UNIVERSITY OF CALIFORNIA, SAN DIEGO

The Total Synthesis and Manipulations of Norcembrenolides

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in

Chemistry

by

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The thesis of Steven D. E. Sullivan is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

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ABSTRACT OF THE THESIS

The Total Synthesis and Manipulations of Norcembrenolides

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Steven D. E. Sullivan

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Professor Emmanuel Theodorakis, Chair

Two natural products, norcembrenolide B and scabrolide D, have been synthesized in a biomimetic fashion. With the synthesis, a strategy has been developed for the transformation of furanocembrenolides to their β-ketotetrahydrofuranone derivatives. Further manipulations, namely C11 and C13 oxidation strategies, have been developed to allow access several natural products of this family.

Chapter 1

The Total Synthesis of Norcembrenolide B and Scabrolide D

1.1 Introduction

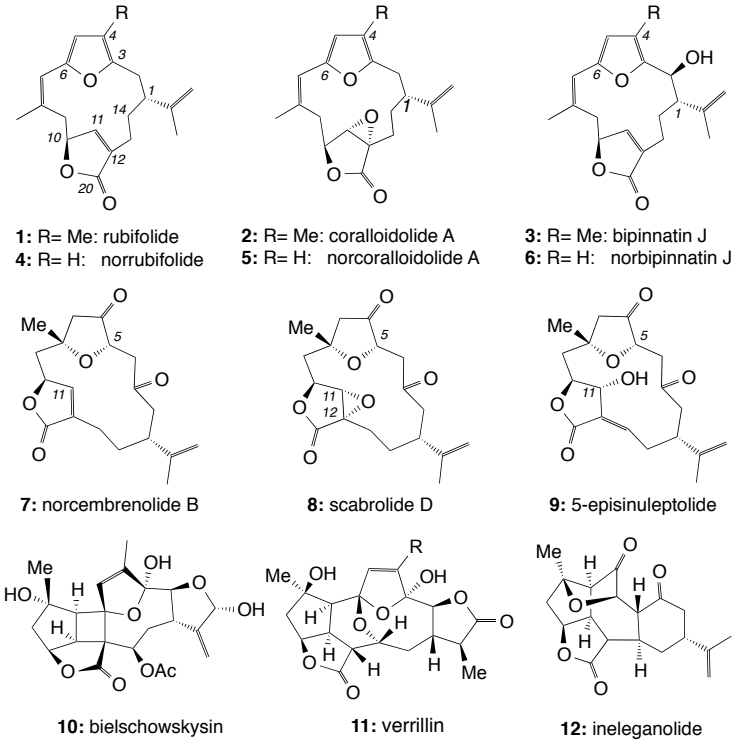


Figure 1.1: Structures of selected cembranes

Cembrenolides are a large family of structurally complex and biologically active diterpenes whose chemical motif is typified by a 14-membered cembrane skeleton (Figure 1.1). [1–4] Isolated from soft corals, these secondary metabolites are proposed to be biologically beneficial to the producing organisms as chemical defense against predation. [5–7] Along these lines, biological testing has revealed that norcembrenolides have a wide array of cytotoxicity and low micromolar activity against several biological assays. [1,2,8] For example, 5-episinuleptolide (**9**) has been shown to inhibit LPS-induced TNF-α production in a dose-dependent manner at 20 μg/mL. [9] More recently, **9** was also found to cause cell cycle arrest during the G_2/M phase in squamous cell carcinoma (SCC25 cell line) at a concentration of 11.2 μM leading to apoptosis. [10] In addition, scabrolide D (**8**) has been shown to inhibit LPS-induced iNOS production up to 47% at 10 μM. [11] The polycyclic and highly intricate cembrane bielschowskysin (**10**) displays very potent *in vitro* cytotoxicity against nonsmall cell lung cancer (EKVX, GI_{50}

ca 0.01 μM) and renal cancer cell line (CAKI-1, GI_{50} ca 0.50 μM). [12] In addition, **10** has demonstrated anti-malarial activity against *plasmodium falciparium* (IC_{50} ca 10 μg/ml). [12] Similarly, ineleganolide (**12**) displays strong cytoxicity against the P-388 cancer cell line (ED_{50} ca 3.82 μg/ml). [13] This diverse biological activity and structural intricacy combined with the lack of availability from natural sources for further biological testing prompted the investigation into the total synthesis of this family of natural products and analogs. Of particular interest was developing a unified biomimetic synthesis allowing for the interconversion of simple norcembrenolides into more complex natural products.

1.2 Retrosynthetic Plan

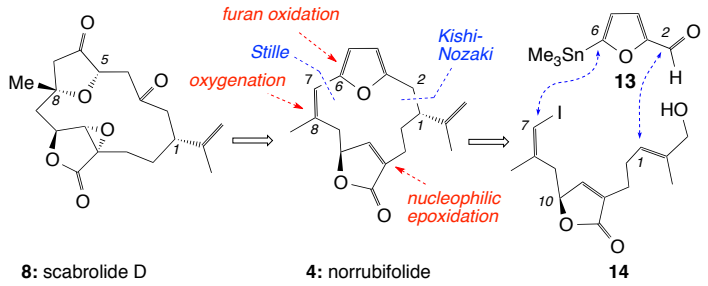
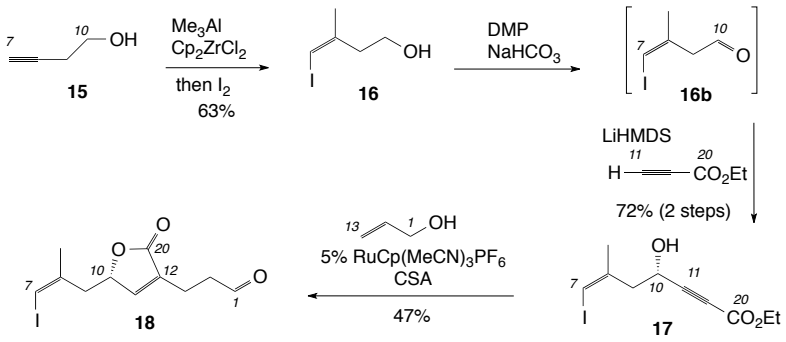


Figure 1.2: Key disconnections towards norcembrenolides

A possible biosynthetic precursor of many cembrenolides is rubifolide (**1**) [14–20], the structure of which is highlighted by the presence of a furan (C3-C6) and a butenolide (C10-C20) ring that are embedded in a 14-membered macrocycle. Oxidative rearrangements of the furan motif in **1** followed by oxidative decarboxylation of the C4 methyl group has been proposed to form the furanone ring of **7**. [1] Additional oxidations of the butenolide motif of **7** [21] would lead to thestructures of **8** [22] and **9**. [21] Taking these biosynthetic pathways into consideration, we designed a divergent synthesis of this family, which involves norrubifolide (**4**) as the key synthetic intermediate (Figure 1.2). We envisioned that **4** could be assembled using the well-established Stille and Kishi-Nozaki couplings of aldehyde **13** and butenolide **14**, followed by reductive deoxygenation of the resulting alcohol at the C2 center. [23, 24] Departing with **4**, we

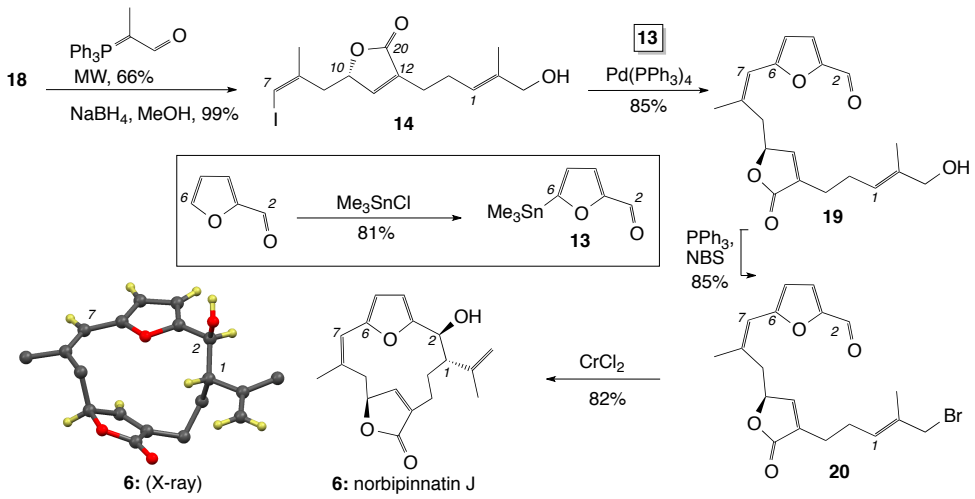
contemplated a diastereoselective hydration at the C8 center. Nucleophilic attack by the resulting tertiary alcohol to an oxidized furan could produce the desired tetrahydrofuranone (C5-C8) motif of norcembrenolide B (**7**). Nucleophilic epoxidation at the butenolide motif of **3** would then yield scabrolide D (**8**) and related natural products. [25]This strategy would allow synthetic access to β-ketotetrahydrofuranone norcembrenolides in from their respective furanocembrenolides.

1.3 Total Synthesis of Norbipinnatin J



Scheme 1.1: Synthesis of intermediate 18

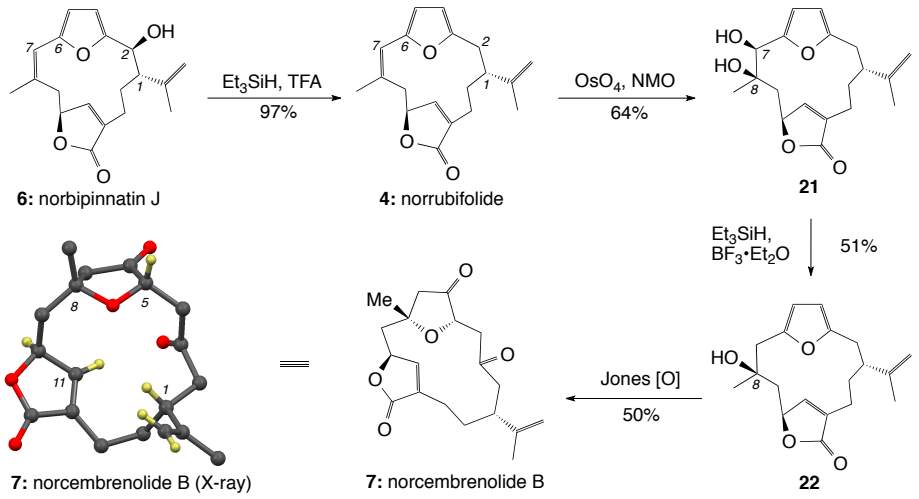
Guided by Trauner's synthesis of bipinnatin J [23], our synthesis began with the methylation of 3-butyn-1-ol (**15**) using neat trimethyl aluminum and zirconocene dichloride (Scheme 1.1). Refluxing this solution for 72 hours and quenching the reaction mixture with iodine selectively afforded the Z-vinyl iodoalcohol **16** in 63% yield. Initially, 1.6M trimethyl aluminum in hexanes was used, however, the lower reflux temperature led to a mixture of the desired Z and but also the E product (4:1), even when refluxed for a week. The increased temperature of reflux by removal of hexanes (85°C to 105°C) allowed for a shift in the equilibrium to completely transform the product to the Z-isomer in good yield (63%). Oxidation using Dess-Martin periodinane provided the sensitive aldehyde **16** that, upon treatment with lithiated ethyl propiolate, formed alcohol **17** in 72% yield over 2 steps. It should be noted that our initial efforts to metalate ethyl propiolate utilized freshly prepared LDA. [26] Under these conditions, however, we formed substantial amounts of a side product arising from the nucleophilic addition



Scheme 1.2: Synthesis of norbipinnatin J

of LDA to ethyl propiolate. Switching to commercially available NaHMDS eliminated the undesired side product, however the reaction yields were inadequate (approximately 15%). To our delight, use of freshly prepared LiHMDS afforded the desired product **17** cleanly and in high yield (72%). Using allyl alcohol as the carbon source, the framework of **17** was extended under ruthenium alder-ene [27] chemistry to produce, after *in situ* lactonization with CSA, butenolide **18** in 47% yield. Additional elongation of the carbon framework of **18** was accomplished via Wittig olefination to afford the corresponding α,β-unsaturated aldehyde in 66% yield. We found that this reaction, which requires 12 hours under conventional heating, could be accelerated without sacrificing yield under microwave conditions (120°C for 40 min). Subsequent reduction using $NaBH_4$ provided alcohol **14** in quantitative yield. Stille coupling of **14** with stannane **13** afforded aldehyde **19** in 78% yield. In preparation for the Kishi-Nozaki coupling, **19** was subjected to Appel conditions [28] to furnish allyl bromide **20** in 85% yield. Treatment of **20** with $CrCl_2$/$NiCl_2$ produced norbipinnatin J (**17**), in a substrate- controlled manner with a diastereoselectivity of 9:1 (82% yield). [29, 30] The structure of norbipinnatin J (**17**) was unambiguously confirmed by single-crystal X-ray diffraction studies (Scheme 1.2).

1.4 Total Synthesis of Norcembrenolide B (3)



Scheme 1.3: Synthesis of norcembrenolide B

Following our retrosynthetic plan, the C2 hydroxyl group of norbipinnatin J (**6**) was deoxygenated using TFA/Et_3SiH [23,31] to afford norrubifolide (**4**) (97% yield). A two-step sequence was then implemented in order to achieve the stereoselective hydration at the C8 center of **4** that included regioselective dihydroxylation of norrubifolide across the C7-C8 alkene followed by deoxygenation of the resulting C7 alcohol. Treatment of **4** under Sharpless dihydroxylation conditions [32] provided the desired diol **21** but this reaction was not amenable to scale-up. Using $KMnO_4$ as the oxidant, the desired diol was produced but it quickly underwent vicinal diol cleavage. To our delight, dihydroxylation of **4** under Upjohn conditions (OsO_4, NMO) [33] at 0 °C afforded diol **21** as a single isomer in 64% yield (Scheme 1.3). The diastereoselectivity of this dihydroxylation was substrate-controlled delivering the hydroxyl groups from the β-face of the macrocycle. Attempts to deoxygenate the C7 alcohol using the TFA/Et_3SiH conditions, as previously employed, were unsuccessful. However, use of a stronger Lewis acid (BF_3OEt_2) [34] at low temperature (–40 °C) afforded alcohol **22** in 51% yield together with a small amount of recovered starting material (11%). Conversion of the furan ring of **22** to the β-keto-tetrahydrofuranone was achieved using Jones reagent [35] giving rise to norcembrenolide B (**3**) in 50% yield. Mechanistically, this conversion

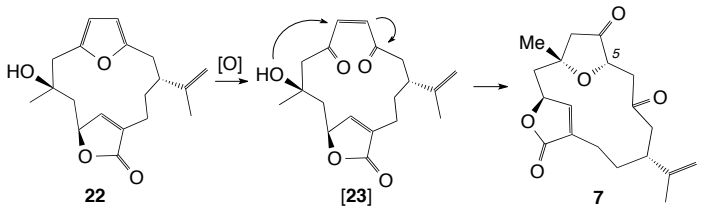


Figure 1.3: Proposed mechanism of jones cyclization

commences with oxidation of the furan to a Z-ene-dione intermediate which cyclizes in a 5-exo-trig fashion under acid catalysis (Figure 1.3). The structures and relative stereochemistry of **4**, **21**, **22**, and **7** were confirmed by X-ray crystallography (Scheme 1.3).

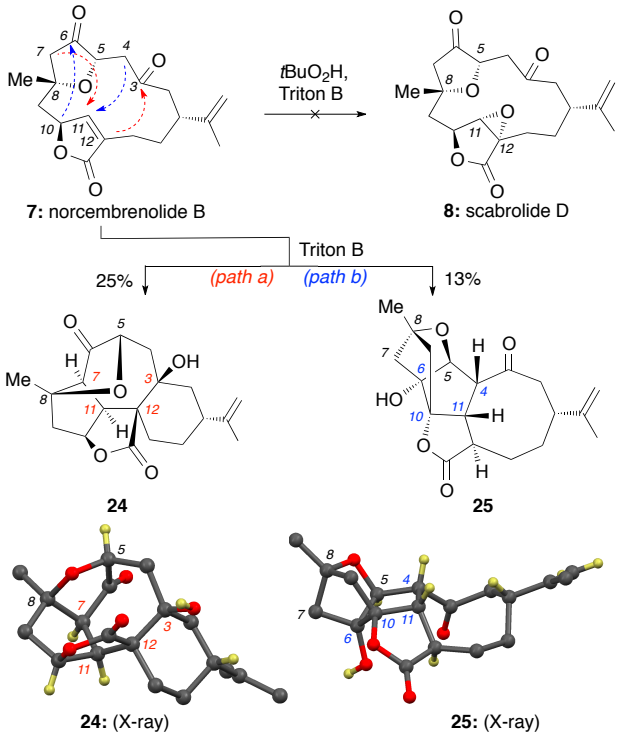
1.5 Total Synthesis of Scabrolide D (4)

1.5.1 Epoxidation Conditions

In principle, a stereoselective epoxidation of the C11-C12 alkene of norcembrenolide B (**7**) would produce scabrolide D (**8**). With this in mind, we screened nucleophilic epoxidation conditions using norrubifolide (**4**) as a model for norcembrenolide B. Sodium hypochlorite, H_2O_2/ NaOH, H_2O_2 / Bu_4NOH, and tBuO$_2$H / Bu_4NOH all failed to produce the desired epoxide neatly in high yield. In all cases significant starting material was also present after 24 hours or more by TLC. However, tBuO$_2$H and catalytic Triton B [36] was found to produce norcoralloidolide A (**5**) in a substrate-directed stereoselective manner and in quantitative yield.

1.5.2 Intramolecular "zip-up" Cyclizations

With the goal of synthesizing scabrolide D (**8**), we attempted the epoxidation of **7** under nucleophilic conditions (tBuO$_2$H and Triton B). To our surprise, we found that this reaction produced two complex polycyclic products (**24, 25**), the structures of which weredetermined via single crystal X-ray diffraction (Scheme 1.4). Mechanistically, **24** is likely formed via an intramolecular Michael addition of the C7 enolate at the C11

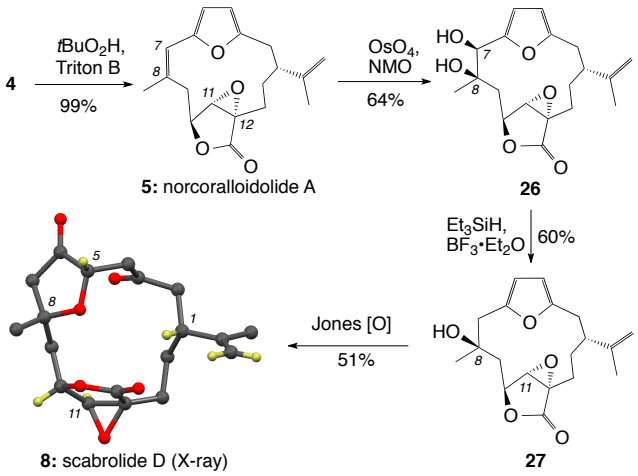


Scheme 1.4: Synthesis of polycyclic norcembrenolides

butenolide and subsequent nucleophilic attack of the C12 enolate at the proximal C3 carbonyl group (*path a*). On the other hand, compound **25** is presumably formed via abstraction of the acidic C10 hydrogen and cyclization of the resulting extended enolate at the C6 carbonyl group (*path b*). Subsequent cyclization across the C4-C11 centers forms the pentacyclic motif of **25** in 13% yield. Although compounds **24** and **25** are not true "natural products", their structures are similar to ineleganolide (**7**) and other polycyclic cembrenoids, suggesting that the latter compounds can also be synthesized in nature via similar intramolecular"zip-up"cyclizations. [37]

1.5.3 Completion of Scabrolide D (4)

To overcome such cyclizations we decided to perform the C11-C12 epoxidation on a less functionalized substrate. To this end,treatment of norrubifolide (**4**) under these conditions (tBuO$_2$H, Triton B) gave rise to norcoralloidolide A (**5**) [38] in a substrate-directed stereoselective manner and in quantitative yield (Scheme 1.5). Following the



Scheme 1.5: Synthesis of scabrolide D

same reaction sequence as above, compound **27** was converted to scabrolide D (**8**) with analogous yields at each step, confirmed by ^{1}H NMR and ^{13}C NMR in $CDCl_3$. However, the structure of scabrolide D described by Sheu *et al* [22] was reported to feature the epoxide on the same face as the lactone oxygen, opposite of our structure confirmed by X-ray crystallographic analysis. This data led to the revision of the relative stereochemistry at the C11 and C12 center, with the epoxide occurring on the opposite face in regard to the lactone oxygen. Interestingly, this proved that the structure of scabrolide D is identical to norcembrenolide C, which was studied in benzene-d_6 and reported by the Fenical group years earlier. [21]

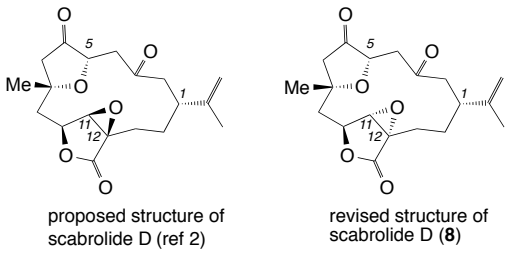


Figure 1.4: Revision of scabrolide D relative stereochemistry

This chapter, in part, has been submitted for publication. Saitman, Alec; Sullivan, Steven D.E.; Theodorakis, E.A. The thesis author was the author and co-investigator of this material.

Chapter 2

Functionalizations of Norcembrenolides and Efforts towards Scabrolide G

2.1 Introduction

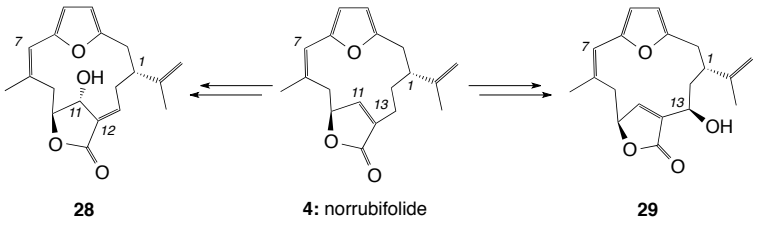
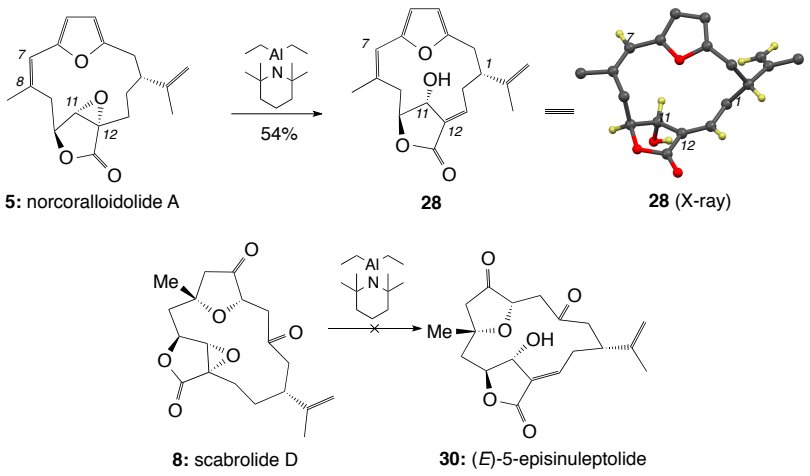


Figure 2.1: Key manipulations of norcembrenolides

With the completion of the norcembrenolide core and our first successful bioinspired transformation complete, we sought to explore additional manipulations that would allow access to more complex natural products from the unified core intermediate, norrubifolide (**4**). Key targets include the opening of the epoxide of norcoralloidolide A into allyl alcohol **28**, allowing access to the biologically active natural product, 5-episinuleptolide. 5-episinuleptolide (**9**) has been shown to inhibit LPS-induced TNF-α production in a dose-dependent manner at 20 μg/mL. [9] as well as cause cell cycle arrest during the G_2/M phase in squamous cell carcinoma (SCC25 cell line) at a concentration of 11.2 μM leading to apoptosis. [10]. Oxidation at the C13 center (**29**) was also a target of high interest, due to its presence in a several sought after polycyclic cembrenolides, including bielschowskysin (**10**), verrillin (**11**), and ineleganolide (**12**). Structural complexity combined with potent biological activity have made these attractive synthetic targets.

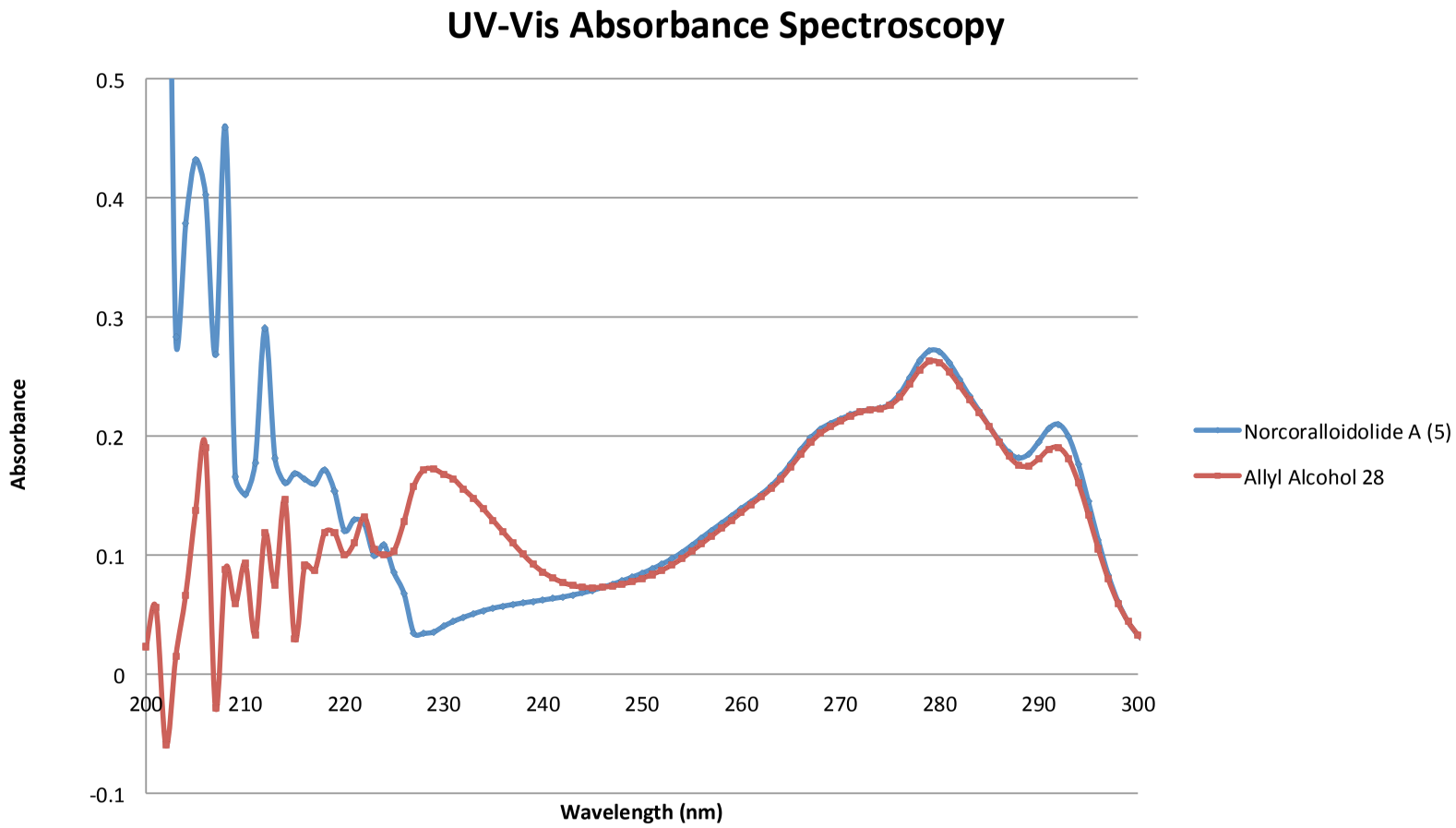
2.2 Studies towards the synthesis of 5-episinuleptolide

Having installed the C11-C12 epoxide, en route to the synthesis of scabrolide D (**8**), we sought to evaluate conditions for its stereoselective opening in order to access the structure of 5-episinuleptolide (**9**). Initially starting with norcoralloidolide (**5**), we screened conditions for this transformation. The only promising reagent was found to be diethylaluminum tetramethylpiperidine (DATMP), [39] producing allylic alcohol **28** norcoralloidolide A (**23**) in 54% yield (Scheme 2.1). Application of DATMP to



Scheme 2.1: Synthesis of allylic alcohol motif

scabrolide D (**8**), however, led to complete degradation of the starting material. Before utilizing a divergent strategy towards the synthesis of 5-episinuleptolide by starting with allylic alcohol **28**, we needed to develop methodology to isomerize the C12-13 alkene to the desired *Z*-isomer. We analyzed the accessibility of selective isomerization of the C12-C13 alkene using UV-Vis absorption spectroscopy. By comparing the spectrum of allylic alcohol **28** and norcoralloidolide (**5**) we were able to deduce the absorbance of the C12-C13 chromophore. Unfortunately, the wavelength of the C12-C13 chromophore was found to be 225-240 nm and the wavelength of the other chromophores was found to be 250-300 nm. These regions are too close to selectively affect the desired chromophore with the available equipment.



Spectrum 2.1: UV-Vis absorbance spectroscopy on compound 5 and compound 28, highlighting the chromophore from 225-240 nm present in compound 28 due to the allyl alcohol (C12-C13). Absorbance (AU) of compound 28 data multiplied by a factor of 1.3.

2.3 Synthesis of C13-hydroxylated Furanocembrenoids

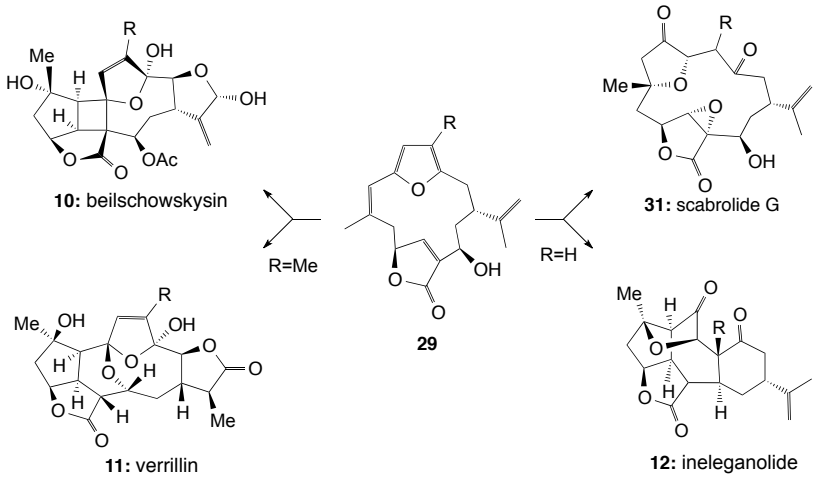
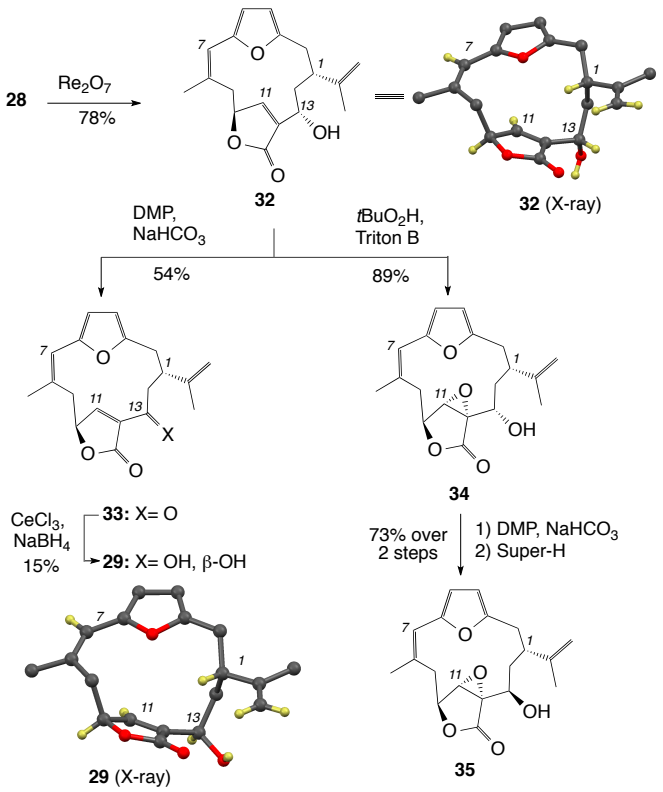


Figure 2.2: Natural products proposed to derive from C13-hydroxylated furanocembrenoids

A number of polycyclic cembrenoids are postulated to derive from oxidation at the C13 center (Figure 2.2). [12, 13, 25, 40] With this in mind, we treated compound **28** with catalytic rhenium (VII) oxide [41] and isolated compound **32** in 78% yield (Scheme 2.2). A single crystal X-ray analysis unambiguously confirmed the structure and relative stereochemistry of **32** and showed that the C13 hydroxyl group was incorporated at the α-face of the macrocycle. Since several related natural products, such as bielschowskysin (**6**), feature the C13 alcohol at the β-face we decided to invert its stereochemistry. To this end, **32** was first oxidized using DMP to afford butenolide **33** in 54% yield (Scheme 2.2). We found that this compound was relatively unstable and was directly reduced under Luche conditions [42] to form the desired β-alcohol **29** in low yield (15%). The structure of **29** was confirmed via a single crystal X-ray diffraction analysis. Attempts to optimize this reaction were unsuccessful, presumably due to the highly electrophilic nature of the α-keto butenolide motif. On the other hand, epoxide **34**, produced from **32** in 89% yield, was oxidized using DMP to the desired ketone. Treatment with $NaBH_4$ reduced the ketone in quantitative yield, but unfortunately delivered the hydride from the wrong face, yielding the initial epoxide **34**. Switching the reductant to superhydride, a bulkier hydride source, switched the stereoselectivity

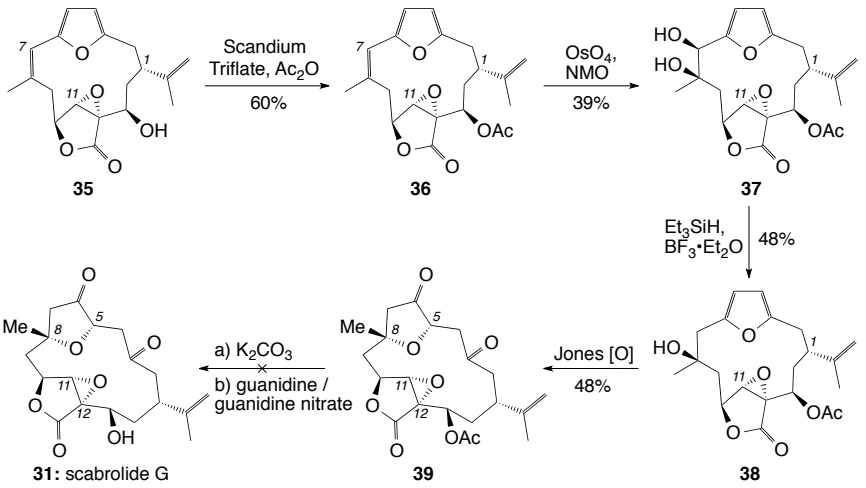


Scheme 2.2: Synthesis and inversion of C13 oxidized norcembrenolides

completely, forming only the desired β-alcohol **35** in 73% yield over two steps. The successful installation of a hydroxyl group at the C13 center of the cembrenolide motif allows access to other natural products of this family.

