工學博士 學位論文

New Synthetic Methods for a Molecular Skeleton of *Cephalotaxus* Troponoids and Regioselective Synthesis of 2,3-Disubstituted Indoles

세파로텍서스 트로포노이드의 분자 골격 및 2,3-이치환된 인돌의 위치 선택적 합성을 위한 새로운 합성 방법

2023年 2月

서울大學校 大學院
化學生物工學部

金 周 喜

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New Synthetic Methods for a Molecular Skeleton of *Cephalotaxus* Troponoids and Regioselective Synthesis of 2,3-Disubstituted Indoles

by

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Abstract

New Synthetic Methods for a Molecular Skeleton of *Cephalotaxus* Troponoids and Regioselective Synthesis of 2,3-Disubstituted Indoles

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This thesis comprises two chapters. Chapter 1 describes the new synthetic method for a molecular skeleton of *Cephalotaxus* troponoids. Chapter 2 describes the regioselective synthesis of 2,3-disubstituted indoles.

Chapter 1.

The first study is the total synthesis of *Cephalotaxus* troponoid isolated from natural products. Among the troponoid compounds, we focused on a harringtonolide, which has been reported as representative plant growth inhibitory, antiviral, and antitumor agent. It is also known as a cytotoxicity to KB tumor cells. Despite showing various biological activities, the effective synthesis of harringtonolide has not been reported so far. In this study, we suggested a total synthesis of the harringtonolide through 12-steps of organic reactions and newly proposed 7-steps. It is possible to complete the target structure reducing the number of reaction steps, and with high overall yield compared to the existing synthetic methods of harringtonolide. Additionally, we have created the benzenoid structure similar to *Cephalotaxus* benzenoid which has recently been spotlighted. This derivative can be completed in 12-steps of organic reactions. The new synthetic pathway presented in this study

will be an important platform for the synthesis of *Cephalotaxus* troponoid and benzenoid derivatives.

Chapter 2.

The second study is the regioselective synthesis of 2,3-disubstituted indole. Since these compounds show interesting biological activities, it is widely used in medicinal chemistry. The most commonly employed method for the preparation of 2,3-disubsituted indoles was Fischer indole synthesis. However, it has difficulty in proceeding by boiling with strong acid, and when an unsymmetrical ketone participates in the reaction, regioisomer mixtures can be formed. In this study, we present a new method for the synthesis of 2,3-disubstituted indoles using amino cyclization that can complete the reaction in a short time under much milder conditions than previous indole synthesis. Moreover, highly regioselective product with various substituents can be achieved. This methodology will be utilized for the synthesis of natural products and fine chemicals containing 2,3-disubstituted indole.

Keyword: *Cephalotaxus* troponoid, *Cephalotaxus* benzenoid Norditerpenoid, Harringtonolide, Radical anionic coupling, Total synthesis, 2,3-Disubstituted indoles, PIFA, Aminocyclization, C-C Cross coupling reaction. Regioselective indole, Stille, Suzuki.

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List of Abbreviations

IC_{50}	Half maximal inhibitory concentration
NMR	Nuclear magnetic resonance
Hz	Hertz
NOESY	Nuclear overhauser effect spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7ene
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TMS	Trimethylsilane
DMF	*N*,*N*-Dimethylformamide
PCC	Pyridinium chlorochromate
OAc	Acetate
OPiv	Pivalate
O*t*Bu	Butoxide
MVK	Methyl vinyl ketone
TEA	Triethylamine
HSAB	Hard and soft acids and bases
LDA	Lithium diisopropylamide
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
HRMS	High resolution mass spectrometry
***p*-TsOH**	*p*-Toluenesulfonic acid
DCM	Dichloromethane
DCE	Dichloroethane
TBAF	Tetrabutylammonium fluoride
THF	Tetrahydrofuran
NBS	*N*-Bromosuccinimide

NIS	*N*-Iodosuccinimide
LHMDS	Lithium bis(tirmethylsilyl)amide
MsCl	Methanesulfonyl chloride
EWG	Electron withdrawing group
EtOAc	Ethyl acetate
AcOH	Acetic acid
***i*-PrOH**	*i*-Propyl alcohol
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
PIDA	(Diacetoxyiodo)benzene
B_2Pin_2	Bis(pinacolato)diboron
HBPin	4,4,5,5-Tetramethyl-1,3,2-dioxaborolane
$HZrCp_2Cl$	Bis(cyclopentadienyl)zirconium chloride
PMA	Phosphomolybdic acid
D*t*BPF	Dichloro[1,1'-bis(di-tert-butylphosphino)ferrocene]palladium
NMP	*N*-Methyl-2-pyrrolidone
IR	Infrared spectroscopy
GC-MS	Gas chromatography mass spectrometry
TLC	Thin layer chromatography
brsm	based on recovered starting material
NSAID	nonsteroidal anti-inflammatory drug
CDK	cyclin denpendent kinase
GSK	glycogen synthase kinase

Chapter 1.

New synthetic methods for a molecular skeleton of *Cephalotaxus* troponoids

Introduction

1. Introduction of *Cephalotaxus* troponoids

Cephalotaxus, called plum yew or cowtail pine, is a genus of coniferous which is evergreen shrubs and small trees reaching 1.0-10 m tall.[1,2] This genus is generally constituted of 6-12 species depending on their length and shape of needles, bark, and stomatal band color, yet the taxonomy of *Cephalotaxus* is difficult.[3] *Cephalotaxus* trees have been harvested for timber, firewood and medicinal purposes which can be related to the anti-cancer alkaloids in which they generally involved.[1,2] Several natural products including harringtonolide (*C. harringtonia*), hainanolidol (*C. hainanensis*), Fortunolide A and B (*C. fortune*), and 7-hydroxyhainanolidol (*C. Koreana*) can also be extracted from *Cephalotaxus*.[1,4] **(Figure 1, 2)**

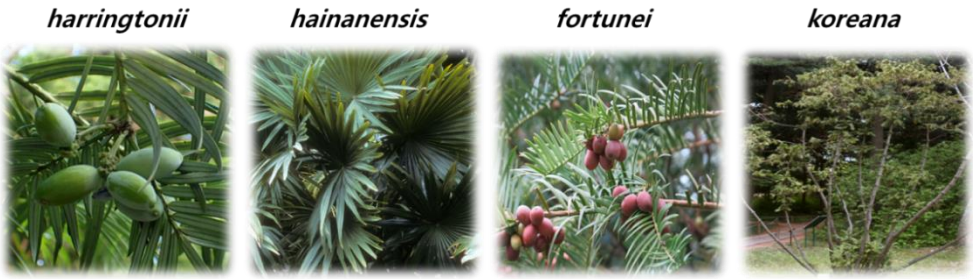


Figure 1. The several *Cephalotaxus* troponoid species

2. *Cephalotaxus* troponoid framework

Harringtonolide was first reported by Buta *et al*. as a new terpenoid material isolated from the seeds of *C. harringtonia,* in 1978.[5] A few months later, Sun *et al*. also discovered the compound from *C. hainanensis*. They also found a new tropone of hainanolidol, whose structure was elucidated a few years later. Interestingly, the harringtonolide was shown to inhibit the growth of tobacco and beans and was found to have antineoplastic and antiviral activities against Walker carcinoma, Lewis lung carcinoma, leukemia cells and influenza type A.[5,6] Furthermore, harringtonolide was described as strongly cytotoxic against KB tumour cells at the IC_{50} concentration of 43 nM.[4] Fortunolide A and fortunolide B were isolated by Du *et al*. from the stems and needles of *C. fortune*[7] and 7-hydroxyhainanolidol was described by Yoon *et al*. from *C. koreana*.[8] However, there was no biological activity for these compounds at all.

These compounds commonly have a tetracyclic carbon skeleton with a compact *cis*-fused tricyclic ring bearing several contiguous stereogenic

centers and an unusual tropone ring structure. Moreover, harringtonolid and Fortunolide B contain additional tetrahydrofuran rings with cage-like framework, and a hydroxyl group still remains on the Hainaolidol, Fortunolide A, 7-hydroxyhainanolidol, and even Fortunolide B **(Figure 2)**. As a result, the tetracyclic carbon skeleton with the hydroxyl group removed and having a cage-like structure generated from the tetrahydrofuran ring have interesting biological activity. Therefore, the following studies have been focused on the synthesis of harringtonolide.

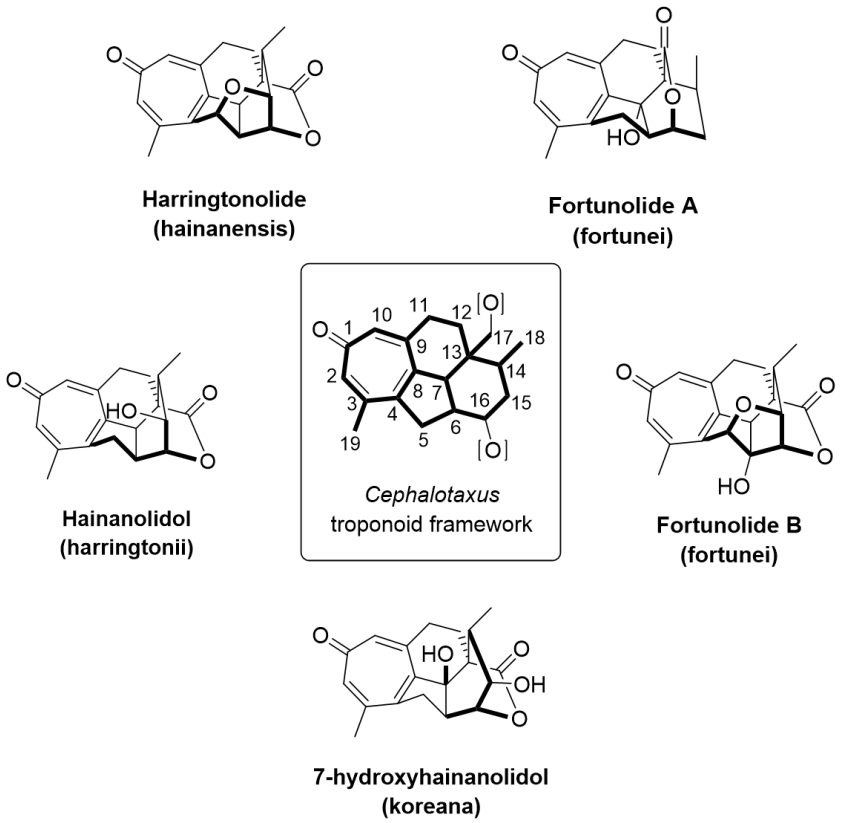


Figure 2. The *Cephalotaxus* troponoid framework

3. Previous synthetic studies toward harringtonolide

The synthetic study of harringtonolide has attracted much attention for organic chemists due to their low natural abundance, unique structure, and various biological activities. First, syntheses of hainanolidol and harringtonolide were reported by the Mander group in 1998.[9] They used intramolecular cyclopropanation of diazocarbonyl catalyzed by rhodium mandelate. The reaction undergoes a Cope rearrangement leading to the formation of cycloheptatriene, which was then transformed to tropone ring structure.[10] **(Scheme 1)**

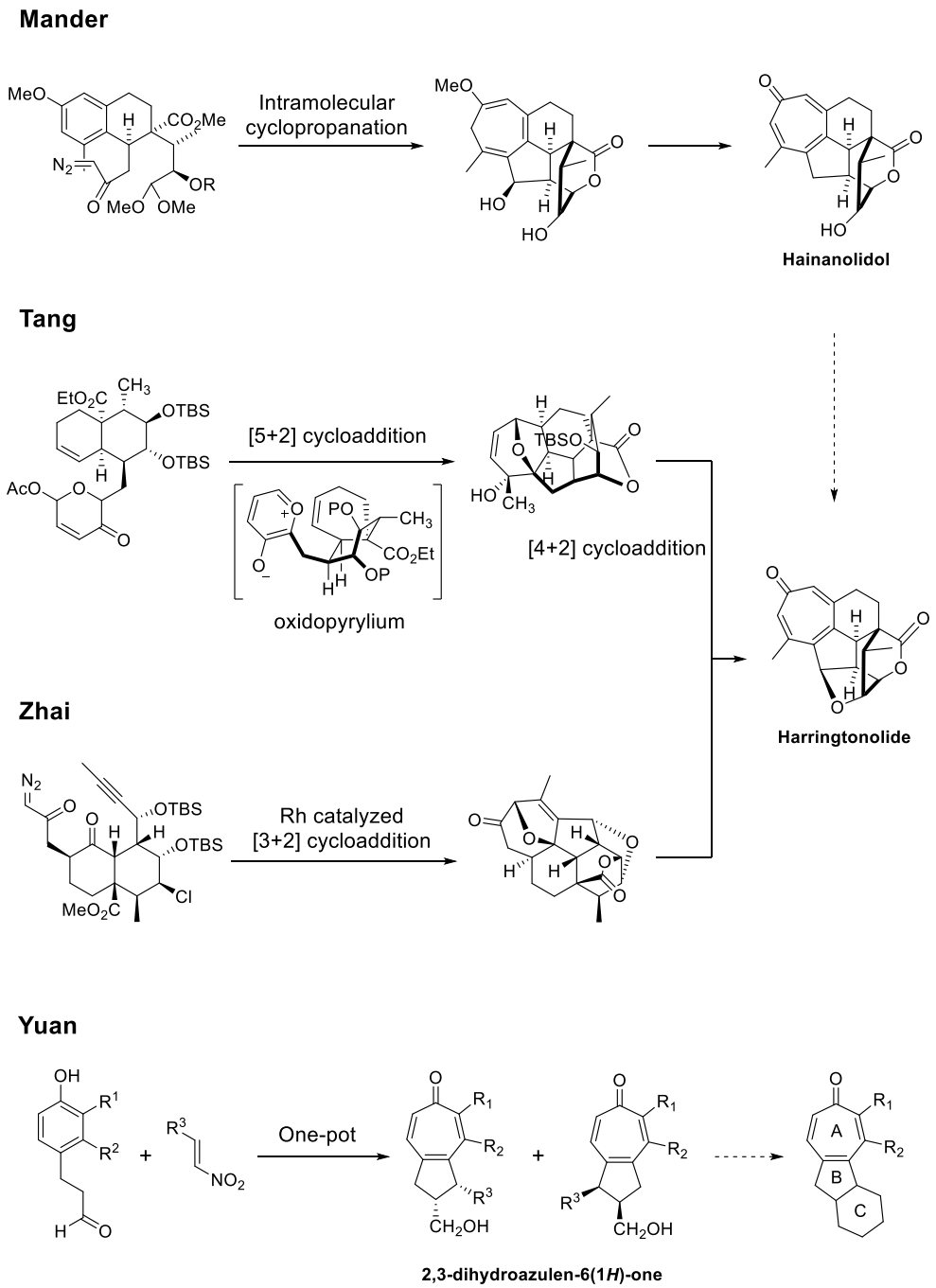
Tang *et al.* developed the tetracyclic carbon skeleton of harringtonolide via an intramolecular oxidopyrylium-based [5+2][11] cycloaddition, then tropone ring was formed through a sequence [4+2] cycloaddition of diene with singlet oxygen, Kornblum−DeLaMare rearrangement, and double elimination.[12] Despite the effort, complicated reactions make it difficult to achieve the asymmetric harringtonolide.

More recently, the Zhai *et al.* reported a first enantioselective total synthesis of (+)-harringtonolide.[13] They described the key transformations of total synthesis include an intramolecular Diels–Alder reaction and a rhodium catalyzed intramolecular [3+2] cycloaddition.[14] The formation of both tetracyclic carbon skeleton and tropone ring structure were accomplished through over twenty steps in less than 0.1% of overall yield.

Finally, Yuan *et al.* demonstrate the one-pot enantioselective synthesis

of *cis*-substituted 2,3-dihydroazulen-6(1H)-one.[15] They used an organocatalyzed Michael reaction to prepare the phenolic nitronate intermediate, which is converted to tropone ring structure by radical anionic coupling reaction in the presence of oxidant and base. This methodology would be successfully utilized to synthesize the tricyclic carbon skeleton of *Cephalotaxus* norditerpenes.

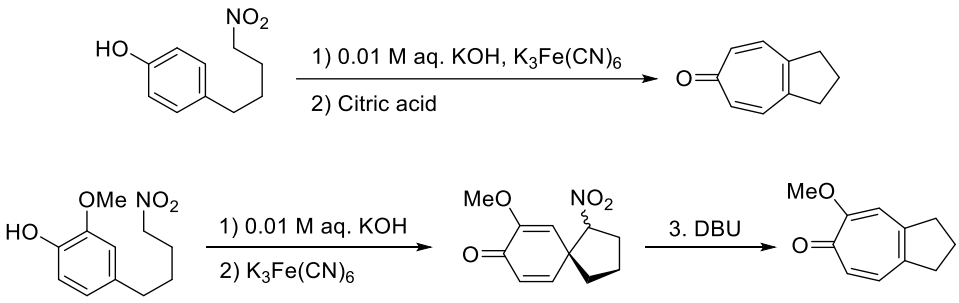
Although many chemists have indulged in the synthesis of harringtonolide, the drawback of previously reported methods is low overall yield due to long reaction steps. In this study, we suggested a new synthetic protocol of harringtonolide using radical anionic coupling reaction previously reported by our research to produce the tropone ring structure.[16] We expect radical anionic coupling reaction for the synthesis of harringtonolide would be a novel and concise strategy.



Scheme 1. Syntheses of harringtonolide and its precursor

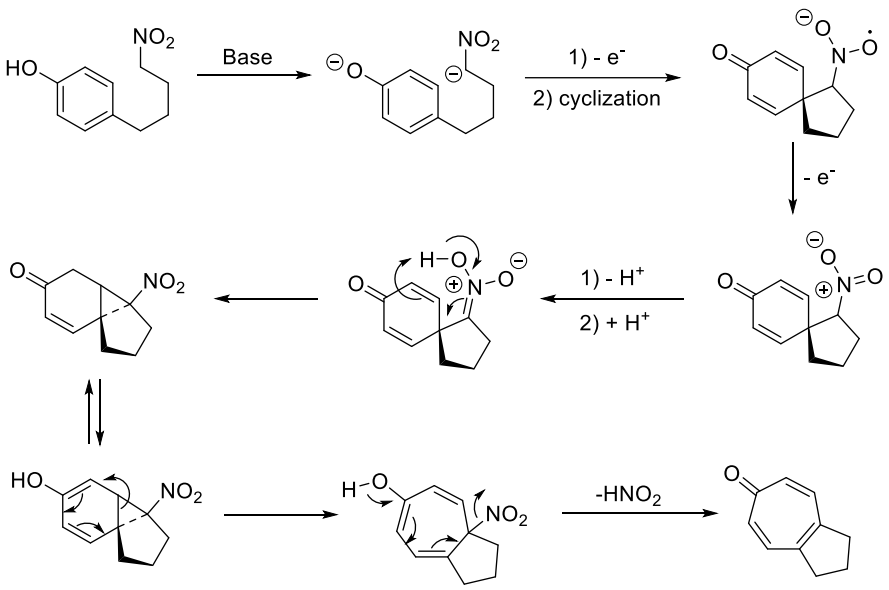
4. Radical anionic coupling reaction

Kende coupling is an oxidative radical anionic coupling, which was first reported by Kende *et al.* in 1986.[17] As a substrate of the reaction, phenolic nitronate was used to achieve the corresponding 7-membered tropone ring structure. A phenolic nitronates under the strong base of potassium hydroxide gave the spirocyclic nitropentane intermediate via intramolecular oxidative coupling reaction initiated by the radical source of $K_3Fe(CN)_6$.[18] A rearrangement of the spirocyclic niropentane in the presence of citric acid or DBU spontaneously led to a 2,3-dihydroazuien-6(1H)-one containing tropone ring.[17] **(Scheme 2)**



Scheme 2. Intramolecular oxidative coupling reaction of phenolic nitronates

The mechanism of Kende coupling reaction was proposed in **Scheme 3**.[17] The phenolic nitronate under strong base condition provided a dianion which undergoes one-electron transfer to the oxidant, and the subsequent cyclization lead to the radical anion. The second electron transfer produced the neutral intermediate which occurs acidification to produce corresponding nitronic acid. Once the cyclopropane intermediate is formed through the "ene" reaction, the subsequent rearrangement provides a tropone system.

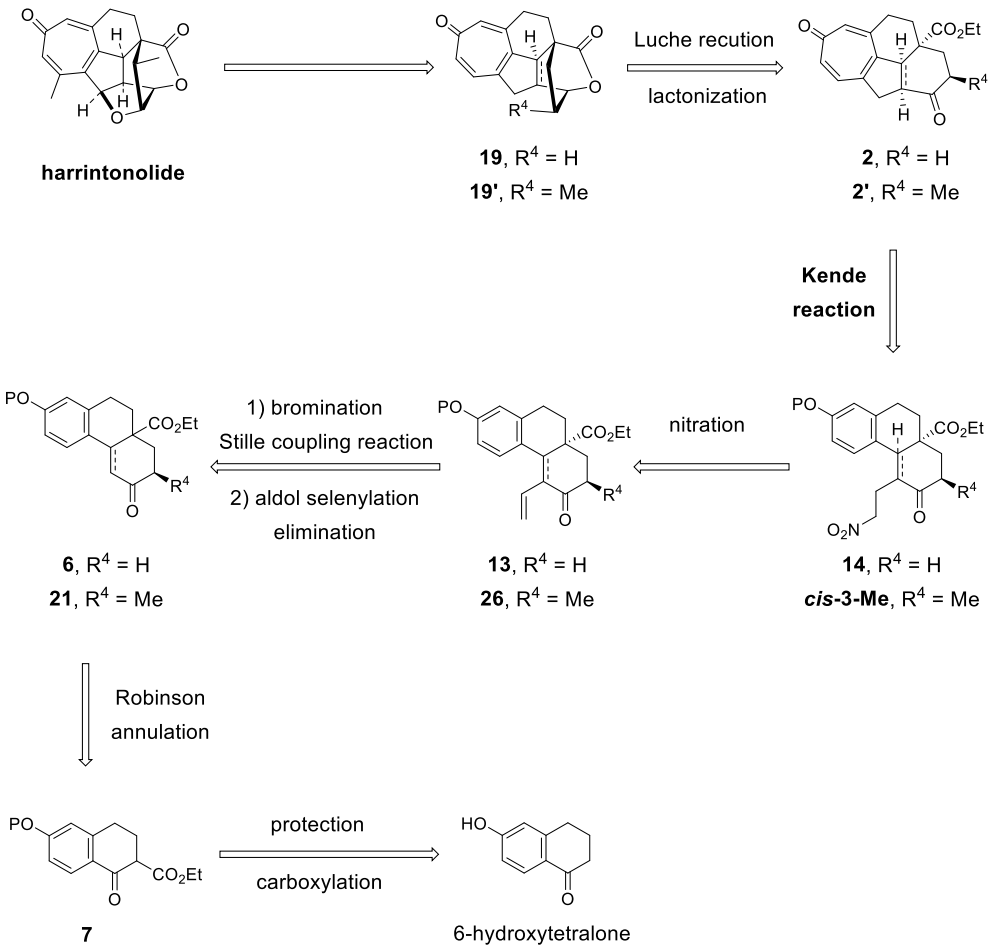


Scheme 3. Mechanism of intramolecular oxidative coupling reaction

Result and Discussion

1. Retrosynthetic analysis of harringtonolide

In this study, concise total synthesis of enantioselective harringtonolide was suggested. The retrosynthesis of harringtonolide was presented in **Scheme 4**. We envisioned the harringtonolide could arise from tetracyclic carbon skeleton **(2)** via late-stage lactonization. The structure could be achieved through oxidative ring expansion of phenolic nitrate **(3)** by radical anionic coupling of Kende reaction. The **3** was produced by the selective hydrogenation of nitroalkenylated tricycloketone **(4)** prepared by Stille coupling reaction and nitration of brominated product **(5)**. The **5** also achieved by selective bromization of α,β-unsaturated tricycloketone **(6)**, which could be disconnected into the commercially available 6-hydroxytetralone **(8)**.



Scheme 4. Retrosynthetic analysis of harringtonolide

2. Preparation of *α,β*-unsaturated tricycloketone (6) and its stereoselective hydrogenation.

2.1. Synthesis of *α,β*-unsaturated tricycloketone **(6)**

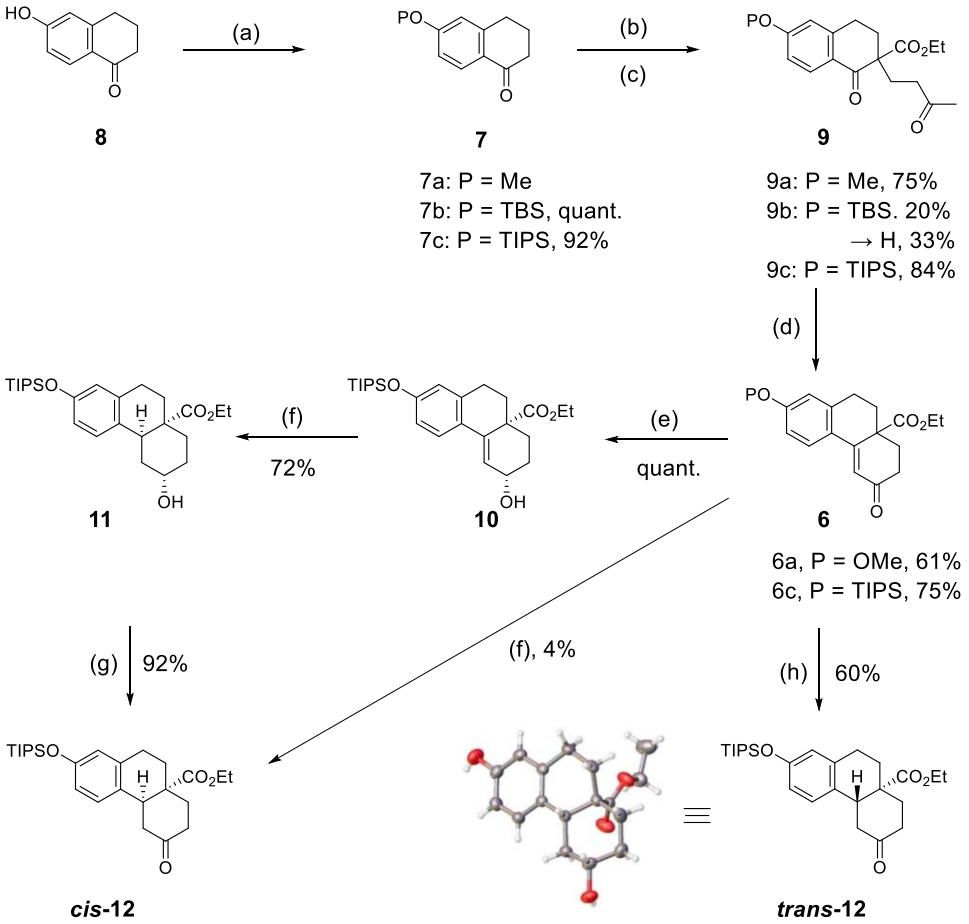
According to the previous retrosynthetic strategy, *α,β*-unsaturated tricycloketone **(6)** was prepared through three steps from 6-hydroxytetralone **(8)**. First, protection of hydroxyl group was accomplished to stabilize the reactants from harsh reaction conditions. When methoxy group was incorporated in the reactant, it was hard to remove the methyl functional moiety from the final product even we used harsh reaction condition. Next, we used the TBS group to protect the hydroxyl function, however, protecting group disappeared in the acidic or basic condition such as Michael addition. Therefore, we attempted the reactions using the TIPS protecting group as shown in **Scheme 5**. TIPS protection of **8** with TIPSCl and imidazole under DMF solvent gave the corresponding **7**. The carboxylation of the **7** using sodium hydride and diethylcarbonate provided carboxylated product[19], which undergoes keto-enol tautomerism in the column purification. Then Michael addition and intramolecualr aldol condensation (Robinson annulation)[20,21] with no further purification of the mixed product **9** gave rise to *α,β*-unsaturated tricycloketone **(6)** in 84% yield over two steps.

2.2. Synthesis of ***trnas*-12** with Pd/C hydrogenation

The hydrogenation of *α,β*-unsaturated cycloketone **(6)** was first attempted using the Pd/C catalyst with H_2 bubbling.[22] The hydrogenation of **6** simply brings tricycle ring structure accompanied with *trans* configuration and with alcohol functionality produced by unexpected ketone reduction. Then PCC oxidation[23] was proceeded to obtain ***trans*-12**. The configuration of product was measured by X-ray crystallography in **Scheme 5**. We planned to achieve the desired *cis* configuration of tricycloketone **(*cis*-12)** involved in natural product of harringtonolide, and further three steps were developed in the next part.

2.3. Synthesis of ***cis*-12** with direct Crabtree hydrogenation

The Crabtree hydrogenation of *α,β*-unsaturated cycloketone **(6)** was next investigated with H_2 bubbling while obtaining *cis*-configuration by directing effect of ester functional group. As a result, most of the starting material was not consumed, and some of the starting materials that participated in the reaction converted to the desired ***cis*-12**. Although the desired ***cis*-12** was produced by the directing effect of ester, the yield was remarkably low. For this reason, we conducted further research on the preparation of ***cis*-12**, as follows by introducing an additional directing effect of the hydroxyl group **(Scheme 5)**.



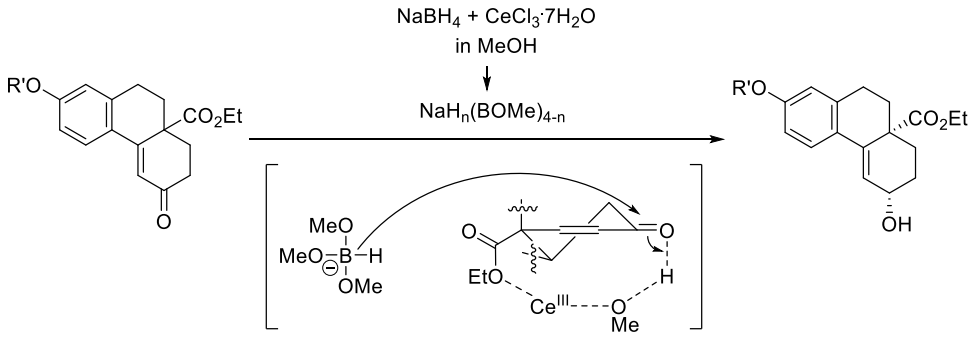
(a) TIPSCl (1.2 eq), Imidazole (2.5 eq), DMF, rt, 18 h (b) 1) $CO(OEt)_2$ (2 eq), NaH (2.1 eq), toluene, 120 ^oC, 3 h (c) MVK (2 eq), TEA (0.5 eq, MeOH, 80 ^oC, 3 h (d) Piperidine (1 eq), AcOH (1 eq), toluene, 120 ^oC, overnight (e) $NaBH_4$ (2 eq), $CeCl_3.7H_2O$ (1 eq), MeOH, DCM, -78 ^oC, 2 h (f) $[(Cod)Ir(Pcy_3)(Py)]PF_6$ (25 mol%), H_2, DCM, 1atm, 3 h (g) PCC (1.5 eq), DCM, rt, 2 h (h) 10 wt% Pd/C, H_2, DCM, 2 h, PCC (1.5 eq), DCM, rt, 2 h

Scheme 5. Synthesis of configurational isomers ***trans*-12** and ***cis*-12**

2.4. Synthesis of ***cis*-12** with Luche and Crabtree reduction

2.4.1. Luche reduction[24] of **6**.

Luche reduction is the selective organic reduction of α,β-unsaturated ketone to allylic alcohols. The reaction was conducted in $NaBH_4$ and $CeCl_3$ in an alcohol solvent. This can be progressed chemoselectively toward only ketone, competing the conjugate 1,4-addition. The selectivity of Luche reduction can be explained in terms of the HSAB theory.[25] The substitution of hydrides in BH_4 by alkoxy groups increases the hardness of the reagent, then carbonyl group demanding hard nucleophiles participated in hydrogenation toward selective 1,2-addition **(Scheme 6)**. Furthermore, moderate *cis* stereoselectivity of carboxylate and hydride was observed by connected $CeCl_3$ providing more favored an axial attack of cyclohexanone **(Scheme 6)**.[26]



Scheme 6. Chemoselective hydrogenation of Luche reduction

2.4.2. Crabtree hydrogenation of cyclic allylic alcohol **(10)**

Crabtree hydrogenation is an effective method in direct reduction of a cyclic allylic alcohol. The direct hydrogenation with Crabtree catalyst occurs *syn* addition to the hydroxyl group. The internal alkene of allylic alcohol can be reached only when the hydroxyl-metal complex is in the pseudoaxial orientation **(Figure 3)**.[27] The Crabtree hydrogenation was applied to the streoselective hydrogenation of the **10** to achieve a *cis*-fused product **(11)**. Even though high catalyst loading (25 mol%) was required to consume the starting material, the corresponding stereoselective hydrogenation of **11** was provided in a high yield of 72%.

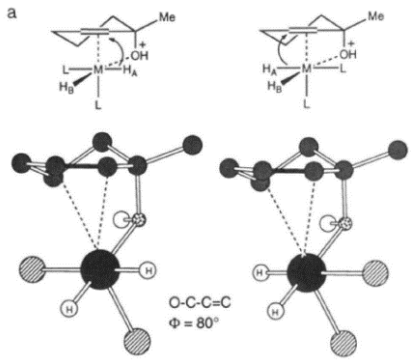


Figure 3. Stereoselective hydrogenation with Crabtree reagent.

2.5. Configurational analysis of ***trans*-12** and ***cis*-12**

The structural difference between the ***trnas*-12** and ***cis*-12** can be detected by ^{1}H NMR spectra as shown in **Figure 4**. A fused proton of ***cis*-12** is down shifted to 4 ppm in proton NMR chemical shift than that of ***trnas*-12** owing to adjacent EWG substituents of carboxylic ester.

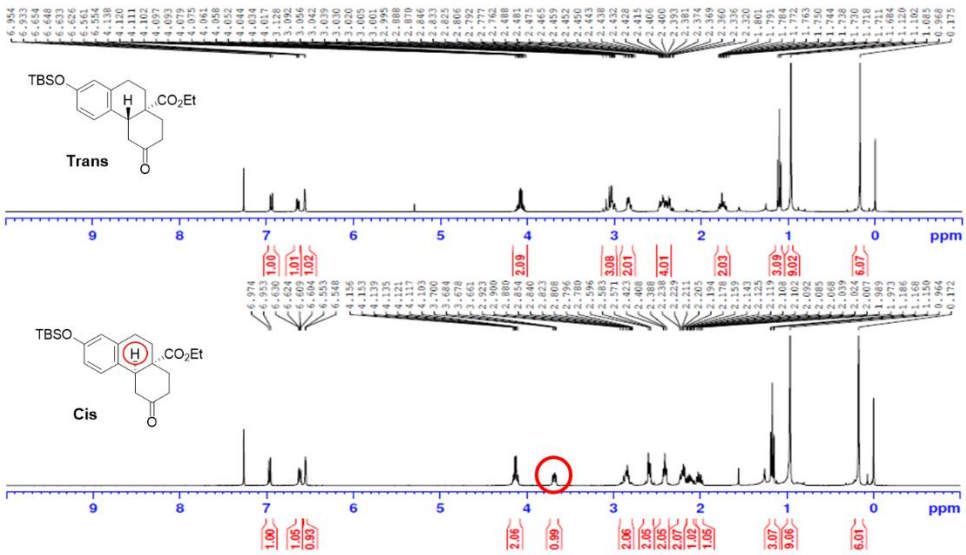
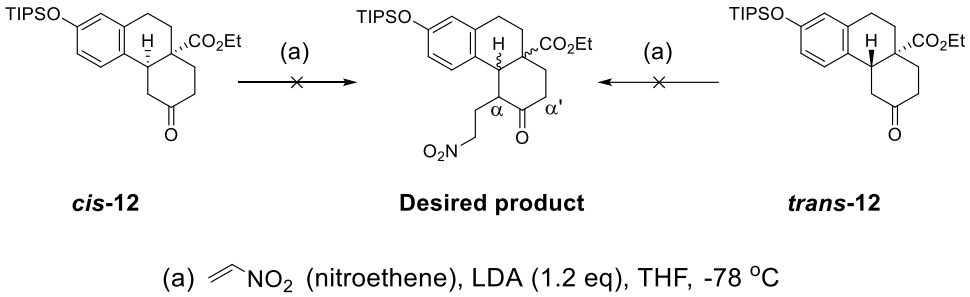


Figure 4. Configurational analysis of ***trans*-12** and ***cis*-12** in ^{1}H NMR

2.6. Nitroethylation of ***trans*-12** and ***cis*-12**

Next, we investigated the first nitration of the prepared ***cis*-12** with a simple method of nitroethylation using LDA and nitroethene. First, nitroethene reagent was produced from 2-nitroethanol through an E2 acid-catalyzed dehydration reaction, then obtained by vacuum distillation. We used the reagent, 1M solution in toluene and stored in the freezer. With the obtained reagent, nitroethylation was carried out to achieve desired phenolic nitronate, which is a precursor of Kende coupling reaction **(Scheme 7)**. However, the result brings out not only extremely low yielded product but also no chemoselectivity of nitration that determines the reactivity of α or α' to both ***cis*-12** and ***trans*-12**. We assumed that selective incorporation of nitro functional group at α position is additionally needed, then selective bromination of α,β-unsaturated tricycloketone **(6)** was performed as following next reaction.

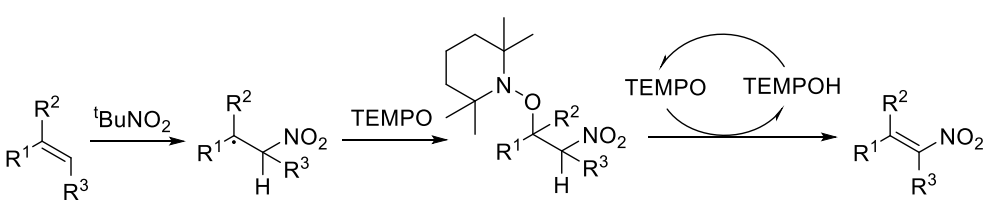


Scheme 7. Chemoselectivity issue of nitroethylation on ***trans*-12** and ***cis*-12**

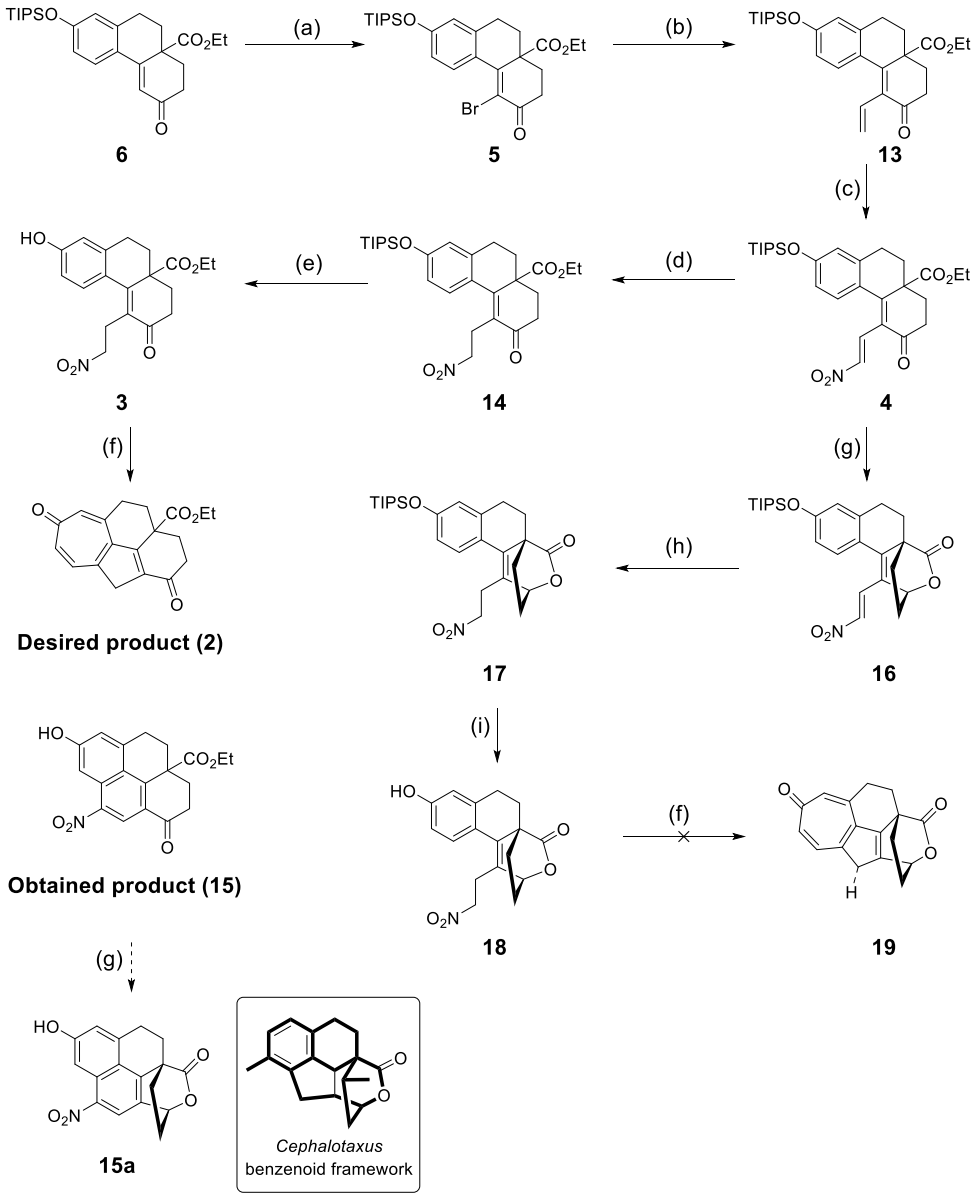
3. Synthesis of phenolic nitronate (3) and its Kende coupling reaction

3.1. Synthesis of α,β-unsaturated phenolic nitronate **(3)**

We have devised a different route started from **6** to offer the regioselectivity on the structure for the incorporation of nitro group. On account of selectivity, a bromination of **6** was attempted with a convenient halogenation of oxone and hydrobromic acid[28] to provide brominated α,β-unsaturated tricycloketone **(5)**. The **5** is able to carbon-carbon coupling reactions as a electrophile. The bromination was optimized by adjusting the concentration and chemical equivalent of oxone to prevent the further bromination on the aromatic ring.[29] Next vinylation was accomplished with palladium-catalyzed Stille coupling reaction. The coupling of vinylstannane as a nucleophile with **5** allowed to provide corresponding vinylated α,β-unsaturated tricycloketone **(13)** in moderate yield. Stereoselective nitration of the **13** with $AgNO_2$ and TEMPO through nitroalkane radical formation leads to the desired nitroolefin **(4)** as a mechanism presented in **Scheme 8**.[30] α,β-Unsaturated phenolic nironate **(3)**, a core precursor of kende coupling reaction, was obtained from simple procedure of reduction, oxidation and TIPS deprotection **(Scheme 9)**.



Scheme 8. Nitration of olefin mechanism



(a) 1) Oxone (0.7 eq), 2N HBr (2 eq), 2 h, 2) TEA (3 eq), 2 h, DCM, rt, 98% (b) $Pd(PPh_3)_2Cl_2$(10 mol%), vinyltributyltin (1.5 eq), dioxane, reflux, 2 h, 56% (c) $AgNO_2$ (2 eq), TEMPO (0.4 eq), dioxane, 90 ^oC, 3 h, 68% (d) 1) $NaBH_4$ (2 eq), EtOH, rt, 2 h, 2) PCC (1.5 eq), DCM, rt, 2 h, 58% (e) TBAF (1.1 eq), THF, rt, 2 h, quant. (f) 1M CsOH, $K_3Fe(CN)_6$ (4 eq), $CHCl_3$, H_2O, 0 ^oC, 1 h, 30% (g) 1) $NaBH_4$ (2 eq), $CeCl_3.7H_2O$ (1 eq), MeOH, DCM, -78 ^oC, 2 h, 2) *p*-TsOH (0.2 eq), toluene, 100 ^oC, 2 h, 55% (h) $NaBH_4$ (1 eq), EtOH, 1 h, 58% (i) TBAF (1.1 eq), THF, 0 ^oC, 2 h, 45%

Scheme 9. Synthesis of α,β-unsaturated phenolic nitronate **(3)** and its Kende coupling reaction

3.2. Kende coupling reaction of **3**

Kende coupling reaction is an oxidative cyclization of phenolic nitronate which can give rise to the fused tropone ring, one of the core freamwork of *Cephalotaxus* troponids. We applied the reaction to phenolic nitronate **(3)** using aqueous potassium ferricyanide and cecium hydroxide as following procedure reported in previous literature.[16] We anticipated a desired product **(2)** with the fused tropone ring was observed, however, 6-membered tetracyclic carbon skeleton with nitro group **(15)** was detected **(Scheme 9)**. The structure was analyzed by ^{1}H NMR, ^{13}C NMR, and HRMS.

Furthermore, we discovered the **15** obtained from Kende coupling reaction shows a structural similarity of *Cephalotaxus* benzenoid which is recently disclosed as natural products. Yue et al. isolated new structurally unique norditerpenoids cephanolides **A−D** from *Cephalotaxus* sinensis (Figure 5).[31] *Cephalotaxus* benzenoids commonly have a tetracyclic carbon skeleton with a compact *cis*-fused tricyclic ring bearing several contiguous stereogenic centers and a benzene ring.[32,33] We anticipated these fascinating architectural would have interesting biological activities, and challenging to targets for total synthesis. Accordingly, our synthetic method using Kende coupling reaction would be an attractive possibility to develop *Cephalotaxus* benzenoid derivatives.

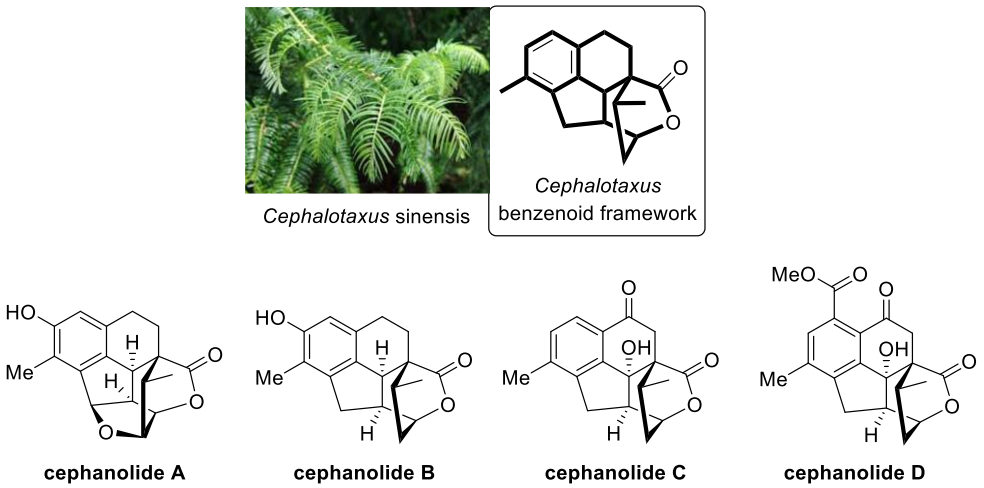
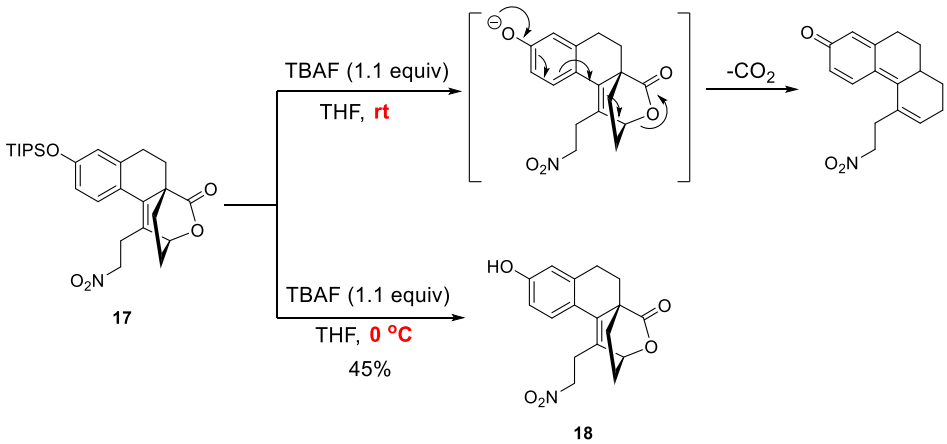


Figure 5. The *Cephalotaxus* benzenoid framework

3.3. Formation of lactone and its Kende coupling reaction

After failed from the formation of the fused tropone ring, we examined how the structural similarity affects the Kende coupling reaction. We believed that the structural similarity of harringtonolide with lactone ring such as **18** would certainly give us the desired tetracyclic carbon **(19)** in the Kende coupling reaction. We first accomplished Luche reduction of **4** with presented method in **Scheme 5**, then intramolecular esterification with catalytic *p*-TsOH was carried out for the formation of lactone **(16)**.[34] Next, simple hydrogenation of **16** gave rise to **17**, then TIPS deprotection of **17** with TBAF was conducted to obtain lactonized α,β-unsaturated phenolic nitronate **(18)**. When the deprotection of **17** was carried out in the room temperature as same condition of **14**, the electron migration occurs through the conjugated system as CO_2 is removed **(Scheme 10)**. The reaction should be proceeded in the ice

water to reduce side product by the opening of lactone ring during the reaction. Then, we expected that the desired **19** could be obtained by the Kende coupling reaction from the obatined latonized **18**. However, it was found that not only desired **19** was not observed, but also the unstable **18** disappeared during the Kende coupling reaction.



Scheme 10. Deprotection condition of lactonized **17**

4. Model structure of phenolic nitronates

We believed that the formation of **15** during the Kende coupling reaction was due to structural hardness of α,β-unsaturated phenolic nitronate **(3)**. Three dimensional structure of phenolic nitronates composed of sp^2 bond **(3)** and sp^3 bond **(*trans*- and *cis*-3)** were constructed by molecular model set as shown in **Figure 6.** This three structures are important factors in determining whether the final product would be 6-membered ring or fused tropone ring structure in the Kende coupling reaction. Following in the **Figure 6**, only the 6-membered ring can be created in the structure of **3** due to strong rigidity of double bond on tricycloketone. On the other hand, 5-membered ring can be formed in the ***trans*-3** and ***cis*-3**, since sp^3 bond on these structures are relatively flexible.

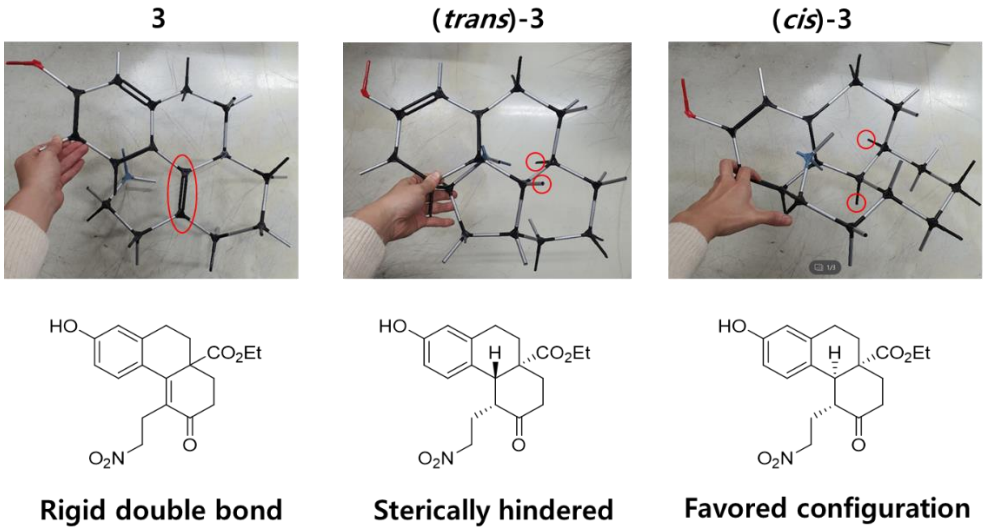


Figure 6. Model structure of phenolic nitronates **(3, *trnas*-3, and *cis*-3)**

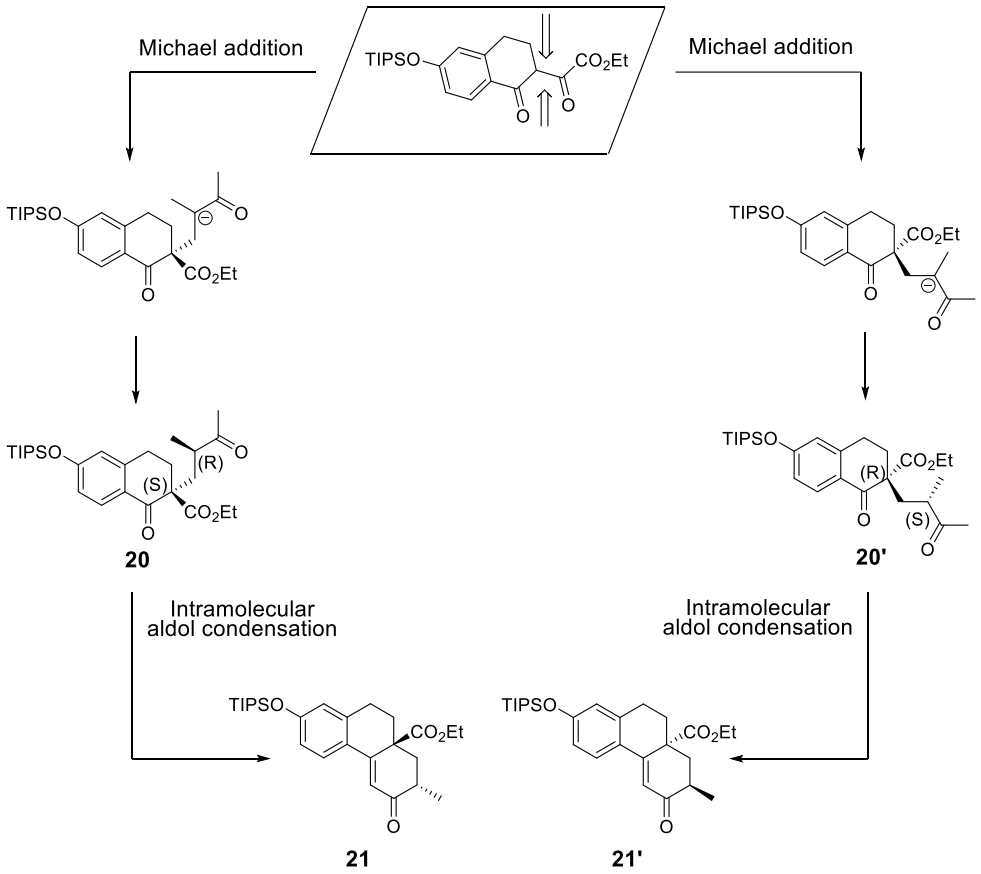
Furthermore, ***trans*-3** is more difficult to make the 5-membered ring than ***cis*-3** as their configuration. When the nitro backbone of ***trans*-3** closed to the phenol ring, a flat shape was observed in the structure, yet ***cis*-3** holds a cage-like structure that makes 5-membered rings more favored. Consequently, we concluded ***cis*-3** would be a proper structure to synthesize the core intermediate **(2)** of harringtoolide from the Kende coupling reaction.

5. Synthesis of *cis*-3-Me and stereochemistry analysis.

5.1. Synthesis of ***cis*-3-Me**

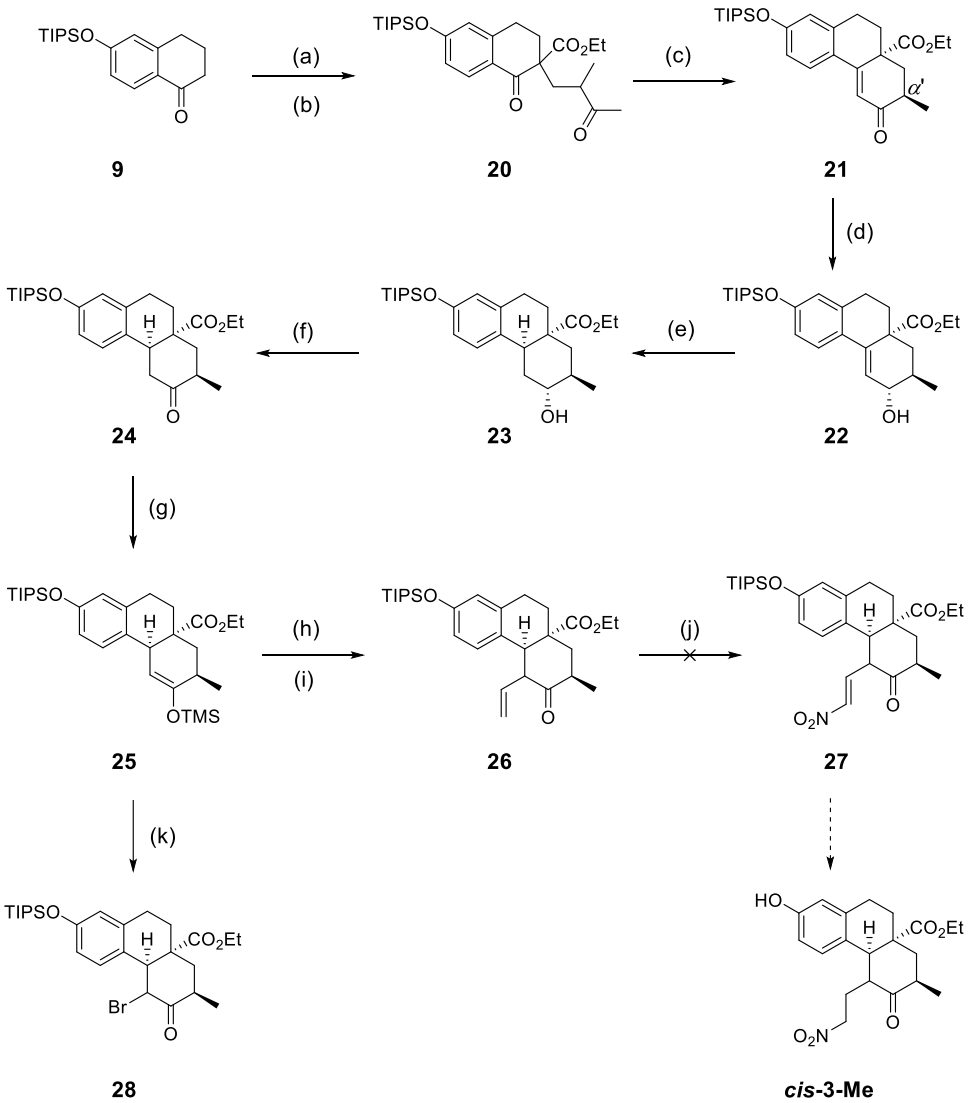
From the previous experimental results, we disclosed a saturated cycloketone having selectivity would be absolutely necessary for further research. Accordingly, 3-methyl-3-butene-2-one instead of MVK was used in the Michael addition followed by intramolecular aldol condensation – Robinson annulation to provide α'-methyl-α,β-unsaturated cycloketone **(21)** **(Scheme 12)**. The Robinson annulation gave one relative stereoisomer of **21** which is formed in preference to another diastereoisomer. We explain that single stereoisomer could be generated as following **Scheme 11**. First, two enantiomers can be observed depending on whether the reagent is approaching upwards or downwards when the Michael reaction occurs. Then, next protonation is determined by the position of the adjacent ester group, generating relatively identical isomers such as **20** and **20'**. After that, one relative stereochemistry (**21** and **21'**) can be also produced from the

intramolecular aldol condensation. The methylated product thus obtained has the following advantages: (1) Selective functionalization towards α side is possible. (2) It enables the introduction of the tetrahydrofuran ring one of the harringtonolide structure that affects biological activity.



Scheme 11. Stereoselective Robinson annulation

Then, **24** was obtained through Luche reduction, Crabtree hydrogenation, and oxidation with the reported condition in **Scheme 5**. We identified the stereochemistry of **24** with chemical shift and coupling constant presented in proton NMR spectra (Figure 7). It was confirmed that the substituent groups of a proton and ester group are oriented in same direction, the diastereomer is referred to as *cis*, and methyl substituent is oriented in opposing direction of the proton and ester group. The reason for being in the upward direction is explained by the stereoselectivity obtained when **20** is generated from Michael addition as in **Scheme 11**. **24** treated with TMSCl allows to regio selective enol silylation, which provides desired product **25**. Direct nitroethylation of **25** with nitroethene was conducted, however, the reaction was not progressed at all. Additional two reaction routes for saturated phenolic nitronate **(*cis*-3-Me)** were suggested. One is aldol condensation and elimination method.[35] From that, vinylated tricycloketone **(26)** was achieved, then nitration of the prepared **26** was carried out. However, this is relatively difficult than the nitration of unsaturated **13** due to the unstable radical intermediate. Another route is bromination of **25** with NBS, which provides the brominated tricycloketone **(28)**. We expected the product can participate in $C(sp^3)$-$C(sp^2)$ cross-coupling reactions that enable the further reactions. These reactions are currently in progress for the formation of ***cis*-3-Me**.



(a) $CO(OEt)_2$ (2 eq), NaH (2.1 eq), toluene, 3 h, 120 ^oC (b) 3-Methyl-3-buten-2-one (2 eq), TEA (0.5 eq), MeOH, 80 ^oC, 3 h, 68% (c) Piperidine (1 eq), AcOH (1 eq), toluene, 120 ^oC, 12 h, 84% (d) $NaBH_4$ (2 eq), $CeCl_3.7H_2O$ (1 eq), MeOH, DCM, -78 ^oC, 2 h, 96%. (e) $[(Cod)Ir(Pcy_3)(Py)]PF_6$ (25 mol%), H_2, DCM, rt, 3 h, 1 atm, 78% (f) PCC (1.5 eq), DCM, rt, 2 h, 95% (g) LHMDS (5 eq), TMSCl (2 eq), THF, 0 ^oC, 5 min, 87% (h) $Sc(OTf)_3$ (10 mol%), $PhSeCH_2CHO$ (1.5 eq), THF, H_2O, rt, 2 h (i) MsCl (4 eq), TEA (3 eq), DCM, 0 ^oC, 2 h, 50% (j) $AgNO_2$ (2 eq), TEMPO (0.4 eq), dioxane, 90 ^oC, 3 h (k) NBS (1.2 eq), $NaHCO_3$ (1.2 eq), THF, -78 ^oC to rt, 2 h, 61%

Scheme 12. Synthesis of stereocontrolled ***cis*-3-Me**

5.2. Stereochemistry and configurational analysis of **24**

The *J*-based NMR configurational analysis was applied to the determination of relative stereochemistry of **24**. Chemical shift and coupling constant of H_a used for its assignment are reported in **Figure 7** and **8**. The chemical shift of H_a was down shifted to 4.0 ppm by the EWG of adjacent carboxylic ester. The carboxylic ester induces a greater deshielding effect to the proton of H_a because both H_a and carboxylic ester present the *cis* configuration **(Figure 7)**. This configuration can be also supplemented by the coupling constant ($J_{H\text{-}H}$) of H_a and adjacent CH_2, which value was observed in 5.4, 5.6 Hz. As their coupling constant, we conclude gauche (60°) conformer of H_a and adjacent CH_2 presented in segment of **Figure 8** is favorable as a data to prove relative *cis* configuration.

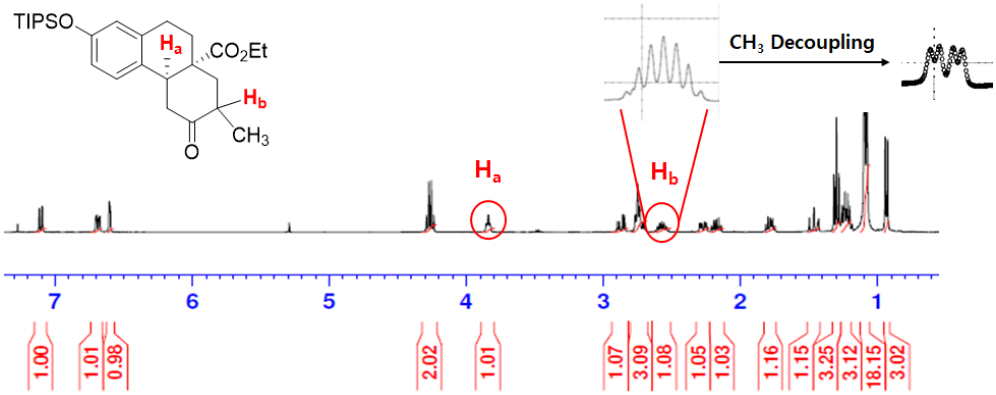
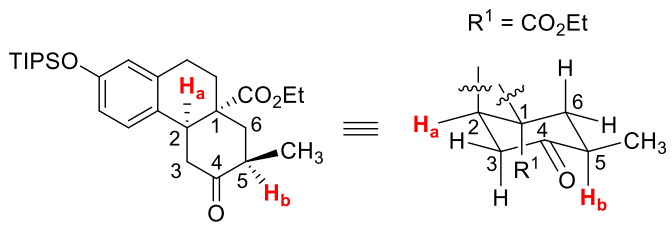


Figure 7. Selective homonuclear decoupling in ^{1}H NMR of **24**

In case of H_b, a multiplet was detected in 2-3 ppm as coupled with adjacent CH_2 and CH_3, which is ambiguous to analyze the its configuration. The resolution of H_b was enhanced by homonuclear decoupling of CH_3 to simplify multiplet to doublet of doublet as shown in **Figure 7**. The coupling constant of H_b and CH_2 was 13.5 and 5.2 Hz, respectively, that is, the dihedral angles of H_b and CH_2 must be positioned at both gauche (60°) and anti (180°) conformer, respectively. **(Figure 8)** Therefore, methyl group in C5 is introduced in the opposite direction of H_b and carboxylic ester.



24

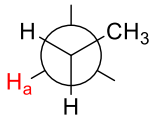
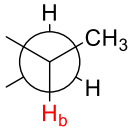
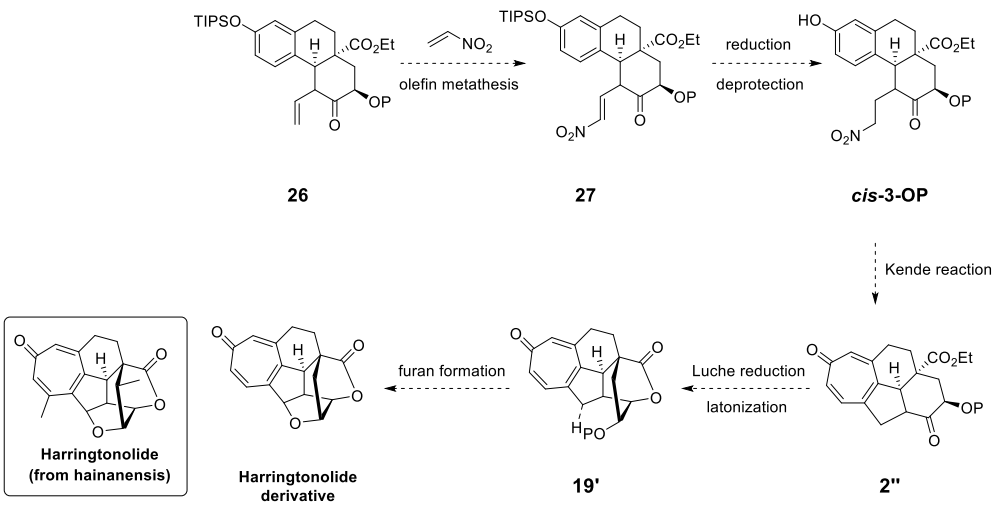
Framment	Segment	$J_{H\text{-}H}$ (Hz)
C3-C2		H_a (J = 5.4, 5.6 Hz)
C6-C5		H_b (J = 13.5, 5.2 Hz)

Figure 8. Stereochemistry and configurational analysis of **24**

6. Finalization of harringtonolide derivative

Due to the failure of the previous nitration reaction using silver nitrate and TEMPO, we newly planned the nitration reaction using the olefin metathesis reaction **(Scheme 13)**. After that, it will be possible to synthesize phenolic nitronate **(cis-3-OP)** by reduction and deprotection. Here, we plan to synthesize the **2''**, which is a key intermediate, while forming a tropone ring through the Kende reaction, and following lactonization gave the 19' The OP group located at α' will complete the introduction of the tetrahydrofunran ring, which is an important structure in the biological activity of harringtonolide. Since the harringtonolide derivative synthesized in this way is simpler than the existing synthetic methods and goes through a short reaction step, it is expected to be very useful reactions for more efficient production of *Cephalotaxus* troponoid.



Scheme 13. Finalization of harringtonolide

Conclusion

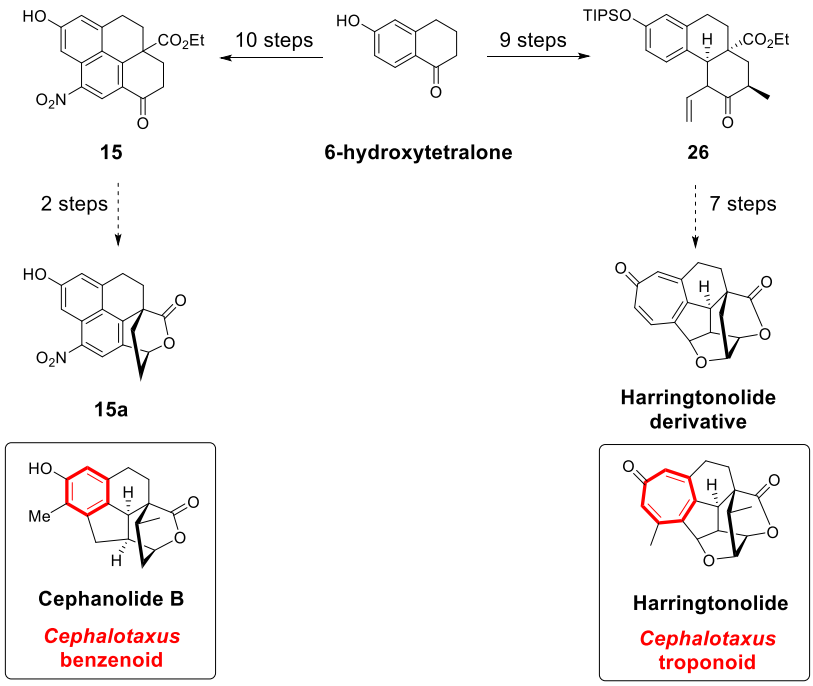
In this study, a key molecular skeleton of harringtonolide derived from the *Cephalotaxus* troponoids was developed by several organic reactions. First, we suggested a retrosynthetic analysis of harringtonolide structure from commercially available 6-hydroxytetralone. The starting material was converted to α,β-unsaturated cycloketone by a sequential TIPS protection, carboxylation, and Robinson annulation. In addition, bromination and Stille coupling reactions were successfully optimized by controlling the amount of reagents, molarities, and reaction temperatures. Also, nitration step can produce α,β-unsaturated phenolic nitronate, a substrate of Kende coupling a reaction.

However, Kednde coupling reaction of phenolic nitronate prepared from above method has rigid double bond on its architecture that prevents tropone ring formation. Accordingly, undesired 6-membered ring product was observed. We assume that a rigid structure of α,β-unsaturated phenolic nitronate triggered 6-memebered cyclization with a favorable bond angle, and saturated phenolic nitronate was absolutely needed to succeed Kende coupling reaction. The accidentally discovered 6-membered ring product has a similar structure to the recently discovered natural product *Cephalotaxus* benzenoid. Therefore, if we reduce one carbon on the α side and proceed with the Kende coupling reaction, we expect that a core architecture of *Cephalotaxus* benzenoid can be completed. Furthermore, biological activity of the obtained 6-membered ring product can be expected.

We investigated an additional synthetic method of α'-methylated saturated phenolic nitronate. Functionalized products at a' position gave two advantageous. One is the advantage of being able to selectively proceed with

the reaction toward α. Another is that the tetrahydrofuran ring, which is a biologically active structure of the harringtonolide, can be inserted. Therefore, ***cis*-3-Me** was prepared througth Luche reduction, Crabtree hydrogenation, selective enol silylation, aldol condensation, and elimination. In this part, we focused on the regio and stereo selectivity of products to reach enantioselective harringtonolide. The structures were analyzed by proton NMR spectra, chemical shift, and coupling constant for the identification of their configuration.

Furthermore, we suggested further synthetic method to achieve target harringtonolide derivatives from the α'-functionalized saturated phenolic nitronate. When the reaction succeeds, we will be able to synthesize enantioselective harringtonolide with 16 steps of organic reaction. This is expected to be able to produce target materials with high yield in a much shorter step than the Zhai group that synthesized the existing enantioselective harritonolide.



Experimental Details

1. General information

All materials were obtained from Sigma-Aldrich, Alfa Aesar, TCI, Merck and were used without further purification. Air- and moisture-sensitive manipulations were carried out under a nitrogen atmosphere using oven-dried glassware and standard syringe/septa techniques. Thin-layer chromatography (TLC) analysis was run on SiO_2 TLC plate under UV light (254 nm) followed by visualization with *p*-anisaldehyde staining solution. Column chromatography was performed with silica gel 60 (70-230 mesh). Compounds were characterized by ^{1}H and ^{13}C NMR spectra with a Bruker 400 AVANCE (400 and 100 MHz, respectively). All ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to TMS as an internal standard using ^{1}H (chloroform-*d*: 7.26 ppm) and ^{13}C (chloroform-*d*: 77.23 ppm) chemical shifts. ^{1}H NMR were presented as following: chemical shifts (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sep = septet, br = broad, dd = doublet of doublets, td = triplet of doublets, tt = triplet of triplets, m = multiplet), coupling constants, and integration. HRMS analyses were obtained on a JMS-700(JEOL, Japan) mass spectrometer.

2. General synthetic method

2.1. 6-((triisopropylsilyl)oxy)-3,4-dihydronaphthalen-1(2H)-one (7)

Imidazole (20.99 g, 308.28 mmol) and TIPSCl (28.53 g, 147.98 mmol) was added to a solution of 6-hydroxytetralone **8** (20 g, 123.33 mmol) in DMF (100 mL) at room temperature. Reaction mixture was stirred for 18 h under argon atmosphere. The resulting mixture was quenched with a deionized water (70 mL) and extracted diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (16:1) to give the corresponding product **7** (36.10 g, 113.45 mmol, 92%) as an orange liquid; ^{1}H NMR ($CDCl_3$): δ 7.94 (d, J = 8.4 Hz, 1H) 6.77 (dd, J = 8.4, 2.4 Hz, 1H) 6.69 (d, J = 2.4 Hz, 1H) 2.87 (t, J = 6.2 Hz, 2H) 2.60 (t, J = 6.4 Hz, 2H) 2.11 (quint, J = 6.3 Hz, 2H) 1.28 (m, 3H) 1.10 (d, J = 7.2 Hz, 18H): ^{13}C NMR ($CDCl_3$): δ 196.9, 160.5, 146.6, 129.4, 126.3, 118.7, 118.3, 38.7, 29.7, 23.2, 17.7, 12.5; HRMS (M^+) calcd for $C_{19}H_{30}O_2Si$ 318.2015, found 318.2019

2.2. Ethyl 1-oxo-2-(3-oxobutyl)-6-((triisopropylsilyl)oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (9)

NaH, 55% dispersion in paraffin liquid (5.76 g, 132.00 mmol) was slowly added to a solution of **7** (20 g, 62.85 mmol) and Diethyl carbonate (14.85 g, 125.71 mmol) in Toluene (100 mL) at 0 ºC. The reaction temperature was increased slowly up to 120 ºC, then the reaction mixture stirred for 3 h under argon atmosphere. The resulting mixture was quenched with MeOH and H_2O, and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, methyl vinyl ketone (10.5 mL, 125.71 mmol) and TEA (4.4 mL, 31.43 mmol) was slowly added to to the crude product in MeOH (100 mL). The reaction mixture was placed to 80 ºC and stirred for 12 h. The resulting mixture was quenched with saturated aqueous NaCl solution (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **9** (24.32 g, 52.80 mmol, 80%) as a brown liquid; ^{1}H NMR ($CDCl_3$): δ 7.94 (d, J = 8.8 Hz, 1H), 6.79 (dd, J = 8.8, 2.4 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 4.19 – 4.13 (m, 2H), 2.96 – 2.89 (m, 2H), 2.71 – 2.67 (m, 1H), 2.62 – 2.51 (m, 2H), 2.22 – 2.15 (m, 1H), 2.15 (s, 3H), 2.10 – 2.04 (m, 2H), 1.32 – 1.23 (m, 3H), 1.18 (t, J = 7.0 Hz, 3H) 1.10 (d, J = 7.2 Hz, 18H);

^{13}C NMR ($CDCl_3$): δ 207.9, 194.2, 172.0, 160.8, 145.1, 130.3, 125.5, 118.8, 118.6, 61.2, 56.2, 39.1, 31.5, 29.8, 27.4, 25.8, 17.7, 13.9, 12.6; HRMS (M^+) calcd for $C_{26}H_{40}O_5Si$ 460.2645, found 460.2650

2.3. Ethyl 6-oxo-2-((triisopropylsilyl)oxy)-7,8,9,10-tetrahydro phenanthrene-8a(6*H*)-carboxylate (6)

Piperidine (4.3 mL, 43.41 mmol) and AcOH (2.5 mL, 43.41 mmol) was slowly added to a solution of **9** (20 g, 43.41 mmol) in Toluene (100 mL). The reaction mixture was stirred for 12 h at 120 ºC under argon atmosphere. The resulting mixture was quenched with saturated aqueous NaCl solution (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, imidazole (5.28 g, 77.49 mmol) and TIPSCl (7.17 g, 37.20 mmol) was added to a solution of crude product in DMF (50 mL) at room temperature. The reaction mixture was stirred for 3 h at room temperature. The resulting mixture was quenched with saturated aqueous NaCl solution (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **6** (19.22 g, 43.41 mmol, 75%) as a light brown solid, mp : 60 ºC; ^{1}H NMR ($CDCl_3$): δ 7.65 (d, J = 8.8 Hz, 1H), 6.75 (dd, J = 8.6,

2.6 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.57 (s, 1H), 4.16 – 4.07 (m, 2H), 2.85 – 2.76 (m, 2H), 2.51 – 2.41 (m, 4H), 2.08 – 2.01 (m, 1H), 1.87 – 1.81 (m, 1H), 1.31 – 1.23 (m, 3H), 1.11 – 1.09 (m, 21H); ^{13}C NMR ($CDCl_3$): δ 199.0, 173.1, 158.3, 155.0, 140.1, 127.3, 124.4, 120.2, 119.8, 118.8, 61.3, 47.6, 34.7, 34.5, 34.3, 27.0, 17.8, 14.0, 12.6; HRMS (M^+) calcd for $C_{26}H_{38}O_4Si$ 442.2539, found 442.2543

2.4. Ethyl (6S,8aR)-6-hydroxy-2-((triisopropylsilyl)oxy)-7,8,9,10-tetra-hydrophenanthrene-8a(6H)-carboxylate (10)

$NaBH_4$ (17.11 g, 45.22 mmol), $CeCl_3.7H_2O$ (8.42 g, 22.61 mmol), and MeOH (25 mL) were placed in reaction vessel at -78 ºC, then a diluted solution of **6** (10 g, 22.61 mmol) in DCM (25 mL) was added dropwise. The reaction mixture was stirred for 2 h under argon atmosphere. The resulting mixture was quenched with H_2O (25 mL) and extracted with DCM (2 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (2:1) to give the corresponding product **10** (10.05 g, 22.61 mmol, quant.); ^{1}H NMR ($CDCl_3$): δ 7.48 (d, J = 8.6 Hz, 1H), 6.69 (dd, J = 8.6, 2.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.17 (d, J = 2.0 Hz, 1H), 4.41 (s, 1H), 4.15 – 4.01 (m, 2H), 2.81 – 2.67 (m, 2H), 2.26 – 2.32 (m, 1H), 2.28 – 2.23 (m, 1H), 2.11 – 2.08 (m, 1H), 1.70 – 1.65 (m, 1H), 1.59 – 1.42 (m, 2H), 1.28 – 1.20 (m, 3H), 1.10 – 1.08 (m,

21H); ^{13}C NMR ($CDCl_3$): δ 175.4, 155.7, 137.1, 137.0, 127.4, 125.9, 124.0, 119.6, 118.5, 68.4, 61.0, 47.2, 34.8, 34.1, 29.7, 27.1, 18.1, 14.3, 12.9.

