EFFORTS TOWARD THE TOTAL SYNTHESIS OF BIELSCHOWSKYSIN

By

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CHAPTER 1

BACKGROUND

Introduction

Isolated from *Pseudopterogorgia kallos* by Rodriguez, bielschowskysin is a unique furanocembranoid natural product.[1] In addition to its structural novelty and complexity, bielschowskysin exhibits antiplasmoidial activity against *Plasmodium falciparum* (IC_{50} = 10 μg/ mL) as well as in vitro cytotoxicity against EKVX nonsmall cell lung cancer (GI50 < 0.01 μM) and CAKI-1 renal cancer (GI50 < 0.51 μM). Its structural and biological profile renders the natural product an interesting target for total synthesis.

Biosynthesis

Bielschowskysin belongs to a unique class of diterpene natural products assembled by gorgonian corals. These marine species are responsible for the production of most known furanocembranoids, pseudopteranes and gersolanes. Differing most markedly in carbocyclic ring size, these natural products are highly oxygenated – often featuring furan and butenolide moieties – and biosynthetically related.[2]

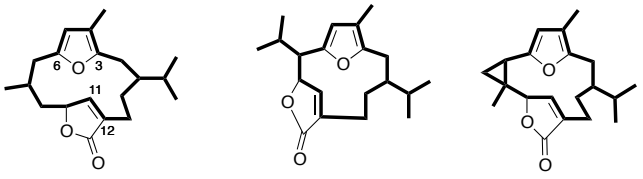
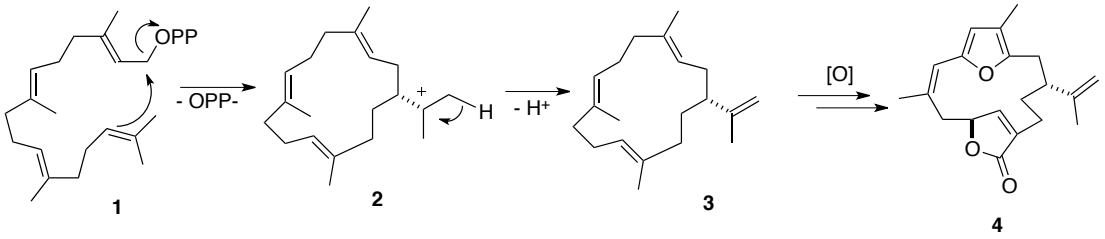


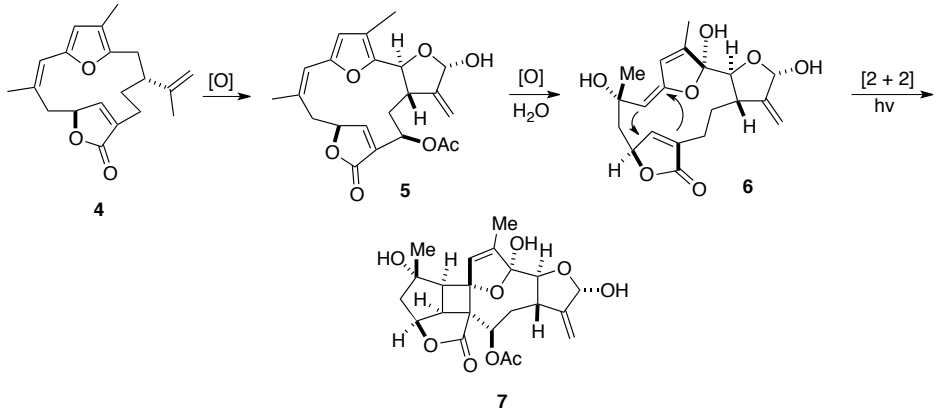
Figure 1: Furanocembranoid skeletons

The proposed biosynthesis of the furanocembranoid ring system begins with geranylgeranyl diphosphate **1**. Cyclization leads to generation of the cembrane skeleton, which upon deprotonation, forms neocembrane **3**. Subsequent oxidation promotes formation of rubifolide **4**, a supposed precursor for more complex furanocembranoids.[2]



Scheme 1: Conversion of geranylgeranyl (**1**) diphosphate to rubifolide (**4**).

Trauner has postulated that biosynthesis of bielschowskysin occurs through rubifolide **4**. Advancement to intermediate **5** is accomplished through various oxidative processes. Further oxidation and hydration generates compound **6** which undergoes [2+2] photocycloaddition to yield the natural product.[2]



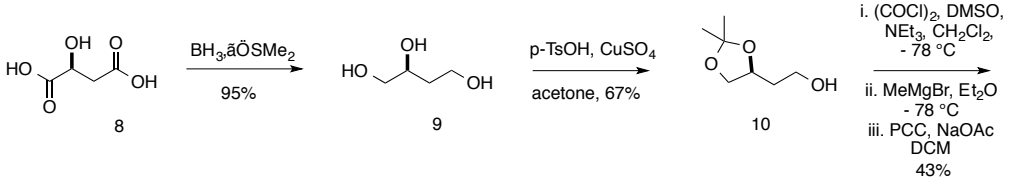
Scheme 2: Proposed biosynthesis of bielschowskysin (**7**).

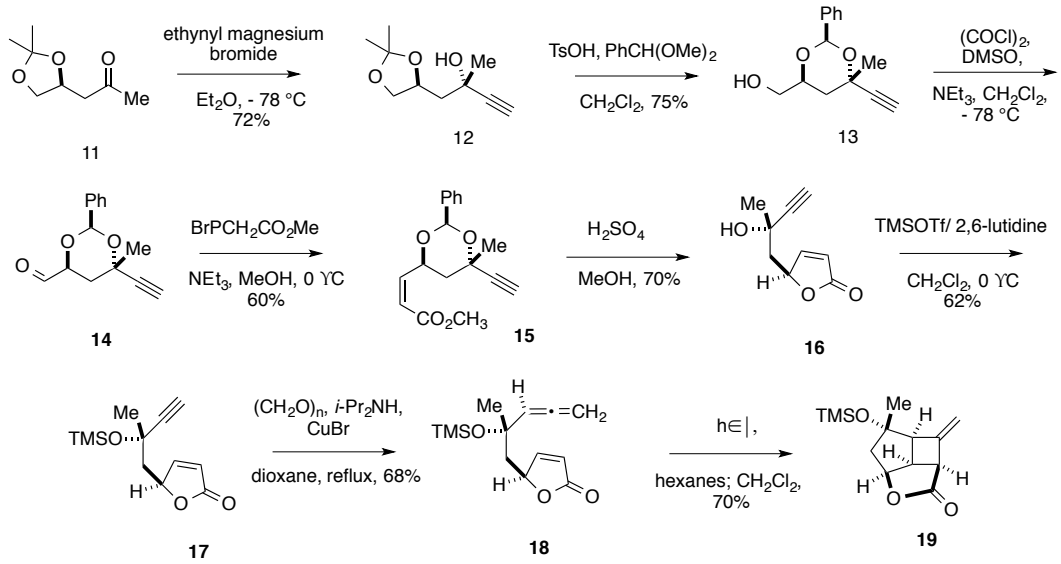
Alternate Routes

Due to its structural complexity, bielschowskysin has proven an interesting yet elusive target. Several groups, in addition to ours, have undertaken a total synthesis program. A noteworthy point of divergence among these routes is the manner in which the core cyclobutane functionality is installed.

Similar to our route, Lear proposes a transannular [2+2]-photocycloaddition between an allene and a butenolide.[3] In order to investigate the feasibility of this transformation, the group implemented a model system.

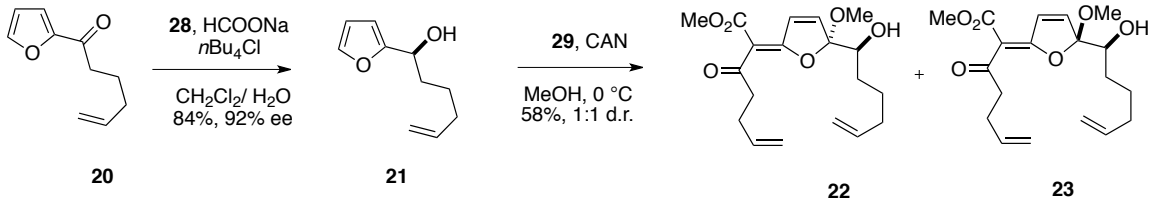
Malic acid was reduced to triol **9** and converted to acetonide **10**. Swern oxidation of the primary alcohol, addition of methyl magnesium bromide, and subsequent oxidation afforded methyl ketone **11**. Ethynyl magnesium bromide addition resulted in tertiary alcohol **12**, which underwent transketalization to the benzylidene acetal. Oxidation of the primary alcohol to the aldehyde followed by Wittig homologation yielded the predominately cis α,β-unsaturated ester **15**. Upon treatment with sulfuric acid, the diol was liberated and spontaneously formed butenolide **16**. Reaction of silyl ether **17** with paraformaldehyde gave photocycloaddition precursor **18**. Upon irradiation in a solution of hexanes and dichloromethane, the allene butenolide was converted to cyclobutane **19**. As of yet, there have been no reports of this methodology being employed in a transannular setting.

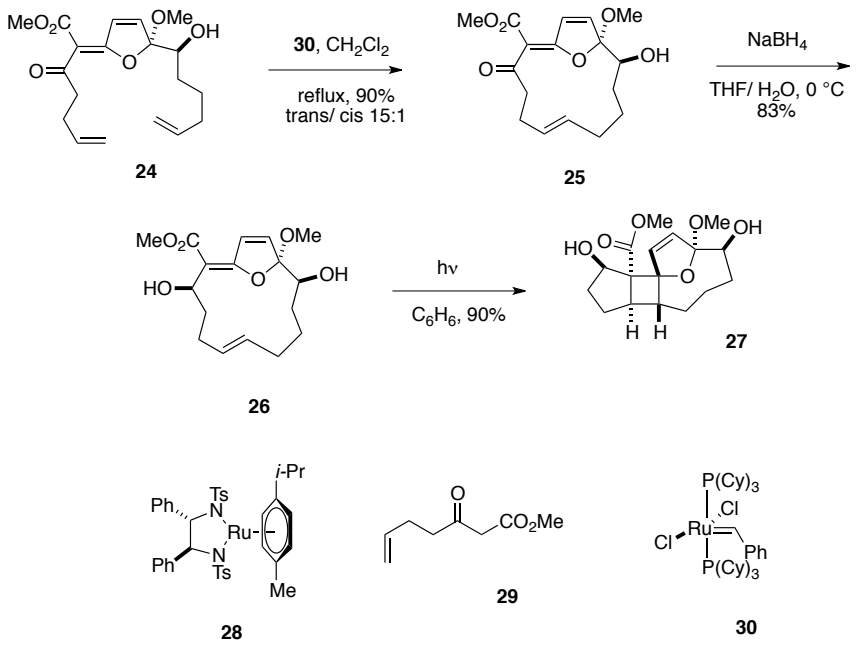




Scheme 3: Lear's Route.

Nicolaou and coworkers also favored a photochemical approach. They are able to access the [9.3.0.0] tetradecane ring system (**27**, Scheme **4**) of bielschowskysin in five steps starting with furan **20**.[4] Noyori reduction to the alcohol followed by CAN mediated coupling with β-ketoester **30** yields compound **21** as a mixture of C3 epimers, **22** and **23**. Grubbs ring closing metathesis of **22** produced macrocycle **24**, with the newly formed olefin in a predominately trans orientation. Attempted photocycloaddition with this substrate was unproductive. In an effort to render the olefin of the enol ether more reactive, ketone **25** was reduced to the allylic alcohol **26**. Irradiation of **26** resulted in **27** as a single diastereomer.

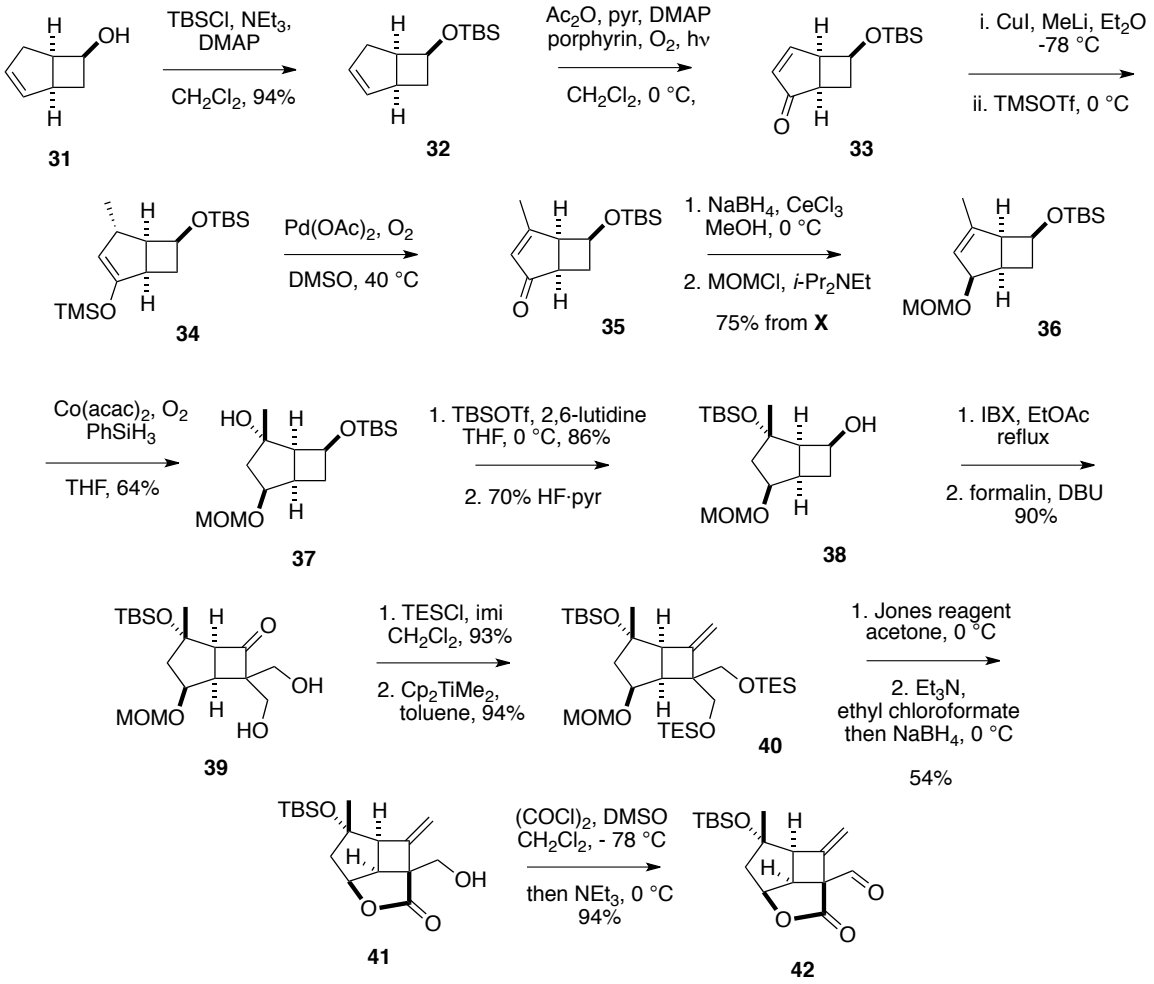




Scheme 4: Nicolaou's Route.

