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 160.4, 157.7, 148.5, 140.0, 136.6, 135.4, 129.2, 129.1, 128.6, 128.1, 128.0, 126.8, 126.7, 125.7, 115.6, 113.6, 106.0, 97.5, 96.2, 82.4, 78.4, 77.8, 75.2, 73.6, 71.7, 66.3, 55.9, 46.9, 41.4, 39.1, 37.2, 36.3, 34.3, 32.1, 31.8, 31.7, 29.9, 28.4, 26.8, 25.3, 23.9, 23.8, 21.4, 20.7, 15.3. MS (ES) *m/z* (%): 899.65 ($[MNa]^+$, 50).



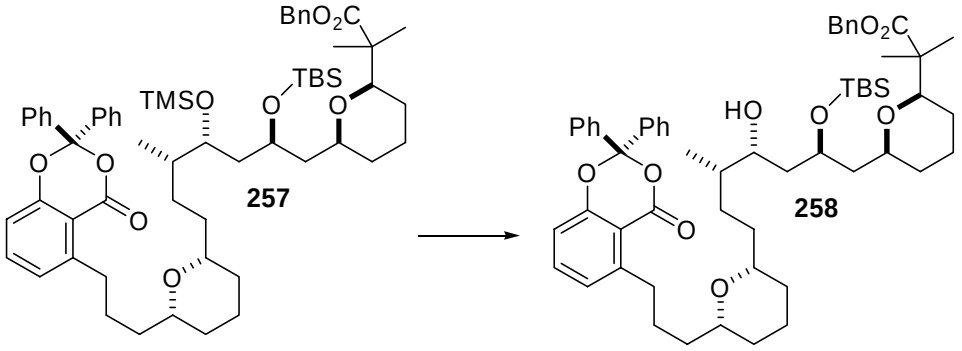
Compound 256. To a stirred solution of alcohol **2** (1.3 g, 2.05 mmol) and Et_3N (5.6 mL, 41.0 mmol), in CH_2Cl_2 (15 mL) at 0 ˚C was added TMSCl (2.6 mL, 20.5 mmol). The reaction was brought to ambient temperature and stirred for 12 hr. The reaction solution was poured into water (100 mL) and extracted with Et_2O (3 × 150 mL). The organic phase was dried over $MgSO_4$, concentrated, and purified by FC (5/95, EtOAc/Hex) to afford 1.2 g (84%) of **256**. $[\alpha]_D$ = +11.5 ($CHCl_3$, *c* 1.0). IR (film) 2936, 2858, 1738, 1472, 1388, 1251, 1086, 838, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.30 (5H, m), 5.77 (1H, dddd, *J* = 7.2, 7.2, 10.4, 17.2 Hz), 5.06 (1H, d, *J* = 12.8 Hz), 5.02 (1H, d, *J* = 12.8 Hz), 4.97 (1H, app d, *J* = 17.2 Hz), 4.92 (1H, app d, *J* = 9.6 Hz), 3.82–3.90 (1H, m),

3.70–3.74 (1H, m), 3.37 (1H, d, *J* = 10.0 Hz), 3.27–3.32 (1H, m), 3.16–3.24 (1H, m), 3.09–3.15 (1H, m), 2.19–2.28 (1H, m), 2.05–2.10 (1H, m), 1.60–1.77 (3H, m), 1.46–1.53 (3H, m), 1.23–1.43 (9H, m), 1.17 (3H, s), 1.07 (3H, s), 0.94–1.20 (6H, m), 0.81 (9H, s), 0.75 (3H, d, *J* = 6.4 Hz), 0.01 (9H, s), -0.01 (3H, s), -0.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 136.6, 135.6, 128.6, 128.1, 128.0, 116.4, 81.9, 78.5, 77.7, 75.2, 73.5, 67.3, 66.2, 47.0, 45.9, 41.3, 40.2, 39.4, 34.9, 32.2, 31.7, 31.4, 29.1, 26.2, 25.9, 23.9, 23.0, 19.9, 18.3, 14.1, 1.1, -3.4, -3.9. MS (ES) *m/z* (%): 739.50 ($[MNa]^+$, 5), 645.45 ($[MH_2$-TMS$]^+$, 100).



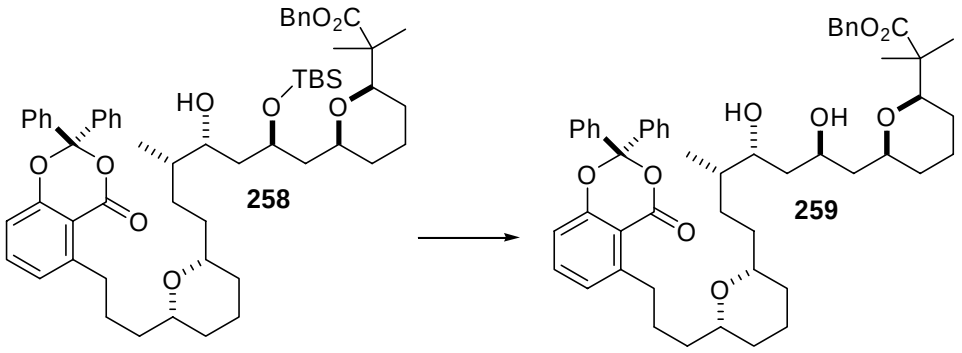
Compound 257. To a roundbottom flask charged with bis-silyl ether **256** (292 mg, 0.408 mmol) and solid 9-BBN (100 mg, 0.816 mmol) was added freshly distilled and degassed THF (2 mL). The reaction was allowed to stir at ambient temperature for 17 hr. To this solution was added aqueous 3 M K_3PO_4 (340 μL, 1.02 mmol), followed by a solution of **93c** (275 mg, 0.612 mmol) and $PdCl_2$dppf (16.6 mg, 0.204 mmol) in degassed DMF (2 mL). After 3 hr the reaction was poured into water (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (5/95→15/85 EtOAc/Hex) rapidly (to avoid silyl deprotection) to afford 363 mg (87%) of **257**. $[\alpha]_D$ = +9.2 ($CHCl_3$, *c* 1.0). IR (film) 2934, 2857, 1742, 1607,

1580, 1266, 1206, 1091, 837, 775, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.51 (4H, m), 7.20–7.30 (12H, m), 6.90 (1H, d, *J* = 8.4 Hz), 6.74 (1H, d, *J* = 8.0 Hz), 5.06 (1H, d, *J* = 12.4 Hz), 5.02 (1H, d, *J* = 12.4 Hz), 3.83–3.86 (1H, m), 3.68–3.72 (1H, m), 3.38 (1H, d, *J* = 10.8 Hz), 3.24–3.32 (1H, m), 3.04–3.13 (2H, m), 2.93–3.01 (1H, m), 2.83–2.90 (1H, m), 1.77–1.82 (2H, m), 1.68–1.75 (2H, m), 1.44–1.54 (4H, m), 1.23–1.42 (13H, m), 1.17 (3H, s), 1.07 (3H, s), 0.94–1.06 (4H, m), 0.78 (9H, s), 0.75 (3H, d, *J* = 6.8 Hz), 0.01 (9H, s), -0.03 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 160.4, 157.7, 148.6, 140.0, 136.6, 135.4, 129.3, 129.2, 128.7, 128.1, 128.0, 126.8, 126.7, 125.7, 115.6, 113.6, 106.0, 81.9, 78.3, 77.9, 75.2, 73.4, 67.3, 66.2, 47.0, 45.9, 40.3, 39.4, 36.3, 34.9, 34.4, 32.2, 31.8, 31.7, 29.0, 26.9, 26.2, 26.0, 24.0, 23.9, 23.0, 19.9, 18.3, 14.2, 1.1, -3.4, -3.9. MS (ES) *m/z* (%): 969.65 ($[MHNa\text{-}TMS]^+$, 90).



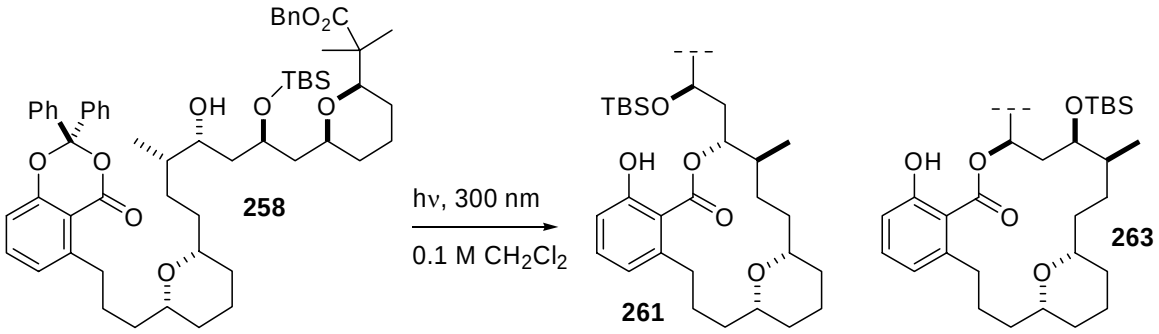
Compound 258. To a stirred solution of bis-silyl ether **257** (322 mg, 0.316 mmol) in THF (5 mL) was added a solution of HF·pyridine [1 mL from a stock solution composed of 70% HF·pyridine (2.15 mL), pyridine (10.75 mL), and THF (29 mL)]. After 1 h at ambient temperature the reaction was poured into water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (1/9 EtOAc/Hex) to afford 264 mg (88%) of **258**. $[\alpha]_D$ = +1.3 ($CHCl_3$,

c 1.0). IR (film) 3498, 2933, 2858, 1739, 1607, 1580, 1474, 1454, 1290, 1267, 1210, 1092, 911, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.52 (4H, m), 7.18–7.30 (12H, m), 6.90 (1H, d, *J* = 8.0 Hz), 6.75 (1H, d, *J* = 7.2 Hz), 5.07 (1H, d, *J* = 12.8 Hz), 4.98 (1H, d, *J* = 12.4 Hz), 4.10–4.17 (1H, m), 3.60–3.67 (1H, m), 3.43 (1H, d, *J* = 10.0 Hz), 3.05–3.18 (3H, m), 2.93–3.01 (1H, m), 2.83–2.92 (1H, m), 1.68–1.79 (3H, m), 1.61–1.65 (2H, m), 1.30–1.56 (12H, m), 0.96–1.24 (8H, m), 1.13 (3H, s), 1.05 (3H, s), 0.81 (9H, s), 0.77 (3H, d, *J* = 6.4 Hz), -0.04 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 160.4, 157.7, 148.5, 140.0, 136.5, 135.4, 129.2, 128.8, 128.6, 128.1, 128.0, 127.8, 126.8, 125.6, 117.3, 115.6, 113.6, 106.0, 82.2, 78.4, 77.8, 75.2, 71.9, 68.6, 66.2, 46.9, 42.6, 39.1, 36.4, 36.3, 34.3, 32.2, 31.8, 31.7, 28.2, 26.8, 26.0, 25.2, 23.9, 23.8, 21.4, 20.4, 18.1, 15.2, -4.5, -4.8. MS (ES) *m/z* (%): 969.50 ($[MNa]^+$, 65).



Compound 259. To a stirred solution of silyl ether **258** (20 mg, 0.021 mmol) was added pyridine (0.020 mL, 0.25 mmol) followed by 70% HF·pyridine (0.020 mL). The reaction was allowed to stir for 10 hr at room temperature. The reaction was diluted with Et_2O (20 mL) and extracted with Et_2O (3 × 20 mL) from saturated $CuSO_4$ (20 mL). The combined organic phase was dried over Na_2SO_4, filtered, and purified by FC (1/3 EtOAc/Hex) to

afford 11.5 mg (66%) of diol **259**. $[\alpha]_D$ = +4.8 ($CHCl_3$, *c* 0.58). IR (film) 3500, 2936, 1732, 1607, 1581, 1455, 1267, 1207, 1093, 1046, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.59 (4H, m), 7.27–7.38 (12H, m), 6.98 (1H, d, *J* = 8.4 Hz), 6.82 (1H, d, *J* = 7.6 Hz), 5.17 (1H, d, *J* = 12.4 Hz), 5.08 (1H, d, *J* = 12.4 Hz), 4.04–4.10 (1H, m), 3.73 (1H, app t, *J* = 6.8 Hz), 3.61 (1H, d, *J* = 11.2 Hz), 3.53–3.59 (1H, m), 3.13–3.22 (2H, m), 2.97–3.22 (1H, m), 2.91–2.97 (1H, m), 1.68–1.88 (3H, m), 1.54–1.64 (4H, m), 1.38–1.54 (12H, m), 0.99–1.32 (6H, m), 1.19 (3H, s), 1.15 (3H, s), 0.85 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 160.5, 157.7, 148.6, 140.0, 136.4, 135.5 129.3, 129.2, 128.7, 128.6, 126.7, 125.7, 115.6, 113.6, 106.0, 83.1, 80.4, 78.5, 77.8, 72.5, 70.7, 66.7, 46.8, 42.6, 39.1, 38.9, 36.3, 34.4, 34.3, 32.1, 31.8, 31.7, 28.3, 26.9, 25.0, 24.0, 23.4, 21.9, 20.1, 15.4. MS (ES) *m/z* (%): 833.50 ($[MH]^+$, 100), 855.45 ($[MNa]^+$, 40).

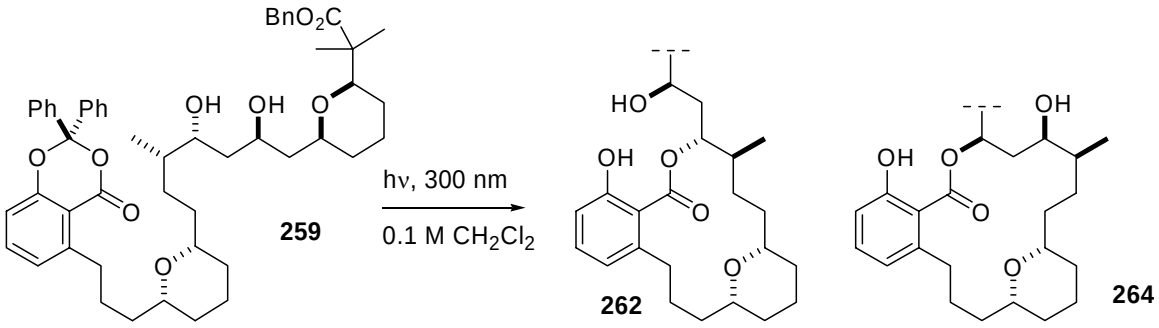


Photolysis of 258 (representative procedure). The starting material **258** was first dried via azeotropic removal of water with benzene (2 × 1 mL) *in-vacuo*. Then alcohol **258** was taken up in freshly distilled CH_2Cl_2 (0.3 mL) and transferred under nitrogen to a flame dried borosilicate test tube fitted with a rubber septum. This solution was then photolyzed for 1 hr at 300 nm. The solvent was then removed and the crude mixture was purified

directly by FC (3/97→15/85 EtOAc/Hex gradient) to afford 11 mg (45%) of **261**, and 2.2 mg (9%) of **263**.

261: $[\alpha]_D$ = -15.1 ($CHCl_3$, *c* 0.55). IR (film) 3401, 2931, 2856, 1725, 1654, 1456, 1259, 1089, 1048, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (1H, s), 7.25–7.37 (4H, m), 7.15–7.22 (2H, m), 6.77 (1H, d, *J* = 8.4 Hz), 6.75 (1H, d, *J* = 7.6 Hz), 5.12–5.18 (1H, m), 5.10 (1H, d, *J* = 12.8 Hz), 5.05 (1H, d, *J* = 12.8 Hz), 3.98–4.04 (1H, m), 3.45 (1H, dd, *J* = 1.6, 11.2 Hz), 3.19–3.38 (4H, m), 2.73 (1H, td, *J* = 3.6, 13.6 Hz), 2.14–2.23 (1H, m), 1.62–1.89 (6H, m), 1.32–1.58 (12H, m), 1.03–1.31 (6H, m), 1.10 (3H, s), 1.08 (3H, s), 0.88 (9H, s), 0.86–0.88 (3H, m), 0.07 (3H, s), 0.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 169.5, 157.9, 145.0, 132.4, 128.8, 128.7, 128.1, 127.8, 127.5, 121.1, 117.8, 115.2, 82.1, 80.2, 78.7, 77.3, 75.1, 66.8, 66.4, 47.0, 44.9, 38.0, 37.0, 36.1, 33.7, 33.1, 32.7, 32.6, 32.2, 31.5, 28.7, 26.3, 26.2, 25.4, 24.3, 23.8, 21.1, 21.0, 18.4, 14.9, -4.0, -4.6. MS (ES) *m/z* (%): 787.50 ($[MNa]^+$, 100).

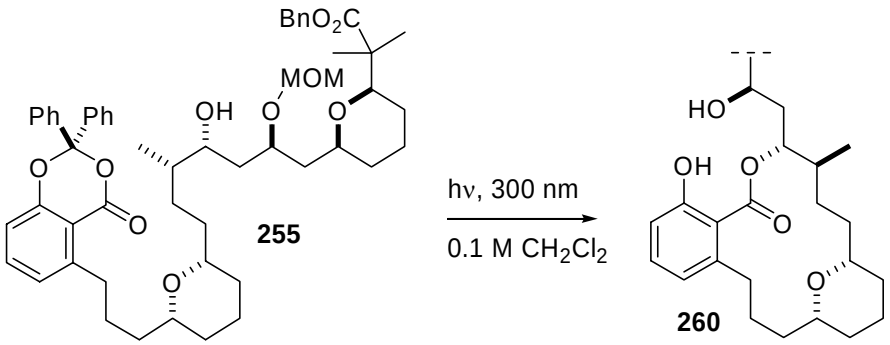
263: ^1H NMR (400 MHz, $CDCl_3$) δ 11.24 (1H, s), 7.24–7.36 (6H, m), 6.82 (1H, d, *J* = 7.2 Hz), 6.69 (1H, d, *J* = 7.2 Hz), 5.52–5.58 (1H, m), 5.10 (2H, s), 3.73–3.76 (1H, m), 3.48 (1H, d, *J* = 10.0 Hz), 3.40–3.47 (1H, m), 3.26 (1H, app t, *J* = 9.2 Hz), 3.13–3.21 (1H, m), 3.00–3.06 (1H, m), 2.73–2.80 (1H, m), 1.92–1.99 (3H, m), 1.72–1.86 (5H, m), 1.34–1.62 (12H, m), 1.06–1.30 (5H, m), 1.23 (3H, s), 1.14 (3H, s), 0.88 (9H, s), 0.85 (3H, d, *J* = 6.4 Hz), 0.03 (6H, s). MS (ES) *m/z* (%): 787.45 ($[MNa]^+$, 100).



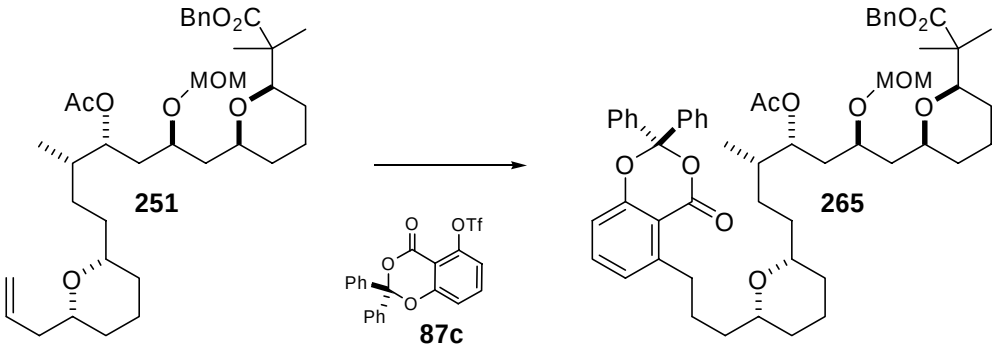
Photolysis of 259. According to the general procedure, compound **259** was photolyzed to produce a mixture of lactones **262** (26%) and **264** (12%), and recovered starting material **259** (30%).

262: $[\alpha]_D$ = -12.0 ($CHCl_3$, *c* 0.11). IR (film) 3369, 2931, 2857, 1723, 1606, 1580, 1455, 1262, 1092, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.33 (1H, *br* s), 7.28–7.36 (5H, m), 7.21 (1H, t, *J* = 8.0 Hz), 6.74 (2H, d, *J* = 8.0 Hz), 5.22 (1H, ddd, *J* = 3.2, 8.8, 8.8 Hz), 5.15 (1H, d, *J* = 12.4 Hz), 5.11 (1H, d, *J* = 12.8 Hz), 3.87–3.95 (1H, m), 3.56 (1H, d, *J* = 10.8 Hz), 3.48–3.55 (1H, m), 3.31 (1H, app t, *J* = 10.0 Hz), 3.25 (1H, app t, *J* = 10.4 Hz), 3.11–3.20 (1H, m), 2.79 (1H, td, *J* = 3.6, 12.4 Hz), 2.08–2.17 (1H, m), 1.08–1.88 (24H, m), 1.15 (3H, s), 1.11 (3H, s), 0.90 (3H, d, *J* = 6.8 Hz). MS (ES) *m/z* (%): 651.45 ($[MH]^+$, 100).

264: $[\alpha]_D$ = -18.3 ($CHCl_3$, *c* 0.06). IR (film) 3437, 2931, 2856, 1732, 1652, 1456, 1374, 1252, 1212, 1087, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.24 (1H, s), 7.23–7.35 (6H, m), 6.82 (1H, d, *J* = 8.4 Hz), 6.69 (1H, d, *J* = 6.8 Hz), 5.61–5.69 (1H, m), 5.18 (1H, d, *J* = 12.4 Hz), 5.10 (1H, d, *J* = 12.8 Hz), 3.52 (1H, dd, *J* = 1.8, 10.8 Hz), 3.48–3.54 (1H, m), 3.39–3.46 (1H, m), 3.23 (1H, app t, *J* = 9.6 Hz), 3.12 (1H, app t, *J* = 10.0 Hz), 2.98–3.06 (1H, m), 2.84–2.92 (1H, m), 1.98–2.06 (2H, m), 1.70–1.89 (4H, m), 1.08–1.70 (19H, m), 1.19 (3H, s), 1.11 (3H, s), 0.83 (3H, d, *J* = 6.8 Hz). MS (ES) *m/z* (%): 651.40 ($[MH]^+$, 100).

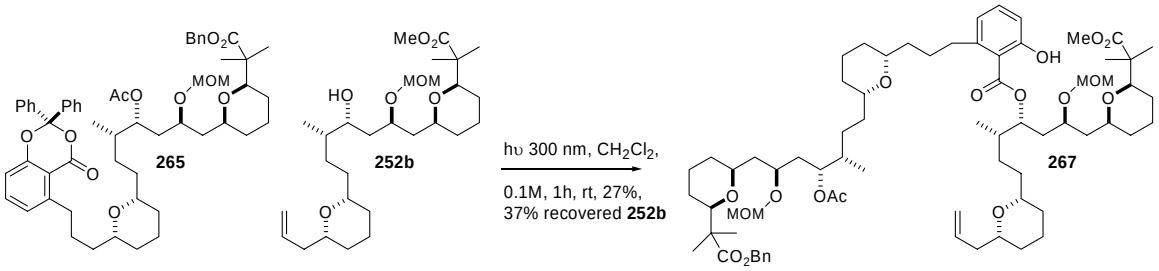


Photolysis of 255. According to the general procedure, compound **255** was photolyzed to produce lactone **260** (34%) and recovered starting material **255** (16%). $[\alpha]_D$ = -28.8 ($CHCl_3$, *c* 0.35). IR (film) 3392, 2933, 1722, 1608, 1456, 1263, 1092, 1035, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (1H, s), 7.29–7.36 (5H, m), 7.19 (1H, t, *J* = 8.0 Hz), 6.75 (2H, app t, *J* = 8.8 Hz), 5.20 (1H, app dd, *J* = 6.4, 9.6 Hz), 5.08 (2H, s), 4.60 (1H, d, *J* = 7.2 Hz), 4.56 (1H, d, *J* = 6.8 Hz), 3.86–3.93 (1H, m), 3.43 (1H, d, *J* = 10.0 Hz), 3.20–3.38 (4H, m), 3.33 (3H, s), 2.60 (1H, td, *J* = 4.0, 13.6 Hz), 2.20–2.28 (1H, m), 1.69–1.93 (6H, m), 1.35–1.65 (12H, m), 1.03–1.27 (6H, m), 1.12 (3H, s), 1.08 (3H, s), 0.87 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 168.9, 156.9, 144.4, 136.5, 132.1, 128.7, 128.1, 127.9, 121.2, 118.4, 115.2, 96.1, 82.5, 80.3, 77.4, 77.1, 75.1, 72.7, 66.3, 56.1, 46.9, 40.6, 36.7, 36.0, 33.9, 33.6, 33.0, 32.6, 32.5, 32.1, 31.8, 31.2, 28.5, 25.4, 24.2, 23.8, 21.1, 14.3. MS (ES) *m/z* (%): 717.45 ($[MNa]^+$, 100).



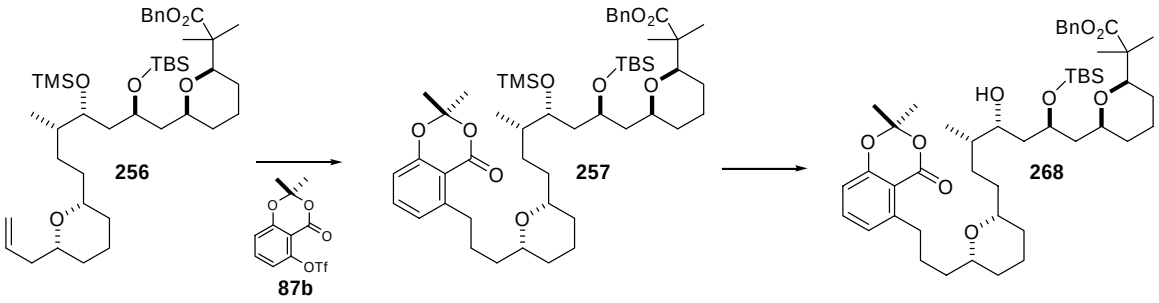
Compound 265. To a roundbottom flask containing **251** (33 mg, 0.053 mmol) was added solid 9-BBN (13 mg, 0.106 mmol) followed by THF (0.4 mL) under N_2. The reaction was allowed to stir for 12 hr at ambient temperature. Then an aqueous solution of K_3PO_4 (0.053 mL, 0.159 mmol) was added followed by a solution of $PdCl_2$dppf (4.3 mg, 0.0053 mmol) and triflate **87c** (48 mg, 0.106 mmol) in anhydrous DMF (0.4 mL). The reaction was allowed to stir for 4 hr at ambient temperature. The reaction was then poured into H_2O (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (15/85, EtOAc/Hex) to afford 28 mg (58%) yield of **265**. $[\alpha]_D$ = -0.75 ($CHCl_3$, *c* 0.88). IR (film) 3521, 2935, 1738, 1607, 1581, 1455, 1266, 1093, 1044, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.59 (4H, m), 7.26–7.38 (12H, m), 6.98 (1H, d, *J* = 8.0 Hz), 6.82 (1H, d, *J* = 7.6 Hz), 5.11 (2H, s), 4.97–5.02 (1H, m), 4.60 (1H, d, *J* = 6.8 Hz), 4.51 (1H, d, *J* = 6.8 Hz), 3.61–3.67 (1H, m), 3.44–3.48 (1H, app d, *J* = 10.8 Hz), 3.30–3.40 (4H, m), 3.13–3.21 (2H, m), 3.00–3.08 (1H, m), 2.90–2.98 (1H, m), 1.97 (3H, s), 1.67–1.85 (6H, m), 1.37–1.64 (12H, m), 1.02–1.28 (7H, m), 1.22 (3H, s), 1.14 (3H, s), 0.85 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 171.4, 170.9, 160.4, 157.7, 148.5, 140.0, 136.6, 135.4, 132.6, 130.3, 129.3, 129.2, 128.6, 128.1, 128.0, 126.8, 126.7, 125.7, 115.6, 113.6, 106.0, 96.5, 82.3, 78.0, 77.8, 74.9, 74.5, 72.4, 66.2, 56.0, 46.9, 42.3, 36.7, 36.3, 35.1,

34.3, 32.1, 31.8, 28.6, 26.8, 25.7, 23.9, 23.8, 22.2, 21.4, 20.4, 14.8. MS (ES) *m/z* (%): 941.70 ([MNa]$^+$, 65).



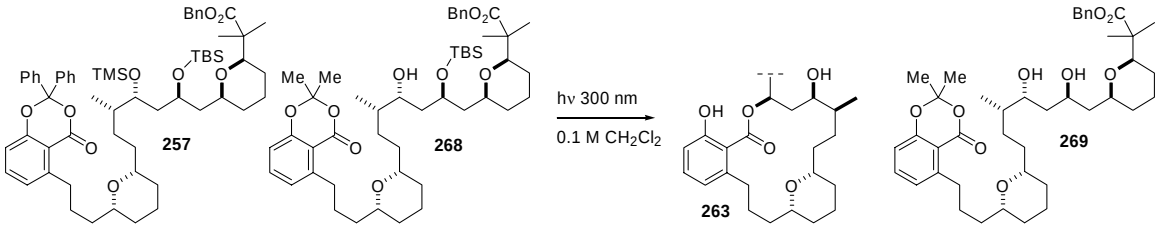
Compound 267. To an oven-dried glass test tube was added **265** (59 mg, 0.064 mmol) and alcohol **252b** (76 mg, 0.153 mmol). The reaction vessel was sealed with a rubber stopper and **265** and **252b** were dissolved in CH_2Cl_2 (0.26 mL). This solution was then photolyzed (300 nm) for 4 hr. The solvent was then removed and the crude mixture was purified directly by FC (10/90→15/85, EtOAc/Hex gradient) to afford 21 mg (27%) of **267**, 30 mg (39%) of sm **252b**. $[\alpha]_D$ = +1.85 ($CHCl_3$, *c* 1.09). IR (film) 3392, 2936, 2860, 1732, 1652, 1455, 1373, 1248, 1089, 1041, 918 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (1H, s), 7.23–7.38 (5H, m), 6.80 (1H, d, *J* = 8.4 Hz), 6.72 (1H, d, *J* = 7.2 Hz), 5.80 (1H, dddd, *J* = 7.2, 7.2, 9.6, 16.8 Hz), 5.41–5.47 (1H, m), 5.11 (2H, s), 4.94–5.08 (3H, m), 4.57–4.65 (2H, m), 4.50–4.55 (2H, m), 3.62–3.73 (2H, m), 3.59 (3H, s), 3.18–3.48 (8H, m), 3.33 (3H, s), 3.32 (3H, s), 2.87–2.93 (2H, m), 2.22–2.34 (1H, m), 2.08–2.17 (1H, m), 1.98 (3H, s), 1.34–1.92 (28H, m), 1.04–1.28 (10H, m), 1.22 (3H, s), 1.14 (3H, s), 1.09 (3H, s), 1.05 (3H, s), 0.96 (3H, d, *J* = 6.4 Hz), 0.85 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 176.7, 171.0, 162.1, 145.4, 136.6, 135.5, 133.8, 128.7, 128.2, 122.3, 116.4, 115.8, 113.2, 96.5, 96.3, 82.3, 82.1, 78.1, 77.9, 77.6, 75.0, 74.7, 74.4, 72.6, 72.3, 66.2, 56.1, 56.0, 51.9, 46.9, 46.8, 42.3, 42.0, 41.2, 37.0, 36.9, 36.7, 36.1, 35.7, 35.1,

34.3, 32.3, 32.2, 32.0, 31.7, 31.4, 28.8, 28.6, 28.2, 25.7, 23.8, 22.2, 22.1, 21.4, 20.4, 20.3, 15.2, 14.7. MS (ES) *m/z* (%): 1257.75 ($[MNa]^+$, 40).



Alcohol 268. To a round bottom flask charged with bis-silyl ether **256** (200 mg, 0.28 mmol) and solid 9-BBN (41 mg, 0.34 mmol) was added freshly distilled THF (1.0 mL). The reaction was allowed to stir for 17 hr at ambient temperature. Then a degassed solution of 3 M K_3PO_4 (0.23 mL, 0.70 mmol) was added, followed by a solution of triflate **87b** (136 mg, 0.42 mmol) and $PdCl_2$dppf (12 mg, 0.014 mmol) in degassed DMF (1.5 mL). The reaction was allowed to stir for 12 hr at ambient temperature at which time the reaction was diluted with Et_2O (20 mL) and extracted with Et_2O (3 × 30 mL) from water (30 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (5/95 EtOAc/Hex) to yield 163 mg (65%) of coupled bis-silyl ether which was taken up in THF (5 mL) and treated with HF·pyridine [1 mL from a stock solution composed of 70% HF·pyridine (2.15 mL), pyridine (10.75 mL), and THF (29 mL)] for 0.5 h. The reaction was then quenched by addition of saturated $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 40 mL) from water (30 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (13/87 EtOAc/Hex) to afford 140 mg (95%) of **268**. $[\alpha]_D$ = -1.1 ($CHCl_3$, *c* 0.80). IR (film) 3514, 2933, 2858, 1739, 1606, 1582, 1476, 1389, 1314, 1269, 1210, 1086, 1046, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

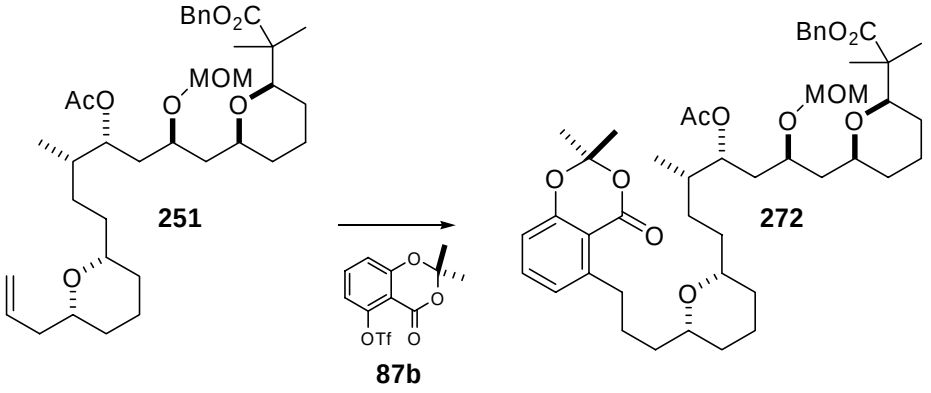
7.27–7.39 (6H, m), 6.92 (1H, d, *J* = 7.6 Hz), 6.77 (1H, d, *J* = 8.0 Hz), 5.13 (1H, d, *J* = 12.4 Hz), 5.04 (1H, d, *J* = 12.8 Hz), 4.16–4.23 (1H, m), 3.66–3.72 (1H, m), 3.49 (1H, s), 3.48 (1H, d, *J* = 9.6 Hz), 3.16–3.30 (3H, m), 3.04–3.12 (2H, m), 1.72–1.86 (3H, m), 1.68 (6H, s), 1.39–1.64 (16H, m), 1.08–1.24 (6H, m), 1.18 (3H, s), 1.11 (3H, s), 0.86 (9H, s), 0.82 (3H, d, *J* = 6.8 Hz), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 160.4, 157.3, 148.4, 136.5, 128.7, 128.2, 127.8, 125.4, 115.3, 112.3, 105.1, 82.2, 78.4, 77.9, 75.3, 72.0, 68.7, 66.3, 47.0, 42.6, 39.1, 36.6, 36.4, 34.4, 34.3, 32.2, 31.9, 31.7, 28.2, 27.3, 26.0, 25.9, 25.8, 25.2, 24.0, 23.8, 21.4, 20.5, 18.1, 15.2, -4.5, -4.8. MS (ES) *m/z* (%): 845.40 ($[MNa]^+$, 100).



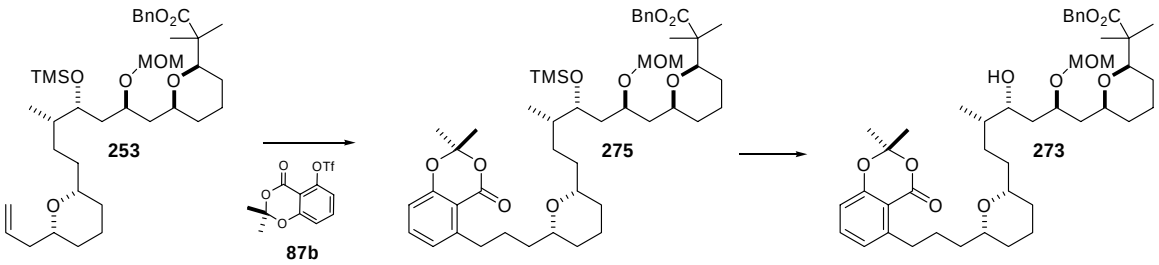
Photolysis of 257 in the presence of alcohol 268. According to the general procedure, photolysis of a mixture of **257** (1 equiv) and **268** (3 equiv) produced a mixture of lactone **263** (10%), diol **269** (65%) and recovered starting material **268** (10%).

269: $[\alpha]_D$ = -8.8 ($CHCl_3$, *c* 0.39). IR (film) 3480, 2935, 2860, 1737, 1606, 1582, 1455, 1314, 1269, 1210, 1083, 1044 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.40 (6H, m), 6.93 (1H, d, *J* = 8.0 Hz), 6.78 (1H, d, *J* = 8.4 Hz), 5.16 (1H, d, *J* = 12.4 Hz), 5.08 (1H, d, *J* = 12.8 Hz), 4.03–4.10 (1H, m), 3.83 (1H, s), 3.70–3.75 (1H, m), 3.61 (1H, d, *J* = 11.2 Hz), 3.53–3.62 (1H, m), 3.17–3.30 (3H, m), 3.05–3.12 (2H, m), 1.72–1.88 (4H, m), 1.69 (6H, s), 1.53–1.66 (8H, m), 1.40–1.52 (8H, m), 1.08–1.33 (5H, m), 1.19 (3H, s), 1.15

(3H, s), 0.85 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 160.5, 157.3, 148.5, 136.4, 135.3, 128.7, 128.3, 125.5, 115.3, 112.2, 105.2, 83.1, 80.4, 78.5, 77.8, 72.5, 70.7, 66.7, 46.8, 42.6, 39.1, 38.9, 36.6, 34.4, 34.3, 32.2, 31.9, 31.8, 28.3, 27.3, 25.9, 25.8, 25.0, 24.0, 23.4, 21.9, 20.1, 15.4. MS (ES) *m/z* (%): 731.35 ([MNa]$^+$, 100).

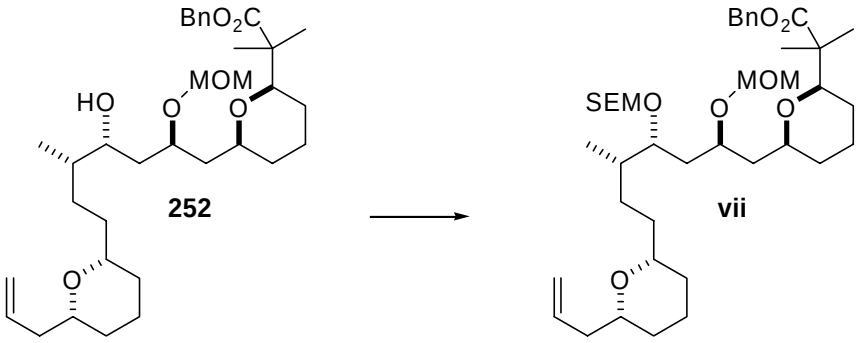


Compound 272. Prepared according to the procedure for **257 (**21-68%). $[\alpha]_D$ = +2.4 ($CHCl_3$, *c* 3.3). IR (film) 2936, 2860, 1738, 1606, 1582, 1477, 1456, 1378, 1314, 1270, 1245, 1149, 1087, 1042, 922 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.39 (6H, m), 6.91 (1H,d, *J* = 7.6 Hz), 6.77 (1H, d, *J* = 8.4 Hz), 5.10 (2H, s), 4.98 (1H, app dd, *J* = 4.0, 10.0 Hz), 4.58 (1H, d, *J* = 6.8 Hz), 4.50 (1H, d, *J* = 6.8 Hz), 3.60–3.67 (1H, m), 3.45 (1H, d, *J* = 10.4 Hz), 3.32–3.38 (2H, m), 3.31 (3H, s), 3.16–3.28 (2H, m), 3.08 (2H, t, *J* = 6.8 Hz), 1.97 (3H, s), 1.35–1.84 (20H, m), 1.68 (6H, s), 1.04–1.28 (4H, m), 1.21 (3H, s), 1.13 (3H, s), 0.83 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 170.8, 160.4, 157.3, 148.8, 136.6, 128.6, 128.1, 127.9, 125.4, 115.3, 112.1, 105.1, 96.5, 82.3, 78.0, 77.8, 74.9, 74.5, 72.4, 66.2, 56.0, 46.8, 42.3, 36.7, 36.6, 35.2, 34.4, 32.0, 31.9, 31.8, 28.6, 27.3, 25.9, 25.8, 25.7, 23.9, 23.8, 22.1, 21.3, 20.4, 14.7. MS (ES) *m/z* (%): 817.50 ([MNa]$^+$, 100).

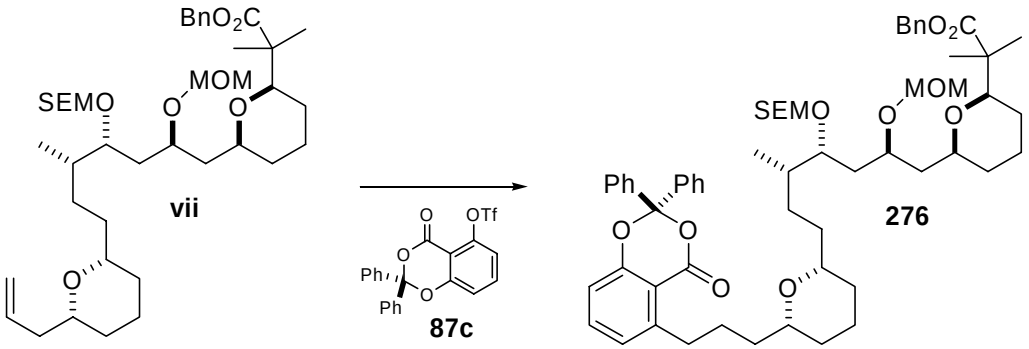


Compound 273. To an ovendried roundbottom flask charged with silyl ether **253** (150 mg, 0.232 mmol) and solid 9-BBN (71 mg, 0.58 mmol) was added THF (1 mL). The reaction was allowed to stir under nitrogen at ambient temperature for 14 hr. At that time an aqueous solution of 3 M K_3PO_4 (155 μL, 0.464 mmol) was added, followed by a solution of $PdCl_2$dppf (9.5 mg, 0.0116 mmol), and **87b** (113 mg, 0.348 mg) in DMF (1 mL). After 24 hr at ambient temperature the reaction was diluted with water (30 mL), and extracted with Et_2O (2 × 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and filtered through a short pad of silicagel (1/4 EtOAc/Hex). After concentration, the residue was treated with HF·pyridine [5 mL from a stock solution composed of 70% HF·pyridine (2.15 mL), pyridine (10.75 mL), and THF (29 mL)]. After 1.5 hr the reaction was poured into water (30 mL), and extracted with Et_2O (2 × 40 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (3/7, EtOAc/Hex) to afford 148 mg (85% for two steps) of **273**. $[\alpha]_D$ = +2.0 ($CHCl_3$, *c* 1.7). IR (film) 3402, 2518, 1655, 1456, 1173, 1031, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, t, *J* = 8.0 Hz), 7.27–7.40 (5H, m), 6.93 (1H, d, *J* = 7.2 Hz), 6.78 (1H, d, *J* = 8.0 Hz), 5.12 (2H, s), 4.61 (1H, d, *J* = 6.4 Hz), 4.58 (1H, d, *J* = 6.4 Hz), 3.90–4.00 (1H, m), 3.63–3.69 (1H, m), 3.51 (1H, d, *J* = 10.0 Hz), 3.17–3.40 (2H, m), 3.35 (3H, s), 3.06–3.13 (2H, m), 2.95 (1H, m), 1.74–1.88 (3H, m), 1.69 (6H, s), 1.39–1.65 (16H, m), 1.07–1.28 (7H, m), 1.20 (3H, s), 1.12 (3H, s), 0.86 (3H, d, *J* = 6.8 Hz);

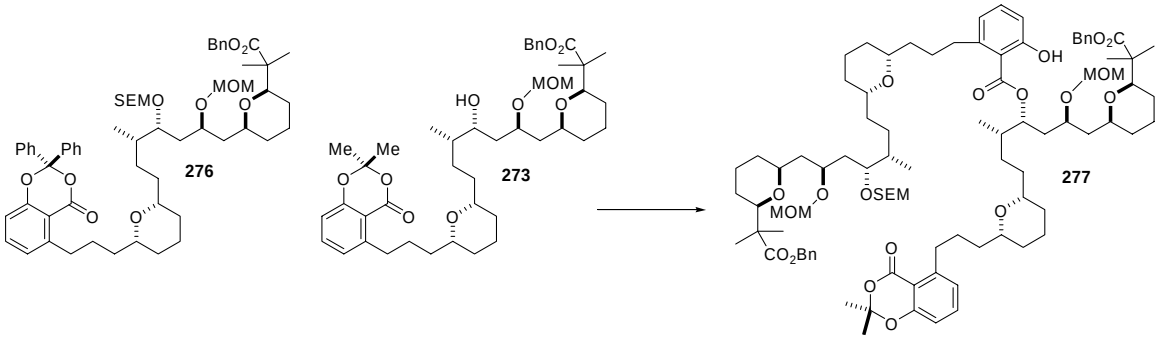
^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 160.4, 157.3, 148.4, 136.6, 135.3, 128.6, 128.1, 127.9, 125.4, 115.3, 112.2, 105.1, 96.2, 82.4, 78.5, 77.8, 75.2, 73.6, 71.7, 66.3, 56.0, 46.9, 41.4, 39.1, 37.2, 36.6, 34.4, 34.3, 32.0, 31.9, 31.7, 28.4, 27.3, 25.9, 25.8, 25.3, 23.9, 23.8, 21.4, 20.7, 15.3. MS (ES) *m/z* (%): 775.40 ([MNa]$^+$, 100).



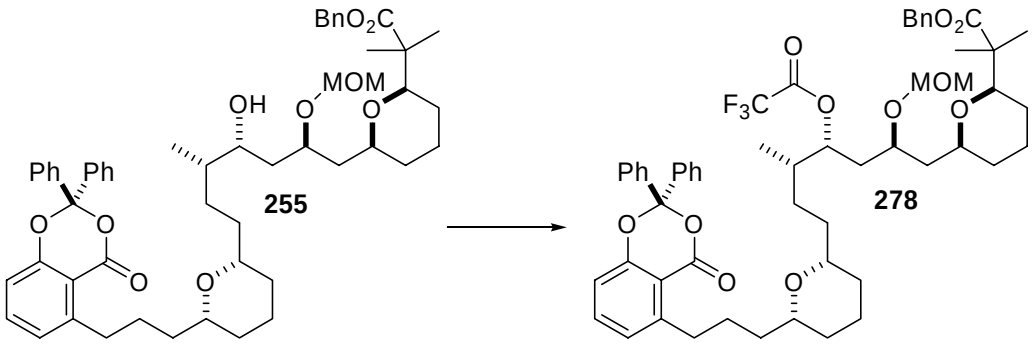
SEM Ether vii. To a stirred solution of alcohol **252** (150 mg, 0.26 mmol) in CH_2Cl_2 (4 mL) was added DIPEA (0.54 mL, 3.14 mmol) and SEMCl (0.28 mL, 1.56 mmol). The reaction was allowed to react at ambient temperature for 2 hr, then at 45 ˚C for 1 hr. The reaction was poured into H_2O (40 mL) and extracted with Et_2O (3 x 40 mL). The organic phase was then dried over $MgSO_4$, filtered, concentrated, and purified by FC (20/80, EtOAc/Hex) to afford 160 mg (87%) of **vii**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.37 (5H, m), 5.83 (1H, dddd, *J* = 7.6, 7.6, 10.4, 17.6 Hz), 5.12 (2H, s), 5.05 (1H, d, *J* = 17.2 Hz), 5.00 (1H, d, *J* = 10.0 Hz), 4.70 (1H, d, *J* = 6.8 Hz), 4.67 (1H, d, *J* = 7.2 Hz), 4.61–4.63 (2H, m), 3.78–3.84 (1H,), 3.48–3.67 (4H, m), 3.28–3.44 (1H, m), 3.36 (3H, s), 3.18–3.32 (2H, m), 2.27–2.33 (1H, m), 2.09–2.16 (1H, m), 1.77–1.85 (4H, m), 1.34–1.61 (15H, m), 1.06–1.28 (10H, m), 0.86 (3H, d, *J* = 6.4 Hz), -0.001 (9H, s).



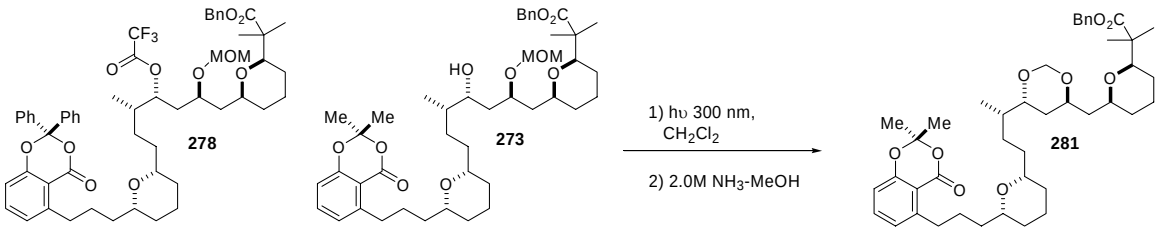
Compound 276. Prepared according to the procedure for **257** (80%). $[\alpha]_D$ = +1.23 ($CHCl_3$, *c* 1.95). IR (film) 2935, 1740, 1607, 1453, 1267, 1094, 1047, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.58 (4H, m), 7.28–7.38 (12H, m), 6.98 (1H, d, *J* = 8.0 Hz), 6.82 (1H, d, *J* = 7.6 Hz), 5.12 (2H, s), 4.58–4.70 (4H, m), 3.47–3.83 (5H, m), 3.32 (3.42 (4H, m), 3.13–3.21 (2H, m), 2.90–3.08 (2H, m), 1.37–1.83 (25H, m), 0.83–1.30 (14H, m), -0.006 (6H, s).



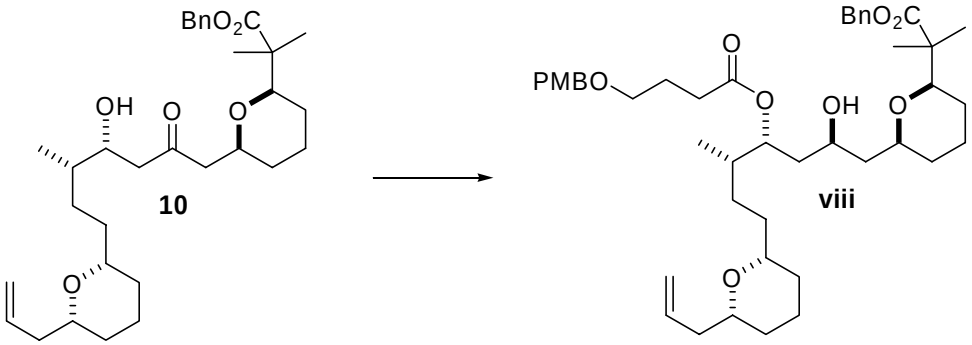
Compound 278. Prepared in a similar manner as **267** (7%). ^1H NMR (400 MHz, $CDCl_3$) δ 10.98 (1H, s), 7.29–7.38 (10H, m), 6.92 (2H, t, *J* = 7.2 Hz), 6.78 (3H, app dd, *J* = 1.6, 8.0 Hz), 6.69 (1H, d, *J* = 7.6 Hz), 5.41–5.45 (1H, m), 5.12 (3H, s), 5.07 (2H, s), 4.57–4.70 (5H, m), 3.28–3.83 (14H, m), 3.17–3.27 (4H, m), 3.05–3.09 (3H, m), 2.86–2.90 (2H, m), 1.34–1.84 (55H, m), 0.85–1.25 (24H, m), -0.001 (6H, s).



Compound 278. To a stirred solution of alcohol **255** (3.5 mg, 0.004 mmol), in CH_2Cl_2 (2 mL) was added pyridine (0.2 mL, 2.48 mmol) followed by trifluoroacetic anhydride (0.03 mL, 0.30 mmol) dropwise at 0 ˚C. After 30 min. the reaction was quenched by addition of ice cold water (10 mL), and extracted with Et_2O (3 x 30 mL). The organic phase was dired over $MgSO_4$, filtered, concentrated, and chromatographed by FC (10/90 EtOAc/Hex) to afford 3.3 mg (85%) of trifluoroacetate **278**. $[\alpha]_D$ = -2.6 ($CHCl_3$, *c* 0.17). IR (film) 2932, 2858, 1781, 1739, 1607, 1581, 1476, 1455, 1267, 1216, 1166, 1092, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.58 (4H, m), 7.27-7.36 (12H, m), 6.97 (1H, d, *J* = 8.0 Hz), 6.81 (1H, d, *J* = 8.0 Hz), 5.21 (1H, app dd, *J* = 4.4, 9.6 Hz), 5.11 (1H, d, *J* = 12.8 Hz), 4.56 (1H, d, *J* = 6.8 Hz), 4.46 (1H, d, *J* = 6.8 Hz), 3.64–3.71 (1H, m), 3.44 (1H, d, *J* = 9.6 Hz), 3.31–3.39 (1H, m), 3.28 (3H, s), 3.11–3.21 (2H, m), 3.00–3.06 (1H, m), 2.88–2.97 (1H, m), 1.74–1.92 (7H, m), 1.34-1.68 (12H, m), 0.90–1.28 (6H, m), 1.20 (3H, s), 1.12 (3H, s), 0.88 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 176.6, 160.5, 157.7, 148.5, 140.1, 136.6, 135.4, 129.3, 129.2, 128.7, 128.2, 128.0, 126.8, 126.7, 125.7, 115.7, 96.2, 82.4, 79.9, 77.9, 77.4, 74.9, 71.9, 66.2, 56.0, 46.9, 41.7, 36.5, 36.3, 34.4, 34.3, 34.2, 32.0, 31.9, 31.7, 29.9, 28.4, 26.8, 25.7, 23.9, 22.2, 20.3, 14.5. MS (ES) *m/z* (%): 995.35 ([MNa^+], 100).

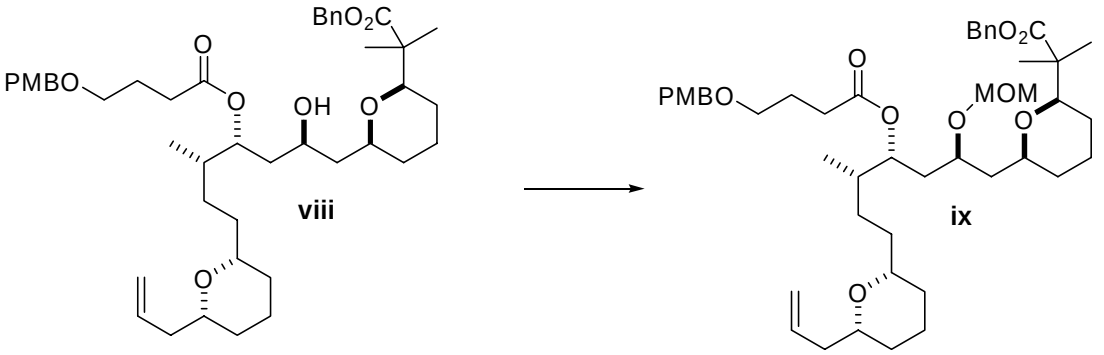


Compound 281. Prepared in a similar manner as **267** followed by treatment with 2.0M MeOH·NH_3 (25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.40 (6H, m), 6.92 (1H, d, *J* = 8.0 Hz), 6.78 (1H, d, *J* = 8.0 Hz), 5.07–5.14 (2H, m), 4.80 (1H, d, *J* = 6.0 Hz), 4.76 (1H, d, *J* = 6.4 Hz), 4.05–4.12 (1H, m), 3.51 (1H, d, *J* = 10.8 Hz), 3.43–3.49 (1H, m), 3.33–3.39 (1H, m), 3.25–3.30 (1H, m), 3.17–3.23 (1H, m), 3.06–3.11 (2H, m), 1.93–2.00 (1H, m), 1.52–1.86 (12H, m), 1.68 (6H, s), 1.40–1.50 (6H, m), 1.04–1.30 (6H, m), 1.19 (3H, s), 1.13 (3H, s), 0.82 (3H, d, *J* = 6.4 Hz). MS (ES) *m/z* (%): 743.40 ([MNa^+], 100).



