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Development of synthetic process for the precursor of Harringtonolide

헤링토놀라이드 전구체의 합성 경로 개발

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이 선 아

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By

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이 논문을 공학석사 학위논문으로 제출함

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Abstract

Development of synthetic process for the precursor of Harringtonolide

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In order to utilize medicinal potentials and explore the related synthetic chemistry of plant extracts, many chemists tried to construct the total synthesis of natural products. Especially, an unusual methylated diterpenoid tropone, Harringtonolide, is one of the most intriguing target compounds for synthetic chemists because of its unique cage-like structures.

The norditerpenoid Harringtonolide, has been extracted and separated from *Cephalotaxus harringtonia*. It is known to show diverse biological activities such as the plant growth inhibitory, cytotoxicity against KB tumor cells, antiviral and antineoplastic properties. Also, it has a thorough tetracyclic structure which is constituted of a tropone, bridged lactone, THF ring and a cis-fused tricyclic ring with continual stereogenic centers. Because of its unique structure and applicable biological activities, several studies were conducted to find the proper synthetic routes for the production of Harringtonolide and its analogs.[4,10,11,12]

Our group also tried to synthesize the precursor of Harringtonolide by 10 steps in order to utilize its biological activities. We have suggested simple and alternative retro-synthetic methods starting with a molecule named 6-hydroxytetralone, with following reaction steps such as Robinson annulation, Bromination and Nitration.[14,16,17] Especially, optimizations for Bromination, Stille coupling and Nitration steps were performed for developing further reactions. Finally, the radical anionic coupling reaction was conducted to generate a tropone ring,[13] but unexpected phenol and nitrobenzene rings were formed. It is believed that a rigid structure of α, β-unsaturated phenolic nitronate triggered a cyclization with a favorable bond angle.

In this study, the synthetic process for the precursor of Harringtonolide and optimizations for some reactions will be illustrated. Also, a new mechanism and molecular model studies which validate the formation of unanticipated phenol and nitrobenzene ring in a radical anionic coupling reaction will be explained. We think that these results can provide a new synthetic perspective towards developing feasible precursors for the total synthesis of Harringtonolide.

Keyword: Harringtonolide, Norditerpenoids, Reaction optimization, Radical anionic coupling, Synthetic process

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List of Abbreviations

CsOH	Cesium hydroxide
DMF	N, N’ −Dimethylformamide
IC_{50}	Half maximal inhibitory concentration
i−PrOH	Isopropyl alcohol
KOH	Potassium hydroxide
MeOH	Methanol
$NaBH_4$	Sodium borohydride
NMR	Nuclear magnetic resonance spectroscopy
$Pb(OAc)_4$	Lead tetraacetate
PCC	Pyridinium chlorochromate
TBAF	Tetrabutylammonium fluoride
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography

1. Introduction

1.1. *Cephalotaxus* Norditerpenes

The member of Cephalotaxaceae, *Cephalotaxus,* is a genus of coniferous trees and evergreen shrubs.[1] Seven species of *Cephalotaxus* have been used to cure leukemia in Chinese traditional remedies.[2] Furthermore, several natural products having a norditerpene structure were extracted and isolated from *Cephalotaxus* including Harringtonolide (*C. Harringtonia*), Hainanolidol (*C. hainanensis*), Fortunolide A and B (*C. fortunei*) (Figure 1).[3,4] These compounds represent similar complex structures featuring fused tetracyclic rings, a tropone ring with methyl group, a cyclohexane with neighboring stereocenters, and a bridged lactone. However, they are somewhat different in that Harringtonolide and Fortunolide B have a THF ring whereas Hainanolidol and Fortunolide A have a hydroxy group instead. Although Harringtonolide and Hainanolidol have almost a same structure except a THF ring, it was discovered that only Harringtonolide is biologically active.[11] This result shows that a THF ring plays an important role in its bioactivity.[5a,5b] There was no result which presented a biological activity of Fortunolide A and B.[1] It could be supposed that the strained structure of Harringtonolide containing lactone and THF rings can interact or bind with biological targets such as N, O, S–based nucleophiles existing in enzymes, nonenzymatic protein, and DNA molecules which is consistent with

Harringtonolide's biological activity.[5c,5d]

Harringtonolide was first extracted from the seeds of *Cephalotaxus harringtonia* by J. Buta in 1978, as a research for developing new natural plant growth regulators and its structure was identified by X-ray crystallography method.[6,10] It was discovered that Harringtonolide can arouse a necrosis and inhibit the plant growth in tobacco and beans. In 1979, Harringtonolide was also detected from *Cephalotaxus hainanensis*, which is one of the Chinese species[5a,10] In the report, it was discovered to represent antiviral and antineoplastic activities against Walker carcinoma, Lewis lung carcinoma, leukemia cells and influenza type A.[1,5,7] In 2008, Nay's group discovered that Harringtonolide has an efficient and selective anticancer activity towards KB tumor cells (IC_{50} = 43 nM) and the antifungal activity, which is due to its tropone moiety.[8a] Antitumor activities of a tropone ring might be related to its lipophilicity, acting as a promising membrane antiporter by delivering protons in exchange for cytoplasmic cations such as K^+.[8c] If the tropone ring of Harringtonolide is functionalized with other functional groups such as the hydroxy group, it can chelate with metals including Mg^{2+}, Zn^{2+} and Cu^{2+}. This can allow the functionalized Harringtonolide to interact with the active site of metalloenzyme.[8b]

Inspired by these medicinal properties, a development of the new and efficient total synthesis of Harringtonolide had been important issues for many synthetic chemists. Therefore, I also attempted to synthesize the precursor for Harringtonolide and its derivatives, with more economic pathways compared to other researchers.

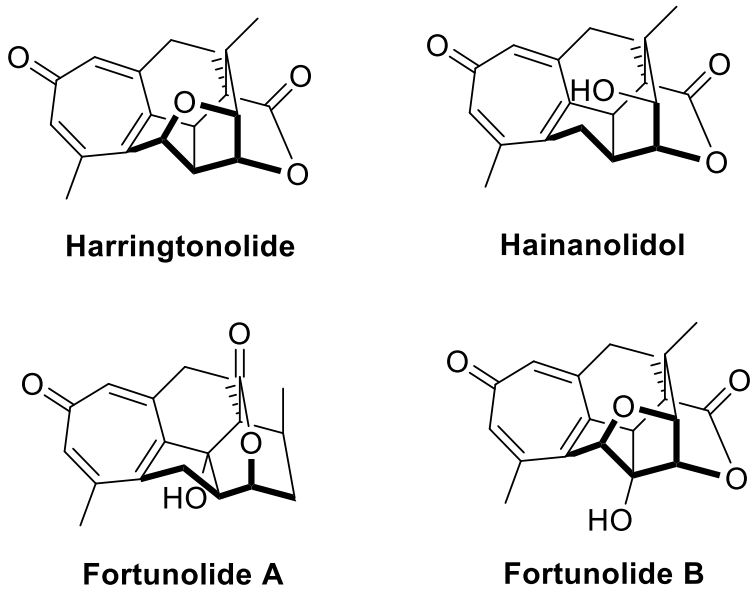


Figure 1. Fused tetracyclic natural products isolated from *Cephalotaxus*

1.2. Previous studies

Due to interesting structural characteristics and anticancer activities of these norditerpenes, there have been several studies on the total synthesis of Harringtonolide and its derivatives (Scheme 1).[4]

Firstly, Mander's group reported the foundational total synthesis of (±)-Hainanolidol in 1998, which can be transformed into Harringtonolide by a transannular oxidation with $Pb(OAc)_4$ under light irradiation.[9] They used a rhodium mandelate-catalyzed intramolecular cyclopropanation and sequential ring expansion to create a cycloheptatriene ring. Lactonization was performed with K_2CO_3 in a later step, because synthesizing a precedent lactone ring before forming a cycloheptatriene ring was sterically hindered. However, continuous tries for the synthesis of Harringtonolide by generating a THF ring at initial steps were not successful.[10]

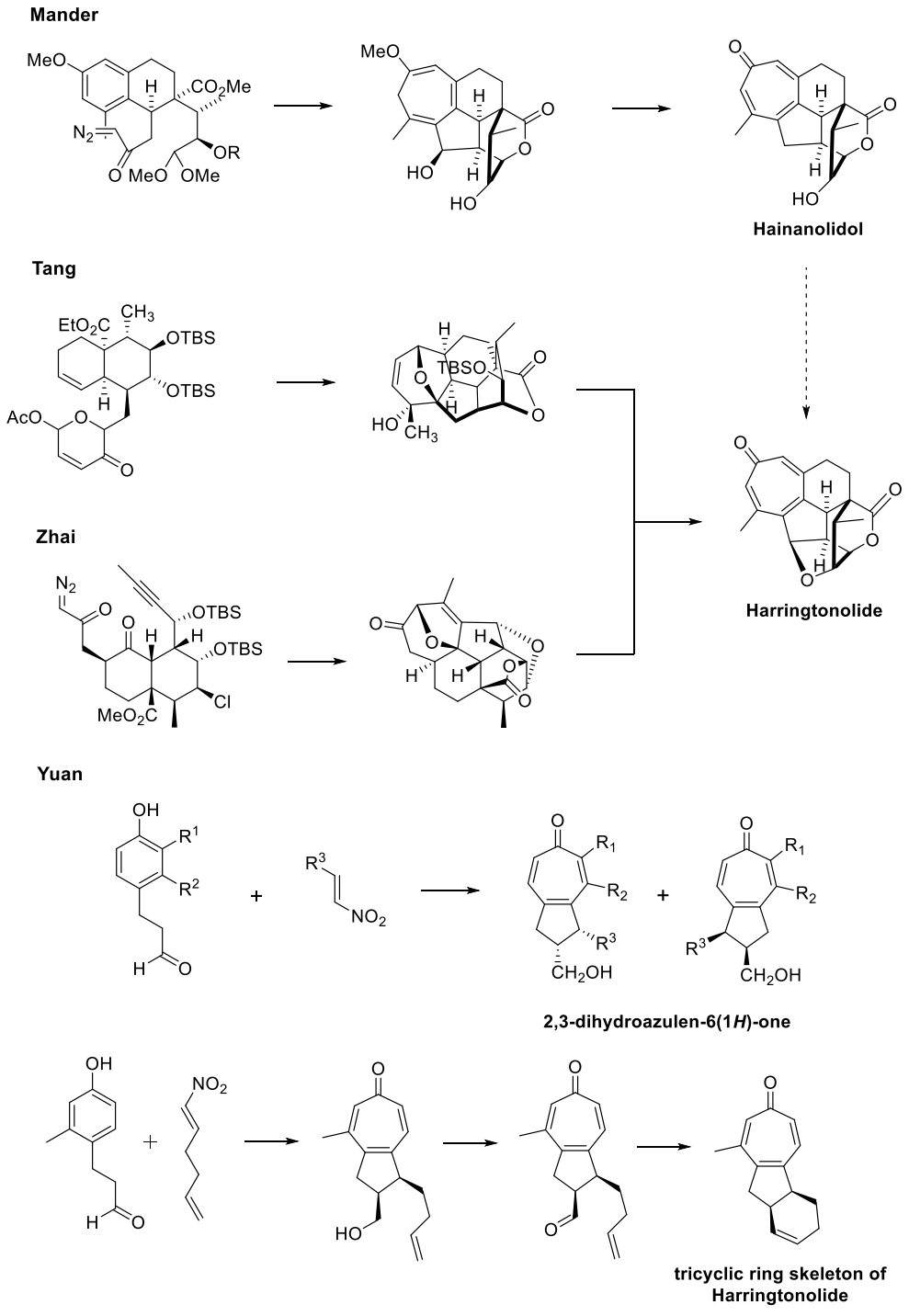
Second, Tang's group produced the report of an effective total synthesis of racemic Harringtonolide and Hainanolidol in 2013. They synthesized the required tetracyclic structure with an intramolecular oxidopyrylium-based [5+2] cycloaddition, which was accompanied by stereoselective reactions to introduce contiguous stereogenic centers. Tropone ring was formed by a serial [4+2] cycloaddition of cycloheptatriene, Kornblum-DelaMare rearrangement, and a double elimination. They finally synthesized Harringtonolide by treating Hainanolidol with $Pb(OAc)_4$.[11]

Third, Zhai's group came up with the first enantioselective total synthesis of (+)-Harringtonolide in 2016 with 20 steps. To introduce a tetracyclic structure, an intramolecular Diels-Alder

reaction and the intramolecular [3+2] cycloaddition catalyzed by rhodium complex was performed. Also, they reacted a silyl enol ether moiety with dimethyl aluminum chloride (Me_2AlCl) to form a tropone ring.[12]

Finally, Yuan's group synthesized the enantioselective 2,3-dihydroazulen-6(1H)-one with a one-pot reaction, which can be utilized as the tricyclic precursor for *Cephalotaxus* norditerpenes. They used an organocatalyzed Michael reaction to install various nitroalkanes to aldehydes followed by a selective oxidative dearomatization to generate tropone moieties. It was revealed that steric and electronic features of spirocyclic Michael acceptors affected the regioselectivity of products. They also prepared a tricyclic ring skeleton with Wittig reaction followed by a ring closing metathesis with Grubb's catalyst.[4]

Afterwards, it will be possible to synthesize Harringtonolide with the biosynthetic and enzymatic pathway. The diterpenoid precursor geranylgeranyl pyrophosphate (GGPP) can interact with various enzymes such as the unidentified cyclases, to create the tetracyclic structure of Harringtonolide. Especially, a tropone ring could be formed by the general shikimate pathway followed by phenylacetate catabolism.[8b,8c,8d]



Scheme 1. Syntheses of Harringtonolide and its precursor[4,10,11,12]

1.3. Radical anionic coupling by Kende

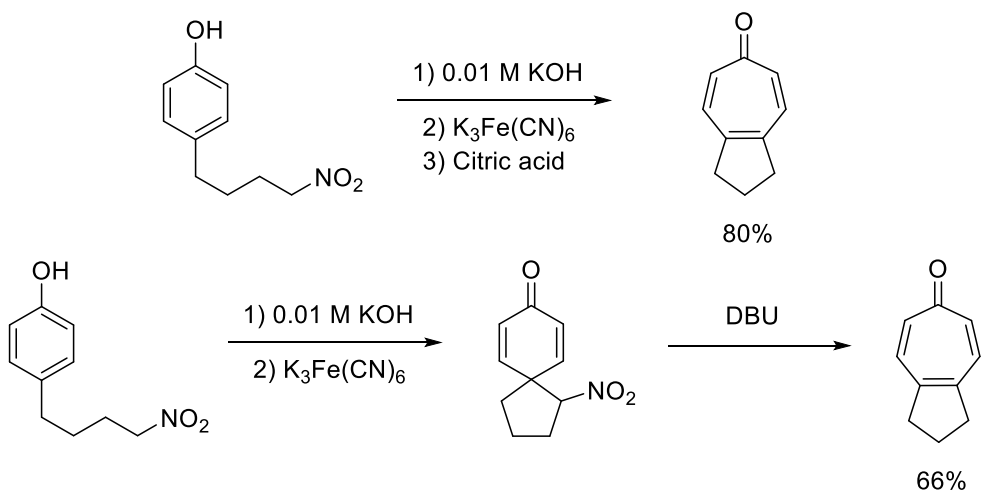
Oxidative radical anionic coupling, which is also called as Kende Tropone coupling, was first reported by A.S. Kende and K. Koch in 1986.[13] They utilized this reaction to generate tropone derivatives starting from the phenolic nitronate anion.

Based on the reaction mechanism, a phenolic nitroalkane reacts with a dilute basic solution to give a dianion in the first step. Then $K_3Fe(CN)_6$ acts as an oxidant in the intramolecular oxidative radical coupling with a phenolic nitronate at the para position of a phenol moiety. Theoretically, only 2 equivalents of base are needed for a deprotonation, but an excess amount of base with the following acid quenching should be used to promote the cyclization.