Mulzer opted for a non-photochemical approach and began his synthesis with known bicyclic alcohol **31**.[5] Silyl ether **32** was converted to enone **33** via photooxygenation. Conjugate addition of a methyl cuprate followed by silyl ether formation and Saegusa oxidation yielded **35**. Luche reduction and MOM-protection afforded compound **36**, which underwent Mukaiyama-Isayama reaction to the tertiary alcohol. Silyl protection, selective deprotection yielded alcohol **38**. Oxidation and alkylation at the α-position with formalin generated the quaternary carbon of the molecule. TES protection of the primary alcohols and treatment with Petasis' reagent gave methylene **40**. Exposure to Jones reagent resulted in tandem liberation of the primary alcohols and oxidation to the dicarboxylic acid. MOM deprotection was accompanied by lactone formation. Selective reduction of the remaining carboxylic acid

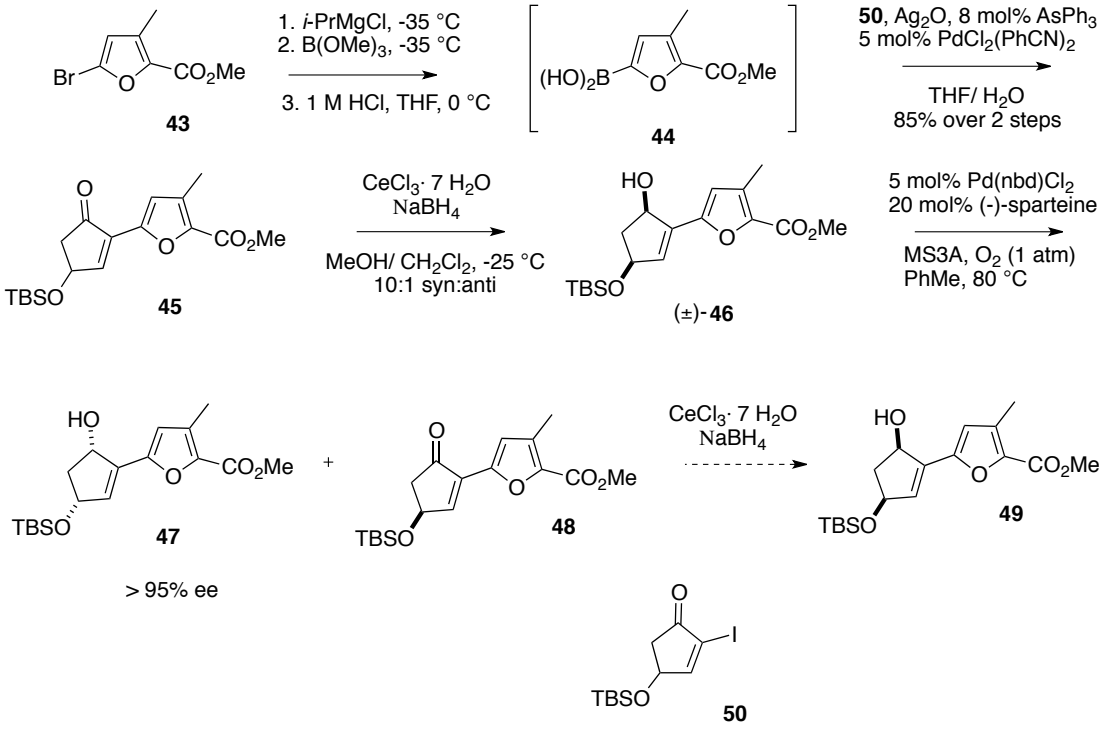
and subsequent oxidation to the aldehyde produced **43**, establishing the eastern portion of bielschowskysin.



Scheme 5: Mulzer's Route.

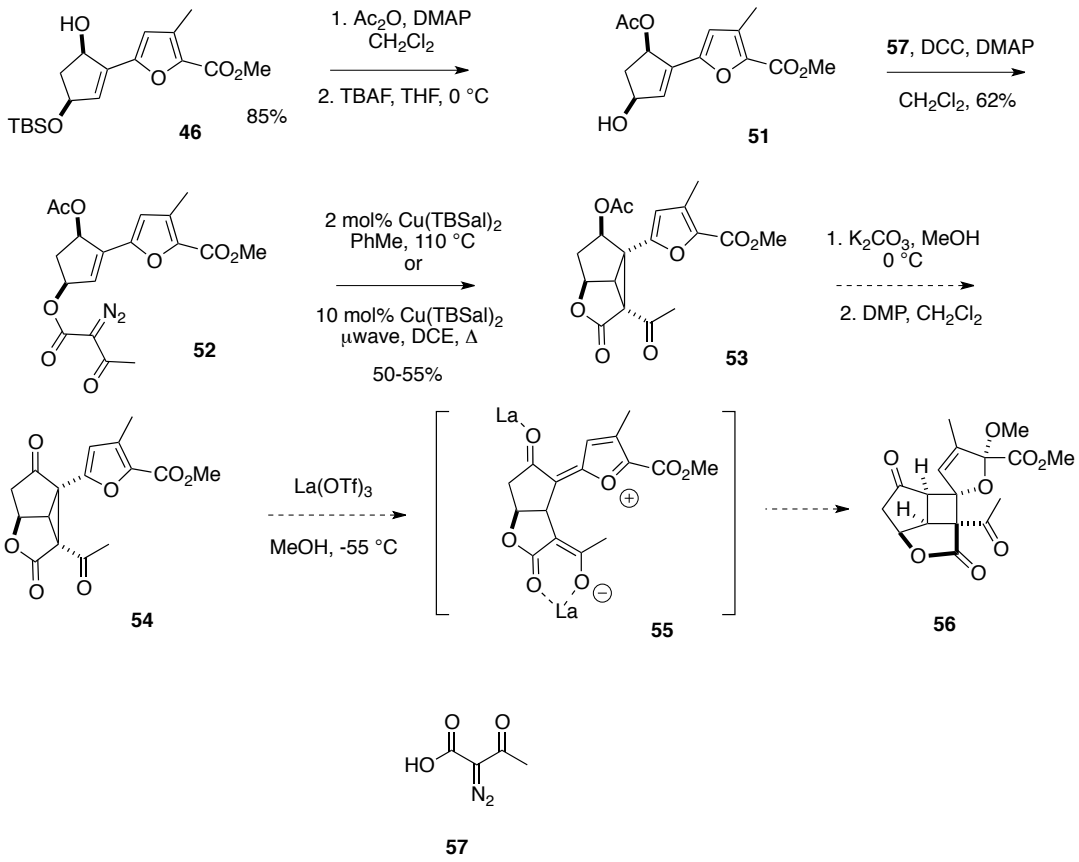
Stoltz and coworkers propose a tandem cyclopropane fragmentation/ Michael addition of intermediate **54** to arrive at **56**. To this end, furan **43** was converted to the boronic acid and coupled with iodide **50**.[6] The group later found that the electron deficient olefin of the enone precluded cyclopropane formation. Thus, ketone **45** was selectively reduced to afford allylic alcohol **46**. This substrate is amenable to an oxidative

kinetic resolution protocol developed in Stoltz's lab. Notably, either enantiomer could be accessed from this method.



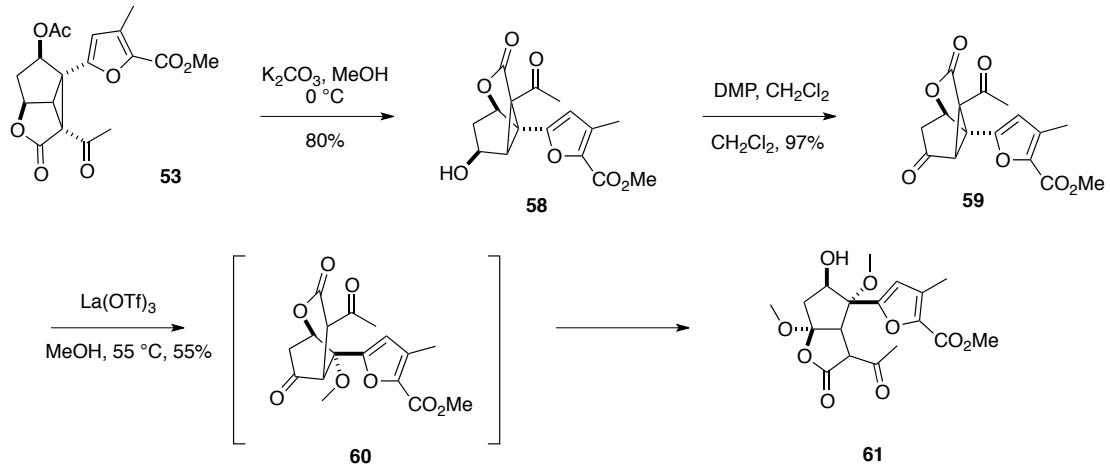
Scheme 6: Stoltz's synthesis of enantiomeric alcohols **(47)** and **(48)**.

Furan **46** was then acylated and coupled with a novel diazoacetoacetic acid reagent. Cyclopropanation with $Cu(TBSal)_2$ afforded **53**. They envisioned acetate removal, followed by oxidation with Dess Martin periodinane would arrive at key intermediate **54**, which would undergo furan-assisted cyclopropane cleavage and subsequent Michael addition yielding the substituted cyclobutane.



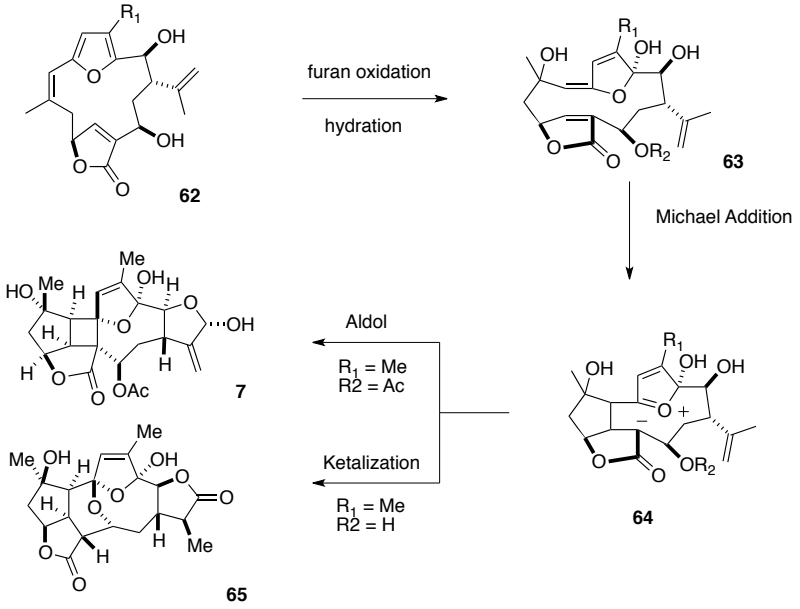
Scheme 7: Stoltz's approach to cyclobutane (**56**).

However, when intermediate **53** was subjected to acetate removal, a drastically different compound, lactone **61**, was obtained. Stoltz postulated that upon acetate cleavage of **53,** intramolecular trans-lactonization affords **58**. Oxidation of the free alcohol at C5, results in **59**. Lewis acid promoted cleavage followed by addition of methanol yields intermediate **60**. Conversion of the cyclic ketone to the hemiacetal via addition of methanol initiates a second trans –esterification to arrive at **61**.



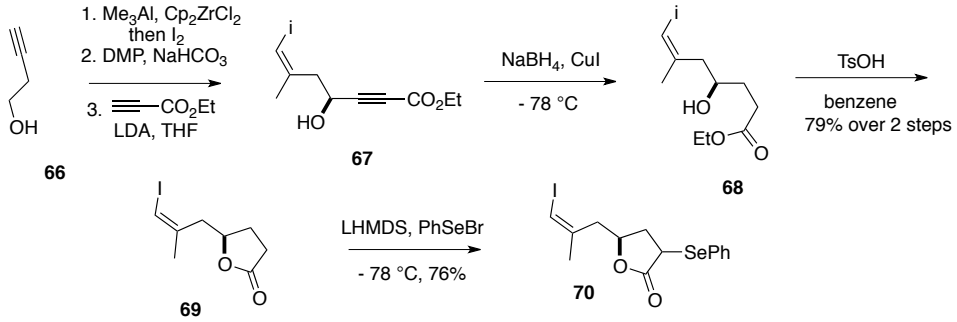
Scheme 8: Stoltz's route to unexpected compound (**61**).

Theodorakis proposes a novel biomimetic synthesis of bielschowskysin via cembrenolide **62**.[7] He postulates that hydration, oxidation, and subsequent Michael addition of this cembrenolide should lead to an intermediate that can undergo either aldol closure to arrive at bielschowskysin or ketalization to arrive at verrillin.



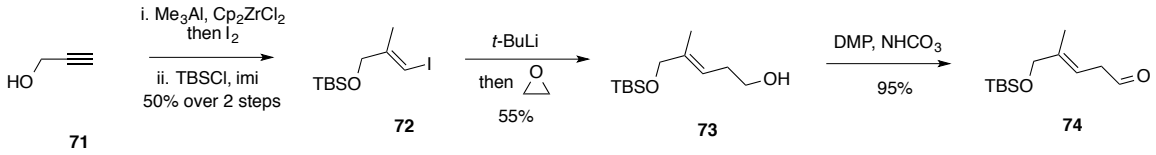
Scheme 9: Theoretical approach to verrillin and bielschowskysin.

The C7-C12 fragment of the cembrenolide was synthesized from butynol **66**. Conversion to ester **67** was accomplished in three steps. Copper mediated reduction of the alkyne followed by acid-induced cyclization afforded lactone **69**. Treatment with LHMDS and PhSeBr effected selenation at the alpha position.



Scheme 10: Theodorakis' synthesis of the C7–C12 fragment.