2.5. Ethyl (4bS,6S,8aR)-6-hydroxy-2-((triisopropylsilyl)oxy)-5,6,7,8,9,10-hexahydrophenanthrene-8a(4bH)-carboxylate (11)

[(Cod)Ir(Pcy_3)(py)]PF_6 (91 mg, 0.11 mmol) was slowly added to a solution of **10** (200 mg, 0.45 mmol) in DCM (5 mL), then the reaction was bubbled with hydrogen balloon. The reaction was stirred for 2 h at hydrogen atmosphere. The resulting mixture was concentrated under reduced pressure and purified by silica gel column chromatography using Hexane/EtOAc (2:1) to give the corresponding product **11** (0.14 g, 0.32 mmol, 72%); ^{1}H NMR ($CDCl_3$): δ 7.04 (d, J = 8.4 Hz, 1H), 6.65 (dd, J = 8.4, 2.5 Hz, 1H), 6.56 (d, J = 2.5 Hz, 1H), 4.15 – 4.01 (m, 2H), 3.85 (s, 1H), 3.54 (q, J = 4.6 Hz, 1H), 2.78 (t, J = 6.7 Hz, 2H), 2.12 – 2.07 (m, 1H), 2.02 – 1.91 (m, 3H) 1.84 – 1.73 (m, 4H), 1.61 – 1.55 (m, 2H), 1.27 – 1.07 (m, 24 H); ^{13}C NMR ($CDCl_3$): δ 177.1, 154.0, 135.8, 128.7, 119.8, 118.0, 66.1, 60.6, 45.7, 38.6, 35.9, 29.8, 27.8, 26.4, 18.1, 14.3, 12.9.

2.6. Ethyl (4bS,8aR)-6-oxo-2-((triisopropylsilyl)oxy)-5,6,7,8,9,10-hexahydrophenanthrene-8a(4bH)-carboxylate (12-*cis*)

Pyridinium chlorochromate (105 mg, 0.32 mmol) was added to a solution of **11** (145 mg, 0.49 mmol) in DCM (3 mL) at room temperature. The reaction mixture was stirred for 2 h under argon atmosphere. The resulting mixture was quenched with a water (3 mL) and extracted diethyl ether (3 x 3 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **(*cis*)-12** (132 mg, 0.30 mmol, 92%); ^{1}H NMR ($CDCl_3$): δ 6.95 (d, J = 8.4 Hz, 1H), 6.66 (dd, J = 8.4, 2.6 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 4.15 – 4.08 (m, 2H), 3.67 (t, J = 6.6 Hz, 1H), 2.88 – 2.82 (m, 2H), 2.59 – 2.57 (m, 2H), 2.41 (t, J = 7.0 Hz, 2H), 2.23 – 1.96 (m, 4H), 1.15 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 7.1 Hz, 18H); ^{13}C NMR ($CDCl_3$): δ 210.3, 176.0, 154.6, 135.7, 130.4, 129.0, 119.9, 118.3, 61.1, 46.0, 45.4, 41.1, 37.3, 32.9, 26.9, 26.5, 18.1, 14.3, 12.9.

2.7. Ethyl (4bR,8aR)-6-oxo-2-((triisopropylsilyl)oxy)-5,6,7,8,9,10-hexa-hydrophenanthrene-8a(4bH)-carboxylate (12-*trans*)

10 wt% Pd/C (75 mg) was slowly added to a solution of **6** (1.50 g, 0.45 mmol) in DCM (10 mL), then the reaction was bubbled with hydrogen balloon. The reaction mixture was stirred for 3 h, then filtered through a pad of Celite with a washing solvent of DCM (3 x 5 mL). The combined organic mixture was concentrated under reduced pressure. Without further purification, Pyridinium chlorochromate (1.10 g, 5.09 mmol) was added to a solution of crude product in DCM (5 mL) at room temperature. The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was quenched with a water (3 mL) and extracted diethyl ether (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **(*trans*)-12** (0.99 g, 2.24 mmol, 66%); ^{1}H NMR ($CDCl_3$): δ 6.93 (d, J = 8.5 Hz, 1H), 6.67 (dd, J = 2.6 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 4.09 – 4.04 (m, 2H), 3.09 – 2.99 (m, 3H), 2.85 – 2.81 (m, 2H), 2.49 – 2.36 (m, 4H), 1.80 – 1.71 (m, 2H), 1.27 – 1.18 (m, 3H), 1.11 – 1.08 (m, 21H); ^{13}C NMR ($CDCl_3$): δ 210.9, 174.2, 154.4, 136.1, 130.6, 125.0, 120.0, 117.8, 60.7, 46.6, 43.8, 42.4, 38.9, 36.1, 34.6, 27.2, 18.2, 14.3, 12.9.

2.8. Ethyl 5-bromo-6-oxo-2-((triisopropylsilyl)oxy)-7,8,9,10-tetrahydro-phenanthrene-8a(6*H*)-carboxylate (5)

Oxone (0.49 g, 0.79 mmol), 2N HBr (1.13 mL) and water (25 mL) was added to a solution of **6** (0.50 g, 1.13 mmol) in DCM (25 mL). The reaction mixture was stirred vigorously for 2 h under argon atmosphere and TEA (0.47 mL, 3.39 mmol) was added dropwise. The reaction mixture was stirred for additional 2 h at room temperature. The resulting mixture was extracted with DCM (3 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (8:1) to give the corresponding product **5** (0.58 g, 1.11 mmol, 98%) as a light yellow solid, mp : 95 ^{o}C; IR 2945, 2867, 1726, 1686, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.98 (d, J = 8.8 Hz, 1H), 6.75 (dd, J = 8.4, 2.4 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 4.08 – 3.95 (m, 2H), 2.88 – 2.79 (m, 2H), 2.73 – 2.69 (m, 2H), 2.43 – 2.34 (m, 2H), 2.10 – 1.96 (m, 2H), 1.31 – 1.23 (m, 3H), 1.10 (d, J = 7.2 Hz, 18H) 0.99 (t, J = 7.0 Hz, 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

2.9. Ethyl 6-oxo-2-((triisopropylsilyl)oxy)-5-vinyl-7,8,9,10-tetrahydroph-enanthrene-8a(6*H*)-carboxylate (13)

Vinyl tributyltin (3.65 g, 11.50 mmol) was added dropwise to a solution of **5** (4.0 g, 7.67 mmol) and $Pd(PPh_3)_2Cl_2$ (0.54 g, 0.77 mmol) in 1,4-dioxane (30 mL). The reaction mixture was stirred for 2 h at 100 ºC. The resulting mixture was quenched with saturated aqueous NaCl solution, and extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (8:1) to give the corresponding product **13** (3.22 g, 6.87 mmol, 90%) as a yellow solid, mp : 53 ºC; ^{1}H NMR ($CDCl_3$): δ 7.48 (d, J = 8.4 Hz, 1H), 6.67 (dd, J = 8.4, 2.4 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.43 (dd, J = 17.6, 11.6 Hz, 1H), 5.94 (dd, J = 11.6, 2.4 Hz, 1H), 5.40 (dd, J = 11.6, 2.4 Hz, 1H), 4.08 – 3.93 (m, 2H), 2.96 – 2.83 (m, 3H), 2.65 – 2.60 (m, 1H), 2.48 – 2.43 (m, 2H), 2.38 – 2.34 (m, 1H), 1.98 – 1.90 (m, 2H), 1.31 – 1.28 (m, 3H), 1.09 (d, J = 7.2 Hz, 18H) 0.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 198.0, 173.5, 157.5, 153.2, 140.5, 133.8, 131.8, 129.2, 126.8, 120.7, 119.2, 117.1, 61.1, 49.1, 35.3, 35.3, 32.2, 26.6, 17.8, 13.9, 12.6; HRMS (M^+) calcd for $C_{28}H_{40}O_4Si$ 468.2696, found 468.2696

2.10. Ethyl (E)-5-(2-nitrovinyl)-6-oxo-2-((triisopropylsilyl) oxy)-7,8,9,10-tetrahydrophenanthrene-8a(6*H*)-carboxylate (4)

$AgNO_2$ (1.78 mL, 14.94 mmol) and TEMPO (0.47 g, 2.99 mmol) was added to a solution of **13** (3.5 g, 7.47 mmol) in 1,4-dioxane (30 mL) at room temperature. The reaction mixture was stirred for 3 h at 90 ^{o}C with O_2 ballon attached. The resulting mixture was concentrated with a rotary evaporator. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **4** (3.37 g, 6.56 mmol, 88%) as a yellow liquid; ^{1}H NMR ($CDCl_3$): δ 8.36 (d, J = 13.2 Hz, 1H), 7.71 (d, J = 13.2 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 9.2, 2.6 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 4.12 – 3.97 (m, 2H), 3.01 – 2.91 (m, 2H), 2.65 – 2.54 (m, 3H), 2.43 – 2.39 (m, 1H), 2.06 – 1.97 (m, 2H), 1.33 – 1.25 (m, 3H) 1.11 (d, J = 7.2 Hz, 18H), 0.97 (t, J = 7.0, 3H); ^{13}C NMR ($CDCl_3$): δ 195.4, 171.8, 164.2, 159.5, 141.7, 140.3, 134.2, 132.9, 125.6, 122.9, 119.6, 117.6, 61.0, 49.6, 34.7, 34.3, 31.2, 26.0, 17.4, 13.4, 12.2; HRMS (M^+) calcd for $C_{28}H_{39}NO_6Si$ 513.2547 found 513.2556

2.11. Ethyl 5-(2-nitroethyl)-6-oxo-2-((triisopropylsilyl)oxy)-7,8, 9,10-tetrahydrophenanthrene-8a(6*H*)-carboxylate (14)

$NaBH_4$ (0.50 g, 13.12 mmol) was slowly added to a solution of **4** (3.37 g, 6.56 mmol) in MeOH (15 mL) and DCM (20 mL) under argon atmosphere. The reaction mixture was stirred for 2 h at room temperature. The resulting mixture quenched with MeOH and saturated $NaHCO_3$ aqueous solution (30 mL), and extracted with EtOAc (3 x 50 mL) and aqueous 1 N HCl solution (5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, PCC (2.83 g, 13.12 mmol) was added to a solution of the crude product in DCM (25 mL). The reaction mixture was stirred for 3 h at 70 ºC. The resulting mixture was quenched with H_2O (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **14** (2.90 g, 5.62 mmol, 86%) as a yellow solid, mp : 83 ºC; ^{1}H NMR ($CDCl_3$): δ 7.13 (d, J = 8.4 Hz, 1H), 6.74 (dd, J = 8.4, 2.4 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 4.59 – 4.57 (m, 1H) 4.46 – 4.44 (m, 1H), 4.06 – 3.94 (m, 2H), 3.39 – 3.36 (m, 1H), 3.20 – 3.15 (m, 1H), 2.78 – 2.70 (m, 2H), 2.57 – 2.49 (m, 2H), 2.40 – 2.37 (m, 1H), 2.29 – 2.25 (m, 1H), 2.05 – 1.94 (m, 1H), 1.93 – 1.89 (m, 1H), 1.30 – 1.21 (m, 3H), 1.10 (d, J = 7.2 Hz, 18H), 1.01 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 198.3, 173.3, 157.6, 156.4,

141.2, 130.3, 128.3, 126.6, 119.2, 117.7, 74.4, 61.1, 49.4, 35.3, 34.4, 31.9, 26.7, 26.0, 17.8, 13.8, 12.5; HRMS (M^+) calcd for $C_{28}H_{41}NO_6Si$ 515.2703 found 515.2702

2.12. Ethyl 2-hydroxy-5-(2-nitroethyl)-6-oxo-7,8,9,10-tetra hydrophenanthrene-8a(6*H*)-carboxylate (3)

1M TBAF solution in THF (6.18 mL) was added dropwise to a solution of **14** (2.9 g, 5.62 mmol) in distilled THF (20 mL) at 0 ºC under argon atmosphere for 1 h. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (20 mL) and extracted with EtOAc (3 x 20 mL) and aqueous 1N HCl solution (3 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (2:1) to give the corresponding product **3** (1.74 g, 4.84 mmol, 86%) as a light yellow solid, mp : 135 ºC; ^{1}H NMR ($CDCl_3$): δ 7.15 (d, J = 8.4 Hz, 1H), 6.68 (dd, J = 8.4, 2.8 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.38 (s, 1H), 4.63 - 4.58 (m, 1H), 4.48 – 4.46 (m, 1H), 4.07 – 4.01 (m, 2H), 3.41 – 3.37 (m, 1H), 3.20 – 3.18 (m, 1H), 2.78 – 2.71 (m, 2H), 2.58 – 2.52 (m, 2H), 2.41 – 2.37 (m, 1H), 2.30 – 2.27 (m, 1H), 2.04 – 1.94 (m, 1H), 1.93 – 1.91 (m, 1H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 198.8, 173.7, 157.6, 156.8, 142.0, 130.8, 128.3, 126.0, 114.7, 113.4, 74.5, 61.5, 49.6, 35.3, 34.4, 31.9, 26.7, 26.1, 13.9; HRMS (M^+) calcd for $C_{19}H_{21}NO_6$ 359.1369 found 359.1364

2.13. Ethyl 7-hydroxy-9-nitro-1-oxo-2,3,4,5-tetrahydropyrene -3a(1*H*)-carboxylate (15)

1.0 M aqueous CsOH (0.67 mL, 0.67 mmol) was added dropwise to a solution of **3** (30 mg, 0.084 mmol) in chloroform (3 mL) at 0 ºC, followed by addition of $K_3Fe(CN)_6$ (0.11 g, 0.33 mmol) in H_2O (3 mL). The reaction mixture was stirred for 1 h, then diluted with *i*-PrOH (5 mL), and filtered through a pad of celite with a washing solvent of *i*-PrOH (3 x 3 mL) and acetone (3 x 3 mL) sequentially. The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (1:1) to give the corresponding product **15** (8.90 mg, 0.025 mmol, 30%) as a yellow solid, mp: 265 ºC; ^{1}H NMR (Acetone-d_6) δ 8.63 (s, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.23 (s, 1H), 4.21 – 4.13 (m, 2H) 3.79 (s, 1H), 3.26 – 3.20 (m, 1H), 3.16 – 3.07 (m, 1H), 2.79 –2.56 (m, 5H), 2.43 – 2.39 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (Acetone-d_6) δ 195.5, 173.8, 161.2, 148.3, 146.4, 141.8, 130.4, 126.1, 125.9, 122.1, 120.2, 105.0, 62.7, 49.6, 35.9, 35.2, 34.4, 28.7, 14.6; HRMS (M^+) calcd for $C_{19}H_{17}NO_6$ 355.1056 found 355.1051

2.14. (3S,10aR)-4-((E)-2-nitrovinyl)-7-((triisopropylsilyl)oxy) -2,3,9,10-tetrahydro-1H-3,10a-(epoxymethano)phenanthren-11-one (16)

$NaBH_4$ (221 mg, 5.85 mmol), $CeCl_3.7H_2O$ (4.54 g, 12.18 mmol), and MeOH (12 mL) were placed in reaction vessel at -78 ºC, then a diluted solution of **4** (2.50 g, 4.87 mmol) in DCM (12 mL) was added dropwise. The reaction mixture was stirred for 2 h under argon atmosphere. The resulting mixture was quenched with H_2O (25 mL) and extracted with DCM (3 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hexane : EtOAc = 2 : 1) to give the corresponding products (1.93 g, 3.75 mmol, 77%). *p*-TsOH (111 mg, 0.58 mmol) was added to a solution of the obtained product (1.50 g, 2.91 mmol) in toluene (15 mL). The reaction mixture was stirred for 2 h at 100 ºC. The resulting mixture was quenched with H_2O (10 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **16** (0.75 g, 1.60 mmol, 55%); ^{1}H NMR ($CDCl_3$): δ 8.14 (d, J = 13.5 Hz, 1H), 7.4 (d, J = 13.5 Hz, 1H), 7.26 (m, 1H), 6.85 (dd, J = 8.4, 2.5 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1 H), 5.44 (d, J = 2.5 Hz, 1H), 2.78 – 2.71 (m, 2H), 2.59 – 2.53 (m, 1H), 2.41 - 2.35 (m, 1H), 1.93 – 1.74 (m, 3H), 1.63 – 1.56 (m, 1H), 1.34 – 1.26 (m, 3H), 1.13 (d, J = 7.3 Hz, 18H).

2.15. (3S,10aR)-4-(2-nitroethyl)-7-((triisopropylsilyl)oxy)-2,3,9,10-tetra-hydro-1H-3,10a-(epoxymethano)phenanthren-11-one (17)

$NaBH_4$ (62 mg, 1.65 mmol) was slowly added to a solution of **16** (772 mg, 1.65 mmol) in EtOH (8 mL) under argon atmosphere. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture quenched with H_2O (8 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **17** (450 mg, 0.95 mmol, 58%); ^{1}H NMR ($CDCl_3$): δ 7.19 (d, J = 8.2 Hz, 1H), 6.78 – 6.75 (m, 2H), 5.11 (dd, J = 3.6, 1.4 Hz, 1H), 4.63 – 4.58 (m, 2H), 3.33 – 3.24 (m, 2H), 2.74 – 2.68 (m, 2H), 2.49 – 2.45 (m, 1H), 2.29 – 2.26 (m, 1H), 1.84 – 1.73 (m, 2H), 1.68 – 1.60 (m, 1H), 1.52 – 1.45 (m, 1H), 1.30 – 1.24 (m, 3H), 1.11 (d, J = 7.3 Hz, 18H); ^{13}C NMR ($CDCl_3$): δ 175.6, 156.6, 142.6, 138.2, 128.4, 127.8, 122.9, 120.0, 118.1, 78.0, 73.4, 47.8, 29.5, 28.5, 27.7, 26.6, 26.5, 18.1, 12.8.

2.16. (3S,10aR)-7-hydroxy-4-(2-nitroethyl)-2,3,9,10-tetrahydro-1H-3,10a-(epoxymethano)phenanthren-11-one (18)

1M TBAF solution in THF (330 µL) was added dropwise to a solution of **17** (140 mg, 0.28 mmol) in distilled THF (2 mL) at 0 ºC under argon atmosphere for 2 h. The reaction mixture was quenched with H_2O (2 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (1:1) to give the corresponding product **18** (42 mg, 0.13 mmol, 45%); ^{1}H NMR ($CDCl_3$): δ 7.19 (d, J = 8.4 Hz, 1H), 6.76 – 6.70 (m, 2H), 5.12 (d, J = 2.4 Hz, 1H), 4.64 – 4.53 (m, 2H), 3.35 – 3.19 (m, 2H), 2.75 – 2.59 (m, 2H), 2.49 – 2.43 (m, 1H), 2.31 – 2.25 (m, 1H), 1.78 – 1.72 (m, 2H), 1.66 – 1.59 (m, 1H), 1.51 – 1.44 (m, 1H), 1.29 – 1.25 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 176.5, 156.8, 142.8, 138.1, 128.7, 127.6, 122.2, 115.7, 113.9, 78.3, 73.3, 47.9, 29.4, 28.5, 27.6, 26.6, 26.5.

2.17. Ethyl 2-(2-methyl-3-oxobutyl)-1-oxo-6-((triisopropyl silyl)oxy)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (20)

NaH, 55% dispersion in paraffin liquid (1.44 g, 33.00 mmol) was slowly added to a solution of **9** (5.00 g, 15.71 mmol) and diethyl carbonate (3.71 g, 31.43 mmol) in toluene (30 mL) at 0 ºC. The reaction temperature was increased slowly up to 120 ºC, then the reaction mixture stirred for 3 h under argon atmosphere. The resulting mixture was quenched with MeOH and H_2O, and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, methyl vinyl ketone (2.6 mL, 31.43 mmol) and TEA (1.1 mL, 7.86 mmol) was slowly added to the crude product in MeOH (30 mL). The reaction mixture was placed to 80 ºC and stirred for 12 h. The resulting mixture was quenched with saturated aqueous NaCl solution (30 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **20** (5.07 g, 10.69 mmol, 68%)

2.18. Ethyl (7R,8aR)-7-methyl-6-oxo-2-((triisopropylsilyl) oxy)-7,8,9,10-tetrahydrophenanthrene-8a(6H)-carboxylate (21)

Piperidine (1.1 mL, 10.69 mmol) and AcOH (0.6 mL, 10.69 mmol) was slowly added to a solution of **20** (5.07 g, 10.69 mmol) in toluene (30 mL). The reaction mixture was stirred for 12 h at 120 ºC under argon atmosphere. The resulting mixture was quenched with saturated aqueous NaCl solution (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Without further purification, imidazole (1.30 g, 19.07 mmol) and TIPSCl (1.77 g, 9.16 mmol) was added to a solution of crude product in DMF (20 mL) at room temperature. The reaction mixture was stirred for 3 h at room temperature. The resulting mixture was quenched with saturated aqueous NaCl solution (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **21** (4.10 g, 8.98 mmol, 84%); ^{1}H NMR ($CDCl_3$): δ 7.64 (d, J = 8.8 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 6.62 (s, 1H), 6.53 (s, 1H), 4.18 – 4.05 (m, 2H), 2.88 – 2.75 (m, 2H), 2.48 – 2.41 (m, 3H), 1.86 – 1.77 (m, 2H), 1.30 – 1.21 (m, 3H), 1.17 (d, J = 6.4, 3H), 1.10 (d, J = 7.2 Hz, 21 H).

2.19. Ethyl (6S,7R,8aR)-6-hydroxy-7-methyl-2-((triisopropyl silyl)oxy)-7,8,9,10-tetrahydrophenanthrene-8a(6H)-carboxylate (22)

$NaBH_4$ (6.14 g, 16.22 mmol), $CeCl_3.7H_2O$ (3.02 g, 8.11 mmol), and MeOH (20 mL) were placed in reaction vessel at -78 ^oC, then a diluted solution of **4** (3.70 g, 8.11 mmol) in DCM (20 mL) was added dropwise. The reaction mixture was stirred for 2 h under argon atmosphere. The resulting mixture was quenched with H_2O (50 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (2:1) to give the corresponding product **22** (3.57 g, 7.79 mmol, 96%); ^1H NMR ($CDCl_3$): δ 7.48 (d, J = 8.7 Hz, 1H), 6.68 (dd, J = 8.6, 2.5 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.14 (d, J = 2.4 Hz, 1H), 4.16 – 4.07 (m, 1H), 4.04 – 3.96 (m, 1H), 3.90 (t, J = 7.3 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.35 – 2.31 (m, 1H), 2.12 (dd, J = 13.4, 2.6 Hz, 1H), 1.86 – 1.84 (m, 1H), 1.68 – 1.54 (m, 2H), 1.39 (t, J = 13.3 Hz, 1H), 1.28 – 1.19 (m, 6H), 1.09 – 1.04 (m, 21H); ^{13}C NMR ($CDCl_3$): δ 175.5, 155.7, 137.0, 136.6, 127.2, 125.9, 123.9, 119.6, 118.4, 74.9, 60.9, 48.0, 42.5, 34.9, 34.9, 27.1, 18.7, 18.1, 14.2, 12.9.

2.20. Ethyl (4bS,6R,7R,8aR)-6-hydroxy-7-methyl-2-((triiso-propylsilyl)-oxy)-5,6,7,8,9,10-hexahydrophenanthrene-8a(4bH)-carboxylate (23)

[(Cod)Ir(Pcy_3)(py)]PF_6 (141 mg, 0.17 mmol) was slowly added to a solution of **22** (320 mg, 0.70 mmol) in DCM (5 mL), then the reaction was bubbled with hydrogen balloon. The reaction was stirred for 2 h at hydrogen atmosphere. The resulting mixture was concentrated under reduced pressure and purified by silica gel column chromatography using Hexane/EtOAc (2:1) to give the corresponding product **23** (257 mg, 0.56 mmol, 80%); ^{1}H NMR ($CDCl_3$): δ 7.26 (d, J = 8.6 Hz, 1H), 6.71 (dd, J = 8.5, 2.6 Hz, 1H), 6.60 (d, J = 2.5 Hz, 1H), 4.21 (q, J = 7.1 H 2H), 3.58 (s, 1H), 3.01 (t, J = 10.5 Hz, 1H), 2.89 – 2.80 (m, 1H), 2.71 – 2.65 (m, 1H), 2.57 – 2.52 (m, 1H), 1.94 – 1.88 (m, 2H), 1.83 – 1.78 (m, 1H), 1.74 – 1.67 (m, 1H), 1.56 – 1.46 (m, 2 H), 1.28 – 1.19 (m, 6H), 1.10 (d, J = 7.0 Hz, 18H); ^{13}C NMR ($CDCl_3$): δ 177.3, 171.3, 153.8, 136.3, 129.7, 127.2, 119.9, 118.3, 71.7, 60.8, 60.6, 46.8, 38.3, 37.6, 36.2, 34.2, 32.5, 26.0, 21.2, 18.5, 18.1, 14.4, 14.4, 12.8.

2.21. Ethyl (4bS,7R,8aR)-7-methyl-6-oxo-2-((triisopropyl silyl)oxy)-5,6,7,8,9,10-hexahydrophenanthrene-8a(4bH)-carboxylate (24)

PCC (181 mg, 0.84 mmol) was added to a solution of **23** (257 mg, 0.56 mmol) in DCM (3 mL) at room temperature. The reaction mixture was stirred for 2 h under argon atmosphere. The resulting mixture was quenched with a water (3 mL) and extracted diethyl ether (3 x 3 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **24** (243 mg, 0.53 mmol, 95%); ^{1}H NMR ($CDCl_3$): δ 7.10 (d, *J* = 8.5 Hz, 1H), 6.69 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 4.26 (t, *J* = 7.1 Hz, 2H), 3.84 (t, *J* = 5.3 Hz, 1H), 2.90 – 2.84 (m, 1H), 2.79 – 2.70 (m, 3H), 2.62 – 2.52 (m, 1H), 2.29 – 2.26 (m, 1H), 2.21 – 2.14 (m, 1H), 1.81 – 1.75 (m, 1H), 1.46 (t, *J* = 13.5 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.27 – 1.18 (m, 3H), 1.08 (d, *J* = 7.2 Hz, 18H), 0.93 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): *δ* 211.9, 176.7, 154.4, 136.6, 128.8, 128.5, 119.6, 118.2, 61.2, 46.3, 43.0, 41.3, 39.7, 38.2, 32.0, 26.5, 18.1, 14.4, 14.3, 12.8.

2.22. Ethyl (4bS,7R,8aR)-7-methyl-2-((triisopropylsilyl)oxy)-6-((trimethylsilyl)oxy)-7,8,9,10-tetrahydrophenanthrene-8a(4bH)-carboxylate (25)

LHMDS 1M solution in THF (21.3 mL, 21.30 mmol) was added dropwise to a solution of **24** (1.95 g, 4.26 mmol) and TMSCl (1.1 mL, 8.52 mmol) in THF (20 mL) at 0 ºC. Reaction mixture was stirred for 5 minutes under argon atmosphere. The resulting mixture was quenched with a deionized water (20 mL) and extracted diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (16:1) to give the corresponding product **25** (1.97 g, 3.71 mmol, 87%); ^{1}H NMR ($CDCl_3$): δ 7.08 (d, *J* = 8.4 Hz, 1H), 6.68 (dd, *J* = 8.4, 2.5 Hz, 1H) 6.59 (d, *J* = 2.4 Hz, 1H), 5.32 (dd, *J* = 6.1, 1.2 Hz, 1H), 4.19 – 4.14 (m, 2H), 3.9 (d, *J* = 5.9 Hz, 1H), 2.78 – 2.63 (m, 2H), 2.37 – 2.31 (m, 1H), 2.07 – 2.00 (m, 2H), 1.68 – 1.62 (m, 1H), 1.28 – 1.20 (m, 6H), 1.09 (d, *J* = 7.2 Hz, 18H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR ($CDCl_3$): *δ* 177.1, 154.2, 153.7, 136.3, 133.0, 128.8, 188.9, 177.9, 106.5, 60.6, 45.5, 38.2, 35.7, 33.5, 32.3, 26.6, 18.7, 18.1, 14.4, 12.8, 0.5.

2.23. Ethyl (4bS,7R,8aR)-7-methyl-6-oxo-2-((triisopropylsilyl) oxy)-5-vinyl-5,6,7,8,9,10-hexahydrophenanthrene-8a(4bH)-carboxylate (26)

$Sc(OTf)_3$ (618 mg, 0.99 mmol) was added to a solution of **25** (1.06 g, 1.99 mmol) and $PhSeCH_2CHO$ (556 μL, 2.40 mmol) in THF (8 mL) and H_2O (2 mL). The reaction mixture was vigorously stirred for 2 h under argon atmosphere. The resulting mixture was quenched with H_2O (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hexane : EtOAc = 4 : 1) to give the corresponding products (0.98 g, 1.49 mmol, 75%). MsCl (347 μL, 4.48 mmol) and TEA (833 μL, 5.97 mmol) was added to a solution of the obtained product (0.98 g, 1.49 mmol) in DCM (10 mL). The reaction mixture was stirred for 30 minutes at room temperature. The resulting mixture was quenched with H_2O (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (8:1) to give the corresponding product **26** (540 mg, 1.11 mmol, 56%); ^{1}H NMR ($CDCl_3$): δ 6.94 (d, J = 8.3 Hz, 1H), 6.64 – 6.59 (m, 2H), 5.86 – 5.77 (m, 1H), 5.10 (dd, J = 11.2, 1.0 Hz, 1H), 4.85 (dd, J = 17.1, 1.0 Hz, 1 H), 4.15 – 4.05 (m, 2H), 3.75 (d, J = 8.0 Hz, 1H), 3.23 (t, J = 7.8 Hz, 1H), 2.86 – 2.72 (m, 3H), 2.35 (dd, J = 13.9, 6.6 Hz, 1H), 2.17 – 2.11 (m, 1H), 1.75 – 1.68 (m, 1H),

1.48 (t, J = 13.9 Hz, 1H), 1.26 – 1.15 (m, 6H), 1.08 – 1.03 (m, 21H).

2.24. Ethyl (4bS,7R,8aR)-5-bromo-7-methyl-6-oxo-2-((triiso propylsilyl)-oxy)-5,6,7,8,9,10-hexahydrophenanthrene-8a(4bH)-carboxylate (28)

NBS (81 mg, 0.45 mmol) and Sodium bicarbonate (38 mg, 0.45 mmol) was added to a solution of **25** (200 mg, 0.38 mmol) in THF (2 mL) at -78 ºC. The reaction mixture was stirred for 2 h under argon atmosphere. The resulting mixture was quenched with a water (3 mL) and extracted diethyl ether (3 x 3 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using Hexane/EtOAc (4:1) to give the corresponding product **28** (123 mg, 0.23 mmol, 61%); ^{1}H NMR ($CDCl_3$): δ 7.16 (d, J = 8.6 Hz, 1H), 6.71 (dd, J = 8.5, 2.6 Hz, 1H), 6.62 (d, J = 2.5 Hz, 1H), 4.72 (d, J = 4.1 Hz, 2H), 4.30 – 4.18 (m, 3H), 3.67 – 3.58 (m, 1H), 2.76 (t, J = 6.7 Hz, 2H), 2.39 – 2.33 (m, 1H), 2.20 – 2.13 (m, 1H), 1.64 – 1.57 (m, 1H), 1.42 (t, J = 13.3 Hz, 1H), 1.28 – 1.18 (m, 6H), 1.08 (d, J = 7.2 Hz, 18H), 1.03 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 206.3, 176.1, 155.1, 137.2, 129.0, 126.7, 120.1, 118.2, 61.3, 51.8, 48.4, 44.1, 38.5, 36.0, 32.6, 26.2, 18.1, 14.3, 14.1, 12.8.

Chapter 2.

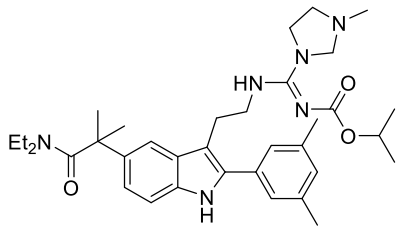
Regioselective synthesis of 2,3-disubstituted indoles

Introduction

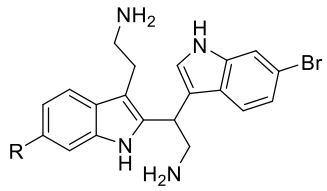
1. Biological activity of indoles

The indole ring motif accounts for the large class of alkaloids and represents undoubtedly one of the most ubiquitous and important heterocycles in nature. The indole alkaloids possess a wide range of structural complexity and diversity, as well as interesting biological activities such as anti-depressant,[36] anti-diabetic,[37] anti-HIV,[38] anti-tubercular,[39] and anti-oxidant.[40] In particular, 2,3-disubstituted indole derivatives are an important class of compounds, which exhibit a wide range of biological activities and they widely used in medicinal chemistry **(Figure 9)**. For example, tryptamine derivative show good affinity for the gonadotropin-releasing hormone (GnRH-antagonist).[41] The (±)Gelliusine E and F isolated from the marine sources exhibit the inhibition of specific ligand binding at neuropeptide Y receptor and somatostatin receptor sites.[42] Indomethacin is also a NSAID with

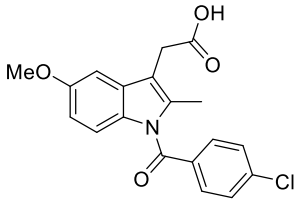
very effective antipyretic, analgesic, and anti-inflammatory activity.[43] Final Ngouniensine found in numerous naturally have proven pharmacological effects as anti-tumour agents, CDK inhibitors, and GSK inhibitors.[44] Accrordingly the synthesis of 2,3-disubstituted indoles in which various substituents are introduced is becoming very important.



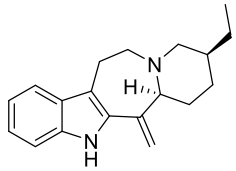
Tryptamine derivative
GnRH-antagonist



R = OH, (±)gelliusine F
R = Br, (±)gelliusine E



Indomethacin

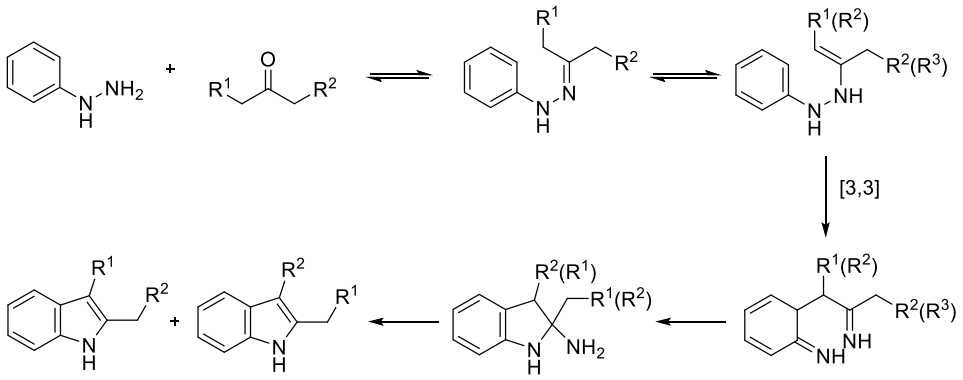


Indole-fused polycycle
Ngouniensine

Figure 9. Representative biologically active 2,3-disubstituted indoles

2. Regioselectivity issue in the classical indole synthesis.

Owing to interesting biological activity of 2,3-disubstittued indoles, the continued importance of the indole to organic synthesis and pharmaceutical chemistry has spurred the development of common synthetic methods. Among indole syntheses, the Fischer indole synthesis, discovered in 1883, is most well known process. The reaction is an important reaction to obtain indoles from hydrazine and an aldehyde or ketone under acidic conditions **(Scheme 14)**.[45] However, two major drawbacks usually identified with the Fischer process are: (1) unsymmetrical ketones give a mixture of isomeric products, depending upon the structure of the hydrazine[46] and (2) harsh reaction conditions are required, typically refluxing in concentrated acid. Accordingly, we have developed a reaction using *o*-haloaniline, which is a condition that can regioselectively synthesize the indoles under much milder conditions than the classical Fisher indole synthesis.



Scheme 14. Regioselectivity issue in the classical Fischer indole synthesis.

3. Indole syntheses from the *o*-haloanilines

o-Haloanilines has been used for indole syntheses, as exemplified by the Castro and Larock methods for the preparation of 2,3-disubstituted indoles, respectively.[47,48] Impressive advances in cross-coupling reactions with the *o*-haloanilines provide easy access to *o*-alkynyl and *o*-alkenyl aniline derivatives that serve as versatile precursors to disubstituted indoles.[49]

3.1. Aminocyclization of *o*-alkynylanilines

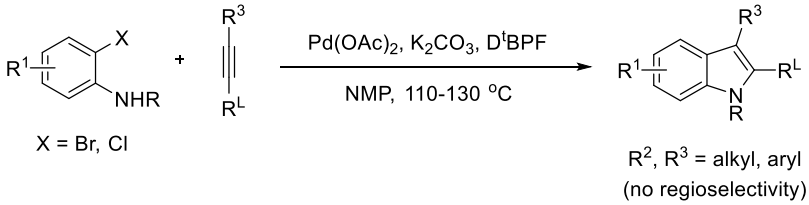
The palladium-catalyzed reaction between *o*-iodoaniline derivatives and internal alkynes for the preparation of 2,3-disubstituted indoles is referred to as the Larock reaction **(Scheme 15)**.[50] The Larock is an attractive method for the preparation of complex indoles in one-pot operation. The reaction generally provides a range of indole targets, since both starting materials possess considerable functionality.

However, consecutive reaction devised by Larock group gave rise to a mixed product of complementary regioisomers not separated each other. Consequently, the stepwise reaction was exploited from the following researcher. Kondo *et al*. was using Sonogashira reaction for the C-C cross-coupling reaction of 2-haloanilines to achieve the 2-alkynylanilines.[51] They utilized the alkoxide-mediated cyclization of 2-alkynylanilines as a sequential step for the preparation of a number of indole derivatives.

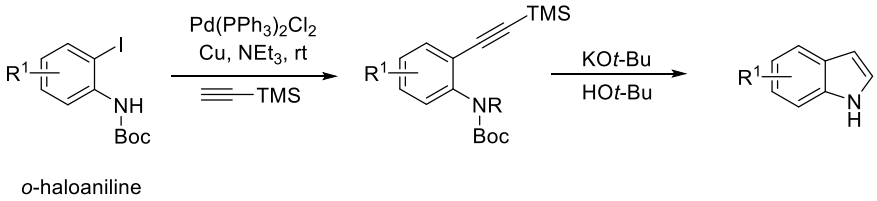
Castro *et al*. also developed indole synthesis from the two pathway. One is the cyclization of *o*-iodoaniline derivatives with cuprous acetylides.[52] Another is the cyclization of 2-alkynylanilines with copper(I) iodide. While reactions employing cuprous acetylides are rare and not amenable to scale up, copper promoted cyclizations of 2-alkynylanilines have received considerable attention as an attractive method for the construction of indoles.

Senanayake *et al*. suggested a practical and economical one-pot process for synthesis of 2,3-disubstituted indoles based on Cacchi original protocol.[53] This Pd-catalyzed domino indolization procedure allows rapid access to a variety of 2,3-disubstituted indoles regiospecifically under fairly mild conditions.

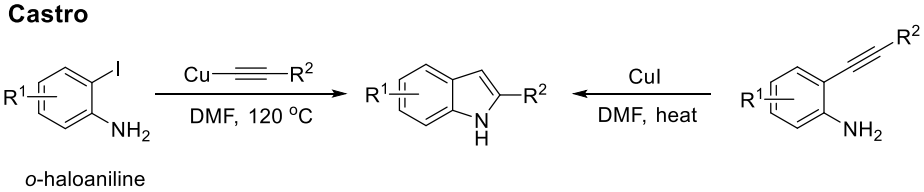
Larock



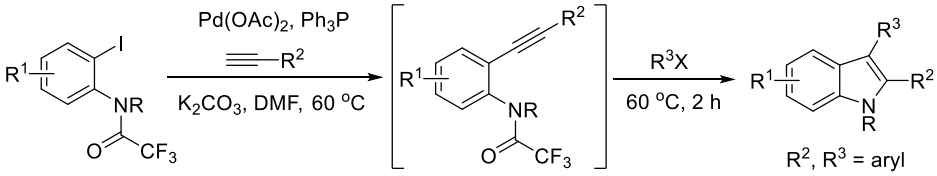
Kondo and Sakamoto



Castro



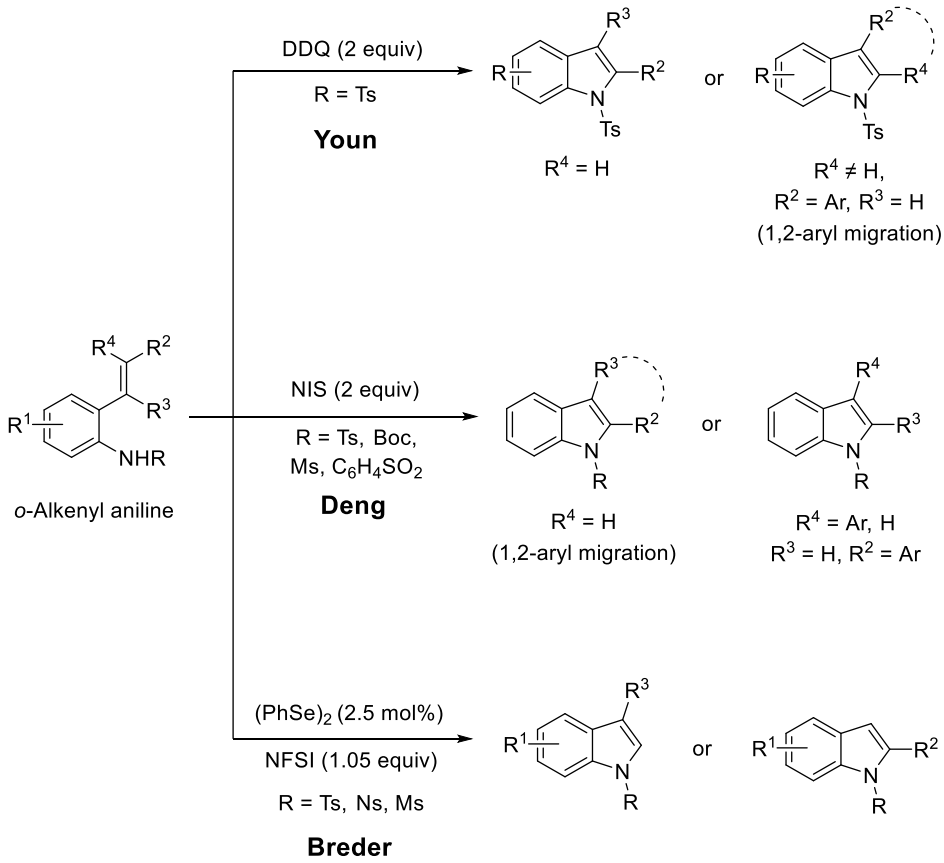
Senanayake



Scheme 15. Aminocyclization of *o*-alkynyl anilines

3.2. Aminocyclization of *o*-alkenyl anilines

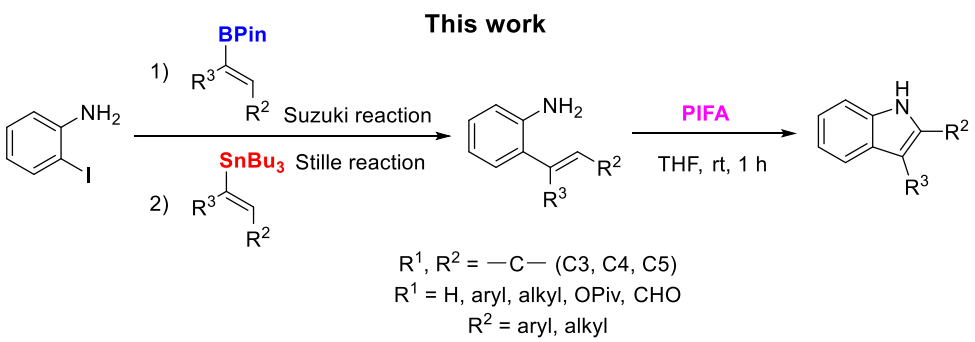
Despite the great progress on the development of indole syntheses derived from *o*-alkynylanilines, new synthetic methods were needed for the formation of 2,3-disubstituted indoles, which possess a wide range of structural complexity and diversity. More recently aminocyclization of *o*-alkenyl anilines was prevalently investigated for the formation of 2,3-disubstituted indoles. The methodology is efficient, simple to perform, which involve the use of metal-free reagents such as DDQ,[54] NIS,[55] and $(PhSe)_2$.[56] However, migration of substituents (i.e., the switch between R^2 and R^3) during the reaction was unavoidable issues and an *N*-protecting group would be crucial to the success of the reactions **(Scheme 16)**.[57,58] Moreover, the introduction of diverse functionality at C2 and C3 still remains challenge.



Scheme 16. Aminocyclization of *o*-alkenyl anilines

3.3. PIFA mediated free *N*-H indole synthesis of *o*-alkenyl anilines

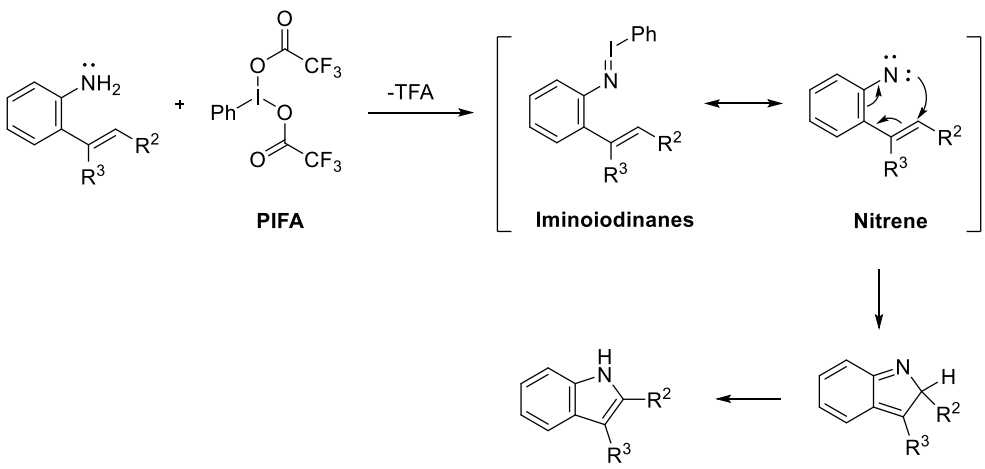
Conspicuously missing from the previous literature was an experimentally expedient, yet conceptually attractive approach involving electrocyclization of *o*-alkenyl nitrene intermediates, leading to free *N*–H indoles without requiring *N*-protecting groups **(Scheme 17)**. We report herein a successful implementation of this strategy which is amenable to the preparation of indoles with all substitutions. We first investigated Suzuki and Stille coupling reaction of *o*-iodoaniline with alkenyl reagents that afforded the corresponding *o*-alkenyl anilines. Among *o*-haloanilines, iodoaniline shows a high yield with a shorter reaction time even in the presence of a small catalyst loading in the cross-coupling reaction.[59] That next undergo the simple and efficient PIFA mediated intramolecular aminocyclization, which leads to the regioselective 2,3-disubstituted indoles. We expect our recommendation would be extended for the development of highly functionalized indoles and their complementary regioisomers.



Scheme 17. PIFA mediated free *N*-H indole synthesis of *o*-alkenyl anilines

4. Plausible mechanism of PIFA mediated aminocyclization

A plausible mechanism of direct PIFA mediated intramolecular aminocyclization is suggested in **Scheme 18** through the nitrene formation. The reaction initiated from the formation of iminoiodinane provided by the reaction of nucleophilic aniline and electrophilic iodine. This would spontaneously decompose to the nitrene as a carbene counterpart. The nitrene intermediate triggers intramolecular aminocyclization with an alkene, providing the indole derivatives. The aminocyclization of *o*-alkenyl anilines gave a chance to produce regioselective 2,3-disubstituted indoles.



Scheme 18. Intramolecular aminocyclization via nitrene intermediate

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Result and Discussion

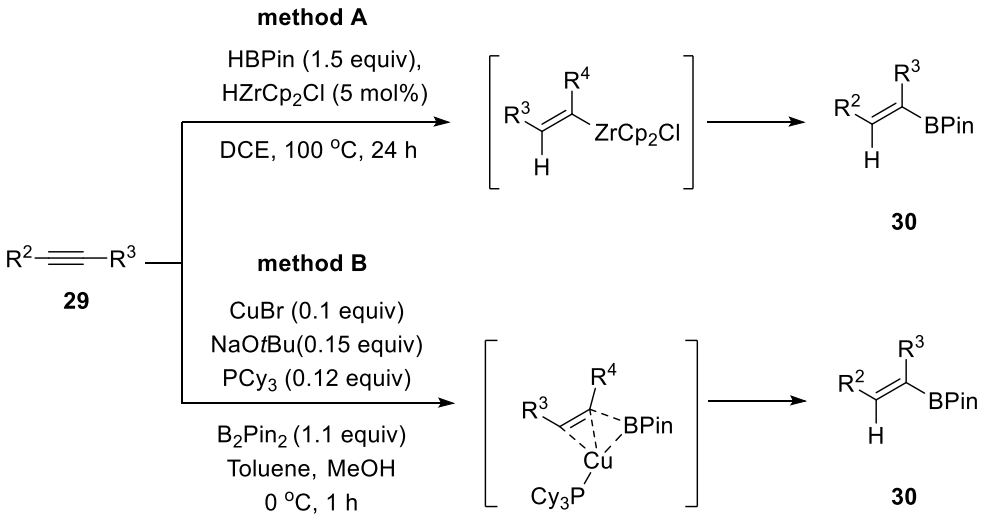
1. Preparation of indole substrate, *o*-alkenyl anilines

1.1. Preparation of alkenyl boronates **(30-BPin)**

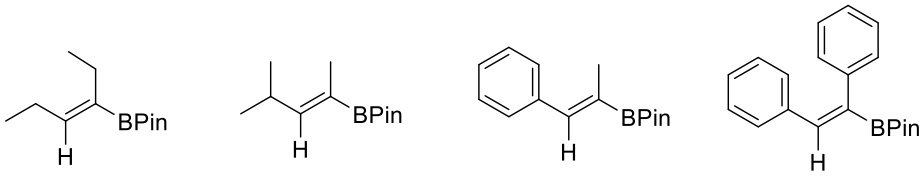
Prior to the Suzuki reaction, alkenyl boronates **(30-BPin)** were prepared by regiocontrolled syn hydroboration of internal alkynes **(29)**. Following two methods were used for the hydroboration. First, Zirconium catalyzed hydroboration of functionalized internal alkynes with pinacolborane was investigated **(Table 1, Method A)**. The reaction allowed the excellent *syn* selectivity and high regioselectivity, but it has a narrow scope of reaction, not applicable to all the internal alkynes.[60]

Accordingly, regiocontrolled Cu(I)-catalyzed borylation was subjected to propargylic-functionalized internal alkynes **(Table 1, Method B)**.[61] A range of propargylic functional groups with steric and electronic properties show uniformly good reactivity and high regiocontrolled result. However, the borylation of a non-functionalized internal alkyne such as 2-pentyne was much less efficient (34% yield) and led to an inseparable mixture of α and β vinylboronates.

Table 1. Preparation of alkenyl boronates with method A and B

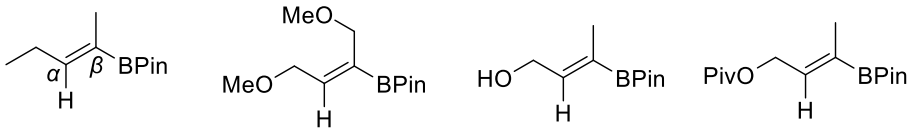


with method A



30e (32%) **30g (81%)** **30h (quant.)** **30i (65%)**

with method B



30f (34%)
***α*/*β* ratio 20:80**

30j (44%) **30k (92%)** **30l (81%)**

1.2. Preparation of alkenyl stannanes **(30-SnBu3)**

Alkenyl stannanes **(30-SnBu3)** were also constructed by the palladium-catalyzed hydrostannation of internal alkynes **29 (Table 2)**. The reaction generally proceeds under much milder conditions, resulting in high yields of products and excellent *syn*-addition. Regioselectivity of the *syn*-addition on the alkyne triple bond is controlled by directing ability which involves steric, electronic, or chelating effect as shown in **Figure 10**.[62]

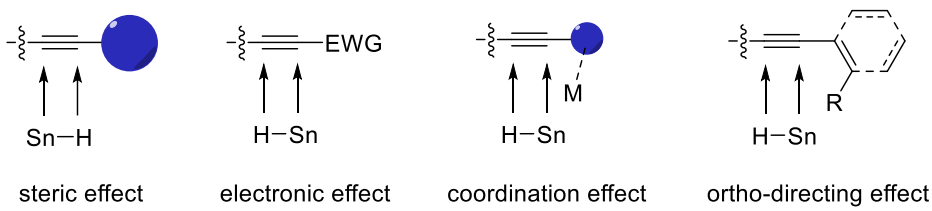
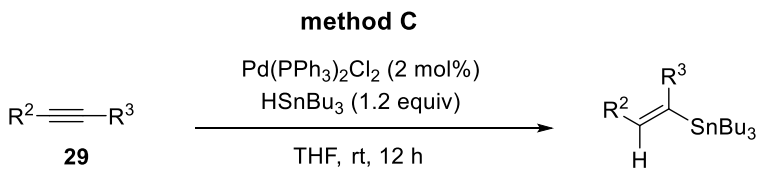


Figure 10. Regioselectivity for alkyne hydrostannation

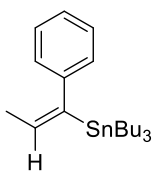
The palladium-catalyzed hydrostannation of 1-phenyl-1-propyne **(29m)** is completely regioselective, delivering a single constitutional isomer. We explain the result by excellent directing effect of aromatic ring for electronic reasons. The selectivity of 2-butyn-1-ol **(29n)** for the hydroboration is influenced by the relative size of proximal substituents, although neighboring hydroxyl groups might have a directing effect. Hydrostannation of diarylalkynes has little effect on selectivity, resulting in two stereoisomers. In case of the isomers, **30o** and **30p** were produced from a single diarylalkyne

(29), and separated by a column chromatography, respectively.[63] On the other hand, **30q** was not separated from another isomer and only a small amount of **30q** was obtained as a major product.

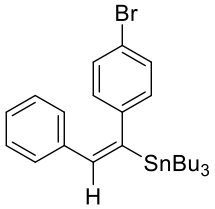
Table 2. Preparation of alkenyl stannanes with method C



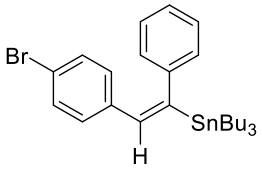
with method C



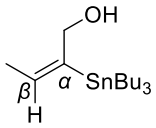
30m (39%)



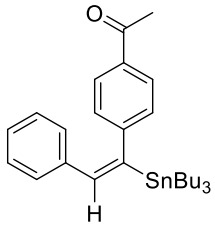
30o (39%)



30p (13%)



30n (56%)
(α:β = 75:25)



30q (49%)

1.3. Suzuki coupling reaction for the preparation of *o*-alkenyl anilines **(32)**

The Suzuki reaction of *o*-iodoaniline **(31)** with obtained alkenyl boronates **(30)** gave the corresponding desired alkene **(32)**. The reaction performed in the presence of $Pd(PPh_3)_2Cl_2$ and K_2CO_3 under a 2:1 mixture of DMF and H_2O in good to excellent yields of 49-97% **(Table 3)**. The reaction of cycloalkenyl boronates **(30a-d)** showed a great result on the formation of **32**, whereas the reaction of disubstituted alkenyl boronates **(32e-l)** provided *E*/*Z* mixtures of **32**, although expected product was *E*-configuration. This is because *E*- to *Z*- isomerization was generated during an organic conjugate reaction, sharing of common Pd species.[64,65] *E*- to *Z*- isomerization occurs through the migratory insertion and *β*-hydride elimination in the presence on the palladium catalyst **(Figure 12)**.

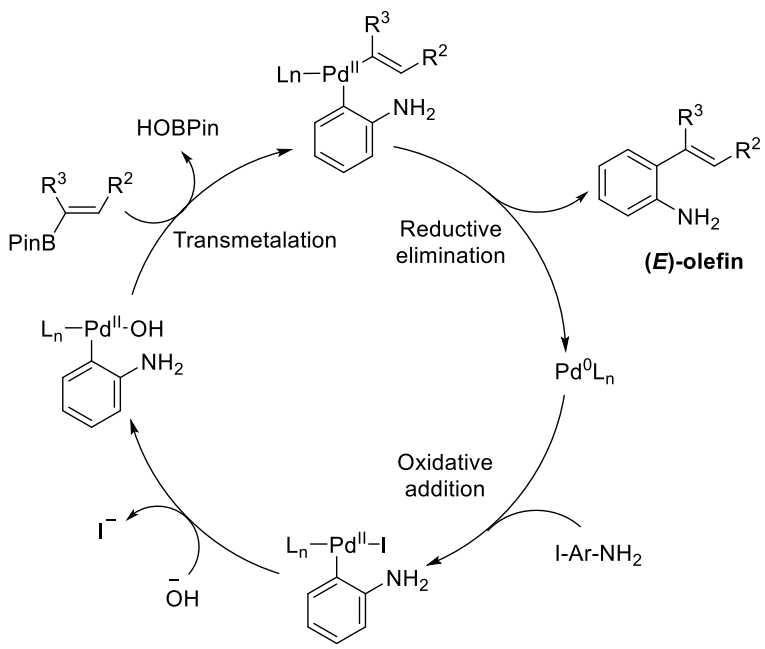


Figure 11. Suzuki coupling reaction mechanism

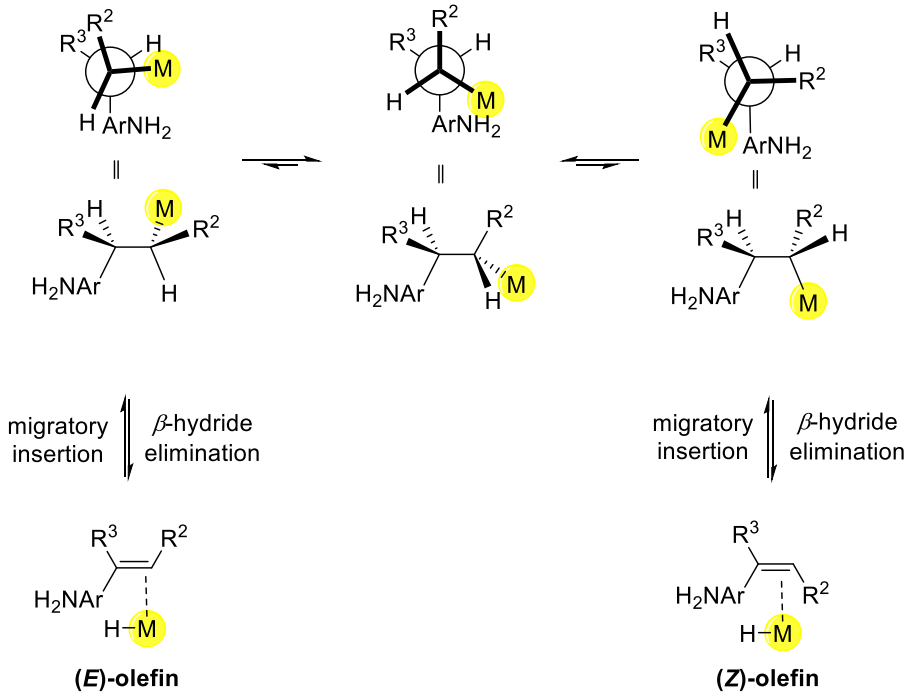
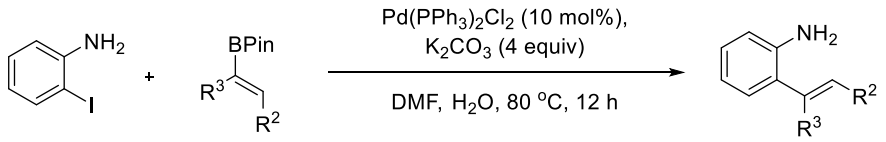


Figure 12. Pd (II)-catalyzed *E*- to *Z*- isomerization

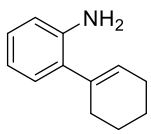
The *E*- and *Z*- ratio of **32** presented on **Table 3**, and all of **32** have slightly *E*-rich configuration. Additionally, we separated *E*- and *Z*-mixture of **32e** and **32f** by column chromatography, then the structure of two stereoisomers were analyzed by 2D NMR in **Figure 13**. *E*-configuration of **32** showed much higher reactivity in the aminocyclization than *Z* of **32**, since *E*-isomer is structurally more accessible for the reaction. Accordingly, we made an effort into preparing *E*-isomer, reducing the Suzuki reaction time to 30 minutes. The desired *E* configuration of **32** was absolutely produced, maintaining the yield of product.

Table 3. Synthesis of *o*-alkenyl anilines via Suzuki coupling reaction

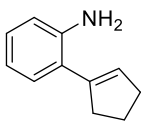


31 **30** **32**

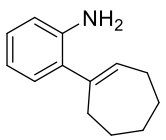
Suzuki reaction[a]



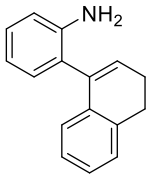
32a, 97%



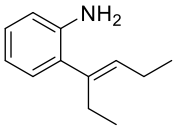
32b, 82%



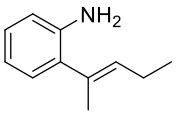
32c, 80%



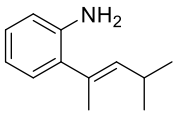
32d, 81%



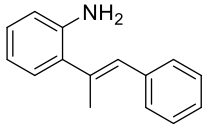
32e, 72% (*E*/*Z*=1:1)[c]
75% (*E*)[b]



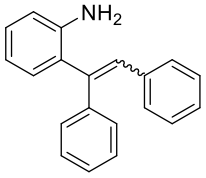
32f, 92% (*E*/*Z*=1:1)[c]
92% (*E*)[b]



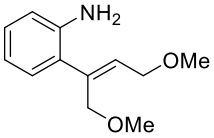
32g, 98% (*E*/*Z*=1.5:1)
84% (*E*)[b]



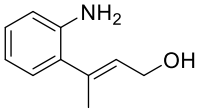
32h, 91% (*E*/*Z*=1.5:1)
92% (*E*)[b]



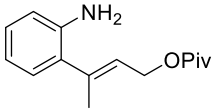
32i, 78% (*E*/*Z*=2.8:1)



32j, 99% (*E*)



32k, 65% (*E*)



32l, 49% (*E*)

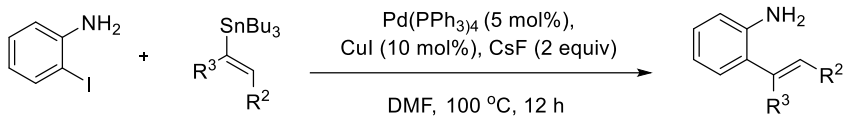
[a] Isolated yield [b] Shortened reaction time to 30 min, *E*/*Z* mixture ratio was detected in NMR [c] *E*/*Z* isomers was separated by column chromatography

1.4. Stille coupling reaction for the preparation of *o*-alkenyl anilines **(32)**

Although the Suzuki coupling reaction is an efficient method for the synthesis of **32**, there have been difficulties in preparing two complementary regioisomer pairs such as **32h** vs **32m**, **32k** vs **32n**, and **32o** vs **32p**. Consequently, another coupling method, Stille reaction has been devised with alkenyl stannanes **(30)**. Performing the Stille reaction with prepared reagents and cesium fluoride in the presence of a catalytic amount of $Pd(PPh_3)_4$ and CuI allows the formation of **32** in 38-88% yields **(Table 4)**.

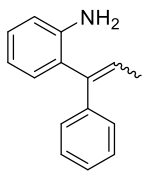
Stille reaction required higher temperature and prolonged reaction times for the consumption of starting material. Although the reaction proceeds under harsher conditions compared to the Suzuki reaction, the product shows a considerably high rate of *E*-configuration. Moreover, regioisomer pairs unable of generating from Suzuki coupling reaction can be prepared from the Stille coupling reaction. It would be a new synthetic strategy for expanding the scope of 2,3-disubstituted indoles.

Table 4. Synthesis of *o*-alkenyl anilines via Stille coupling reaction

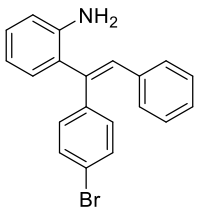


31 **30** **32**

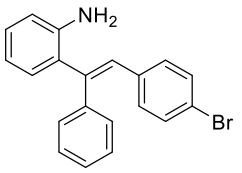
Stille reaction[a]



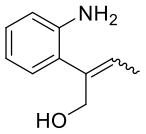
32m, 69% (*E*/*Z*=8:1)[b]



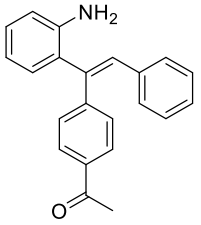
32o, 48%



32p, 38%



32n, 58% (*E*/*Z*=4:1)[b]



32q, 80%

[a] Isolated yield. [b] The ratio of *E*/*Z* mixture was detected in NMR.

1.5. Stereochemistry analysis with NOESY

For more details on stereochemistry, we separated *E*- and *Z*- mixture of **32e** and **32f** by column chromatography. The assignment and configurational analysis of separated *E*- and *Z*- stereoisomers of **32e** and **32f** was supported by ^{1}H and NOESY spectra **(Figure 13)**. All protons of the **32e** and **32f** were assigned as their chemical shift, integration, and NOE correlation. NOE cross peak signals between H–C (4) and H–C (5) with a red circle indicated the *E* configuration of **32e** and **32f** as the alkenyl substituent rotates, while no appearance of the signal is shown in the *Z* configuration.

In the case of **32e**, NOESY cross peak signals between H-C (4) and H-C (6)/ H-C (4) and H-C (7) with a blue circle of ***Z*-32e** suggested the *Z*-alkenyl aniline. The signal between H-C (10) and H-C (5) with a yellow circle additionally confirmed the ***E*-32** by correlating adjacent amine and vinyl proton. These two results present the stereoisomer of ***Z*-** and ***E*-32e**, respectively **(Figure 13, (a))**.

In the case of **32f**, NOESY cross peak signals between H-C (4) and H-C (6) with a green circle of ***Z*-32f** suggested the *Z*-alkenyl aniline, and the signal between H-C (9) and H-C (5) with a purple circle additionally confirmed the ***E*-32f** by correlating adjacent amine and vinyl proton. These two results present the stereoisomer of ***Z*-** and ***E*-32f**, respectively **(Figure 13, (b))**.

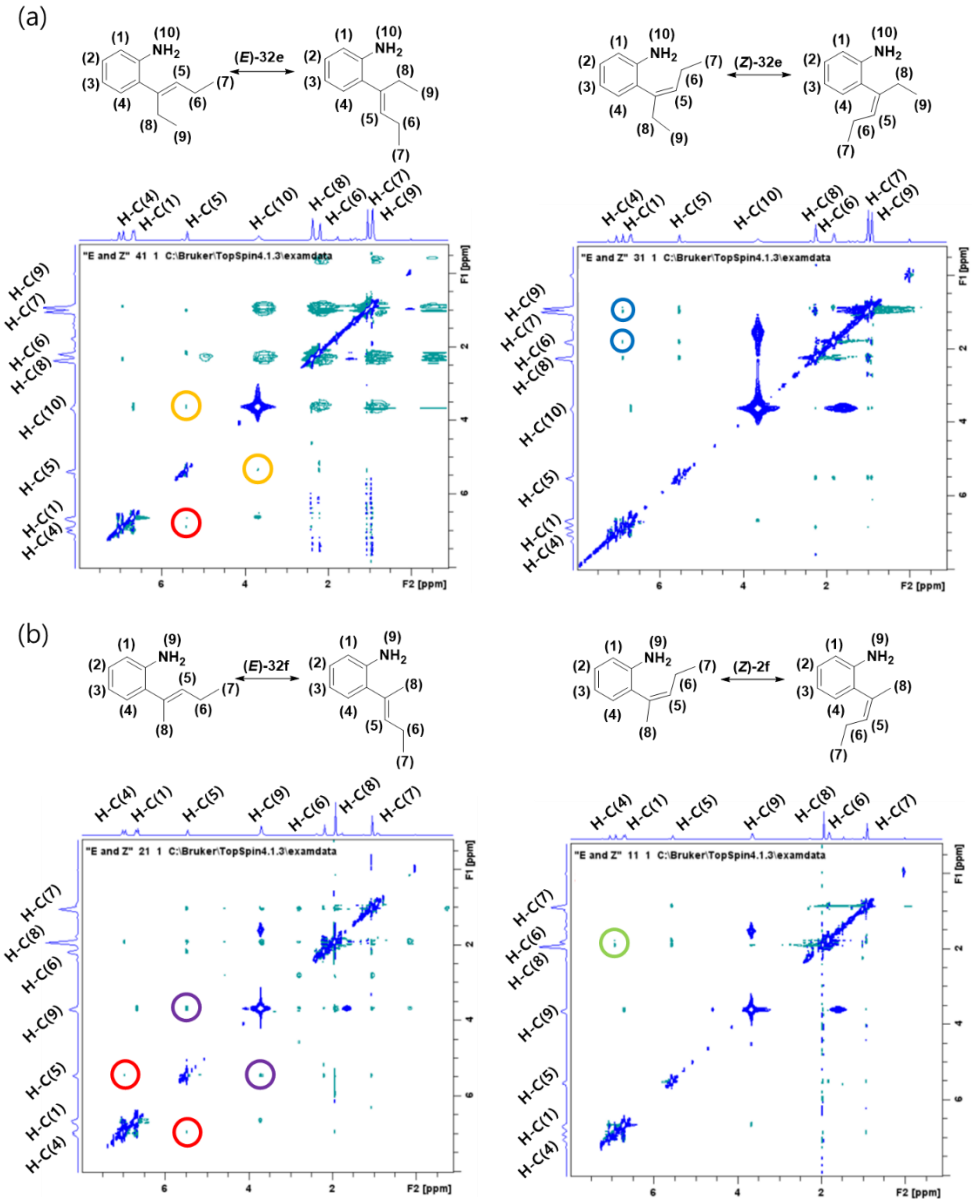


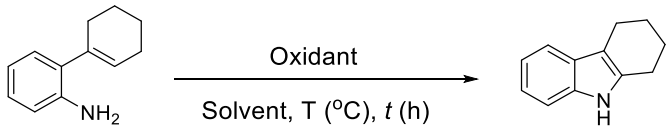
Figure 13. Stereochemistry analysis of (a) ***E***- and ***Z*-32e**, (b) ***E***- and ***Z*-32f**

2. Intramolecular aminocyclization with hypervalent iodines (PIFA)

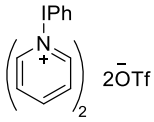
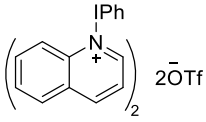
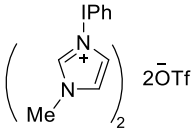
2.1. Optimization studies

As an effective metal-free reaction, intramolecular aminocyclization of **32** with hypervalent iodines has been presented in **Table 5**. First, we used PIFA reagent for the aminocyclization of **32a** that produced the indole product **33a**. Screening of solvent and reaction temperature for the reaction revealed a satisfactory yield shows at room temperature in THF. Comparable yields of **32a** were obtained with PIDA in THF. Iodosobenzene was also used as a mild oxidant, reducing further oxidation. However, the product yield from the reaction with iodosobenzene was not as good as with PIDA and PIFA even in the increased temperature. Finally, this synthetic approach has been expanded to the Weiss reagents, the strong oxidizing agent, however the reactivity of aminocyclization was extremely low due to decomposition of starting material.

Table 5. Optimization studies with hypervalent iodines.



32a **33a**

Entry	Oxidant	Solvent	T (°C)	Yield (%)[b]
1	PIDA	THF	rt	61
2	PIFA	THF	rt	58
3	PhIO	THF	rt	3[c]
4	PhIO	THF	50 °C	12[c]
5	PhIO	THF	80 °C	41[c]
6	PhIO	DMF	100 °C	37[c]
7		THF	rt	5
8		THF	rt	4
9		THF	rt	14

[a] Reaction conditions: **32a** (0.28 mmol), oxidant (2 equiv.) in solvent for 1 h.
[b] Isolated yield of purified products.
[c] Yield brsm by ^{1}H NMR.

2.2. Scope of PIFA mediated intramolecular aminocyclization.

The substrate scope was broad, and alkyl- and aryl- 2,3-disubstituted indoles were obtained in comparable (40–83%) yields **(Table 6)**. The formation of free *N*–H indoles is a noteworthy feature of this method, whereas many known methods required protecting groups at the indole nitrogen. As expected, this protocol is tolerant of common functional groups such as bromo and keto substituents. Indoles **33i** and **33m** were prepared from a mixture of *E*- and *Z*-alkenyl anilines (8:1 and 1:2.8, respectively). The similar yields obtained was suggestive of the indole formation from both *E*- and *Z*-alkenes. In the case of **33e** and **33f**, an *E*- and *Z*- mixture of the staring substrates was separated by column chromatography. Each geometrical isomer was subjected to indole formation: both isomers afforded the identical indoles, where higher yields (70% and 80% for **33e** and **33f**) were obtained from the *E*-alkenes than the *Z*-isomers (38% and 56%). This is because *E*-alkenes are structurally more favored for cyclization than *Z*-alkenes. **(Figure 14)**. Overall, this method offers a regioselective alternative to the Larock indole synthesis.

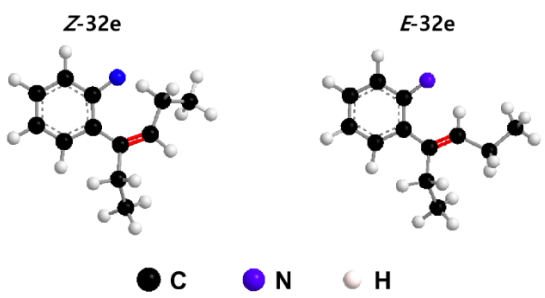
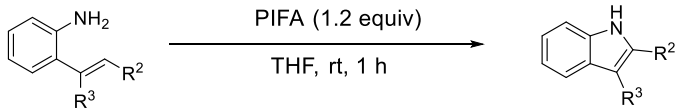
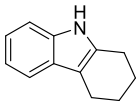
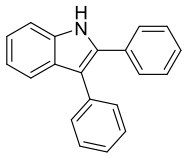
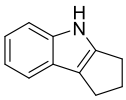
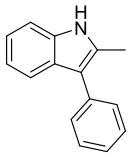
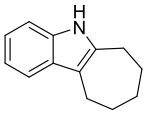
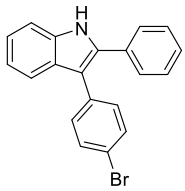
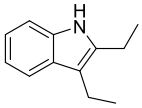
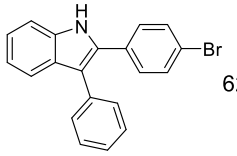
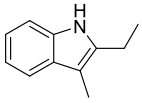
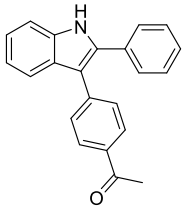
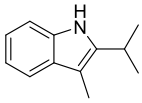
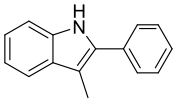


Figure 14. 3D structure of ***E*- and *Z*-32e**

Table 6. Intramolecular aminocyclization of *o*-alkenyl anilines



32 **33**

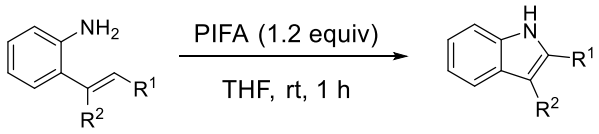
Entry	32	33	Yield (%)[a]	Entry	32	33	Yield (%)[a]
1	32a	 **33a**	58%	**8**	*E*/*Z*-32i	 **33i**	62%
2	32b	 **33b**	57%	**9**	*E*/*Z*-32m	 **33m**	57%
3	32c	 **33c**	83%	**10**	32o	 **33o**	62%
4	*E*-32e *Z*-32e	 **33e**	70% 38%	**11**	32p	 **33p**	62%
5	*E*-32f *Z*-32f	 **33f**	80% 56%	**12**	32q	 **33q**	58%
6	*E*-32g	 **33g**	61%				
7	*E*-32h	 **33h**	54%				

[a] Isolated yield.

