AN ABSTRACT OF THE DISSERTATION OF

Eric A. Korf for the degree of Doctor of Philosophy in Chemistry presented on July 24, 2006.

Title: Studies Toward the Synthesis of Halichlorine and Pinnaic Acid.

Abstract approved:_____

James D. White

Three approaches toward the core of halichlorine and pinnaic acid are described. The first approach entails a racemic transannular nitrone-olefin [3+2] cycloaddition from nitrone **238**. Construction of the nitrone **238** began with aldehyde **241**. Another key feature in this route involved a ring-closing metathesis for the formation of a 14-membered ring. The route ended upon formation of a key diol **237**.

The second approach incorporated the C_{14} methyl group at an early stage to probe its influence upon an intramolecular nitrone-olefin [3+2] cycloaddition. The approach began with dithiane **258**. A key feature in the second plan involved asymmetric induction at the C_5 carbon through a conjugate addition of an azide to an α,β-unsaturated imide to form azide **290** with both excellent yield and stereocontrol for this additon. The route was advanced to oxaziridine **299**. Conversion of **299** to the nitrone **300** and ultimately the intramolecular nitrone-olefin [3+2] cycloaddition was unsuccessful.

The third and final approach involved using the basic plan of our first successful approach and employing the asymmetric induction of the second approach. This blending of strategies led to an asymmetric intermediate that links up with the first approach. The route began with dithiane **258**. Again, the use of an azide addition

to a α,β-unsaturated imide led to azide **309**. Upon formation of the 14-membered lactone, the azide function was first reduced and protected as carbamate **320** which in turn, increased the yield substantially over this same transformation from the first route. Amine **318** now stands ready to complete a formal synthesis of halichlorine and pinnaic acid.

Studies Toward the Synthesis of Halichlorine and Pinnaic Acid.

by

Eric A. Korf

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APPROVED:

_____

Major Professor, representing Chemistry

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Chair of the Department of Chemistry

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Dean of the Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

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Eric A. Korf, Author

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STUDIES TOWARD THE SYNTHESIS OF HALICHLORINE AND PINNAIC ACID

CHAPTER 1 BACKGROUND

1.1 GENERAL INTRODUCTION

Marine life continues to provide an abundance of novel metabolites which are of interest structurally and which often possess significant biological activities. These compounds are formed within slowly growing creatures in areas of the oceans where the ecology is too fragile for continuous harvesting, e.g, coral reefs. These precious compounds are typically collected in minute quantities using multiple extractions and separations. This, in turn, gives chemists an opportunity for structure elucidation, as well as designing and implementing a synthetic plan. This leads to advancement in the frontier of natural product isolation and synthesis, while being ecologically responsible.

1.2 ISOLATION, BIOLOGICAL ACTIVITY, AND STRUCTURE DETERMINATION OF HALICHLORINE

Halichlorine (**1**) is a substance isolated from a family of marine species and is characterized by the presence of an azaspiro[4.5]decane nucleus (figure 1). It was discovered initially by Uemura in a marine sponge, *Halichondria okadai* Kadota, collected in Japanese waters.[1] Fortunately, **1** is produced in relatively large amounts (200 kg of wet sponge yielded 70.9 mg). The purification to obtain the crystalline alkaloid was tedious, requiring three column chromatographic separations followed by preparative thin-layer chromatography. The structure of halichlorine was established by using extensive spectroscopic techniques (mainly NMR). The absolute configuration at C_5, C_9, C_{13}, C_{14}, and C_{17} of **1** was initially assigned as enantiomeric with that shown.

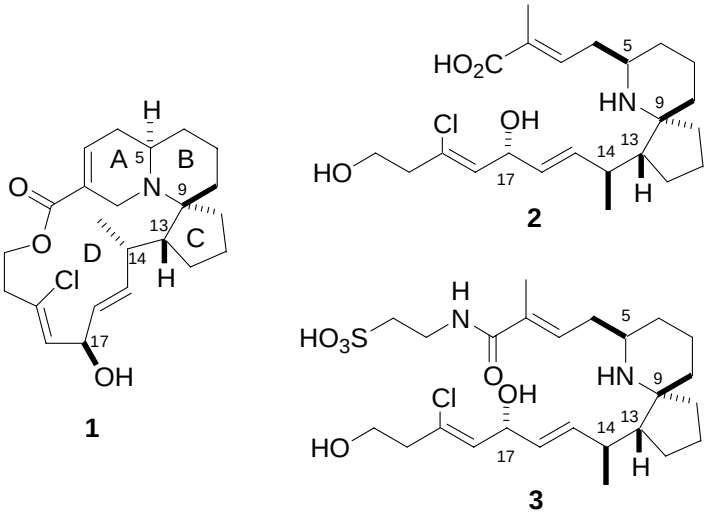
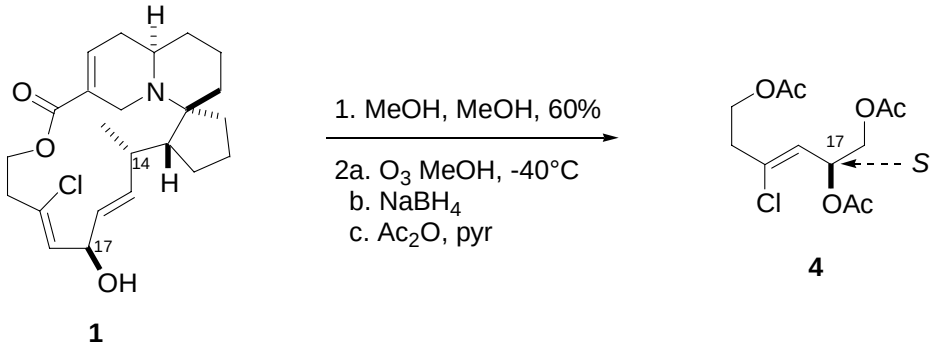


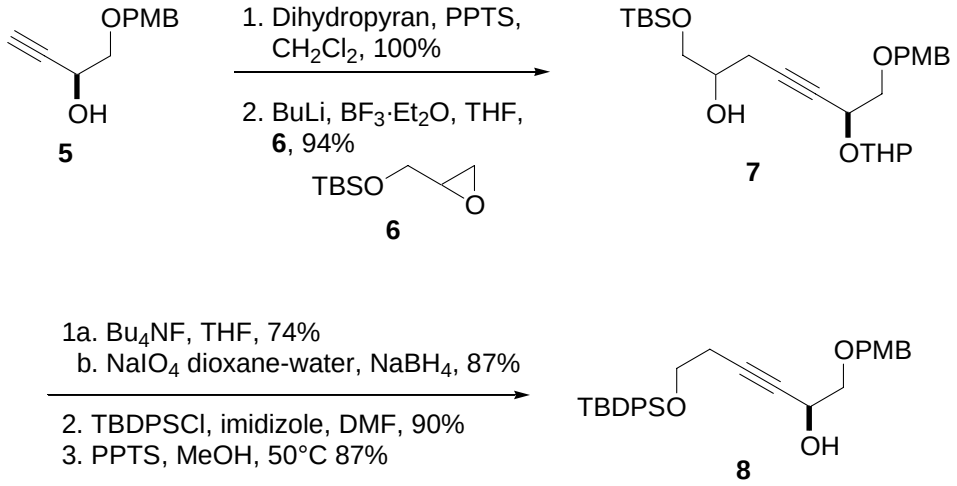
Figure 1. Structure of halichlorine (**1**) pinnaic acid (**2**), and tauropinnaic acid (**3**).

Uemura and co-workers published a second paper verifying the absolute configuration of **1** via a degradation study (Scheme 2).[2] Methanolysis of **1**, followed by ozonolysis with reductive workup and global acetyl protection of the exposed alcohol functionalities yielded **4**. The degradation product was compared to a sample prepared from D-(+)-tartaric acid via alcohol **5**. After alcohol **5** was protected, subsequent addition to epoxide **6** afforded alcohol **7**. Desilylation, diol oxidation with reductive workup, primary alcohol silylation, and final acetal removal yielded **8**. A sequence involving chlorine addition to the alkyne, followed by debenzylation and desilylations ended with global acetyl protection to form **4**. The two **4**'s were analyzed by chiral HPLC, which showed them to have the same retention time. This established the absolute stereochemistry of C_{17} and therefore of **1**. This assignment was later confirmed with the first synthesis of **1** by Danishefsky.[3]



1 **4**

Scheme 1. Degradation of **1**



Scheme 2. Confirmation of C_{17} stereochemistry of halichlorine

Halichlorine was shown to inhibit the induction of vascular cell adhesion molecule-1 (VCAM-1) in cultured human umbilical vein endothelial cells.[4] The IC_{50} for **1** in this bioassay is 7 μg/mL. Substances that selectively inhibit the induction of

VCAM-1 are potential candidates for treatment of atherosclerosis, coronary artery diseases, angina and other noncardiovascular inflammatory diseases.[5]

1.3 ISOLATION, BIOLOGICAL ACTIVITY, AND STRUCTURE DETERMINATION OF PINNAIC AND TAUROPINNAIC ACID

Pinnaic acid (**2**) and tauropinnaic acid (**3**) are closely related structurally to halichlorine (**1**) (Figure 1). These alkaloids were isolated in the amounts of 1 mg and 4 mg respectively from 10 kg of viscera acquired from 3000 individual specimens of the Okinawan bivalve, *Pinna muricata,* again in Japanese waters [6] The structures of **2** and **3** were established using spectroscopic analysis, including NMR techniques. In this case, however, it was not possible to assign the C_{17} stereochemistry, and that proposed for C_{14} was not on a very secure basis. The first synthesis of **2** by Danishefsky[7,8] allowed assignment of both stereocenters and showed that the stereochemistry at C_{14} required revision from that initially proposed by Uemura. The synthetic studies of Danishefsky finalized the structural details as shown in **2** and **3**. Later synthetic work by Heathcock,[9] and by Hayakawa, Arimoto, and Uemura[10] was in accord with these new assignments.

It was the search for natural substances which inhibit phospholipase A_2 (PLA_2) that led to the discovery of pinnaic and tauropinnaic acids. PLA_2 is linked to the initial step of the cascade for enzymatic reactions leading to the generation of inflammatory mediators. Specific inhibitors of PLA_2 are considered potential drug candidates for the treatment of various inflammations. Pinnaic and tauropinnaic acids are known inhibitors of a cytosolic 85-KDa phospholipase ($cPLA_2$); their IC_{50} values

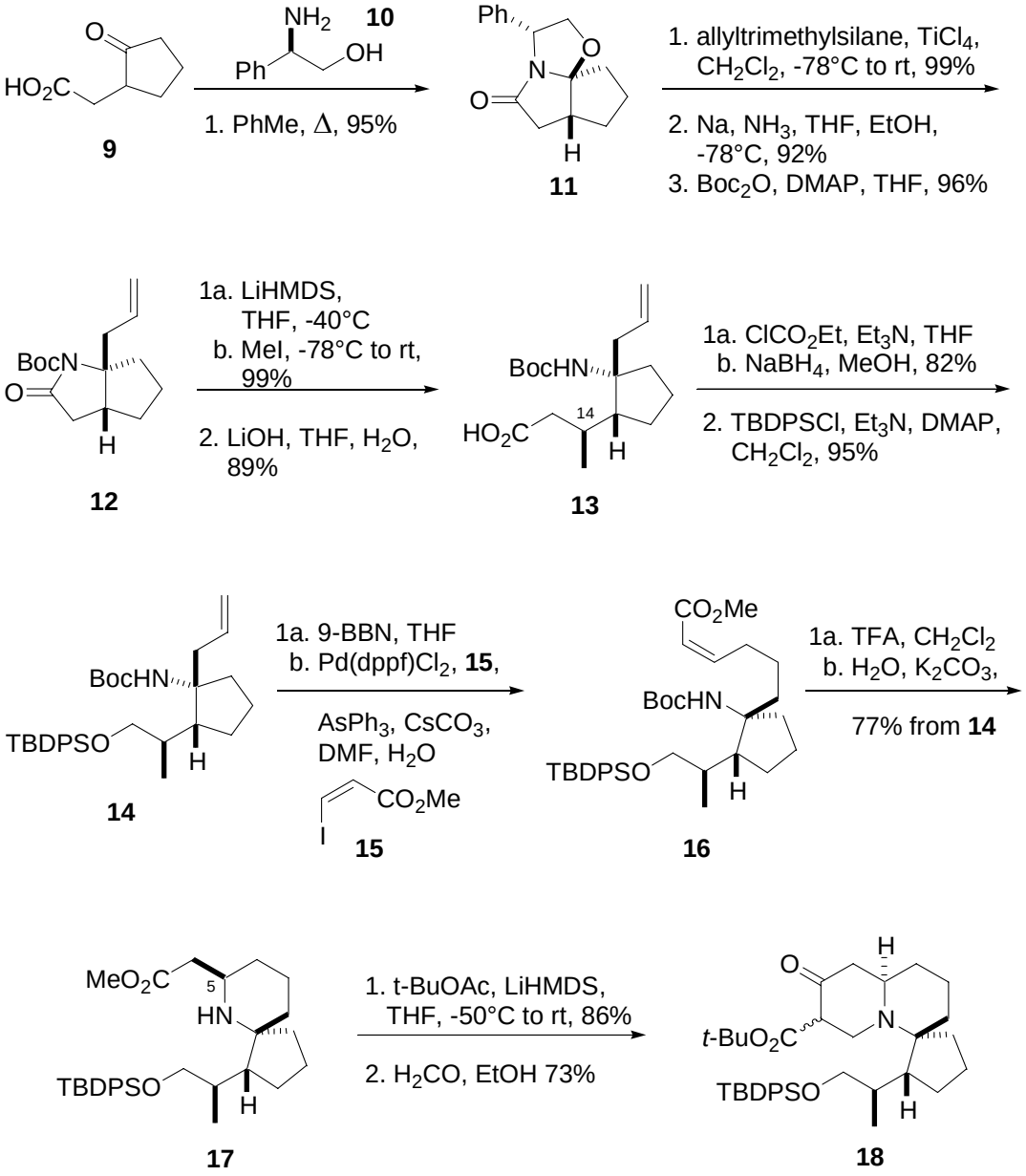
in vitro are 0.2 mM and 0.09 mM, respectively.[11] In turn, $cPLA_2$ has been shown to exhibit specificity for the release of arachidonic acid from membrane phospholipids.[12]

1.4 SYNTHETIC STUDIES

Halichlorine and pinnaic acid have invited a broad range of efforts directed towards their total synthesis. Many conceptually different synthetic strategies have been compiled in a comprehensive review by Clive.[13]

1.4.1 DANISHEFSKY'S TOTAL SYNTHESIS OF (+)-HALICHLORINE

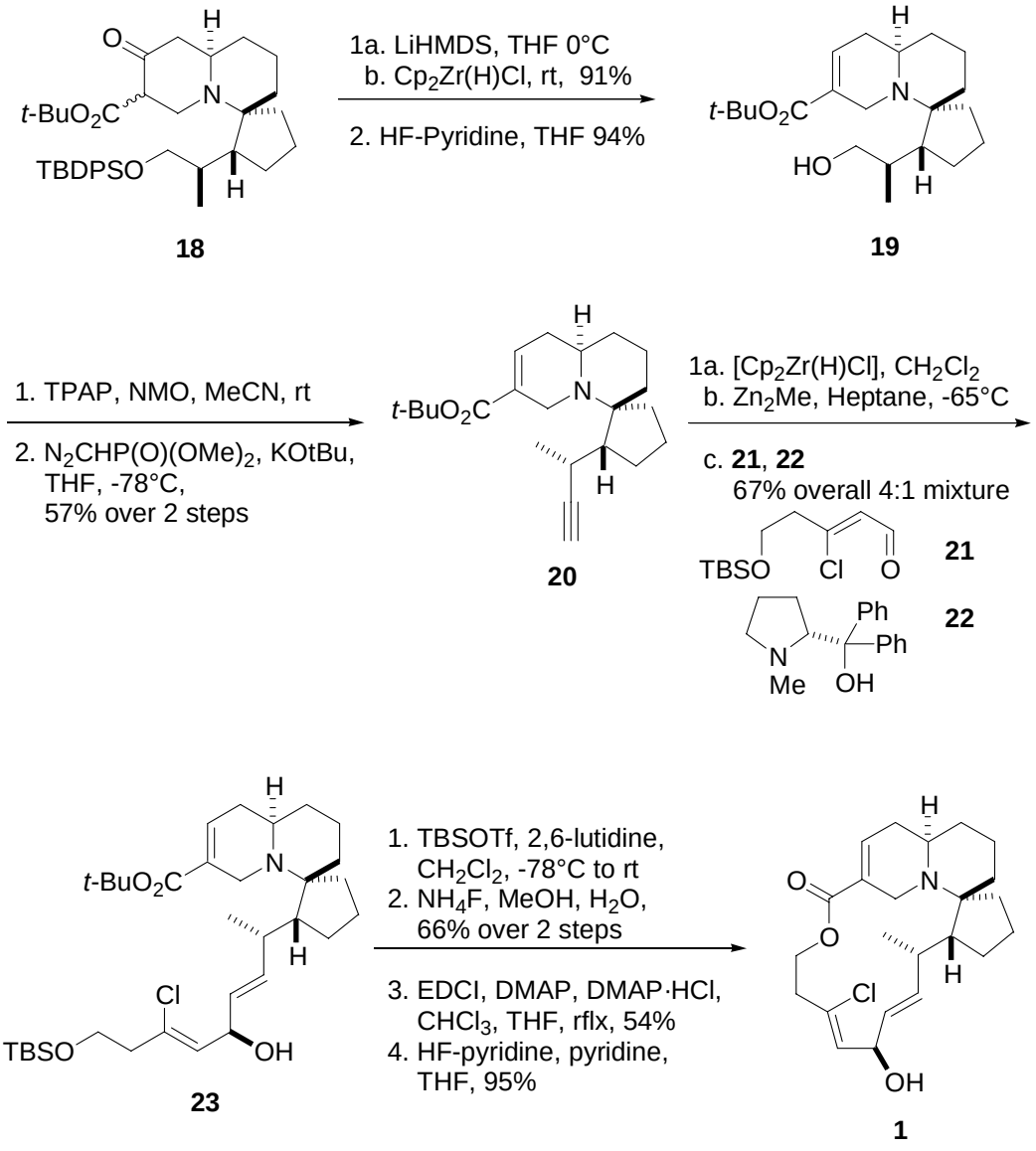
The first report from Danishefsky et al. described the asymmetric synthesis of the spiroquinazoline core.[14] The starting point was a "Meyers lactam" (**11**) which was made by addition of a γ-keto acid **9** to D-(-)-phenylglycinol (**10**) (Scheme 3).[15] The lactam reacted with allyltrimethylsilane in the presence of a Lewis acid; subsequent dissolving metal reduction and amine carbamate formation afforded alkene **12**. This set the stage for the introduction of the C_{14} methyl group from the convex face through an alkylation, which was followed by lactam hydrolysis to form **13**. Reduction of the carboxylic acid via a mixed anhydride followed by silylation yielded amine **14**. The allylic side chain was extended by hydroboration and Suzuki coupling of the resulting borane with iodide **15** to afford α,β-unsaturated ester **16**. Carbamate cleavage facilitated spontaneous Michael addition affording spirocycle **17** with the desired configuration at C_5. Claisen condensation followed by a Mannich reaction with formaldehyde was used for the construction of the A ring and gave a mixture of diastereomeric esters **18**.



Scheme 3. Danishefsky's synthesis of the tricyclic core of halichlorine

Introduction of the α,β-unsaturated olefin into **18** was achieved using Ganem's protocol.[16] Desilylation of the product led to alcohol **19** (Scheme 4). Oxidation of **19** and conversion to the alkyne was achieved with the Gilbert reagent, affording alkyne **20**. The terminal alkyne was subjected to hydrozirconation followed by metal exchange with dimethylzinc. The resultant zinc species was coupled with aldehyde **21**

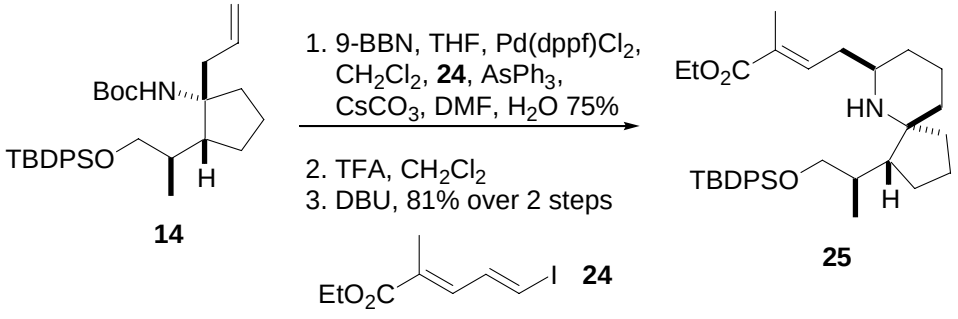
in the presence of amino alcohol **22.** This led to alcohol **23** as a 4:1 mixture containing the desired $C_{17}(R)$ and the undesired $C_{17}(S)$ configuration, which was carried forward without separation. Protection of the secondary alcohol allowed for the selective deprotection of the primary alcohol. Ester hydrolysis produced a seco acid, which formed the D ring after macrolactonization. Final desilylation gave **(+)**-halichlorine.

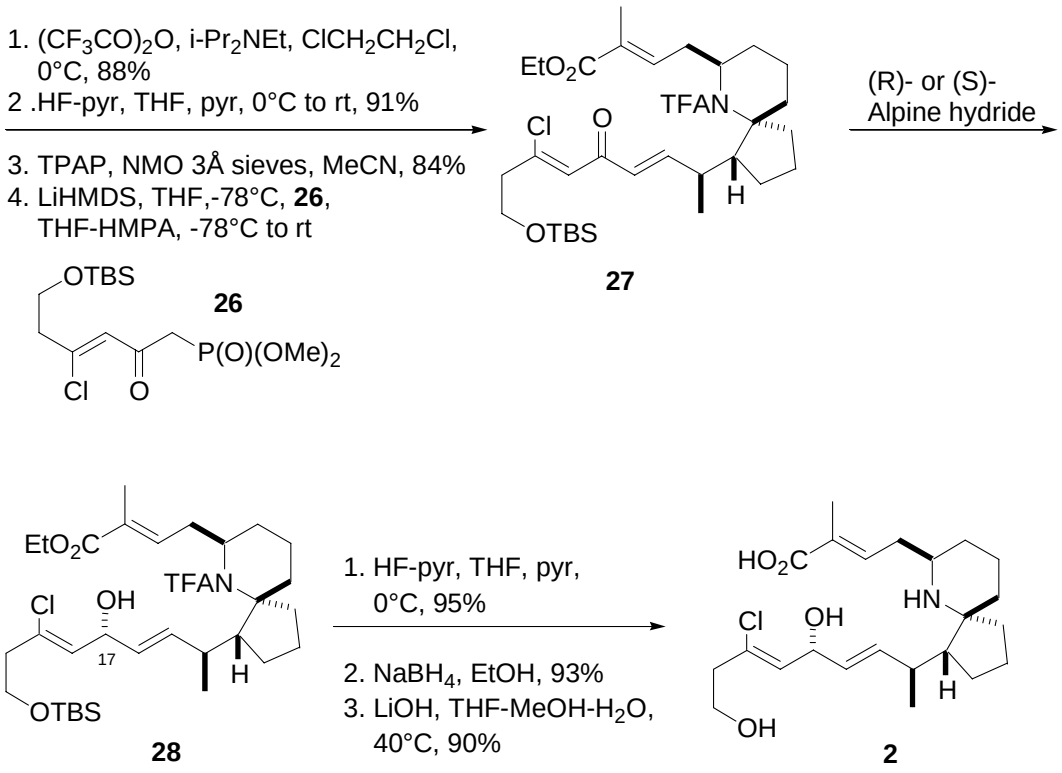


Scheme 4. Danishefsky's synthesis of **(+)**-halichlorine

1.4.2 DANISHEFSKY'S TOTAL SYNTHESIS OF NATURAL AND UNNATURAL PINNAIC ACIDS

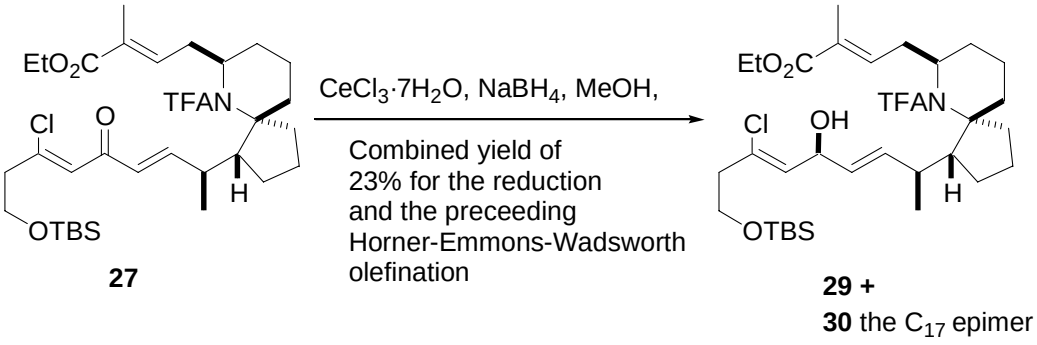
With the absolute configuration of C_{14} and C_{17} in **2** and **3** still to be determined, a study was undertaken to synthesize all four diastereomeric derivatives. Fragment **14** was again subjected to hydroboration and subsequently coupled with iodide **24** in the presence of a palladium(II) catalyst. Removal of the carbamate group and treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to clean and stereoselective cyclization while retaining the *E* geometry of the resultant olefin **25** (Scheme 5).[7,8] Nitrogen acylation and desilylation, was followed by alcohol oxidation to the aldehyde. This product was used in a Horner-Wadsworth-Emmons olefination with known phosphonate **26**,[17] yielding α,β-unsaturated ketone **27**. The ketone was reduced with Alpine-hydride,[18] and surprisingly, the resultant alcohol **28** had the desired C_{17} configuration regardless of which chiral (*R*)- or (*S*)-Alpine-hydride was used. Desilylation, *N*-acetyl cleavage and final ester hydrolysis led to natural pinnaic acid (**2**).

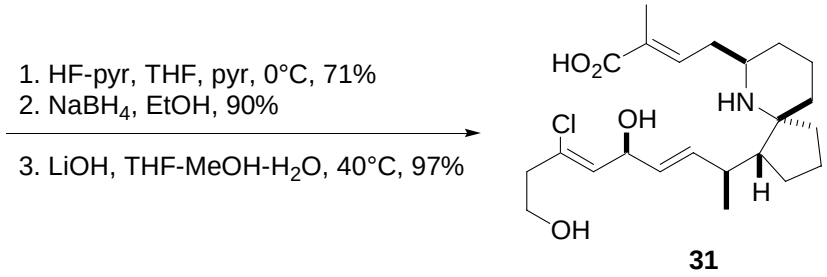




Scheme 5. Danishefsky's synthesis of pinnaic acid

In Danishefsky's studies, it had been observed that sodium borohydride reduction of ketone **27** gave predominantly alcohol **29**, and the C_{17} epimer alcohol **30** (Scheme 6). Desilylation, *N*-acetyl cleavage and final ester hydrolysis yielded **31** the spectral data of which did not match that of **2**.





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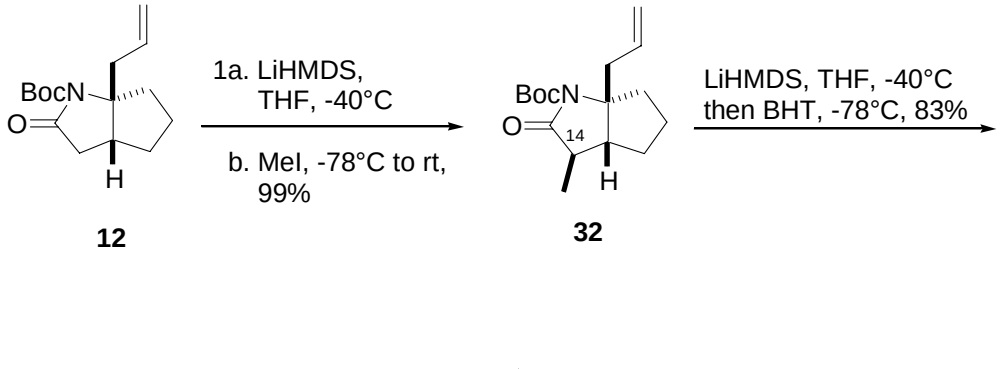
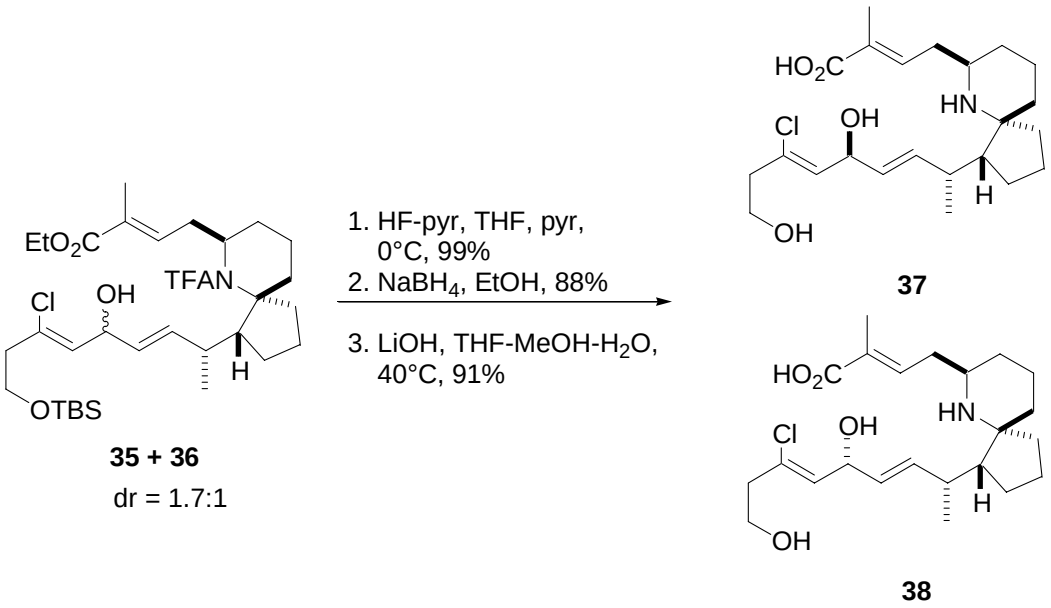
Scheme 6. Danishefsky's synthesis of non-natural pinnaic acid

To prepare the C_{14} epimer of pinnaic acid, lactam **12** was alkylated as in Scheme 3, but was then deprotonated and reprotonated with 2,3-di-*tert*-butyl-4-methylphenol (BHT). This gave the epimer of the corresponding C_{14} carbon in **1-3** (Scheme 7). The subsequent reactions were the same as previously described and led to ketone **34**. Alpine hydride reduction was employed again but this time was not as selective, giving a 1.7:1 mixture of epimeric alcohols **35**, and **36** respectively. These diastereomers were separated and carried on to the putative pinnaic acids **37** and **38**.

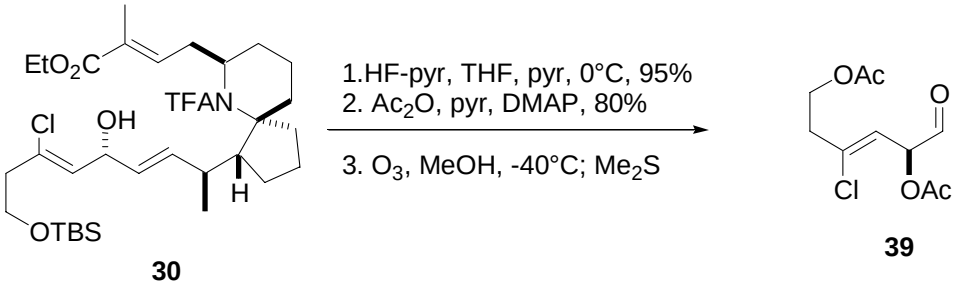


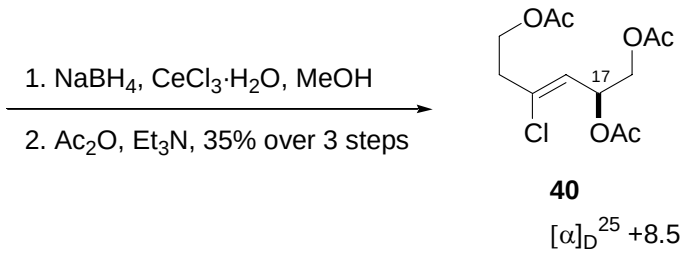
12 **32** **33** **34**



Scheme 7. Danishefsky's synthesis of non-natural pinnaic acids

With all four diastereomers in hand, only **2** (Scheme 5) exhibited spectra that matched the spectral data from natural pinnaic acid. The only remaining task was to confirm the absolute C_{17} configuration, which was done by degradation studies (Scheme 8). Key intermediate **30** was subjected to desilylation and acetylation followed by ozonolysis to excise the requisite segment. This afforded aldehyde **39**. Reduction and final acetylation of **39** was shown by direct comparison to yield a known compound **40**[2] having an established absolute configuration at C_{17}. This correlation confirmed the absolute configuration of **2.**





40

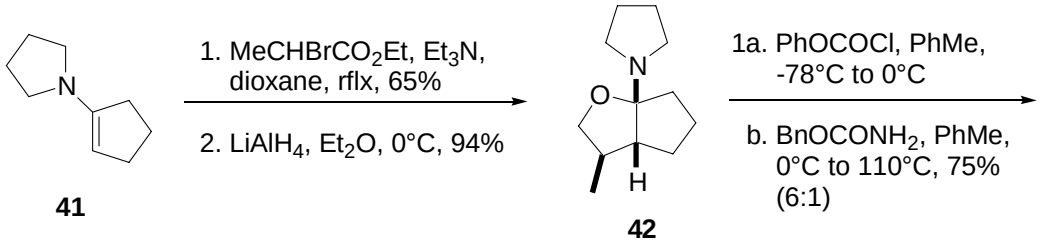
$[\alpha]_D^{25}$ +8.5

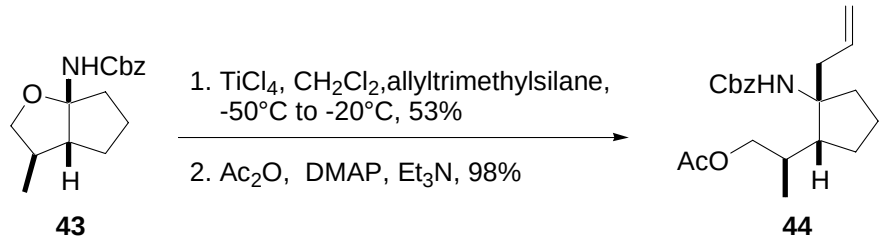
Scheme 8. Danishefsky's confirmation of C_{17} stereochemistry of pinnaic acid

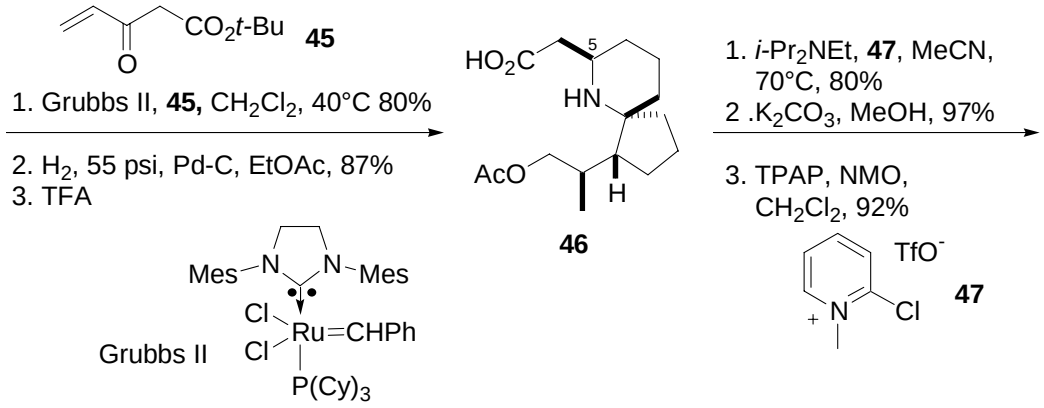
1.4.3 HEATHCOCK'S TOTAL SYNTHESIS OF (±)-PINNAIC AND (±)-TAUROPINNAIC ACIDS.

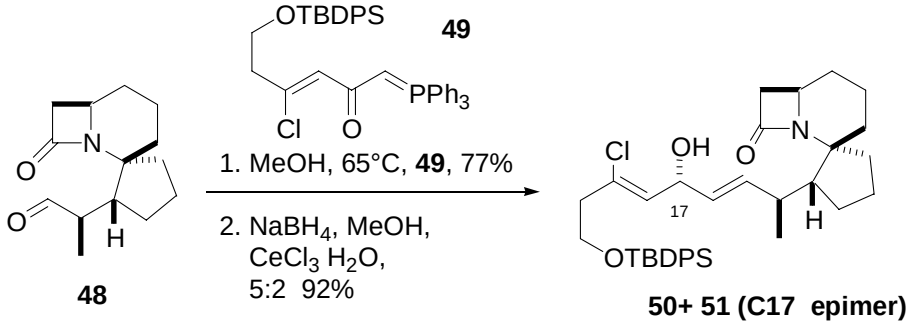
The total synthesis of pinnaic acid reported by Heathcock et al.[9] commenced with alkylation of enamine **41** followed by ester reduction. Subsequent aminal formation as described previously by Lawesson[19] gave **42** (Scheme 9), and condensation with benzyl carbamate afforded the cis-fused bicyclic carbamate **43** as a 6:1 isomeric mixture. With the mixture in hand, titanium tetrachloride facilitated the capture of the resulting iminium ion by allyltrimethylsilane and subsequent acetylation yielded alkene **44**. An olefin cross metathesis of **44** with α,β-unsaturated ester **45** using Grubbs II catalyst was followed by hydrogenation and hydrogenolysis of the resultant alkene and *N*-benzyl carbamate which led to spontaneous cyclization. The latent imine was reduced, resulting in formation of the correct C_5 stereocenter present in **1**-**3**, and hydrolysis of the *tert*-butyl ester afforded carboxylic acid **46**. Formation of a β-lactam with pyridinium salt **47**, followed by acetate hydrolysis, gave a crystalline alcohol whose structure was confirmed by X-ray analysis. Oxidation of the alcohol then gave aldehyde **48**. Chain elongation of **48** was achieved with ylide **49**, and reduction of the carbonyl function afforded alcohols **50** and **51** as a 5:2 mixture, respectively. Silylation and β-lactam cleavage, the latter facilitated by partial

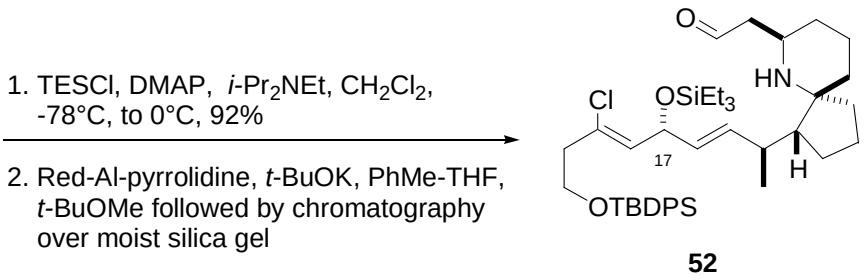
reduction with sodium bis-(2-methoxyethoxy)aluminum hydride (Red-Al), modified by treatment with pyrrolidine and potassium *tert*-butoxide,[20] gave aldehyde **52**.





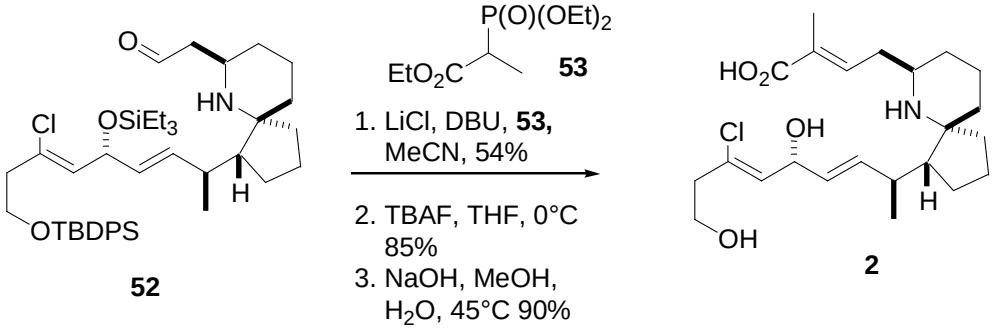




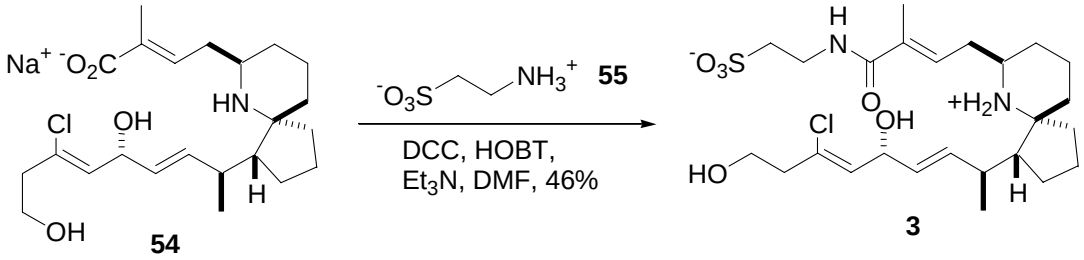


Scheme 9. Heathcock's synthesis of the core of pinnaic acid

Horner-Emmons-Wadsworth olefination of aldehyde **52**, with subsequent desilylation and ester hydrolysis, yielded (±)-pinnaic acid (Scheme 10). The sodium salt **54** was coupled with taurine **55** in the presence of *N, N'*-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole hydrate (HOBT) to afford (±)-tauropinnaic acid (Scheme 11).



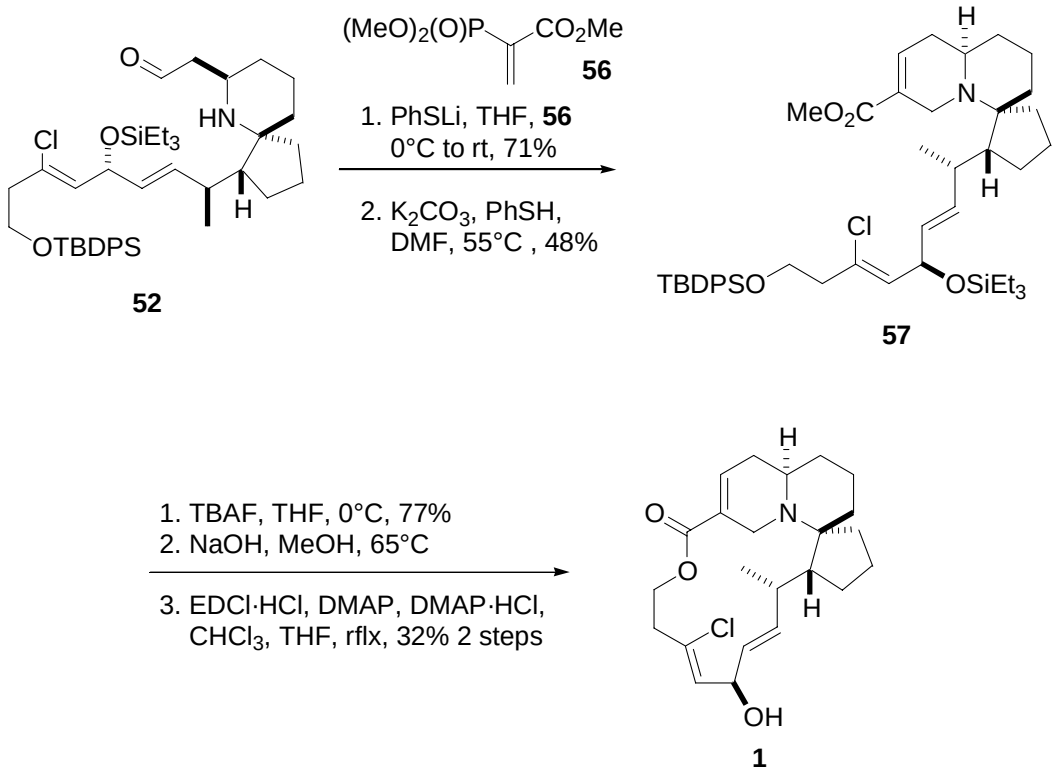
Scheme 10. Heathcock's synthesis of (±)-pinnaic acid



Scheme 11. Heathcock's synthesis of (±)-tauropinnaic acid

1.4.4 HEATHCOCK'S TOTAL SYNTHESIS OF (±)-HALICHLORINE

The aldehyde **52** was converted to the dehydroquinolizidine **57** with phosphonate **56** and lithium thiophenoxide, followed by heating with potassium carbonate and lithium thiophenol (Scheme 12). Two desilylations were followed by ester hydrolysis, and the resultant seco acid was macrolactonized with (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) to yield (±)-halichlorine.

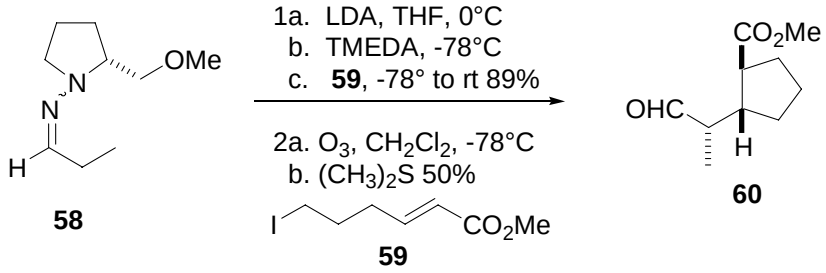


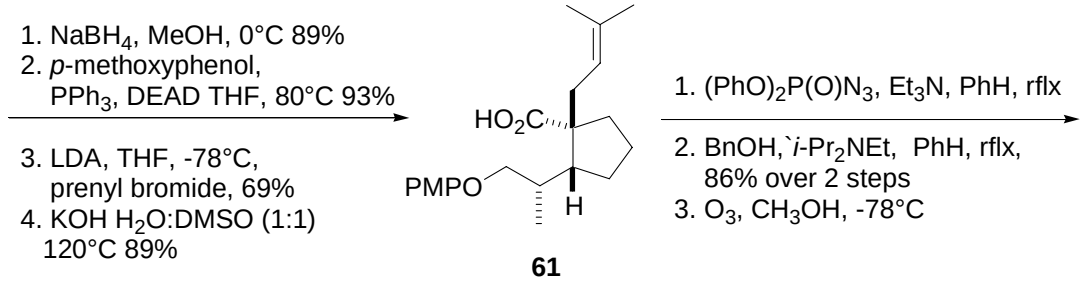
Scheme 12. Heathcock's synthesis of (±)-halichlorine (**1**)

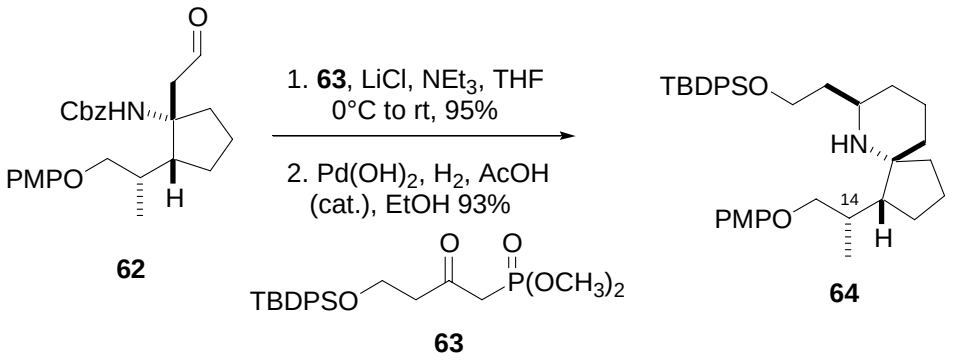
1.4.5 ARIMOTO-UEMURA SYNTHESIS OF THE AZABICYCLIC CORE OF HALICHLORINE AND PINNAIC ACID

The Arimoto-Uemura group's synthesis[21] of the azabicyclic core of **1**-**3** began with **(***S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone **58**.

Treatment of **58** with Michael acceptor **59** provided the desired aldehyde **60** (>97% ee) after oxidative cleavage of the chiral auxiliary. Aldehyde **60** was reduced and the alcohol was protected as its *p*-methoxyphenyl ether (PMP) under Mitsunobu conditions. A facially selective alkylation with prenyl bromide followed by ester hydrolysis then gave carboxylic acid **61**. Treatment of **61** under Curtius rearrangement conditions provided a stable isocyanate that was added to benzyl alcohol to form the carboxybenzyl (Cbz) protected amine. Cleavage of the resulting olefin with ozone gave aldehyde **62**. Horner-Emmons-Wadsworth olefination with phosphonate **63** followed by catalytic hydrogenation/hydrogenolysis of the resultant alkene and Cbz group liberated the free amine which underwent spontaneous cyclization to the imine. The imine was reduced to afford amine **64** with the correct C_5 stereochemistry as found in **1**-**3**. Amine **64** represents a portion of the halichlorine core which has C_{14} stereochemistry in accord with the original assignment made to **1**.[1]



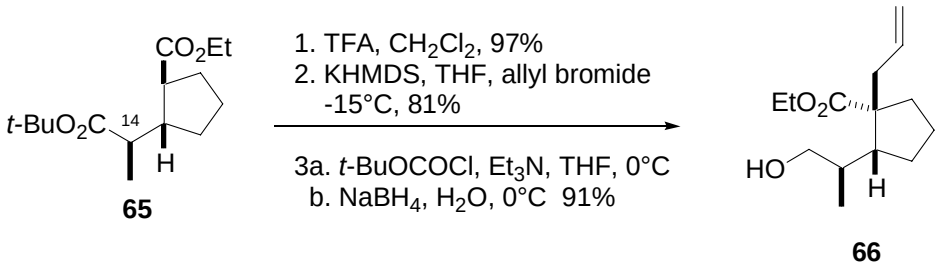


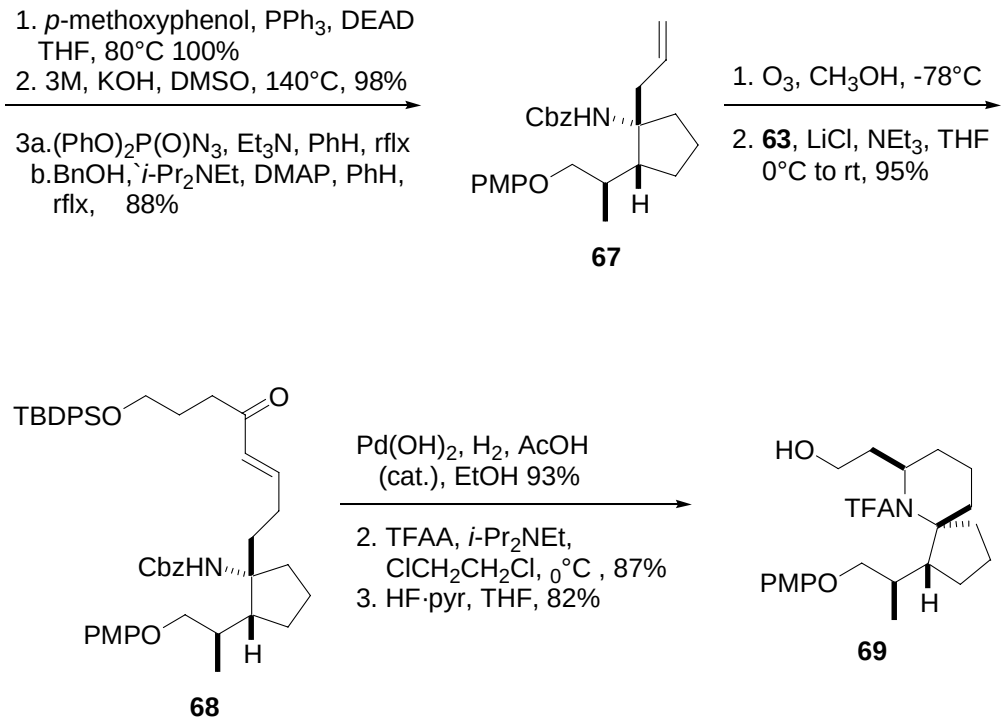


Scheme 13. Arimoto-Uemura's synthesis of the azabicyclic core in halichlorine and pinnaic acid

1.4.6 ARIMOTO-UEMURA SYNTHESIS OF PINNAIC ACID

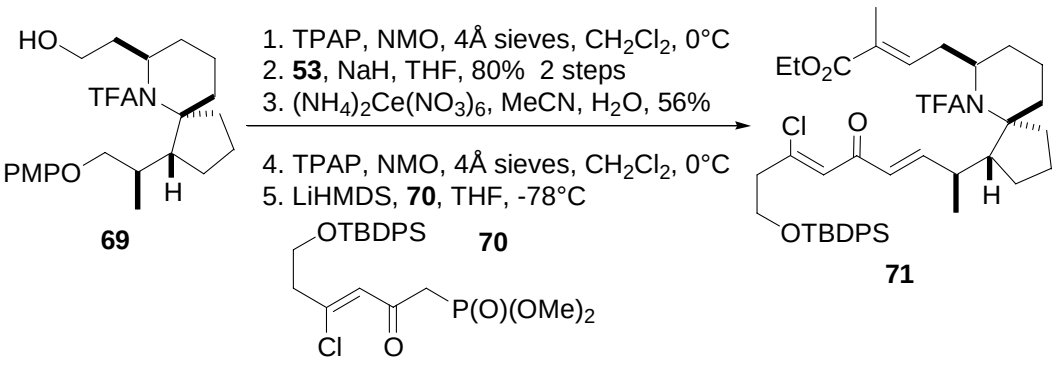
With a revision of stereochemistry having been established at C_{14}, an alternative synthetic route was undertaken by Arimoto and Uemura[21]. Known diester **65**[22] was selectively hydrolyzed with trifluoroacetic acid (TFA) and alkylated with allyl bromide (Scheme 14).[10] The resultant acid was converted to a mixed anhydride and reduced to alcohol **66** which was protected as its PMP ether. Ester hydrolysis and Curtius rearrangement as previously described gave Cbz protected amine **67**. Ozonolysis and Horner-Emmons-Wadsworth olefination led to ketone **68**. Reduction of the olefin and Cbz group led to the spirobicyclic amine. Acetylation and desilylation then gave alcohol **69**.

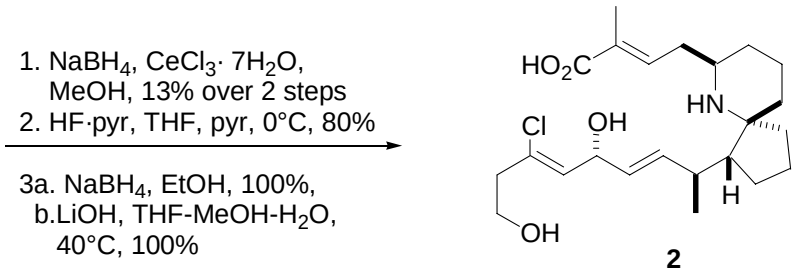




Scheme 14. Arimoto-Uemura's synthesis of the core of pinnaic acid

Alcohol **69** was oxidized to an aldehyde which was olefinated with phosphonate **53.** The *p*-methoxyphenyl (PMP) ether was cleaved with cerium ammonium nitrate (CAN) (Scheme 15) and the alcohol was oxidized to an aldehyde. This was homologated with phosphonate **70** to afford ketone **71** and reduced to an alcohol under Luche conditions. Desilylation and hydrolysis of the trifluoroacetyl and ester functionalities completed the synthesis of (±)-pinnaic acid.

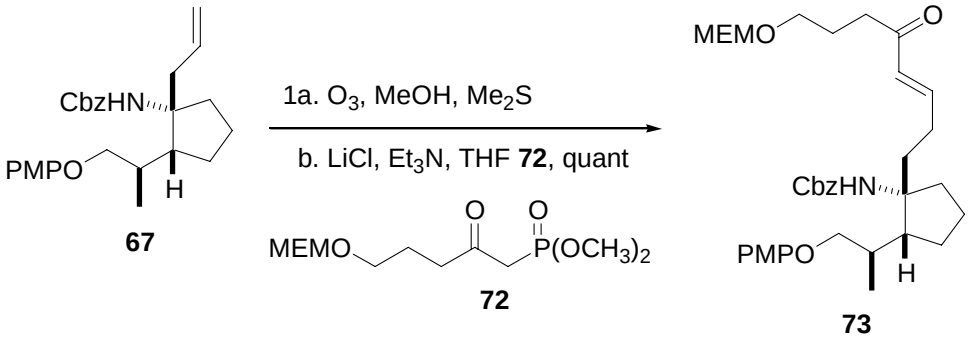


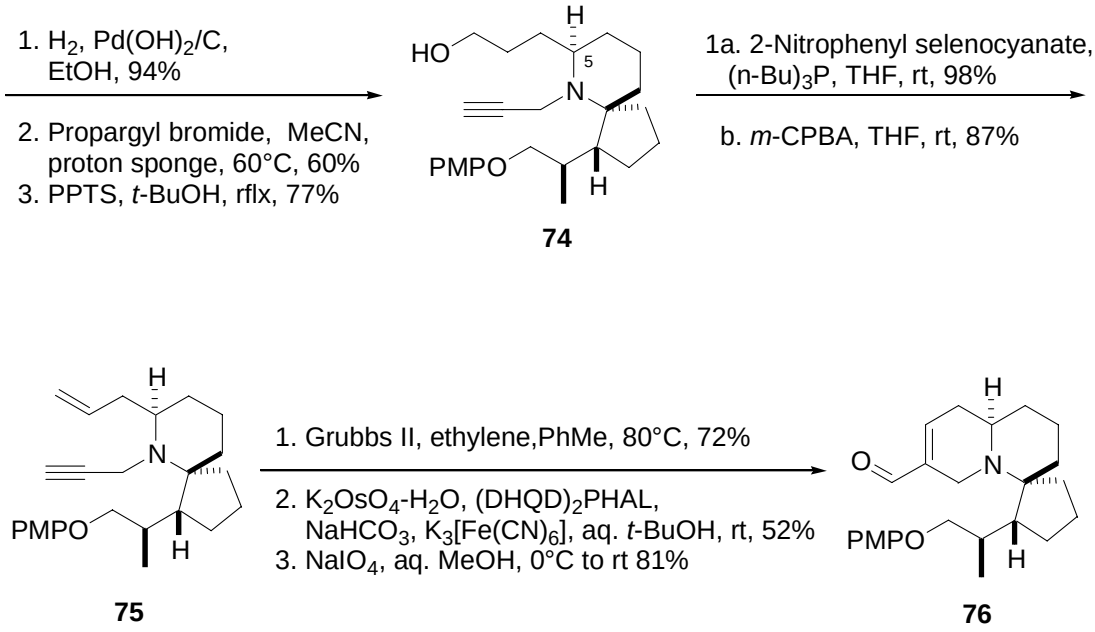


Scheme 15. Arimoto-Uemura's synthesis of (±)-pinnaic acid

1.4.7 ARIMOTO-UEMURA SYNTHESIS OF THE TRICYCLIC CORE OF HALICHLORINE

Arimoto and Uemura used intermediate **67** for the formation of the halichlorine core. Ozonolysis of the olefin followed by Horner-Emmons-Wadsworth condensation with phosphonate **72** led to ketone **73**. Catalytic reduction of ketone **73**'s carbamate induced spirobicycle formation which resulted in the desired C_5 stereochemistry found in **1**. The free amine was alkylated with propargyl bromide, and the acetal hydrolyzed to give alcohol **74**. Transformation of **74** to an alkene was achieved using standard selenium chemistry which led to ene-yne **75**. Ring-closing metathesis with ene-yne **75** using Grubbs II catalyst afforded an olefin which was dihydroxylated and subsequently cleaved to liberate the target aldehyde **76**.

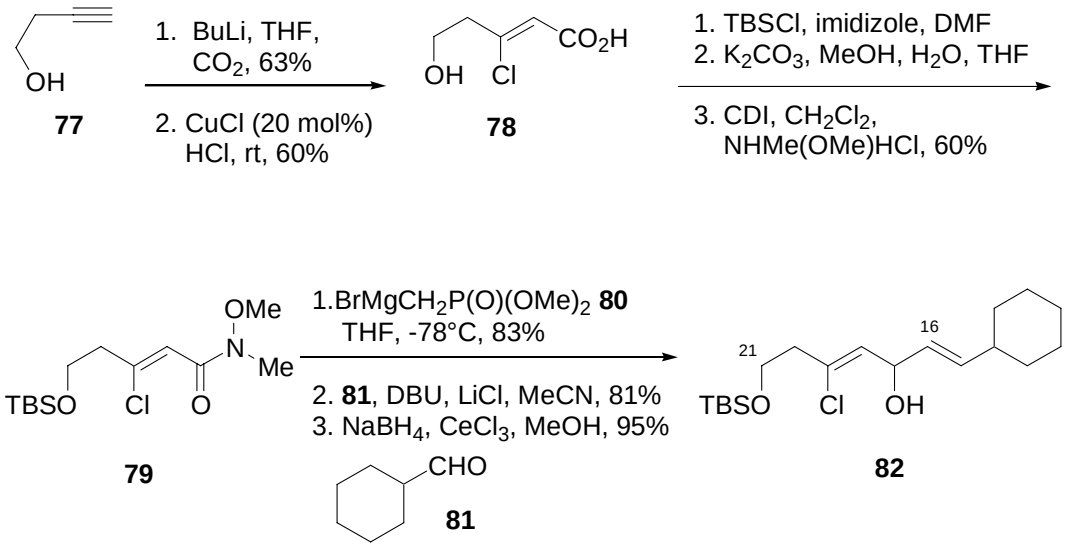




Scheme 16. Arimoto-Uemura's approach toward halichlorine

1.4.8 WEINREB'S SYNTHESIS OF THE C_{16}-C_{21} SUBUNIT IN HALICHLORINE AND PINNAIC ACID

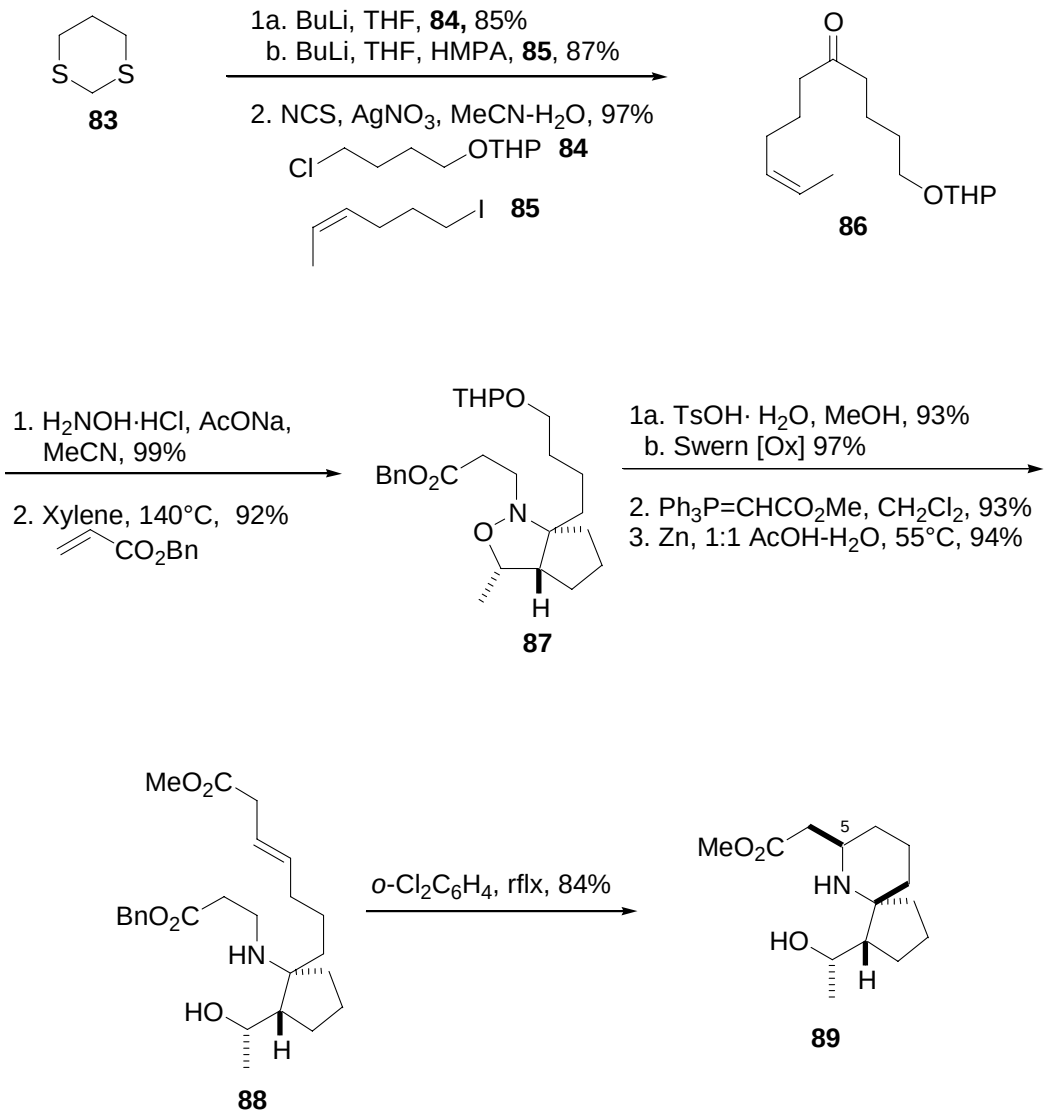
Weinreb's laboratory was first to report[23] the introduction of the C_{16}-C_{21} subunit which was intended to be coupled to a larger fragment in a Horner-Wadsworth-Emmons olefination. Commercially available alkyne **77** was carboxylated, and the resulting acetylenic acid upon treatment with copper(I) chloride, gave the *Z* vinyl chloride **78** (Scheme 17). Global silylation with subsequent release of the free acid was followed by conversion to the Weinreb amide **79**. The Grignard reagent with pendant phosphonate **80** was added to the amide, demonstrating its use as a linchpin reaction with aldehyde **81**, to yield an α,β–unsaturated ketone. Final reduction of the ketone led to alcohol **82**.



Scheme 17. Weinreb's approach of the C_{16}-C_{21} subunit of halichlorine and pinnaic acid

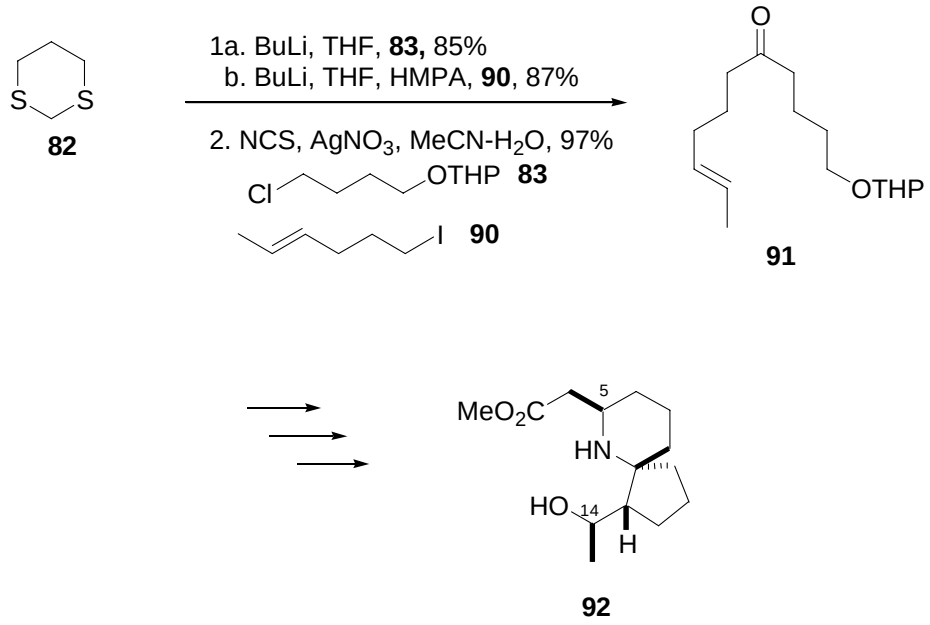
1.4.9 ZHAO'S SYNTHESIS OF THE BICYCLIC CORE OF HALICHLORINE AND PINNAIC ACID

Zhao et al. employed a nitrone [3+2] cycloaddition to construct a spirocyclic intermediate. Dithiane **83** was converted to ketone **86** via two consecutive alkylations using chloride **84** and (*Z*)-iodide **85** followed by thioketal hydrolysis (Scheme 18).[24] Treatment of ketone **86** with hydroxylamine hydrochloride yielded an oxime which was heated with benzyl acrylate. This formed a nitrone which underwent spontaneous intamolecular [3+2] cycloaddition yielding cycloadduct **87**. Hydrolysis of the tetrahydropyran (THP) ether from cycloadduct **87** was followed by oxidation to an aldehyde which was homologated with a stabilized Wittig reagent. Cleavage of the N-O bond afforded amino alcohol **88**. Heating **88** facilitated a Michael addition that resulted in the incorrect C_5 stereochemistry as well as elimination of the benzyl acrylate moiety. It was shown that continued heating favors a reversible Michael addition which delivers the correct C_5 stereochemistry shown as amino alcohol **89**.



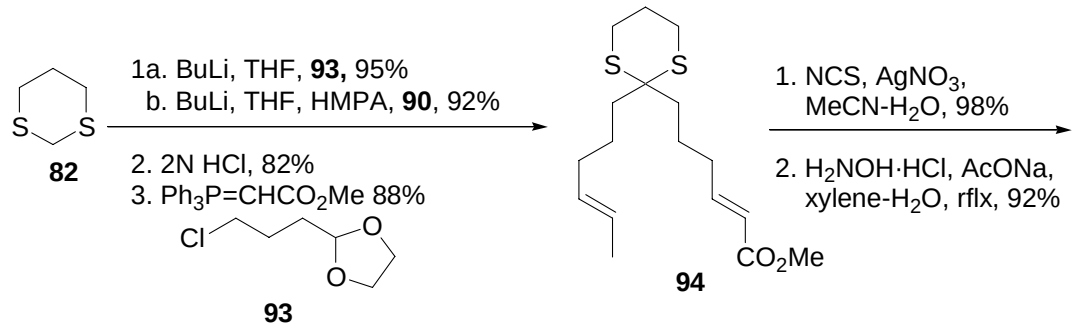
Scheme 18. Zhao's approach toward halichlorine and pinnaic acid

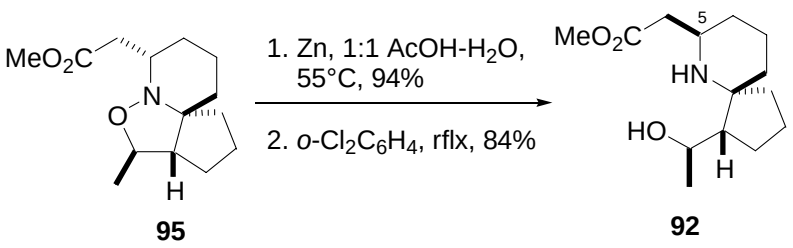
In the same report,[24] Zhao reversed the C_{14} stereochemistry by using for the second alkylation the (*E*)-iodide **90**. Thioketal hydrolysis led to ketone **91** (Scheme 19), and the same chemistry as was shown in Scheme 18 was employed to give desired alcohol **92**. This substance has the same stereochemistry at C_5 and C_{14} as **1**-**3**.



Scheme 19. Zhao's approach toward halichlorine and pinnaic acid

In a subsequent publication,[25] Zhao incorporated a slightly modified route to **2**. Dithiane **82** was alkylated consecutively with **93** and **90** and this was followed by acetal hydrolysis to give an aldehyde (Scheme 20). The aldehyde was olefinated with a stabilized Wittig ylide to afford **94**. Hydrolysis of the thioketal and treatment of the resultant ketone with hydroxylamine hydrochloride resulted in tandem Michael addition-nitrone [3+2] cycloaddition to yield cycloadduct **95**. Cleavage of the N-O bond in cycloadduct **95** and epimerization at C_5 was facilitated by the reversible Michael addition as previously described.



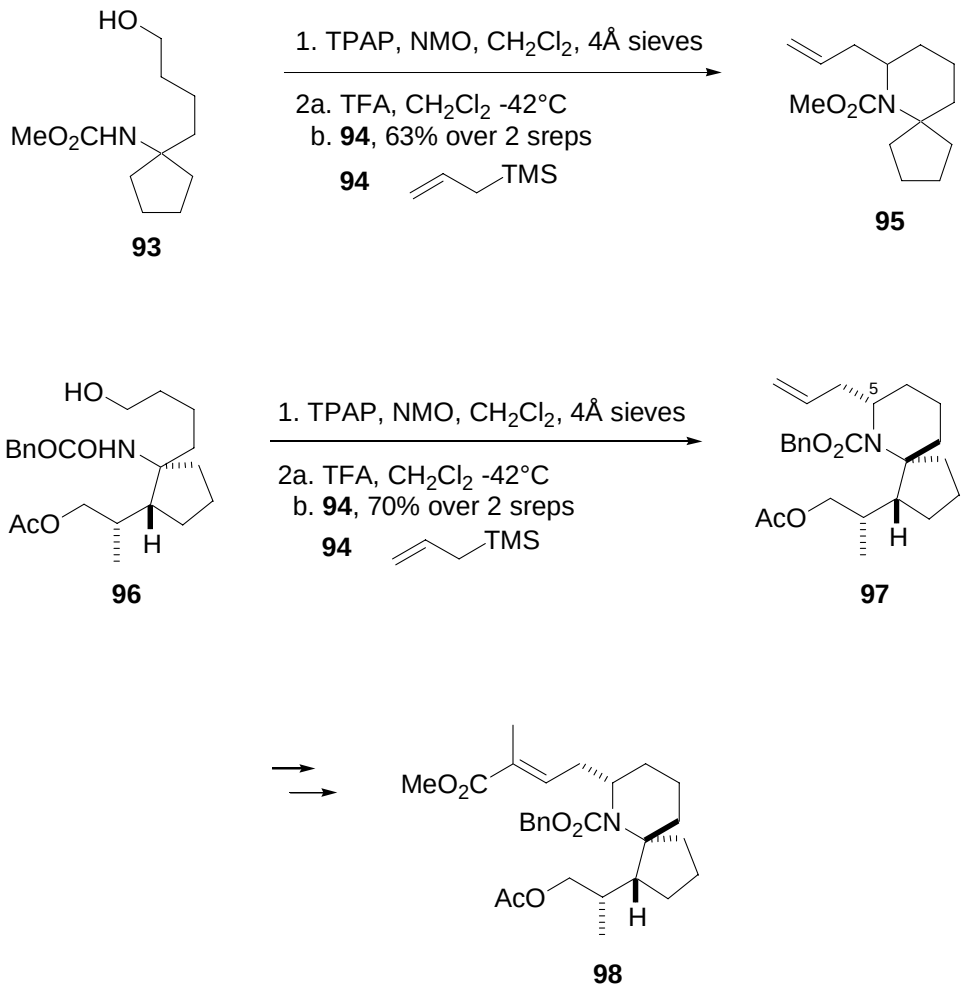


95 **92**

Scheme 20. Zhao's approach toward halichlorine and pinnaic acid

1.4.10 FORSYTH'S SYNTHESIS OF THE BICYCLIC CORE OF PINNAIC ACID

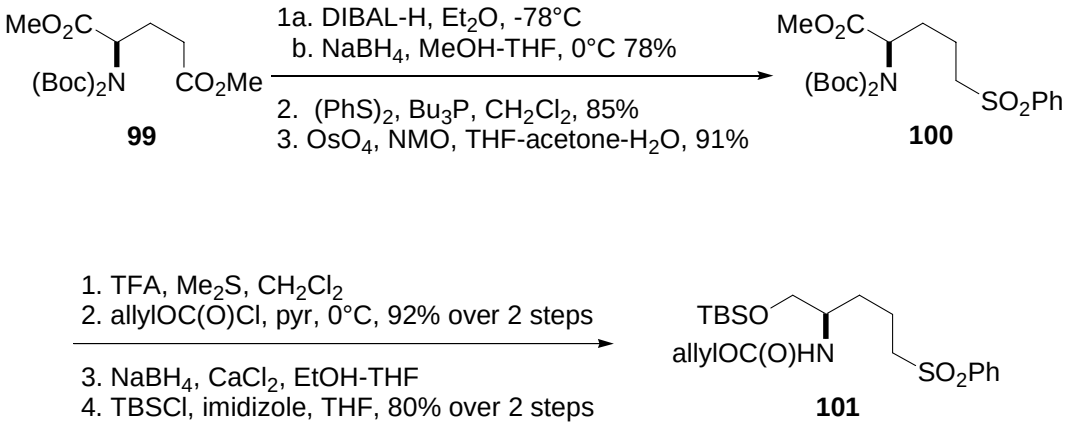
Forsyth et al. reported[26] two pathways for the formation of the bicyclic core found in **1** and **2**. Alcohol **93** was oxidized to a transient aldehyde which underwent spontaneous cyclization and dehydration to an enamine (Scheme 21). Treatment of this enamine with trifluoroacetic acid served to generate an iminium ion which was captured by allyltrimethylsilane **94** to afford olefin **95**. The first route did not provide information about the stereochemical outcome of the allylation, and a second more complex approach was undertaken. The racemic alcohol **96**[27] was oxidized as before but this time cyclization and dehydration were not spontaneous. Treatment of the crude aldehyde with trifluoroacetic acid resulted in the cyclized iminium ion which further reacted with allyltrimethylsilane to form spirocycle **97** having the desired C_5 stereochemistry. Oxidative cleavage of the alkene to an aldehyde and homologation via a Wittig olefination proceeded as far as ester **98**. 2D NMR studies were used to determine the stereochemistry of this substance.



Scheme 21. Forsyth's approach toward halichlorine and pinnaic acid

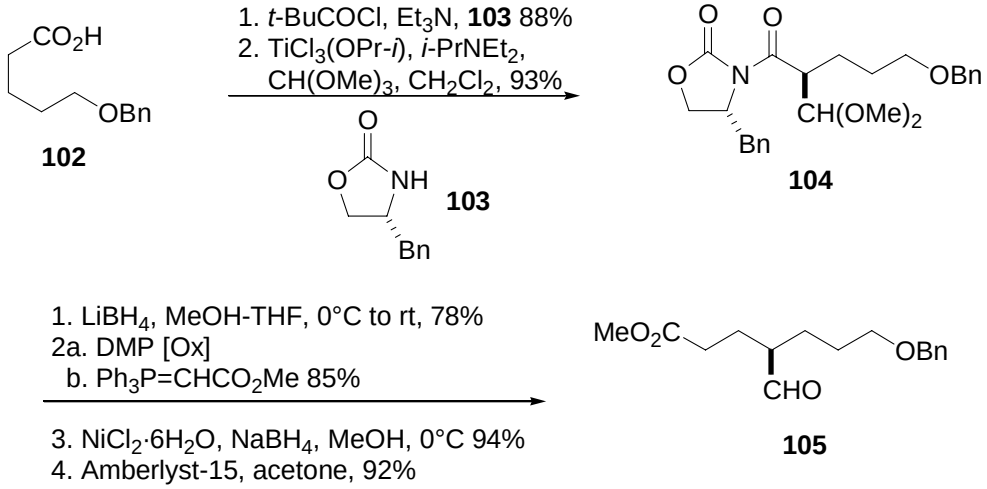
1.4.11 CLIVE'S APPROACHES TO THE SPIROCYCLIC CORES OF HALICHLORINE AND PINNAIC ACID

Clive et al. reported a number of exploratory routes that have led to spiro compounds resembling the core structures of **1**-**3**. The first report[28] from Clive was based on a radical cyclization. Known diester **99**[29] was selectively reduced first with diisobutylaluminum hydride (DIBAL-H) and then with sodium borohydride, to a primary alcohol (Scheme 22). The resulting alcohol was converted to sulfone **100** in two steps and the bis *tert*-butyl carbamate (Boc) was replaced with a single allyl carbamate. Ester reduction followed by alcohol silylation led to sulfone **101**.



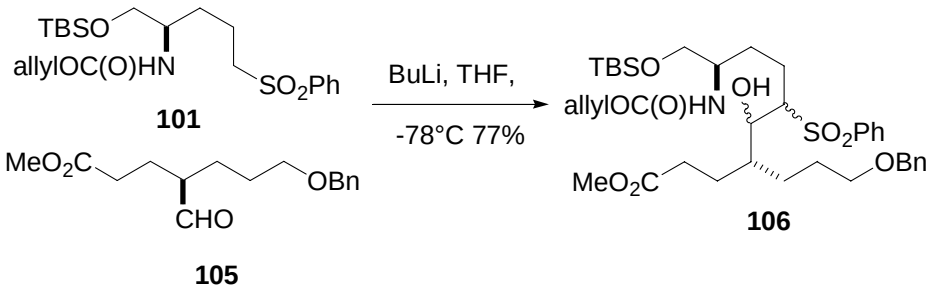
Scheme 22. Clive's approach toward halichlorine and pinnaic acid

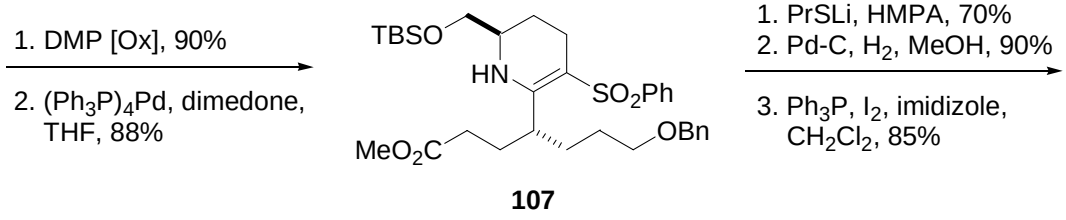
The second coupling subunit was prepared by an asymmetric alkylation using an oxazolidinone as a chiral auxiliary. The oxazolidinone was alkylated with trimethyl orthoformate following a literature procedure[30] which yielded acetal **104** (Scheme 23). Reductive removal of the chiral auxiliary followed by alcohol oxidation yielded an aldehyde which was homologated to a α,β-unsaturated ester using a stabilized Wittig ylide. The resultant alkene was reduced and the acetal was hydrolyzed to afford aldehyde **105**.

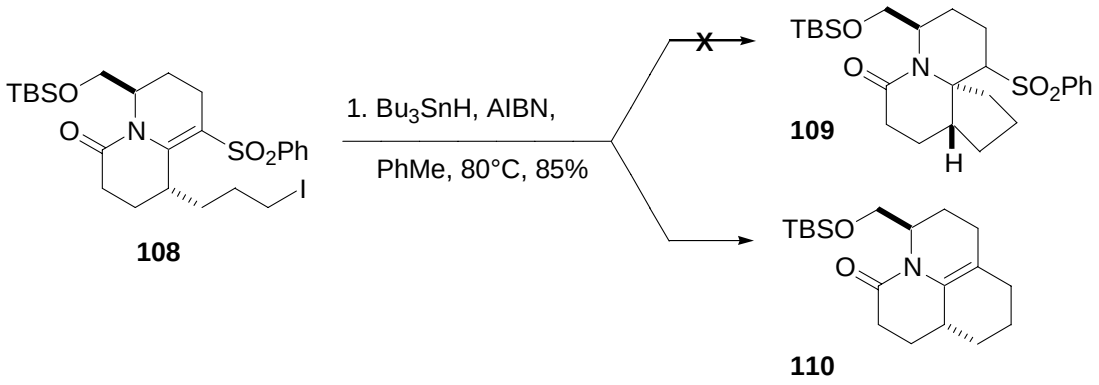


Scheme 23. Clive's approach toward halichlorine and pinnaic acid.

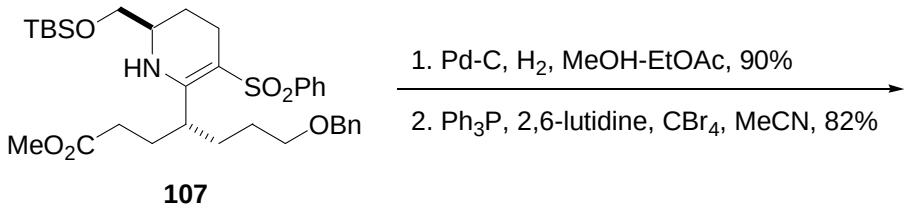
At this point, the two subunits were joined by addition of the sulfone anion of **101** to aldehyde **105** (Scheme 24). The resultant alcohol **106** was oxidized and the allyl carbamate was removed to yield the free amine that spontaneously cyclized to enamine **107**. Cyclization of **107** to a α,β-unsaturated lactam was achieved with lithium thiopropoxide in hexamethylphosphoramide (HMPA).[31] Hydrogenolysis of the benzyl ether was followed by conversion of the liberated alcohol to iodide **108**. Upon treatment with tributyltin hydride, the expected cyclization product spirocycle **109**, was not observed; instead, tricycle **110** resulting from a 6-endo closure was isolated in high yield. The cyclization problem was circumvented by conversion of the alcohol from **107** to bromide **111** (Scheme 25). Final desulfonation gave the target spiro amine **112**.

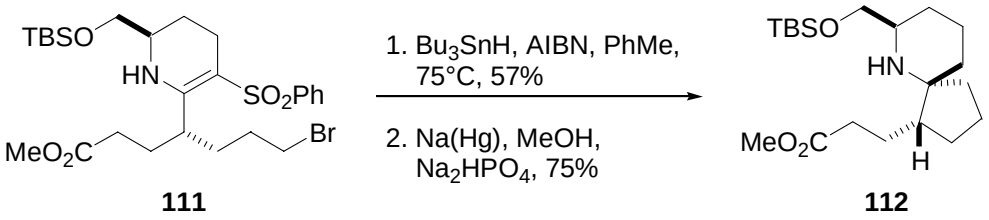






Scheme 24. Clive's approach toward halichlorine and pinnaic acid



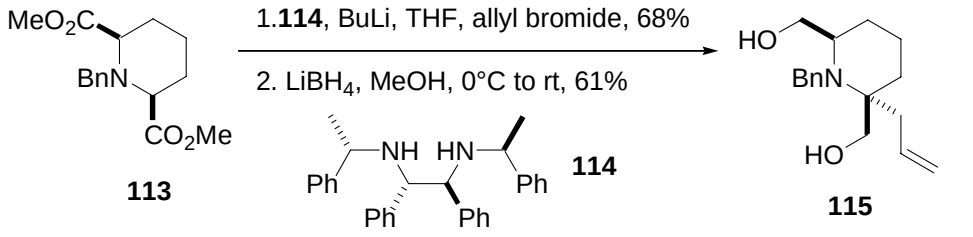


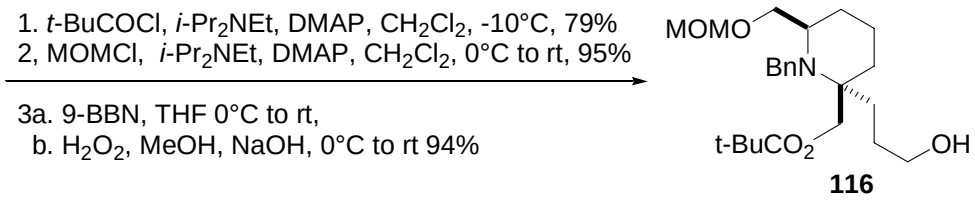
Scheme 25. Clive's approach toward halichlorine and pinnaic acid

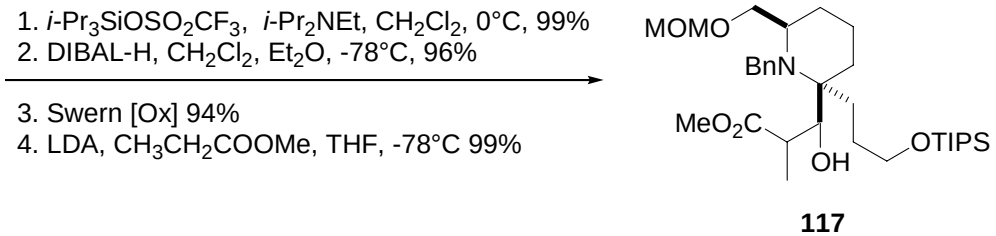
1.4.12 CLIVE'S APPROACH TO THE TRICYCLIC CORE OF HALICHLORINE

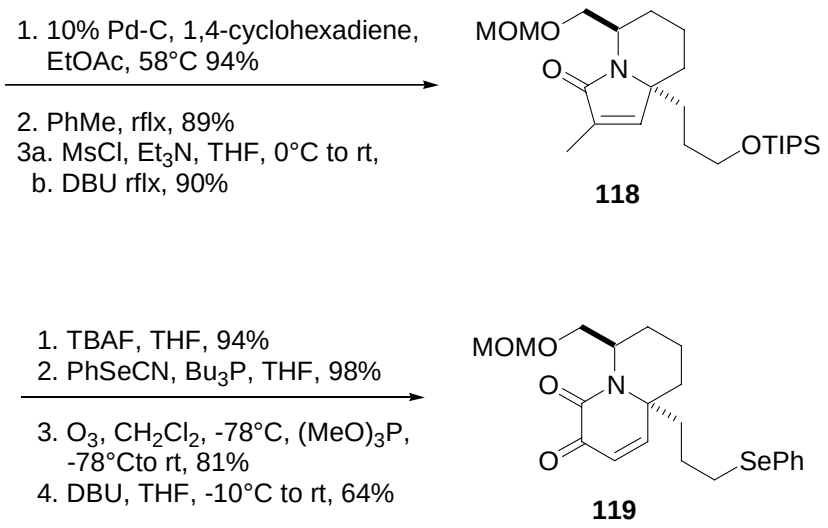
A second report[32] by Clive used a different radical cyclization to form the tricyclic core of halichlorine. The readily available piperidine diester **113**[33] was subjected to asymmetric allylation according to a literature procedure[34] using a chiral lithium amide base **114** (Scheme 26). Reduction of the diester led to diol **115**. Selective formation of a *tert*-butyl carbonate and protection of the second alcohol was

followed by hydroboration of the alkene to give alcohol **116**. Alcohol silylation was followed by ester reduction and the newly formed alcohol was oxidized to its corresponding aldehyde. Condensation of the aldehyde with the anion of methyl propionate gave alcohol **117** as a mixture of epimers. Reductive debenzylation of epimeric alcohols **117** with prolonged heating facilitated the lactam formation. The epimeric alcohols **117** were then mesylated and eliminated to afford lactam **118**. Desilylation of lactam **118** was followed by conversion of the liberated alcohol to the phenyl selenide. Exposure to ozone opened the lactam which underwent intramolecular aldol condensation in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give re-cyclized ketolactam **119**.



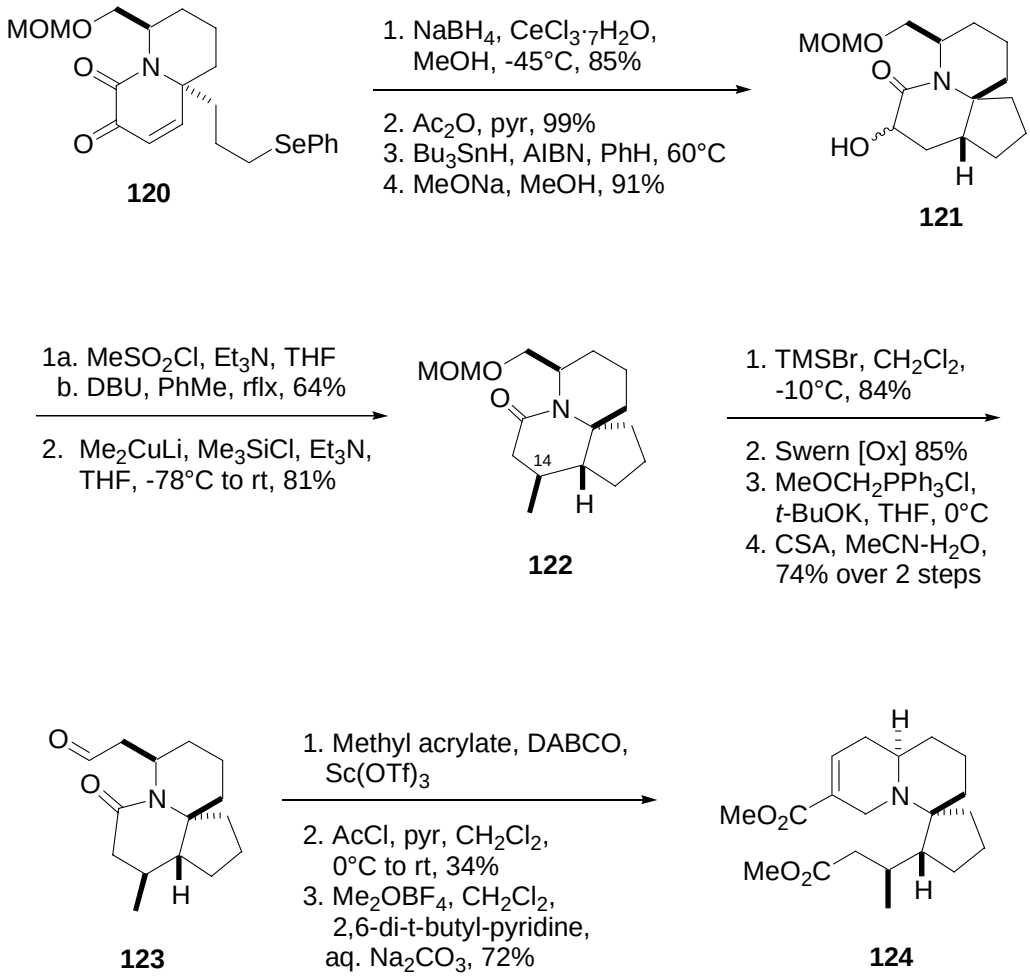






Scheme 26. Clive's approach toward the tricyclic core of halichlorine

With ketolactam **120** in hand, the ketone function was reduced, and the resulting alcohol was acetylated (Scheme 27). The acetate underwent radical cyclization when treated with tributyltin hydride, and subsequent acetate hydrolysis gave an epimeric mixture of spirocyclic alcohols **121**. The pair of epimeric alcohols were then eliminated forming an α, β–unsaturated lactam. The required C_{14} methyl group was installed via an organocuprate conjugate addition affording lactam **122**. The MOM ether was hydrolyzed to liberate an alcohol which was oxidized to an aldehyde. The latter was homologated via Wittig olefination and the resulting enol-ether was hydrolyzed to aldehyde **123**. Baylis-Hillman-Morita coupling to the aldehyde was carried out with methyl acrylate and the resultant alcohol was acetylated. Final treatment with trimethyloxonium tetrafluoroborate produced the desired tricyclic dehydroquinolizidine core **124**.

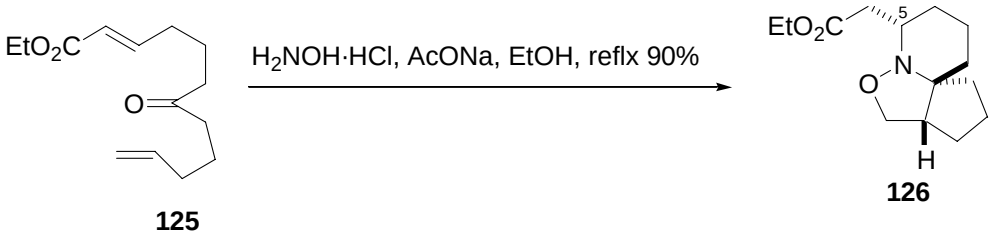


Scheme 27. Clive's approach toward the tricyclic core of halichlorine

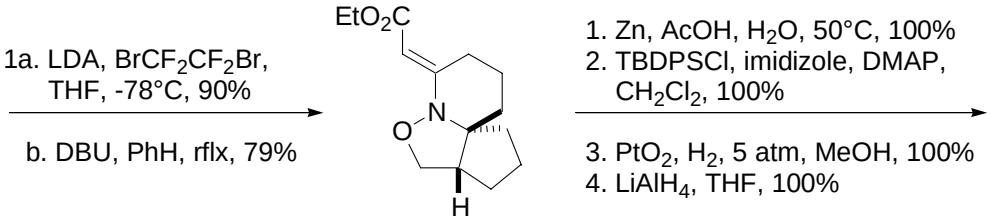
1.4.13 SHISHIDO'S APPROACH TO THE SPIROCYCLIC CORES OF HALICHLORINE AND PINNAIC ACID

Shishido's route was also based on an intramolecular [3+2] nitrone cycloaddition.[35] Known ketoester **125**[36] was heated with hydroxylamine hydrochloride which yielded cycloadduct **126** via an intramolecular Michael addition to the nitrone followed by spontaneous intramolecular [3+2] nitrone cycloaddition (Scheme 28). The stereochemistry of cycloadduct **126** was confirmed by X-ray analysis. To achieve the desired stereochemistry at C_5, **126** was brominated and eliminated giving the (*E*) α,β-unsaturated ester **127**. Hydrogenation led exclusively to

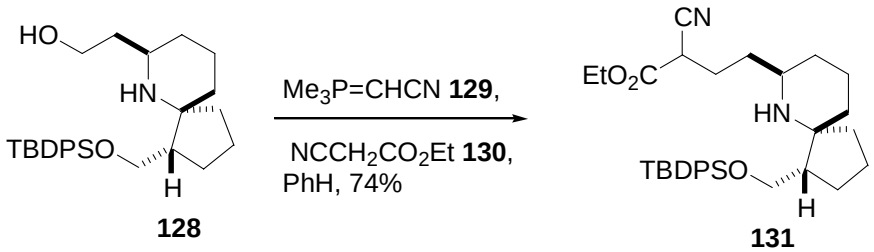
the undesired C_5 epimer. To circumvent this problem, the N-O bond in alkene **127** was cleaved and the liberated alcohol was protected, resulting in the hydrogenation of the olefin from the desired face. Reduction of the ester led to alcohol **128**. Homologation of **128** was achieved with phosphonate **129** in the presence of cyano ester **130**,[37] a reagent combination that afforded cyanoester **131**. Ester hydrolysis to the carboxylic acid produced a δ–lactam, and the α, β unsaturated olefin in lactam **132** was introduced by the standard method of selenation and selenoxide elimination.



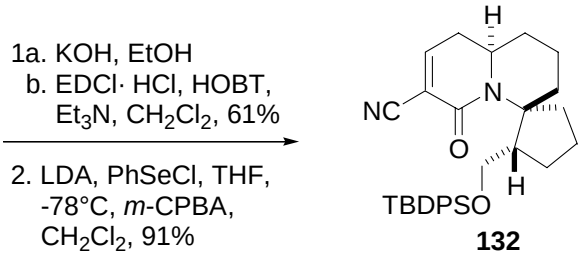
125 **126**



127

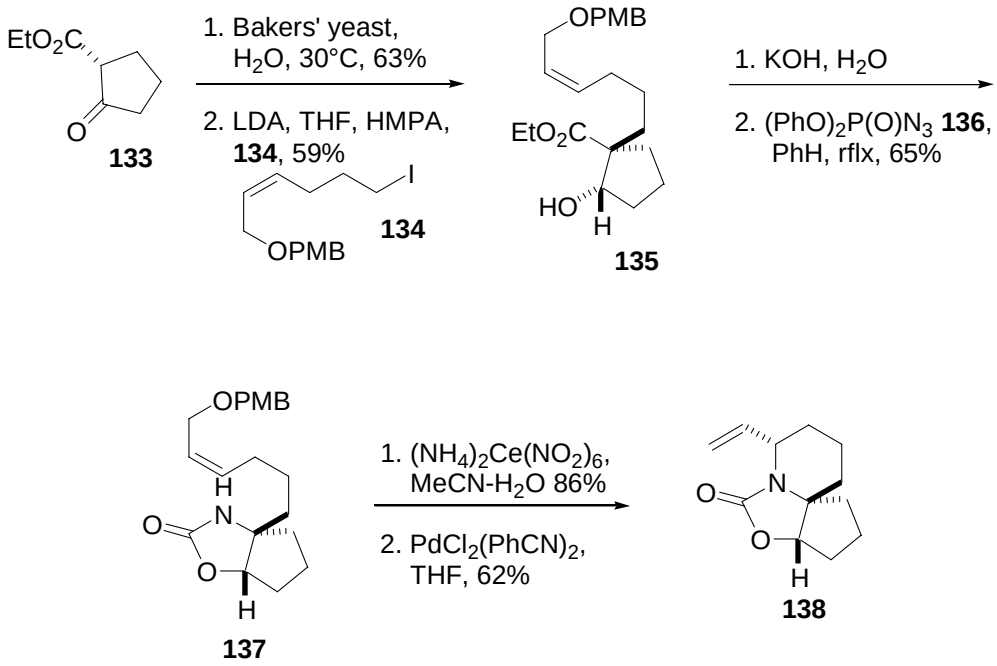


128 **131**



Scheme 28. Shishido's approach toward halichlorine and pinnaic acid.