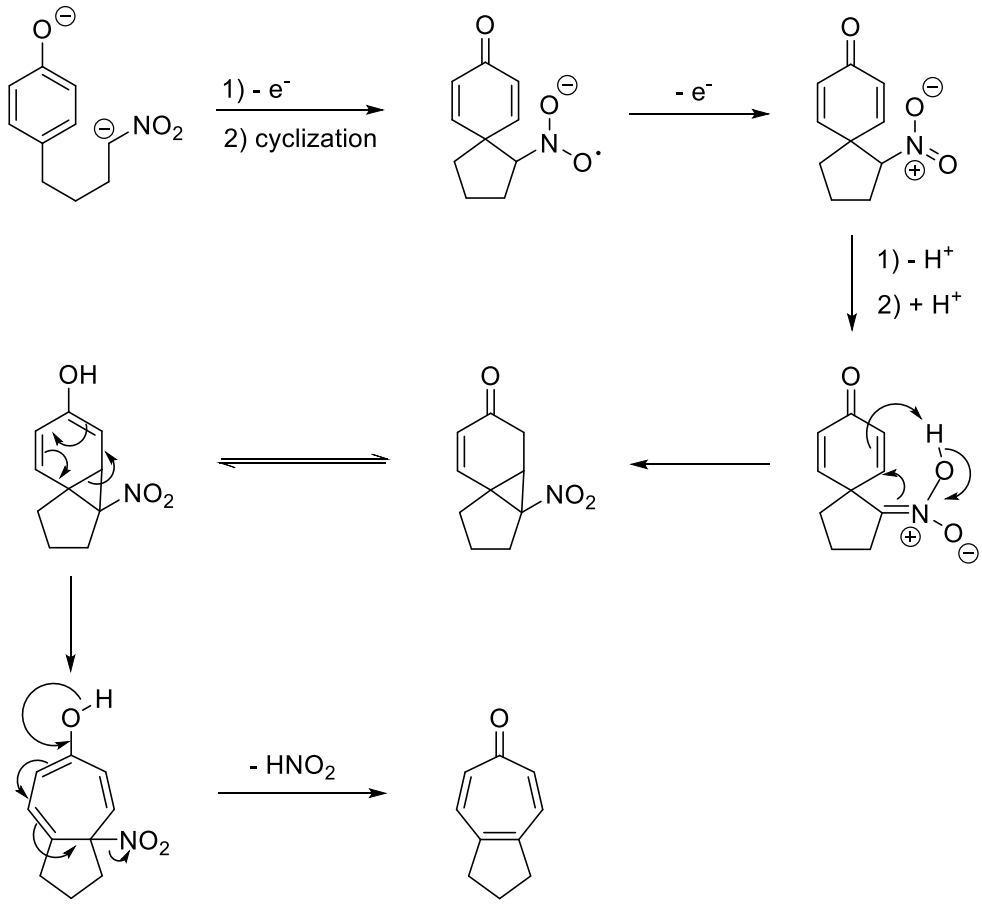
According to Kende's original paper, the reactant does not cyclize below pH 11, which means that a deprotonation of both phenol and nitroalkane are required. Also, if only 2 equivalents of base were used, the spirocyclic hexadienone could be isolated, which rearranged to a tropone ring by a treatment with DBU (Scheme 2). Kende also performed kinetic studies under the same base concentration by changing the amount of $K_3Fe(CN)_6$ from 2.5 to 9 equivalents. The result was that the rate of nitronate cyclization is proportional to a $K_3Fe(CN)_6$ concentration. This is consistent with the mechanism, because the one-electron transfer from a dianion to an oxidant is slower than a subsequent cyclization and a second electron transfer from a radical anion.

After the first oxidative radical coupling, the spirocyclic nitropentane appears as a nitronate anion when the excess amount of base is used. Under basic conditions, the proton is removed from

the alpha position of a nitro group. The resulting phenolic nitronate undergoes an intramolecular conjugate addition, forming a norcaradiene. The enol form of a norcaradiene rearranges to a cycloheptatrienone and a consecutive nitrous acid (HNO_2) elimination results in the annulated tropone ring. This final product of Kende coupling reaction, tropone, is a key structure of few *Cephalotaxus* Norditerpenes. As rearrangements occurred very slowly in basic condition, Kende acidified a nitronate into a nitronic acid by the ene-forming reaction. Desired by Kende's efficient coupling reaction, we planned to develop the total synthesis of the precursor for Harringtonolide and its analogs, by applying radical anionic coupling as a key concept (Scheme 3).



Scheme 2. Intramolecular oxidative radical coupling of the phenolic nitronates[13]



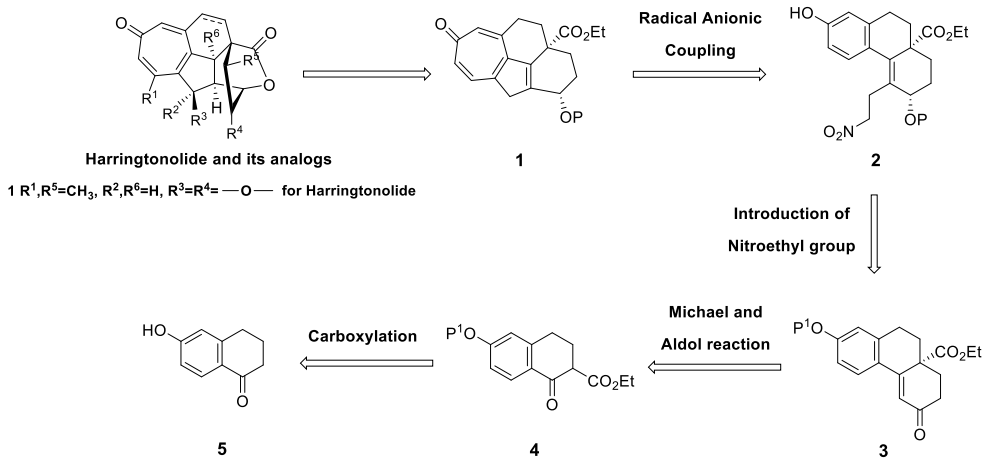
Scheme 3. Proposed mechanism of Kende tropone coupling[13]

2. Results and Discussion

2.1. Retrosynthetic analysis

As stated earlier, various methods for the total synthesis of Harringtonolide had highly long steps and low total yields. Also, useful research by Yuan's group was only suitable for synthesizing simple tricyclic structures of Harringtonolide.

In order to resolve these problems, our group tried to use Kende radical anionic coupling reaction as a key step for synthesizing the precursor for Harringtonolide and its analogs, which have a more complicated structure than the precursors synthesized by Yuan's group. To use Kende's coupling method, the phenolic nitronate (nitroethyl group) was required. We have designed a new and simple retrosynthetic method to prepare the phenolic nitronate precursor **2** by successive Bromination, Stille coupling and Nitration. Furthermore, the α, β-unsaturated cycloketone moiety **3** was prepared by Carboxylation and Robinson annulation of starting material, 6-hydroxytetralone which is commercially available (Scheme 4).

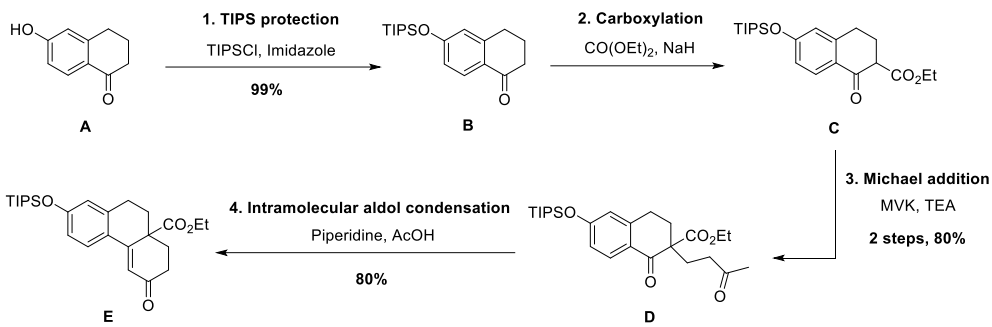


Scheme 4. Retrosynthetic analysis of the precursor for Harringtonolide

2.2. Synthetic route

Our attempts to develop the total synthesis of the precursor for Harringtonolide started from a commercially available 6-hydroxytetralone **A**. First of all, a phenol moiety of 6-hydroxytetralone was protected with TIPSCl in 99% yield. The corresponding tetralone **B** was reacted with NaH to generate enolate which went a nucleophilic addition reaction with diethyl carbonate. The crude mixture was directly subjected to Michael addition with methyl vinyl ketone (MVK) and triethylamine, because a keto-enol tautomerization of 1,3-diketone made it difficult to attain the pure NMR data of our desired product **C**. The total yield for consecutive Carboxylation and Michael addition was 80% and the purity was checked by NMR data of compound **D**. Then, aldol reaction for compound **D** was conducted to afford tricycloketone moiety **E**. In this step, acetic acid participated not only as an acid

catalyst for nucleophilic addition, but also as a reagent for cleaving Si–O bond. This resulted in 25% yield of product **E,** as a phenol and **E** coexisted in a reaction mixture. To increase the yield of product **E**, a reaction with protecting group TIPSCl was done again after a work–up process of aldol reaction. Purification by column chromatography afforded product **E** selectively with 80% yield (Scheme 5).

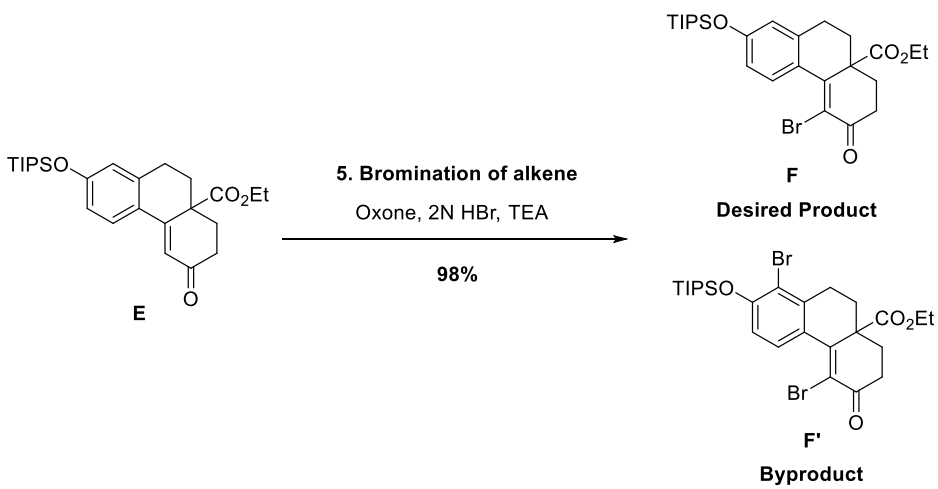


Scheme 5. Synthetic route for tricycloketone moiety **E**

After that, regioselective Bromination of tricycloketone **E** was conducted with 2N HBr aqueous solution, Oxone and TEA (Scheme 6).[14] The proposed mechanism of Bromination based on the reported paper was that Oxone produces a bromine radical and a radical cation at the reactive site which has double bonds. These two radicals combine with each other followed by a deprotonation of TEA to recover α, β–unsaturated cycloketone form.[15] This mechanism is more consistent with our undesired product formation than the electrophilic addition with Br_2 followed by HBr elimination with TEA. This is due to the fact that benzene rings resist the electrophilic addition to retain their stability.

As a high concentration of HBr and Oxone generated

undesired dibrominated product based on the mechanism, Bromination step was optimized by controlling the amount of 2N HBr solution, TEA and Oxone. In entry 1 to 4, the dibrominated product was also formed in the reaction, and the separation was difficult because R_f values in TLC were similar for both desired product and byproduct. As the amount of byproduct decreased from entry 1 to 4, we attempted to adjust the conditions in entry 4. In entry 5, a molarity of Oxone was decreased to 0.075 M, which led to the selective formation of the desired product. From this result, we could conclude that a molarity of Oxone was crucial for the selective formation of the mono-brominated product (Table 1).



Scheme 6. Synthetic route of Bromination

Table 1. Optimization conditions of Bromination

Entry	2N HBr	TEA	Oxone	Molarity of Oxone	Yield
1	10 eq	5 eq	1.2 eq	0.2 M	92%[a]
2	5 eq	3 eq	1.2 eq	0.2 M	98%[a]
3	2 eq	3 eq	1.2 eq	0.1 M	83%[a]
4	2 eq	3 eq	0.7 eq	0.1 M	99%[a]
5	2 eq	3 eq	0.7 eq	0.075 M	98%[b]

a. The yield was based on a purified mixture of **F** and **F'**.

b. The yield was based on a purified product **F**.

Then Brominated compound **F** was subjected to Stille coupling reaction to generate a vinyl compound **G** in 90% yield (Scheme 7). In this reaction, R_f value in TLC for a starting material and a product was almost same which made the purification by column chromatography unmanageable. In order to solve this problem, the optimization was conducted to fully convert a starting material into a product. The amount of a palladium catalyst and a reaction temperature were controlled through entry 1 to 4. In entry 2, it was discovered that increasing temperature up to 100 °C was more important than adding more palladium catalyst to the reaction mixture (Table 2).

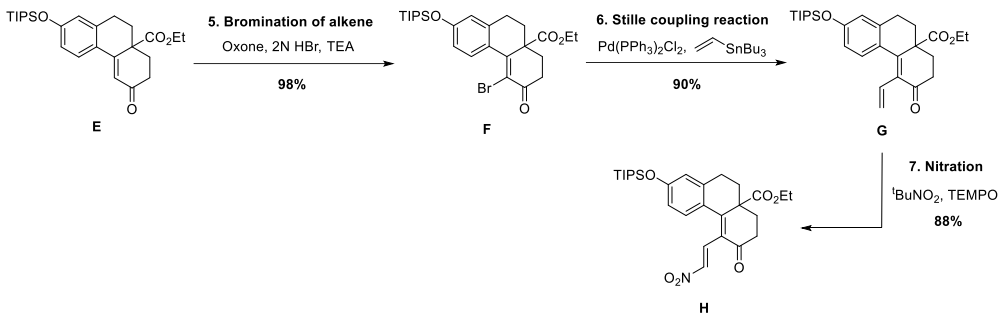
Table 2. Optimization conditions of Stille coupling

Entry	Pd catalyst	Temperature	F : G[a]
1	0.05 eq	90 °C	4.3 : 1
2	0.1 eq	Reflux[b]	0 : 1
3	0.2 eq	90 °C	1.7 : 1
4	0.5 eq	90 °C	0.1 : 1

a. The ratio of compound **F** and **G**
b. 100 °C

To introduce a nitro group, Nitration with two different nitrite reagents was conducted (Scheme 7). At the beginning, silver nitrite was used as a nitrating agent under Argon purging.[16] However, Celite filtration was crucial to remove silver before a column chromatography purification and the reaction yield was 62%, which was moderate but not satisfactory. Then tert-butyl nitrite was alternatively used as a nitrating agent.[17] The reaction with tert-butyl nitrite was more convenient than with silver nitrite, as the reaction was not sensitive to air or moisture and no work-up process is needed before a purification by column chromatography. It was observed that purging a reaction flask with O_2 balloon is important for our Nitration step. Although a nitro radical was generated even in aerobic condition, only 50% of the starting material **G** converted into nitrated product **H**. So, we promoted a radical generation by purging O_2 and obtained the product **H** with 88% yield in the same 4 h reaction. According to the coupling

constant values in NMR data, only trans-nitroalkene was selectively formed. It is believed that our bulky tricyclic system triggered a nitro group to reside at the less hindered position (trans) of a vinyl group (Table 3).[16]



Scheme 7. Synthetic route for introducing a nitroethyl group

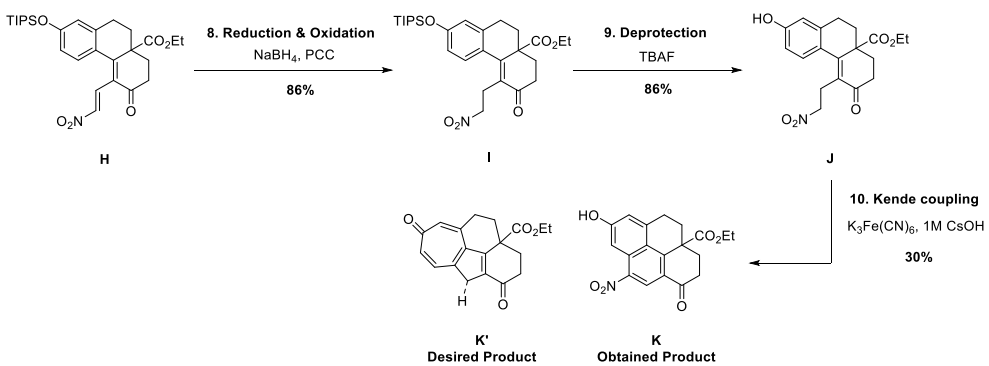
Table 3. Optimization conditions of Nitration

Entry	Reagent	Temperature	Reaction condition	Yield
1	$AgNO_2$	60 °C	Ar purging	62%
2	$^tBuNO_2$	90 °C	Aerobic	80%[a]
3	$^tBuNO_2$	90 °C	O_2 purging	88%

a. The yield for a mixture of product **H** and starting material **G** (1:1 ratio)

After that, we tried to produce a reduced nitroethyl group which is one of the reaction centers used in Kende tropone coupling. The reduction of nitroalkene was conducted with $NaBH_4$ and both nitroalkene and ketone were reduced. So, oxidation using PCC was performed in order to oxidize a resulting alcohol, which afforded

compound **I** with 86% yield for 2 step-reactions. Then a deprotection of a TIPS protecting group was conducted in 1 M TBAF solution with 86% yield. To prevent a degradation of the product, a reaction temperature was decreased to 0 °C. Finally, Kende coupling reaction was performed using 1M CsOH as a base and $K_3Fe(CN)_6$ as an oxidant.[13] Recrystallization with chloroform after a column chromatography was done to remove the undefined byproducts. We also tested Kende coupling reaction with other reagents, KOH as a base or $Fe(acac)_3$ as an oxidant, but only starting material recovered in these cases.[18] After NMR and GC-MS analysis, we found out that the product of Kende coupling reaction was different from what we had expected. According to NMR spectra, compound **K** with phenol and nitrobenzene ring was formed with 30% yield instead of the desired product **K'**. It was confirmed that protons in a benzene ring have weak couplings with each other, which was well represented in our NMR data of compound **K** (Scheme 8).