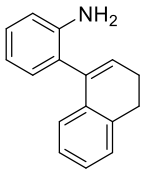
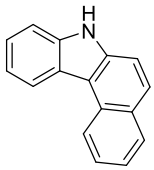
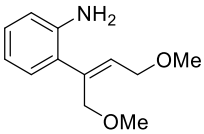
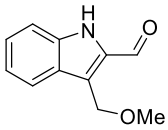
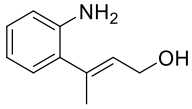
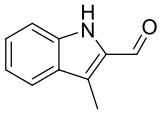
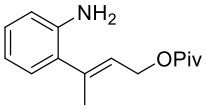
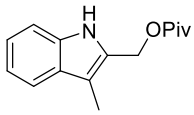
2.3. Further oxidation in aminocyclization

Along with the advantage of being able to prepare various indoles, aminocyclization also delivered interesting indole structures through further oxidation reactions **(Table 7)**. A remarkable result was confirmed in aminocyclization of **32d**, which provides unexpected benzocarbazole **(33d)** via additional PIFA oxidation of dihydrobenzocarbazole. Furthermore, when the oxygenated **32j** and **32k** are exposed to the reaction, it miraculously brings a new product with aldehyde via the additional oxidation of alcohol **(Scheme 19)**. However, when the pivalated substrate bearing an EWG beside on the oxygen lone pair **(32l)** is applied to the reaction, aldehyde product was not observed. We conclude the ester functional group is not appropriate for the further oxidation reaction such as Dess-Martin oxidation to obtain aldehyde product.

Table 7. Further oxidation of intramolecular aminocyclization



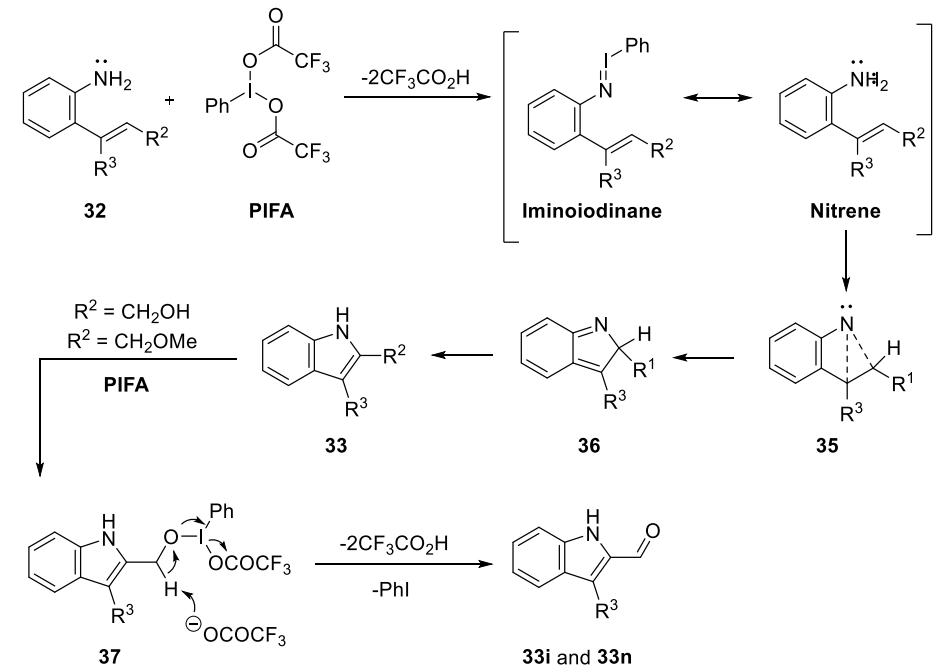
32 **33**

Entry	Substrate	Product	Yield (%)[a]
1	 **32d**	 **33d**	38
2	 **32j**	 **33j**	22
3	 **32k**	 **33k**	24
4	 **32l**	 **33l**	21[b]

[a] Isolated yield. [b] Deprotection affects the yield of the product.

2.4. Plausible mechanism of PIFA mediated aminocyclization

A plausible pathway of direct PIFA mediated intramolecular amination is proposed in **Scheme 18**. The reaction initiated from the formation of iminoiodinane through the reaction between nucleophilic aniline and electrophilic iodine. This would spontaneously decompose to the nitrenes as a carbene counterpart.[66,67] The nitrene triggers cyclization with an adjacent alkene, providing indole derivatives. However, when the oxygenated functional group is introduced into the substituent R^2, the aldehyde product could be generated through an additional oxidation step with PIFA reagent such as Dess-Martin oxidation, then aldehydes (**33i** and **33n**) were observed.



Scheme 19. Plausible mechanism of PIFA-mediated aminocyclization

Conclusion

A novel synthetic methodology of 2,3-disubsituted indole was suggested in this study. Since these compounds show interesting biological activities, it is widely used in medicinal chemistry. Although the preparation of indole compounds has been studied by many chemists for a long time, the synthesis of 2,3-disubstituted indole suffers from the migration of substituents and structural instability. We suggested an efficient synthetic method of 2,3-disubstituted indole with PIFA mediated aminocyclization via nitrene intermediate. *o*-Alkenylaniline as a precursor of the aminocyclization were prepared from Suzuki and Stille coupling reactions. The precursors exist as a mixture of *trans* and *cis*-isomers, whereas the selective *trans*-isomer can be exclusively obtained when the reaction time was shortened. It was also possible to separate the two stereoisomers for the analysis of respective structures by detection of 2D NMR. Furthermore, we reported here synthetic method of alkenyl boronate (BPin) and stannane ($SnBu_3$) reagents from regioselective hydroboration and stannation. Since the aminocyclization reaction proposed in this study proceeds through a nitrene intermediate, free *N*-H indole can be efficiently synthesized without protecting group. Furthermore, it enables the regioselective synthesis of indoles having various substituents, which have not been reported in many existing papers. This methodology will be utilized in a concise synthetic method of valuable 2,3-disubstituted indoles in the field of fine chemicals and natural products.

Experimental Details

1. General information

All materials were obtained from Sigma-Aldrich, Alfa Aesar, TCI, Merck and were used without further purification. Air- and moisture-sensitive manipulations were carried out under a nitrogen atmosphere using oven-dried glassware and standard syringe/septa techniques. Thin-layer chromatography (TLC) analysis was run on SiO_2 TLC plate under UV light (254 nm) followed by visualization with PMA and ninhydrin staining solution, and I_2 . Column chromatography was performed on glass plates coated with silica gel 60 (70-230 mesh). Compounds were characterized by ^{1}H and ^{13}C NMR spectra recorded on a Bruker 400 AVANCE spectrometer (400 and 100 MHz, respectively). All ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to TMS as an internal standard using ^{1}H (chloroform-*d*: 7.26 ppm) and ^{13}C (chloroform-*d*: 77.23 ppm) chemical shifts. ^{1}H NMR were presented as following: chemical shifts (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sep = septet, br = broad, dd = doublet of doublets, td = triplet of doublets, tt = triplet of triplets, m = multiplet), coupling constants (Hz), and integration.

2. General synthetic method

2.1. General procedure for first hydroboration

$HZrCp_2Cl$ (0.16 g, 0.61 mmol), disubstituted 3-hexyne **29e** (1.00 g, 12.10 mmol) were placed in pressure tube and dichloroethane (5 mL) was charged to the vessel. The HBPin (2.32 g, 18.15 mmol) was added dropwise and the mixture was stirred at 100 ºC for 24 h. The reaction was quenched with water (5 mL) and washed with dichloromethane (5 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

2.1.1. (*Z*)-2-(hex-3-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30e)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (16:1) with PMA staining to give the corresponding product **30e**. (0.81 g, 3.86 mmol, 32%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 – 6.26 (m, 1 H), 2.20 – 2.13 (m, 4 H), 1.28 (s, 12 H), 1.04 – 0.94 (m, 6 H). MS (EI) m/z (relative intensity): 210 (M, 24), 195 (38), 181 (44), 167 (11), 153 (100), 139 (17), 124 (17), 111 (79), 101 (89), 93 (3), 84 (90), 69 (45), 55 (57).

2.1.2. (*Z*)-4,4,5,5-tetramethyl-2-(4-methylpent-2-en-2-yl)-1,3,2-dioxaborolane (30g)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (4:1) with PMA staining to give the corresponding product **30g** (3.93 g, 18.71 mmol, 81%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 – 6.11 (m, 1 H), 2.73 – 2.64 (m, 1 H), 1.69 (s, 3 H), 1.26 (s, 12 H), 0.98 – 0.95 (m, 6 H). MS (EI) m/z (relative intensity): 210 (M, 44), 195 (28), 181 (1), 167 (20), 153 (73), 139 (7), 125 (18), 112 (4), 101 (85), 84 (100), 69 (56), 55 (28).

2.1.3. (*Z*)-2-(1,2-diphenylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30i)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **30i** (0.60 g, 1.96 mmol, 65%) as a yellow solid, mp : 96 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 1 H), 7.31 – 7.27 (m, 3 H), 7.20 – 7.18 (m, 2 H), 7.15 – 7.12 (m, 3 H), 7.08 – 7.06 (m, 2 H), 1.33 (s, 12 H). MS (EI) m/z (relative intensity): 306 (M, 100), 290 (11), 273 (2), 249 (8), 233 (8), 206 (23), 190 (100), 165 (15), 147 (3), 129 (0.9), 103 (29), 77 (8), 55 (3).

2.2. General procedure for second hydroboration

CuBr (0.22 g, 1.46 mmol), NaO*t*Bu (0.21 g, 2.19 mmol), PCy_3 (0.48 g, 1.75 mmol), and B_2Pin_2 (4.08 g, 16.06 mmol) were placed in round bottom flask, then toluene (2 mL) and methanol (3 mL) were charged to the vessel. 2-Pentyne **29f** (1.00 g, 14.60 mmol) in toluene (2 mL) was added dropwise and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with water (5 mL) and washed with diethyl ether (5 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

2.2.1. (Z)-4,4,5,5-tetramethyl-2-(pent-2-en-2-yl)-1,3,2-dioxaborolane (30f)

Following the procedure as above, residue was purified by silica gel column chromatography with hexane followed by using Hexane/EA (4:1) with PMA staining to give the corresponding product **30f** (0.90 g, 4.59 mmol, 34% – 4.5:1 of regioisomer) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (q, J = 6.9 Hz, 0.22 H, minor isomer), 6.33 – 6.29 (m, 1 H, major isomer), 2.17 – 2.10 (m, 2.44 H, major and minor isomers), 1.72 (d, J = 6.9 Hz, 0.66, minor isomers), 1.67 (s, 3 H, major isomer), 1.26 (s, 12 H, major isomer), 1.26 (s, 2.64 H, minor isomer), 1.02 – 1.00 (m, 3 H, major isomer), 0.98 – 0.92 (m, 0.66 H, minor isomer). MS (EI) m/z (relative intensity for major isomer): 196 (M, 32), 181 (67), 167 (29), 153 (6), 139 (78), 125 (26), 110 (50), 97 (100), 83 (45), 69 (38), 55 (62). MS (EI) m/z (relative intensity for

minor isomer): 196 (M, 25), 181 (42), 167 (73), 152 (4), 139 (56), 125 (26), 110 (46), 97 (100), 83 (32), 69 (44), 55 (31).

2.2.1. (*Z*)-4,4,5,5-tetramethyl-2-(1-phenylprop-1-en-2-yl)-1,3,2-dioxaborolane (30h)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **30h** (2.35 g, 9.63 mmol, quant.) as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.32 (m, 4 H), 7.25 – 7.23 (m, 2 H), 1.99 (s, 3 H), 1.31 (s, 12 H). MS (EI) m/z (relative intensity): 244 (M, 100), 229 (28), 187 (15), 171 (10), 158 (18), 143 (82), 128 (75), 116 (37), 103 (23), 91 (14), 77 (8).

2.2.2. (*Z*)-2-(1,4-dimethoxybut-2-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30j)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (4:1) with PMA staining to give the corresponding product **30j** (0.57 g, 2.36 mmol, 44%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (t, J = 5.6 Hz, 1 H), 4.16 (d, J = 5.6 Hz, 2 H), 4.04 (s, 2 H), 3.36 (s, 3 H), 3.30 (s, 3 H), 1.26 (s, 12 H). MS (EI) m/z (relative intensity): 210 (M-32, 100), 182 (1), 153 (12), 137 (25), 110 (36), 84 (37), 59 (20).

2.2.3. (*Z*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-en-1-ol (30k)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (2:1) with PMA staining to give the corresponding product **30k** (2.44 g, 12.32 mmol, 92%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (t, J = 4.9 Hz, 1 H), 4.3 (d, J = 4.9 Hz, 2 H), 1.71 (s, 3 H), 1.68 (d, J = 4.4 Hz, 1H), 1.27 (s, 12 H). MS (EI) m/z (relative intensity): 197 (M, 1), 183 (22), 141 (12), 123 (10), 115 (18), 101 (100), 94 (6), 84 (67), 69 (31), 55 (31).

2.2.4. (*Z*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-en-1-yl pivalate (30l)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (4:1) with PMA staining to give the corresponding product **30l** (0.694 g, 2.46 mmol, 81%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 – 6.32 (m, 1 H), 4.73 – 4.71 (m, 2 H), 1.74 (s, 3 H), 1.27 (s, 18 H), 1.21 (s, 9 H). MS (EI) m/z (relative intensity): 282 (M, 1), 267 (4), 225 (2), 197 (44), 181 (19), 165 (11), 138 (9), 123 (11), 97 (59), 83 (28), 69 (6), 57 (100).

2.3. General procedure for hydrostannation

$Pd(PPh_3)_2Cl_2$ (0.12 g, 0.17 mmol), 1-Phenyl-1-propyne **29m** (1.00 g, 8.60 mmol) were placed in a flame-dried round bottom flask and tetrahydrofuran (5 mL) was charged to the vessel. The tributyltin hydride – HSnBu3 (3.00 g, 10.32 mmol) was added dropwise and the mixture was stirred at rt for 2 h. The reaction was quenched with water (5 mL) and washed with diethyl ether (5 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding products **30m**.

2.3.1. (*E*)-tributyl(1-phenylprop-1-en-1-yl)stannane (30m)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane with I_2 staining to give the corresponding product **30m** (1.20 g, 2.95 mmol, 39%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.27 (m, 2 H), 7.13 (t, J = 7.4 Hz, 1 H), 6.95 (d, J = 7.4 Hz, 2 H), 5.90 (q, J = 6.4 Hz, 1 H), 1.68 (d, J = 6.4 Hz, 3 H), 1.49 – 1.41 (m, 6 H), 1.33 – 1.24 (m, 6 H), 0.89 – 0.86 (m, 15 H). MS (EI) m/z (relative intensity): 351 (M-57, 100), 295 (66), 237 (93), 215 (1), 197 (21), 177 (28), 159 (1), 135 (8), 117 (43), 91 (15), 65 (2).

2.3.2. (*E*)-2-(tributylstannyl)but-2-en-1-ol (30n)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with I_2 staining to give the corresponding product **30n** (2.00 g, 5.54 mmol, 42%) as a black oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 – 5.57 (m, 1 H), 4.44 – 4.33 (m, 2 H), 1.69 (d, J = 6.6 Hz, 3 H), 1.55 – 1.43 (m, 8 H), 1.36 – 1.26 (m, 8 H), 0.98 – 0.87 (m, 20 H).

2.3.3. (*E*)-(1-(4-bromophenyl)-2-phenylvinyl)tributylstannane (30o)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane with I_2 staining to give the corresponding product **30o** (1.00 g, 1.82 mmol, 39%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.37 (m, 2 H), 7.15 – 7.09 (m, 3 H), 7.00 – 6.98 (m, 2 H), 6.86 - 6.84 (m, 2 H), 6.66 (s, 1 H), 1.51 – 1.41 (m, 6 H), 1.34 – 1.20 (m, 6 H), 1.12 – 0.82 (m, 18 H). MS (EI) m/z, (relative intensity): 491 (M-57, 100), 435 (31), 377 (39), 297 (7), 259 (11), 235 (12), 201 (28), 178 (98), 152 (12), 121 (20).

2.3.4. (*E*)-(2-(4-bromophenyl)-1-phenylvinyl)tributylstannane (30p)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane with I_2 staining to give the corresponding product **30p** (0.37 g, 0.67 mmol, 13%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.10 (m, 5 H), 6.95 – 6.93 (m, 2 H), 6.86 – 6.83 (m, 2 H), 6.57 (s, 1 H), 1.51 – 1.43 (m, 6 H), 1.33 – 1.24 (m. 6 H), 1.12 – 0.85 (m, 18 H). MS (EI) m/z (relative intensity): 491 (M-57, 97), 435 (38), 377 (47), 297 (7), 275 (12), 235 (12), 201 (29), 178 (100), 152 (11), 121 (24).

2.3.5. (E)-1-(4-(2-phenyl-1-(tributylstannyl)vinyl)phenyl) ethan-1-one (30q)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (16:1) with I_2 staining to give the corresponding product **30q** (1.15 g, 2.25 mmol, 49%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.4 Hz, 1 H), 7.15 – 7.11 (m, 5 H), 7.03 (d, J = 8.4 Hz, 1 H), 6.76 (s, 1 H), 2.59 (s, 3 H), 1.58 – 1.51 (m, 6 H), 1.40 – 1.31 (m, 6 H), 1.10 – 1.00 (m, 6 H), 0.95 – 0.91 (m, 12 H). MS (EI) m/z (relative intensity): 455 (M-57, 77), 429 (8), 399 (14), 341 (39), 281 (21), 253 (22), 207 (100), 179 (29), 135 (19), 73 (19).

2.4. General procedure for Suzuki coupling reaction

A suspension of $Pd(PPh_3)_2Cl_2$ (0.28 g, 0.40 mmol), K_2CO_3 (2.21 g, 16.00 mmol), and *o*-iodoaniline **31** (0.88 g, 4.00 mmol) in a 2:1 DMF/H_2O were stirred at room temperature followed by the addition of 1-cyclohexen-1-yl-boronic acid pinacol ester **30a** (1.00 g, 4.80 mmol) in DMF (10 mL) solution. The reaction mixture was placed at 80 ºC, then stirred for 30 minutes to reduce regio-conversion. The reaction was quenched with water (10 mL) and washed with diethyl ether (10 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding products **32a**.

2.4.1. 2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-amine (32a)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product **32a** (0.597 g, 3.45 mmol, 86%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 – 7.01 (m, 1 H), 6.99 – 6.97 (m, 1 H), 6.74 – 6.68 (m, 2 H), 5.75 (sep, 1 H), 3.76 (br, 2H), 2.26 – 2.22 (m, 2 H), 2.20 – 2.12 (m, 2 H), 1.78 – 1.74 (m, 2H), 1.72 – 1.66 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 136.5, 130.5, 128.7, 127.5, 126.8, 118.3, 115.4, 29.4, 25.5, 23.2, 22.2. MS (EI) m/z (relative intensity): 173 (M, 100), 144 (100), 119 (26), 93 (7), 77 (12), 51 (4).

2.4.2. 2-(cyclopent-1-en-1-yl)aniline (32b)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product **32b** (0.563 g, 3.54 mmol, 82%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 – 7.10 (m, 1 H), 7.06 – 7.01 (m, 1 H), 6.76 – 6.70 (m, 2 H), 6.00 – 5.99 (m, 1 H), 3.93 (br, 2 H) 2.72 – 2.68 (m, 2 H), 2.58 – 2.54 (m, 2 H), 1.97 (p, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 141.3, 128.3, 128.2, 127.6, 123.7, 118.2, 115.8, 36.4, 33.9, 23.2. MS (EI) m/z (relative intensity): 159 (M, 100), 144 (49), 130 (67), 117 (18), 103 (9), 90 (6), 77 (12), 63 (5), 50 (2).

2.4.3. 2-(cyclohept-1-en-1-yl)aniline (32c)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product **32c** (0.159 g, 0.85 mmol, 83%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 – 6.96 (m, 2 H), 6.71 – 6.68 (m, 1 H), 6.64 (d, J = 6.5 Hz, 1 H), 5.92 (t, J = 6.5 Hz, 1 H), 3.67 (br, 2 H), 2.46 – 2.44 (m, 2 H), 2.28 – 2.24 (m, 2 H), 1.84 – 1.80 (m, 2 H), 1.66 – 1.55 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 142.9, 132.6, 132.3, 128.8, 127.5, 118.4, 115.4, 34.2, 32.8, 29.0, 27.6, 27.3. MS (EI) m/z (relative intensity): 187 (M, 92), 158 (19), 130 (100), 106 (24), 77 (9), 51 (3).

2.4.4. 2-(3,4-dihydronaphthalen-1-yl)aniline (32d)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product **32d** (0.174 g, 0.79 mmol, 81%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.16 (m, 3 H), 7.13 – 7.10 (m, 2 H), 6.86 – 6.81 (m, 2 H), 6.76 (d, J = 8.0 Hz, 1 H), 3.59 (br, 2 H), 2.95 – 2.92 (m, 2 H), 2.50 – 2.46 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 137.1, 136.2, 134.0, 131.0, 129.6, 128.6, 127.8, 127.4, 126.8, 126.4, 124.9, 118.6, 115.4, 28.2, 23.6. HRMS (EI) m/z: calcd for $C_{16}H_{15}N^+$ ($[M]^+$) 221.1198; Found 221.1198.

2.4.5. *E*-2-(hex-3-en-3-yl)aniline (*E*-32e)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product ***E*-32e** (0.112 g, 0.64 mmol, 36%) detected on a higher spot in the TLC as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 – 7.02 (m, 1 H), 6.96 – 6.94 (m, 1 H), 6.74 – 6.68 (m, 2 H), 5.42 – 5.38 (m, 1 H), 3.71 (br, 2 H), 2.41 – 2.35 (m, 2 H), 2.24 – 2.16 (m, 2 H), 1.05 (t, J = 7.5 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 139.4, 131.9, 130.3, 129.6, 127.5, 118.1, 115.3, 24.4, 21.4, 14.7, 13.4. HRMS (EI) m/z: calcd for $C_{12}H_{17}N^+$ ($[M]^+$) 175.1361; Found 175.1361.

2.4.5. (*Z*)-2-(hex-3-en-3-yl)aniline (*Z*-32e)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product ***Z*-32e** (0.110 g, 0.63 mmol, 36%) detected on a lower spot in the TLC as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 – 7.03 (m, 1 H), 6.90 – 6.87 (m, 1 H), 6.74 – 6.68 (m, 2 H), 5.55 – 5.52 (m, 1 H), 3.63 (br, 2 H), 2.29 – 2.23 (m, 2 H), 1.84 – 1.80 (m, 2 H), 0.99 (t, J = 7.5 Hz, 3 H), 0.90 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 139.1, 129.8, 129.4, 127.7, 127.3, 118.2, 115.0, 31.4, 22.5, 14.5, 13.0. HRMS (EI) m/z: calcd for $C_{12}H_{17}N^+$ ($[M]^+$) 175.1362; Found 175.1362.

2.4.6. (*E*)-2-(pent-2-en-2-yl)aniline (*E*-32f)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product ***E*-32f** (0.160 g, 0.99 mmol, 44%) detected on a higher spot in the TLC as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 – 7.02 (m, 1 H), 6.99 – 6.97 (m, 1 H), 6.74 – 6.68 (m, 2 H), 5.50 – 5.45 (m, 1H), 3.73 (br, 2 H), 2.19 (p, J = 7.5 Hz, 2 H), 1.94 (s, 3 H), 1.05 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 133.0, 132.5, 131.7, 128.9, 127.6, 118.4, 115.5, 21.8, 17.3, 14.3. HRMS (EI) m/z: calcd for $C_{11}H_{15}N^+$ ($[M]^+$) 161.1202; Found 161.1202.

2.4.7. (*Z*)-2-(pent-2-en-2-yl)aniline (*Z*-32f)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product ***Z*-32f** (0.176 g, 1.09 mmol, 48%) detected on a lower spot in the TLC as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 – 7.04 (m, 1 H), 6.93 – 6.91 (m, 1 H), 6.76 – 6.69 (m, 2 H), 5.58 – 5.54 (m, 1 H), 3.66 (br, 2 H), 1.95 (s, 3 H), 1.81 (p, J = 7.5 Hz, 2 H), 0.90 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 133.1, 131.4, 128.9, 128.0, 127.8, 118.4, 115.1, 24.6, 22.7, 14.4. HRMS (EI) m/z: calcd for $C_{11}H_{15}N^+$ ($[M]^+$) 161.1201; Found 161.1201.

2.4.8. (*E*)-2-(4-methylpent-2-en-2-yl)aniline (*E*-32g)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product ***E*-32g** (0.336 g, 1.92 mmol, 84%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (td, J = 7.6, 1.5 Hz, 1 H), 7.01 (dd, J = 7.6, 1.5 Hz, 1 H), 6.78 – 6.71 (m, 2 H), 5.34 (dd, J = 9.2, 1.2 Hz, 1 H), 3.76 (br, 2 H), 2.76 – 2.68 (m, 1 H), 1.98 (d, J = 1.2 Hz, 3 H), 1.08 (s, 3 H), 1.06 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 138.2, 131.5, 131.1, 128.8, 127.4, 118.3, 115.4, 27.6, 22.9, 17.2. HRMS (EI) m/z: calcd for $C_{12}H_{17}N^+$ ($[M]^+$) 175.1361; Found 175.1361.

2.4.9. (*E*)-2-(1-phenylprop-1-en-2-yl)aniline (*E*-32h)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product ***E*-32h** (0.435 g, 2.08 mmol, 92%) as a pale yellow solid, mp: 45 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.38 (m, 4 H), 7.28 – 7.23 (m, 1 H), 7.11 – 7.08 (m, 2 H), 6.80 - 6.72 (m, 2 H), 6.56 (d, J = 1.4 Hz, 1 H), 3.81 (br, 2 H), 2.23 (d, J = 1.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 137.9, 136.8, 131.7, 130.1, 129.1, 128.9, 128.4, 128.1, 126.8, 118.6, 115.8, 19.4. MS (EI) m/z (relative intensity): 209 (M, 100), 194 (35), 165 (15), 152 (6), 132 (11), 118 (62), 91 (20), 77 (7).

2.4.10. 2-(1,2-diphenylvinyl)aniline (32i)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product **32i** (0.220 g, 0.81 mmol, 78% – 2.8:1 of regioisomer) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.36 (m, major and minor isomer), 7.28 – 6.96 (m, major and minor isomer), 6.98 – 6.96 (m, major and minor isomer), 6.75 – 6.70 (m, major and minor isomer), 6.66 – 6.64 (m, 1H, major isomer), 6.57 – 6.55 (m, 0.36 H, minor isomer), 3.50 (br, 2 H, major and minor isomer). ^{13}C NMR (100 MHz, $CDCl_3$) of mixture of two isomers: δ 144.4, 144.2, 141.9, 140.9, 139.8, 139.0, 137.3, 137.1, 131.2, 131.1, 130.7, 130.0, 129.8, 129.6, 129.5, 129.1, 129.0, 128.8,

128.7, 128.6, 128.3, 128.1, 127.9, 127.7, 127.4, 127.0, 126.8, 125.5, 119.0, 118.4, 116.1, 115.9. HRMS (EI) m/z: calcd for $C_{20}H_{17}N^+$ ($[M]^+$) 271.1354; Found 271.1354.

2.4.11. (*E*)-2-(1,4-dimethoxybut-2-en-2-yl)aniline (32j)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (1:1) with Ninhydrin staining to give the corresponding product **32j** (0.472 g, 2.28 mmol, 99%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (td, J = 7.6, 1.5 Hz, 1 H), 7.03 (dd, J = 7.6, 1.5 Hz, 1 H), 6.72 – 6.66 (m, 2 H), 5.92 (t, J = 6.4 Hz, 1 H), 4.19 (d, J = 6.4 Hz, 2 H), 4.14 (s, 2 H), 4.04 (br, 2 H), 3.41 (s, 3 H), 3.37 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 138.7, 132.6, 129.7, 128.6, 128.1, 118.1, 115.6, 70.9, 68.9, 58.7, 58.5. HRMS (EI) m/z: calcd for $C_{12}H_{17}NO_2^+$ ($[M]^+$) 207.1260; Found 207.1260.

2.4.12. (*E*)-3-(2-aminophenyl)but-2-en-1-ol (32k)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (1:1) with Ninhydrin staining to give the corresponding product **32k** (0.171 g, 1.05 mmol, 65%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (td, J = 7.7, 1.6 Hz, 1 H), 6.93 (dd, J = 7.5, 1.6 Hz, 1 H), 6.79 (dd, J = 7.5, 1.1 Hz, 1 H), 6.73 (d, J = 7.7 Hz, 1 H), 5.91 – 5.87 (m, 1 H), 3.84 (d, J = 7.4 Hz, 2 H), 2.03 (s, 3 H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ 142.4, 137.5, 128.7, 128.3, 128.2, 127.5, 119.1, 115.9, 75.1, 60.5, 24.9, 24.9. HRMS (EI) m/z: calcd for $C_{10}H_{13}NO^+$ ($[M]^+$) 163.0998; Found 163.0998.

2.4.13. (*E*)-3-(2-aminophenyl)but-2-en-1-yl pivalate (32l)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (4:1) with Ninhydrin staining to give the corresponding product **32l** (0.107 g, 0.43 mmol, 49%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (t, J = 7.5 Hz, 1 H), 6.98 (d, J = 7.5 Hz, 1 H), 6.73 (t, J = 7.5 Hz, 1 H), 6.68 (d, J = 6.5 Hz, 1 H), 5.62 (t, J = 6.5 Hz, 1 H), 4.75 (d, J = 6.5 Hz, 2 H), 3.74 (br, 2 H), 2.03 (s, 3H), 1.21 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.7, 143.0, 139.2, 130.1, 128.6, 128.2, 124.6, 118.4, 115.7, 61.5, 39.0, 27.4, 18.0. HRMS (EI) m/z: calcd for $C_{15}H_{21}NO_2^+$ ($[M]^+$) 247.1569; Found 247.1569.

2.5. General procedure for Stille coupling reaction

A suspension of $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol), CuI (0.048 g, 0.25 mmol), CsF (0.76 g, 5.00 mmol), and *o*-iodoaniline 5 (0.56 g, 2.50 mmol) in a DMF were stirred at room temperature followed by the addition of (*E*)-tributyl(1-phenylprop-1-en-1-yl)stannane **30m** (1.22 g, 3.00 mmol) in DMF solution. The reaction mixture was placed at 100 ºC, then stirred for 12 h. The reaction was quenched with water (10 mL) and washed with diethyl ether (10 mL ×

3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding products **32m**.

2.5.1. 2-(1-phenylprop-1-en-1-yl)aniline (32m)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product **32m** (0.368 g, 1.76 mmol, 70% - *E*/*Z*=8:1 of regioisomer) as a white solid, mp : 66 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.26 (m, 6 H), 7.10 – 7.06 (m, 2H), 6.76 – 6.72 (m, 1 H), 6.63 – 6.61 (m, 1 H), 5.95 (q, J = 7.1 Hz, 1 H), 3.53 (br, 2 H), 1.91 (d, J = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 140.2, 139.5, 131.1, 130.2, 129.4, 128.4, 128.3, 127.2, 126.3, 118.3, 115.8, 15.6. MS (EI) m/z (relative intensity): 209 (M, 100), 194 (40), 180 (69), 165 (19), 152 (9), 139 (3), 130 (12), 115 (16), 103 (4), 91 (8), 77 (7), 65 (3), 51 (3).

2.5.2. 2-(2-aminophenyl)but-2-en-1-ol (32n)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (1:1) with Ninhydrin staining to give the corresponding product **32n** (0.215 g, 1.32 mmol, 58% - *E*/*Z*=4:1 of regioisomer) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 - 7.06 (m, 1 H, major and minor isomer), 7.00 (dd, J = 7.5, 1.5 Hz, 1 H, major isomer),

6.94 (dd, J = 7.5, 1.5 Hz, 1 H, minor isomer), 6.79 – 6.71 (m, 1 H for major and 2 H for minor isomer), 6.82 (dd, J = 7.8, 1.0 Hz, 1H, major isomer), 5.92 (q, J = 6.8 Hz, 1 H, minor isomer), 5.71 (q, J = 7.0 Hz, 1 H, major isomer), 4.43 (d, J = 0.4 Hz, 2 H, major isomer), 4.23 (s, 2 H, minor isomer), 1.85 (d, J = 7.0 Hz, 3 H, major isomer), 1.53 (d, J = 6.8 Hz, 3 H, minor isomer). ^{13}C NMR (100 MHz, $CDCl_3$) of mixture of two isomers: δ 144.0, 143.9, 138.6, 138.3, 129.8, 129.5, 129.2, 128.5, 128.3, 128.1, 124.8, 124.4, 118.7, 118.5, 115.9, 115.4, 67.3, 60.5, 14.2, 13.8. HRMS (EI) m/z: calcd for $C_{10}H_{13}NO^+$ ($[M]^+$) 163.0995; Found 163.0995.

2.5.3. (*E*)-2-(1-(4-bromophenyl)-2-phenylvinyl)aniline (32o)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product **32o** (0.153 g, 0.44 mmol, 48%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 8.5 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 2 H), 7.22 – 7.08 (m, 7 H), 6.96 – 6.95 (m, 1 H), 6.78 – 6.71 (m, 2 H), 3.56 (br, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 140.8, 137.8, 136.7, 131.6, 130.9, 129.7, 129.1, 129.0, 128.4, 128.3, 127.6, 124.8, 121.8, 119.1, 115.9. HRMS (EI) m/z: calcd for 50% of $C_{20}H_{16}{}^{79}BrN^+$ ($[M]^+$) 349.0463; Found 349.0461. HRMS (EI) m/z: calcd for 50% of $C_{20}H_{16}{}^{81}BrN^+$ ($[M]^+$) 351.0455; Found 351.0455.

2.5.4. (*E*)-2-(2-(4-bromophenyl)-1-phenylvinyl)aniline (32p)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with Ninhydrin staining to give the corresponding product **32p** (0.122 g, 0.35 mmol, 38%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.38 (m, 2 H), 7.41 – 7.25 (m, 4 H), 7.20 – 7.08 (m, 2 H), 7.02 (s, 1 H), 6.96 – 6.94 (m, 2 H), 6.81 – 6.68 (m, 2 H), 3.56, (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 141.6, 139.9, 136.1, 131.5, 131.0, 130.6, 129.3, 128.8, 128.2, 128.2, 126.9, 125.0, 121.3, 119.2, 116.0. HRMS (EI) m/z: calcd for 50% of $C_{20}H_{16}{}^{79}BrN^+$ ($[M]^+$) 349.0461; Found 349.0461. HRMS (EI) m/z: calcd for 50% of $C_{20}H_{16}{}^{81}BrN^+$ ($[M]^+$) 351.0452; Found 351.0452.

2.5.5. (*E*)-2-(2-(4-bromophenyl)-1-phenylvinyl)aniline (32q)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (4:1) with Ninhydrin staining to give the corresponding product **32q** (0.169 g, 0.54 mmol, 80%) as a pale yellow solid, mp : 126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.6 Hz, 2 H), 7.49 (d, J = 8.6 Hz, 2 H), 7.22 – 7.13 (m, 7 H), 6.99 – 6.97 (m, 1 H), 6.82 – 6.75 (m, 2 H), 3.58 (br, 2 H), 2.59 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 146.7, 144.2, 138.0, 136.6, 136.3, 131.6, 131.0, 129.7, 129.4, 128.8, 128.5, 128.1, 127.0, 124.8, 119.3, 116.1, 26.8. HRMS (EI) m/z: calcd for $C_{22}H_{19}NO^+$ ($[M]^+$) 313.1470; Found 314.1470.

2.6. General procedure for PIFA mediated aminocyclization

The PIFA (0.15 g, 0.35 mmol) was placed to the reaction vessel, then tetrahydrofuran (1 mL) was charged. *o*-alkenyl aniline **32a** (0.050 g, 0.29 mmol) in tetrahydrofuran (1 mL) was added dropwise to the vessel with stirring. After 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding products **33a**.

2.6.1. 2,3,4,9-tetrahydro-1H-carbazole (33a)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33a** (0.030 g, 0.18 mmol, 60%) as a yellow solid, mp: 106 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (br, 1 H), 7.46 – 7.45 (m, 1 H), 7.28 – 7.25 (m, 1 H), 7.13 – 7.04 (m, 2 H), 2.74 – 2.69 (m, 4 H), 1.92 – 1.86 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 134.2, 128.0, 121.2, 119.3, 117.9, 110.5, 110.4, 23.5, 23.5, 23.4, 21.1. MS (EI) m/z (relative intensity): 171 (M, 54), 154 (5), 143 (100), 115 (9), 77 (1).

2.6.2. 1,2,3,4-tetrahydrocyclopenta[b]indole (33b)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33b** (0.028 g, 0.18 mmol, 57%) as a brown solid, mp : 106 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (br, 1 H), 7.44 – 7.41 (m, 1 H), 7.30 – 7.25 (m, 1 H), 7.11 – 7.04 (m, 2 H), 2.88 – 2.81 (m, 4 H), 2.57 – 2.50 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 141.2, 124.9, 120.7, 120.0, 119.7, 118.7, 111.5, 28.9, 26.0, 24.6. MS (EI) m/z (relative intensity): 156 (M, 100), 130 (25), 115 (4), 102 (4), 77 (8), 65 (4).

2.6.3. 5,6,7,8,9,10-hexahydrocyclohepta[b]indole (33c)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33c** (0.041 g, 0.22 mmol, 83%) as a white solid, mp : 143 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (br, 1 H), 7.51 – 7.46 (m, 1 H), 7.28 – 7.24 (m, 1 H), 7.01 – 7.06 (m, 2 H), 2.85 – 2.80 (m, 4 H), 1.92 – 1.87 (m, 2 H), 1.81 – 1.74 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 134.4, 132.2, 129.5, 120.8, 119.2, 117.8, 110.3, 32.0, 29.8, 28.9, 27.7, 24.9. MS (EI) m/z (relative intensity): 185 (M, 100), 156 (82), 143 (34), 130 (27), 115 (9), 102 (4), 77 (6).

2.6.4. 2,3-diethyl-1H-indole (33e)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33e** (0.035 g, 0.20 mmol, 70% from ***E*-32e** and 0.019 g, 0.11 mmol, 38% from ***Z*-32e** as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (br, 1 H), 7.54 – 7.52 (m, 1 H), 7.36 – 7.25 (m, 1 H), 7.13 – 7.05 (m, 2 H), 2.79 – 2.69 (m, 4 H), 1.28 (t, J = 7.6 Hz, 3 H), 1.23 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.2, 135.4, 128.6, 121.0, 119.1, 118.4, 113.3, 110.5, 19.5, 17.5, 16.0, 14.7. MS (EI) m/z (relative intensity): 173 (M, 40), 158 (100), 143 (24), 130 (15), 117 (4), 77 (5), 65 (4), 51 (5).

2.6.5. 2-ethyl-3-methyl-1H-indole (33f)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33f** (0.040 g, 0.25 mmol, 80% from ***E*-32f** and 0.028 g, 0.18 mmol, 56% from ***Z*-32f** as a pale orange solid, mp : 57 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (br, 1 H), 7.49 – 7.47 (m, 1 H), 7.28 – 7.26 (m, 1 H), 7.13 – 7.06 (m, 2 H), 2.76 (q, J = 7.6 Hz, 2 H), 2.24 (s, 3 H), 1.27 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 135.3, 129.6, 121.1, 119.2, 118.2, 110.3, 106.4, 19.6, 14.2, 8.5. MS (EI) m/z (relative intensity): 159 (M, 52), 144 (100), 130 (11), 115 (7), 102 (3), 89 (2), 77 (7), 65 (2), 51 (2).

2.6.5. 2-ethyl-3-methyl-1H-indole (33f)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33f** (0.040 g, 0.25 mmol, 80% from ***E*-32f** and 0.028 g, 0.18 mmol, 56% from ***Z*-32f** as a pale orange solid, mp : 57 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (br, 1 H), 7.49 – 7.47 (m, 1 H), 7.28 – 7.26 (m, 1 H), 7.13 – 7.06 (m, 2 H), 2.76 (q, J = 7.6 Hz, 2 H), 2.24 (s, 3 H), 1.27 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 135.3, 129.6, 121.1, 119.2, 118.2, 110.3, 106.4, 19.6, 14.2, 8.5. MS (EI) m/z (relative intensity): 159 (M, 52), 144 (100), 130 (11), 115 (7), 102 (3), 89 (2), 77 (7), 65 (2), 51 (2).

2.6.6. 2-isopropyl-3-methyl-1H-indole (33g)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33g** (0.030 g, 0.17 mmol, 61% from ***E*-32g** and 0.016 g, 0.09 mmol, 32% from ***E*/*Z*-32f** as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (br, 1 H), 7.50 – 7.48 (m, 1 H), 7.29 – 7.27 (m, 1 H), 7.13 – 7.06 (m, 2 H), 3.26 (p, J = 7.0 Hz, 1 H), 2.25 (s, 3 H), 1.31 (d, J = 7.0 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 134.9, 129.5, 120.9, 119.0, 118.1, 110.3, 105.3, 25.7, 22.4, 8.4. MS (EI) m/z (relative intensity): 173 (M, 40), 158 (100), 143 (24), 130 (13), 117 (5), 103 (2), 89 (1), 77 (5), 65 (2), 51 (1).

2.6.7. 3-methyl-2-phenyl-1H-indole (33h)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33h** (0.027 g, 0.13 mmol, 54% from ***E*-32g** and 0.018 g, 0.09 mmol, 36% from ***E*/*Z*-32g** as a pale yellow solid, mp : 90 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (br, 1 H), 7.63 – 7.56 (m, 3 H), 7.51 – 7.45 (m, 2 H), 7.39 – 7.32 (m, 2 H), 7.24 – 7.12 (m, 2 H), 2.46 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 134.2, 133.5, 130.2, 129.0, 127.9, 127.5, 122.5, 119.7, 119.2, 110.9, 108.9, 9.9. MS (EI) m/z (relative intensity): 207 (M, 100), 178 (12), 152 (2), 130 (21), 102 (9), 77 (9), 51 (4).

2.6.8. 2,3-diphenyl-1H-indole (33i)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33i** (0.031 g, 0.12 mmol, 62% from ***E*/*Z*-32i** as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (br, 1 H), 7.73 – 7.71 (m, 1 H), 7.49 – 7.26 (m, 12 H), 7.19 – 7.17 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 135.3, 134.3, 132.9, 131.4, 130.4, 128.9, 128.7, 128.4, 127.9, 126.4, 122.9, 120.6, 119.9, 115.3, 111.1 MS (EI) m/z (relative intensity): 269 (M, 100), 239 (5), 207 (1), 190 (1), 165 (7), 134 (8), 113 (1), 94 (1), 77 (1), 51 (1).

2.6.9. 2-methyl-3-phenyl-1H-indole (33m)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33m** (0.028 g, 0.14 mmol, 57% from ***E*/*Z*-32m** as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (br, 1 H), 7.68 – 7.66 (m, 1 H), 7.52 – 7.43 (m, 4 H), 7.31 – 7.28 (m, 2 H), 7.18 – 7.09 (m, 2 H), 2.47 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 135.4, 131.6, 129.6, 128.7, 128.0, 126.0, 121.7, 120.2, 119.0, 114.7, 110.5, 12.7. MS (EI) m/z (relative intensity): 207 (M, 100), 178 (12), 152 (2), 130 (14), 102 (6), 77 (4), 51 (1).

2.6.10. 3-(4-bromophenyl)-2-phenyl-1H-indole (33o)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33o** (0.021 g, 0.06 mmol, 43%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (br, 1 H), 7.65 – 7.63 (m, 1 H), 7.50 – 7.37 (m, 6 H), 7.35 – 7.30 (m, 4 H), 7.26 – 7.24 (m, 1 H), 7.19 – 7.15 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 134.6, 134.3, 132.6, 131.9, 129.1, 128.6, 128.4, 128.2, 123.1, 120.9, 120.3, 119.6, 113.9, 11.2. MS (EI) m/z (relative intensity): 347 (M, 100), 267 (59), 239 (11), 165 (14), 134 (24).

2.6.11. 2-(4-bromophenyl)-3-phenyl-1H-indole (33p)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33p** (0.020 g, 0.06 mmol, 40%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (br, 1 H), 7.67 – 7.65 (m, 1 H), 7.48 – 7.35 (m, 7 H), 7.32 – 7.24 (m, 4 H), 7.16 –7.14 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.2, 134.9, 133.0, 132.1, 131.9, 131.8, 130.3, 129.8, 128.9, 126.7, 123.3, 122.0, 120.8, 120.0, 115.9, 111.1. MS (EI) m/z (relative intensity): 347 (M, 100), 267 (65), 239 (11), 165 (15), 134 (21).

2.6.12. 1-(4-(2-phenyl-1H-indol-3-yl)phenyl)ethan-1-one (33q)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (4:1) with PMA staining to give the corresponding product **33q** (0.029 g, 0.09 mmol, 58%) as a pale yellow solid, mp: 207 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (br, 1 H) 7.96 (d, J = 8.5, 2 H), 7.71 (d, J = 8.1 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 2 H), 7.46 (d, J = 8.1 Hz, 1 H), 7.43 – 7.41 (m, 2 H), 7.38 – 7.33 (m, 3 H), 7.30 – 7.26 (m, 1 H), 7.19 – 7.17 (m, 1 H), 2.63 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 140.8, 136.2, 135.4, 135.0, 132.5, 131.0, 130.2, 129.1, 128.9, 128.6, 128.4, 123.2, 121.1, 119.6, 114.1, 111.3, 26.8. MS (EI) m/z (relative intensity): 311 (M, 99), 267 (34), 239 (7), 207 (6), 165 (6), 134 (16), 107 (1), 73 (2), 51 (1).

2.6.13. 7H-benzo[c]carbazole (33d)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33d** (0.058 g, 0.27 mmol, 38%) as a white solid, mp : 137 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 8.2 Hz, 1 H), 8.57 (d, J = 7.9 Hz, 1 H), 8.42 (br, 1 H), 8.00 (d, J = 8 Hz, 1 H), 7.86 (d, J = 8.7 Hz, 1 H), 7.71 (td, J = 7, 1.2 Hz, 1 H), 7.63 (d, J = 8.7 Hz, 1 H), 7.58 (d, J = 8 Hz, 1 H), 7.47 (q, J = 8 Hz, 2 H), 7.39 (td, J = 7.5, 1.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 137.3, 130.1, 129.5, 129.4, 127.6, 127.1, 124.5, 124.3, 123.5, 123.2, 122.2, 120.5, 112.7, 111.3. MS (EI) m/z (relative intensity): 217 (M, 100), 189 (6), 163 (3), 133 (1), 109 (7), 82 (1), 63 (1).

2.6.14. 3-(methoxymethyl)-1H-indole-2-carbaldehyde (33j)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (2:1) with PMA staining to give the corresponding product **33j** (0.010 g, 0.05 mmol, 22%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.16 (s, 1 H), 7.81 (br, 1 H), 7.80 (dd, J = 8.2, 0.9 Hz, 1 H), 7.44 – 7.38 (m, 2 H), 7.22 – 7.18 (m, 1 H), 4.98 (s, 2 H), 3.48 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.8, 137.3, 133.1, 127.7, 127.3, 123.8, 121.9, 121.4, 112.5, 64.9, 58.5. MS (EI) m/z (relative intensity): 189 (M, 100), 174 (73), 158 (50), 144 (18), 130 (51), 118 (23), 103 (23), 89 (14), 77 (23), 63 (8), 51 (8).

2.6.15. 3-methyl-1H-indole-2-carbaldehyde (33k)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (4:1) with PMA staining to give the corresponding product **33k** (0.012 g, 0.075 mmol, 24%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1 H), 7.71 (d, J = 7.4 Hz, 1 H), 7.42 – 7.37 (m, 2 H), 7.18 – 7.14 (m, 1 H). 2.65 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6, 137.6, 132.4, 128.5, 127.8, 125.0, 121.6, 120.7, 112.3, 8.6. MS (EI) m/z (relative intensity): 159 (M, 99), 130 (81), 103 (21), 89 (2), 77 (25), 65 (6), 51 (9).

2.6.16. (3-methyl-1H-indol-2-yl)methyl pivalate (33l)

Following the procedure as above, residue was purified by silica gel column chromatography by using Hexane/EA (8:1) with PMA staining to give the corresponding product **33l** (0.22 g, 0.898 mmol, 21%) as a pale yellow solid, mp : 75 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (br, 1 H), 7.58 (d, J = 8.2 Hz, 1 H), 7.35 (d, J = 8.4 Hz, 1 H), 7.24 (t, J = 7 Hz, 1 H), 7.14 (t, J = 7.6 Hz, 1 H), 5.26 (s, 2 H), 2.38 (s, 3 H), 1.22 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 135.7, 129.2, 128.2, 122.7, 119.2, 119.1, 111.4, 110.9, 57.7, 38.9, 27.2, 8.5.

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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 **6**
2. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **10**
3. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **11**
4. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***cis*-12**
5. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***trans*-12**
6. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **5**
7. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **13**
8. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **4**
9. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **14**
10. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **3**
11. 400 MHz ^{1}H-NMR spectrum (Acetone-d_6) of compound **15**
12. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **16**
13. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **17**
14. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **18**
15. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **20**
16. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **21**
17. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **22**
18. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **23**
19. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **24**

20. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **25**

21. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **26**

22. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **28**

23. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32a**

24. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32b**

25. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32c**

26. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32d**

27. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32e**

28. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***Z*-32e**

29. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32f**

30. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***Z*-32f**

31. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32g**

32. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32h**

33. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32i**

34. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32j**

35. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***Z*-32k**

36. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32l**

37. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32m**

38. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32n**

39. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32o**

40. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32p**

41. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32q**

42. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33a**

43. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33b**

44. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33c**

45. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33d**

46. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33e**

47. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33f**

48. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33g**

49. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33h**

50. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33i**

51. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33j**

52. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33k**

53. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33l**

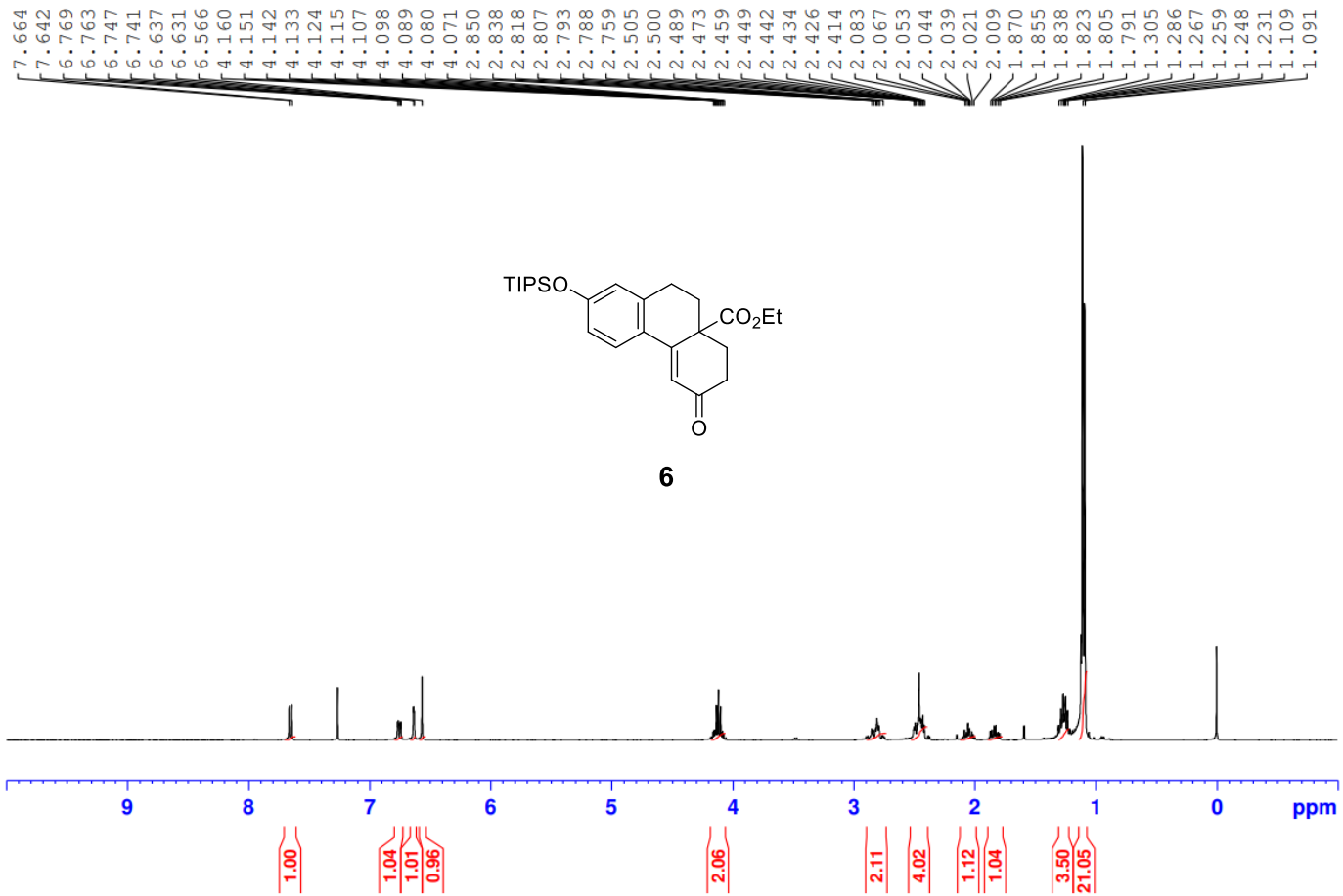
54. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33m**

55. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33n**

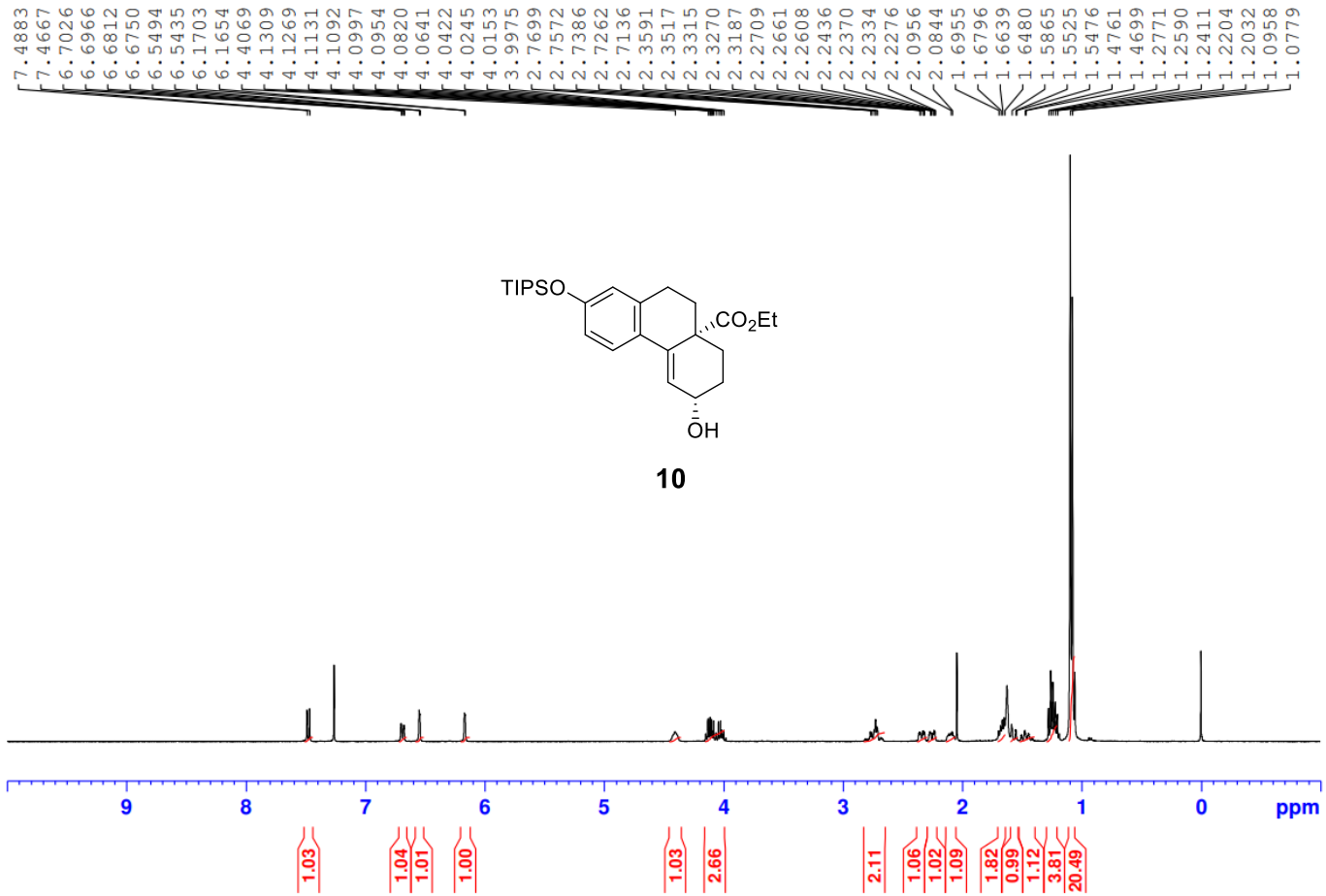
56. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33o**

57. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33p**

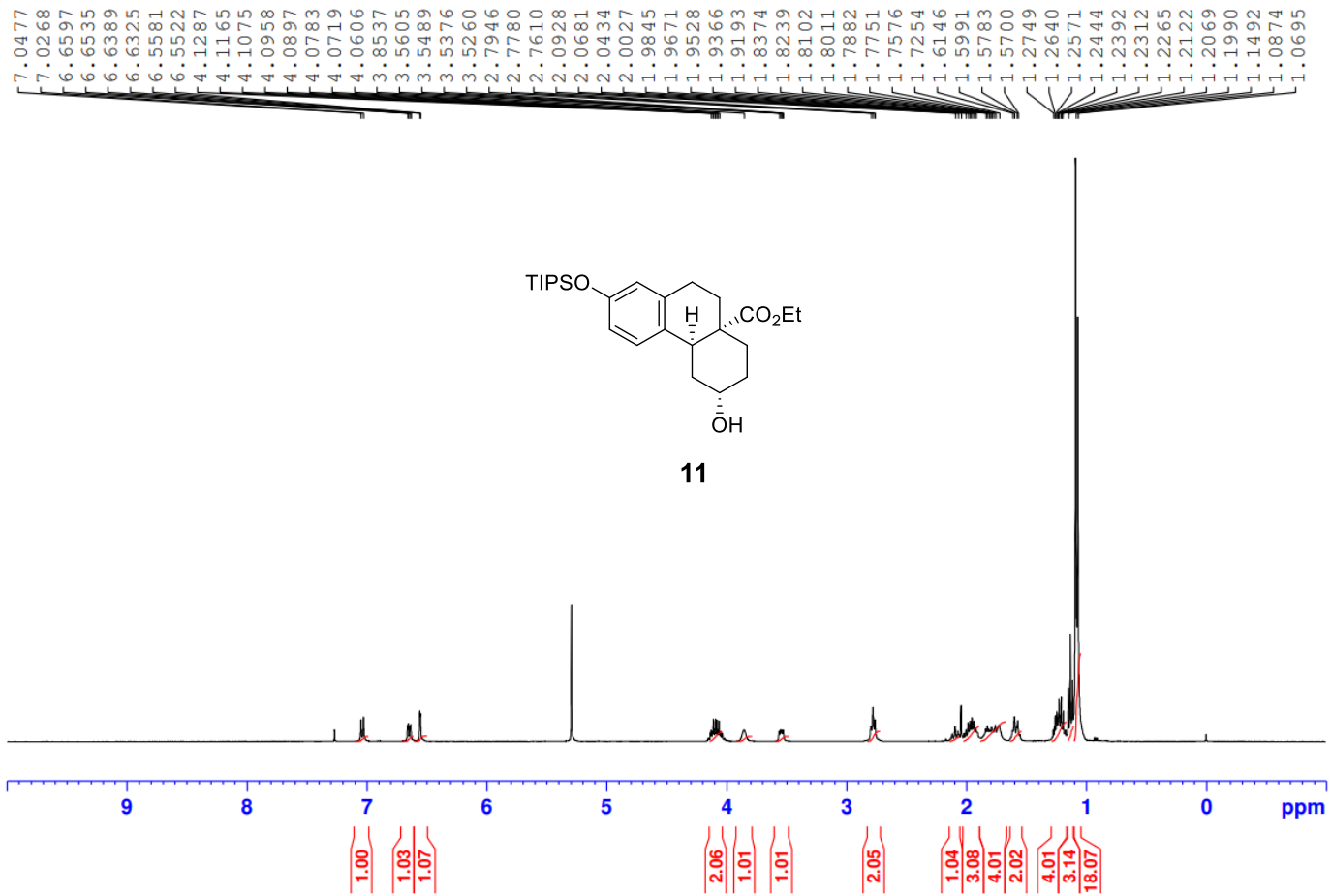
58. 400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33**



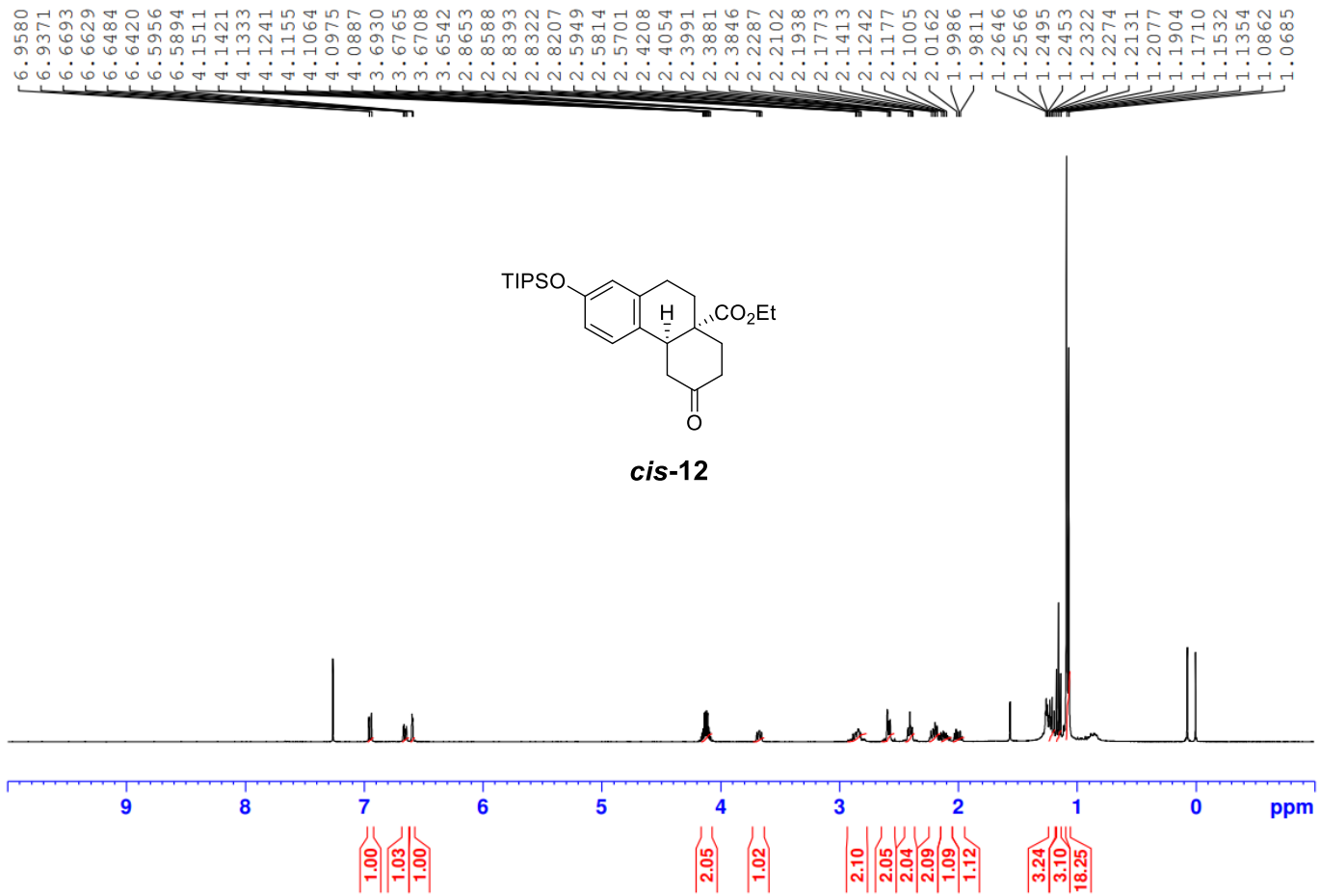
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **6**



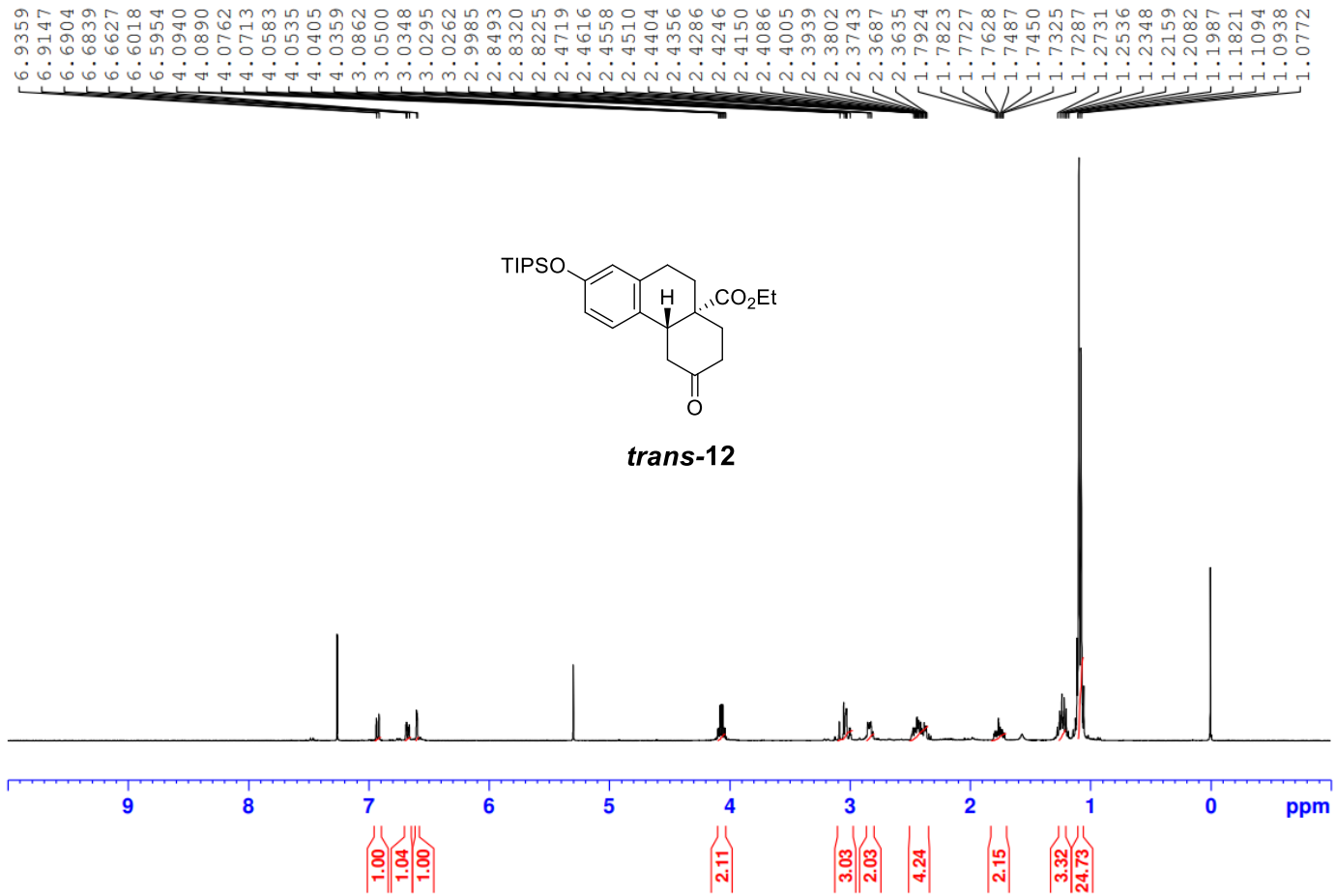
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **10**



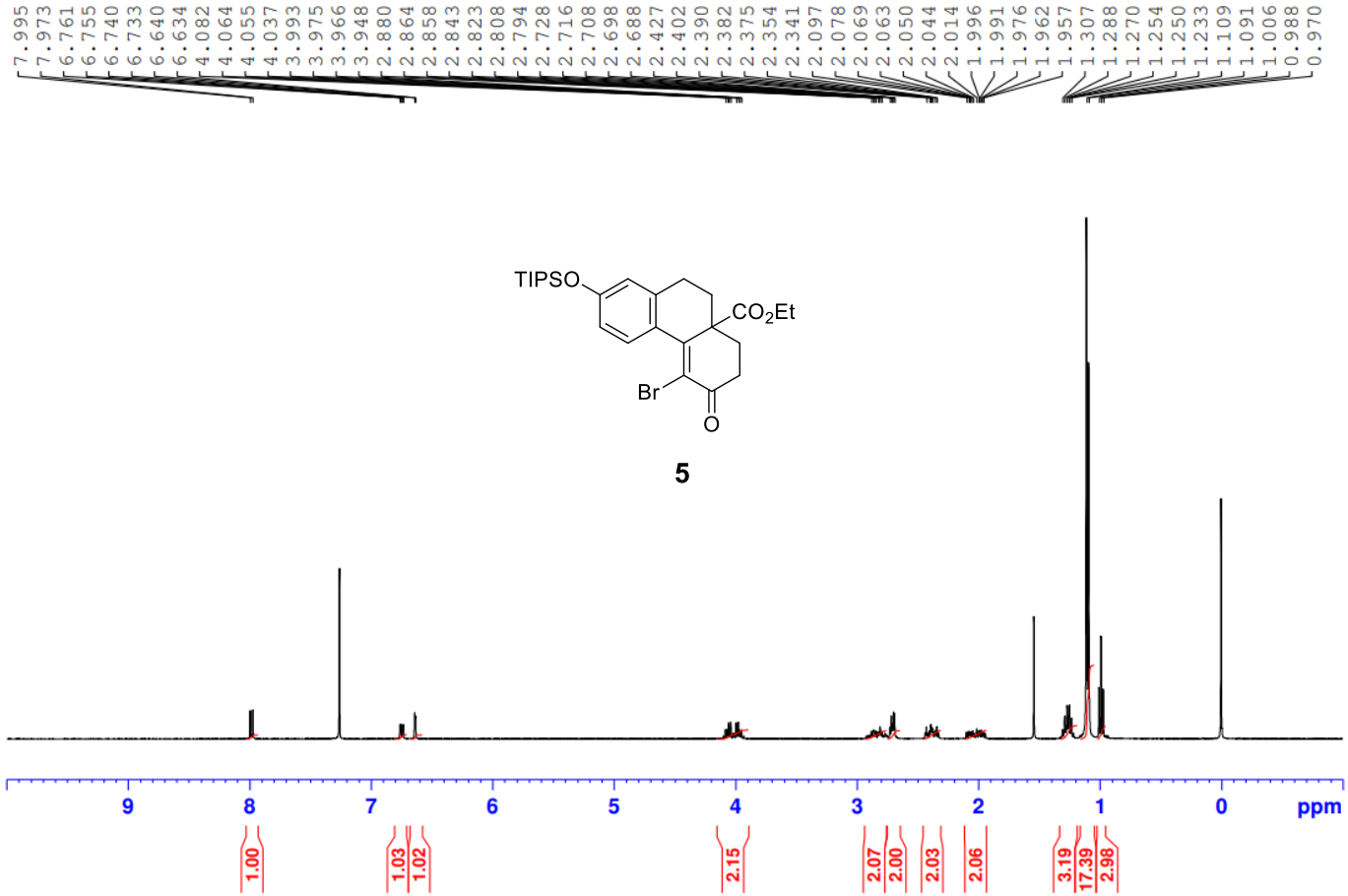
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **11**



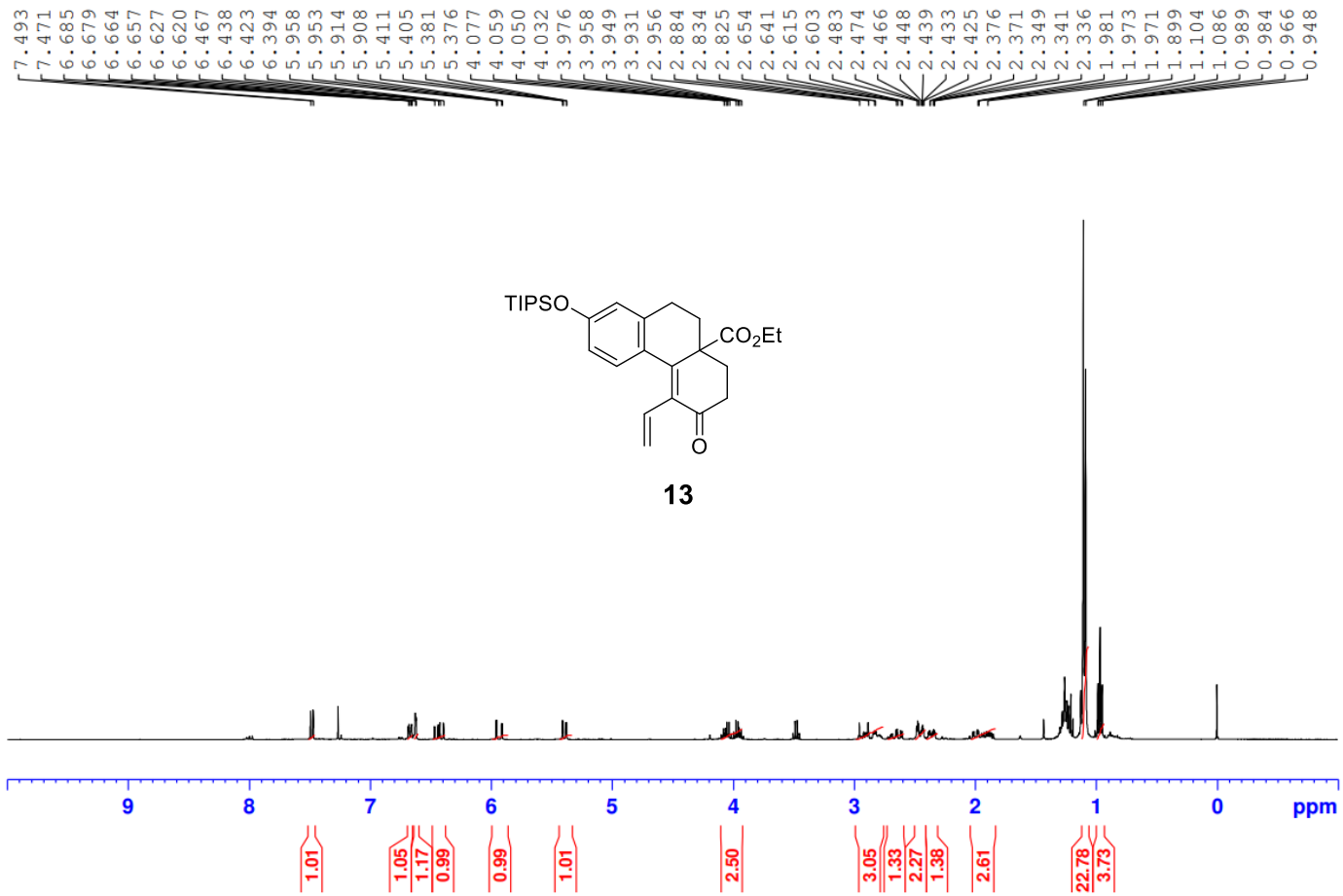
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***cis*-12**



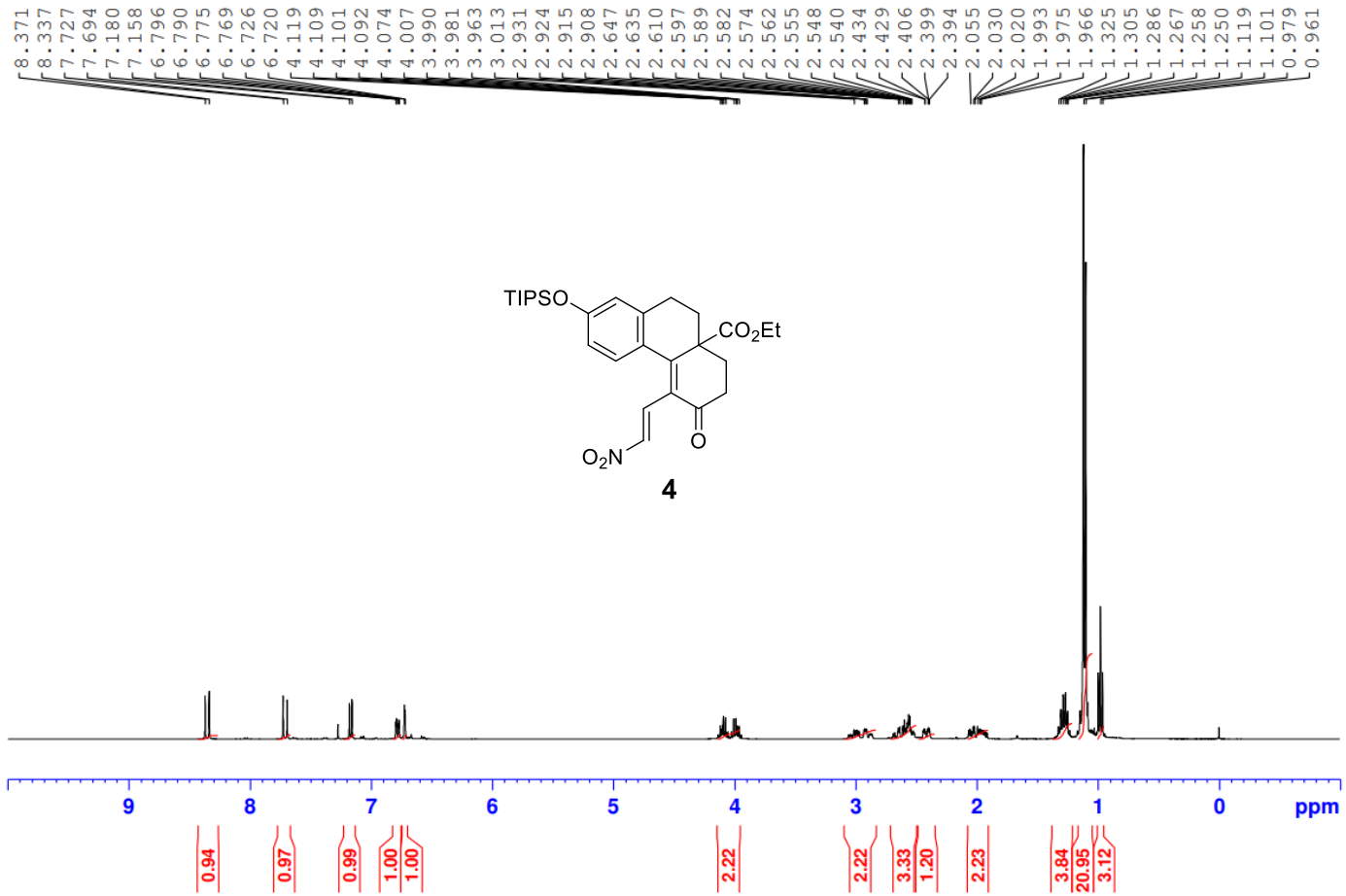
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***trans*-12**