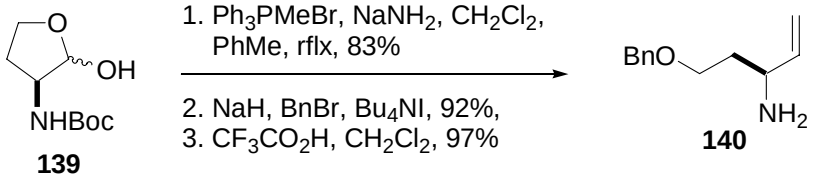
In a later study,[38] Shishido examined the possibility of making the tricyclic core via palladium-mediated cyclization (Scheme 31). The ketone of **133** was reduced with Baker's yeast to the (*S*) alcohol (99% ee) and the ester was alkylated with iodide **134** leading to ester **135**. Hydrolysis of ester **135** and treatment with diphenyl phosphoryl azide (DPPA) [39] (**136**) led directly to cyclic carbamate **137**. Cleavage of the PMB ether and exposure to palladium(II) chloride gave the tricyclic carbamate **137**, albeit with the undesired C_5 stereochemistry. This configuration of **138** was established by X-ray analysis.



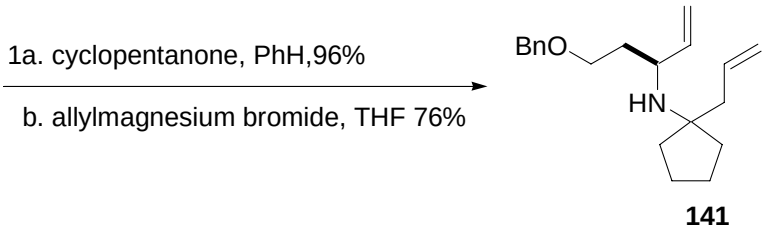
Scheme 31. Shishido's approach toward halichlorine and pinnaic acid.

1.4.14 WRIGHT'S APPROACH TO SPIROCYCLIC CORES SIMILAR TO THOSE IN HALICHLORINE AND PINNAIC ACID

A general method for constructing spirocyclic compounds similar to the bicyclic core of **1-3** has been developed by Wright et al.[40] A key feature of the method is ring-closing metathesis for construction of the piperidine ring system (Scheme 32). Lactol **139** readily available from a DIBAL-H reduction of the corresponding lactone,[41] was opened with Wittig olefination. Benzylation followed by *N*-carbamate cleavage led to amine **140**. Condensation with cyclopentanone and addition of allylmagnesium bromide to the resultant imine yielded diene **141**. When **141** was exposed to either the Grubb's I or II catalyst in the presence of *p*-toluenesulfonic acid (*p*-TsOH), piperidine **142** was formed. The superior method for this metathesis employed the Grubb's II catalyst. A further improvement was realized in the formation of piperidine **143** when amine **141** was first converted to a carbamate and then exposed to Grubb's II catalyst.



139 **140**



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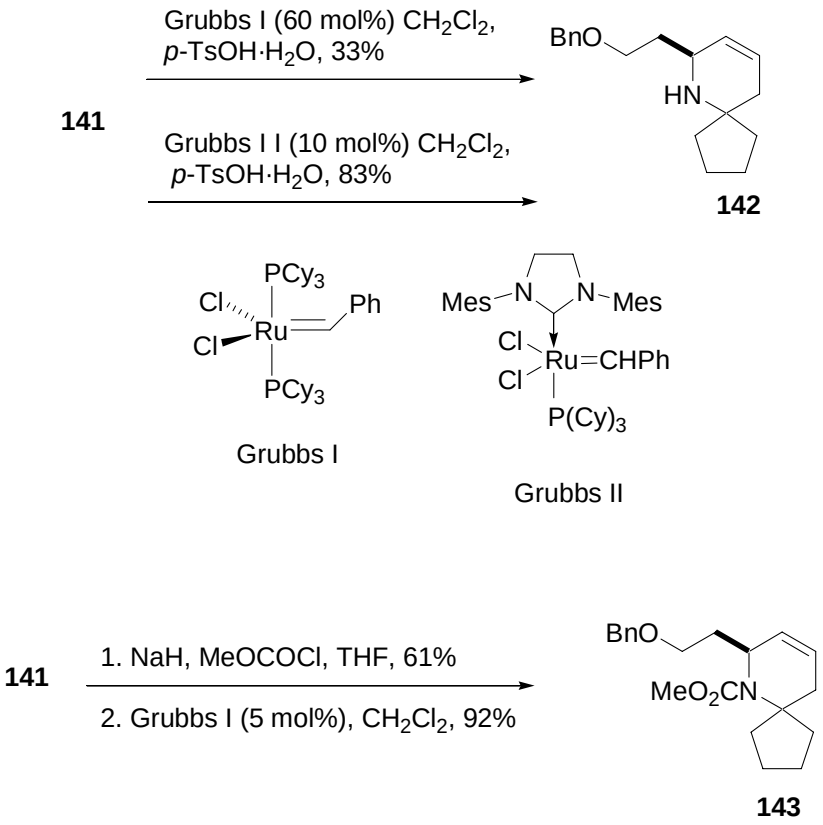
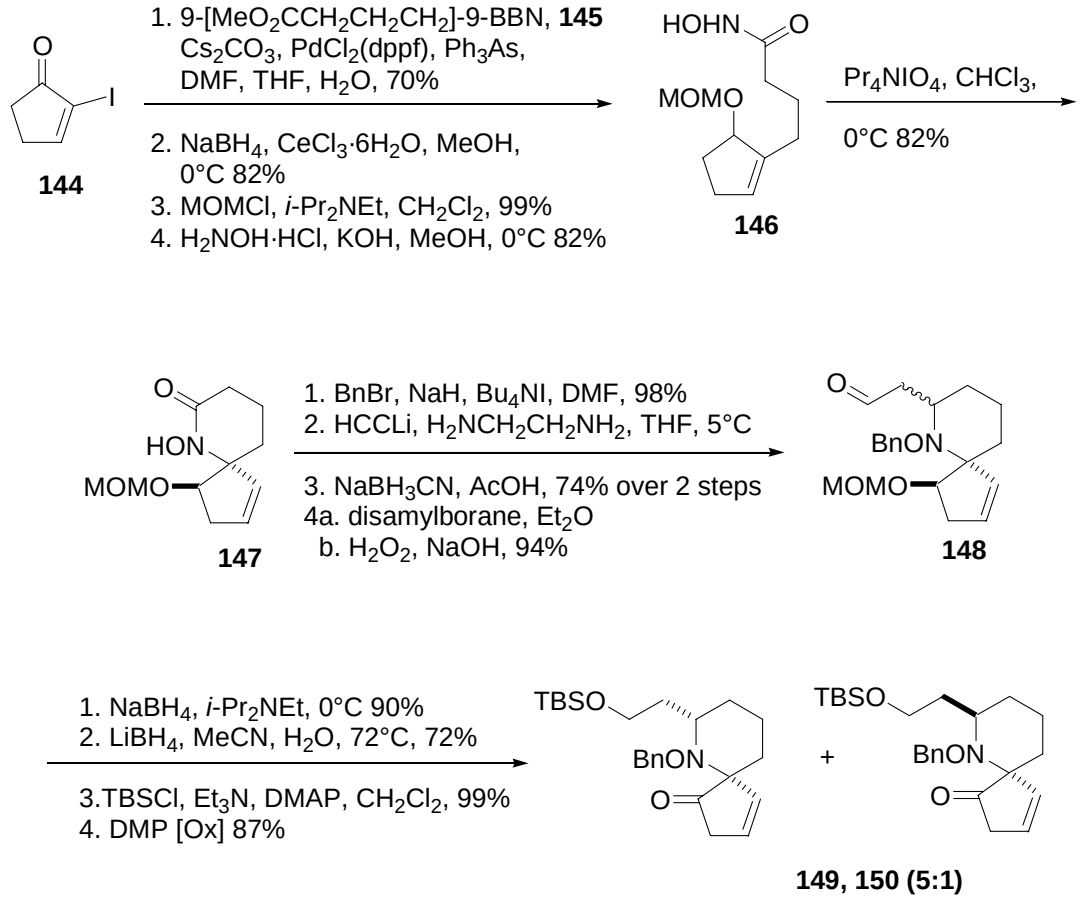


Scheme 32. Wright's approach toward spirocyclic cores similar to that of halichlorine and pinnaic acid

1.4.15 KIBAYASHI'S FORMAL SYNTHESIS OF PINNAIC ACID

Kibayashi et al.[42] constructed the azaspiro[4.5]decane core by means of an intramolecular ene reaction. Suzuki-Miyaura coupling of iodoenone **144** with borane **145** in the presence of a Pd(II) catalyst (Scheme 33) was followed by ketone reduction and MOM ether formation. The pendant ester was converted to the hydroxamic acid **146** upon treatment with a basic solution of hydroxylamine. Oxidation of the hydroxamic acid to the acylnitroso species led to a spontaneous ene reaction which yielded spirocycle **147** whose structure was confirmed by X-ray analysis. Benzylation of **147** and treatment with lithium acetylide-ethylenediamine complex served to introduce an alkynyl subunit. Reduction of the resultant aminal

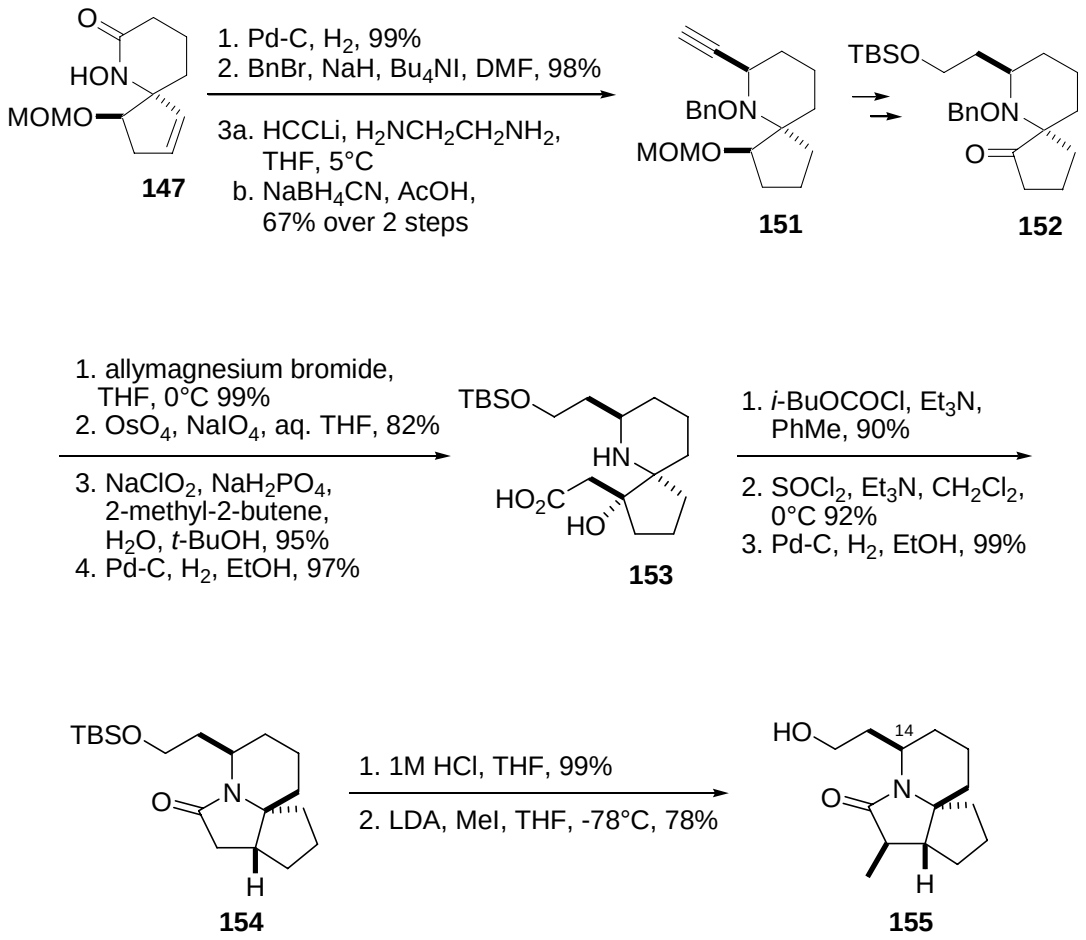
gave a 5:1 mixture of epimers. The terminal alkyne was then converted to aldehyde **148** by hydroboration. Reduction of **148** and hydrolysis of the MOM ether was followed by selective silylation of the primary alcohol. The secondary alcohol was then oxidized to give ketones **149** and **150** as a 5:1 mixture respectively.



Scheme 33. Kibayashi's approach

The sequence in scheme 33 was improved by first reducing the olefin in spirocycle **147** and subjecting it to the same series of reactions as described above (Scheme 34).[43] With this modification the desired spirocycle **152** was completely free of the undesired epimer. To explain the result it was rationalized that the proximal vinyl hydrogen of the five-member ring blocked access of hydride from one face.

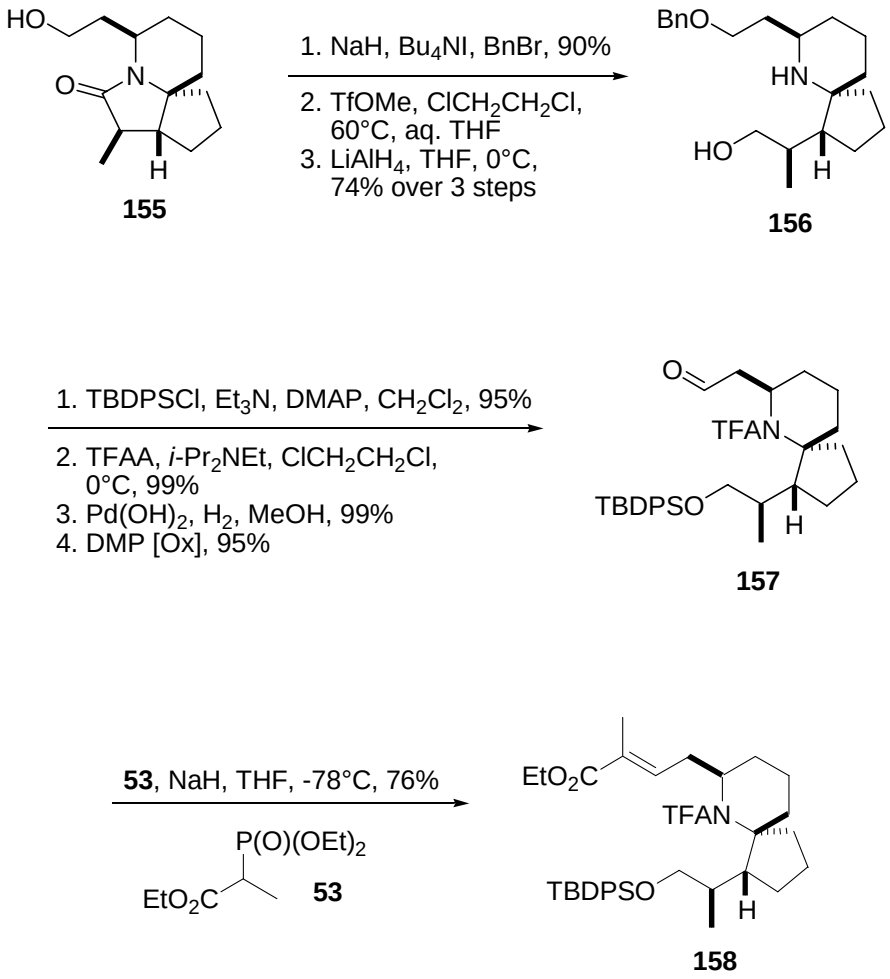
Addition of allylmagnesium bromide to spirocycle **152** was followed by a two-step oxidation to a carboxylic acid. Cleavage of the benzyl moiety yielded amine **153**, and conversion of this carboxylic acid to a mixed anhydride resulted in lactam formation. Alcohol dehydration with thionyl chloride resulted in a mixture of regioisomers, both of which were hydrogenated to yield amide **154**. Desilylation and alkylation with methyl iodide afforded tricycle **155** with the correct C_{14} stereochemistry.



Scheme 34. Kibayashi's approach to a formal synthesis of pinnaic acid

Alcohol **155** was protected as its benzyl ether after which lactam cleavage was accomplished by *O*-methylation with methyl triflate and hydrolysis the resultant iminium ion. This yielded an ester that was reduced to give amine **156** (Scheme 35).

Alcohol silylation, nitrogen acylation, cleavage of the benzyl ether by hydrogenolysis, and final alcohol oxidation led to aldehyde **157**. Olefination of **157** using phosphonate **53** afforded ester **158**, which is the racemic version of an intermediate in Danishefsky's synthesis[7,8] of **2**.

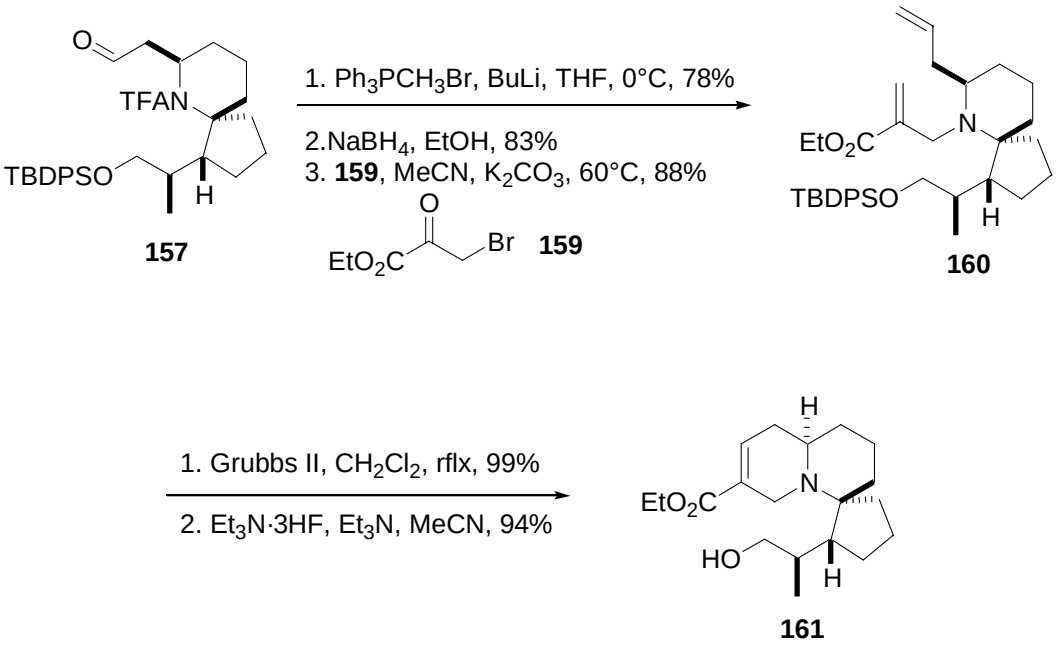


Scheme 35. Kibayashi's completion of the formal synthesis of pinnaic acid

1.4.16 KIBAYASHI'S APPROACH TO THE TRICYCLIC CORE OF HALICHLORINE

A synthetic route toward (±)-halichlorine from Kibayashi[42] used the previously synthesized aldehyde **157**. Wittig methylenation of **157** was followed by reduction of the *N*-trifluoroacetal linkage and the free amine was alkylated with bromide **159**

yielding diene **160** (Scheme 36). Grubb's II catalyst was used for ring-closing metathesis, and final desilylation provided the advanced tricycle **161**.

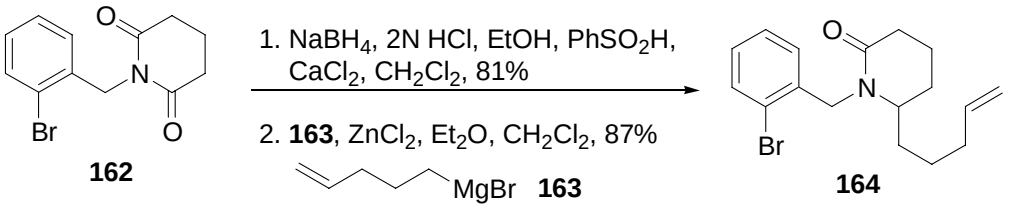


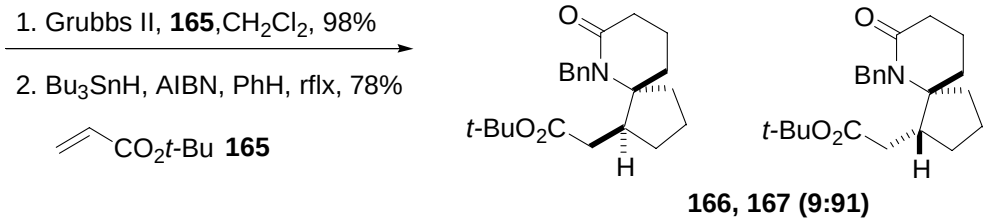
Scheme 36. Kibayashi's approach toward halichlorine

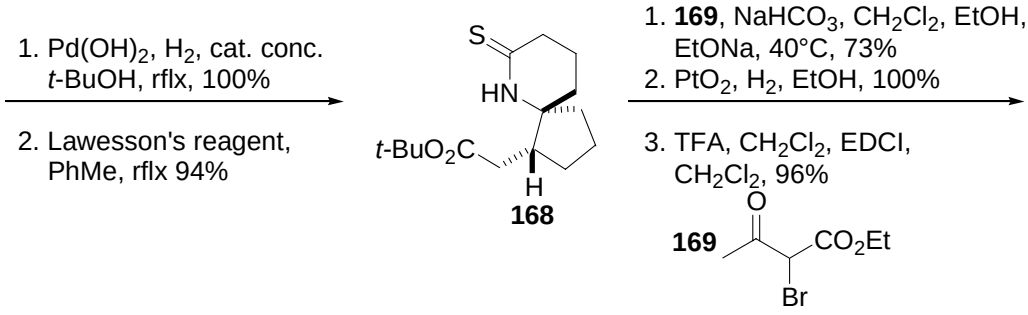
1.4.17 IHARA'S APPROACH TO THE BICYCLIC CORE OF HALICHLORINE AND PINNAIC ACID

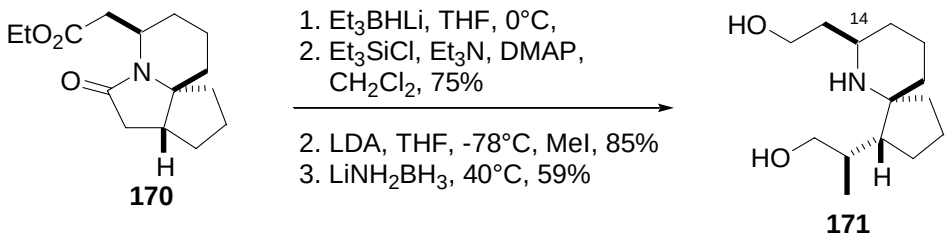
Ihara's approach involved radical translocation for the formation of the spirobicyclic core. The *N*-substituted glutarimide **162** underwent mono-reduction, and was then converted to a sulfone by treatment with benzenesulfinic acid (Scheme 37).[44] The sulfone was reacted with 4-pentenylmagnesium bromide **163** in the presence of zinc(II) chloride to yield olefin **164**. Olefin cross-metathesis with acrylate **165** set the carbon framework for radical cyclization. Tributyltin hydride and 2, 2′-azobis(2-methylpropionitrile) (AIBN) generated the aryl radical, and upon transfer of hydrogen resulted in a 5-exo trigonal cyclization that yielded spiro lactams **166** and **167**, 9:91 mixture, respectively. The spiro lactam **167** was first debenzylated and then converted

to its corresponding thiolactam **168** with Lawesson's reagent. A vinylogous carbamate was formed by Eshenmoser sulfide contraction[45] with bromide **169** and the resultant α,β-unsaturated olefin was subsequently hydrogenated. The *tert*-butyl ester was hydrolyzed to the carboxylic acid which was converted to lactam **170**. Ester reduction of **170** was followed by alcohol silylation, and installation of C_{14} methyl group with the desired stereochemistry was accomplished by alkylation with methyl iodide. Lactam reduction was accomplished by desilylation which yielded diol **171**.





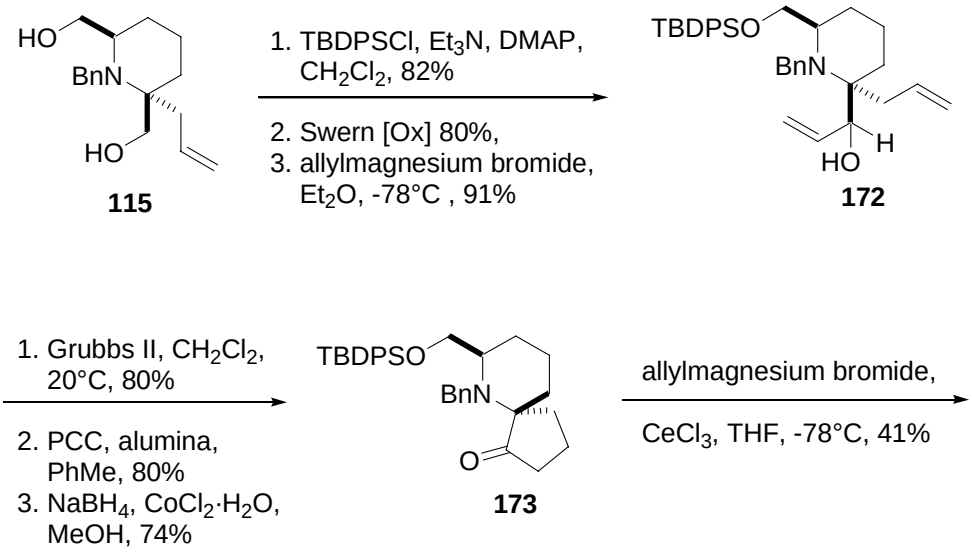


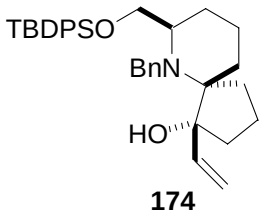


Scheme 37. Ihara's approach toward halichlorine and pinnaic acid

1.4.18 SIMPKINS APPROACH TO A BICYCLIC CORE SIMILAR TO THAT FOUND IN HALICHLORINE AND PINNAIC ACID

Simpkins et al. in a similar manner to Clive's work,[30] has developed a route to the spirocyclic core. Diol **155** (90-95% ee) was selectively silylated and the remaining alcohol was oxidized to an aldehyde (Scheme 38).[46] Addition of allylmagnesium bromide to the aldehyde led to epimeric alcohols **172**. Olefin metathesis using Grubb's II catalyst was followed by alcohol oxidation to a ketone; subsequent reduction of the α,β-unsaturated olefin resulted in spirocycle **173**. The ketone function was treated with allylmagnesium bromide which gave a single alcohol **174**.



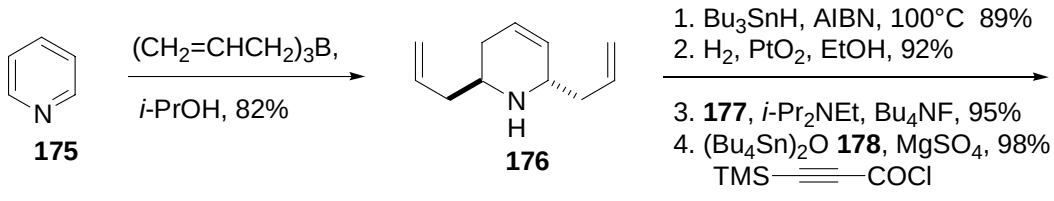


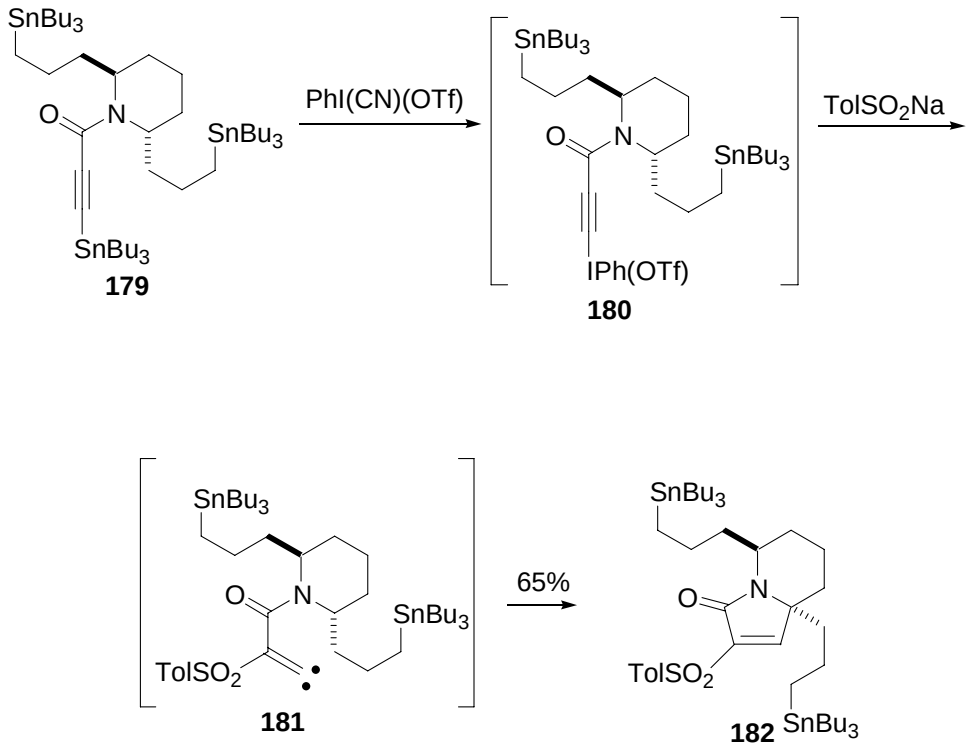
174

Scheme 38. Simpkin's approach toward a bicyclic core similar to that found in halichlorine and pinnaic acid

1.4.19 FELDMAN'S APPROACH TO THE TRICYCLIC CORE OF HALICHLORINE

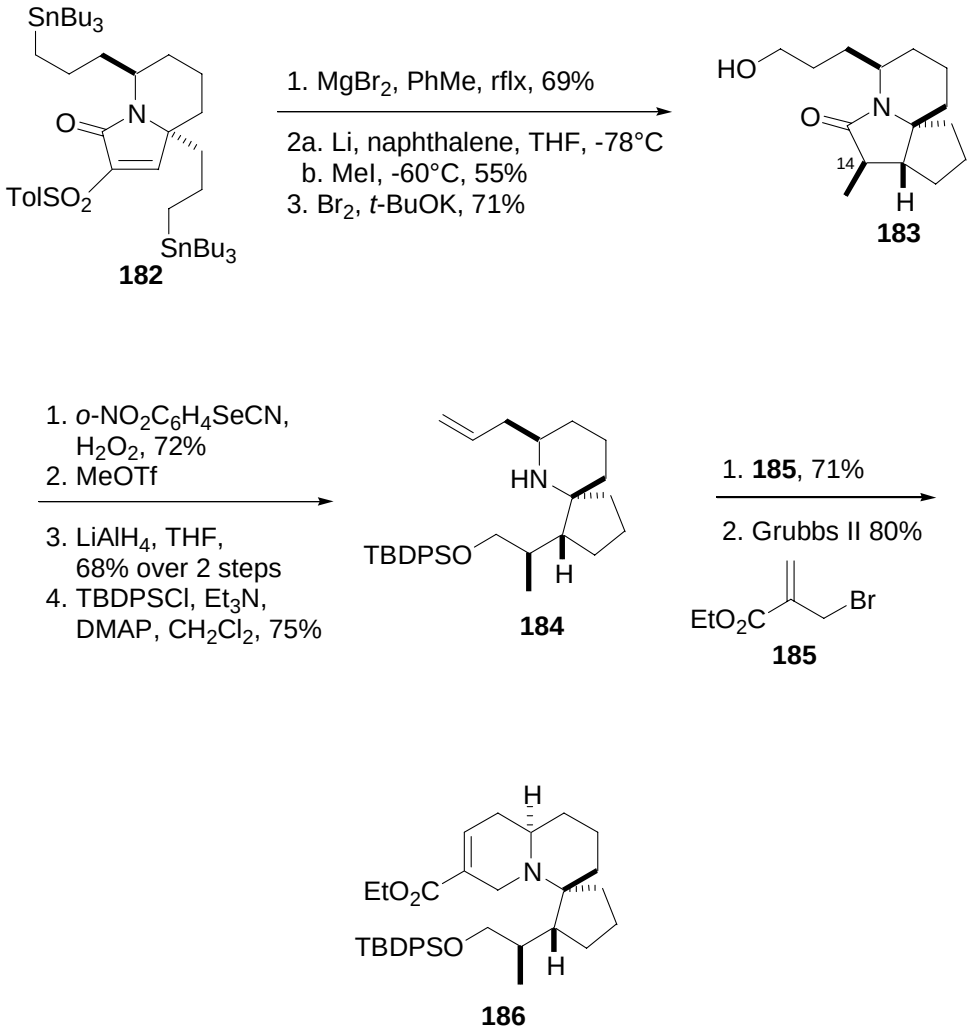
Feldman's approach to the tricyclic dehydroquinolizidine core was based on the insertion of an alkylidene carbene into the C-H bond of a tertiary carbon (Scheme 39).[47] Tetrahydropyridine **176** was constructed from pyridine **175** in one step. Hydrostannylation, olefin hydrogenation, and acylation of the amino group with acyl chloride **177** in the presence of stannoxane **178** afforded tristannane **179**. Treatment of the acetylenic stannane with Stang's reagent[48] yielded the presumed iodonium species **180** and exposure to *p*-toluenesulfinate led to the carbene insertion product **182**, presumably *via* carbene **181**.





Scheme 39. Feldman's approach toward halichlorine

Differentiation between the two stannanes present in **182** was achieved with magnesium bromide which facilitated the conjugate addition of one of the Sn-C bonds to the α,β-unsaturated δ-lactone (Scheme 40).[49] Reduction and methylation served to install the methyl group with the desired C_{14} stereochemistry. Conversion of this material to a monobromodibutyltin derivative followed by a Tamao-Fleming type oxidation resulted in formation of alcohol **183**. Elimination of this alcohol to a mono-substituted olefin was achieved via Grieco's selenoxide chemistry.[50] Opening of the δ-lactam employed the same procedure used by Kibayashi,[29,30] with silylation of the resultant alcohol to yield amine **184**. Acylation of **184** with **185** followed by olefin metathesis with Grubbs II catalyst resulted in the tricyclic core **186**.

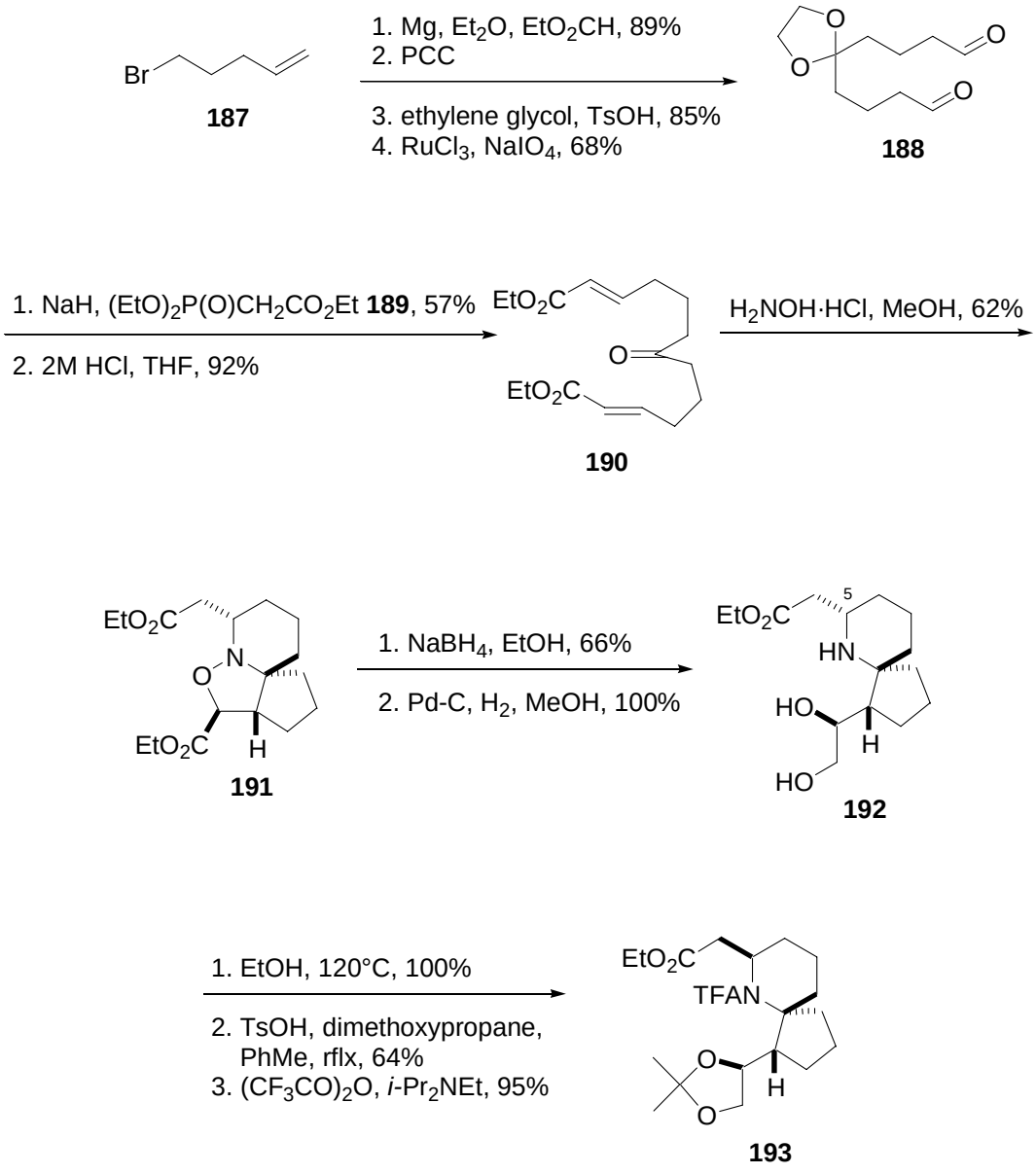


Scheme 40. Feldman's approach toward halichlorine

1.4.20 STOCKMAN'S APPROACH TO THE BICYCLIC CORE OF HALICHLORINE AND PINNAIC ACIDS

In Stockman's approach, a [3+2] nitrone cycloaddition was employed to construct the core ring system (Scheme 41).[51] The synthesis commenced with a double Grignard addition to ethyl formate. The resultant alcohol was oxidized and the ketone protected as a ketal. The terminal olefins were then oxidatively cleaved to dialdehyde **182**. Horner-Wadsworth-Emmons olefination of the dialdehyde **188** with phosphonate **189** followed by acetal cleavage yielded ketone **190**. Condensation of

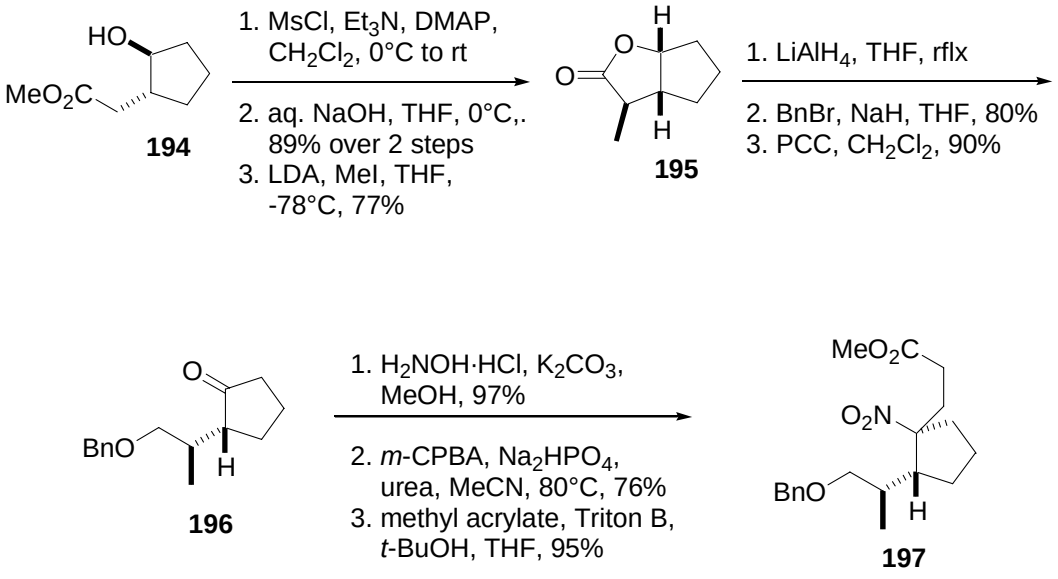
this ketone with hydroxylamine hydrochloride resulted in intramolecular Michael addition which was followed by a [3+2] intramolecular cycloaddition of the intermediate nitrone to produce cycloadduct **191**. Selective ester reduction and subsequent N-O bond cleavage led to diol **192**. Epimerization of the C_5 stereocenter was realized by a reversible Michael addition. Diol ketalization and *N*-acetylation led to the formation of acetonide **193**.

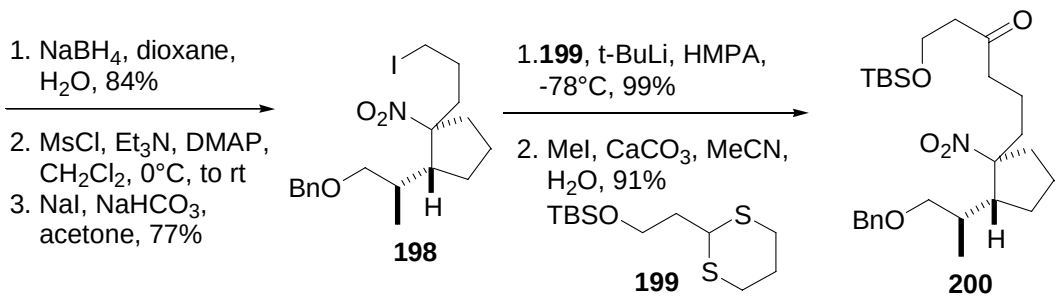


Scheme 41. Stockman's approach toward halichlorine and pinnaic acids

1.4.21 ZHAO AND DING'S APPROACH TO THE FORMAL SYNTHESIS OF PINNAIC ACID

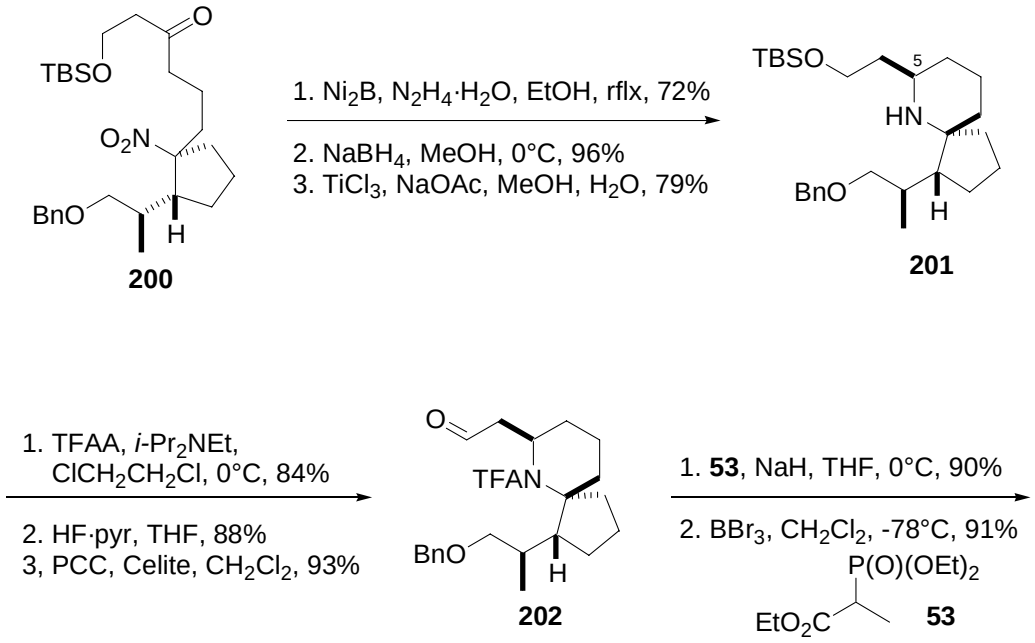
Zhao and Ding achieved a formal synthesis[52] of pinnaic acid that merges with the Danishefsky route to the azabicyclic core of **1**. The enantiomerically pure hydroxy ester **194** was converted to a γ-lactone via displacement of the mesylated alcohol by the free acid (Scheme 42). The newly formed lactone was alkylated with methyl iodide to give ester **195**. The latter was reduced, the ensuing primary alcohol was benzylated, and the secondary alcohol was oxidized to ketone **196**. Treatment with hydroxylamine hydrochloride followed by oxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) resulted in the nitro derivative which was treated with methyl acrylate to give conjugate addition product ester **197**. The ester was reduced and the alcohol was converted to the corresponding iodide **198**. Alkylation of dithiane **199** with iodide **198** was followed by hydrolysis of the thioketal which yielded ketone **200**.

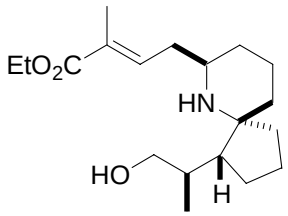




Scheme 42. Zhao and Ding's approach toward the formal synthesis of pinnaic acid

With ketone **200** in hand, the nitro functionality was reduced to the hydroxyl amine which spontaneously condensed with the ketone to form a cyclic nitrone. The cyclic nitrone was reduced to a hydroxyl amine and then finally reduced to amine **201** having the desired C_5 stereochemistry. Amine acylation, alcohol desilylation and oxidation afforded aldehyde **202**. Horner-Wadsworth-Emmons olefination to aldehyde **202** and debenzylation afforded alcohol **203**, which corresponded to an intermediate made by Danishefsky.



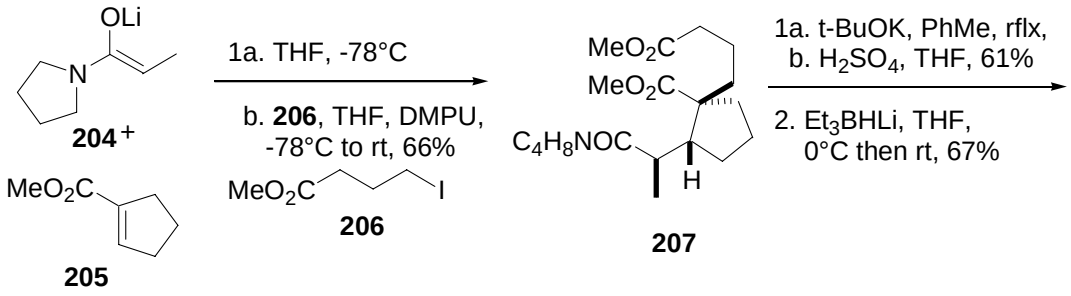


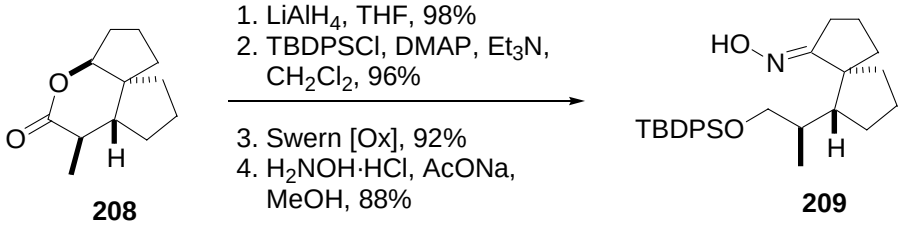
203

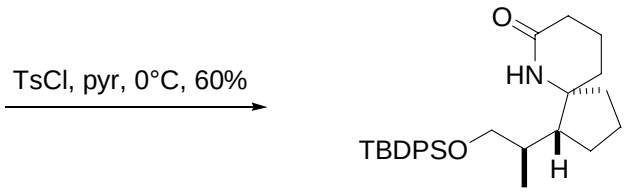
Scheme 43. Zhao and Ding's formal synthesis of pinnaic acid

1.4.22 PILLI'S APPROACH TO THE BICYCLIC CORE OF HALICHLORINE AND PINNAIC ACID

Studies in Pilli's laboratory[53] focused on a stereoselective Michael addition of the (*Z*)-enolate **204** to ester **205** followed by *in situ* trapping with iodide **206** to yield diester **207** (Scheme 44). Dieckmann cyclization followed decarboxylation and amide hydrolysis led to spiro lactone **208**. The lactone was reduced, the resulting primary alcohol was silylated, and the secondary alcohol was oxidized to a ketone. Hydroxylamine hydrochloride was used to form the oxime **209** which underwent Beckmann rearrangement to give the spirocyclic lactam **210**.





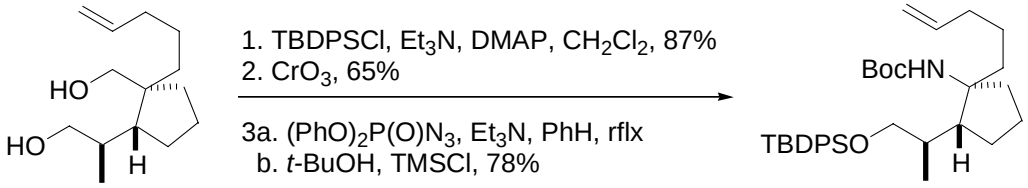


210

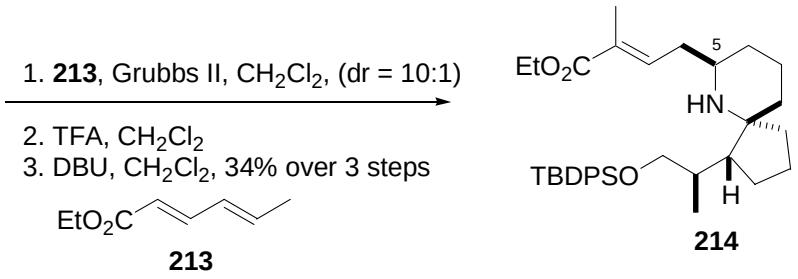
Scheme 44. Pilli's approach toward halichlorine and pinnaic acid

1.4.23 MARTIN'S FORMAL SYNTHESIS OF PINNAIC ACID

A formal synthesis of pinnaic acid was achieved by Martin et al.[54] The synthesis commenced with selective silylation of diol **211** followed by oxidation or the remaining alcohol to the carboxylic acid (Scheme 45). The carboxylic acid was then subjected to Curtius rearrangement **136** and *tert*-butanol to afford carbamate **212**. Olefin cross-metathesis between diene **213** and **212** gave a carbamate with Grubbs II catalyst and this was followed by carbamate cleavage to yield the free amine. The amine spontaneously underwent intramolecular conjugate addition to the unsaturated ester which afforded α,β-unsaturated ester **214.** Having achieved the desired C_5 stereochemistry, ester **214** was compared to a previously synthesized intermediate of Danishefsky's.



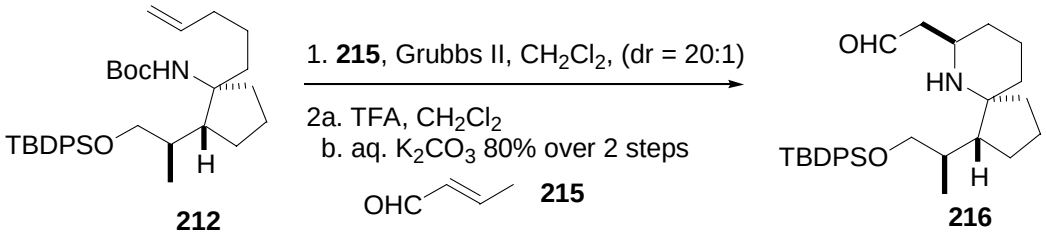
211 **212**

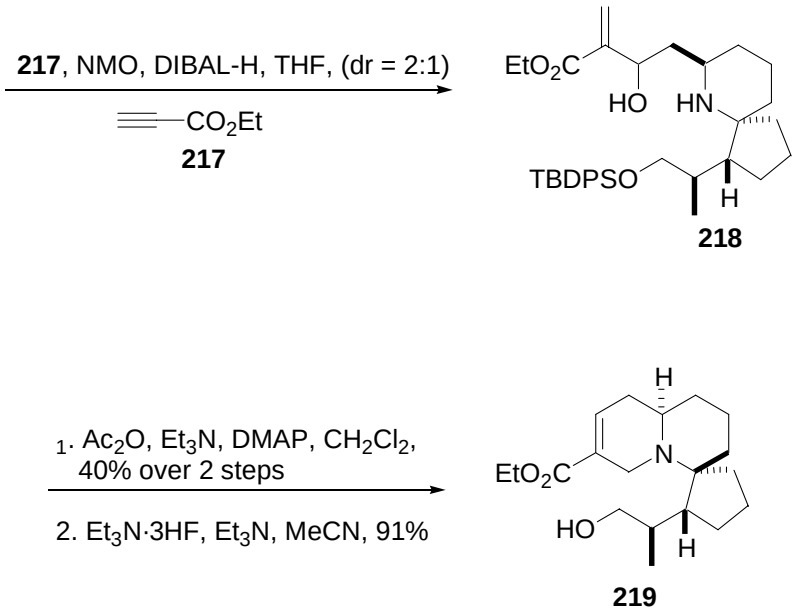


Scheme 45. Martin's formal synthesis of pinnaic acid

1.4.24 MARTIN'S FORMAL SYNTHESIS OF HALICHLORINE

Martin's formal synthesis[53] of halichlorine used carbamate **212**. A cross-metathesis of **212** with α,β-unsaturated aldehyde **215** in the presence of Grubb's II catalyst was followed by carbamate cleavage to yield an amine (Scheme 46). The resulting amine was cyclized via conjugate addition to the α,β-unsaturated aldehyde affording aldehyde **216**. Ramachandran's vinylaluminum methodology[55] was used to homologate aldehyde **216** which leading to α,β-unsaturated ester **218** (dr = 2:1). Acylation of the resultant alcohol led to facile cyclization. Final desilylation provided ester **219**, a substance synthesized previously by Kibayashi.





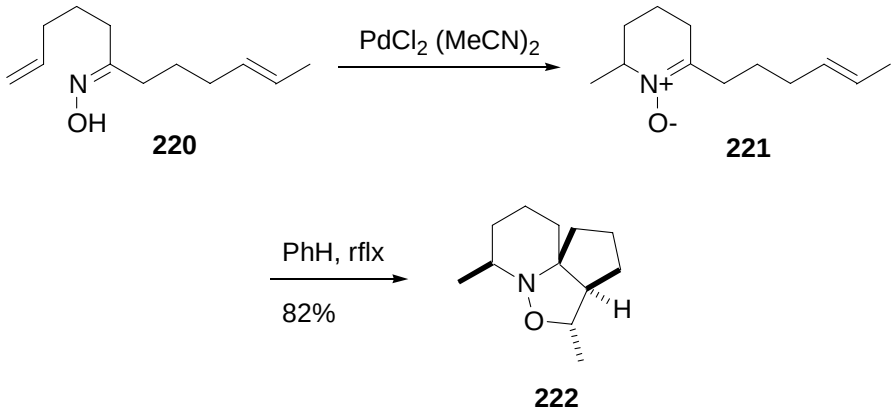
Scheme 46. Martin's formal synthesis of halichlorine

In summary, several conceptually different synthetic approaches to halichlorine and pinnaic acid have been reported.

CHAPTER 2. SYNTHESIS OF THE SPIROCYCLIC CORE OF HALICHLORINE AND PINNAIC ACID VIA A TRANSANNULAR NITRONE CYCLOADDITION

2.1 INTRODUCTION TO TRANSANNULAR CYCLOADDITION REACTIONS

The unique and complex structure of halichlorine and pinnaic acid, coupled with their largely unexplored potential in medicine, makes these natural products attractive targets for synthetic studies. Our initial interest in developing a synthetic approach to the spirocyclic core was inspired by a [3+2] nitrone cycloaddition based on Grigg's pioneering work on intramolecular cycloaddition of nitrones, particularly on his finding that the cycloaddition of nitrone **221** gives cycloadduct **222** in high yield and with complete stereoselectivity (Scheme 47).[56]

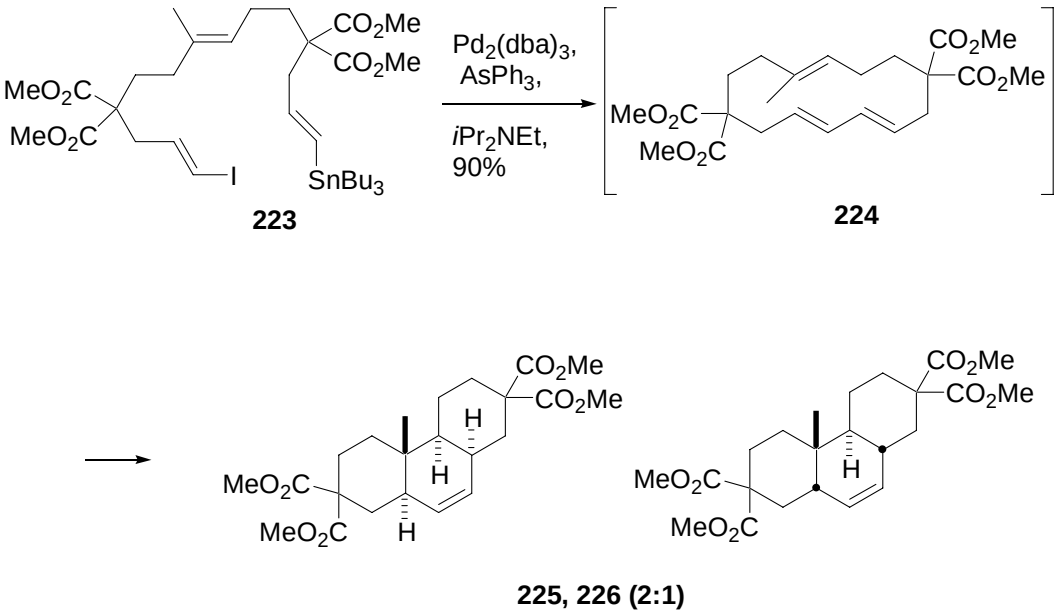


Scheme 47. Grigg's stereoselective intramolecular nitrone cycloaddition

With Grigg's nitrone cycloaddition methodology established for construction of the spiro ring system, it was perceived that a possible cycloaddition in which the pair of addends are tethered to each other at both termini represents a special class of intramolecular reactions that offers unique advantages for synthesis. If the ring formed by connecting the addends in this manner is conformationally constrained, a

predicted stereochemical outcome from the process of transannular cycloaddition should be possible.

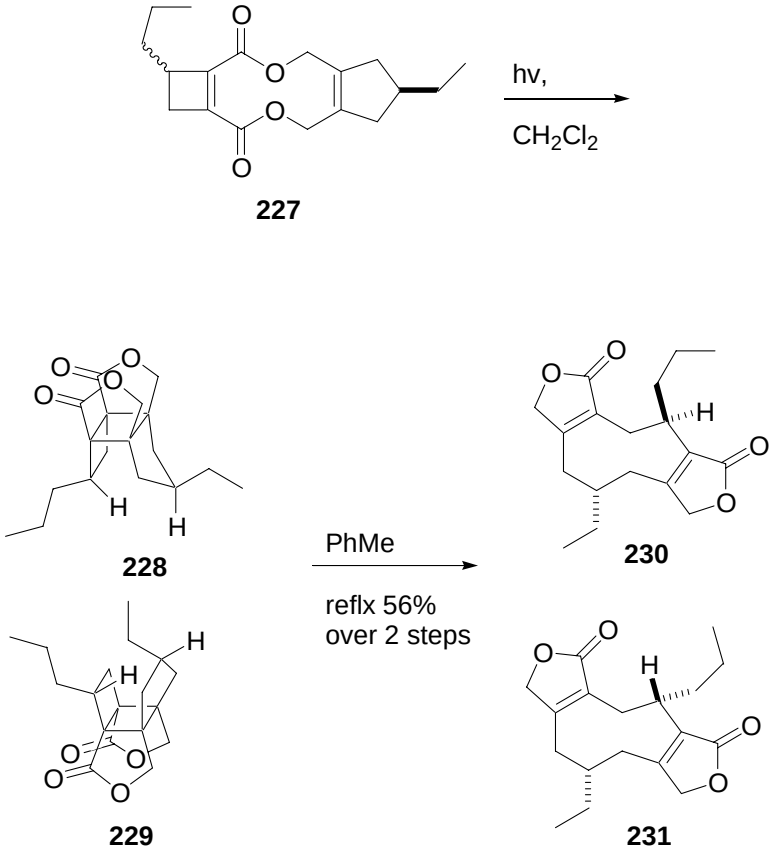
The best studied examples of transannular cycloadditions are Diels-Alder (TADA) reactions.[57] Deslongchamps has demonstrated the practical use of TADA for the elaboration of complex polycyclic systems with a high degree of stereocontrol from relatively simple precursors. A recent example by Deslongchamps has stannyl iodide **223** under Stille coupling conditions forming transient triene **224** which undergoes a TADA to give a mixture of cycloadducts. Isomeric tricycles *trans-anti-cis* **225** and *cis-anti-trans* **226** are produced in a ratio of 2:1(Scheme 48).[58]



Scheme 48. An example of a TADA by Deslongchamps.[57]

Another recent example, which involved a transannular [2+2] photoaddition, was employed for the synthesis of (+)-Byssochlamic Acid by White[59] (Scheme 49). When the 1:1 mixture of diene **227** was irradiated, *exo*, *exo* and *exo*, *endo* photoadducts **228** and **229** were isolated in equal quantity. This was followed by cycloreversion to give α,β-unsaturated γ-lactones **230** and **231**. Compound **231** was

carried on to form (+)-Byssochlamic Acid. Despite these groundbreaking examples, transannular cycloadditions are still a largely unexplored class of reactions.

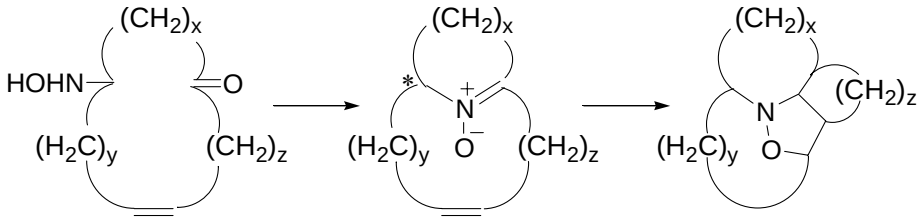


Scheme 49. White's transannular [2+2] photoaddition

2.2 INCORPORATION OF A TRANSANNULAR NITRONE-OLEFIN CYCLOADDITION IN THE SYNTHETIC PLAN FOR HALICHLORINE AND PINNAIC ACID

Halichlorine's and pinnaic acid's structure provided the opportunity to further extend the scope of transannular cycloaddition by incorporating a nitrone and an olefin as dipole and dipolarophile respectively, within a ring. A basic representation of our proposed transannular nitrone cycloaddition (TANCA) begins with a tetracyclic ($x \neq 0$) isoxazolidine **232** bearing three new stereocenters which is produced from nitrone

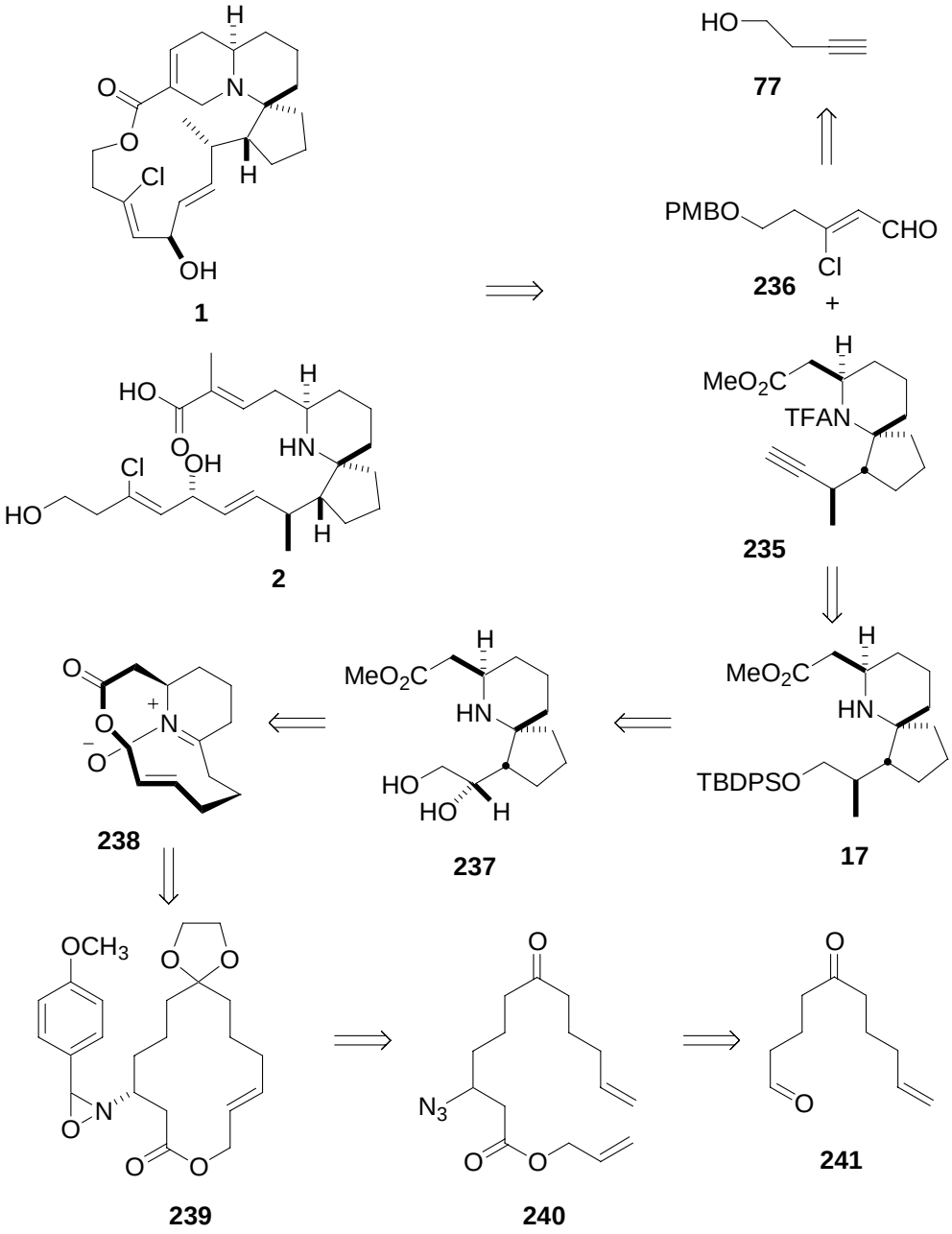
233 (Scheme 50). The latter is prepared from transannular condensation of a hydroxylamine with the ketone **234**. A requirement for stereocontrol in the reaction is that y and z must be large enough to permit flexibility in the approach of the nitrone to its olefin partner, but not so large to allow the nitrone oxygen to pass through the plane of the macrocycle. If these conditions are met, the face of the olefin to which the nitrone adds will be determined by the single stereocenter (*) in **233** which originated from the configuration of the hydroxylamine in **234**.



234 **233** **232**

Scheme 50

Halichlorine and pinnaic acid were envisioned coming from the coupling of alkyne **235** with aldehyde **236** (Scheme 51). Compound **236** would be synthesized from commercially available alcohol **77**. The pivotal branching intermediate **235** would arise from amine **17** which has been previously synthesized by Danishefsky.[3] A further disconnection of **17** leads to diol **237**. The spirobicylic core of **237** would be formed by the key step in our synthesis plan, namely transannular nitrone-olefin [3+2] cycloaddition of **238**. Access to the nitrone would be from oxaziridine **239**, and the 14-membered macrolactone ring would be realized in a ring-closing-metathesis of diene **240**. The latter originates from known aldehyde **241**.[60]

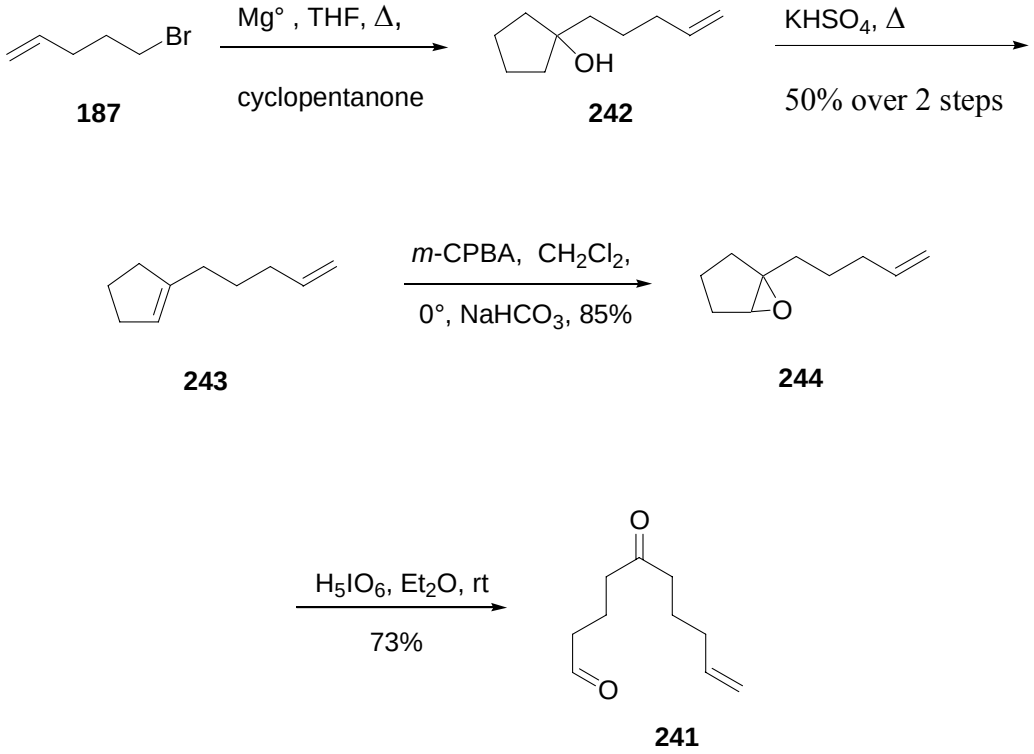


Scheme 51. Retrosynthetic analysis for the synthesis of halichlorine and pinnaic acid

2.3 RACEMIC SYNTHESIS OF DIOL 237

A convenient synthesis of aldehyde **241** was developed by Kitching.[60] The synthesis began with a Grignard reaction with bromide **187** and cyclopentanone to yield alcohol **242** (Scheme 52). The alcohol was then dehydrated with potassium hydrogen sulfate to give cyclopentene **243**. Upon oxidation, the more substituted

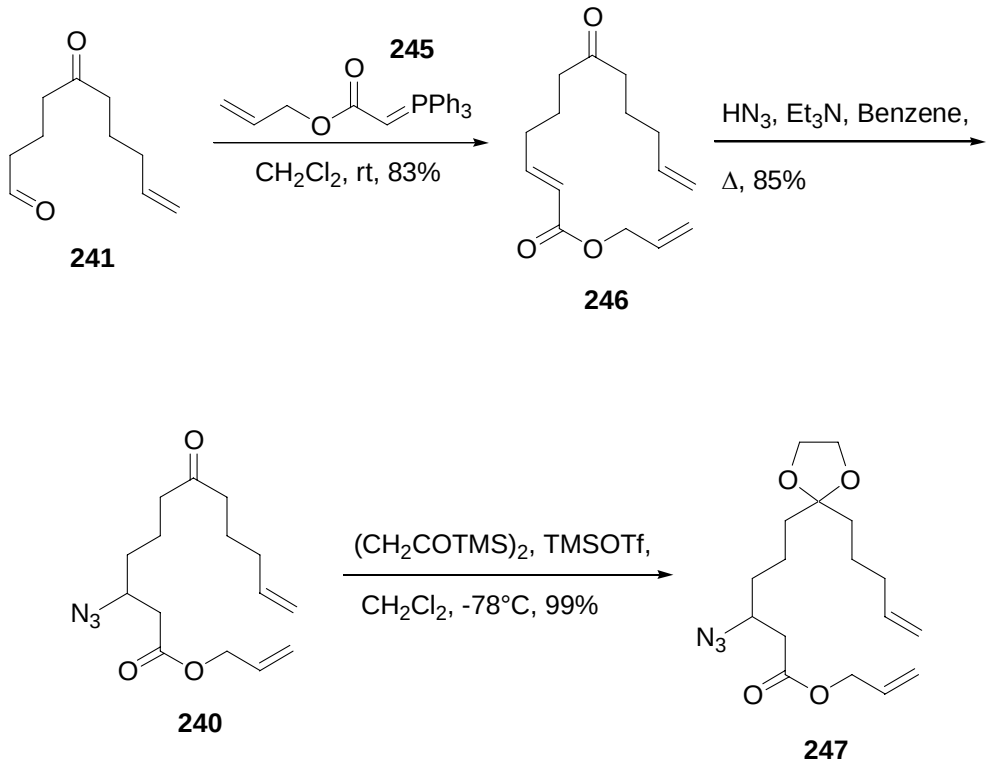
olefin quickly formed epoxide **244**. Further oxidation, presumably through hydrolysis of the epoxide to the diol, resulted in **241** uneventfully.



187 **242** **243** **244** **241**

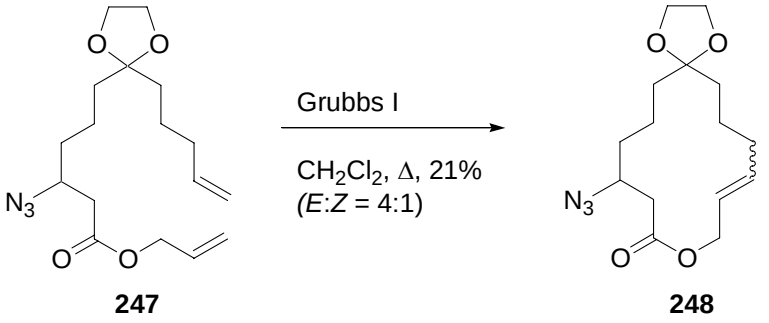
Scheme 52. Synthesis of known aldehyde **241**

Aldehyde **241** was elongated using a stabilized Wittig olefination with ylide **245** to give (*E*) allylic ester **246** without consequence (Scheme 53).[61] A nitrogen function was introduced into **246** as an azide by employing methodology due to Rao.[62] This involved conjugate addition of hydrazoic acid in the presence of catalytic triethylamine to afford azide **240** in high yield. The ketone function was then protected as its ethylene ketal using Noyori's procedure[63] to yield ketal **247**.



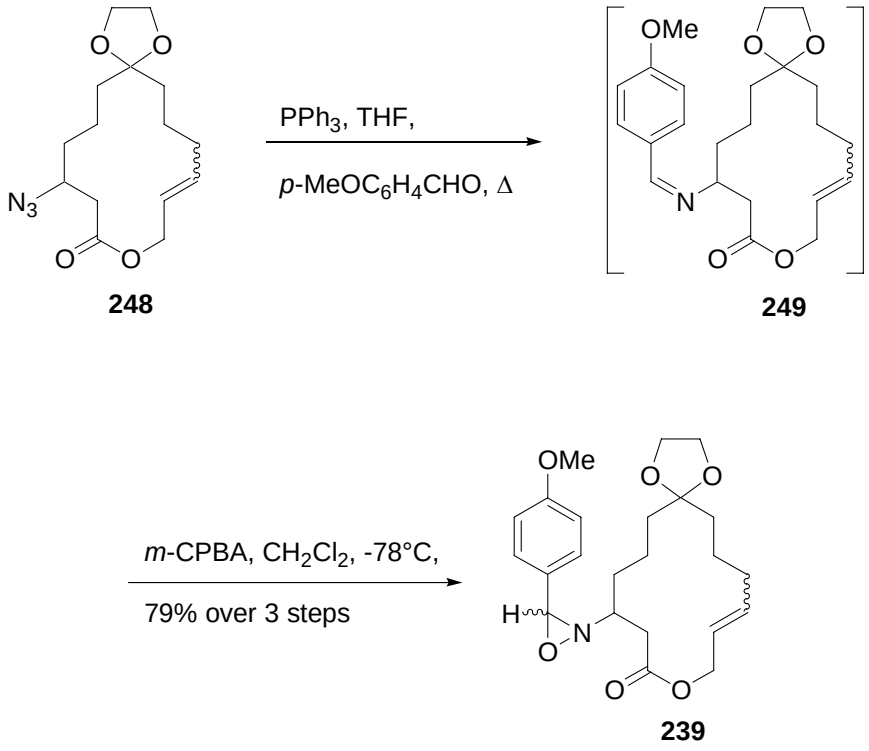
Scheme 53. Azide installation at C_3

Our next task was to close the macrocycle form **247**. The use of Grubbs I catalyst in the formation of 14-membered rings is well precedented in the literature.[64,65] Ring closing metathesis of **247** required 20 mol% of Grubbs I catalyst and gave tridecanolide **248** in low yield as an inseparable mixture of olefin isomers (*E:Z* = 4:1) (Scheme 54). The use of the newer Grubbs II catalyst[66] was found to offer no improvement for this conversion. Deleterious side reaction such as polymerization of **247** could account for the low yield of the closure.



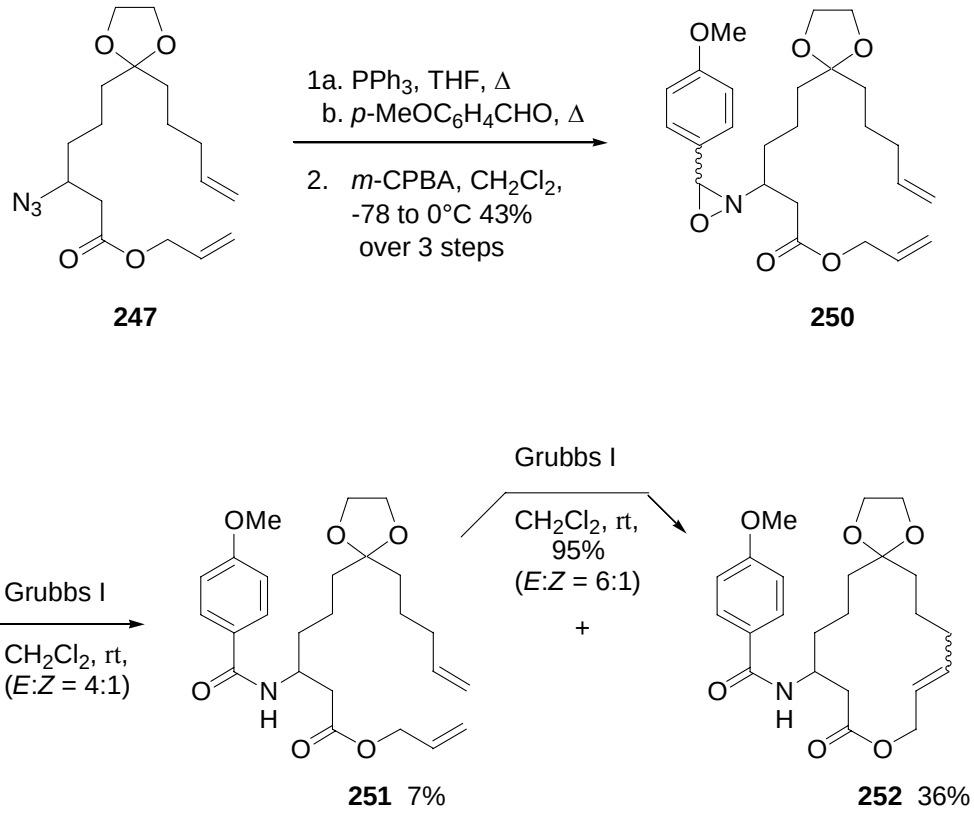
Scheme 54. Ring closing metathesis

Holmes' elegant chemistry[67] was employed as a way to formally oxidize an amine through an imine to an oxaziridine without over-oxidation at nitrogen. First, a Staudinger reaction[68] of the azide **248** was followed by an aza-Wittig reaction of the resultant iminophosphorane with *p*-anisaldehyde to form transiently imine **249**. The latter underwent selective oxidation with *m*-chloroperoxybenzoic acid at the more electron rich π bond to yield oxaziridine **239** (Scheme 55).



Scheme 55. Oxaziridine formation from **239**

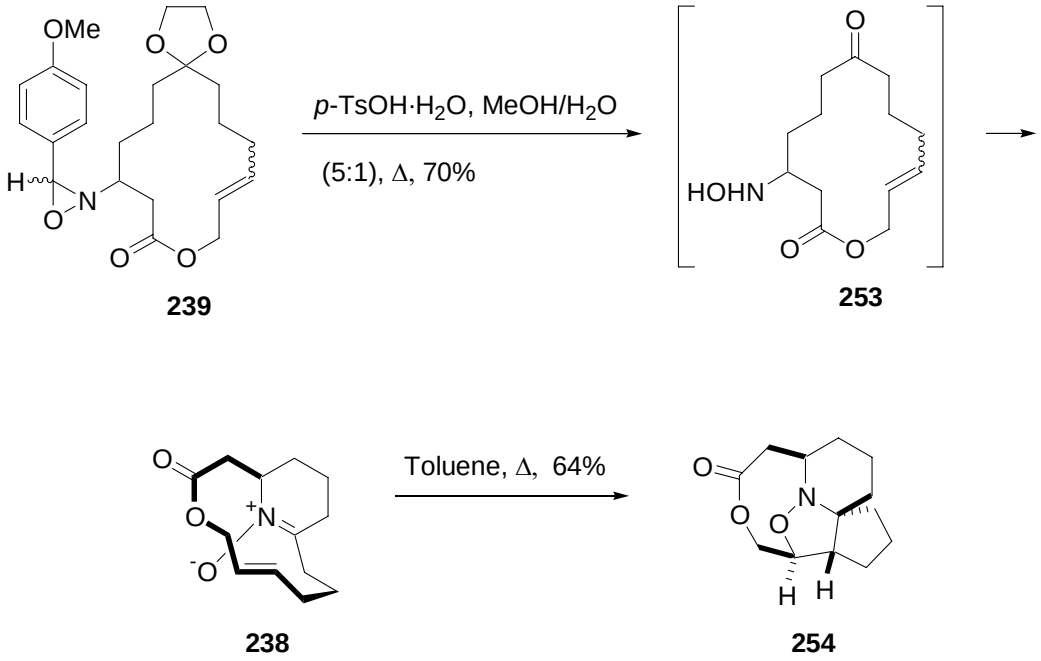
With the successful acquisition of oxaziridine **239** we explored RCM again in an attempt to improve its efficiency. Azide **247** was converted to oxaziridine **250** similar to the transformation of **239** (Scheme 56). However, treatment of **250** with Grubbs I catalyst gave only allyl dodecanoate **251** and the tridecanolide **252** in low yield. Analysis by thin layer chromatography (TLC) of the reaction mixture suggested that isomerization of the oxaziridine occurred before RCM and none of the desired **239** was formed. In a separate experiment **251** was converted to **252** in almost quantitative yield with just 5 mol% of Grubbs I. The isomerization of oxaziridines to amides is typically base catalyzed[69] and is somewhat puzzling in this context.



Scheme 56. Alternative approach to the RCM

Exposure of **239** with *p*-toluenesulfonic acid in aqueous methanol resulted in simultaneous hydrolysis of the ethylene ketal and the oxaziridine to give transiently

the keto hydroxylamine **253** (Scheme 57). The latter underwent spontaneous intramolecular condensation to produce *E* nitrone **238** and its *Z* isomer as a 4:1 mixture, i.e, the same ratio as was obtained in the RCM of **247**. At this stage, it was possible through careful chromatography to remove the minor *Z* isomer. Conformational analysis of **238** indicated that the macrocycle is too small to allow the nitrone oxygen to pass through the ring; therefore, transannular cycloaddition should occur preferentially at only the rear face of the olefin in the conformation shown. When the nitrone **238** was heated to reflux in toluene a single crystalline product was formed in good yield. X-ray analysis of this product confirmed its structure to be the cycloadduct **254** (Figure 2). The relative configuration of the three new stereocenters in **254** originate from the single stereocenter in **238** along with the *E* geometry of the olefin and affirms that good stereocontrol can be achieved in transannular dipolar cycloadditions of this type.



Scheme 57. Transannular nitrone-olefin [3+2] cycloaddition

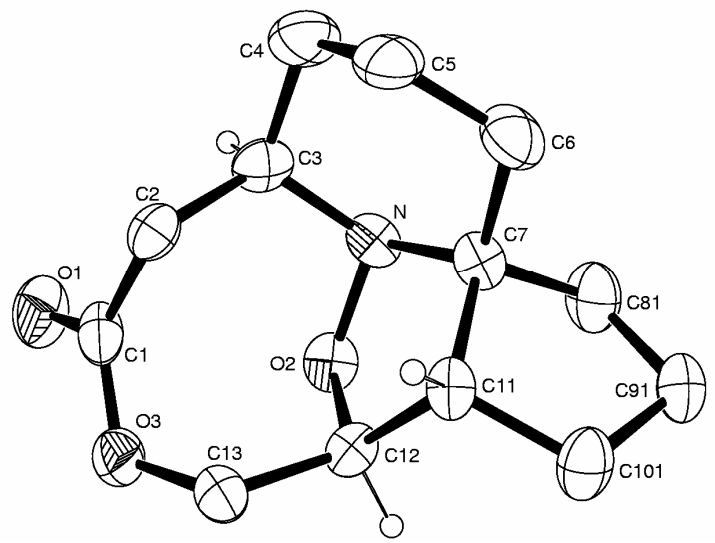
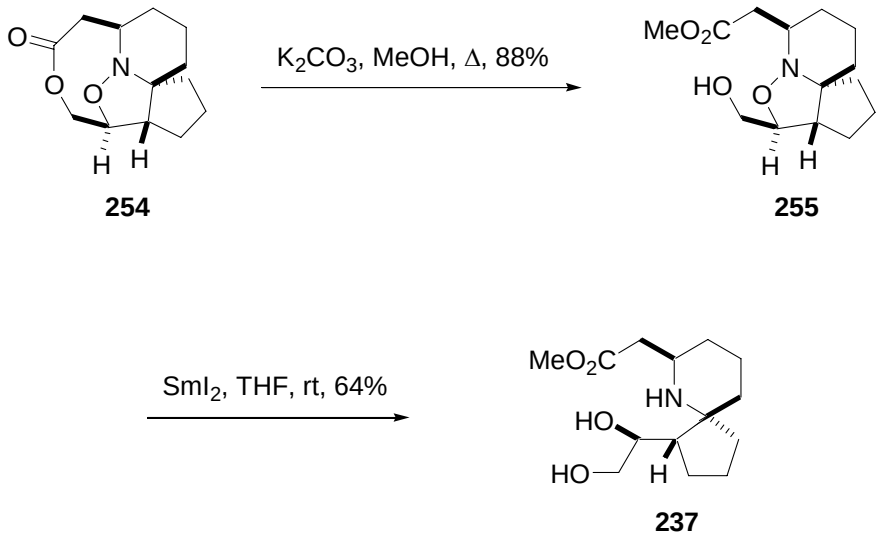


Figure 2. ORTEP diagram of **254**.

With our key step realized, base-catalyzed methanolysis of **254** yielded hydroxy ester **255**. This in turn, relieved some of the steric strain in the isoxazolidine, and cleavage of the N-O bond with samarium diiodide afforded amino diol **237** (Scheme 58). The azaspirocyclic core that was constructed in this way had now established a practical entry to the central portion of halichlorine and pinnaic acid.



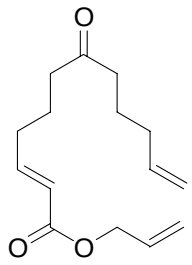
Scheme 58. Synthesis of alcohol **237**.

2.4 EXPERIMENTAL SECTION

General techniques: All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of argon. THF and Et_2O were freshly distilled from sodium benzophenone ketyl prior to use. DMSO and DMF were distilled from CaH_2 at 15 mm Hg. CH_2Cl_2 was freshly distilled from CaH_2, and PhMe was distilled from molten sodium metal. Anhydrous MeOH was obtained by distillation from magnesium alkoxide and stored under argon over activated 4Å molecular sieves. Preparative chromatographic separations were performed on silica gel (35-75 μm); reactions were followed by TLC analysis using silica plates with fluorescent indicator (254 nm) and visualized with UV, phosphomolybdic acid or 4-hydroxy-3-methoxybenzaldehyde. All commercially available reagents were purchased from Aldrich and were typically used as supplied.

Melting points were recorded using open capillary tubes on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured at ambient temperature (22 °C) on $CHCl_3$ solutions with a polarimeter using a 1 mL capacity cell with 1 dm path length. Infrared spectra were recorded on a Nicolet 5DXB spectrometer using a thin film supported between NaCl plates or KBr discs. ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified either on a Bruker AC300 or AM400 spectrometer. Spectra were obtained on $CDCl_3$ solutions in 5 mm diameter tubes, and the chemical shift in ppm is quoted relative to the residual signals of chloroform (δ_H 7.25 ppm, or δ_C 77.0 ppm). Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q= quartet, m = multiplet, br = broad; coupling constants are reported in Hz.

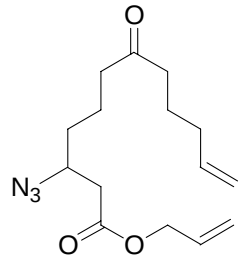
Low (MS) and high (HRMS) resolution mass spectra were measured on a Kratos MS50 spectrometer. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units.



246

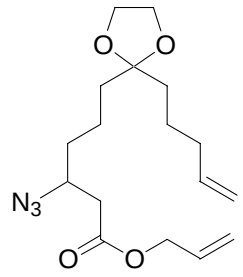
Allyl (*E*)-7-Oxo-2,11-dodecadienoate (**246**). A solution of allyl (triphenylphosphoranylidene)acetate (4.13 g, 11.5 mmol) in CH_2Cl_2 (80 mL) at rt under Ar, was treated with freshly prepared **241** (0.91 g, 5.42 mmol) in CH_2Cl_2 (20 mL). After stirring for 1 h the reaction mixture was concentrated *in vacuo* and the crude residue was further purified *via* column chromatography (eluting with 3:7 Et_2O:hexanes) to yield the enoate **246** (1.13 g, 4.52 mmol, 83%) as a colorless oil.: IR (neat) 2935, 1718, 1649, 1365, 1262, 1174, 992, 904, 712, 634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) ^1H NMR analysis indicated only the *trans* isomer δ 1.55 (quintet, *J* = 7 Hz, 2H), 1.64 (quintet, *J* = 7 Hz, 2H), 1.93 (qm, *J* = 7 Hz, 2H), 2.11 (qm, *J* = 7 Hz, 2H), 2.29 (t, *J* = 7 Hz, 2H), 2.32 (t, *J* = 7 Hz, 2H), 4.51 (dt, *J* = 6, 1 Hz, 2H), 4.85 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.89 (dq, *J* = 17, 2 Hz, 1H), 5.12 (dq, *J* = 10, 1 Hz, 1H), 5.21 (dq, *J* = 17, 2 Hz, 1H), 5.64 (ddt, *J* = 17, 10, 7 Hz, 1H), 5.74 (dt, *J* = 16, 2 Hz, 1H), 5.83 (ddt, *J* = 17, 10, 6 Hz, 1H), 6.84 (dt, *J* = 16, 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 22.5, 31.2, 32.8, 41.4, 41.6, 64.6, 114.9, 117.7, 121.4, 132.1, 137.6, 148.4, 165.7; MS (CI) *m/z*

251, 192, 175, 165, 147, 97; HRMS (CI) *m/z* 251.1648 (calcd for $C_{15}H_{23}O_3$: 251.1647).



240

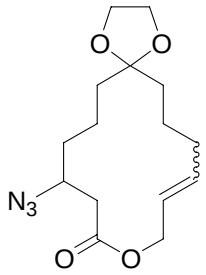
Allyl (±)-3-Azido-7-oxo-11-dodecenoate (**240**). The enoate **246** (250 mg, 1.0 mmol) was treated with a freshly prepared solution of hydrazoic acid (6.5 mL, 1.58 M in PhH, 10.3 mmol) followed by triethylamine (0.28 mL, ρ = 0.726, 203 mg, 2.0 mmol). The resulting solution was then heated to a gentle reflux and stirred under Ar for 27 h. After this time the mixture was allowed to cool and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 1:4 Et_2O:hexanes) to afford the alkyl azide **240** (249 mg, 0.85 mmol, 85%) as a colorless oil: IR (neat) 2934, 2103, 1732, 1713, 1371, 1271, 989, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40-1.80 (m, 6H), 2.05 (qm, *J* = 7 Hz, 2H), 2.40 (t, *J* = 7 Hz, 2H), 2.43 (t, *J* = 7 Hz, 2H), 2.53 (d, *J* = 7 Hz, 2H), 3.80 (quintet, *J* = 7 Hz, 1H), 4.62 (dt, *J* = 6, 1 Hz, 2H), 4.97 (dq, *J* = 10, 2 Hz, 1H), 5.00 (dq, *J* = 17, 2 Hz, 1H), 5.25 (dq, *J* = 10, 1 Hz, 1H), 5.33 (dq, *J* = 17, 1 Hz, 1H), 5.75 (ddt, *J* = 17, 10, 7 Hz, 1H), 5.91 (ddt, *J* = 17, 10, 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 22.8, 33.1, 33.8, 39.4, 42.0 (2C), 58.9, 65.6, 115.3, 118.7, 131.8, 137.9, 170.3; MS (CI) *m/z* 294, 266, 208, 168, 154; HRMS (CI) *m/z* 294.1818 (calcd for $C_{15}H_{24}N_3O_3$: 294.1818).



247

Allyl (±)-3-Azido-6-(2-pent-4-enyl[1,3]dioxolan-2-yl)hexanoate (**247**)**.** A solution of the ketone (564 mg, 1.92 mmol) and bis(trimethylsilyl)ethylene glycol (0.94 mL, 791 mg, 3.83 mmol) in anhydrous CH_2Cl_2 (2 mL) at –78°C under Ar, was treated with trimethylsilyl triflate (35 μL, 43 mg, 0.19 mmol). After stirring for 20 min the solution was allowed to warm to rt and then quenched 35 min later by the addition of pyridine (1 mL). The mixture was then diluted with CH_2Cl_2 (20 mL) and shaken with sat. $NaHCO_{3(aq)}$ (20 mL). The layers were separated and the aqueous phase extracted (2x10 mL CH_2Cl_2). The combined organic fractions were then washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 1:3 Et_2O:hexane) to yield **247** (640 mg, 1.90 mmol, 99%) as a colorless oil: IR (neat) 2945, 2100, 1736, 1639, 1462, 1375, 1272, 1166, 1069, 992, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30-1.70 (m, 10H), 2.04 (qt, *J* = 7, 1 Hz, 2H), 2.51 (d, *J* = 7 Hz, 2H), 3.78 (q, *J* = 7 Hz, 1H), 3.91 (s, 4H), 4.60 (dt, *J* = 6, 1 Hz, 2H), 4.93 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.99 (dq, *J* = 17, 2 Hz, 1H), 5.24 (dq, *J* = 10, 1 Hz, 1H), 5.32 (dq, *J* = 17, 1 Hz, 1H), 5.78 (ddt, *J* = 17, 10, 7 Hz, 1H), 5.91 (ddt, *J* = 17, 10, 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 23.1, 33.8, 34.5, 36.6, 36.6, 39.5, 59.1, 64.9 (2C), 65.5, 111.3, 114.7, 118.6, 131.8, 138.5, 170.3; MS

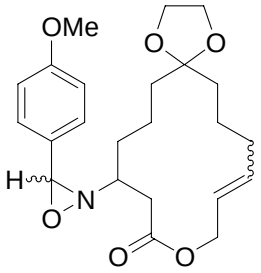
(FAB) *m/z* 338, 336, 310, 268, 240, 141; HRMS (FAB) *m/z* 338.2074 (calcd for $C_{17}H_{28}N_3O_4$: 338.2080).



248

(*E*, ±)-9-Azido-1,4,12-trioxaspiro[4.13]octadec-14-en-11-one (**248**)**.** A stirred solution of **247** (27 mg, 80 μmol) in anhydrous CH_2Cl_2 (8 mL) at rt under Ar, was treated with a portion of bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (7 mg, 8.5 μmol) followed by another such addition after 4 h. After stirring for an additional 19 h the solvent was removed *in vacuo.* The resulting black residue was further purified *via* column chromatography (eluting with CH_2Cl_2) to yield, in order of elution, unreacted starting material (11.0 mg, 33 μmol, 41%) and the desired lactone as an inseparable mixture of isomers **248** (5.2 mg, 17 μmol, 21%), both as colorless oils: IR (neat) 2924, 2092, 1733, 1462, 1376, 1260, 1168, 1063, 971 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *E:Z* = 4:1 δ 1.20-1.70 (m, $10H_{E+Z}$), 2.00-2.20 (m, $2H_{E+Z}$), 2.43 (dd, *J* = 15, 11 Hz, $1H_E$), 2.46 (dd, *J* = 14, 11 Hz, $1H_Z$), 2.70 (dd, *J* = 15, 4 Hz, $1H_E$), 2.71 (dd, *J* = 14, 4 Hz, H_Z), 3.78 (dtd, *J* = 10, 6, 4 Hz, $1H_{E+Z}$), 3.88 (s, $4H_{E+Z}$), 4.44 (ddd, *J* = 12, 6, 1 Hz, $1H_E$), 4.45-4.53 (m, $1H_Z$), 4.59-4.66 (m, $1H_Z$), 4.68 (dd, *J* = 12, 7 Hz, $1H_E$), 5.64 (dddt, *J* = 15, 7, 6, 1 Hz, $1H_E$), 5.72-5.86 (m, $1H_E$+$2H_Z$); ^{13}C NMR (75 MHz, $CDCl_3$) *E*-isomer δ 20.8, 21.9, 30.6, 32.9, 33.1, 35.2, 38.8, 58.9, 64.1, 64.5, 64.6, 111.7, 125.8, 138.3, 169.6, *Z*-isomer δ 19.7, 21.8, 26.7, 33.0, 34.4,

35.0, 39.5, 58.3, 59.9, 64.7, 64.8, 111.9, 122.9, 138.2, 170.0; MS (CI) *m/z* 267 (M-N_3)$^+$, 141, 99; HRMS (CI) *m/z* 308.1608 (calcd for $C_{15}H_{22}N_3O_4$: 308.1610).



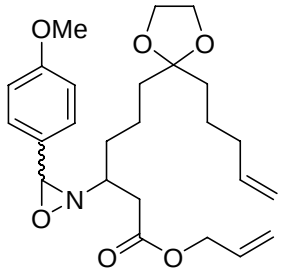
239

(*E*,±)-9-[3-(4-Methoxyphenyl)oxaziridin-2-yl]-1,4,12-trioxaspiro[4.13]octadec-14-en-11-one (**239**)**.** A solution of **248** (10.7 mg, 34.6 μmol, *E:Z* ~ 4:1) in anhydrous THF (0.5 mL) at rt under Ar, was treated with triphenylphosphine (9.2 mg, 35.1 μmol) and the resulting mixture heated to reflux and stirred for 23 h. After this time *p*-anisaldehyde (4.3 μL, 4.8 mg, 35.4 μmol) was added and reflux continued for 35 h. The reaction mixture was then allowed to cool to rt and stirred for 14 h before being further cooled to –78°C and treated with a solution of dried 3-chloroperoxybenzoic acid (9.3 mg, 85 wt% 3-chlorobenzoic acid, 46 μmol) in anhydrous CH_2Cl_2 (0.5 mL). The mixture was allowed to warm to rt over 1.5 h and then quenched by the addition of sat. $Na_2S_2O_{3(aq)}$ (3 mL) and stirred vigorously for 10 min. After dilution with CH_2Cl_2 (5 mL), 10% $Na_2CO_{3(aq)}$ (5 mL) was added and the layers well shaken and then separated. The aqueous phase was then extracted CH_2Cl_2 (2x5 mL) and the combined organic fractions dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 3:7 EtOAc:hexanes) to yield the oxaziridine product (11.4 mg, 27.3 μmol, 79%, colorless oil) as a mixture of isomers **239** (dr (oxaziridine) = 59:41, *E:Z* ~ 4:1).

Diastereoisomers resulting from oxaziridine stereogenicity could be separated by careful column chromatography (eluting with 1:1 Et_2O:hexanes) but olefinic mixtures could not be resolved (*E:Z* ~ 4:1).