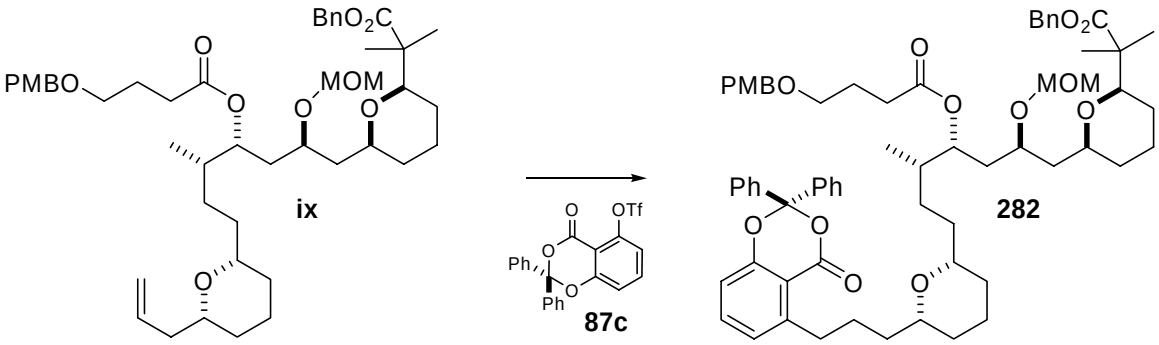
Alcohol viii. Prepared in a similar manner as **250** with 4-(4-Methoxy-benzyloxy)-butyraldehyde (97%). $[\alpha]_D$ = +7.0 ($CHCl_3$, *c* 1.0). IR (film) 3525, 2936, 2860, 1732, 1613, 1514, 1372, 1249, 1172, 1086, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.37 (5H, m), 7.24 (2H,d , *J* = 8.8 Hz), 6.87 (2H, d, *J* = 8.8 Hz), 5.83 (1H, dddd, *J* = 7.2, 7.2, 10.0, 17.2 Hz), 5.12 (1H, s), 5.11 (1H, s), 4.98–5.08 (3H, m), 4.41 (2H, s), 3.80 (3H, s), 3.65–3.71 (1H, s), 3.56 (1H, dd, *J* = 1.0, 11.2 Hz), 3.48–3.52 (1H, m), 3.46 (2H, t, *J* = 6.0 Hz), 3.24–3.31 (1H, m), 3.16–3.22 (1H, m), 2.37–2.41 (2H, m), 2.26–2.34 (1H, m), 2.08–

2.17 (1H, m), 1.88–1.93 (2H, m), 1.7–1.84 (2H, m), 1.29–1.74 (16H, m), 1.04–1.30 (4H, m), 1.18 (3H, s), 1.13 (3H, s), 0.85 (3H, d, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 173.5, 159.2, 136.5, 135.5, 130.6, 129.3, 128.5, 128.1, 116.3, 113.8, 82.8, 78.8, 78.2, 77.4, 74.8, 72.6, 69.1, 67.5, 66.4, 55.3, 46.7, 43.5, 41.1, 38.3, 36.9, 34.2, 31.9, 31.6, 31.4, 31.3, 28.2, 25.3, 25.0, 23.7, 23.4, 21.4, 20.3, 15.1. MS (ES) *m/z* (%): 759.55 ([MNa^+], 100).

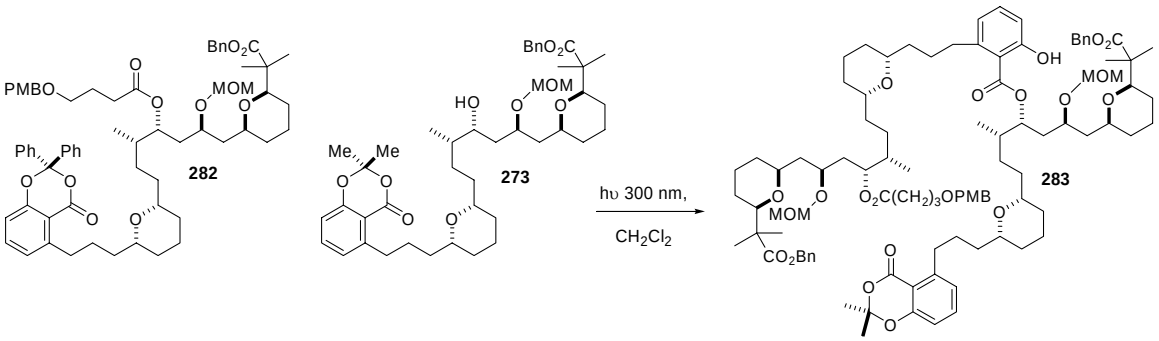


Compound ix. Prepared in a similar manner as **251** (96%). $[\alpha]_D$ = +0.5 ($CHCl_3$, *c* 1.2). IR (film) 2935, 1738, 1614, 1514, 1442, 1372, 1248, 1087, 1039, 915, 821, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.35 (5H, m), 7.23 (2H, d, J = 8.4 Hz), 6.85 (2H, d, J = 8.4 Hz), 5.83 (1H, dddd, J = 7.2, 7,2, 10.8, 17.2 Hz), 5.11 (2H, s), 4.98–5.07 (3H, m), 4.60 (1H, d, J = 6.8 Hz), 4.52 (1H, d, J = 6.4 Hz), 4.41 (2H, s), 3.78 (3H, s), 3.60–3.68 (1H, m), 3.38–3.48 (4H, m), 3.31–3.45 (1H, m), 3.33 (3H, s), 3.25–3.29 (1H, m), 3.18–3.24 (1H, m), 2.39 (2H, t, J = 7.6 Hz), 2.26–2.33 (1H, m), 2.09–2.16 (1H, m), 1.87–1.94 (2H, m), 1.68–1.85 (5H, m), 1.36–1.60 (11H, m), 1.04–1.30 (4H, m), 1.22 (3H, s), 1.14 (3H, s), 0.84 (3H, d, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 173.2, 159.2, 136.5, 130.6, 129.3, 128.6, 128.1, 127.9, 116.3, 113.9, 96.5, 82.2, 78.1, 77.5, 74.9, 74.3,

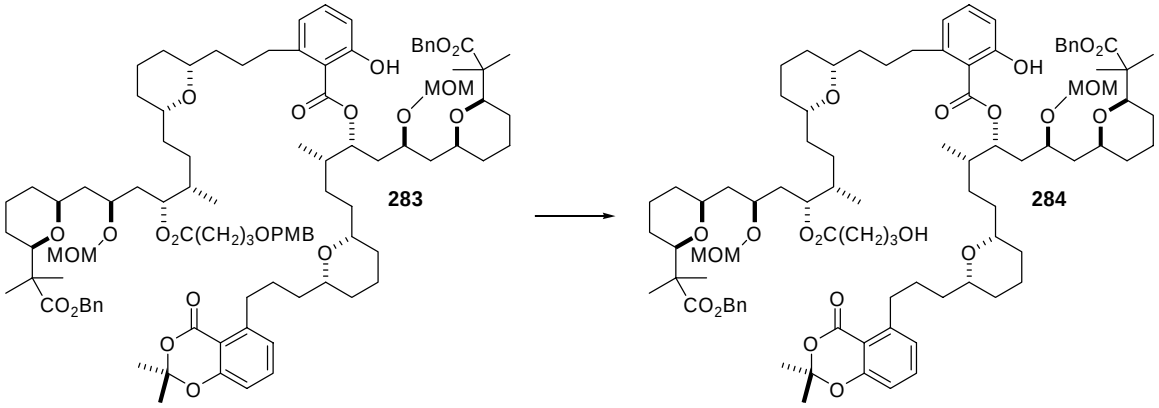
72.7, 72.4, 69.1, 66.1, 55.9, 55.3, 46.8, 42.2, 41.2, 36.7, 35.1, 34.3, 32.0, 31.6, 31.4, 31.3, 28.5, 25.6, 25.4, 23.8, 22.1, 20.4, 14.7. MS (ES) *m/z* (%): 803.40 ([MNa^+], 100).



Compound 282. Prepared in a similar manner as **257** (14%). $[\alpha]_D$ = +5.3 ($CHCl_3$, *c* 1.6). IR (film) 2934, 2859, 1732, 1608, 1580, 1514, 1455, 1266, 1094, 1038, 917, 758, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.59 (4H, m), 7.28–7.38 (12H, m), 7.23 (2H, d, *J* = 8.8 Hz), 6.98 (1H, d, *J* = 8.4 Hz), 6.85 (2H, d, *J* = 8.4 Hz), 6.82 (1H, d, *J* = 7.2 Hz), 5.11 (2H, s), 5.02 (1H app dd, *J* = 4.0, 9.6 Hz), 4.59 (1H, d, *J* = 6.4 Hz), 4.50 (1H, d, *J* = 7.2 Hz), 4.40 (2H, s), 3.78 (3H, s), 3.60–3.68 (1H, m), 3.36–3.50 (3H, m), 3.29–3.34 (1H, m), 3.31 (3H, s), 3.13–3.20 (2H, m), 3.01–3.08 (1H, m), 2.90–2.97 (1H, m), 2.38 (2H, t, *J* = 8.0 Hz), 1.86–1.93 (2H, m), 1.68–1.84 (5H, m), 1.36–1.64 (14H, m), 1.02–1.28 (6H, m), 1.22 (3H, s), 1.14 (3H, s), 0.84 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 173.2, 160.4, 159.3, 157.7, 148.5, 140.0, 136.6, 135.4, 130.7, 129.4, 129.2, 128.6, 128.1, 128.0, 126.8, 126.7, 125.7, 115.6, 113.9, 106.0, 96.5, 82.3, 78.1, 77.8, 75.0, 74.4, 72.7, 72.4, 69.2, 66.2, 56.0, 55.4, 46.9, 42.2, 37.4, 36.7, 36.2, 35.1, 34.3, 32.0, 31.8, 31.5, 29.9, 28.5, 26.8, 25.7, 25.4, 23.9, 23.8, 22.3, 21.8, 20.7, 20.4, 14.7. MS (ES) *m/z* (%): 1105.55 ([MNa^+], 100).

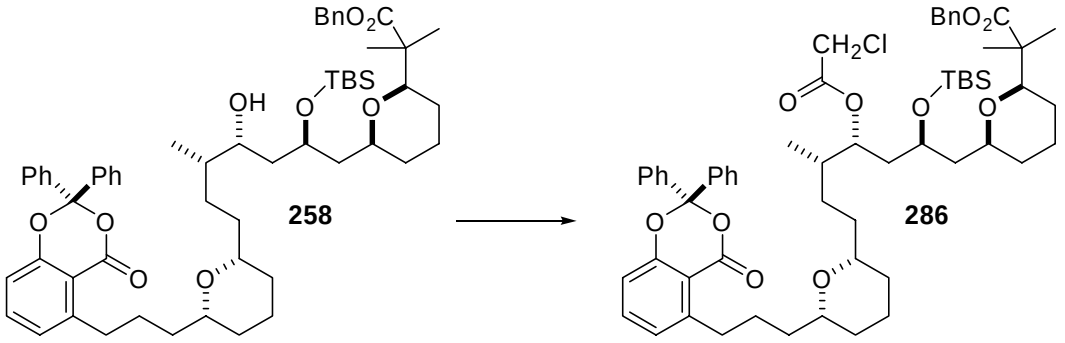


Compound 283. Prepared in a similar manner as **267** (10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (1H, s), 7.22–7.40 (13H, m), 6.92 (2H, t, *J* = 8.0 Hz), 6.85 (2H, d, *J* = 8.4 Hz), 6.78 (2H, d, *J* = 7.2 Hz), 5.41–5.45 (1H, m), 5.00–5.12 (5H, m), 4.48–4.63 (4H, m), 4.40 (2H, s), 3.96–3.99 (1H, m), 3.79 (3H, s), 3.60–3.70 (3H, m), 3.15–3.54 (14H, m), 3.05–3.09 (4H, m), 2.85–2.90 (2H, m), 2.35–2.38 (2H, m), 0.82–1.90 (74 H, m).



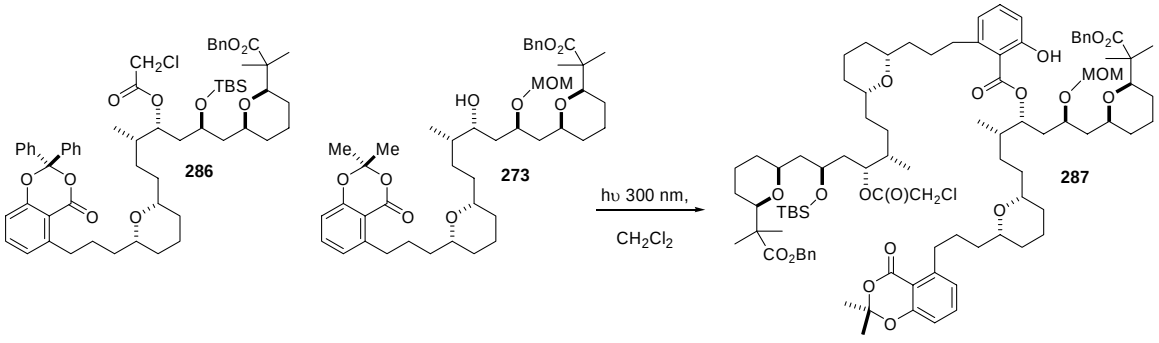
Compound 284. To a stirred solution of **283** (10 mg, 0.006 mmol) in CH_2Cl_2:H_2O (1 mL, 10:1) was added DDQ (6 mg, 0.027 mmol). The reaction was allowed to stir for 10 hr at ambient temperature prior to quenching with sat. $NaHCO_3$ (10 mL). The reaction was extracted with Et_2O (3 x 50 mL) from H_2O (30 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (35/65, EtOAc/Hex) to afford 3.5 mg (38%) of alcohol **284**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (1H, s), 7.27–7.29 (12H,

m), 6.91 (1H, d, *J* = 7.2 Hz), 6.79 (2H, dd, *J* = 1.4, 8.0 Hz), 6.69 (1H, d, *J* = 7.6 Hz), 5.41–5.44 (1H, m), 5.12 (2H, s), 5.07 (2H, s), 4.99–5.04 (1H, m), 4.49–4.60 (4H, m), 3.62–3.72 (4H, m), 3.28–3.48 (10H, m), 3.14–3.27 (4H, m), 3.07 (2H, t, *J* = 7.2 Hz), 2.84–2.90 (2H, m), 2.36–2.46 (2H, m), 1.06–1.86 (70H, m), 0.94 (3H, d, *J* = 6.8 Hz), 0.84 (3H, d, *J* = 6.8 Hz).



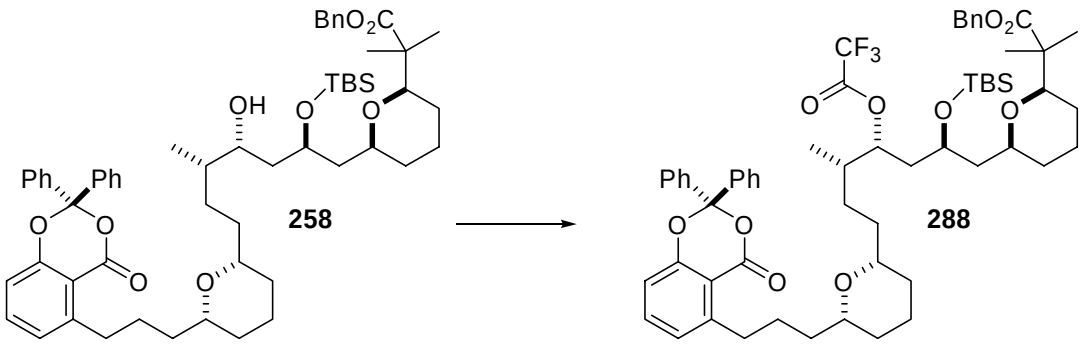
Compound 286. To a stirred solution of alcohol **258** (106 mg, 0.11 mmol) in CH_2Cl_2:Pyridine (2.5 mL, 5:1) was added chloroacetic anhydride (94 mg, 0.55 mmol). After ½ hr the reaction was poured into H_2O (30 mL) and extracted with Et_2O (3 x 25 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (15/85, EtOAc/Hex) to afford 98 mg (87%) of chloroacetate **286**. $[\alpha]_D$ = +9.8 ($CHCl_3$, *c* 1.5). IR (film) 2934, 1738, 1607, 1580, 1455, 1291, 1266, 1202, 1089, 915 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.59 (4H, m), 7.28–7.38 (12H, m), 6.98 (1H, d, *J* = 8.0 Hz), 6.82 (1H, d, *J* = 7.6 Hz), 5.03–5.14 (3H, m), 4.08 (1H, d, *J* = 14.8 Hz), 4.01 (1H, d, *J* = 14.6 Hz), 3.82–3.88 (1H, m), 3.47 (1H, d, *J* = 11.6 Hz), 3.27–3.33 (1H, m), 3.12–3.33 (1H, m), 3.02–2.09 (1H, m), 2.90–2.97 (1H, m), 1.68–1.83 (5H, m), 1.36–1.52 (12H, m), 1.02–1.28 (8H, m), 1.22 (3H, s), 1.14 (3H, s), 0.82–0.86 (12H, m), 0.01 (3H, s), -0.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 167.2, 160.4, 157.7,

148.5, 140.0, 139.9, 136.5, 132.6, 130.3, 129.3, 129.2, 128.7, 128.6, 128.2, 127.9, 126.8, 126.7, 125.7, 115.6, 113.6, 106.0, 82.0, 77.8, 77.4, 75.0, 66.3, 66.0, 46.9, 45.5, 41.4, 36.5, 36.2, 36.0, 34.3, 34.1, 32.3, 31.9, 31.8, 28.7, 26.8, 26.1, 25.6, 23.9, 23.8, 21.8, 20.6, 18.1, 14.6, -3.9, -4.7. MS (ES) *m/z* (%): 1045.80 ([MNa^+], 100).



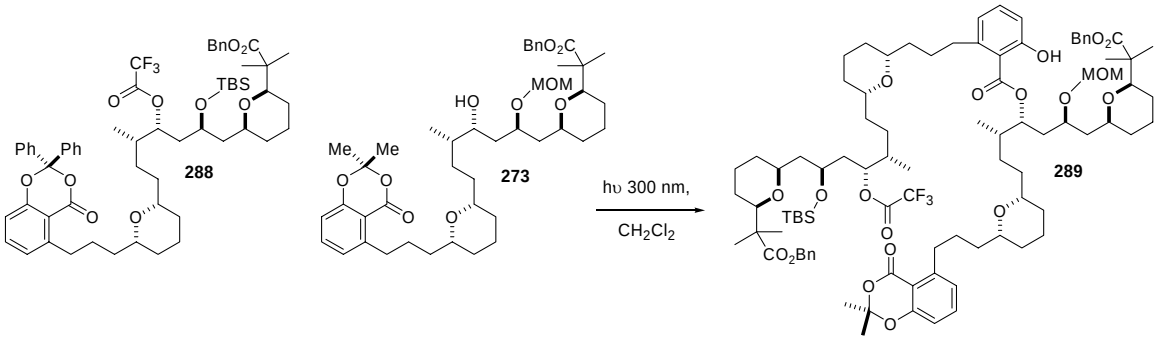
Compound 287. Prepared in a similar manner as **267** (31%). $[\alpha]_D$ = +2.5 ($CHCl_3$, *c* 0.65). IR (film) 2934, 1736, 1654, 1606, 1450, 1087, 1046, 919, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.98 (1H, s), 7.21–7.39 (12H, m), 6.91 (1H, d, *J* = 7.6 Hz), 6.78 (2H, d, *J* = 2.4, 8.0 Hz), 6.69 (1H, d, *J* = 7.6 Hz), 5.41–5.45 (1H, m), 5.03–5.14 (5H, m), 4.58 (1H, d, *J* = 6.4 Hz), 4.51 (1H, d, *J* = 7.2 Hz), 4.08 (1H, d, *J* = 14.8 Hz), 3.98 (1H, d, *J* = 14.0 Hz), 3.82–3.87 (1H, m), 3.68–3.72 (1H, m), 3.46 (2H, t, *J* = 11.2 Hz), 3.35–3.41 (1H, m), 3.18–3.35 (5H, m), 3.30 (3H, s), 3.05–3.09 (2H, m), 2.85–2.91 (2H, m), 1.34–1.84 (38H, m), 1.68 (6H, s), 1.04–1.28 (8H, m), 1.22 (3H, s), 1.14 (3H, s), 1.11 (3H, s), 1.08 (3H, s), 0.94 (3H, d, *J* = 6.4 Hz), 0.83–0.87 (12H, m), 0.01 (3H, s), -0.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 176.6, 171.0, 167.2, 162.1, 160.4, 157.3, 148.4, 145.4, 136.6, 135.3, 133.8, 128.7, 128.6, 128.2, 128.0, 127.9, 125.4, 122.2, 115.8, 115.3, 113.2, 112.3, 105.1, 96.3, 82.1, 82.0, 78.0, 77.9, 77.8, 77.3, 75.0, 74.7, 72.5, 66.3, 66.2, 66.0, 56.1, 46.9, 46.8, 45.5, 42.0, 41.4, 36.9, 36.8, 36.6, 36.5, 36.0, 35.7, 34.4, 34.1, 32.3, 32.1, 32.0,

31.8, 31.7, 29.9, 28.8, 28.7, 28.2, 27.3, 26.2, 25.9, 25.8, 25.7, 25.6, 23.9, 23.8, 15.0, 14.6, -3.9, -4.7. MS (ES) *m/z* (%): 1616.75 ([MNa^+], 10).



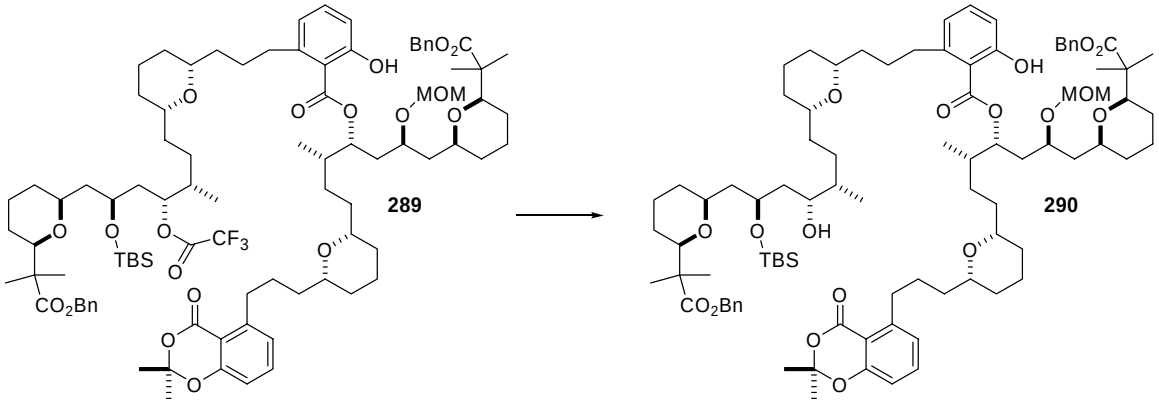
Trifluoroacetate 288. To a stirred solution alcohol **258** (95 mg, 0.10 mmol) in CH_2Cl_2:Pyridine (6 mL, 5:1) at 0 ˚C was added trifluoroacetic anhydride (55 μL, 0.30 mmol). After 0.5 hr, the reaction was poured into water (50 mL) and extracted with Et_2O (3 × 25 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (1/9 EtOAc/Hex) to afford 96 mg (92%) of **288**. $[\alpha]_D$ = +14.0 ($CHCl_3$, *c* 0.83). IR (film) 2934, 2858, 1779, 1741, 1607, 1581, 1475, 1455, 1266, 1217, 1166, 1090, 912, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.58 (4H, m), 7.27–7.38 (12H, m), 6.98 (1H, d, *J* = 8.4 Hz), 6.82 (1H, d, *J* = 8.0 Hz), 5.18 (1H, app dd, *J* = 4.0, 10.0 Hz), 5.10 (2H, s), 3.88 (1H, app t, *J* = 9.2 Hz), 3.43 (1H, d, *J* = 11.2 Hz), 3.33 (1H, app t, *J* = 14 Hz), 3.11–3.24 (2H, m), 3.01–3.10 (1H, m), 2.88–2.99 (1H, m), 1.68–1.96 (5H, m), 1.30–1.61 (12H, m), 0.97–1.29 (8H, m), 1.21 (3H, s), 1.14 (3H, s), 0.85–0.89 (12H, m), 0.02 (3H, s), –0.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 160.4, 157.7, 157.0, 148.4, 140.0, 136.5, 135.4, 129.2, 128.6, 128.1, 127.9, 126.7, 126.6, 125.7, 115.6, 113.6, 106.0, 82.1, 80.5, 77.8, 77.6, 74.8, 66.1, 65.6, 46.8, 45.2, 42.1, 36.2, 35.9, 35.8, 34.3,

34.0, 32.1, 31.8, 31.7, 28.6, 27.3, 26.7, 26.1, 25.8, 23.9, 23.8, 22.7, 19.7, 18.1, -3.8, -5.0. MS (ES) *m/z* (%): 1065.65 ($[MNa]^+$, 100).



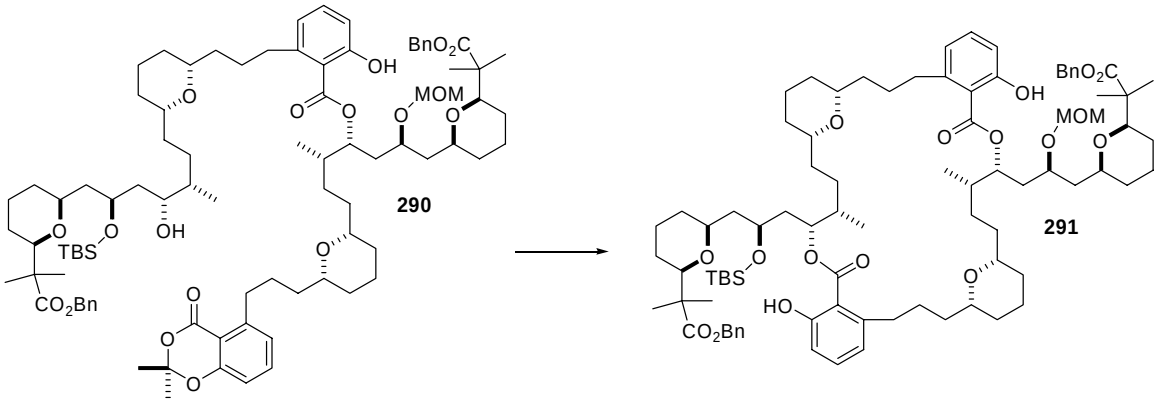
Trifluoroacetate 289. To an ovendried flask was added alcohol **273** (144 mg, 0.192 mmol) and **288** (100 mg, 0.095 mmol). These starting materials were dried via azeotropic removal of water with benzene *in-vacuo* (3 × 2 mL). The combined starting materials were then dissolved in freshly distilled CH_2Cl_2 (0.48 mL) and transferred to a flame dried borosilicate test tube fitted with a rubber septum under nitrogen. This test tube was sealed with parafilm and the solution was photolyzed for 1 hr at 300 nm in a Rayonett® photochemical reactor at ambient temperature. The solvent was then removed and the crude material was purified directly by FC (3/97→30/70 EtOAc/Hex gradient) to afford 41.4 mg (27%) of **289**, along with 50 mg (50%) of **288** and 114 mg (80%) of **273**. $[\alpha]_D$ = +6.8 ($CHCl_3$, *c* 0.83). IR (film) 2935, 2859, 1780, 1737, 1652, 1606, 1581, 1450, 1313, 1269, 1216, 1165, 1087, 1046, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.98 (1H, s), 7.27–7.40 (11H, m), 7.23 (1H, t, *J* = 8.0 Hz), 6.92 (1H, d, *J* = 7.6 Hz), 6.79 (2H, dd, *J* = 3.2, 8.0 Hz), 6.68 (1H, d, *J* = 8.0 Hz), 5.42–5.44 (1H, m), 5.18 (1H, app dd, *J* = 3.6, 10.0 Hz), 5.10 (2H, s), 5.07 (2H, s), 4.58 (1H, d, *J* = 6.8 Hz), 4.51 (1H, d, *J* = 6.8 Hz), 3.89 (1H, app t, *J* = 9.2 Hz), 3.64–3.74 (1H, m), 3.38–3.48 (3H, m), 3.28–3.34 (1H, m), 3.30

(3H, s), 3.14–3.27 (4H, m), 3.08 (2H, t, *J* = 7.2 Hz), 2.84–2.94 (2H, m), 1.34–1.96 (40H, m), 1.69 (6H, s), 1.07–1.28 (10H, m), 1.21 (3H, s), 1.14 (3H, s), 1.11 (3H, s), 1.08 (3H, s), 0.95 (3H, d, *J* = 6.4 Hz), 0.86–0.88 (3H, m), 0.85 (9H, s), 0.02 (3H, s), -0.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 176.5, 171.0, 162.1, 160.4, 157.3, 148.4, 145.4, 136.6, 135.3, 133.8, 128.7, 128.2, 128.0, 125.4, 122.2, 115.8, 115.3, 113.3, 112.3, 105.1, 96.4, 82.1, 80.5, 77.9, 77.7, 74.9, 74.7, 72.5, 66.2, 65.6, 56.1, 46.8, 45.3, 42.0, 36.9, 36.8, 36.6, 36.1, 36.0, 35.8, 35.7, 34.4, 34.0, 32.2, 31.9, 31.8, 28.9, 28.6, 28.1, 27.3, 26.1, 25.9, 25.8, 23.9, 23.8, 22.8, 22.2, 20.3, 19.7, 18.1, 15.0, 14.3, -3.8, -5.0. MS (ES) *m/z* (%): 1636.55 ($[MNa]^+$, 35).



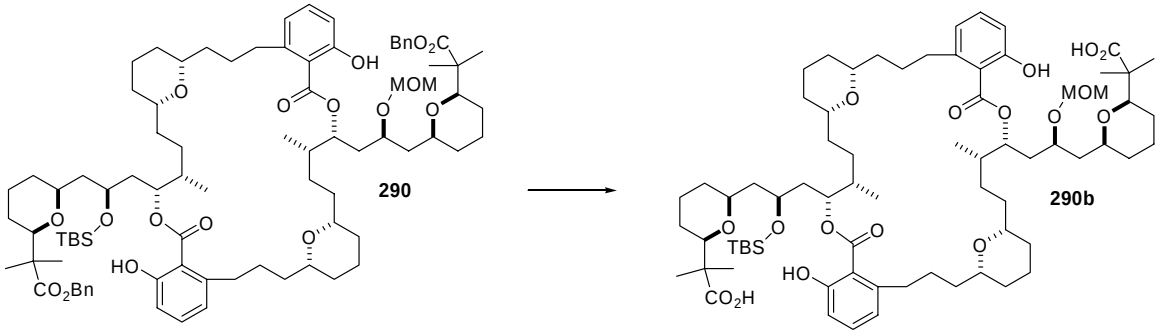
Alcohol 290. To a stirred solution of trifluoroacetate **289** (41.4 mg, 0.025 mmol) in THF (5 mL) was added 2.0 M NH_3 in MeOH (2 mL). The reaction was allowed to stir at ambient temperature for 12 hr. The solvent was removed and the crude material was purified by FC (25/75 EtOAc/Hex) to afford 35.5 mg (94%) of alcohol **290**. $[\alpha]_D$ = -1.3 ($CHCl_3$, *c* 0.78). IR (film) 3508, 2934, 2858, 1738, 1652, 1606, 1582, 1454, 1313, 1269, 1212, 1087, 1044, 919 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.99 (1H, s), 7.27–7.40 (11H, m), 7.23 (1H, t, *J* = 8.0 Hz), 6.91 (1H, d, *J* = 8.0 Hz), 6.78 (2H, dd, *J* = 1.6, 8.0 Hz), 6.68 (1H, d, *J* = 7.2 Hz), 5.40–5.44 (1H, m), 5.03–5.15 (4H, m), 4.57 (1H, d, *J* = 7.6

Hz), 4.51 (1H, d, *J* = 6.4 Hz), 4.17–4.24 (1H, m), 3.65–3.72 (2H, m), 3.49 (1H, d, *J* = 11.2 Hz), 3.44 (1H, d, *J* = 10.8 Hz), 3.36–3.3.41 (1H, m), 3.30 (3H, s), 3.16–3.27 (5H, m), 3.07 (2H, t, *J* = 7.2 Hz), 2.85–2.91 (2H, m), 1.34–1.86 (40H, m), 1.68 (6H, s), 1.07–1.29 (10H, m), 1.19 (3H, s), 1.12 (3H, s), 1.10 (3H, s), 1.08 (3H, s), 0.94 (3H, d, *J* = 6.8 Hz), 0.87 (9H, s), 0.83 (3H, d, *J* = 6.4 Hz), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 176.6, 171.0, 162.1, 160.4, 157.3, 148.4, 145.4, 146.6, 136.5, 135.3, 133.8, 128.7, 128.2, 128.0, 127.8, 125.4, 122.3, 115.8, 115.3, 113.2, 112.2, 105.1, 97.2, 96.4, 82.2, 82.1, 78.5, 78.0, 77.9, 77.8, 75.3, 74.7, 72.5, 72.0, 68.6, 66.3, 66.2, 56.1, 46.9, 46.8, 42.6, 42.0, 39.1, 36.9, 36.6, 36.1, 35.7, 34.4, 34.2, 32.2, 32.1, 32.0, 31.8, 31.6, 28.8, 28.2, 28.1, 27.3, 26.2, 26.0, 25.9, 25.8, 25.7, 25.2, 23.9, 23.8, 22.2, 21.4, 20.5, 20.2, 18.1, 15.2, 15.1, -4.5, -4.8. MS (ES) *m/z* (%): 1541.45 ([MNa]$^+$, 30).



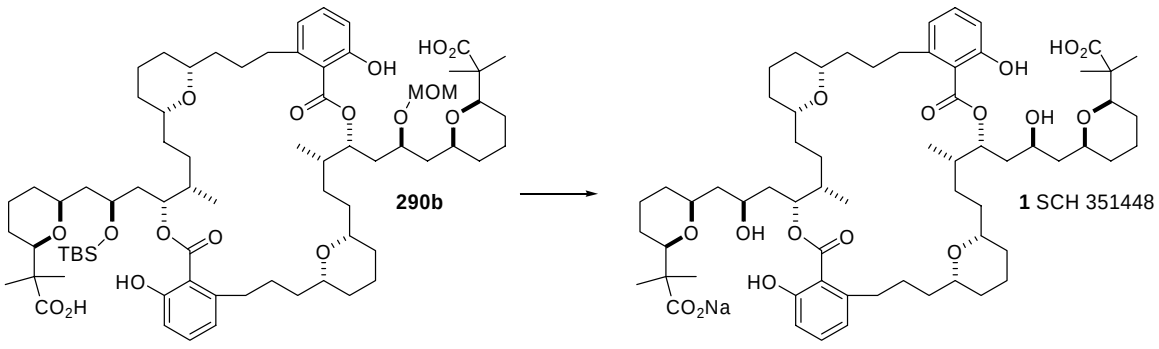
Macrocycle 291. To a stirred solution of alcohol **290** (22.3 mg, 0.0147 mmol) in THF (2 mL) at -78 ˚C was added NaHMDS (74 μL, 0.074 mmol). The reaction was allowed to warm to -20 ˚C over the course of 1 hr and kept at that temperature for 30 min before addition of pH = 7 phosphate buffer (3 mL). The quenched reaction was then diluted with water (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organic phase was dried over Na_2SO_4, filtered, concentrated, and purified by FC (1/15/84 Et_3N/EtOAc/Hex)

to afford 11 mg (50%) of macrocycle **291**. $[\alpha]_D$ = +12.7 ($CHCl_3$, *c* 0.70). IR (film) 3400, 2933, 2858, 1732, 1652, 1606, 1578, 1450, 1371, 1311, 1253, 1214, 1089, 1047, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.35 (1H, s), 11.06 (1H, s), 7.27–7.38 (10H, m), 7.16–7.23 (2H, m), 6.78 (2H, dd, *J* = 2.0, 8.0 Hz), 6.61 (1H, d, *J* = 7.6 Hz), 6.56 (1H, d, *J* = 7.6 Hz), 5.37–5.43 (1H, m), 5.30–5.35 (1H, m), 5.06 (2H, s), 5.04 (2H, s), 4.57 (1H, d, *J* = 6.8 Hz), 4.51 (1H, d, *J* = 6.8 Hz), 3.84–3.91 (1H, m), 3.64–3.71 (1H, m), 3.41 (1H, d, *J* = 10.8 Hz), 3.35 (1H, d, *J* = 11.2 Hz), 3.30 (3H, s), 3.15–3.23 (4H, m), 3.06–3.13 (4H, dd, *J* = 4.4, 6.8 Hz), 2.46–2.58 (2H, m), 1.36–1.94 (43H, m), 0.94–1.29 (22H, m), 0.86–0.87 (3H, m), 0.85 (9H, s), -0.01 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 176.5, 171.6, 171.3, 162.8, 162.3, 145.8, 145.6, 136.6, 133.9, 133.8, 128.7, 128.2, 128.0, 122.8, 115.8, 112.9, 112.5, 96.5, 82.1, 81.8, 78.1, 77.2, 75.0, 74.9, 72.6, 66.5, 66.2, 66.1, 56.0, 53.6, 46.8, 46.4, 45.6, 42.1, 39.0, 37.1, 37.0, 36.9, 36.8, 36.7, 33.9, 32.2, 32.0, 31.5, 31.4, 29.2, 29.0, 28.3, 28.2, 26.1, 25.9, 25.7, 23.9, 23.8, 22.7, 22.3, 22.0, 19.4, 18.2, 15.9, 15.7, -3.9, -4.7. MS (ES) *m/z* (%): 1482.95 ($[MNa]^+$, 100).

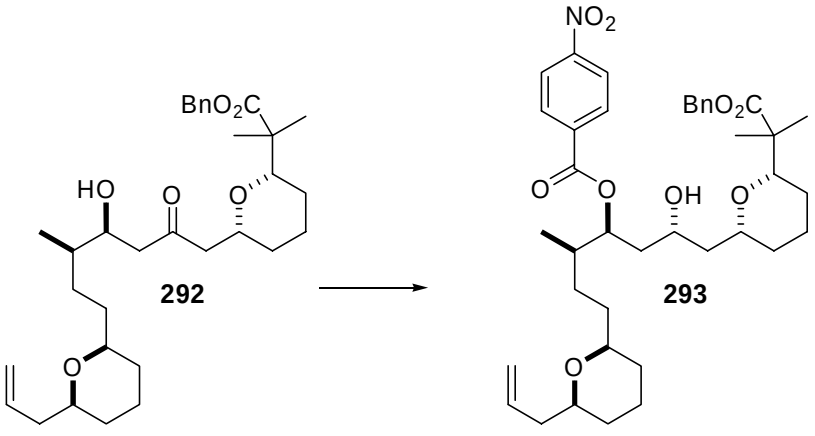


Bis-Acid 290b. To a stirred solution of bis-benzyl ester **290** (11 mg, 0.0075 mmol) in MeOH (2 mL) at ambient temperature was quickly added 10% Pd/C (~ 1–2 mg). The reaction flask was then sealed with a three way stopper fitted with a H_2 balloon. The flask was placed under house vacuum and flushed with H_2 then placed under vacuum once

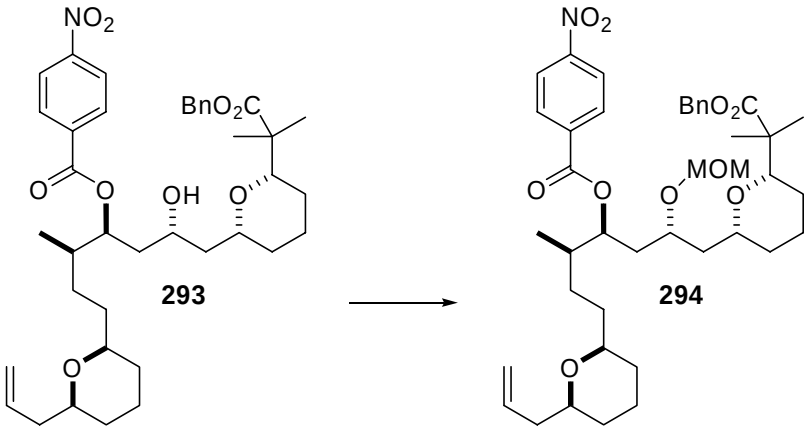
again. This process was repeated (6×). The reaction was then allowed to stir under balloon pressure of H_2 for 3.5 hr. The reaction was filtered through a short pad of celite, and the catalyst was washed extensively with CH_2Cl_2 and MeOH. After concentration, and purification by FC (1/2/97 AcOH/MeOH/CH_2Cl_2) 9.0 mg (93%) of bis-acid **290b** was isolated. $[\alpha]_D$ = +19.3 ($CHCl_3$, *c* 0.61). IR (film) 3300, 2934, 2859, 1705, 1652, 1606, 1450, 1369, 1295, 1252, 1214, 1089, 1047, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, t, *J* = 8.0 Hz), 6.79–6.84 (2H, m), 6.65–6.70 (2H, m), 5.33–5.40 (2H, m), 4.61 (1H, d, *J* = 6.8 Hz), 4.57 (1H, d, *J* = 6.8 Hz), 3.85–3.92 (1H, m), 3.64–3.72 (1H, m), 3.43–3.53 (2H, m), 3.34–3.36 (2H, m), 3.37 (3H, s), 3.05–3.23 (6H, m), 2.53–2.63 (2H, m), 1.66–1.94 (14H, m), 1.38–1.64 (24H, m), 1.12–1.26 (12H, m), 1.25 (3H, s), 1.09 (3H, s), 1.07 (3H, s), 0.96–1.02 (6H, m), 0.88 (3H, s), 0.86 (9H, s), 0.01 (3H, s), -0.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 178.8, 171.4, 171.3, 162.8, 162.4, 145.8, 145.6, 134.0, 122.8, 116.0, 112.8, 112.5, 96.9, 82.7, 82.6, 78.6, 78.2, 78.1, 77.4, 75.3, 75.1, 73.1, 66.8, 56.0, 46.5, 45.1, 42.1, 39.3, 37.3, 37.1, 37.0, 36.8, 33.8, 33.7, 32.2, 32.0, 31.5, 29.9, 29.8, 29.2, 29.1, 28.4, 28.3, 26.1, 25.5, 23.9, 23.7, 23.6, 23.2, 23.0, 18.2, 16.2, 16.0, -3.9, -4.7. MS (ES) *m/z* (%): 1301.75 ($[MNa]^+$, 80).



SCH 351448 1. To a stirred solution of bis-acid **290b** (6.5 mg, 0.005 mmol) in CH_3CN (0.3 mL), was added 48% aqueous HF (0.030 mL, 3.13 mmol). The reaction was allowed to stir at ambient temperature in a plastic vial for 48 hr. The reaction was then diluted with hexane (5 mL) and extracted with hexane (3 × 5 mL) from 4 N aq. HCl (saturated with NaCl, 2 mL). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated to afford 4.4 mg (77%) of crude **1** as a fine white powder. Crude **1** contained detectable amounts of a by-product by ^{1}H NMR which is also present in the natural isolated **1**. Purification by reversed phase HPLC (C18 column, 8/92 H_2O/MeOH) provided pure **1**. $[\alpha]_D$= +29.8 ($CHCl_3$, *c* 0.10). IR (film) 3445, 2930, 2857, 1704, 1668, 1605, 1463, 1295, 1086, 1047, 757 cm^{-1}; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.25 (2H, t, *J* = 8.0 Hz), 6.81 (2H, d, *J* = 8.0 Hz), 6.72 (2H, d, *J* = 7.2 Hz), 5.61–5.66 (2H, m), 3.71–3.77 (2H, m), 3.56–3.63 (2H, m), 3.50 (2H, d, *J* = 10.4 Hz), 3.09–3.19 (6H, m), 2.54 (2H, td, *J* = 4.6, 12.4 Hz), 2.20–2.10 (2H, m), 1.82–1.88 (6H, m), 1.57–1.79 (10H, m), 1.38–1.60 (22H, m), 1.14–1.29 (10H, m), 1.13 (6H, s), 1.10 (6H, s), 1.01 (6H, d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 178.7, 171.2, 160.2, 145.2, 133.6, 122.5, 116.0, 115.8, 83.4, 79.3, 78.5, 78.3, 77.8, 67.6, 46.6, 43.8, 37.9, 37.6, 37.0, 36.8, 35.3, 33.1, 32.7, 32.1, 30.3, 29.7, 25.3, 24.5, 23.7, 23.4, 19.4, 15.2. MS (ES) *m/z* (%): 1143.65 ([MH]$^+$, 100).

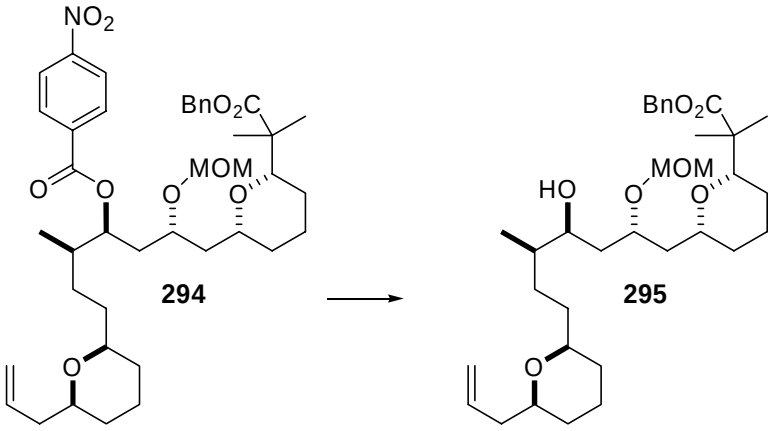


Ester 293. Prepared in a similar manner as **250** with 4-nitrobenzaldehyde (71%). $[\alpha]_D$= -19.9 ($CHCl_3$, *c* 0.72). IR (film) 3401, 2979, 1792, 1771, 1705, 1446, 1368, 1251, 1170, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (2H, d, *J* = 8.4 Hz), 8.12 (2H, d, *J* = 8.8 Hz), 7.24–7.40 (5H, m), 5.78 (1H, dddd, *J* = 6.8, 6.8, 10.0, 17.2 Hz), 5.37–5.45 (1H, m), 3.72–3.80 (1H, m), 3.49–3.60 (2H, m), 3.18–3.30 (2H, m), 2.22–2.32 (1H, m), 2.04–2.16 (1H, m), 1.40–1.90 (17H, m), 1.06–1.30 (4H, m), 1.13 (3H, s), 1.08 (3H, s), 0.94 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 164.2, 150.2, 136.1, 136.0, 135.2, 130.5, 128.3, 128.2, 127.9, 127.8, 123.3, 116.0, 82.7, 79.2, 77.9, 76.6, 76.5, 67.6, 66.3, 46.5, 43.3, 40.9, 38.1, 36.8, 34.0, 31.8, 31.4, 31.1, 28.1, 24.6, 23.5, 23.1, 21.4, 19.6, 15.0. MS (ES) *m/z* (%): 702.35 ($[MNa]^+$, 100).

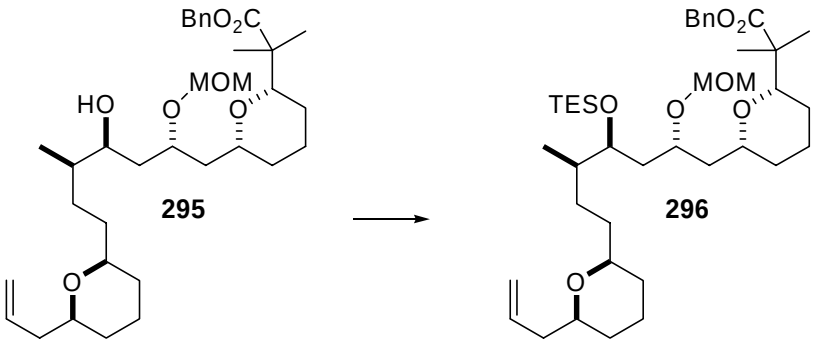


Compound 294. Prepared in a similar manner as **251**. $[\alpha]_D$= +0.33 ($CHCl_3$, *c* 2.75). IR (film) 3343, 2919, 1742, 1465, 1377 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (2H, d, *J* = 8.0 Hz), 8.16 (2H, d, *J* = 8.4 Hz), 7.22–7.34 (5H, m), 5.72–5.82 (1H, m), 5.27–5.34 (1H, m), 5.04 (2H, s), 4.98 (1H, d, *J* = 17.6 Hz), 4.92 (1H, d, *J* = 10.0 Hz), 4.55 (1H, d, *J* = 6.8 Hz), 4.48 (1H, d, *J* = 6.8 Hz), 3.68–3.76 (1H, m), 3.43 (1H, d, *J* = 11.2 Hz), 3.36–3.39 (1H, m), 3.20–3.31 (2H, m), 3.27 (3H, s), 2.21–2.26 (1H, m), 1.73–1.97 (6H, m), 1.34–

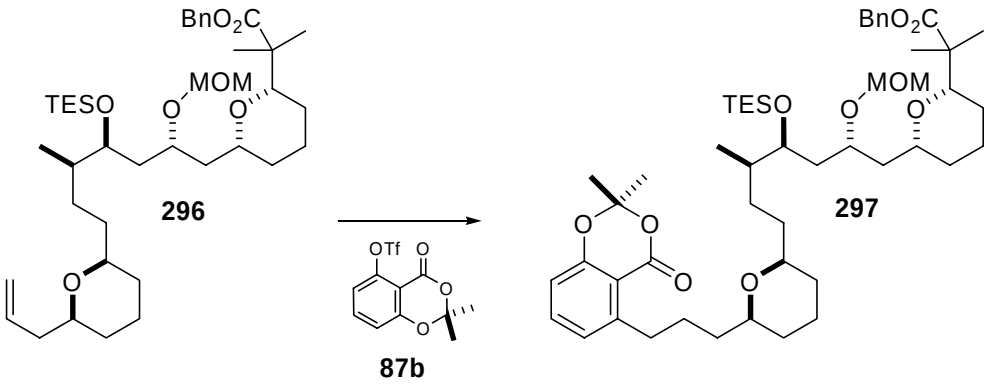
1.72 (12H, m), 1.06–1.25 (4H, m), 1.11 (3H, s), 1.09 (3H, s), 0.92 (3H, d, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 164.4, 150.5, 136.4, 136.3, 135.4, 130.8, 128.6, 128.1, 127.9, 123.6, 116.3, 96.3, 82.3, 78.1, 77.5, 76.5, 74.9, 72.2, 66.1, 55.9, 46.7, 42.1, 41.1, 36.9, 35.1, 34.3, 32.0, 31.7, 31.3, 28.6, 25.6, 23.7, 22.0, 20.5, 14.9. MS (ES) *m/z* (%): 746.40 ($[MNa]^+$, 100).



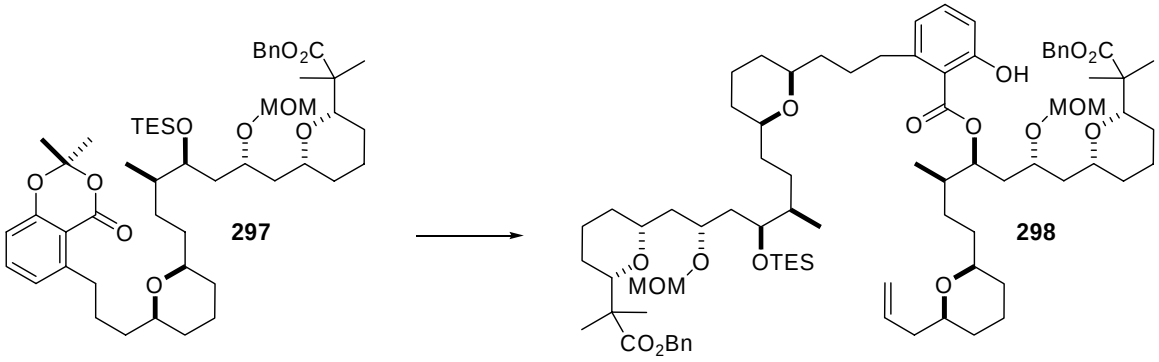
Alcohol 295. To a stirred solution of ester **294** (5.65 g, 7.81 mmol) in MeOH (100 mL) was added K_2CO_3 (3.2 g, 23.4 mmol). The reaction was allowed to stir overnight at ambient temperature. The reaction was then poured into H_2O (100 mL), and extracted with Et_2O (2 x 200 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (15/85, EtOAc/Hex) to afford 3.77g (84%) of alcohol **295** (for data see **252**, *ent*-**295**).



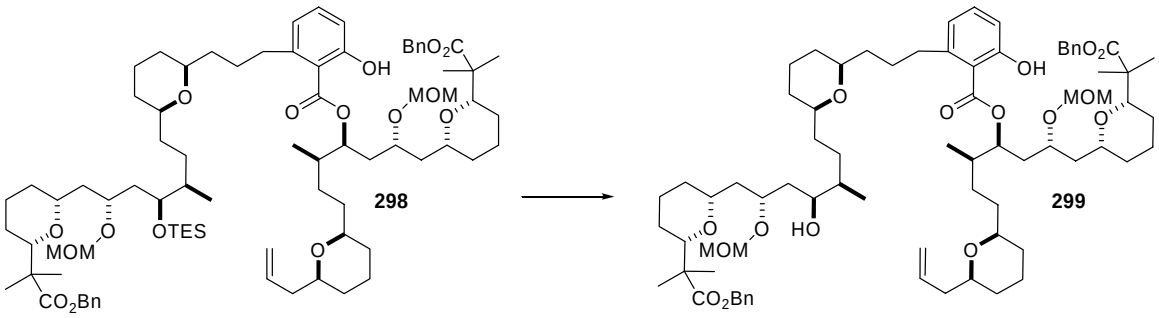
Silyl Ether 296. To a stirred solution of alcohol **295** (1.5 g, 2.61 mmol) in CH_2Cl_2 (20 mL) was added 2,6-lutidine (0.91 mL, 7.83 mmol) followed by TESOTF (0.84 mL, 3.7 mmol) at 0 ˚C. After 2 hr the reaction was quenched by addition of $NaHCO_3$ (100 mL), and extracted with Et_2O (3 x 200 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (5/95, EtOAc/Hex) to afford 1.32 g (78%) of silyl ether **296**. $[\alpha]_D$= -5.8 ($CHCl_3$, *c* 1.0). IR (film) 2936, 1735, 1457, 1376, 1264, 1151, 1087, 1041, 916, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.37 (5H, m), 5.83 (1H, dddd, *J* = 6.8, 6.8, 10.0, 16.8 Hz), 5.10–5.11 (2H, m), 5.05 (1H, d, *J* = 18.4 Hz), 5.01 (1H, d, *J* = 10.0 Hz), 4.64 (2H, s), 3.75–3.80 (2H, m), 3.46 (1H, dd, *J* = 1.6, 11.2 Hz), 3.40–3.43 (1H, m), 3.35 (3H, s), 3.26–3.32 (1H, m), 3.17–3.23 (1H, m), 2.27–2.34 (1H, m), 2.10–2.17 (1H, m), 1.79–1.83 (3H, m), 1.32–1.62 (14H, m), 1.10–1.29 (4H, m), 1.24 (3H, s), 1.14 (3H, s), 0.94 (9H, t, *J* = 8.0 Hz), 0.84 (3H, d, *J* = 6.8 Hz), 0.58 (6H, d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 136.6, 135.4, 128.5, 128.0, 127.9, 116.4, 96.4, 82.1, 78.4, 77.5, 75.1, 74.0, 72.9, 66.1, 55.7, 46.8, 42.7, 41.2, 39.7, 37.7, 34.9, 31.8, 31.6, 31.3, 29.2, 25.7, 23.8, 23.7, 22.4, 20.1, 13.6, 7.2, 5.4. MS (ES) *m/z* (%): 597.30 ([MHNa-TES]$^+$, 100).