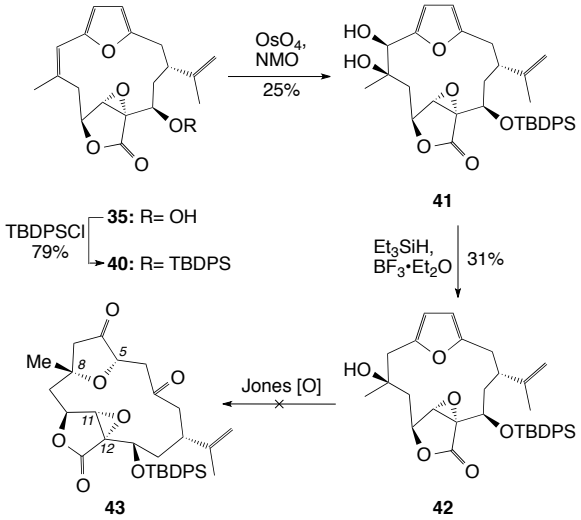
2.4 Efforts towards Scabrolide G

With the chemistry developed to make the epoxidized and C13 oxidized norrubifolide, we then set out to synthesize the natural product scabrolide G (**31**), which features the same motif except in a β-ketotetrahydrofuranone skeleton. To achieve this goal, alcohol **35** was first acetate protected using scandium (III) triflate and acetic anhydride to afford **36** in 60% yield (Scheme 2.3). Using the same conditions presented in chapter 1, **36** was successfully converted to the β-ketotetrahydrofuranone **39** in 9% yield over three steps. Deprotection using a 1% solution of potassium carbonate in methanol,



Scheme 2.3: Efforts towards scabrolide G: acetate protection.

however, led to the decomposition of the starting material. Postulating this failure due the extreme sensitivity experienced on other β-ketotetrahydrofuranone norcembrenolides with the added complexity of further oxidations, we sought the mildest conditions available. However, treatment with a mixture of guanidine and guanidine nitrate [43] also led to decomposition of the starting material. The protecting group strategy was



Scheme 2.4: Efforts towards scabrolide G: TBDPS protection.

then modified to avoid base conditions by once again starting with alcohol (**35**) and protecting it with TBDPS-Cl, affording **41** in 79% yield (Scheme 2.4). Conversion to

the β-ketotetrahydrofuranone, however, proved unsuccessful when the material decomposed upon treatment of alcohol **42** with Jones reagent. Further attempts were ceased due to the dearth of the material.

2.5 Conclusion

In conclusion, the total synthesis of several norcembrenolides including norcembrenolide B (**7**) and scabrolide D (**8**) was achieved. The synthetic strategy is divergent and builds upon an efficient construction of norrubifolide (**4**). A sequence of various transformations, such as dihydroxylation (C7-C8 alkene), epoxidation (C11-C12 enone), epoxide opening (hydroxylation at C11), allylic alcohol migration (oxidation at C13) and furan oxidation (formation of a β-keto-tetrahydrofuranone), has been developed in order to access several natural products of this family.

This chapter, in part, has been submitted for publication. Saitman, Alec; Sullivan, Steven D.E.; Theodorakis, E.A. The thesis author was the author and co-investigator of this material.

Chapter 3

Supporting Information

3.1 Experimental

General Techniques. All reagents were commercially obtained (Aldrich, Acros, Strem) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 40 °C at approximately 15 mmHg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), toluene ($PhCH_3$) and benzene (PhH) were purified by passage through a bed of activated alumina. Dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4Å molecular sieves until needed. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or Potassium Permanganate solution ($KMnO_4$) in water and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Jeol Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, dd = doublet of doublet, dt = doublet of triplet. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS or on a VG ZAB-ZSE mass spectrometers. X-ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

Vinyl-iodo alcohol (16): To a solution of $ZrCp_2Cl_2$ (5.00 g, 17.12 mmol, 0.2 eq) in 1,2-dichloroethane (140 mL) at 0 °C was added a solution of trimethylaluminum (2M, 107 mL, 214 mmol, 2.5 eq) in hexanes dropwise. A solution of but-3-yn-1-ol (6.49 mL, 86 mmol) in 1,2-dichloroethane (20 mL) was then added dropwise. The

solution was stirred at rt for 24h. The solution was then warmed to 86 °C and gently refluxed for 4 days. The reaction was then cooled to –40 °C and a solution of iodine (43.5 g, 171 mmol, 2 eq) in 100 mL of dry THF was added via cannula. The solution turned black and was stirred for 30 minutes. The reaction was warmed up to 0 °C and a solution of sat. K_2CO_3 was added very slowly (the solution frothed and bubbled) until eventually turning yellow with aluminum gel precipitate. Ether (250 mL) was added and the solution was filtered through fritted funnel. The gel was extracted with a large amount of ether to remove all organics. 200 mL of water was added to the organic layer which was separated. The aqueous layer was then extracted 3x with ether. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 20% EtOAc in hexanes) of the crude mixture gave alcohol **16** (9.3 g, 43.9 mmol, 51% yield) as a light brown oil. R_f=0.30 (20% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$)δ: 6.01 (d, 1H, *J*=1.4 Hz), 3.78 (t, 2H, *J*=6.7 Hz), 2.53 (t, 2H, *J*=6.7 Hz), 1.94 (d, 3H, *J*=1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.3, 76.3, 60.1, 41.6, 23.8.

Alkyne 17: To an oven-dried flask was added dry HMDS (bis(trimethylsilyl)-amine) (19.93 mL, 94 mmol, 3 eq) and THF (95 mL). The solution was cooled to -78 °C and n-BuLi (1.6M in hexanes, 56.7 mL, 91 mmol, 2.9 eq) was added dropwise. The solution turned yellow and was then warmed up to 0 °C and stirred for 20 minutes. The reaction was cooled back down to -78 °C and a solution of ethyl propiolate (9.51 mL, 94 mmol, 3 eq) in THF (60 mL) was added dropwise over 30 minutes. The solution remained pale yellow. The reaction was stirred at -78 °C for 1 hour. During this time, to a solution of the alcohol **16** (6.63 g, 31.3 mmol) in CH_2Cl_2 (156 mL) at rt was added $NaHCO_3$ (15.76 g, 188 mmol, 6 eq) followed by Dess-Martin periodinate (17.24 g, 40.7 mmol, 1.3 eq) in one portion. After 15 minutes, the reaction was completed. A 1:1:1 mixture of aq. sat. $Na_2S_2O_3$, aq. sat. $NaHCO_3$ and water (160 mL) was added slowly to the CH_2Cl_2solution and was stirred vigorously for 20 minutes. Layers were separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure at rt to yield aldehyde **16b** which was used without further purification. The aldehyde **16b** was then taken up in dry THF (50 mL) and was cooled to -78 °C in a separate cooling bath. The cold

aldehyde solution was added via cannula quickly to the solution of the alkyne at -78 °C. The solution turned dark red and was stirred for 30 minutes at -78 °C. The reaction was then quenched with sat. NH_4Cl solution (100 mL). The organic layer was separated, and the aqueous layer was extracted 3x with ether. The combined organic layers were washed once with Brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 18% EtOAc in hexanes) of the crude mixture gave alkyne **17**(5.54 g, 17.98 mmol, 65% yield over 2 steps) as a light red oil. R_f=0.34 (silica, 20% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.13 (d, 1H, *J*=1.4 Hz), 4.72 (td, 1H, *J*=6.1 Hz, *J*=8.3 Hz), 4.25 (q, 2H, *J*=7.1 Hz), 2.80 (dd, 1H, *J*=8.3 Hz, *J*= 13.6Hz), 2.65 (dd, 1H, *J*=6.0 Hz, *J*=13.6 Hz), 2.00 (d, 3H, *J*=1.4 Hz), 1.32 (t, 3H, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.3, 142.4, 86.9, 78.4, 76.7, 62.2, 60.1, 45.3, 24.6, 13.9; HRMS calcd. for ($M+Na^+$) 330.9802, found 330.9803.

Aldehyde 18: To a solution of the alkyne **17** (0.592 g, 1.921 mmol) in dry DMF (3.84 mL) was added allyl alcohol (0.261 mL, 3.84 mmol), CSA (0.112 g, 0.480 mmol) under an argon atmosphere. The reaction mixture was sparged with argon for 15 minutes before adding Tris(acetonitrile)cyclopentadienylruthenium (II) hexafluorophosphate (0.042 g, 0.096 mmol). The reaction was heated to 50 °C for 1.5 hrs. The reaction mixture was then quenched with saturated $NaHCO_3$ solution and extracted 4x with diethyl ether. Organics were combined dried and concentrated. Flash chromatography (up to 40% EtOAc in hexanes) of the crude mixture gave aldehyde **18** (0.314 g, 0.98 mmol, 51% yield) as a dark orange oil, R_f=0.32 (silica, 40% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 7.11 (q, 1H, *J*=1.4 Hz), 6.06 (d, 1H, *J*=1.4 Hz), 5.01 (qdd, 1H, *J*=1.6 Hz, *J*=6.1 Hz, *J*=7.7 Hz), 2.73 (t, 2H, *J*=7.0 Hz), 2.57 (m, 3H), 2.49 (dd, 1H, *J*=7.5 Hz, *J*=13.6 Hz), 1.92 (d, 3H, *J*=1.5 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.3, 172.7, 148.6, 142.0, 132.4,79.3, 78.6, 42.2, 40.9, 24.6, 17.8; HRMS calcd. for ($M+H^+$) 320.9982, found 320.9884.

α,β-Unsaturated Aldehyde 18b: To a solution of aldehyde **18** (0.680 g, 2.124 mmol) in dry benzene (14.16 mL) was added 2-(triphenylphosphoranylidene) propanal (1.352 g, 4.25 mmol, 2eq) in a microwave tube. The reaction mixture was sparged with argon for 10 minutes. The reaction was then microwaved for 40 minutes at 120 °C. The reaction was quenched with sat. NH_4Cl solution (10 mL), the organic layer was

separated and the aqueous layer was extracted 3x with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 30% EtOAc in hexanes) of the crude mixture gave aldehyde **18b** (0.513 g, 1.423 mmol, 67% yield) as a yellow oil. R_f=0.52 (silica, 50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.36 (s, 1H), 7.14 (d, 1H, *J*=1.3 Hz), 6.42 (dt, 1H, *J*=1.2 Hz, *J*=7.1 Hz), 6.08 (d, 1H, *J*=1.4 Hz), 5.05 (dt, 1H, *J*=1.6 Hz, *J*=7.1 Hz), 2.57 (m, 6H), 1.94 (d, 3H, *J*=1.3 Hz), 1.71 (d, 3H, *J*=0.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.8, 172.8, 151.7, 148.2, 142.1, 140.2, 132.9, 79.4, 78.7, 42.2, 26.5, 24.7, 24.0, 9.3; HRMS calcd. for ($M+Na^+$) 383.0112, found 383.0115.

Allyl Alcohol 14: To a solution of aldehyde **18b** (1.58 g, 4.39 mmol) in MeOH (88 mL) at -20 °C was added sodium borohydride (0.183 g, 4.83 mmol, 1.1eq) in one portion. The solution went from orange-red to yellow. The reaction was stirred at -20 °C for 15 minutes. The reaction was quenched with sat. NH_4Cl solution (50 mL), the organic layer was separated and the aqueous layer was extracted 3x with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 55% EtOAc in hexanes) of the crude mixture gave allyl alcohol **14** (1.589 g, 4.39 mmol, 100% yield), as a pale yellow oil, R_f= 0.30 (silica, 50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (d, 1H, *J*=1.4 Hz), 6.07 (d, 1H, *J*=1.4 Hz), 5.35 (m, 1H), 5.02 (ddd, 1H, *J*=1.5 Hz, *J*=6.1 Hz, *J*=7.5 Hz), 3.94 (s, 2H), 2.61 (dd, 1H, *J*=6.0 Hz, *J*=13.6 Hz), 2.50 (dd, 1H, *J*=7.5 Hz, *J*=13.6 Hz), 2.29 (m, 4H), 2.12 (s, 1H), 1.94 (d, 3H, *J*=1.4 Hz), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7, 148.2, 142.6, 136.5, 134.1, 123.9, 79.7, 78.8, 68.5, 42.6, 25.6, 25.3, 25.0, 14.0; HRMS calcd. for ($M+Na^+$) 385.0271, found 385.0273.

Furfural stannane (13): To a suspension of N,O-dimethylhydroxylammonium chloride (3.62 g, 37.1 mmol, 1.3 eq) in THF (190 mL) was added the first amount of butylithium (46.3 mL, 74.1 mmol, 2.6 eq) at -40 °C over 15 minutes. After 30 minutes stirring, furan-2-carbaldehyde (2.362 mL, 28.5 mmol) was added dropwise over 10 minutes. The reaction was stirred at -40 °C for 45 minutes. The second amount of butylithium (26.7 mL, 42.8 mmol, 1.5 eq) was added dropwise over 10 minutes. The reaction was stirred at -40 °C for 1 hour. Then a solution of the chlorotrimethylstannane

(6.82 g, 34.2 mmol, 1.2 eq) in 20 mL of dry THF was added over 5 minutes. The reaction was stirred for 30 minutes then was quenched with sat. NH_4Cl solution (150 mL), the organic layer was separated and the aqueous layer was extracted 3x with ether. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 10% EtOAc in hexanes) of the crude oil yielded stannane **13** (5.32 g, 20.53 mmol, 72% yield) as a pale yellow oil, R_f= 0.33 (silica, 10% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.64 (s, 1H), 7.22 (d, 1H, *J*=3.5 Hz), 6.71 (d, 1H, *J*=3.4 Hz), 0.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.3, 171.3 157.5, 123.1, 121.4, -9.1; HRMS calcd. for ($M+H^+$) 252.9958, found 252.9961.

Carbaldehyde 19: To a solution of alcohol **14** (1.59 g, 4.39 mmol) in DMF (29.3 mL) was added stannane **13** (1.364g, 5.27 mmol, 1.2 eq). The solution was sparged with argon for 15 minutes. To this solution was added $Pd(PPh_3)_4$ (0.203 g, 0.176 mmol, 0.04 eq), copper iodide (0.067 g, 0.351 mmol, 0.08 eq) and cesium fluoride (1.334 g, 8.78 mmol, 2 eq) in one portion at rt. The solution went from yellow to brownish-grey and became heterogeneous. After 10 minutes of stirring, the reaction was quenched with sat. NH_4Cl solution (10 ml), the organic layer was separated and the aqueous layer was extracted 3x with ether. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 70% EtOAc in hexanes) of the crude mixture gave carbaldehyde **19** (1.13 g, 3.42 mmol, 78% yield) as a yellow oil, R_f=0.23 (silica, 60% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.48 (s, 1H), 7.32 (d, 1H, *J*=1.4 Hz), 7.22 (d, 1H, *J*=3.7 Hz), 6.35 (d, 1H, *J*=3.7 Hz), 6.23 (s, 1H), 5.39 (ddd, 1H, *J*=1.3 Hz, *J*=5.5 Hz, *J*=7.9 Hz), 5.13 (qdd, 1H, *J*=1.6 Hz, *J*=3.5 Hz, *J*=8.6 Hz), 3.98 (s, 2H), 3.24 (dd, 1H, *J*=3.5 Hz, *J*=13.8 Hz), 2.44 (dd, 1H, *J*=8.6 Hz, *J*=13.8 Hz), 2.33 (m, 4H), 2.06 (d, 3H, *J*=1.4 Hz), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 173.8, 157.9, 151.2, 148.9, 141.8, 136.4, 133.4, 124.4, 123.6, 115.4, 111.2, 81.4, 68.3, 38.2, 26.6, 25.2, 24.8, 13.6; HRMS calcd. for ($M+Na^+$) 353.1359, found 353.1356.

Allyl Bromide 20: To a solution of carbaldehyde **19** (1.13 g, 3.42 mmol) in dry CH_2Cl_2 (86 mL) at -20 °C was added triphenylphosphine (0.987 g, 3.76 mmol, 1.1 eq), the reaction mixture was stirred until it dissolved. N-bromosuccinimide (0.670 g, 3.76

mmol, 1.1 eq) was then added. After 15 minutes the reaction was complete. The reaction was diluted with water (50 mL), the organic layer was separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 30% EtOAc in hexanes) of the crude mixture gave allyl bromide **20** (1.264 g, 3.22 mmol, 94% yield) as a pale yellow oil, R_f=0.49 (silica, 40% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (s, 1H), 7.26 (s, 1H), 7.20 (d, 1H, *J*=3.7 Hz), 6.35 (d, 1H, *J*=3.7 Hz), 6.24 (s, 1H), 5.54 (t, 1H, *J*=6.8 Hz), 5.13 (ddd, 1H, *J*=1.7 Hz, *J*=3.9 Hz, *J*=8.3 Hz), 3.93 (s, 2H), 3.19 (dd, 1H, *J*=4.0 Hz, *J*=13.8 Hz), 2.53 (dd, 1H, *J*=8.4 Hz, *J*=13.8 Hz), 2.36 (m, 2H), 2.28 (m, 2H), 2.05 (d, 3H, *J*=1.3 Hz), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 176.3, 173.5, 157.8, 151.4, 148.9, 141.3, 133.5, 133.2, 129.3, 123.9, 123.8, 115.6, 111.2, 81.2, 41.2, 38.2, 26.7, 25.9, 24.6, 14.7; HRMS calcd. for ($M+Na^+$) 415.0515, found 415.0516.

Norbipinnatin J (6): Under an argon atmosphere, to dry THF (399 mL) were added powdered molecular sieves (11 g), $CrCl_2$ (3.24 g, 26.4 mmol, 12 eq) and Ni-$(DME)_2Cl_2$ (1.448 g, 6.59 mmol, 3 eq). The reaction was stirred vigorously and sparged with argon for 10 minutes. The amount of allyl bromide **20** (0.864 g, 2.197 mmol) was taken up in dry THF (50 mL) and added to the stirring mixture via syringe pump over 1.5 Hrs at rt. The reaction was left to stir at rt overnight. 100 mL of water was then added and the solution and was diluted in 300 mL of ether. The organic layer was separated and the aqueous layer was extracted 3x with ether. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 25% EtOAc in hexanes) of the crude mixture gave norbipinnatin J (**6**) (0.566 g, 1.80 mmol, 82% yield) as a white solid. R_f=0.21 (silica, 30% EtOAc in hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.82 (t, 1H, *J*=1.6 Hz), 6.36 (d, 1H, *J*=3.2 Hz), 6.16 (s, 1H), 6.14 (d, 1H, *J*=3.2 Hz), 5.15 (m, 1H), 5.05 (s, 1H), 4.99 (m, 1H), 4.46 (dd, 1H, *J*=2.3 Hz, *J*=11.0 Hz), 3.22 (t, 1H, *J*=11.9 Hz), 2.74 (dd, 1H, *J*=4.4 Hz, *J*=11.8Hz), 2.40 (dt, 1H, *J*=3.1 Hz, *J*=14.5 Hz), 2.35 (t, 1H, *J*=10.9 Hz), 2.09 (m, 1H), 2.00 (d, 3H, *J*=1.2 Hz), 1.97 (d, 1H, *J*=2.6 Hz), 1.77 (d, 3H, *J*=0.6 Hz), 1.67 (tdd, 1H, *J*=3.4 Hz, *J*=10.9 Hz, *J*=13.9 Hz), 0.88 (dt, 1H, *J*=3.6 Hz, *J*=13.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3, 153.8, 152.3, 152.1, 141.9, 132.6, 129.2, 118.7, 117.4, 112.0, 111.0, 78.6,

67.4, 51.2, 39.6, 30.0, 25.9, 19.6, 17.4; HRMS calcd. for (M+Na^+) 337.1410, found 337.1414.

Norrubifolide (4): To a solution of Norbipinnatin J (**6**) (0.456 g, 1.450 mmol) in dry CH_2Cl_2 (58.0 mL) was first added triethylsilane (1.019 mL, 6.38 mmol, 4.4 eq), then trifluoroacetic acid (0.246 mL, 3.19 mmol, 2.2 eq) dropwise. After 15 minutes, the reaction was quenched with sat. $NaHCO_3$ solution (25 mL), the organic layer was separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 15% EtOAc in hexanes) of the crude mixture gave norrubifolide **4** (0.407 g, 1.407 mmol, 97% yield) as a white solid, R_f=0.70 (silica, 30% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.88 (s, 1H), 6.11 (s, 1H), 6.09 (d, 1H, *J*=3.2 Hz), 6.03 (dd, 1H, *J*=1.4 Hz, *J*=3.1 Hz), 4.97 (tdd, 1H, *J*=1.8 Hz, *J*=4.0 Hz, *J*=11.8 Hz), 4.90 (m, 1H), 4.88 (s, 1H), 3.25 (t, 1H, *J*=11.8 Hz), 2.69 (m, 2H), 2.58 (dd, 1H, *J*=12.5 Hz, *J*=15.3 Hz), 2.39 (m, 2H), 2.09 (m, 1H), 1.99 (s, 3H), 1.72 (s, 3H), 1.65 (tdd, 1H, *J*=3.4 Hz, *J*=10.8 Hz, *J*=14.0 Hz), 1.18 (ddt, 1H, *J*=0.9 Hz, *J*=3.5 Hz, *J*=13.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)d; 174.5, 154.1, 152.0, 151.2, 145.2, 132.9, 127.3, 117.5, 113.2, 111.1, 108.7, 78.7, 43.4, 39.6, 32.9, 31.1, 25.8, 20.0, 19.1; HRMS calcd. for (M+Na^+) 321.1461, found 321.1460.

Diol 21: To a solution of norrubifolide (**4**) (0.064 g, 0.214 mmol) in a 1:1:1 ratio of water (0.298 mL), THF (0.298 mL) and acetone (0.298 mL) was added NMO (0.030 g, 0.257 mmol, 1.2 eq). The mixture was cooled to 0 °C and treated with osmium tetroxide 4% solution in water (0.136 mL, 0.021 mmol, 0.1eq) added dropwise. The reaction went from light yellow to brown and then turned dark green. It was stirred at 0 °C for 1.5h and then warmed up to rt and stirred for an additional 1.5h. The solution was quenched with sat. Na_2SO_3 solution, the organic layer was separated and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure. Flash chromatography (up to 80% EtOAc in hexanes) of the crude mixture gave diol **21** (0.046 g, 0.137 mmol, 64% yield) as a white solid, R_f=0.20 (silica, 50% Ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.24 (d, 1H, *J*=3.0 Hz), 6.12 (d, 1H, *J*=3.0 Hz), 5.74 (s, 1H), 4.94 (d, 1H, *J*=11.4 Hz), 4.81 (s, 1H), 4.77 (s, 1H), 4.55 (s, 1H), 2.70 (d, 1H, *J*=13.3 Hz), 2.51 (dd,

1H, *J*=12.3 Hz, *J*=14.3 Hz), 2.34 (m, 2H), 2.24 (dd, 1H, *J*=11.5 Hz, *J*=14.4 Hz), 2.11 (m, 2H), 1.73 (s, 3H), 1.70 (m, 2H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:173.7, 154.4, 149.8, 148.7, 146.3, 133.3, 112.4, 109.4, 108.7, 79.2, 75.7, 73.3, 43.9, 40.0, 33.1, 27.8, 23.4, 21.6, 18.9; HRMS calcd. for (M+Na^+) 355.1516, found 355.1518.

Teriary Alcohol (**22**)**:** To a solution of diol **21** (0.0496 g, 0.149 mmol) in CH_2Cl_2 (9.95 mL) at - 40 °C was added boron trifluoride diethyl etherate (0.057 mL, 0.448 mmol, 3 eq) and triethylsilane (0.143 mL, 0.895 mmol, 6 eq). After 10 minutes, the reaction was quenched with sat. NH_4Cl solution (3 mL), the organic layer was separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 60% EtOAc in hexanes) of the crude mixture gave tertiary alcohol **22** (0.024 g, 0.075 mmol, 51% yield) as clear crystals, R_f=0.29 (silica, 50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.08 (m, 2H), 6.02 (d, 1H, *J*=3.0 Hz), 4.88 (d, 1H, *J*=11.3 Hz), 4.79 (m, 1H), 4.77 (s, 1H), 2.88 (q, 2H, *J*=14.7 Hz), 2.65 (dd, 1H, *J*=1.5 Hz, *J*=14.7 Hz), 2.49 (dd, 1H, *J*=11.6 Hz, *J*=14.7 Hz), 2.42 (dd, 1H, *J*=4.0 Hz, *J*=14.0 Hz), 2.33 (ddd, 1H, *J*=4.2 Hz, *J*=11.5 Hz, *J*=15.9 Hz), 2.13 (m, 2H), 1.93 (bs, 1H), 1.85 (dd, 1H, *J*=11.4 Hz, *J*=14.0 Hz), 1.77 (m, 2H), 1.72 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7, 153.9, 149.7, 149.3, 146.5, 133.0, 112.2, 108.9, 108.2, 79.1, 71.2, 45.6, 44.3, 43.2, 33.0, 28.4, 26.6, 21.6, 18.8; HRMS calcd. for (M+Na^+) 339.1567, found 339.1565.

Norcembrenolide B (7): To a solution of alcohol **22** (0.124 g, 0.392 mmol) in acetone (1.3 mL) at 0 °C was added Jones reagent (0.161 mL, 0.431 mmol, 1.1 eq) dropwise. After 20 minutes, the reaction was quenched with sat. $NaHCO_3$ solution (100 mL), the organic layer was separated and the aqueous layer was extracted 3x with ethyl acetate. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 6% Acetone in CH_2Cl_2) of the crude mixture gave Norcembrenolide B **3** (0.0646 g, 0.194 mmol, 50% yield) as a white solid, R_f: 0.30 (silica, 5% Acetone in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ:7.21 (s, 1H), 5.13 (bs, 1H), 4.80 (s, 1H), 4.68 (s, 1H), 4.15 (dd, 1H, *J*=3.5 Hz, *J*=8.3 Hz), 2.97 (dd, 1H, *J*=3.4 Hz, *J*=15.3 Hz), 2.59 (dd, 1H, *J*=6.8 Hz, *J*=16.9 Hz), 2.53 (dd, 1H, *J*=10.7 Hz, *J*=24.6 Hz), 2.50 (m, 1H) 2.44 (d, 1H, *J*=18.1 Hz), 2.39

(m, 2H), 2.35 (dd, 1H, *J*=5.9 Hz, *J*=12.8 Hz), 2.22 (m, 3H), 1.94 (ddd, 1H, *J*=2.4 Hz, *J*=4.7 Hz, *J*=14.6 Hz), 1.76 (m, 1H), 1.66 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6)δ:211.6, 206.5, 173.4, 150.3, 146.1, 127.6, 112.9, 78.2, 77.8, 74.6, 47.8, 46.1, 45.6, 42.7, 40.8, 27.8, 24.6, 21.1, 18.0; HRMS calcd. for (M+Na^+) 355.1516, found 355.1514.

Polycyclic cembrenoids 24 and 25: To a solution of norcembrenolide B (**3**) (0.004 g, 0.012 mmol) in dry THF at 0 °C was added a 40 wt. % Triton B solution in methanol (0.001 mL, 0.002 mmol, 0.2 eq) dropwise. The reaction was stirred at 0 °C for 10 minutes, and then quenched with solid sodium sulfite and allowed to stir for 30 minutes. The reaction was diluted in dry ether, filtered over celite, and concentrated under reduced pressure. Flash chromatography (up to 3% Acetone in DCM) of the crude mixture gave polycyclic cembrenoid **24** (0.5 mg, 1.5 μmol, 13% yield) as a white solid, R_f: 0.34 (silica, 40% EtOAc in hexanes), and polycyclic cembrenoid **25** (1.0 mg, 3.0μmol, 25% yield) as a white solid, R_f: 0.19 (silica, 40% EtOAc in hexanes); **24:**^{1}H NMR (400 MHz, $CDCl_3$)δ: (400 MHz) 4.74 (s, 1H) 4.72 (s, 1H) 4.29 (s, 1H) 3.67 (d, 1H, J=9.8Hz) 3.02 (dd, 1H, J=10.2 Hz, J=11.3 Hz) 2.64 (dd, 1H, J=1.6 Hz, J=12.7 Hz)2.53 (m, 1H) 2.41 (m, 3H) 2.30 (t, 1H, J=11.3 Hz) 2.09 (s, 1H) 1.98 (dd, 2H, J=2.7 Hz, J=10.3 Hz) 1.73 (m, 3H) 1.38 (s, 3H);HRMS calcd. for (M+Na^+) 355.1516, found 355.1517; **25:** 1H-NMR (400 MHz)5.18 (s, 1H)4.72 (s, 1H) 4.66 (s, 1H) 4.12 (dd, 1H, J=2.5Hz, J=4.7Hz) 3.33 (m, 1H) 2.64 (d, 1H, J=9.2Hz) 2.58 (d, 1H, J=15.4Hz) 2.46 (dt, 1H, J=3.7Hz, J=13.2Hz) 2.17 (s, 1H) 1.97 (dd, 1H, J=4.6Hz, J=15.4Hz) 1.43 (s, 3H) 1.24 (s, 3H);HRMS calcd. for (M+Na^+) 355.1516, found 355.1518.

Norcoralloidolide A (5): To a solution of norrubifolide **4** (0.288 g, 0.965 mmol) in dry THF (3.11 mL) at 0 °C was added tBuOOH (0.241 mL, 1.448 mmol, 1.5 eq) dropwise. The reaction was stirred for 5 minutes at 0 °C. triton B (4.39 μl, 9.65 μmol, 0.01 eq) was then immediately added dropwise. The reaction was then stirred at 0 °C and monitored by TLC. The reaction completed within 10 minutes. The reaction was quenched by adding solid Na_2SO_3 and stirred for 30 minutes. The reaction was then diluted with dry ether and filtered over celite. The reaction was concentrated under reduced pressure and yielded norcoralloidolide A(**5**)(0.300 g, 0.956 mmol, 99% yield) as a white solid which was used without further purification. R_f=0.55 (silica, 20%

EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.18 (s, 1H), 6.11 (d, 1H, *J*=3.1 Hz), 6.04 (dd, 1H, *J*=1.5 Hz, *J*=3.1 Hz), 4.96 (m, 1H), 4.87 (s, 1H), 4.56 (dd, 1H, *J*=4.3 Hz, *J*=12.7 Hz), 3.76 (s, 1H), 3.68 (t, 1H, *J*=12.7 Hz), 2.78 (d, 1H, *J*=14.8 Hz), 2.60 (m, 1H), 2.55 (m, 3H), 1.98 (s, 3H), 1.73 (s, 3H), 1.55 (m, 2H), 1.03 (dd, 1H, *J*=12.3 Hz, *J*=14.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 172.3, 152.9, 150.7, 144.5, 127.0, 117.9, 113.4, 110.8, 108.4, 77.1, 61.3, 60.7, 44.1, 36.1, 32.9, 27.6, 25.0, 21.5, 19.1; HRMS calcd. for (M+Na^+) 337.1410, found 337.1408.

Diol 26: Norcoralloidolide A (**5**) (0.059 g, 0.188 mmol) was subjected to identical conditions found for diol **21**. Flash chromatography (up to 80% EtOAc in hexanes) of the crude mixture gave diol **24** (0.027 g, 0.076 mmol, 42% yield) as a white solid, R_f=0.20 (silica, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$)δ: 6.24 (d, 1H, *J*=3.1 Hz), 6.04 (dd, 1H, *J*=1.1 Hz, *J*=3.1 Hz), 4.92 (s, 2H), 4.67 (dd, 1H, *J*=6.9 Hz, *J*=8.9 Hz), 4.53 (s, 1H), 3.54 (s, 1H), 2.77 (d, 1H, *J*=13.7 Hz), 2.62 (m, 2H), 2.40 (m, 1H), 2.00 (dd, 1H, *J*=9.0 Hz, *J*=15.1 Hz), 1.81 (dd, 1H, *J*=6.9 Hz, *J*=15.1 Hz), 1.74 (s, 3H), 1.55 (m, 2H), 1.38 (s, 3H), 1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 171.5, 153.8, 150.4, 145.3, 112.8, 109.6, 107.9, 75.4, 75.3, 73.1, 62.6, 60.5, 43.2, 39.8, 32.0, 27.2, 25.9, 21.3, 19.3; HRMS calcd. for (M+Na^+) 371.1465, found 371.1463.