Minor oxaziridine isomers **239** (less polar): IR (neat) 2919, 1738, 1620, 1516, 1459, 1376, 1254, 1167, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *E*-isomer δ 1.30-1.90 (m, 10H), 2.00-2.10 (m, 2H), 2.42-2.56 (m, 2H), 2.57-2.67 (m, 1H), 3.80 (s, 3H), 3.89-3.91 (m, 4H), 4.29 (ddm, *J* = 12, 6 Hz, 1H), 4.53 (s, 1H), 4.85 (dd, *J* = 12, 7 Hz, 1H), 5.65 (dddt, *J* = 15, 7, 6, 1 Hz, 1H), 5.75-5.88 (m, 1H), 6.89 (d, *J* = 9 Hz, 2H), 7.33 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) *E*-isomer δ 20.8, 22.4, 30.5, 32.6, 33.6, 35.5, 36.9, 55.3, 64.0, 64.4 (2C), 68.3, 79.7, 111.9, 114.0 (2C), 125.8, 126.7, 128.9 (2C), 138.1, 161.1, 170.0; MS (FAB) *m/z* 418 $(M+H)^+$, 282, 217, 136; HRMS (FAB) *m/z* 418.2225 (calcd for $C_{23}H_{32}NO_6$: 418.2230).

Major oxaziridine isomers **239** (more polar): IR (neat) 2949, 1739, 1614, 1515, 1459, 1373, 1304, 1248, 1170, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *E*-isomer δ 1.30-1.70 (m, 10H), 2.00-2.20 (m, 2H), 2.55-2.67 (m, 2H), 2.87-2.97 (m, 1H), 3.81 (s, 3H), 3.85-3.90 (m, 4H), 4.42 (dd, *J* = 12, 5 Hz, 1H), 4.56 (s, 1H), 4.73 (dd, *J* = 12, 7 Hz, 1H), 5.67 (dddm, *J* = 16, 7, 6 Hz, 1H), 5.74-5.85 (m, 1H), 6.89 (d, *J* = 9 Hz, 2H), 7.33 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) *E*-isomer δ 21.6, 22.3, 30.6, 31.9, 33.0, 35.6, 39.1, 55.3, 63.8, 64.5 (2C), 68.7, 81.4, 111.8, 114.0 (2C), 126.1, 126.6, 129.0 (2C), 137.8, 161.1, 170.7; MS (FAB) *m/z* 418 $(M+H)^+$, 282, 154; HRMS (FAB) *m/z* 418.2232 (calcd for $C_{23}H_{32}NO_6$: 418.2230).

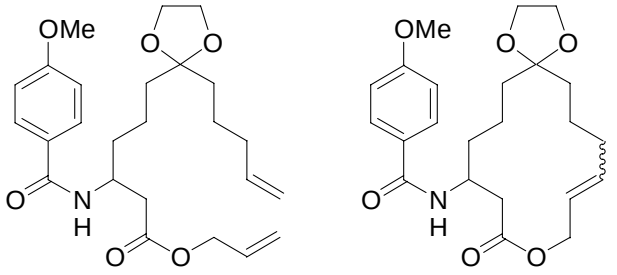


250

Allyl 3-[3-(4-Methoxyphenyl)oxaziridin-2-yl]-6-(2-pent-4-enyl[1,3]dioxolan-2-yl)hexanoate (**250**)**.** A stirred solution of **247** (50 mg, 0.15 mmol) in anhydrous THF (2 mL) at rt under Ar, was treated with triphenylphosphine (39 mg, 0.15 mmol) and the resulting solution heated to reflux and stirred for 24 h. After this time *p*-anisaldehyde (18 μL, 20 mg, 0.15 mmol) was added and heating continued for 32 h. The mixture was then allowed to cool and allowed to stir for 18 h at rt. Following this period the reaction was further cooled to –78 °C and then treated with a solution of dried 3-chloroperoxybenzoic acid (36 mg, 85 wt.%, 0.18 mmol) in anhydrous CH_2Cl_2 (1 mL). After 30 min the cooling bath was removed and the reaction allowed to warm to rt over 30 min. Saturated $Na_2S_2O_{3(aq)}$ (5 mL) was added and the mixture stirred vigorously for 5 min. Et_2O (10 mL) and 10% $Na_2CO_{3(aq)}$ (5 mL) were then added and the layers separated. The aqueous phase was extracted (5 mL, Et_2O) and the combined organic fractions washed with brine (5 mL), dried (Na_2SO_4) and then concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 2:3, 1:1 Et_2O in hexanes) to yield **250** as isomers (29 mg, 65 μmol, 43%, dr = 1:1) as a colorless oil. Diastereoisomers could be separated if desired by careful column chromatography (eluting with 30% Et_2O in hexanes).

Less polar isomer **250**: IR (neat) 2927, 1739, 1615, 1521, 1459, 1306, 1249, 1174, 1030, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.70 (m, 9H), 1.75-1.90 (m, 1H), 2.05 (qt, *J* = 7, 1 Hz, 2H), 2.57-2.70 (m, 3H), 3.80 (s, 3H), 3.93 (s, 4H), 4.44 (ddt, *J* = 13, 6, 1 Hz, 1H), 4.52 (ddt, *J* = 13, 6, 1 Hz, 1H), 4.72 (s, 1H), 4.95 (ddt, *J* = 10, 2, 1 Hz, 1H), 5.00 (dq, *J* = 17, 2 Hz, 1H), 5.16 (dq, *J* = 9, 1 Hz, 1H), 5.21 (dq, *J* = 17, 2 Hz, 1H), 5.70-5.87 (m, 2H), 6.87 (d, *J* = 9 Hz, 2H), 7.32 (d, *J* = 9 Hz, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 23.1, 33.9, 34.3, 36.6, 36.7, 37.1, 55.3, 65.0, 65.5 (2C), 66.7, 80.5, 111.5, 113.8 (2C), 114.6, 118.6, 126.9, 128.9 (2C), 131.7, 138.7, 160.9, 171.0; MS (FAB) *m/z* 446 $(M+H)^+$, 402, 307, 273, 250, 154; HRMS (FAB) *m/z* 446.2537 (calcd for $C_{25}H_{36}NO_6$: 446.2543).

More polar isomer **250**: IR (neat) 2945, 1733, 1613, 1511, 1463, 1378, 1305, 1245, 1168, 1035, 907 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30-1.64 (m, 10H), 1.96 (q, *J* = 7, 2H), 2.58 (dd, *J* = 14, 8 Hz, 1H), 2.59-2.70 (m, 1H), 2.87 (dd, *J* = 14, 4 Hz, 1H), 3.80 (s, 3H), 3.80-3.90 (m, 4H), 4.56 (s, 1H), 4.61 (dm, *J* = 6 Hz, 2H), 4.91 (ddt, *J* = 9, 2, 1 Hz, 1H), 4.96 (dq, *J* = 16, 2 Hz, 1H), 5.24 (dq, *J* = 10, 1 Hz, 1H), 5.34 (dq, *J* = 17, 1 Hz, 1H), 5.73 (ddt, *J* = 17, 10, 7 Hz, 1H), 5.94 (ddt, *J* = 17, 11, 6 Hz, 1H), 6.88 (d, *J* = 9 Hz, 2H), 7.33 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 23.1, 32.5, 33.8, 36.7, 36.9, 39.3, 55.3, 64.9 (2C), 65.3, 67.6, 81.3, 111.3, 113.9 (2C), 114.6, 118.3, 126.4, 128.9 (2C), 132.1, 138.5, 161.1, 171.2; MS (FAB) *m/z* 446 $(M+H)^+$, 402, 310, 250; HRMS (FAB) *m/z* 446.2539 (calcd for $C_{25}H_{36}NO_6$: 446.2543).



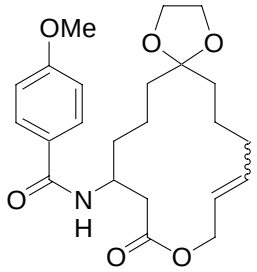
251 **252**

***N*-(11-Oxo-1,4,12-trioxaoxospiro[4.13]octadec-14-en-9-yl)-4-methoxybenzamide (252).** Bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (3 mg, 3.6 μmol) was added to a stirred solution of **250** (16 mg, 36 μmol) in CH_2Cl_2 (7 mL) at rt under Ar. The initially purple mixture gradually turned a muddy brown and then black. After 22 h the solvent was removed *in vacuo* and the residue further purified *via* column chromatography (eluting with 4:6, 6:4 EtOAc:hexanes) to yield in order of elution: *p*-anisaldehyde (2.1 mg, 15 μmol, 43%), **251** (1.1 mg, 2.5 μmol, 7%) and then **252** (5.4 mg, 13 μmol, 36%) as an inseparable mixture of olefin isomers.

Amidodiene **251**: IR (neat) 3314, 2945, 1735, 1629, 1609, 1539, 1502, 1303, 1256, 1180, 1034, 914, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35-1.50 (m, 4H), 1.52-1.80 (m, 6H), 2.02 (qt, *J* = 7, 1 Hz, 2H), 2.63 (dd, *J* = 16, 5 Hz, 1H), 2.71 (dd, *J* = 16, 5 Hz, 1H), 3.84 (s, 3H), 3.88-3.90 (m, 4H), 4.38-4.48 (m, 1H), 4.59 (dq, *J* = 6, 1 Hz, 2H), 4.92 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.97 (dq, *J* = 17, 2 Hz, 1H), 5.24 (dq, *J* = 10, 1 Hz, 1H), 5.31 (dq, *J* = 17, 1 Hz, 1H), 5.76 (ddt, *J* = 17, 10, 7 Hz, 1H), 5.90 (ddt, *J* = 17, 10, 6 Hz, 1H), 6.77 (d, *J* = 9 Hz, 1H), 6.91 (d, *J* = 9 Hz, 2H), 7.73 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.1, 33.8, 34.2, 36.5, 36.7, 38.2, 46.2, 55.4, 64.9 (2C), 65.3, 111.4, 113.7 (2C), 114.6, 118.7, 126.9, 128.7 (2C), 131.8, 138.6,

162.1, 166.2, 171.9; MS (CI) *m/z* 446 $(M+H)^+$, 400, 376, 277, 141; HRMS (CI) *m/z* (calcd for calcd for $C_{25}H_{36}NO_6$: 446.2543).

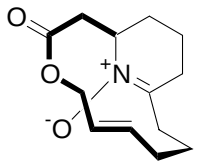
Amidolactone **252**: IR (neat) 3338, 2920, 1731, 1633, 1604, 1541, 1505, 1455, 1308, 1255, 1176, 1027, 974, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *E:Z* = 80:20, *E*-isomer δ 1.30-1.80 (m, 9H), 1.93-2.40 (m, 3H), 2.59 (dd, *J* = 16, 5 Hz, 1H), 2.69 (dd, *J* = 16, 4 Hz, 1H), 3.84 (s, 3H), 3.86-3.90 (m, 4H), 4.18 (dd, *J* = 12, 6 Hz, 1H), 4.35-4.45 (m, 1H), 5.02 (dd, *J* = 12, 7 Hz, 1H), 5.69 (dtm, *J* = 15, 7 Hz, 1H), 5.85 (dt, *J* = 15, 7 Hz, 1H), 6.91 (d, *J* = 9 Hz, 2H), 7.15-7.30 (obscured, 1H), 7.76 (d, *J* = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) *E*-isomer δ 21.3, 22.2, 30.5, 32.6, 33.3, 35.3, 36.6, 46.3, 55.4, 63.8, 64.4, 64.6, 111.8, 113.7 (2C), 126.0, 126.8, 128.7 (2C), 138.3, 162.1, 165.8, 172.2; MS (FAB) *m/z* 418 $(M+H)^+$, 307, 289, 135; HRMS (FAB) *m/z* 418.2221 (calcd for $C_{23}H_{32}NO_6$: 418.2230).



252

***N*-(11-Oxo-1,4,12-trioxaoxospiro[4.13]octadec-14-en-9-yl)-4-methoxybenzamide (252).** Bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (1 mg, 1.2 μmol) was added to a stirred solution of **251** (8.0 mg, 18 μmol) in CH_2Cl_2 (4 mL) at rt under Ar. After stirring for 6 h the mixture was concentrated *in vacuo* and the resulting residue further purified *via* column chromatography (eluting with 60%

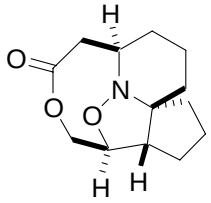
EtOAc in hexanes) to yield **252** (7.1 mg, 17 μmol, 95%) as an inseparable mixture of olefin isomers. ^{1}H NMR analysis indicated *E:Z* = 86:14 and that the product was identical to that previously obtained from the oxaziridinyldiene.



238

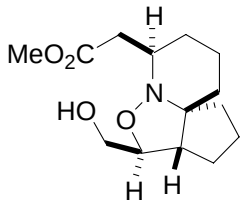
(*E*,±)-15-Oxy-4-oxa-15-azabicyclo[9.3.1]pentadeca-6,11(15)-dien-3-one (**238**)**.** A stirred solution of **239** (3.5 mg, 8.4 μmol, *E:Z* ~ 4:1) in MeOH-H_2O (5:1, 1.2 mL) was treated with 4-methylphenylsulfonic acid monohydrate (0.6 mg, 3 μmol) and then heated to a gentle reflux and stirred for 6 h. After this time the mixture was allowed to cool, diluted with CH_2Cl_2 (5 mL) and shaken with sat. $NaHCO_{3(aq)}$ (5 mL). The layers were separated and then the aqueous phase extracted (2x5 mL CH_2Cl_2). The combined organic fractions were then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with 1:20 MeOH:CH_2Cl_2) to yield **238** (1.4 mg, 5.9 μmol, 70%) as a colorless oil. Repeated careful chromatography (5% MeOH in CH_2Cl_2) yields material with good isomeric purity (*E:Z* ≥ 92:8): IR (neat) 2921, 1729, 1591, 1462, 1370, 1250, 1195, 1144, 969 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *E:Z* = 4:1, δ 1.44-1.63 (m, 2H), 1.82-1.95 (m, 2H), 1.96-2.08 (m, 4H), 2.19-2.30 (m, 1H), 2.25 (dd, *J* = 14, 2 Hz, 1H), 2.32-2.44 (m, 1H), 2.57 (tdd, *J* = 14, 11, 4 Hz, 1H), 3.44 (ddd, *J* = 16, 12, 1 Hz, 1H), 3.54 (dd, *J* = 14, 6 Hz, 1H), 4.03-4.14 (m, 1H), 4.43 (dd, *J* = 12, 7 Hz, 1H), 4.60 (dd, *J* = 11, 3 Hz, 1H), 5.72-5.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 23.3, 28.4, 28.9, 30.3, 33.1, 35.9,

63.0, 64.3, 125.2, 135.6, 151.2, 170.4; MS (FAB) *m/z* 238 $(M+H)^+$, 154, 136; HRMS (FAB) *m/z* 238.1439 (calcd for $C_{13}H_{20}NO_3$: 238.1443).



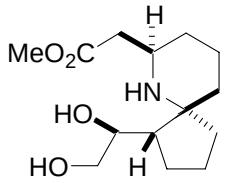
254

Transannular Cycloadduct (**254**). A solution of **238** (10.4 mg, *E:Z* = 92:8, 40 μmol) in toluene (2 mL) under Ar was heated to reflux and stirred for 2 h. After this time the mixture was allowed to cool and concentrated *in vacuo.* The residue was then further purified *via* column chromatography (eluting with 9:1 EtOAc:hexanes) to yield the isomerically pure **254** (6.1 mg, 26 μmol, 64%) as a colorless crystalline solid: mp 105-108 °C (CH_2Cl_2); IR (neat) 2914, 1732, 1453, 1294, 1143, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) dr = 88:12 δ 1.40-2.10 (m, 12H), 2.44 (dm, *J* = 13 Hz, 1H), 2.52 (ddd, *J* = 6, 4, 2 Hz, 1H), 2.64 (dd, *J* = 13, 10 Hz, 1H), 4.05 (ddd, *J* = 7, 6, 4 Hz, 1H), 4.19-4.25 (obscured, 1H), 4.21 (dd, *J* = 13, 7 Hz, 1H), 4.55 (dd, *J* = 13, 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 22.8, 27.8, 31.2, 33.2, 35.9, 42.8, 55.8, 60.5, 70.6, 75.1, 84.9, 175.9; MS (FAB) *m/z* 238 $(M+H)^+$, 217, 139; HRMS (FAB) *m/z* 238.1440 (calcd for $C_{13}H_{20}NO_3$: 238.1443).



255

Methyl (4-Hydroxymethyloctahydrocyclopenta[3,4]isoxazolo[2,3-*a*]pyrindin-7-yl)acetate (**255**)**.** A solution of **254** (3.4 mg, 14.3 μmol) in MeOH (2 mL) was treated with K_2CO_3 (2 mg, 14.4 μmol) and the resulting suspension heated to a gentle reflux and stirred for 3 h. After this time the mixture was allowed to cool to rt and partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated and then the aqueous phase extracted (2x5 mL CH_2Cl_2). The combined organic fractions were washed with brine (5 mL), dried (Na_2SO_4) and then concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 1:20 MeOH:CH_2Cl_2) to yield **255** (3.4 mg, 12.6 μmol, 88%) as a colorless oil: IR (neat) 3441, 2935, 2862, 1731, 1442, 1290, 1175, 1040, 879 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO, T = 60°C, one signal obscured by H_2O resonance) δ 1.20-1.50 (m, 6H), 1.50-1.90 (m, 6H), 2.10-2.17 (m, 1H), 2.37 (dd, *J* = 15, 8 Hz, 1H), 2.61 (dd, *J* = 15, 6 Hz, 1H), 3.40-3.50 (m, 3H), 3.59 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO, T = 60°C, four signals obscured by DMSO septet) δ 20.9, 25.5, 29.9, 50.8, 54.3, 57.0, 61.9, 73.5, 84.5, 171.5; MS (FAB) *m/z* 270 $(M+H)^+$, 196, 154, 136; HRMS (FAB) *m/z* 270.1707 (calcd for $C_{14}H_{24}NO_4$: 270.1705).



237

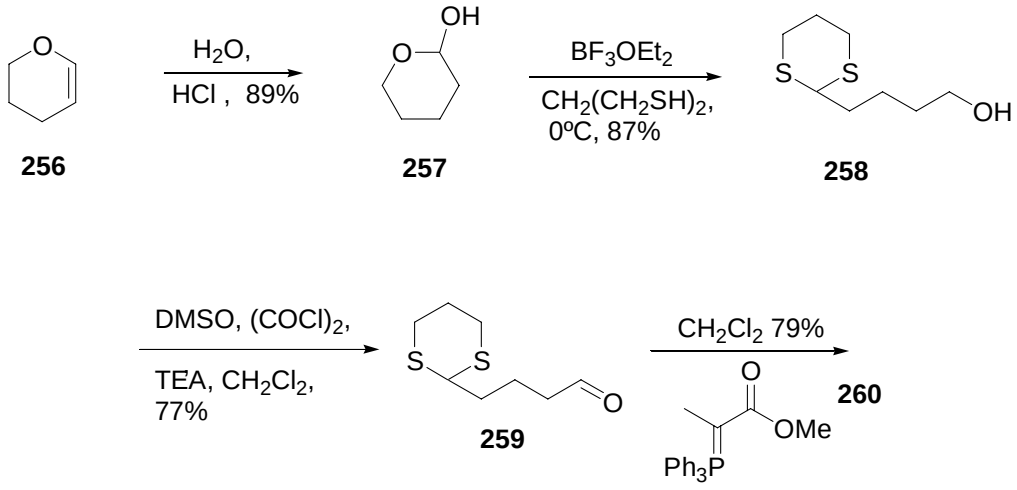
Methyl (±)-[(1*S,5*S**,7*R**)-1-[(1*S**)-1,2-Dihydroxyethyl]-6-azaspiro[4.5]dec-7-yl]acetate** (**237**)**. 255** (3.4 mg, 12.6 μmol) was treated with samarium (II) diiodide (4 mL, 0.1 M in THF, 0.4 mmol) and the resulting solution stirred at rt under Ar for 48

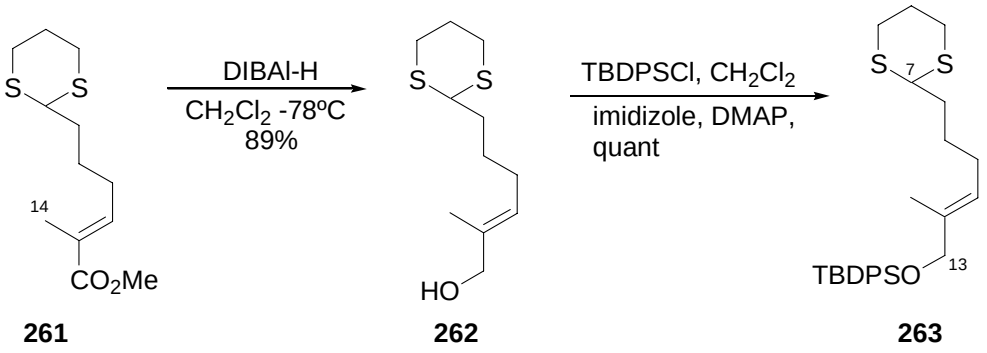
h. After this time the mixture was quenched with 5% w/v aq. $Na_2S_2O_3$ (5 mL) and stirred vigorously for 10 min. CH_2Cl_2 (10 mL) and sat. aq. $NaHCO_3$ (10 mL) were then added and the layers shaken and then separated. The aqueous phase was then extracted (3x5 mL CH_2Cl_2) and the combined organic fractions were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was then further purified *via* column chromatography (eluting with 1:20 MeOH:CH_2Cl_2) to yield **237** (2.2 mg, 8.1 μmol, 64%) as a colorless oil: IR (neat) 3315, 2939, 2860, 1729, 1602, 1440, 1381, 1290, 1215, 1171, 1072, 867, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35-2.00 (m, 13H), 2.71 (dd, *J* = 17, 6 Hz, 1H), 2.94 (ddm, *J* = 17, 5 Hz, 1H), 3.21-3.31 (m, 1H), 3.46 (dd, *J* = 11, 6 Hz, 1H), 3.70 (s, 3H), 3.76 (dd, *J* = 11, 3 Hz, 1H), 3.98 (ddd, *J* = 9, 6, 3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 24.4, 28.9, 29.4, 35.3, 36.4, 38.3, 49.6, 51.7, 52.0, 65.9, 66.4, 72.9, 172.1; MS (CI) *m/z* 272 $(M+H)^+$, 240; HRMS (CI) *m/z* 272.1857 (calcd for $C_{14}H_{26}NO_4$: 272.1862).

CHAPTER 3. ALTERNATIVE RACEMIC MACROLACTONIZATION AND ASYMMETRIC INDUCTION AT C_3

3.1 AN ALTERNATIVE ROUTE TO RACEMIC MACROLACTONE 274

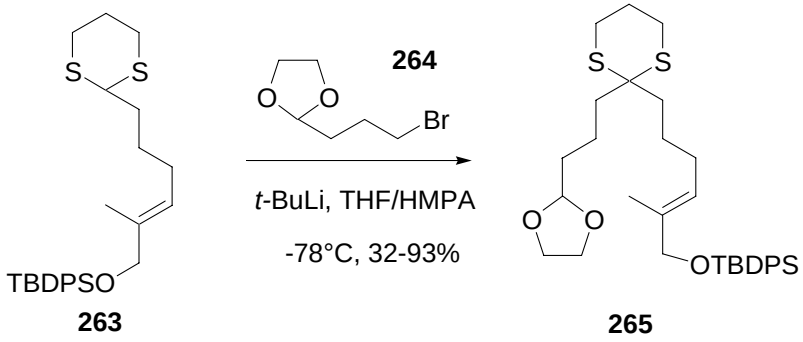
To improve on the formation of the 14-membered lactone a second generation synthesis was undertaken. We decided to incorporate the C_{14} methyl group at an early stage in order to probe its influence on the TANCA. Commercially available 2,3-dihydropyran (**256**) was transformed under literature conditions to dithiane **259**[70] (Scheme 59). Swern oxidation of alcohol **258** formed aldehyde **259**, and this was followed by homologation with ylide **260** to yield α, β-unsaturated ester **261**. Ester reduction to alcohol **262** was followed by silylation to afford dithiane **263**.

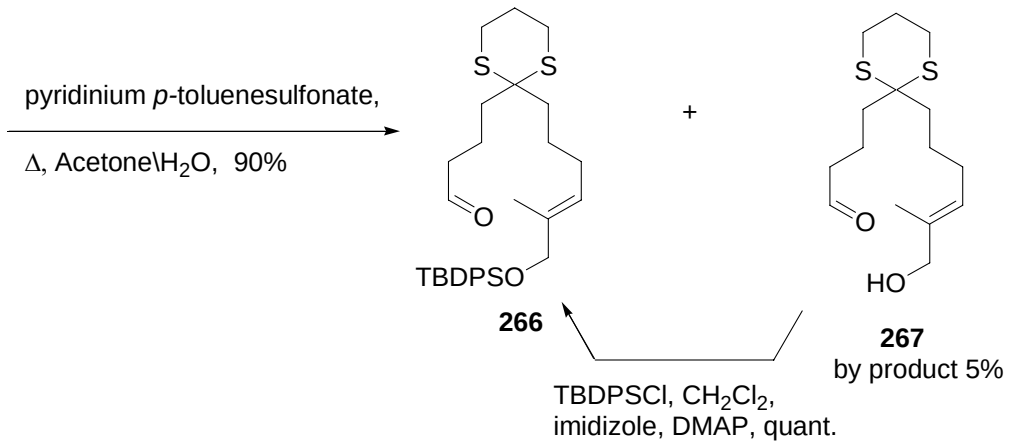




Scheme 59. Synthesis of the C_7-C_{13} subunit.

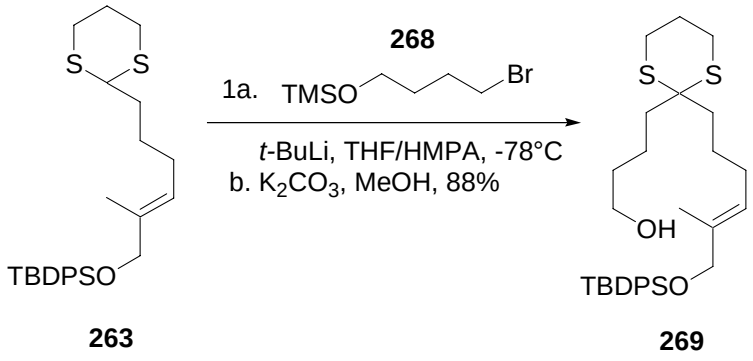
Our first alkylation attempts on dithiane **263** used known bromide **264**[71] and gave acetal **265** in modest, but highly inconsistent yields (Scheme 60). The acetal **265** was hydrolyzed with aqueous acid to give aldehyde **266**. The drawback to this approach is the three step procedure required for the preparation of **264.** Also, the sluggish deprotection of the acetal required many days to achieve an acceptable yield. A small amount of silyl cleavage product, alcohol **267**, was also isolated after longer reaction times, but **267** could easily be converted back to **266** *via* a resilylation.

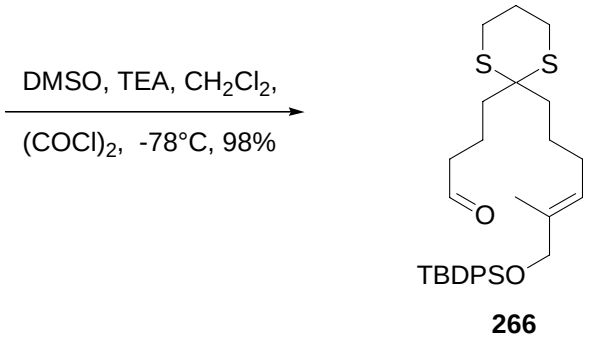




Scheme 60. Initial dithiane alkylation

A more efficient way to synthesize **266** proved to be alkylation of **263** with known bromide **268**.[72] The latter required only one step for its preparation. A mild alkaline workup to hydrolyze the trimethylsilyl ether following the alkylation yielded alcohol **269** (Scheme 61). Final Swern oxidation of alcohol **269** yielded aldehyde **266** uneventfully.

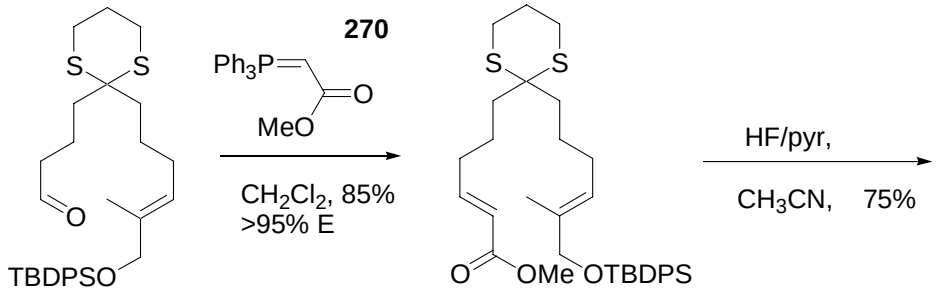




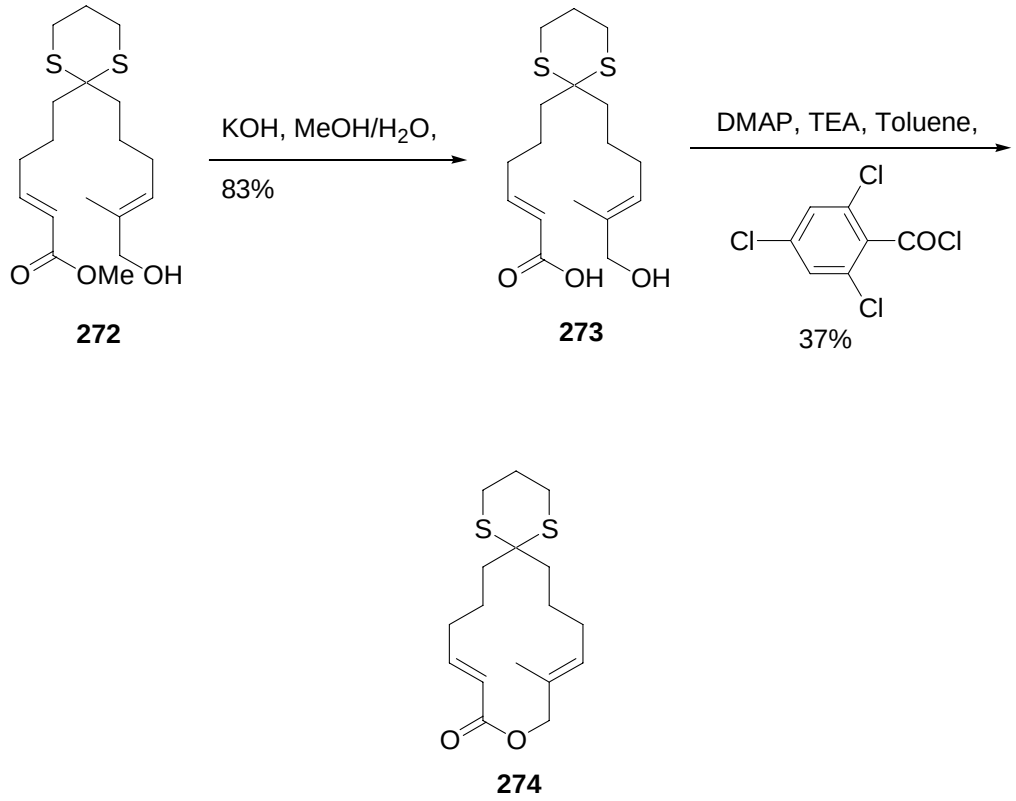
266

Scheme 61. Improved alkylation of dithiane **263**

Wittig olefination of **266** with stabilized ylide **270** was followed by saponification and silyl deprotection to afford hydroxy acid **273** (Scheme 62). Macrolactonization of **273** using Yamaguchi's conditions[73] provided macrolactone **274** whose structure was confirmed by X-ray analysis (Figure 3). In view of the modest yield of **274** an alternative macrolactonization of **273** was investigated using the Keck-Steglich procedure[74] with dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine hydrochloride (DMAP HCl). However, no lactone was isolated from this reaction.



266 **271**



Scheme 62. Yamaguchi macrolactonization

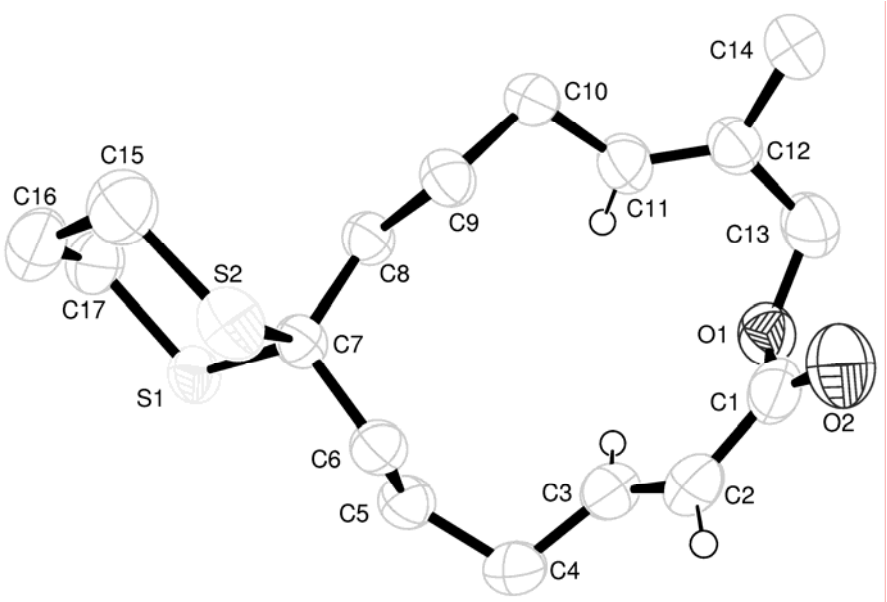
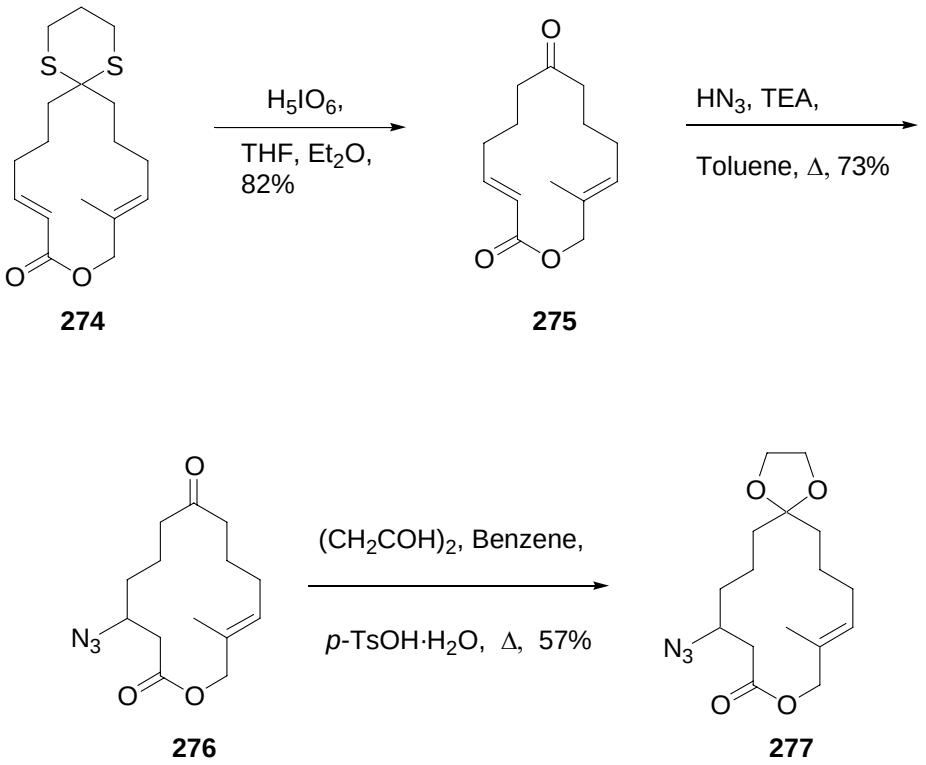


Figure 3. ORTEP diagram of **274**

Oxidative cleavage of the dithiane function in **274** with periodic acid[75] afforded ketone **275**. Conjugate addition of hydrazoic acid to **275** yielded azide **276**, and this was followed ketolization to form dioxolane **277**.



274 **275** **276** **277**

Scheme 63. Azide conjugate addition to lactone **275**.

At this juncture, a modest improvement had been made in the formation of the 14-membered lactone **277**, and we then turned our attention to incorporating the azide function in an asymmetric fashion.

3.2. JACOBSEN'S CATALYTIC CONJUGATE ADDITION OF AZIDE TO α, β-UNSATURATED IMIDES

Catalysts for asymmetric additions of nucleophiles to electrophiles have typically been designed employing Lewis acid activation of the electrophilic reacting partner (Figure 4, type 1).[76] In this way, cooperative activation of both reacting partners may lead to enhanced reactivity and more specific control of the transition structure with respect to the catalyst's asymmetric environment. This concept can be used to rationalize why two-metal ion catalysis is a common feature in enzyme-catalyzed reactions.[77] Dual activation with bimetallic systems has been established recently in small-molecule-catalyzed asymmetric reactions, with the identification of two additional classes of cooperative catalysis. Complexes of a single chiral ligand bearing two different metal ions have been developed by Shibasaki and co-workers.[78] In these catalysts, the M_1 (typically a lanthanide or main group metal) ion serves as a Lewis acid activator for the electrophile and the M_2 (typically an alkali metal ion) serves as a counterion to the nucleophile (type 2). Furthermore, several catalyst systems have been identified that promote addition reactions through dual activation of both substrates in nucleophile-electrophile additions by the same metal-ligand framework (type 3).[79] Catalyst oligomerization[80] strategies have provided a path to achieve type 3 systems with increased reactivity, but homobimetallic catalysis is inherently limited to systems in which the same metal-ligand complex is capable of activating both the electrophile and the nucleophile. Yet another approach in which two distinct chiral metal complexes act cooperatively in highly enantioselective conjugate additions (type 4)[69,81] has been investigated.

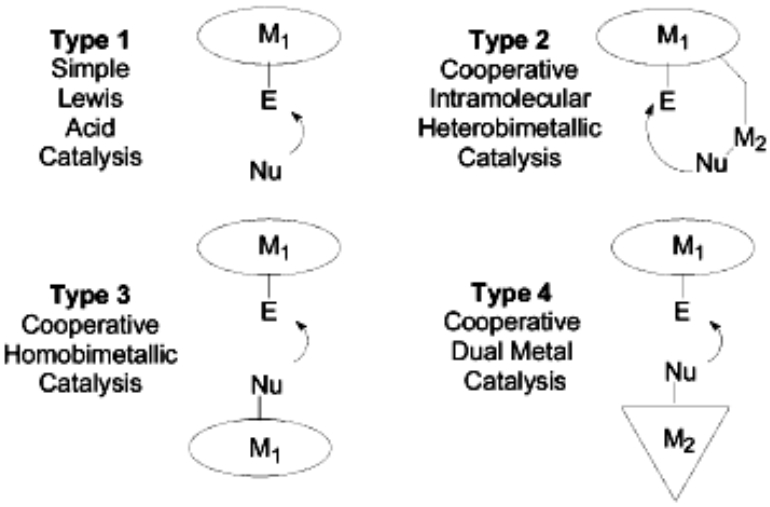
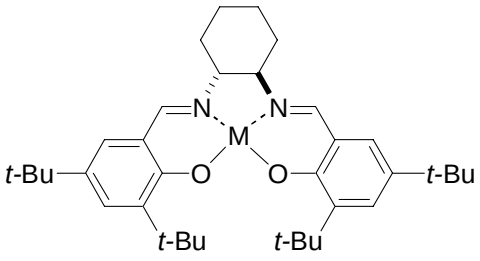


Figure 4. Approaches to the catalysis of nucleophile (Nu)- electrophile (E) reactions. Geometric shapes (ovals, triangle) symbolize chiral ligands.

Metal complexes of the salen ligand **278a** (Figure 5) have been effective for a wide variety of asymmetric nucleophilic-electrophilic reactions; including (a) opening of epoxides by azide,[82] water,[83] carboxylic acids,[84] and phenols,[85] (b) the addition of hydrogen cyanide to imines,[86] and (c) hetero-Diels-Alder reactions between electron-rich dienes and aldehydes.[87]

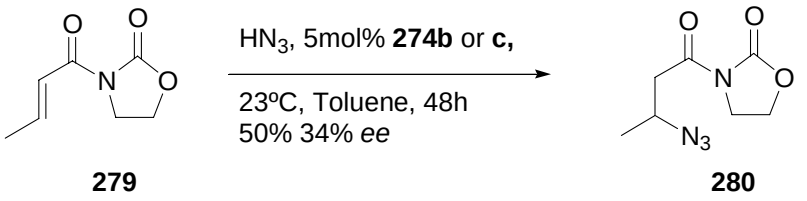


(*R*, *R*)-**278a** M= H, H
(*R*, *R*)-**278b** M= AlN_3
(*R*, *R*)-**278c** M= AlMe

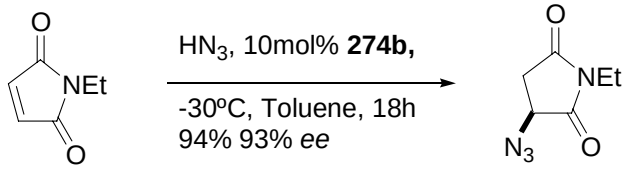
Figure 5. Salen complexes

Over the past several years Jacobsen has demonstrated the utility of the (salen)aluminum complexes **278b-c** as catalysts for the highly enantioselective

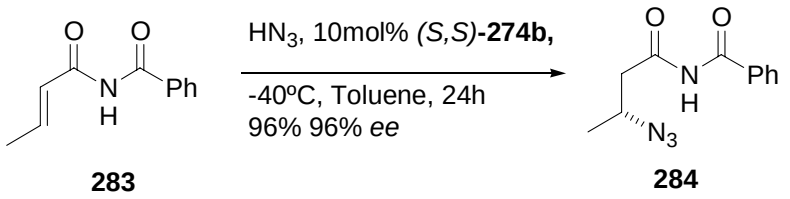
conjugate addition of a variety of weakly acidic nucleophiles including hydrazoic acid,[88] hydrogen cyanide,[89] malononitrile, substituted cyanoacetates,[90] and oximes.[91] Jacobsen's preliminary work with conjugate additions of hydrazoic acid to α,β-unsaturated systems has shown catalyst **278b** to be effective in the addition reaction, but it proved to have a short shelf life. A more stable catalyst **278c** could be conveniently generated *in situ* from **278b** and used effectively in its place. In early screenings, oxazolidinone **279** with either **278b** or **278c** was used to generate azide **280** in modest yield and facial selectivity (Scheme 64). With these encouraging results, a wide variety of easily accessible conjugate acceptors for asymmetric addition of azide were further screened. Of these, *N*-alkylmaleimide **281** displayed both excellent reactivity and enantioselectivity in the conjugate addition to form azide **282**. These conjugate addition reactions appeared to work best if the α,β-unsaturated olefin is conjugated to an imide derivative. Thus, the unsaturated imide function present in **283** formed azide **284** with outstanding yield and stereocontrol.



279 **280**



281 **282**



Scheme 64. Hydrazoic acid addition to α,β-unsaturated systems.

The rationale for the stereochemical outcome of addition is a cooperative homobimetallic catalysis of type 3 (Figure 4) with one of the salen ligands complexed to the azide and a second salen ligand complexed to the α,β-unsaturated imide (Figure 6).[81,92] Our interest in these results led us to apply Jacobsen conjugate addition of hydrazoic acid to our substrate in order to introduce nitrogen functionality in a highly enantioselective fashion.

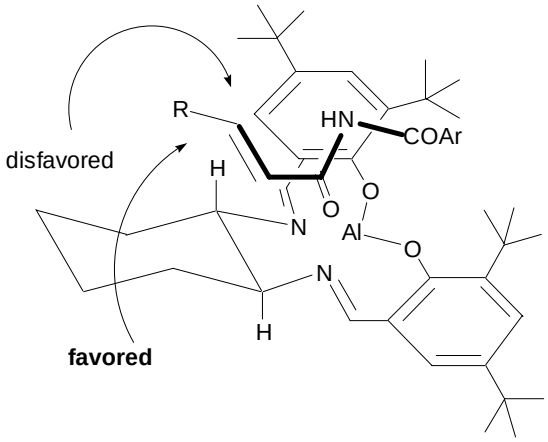
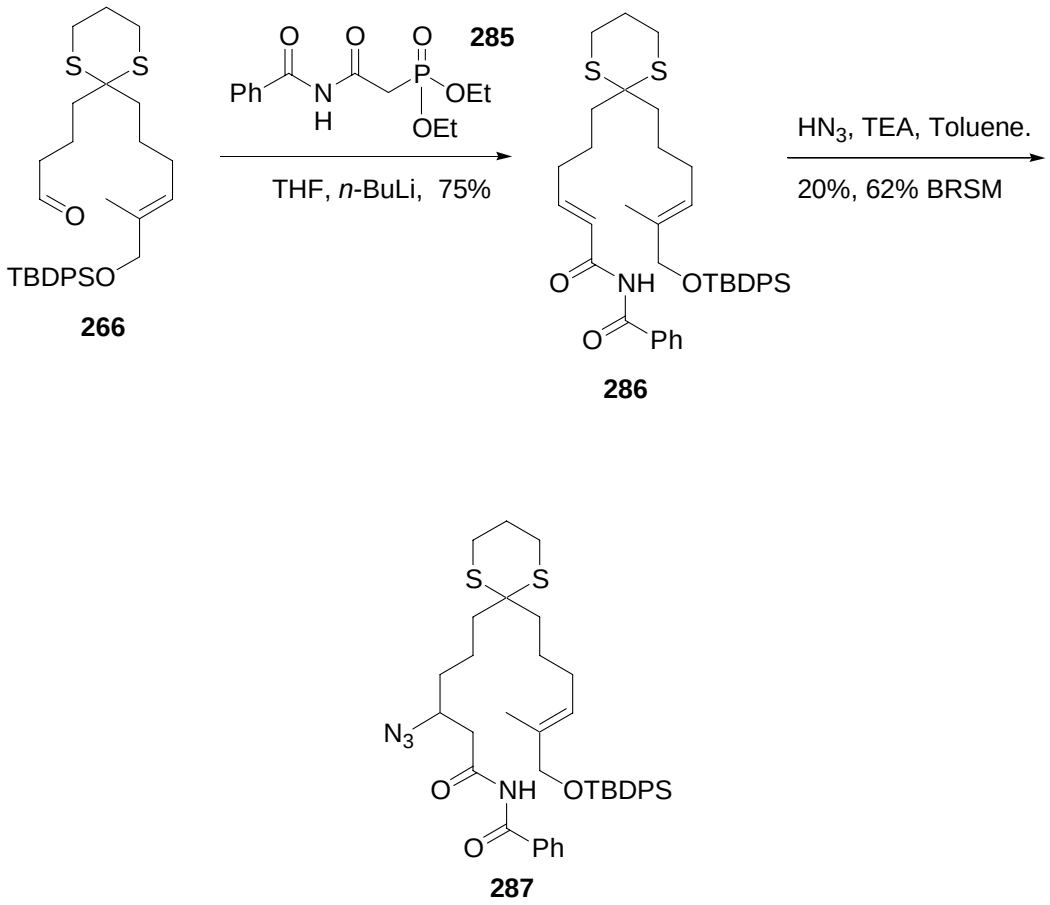


Figure 6. The proposed complex of an α,β-unsaturated imide with Jacobsen's (salen)aluminum system.

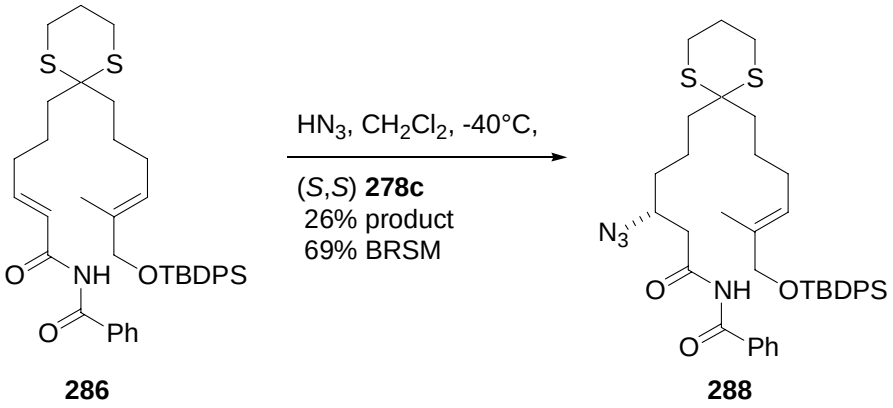
3.3. ASYMMETRIC AZIDE ADDITON

In order to use the methodology pioneered by Jacobsen, aldehyde **266** was first converted to imide **286** via a Horner-Emmons-Wadsworth reaction with phosphonate **285** (Scheme 65). When **286** was treated with hydrazoic acid in the presence of triethylamine it gave racemic azide **287** in low yield with recovery of starting material.

To incorporate the azide function asymmetrically salen catalyst (***S***,***S***)-**278c** was used with hydrazoic acid and **286** (Scheme 66)**.** Azide **287** was produced in modest yield again with recovery of starting material. The need for improvement of the yield of the conjugate addition led us to replace the dithiane function with a different ketone surrogate. The low yields could be rationalized by the dithiane function binding to the salen catalyst or/and the α,β-unsaturated imide might not be in complete conjugation.

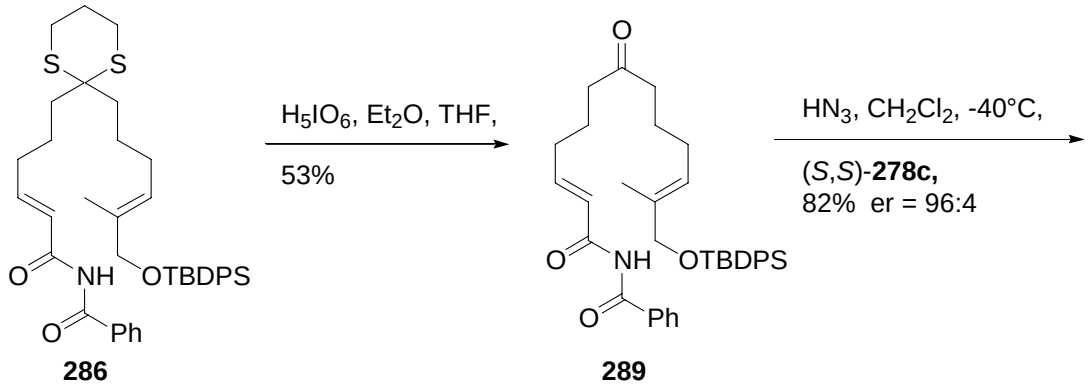


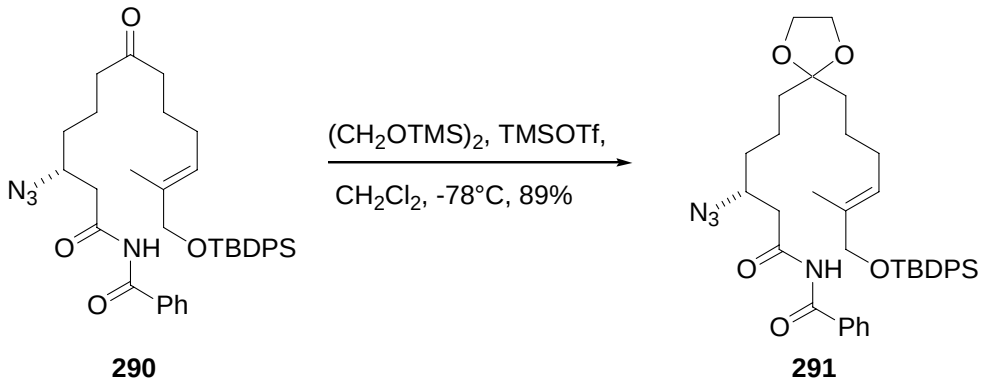
Scheme 65. Racemic azide addition



Scheme 66. Initial asymmetric azide addition.

Removal of the dithiane from **286** with periodic acid led to ketone **289**. Upon treatment with hydrazoic acid and (***S***,***S***)-**278c** catalyst, **289** gave the conjugate addition product, azide **290**, in high yield and with excellent enantiomeric excess (Scheme 67). The enantiomeric ratio of **290** was determined using a chiral column (OD) and high pressure liquid chromatography (HPLC). Protection of the ketone using Noyori's protocol[63] provided dioxolane **291**. The improved yield of the conjugate addition of hydrazoic acid to **288** confirmed that the disappointing result with **286** was due to the dithiane moiety.



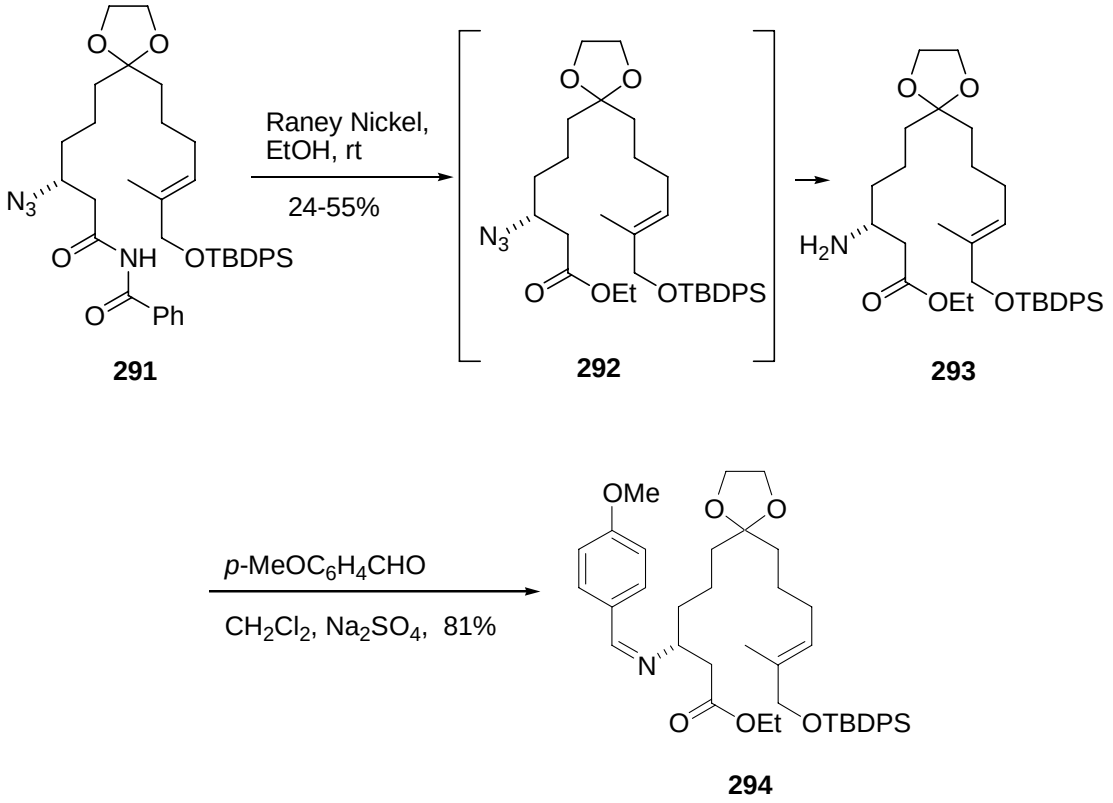


290 **291**

Scheme 67. Improved azide addition.

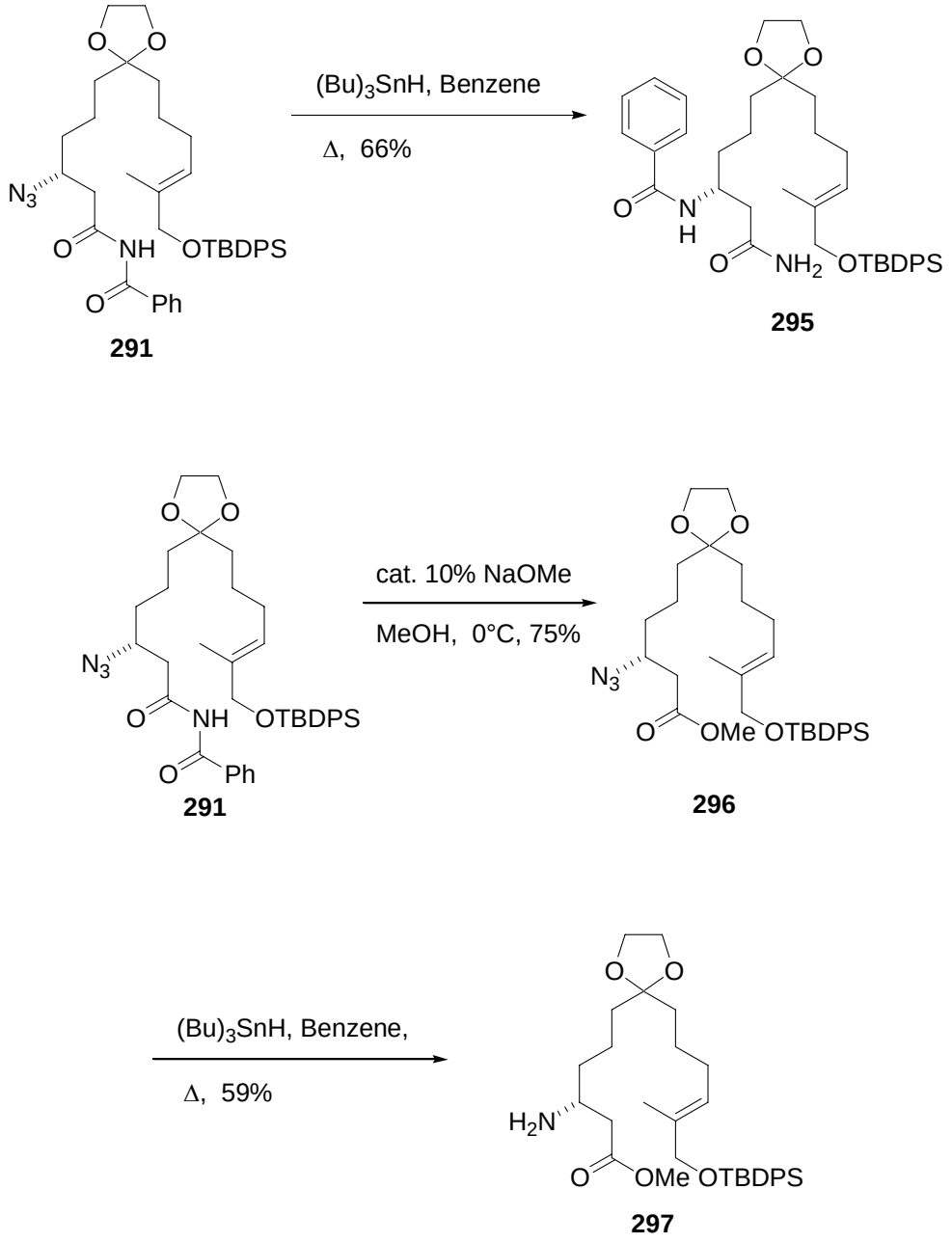
With incorporation of the asymmetric nitrogen function now realized, we moved on to explore the intramolecular [3+2] nitrone cycloaddition envisioned in our retrosynthetic scheme. Our task therefore became to convert azide **291** to the nitrone **300**.

Attempted reduction of azide **291** under Staudinger conditions proved to be an ineffective means for this transformation and we turned to hydrogenation with Raney-nickel[93] complex for this conversion. During reduction of **291**, in ethanol, it was found that ethanolysis of the imide had occurred first to ester **292** through its isolation before the reduction occurred to amine **293.** The reduction also occurred with inconsistent yields (Scheme 68). Although, ethanolysis of imide **291** was inconsequential, it was rationalized that the mildly alkaline reduction conditions facilitate cleavage of the imide due to the presence of ethoxide. The amine **293** was treated with *p*-anisaldehyde to form imine **294** in good yield but, due to the inconsistent yields from the Raney-nickel reduction of **291**, we decided to look elsewhere for a more efficient reagent for the reduction.



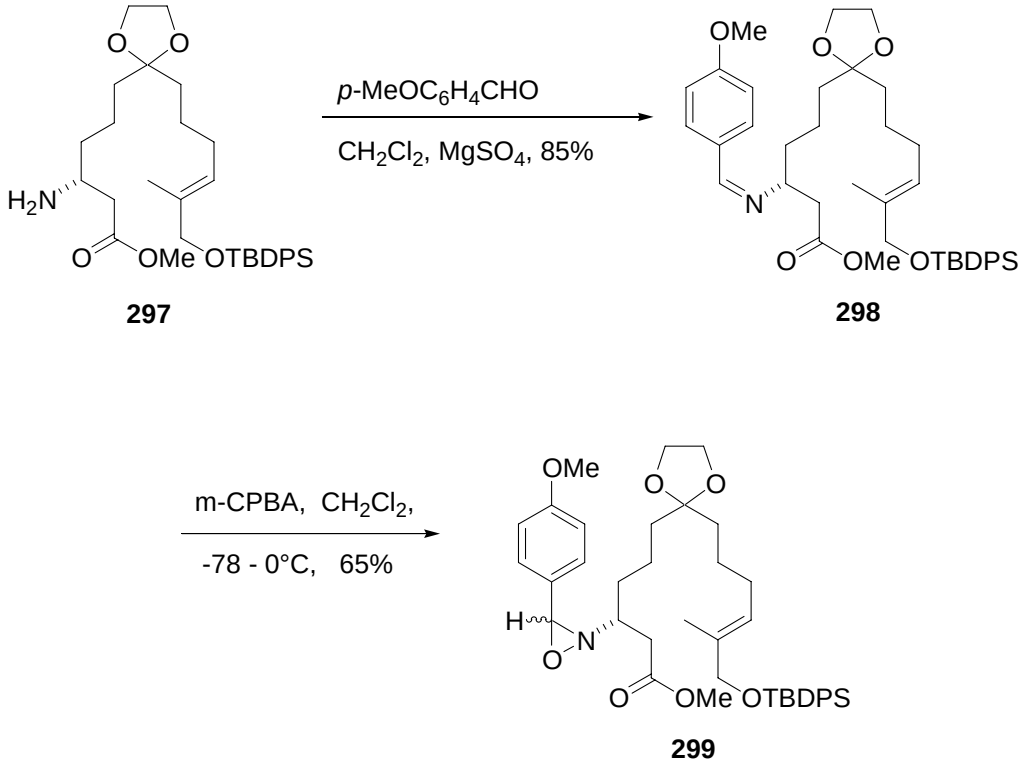
Scheme 68. Reduction with W2 Raney-nickel.

Reduction of **291** with tributyltin hydride gave diamide **295** as the only isolated product (Scheme 69). This can be rationalized by the newly formed amine nucleophilically attacking the benzamide carbonyl and displacing the imide nitrogen leading to the diamide. With this unexpected result, we clearly saw the need to remove the imide function immediately after the acetalization step. The results from the Raney-nickel experiments provided an advantageous way to cleave the imide to an ester in mildly alkaline conditions. With this in mind, compound **291** and catalytic 10% sodium methoxide in methanol cleaved the imide to methyl ester **296**. Reduction of the azide with tributyltin hydride[94] proceeded as expected to form amine **297**.



Scheme 69. Azide reduction with tributyltin hydride

Amine **297** was treated with *p*-anisaldehyde to form imine **298** (Scheme 70). The imine was oxidized using Holmes' chemistry[65] to form oxaziridine **299** with no oxidation of the trisubstituted olefin in **298**.



Scheme 70. Oxaziridine formation

The oxaziridine now stood ready to be converted to nitrone **300**. The nitrone **300** bearing one stereocenter could produce two diastereomeric cycloadducts **301** and **302** respectively (Figure 7). The oxaziridine **299** was treated with conditions from our previous work and conditions from Holmes' work but nitrone **300** was never isolated. Crude NMR data did show free *p*-anisaldehyde as well as cleavage of the dioxolane moiety (Scheme 71). The crude reaction mixtures were also heated to reflux in toluene but, no cycloadducts were isolated.

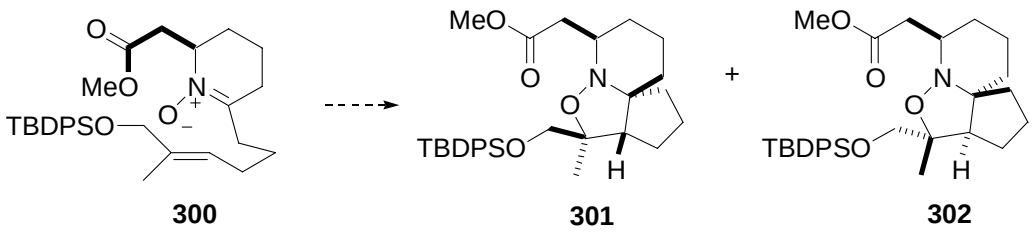
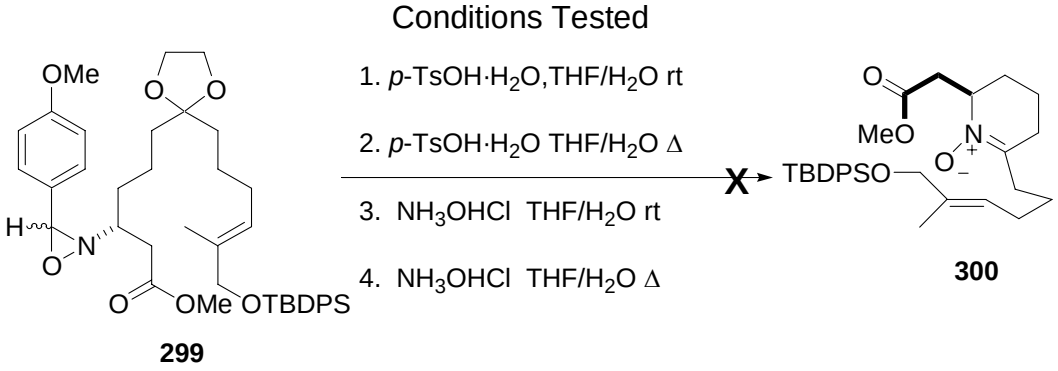


Figure 7. The potential cycloadduct outcomes from the intramolecular [3+2] nitrone cycloaddition

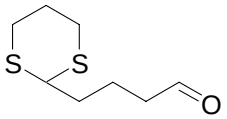


Scheme 71. Unsuccessful nitrone formation.

The discouraging results from attempted nitrone formation from **299** led us to move in a new direction, again revisiting the RCM route, while blending in Jacobsen's methodology to add our nitrogen functionality asymmetrically.

3.4 EXPERIMENTAL SECTION

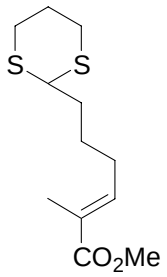
General experimental techniques and instrumentation used in this work are described in section 2.4.



259

4-[1,3]Dithian-2-yl-butyraldehyde (**259**). A stirred solution of oxalyl chloride (0.63 mL, 0.917 g, 7.27 mmol) in anhydrous CH_2Cl_2 (15 mL) at –78 ºC under Ar was

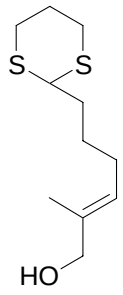
treated dropwise with a –78 ºC solution of anhydrous dimethyl sulfoxide (0.85 mL, 0.936 g, 11.9 mmol) in anhydrous CH_2Cl_2 (15 mL) over 20 min. After stirring an additional 20 min, a solution of **258** (0.910 g 4.73 mmol) in anhydrous CH_2Cl_2 (10 mL) at –78 ºC under Ar was added dropwise over 10 min. The resulting cloudy solution was stirred for 25 min, then triethylamine (4.7 mL, 3.41 g, 33.7 mmol) was added. The reaction was then allowed to warm up to rt over the next 1.5 h, H_2O (20 mL) was added, and the layers well shaken and separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL), the organic fractions were combined, washed with brine (50 mL), dried over (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 4:1, 2:1 hexanes:EtOAc) to yield **259** (0.692 g, 3.46 mmol, 77%) as a colorless oil: IR (Neat) 2933, 2901, 2724, 1718, 1558, 1455, 1419, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75–1.92 (m, 4H), 2.04-2.17 (m, 2H) 2.47 (td, *J* = 7, 1 Hz, 2H), 2.79-2.89 (m, 4H), 4.03 (t, *J* = 6.5 Hz, 1H), 9.76 (t, *J* = 1 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 19.3, 25.9, 30.3(2c), 34.7, 43.2, 47.0, 201.9; MS (CI) *m/z* 190 $(M)^+$, 165, 119, 85; HRMS (CI) *m/z* 190.0485 (calcd for $C_8H_{14}OS_2$: 190.0486).



261

6-[1,3]Dithian-2-yl-2-methyl-hex-2-enoic acid methyl ester (**261**). To a solution of aldehyde **259** (2.5 g, 13 mmol) in CH_2Cl_2 (70 mL) was added the ylide **260** (4.9 g, 14

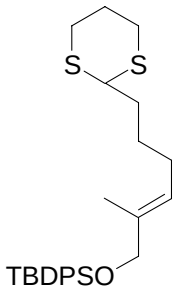
mmol) and the solution was stirred for 12 h at rt The resulting solution was concentrated and triturated with ether and filtered to remove the triphenylphosphine oxide. The solution was concentrated *in vacuo*. The resulting residue was purified *via* column chromatography (eluting with 4:1, 3:1 hexanes:EtOAc) to yield **261** (2.7 g, 10 mmol, 79%) as a colorless oil: IR (Neat) 2986, 2844, 2887, 2858, 1713, 1647, 1441, 1270, 1188, 1118 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62-1.89 (m, 4H), 1,79 (s, 3H), 2.03-2.23 (m, 4H), 2.73-2.89 (m, 4H), 3.69 (s, 3H), 4.01 (s, 1H), 6.69 (t, *J* = 7Hz, 1H) ; ^{13}C (75 MHz, $CDCl_3$) δ, 12.3, 25.5, 25.8, 28.0, 30.3(2c), 34.8, 47.1, 51.6, 127.9, 141.4, 168.3; MS (CI) *m/z* 260 $(M)^+$ 229, 201, 145, 119, 108, 84; HRMS (CI) *m/z* 260.0905 (calcd for $C_{12}H_{20}O_2S_2$: 260.0905).



262

6-[1,3]Dithian-2-yl-2-methyl-hex-2-en-1-ol (**262**). A solution of ester **261** (0.60 g, 2.3 mmol) in CH_2Cl_2 (20 mL) was cooled to –78 ºC. DIBAL-H (5.7 mL, 5.7 mmol of a 1M solution of DIBAL-H in hexane) was added dropwise over 20 min and the solution was stirred for 3h. The reaction was quenched with MeOH (5 mL) and allowed to warm to rt. Saturated Rochelle's $salt_{(aq)}$ (50 mL) was added and the mixture was stirred overnight. The layers were separated and the aqueous phases were extracted with CH_2Cl_2 (3x30 mL). The organic fractions were combined, washed with

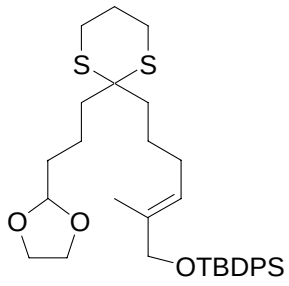
brine (50 mL), dried over (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 3:1, 2:1, 1:1, hexanes:EtOAc) to yield **262** (0.48 g, 2.1 mmol 89%) as a colorless oil: IR (Neat) 3421, 2936, 2901, 2358, 1465, 1274, 1184, 1068, 1006, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ1.43-1.82 (m, 4H), 1.56 (s, 3H), 1.93-2.1 (m, 4H), 2.24 (s, 1H), 2.69-2.84 (m, 4H), 3.87 (s, 2H), 3.95 (t, *J* = 7 Hz, 1H), 5.28 (t, *J* = 7 Hz, 1H) ; ^{13}C (75 MHz, $CDCl_3$) δ 13.4, 25.7, 26.2, 26.8, 30.1(2c), 34.6, 47.2, 68.2, 124.8, 135.1; MS (CI) *m/z* 232 $(M)^+$, 215, 204, 145, 134, 119, 106, 67; HRMS (CI) *m/z* 232.0956 (calcd for $C_{11}H_{20}OS_2$: 232.0956).



263

***tert*-Butyl (6-[1,3]dithian-2-yl-2-methylhex-2-enyloxy) diphenylsilane** (**263**). To a solution of alcohol **262** (8.98 g, .38.7mol) in CH_2Cl_2 (250 mL) was added imidazole (7.9 g, 116 mmol), DMAP (25 mg, 0.205 mmol) and, TBDPSCl (12.9g, 46.9 mmol) and the solution was stirred at rt for 48 h. H_2O (200 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (200 mL), and the organic layers were combined, washed with brine (200 mL), dried with (Na_2SO_4), and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 5:1, 3:1 hexanes:Et_2O) to yield **263** (18.2 g, 38.7 mmol, 97%) as a colorless oil: IR (Neat) 3071, 2930, 2852, 1464, 1425, 1186, 1115, 1055, 823 cm^{-1}; ^1H NMR (300

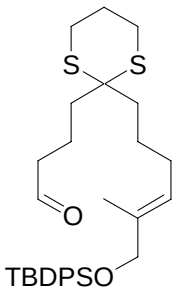
MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.54-1.63 (m, 2H), 1.59 (d, *J* = 1 Hz, 3H), 1.71-1.43 (m, 3H), 2.01-2.16 (m, 3H), 2.77-2.93(m, 4H), 4.04 (q, *J* = 1 Hz, 2H), 4.05 (t, *J* = 7 Hz, 1H), 5.42 (tq, *J* = 7, 1 Hz, 1H), 7.34-7.50 (m, 6H), 7.61-7.70 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 13.5, 19.3, 26.0, 26.2, 26.9(2C), 27.0, 30.5(2C), 35.1, 47.5, 69.0, 123.7, 127.6(4C), 129.5(2C), 13.9, 134.6, 135.6(4C); MS (CI) *m/z* 470 $(M)^+$ 455, 427, 413, 289, 211, 199, 125, 67; HRMS (CI) *m/z* 470.2130 (calcd for $C_{27}H_{38}OSiS_2$: 470.2133)



265

***tert*-Butyl-{6-[2-(3-[1,3]dioxolan-2-yl-propyl)[1,3]dithian-2-yl]-2-methylhex-2-enyloxy} diphenylsilane** (**265**). A solution of dithiane **263** (380 mg, 0.807 mmol) in 10% HMPA/THF (10 mL) was cooled to –78 ºC. *t*-BuLi (1.07 M solution in pentane, 2.3 mL, 2.45 mmol) was added, and immediately thereafter a similarly cooled solution of bromide **264** (321 mg, 1.65 mmol) in 10% HMPA/THF (1 mL) was added *via* cannula. The mixture was allowed to warm to rt and sat. $NH_4Cl_{(aq)}$ (20 mL) was added. The layers were separated, and the aqueous layer was extracted with ether (2 x 20 mL). The organic fractions were combined, washed with H_2O (3 x 20 mL), brine (40 mL), dried with (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 5:1, 3:1, hexanes:Et_2O) to yield **265** (442.4 mg, 0.756 mmol, 93%) as a colorless oil. IR (neat) 2929, 1423, 1113, 1060, 936cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.45-1.71 (m, 6H), 1.59 (s, 3H), 1.81-1.96

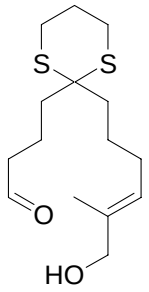
(m, 6H), 2.04 (qm, *J* = 7 Hz, 2H), 2.71- 2.81 (m, 4H), 3.79-3.84 (m, 2H), 3.91-3.97 (m, 2H), 4.02-4.05 (m, 2H), 4.81 (t, *J* = 5 Hz, 1H), 5.44 (tq, *J* = 6, 2 Hz, 1H), 7.34-7.42 (m, 6H), 7.65-7.69 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) ẟ 13.6, 18.8, 19.3, 24.1, 25.5, 26.0(2C), 26.9(3C), 27.5, 33.8, 37.8, 38.1, 53.2, 64.8(2C), 69.0, 104.3, 124.0, 127.6(4C), 129.5(2C), 133.9, 134.6, 135.5(4C); MS (CI) *m/z* 584 (M)+, 527, 477, 413, 328, 289, 199, 99, 73; HRMS (CI) *m/z* 584.2812 (calcd for $C_{33}H_{48}O_3SiS_2$: 584.2814)



266

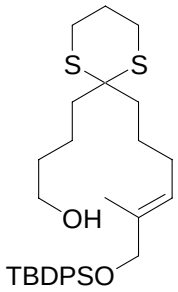
4-{2-[6-(tert-Butyldiphenylsilanyloxy)-5-methyl-hex-4-enyl]-[1,3]dithian-2-yl}-butyraldehyde (**266**). To a solution of acetal **265** (1.38 g, 2.37 mmol) in acetone/H_2O (3:1 28 mL) was added pyridinium *p*-toluenesulfonate (59.5 mg, .237 mmol) and the solution was heated to reflux for 72 h. The reaction was allowed to cool to rt. Saturated. $NaHCO_{3(aq)}$ (30 mL) and Et_2O (30mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 20 mL), the organic fractions were combined, washed with brine (50 mL), and dried with (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 1:1 hexanes:Et_2O) to yield **266** (1.15 g 2.13 mmol, 90%) and **267** (35.8 g, 0.119 mmol, 5% as a yellowish oil: IR (Neat) 2932, 2856, 2719, 1725, 1427, 1112, 1067 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.50-1.58 (m, 2H), 1.62 (s, 3H), 1.76-1.85 (m, 2H), 1.88-1.98 (m, 6H), 2.09 (q, J = 7 Hz, 2H), 2.47 (t, J = 7 Hz, 2H),

2.76-2.86 (m, 4H), 4.07 (s, 2H), 5.47 (t, J = 7 Hz, 1H), 7.37-7.45 (m, 6H), 7.68-7.70 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 13.6, 17.1, 19.3, 24.0, 25.4, 26.0(2c), 26.3(2c), 27.4, 37.5, 37.9, 43.6, 53.0, 68.9, 123.7, 127.6(4c), 129.5(2c), 133.8(2c), 134.7, 135.5(4c), 201.9; MS (CI) *m/z* 540 $(M)^+$ 483, 350, 244, 199, 167, 91 HRMS (FAB) *m/z* 540.2554 (calcd for $C_{31}H_{46}O_2S_2Si$: 540.2552).



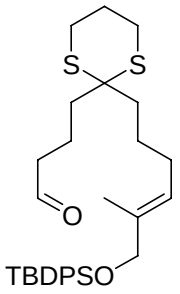
267

4-[2-(6-Hydroxy-5-methyl-hex-4-enyl)-[1,3]dithian-2-yl]-butyraldehyde (**267**). IR (Neat) 3409, 2935, 2862, 2721, 1721, 1452, 1442, 1276, 1240, 1118, 1073, 1015 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ1.51-1.60 (m, 4H), 1.68 (s, 3H), 1.75-1.99 (m, 6H), 2.04-2.12 (m, 2H), 2.47-2.52 (m, 2H), 2.79-2.85 (m, 4H), 4.02 (s, 2H), 5.44 (t, *J* = 7 Hz, 1H), 9.72 (t, *J* = 2 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ13.4, 16.7, 23.6(2c), 27.2, 37.0, 37.5, 43.4, 52.6, 68.1, 124.8, 135.2, 201.9; MS (CI) *m/z* 302 $(M)^+$ 285, 227, 204, 189, 145, 105, 98; HRMS (CI) *m/z* 302.1378 (calcd for $C_{15}H_{26}O_2S_2$: 302.1374).



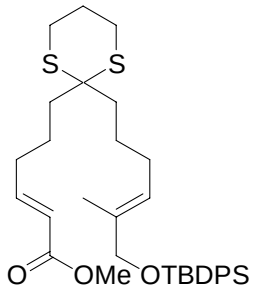
269

4-{2-[6-(tert-Butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dithian-2-yl}-butan-1-ol (**269**). A solution of **263** (6.88 g, 14.6 mmol) in 10% HMPA/THF (110 mL) was cooled to -78 ºC. *t*-BuLi (29.2 mmol, 30 mL, 0.97 M solution in pentane) was added dropwise over 20 min and the solution was stirred for an additional 10 min. A solution of bromide **268** (3.94 g, 17.5 mmol) in 10% HMPA/THF (10 mL) at -78 ºC was added to the initial flask via cannula over 15 min and allowed to warm to rt. $NH_4Cl_{(aq)}$ (100 mL) and ether (200mL) were added and the layers separated. The organic layer was extracted with H_2O (3 x 100mL). The aqueous layer was extracted with ether (3 x 100 mL). The organic layers were combined and concentrated *in vacuo*. The wet oil was then added to a flask containing MeOH (100mL) sat with K_2CO_3 (100 mg), and the solution was stirred for 10 min. Et_2O (100 mL), H_2O (100 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 100mL), and the organic fractions were combined, washed with brine (100 mL), dried over (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 2:1, 1:1 hexanes:Et_2O) to yield **269** (6.98g 12.8 mmol, 88%). IR (Neat) 3385, 2934, 2857, 1962, 1886, 1823, 1472, 1458, 1427, 1112, 1067 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.49-1.60 (m, 6H), 1.62 (s, 3H), 1.87-1.97 (m, 6H), 2.08 (q, *J* = 7 Hz, 2H), 2.75-2.86 (m, 4H), 3.65 (t, *J* = 6 Hz, 2H), 4.07 (s, 2H),5.48 (t, J = 7 Hz, 1H), 7.37-7.45 (m, 6H), 7.66-7.73(m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 13.6, 19.3, 20.4, 24.1, 25.4, 26.0(2c), 26.8(3c), 27.4, 32.8, 37.7, 38.0, 53.2, 62.6, 68.9, 123.8, 127.6(4c), 129.5(2c), 133.8, 134.6(2c), 135.5(4c); MS (FAB) *m/z* 542 $(M)^+$, 435, 287, 199, 135; HRMS (FAB) *m/z* 542.2717 (calcd for $C_{31}H_{46}O_2S_2Si$: 542.2709).



266

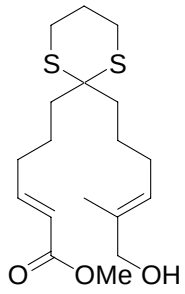
4-{2-[6-(tert-Butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dithian-2-yl}-butyraldehyde (**266**). A solution of oxalyl chloride (2.43 g, 19.1 mmol) in CH_2Cl_2 (150 mL) was cooled to -78 ºC. DMSO (3.49 g, 32.0 mmol) in CH_2Cl_2 (50 mL) at -78 ºC was added dropwise over 30 min and the solution was left to stir an additional 10 min. Alcohol **269** (6.93 g, 12.8 mmol) in CH_2Cl_2 (20 mL) at -78 ºC was added to the initial flask via cannula over 20 min. Triethylamine (6.5 g, 64.0 mmol) was added dropwise while warming to rt. H_2O (200 mL) was added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (100 mL) and the organic fractions were combined, washed with brine, dried with (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 1:1 hexanes:Et_2O) to yield **266** (6.79 g, 12.5 mmol, 98%) as a colorless oil.



271

6-{2-[6-(tert-Butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dithian-2-yl}-hex-2-enoic acid methyl ester (**271**). To a solution of aldehyde **266** (3.65g, 6.76

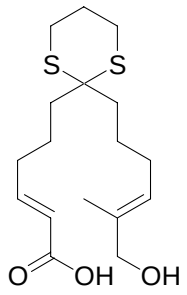
mmol) in DCM (100mL) was added ylide **270** (3.10g, 7.44mmol) and the solution was stirred at rt for 12 h. The reaction was concentrated *in vacuo* and triturated with ether (2x50mL) to remove triphenylphosphine oxide crystals by filtration. The residue was purified *via* column chromatography (eluting with 3:1 hexanes:Et_2O) to yield **271** (5.74 g, 9.62 mmol, 85%): IR (Neat) 2929, 2856, 1725, 1654, 1427, 1267, 1107 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9H), 1.51-1.59 (m, 2H), 1.65 (s, 3H), 1.61-1.71(m, 2H), 1.87-1.98 (m, 6H), 2.09-2.14 (m, 2H), 2.22-2.27 (m, 2H), 2.73-2.86 (m, 4H), 3.73 (s, 3H), 4.11 (s, 2H), 5.51 (t, *J* = 7Hz, 1H), 5.89 (d J = 16, 1H), 6.99 (td *J* = 7, 16 Hz, 1H) 7.37-7.45 (m, 6H), 7.70-7.78 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 13.5, 19.1, 22.5, 24.0, 25.3, 25.8(2c), 264, 26.7(3c), 27.2, 32.0, 37.7, 51.2, 52.9, 68.7, 121.3, 123.7, 127.5(4c), 129.4(2c), 133.7, 134.5, 134.7, 135.4(4c), 148.5, 166.7; MS (FAB) *m/z* 595 $(M-H)^+$, 539, 489, 341, 199, 135; HRMS (FAB) *m/z* 595.2743 (calcd for $C_{34}H_{47}O_3SiS_2$: 595.2736).



272

6-[2-(6-Hydroxy-5-methyl-hex-4-enyl)-[1,3]dithian-2-yl]-hex-2-enoic acid methyl ester (**272**). To a solution of HF (48% in H_2O, 0.6 mL), pyridine (1.6 mL) and CH_3CN (25 mL) was added a solution of ester **271** (2.51 g, 6.99 mmol) in CH_3CN (10 mL) at rt and the solution was stirred for 12 h. The reaction was quenched with $NaHCO_{3(aq)}$ (20 mL), Et_2O (40 mL) was added and the layers were separated. The

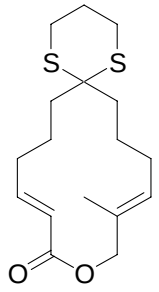
aqueous layer was extracted with Et_2O (20 mL) and the organic phases were combined, washed with brine, dried with (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 2:1 hexanes:Et_2O) to yield **272** (1.87 g, 5.24 mmol, 75%) as a pale yellow oil: IR (Neat) 3446, 2942, 2860, 1723, 1655, 1432, 1314, 1274, 1202, 1164, 1011 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46-1.66 (m, 4H), 1.68 (s, 3H), 1.81-1.99 (m, 6H), 2.07 (q, J = 7 Hz, 2H) 2.24 (q, J = 7Hz, 2H), 2.48 (s, 1H), 2.80 (t, J = 6Hz, 4H), 3.74 (s, 3H), 4.02 (s, 2H), 5.42 (t, J = 7Hz, 1H), 5.86 (d, J = 16Hz, 1H), 6.97 (dt J = 16.7Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 13.7, 22.7, 24.0, 25.3, 25.9(2c), 27.5, 32.1, 37.5, 37.9, 51.4, 52.9, 68.7, 121.3, 125.4, 135.4, 148.7, 167.0; MS (FAB) *m/z* 359 $(M+H)^+$ 341, 327, 307, 289, 235, 219, 186; HRMS (FAB) *m/z* 359.1714 (calcd for $C_{18}H_{31}O_3S_2$:).



273

6-[2-(6-Hydroxy-5-methyl-hex-4-enyl)-[1,3]dithian-2-yl]-hex-2-enoic acid (**273**). To a solution of **272** (1.28g, 3.58 mmol) in THF/H_2O/MeOH (20mL/5mL/5mL) was added LiOH (451 mg, 10.74 mmol) and the solution was heated to reflux for 12 h. The solution was cooled to rt and acidified with 10% HCl to pH~1. CH_2Cl_2 (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) The organic fractions were combined, washed with brine (50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column

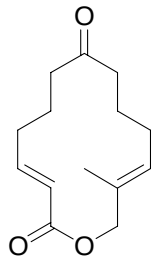
chromatography (eluting with 5% MeOH/CH_2Cl_2) to yield **273** (1.02 g, 2.97 mmol, 83%) as a colorless oil: IR (Neat) 3355, 2938, 2861, 1698, 1653, 1456, 1419, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44-1.52 (m, 2H), 1.59-1.64 (m, 2H), 1.66 (s, 3H), 1.82-1.90 (m, 6H), 1.91-1.95 (m, 2H), 2.04 (q, *J* = 7 Hz, 2H), 2.25 (q, *J* = 6 Hz, 2H), 2.75-2.81 (m, 4H), 4.0 (s, 2H), 5.40 (t, *J* = 7 Hz, 1H), 5.85 (d, *J* = 14 Hz, 1H), 7.04 (dt, *J* = 14, 7 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ13.7, 22.6, 24.0, 25.3, 26.0(2c), 27.5, 32.1, 37.3, 37.8, 52.8, 68.7, 121.2, 125.6, 135.1, 151.1, 171.2 ; MS (FAB) *m/z* $(M+H)^+$,327, 307, 217, 136, 107, 89, HRMS (FAB) *m/z* 347.1716 (calcd for $C_{17}H_{31}O_3S_2$: 347.1714).



274

15-Methyl-13-oxa-1,5-dithia-spiro[5.13]nonadeca-10,15-dien-12-one (**274**). To a solution of **273** (440 mg, 1.30 mmol) in THF (18 mL) was added triethylamine (210 mg, 2.07 mmol) and 2,4,6-trichlorobenzoyl chloride (461 mg, 1.89 mmol) and the solution was stirred for 2 h. The solution was then added via a cannula to a flask containing toluene (945 mL). This new solution was added *via* cannula over 12 h to another flask containing DMAP (693 mg, 5.67 mmol) in refluxing toluene (190 mL). After the addition was complete the reaction was left refluxing an additional 3 h. The reaction was cooled to rt, the solvent was removed by water aspirator distillation until

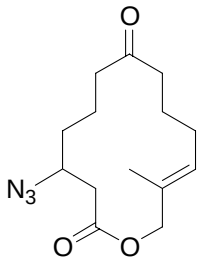
50 mL remained. H_2O (40 mL) was added, and layers were separated. The aqueous phase was extracted with Et_2O (2 x 40 mL). The organic fractions were combined, washed with brine (20 ml), dried with (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 4:1 hexanes:Et_2O) to yield **274** (154 mg, 0.472 mmol, 37%) as a colorless solid mp 102 °C; IR (Neat) 2932, 2853, 1718, 1681, 1647, 1556, 1457, 1263, 1245cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37-1.46 (m, 2H), 1.59 (s, 3H), 1.59-1.71 (m, 2H), 1.22-1.86 (m, 2H), 1.92-2.01 (m, 2H), 2.18-2.26 (m, 2H), 2.69-2.81 (m, 4H), 4.59 (s, 2H), 5.26 (t, *J* = 7 Hz, 1H), 5.88 (d, *J* = 16 Hz, 1H), 7.03 (dt, *J* = 16, 8 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.3, 24.1, 24.7, 24.9, 25.2, 26.7(2c), 30.3, 33.7, 35.8, 52.9, 66.6, 123.1, 123.9, 131.2, 150.6, 166.3; MS (CI) *m/z* 326 $(M)^+$ 251, 245, 223, 207, 145, 106; HRMS (CI) *m/z* 326.1367 (calcd for $C_{17}H_{26}O_2S_2$:326.1374).



275

13-Methyl-oxacyclotetradeca-3,12-diene-2,8-dione (**275**). A solution of lactone **274** (124 mg, 0.380 mmol) in Et_2O (8 mL) and THF (3 mL) was cooled to 0 ºC. H_5IO_6 in THF (2 mL) was added slowly to the initial reaction, which turned yellow and which was stirred for 20 min. Saturated sodium sulfite$_{(aq)}$ (10 mL) was added with the reaction turning clear. H_2O (10 mL) and Et_2O (20 mL) were added. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 10 mL). The organic

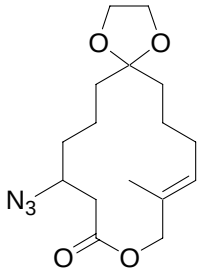
fractions were combined, washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 3:1 hexanes:Et_2O) to yield **275** (71.7 mg, 0.312 mmol, 82%) as a colorless oil: IR (Neat) 2931, 1719, 1654, 1438, 1654, 1271, 1253, 1151cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 3H), 1.74 (quintet, *J* = 6 Hz, 2H), 1.96-2.02 (m, 2H), 2.08 (q, *J* = 7 Hz, 2H), 2.28 (q, *J* = 7 Hz, 2H), 2.34 (t, *J* = 6 Hz, 2H), 2.38 (t, *J* = 6 Hz, 2H), 4.58 (s, 2H), 5.09 (t, *J* = *7* Hz, 1H), 5.81 (d, *J* = 16 Hz, 1H), 6.80 (dt, *J* = 1, 7 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.4, 19.5, 19.7, 26.3, 33.1, 40.2, 67.0, 123.2, 123.6, 131.2, 149.3, 166.0, 209.1; MS (CI) *m/z* 236 $(M)^+$ 218, 173, 141, 123, 113, 95; HRMS (CI) *m/z* 236.1410 (calcd for $C_{14}H_{20}O_3$:236.1412).



276

4-Azido-13-methyl-oxacyclotetradec-12-ene-2,8-dione (**276**). A solution of ester **275** (12.0 mg, 0.051 mmol) in toluene with HN_3 (1.1 M solution in toluene, 5 mL) and triethylamine (50 μL, 36 mg, 0.3556 mmol) was heated to reflux for 12 h. The solution was cooled to rt , opened to air under a stream of Ar to remove excess HN_3, and then concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 4:1 hexanes:Et_2O) to yield **276** (10.4 mg, 0.037 mmol, 73%) as a yellowish oil: IR (Neat) 2927, 2844, 2099, 1732, 1440, 1368, 1256, 1201,

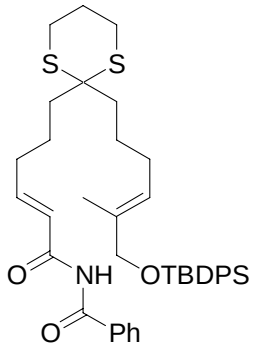
1165cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.51 (q, *J* = 7 Hz, 2H), 1.58-1.64 (m, 2H), 1.69 (s, 3H), 1.78-1.97 (m, 2H), 2.07-2.17 (m, 1H), 2.19-2.27 (m, 1H) 2.30-2.48 (m, 5 H), 5.58 (dd, *J* = 3, 15 Hz, 1H), 3.71-3.78 (m, 1H), 4.47 (s, 2H), 5.38 (t, *J* = 8 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 14.7, 20.0, 20.9, 26.7, 32.1, 39.8, 40.4, 40.7, 57.6, 70.9, 130.5, 131.8, 169.4, 210.2; MS (CI) *m/z* 279 $(M)^+$ 260, 244, 233, 191, 167, 149, 111, 98;HRMS (CI) *m/z* 279.1591 (calcd for $C_{14}H_{21}O_3N_3$:279.1583).



277

9-Azido-14-methyl-1,4,12-trioxa-spiro[4.13]octadec-14-en-11-one (**277**). To a solution of ketone **276** (10.4 mg, 0.037 mmol) in benzene (20 mL) was added ethylene glycol (4.59 mg, 0.074 mmol), and *p*-toluenesulfonic acid (1 mg) and the solution was heated to reflux for 12 h using a Dean-Stark trap. The reaction was cooled to rt. Saturated $NaHCO_{3(aq)}$ (10 mL), H_2O (20 mL) and Et_2O (50 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 10 mL). The organic phases were combined, washed with brine (20 ml), dried with (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 3:1 hexanes:Et_2O) to yield **277** (6.8 mg, 0.021 mmol, 57%) as a yellowish oil: IR (Neat) 2950, 2872, 2096, 1735, 1373, 1257, 1163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ1.23-1.43 (m, 3H), 1.46-1.73 (m, 7H), 1.69 (s, 3H), 1.98-2.09 (m, 2H), 2.47 (dd, *J* = 10, 15 Hz, 1H), 2.71 (dd, *J* = 4, 15 Hz, 1H), 3.77-3.85 (m, 1H), 3.89 (s, 4H), 4.32 (d, *J*

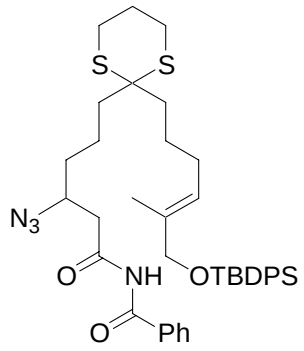
= 12 Hz, 1H), 4.75 (d, *J* = 12 Hz, 1H) 5.47 (t, *J* = 9 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 15.0, 20.7, 23.1, 26.1, 32.9, 3.3, 34.6, 38.6, 58.6, 64.3, 64.4, 68.7, 111.7, 129.7, 131.7, 169.6; MS (CI) *m/z* 322 $(M-H)^+$ 281, 234, 167, 141, 98; HRMS (CI) *m/z* 323.1847 (calcd for $C_{16}H_{25}O_4N_3$:323.1845).



286

***N*-(6-{2-[6-(tert-Butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dithian-2-yl}-hex-2-enoyl)-benzamide** (**286**). A solution of phosphonate **285** (2.16 g, 7.21 mmol) in THF (35 mL) was cooled to –78 ºC. *n*-BuLi (2.55 M solution in hexanes 7.21 mL, 18.03 mmol) was added dropwise over 15 min, and the solution was left to stir an additional 20 min. Aldehyde **266** (3.25 g, 6.01 mmol) in THF (10 mL) was cooled to –78 ºC and added *via* cannula to the first flask over a period of 20 min. The reaction warmed to rt over 4 h and was quenched first with 1M HCl (50 mL) stirred for 10 min and then H_2O (25 mL) and Et_2O (50 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2x50 mL). The organic phases were combined, washed with brine (40 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 2:1, 1:1, hexanes:Et_2O) to yield **286** (3.09 g, 4.51 mmol, 75%): IR (Neat) 3262, 2934, 2854,

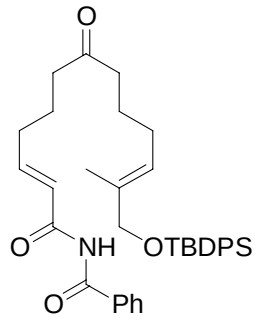
1710, 1670, 1670, 1627, 1477, 1357, 1237, 1106, 902 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.47-1.56 (m, 2H), 1.61 (s, 3H), 1.63-1.72 (m, 2H), 1.86-1.95 (m, 6H), 2.07 (q, *J* = 7 Hz, 2H), 2.31-2.36 (m, 2H), 2.76-2.81 (m, 4H), 4.05 (s, 2H), 5.45 (tq, *J* = 7, 1 Hz, 1H), 7.16-7.18 (m, 2H), 7.34-7.41 (m, 6H), 7.47-7.51 (m, 2H), 7.59 (tt, *J* = 1, 7 Hz, 1H), 7.66-7.69 (m, 4H), 7.86-7.89 (m, 2H), 8.74 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ13.6, 19.3, 22.9, 24.1, 25.4, 26.0(2c), 26.8(3c), 27.4, 32.7, 37.8, 37.9, 53.1, 68.9, 123.2, 123.8, 127.6(4c), 127.7, 128.9(2c), 129.5(2c), 133.0, 133.1, 133.8, 134.6, 135.5(4c), 151.0, 165.7, 167.2; MS (FAB) *m/z* 708 $(M + Na)^+$, 628, 430, 335, 199, 135, 105; HRMS (FAB) *m/z* 685.3076 (calcd for $C_{40}H_{51}NO_3SiS_2$: 685.3080)



287

***N*-(3-Azido-6-{2-[6-(tert-butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dithian-2-yl}-hexanoyl)-benzamide** (**287**). A solution of HN_3 (0.252 mmol, 0.18 mL of a 1.4M solution in toluene) was added to a –78 ºC suspension of **286** (25 mg, 0.037 mmol) and salen complex **278c** (1 mg, 1.80 μmol) in CH_2Cl_2 (1 mL). The reaction was warmed to -40°C and maintained at that temperature for 24h. The reaction was allowed to warm to rt and flushed with Ar to remove the remaining HN_3. The reaction concentrated *in vacuo* and purified *via* flash chromatography (eluting

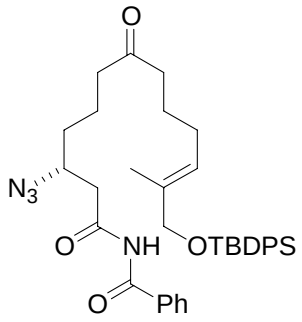
with 2:1, 1:1, hexanes:Et_2O) to yield **287** (7 mg, 9.60 μmol, 26%) and **286** (11 mg, 16.0 μmol, 69%): $[\alpha]_D^{23}$ -.77 (c 1.3, $CHCl_3$); IR (neat) 2931, 2856, 2109, 1714, 1682, 1471, 1427, 1240, 1112, 705, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.49-1.70 (m, 6H), 1.63 (s, 3H), 1.85-2.00 (m, 6H), 2.09 (q, *J* = 7 Hz, 2H), 2.81 (t, *J* = 5 Hz, 4H), 3.17 (dd, *J* = 17, 4 Hz, 1H), 3.29 (dd, *J* = 9, 17 Hz, 1H), 3.97-4.04 (m, 1H), 4.07 (s, 2H), 5.47 (t, *J* = 6 Hz, 1H), 7.35-7.71 (m, 13H), 7.87 (d, *J* = 7 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 13.6, 19.3, 20.9, 24.1, 25.4, 26.0 (2C), 26.8 (3C), 27.4, 29.7, 34.7, 37.9 (2C), 42.8, 53.1, 58.1, 68.9, 123.9, 127.7 (4C), 129.1 (2C), 129.5 (2C), 132.3, 133.5, 133.9, 134.6, 135.5(4C), 165.5, 173.1; MS (CI) *m/z* 685, 671, 613, 307, 154, 136.