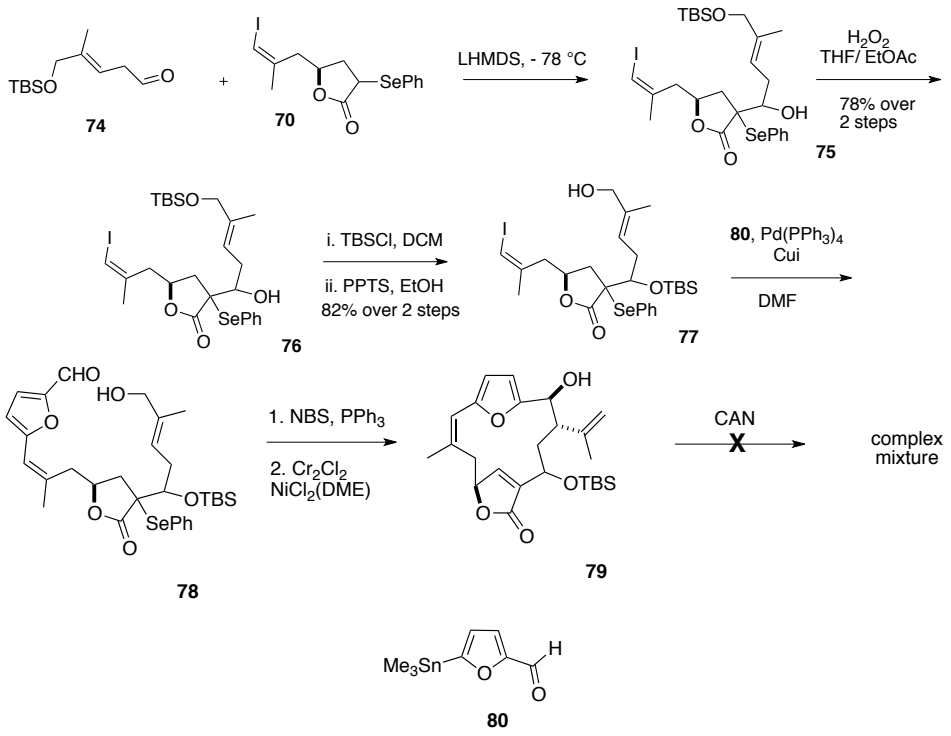
Methyl zirconation and iodination of propargyl alcohol followed by silylation yielded vinyl iodide **72**. Lithium halogen exchange and addition of oxirane resulted in homoallylic alcohol **73** which was further oxidized to the aldehyde completing the C1 – C13 fragment of the cembrenolide intermediate.



Scheme 11: Theodorakis' synthesis of the C1–C13.

Coupling of the two fragments and oxidation/ elimination of the selenide moiety proceeded to give butenolide **75** as a mixture of diastereomers. Silyl protection followed

by selective deprotection gave primary alcohol **76**. Coupling of fufural **80** and iodide **77** was accomplished via a modified Stille. Appel reaction of the allylic alcohol resulted in formation of the bromide, which underwent NHK cyclization to macrocycle **79**. However, attempted oxidation of the furan moiety with CAN led to a complex mixture of products rather than enol ether **63**.



Scheme 12: Theodorakis' completion of route to common intermediate (**79**)

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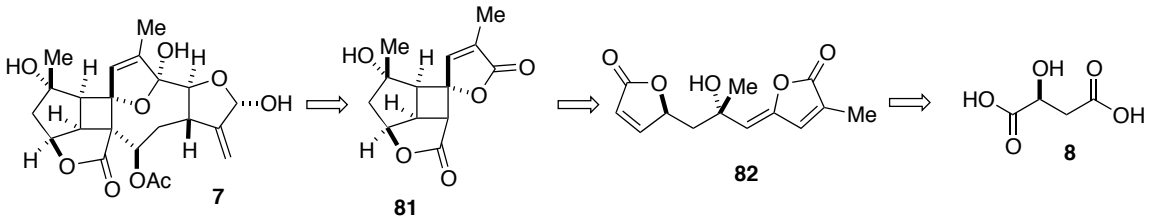
CHAPTER II

CURRENT PROGRESS

Sulikowski Route

Initially, efforts toward the molecule centered on construction of the tetracyclic core. With this strategy in mind, bis-butenolide **82** was envisioned as a precursor to cyclobutane **81** via a [2+2] photocycloaddition. The required bis-butenolide could ultimately be derived from (-)-malic acid.



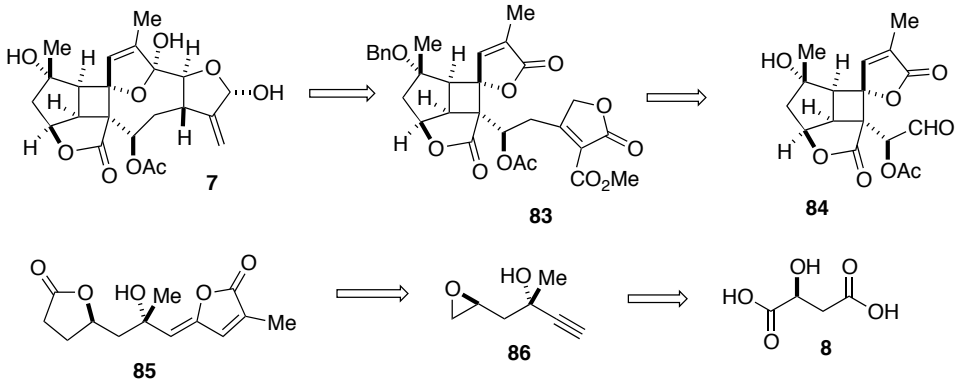
Scheme 13: Retrosynthetic analysis of bielschowskysin (**7**).

In a 2006 manuscript, Doroh and Sulikowski disclosed the synthesis of intermediate **82** and its subsequent photocyclization to cyclobutane **81**.[8] Irradiation of an acetone solution of bis-butenolide **9** resulted in a 5:1 mixture of [2+2] photoadducts with the major product having the desired stereochemistry. Stereochemical assignments were confirmed by NOE and single-crystal x-ray analysis.

With an established protocol for the [2+2] photocycloddition, the group's focus shifted to synthesis of an α–substituted butenolide which would provide a handle for elaboration of the eastern portion of the molecule. After several failed attempts to install

the substituted butenolide directly, the group resorted to Grieco's method of selenation-oxidation, accessing this moiety through lactone **85**.[9]

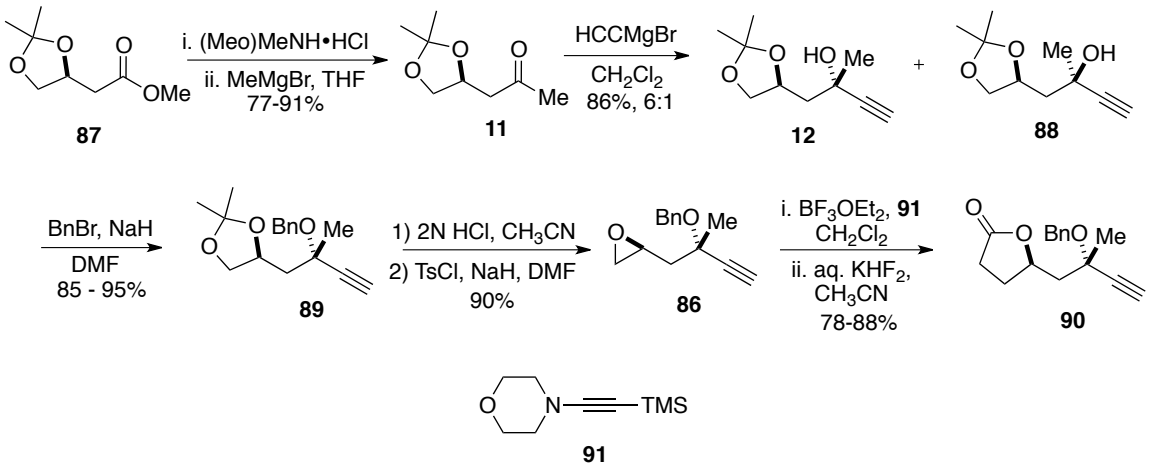
In a revised synthetic analysis, it was envisioned that formation of the macrocycle would arise from an intramolecular vinylogous aldol reaction of **83**. Aldehyde **84** would enable installation of the required butenolide for this key reaction. The photocycloaddition precursor could be accessed from lactone **85**, which could be derived from epoxide **86**. As before (-)-malic acid would serve as the starting point of the synthesis.



Scheme 14: Revised synthetic analysis of bielschowskysin (**7**).

Dr. Steve Townsend developed the route to advanced intermediate **84**. At the outset of the synthesis, (-)-malic acid was converted to methyl ester **87** in three steps via a protocol reported by Saito.[8, 10] Formation of the Weinreb amide and subsequent reaction with methyl Grignard generated ketone **11**.[11] Chelation-controlled addition of ethynyl magnesium bromide resulted in a 6:1 mixture of tertiary alcohols **12** and **88**, with the major product having the desired 1,3 anti-oxygenated relationship observed in bielschowskysin.[12, 13] Subsequent benzyl protection of the free alcohol gave benzyl ether

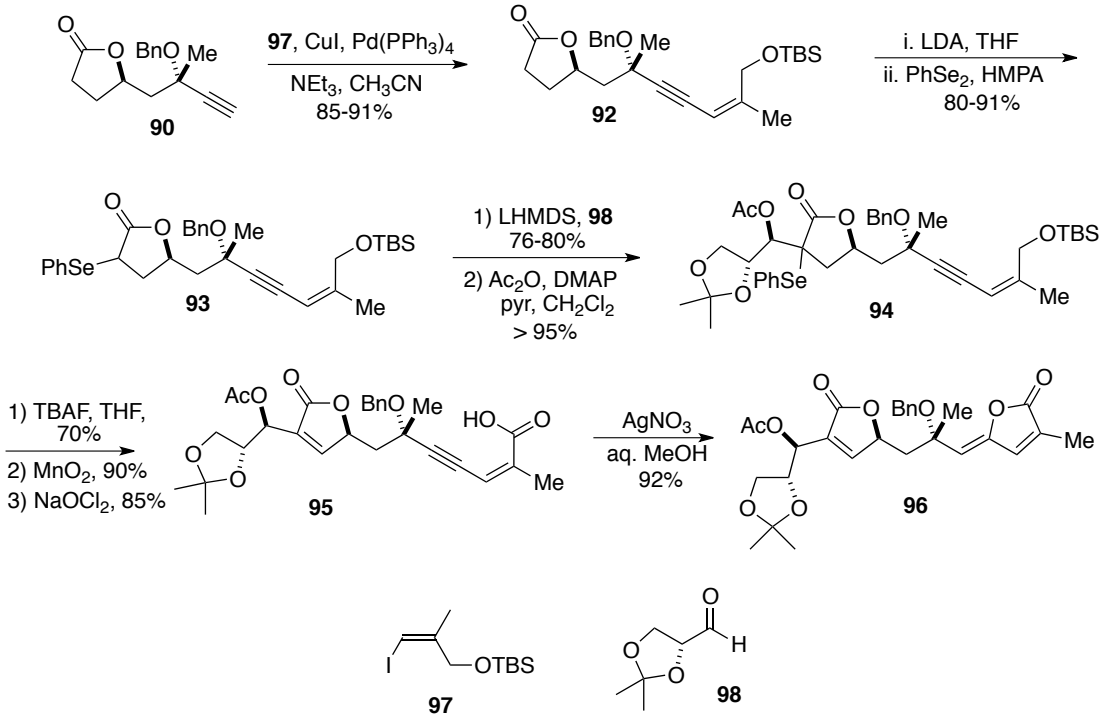
89. Exposure to acid liberated the diol, which upon addition to a slurry of sodium hydride and tosyl chloride resulted in concomitant formation of epoxide **86**[14, 15] The action of ynamine **91** on the epoxide followed by desilylation gave lactone **90** in 88% yield.[16]



Scheme 15: Synthesis of lactone (**90**).

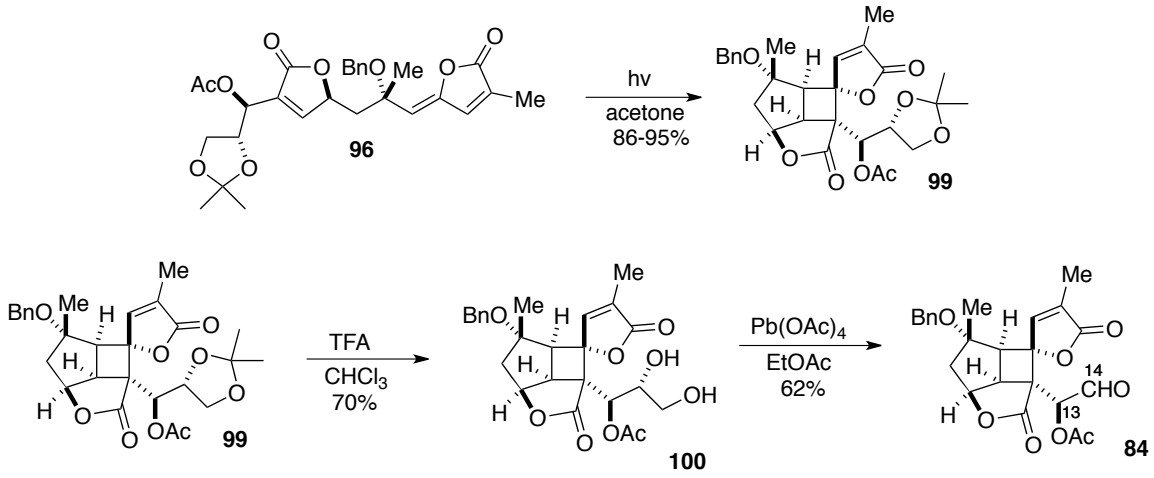
With formation of the lactone complete, the synthesis was directed toward extension of the carbon chain for construction of the alkylidene butenolide. Sonogashira coupling of alkyne **90** and vinyl iodide **97** resulted in enyne **92**.[17, 18] Generation of the lithium enolate of **92** followed by addition of diphenyl diselenide resulted in **93**. In the same manner, conversion to the disubstitued lactone was achieved upon aldol reaction with D-glyceraldehyde acetonide (**98)**, producing the aldol adduct as a single diastereomer. Acylation was followed by TBAF deprotection and allylic oxidation to the aldehyde. Pinnick oxidation simultaneously resulted in conversion of the aldehyde to the carboxylic acid and oxidative elimination of the phenyl selenoxide to give the butenolide.

Completion of photocycloadditon precursor **96** was realized upon silver catalyzed cycloisomerization of acid **95**.[19, 20]



Scheme 16: Synthesis of bis-butenolide (**96**).

Using the previously established protocol for the [2+2] photocycloaddition, irradiation of bis-butenolide **96** in acetone afforded cyclobutane **99** as a single isomer.[8] Subsequent TFA removal of the acetonide and lead tetraacetate cleavage of the resultant diol provided aldehyde **84**. With the aldehyde in place, our focus shifted to functionalization of the eastern portion of the molecule and pursuit of an end-game strategy for bielschowskysin.