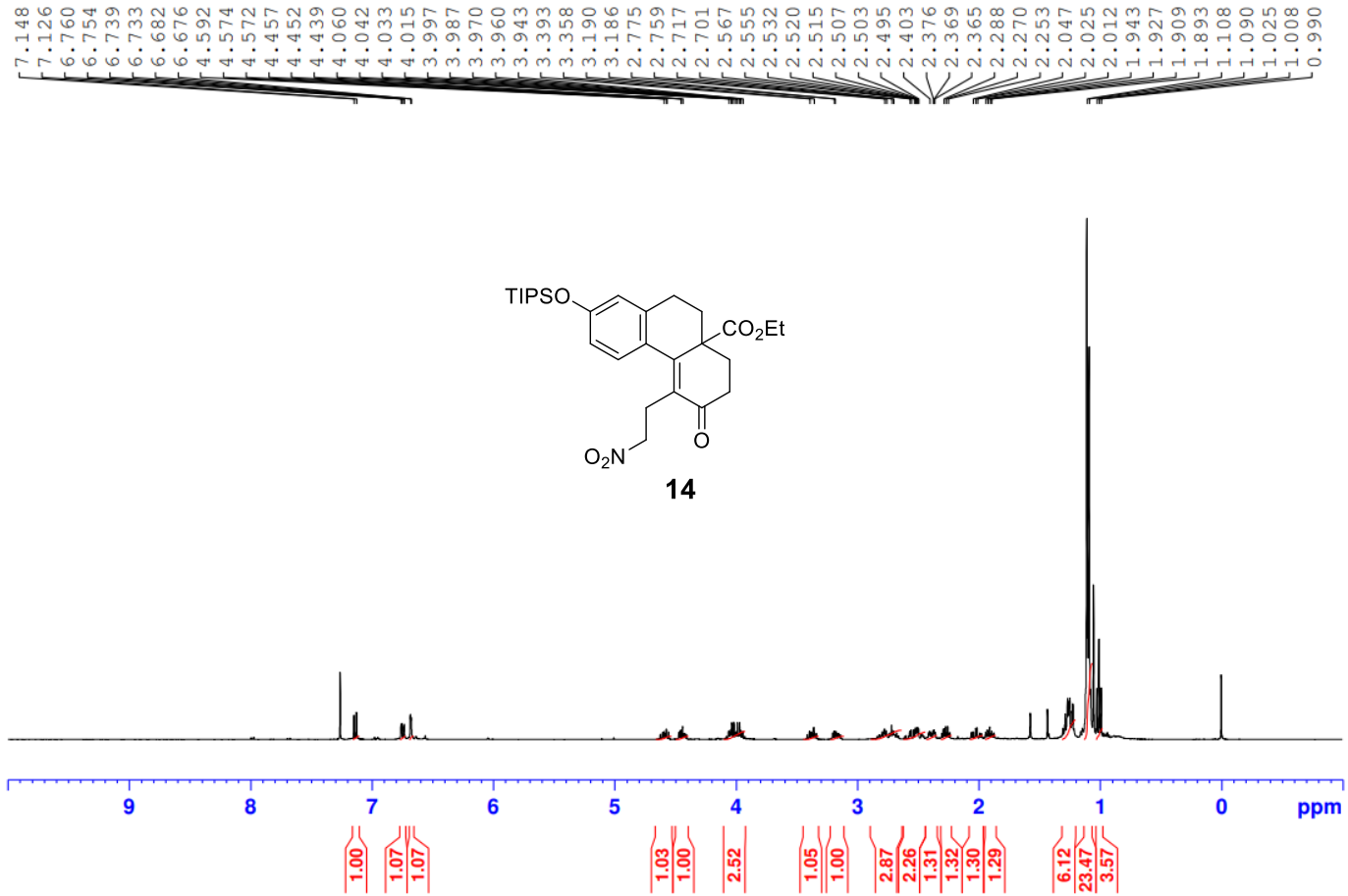
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **5**



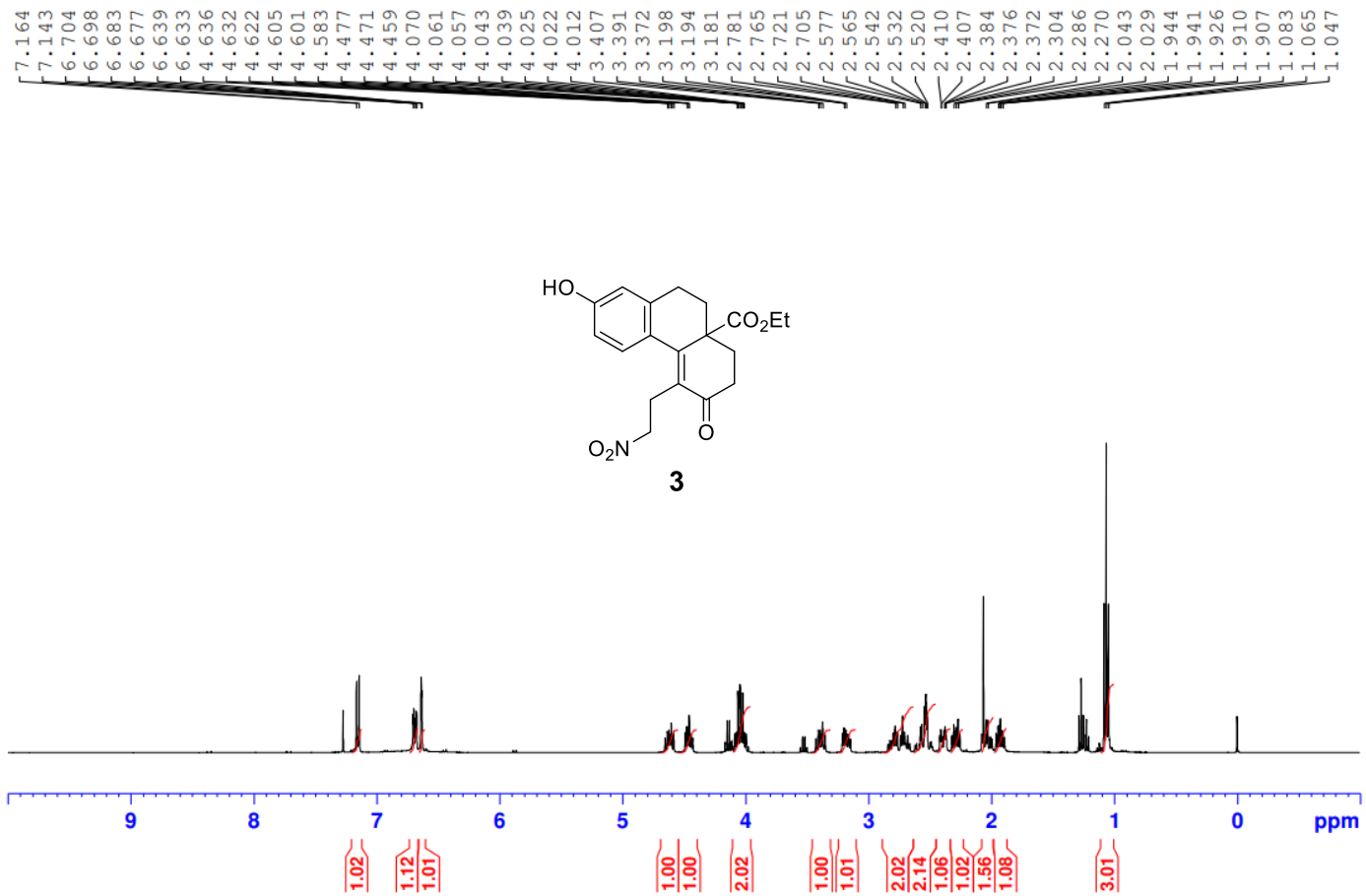
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **13**



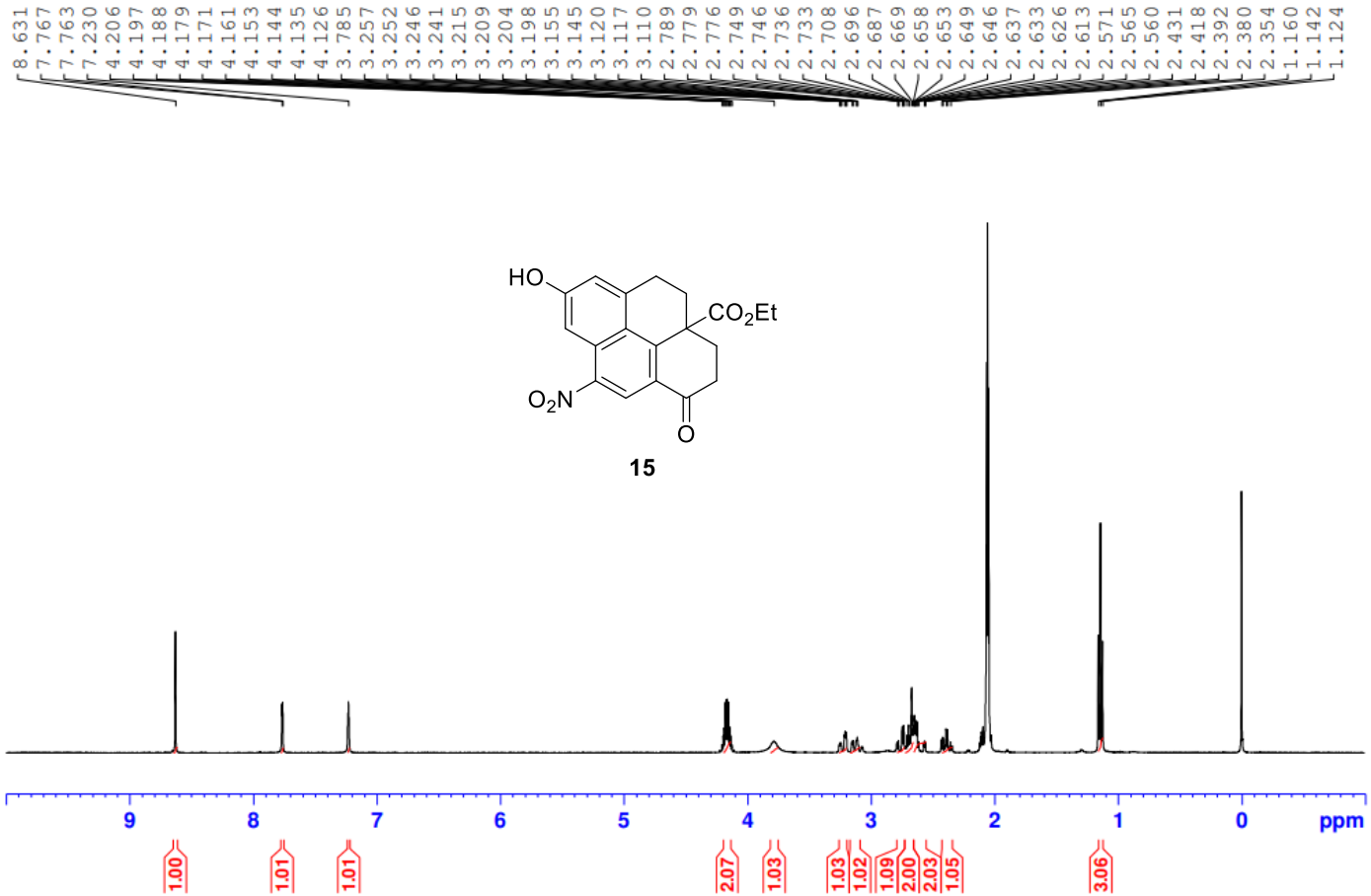
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **4**



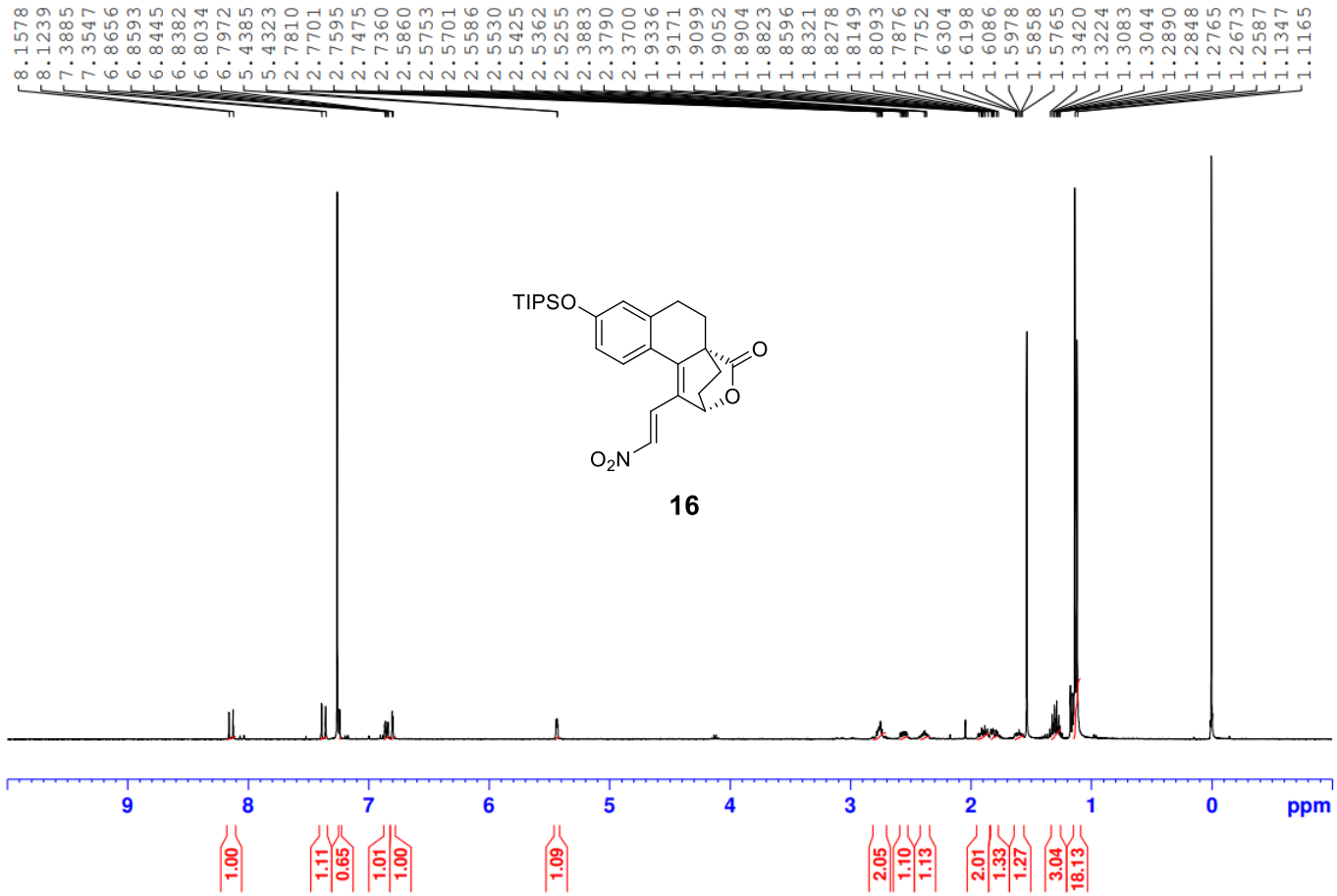
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **14**



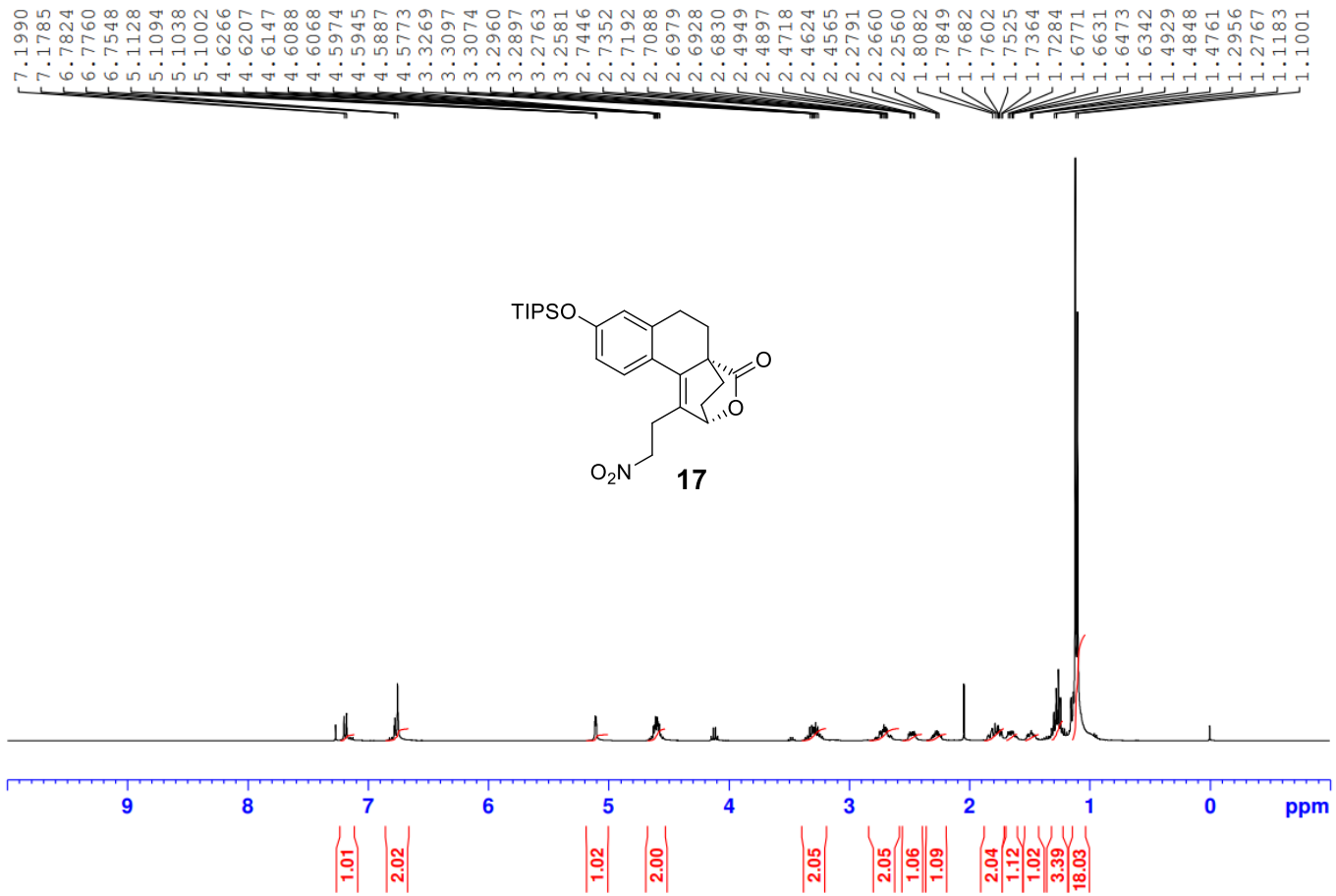
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **3**



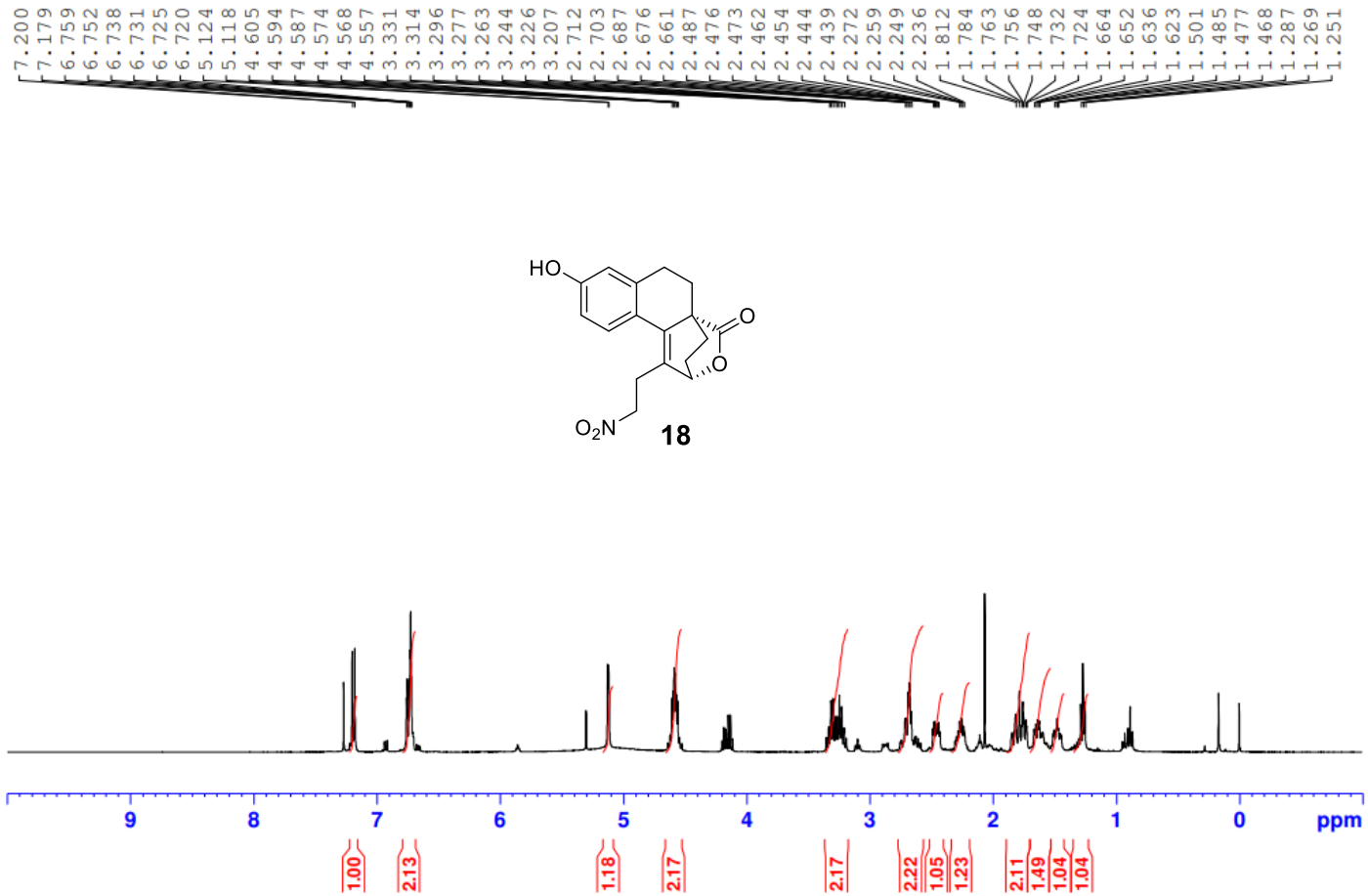
400 MHz ^{1}H-NMR spectrum (Acetone-d_6) of compound **15**



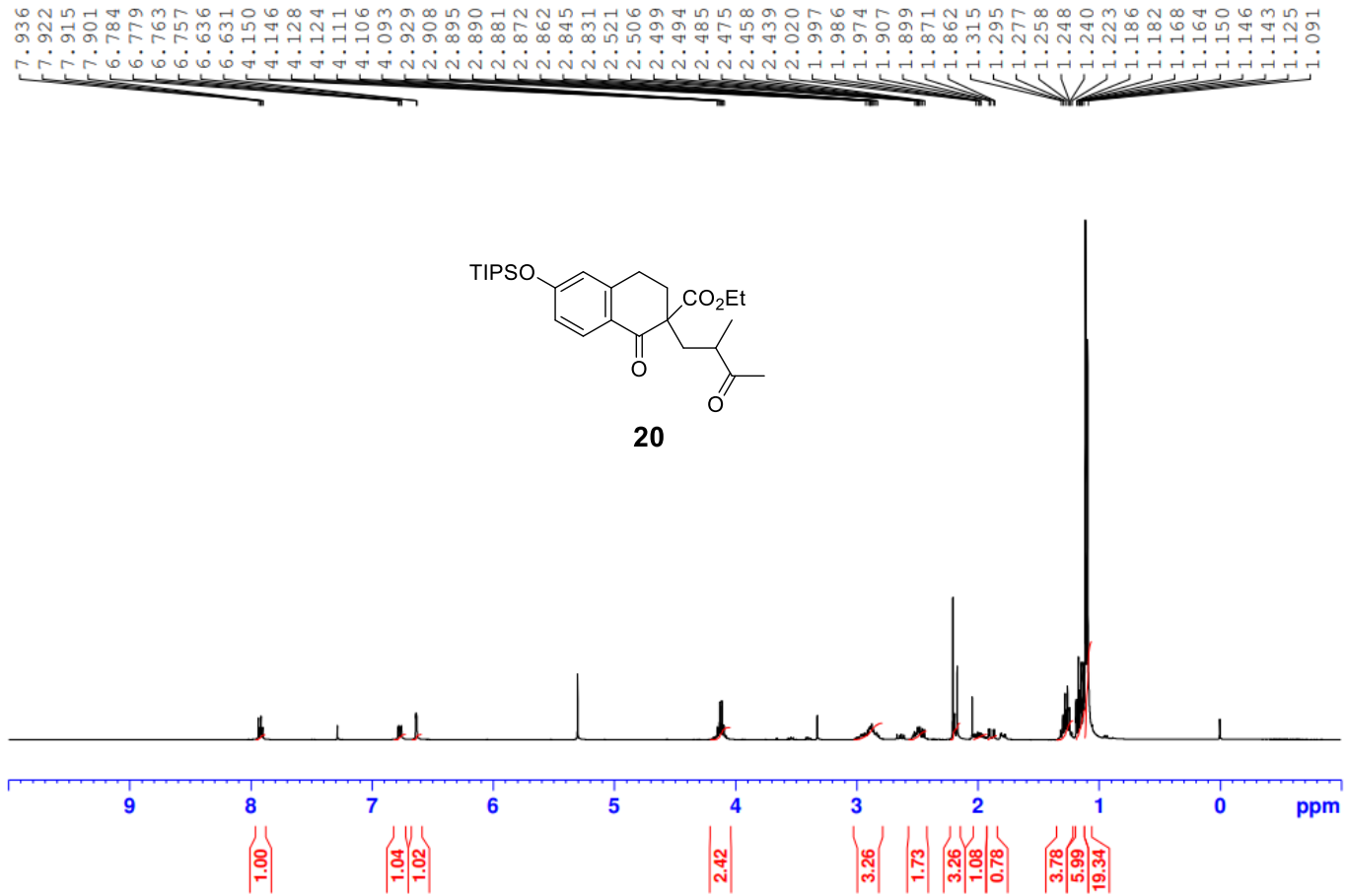
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **16**



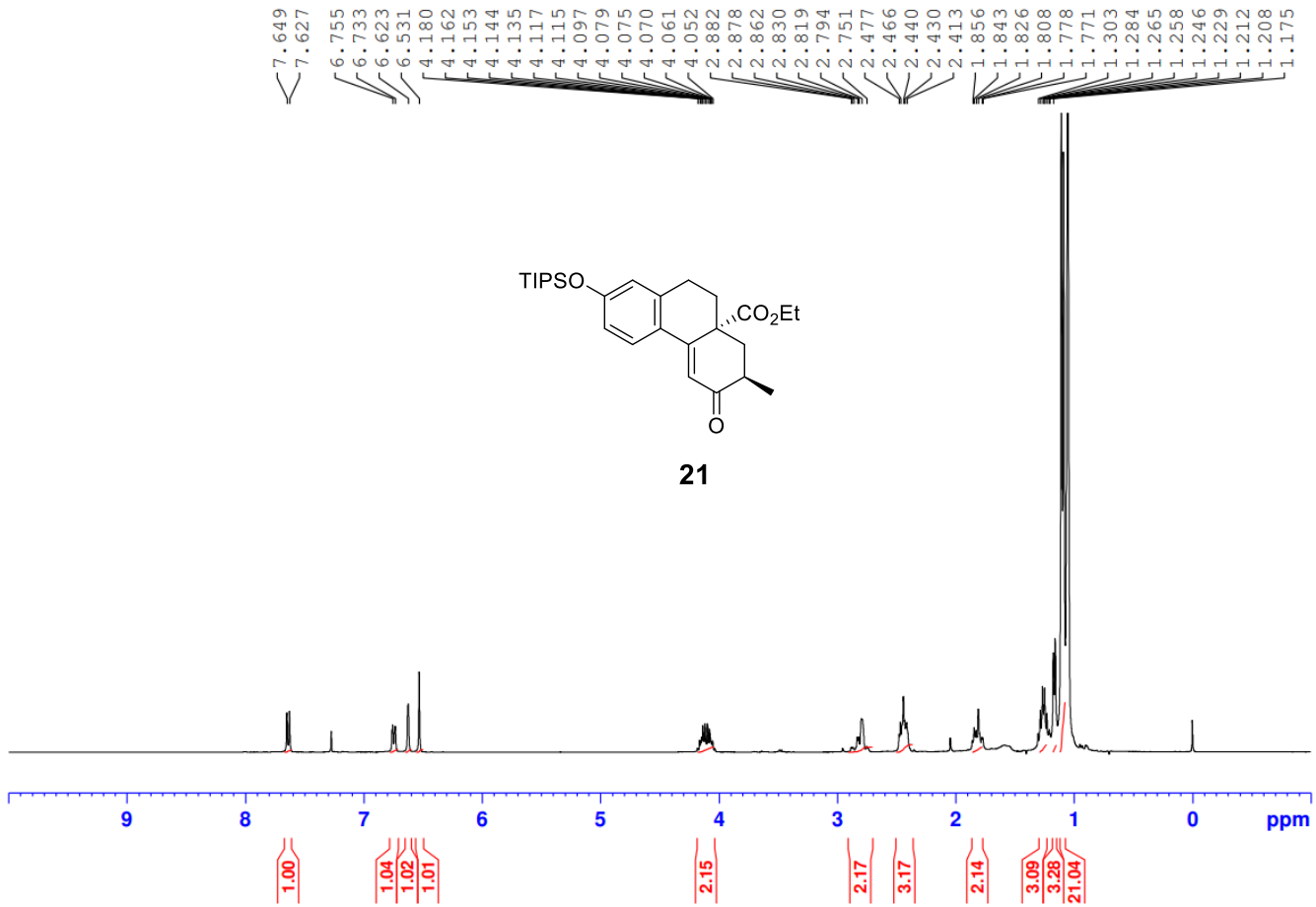
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **17**



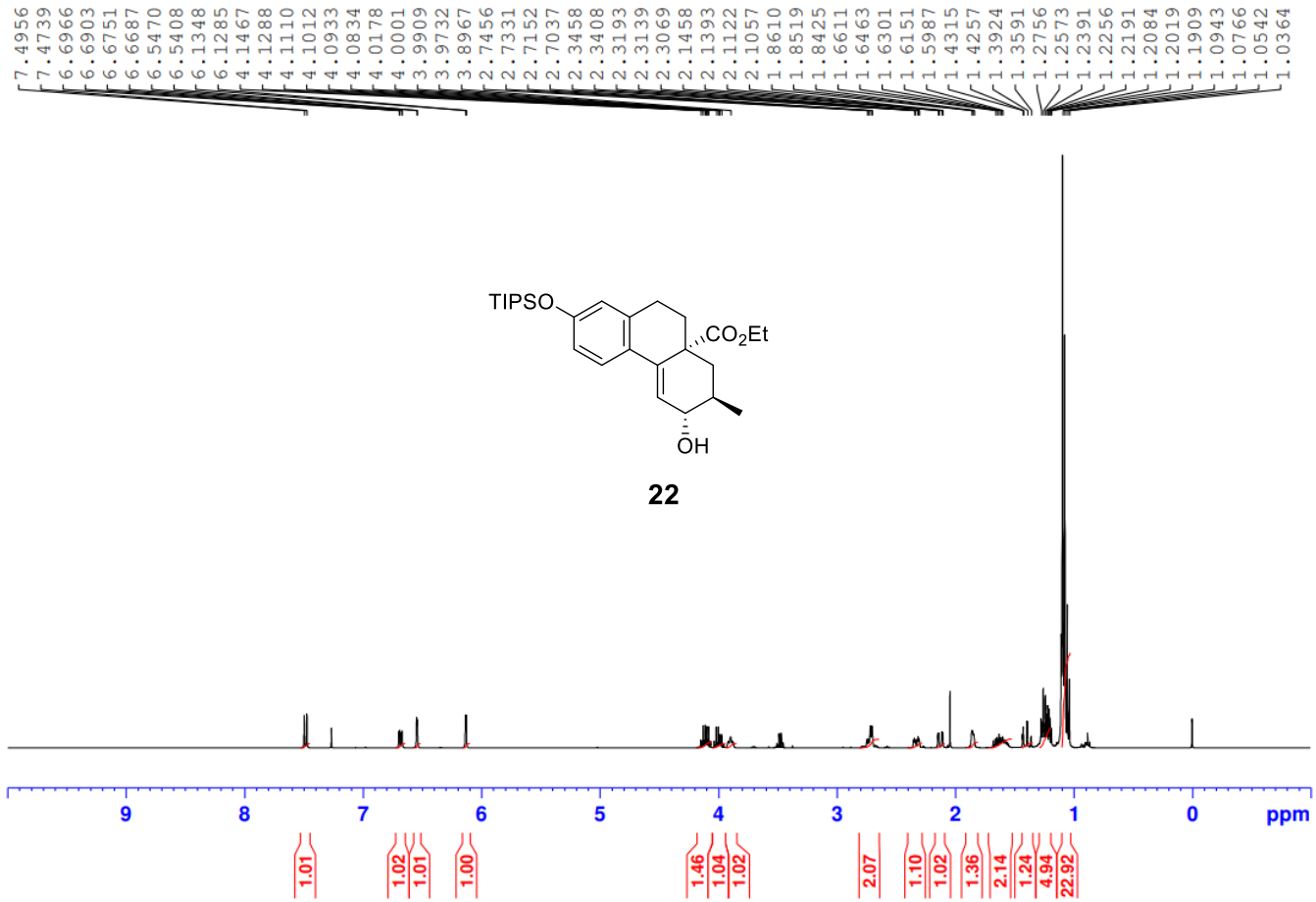
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **18**



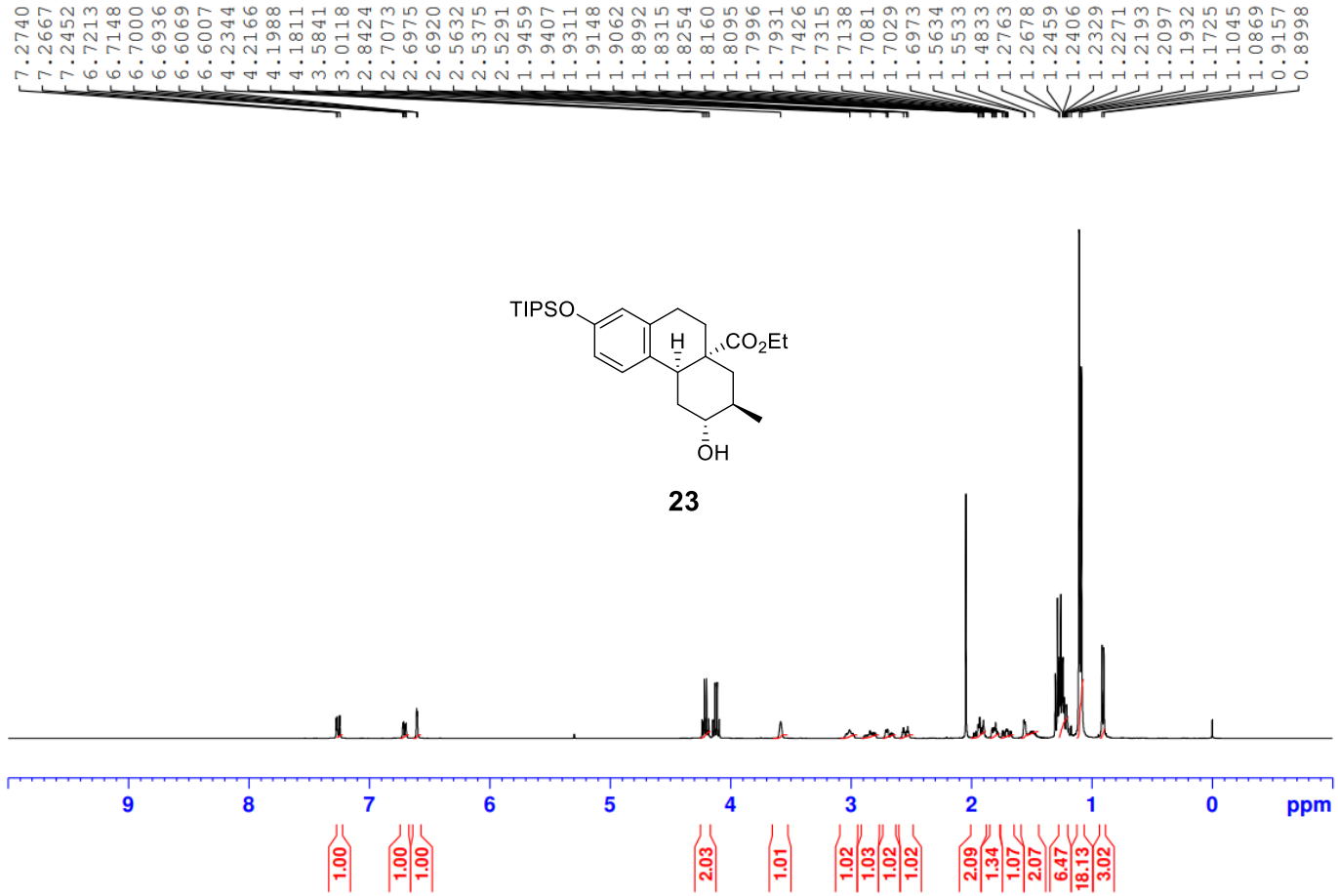
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **20**



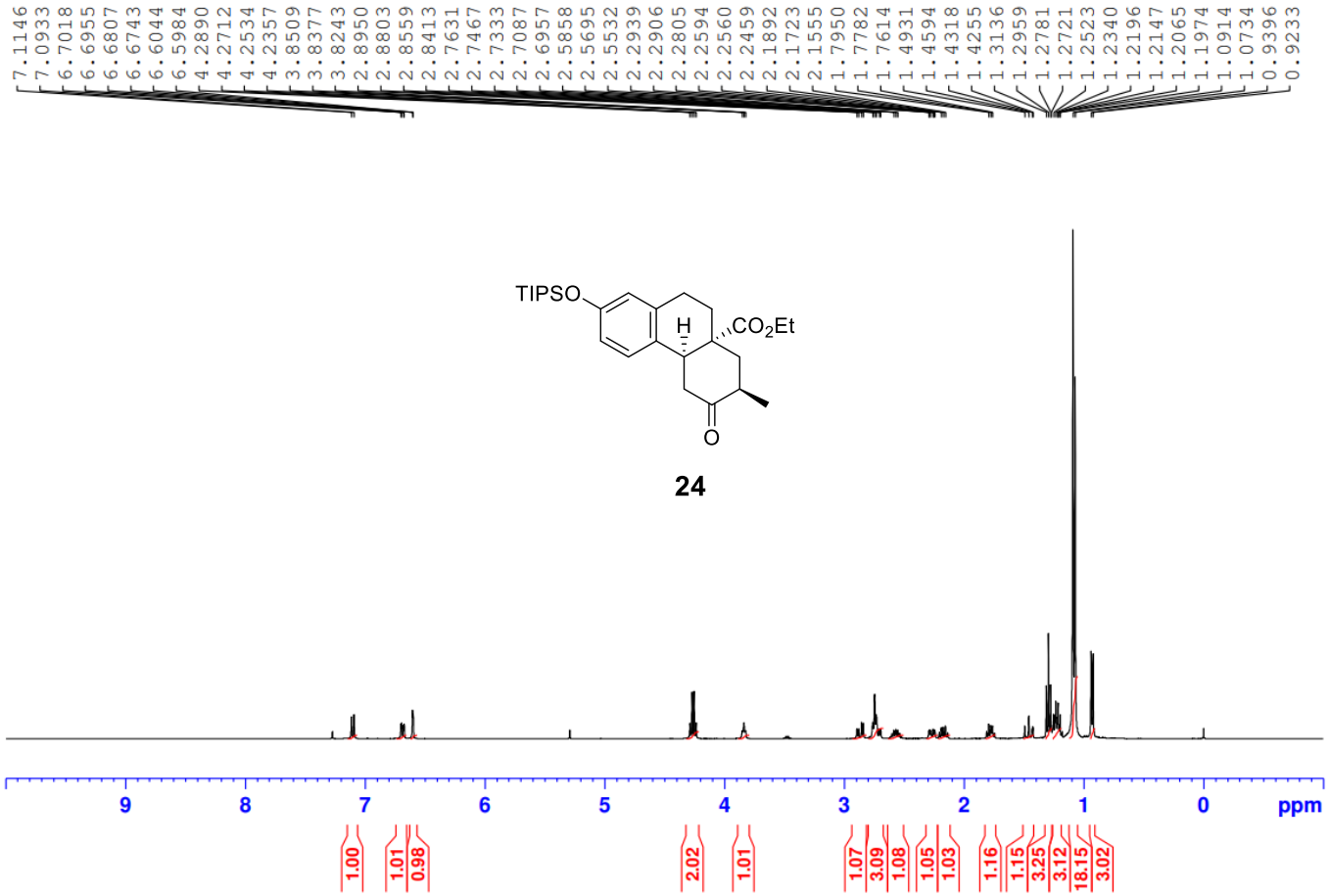
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **21**



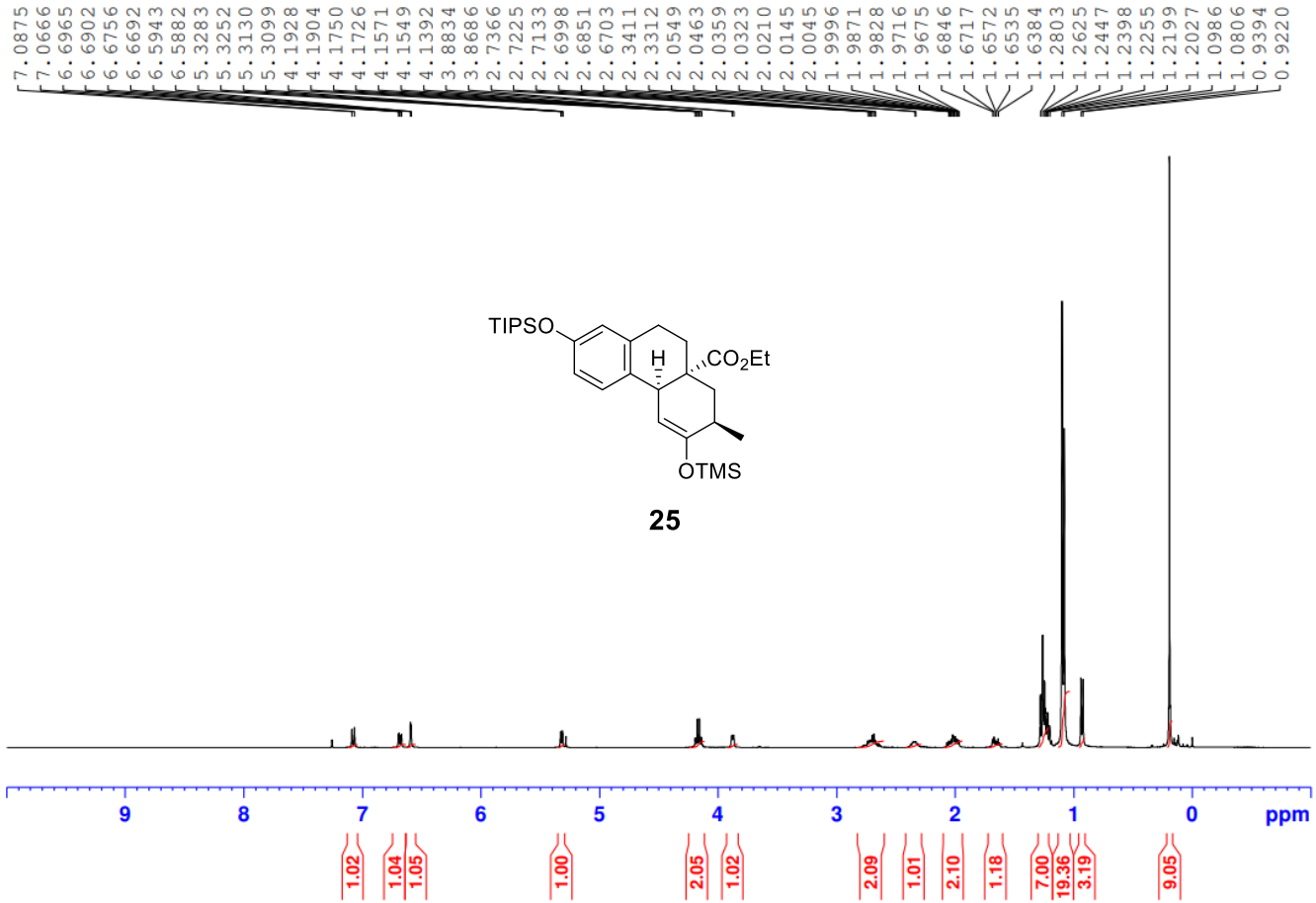
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **22**



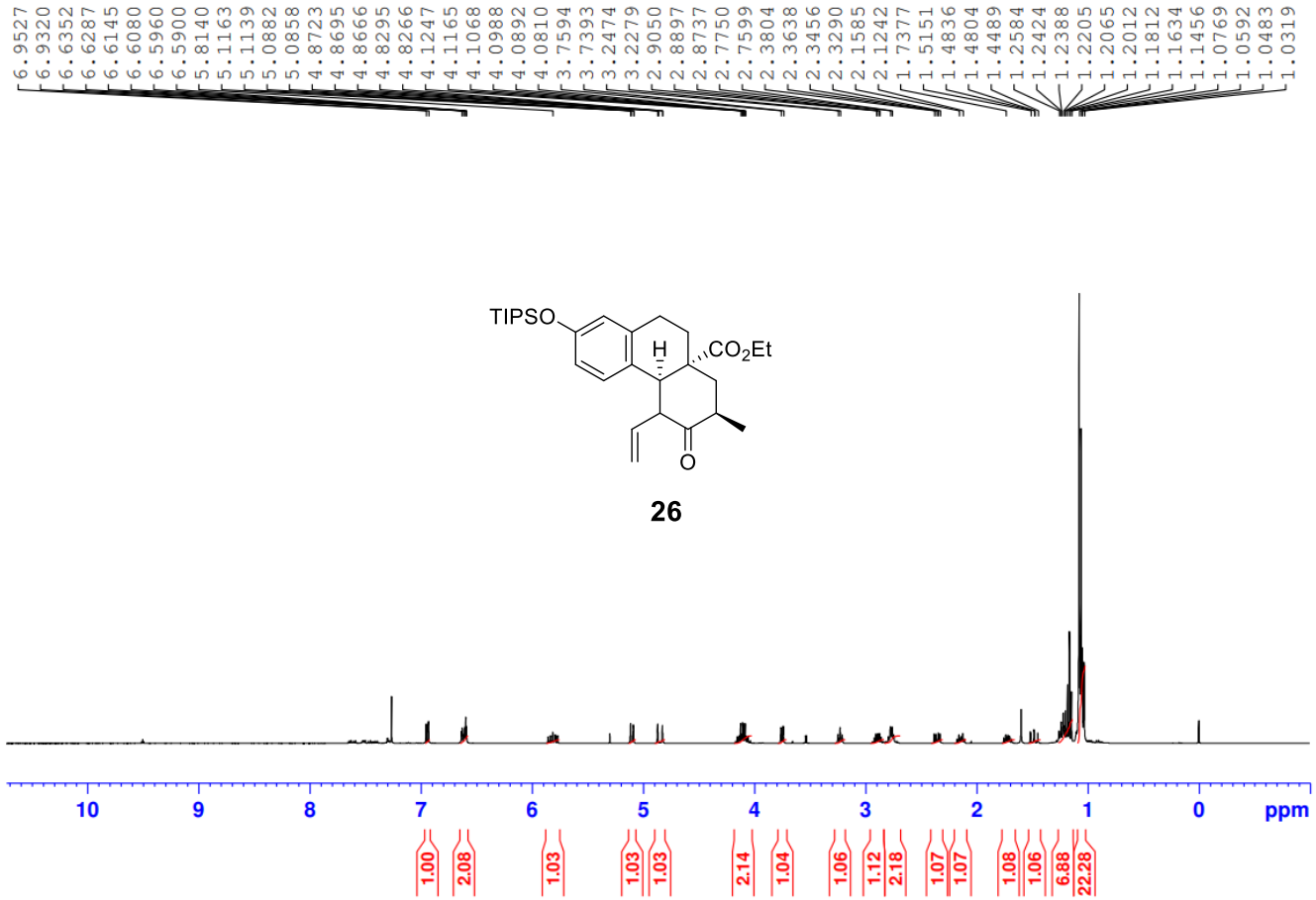
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **23**



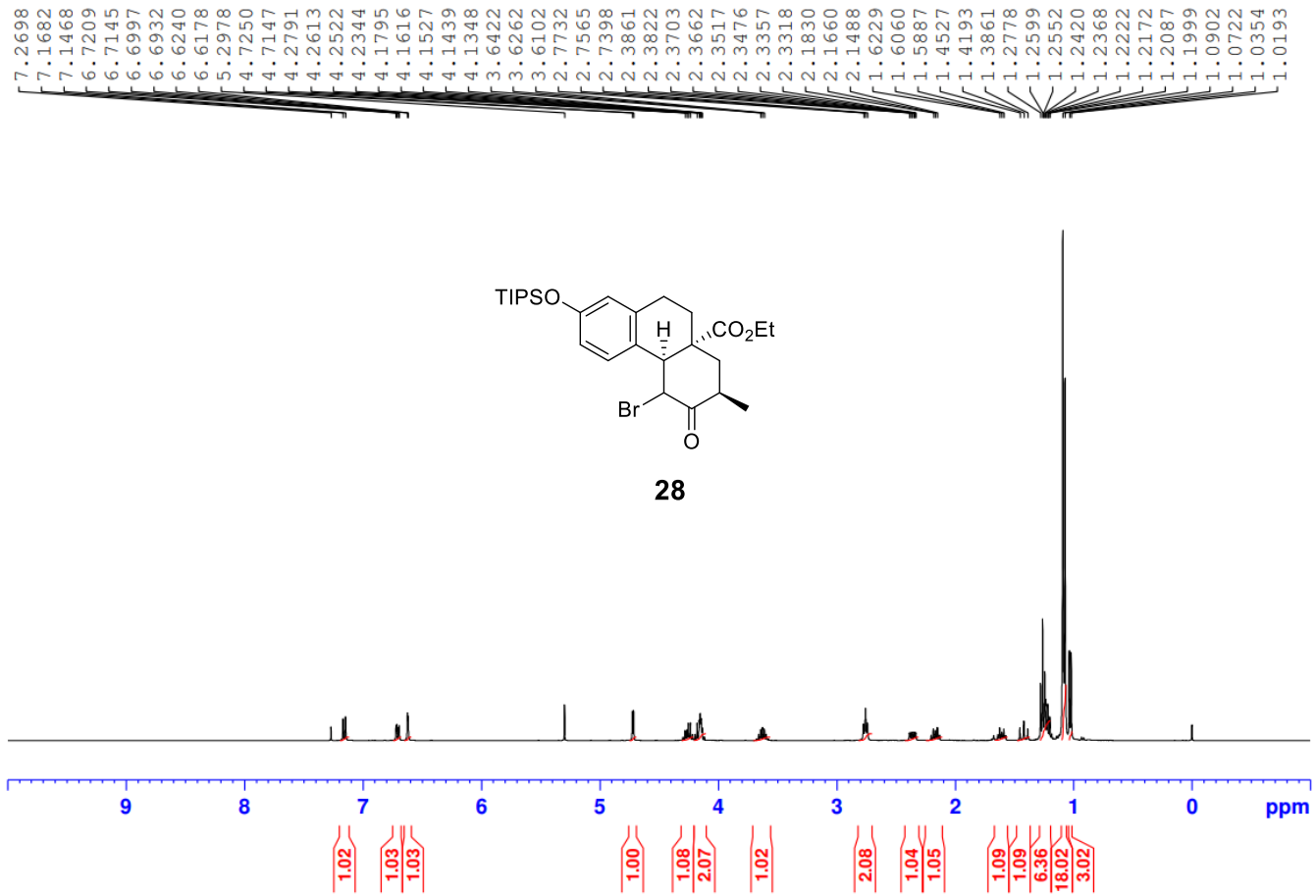
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **24**



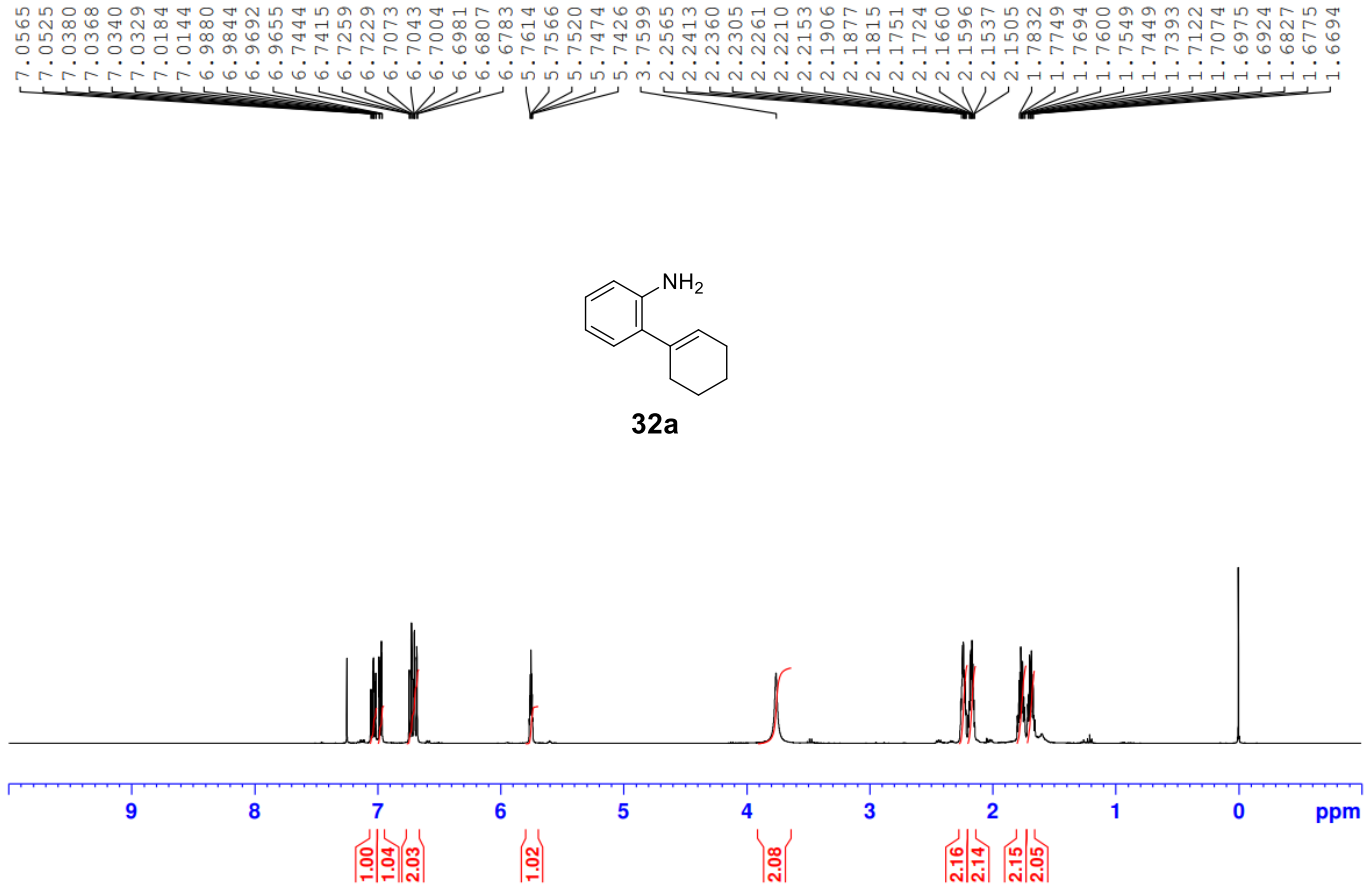
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **25**



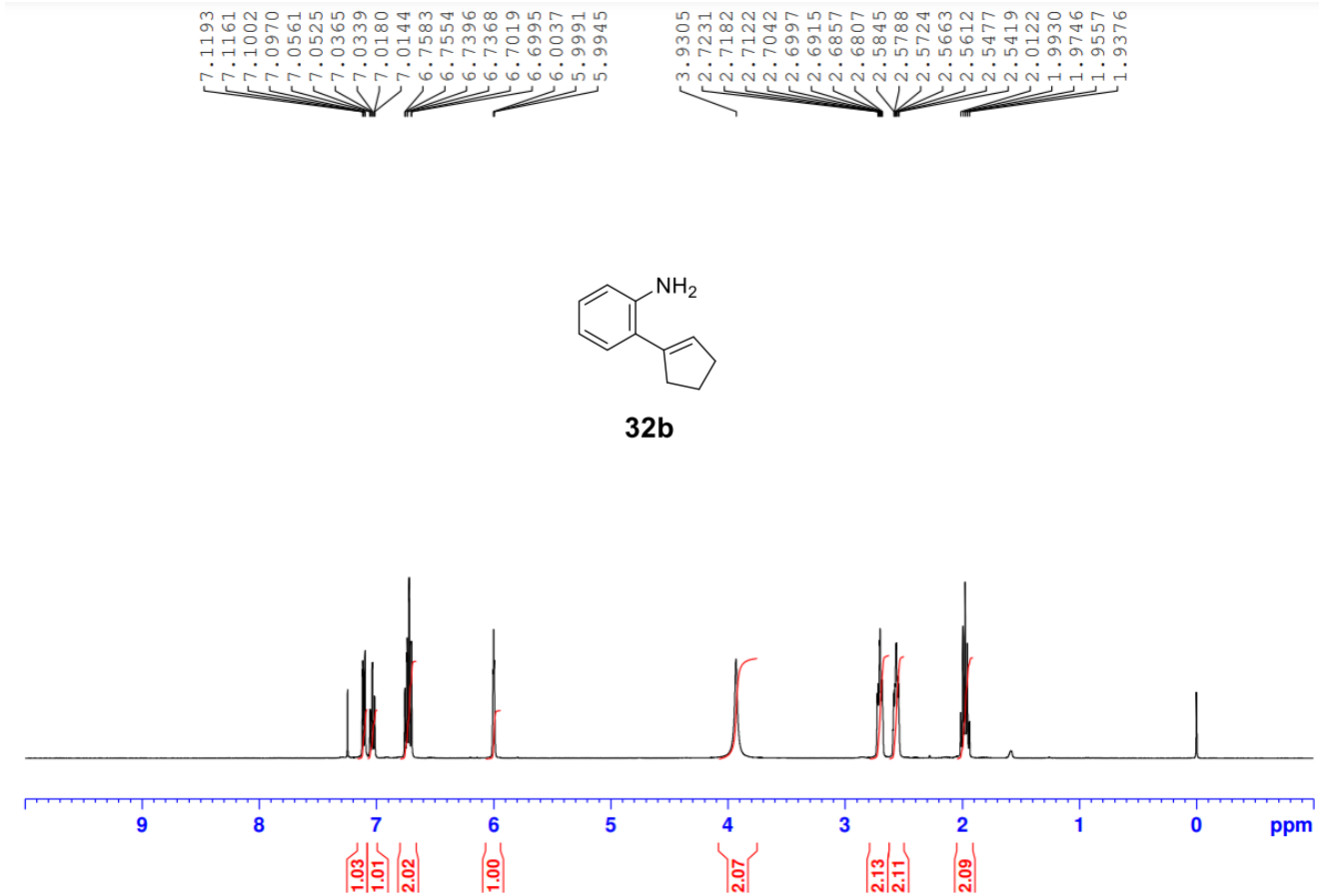
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **26**



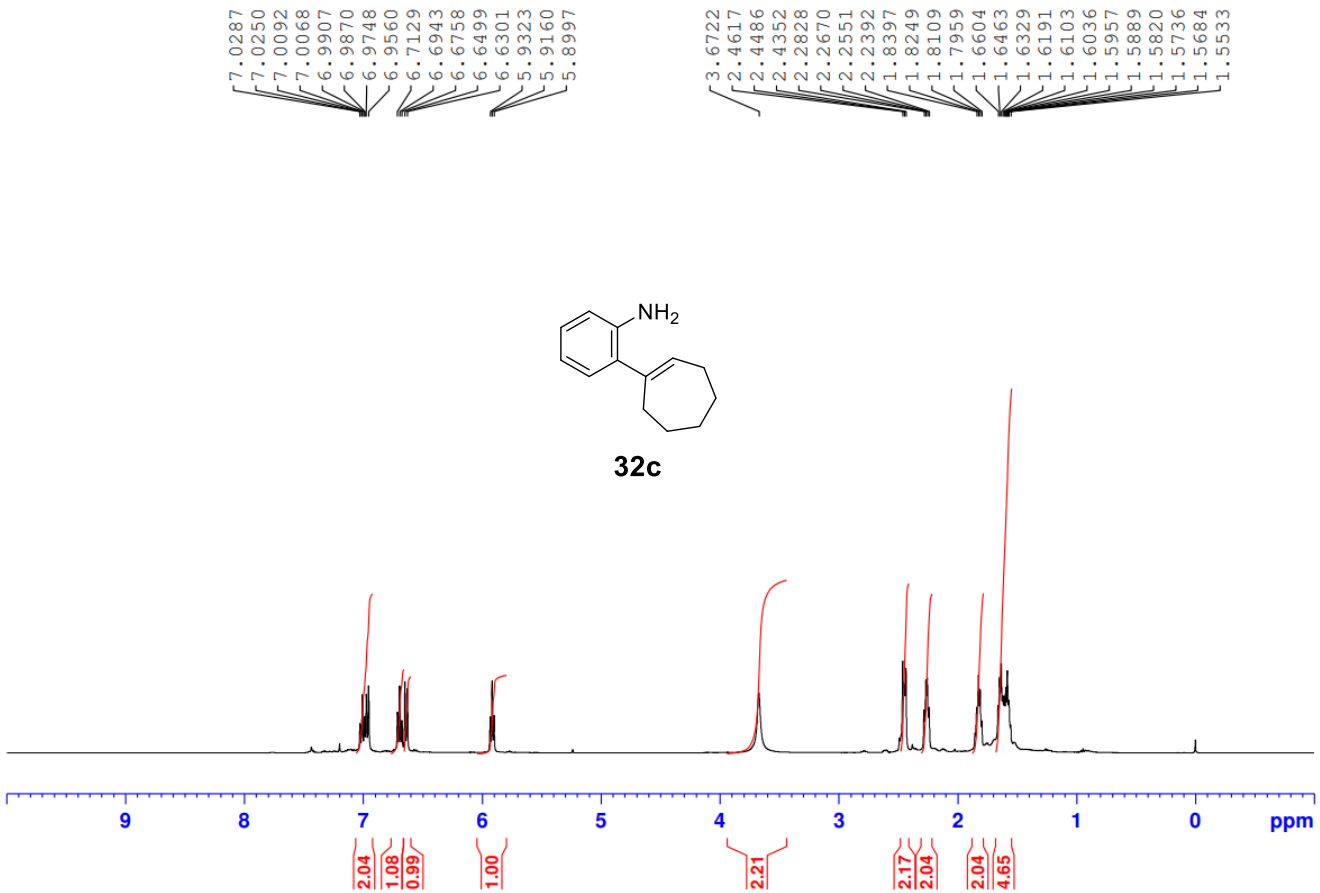
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **28**



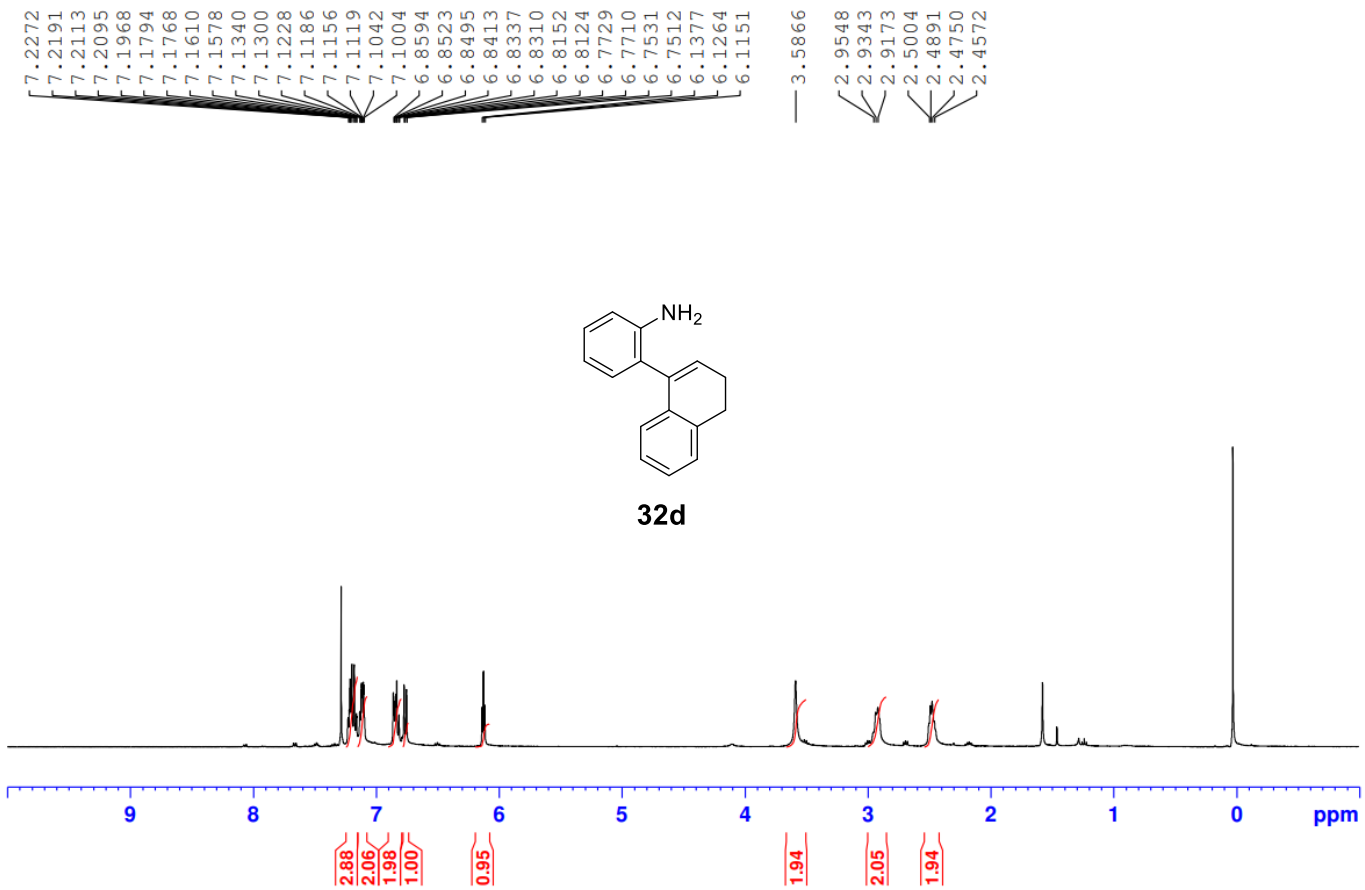
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32a**



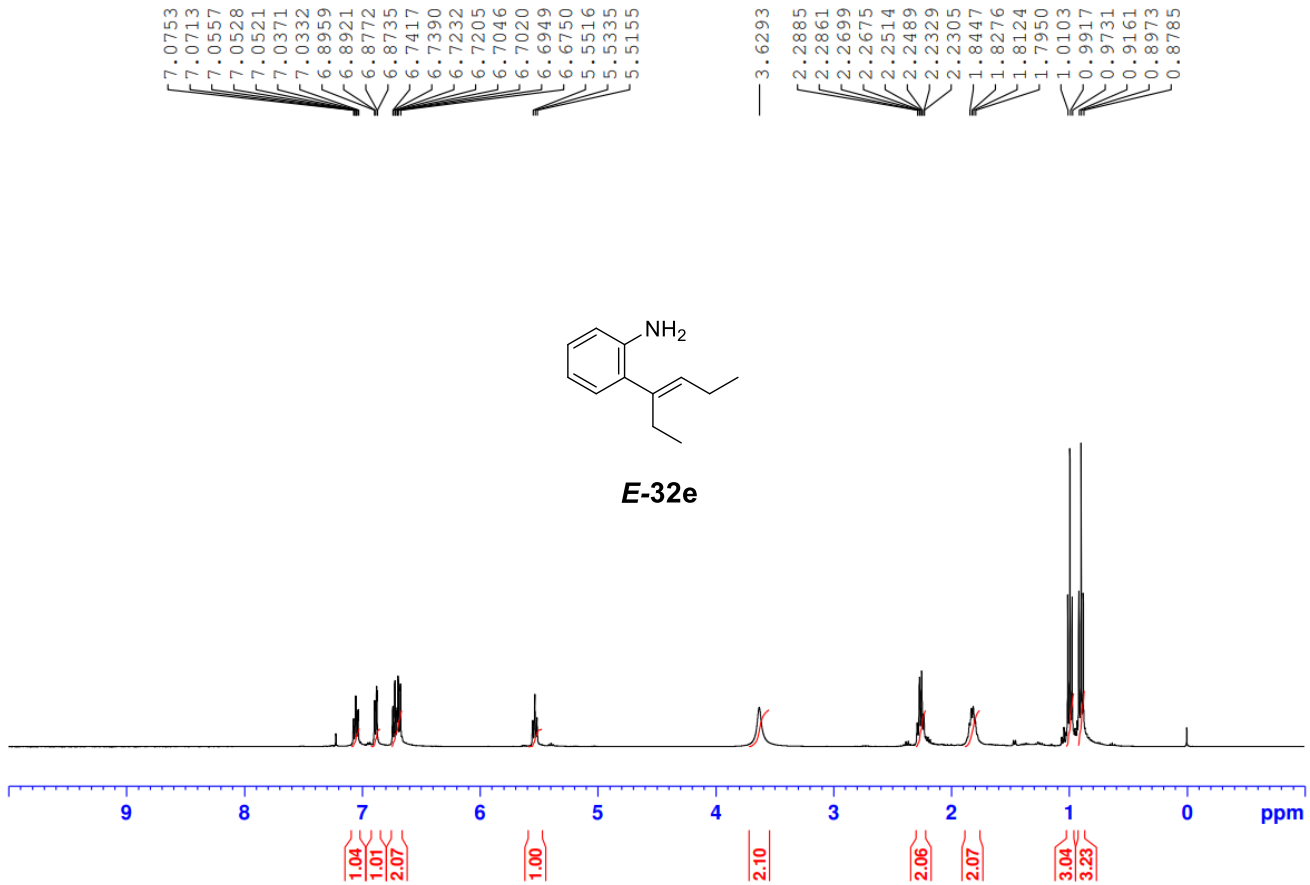
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32b**



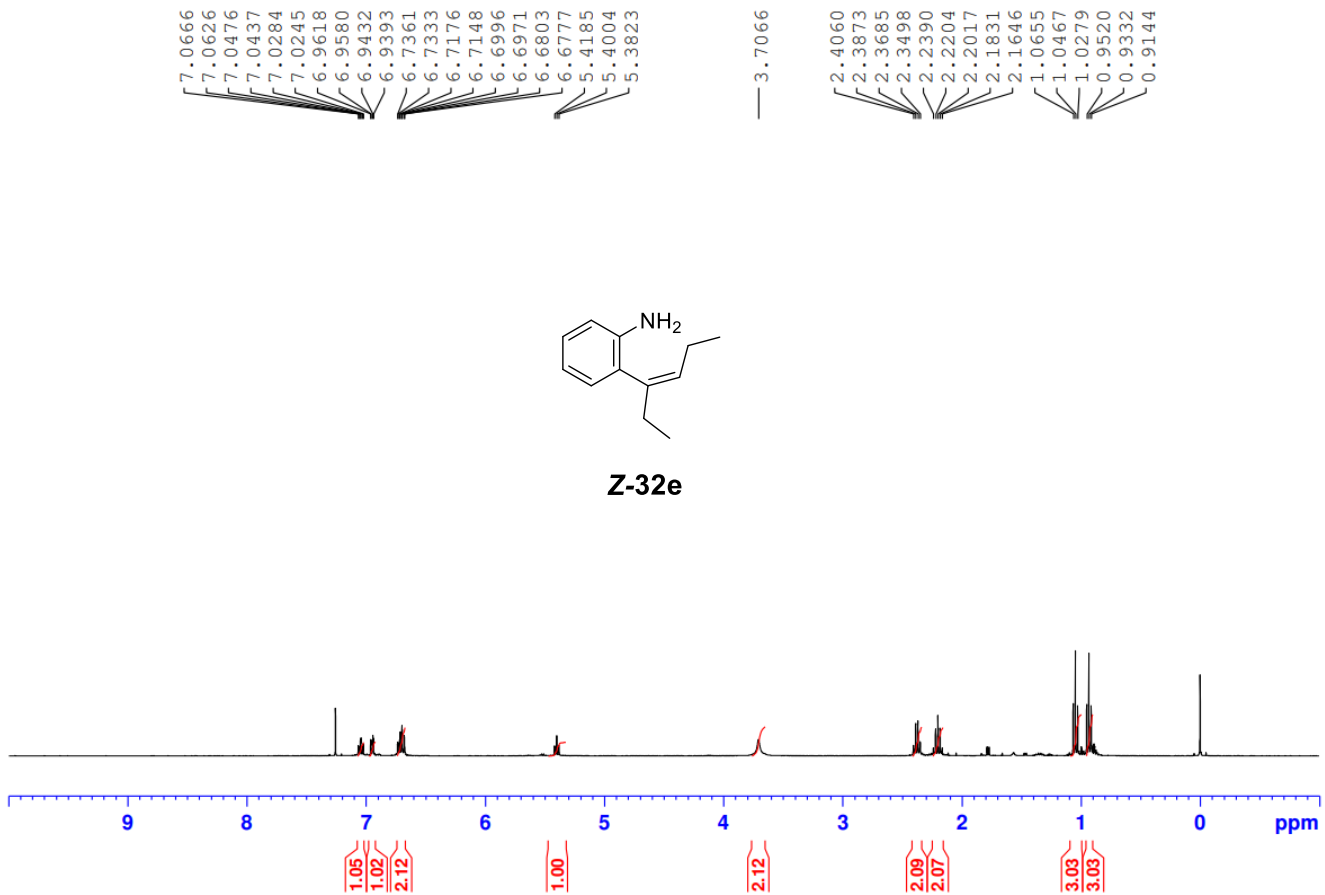
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32c**



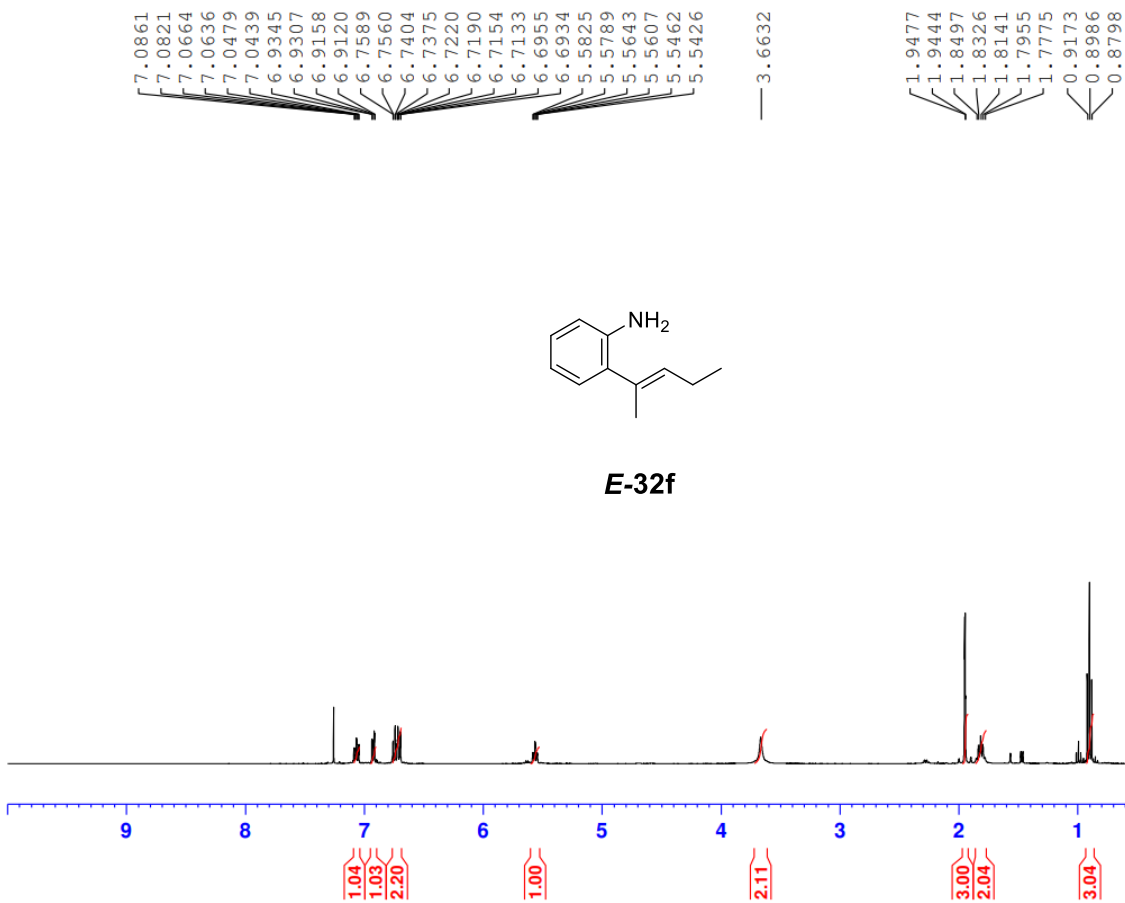
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32d**