289

***N*-[13-(tert-Butyl-diphenyl-silanyloxy)-12-methyl-7-oxo-trideca-2,11-dienoyl]-benzamide** (**289**). A solution of dithiane **286** (327 mg, 0.477 mmol) in Et_2O (5 mL) and THF (2 mL) was cooled to 0 ºC. H_5IO_6 in THF (2 mL) was added slowly to the initial reaction, which turned yellow and which was stirred for 20 min. Saturated sodium $sulfite_{(aq)}$ (10 mL) was added with the reaction turning clear. H_2O (10 mL) and Et_2O (20 mL) was added. The layers were separated, and the aqueous phase was

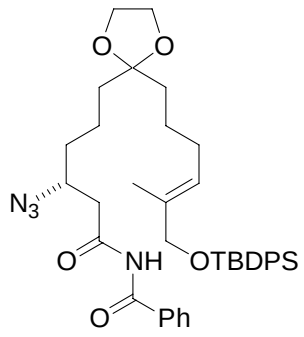
extracted with Et_2O (2 x 10 mL). The organic fractions were combined, washed with brine (20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 1:1 hexanes:Et_2O) to yield **289** (161 mg, 0.253 mmol, 53%): IR (Neat) 2954, 2857, 1708, 1683, 1672, 1635, 1506, 1472, 1361, 1248, 1134, 1109, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ1.07 (s, 9H), 1.59 (s, 3H), 1.62-1.70 (m, 2H), 1.82 (quintet, *J* = 7 H, 2H), 2.05 (q, *J* = 8 Hz, 2H), 2.41, (t, *J* = 8 Hz, 2H), 2.47 (t, *J* = 8 Hz, 2H), 4.06 (s, 2H), 5.41 (t, *J* = 8 Hz, 1H), 7.15-7.18 (m, 2H), 7.35-7.45 (m, 6H), 7.48-7.53 (m, 2H), 7.59-7.70 (m, 5H), 7.87 (d, *J* = 7 Hz, 2H), 8.64 (s 1H); ^{13}C (75 MHz, $CDCl_3$) δ 13.5, 19.3 22.0, 23.6, 26.8(3c), 29.7, 31.9, 41.7, 42.2, 68.9, 123.3, 123.5, 127.6(4c), 127.7(2c), 129.0(2c), 129.5(2c), 132.9, 133.2, 133.8, 134.9, 135.5(4c), 150.7 156.6, 165.7, 167.2, 210.3; MS (FAB) *m/z* 596 $(M+H)^+$ 538, 307, 289, 136, 107; HRMS (FAB) *m/z* 596.3194 (calcd for $C_{37}H_{46}O_4NSi$: 596.3196).



290

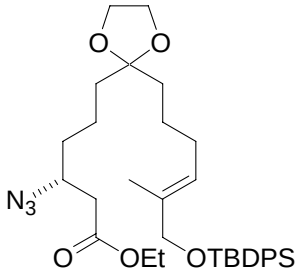
***N*-[3-Azido-13-(tert-butyl-diphenyl-silanyloxy)-12-methyl-7-oxo-tridec-11-enoyl]-benzamide** (**290**). To a solution of imide **289** (157 mg, 0.264 mmol) in CH_2Cl_2 (2 mL) was added salen cat. **278c** (4 mg) and the solution was cooled to -78 ºC. A solution of HN_3 in toluene (1.1M solution, 1.5mL, 1.58 mmol) was added and then the solution was allowed to warm to -40 °C and stirred for 12 h. Another quantity of **278c**

(4 mg) and HN_3 in toluene (1.1 M solution, 1.5 mL, 1.58 mmol) was added and the solution was stirred for an additional 24 h. The solution was allowed to warm to rt while open to atmosphere under a stream of Ar to remove excess HN_3. The solution was concentrated *in vacuo*, and purified *via* column chromatography (eluting with 4:1 hexanes:Et_2O) to yield **290** (139 mg, 0.219 mmol, 83%, 92% ee as separated on a chiral OD column) as a colorless oil: $[\alpha]_D^{23}$ +3.70 (c = 0.135, $CHCl_3$); IR (Neat) 3291, 2931, 2857, 2105, 1715, 1684, 1506, 1472, 1428, 1378, 1241, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ1.07 (s, 9H), 1.60-1.84 (m, 6H), 1.62 (s, 3H), 2.06 (q, *J* = 7 Hz, 2H), 2.41 (t, *J* = 8 Hz, 2H), 2.47 (t, *J* = 7 Hz, 2H), 3.17 (dd, *J* = 17, 4 Hz, 1H), 3.27 (dd, *J* = 17, 8 Hz, 1H) 3.94-4.02 (m, 1H), 4.06 (s, 2H), 5.42 (t, *J* = 8 Hz, 1H), 7.34-7.40 (m, 4H), 7.49-7.51 (m, 4H), 7.61-7.73 (m, 5H), 7.86 (d, *J* = 8 Hz, 2H), 8.74 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 13.5, 19.3, 20.1, 23.7, 26.9(3c), 34.0, 42.0, 42.2, 42.7, 58.2, 68.9, 123.3, 127.5(2c), 127.6(2c), 129.1(2c), 129.5, 132.4(2c), 133.5, 133.9, 133.5, 134.2, 134.4, 134.7(2c), 134.8, 135.0, 135.5(2c), 134.8, 135.0, 135.5(2c), 134.8, 135.0, 135.5(2c), 165.4, 173.0, 210.2; MS (FAB) *m/z* 639 $(M+H)^+$ 637, 234, 199, 105, 91; HRMS (FAB) *m/z* 639.3346 (calcd for $C_{37}H_{47}O_4N_4Si$: 639.3367).

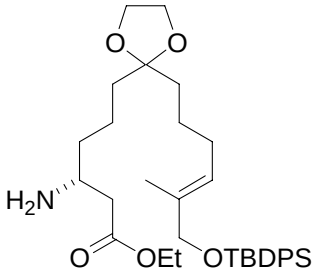


291

***N*-(3-Azido-6-{2-[6-(tert-butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dioxolan-2-yl}-hexanoyl)-benzamide** (**291**). To a solution of ketone **290** (117 mg, 0.183 mmol) in CH_2Cl_2 (10 mL) was added 1,2-bis(trimethylsilyloxy)ethane (189 mg, 0.915 mmol) and the solution was cooled to –78 ºC. TMSOTf (20 mg, 0.111 μmol) was added and the solution was left to stir for an additional 3 h while warming to 0 °C. The reaction was quenched by the addition of dry pyridine (1 mL) at 0 ºC, and poured into a solution of sat. $NaHCO_{3(aq)}$ (10 mL), shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The organic fractions were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 3:1 hexanes:Et_2O) to yield **291** (111 mg, 0.067 mmol, 89%) as a yellowish oil: $[\alpha]_D^{23}$+1.81 (c = 0.995, $CHCl_3$); IR (Neat) 3285, 3066, 2951, 2857, 2107, 1715, 1683, 1471, 1241, 1112, 1070 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.39-1.49 (m, 2H), 1.55-1.69 (m, 11H), 1.58 (s, 3H), 2.06 (q, *J* = 7 Hz, 2H), 3.16 (dd, *J* = 17, 4 Hz, 1H), 3.27 (dd, *J* = 17, 9 Hz, 1H), 3.95 (s, 4H), 3.9-4.01(m, 1H), 4.06 (s, 2H), 5.44 (t, *J* = 8 Hz, 1H), 7.36-7.45 (m , 6H), 7.53, (t, *J* = 7 Hz, 1H), 7.53 (t, *J* = 7 Hz, 2H), 7.61-7.70 (m, 5H), 7.85 (d, *J* = 7 Hz, 2H), 8.63 (s, 1H) ; ^{13}C (75 MHz, $CDCl_3$) δ14.0, 19.7, 20.8, 24.3, 27.2(3c), 28.0, 35.2, 37.1, 37.3, 43.3, 58.8, 65.4(2c), 69.4, 111.9, 124.7, 128.0(4c), 128.2(2c), 129.4(2c), 130.0(2c), 132.8, 133.8, 134.3, 134.6, 136.0(4c), 166.1, 174.1; MS (FAB) *m/z* 681 $(M-H)^+$ 625, 534, 199, 135, 99; HRMS (FAB) *m/z* 682.3563 (calcd for $C_{39}H_{50}O_5N_4Si$: 682.3551).



292

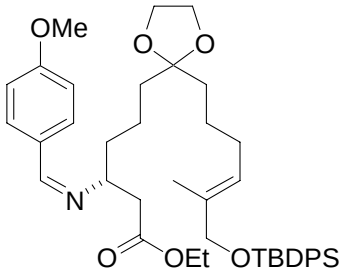


293

3-Amino-6-{2-[6-(tert-butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dioxolan-2-yl}-hexanoic acid ethyl ester (**293**). To a solution of imide **291** (25.0 mg, 0.032 mmol) in EtOH (2 mL) was added Raney Nickel (150 mg, a black powder in a suspension of EtOH) and the suspension was stirred at rt for 24 h. The suspension was filtered over Celite, washed with EtOH and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 8% MeOH in CH_2Cl_2) to yield **293** (10.1 mg, 0.018 mmol, 55%) as a colorless oil: $[\alpha]_D^{23}$+5.0 (c = 0.1, $CHCl_3$); IR (Neat) 3375, 2923, 2855, 1732, 1453cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ;1.06 (s, 9H), 1.27 (t, *J* = 7 Hz, 3H), 1.37-1.48 (m, 7H), 1.59-1.65 (m, 4H), 1.60 (s, 3H), 2.04 (q, *J* = 7 Hz 2H), 2.20 (s-br, 2H), 2.34 (dd , *J* = 9, 16 Hz, 1H), 2.52 (dd, *J* = 4, 16 Hz, 1H), 3.93 (s, 4H), 4.04 (s, 2H), 4.16 (q, *J* = 7 Hz, 2H), 5.4 (t *J* = 7 Hz, 1H), 7.35-7.40 (m, 6H), 7.67-7.70 (m, 4H); MS (FAB) *m/z* 582 $(M+H)^+$ 520, 391, 149, 89; HRMS (FAB) *m/z* $(M+H)^+$ 582.3593 (calcd for $C_{34}H_{52}O_5NSi$: 582.3615).

3-Azido-6-{2-[6-(tert-butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dioxolan-2-yl}-hexanoic acid ethyl ester (**292**). $[\alpha]_D^{23}$-1.5 (c = 0.8, $CHCl_3$); IR (Neat) 3072, 2953, 2935, 2856, 2101, 1739, 1431, 1112cm^{-1}; ^{1}H NMR (300 MHz,

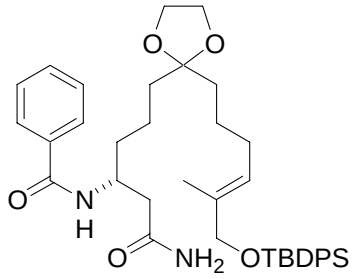
$CDCl_3$) δ 1.07 (s, 9H), 1.28 (t, J = 7 Hz, 3H), 1.38-1.49 (m, 2H), 1.51-1.66 (m, 5H), 1.61 (s, 3H), 1.83-1.88 (m, 2H), 2.05 (q, J = 7 Hz, 2H), 2.49 (d, J = 7 Hz, 2H), 3.94 (s, 4H) 4.05 (s, 2H), 4.19 (q, J = 7 Hz, 2H), 5.44 (t, J = 7 Hz, 1H), 7.36-7.45 (m, 6H), 7.67-7.70 (m, 4H);. ^{13}C (75 MHz, $CDCl_3$) δ; 13.5, 14.1, 19.3, 20.2, 23.9, 26.8(3c), 27.6, 34.6, 36.7, 36.9, 39.7, 59.2, 66.8, 65.0(2c), 69.0, 111.4, 124.2, 127.6(4c), 129.5(2c), 133.9, 134.3, 135.5(4c), 170.7; MS (FAB) *m/z* 681 $(M-H)^+$ 606, 550, 391, 149, 91.1; HRMS (FAB) *m/z* 606.3376 (calcd for $C_{34}H_{48}O_5N_3Si$: 606.3363).



294

6-{2-[6-(tert-Butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dioxolan-2-yl}-3-[(4-methoxy-benzylidene)-amino]-hexanoic acid ethyl ester (**294**). To a solution of **293** (7.02 mg, 12.1 μmol) in CH_2Cl_2 (10 mL) was added Na_2SO_4 (847 mg, 6.06 mmol) and *p*-methoxybenzaldehyde (2.47 mg, 18.15 μmol) with stirring for 48 h at rt. The suspension was filtered and concentrated *in vacuo*. The residue was further purified *via* column chromatography (the column was flushed with triethylamine before applying **294**, eluting with 1:2 Et_2O:hexane) to yield **294** (9.80 mg, 14.0 μmol, 81%) as a colorless oil: $[\alpha]_D^{23}$+6.21 (c = 0.36, $CHCl_3$); IR (neat) 2950, 2856, 1734, 1643, 1607, 1512, 1428, 1251, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.22-1.68 (m, 16H), 1.23 (s, 3H), 1.93-2.07 (m, 2H), 3.55-3.61 (m, 2H), 3.87 (s,

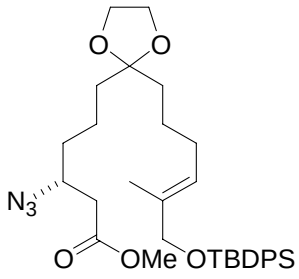
4H), 3.94 (s, 3H), 4.05-4.14 (m 4H), 5.35-5.45 (m, 1H), 6.89-6.92 (m, 2H), 7.40-7.49 (m, 6H), 7.62-7.87 (m, 6H), 8.20 (s, 1H) ; ^{13}C (100 MHz, $CDCl_3$) δ 13.5, 14.3 19.3 20.6, 23.8, 26.9 (3C), 27.6, 36.3, 36.8 (2C), 41.5, 55.4, 60.2, 64.9 (2C), 67.6, 69.0, 111.6, 113.9 (2C), 124..3, 127.6 (4C), 129.1, 129.6 (2C), 129.8 (2C), 133.9, 134.2, 135.6 (4C), 160.4, 161.6, 171.9; MS (EI) *m/z* 700 $(M+H)^+$, 582, 520; HRMS (EI) *m/z* 700.4072 (calcd for $C_{42}H_{58}NO_6Si$: 700.4033).



295

***N*-(4-{2-[6-(tert-Butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dioxolan-2-yl}-1-carbamoylmethyl-butyl)-benzamide** (**295**). To a solution of **291** (55.0 mg, 80.5 μmol) in benzene (10 mL) was added tributyltin hydride (58.2 mg, 241 μmol) and the solution was heated to reflux for 12 h. The solution was concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with hexanes followed by 20:1 CH_2Cl_2:MeOH) to yield **295** (34.9 mg, 53.1 μmol, 66%) as a colorless oil: $[\alpha]_D^{23}$ +13.6 (c = 1.49, $CHCl_3$); IR (neat) 3396, 3296, 3196, 2950, 2857, 1656, 1634, 1536, 1428, 1112, 1073 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.38-1.84 (m, 10H), 1.51 (s, 3H), 2.02-2.10 (m, 2H), 2.50-2.64 (m, 2H), 3.85-3.94 (m, 1H), 3.91 (s, 4H), 4.05 (s, 2H), 4.35-4.42 (m, 2H), 5.38-5.46 (m, 1H), 5.75 (s, br, 1H), 6.27 (s, br, 1H), 7.37-7.48 (m, 9H), 7.69-7.73 (m, 4H), 7.78-7.81 (m, 2H); ^{13}C (100

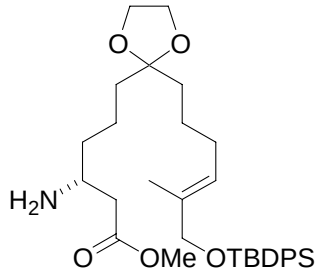
MHz, $CDCl_3$) δ 13.5, 13.6, 17.5, 19.2, 20.6, 21.1, 23.8, 24.0, 26.8 (3C), 27.6, 27.8, 29.6, 34.3, 36.6, 36.7, 39.4, 47.0, 62.5, 64.8 (2C), 69.0, 76.7, 77.0, 77.3, 111.4, 124.2, 126.4, 126.9, 127.3, 127.5, 128.5, 129.5, 131.4, 131.9, 133.9, 134.2, 134.5, 134.6, 135.5, 167.1, 173.8; MS (CI) *m/z* 655, 401, 383, 179, 122; HRMS (CI) *m/z* 657.3729 $(M+H)^+$ (calcd for $C_{39}H_{53}N_2O_5Si$: 657.3724).



296

3-Azido-6-{2-[6-(tert-butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dioxolan-2-yl}-hexanoic acid methyl ester (**296**). A solution of **291** (1.33 g, 1.95 mmol) in MeOH (20 mL) was cooled to 0 ºC. NaOMe (5 mol%, 5.26 mg, 97 μmol) was added and the solution was stirred for 12 h. at 0 °C. Saturated $NH_4Cl_{(aq)}$ (10 mL), H_2O (10 mL) and Et_2O (50 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (2x50 mL). The combined organic extracts were then washed with brine (40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 1:1 Et_2O:hexane) to yield **296** (864 mg, 1.46 mmol, 75 %) as a colorless oil: $[\alpha]_D^{23}$ -1.98 (c = 2.32, $CHCl_3$); IR (neat) 2952, 2857, 2105, 1741, 1429, 1112, 1067 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.34-1.62 (m, 10H), 1.52 (s, 3H), 1.98-2.08 (m, 2H), 2..36-

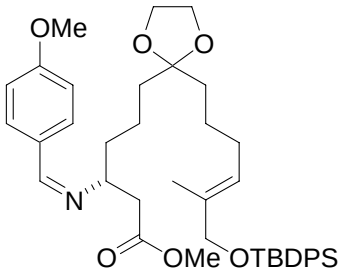
2..58 (m, 2H), 3.59-3.68 (m, 1H), 3.67 (s, 4H), 3.90 (s, 3H), 4.02 (s, 2H), 5..36-5..54 (m, 1H), 7.31-7.42 (m, 6H), 7.65-7.71 (m 4H); ^{13}C (75 MHz, $CDCl_3$) δ 13.5, 19.2, 20.3, 22.8, 26.8 (3C), 27.5, 34.7, 36.6, 36.8, 42.8, 58.3, 64.9 (2C), 68.9, 111.3, 124.2, 127.5, 127.7, 129.0 129.4, 132.2, 133.4, 133.8, 134.2, 135.5, 165.6, 173.4; MS (CI) *m/z* 594, 582, 524, 423, 335, 198, 97; HRMS (CI) *m/z* 593.3271 (calcd for $C_{33}H_{47}O_5N_3Si$: 593.3285).



297

3-Amino-6-{2-[6-(tert-butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dioxolan-2-yl}-hexanoic acid methyl ester (**297**). To a solution of **296** (166 mg, 0.280 mmol) in benzene (15 mL) was added tributyltin hydride (93.8 mg, 839 μmol) and the solution was heated to reflux for 12 h. The solution was concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with hexanes followed by 20:1 CH_2Cl_2:MeOH) to yield **297** (93.8 mg, 165 μmol, 59%) as a colorless oil: $[\alpha]_D^{23}$ +13.6 (c = 1.49, $CHCl_3$); IR (neat) 3382, 2951, 2857, 1735, 1428, 1112, 1175, 1058 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.27-2.67 (m, 10H), 1.58 (s, 3H), 2.01-2.09 (m, 2H), 2.35-2.48 (m, 2H), 3.09 (s, br, 2H), 3.29 (s, br, 1H), 3.31 (s, 3H), 3.89-3.98 (m, 1H), 3.95 (s, 4H), 4.08 (s, 2H), 5.42-5.49 (m, 1H), 7.36-7.44 (m, 6H), 7.68-7.72 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 13.6, 19.3, 20.3, 23.9,

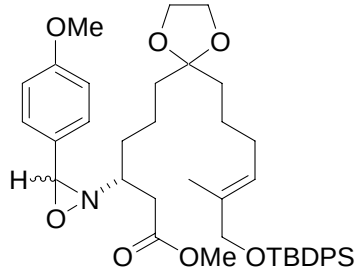
26.9 (3C), 27.6, 36.9, 37.0, 37.8, 42.4, 48.3 (2C), 51.6, 65.0, 69.0, 111.6, 124.3, 127.6, 129.6, 133.4, 134.3, 135.6, 173.1; MS (CI) *m/z* 568 $(M+H)^+$ 530, 352, 239, 179, 107; HRMS (CI) *m/z* 568.3461 (calcd for $C_{33}H_{50}NO_5Si$: 568.3458).



298

6-{2-[6-(tert-Butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dioxolan-2-yl}-3-[(4-methoxy-benzylidene)-amino]-hexanoic acid methyl ester (**298**). To a solution of **297** (93.8 mg, 165 μmol) in CH_2Cl_2 (15 mL) was added Na_2SO_4 (2.34 g, 16.5 mmol) and *p*-methoxybenzaldehyde (27.0 mg, 198 μmol) with stirring for 48 h at rt. The suspension was filtered and concentrated *in vacuo*. The residue was further purified *via* column chromatography (the column was flushed with and triethylamine before applying **298**, eluting with 1:2 Et_2O:hexane) to yield **298** (96.2 mg, 140 μmol, 85%) as a colorless oil: $[\alpha]_D^{23}$ +5.1 (c = 0.36, $CHCl_3$); IR (neat) 2950, 2857, 1739, 1645, 1607, 1512, 1428, 1250, 1165, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.09-1.80 (m, 10H), 1.05 (s, 3H), 1.92-2.03 (m, 2H), 2.55-2.67 (m, 2H), 3.51-3.66 (m, 1H), 3.60 (s, 3H), 3.80 (s, 3H), 3.86 (s, 4H), 4.02 (s, 2H), 5.31-5.42 (m, 1H), 6.82-6.92 (m, 2H), 7.32-7.45 (m, 6H), 7.59-7.73 (m, 6H), 8.02 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 13.4, 19.2, 20.5, 23.7, 26.8(3C), 27.5, 36.0, 36.6, 36.7, 41.0, 51.4, 55.3, 64.8 (2C), 67.3, 68.9, 111.5, 113.8, 114.7, 116.0, 124.2, 127.5, 128.9, 129.5, 129.8, 133.8

135.1, 135..5, 160.5, 161.6, 172.3; MS (FAB) *m/z* 686, 199, 135; HRMS (FAB) *m/z* 686.3941 (calcd for $C_{41}H_{56}NO_6Si$: 686.3877).



299

6-{2-[6-(tert-Butyl-diphenyl-silanyloxy)-5-methyl-hex-4-enyl]-[1,3]dioxolan-2-yl}-3-[3-(4-methoxy-phenyl)-oxaziridin-2-yl]-hexanoic acid methyl ester (**299**). A solution of **298** (9.10 mg, 13.2 μmol) in CH_2Cl_2 (5 mL) was cooled to –78 ºC and treated with a solution of dried 3-chloroperoxybenzoic acid (2.96 mg, 85 wt% 3-chlorobenzoic acid, 14.6 μmol) in anhydrous CH_2Cl_2 (0.5 mL). The mixture was allowed to warm to 0 °C over 1.5 h and then quenched by the addition of sat. $Na_2S_2O_{3(aq)}$ (5 mL) and stirred vigorously for 10 min. After dilution with CH_2Cl_2 (5 mL), 10% $Na_2CO_{3(aq)}$ (10 mL) was added and the layers were well shaken and then separated. The aqueous phase was extracted (2x10 mL CH_2Cl_2), and the organic fractions were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was then further purified *via* column chromatography (eluting with 1:1 Et_2O:hexanes) to yield **299** (6.02 mg, 8.58 μmol, 65%) as a colorless oil: $[\alpha]_D^{23}$ +4.17 (c = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) dr = 4.5:3, major diastereomer δ 1.02 (s, 9H), 1.29-1.78 (m, 10H), 1.58 (s, 3H), 1.90-2.00 (m, 2H), 2.52-2.69 (m, 2H), 3.70

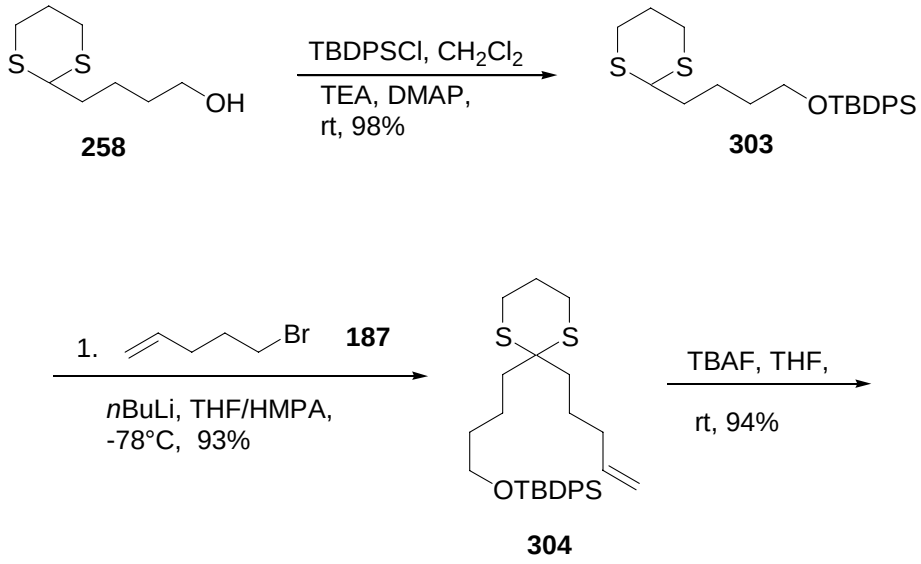
(s, 3H), 3.78 (s, 4H), 3.80 (s, 1H), 3.82-3.9 (m, 1H), 4.00 (s, 2H), 4.53 (s, 1H), 5.32-5.47 (m, 1H), 6.82-6.88 (m, 2H), 7.26- 7.39 (m, 6H), 7.62-7.69 (m, 6H).

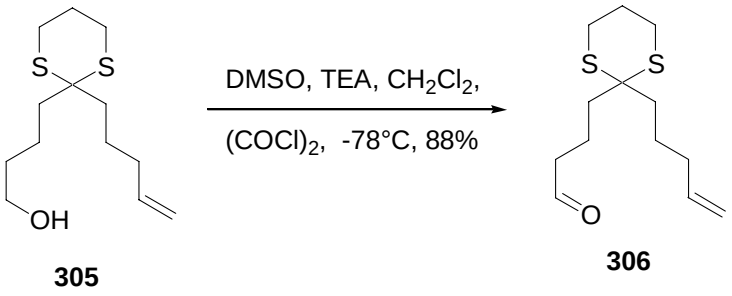
CHAPTER 4. ASYMMETRIC REINVESTIGATION OF THE RCM AND ENDGAME STRATEGY.

4.1 ASYMMETRIC VARIANT OF THE RCM STRATEGY

The advantageous results from the Jacobsen azide addition in conjunction with the discouraging results in efforts to form the nitrone led us to blend what we had accomplished with the racemic route that led us past the TANCA with the route that incorporated the azide asymmetrically.

For this plan we returned to alcohol **258** which was protected as its silyl ether to form dithiane **303** (Scheme 72). Alkylation of **303** with commercially available bromide **187** formed dithiane **304**. Desilylation of **304** yielded alcohol **305**. Swern oxidation of **305** led to aldehyde **306** uneventfully.

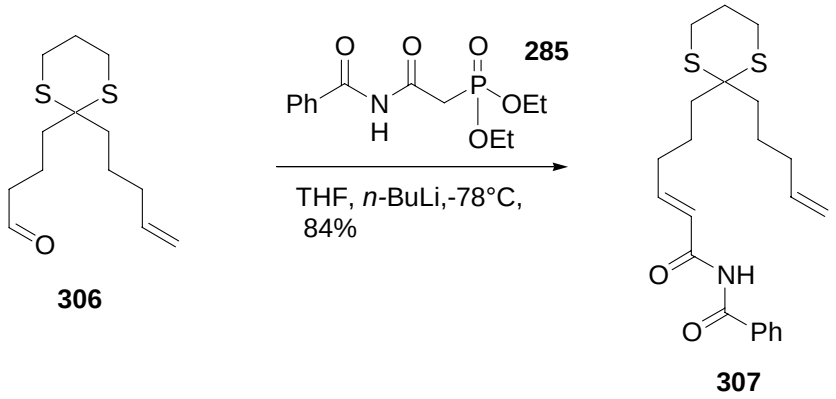




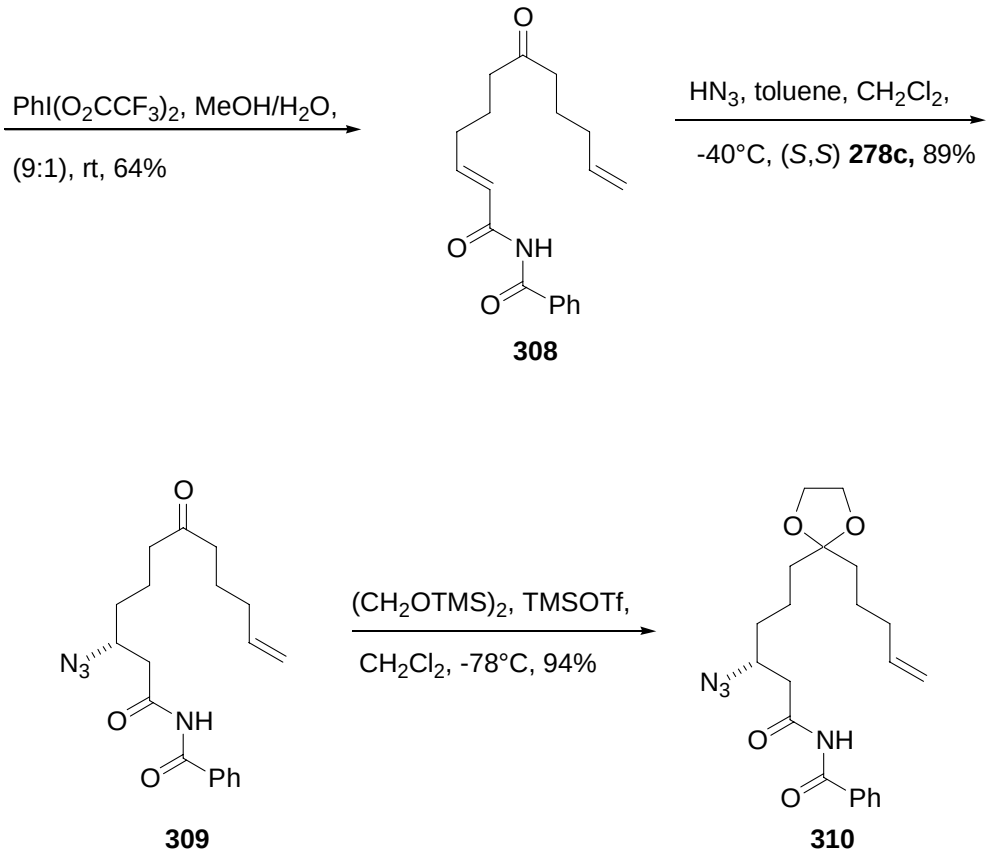
305 **306**

Scheme 72. Synthesis of aldehyde **306**.

Our next task was to incorporate the azide function into our substrate. Phosphonate **285** was used to homologate aldehyde **306** to furnish imide **307** (Scheme 73). For dithiane hydrolysis of **307**, periodic acid was not the best choice in this series; instead, the use of bis(trifluoroacetoxy) iodobenzene (PIFA) proved to give a higher yield for this transformation[95] which led to ketone **308**. The azide addition again used Jacobsen's salen chemistry to furnish azide **309**. Ketalization of **309** through Noyori's method[63] yielded dioxolane **310**.

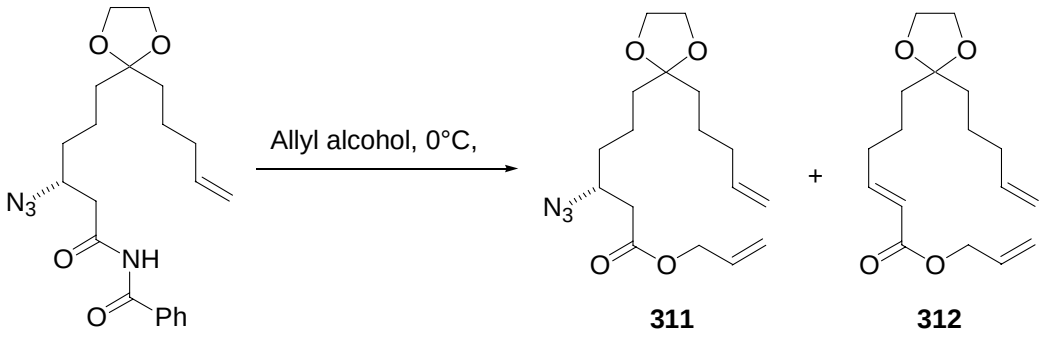


306 **307**



Scheme 73. Asymmetric azide addition.

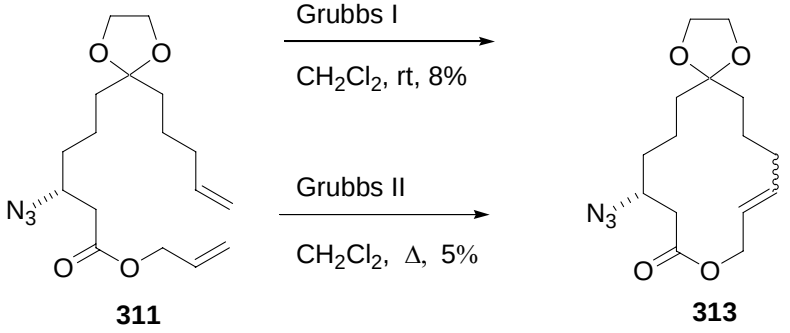
Our experience in the previous synthetic route with cleaving of the imide function with methanol and ethanol under alkaline conditions proved to be too harsh in this series. The lower yields of allyl ester **311** and the isolation of the elimination product **312** under a variety of catalytic alkaline conditions led us seek an alternative pathway (Scheme 74). The use of magnesium(II) bromide diethyletherate complex provided a means to cleave the imide with allyl alcohol to form **311** in good yield without elimination to **312**.



cat. 10% NaH,	36%	52%
cat. 10% LiH,	15%	67%
cat. 10% Li°,	25%	59%
cat. 10% $MgBr_2 \cdot (Et)_2O$, 40°C	**75%**	**0%**

Scheme 74. Cleavage of the imide function with allyl alcohol.

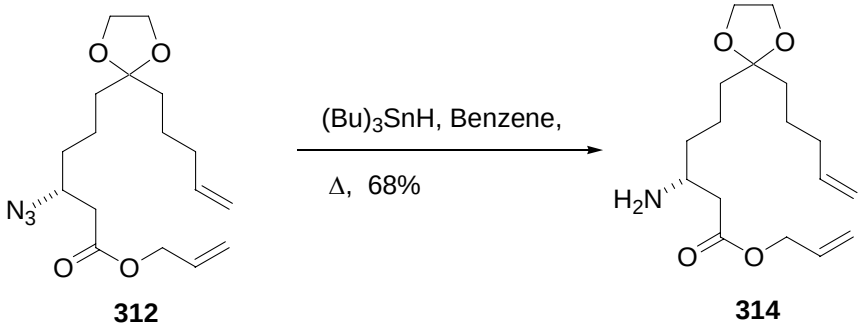
With our diene **311** in hand, we revisited the RCM of **311** with the use of the now commercially available Grubbs II catalyst. Neither the first generation Grubbs I, nor the second generation Grubbs II catalyst provided an acceptable yield of macrolactone **313** (Scheme 75).

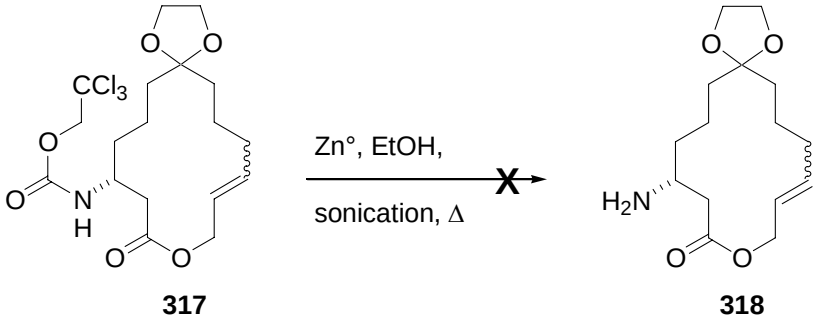


Scheme 75. RCM of azide **311**.

The outcome from the RCM with **311** required that we first protect the nitrogen as a carbamate and then proceed with the metathesis. It should be noted that the choice for protecting groups is quite limited because of other sensitive

functionality in **314** i. e, (a) the dioxolane is acid/electrophile sensitive, (b) the ester is base/nucleophile sensitive and (c) the olefin would be easily reduced with hydrogenation. Fortunately reduction of the azide function in **312** with tributyltin hydride led to amine **314** in satisfactory yield (Scheme 76). The first carbamate forming group chosen for the protection of amine **314** was 2,2,2-trichloroethoxycarbonyl chloride (TrocCl) (**315**) which gave carbamate **316**. Ring closing metathesis of the dienes present in **361** with Grubbs II catalyst gave macrolactone **317** in excellent yield with (*E*:*Z* 4:1) selectivity. Removal of the troc carbamate under non-typical neutral conditions[96] proved to be unsuccessful, with only the recovery of starting material. This deprotection often requires the use of acetic acid which was not used due to the sensitivity of the dioxolane moiety.

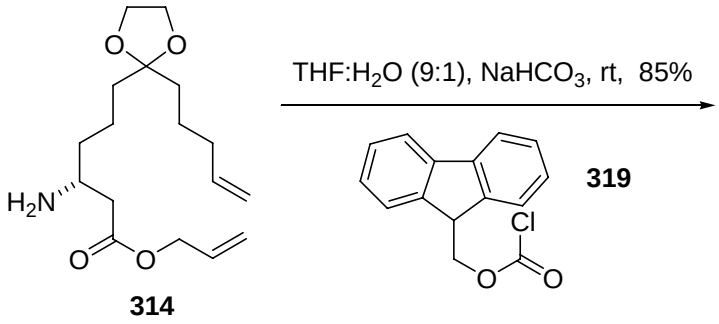




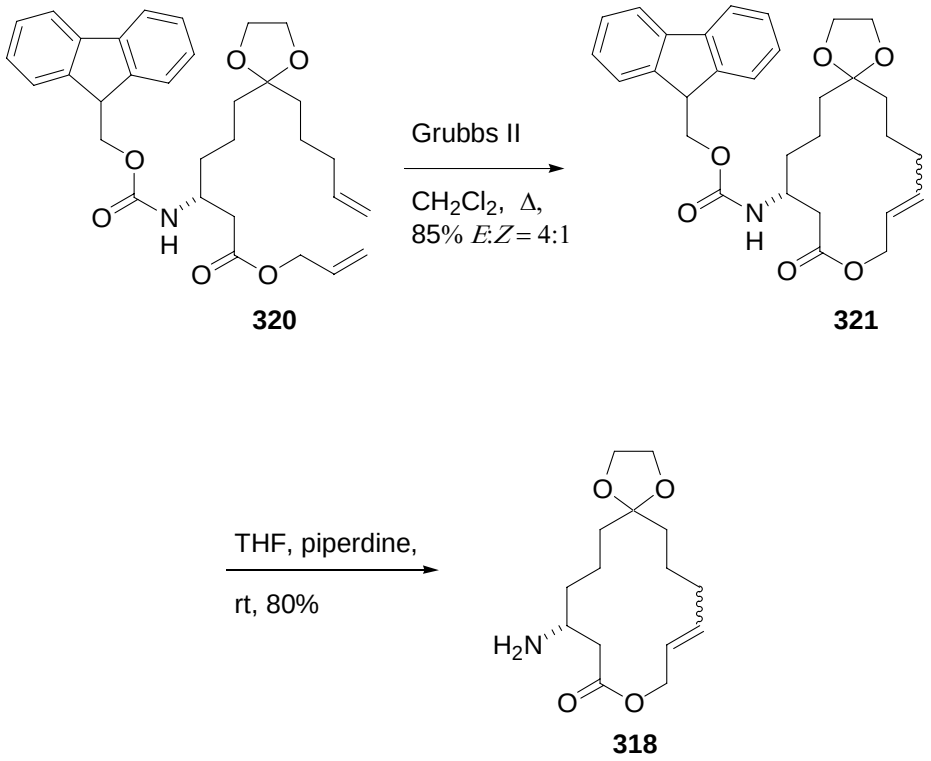
317 **318**

Scheme 76. Improved RCM 1

The difficulties with troc deprotection led us to switch to (9H-fluoren-9-yl)methyl chloroformate[97] (FmocCl) (**319**) as the protecting reagent for amine **314**. This gave carbamate **320** (Scheme 77). The RCM with **320** and Grubbs II catalyst provided macrolactone **321** in high yield with (*E*:*Z* 4:1) selectivity. Removal of the Fmoc derivative with piperidine provided amine **318** without consequence. Amine **318** now stands ready for further elaboration to the TANCA and formal synthesis of the core of halichlorine and pinnaic acid.



314 **319**

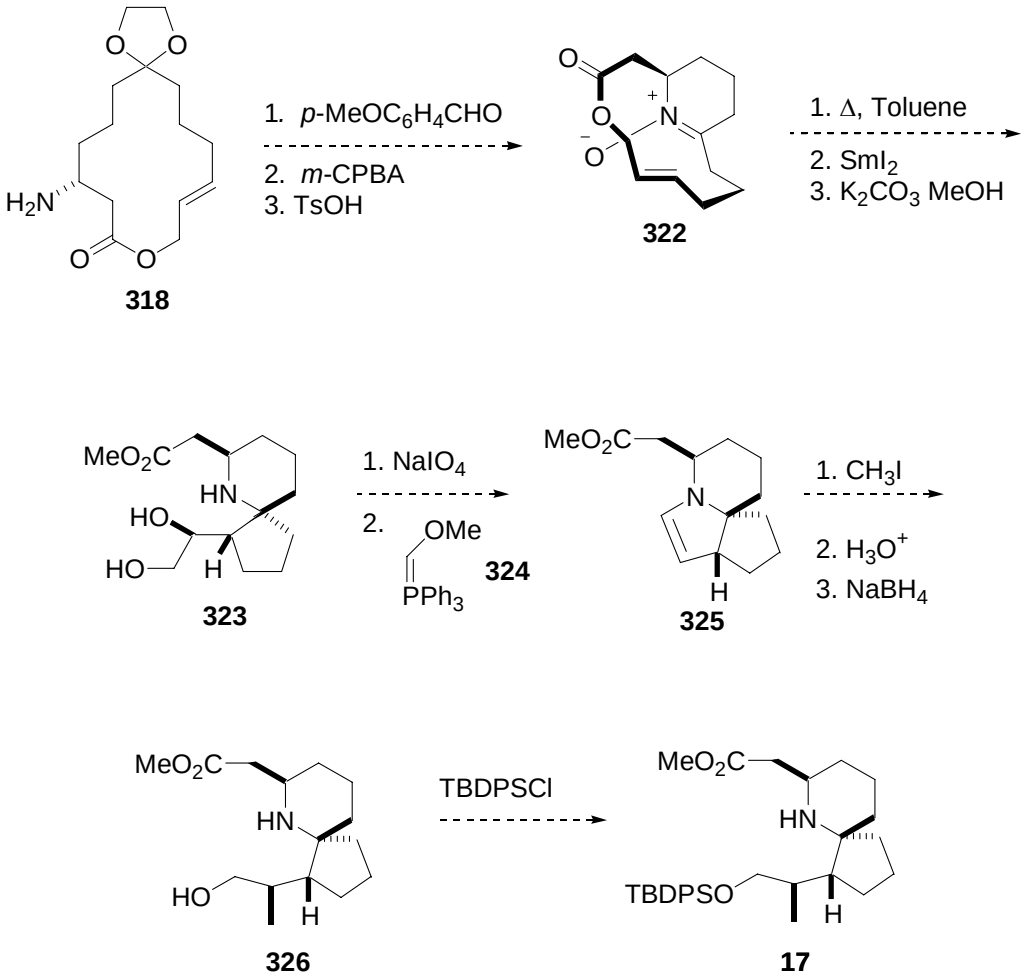


320 **321** **318**

Scheme 77. Improved RCM 2.

4.2 CONCLUSION AND POSSIBLE ENDGAME STRATEGY

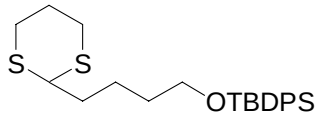
The completion of a formal synthesis of halichlorine and/or pinnaic acid would begin with amine **318**. When **318** is treated with *p*-anisaldehyde an imine should be formed. Oxidation with *m*-CPBA followed by acidic hydrolysis would lead to nitrone **322** (Scheme 76). As previously shown with nitrone **238**, when **322** is heated to reflux in toluene TANCA should occur. Cleavage of the N-O bond with samarium diiodide and alkaline hydrolysis with methanol would lead to diol **323**. Diol cleavage of **323** with sodium periodate followed by treatment with ylide **324** would provide enamine **325**. Methyl alkylation on the open face of **325** would be followed by hydrolysis of the iminium ion to the aldehyde. The aldehyde would be reduced and the ensuing alcohol **326** would be silylated to form amine **17**. This amine has been previously synthesized by Danishefsky.



Scheme 76. Planned formal synthesis of known amine **17**.

4.3 EXPERIMENTAL SECTION

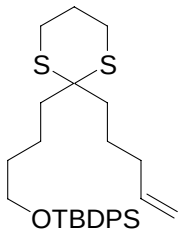
General experimental techniques and instrumentation used in this work are described in section 2.4.



303

***tert*-Butyl-(4-[1,3]dithian-2-yl-butoxy)-diphenyl-silane** (**303**). To a solution of alcohol **258** (28.6 g, 148 mmol) in CH_2Cl_2 (350 mL) was added triethylamine (44.8 g,

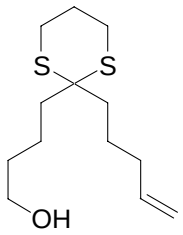
444 mmol), DMAP (50 mg, 0.410 mmol), and over 15 min TBDPSCl (45.0g, 164 mmol) and the solution was stirred at rt for 48 h. H_2O (200 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (200 mL), and the organic fractions were combined, washed with brine (200 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 7:1, 5:1 hexanes:Et_2O) to yield **303** (62.5 g, 145 mmol, 98%) as a yellowish oil: IR (Neat) 2932, 2897, 2857, 1961, 1888, 1827, 1472, 1427, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 9H), 1.59-1.69 (m, 4H), 1.78-1.97 (m, 3H), 2.08-2.19 (m, 1H), 2.78-2.97 (m, 4H), 3.68-3.77 (m, 2H), 4.04-4.12 (m, 1H), 7.37-7.45 (m, 6H), 7.68-7.75 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 19.1, 22.9, 26.0, 26.7, 30.4, 32.0, 35.1, 47.5, 63.5, 127.5 (4c), 129.5 (2C), 133.9 (2C), 135.5 (2C); MS (CI) *m/z* 431 $(M+H)^+$ 373,289, 211, 199; HRMS (CI) *m/z* 431.1888 (calcd for $C_{27}H_{38}OSiS_2$: 431.1899).



304

***tert*-Butyl-[4-(2-pent-4-enyl-[1,3]dithian-2-yl)-butoxy]-diphenyl-silane** (**304**). A solution of **303** (1.25 g, 2.90 mmol) in 10% HMPA/THF (50 mL) was cooled to -78 ºC. *n*-BuLi (2.5 M solution in hexanes 3.5 mL, 8.71 mmol) was added dropwise over 20 min and the solution was stirred for an additional 10 min. A solution of bromide

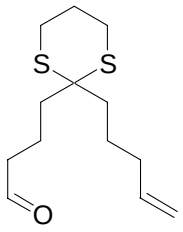
187 (475 mg, 3.19 mmol) in 10% HMPA/THF (5 mL) at -78 ºC was added to the initial flask via cannula over 15 min and the solution was allowed to warm to rt. $NH_4Cl_{(aq)}$ (50 mL) and ether (100mL) were added and the layers were separated. The organic layer was extracted with H_2O (2x50mL). The aqueous layer was extracted with ether (2x50 mL). The combined organic extracts were then washed with brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 7:1 Et_2O:hexane) to yield **304** (1.29 g, 2.61 mmol, 93%) as a yellowish oil: IR (neat) 3070, 2932, 2857, 1955, 1888, 1821, 1472, 1459, 1427, 1110cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.49-1.61 (m, 6H), 1.83-1.92 (m, 4H), 1.93-2.02 (m, 2H), 2.06-2.16 (m, 2H), 2.79-2.85 (m, 4H), 3.68-3.75 (m, 2H), 4.96-5.09 (m, 2H), 5.78-5.89 (m, 1H), 7..37-7.47 (m, 6H), 7.68-7.75 (m, 4H); MS (CI) *m/z* 499 $(M+H)^+$ 434, 243; HRMS (CI) *m/z* 499.2510 (calcd for $C_{29}H_{43}O_2S_2Si$: 499.2525).



305

4-(2-Pent-4-enyl-[1,3]dithian-2-yl)-butan-1-ol (**305**). To a solution of **304** (30.5 g, 61.1 mmol) in THF (100 mL) at rt was added TBAF (30.5 g, 73.3 mmol) and the solution was stirred for 6 h. Saturated $NH_4Cl_{(aq)}$ (100 mL) and Et_2O (200 mL) were added, the solution was shaken, and the layers were separated. The aqueous layer was

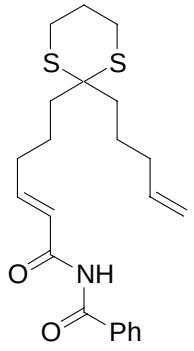
extracted with Et_2O (2x100 mL). The combined organic fractions were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 1:1 Et_2O:hexane) to yield **305** (14.9 g, 57.5 mmol, 94%) as a yellowish oil: IR (neat) 3373 br, 3070, 2939, 2864, 1639, 1456, 1423, 1068 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45-1.67 (m, 7H), 1.81-1.98 (m, 6 H), 2.03-2.12 (m, 2H), 2.75- 2.81 (m, 4H), 3.61-3.70 (m, 2H), 4.92-5.06 (m, 2H), 5.07-5.98 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 20.5, 23.4, 25.5, 26.0 (2C), 32.8, 33.7, 37.6, 38.4, 53.2, 62.7, 115.0, 138.3; MS (EI) *m/z* 260, 185, 153, 106; HRMS (EI) *m/z* 261.1335 $(M+H)^+$ (calcd for $C_{13}H_{25}OS_2$: 261.1347).



306

4-(2-Pent-4-enyl-[1,3]dithian-2-yl)-butyraldehyde (**306**). A solution of DMSO (7.95 g, 61.1 mmol) in CH_2Cl_2 (200 mL) was cooled to -78 ºC. Oxalyl chloride (7.70 g, 61.1 mmol) in CH_2Cl_2 (50 mL) at -78 ºC was added dropwise over 30 min and the solution was left to stir for an additional 10 min. Alcohol **305** (10.6 g, 40.7 mmol) in CH_2Cl_2 (40 mL) at -78 ºC was added to the initial flask via cannula over 20 min. Triethylamine (20.4 g, 202 mmol) was added dropwise while warming to rt. H_2O (200 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (200 mL) and the organic phases were combined, washed with brine, dried

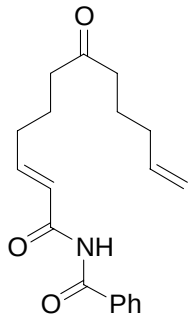
(Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 2:1 hexanes:Et_2O) to yield **306** (10.3 g, 35.8 mmol, 88%) as a yellowish oil: IR (neat) 3075, 2939, 2907, 2825, 2722, 1723, 1642, 1453, 1413 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47-1.59 (m, 2H), 1.7-1.97 (m, 8H), 2.03-2.15 (m, 2H), 2.42-2.51 (m, 2H), 3.72-3.84 (m, 4H), 4.92- 5.08 (m, 2H), 5.70-5.88 (m, 1H), 9.33 (s, 1H);^{13}C (75 MHz, $CDCl_3$) δ 17.0, 23.1, 25.3, 25.9 (2C), 33.6, 37.4, 37.6, 43.6, 52.7, 115.0, 138.1; MS (EI) *m/z*259 $(M+H)^+$ 183, 151, 133, 106, 85; HRMS (EI) *m/z* 259.1183 (calcd for $C_{13}H_{23}OS_2$: 259.1190).



307

***N*-[6-(2-Pent-4-enyl-[1,3]dithian-2-yl)-hex-2-enoyl]-benzamide** (**307**). A solution of phosphonate **285** (2.32 g, 7.77 mmol) in THF (45 mL) was cooled to –78 ºC. *n*-BuLi (2.45 M solution in hexanes 6.34 mL, 15.6 mmol) was added dropwise over 15 min, and the solution was left to stir an additional 20 min. Aldehyde **306** (1.67 g, 6.47 mmol) in THF (10 mL) was cooled to –78 ºC and the solution was added *via* cannula to the first flask over a period of 20 min. The reaction warmed to rt over 4 h and was quenched with first 1M HCl (50 mL) with stirring for 10 min then added H_2O (25 mL) and Et_2O (50 mL), The layers were separated, and the aqueous layer was extracted

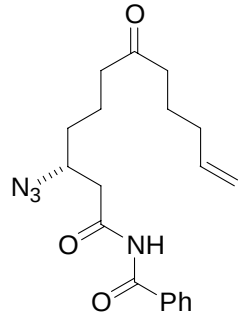
with Et_2O (2x50 mL). The organic fractions were combined, washed with brine (40 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 2:1, 1:1, hexanes:Et_2O) to yield **307** (2.20 g, 5.43 mmol, 84%): IR (Neat) 3276, 3069, 2940, 2244, 1707, 1673, 1637, 1506, 1474, 1346, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48-1.70 (m, 4H), 1.80-1.93 (m, 6H), 1.94-2.01 (m, 2H), 2.21-2.38 (m, 2H), 3.69-3.83 (m, 4H), 4.92-5.09 (m, 2H), 5.70-5.87 (m, 1H), 7.10-7.20 (m, 2H), 7.42-7.61 (m, 3H), 7.89-7.97 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 22.8, 23.2, 25.3, 25.9 (2C), 32.6, 33.6, 37.6 (2C), 52.9, 115.5, 123.3, 127.9 (2C), 128.8 (2C), 132.9, 133.1, 138.1, 150.8, 166.0, 167.7; MS (EI) *m/z* 404 $(M + H)^+$,296, 283, 241, 187, 122, 105; HRMS (EI) *m/z* 403.1610 (calcd for $C_{22}H_{29}NO_2S_2$: 403.1640).



308

***N*-(7-Oxo-dodeca-2,11-dienoyl)-benzamide** (**308**). Bis(trifluoroacetoxy)iodobenzene (907 mg, 2.11 mmol) was added at rt to a solution of **307** (568 mg, 1.41 mmol) in MeOH:H_2O (9:1, 20 mL) and the solution was left for 5 h. The reaction was quenched with the addition of sat. $NaHCO_{3(aq)}$ (20 mL) and Et_2O (30 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2x30 mL). The combined organic extracts were then washed with brine (50 mL), dried (Na_2SO_4) and

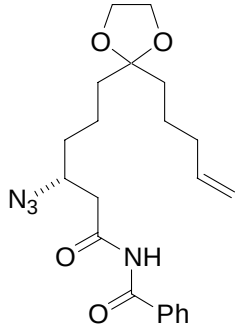
concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 1:1 Et_2O:hexane) to yield **308** (282 mg, 0.902 mmol, 64 %) as a colorless oil: IR (neat) 3282, 2935, 1716, 1683, 1641, 1506, 1484, 1242, 1153 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68-1.74 (m, 2H), 1.79-1.87 (m, 2H), 2.04-2.11 (m, 2H), 2.30-2.38 (m, 2H), 2.41-2.51 (m, 6H), 4.98-5.08 (m, 2H), 5.71-5.83 (m, 1H), 7.23-7.31 (m, 2H), 7.50-7.58 (m, 2H), 7.60-7.67 (m, 1H), 7.89-7.96 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 21.8, 22.7, 31.8, 33.0, 41.6, 41.9, 115.2, 123.3, 127.7 (2C), 128.8 (2C), 132.8, 137.1, 137.9, 150.5, 165.8, 167.4, 210.2; MS (EI) *m/z* 314 $(M+H)^+$ 193, 122, 105; HRMS (CI) *m/z* 313.1681 (calcd for $C_{19}H_{23}O_3N$:313.1678).



309

***N*-(3-Azido-7-oxo-dodec-11-enoyl)-benzamide** (**309**). To a solution of **308** (1.98 g, 6.32 mmol) in CH_2Cl_2 (10 mL) was added salen cat. **278c** (185 mg, 0.316 mmol) and the solution was cooled to -78 ºC. A solution of HN_3 in toluene (1.1M solution, 28.7 mL, 31.6 mmol) was slowly added over 20 min and then the solution was allowed to warm to -40 ºC while stirring for an additional 12 h. Another quantity of **278c** (185 mg, 0.316 mmol) and HN_3 in toluene (1.1M solution, 28.7 mL, 31.6 mmol) was added and the solution was stirred for an additional 24 h. The solution was allowed to warm to rt while open to atmosphere under a stream of Ar to remove excess HN_3. The

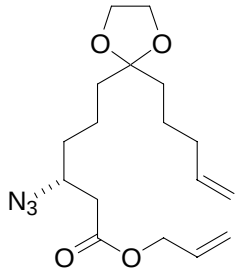
solution was concentrated *in vacuo*, and the residue was purified *via* column chromatography (eluting with 4:1 hexanes:Et_2O) to yield **309** (2.00 g, 5.62 mmol, 89%) as a colorless oil: $[\alpha]_D^{23}$ -1.42 (c =`2.25, $CHCl_3$); IR (Neat) 3288, 3072, 2931, 2106, 1713, 1693, 1504, 1471, 1379, 1242, 1195cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57-1.81 (m, 6H), 2.01-2.11 (m, 2H), 2.38-2.50 (m, 4H), 3.11-3.31 (m, 2H), 3.90-4.02 (m, 1H), 4.93-5.10 (m, 2H), 5.68-5.88 (m, 1H), 7.45-7.60 (m, 2H), 7.61-7.70 (m, 2H), 7.86-7.95 (m, 2H), 9.12 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 20.0, 22.5, 32.8, 33.7, 41.7, 41.8, 42.6, 58.0, 115.0, 127.8 (2C), 128.6 (2C), 132.2, 133.1, 137.7, 165.9, 173.8, 210.1; MS (CI) *m/z* 357 $(M+H)^+$ 314, 208, 160; HRMS (CI) *m/z* 357.1925 (calcd for $C_{19}H_{25}O_3N_4$: 357.1927).



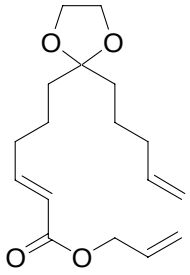
310

***N*-[3-Azido-6-(2-pent-4-enyl-[1,3]dioxolan-2-yl)-hexanoyl]-benzamide** (**310**). To a solution of ketone **309** (2.00 g, 5.62 mmol) in CH_2Cl_2 (50 mL) was added 1,2-bis(trimethylsilyloxy)ethane (3.48 mg, 16.8 mmol) and the solution was cooled to –78 ºC. TMSOTf (62 mg, 0.281 mmol) was added and the solution was left to stir for an additional 3 h while warming to 0 ºC. The reaction was quenched by the addition of dry pyridine (2 mL) at 0 ºC, and poured into a solution of sat. $NaHCO_{3(aq)}$ (30 mL), and extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried

(Na_2SO_4), and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 3:1 hexanes:Et_2O) to yield **310** (2.11 g, 5.28 mmol, 94%) as a yellowish oil: $[\alpha]_D^{23}$ +1.58 (c = 0.76, $CHCl_3$); IR (Neat) 3276, 2949, 2876, 2106, 1714, 1683, 1504, 1496, 1381, 1241 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.70 (m, 10H), 2.00-2.11 (m, 2H), 3.09-3.30 (m, 2H), 3.83-3.98 (m, 1H), 4.89 (s, 4H), 4.90-5.03 (m, 2H), 5.72-5.86 (m, 1H), 7.46-7.55 (m, 2H), 7.56-7.65 (m, 1H), 7.85-7.92 (m, 2H), 9.28 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 20.3, 23.0, 33.8, 34.7, 36.5, 36.6, 42.8, 58.3, 64.9, 111.3, 114.6, 123.8 (2C), 128.9 (2C) 132.3, 133.4, 138.5, 165.8, 173.8; MS (CI) *m/z* 401 $(M-H)^+$, 373, 357, 252; HRMS (CI) *m/z* 401.2364 (calcd for $C_{21}H_{29}O_4N_4$: 401.2189).



311

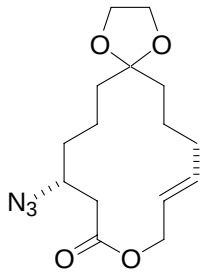


312

3-Azido-6-(2-pent-4-enyl-[1,3]dioxolan-2-yl)-hexanoic acid allyl ester (**311**). A solution of **310** (1.25 g, 4.38 mmol) in allyl alcohol (20 mL) was added $MgBr_2 \cdot Et_2O$ (113 mg, 0.43 mmol) at rt and heated to 40 ºC for 6 h. H_2O (20 mL) Et_2O (20 mL) were added shaken and seperated. The aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic fractions were then washed with brine (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column

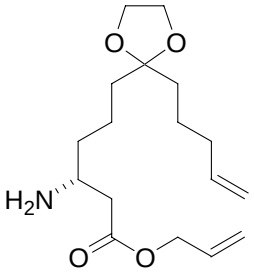
chromatography (eluting with 1:2 Et_2O:hexane) to yield **311** (1.11 g, 3.29 mmol, 75%) as a colorless oil: $[\alpha]_D^{23}$ -1.79 (c = 3.8, $CHCl_3$); IR (neat) 2945, 2100, 1736, 1639, 1462, 1375, 1272, 1166, 1069, 992, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30-1.70 (m, 10H), 2.04 (qt, *J* = 7, 1 Hz, 2H), 2.51 (d, *J* = 7 Hz, 2H), 3.78 (q, *J* = 7 Hz, 1H), 3.91 (s, 4H), 4.60 (dt, *J* = 6, 1 Hz, 2H), 4.93 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.99 (dq, *J* = 17, 2 Hz, 1H), 5.24 (dq, *J* = 10, 1 Hz, 1H), 5.32 (dq, *J* = 17, 1 Hz, 1H), 5.78 (ddt, *J* = 17, 10, 7 Hz, 1H), 5.91 (ddt, *J* = 17, 10, 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 23.1, 33.8, 34.5, 36.6, 36.6, 39.5, 59.1, 64.9 (2C), 65.5, 111.3, 114.7, 118.6, 131.8, 138.5, 170.3; MS (FAB) *m/z* 338, $(M-H)^+$, 336, 310, 268, 240, 141; HRMS (FAB) *m/z* 338.2074 (calcd for $C_{17}H_{28}N_3O_4$: 338.2080).

6-(2-Pent-4-enyl-[1,3]dioxolan-2-yl)-hex-2-enoic acid allyl ester (**312**). Isolated from the alkaline hydrolysis reactions from **310** in yields ranging from 52-67%
IR (neat) 2944, 1714, 1650, 1433, 1365, 1263, 1173, 1028, 990, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35-1.70 (m, 8H), 2.02 (qt, *J* = 7, 1 Hz, 2H), 2.19 (qd, *J* = 7, 2 Hz, 2H), 3.90 (s, 4H), 4.61 (dt, *J* = 6, 1 Hz, 2H), 4.93 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.98 (dq, *J* = 17, 2 Hz, 1H), 5.21 (dq, *J* = 10, 1 Hz, 1H), 5.30 (dq, *J* = 17, 2 Hz, 1H), 5.77 (ddt, *J* = 17, 10, 7 Hz, 1H), 5.83 (dt, *J* = 16, 1 Hz, 1H), 5.92 (ddt, *J* = 17, 10, 6 Hz, 1H), 6.96 (dt, *J* = 16, 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 23.0, 32.2, 33.8, 36.6, 36.6, 64.8, 64.9 (2C), 111.4, 114.6, 118.0, 121.2, 132.3, 138.5, 149.4, 166.2; MS (CI) *m/z* 295, 237, 225, 141; HRMS (CI) *m/z* 295.1904 (calcd for $C_{17}H_{27}O_4$: 295.1909).



313

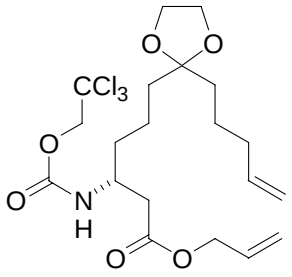
9-Azido-1,4,12-trioxa-spiro[4.13]octadec-14-en-11-one (**313**). $[\alpha]_D^{23}$ -10.5 (c = 0.315, $CHCl_3$). Spectral data are the same as for compound **248**.



314

3-Amino-6-(2-pent-4-enyl-[1,3]dioxolan-2-yl)-hexanoic acid allyl ester (**314**). To a solution of **290** (1.107 g, 3.28 mmol) in benzene (30 mL) was added tributyltin hydride (2.80 mg, 9.85 mmol) and the solution was heated to reflux for 14 h. The solution was concentrated *in vacuo*. The residue was further purified *via* column chromatography (eluting with hexanes followed by 20:1 CH_2Cl_2:MeOH) to yield **314** (694 mg, 2.33 mmol, 68%) as a colorless oil: $[\alpha]_D^{23}$ -2.8 (c = 0.43, $CHCl_3$); IR (neat) 2940, 1732, 1636, 1456, 1373, 1160, 1059, 991, 914 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 1.30-1.70 (m, 10H), 2.04 (qt, *J* = 7, 1 Hz, 2H), 2.31 (dd, *J* = 16, 9 Hz, 1H), 2.51 (dd, *J* = 16, 4 Hz, 1H), 3.15-3.25 (m, 1H), 3.91 (s, 4H), 4.59 (dt, *J* = 6, 1 Hz, 2H),

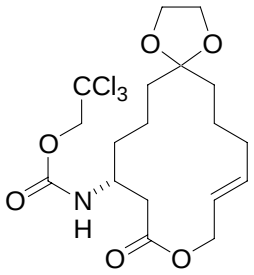
4.94 (ddt, *J* = 10, 2, 1 Hz, 1H), 4.99 (dq, *J* = 17, 2 Hz, 1H), 5.23 (dq, *J* = 10, 1 Hz, 1H), 5.31 (dq, *J* = 17, 2 Hz, 1H), 5.78 (ddt, *J* = 17, 10, 7 Hz, 1H), 5.91 (ddt, *J* = 17, 10, 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 23.1, 33.8, 36.6, 37.0, 37.5, 42.2, 48.3, 64.9 (2C), 65.1, 111.5, 114.6, 118.4, 132.1, 138.6, 172.2; MS (FAB) *m/z* 312 $(M+H)^+$, 250; HRMS (FAB) *m/z* 312.2180 (calcd for $C_{17}H_{30}NO_4$: 312.2175).



316

6-(2-Pent-4-enyl-[1,3]dioxolan-2-yl)-3-(2,2,2-trichloro-ethoxycarbonylamino)-hexanoic acid allyl ester (**316**). To a solution of **314** (55.0 mg, 177 μmol) in CH_2Cl_2 (5 mL) and pyridine (2 mL) was added TrocCl (89.8 mg, 414 μmol) and the solution was left to stir for 12 h at rt. H_2O (7 mL) was added, the mixture was shaken and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x5 mL). The combined organic fractions were then washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 1:1 Et_2O:hexane) to yield **316** (76.6 mg, 158 μmol, 89%) as a colorless oil: $[\alpha]_D^{23}$ +10.1 (c = 0.84, $CHCl_3$); IR (neat) 3343, 3078, 2950, 2880, 1739, 1530, 1231, 1129 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35-1.69 (m, 10H), 2.00-2.09 (m, 2H), 2.52-

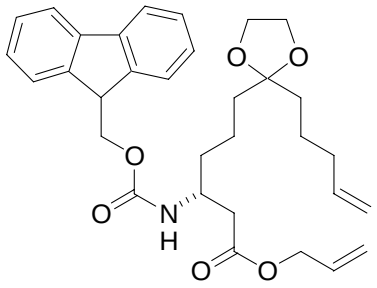
2.69 (m, 2H), 3.91 (s, 4H), 3.92-4.06 (m, 1H), 4.55-5.02 (m, 5H), 5.20-5.47 (m, 3H), 5.70-5.98 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 20.4, 23.1, 33.8, 34.4, 36.6, 38.8, 48.5, 64.9, 65.4 (2C), 74.4, 46.1, 111.4, 114.7, 118.7, 131.8, 138.6, 154.8, 172.1; MS (CI) *m/z* 488 $(M+H)^+$ 426, 338, 113, 98; HRMS (CI) *m/z* 486.1211 (calcd for $C_{20}H_{31}NO_6Cl_3$: 486.1217).



317

(11-Oxo-1,4,12-trioxa-spiro[4.13]octadec-14-en-9-yl)-carbamic acid 2,2,2-trichloro-ethyl ester (**317**). A solution of **316** (12.3 mg, 2.53 μmol) in anhydrous CH_2Cl_2 (8 mL) at rt under Ar, was treated with [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (1 mg, 1.27 μmol) followed by another such additon after 6 h. After stirring for an additional 24 h the solvent was removed *in vacuo.* The resulting black residue was further purified *via* column chromatography (eluting with 1:1 Et_2O:hexane) to yield **317** (10.6 mg, 23.0 μmol, 91%) as a colorless oil: $[\alpha]_D^{23}$ +17.8 (c = 0.89, $CHCl_3$); IR (neat) 3331, 2952, 1734, 1522, 1233, 1171, 1141, 1064 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *E:Z* = 4:1 δ 1.16-1.68 (m, 10H), 1.94-2.29 (m, 2H), 2.49-2.72 (m, 2H), 3.83-4.00 (m 1H), 3.9 (s, 4H), 4.21-4.30 (m, 1H), 4.68-4.71 (m, 2H), 4.86-4.98 (m, 1H),

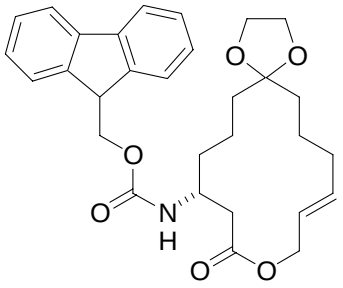
5.65-5.72 (m, 1H), 6.79-6.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 23.1, 30.9, 32.6, 32.9, 70.3, 37.1, 49.0, 63.8, 64.6, 64.7, 74.8, 96.0, 112.0, 126.1, 138.2, 154.1, 172.3; MS (CI) *m/z* 460 $(M-H)^+$, 424, 310, 248, 153; HRMS (CI) *m/z* 458.0926 (calcd for $C_{18}H_{27}NO_6Cl_3$: 458.0904).



320

3-(9H-Fluoren-9-ylmethoxycarbonylamino)-6-(2-pent-4-enyl-[1,3]dioxolan-2-yl)-hexanoic acid allyl ester (**320**). To a solution of **314** (101 mg, 325 μmol) in THF:H_2O (9:1, 10 mL) was added $NaHCO_3$ (81.0 mg, 975 μmol) and then FmocCl (101 mg, 390 μmol) and the solution was left to stir for 12 h at rt. H_2O (7 mL) and CH_2Cl_2 (10 mL) were added, the mixture was shaken and the solution were separated. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic fractions were then washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 1:1 Et_2O:hexane) to yield **320** (147 mg, 276 μmol, 85%) as a colorless oil: $[\alpha]_D^{23}$ +7.13 (c = 2.82, $CHCl_3$); IR (neat) 3337, 2948, 2880, 1728, 1528, 1450, 1241, 1181 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41-1.72 (m, 10H), 2.02-2.12 (m, 2H), 2.58-2.70 (m, 2H), 3.97 (s, 4H), 4.00-4.01 (m, 1H), 4.22-4.29 (m, 1H), 4.38-4.45 (m, 2H), 4.59-4.67 (m, 2H), 4.97-5.08 (m, 2H), 5.35-5.40 (m, 2H), 5.78-6.02 (m, 2H), 7.30-7.44 (m, 4H),

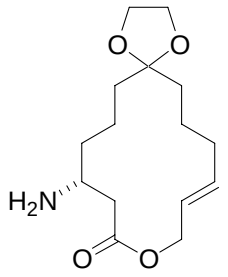
7.58-7.64 (m, 2H), 7.76-7.83 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 20.4, 23.1, 33.8, 34.4, 36.5, 36.6, 38.9, 47.2, 48.1, 64.9, 65.2, 66.6, 111.4, 114.6, 118.5, 119.6, 125.0, 127.0, 127.6, 131.8, 136.2, 138.5, 141.2, 143.9, 155.7, 171.2; MS (CI) *m/z* 534 $(M+H)^+$ 472, 338,`207, 195, 180.



321

(**11-Oxo-1,4,12-trioxa-spiro[4.13]octadec-14-en-9-yl)-carbamic acid 9H-fluoren-9-ylmethyl ester** (**321**). A solution of **320** (25.0 mg, 46.9 μmol) in anhydrous CH_2Cl_2 (8 mL) at rt under Ar was treated with [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (2 mg, 2.34 μmol) followed by another such additon after 7 h. After stirring for an additional 12 h the solvent was removed *in vacuo.* The resulting black residue was further purified *via* column chromatography (eluting with 1:1 Et_2O:hexane) to yield **321** (20.2 mg, 39.7 μmol, 85%) as a colorless oil: $[\alpha]_D^{23}$ +24.7 (c = 0.45, $CHCl_3$); IR (neat) 3337, 2959, 2877, 1723, 1509, 1450, 1235, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.73 (m, 10H), 1.95-2.20 (m, 2 H), 2.42-2.68 (m, 2H), 3.90 (s, 4H), 3.82.4.02 (m, 1H), 4.16-4.20 (m, 2H), 4.32-4.41 (m, 2H), 4.85-4.98 (m, 1H), 5.53-5.90 (m, 2H), 7.18-7.42 (m, 4H), 7.50-7.61 (m, 2H), 7.64-7.79 (m, 2H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 21.3, 22.2, 30.6, 31.6, 32.7, 33.5, 34.0, 35.3, 37.4, 47.3, 48.2, 63.8, 64.5, 64.7, 64.8, 66.7, 111.8, 120.0, 125.2, 126.1, 127.1, 127.7, 138.3, 141.3, 144.0, 155.7, 171.4.5, 6; MS (CI) *m/z* 506 $(M-H)^+$, 310, 284, 207, 180; HRMS (CI) *m/z* 506.2547 (calcd for $C_{30}H_{36}NO_6$: 506.2543).



318

9-Amino-1,4,12-trioxa-spiro[4.13]octadec-14-en-11-one (**318**). To a solution of **321** (55.8 mg, 109 μmol) in CH_2Cl_2 (10 mL) was added piperidine (46.3 mg, 545 μmol) and the solution was stirred for 30 min. H_2O (10 mL) was added, the mixture was shaken, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic fractions were then washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified *via* column chromatography (eluting with 20:1 CH_2Cl_2:MeOH) to yield **318** (24.7 mg, 87.2 μmol, 80%) as a yellowish oil: $[\alpha]_D^{23}$ +6.01 (c = 0.715, $CHCl_3$); IR (neat) 3367, 2950, 2874, 1728, 1587, 1447, 1371, 1207, 1145 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17-1.67 (m, 10H, 1.91-2.27 (m, 2 H), 2.25-2.36 (m, 1H), 2.49-2.59 (m, 1H), 3.06-3.20 (m, 1H), 3.85 (s, 4H), 4.43-4.60 (m, 2H), 5.58-5.85 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ

21.1, 22.1, 30.4, 32.8, 35.4, 37.2, 41.9, 49.4, 63.4, 64.3, 64.4, 111.7, 126.1, 137.8, 171.2.

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CHAPTER 5. GENERAL CONCLUSION

The studies described in this dissertation outline a conceptually new approach to the halichlorine and pinnaic acid core structures. Central to the success of our approach was the discovery of transannular nitrone cycloaddition the first (TANCA) and its utility in the formation of the azaspirocyclic cores found in halichlorine and pinnaic acid. Other pivotal features in our synthesis included asymmetric introduction of a nitrogen moiety via Jacobsen's salen catalyzed conjugate addition of hydrozoic acid. Improvement in yield over the original RCM used in the racemic route for macrolactone formation is also significant.

An advanced intermediate now stands ready to complete a formal synthesis of the spirocyclic core of the natural products.

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APPENDICES

A 1. Crystal data and structure refinement for 254.

Identification code	PA092000	
Empirical formula	$C_{13}H_{19}NO_3$	
Formula weight	237.29	
Temperature	288(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_1 2_1$	
Unit cell dimensions	a = 5.798(3) Å	α= 90°.
d	b = 12.687(6) Å	β= 90°.
	c = 15.244(8) Å	γ = 90°.
Volume	1121.3(10) $Å^3$	
Z	4	
Density (calculated)	1.406 Mg/m^3	
Absorption coefficient	0.808 mm^{-1}	
F(000)	512	
Crystal size	0.30 x 0.05 x 0.05 mm^3	
Theta range for data collection	4.53 to 69.94°.	
Index ranges	-1<=h<=3, -15<=k<=1, -18<=l<=1	
Reflections collected	1239	
Independent reflections	1092 [R(int) = 0.0283]	
Completeness to theta = 69.94°	96.7 %	
Absorption correction	Psi-scans	
Max. and min. transmission	0.9607 and 0.7935	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1092 / 12 / 163	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.0753	
R indices (all data)	R1 = 0.0704, wR2 = 0.0874	
Absolute structure parameter	0.4(5)	
Largest diff. peak and hole	0.100 and -0.103 e.$Å^{-3}$	

A 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 254. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor..

	x	y	z	U(eq)
O(1)	5346(8)	1857(3)	6923(2)	82(2)
O(2)	2806(6)	488(2)	5426(2)	57(1)
O(3)	2626(6)	2364(2)	6067(2)	66(1)
N	2142(8)	-417(2)	5927(2)	52(1)
C(1)	3418(12)	1735(4)	6694(3)	60(2)
C(2)	1833(8)	970(3)	7102(2)	52(2)
C(3)	2426(8)	-138(3)	6845(2)	59(1)
C(4)	1124(12)	-920(4)	7397(3)	80(2)
C(5)	-1325(12)	-952(4)	7132(3)	76(2)
C(6)	-1507(10)	-1322(3)	6216(2)	74(2)
C(7)	-101(10)	-688(3)	5576(3)	49(2)
C(81)	255(10)	-1303(3)	4731(3)	74(2)
C(91)	-1910(30)	-1044(10)	4184(9)	74(5)
C(101)	-2424(9)	43(3)	4425(3)	68(1)
C(82)	255(10)	-1303(3)	4731(3)	74(2)
C(92)	-830(30)	-737(11)	4058(9)	73(5)
C(102)	-2424(9)	43(3)	4425(3)	68(1)
C(11)	-1187(8)	317(3)	5262(2)	47(1)
C(12)	788(11)	1046(3)	5156(2)	50(1)
C(13)	577(9)	2085(3)	5638(3)	60(2)

A 3. Bond lengths [Å] and angles [°] for 254.

O(1)-C(1)	1.182(5)
O(2)-C(12)	1.428(5)
O(2)-N)	1.432(3)
O(3)-C(1)	1.326(5)
O(3)-C(13)	1.402(5)
N-C(7)	1.448(5)
N-C(3)	1.453(5)
C(1)-C(2)	1.475(6)
C(2)-C(3)	1.499(5)
C(3)-C(4)	1.504(6)
C(4)-C(5)	1.477(6)
C(5)-C(6)	1.477(5)
C(6)-C(7)	1.504(5)
C(7)-C(11)	1.501(5)
C(7)-C(81)	1.521(5)
C(81)-C(91)	1.541(15)
C(91)-C(101)	1.458(14)
C(101)-C(11)	1.503(5)
C(11)-C(12)	1.481(5)
C(12)-C(13)	1.514(5)
C(12)-O(2)-N	109.3(3)
C(1)-O(3)-C(13)	118.5(4)
O(2)-N-C(7)	103.6(3)
O(2)-N-C(3)	106.8(3)
C(7)-N-C(3)	121.0(3)
O(1)-C(1)-O(3)	117.4(5)
O(1)-C(1)-C(2)	123.5(5)
O(3)-C(1)-C(2)	119.0(5)
C(1)-C(2)-C(3)	111.3(4)
N-C(3)-C(2)	117.0(3)
N-C(3)-C(4)	108.8(4)
C(2)-C(3)-C(4)	110.9(4)
C(5)-C(4)-C(3)	110.4(4)
C(4)-C(5)-C(6)	109.7(5)

C(5)-C(6)-C(7)	113.9(4)
N-C(7)-C(11)	107.0(4)
N-C(7)-C(6)	112.0(4)
C(11)-C(7)-C(6)	115.7(4)
N-C(7)-C(81)	108.3(4)
C(11)-C(7)-C(81)	102.8(3)
C(6)-C(7)-C(81)	110.5(3)
C(7)-C(81)-C(91)	103.8(6)
C(101)-C(91)-C(81)	103.5(9)
C(91)-C(101)-C(11)	109.5(7)
C(12)-C(11)-C(7)	103.9(4)
C(12)-C(11)-C(101)	114.9(3)
C(7)-C(11)-C(101)	106.0(3)
O(2)-C(12)-C(11)	107.0(3)
O(2)-C(12)-C(13)	111.0(4)
C(11)-C(12)-C(13)	115.3(4)
O(3)-C(13)-C(12)	112.2(4)

Symmetry transformations used to generate equivalent atoms:

A 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 254. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	55(4)	101(3)	90(2)	-15(2)	-10(3)	-30(3)
O(2)	39(3)	68(2)	63(2)	-7(2)	11(2)	-1(2)
O(3)	74(3)	60(2)	64(2)	1(2)	-5(2)	-22(2)
N	39(4)	48(2)	70(2)	0(2)	10(2)	0(2)
C(1)	62(7)	61(3)	57(3)	-17(2)	9(3)	-18(4)
C(2)	46(5)	65(2)	45(2)	-4(2)	1(2)	0(3)
C(3)	41(4)	68(3)	67(2)	11(2)	-15(3)	8(3)
C(4)	79(6)	78(3)	82(3)	26(3)	-20(4)	5(3)
C(5)	79(7)	81(3)	68(3)	24(3)	3(3)	-25(3)
C(6)	73(5)	66(3)	85(3)	3(2)	11(3)	-21(3)
C(7)	35(5)	46(2)	66(2)	-6(2)	6(3)	1(3)
C(81)	77(5)	66(3)	80(3)	-29(3)	5(3)	11(3)
C(91)	87(10)	66(6)	69(6)	-21(5)	-13(7)	-12(7)
C(101)	49(4)	77(3)	79(3)	-17(2)	-13(3)	3(3)
C(82)	77(5)	66(3)	80(3)	-29(3)	5(3)	11(3)
C(92)	69(10)	90(8)	59(6)	-24(6)	-1(7)	-1(7)
C(102)	49(4)	77(3)	79(3)	-17(2)	-13(3)	3(3)
C(11)	32(4)	56(2)	53(2)	-13(2)	10(2)	-1(3)
C(12)	42(5)	64(3)	45(2)	0(2)	3(3)	0(3)
C(13)	66(5)	48(2)	66(2)	-3(2)	-10(3)	1(3)

A 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 254..

	x	y	z	U(eq)
H(2A)	264	1125	6923	62
H(2B)	1915	1038	7735	62
H(3)	4064	-235	6982	71
H(4A)	1802	-1614	7329	95
H(4B)	1235	-722	8011	95
H(5A)	-1996	-255	7184	91
H(5B)	-2169	-1425	7516	91
H(6A)	-3113	-1297	6039	89
H(6B)	-1012	-2051	6189	89
H(81A)	360	-2053	4846	89
H(81B)	1645	-1075	4431	89
H(91A)	-1593	-1104	3561	89
H(91B)	-3175	-1509	4335	89
H(10A)	-4074	127	4505	82
H(10B)	-1935	514	3960	82
H(82A)	1889	-1376	4607	89
H(82B)	-412	-2001	4781	89
H(92A)	-1679	-1220	3683	87
H(92B)	317	-384	3702	87
H(10C)	-3933	-258	4539	82
H(10D)	-2586	651	4045	82
H(11)	-2274	589	5699	56
H(12)	946	1202	4529	60
H(13A)	172	2634	5223	72
H(13B)	-658	2034	6065	72

Table 1. Crystal data and structure refinement for ek102401.

A 6. Crystal data and structure refinement for 274.

Identification code	ek102401	
Empirical formula	$C_{17}H_{26}O_2S_2$	
Formula weight	326.50	
Temperature	290(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	Pbca (#61)	
Unit cell dimensions	a = 18.5980(7) Å	α= 90°.
	b = 7.8240(3) Å	β= 90°.
	c = 24.0410(9) Å	γ = 90°.
Volume	3498.2(2) $Å^3$	
Z	8	
Density (calculated)	1.240 Mg/m^3	
Absorption coefficient	2.766 mm^{-1}	
F(000)	1408	
Crystal size	0.30 x 0.20 x 0.20 mm^3	
Theta range for data collection	3.68 to 67.72°.	
Index ranges	-22<=h<=1, -8<=k<=1, -28<=l<=1	
Reflections collected	3862	
Independent reflections	2992 [R(int) = 0.0316]	
Completeness to theta = 67.72°	94.3 %	
Max. and min. transmission	0.6077 and 0.4909	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2992 / 0 / 192	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0379, wR2 = 0.0984	
R indices (all data)	R1 = 0.0488, wR2 = 0.1093	
Largest diff. peak and hole	0.183 and -0.234 e.$Å^{-3}$	

A 7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 274. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-824(1)	6877(2)	2713(1)	60(1)
O(2)	-905(1)	8979(3)	3346(1)	86(1)
S(1)	1776(1)	1491(1)	3876(1)	48(1)
S(2)	1241(1)	3420(1)	4874(1)	57(1)
C(1)	-543(1)	8060(3)	3062(1)	58(1)
C(2)	244(1)	8038(3)	3069(1)	59(1)
C(3)	629(1)	6777(3)	2873(1)	55(1)
C(4)	1413(1)	6476(3)	2950(1)	59(1)
C(5)	1535(1)	4766(3)	3248(1)	51(1)
C(6)	1321(1)	4808(3)	3862(1)	46(1)
C(7)	1123(1)	3075(3)	4128(1)	41(1)
C(8)	355(1)	2512(3)	3970(1)	43(1)
C(9)	-258(1)	3459(3)	4261(1)	47(1)
C(10)	-988(1)	3182(3)	3980(1)	50(1)
C(11)	-1076(1)	4249(3)	3471(1)	54(1)
C(12)	-1610(1)	5297(3)	3339(1)	51(1)
C(13)	-1560(1)	6395(4)	2828(1)	67(1)
C(14)	-2286(1)	5529(4)	3672(1)	71(1)
C(15)	1130(2)	1303(4)	5155(1)	73(1)
C(16)	1681(2)	41(4)	4938(1)	77(1)
C(17)	1608(1)	-321(3)	4326(1)	64(1)

A 8. Bond lengths [Å] and angles [°] for 274.