Tertiary alcohol 27: Diol **26** (0.0245 g, 0.070 mmol) was subjected to identical conditions found for tertiary alcohol **22** to afford compound **27** (0.014 g, 0.042 mmol, 60% yield) as clear crystals, R_f=0.32 (silica, 50% EtOAc in hexanes), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.06 (d, 1H, *J*=3.0 Hz), 5.96 (d, 1H, *J*=2.9 Hz), 4.99 (s, 1H), 4.90 (m, 1H), 4.71 (t, 1H, *J*=8.1 Hz), 3.83 (s, 1H), 3.20 (d, 1H, *J*=14.7 Hz), 2.93 (m, 1H), 2.81 (d, 1H, *J*=14.7 Hz), 2.72 (dd, 1H, *J*=2.1 Hz, *J*=15.7 Hz), 2.59 (dd, 1H, *J*=11.8 Hz, *J*=15.8 Hz), 2.44 (m, 1H), 1.73 (s, 3H), 1.66 (dd, 2H, *J*=5.1 Hz, *J*=8.1 Hz), 1.62 (dd, 1H, *J*=3.9 Hz, *J*=8.1 Hz), 1.45 (m, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8, 152.9, 149.8, 145.7, 112.7, 108.9, 107.4, 75.3, 71.6, 62.7, 60.9, 42.1, 41.9, 41.0, 31.7, 29.1, 27.7, 22.0, 19.1; HRMS calcd.for (M+Na^+) 355.1516, found 355.1511.

Scabrolide D (Norcembrenolide C, 8): Tertiary alcohol **27** (0.0363 g, 0.109 mmol) was subjected to identical conditions as norcembrenolide B (**7**). Flash chromatography (up to 4% Acetone in CH_2Cl_2) of the crude mixture gave scabrolide D (**8**)

(0.019 g, 0.055 mmol, 51% yield) as a white solid, R_f=0.45 (silica, 5% Acetone in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.93 (s, 1H), 4.86 (s, 1H), 4.74 (t, 1H, *J*=6.6 Hz), 4.20 (dd, 1H, *J*=4.0 Hz, *J*=5.7 Hz), 3.95 (s, 1H), 3.09 (dd, 1H, *J*=4.0 Hz, *J*=16.4 Hz), 2.73 (dd, 1H, *J*=5.8 Hz, *J*=16.4 Hz), 2.63 (d, 1H, *J*=18.2 Hz), 2.61 (m, 1H), 2.52 (dd, 1H, *J*=2.4 Hz, *J*=12.0 Hz), 2.49 (d, 1H, *J*=18.2 Hz), 2.31 (dd, 1H, *J*=7.0 Hz, *J*=14.9 Hz), 2.20 (m, 2H), 2.11 (dd, 1H, *J*=6.2 Hz, *J*=14.9 Hz), 1.75 (m, 1H), 1.68 (s, 3H), 1.65 (dd, 1H, *J*=3.5 Hz, *J*=8.2 Hz), 1.47 (s, 3H), 1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.8, 207.6, 172.3, 145.7, 112.7, 79.1, 75.8, 75.0, 62.7, 60.7, 49.7, 48.3, 44.7, 42.4, 40.7, 26.9, 25.6, 21.3, 18.7; HRMS calcd. for (M+Na^+) 371.1465, found 371.1466.

Allyl Alcohol 28: To a solution of 2,2,6,6-tetramethylpiperidine (0.149 mL, 0.878 mmol, 12 eq) in dry toluene (0.290 mL) at 0 °C was added butylithium (0.549 mL, 0.878 mmol, 12 eq) dropwise. The solution was warmed to rt and stirred for 30 minutes. The solution was then cooled to 0 °C and diethylaluminum chloride (0.975 mL, 0.878 mmol, 12 eq) added dropwise and stirred for 40 minutes. In a separate container, Norcoralloidolide A (**5**) (.023 g, 0.073 mmol) was dissolved in dry toluene (0.602 mL) and cooled to 0 °C. The first solution was transferred via cannula into the solution containing norcoralloidolide A (**5**) and stirred at 0 °C. Reaction was completed in 5 minutes and quenched with sat. NH_4Cl (5 mL). The organic layer was dilute with EtOAc, separated, and the aqueous layer was extracted 3x with EtOAc. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 35% EtOAc in hexanes) of the crude mixture gave allyl alcohol **28** (0.011 g, 0.035 mmol, 48% yield) as a white solid, R_f: 0.36 (silica, 20% EtOAc in hexanes) and recollection of starting material; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.00 (dd, 1H, J=2.5 Hz, J=12.3 Hz) 6.11 (s, 1H) 6.07 (d, 1H, J=3.2 Hz) 5.90 (d, 1H, J=3.1 Hz) 4.89 (s, 1H) 4.72 (s, 1H) 4.61 (dd, 1H, J=3.8 Hz, J=12.6 Hz) 4.49 (s, 1H) 3.18 (t, 1H, J=12.6 Hz) 2.82 (d, 1H, J=14.8 Hz) 2.71 (dd, 1H, J=5.1 Hz, J=14.9 Hz) 2.60 (m, 1H) 2.40 (d, 1H, J=15.0 Hz) 2.29 (dd, 1H, J=3.6 Hz, J=12.8 Hz) 2.19 (td, 1H, J=12.3 Hz, J=15.1 Hz) 1.96 (s, 3H) 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 151.2, 145.4, 145.1, 131.4, 128.7, 118.0, 111.8, 111.0, 109.7, 84.0, 69.5, 44.1, 37.4, 31.9, 29.9, 29.1, 25.2, 22.9; HRMS calcd. for (M+Na^+) 315.1591, found 315.1589.

Alcohol 32: To a solution of allyl alcohol **28** (0.02 g, 0.064 mmol) in dry, degassed chloroform (0.636 mL) and 4 Å activated molecular sieves (0.3 g) at rt was added rhenium(VII) oxide (3 mg, 0.006 mmol, 0.1 eq). The reaction was stirred overnight and quenched with sat. $NaHCO_3$. The organic layer was dilute with DCM, separated, and the aqueous layer was extracted 3x with DCM. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 40% EtOAc in hexanes) of the crude mixture gave alcohol **32** (0.016 g, 0.050 mmol, 78% yield) as a white solid, R_f: 0.22 (silica, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.17 (d, 1H, J=1.3 Hz) 6.13 (s, 1H) 6.11 (d, 1H, J=3.2 Hz) 6.07 (dd, 1H, J=1.1 Hz, J=3.1 Hz) 5.04 (ddd, 1H, J=1.3 Hz, J=4.5 Hz, J=11.8 Hz) 4.89 (s, 2H) 4.57 (dd, 1H, J=4.0 Hz, J=11.8 Hz) 3.21 (t, 1H, J=11.8 Hz) 2.75 (dd, 1H, J=4.6 Hz, J=11.9 Hz) 2.61 (m, 2H) 2.17 (dt, 1H, J=5.0 Hz, J=11.6 Hz) 2.00 (s, 3H) 1.94 (m, 1H) 1.75 (s, 3H) 1.30 (t, 1H, J=12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.0, 153.9, 153.6, 151.1, 145.3, 135.9, 126.9, 117.6, 113.0, 111.4, 109.2, 79.1, 62.7, 42.2, 39.7, 39.3, 32.8, 25.7, 19.2; HRMS calcd. for (M+Na^+) 377.1410, found 377.1407.

α-keto butenolide 33: To a solution of the alcohol **32** (0.020 g, 0.064 mmol) in CH_2Cl_2(0.318 mL) at rt was added $NaHCO_3$ (0.080 g, 0.954 mmol, 15 eq) followed by Dess-Martin periodinate (0.108 g, 0.254 mmol, 4 eq) in one portion. After 15 minutes, the reaction was completed. A 1:1:1 mixture of aq. sat. $Na_2S_2O_3$, aq. sat. $NaHCO_3$ and water (0.5 mL) was added slowly to the CH_2Cl_2solution and was stirred vigorously for 20 minutes. Layers were separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield the sensitive a-keto butenolide **33** (0.011 g, 0.034 mmol, 54% yield) as a white solid, which was used without further purification. R_f: 0.37 (silica, 40% EtOAc in hexanes).

Alcohol 29: To a solution of α-keto butenolide **33** (0.020, 0.064 mmol) in dry methanol (0.26 mL) at 0 °C was added cerium(III) chloride (0.021 g, 0.083 mmol, 1.3 eq) followed by $NaBH_4$ (0.0032 g, 0.085 mmol, 1.3 eq). The reaction was stirred for 15 minutes and then quenched sat. NH_4Cl (0.50 mL). The organic layer was dilute with EtOAc, separated, and the aqueous layer was extracted 3x with EtOAc. The combined

organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 40% EtOAc in hexanes) of the crude mixture gave allyl alcohol **29** (0.003 g, 0.0095 mmol, 15% yield) as a white solid, R_f: 0.22 (silica, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.79 (s, 1H) 6.11 (s, 1H) 6.08 (d, 1H, J=3.2 Hz) 6.03 (d, 1H, J=2.8 Hz) 5.06 (tdd, 1H, J=1.4 Hz, J=4.8 Hz, J=11.7 Hz) 4.97 (s, 1H) 4.85 (m, 2H) 4.25 (d, 1H, J=8.7 Hz) 3.30 (t, 1H, J=11.8 Hz) 2.77 (dd, 1H, J=4.9 Hz, J=11.9 Hz) 2.64 (s, 3H) 2.22 (ddd, 1H, J=4.2 Hz, J=7.5 Hz, J=13.0 Hz) 1.99 (s, 3H) 1.80 (m, 3H) 1.22 (dd, 1H, J=2.2 Hz, J=4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.9, 173.6, 153.8, 151.1, 148.3, 131.4, 127.3, 117.6, 112.0, 111.1, 108.9, 79.2, 68.9, 41.7, 39.7, 39.5, 34.0, 25.5, 19.0; HRMS calcd. for ($M+Na^+$) 377.1410, found 377.1411.

Epoxide 34: Alcohol **32** (0.175 g, 0.557 mmol) was subjected to identical conditions found for norcoralloidolide A (**5**). Flash chromatography (up to 30% EtOAc in hexanes) of the crude mixture gave epoxide **34** (0.171 g, 0.517 mmol, 93% yield) as a white solid, R_f: 0.41 (silica, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.19 (s, 1H) 6.11 (d, 1H, J=3.0 Hz) 6.05 (s, 1H) 4.96 (s, 1H) 4.91 (s, 1H) 4.67 (dd, 1H, J=4.8 Hz, J=12.6 Hz) 4.56 (dd, 1H, J=3.2 Hz, J=11.2 Hz) 3.90 (s, 1H) 3.70 (t, 1H, J=12.7 Hz) 2.82 (dd, 1H, J=2.7 Hz, J=15.4 Hz) 2.59 (td, 2H, J=8.7 Hz, J=12.6 Hz) 2.46 (dt, 1H, J=1.6 Hz, J=11.7 Hz) 1.98 (s, 3H) 1.94 (dd, 1H, J=2.5 Hz, J=13.2 Hz) 1.78 (s, 3H) 1.06 (t, 1H, J=12.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 152.6, 150.7, 144.7, 126.6, 118.1, 112.8, 111.0, 108.7, 77.0, 61.8, 61.3, 60.8, 40.8, 36.7, 36.0, 33.0, 24.9, 19.6; HRMS calcd. for ($M+Na^+$) 353.1359, found 353.1358.

Ketone 34b: To a solution of the epoxide **34** (0.171 g, 0.514 mmol) in CH_2Cl_2 (2.58 mL) at rt was added $NaHCO_3$ (0.260 g, 3.10 mmol, 6 eq) followed by Dess-Martin periodinate (0.285 g, 0.672 mmol, 1.3 eq) in one portion. After 15 minutes, the reaction was completed. A 1:1:1 mixture of aq. sat. $Na_2S_2O_3$, aq. sat. $NaHCO_3$ and water (3 mL) was added slowly to the CH_2Cl_2solution and was stirred vigorously for 20 minutes. Layers were separated and the aqueous layer was extracted 3x with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield ketone **34b** as a white solid that was used without further purification. R_f: 0.56 (silica, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.23 (s, 1H)

6.10 (d, 1H, J=3.2 Hz) 6.00 (dd, 1H, J=1.2 Hz, J=3.2 Hz) 4.87 (s, 1H) 4.80 (s, 1H) 4.62 (dd, 1H, J=5.1 Hz, J=12.2 Hz) 3.95 (s, 1H) 3.52 (t, 1H, J=12.5 Hz) 3.35 (d, 1H, J=13.6 Hz) 3.02 (m, 1H) 2.88 (dd, 1H, J=2.9 Hz, J=15.6 Hz) 2.75 (dd, 1H, J=9.7 Hz, J=15.7 Hz) 2.64 (dd, 1H, J=5.9 Hz, J=11.9 Hz) 2.60 (dd, 1H, J=11.8 Hz, J=13.7 Hz) 1.99 (s, 3H) 1.83 (s, 3H).

Alcohol 35: To a solution of ketone **34b** (0.170 g, 0.518 mmol) in DCM (17.3 mL) at -78 °C was added a 1 molar solution of Super hydride in DCM (0.518 mL, 0.518 mmol, 1 eq) dropwise. The reaction was stirred for 5 minutes and then quenched with a few drops of methanol followed by sat. NH_4Cl (17 mL). The organic layer was dilute with DCM, separated, and the aqueous layer was extracted 3x with DCM. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 30% EtOAc in hexanes) of the crude mixture gave alcohol **35** (0.152 g, 0.460 mmol, 89% yield) as a white solid, R_f: 0.41 (silica, 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.19 (s, 1H) 6.09 (d, 1H, J=3.2 Hz) 6.03 (d, 1H, J=3.1 Hz) 4.92 (s, 1H) 4.87 (s, 1H) 4.66 (dd, 1H, J=5.1 Hz, J=12.5 Hz) 3.88 (m, 1H) 3.84 (m, 1H) 3.62 (t, 1H, J=12.7 Hz) 3.38 (d, 1H, J=9.3 Hz) 2.69 (m, 4H) 2.22 (ddd, 1H, J=6.4 Hz, J=7.9 Hz, J=14.6 Hz) 1.97 (s, 3H) 1.80 (s, 3H) 1.49 (td, 1H, J=4.5 Hz, J=14.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 152.8, 150.6, 147.4, 127.7, 118.2, 112.3, 110.6, 108.2, 77.0, 70.9, 62.3, 59.0, 41.8, 36.4, 36.3, 33.3, 24.8, 19.1.

Acetate 36: To a solution of alcohol **35** (0.039 g, 0.118 mmol) in acetonitrile (2.4 mL) at rt was added acetic anhydride (0.024 g, 0.236 mmol, 2 eq) followed by scandium (III) triflate (2.9 mg, 0.006 mmol, 0.05 eq). The solution was stirred for 10 minutes and then quenched with Sat. bicarb. The organic layer was dilute with ether, separated, and the aqueous layer was extracted 3x with ether. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (up to 40% EtOAc in hexanes) of the crude mixture gave acetate **36** (0.026 g, 0.070 mmol, 60% yield) as a white solid, R_f: 0.69 (silica, 40% EtOAc in hexanes);^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.24 (s, 1H) 6.10 (d, 1H, J=3.2Hz) 6.06 (d, 1H, J=3.1Hz) 4.98 (dd, 1H, J=5.0Hz, J=9.6Hz) 4.77 (s, 1H) 4.71 (s, 1H) 4.60 (dd, 1H, J=4.4Hz, J=12.6Hz) 3.94 (s, 1H) 3.41 (t, 1H, J=12.7Hz) 2.80 (dd, 1H,

J=6.2Hz, J=8.6Hz) 2.80 (dd, 1H, J=6.1Hz, J=40.7Hz) 2.63 (td, 1H, J=4.5Hz, J=11.3Hz) 2.54 (dd, 1H, J=4.4Hz, J=12.7Hz) 2.45 (ddd, 1H, J=3.9Hz, J=9.6Hz, J=13.7Hz) 2.10 (s, 3H) 1.97 (s, 3H) 1.90 (m, 1H) 1.75 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ:170.2, 168.5, 152.9, 150.2, 147.4, 129.0, 118.6, 110.6, 110.5, 107.8, 76.2, 69.1, 64.2, 57.7, 41.2, 36.8, 35.2, 32.3, 25.0, 20.9, 20.3;

Diol 37: Epoxide **36** (0.026 g, 0.070 mmol) was subjected to identical conditions found for diol **18**. Flash chromatography (up to 80% EtOAc in hexanes) of the crude mixture gave diol **24** (0.011 g, 0.027 mmol, 39% yield) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ:6.32 (d, 1H, J=3.2 Hz) 6.09 (d, 1H, J=3.3 Hz) 5.11 (t, 1H, J=5.8 Hz) 4.79 (s, 1H) 4.72 (s, 1H) 4.62 (m, 2H) 4.01 (m, 1H) 2.06 (s, 3H) 1.80 (s, 1H) 1.46 (s, 1H);

Tertiary alcohol 38: Diol **37** (0.004 g, 0.010 mmol) was subjected to identical conditions found for tertiary alcohol **19** to afford compound **38** (0.018 g, 4.6 μmol, 48% yield) as a white solid;^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.11 (d, 1H, J=3.1 Hz) 6.00 (d, 1H, J=3.0 Hz) 5.13 (t, 1H, J=5.4 Hz) 4.80 (s, 1H) 4.74 (s, 1H) 4.66 (dd, 1H, J=6.3 Hz, J=9.6 Hz) 4.34 (s, 1H) 2.06 (s, 3H) 1.81 (s, 3H) 1.42 (s, 3H).

Scabrolide G acetate (39): Tertiary alcohol **25** (0.018 g, 4.6 μmol) was subjected to identical conditions as norcembrenolide B (**3**) to afford **39** (0.0009 g, 2.2 μmol, 48% yield) as a white solid;^{1}H NMR (400 MHz, $CDCl_3$) δ:4.76 (s, 1H) 4.68 (s, 1H) 4.23 (dd, 1H, J=2.5 Hz, J=7.7 Hz) 4.20 (s, 1H) 2.53 (s, 1H) 2.04 (s, 3H) 1.77 (s, 3H) 1.49 (s, 3H)

TBDPS Alcohol 40: To a solution of Alcohol X in DMF (1.725 mL) at 0°C was added imidazole (0.117 g, 1.725 mmol, 10 eq) followed by tert-butyldiphenylchlorosilane (0.133 mL, 0.518 mmol, 3 eq). The reaction was allowed to stir until complete by TLC. Reaction was then quenched with methanol and allowed to warm to RT and stir for 15 minutes. Sat. Ammonia chloride was then added and stirred for 10 minutes. Extracted with ether. The organic layer was dilute with ether, separated, and the aqueous layer was extracted 3x with ether. The combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

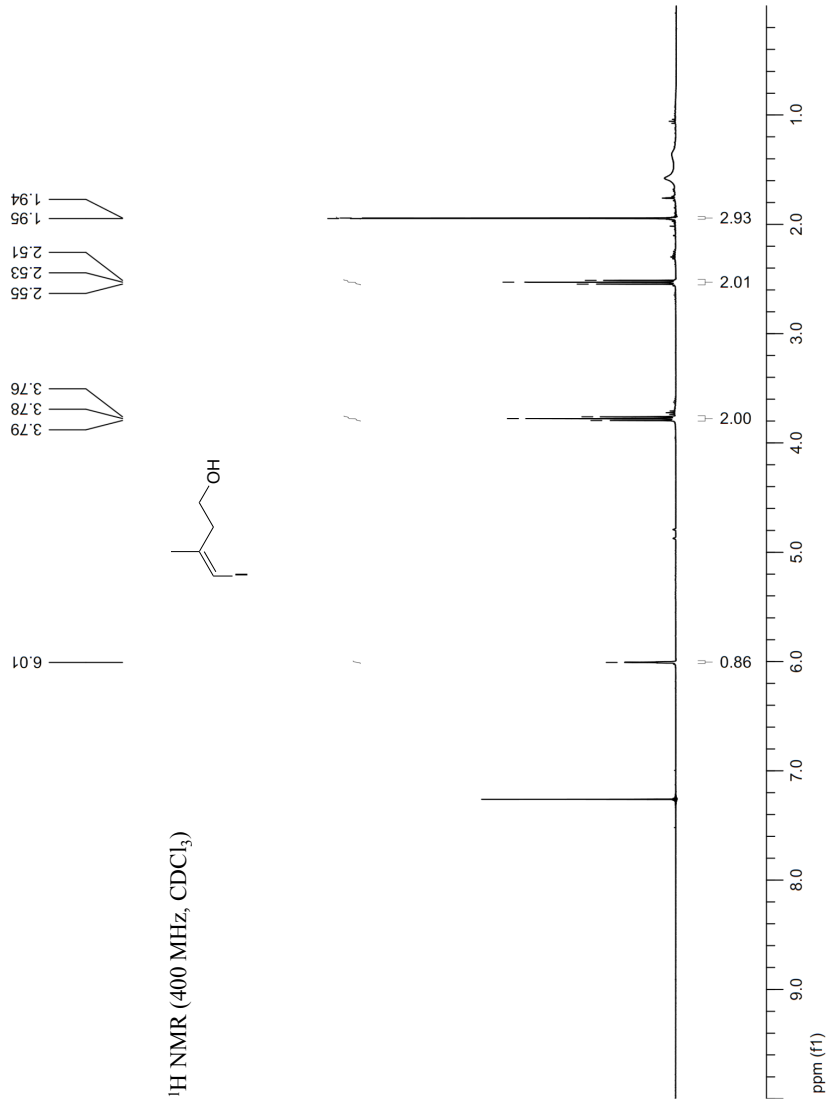
Flash chromatography (up to 7% EtOAc in hexanes) of the crude mixture gave compound **40** (0.777 g, 0.137 mmol, 79% yield) as a white solid, R_f: 0.74 (silica, 10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (m, 4H) 7.41 (m, 6H) 6.16 (s, 1H) 5.92 (d, 1H, J=3.1 Hz) 5.63 (d, 1H, J=3.1 Hz) 4.67 (m, 1H) 4.58 (s, 1H) 4.49 (dd, 1H, J=4.5 Hz, J=12.6 Hz) 3.62 (dd, 1H, J=4.9 Hz, J=11.0 Hz) 3.43 (s, 1H) 3.38 (t, 1H, J=12.7 Hz) 2.58 (ddd, 1H, J=2.5 Hz, J=11.1 Hz, J=13.7 Hz) 2.47 (m, 4H) 2.10 (dd, 1H, J=6.9 Hz, J=15.7 Hz) 1.93 (s, 3H) 1.62 (s, 3H) 1.06 (s, 9H); HRMS calcd. for ($M+Na^+$) 591.2537, found 591.2534.

Diol 41: TBDPS Alcohol **40** (0.117 g, 0.021 mmol) was subjected to identical conditions found for diol **18**. Flash chromatography (up to 80% EtOAc in hexanes) of the crude mixture gave diol **41** (0.0031 g, 5.2 μmol, 25% yield) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (m, 4H) 7.41 (m, 6H) 6.11 (d, 1H, J=3.1 Hz) 5.51 (d, 1H, J=3.0 Hz) 4.67 (s, 1H) 4.55 (s, 1H) 4.51 (dd, 1H, J=4.8 Hz, J=12.3 Hz) 4.44 (s, 1H) 3.65 (s, 1H) 3.64 (dd, 1H, J=4.7 Hz, J=10.9 Hz) 2.75 (s, 1H) 1.65 (s, 3H) 1.35 (s, 3H) 1.07 (s, 9H); HRMS calcd. for ($M+Na^+$) 625.2592, found 625.2582.

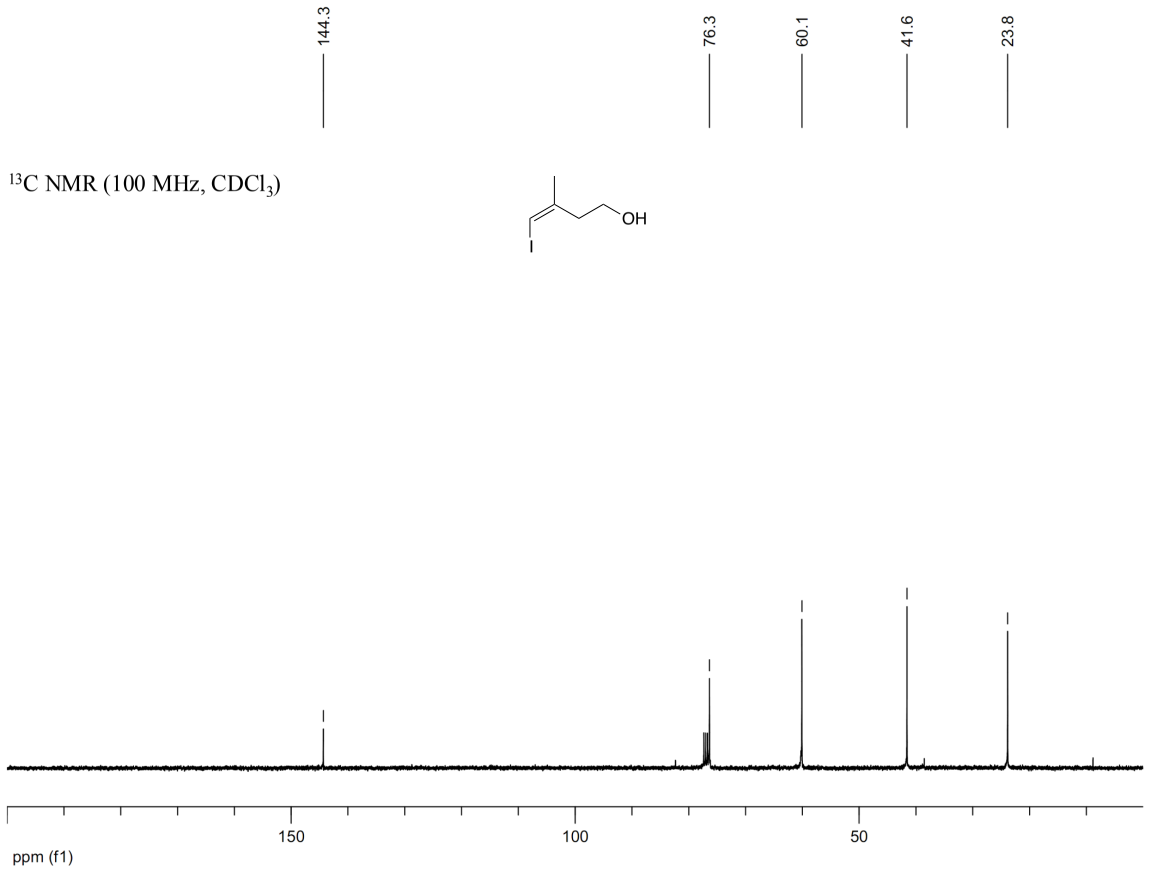
Tertiary alcohol 42: Diol **41**(0.0053 g, 8.8 μmol) was subjected to identical conditions found for tertiary alcohol **19** to afford compound **42** (0.016 g, 2.7 μmol, 31% yield) as a white solid;^{1}H NMR (400 MHz, $CDCl_3$)δ:7.67 (m, 4H) 7.40 (ddd, 1H, J=6.3 Hz, J=10.7 Hz, J=20.5 Hz) 5.98 (d, 1H, J=3.1 Hz) 5.64 (d, 1H, J=2.9 Hz) 4.64 (s, 1H) 4.48 (s, 1H) 3.80 (dd, 1H, J=4.4 Hz, J=10.7 Hz) 3.77 (s, 1H) 3.34 (m, 1H) 2.82 (dd, 1H, J=14.9 Hz, J=44.4 Hz) 1.61 (s,3H) 1.37 (s, 3H) 1.08 (s, 9H); HRMS calcd. for ($M+Na^+$) 609.2643, found 609.2641.