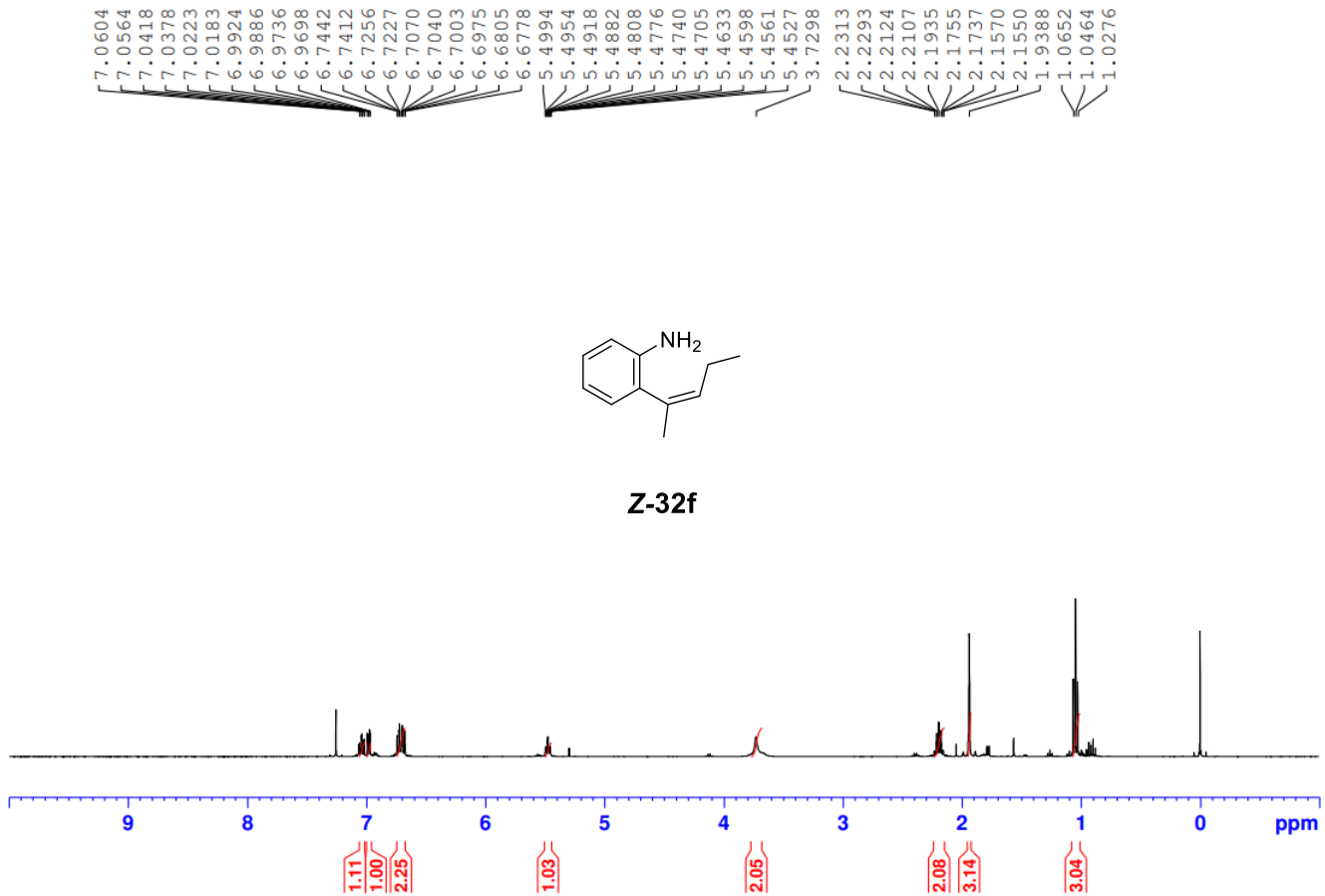
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32e**



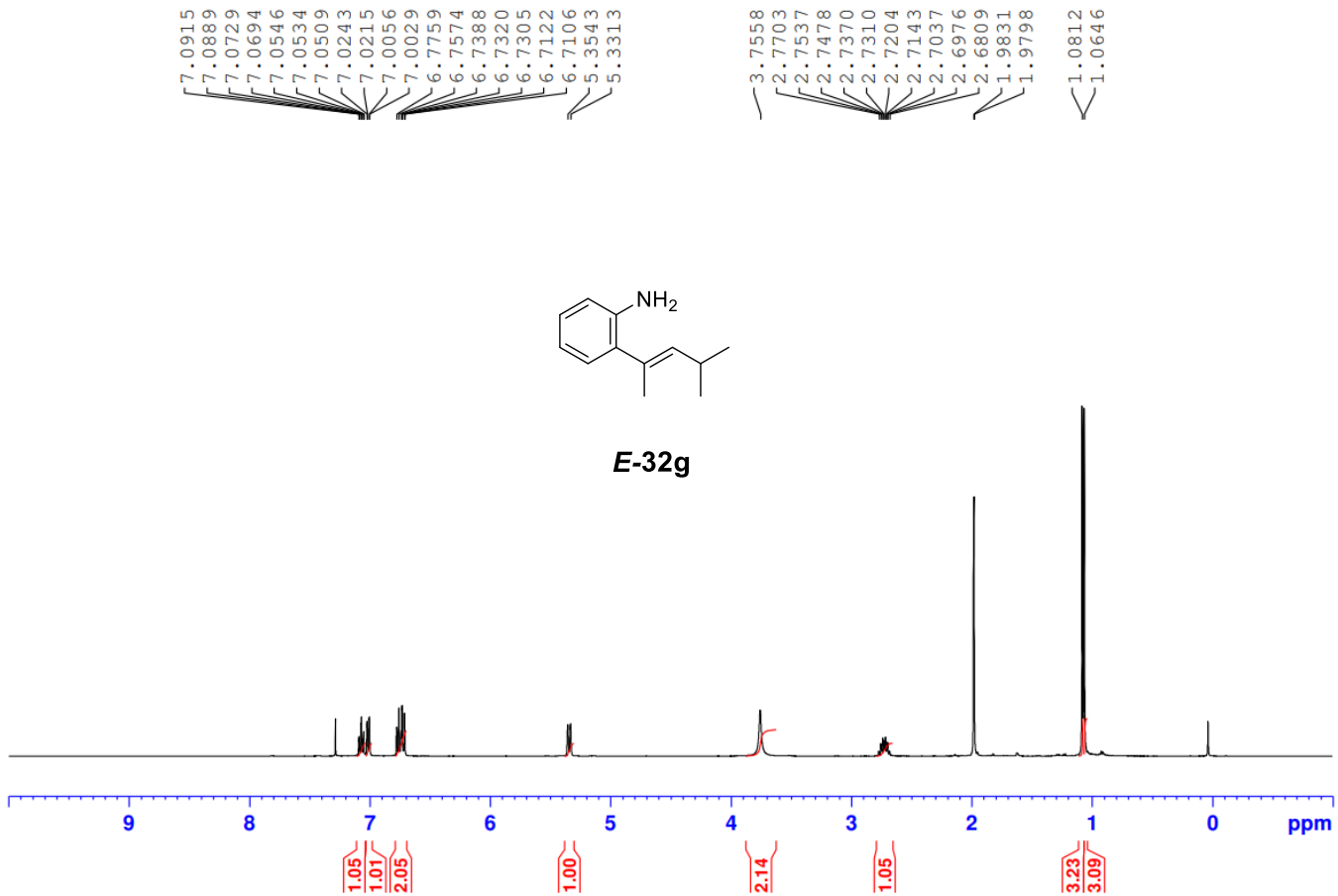
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***Z*-32e**



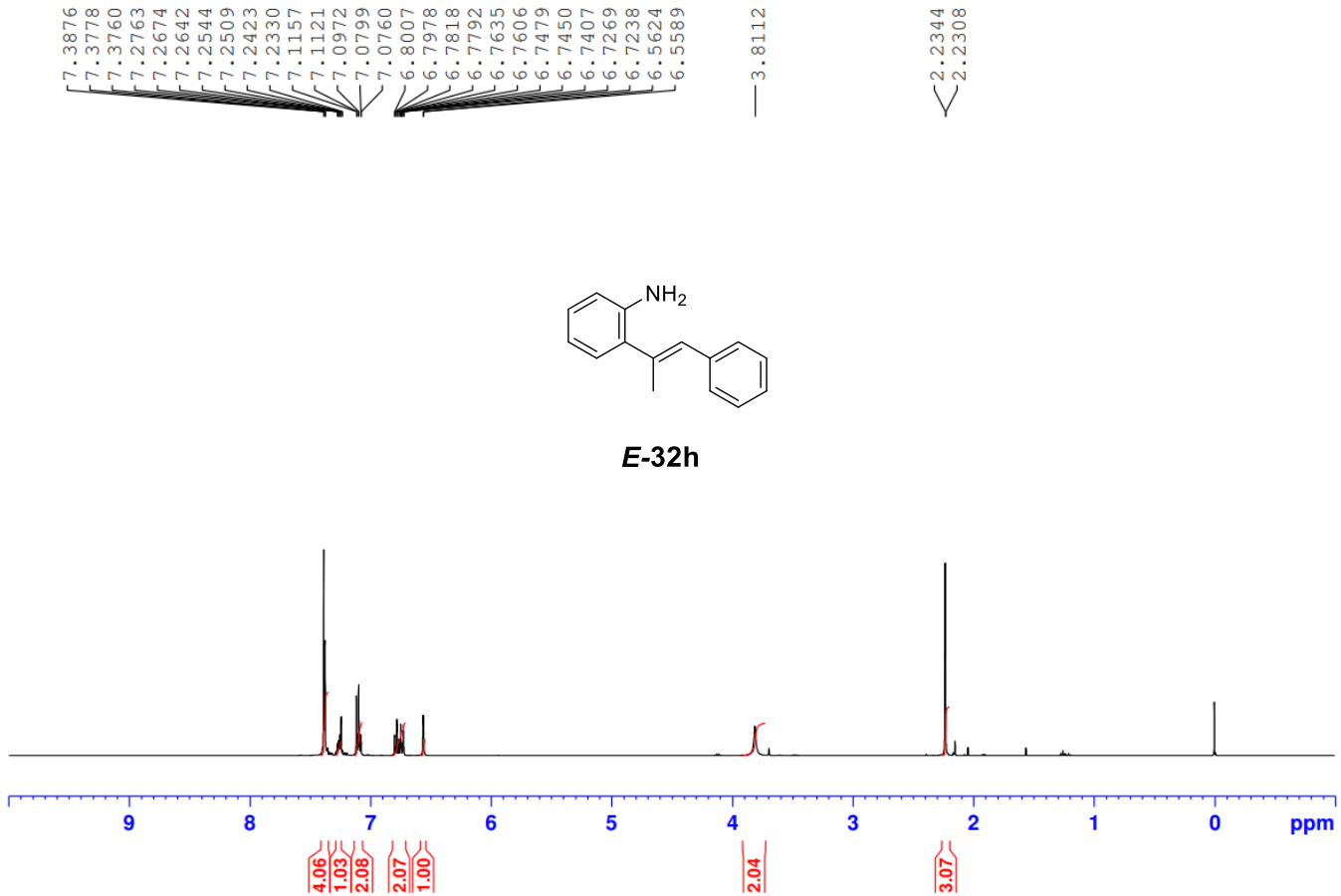
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32f**



400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***Z*-32f**

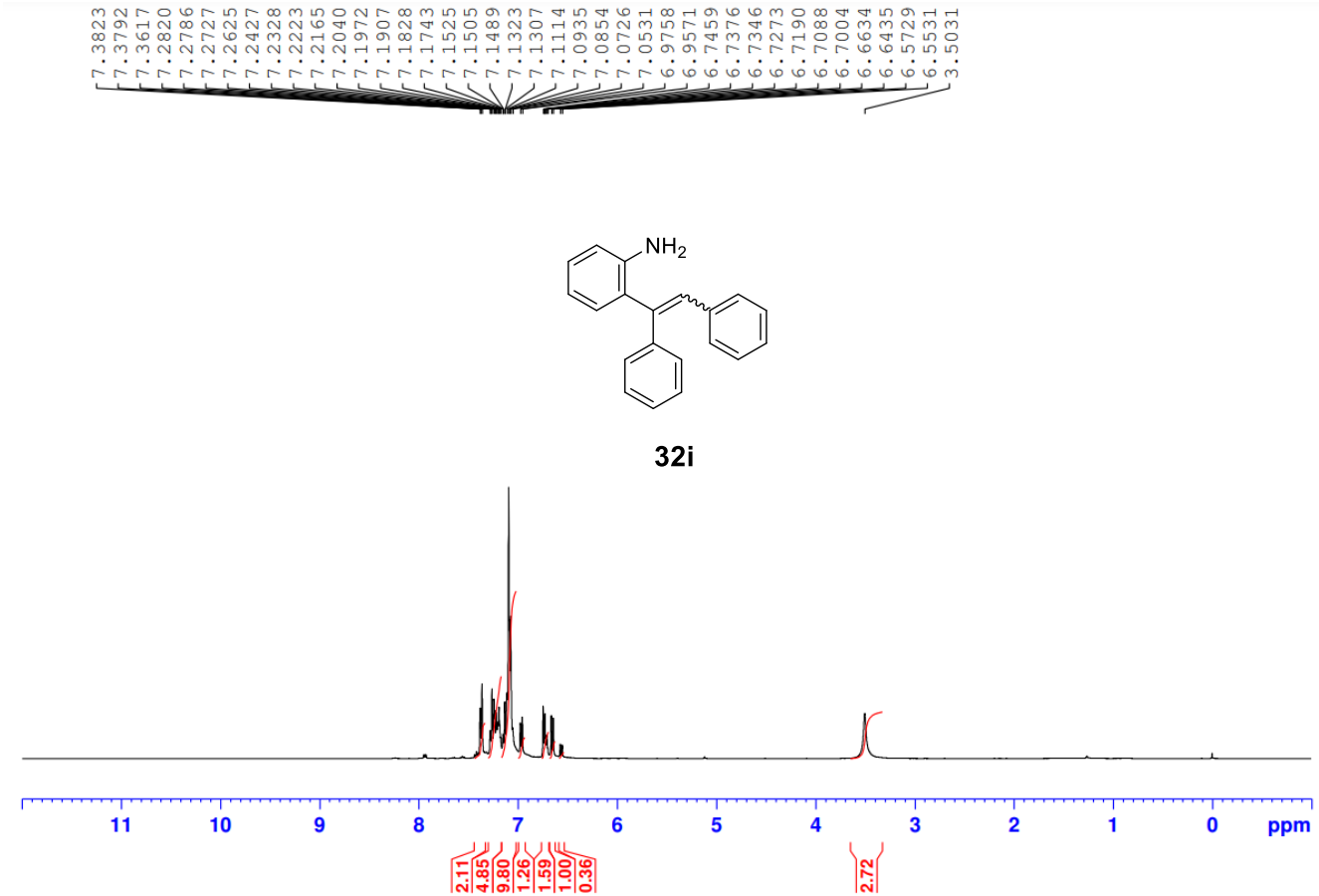


400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32g**

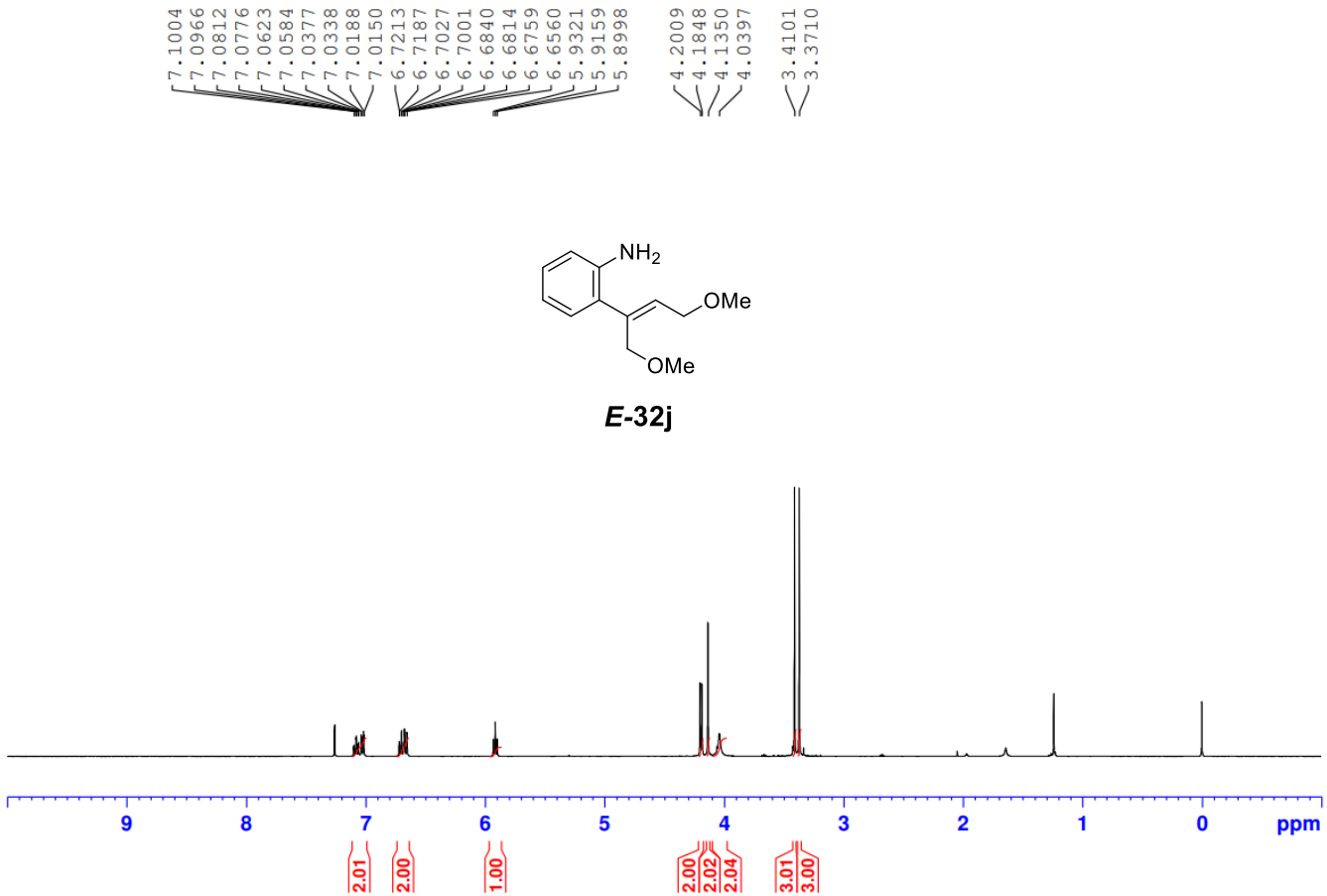


***E*-32h**

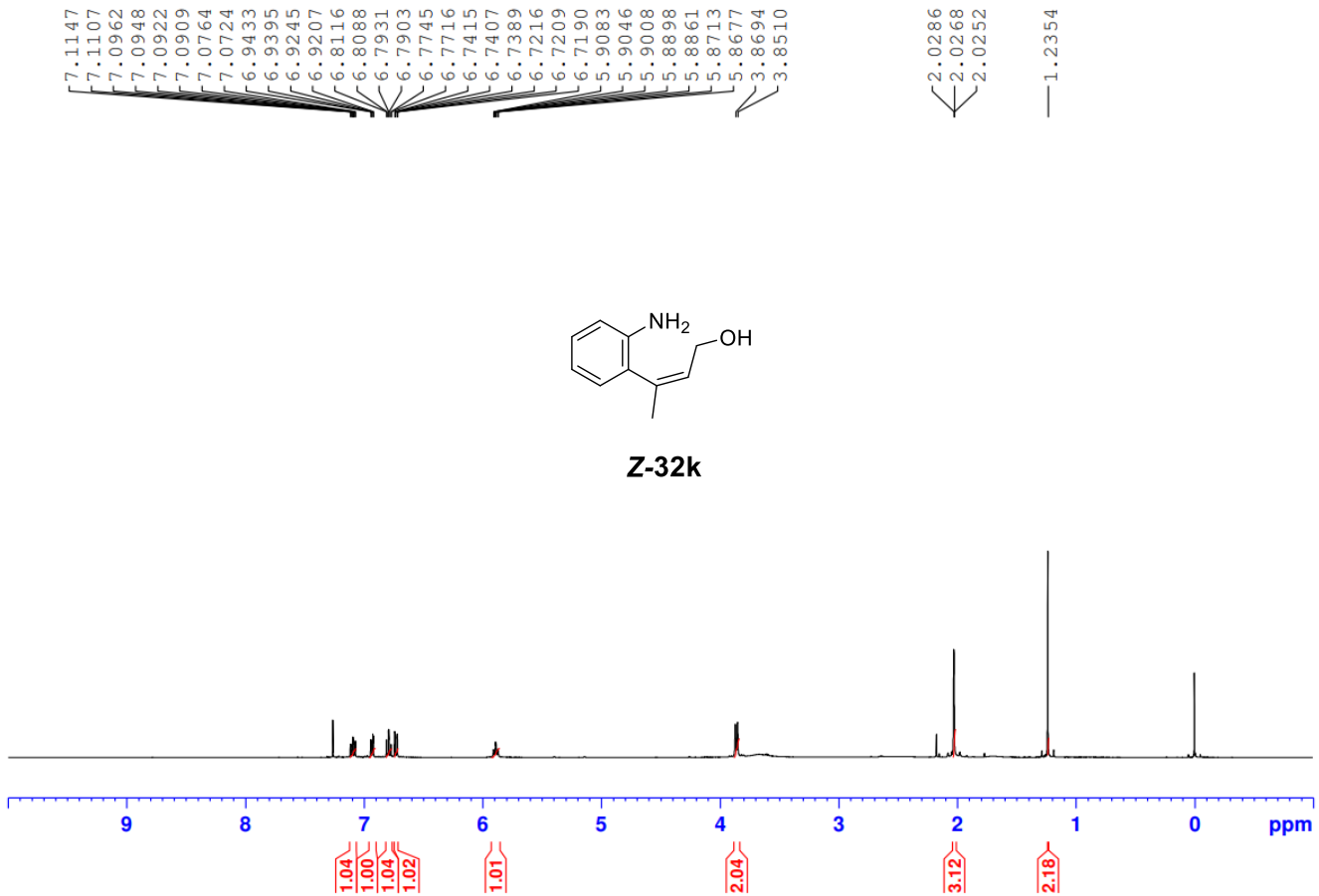
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32h**



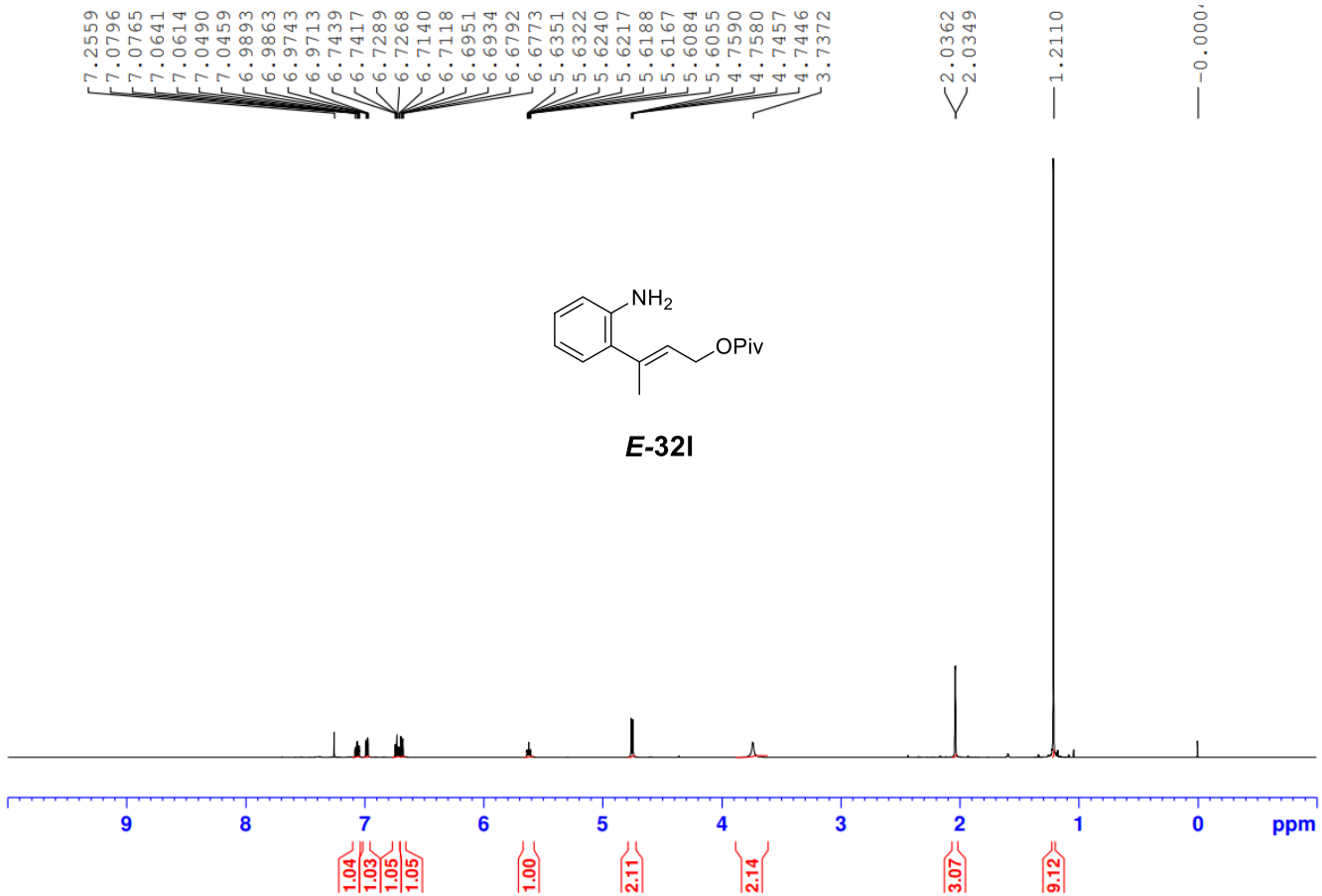
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32i**



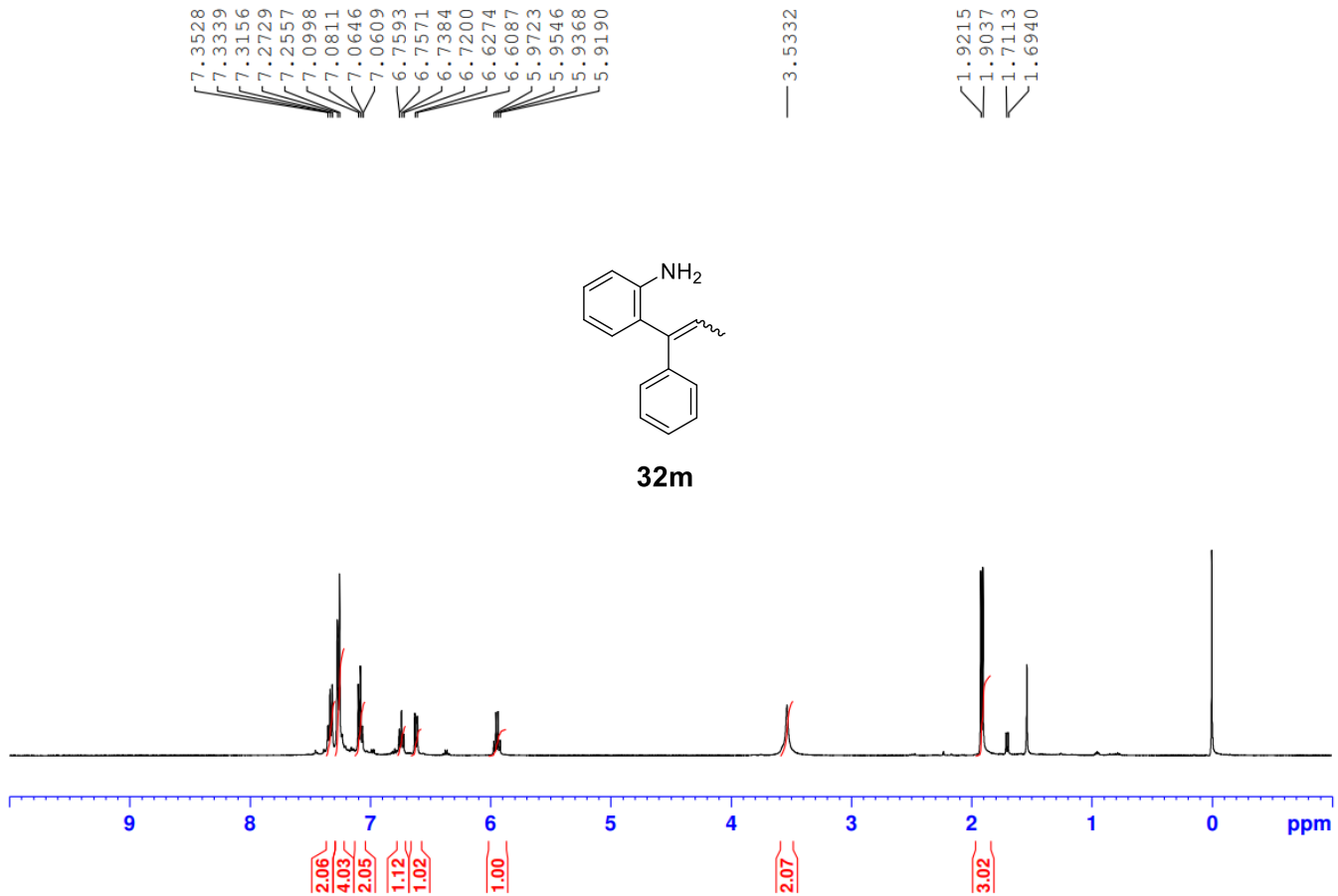
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32j**



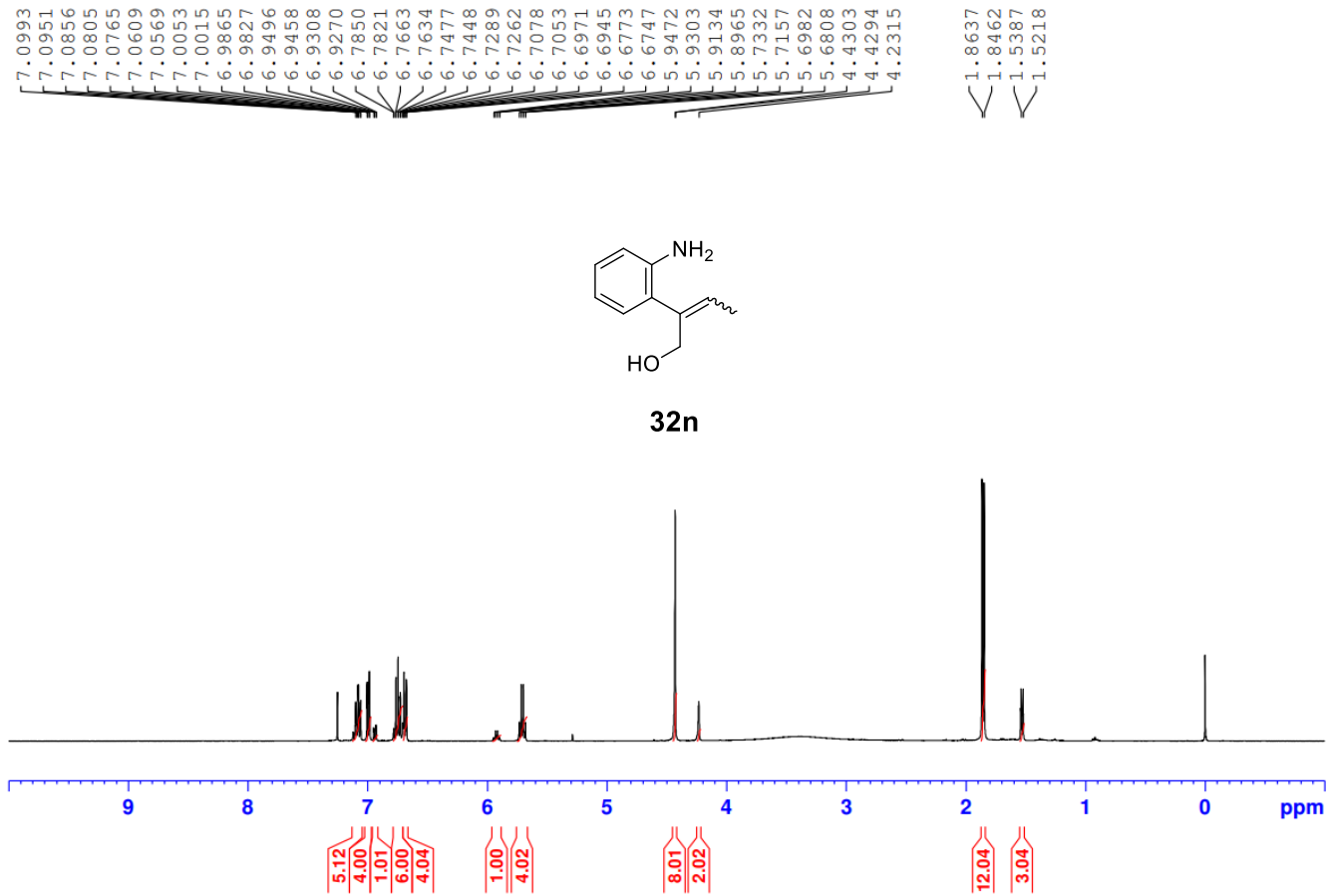
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***Z*-32k**



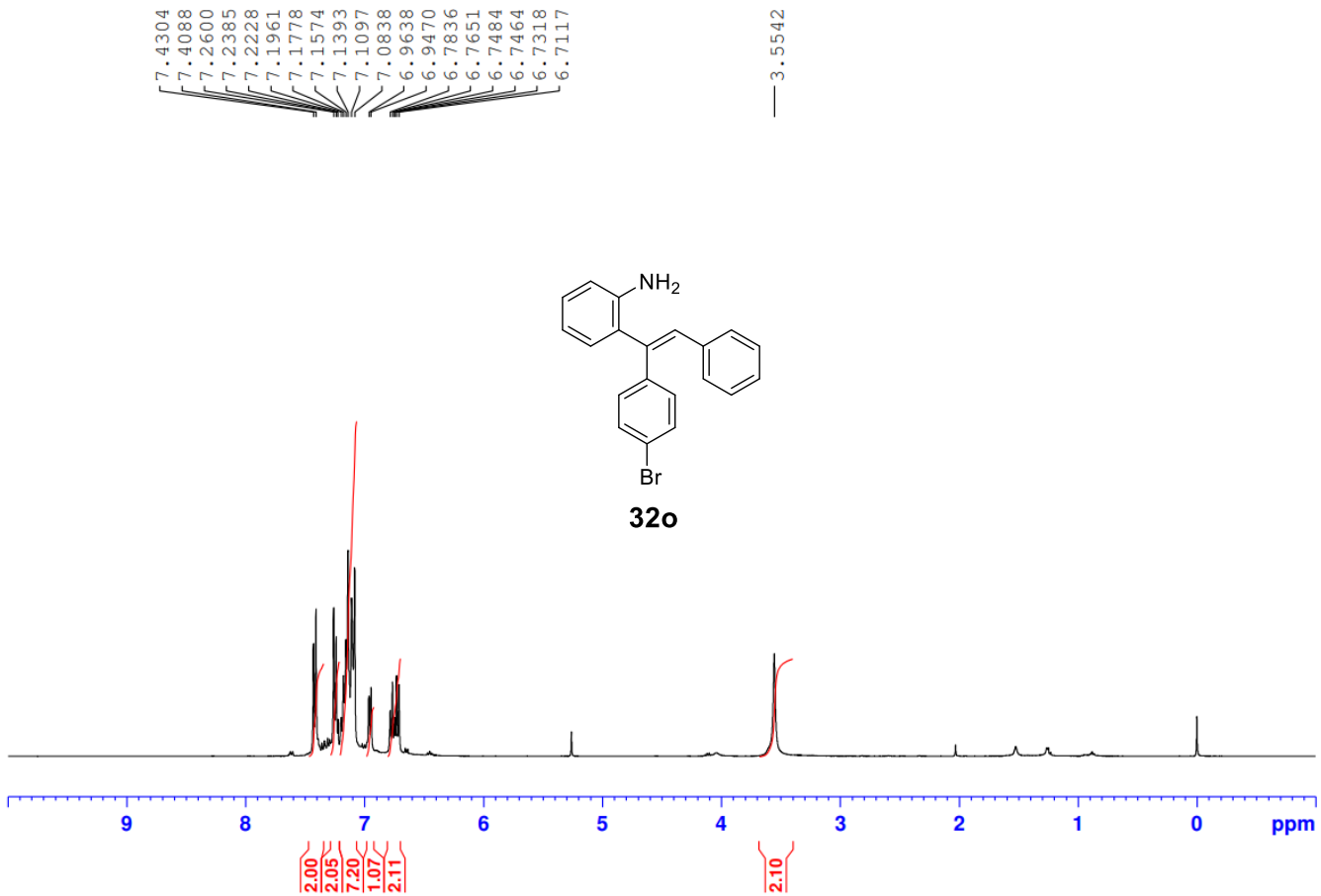
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound ***E*-32l**



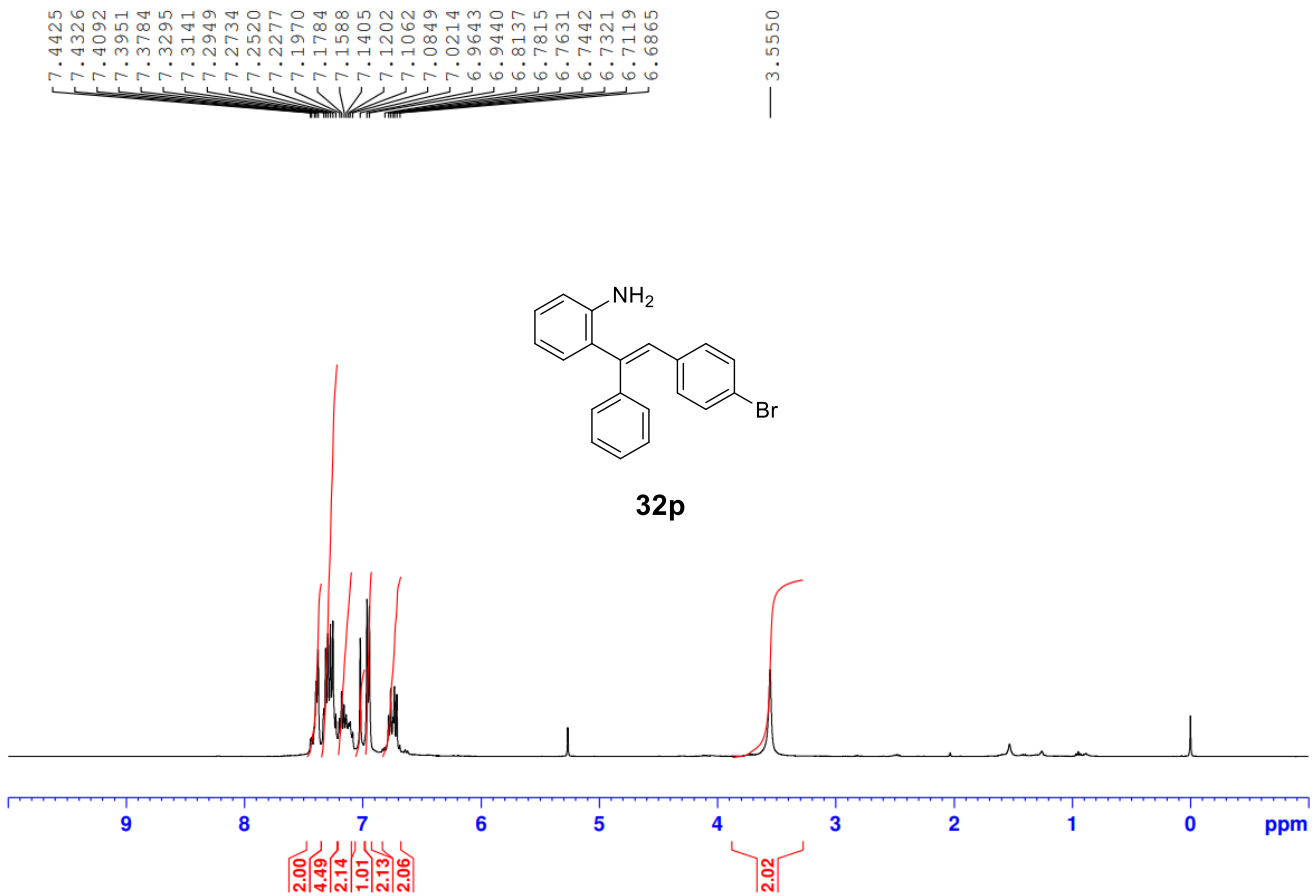
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32m**



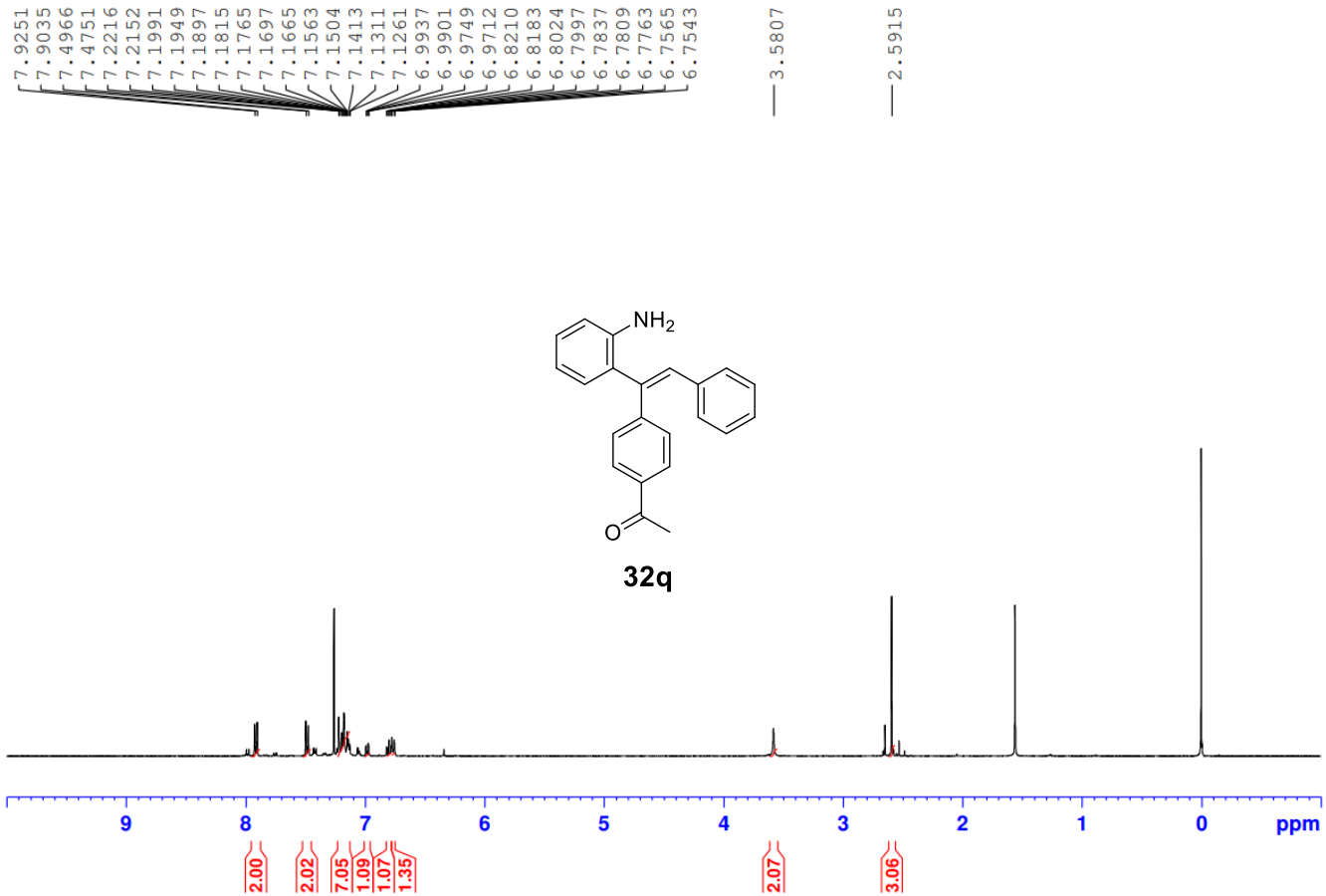
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32n**



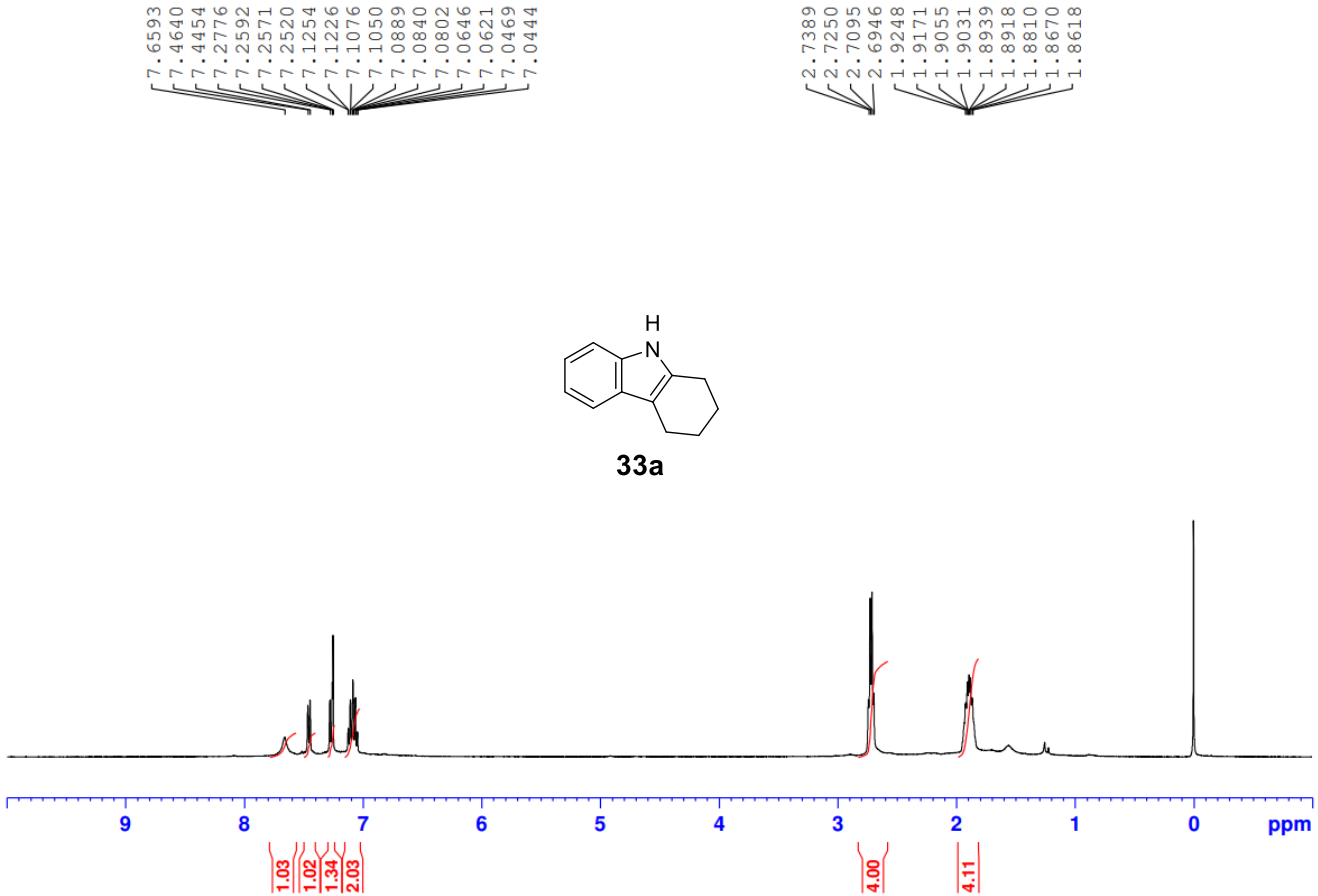
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32o**



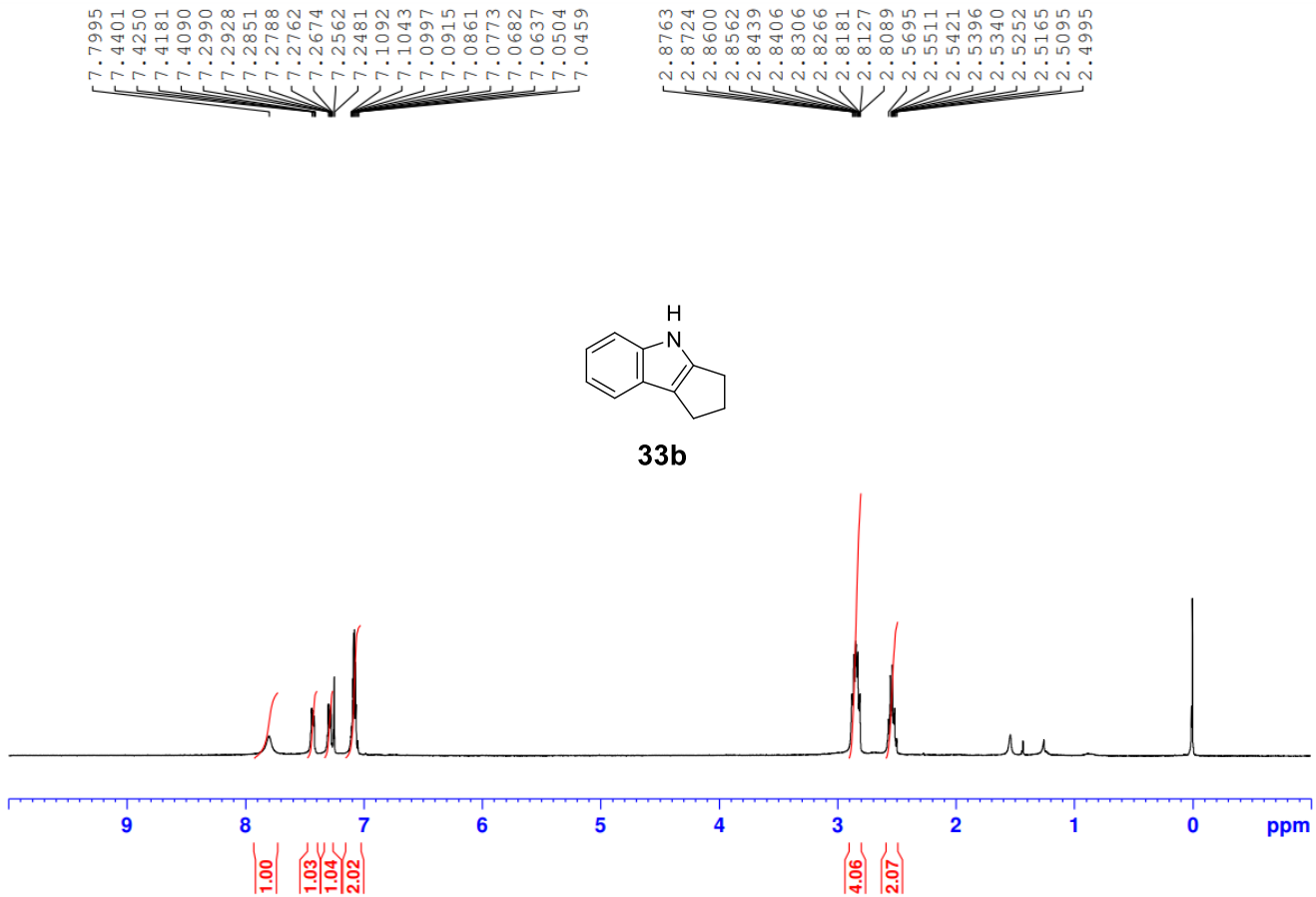
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32p**



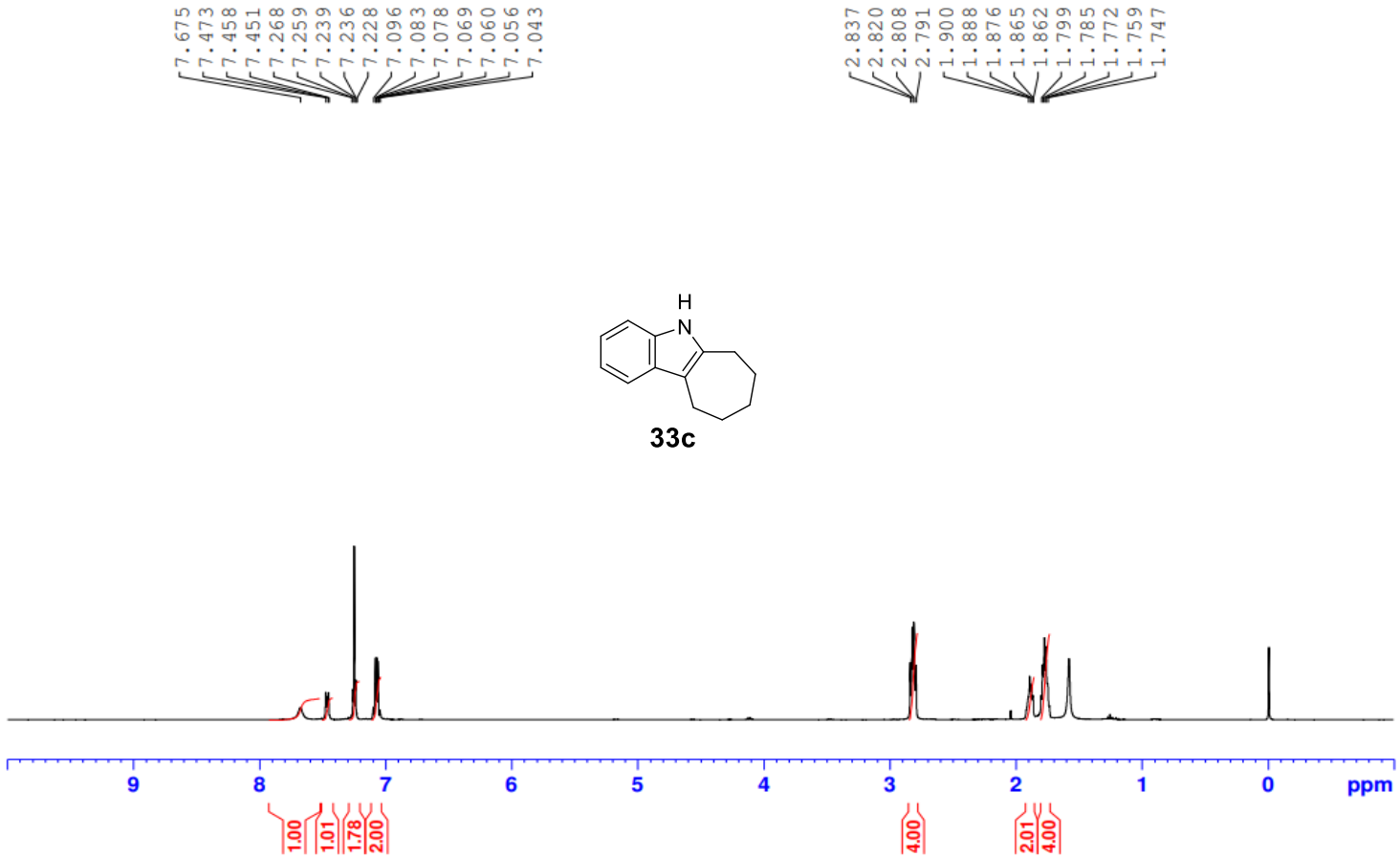
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **32q**



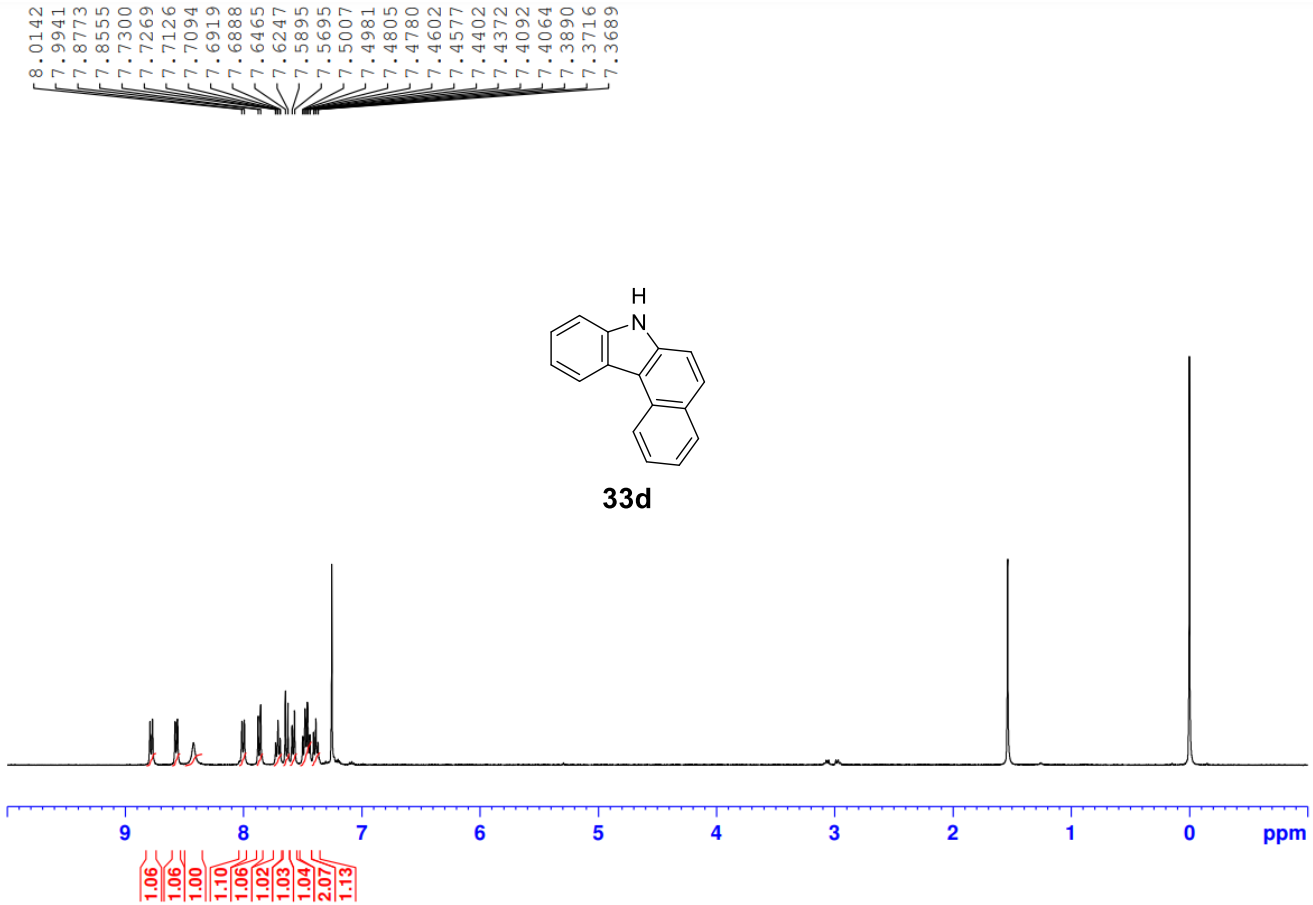
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33a**



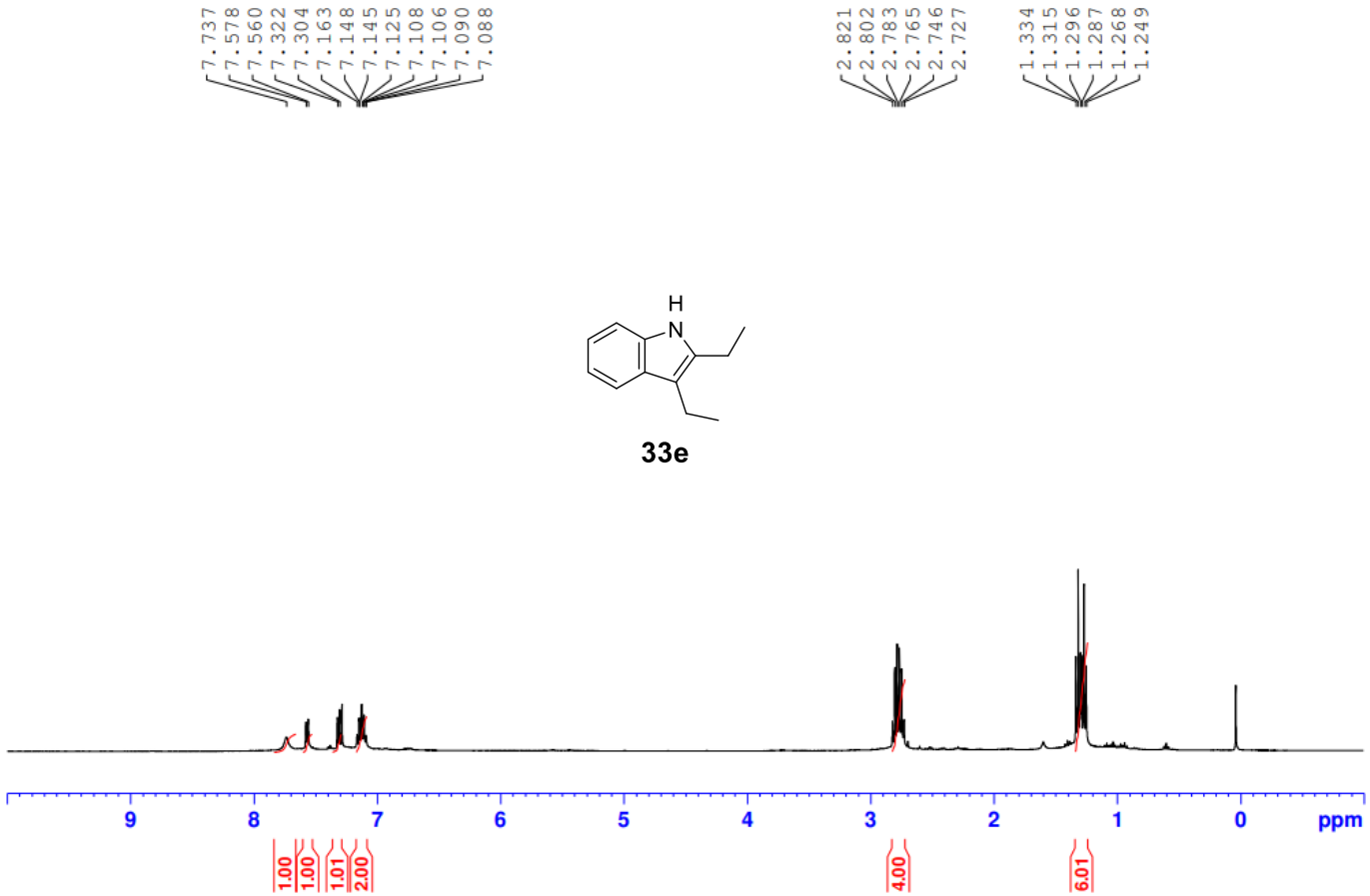
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33b**



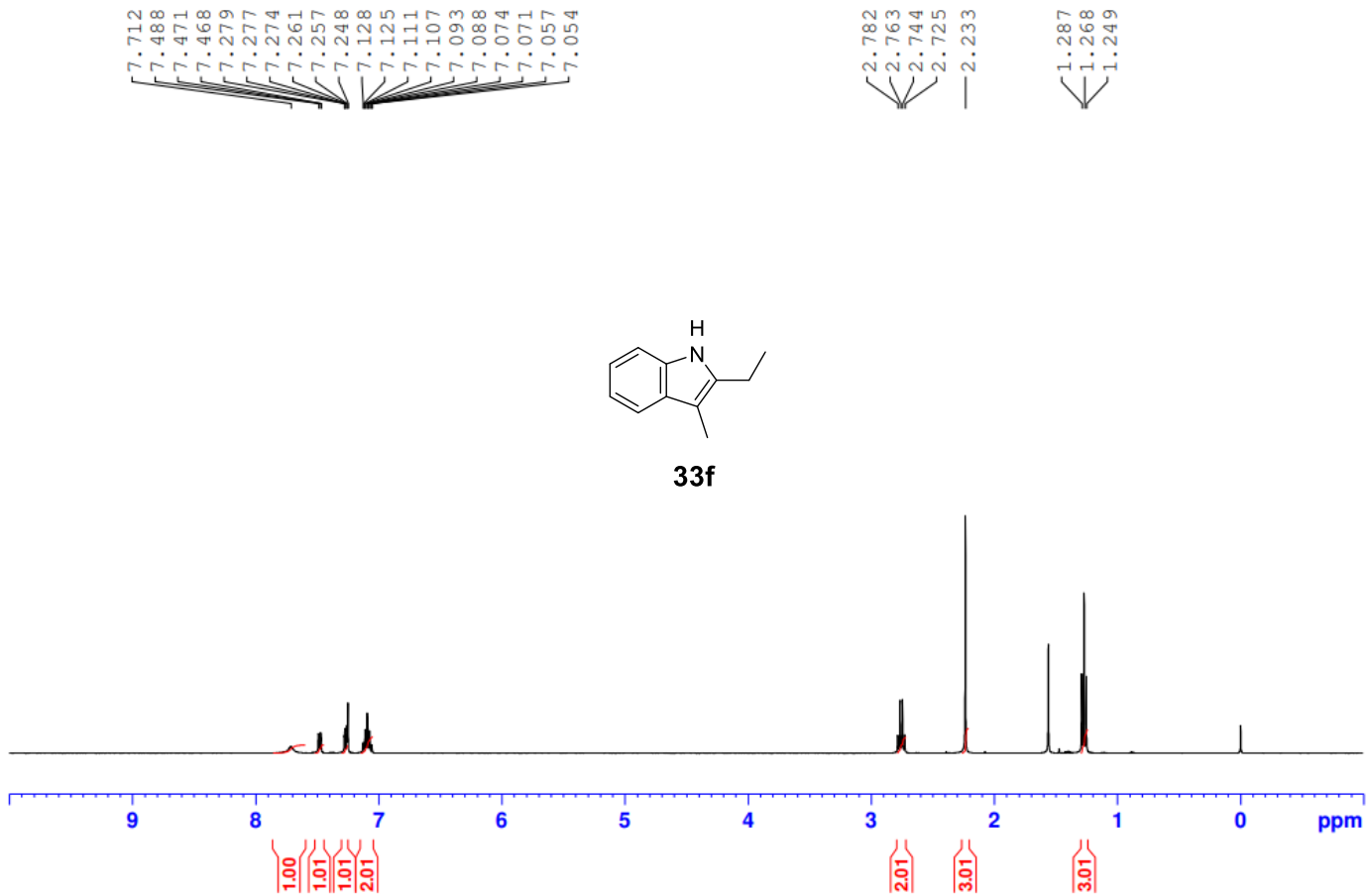
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33c**



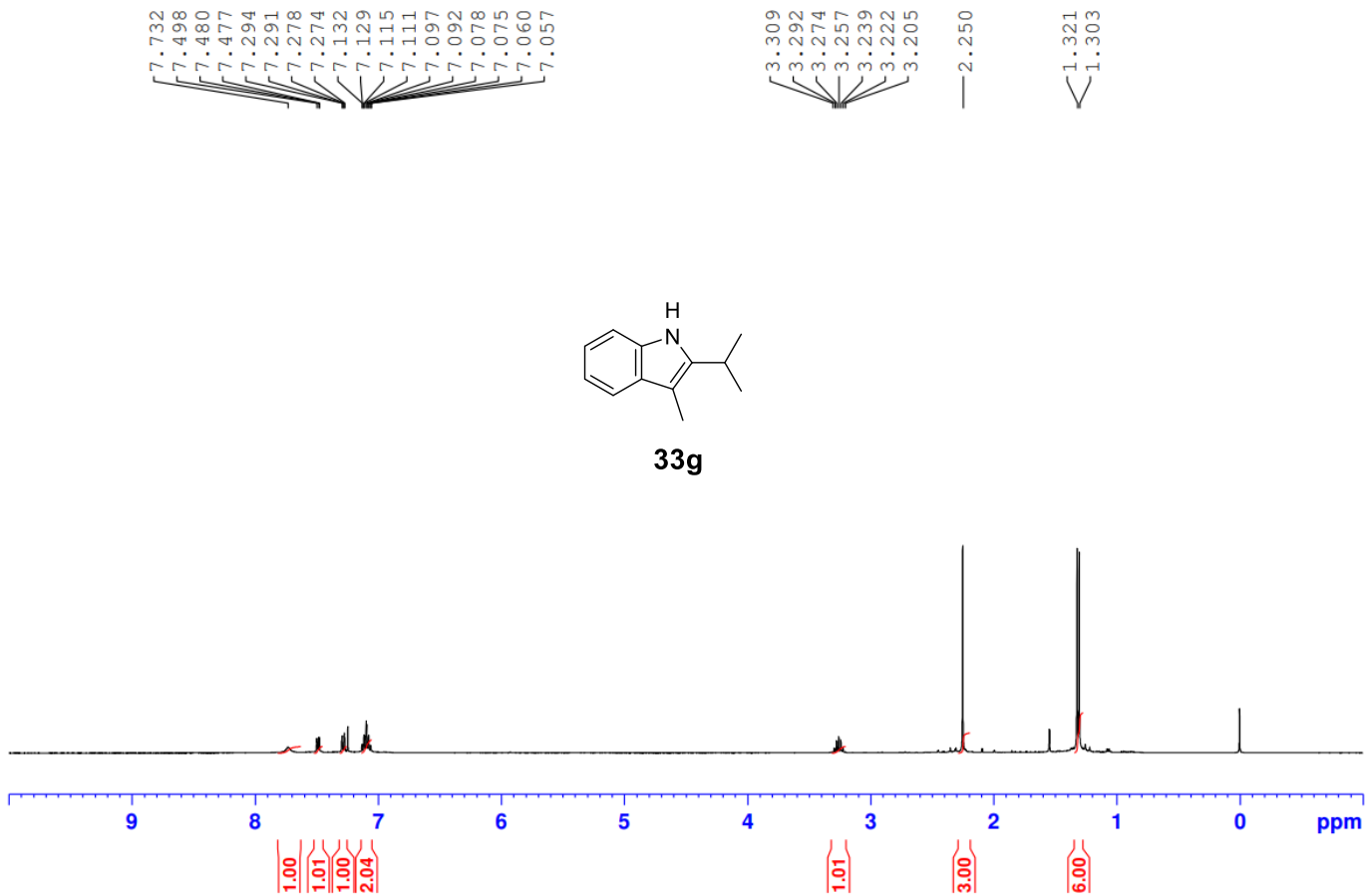
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33d**



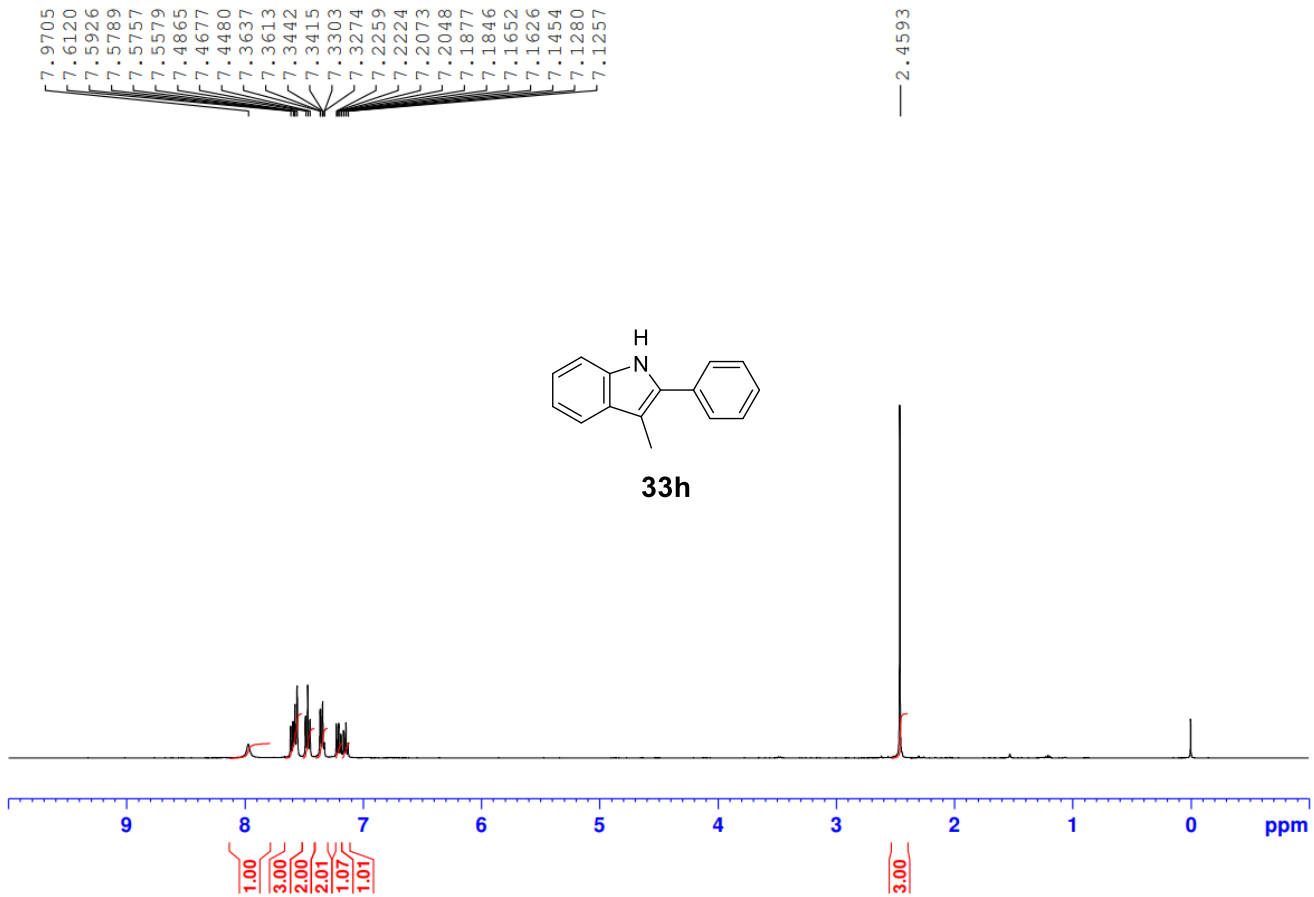
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33e**



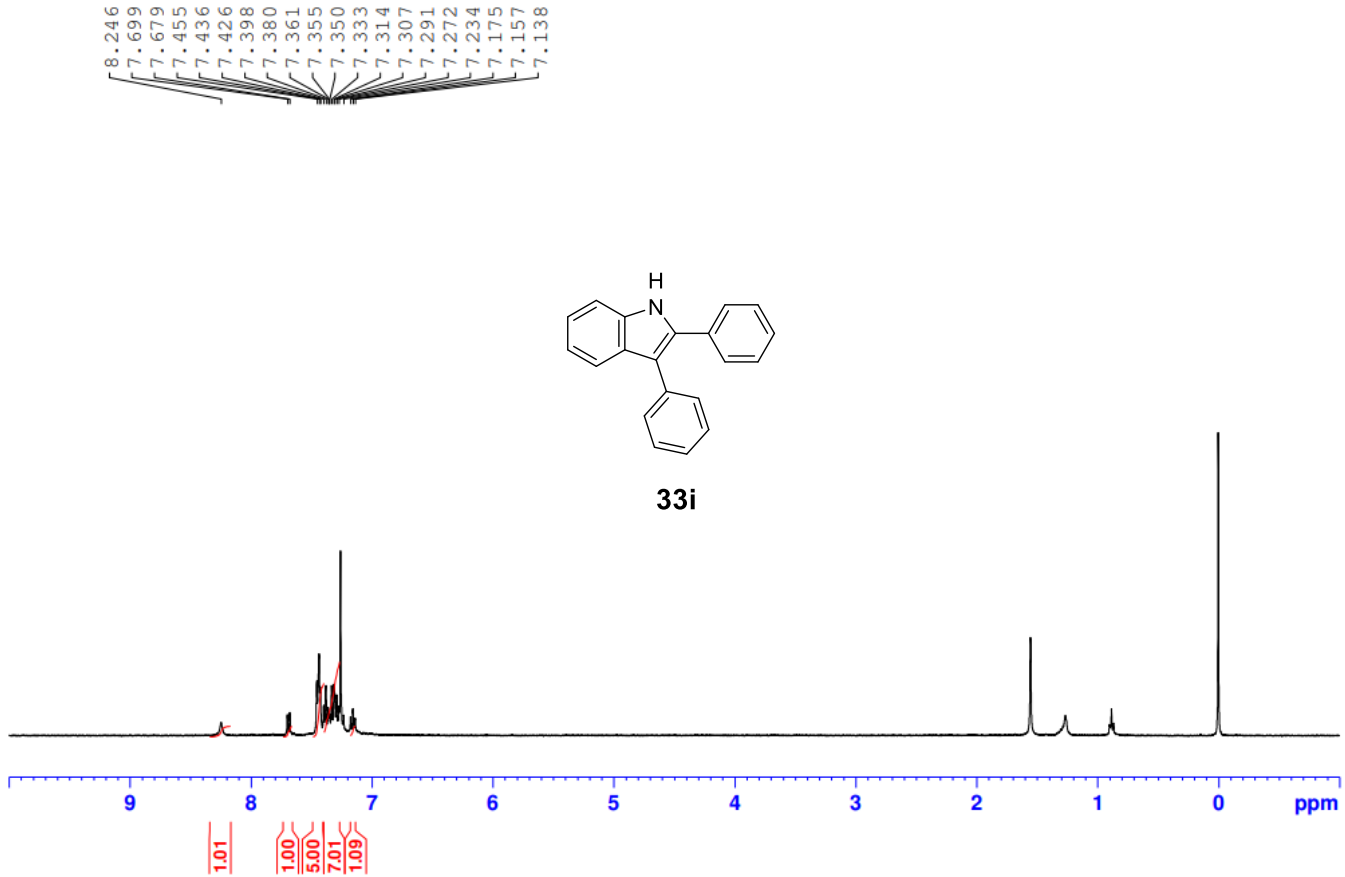
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33f**