O(1)-C(1)	1.354(3)
O(1)-C(13)	1.446(3)
O(2)-C(1)	1.198(3)
S(1)-C(17)	1.810(2)
S(1)-C(7)	1.8376(19)
S(2)-C(15)	1.801(3)
S(2)-C(7)	1.827(2)
C(1)-C(2)	1.464(3)
C(2)-C(3)	1.308(3)
C(3)-C(4)	1.488(3)
C(4)-C(5)	1.535(3)
C(5)-C(6)	1.530(3)
C(6)-C(7)	1.543(3)
C(7)-C(8)	1.543(3)
C(8)-C(9)	1.530(3)
C(9)-C(10)	1.532(3)
C(10)-C(11)	1.490(3)
C(11)-C(12)	1.327(3)
C(12)-C(14)	1.501(3)
C(12)-C(13)	1.503(3)
C(15)-C(16)	1.516(4)
C(16)-C(17)	1.504(4)
C(1)-O(1)-C(13)	115.14(19)
C(17)-S(1)-C(7)	102.58(10)
C(15)-S(2)-C(7)	102.65(11)
O(2)-C(1)-O(1)	123.1(2)
O(2)-C(1)-C(2)	124.2(3)
O(1)-C(1)-C(2)	112.7(2)
C(3)-C(2)-C(1)	123.6(2)
C(2)-C(3)-C(4)	127.7(2)
C(3)-C(4)-C(5)	109.89(18)
C(6)-C(5)-C(4)	113.19(19)
C(5)-C(6)-C(7)	116.25(17)
C(8)-C(7)-C(6)	111.73(16)

C(8)-C(7)-S(2)	113.28(13)
C(6)-C(7)-S(2)	104.32(13)
C(8)-C(7)-S(1)	109.76(13)
C(6)-C(7)-S(1)	107.38(13)
S(2)-C(7)-S(1)	110.10(10)
C(9)-C(8)-C(7)	116.00(16)
C(8)-C(9)-C(10)	112.94(17)
C(11)-C(10)-C(9)	112.28(18)
C(12)-C(11)-C(10)	128.6(2)
C(11)-C(12)-C(14)	125.1(2)
C(11)-C(12)-C(13)	120.1(2)
C(14)-C(12)-C(13)	114.8(2)
O(1)-C(13)-C(12)	111.37(18)
C(16)-C(15)-S(2)	113.10(19)
C(17)-C(16)-C(15)	113.5(2)
C(16)-C(17)-S(1)	114.9(2)

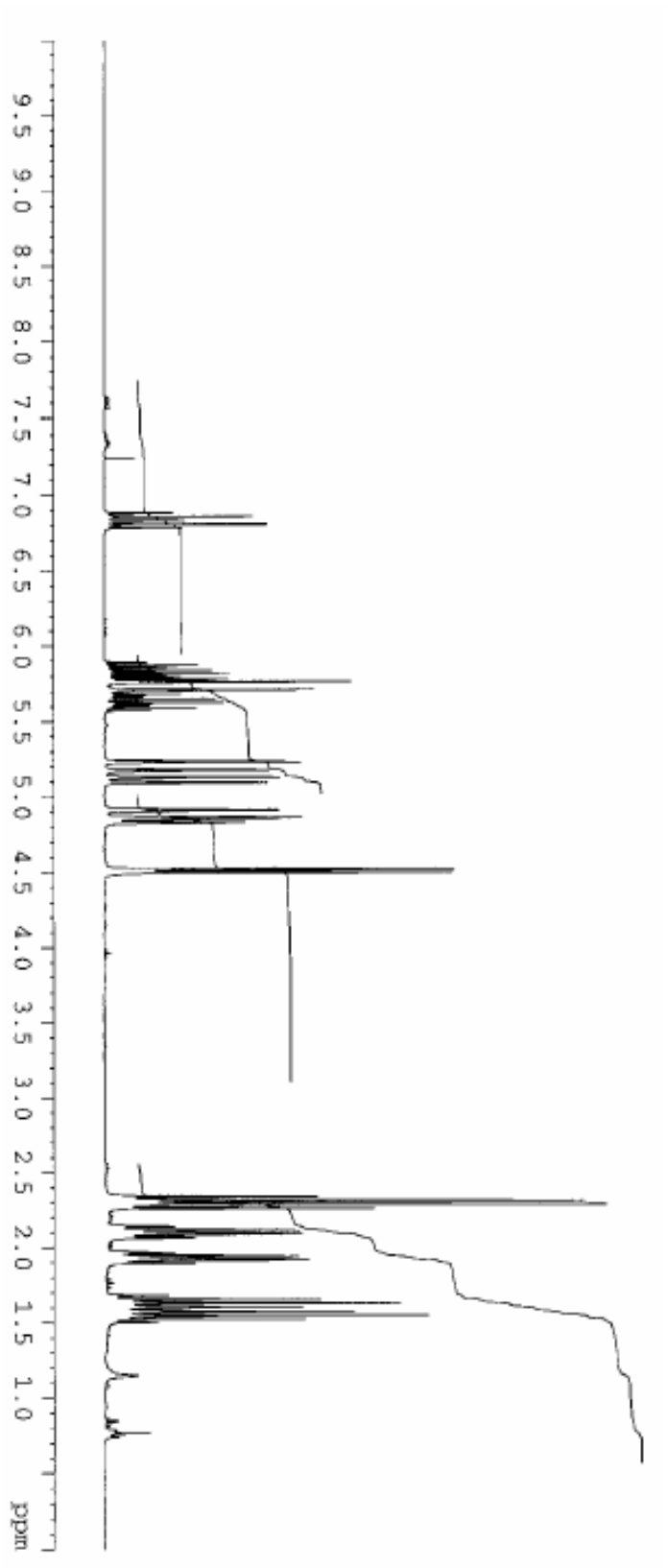
Symmetry transformations used to generate equivalent atoms:

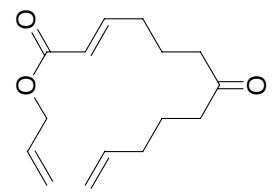
A 9. Anisotropic displacement parameters ($Å^2$x 10^3)for 274. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	58(1)	67(1)	54(1)	10(1)	0(1)	7(1)
O(2)	84(1)	70(1)	103(2)	-12(1)	11(1)	24(1)
S(1)	44(1)	42(1)	58(1)	-3(1)	3(1)	10(1)
S(2)	55(1)	68(1)	48(1)	-12(1)	-4(1)	3(1)
C(1)	66(1)	49(1)	59(1)	12(1)	2(1)	11(1)
C(2)	69(2)	42(1)	66(1)	5(1)	-1(1)	-1(1)
C(3)	60(1)	49(1)	57(1)	5(1)	3(1)	-3(1)
C(4)	54(1)	56(2)	68(1)	9(1)	10(1)	-7(1)
C(5)	44(1)	48(1)	62(1)	-1(1)	7(1)	1(1)
C(6)	43(1)	38(1)	57(1)	-6(1)	-1(1)	-1(1)
C(7)	38(1)	37(1)	47(1)	-6(1)	-1(1)	2(1)
C(8)	40(1)	37(1)	52(1)	-3(1)	-1(1)	1(1)
C(9)	40(1)	47(1)	55(1)	-1(1)	3(1)	4(1)
C(10)	40(1)	45(1)	64(1)	5(1)	4(1)	0(1)
C(11)	47(1)	60(2)	56(1)	4(1)	5(1)	8(1)
C(12)	42(1)	51(1)	60(1)	-2(1)	-4(1)	1(1)
C(13)	53(1)	81(2)	68(2)	13(1)	-8(1)	8(1)
C(14)	49(1)	69(2)	96(2)	14(2)	7(1)	10(1)
C(15)	71(2)	93(2)	54(1)	14(1)	2(1)	5(2)
C(16)	76(2)	76(2)	79(2)	30(2)	3(1)	14(2)
C(17)	61(1)	45(1)	84(2)	8(1)	4(1)	11(1)

A 10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 274.

	x	y	z	U(eq)
H(2)	482	8971	3222	68(2)
H(3)	385	5972	2660	68(2)
H(4A)	1619	7397	3168	68(2)
H(4B)	1650	6459	2591	68(2)
H(5A)	1258	3886	3061	68(2)
H(5B)	2039	4460	3219	68(2)
H(6A)	914	5571	3903	68(2)
H(6B)	1717	5297	4072	68(2)
H(8A)	297	2654	3571	68(2)
H(8B)	308	1302	4050	68(2)
H(9A)	-151	4672	4266	68(2)
H(9B)	-287	3074	4644	68(2)
H(10A)	-1037	1986	3881	68(2)
H(10B)	-1368	3459	4242	68(2)
H(11)	-706	4170	3212	68(2)
H(13A)	-1753	5775	2512	68(2)
H(13B)	-1847	7417	2880	68(2)
H(14A)	-2263	4836	4001	127(8)
H(14B)	-2693	5192	3452	127(8)
H(14C)	-2334	6709	3776	127(8)
H(15A)	1166	1358	5557	68(2)
H(15B)	652	891	5063	68(2)
H(16A)	2159	488	5009	68(2)
H(16B)	1633	-1024	5142	68(2)
H(17A)	1126	-738	4255	68(2)
H(17B)	1941	-1228	4228	68(2)





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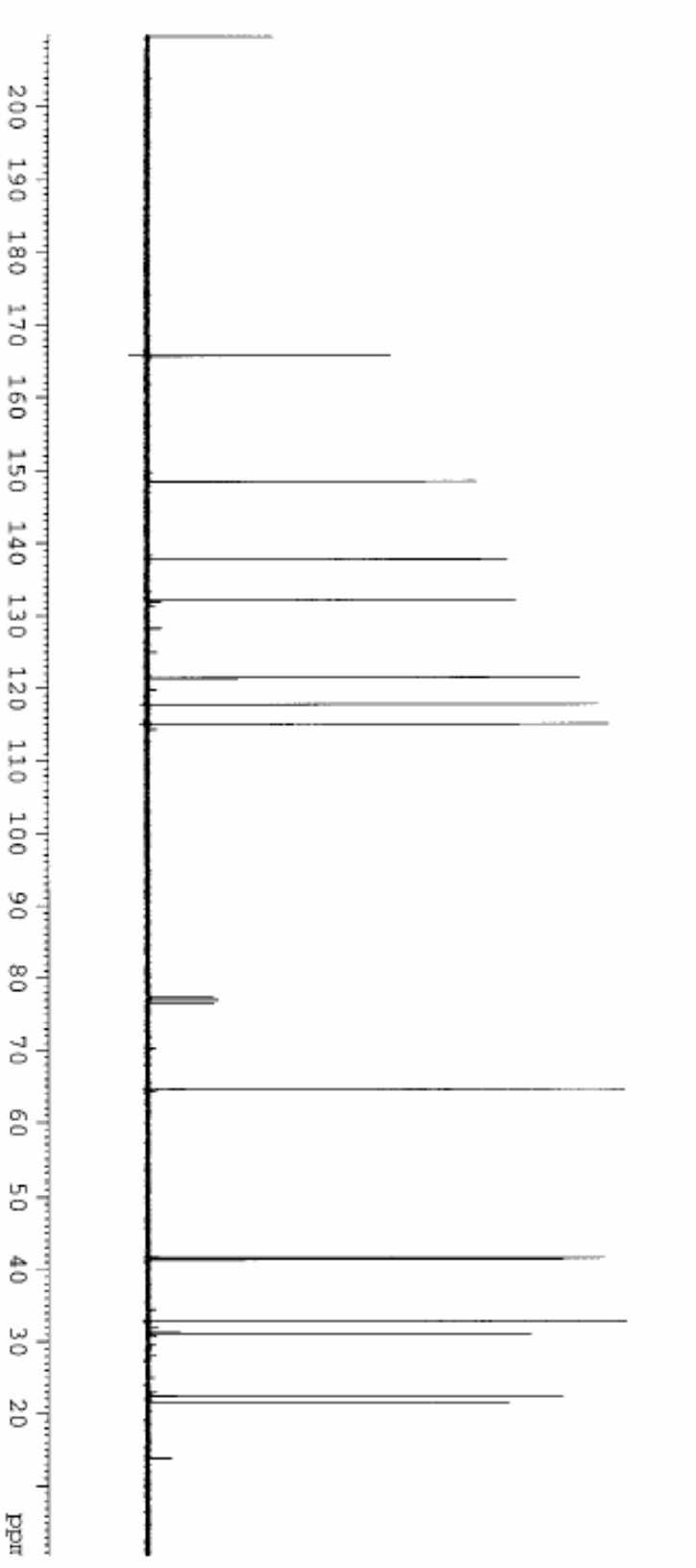
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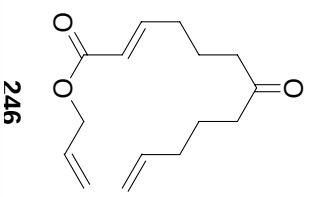

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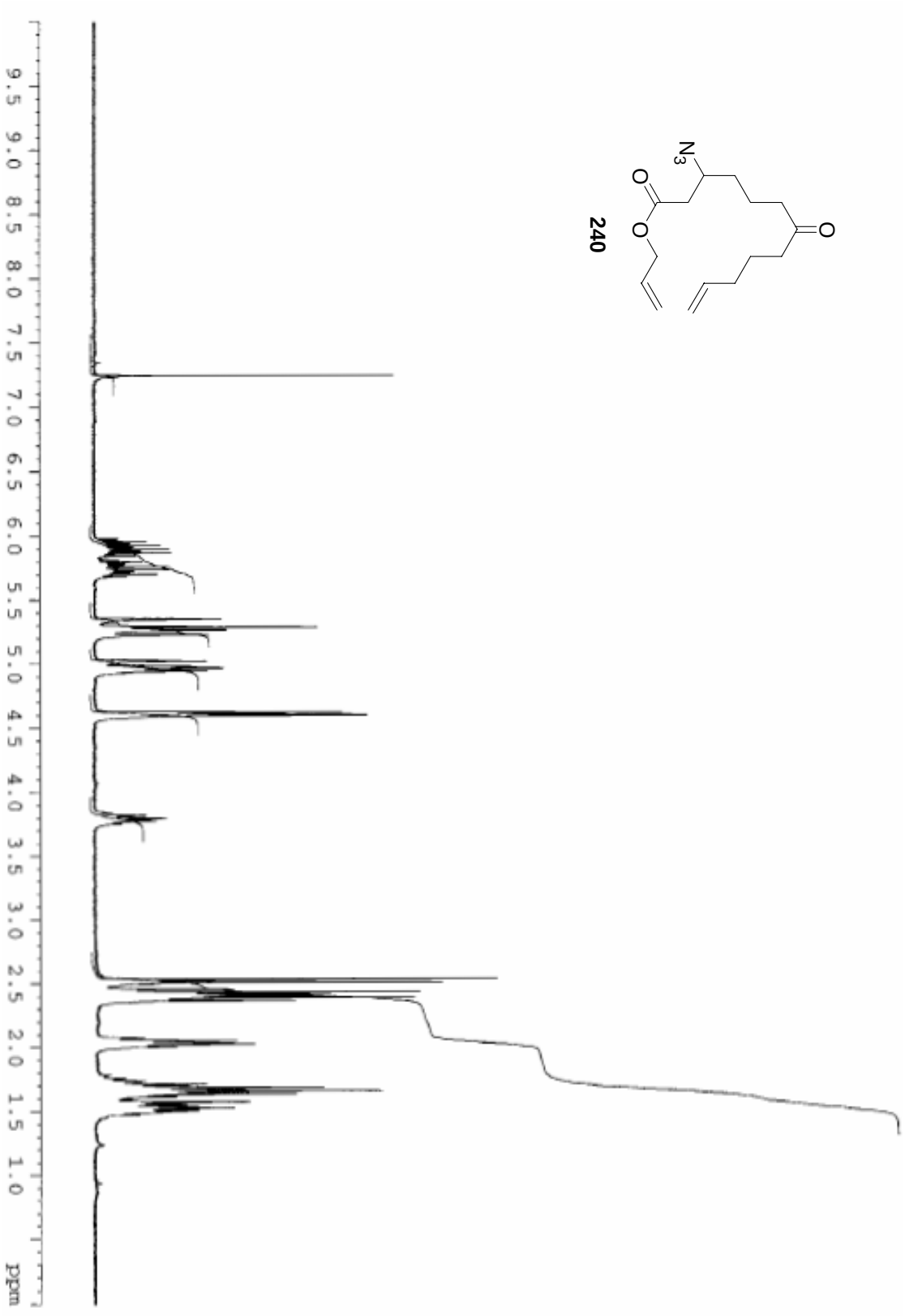
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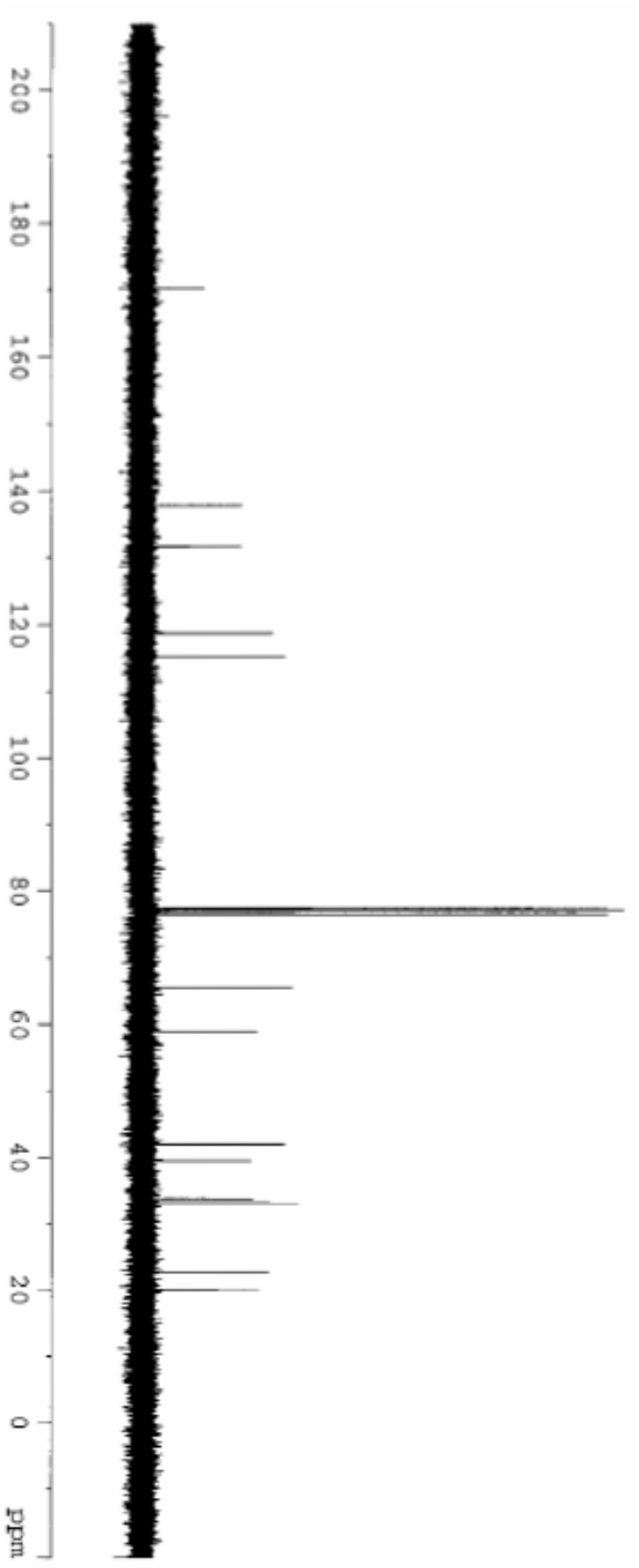
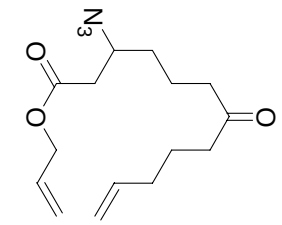
ppm





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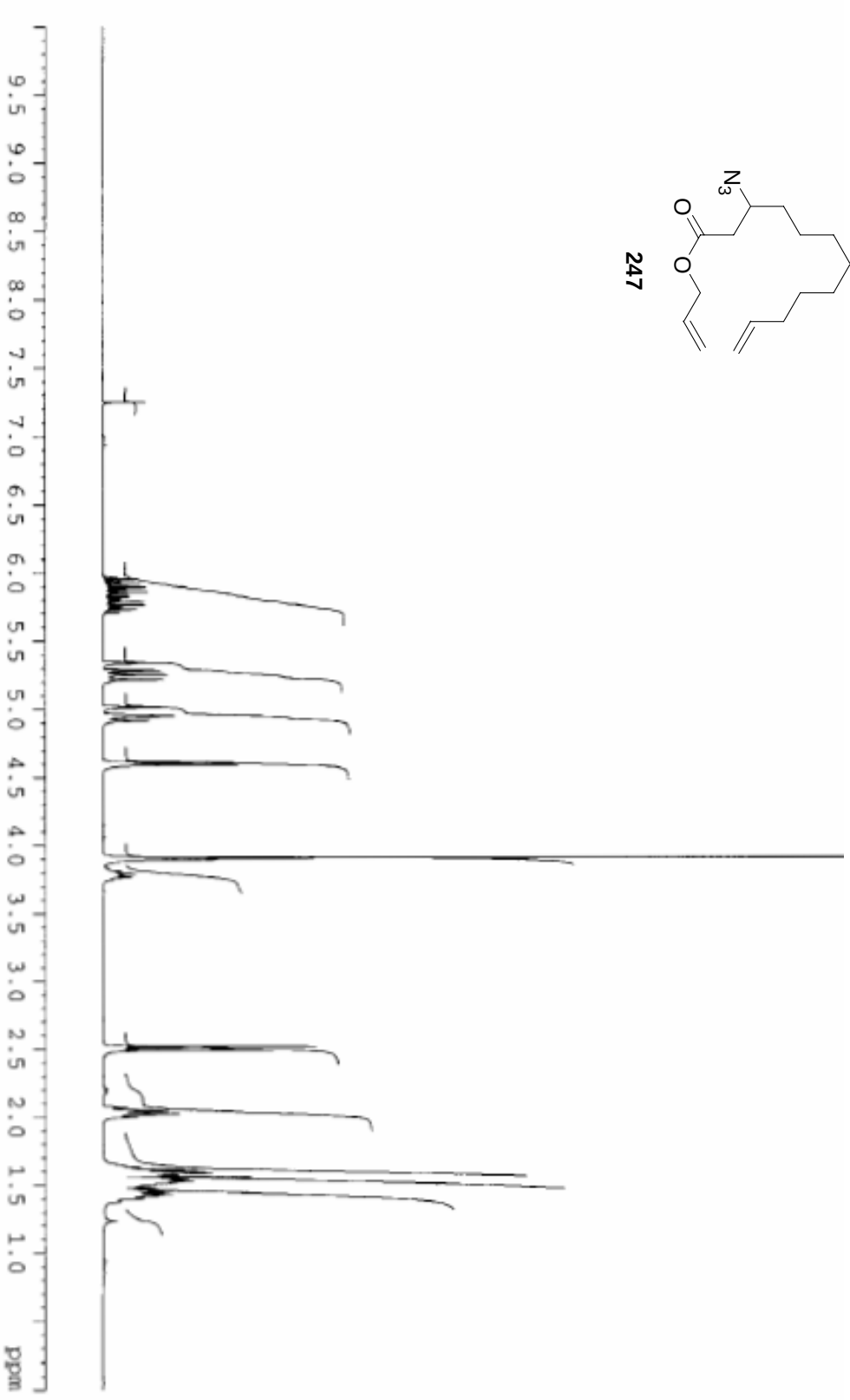
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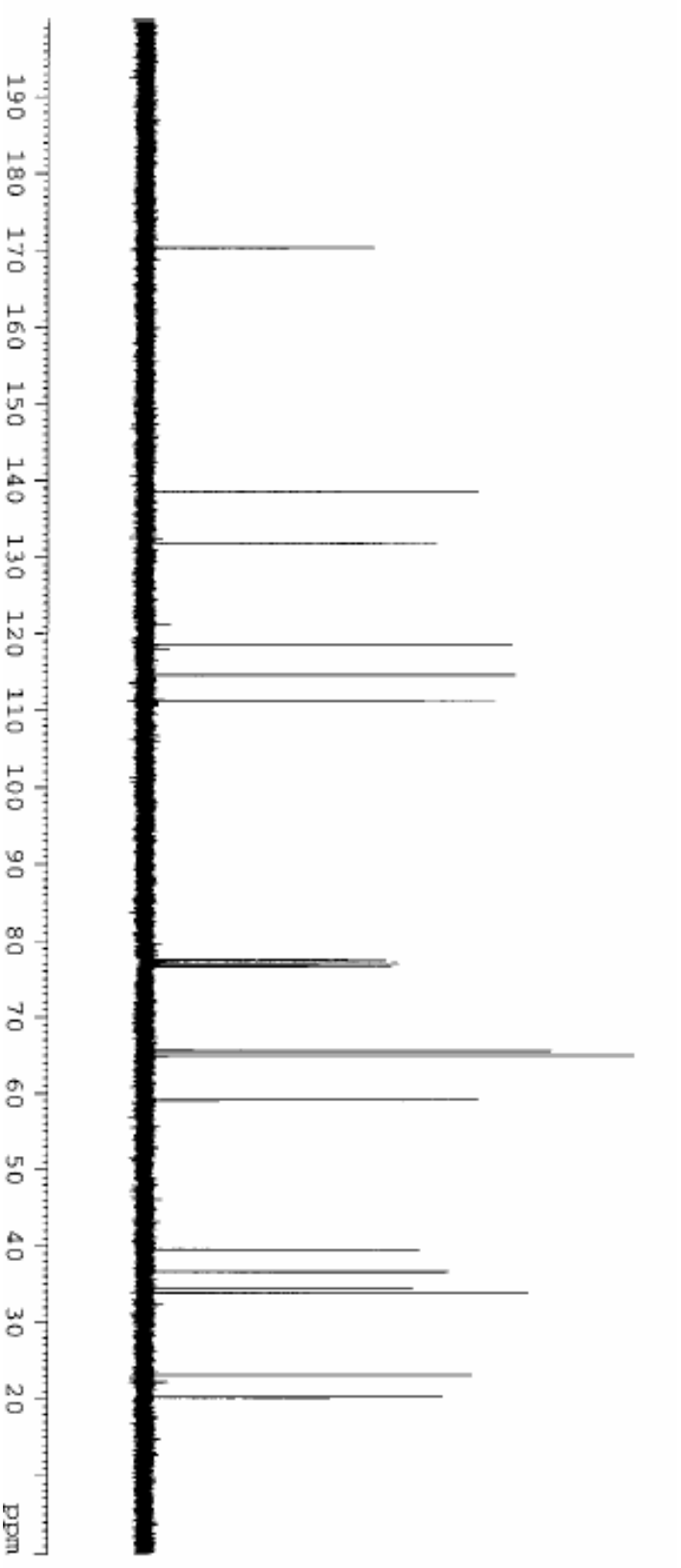
ppm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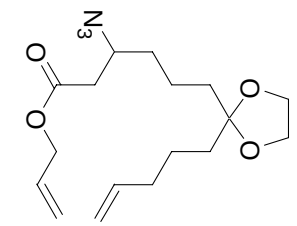
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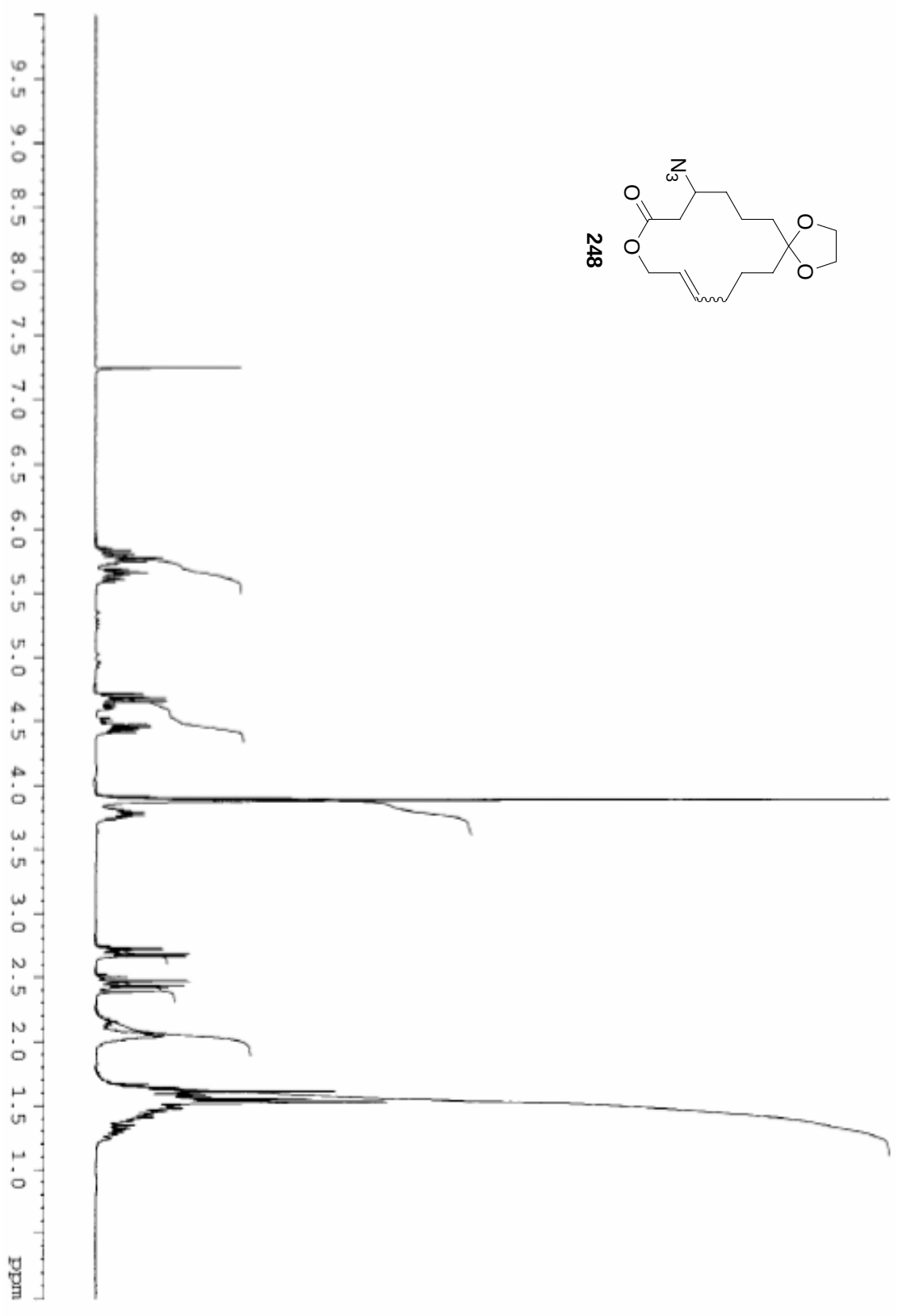
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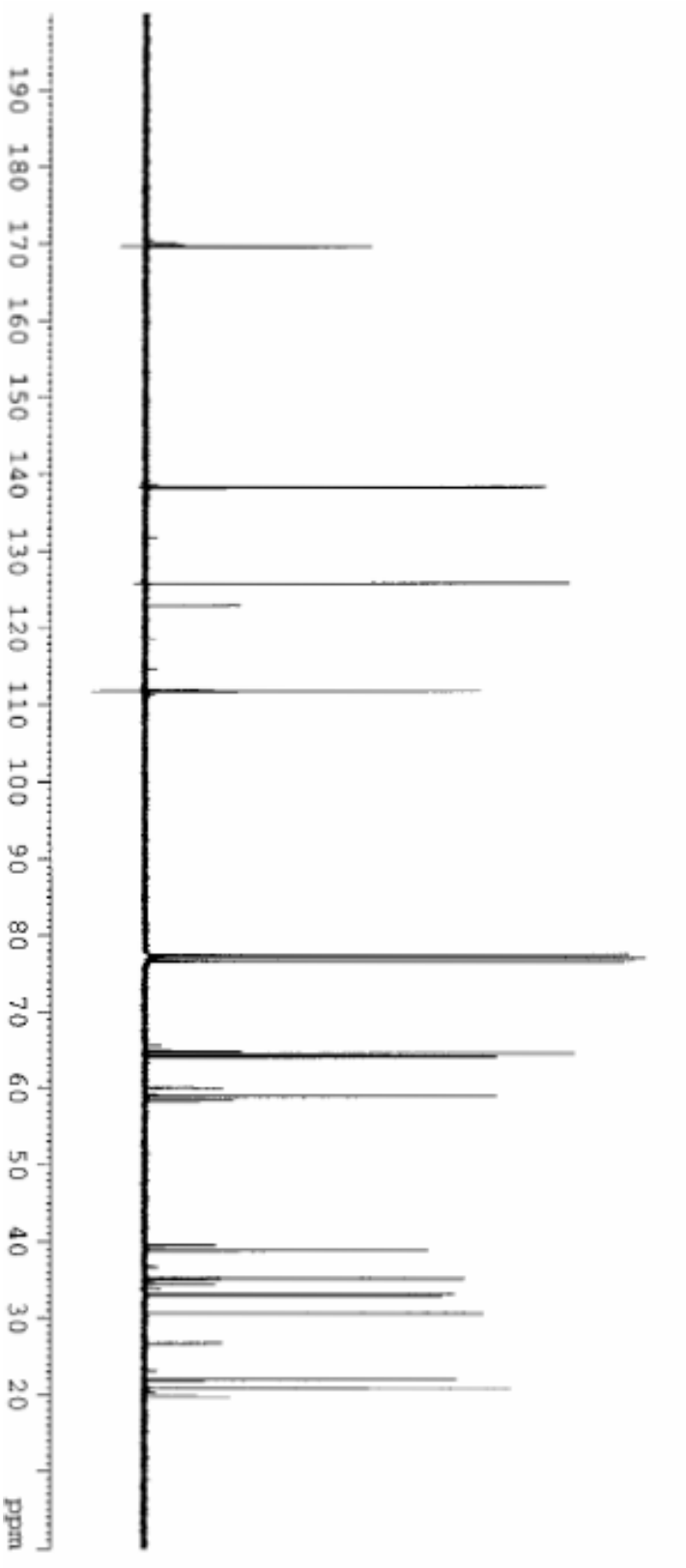
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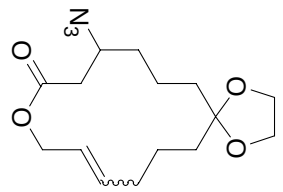
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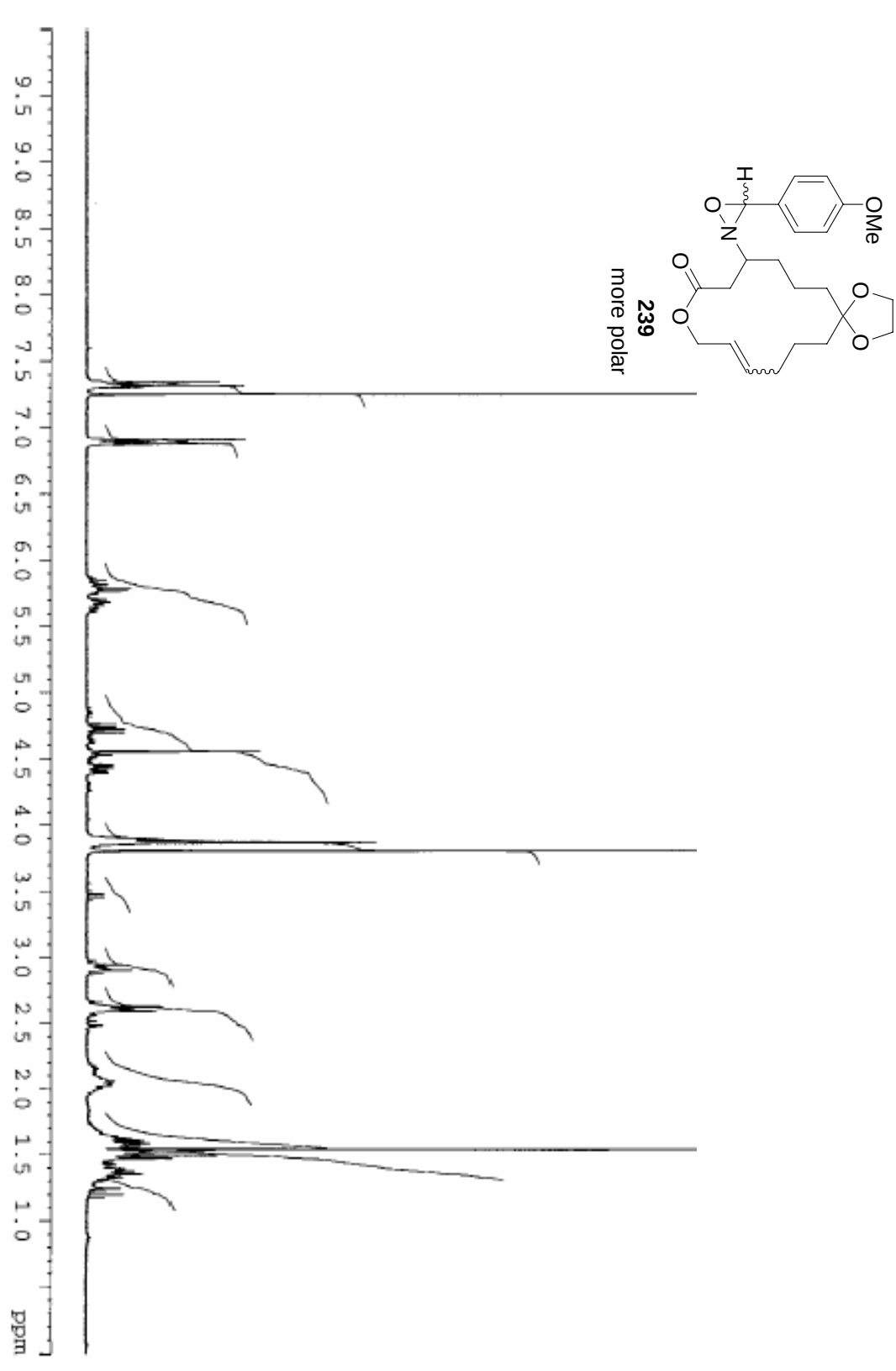
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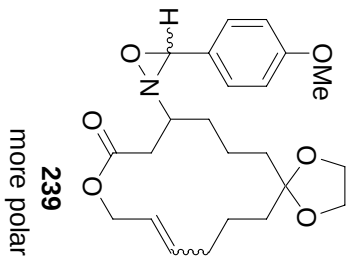

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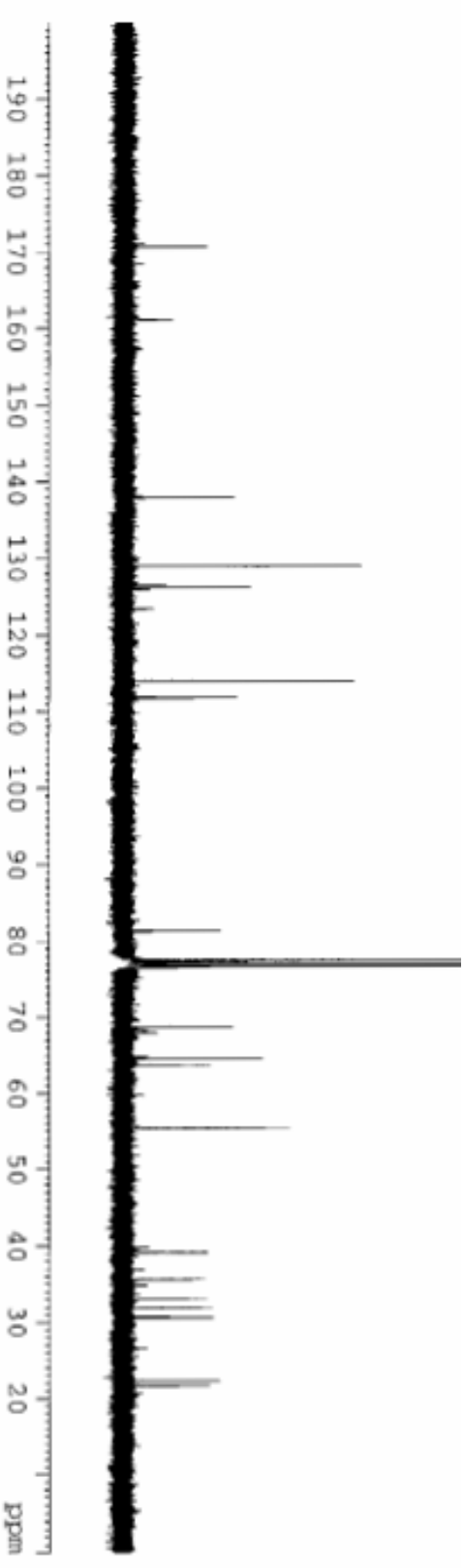

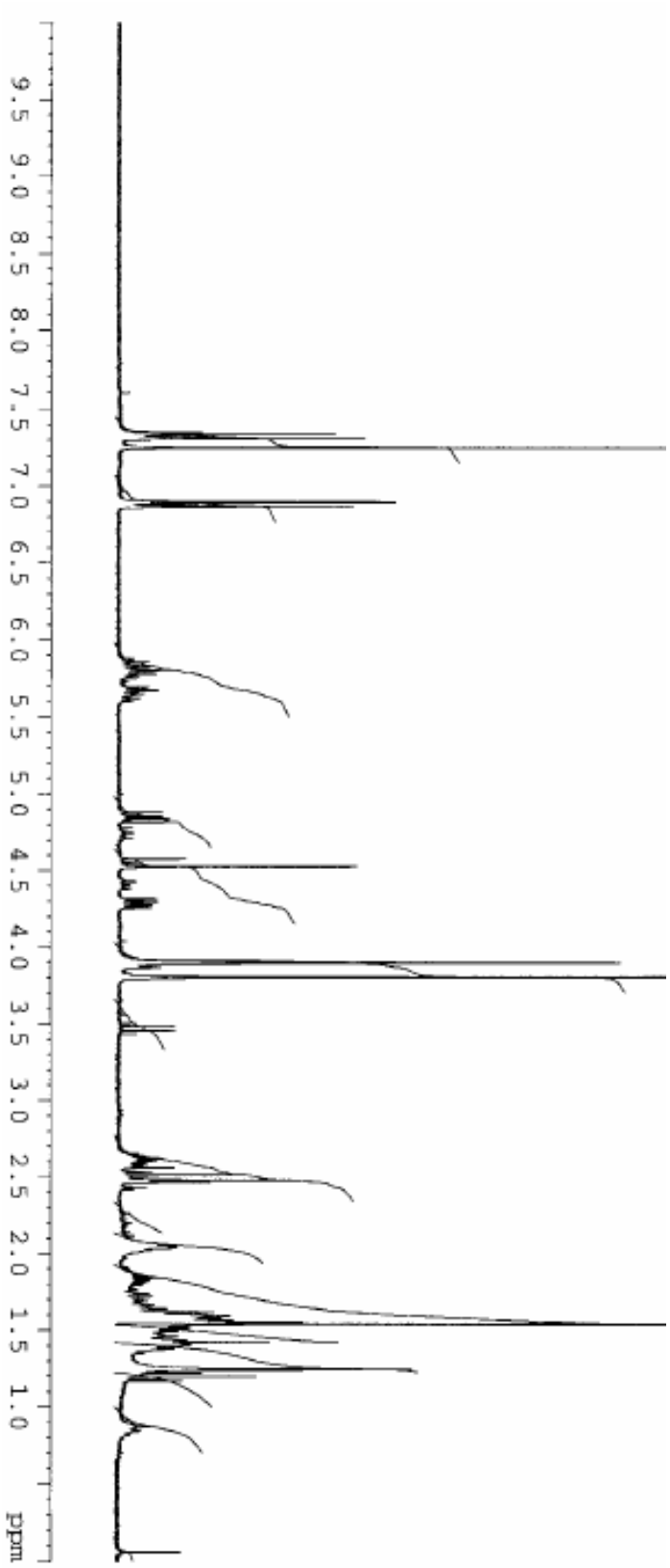
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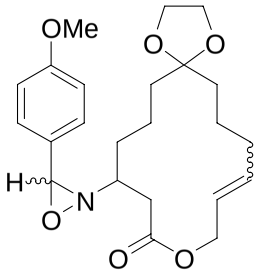

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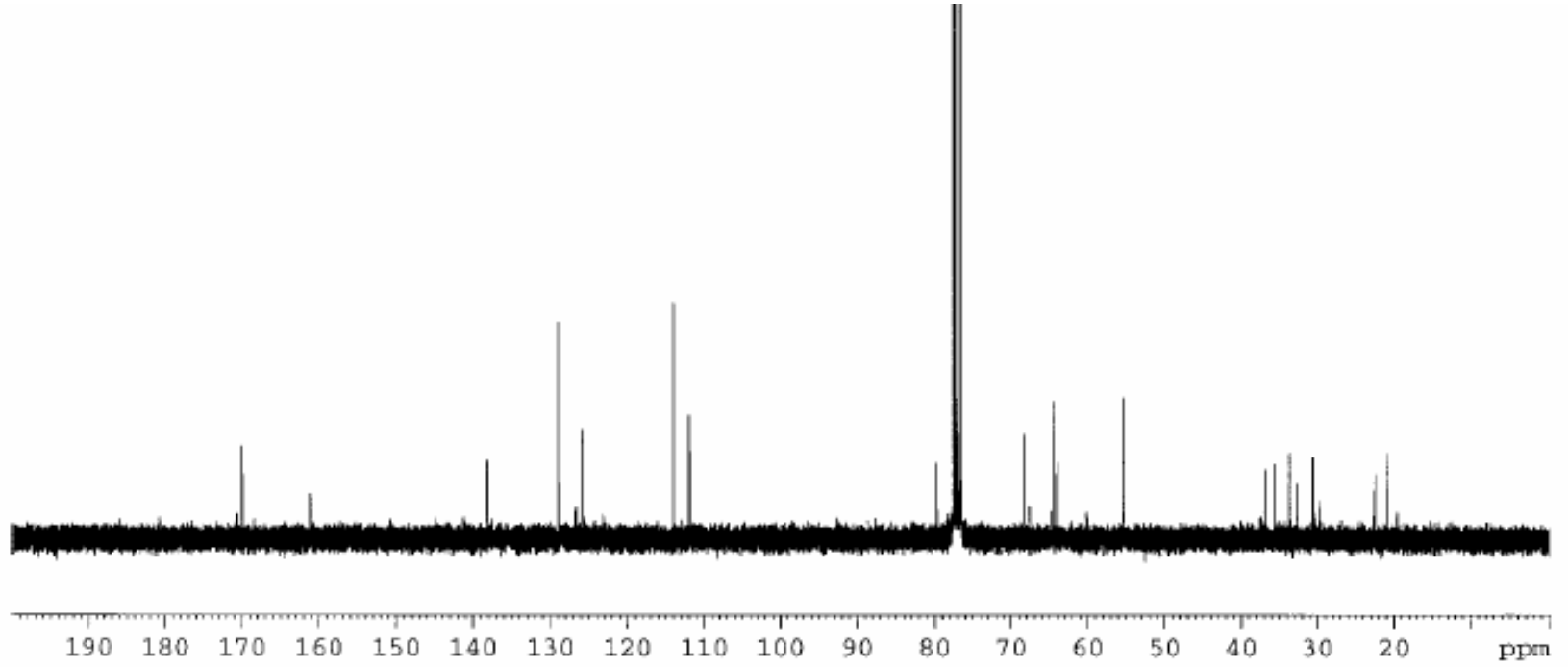
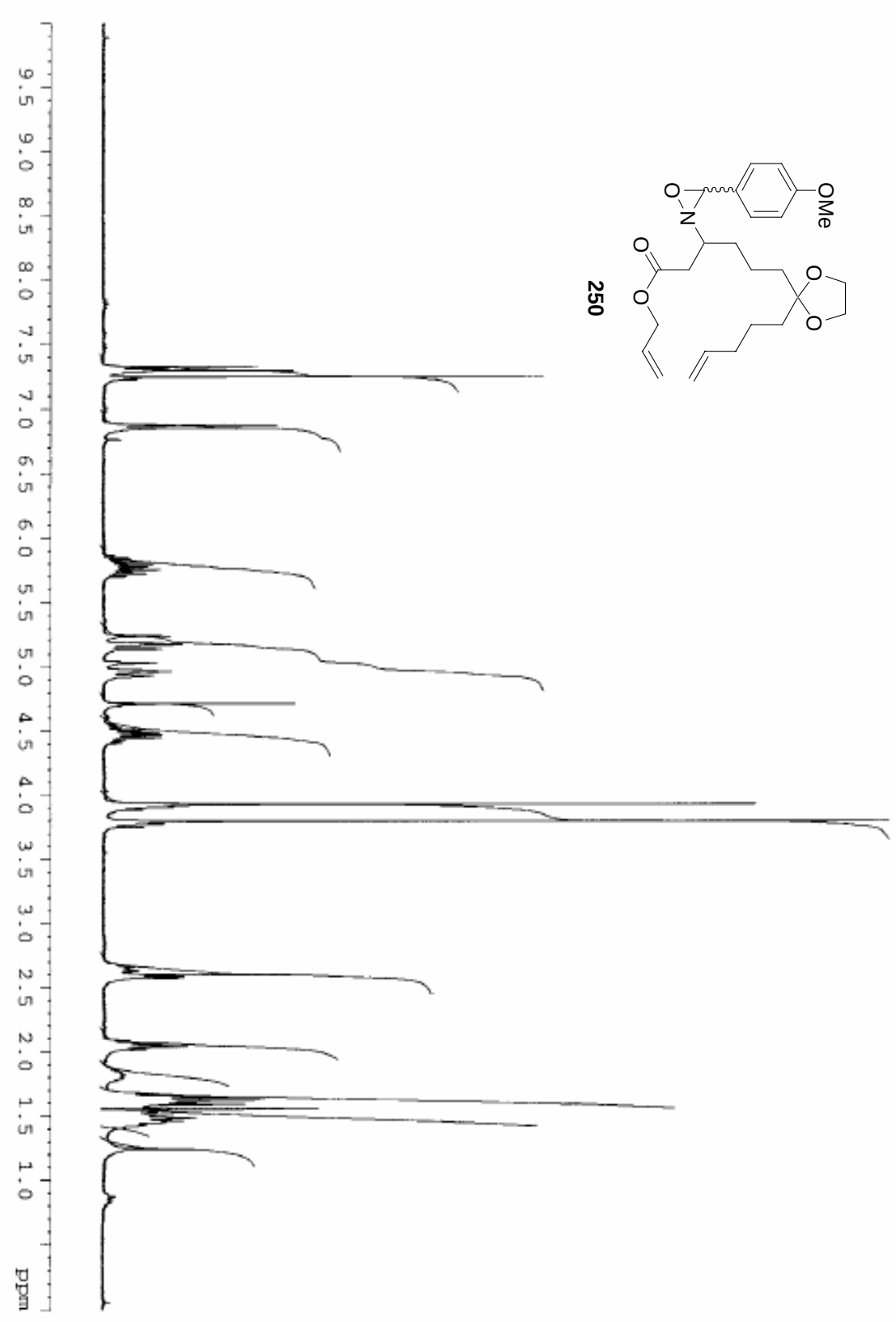
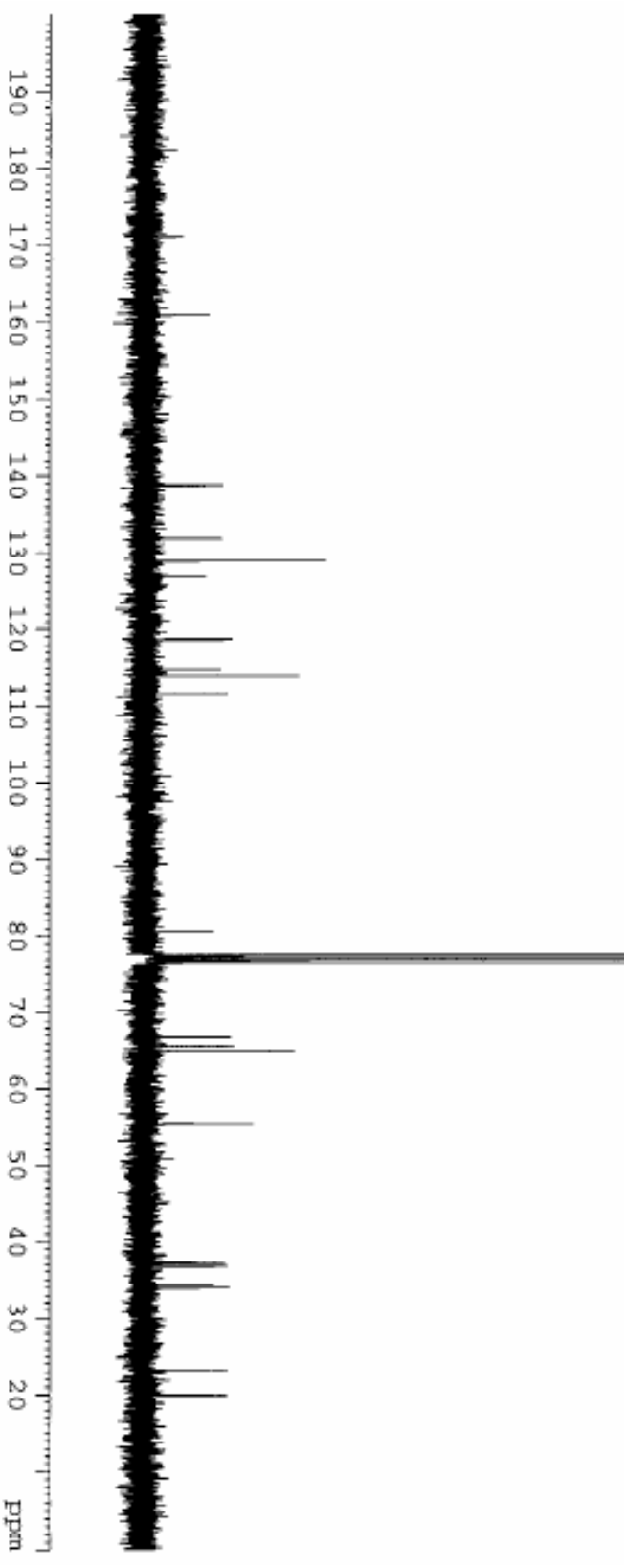
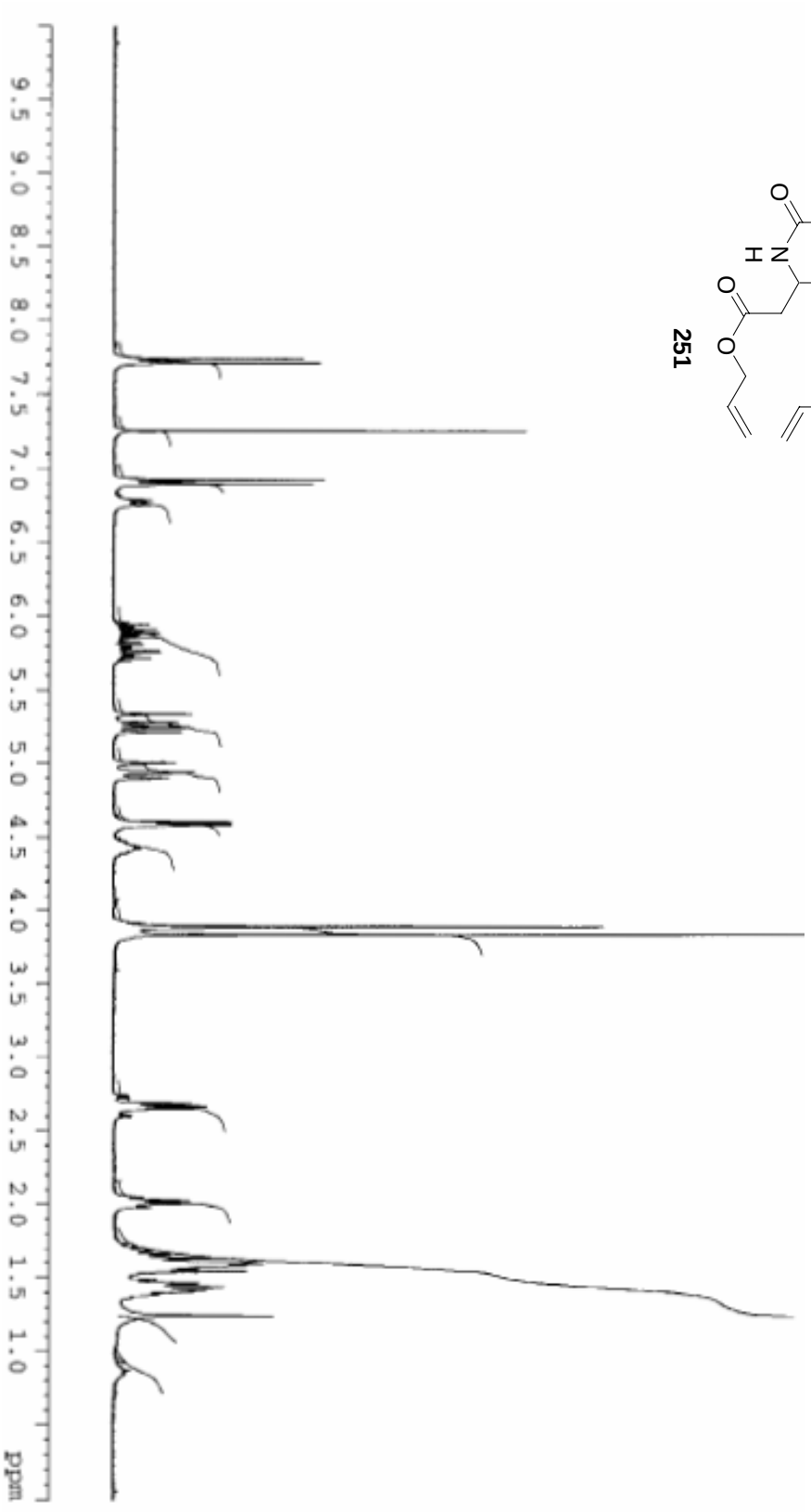
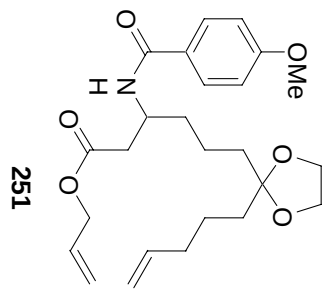



OMe
O
N
O
O
O
O
O
250
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm


OMe
O
N
O
O
O
O
O
250
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


OMe
O
N
H
O
O
O
O
251
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm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O
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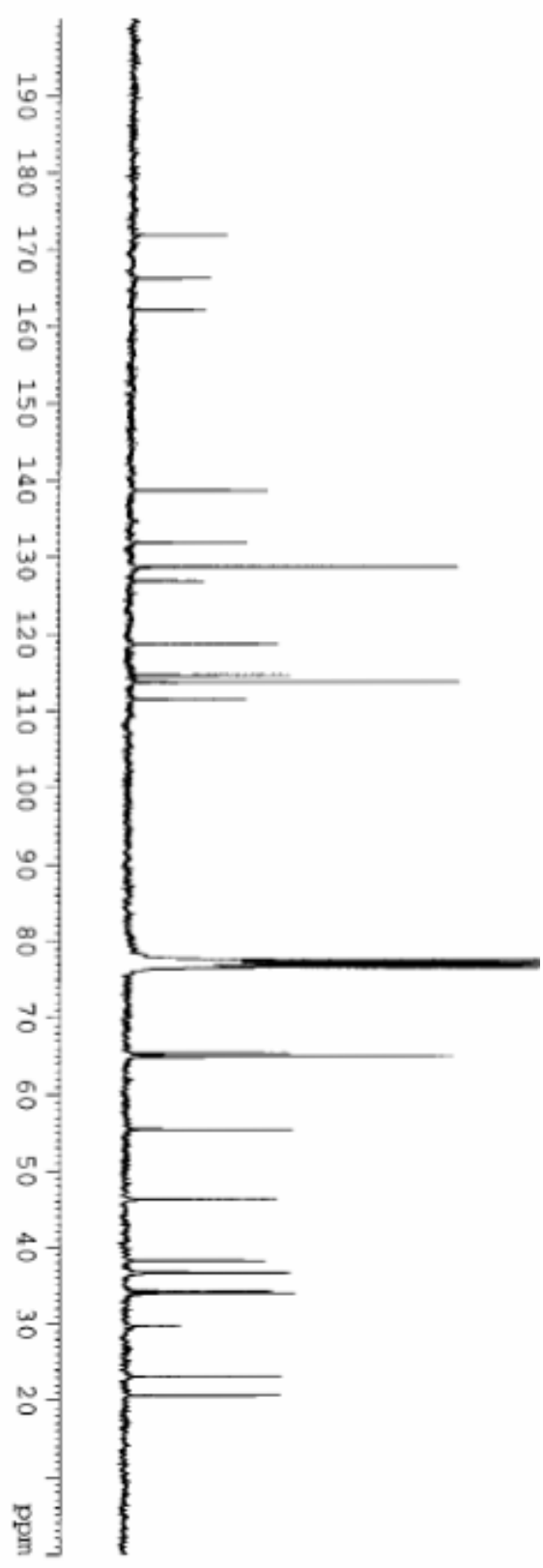
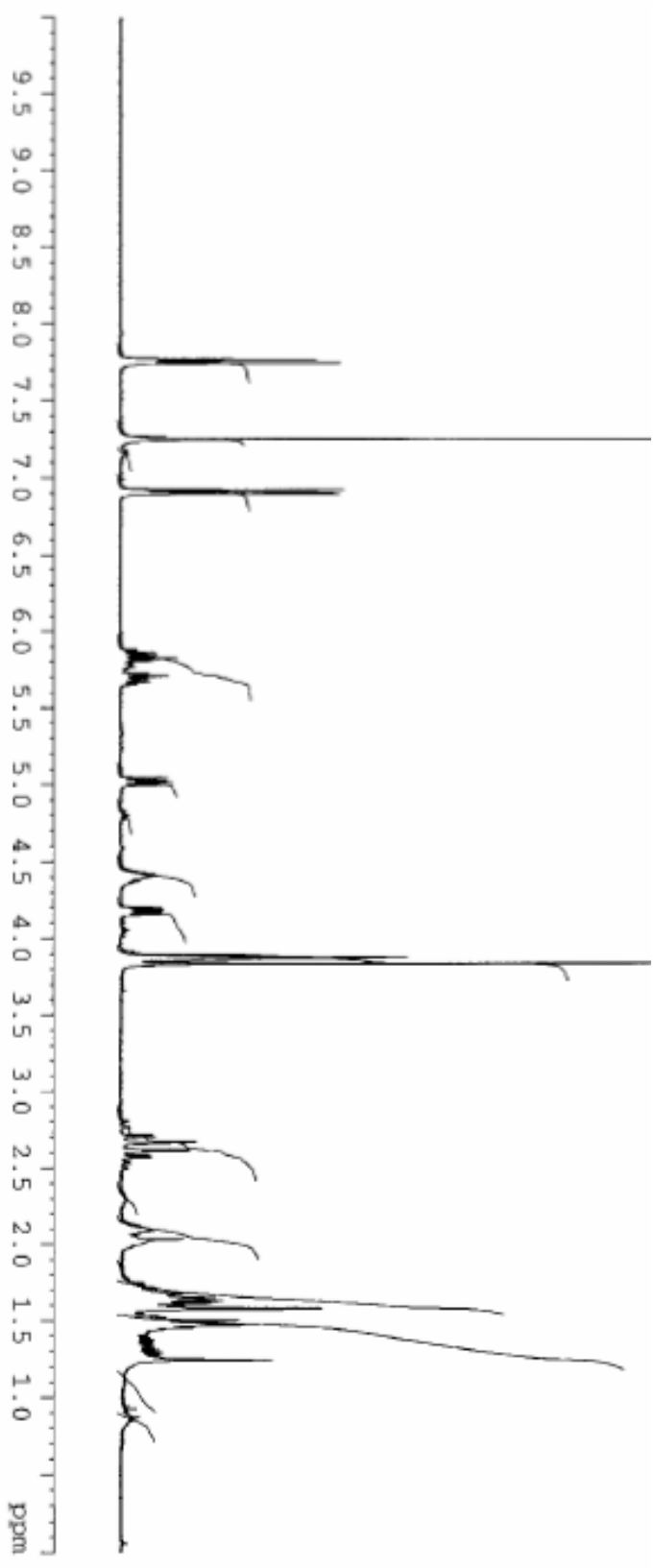
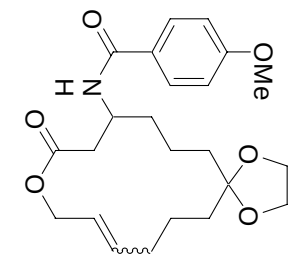
O

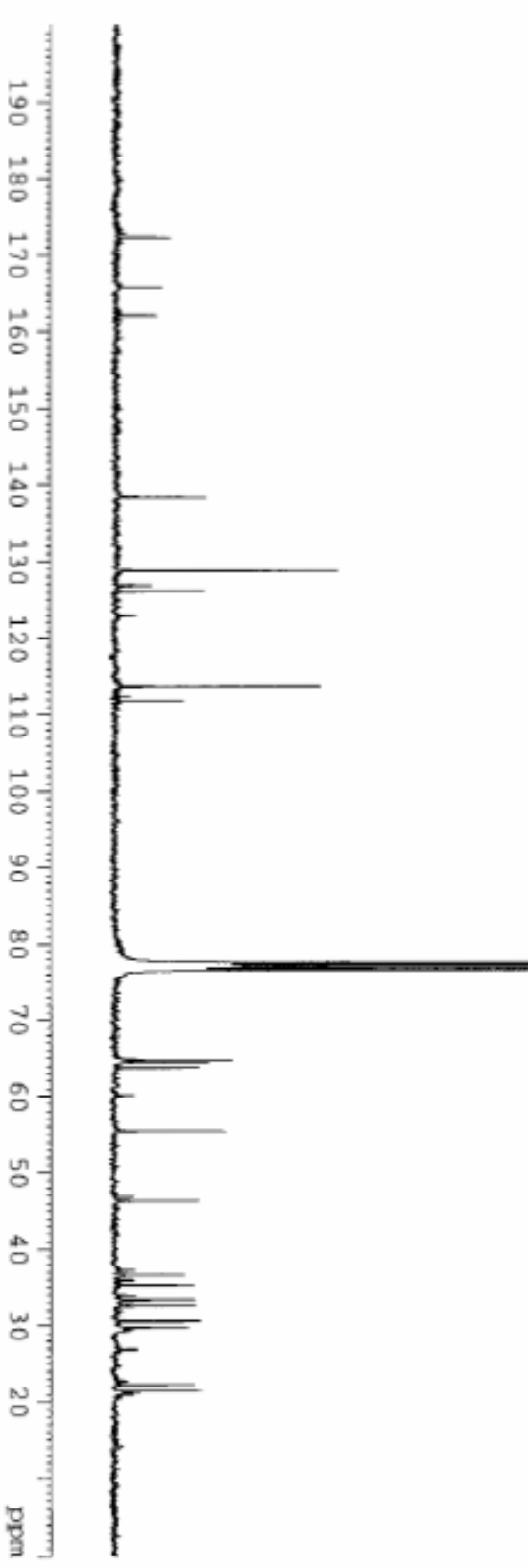
251


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm





252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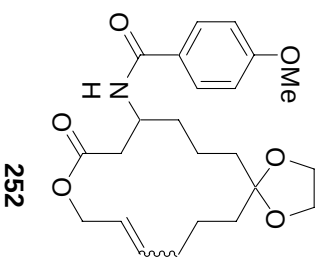
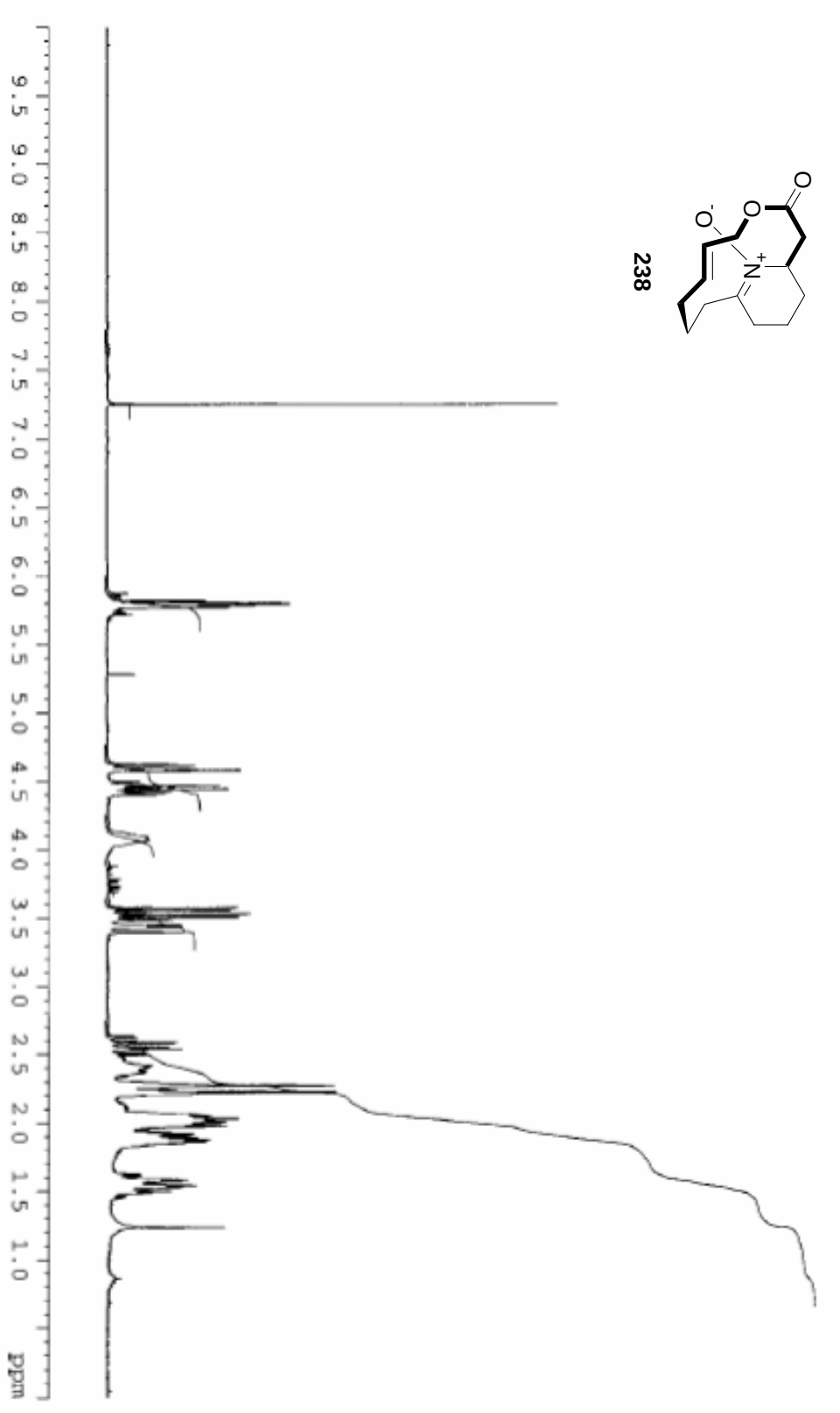
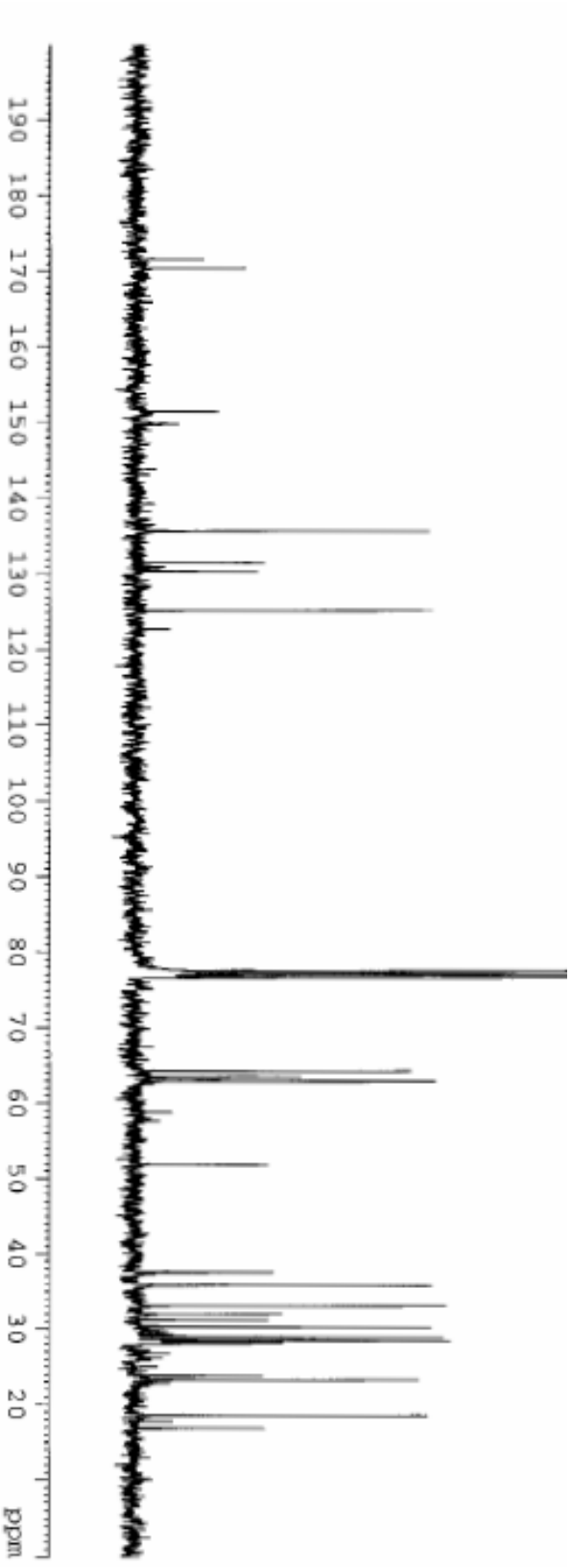
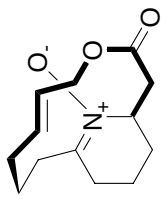

O
N
H
O
O
O
O
OMe

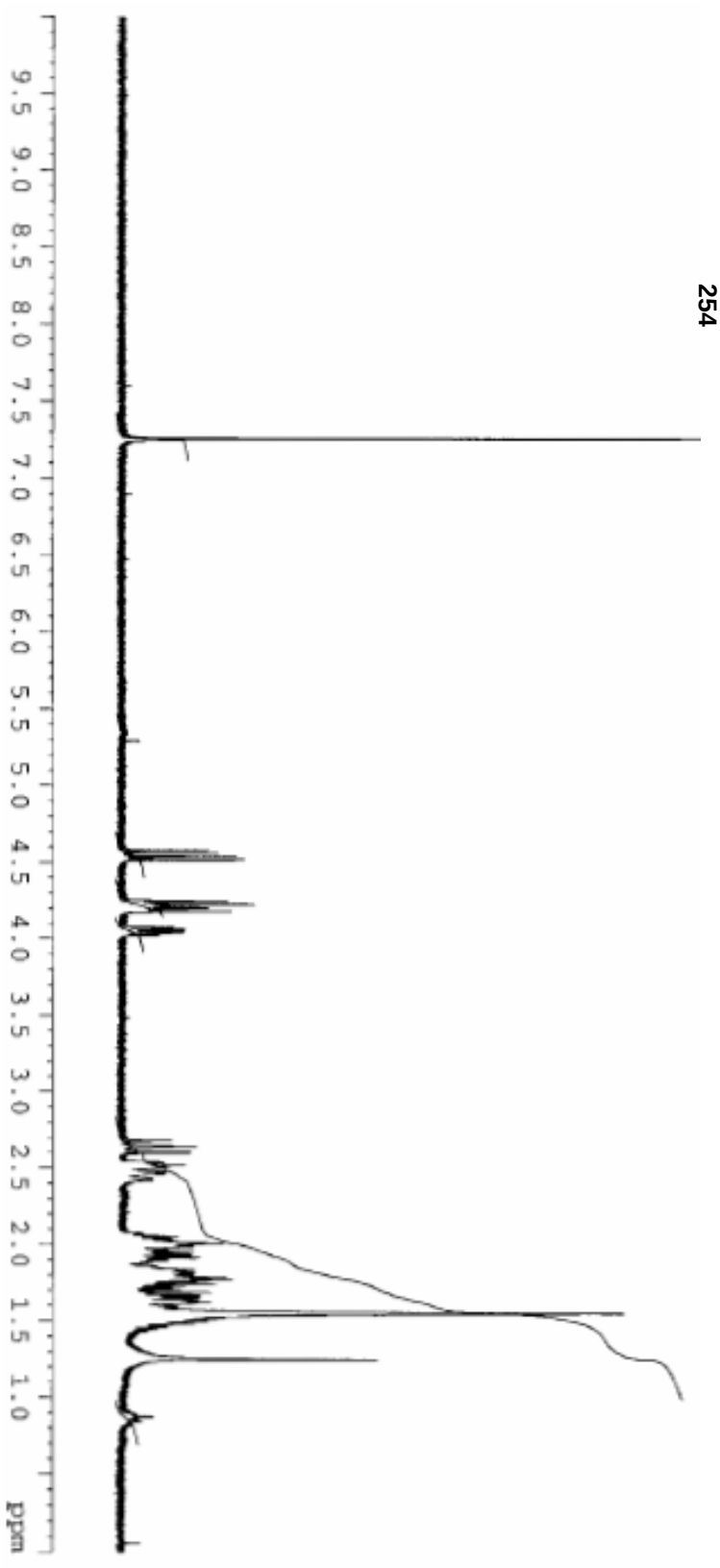
252


238
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

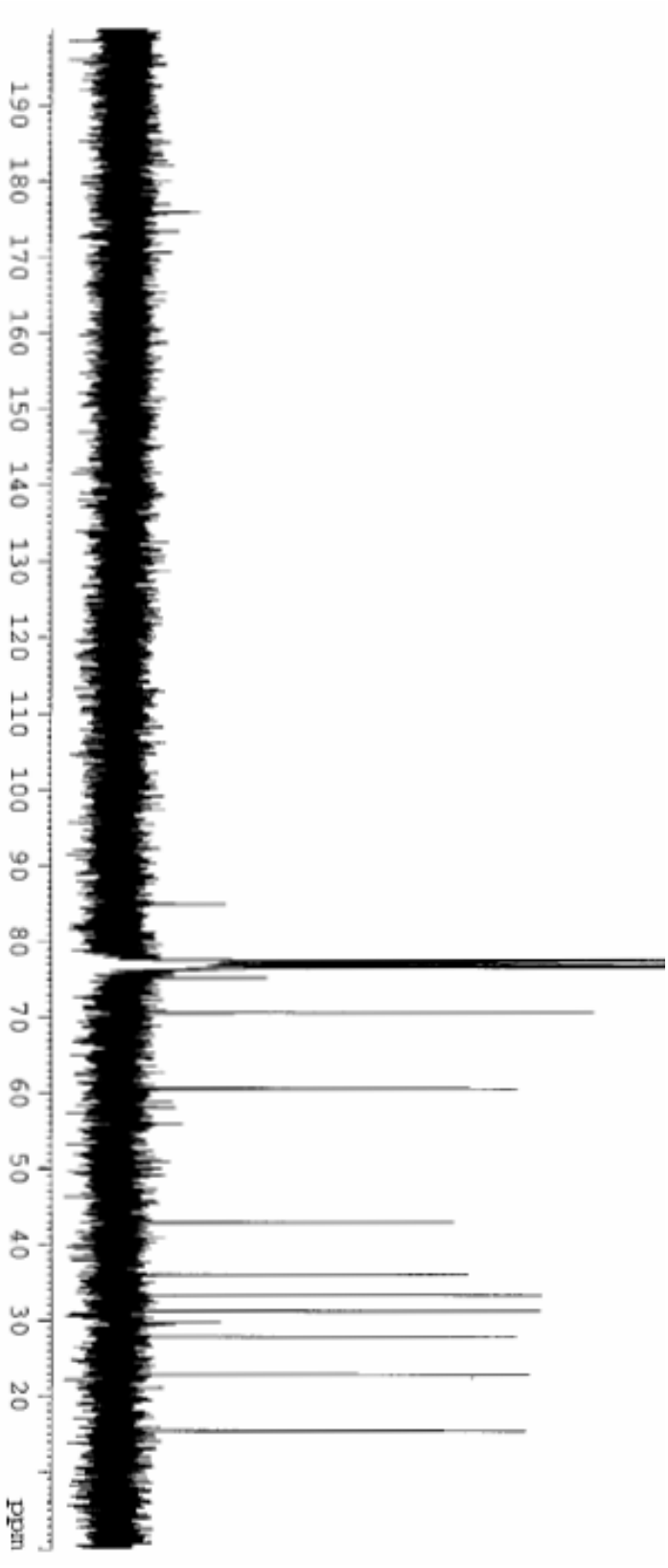




238



254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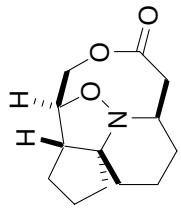
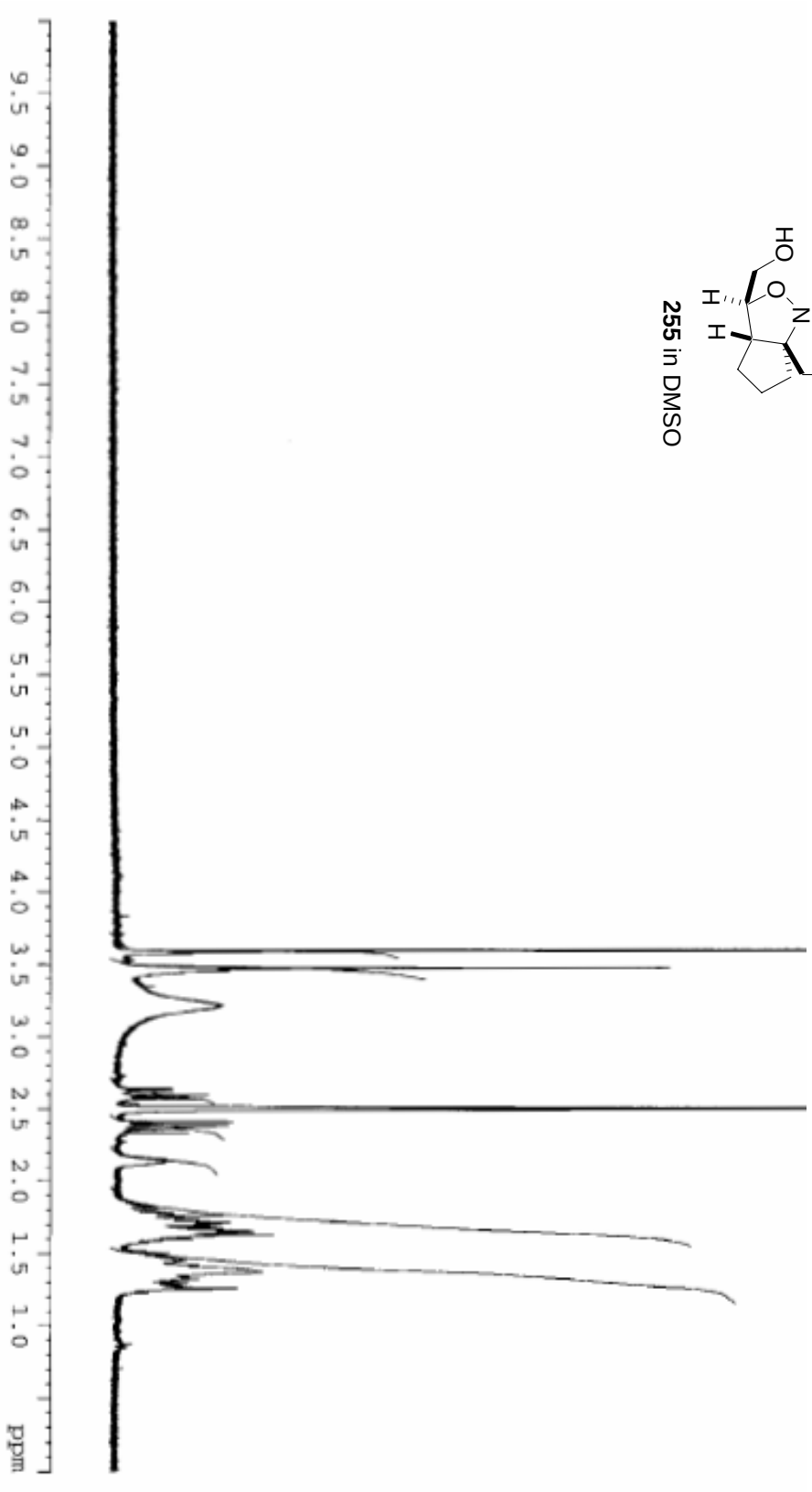
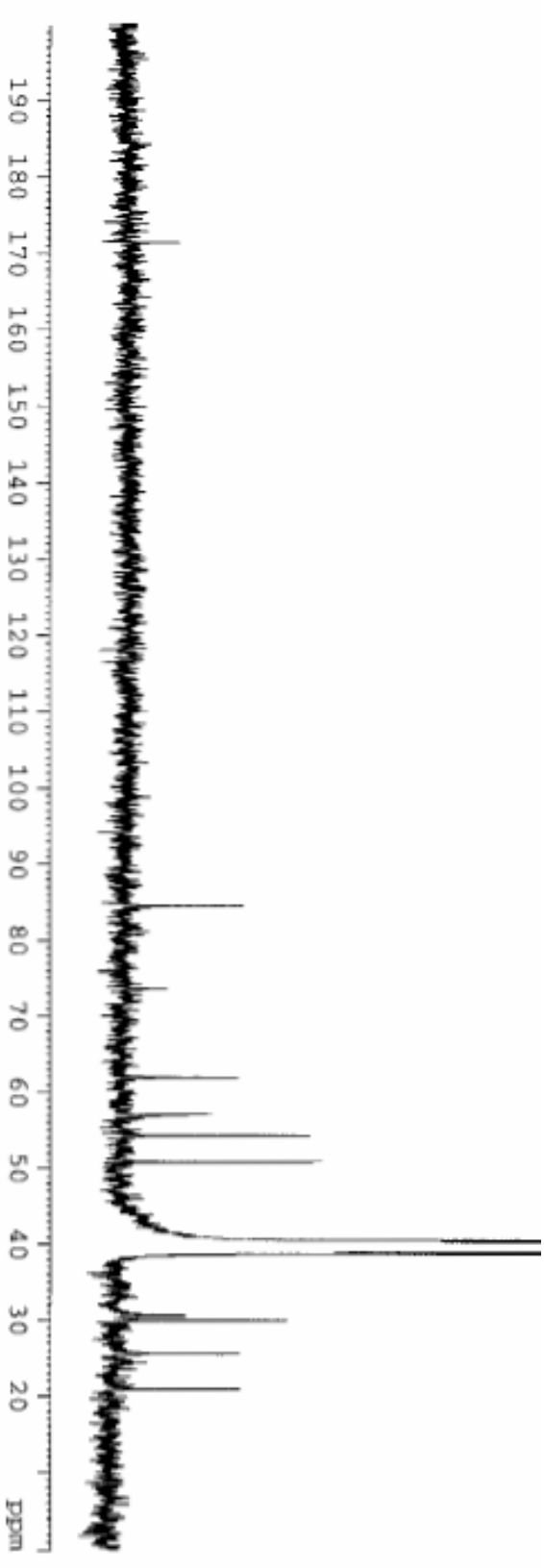
ppm


O
O
O
N
H
H

254


MeO2C
HO
O
N
H
H
255 in DMSO
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm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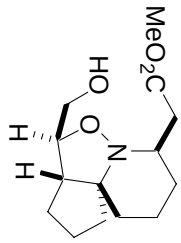
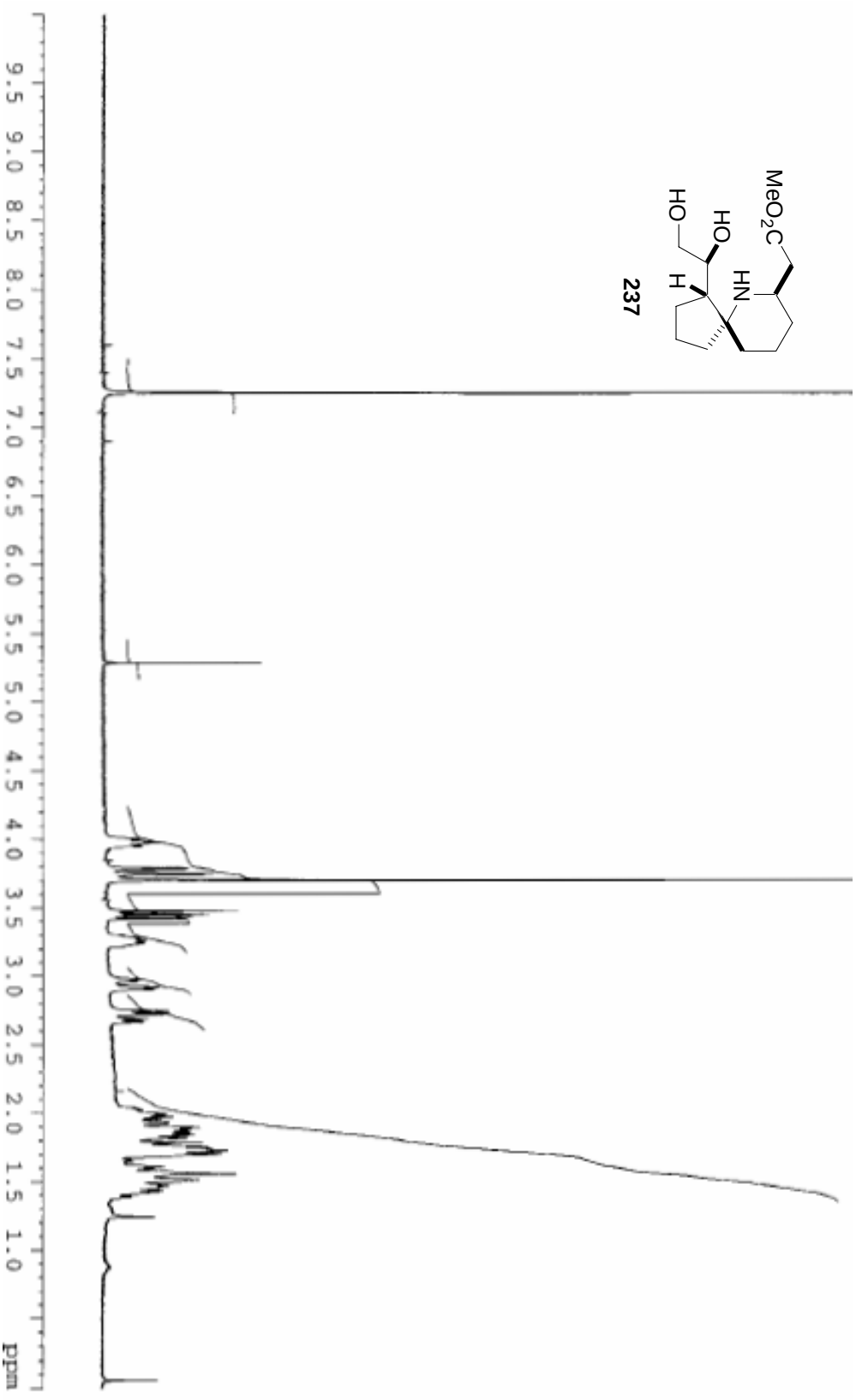
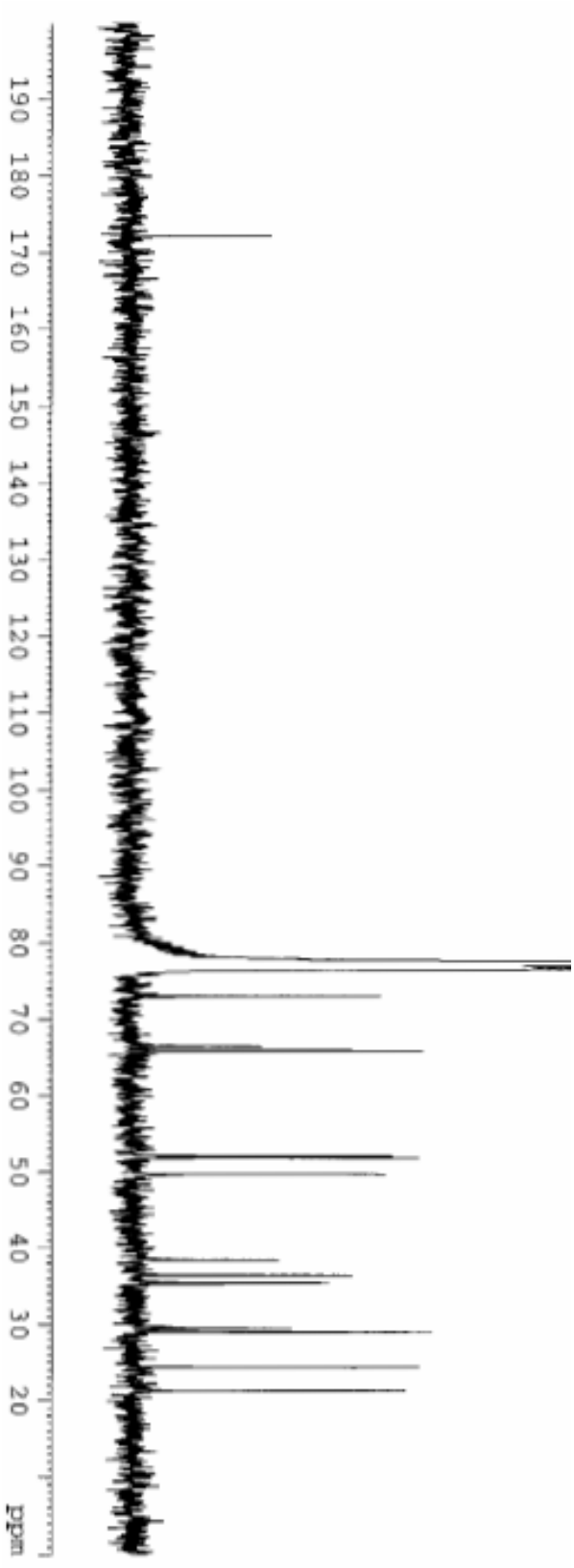
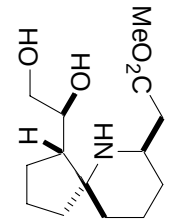