3.2 Spectral Data

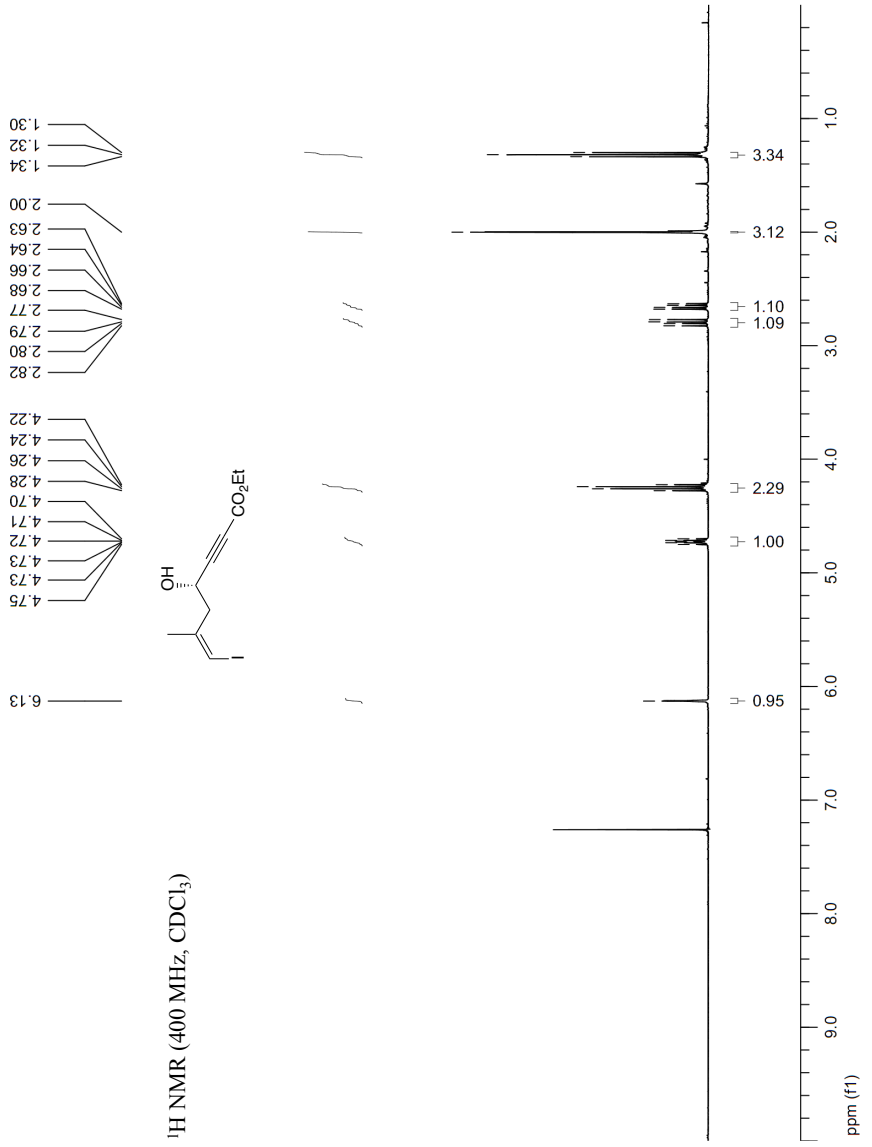
3.2.1 NMR Spectra



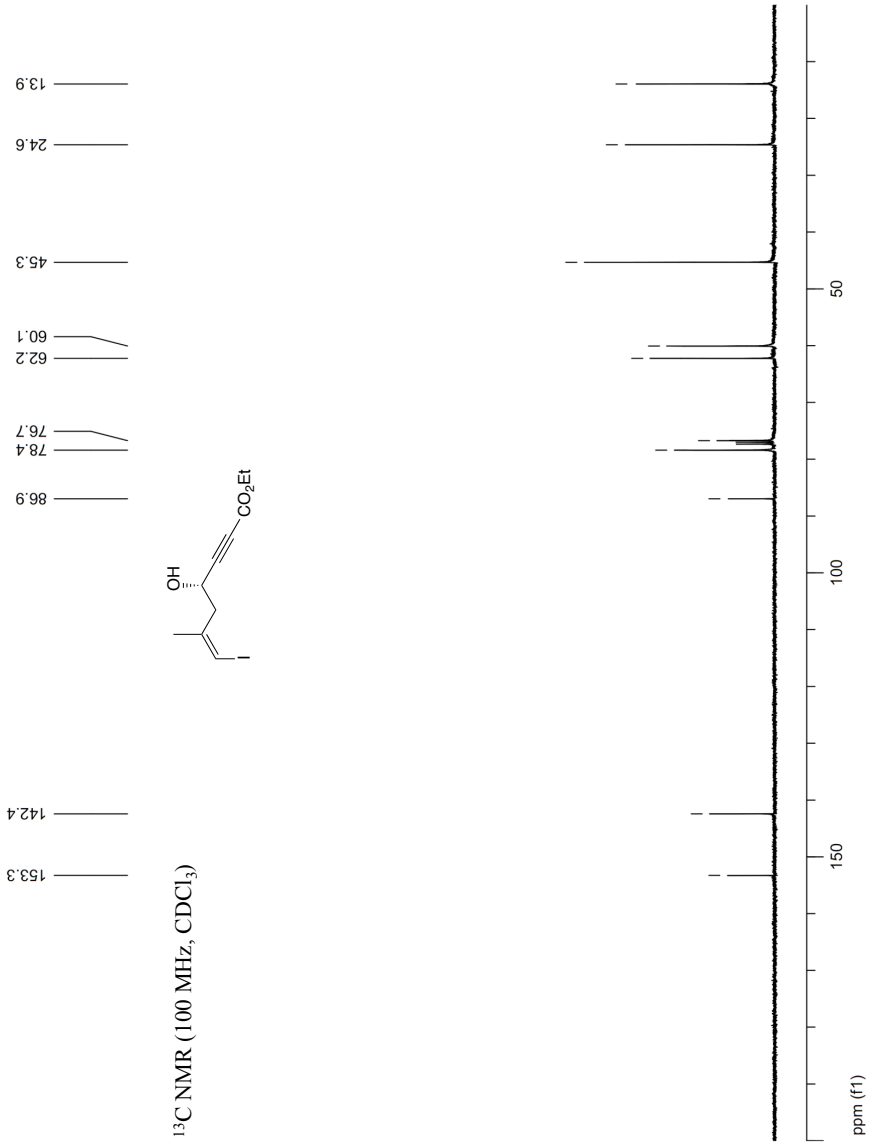
Spectrum 3.1: Compound 16: ^{1}H NMR



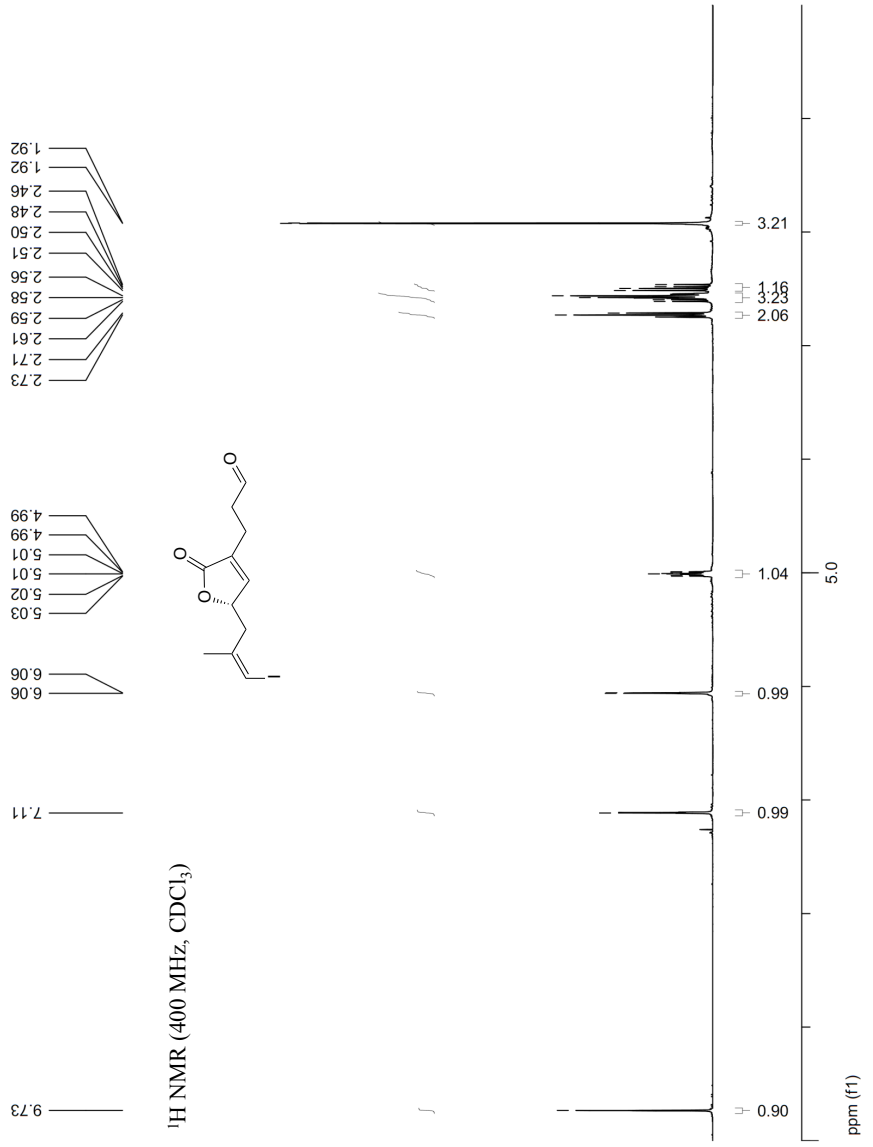
Spectrum 3.2: Compound 16: ^{13}C NMR



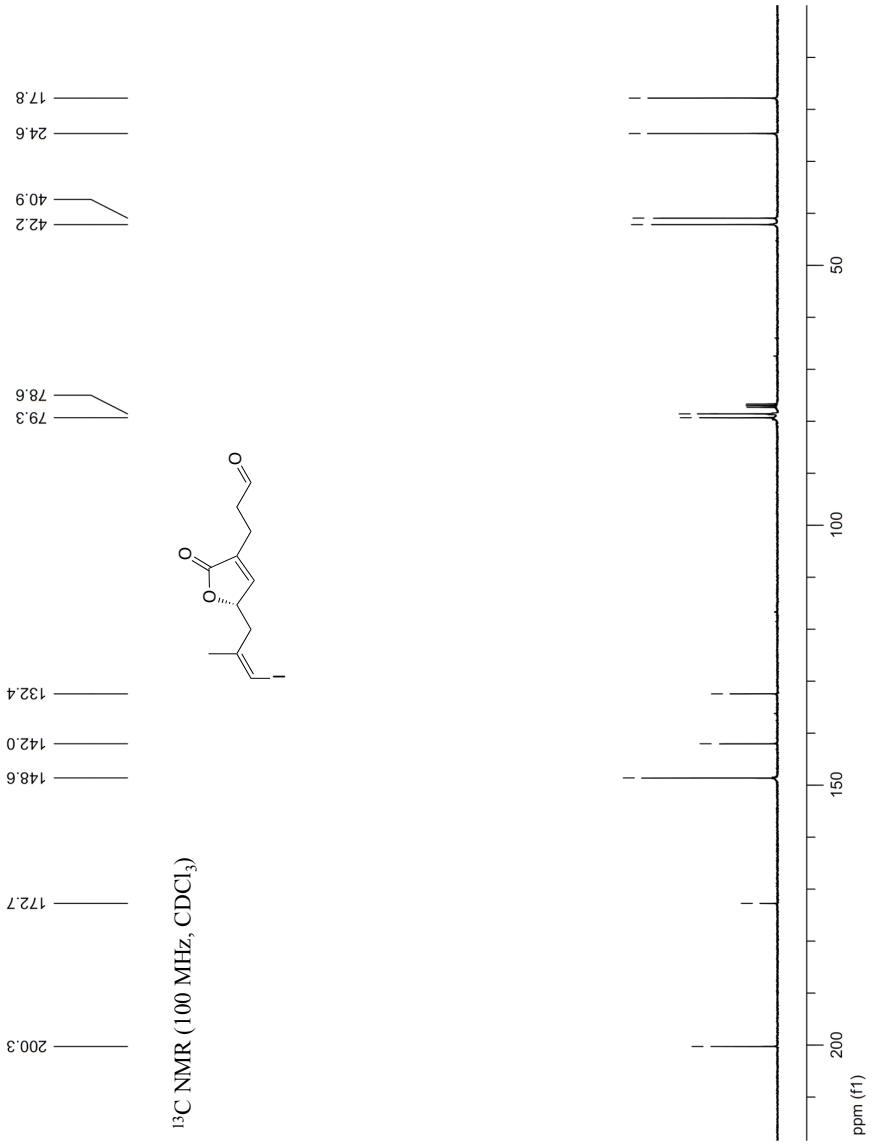
Spectrum 3.3: Compound 17: ^{1}H NMR



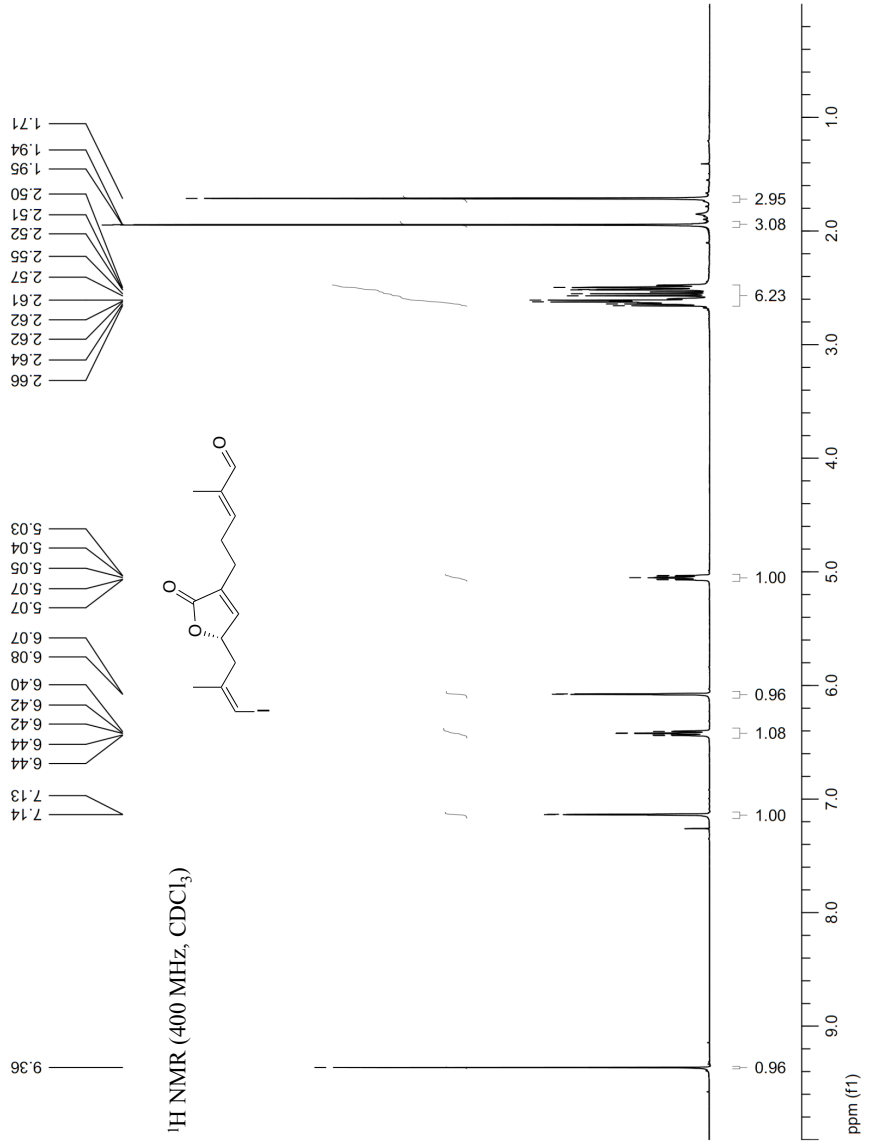
Spectrum 3.4: Compound 17: ^{13}C NMR



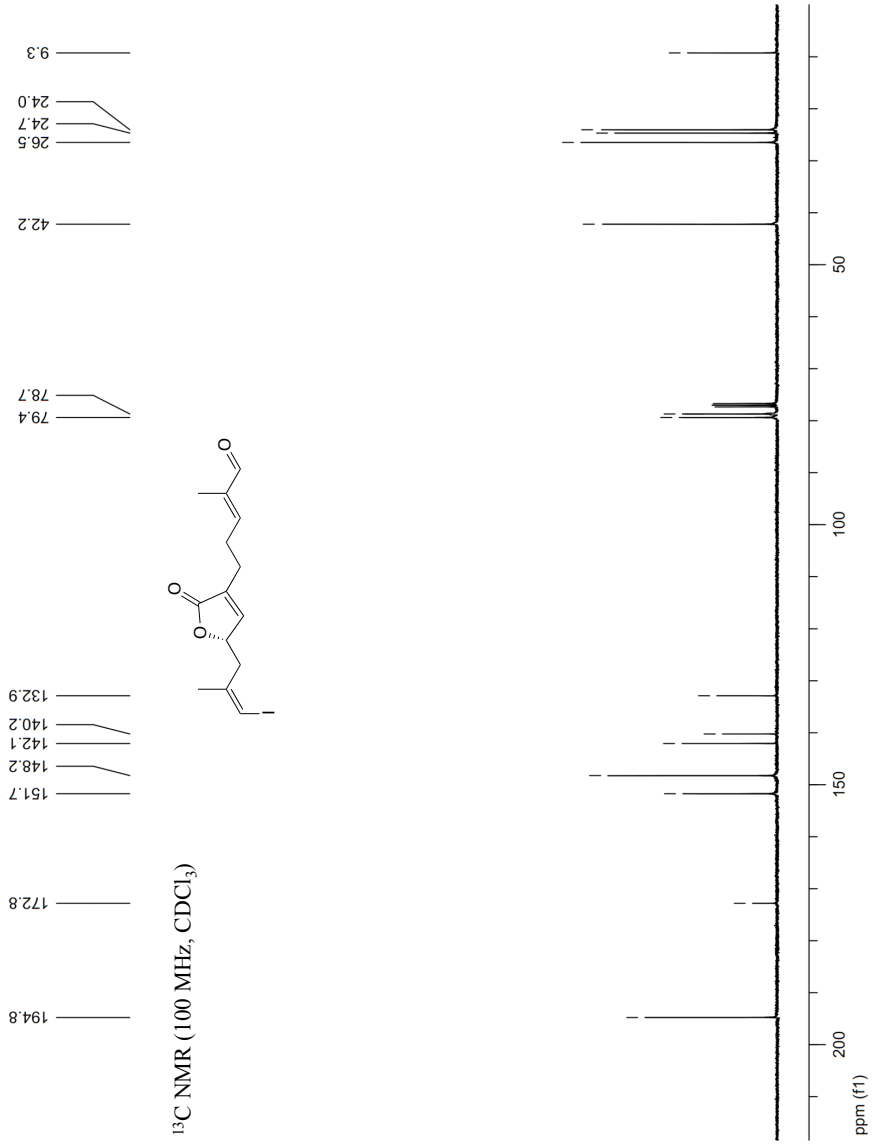
Spectrum 3.5: Compound 18: ^{1}H NMR



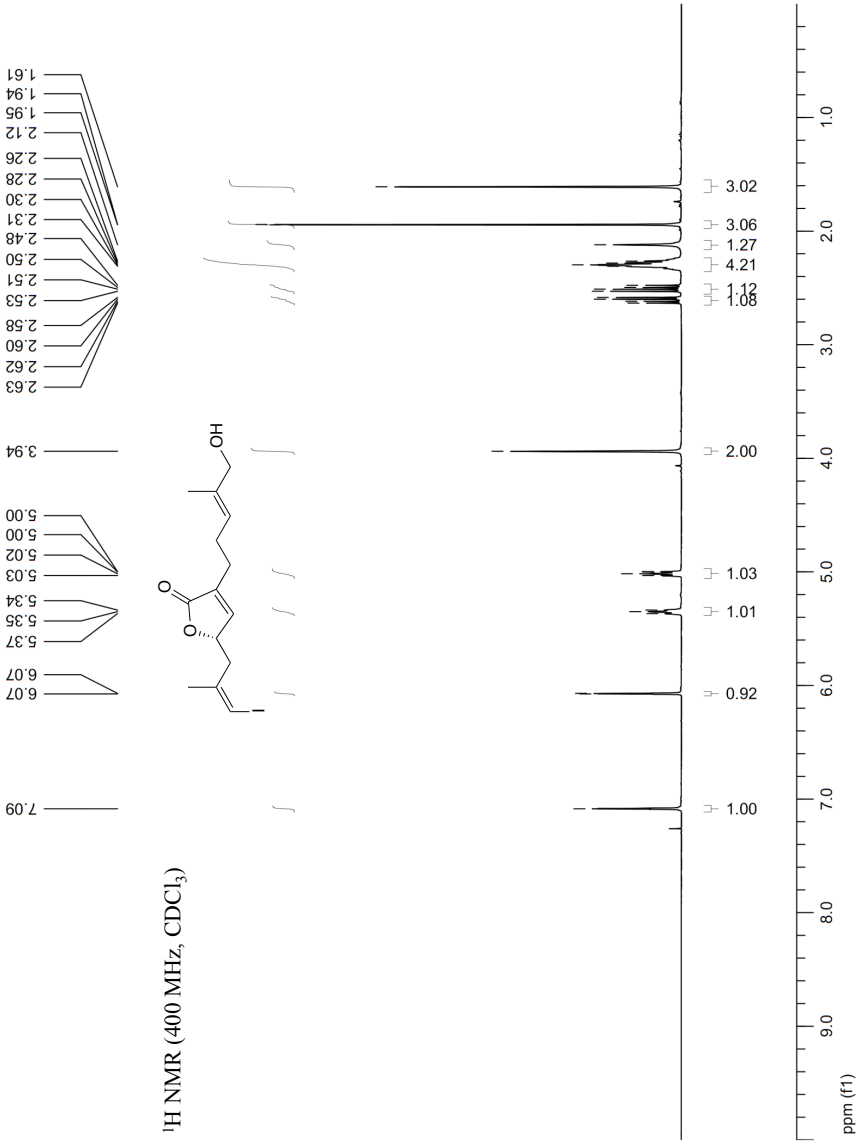
Spectrum 3.6: Compound 18: ^{13}C NMR



Spectrum 3.7: Compound 18b: ^{1}H NMR

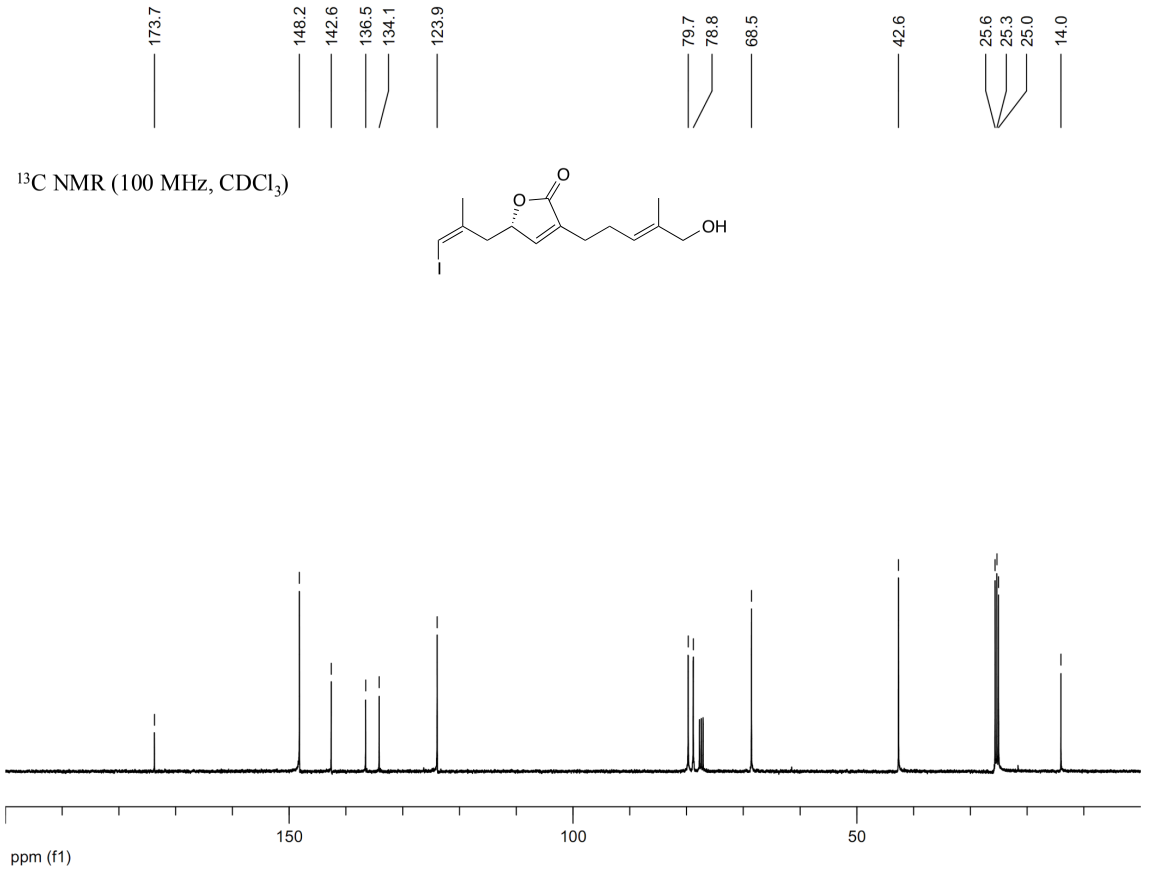


Spectrum 3.8: Compound 18b: ^{13}C NMR

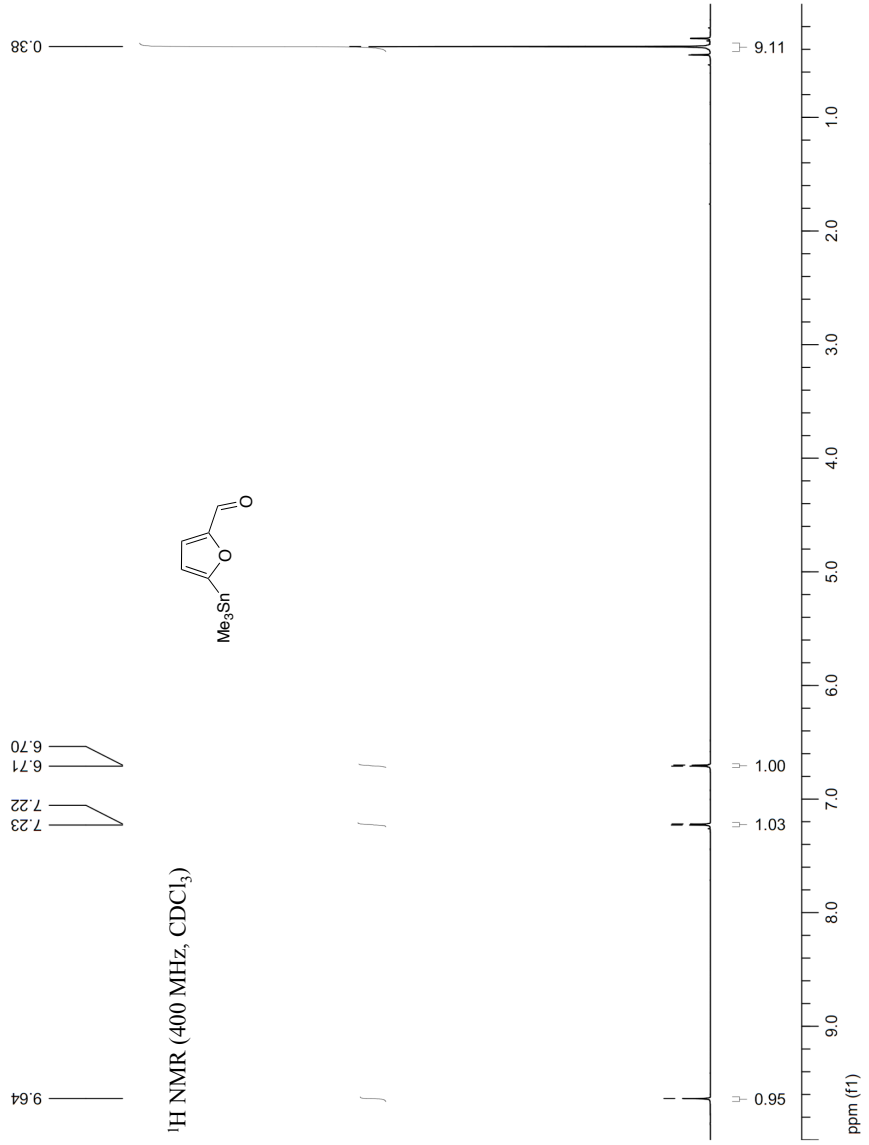


^{1}H NMR (400 MHz, $CDCl_3$)