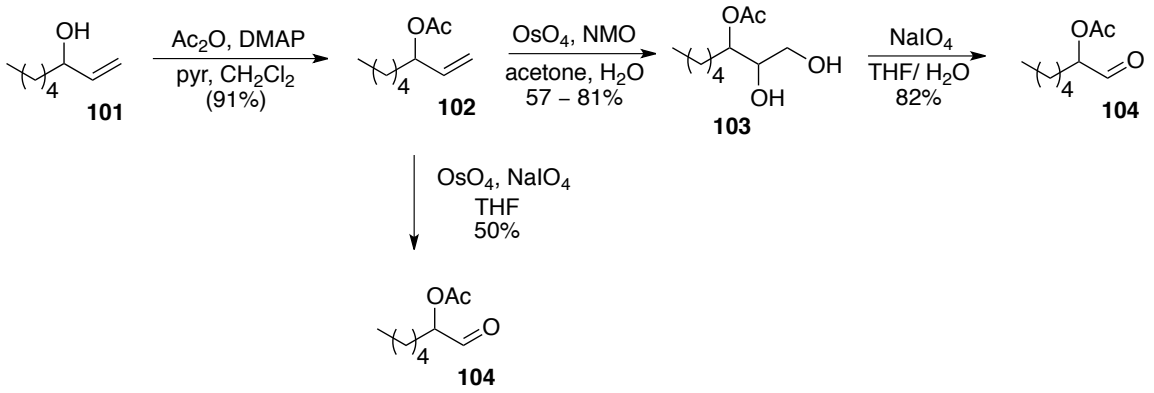


Scheme 17: Synthesis of advanced intermediate (**84**).

Model System

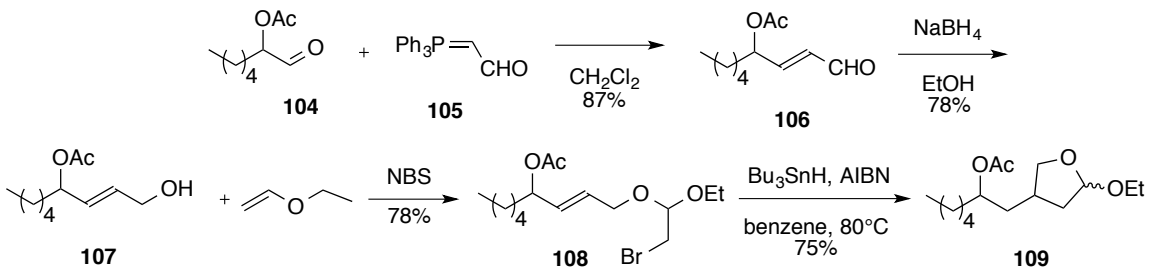
To complete our synthetic vision of a vinylogous aldol to install the C2, C3 bond, a final butenolide must be constructed from aldehyde **12**. In the interest of conserving valuable material, a model system was adopted to develop methodology before applying it to any advanced intermediates.

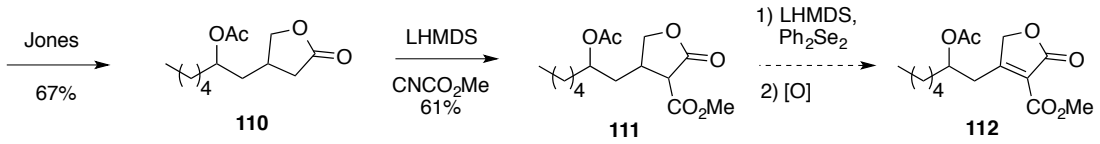
Octenol, **101**, serves as the starting point of our exploratory synthesis. The alcohol was smoothly converted to ester **102**. Lemieux Johnson oxidation resulted in aldehyde **104** in modest yield.[21] The aldehyde was also obtained via a separate dihydroxylation/ sodium periodate cleavage pathway, a route more consistent with the reactions to be applied to the actual system.[22] At this point the model system resembles C13 and C14 of intermediate **84**.



Scheme 18: Synthesis of aldehyde (**104**).

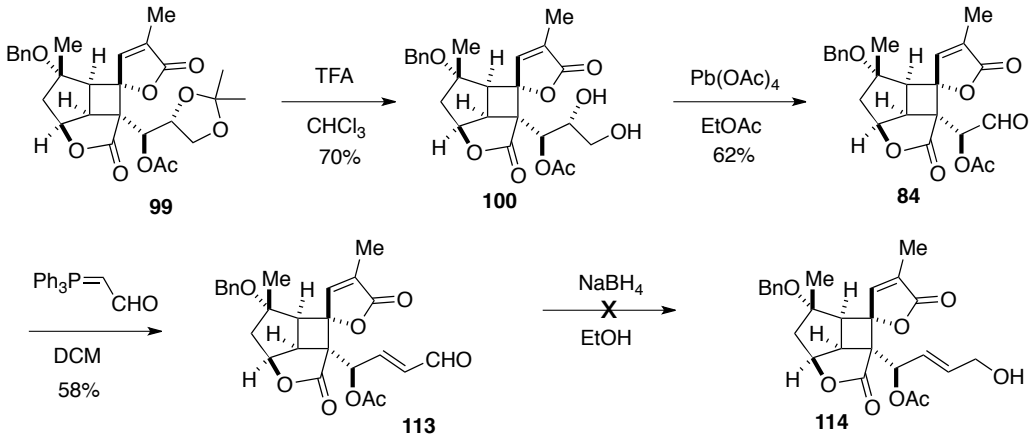
Wittig olefination with triphenyl phosphorane **105** afforded homologated aldehyde **106**. Sodium borohydride reduction resulted in allylic alcohol **107**, an important intermediate allowing for synthetic divergence within the model system. Transformation of **107** to bromoacetal **108** was accomplished with NBS and neat ethyl vinyl ether. Employing a protocol established by Stork, radical cyclization of the bromoacetal was observed upon reflux with Bu_3SnH and AIBN in benzene for five hours.[23] Jones' oxidation of the lactol yielded lactone **110**. Subsequent enolization and reaction with Mander's reagent provided the substituted lactone. Presumably, selenation followed by oxidation elimination would provide butenolide **112**. Satisfied with the preliminary findings of the model system, we shifted our efforts toward scale-up of material and application of the newly explored chemistry to the front end.





Scheme 19: Synthesis of butenolide (**112**).

Aldehyde **84** was converted to α,β-unsaturated aldehyde **113** without incident. However, attempted reduction to the allylic alcohol resulted in decomposition.

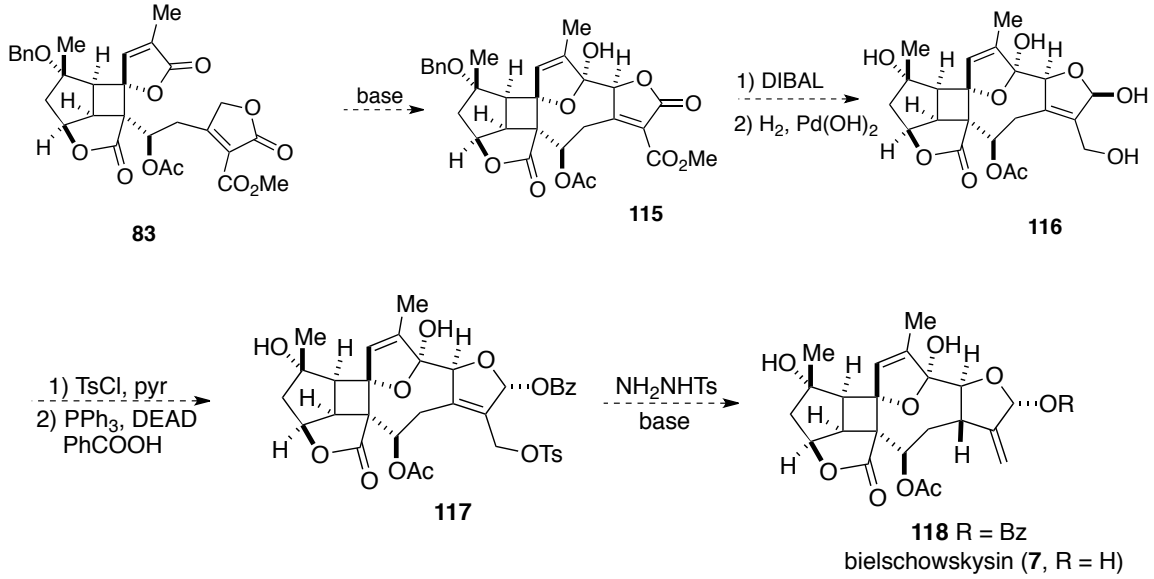


Scheme 20: Application of model system chemistry to front end.

Future Plans

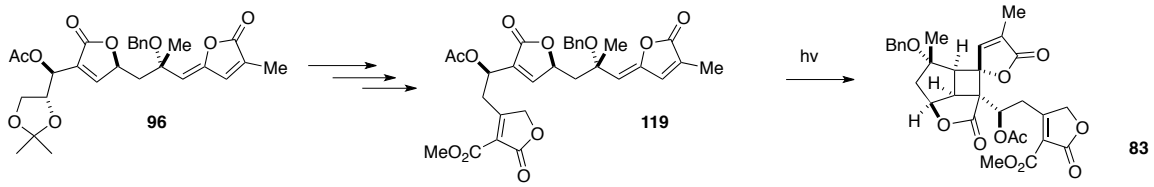
Once intermediate **84** is advanced to butenolide **83**, we will turn our attention to the completion of the molecule. We propose deprotonation at C2 will lead to a vinylogous aldol reaction resulting in formation of macrocycle **115**. DIBAL reduction and subsequent hydrogenation is expected to provide lactol **116**. Tosylation of the free primary alcohol followed by Mitsunobu reaction should correct the stereochemistry at C16. Subsequent reaction of **117** with p-toluensulfonyl hydrazide is expected to install

the exocyclic olefin and trans ring juncture simultaneously via an intermediate diazene.[24] Finally benzoate removal will result in bielschowskysin, **7**.



Scheme 21: Bielschowskysin end-game strategy.

In an alternate strategy, we envision advancing bis-butenolide **96** to tris-butenolide **119** via the model system chemistry and then attempting the photocycloaddition.

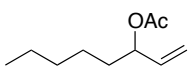


Scheme 22: Proposed conversion to tris-butenolide **119**.

Experimental Methods

General. All non-aqueous reactions were performed under an argon atmosphere in oven-dried glassware. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Diethyl ether (Et_2O), acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), and dimethylformamide (DMF) were obtained by passing commercially available formulations through activated alumina columns (MBraun MB-SPS solvent system). Tetrahydrofuran (THF) was obtained by distillation from benzophenone-sodium. Triethylamine (Et_3N) and diisopropylamine were distilled from calcium hydride and stored over potassium hydroxide. Reactions were monitored by thin-layer chromatography (TLC) using E. Merck precoated silica gel 60 F254 plates. Visualization was accomplished with UV light and aqueous stain followed by charring on a hot plate. Flash chromatography was conducted using the indicated solvents and silica gel (230-400 mesh). Yields refer to chromatographically and spectroscopically homogenous materials. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer and are reported relative to deuterated solvent signals (7.26 and 77.2).

Preparative Procedures



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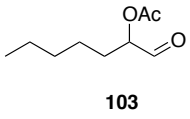
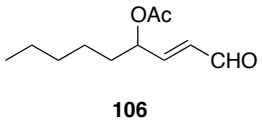
To a solution of alcohol **101** (1.0 eq, 9.5 g, 74.1 mmol) in CH_2Cl_2 (120 mL) at ambient temperature was added pyridine (100 mL), acetic anhydride (60 mL), and DMAP (1 crystal). The reaction was stirred 1 h, washed with 1 N HCl (3 x 50 mL), brine (1 x50 mL), dried (MgSO4), filtered, and concentrated *in vacuo*.

The crude residue was purified by distillation (72-74 °C) to provide acetate **102** (12.0 g, 70.0 mmol, 95%) as colorless oil. Spectral data was consistent with reported values.[25]



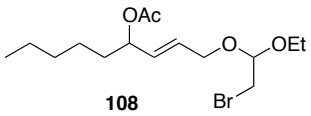
103

To a solution of acetate **102** (1.0 eq, 3.0 g, 17.6 mmol) in THF (90 mL) at ambient temperature was added OsO_4 (1 crystal) and sodium periodate (1.5 eq, 5.7 g, 26.5 mmol) as a slurry in water (25 mL). The reaction was stirred 4 h, diluted with Et_2O (100 mL) and washed with saturated sodium bicarbonate (3 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (7:1 hexanes/ ethyl acetate) to provide aldehyde **104** (1.84 g, 10.7 mmol, 61%) as a colorless oil. Spectral data was consistent with reported values. [25]



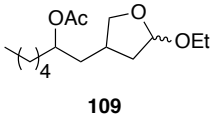
106

To a solution of aldehyde **104** (1.0 eq, 900 mg, 5.2 mmol) in CH_2Cl_2 (50 mL) at ambient temperature was added formylmethylene triphenylphosphorane (1.0 eq, 1.6 g, 5.2 mmol). After warming to reflux, the reaction was stirred 3 h. Celite (1 g) was added and the reaction was concentrated *in vacuo*. The crude residue was purified by column chromatography (4:1 hexanes/ ethyl acetate) to provide aldehyde **106** (680 mg, 3.4 mmol, 66%) as a pale yellow oil. ^{1}H NMR (400 MHz $CDCl_3$): δ 9.7 (d, J = 7.6 Hz, 1H), 6.75 (dd, J = 15.6, 4.8 Hz, 1 H), 6.21 (dd, J = 15.6, 7.6 Hz, 1H), 5.52 (dd, J = 6.8, 5.2, 1H), 2.13 (s, 3H), 1.75-1.69 (m, 2H), 1.44-1.27 (m, 6H), 0.93-0.89 (m, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 192.9, 170.0, 153.9, 131.4, 33.5, 31.3, 24.6, 22.3, 20.9, 13.9.



108

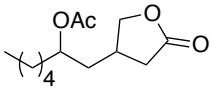
To a solution of aldehyde **106** (1.0 eq, 198 mg, 1 mmol) in EtOH (10 mL) at ambient temperature was added sodium borohydride (1,0 eq, 380 mg, 10 mmol) and the reaction was stirred 1 h. The reaction mixture was concentrated *in vacuo* and the crude residue dissolved in ethyl acetate (10 mL). The organics were washed with water (1 x 10 mL), brine (1 x 10 mL), dried (MgSO4), filtered and concentrated *in vacuo*. The crude alcohol was lowered to – 20 °C. Ethyl vinyl ether (10 eq, 740 mg, 10 mmol) was added and the reaction was allowed to stir 5 minutes. N-bromosuccinimide (1.0 eq, 178 mg, 1 mmol) was added while maintaining an internal temperature below 0 C. After 30 min, hexanes (10 mmol) was added and the reaction filtered through a plug of celite. The organics were washed with 1N HCl (3 x 10 mL), dried (MgSO4), filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (6:1 hexanes/ ethyl acetate) to provide acetal **108** (284 mg, 0.81 mmol, 81%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83-5.68 (m, 2H), 5.27 (dd, *J* = 6.8, 6.4 Hz, 1 H), 4.71 (t, *J* = 5.6 Hz, 1H), 4.19-4.07 (m, 2H), 3.74-3.56 (m, 2H), 3.38 (d, *J* = 5.6 Hz, 1H), 2.06 (s, 3H), 1.66-1.54 (m, 2H), 1.30-1.21 (m, 6H), 0.91-0.88 (m, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 170.3, 131.4, 128.3, 100.9, 73.9, 66.3, 62.4, 34.2, 31.6, 31.4, 24.7, 22.4, 21.2, 15.1, 13.9.