MeO2C
HO
O
N
H
H

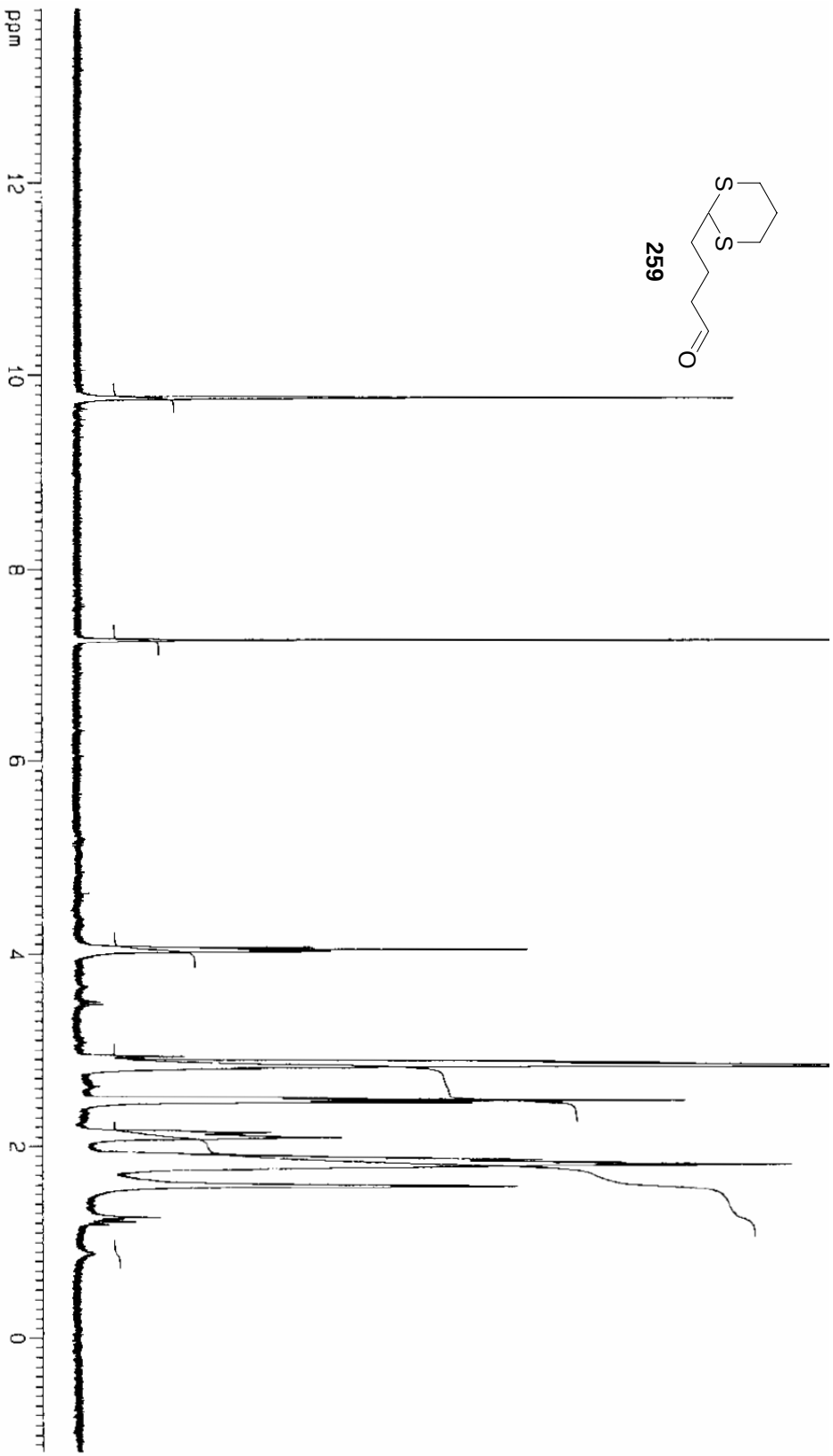
255 in DMSO

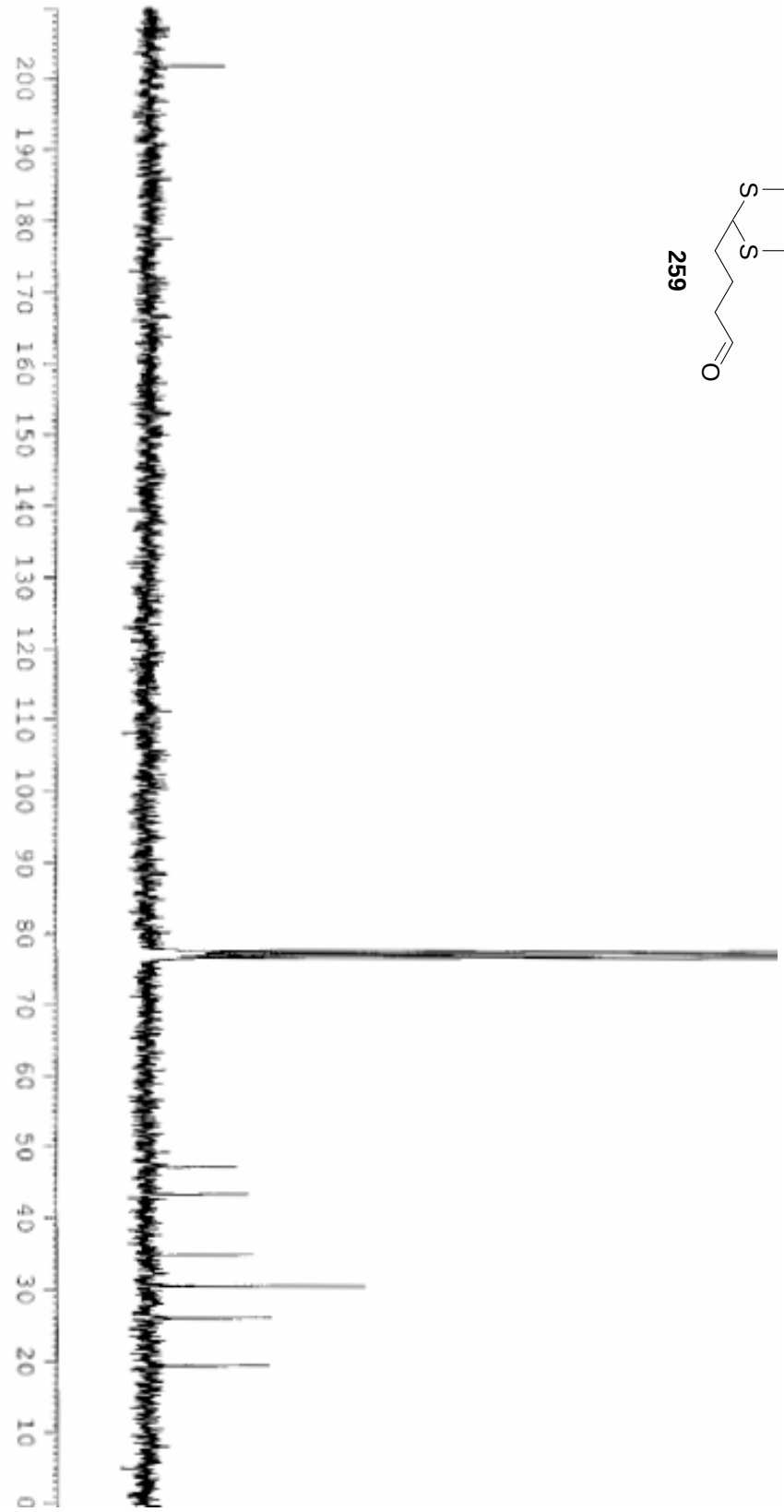

MeO2C
HO
HO
H
HN
237
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


HO
H
HO
HN
MeO2C

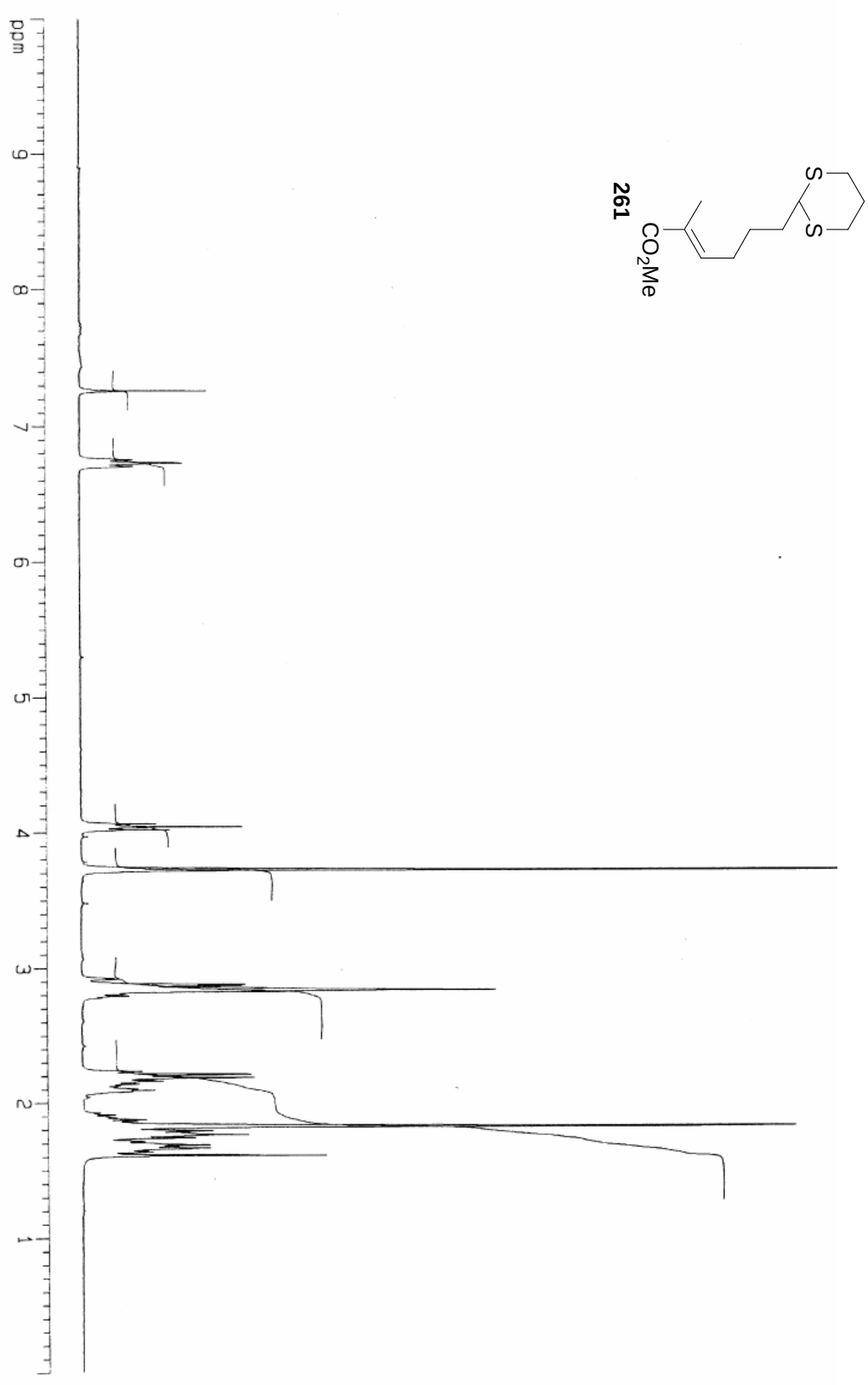
237


ppm
12
10
8
6
4
2
0
S
S
O
259

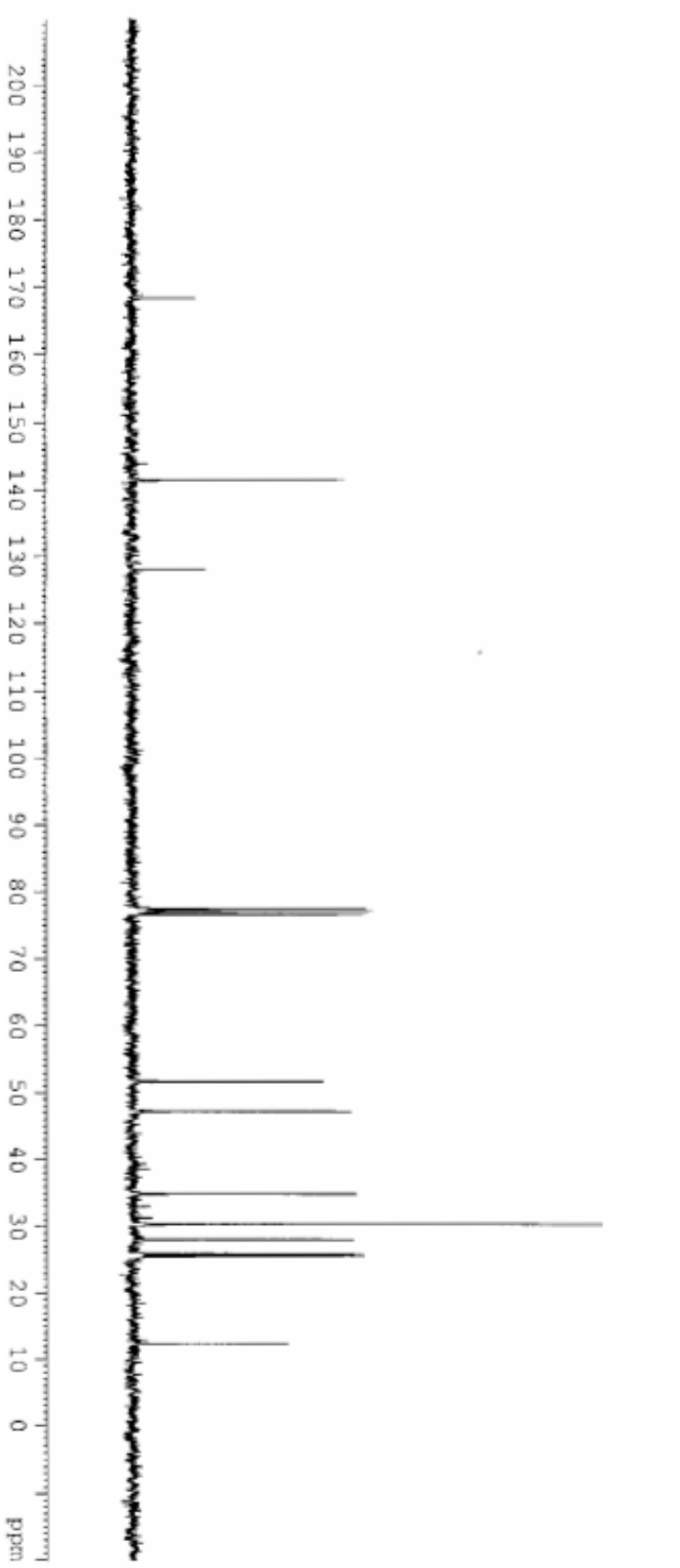

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

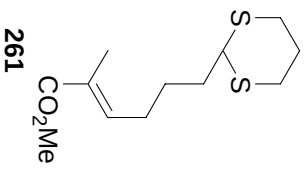
S
S
O

259

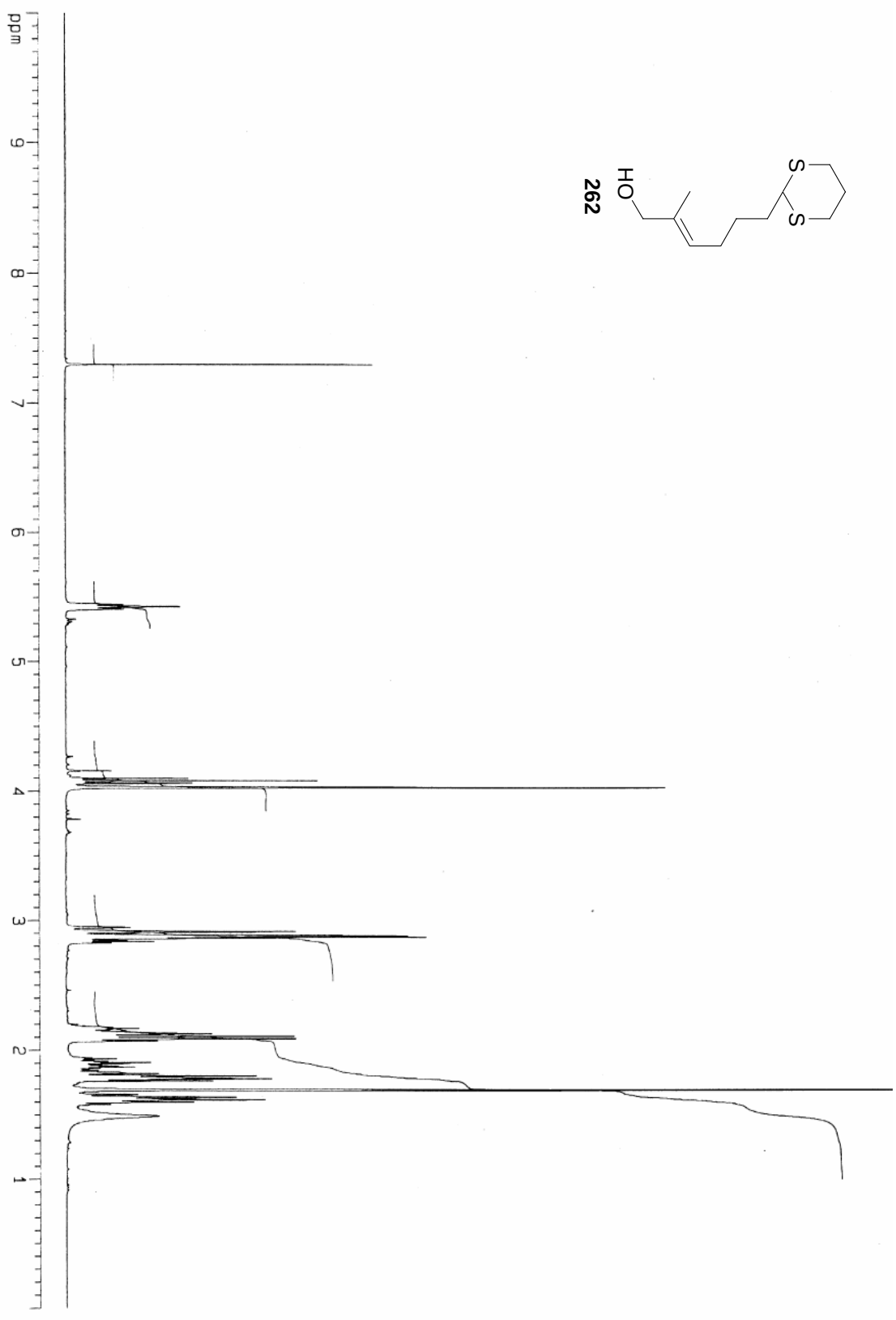


261

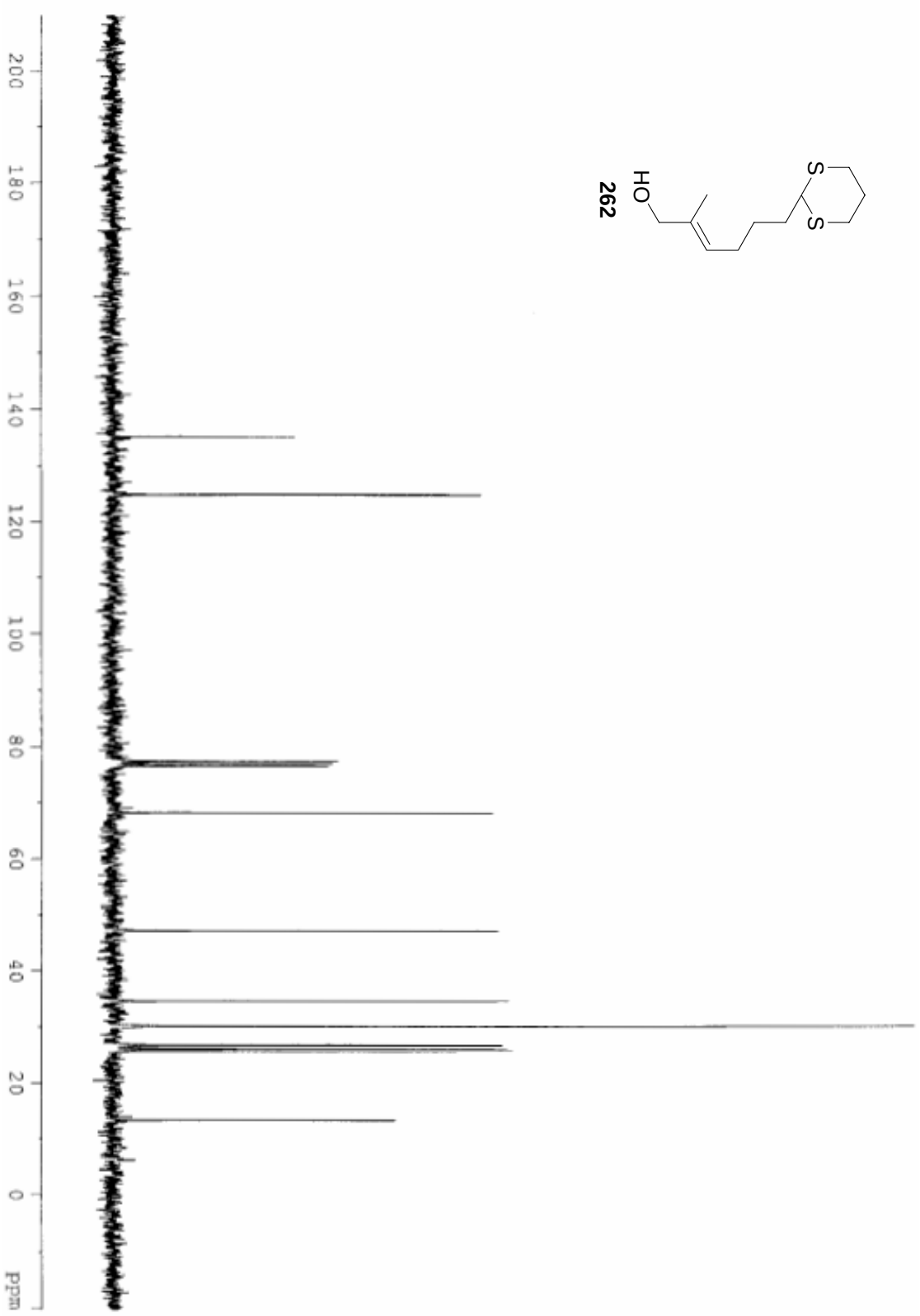

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

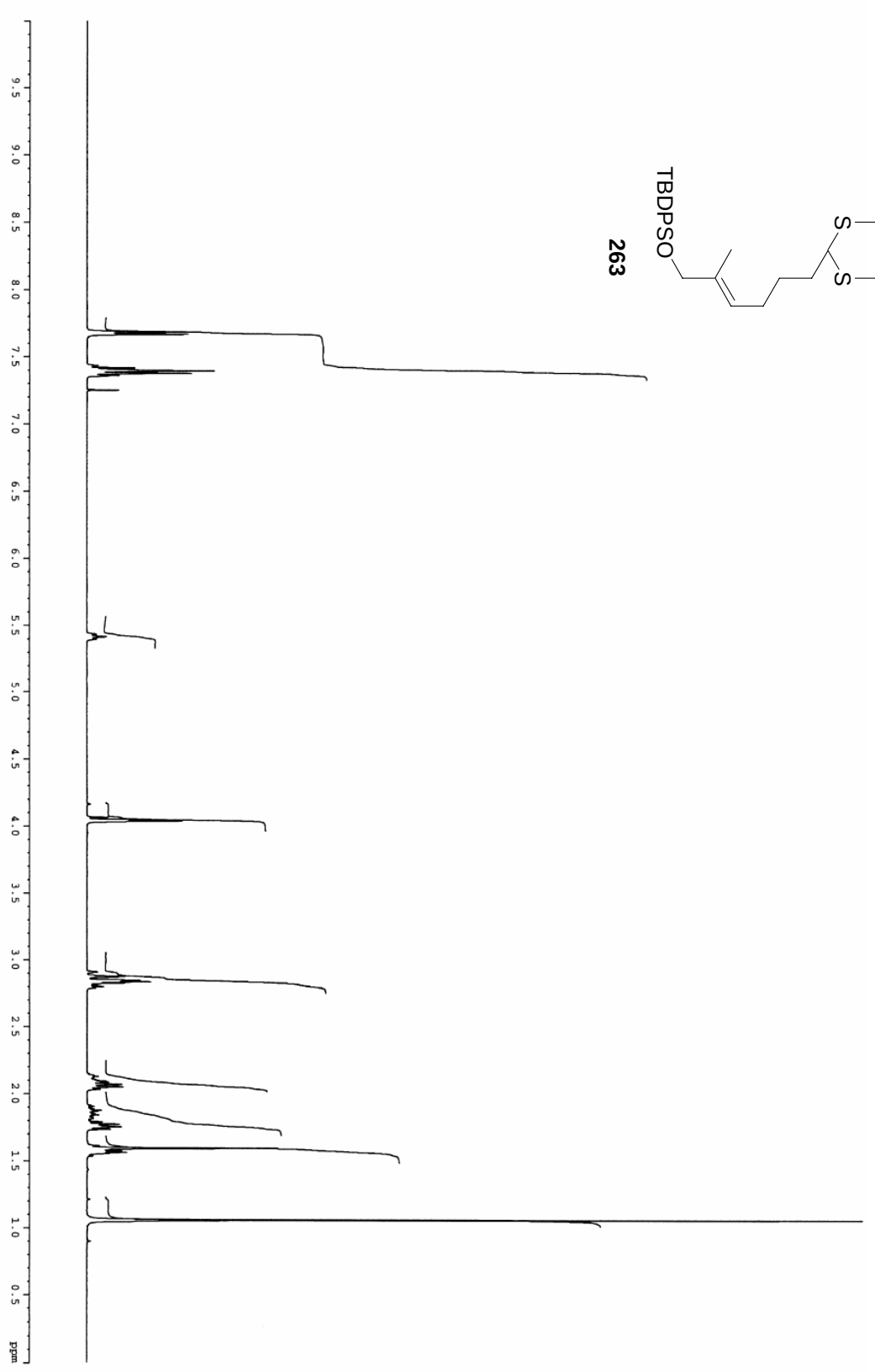

S
S
CO2Me

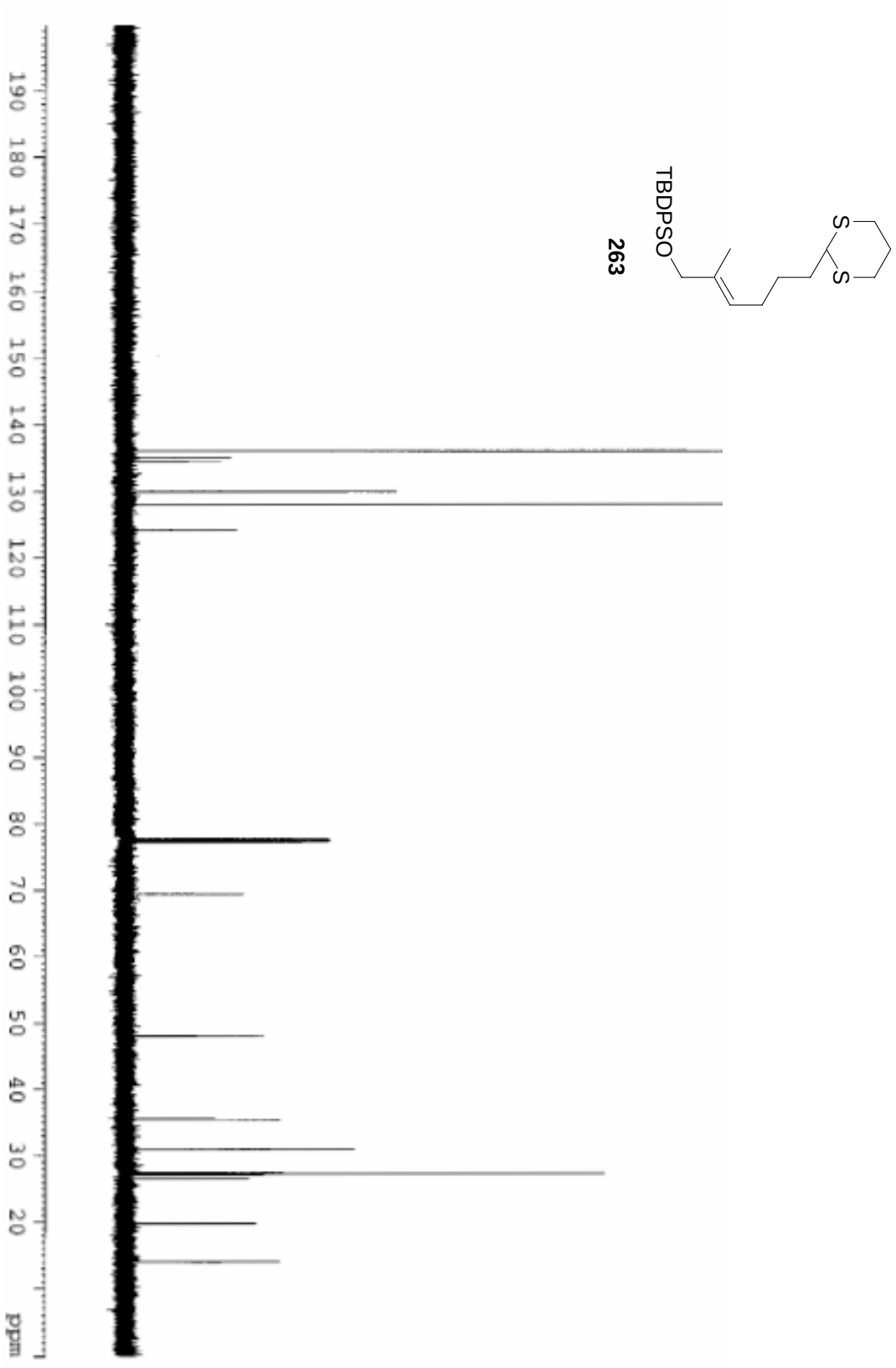
261

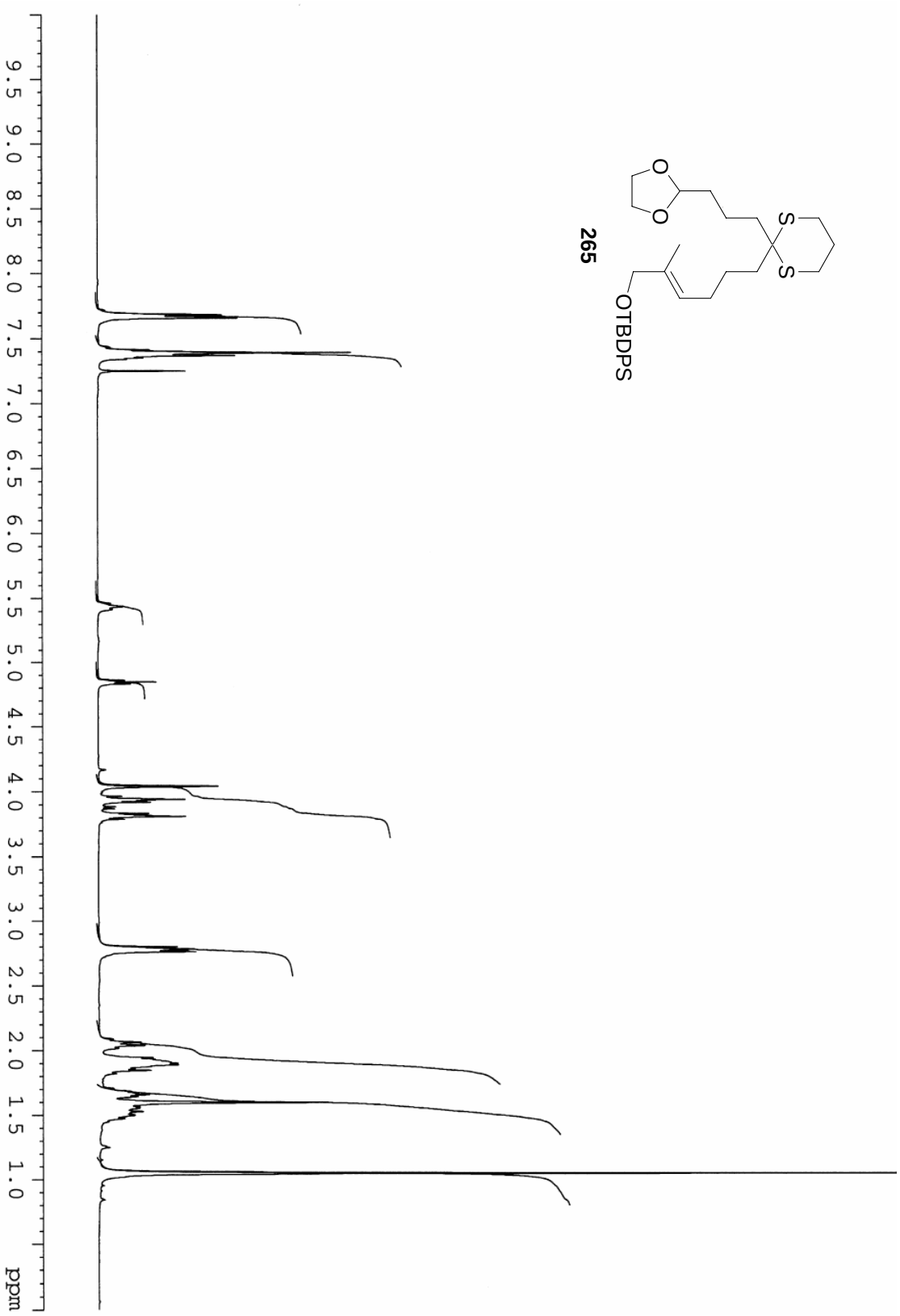


262

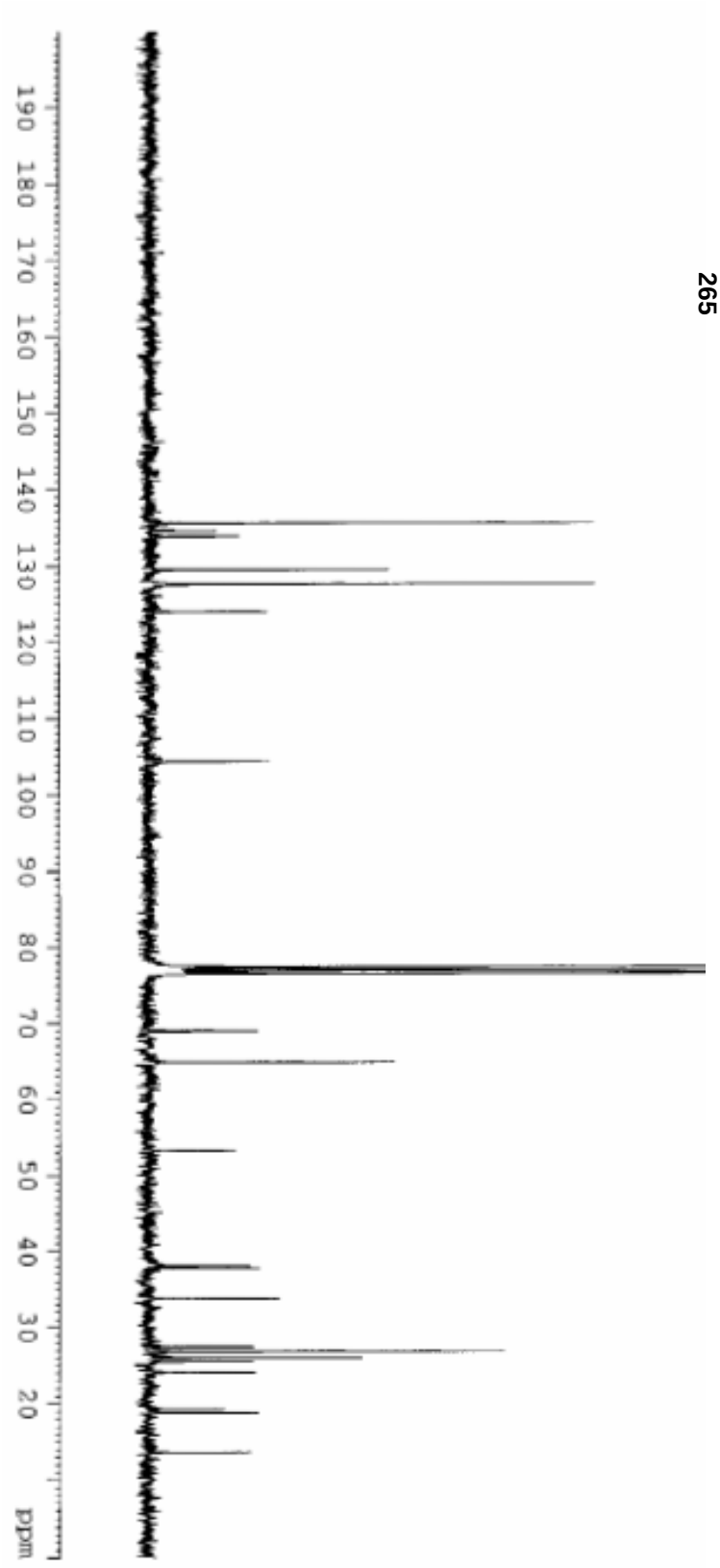

HO
S
S
262
200
180
160
140
120
100
80
60
40
20
0
ppm


TBDPSO
S
S
263
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

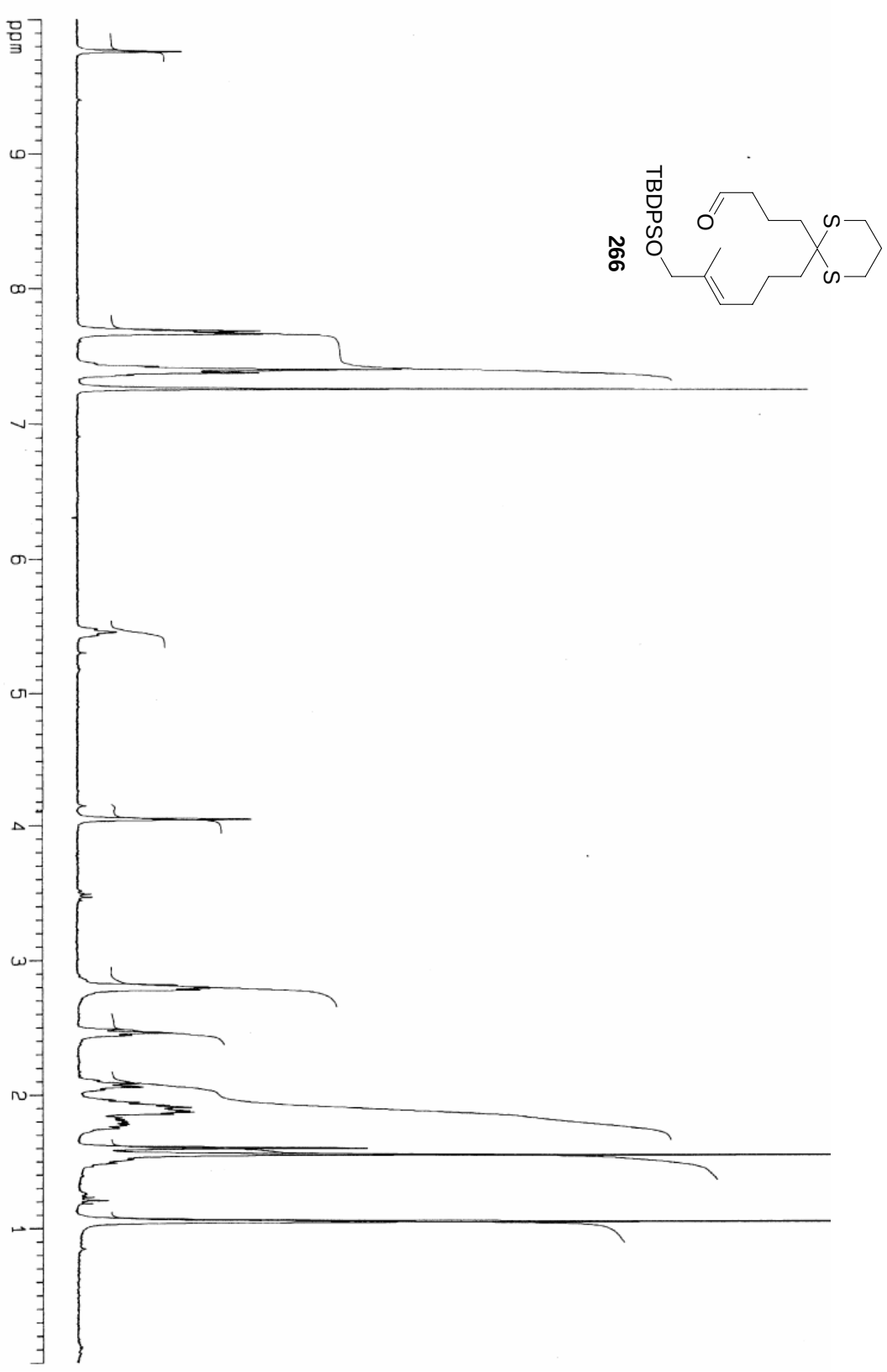

TBDPSO
S
S
263
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm



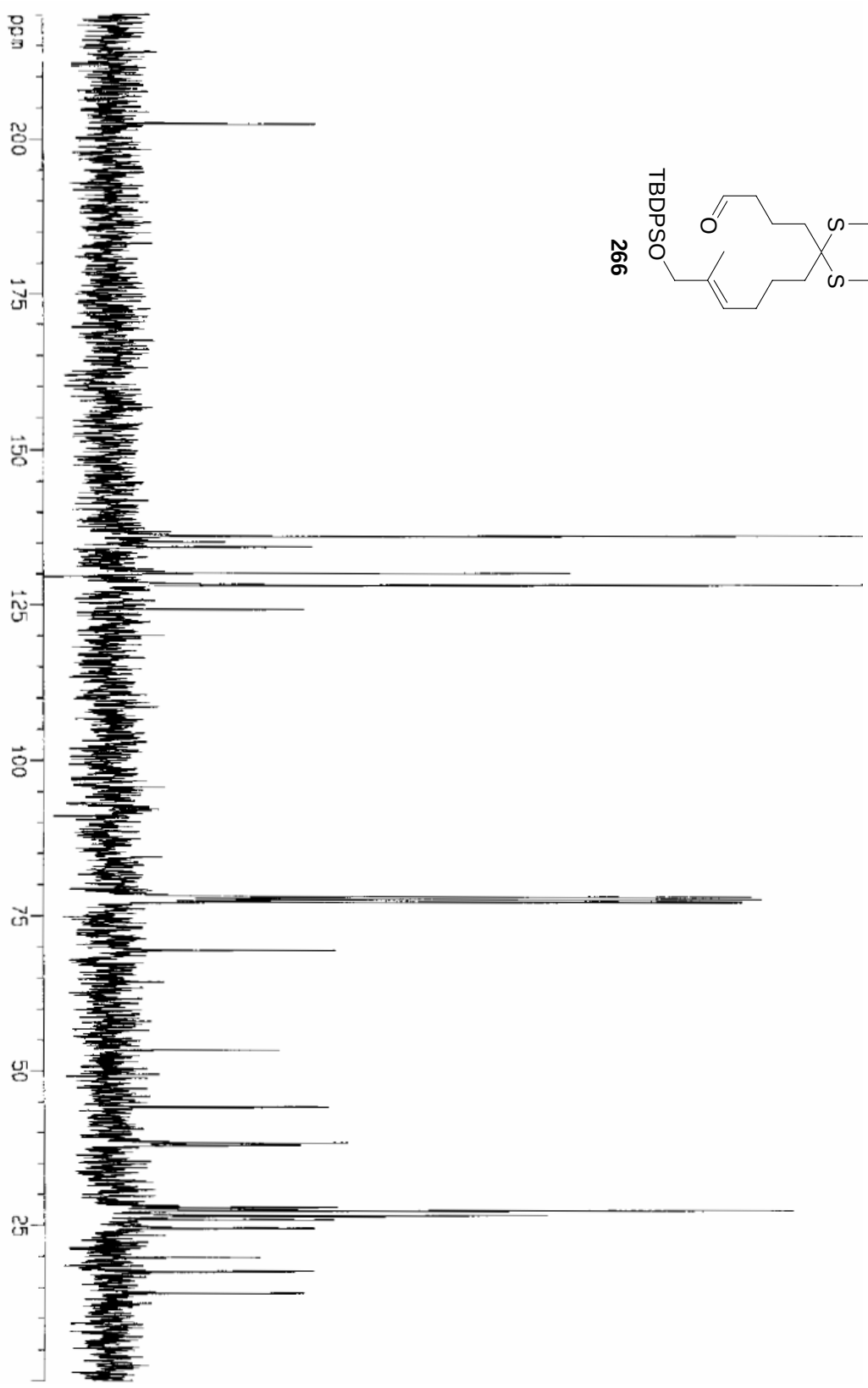
265


O
O
S
S
OTBDPS
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

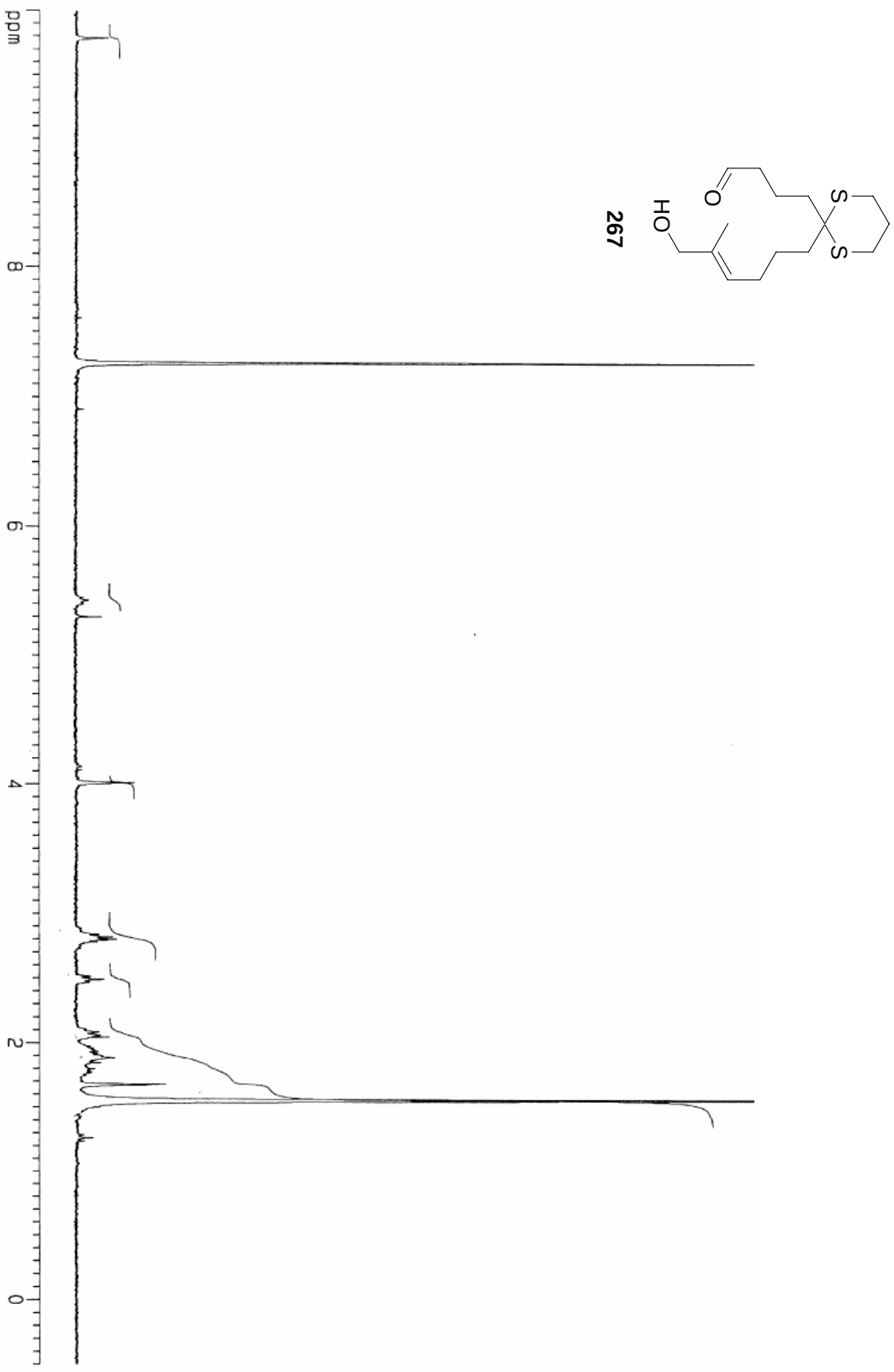
265



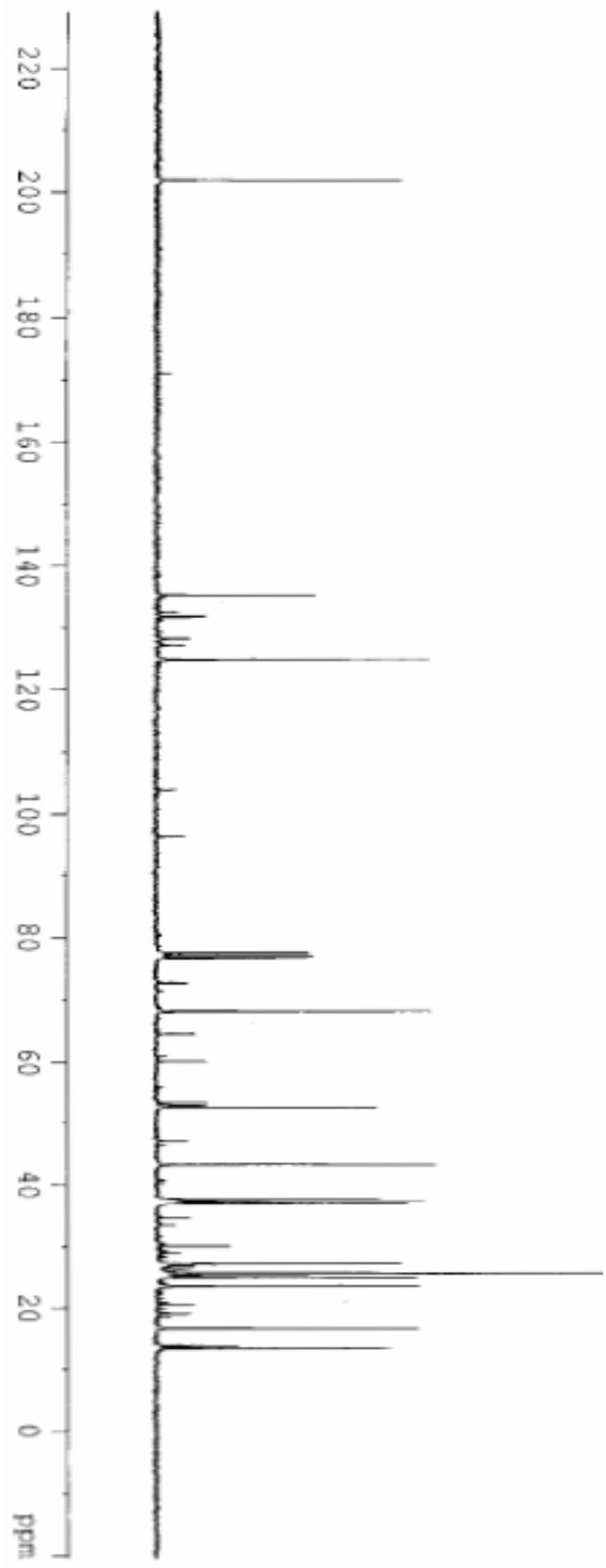
266

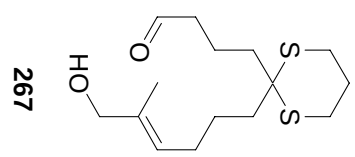


266

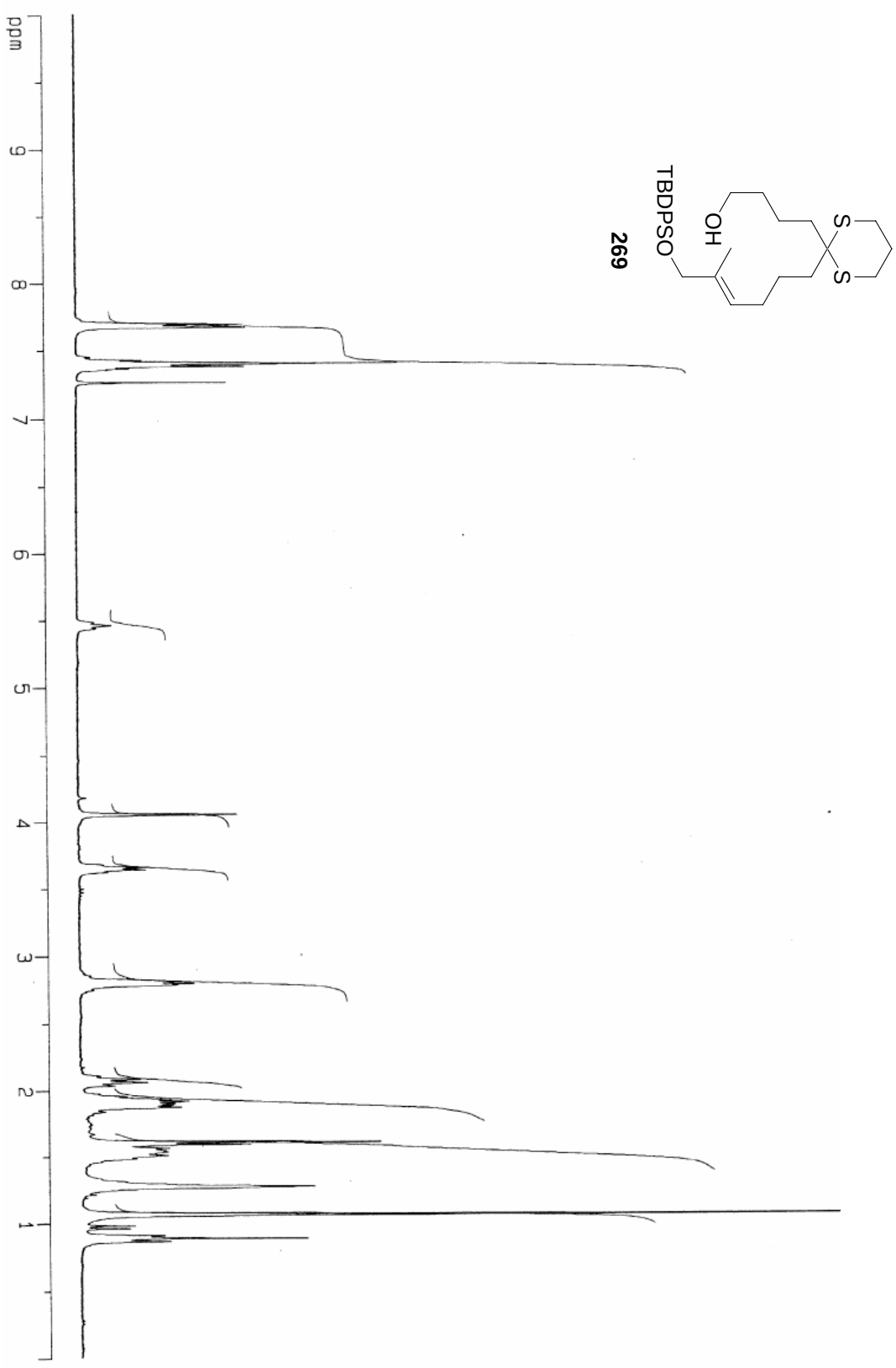


267

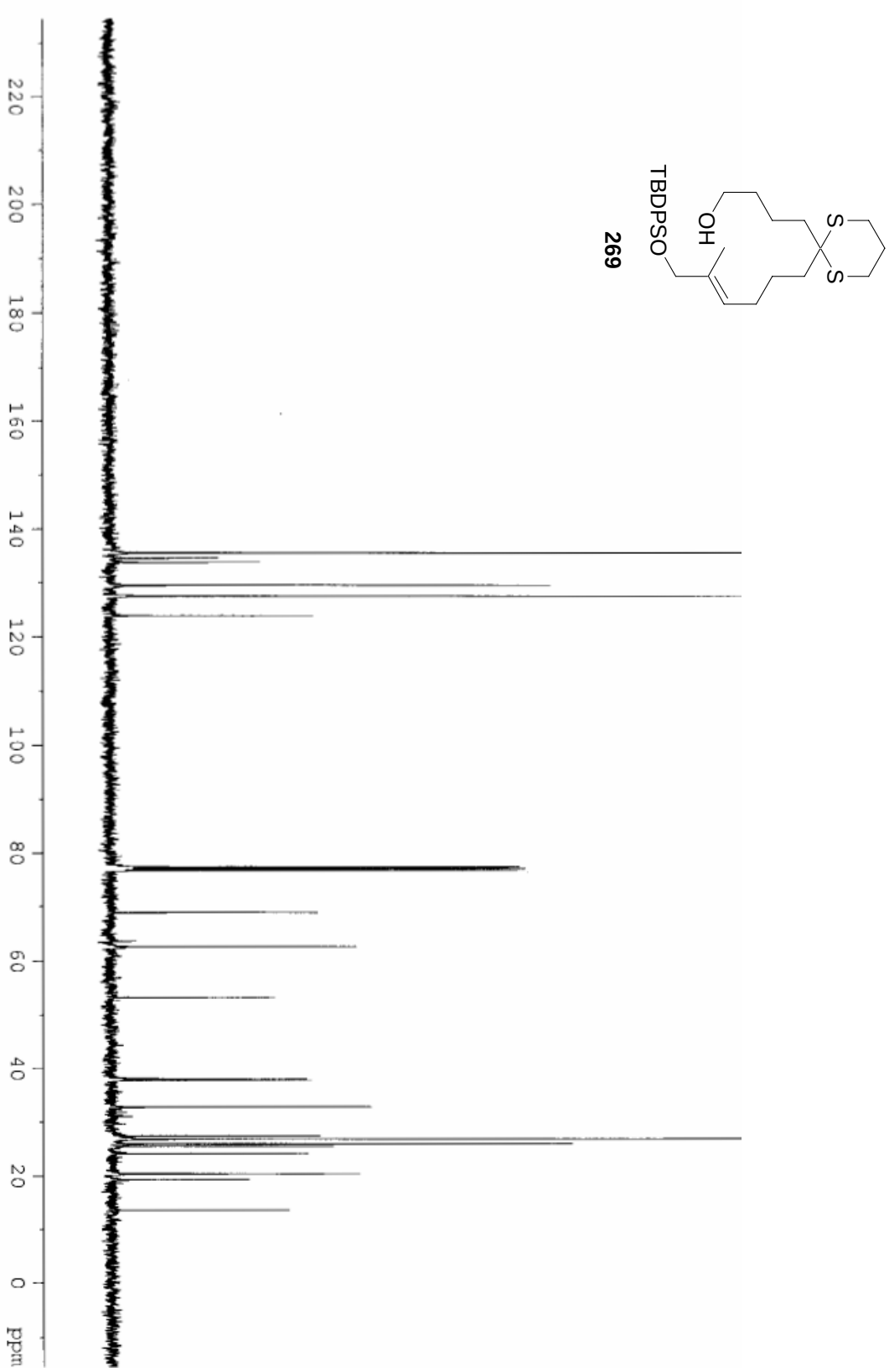


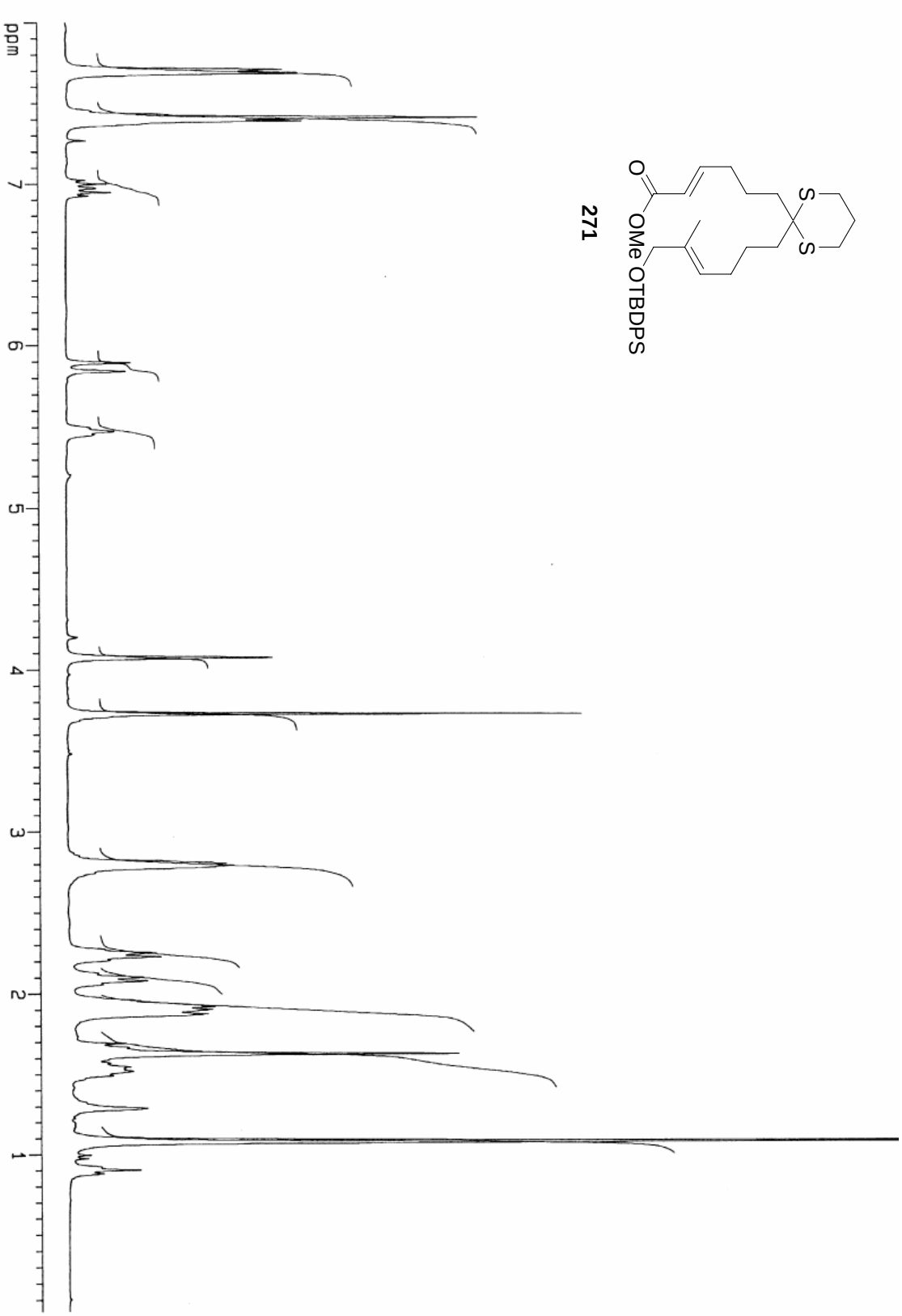


267

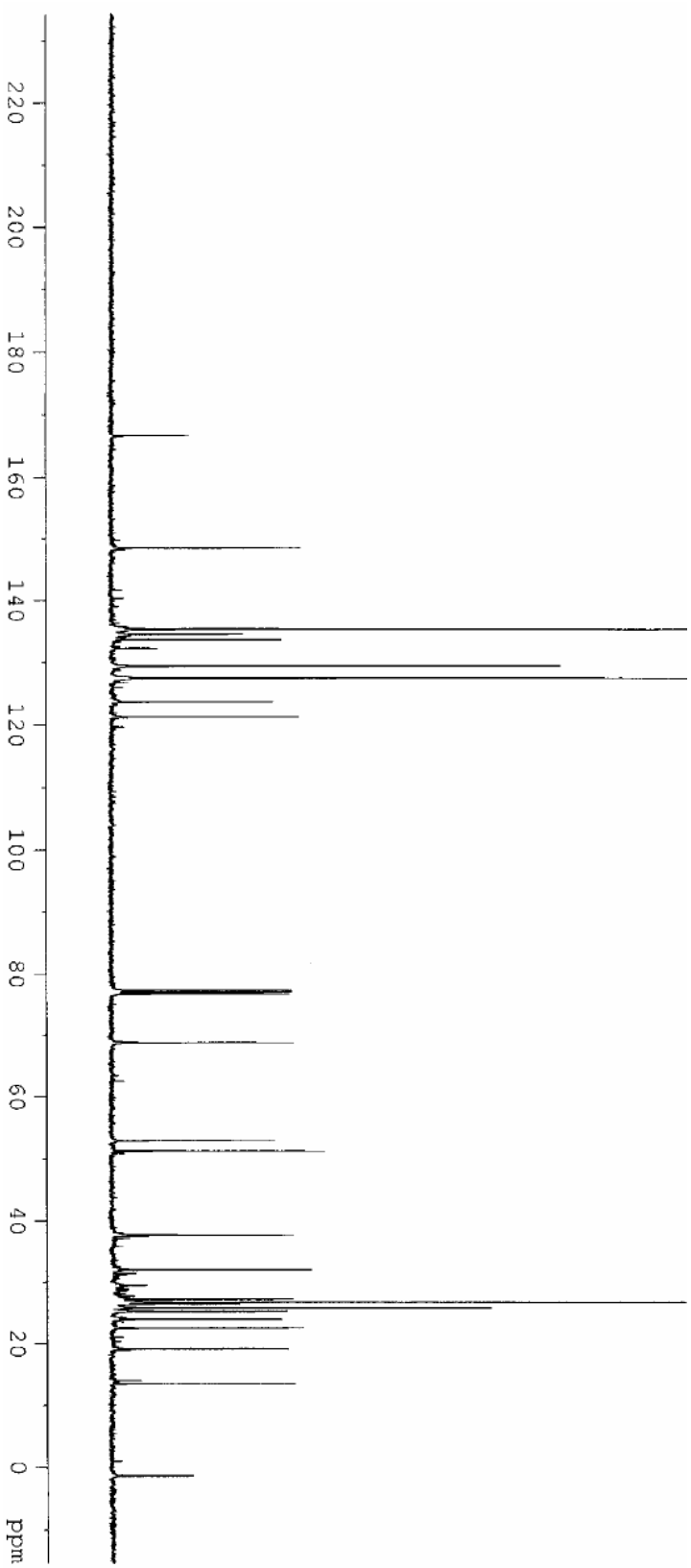


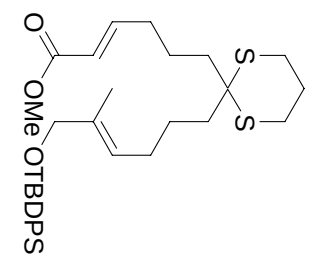
269


TBDPSO
OH
S
S
269
220
200
180
160
140
120
100
80
60
40
20
0
ppm

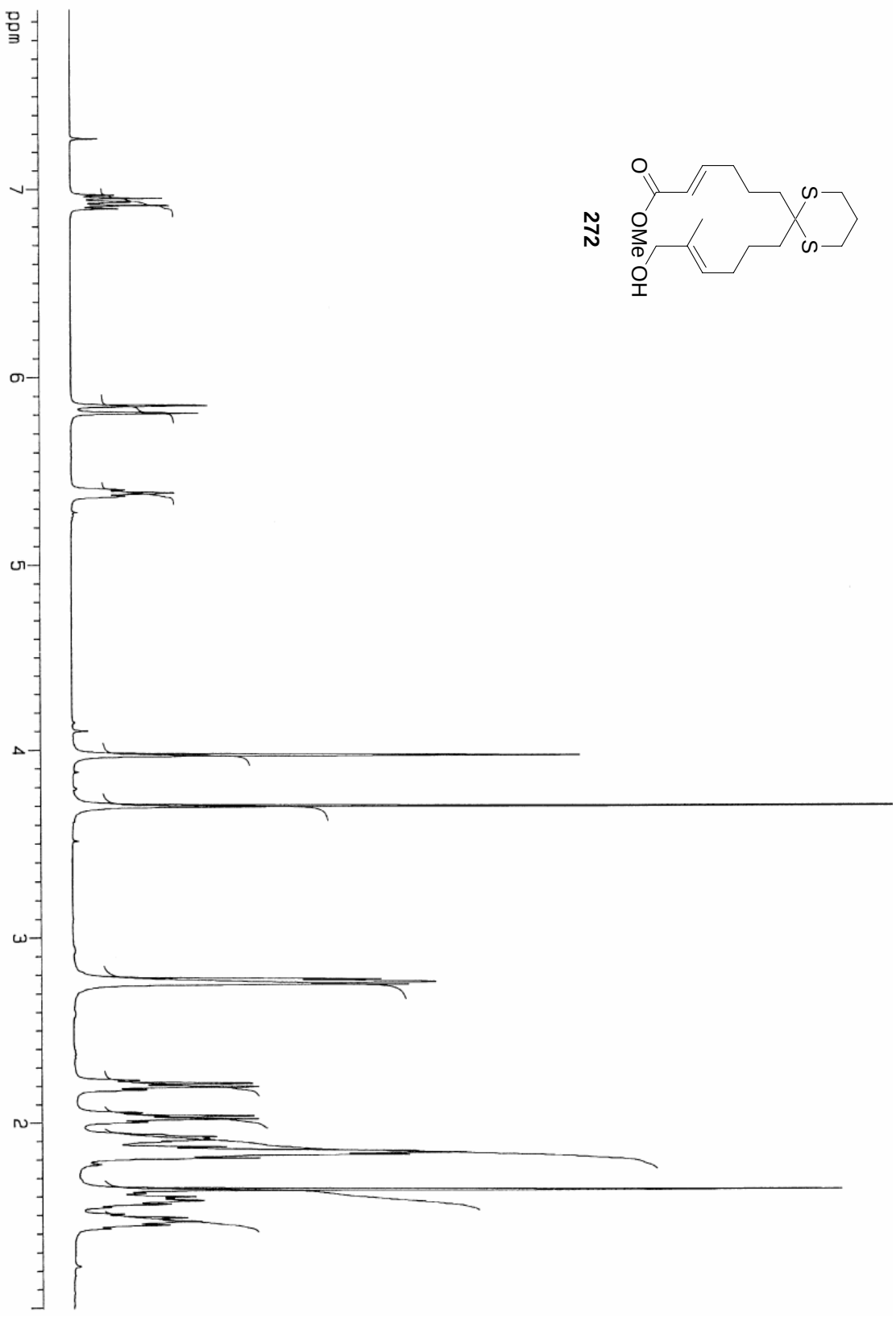


271

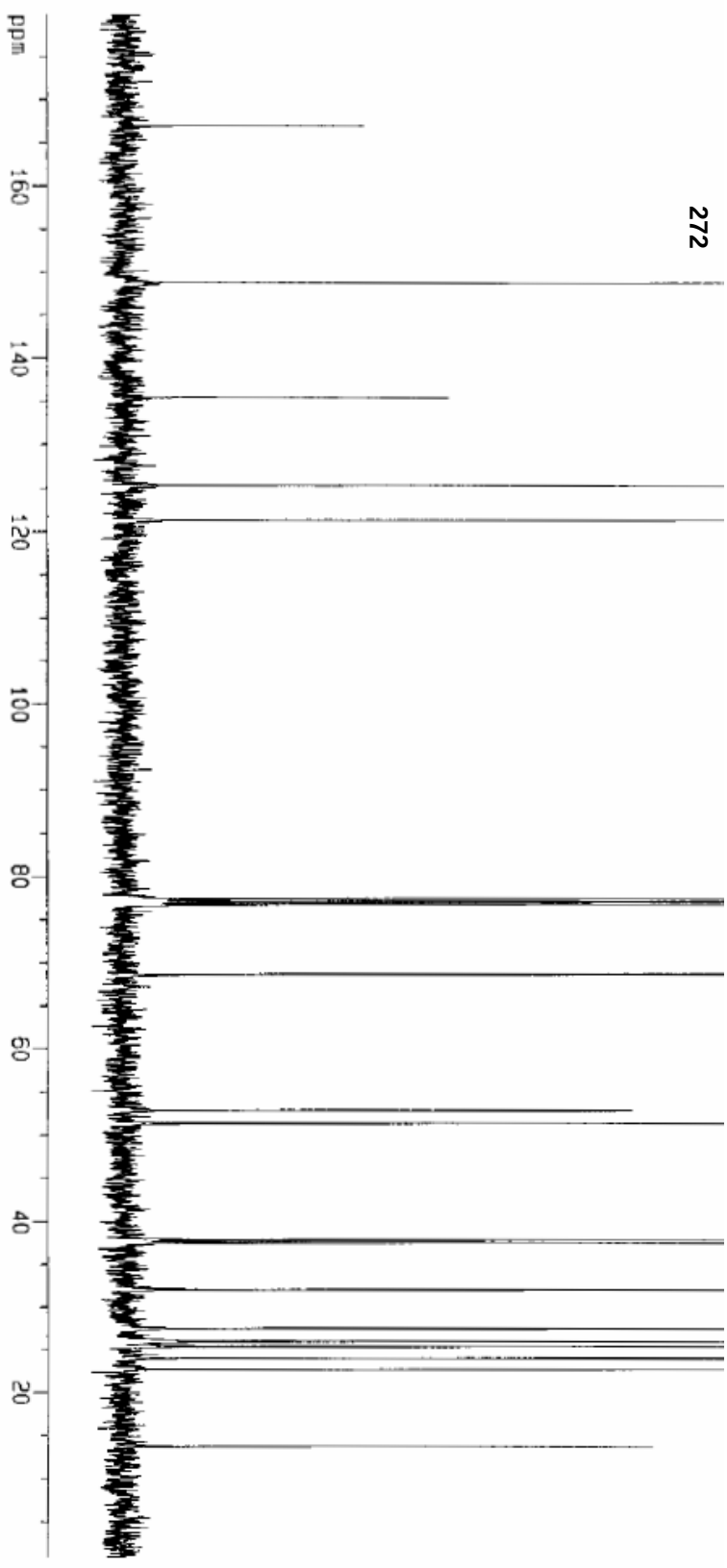


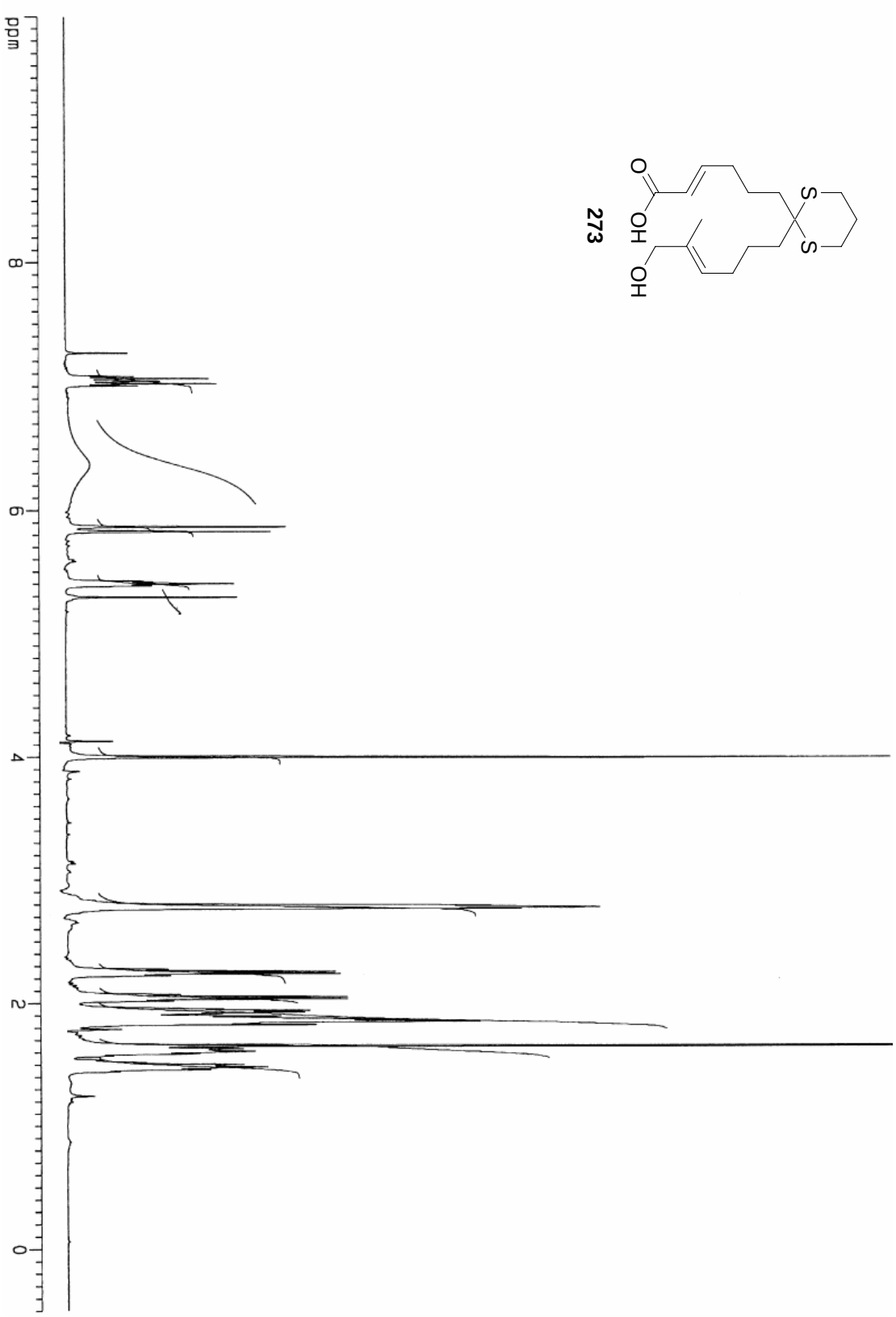


271

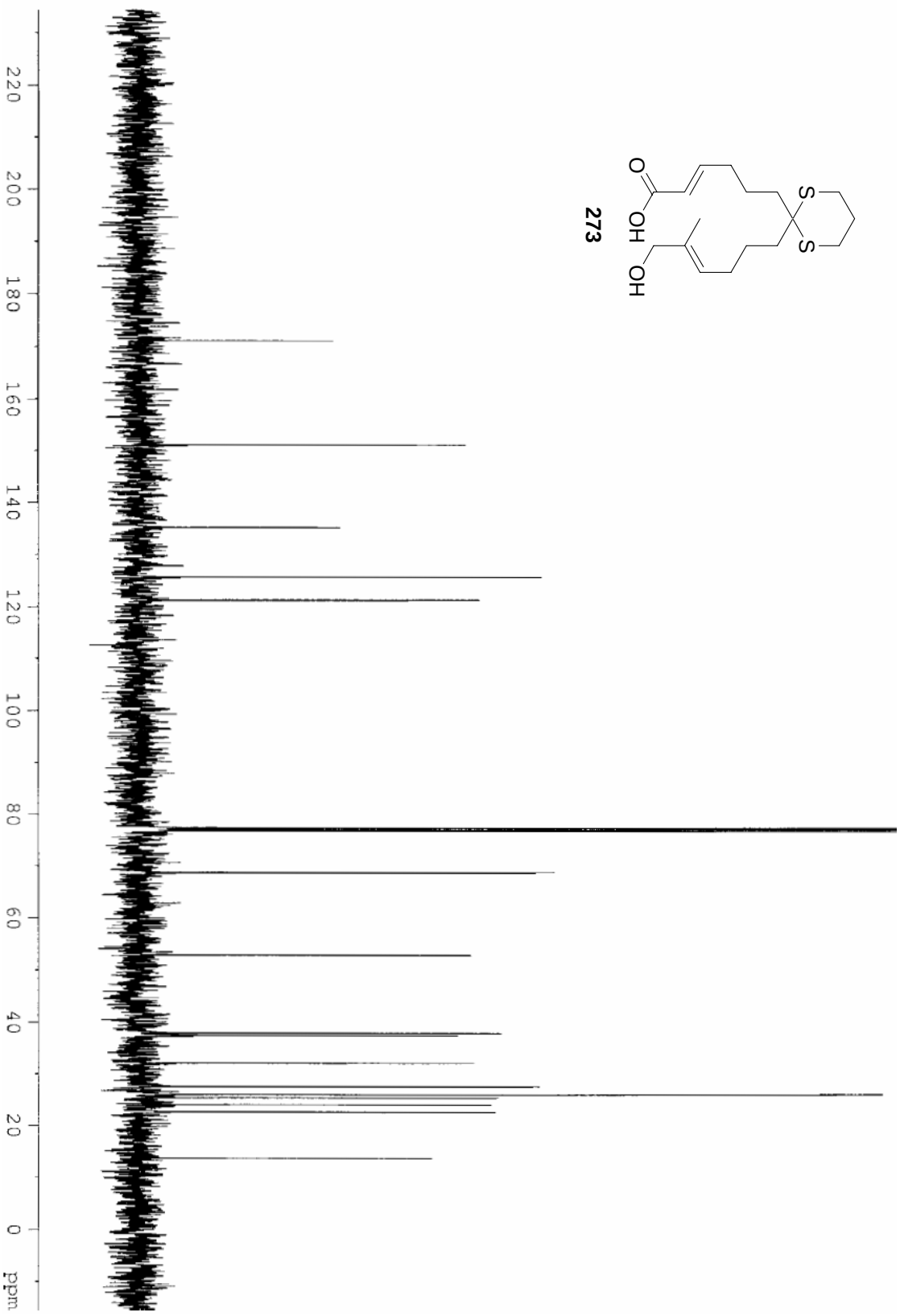


272


ppm
160
140
120
100
80
60
40
20
272
O
OMe
OH
S
S



273


O
OH
OH
S
S
273
220
200
180
160
140
120
100
80
60
40
20
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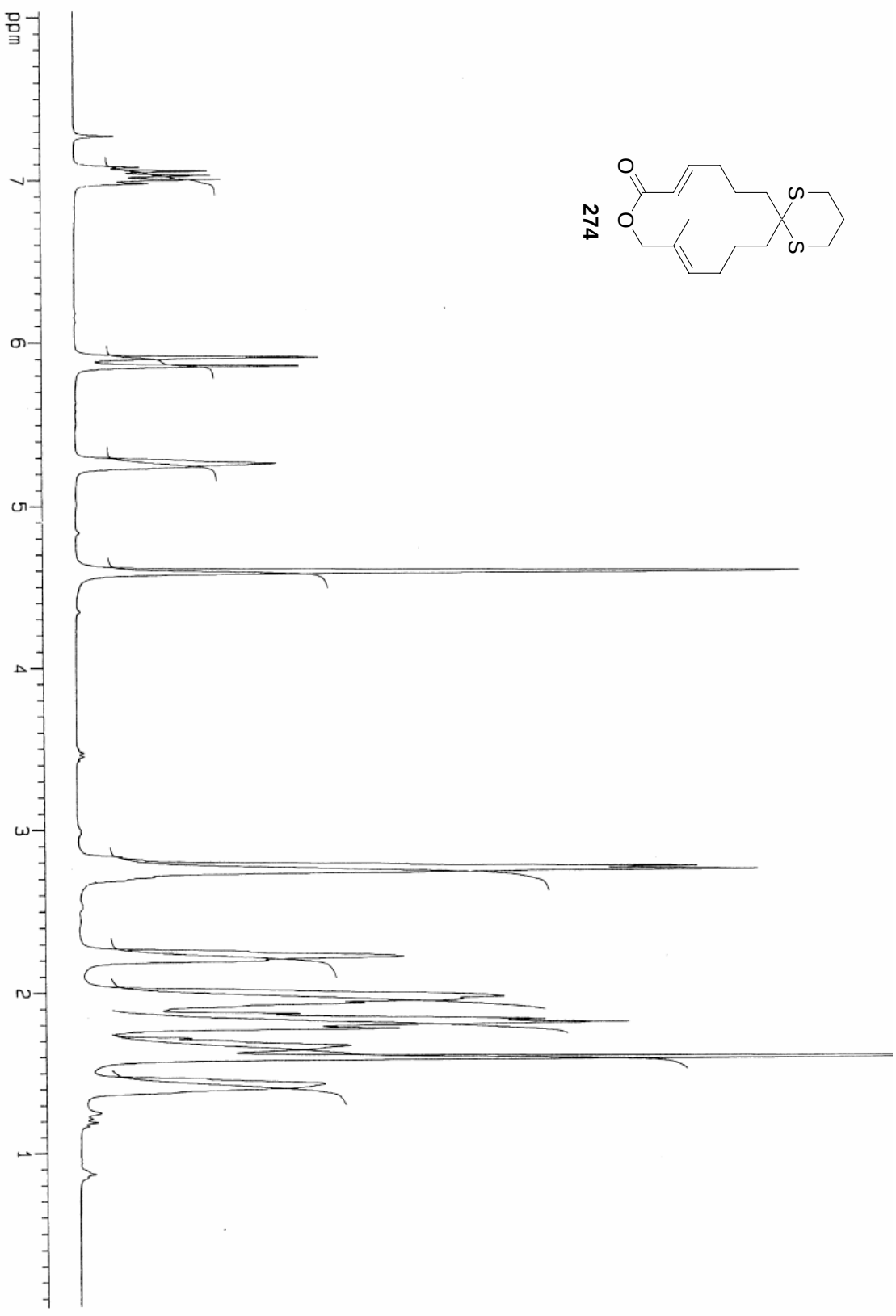

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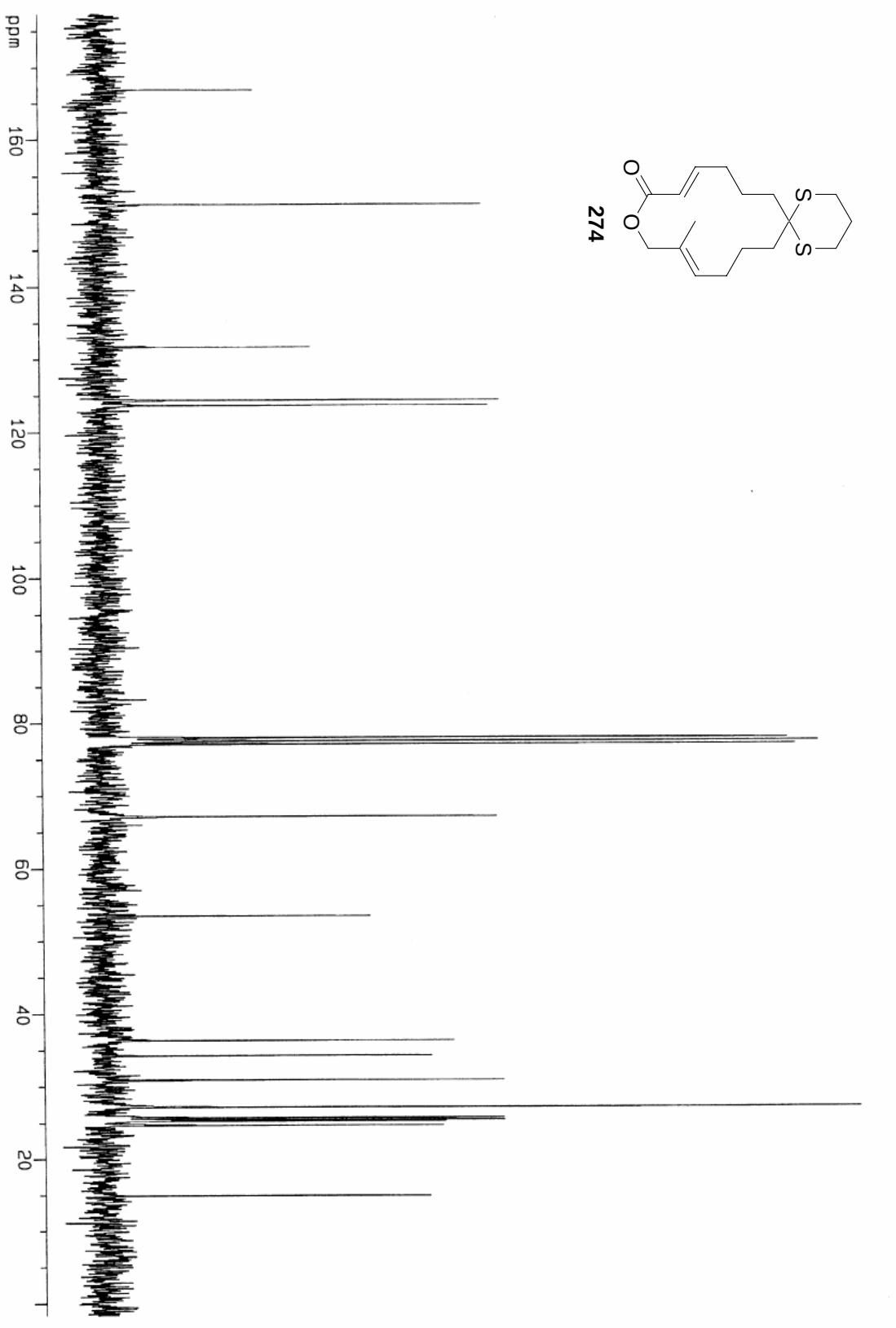
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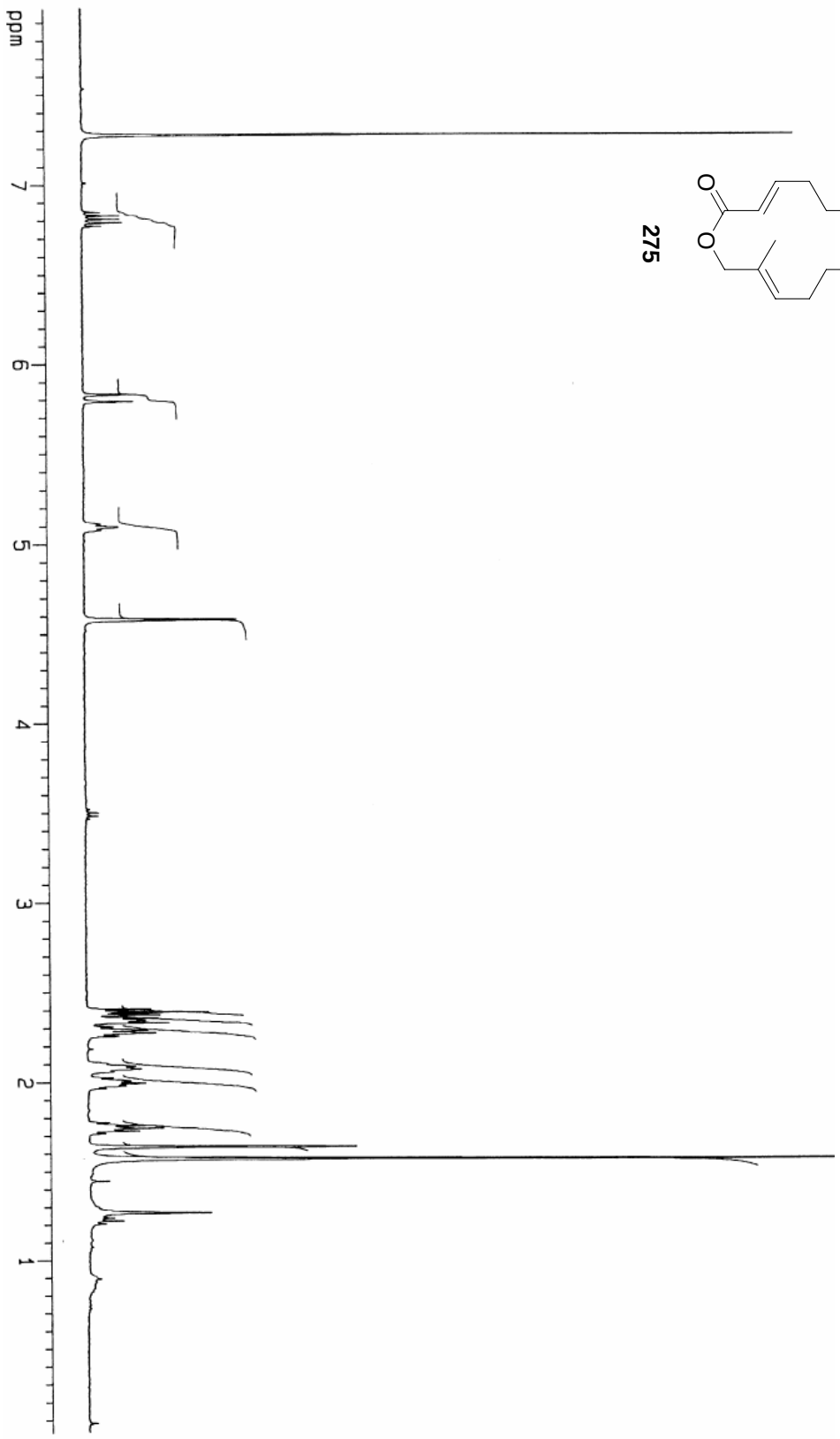
S
S
274



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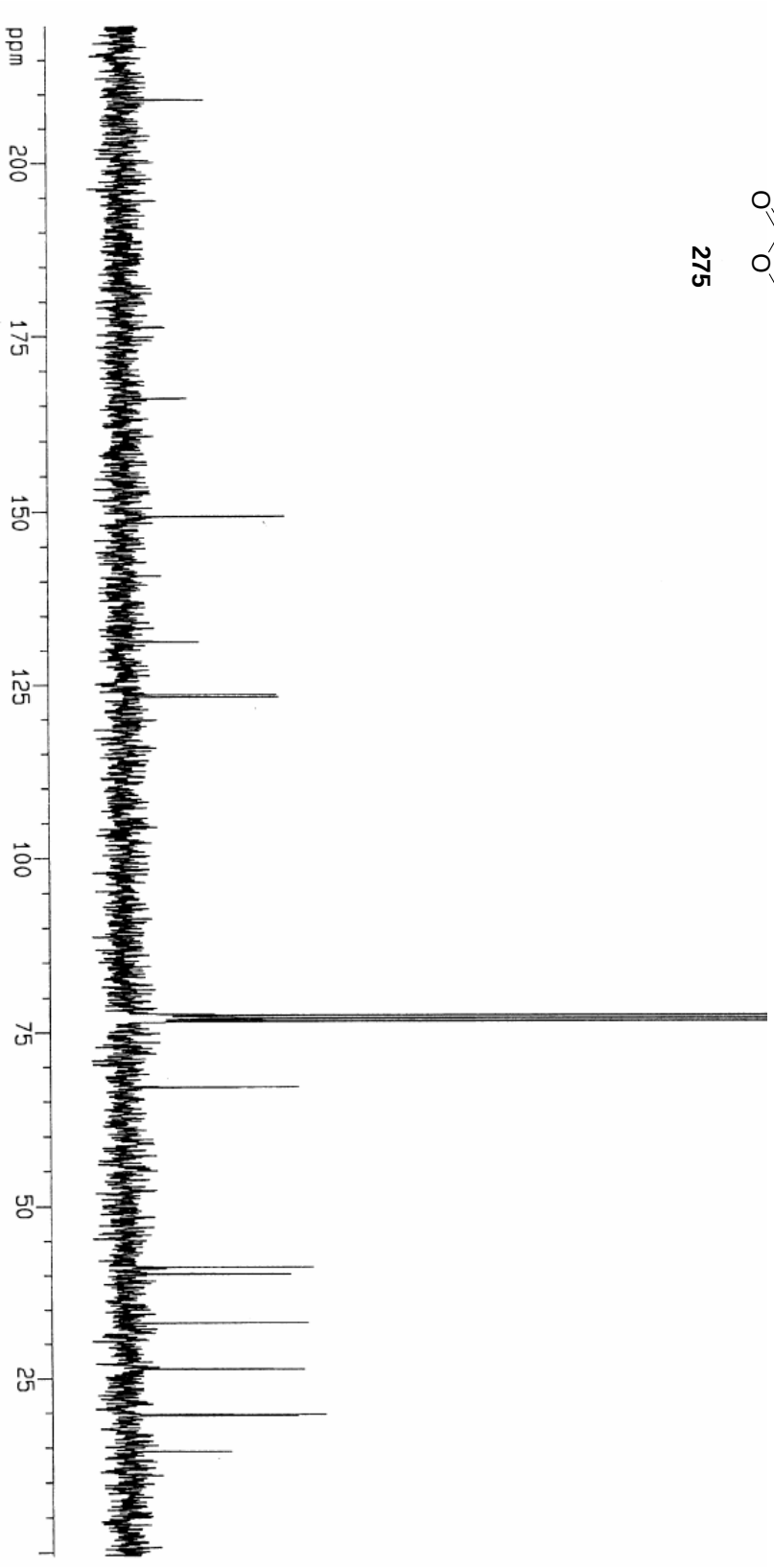

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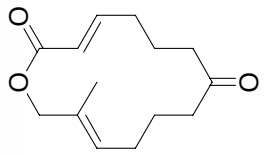

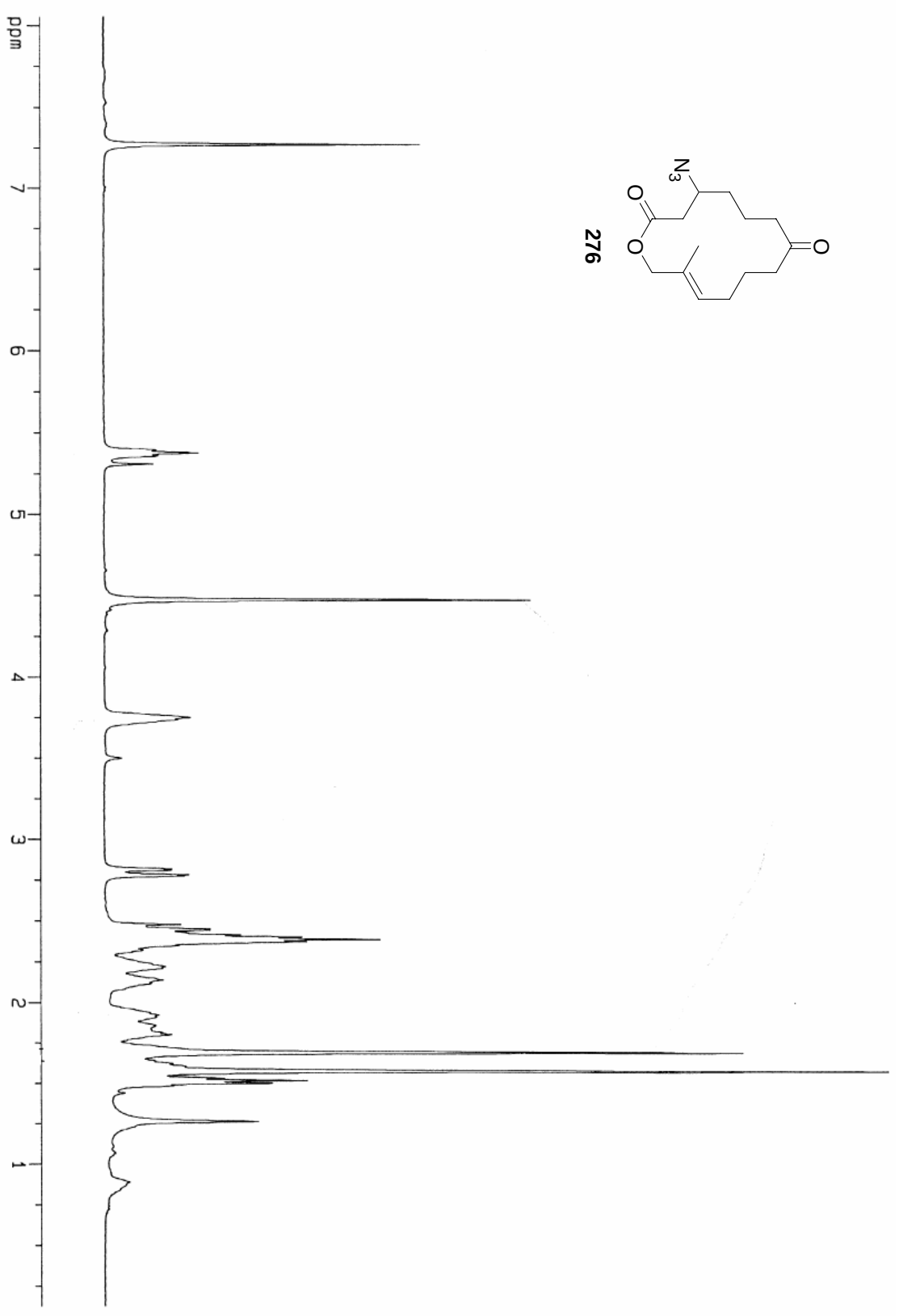

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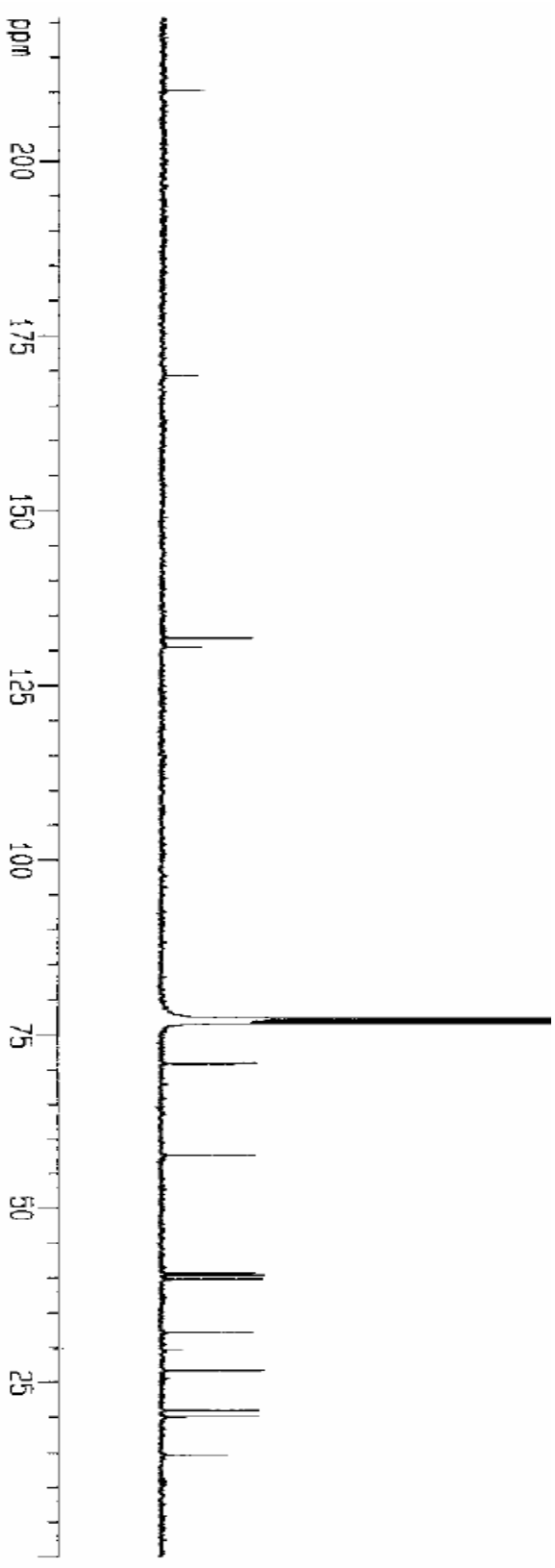

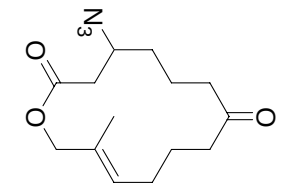

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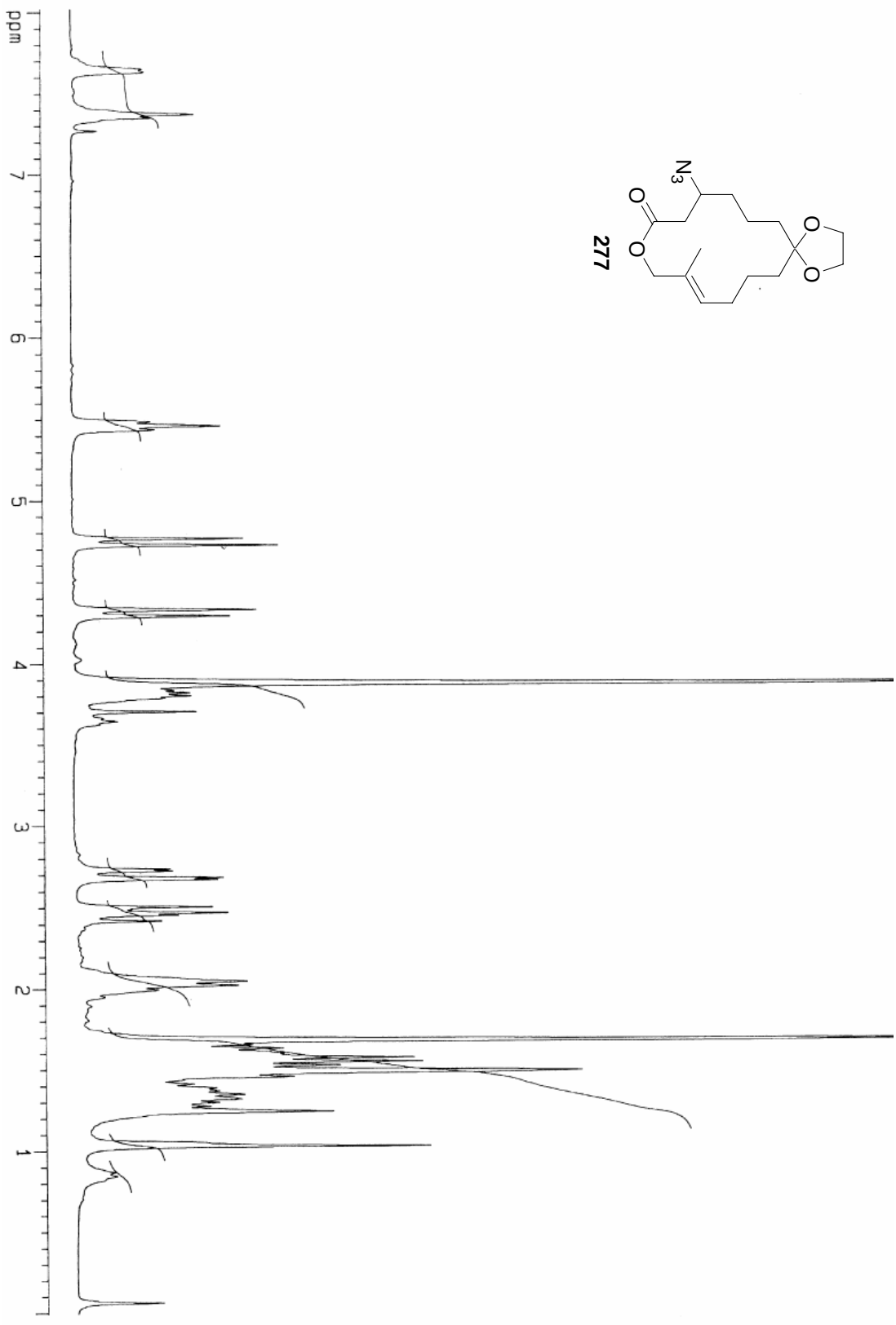

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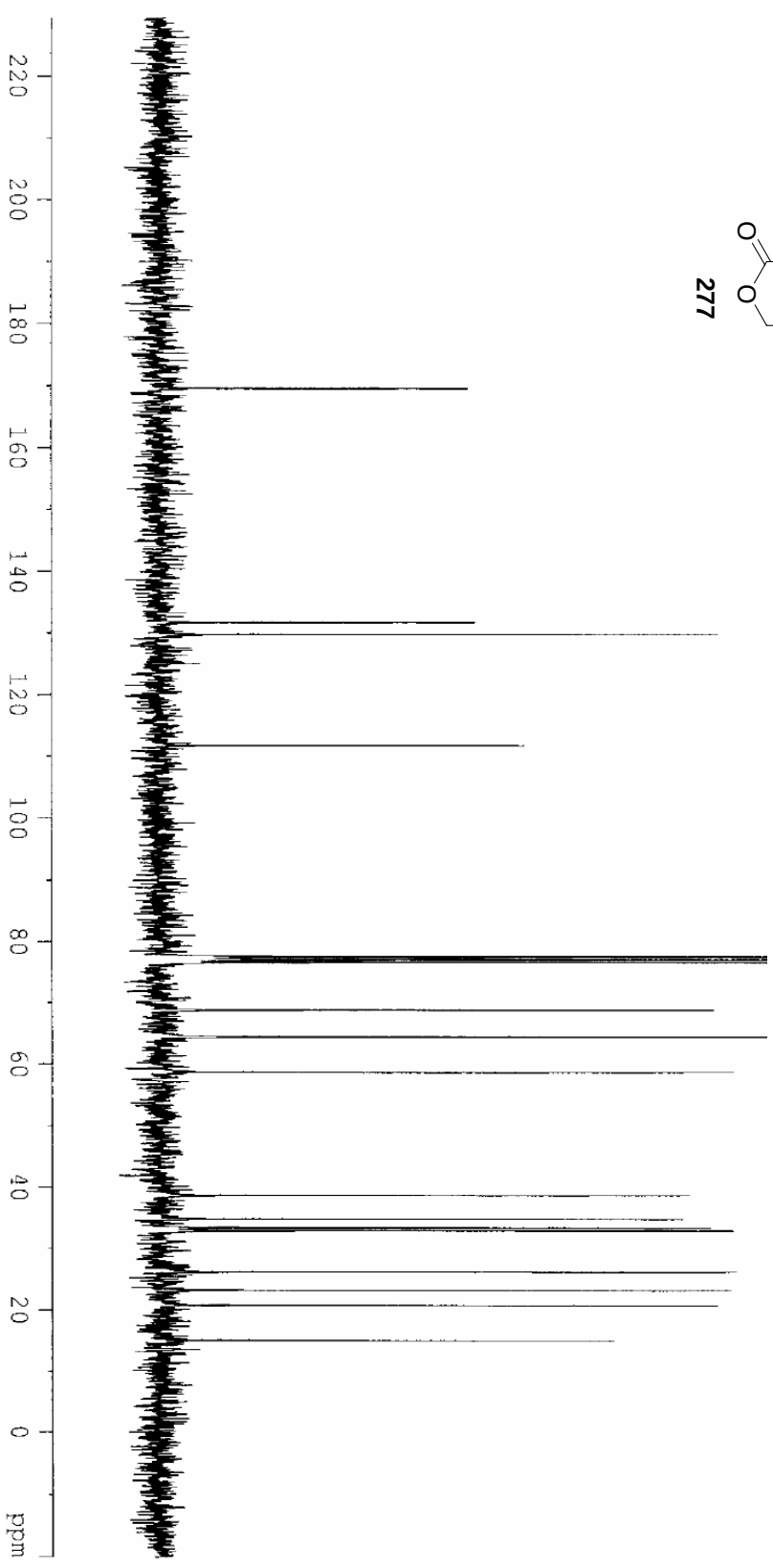

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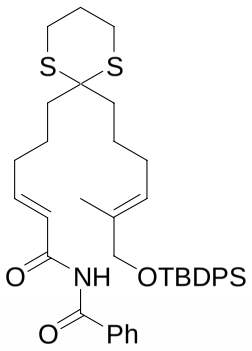
S
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OTBDPS
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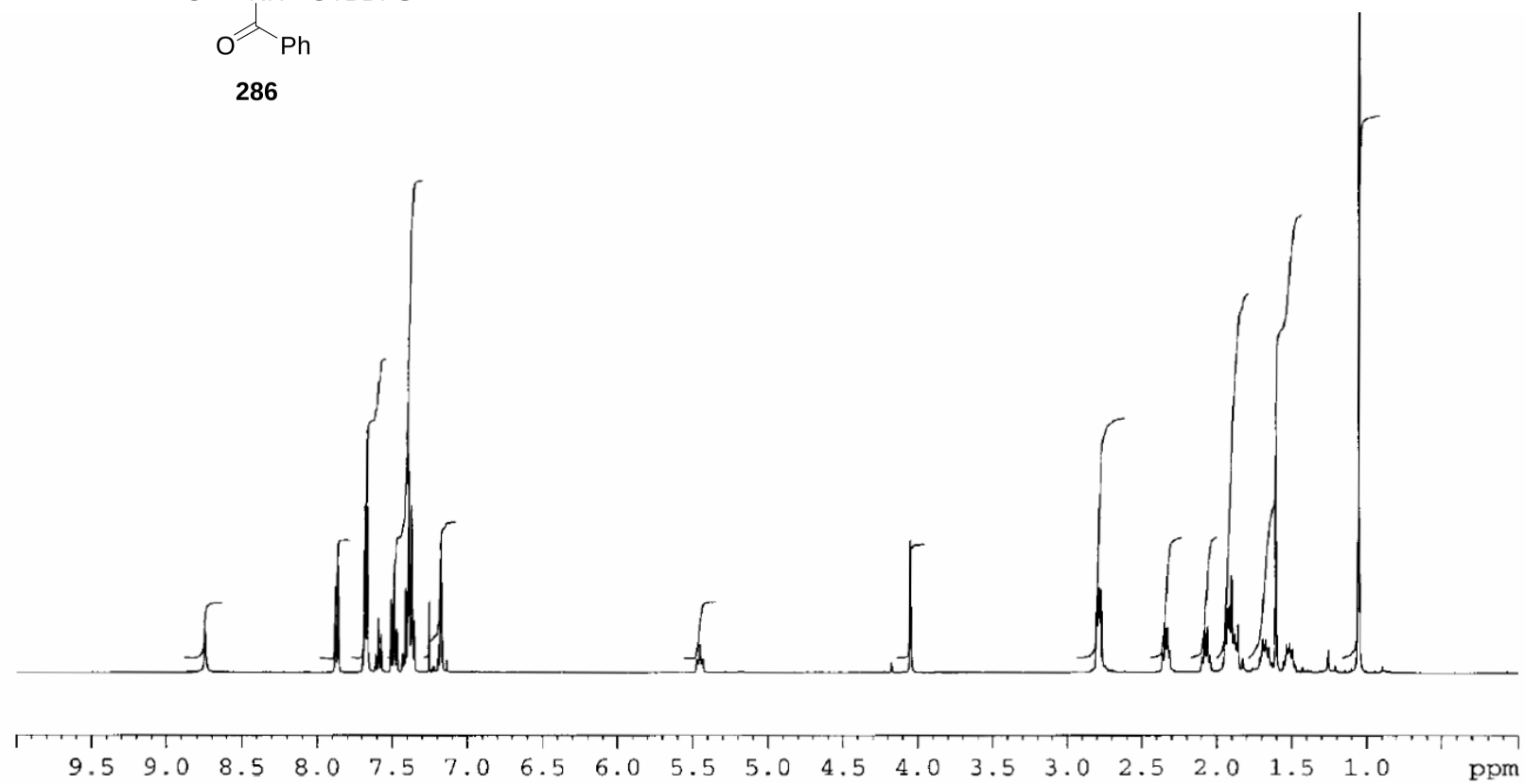
Ph

286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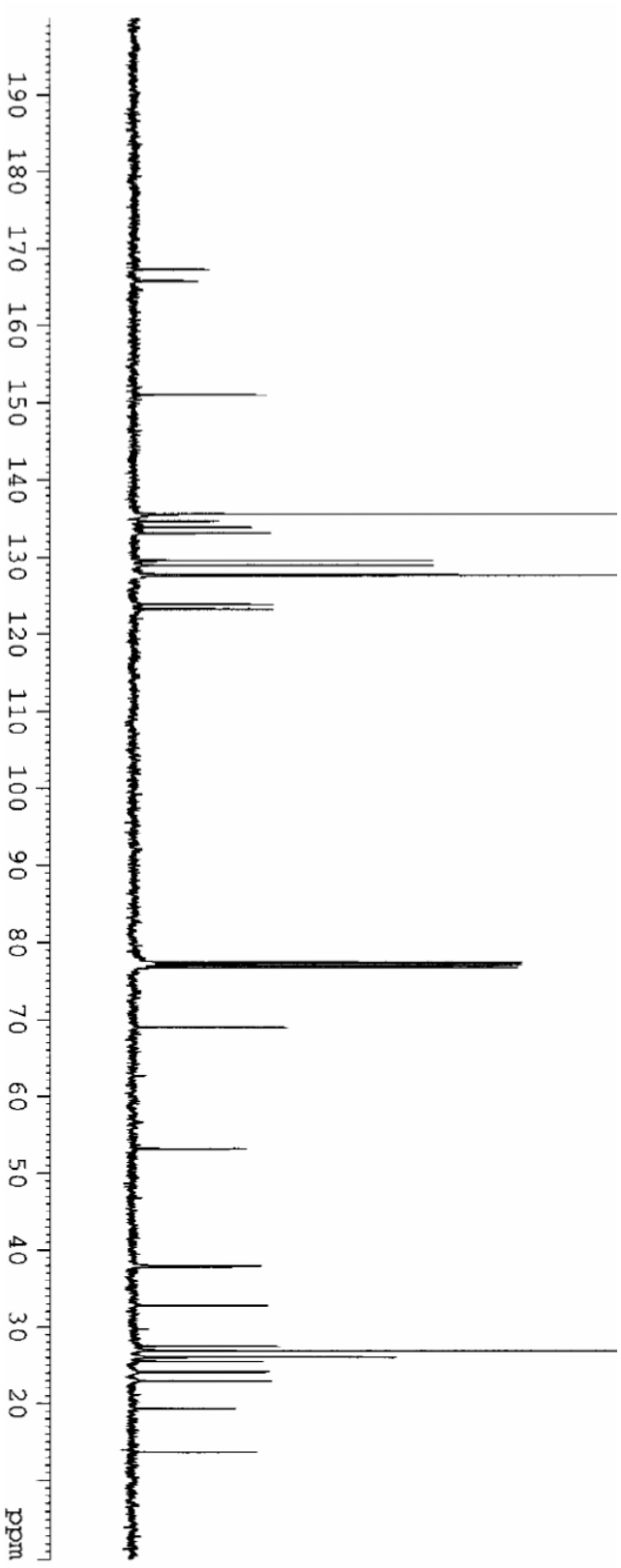
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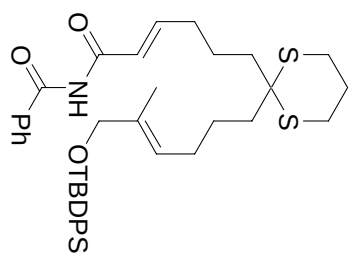
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NH
OTBDPS
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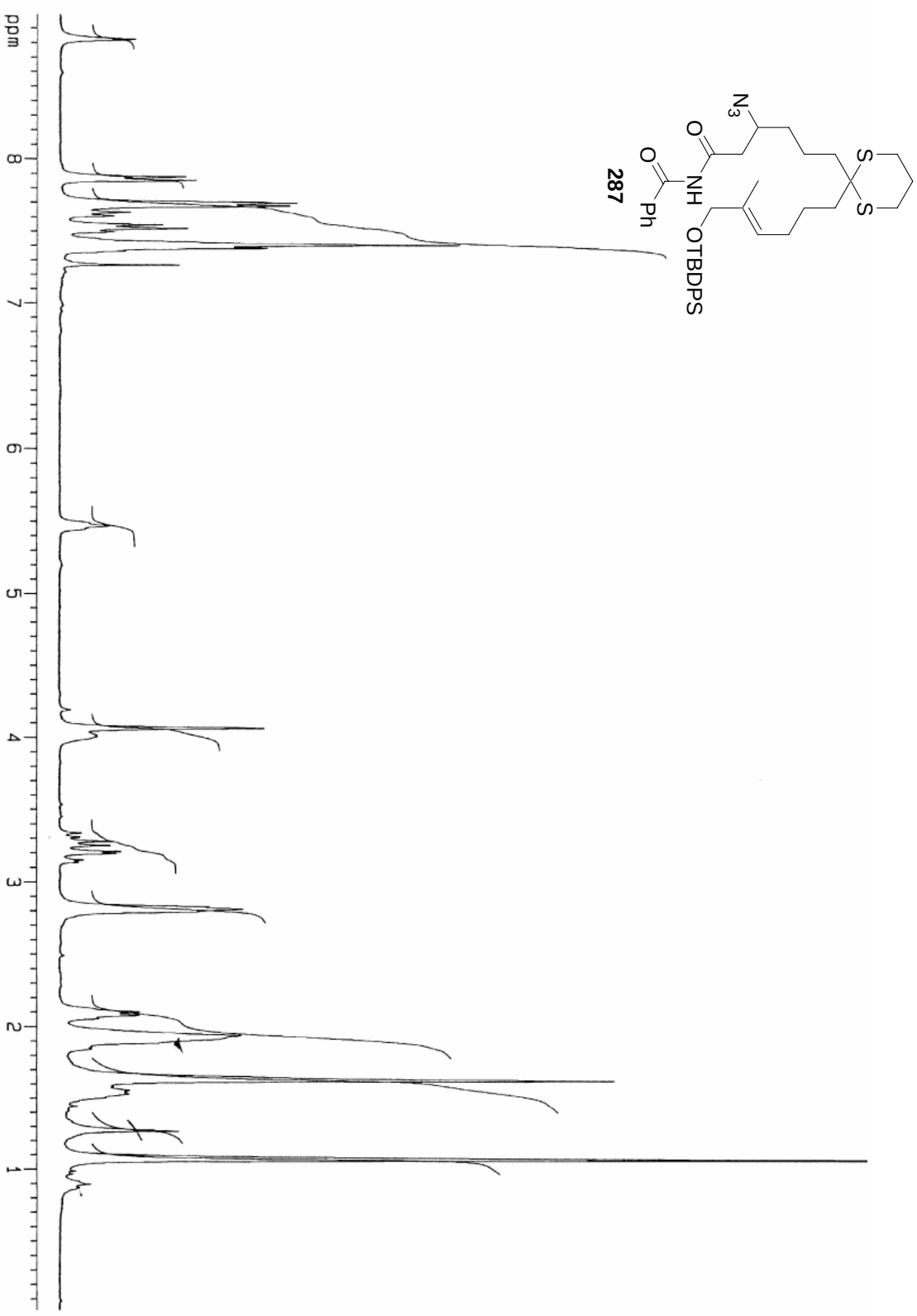
Ph
S
S