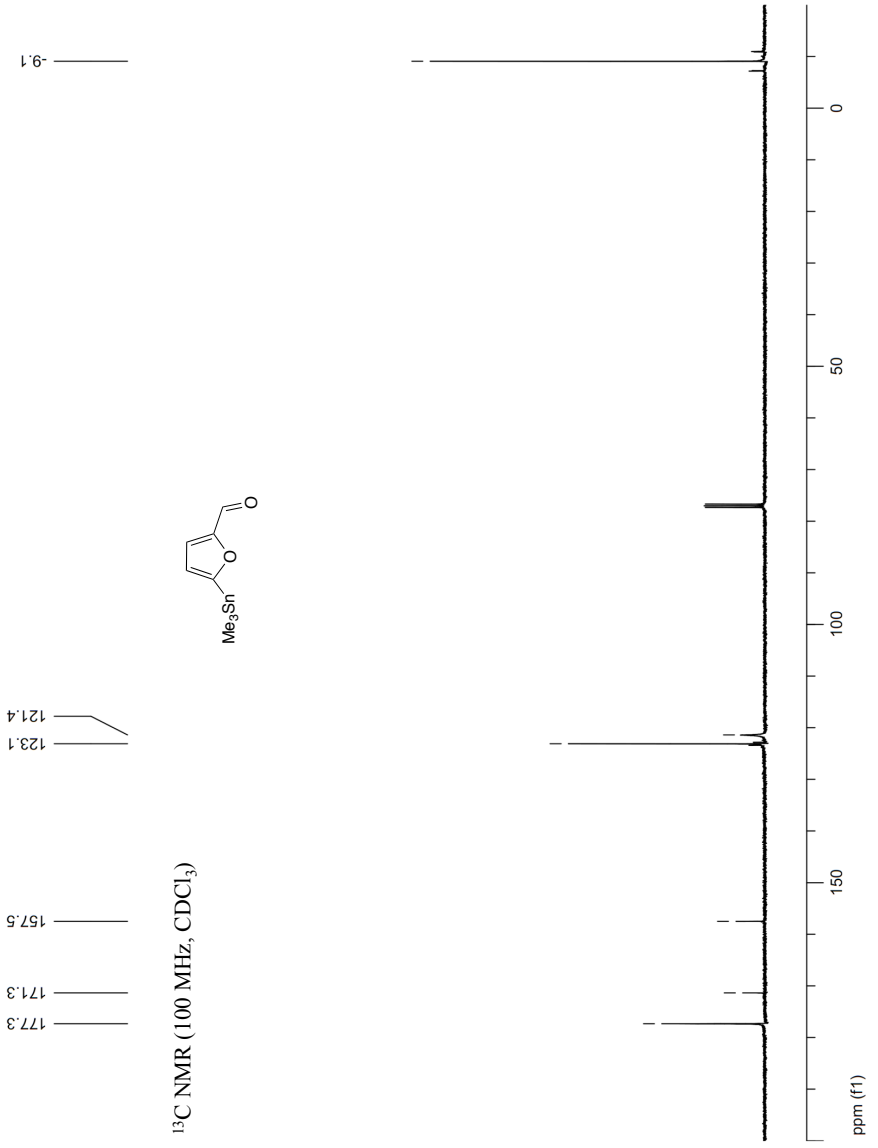
Spectrum 3.9: Compound 14: ^{1}H NMR



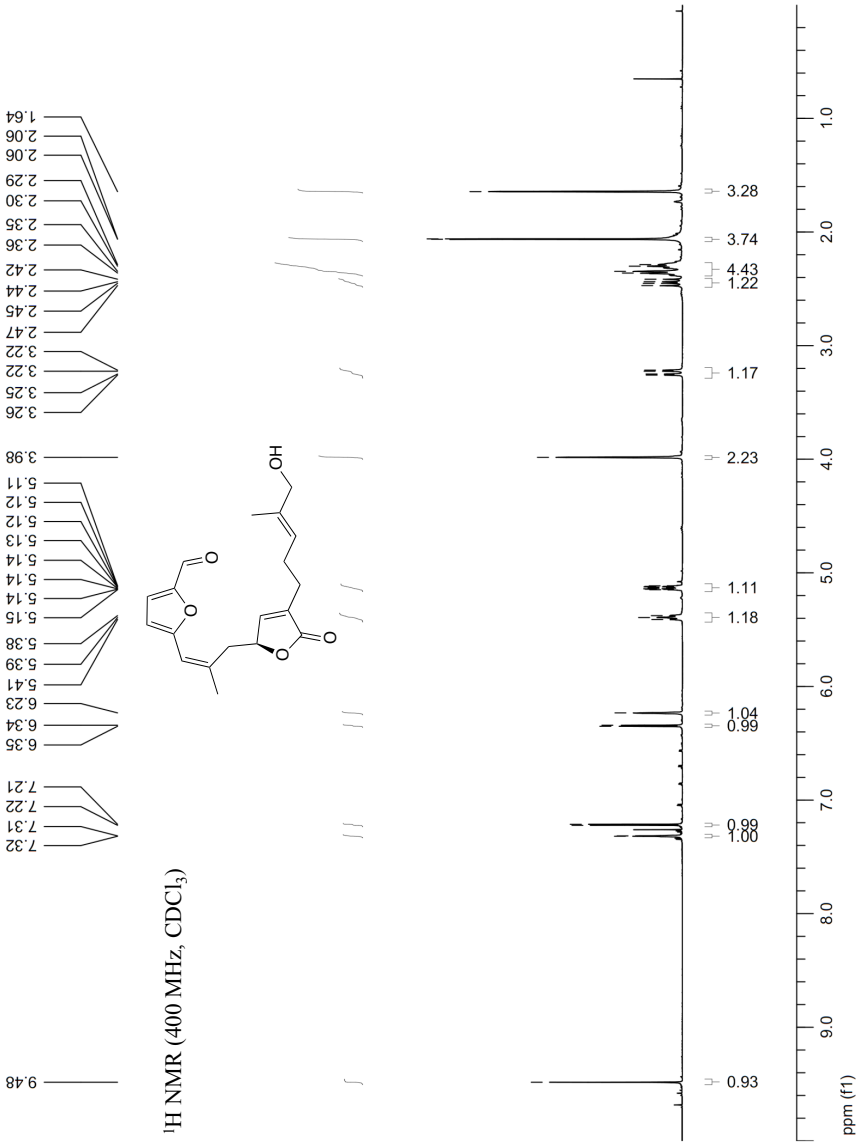
Spectrum 3.10: Compound 14: ^{13}C NMR



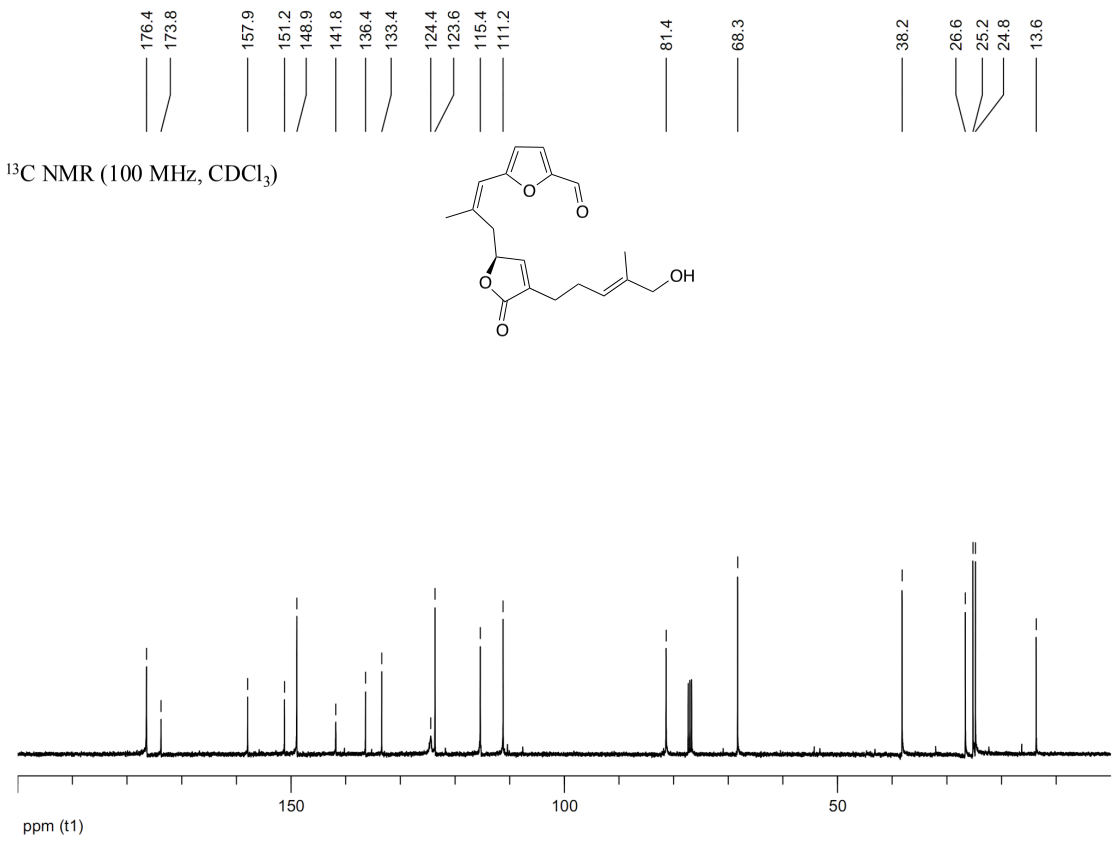
Spectrum 3.11: Compound 13: ^{1}H NMR



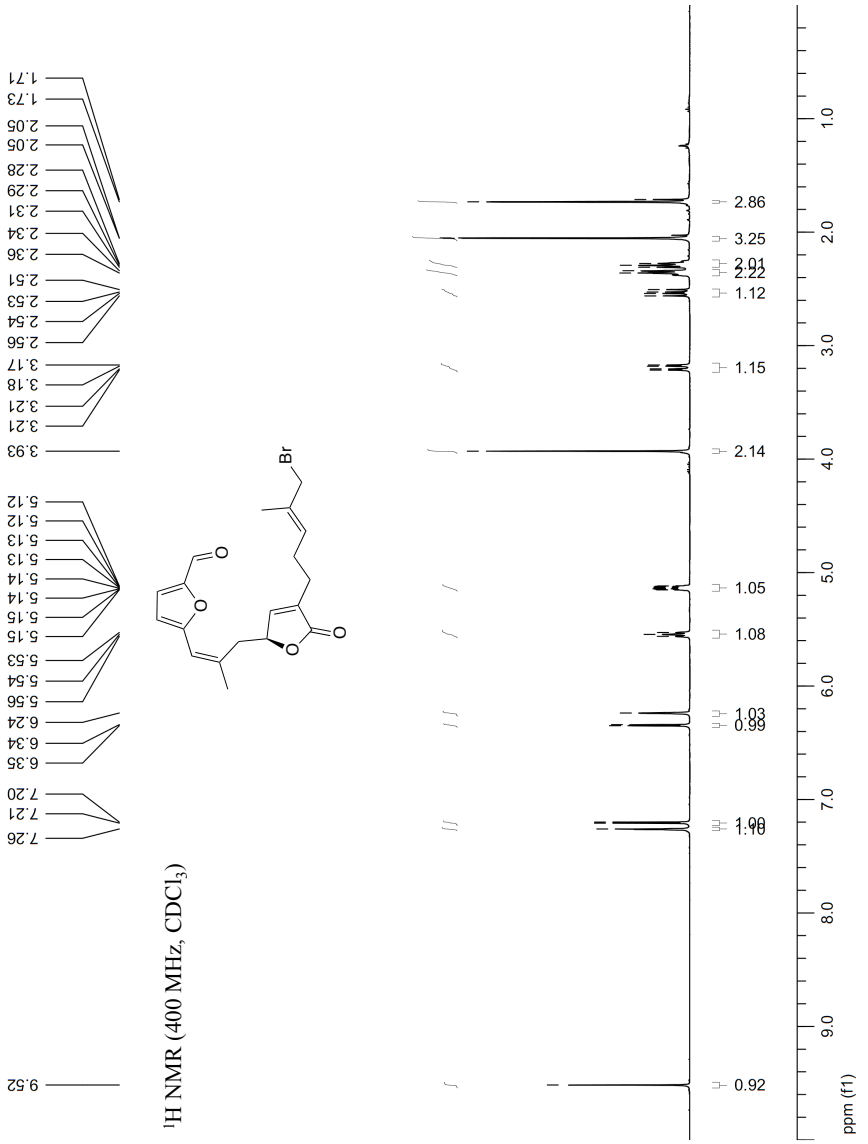
Spectrum 3.12: Compound 13: ^{13}C NMR



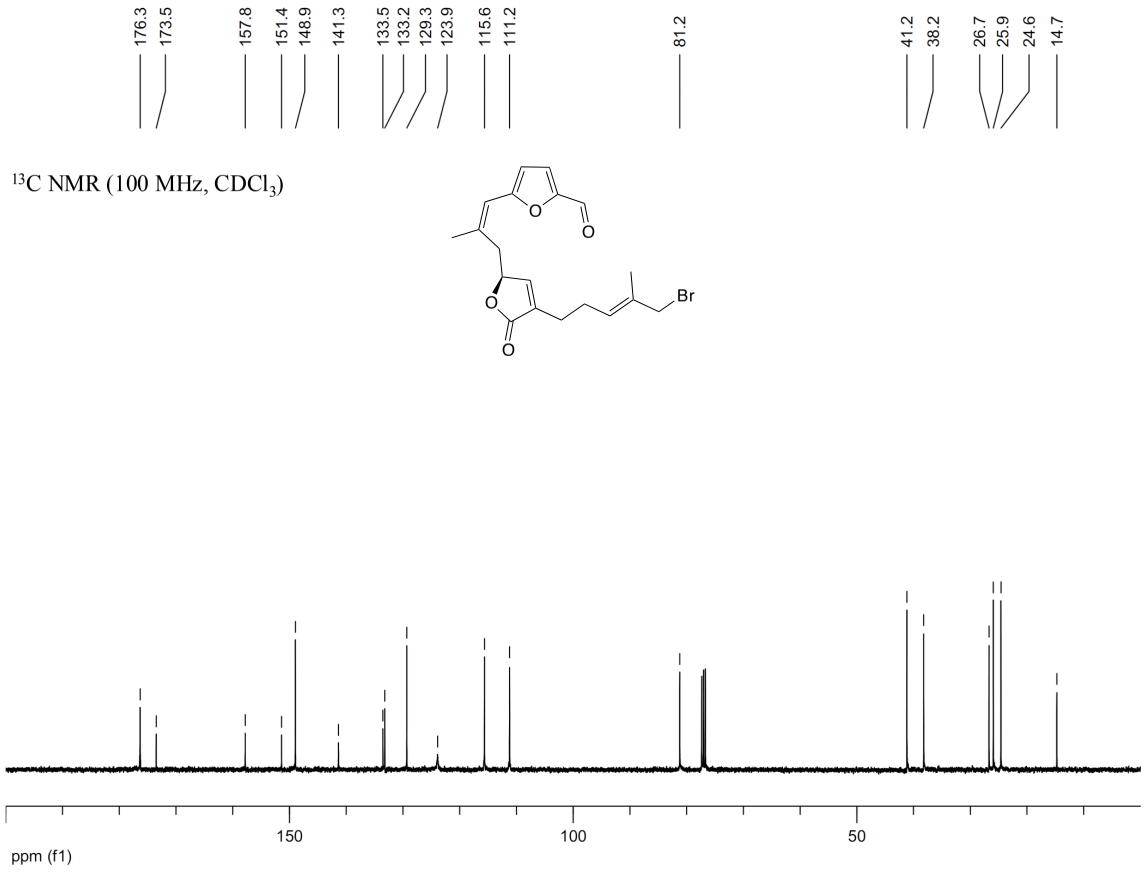
Spectrum 3.13: Compound 19: ^{1}H NMR



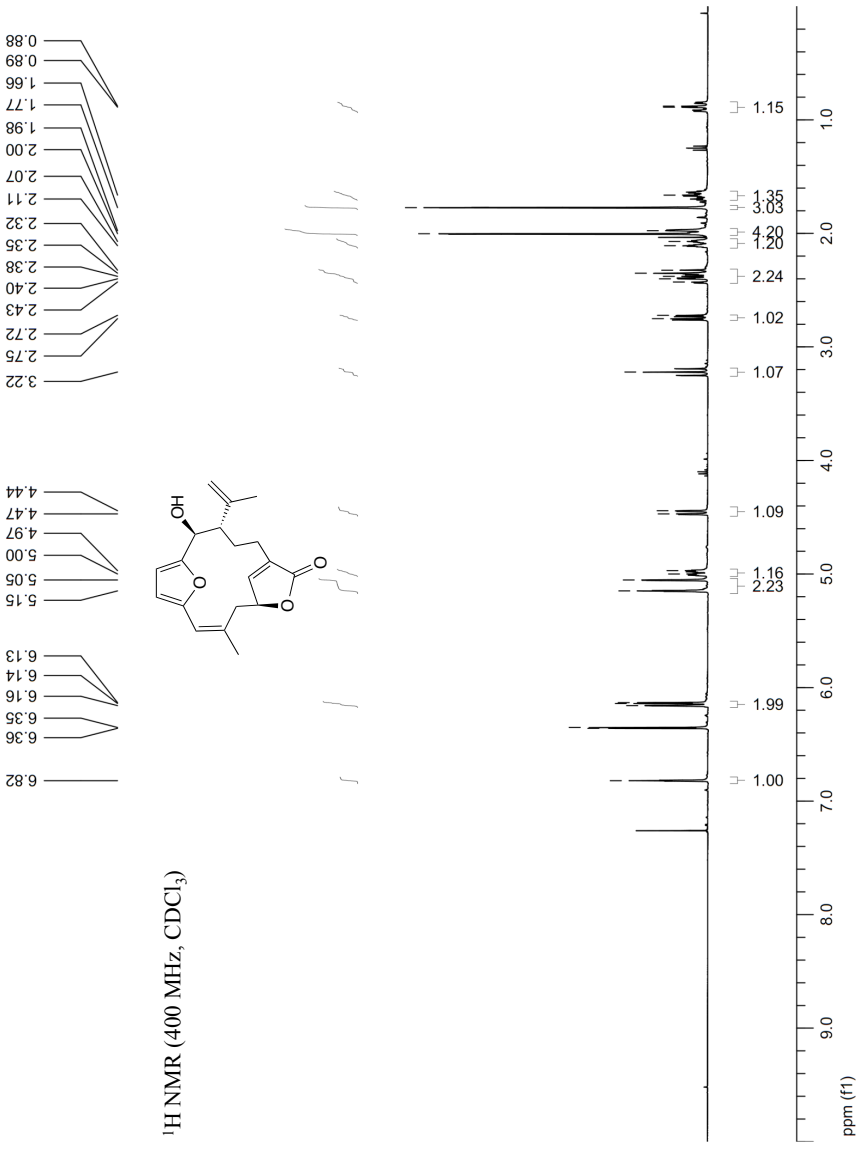
Spectrum 3.14: Compound 19: ^{13}C NMR



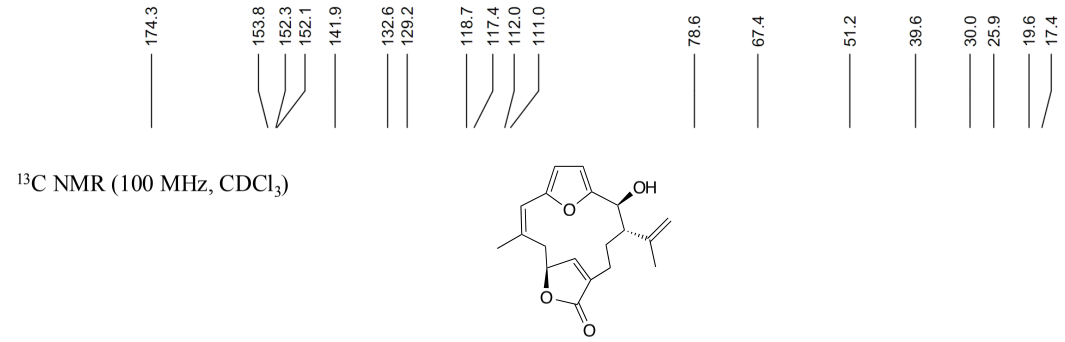
Spectrum 3.15: Compound 20: ^{1}H NMR

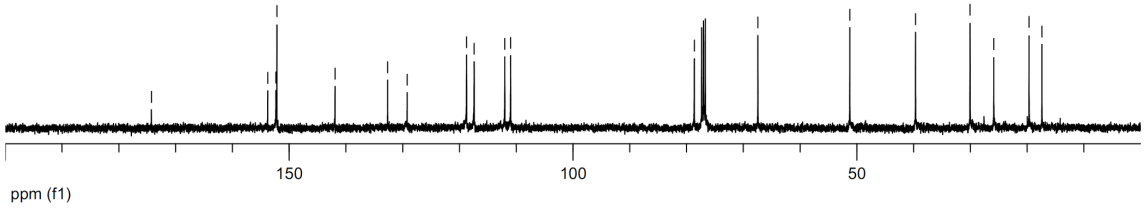


Spectrum 3.16: Compound 20: ^{13}C NMR

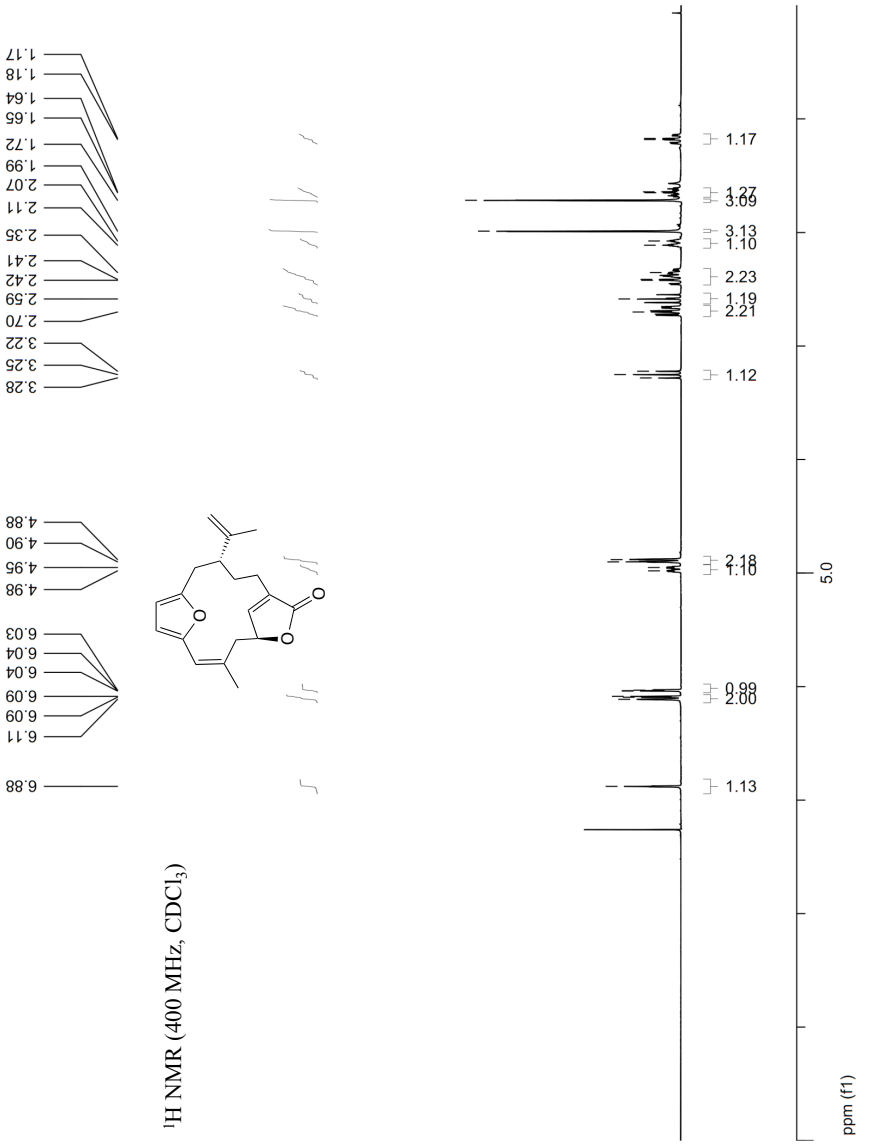


Spectrum 3.17: Compound 6: ^{1}H NMR

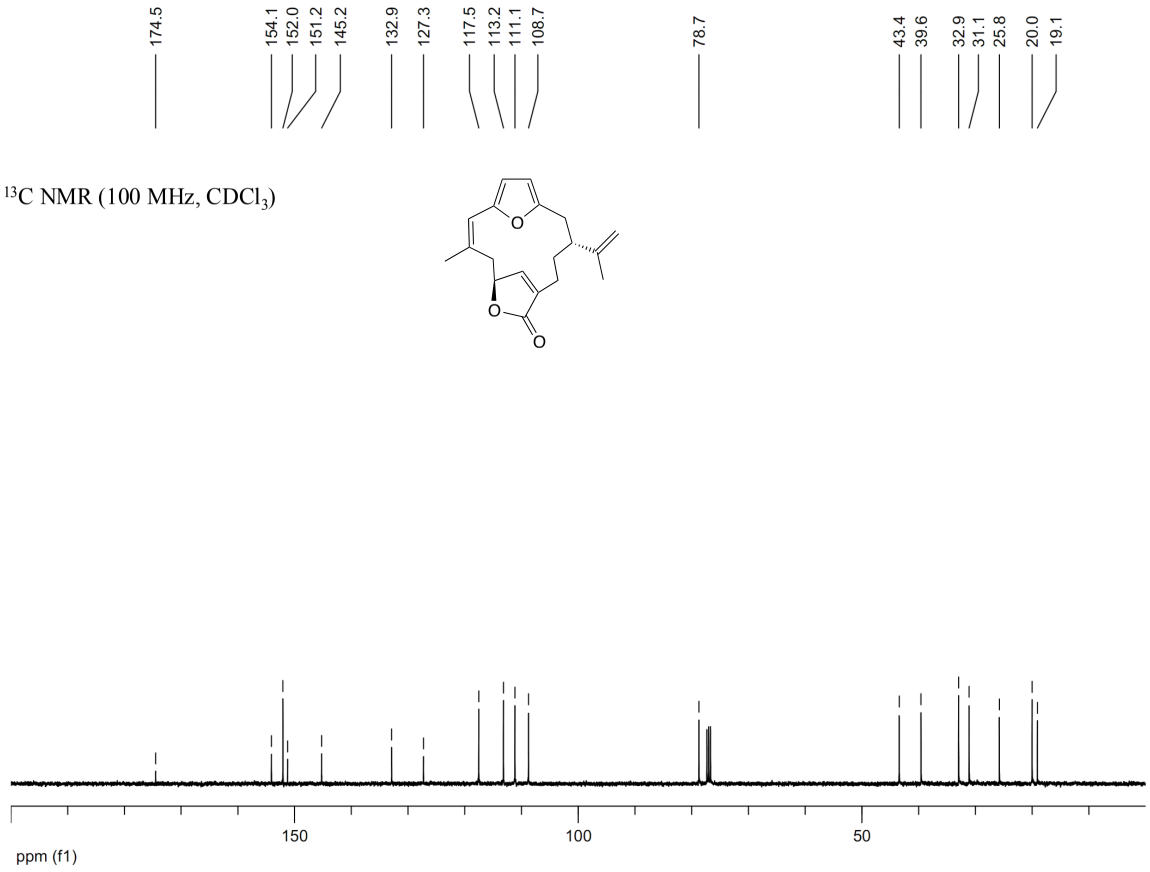




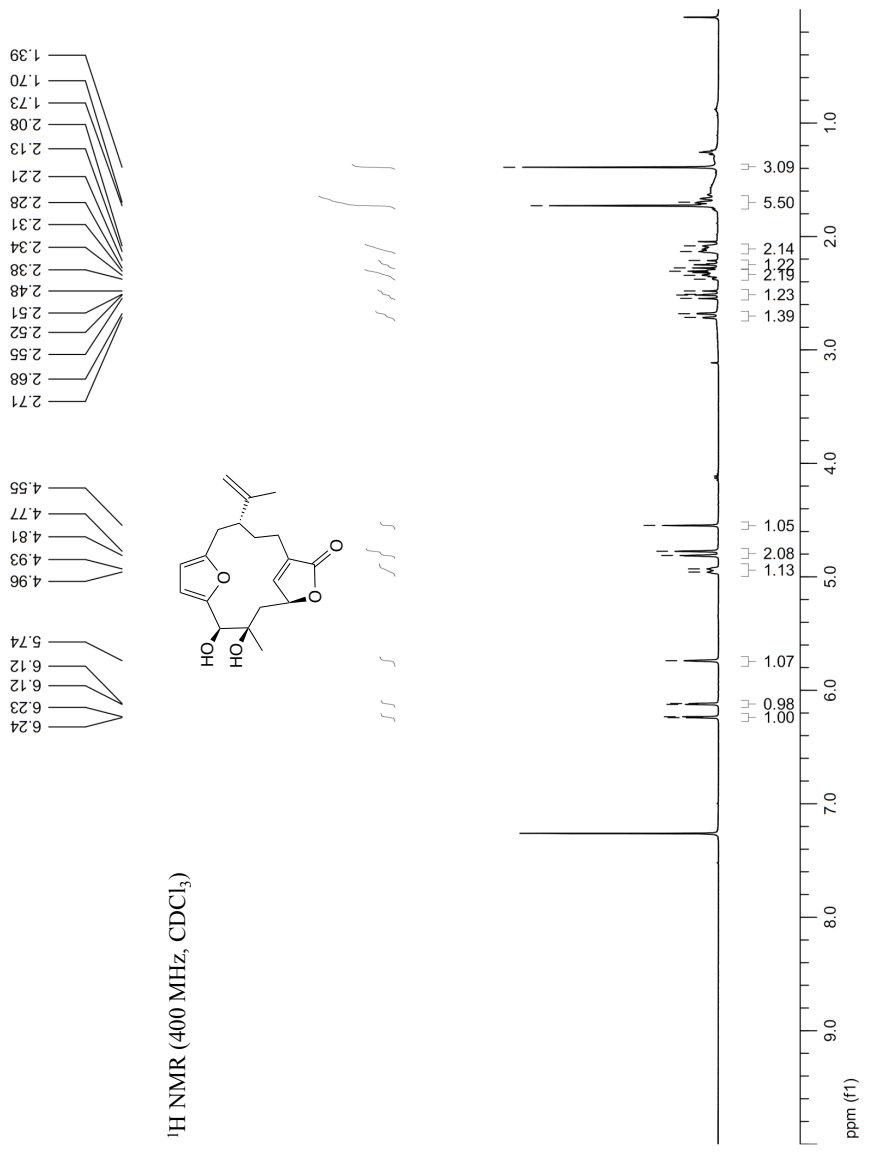
Spectrum 3.18: Compound 6: ^{13}C NMR



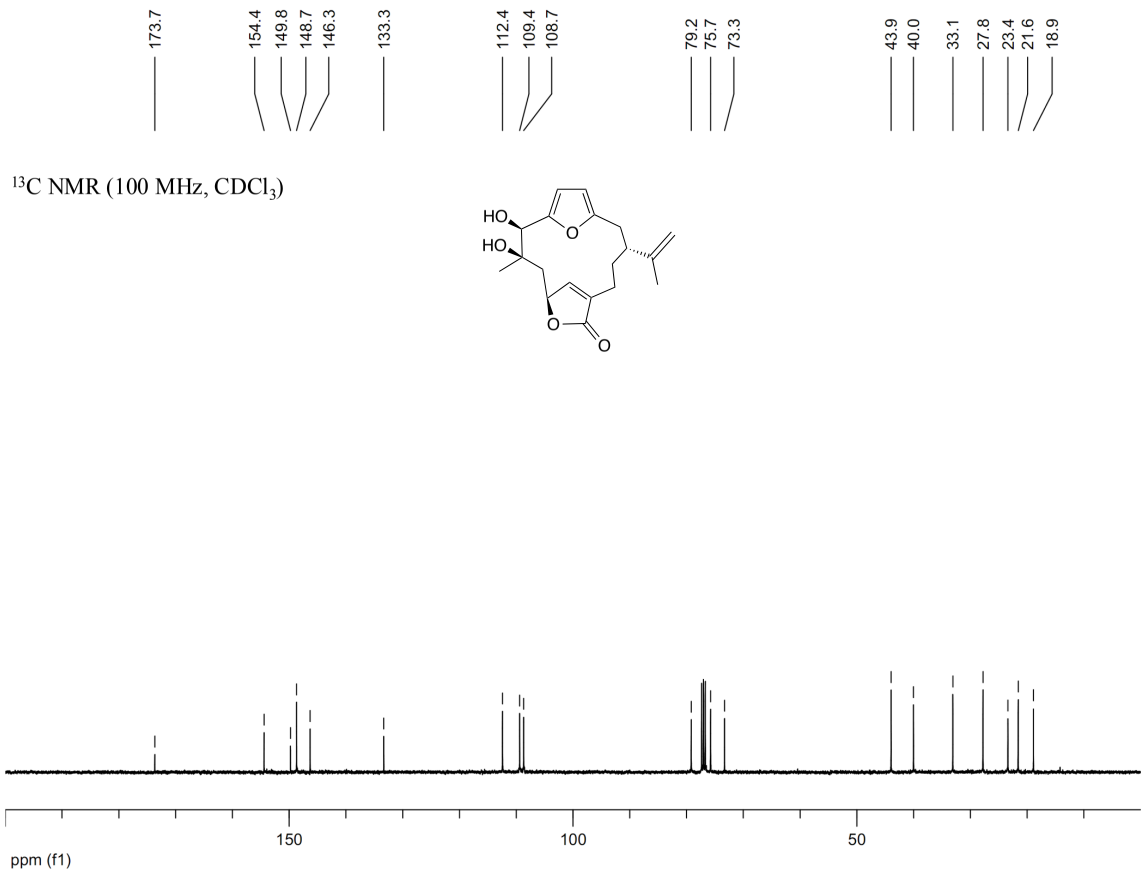
Spectrum 3.19: Compound 4: ^{1}H NMR



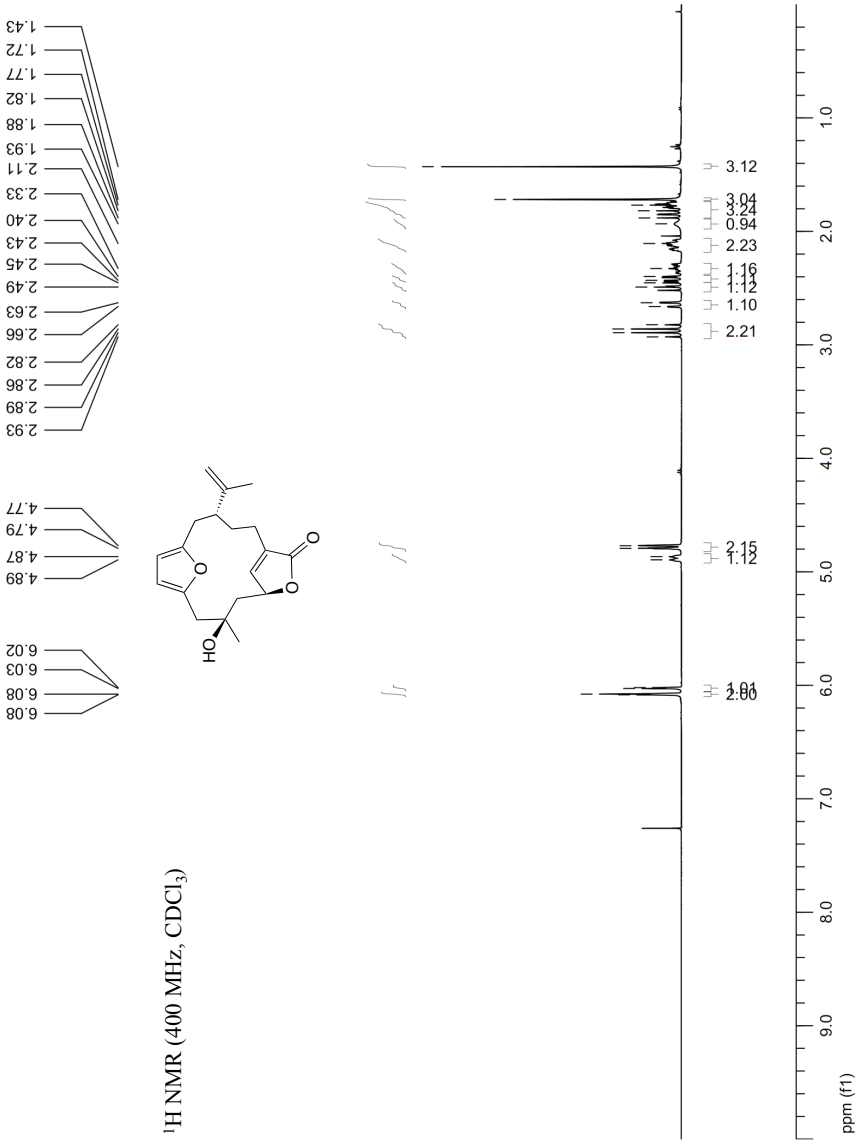
Spectrum 3.20: Compound 4: ^{13}C NMR



