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**Development of Nef reaction for aldehyde synthesis and its application
toward total synthesis of Alyterinate A**

(アルデヒドを合成するための Nef 反応の開発とアリテリネート A の全
合成に向けた応用)

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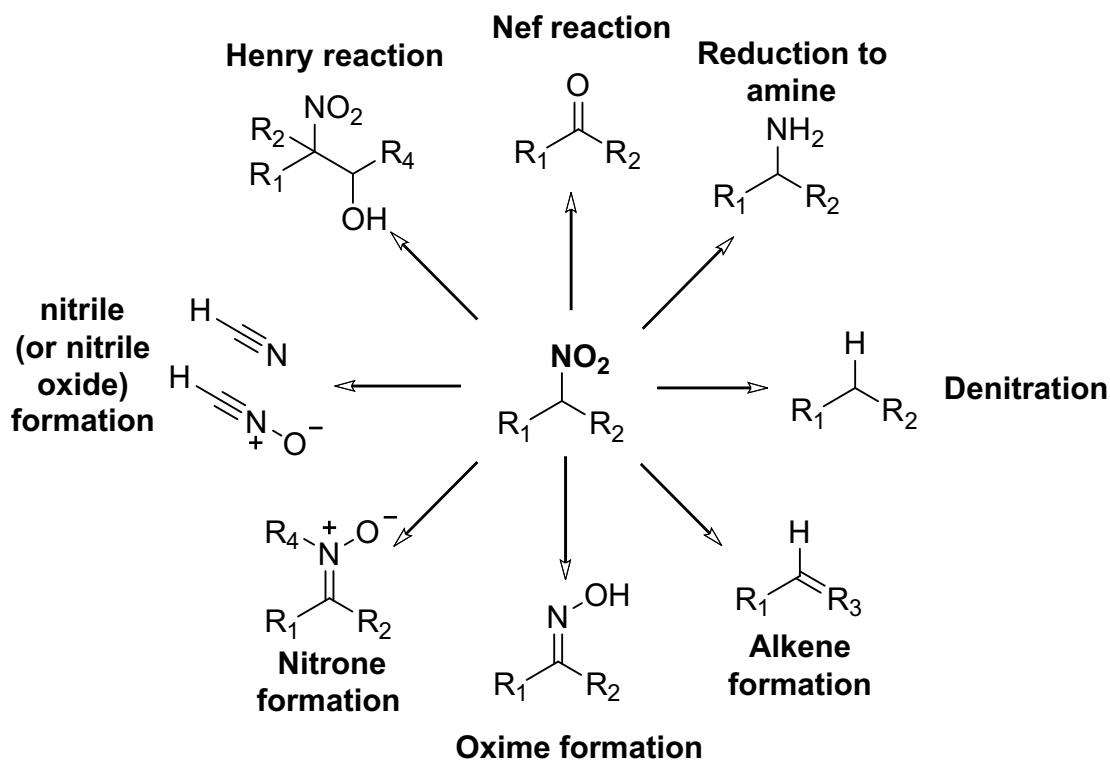
CHAPTER 1

General Introduction

1-1 Overview the Importance of Nitro Group

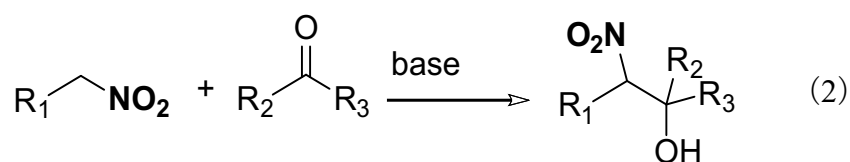
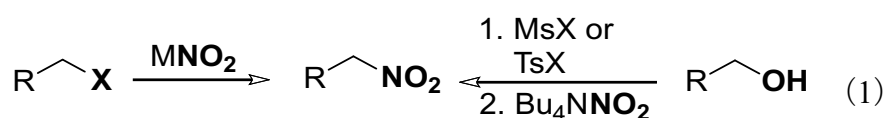
The nitro group is a highly versatile functional group in organic chemistry, renowned for its dual reactivity, capable of acting as both a nucleophile and an electrophile. Because of this adaptability, it is often referred to as a "synthetic chameleon," serving as a latent precursor to a wide range of functional groups through diverse chemical transformations.¹ As illustrated in Figure 1-1, typical transformations of the nitro group include the Nef reaction, the Henry reaction, reduction to amines and their derivatives, as well as conversions to oximes, nitriles, nitrile oxides, nitrones, and even substitution or elimination of the nitro group itself.² These transformations are frequently employed in the total synthesis of natural products, underscoring the nitro group as a pivotal intermediate in constructing complex molecular architectures.

Figure 1-1. Representative Transformations of the Nitro Group into Various Functionalities.



Commonly, nitro groups can be introduced into organic molecules through various synthetic strategies. One of the most common methods involves the nucleophilic displacement of a suitable leaving group, such as an alkyl halide or an alcohol derivative (e.g., mesylate or tosylate), using a nitrite source (Figure 1-2. eqn (1)). Alternatively, the oxidation of nitrogen-containing precursors offers a valuable route to access nitro compounds that are challenging to obtain via direct nitration, particularly in sterically hindered halo derivatives.³ In addition, nitroalkanes can be readily synthesized through the nitroaldol (Henry) condensation (Figure 1-2. eqn (2)) or by the direct nitration of corresponding olefins (Figure 1-2. eqn (3)). As the importance of nitroalkanes has grown in the context of organic synthesis, they have become indispensable feedstock chemicals for the production of fine chemicals. Their widespread availability, both commercially and synthetically, combined with their versatile reactivity, has facilitated the development of numerous robust and efficient synthetic methodologies.

Figure 1-2. Common Approaches to Nitro Group Installation.



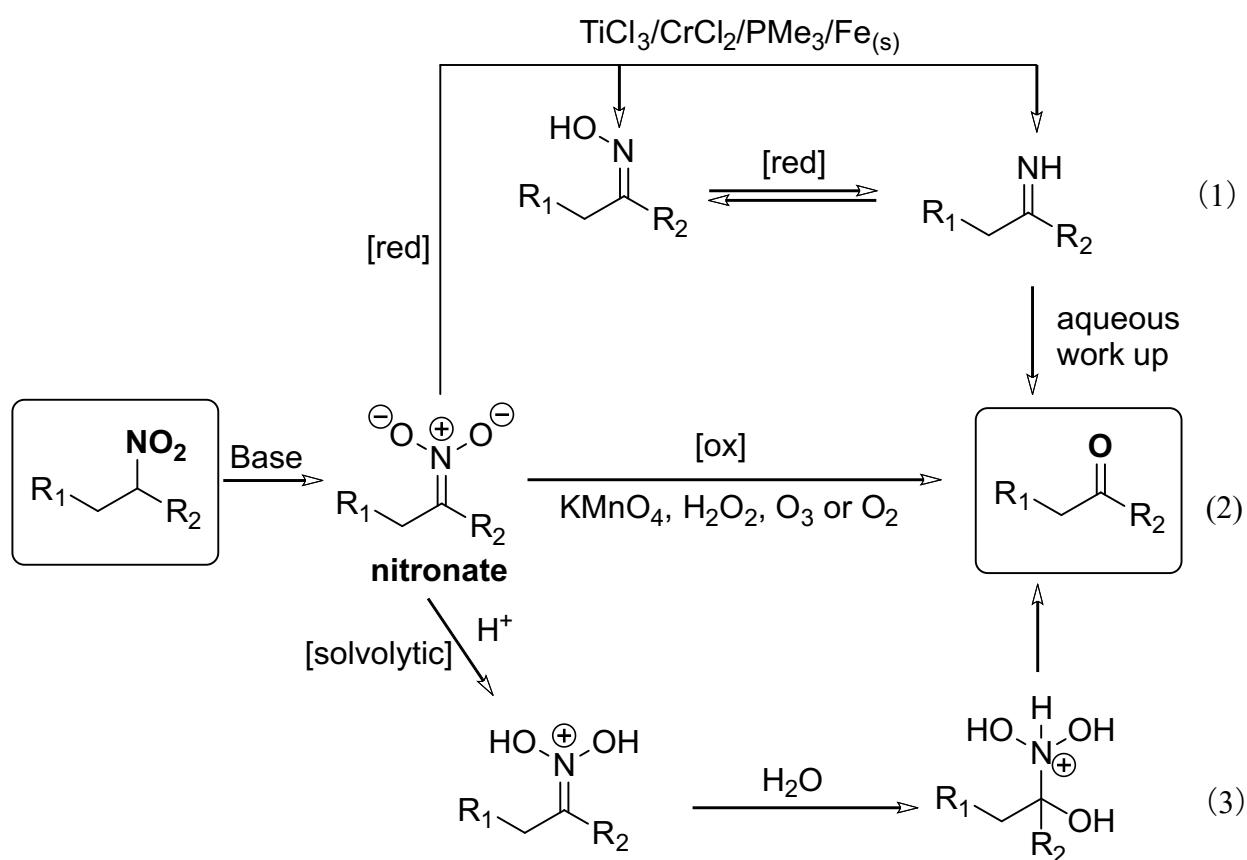
1-2 Nef Reaction and Its Methodologies

Among the various transformations of the nitro group, its conversion to carbonyl compounds, called Nef reaction, continues to be of significant synthetic interest and can be achieved through a variety of strategies. Typically, the introduction of carbonyl group into molecular frameworks is accomplished via the oxidation of alcohols or alkenes or through the rearrangement of oxygen-containing substrates.⁴ In contrast, the Nef reaction, converting nitroalkanes into aldehydes or ketones via oxidative or acidic activation, offers a direct and valuable alternative for accessing carbonyl compounds from readily available nitro precursors. For example, oxidative Nef methods (Scheme 1-1. eqn (2)) are a popular strategy for obtaining carbonyl compounds from the nitronate intermediate using stoichiometric oxidants such as KMnO_4 ,^{5a} hydrogen peroxide,^{5b} dimethyl dioxirane,^{5c} oxone,^{5d} ozone,^{5e} or singlet oxygen,^{5f} which require an excess amount of base.

Reductive protocols (Scheme 1-1. eqn (1)) for nitro compound transformation typically proceed through a stepwise mechanism involving initial N–O bond cleavage, leading to the formation of an oxime intermediate, followed by a second reduction step and subsequent imine hydrolysis. Among these methods, classified broadly under Nef-type reactions, the TiCl_3 -mediated McMurry protocol has gained considerable popularity.^{6a} Other reducing agents, such as CrCl_2 ,^{6b} trimethylphosphine,^{6c} and iron powder,^{6d} have also been successfully employed for similar transformations. Additionally, a number of studies have described solvolytic Nef reactions,⁷ wherein the reaction proceeds through the generation of nitronate and nitronic acid intermediates (Scheme 1-1. eqn (3)). These intermediates require carefully controlled stoichiometric amounts of both base and acid to promote subsequent hydrolysis, ultimately yielding the corresponding carbonyl compounds. Classical Nef protocols usually require strongly acidic conditions or the use of stoichiometric oxidants, which limit their

functional group compatibility and reduce their applicability in late-stage functionalization of complex molecules.

Scheme 1-1. Classical approaches of the Nef reaction to carbonyl compounds: (1) reductive, (2) oxidative, and (3) solvolytic methods.

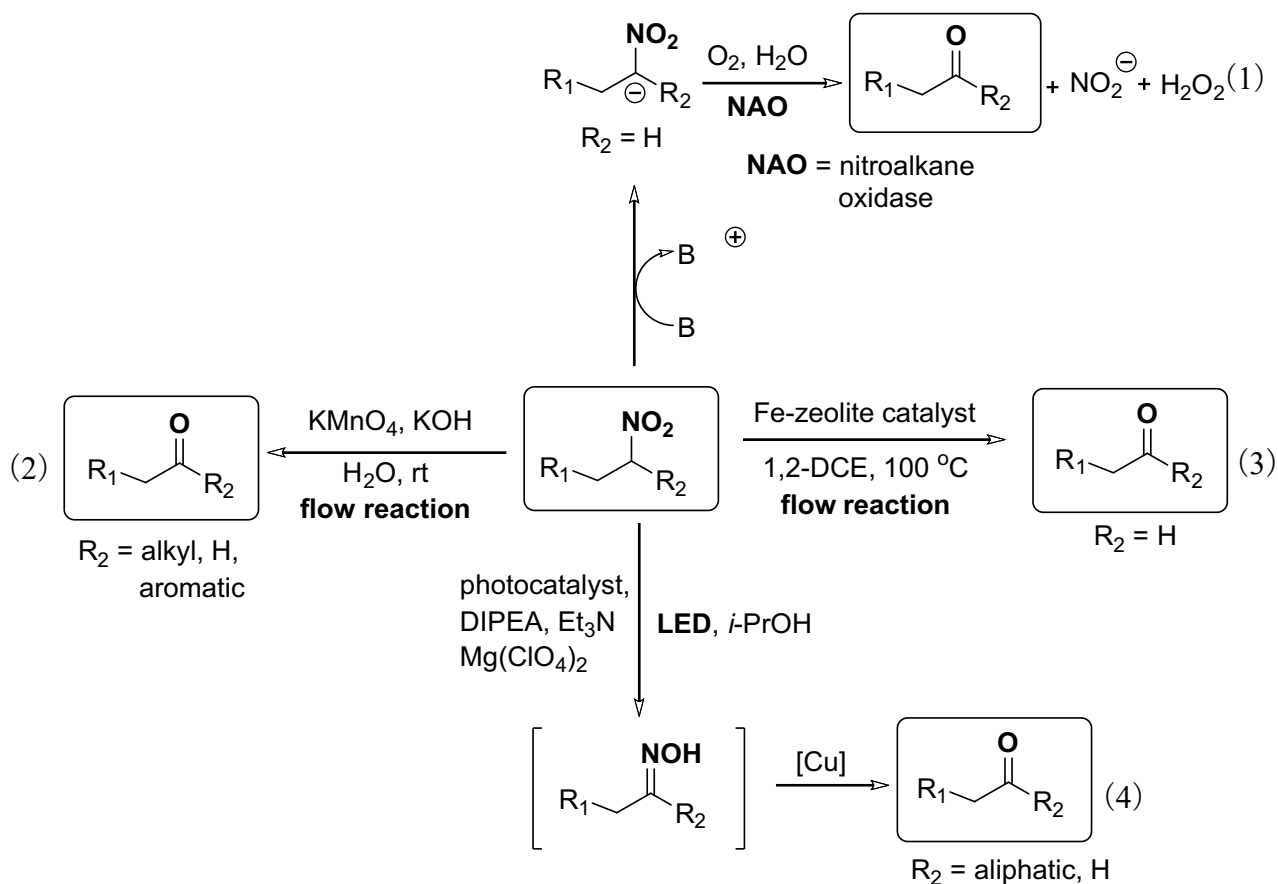


Despite numerous advancements aimed at expanding the substrate scope and optimizing reaction conditions, the development of greener, milder, and more versatile alternatives remains a significant challenge. These alternatives should ideally offer enhanced substrate tolerance, improved operational simplicity, and reduced environmental

impact. In recent years, biocatalytic approaches have emerged as promising strategies for converting nitroalkanes into carbonyl compounds. For instance, flavoprotein enzymes such as nitroalkane oxidase (NAO)^{8a} and propionate-3-nitronate oxidase^{8b} have been employed under aerobic conditions to catalyze the oxidative transformation of nitroalkanes into their corresponding carbonyl derivatives. During this transformation, a nitro group is released in the form of a nitrite anion (Scheme 1-2. eqn (1)). This makes the biological process somewhat different from the transformation using the traditional method of converting a nitroalkane to a carbonyl compound. Additionally, reductase enzymes have been explored for this transformation. However, the yields achieved thus far remain relatively modest.^{8c} Nonetheless, these enzyme-catalyzed processes underscore the potential of biocatalysis as a sustainable alternative to traditional chemical methods for nitro to carbonyl conversions.

Further advancements in the reactivity and synthetic utility of nitroalkanes have been realized through the integration of external stimuli and emerging technologies. Sedelmeier and co-workers initially demonstrated that Nef oxidation of aliphatic nitro compounds could be effectively carried out using stoichiometric potassium permanganate (KMnO₄) under continuous flow conditions (Scheme 1-2. eqn (2)), affording the corresponding carbonyl compounds in good yield.^{9a} Subsequently, in 2018, Gnanaprakasam reported a highly selective synthesis of various aldehydes using a similar continuous flow approach, notably without the need for additional additives such as bases or oxidants.^{9b} This transformation was catalyzed by a robust heterogeneous Fe-zeolite catalyst (Scheme 1-2. eqn (3)), highlighting the potential of catalyst-driven, additive-free protocols for green and scalable oxidation reactions.

Scheme 1-2. Alternative protocols of Nef reaction



In parallel, photochemical methods have also contributed to the development of novel nitro to carbonyl transformations. Chien *et al* (2022) reported a visible-light photoredox catalysis strategy, employing blue LEDs (Scheme 1-2. eqn (4)) in conjunction with additives such as triethylamine and diisopropylethylamine (DIPEA).¹⁰ This method enabled a mild, one-pot transformation of nitroalkanes into their corresponding aldehydes and ketones via a photoinitiated reduction-hydrolysis sequence. The process is particularly attractive due to its operational simplicity, mild reaction conditions, high efficiency, and broad functional group tolerance, making it a promising approach for the synthesis of sensitive or complex molecules.

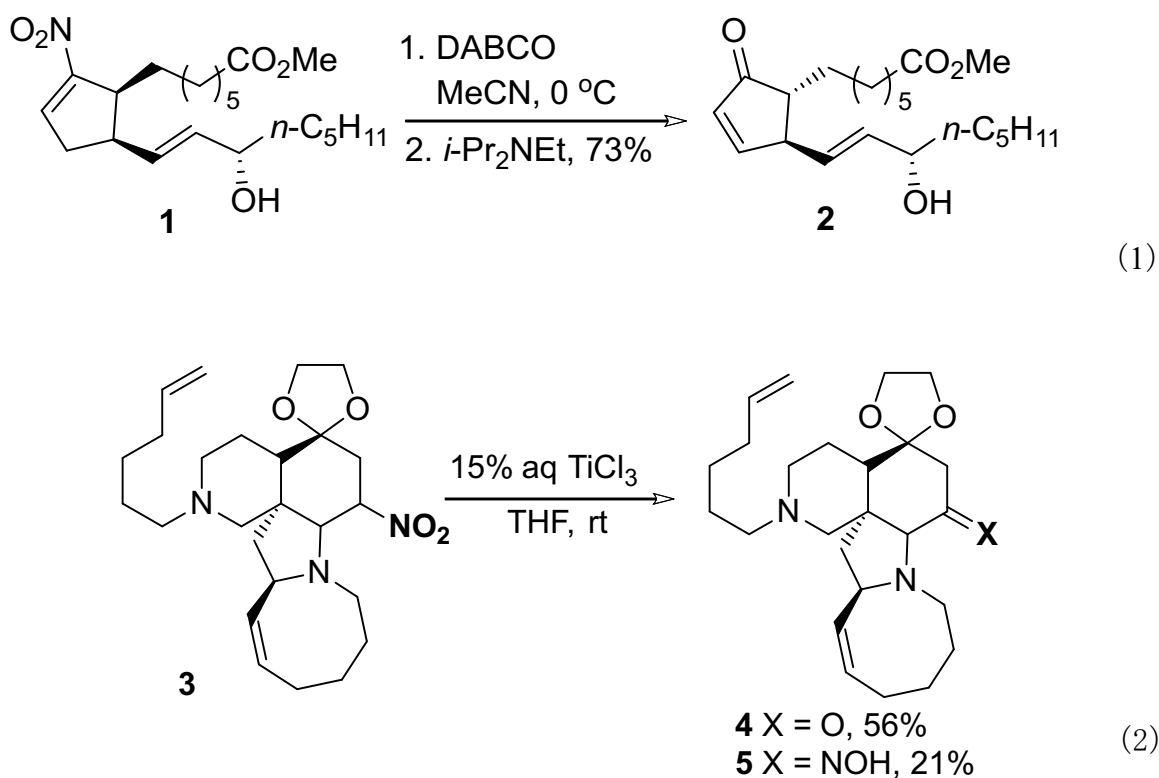
1-3 Application and Limitations of Nef Reaction in Natural Product Synthesis

The Nef reaction has found significant utility in the total synthesis of complex natural products, particularly for the late-stage conversion of nitroalkanes to carbonyl compounds under controlled conditions. One illustrative example of ketone formation is the final step in the synthesis of PGA₁ methyl ester **2**, which was accomplished using a one-pot protocol starting from nitrocyclopentene **1** (Scheme 1-3, eqn (1)). This transformation involved an initial isomerization of the endocyclic double bond, followed by the addition of *N,N*-diisopropylethylamine (DIPEA), which promoted both the nitro-to-carbonyl conversion and epimerization at the α -position adjacent to the carbonyl functionality.¹¹ In another example, special consideration was required when applying Nef conditions to polyfunctionalized intermediates bearing acid-labile groups (Scheme 1-3, eqn (2)). Remarkably, despite the presence of these sensitive moieties, the substrate underwent successful Nef conversion using TiCl₃ under strongly acidic conditions (pH < 1). However, a significant amount of oxime **5** was formed alongside the desired ketone **4**, indicating a competitive side reaction. This outcome highlights the need for further optimization when applying the Nef reaction to highly functionalized and reactive systems.¹²

While the majority of synthetic applications of the Nef reaction have focused on ketone formation, the aldehyde-forming variant has received comparatively less attention. One successful example involves the conversion of nitroalkane precursor **6** into the desired aldehyde **7** under optimized Nef conditions (Scheme 1-4, eqn (1)). This aldehyde was immediately subjected to condensation with (*R*)-(+)-2-methyl-2-propanesulfinamide, affording compound **8** in an overall 73% yield and a favorable diastereomeric ratio (>93:7 dr). Notably, the Nef reaction also generated a dimethyl acetal as a major byproduct during the reaction.¹³ Although no epimerization was observed in the freshly isolated aldehyde, a noteworthy limitation was revealed during storage under house vacuum overnight,

where partial epimerization was detected based on the formation of a diastereomeric mixture in the subsequent product **8**. This highlights the chemical lability of Nef-derived aldehydes, especially in the presence of an acidic α -proton, which facilitates enolization and subsequent epimerization(Scheme 1-4, eqn (2)).

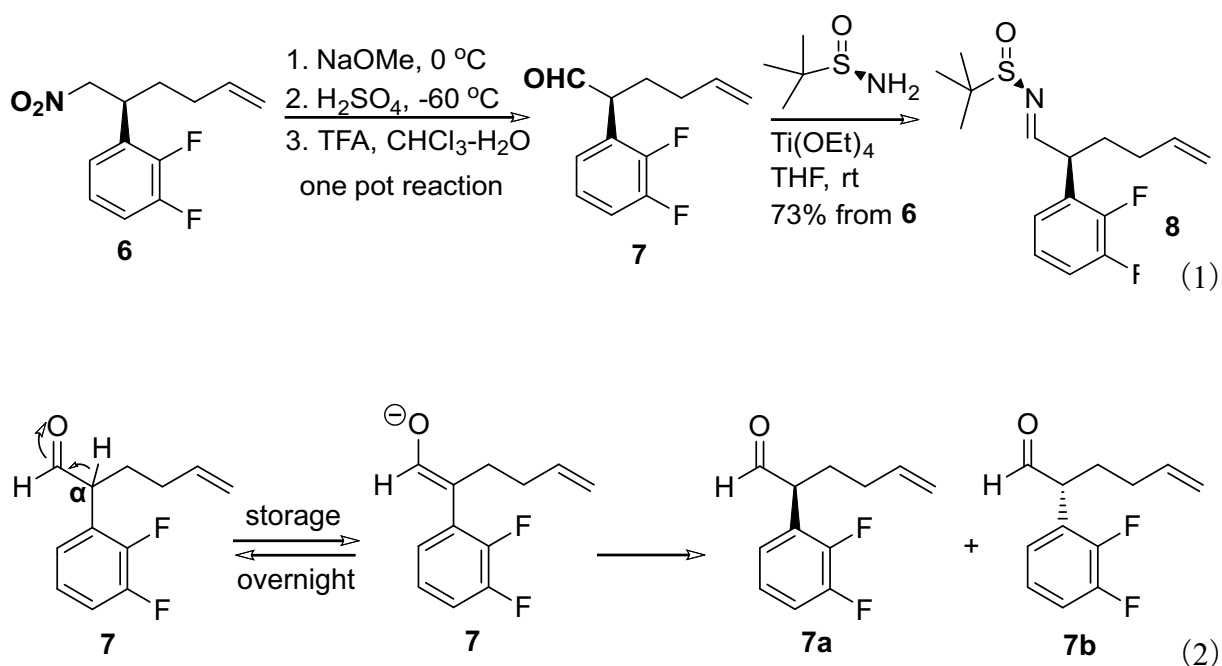
Scheme 1-3. Nef reaction in the : (1) Synthesis of PGA₁ methyl ester, (2) Synthesis of an advanced intermediate to manzamine A.



As reported by Luo and co-workers,¹³ a key challenge in the aldehyde-forming Nef reaction is the inherent instability of the resulting aldehydes. The presence of an enolizable α -proton renders these compounds susceptible to epimerization and degradation, complicating

both their isolation and downstream use. This issue, coupled with the formation of side products such as acetals or oximes, has partly limited the broader adoption of aldehyde-forming Nef protocols in complex molecule synthesis.

Scheme 1-4. (1) Nef reaction in the asymmetric synthesis of a novel heterocyclic analogue of the CGRP receptor antagonist Rimegepant (BMS-927711), and (2) Instability of aldehydes during storage due to enolizable α -proton.



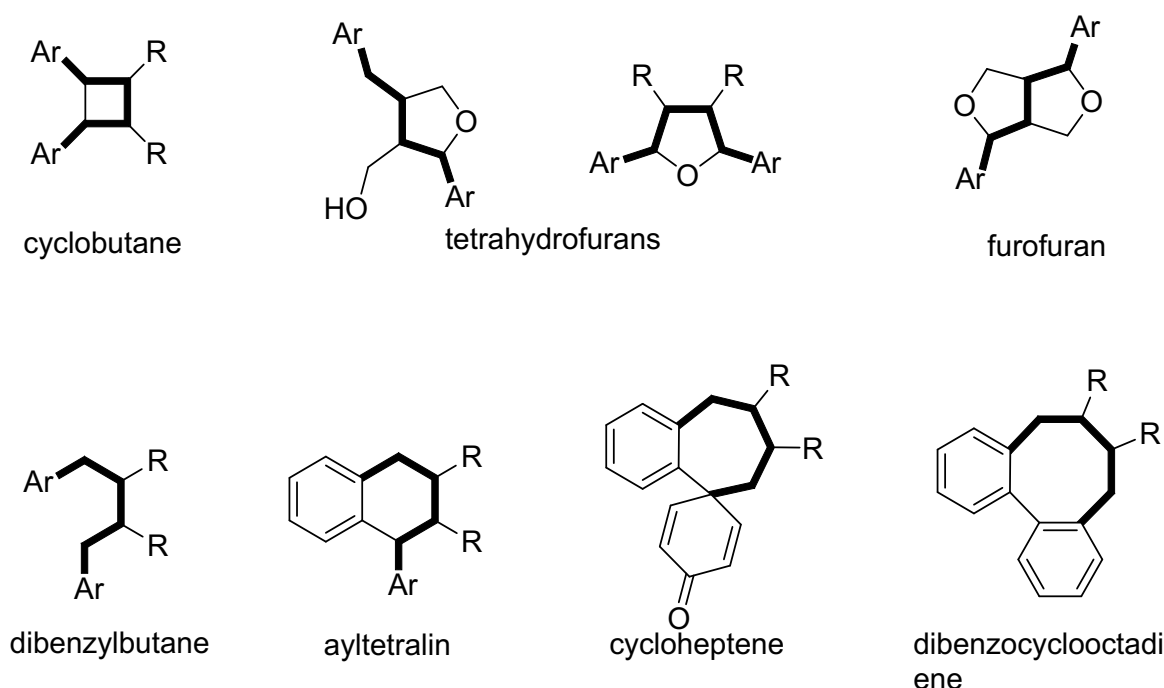
Motivated by these challenges, the current study aims to investigate and optimize Nef reactions that specifically yield aldehyde products. Notably, Yamashita and co-workers pioneered a strategy for aldehyde formation via a Nef reaction involving singlet oxygen. In their methodology, phosphonate precursors **9** are first deprotonated using sodium methoxide in methanol to generate the corresponding nitronate ions **10** (Scheme 1-5. eqn (1)).

photosensitizer under visible-light irradiation (470 nm) in the presence of molecular oxygen (Scheme 1-5. eqn (2)). Despite the need for a prolonged reaction time (48 hours), the conditions described afforded the desired aldehyde intermediates, which were directly utilized in a subsequent Wittig olefination to furnish the target compound **13** in an overall yield of 48% over two steps. Notably, under these optimized conditions, 9% of the starting nitroalkane **12** was recovered, indicating that incomplete conversion or reverse reaction might have proceeded.¹⁵ Nevertheless, the transformation demonstrated acceptable efficiency given its mild and operationally simple conditions.

1-4 Lignan Natural Product

Lignans have garnered significant attention due to their widespread occurrence in plant and human food sources, with a diverse range of biological activities.¹⁶ These compounds are naturally occurring secondary metabolites biosynthesized via the oxidative dimerization of two phenylpropanoid (C_6-C_3) units. The various modes of dimerization among these simple monomers result in a broad array of lignan structures (Figure 1-2), contributing to the remarkable structural and functional diversity observed within this class of natural products.¹⁷ Although the precise biological role of lignans in plants remains incompletely understood, they are often associated with defensive mechanisms against biotic and abiotic stressors. To date, numerous promising bioactivities have been identified for lignan natural products and their unnatural analogues. These include antibacterial, antiviral, antitumor, antiplatelet, phosphodiesterase inhibitory, 5-lipoxygenase inhibitory, HIV reverse transcriptase inhibitory, cytotoxic, antioxidant, immunosuppressive, and antiasthmatic activities.¹⁸

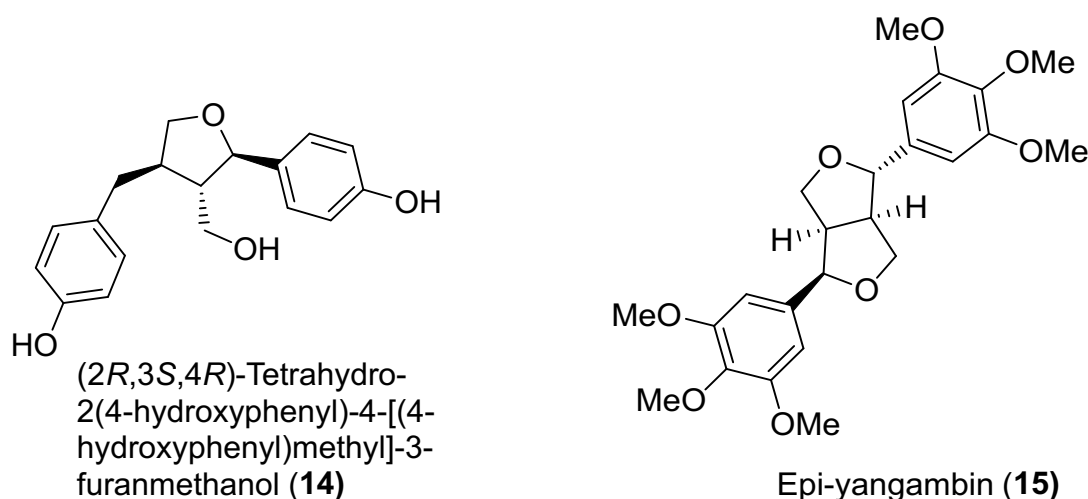
Figure 1-2. Several classes of lignan scaffold



These reports discuss the activities of isolated lignan compounds. For example, the Wu group in 2012 enabled isolating (2*R*,3*S*,4*R*)-Tetrahydro-2(4-hydroxyphenyl)-4-[(4-hydroxyphenyl)methyl]-3-furanmethanol (**14**) from *Carya cathayensis* tree shell. This compound has cytotoxicity against three different human tumor types, which are human colorectal cancer cell lines (HT-29), human lung cancer cell line (A549), and human breast cancer cell line (MCF-7).¹⁹ Garcia (2024) also identified bioactive tetrahydrofurofuran lignans isolated from *Croton floribundus*. In this study, four tetrahydrofurofuran lignans were isolated for the first time from the most bioactive fraction of the *C. floribundus* extract. Metabolomic profiling combined with multivariate statistical analysis revealed that the isolated lignan Epi-yangambin (**15**) was the principal compound responsible for the antiproliferative effect against the SK-MEL-147 melanoma cell line. Epi-yangambin **15** demonstrated selective antiproliferative activity, with an IC₅₀ value of 13.09 µg/mL and a selectivity index of 3.82.

This finding is particularly significant given the well-documented resistance of melanoma cells to current chemotherapeutic agents. As such, Epi-yangambin **15** holds promise as a lead compound for the development of novel antiproliferative therapeutics targeting drug-resistant melanoma.²⁰

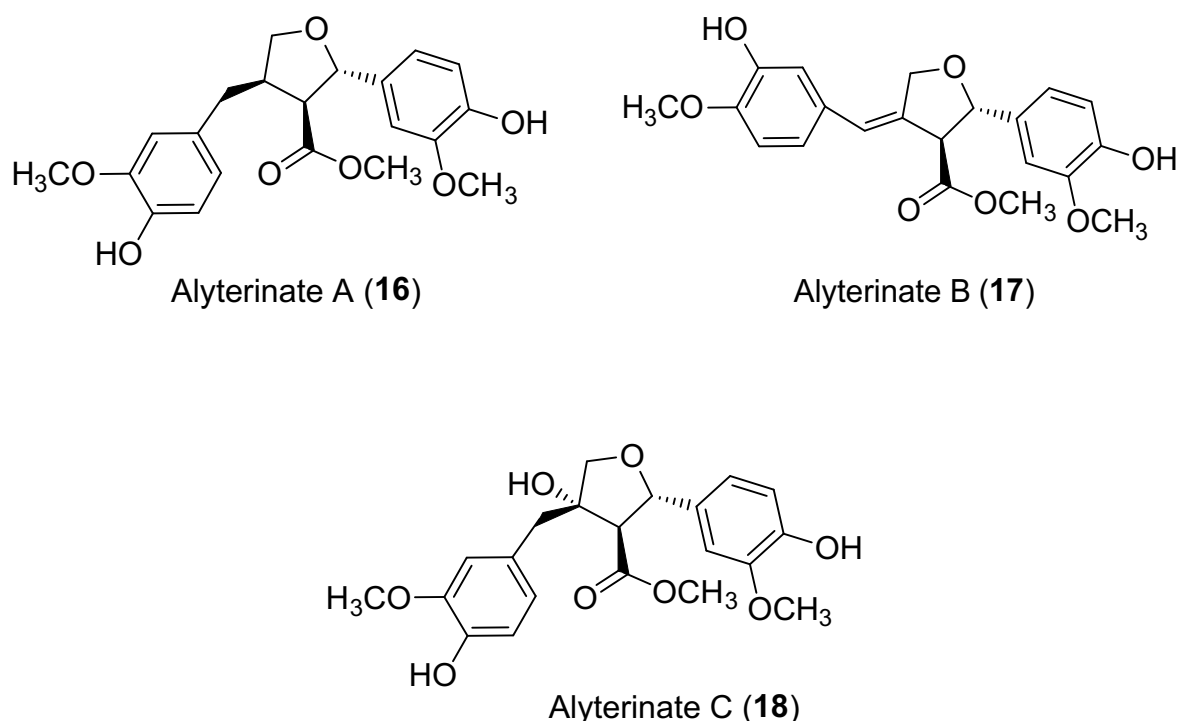
Figure 1-3. Structure of (2*R*,3*S*,4*R*)-Tetrahydro-2(4-hydroxyphenyl)-4-[(4-hydroxyphenyl)methyl]-3-furanmethanol (**14**) and Epi-yangambin (**15**)



Earlier, Sriphana *et al.* successfully isolated three novel lignan compounds, Alyterinates A (**16**), Alyterinates B (**17**), Alyterinates C (**18**) alongside four previously identified furofuran-type lignans from the plant *Alyxia schlechteri*. These bioactive compounds have been the subject of intensive screening for their potential activity against *Pythium insidiosum*, an oomycete responsible for the disease pythiosis. This pathogen affects various animal species, including dogs, horses, calves, and cats. Notably, *P. insidiosum* is not classified as a true fungus, as its cellular membranes lack ergosterol, a sterol typically present in fungal membranes.²¹ Consequently, conventional antifungal agents such as terbinafine and

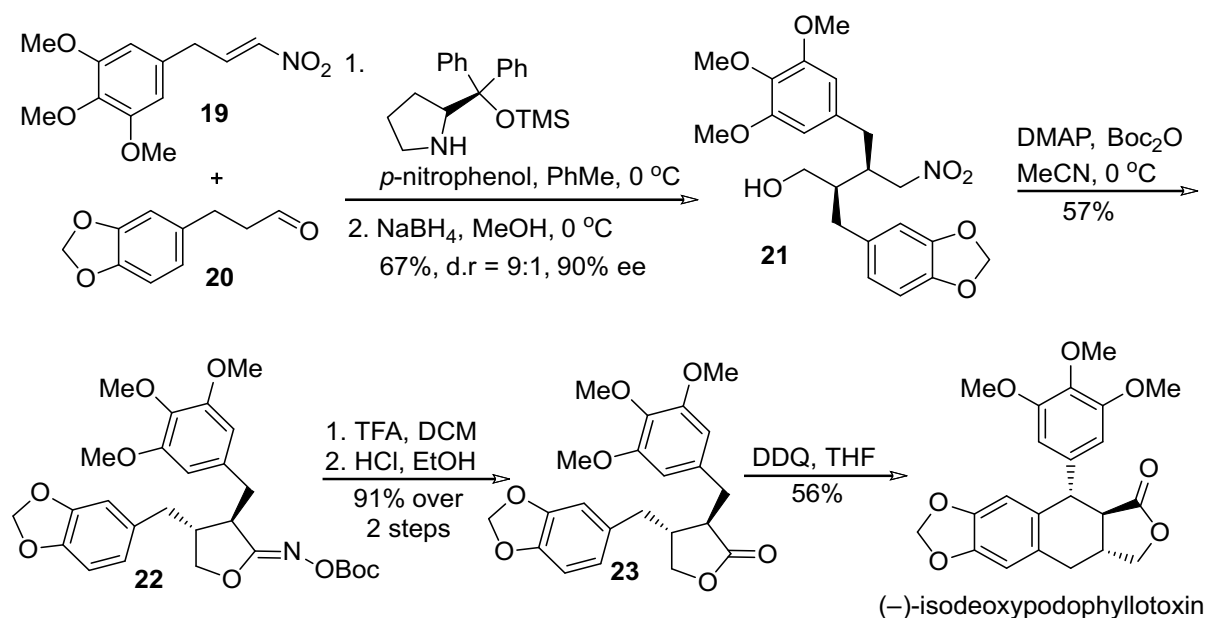
itraconazole, both of which target ergosterol synthesis, are generally ineffective in treating infections caused by this organism.²² Among the isolated lignan compounds, alyterinate C (**18**), which possesses a hydroxy group at the C-8' position, exhibited notable activity against *Pythium insidiosum*, as demonstrated by the disk diffusion assay. Moreover, in a recent study, Tanjung and coworkers (2020 and 2023) also isolated lignan derivatives, including Alyterinate A, from the roots and stem bark of *Willughbeia coriacea* Wall (Apocynaceae). This compound showed moderate activity against murine leukemia cells (P-388) with an IC₅₀ value of 3.04 ± 0.27 µg/mL and against cervical cancer cells (HeLa) with an IC₅₀ value of 12.5 µg/mL.^{23a, 23b.}

Figure 1-3. Structure of Alyteriante A (**16**), Alyteriante B (**17**) and Alyteriante C (**18**)



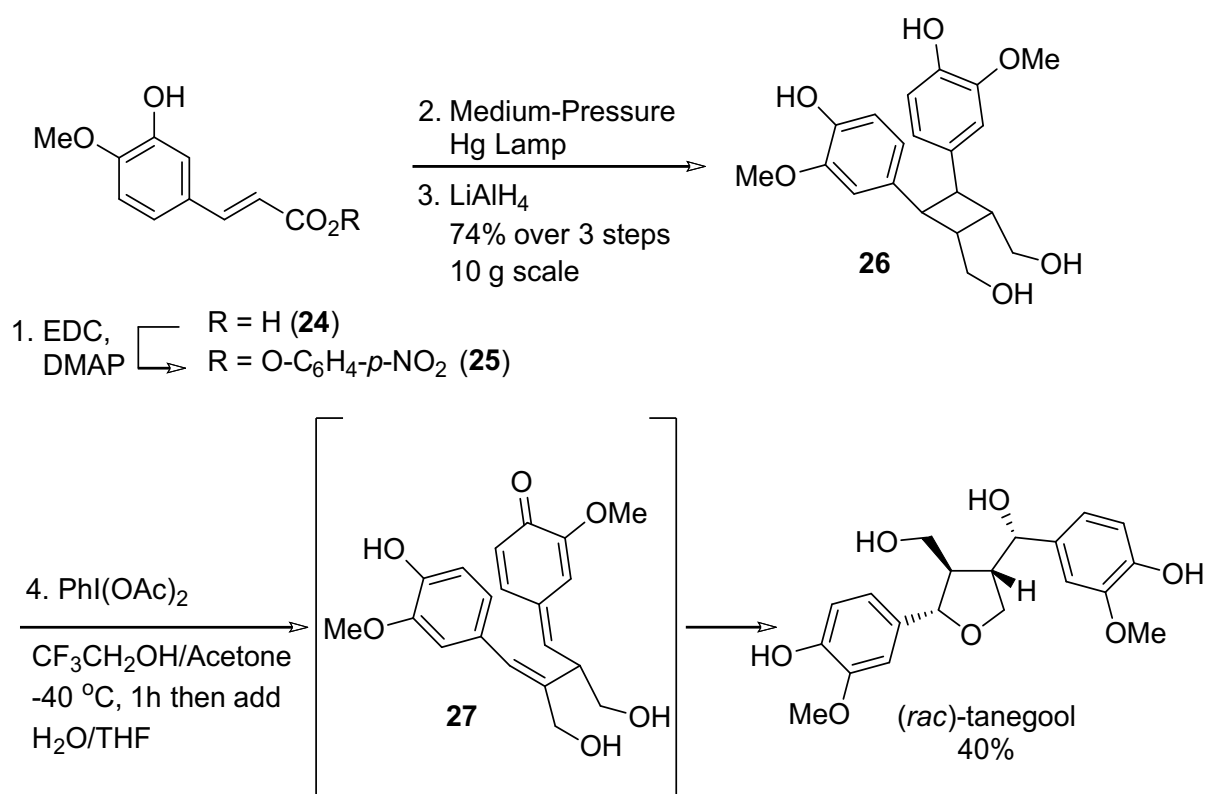
Given interest in its biological activities, significant efforts have been dedicated to understanding the synthesis of lignans over the past decade. Tremendous synthetic efforts on this family have been well documented by reviews. In recent years, several reports have outlined progress of particular topics related to the synthesis of furofuran lignans, aryl-naphthalene lactone analogues and aryltetralin glycosides.²⁴ However, synthesizing lignans presents several challenges, including achieving stereochemical control, controlling selectivity in oxidative coupling reactions, and the complexity of building highly strained ring systems. Researchers have developed various synthetic methodologies to tackle these challenges, inspired by biosynthetic pathways and employing novel reactions like the Catellani reaction.