109

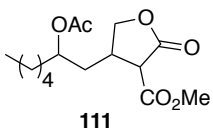
To a solution of bromoacetal **108** (1.0 eq, 40 mg, 0.11 mmol) in benzene (5 mL) was added tributyl tin hydride (1.1 eq, 30 μL, 0.12 mmol). The solution was degassed and then AIBN (1 crystal) was added. Heated to reflux (80 °C). After 3 hours, concentrated *in vacuo*. The residue was dissolved in Et_2O (5 ml), washed 2 x 5 mL 10% KF, dried ($MgSO_4$), filtered through Celite, and concentrated *in*

vacuo. The crude residue was purified by column chromatography (8:1 hexanes/ ethyl acetate) to provide lactol **109** (23 mg, 0.08 mmol, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (s, 1H), 5.12-5.08 (m, 1H), 4.91-4.83 (m, 1H), 3.78 (dt, *J* = 24, 8 Hz, 1H), 3.72 (ddd, *J* = 8, 7, 1 Hz, 1H), 3.47 (m, 2H), 2.35-2.15 (m, 2H), 2.04 (s, 3H), 1.73-1.60 (m, 2H), 1.49-1.43 (m, 4H), 1.30-1.19 (m, 6H), 0,9-0.86 (m, 3H) ^{13}C (100 MHz, $CDCl_3$) δ 170.7, 104.1, 73.4, 73.2, 71.6, 71.5, 39.3, 39.1, 37.3, 37.2, 35.4, 31.2, 24.8, 22.4, 15.1, 13.9.



110

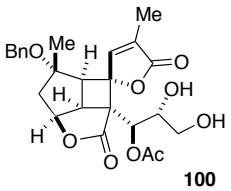
To a solution of lactol **109** (1.0 eq, 80 mg, 0.30 mmol) in acetone (3 mL) added 1 mL of a solution of Jones reagent (1:9 Jones reagent: acetone). The reaction was monitored by TLC. After 30 minutes, the reaction was quenched with ethanol (1 mL). The reaction was diluted with ether (5 mL) and washed with H_2O (1 x 5 mL), sodium bicarbonate (1 x 5 mL), and brine (1 x 5 mL). The organics were dried ($MgSO_4$) and filtered. The crude residue was purified by column chromatography (4:1 hexanes/ ethyl acetate) to provide lactone **110** (50 mg, 0.20 mmol, 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (m, 1H), 4,42 (m, 1H), 3.93 (dd, *J* = 16, 8 Hz, 1H), 2.70-2.55 (m, 2H), 2.21 (dd, *J* = 16, 8 Hz, 2H), 2.06 (s, 3H), 1.73 (m, 2H), 1.58-1.53 (m, 3H), 1.27 (m, 6H), 0.90-0.87 (m, 3H) ^{13}C (100 MHz, $CDCl_3$) δ 176.7, 170.7, 73.2, 72.9, 72.4, 72.1, 37.4, 32.8, 31.5, 24.8, 22.4, 21.1, 13.9.



111

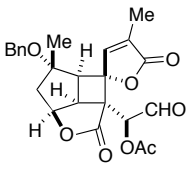
To a freshly prepared solution of LDA (1.0 eq, 0.10 mmol) in THF (1 mL) was added lactone **110 (**1.0 eq, 25 mg, 0.10 mmol**)** at 0 °C. Stirred at 0 °C for 1 hour, then cooled to -78 °C and added HMPA (20 μL) and methyl

cyanoformate (1.0 eq, 10 μL, 0.10 mmol). Stirred 30 min at -78 °C then poured reaction into cold water (1 mL). Extracted (3 x 5 mL) Et_2O, dried ($MgSO_4$), and concentrated with Celite. The crude residue was purified by column chromatography (4:1 hexanes/ ethyl acetate) to provide ester **111** (18 mg, 0.07 mmol, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (m, 1H), 4.46 (t, *J* = 8 Hz, 1H), 3.94 (t, *J* = 8 Hz, 1 H), 3.78 (s, 3H), 3.47 (d, *J* = 8 Hz, IH), 3.15 (dd, *J* = 16, 8 Hz, 1H), 2.43 (s, 3H), 1.78 – 1.74 (m, 2H), 1.35-1.20 (m, 6H), 0.90-0.88 (m, 3H).



100

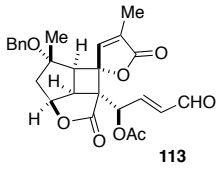
To a solution of acetonide **99** (1.0 eq, 5 mg, 10 μmol) in $CDCl_3$ (600 μL) in an NMR tube was added 1 drop of trifluoroacetic acid. Reaction progress was monitored by NMR. After 1 hour, the reaction was concentrated *in vacuo* and the crude residue was purified by column chromatography (1:1 hexanes/ ethyl acetate) to provide diol **100** (2 mg, 4.0 μmol, 50%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 5H), 6.95 (d, *J* = 1.5 Hz, 1H), 5.69 (d, *J* = 4, 1 Hz, 1H), 5.33 (td, *J* = 11.4, 4 Hz, 1H), 4.37 (dd, *J* = 18, 11.2 Hz, 2H), 4.14 (dd, *J* = 14, 6.7 Hz, 1H), 3.95 (m, 1H), 3.68-3.63 (m, 2H), 3.55 (dd, *J* = 7.8, 1.5 Hz, 1H), 3.35 (t, *J* = 8 Hz, 1H), 3.15 (t, *J* = 6 Hz, 1H), 2.90 (ddd, *J* = 10, 8, 1.8 Hz, 1H), 2.15 (s, 3H), 2.05 (d, *J* = 1.8 Hz, 1H), 1.95 (s, 3H), 1.34 (s, 3H).



84

To a solution of diol **100** (1.0 eq, 3 mg, 6.0 μmol) in ethyl acetate (500 μL) at ambient temperature was added lead tetraacetate (3 mg). After 30 min, filtered reaction through a plug of celite and obtained aldehyde **84** (2 mg, 4 μmol, 75%) as a pure white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H),

7.38-7.31 (m, 5H), 7.02 (d, *J* = 1.4 Hz, 1H), 5.76 (s, 1H), 5.35 m, 1H), 4.37 (dd, *J* = 19, 11.4 Hz, 2H), 4.14 (dd, *J* = 14, 7 Hz, 1H), 3.59-3.51 (m, 2H), 2.90 (ddd, *J* = 10, 8, 2 Hz, 1H), 2.23 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H).



113

To a solution of aldehyde **84** (1.0 eq, 3 mg, 7.0 μmol) in CH_2Cl_2 (1 mL) was added formylmethylene triphenylphosphorane (1.0 eq, 2 mg, 7.0 μmol). The reaction was heated to reflux (40 °C). After 2 hours, concentrated reaction with Celite and purified residue by column chromatography (1:1 hexanes/ ethyl acetate) to provide aldehyde **113** (2 mg, 4.0 μmol, 61%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, *J* = 7.6 Hz, 1H), 7.38-7.31 (m, 5H), 7.02 (d, *J* = 1.4 Hz, 1H), 6.73 (dd, *J* = 15, 6 Hz, 1H), 6.29 (dd *J* = 15.7, 6.7 Hz, 1H), 6.1 (d, *J* = 5.1 Hz, 1H), 5.29-5.25 (m, 1H), 4.35 (dd, *J* = 20, 11.3 Hz, 1H), 2.87 (dd, *J* = 16, 8 Hz, 1H), 2.16 (s, 3H), 1.91 (s, 3H), 1.5 (s, 3H).

Appendix A:

Spectra of Relevant Compounds

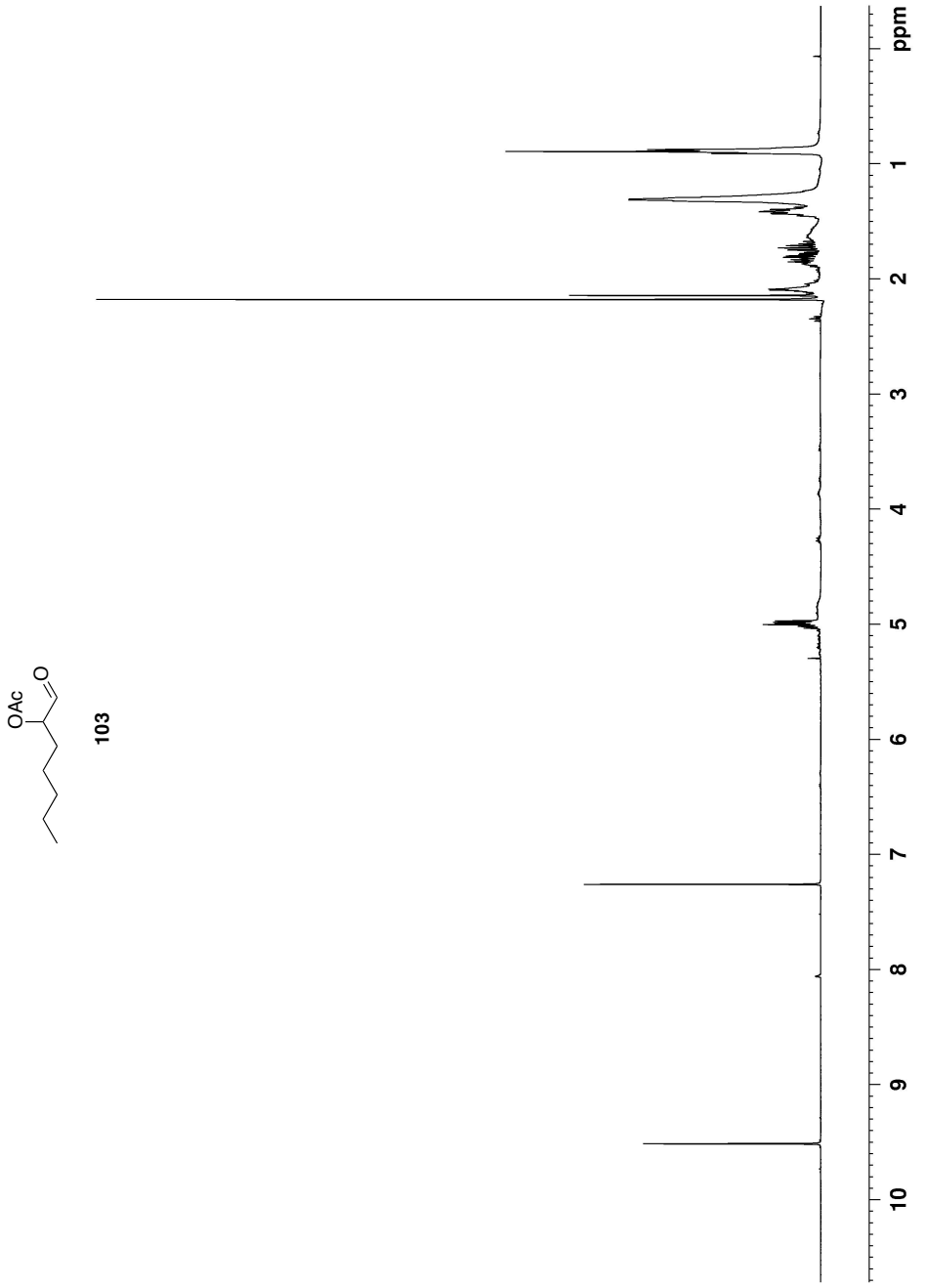


Figure A1 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **103**

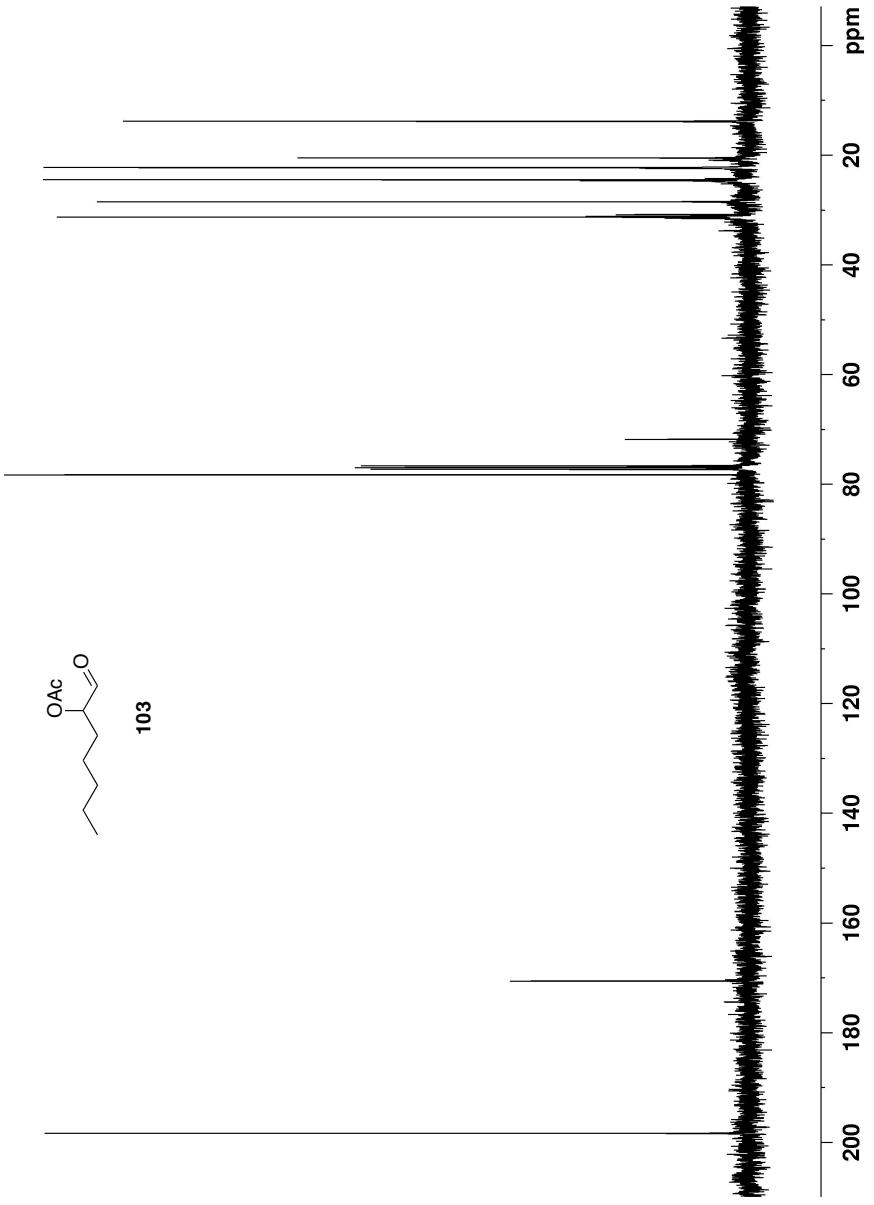


Figure A2 ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **103**

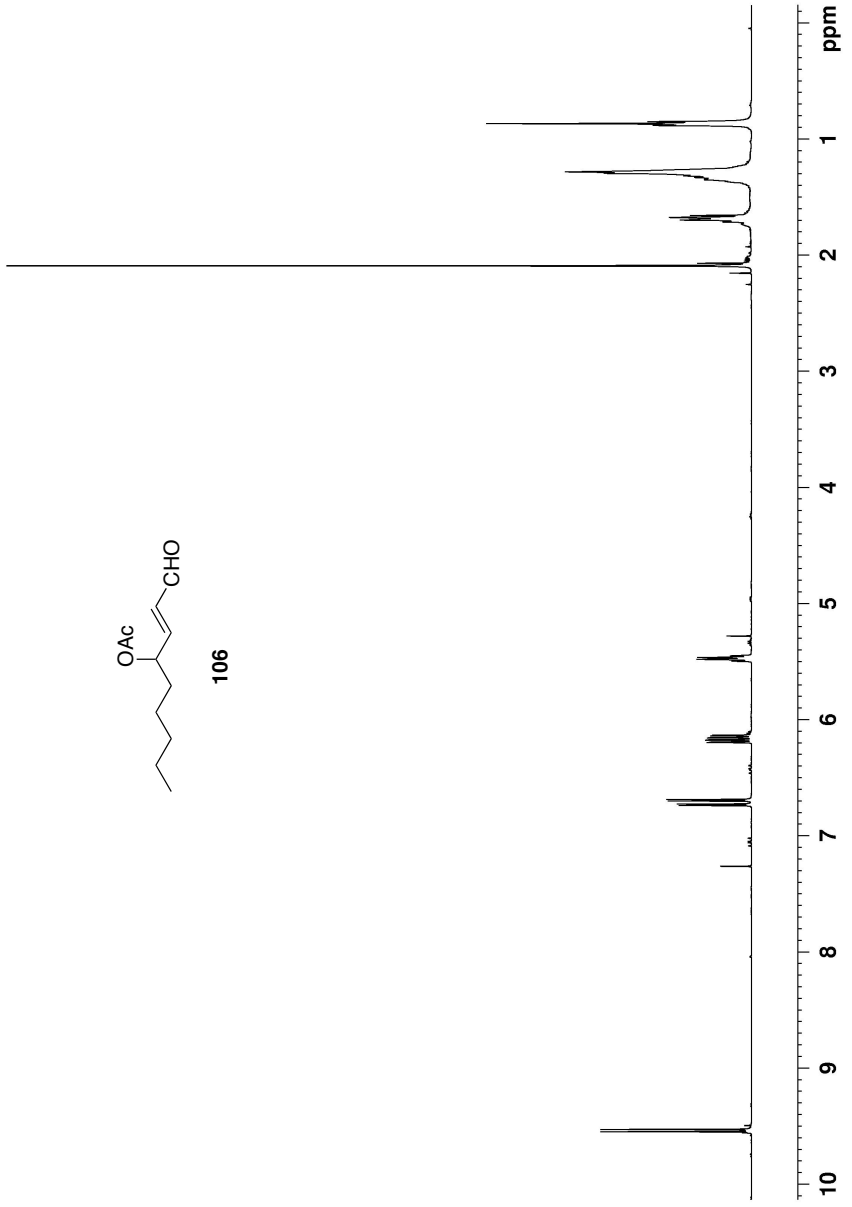


Figure A3 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **106**

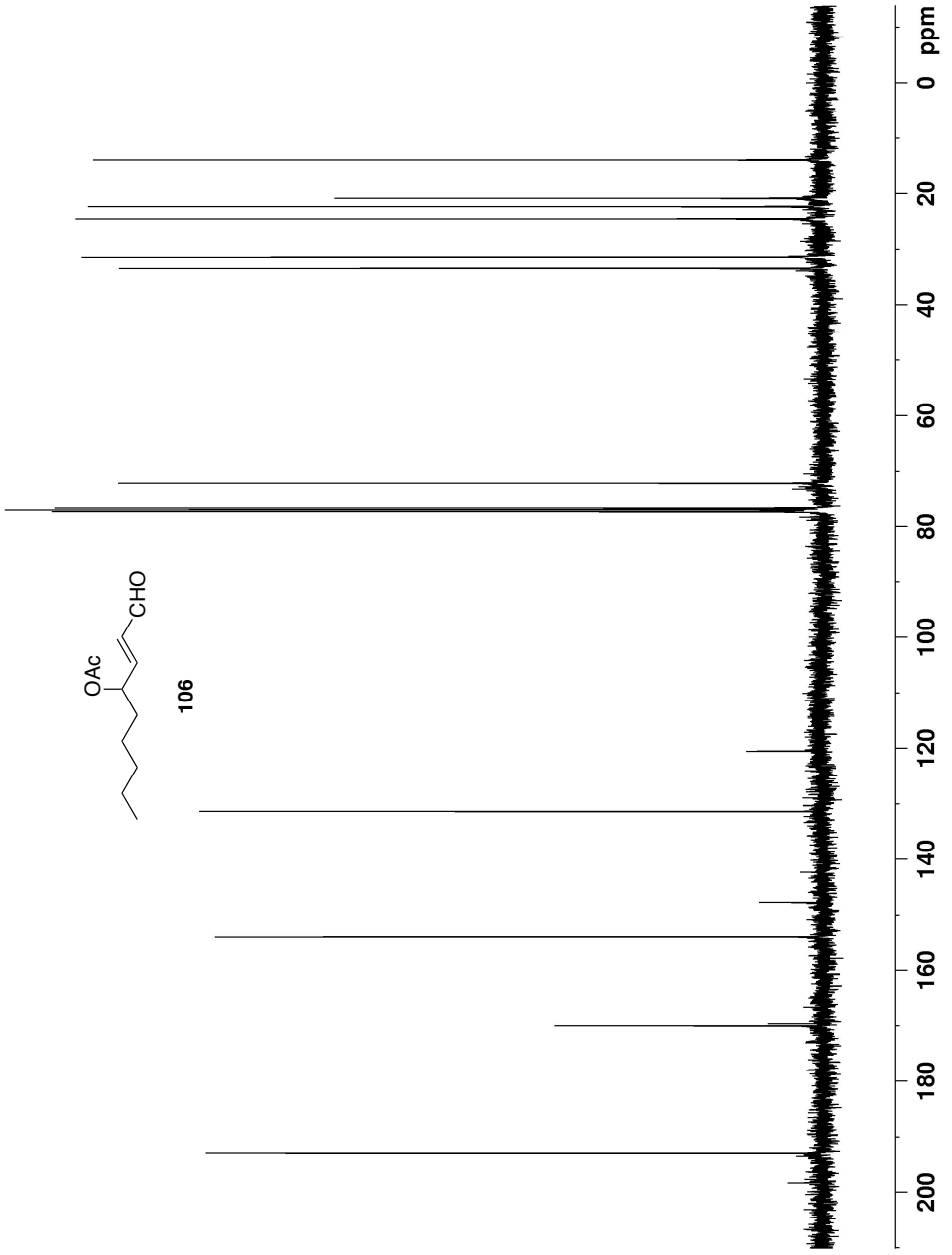


Figure A4 ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **106**

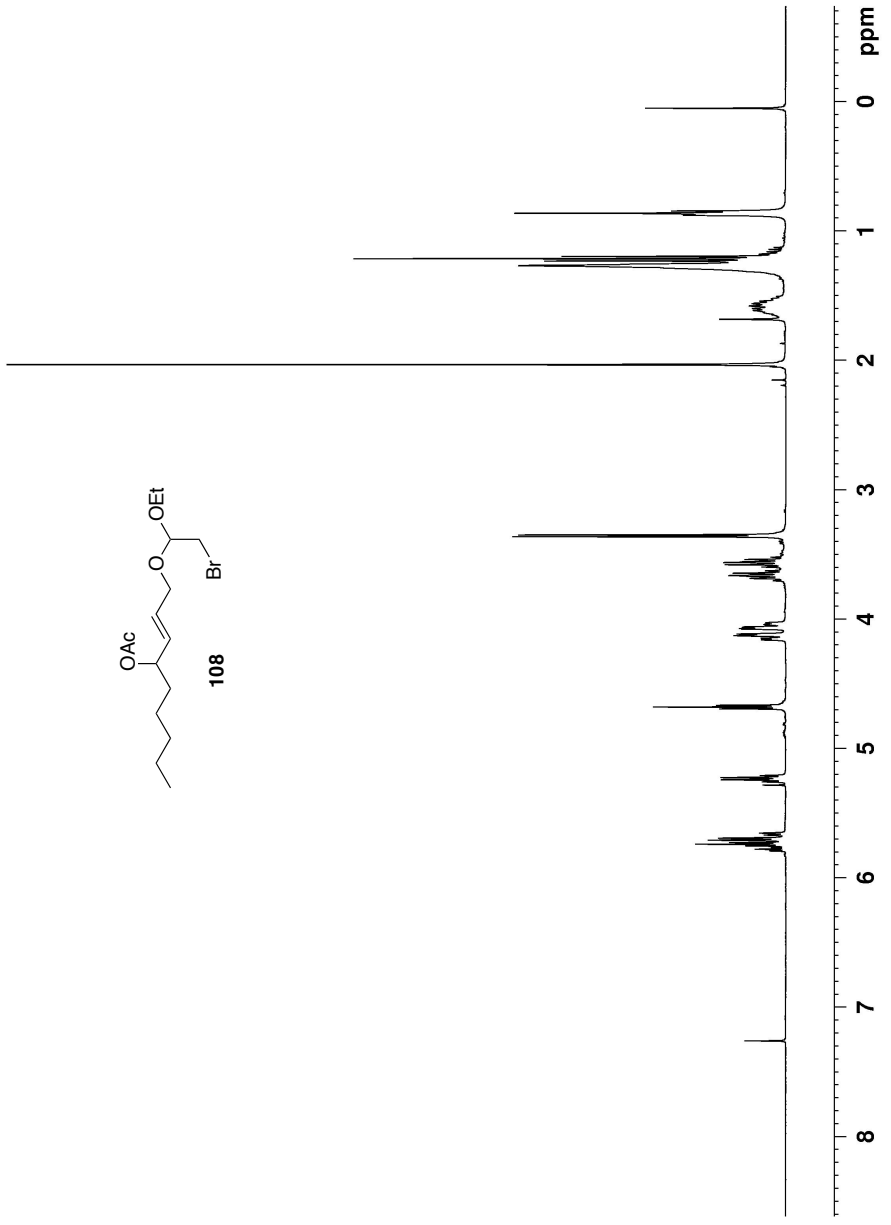