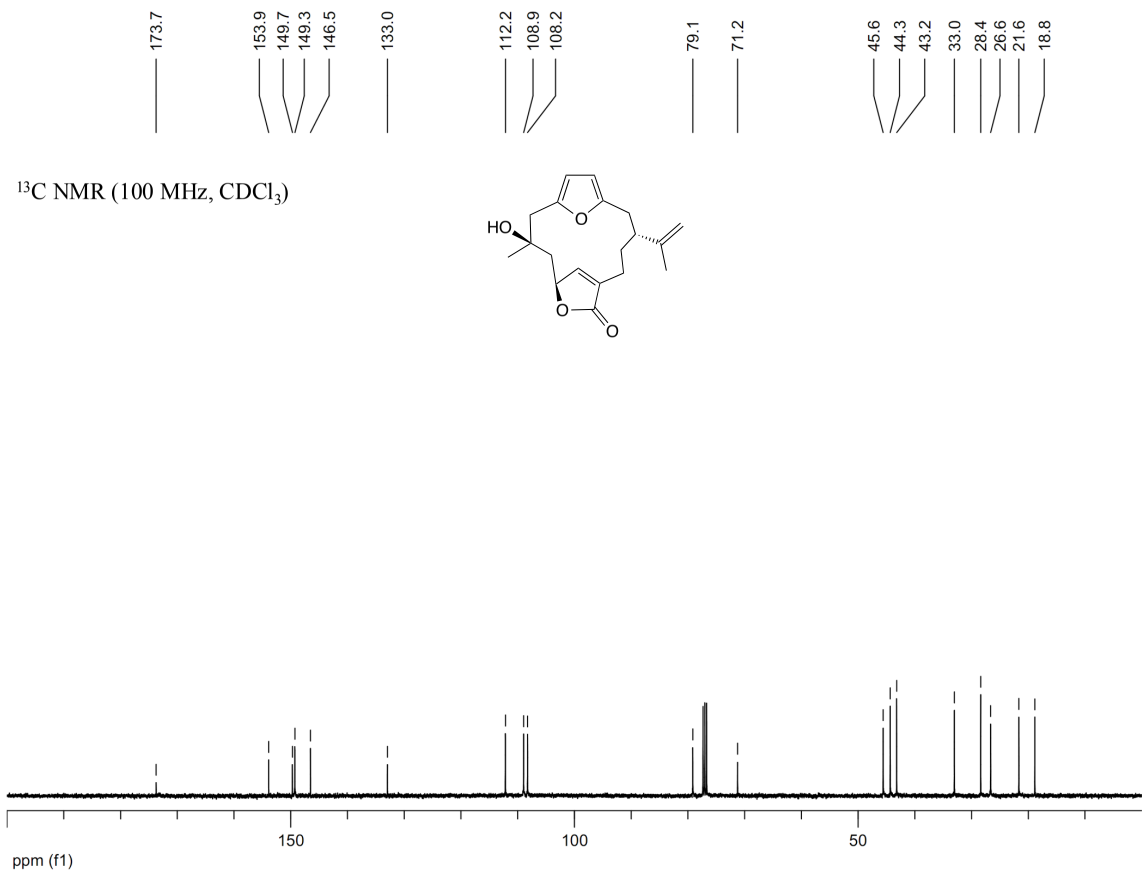
Spectrum 3.21: Compound 21: ^{1}H NMR



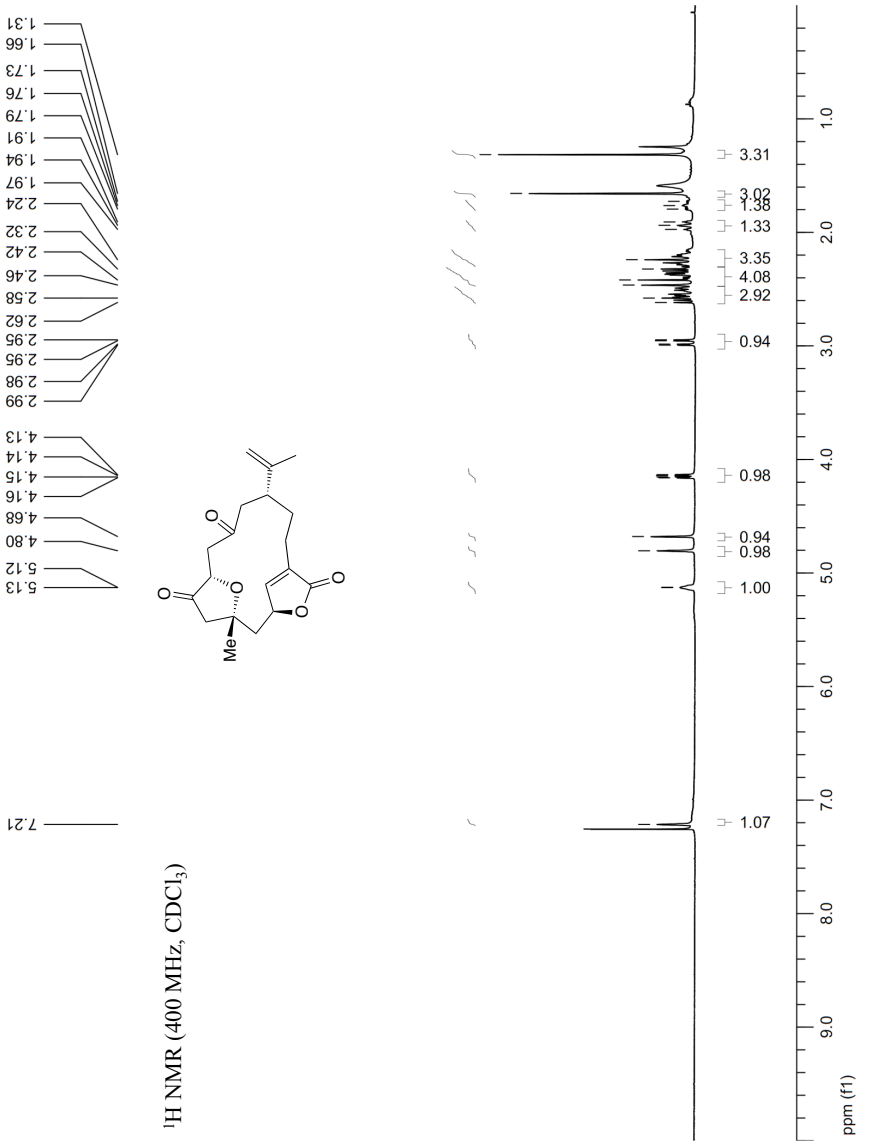
Spectrum 3.22: Compound 21: ^{13}C NMR



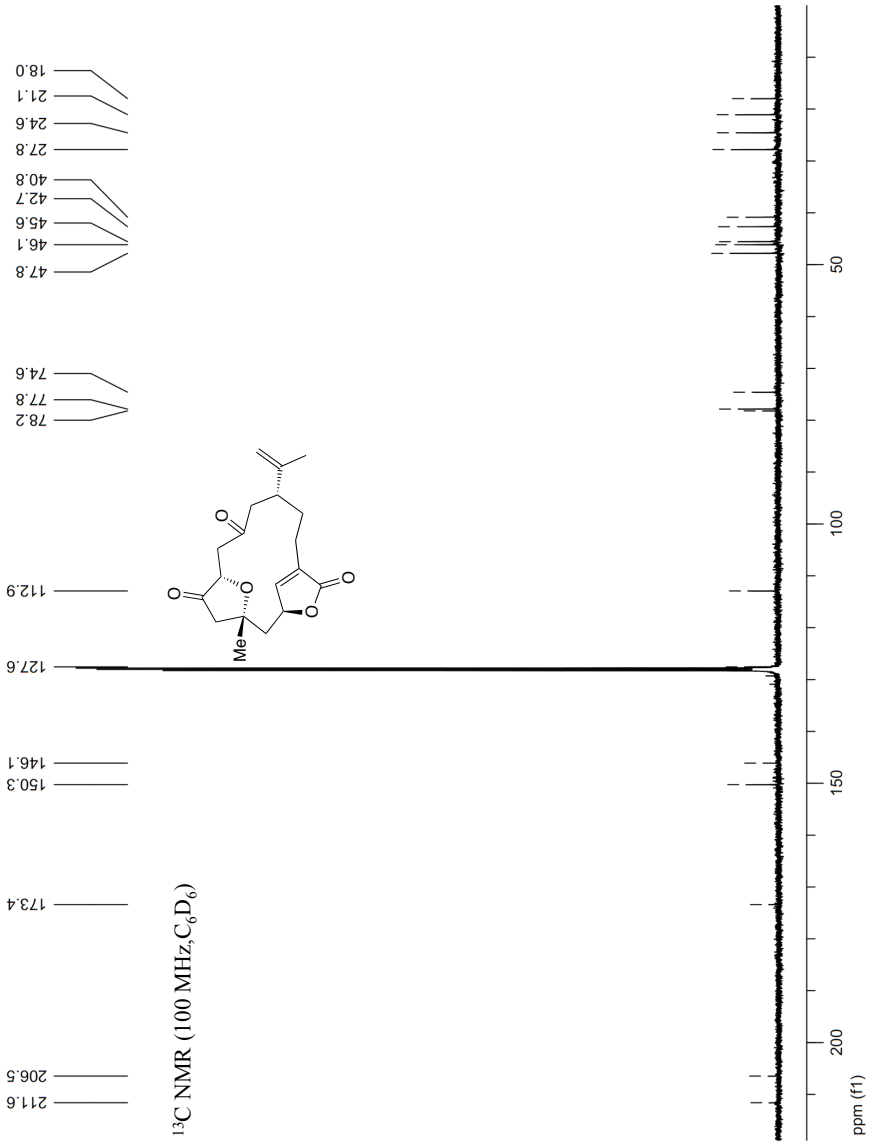
Spectrum 3.23: Compound 22: ^{1}H NMR



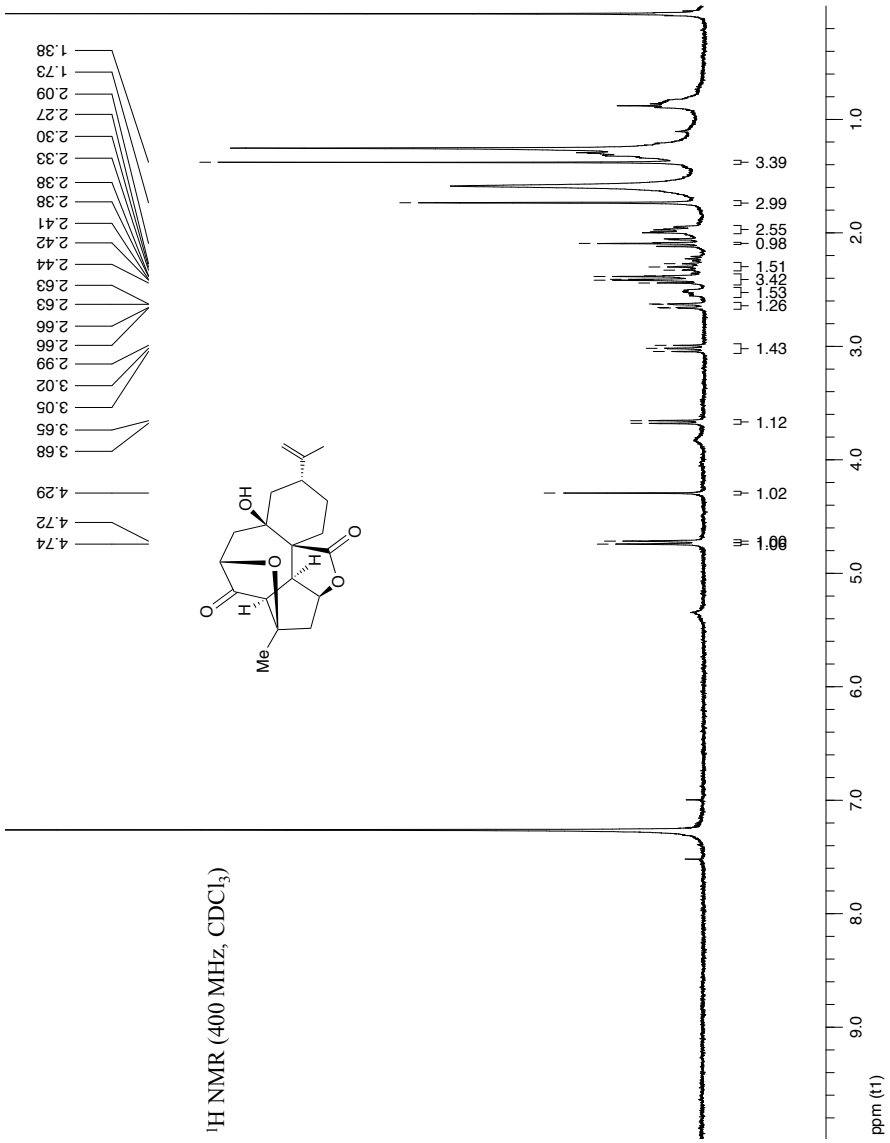
Spectrum 3.24: Compound 22: ^{13}C NMR



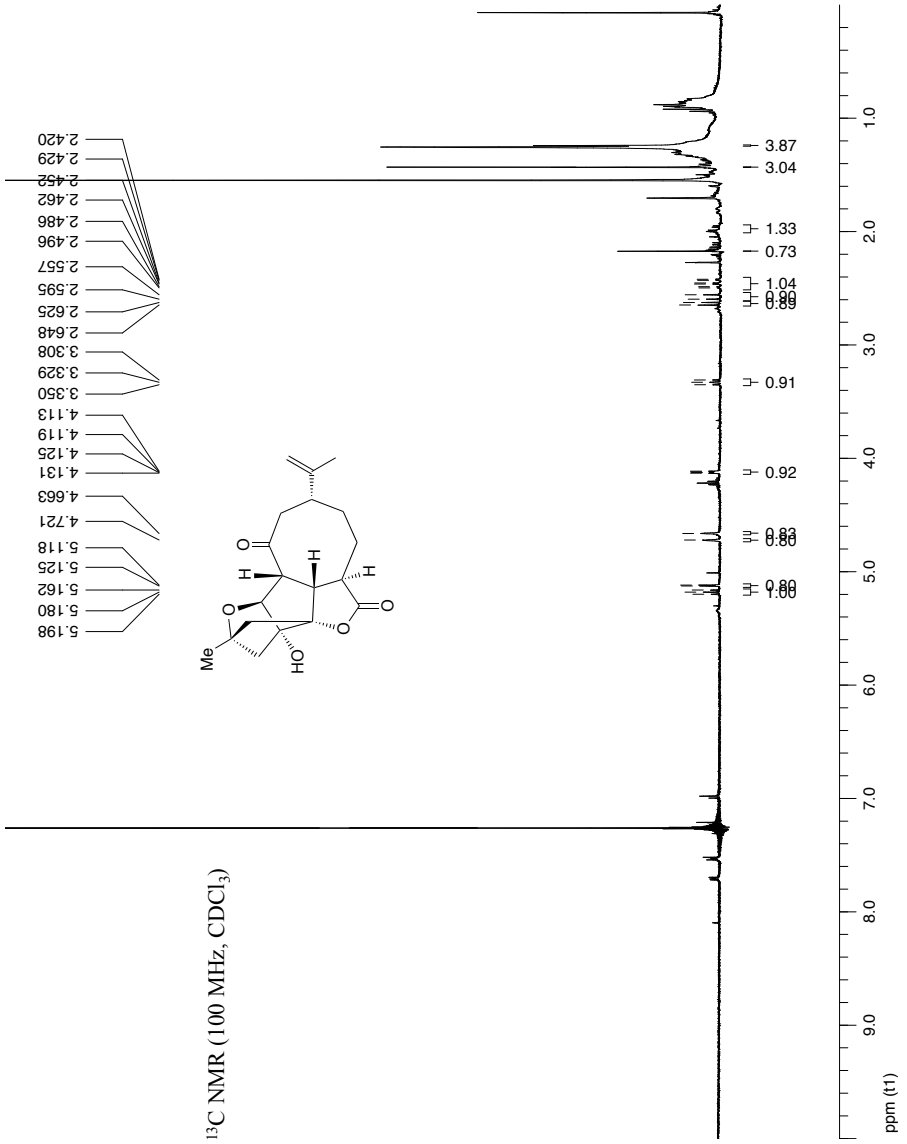
Spectrum 3.25: Compound 7: ^{1}H NMR



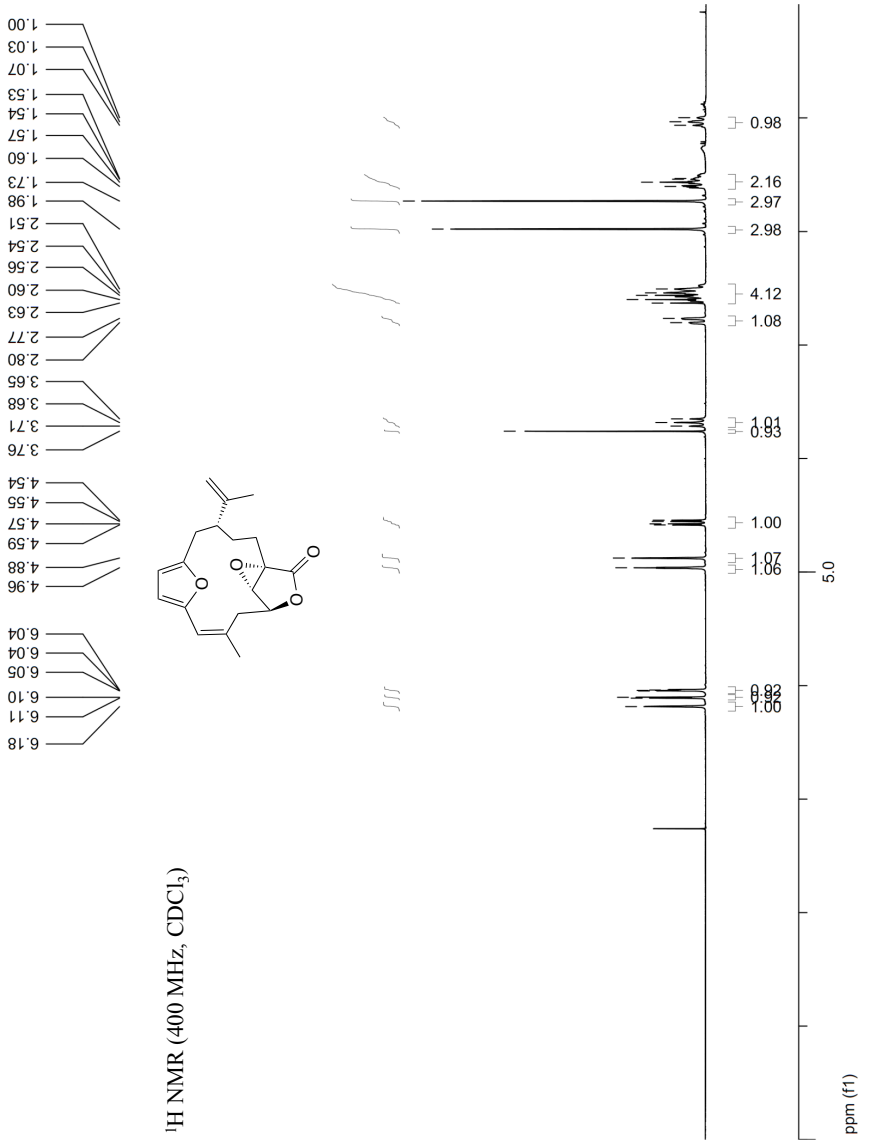
Spectrum 3.26: Compound 7: ^{13}C NMR



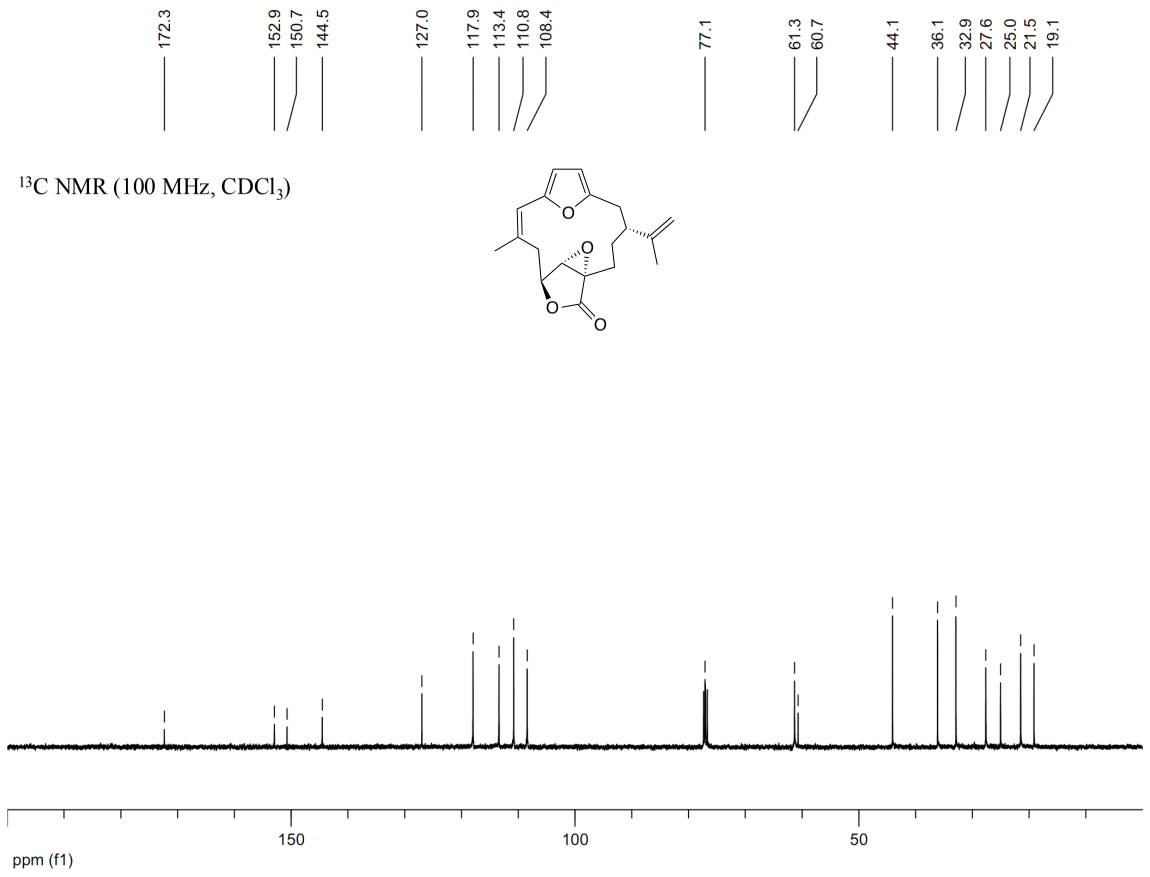
Spectrum 3.27: Compound 24: ^{1}H NMR



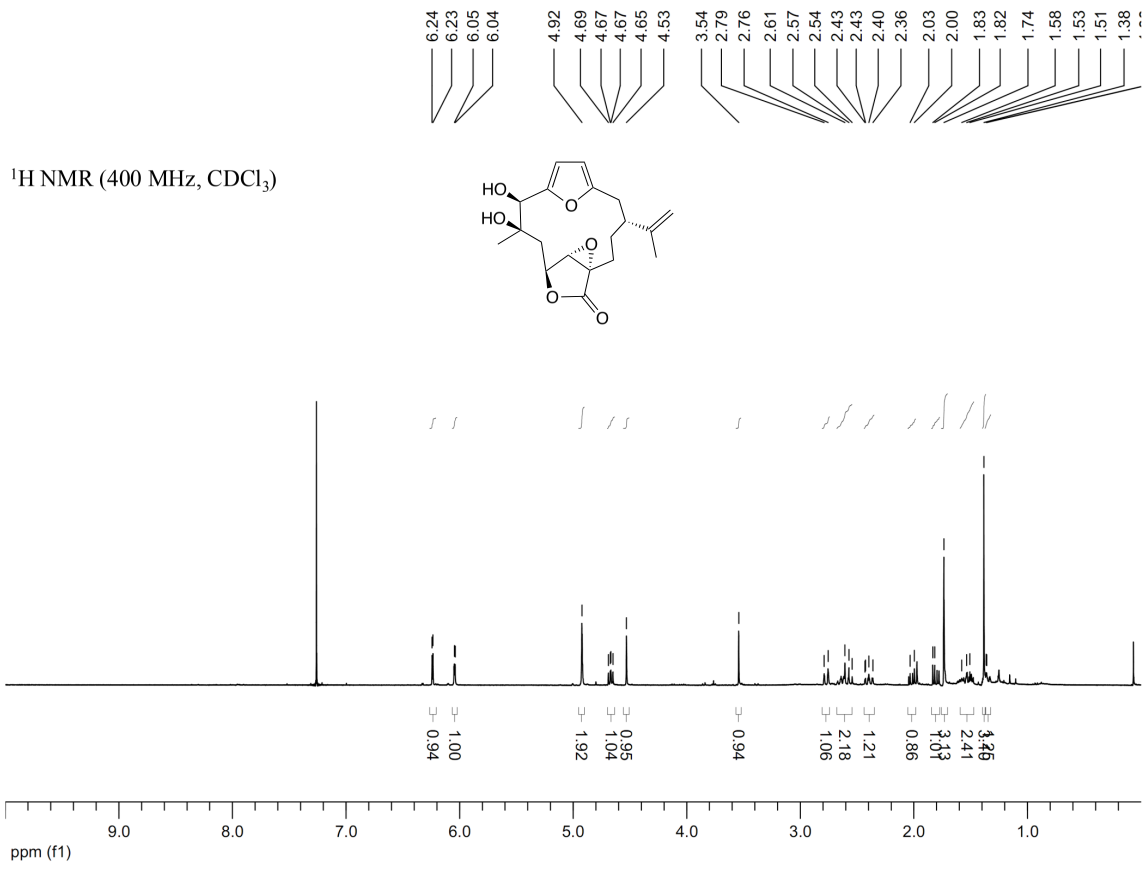
Spectrum 3.28: Compound 25: ^{1}H NMR



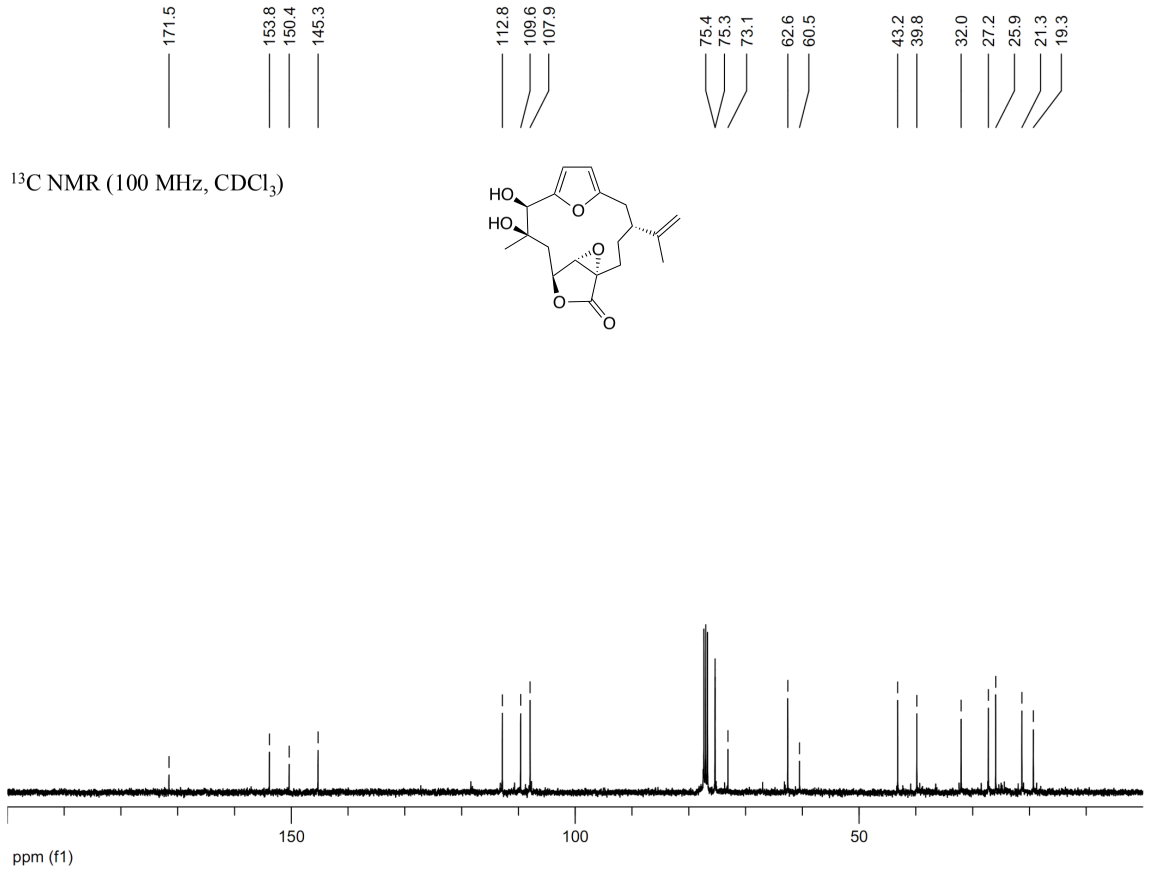
Spectrum 3.29: Compound 5: ^{1}H NMR



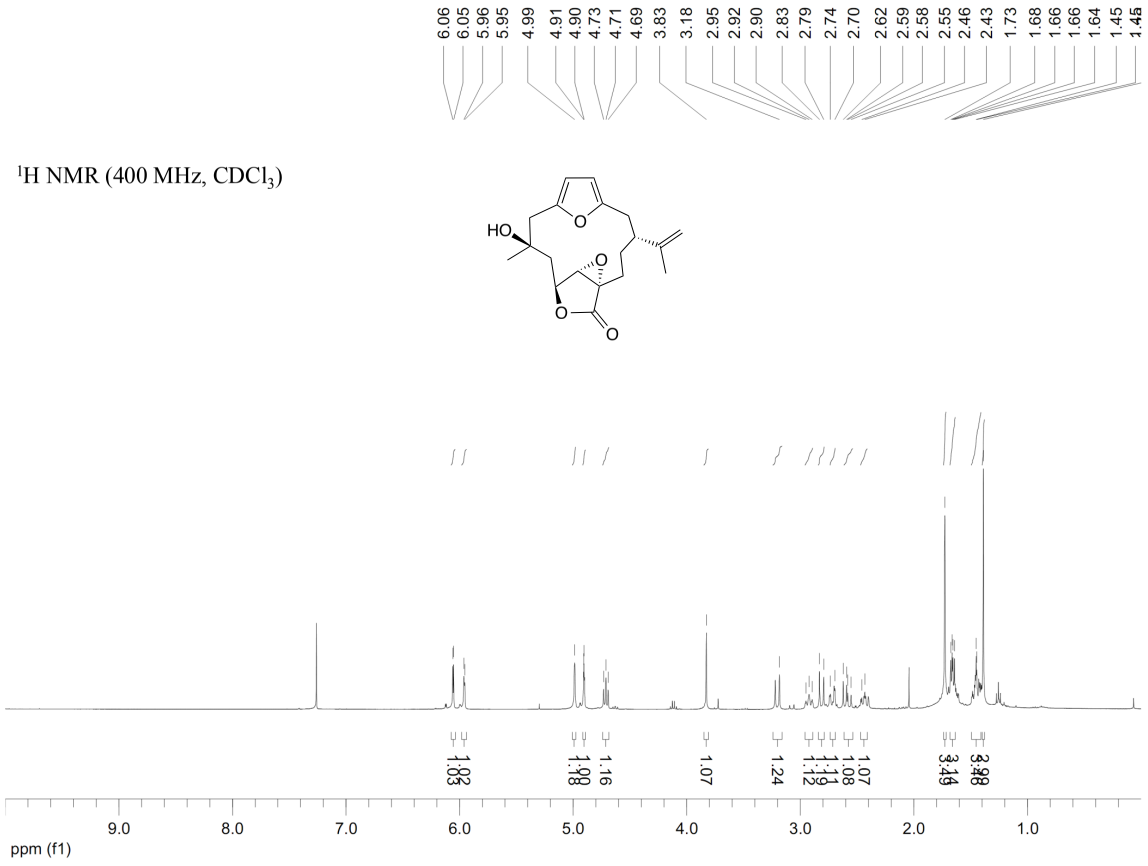
Spectrum 3.30: Compound 5: ^{13}C NMR



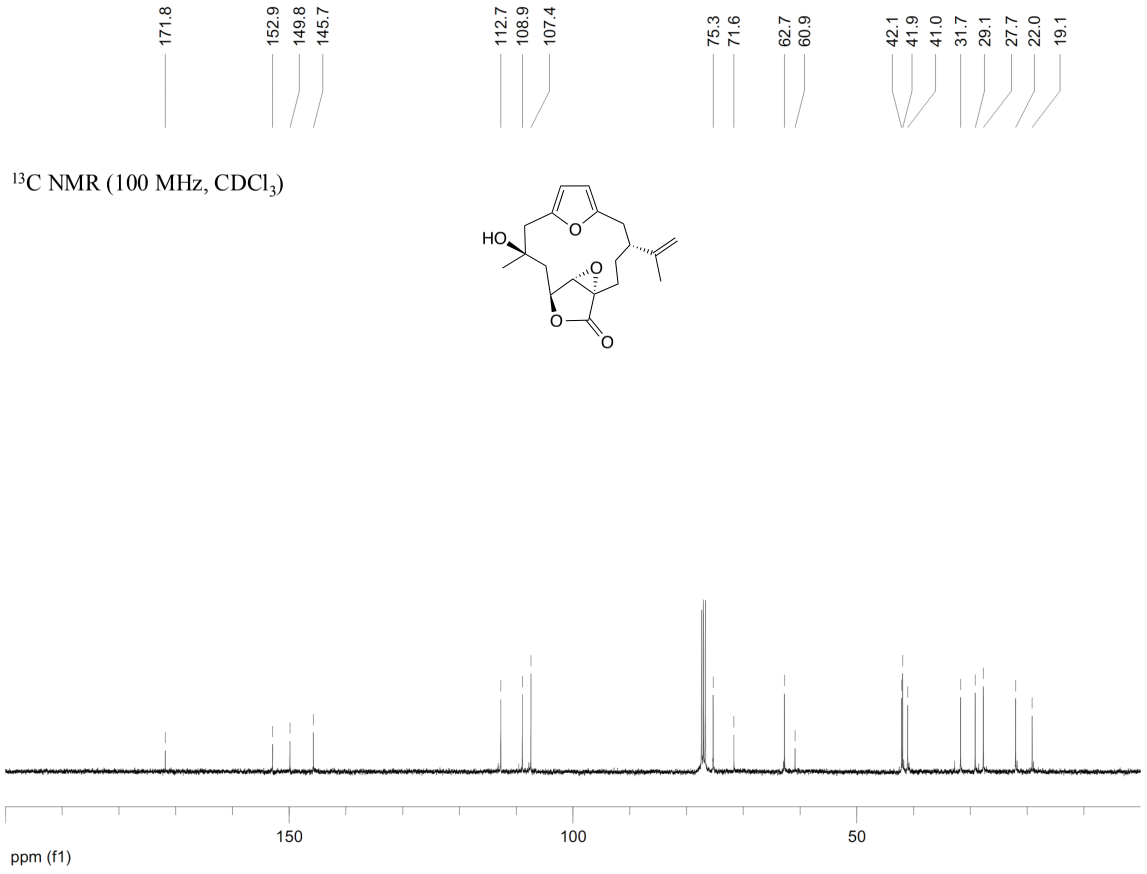
Spectrum 3.31: Compound 26: ^{1}H NMR



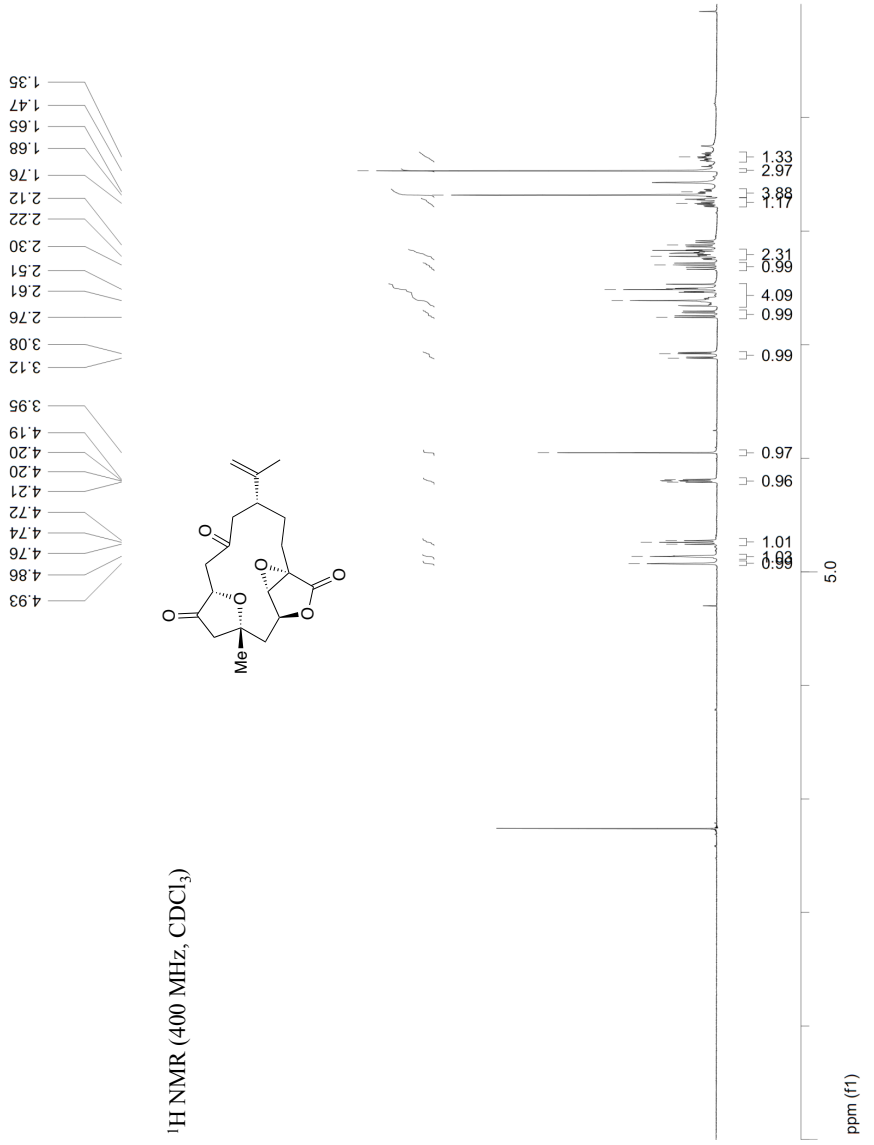
Spectrum 3.32: Compound 26: ^{13}C NMR



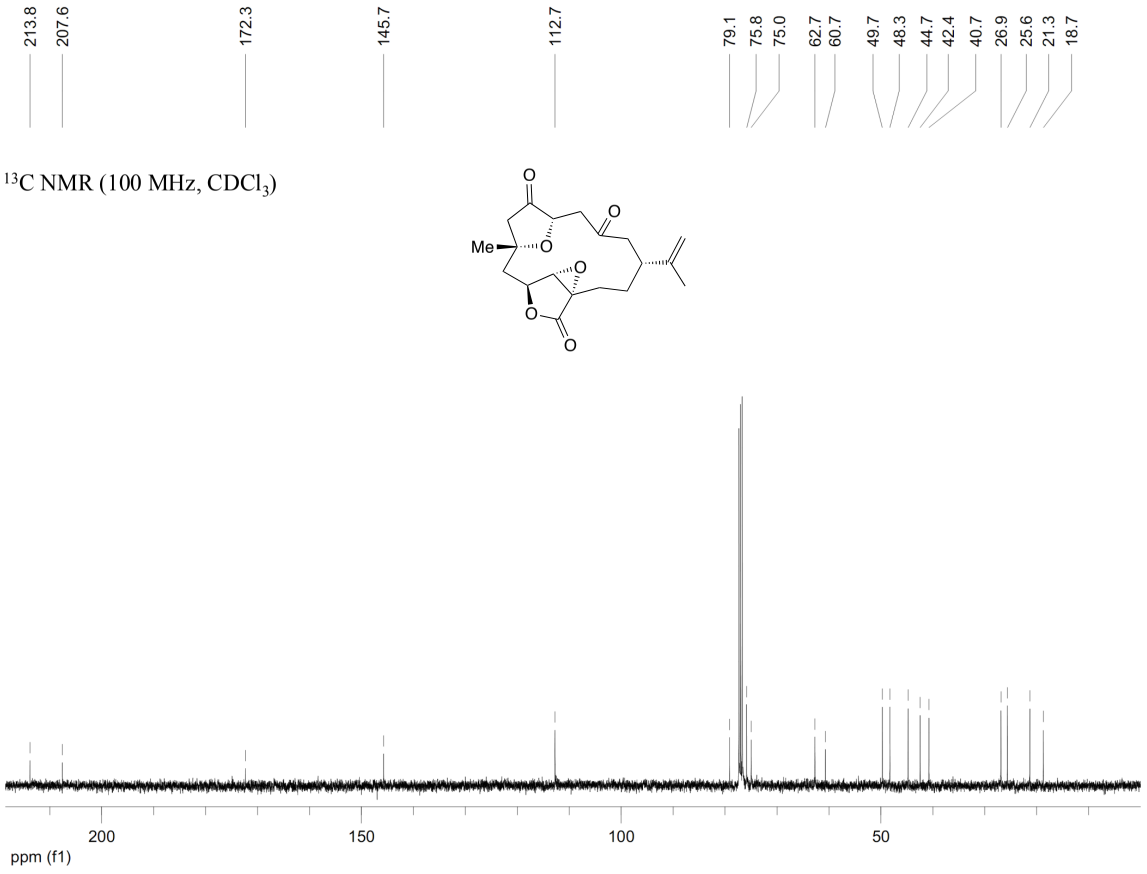
Spectrum 3.33: Compound 27: ^{1}H NMR