Scheme 1-6. Synthesis route of (–)-isodeoxypodophyllotoxin



These are some reports that gave some alternative reactions affording the tetrahydrofuran ring as an important part of lignan derivatives in the natural products. For example, Bobek (2023) did a total synthesis of (–)-isodeoxypodophylotoxin. In the part of their synthetic procedure, they study an unexplored pathway to α,β -disubstituted γ -butyrolactone natural products through the oxime functional group (Scheme 1-6).²⁵ This methodology selectively prepares *trans*- α,β -substituted butyrolactone *O*-(Boc) oxime carbonates **22** via activation of δ -nitro alcohol **21** precursors under mild conditions, using cost-effective reagents: 4-dimethylamino pyridine (DMAP) and di-*tert*-butyl carbonate (Boc₂O). In this approach, δ -nitro alcohols can be conveniently obtained by Michael addition of carbonyl α -carbons **20** to nitroolefin **19**.

Scheme 1-7. A Bio-Inspired Total Synthesis of Tetrahydrofuran Lignans of (*rac*)-tanegool

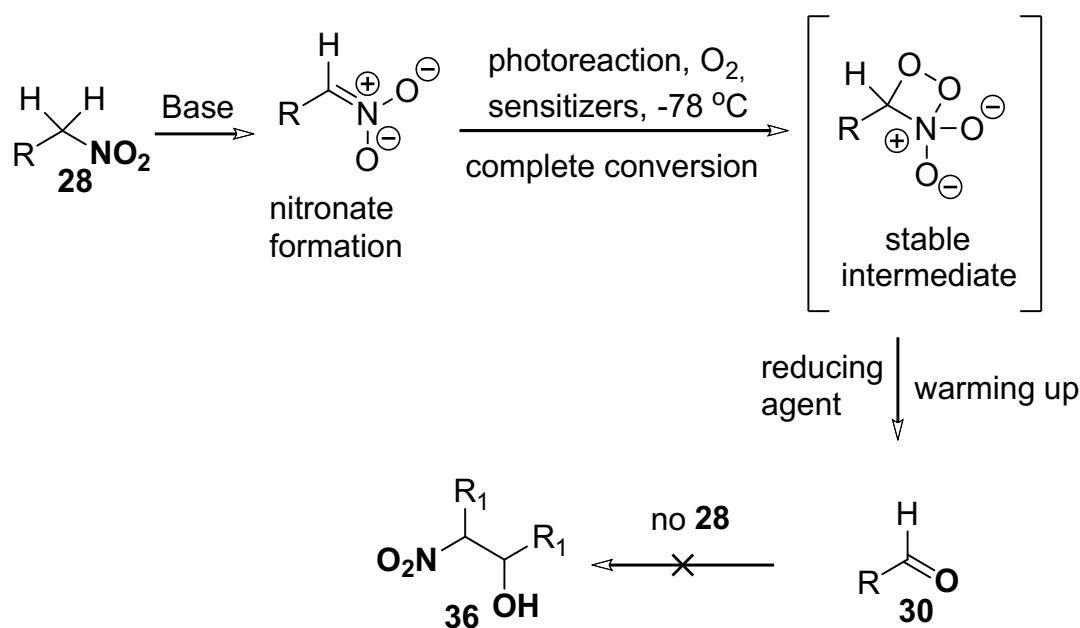


The total synthesis of (*rac*)-tanegool was also discussed other methods achieve tetrahydrofuran ring formation. Lignan synthesis is often inspired by common biosynthesis, which involves regio- and chemoselective oxidative coupling of propenyl phenols. Researchers attempt to replicate this oxidative coupling, which revealed significant challenges for controlling selectivity, and these challenges have thus far prevented the development of a unified biomimetic route to compounds of the lignan family. Then Albertson's group gave a practical solution that hinges on the oxidative ring-opening of a diarylcyclobutane diol **26** by Phenylido diacetate (PIDA) to intercept a putative biosynthetic intermediate. The resulting para-quinone methides **27** undergo stereospecific cyclization to give the natural product tanegool. The effectiveness of this approach is demonstrated by the first total synthesis of (*rac*)-tanegool in 4 steps starting from ferulic acid **24** (Scheme 1-7).²⁶

1-5 Development of Aldehyde-forming Nef Reaction Mediated Singlet Oxygen and Its Application for the Synthesis of Lignan Ester Alyterinate A

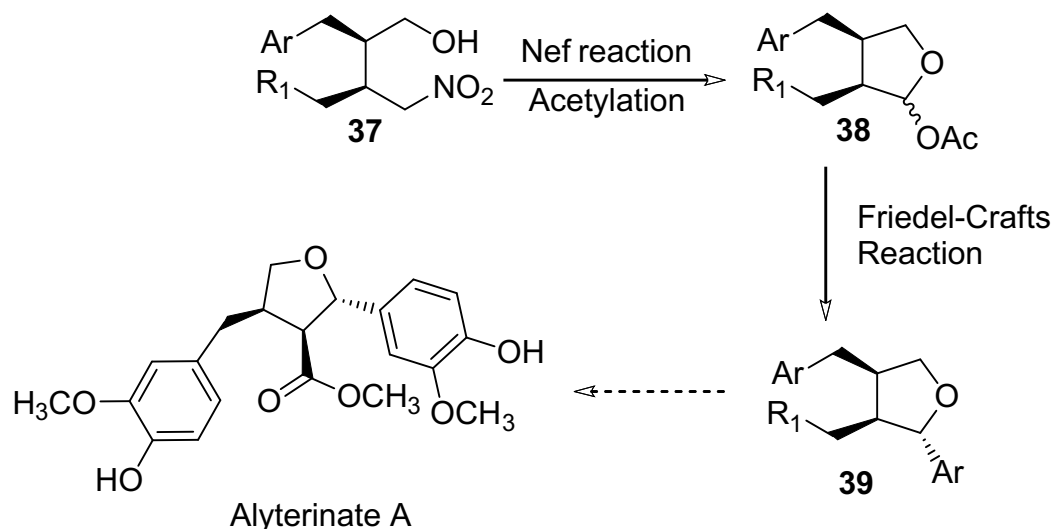
The Nef reaction is a valuable transformation in organic synthesis, enabling the conversion of nitro compounds into their corresponding carbonyl derivatives, either ketones, aldehydes, or carboxylic acids. While the ketone- and carboxylic acid-forming variants are well established, aldehyde-forming Nef reactions have received comparatively less attention. This is largely due to the intrinsic instability of aldehydes, which are more prone to degradation and epimerization than ketones, particularly under conventional reaction conditions. Additionally, aldehyde-forming Nef reactions often suffer from competitive side reactions, such as the Henry (nitroaldol) reaction, in which the aldehyde product reacts with residual nitro compounds, complicating purification and lowering yields. Traditional methods also frequently rely on strong oxidants or highly basic/acidic environments, thereby limiting substrate scope and functional group compatibility.

Scheme 1-8. Strategy for the development of the aldehyde-forming Nef reaction



To address these limitations, there is growing interest in developing milder, more selective, and functionally tolerant protocols for aldehyde synthesis via the Nef reaction. Recent studies have demonstrated that photochemical strategies offer a promising alternative. For example, prior work from our group¹⁵ has shown that singlet oxygen generated under visible light irradiation can mediate the conversion of nitronate intermediates to aldehydes, albeit with extended reaction times of up to 48 hours. According to results in Chapter 2, the optimization of reaction conditions would be explored to achieve more effective results in aldehyde formation (Schemes 1-8). The addition of a reducing agent would prevent the reverse reaction, thus avoiding the competing Henry reaction. Additionally, substrate scopes toward various functional groups will also be investigated to determine the generality of the newly developed protocols. The reaction mechanism will also be examined to enhance understanding.

Scheme 1-9. Strategy in the total synthesis of Alyterinate A.



Furthermore, in Chapter 3, application of this method to the synthesis of lignan derivatives is described. Alyterinate A is a lignan derivative that has bioactivities against *Pythium insidiosum*, an oomycete responsible for the disease pythiosis.²¹ It also demonstrated moderate cytotoxic activity against P-388 murine leukemia cells with an IC₅₀ value of 3.04 ± 0.27 $\mu\text{g/mL}$ and against cervical cancer cells (HeLa) with an IC₅₀ value of 12.5 $\mu\text{g/mL}$.^{23a, 23b} Due to its intriguing bioactivities and unique structural features, Chapter 3 would explore a synthetic route for the chemical production of Alyterinate A, thereby enabling the generation of sufficient quantities of the compound for comprehensive biological evaluation. Naturally isolated compounds are often obtained in limited amounts, posing challenges for further pharmacological investigations. To overcome this limitation, this study propose a synthetic approach based on our established Nef reaction protocols.²⁷ As seen in Figure 1-3, Alyterinate A (**16**) is a lignan ester with a tetrahydrofuran (THF) ring. The developed Nef reaction procedure could be applied in the synthetic route, especially in the THF ring formation (Scheme 1-9). Next, an aryl group is introduced into the THF ring via a Friedel-Crafts reaction

as the next key step to afford adduct **39**. The esterification reaction would complete the total synthesis of Alyterinate A.

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CHAPTER 2

Development of the Aldehyde-forming Nef Reaction Initiated by Singlet Oxygen under Mild Conditions and Investigation of the Reaction Mechanism

2-1 Introduction

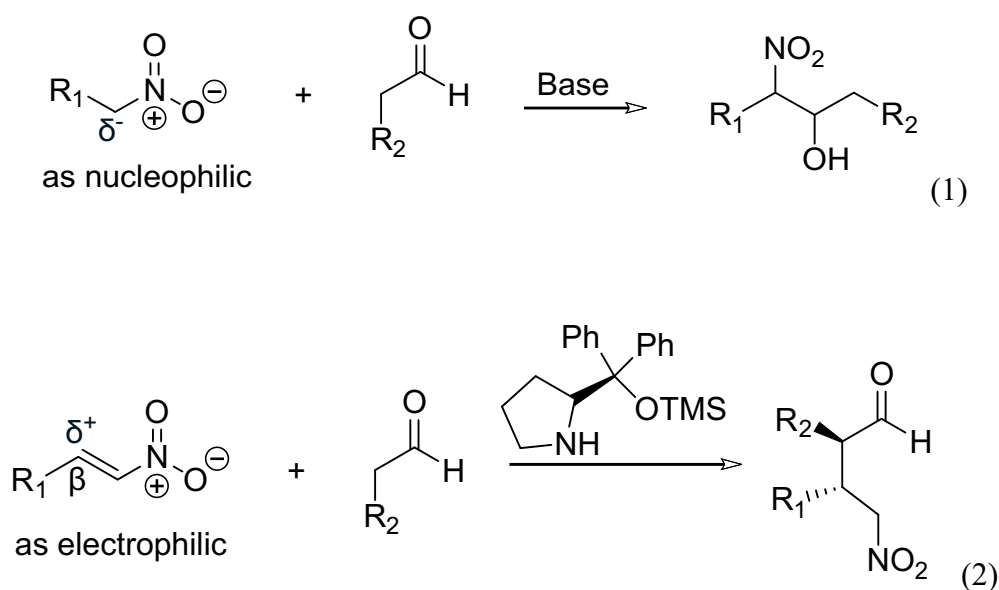
The strategic interconversion of functional groups forms a foundational element in modern organic synthesis, particularly in the construction of structurally complex and well-defined molecules. Functional groups are frequently introduced in the early stages of a synthetic sequence to enable or enhance key transformations such as carbon–carbon bond formation. However, these groups often serve a transient role and must be subsequently modified or replaced to achieve the structural and functional requirements of the target molecule. The synthetic value of a given functional group is thus heavily dependent on the range and reliability of available interconversion methodologies, which in turn influence the development of robust and versatile synthetic routes.

Nitroalkanes represent a fundamental class of compounds in this context, due to their ability to undergo facile deprotonation at the α -position to generate nitronate anions. This reactivity is enabled by the strong electron-withdrawing character of the nitro group, which significantly enhances the acidity of the adjacent C–H bond (e.g., the pK_a of MeNO_2 is approximately 10).¹ The resulting nitronate species serve as potent carbon nucleophiles. They can engage in carbon–carbon bond forming reactions with a variety of electrophilic partners, including alkyl halides, aldehydes, and Michael acceptors.² These transformations are widely utilized to increase molecular complexity and to introduce structural diversity in synthetic intermediates.

Although nitro groups are often essential during intermediate stages of synthesis, they are rarely retained in the final product. Consequently, they are commonly subjected to further transformations, either by reduction to form amines or through oxidative or hydrolytic pathways to yield carbonyl group. One of the most well-established methods for converting a nitro group into a carbonyl group is the Nef reaction.³ This transformation, which produces either aldehydes or ketones, is particularly important because it inverts the electronic nature of the α -carbon from nucleophilic to electrophilic. This change in polarity allows for further

functionalization and is frequently utilized in multistep synthesis. Additionally, the nitro group has proven extremely valuable in catalytic asymmetric reactions, where it can be employed to construct multiple stereocenters in a single transformation. When attached to a sp^3 -hybridized carbon, the nitroalkyl group typically acts as a carbon nucleophile (Scheme 2-1. eqn (1)),⁴ while in nitroalkenes, the electrophilic reactivity is focused at the β -position (Scheme 2-1. eqn (2)), offering diverse reactivity profiles depending on the molecular context.⁵

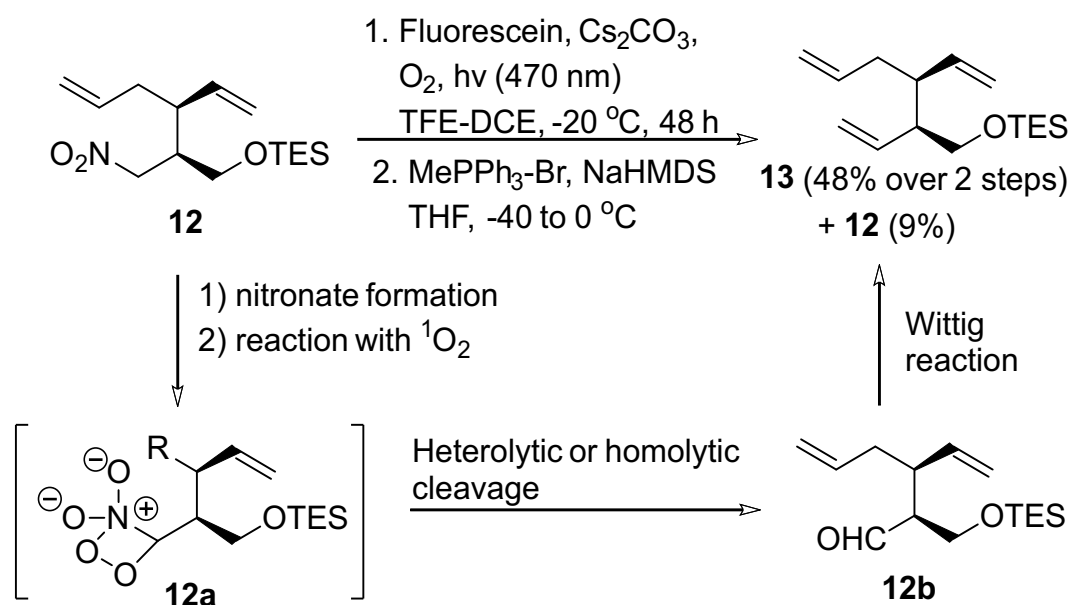
Scheme 2-1. Reactivity Profiles of Nitro Groups.



The classical Nef reaction involves the hydrolysis of a nitronate salt, which is formed by the base-catalyzed deprotonation of a nitroalkane, under highly acidic conditions ($pH < 1$). While this method effectively generates carbonyl compounds, the harsh conditions are required, limiting its applicability, especially in the presence of acid-sensitive functional groups.⁶ In response to these limitations, various alternative protocols have been developed that allow the

Nef reaction to proceed under oxidative, reductive, or neutral conditions.¹ These advancements have significantly enhanced the practicality of the reaction, particularly for the synthesis of ketones. However, equivalent transformations to access aldehydes remain considerably less developed. The limited availability of mild and selective Nef conditions for aldehyde formation highlights an ongoing challenge in the field and encourages further investigation into reaction designs that bypass these constraints while maintaining high chemoselectivity and functional group tolerance.

Scheme 2-2. Nef reaction induced by singlet oxygen in the total synthesis of multifidene.



Our group previously reported the total synthesis of multifidene, a sex pheromone of brown algae, in which the Nef reaction for an aldehyde was used under visible light irradiation ($\lambda_{\text{max}} = 470 \text{ nm}$) in the presence of oxygen gas and fluorescein as a photocatalyst at -20°C based on

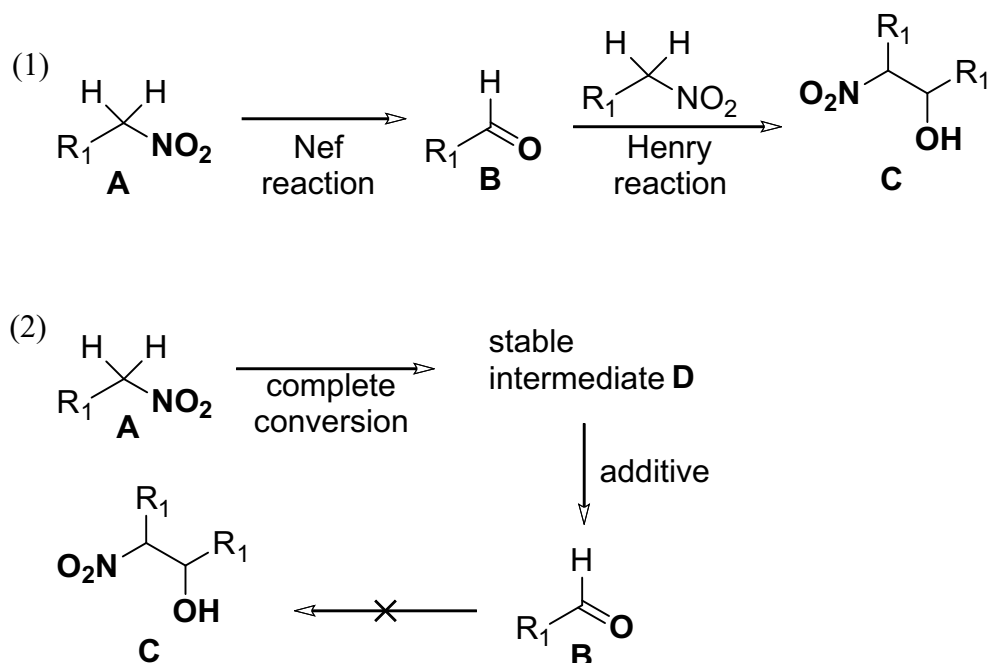
the literature,⁷ as shown in Scheme 2-2. In this transformation, a long reaction time (48 h) was necessary to obtain a higher yield of **13**. In this reaction, the target product **13** and recovered starting nitro compound **12** were obtained after the Wittig reaction. In these reactions, products derived from the Henry reaction were not observed. The author suspected a unique property of the proposed intermediate **12a**, as described in the previous report, with this outcome. Intermediate **12a** was formed completely from **12** via nitronate ion *in situ*, which was then gradually transformed to **12b**, shortening the reaction time between **12** and **12b** and thus avoiding the competing Henry reaction.

2-2 Study Plan

Despite these advances, the Nef reaction for aldehyde synthesis remains challenging due to the requirement for harsh reaction conditions, such as strong acids or bases, which limit the functional group tolerance of the methodology. A primary difficulty arises from a competing side reaction, the Henry (nitroaldol) reaction, which occurs between the starting nitro compound **A** and the newly formed aldehyde **B**, resulting in byproducts such as compound **C** (Figure 2-1. eqn (1)). Aldehydes, being more reactive than ketones, are particularly susceptible to this side reaction.

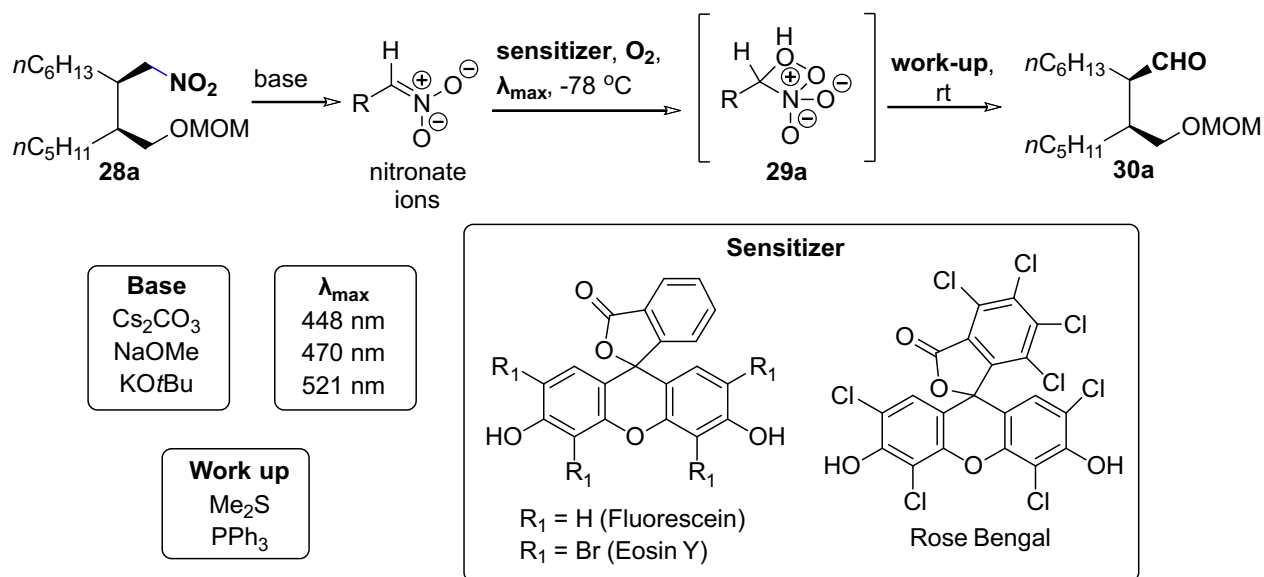
To overcome this issue, it has been proposed that the complete consumption of the starting material **A** prior to aldehyde formation is essential. By generating a stable intermediate **D** that can be selectively converted into the aldehyde **B** in the absence of residual **A**, the Henry side reaction can be effectively suppressed (Figure 2-1. eqn (2)). This strategy offers a promising approach for the selective and efficient synthesis of aldehydes via the Nef reaction, while minimizing undesired byproduct formation.

Figure 2-1. (1) Competing Henry reaction pathway in Nef reaction for aldehydes, (2) concept of effective Nef reaction for aldehydes.



For the development of the aldehyde-forming Nef reaction, a model study of nitro compound **28a** is first investigated to optimize the reaction conditions, as shown in Figure 2-2. Commercially available sensitizers of fluorescein, Eosin Y, and Rose Bengal, along with bases such as Cs_2CO_3 , NaOMe, and KO^tBu , are employed to reach complete conversion of **28a** to intermediate **29a**. Screening of the light wavelength was also conducted to obtain optimum results. After work-up and warming to room temperature, aldehyde **30a** is expected to be formed.

Figure 2-2. Optimization condition of the aldehyde-forming Nef reaction.



2-3 Optimization of Aldehyde-forming Nef reaction

The initial optimization studies were conducted using **28a** as a model compound to evaluate the formation and stability of the desired aldehyde **30a** under photochemical Nef conditions. This particular compound was chosen because it allowed us to observe whether any isomerization occurred at the α -position of the resultant aldehyde. Such isomerization can negatively affect the purity of the target compound. This is especially important when reactions are conducted toward chiral centers, as even small configurational changes can lead to significant differences in biological activity or reactivity. Therefore, maintaining stereochemical integrity during the reaction was a key consideration.

As summarized in Table 2-1, a series of photochemical reactions using rose bengal as the photosensitizer and a blue LED light source ($\lambda_{\max}$ = 448 nm) was examined. Rose bengal was chosen because of its well-established ability to generate singlet oxygen (¹O₂) upon visible-

light irradiation, a reactive species believed to be central to the transformation.⁸ Upon irradiation of **28a** in the presence of rose bengal for 1 hour, the reaction yielded aldehyde **30a** along with **28a** as an inseparable mixture (Table 2-1, entry 1). This partial conversion prompted further investigation into the incomplete conversion or the possibility of a reverse reaction that might proceed, reforming the starting nitro compound **28a**. Next, A control experiment conducted in the absence of rose bengal resulted in no observable product formation (Table 2-1, entry 2), thus confirming that singlet oxygen is crucial for initiating the formation of the peroxide intermediate, which is important in the generation of aldehyde species.

To probe the involvement of a peroxide intermediate, postulated to form via reaction of singlet oxygen with the nitronate species, various reductants were introduced post-irradiation to cleave the peroxide bond. When dimethyl sulfide (Me₂S) was introduced after 1 hour of irradiation, the crude ¹H NMR spectrum revealed neither unreacted starting material nor signals corresponding to α -epimerized aldehydes, indicating complete and selective transformation into **30a** with 85% yield (Table 2-1, entry 3). This finding supports the efficient cleavage of the suspected peroxidic intermediate without the formation of detectable side products. Interestingly, no evidence of side reactions, such as Henry-type adducts arising from condensation between the starting nitroalkane **28** and the aldehyde product **30a**, was observed in any of the reaction mixtures. This suggests a clean reaction profile under the specified conditions. Further, substitution of Me₂S with triphenylphosphine (PPh₃) also led to the formation of **30a**, albeit with a slightly lower yield as much as 67% (Table 2-1, entry 4), possibly due to complications in purification caused by the formation of triphenylphosphine oxide (TPPO).⁹

Subsequent trials were conducted to assess the effects of modifying other key variables. Lowering the amounts of Cs₂CO₃ resulted in reduced product formation and incomplete conversion (Table 2-1, entries 5-7), likely due to a decreased concentration of nitronate anions

necessary for reaction progression. Additionally, altering the LED light source to emit wavelengths other than 448 nm significantly diminished the efficiency of the reaction. LEDs emitting at 521 nm (Table 2-1, entry 5) and 470 nm (Table 2-1, entry 6), for example, provided only partial conversion of the starting nitro compound. This indicates that the efficiency of singlet oxygen generation and overall photoreaction progress is highly dependent on aligning the light source with the absorption profile of the photosensitizer.

Alternative bases were then evaluated to optimize deprotonation and facilitate the formation of nitronates. Compared to Cs_2CO_3 , which gave the highest conversion, both K_2CO_3 and NaOMe were less effective, particularly NaOMe, which showed significantly reduced yields (Table 2-1, entries 8-11). The utilization of K_2CO_3 could produce aldehyde in 72% yield, while using NaOMe could not convert all nitro compounds to aldehyde. One key reason for Cs_2CO_3 effectiveness is the large size of the cesium ion (Cs^+), which weakly interacts with the nitronate anion.¹⁰ This weak interaction allows the anion to remain more reactive and accessible in solution. In contrast, smaller alkali metal ions like Na^+ or K^+ tend to bind more tightly to the nitronate, making it less reactive. Moreover, Cs_2CO_3 is more soluble in organic solvents than other carbonates, allowing for better homogeneity and more efficient deprotonation.

Further, the addition of 15-crown-5 to the reaction when using NaOMe as base (Table 2-1, entry 10) could slightly increase the formation of **2b**, but could not convert all starting nitro compound **1a**. Base of Cs_2CO_3 and K_2CO_3 , both enabled full conversion, was likely due to their ability to generate nitronate ions efficiently because of their weakly bonding cations (Cs^+ and K^+) to the carbonate anions, which allows effective deprotonation of the nitro compound. In contrast, NaOMe, although fully soluble in methanol, was far less effective, generating only 5% aldehyde without additives and 15% with the addition of 15-crown-5. This reduced efficiency is attributed protic nature of methanol, which stabilizes ion pairs and reduces base

strength, while also favoring proton exchange that can reverse nitronate formation. The crown ether improved performance slightly by sequestering Na^+ and freeing methoxide, but this effect was limited in the protic environment.

Lastly, the generality of the photosensitization was examined by replacing rose bengal with other visible-light photosensitizers. As shown in entries 12-19 of Table 2-1, both Eosin Y and fluorescein successfully promoted the transformation, resulting in the formation of aldehyde product **30a** with different conversion percentages (particularly using eosin Y with entry 12 condition could generated aldehyde in 75% yield). These findings demonstrate the flexibility of the photochemical system and its compatibility with a variety of photocatalysts, thus expanding the range of conditions under which the Nef reaction can be implemented. The different amount of conversion underscores the critical importance of selecting a light source that matches the absorption characteristics of the photosensitizer to ensure optimal excitation, singlet oxygen generation, and overall reaction efficiency.

Collectively, these results reinforce the notion that both the base and the photonic parameters must be carefully tuned for effective execution of the mild Nef protocol. Cs_2CO_3 remains a base of choice due to its high solubility and efficacy in generating reactive nitronate intermediates under mild conditions. When combined with appropriately matched visible-light photosensitizers and irradiation wavelengths (most effectively with rose bengal and 448 nm LED light), this system provides a reliable and robust platform for the oxidative conversion of nitroalkanes to aldehydes. These insights into the photochemical parameters further expand the synthetic utility of the method, enabling researchers to tailor the protocol to specific experimental setups or substrate requirements without compromising on efficiency or selectivity.

Table 2-1. Optimization of reaction conditions^a

CCCCCCCC[C@H](NO2)[C@H](OC(=O)OC(C)C)CCCC
 $\xrightarrow[\text{then reducing agent, } 0\text{ }^{\circ}\text{C for 10 min}]{\text{Base, Sensitizer, O}_2, \lambda_{\text{max}}, \text{MeOH:DCM (9:1) 0.1 M, } -78\text{ }^{\circ}\text{C, 1 h}}$
CCCCCCCC[C@H](C=O)[C@H](OC(=O)OC(C)C)CCCC

28a (dr = 7.3:1)
 30a (dr = 7.3:1)

Entry	Base [eq]	Sensitizer [0.05 eq]	Reducing Agent [eq]	hν [nm]	Ratio (30a : 28a) ^b Yield 30a ^c
1	Cs ₂ CO ₃ (1.5)	Rose Bengal	-	448	69:31
2	Cs ₂ CO ₃ (1.5)	-	Me ₂ S (3.0)	-	0:100
3	Cs₂CO₃ (1.5)	Rose Bengal	Me₂S (3.0)	448	100:0, 85%
4	Cs ₂ CO ₃ (1.5)	Rose Bengal	Me ₂ S (1.0)	448	76:24
5	Cs₂CO₃ (1.5)	Rose Bengal	PPh₃ (1.5)	448	100:0, 67%
6	Cs ₂ CO ₃ (1.0)	Rose Bengal	Me ₂ S (3.0)	521	72:28
7	Cs ₂ CO ₃ (1.0)	Rose Bengal	Me ₂ S (3.0)	470	76:24
8	Cs ₂ CO ₃ (1.0)	Rose Bengal	Me ₂ S (3.0)	448	87:13
9	K ₂ CO ₃ (1.0)	Rose Bengal	Me ₂ S (3.0)	448	60:40
10	K₂CO₃ (1.5)	Rose Bengal	Me₂S (3.0)	448	100:0, 72%
11	NaOMe (1.0)	Rose Bengal	Me ₂ S (3.0)	448	21:79
12	NaOMe (1.5)	Rose Bengal	Me ₂ S (3.0)	448	5:95^d
13	Cs₂CO₃ (1.5)	Eosin Y	Me₂S (3.0)	448	100:0, 75%
14	Cs ₂ CO ₃ (1.5)	Eosin Y	Me ₂ S (3.0)	470	85:15
15	Cs ₂ CO ₃ (1.5)	Eosin Y	Me ₂ S (3.0)	521	90:10
16	K ₂ CO ₃ (1.5)	Eosin Y	Me ₂ S (3.0)	448	89:11
17	NaOMe (1.5)	Eosin Y	Me ₂ S (3.0)	448	6:94
18	Cs ₂ CO ₃ (1.5)	Fluorescein	Me ₂ S (3.0)	448	90:10
19	Cs ₂ CO ₃ (1.5)	Fluorescein	Me ₂ S (3.0)	470	80:20
20	Cs ₂ CO ₃ (1.5)	Fluorescein	Me ₂ S (3.0)	521	83:17

^a Reaction conditions: 0.200 mmol of **28a** was used; ^bThe ratio was estimated by crude ¹H NMR; ^cDue to the difficulty in separating **28a** and **30a**, the isolated yield of **30a** was given when **28a** was not obtained, ^dIn the presence of 15-crown-5, the ratio changed to **30a:28a** = **15:85**.

2-4 Substrate Scope

With the optimized reaction conditions established, a comprehensive evaluation of the functional group tolerance was undertaken, focusing specifically on functional groups known to be labile under acidic, basic, or oxidative environments. These studies are summarized in Figure 2-3. According to these results, the newly developed protocol, which employs significantly milder reagents and reaction conditions, allows for the preservation of these functional groups while enabling the efficient conversion of nitroalkanes to aldehydes.

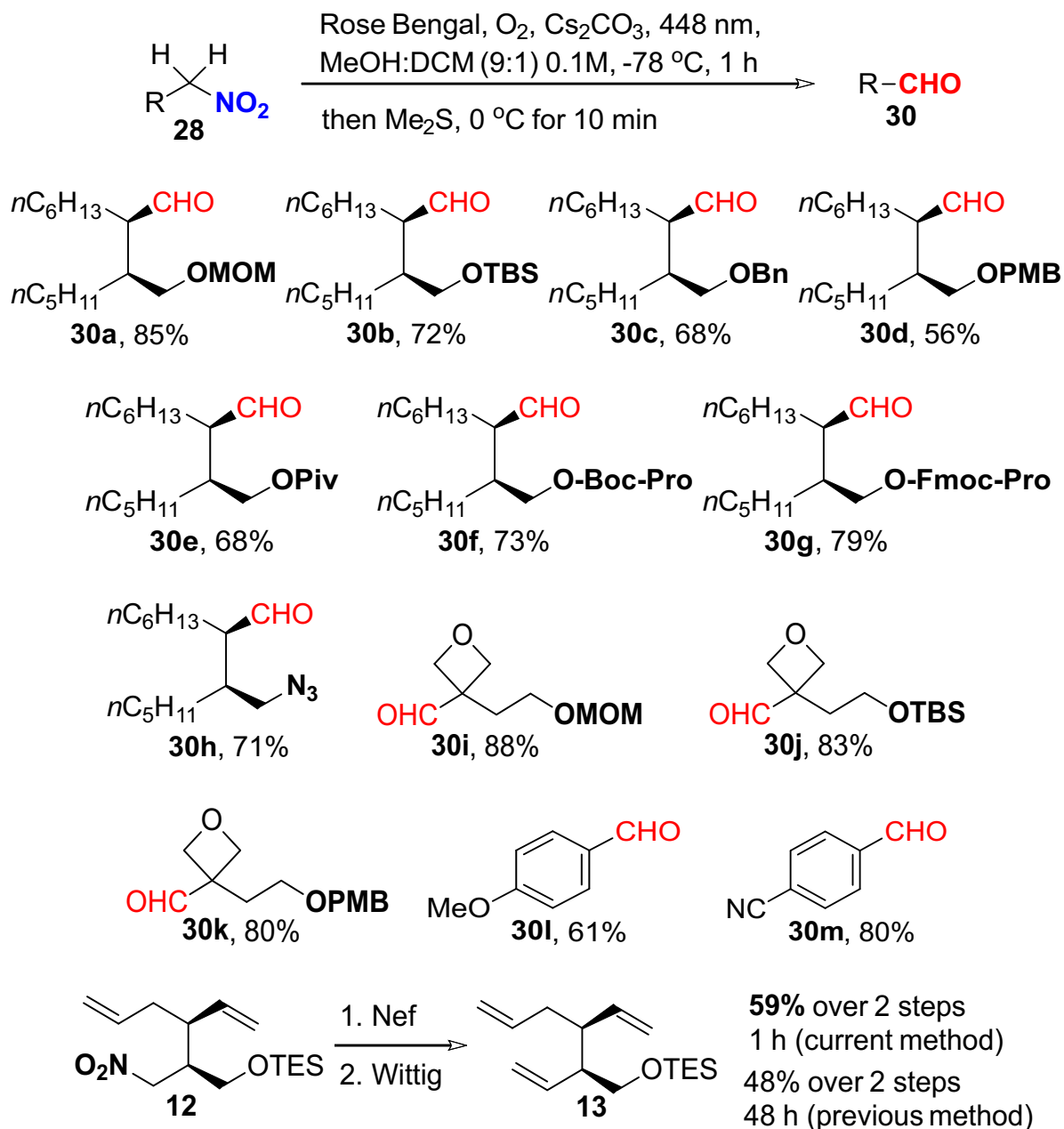
Acid-sensitive protecting groups such as *tert*-butyldimethylsilyl (TBS) and benzyl ethers were evaluated using nitroalkane substrates and were found to remain intact under the new reaction system. The corresponding aldehydes (**30b–30d**) were isolated in moderate yields, confirming that the conditions did not trigger deprotection or decomposition of these groups. This represents a substantial advantage over conventional methods, wherein silyl ethers are typically cleaved under even mildly acidic conditions, and benzyl ethers are unstable in the presence of strong acid.

Moreover, the protocol demonstrated compatibility with base-sensitive carbonyl functionalities. Aldehyde **30f–30h** were obtained under mild basic conditions, indicating that the conditions did not induce base-catalyzed hydrolysis, which is common under stronger basic conditions. Impressively, azides (**30e**) also survived the reaction sequence. The successful transformation in the presence of these groups validates the mildly basic nature of the reaction environment and underscores the method's synthetic utility in complex molecule construction.