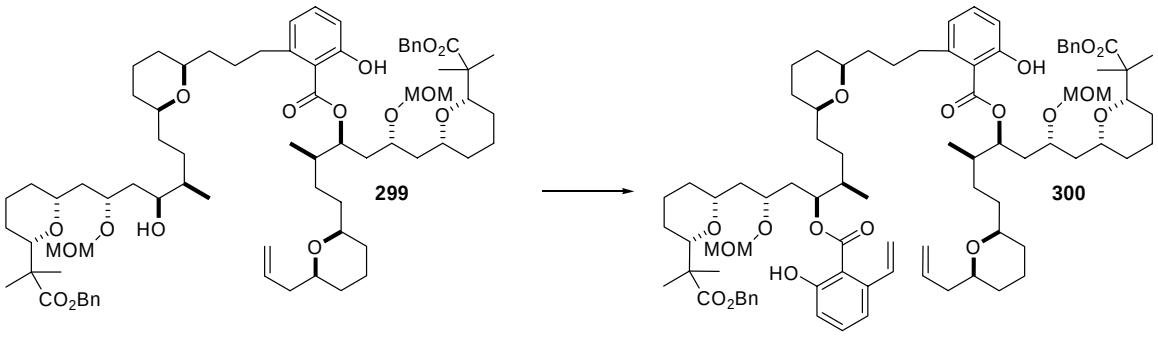
Compound 297. Prepared in a similar manner as **257** (81%). $[\alpha]_D$= -5.6 ($CHCl_3$, *c* 0.9). IR (film) 2936, 1737, 1606, 1582, 1476, 1389, 1314, 1270, 1211, 1042, 920, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.39 (6H, m), 6.91 (1H, d, *J* = 7.6 Hz), 6.78 (1H, d, *J* = 8.0 Hz), 5.07–5.14 (2H, m), 4.59–4.64 (2H, m), 3.74–3.82 (2H, m), 3.45 (1H, dd, *J* = 1.6, 7.2 Hz), 3.38–3.42 (1H, m), 3.31 (3H, s), 3.23–3.29 (1H, m), 3.17–3.20 (1H, m), 3.08 (2H, t, *J* = 6.8 Hz), 1.75–1.83 (4H, m), 1.68 (6H, s), 1.33–1.64 (16H, m), 1.04–1.27 (5H, m), 1.23 (3H, s), 1.13 (3H, s), 0.93 (9H, t, *J* = 8.0 Hz), 0.83 (3H, d, *J* = 6.8 Hz), 0.57 (6H, q, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 160.4, 157.3, 148.4, 136.6 136.4, 135.3, 134.0, 128.6, 128.5, 128.1, 127.9, 125.8, 125.4, 118.0, 115.3, 112.2, 105.1, 96.4, 82.1, 78.3, 77.9, 75.2, 74.0, 72.9, 66.1, 55.7, 46.9, 42.8, 39.7, 37.7, 36.6, 35.0, 34.4, 31.8, 31.7, 29.2, 27.3, 25.9, 25.8, 23.9, 23.8, 22.5, 20.1, 13.7, 7.3, 5.5. MS (ES) *m/z* (%): 775.50 ([MHNa-TES]$^+$, 100).



Compound 298. To a stirred solution of **295** (200 mg, 0.348 mmol) in THF (2 mL) was added NaHMDS (0.317 mL, 0.317 mmol, 1M soln.) dropwise at 0 ˚C. After 45 min. a solution of **297** (274 mg, 0.317 mmol) in THF (1 mL) was added dropwise. The reaction was allowed to stir for 1 hr at 0 ˚C and 1 hr at ambient temperature. The reaction was then quenched by addition of sat. $NH_4^+Cl^-$ (10 mL). The crude solution was then extracted with Et_2O (3 x 50 mL). The combined organic phase was dried over $MgSO_4$, filtered, concentrated, and purified by FC (7/93→15/85, EtOAc/Hex gradient) to afford 195 mg (45%) of ester **298**. $[\alpha]_D$= -3.5 ($CHCl_3$, *c* 0.57). IR (film) 2935, 1734, 1653, 1454, 1374, 1264, 1088, 1041, 918, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.01 (1H, s), 7.21–7.35 (11H, m), 6.78 (1H, d, *J* = 8.0 Hz), 6.67 (1H, d, *J* = 8.0 Hz), 5.78 (1H, dddd, *J* = 7.2, 7.2, 10.0, 17.2 Hz), 5.41–5.44 (1H, m), 4.93–5.10 (6H, m), 4.60 (2H, s), 4.58–4.59 (1H, m), 4.52 (1H, d, *J* = 6.8 Hz), 3.74–3.80 (2H, m), 3.66–3.72 (1H, m), 3.43 (2H, d, *J* = 11.2 Hz), 3.37–3.40 (2H, m), 3.31 (6H, m), 3.16–3.28 (4H, m), 2.86–2.89 (2H, m), 2.22–2.29 (1H, m), 2.06–2.15 (1H, m), 1.67–1.90 (10H, m), 1.32–1.62 (28H, m), 1.04–1.23 (8H, m), 1.22 (3H, s), 1.13 (3H, s), 1.10 (3H, s), 1.07 (3H, s), 0.90–0.94 (3H, m), 0.93 (9H, t, *J* = 8.0 Hz), 0.83 (3H, d, *J* = 6.4 Hz), 0.56 (6H, q, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 176.4, 170.9, 162.0, 145.3, 136.5, 135.4, 133.7, 128.5, 128.0, 127.9, 127.8, 122.1, 116.3, 115.7, 113.1, 96.3, 96.2, 82.1, 82.0, 78.2, 77.8, 77.7, 75.1, 74.6, 73.9, 72.8, 72.4, 66.1, 66.0, 55.9, 55.6, 46.8, 46.7, 42.8, 41.8, 41.1, 39.6, 37.7, 36.8, 36.0, 35.7, 34.9, 34.2, 32.0, 31.8, 31.6, 31.5, 31.3, 29.0, 28.7, 28.1, 25.7, 25.6, 23.8, 23.7, 22.4, 22.0, 20.2, 20.1, 15.1, 13.6, 7.2, 5.4.

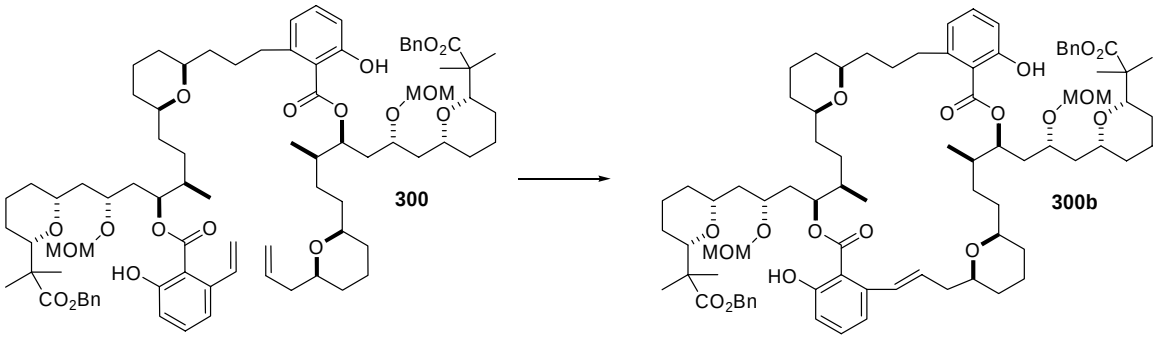


Compound 299. Prepared in a similar manner as **258** (96%). $[\alpha]_D$= -6.1 ($CHCl_3$, *c* 2.0). IR (film) 3516, 2935, 2250, 1732, 1652, 1606, 1454, 1373, 1266, 1150, 1088, 1039, 917, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.02 (1H, s), 7.20–7.35 (11H, m), 6.77 (1H, d, *J* = 8.4 Hz), 6.67 (1H, d, *J* = 7.6 Hz), 5.78 (1H, dddd, *J* = 6.8, 6.8, 10.4, 17.2 Hz), 5.40–5.44 (1H, m), 5.10 (2H, s), 5.05 (2H, s), 4.99 (1H, d, *J* = 16.8 Hz), 4.94 (1H, d, *J* = 10.0 Hz), 4.50–4.61 (4H, m), 3.90–3.96 (1H, m), 3.61–3.69 (2H, m), 3.48 (1H, d, *J* = 11.2 Hz), 3.42 (1H, d, *J* = 10.8 Hz), 3.34–3.39 (2H, m), 3.33 (3H, s), 3.31 (3H, s), 3.19–3.26 (4H, m), 2.84–2.90 (2H, m), 2.03–2.29 (2H, m), 1.32–1.89 (38H, m), 1.03–1.24 (8H, m), 1.18 (3H, s), 1.11 (3H, s), 1.09 (3H, s), 1.06 (3H, s), 0.94 (3H, d, *J* = 6.4 Hz), 0.85 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 176.5, 171.0, 162.1, 145.3, 136.5, 136.4, 135.4, 133.7, 128.5, 128.1, 128.0, 127.9, 122.2, 116.3, 115.7, 113.1, 96.3, 96.1, 82.3, 82.0, 78.4, 78.0, 77.8, 76.8, 75.0, 74.6, 73.5, 72.4, 71.5, 66.2, 66.1, 60.5, 56.0, 55.8, 46.8, 46.7, 41.8, 41.1, 39.0, 37.2, 36.9, 36.8, 36.1, 35.8, 34.2, 32.1, 31.9, 31.8, 31.6, 31.5, 31.3, 28.7, 28.3, 28.1, 25.6, 25.2, 23.8, 23.7, 22.0, 21.4, 20.5, 20.1, 15.2, 15.1, 14.3.



Diene 300. To a stirred solution of alcohol **299** (91 mg, 0.072 mmol) in THF (1 mL) was added NaHMDS (0.18 mL, 0.18 mmol, 1M soln.) at 0 ˚C. After 45 min. a solution of benzodioxinone **7** (22 mg, 0.11 mmol) in THF (0.5 mL) was added dropwise. After 1.5 hr at 0 ˚C, the reaction was quenched by addition of sat. $NH_4^+Cl^-$ (20 mL). The crude material was extracted with Et_2O (3 x 50 mL), dried over $MgSO_4$, filtered, concentrated, and purified by FC (15/85, EtOAc/Hex) to afford 58 mg (45%) of diene **300**. $[\alpha]_D$= -3.2 ($CHCl_3$, *c* 1.45). IR (film) 2935, 1735, 1654, 1603, 1450, 1252, 1215, 1088, 1039, 918, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.31 (1H, s), 11.02 (1H, s), 7.19–7.36 (12H, m), 6.88 (1H, d, *J* = 8.8 Hz), 6.86 (1H, d, *J* = 7.6 Hz), 5.79 (1H, dddd, *J* = 6.8, 6.8, 10.0, 16.8 Hz), 5.37–5.44 (3H, m), 5.18 (1H, d, *J* = 6.8 Hz), 5.06 (2H, s), 5.01 (1H, d, *J* = 17.6 Hz), 4.95 (1H, d, *J* = 6.0 Hz), 4.59 (1H, d, *J* = 6.8 Hz), 4.56 (1H, d, *J* = 6.8 Hz), 4.52 (1H, d, *J* = 6.8 Hz), 4.49 (1H, d, *J* = 6.8 Hz), 3.65–3.71 (2H, m), 3.37–3.45 (3H, m), 3.32–3.34 (1H, m), 3.31 (3H, s), 3.29 (3H, s), 3.20–3.25 (4H, m), 2.84–2.90 (2H, m), 2.22–2.28 (1H, m), 2.07–2.13 (1H, m), 1.67–1.89 (14H, m), 1.33–1.63 (30H, m), 1.04–1.24 (5H, m), 1.10 (3H, s), 1.07 (9H, s), 0.94 (6H, app t, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 176.5, 171.0, 170.9, 162.3, 162.1, 145.4, 141.9, 138.8, 136.5, 135.5, 134.3, 133.8, 128.6, 128.1, 127.9, 122.2, 120.1, 117.4, 116.4, 115.8, 115.7, 113.1, 111.4, 96.3, 96.2, 82.1, 82.0, 78.1, 77.9, 77.8, 77.5, 77.1, 74.9, 74.6, 72.5, 72.3, 66.2, 66.1, 56.1, 56.0,

46.8, 42.1, 41.9, 41.2, 36.9, 36.8, 36.7, 36.7, 36.1, 35.8, 35.5, 34.3, 32.1, 31.9, 31.7, 31.6, 31.4, 28.8, 28.5, 28.2, 25.6, 23.8, 22.1, 22.0, 20.3, 20.2, 15.1, 15.0.



Macrocycle 300b. A roundbottom flask charged with diene **300** (25 mg, 0.0176 mmol) and Grubbs' 2nd generation catalyst (4.5 mg, 0.0052 mmol) was heated to 55 ˚C for 10 hr. The solvent was removed and the crude residue was purified directly by FC (15/85, EtOAc/Hex) to afford 8 mg (33%) of macrocycle **300b**. $[\alpha]_D$= -31.5 ($CHCl_3$, *c* 0.4). IR (film) 3401, 2933, 1731, 1652, 1450, 1253, 1215, 1089, 1039, 916, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.20 (1H, s), 10.97 (1H, s), 7.18–7.37 (12H, s), 6.98 (1H, d, *J* = 7.6 Hz), 5.78–5.86 (1H, m), 5.34–5.42 (2H, m), 5.02–5.09 (4H, m), 4.51–4.57 (4H, m), 3.64–3.72 (4H, m), 3.25–3.42 (11H, m), 3.09–3.21 (3H, m), 2.99–3.06 (1H, m), 2.62–2.72 (1H, m), 2.36–2.44 (1H, m), 2.24–2.32 (1H, m), 1.68–1.90 (12H, m), 1.31–1.64 (28H, m), 1.01–1.27 (18H, m), 0.94–0.99 (6H, m).

Representative Procedure for Ion Transport Studies.

To a quartz cuvette containing a magnetic stir bar was added 1.6 mL of 150 mM Bis-Tris buffer (pH = 7.5) followed by acridine orange (10 μL), and potassium loaded unilamellar vesicles (2 μL). After establishing a stable absorbance reading SCH 351448

1 (1.6 μL of 1 mM soln. in EtOH) was rapidly added to the cuvette. Once the drop in absorbance had tapered, a solution of $CaCl_2$ (1.6 μL of 1 M soln.) was added.

5.7 Notes and References

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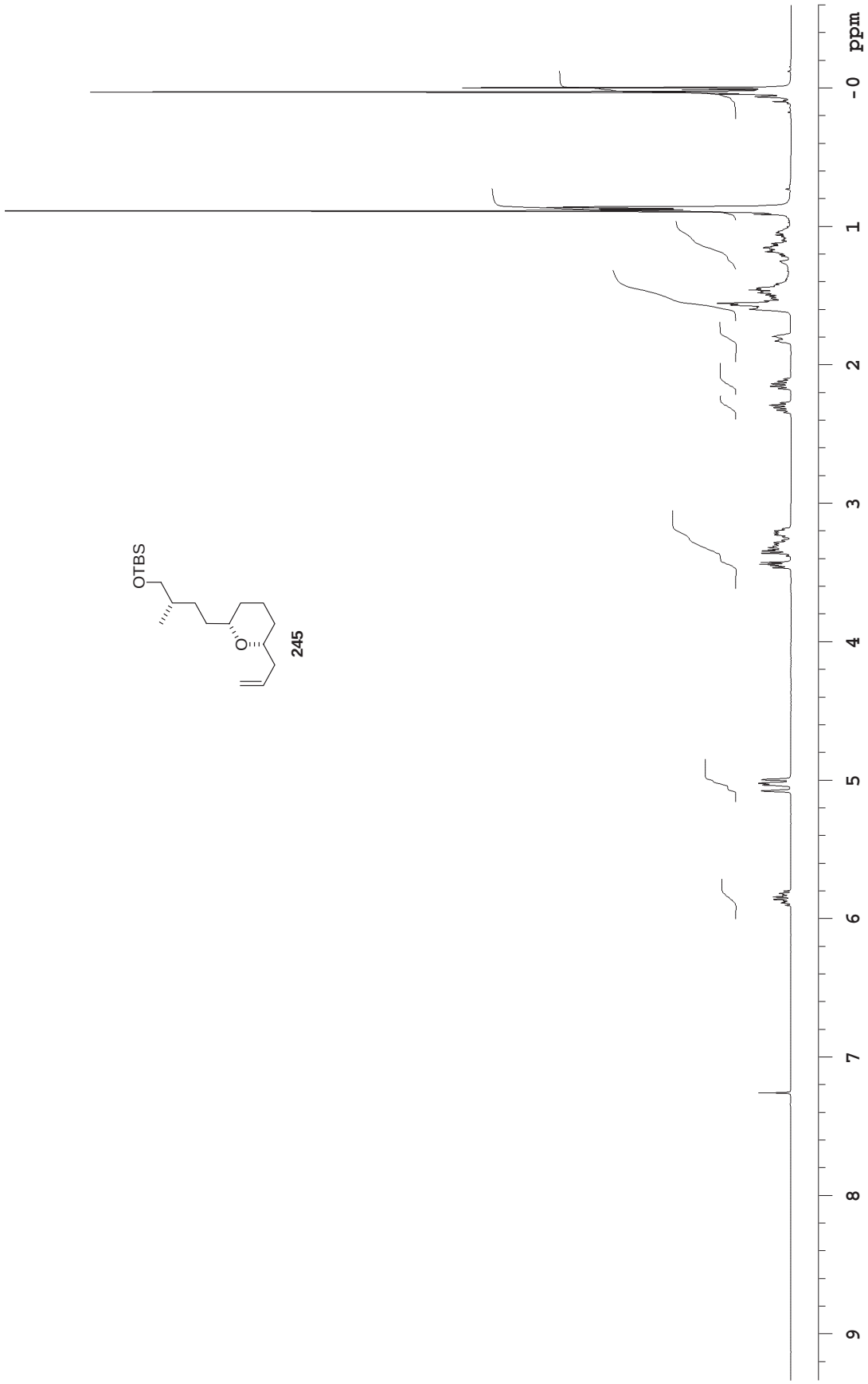
Appendix Three: Spectra of Compounds Appearing in Chapter 5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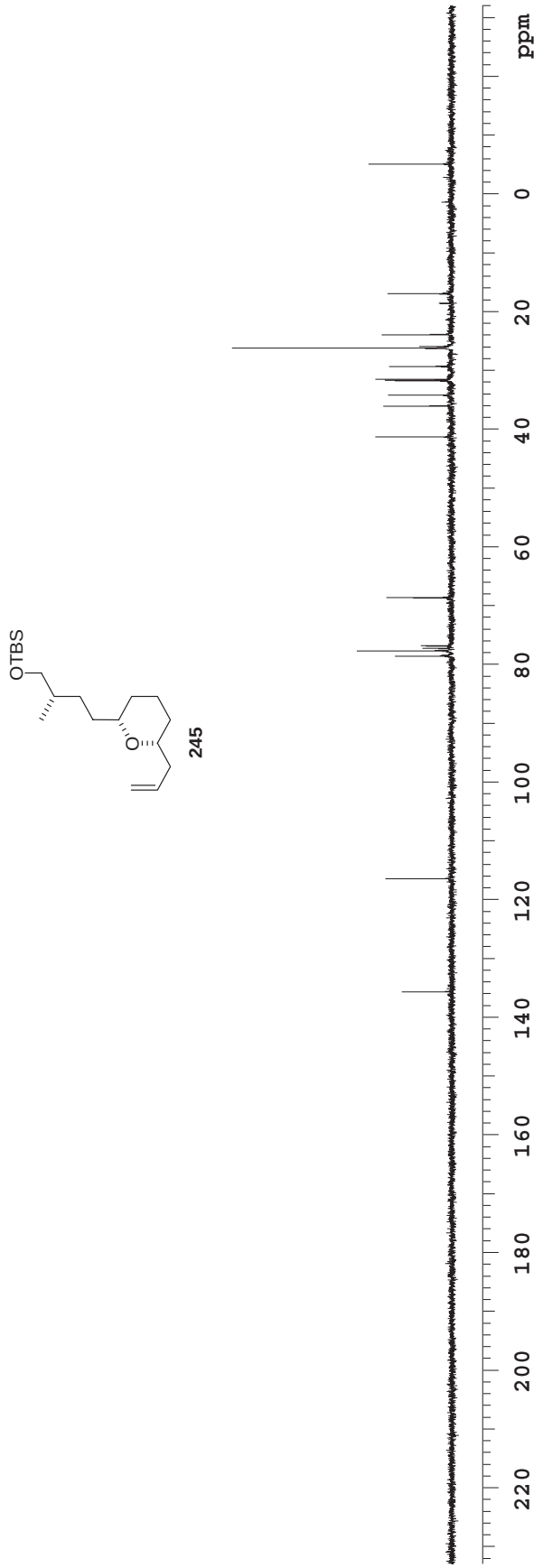
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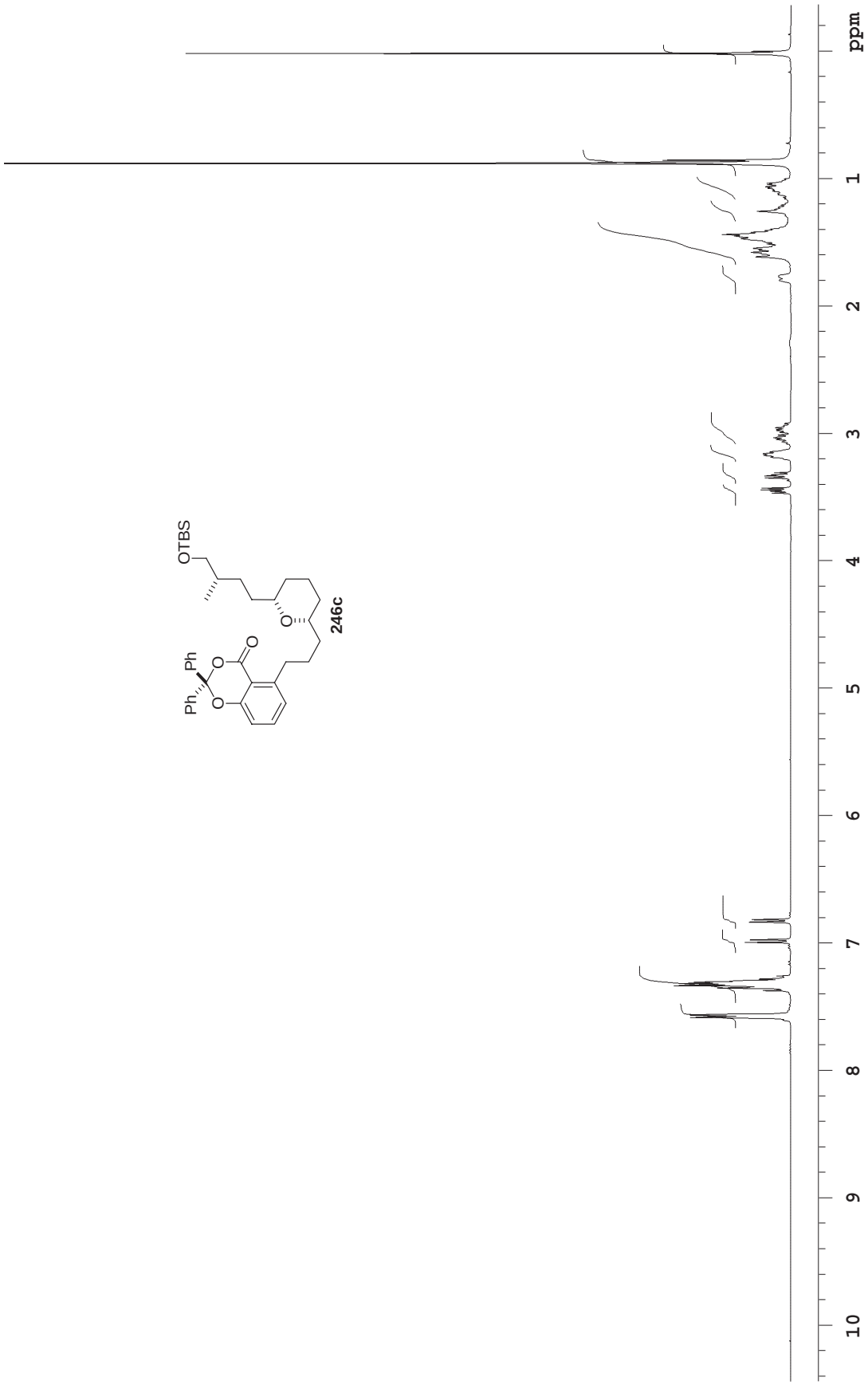
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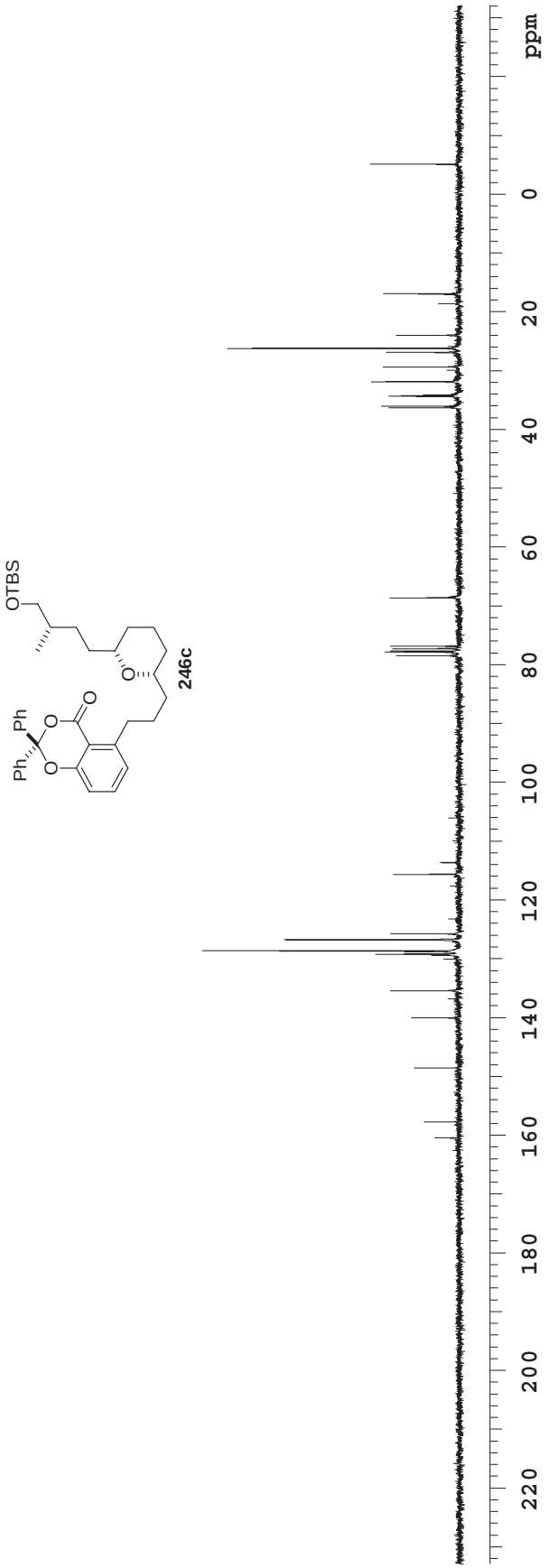
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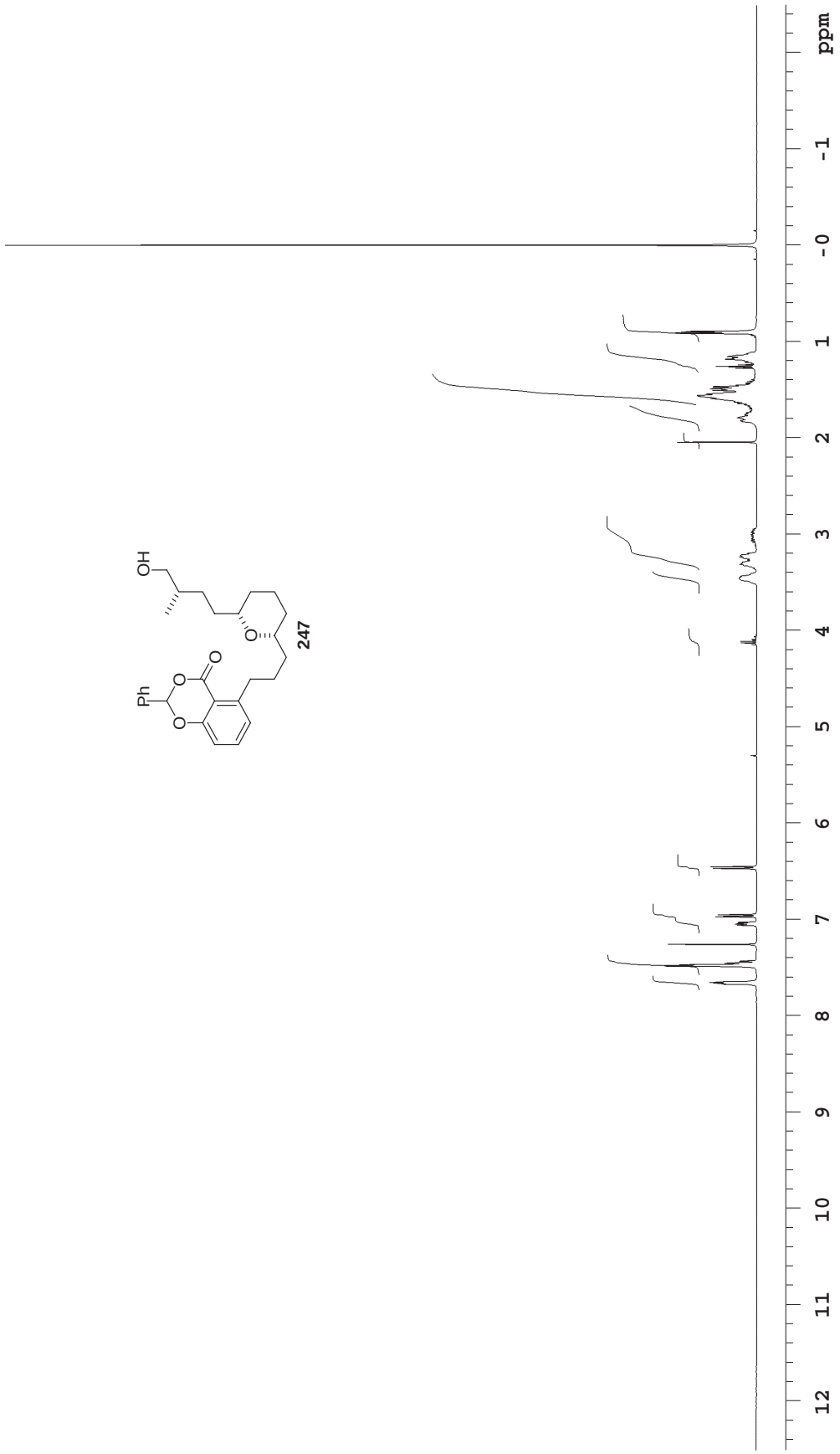
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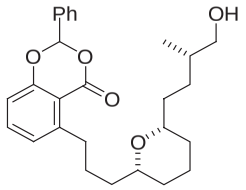

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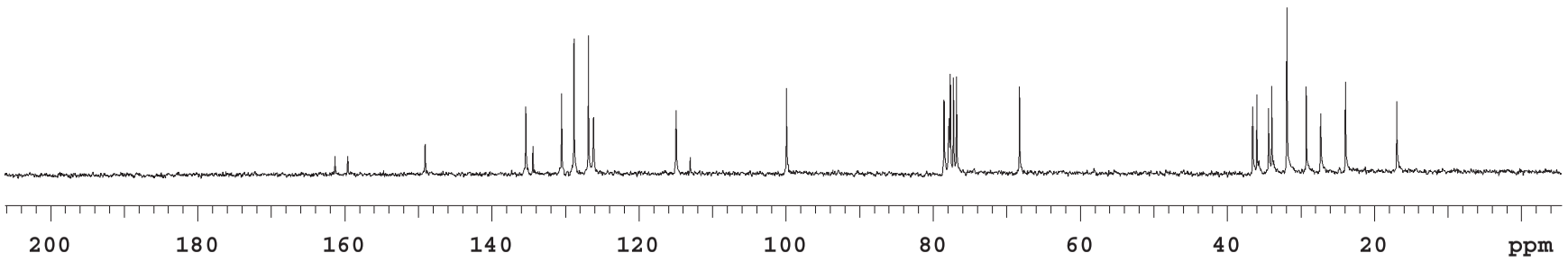

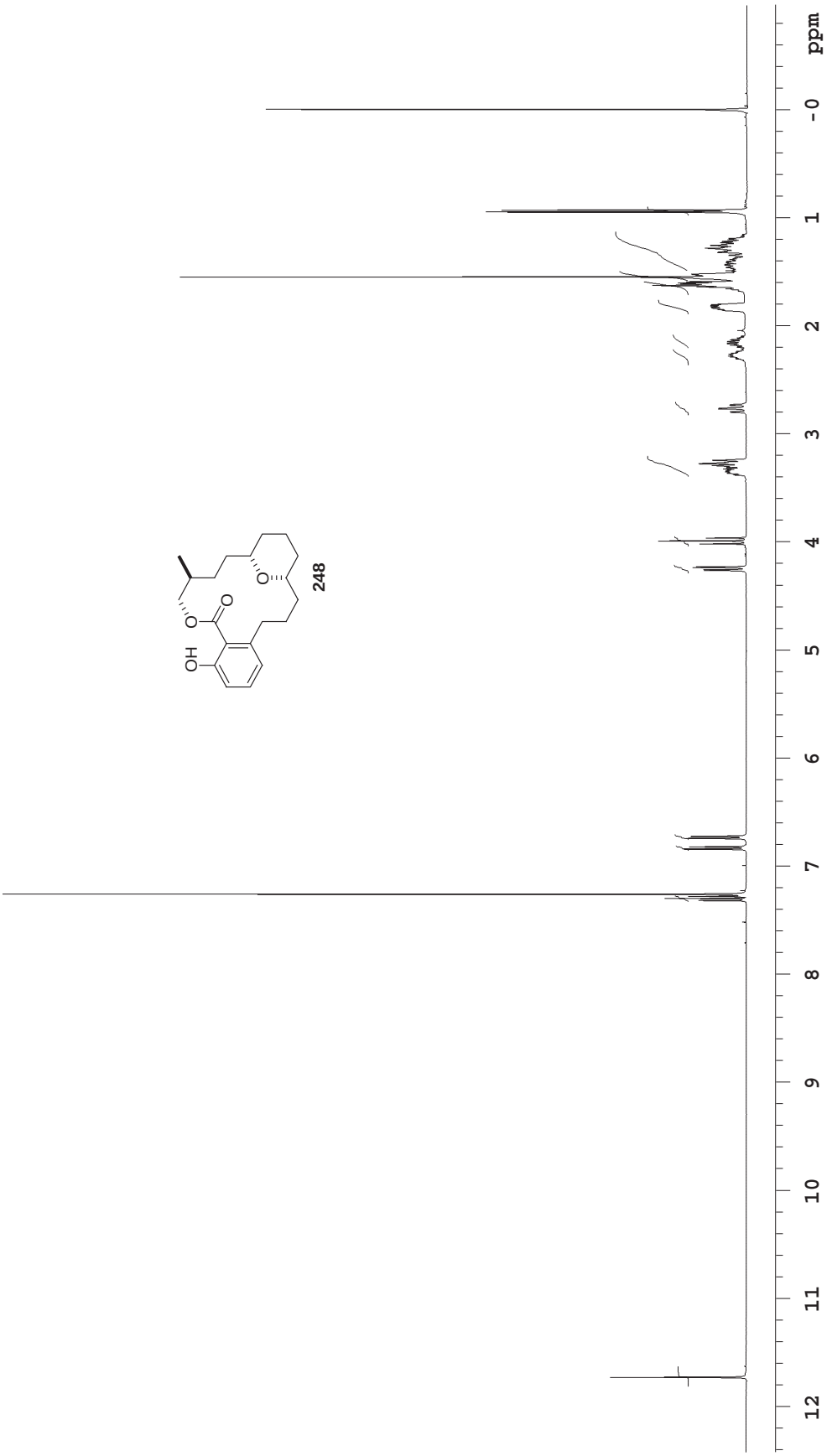
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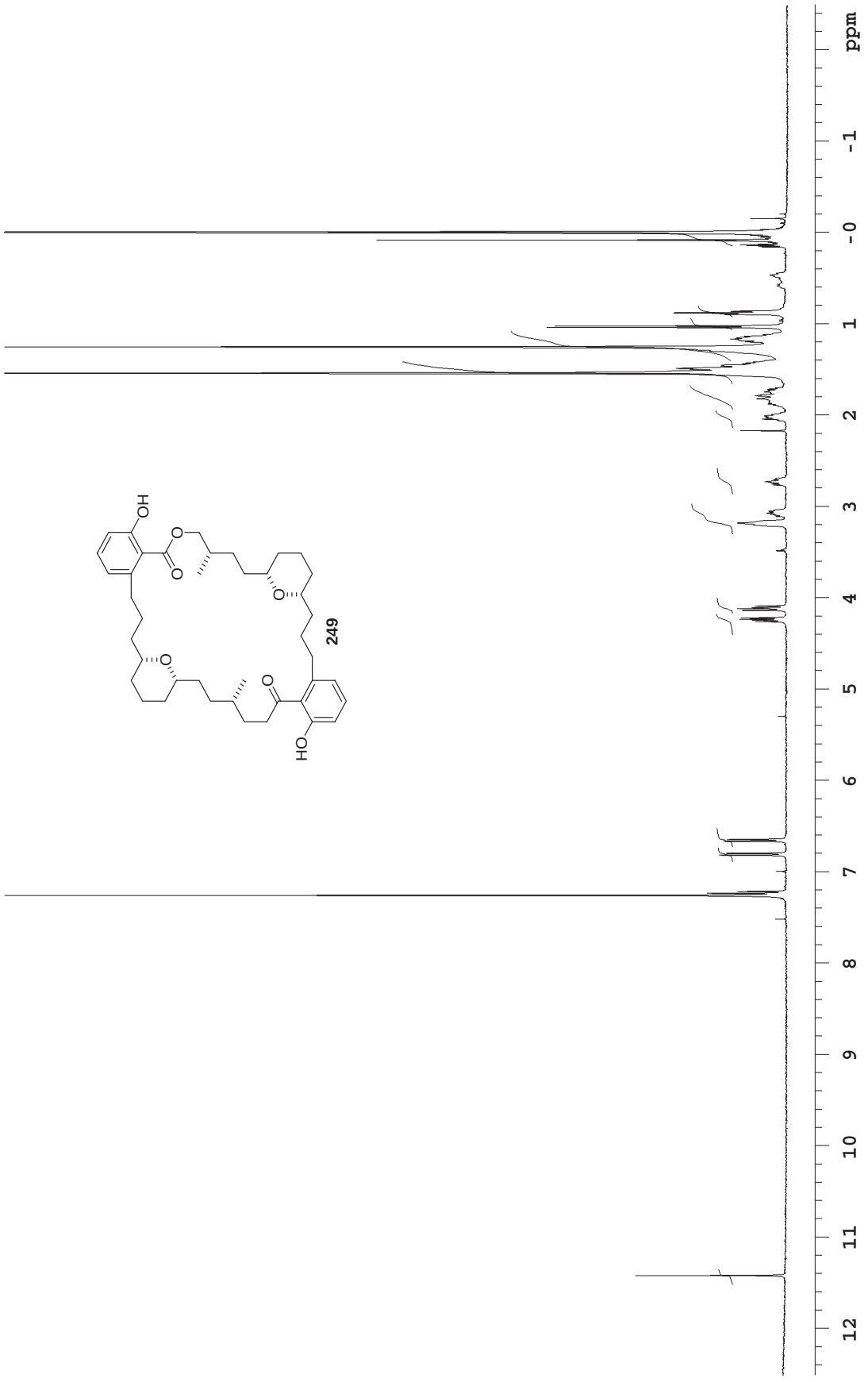
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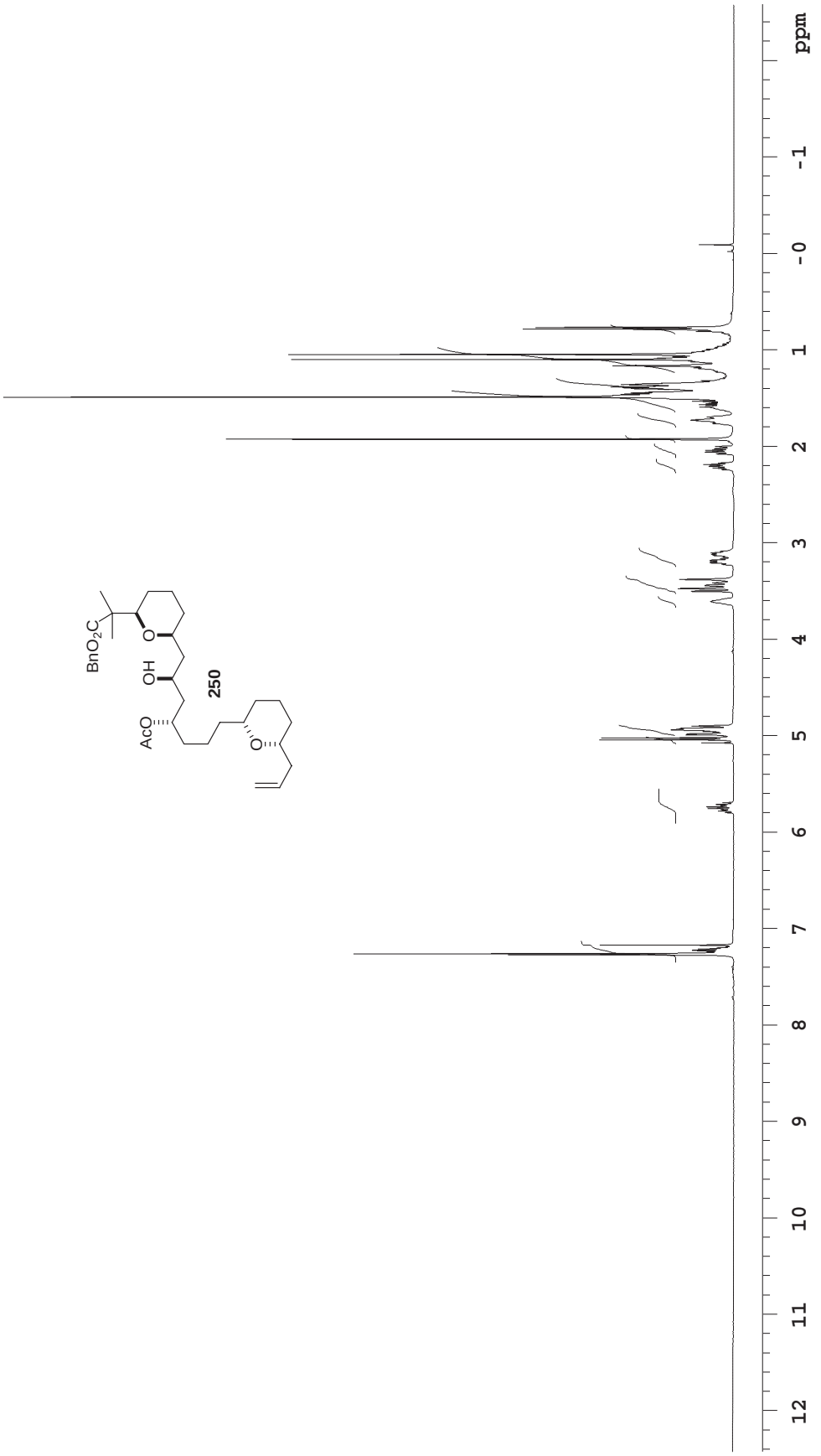
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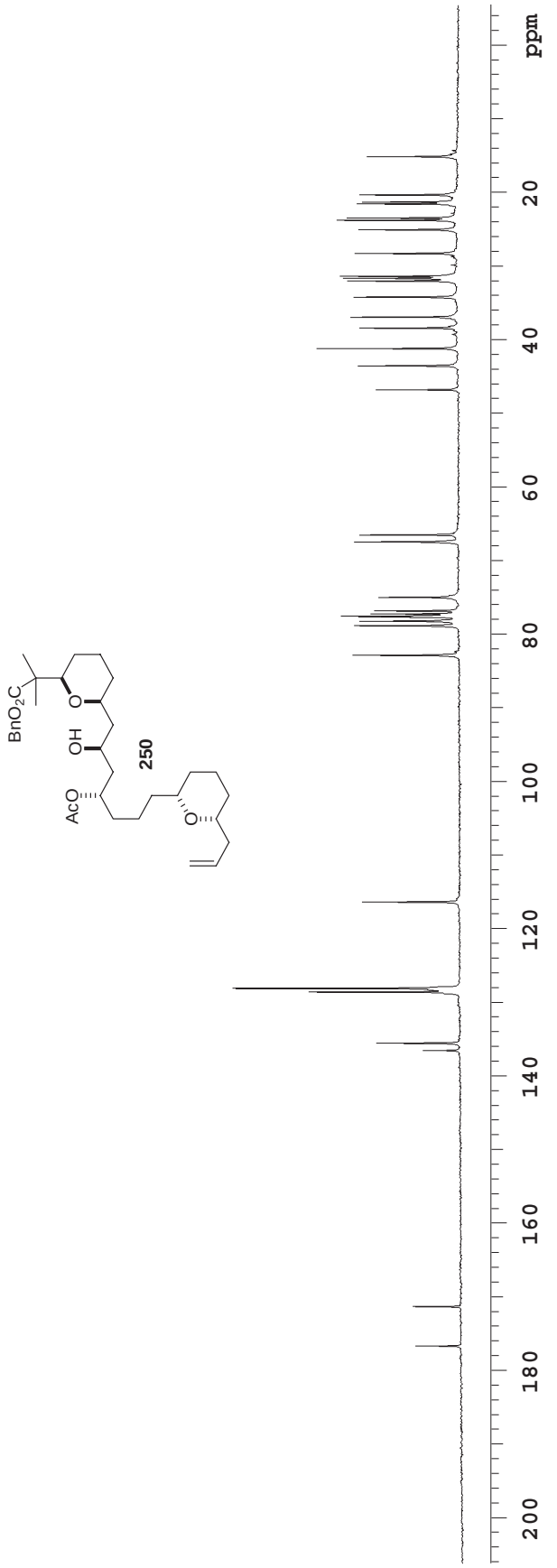
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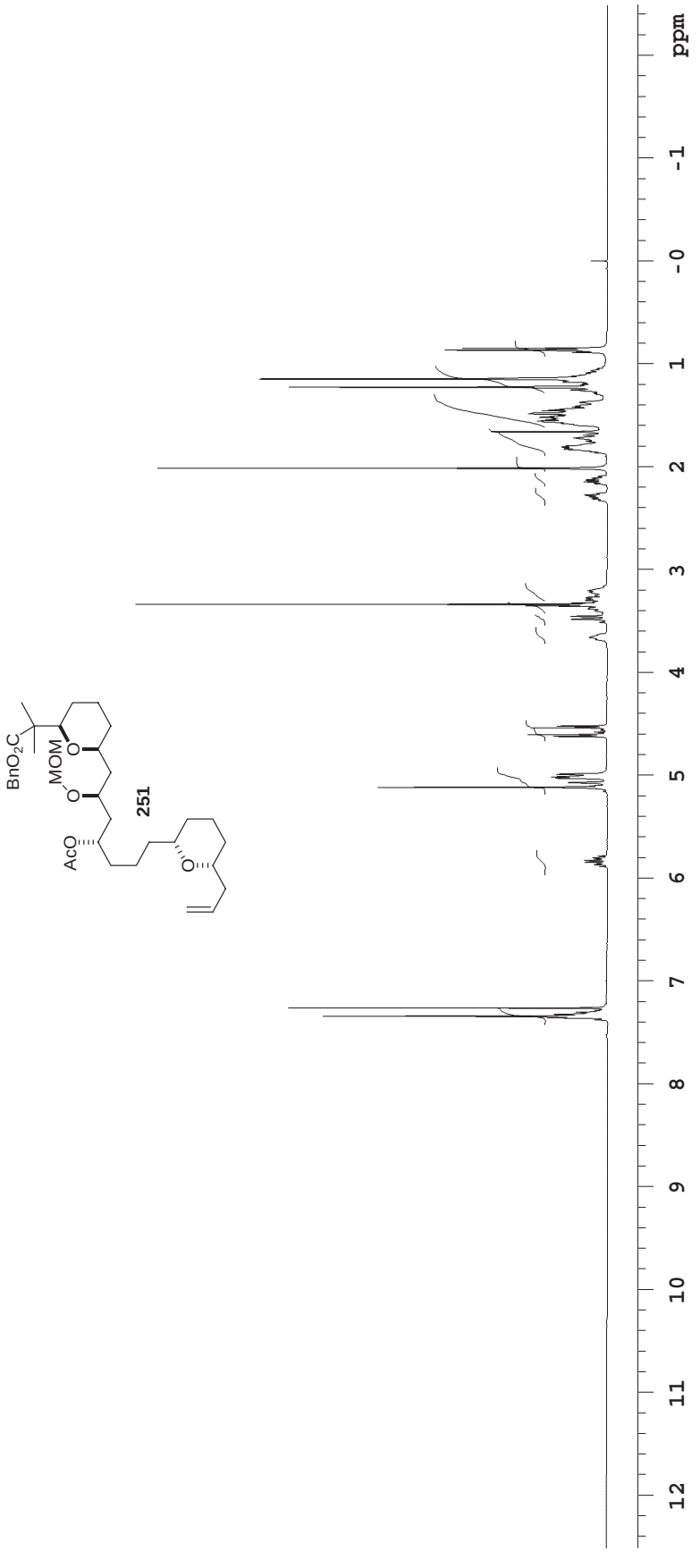
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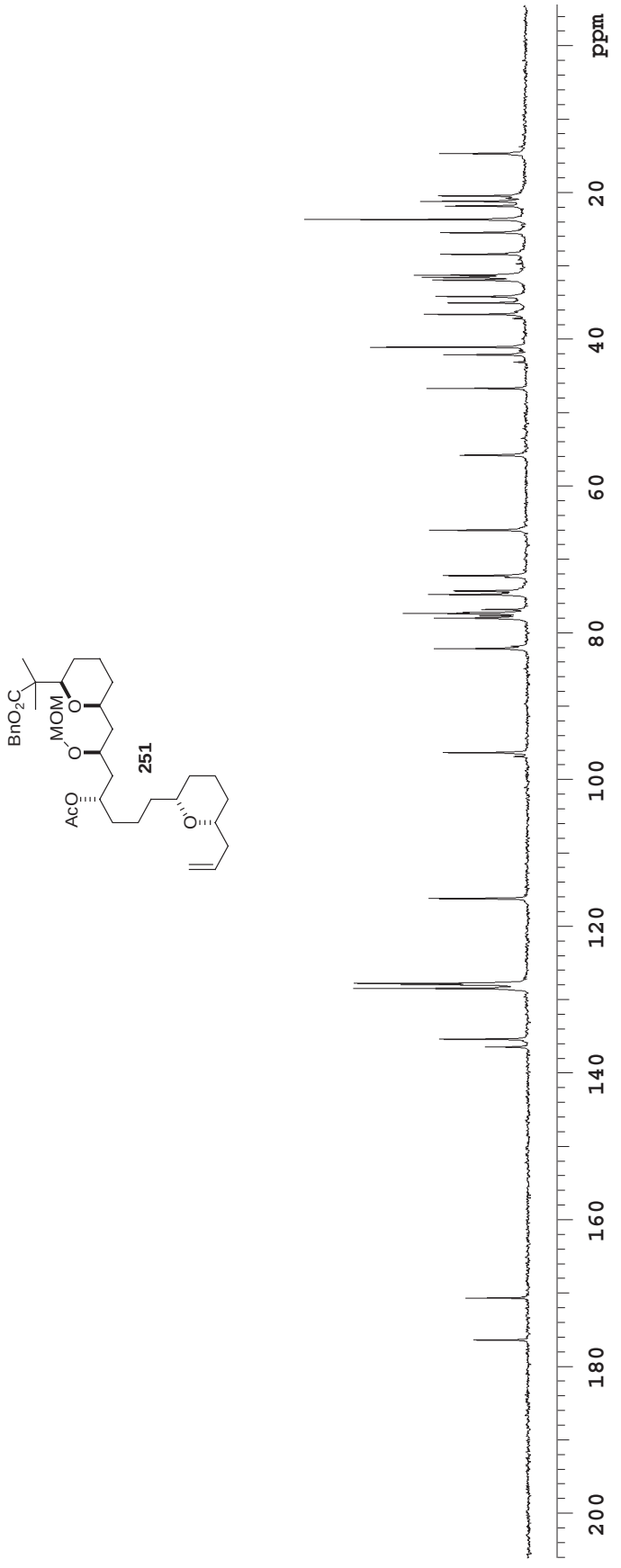
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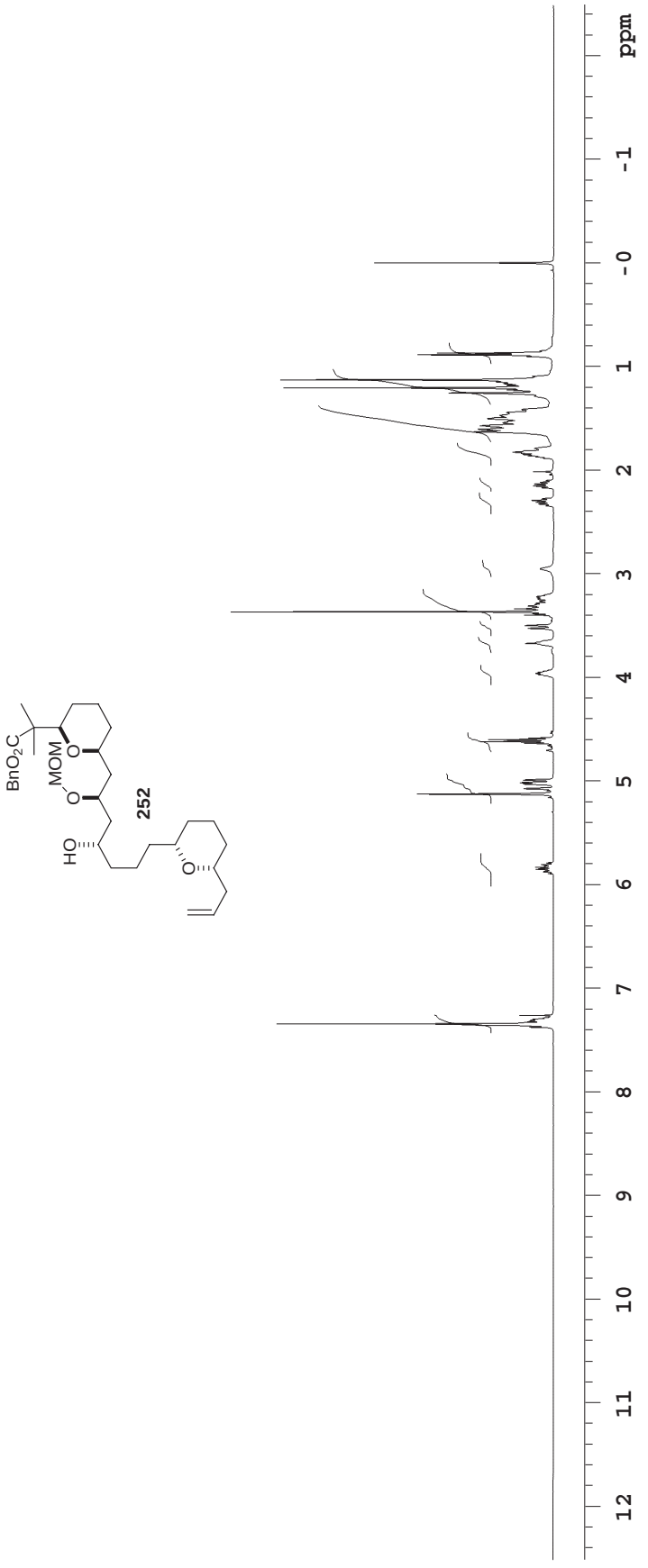
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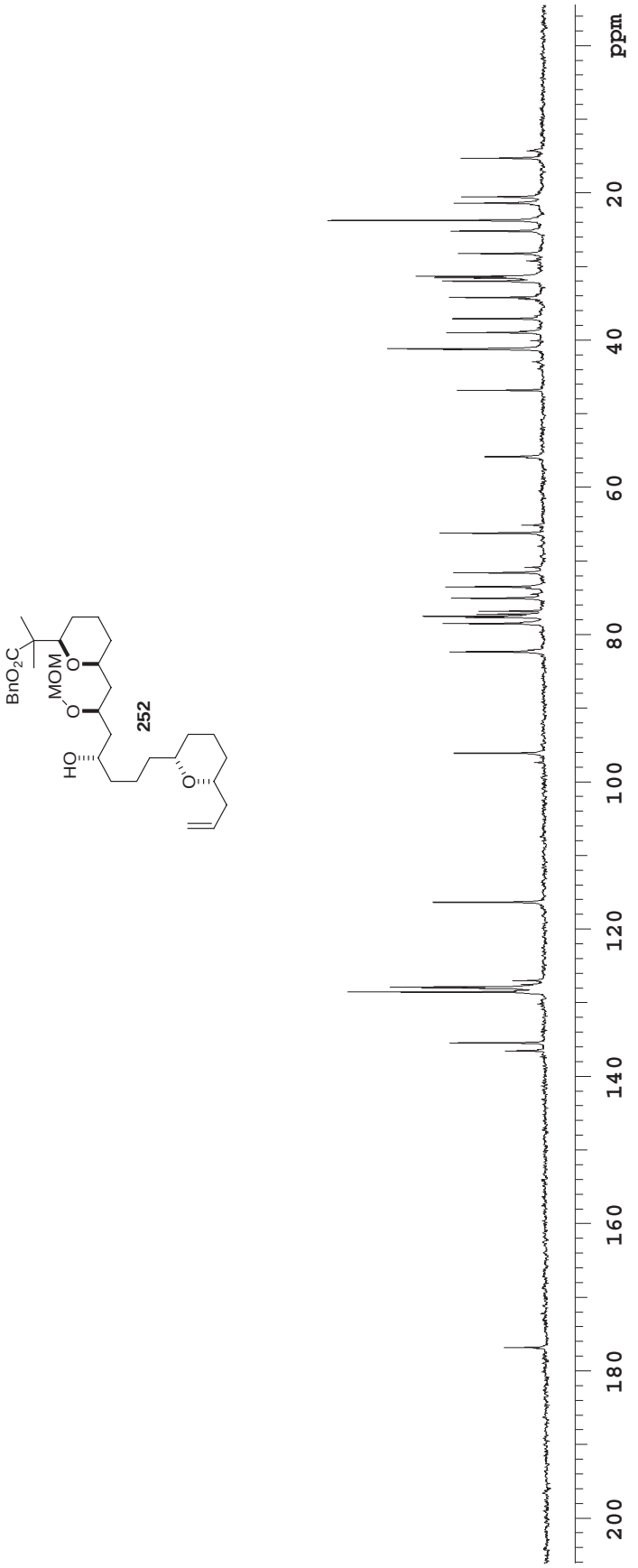
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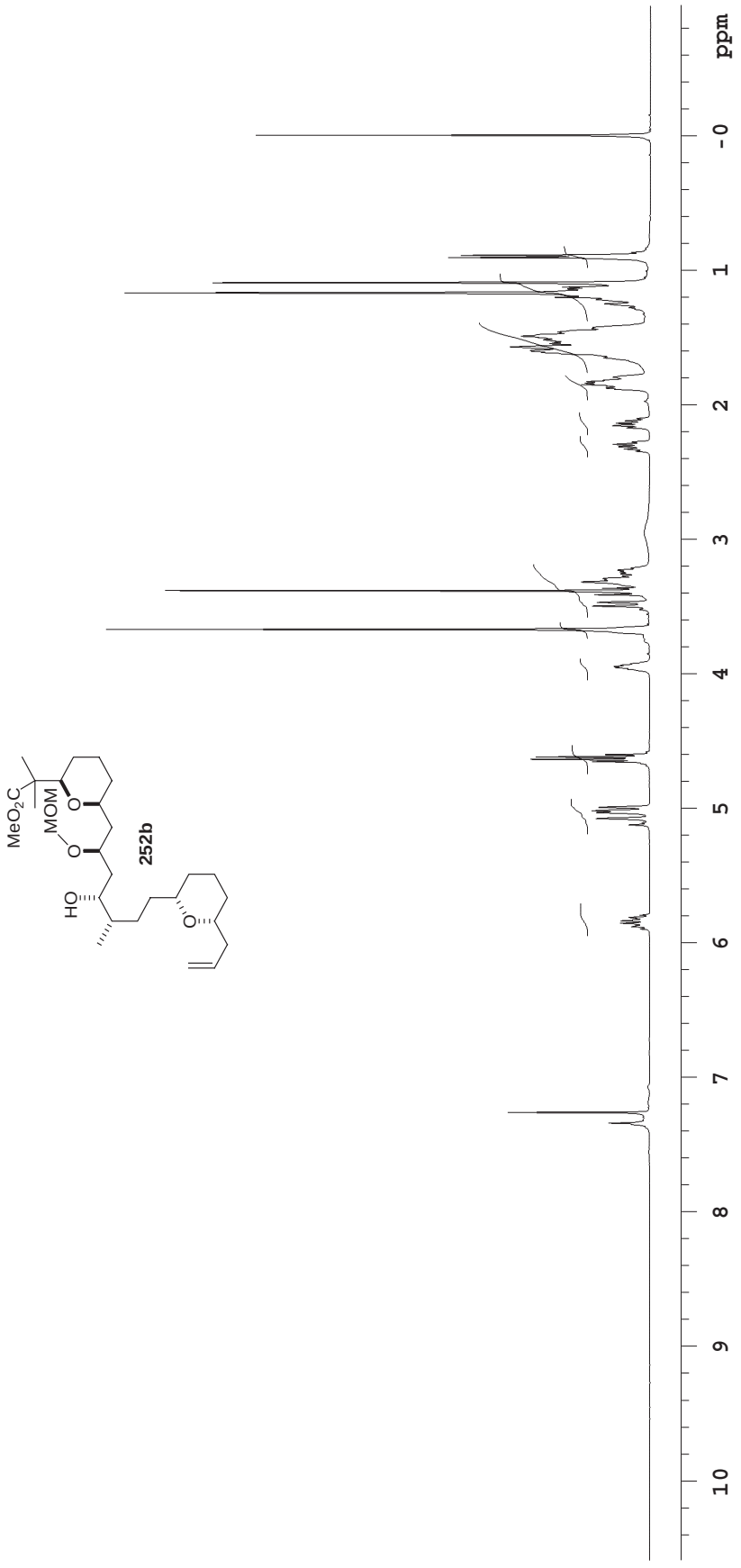
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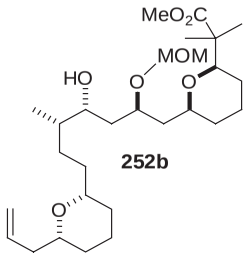