286



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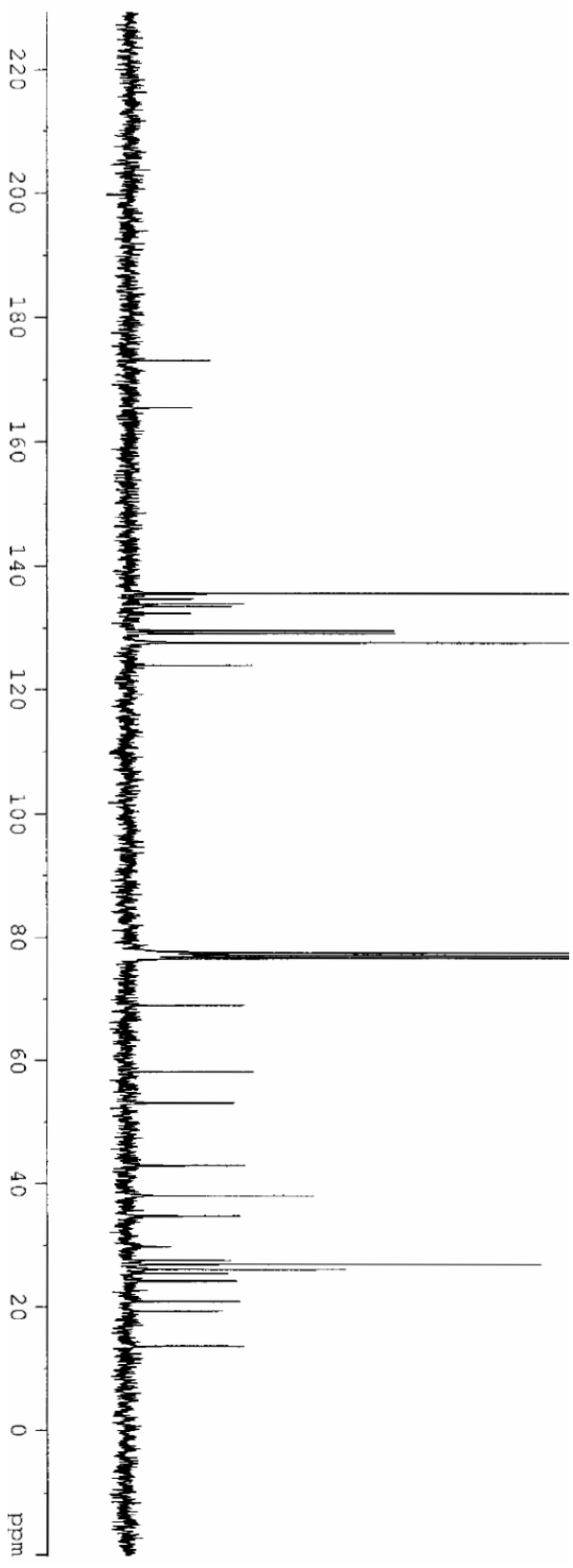

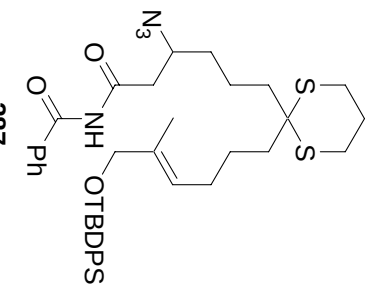

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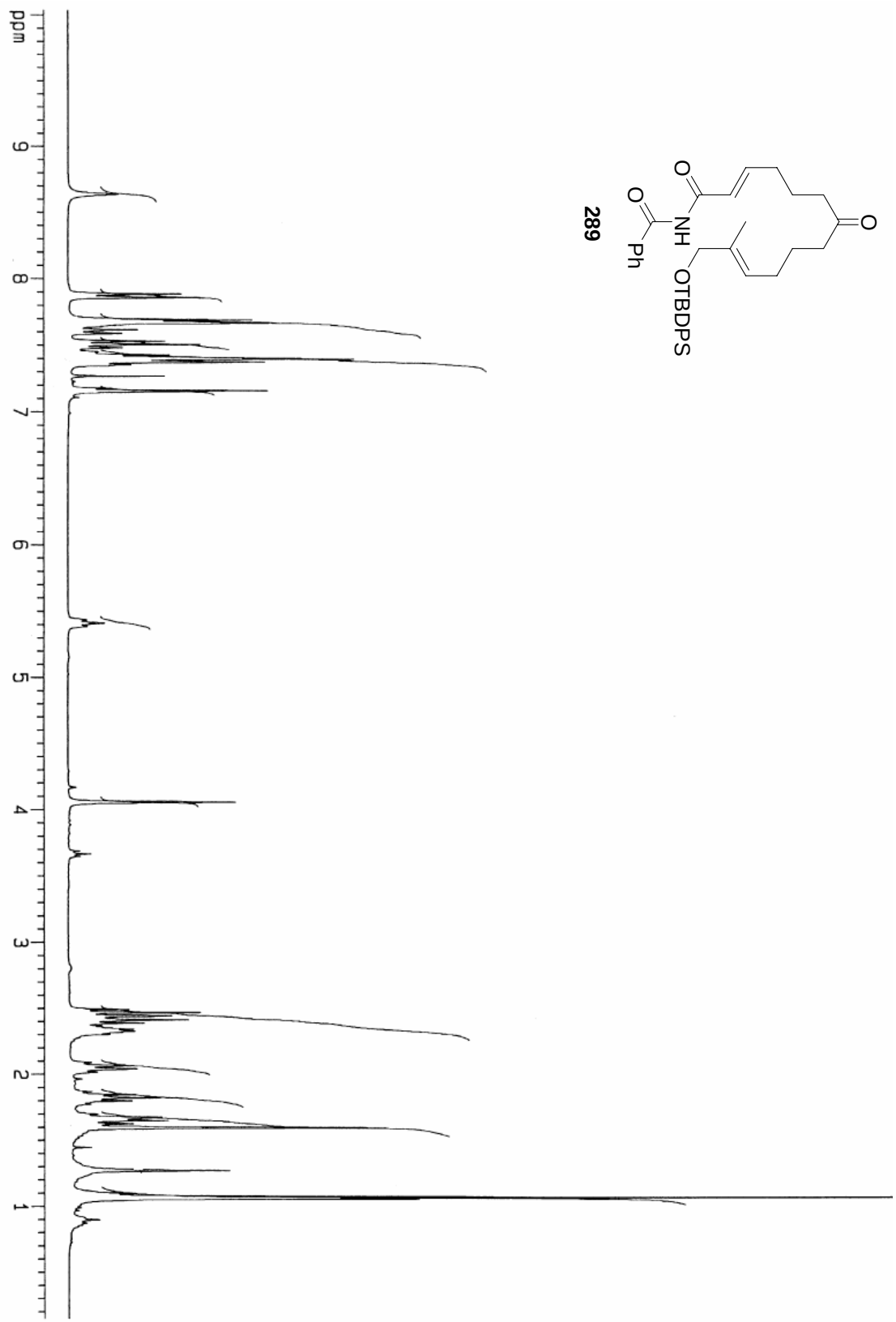

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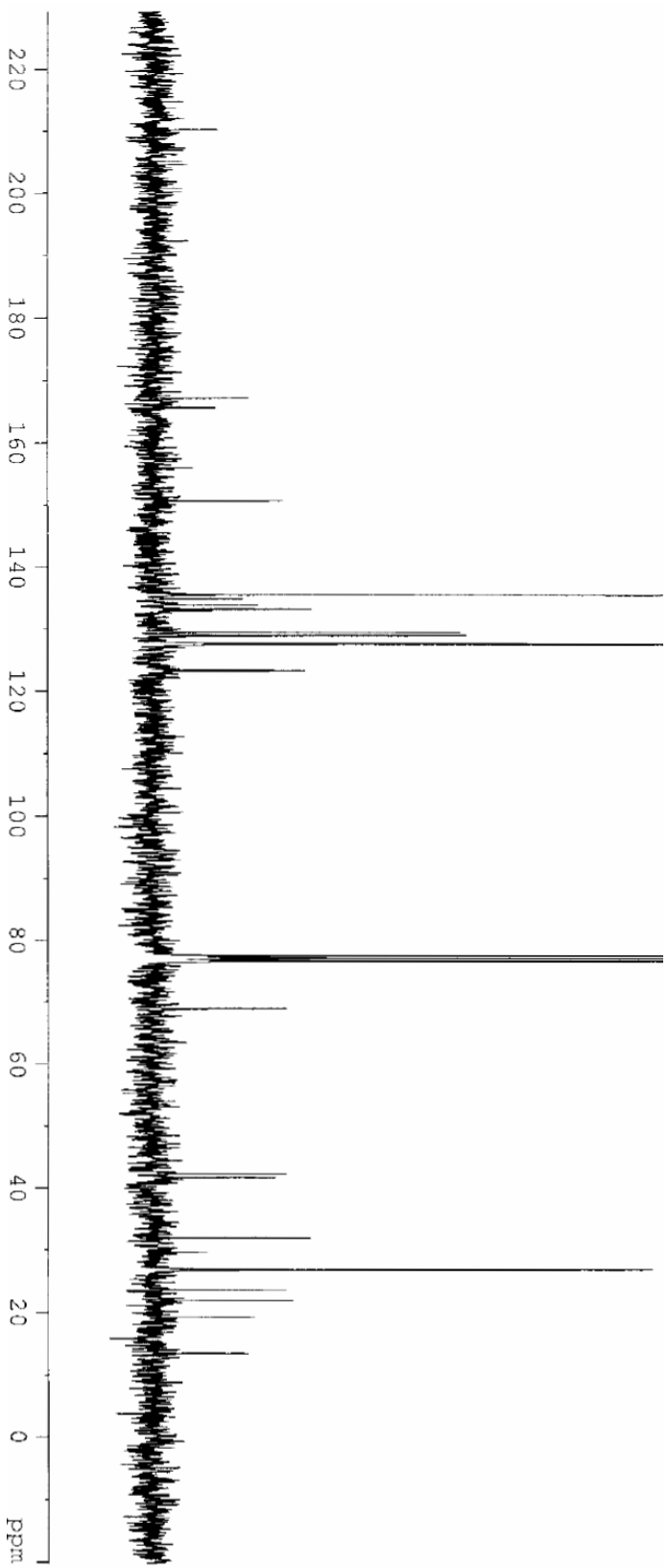

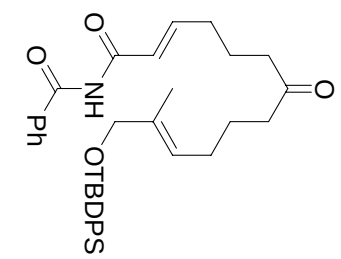

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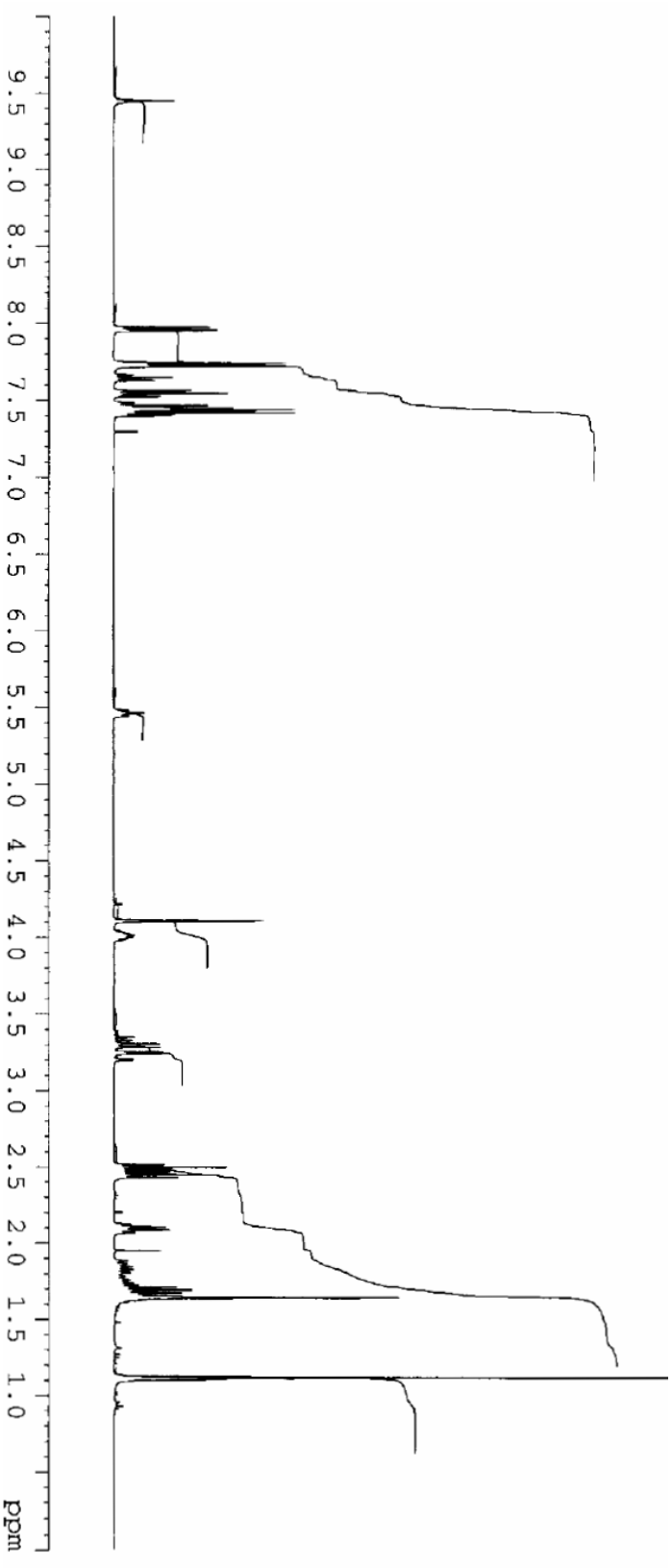
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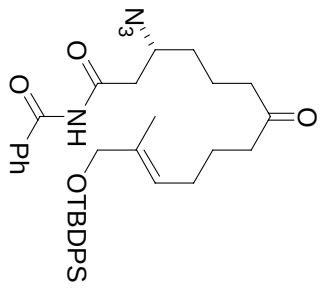
ppm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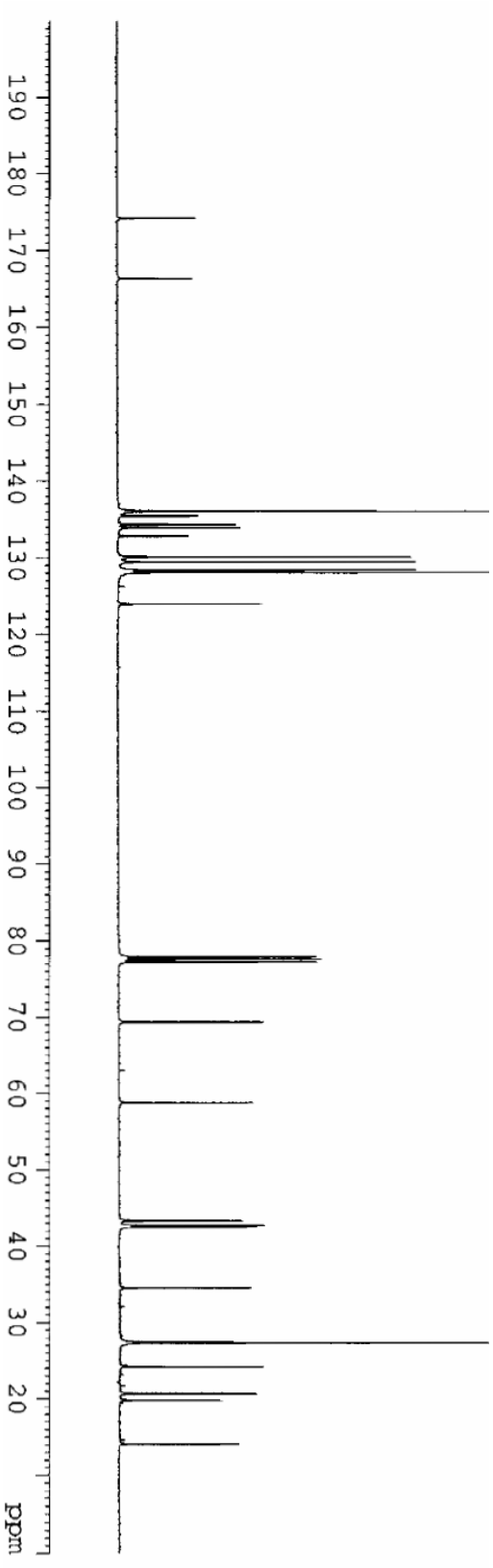
NH
O
Ph
OTBDPS
O

290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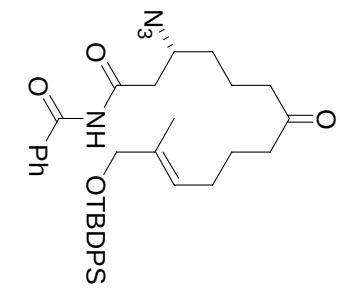
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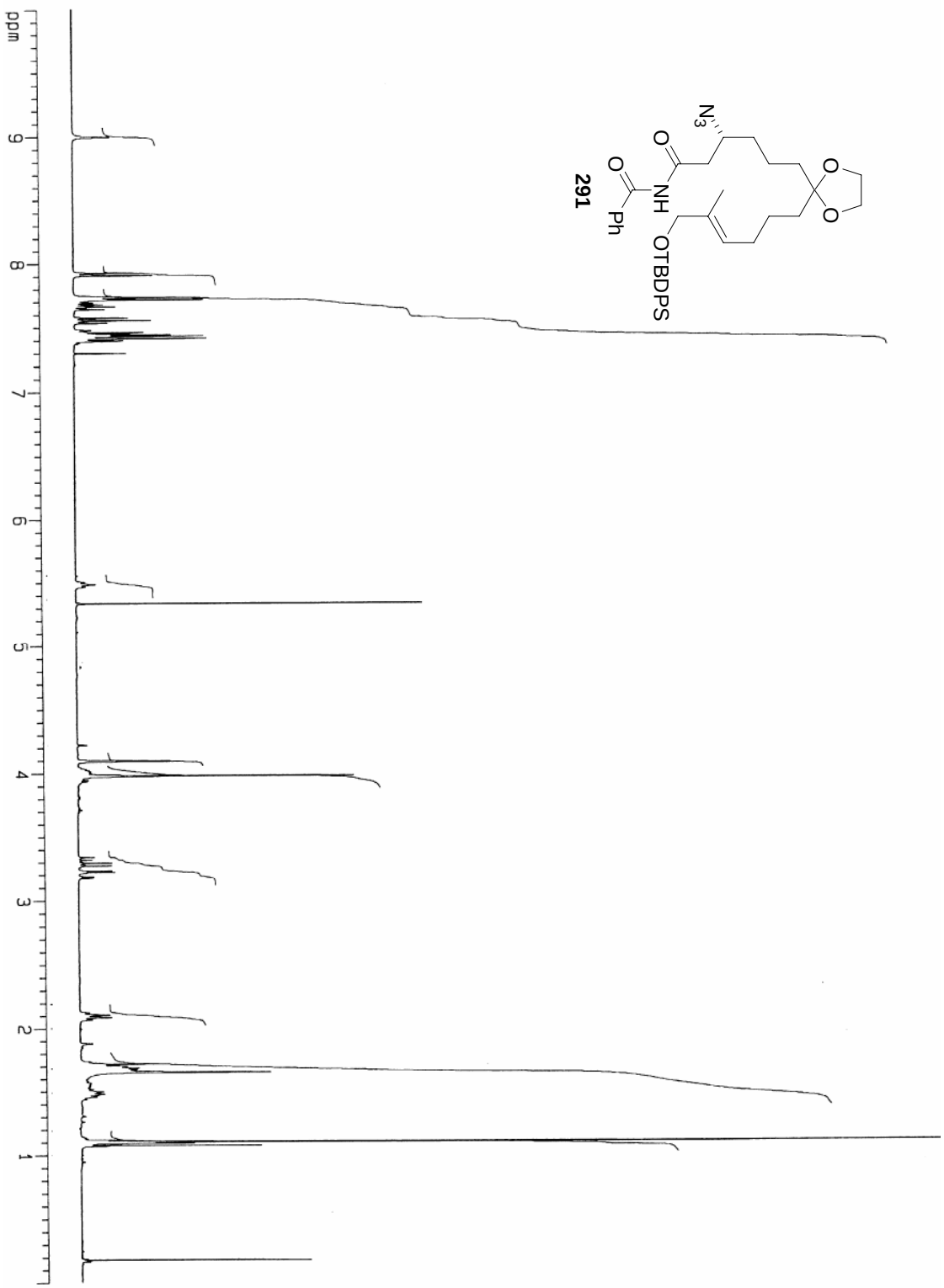
Ph
OTBDPS
O

290



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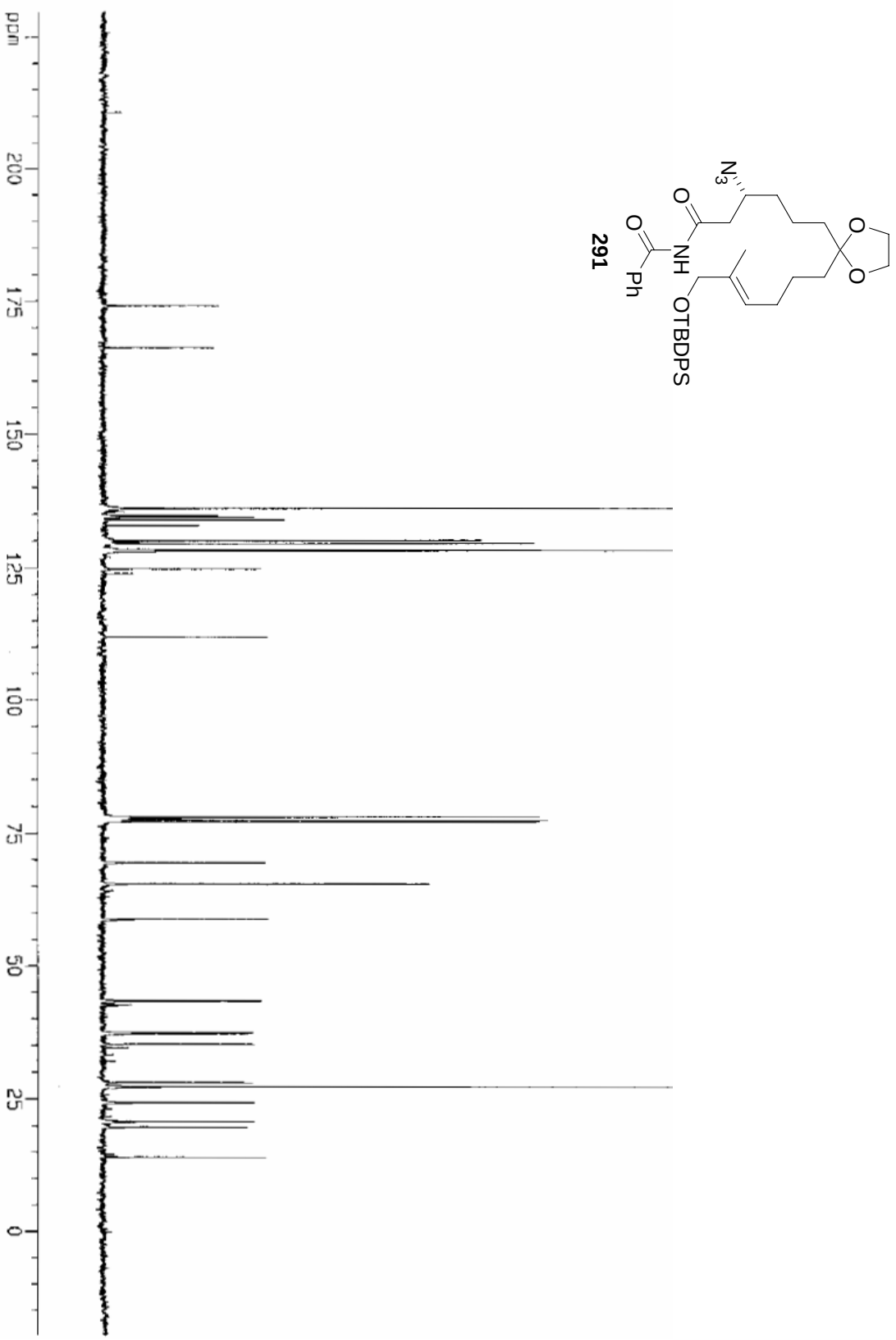

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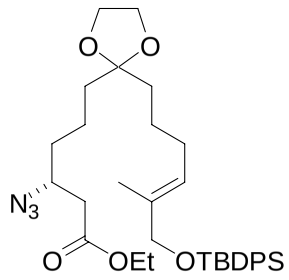
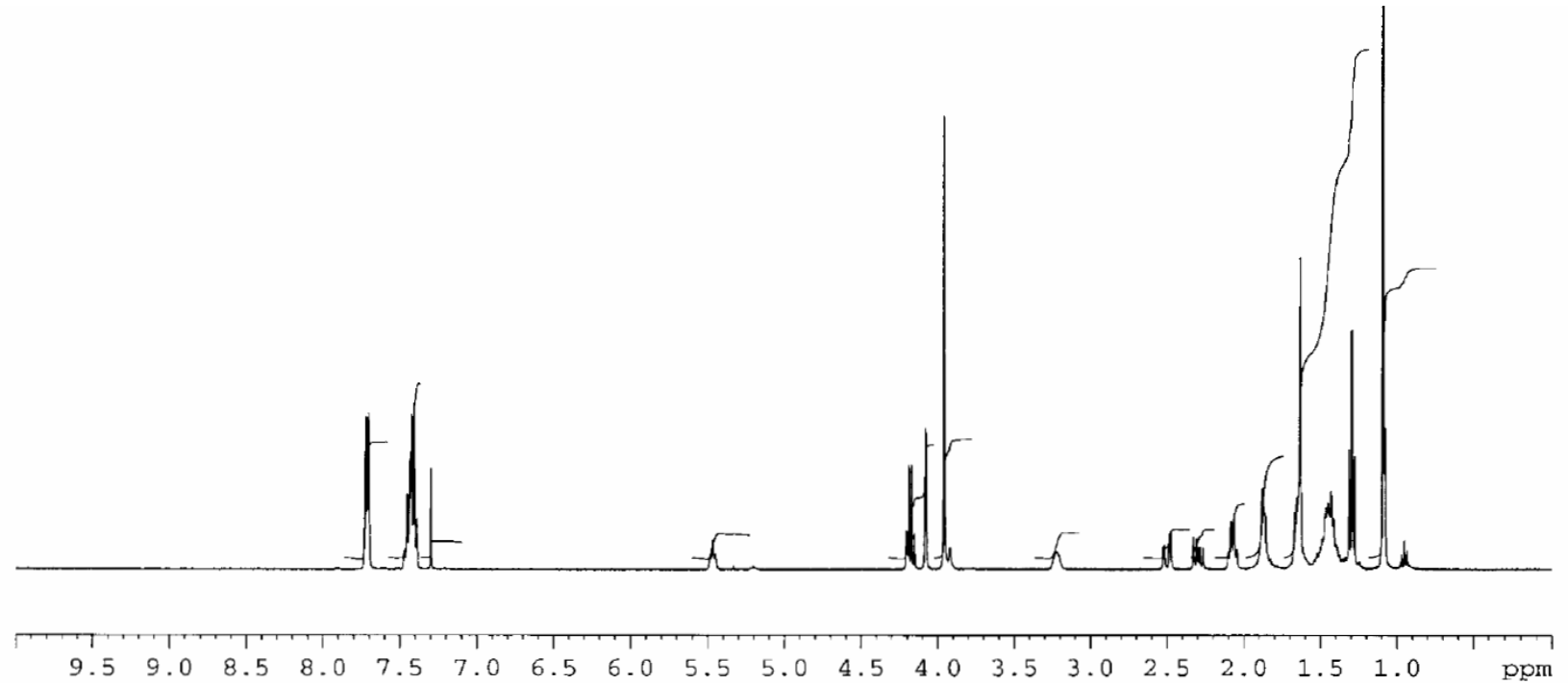

O
O
N3
O
OEt
OTBDPS

292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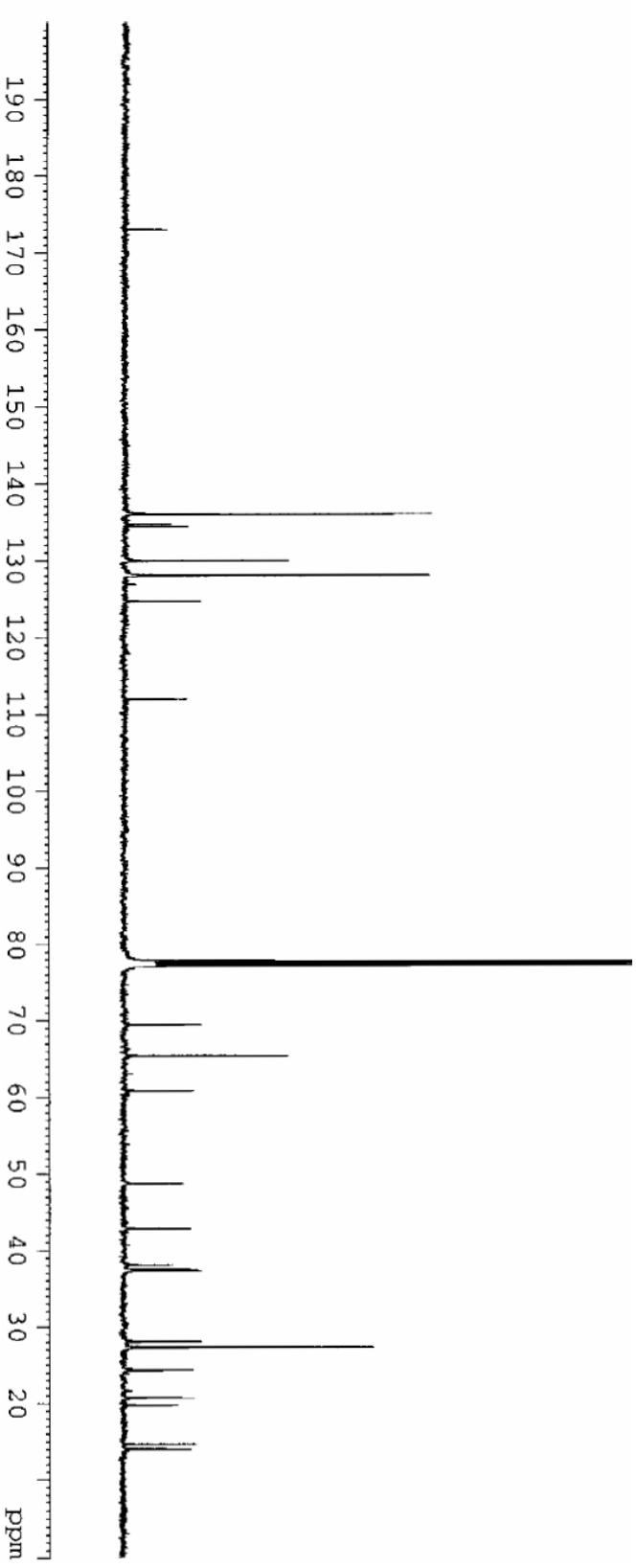
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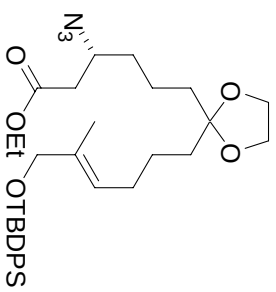
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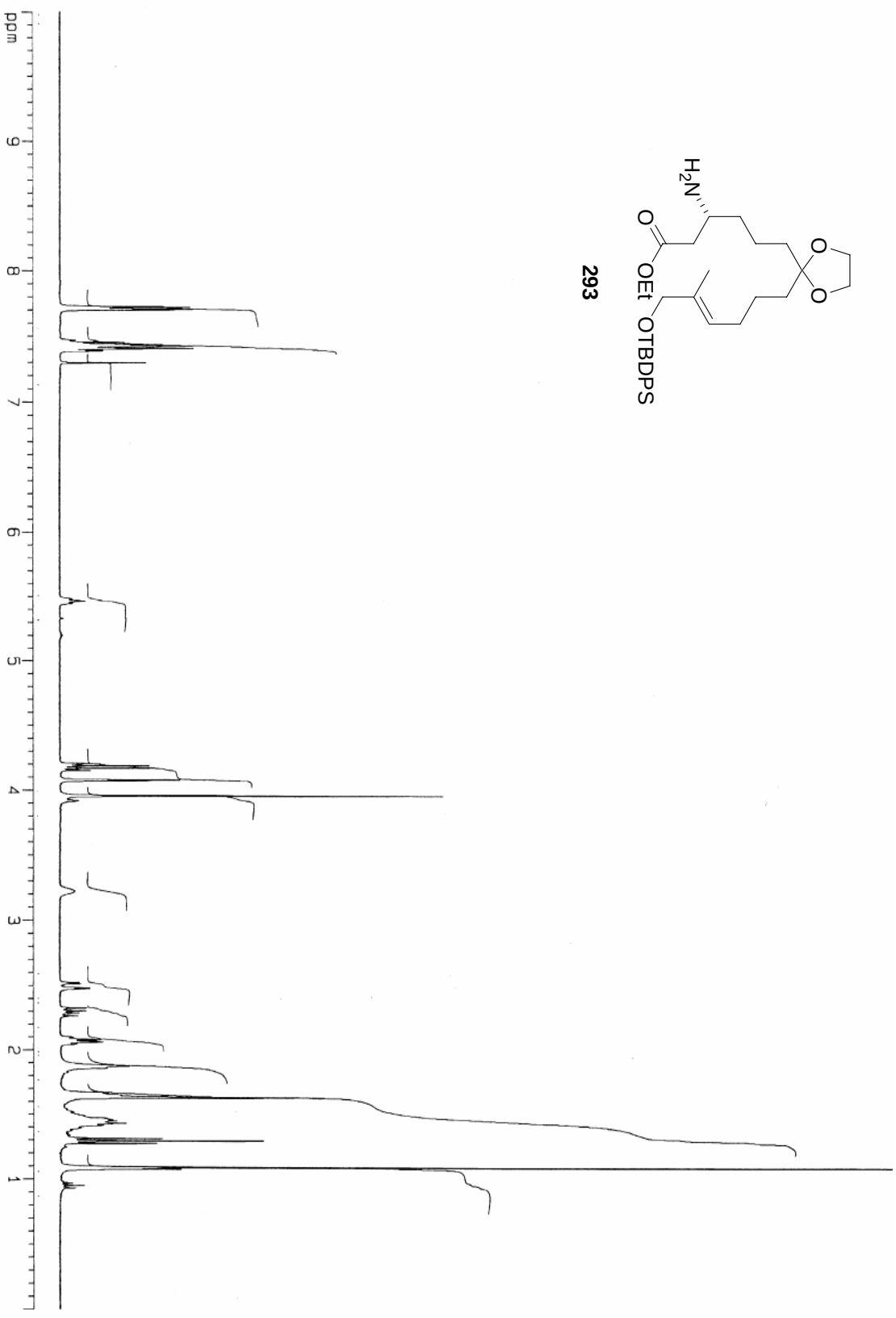
OEt
OTBDPS
O
O

292



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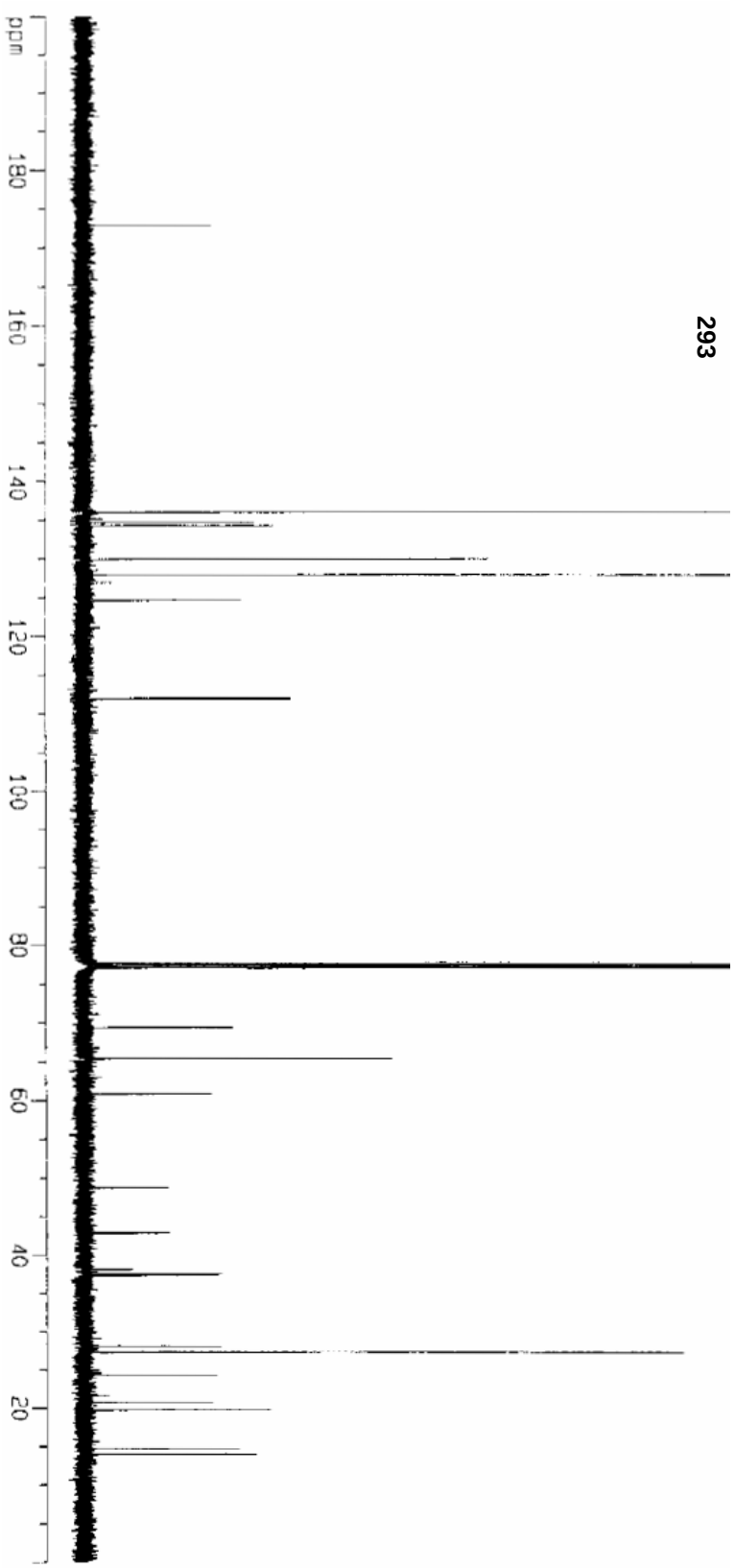

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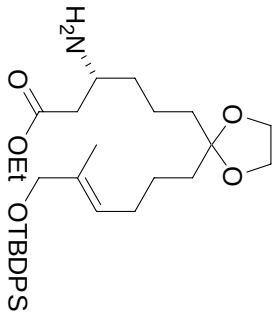

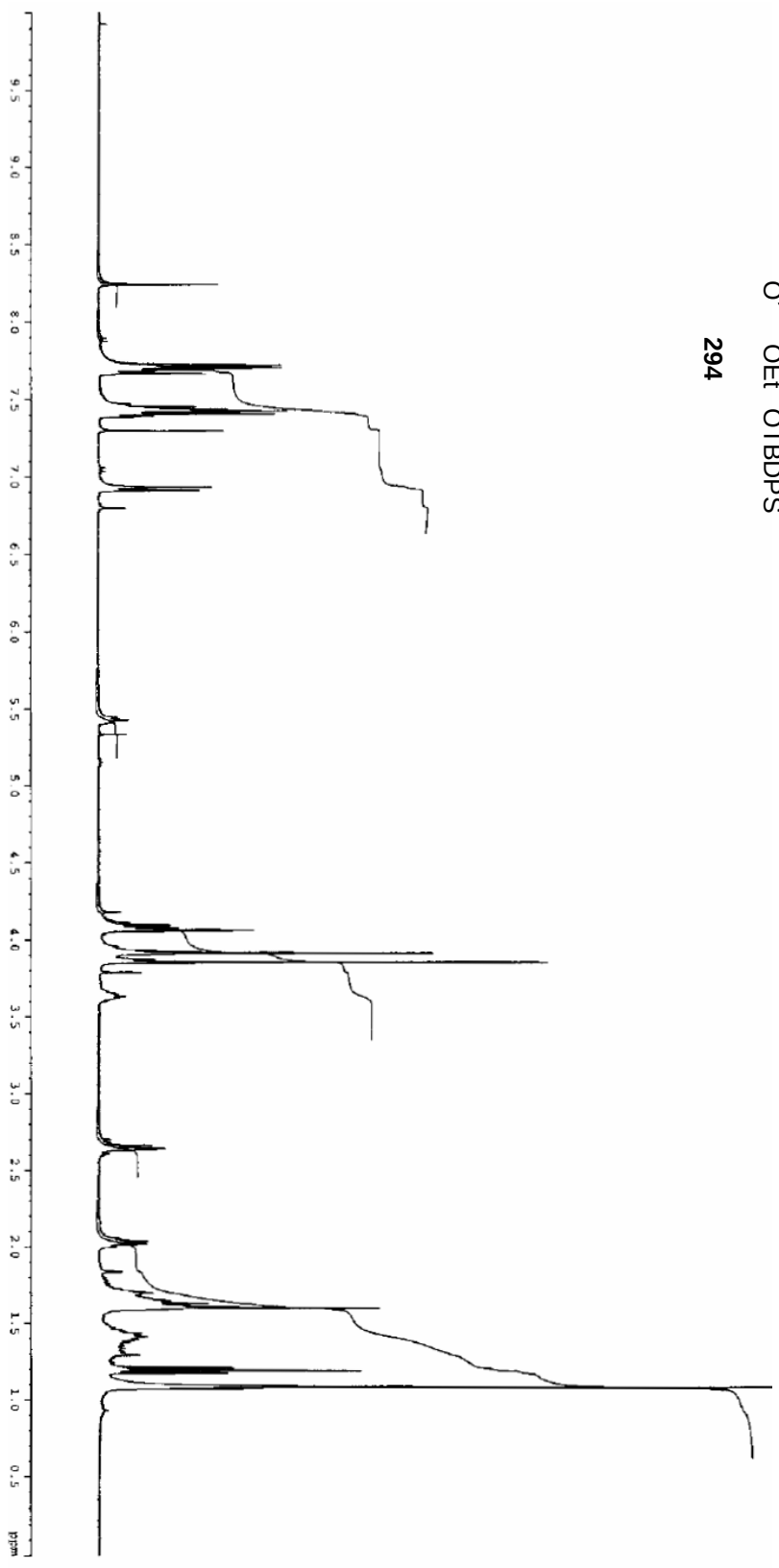
OMe
N
O
O
O
OEt
OTBDPS
294
9.5
9.0
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8.0
7.5
7.0
6.5
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4.5
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2.0
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1.0
0.5
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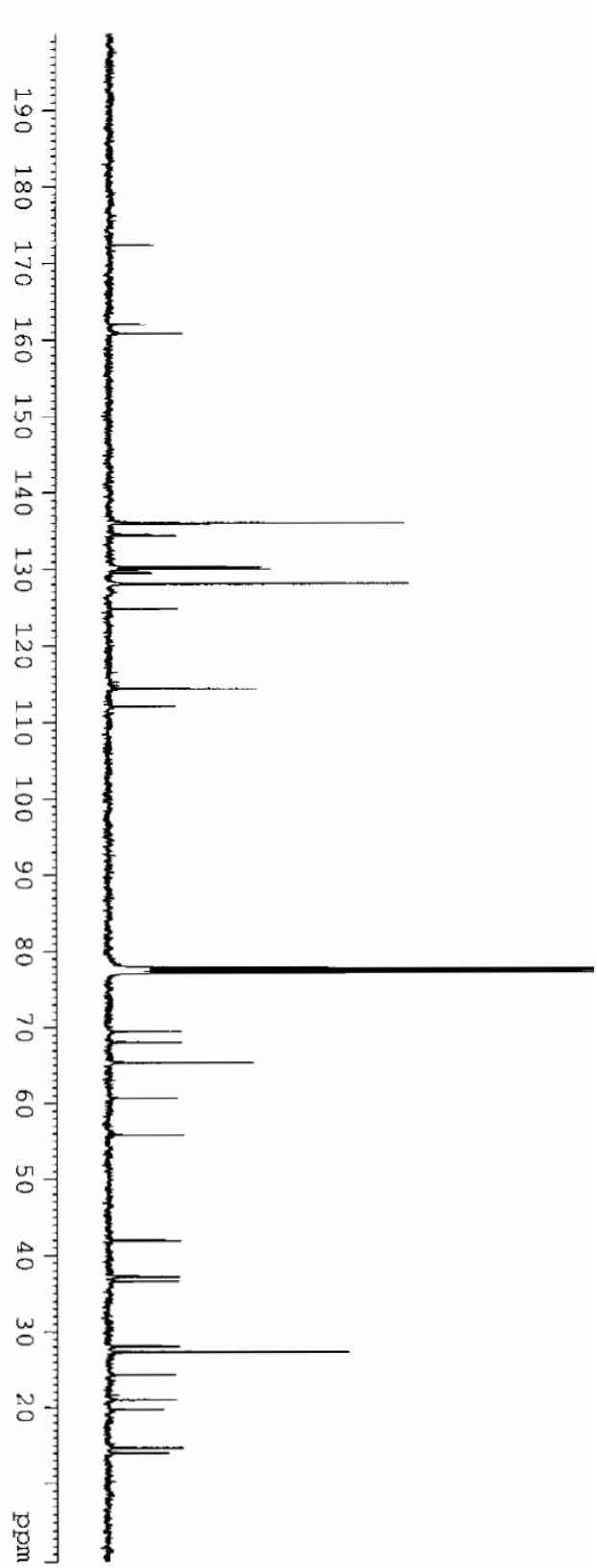
OMe
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O
O
OEt
OTBDPS
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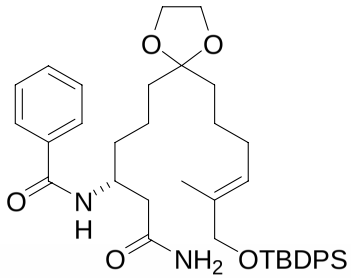
ppm


O
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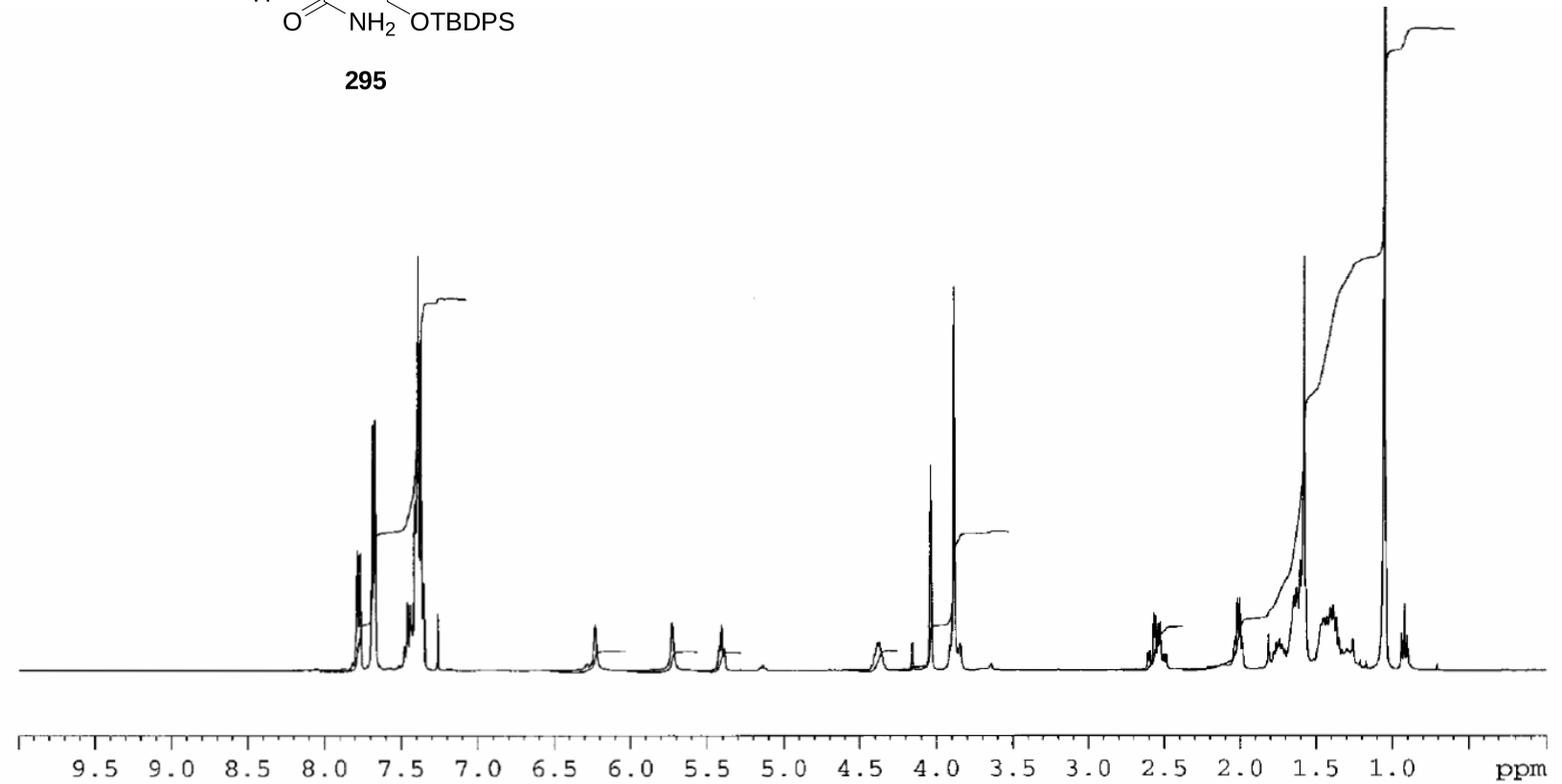
N
H
O
NH2
OTBDPS

295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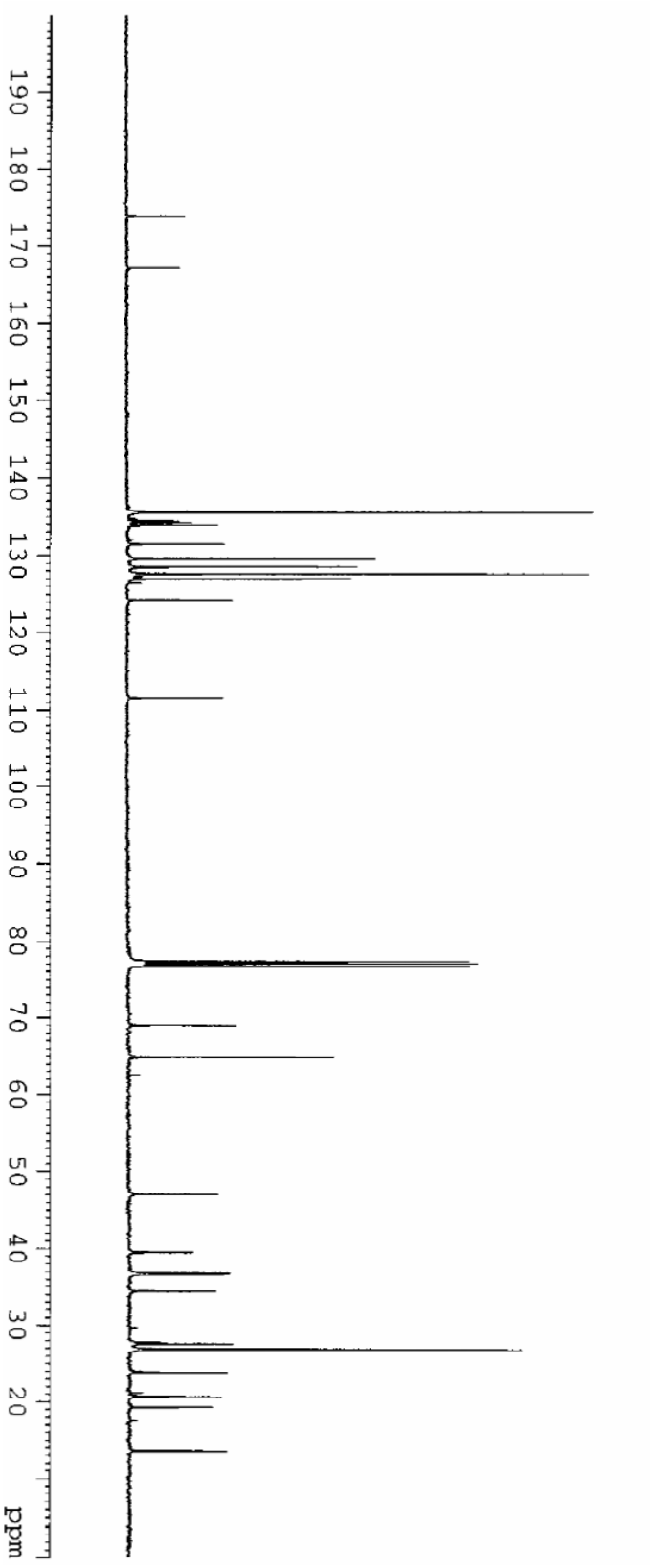
ppm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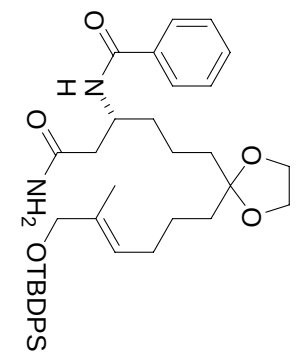
ppm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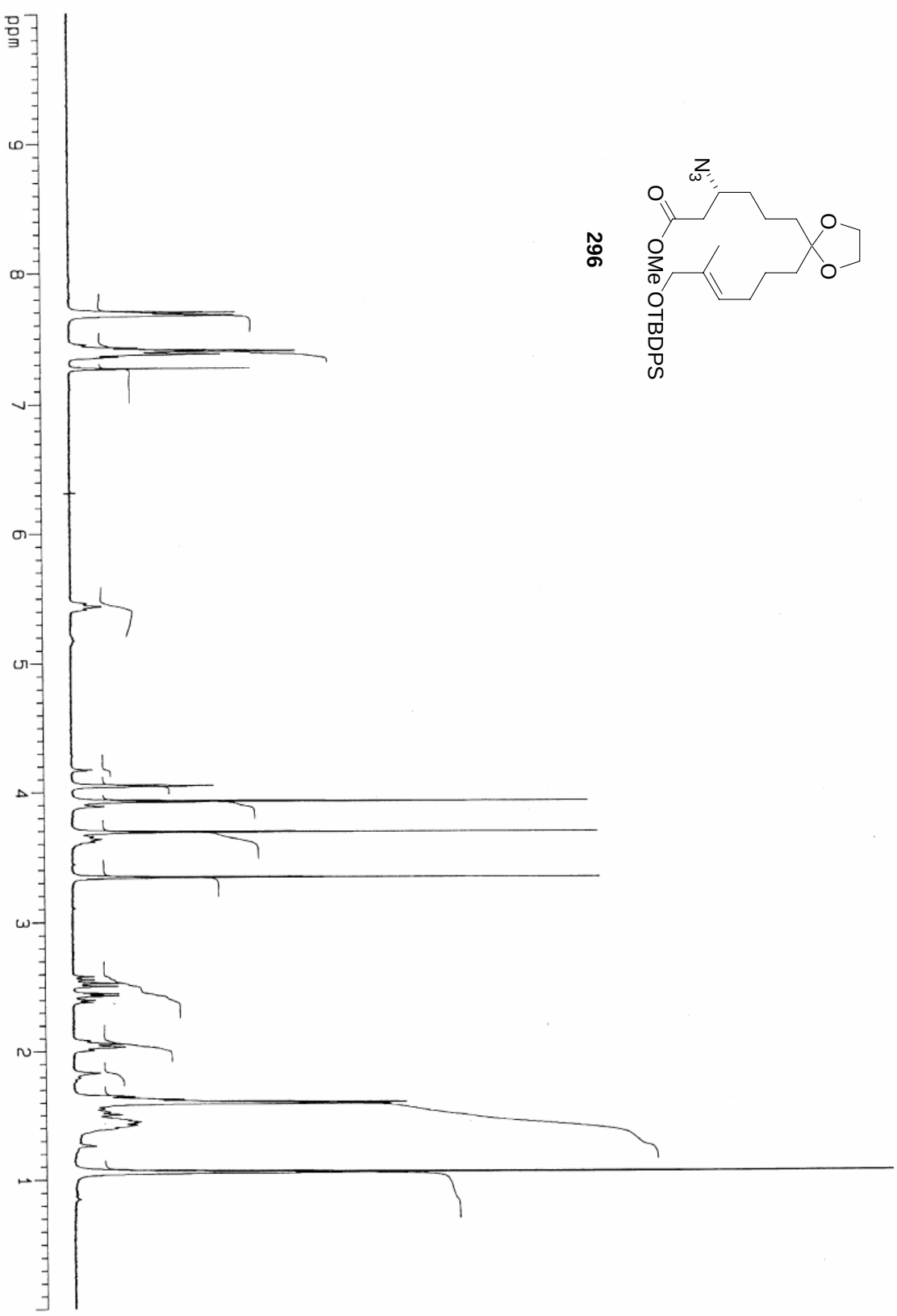
NH2
OTBDPS
O
O

295



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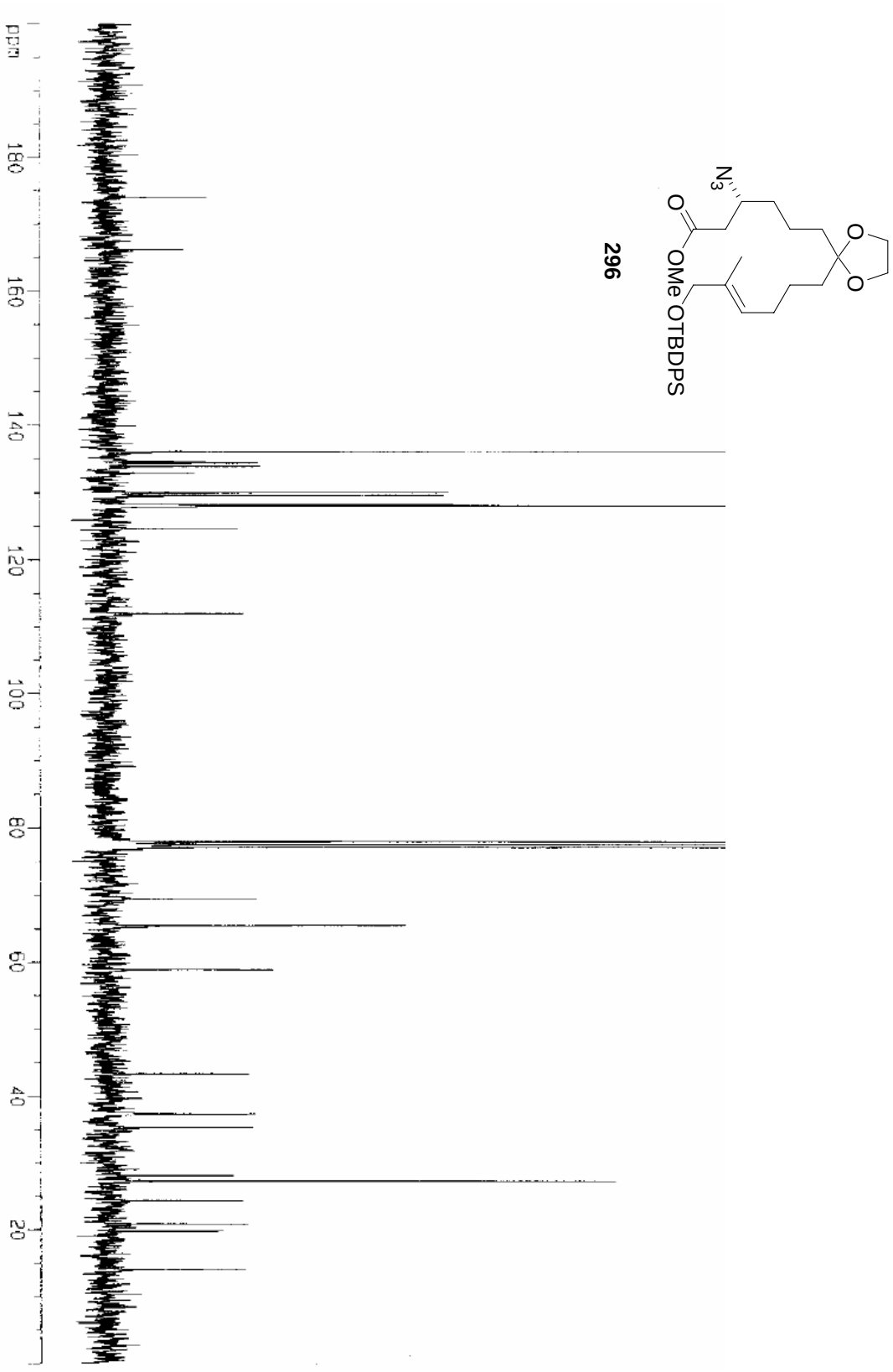

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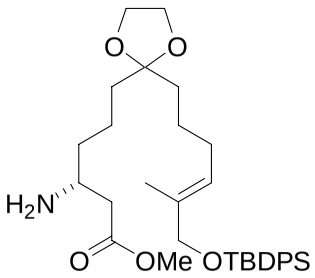
O
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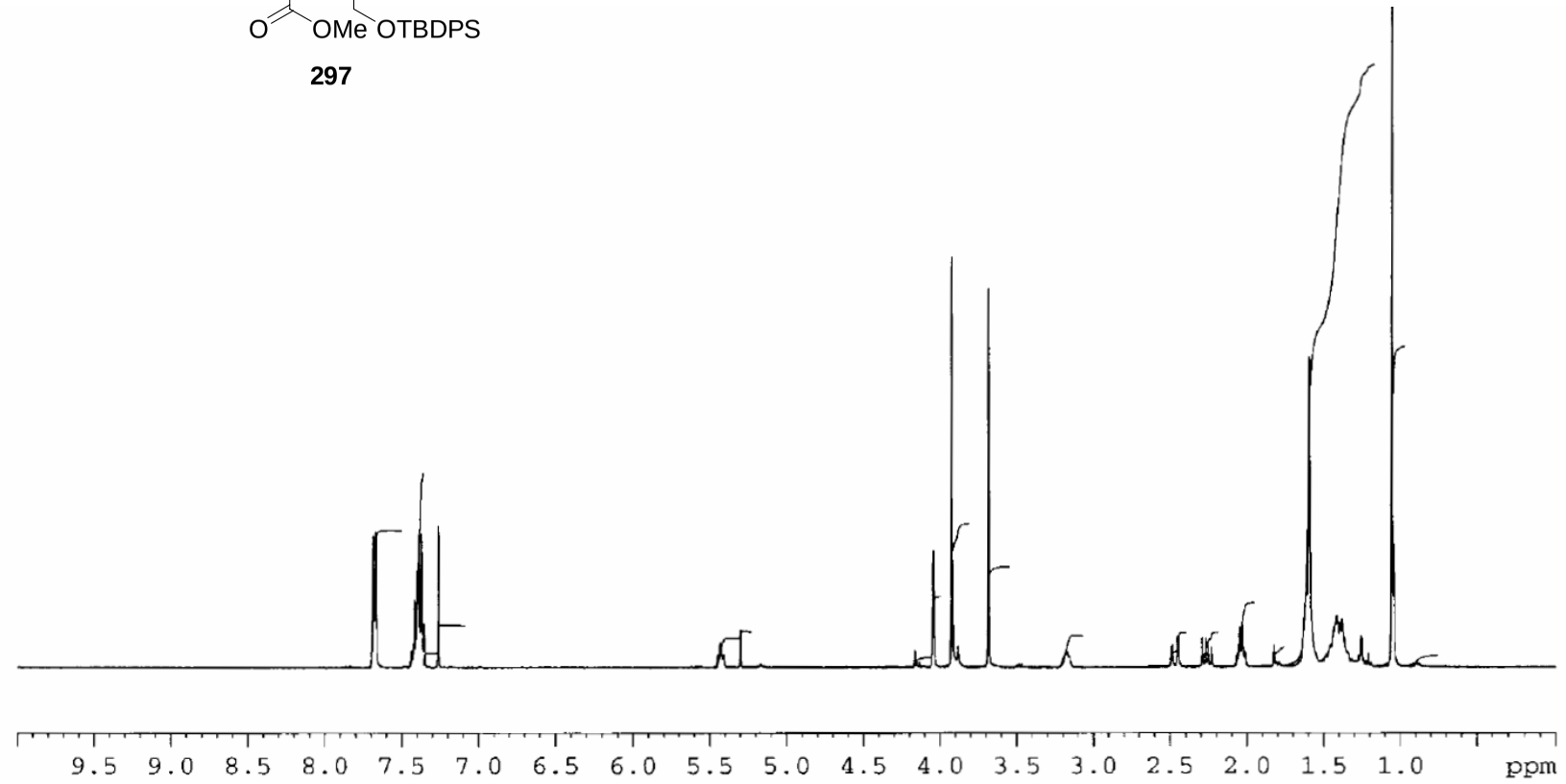
H_2N
O
OMe
OTBDPS

297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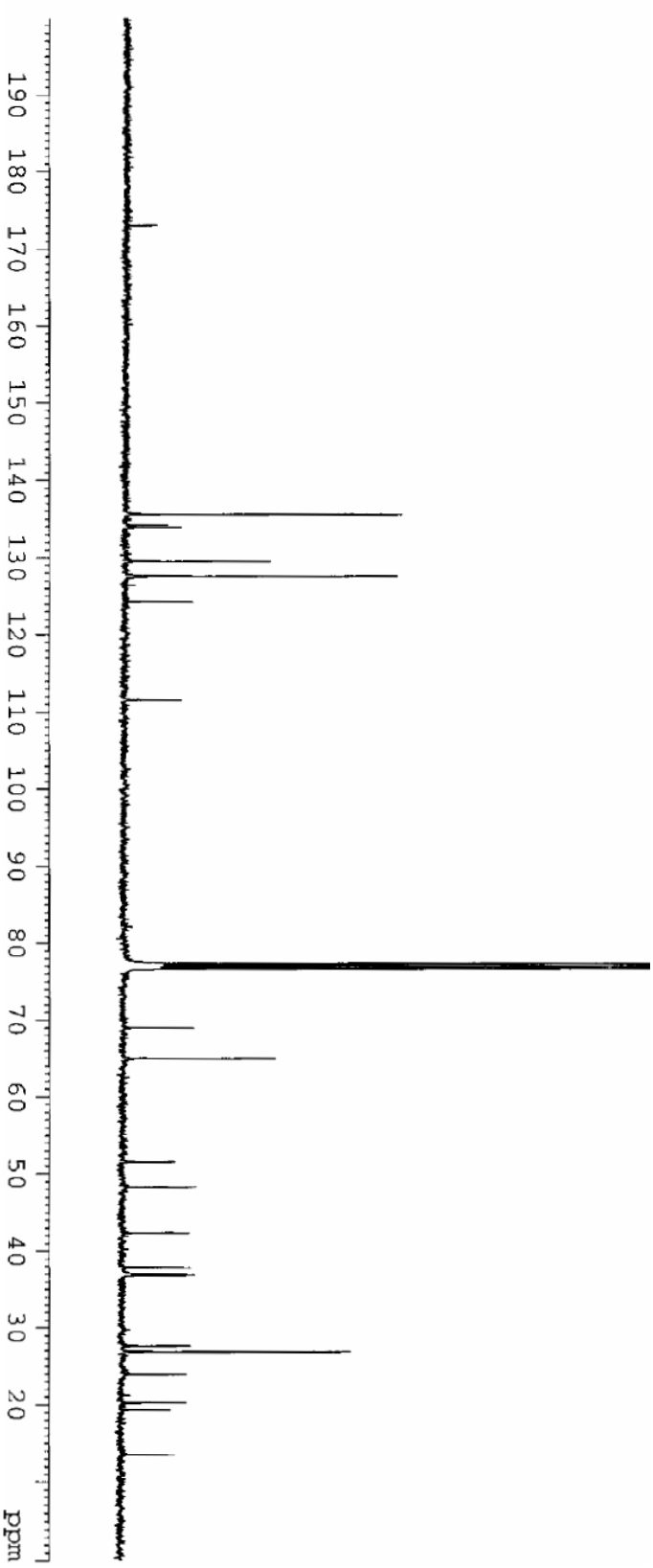
ppm


H2N
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OMe
OTBDPS
O
O
297
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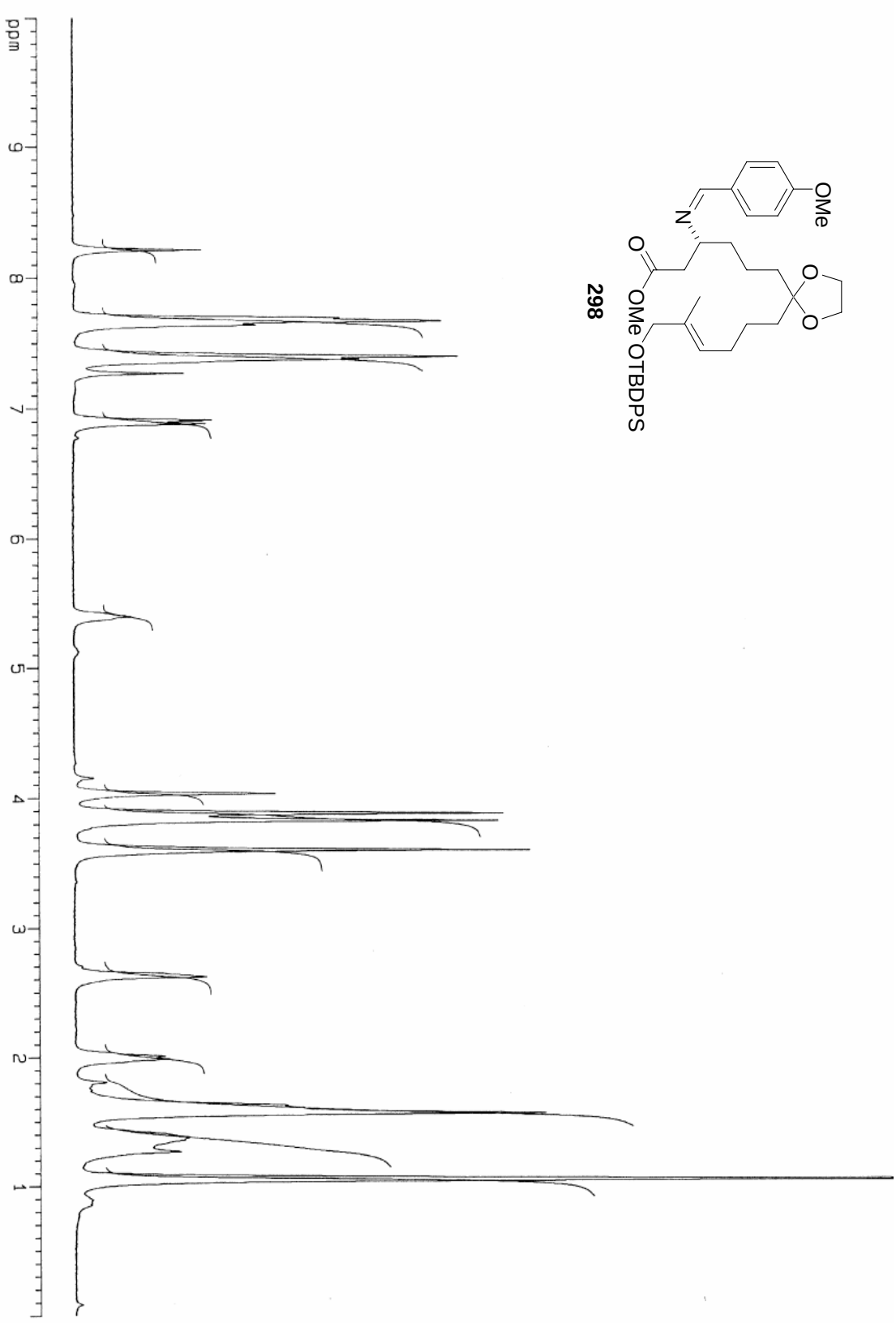
ppm



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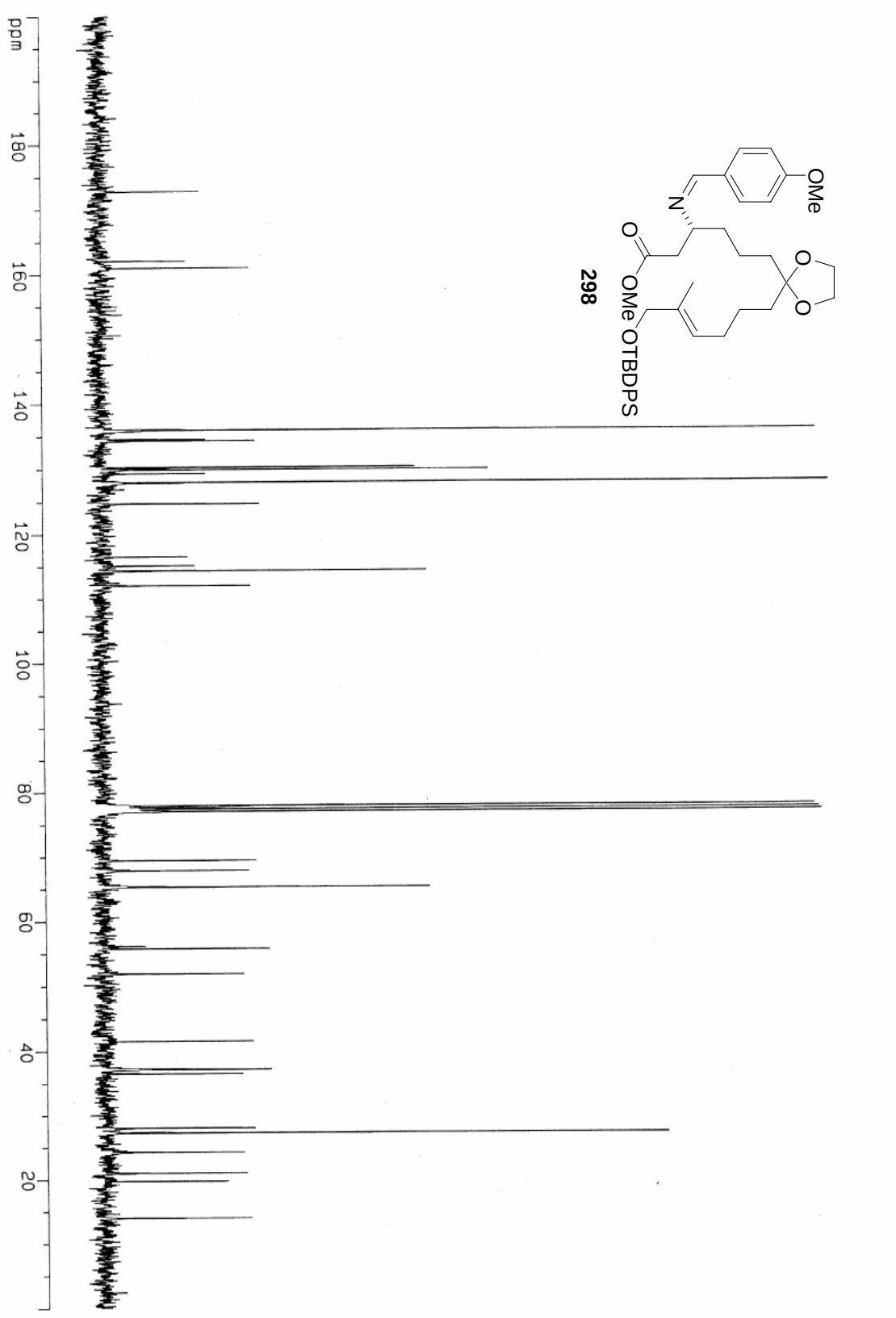
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OMe OTBDPS
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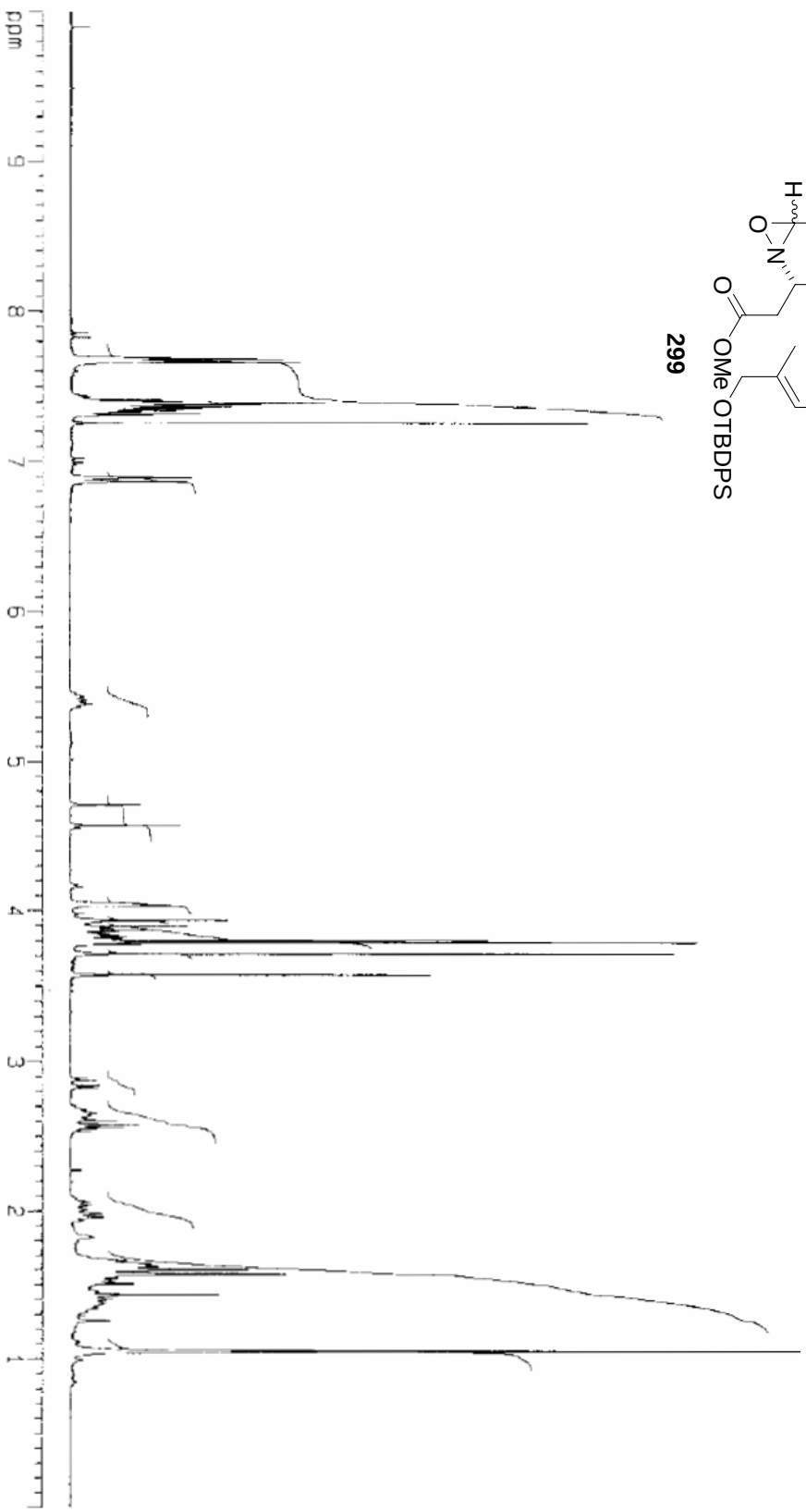
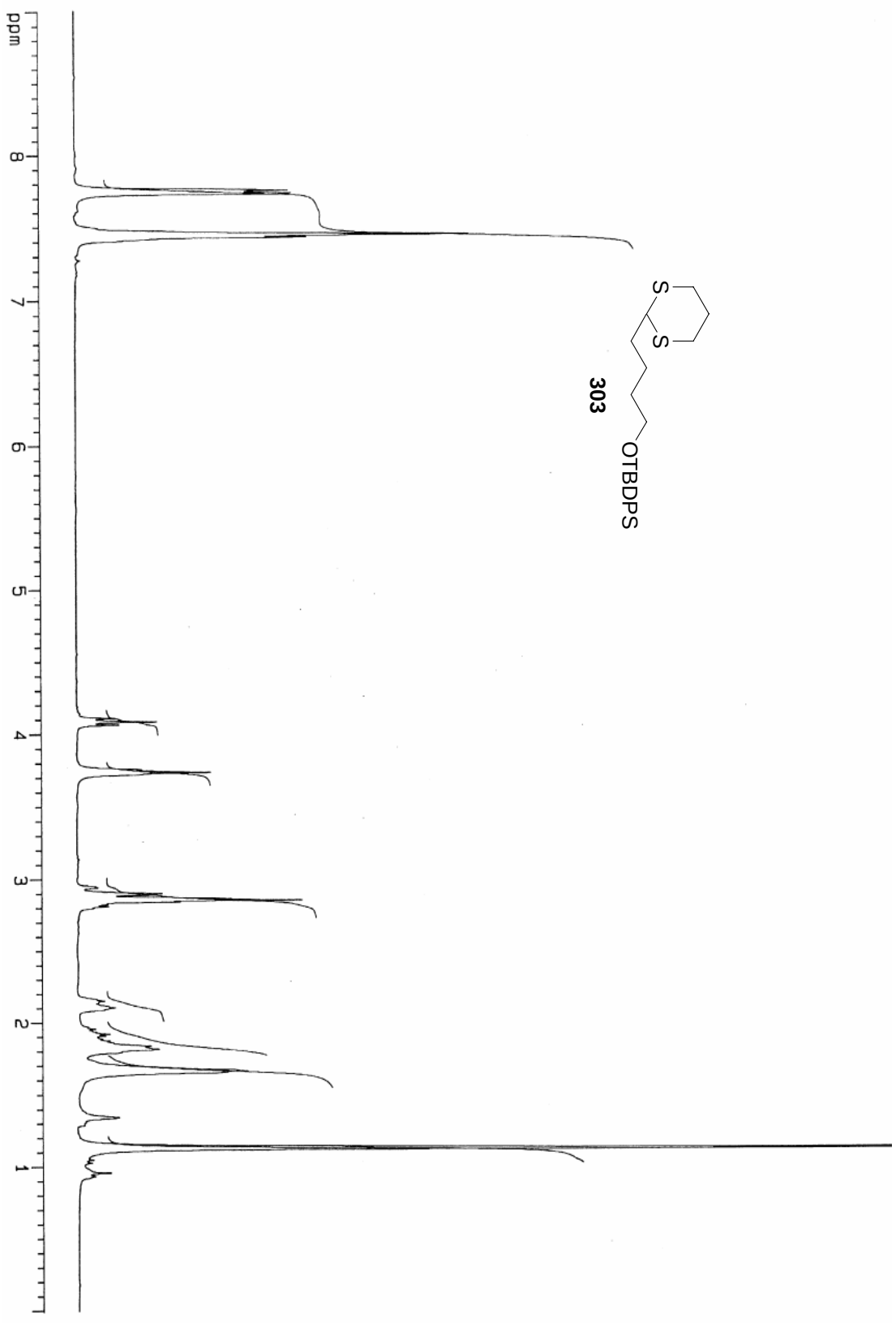
60
40
20



299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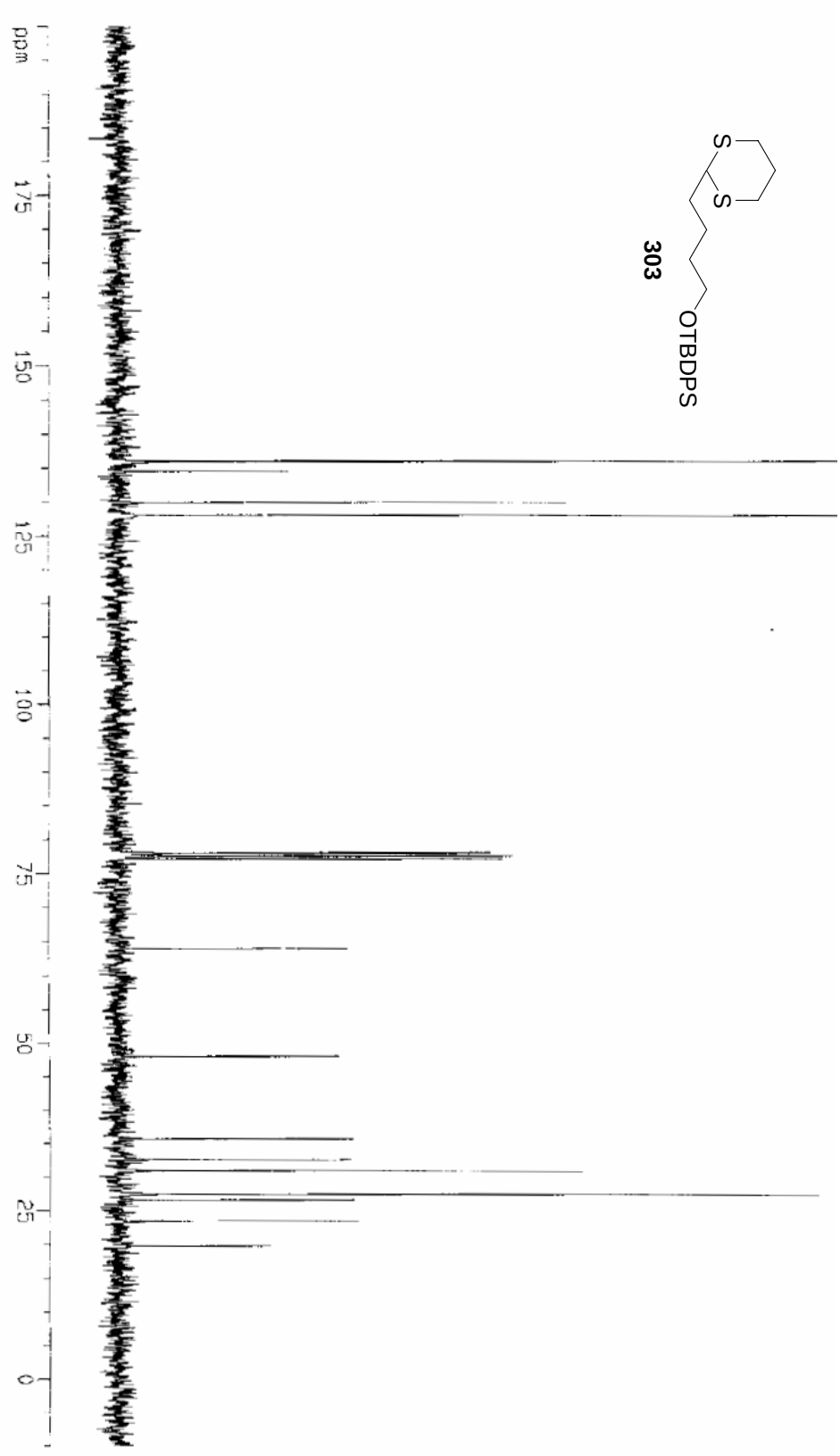

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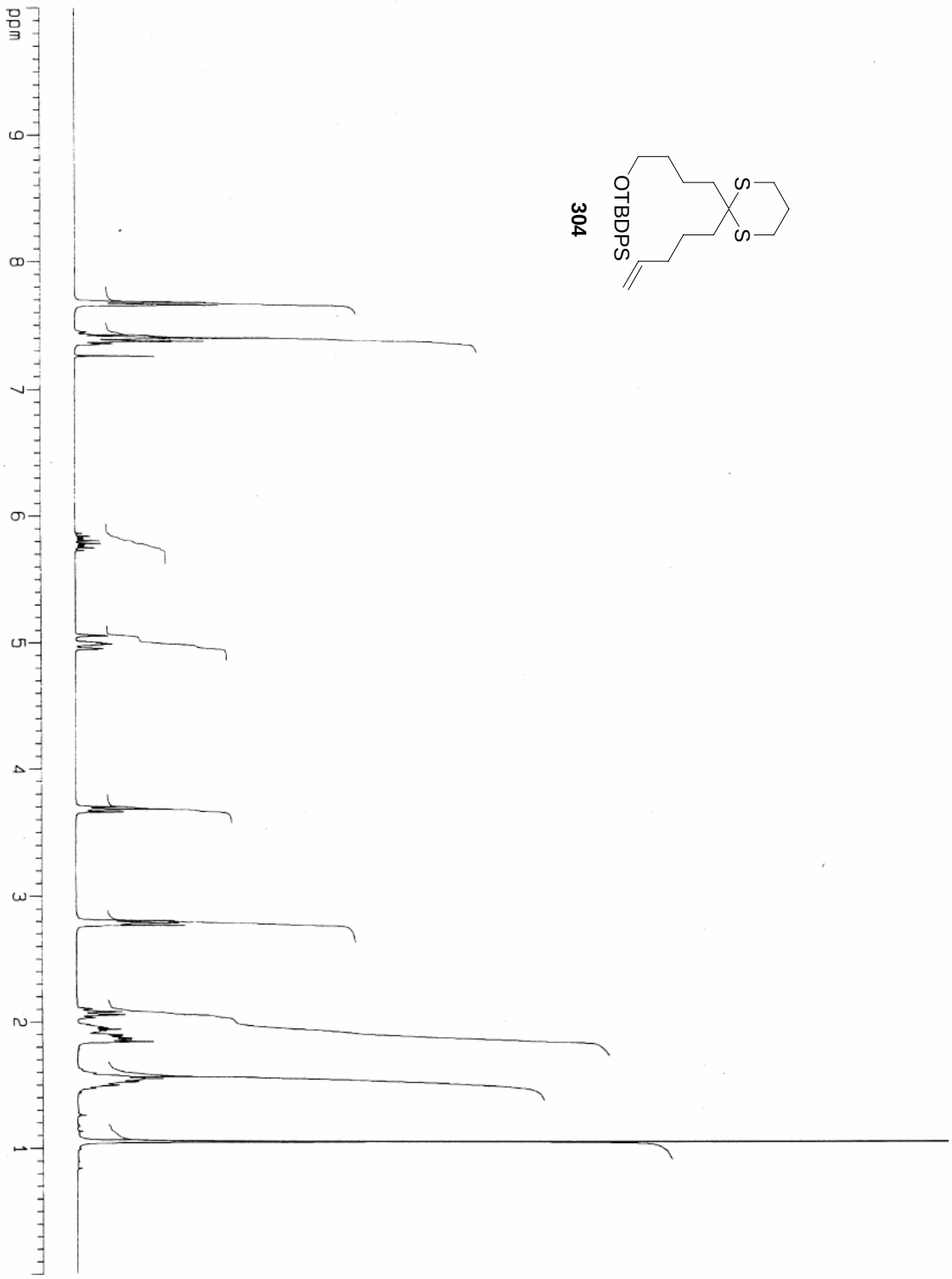

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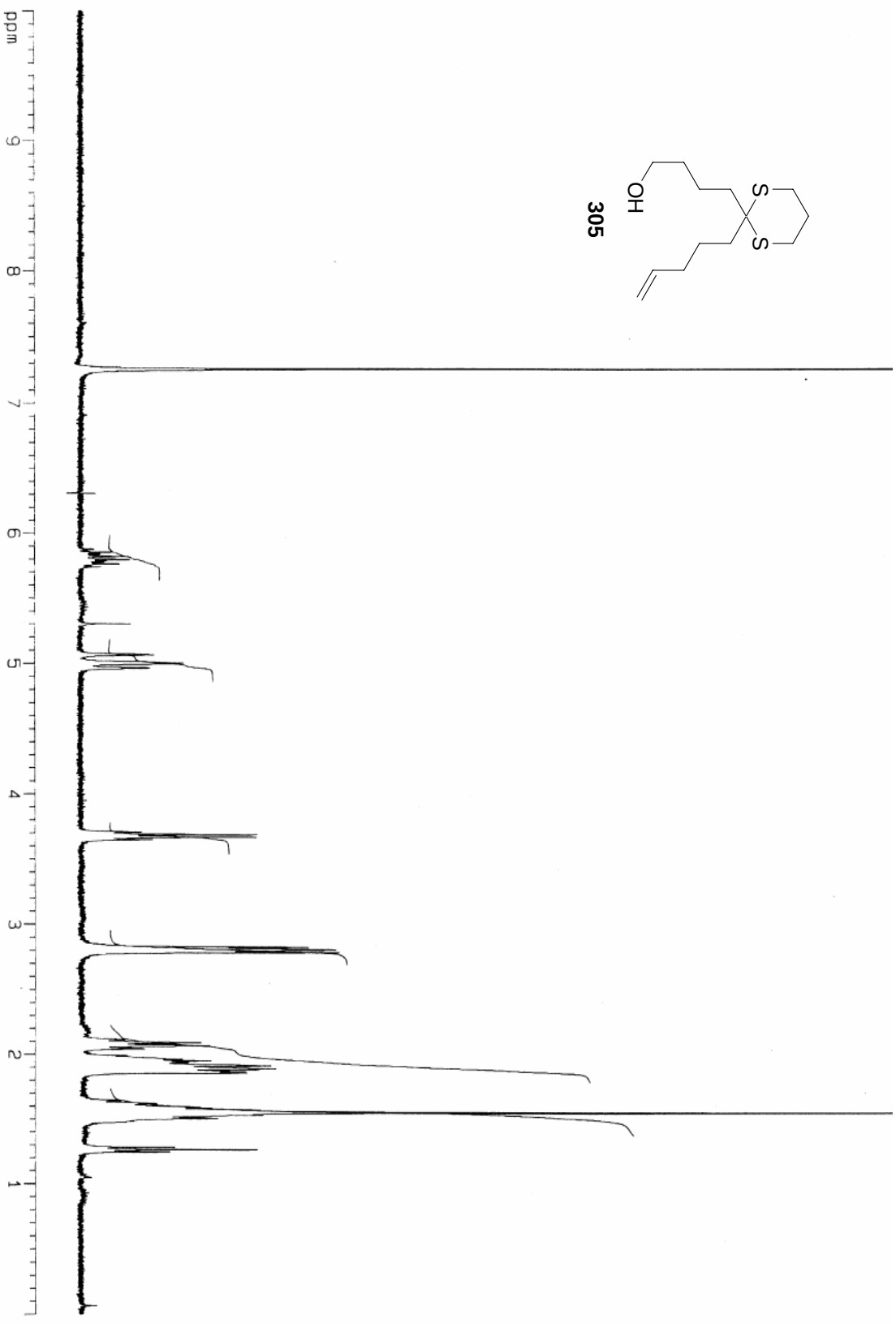

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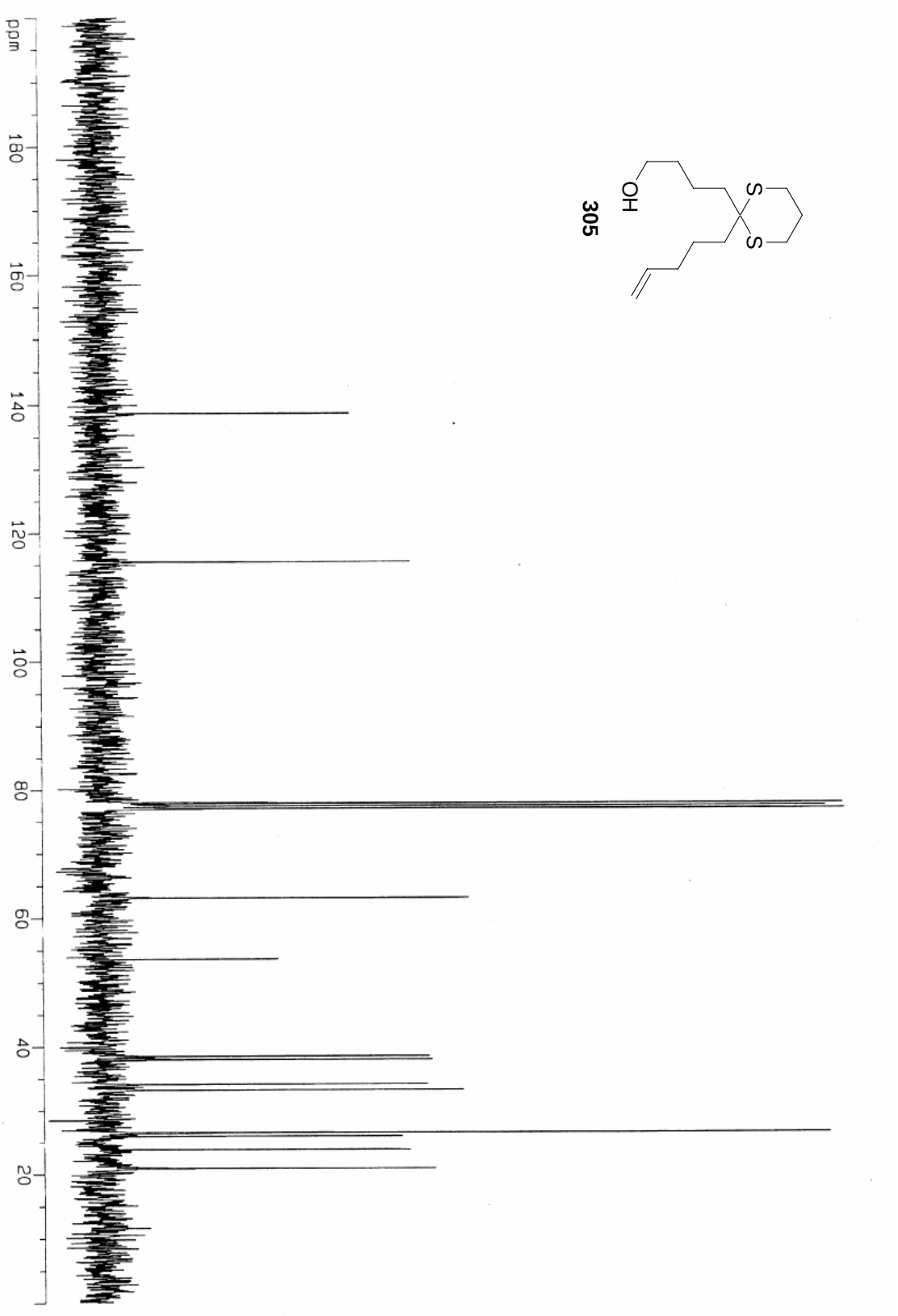

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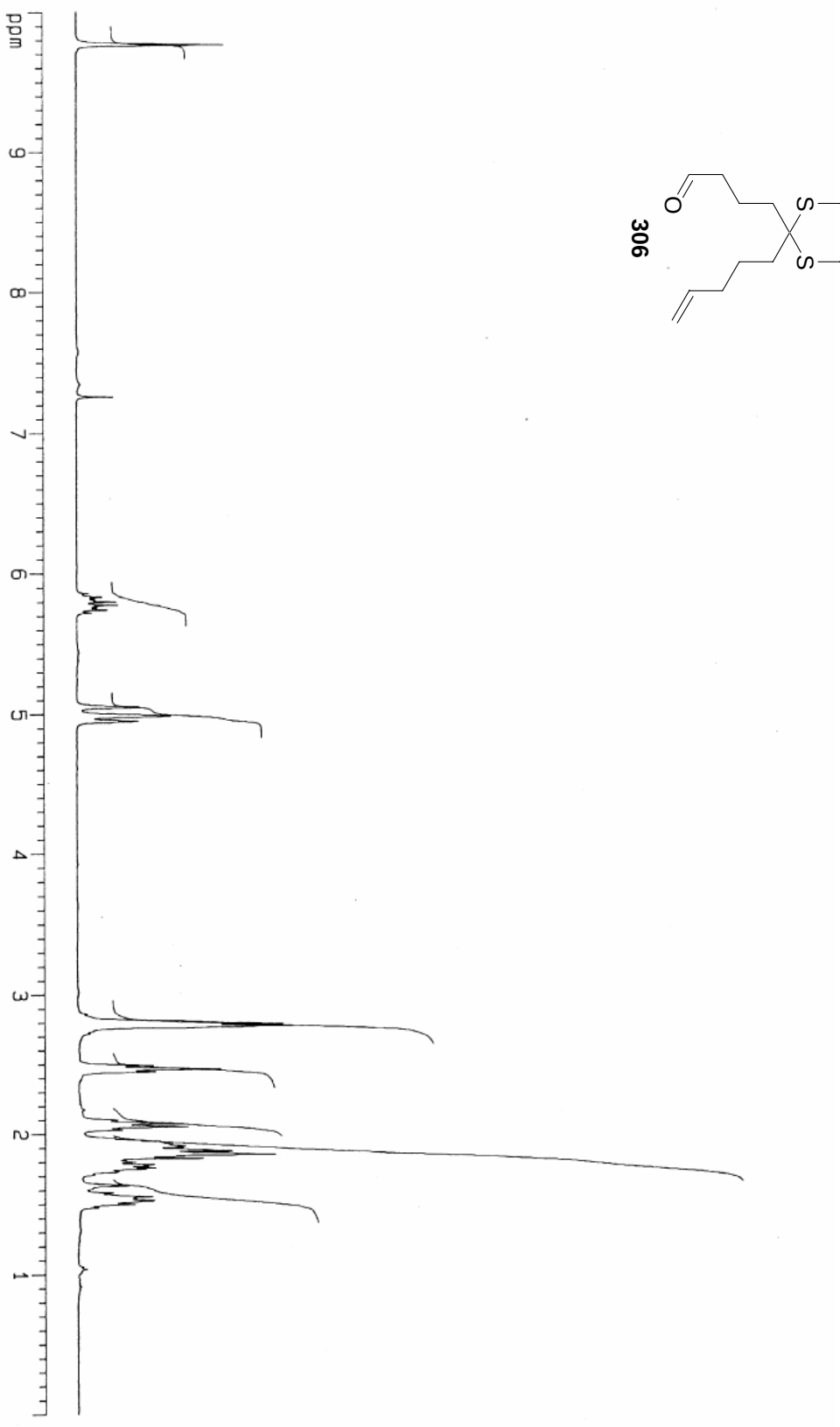