Furthermore, substrates bearing sterically hindered nitroalkanes were also well tolerated under the optimized conditions. The resulting aldehydes **30i–30k**, each bearing a formyl group directly attached to a quaternary carbon center, were obtained in high yields. Such transformations are typically challenging due to steric hindrance around the reaction center,

yet the mild protocol enabled smooth conversion without requiring elevated temperatures or prolonged reaction times.

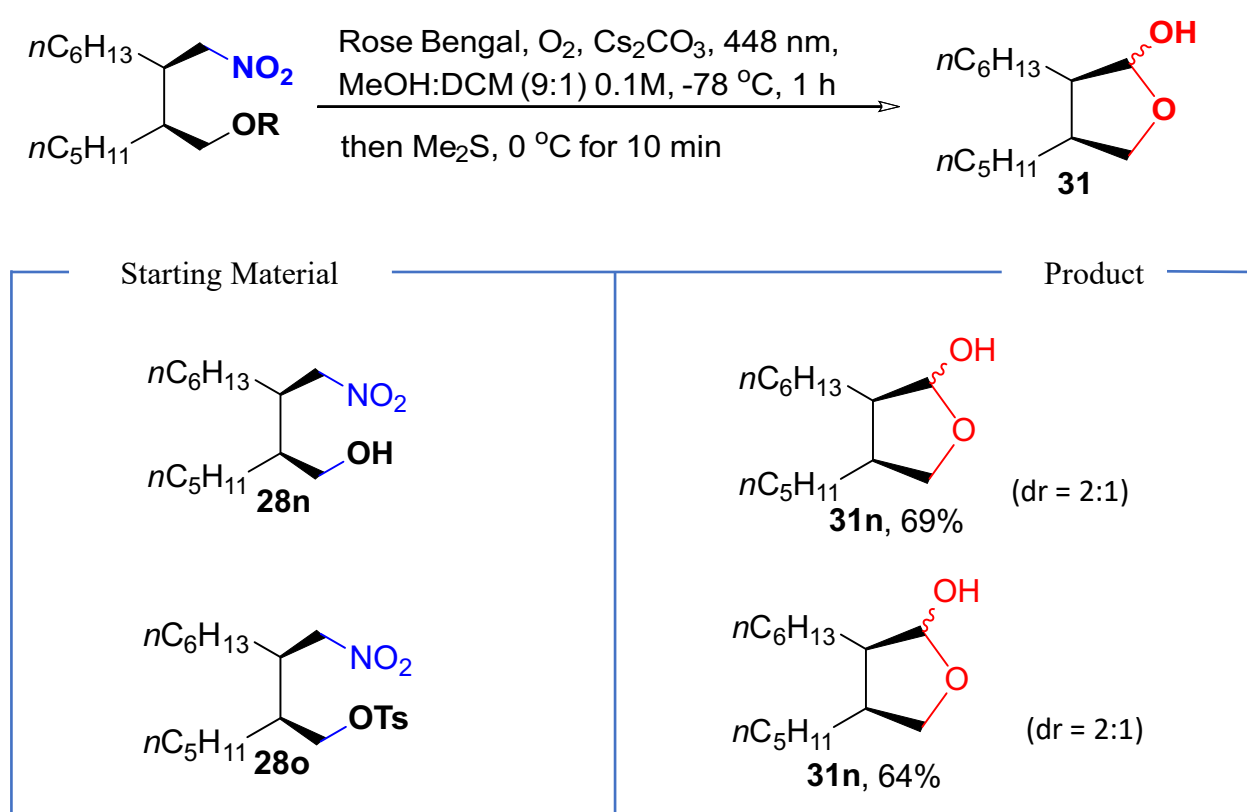
Figure 2-3. Substrate scope of the Nef reaction



In addition, the methodology proved effective in generating aromatic aldehydes **30l** and **30m** in moderate to high yields. These substrates, often susceptible to electrophilic aromatic substitution or undesired side reactions in harsh acidic media, remained intact, further

reinforcing the chemoselectivity of the current reaction system. The optimized conditions were also successfully applied to a previously reported substrate (**12**), which had required 48 hours and yielded **13** in only 48% over two steps under older conditions. In contrast, the present method afforded the same product in just 1 hour with an improved overall yield of 59%. This study exemplifies the practical advantages of the refined procedure, including enhanced reaction efficiency, reduced reaction times, and improved yields. These collective results affirm the mild Nef reaction as a robust and versatile strategy for the synthesis of structurally and functionally diverse aldehydes from nitroalkane precursors.

Figure 2-4. Substrate scope of the Nef reaction forming cyclic acetal



The application of the Nef reaction to nitro-containing alcohol substrates led to the formation of cyclic acetals in synthetically useful yields. Specifically, treatment of a nitro alcohol (**28n**) under standard Nef conditions resulted in the corresponding cyclic acetal in 69%

yield (**31n**). Interestingly, the same product was obtained even when the substrate contained a tosyl group (**28o**). Mechanistically, we propose that the transformation proceeds via initial oxidative conversion of the nitro group to an aldehyde, a hallmark of the Nef reaction. The resulting aldehyde intermediate is prone to hydration under aqueous or protic conditions, forming a gem-diol. This hydrated aldehyde intermediate then undergoes intramolecular nucleophilic substitution (S_N2), wherein a hydroxy group (or an oxygen nucleophile derived from hydrolysis) attacks the electrophilic carbon center bearing the tosyl leaving group. This results in ring closure to afford a cyclic acetal. The S_N2 nature of the ring closure is supported by the requirement for a good leaving group (tosylate) and a suitably positioned nucleophile, which are both present in the substrates employed.

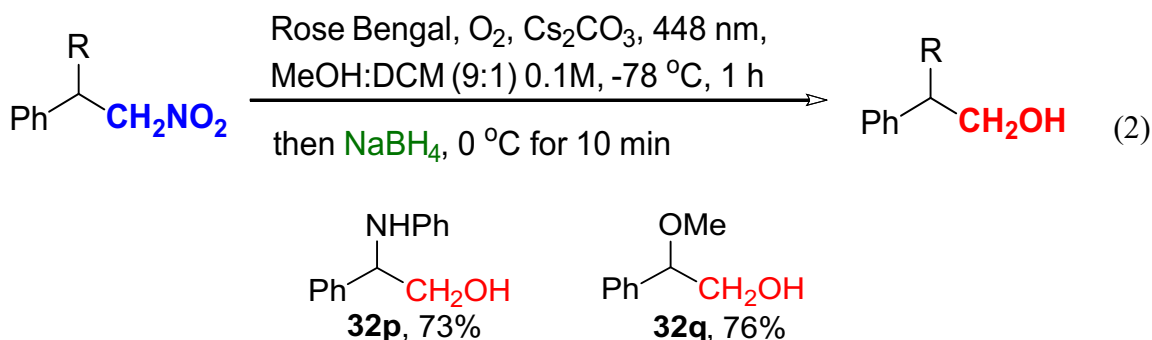
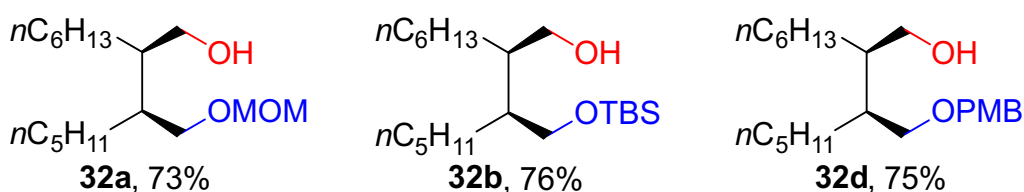
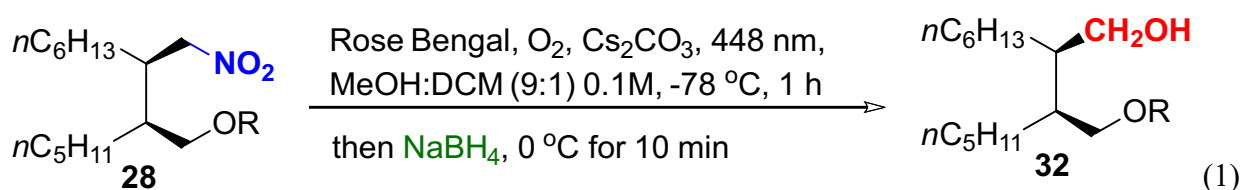
2-5 One-pot Reaction to Alcohol Derivatives

The one-pot reduction of nitromethyl compounds to hydroxymethyl derivatives using sodium borohydride (NaBH_4) demonstrates a significant improvement over conventional multi-step protocols. Traditionally, the conversion of a nitromethyl group to a hydroxymethyl group proceeds through oxidation to an intermediate aldehyde or carboxylic acid, followed by a separate reduction step. Such methods often require intermediate purification and the use of additional reagents such as $\text{BH}_3\text{-SMe}_2$. This was illustrated by Jørgensen (2008), who reported a two-step protocol involving aldehyde isolation prior to reduction.¹¹ These multi-step routes can lead to lower overall yields, increased material loss, and extended reaction times, particularly when sensitive or multifunctional substrates are involved.

In contrast, the current NaBH_4 -mediated one-pot protocol provides an operationally simple and highly efficient alternative. The reaction exhibits excellent reactivity, preserving a variety of common protecting groups, including acetals, silyl ethers, and PMB ethers, under the reduction conditions. This is evident from the high-yielding syntheses of alcohols **32a**, **32b**,

and **32d** (Figure 2-5. eqn (1)), indicating the method's tolerance toward acid- and base-sensitive functionalities.

Figure 2-5. One-pot conversion of nitromethyl group to hydroxymethyl group.



Notably, the protocol is also applicable to the preparation of more complex molecules, such as 1,2-aminoalcohol (**32p**) and 1,2-diol (**32q**) derivatives from nitro precursors **28p** and **28q**, respectively (Figure 2-5. eqn (2)). These substrates, which contain additional nucleophilic or electrophilic centers, could be prone to side reactions or competing reductions under less selective conditions. The successful conversion of these compounds highlights the method's functional group compatibility and substrate scope.

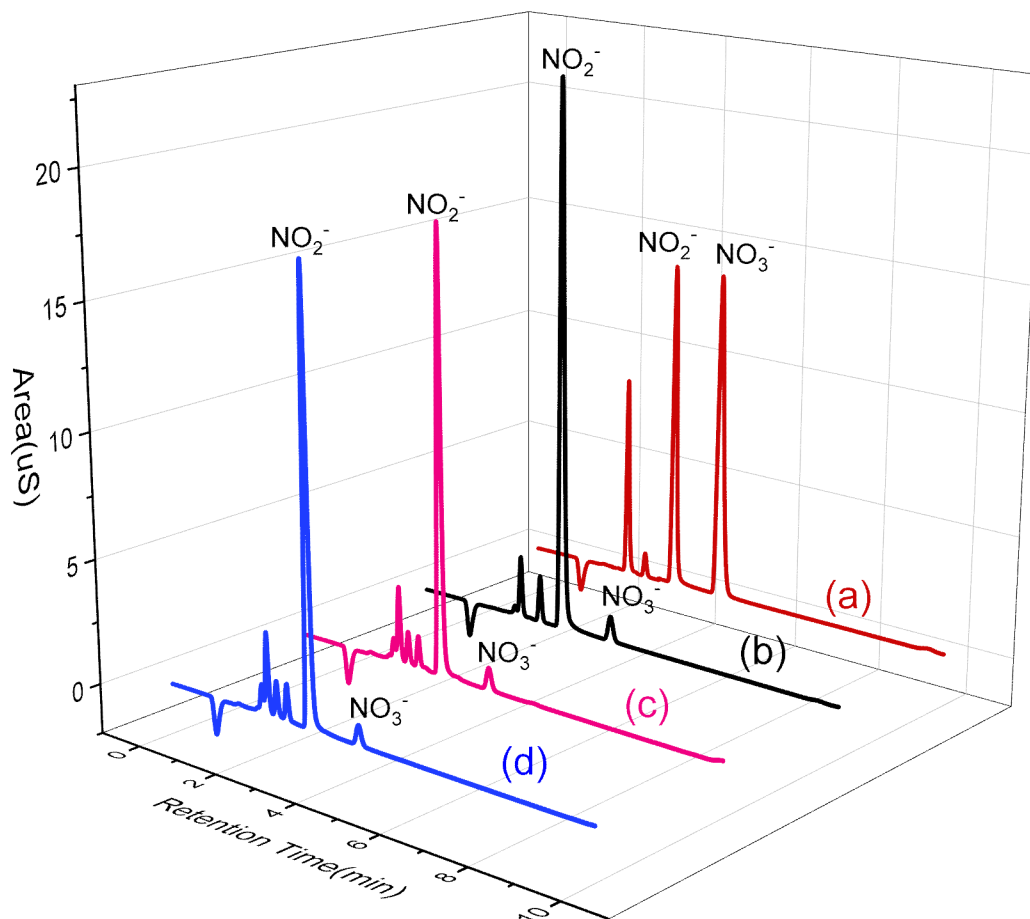
Overall, this one-pot NaBH_4 reduction offers a synthetically efficient route to hydroxymethylated products directly from nitromethyl precursors, avoiding the need for intermediate oxidation and purification. Its simplicity, selectivity, and broad applicability make it a valuable tool for synthesis of nitroalkane derivatives and polyfunctional substrates.

2-6 Mechanistic Investigation of the Aldehyde-Forming Nef Reaction

The Nef reaction serves as a valuable transformation for converting nitroalkanes into their corresponding carbonyl compounds. However, when aldehydes are the desired products, the reaction presents unique mechanistic challenges, particularly under mild or selective conditions. One significant complication is the regeneration of the starting material. Notably, the formation of peroxide intermediates has been proposed as a crucial step in determining the reaction's outcome.⁷ To better understand the influence of peroxide intermediates and to differentiate between the ionic and radical pathways involved in the Nef transformation, we investigated the role of dimethyl sulfide (Me_2S), a known peroxide-reducing agent, and *p*-benzoquinone (BQ), a commonly used radical scavenger. Diagnostic anions, namely nitrite (NO_2^-) and nitrate (NO_3^-), were monitored using ion chromatography, providing insight into the underlying mechanistic pathways.

Crude reaction mixtures derived from nitro compound **28a** were analyzed under various conditions. In the absence of Me_2S , both NO_2^- and NO_3^- ions were observed in the chromatogram (Figure 2-6 (a), red line), indicating the operation of at least two concurrent pathways. This finding was unexpected, as prior mechanistic proposals suggested that only NO_3^- would be formed, involving a proposed peroxide intermediate (denoted **12a**).¹² However, when Me_2S was added (Figure 2-6 (b), black line), the formation of NO_3^- was almost entirely suppressed. This supports the hypothesis that Me_2S reduces the peroxide bond, favoring the ionic pathway that selectively produces NO_2^- .

Figure 2-6. Ion chromatograms for detection of NO_2^- and NO_3^- .

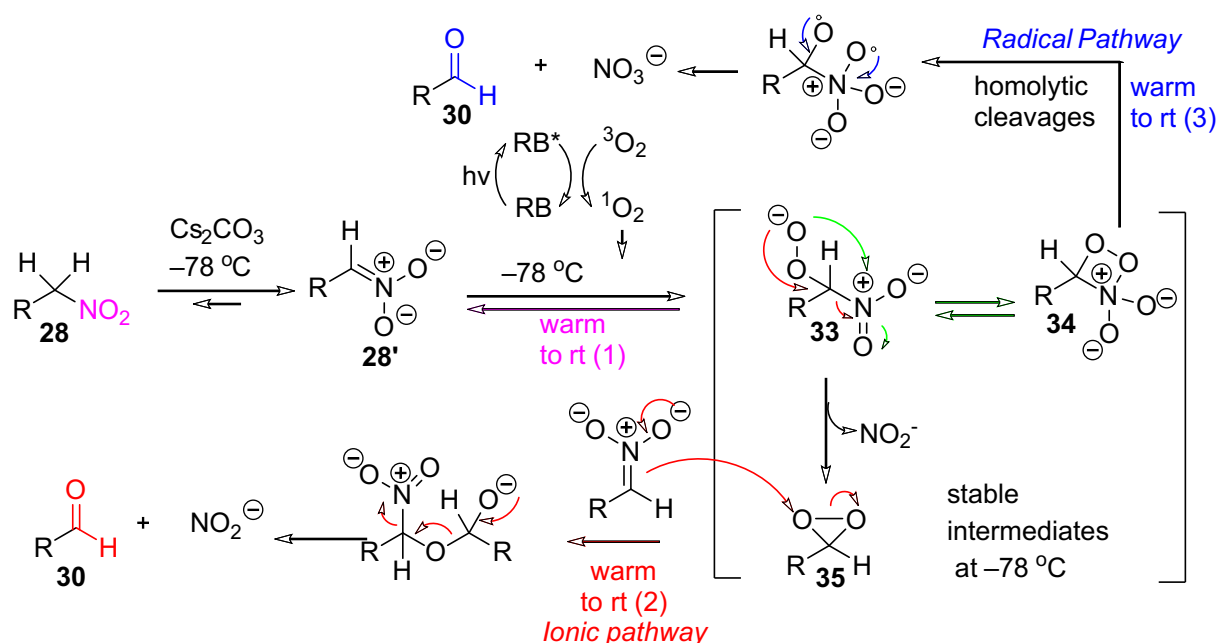


(a) Without Me_2S addition (**28a:30a** = 31:69; $[\text{NO}_2^-]$ = 0.403 mM and $[\text{NO}_3^-]$ = 0.456 mM), (b) With Me_2S addition (**28a:30a** = 0:100; $[\text{NO}_2^-]$ = 0.730 mM and $[\text{NO}_3^-]$ = 0.081 mM), (c) Radical Scavenger (*p*-benzoquinone 1.0 equiv)– without Me_2S addition (**28a:30a** = 42:58; $[\text{NO}_2^-]$ = 0.501 mM and $[\text{NO}_3^-]$ = 0.074 mM), (d) Radical Scavenger (*p*-benzoquinone 1.0 equiv)– with Me_2S addition (**28a:30a** = 17:83; $[\text{NO}_2^-]$ = 0.514 mM and $[\text{NO}_3^-]$ = 0.071 mM).

To further probe the radical contribution both in peroxide bond cleavage and reaction between oxygen species ($^1\text{O}_2$, O_2 radical anions) and nitronate ions, we carried out the Nef reaction in the presence of BQ.¹³ Ion chromatography revealed that NO_2^- was the dominant product (Figure 2-6 (c), pink line), suggesting that BQ inhibits the radical pathway responsible

for NO_3^- formation while leaving the ionic pathway unaffected. When both Me_2S and BQ were present (Figure 2-6 (d), blue line), the observed chromatographic profile was nearly identical to that seen with BQ alone. This reinforces the conclusion that NO_3^- arises exclusively from a radical-mediated pathway, whereas NO_2^- is formed through an ionic route.

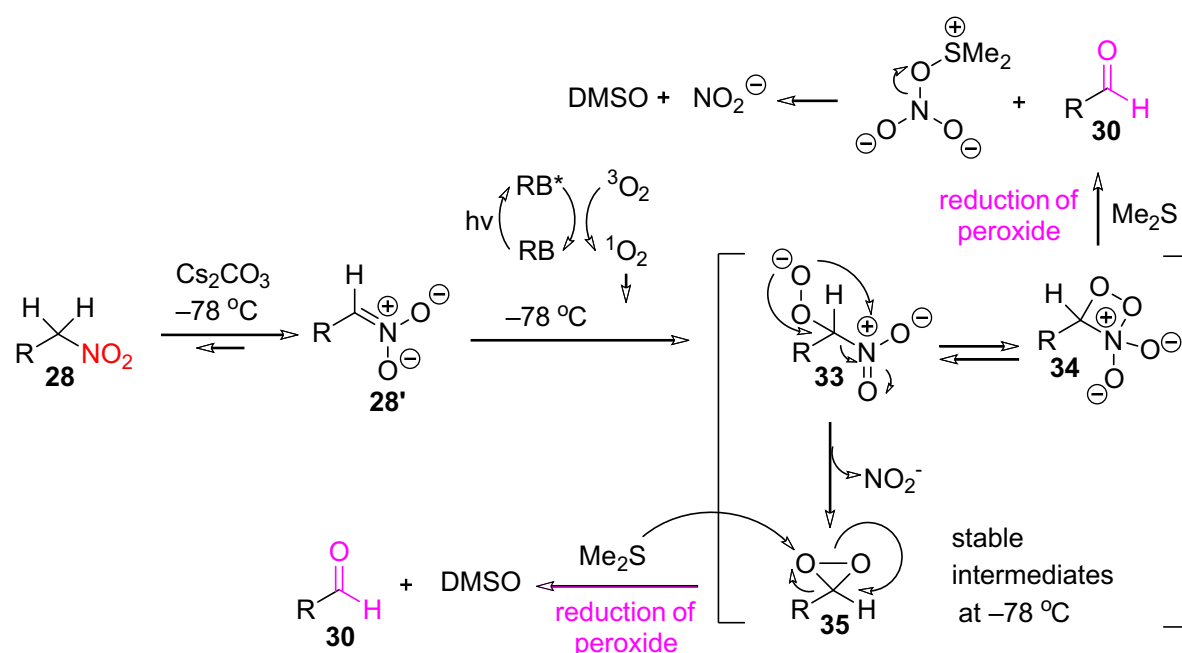
Figure 2-7. Proposed reaction mechanism without Me_2S .



A proposed mechanism consistent with the observations from Table 2-1 and Figure 2-6 is outlined in Figure 2-7. The reaction begins with the formation of nitronate ions **28'**, generated by deprotonation of the nitromethyl group in compound **28** using Cs_2CO_3 . This nitronate then reacts with singlet oxygen ($^1\text{O}_2$), an electrophilic oxygen species known to form peroxides under low-temperature conditions,¹⁴ yielding peroxide intermediates **33**, **34**, and **35**, which are stable at -78°C . The radical scavenger BQ does not inhibit the formation of these peroxides, indicating that this initial step is ionic in nature.

Upon warming to room temperature in the absence of Me₂S, the peroxides decompose via three possible pathways: (1) Regeneration of **28**: Reverse reaction undergoes by releasing oxygen species, which convert nitronate intermediate back into the starting nitro compound **28**, (2) Ionic pathway: Nitronate ions react with **35**, releasing NO₂[−] and generating aldehyde **30**, consistent with the pathway described by Hayashi¹⁵, (3) Radical pathway: A reaction involving radical species leads to the formation of NO₃[−] and **30**, which is significantly suppressed in the presence of BQ, confirming its radical character.

Figure 2-8. Proposed reaction mechanism with Me₂S.



When Me₂S is introduced at −78 °C (Figure 2-8), it reduces the peroxide intermediates, yielding aldehyde **30**, dimethyl sulfoxide (DMSO), and NO₂[−] as byproducts. This reductive pathway effectively prevents the regeneration of **28** by stabilizing the peroxides and avoiding

the release of reactive oxygen species. As a result, the stability of the peroxide intermediate at -78 °C and the use of Me₂S enables a more selective and efficient aldehyde-forming Nef reaction, minimizing side reactions such as the Henry condensation between the starting material **28** and the aldehyde product **30**. These mechanistic insights provide a basis for improving the selectivity and control of the Nef reaction under mild conditions, thereby facilitating its application in the synthesis of sensitive aldehydes.

Conclusion of Chapter 2

In conclusion of this chapter, the study presents a comprehensive optimization of a visible-light-mediated Nef reaction protocol for converting nitroalkanes into aldehydes under mild, selective, and functionally tolerant conditions. A detailed examination using model substrate **28a** demonstrated the importance of preserving stereochemical integrity and avoiding side reactions such as α -isomerization. Rose bengal, in combination with a 448 nm LED light source, was identified as the optimal photosensitizer for singlet oxygen generation, enabling efficient peroxide formation necessary for the transformation. Key reaction parameters, including base choice, light wavelength, and reducing agent, were finely tuned. Among the tested conditions, the use of Cs_2CO_3 and dimethyl sulfide (Me_2S) yielded the highest conversion to aldehyde **30a**, with minimal byproducts and excellent selectivity.

Substrate scope studies confirmed that the protocol is broadly applicable and compatible with various acid-, base-, and oxidation-sensitive functional groups. Protecting groups, TBS, PMB, and benzyl ethers remained intact, and even sterically hindered nitroalkanes were successfully converted to aldehydes. Moreover, the reaction's ability to proceed under mild conditions allowed it to outperform previously reported two-step protocols both in terms of yield and operational simplicity. The method's chemoselectivity was further highlighted by its tolerance to complex substrates, enabling the synthesis of cyclic acetals and aromatic aldehydes without compromising sensitive functional groups.

A one-pot extension of the method was developed for the reduction of nitromethyl groups to hydroxymethyl groups using NaBH_4 . This streamlined alternative to traditional multi-step routes eliminates the need for intermediate oxidation and purification. The protocol maintained compatibility with a wide range of functional groups and proved effective for synthesizing complex alcohol products, such as 1,2-amino alcohols and diols, from multifunctional nitro

precursors. This step-economical process demonstrates the method's potential in facilitating rapid access to valuable building blocks in organic synthesis.

Mechanistic studies, supported by ion chromatography, revealed a dual-pathway system involving both ionic and radical intermediates. The presence of Me₂S favored the ionic pathway, selectively yielding NO₂⁻ and aldehyde product while suppressing the formation of NO₃⁻ associated with the radical route. These insights into peroxide formation and decomposition underscore the value of precise control over the reaction environment. Collectively, this work provides a robust and general strategy for aldehyde synthesis from nitroalkanes and initiating the applications of photochemically driven Nef reactions in complex molecule synthesis.

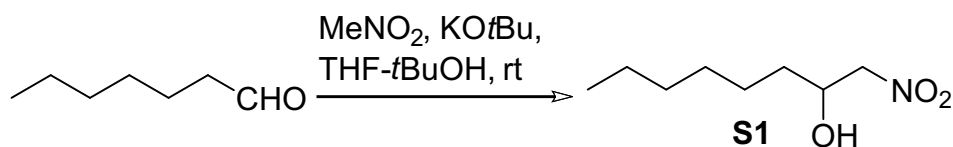
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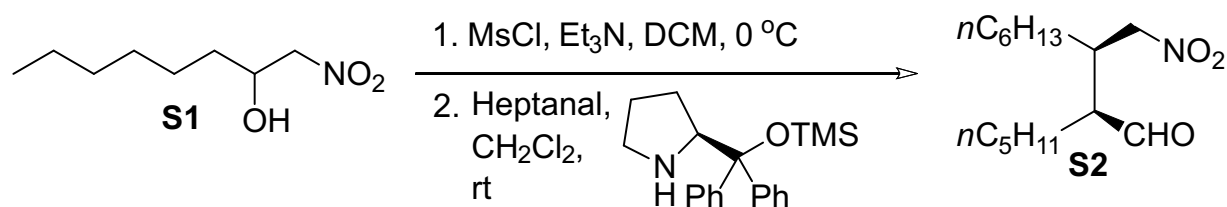
Experimental Section of Chapter 2

Tetrahydrofuran (THF), methanol (CH₃OH), and acetonitrile (CH₃CN) were purchased from Kanto Chemical Co. Inc. Dichloromethane (CH₂Cl₂) and triethylamine (Et₃N) were distilled from CaH₂. All commercially obtained reagents were employed as received. Analytical TLC was carried out using pre-coated silica gel plates (Wako TLC Silicagel 70F₂₅₄, FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan). Wakogel 60N 63-212 μ m was used for column chromatography. Optical rotation was measured with a JASCO P2200 polarimeter. ESI-MS were obtained on a JEOL JMS-700TZ (JEOL Ltd., Tokyo, Japan) or BRUKER DALTONICS micro TOF-HS focus spectrometer (Bruker Japan Ltd., Yokohama, Japan). Irradiations of photoreactions were carried out using a blue LED lamp (PER-AMR-448, λ_{max} = 448 nm, Techno Sigma Co., Ltd.) with the following operating conditions: 3.5 V, 350 mA. The ¹H NMR and ¹³C NMR spectra were recorded using a JNM-ECZR 500 (500 MHz and 126 MHz, respectively) spectrometer (JEOL Ltd., Tokyo, Japan). Chemical shifts were reported in ppm relative to CHCl₃ in CDCl₃ for ¹H NMR (δ = 7.24) and ¹³C NMR (δ = 77.0). Splitting patterns for ¹H NMR were designated as “s, d, t, q, m, dt, dd, and td”. These symbols indicate “singlet, doublet, triplet, quartet, multiplet, doublettriplet, doubletdoublet, and tripletdoublet” respectively.



1-nitrooctan-2-ol (S1). To a solution of heptanal (3.00 mL, 21.7 mmol) in THF-*t*BuOH (72 mL, 1:1 v/v) was added MeNO₂ (2.60 mL, 47.7 mmol) and KOtBu (970 mg, 8.70 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 1 h, quenched with saturated NaHCO₃, extracted with AcOEt, dried over Na₂SO₄, filtered and concentrated *in*

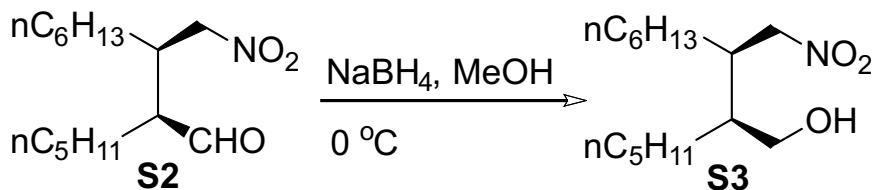
vacuo. The residue was purified by silica gel column chromatography (hexane: AcOEt = 98:2, 96:4 then 94:6) to obtain **S1** (1.56 g, 13.4 mmol, 62%) as a colorless oil: IR (neat) 3424, 2955, 2930, 2858, 1556, 1465, 1421, 1382, 1287, 1207, 1132, 1091, 970, 889, 790, 648 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 4.42 (1H, dd, $J = 12.5, 2.6$ Hz), 4.36 (1H, dd, $J = 13.0, 8.5$ Hz), 4.28-4.33 (1H, m), 2.47 (1H, d, $J = 4.4$ Hz), 1.45-1.58 (4H, m), 1.23-1.40 (6H, m), 0.87 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) δ 80.6, 68.6, 33.7, 31.6, 28.9, 25.1, 22.5, 14.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$; Calcd for $\text{C}_8\text{H}_{17}\text{NNaO}_3$ 198.1108; Found 198.1108.



(2S,3R)-3-(nitromethyl)-2-pentylnonanal (S2). To a solution of **S1** (1.20 g, 10.3 mmol) in CH_2Cl_2 (35 mL) were added NEt_3 (3.65 mL, 25.8 mmol) and MsCl (1.12 mL, 14.5 mmol) at 0 $^\circ\text{C}$ under Ar atmosphere. After stirring for 5 min, the mixture was quenched with saturated NH_4Cl , extracted with AcOEt, washed with brine, dried over Na_2SO_4 , filtered through a short silica gel pad and concentrated *in vacuo*. The crude nitro compound was employed directly in the next reaction.

To a solution of (*S*)-Hayashi-Jørgensen catalyst (340 mg, 1.03 mmol) in DCM (7.0 mL) were added the crude nitro in DCM (14 mL) and heptanal (141 μL , 12.4 mmol) at 0 $^\circ\text{C}$ to room temperature under Ar atmosphere. The mixture was stirred for 18 h at 0 $^\circ\text{C}$, quenched with HCl 0.1 N, extracted with AcOEt, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane: AcOEt = 99.5:0.5, 99.2:0.8 then 99:1) to obtain the **S2** (2.12 g, 7.43 mmol, 72% over 2 steps) as a colorless oil. The following data were collected from a mixture of diastereomers ($\text{dr} = 7.3:1$): $[\alpha]_{\text{D}}^{24} +135.0$ (c 0.40, CHCl_3); IR (neat) 2956, 2930, 2858, 1706, 1555, 1465, 1434, 1379, 1231, 1173, 1117,

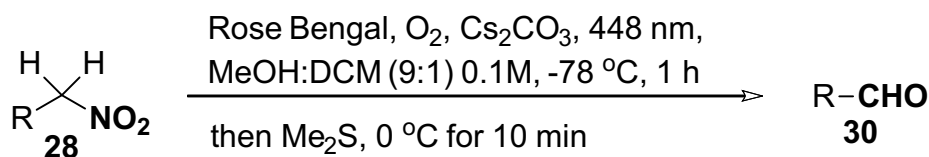
940, 837, 724 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.66 (1H, d, $J = 1.6$ Hz), 4.36-4.46 (2H, m), 2.59-2.62 (1H, m), 2.42-2.43 (1H, m), 1.69-1.71 (1H, m), 1.36-1.40 (1H, m), 1.23-1.33 (16H, m), 0.83-0.88 (6H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 203.2, 52.3, 37.1, 31.8, 31.5, 29.1, 29.1, 29.0, 27.3, 26.7, 25.4, 22.5, 22.4, 14.0, 13.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$; Calcd for $\text{C}_{15}\text{H}_{29}\text{NNaO}_3$ 294.2030; Found 294.2040.



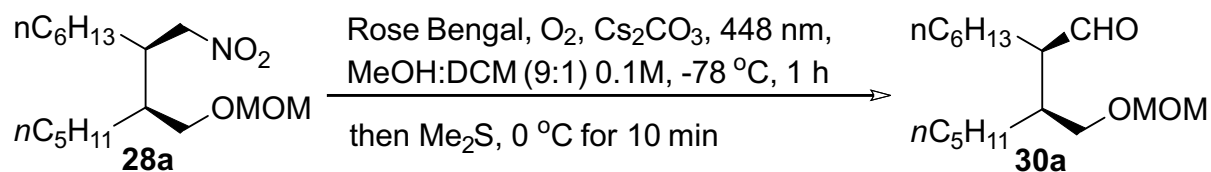
(2S,3R)-3-(nitromethyl)-2-pentynon-1-ol (S3). To a solution of **S2** (2.00 g, 7.31 mmol) in MeOH (21 mL) was added NaBH_4 (400 mg, 10.5 mmol) at 0 $^\circ\text{C}$ under Ar atmosphere. After stirring for 15 min, the mixture was quenched with saturated NaHCO_3 , extracted with AcOEt, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane: AcOEt = 98:2 then 95:5) to obtain **S3** (1.78 g, 6.51 mmol, 93%) as a colorless oil: $[\alpha]_{\text{D}}^{24} +24.5$ (c 0.35, CHCl_3); IR (neat) 3407, 2958, 2928, 2857, 1712, 1551, 1465, 1433, 1379, 1212, 1121, 1038, 908, 724, 637 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 4.44 (1H, dd, $J = 12.4, 6.1$ Hz), 4.36 (1H, dd, $J = 12.4, 7.9$ Hz), 3.66 (1H, dd, $J = 11.0, 4.2$ Hz), 3.56 (1H, dd, $J = 10.9, 6.0$ Hz), 2.41-2.44 (1H, m), 1.59-1.62 (1H, m), 1.42-1.46 (1H, m), 1.25-1.34 (17H, m), 0.84-0.89 (6H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 78.3, 62.3, 41.0, 38.9, 32.0, 31.6, 29.3, 29.1, 28.1, 27.4, 27.0, 22.6, 22.5, 14.0, 14.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$; Calcd for $\text{C}_{15}\text{H}_{31}\text{NNaO}_3$ 296.2193; Found 296.2196.



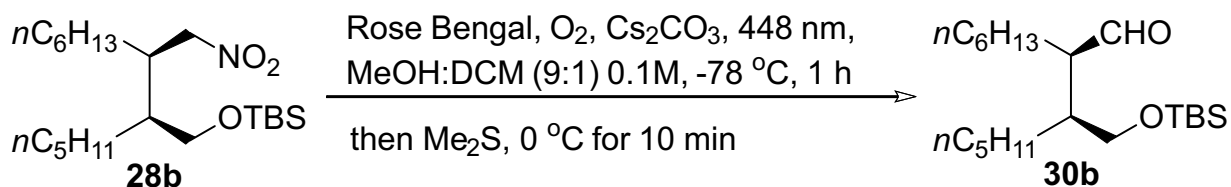
2-(3-(nitromethyl)oxetan-3-yl)ethan-1-ol (S4). To a solution of ethyl 2-(3-(nitromethyl)oxetan-3-yl)acetate (150 mg, 0.738 mmol) in CH₂Cl₂ (2.5 mL) was added a solution of DIBAL-H (2.21 mL, 1M in hexane, 2.21 mmol) dropwise at 0 °C under Ar atmosphere. After stirring for 30 min, the mixture was quenched with saturated Na-K tartrate. The biphasic mixture was stirred for 2 h, extracted with AcOEt, washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane: AcOEt = 60:40, 55:45 then 50:50) to obtain **S4** (92.8 mg, 0.583 mmol, 78%) as a colorless oil : IR (neat) 3408, 2925, 2885, 1550, 1435, 1383, 1277, 1146, 1061, 1020, 976, 902, 840, 689cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 2.07 (2H, t, *J* = 5.9 Hz), 3.78 (2H, t, *J* = 5.9 Hz), 4.58 (4H, dd, *J* = 12.0, 6.8 Hz), 4.88 (2H, s); ¹³C NMR (CDCl₃, 126 MHz) δ 35.6, 41.7, 58.7, 78.9, 79.2, 79.2; HRMS (ESI) *m/z*: [M+Na]⁺; Calcd for C₆H₁₁NNaO₄ 184.0590; Found 184.0580.



General Procedure for Aldehyde-forming Nef reaction. A two-neck glass vessel was charged with a solution of **28** (0.200 mmol) in MeOH-DCM (2.0 mL, 9:1 v/v), Cs₂CO₃ (97.6 mg, 0.300 mmol), rose Bengal (10.0 mg, 0.0100 mmol). The mixture was stirred and bubbled with O₂ gas at 0 °C for 1 min, cooled to at -78 °C, irradiated LED light (λ_{max} = 448 nm, 680 mW) directly in the solution under O₂ atmosphere with stirring at -78 °C. After 1 h, Me₂S (44.0 μL, 0.600 mmol) was added to the mixture, stirred for 10 min at room temperature. The mixture was then filtered through a short path silica gel pad and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane: AcOEt) to give **30**.

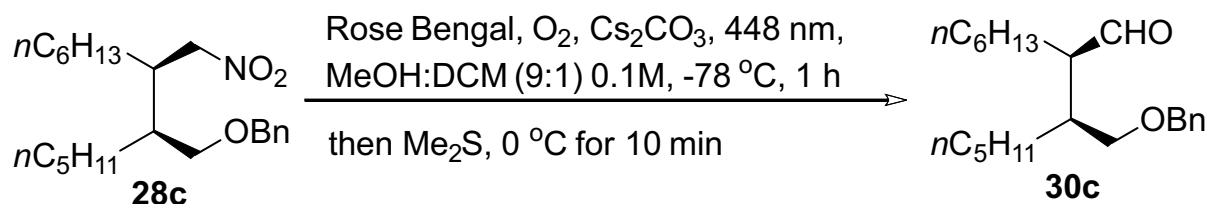


(2R,3S)-2-hexyl-3-((methoxymethoxy)methyl)octanal (30a). Starting from **28a** (63.5 mg, 0.200 mmol) to obtain **30a** (48.7 mg, 0.169 mmol, 85%, for silica gel column chromatography (hexane: AcOEt = 99.5:0.5 then 99:1) as a colorless oil: $[\alpha]_{\text{D}}^{24} +155.7$ (c 0.56, CHCl_3); IR (neat) 2928, 2857, 1724, 1703, 1552, 1465, 1379, 1214, 1152, 1110, 1046, 920, 725 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.62 (1H, d, $J = 2.7$ Hz), 4.54 (2H, dd, $J = 2.8$ Hz), 3.54 (1H, dd, $J = 9.7, 4.3$ Hz), 3.40 (1H, dd, $J = 9.8, 6.7$ Hz), 3.31 (3H, s), 2.31-2.33 (1H, m), 1.95-1.98 (1H, m), 1.64-1.68 (1H, m), 1.24-1.35 (17H, m), 0.83-0.87 (6H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 205.3, 96.6, 68.0, 55.4, 53.8, 39.6, 32.0, 31.6, 29.4, 29.0, 27.8, 27.0, 25.8, 22.6, 22.5, 14.0, 14.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$; Calcd for $\text{C}_{17}\text{H}_{34}\text{NaO}_3$ 309.2379; Found 309.2400.