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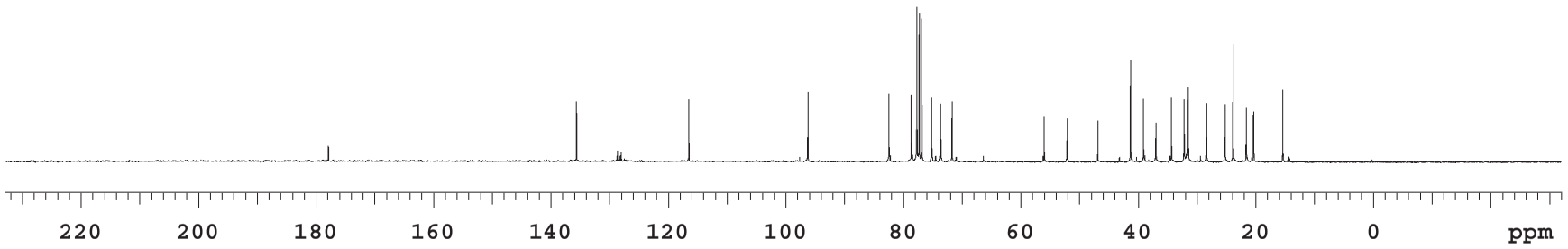

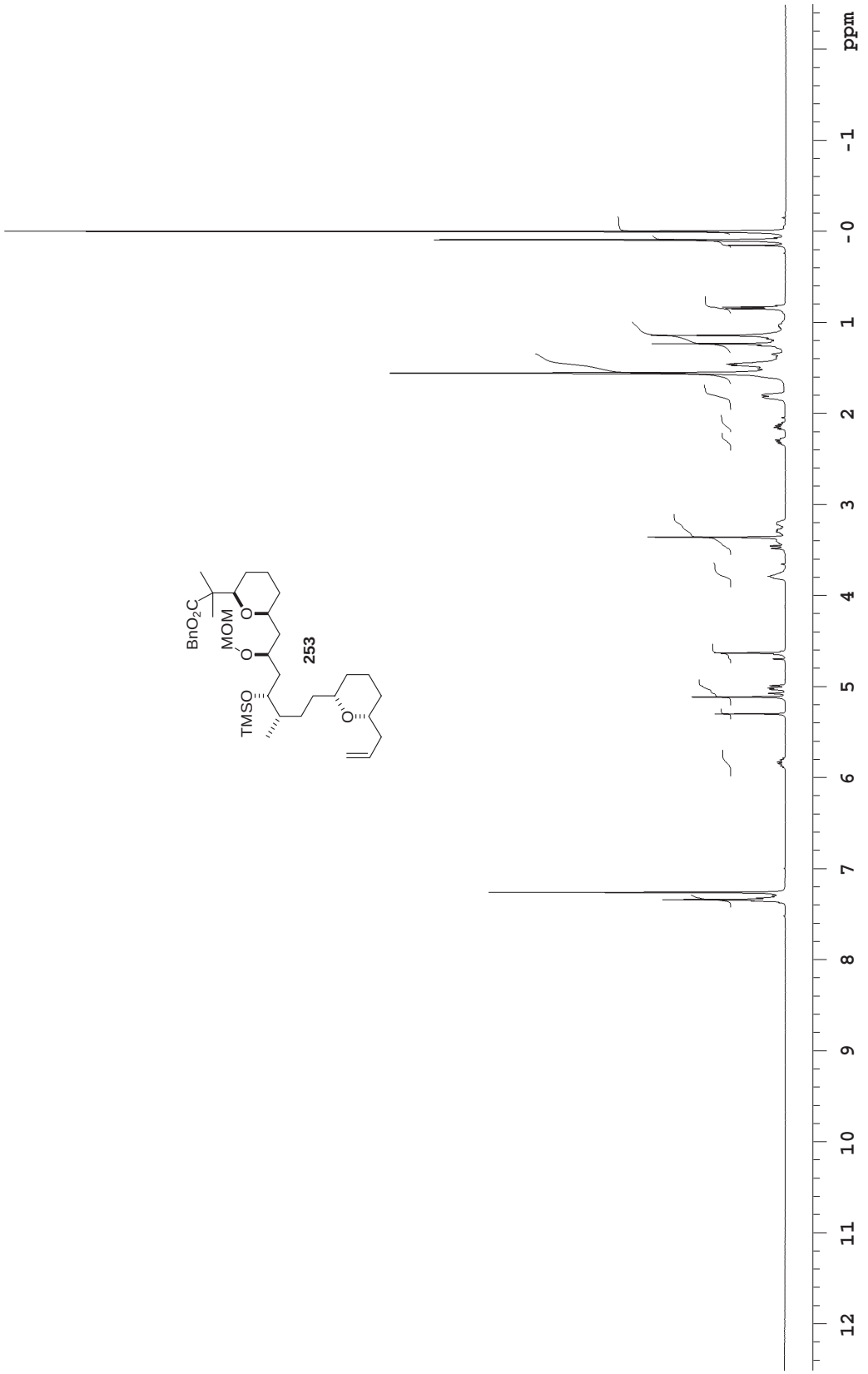
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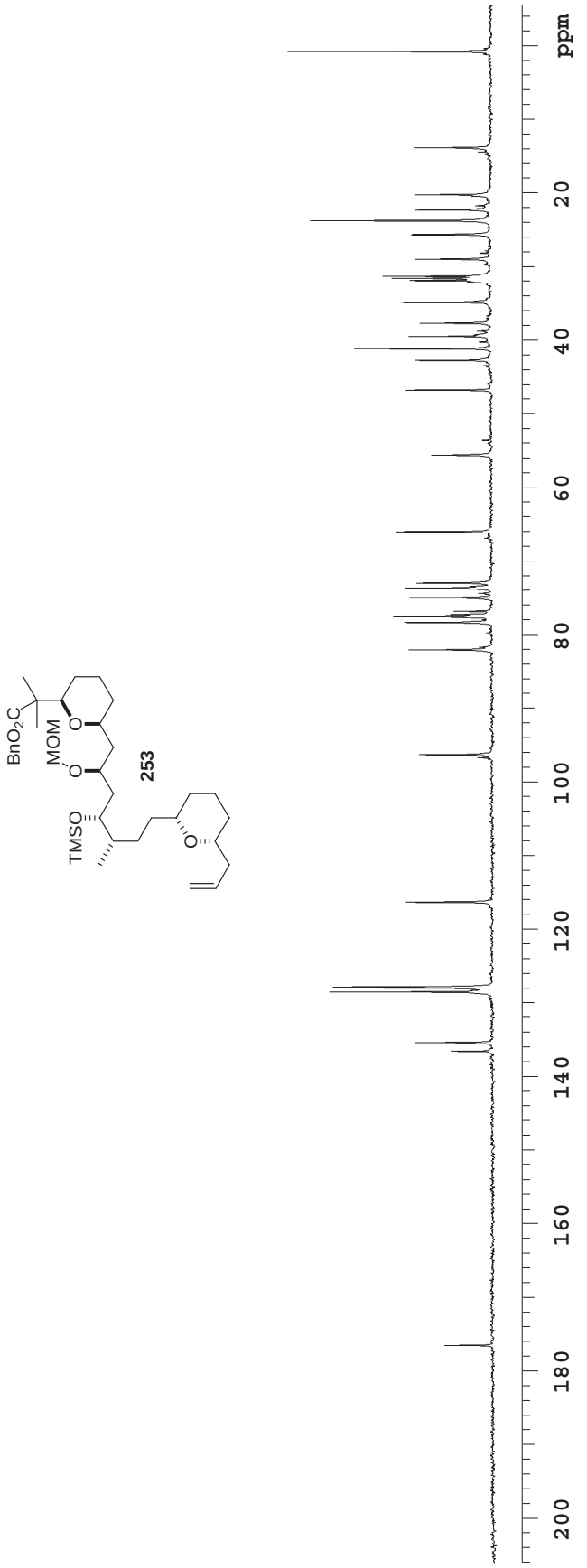
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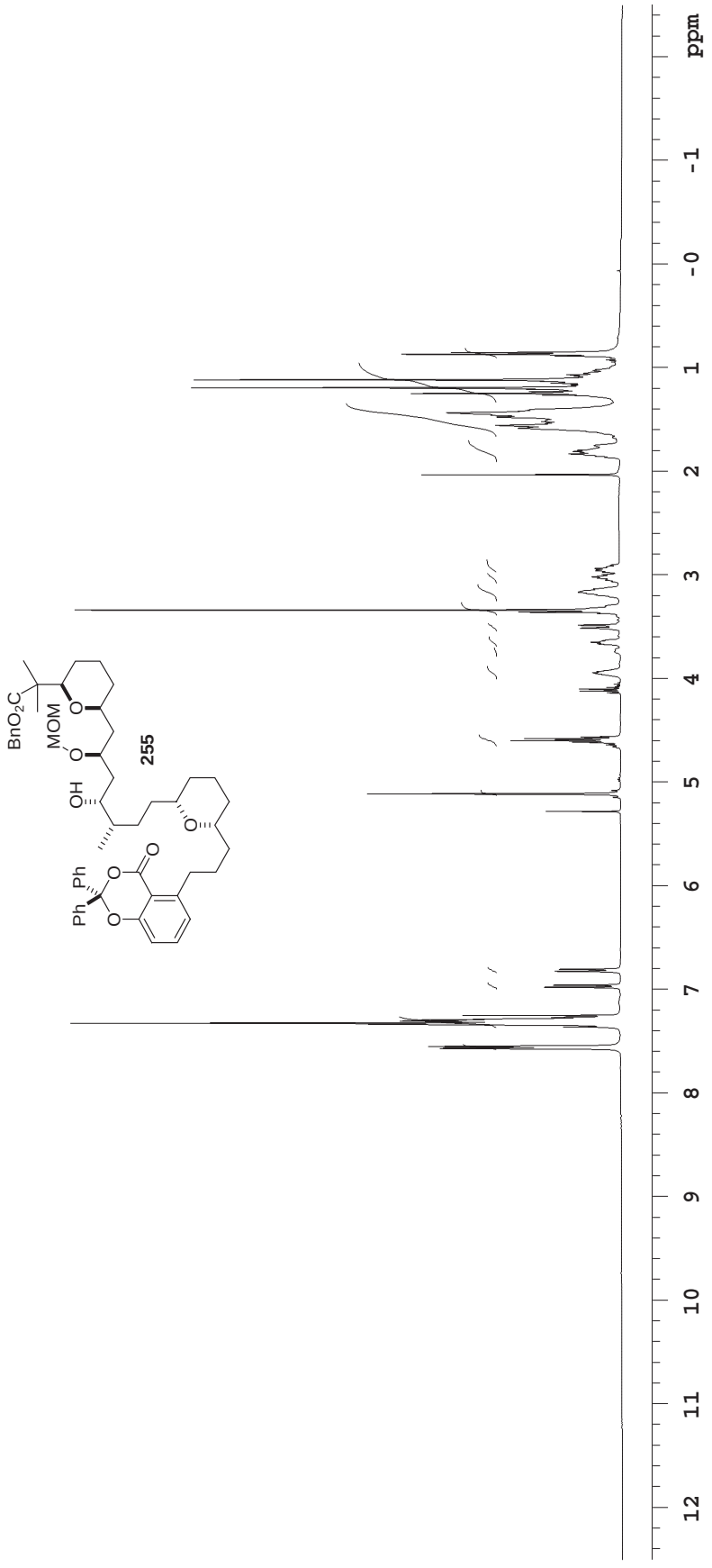
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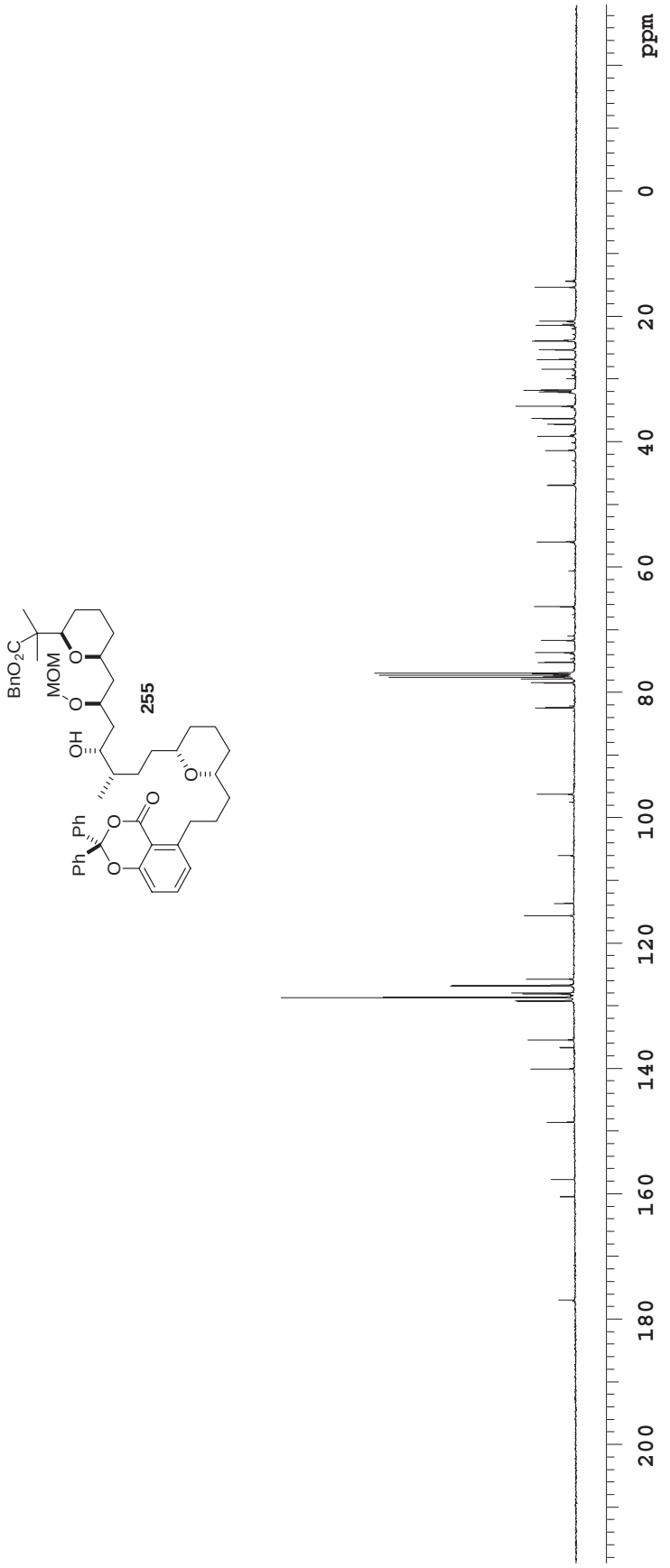
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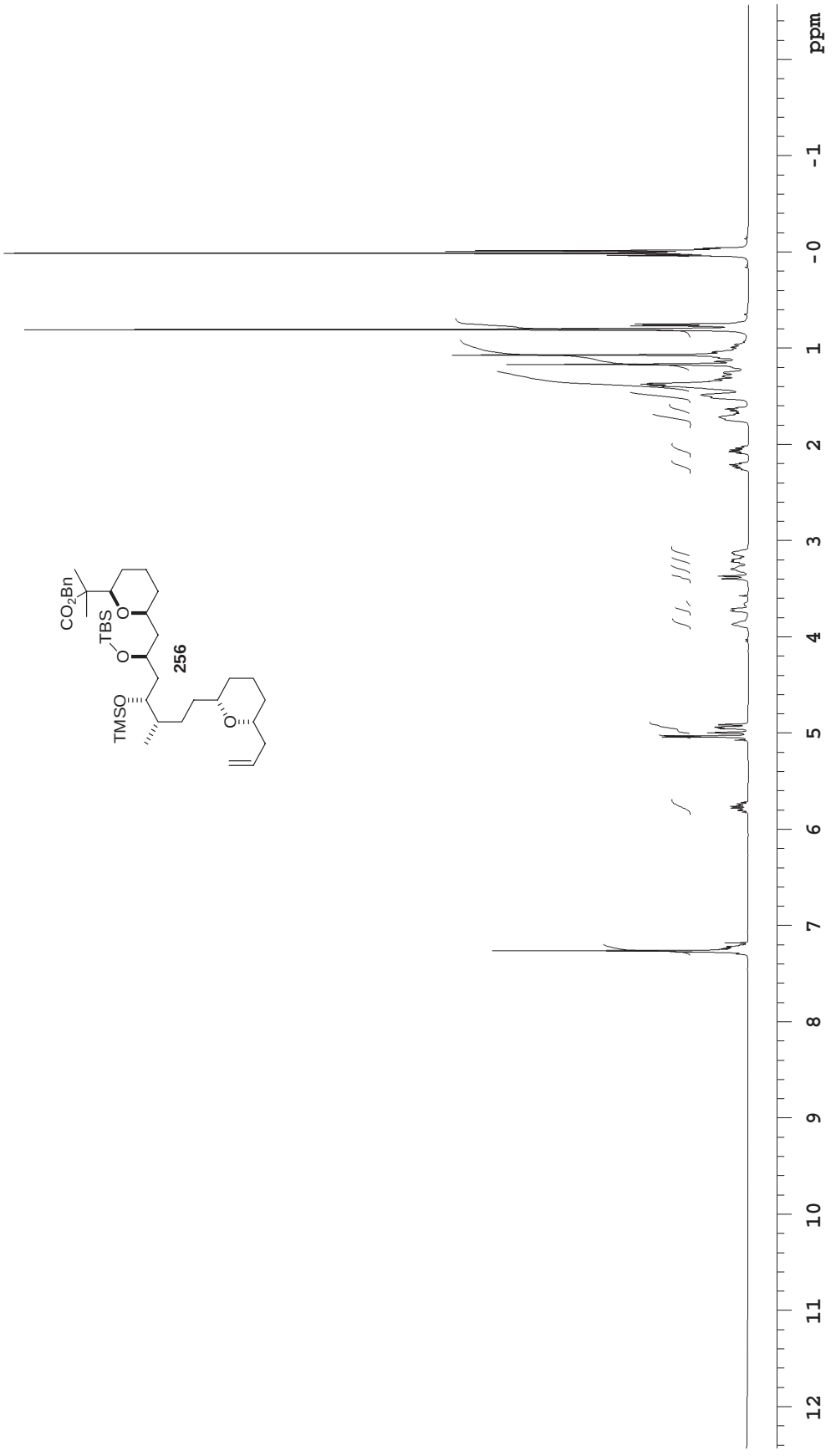
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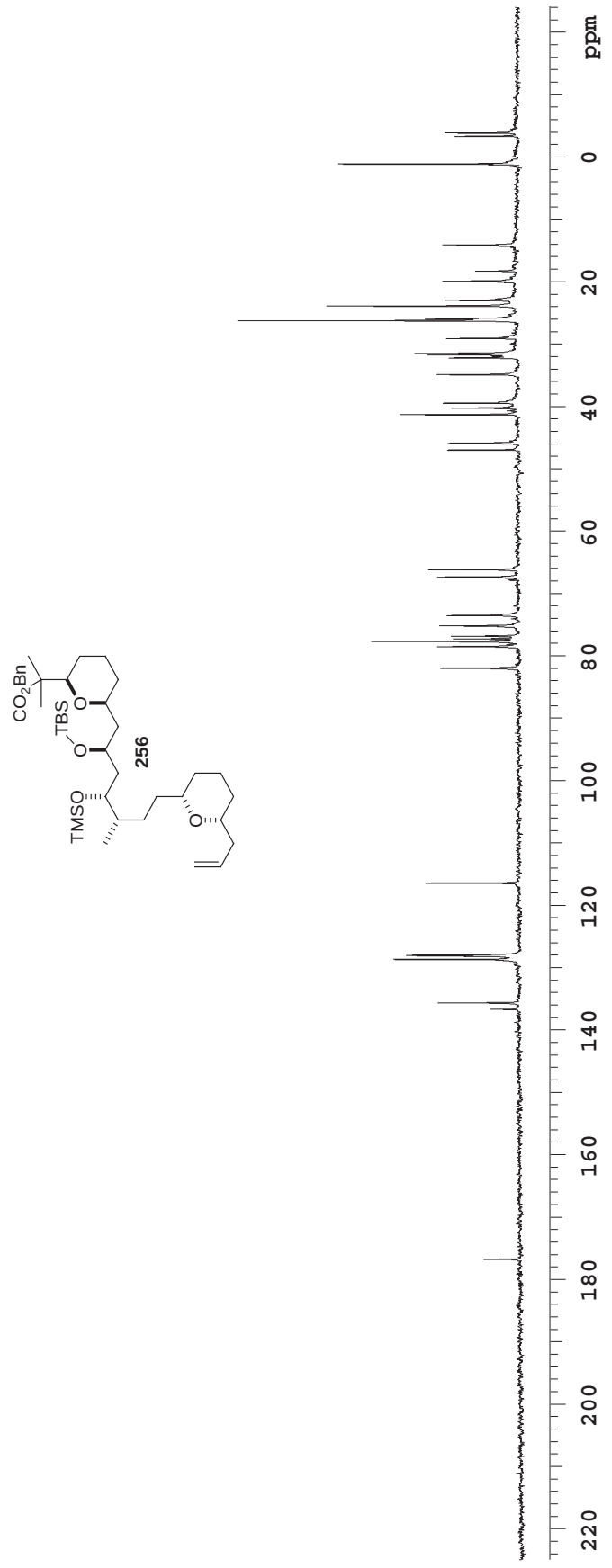
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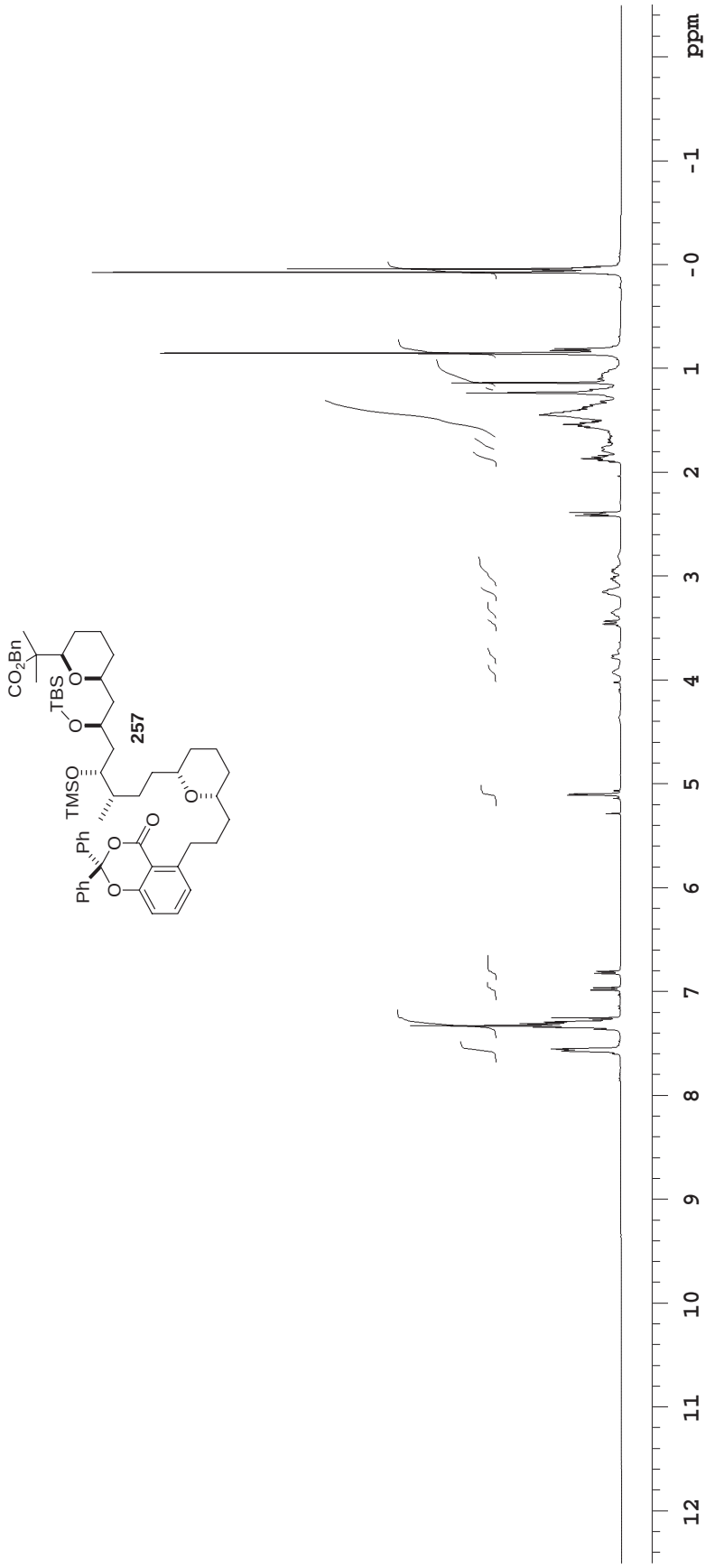
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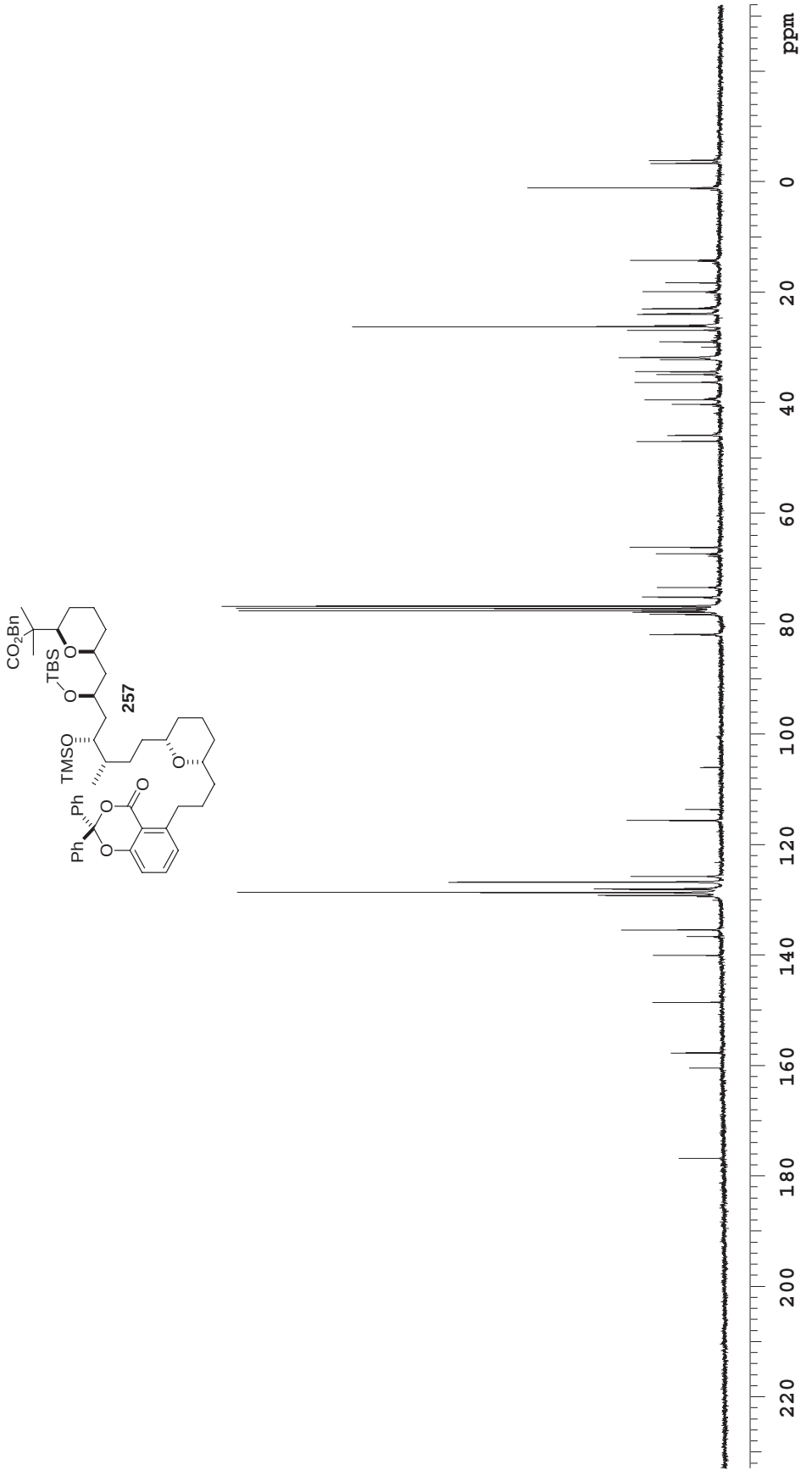
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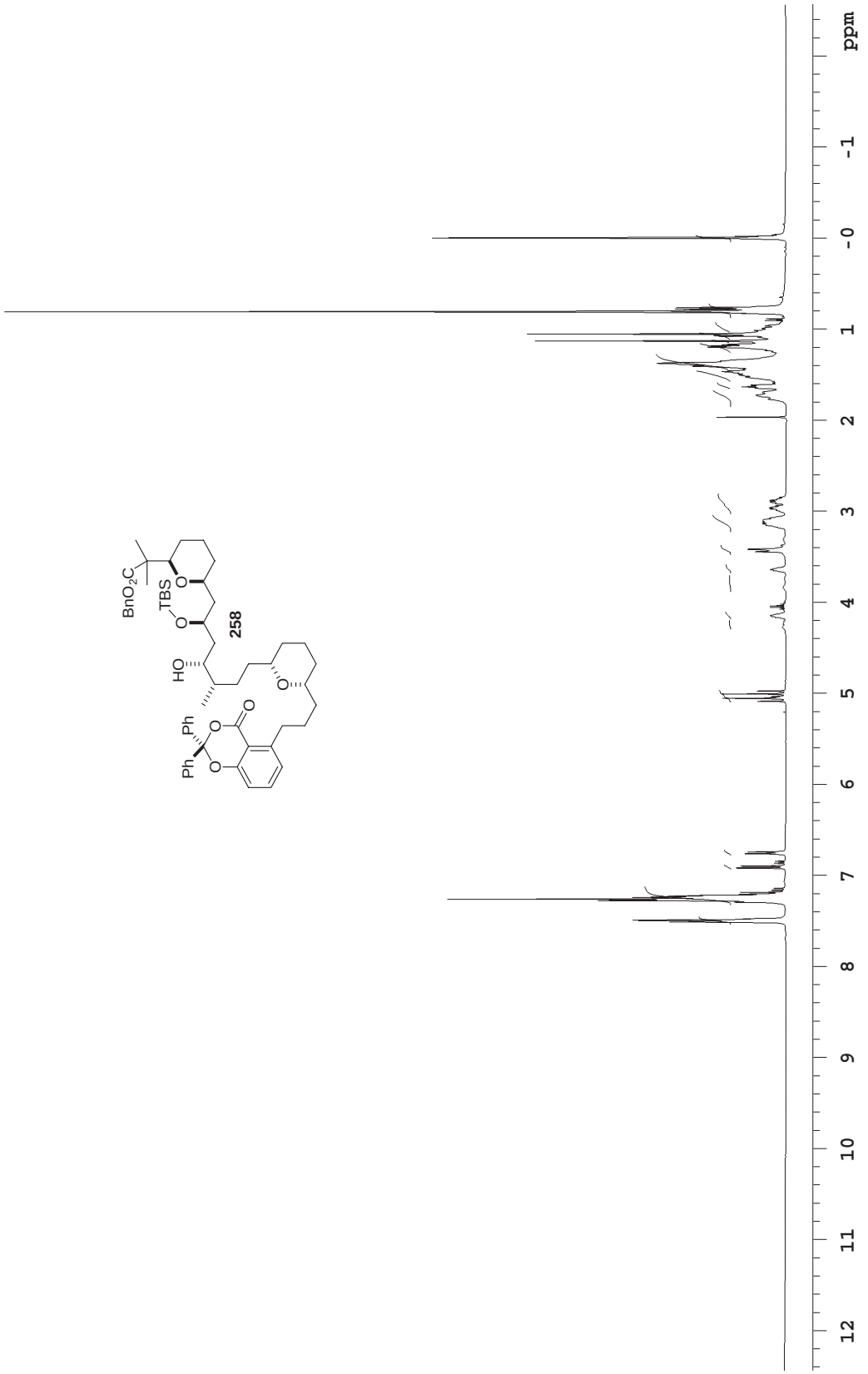
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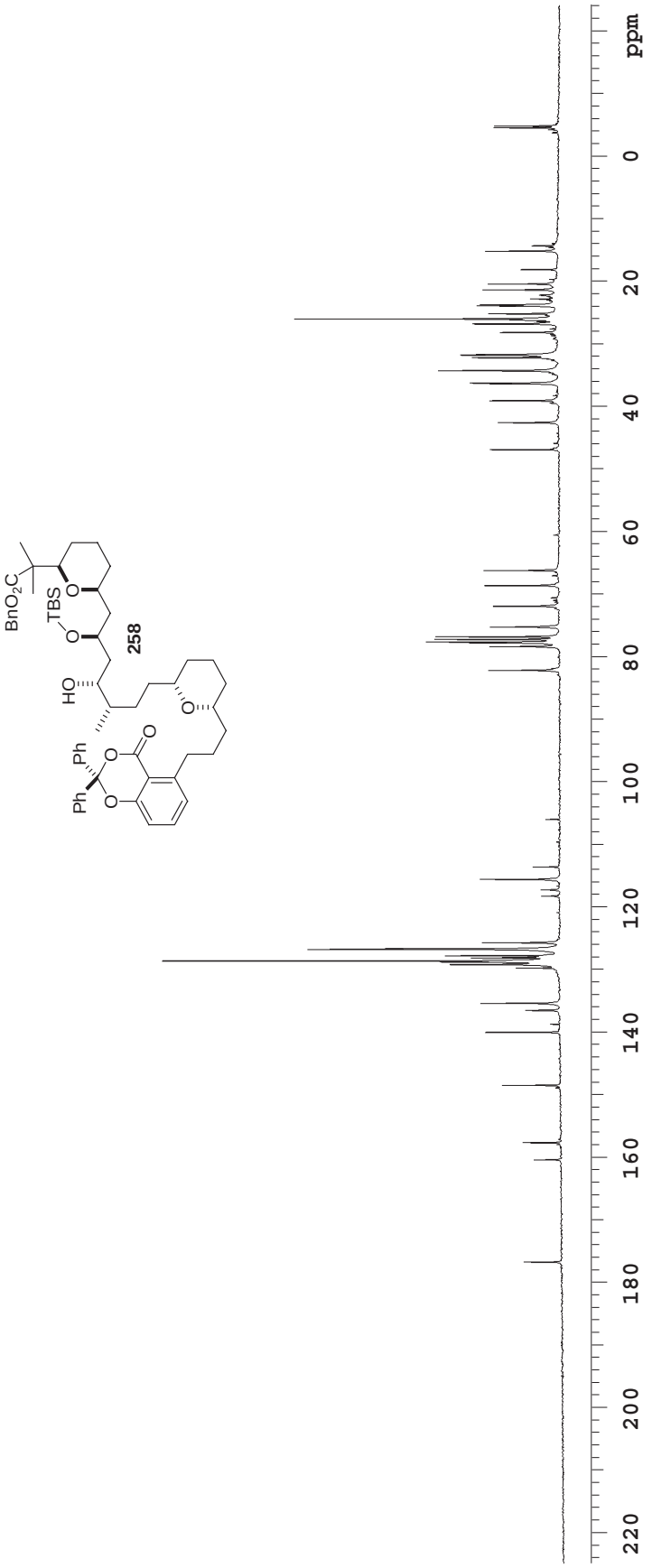
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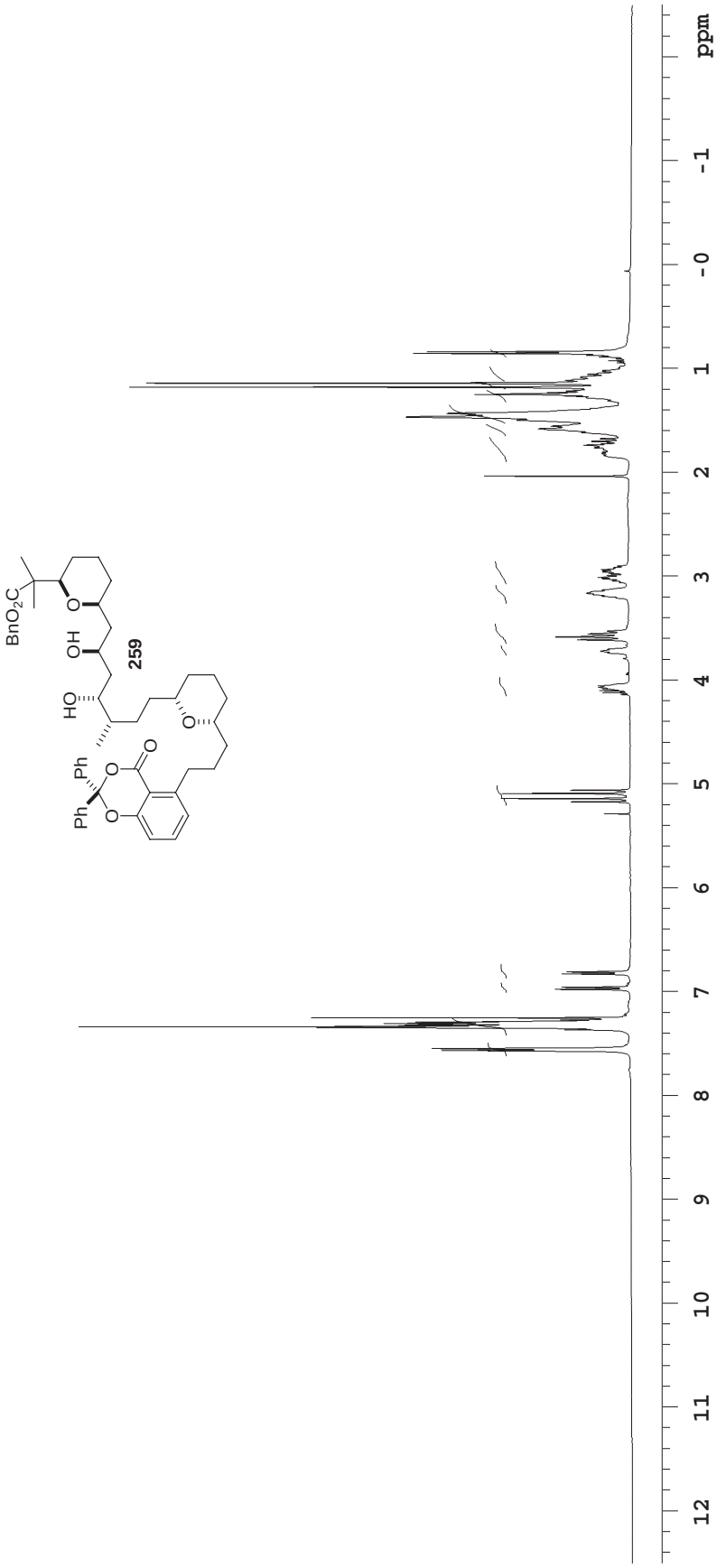
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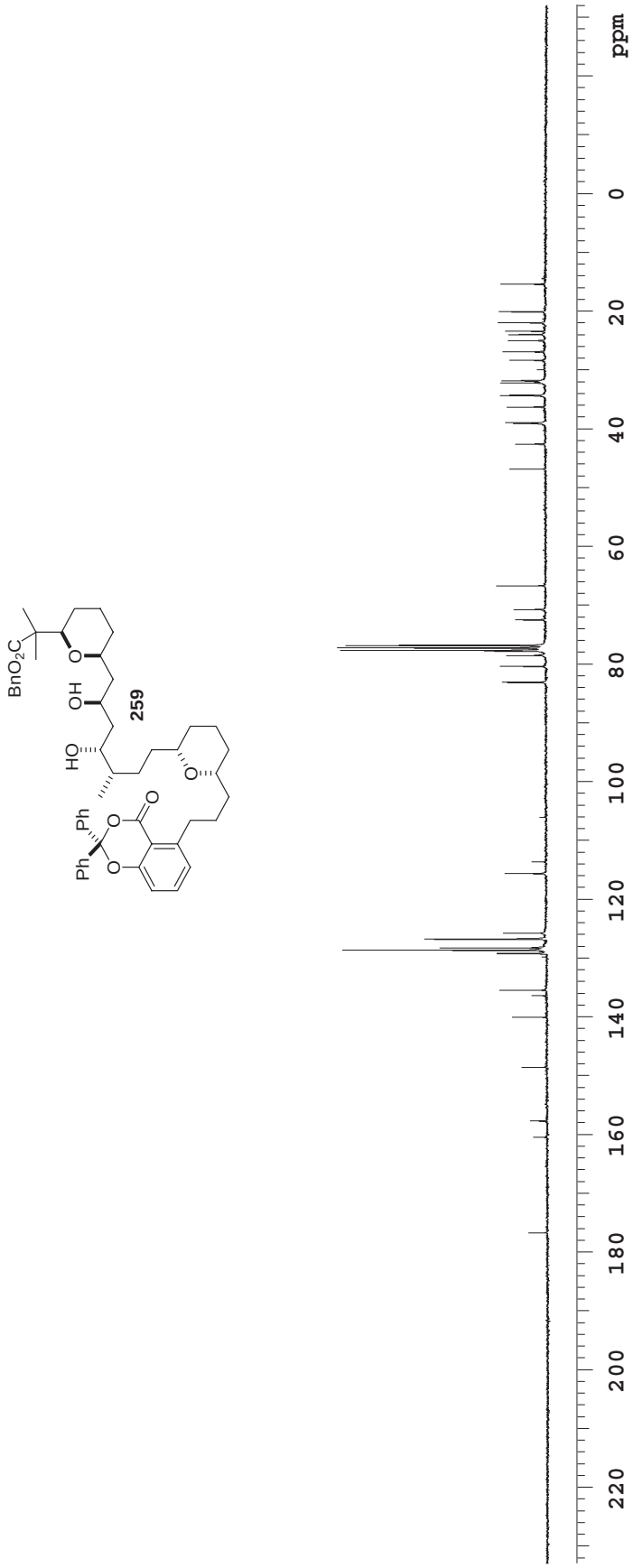
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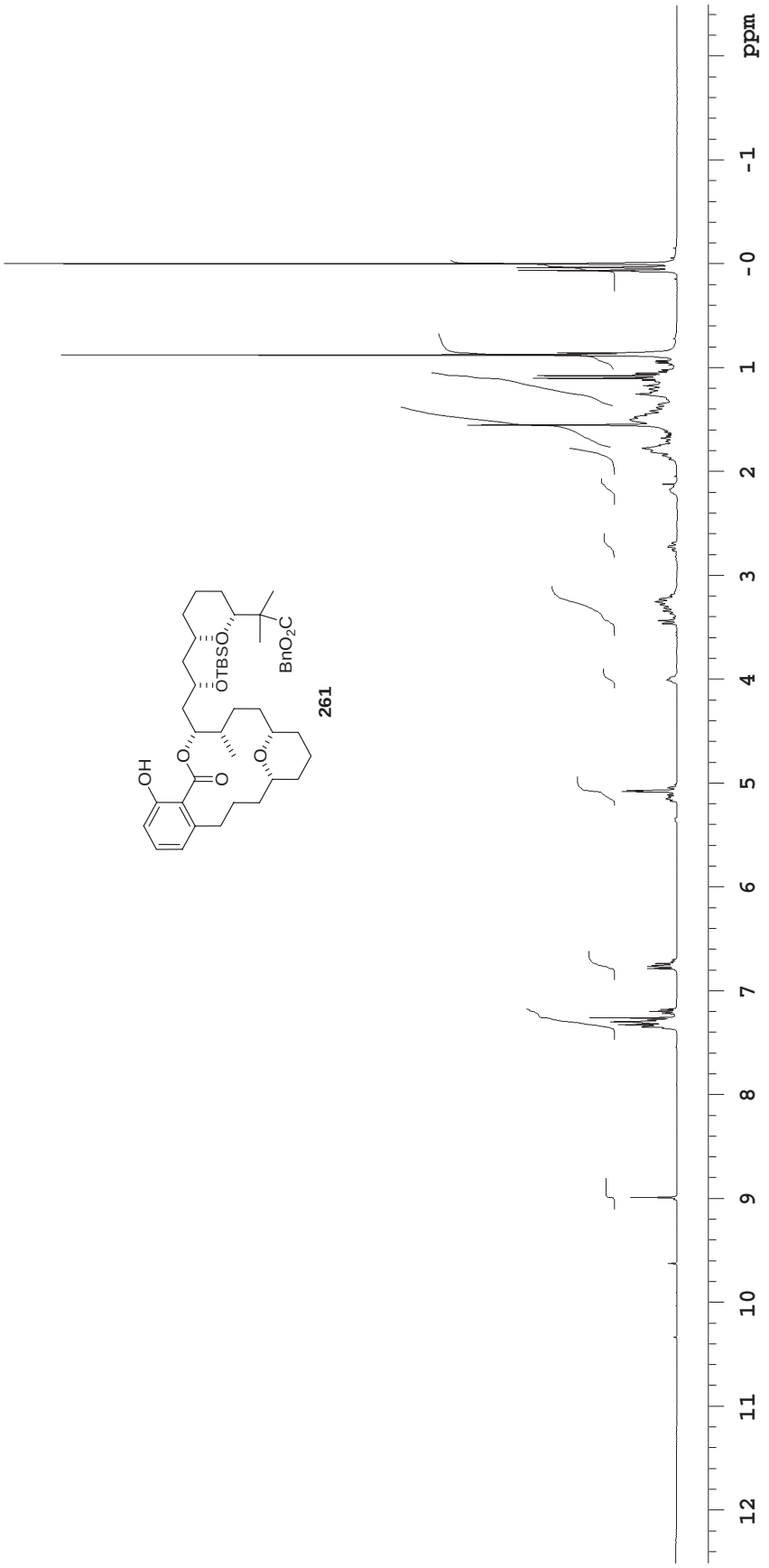
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BnO2C
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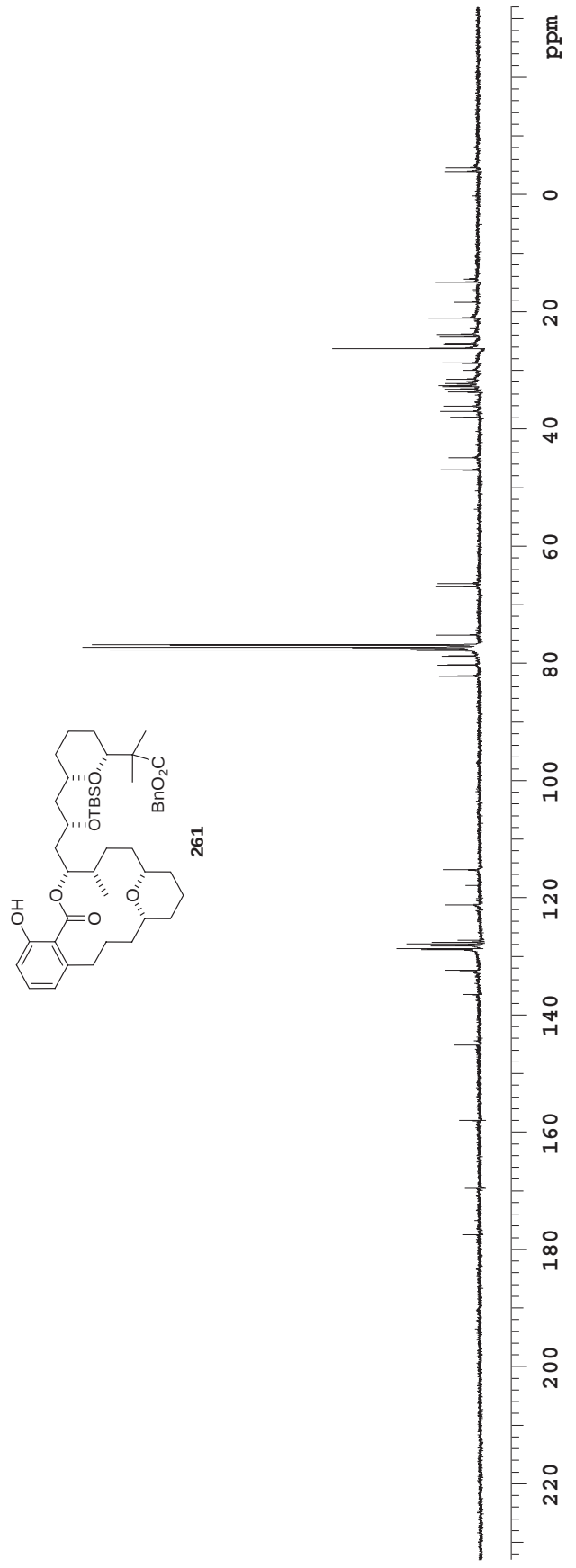
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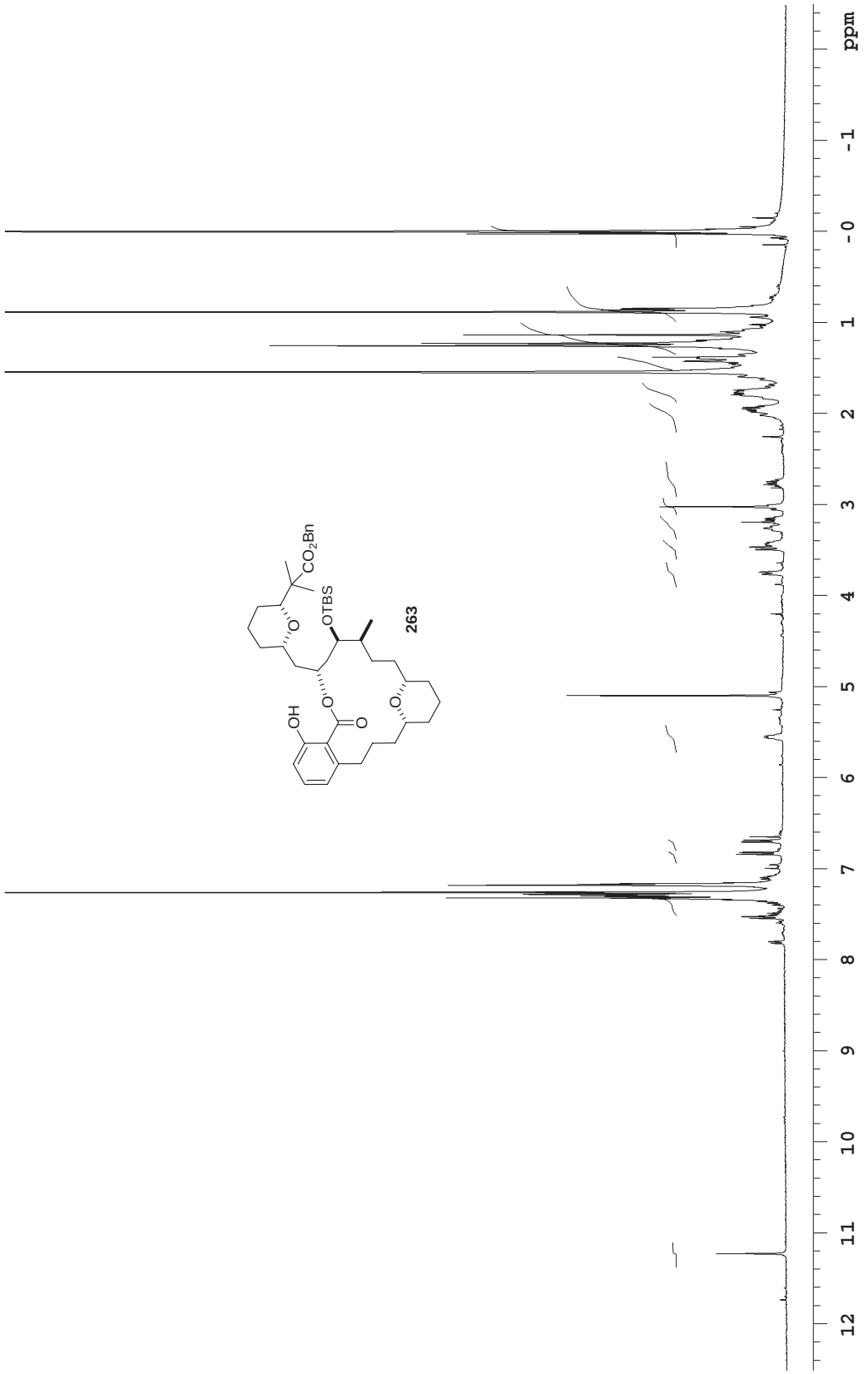
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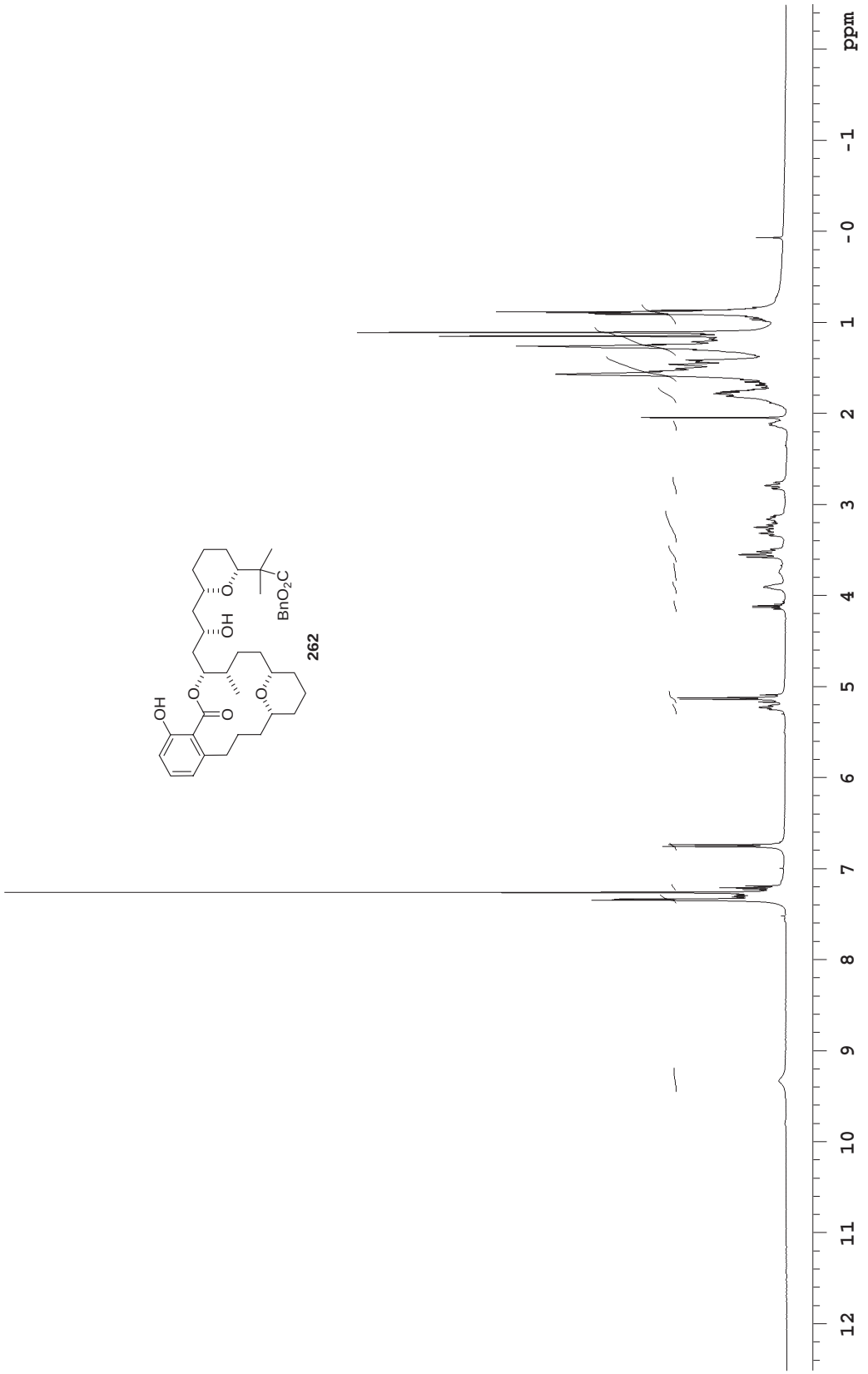