Figure A5 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **108**

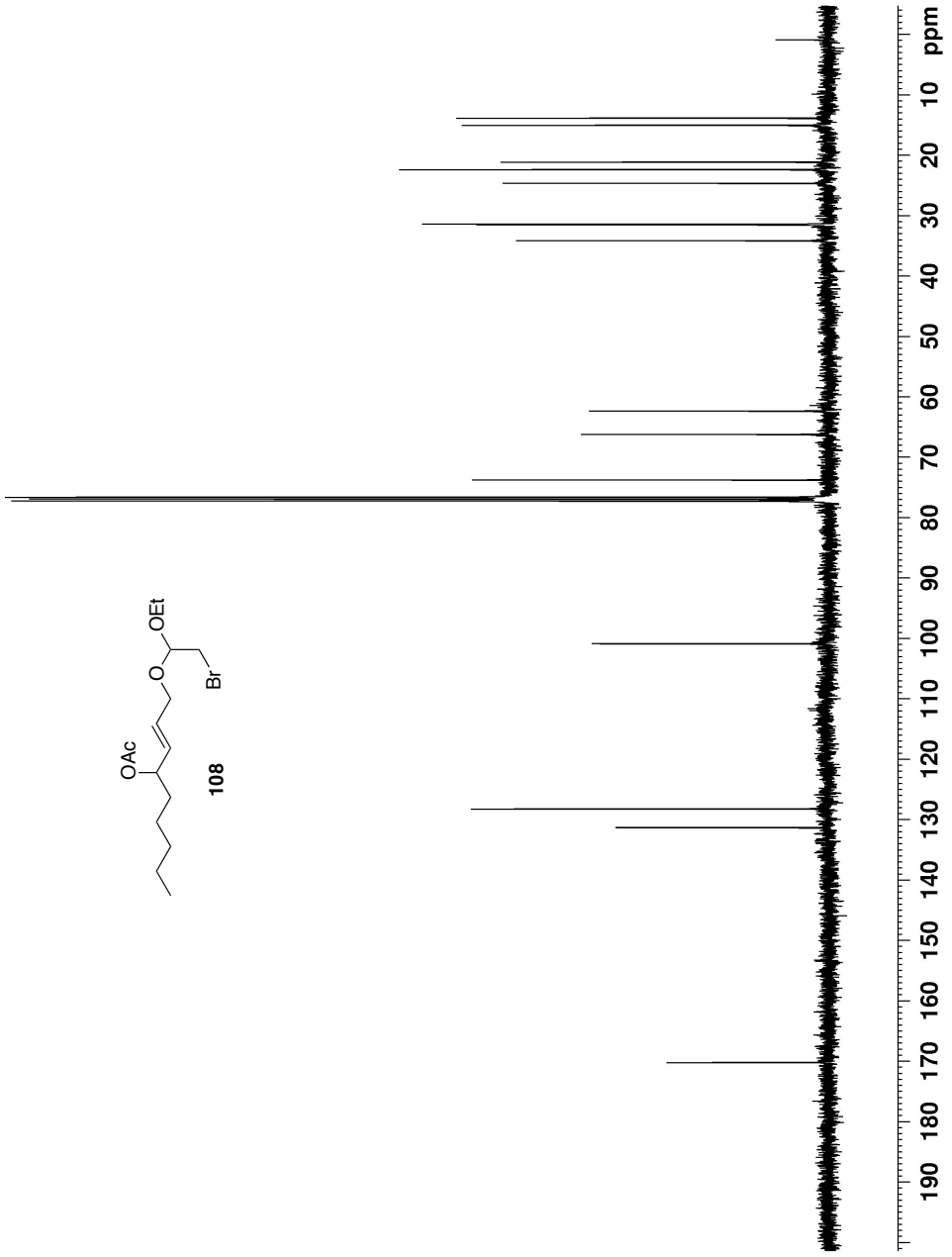


Figure A6 ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **108**

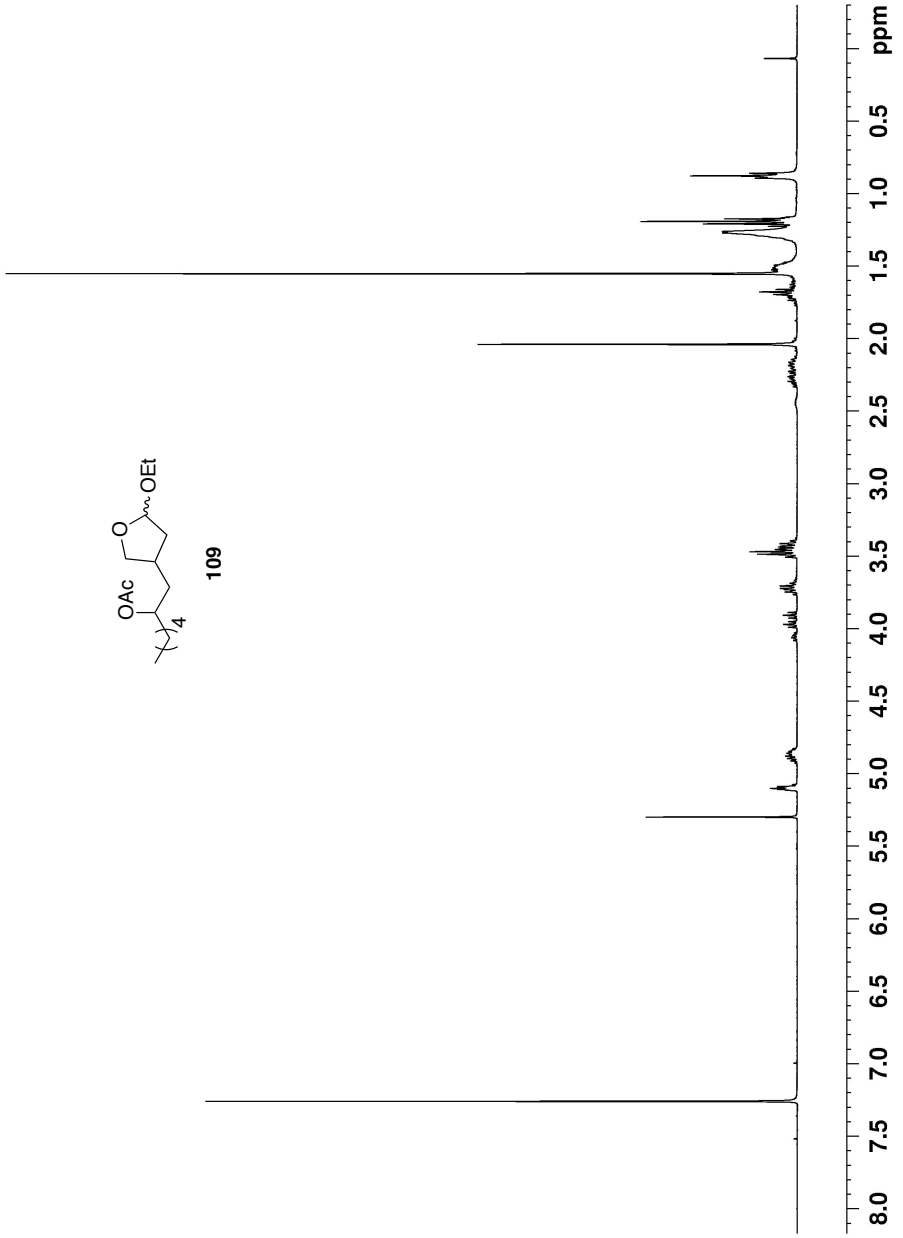


Figure A7 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **109**

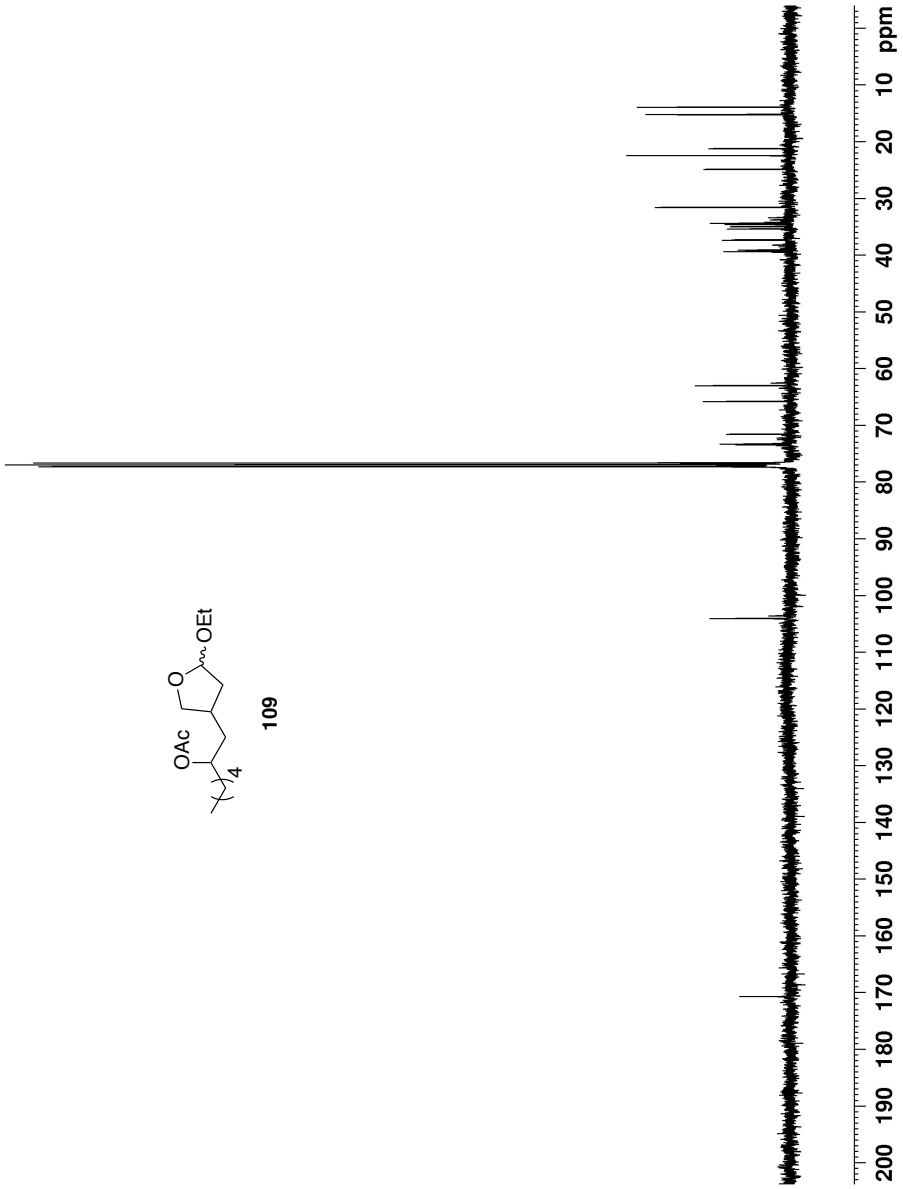


Figure A8 ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **109**

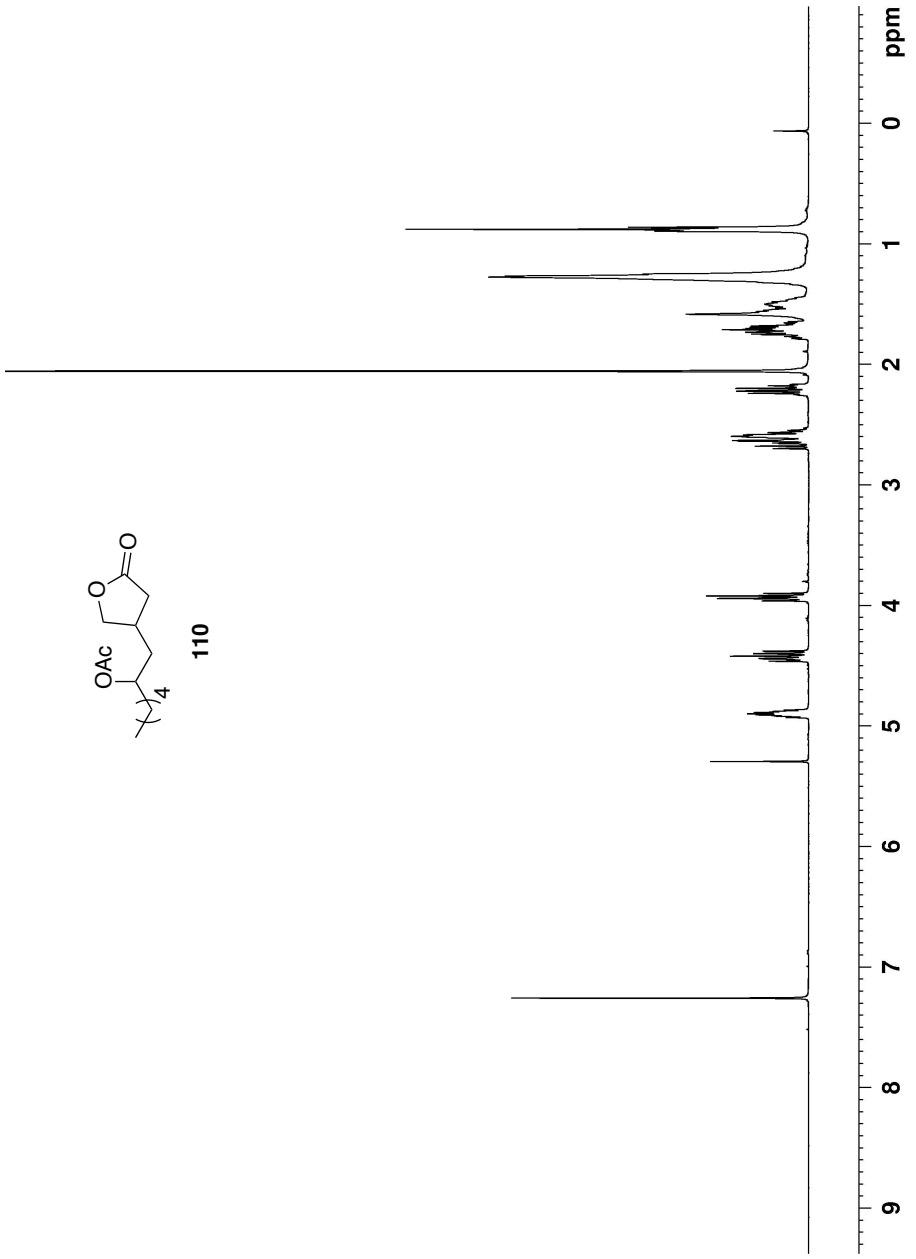


Figure A9 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **110**

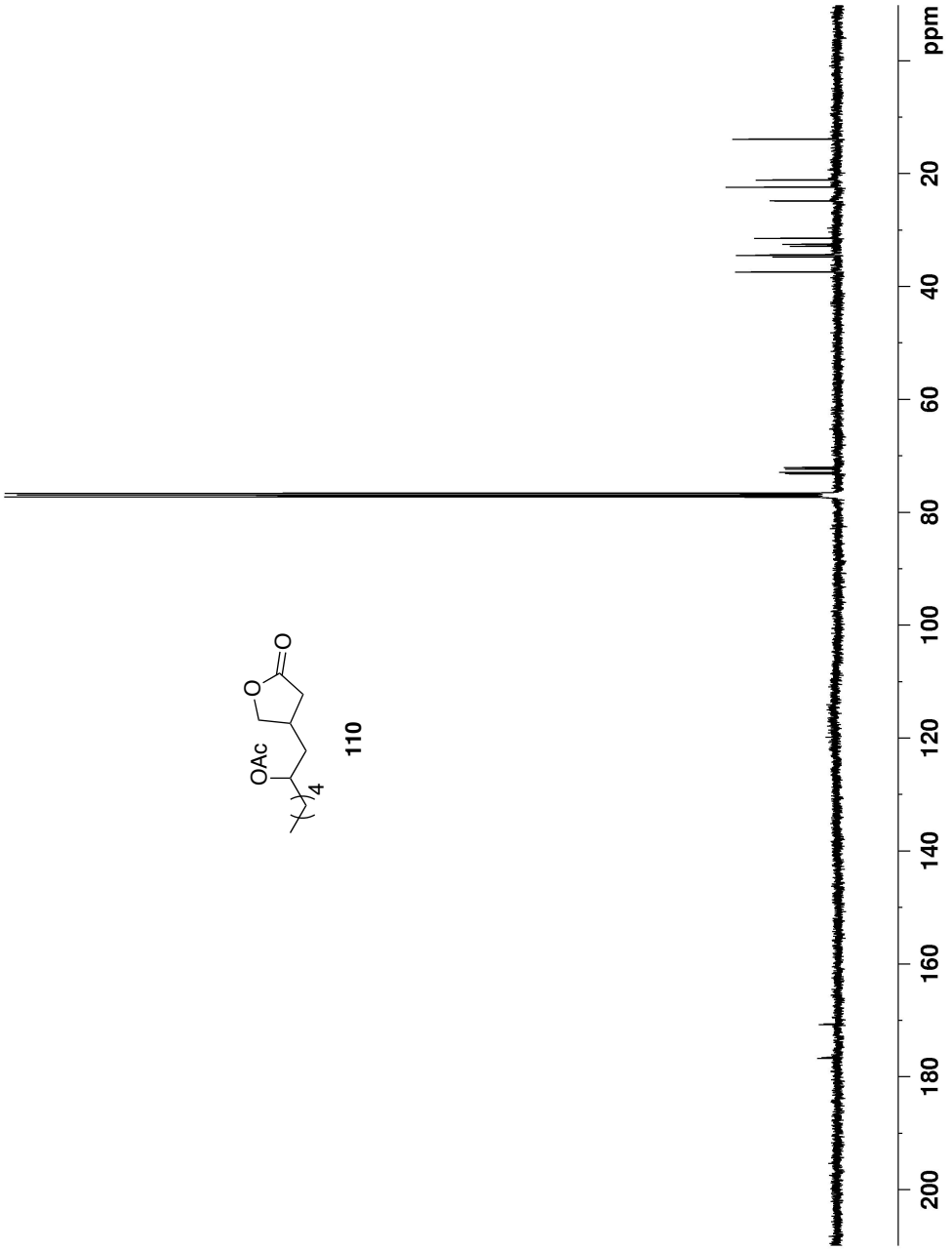