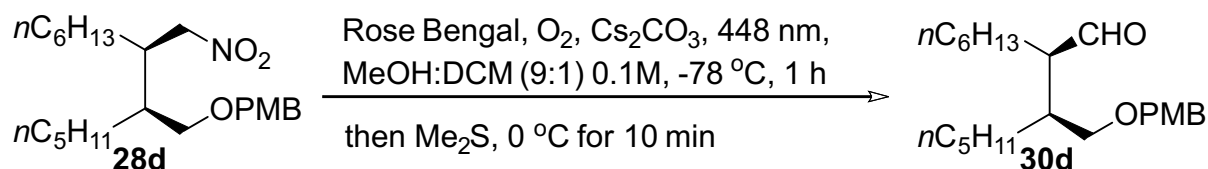


(2R,3S)-3-(((tert-butyldimethylsilyl)oxy)methyl)-2-hexyloctanal (30b). Starting from **28b** (77.5 mg, 0.200 mmol) to obtain **30b** (51.4 mg, 0.144 mmol, 72%), for silica gel column chromatography (hexane: AcOEt = 99.8:0.2, 99.6:0.4 then 99.5:0.5) as a colorless oil and starting from **28b** (388 mg, 1.00 mmol) to obtain **30b** (250 mg, 0.701 mmol, 70%) as a colorless oil: $[\alpha]_{\text{D}}^{24} +130.9$ (c 0.42, CHCl_3); IR (neat) 2955, 2928, 2857, 1703, 1553, 1463, 1414, 1379, 1361, 1254, 1099, 837, 776, 668 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.63 (1H, d, $J = 2.7$ Hz), 3.64 (1H, dd, $J = 10.0, 4.5$ Hz), 3.46 (1H, dd, $J = 10.2, 6.2$ Hz), 2.29-2.34 (1H, m), 1.82-1.88

(1H, m), 1.62-1.70 (1H, m), 1.25-1.31 (17H, m), 0.85-0.86 (15H, m), 0.01 (6H, s); ^{13}C NMR (CDCl_3 , 126 MHz) δ 205.6, 62.8, 53.6, 42.1, 32.0, 31.7, 29.4, 28.7, 27.9, 27.1, 25.8, 25.7, 22.6, 22.5, 18.2, 14.0, -5.6, -5.6; HRMS (ESI-TOF) m/z : $[\text{M} - \text{H}]^-$; Calcd for $\text{C}_{21}\text{H}_{43}\text{O}_2\text{Si}$ 355.3032; Found 355.3027.

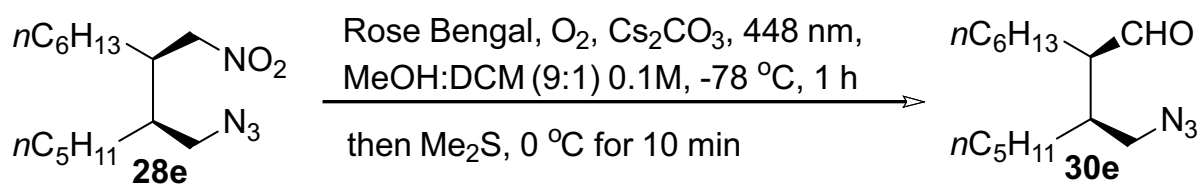


(2R,3S)-3-((benzyloxy)methyl)-2-hexyloctanal (30c). Starting from **28c** (72.7 mg, 0.200 mmol) to obtain **30c** (45.2 mg, 0.136 mmol, 68%), for silica gel column chromatography (hexane: AcOEt = 99.8:0.2, 99.6:0.4 then 99.4:0.6) as a colorless oil: $[\alpha]_{\text{D}}^{24} +253.6$ (c 0.28, CHCl_3); IR (neat) 2954, 2928, 2857, 2349, 1721, 1612, 1513, 1465, 1361, 1302, 1248, 1172, 1096, 1036, 821, 725 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.66 (1H, d, $J = 4.0$ Hz), 7.25-7.35 (5H, m), 4.47 (2H, s), 3.46-3.48 (2H, m), 2.62-2.64 (1H, m), 2.48-2.50 (1H, m), 1.80-1.83 (1H, m), 1.67-1.72 (1H, m), 1.52-1.62 (2H, m), 1.24-1.31 (14H, m), 0.81-0.90 (6H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 205.4, 138.3, 128.4, 128.4, 127.8, 127.7, 127.6, 73.1, 72.1, 70.6, 54.0, 39.9, 32.0, 31.7, 29.4, 29.0, 27.9, 27.1, 25.9, 22.6, 14.1, 14.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$; Calcd for $\text{C}_{22}\text{H}_{36}\text{NaO}_2$ 355.2586; Found 355.2608.

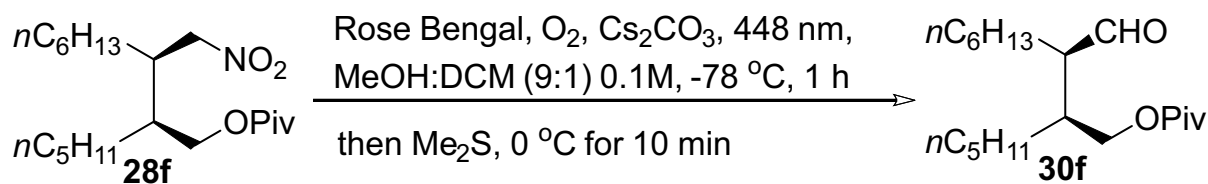


(2R,3S)-2-hexyl-3-(((4-methoxybenzyl)oxy)methyl)octanal (30d). Starting from **28d** (78.7 mg, 0.200 mmol) to obtain **30d** (40.7 mg, 0.112 mmol, 56%), for silica gel column

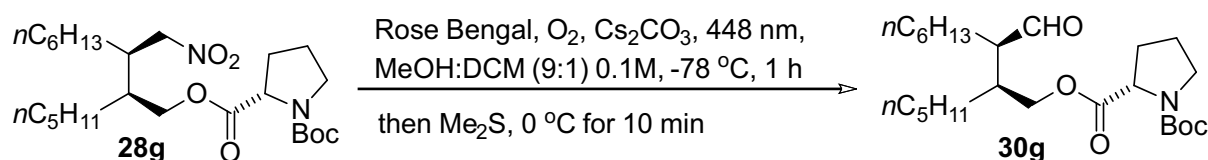
chromatography (hexane: AcOEt = 99.2:0.8 then 99:1) as a colorless oil: $[\alpha]_{\text{D}}^{24} -214.7$ (c 0.34, CHCl_3); IR (neat) 3031, 2954, 2927, 2857, 1702, 1496, 1454, 1362, 1205, 1099, 1028, 735, 697 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.60 (1H, d, $J = 3.0$ Hz), 7.21 (2H, d, $J = 8.9$ Hz), 6.86 (2H, d, $J = 8.4$ Hz), 4.43 (1H, d, $J = 9.9$ Hz), 4.36 (1H, d, $J = 7.2$ Hz), 3.79 (3H, s), 3.42-3.46 (1H, m), 3.28 (1H, dd, $J = 9.4, 7.2$ Hz), 2.56-2.61 (1H, m), 1.86-1.89 (1H, m), 1.84-1.89 (1H, m), 1.32-1.41 (1H, m), 1.15-1.31 (16H, m), 0.84-0.87 (6H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 205.4, 159.1, 130.2, 129.4, 129.3, 113.8, 113.7, 72.7, 70.3, 55.2, 54.0, 39.9, 32.0, 31.6, 29.4, 29.0, 27.8, 27.0, 25.8, 22.6, 22.5, 14.0, 14.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$; Calcd for $\text{C}_{23}\text{H}_{38}\text{NaO}_3$ 385.2704; Found 385.2713.



(2R,3S)-3-(azidomethyl)-2-hexyloctanal (30e). Starting from **28e** (59.7 mg, 0.200 mmol) to obtain **30e** (37.9 mg, 0.142 mmol, 71%), for silica gel column chromatography (hexane: AcOEt = 99.8:0.2 then 99.6:0.4) as a colorless oil: $[\alpha]_{\text{D}}^{24} +132.1$ (c 0.56, CHCl_3); IR (neat) 2956, 2929, 2859, 2099, 1704, 1553, 1459, 1419, 1379, 1349, 1285, 1237, 1175, 1117, 937, 795, 725, 664 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.65 (1H, d, $J = 2.3$ Hz), 3.40 (1H, dd, $J = 12.4, 5.2$ Hz), 3.29 (1H, dd, $J = 12.5, 6.8$ Hz), 2.34-2.37 (1H, m), 1.95-2.00 (1H, m), 1.64-1.68 (1H, m), 1.23-1.36 (17H, m), 0.85-0.87 (6H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 204.6, 53.3, 52.7, 38.9, 31.9, 31.6, 29.4, 29.1, 27.8, 26.8, 25.3, 22.6, 22.5, 14.0, 14.0; HRMS (ESI-TOF) m/z : $[\text{M} - \text{N}_2]^-$; Calcd for $\text{C}_{15}\text{H}_{30}\text{NO}$ 240.2322; Found 240.2322.

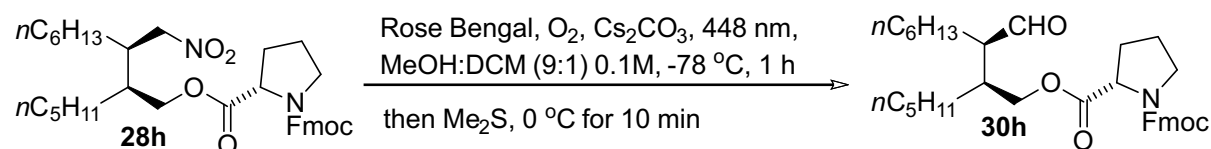


(2*S*,3*R*)-3-formyl-2-pentynonyl pivalate (30f). Starting from **28f** (71.5 mg, 0.200 mmol) to obtain **30f** (44.4 mg, 0.136 mmol, 68%), for silica gel column chromatography (hexane: AcOEt = 99.8:0.2, 99.6:0.4 then 99.2:0.8) as a colorless oil: $[\alpha]_{\text{D}}^{24} +67.9$ (c 0.28, CHCl_3); IR (neat) 2957, 2930, 2859, 1732, 1706, 1554, 1480, 1462, 1398, 1379, 1366, 1283, 1228, 1158, 1035, 940, 770, 725 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.63 (1H, d, $J = 1.6$ Hz), 3.98-4.07 (2H, m), 2.28-2.31 (1H, m), 2.04-2.08 (1H, m), 1.65-1.70 (1H, m), 1.23-1.31 (17H, m), 1.14-1.15 (9H, m), 0.82-0.85 (6H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 204.6, 178.3, 64.4, 53.5, 38.8, 38.4, 31.9, 31.6, 29.3, 28.7, 27.8, 27.1, 26.9, 25.6, 22.5, 22.4, 14.0, 13.9; HRMS (APCI) m/z : $[\text{M} - \text{CHO}]^+$; Calcd for $\text{C}_{19}\text{H}_{37}\text{O}_2$ 297.2793; Found 297.2788.

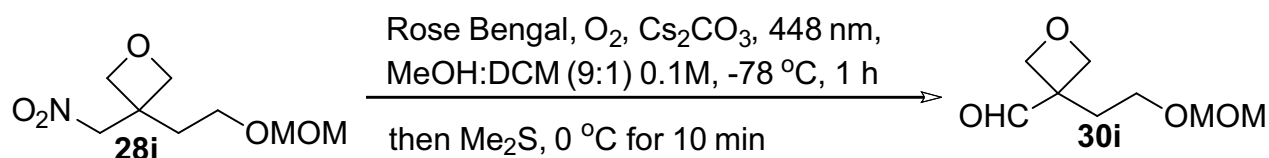


1-(*tert*-butyl) 2-((2*S*,3*R*)-3-(nitromethyl)-2-pentynonyl) (*R*)-pyrrolidine-1,2-dicarboxylate (30g). Starting from **28g** (94.1 mg, 0.200 mmol) to obtain **30g** (64.1 mg, 0.146 mmol, 73%), for silica gel column chromatography (hexane: AcOEt = 95:5 then 92:8) as a colorless oil: $[\alpha]_{\text{D}}^{20} -27.3$ (c 1.00, CHCl_3); IR (neat) 2955, 2929, 2859, 1742, 1395, 1366, 1257, 1165, 1126, 1087, 1031, 974, 856 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) (mixture of rotamers) δ 9.65 (1H, d, $J = 7.5$ Hz), 4.05-4.25 (3H, m), 3.35-3.62 (2H, m), 2.06-2.39 (3H, m), 1.66-1.88 (3H, m), 1.37-1.41 (9H, m), 1.10-1.31 (18H, m), 0.72-0.95 (6H, m); ^{13}C NMR (CDCl_3 , 126

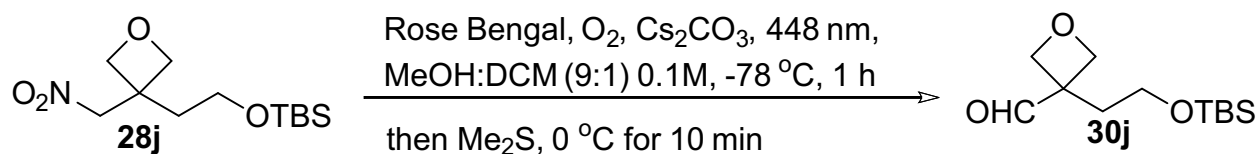
MHz) (mixture of rotamers) δ 205.0, 204.5, 173.1, 172.9, 154.4, 153.8, 80.0, 79.8, 77.4, 77.1, 76.9, 65.2, 59.2, 59.0, 53.5, 53.3, 46.6, 46.4, 38.4, 38.3, 31.9, 31.8, 31.7, 30.9, 30.0, 29.4, 28.8, 28.6, 28.5, 28.4, 27.9, 27.9, 27.1, 27.0, 25.8, 25.6, 24.5, 23.7, 22.6, 22.6, 14.1, 14.1; HRMS (ESI- TOF) m/z : $[M + H]^+$; Calcd for $C_{25}H_{46}NO_5$ 440.3366; Found 440.3370.



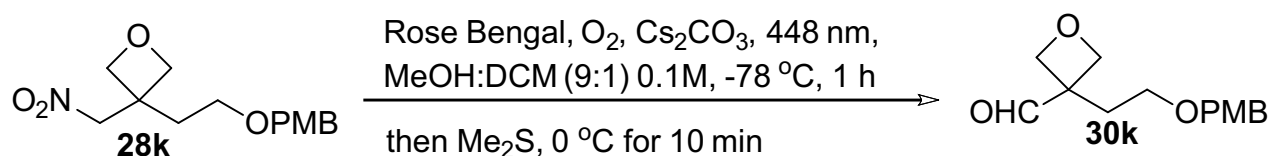
1-((9H-fluoren-9-yl)methyl) 2-((2S,3R)-3-(nitromethyl)-2-pentynonyl) (R)-pyrrolidine-1,2-dicarboxylate (30h). Starting from **28h** (118 mg, 0.200 mmol) to obtain **30h** (88.8 mg, 0.158 mmol, 79%), for silica gel column chromatography (hexane: AcOEt = 95:5 then 93:7) as a colorless oil: $[\alpha]_D^{20}$ -36.8 (c 1.00, CHCl₃); IR (neat) 2954, 2927, 2857, 1710, 1556, 1451, 1417, 1349, 1278, 1174, 1120, 1089, 990, 759, 740 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) (mixture of rotamers) δ 9.58 (1H, d, J = 7.2 Hz), 7.72-7.75 (2H, m), 7.53-7.62 (2H, m), 7.25-7.39 (4H, m), 4.25-4.42 (4H, m), 4.00-4.17 (2H, m), 3.58-3.67 (1H, m), 3.47-3.58 (1H, m), 2.18-2.31 (2H, m), 1.93-2.09 (4H, m), 1.13-1.46 (18H, m), 0.81-0.91 (6H, m); ¹³C NMR (CDCl₃, 126 MHz) (mixture of rotamers) δ 204.7, 204.3, 172.4, 172.4, 154.8, 144.1, 144.0, 141.2, 127.6, 127.0, 125.1, 125.0, 125.0, 120.0, 119.9, 67.6, 67.5, 65.3, 65.3, 59.3, 58.9, 53.4, 53.3, 47.2, 47.2, 47.0, 46.5, 46.4, 38.3, 38.1, 31.8, 31.7, 31.6, 31.0, 29.8, 29.6, 29.3, 28.8, 28.6, 28.6, 28.2, 28.1, 27.8, 27.0, 26.8, 25.7, 25.6, 24.7, 24.4, 23.4, 23.4, 22.5, 22.4, 14.0, 14.0, 13.9, 13.9; HRMS (ESI-TOF) m/z : $[M + Na]^+$; Calcd for $C_{35}H_{47}NNaO_5$ 584.3351; Found 584.3346.



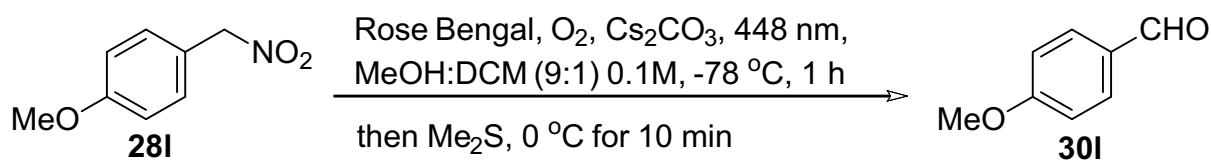
3-(2-(methoxymethoxy)ethyl)oxetane-3-carbaldehyde (30i). Starting from **28i** (41.0 mg, 0.200 mmol) to obtain **30i** (30.7 mg, 0.176 mmol, 88%), for silica gel column chromatography (hexane: AcOEt = 90:10 then 80:20) as a colorless oil: IR (neat) 2928, 2858, 1724, 1703, 1552, 1466, 1379, 1215, 1152, 1110, 1046, 920, 725 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.83 (1H, s), 4.82 (2H, d, $J = 6.3$ Hz), 4.57 (2H, d, $J = 6.3$ Hz), 4.48 (2H, s), 3.54 (2H, t, $J = 5.9$ Hz), 3.26 (3H, s), 2.30 (2H, t, $J = 5.9$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) δ 200.2, 96.3, 75.6, 75.5, 63.2, 55.3, 51.7, 32.8; HRMS (APCI) m/z : $[\text{M} - \text{OMe}]^+$; Calcd for $\text{C}_7\text{H}_{11}\text{O}_3$ 143.0712; Found 143.0703.



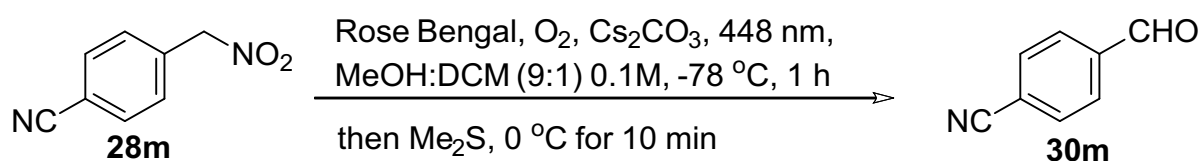
3-(2-((tert-butyldimethylsilyl)oxy)ethyl)oxetane-3-carbaldehyde (30j). Starting from **28j** (55.1 mg, 0.200 mmol) to obtain **30j** (40.6 mg, 0.166 mmol, 83%), for silica gel column chromatography (hexane: AcOEt = 95:5 then 93:7) as a colorless oil: IR (neat) 2955, 2929, 2885, 2858, 1735, 1710, 1558, 1472, 1436, 1390, 1361, 1255, 1208, 1104, 984, 939, 835, 811 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.83 (1H, s), 4.80 (2H, d, $J = 6.4$ Hz), 4.56 (2H, d, $J = 6.4$ Hz), 3.64 (2H, t, $J = 5.7$ Hz), 2.24 (2H, t, $J = 5.7$ Hz), 0.83 (9H, t, $J = 2.9$ Hz), -0.02 (6H, s); ^{13}C NMR (CDCl_3 , 126 MHz) δ 200.6, 75.9, 75.9, 58.9, 51.7, 35.9, 25.8, 18.5, 18.1, 17.5, -5.7 , -5.7 ; HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$; Calcd for $\text{C}_{12}\text{H}_{25}\text{O}_3\text{Si}$ 245.1564; Found 245.1567.



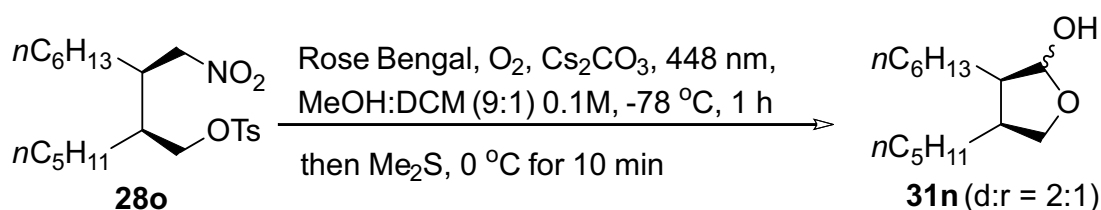
3-(2-((4-methoxybenzyl)oxy)ethyl)oxetane-3-carbaldehyde (30k). Starting from **28k** (56.3 mg, 0.200 mmol) to obtain **30k** (40.0 mg, 0.159 mmol, 80%), for silica gel column chromatography (hexane: AcOEt = 93:7, 90:10 then 85:15) as a white solid: IR (neat) 3372, 3320, 3245, 3188, 1694, 1614, 1513, 1382, 1247, 1109, 834, 649 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 9.66 (1H, s), 7.18-7.21 (2H, m), 6.85-6.87 (2H, m), 4.43 (2H, s), 4.05 (1H, d, $J = 9.5$ Hz), 3.79 (2H, s), 3.69 (1H, d, $J = 9.5$ Hz), 3.65 (1H, d, $J = 9.0$ Hz), 3.57 (1H, d, $J = 9.2$ Hz), 2.14-2.19 (1H, m), 1.76-1.81 (1H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 200.5, 179.2, 129.8, 129.2, 129.2, 116.2, 113.7, 76.7, 75.7, 72.8, 65.4, 55.2, 51.7, 33.1; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$; Calcd for $\text{C}_{14}\text{H}_{18}\text{NaO}_4$ 273.1113; Found 273.1097.



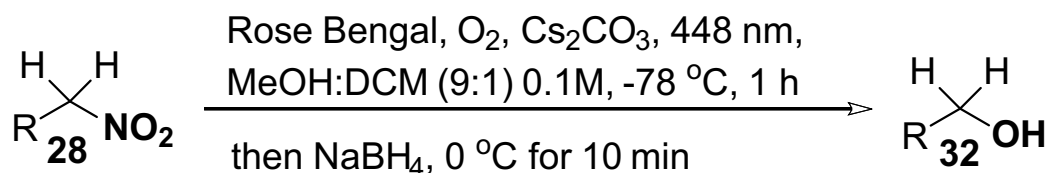
4-methoxybenzaldehyde (30l). Starting from **28l** (33.4 mg, 0.200 mmol) to obtain **30l** (16.6 mg, 0.122 mmol, 61%), for silica gel column chromatography (hexane: AcOEt = 98:2 then 95:5) as a colorless oil: ^1H NMR (CDCl_3 , 500 MHz) δ 9.79 (1H, s), 7.83-7.80 (2H, m), 6.97 (2H, m), 3.86 (3H, s); ^{13}C NMR (CDCl_3 , 126 MHz) δ 189.8, 161.8, 128.4, 124.7, 111.6, 55.6.



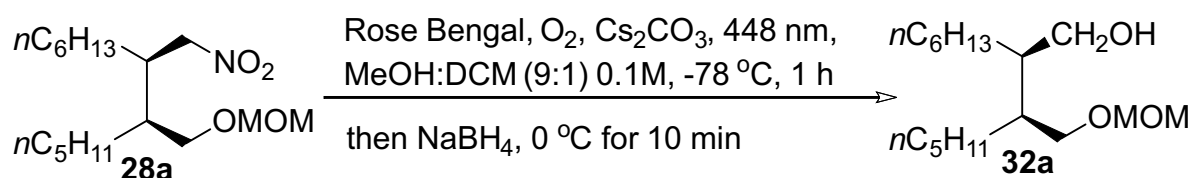
4-formylbenzonitrile (30m). Starting from **28m** (32.4 mg, 0.200 mmol) to obtain **30m** (20.9 mg, 0.159 mmol, 80%), for silica gel column chromatography (hexane: AcOEt = 99:1 then 97:3) as a white solid: ^1H NMR (CDCl_3 , 500 MHz) δ 10.07 (1H, s), 7.97 (2H, d, $J = 8.3$ Hz), 7.83 (2H, d, $J = 8.0$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) δ 190.6, 138.7, 132.9, 129.9, 117.7, 117.6.



(3R,4S)-3-hexyl-4-pentyltetrahydrofuran-2-ol (31n). Starting from **28o** (53.5 mg, 0.200 mmol) to obtain **31n** (33.4 mg, 0.138 mmol, 69%), for silica gel column chromatography (hexane: AcOEt = 90:10 then 85:15) as a colorless oil: IR (neat) 3404, 2955, 2925, 2856, 1714, 1551, 1465, 1378, 1277, 1121, 1004, 925, 725 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 5.33-5.34 (1/3x1H, m) 5.12 (2/3x1H, t, $J = 2.6$ Hz), 4.17 (1/3x1H, t, $J = 8.2$ Hz), 3.99 (2/3x1H, t, $J = 7.9$ Hz), 3.62 (2/3x1H, t, $J = 8.7$ Hz), 3.42 (1/3x1H, t, $J = 8.4$ Hz), 3.05 (2/3x1H, d, $J = 3.0$ Hz), 2.88 (1/3x1H, d, $J = 2.4$ Hz), 1.97-2.01 (1H, m), 1.71-1.79 (1H, m), 1.51-1.64 (2H, m), 1.40-1.41 (1H, m), 1.24-1.33 (14H, m), 0.84-0.87 (6H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 104.3, 99.0, 73.2, 72.4, 52.9, 50.1, 45.4, 41.5, 32.9, 32.7, 32.6, 31.8, 31.7, 29.7, 29.4, 28.2, 28.1, 27.9, 27.7, 22.6, 22.6, 22.5, 14.1, 14.0; HRMS (ESI-TOF) m/z : $[\text{M} - \text{OH}]^+$; Calcd for $\text{C}_{15}\text{H}_{29}\text{O}$ 225.2213; Found 225.2210.

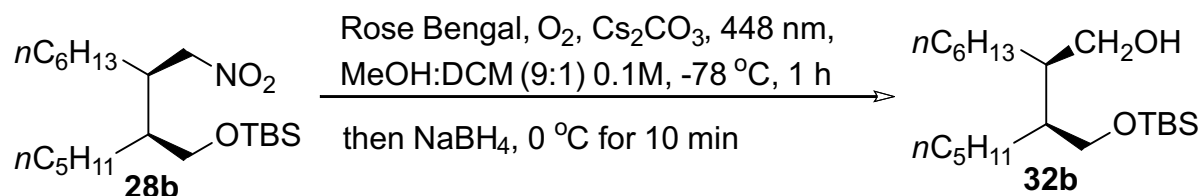


General Procedure for Alcohol Formation. A two-neck glass vessel was charged with a solution of **28** (0.200 mmol) in MeOH-DCM (2.0 mL, 9:1 v/v), Cs₂CO₃ (97.6 mg, 0.300 mmol), rose Bengal (10.0 mg, 0.0100 mmol). The mixture was stirred and bubbled with O₂ gas at 0 °C for 1 min, cooled to at –78 °C, irradiated LED light (λ_{max} = 448 nm, 680 mW) directly in the solution under O₂ atmosphere with stirring at –78 °C. After 1 h, NaBH₄ (11.2 mg, 0.300 mmol) was added to the mixture, and stirred for 10 min at 0 °C. The mixture was quenched with saturated NaHCO₃, extracted with AcOEt, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane : AcOEt) to give **32**.

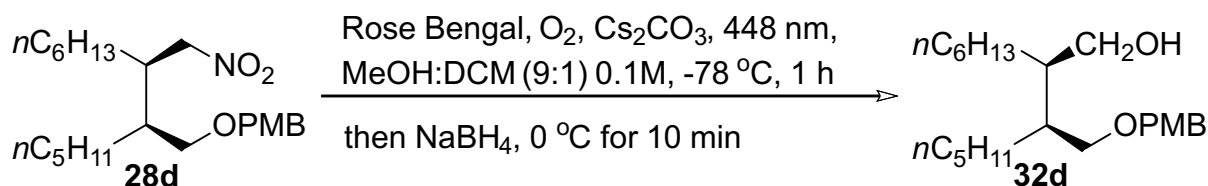


(2*R*,3*S*)-2-hexyl-3-((methoxymethoxy)methyl)octan-1-ol (32a). Starting from **28a** (63.5 mg, 0.200 mmol) to obtain **32a** (42.1 mg, 0.146 mmol, 73%), for silica gel column chromatography (hexane: AcOEt = 97:3 then 95:5) as a colorless oil and starting from **28a** (318 mg, 1.00 mmol) to obtain **32a** (215 mg, 0.750 mmol, 75%), for silica gel column chromatography (hexane: AcOEt = 97:3 then 95:5) as a colorless oil : $[\alpha]_{\text{D}}^{25} +84.7$ (*c* 0.52, CHCl₃); IR (neat) 3448, 2954, 2926, 2858, 1466, 1378, 1213, 1152, 1108, 1047, 919, 724 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.58-4.62 (2H, m), 3.65 (1H, dd, *J* = 11.6, 3.3 Hz), 3.56-3.59 (1H, m), 3.46-3.51 (2H, m), 3.35 (3H, s), 1.59-1.64 (1H, m), 1.50-1.52 (1H, m), 1.25-1.36 (18H, m), 0.84-0.87 (6H, m); ¹³C

NMR (CDCl₃, 126 MHz) δ 96.7, 67.6, 61.9, 55.6, 42.7, 40.2, 32.1, 31.8, 29.8, 29.6, 29.2, 27.7, 27.4, 22.6, 22.6, 14.1, 14.1; HRMS (ESI-TOF) m/z : [M + Na]⁺; Calcd for C₁₇H₃₆NaO₃ 311.2545; Found 311.2557.

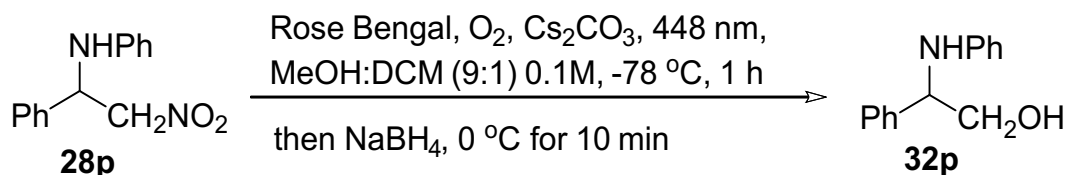


(2*R*,3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-hexyloctan-1-ol (32b). Starting from **28b** (77.5 mg, 0.200 mmol) to obtain **32b** (54.5 mg, 0.152 mmol, 76%), for silica gel column chromatography (hexane: AcOEt = 98:2 then 96:4) as a colorless oil: [α]_D²⁰ +109.1 (*c* 1.0, CHCl₃); IR (neat) 3460, 2955, 2928, 2857, 1725, 1702, 1613, 1514, 1465, 1362, 1249, 1172, 1097, 821 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 3.64-3.71 (2H, m), 3.45-3.56 (2H, m), 1.46-1.72 (2H, m), 1.25-1.38 (19H, m), 0.85-0.95 (15H, m), 0.06 (6H, s); ¹³C NMR (CDCl₃, 126 MHz) δ 62.2, 61.2, 43.0, 42.6, 32.1, 31.9, 29.8, 29.8, 29.7, 29.6, 27.7, 27.6, 27.3, 25.8, 22.7, 22.7, 18.2, 14.1, 14.1, -5.6, -5.6; HRMS (ESI-TOF) m/z : [M + H]⁺; Calcd for C₂₁H₄₇O₂Si 359.3327; Found 359.3340.

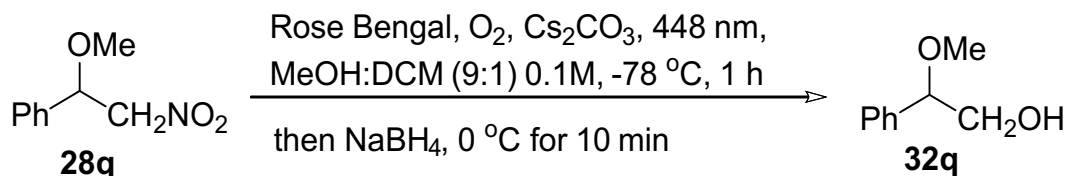


(2*R*,3*S*)-2-hexyl-3-(((4-methoxybenzyl)oxy)methyl)octan-1-ol (32d). Starting from **28d** (78.7 mg, 0.200 mmol) to obtain **32d** (54.7 mg, 0.151 mmol, 75%), for silica gel column chromatography (hexane: AcOEt = 95:5 then 90:10) as a colorless oil: [α]_D²⁵ -117.9 (*c* 0.28, CHCl₃); IR (neat) 3460, 2955, 2928, 2857, 1725, 1702, 1613, 1514, 1465, 1362, 1249, 1172,

1097, 821 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 7.24-7.27 (2H, m), 6.87-6.90 (2H, m), 4.48 (1H, d, $J = 11.5$ Hz), 4.41 (1H, d, $J = 11.5$ Hz), 3.81 (3H, s), 3.66 (1H, d, $J = 11.5$ Hz), 3.52 (1H, dd, $J = 9.5, 2.4$ Hz), 3.47 (1H, d, $J = 15.5$ Hz), 3.38 (1H, dd, $J = 9.6, 5.3$ Hz), 1.57-1.60 (1H, m), 1.41-1.49 (2H, m), 1.22-1.36 (17H, m), 0.88 (6H, t, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) δ 159.3, 129.6, 129.5, 113.8, 113.8, 73.0, 69.3, 61.4, 60.4, 55.2, 43.0, 40.8, 32.1, 31.8, 30.1, 29.6, 29.5, 27.7, 27.3, 22.6, 22.6, 14.1, 14.0; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$; Calcd for $\text{C}_{23}\text{H}_{40}\text{NaO}_3$ 387.2854; Found 387.2870.



2-phenyl-2-(phenylamino)ethan-1-ol (32p). Starting from **28p** (48.5 mg, 0.200 mmol) to obtain **31o** (31.1 mg, 0.147 mmol, 73%), for silica gel column chromatography (hexane: AcOEt = 92:8 then 90:10) as a yellow oil: ^1H NMR (CDCl_3 , 500 MHz) δ 7.39-7.35 (4H, m), 7.20-7.16 (2H, m), 6.7 (1H, t, $J = 7.4$ Hz), 6.64 (2H, d, $J = 7.7$ Hz), 4.58-4.61 (1H, m), 4.33 (1H, s), 3.33-3.27 (2H, m); ^{13}C NMR (CDCl_3 , 126 MHz) δ 148.1, 139.4, 129.2, 128.6, 127.5, 127.2, 117.5, 112.8, 60.7, 48.3.



2-methoxy-2-phenylethan-1-ol (32q). Starting from **28q** (36.2 mg, 0.200 mmol) to obtain **32q** (23.1 mg, 0.152 mmol, 76%), for silica gel column chromatography (hexane: AcOEt = 90:10

then 88:12) as a colorless oil: IR (neat) 3404, 2928, 1750, 1557, 1494, 1455, 1240, 1198, 1173, 1107, 732, 699 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 7.37-7.30 (5H, m), 4.70 (1H, s), 4.32-4.28 (1H, m), 4.14-4.09 (1H, m), 3.67-3.60 (1H, m), 3.31 (3H, s); ^{13}C NMR (CDCl_3 , 126 MHz) δ 135.9, 129.1, 129.1, 126.8, 80.4, 67.2, 57.1; HRMS (ESI-TOF) m/z : $[\text{M} - \text{OMe}]^+$; Calcd for $\text{C}_8\text{H}_9\text{O}$ 121.0648; Found 121.0658.

Procedure for Ion Chromatographic analysis. Crude samples were analyzed by ion chromatography to examine the presence of NO_2^- and NO_3^- in the samples. An ion chromatograph (IC-8100, Tosoh Co.) equipped with a TSK gel Super IC-AZ column was used with an aqueous solution of NaHCO_3 and Na_2CO_3 as eluent.

Procedure for ion chromatography analysis

- a) Without Me_2S addition.** A two-neck glass vessel was charged with a solution of **28a** (0.200 mmol) in MeOH-DCM (2.0 mL, 9:1 v/v), Cs_2CO_3 (97.6 mg, 0.300 mmol), rose bengal (10.0 mg, 0.0100 mmol). The mixture was stirred and bubbled with O_2 gas at 0°C for 1 min, cooled to at -78°C , irradiated LED light ($\lambda_{\text{max}} = 448 \text{ nm}$, 680 mW) directly in the solution under O_2 atmosphere with stirring at -78°C for 1h. The mixture was then diluted to 1 mM with distilled water and was analyzed using ion chromatography instrument immediately.
- b) With Me_2S addition.** A two-neck glass vessel was charged with a solution of **28a** (0.200 mmol) in MeOH-DCM (2.0 mL, 9:1 v/v), Cs_2CO_3 (97.6 mg, 0.300 mmol), rose bengal (10.0 mg, 0.0100 mmol). The mixture was stirred and bubbled with O_2 gas at 0°C for 1 min, cooled to at -78°C , irradiated LED light ($\lambda_{\text{max}} = 448 \text{ nm}$, 680 mW) directly in the solution under O_2 atmosphere with stirring at -78°C . After 1 h, Me_2S (44.0 μL , 0.600 mmol) was added to the mixture, stirred for 10 min at room temperature. The mixture was

then diluted to 1 mM concentration with distilled water and was analyzed using ion chromatography instrument immediately.