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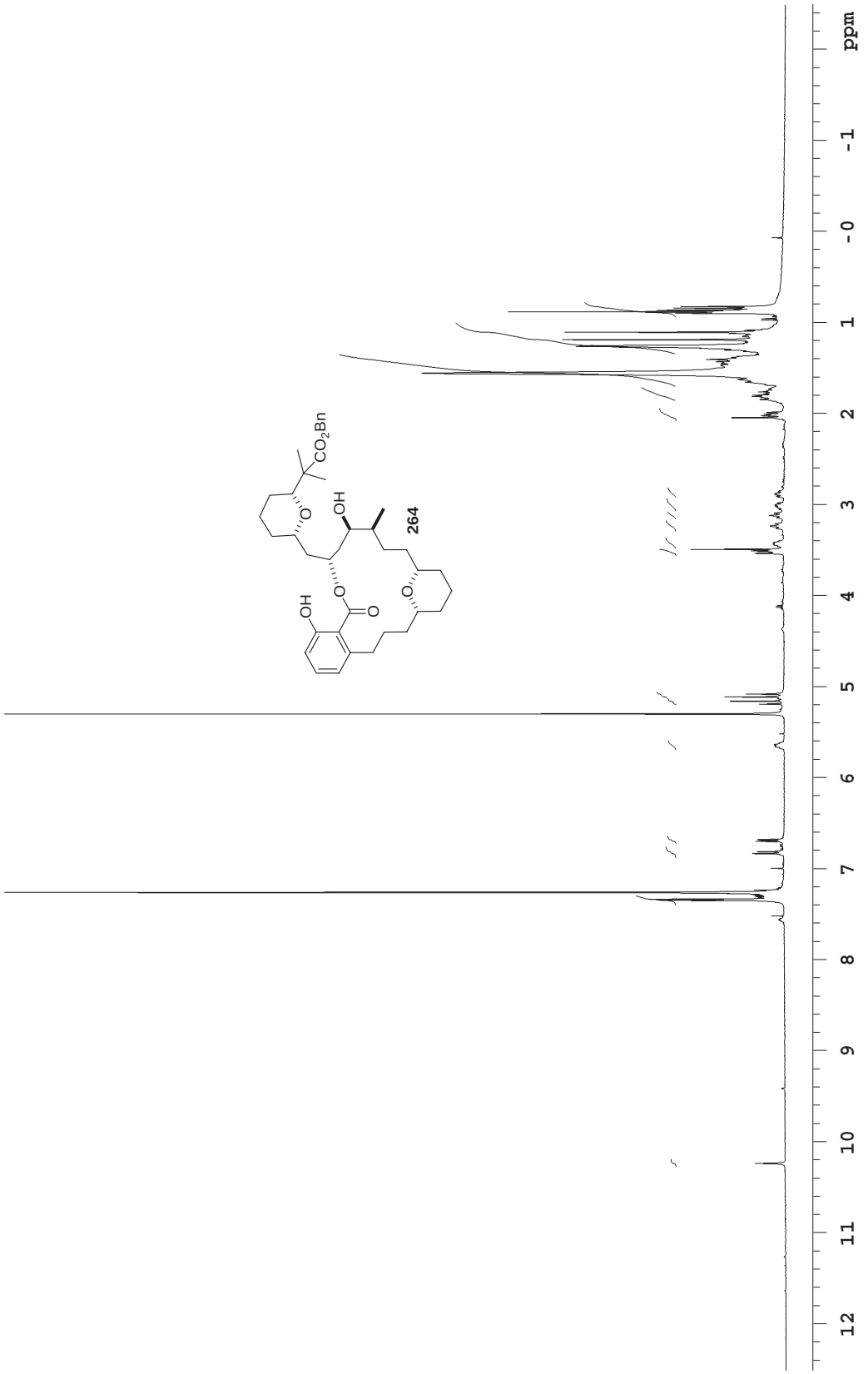
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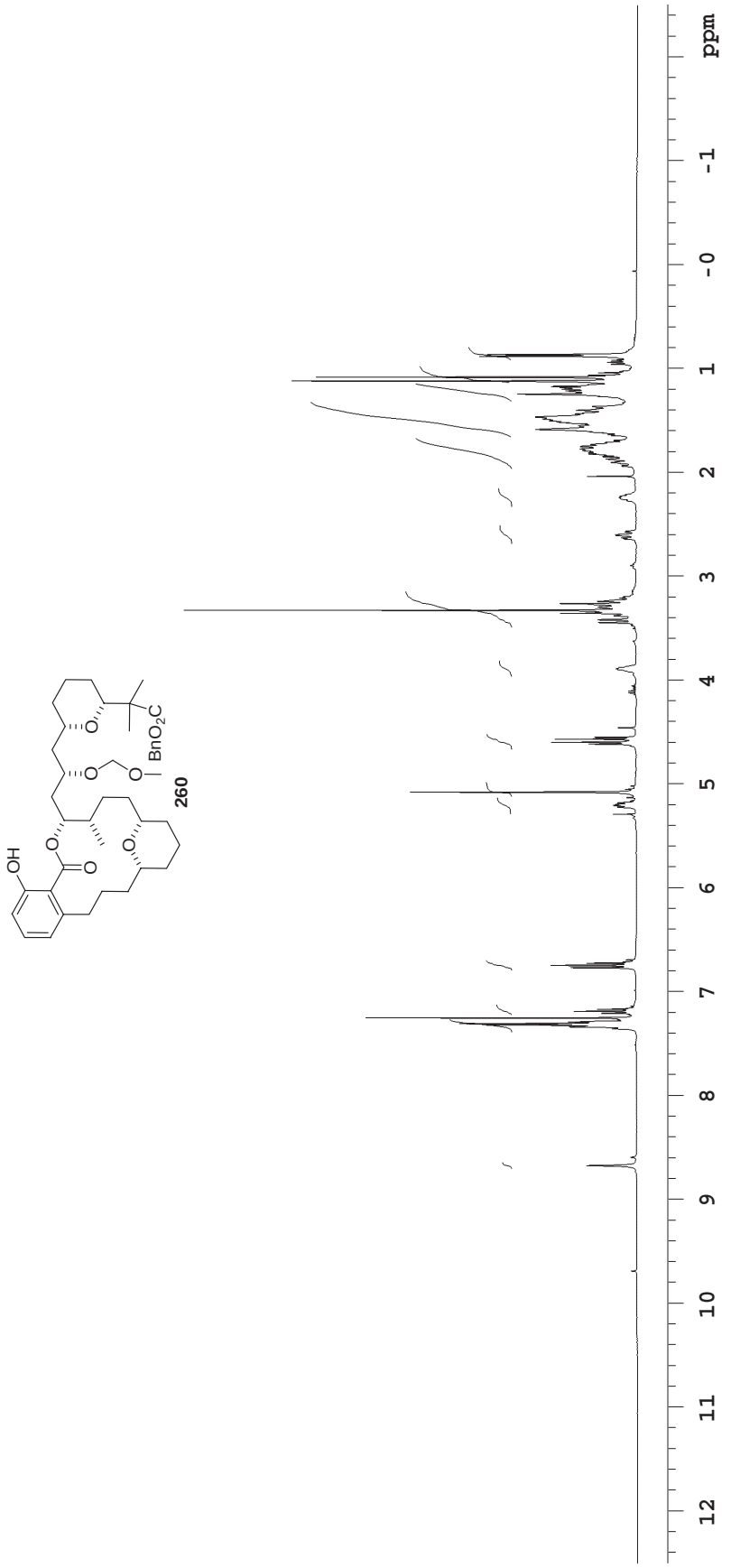
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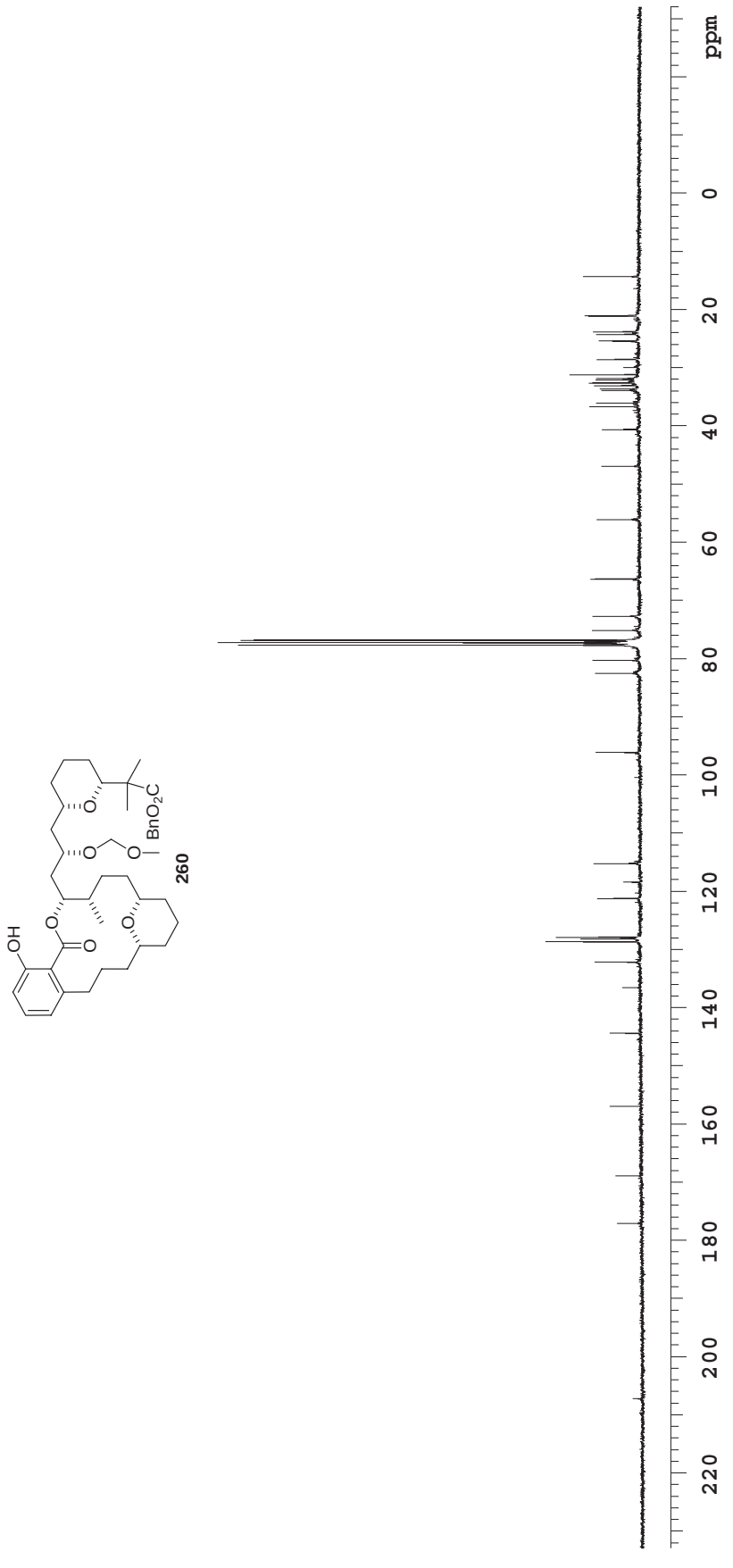
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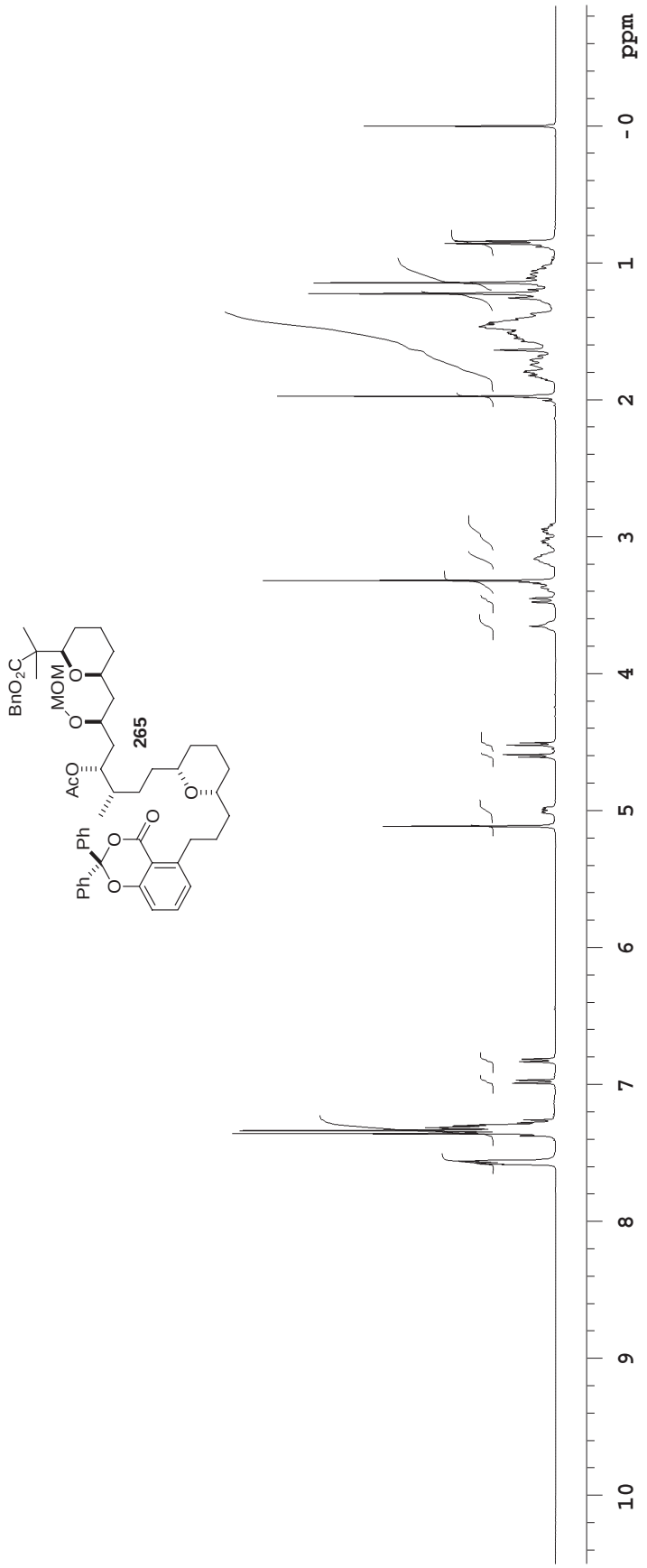
BnO2C
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AcO
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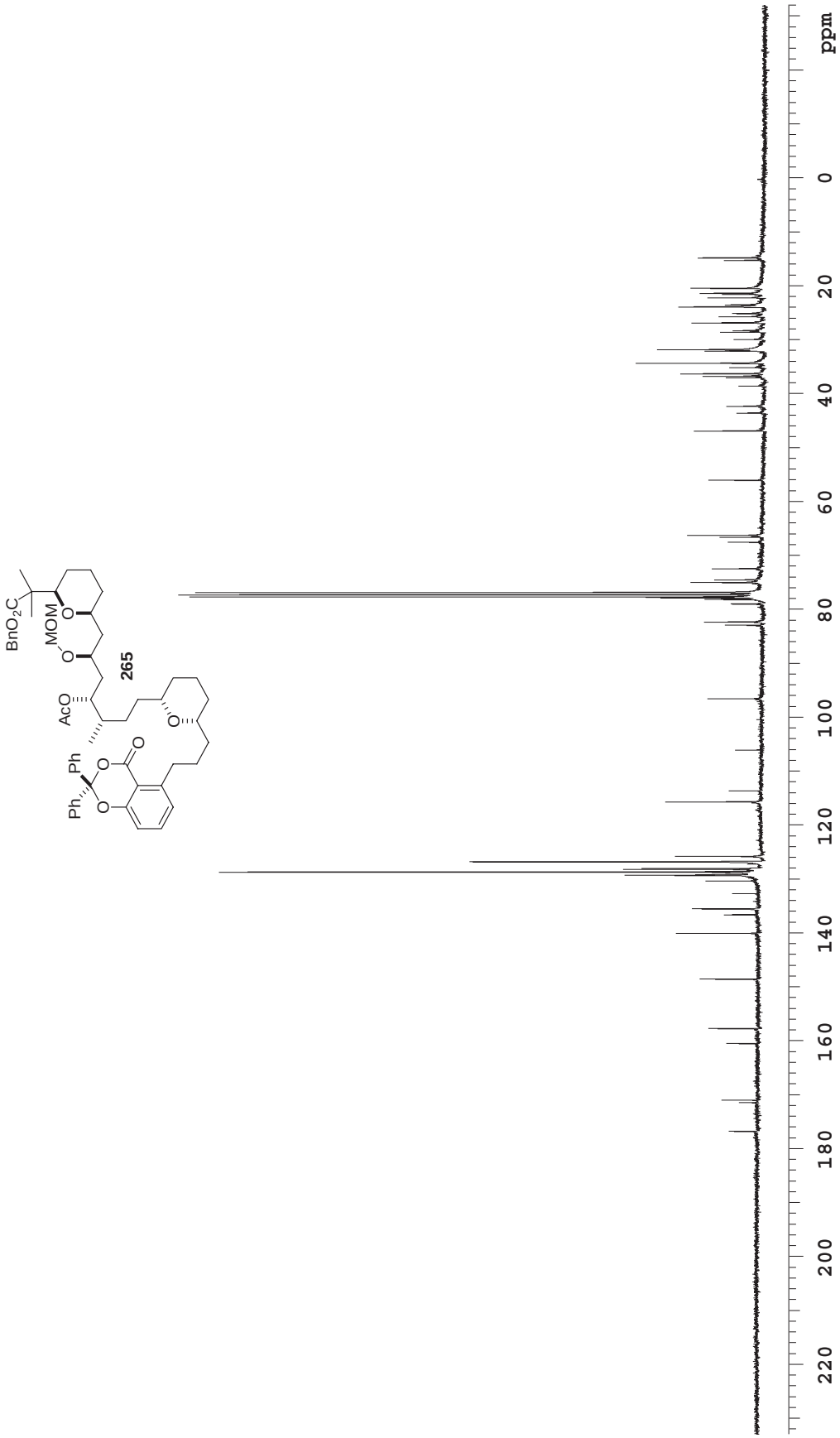
BnO2C
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AcO
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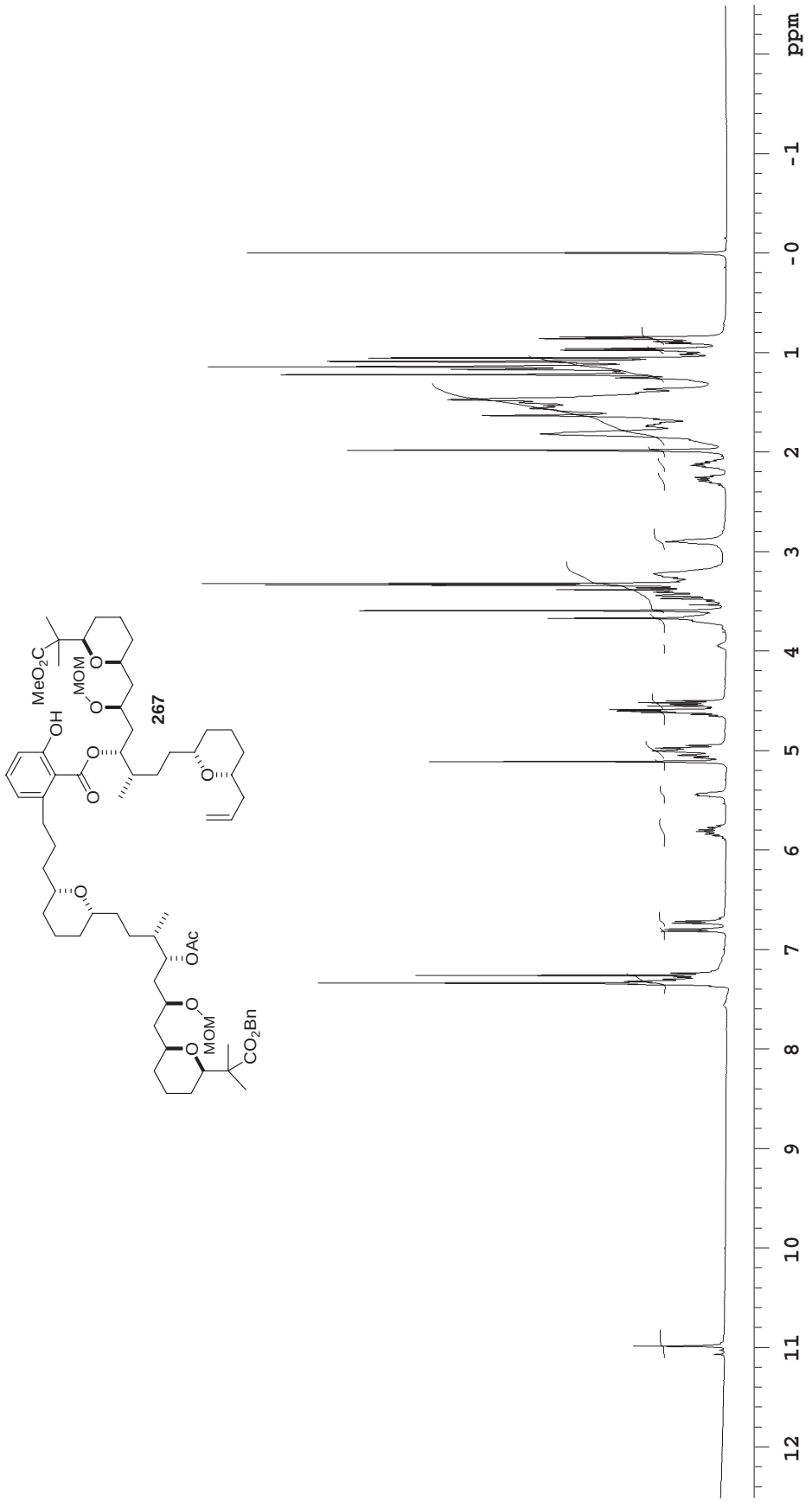
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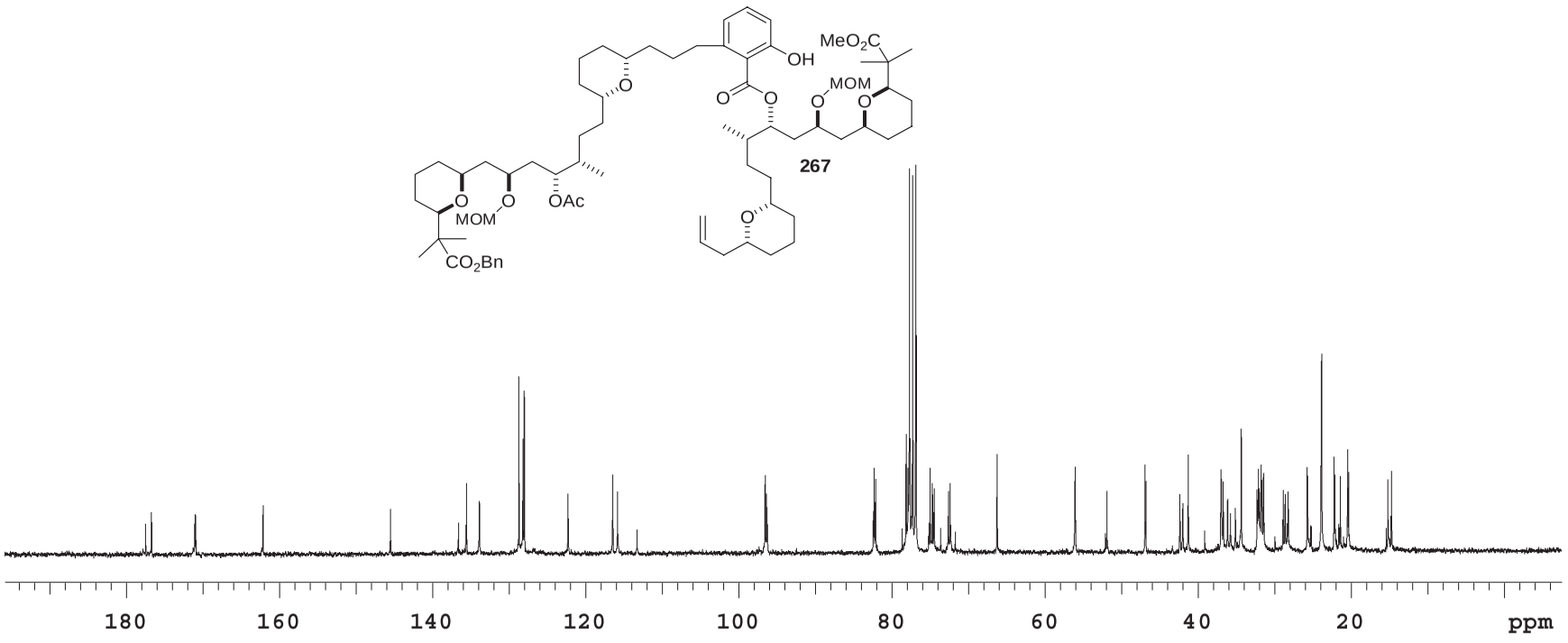
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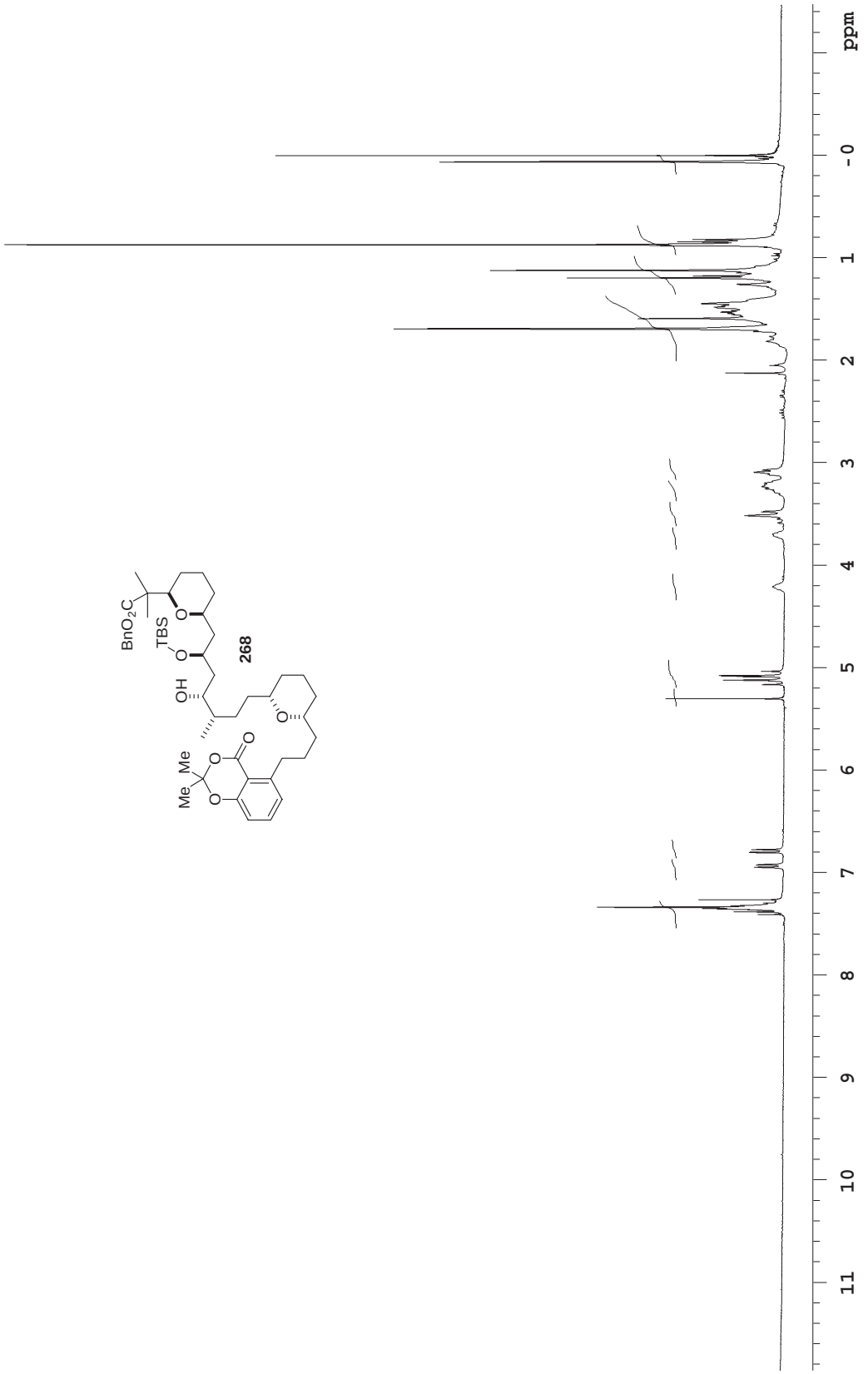
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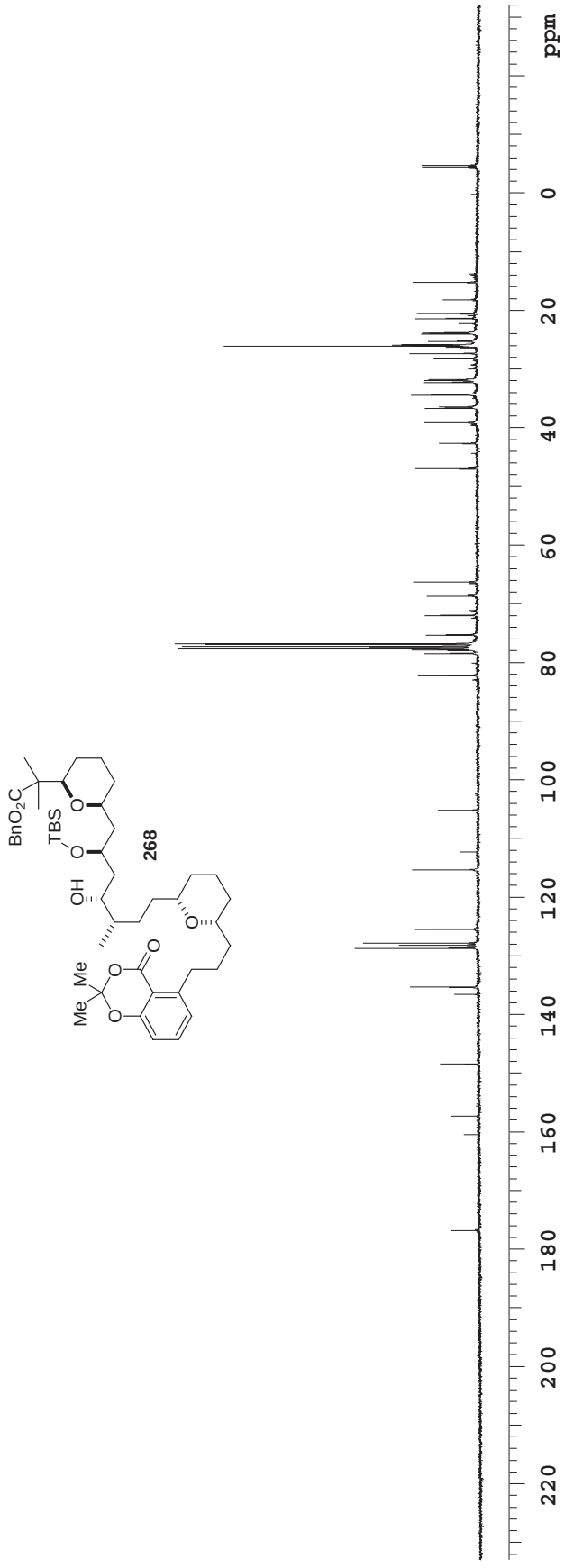
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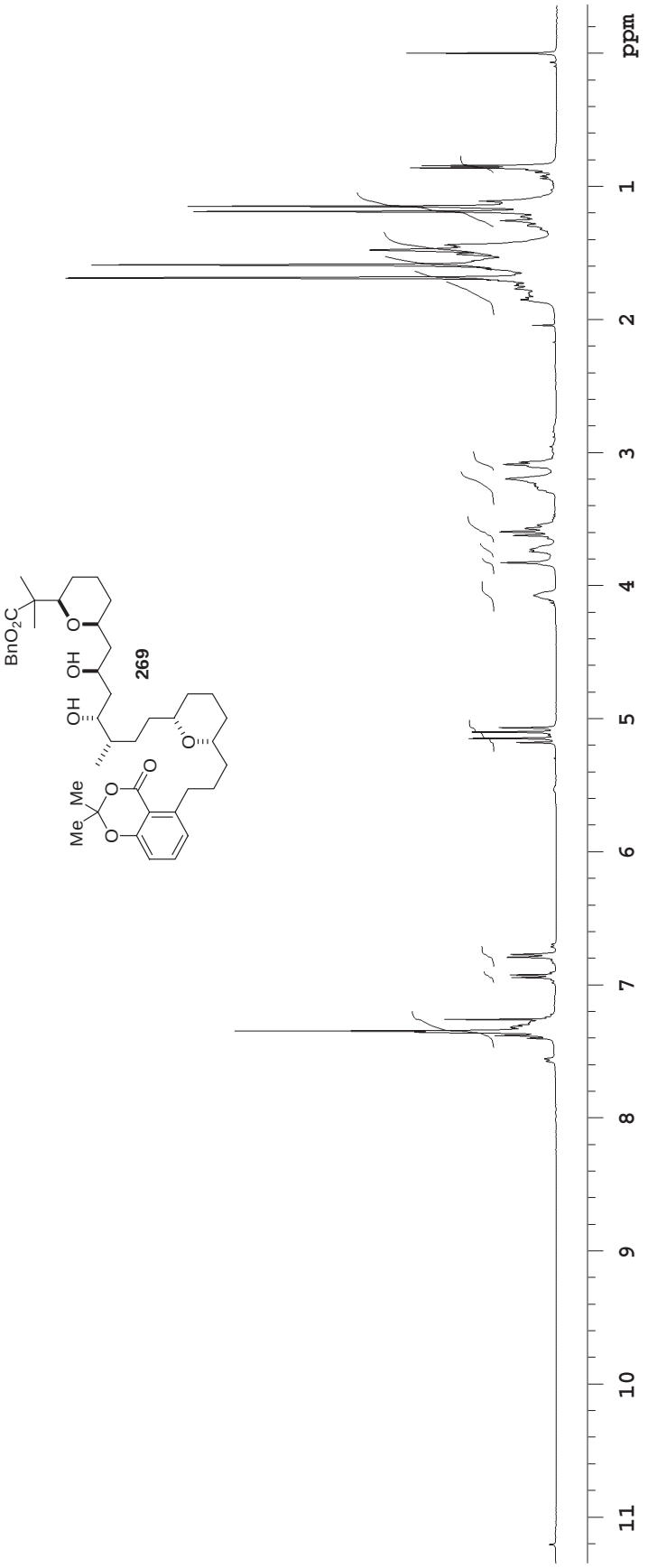
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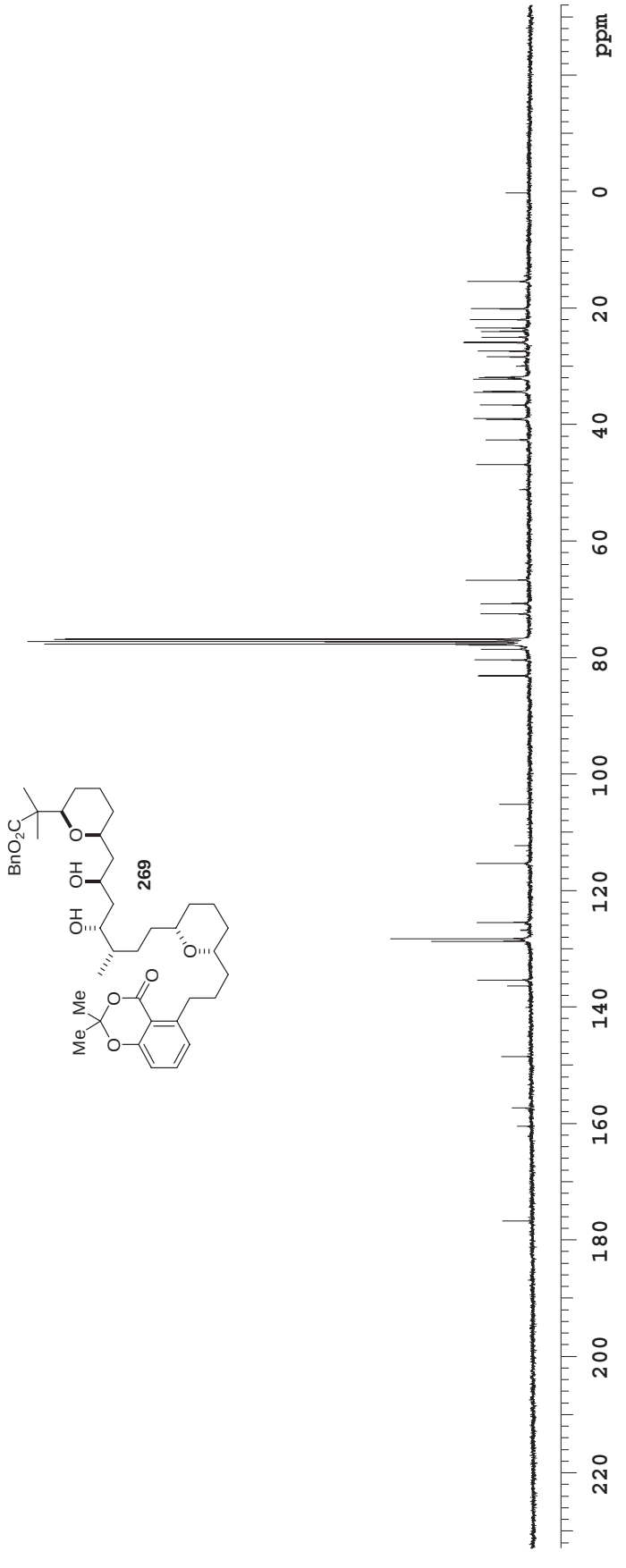
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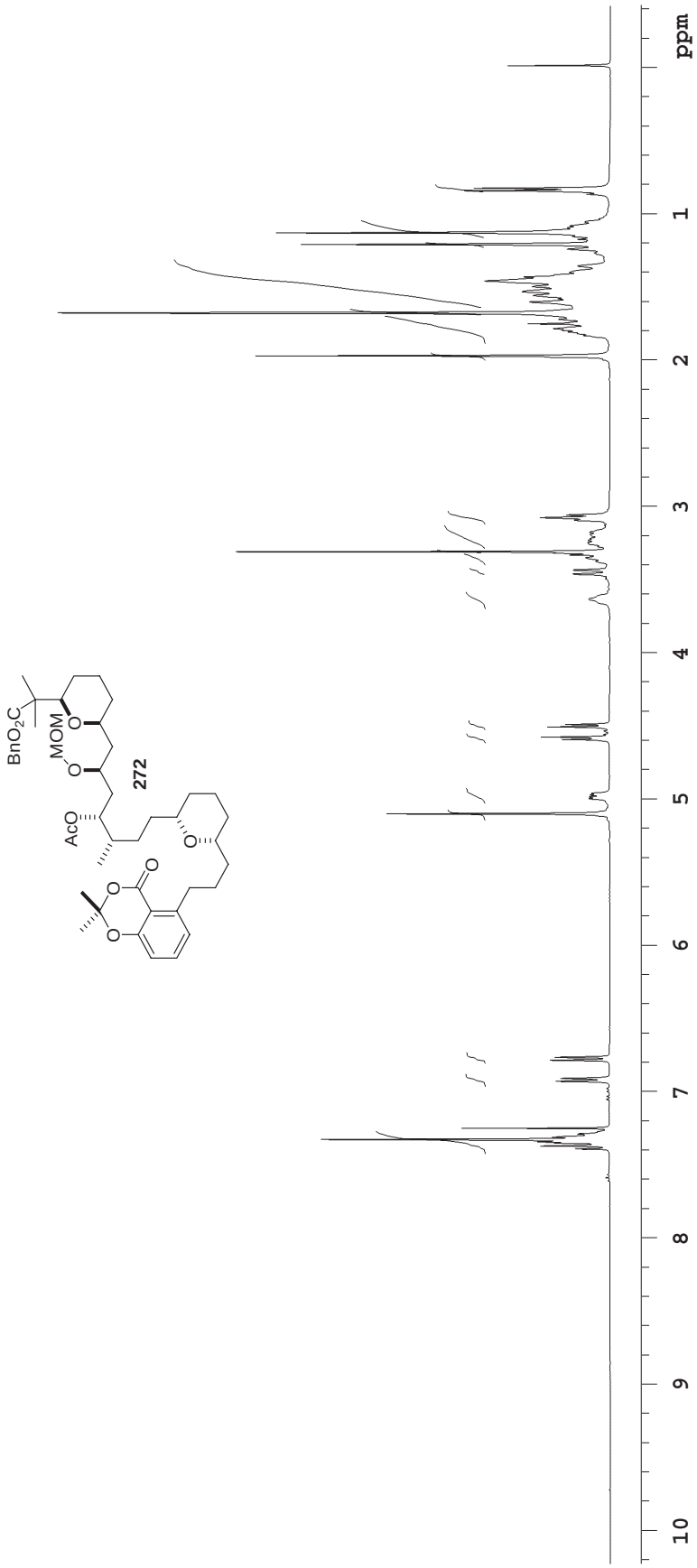
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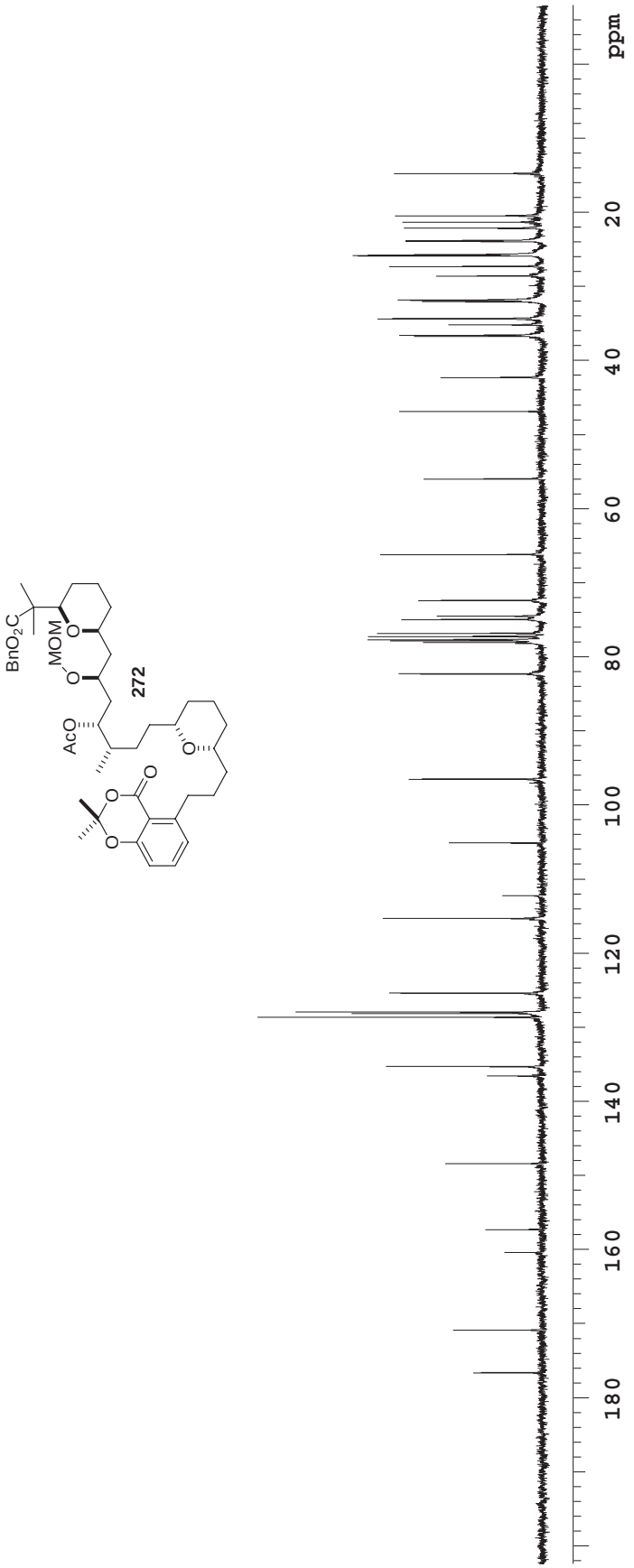
BnO2C
MOM
O
AcO
O
O
O
O
O
O
272
ppm
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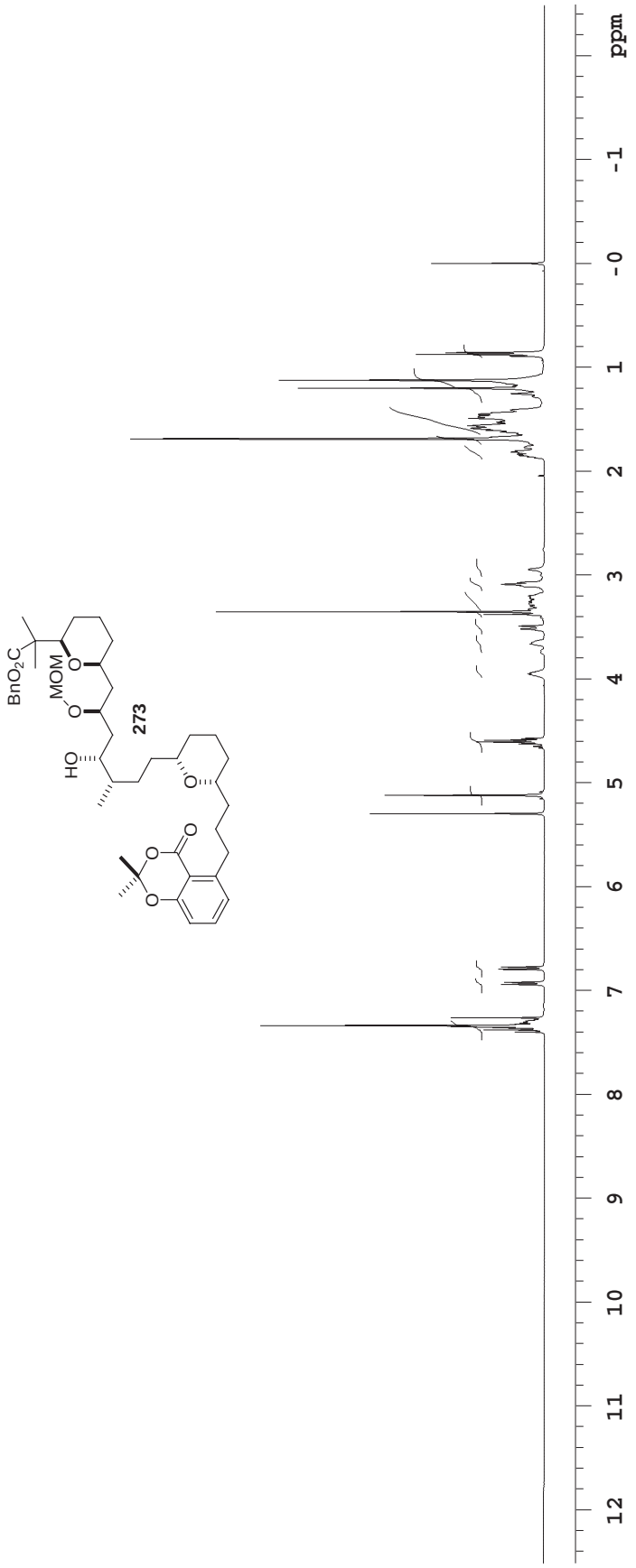
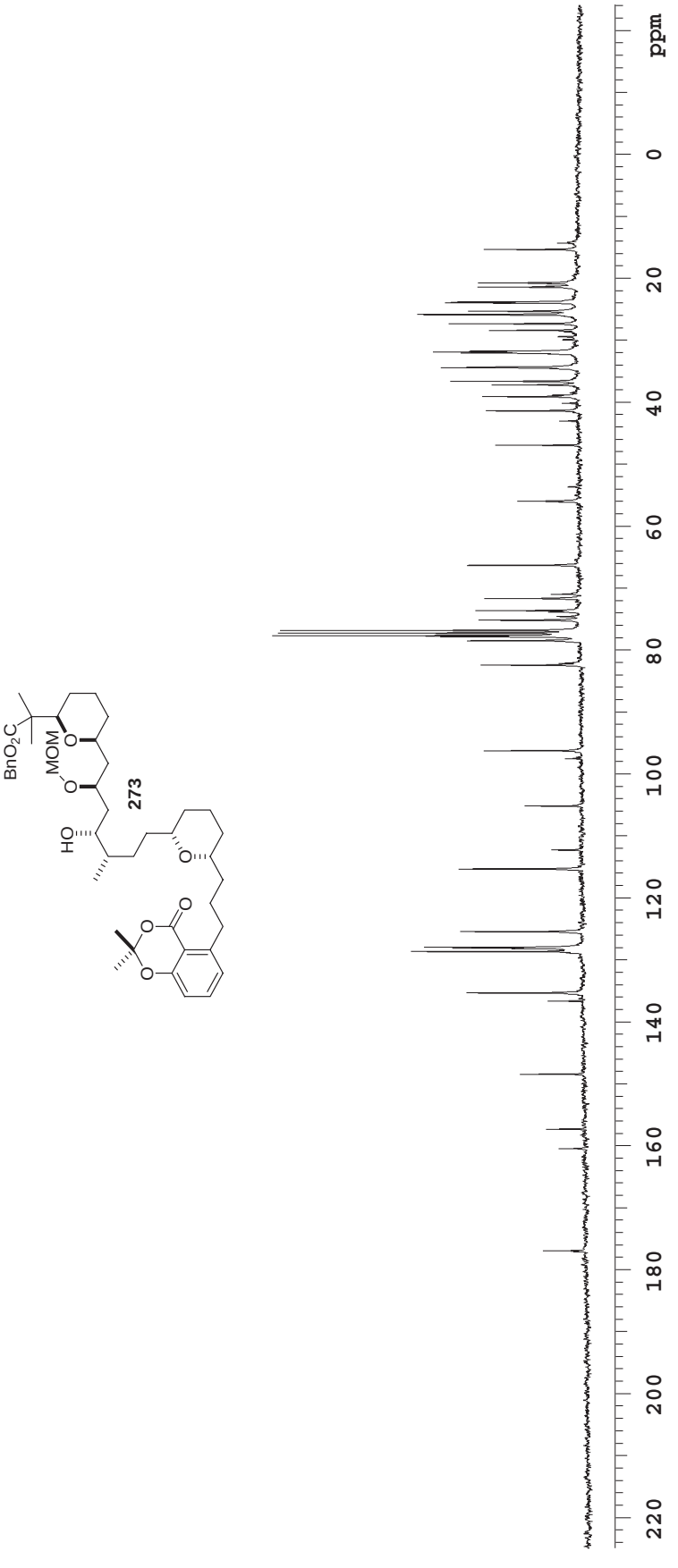
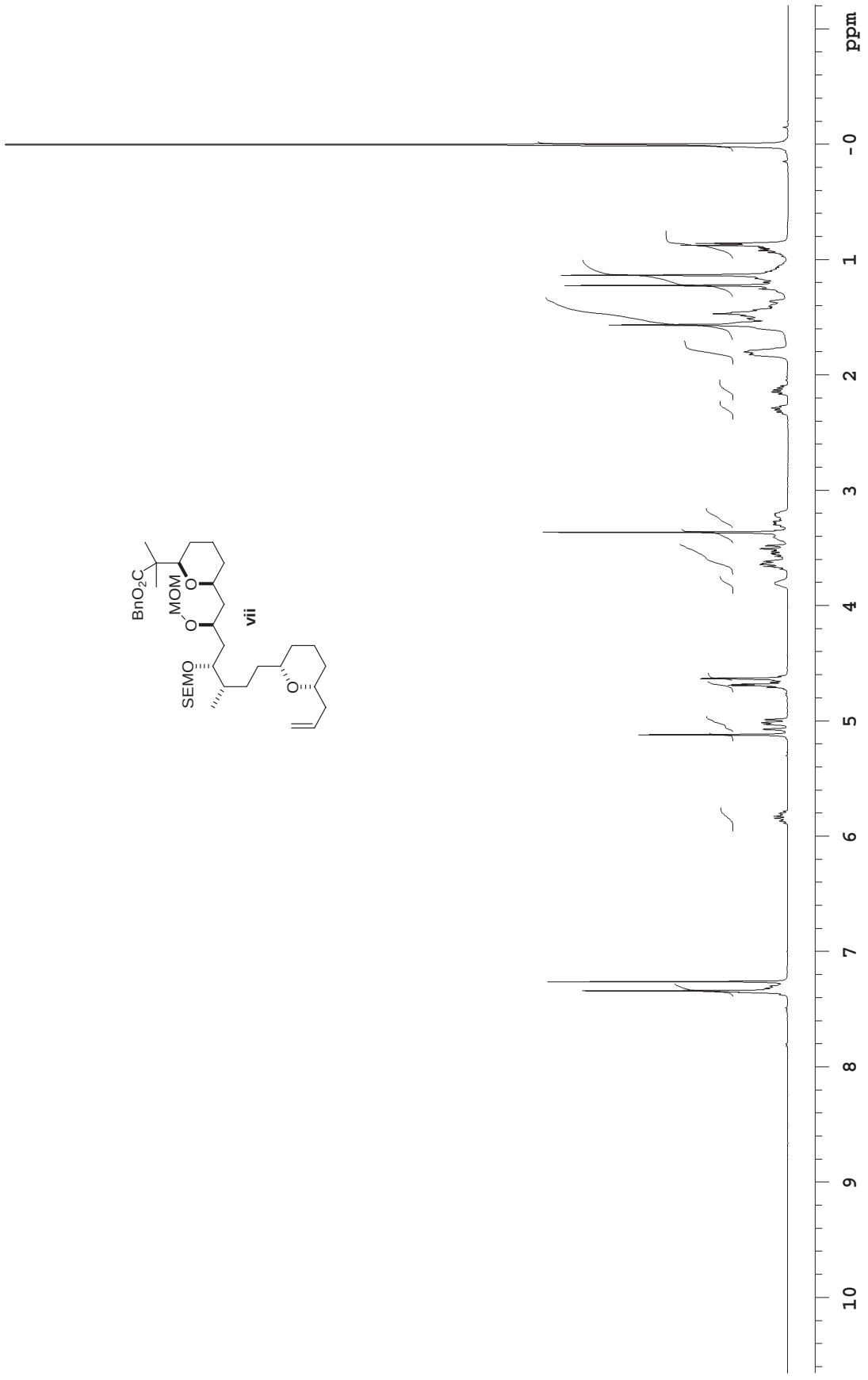
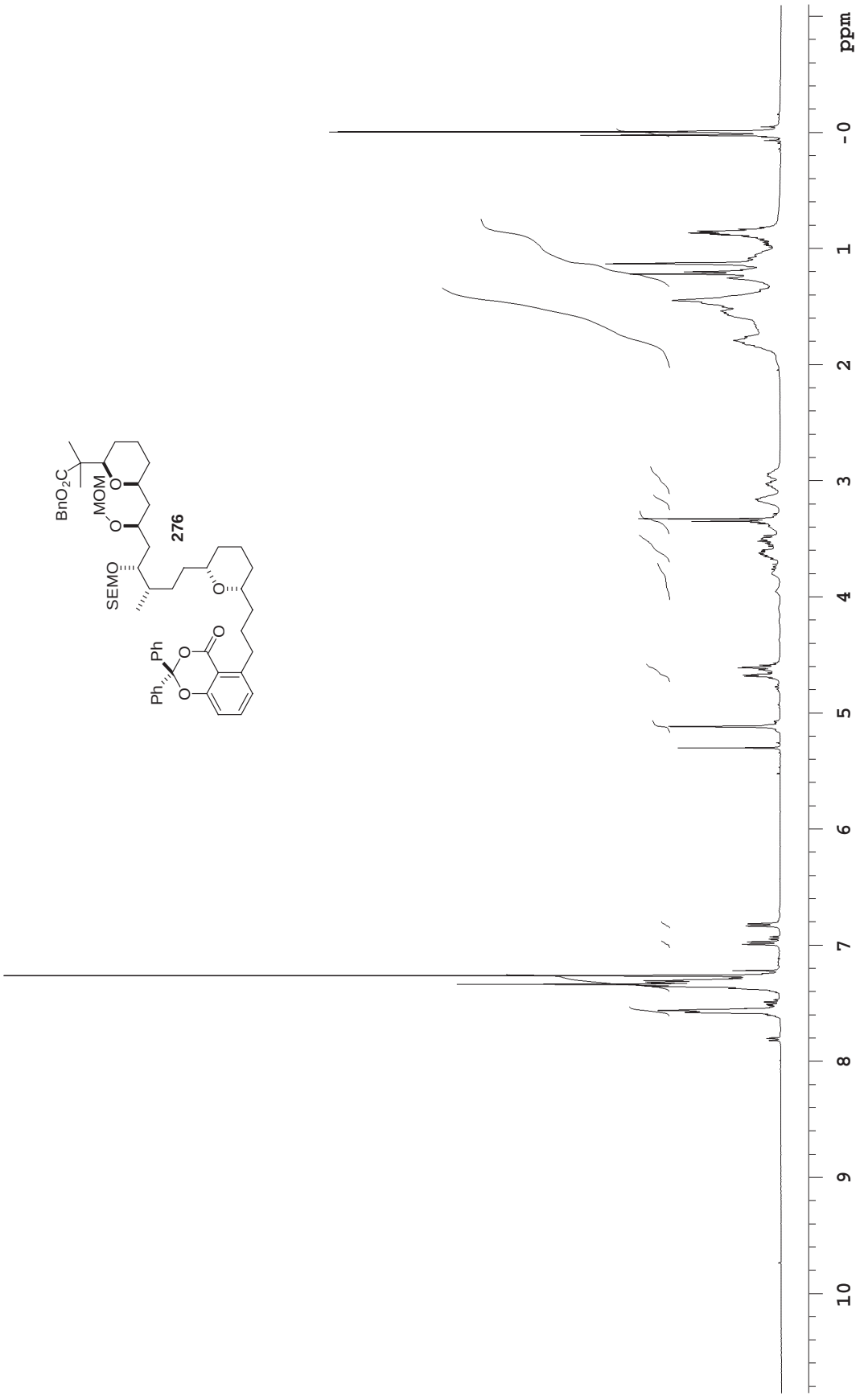
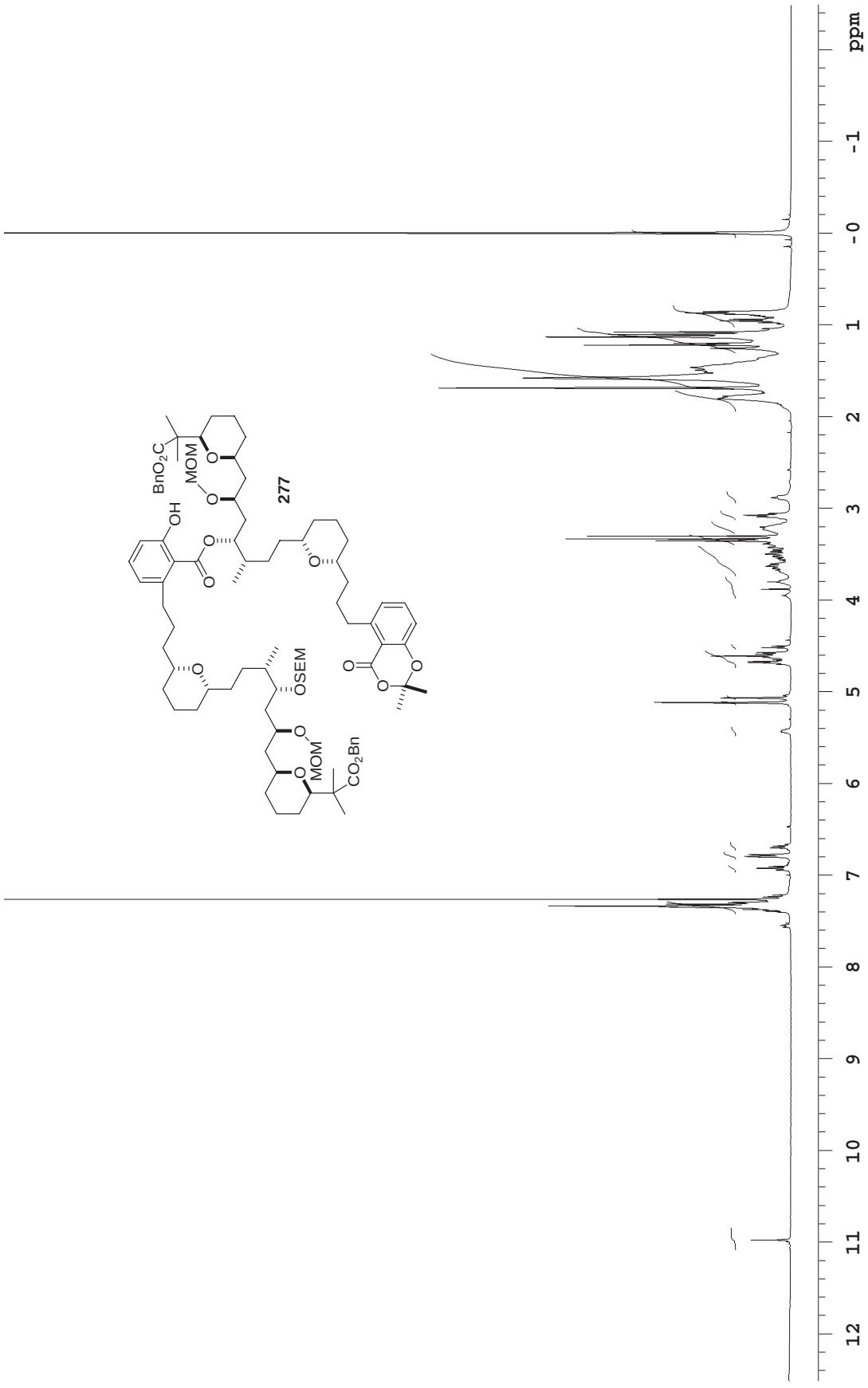
160
140
120
100
80
60
40
20