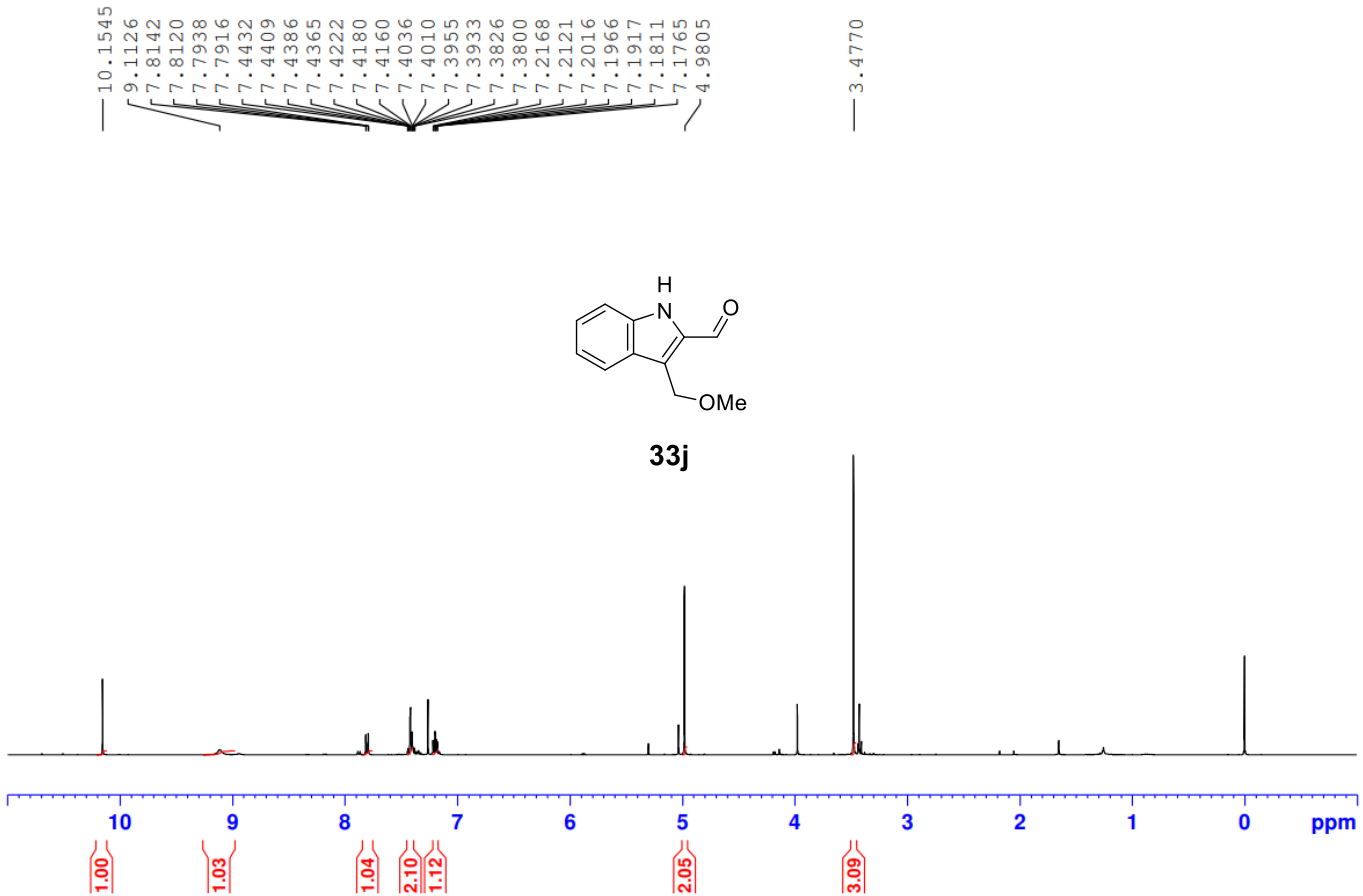
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33g**



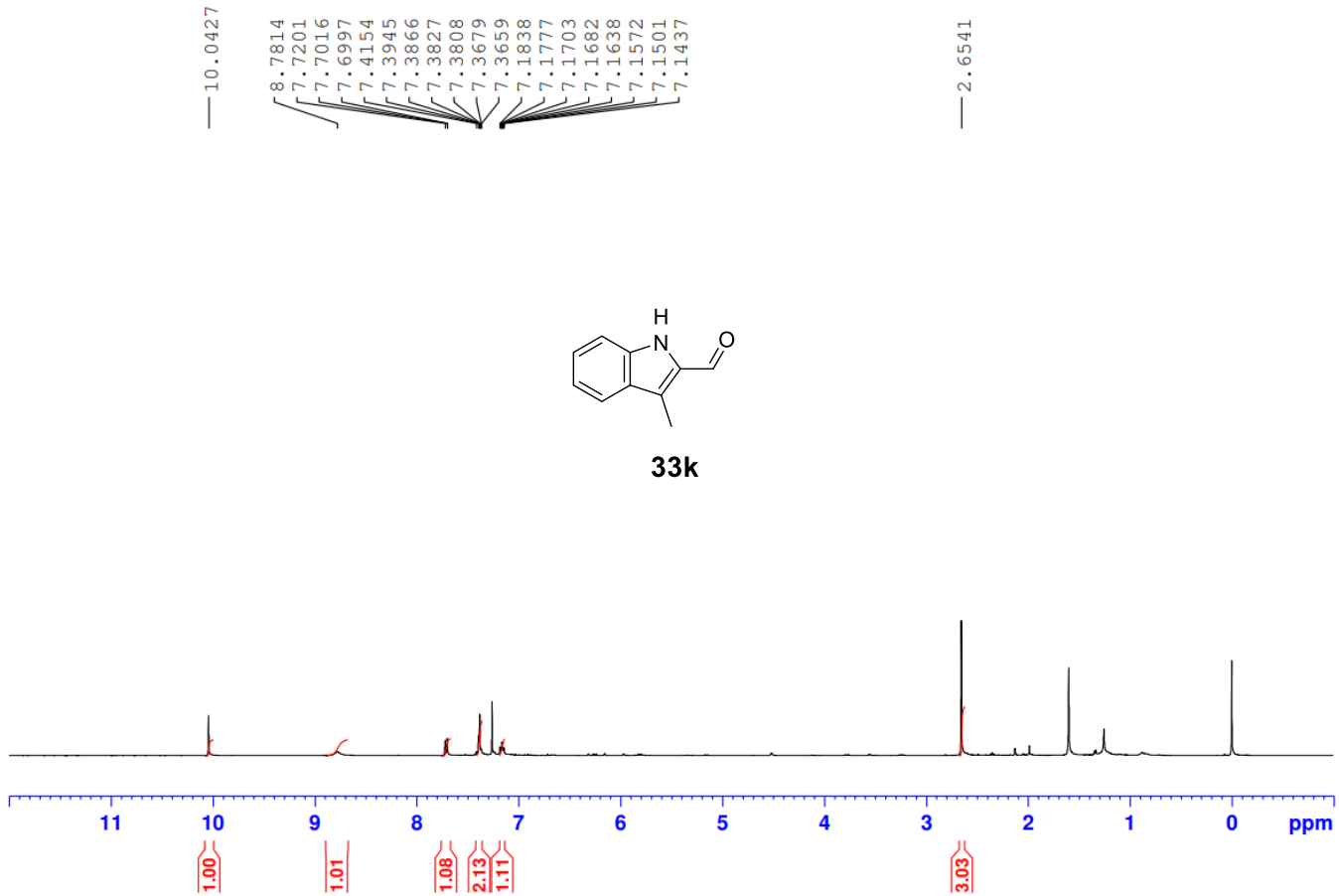
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33h**



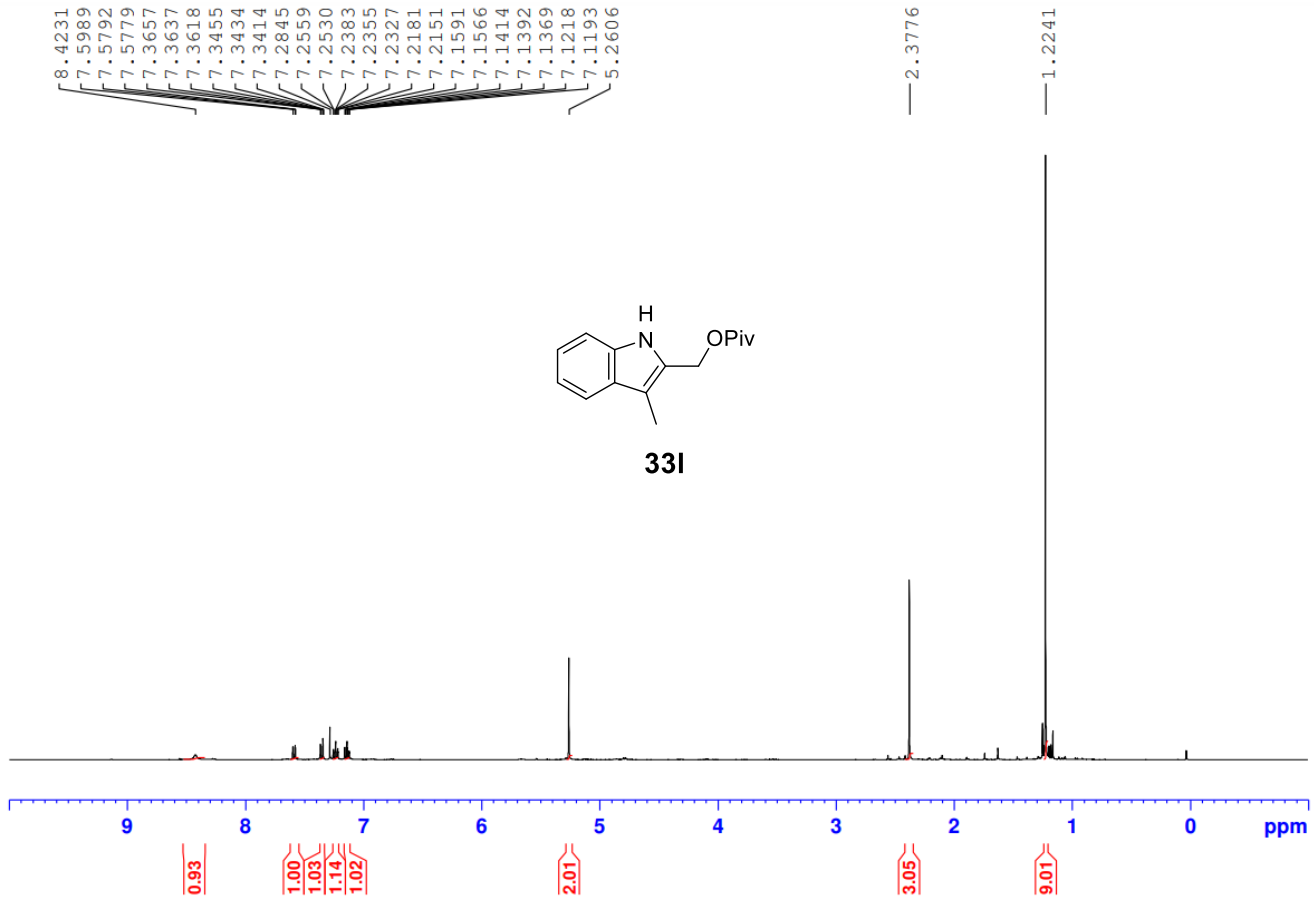
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33i**



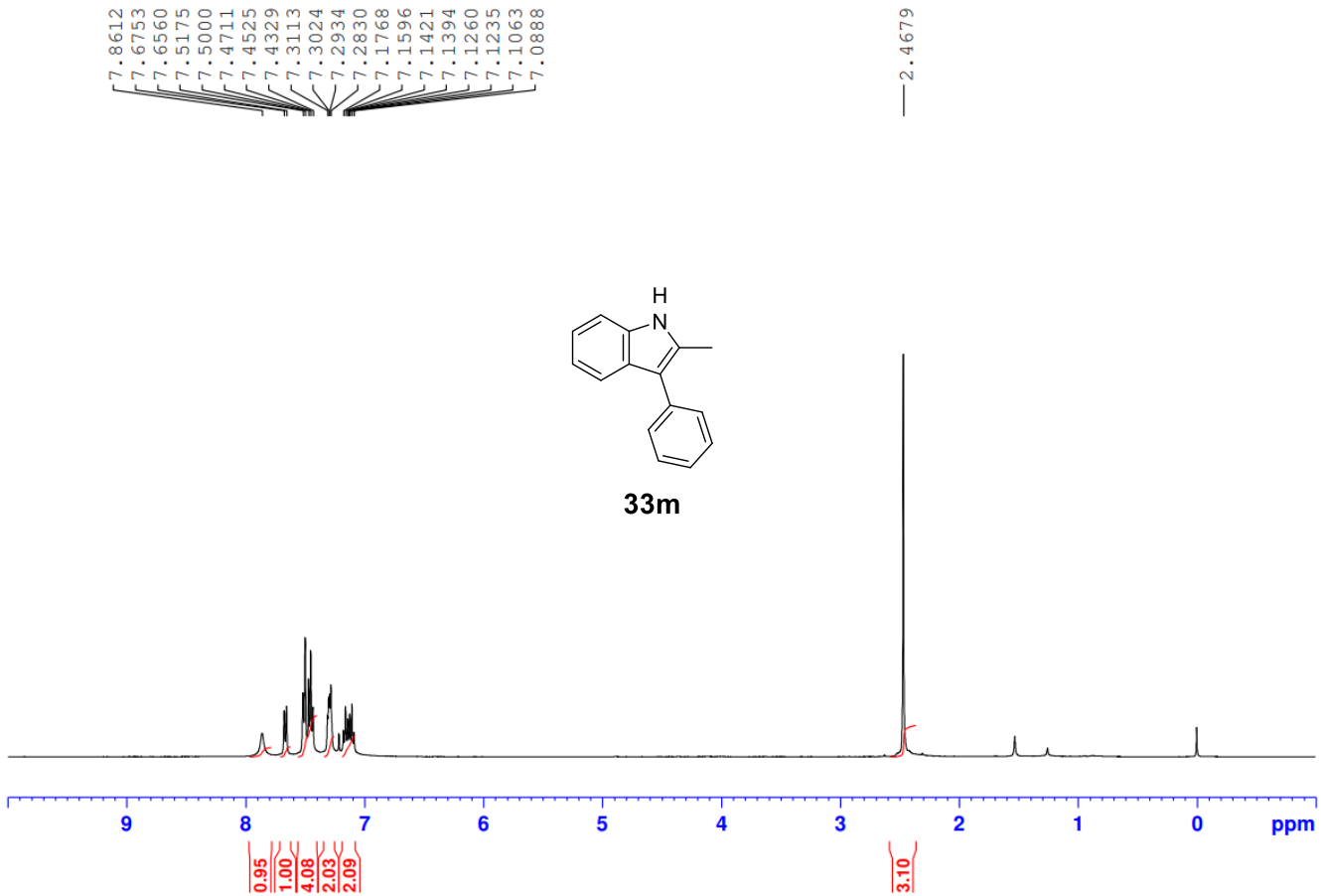
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33j**



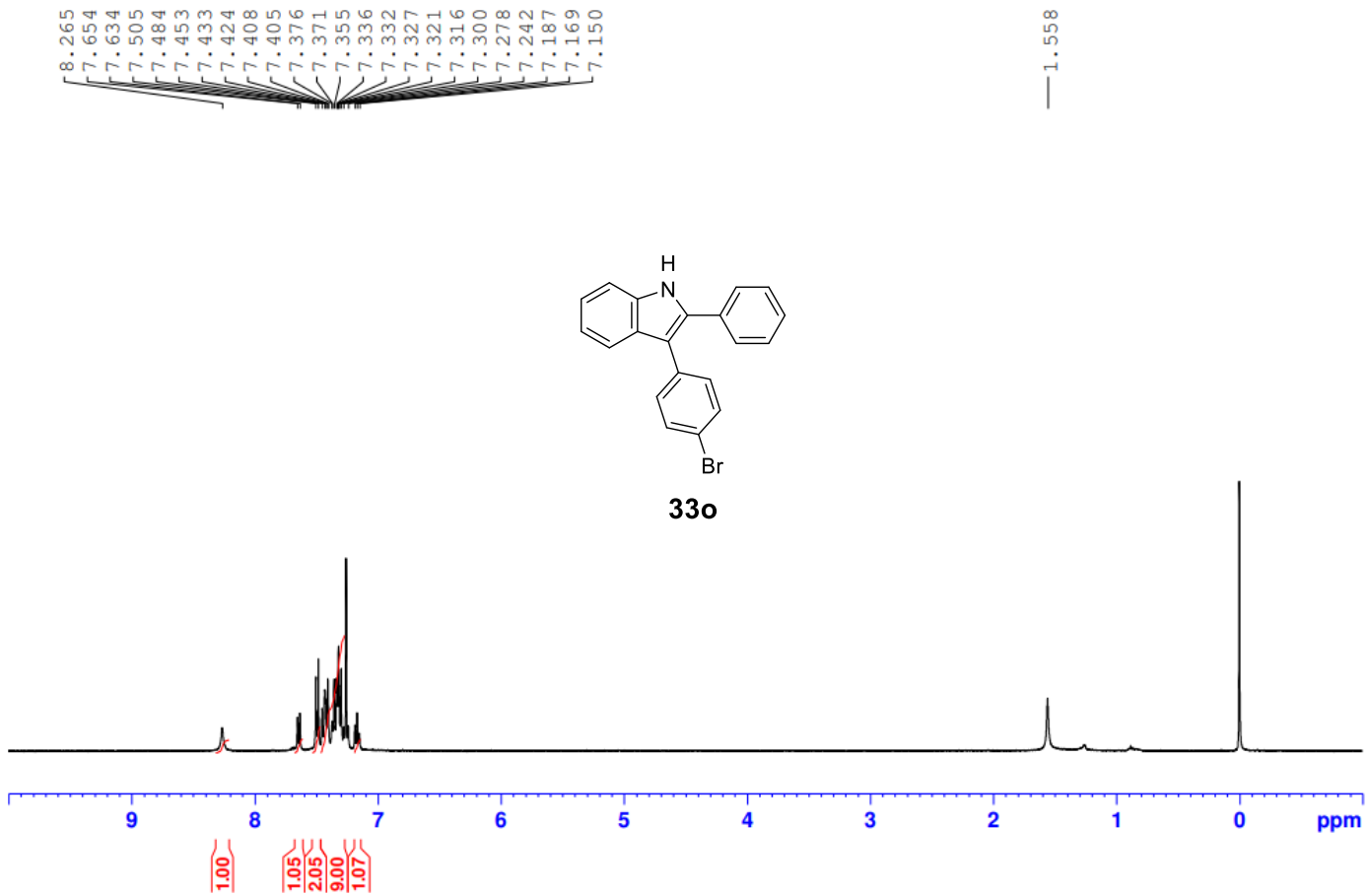
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33k**



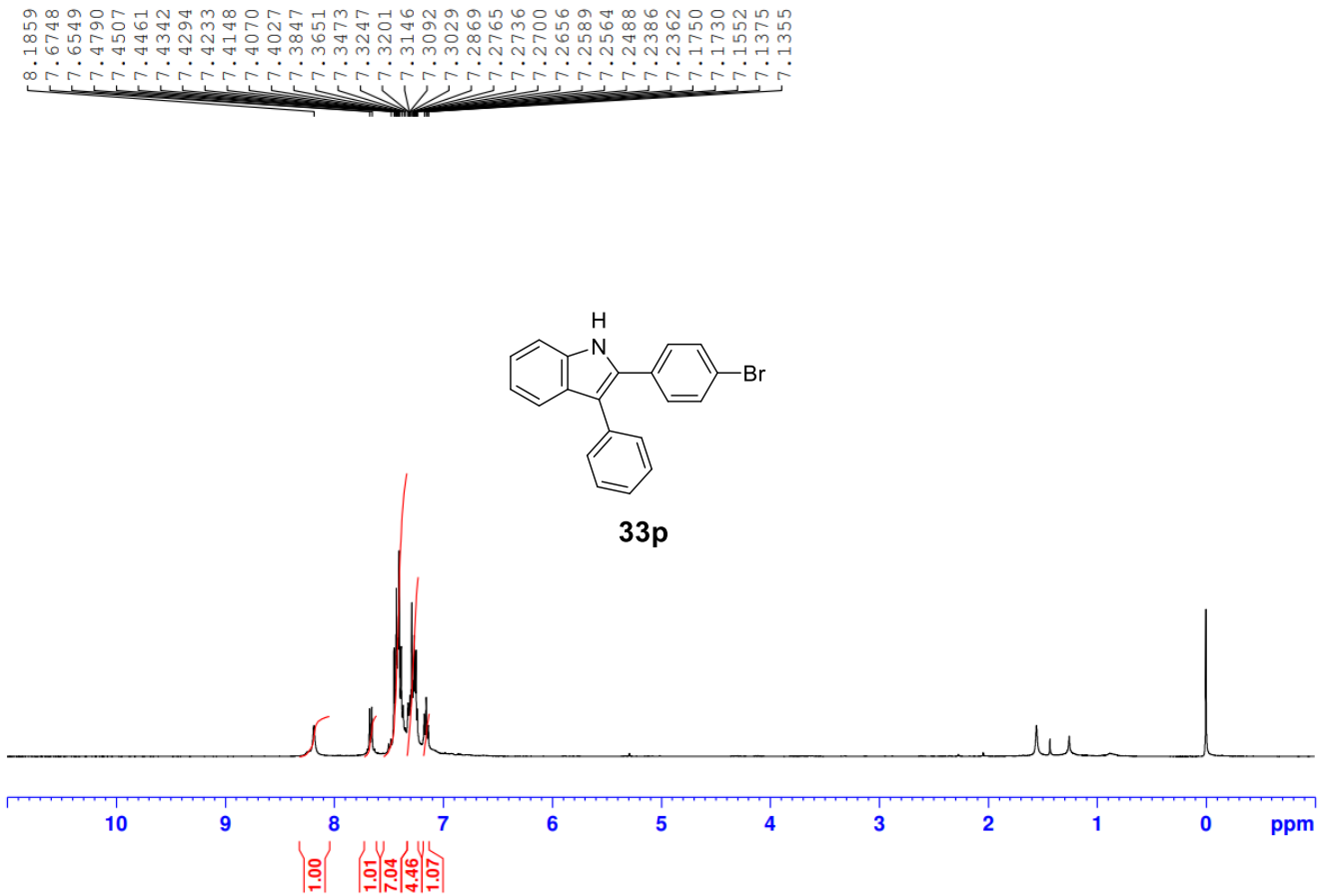
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33l**



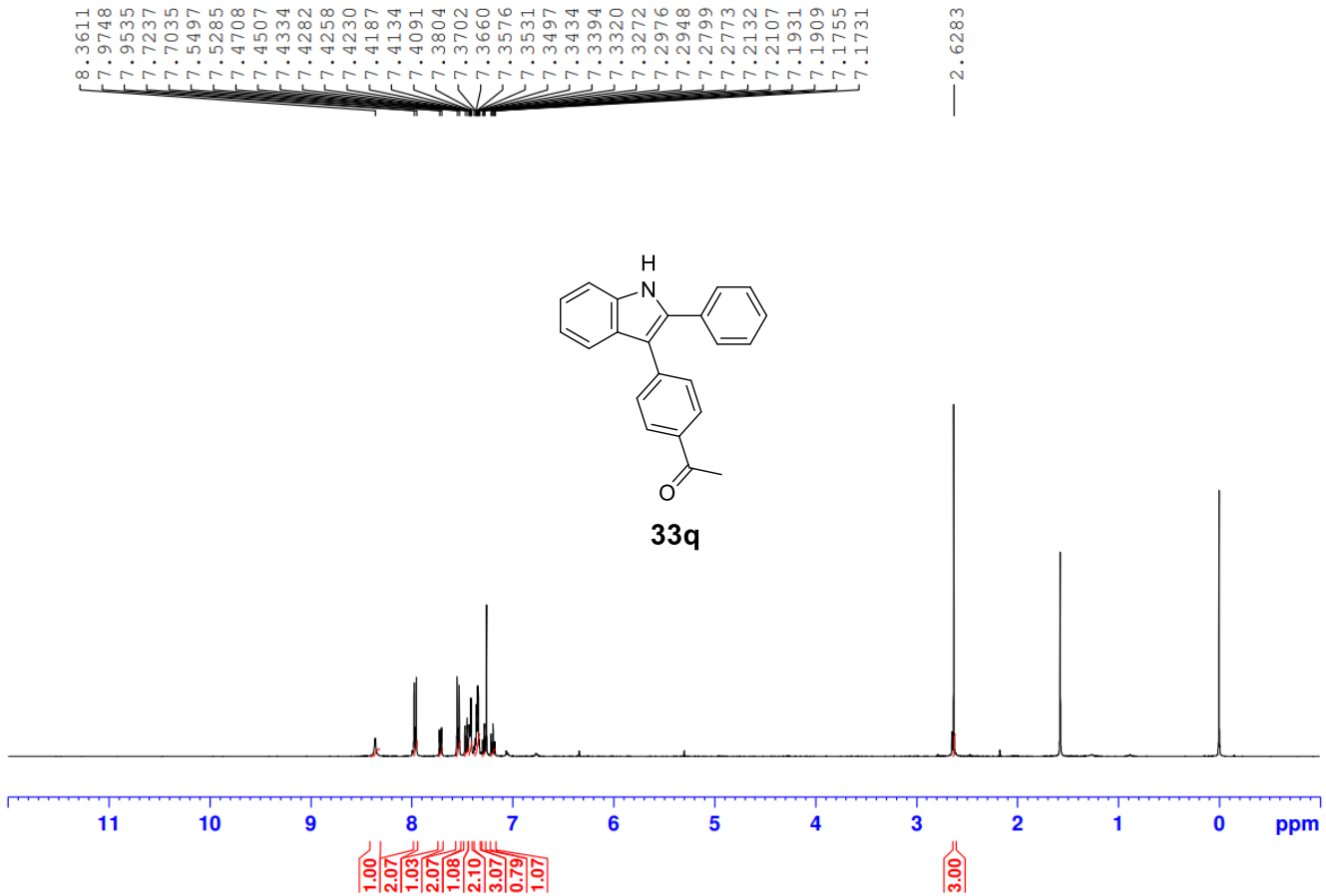
400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33m**



400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33o**



400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33p**



400 MHz ^{1}H-NMR spectrum ($CDCl_3$) of compound **33q**

List of ^{13}C-NMR Spectra of Selected Compounds

1. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **6**
2. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **10**
3. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **11**
4. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***cis*-12**
5. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***trans*-12**
6. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **5**
7. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **13**
8. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **4**
9. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **14**
10. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **3**
11. 100 MHz ^{13}C-NMR spectrum (Acetone-d_6) of compound **15**
12. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **17**
13. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **18**
14. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **20**
15. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **22**
16. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **23**
17. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **24**
18. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **25**
19. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **28**
20. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32a**

21. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32b**

22. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32c**

23. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32d**

24. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32e**

25. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***Z*-32e**

26. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32f**

27. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***Z*-32f**

28. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32g**

29. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32h**

30. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32i**

31. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32j**

32. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***Z*-32k**

33. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32l**

34. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32m**

35. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32n**

36. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32o**

37. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32p**

38. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32q**

39. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33a**

40. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33b**

41. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33c**

42. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33d**

43. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33e**

44. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33f**

45. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33g**

46. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33h**

47. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33i**

48. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33j**

49. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33k**

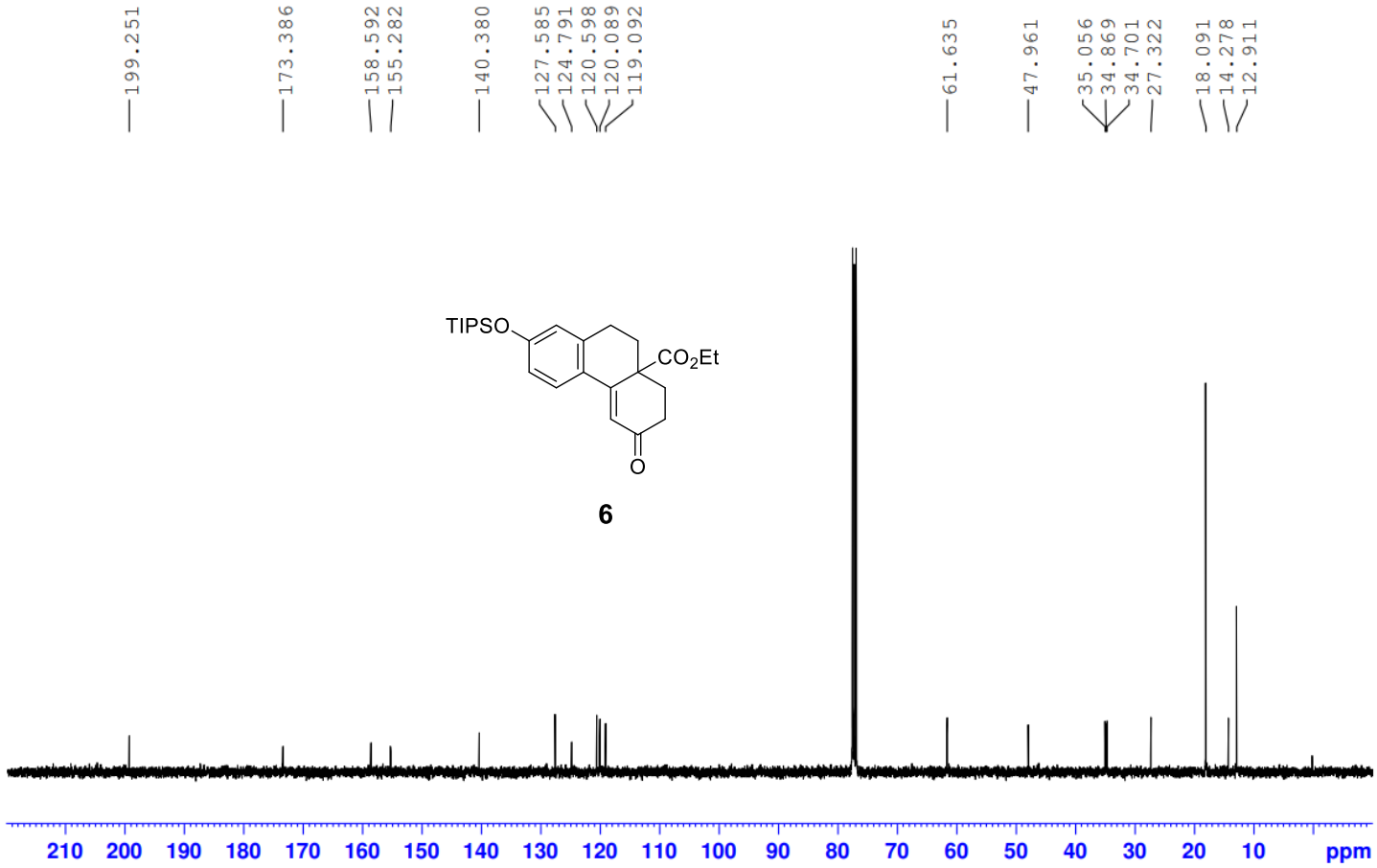
50. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33l**

51. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33m**

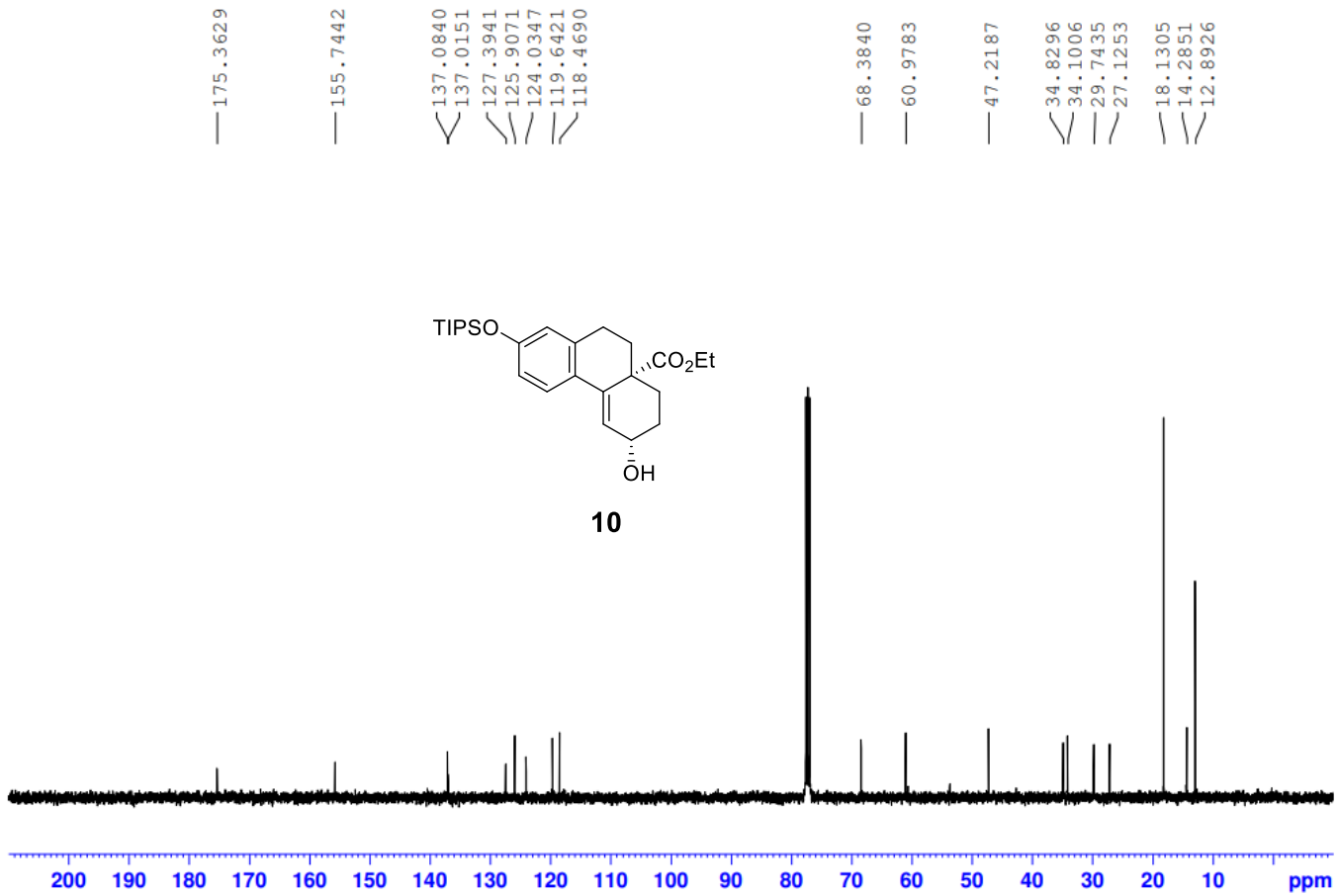
52. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33o**

53. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33p**

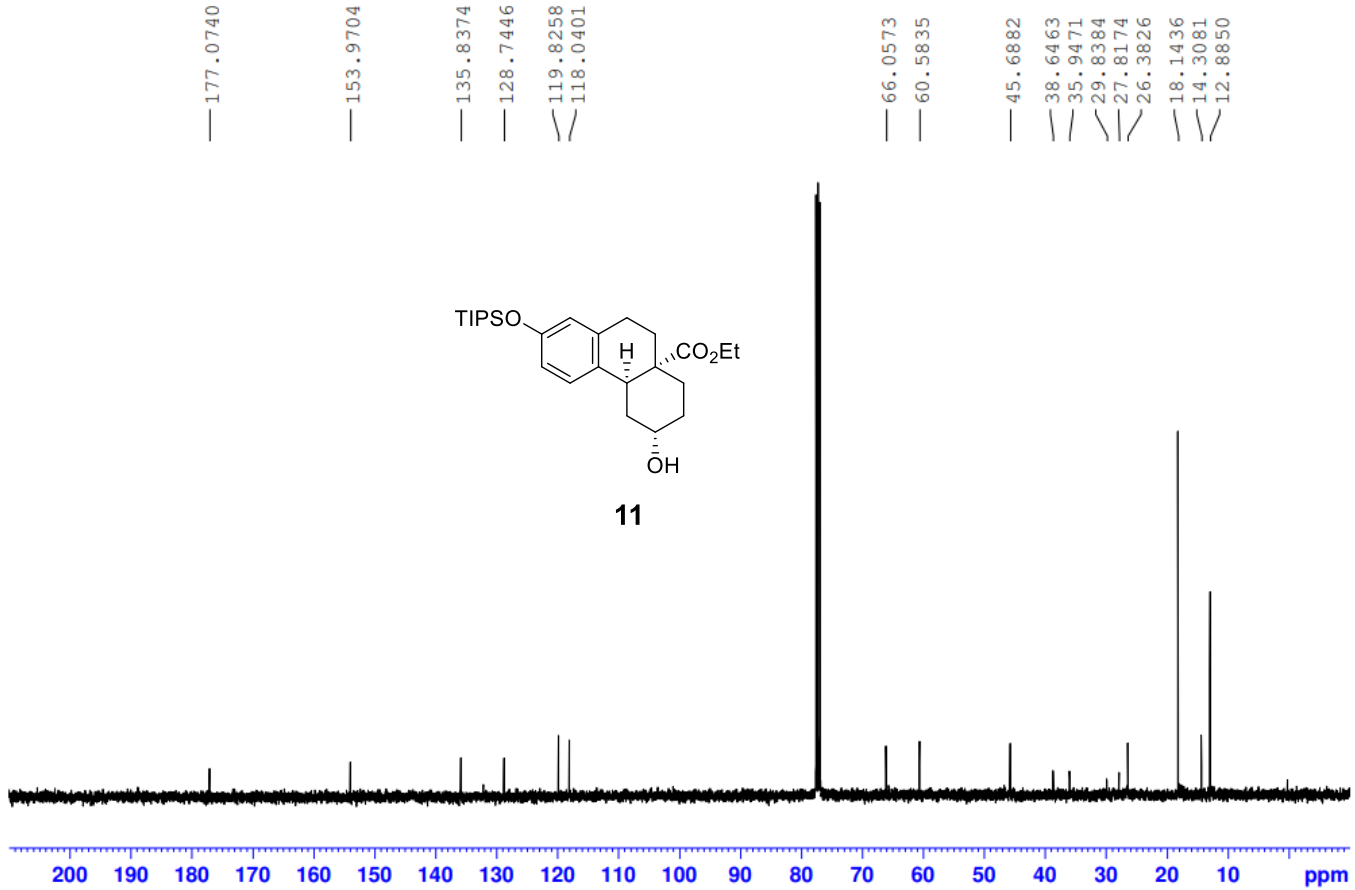
54. 100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33q**



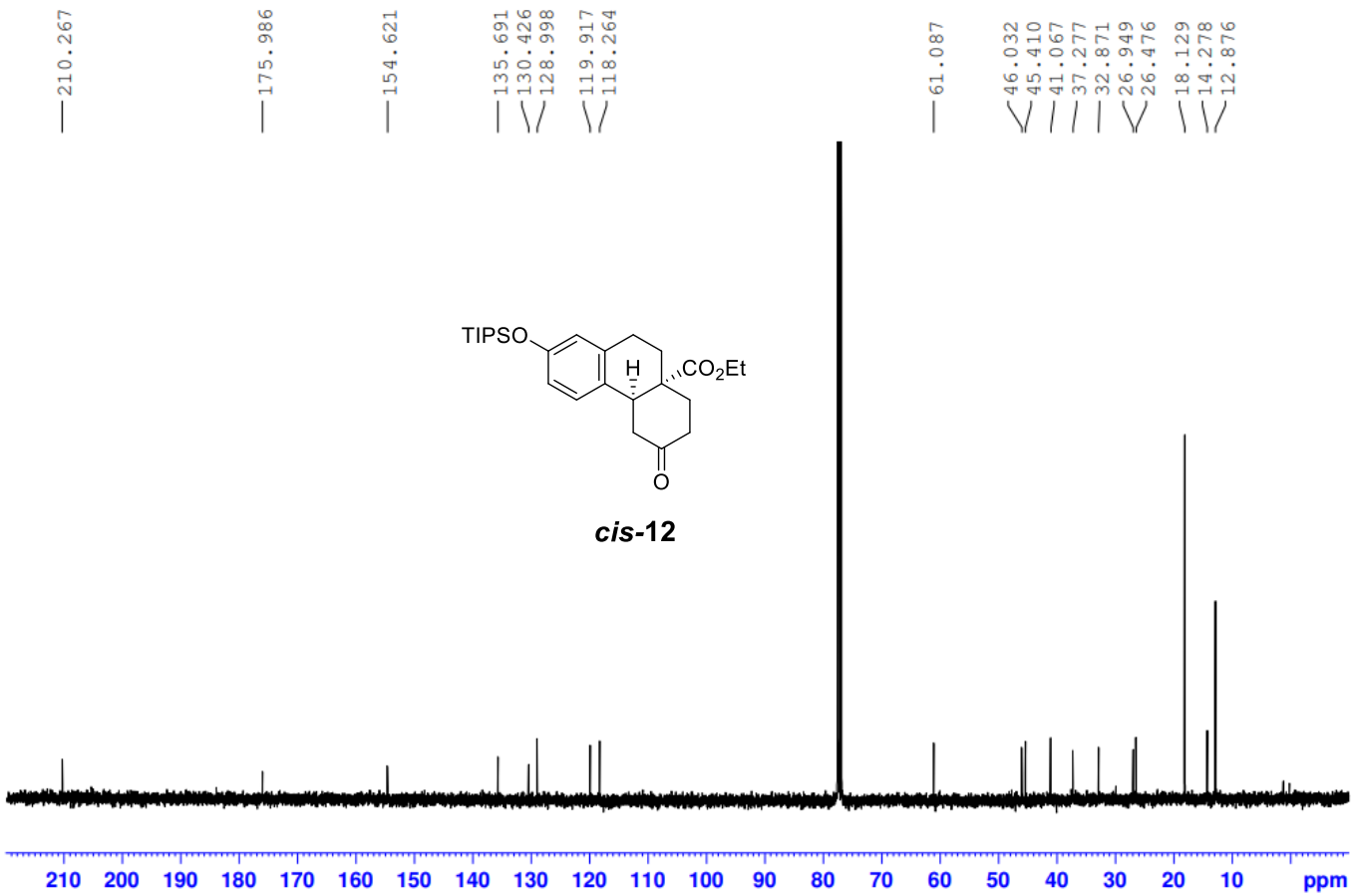
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **6**



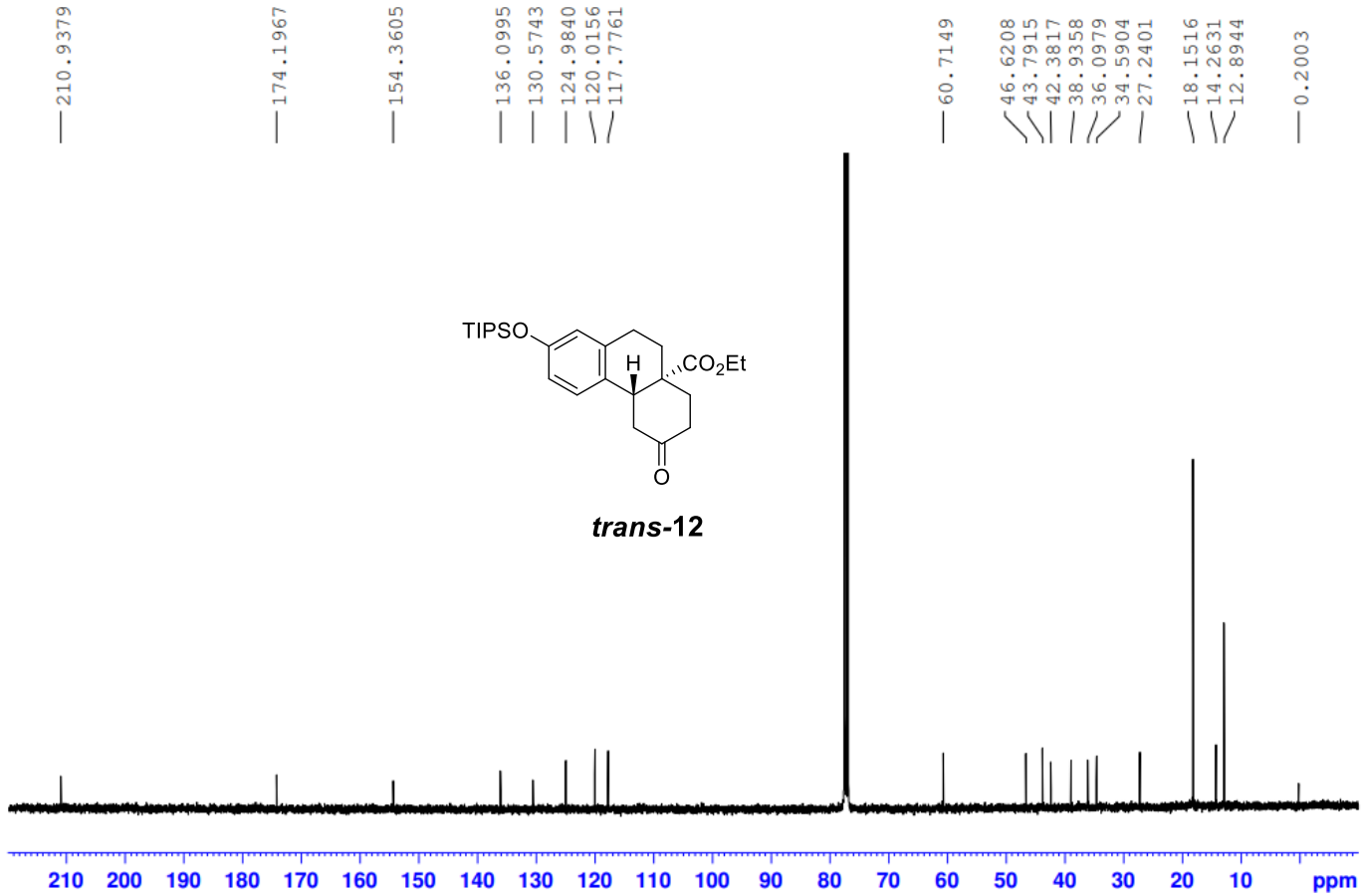
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **10**



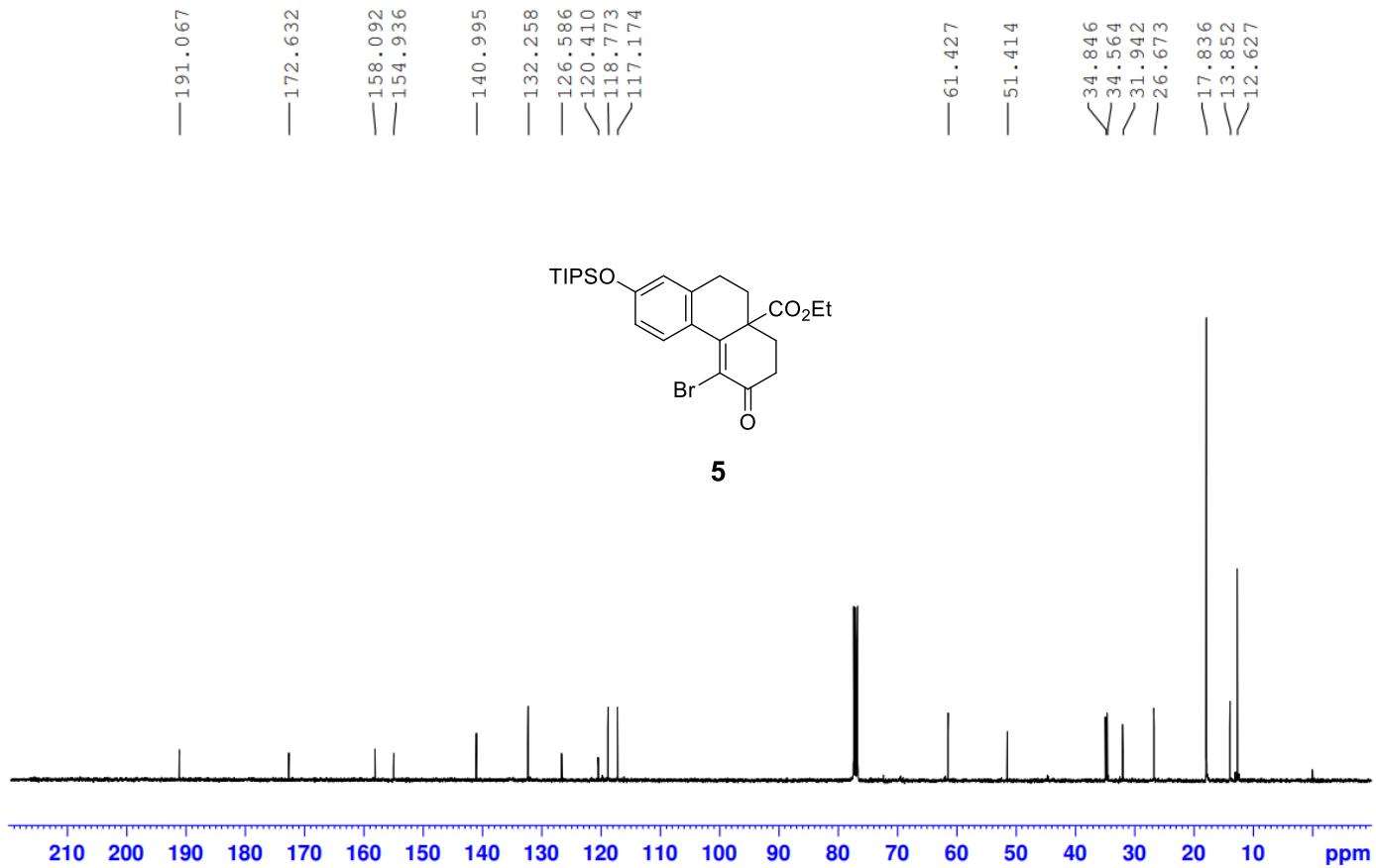
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **11**



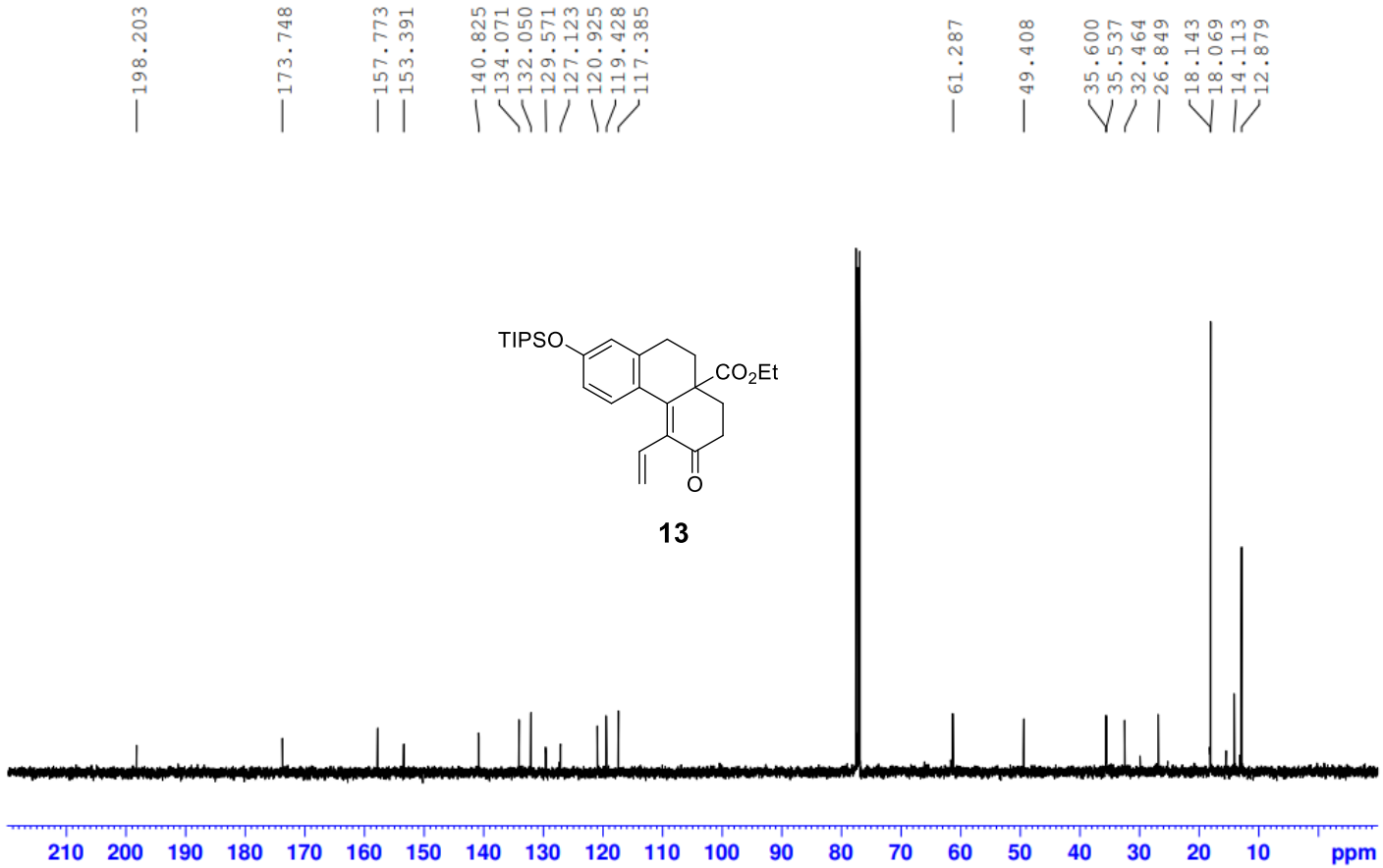
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***cis*-12**



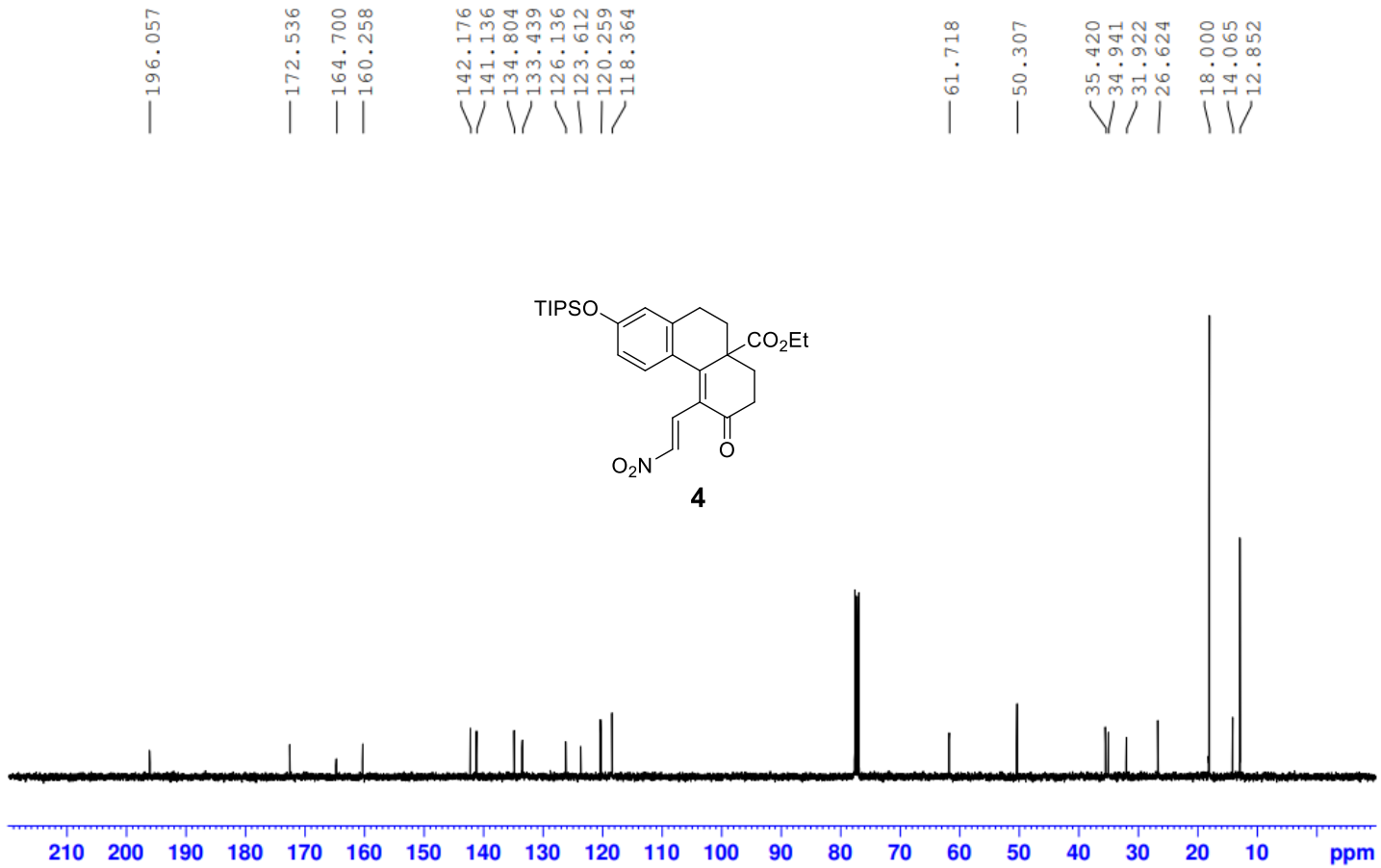
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***trans*-12**



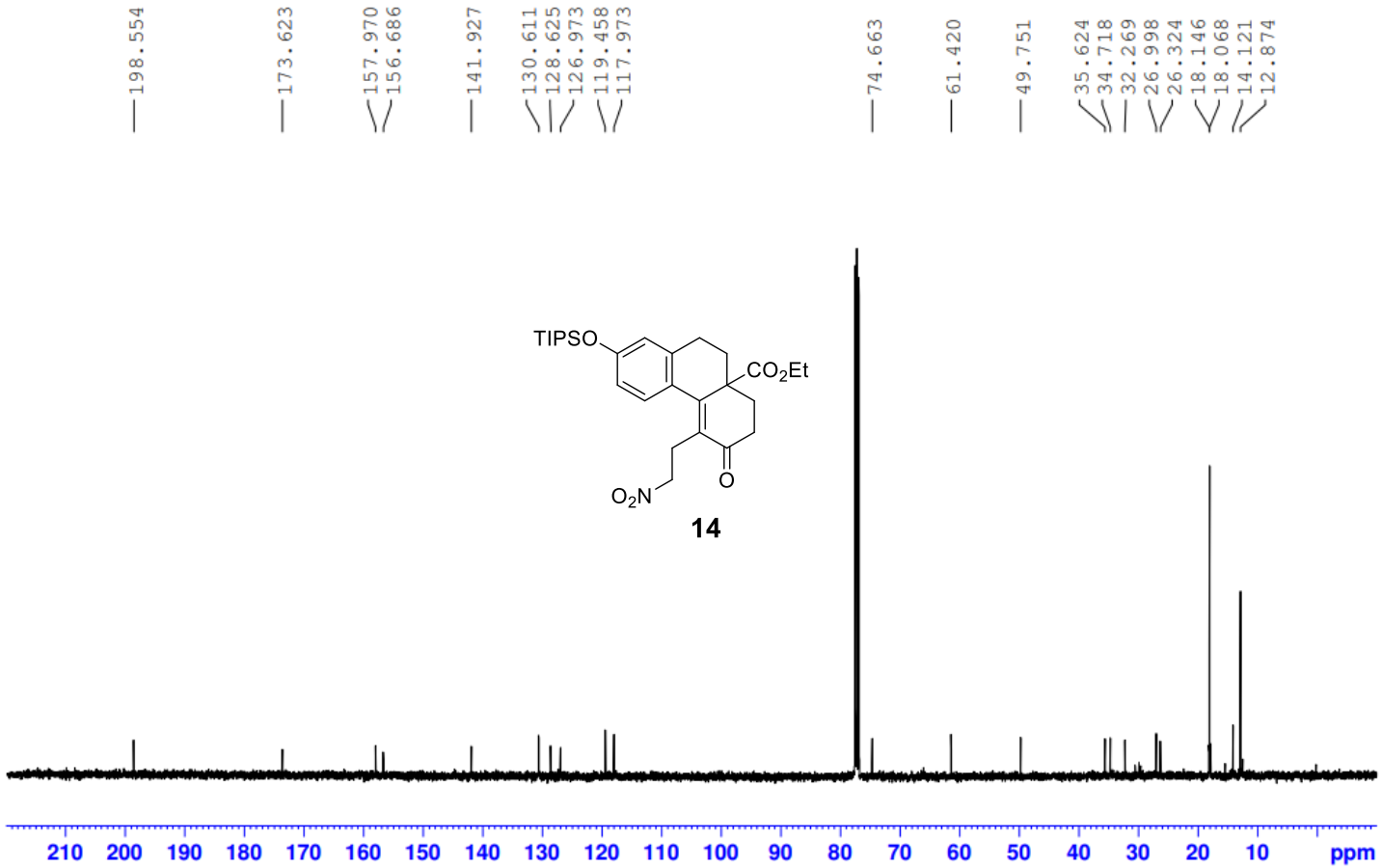
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **5**



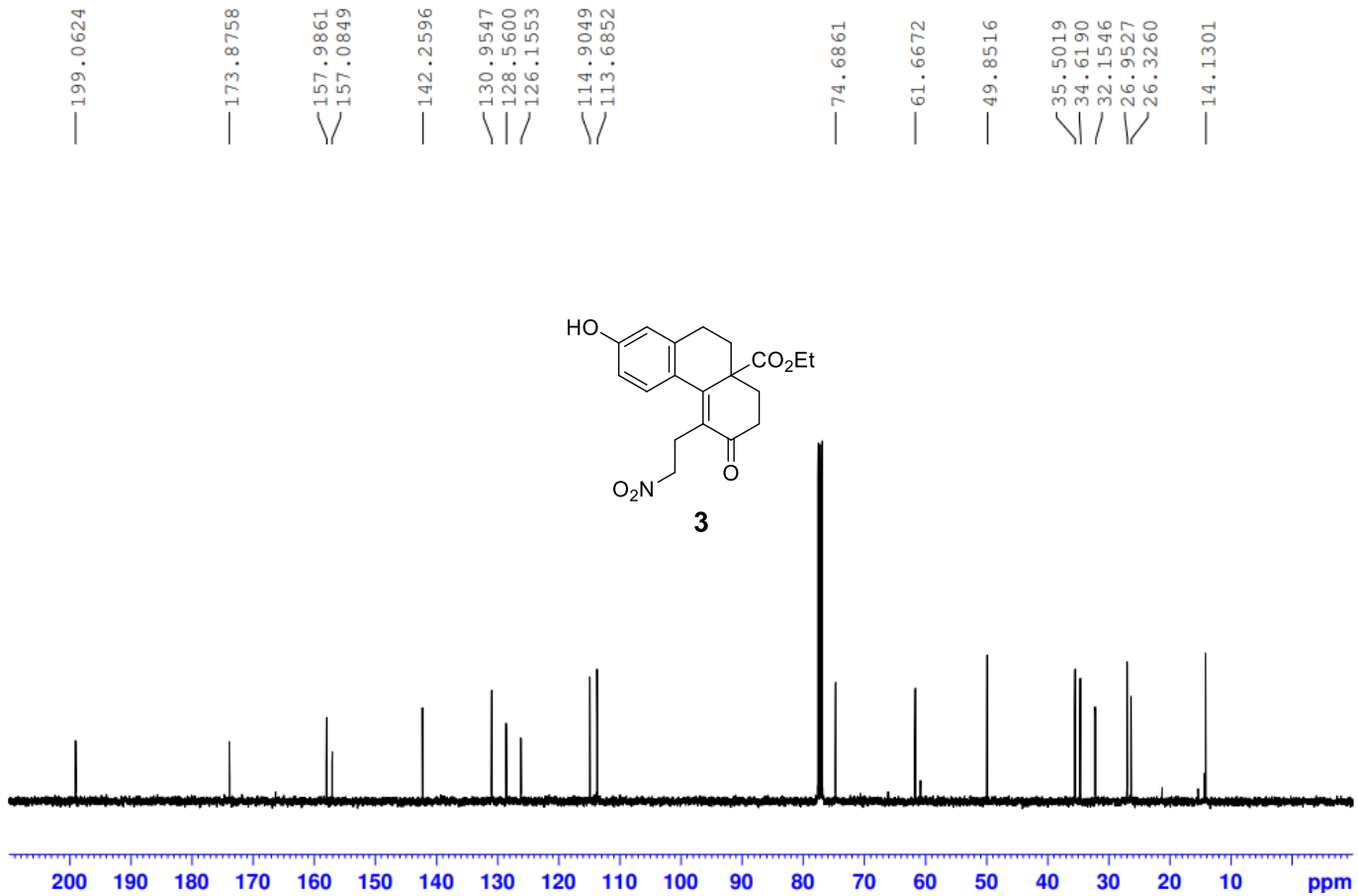
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **13**



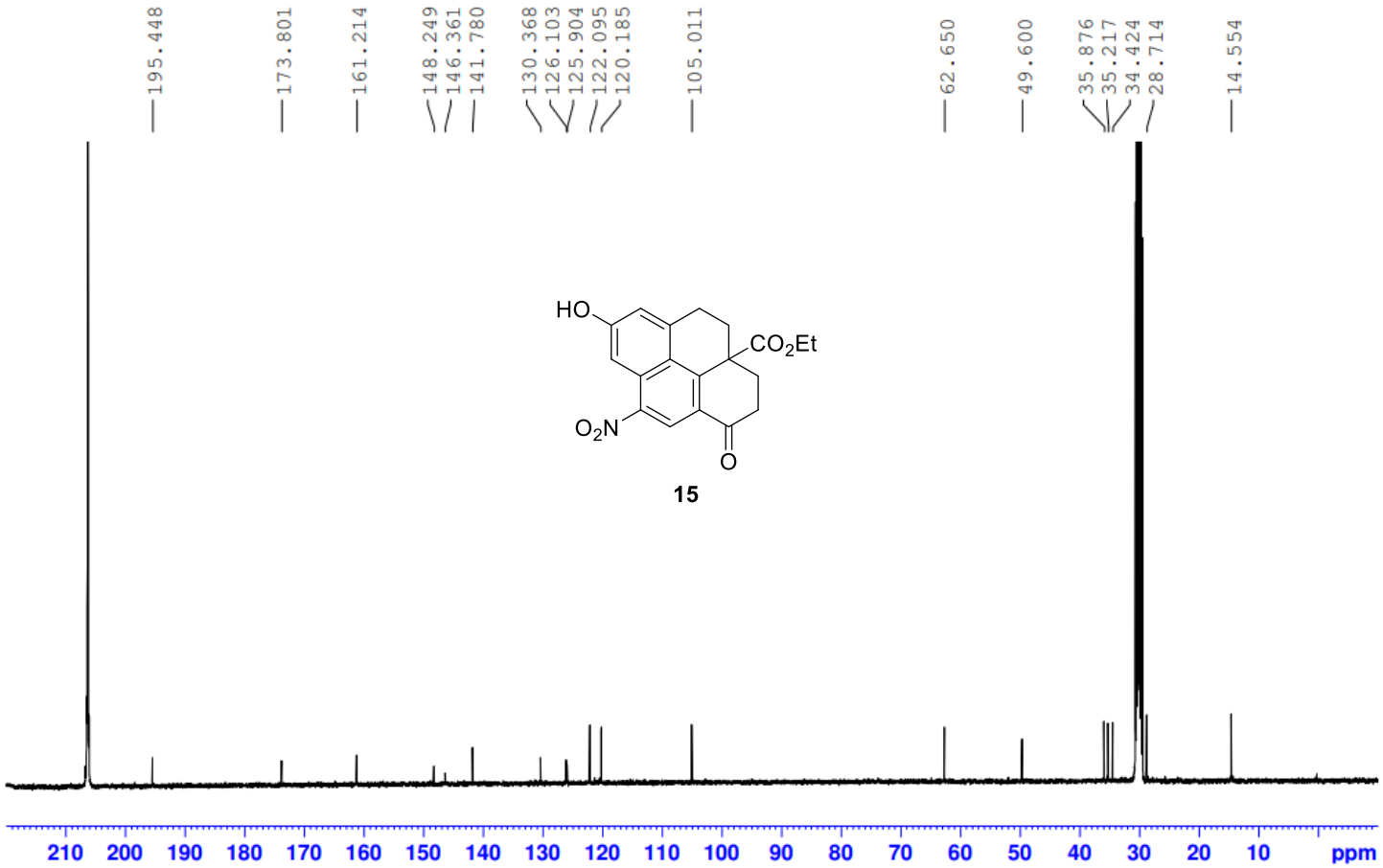
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **4**



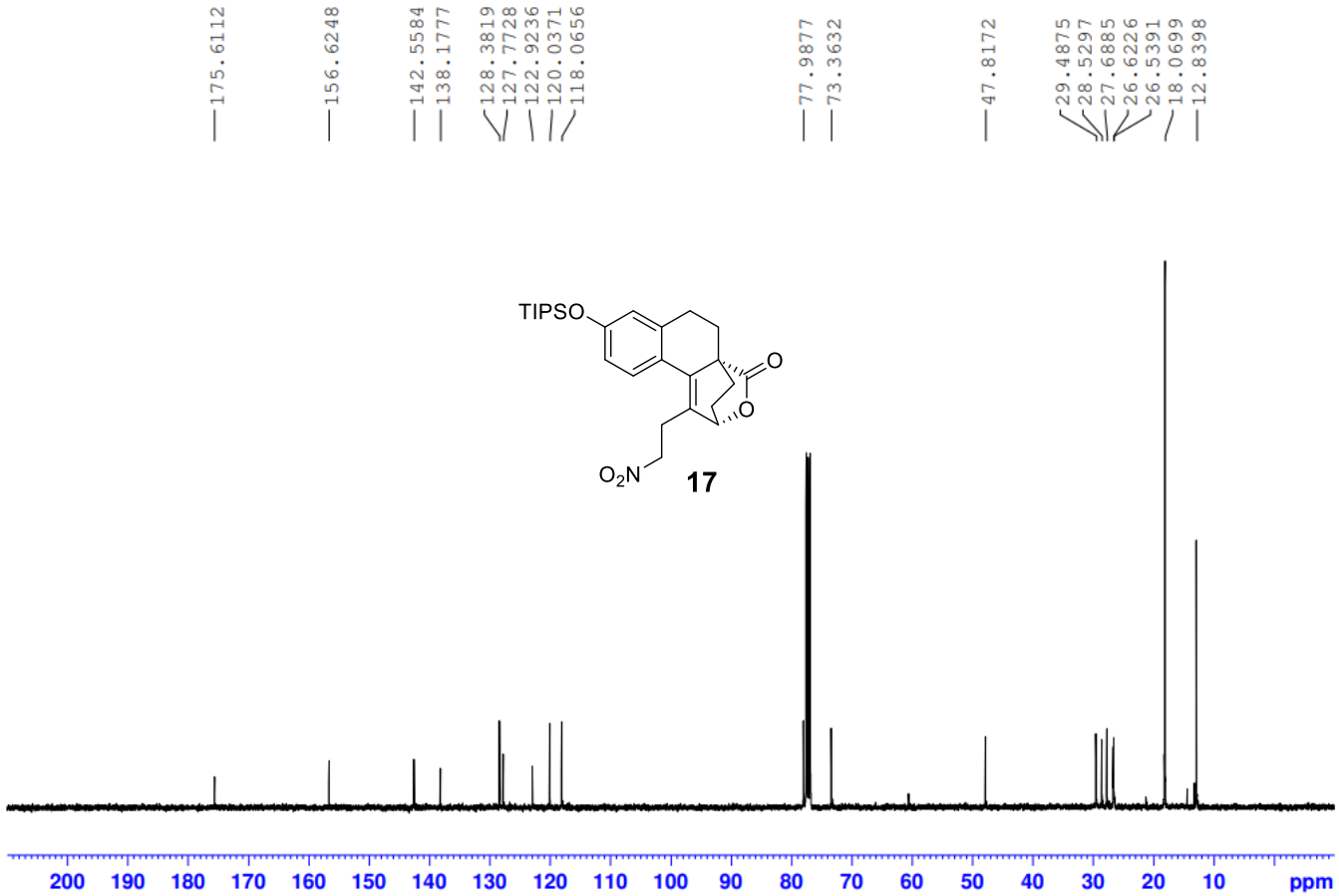
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **14**



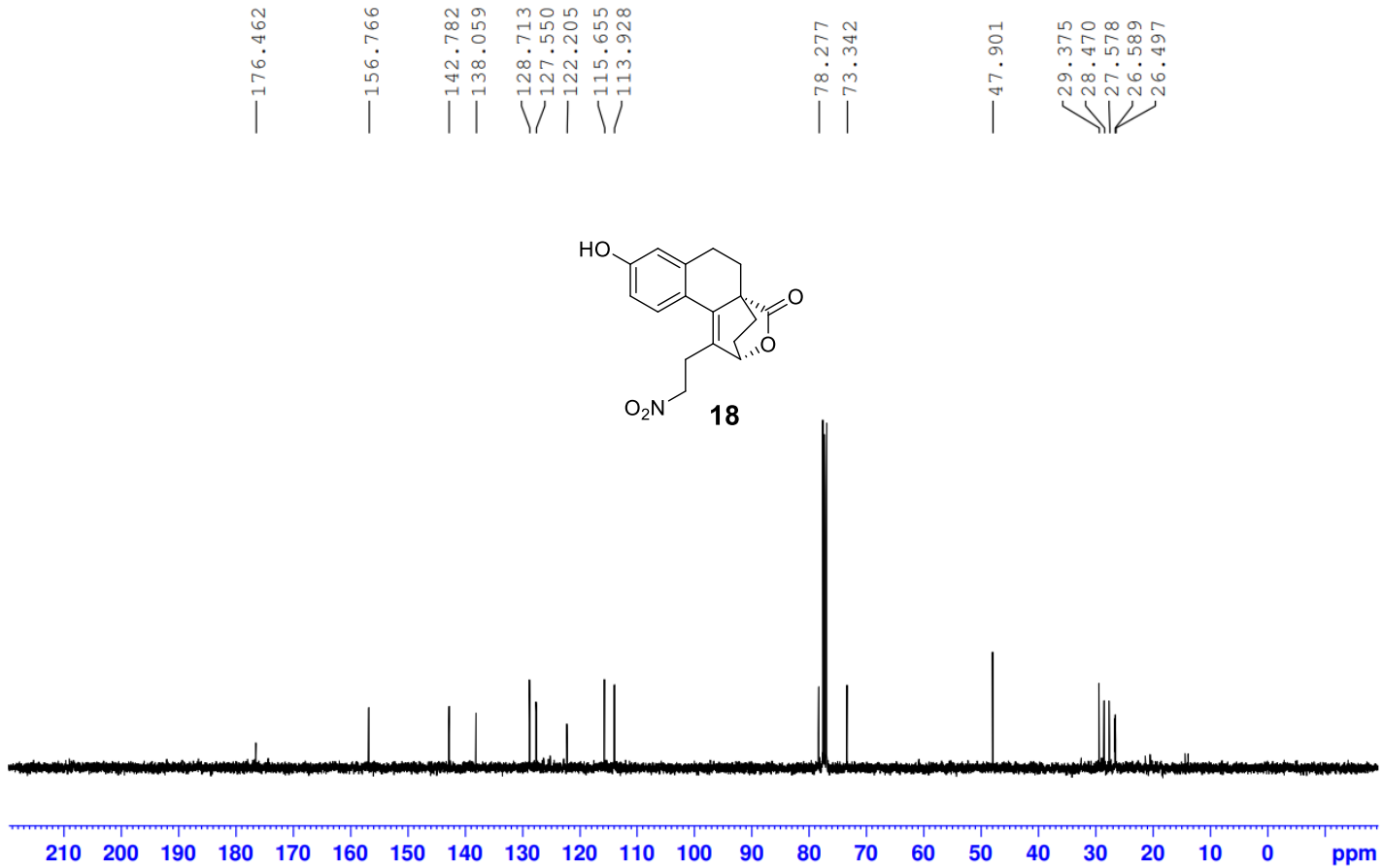
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **3**