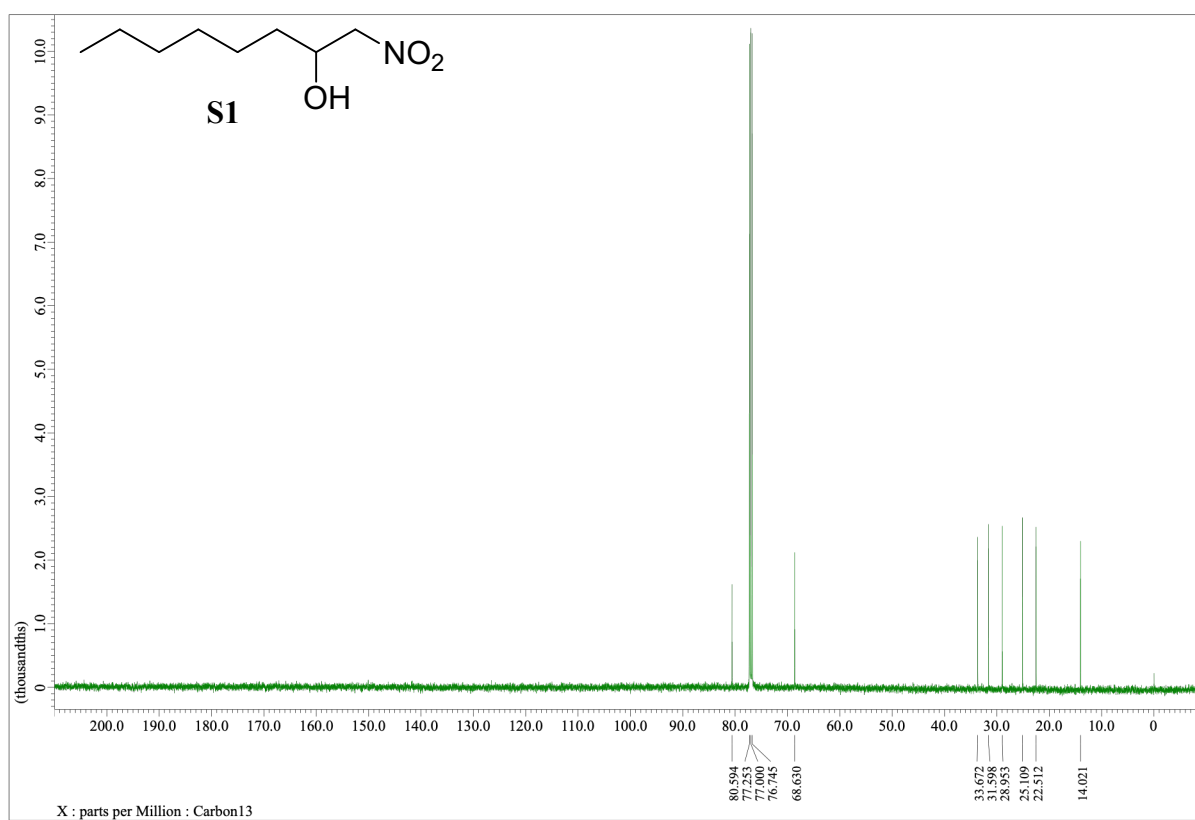
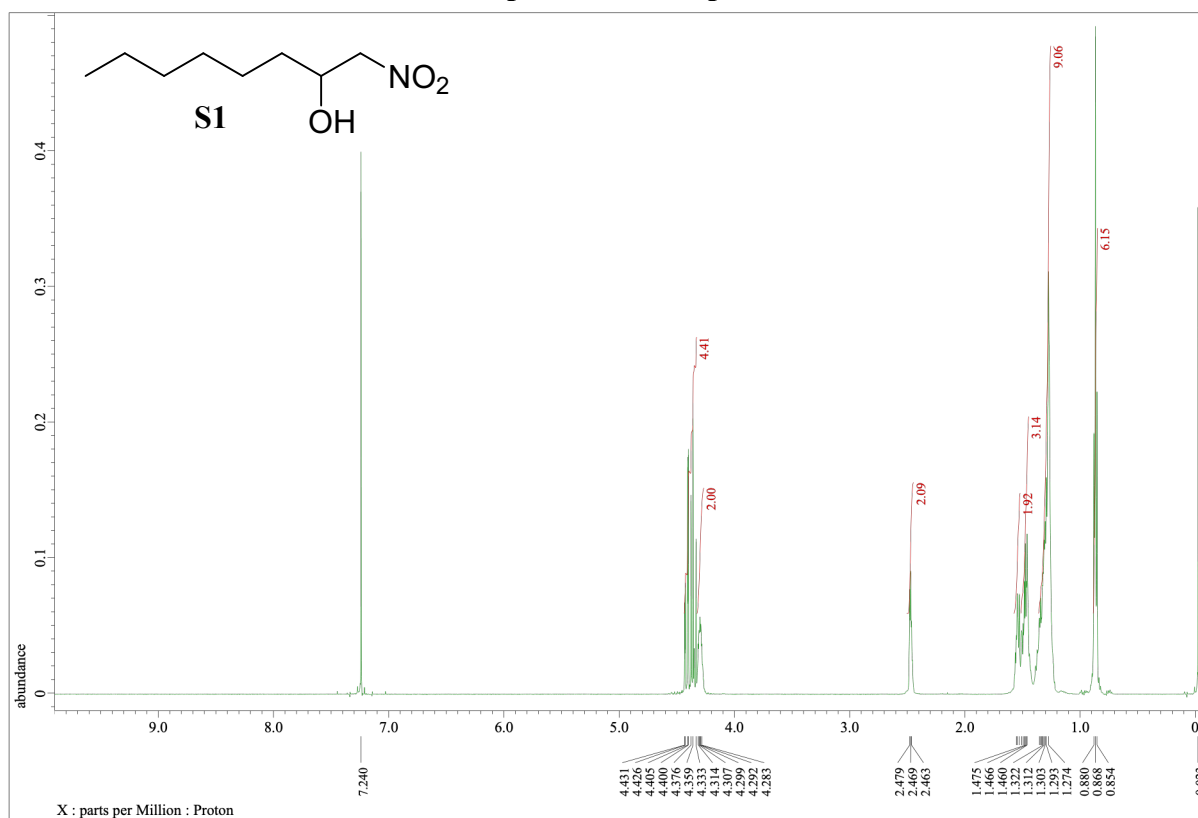
- c) **Radical scavenger *p*-benzoquinone (1.0 eq) - without Me₂S addition.** A two-neck glass vessel was charged with a solution of **28a** (0.200 mmol) in MeOH-DCM (2.0 mL, 9:1 v/v), Cs₂CO₃ (97.6 mg, 0.300 mmol), rose bengal (10.0 mg, 0.0100 mmol) and *p*-benzoquinone (21.6 mg, 0.200 mmol). The mixture was stirred and bubbled with O₂ gas at 0 °C for 1 min, cooled to at –78 °C, irradiated LED light (λ_{max} = 448 nm, 680 mW) directly in the solution under O₂ atmosphere with stirring at –78 °C for 1 h. The mixture was then diluted to 1 mM concentration with distilled water and was analyzed using ion chromatography instrument immediately.

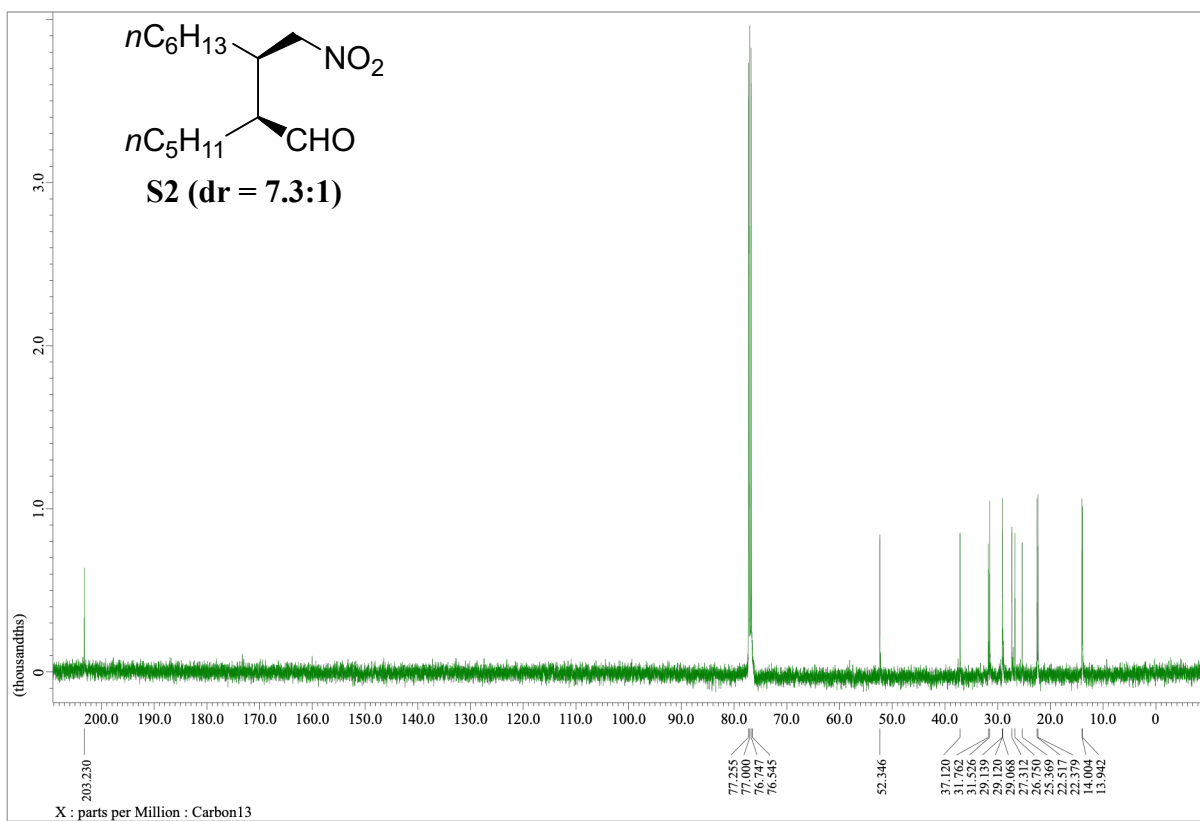
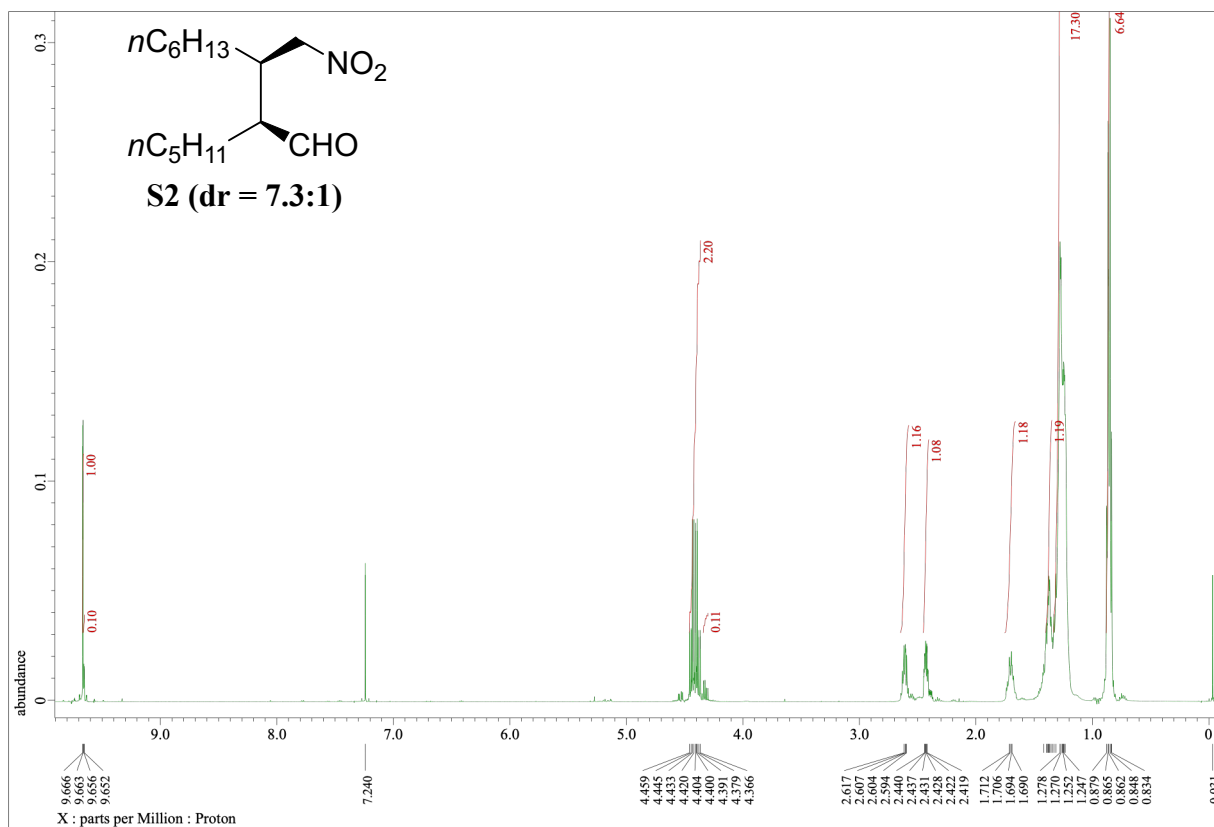
Starting from **28a** (63.5 mg, 0.200 mmol) to obtain **30a** as colorless oil (30.9 mg, 52%) and **30a** as colorless oil (15.2 mg, 24%).

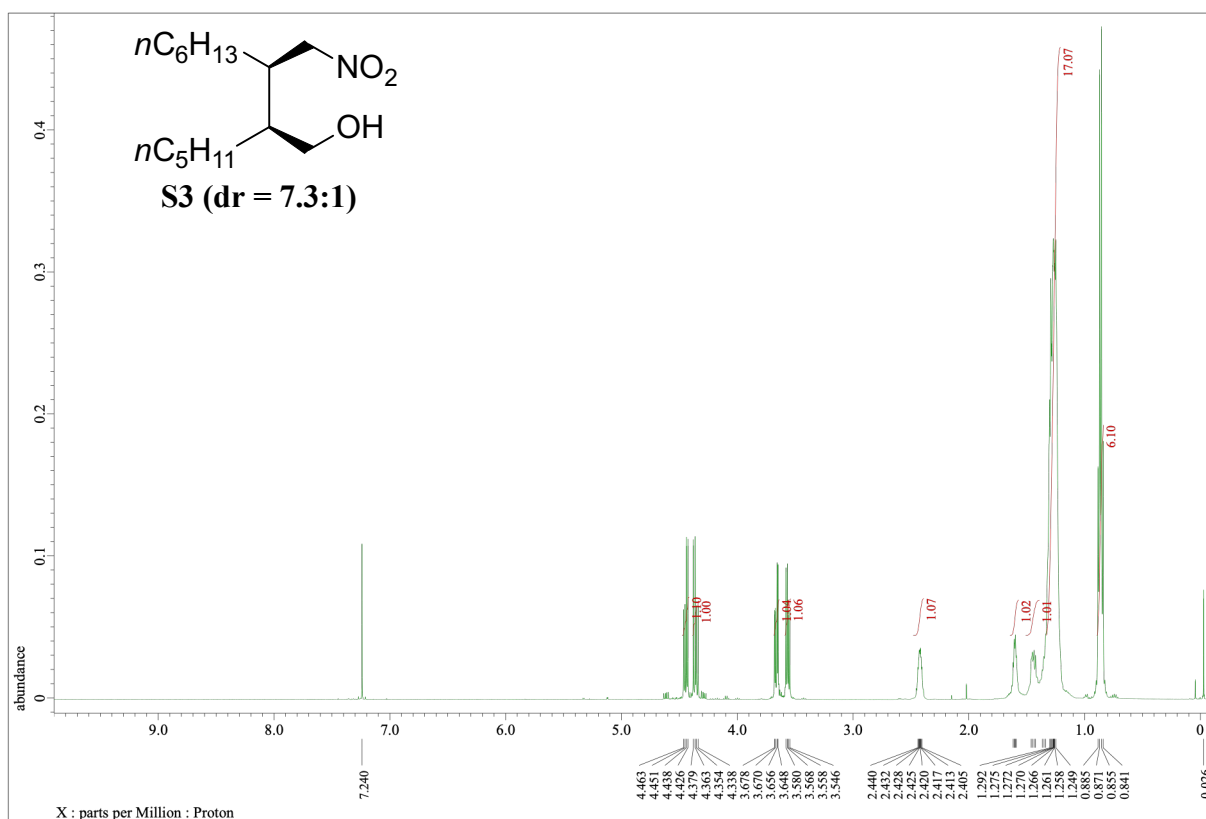
- d) **Radical scavenger *p*-benzoquinone (1.0 eq) - with Me₂S addition.** A two-neck glass vessel was charged with a solution of **28a** (0.200 mmol) in MeOH-DCM (2.0 mL, 9:1 v/v), Cs₂CO₃ (97.6 mg, 0.300 mmol), rose bengal (10.0 mg, 0.0100 mmol) and *p*-benzoquinone (21.6 mg, 0.200 mmol). The mixture was stirred and bubbled with O₂ gas at 0 °C for 1 min, cooled to at –78 °C, irradiated LED light (λ_{max} = 448 nm, 680 mW) directly in the solution under O₂ atmosphere with stirring at –78 °C. After 1 h, Me₂S (44.0 μ L, 0.600 mmol) was added to the mixture, stirred for 10 min at room temperature. The mixture was then diluted to 1 mM concentration with distilled water and was analyzed using ion chromatography instrument immediately.

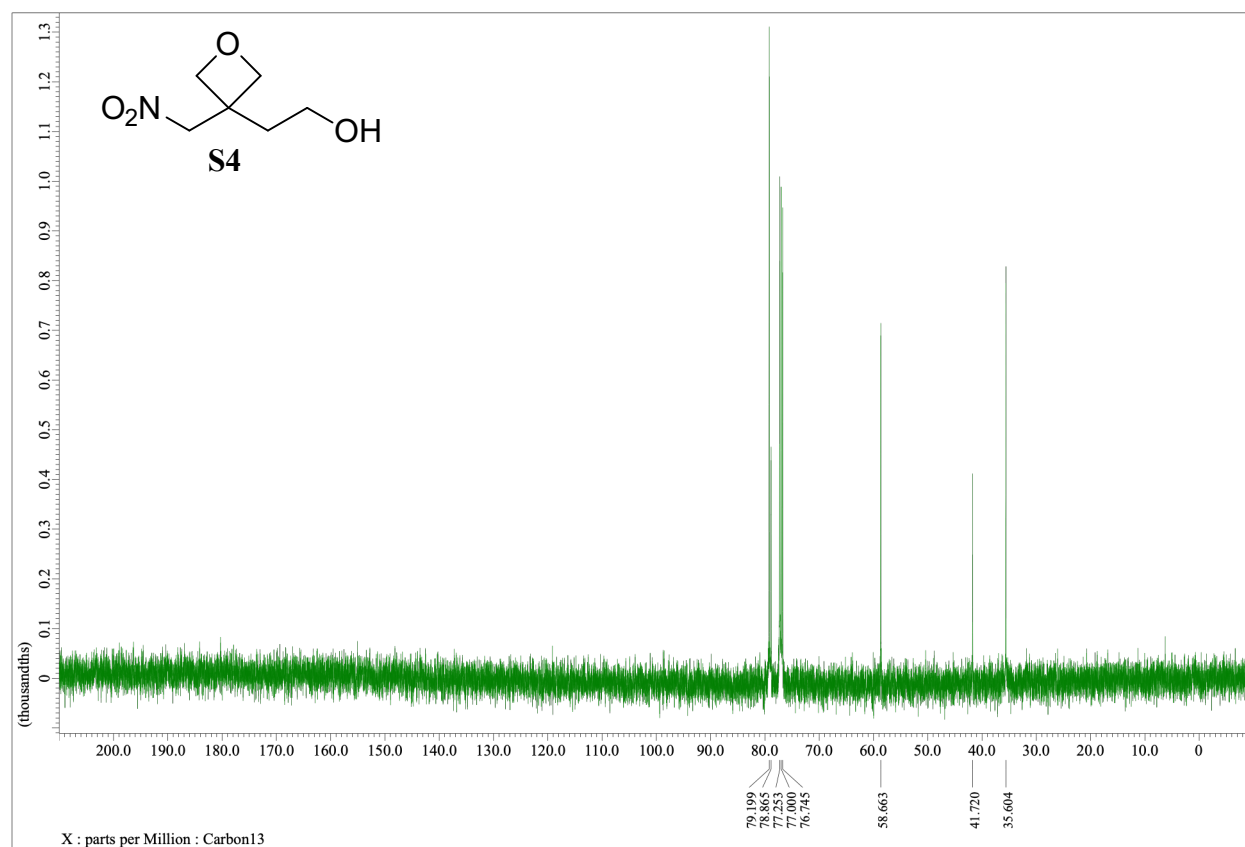
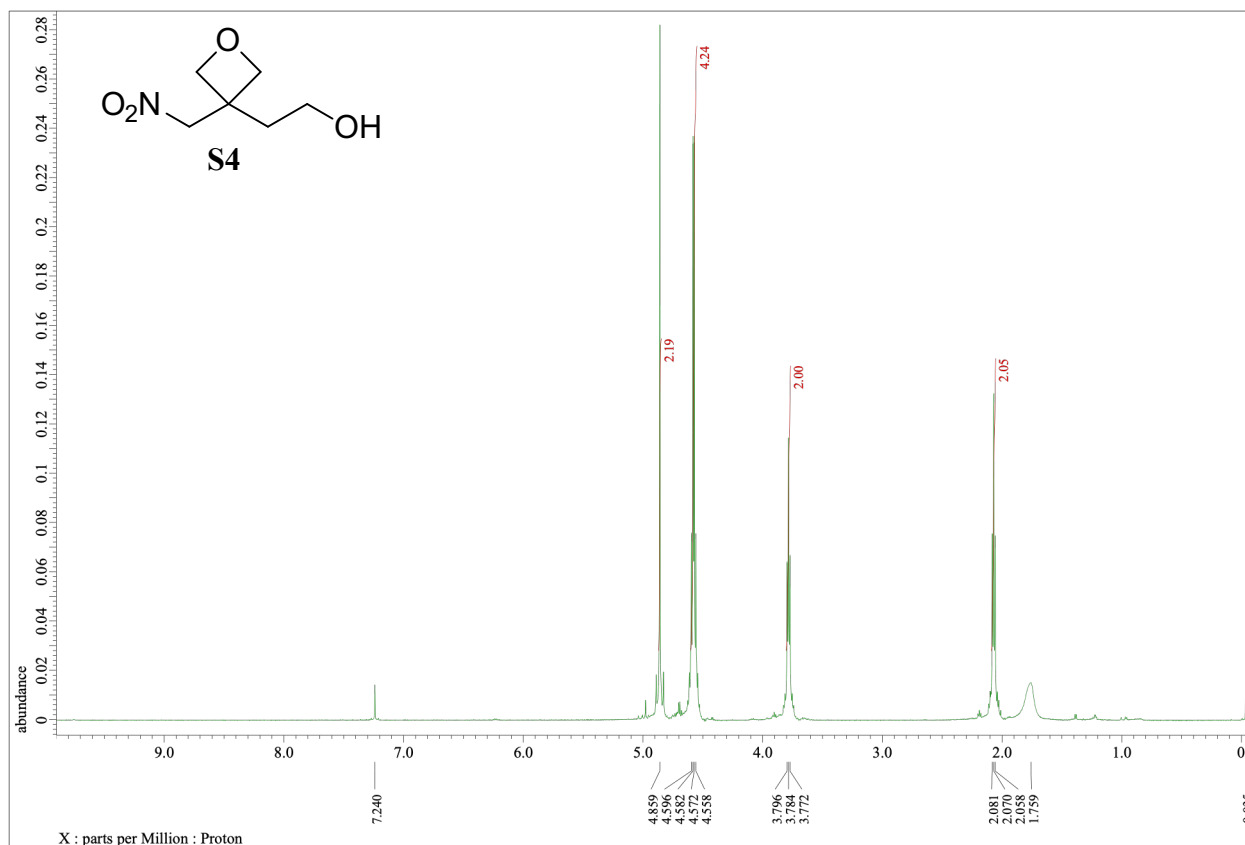
Starting from **28a** (63.5 mg, 0.200 mmol) to obtain **30a** as colorless oil (46.4 mg, 81%) and **30a** as colorless oil (6.35 mg, 10%).

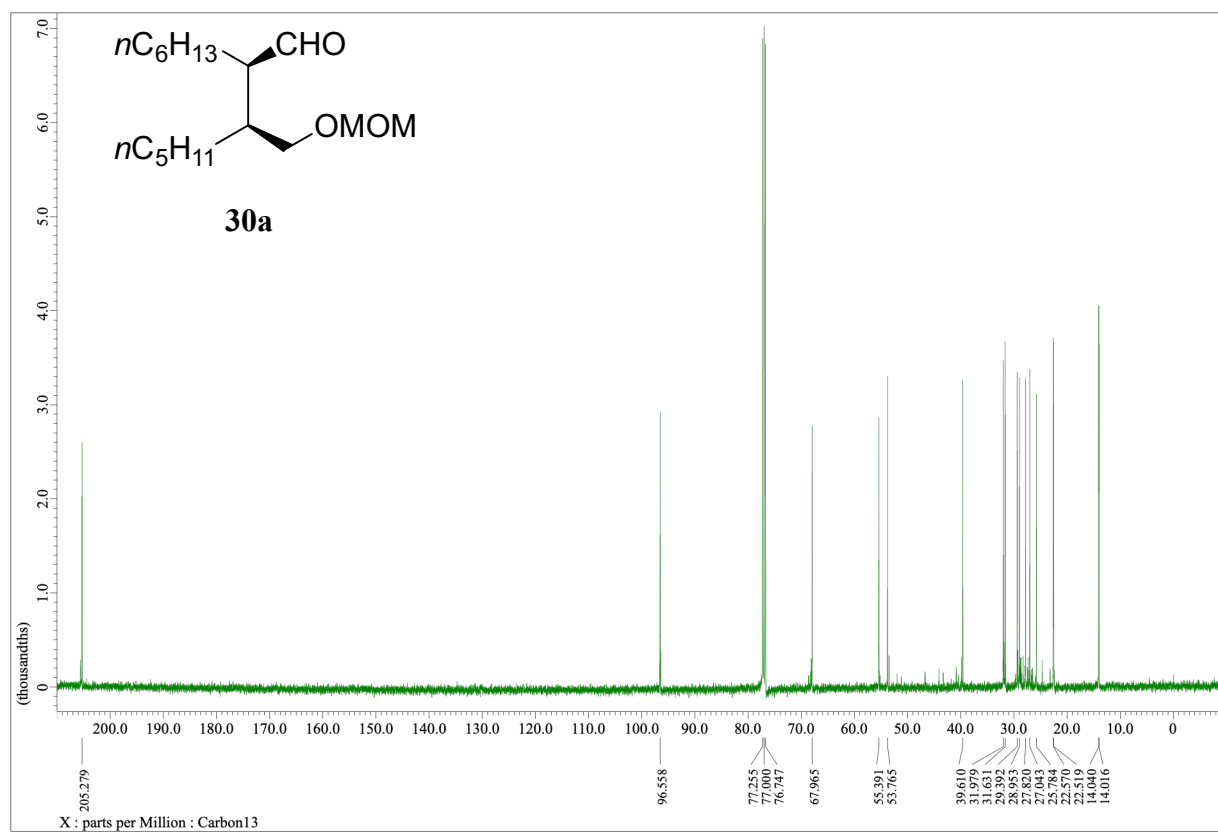
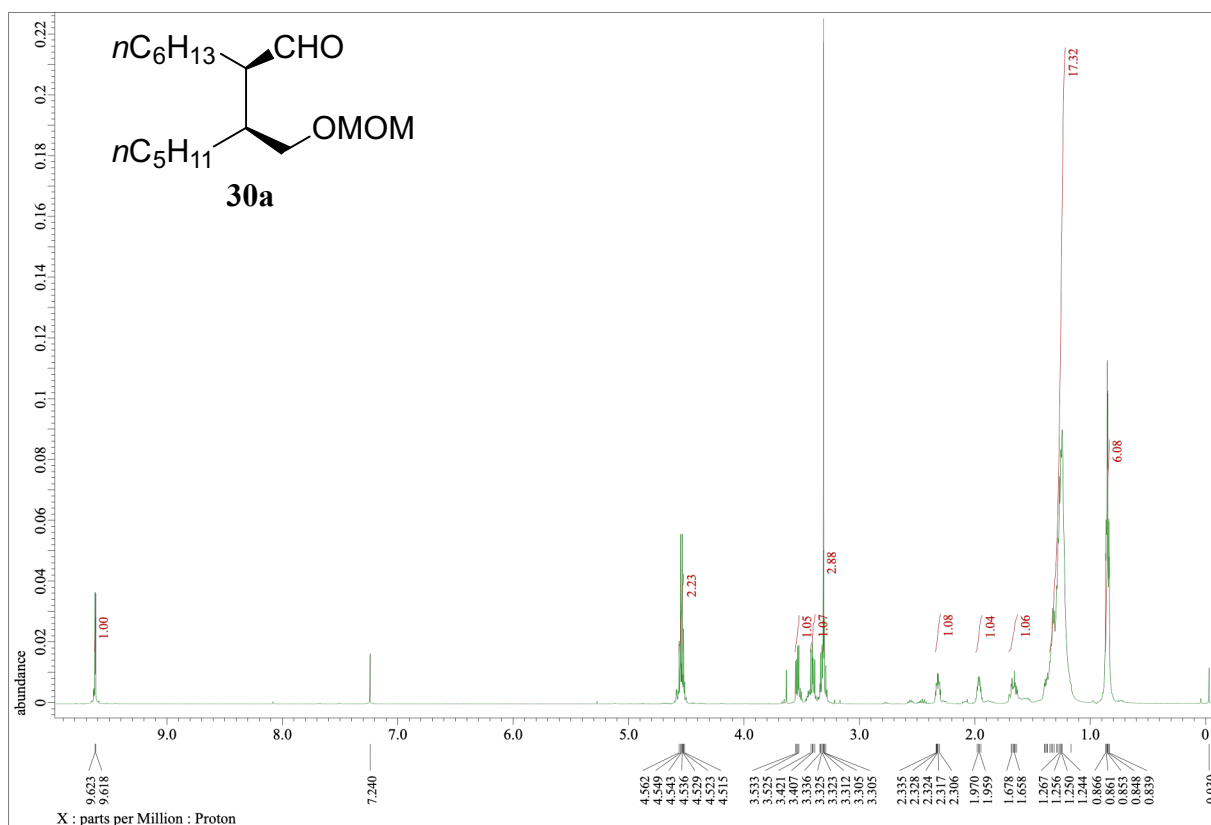
NMR Spectra for Chapter 2

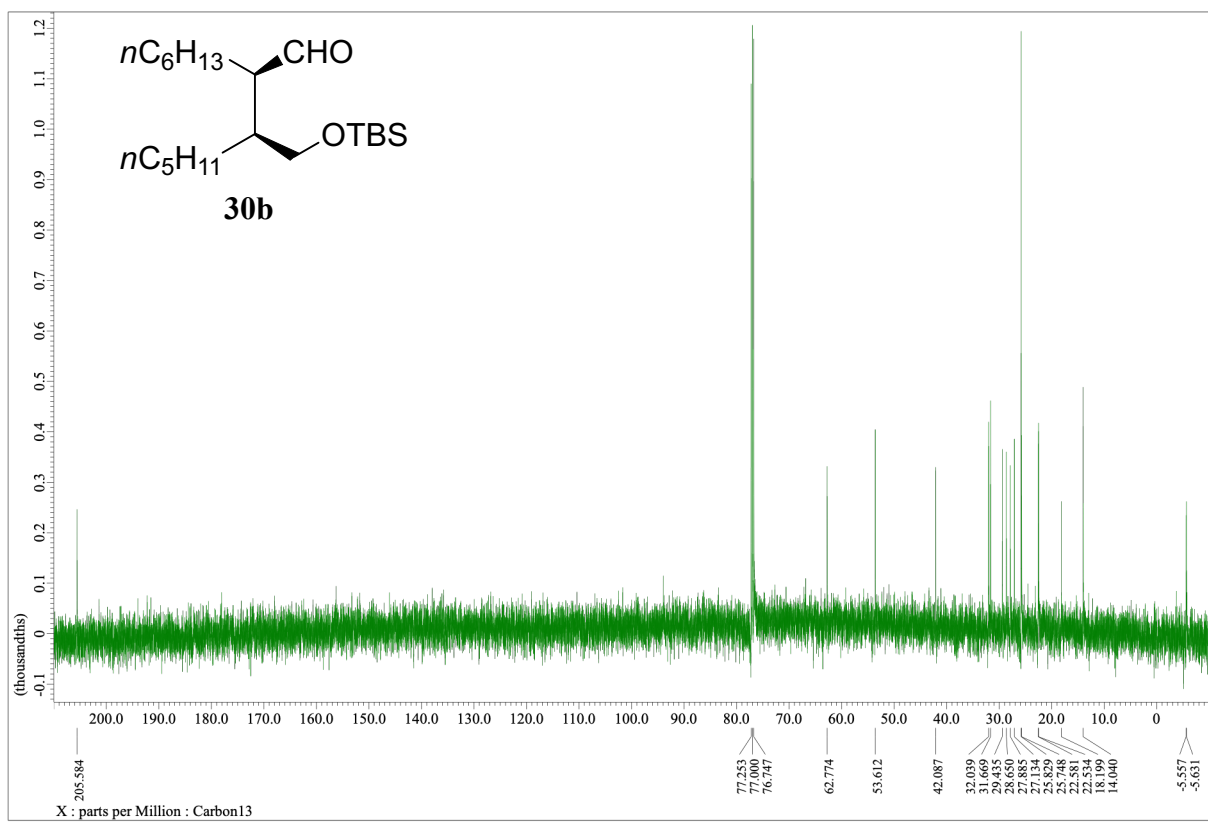
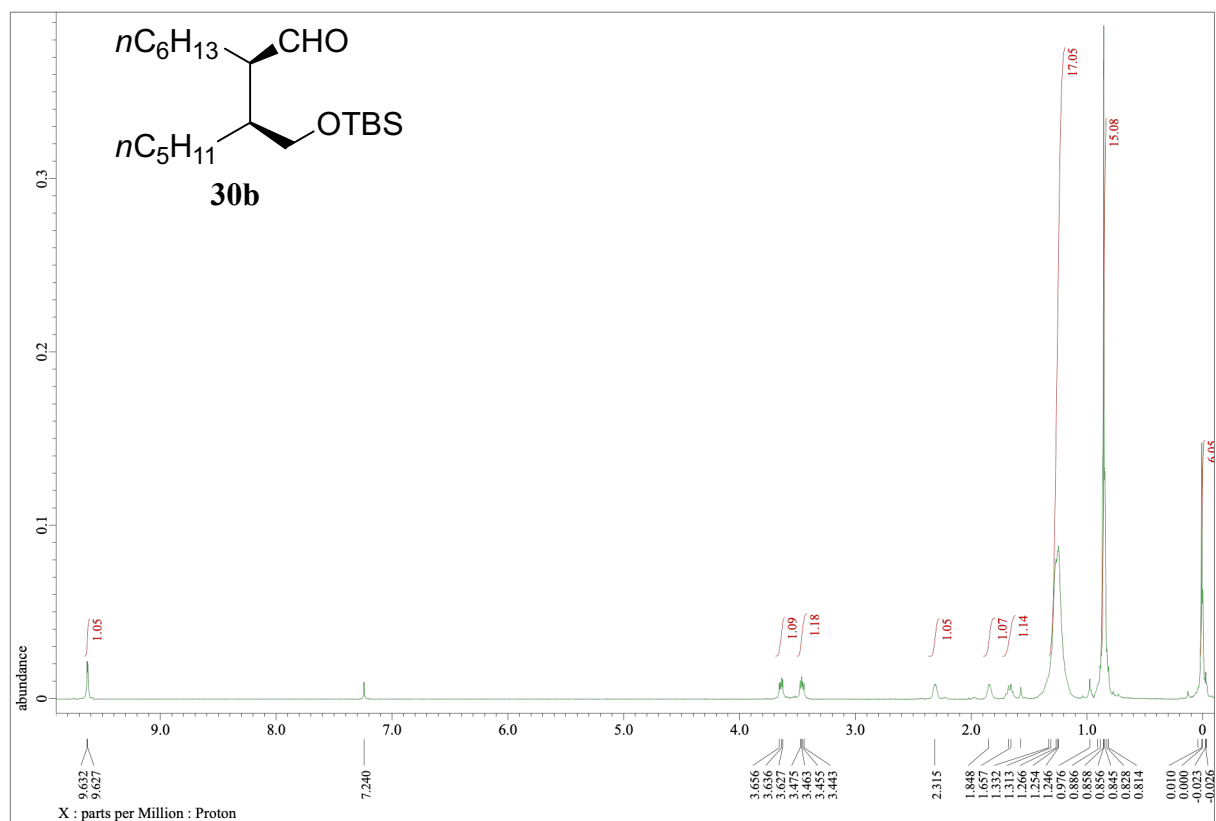


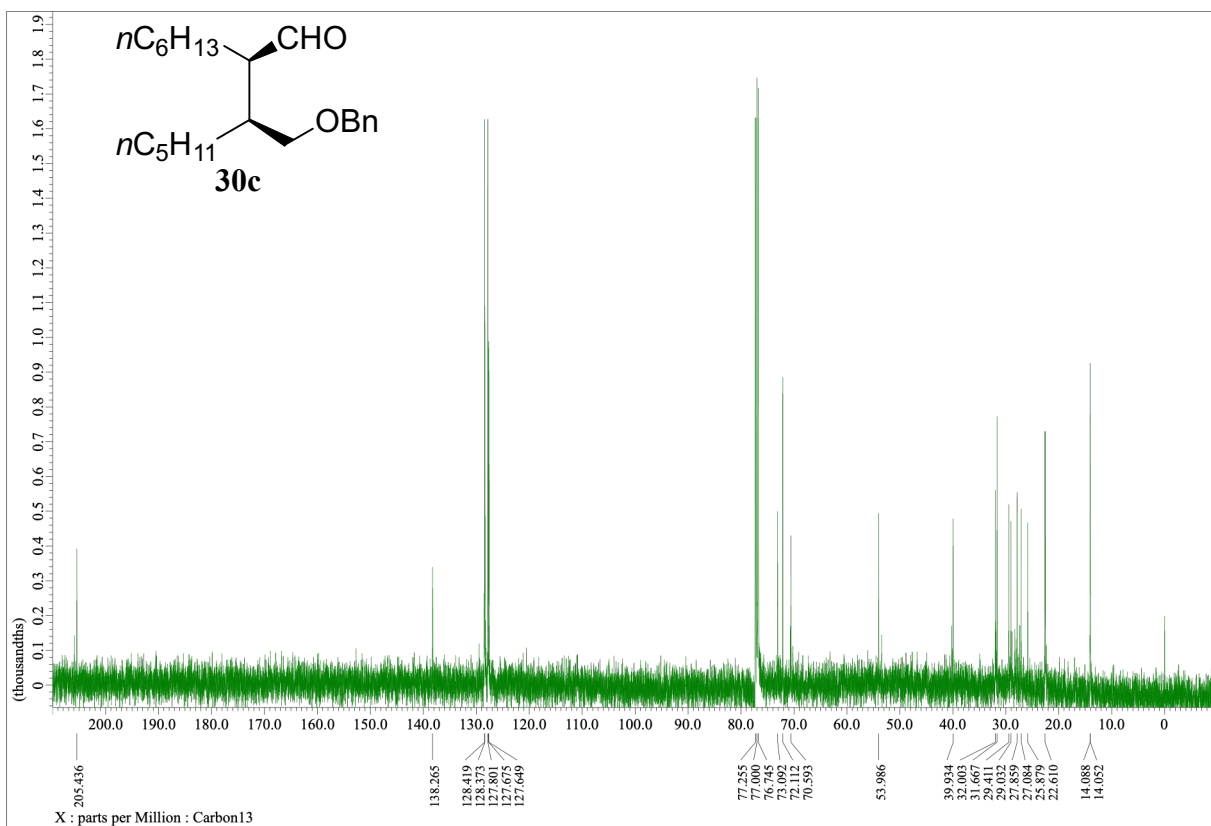
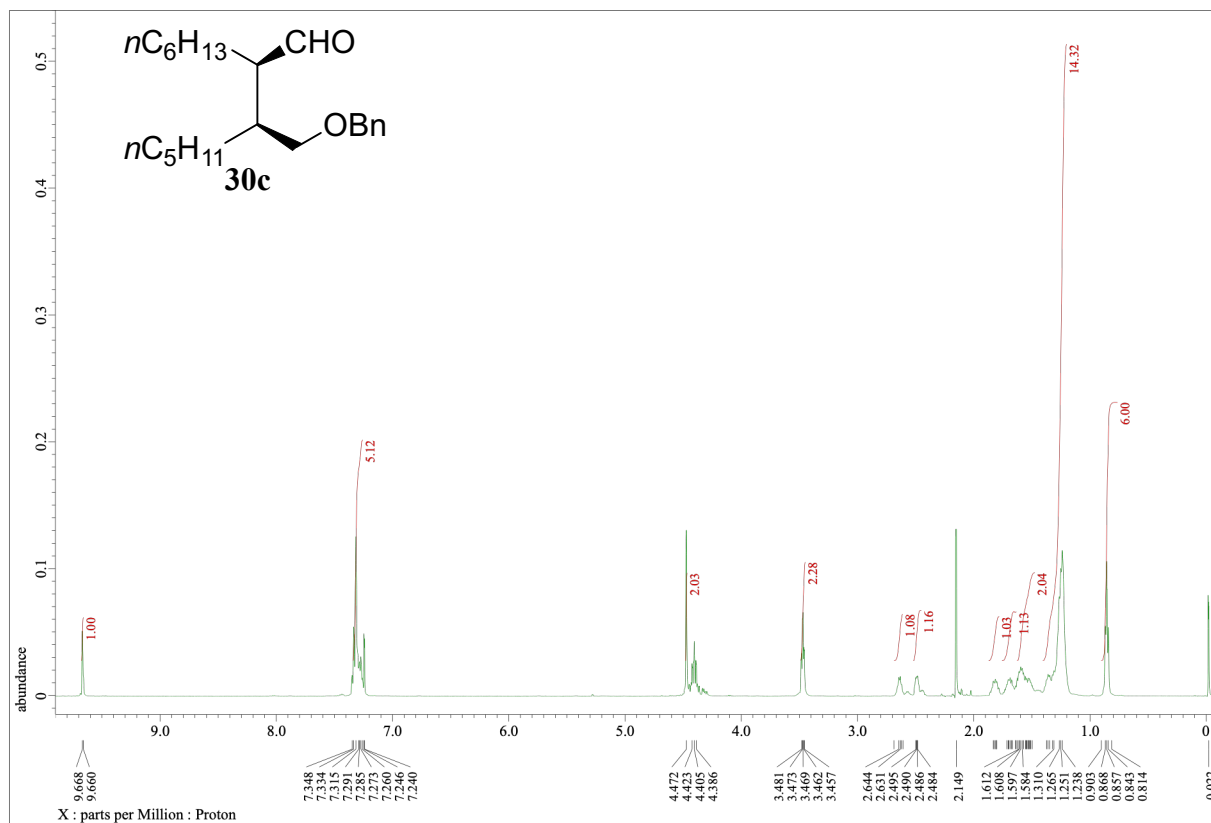