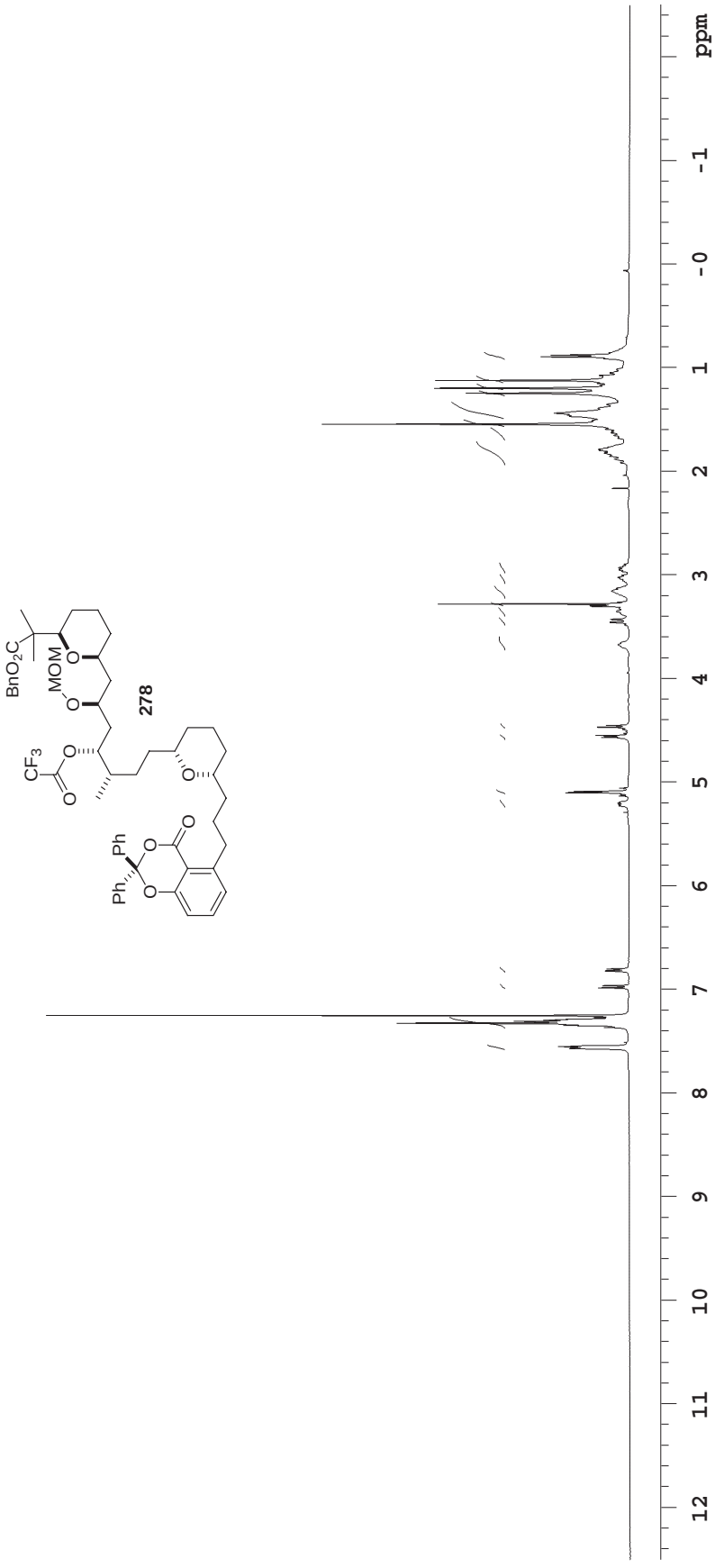

BnO2C
MOM
O
O
HO
O
O
O
O
O
O
273
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1

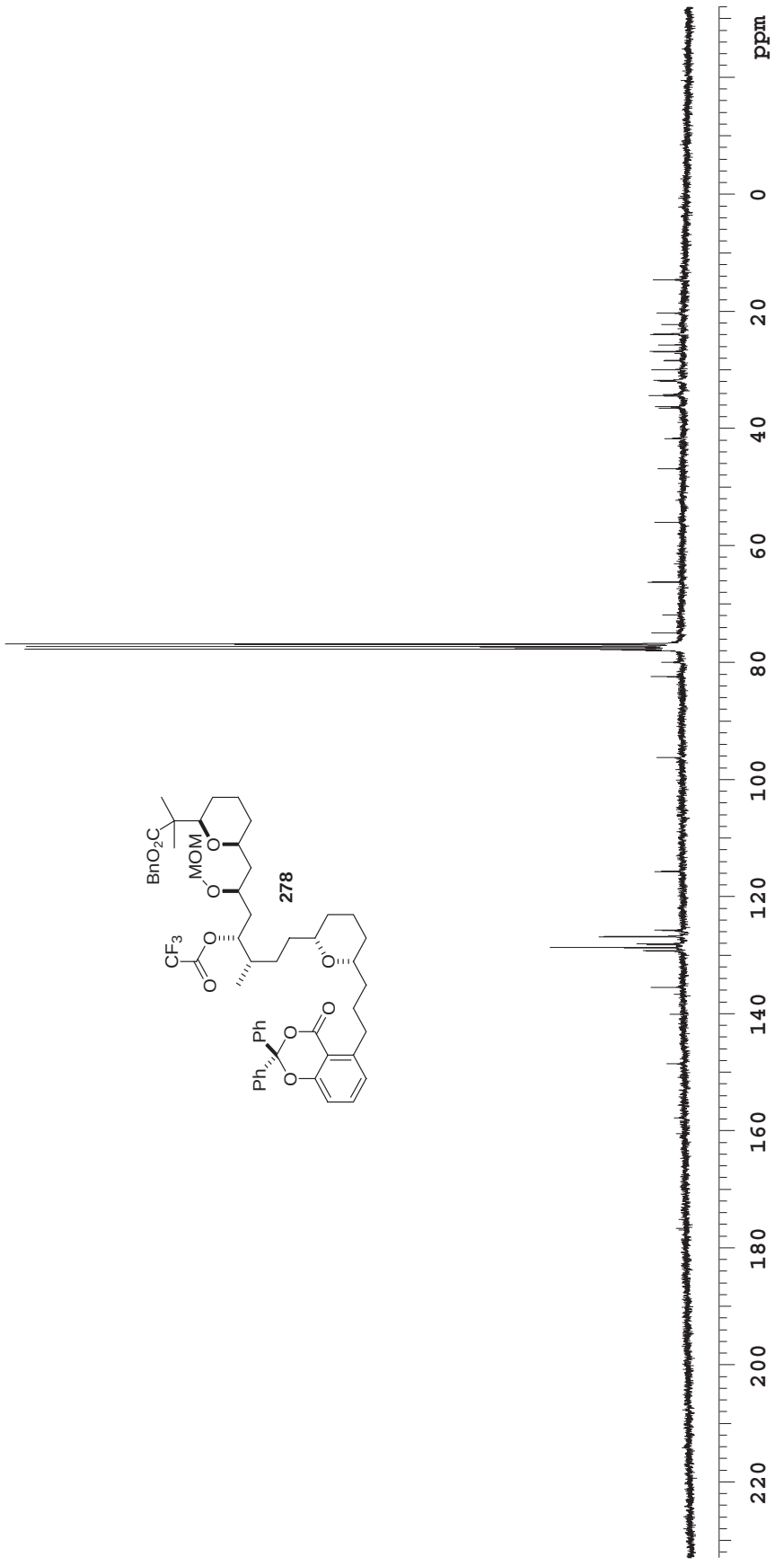

BnO2C
MOM
O
HO
O
O
O
O
O
O
273
ppm
220
200
180
160
140
120
100
80
60
40
20
0

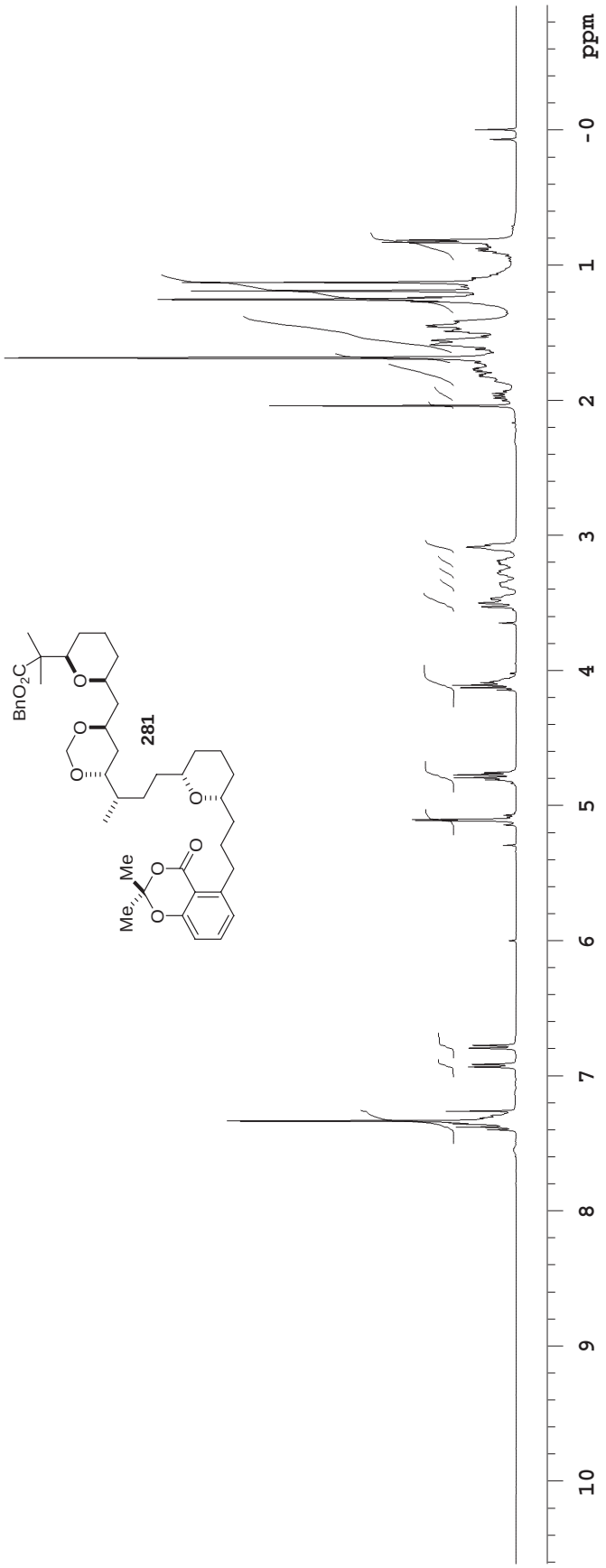

BnO2C
MOM
O
O
SEMO
O
vii
ppm
10
9
8
7
6
5
4
3
2
1
0

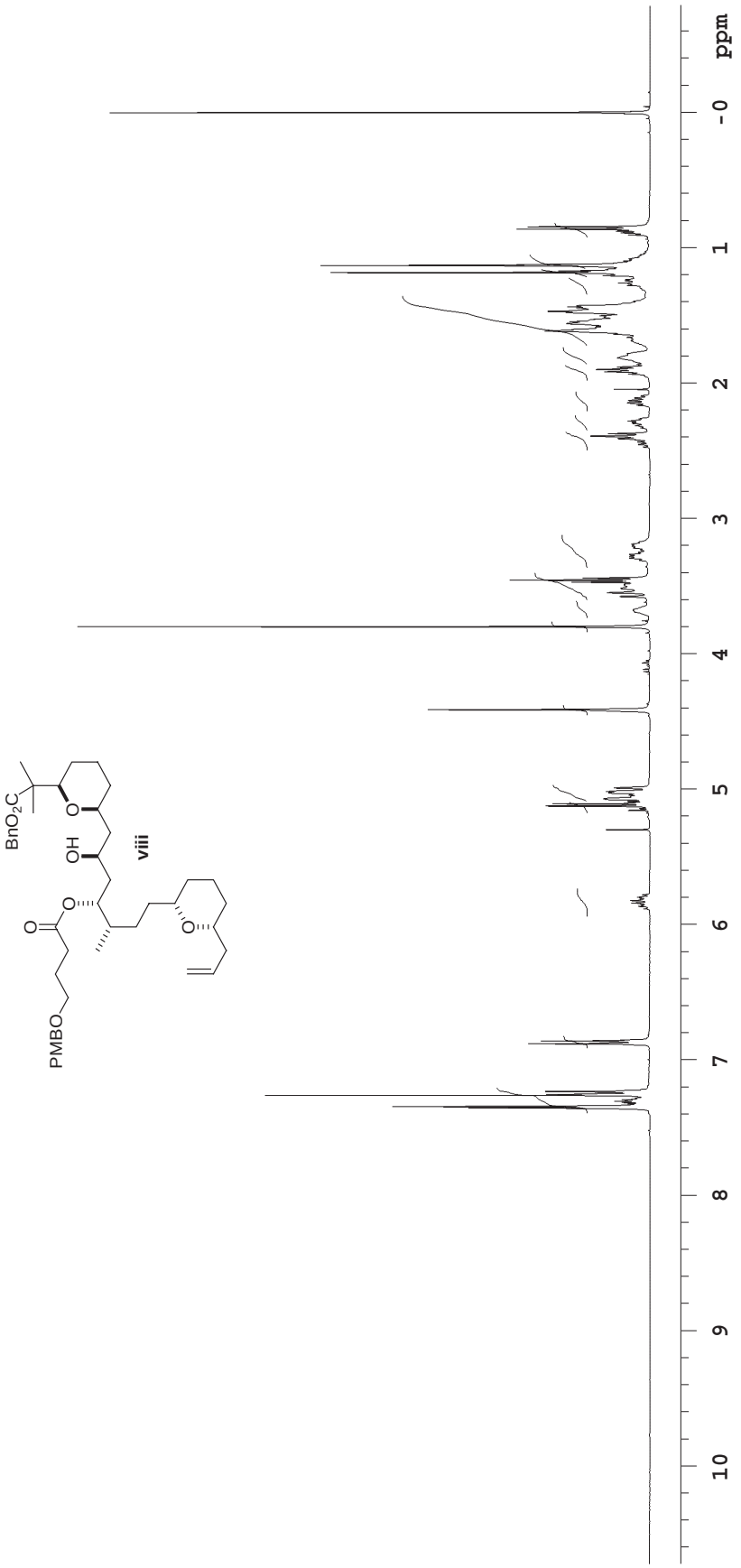

BnO2C
MOM
O
O
276
SEMO
O
O
Ph
Ph
O
O
O
ppm
10
9
8
7
6
5
4
3
2
1
0

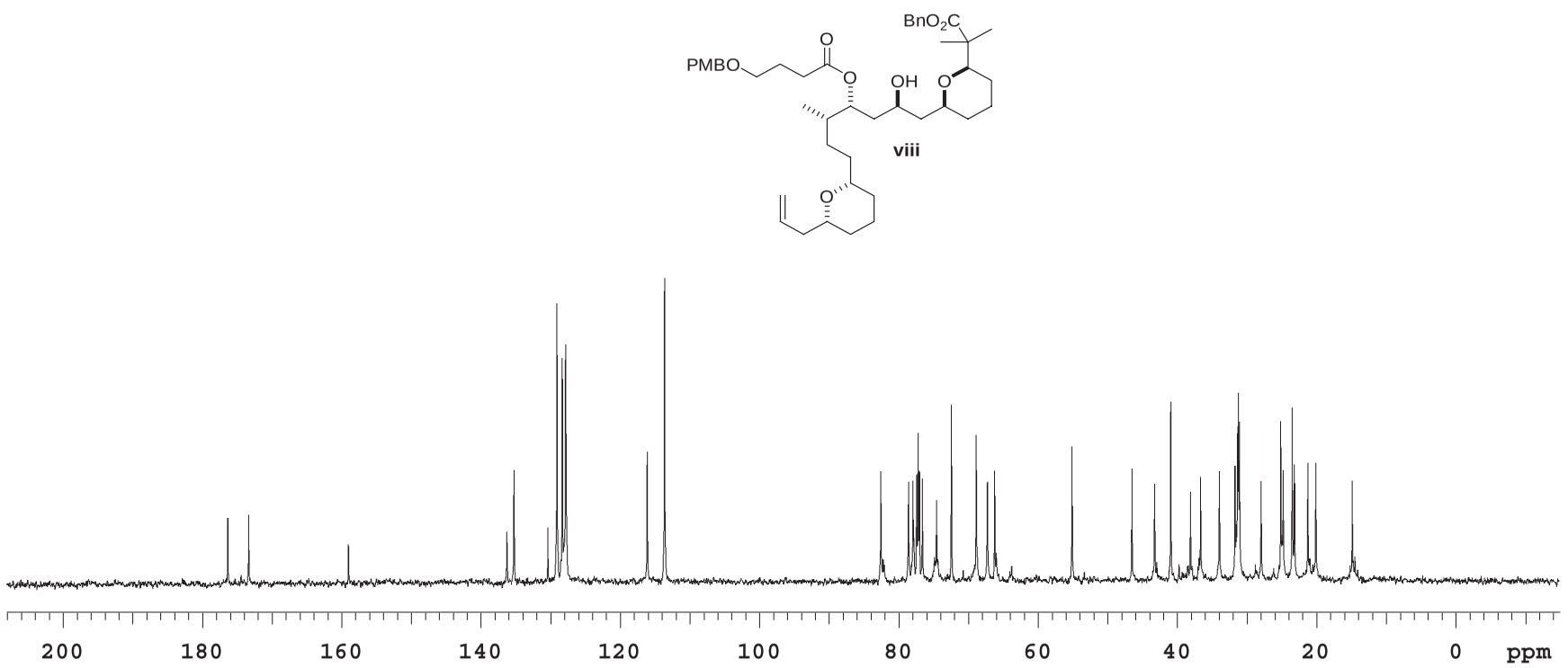

277
BnO2C
MOM
OH
OSEM
MOM
CO2Bn
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1


BnO2C
MOM
O
O
CF3
O
O
278
O
Ph
Ph
O
O
O
O
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1

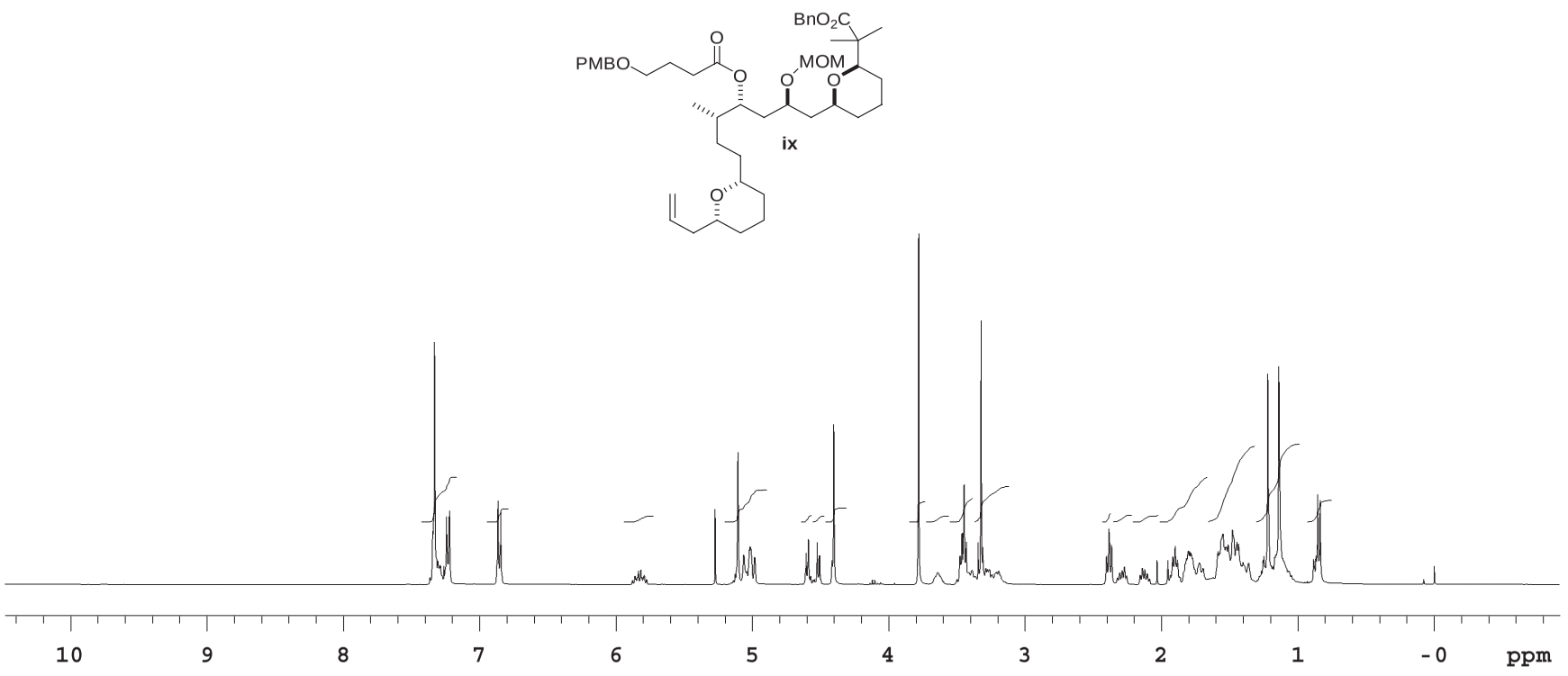

BnO2C
MOM
O
O
CF3
O
O
278
O
Ph
Ph
O
O
O
ppm
220
200
180
160
140
120
100
80
60
40
20
0