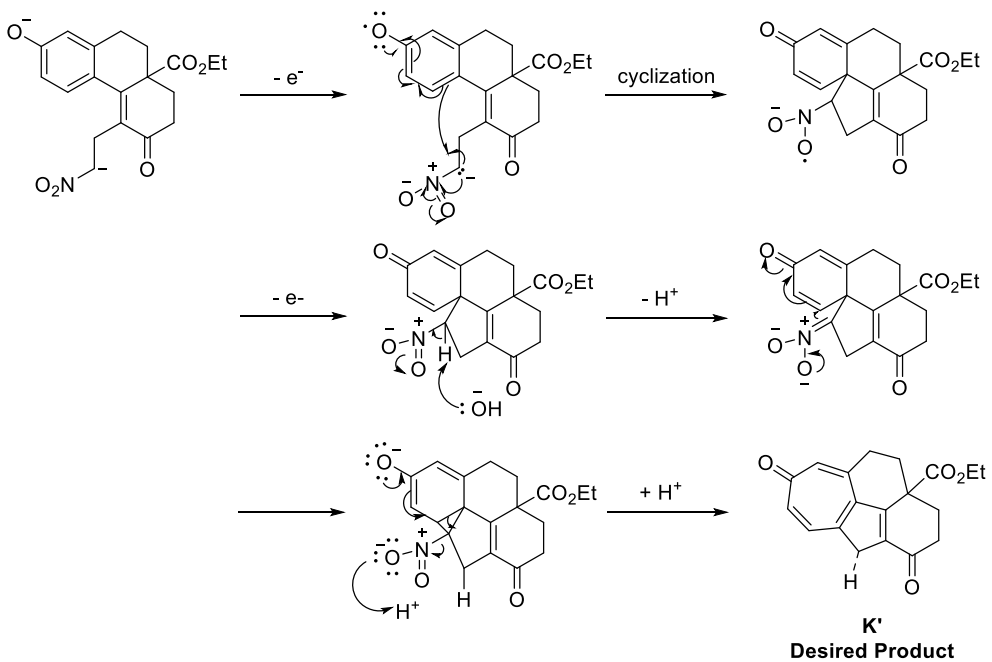


Scheme 8. Synthetic route for the resulting final product **K**

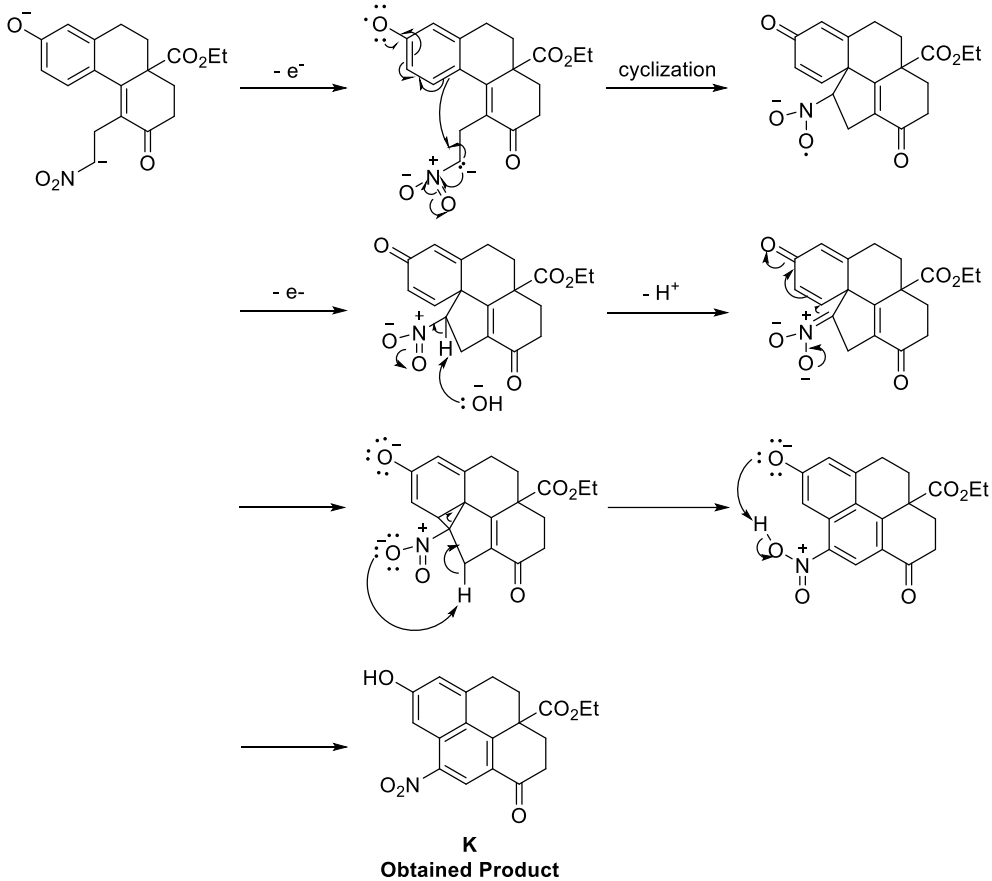
2.3. Mechanism and molecular model studies

To interpret the reason for 6-membered ring formation in Kende coupling reaction, the mechanism and molecular model studies were conducted.

Firstly, we proposed a new mechanism for the 6-membered ring formation. Theoretically, the rearrangement of a cyclic hexadienone and a nitrous acid elimination should be performed in order to produce a tropone ring, after the consecutive electron transfer reactions, cyclization and intramolecular conjugate addition (Scheme 9).[13] However, in our proposed mechanism, only proton transfer occurs after the intramolecular conjugate addition. This mechanism corresponds to a phenol and a nitrobenzene ring formation with a stable, conjugated tetracyclic structure (Scheme 10).



Scheme 9. Required mechanism for the synthesis of the desired product K'



Scheme 10. Proposed mechanism for the synthesis of the obtained product K

Secondly, we designed molecular models for three phenolic nitronates to explain this phenomenon intuitionally (Figure 2). It was valid that a rigid double bond of unsaturated phenolic nitronate prohibited cyclopentene ring formation. Instead, the cyclization to produce benzene rings with a favorable bond angle was prevalent. This rigidity of compound K could correspond to its higher melting point than other products' cases in our synthetic methods. We also discovered that a saturated phenolic nitronate with cis selectivity of

the internal hydrogen and the ester group has an appropriate configuration for cyclization, compared to the trans isomer having a sterically hindered configuration. To conclude, in order to synthesize a tropone-based precursor for Harringtonolide by Kende coupling, it is essential to saturate the internal alkene located at γ and δ position of a nitro group and provide a cis selectivity for the internal hydrogen and the ester. Our developments on the enantioselective total synthesis of Harringtonolide will continue based on the results of these two studies.

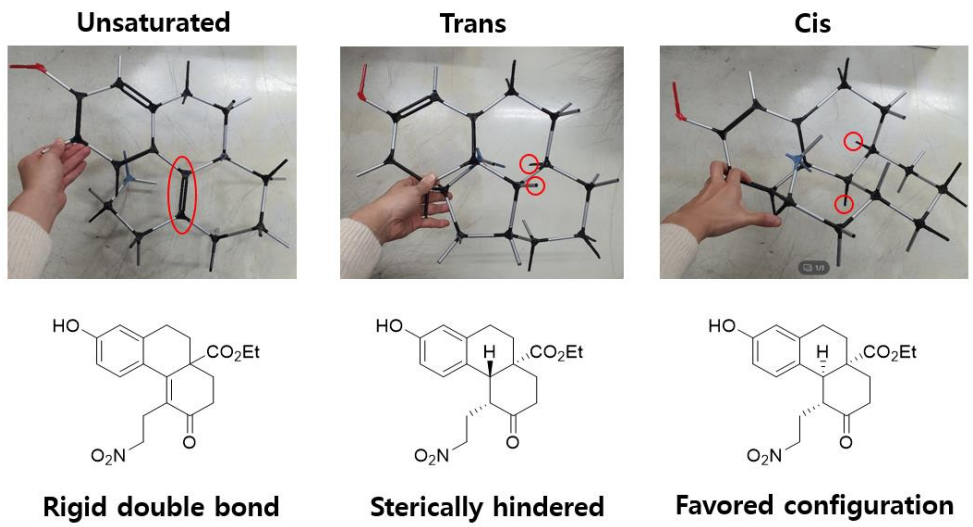


Figure 2. Molecular model studies of phenolic nitronates

3. Conclusion

In this study, new ways for synthesizing the precursor of Harringtonolide were suggested. The synthetic method contained 10 steps with a key reaction of radical anionic coupling.

Our total scheme started with a commercially available 6-hydroxytetralone. The starting material was converted to α, β-unsaturated cycloketone moiety **E** by sequential TIPS protection, Carboxylation and Robinson annulation. In addition, consecutive Bromination, Stille coupling, Nitration was conducted. At these steps, Bromination and Stille coupling reactions were successfully optimized by controlling the amount of reagents, molarities and reaction temperatures. Also, Nitration step became more convenient and fruitful by changing the nitrating agent which had a different reaction mechanism with the previous one. Also, a nitroethyl group was formed by sequential reduction and oxidation steps, followed by a deprotection of TIPS protecting group.

Finally, Kende coupling reaction was conducted to generate a tropone ring, but NMR and GC-MS analysis revealed that the unexpected phenol and nitrobenzene rings were formed. With mechanism and molecular model studies, we could assume that a rigid structure of α, β-unsaturated phenolic nitronate triggered cyclization with a favorable bond angle. Although the undesired tetracyclic structure was formed at the final Kende coupling step, we think that these results can provide a new synthetic perspective for developing feasible precursors for the total synthesis of Harringtonolide and its analogs.

4. Experimental Details

4.1. General information

Materials were obtained from commercial suppliers and were used without further purifications. Air or moisture sensitive reactions were conducted under argon or nitrogen atmosphere using oven-dried glassware and standard syringe/septa techniques. All reaction solvents were dehydrated and purified prior to use. THF were distilled by sodium benzophenone ketyl. MeOH was distilled from potassium carbonate. The reactions were monitored by the analytical thin layer chromatography (TLC) using Merck 60, F254 glass plates precoated with a 0.25 nm thickness of silica gel under UV light (254 nm, 365 nm) followed by visualization with a p-anisaldehyde staining solution. Column chromatography was performed on a silica gel 60 (70-230 mesh) obtained from Sigma Aldrich. IR spectra were obtained on a commercially available ATR-FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were measured at 400 MHz and 100 MHz, respectively in $CDCl_3$ unless stated otherwise and the data were reported as follows in ppm(δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, coupling constant in Hz, integration). High resolution mass spectra were measured by the EI ionization method. Melting points were determined with an open capillary melting point apparatus and are uncorrected.

4.2. General synthetic methods

6-((triisopropylsilyl)oxy)-3,4-dihydronaphthalen-1(2H)-one (B)

To a solution of 6-hydroxytetralone **A** (10 g, 61.66 mmol) in DMF (100 mL) was added imidazole (10.49 g, 154.15 mmol) and TIPSCl (14.26 g, 73.99 mmol) at room temperature. Reaction mixture was stirred for 18 h under argon atmosphere and then quenched with a deionized water (70 mL). Organic layer was separated by extraction with diethyl ether (3 x 50 mL), dried over $MgSO_4$ and concentrated with a rotary evaporator. Purification by column chromatography (16:1 Hexane-EtOAc) afforded **B** (18.14 g, 56.95 mmol, 99%) as an orange liquid: IR 2943, 2891, 2865, 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (d, J=8.4, 1H) 6.77 (dd, J_1=8.4, J_2=2.4, 1H) 6.69 (d, J=2.4, 1H) 2.87 (t, J=6.2, 2H) 2.60 (t, J=6.4, 2H) 2.11 (quint, J=6.3, 2H) 1.28 (m, 3H) 1.10 (d, J=7.2, 18H); ^{13}C NMR ($CDCl_3$) δ 196.93, 160.48, 146.63, 129.35, 126.31, 118.69, 118.29, 38.68, 29.72, 23.18, 17.65, 12.48; HRMS (M^+) calcd for $C_{19}H_{30}O_2Si$ 318.2015, found 318.2019

Ethyl 1-oxo-6-((triisopropylsilyl)oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (C),
Ethyl 1-oxo-2-(3-oxobutyl)-6-((triisopropylsilyl)oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (D)

NaH (3.14 g, 130.9 mmol) and diethyl carbonate (14.73 g, 125 mmol) was added slowly to a solution of **B** in toluene (100 mL) at 0 °C. The temperature was increased slowly up to 120 °C and the reaction mixture was stirred for 3 h under argon atmosphere, quenched with MeOH and saturated aqueous NaCl solution (100

mL) consecutively. Separation of organic layer was conducted by extraction with diethyl ether (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Without further purification, to a solution of the crude product **C** in MeOH (100 mL) was added methyl vinyl ketone (7.59 g, 108.29 mmol) and triethylamine (2.74 g, 27.07 mmol). The reaction mixture was stirred for 12 h and then quenched by saturated aqueous NaCl solution (100 mL). The resulting mixture was extracted with diethyl ether (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (4:1 Hexane–EtOAc) afforded **D** (18.95 g, 41.13 mmol, 80%) as a brown liquid: IR 2944, 2867 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.94 (d, J=8.8, 1H) 6.79 (dd, J_1=8.8, J_2=2.4, 1H) 6.65 (d, J=2.4, 1H) 4.16 (m, 2H) 2.93 (m, 2H) 2.71 (m, 1H) 2.54 (m, 2H) 2.21 (m, 1H) 2.15 (s, 3H) 2.08 (m, 2H) 1.28 (m, 3H) 1.18 (t, J=7.0, 3H) 1.10 (d, J=7.2, 18H); ^{13}C NMR ($CDCl_3$) δ 207.87, 194.15, 171.96, 160.81, 145.09, 130.26, 125.53, 118.76, 118.62, 61.17, 56.22, 39.08, 31.48, 29.82, 27.39, 25.82, 17.74, 13.92, 12.55; HRMS (M+) calcd for $C_{26}H_{40}O_5Si$ 460.2645, found 460.2650

Ethyl 6–oxo–2–((triisopropylsilyl)oxy)–7,8,9,10–tetrahydrophenanthrene–8a(6*H*)–carboxylate (E)

To a solution of **D** (16.31 g, 35.40 mmol) in toluene (100 mL) was added piperidine (3.50 g, 35.40 mmol) and acetic acid (2.47 g, 35.40 mmol) at room temperature. The reaction mixture was stirred for 12 h at 120 °C under argon atmosphere and quenched by saturated aqueous NaCl solution (100 mL). The resulting mixture was extracted with diethyl ether (2 x 50 mL) and ethyl acetate (2 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Without further purification, to a solution of crude mixture was added

imidazole (3.14 g, 46.06 mmol) and TIPSCl (4.26 g, 22.11 mmol) in DMF (70 mL). The reaction mixture was stirred for 3 h at room temperature and then quenched by saturated aqueous NaCl solution (100 mL). The resulting mixture was extracted with diethyl ether (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (4:1 Hexane−EtOAc) afforded **E** (13.62 g, 30.77 mmol, 80%) as a light brown solid: mp 60 °C; IR 2944, 2866, 1718, 1665, 1607, 1587 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (d, J=8.8, 1H) 6.75 (dd, J_1=8.6, J_2=2.6, 1H) 6.63 (d, J=2.4, 1H) 6.57 (s, 1H) 4.12 (m, 2H) 2.82 (m, 2H) 2.49 (m, 2H) 2.43 (m, 2H) 2.05 (m, 1H) 1.83 (m, 1H) 1.26 (m, 6H) 1.10 (d, J=7.2, 18H); ^{13}C NMR ($CDCl_3$) δ 198.99, 173.05, 158.25, 155.01, 140.08, 127.26, 124.41, 120.21, 119.77, 118.75, 61.33, 47.61, 34.69, 34.53, 34.34, 26.99, 17.77, 13.97, 12.56; HRMS (M+) calcd for $C_{26}H_{38}O_4Si$ 442.2539, found 442.2543