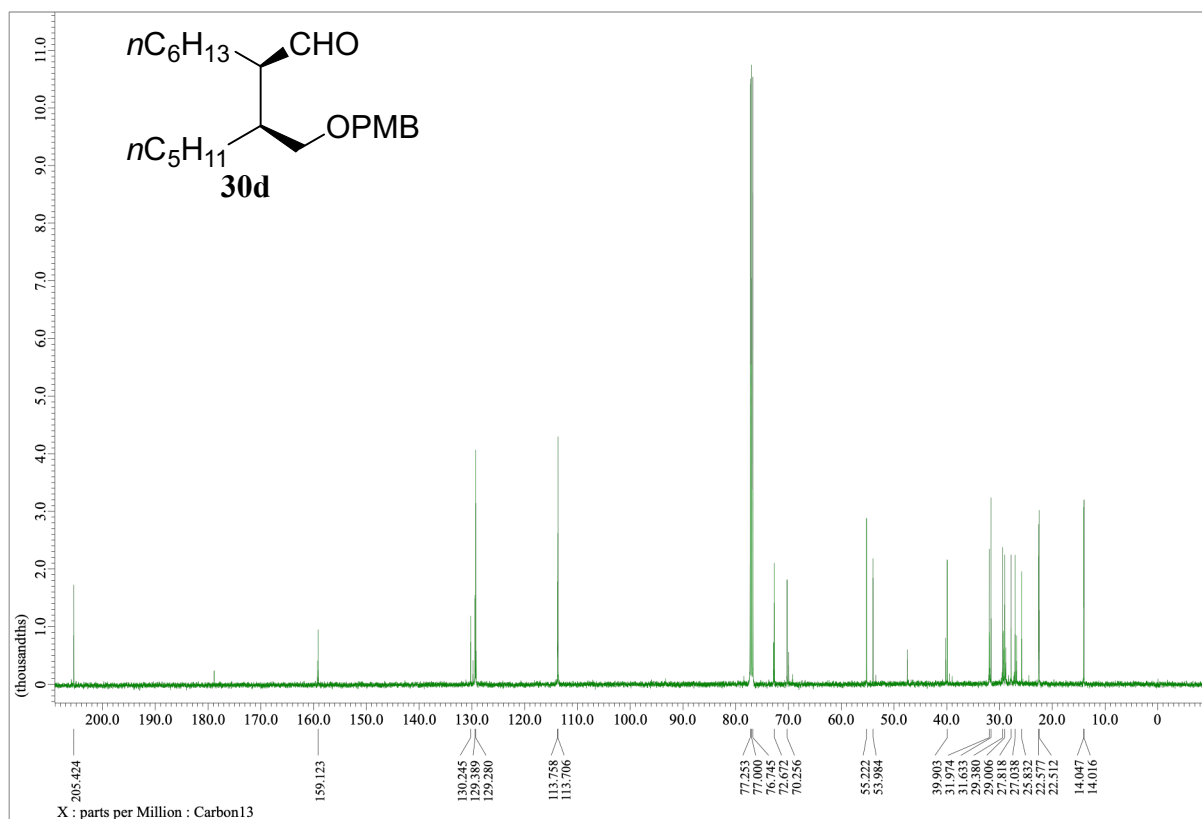
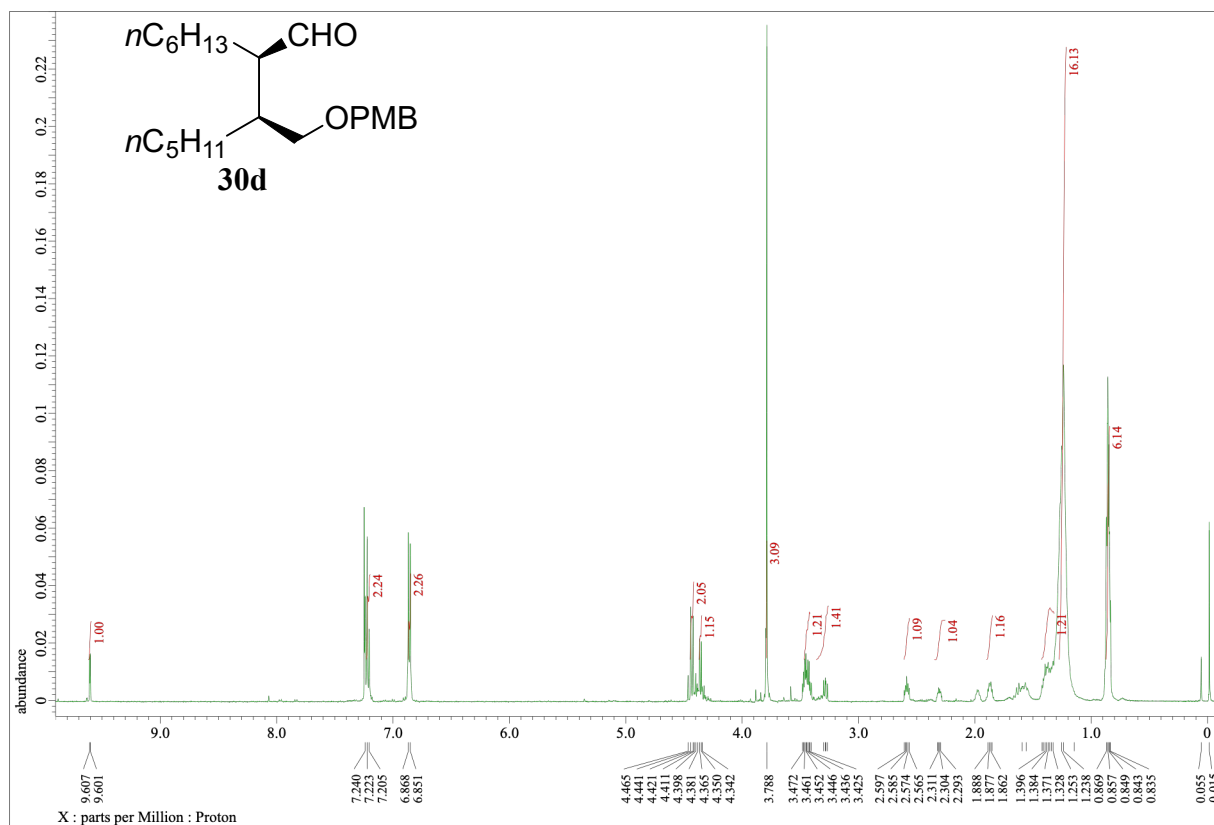


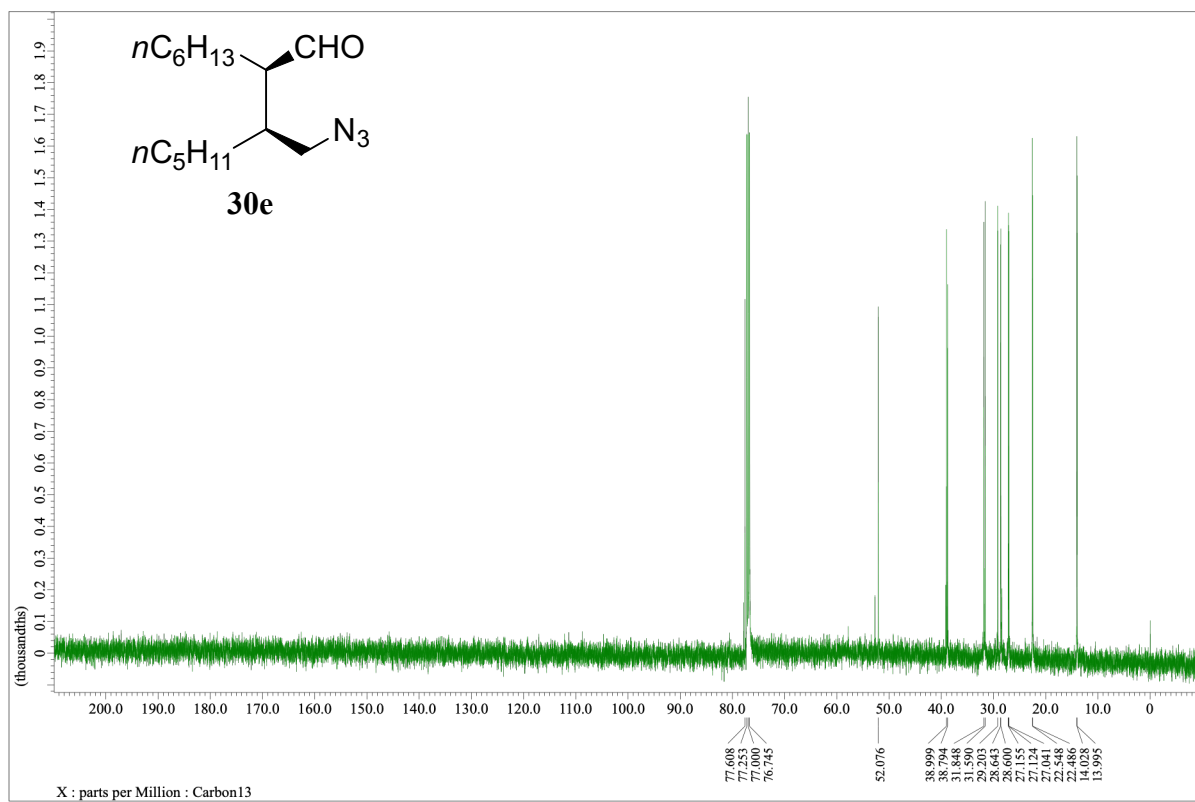
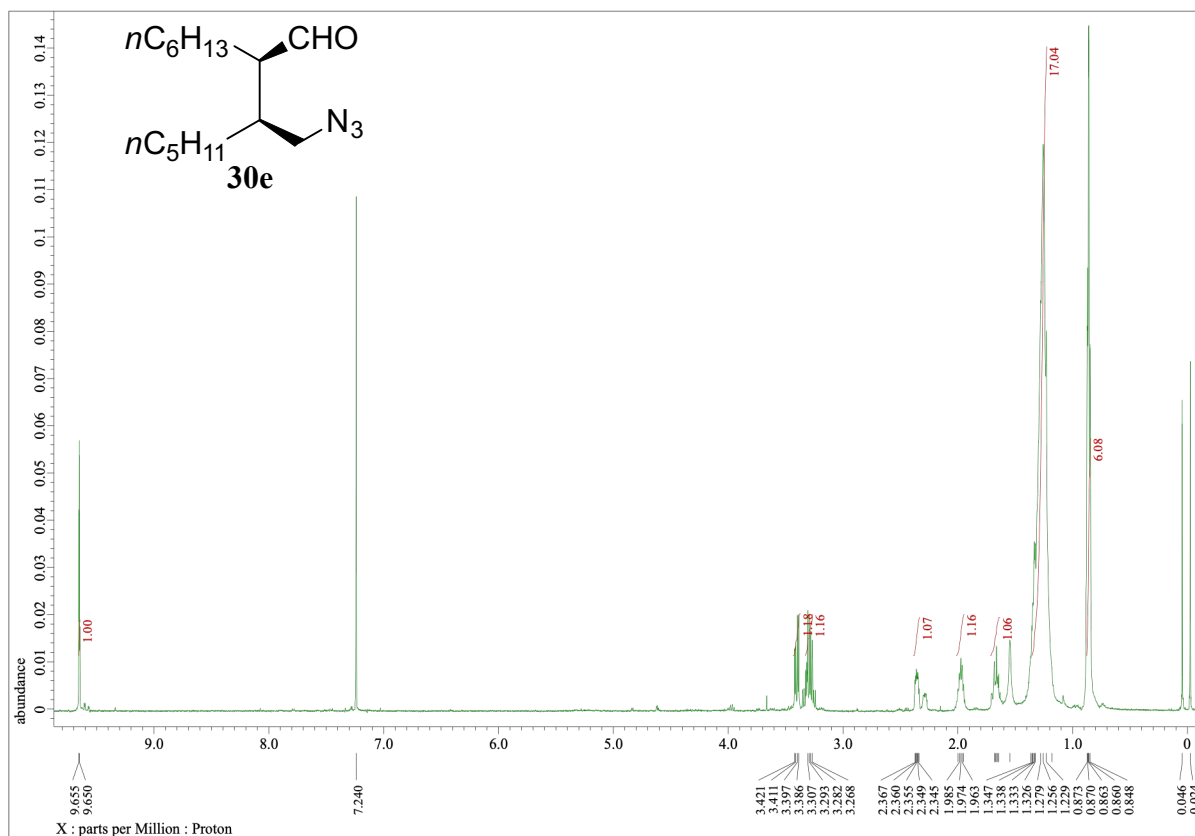


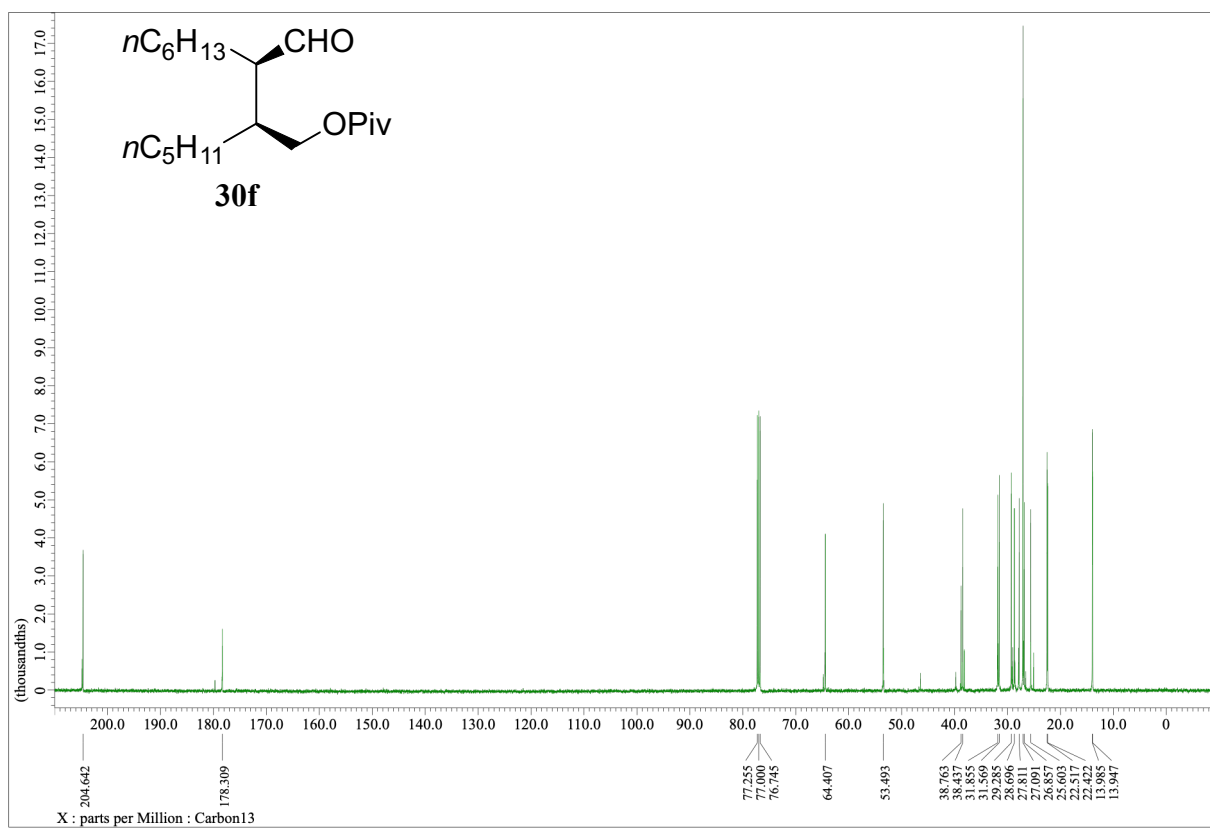
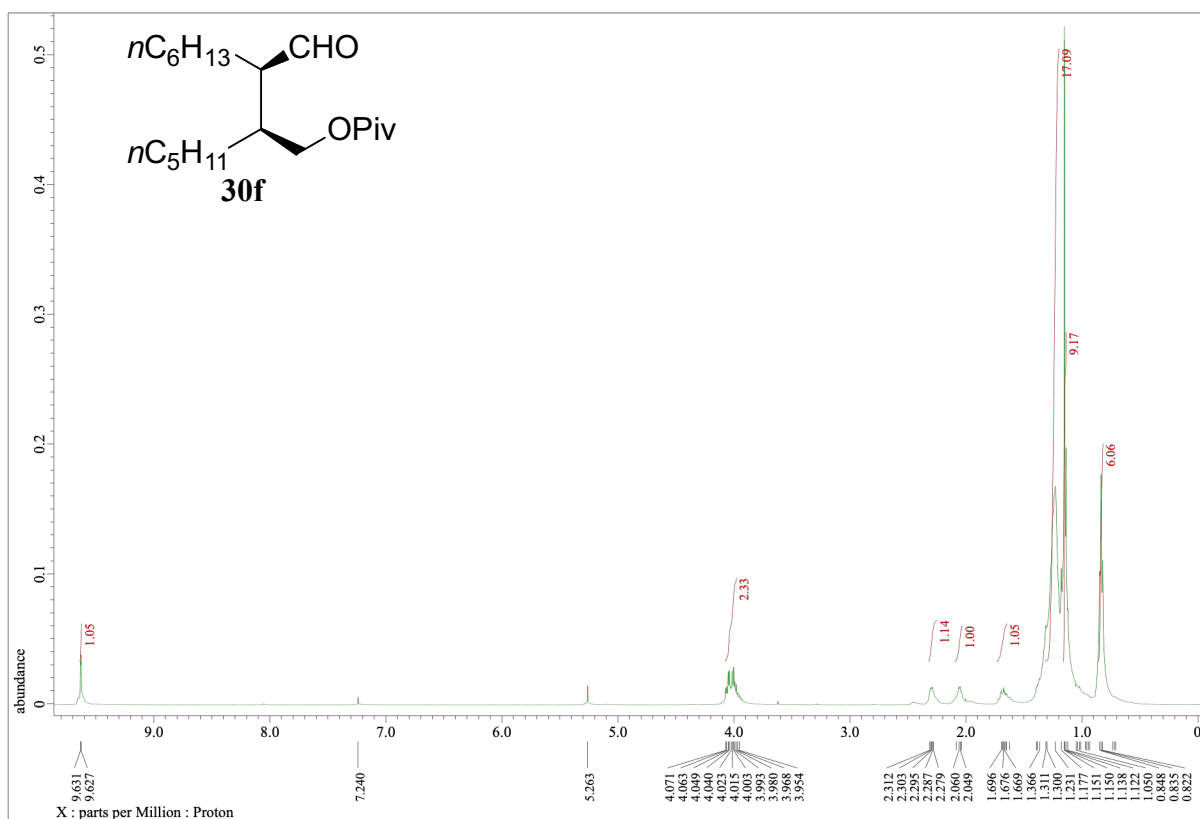


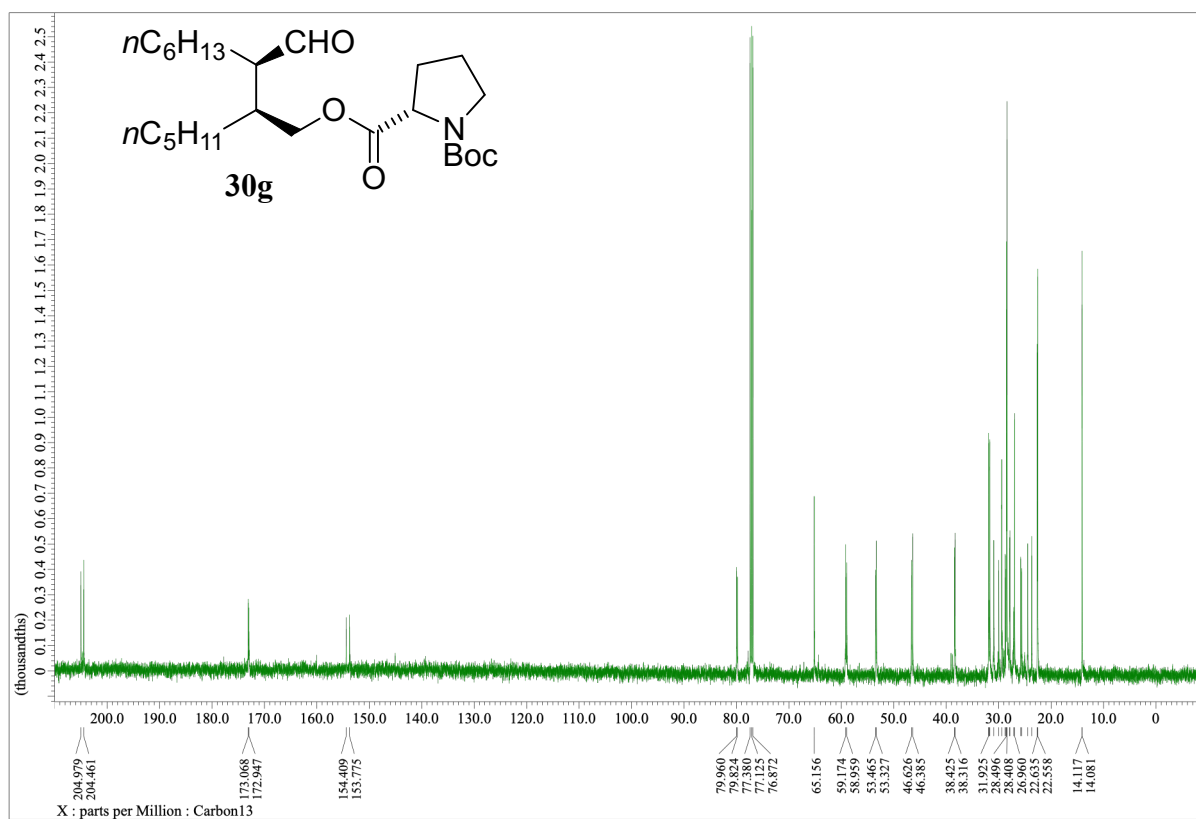
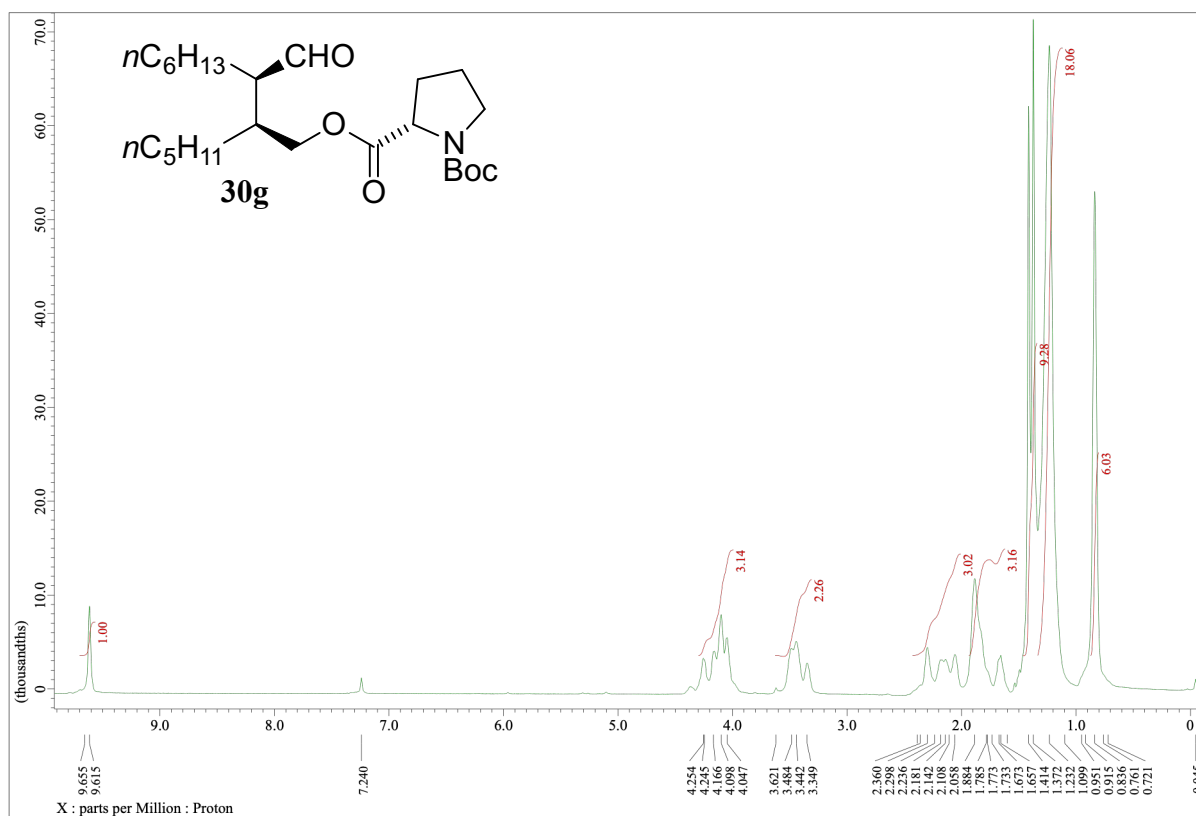


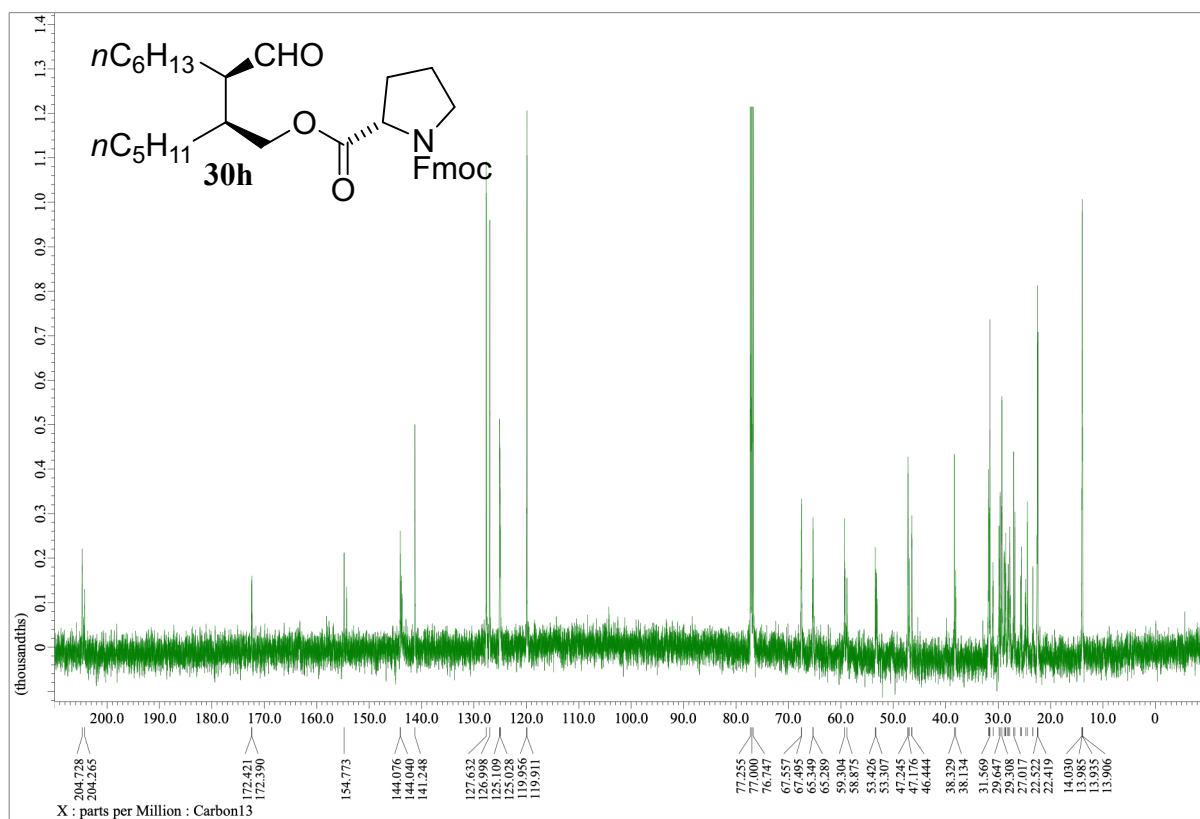
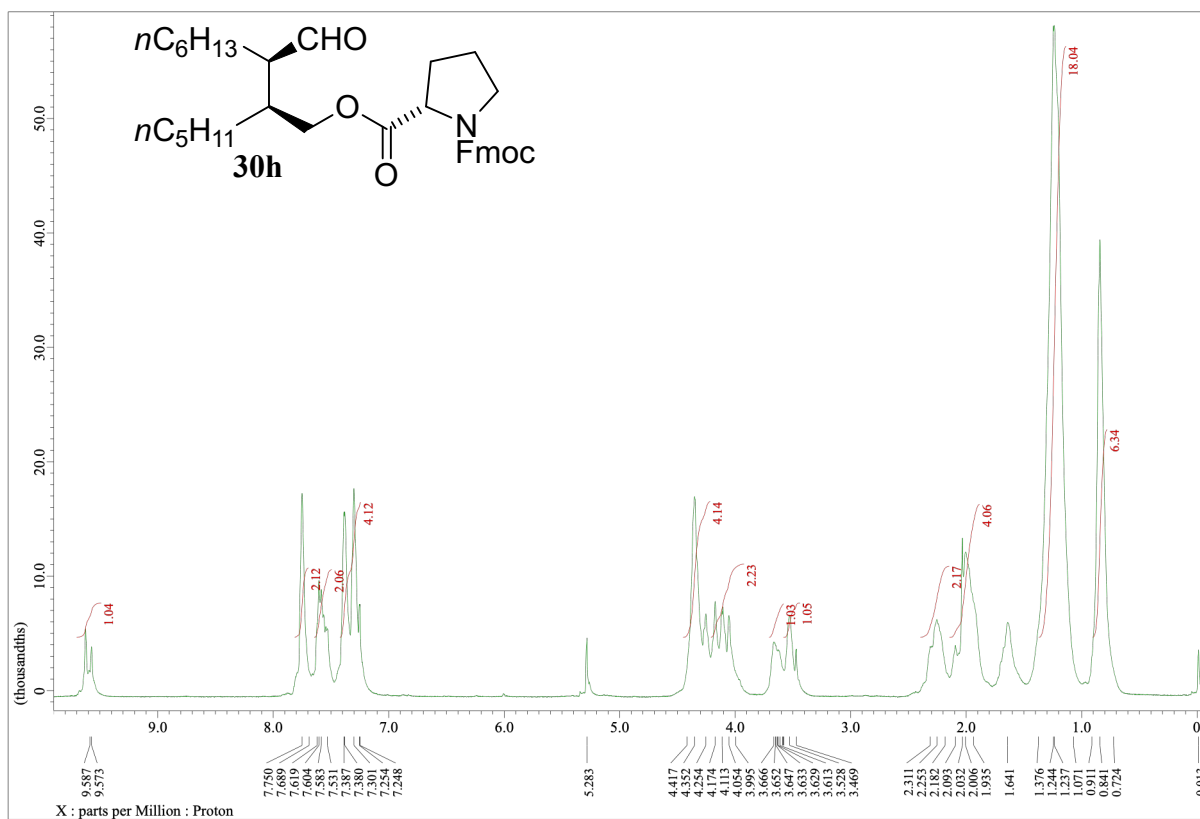


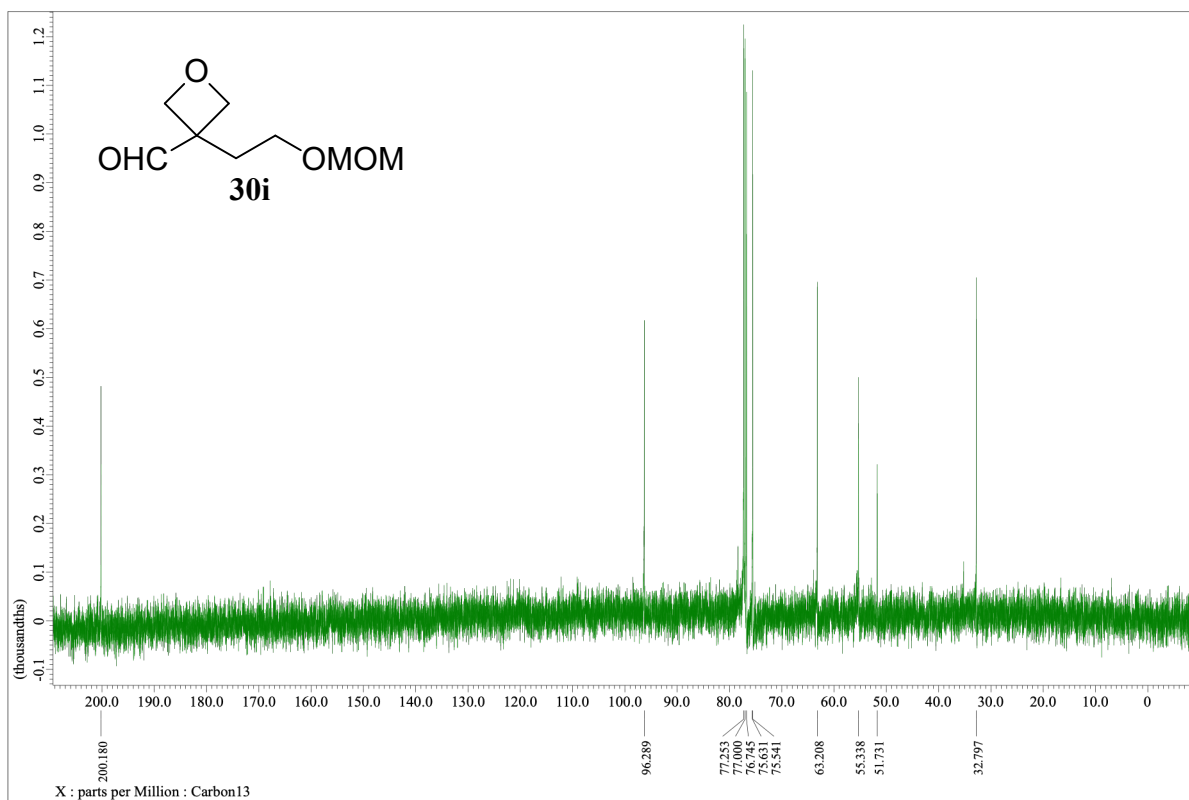
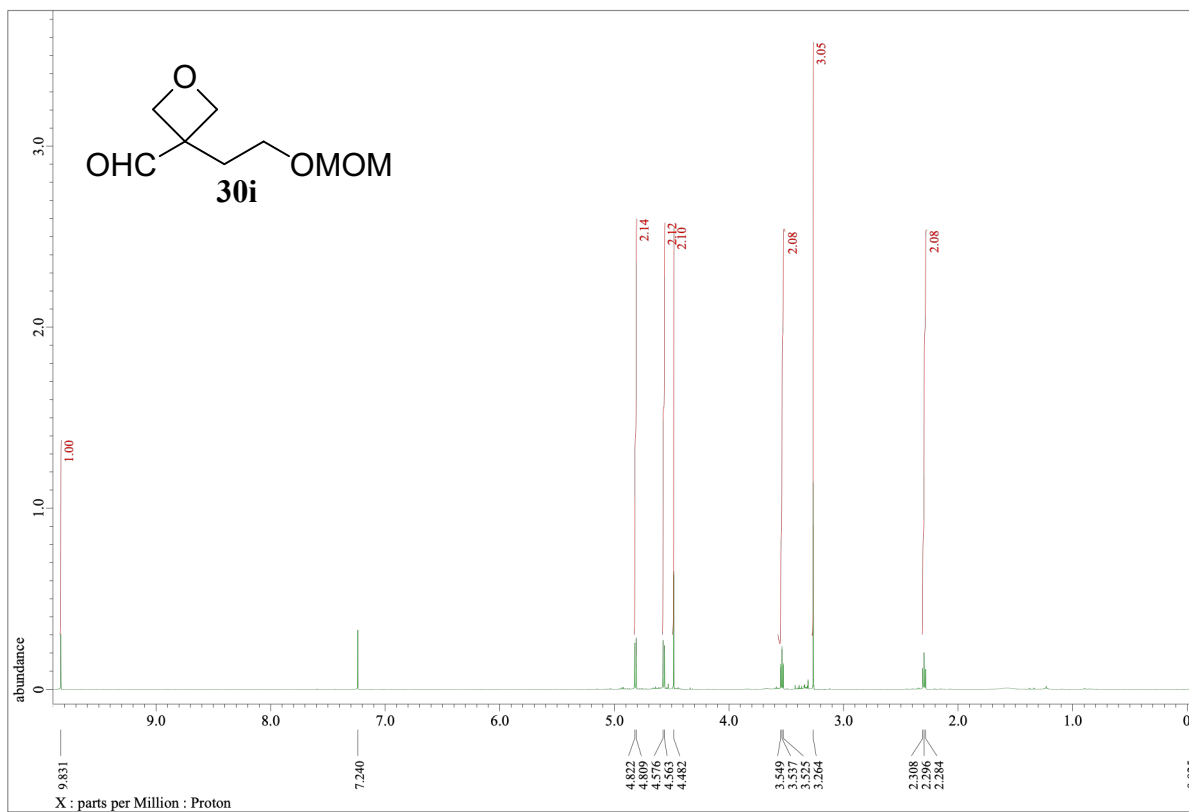


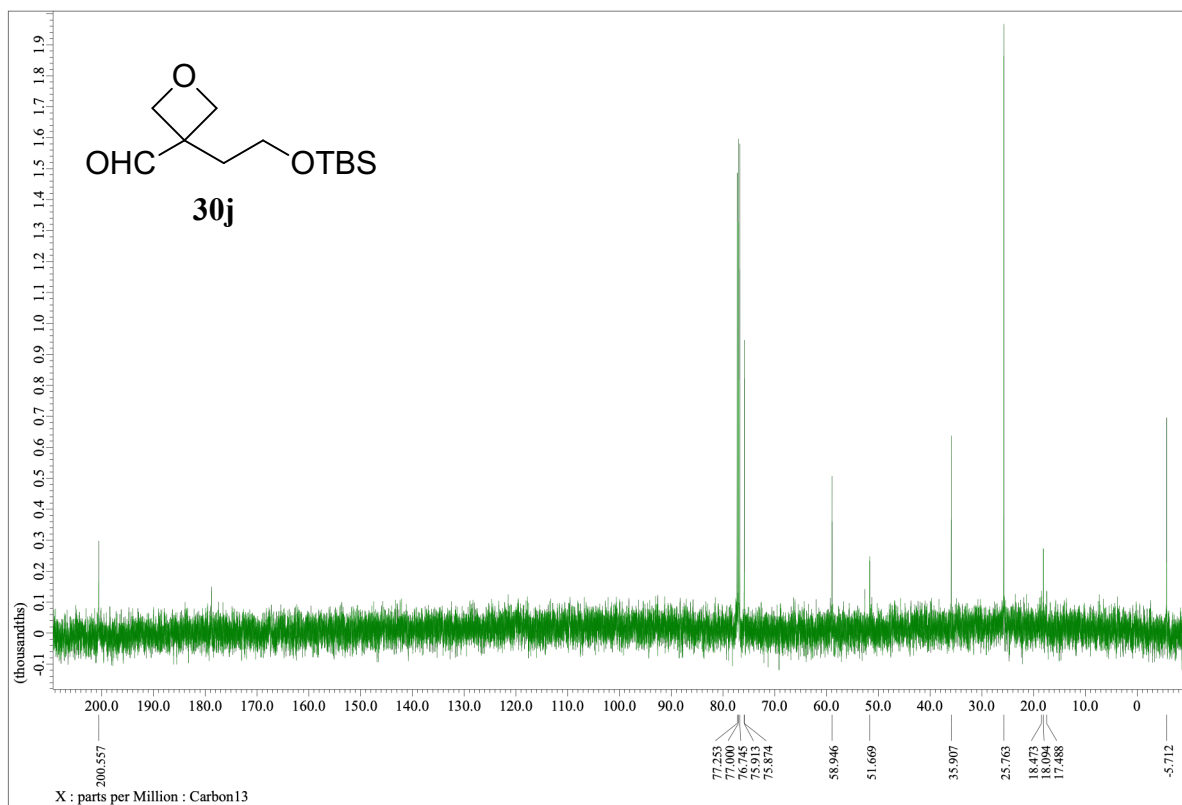
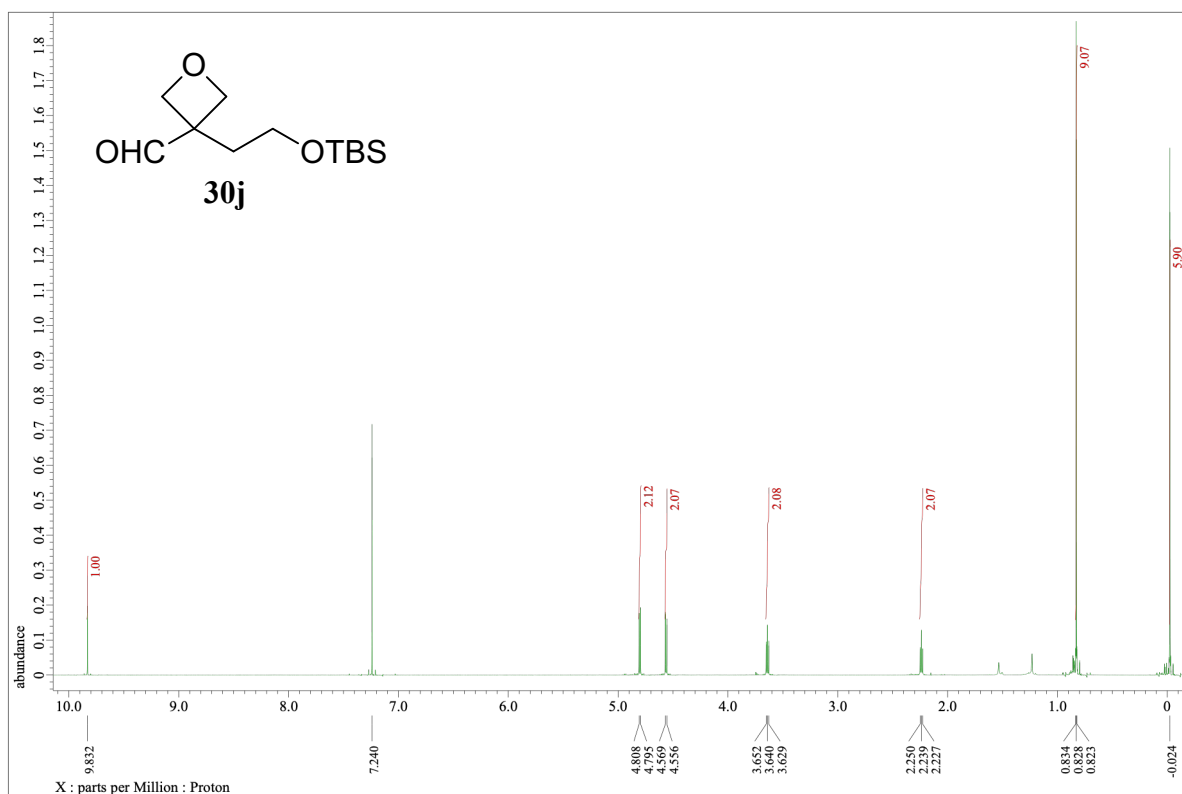