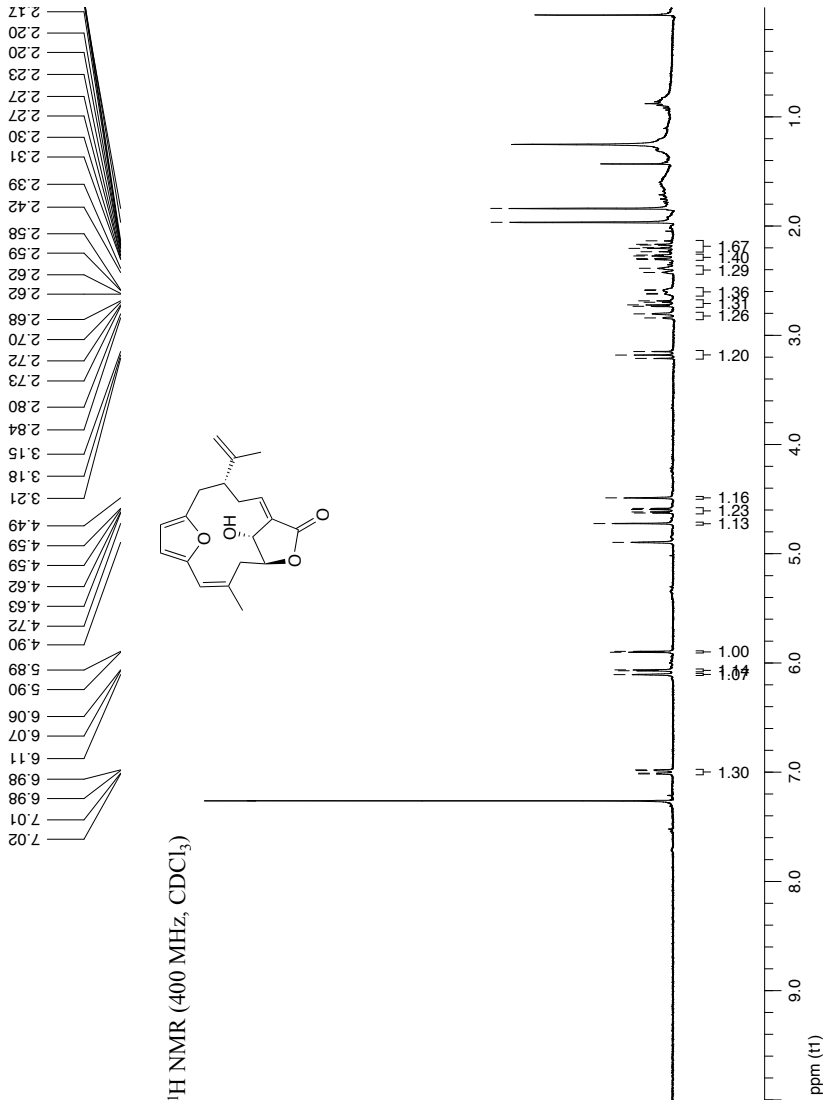
Spectrum 3.34: Compound 27: ^{13}C NMR



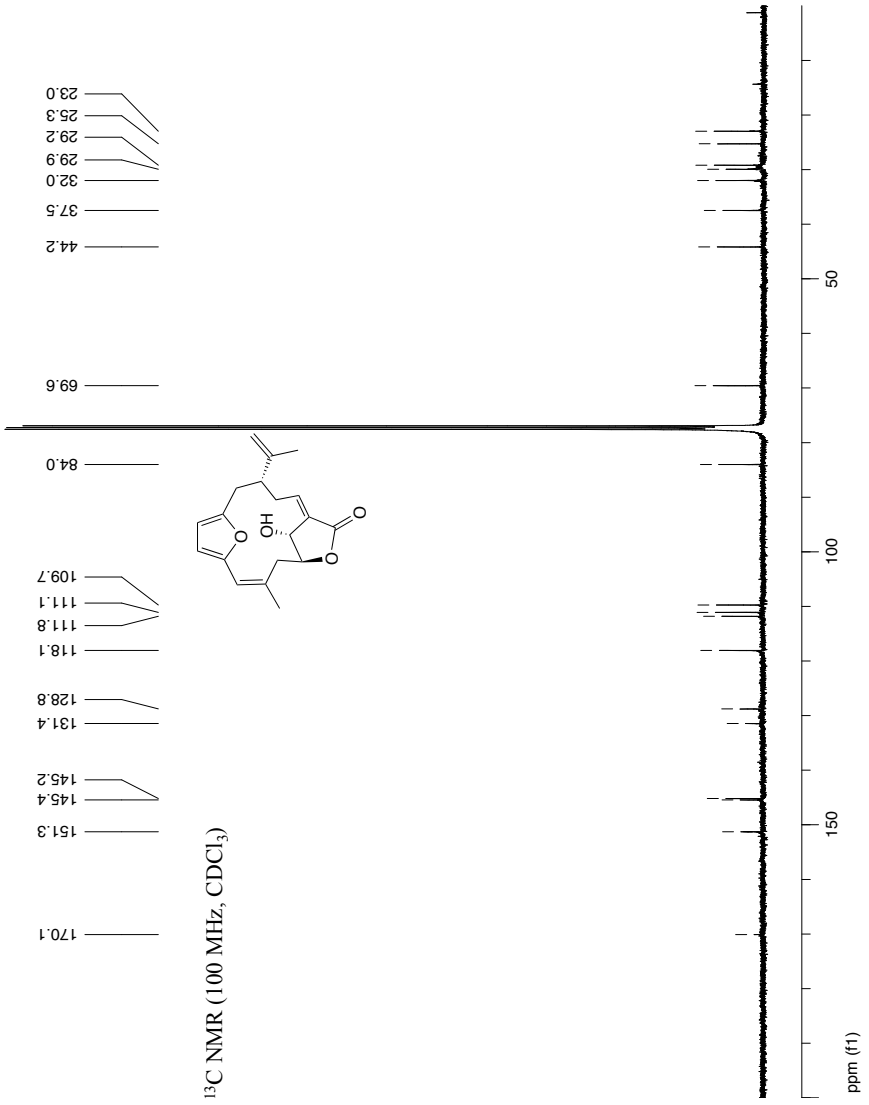
Spectrum 3.35: Compound 8: ^{1}H NMR



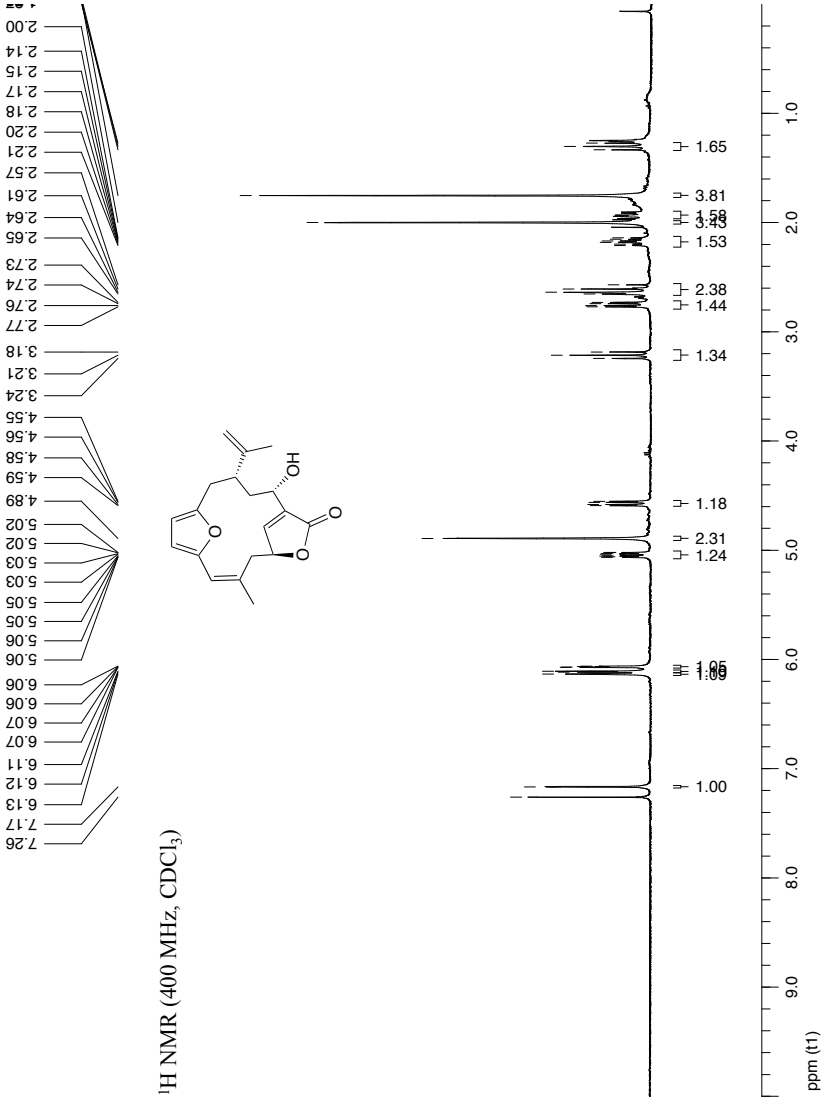
Spectrum 3.36: Compound 8: ^{13}C NMR



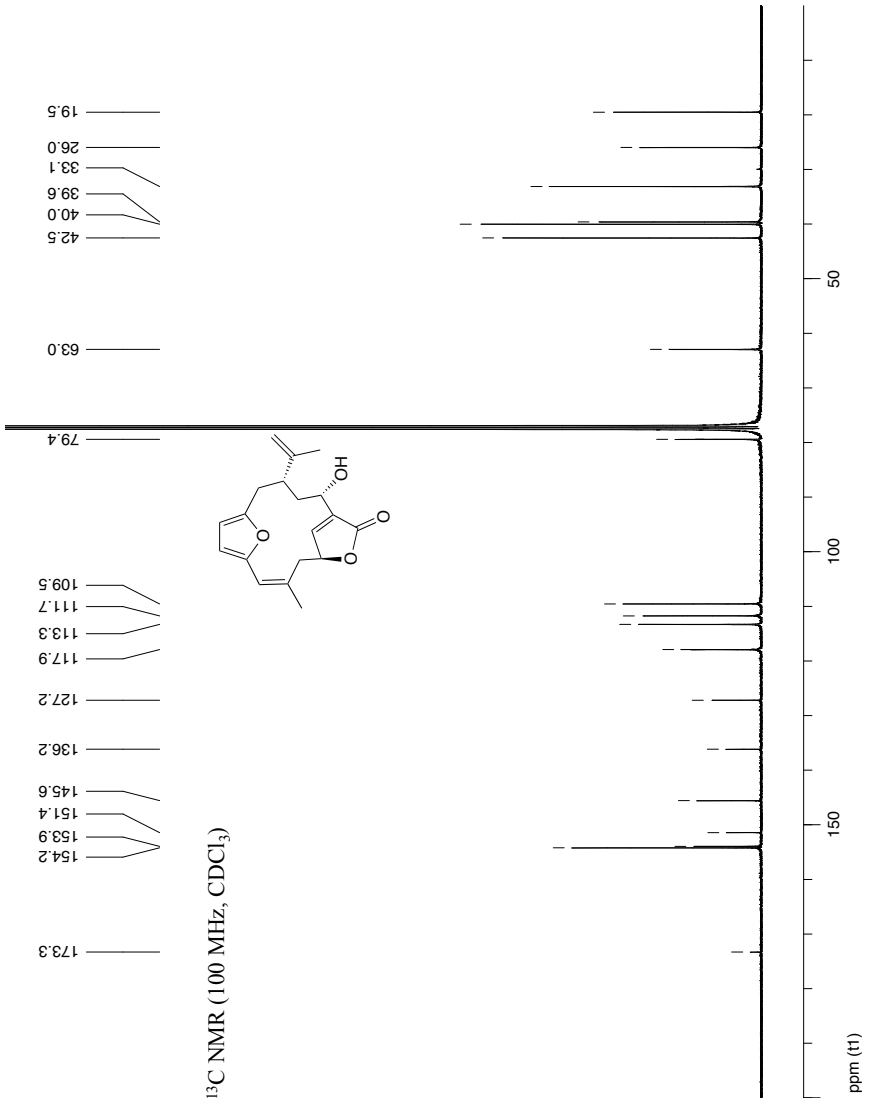
Spectrum 3.37: Compound 28: ^{1}H NMR



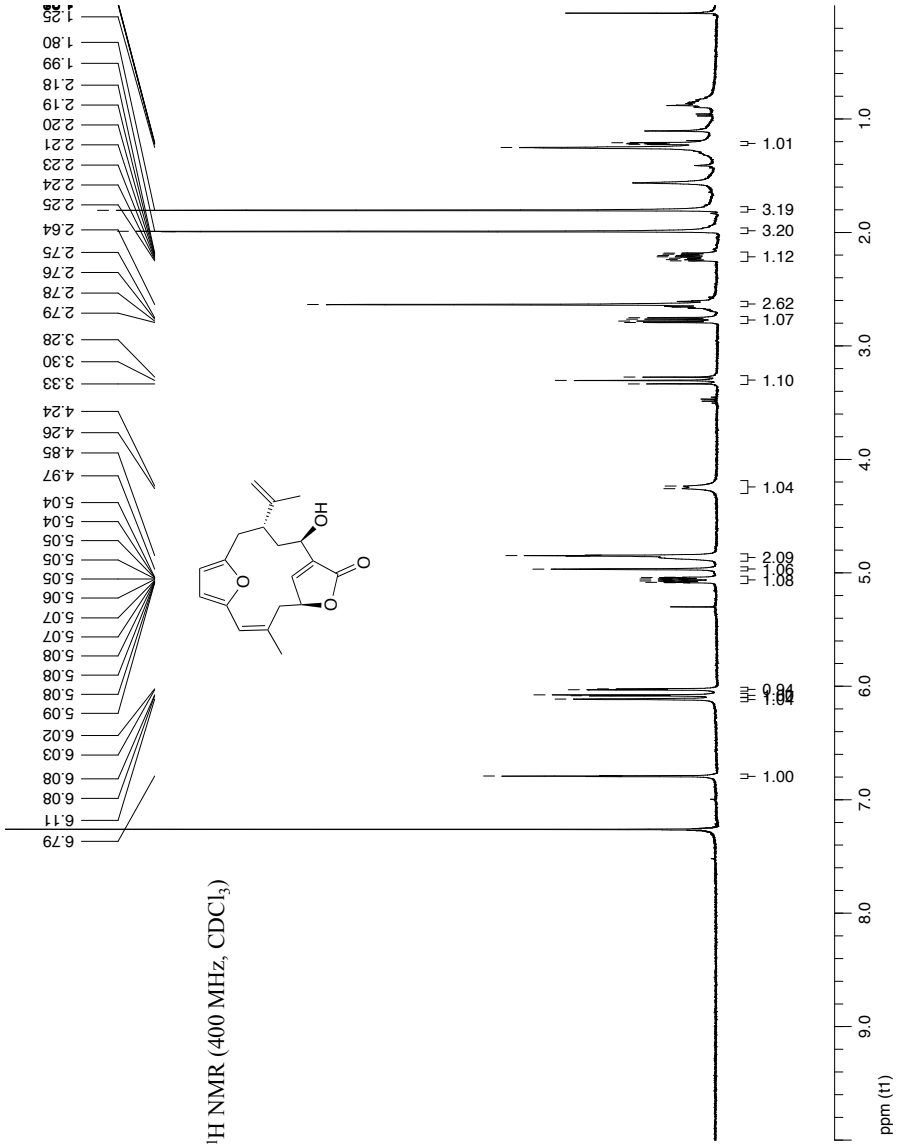
Spectrum 3.38: Compound 28: ^{13}C NMR



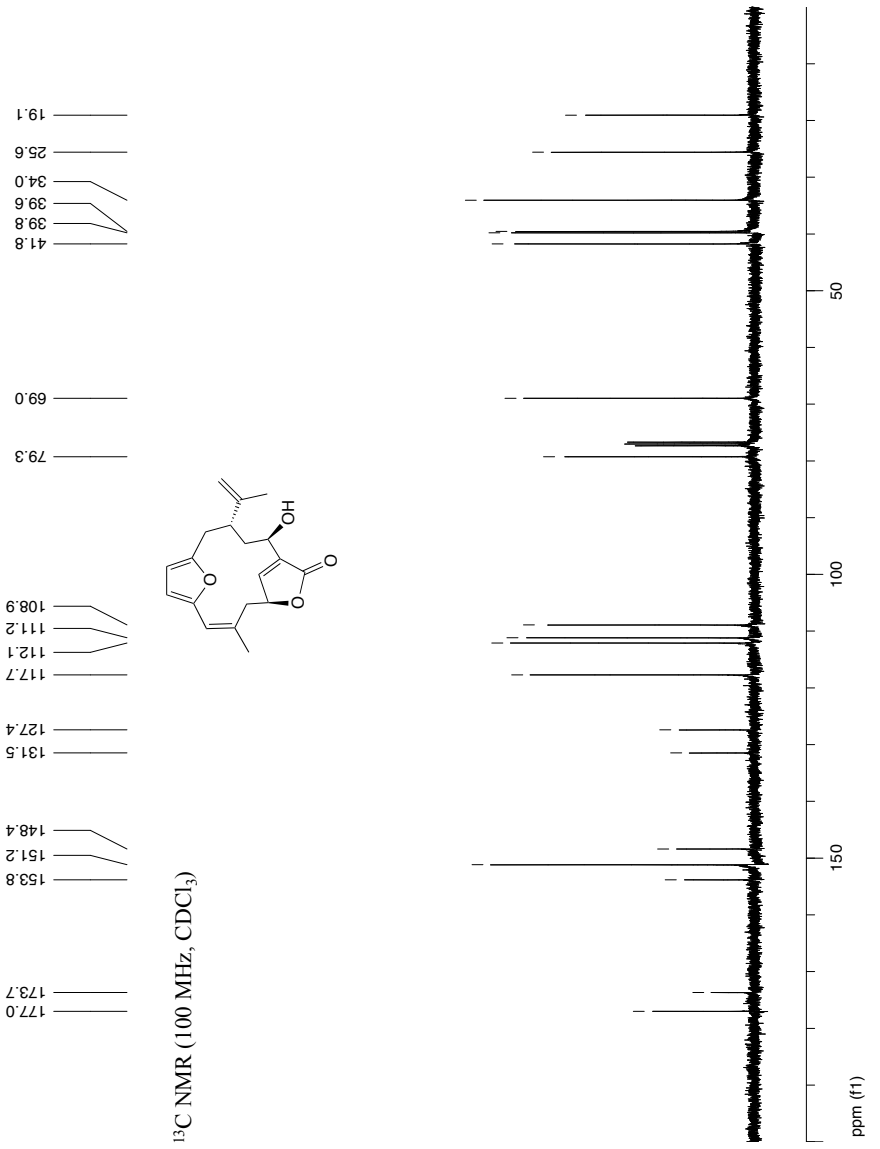
Spectrum 3.39: Compound 32: ^{1}H NMR



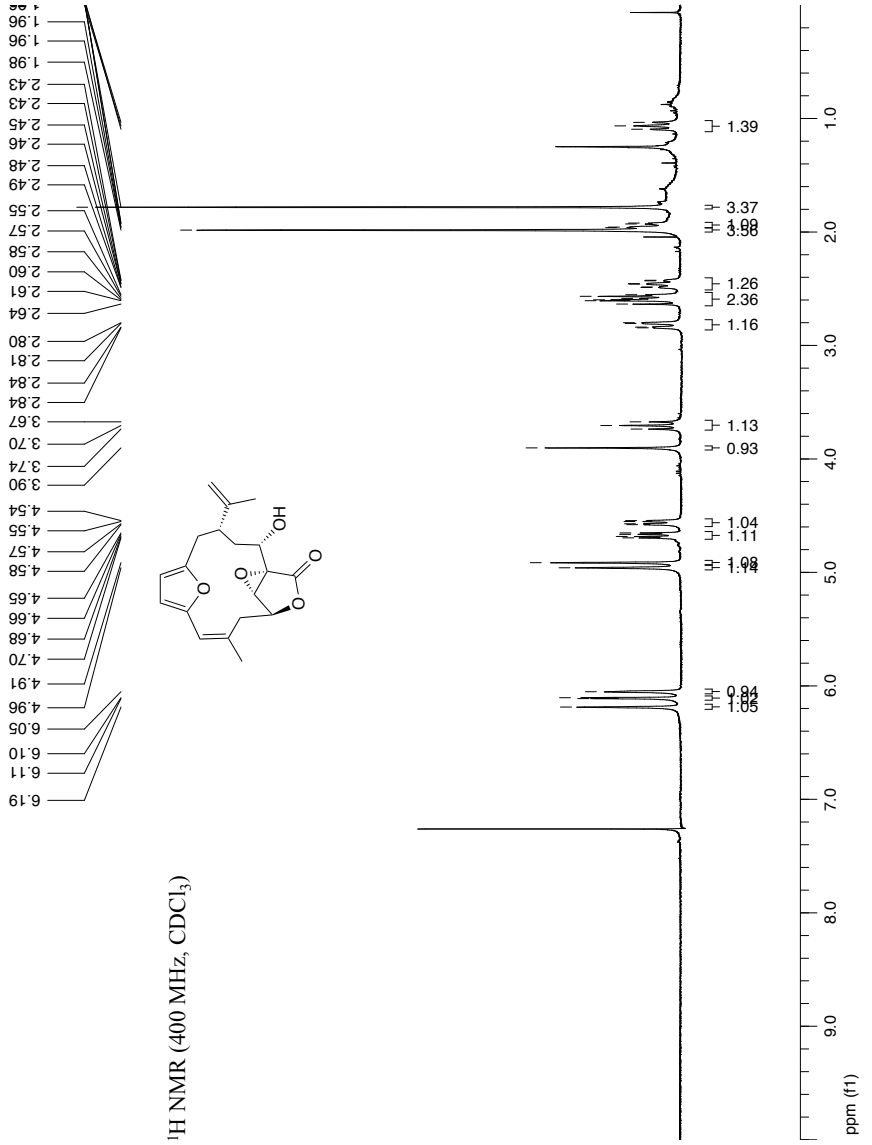
Spectrum 3.40: Compound 32: ^{13}C NMR



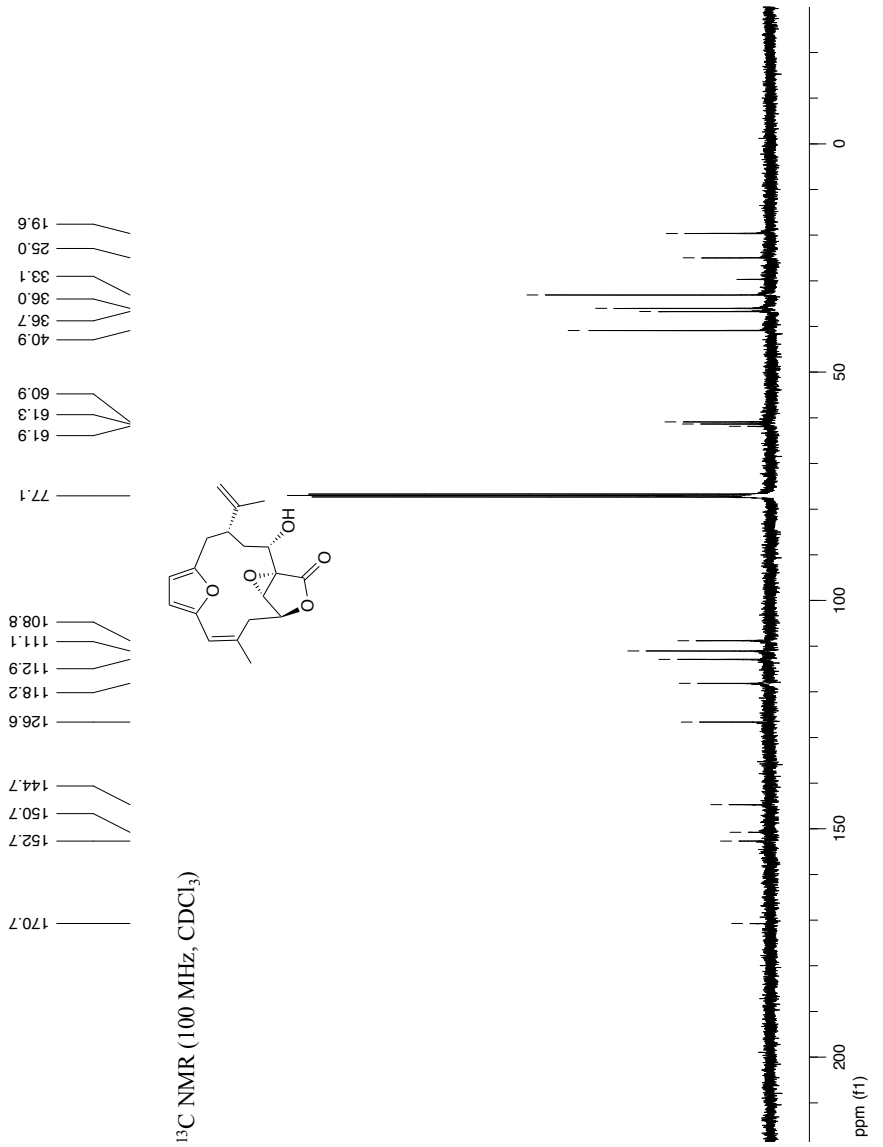
Spectrum 3.41: Compound 29: ^{1}H NMR



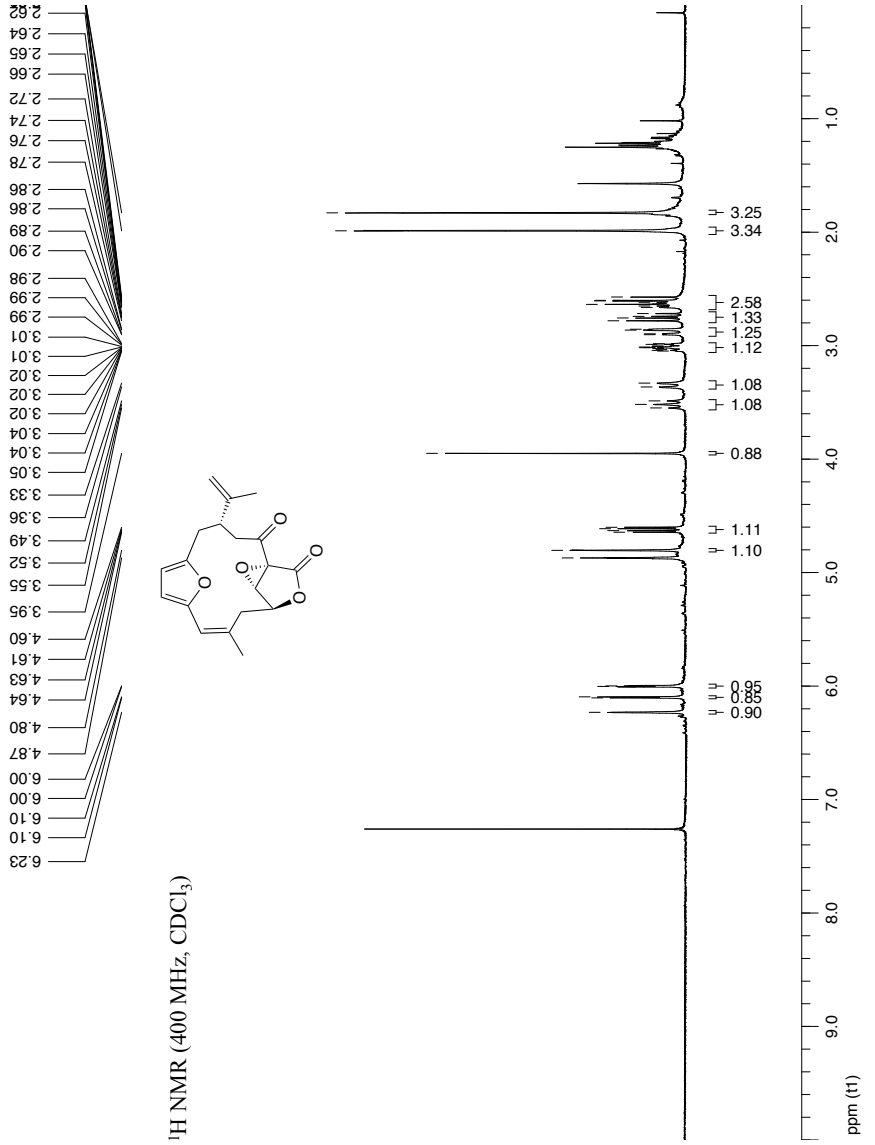
Spectrum 3.42: Compound 29: ^{13}C NMR



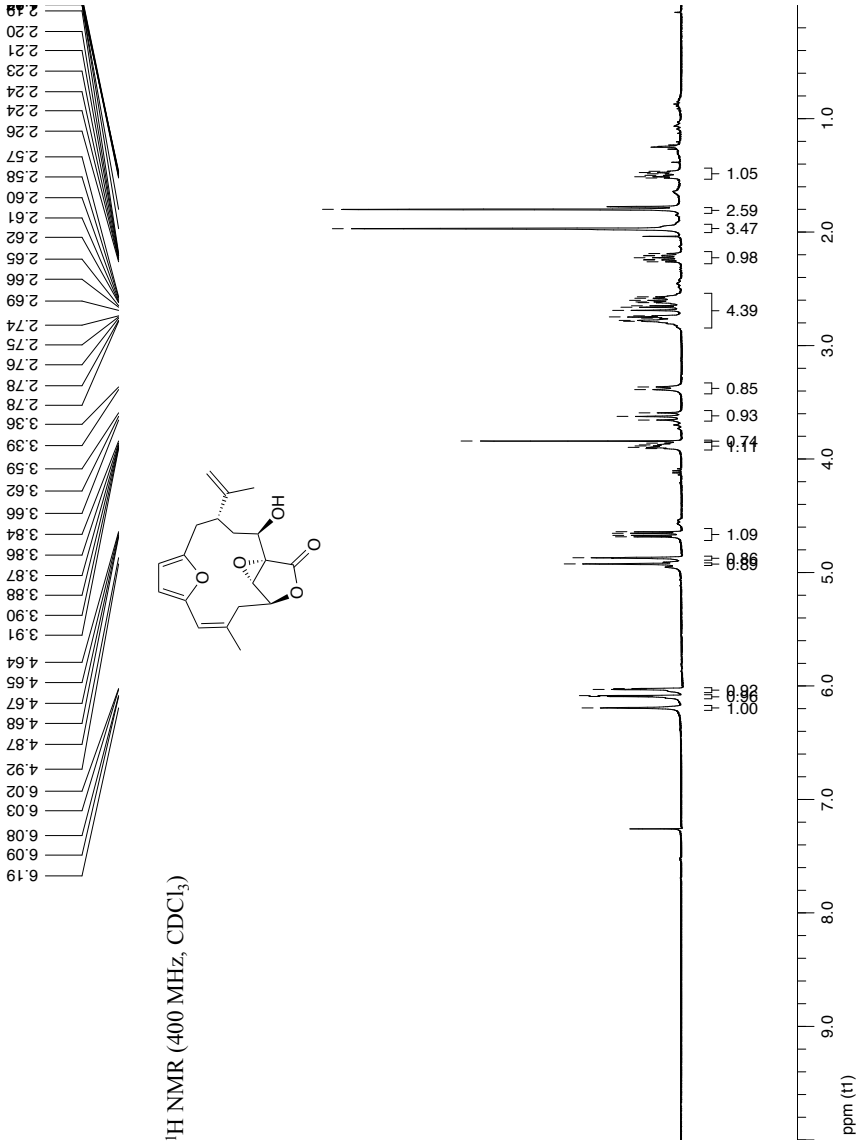
Spectrum 3.43: Compound 34: ^{1}H NMR



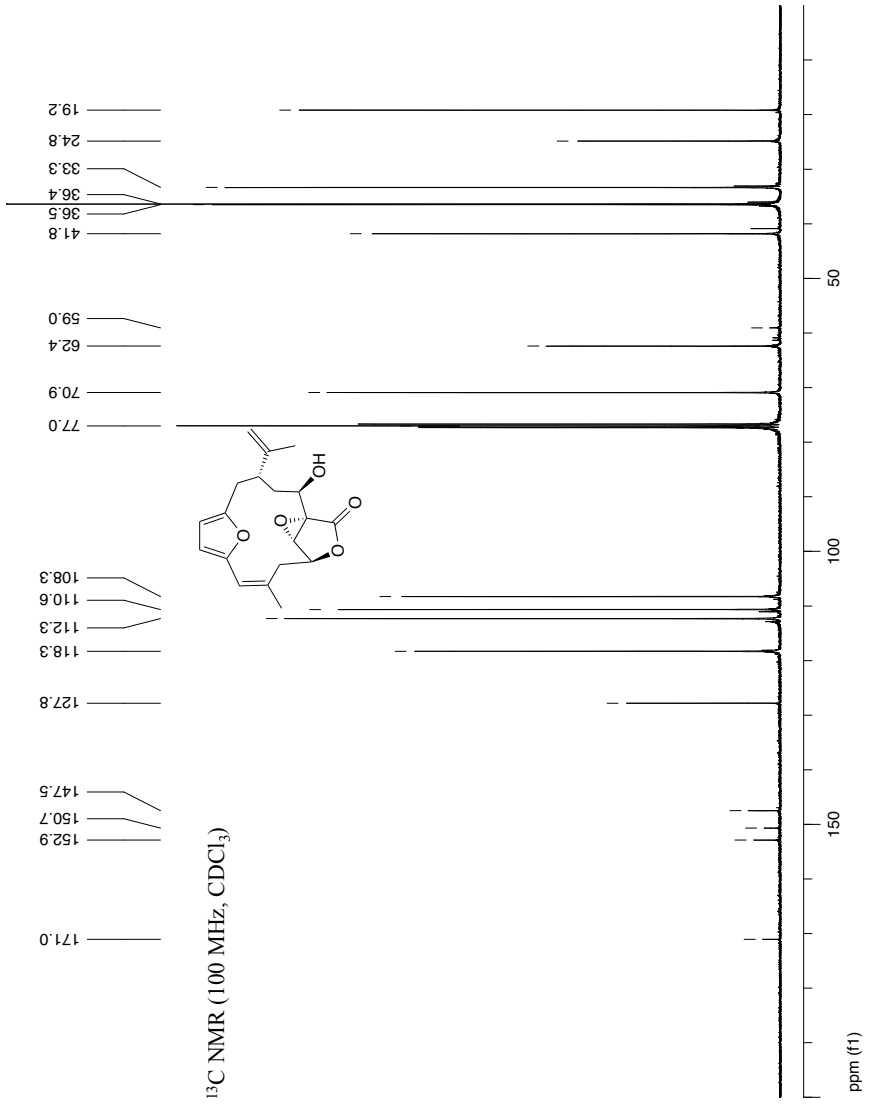
Spectrum 3.44: Compound 34: ^{13}C NMR



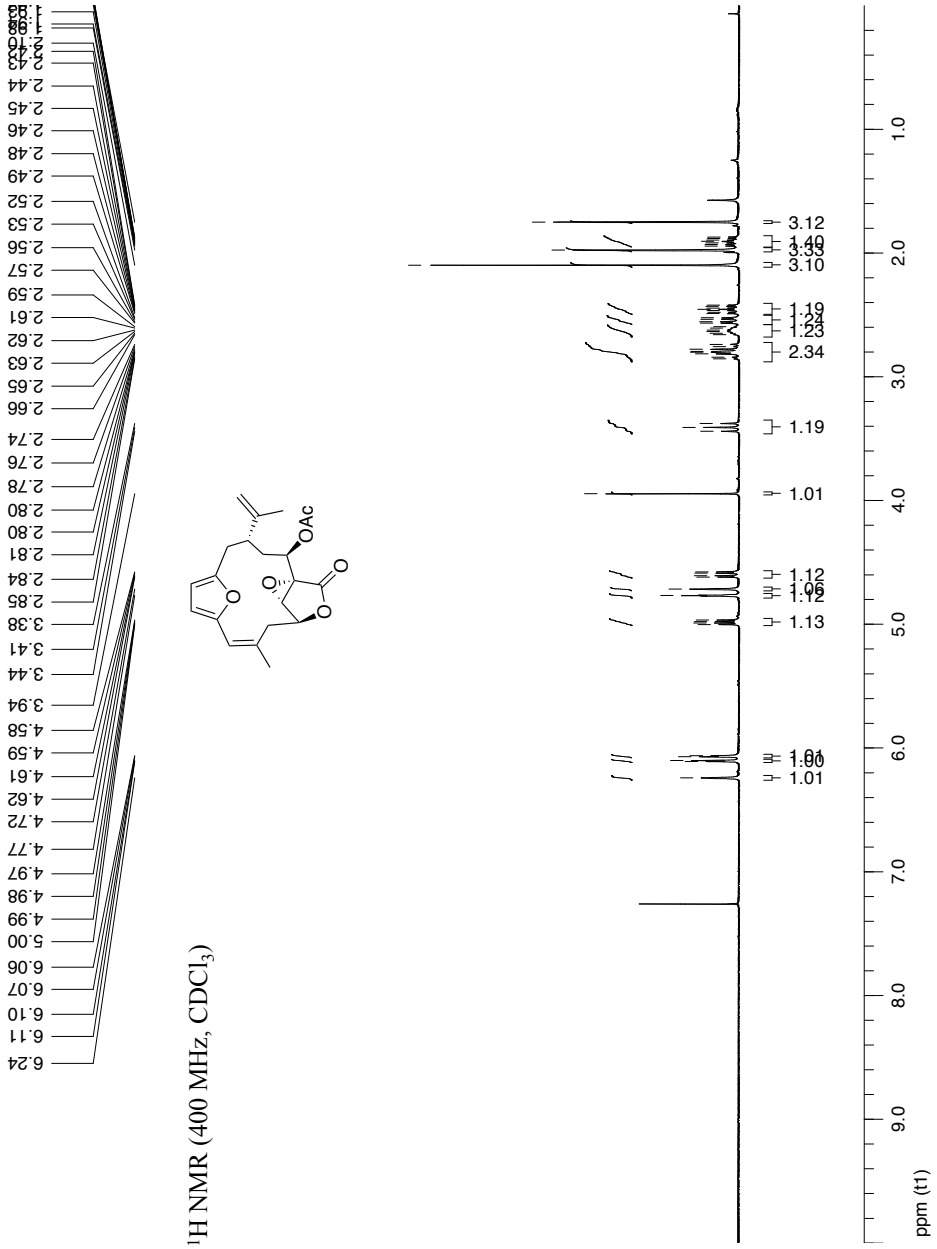
Spectrum 3.45: Compound 34b: ^{1}H NMR



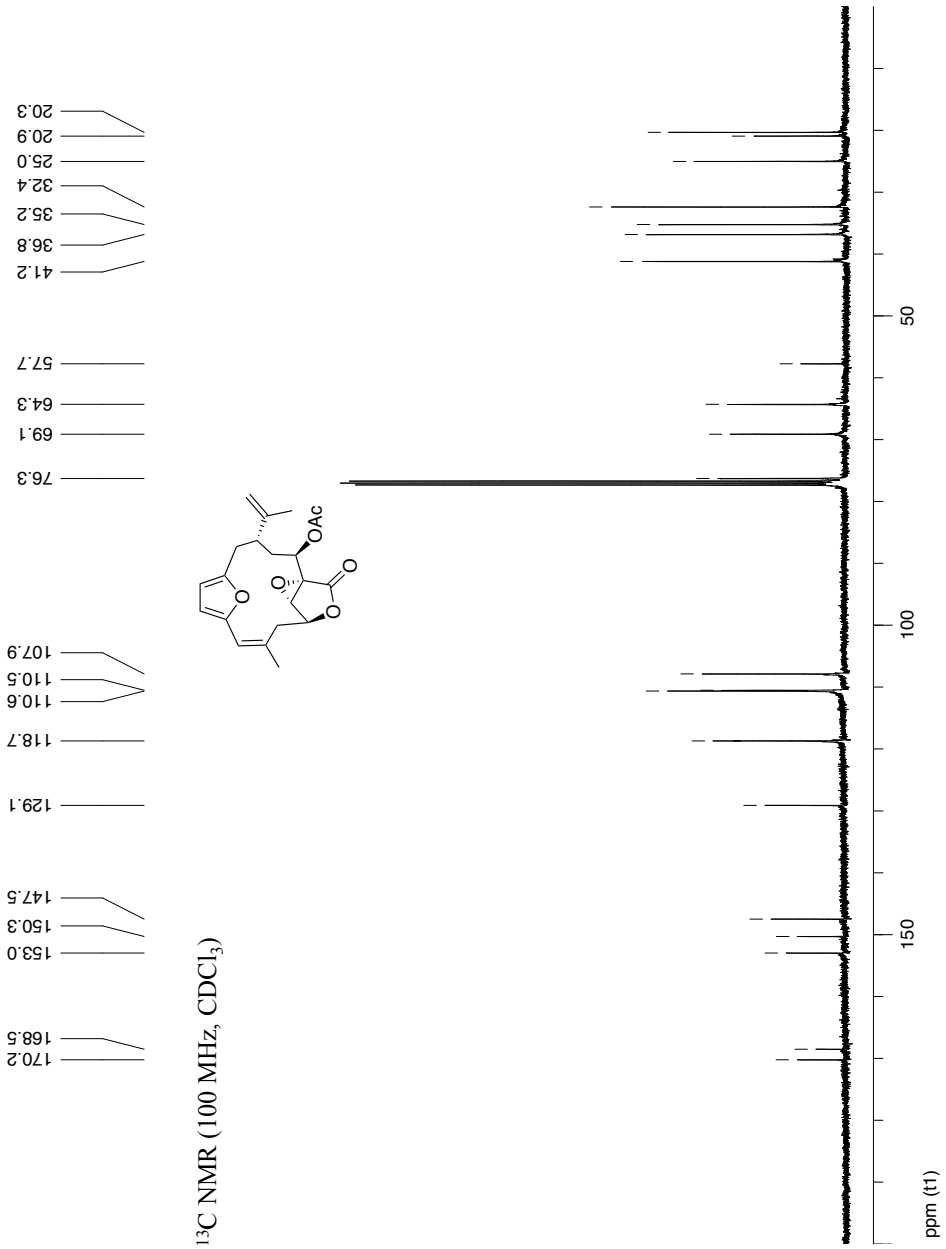