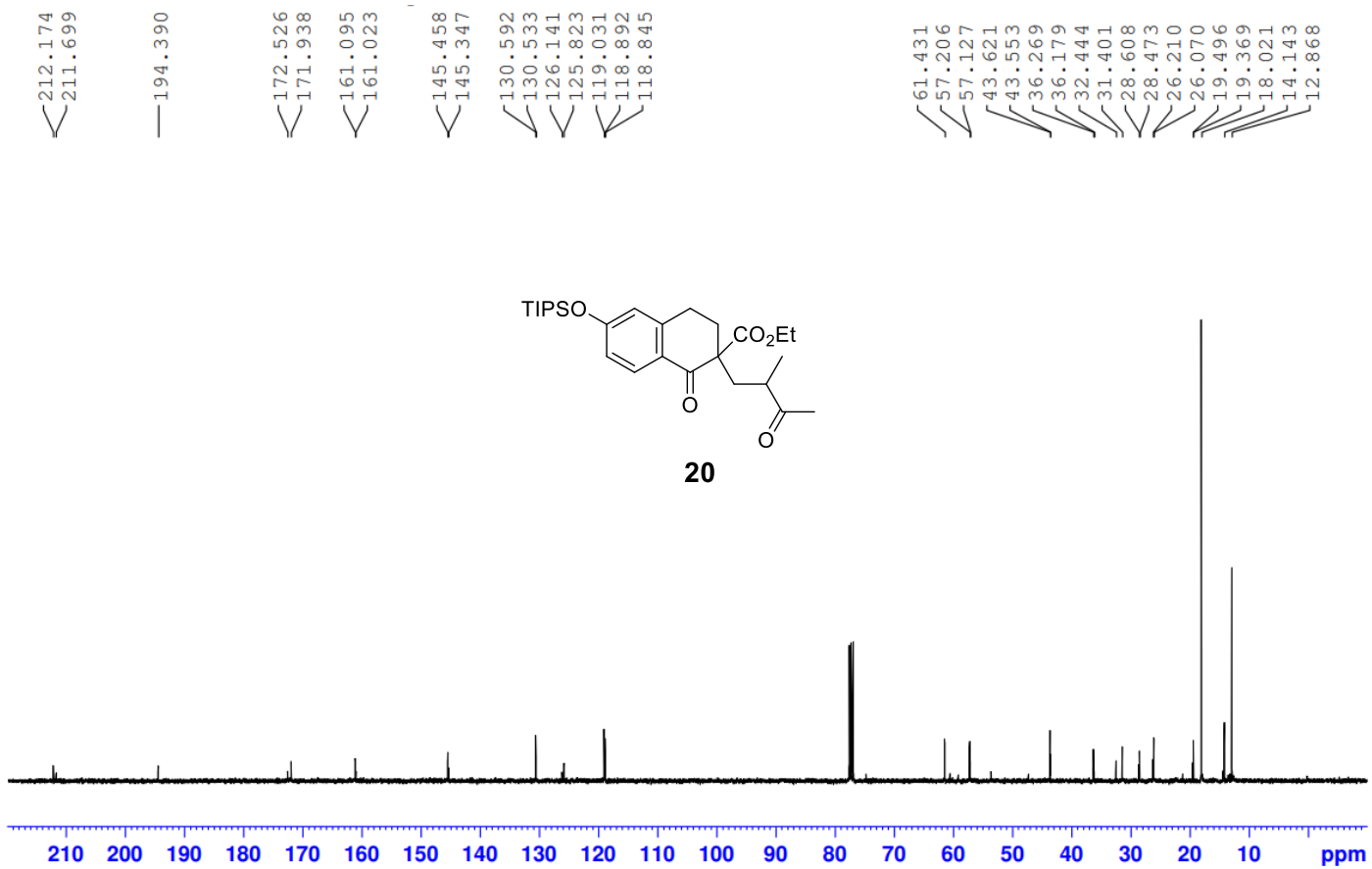
100 MHz ^{13}C-NMR spectrum (Acetone-d_6) of compound **15**



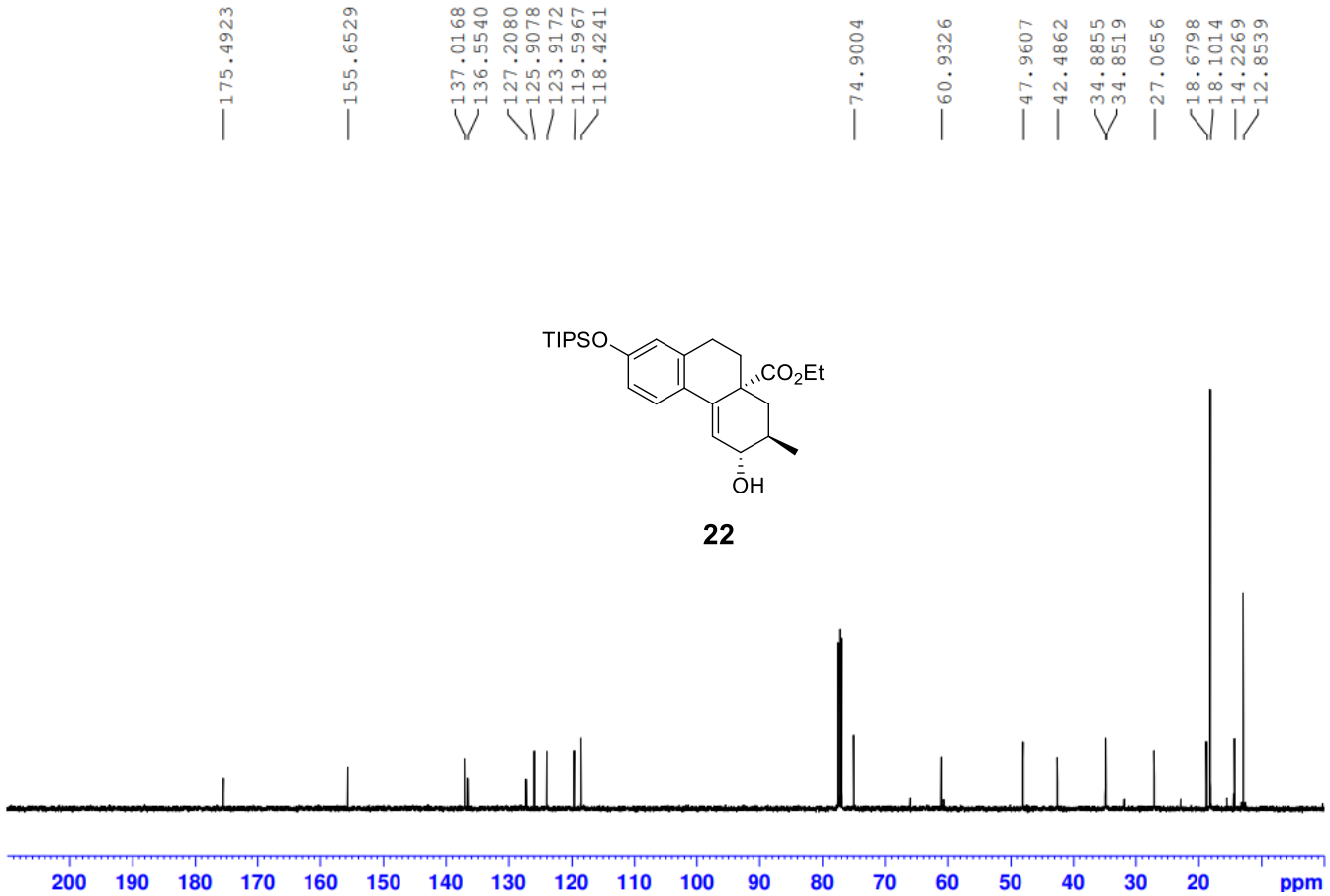
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **17**



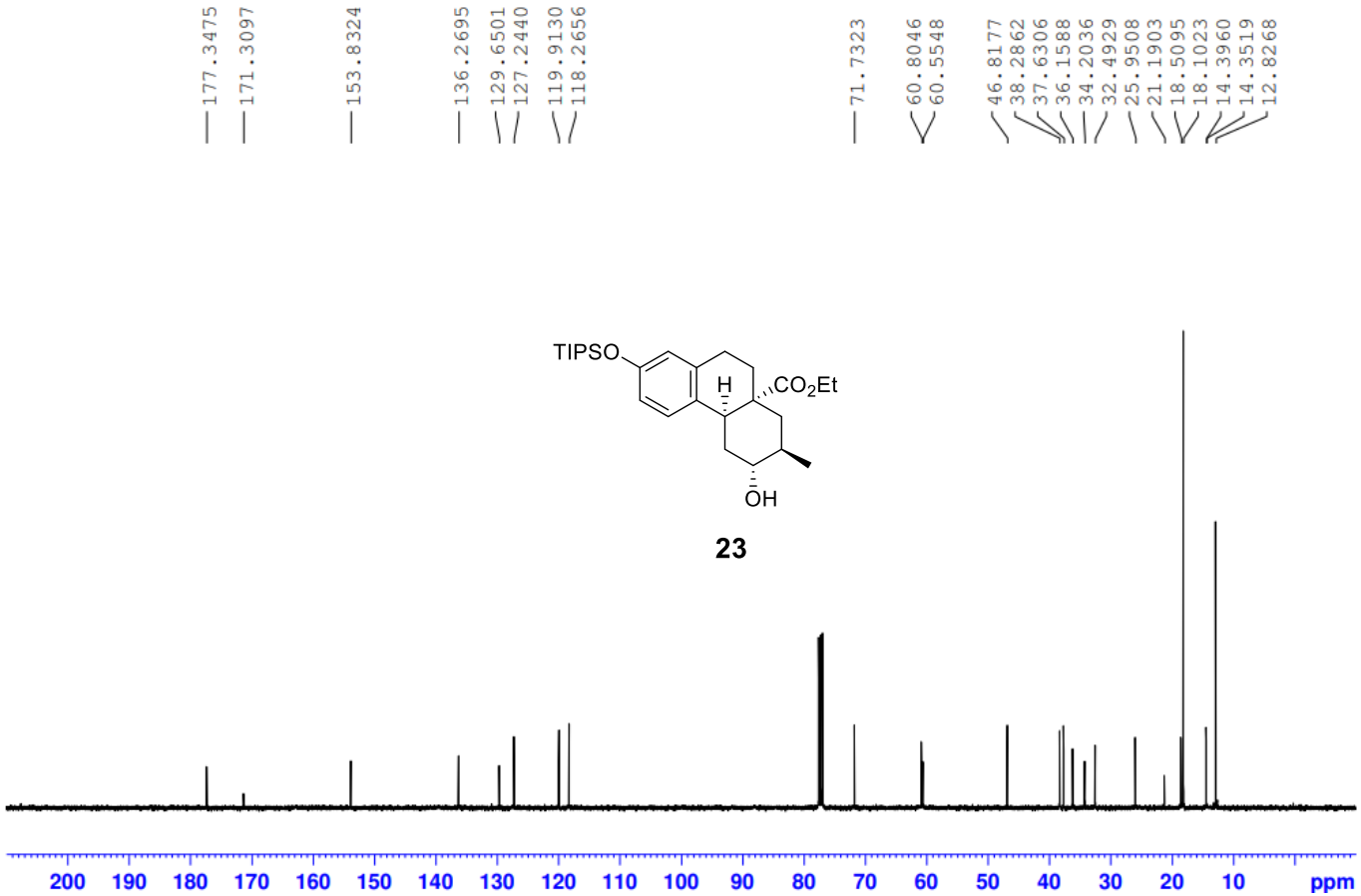
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **18**



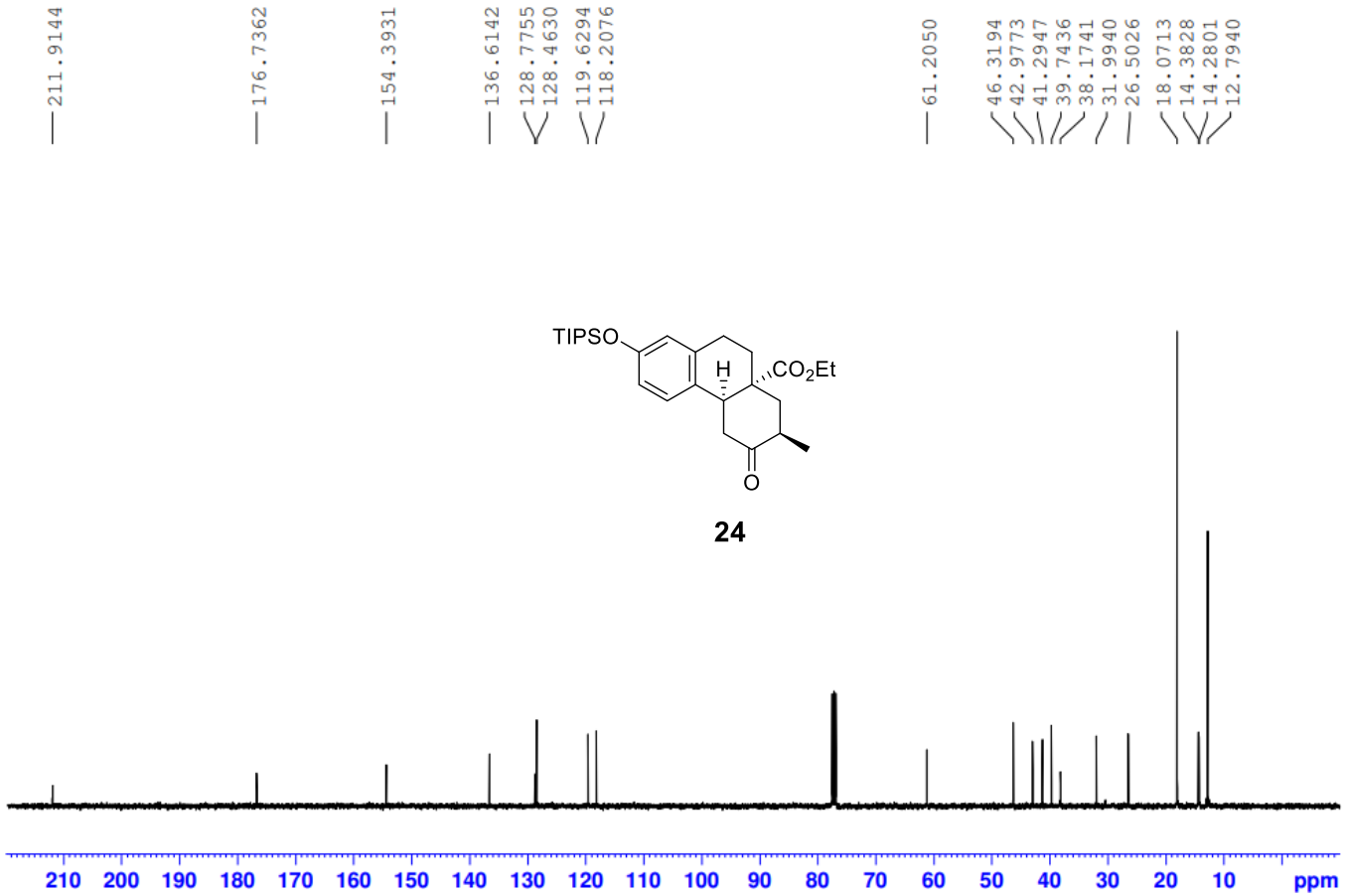
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **20**



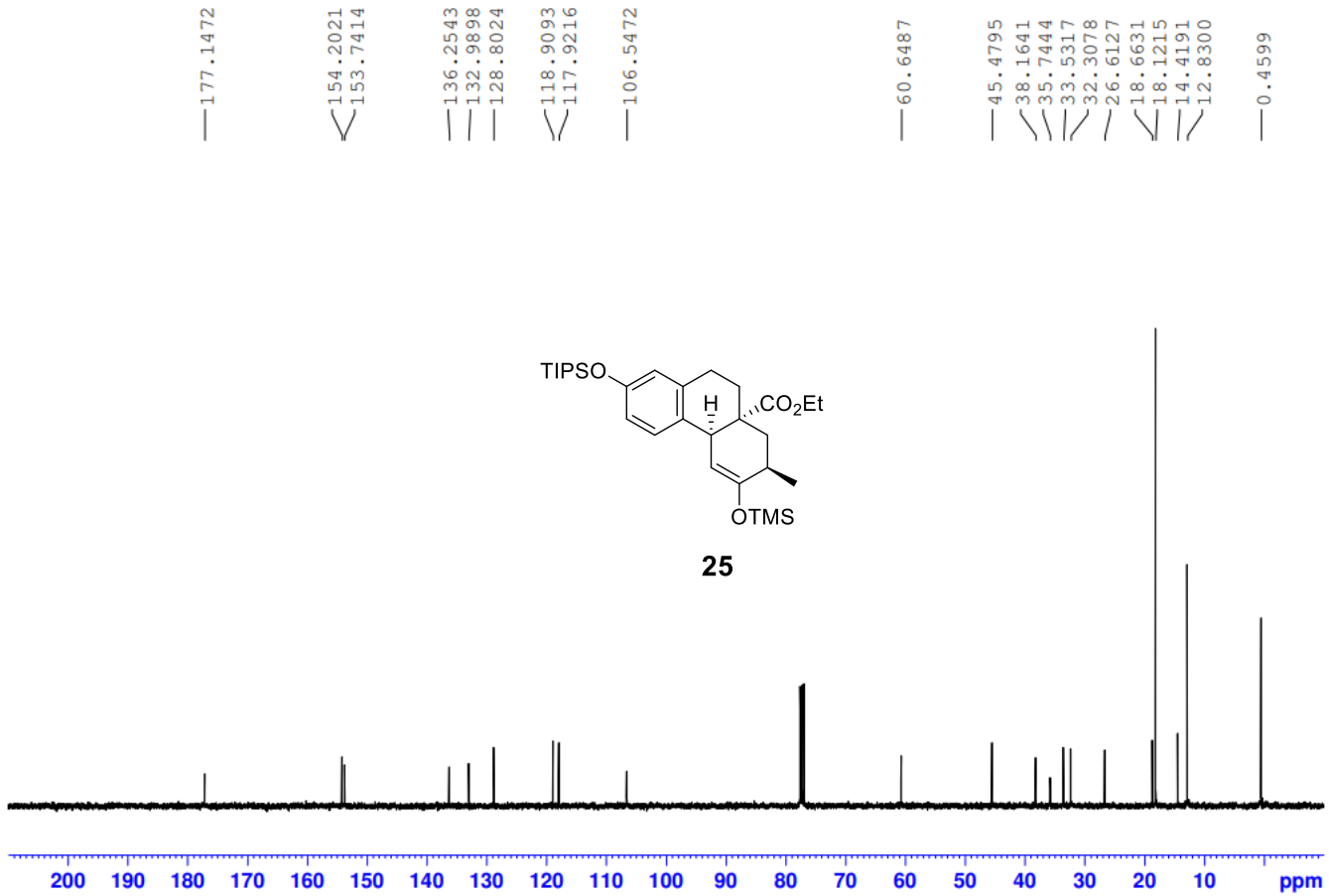
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **22**



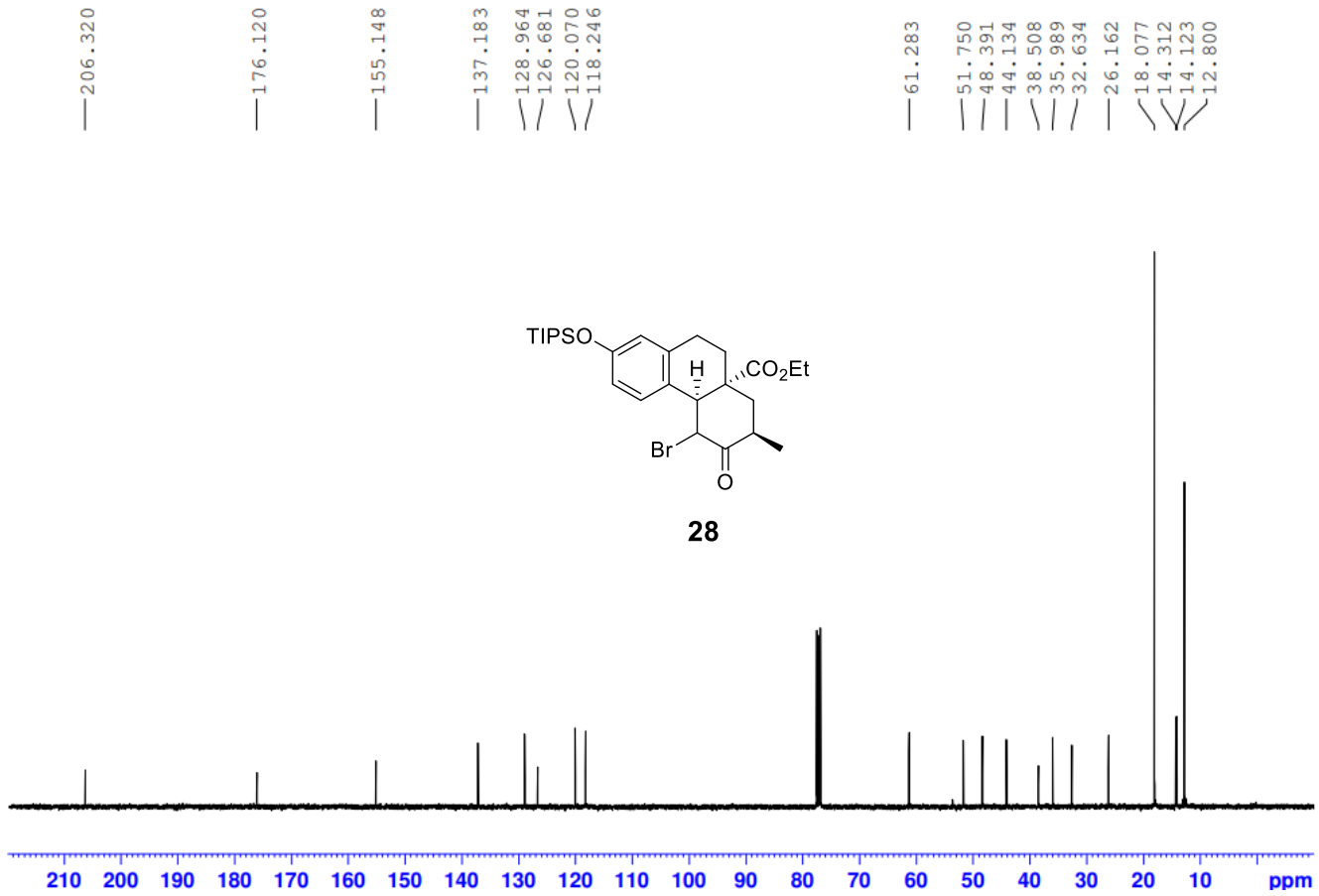
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **23**



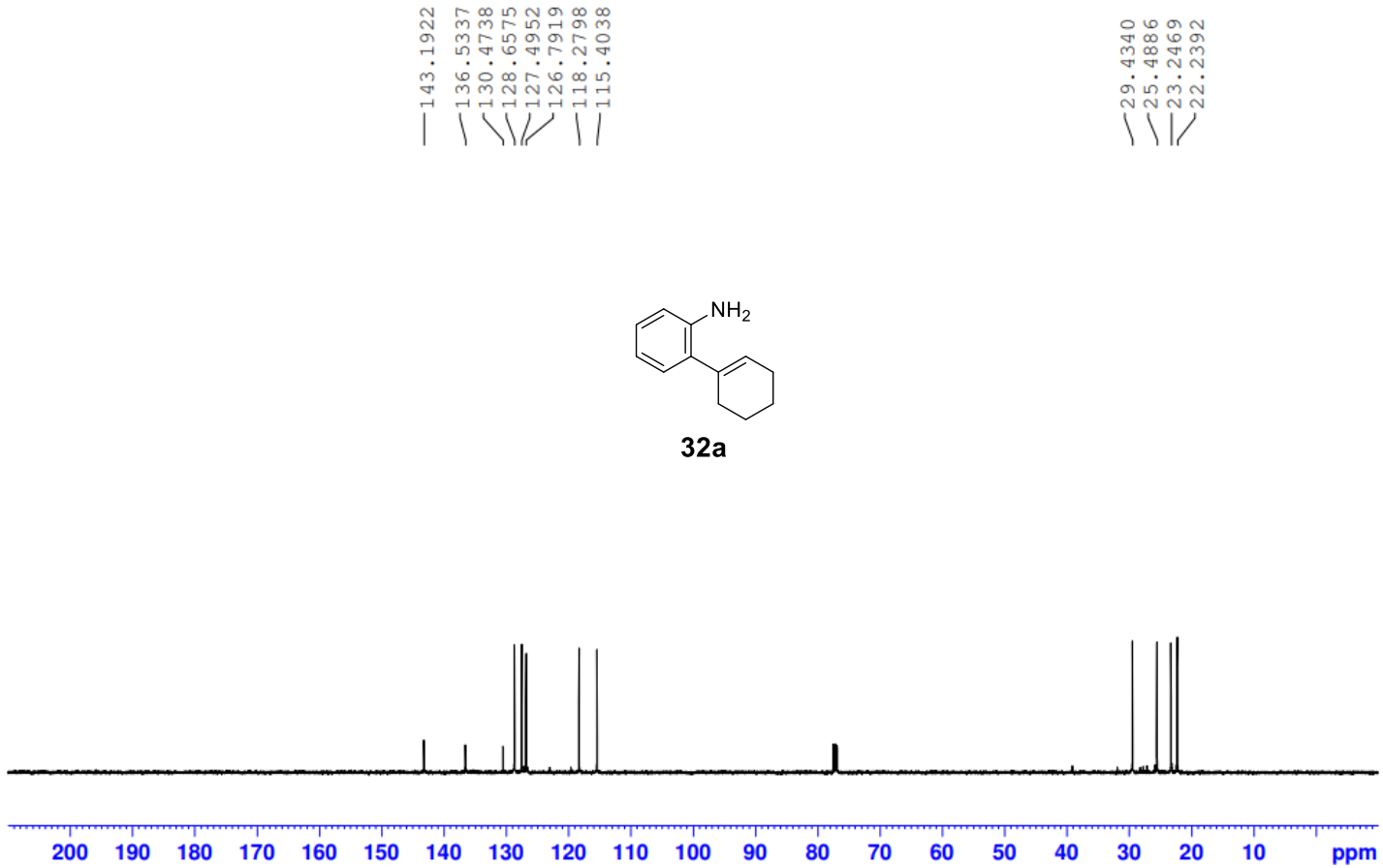
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **24**



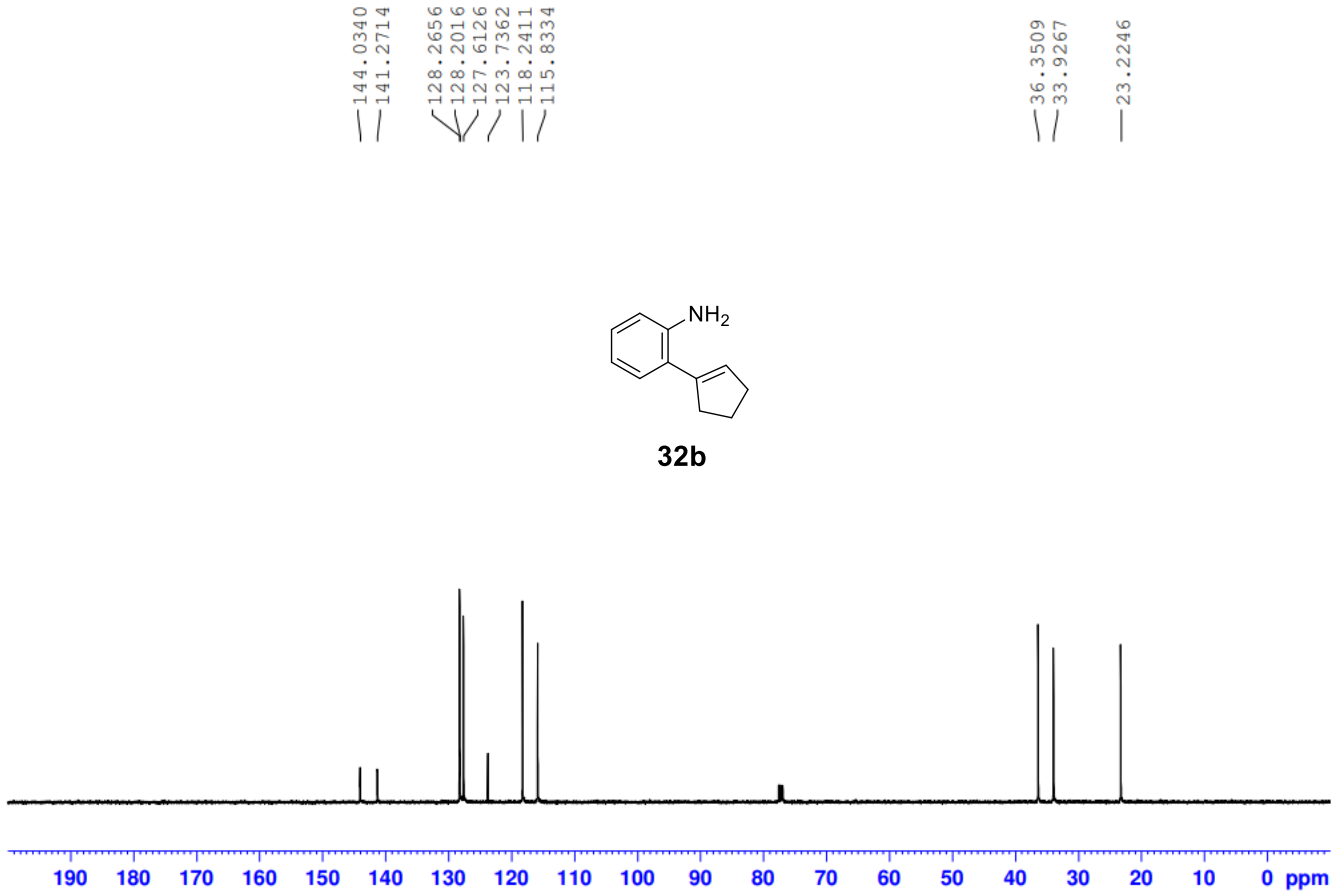
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **25**



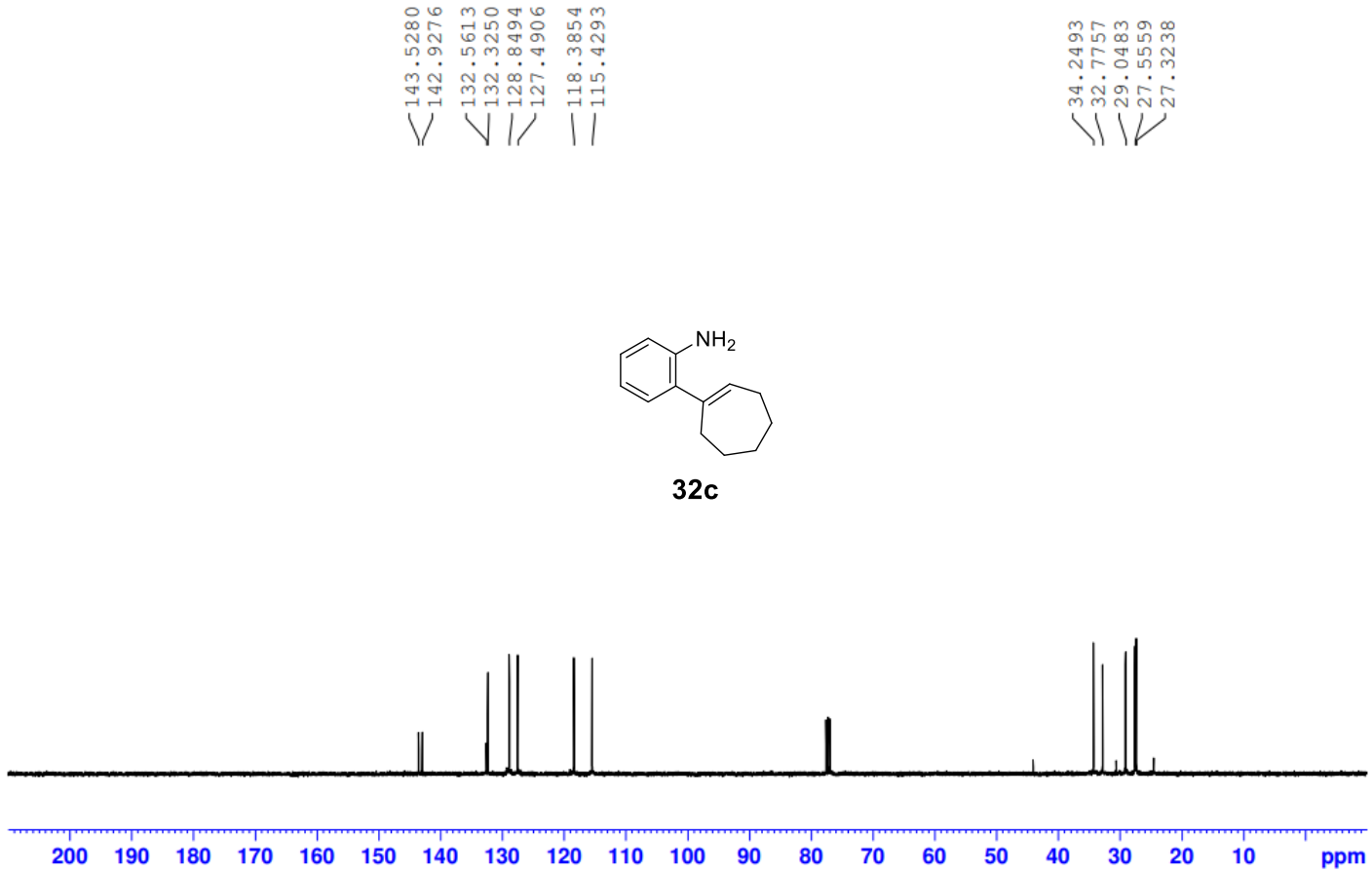
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **28**



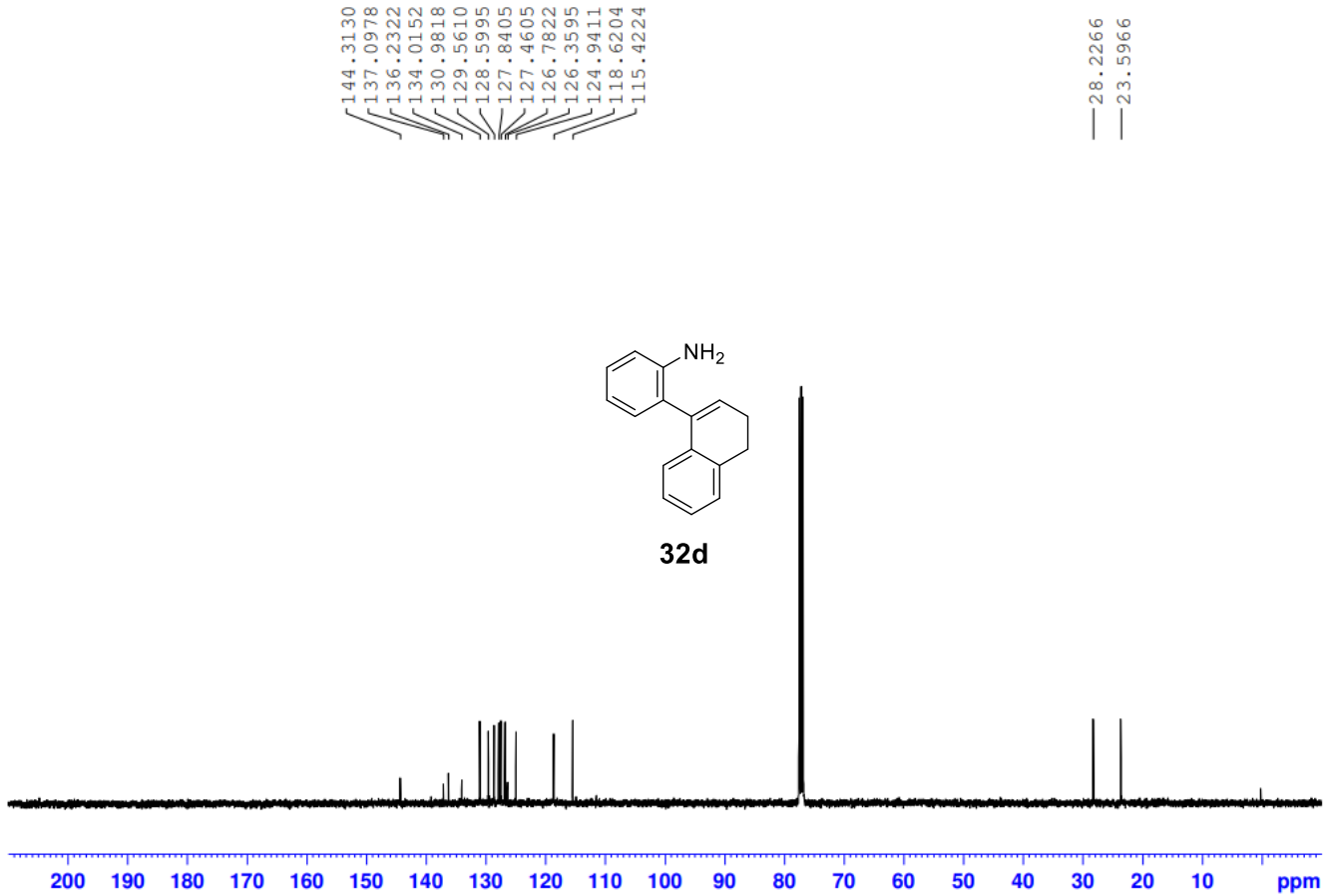
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32a**



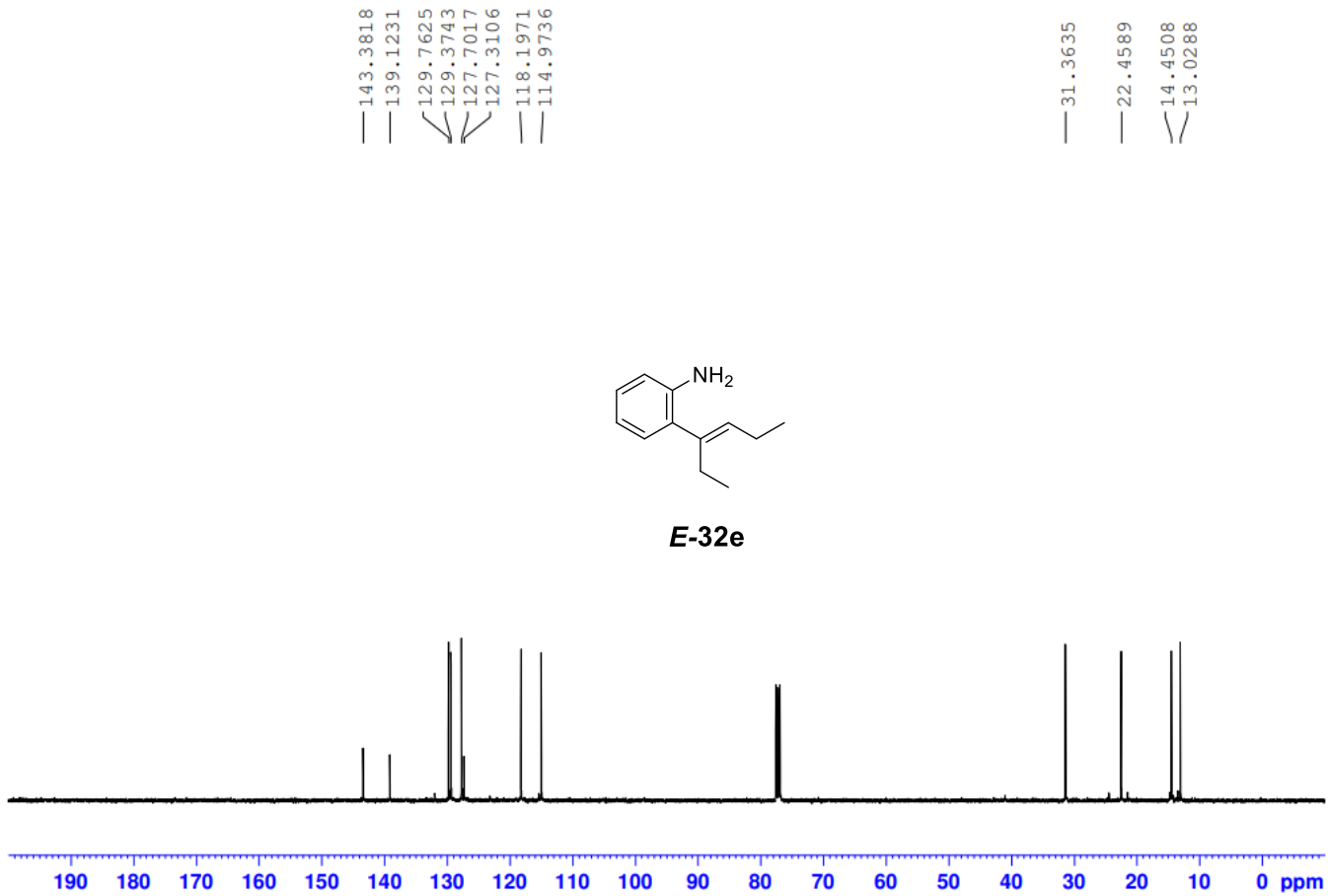
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32b**



100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32c**

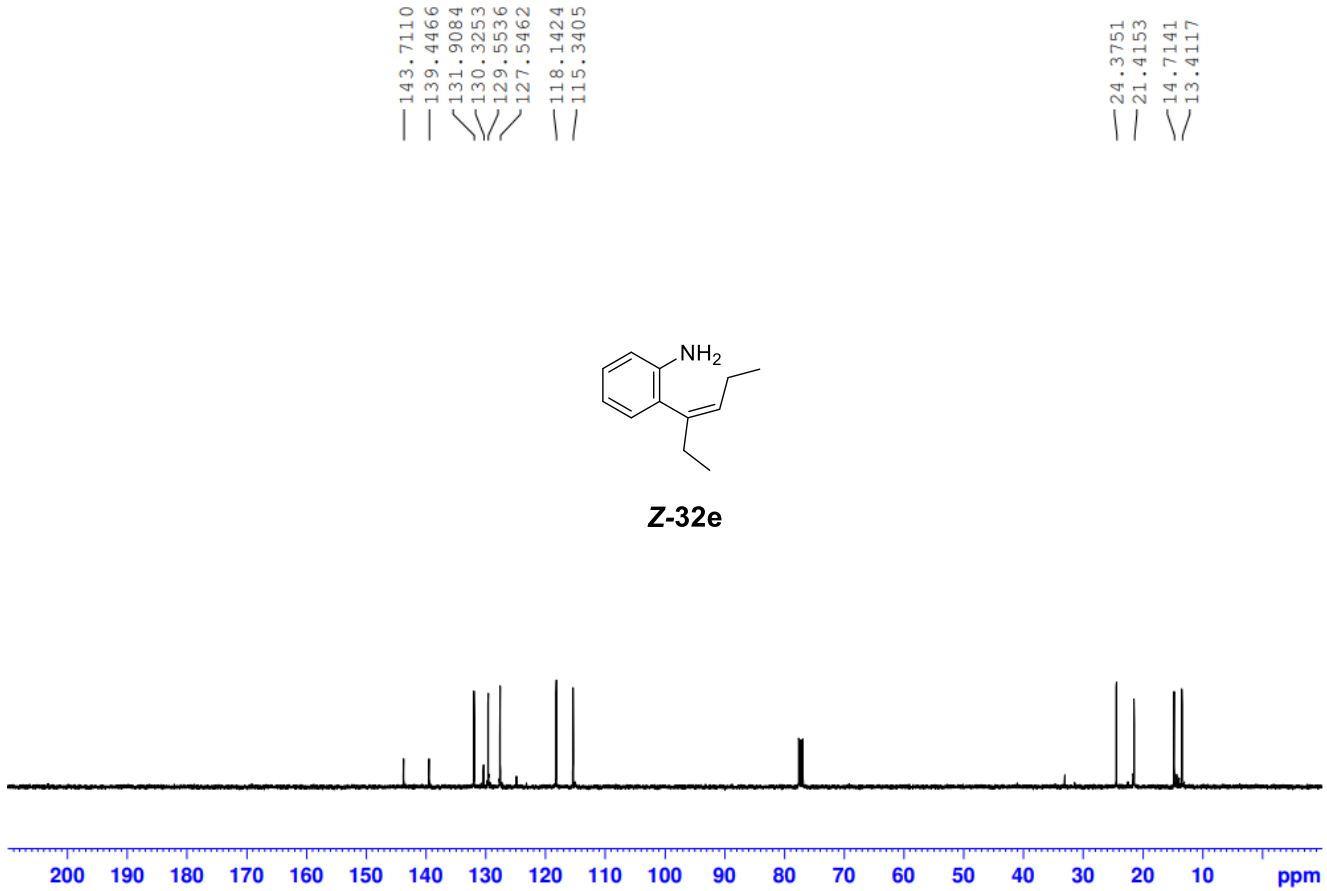


100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32d**



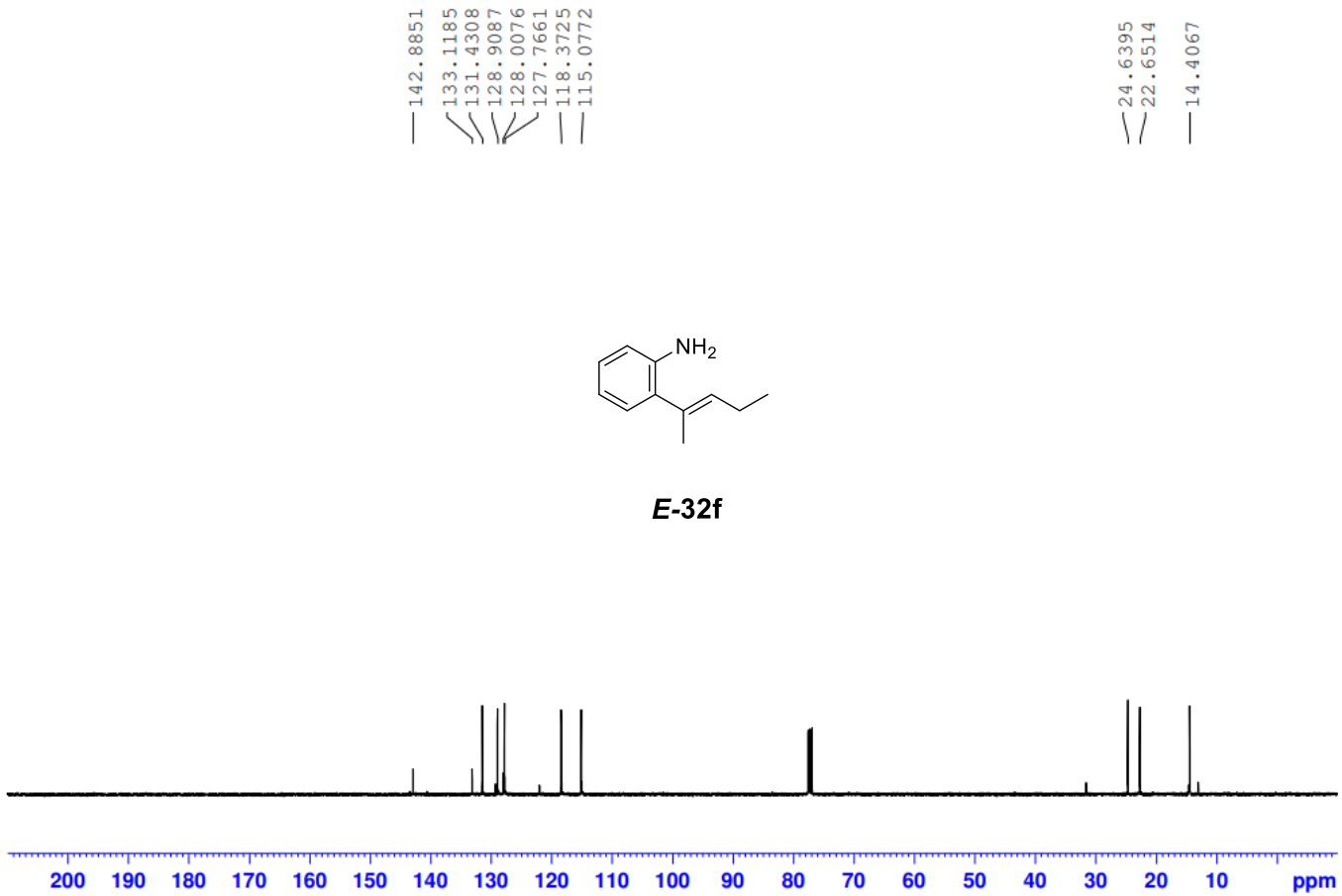
***E*-32e**

100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32e**



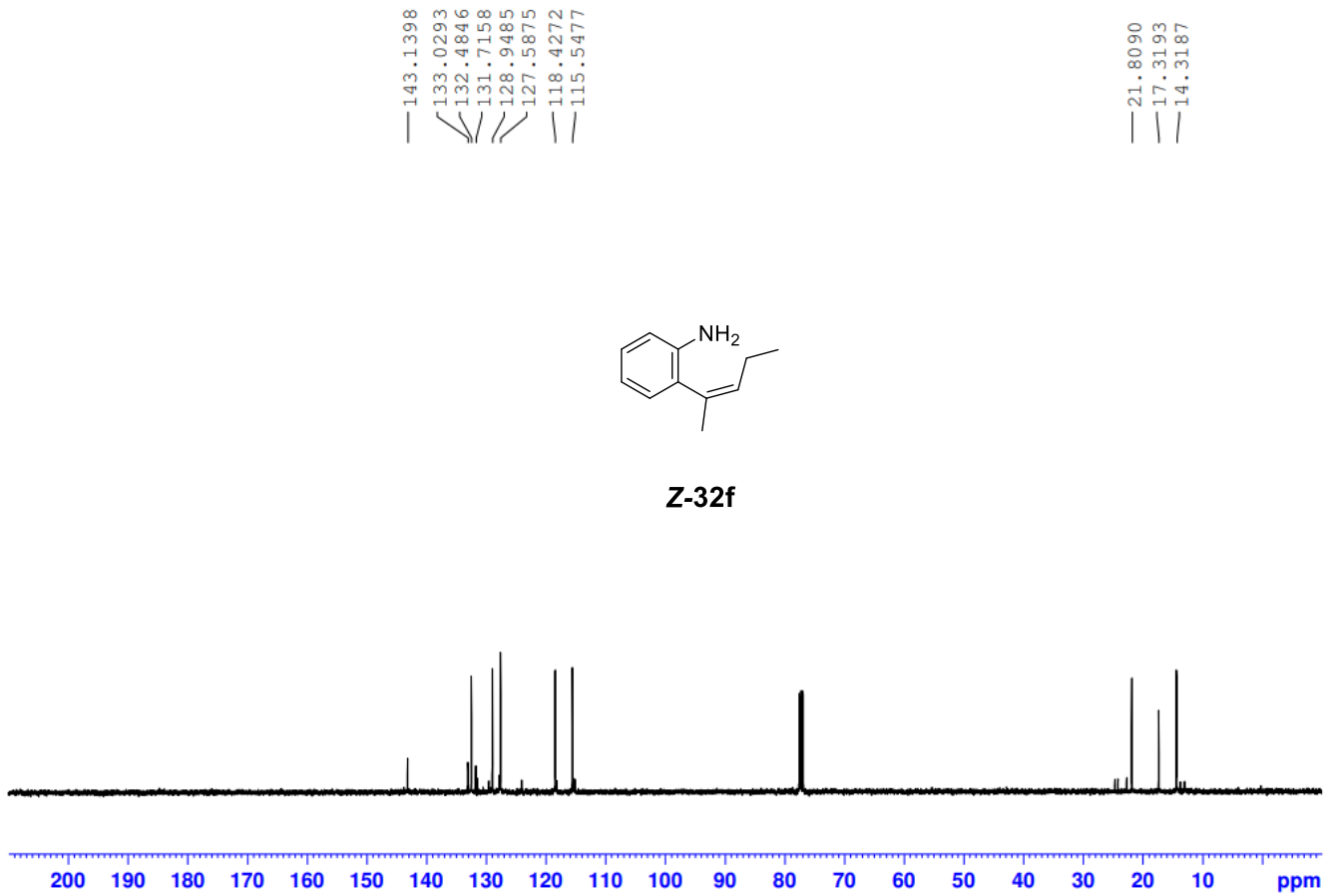
***Z*-32e**

100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***Z*-32e**



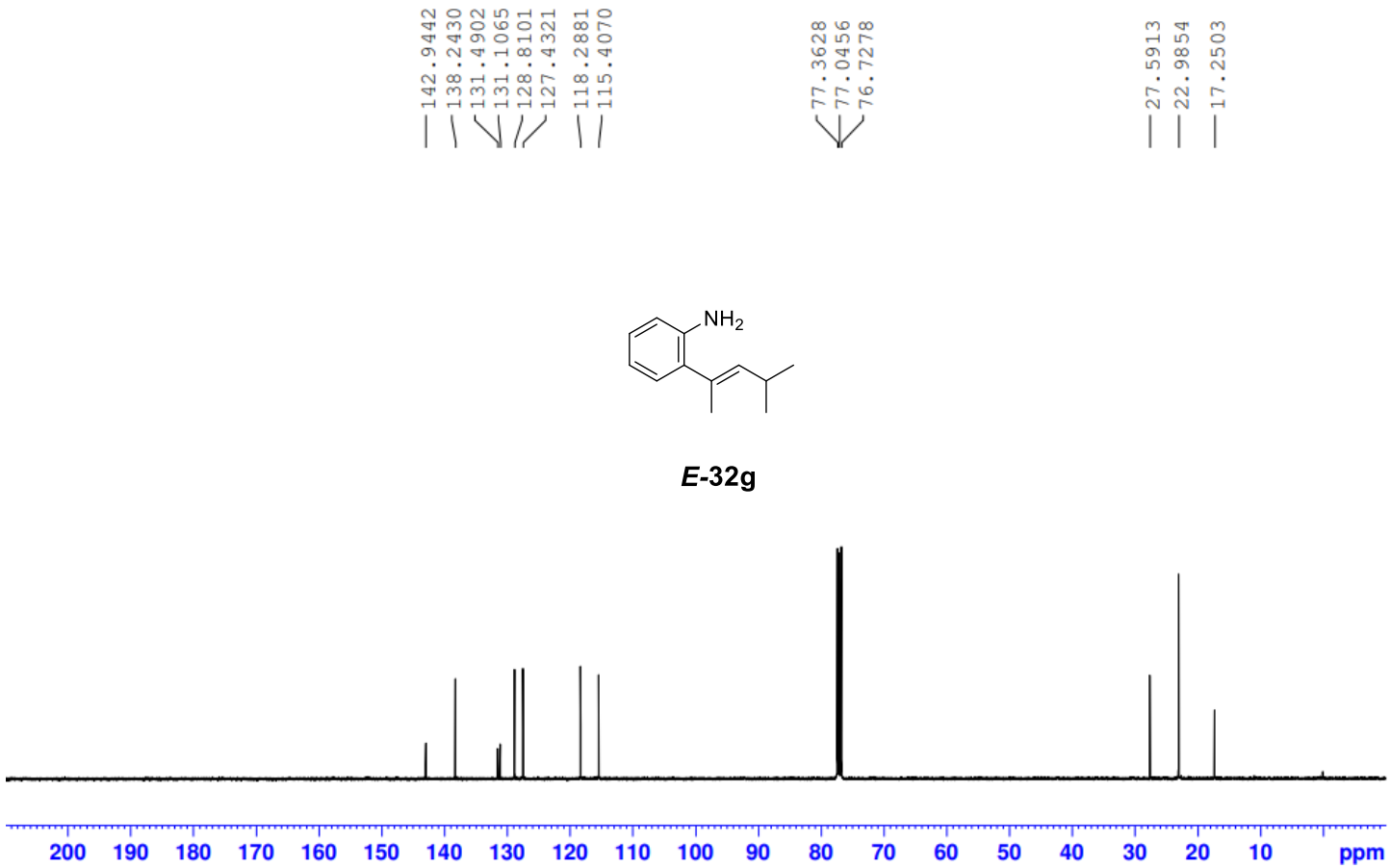
***E*-32f**

100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32f**

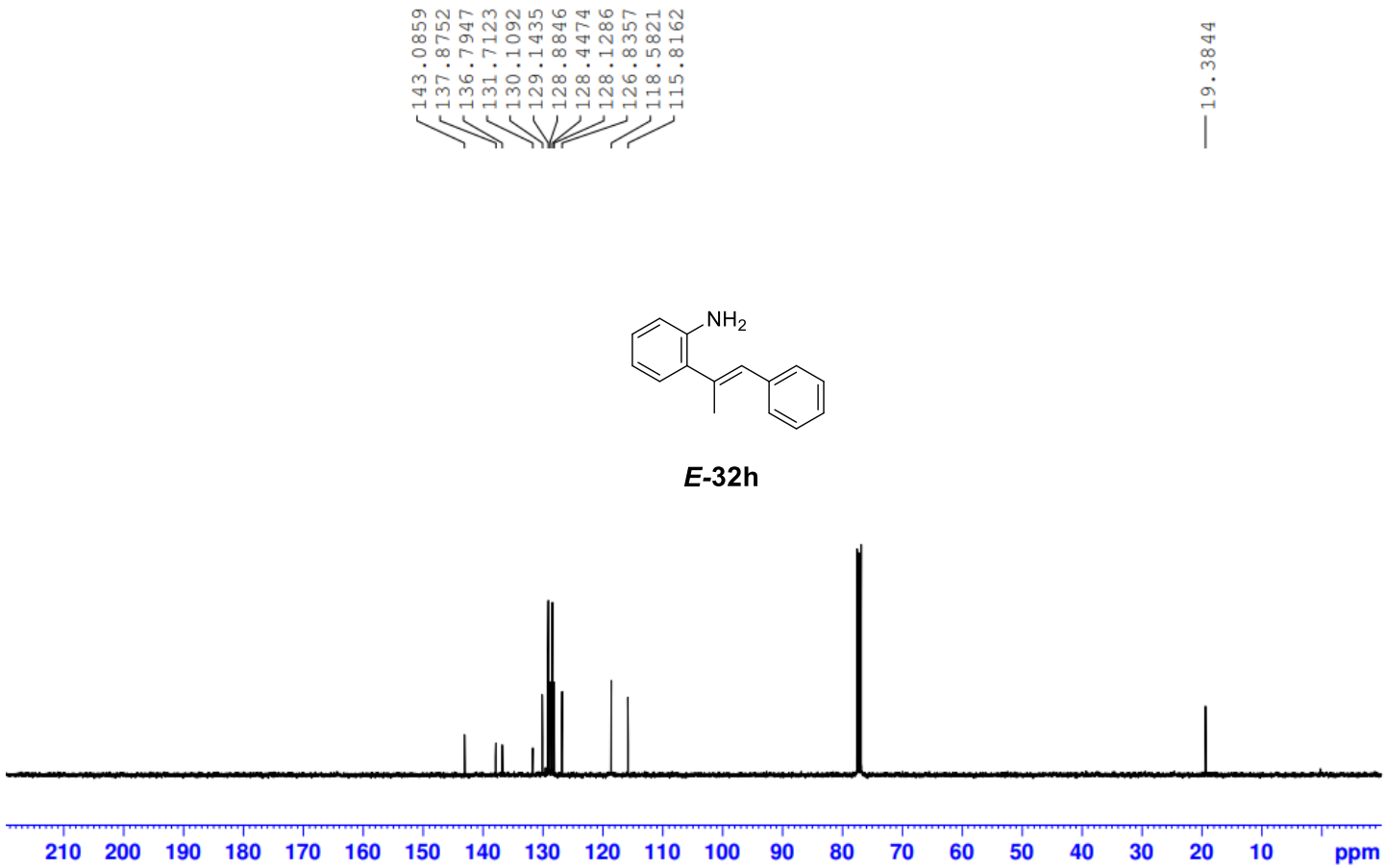


***Z*-32f**

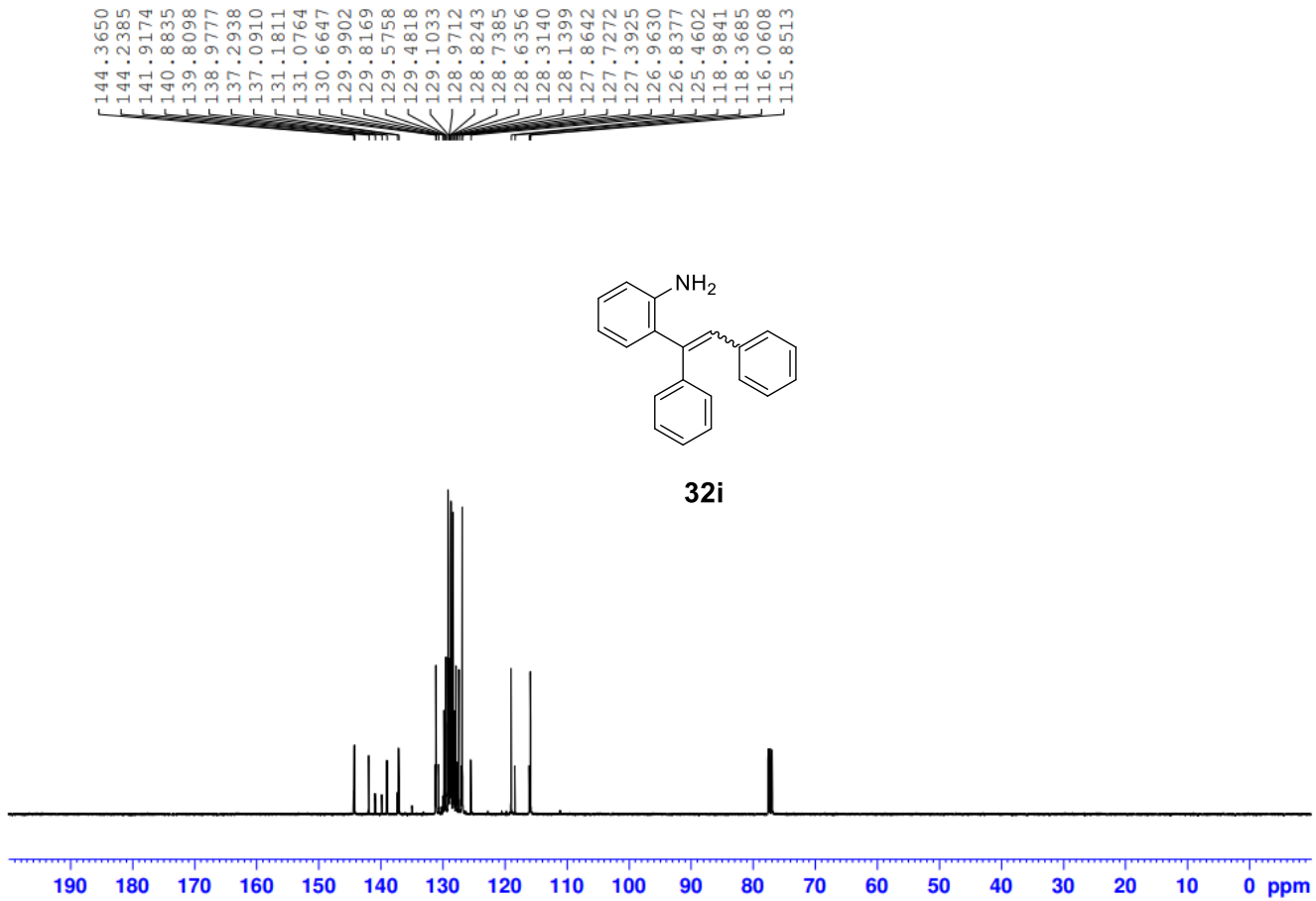
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***Z*-32f**



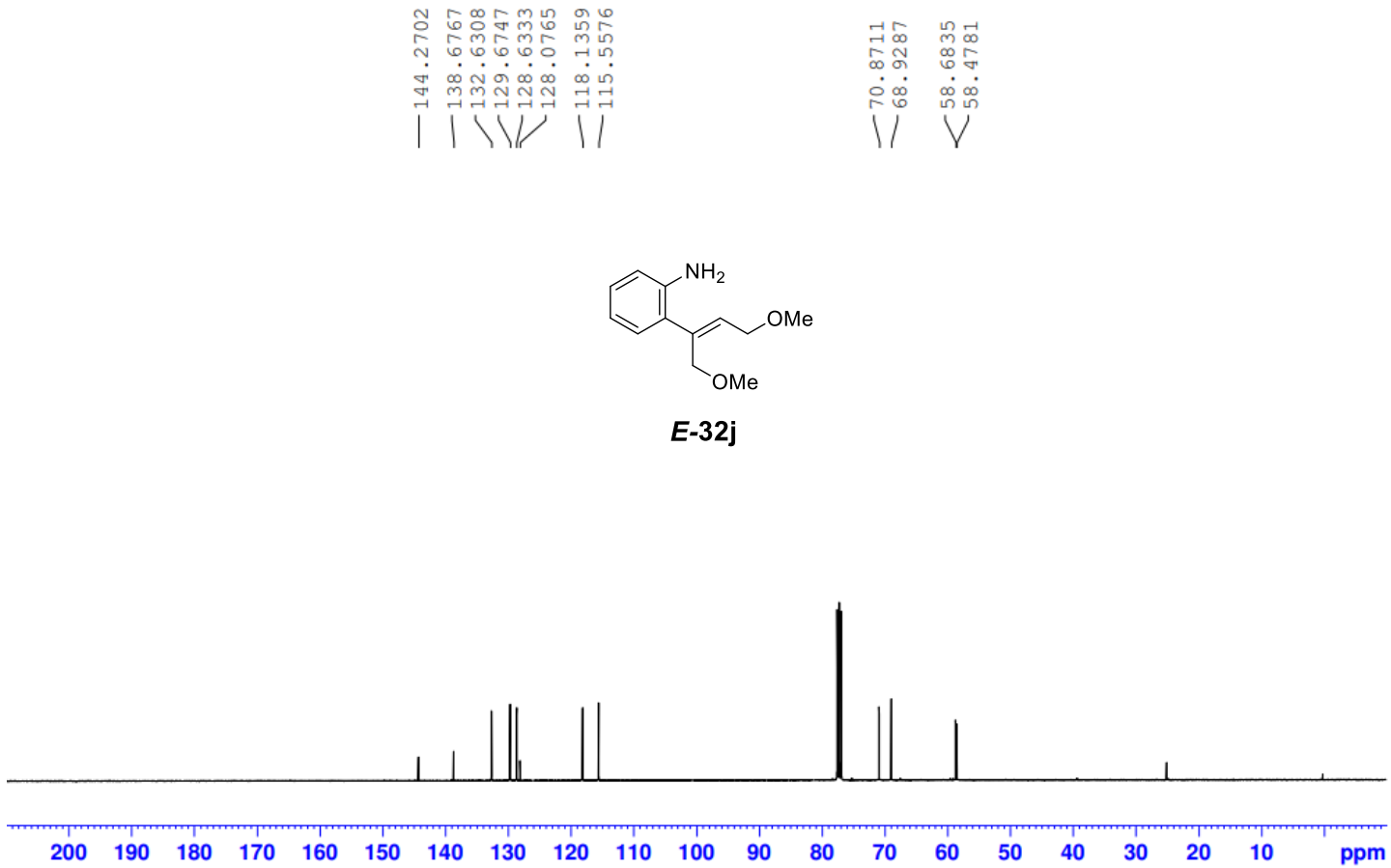
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32g**



100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32h**

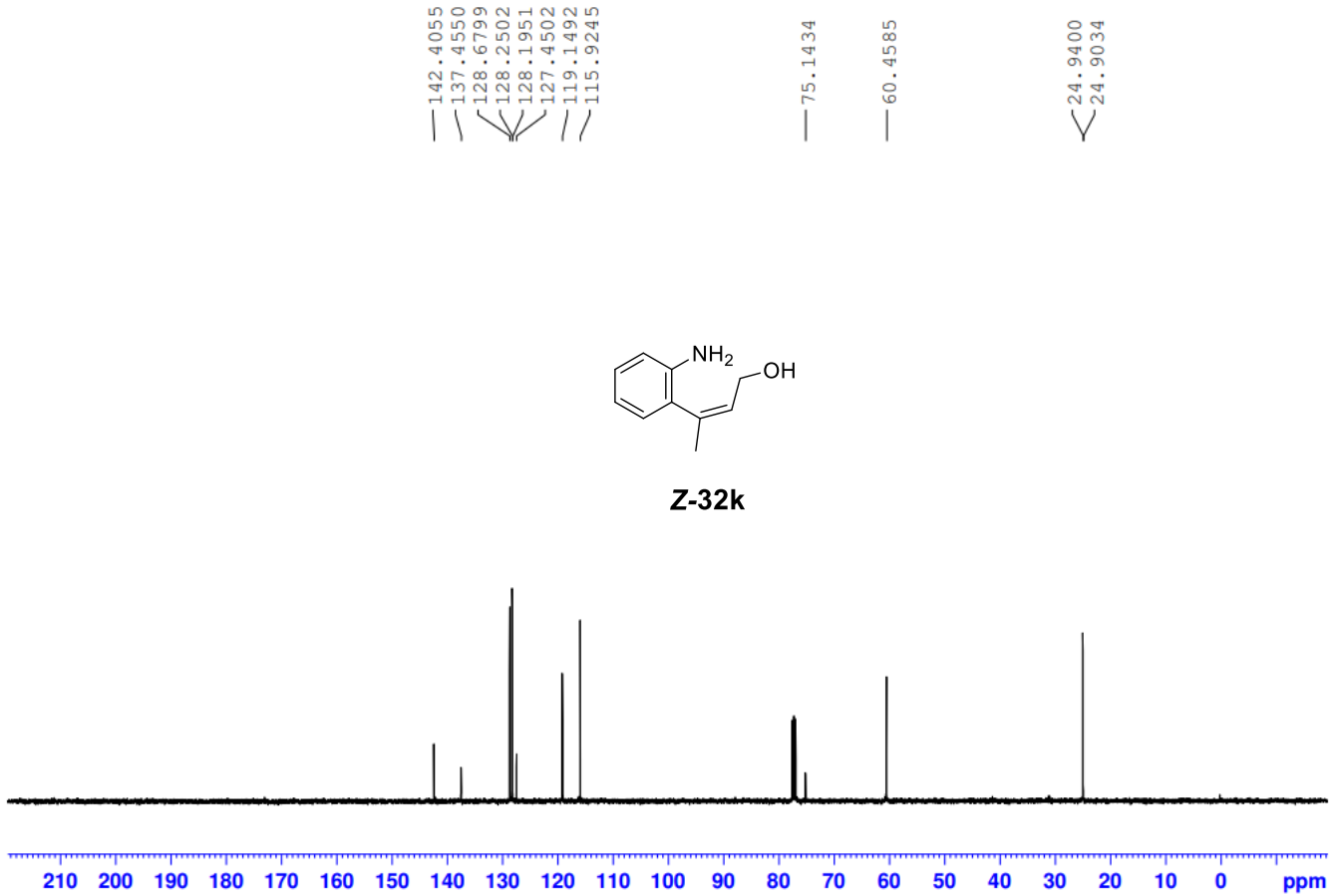


100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32i**

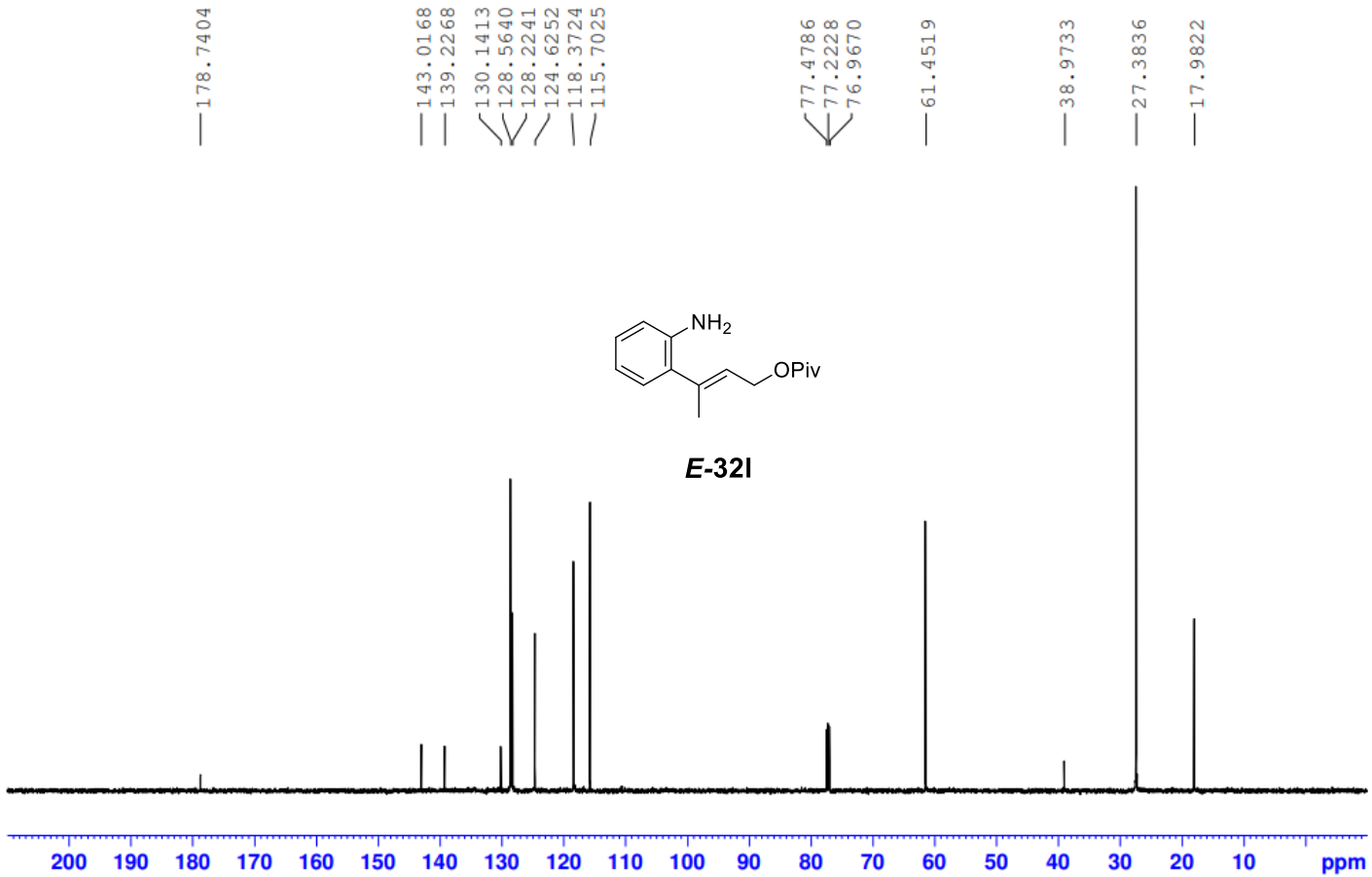


***E*-32j**

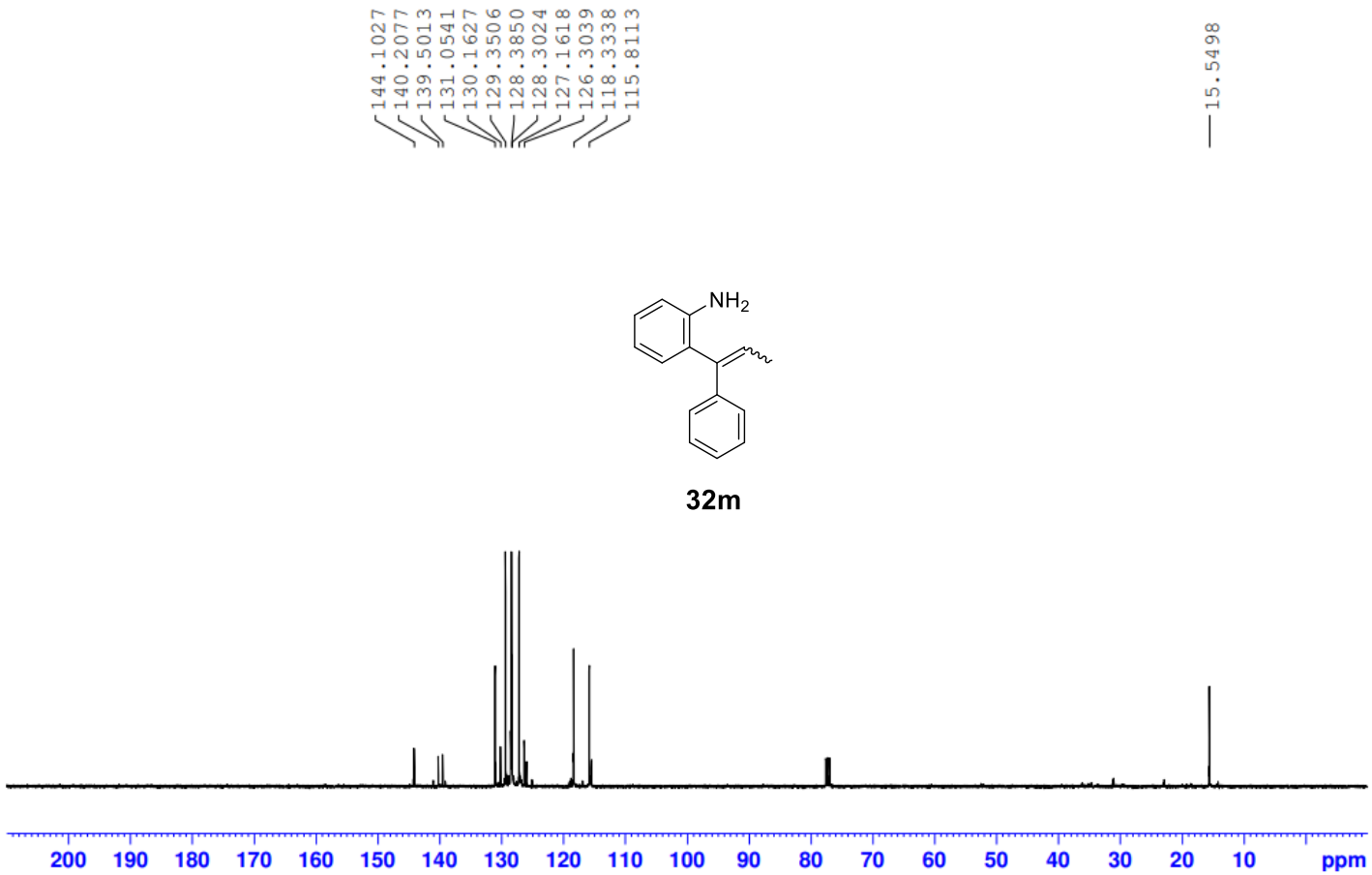
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32j**