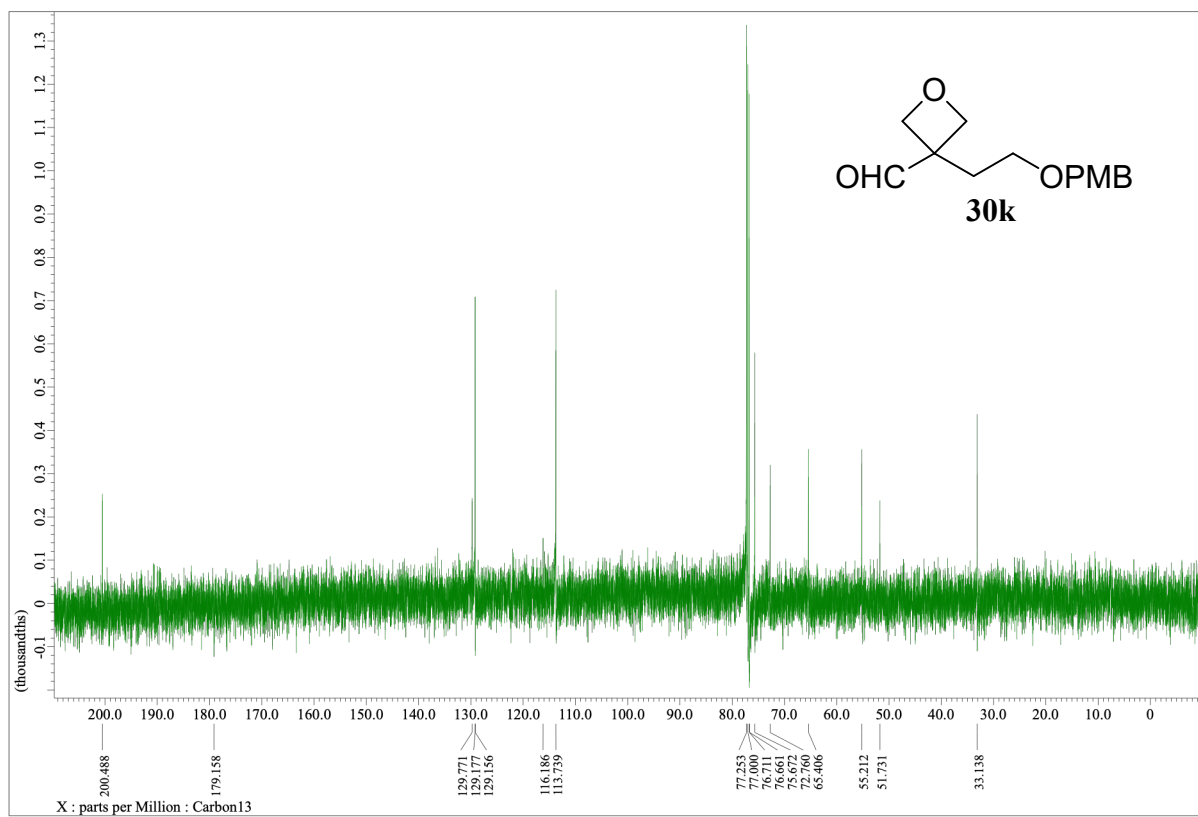
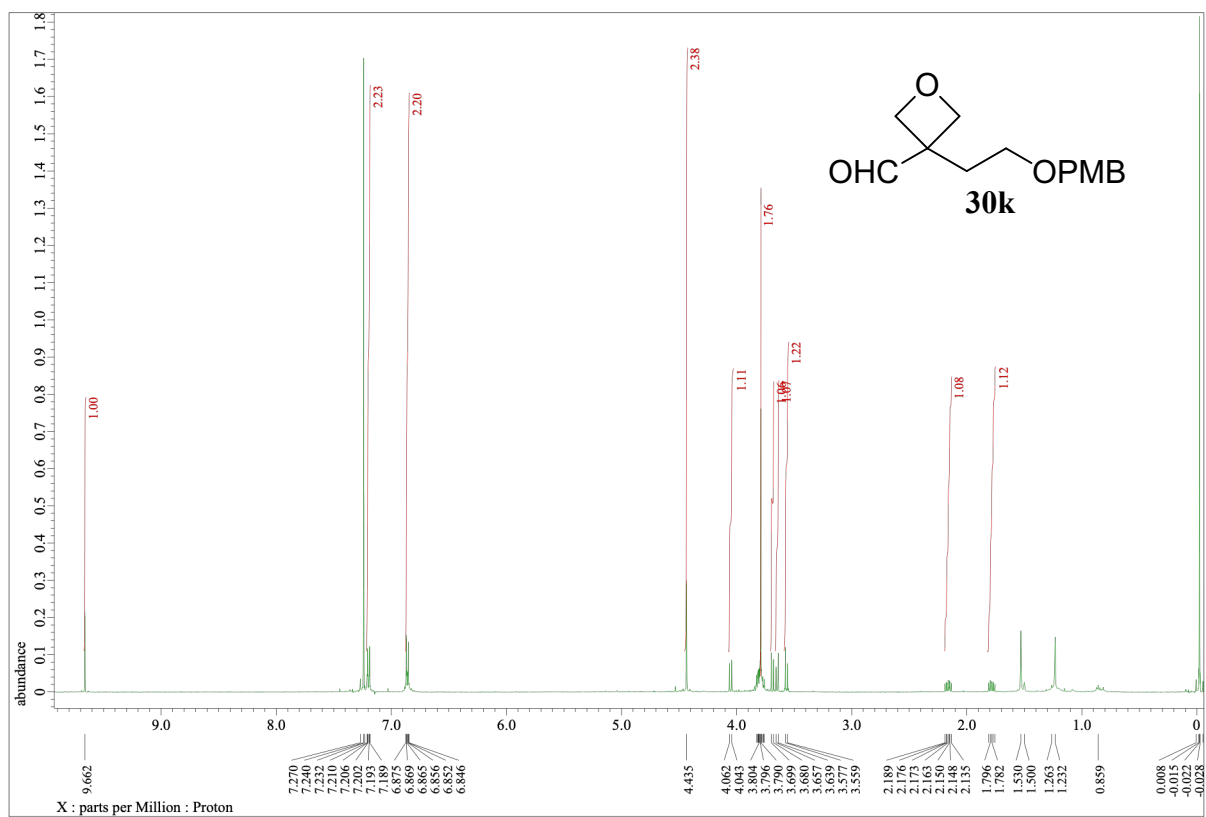


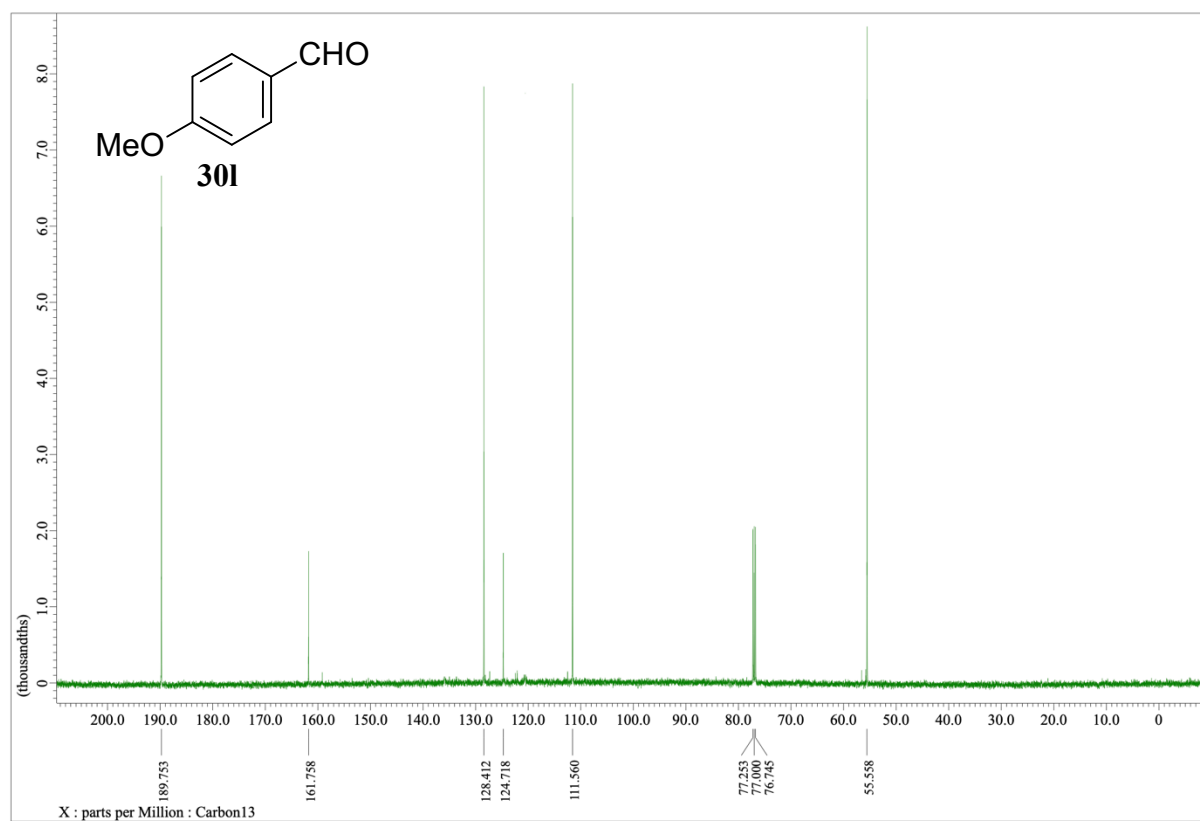
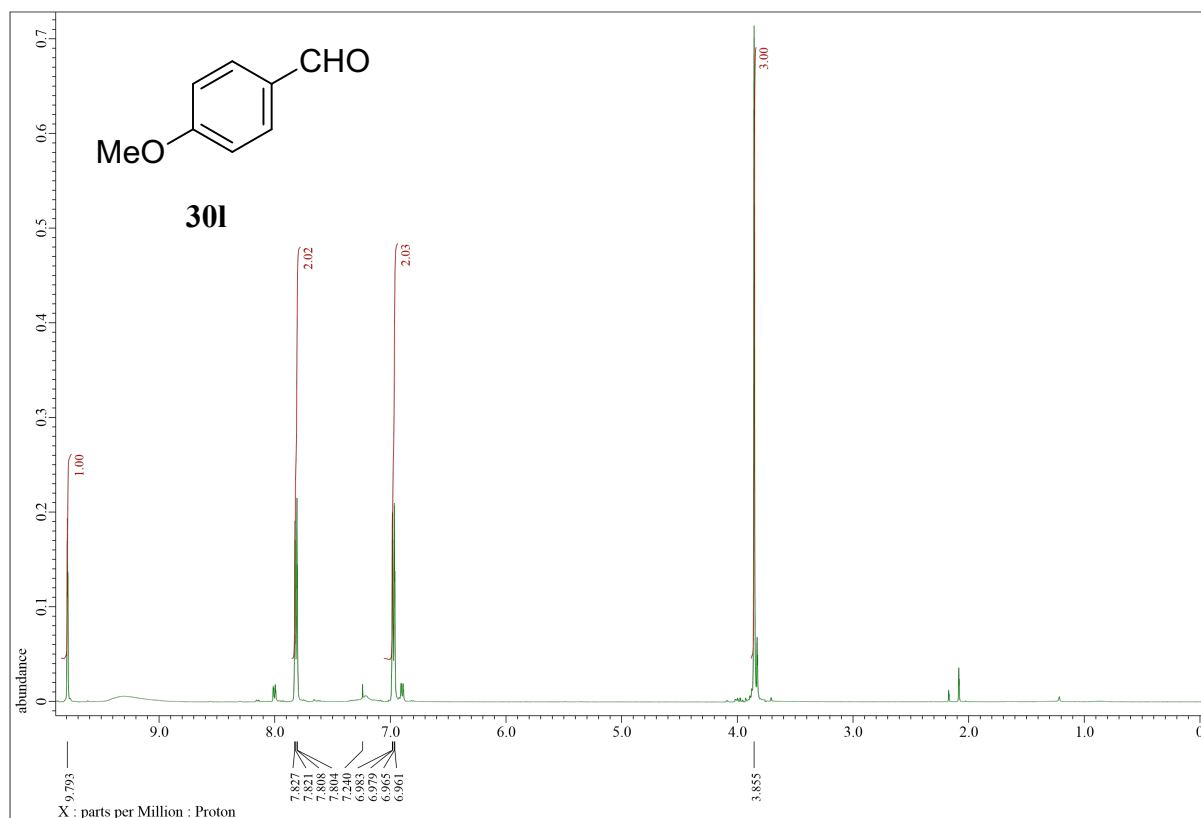


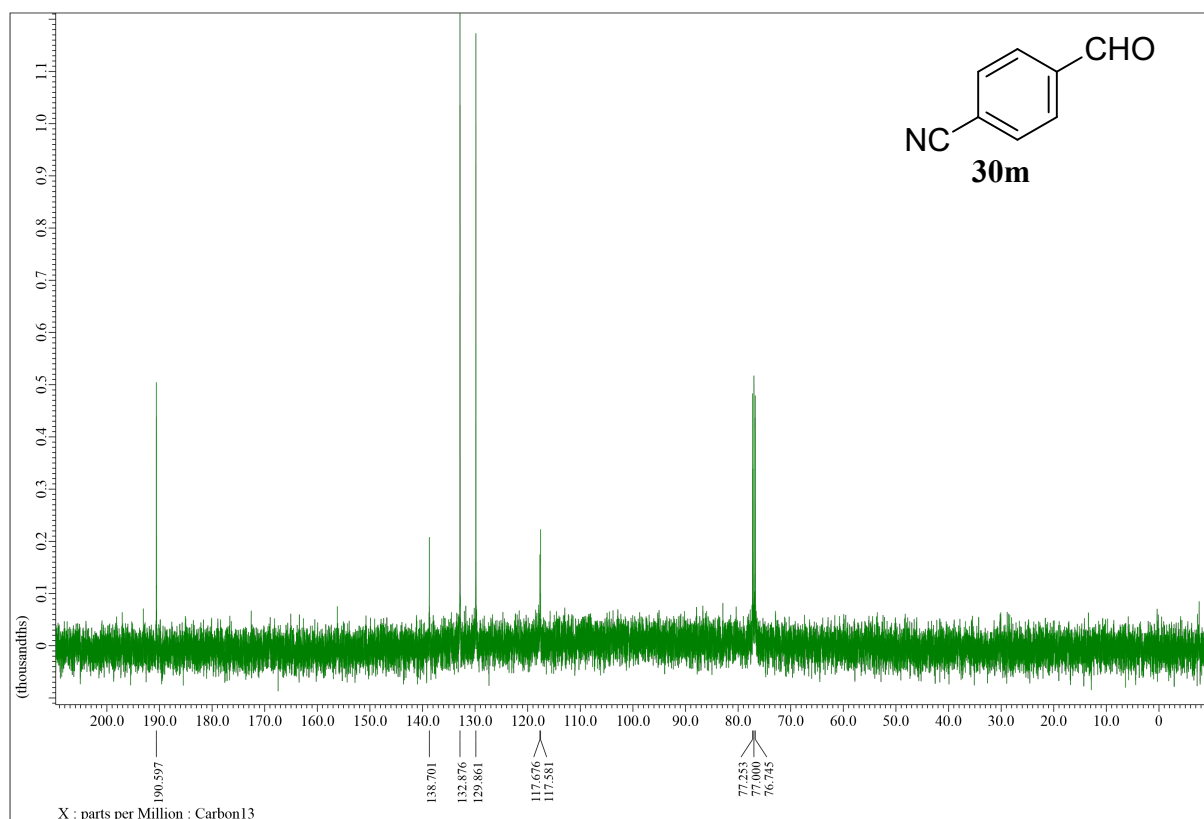
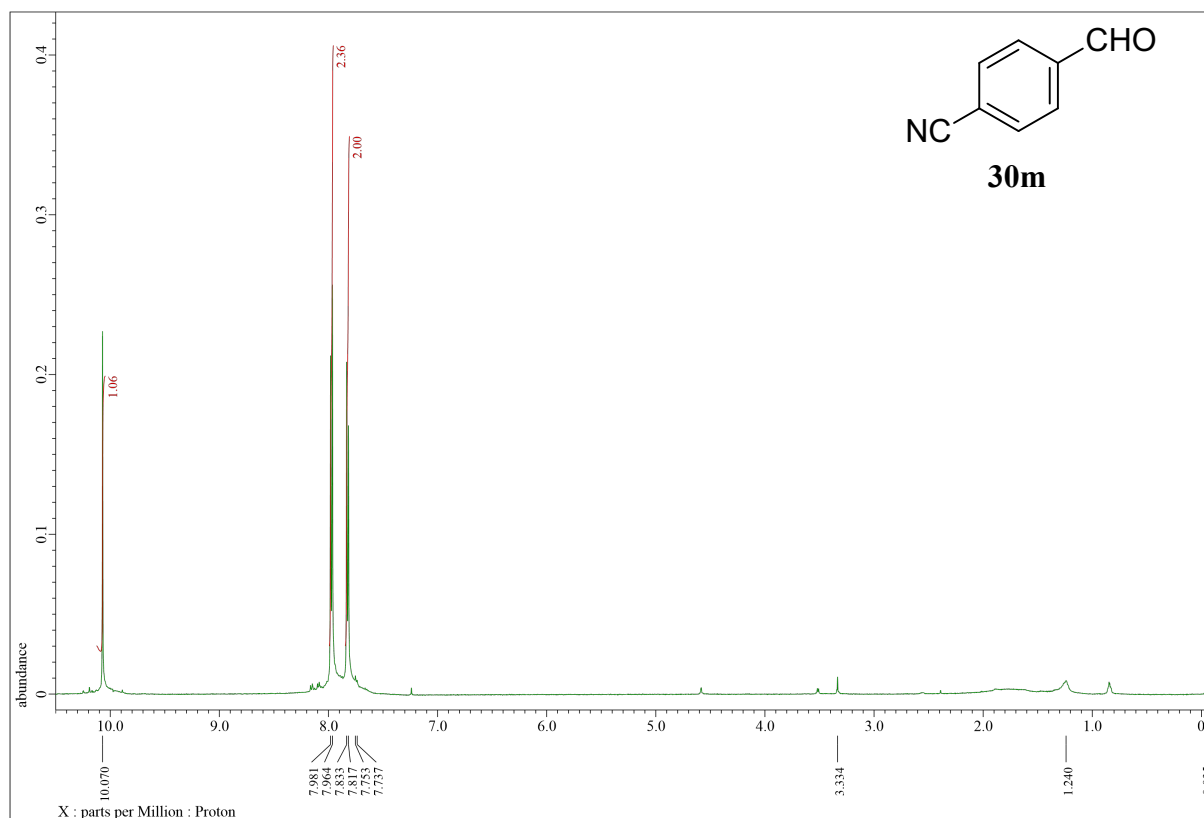


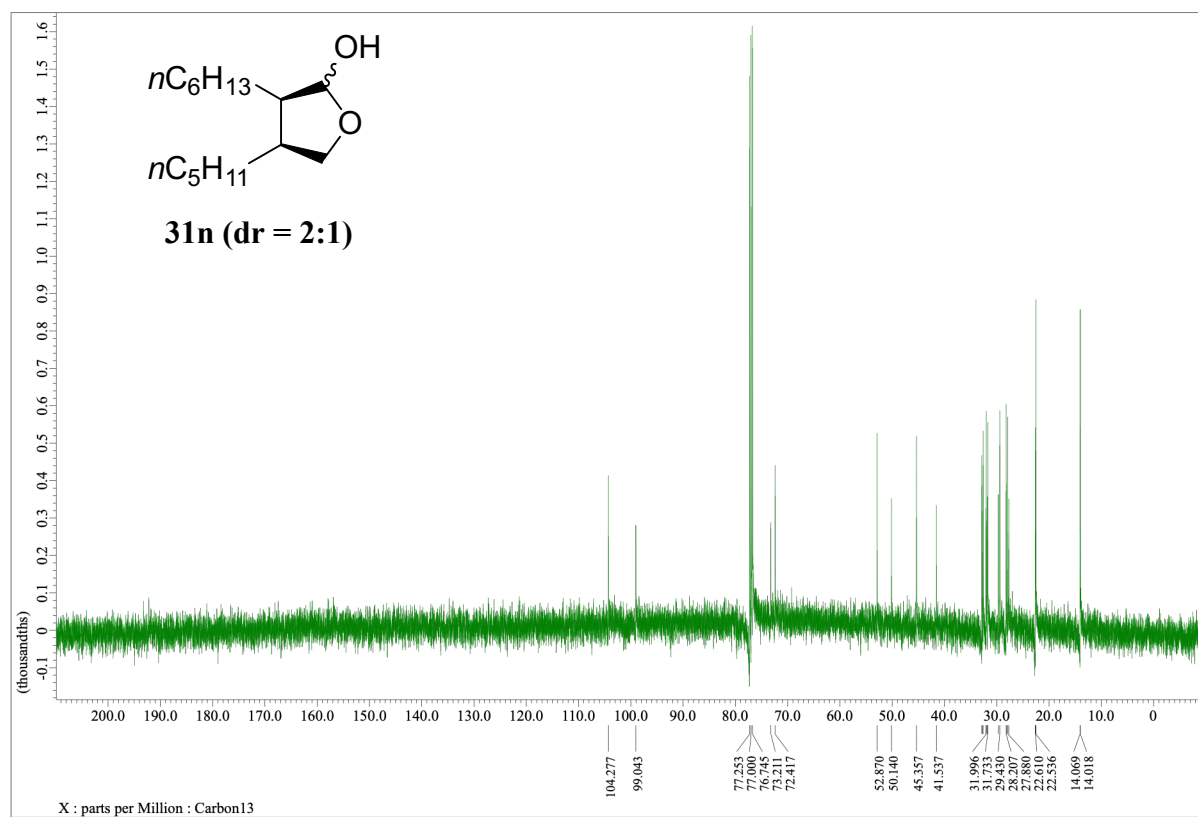
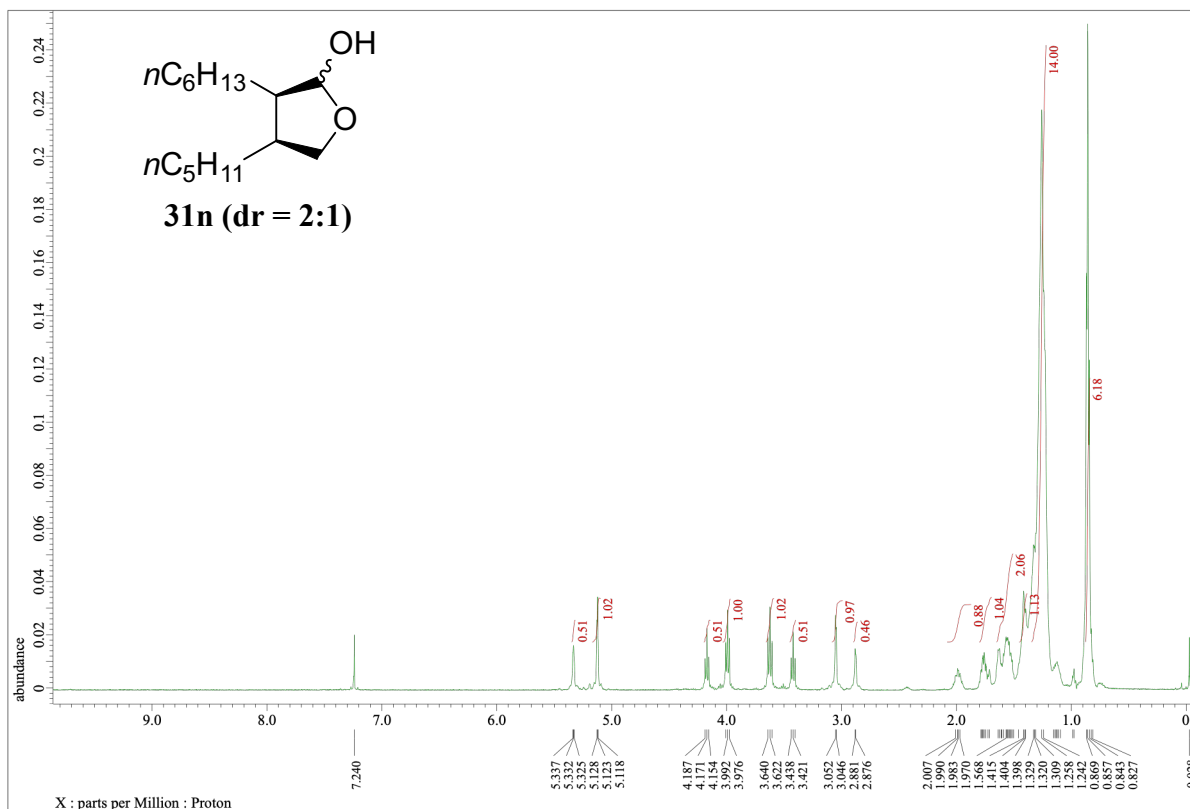


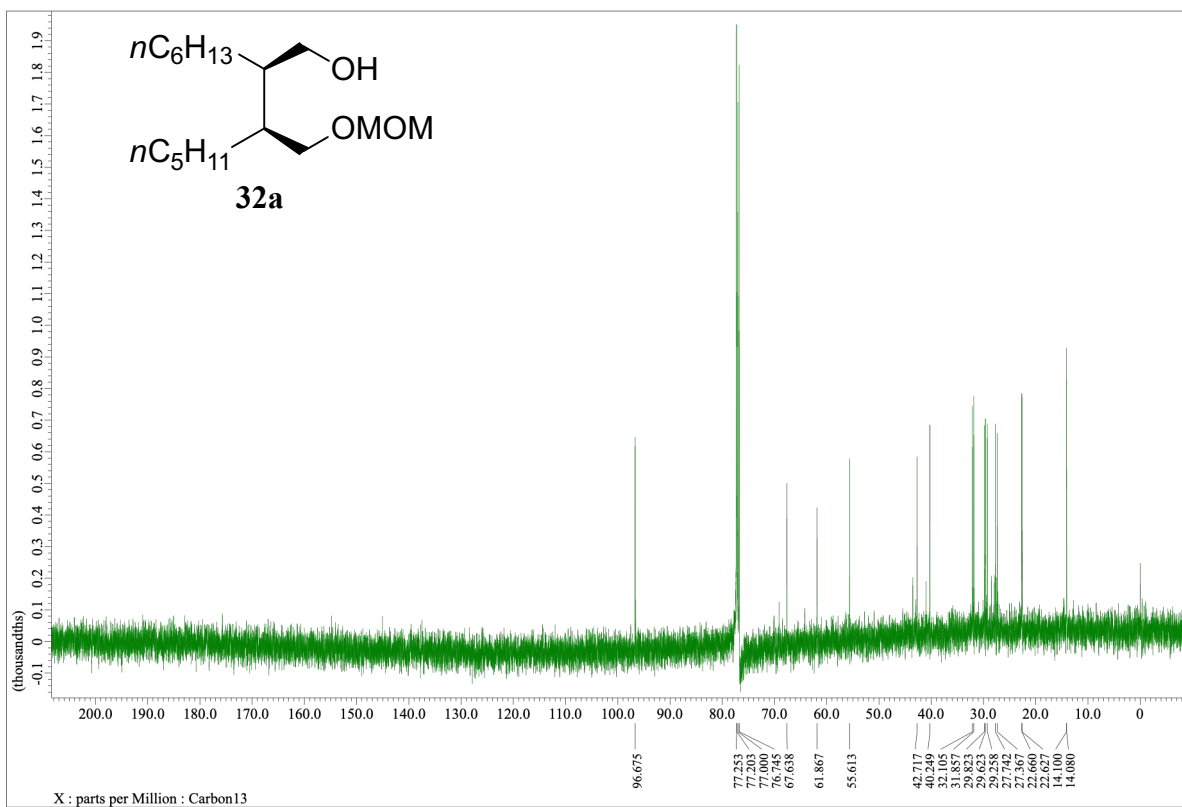
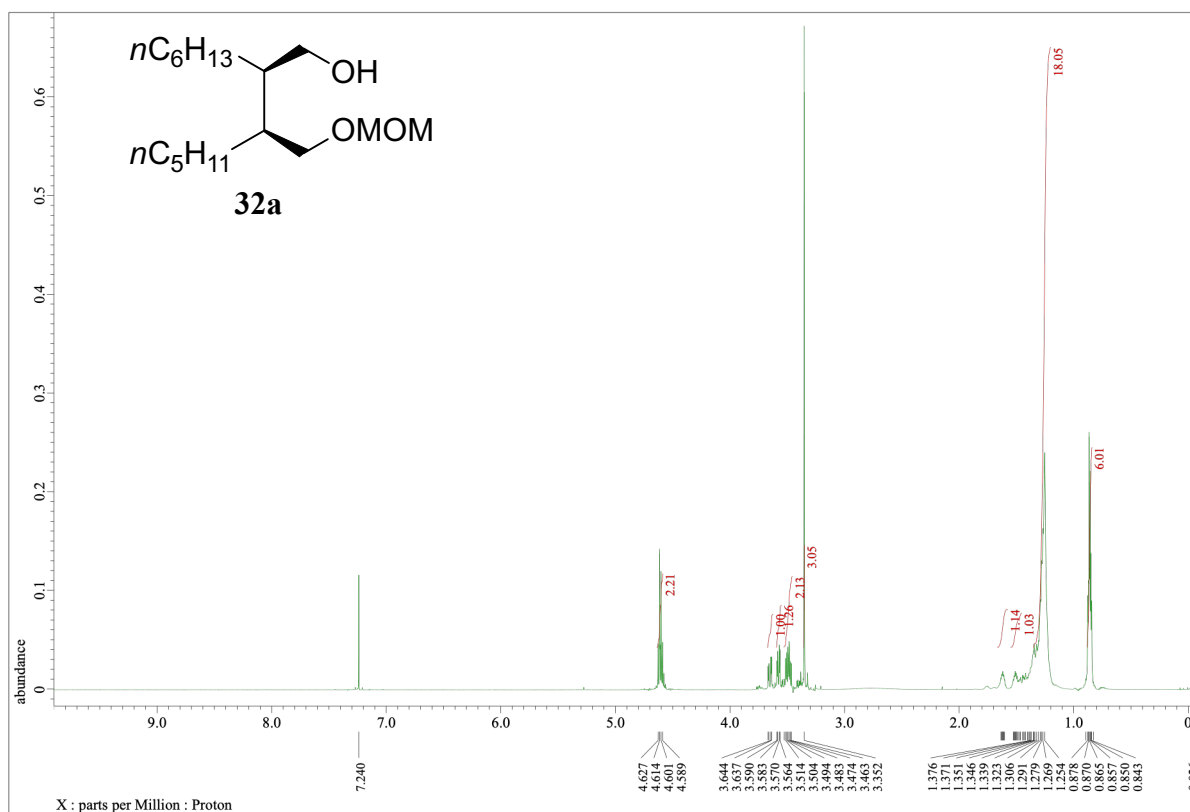


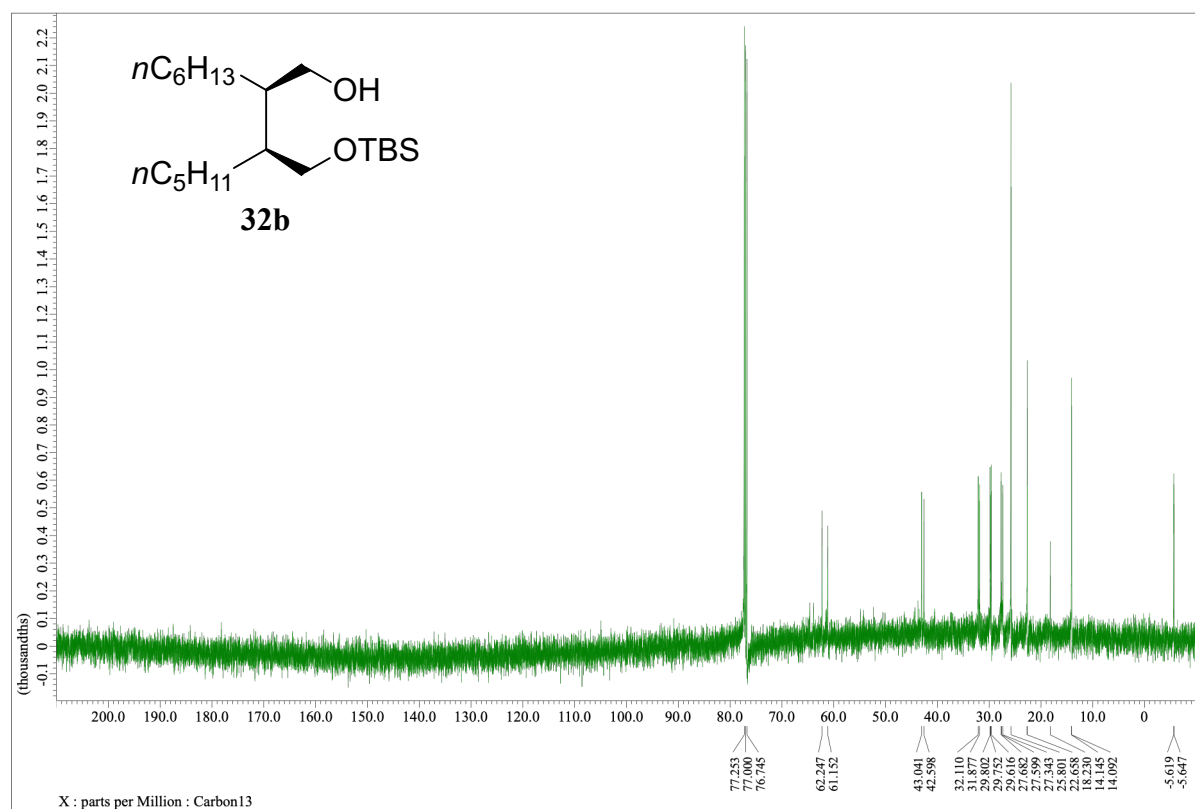
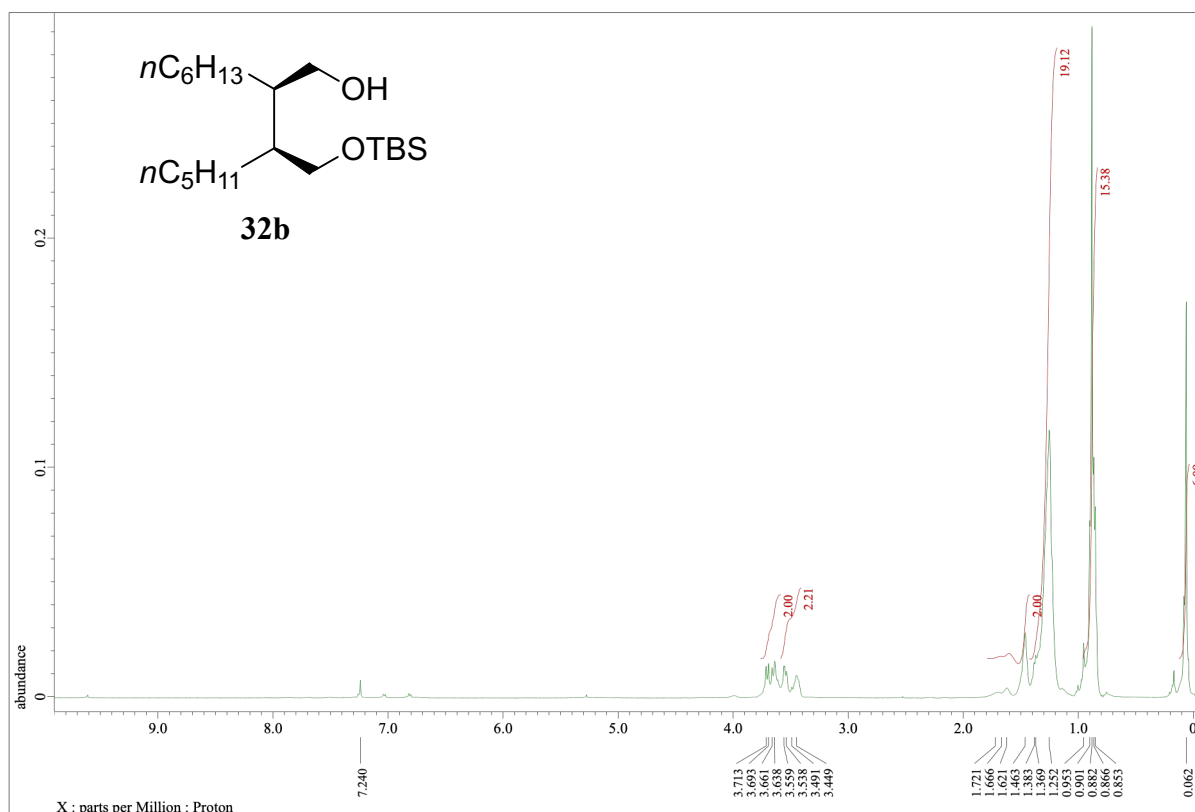