Ethyl 5−bromo−6−oxo−2−((triisopropylsilyl)oxy)−7,8,9,10−tetrahydrophenanthrene−8a(6*H*)−carboxylate (F)

To a solution of **E** (0.50 g, 1.13 mmol) in methylene chloride (25 mL) was added Oxone (0.49 g, 0.79 mmol), 2N HBr (1.13 mL) and deionized water (25 mL) at room temperature. The reaction mixture was stirred vigorously for 2 h under argon atmosphere and triethylamine (0.47 mL, 3.39 mmol) was added dropwise. The resulting mixture was stirred for 2 h, quenched by saturated aqueous NaCl solution, extracted with methylene chloride (3 x 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (8:1 Hexane−EtOAc) afforded **F** (0.58 g, 1.11 mmol, 98%) as a light yellow solid: mp 95 °C; IR 2945, 2867, 1726, 1686, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (d, J=8.8, 1H)

6.75 (dd, J_1=8.4, J_2=2.4, 1H) 6.64 (d, J=2.0, 1H) 4.01 (m, 2H) 2.83 (m, 2H) 2.71 (m, 2H) 2.38 (m, 2H) 2.02 (m, 2H) 1.31 (m, 3H) 1.10 (d, J=7.2, 18H) 0.99 (t, J= 7.0, 3H); ^{13}C NMR ($CDCl_3$) δ 191.07, 172.63, 158.09, 154.94, 141.00, 132.26, 126.59, 120.41, 118.77, 117.17, 61.43, 51.41, 34.85, 34.56, 31.94, 26.67, 17.84, 13.85, 12.63; HRMS (M+) calcd for $C_{26}H_{37}BrO_4Si$ 520.1644, found 520.1648

Ethyl 6-oxo-2-((triisopropylsilyl)oxy)-5-vinyl-7,8,9,10-tetrahydrophenanthrene-8a(6*H*)-carboxylate (G)

To a solution of **F** (4.0 g, 7.67 mmol) in 1,4-dioxane (30 mL) was added vinyl tributyltin (3.65 g, 11.50 mmol) dropwise and bis(triphenylphosphine)palladium(Ⅱ) dichloride (0.54 g, 0.77 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 2 h at 100 °C, quenched by saturated aqueous NaCl solution, extracted with methylene chloride (3 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (8:1 Hexane-EtOAc) afforded **G** (3.22 g, 6.87 mmol, 90%) as a yellow solid: mp 53 °C; IR 2950, 2867, 1728, 1678, 1598, 1562 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.48 (d, J=8.4, 1H) 6.67 (dd, J_1=8.4, J_2=2.4, 1H) 6.62 (d, J=2.4, 1H) 6.43 (dd, J_1=17.6, J_2=11.6, 1H) 5.94 (dd, J_1=11.6, J_2=2.4, 1H) 5.40 (dd, J_1=11.6, J_2=2.4, 1H) 4.01 (m, 2H) 2.93 (m, 1H) 2.81 (m, 1H) 2.64 (m, 1H) 2.47 (m, 1H) 2.44 (m, 1H) 2.36 (m, 1H) 1.98 (m, 1H) 1.89 (m, 1H) 1.25 (m, 3H) 1.09 (d, J=7.2, 18H) 0.96 (t, J= 7.0, 3H); ^{13}C NMR ($CDCl_3$) δ 198.03, 173.49, 157.50, 153.21, 140.54, 133.84, 131.80, 129.20, 126.80, 120.70, 119.20, 117.11, 61.05, 49.11, 35.33, 35.26, 32.15, 26.55, 17.82, 13.87, 12.59; HRMS (M+) calcd for $C_{28}H_{40}O_4Si$ 468.2696, found 468.2696

Ethyl (E)-5-(2-nitrovinyl)-6-oxo-2-((triisopropylsilyl)oxy)-7,8,9,10-tetrahydrophenanthrene-8a(6*H*)-carboxylate (H)

Nitration step was performed with two different nitrating agents, tert-butyl nitrite and silver nitrite.

$^{t}BuNO_2$: To a solution of **G** (3.5 g, 7.47 mmol) in 1,4-dioxane (30 mL) was added tert-butyl nitrite (1.78 mL, 14.94 mmol) and TEMPO (0.47 g, 2.99 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 4 h at 100 °C with O_2 balloon attached. The reaction mixture was concentrated with a rotary evaporator and purification by column chromatography (4:1 Hexane-EtOAc) afforded **H** (3.37 g, 6.56 mmol, 88%) as a yellow liquid.

$AgNO_2$: To a solution of **G** (4.82 g, 10.28 mmol) in 1,2-dichloroethane (40 mL) was added silver nitrite (4.75 g, 30.84 mmol) and TEMPO (0.64 g, 4.11 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 3 h at 70 °C and was filtered through a Celite bed filter with ethyl acetate as a washing solvent. Organic extract was concentrated with a rotary evaporator and purification by column chromatography (4:1 Hexane-EtOAc) afforded **H** (3.30 g, 6.42 mmol, 62%) as a yellow liquid: IR 2945, 2867, 1728, 1678, 1598, 1558 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.36 (d, J=13.2, 1H) 7.71 (d, J=13.2, 1H) 7.16 (d, J=8.8, 1H) 6.78 (d, J_1=9.2, J_2=2.6, 1H) 6.71 (d, J=2.4, 1H) 4.04 (m, 2H) 2.96 (m, 2H) 2.65 (m, 2H), 2,56 (m, 1H) 2.41 (m, 1H) 1.99 (m, 2H) 1.27 (m, 3H) 1.11 (d, J=7.2, 18H) 0.97 (t, J=7.0, 3H); ^{13}C NMR ($CDCl_3$) δ 195.37, 171.79, 164.20, 159.52, 141.67, 140.33, 134.20, 132.88, 125.56, 122.88, 119.63, 117.64, 61.02, 49.63, 34.71, 34.26, 31.16, 25.97, 17.35, 13.41, 12.17; HRMS (M+) calcd for $C_{28}H_{39}NO_6Si$ 513.2547 found 513.2556

Ethyl 5-(2-nitroethyl)-6-oxo-2-((triisopropylsilyl)oxy)-7,8,9,10-tetrahydrophenanthrene-8a(6*H*)-carboxylate (I)

To a solution of H (3.37 g, 6.56 mmol) in MeOH (15 mL) and methylene chloride (20 mL) was added sodium borohydride (0.50 g, 13.12 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 2 h, quenched with methanol and saturated $NaHCO_3$ aqueous solution (30 mL). The separation of organic layer was conducted by extraction with ethyl acetate (3 x 50 mL) and aqueous 1 N HCl solution (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Without further purification, to a solution of the crude product in methylene chloride (50 mL) was added PCC (2.83 g, 13.12 mmol). The reaction mixture was stirred at room temperature for 2 h and quenched by saturated aqueous NaCl solution (50 mL). The resulting mixture was extracted with ethyl acetate (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (4:1 Hexane-EtOAc) afforded I (2.90 g, 5.62 mmol, 86%) as a yellow solid: mp 83 °C; IR 2952, 2866, 1718, 1666, 1607, 1589, 1551 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (d, J=8.4, 1H) 6.74 (dd, J_1=8.4, J_2=2.4, 1H) 6.68 (d, J=2.4, 1H) 4.58 (m, 1H) 4.45 (m, 1H) 4.00 (m, 2H) 3.38 (m, 1H) 3.17 (m, 1H) 2.80 (m, 1H) 2.70 (m, 1H) 2.58 (m, 2H) 2.38 (m, 1H) 2.27 (m, 1H) 2.02 (m, 1H) 1.91 (m, 1H) 1.26 (m, 3H) 1.10 (d, J=7.2, 18H) 1.01 (t, J=7.0, 3H); ^{13}C NMR ($CDCl_3$) δ 198.26, 173.32, 157.63, 156.40, 141.61, 130.33, 128.26, 126.64, 119.16, 117.66, 74.36, 61.12, 49.41, 35.32, 34.41, 31.93, 26.67, 26.03, 17.77, 13.83, 12.54; HRMS (M+) calcd for $C_{28}H_{41}NO_6Si$ 515.2703 found 515.2702

Ethyl 2-hydroxy-5-(2-nitroethyl)-6-oxo-7,8,9,10-tetrahydrophenanthrene-8a(6*H*)-carboxylate (J)

To a solution of **I** (2.9 g, 5.62 mmol) in distilled THF (20 mL) was added 1M TBAF solution in THF (6.18 mL) dropwise at 0 °C under argon atmosphere for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (20 mL) and extracted with ethyl acetate (3 x 20 mL) and aqueous 1N HCl solution (3 mL). The organic extract was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (2:1 Hexane-EtOAc) afforded **J** (1.74 g, 4.84 mmol, 86%) as a light yellow solid: mp 135 °C; IR 3346, 2957, 1714, 1636, 1595, 1552 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (d, J=8.4, 1H) 6.68 (dd, J_1=8.4, J_2=2.8, 1H) 6.63 (d, J=2.4, 1H) 6.38 (s, 1H), 4.62 (m, 1H) 4.47 (m, 1H) 4.04 (m, 2H) 3.39 (m, 1H) 3.17 (m, 1H) 2.80 (m, 1H) 2.70 (m, 1H) 2.54 (m, 2H) 2.39 (m, 1H) 2.29 (m, 1H) 2.04 (m, 1H) 1.93 (m, 1H) 1.07 (t, J=7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 198.81, 173.66, 157.60, 156.83, 142.03, 130.76, 128.33, 125.98, 114.67, 113.44, 74.48, 61.46, 49.60, 35.29, 34.40, 31.91, 26.72, 26.12, 13.93; HRMS (M+) calcd for $C_{19}H_{21}NO_6$ 359.1369 found 359.1364

Ethyl 7-hydroxy-9-nitro-1-oxo-2,3,4,5-tetrahydropyrene-3a(1*H*)-carboxylate (K)

A solution of **J** (0.03 g, 0.084 mmol) in chloroform (3 mL) was dissolved in 1.0 M aqueous CsOH (0.67 mL, 0.67 mmol) at 0 °C. $K_3Fe(CN)_6$ (0.11 g, 0.33 mmol) in H_2O (3 mL) was added to the dianion solution and the reaction mixture was stirred for 1 h, diluted with i-PrOH (5 mL), and filtered through a pad of Celite. The filter cake was washed with i-PrOH (3 x 3 mL) and acetone (3 x 3 mL) sequentially. The combined filtrates were concentrated *in vacuo*.

Purification by column chromatography (1:1 Hexane−EtOAc) followed by the recrystallization with chloroform (5 mL) afforded **K** (8.90 mg, 0.025 mmol, 30%) as a yellow solid: mp 265 °C; IR 3675, 2988, 1701 cm^{-1}; ^{1}H NMR (Acetone−d_6) δ 8.63 (s, 1H) 7.76 (d, J=1.6, 1H) 7.23 (s, 1H) 4.17 (m, 2H) 3.79 (s, 1H) 3.21 (m, 1H) 3.12 (m, 1H) 2.76 (m, 1H) 2.71 (m, 2H), 2.61 (m, 2H) 2.39 (m, 1H) 1.14 (t, J=7.2, 3H); ^{13}C NMR (Acetone−d_6) δ 195.45, 173.80, 161.21, 148.25, 146.36, 141.78, 130.37, 126.10, 125.90, 122.10, 120.19, 105.01, 62.65, 49.60, 35.88, 35.22, 34.42, 28.71, 14.55; HRMS (M+) calcd for $C_{19}H_{17}NO_6$ 355.1056 found 355.1051

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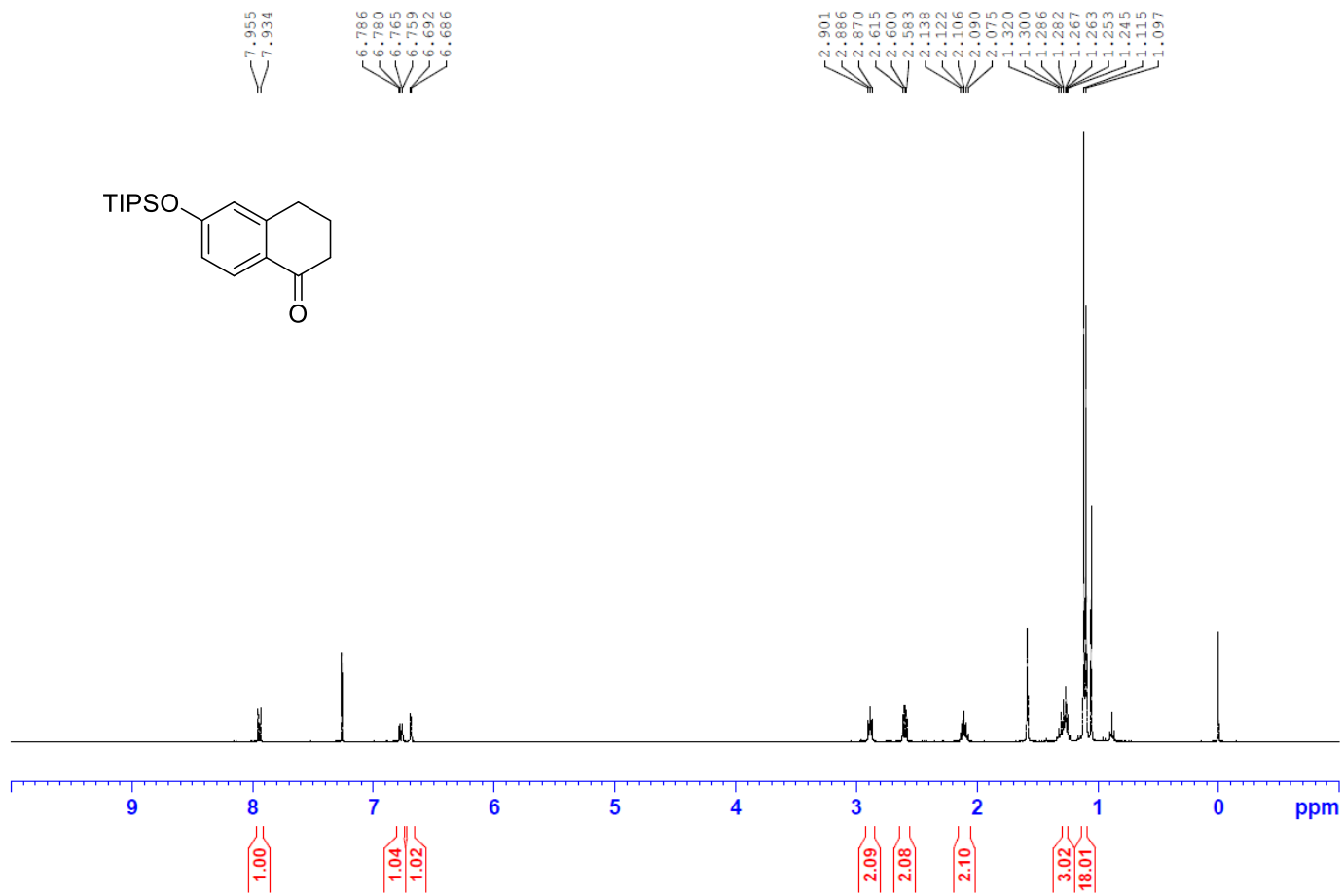
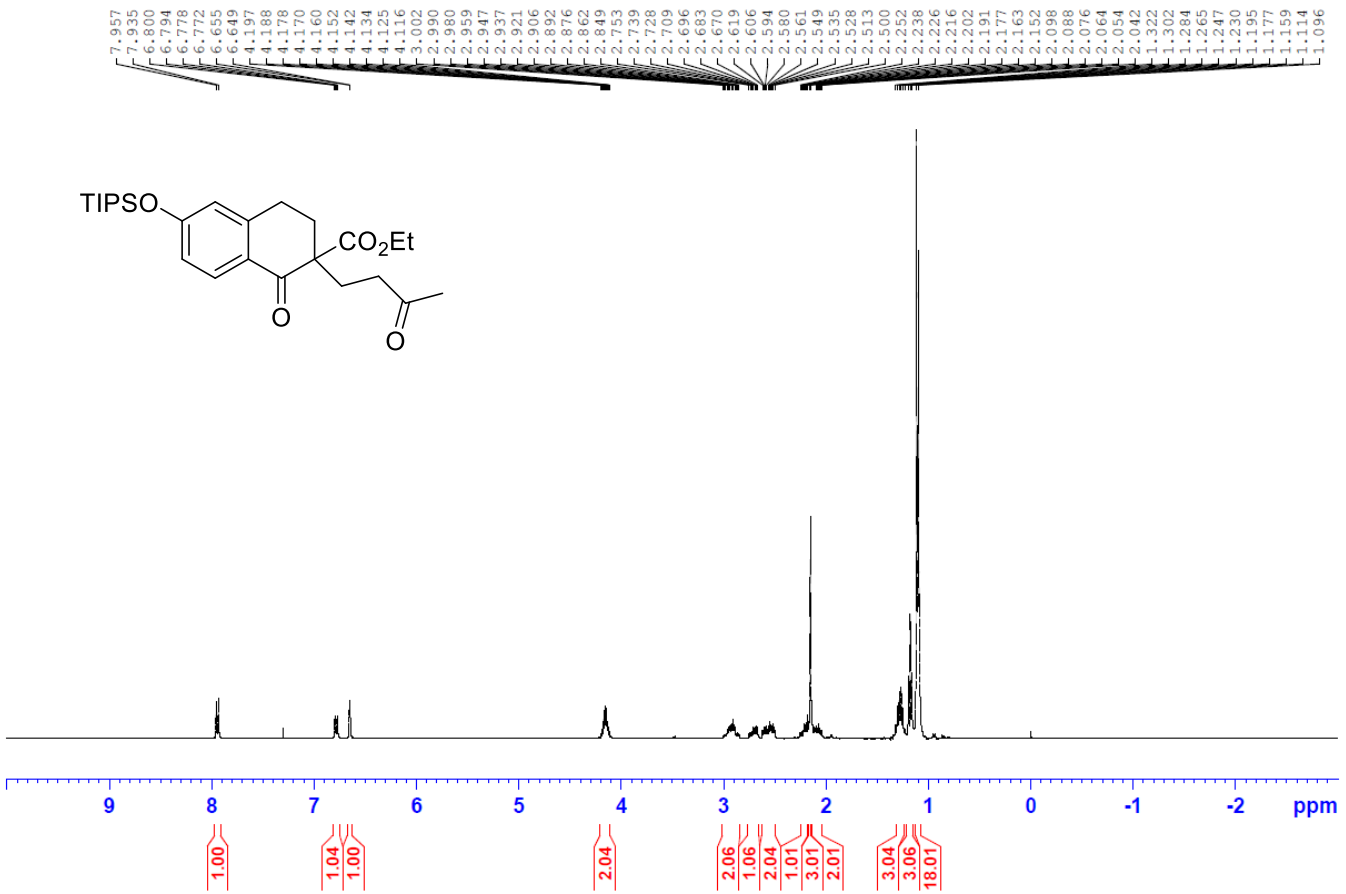
Appendices