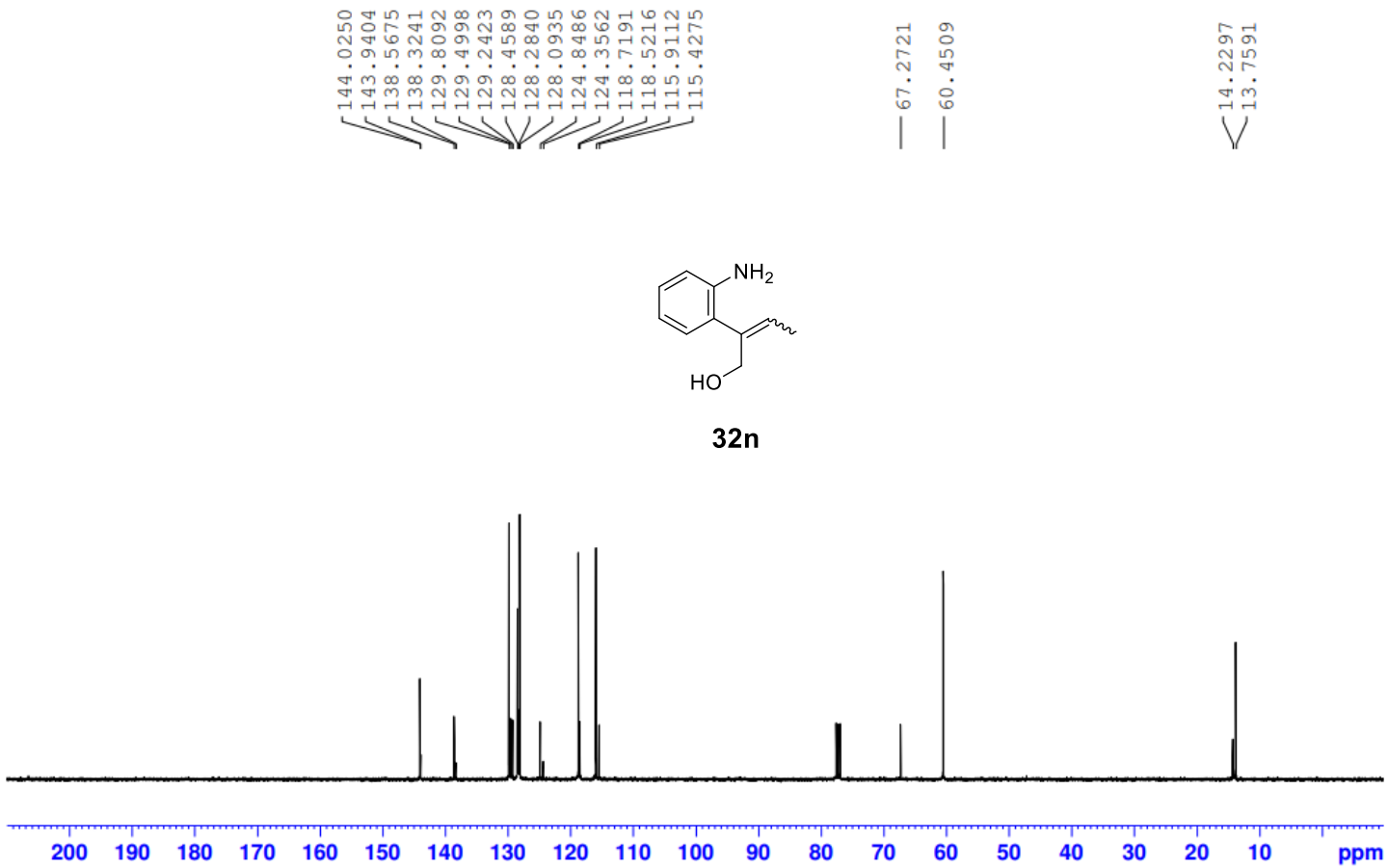
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***Z*-32k**



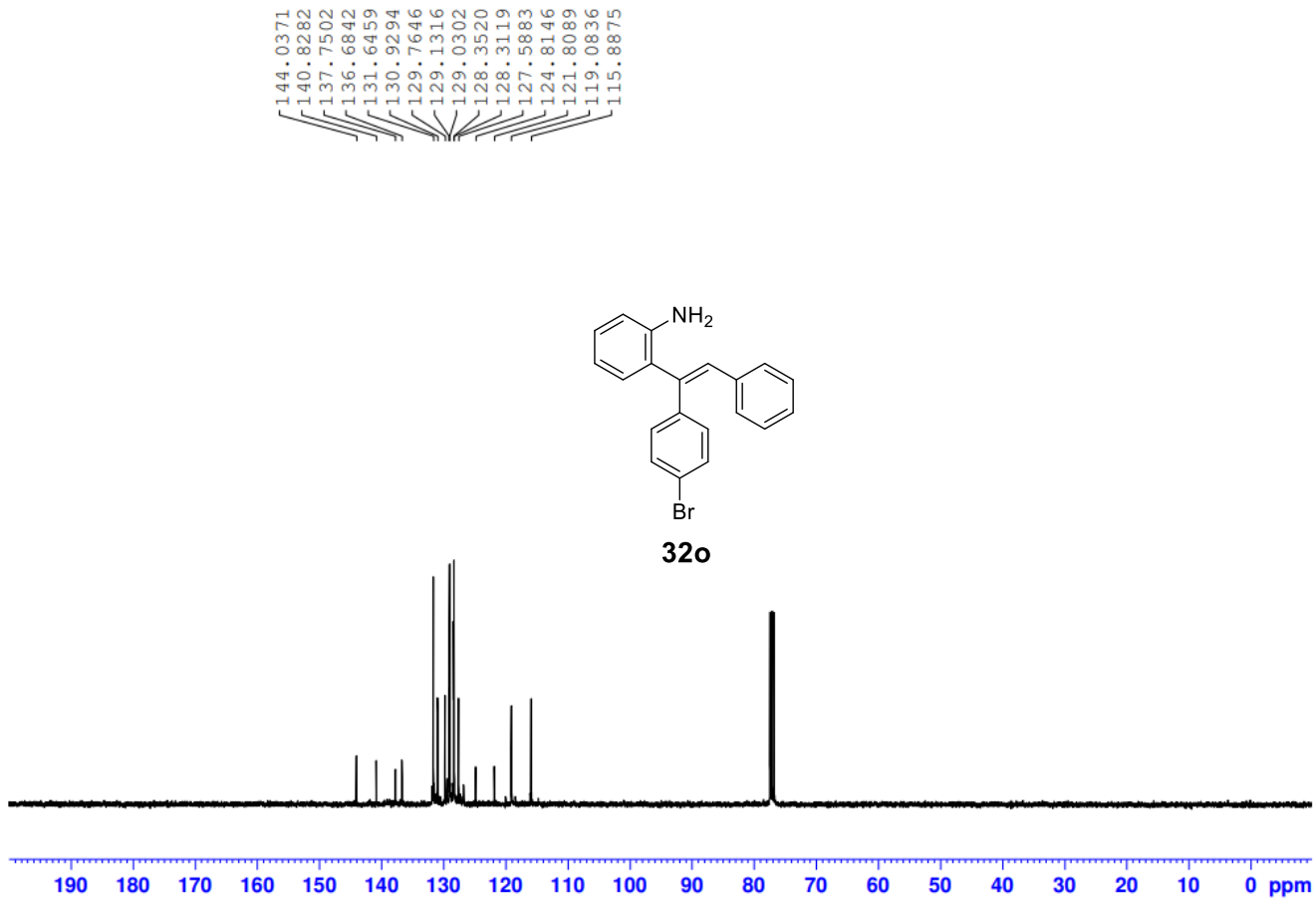
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound ***E*-32l**



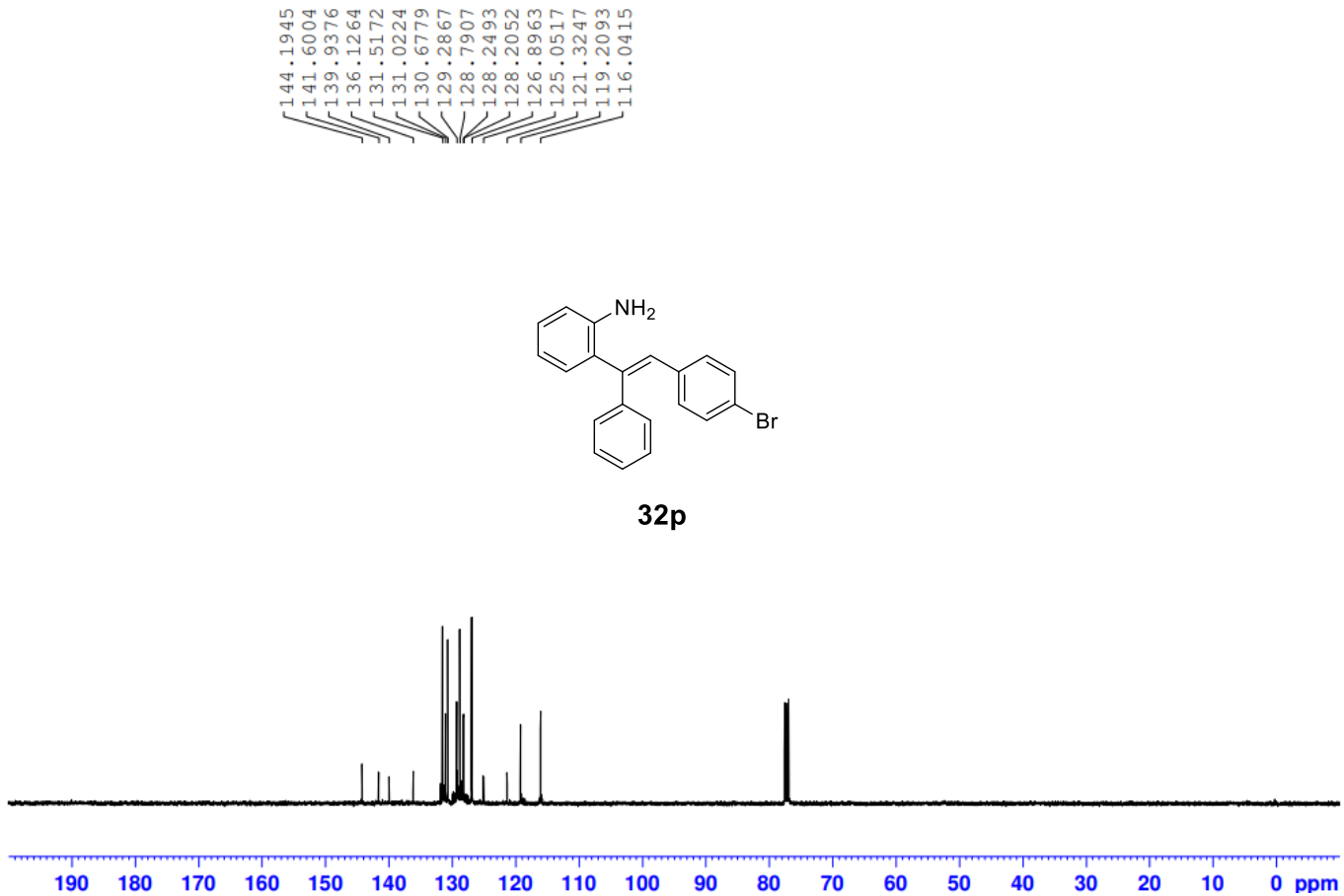
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32m**



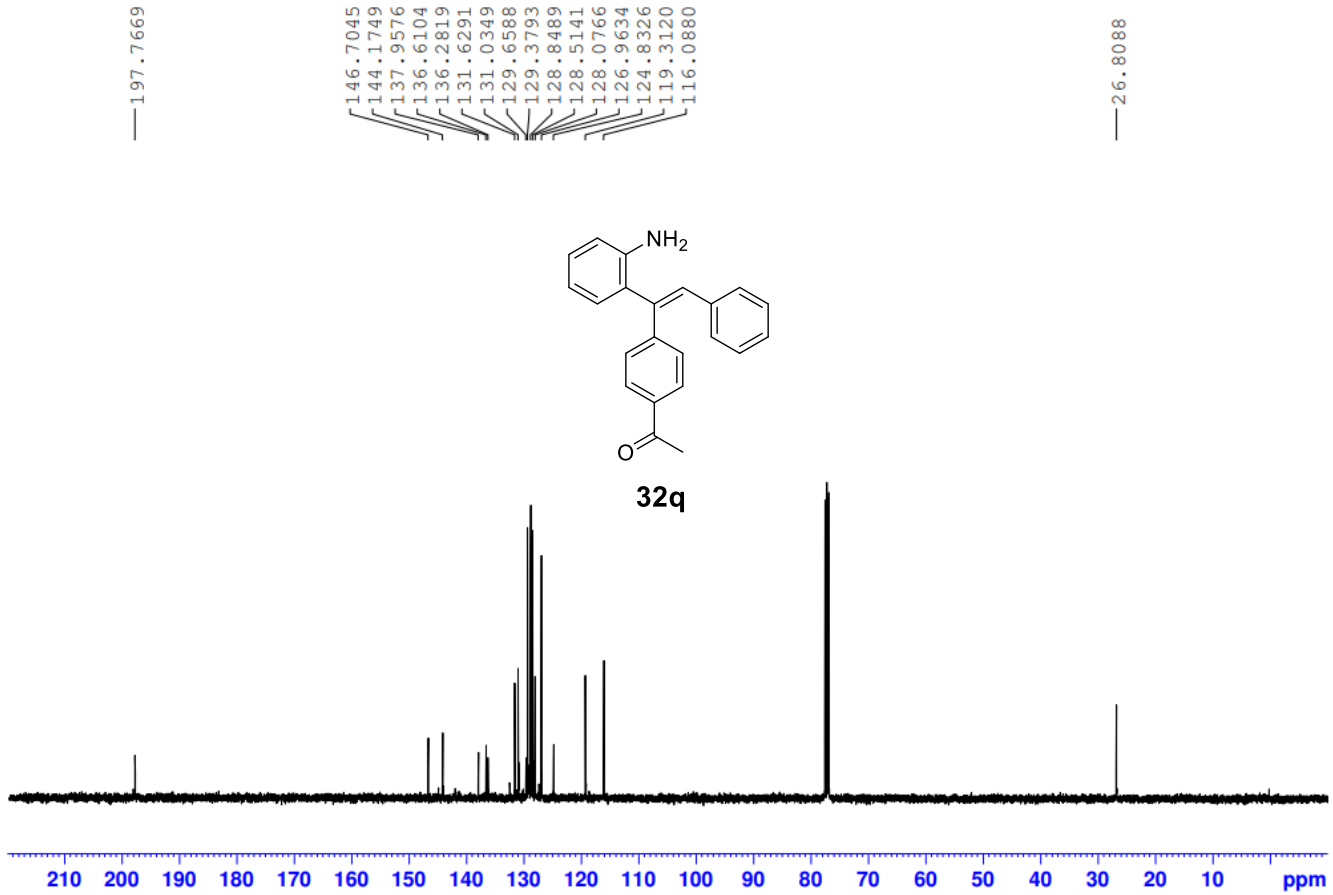
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32n**



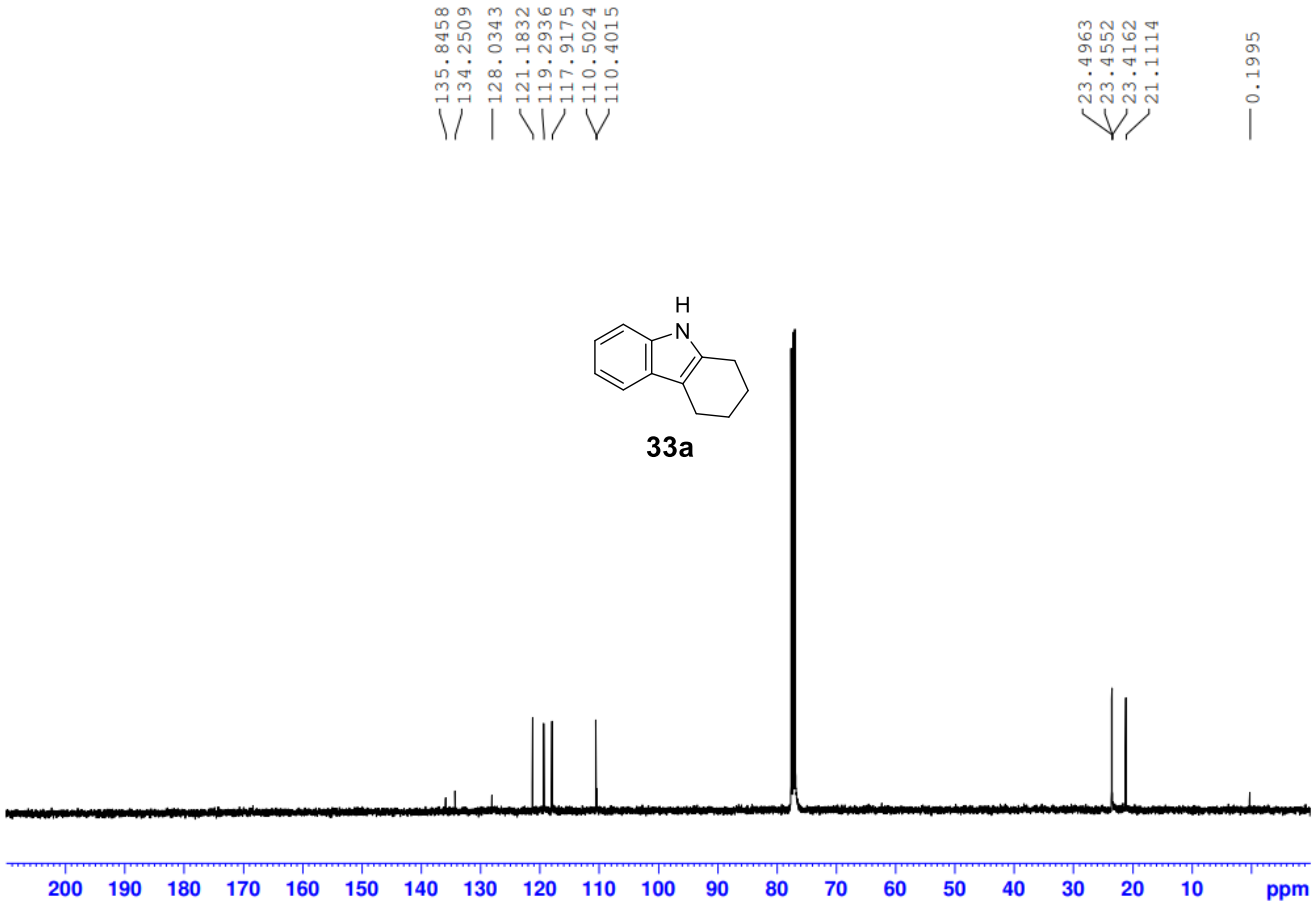
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32o**



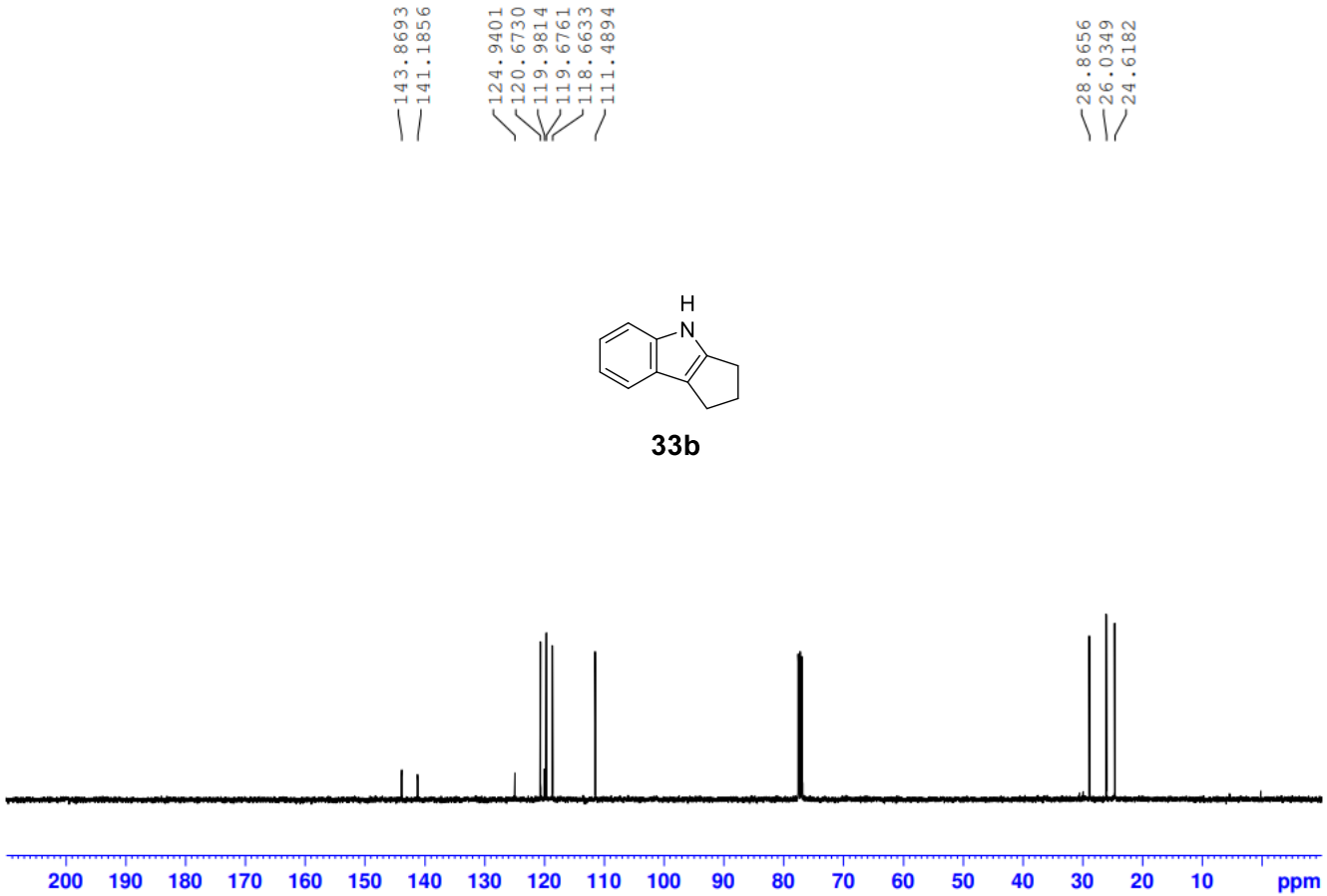
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32p**



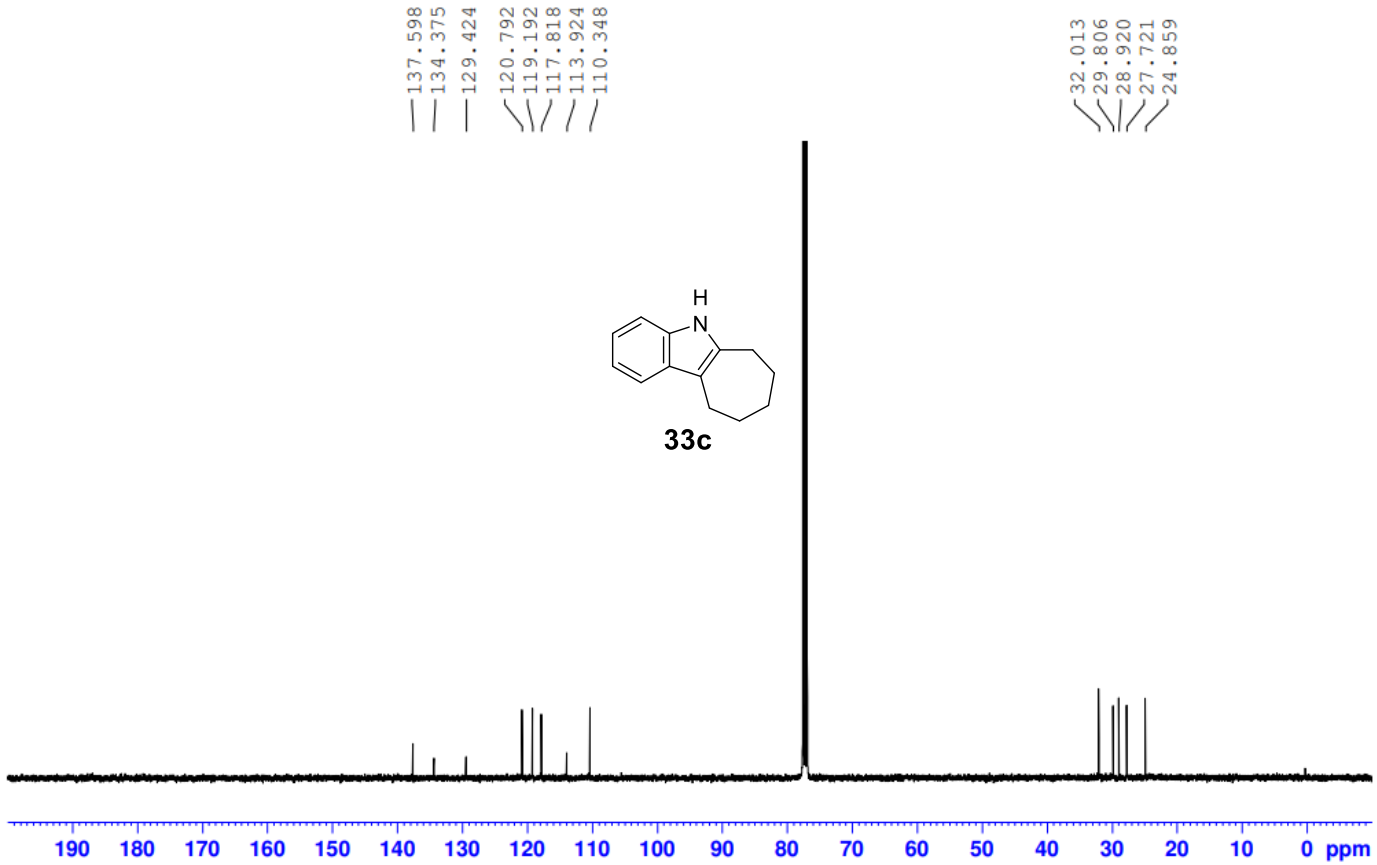
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **32q**



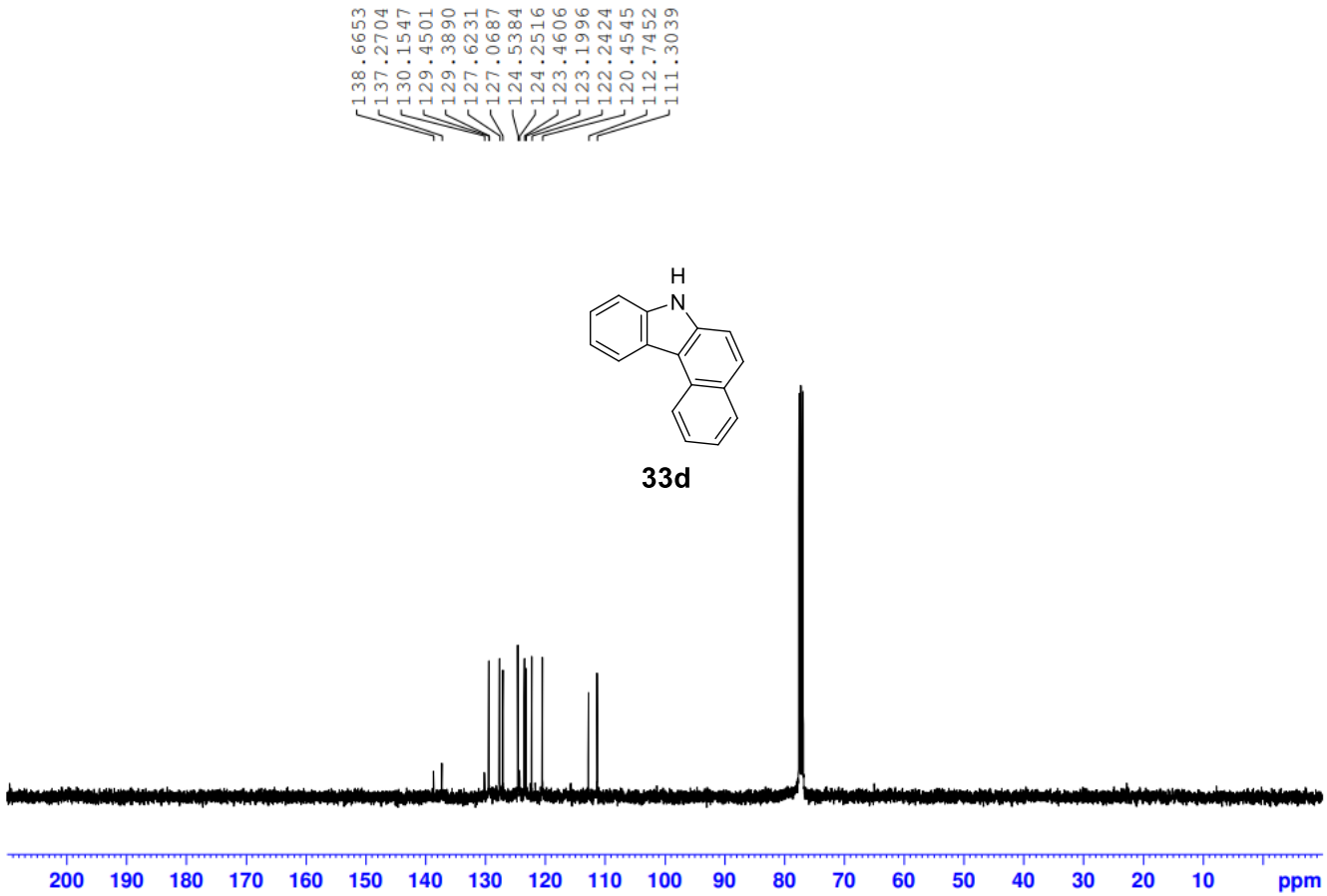
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33a**



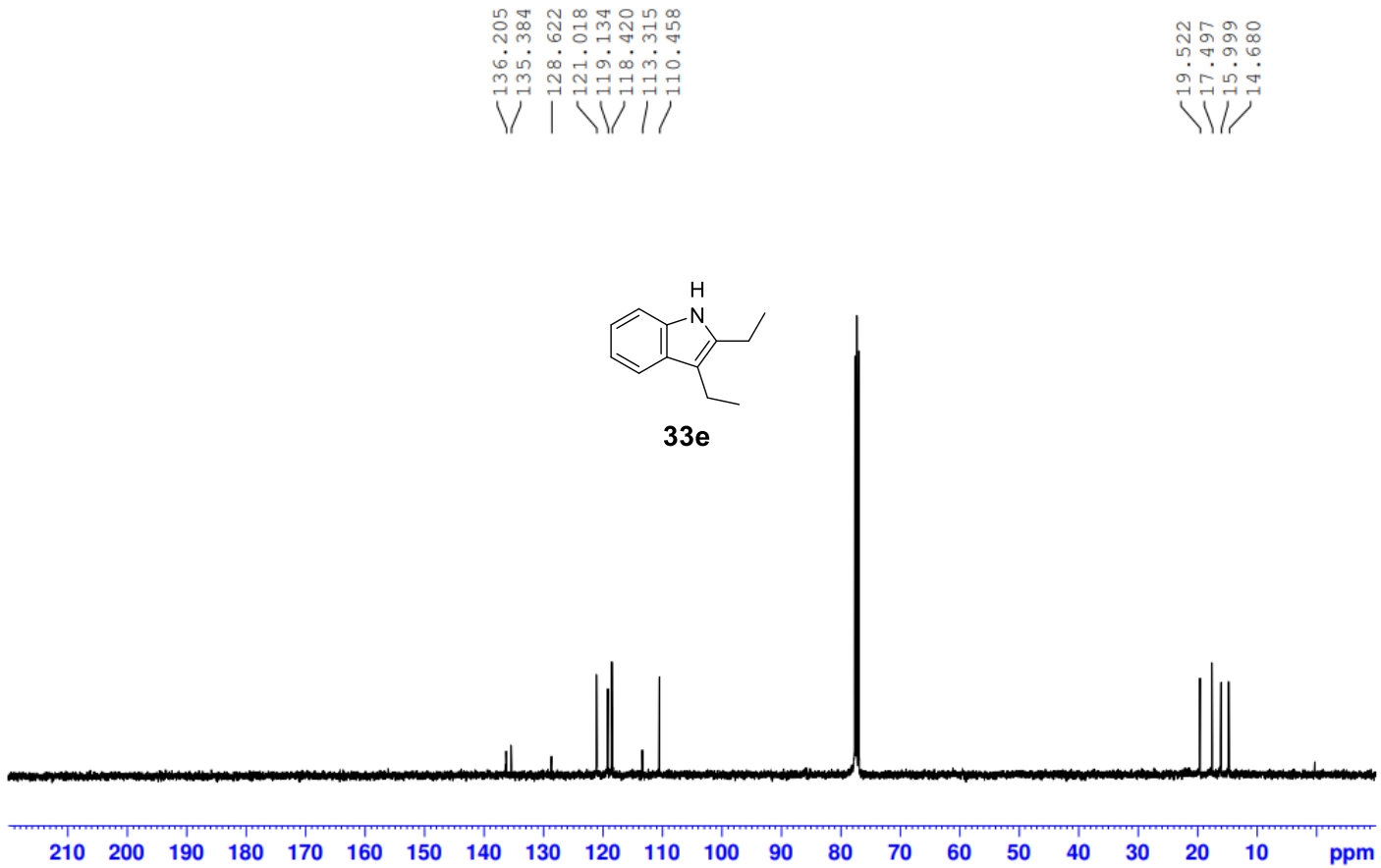
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33b**



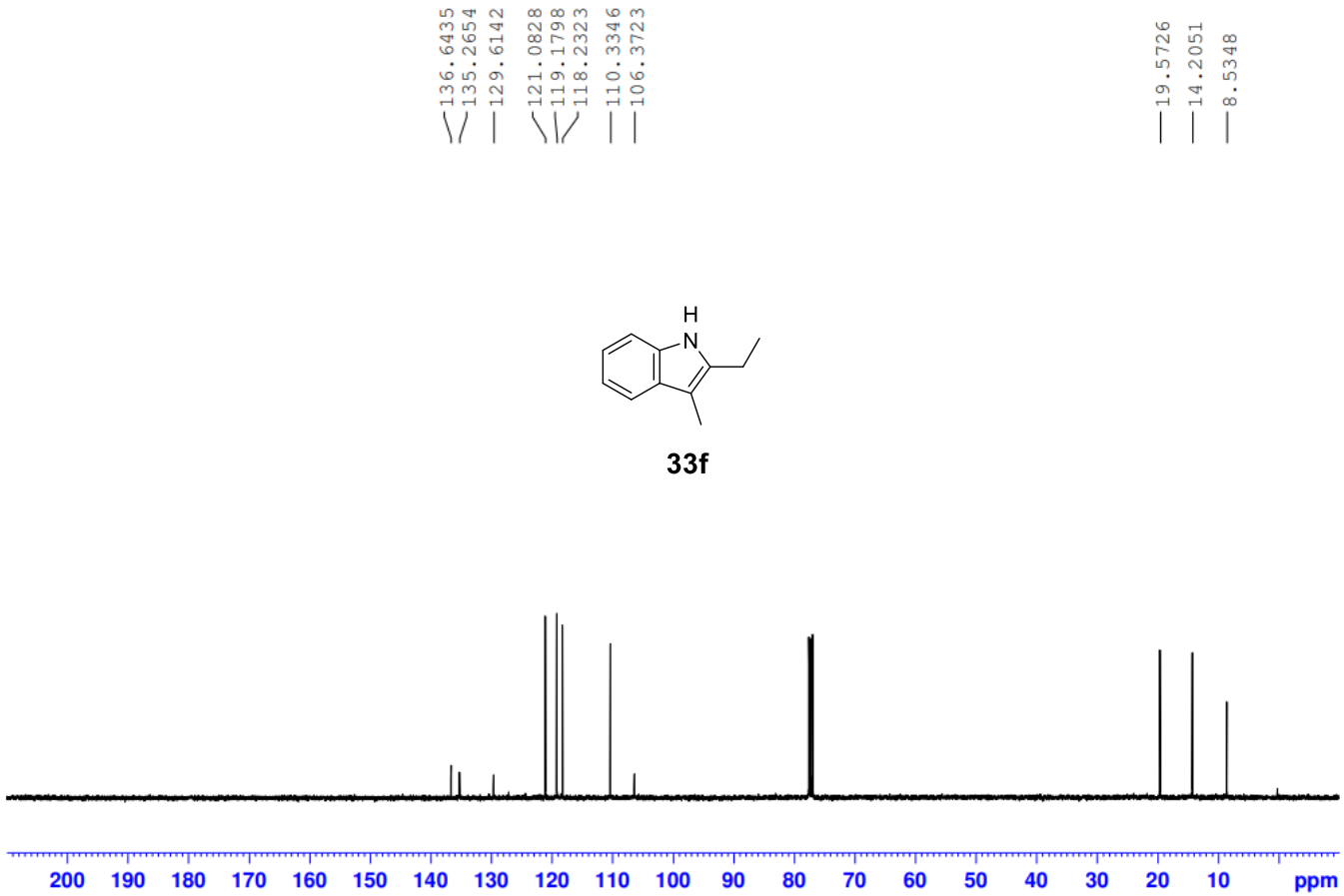
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33c**



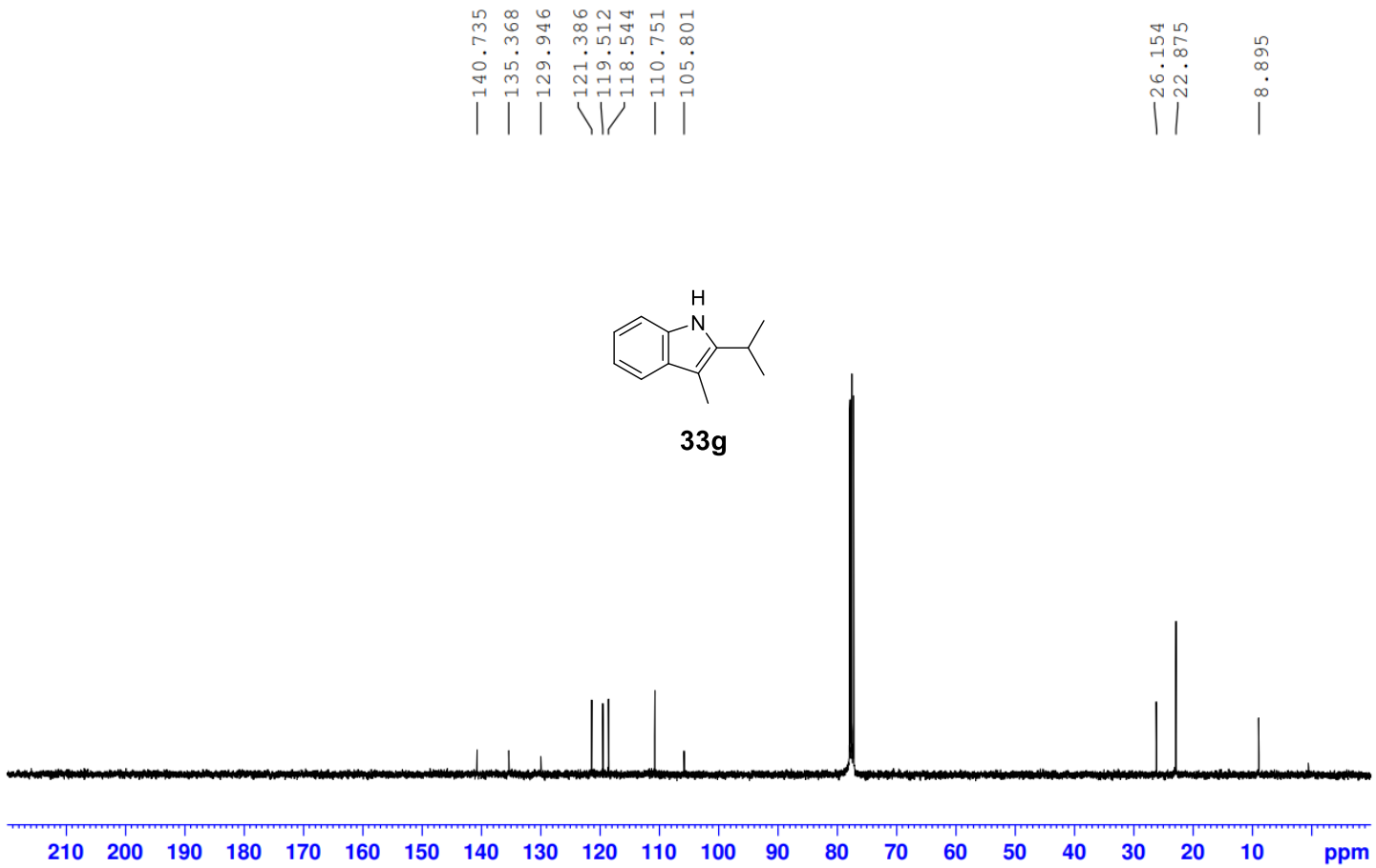
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33d**



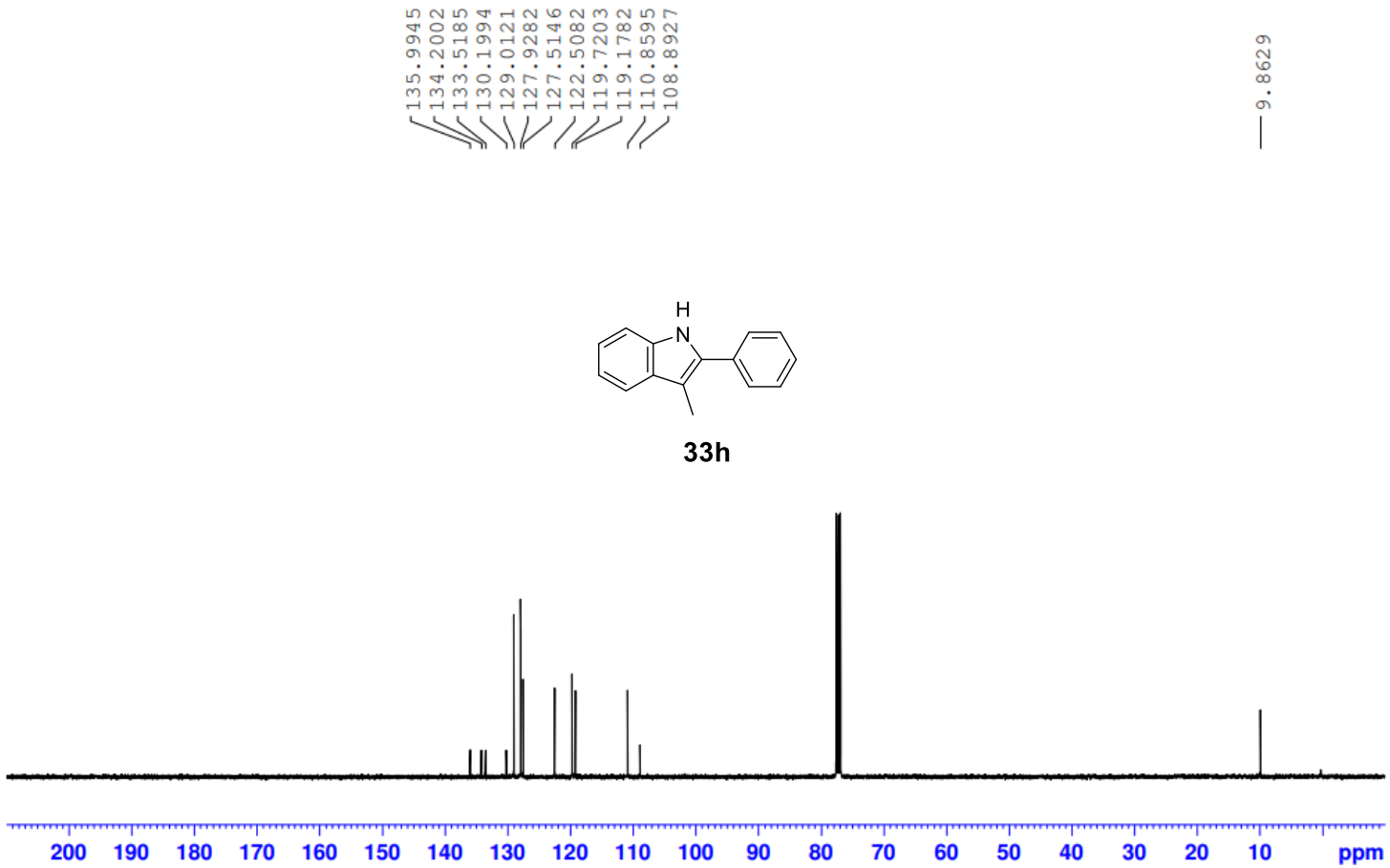
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33e**



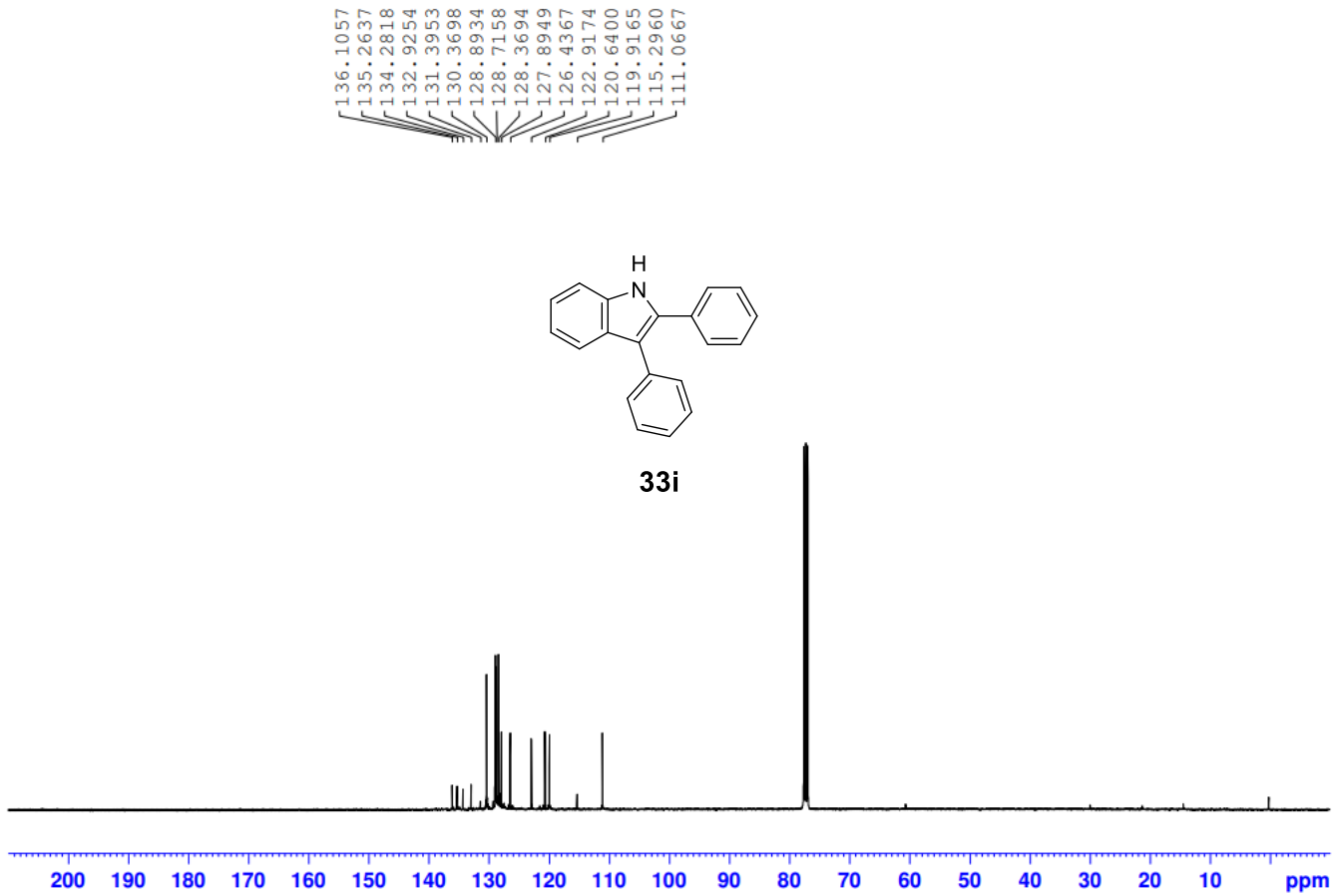
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33f**



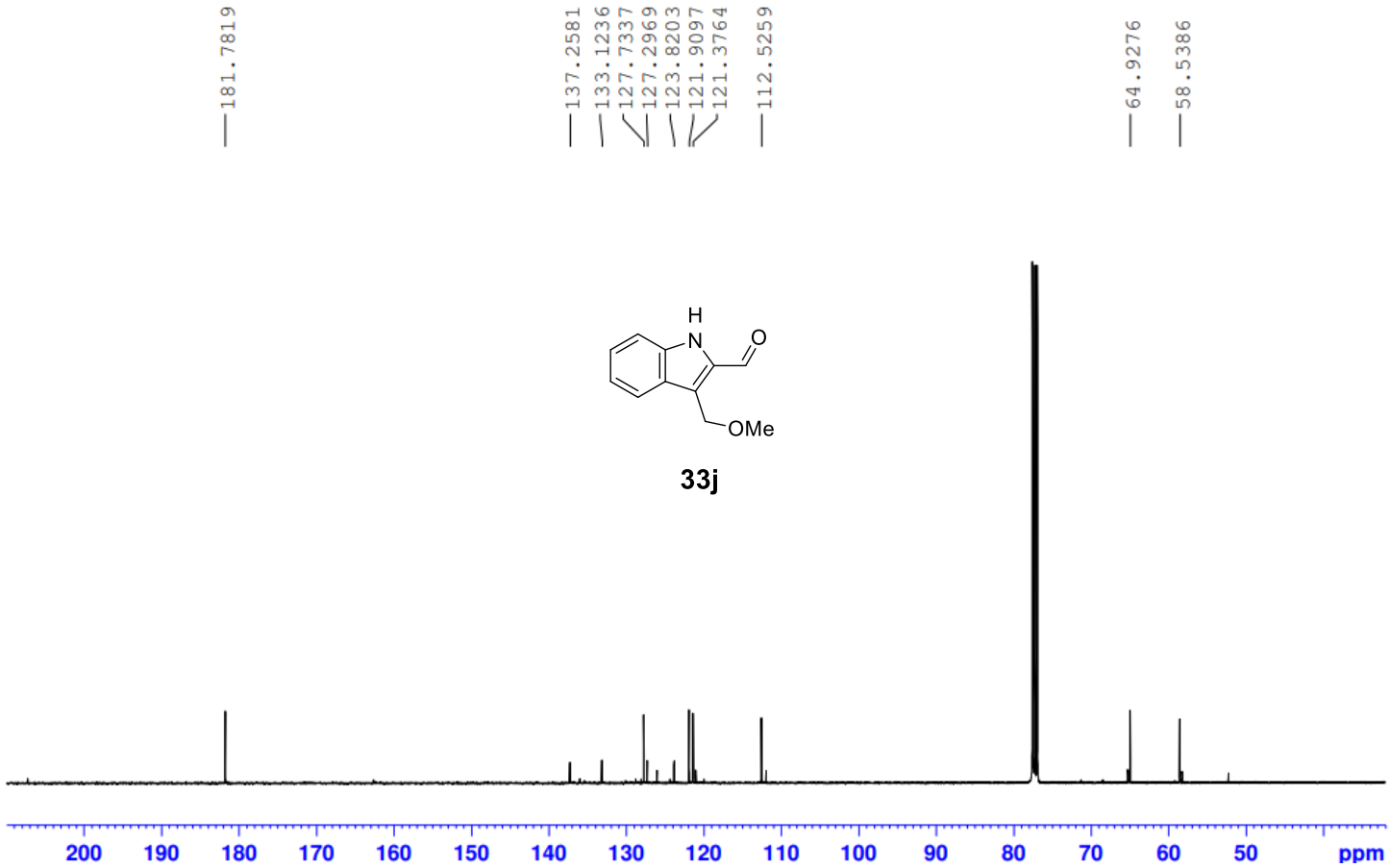
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33g**



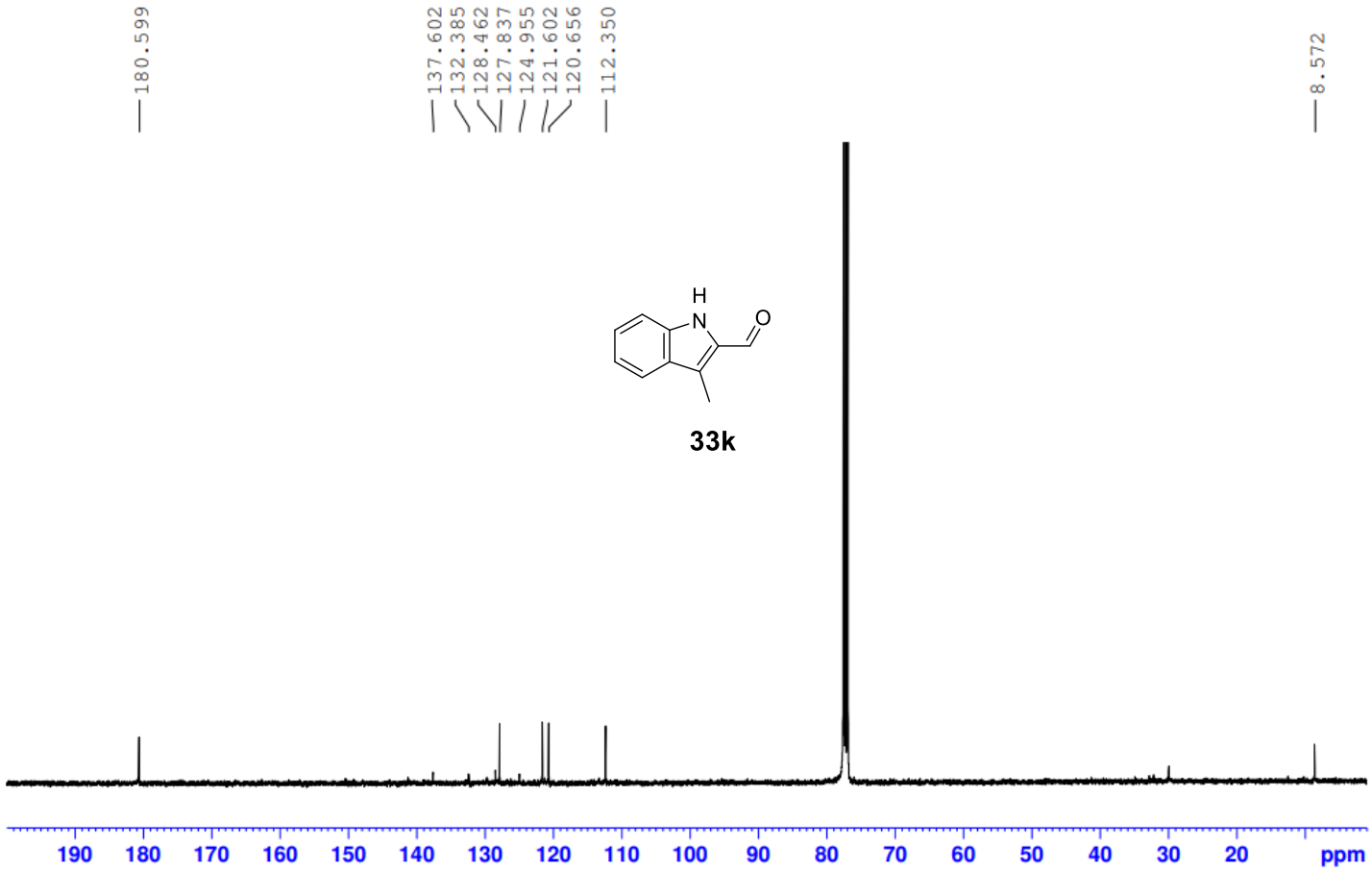
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33h**



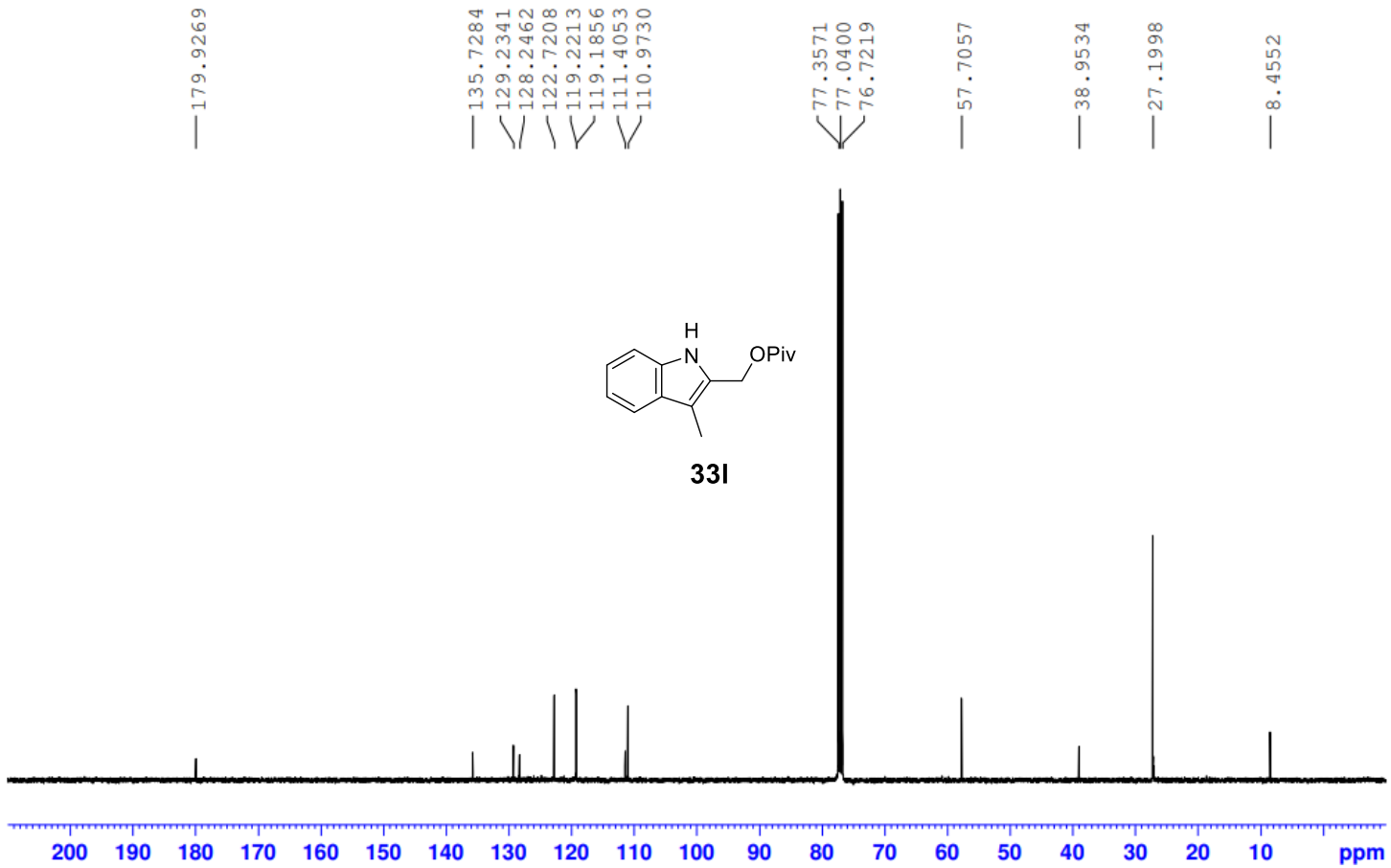
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33i**



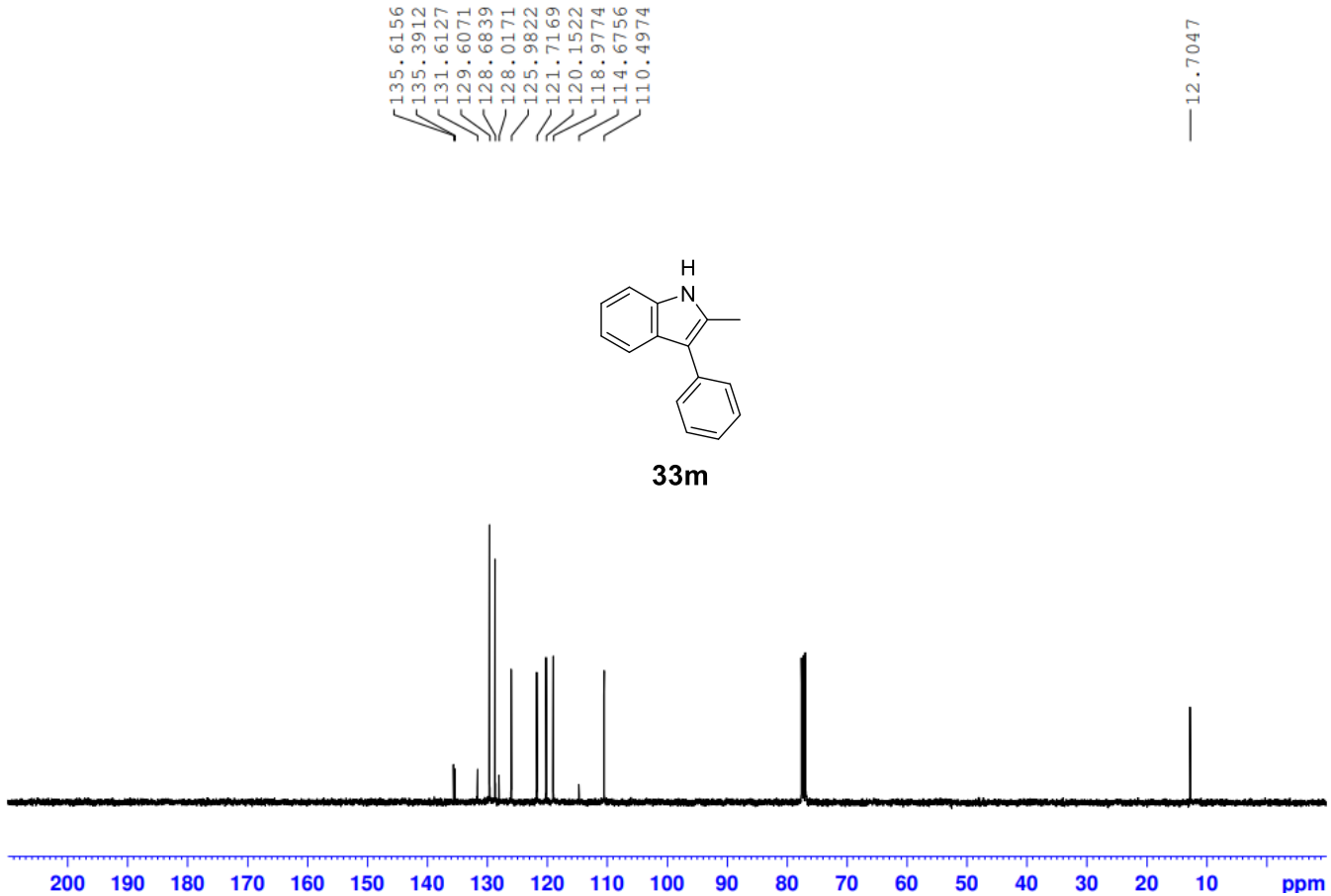
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33j**



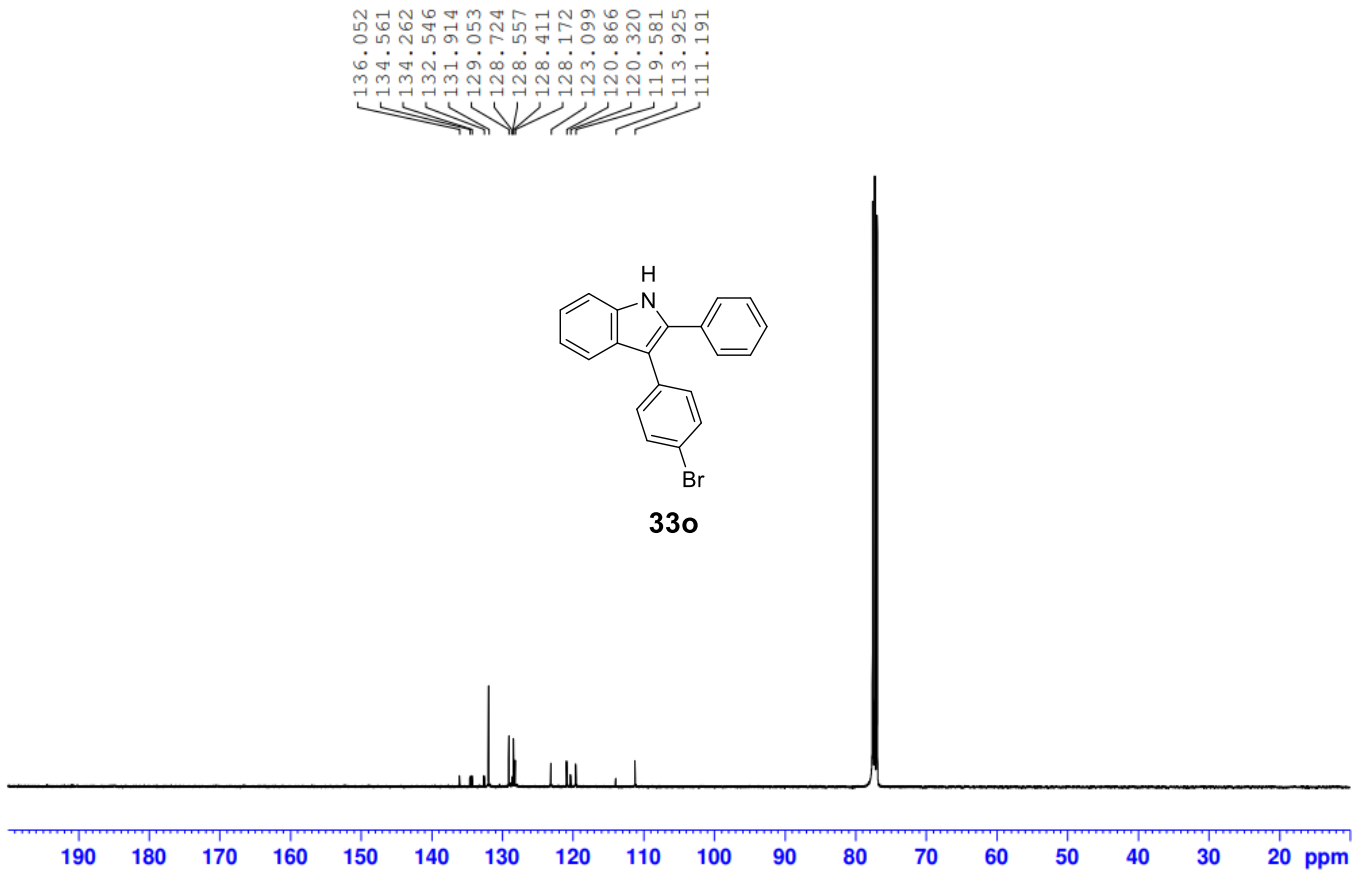
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33k**



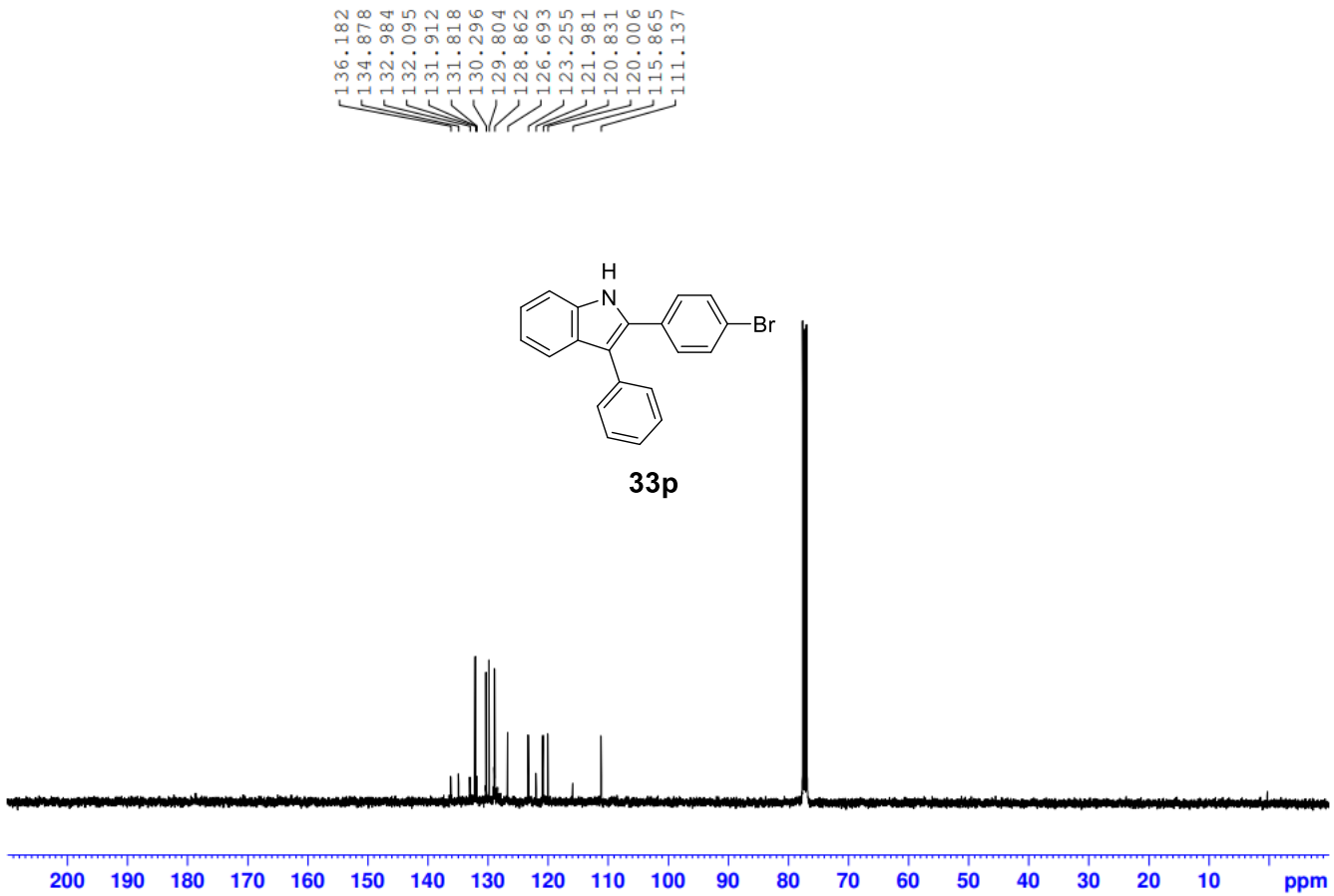
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33l**



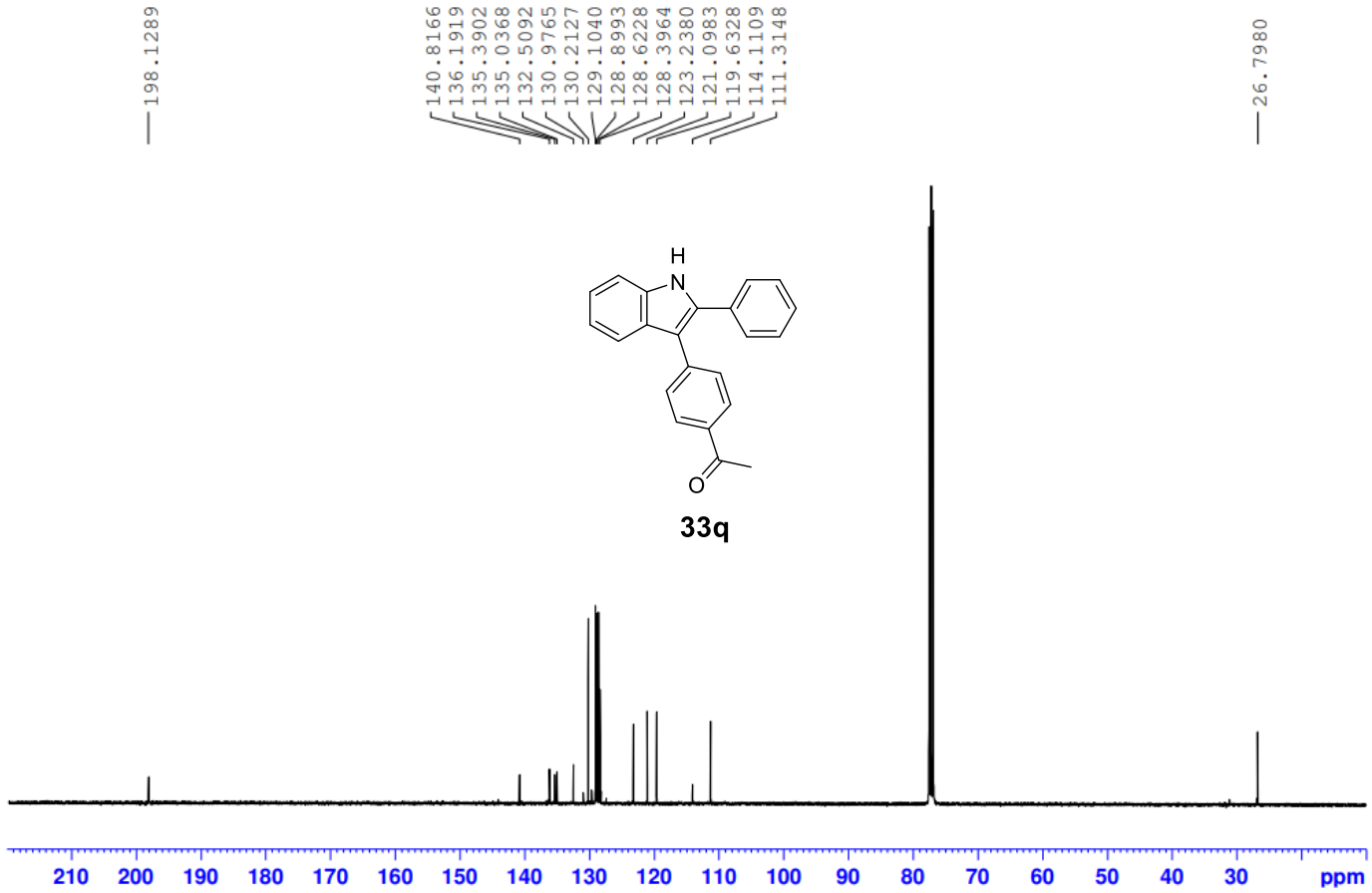
100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33m**



100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33o**



100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33p**



100 MHz ^{13}C-NMR spectrum ($CDCl_3$) of compound **33q**

국문초록

첫번째 연구는 식물 추출물의 의약학적 효능을 가진 천연물의 전합성에 관한 것이다. 본 연구에서는 5가지 종류의 세파로텍서스 트로포노이드 화합물을 제시하였으며, 그 중 항종양, 항바이러스의 활성을 보여주며, 더욱이 KB 종양세포에서도 강한 세포독성을 띄는 물질이라고 보고된 헤링토놀라이드 화합물의 합성에 초점을 맞추었다. 헤링토놀라이드에 존재하는 7각형, 5각형이 결합된 특이한 2중고리 구조를 포함하는 4중고리 골격구조를 라디칼 음이온 중합반응을 이용해서 기존보다 효율적으로 합성하고자 하였다. 먼저 상업적으로 쉽게 구매 가능한 6-하이드록시테트라론을 출발 물질로 하여 로빈슨 고리화를 포함한 4단계 반응을 통해 헤링토놀라이드 분자골격인 A, B, C, D 고리에서 A, B, D고리로 이루어진 3중고리 화합물을 얻었다. 다음은 브로민 도입, 스틸레 커플링, 나이트로화 반응을 거쳐 페놀릭 니트로네이트의 합성을 완료하였다. 이 화합물로 라디칼 음이온 중합반응을 시도하였으나, 기대하였던 7각형, 5각형이 결합된 트로포노이드 화합물이 아닌 6각형, 6각형이 결합된 파이렌계의 4중고리를 갖는 벤제노이드가 합성되었다. 생성된 벤제노이드계 화합물들은 세파로텍서스 트로포노이드 화합물과 유사한 생리활성을 보이는 것으로 알려져 있어, 본 연구에서 얻어진 결과를 이용하면 생리활성을 갖는 새로운 벤제노이드 유도체를 합성하는데 중요한 플렛폼이 될 것으로 예상한다. 벤제노이드 화합물의 생성은 전구체에 존재하는 이중고리의 경직성에서 기인한 것으로 추정되며, 단단한 이중구조를 포화시키면, 라디칼 음이온 중합반응을 통해 7각형, 5각형이 결합된 2중고리 구조를 형성할 수 있을 것이라고 기대하였다. 포화된 페놀릭 니트로네이트를 합성하기 위해 루체 환원, 크랩트리 수소화, 선택적인 인올실란화, 알돌 축합 및 제거 반응을 추가로 완료하였으며, 현재는 마지막 니이트로화 반응을 진행 중이다. 현재까지 진행된 반응에 본 연구에서는 제안하는 새로운 7단계의 반응을 진행하면 헤링토놀라이드 화합물의 합성을

완료할 수 있을 것으로 예상되며, 이는 기존에 보고된 합성법 보다도 훨씬 효율적으로 입체선택성을 가진 헤링토놀라이드의 합성을 가능하게 할 것이다.

두번째 연구에서는 다양한 생리활성을 가진 2,3-이치환된 인돌의 효율적인 합성방법을 소개하고자 한다. 이전에 많이 사용된 인돌 합성법들은 강한 산성 조건에서의 반응으로 위험성이 존재하고, 비대칭 케톤 등이 반응에 참여할 경우 위치이성질체 혼합물이 형성되어 원하는 화합물을 선택적으로 얻지 못한다는 단점이 있다. 그러나 본 연구에서는 기존의 인돌 합성법들 보다 훨씬 온화한 조건에서 짧은 시간 안에 효율적으로 위치이성체를 갖는 2,3-이치환된 인돌의 합성을 두 단계 반응을 이용하여 제시하였다. 첫 번째 반응으로는 *o*-아이오도아닐린에 탄소-탄소 결합 반응을 이용하여 *o*-알케닐아닐린 화합물을 합성하는 반응이다. 이 반응으로부터 얻어진 *o*-알케닐아닐린 화합물은 트렌스-와 시스-아이소머로 존재하며, 원하는 트렌스-아이소머를 선택적으로 얻는 방법 또한 제시하였다. 두 번째 반응으로는 hypervalent iodine 시약인 PIFA를 이용한 아미노 고리화 반응이다. 아미노 고리화 반응은 나이트렌 중간체를 거쳐 반응이 진행되기 때문에 보호기를 갖지 않는 인돌을 효율적으로 합성할 수 있으며, 빠른 시간 안에 반응이 완료 되어 치환기들의 이동 현상 없이 위치 선택적으로 반응이 진행된다. 본 연구에서 제안한 방법은 향후 생리활성이 뛰어난 인돌 화합물은 물론이고 새로운 2,3-이치환된 인돌 화합물의 합성에도 매우 유용하게 활용될 수 있을 것으로 기대된다.

주요어: 세파로텍서스 트로포노이드, 헤링토놀라이드, 라이칼 음이온 중합반응, 입체선택성, 2,3-이치환된 인돌, 스즈키, 스틸레, 아미노고리화 반응.

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