Spectrum 3.46: Compound 35: ^{1}H NMR



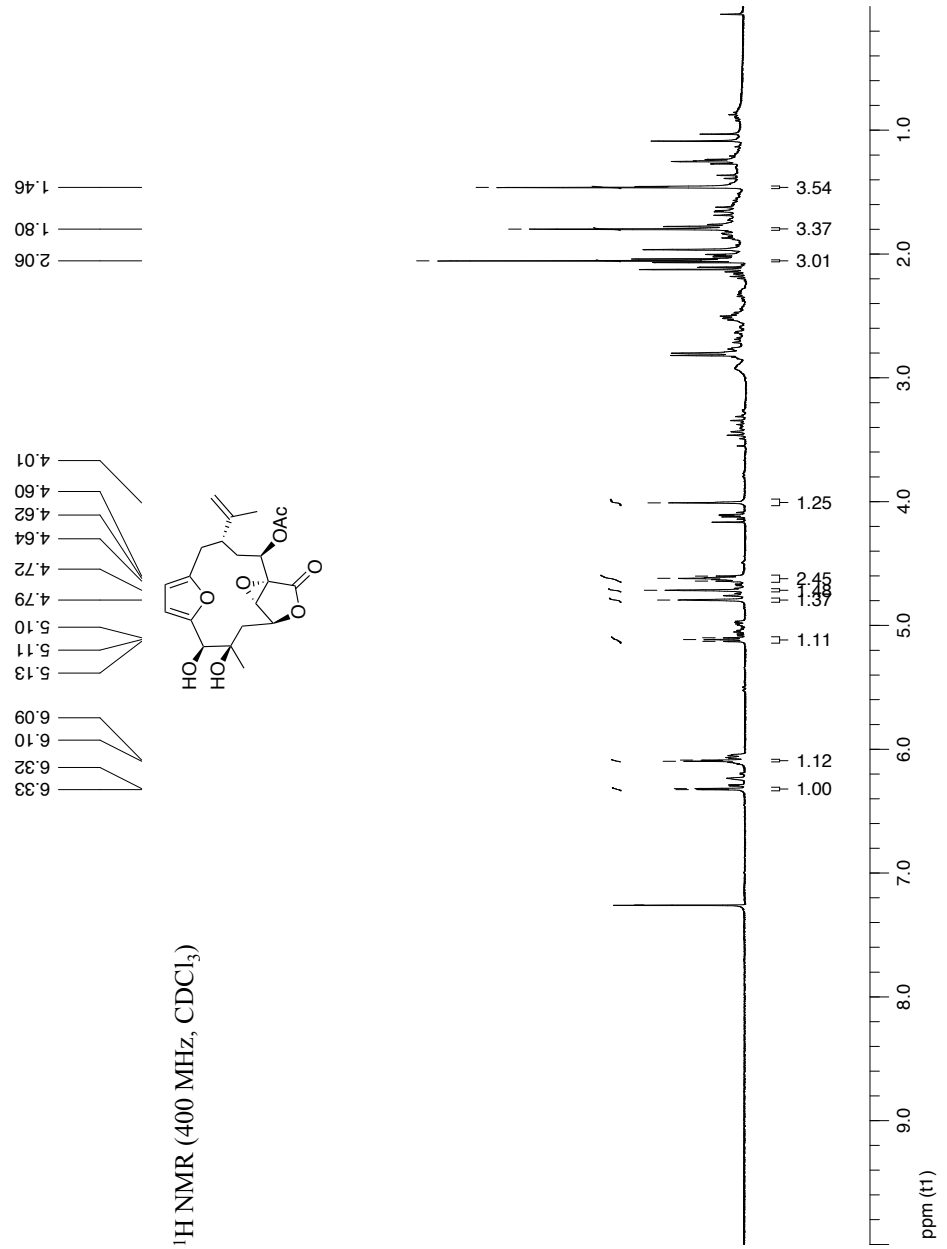
Spectrum 3.47: Compound 35: ^{13}C NMR



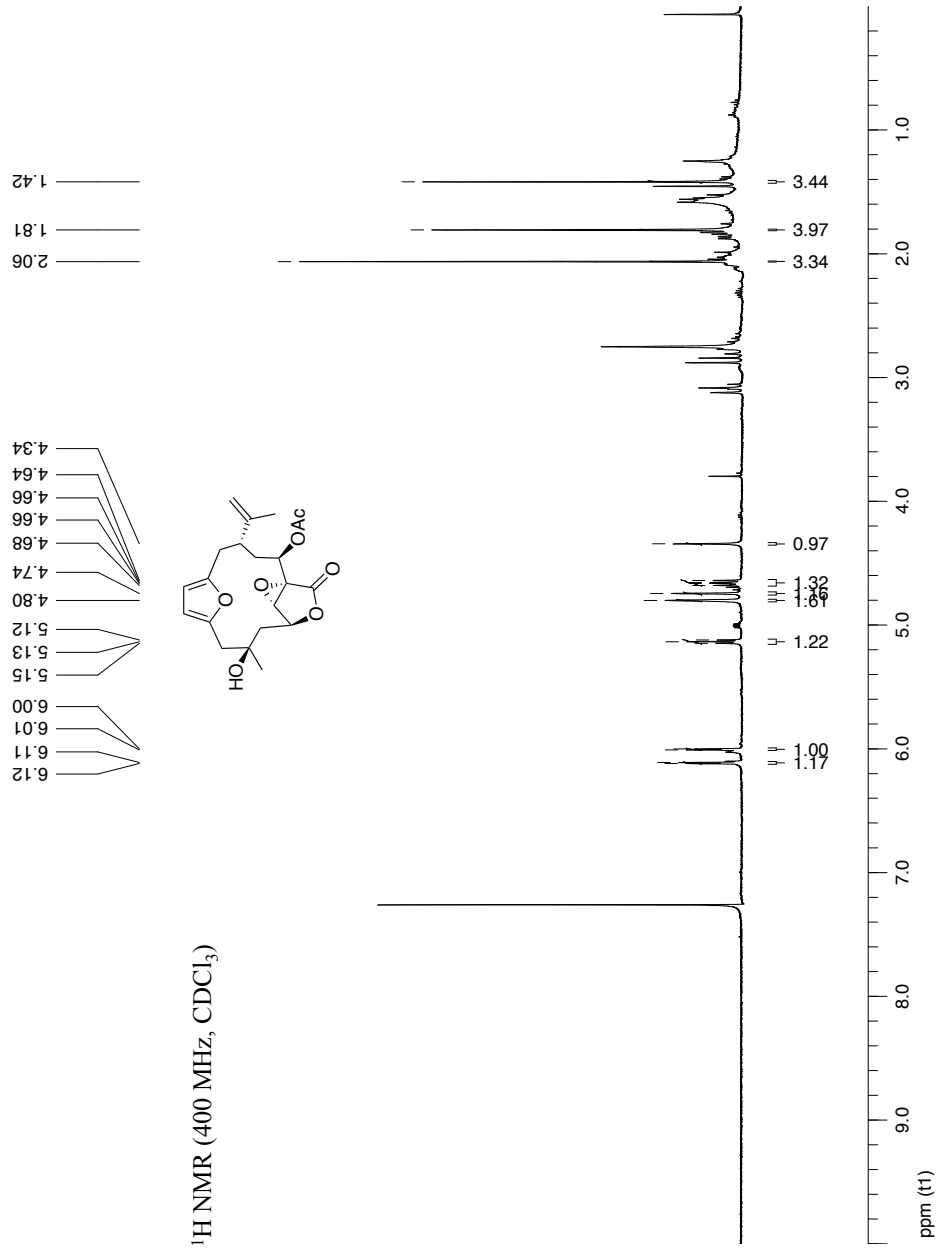
Spectrum 3.48: Compound 36: ^{1}H NMR



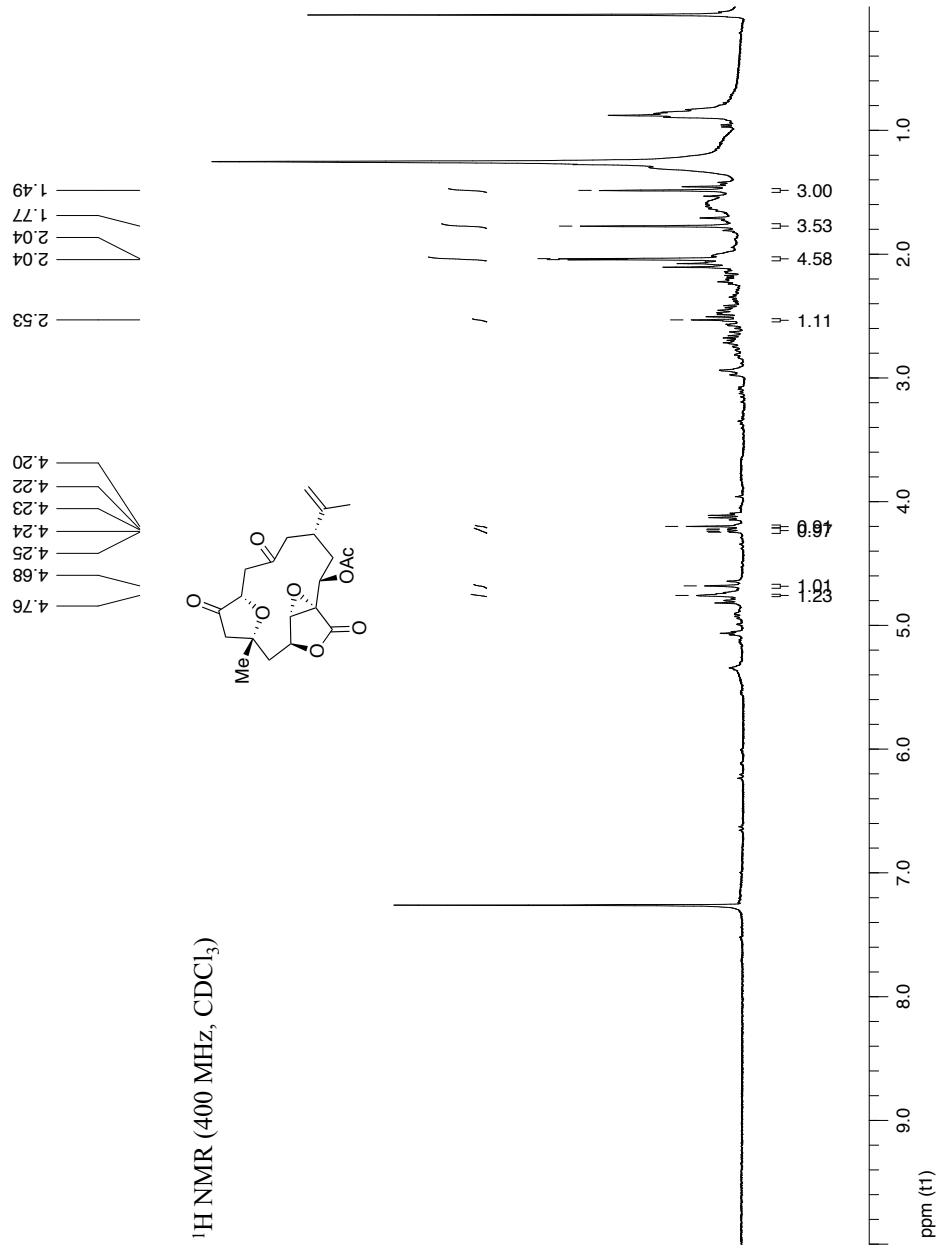
Spectrum 3.49: Compound 36: ^{13}C NMR



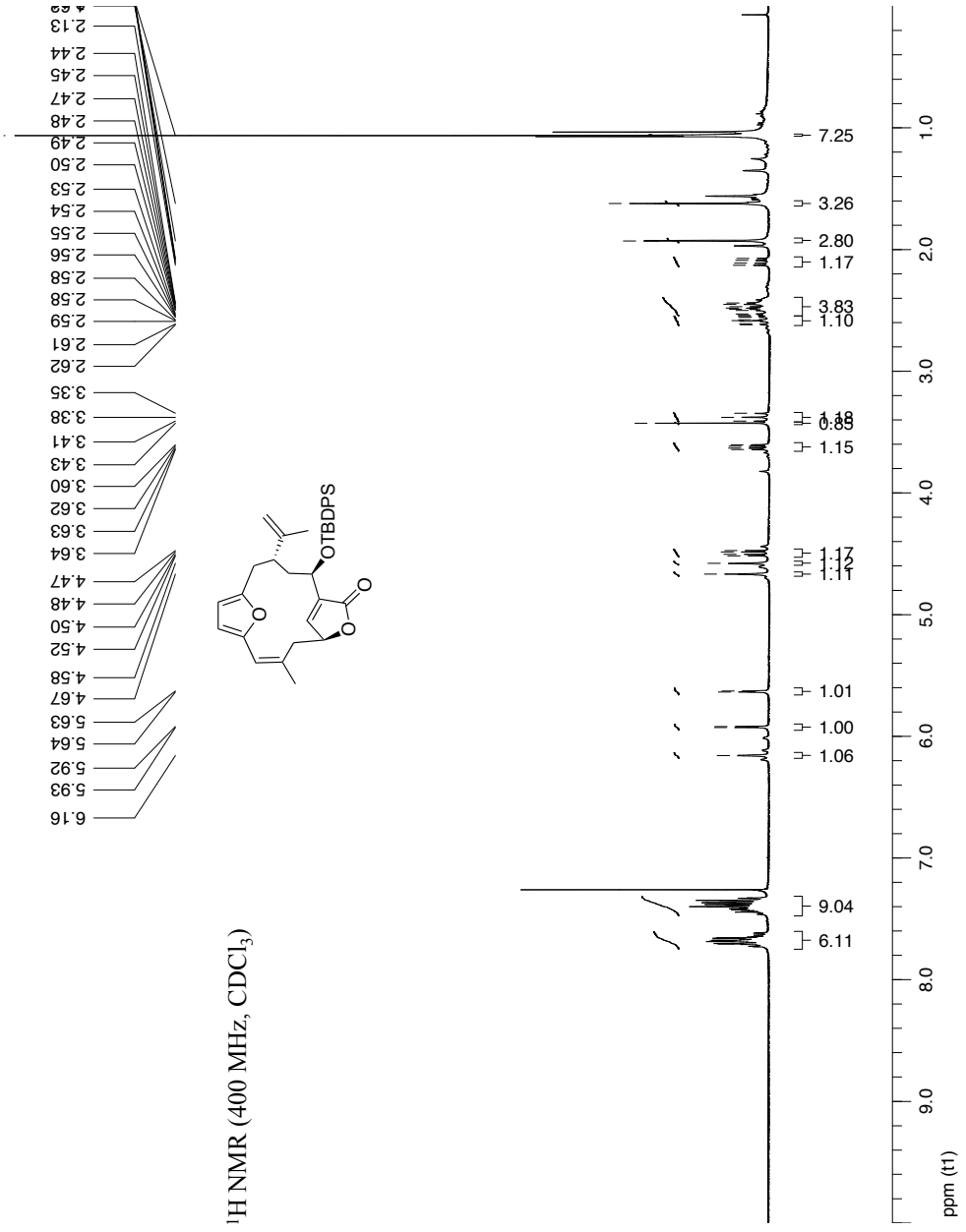
Spectrum 3.50: Compound 37: ^{1}H NMR



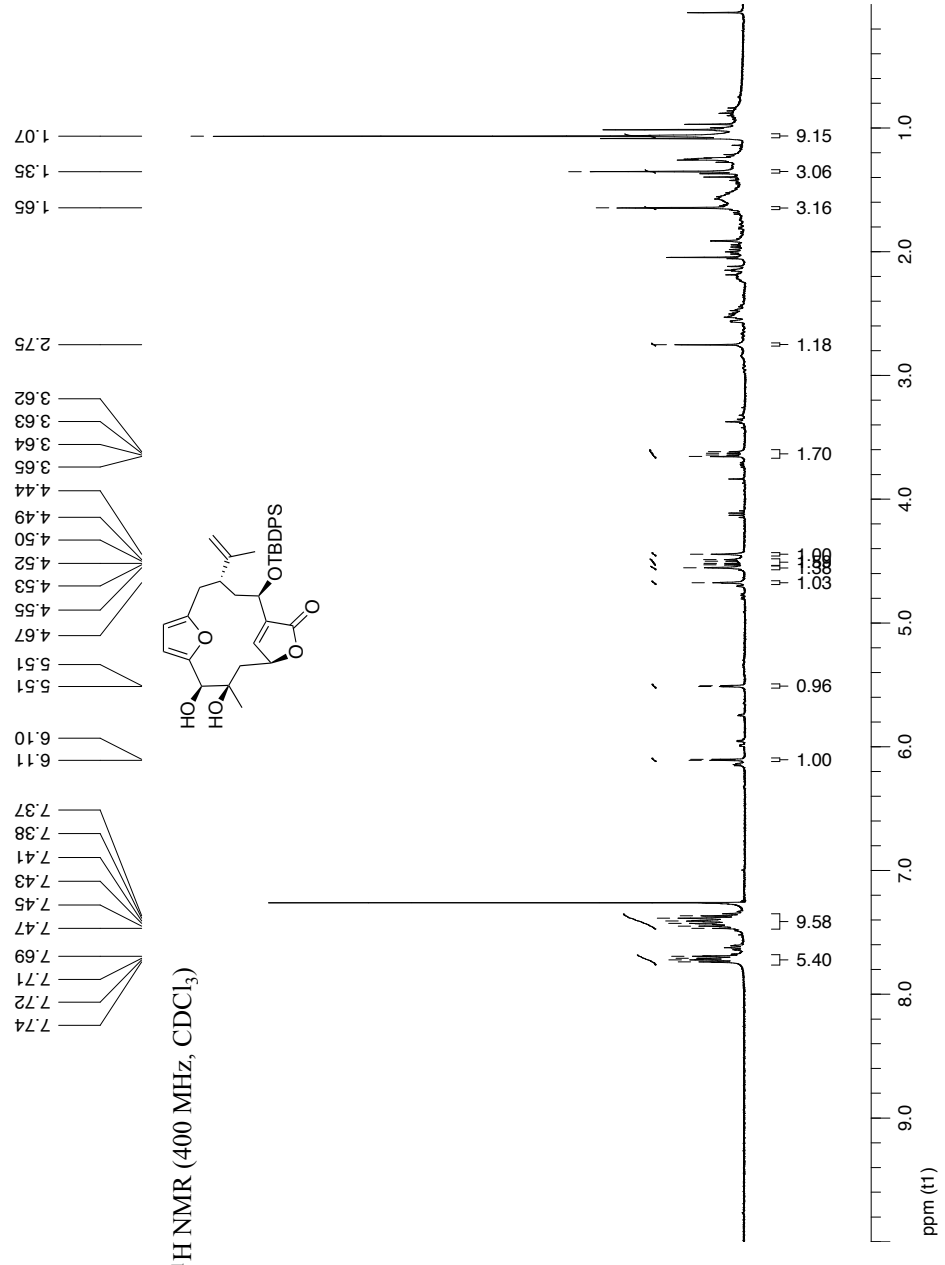
Spectrum 3.51: Compound 38: ^{1}H NMR



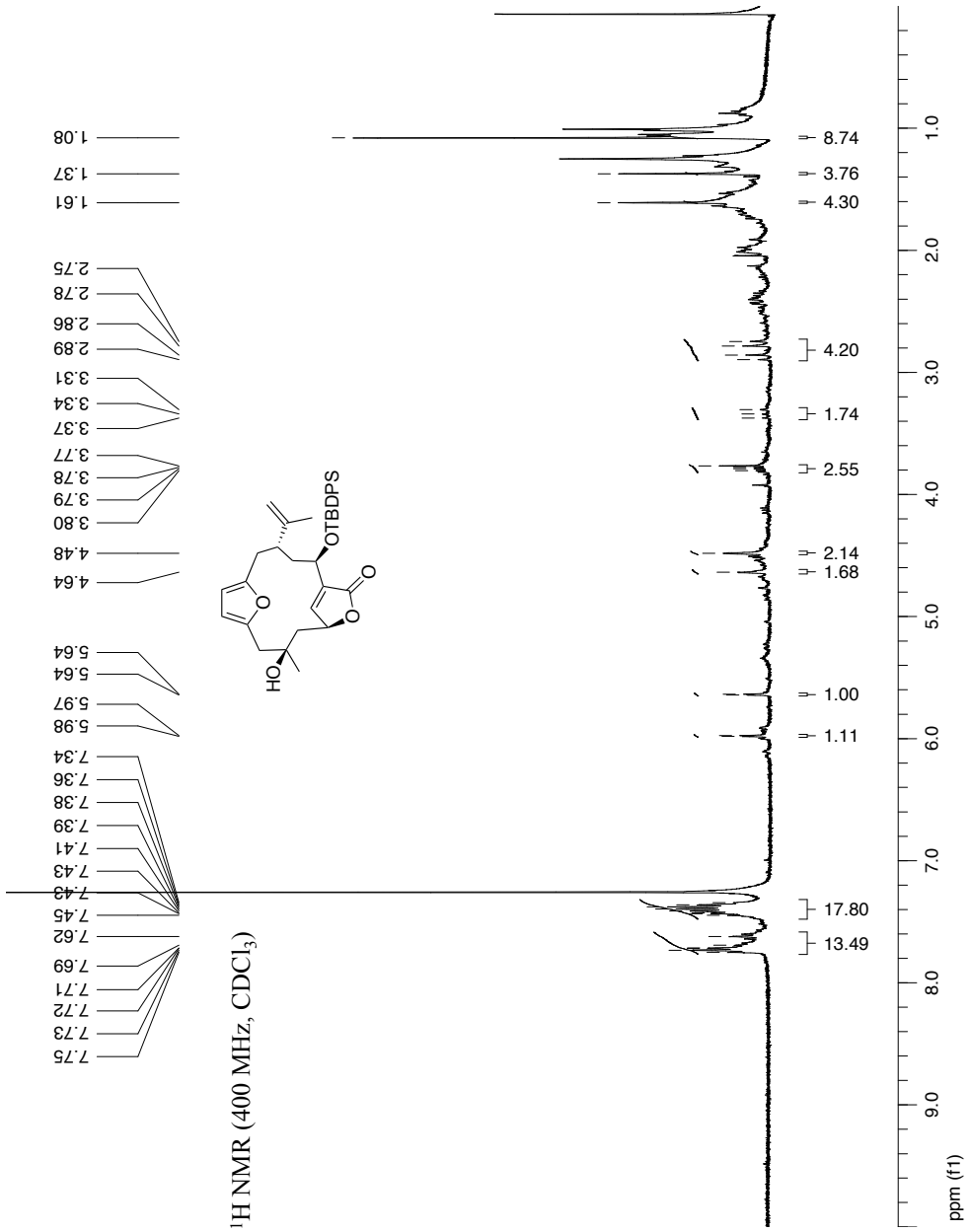
Spectrum 3.52: Compound 39: ^{1}H NMR



Spectrum 3.53: Compound 40: ^{1}H NMR



Spectrum 3.54: Compound 41: ^{1}H NMR



Spectrum 3.55: Compound 42: ^{1}H NMR

3.2.2 X-ray crystal data

CCDC 831516 **(4)**, 831512 **(5)**, 831511 **(6)**, 831510 **(7)**, 831515 **(8)**, 831509 **(21)**, 831766 **(22)**, 831513 **(24)**, 831514 **(25)**, 889637 **(28)**, 888994 **(29)**, and 888992 **(32)** contain the supplementary crystallographic data. This information can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/.

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