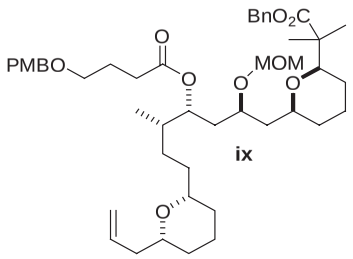

BnO2C
281
Me
Me
ppm
10
9
8
7
6
5
4
3
2
1
0


BnO2C
O
OH
viii
O
O
PMBO
ppm
10
9
8
7
6
5
4
3
2
1
0

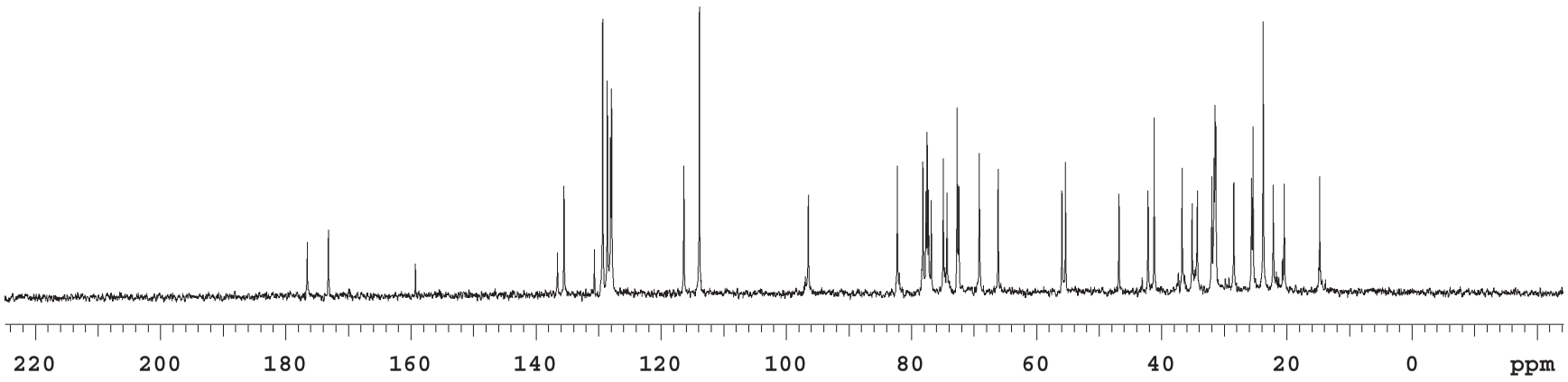


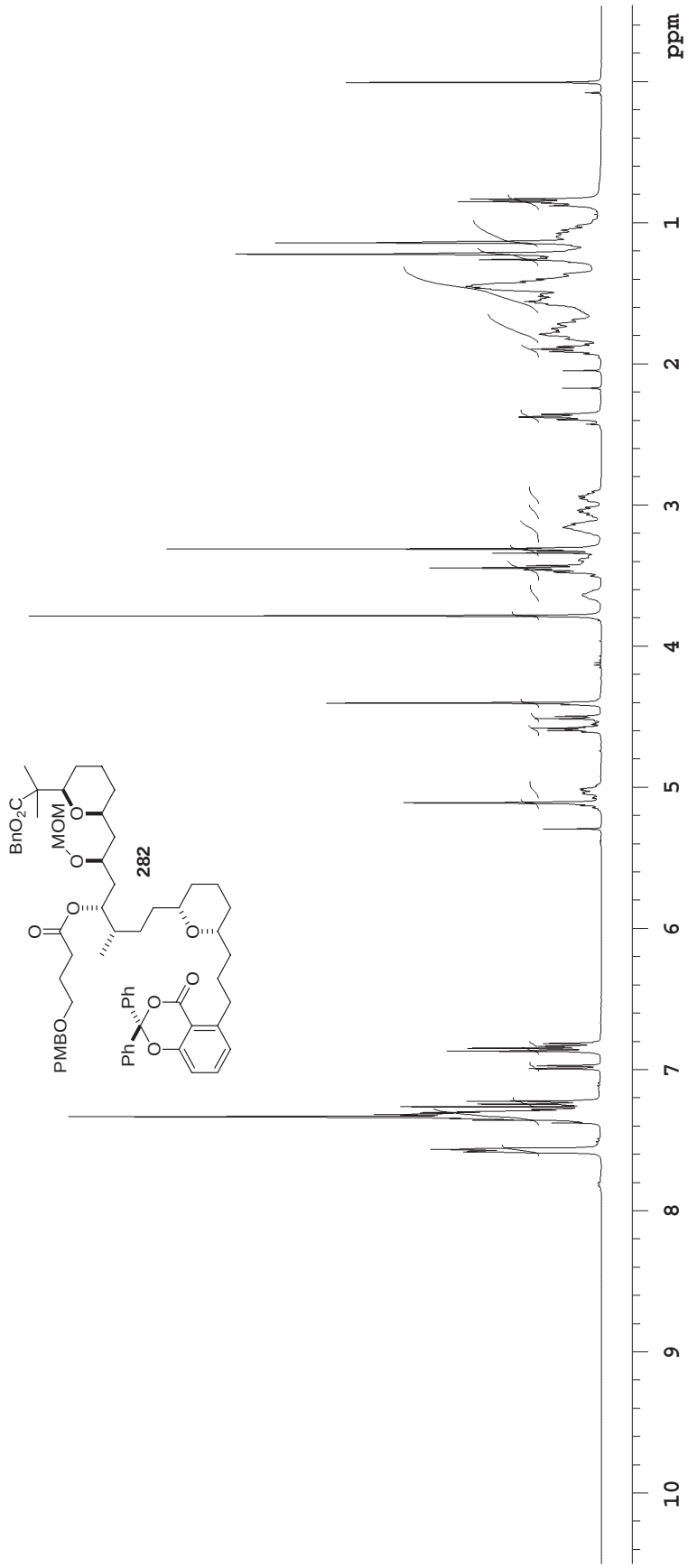
viii

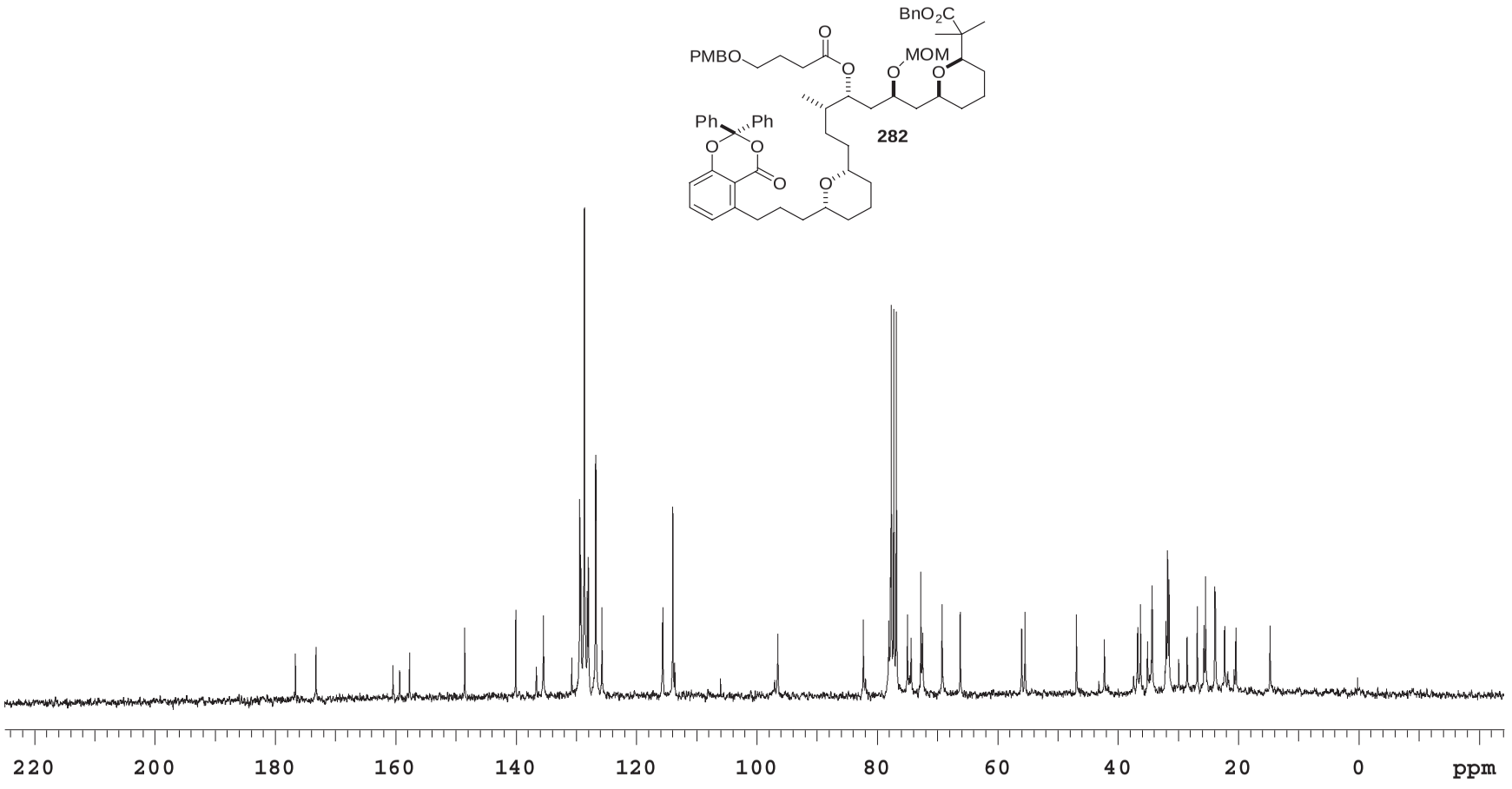

BnO2C
PMBO
MOM
O
O
O
O
O
O
ix
10
9
8
7
6
5
4
3
2
1
-0
ppm

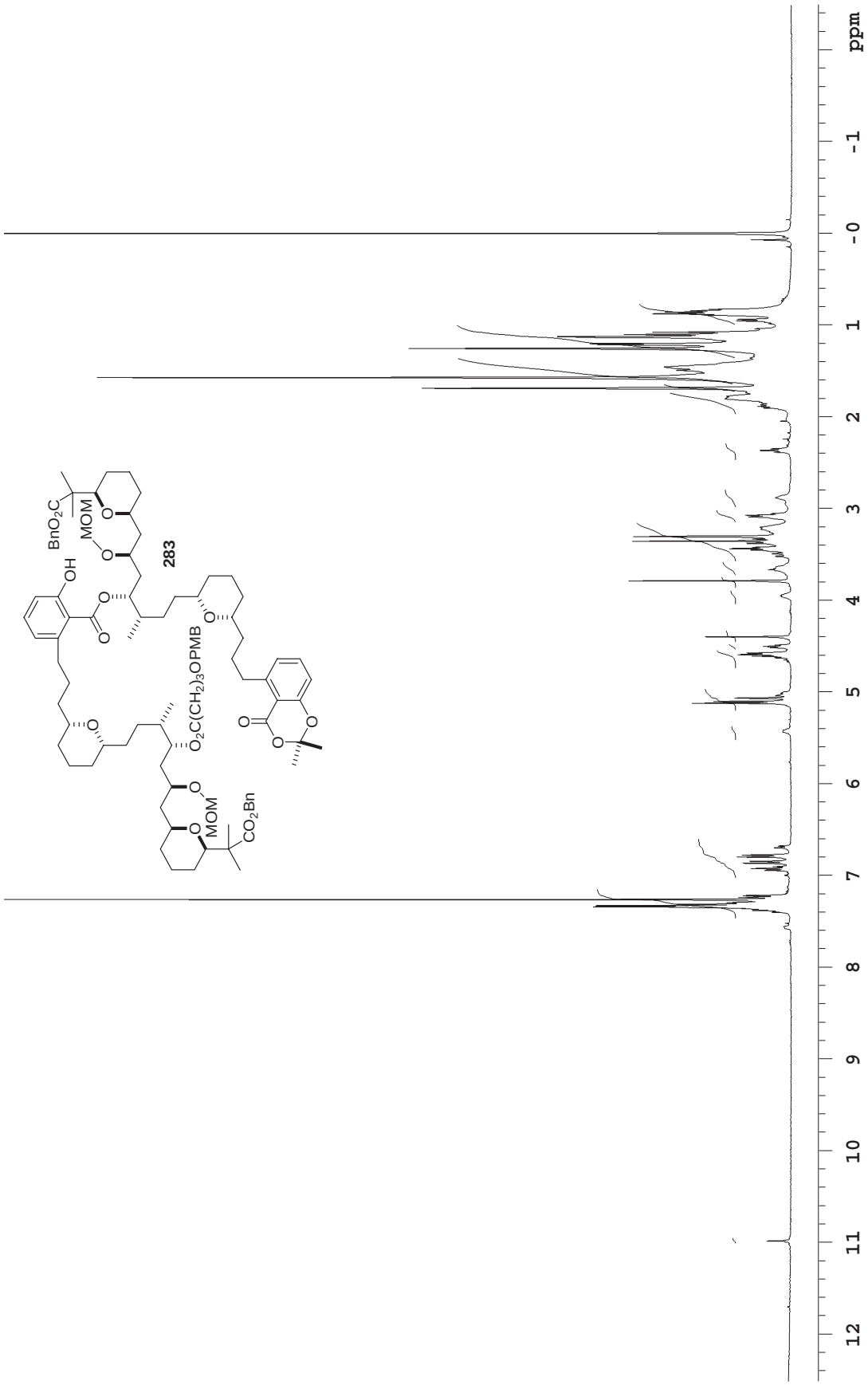

BnO2C
O
PMBO
MOM
O
O
O
O
O

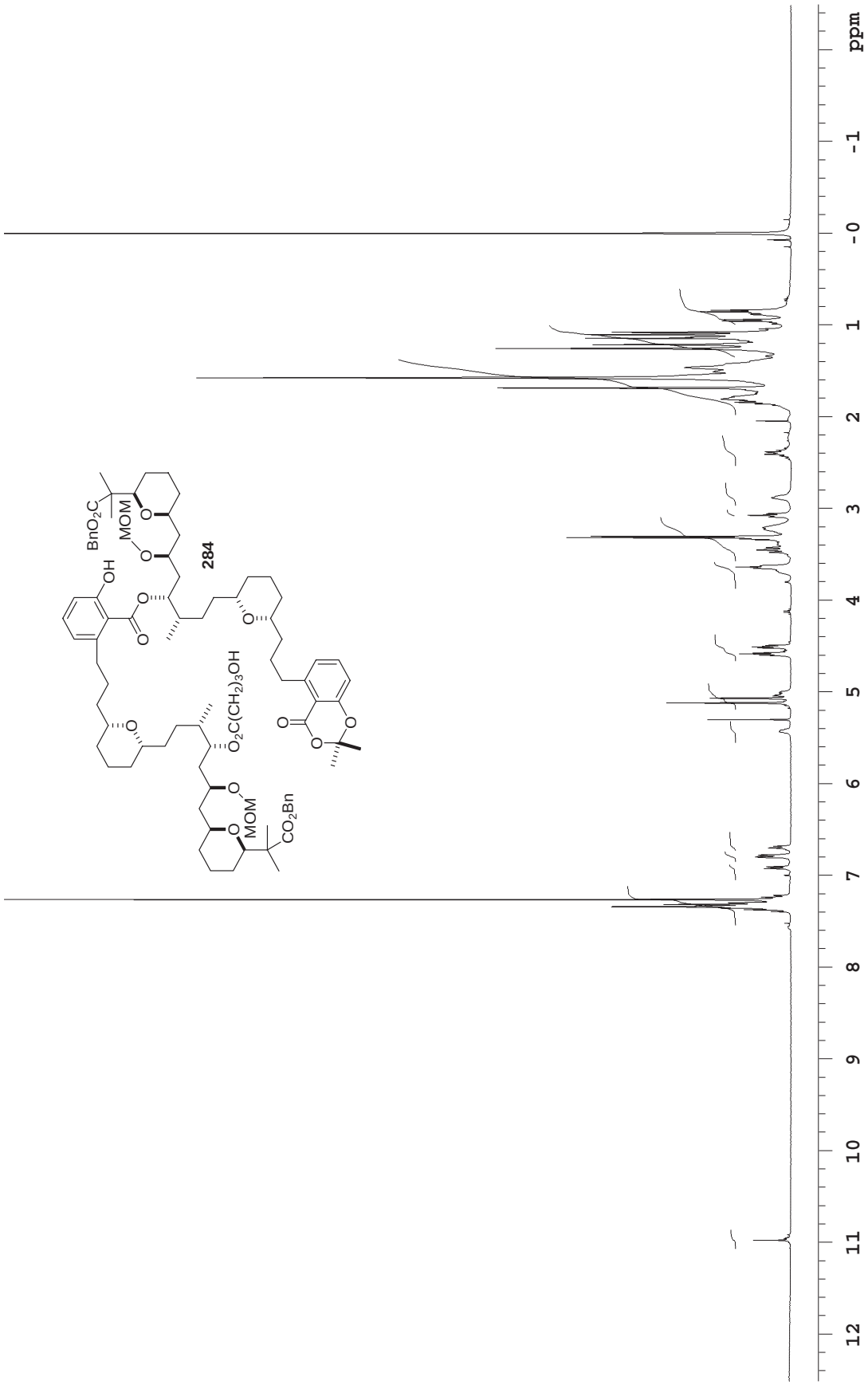
ix

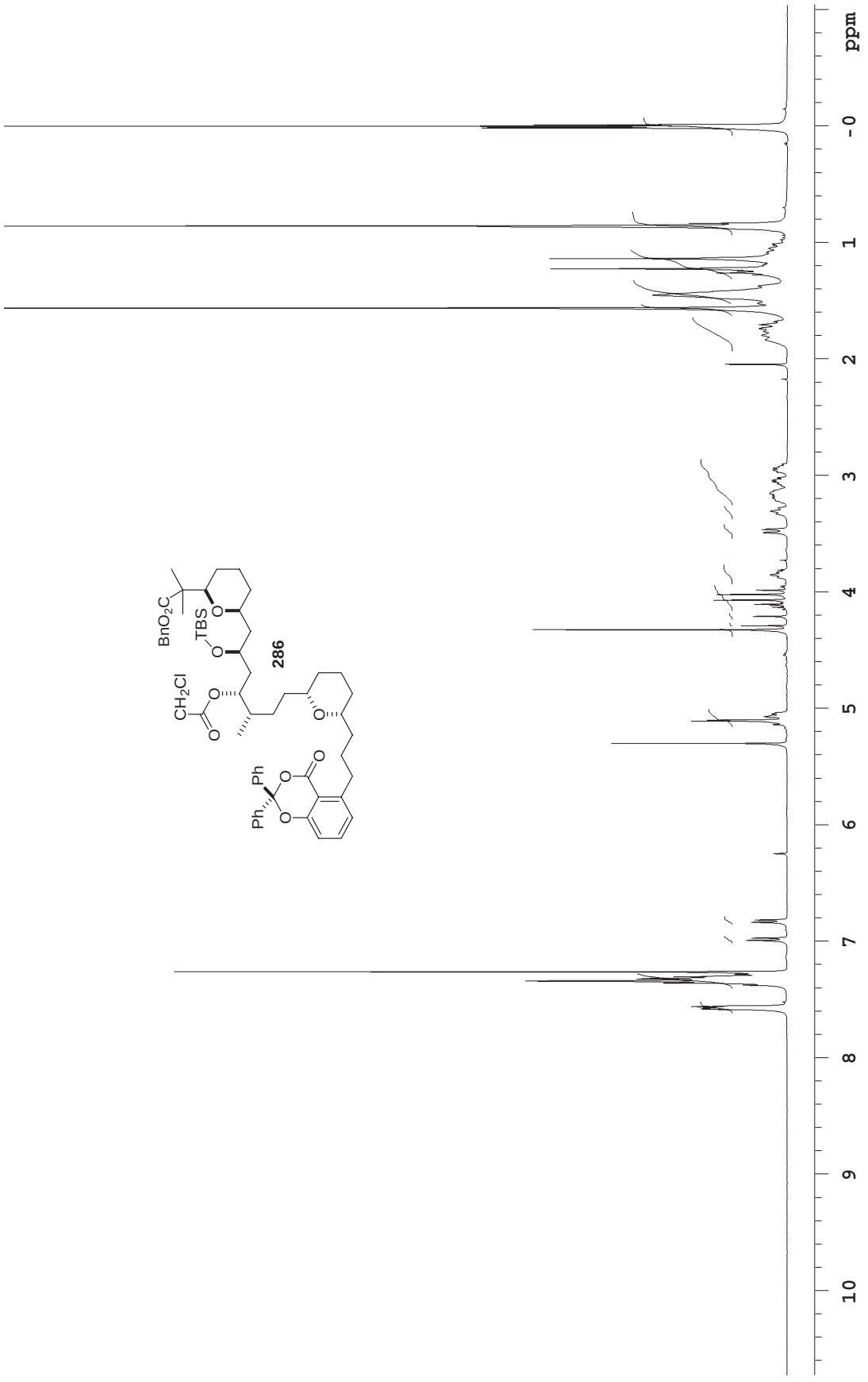

220
200
180
160
140
120
100
80
60
40
20
0
ppm

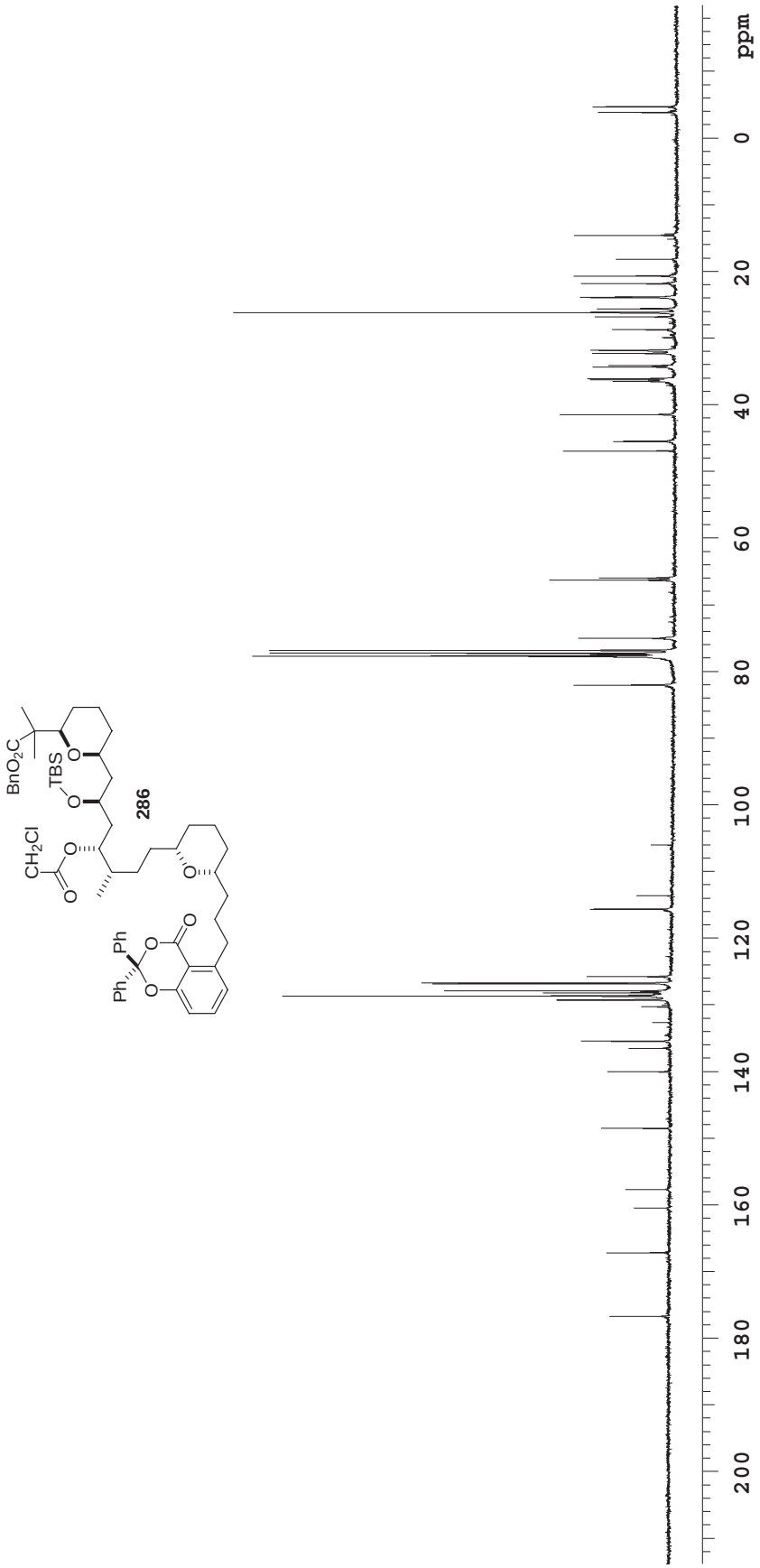

ppm
1
2
3
4
5
6
7
8
9
10
BnO2C
MOM
O
O
O
O
O
O
PMBO
Ph
Ph
O
O
O
O
282

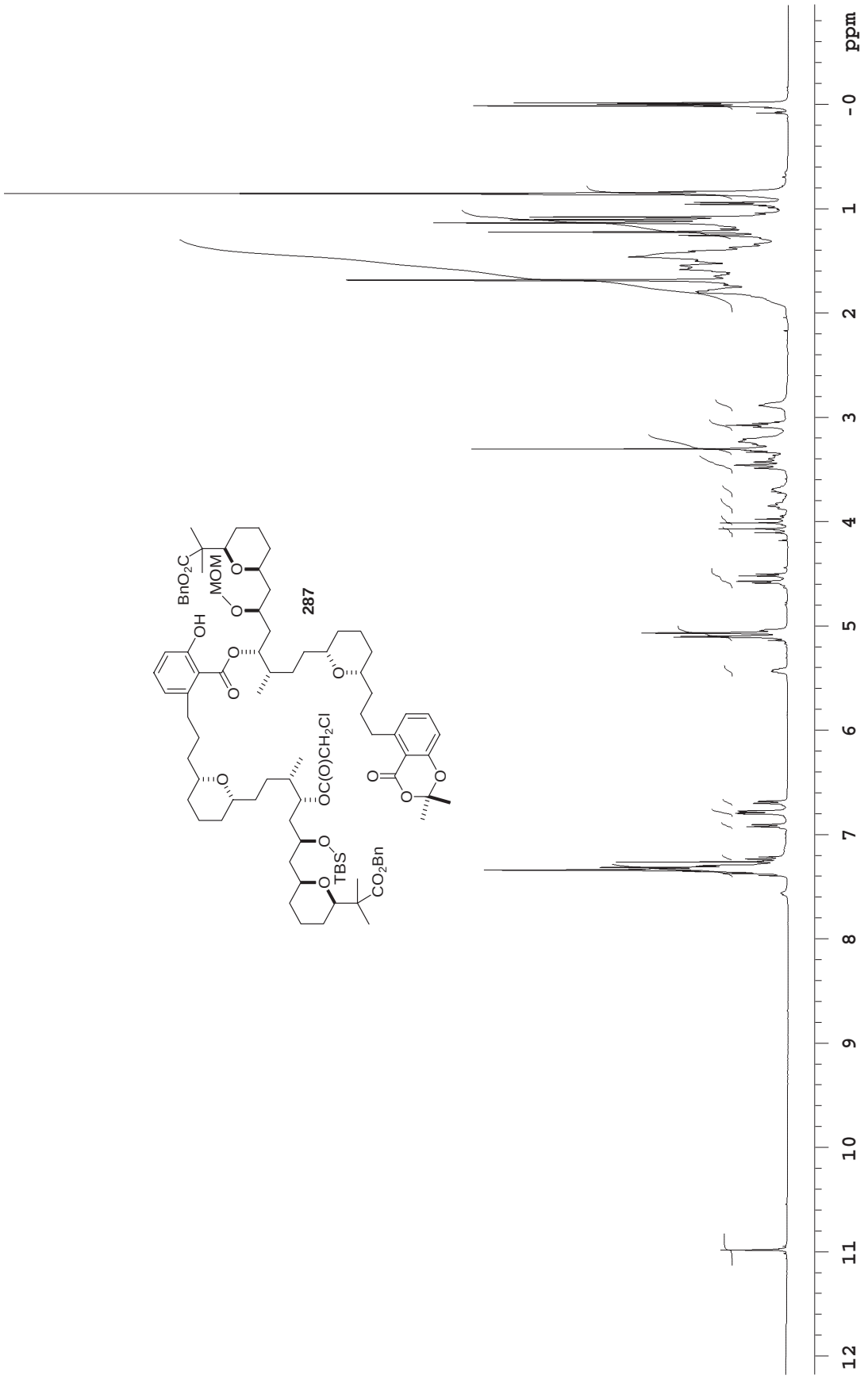

BnO2C
O
PMBO
O
MOM
O
O
Ph
Ph
O
O
O
O
O
282
220
200
180
160
140
120
100
80
60
40
20
0
ppm

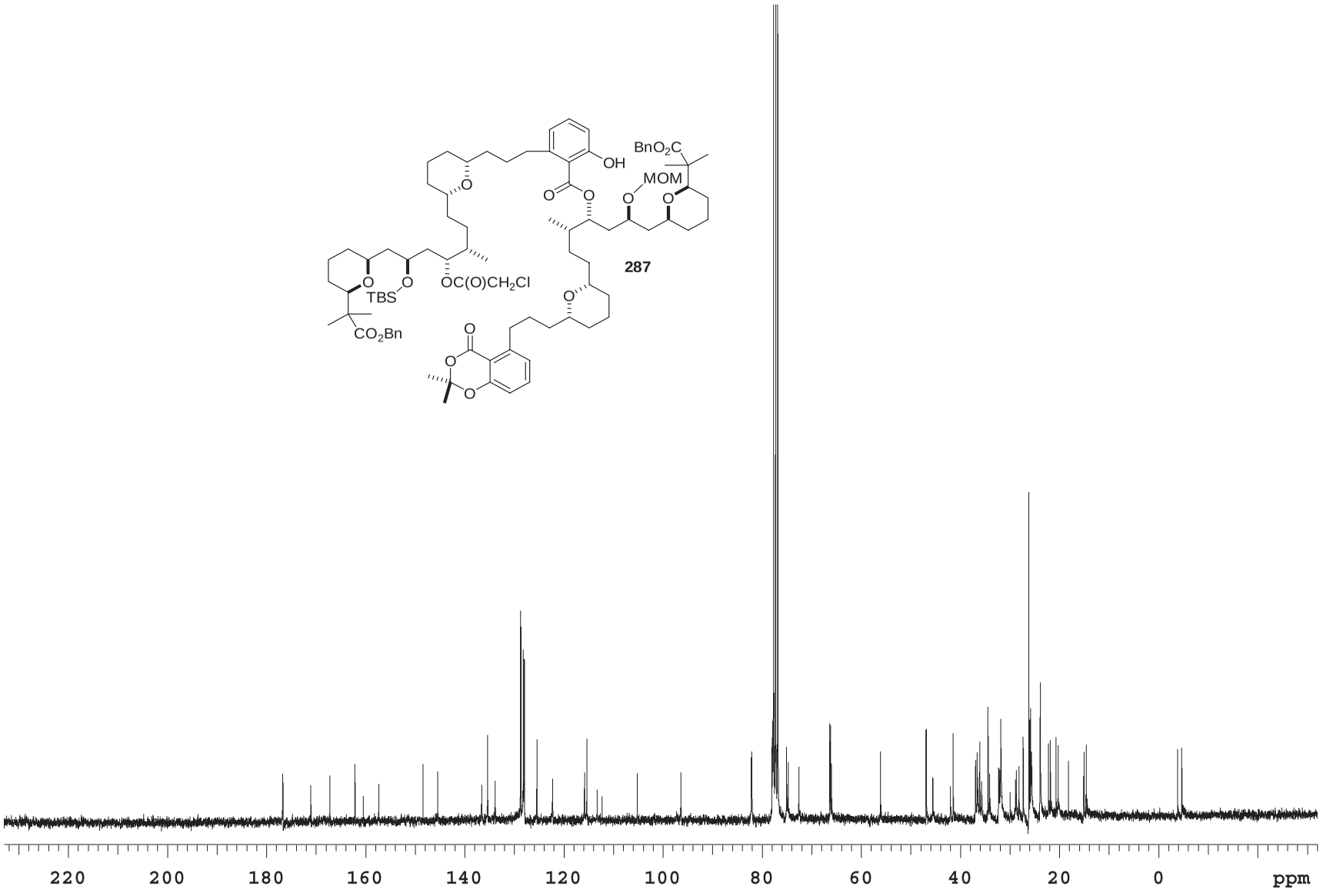

283
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1

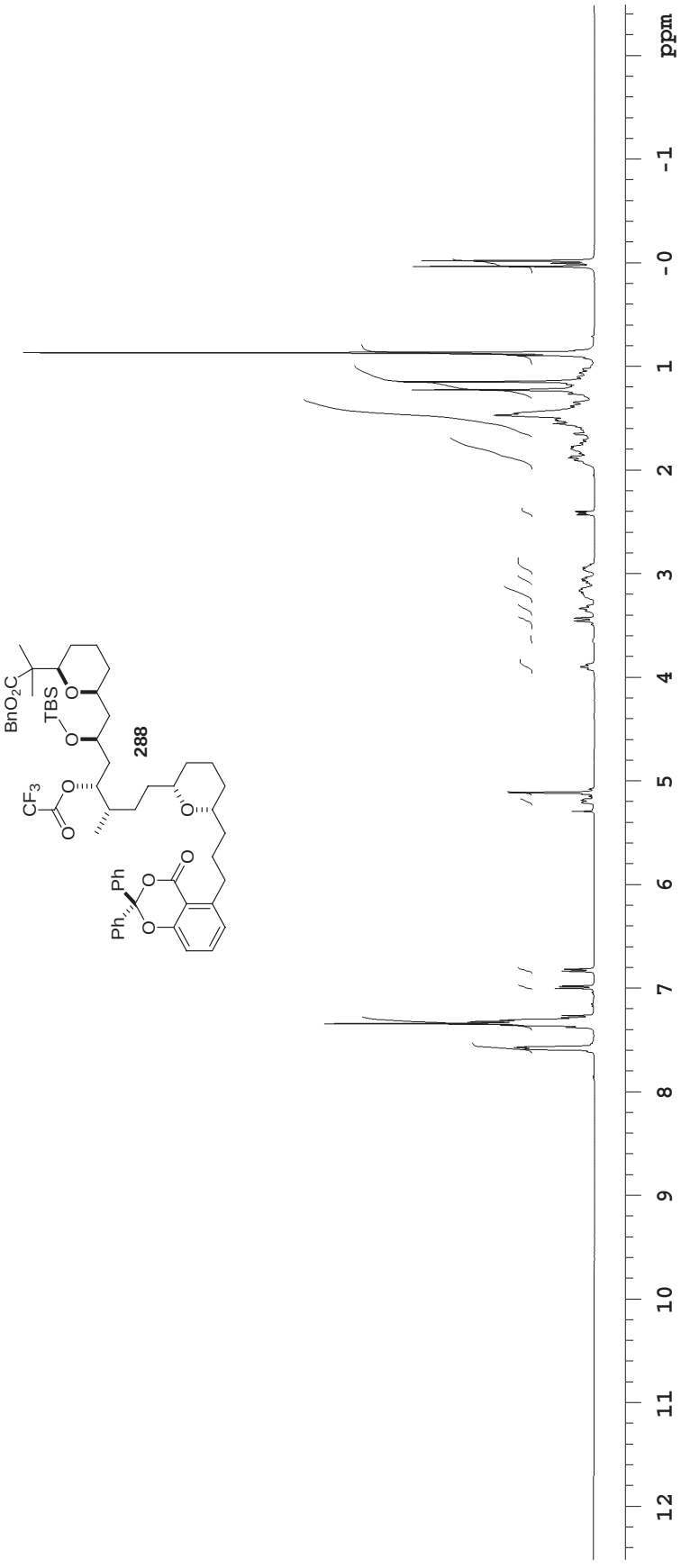

ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
284
BnO2C
MOM
OH
O2C(CH2)3OH
MOM
CO2Bn

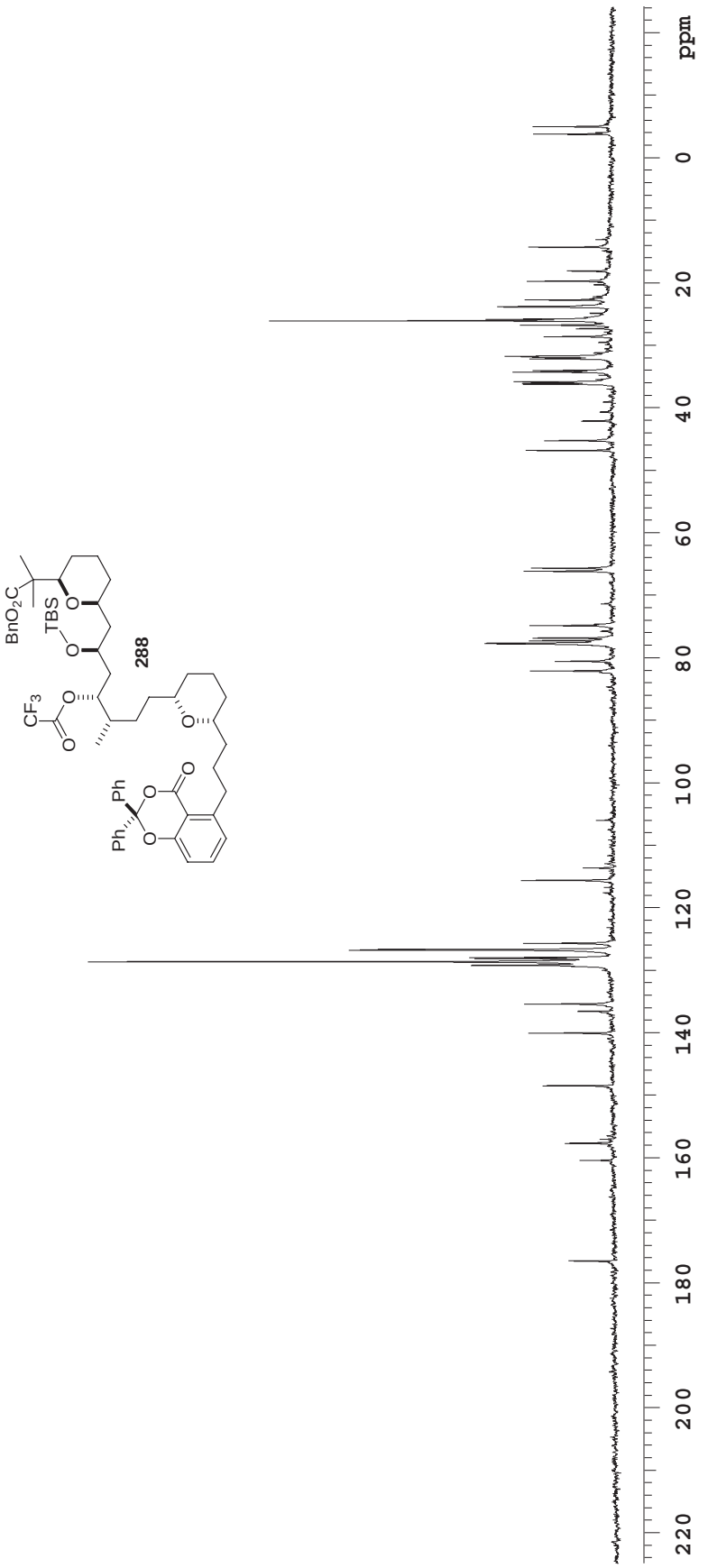

BnO2C
TBS
O
O
286
CH2Cl
O
O
O
O
Ph
Ph
O
O
O
ppm
10
9
8
7
6
5
4
3
2
1
0

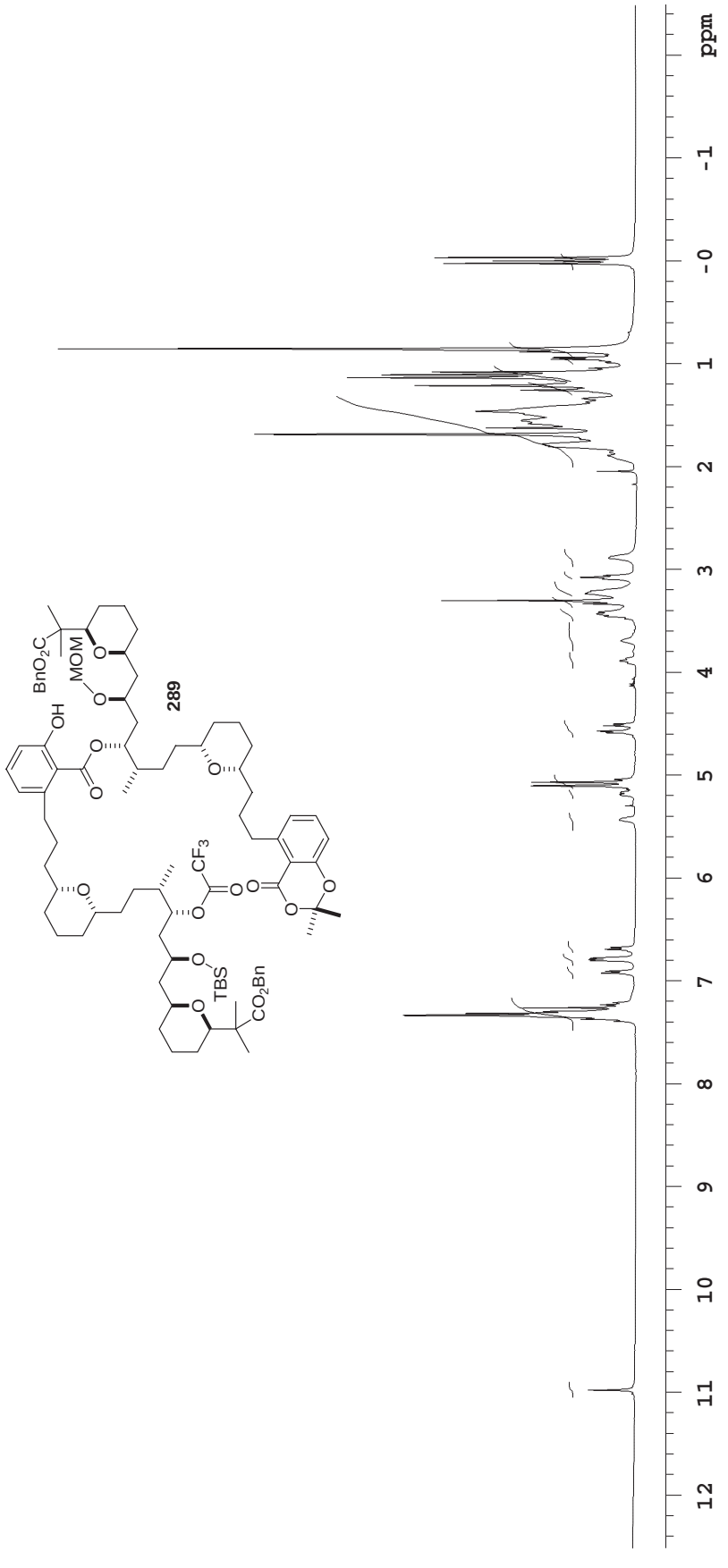

BnO2C
TBS
O
O
286
CH2Cl
O
O
O
O
Ph
Ph
O
O
O
ppm
200
180
160
140
120
100
80
60
40
20
0

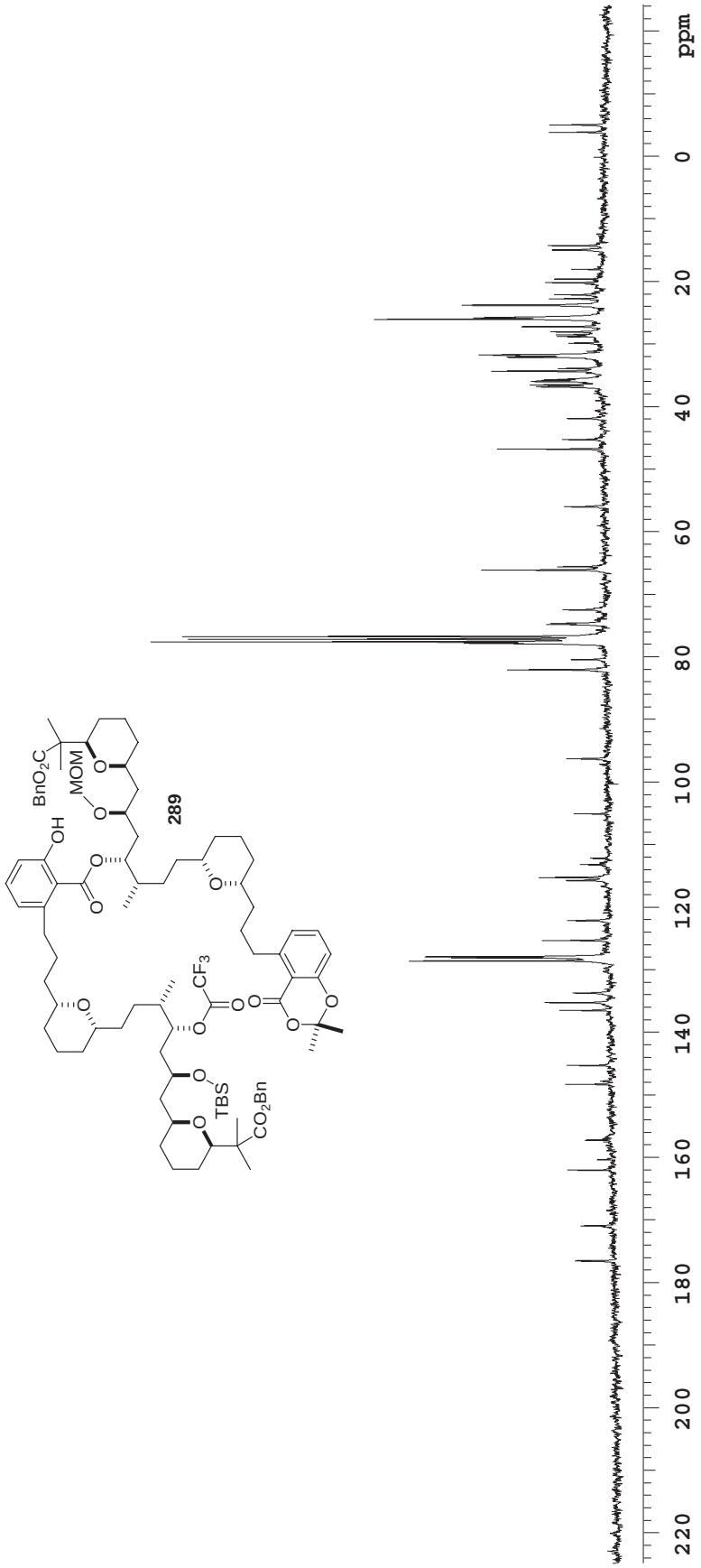

287
BnO2C
MOM
OH
OC(O)CH2Cl
TBS
CO2Bn
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0


BnO2C
OH
MOM
O
O
O
O
O
O
O
O
O
O
O
O
O
O
O
TBS
OC(O)CH2Cl
CO2Bn
287
220
200
180
160
140
120
100
80
60
40
20
0
ppm

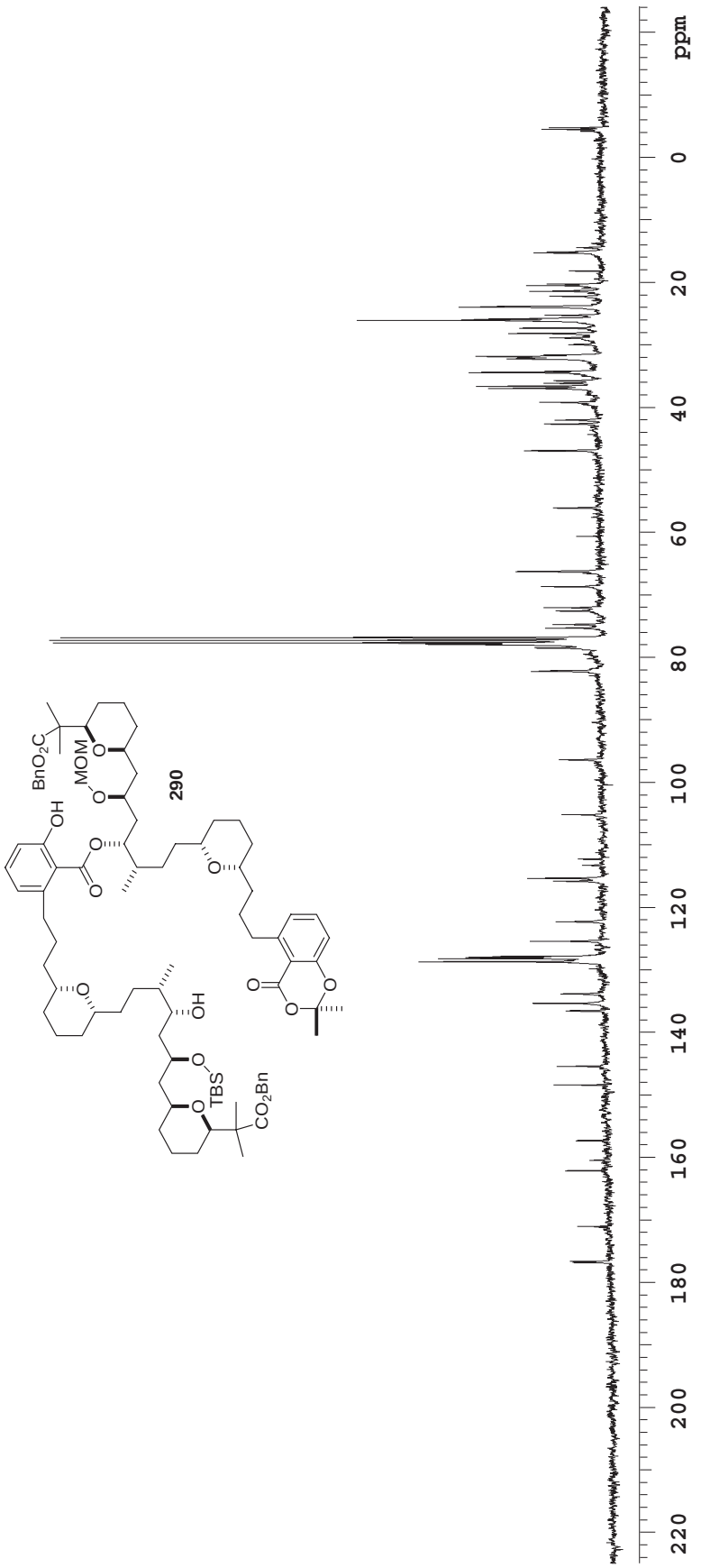

BnO2C
TBS
O
O
CF3
O
O
O
O
O
Ph
Ph
O
O
288
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1

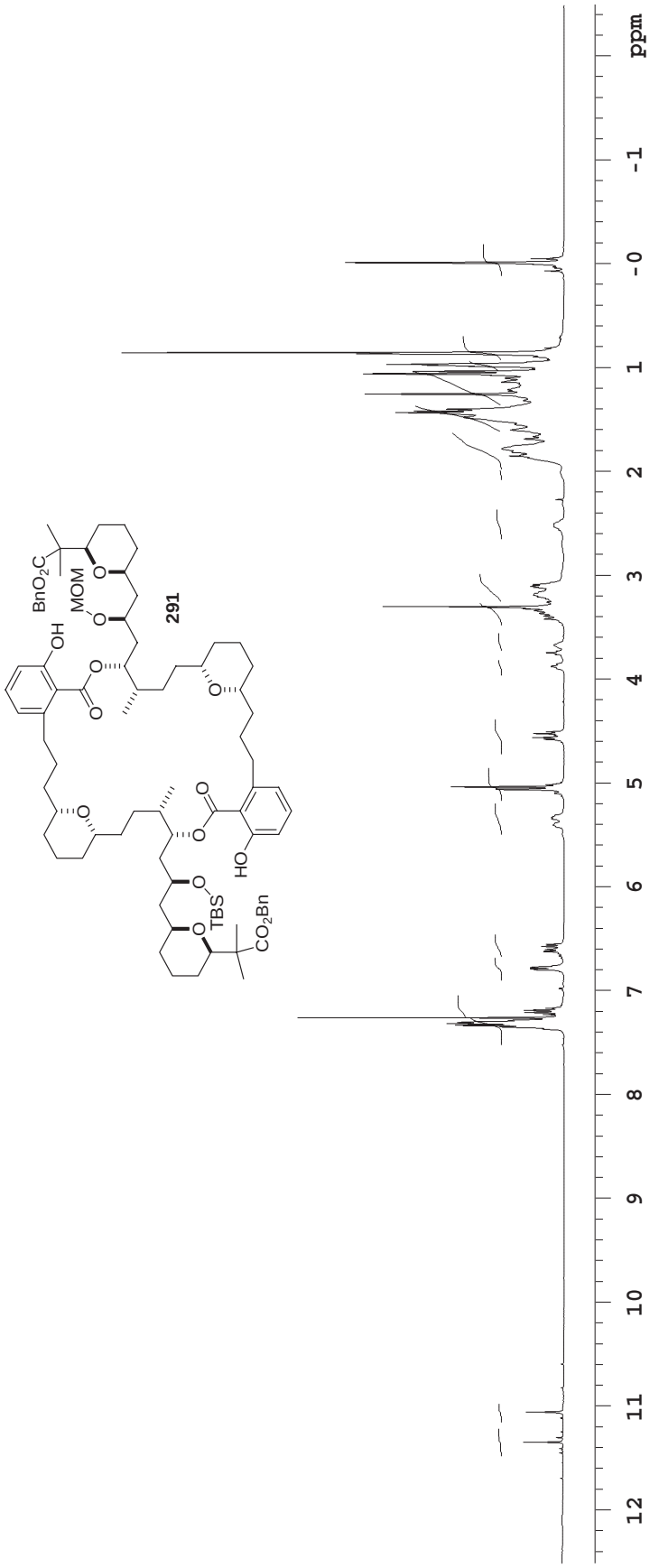

BnO2C
TBS
O
O
CF3
O
O
O
O
O
O
Ph
Ph
O
288
ppm
220
200
180
160
140
120
100
80
60
40
20
0

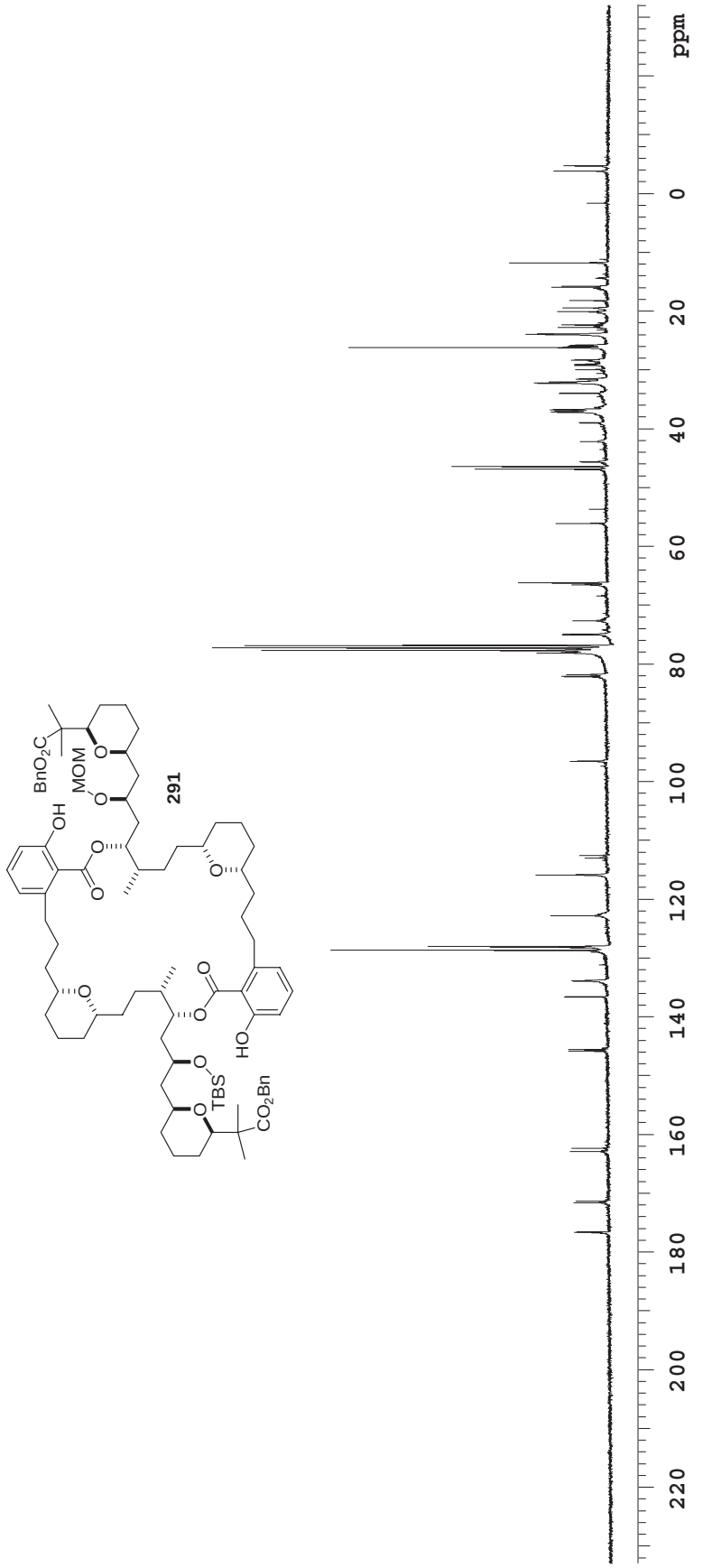

289
BnO2C
MOM
OH
CF3
TBS
CO2Bn
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1

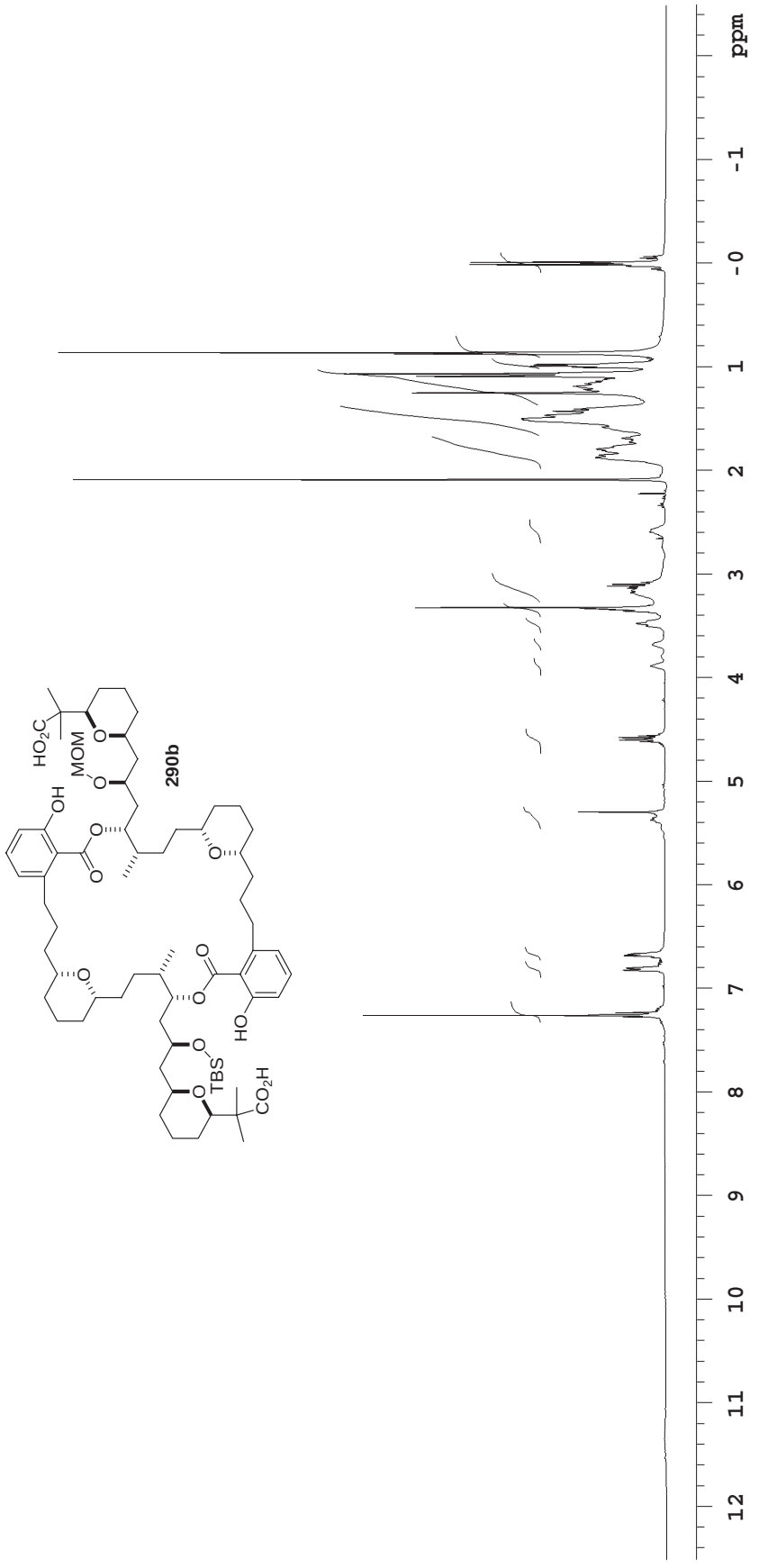

BnO2C
MOM
OH
289
CF3
TBS
CO2Bn
ppm
220
200
180
160
140
120
100
80
60
40
20
0

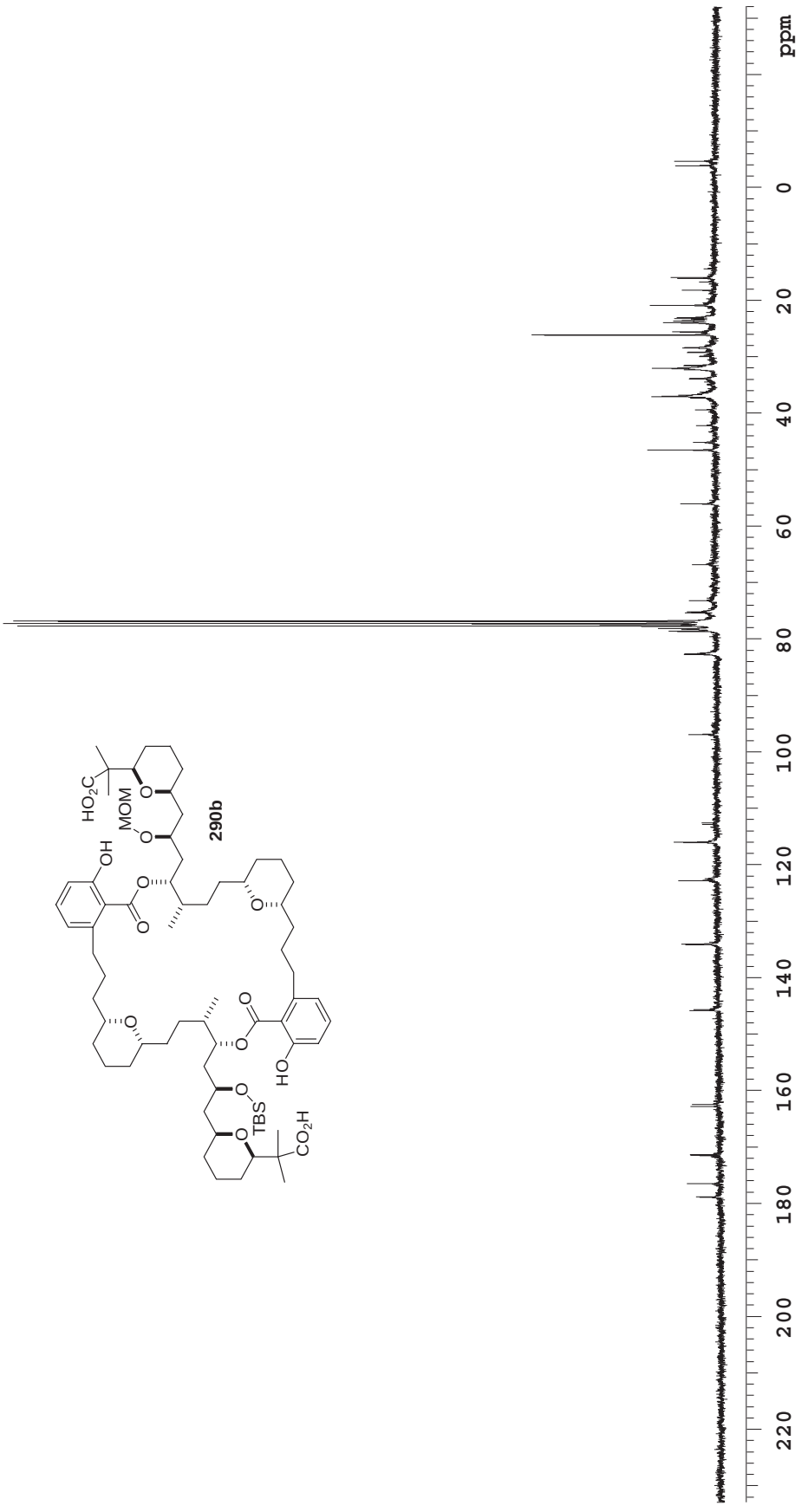

290
BnO2C
MOM
OH
TBS
CO2Bn
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1


BnO2C
MOM
OH
290
OH
TBS
CO2Bn
ppm
220
200
180
160
140
120
100
80
60
40
20
0

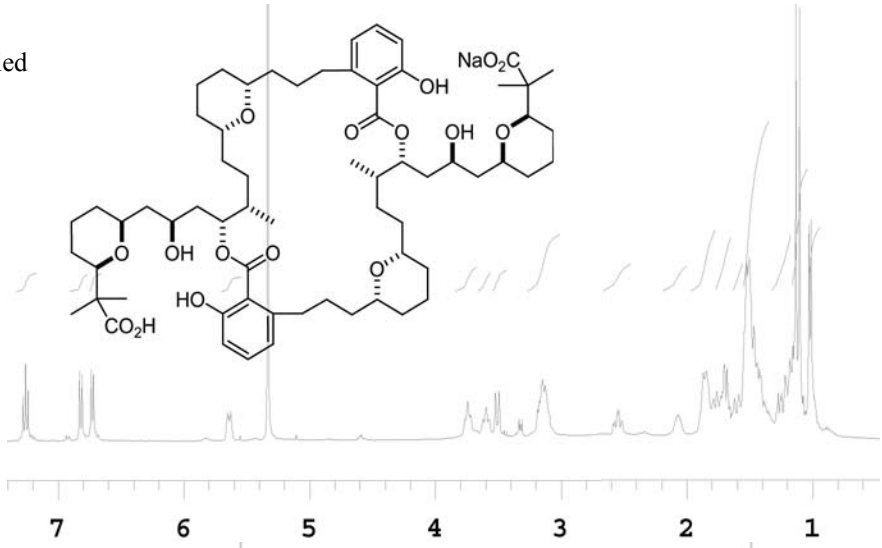

291
BnO2C
MOM
OH
HO
TBS
CO2Bn
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1


291
BnO2C
MOM
OH
HO
TBS
CO2Bn
ppm
220
200
180
160
140
120
100
80
60
40
20
0

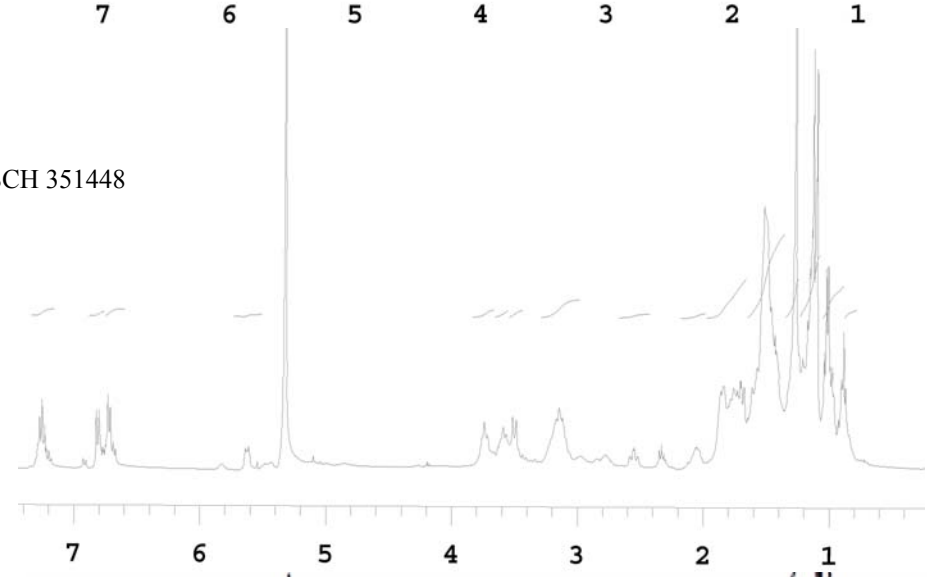

290b
HO2C
MOM
OH
TBS
CO2H
HO
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1