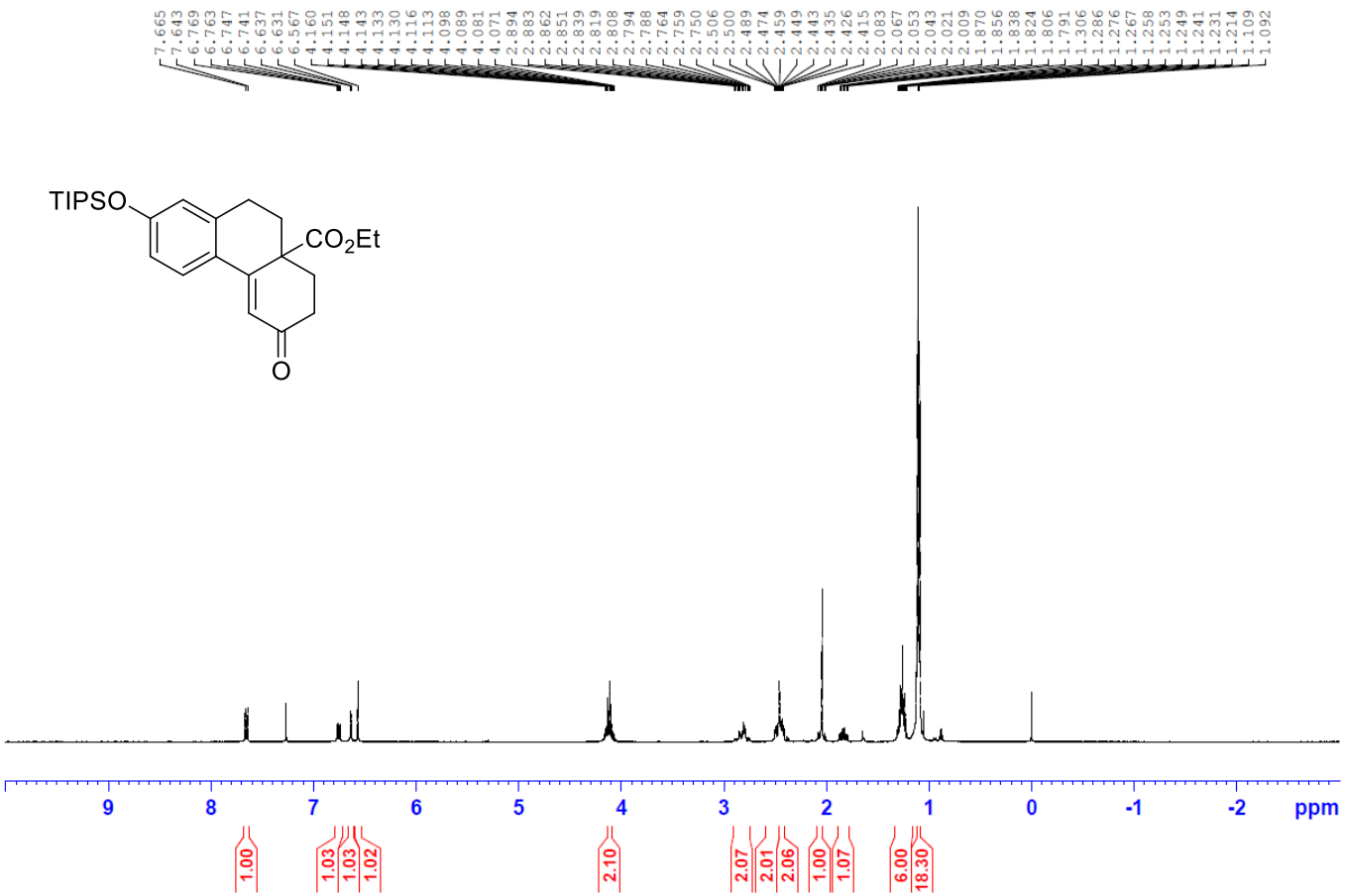
List of ^{1}H NMR Spectra of Selected compounds



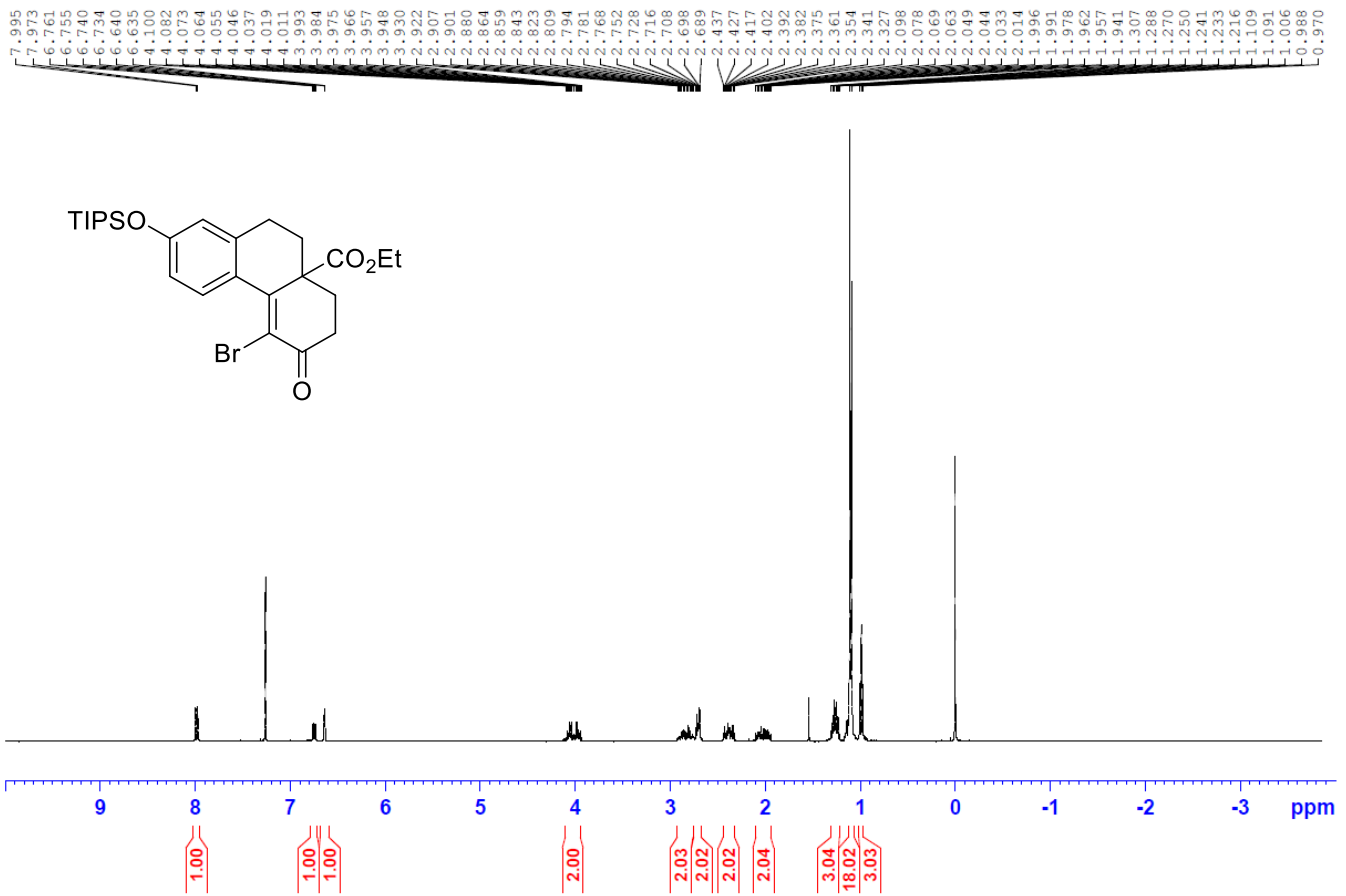
1. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **B**



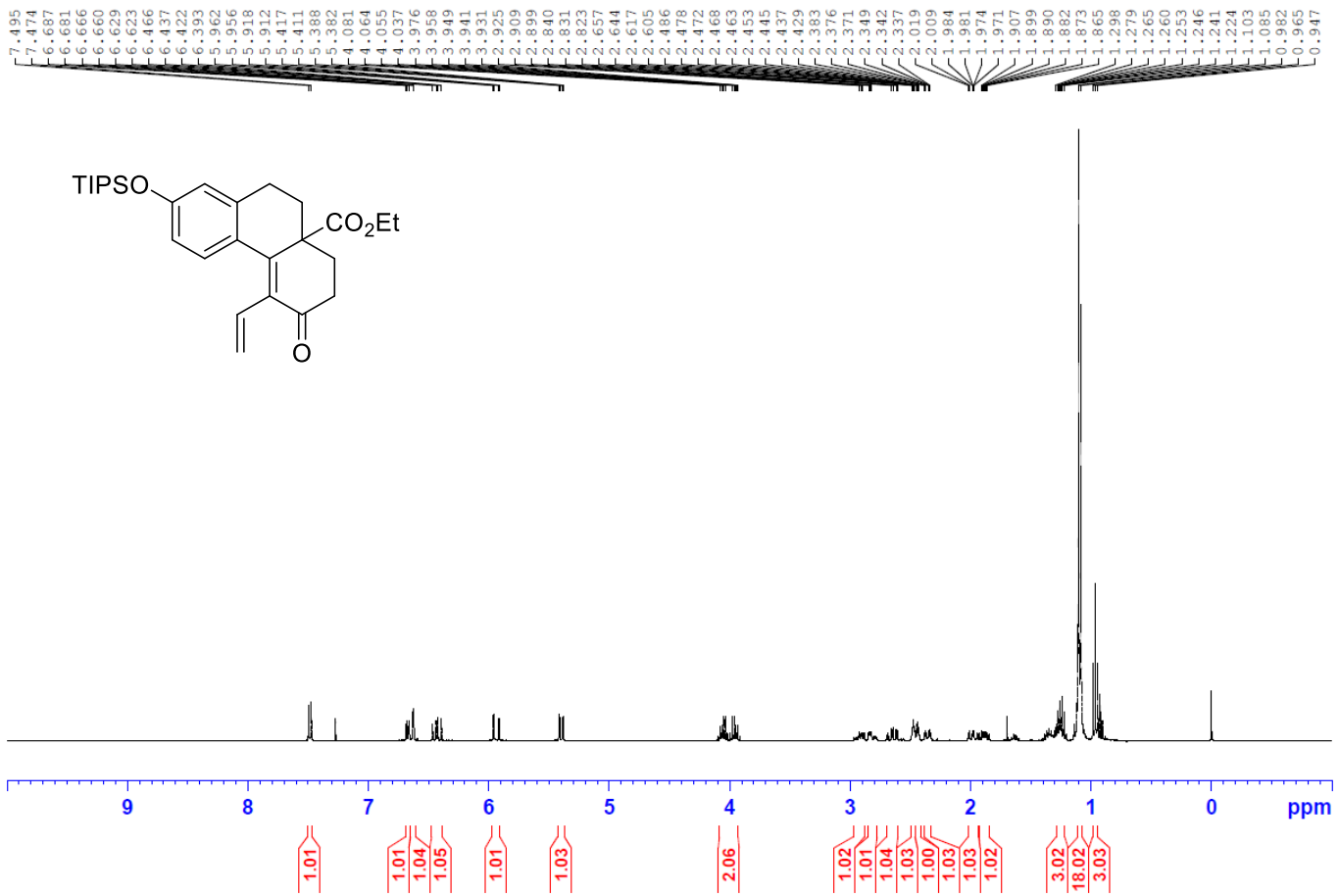
2. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound D



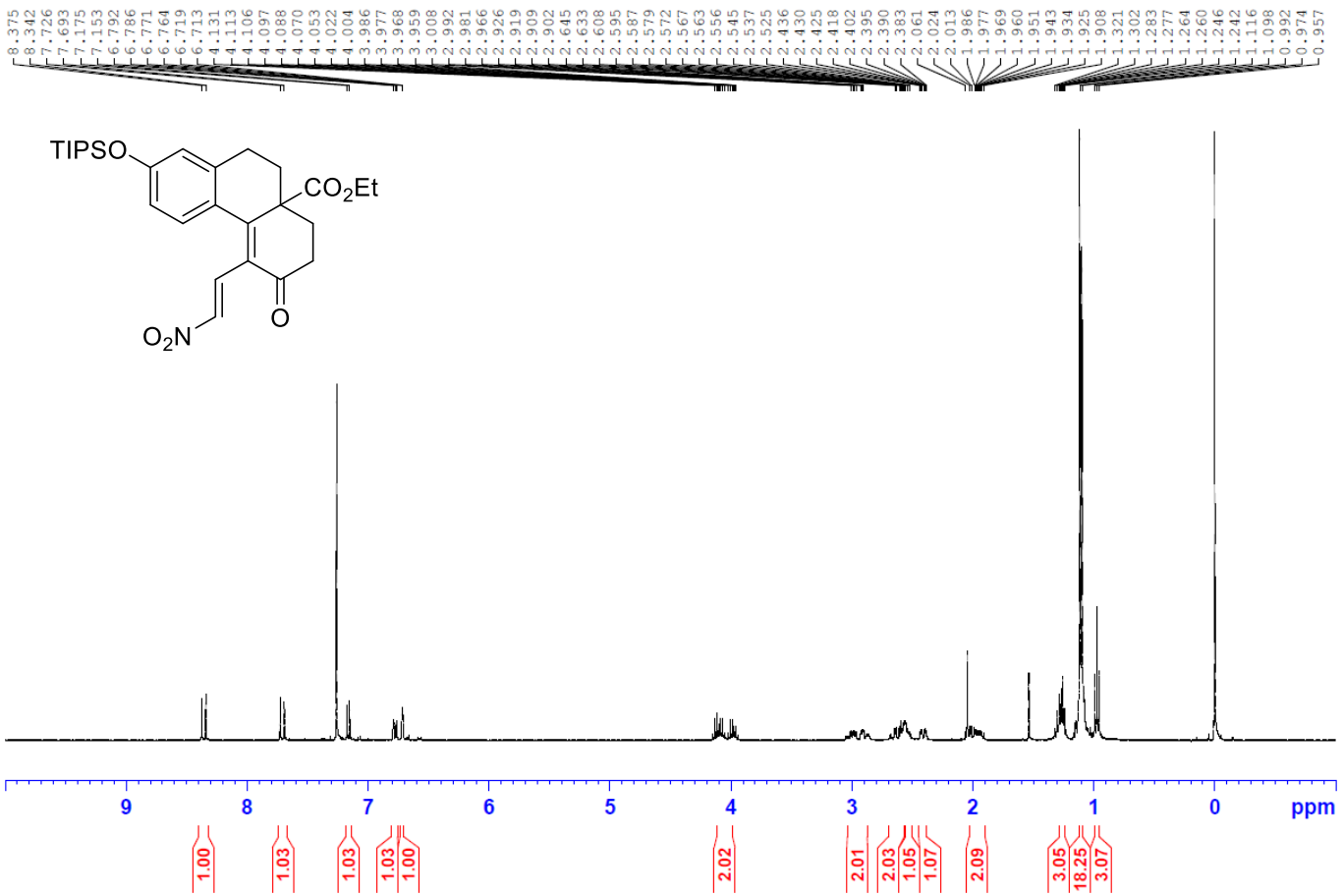
3. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **E**