Figure A10 ^{13}C NMR spectra (100 MHz, $CDCl_3$) of compound **110**

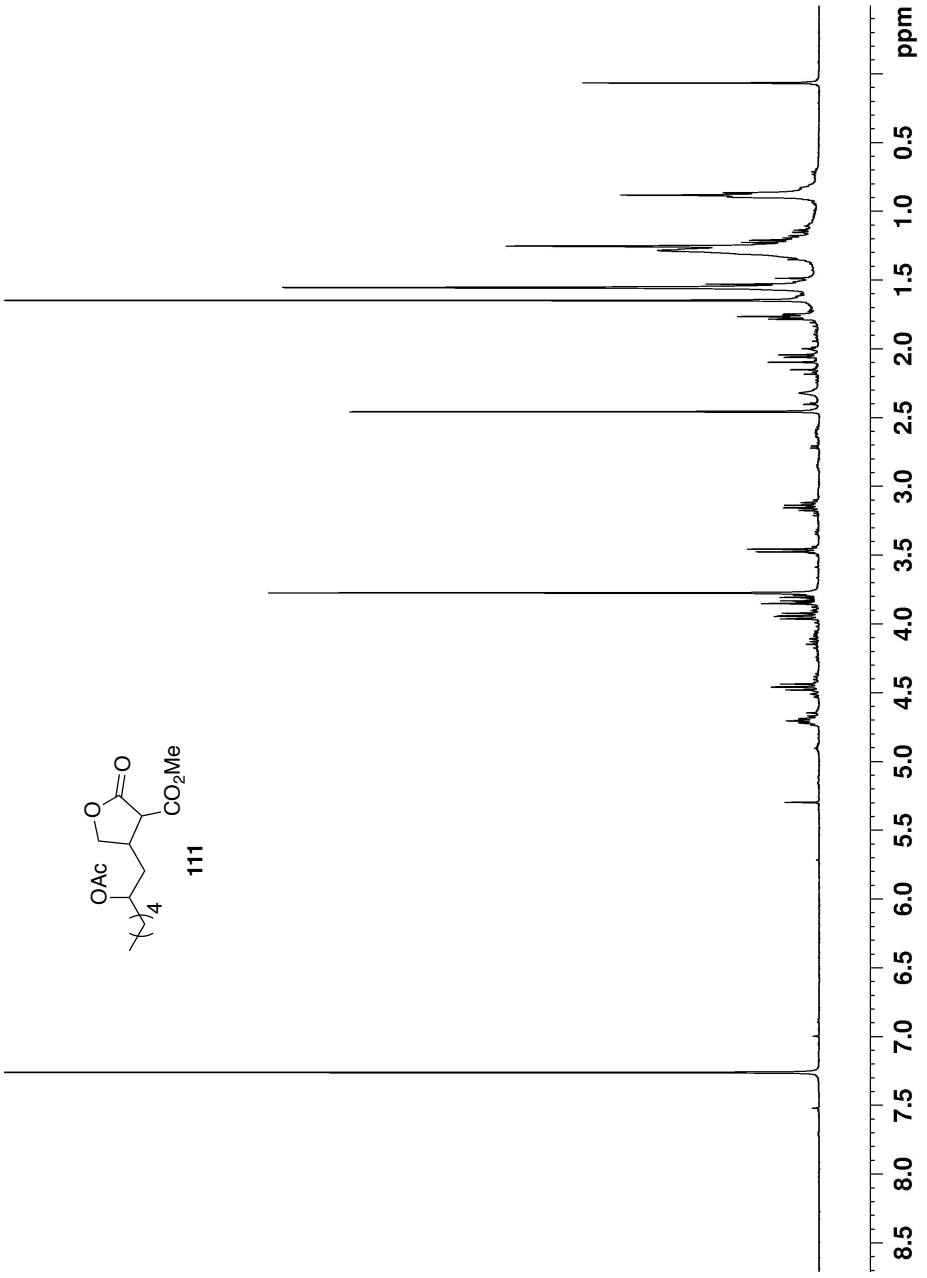


Figure A11 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **111**

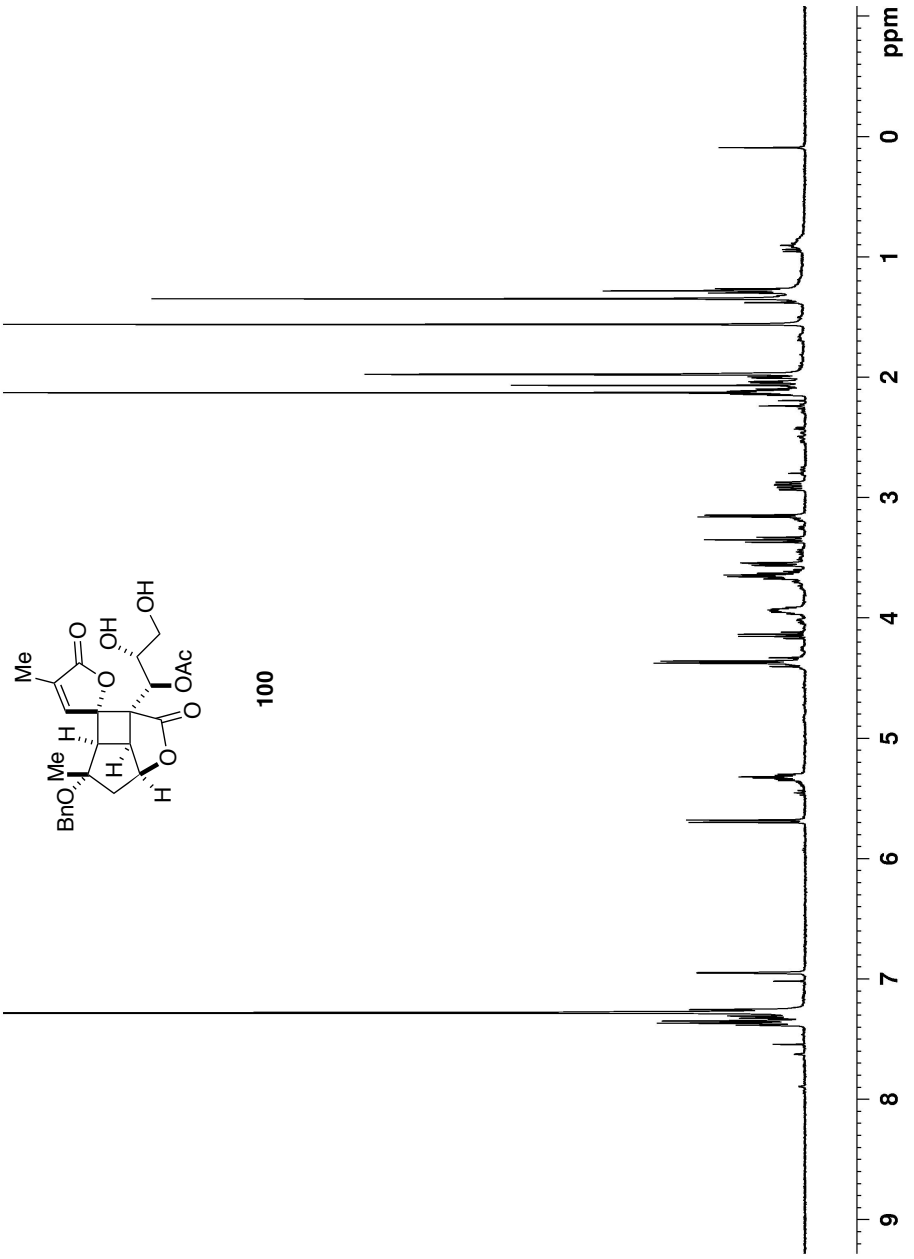


Figure A12 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **100**

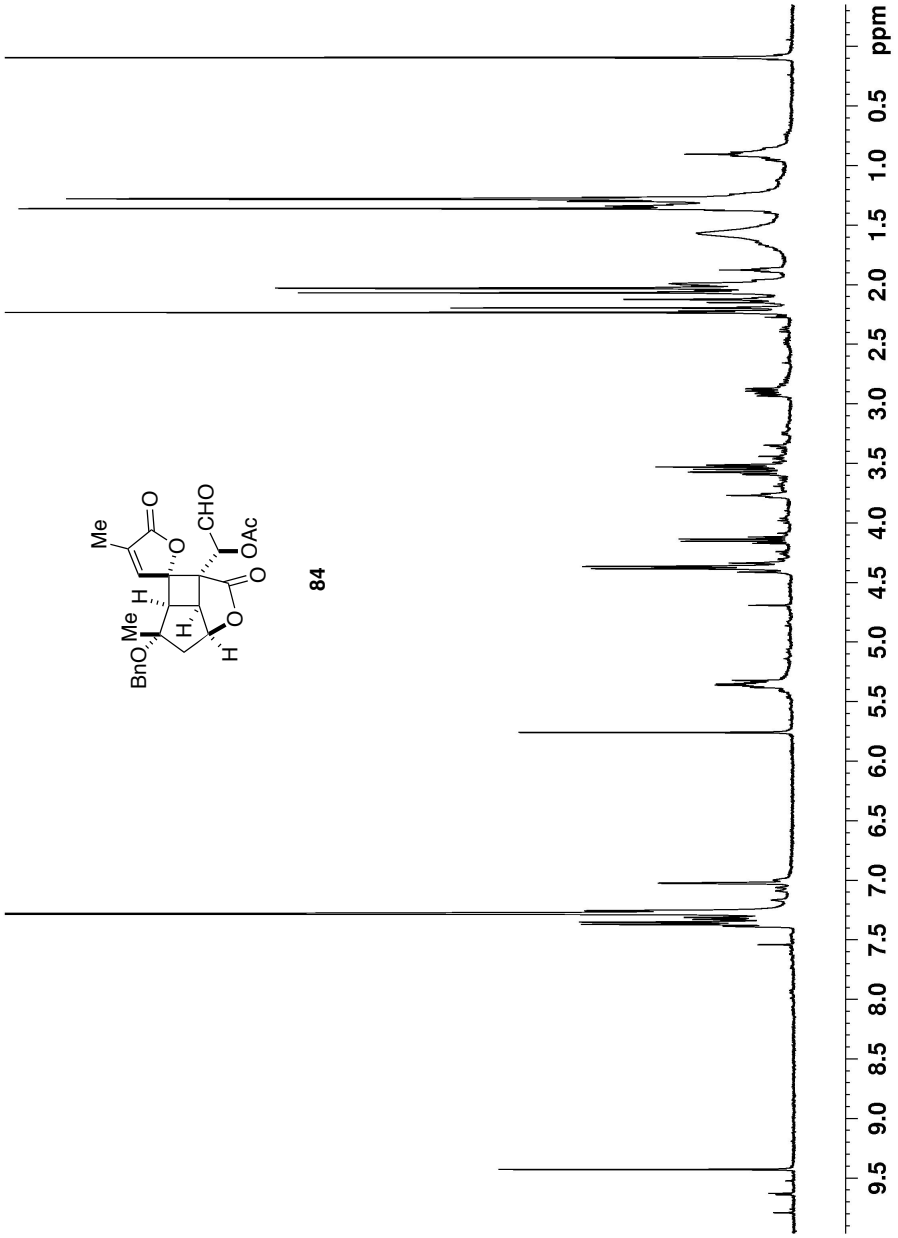


Figure A13 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **84**

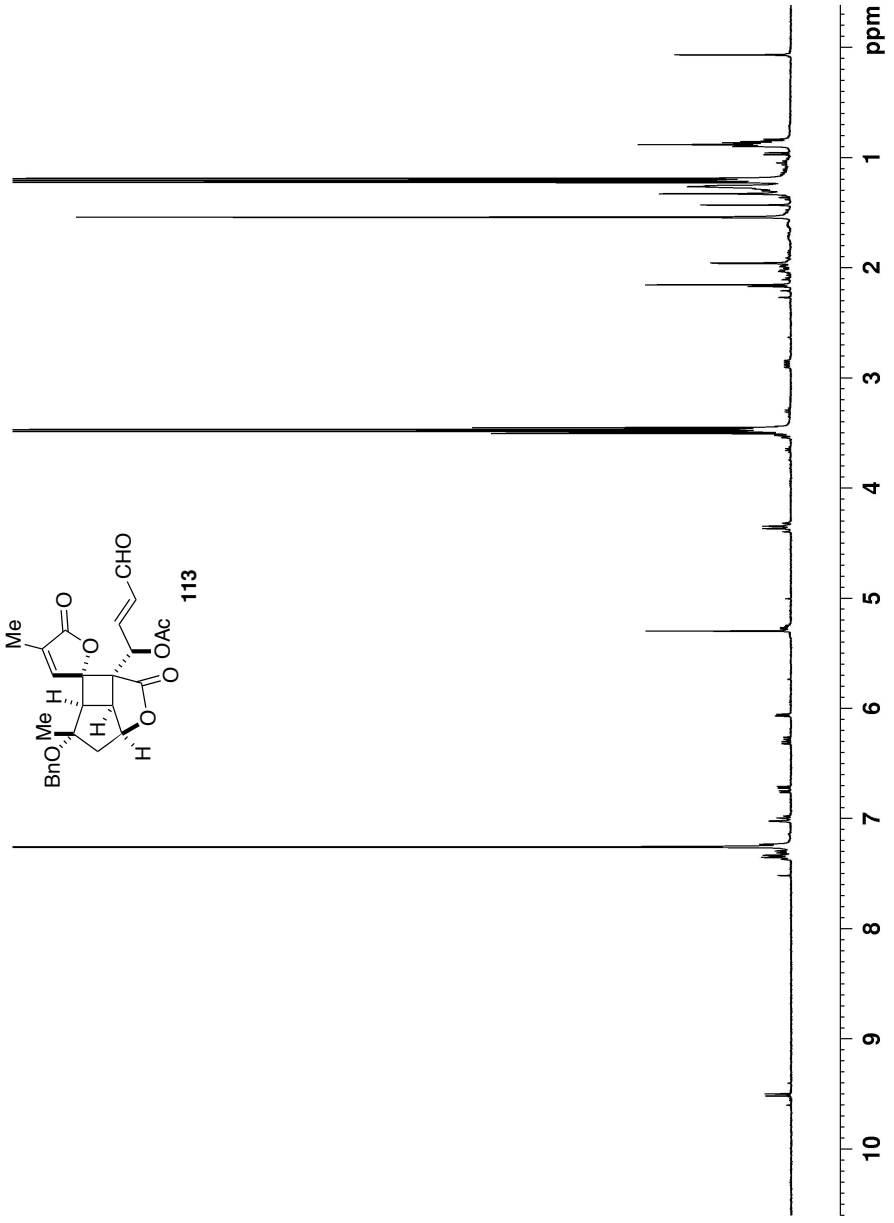


Figure A14 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **113**

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