290b
HO2C
MOM
OH
TBS
CO2H
HO
ppm
220
200
180
160
140
120
100
80
60
40
20
0

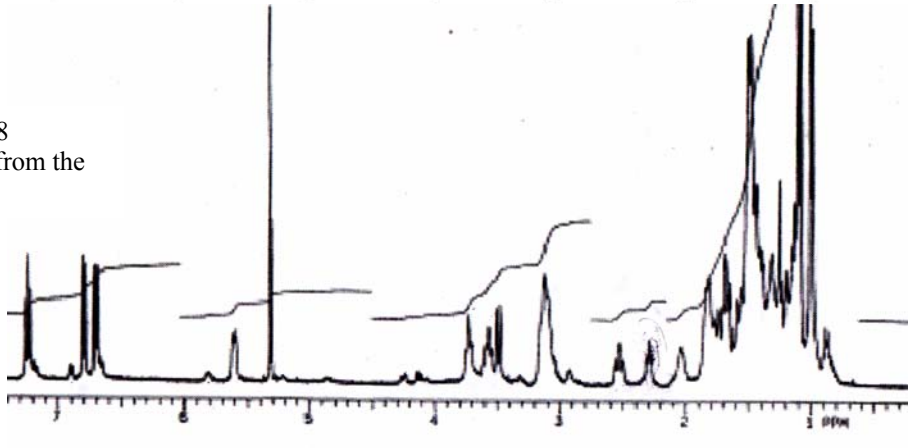
Synthetic HPLC Purified
SCH 351448

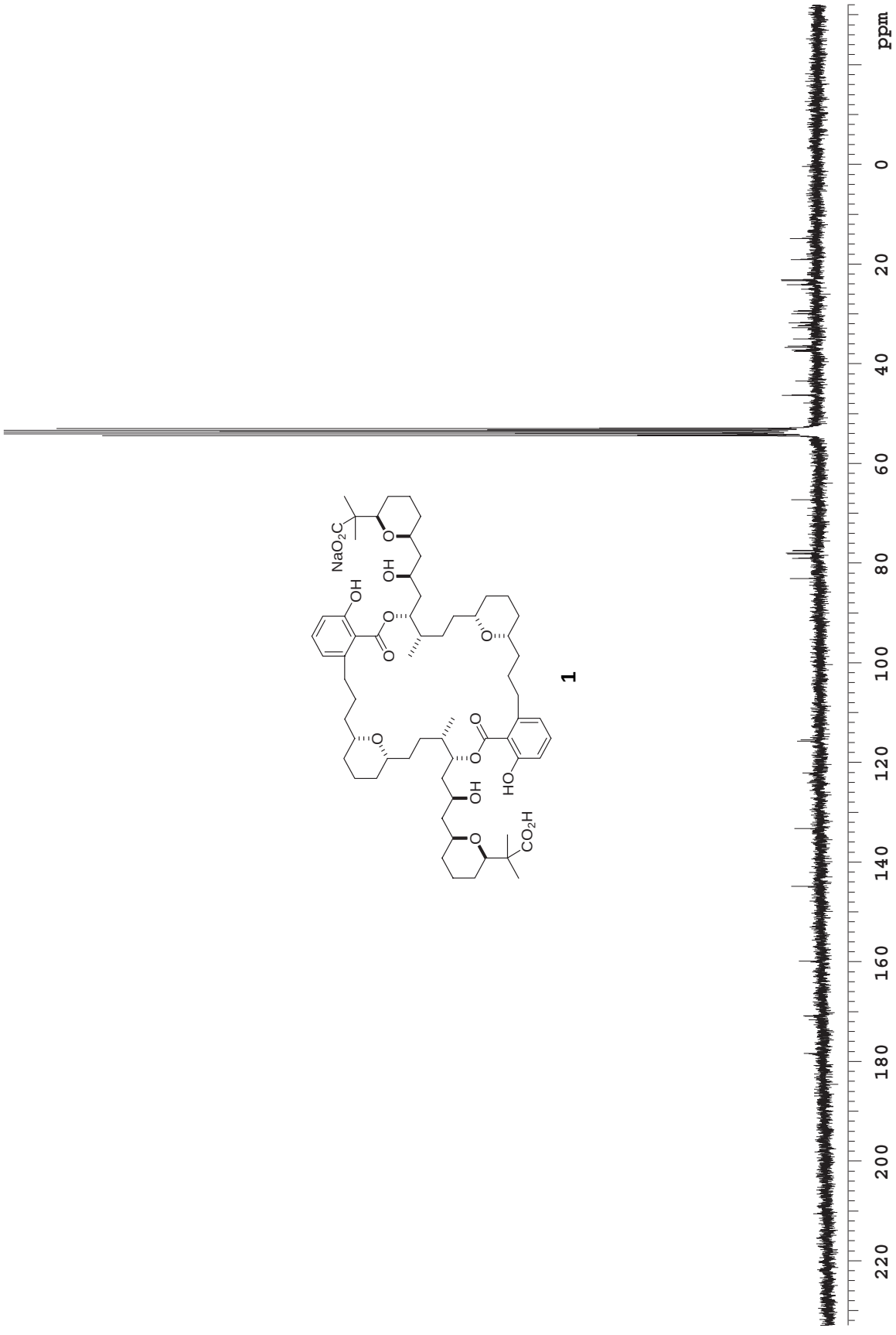


Synthetic Crude SCH 351448

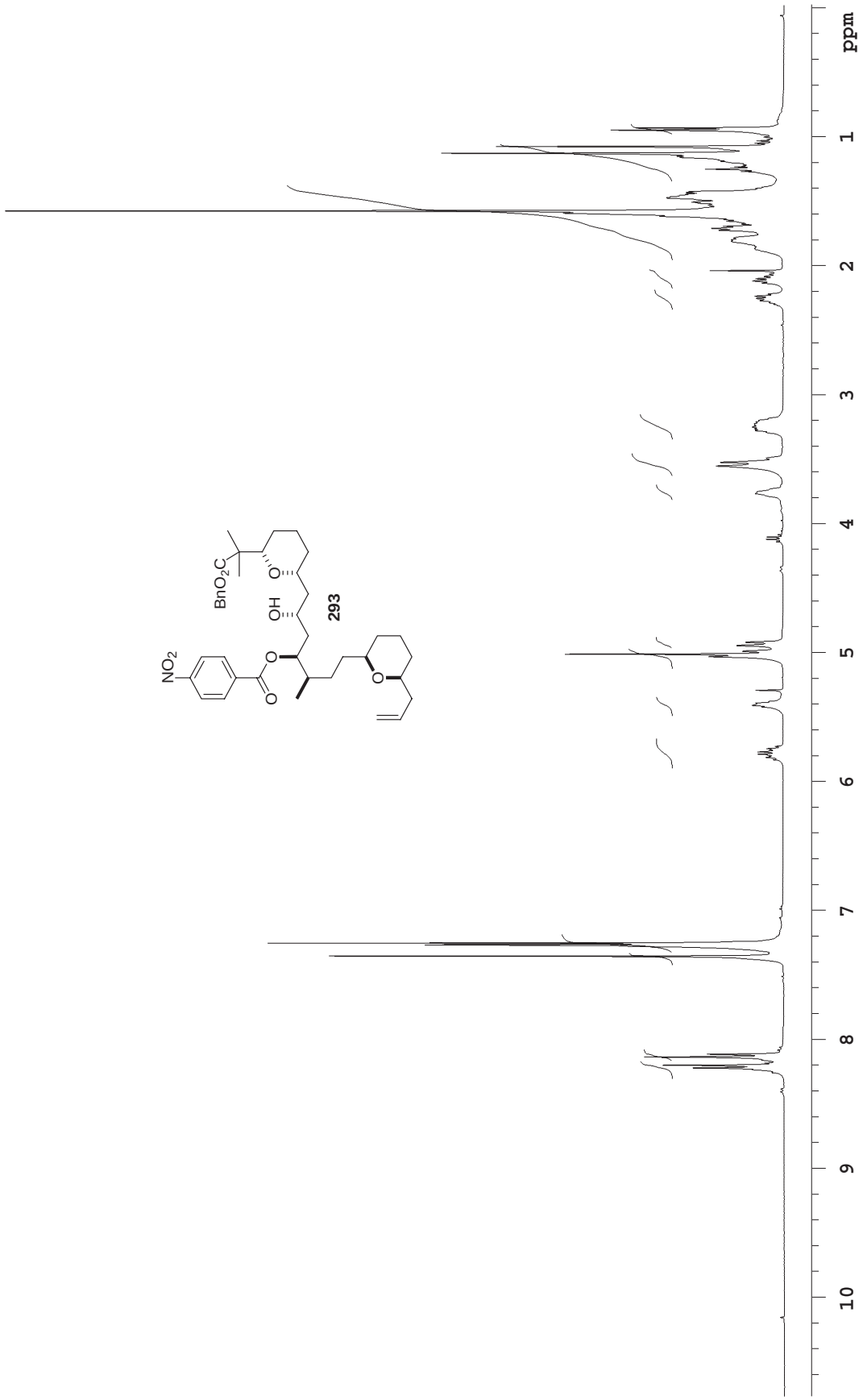


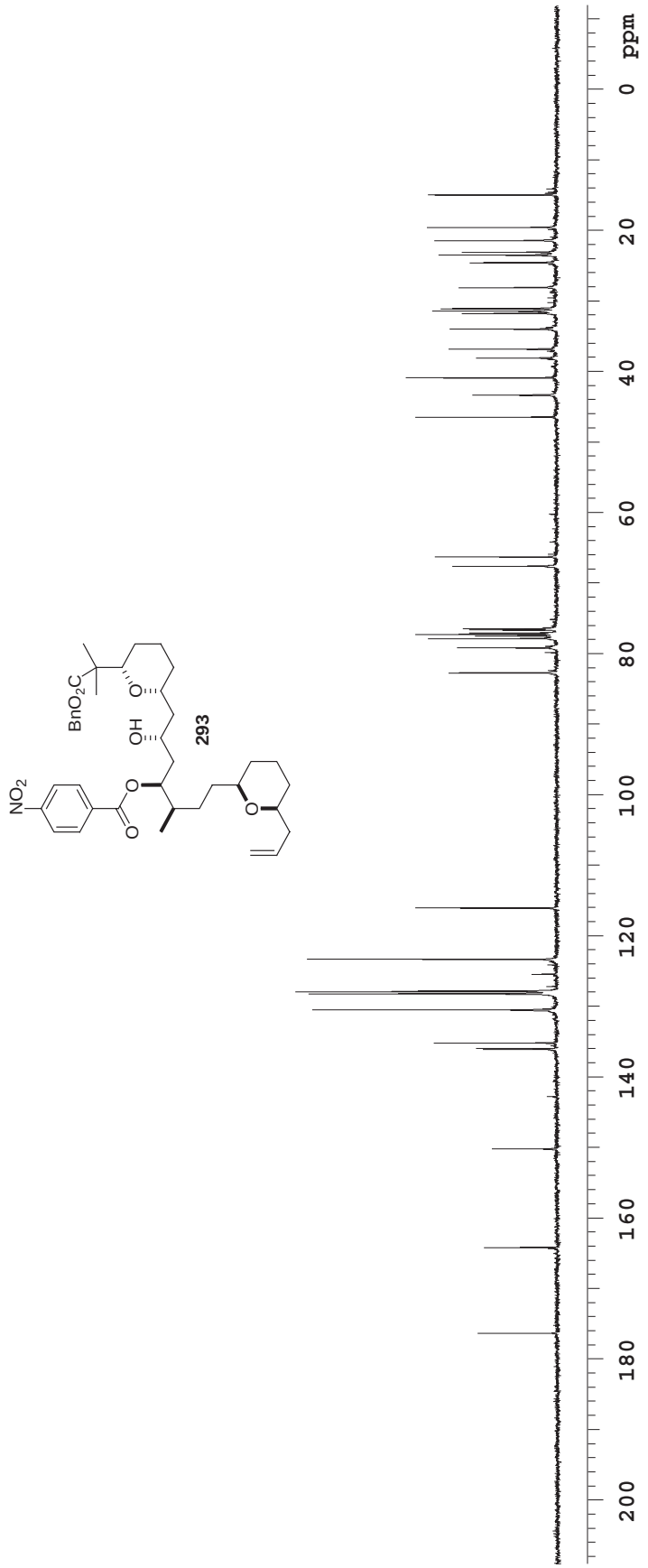
Natural SCH 351448
(Spectrum scanned from the
Supp. Info. of ref [1])

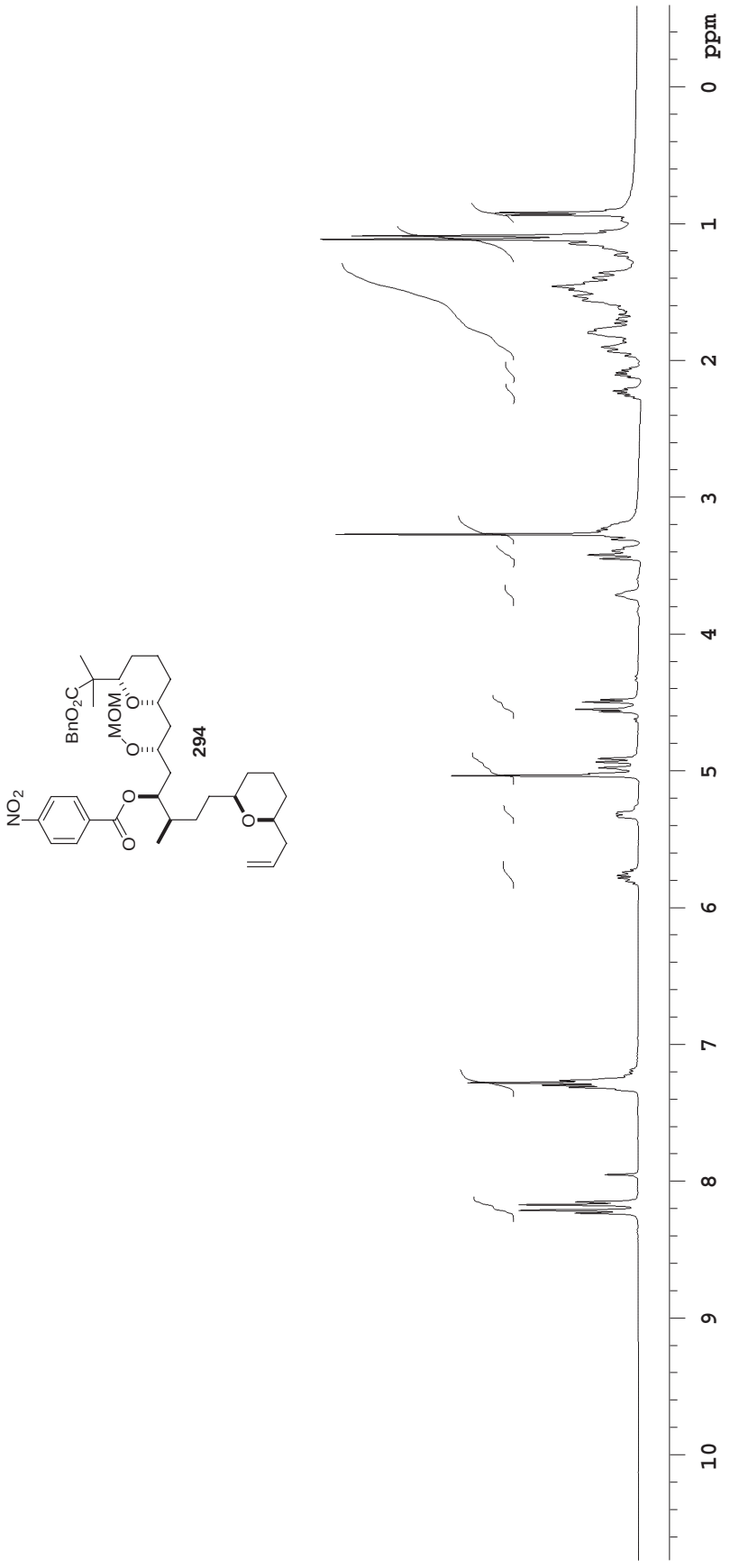



ppm
0
20
40
60
80
100
120
140
160
180
200
220
NaO2C
OH
OH
O
O
O
O
O
O
O
O
OH
HO
CO2H

1


293
BnO2C
OH
NO2
ppm
1
2
3
4
5
6
7
8
9
10


293
NO_2
BnO_2C
OH
O
O
O
O
200
180
160
140
120
100
80
60
40
20
0 ppm


BnO2C
MOM
O
O
O
O
O
O
NO2
294
0
1
2
3
4
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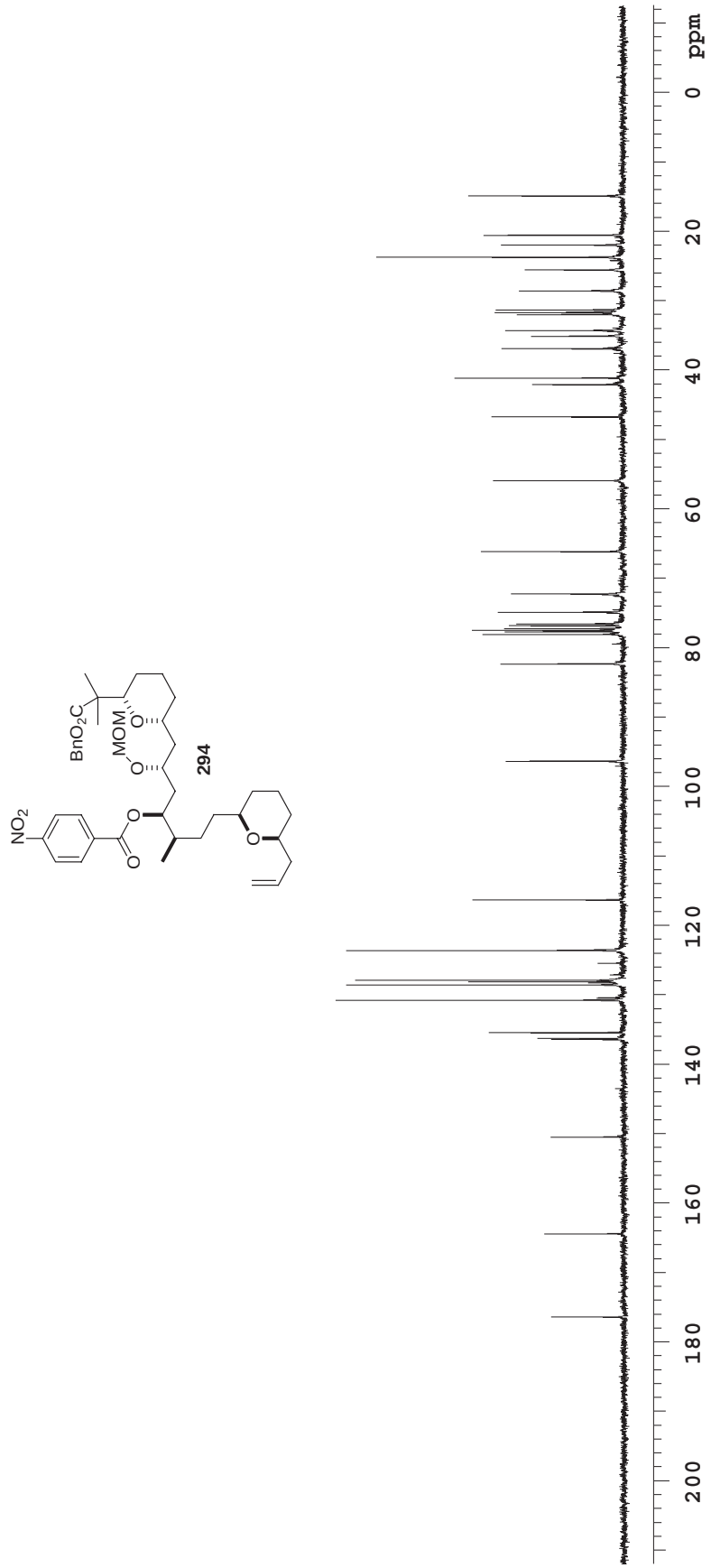
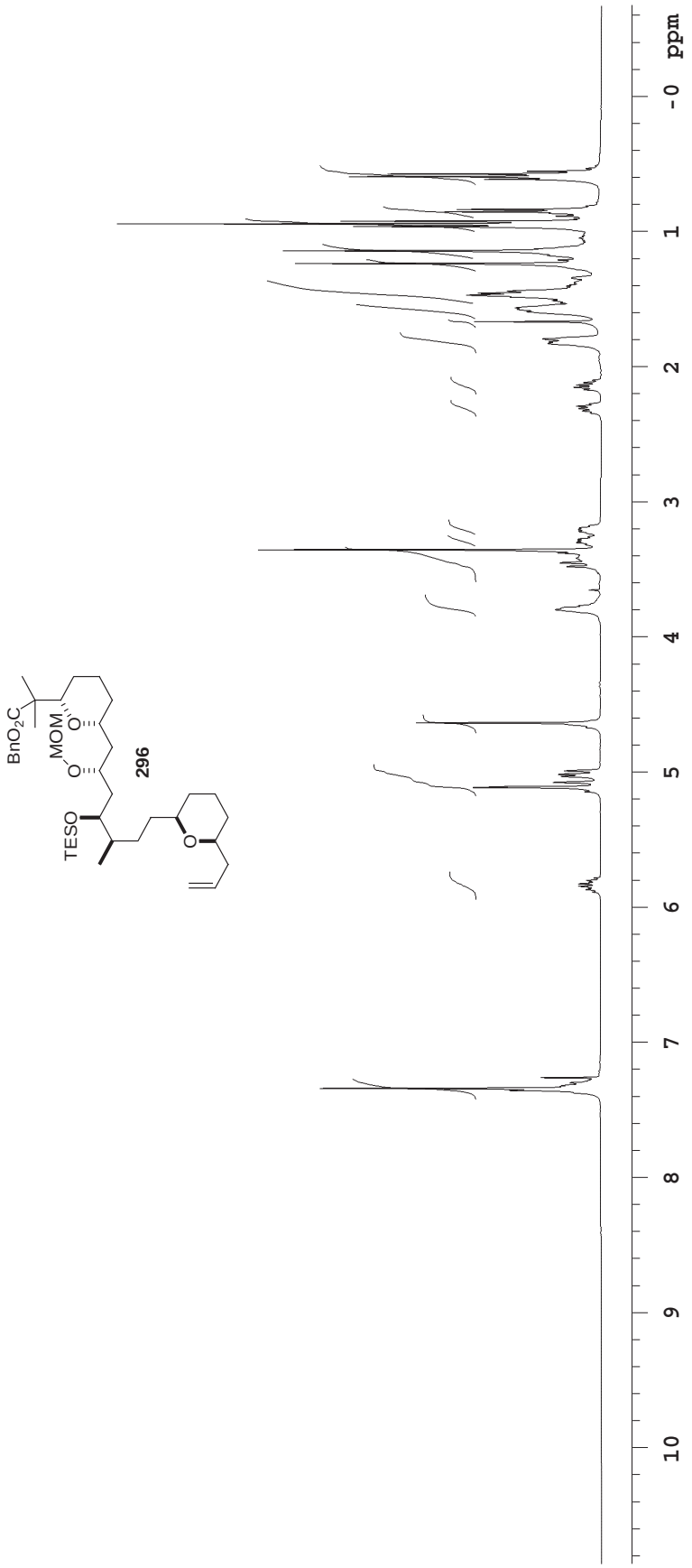
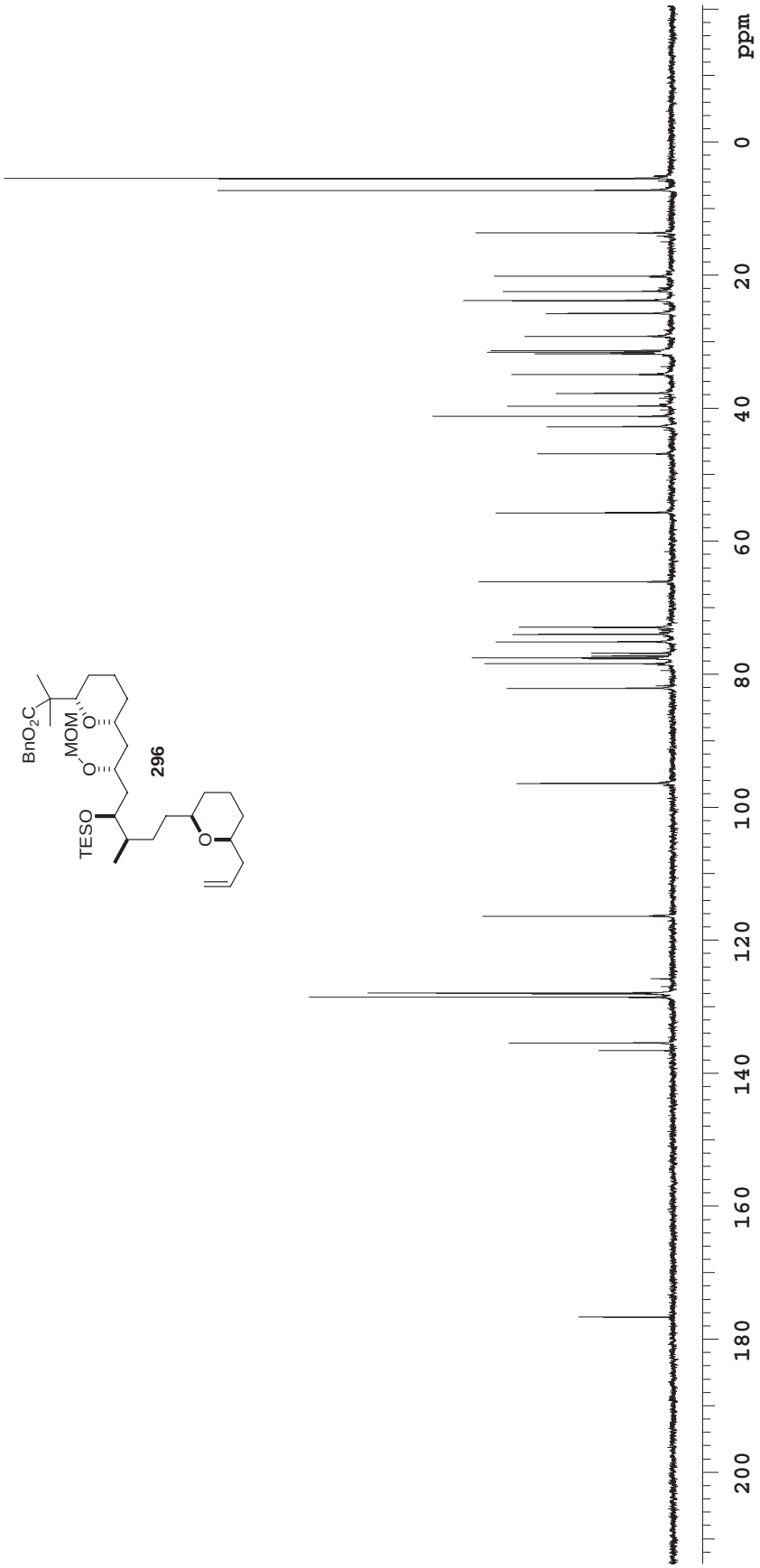
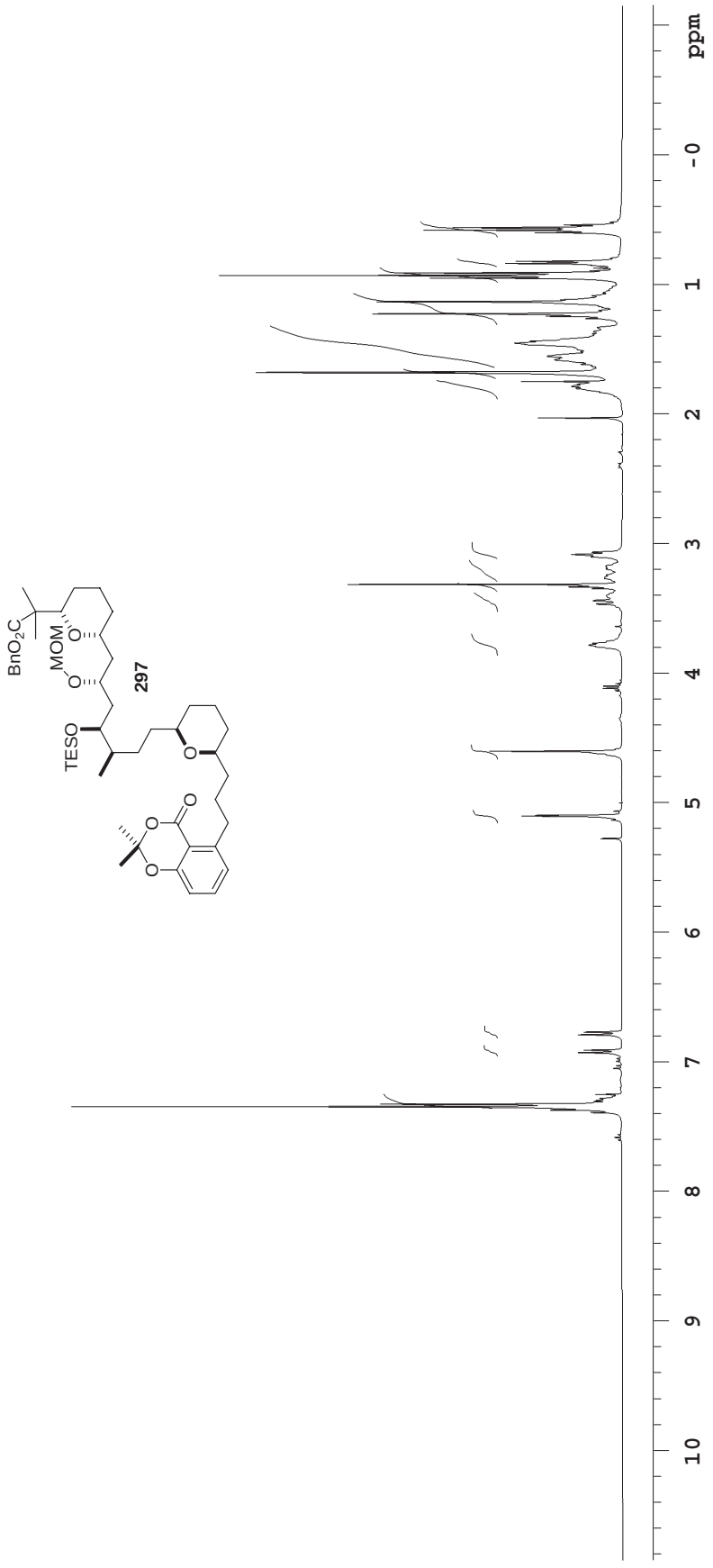
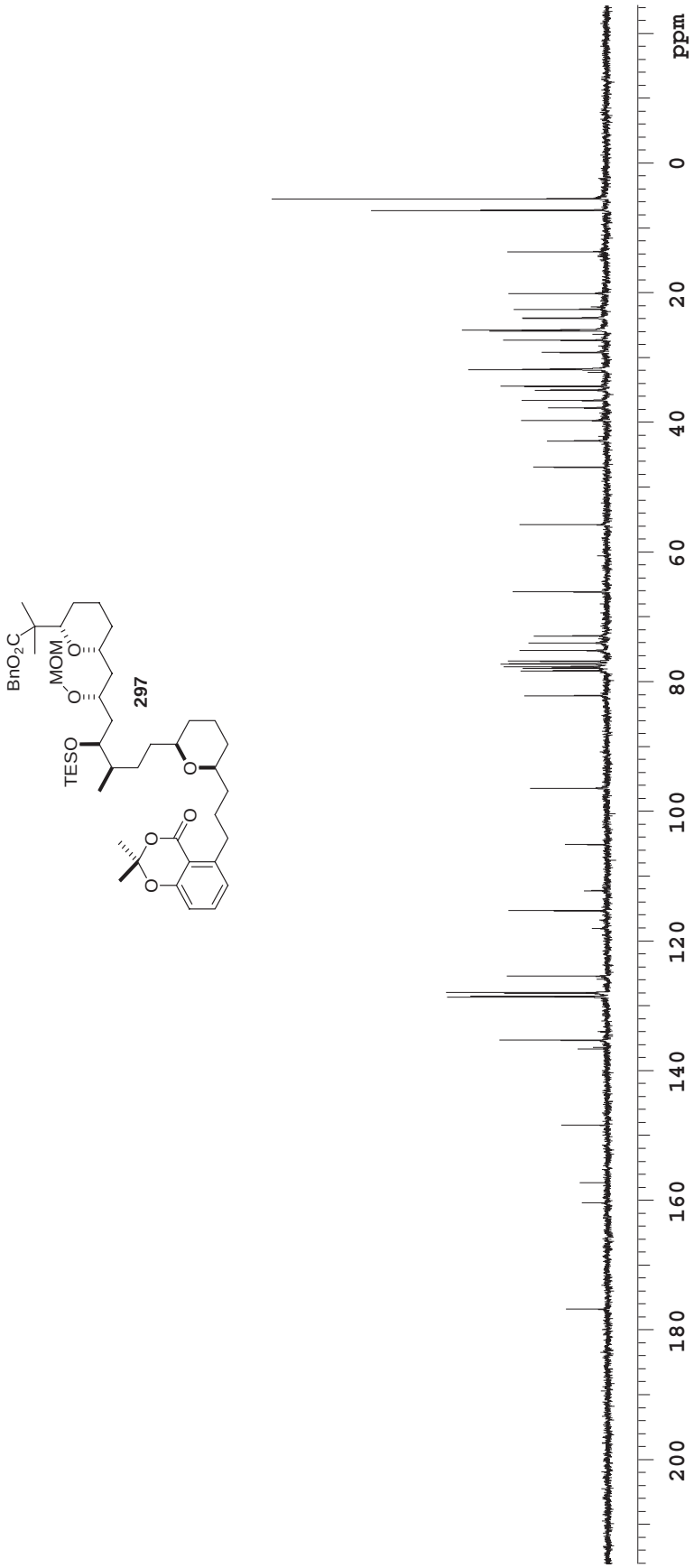
6
7
8
9
10
ppm

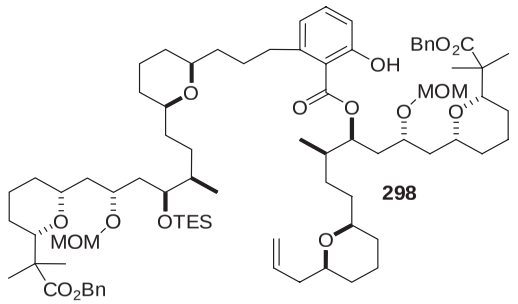

BnO2C
MOM
O
O
O
O
O
O
NO2
294
0
20
40
60
80
100
120
140
160
180
200
ppm


BnO2C
MOM
O
O
TESO
O
296
10
9
8
7
6
5
4
3
2
1
0
ppm

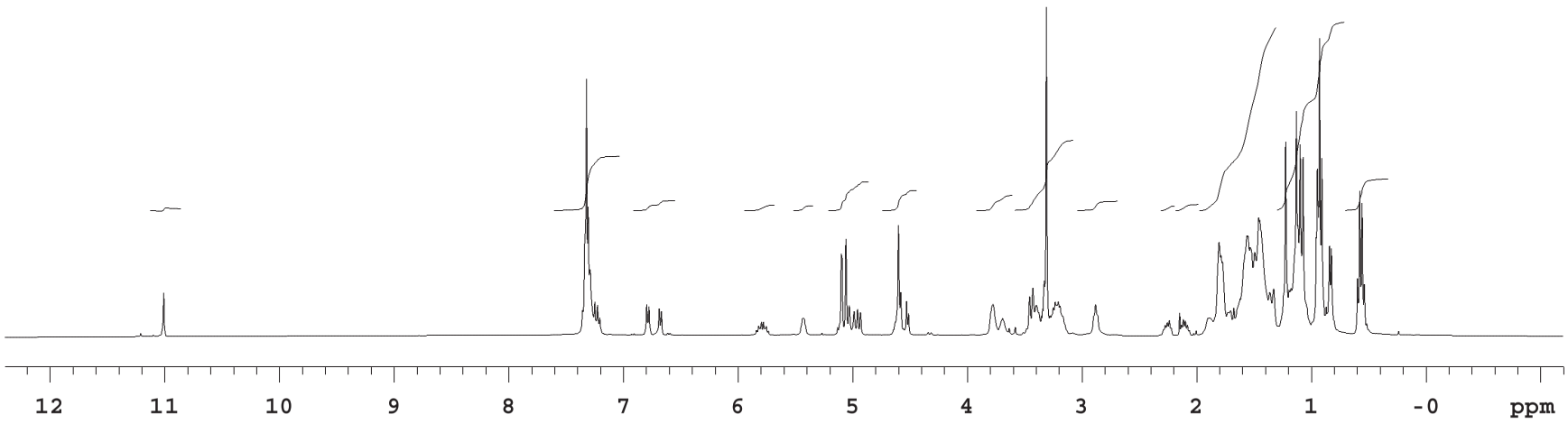

BnO2C
MOM
O
O
TESO
O
296
ppm
0
20
40
60
80
100
120
140
160
180
200


BnO2C
MOM
O
TESO
297
O
O
O
O
O
ppm
10
9
8
7
6
5
4
3
2
1
0


BnO2C
MOM
TESO
297
ppm
0
20
40
60
80
100
120
140
160
180
200


BnO2C
OH
MOM
O
O
O
O
O
O
O
O
O
MOM
O
OTES
CO2Bn

298


12
11
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9
8
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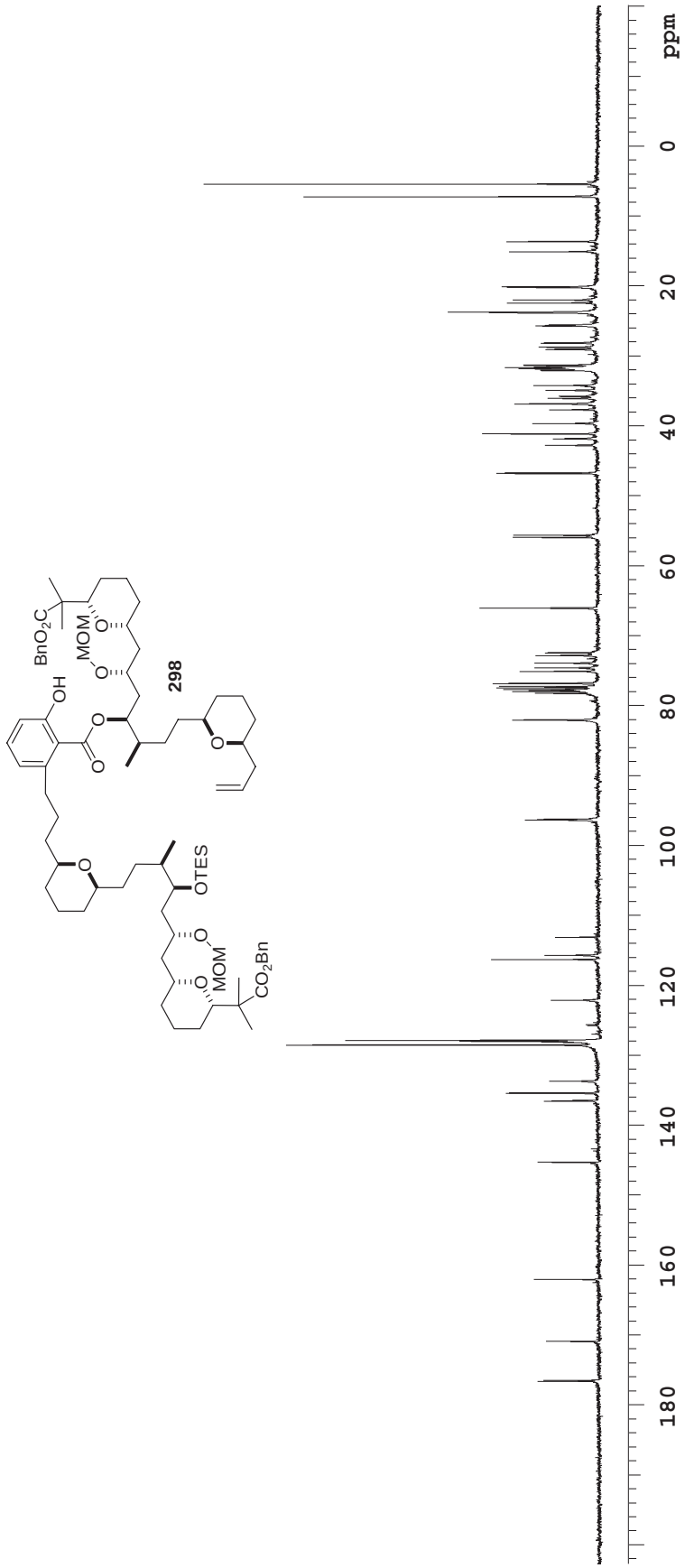
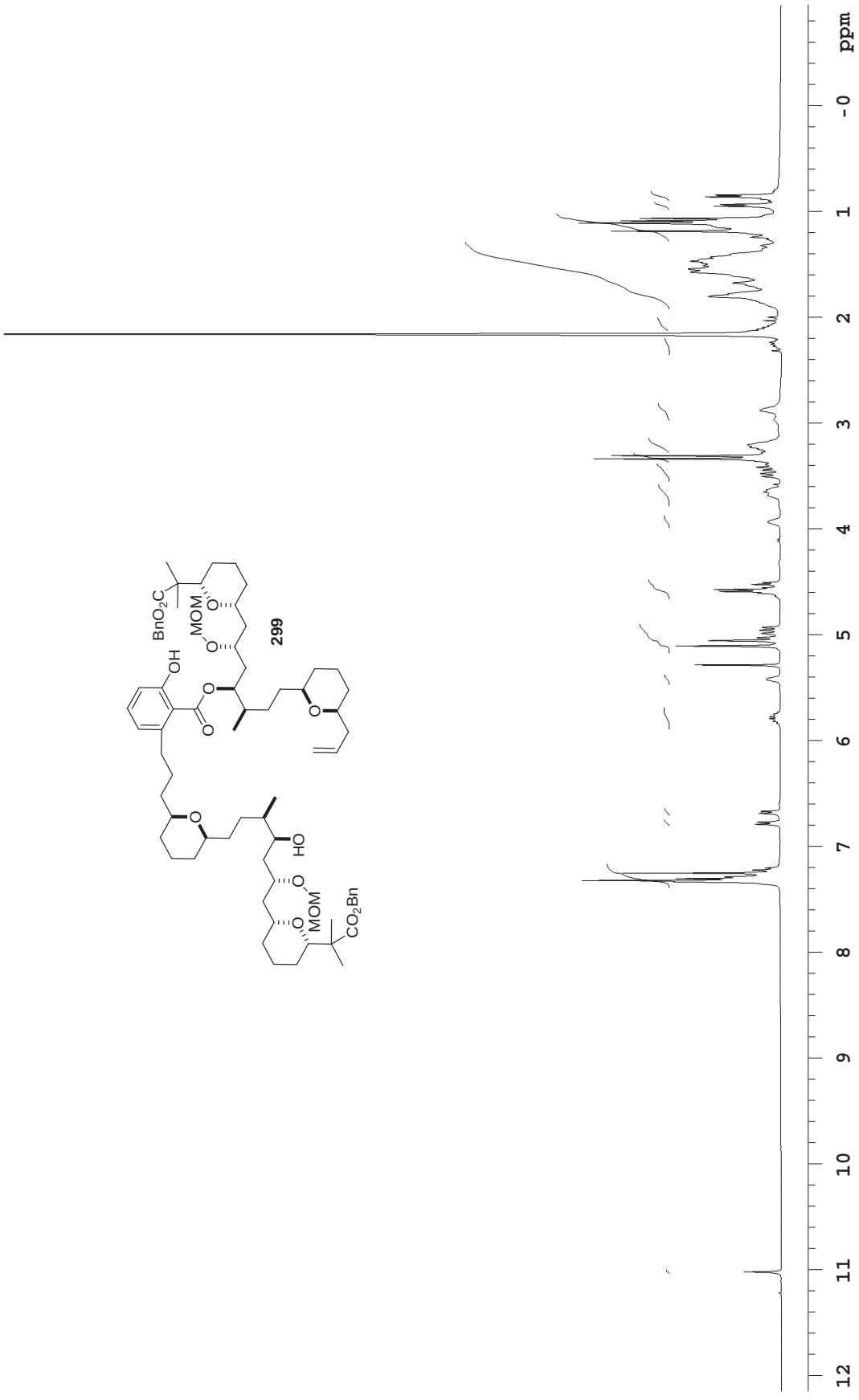
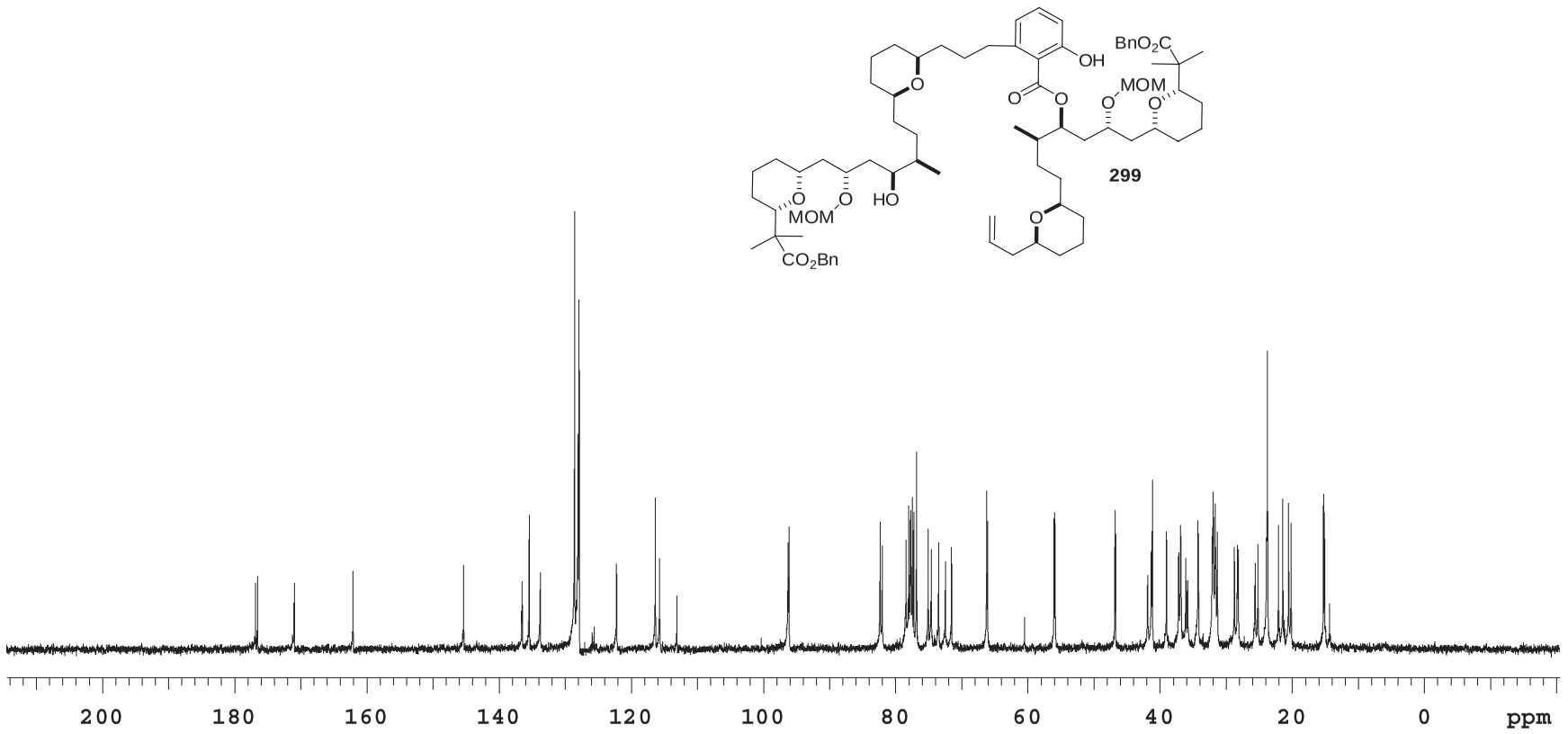
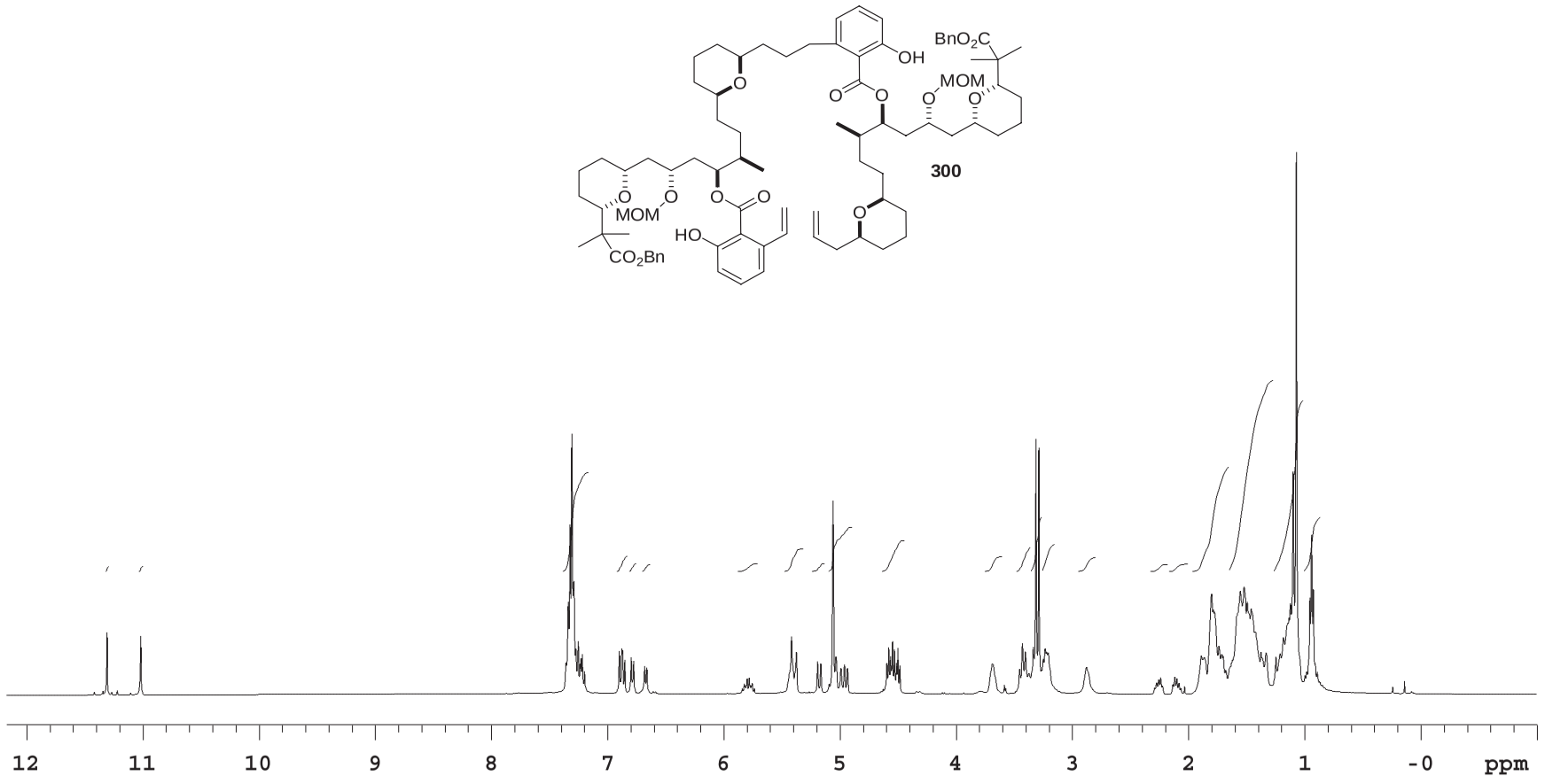
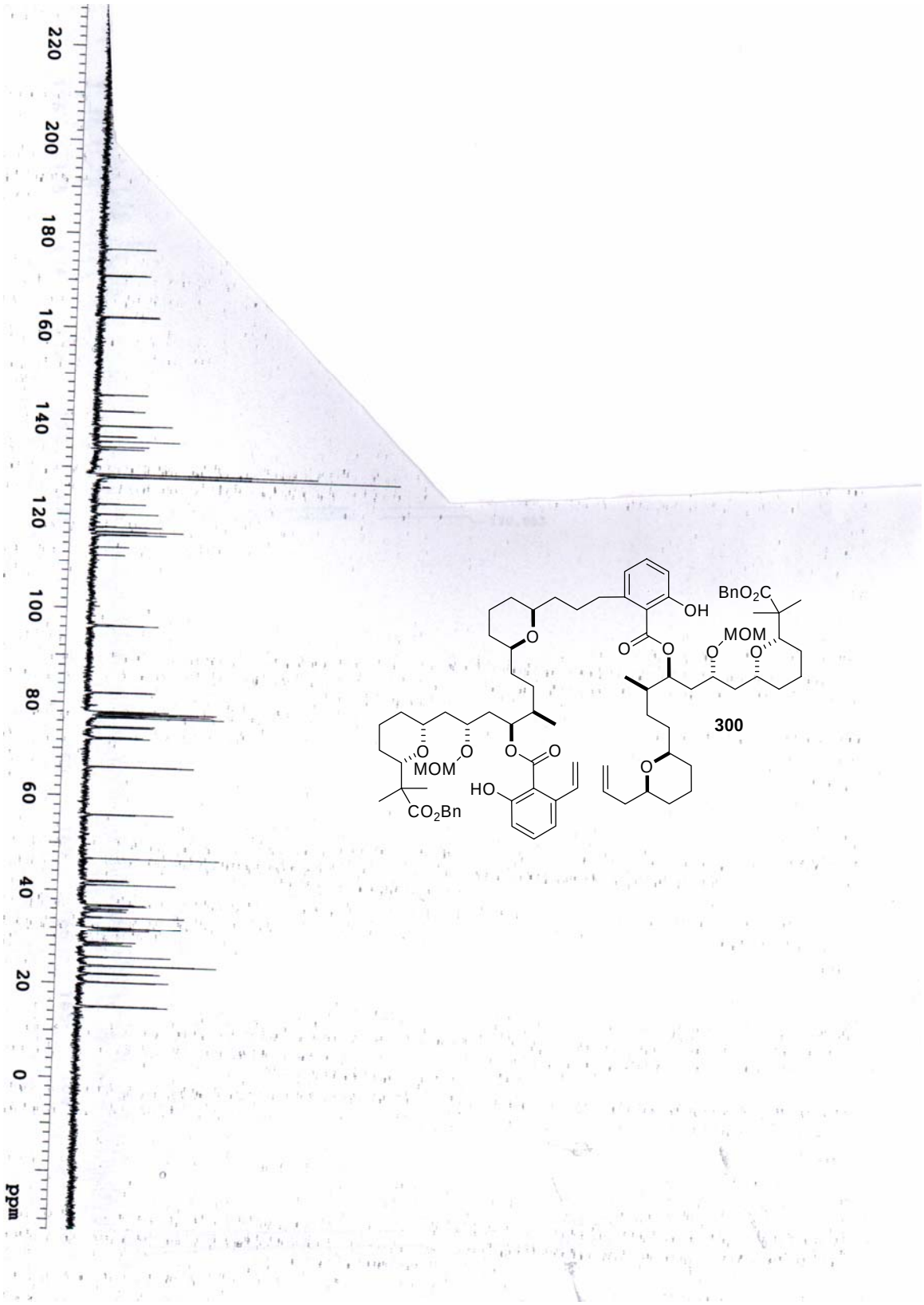
6
5
4
3
2
1
-0
ppm

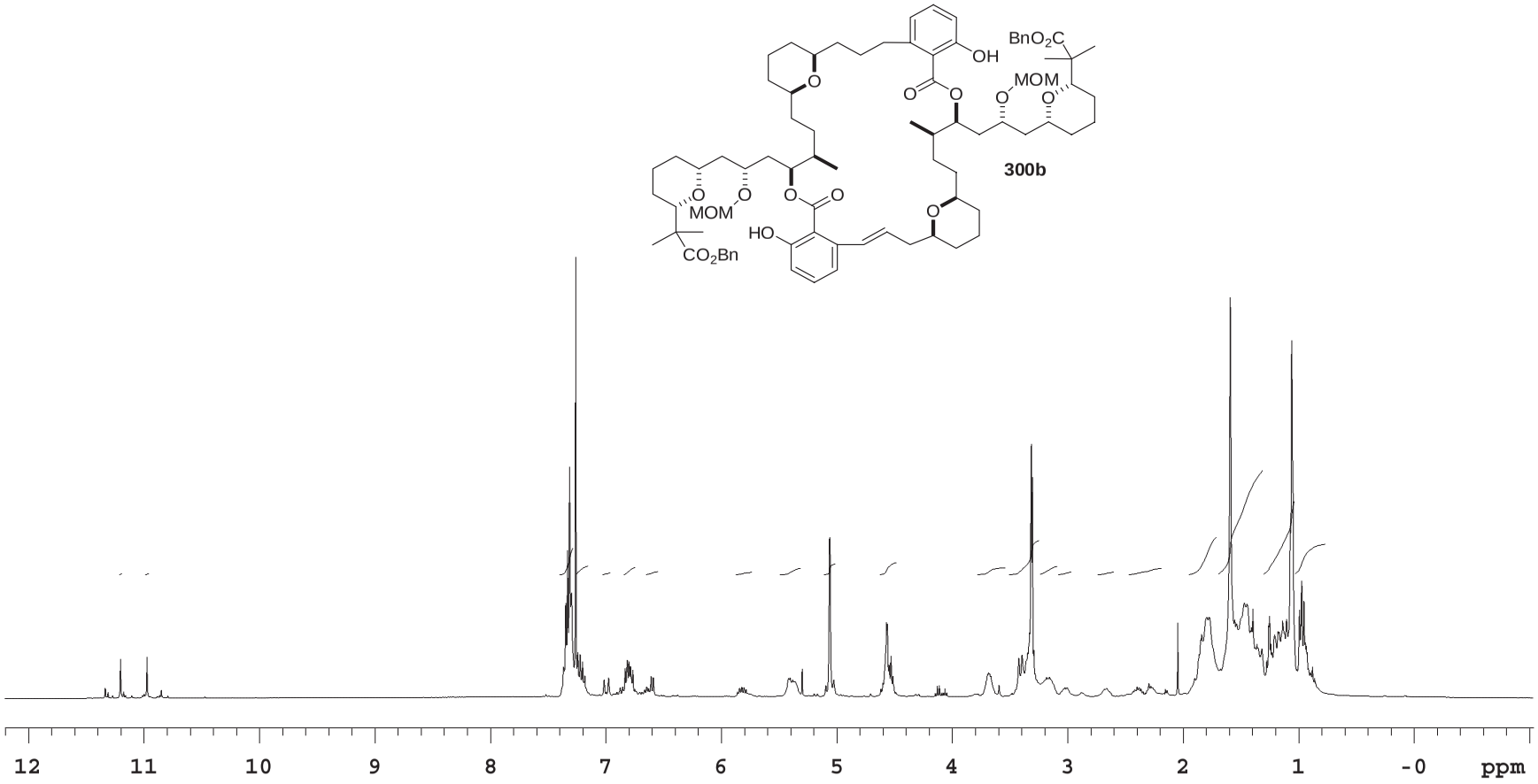

BnO2C
MOM
OH
298
OTES
MOM
CO2Bn
ppm
0
20
40
60
80
100
120
140
160
180


ppm
12
11
10
9
8
7
6
5
4
3
2
1
0
299
BnO2C
MOM
OH
HO
MOM
CO2Bn


OH
BnO2C
MOM
O
HO
MOM
CO2Bn
299
200
180
160
140
120
100
80
60
40
20
0
ppm


BnO2C
OH
MOM
O
O
O
O
O
O
O
O
MOM
HO
CO2Bn
300
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm
OH
BnO2C
MOM
O
O
O
O
O
O
O
O
MOM
HO
CO2Bn
300


BnO2C
OH
MOM
O
O
O
O
O
O
O
O
O
MOM
HO
CO2Bn
300b
12
11
10
9
8
7
6
5
4
3
2
1
-0
ppm

Vitae

Omid Soltani was born in Isfahan, Iran on November 28, 1977, the son of Ali and Zohreh Soltani. At the age of one his family moved to the Dallas/Fort Worth area where he was raised. During his formative years he developed an interest in the sciences and the sport of tennis. After graduating with honors from Lamar high school in 1996, he attended St. Mary's University in San Antonio, Texas. Following a brief stint on the tennis team at St. Mary's, his focused turned to the his studies where he developed a passion for organic chemistry that culminated in a Bachelor of Science degree with honors in chemistry. In 2000, he began graduate studies in organic synthesis in the laboratory of Jef K. De Brabander at U.T. Southwestern Medical Center at Dallas. He then obtained his Doctorate of Philosophy from U.T. Southwestern in April 2006.

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