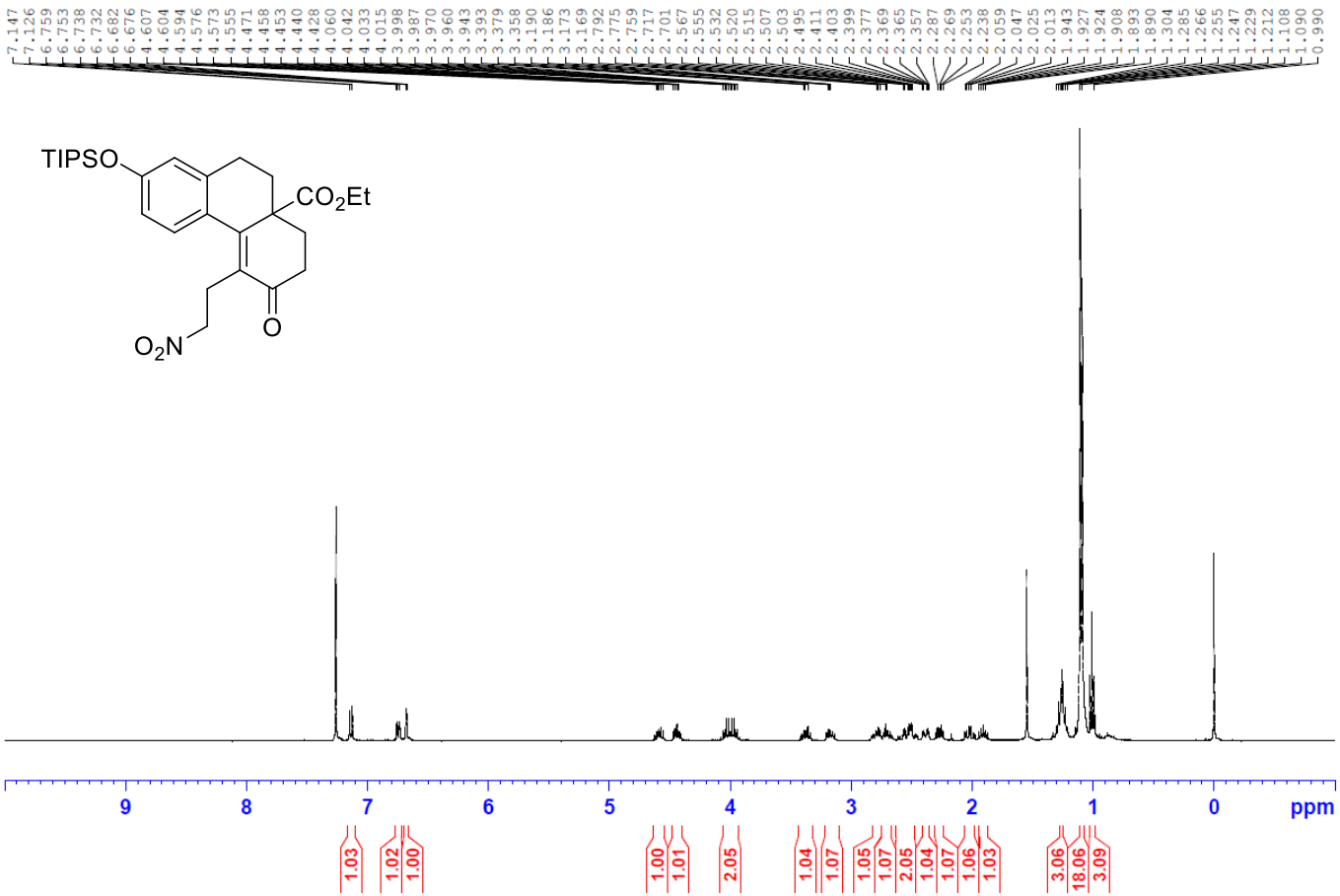
4. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **F**



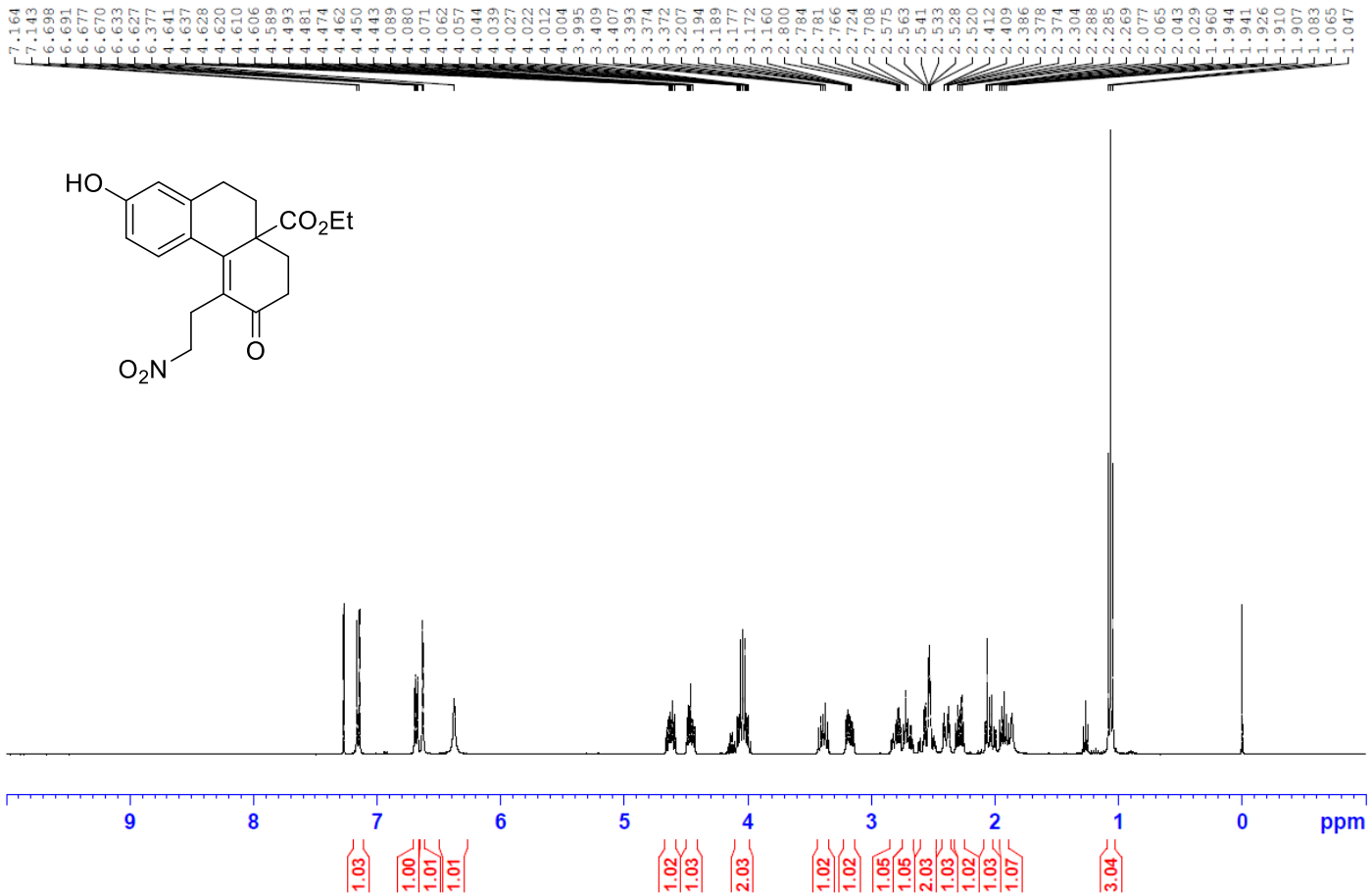
5. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound G



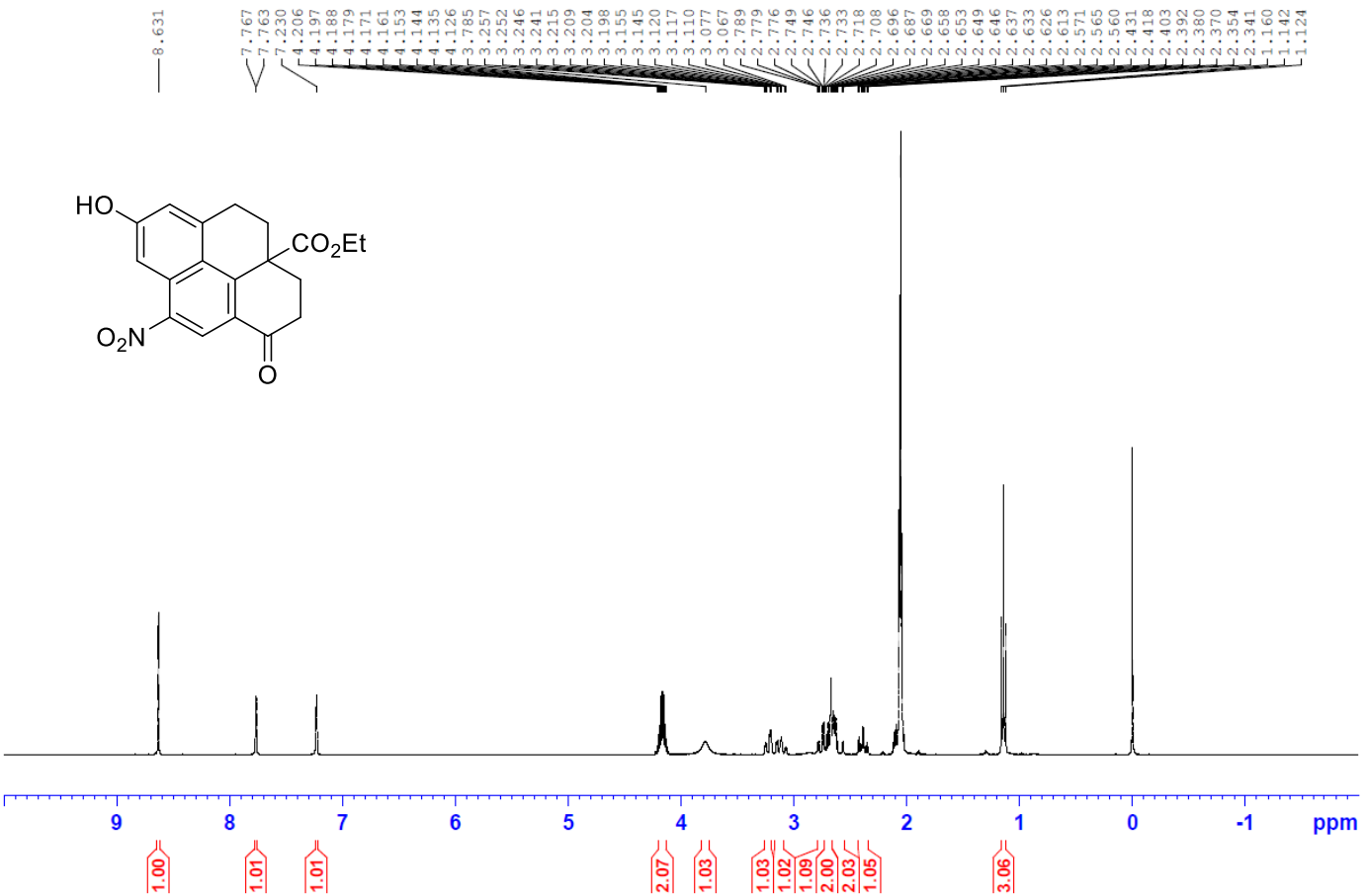
6. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **H**



7. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **I**

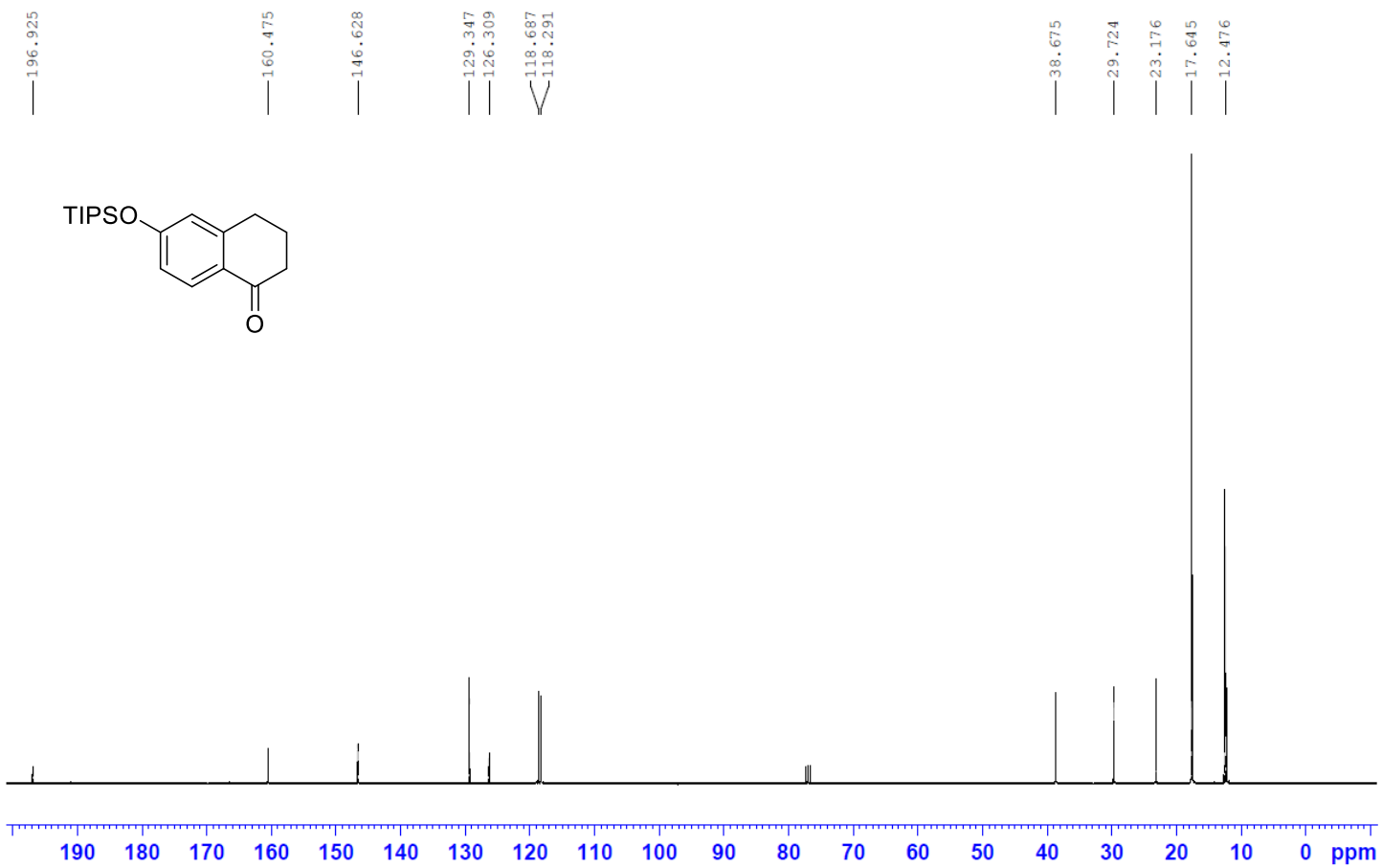


8. 400 MHz ^{1}H NMR Spectrum ($CDCl_3$) of compound **J**

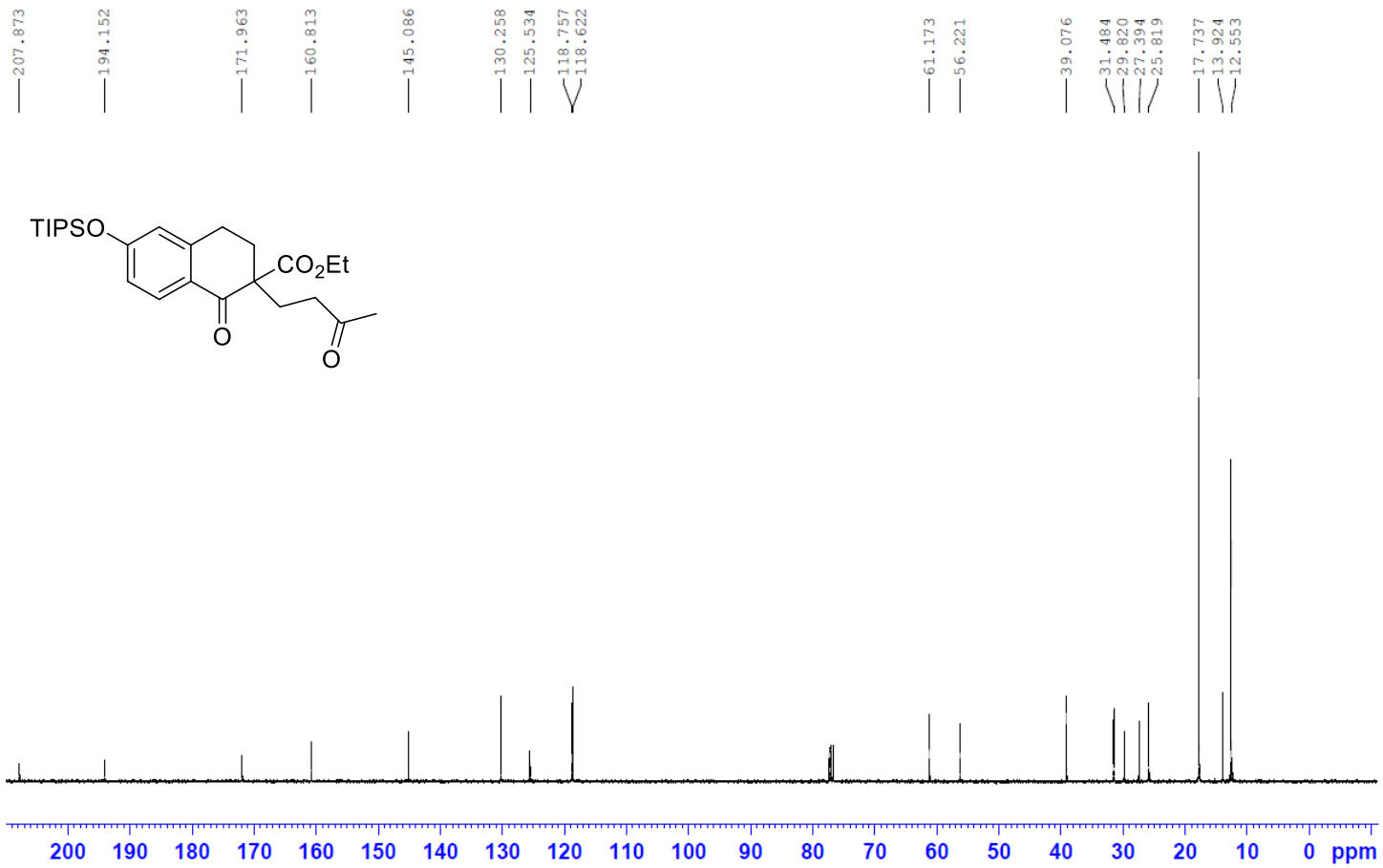


9. 400 MHz ^{1}H NMR Spectrum (Acetone−d_6) of compound **K**

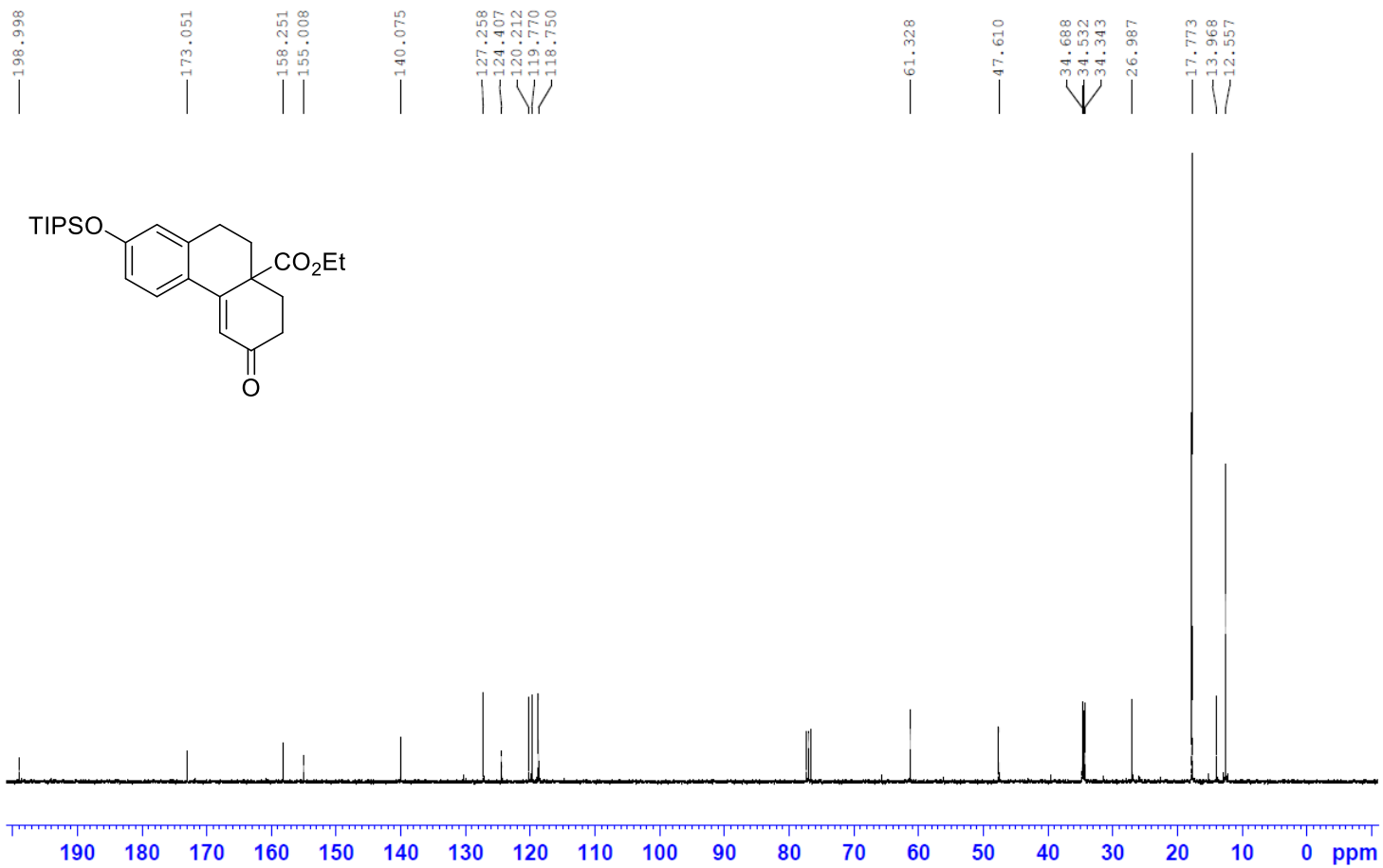
List of ^{13}C NMR Spectra of Selected compounds



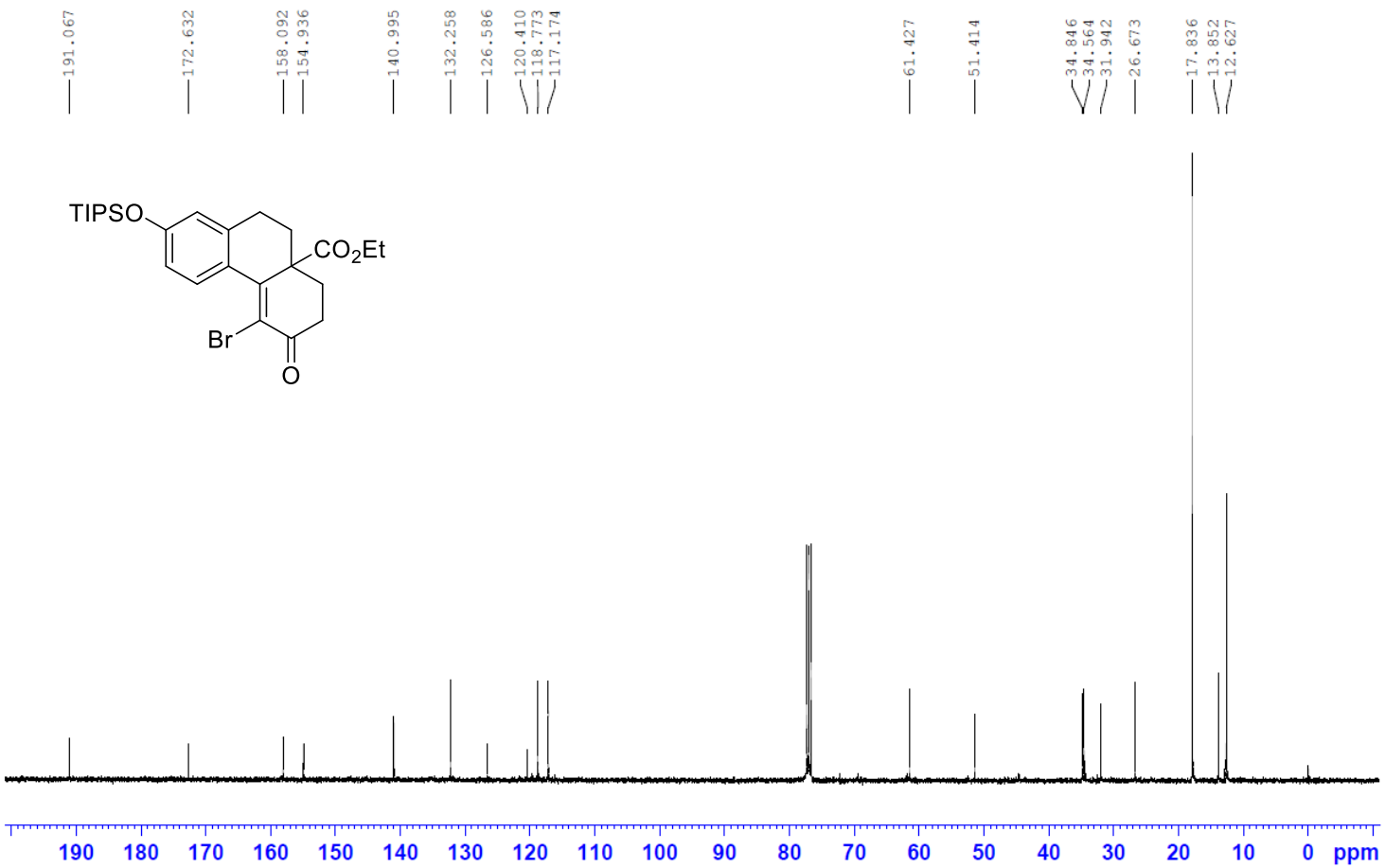
1. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **B**



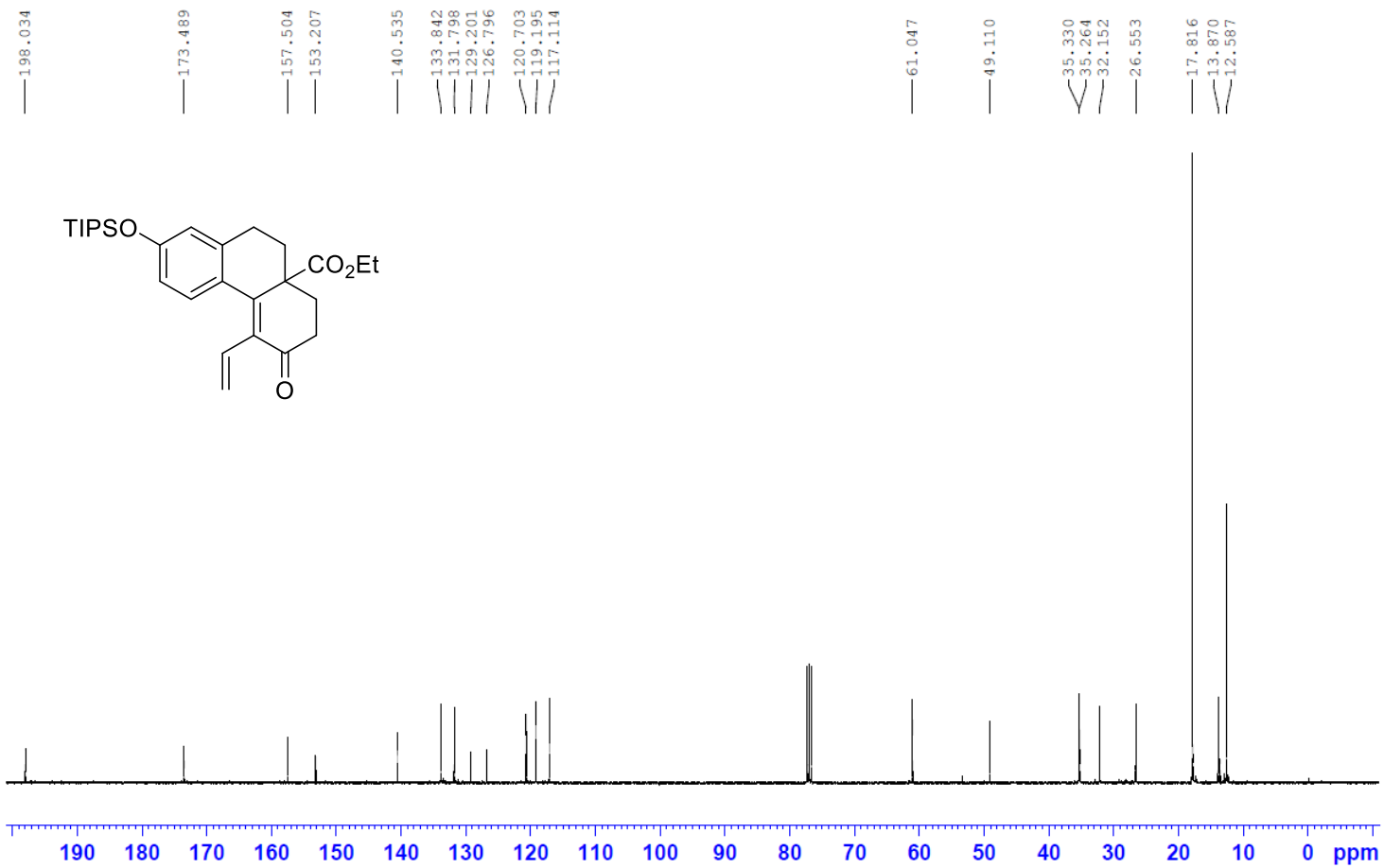
2. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **D**