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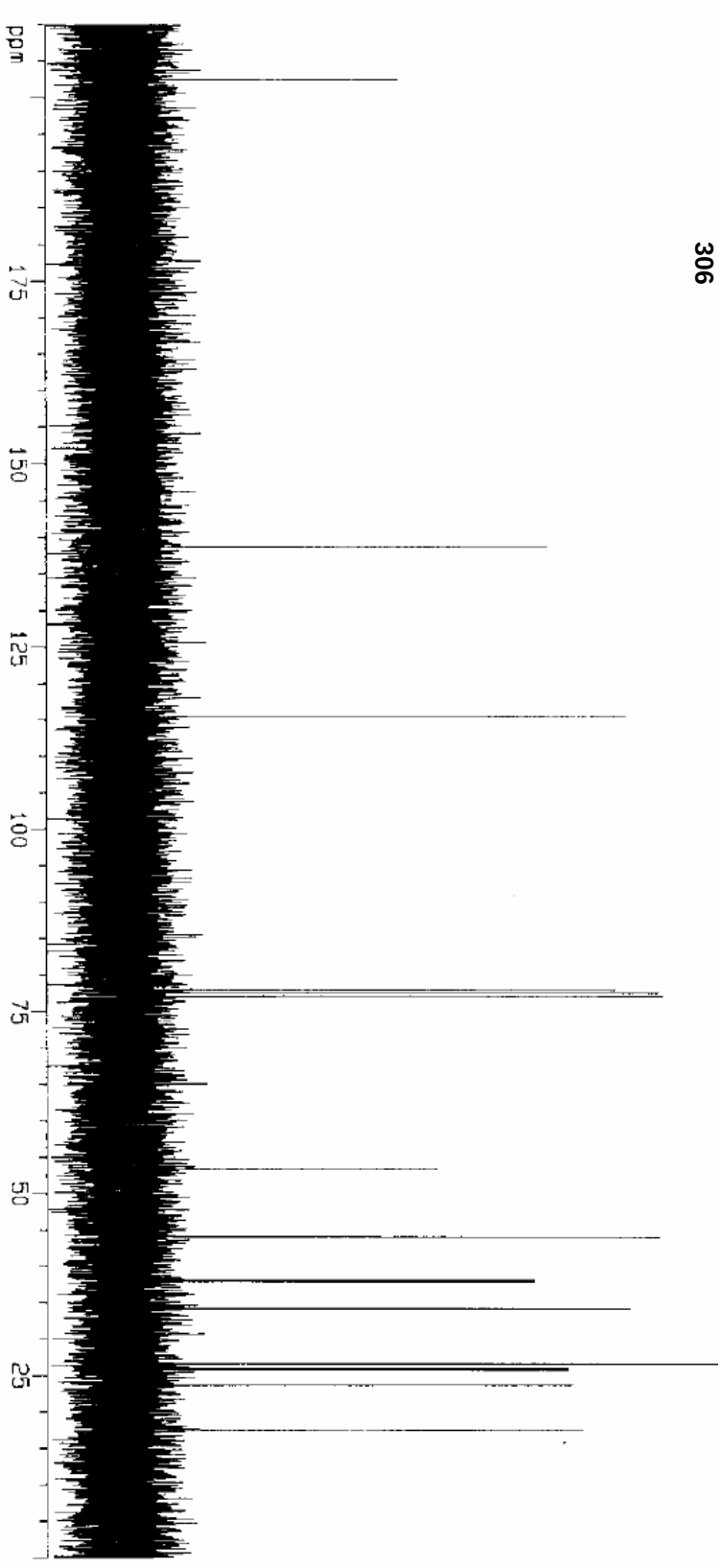

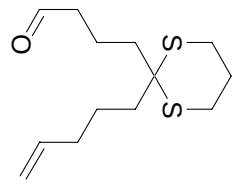

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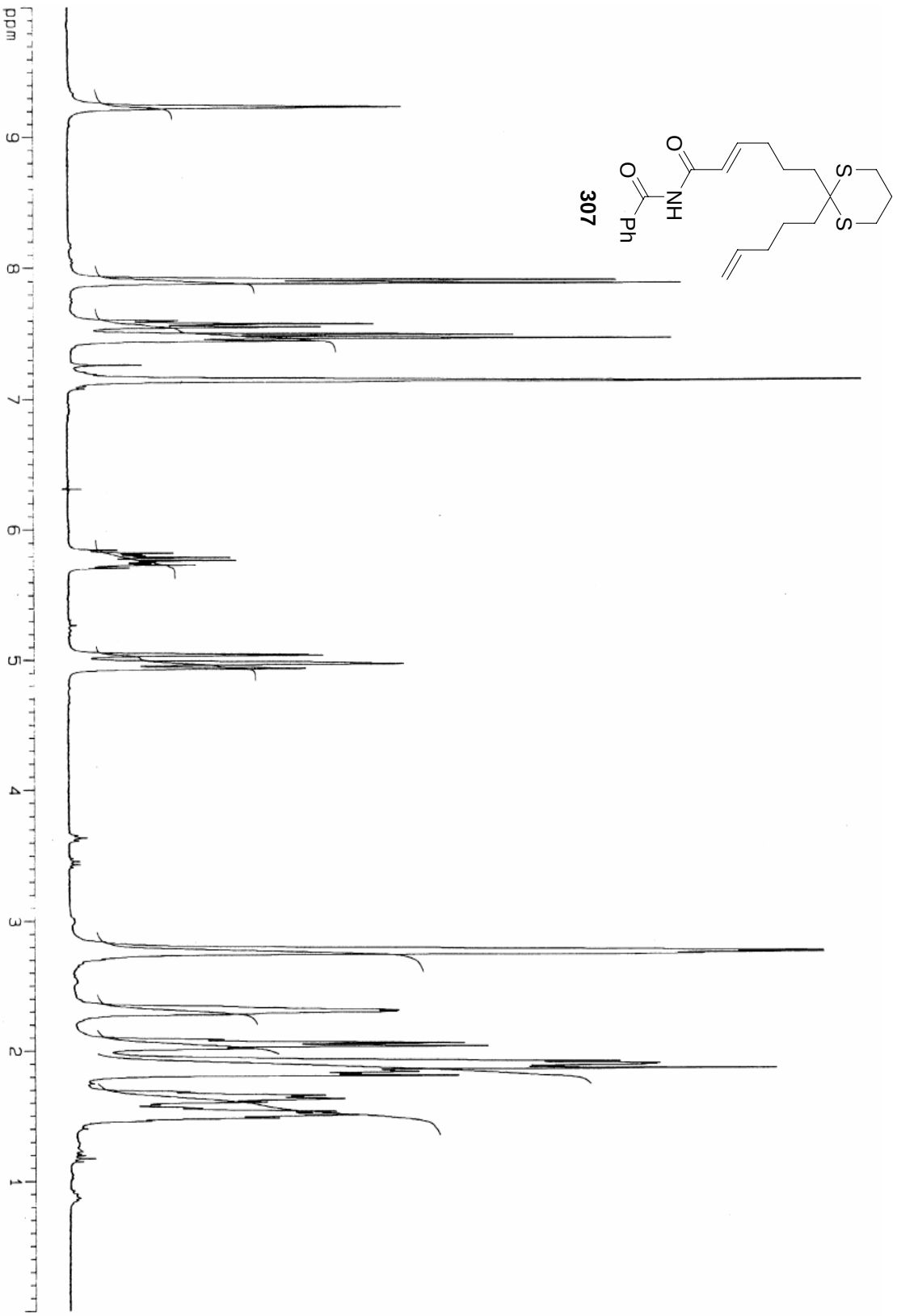

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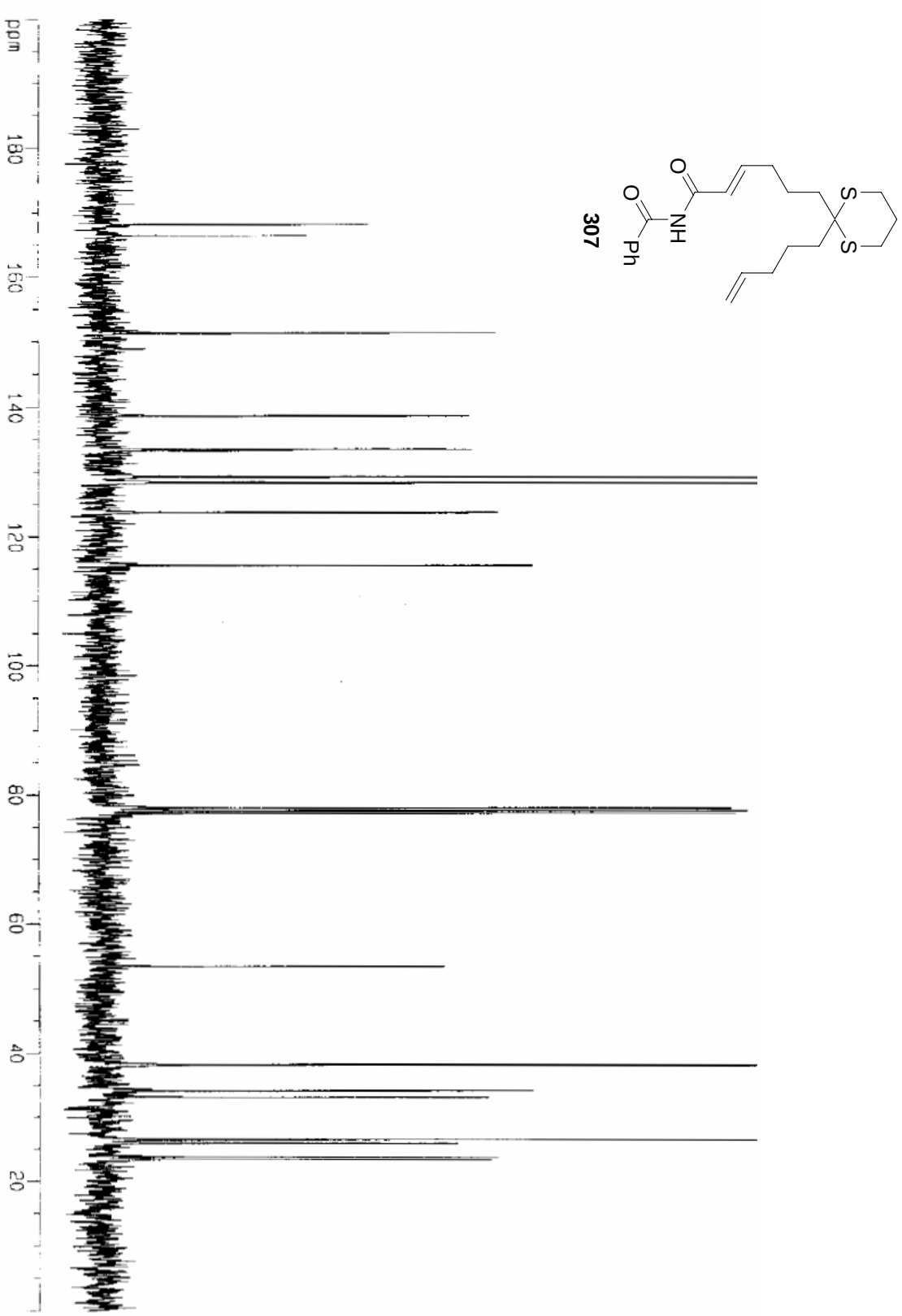

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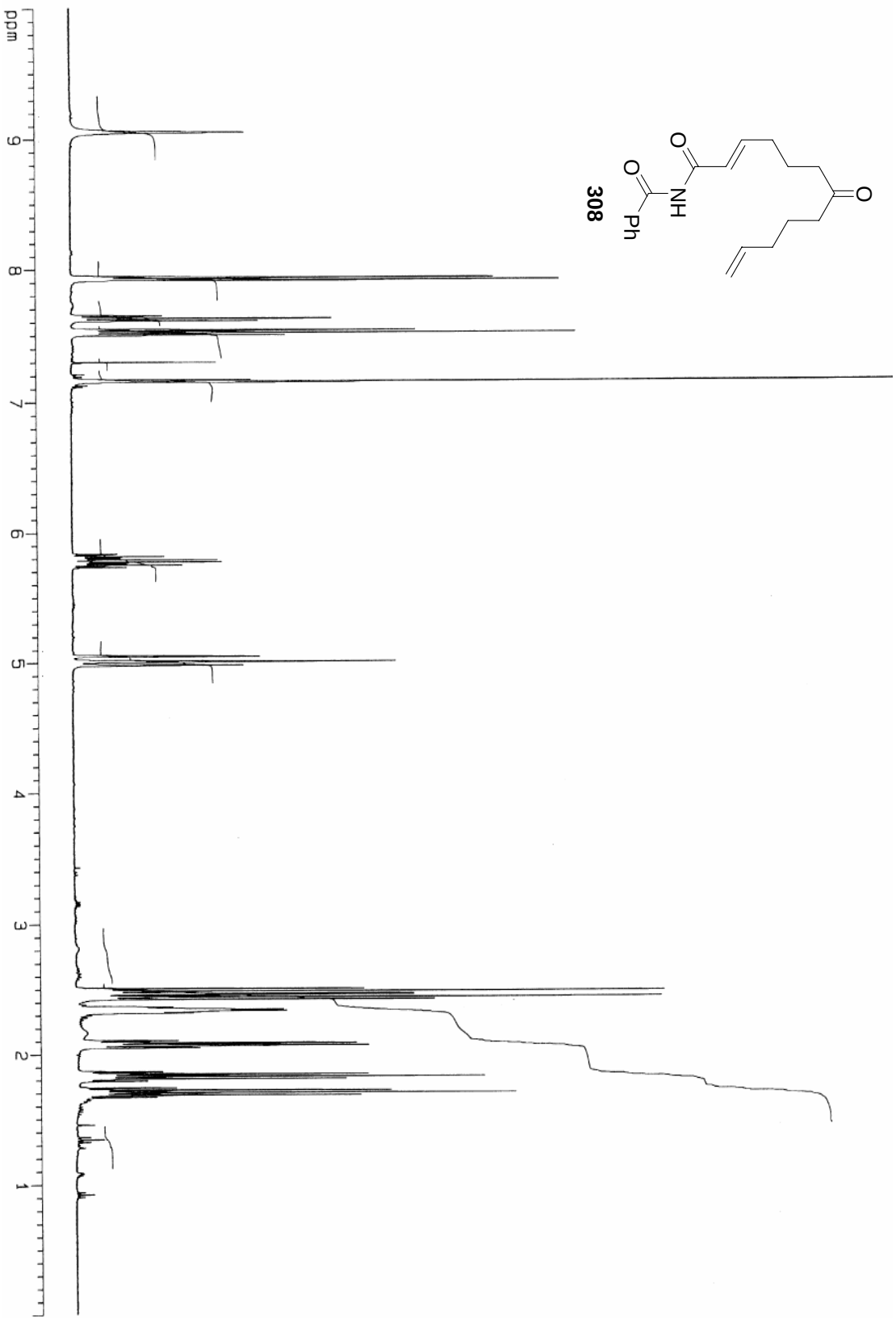
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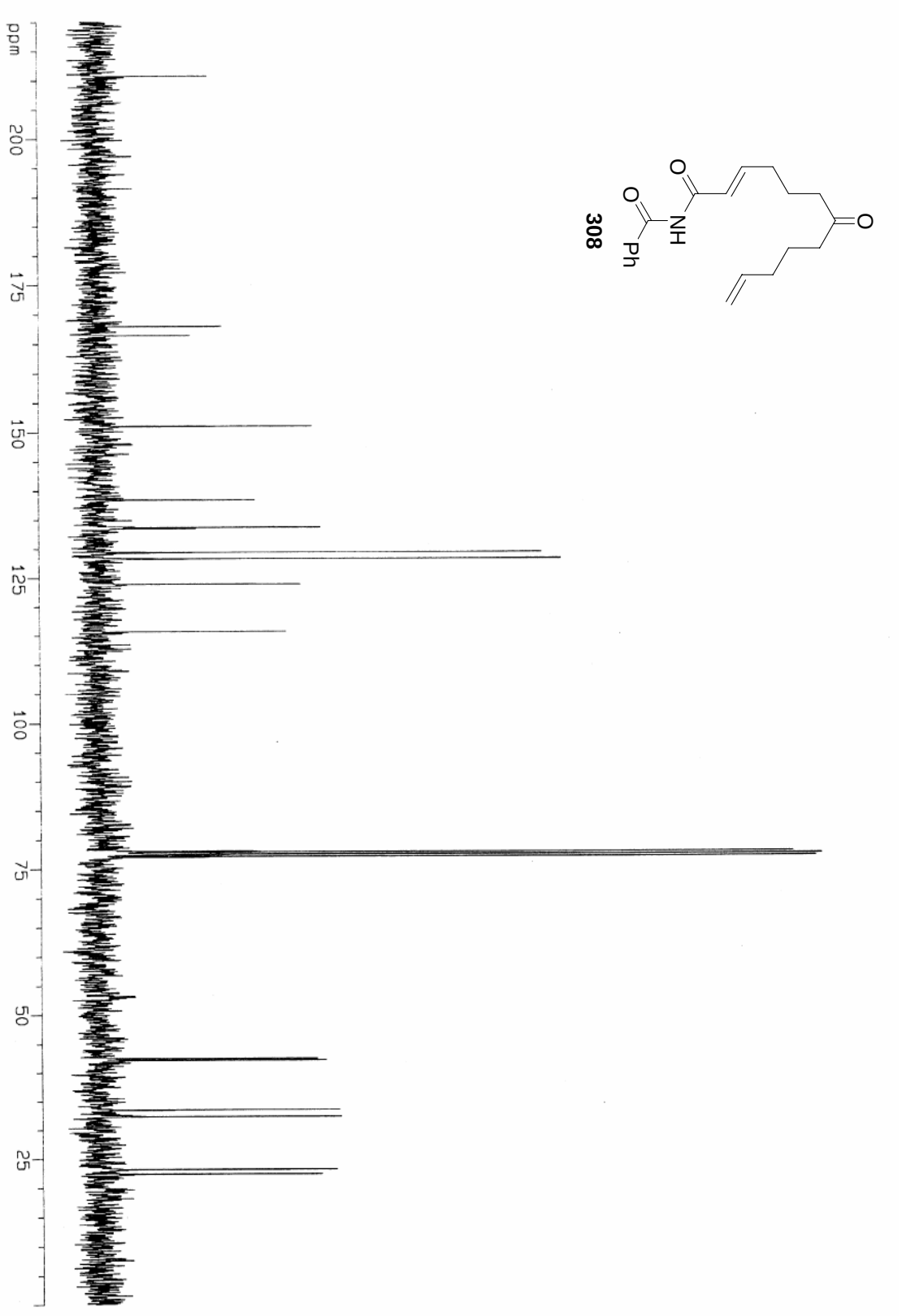

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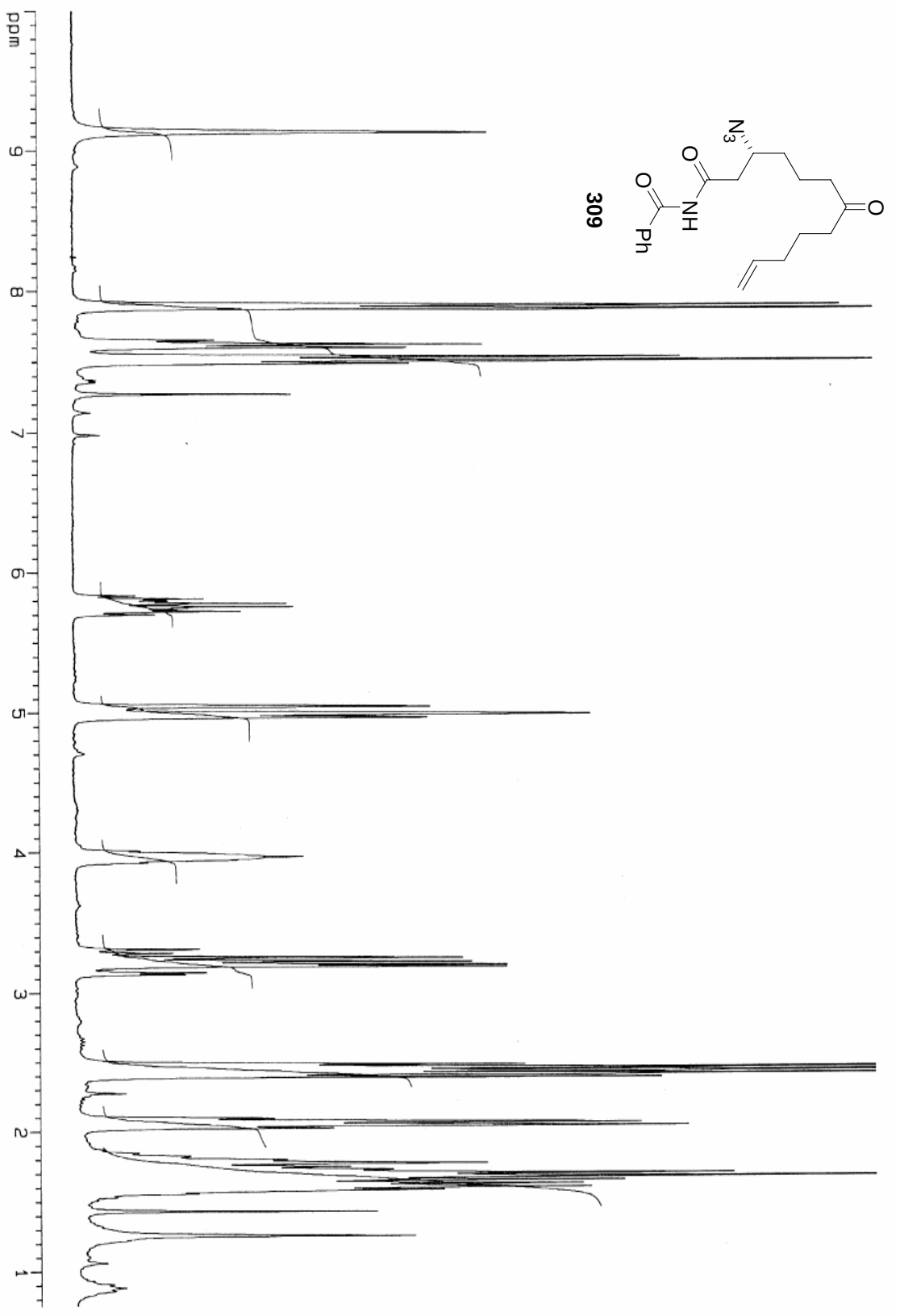

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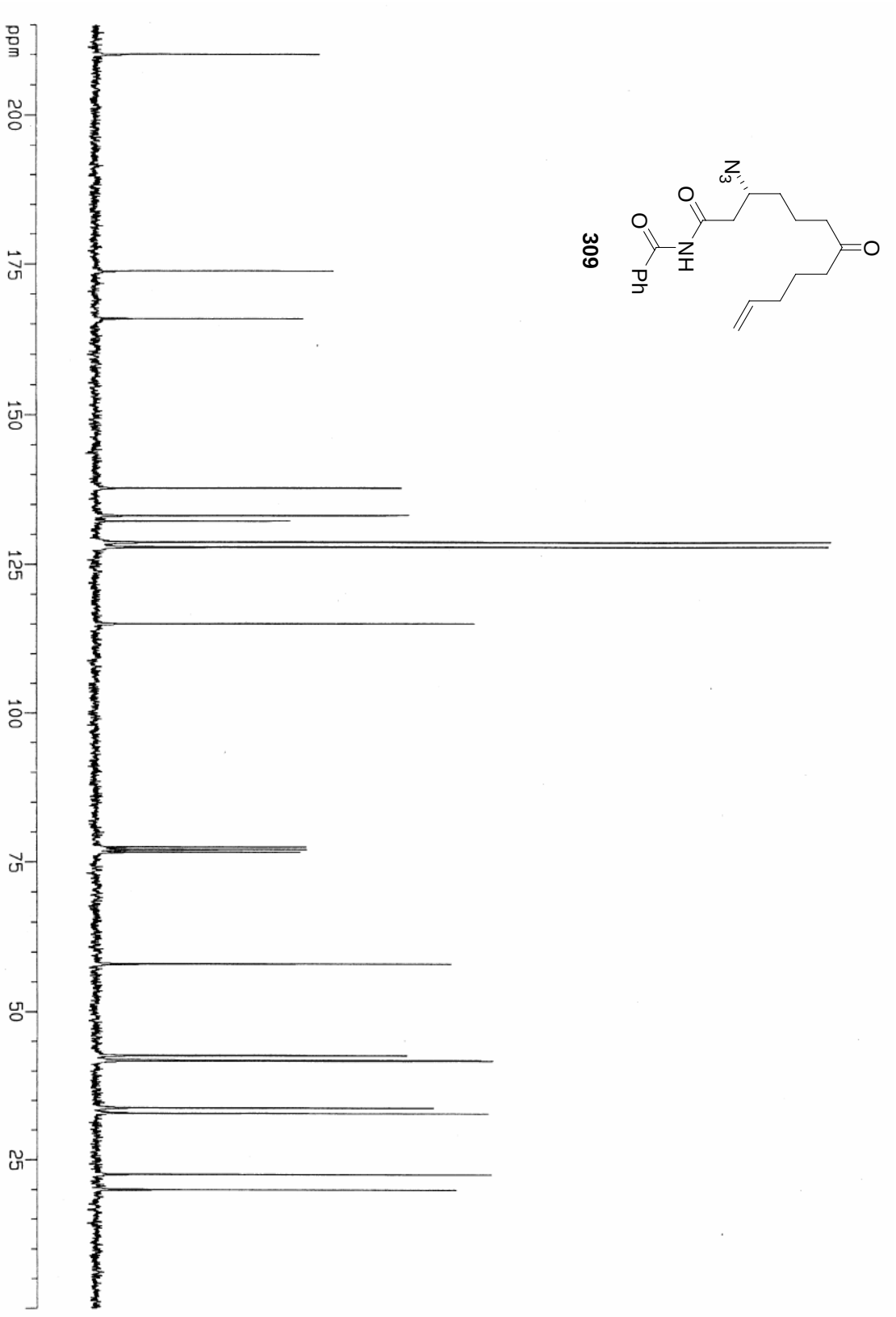

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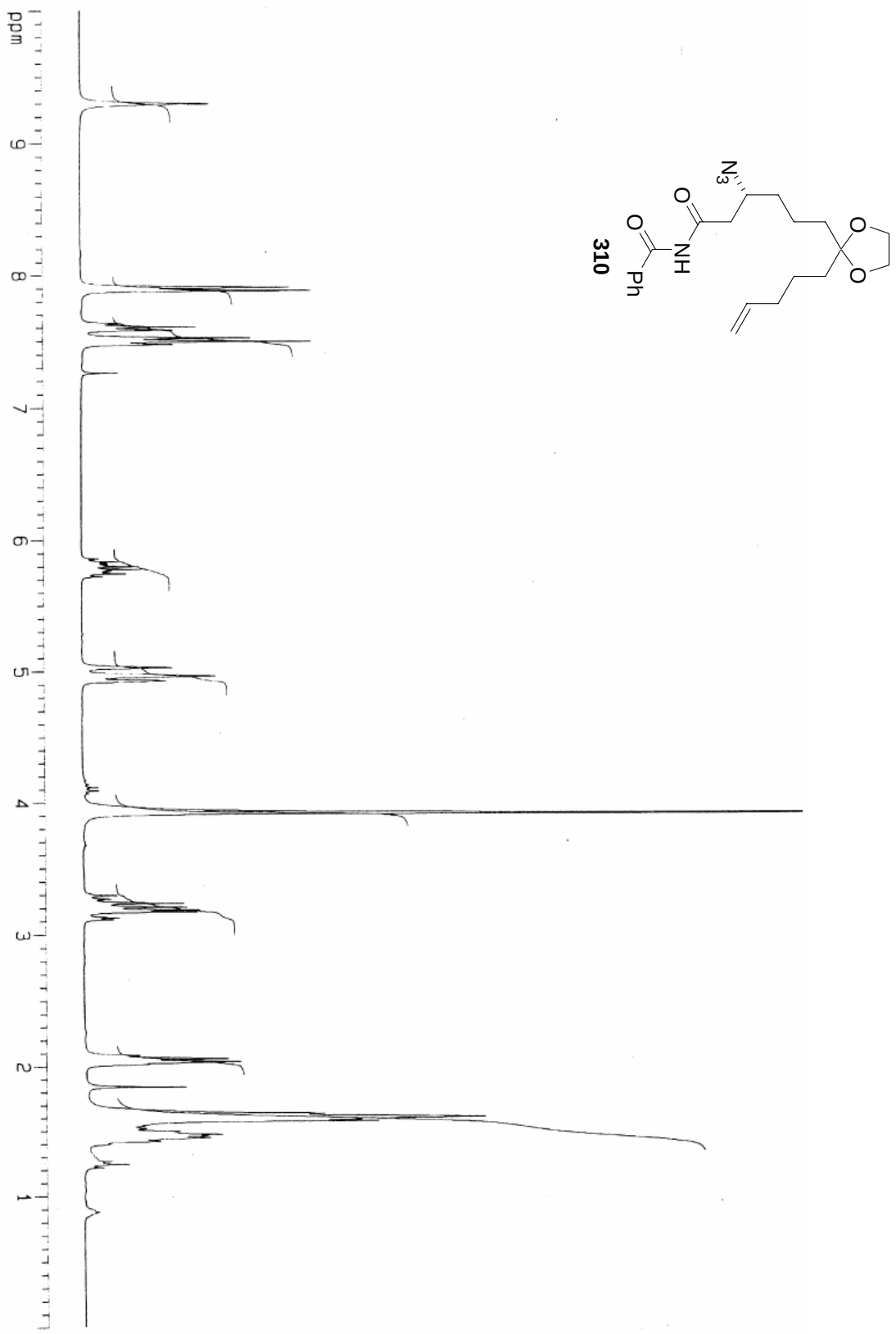

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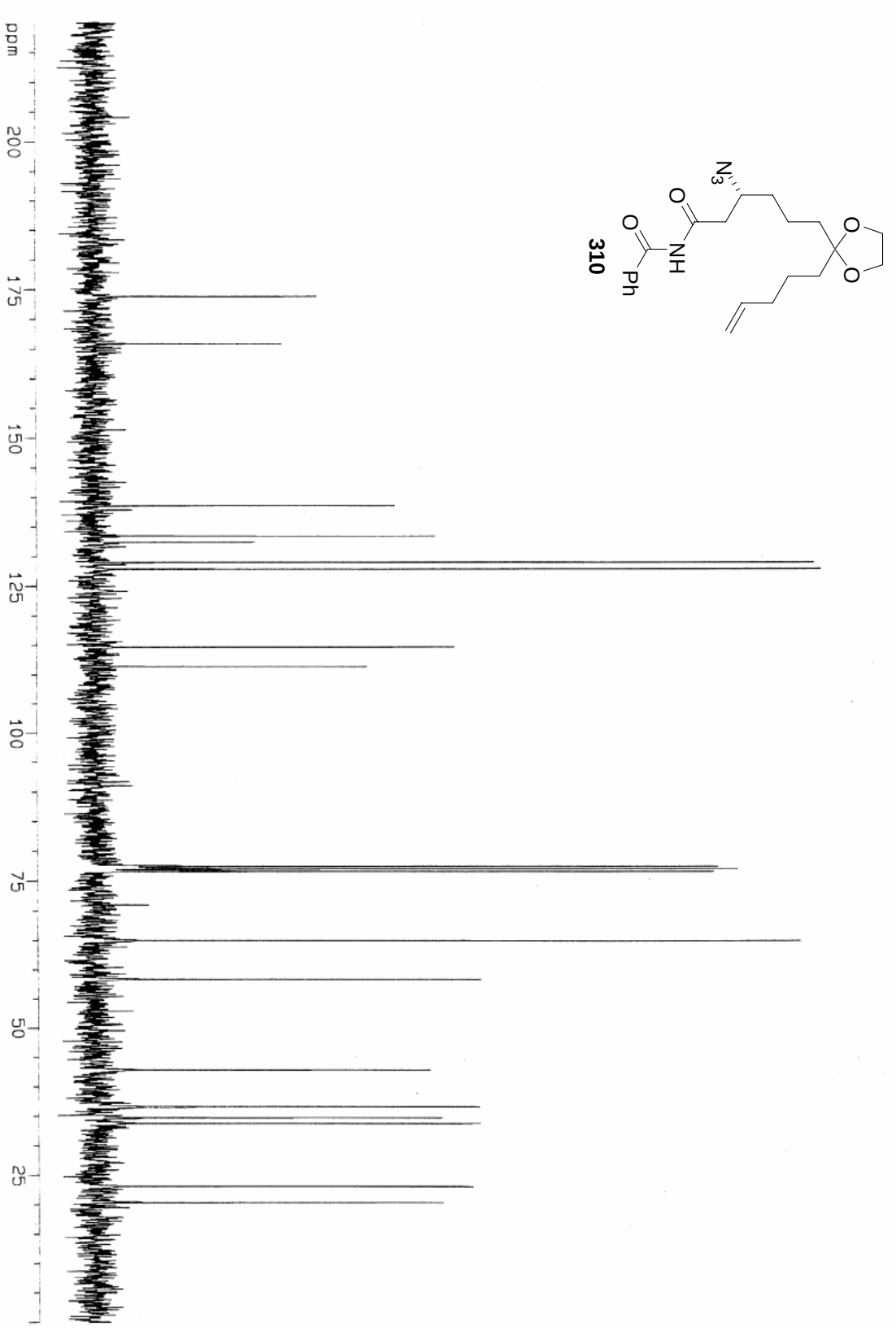
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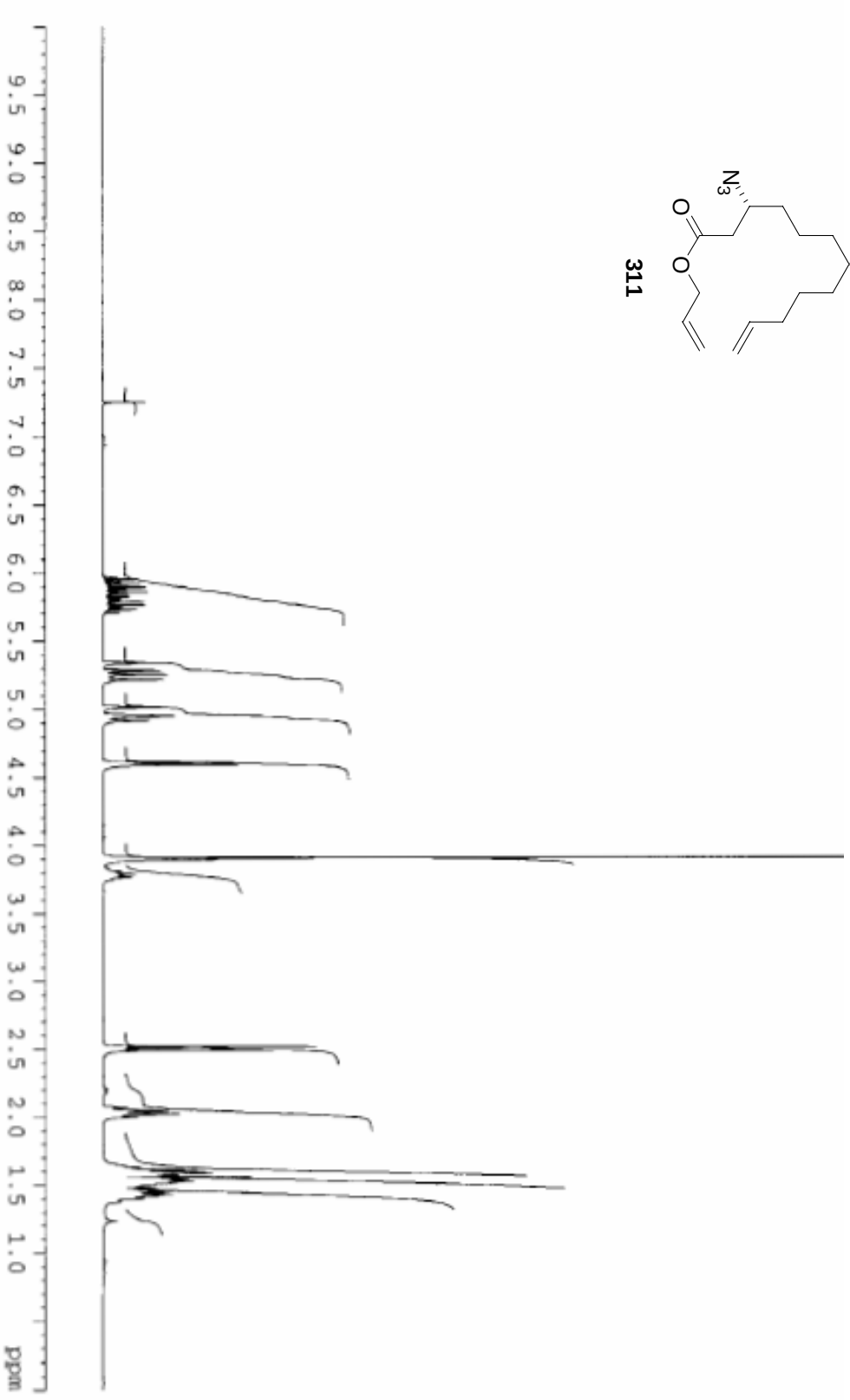
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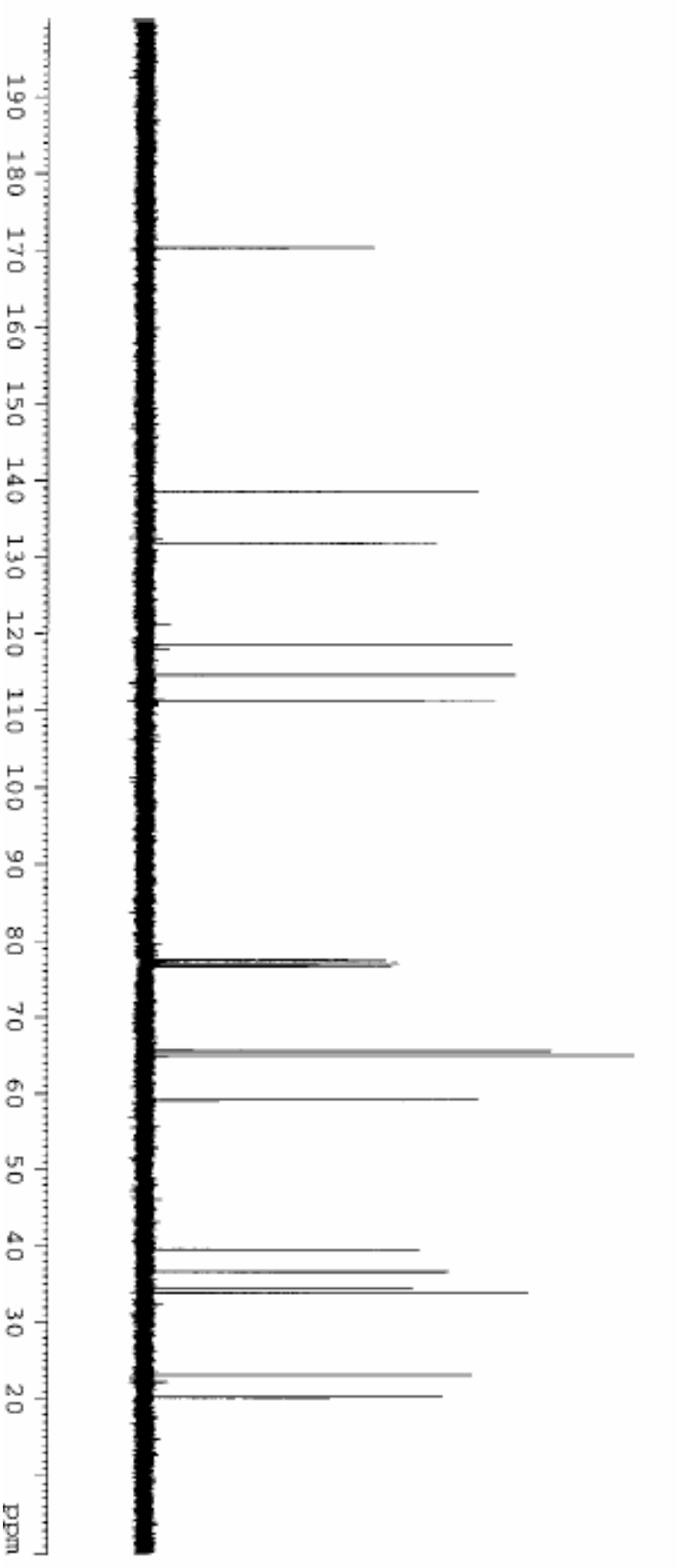
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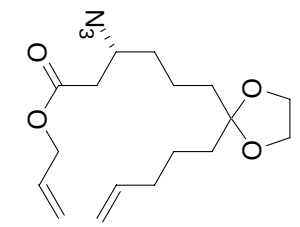
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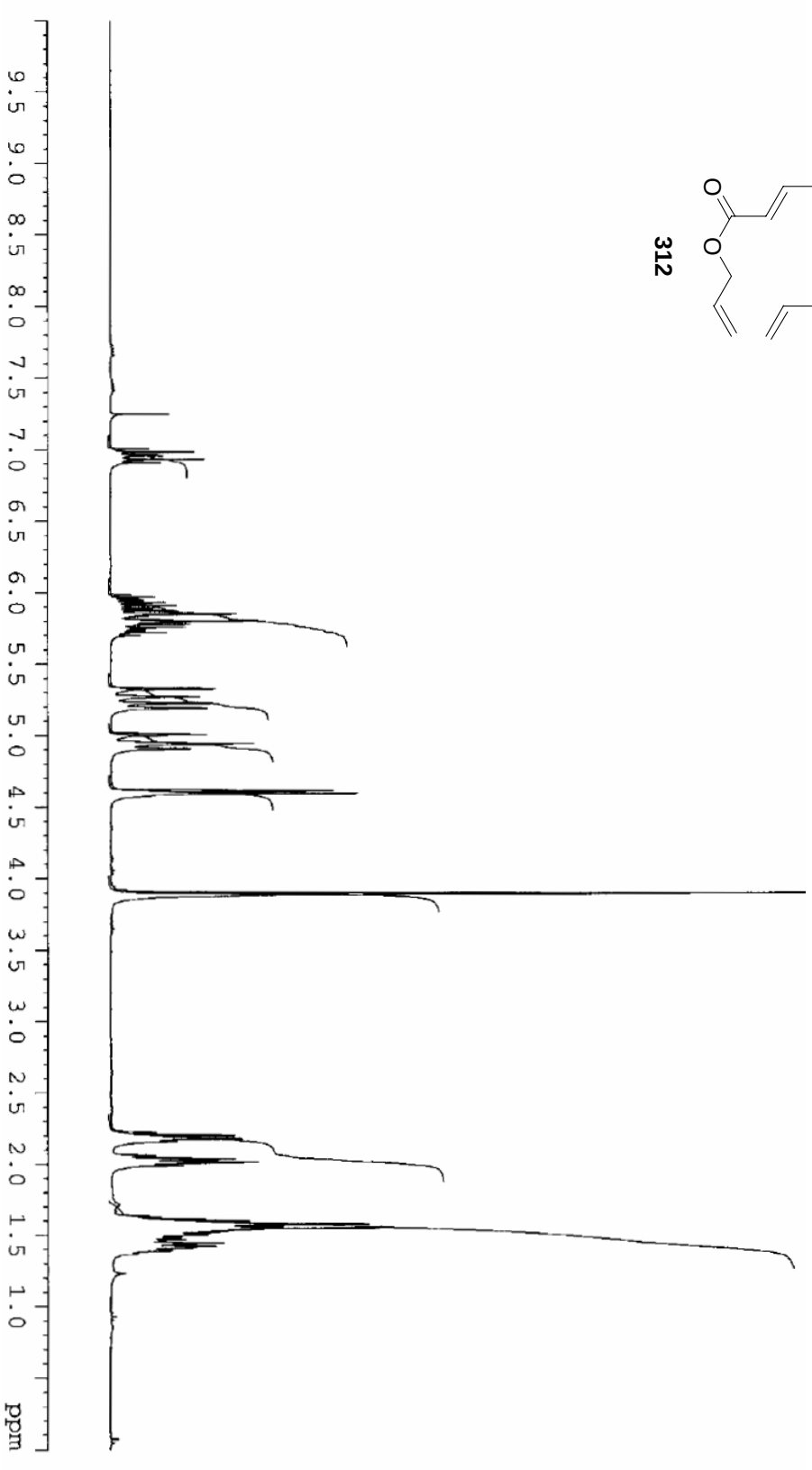
311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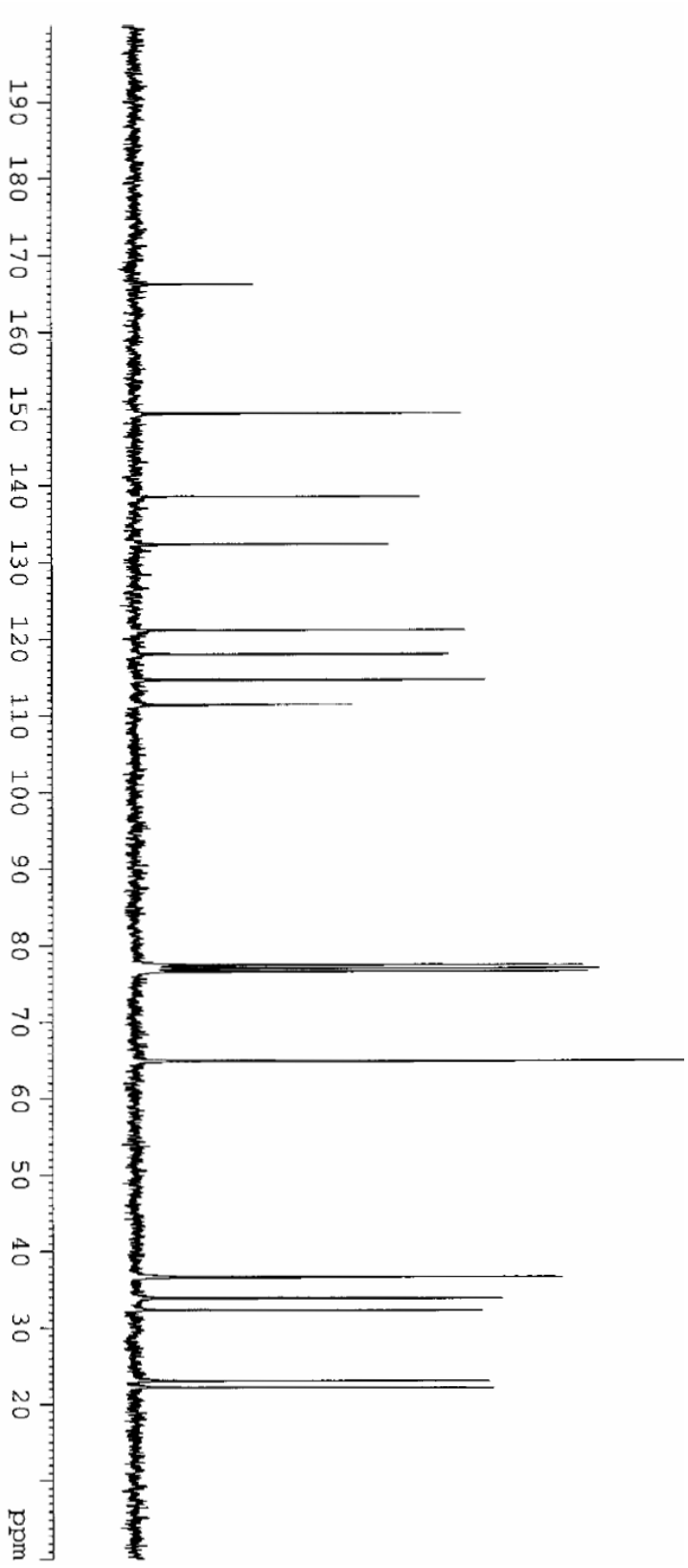

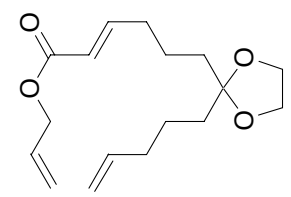

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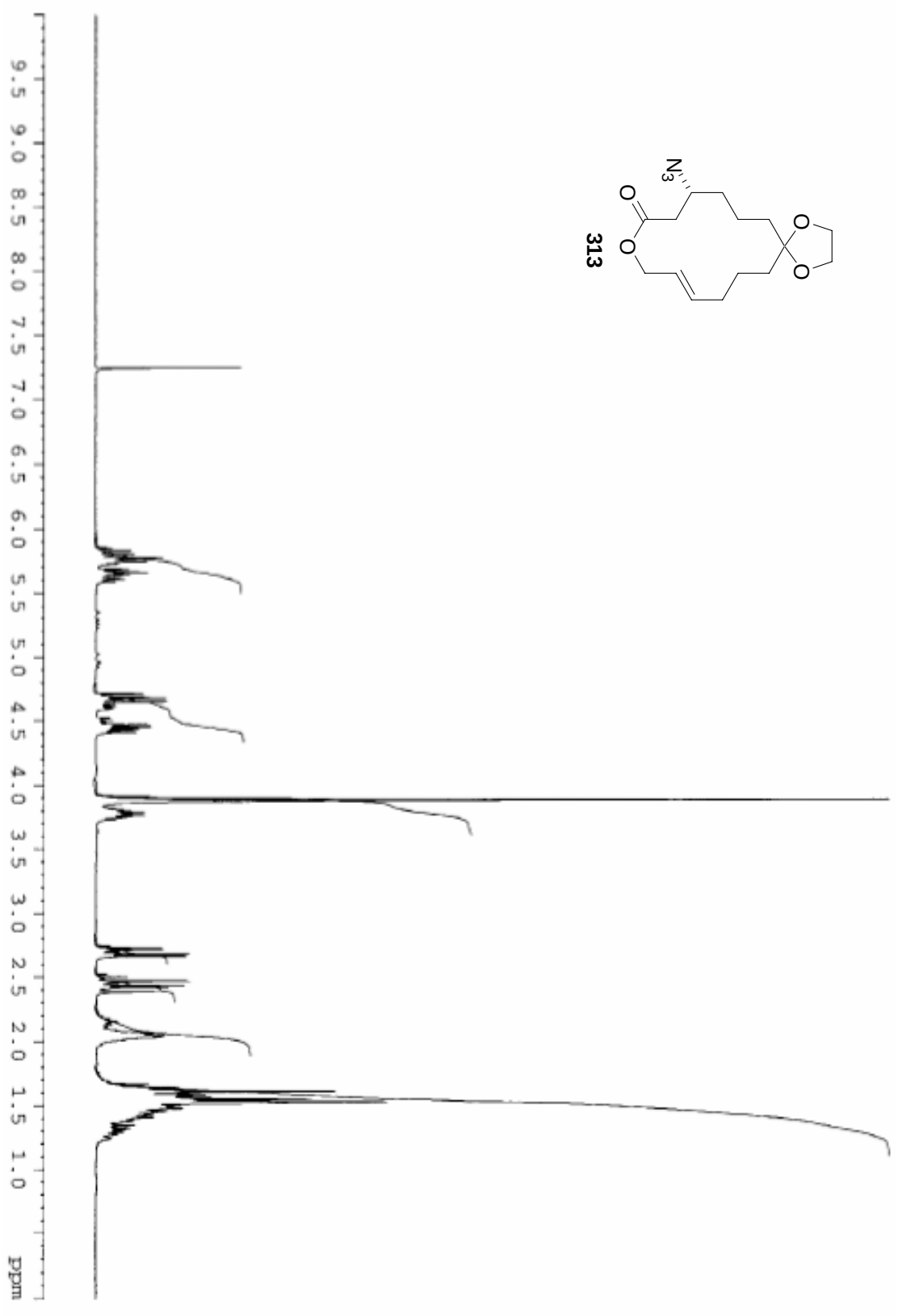
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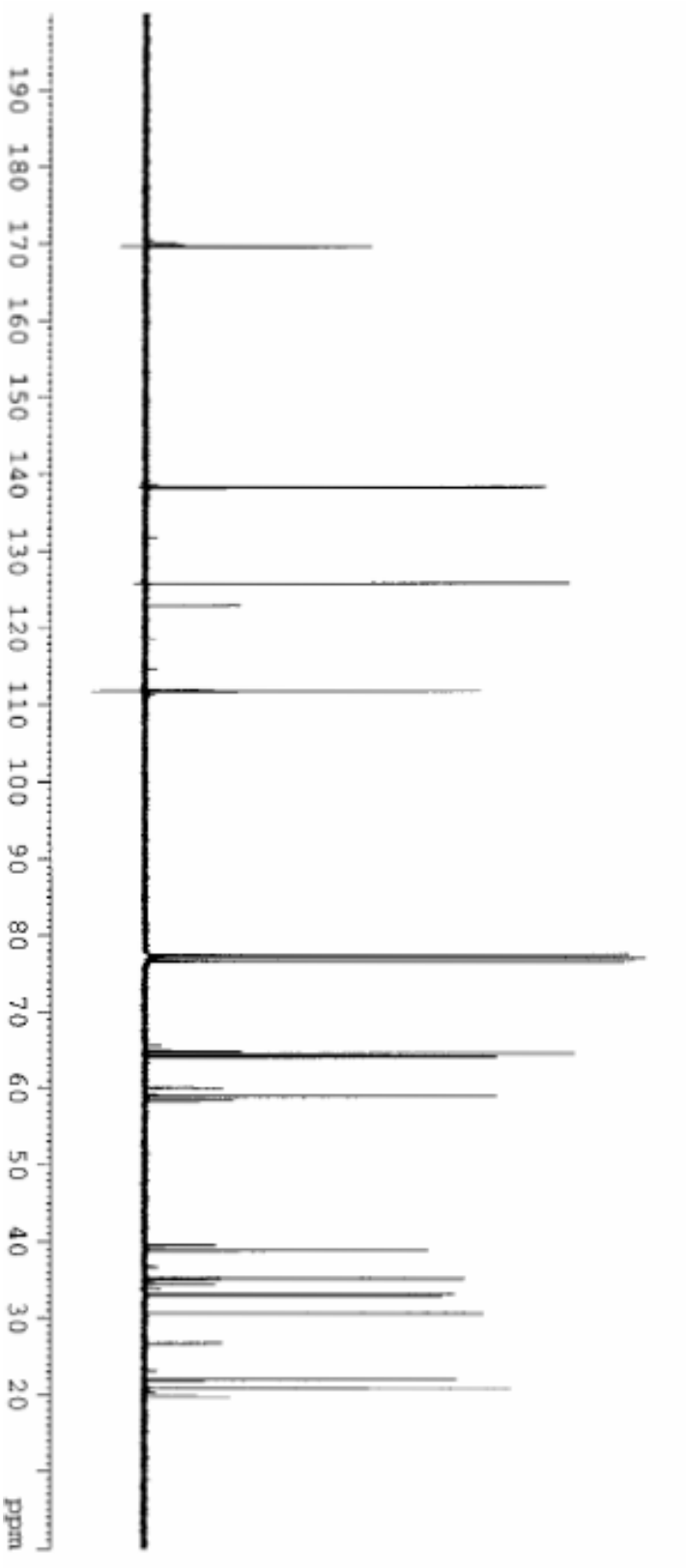
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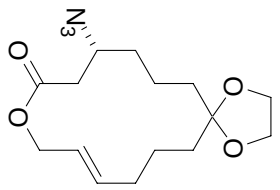
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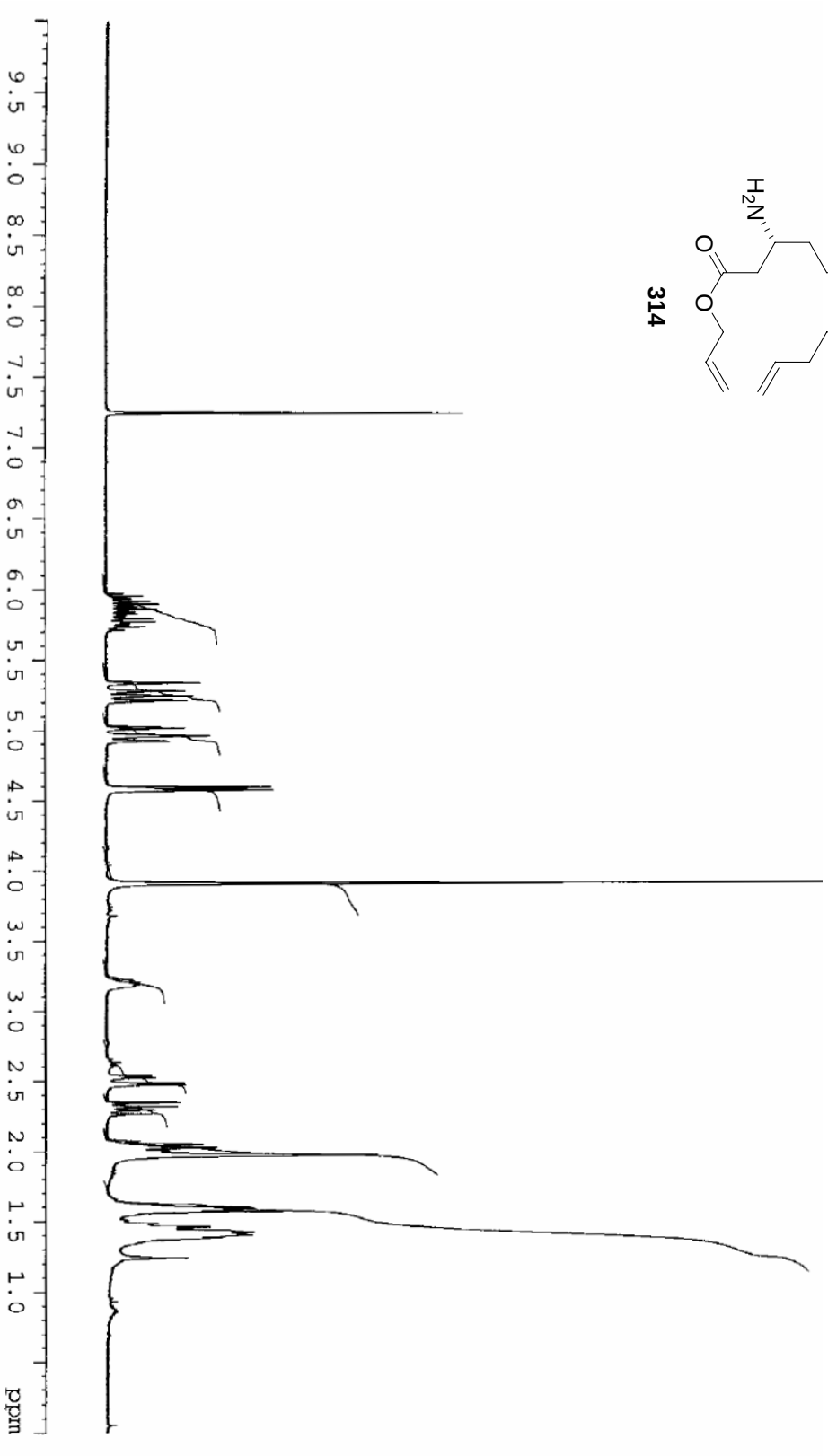
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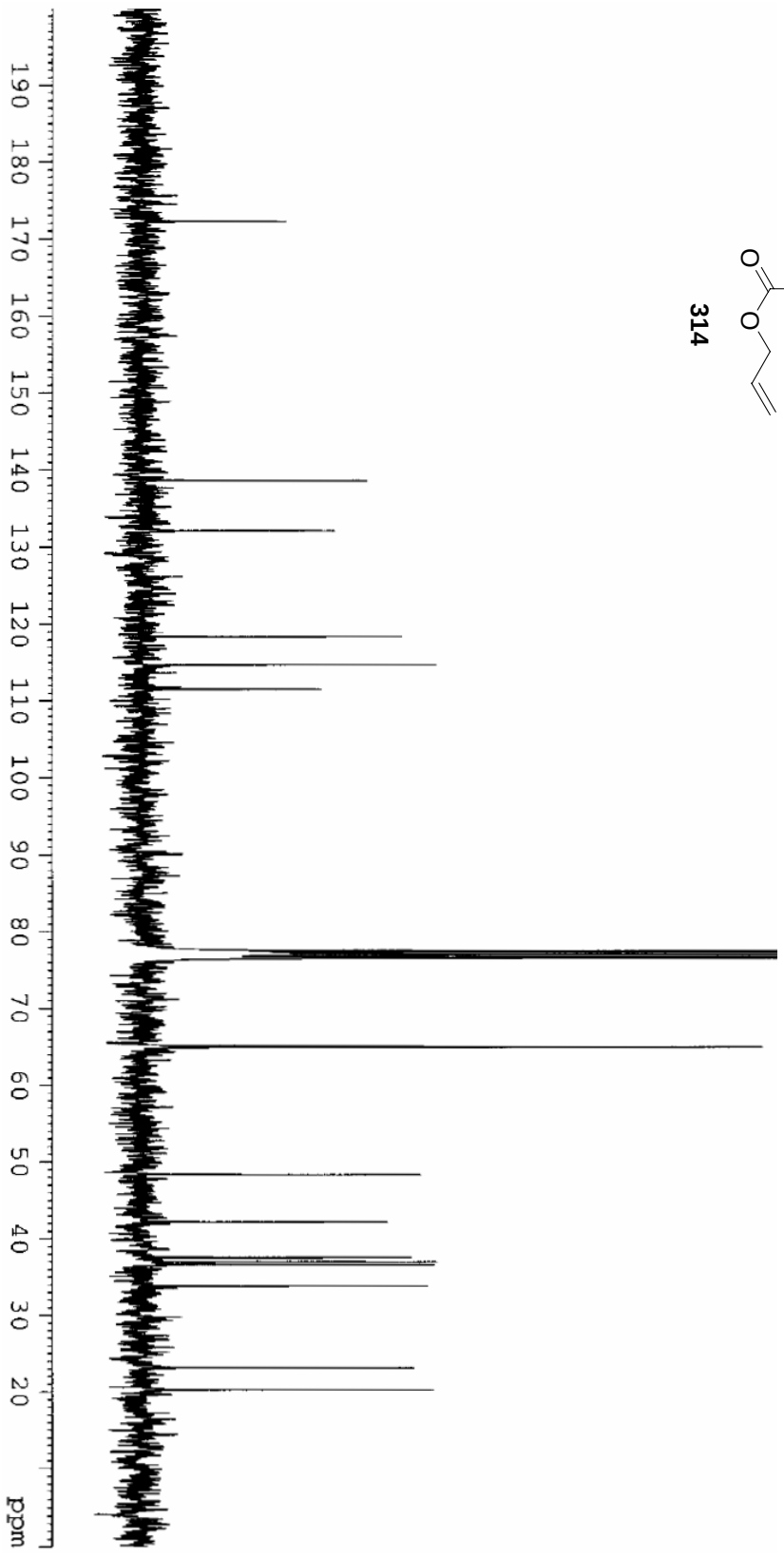
ppm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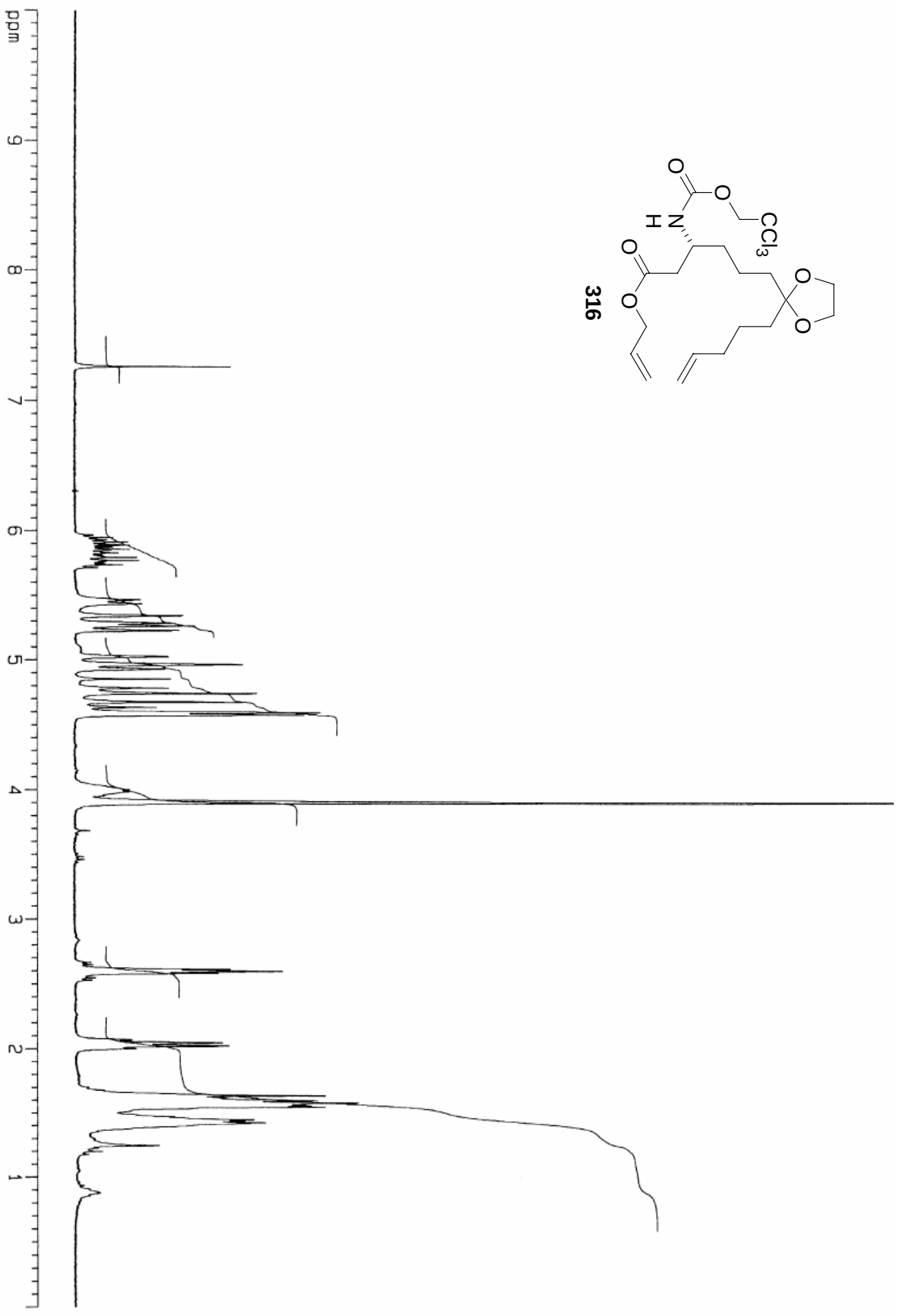

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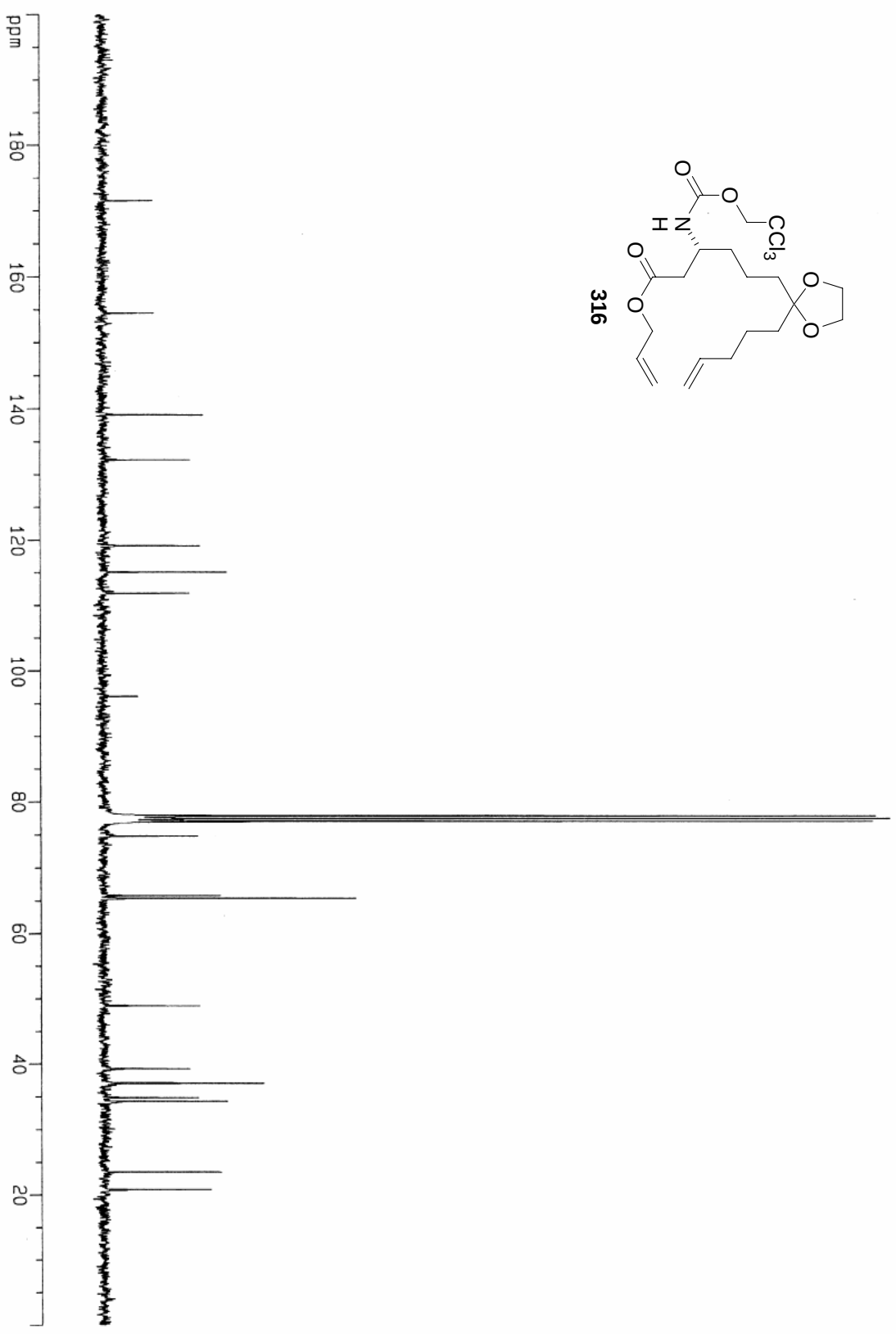

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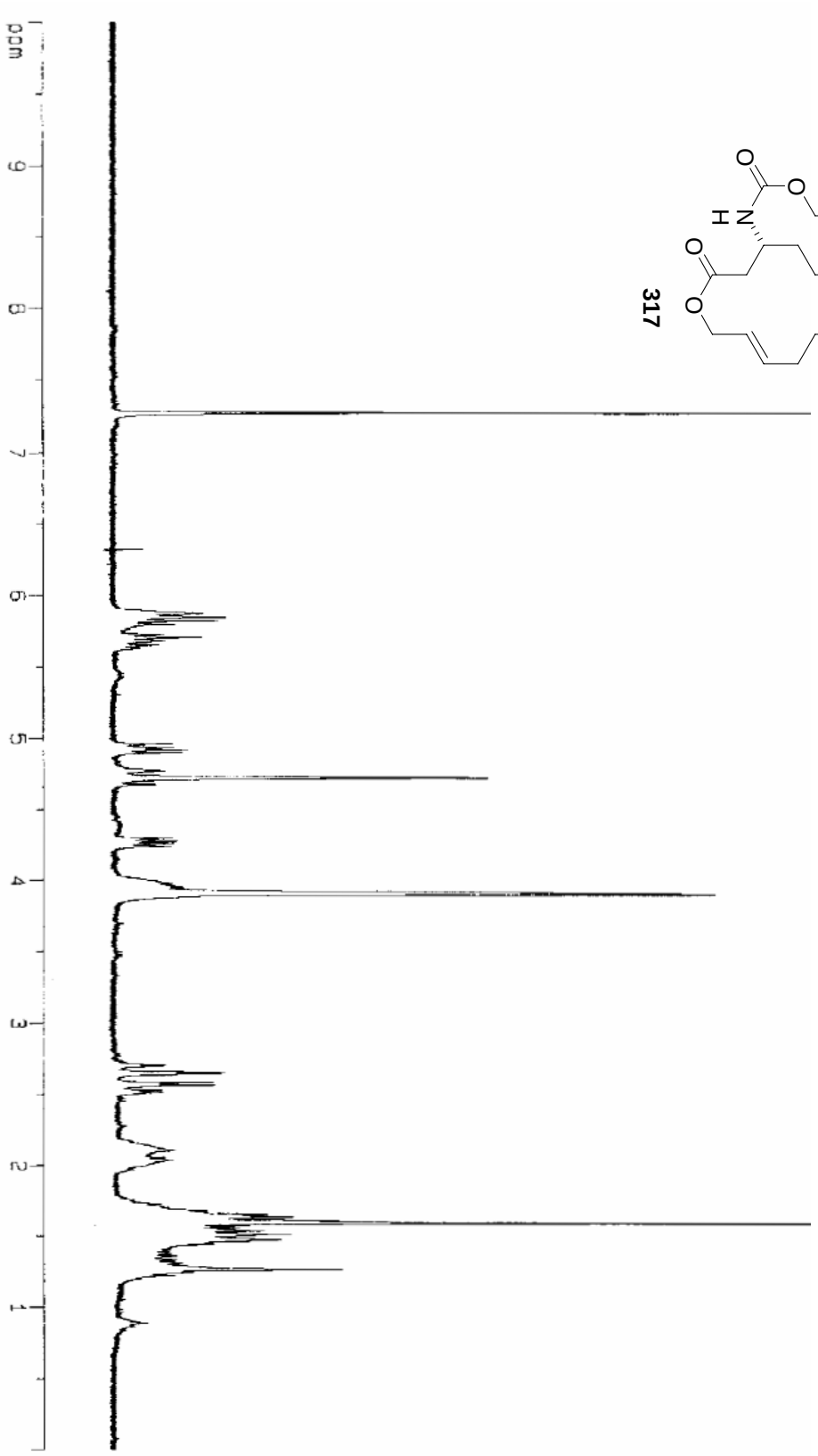
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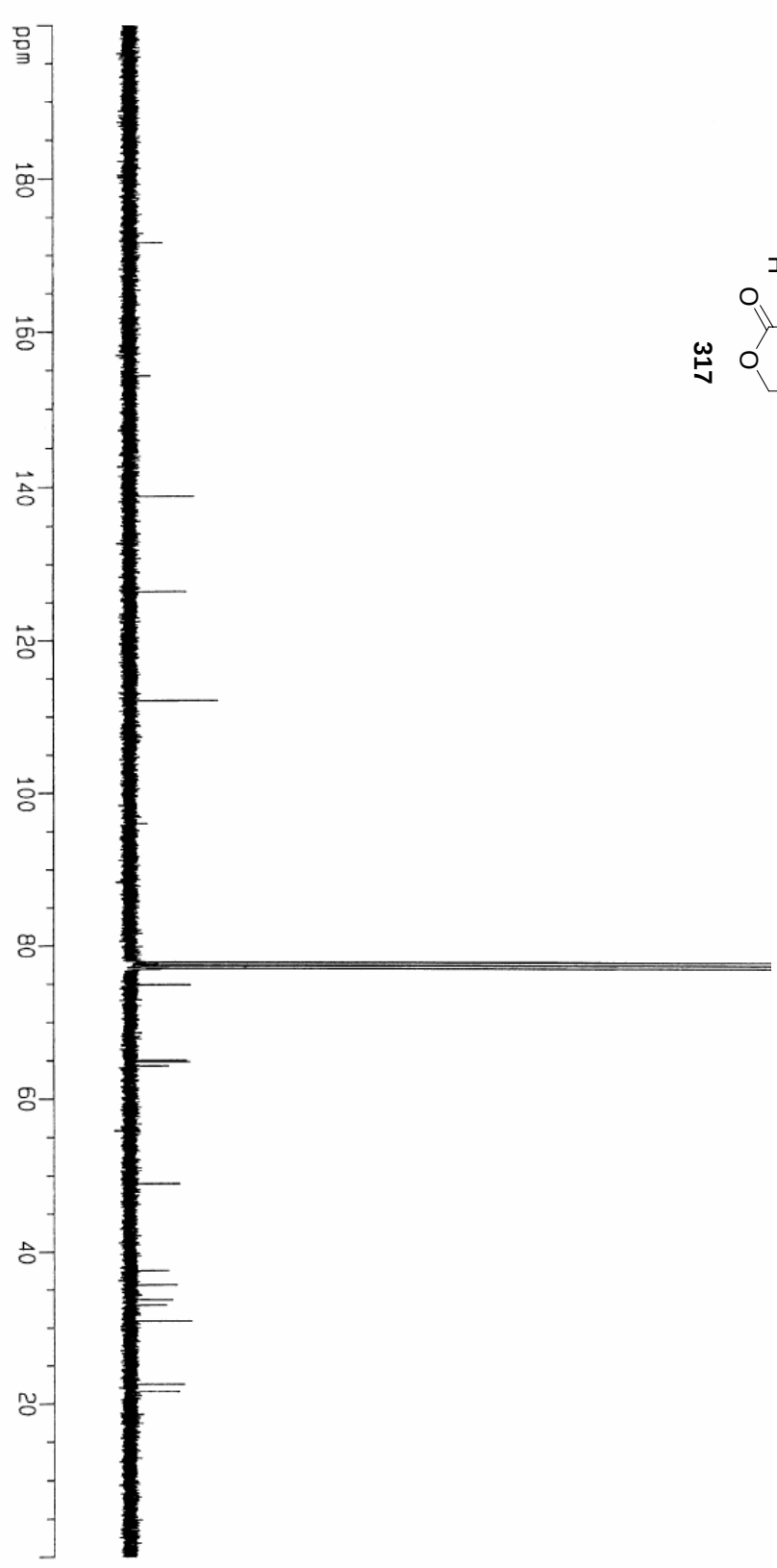
317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CCl3
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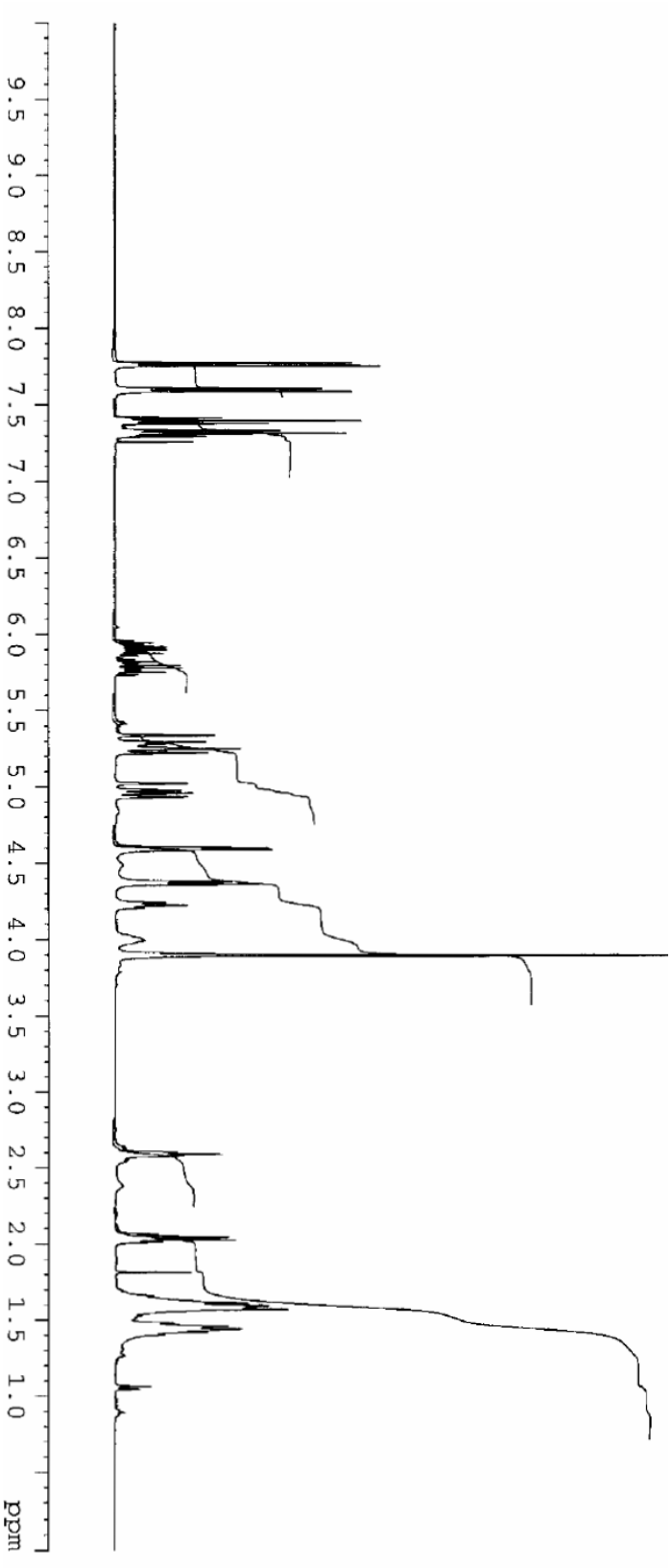

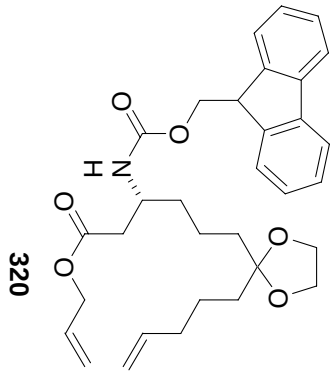

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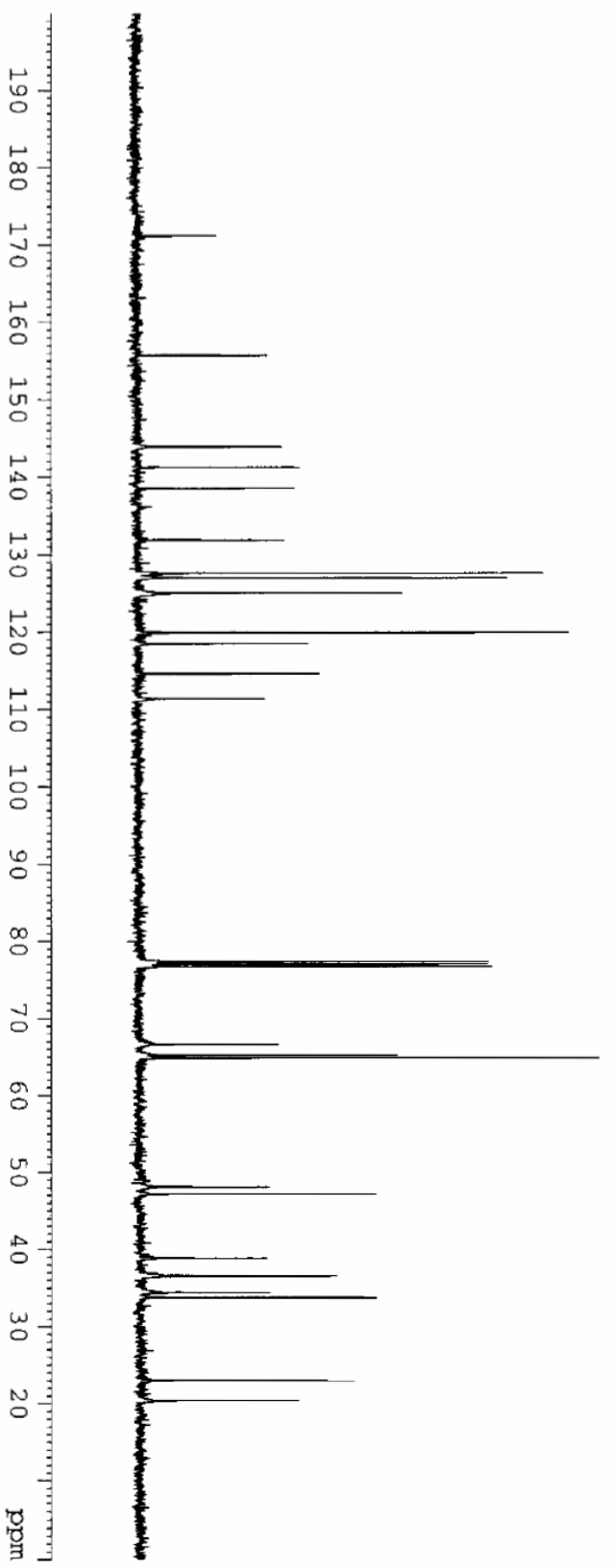

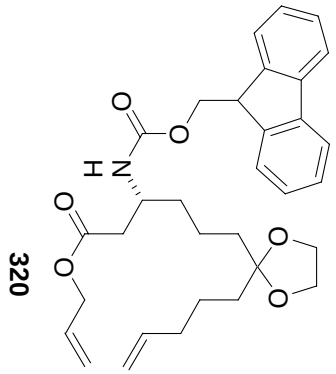

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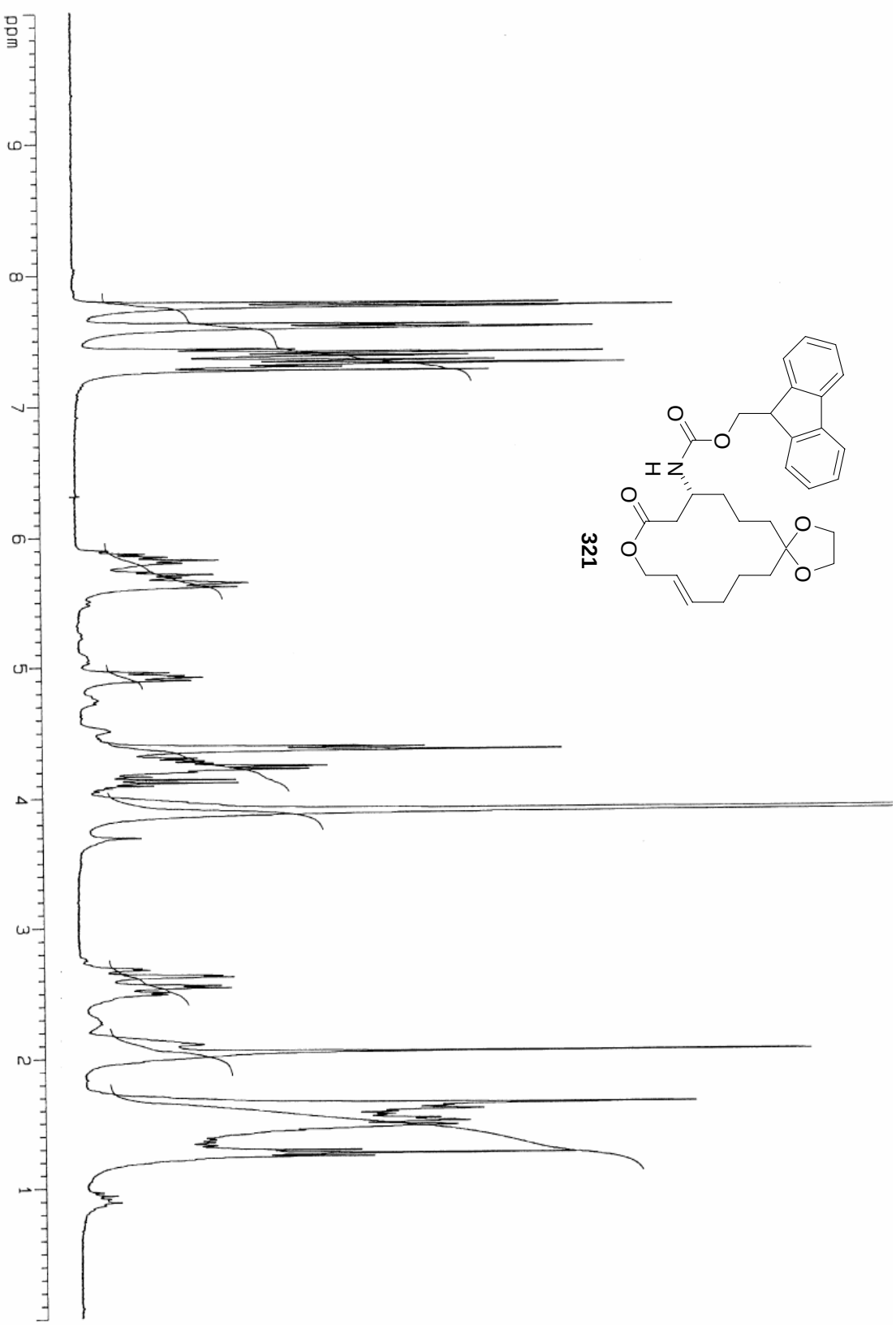
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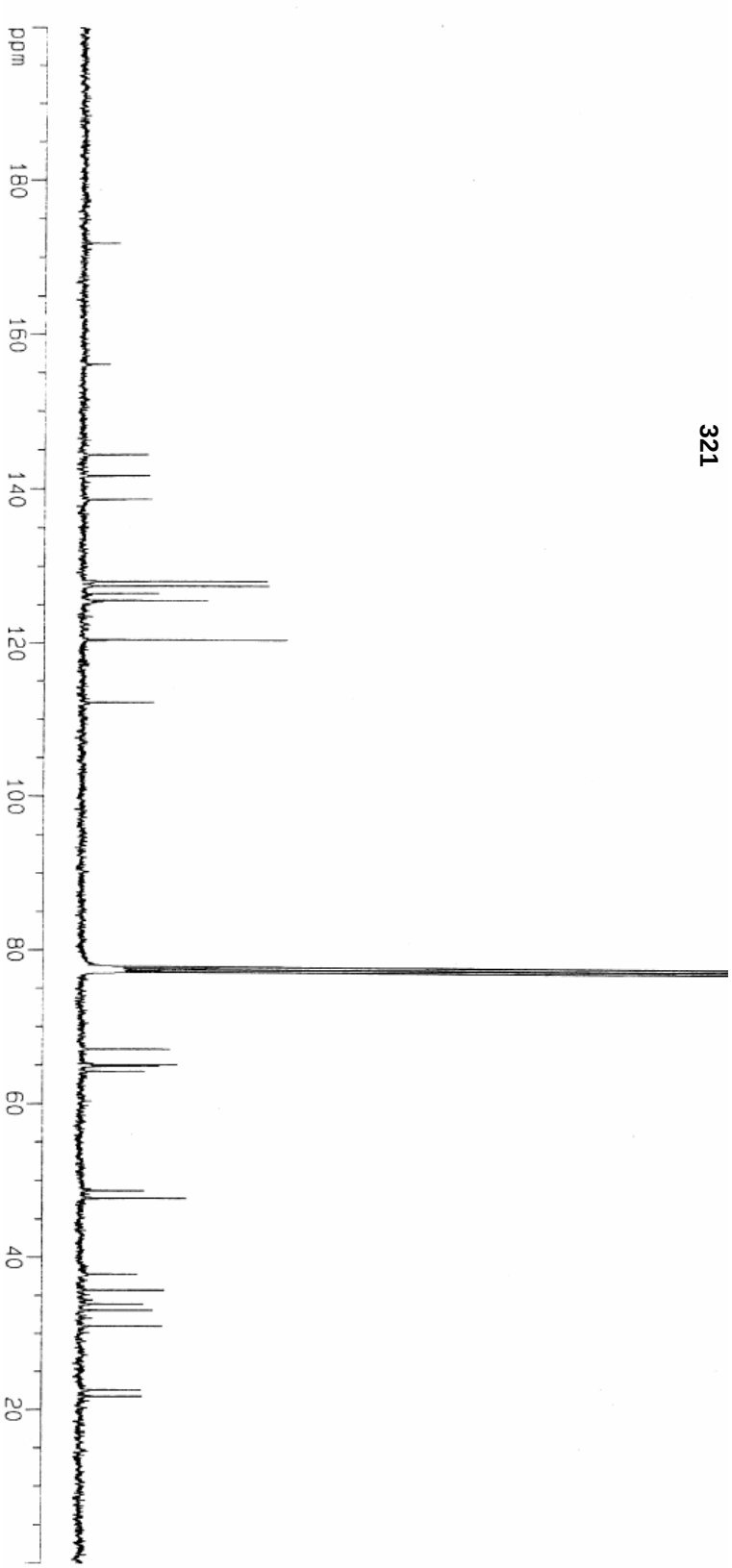

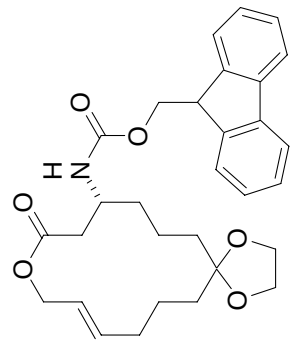

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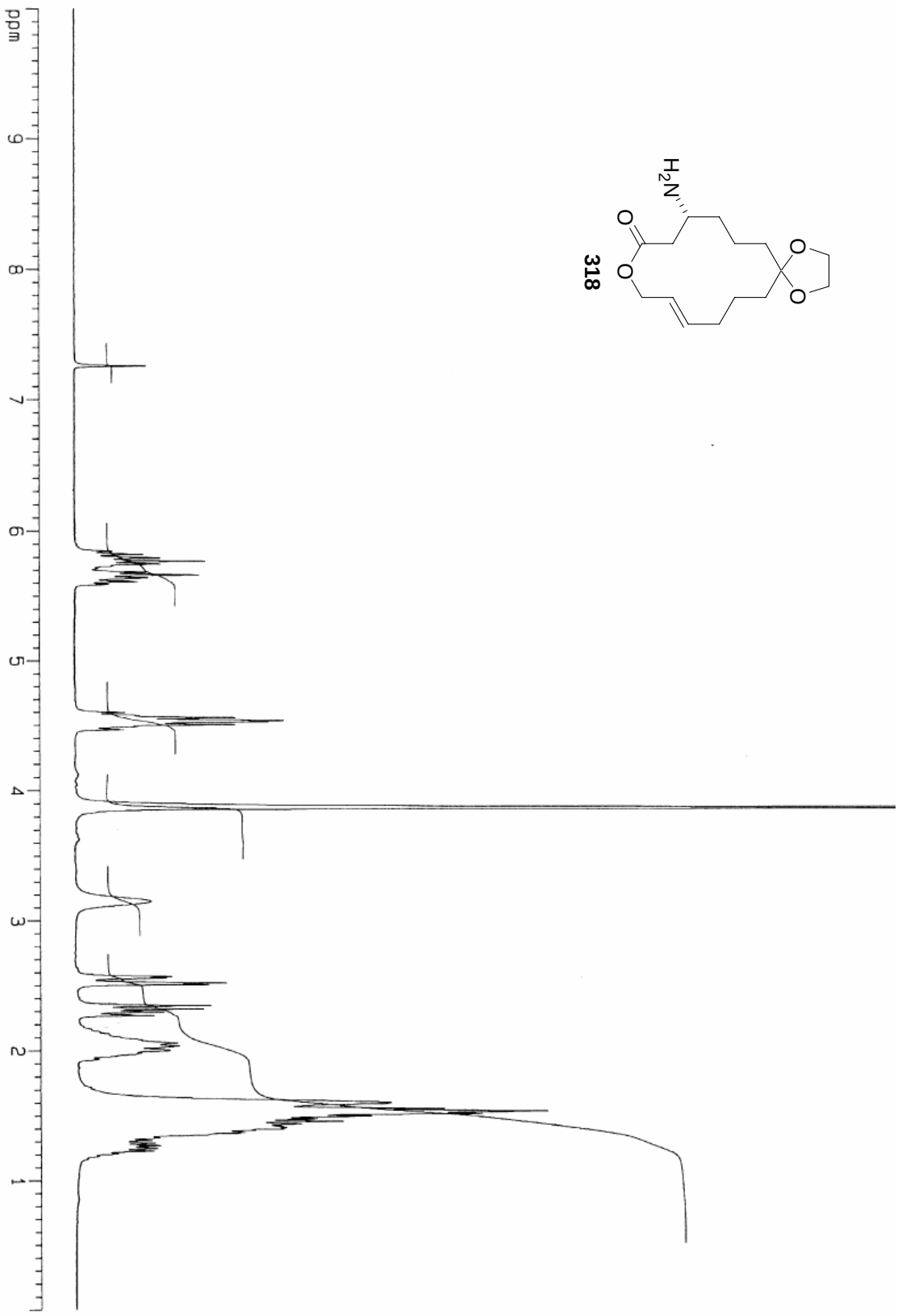

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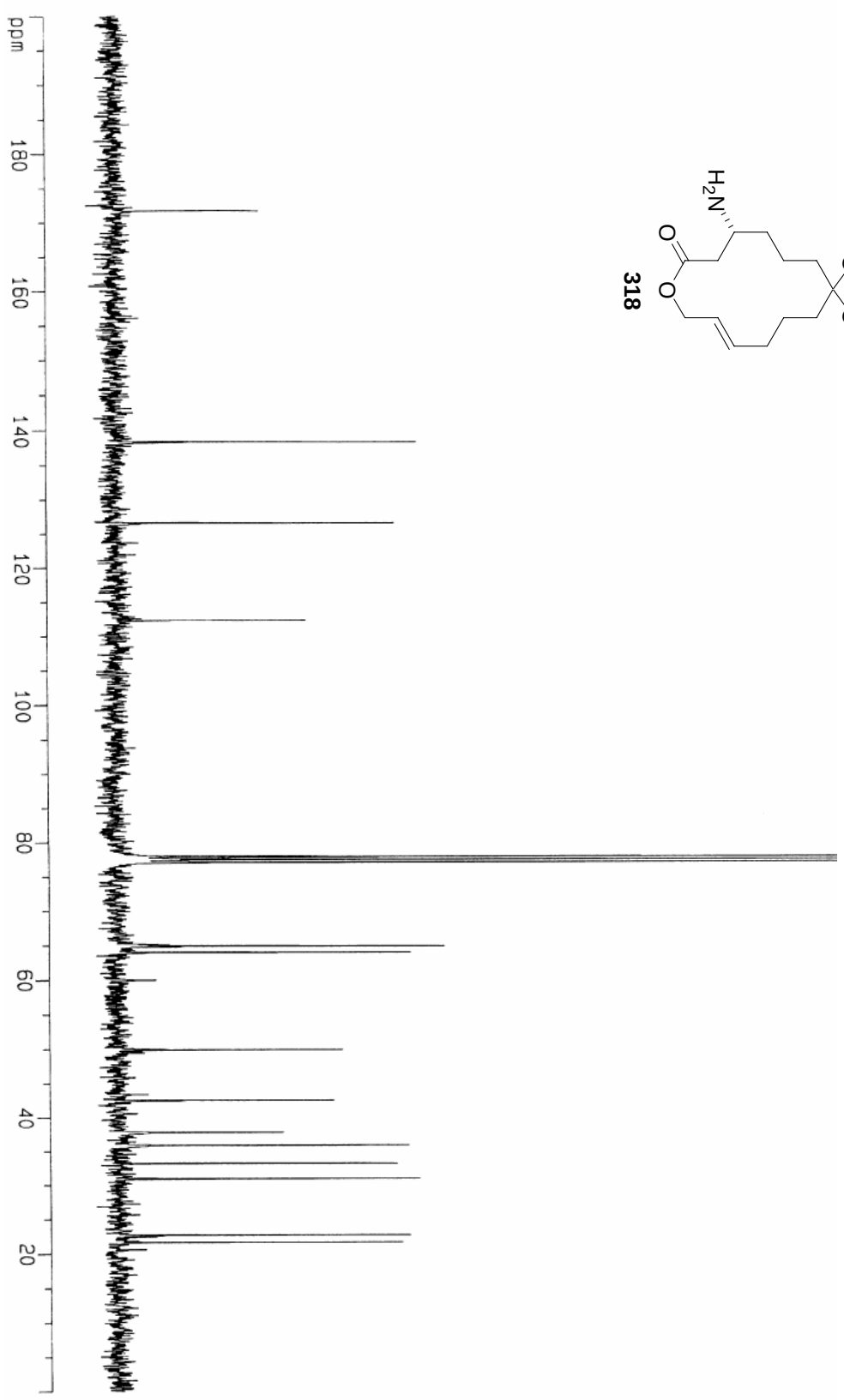

318