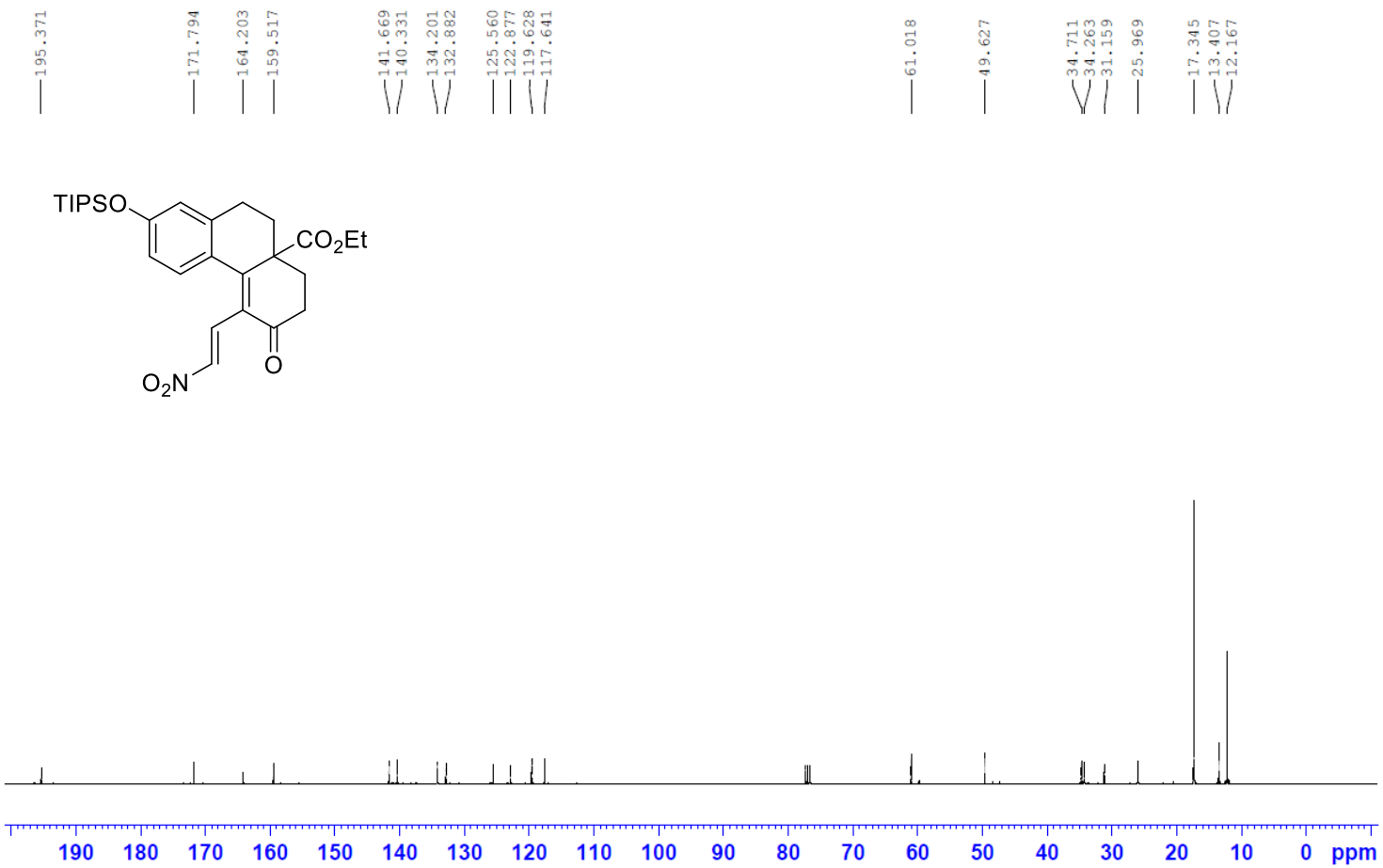
3. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **E**



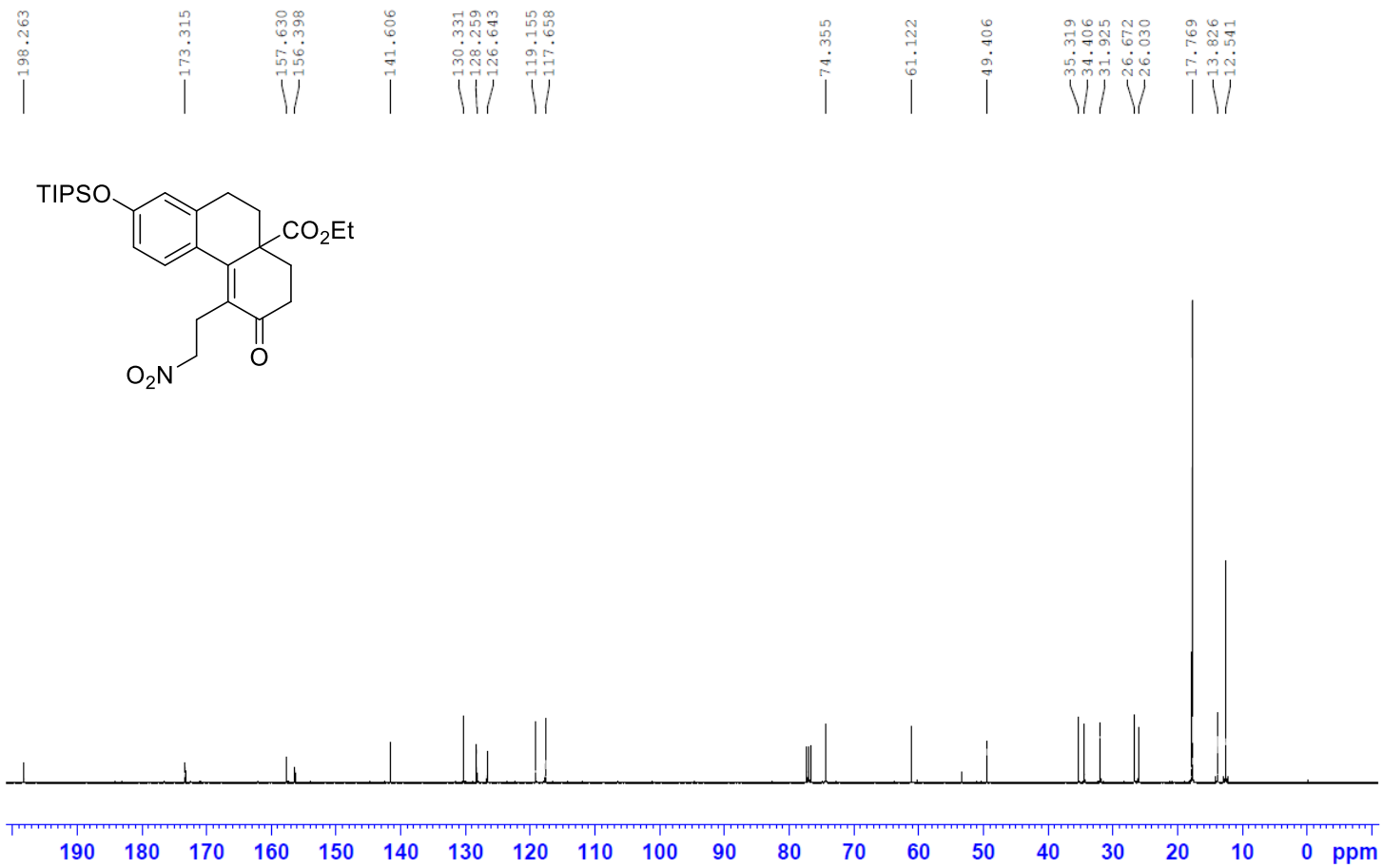
4. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **F**



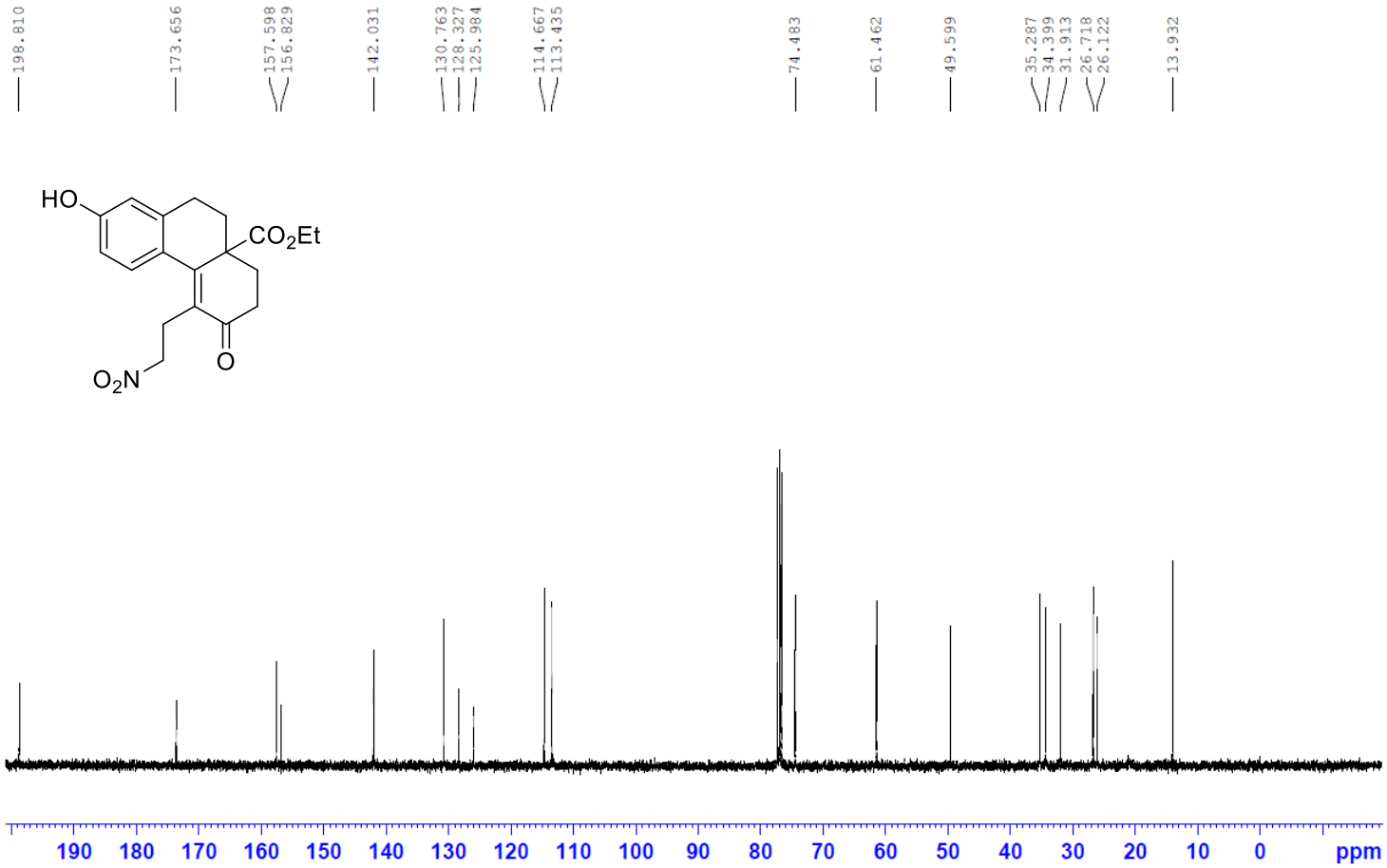
5. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **G**



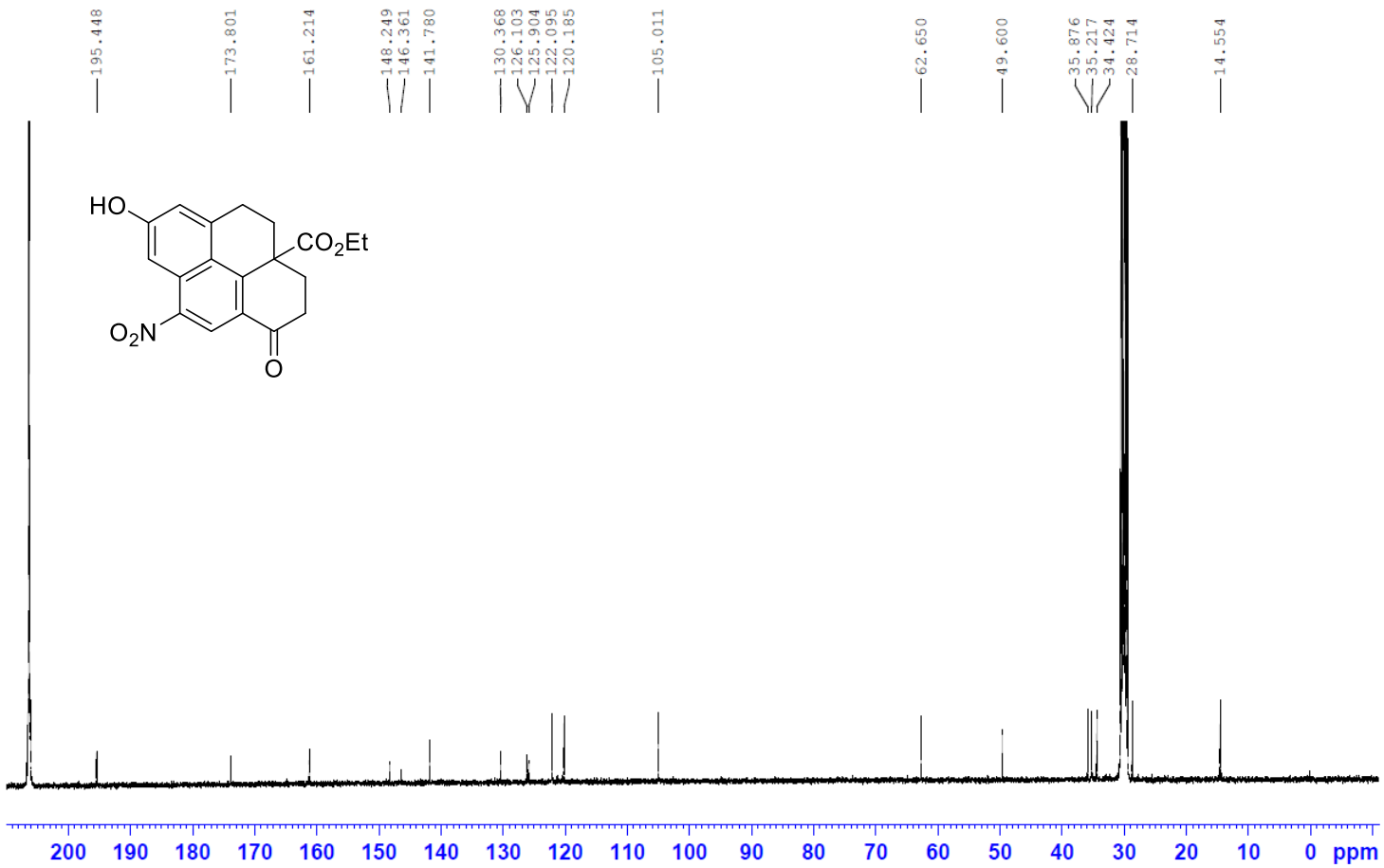
6. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **H**



7. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound I



8. 100 MHz ^{13}C NMR Spectrum ($CDCl_3$) of compound **J**



9. 100 MHz ^{13}C NMR Spectrum (Acetone-d_6) of compound **K**

국 문 초 록

식물 추출물의 의약학적 효능과 합성 방법에 대하여 연구하기 위해서 많은 화학자들은 천연물의 전합성 실험을 시도하였다. 특히 메틸기로 치환된 트로폰 고리를 가지고 있는 헤링토놀라이드는 새장과 같은 독특한 구조로 이루어져 있어서 합성 화학자들의 흥미를 불러 일으키는 목표 물질이다.

헤링토놀라이드는 개비자나무에서 추출한 노디테르페노이드 계열 파생 물질의 한 종류로, KB 종양 세포에 대한 세포 독성, 식물 성장 억제, 항생성과 항종양성 등의 생리활성을 가지고 있는 독특한 물질이다. 또한, 다리 구조의 락톤, 트로폰, 테트라하이드로퓨란과 시스로 접합된 4개의 고리에 연속적인 입체 중심이 존재하는 복잡한 구조를 가지고 있다. 이러한 독특한 구조와 활용성이 높은 생리활성으로 인하여, 헤링토놀라이드와 그 유사 물질들을 합성하는 적절한 경로를 찾기 위한 다양한 연구가 진행되었다.

우리 연구실에서도 이러한 생리활성을 활용하기 위하여 헤링토놀라이드의 전구체를 10단계의 화학 반응을 거쳐 합성하고자 하였다. 따라서 6-하이드록시테트라론을 출발 물질로 하는 간단한 역합성 방법을 제안하였고, 로빈슨 고리화, 브로민 도입 반응, 나이트로화 반응 등을 진행하였다. 특히 다음 반응을 진행하기 위하여 브로민 도입 반응, 스틸레 커플링 반응, 나이트로화 반응 등을 최적화하였다. 또한, 라디칼 음이온 중합 반응을 진행하여 트로폰 고리를 생성하려고 하였으나, 예상하지 못한 육각형 고리 화합물인 페놀과 나이트로벤젠이 생성되었다. 알파와 베타 위치가 불포화된 페놀릭 나이트로네이트 물질의 단단한 구조 때문에, 고리화가 일어나기 쉬운 결합 각도를 통하여 반응이 진행되는 것으로 추측된다. 이번 연구를 통해 헤링토놀라이드 전구체의 합성 과정과 최적화 작업을

소개하였다. 그리고 라디칼 음이온 중합 반응에서 육각형 고리 화합물인 페놀과 나이트로벤젠이 생성된 이유를 증명하기 위한 새로운 메커니즘과 분자 모형 연구에 대해서 설명하였다. 이러한 연구 결과는 헤링토놀라이드의 전합성을 가능하게 하는 전구체 물질을 개발하는 연구에 새로운 관점을 제시해줄 것이라고 생각한다.

주요어: 헤링토놀라이드, 노디테르페노이드, 반응 최적화, 라디칼 음이온 중합, 합성 과정
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