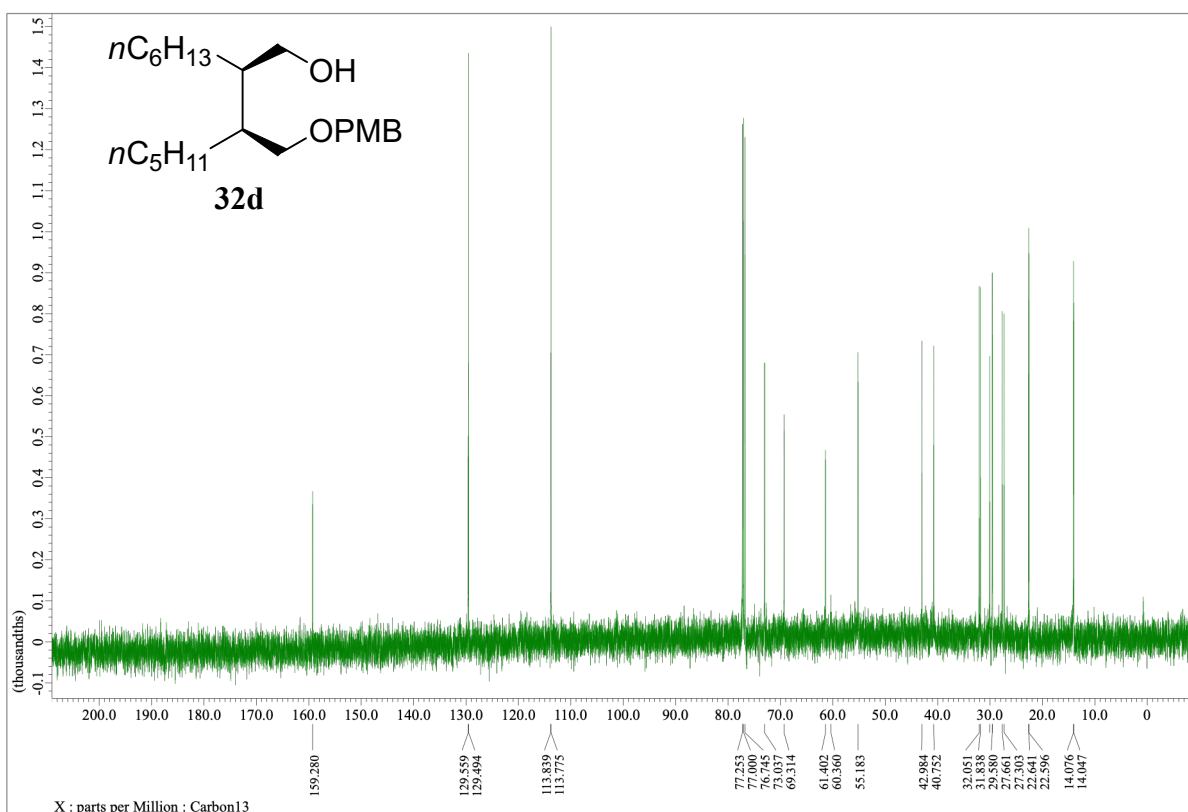
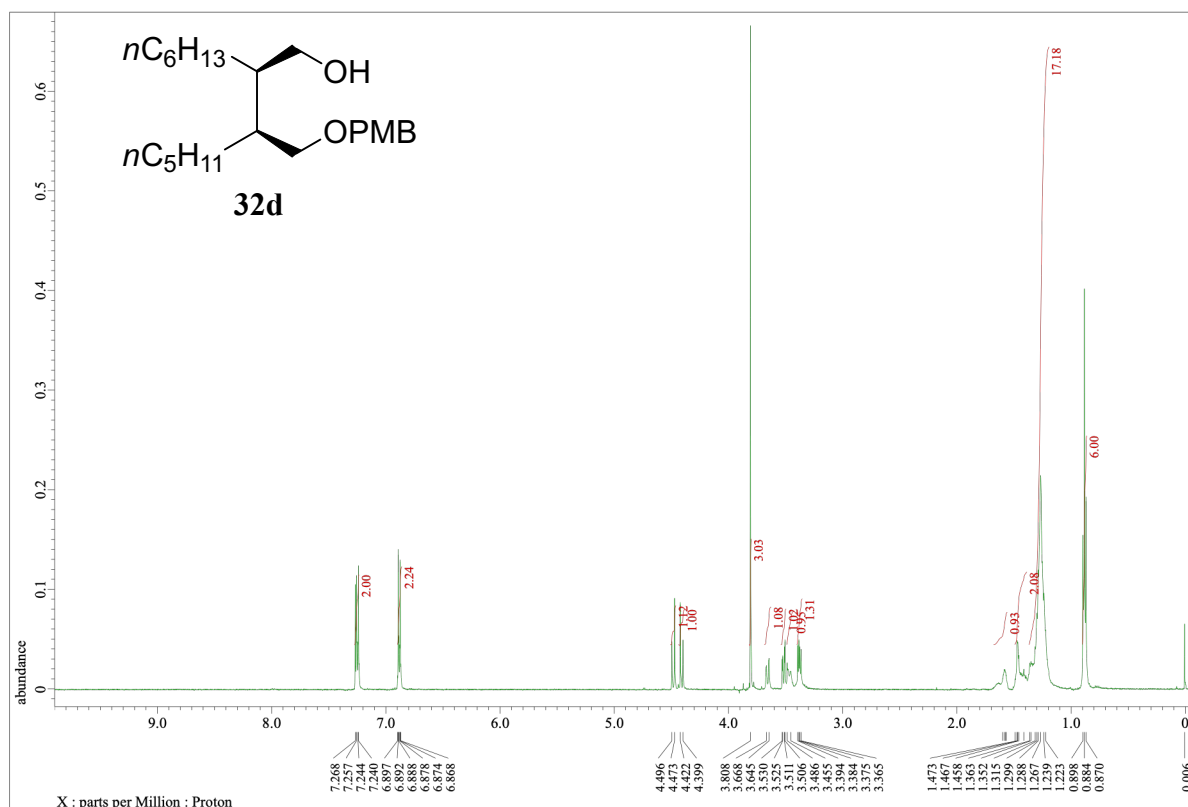


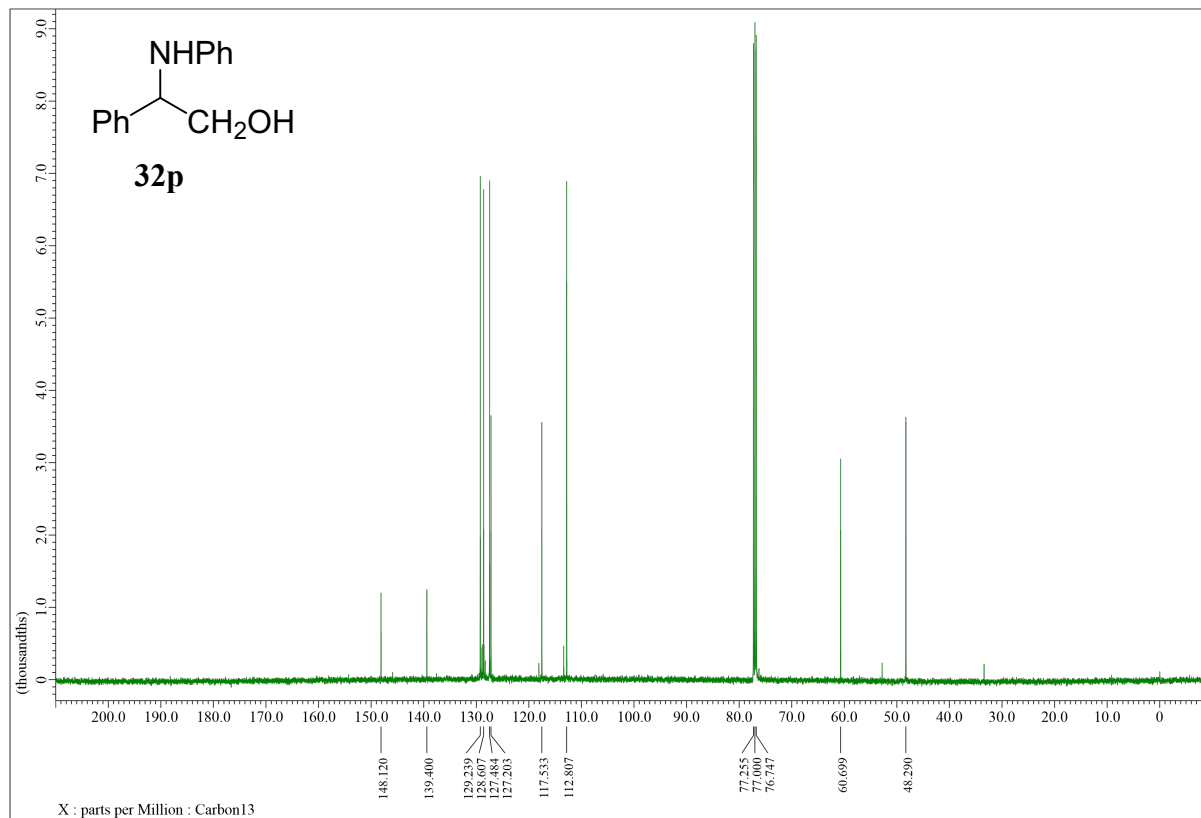
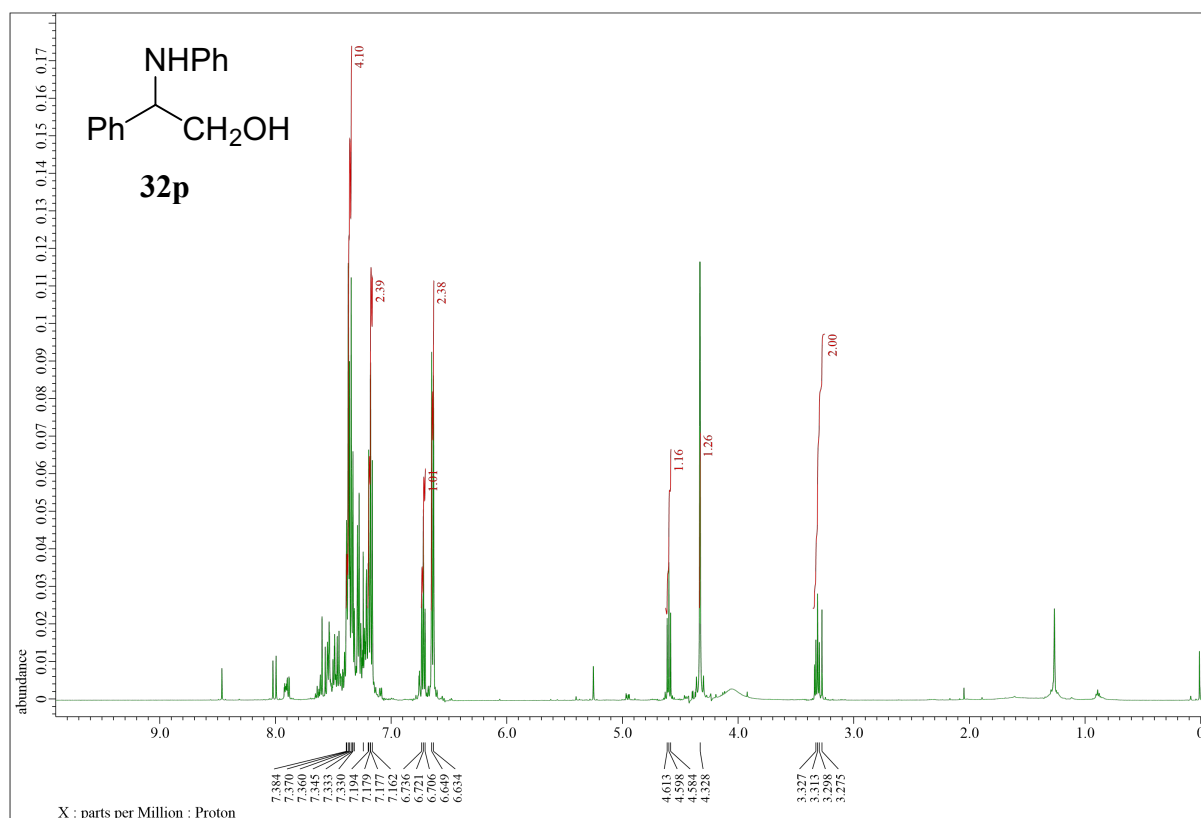


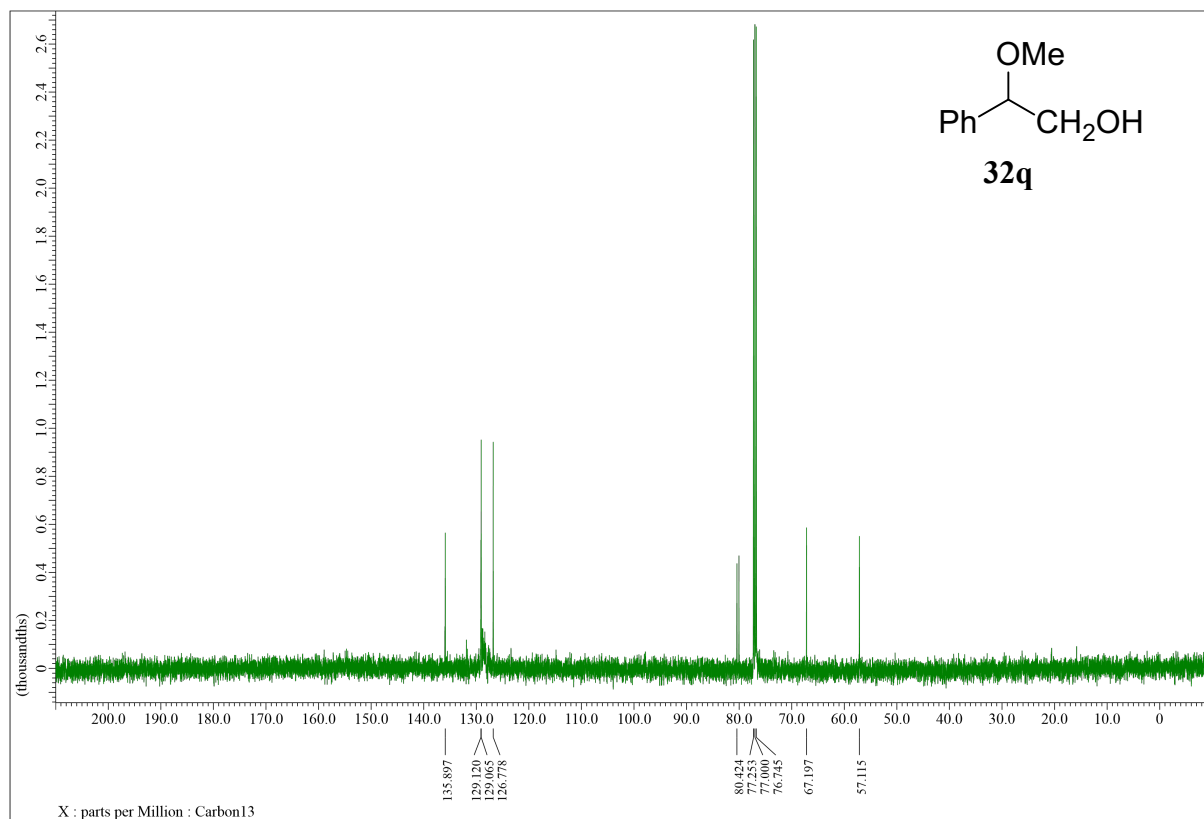
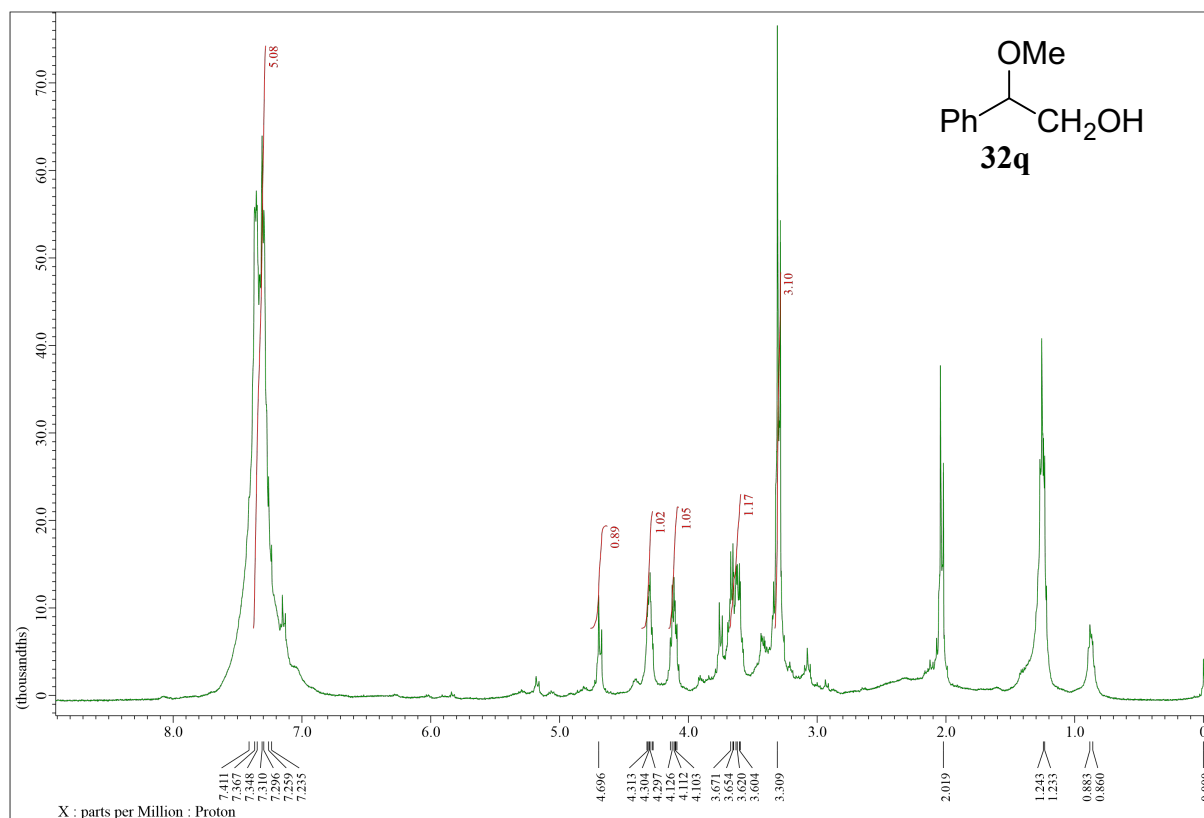












Chapter 3
Synthetic Study of Alyterinate A

3-1 Introduction

Lignans comprise a class of plant-derived secondary metabolites featuring β - β -linked diphenolic structures, widely distributed across plant parts. These compounds have garnered considerable interests due to their reported health benefits, including potential roles in reducing the risk of cardiovascular disease, alleviating menopausal symptoms, and preventing osteoporosis and breast cancer.¹ More importantly, lignans have pronounced biological activities, such as antibacterial, antiviral, antitumor, antioxidant, cytotoxic, and immunosuppressive properties. These are gaining traction in both chemical synthesis and synthetic biology.²

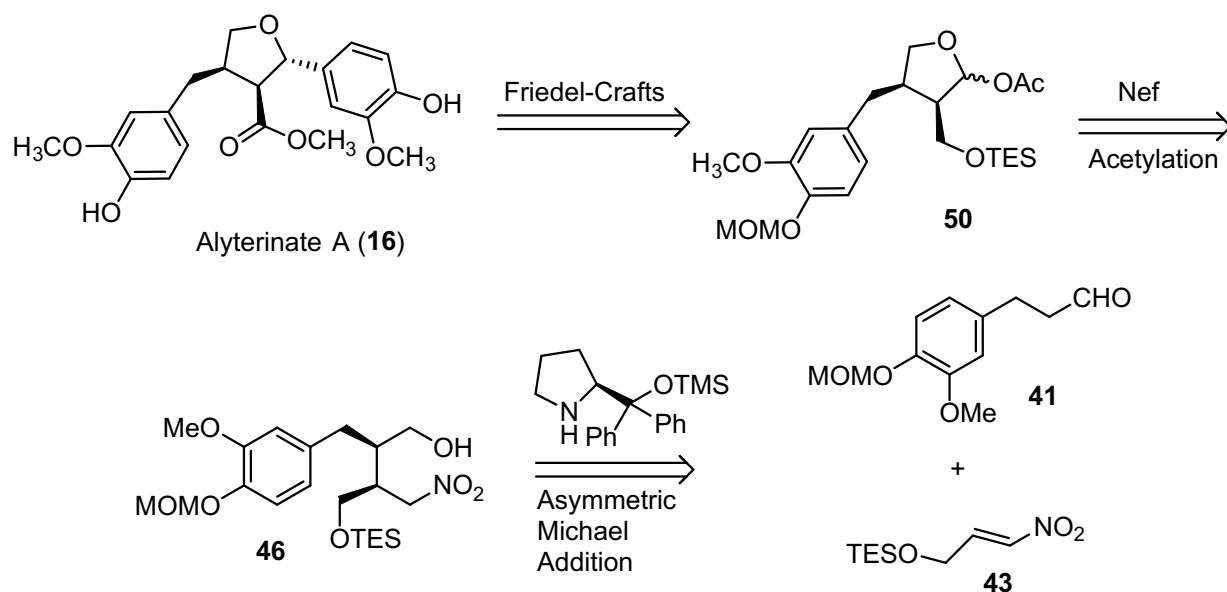
Among these, Alyterinate A, isolated from *Alyxia schlechteri* and also identified in *Willughbeia coriacea*, has demonstrated noteworthy bioactivity. Root-derived lignan esters *Alyterinate A* have potential as an effective agent against the pathogen of *Pythium insidiosum*. It is an oomycete rather than a true fungus, which lacks ergosterol in its cell membrane, rendering conventional antifungals such as itraconazole and terbinafine largely ineffective.³ This resistance profile elevates the importance of alternative agents like Alyterinate A.

Moreover, the compound isolated from *Willughbeia coriacea* exhibits moderate cytotoxicity against murine leukemia (P-388) cells ($IC_{50} = 3.04 \mu\text{g/mL}$)⁴ and against HeLa cervical cancer cells ($IC_{50} = 12.05 \mu\text{g/mL}$)⁵, indicating promise as an antitumor lead. Given these multifaceted activities and considering the challenges of naturally sourcing sufficient quantities, this research focuses on developing a scalable synthetic route for Alyterinate A. This effort may support the formation of optimized analogs for therapeutic evaluation.

3-2 Retrosynthetic Analysis

The synthetic route toward Alyterinate A was devised based on a retrosynthetic strategy that emphasizes stepwise construction of key structural groups (Scheme 3-1). Retrosynthetically, Alyterinate A can be traced back to a precursor bearing a hydroxy-functionalized tetrahydrofuran (THF) ring. Prior to this, installation of the aryl moiety is achieved through a Friedel-Crafts acylation, in which an aryl group adds to the cyclic acetal **50** intermediate. This transformation represents a key step in forming carbon–carbon bonds and requires optimization for efficient and selective acylation.

Scheme 3-1. Retrosynthetic analysis towards the synthesis of Alyterinate A



The THF ring system itself is created from a nitro adduct **46** precursor via a Nef-based cyclization strategy developed in our group⁶. This method enables the formation of a five-membered cyclic acetal **47** through intramolecular cyclization of the nitro-containing

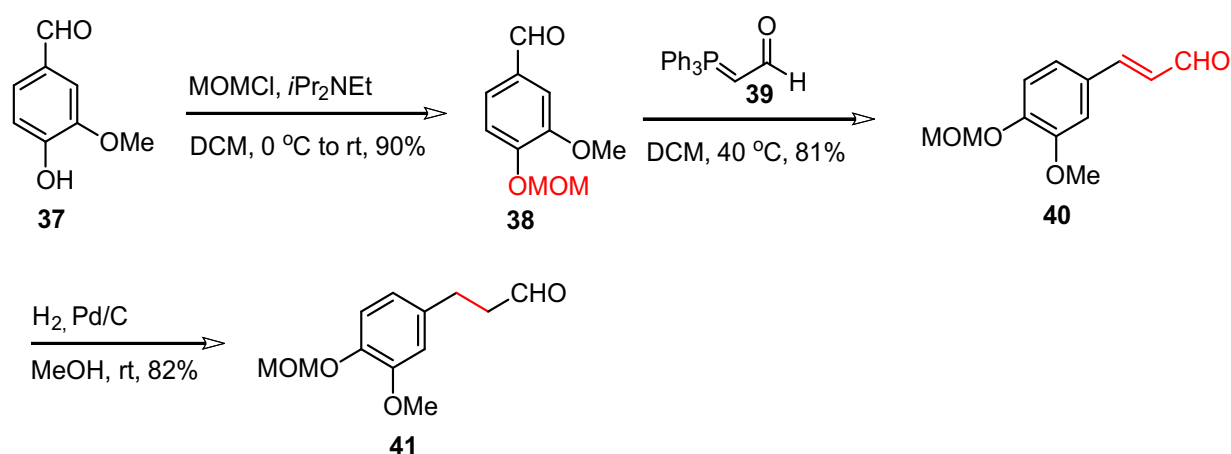
compounds. The precursor nitro adduct **46** is formed through an asymmetric Michael addition reaction between an α,β -unsaturated nitroalkene **42** and an aldehyde **40**. Subsequently, the aldehyde functionality is chemoselectively reduced to the corresponding secondary alcohol, setting the stage for ring closure. Overall, this retrosynthetic approach strategically assembles Alyterinate A (**16**), leveraging robust carbon-carbon bond-forming reactions and a novel application of Nef-based cyclization to construct the core THF ring with high efficiency.

3-3 Synthesis of Alyterinate A

3-3-1 Synthesis of aldehyde **41** and nitro olefin **43**

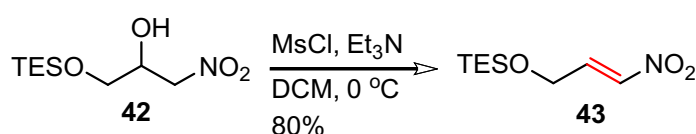
The synthesis commenced with the preparation of two pivotal intermediates: aldehyde **41** and nitro-olefin **43**. Aldehyde **41** was accessed from vanillin **37** via a sequence of protecting, olefination, and hydrogenation. First, the phenolic group of **37** was protected by MOM-Cl in the presence of a base to yield the MOM-ether **38** in 90% yield. Next, a Wittig reaction employing **39** was performed to install the α,β -unsaturated aldehyde functionality, furnishing compound **40**. The use of a stabilized ylide promoted *E*-alkene formation. The resulting **40** was then subjected to catalytic hydrogenation using H_2 over Pd/C, selectively reducing the C=C double bond to afford aldehyde **41**.

Scheme 3-2



In parallel, nitroalkane **43** was generated from the corresponding nitro alcohol **42**. The secondary nitro alcohol **42** was treated with MsCl and Et₃N, to convert the hydroxy group into a mesylate. This activated leaving group then underwent elimination under mild conditions to yield the nitroalkene **43** in 80% yield.

Scheme 3-3



3-3-2 Optimization of asymmetric Michael addition reaction

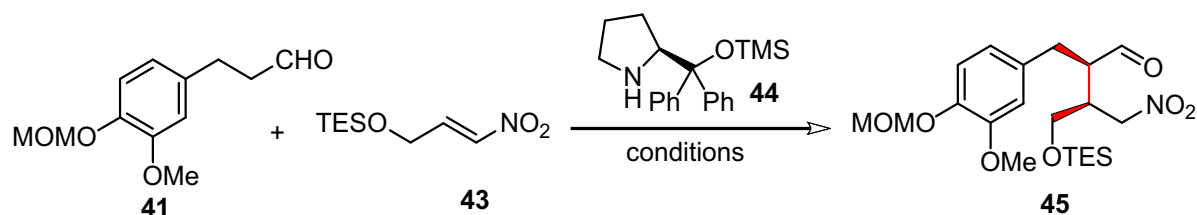
The optimization of the asymmetric Michael addition between aldehyde **41** and nitroolefin **43** was investigated using the Hayashi–Jørgensen catalyst (**44**) under various reaction conditions⁷. Key parameters, including catalyst loading, solvent, temperature, reaction time, and additive presence, were systematically varied to enhance the overall efficiency and stereoselectivity of the transformation. The initial experiments explored the influence of catalyst loading by comparing 0.1 and 0.2 equivalents of the catalyst (Entries 1 vs 2 and Entries 3 vs 4). An increase in catalyst loading generally improved both the reaction yield and diastereoselectivity⁸. This occurred because the higher catalyst concentrations promote more efficient formation of the reactive iminium ion intermediate (Scheme 3-4). For instance, in dichloromethane (DCM) at 0 °C, the yield increased from 77% to 96%, and the diastereomeric ratio improved from 88:12 to 90:10 when the catalyst loading was increased from 0.1 to 0.2 equivalents (Entries 3 and 4). These results underscore the importance of sufficient catalytic activation to achieve high stereoselectivity and product formation.

The choice of solvent was found to be a critical factor in the reaction outcome. Reactions performed in toluene (PhMe) resulted in moderate yields and lower diastereoselectivity up to 85:15 dr (Entries 1 and 2), whereas DCM consistently led to higher yields and better stereoselectivity (Entries 3 to 7). The superior performance in DCM can be attributed to its moderate polarity and ability to stabilize charged intermediates in the catalytic cycle, thereby facilitating iminium ion formation and enhancing transition state stabilization^{9,10}. Moreover, the temperature of the reaction significantly influenced both the rate and selectivity.

Reactions conducted at 0 °C provided the highest overall yields (Entry 5, 96% yield, 90:10 dr). However, when the temperature was lowered to –15 °C (Entries 6 and 7), product yields decreased to 55–71%, while the diastereomeric ratio improved to 91:9–92:8. This trend indicates that, although reduced temperatures slow down the catalytic cycle and limit the formation of key intermediates, they promote a more selective transition state, resulting in enhanced stereochemical control. Thus, at lower temperatures, the gain in selectivity comes at the expense of overall reactivity.

A notable aspect of the optimization study was the effect of *p*-nitrophenol as an additive. Its omission in Entry 9 resulted in a substantial decrease in yield (from 71% to 38%) despite maintaining selectivity. This suggests that *p*-nitrophenol plays a critical role in the proton transfer steps or stabilization of catalytic intermediates, thereby enhancing overall efficiency. The improved selectivity is likely due to a more rigid and well-defined transition state enabled by the iminium ion activation mechanism, which is facilitated by the electron-deficient *p*-nitrophenol and stabilized in a more polar solvent environment (Scheme 3-4). The high diastereomeric ratio is consistent with previous reports utilizing the Hayashi–Jørgensen catalyst (**44**) in similar Michael-type additions¹¹.

Table 3-1. Optimization of asymmetric Michael addition reaction

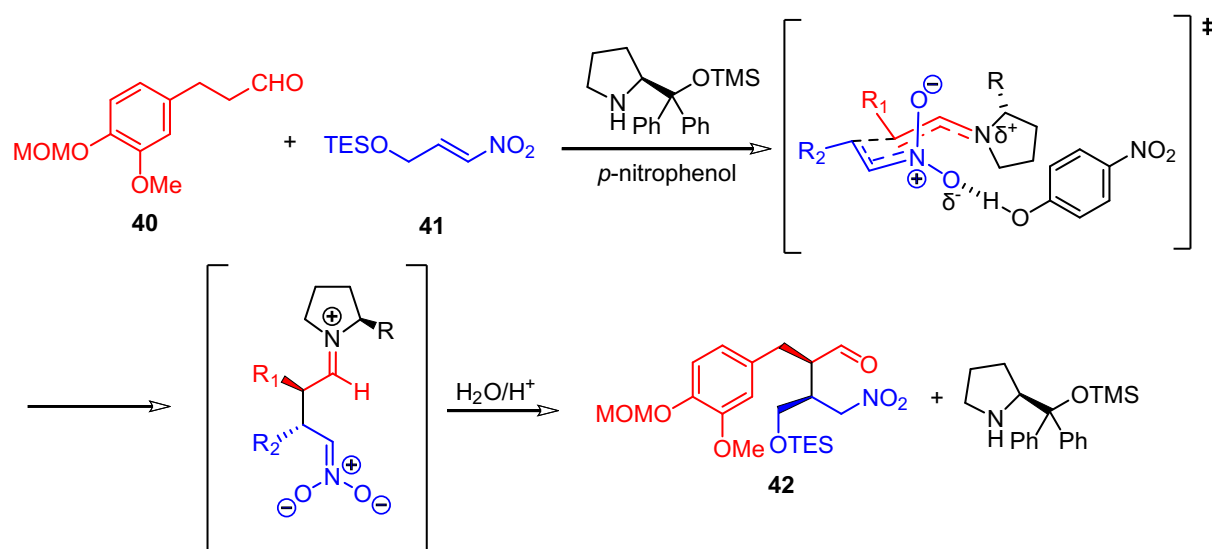


Entry	44 (eq)	Solvent (0.5 M)	Temp. (°C)	Time (h)	Yield ^b (%)	dr ^c	ee(%)
1	0.1	PhMe	-15	24	65	80:20	92
2	0.2	PhMe	-15	24	68	85:15	93
3	0.1	DCM	0	24	77	88:12	91
4	0.2	DCM	0	18	94	90:10	92
5	0.2	DCM	0	24	96	90:10	92
6	0.2	DCM	-15	24	55	91:9	94
7	0.2	DCM	-15	48	71	92:8	96
8	0.2	DCM	-15	24	87	92:8	96
9	0.2	DCM ^d	-15	24	38	90:10	-

^aunless otherwise shown, reactions were performed by employing aldehyde **41** (0.120 mmol), nitro olefin **43** (0.100 mmol), *p*-nitrophenol (0.020 mmol) for the indicated time; ^bisolated yield; ^cthe dr was determined by ¹H NMR of the crude reaction mixture; ^dthe asymmetric reaction was conducted without the addition of *p*-nitrophenol.

Moreover, longer reaction times seem to be detrimental to the yield of the product as well as its stereochemical integrity. The longer reaction time (72 h vs 24 h in Table 3-1, entry 8) allowed for greater conversion with excellent selectivity, reinforcing that the transformation is kinetically controlled. Taken together, the optimal conditions were found to involve 0.2 equivalents of the Hayashi-Jørgensen catalyst (**44**) in DCM at -15 °C for 72 hours, in the presence of *p*-nitrophenol, which afforded the desired product in 87% yield with 92:8 dr.

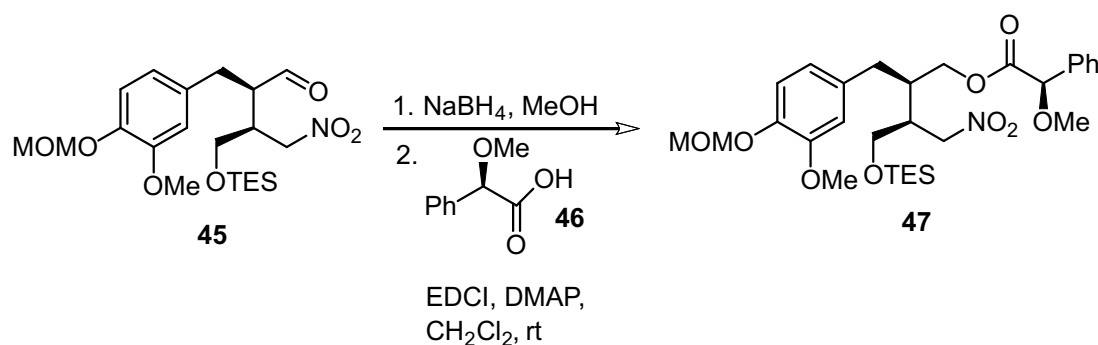
Scheme 3-4



To further evaluate the stereocontrol of the asymmetric Michael addition, the enantiomeric excess (ee) of the resulting aldehyde adduct **45** was examined. The major isomer of aldehyde **45** was isolated and subsequently reduced with NaBH₄ to afford the corresponding secondary alcohol. This chiral alcohol was then derivatized with (*R*)-(-)- α -methoxyphenylacetic acid (MPA) **46** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and DMAP in DCM to generate the corresponding MPA esters **47** (Scheme 3-5). The diastereomeric ratio of these esters was analyzed by ¹H NMR spectroscopy to determine the enantiomeric excess of the original aldehyde adduct **45**. Across all examined conditions (Entries 1–8), the reaction consistently delivers high enantiomeric excess (91–96%), demonstrating robust asymmetric induction. The ee is only slightly affected by reagent loading and reaction time, whereas solvent and temperature play more significant roles. Reactions conducted in dichloromethane generally afford higher ee values than those in toluene, indicating a more favorable environment for enantioselective control. Notably, lowering the reaction temperature

from 0 °C to −15 °C leads to a clear improvement in ee, reaching up to 96%, likely due to suppression of nonselective background pathways. Overall, the highest enantioselectivity is achieved under low-temperature conditions in DCM, highlighting temperature as the key parameter governing ee.

Scheme 3-5

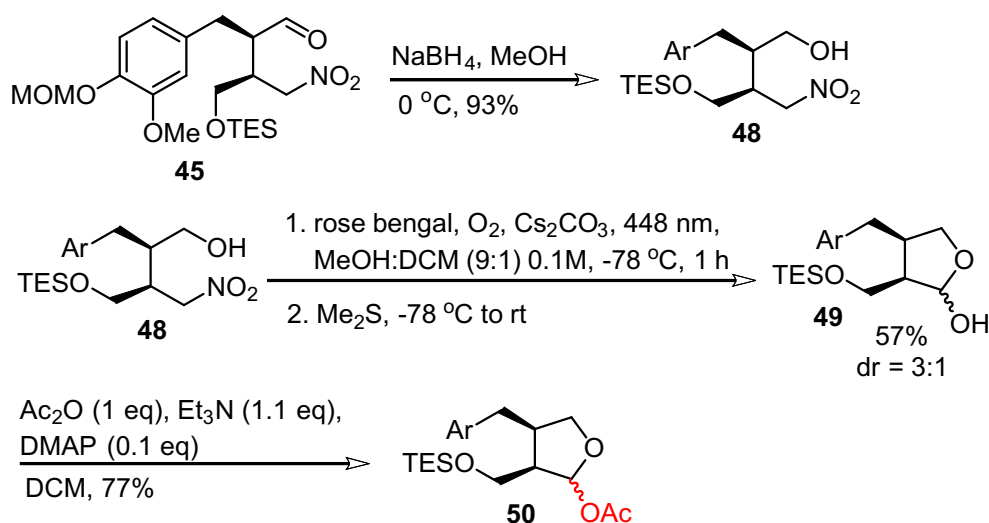


3-3-3 Nef reaction

The aldehyde functionality in compound **45** was successfully reduced to the corresponding primary alcohol **48** using NaBH₄ in 93% yield. In this case, NaBH₄ enabled selective reduction of the aldehyde without affecting the adjacent stereocenters or other potentially sensitive moieties, making it an ideal choice for this transformation. Following the successful reduction of compound **45** to alcohol **48**, the Nef reaction was employed to convert the nitro group into a carbonyl functionality, enabling the formation of cyclic acetal **49**. This transformation was accomplished using a method developed within our group, which leverages singlet oxygen (¹O₂) as the key oxidant⁶. The reaction proceeded in 57% yield with a diastereomeric ratio of 3:1, indicating moderate stereocontrol during the formation of the new stereocenter. The process resulted in a carbonyl species, which underwent intramolecular acetalization, yielding the cyclic acetal **49**.

In the next step, the free hydroxy group **49** was acetylated under standard conditions to give **50** in 77% yield. This functional group modification is a critical transformation in this synthetic sequence, as the acetate moiety not only provides protection but also introduces additional functionality for further derivatization.

Scheme 3-6



3-3-3 Friedel-Crafts acylation

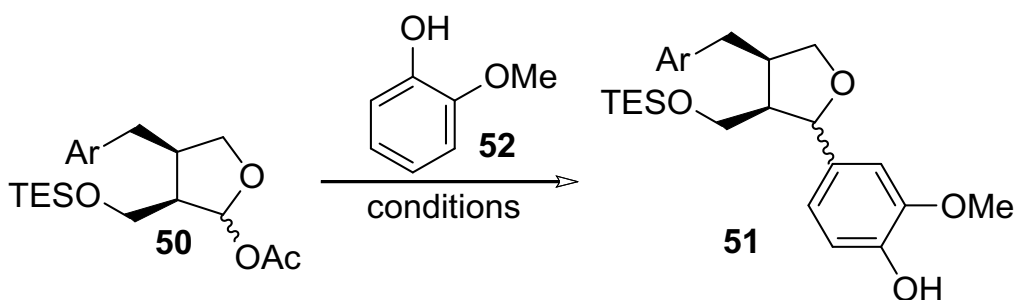
The Friedel–Crafts acylation was investigated under various conditions using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as the Lewis acid in DCM at a concentration of 0.5 M (Table 3-2). The reaction employed 5.0 equivalents of the acylating reagent and 6.0 equivalents of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, and the effects of temperature and reaction time on the yield of product **51** were examined. At $-78\text{ }^\circ\text{C}$, the desired acylated product was obtained in modest yield. After 1 hour, a yield of 30% was observed (Entry 1), and extending the reaction time to 5 hours led to only a slight improvement, affording a 33% yield (Entry 2). These results indicate that prolonging the reaction time at low temperature does not significantly enhance conversion, suggesting that the reaction is

intrinsically inefficient under these conditions. When the reaction temperature was increased to $-40\text{ }^{\circ}\text{C}$, the desired product was not obtained (Entry 3). Instead, a complex mixture of unidentified byproducts was formed, indicating that higher temperatures promote competing side reactions or decomposition pathways. This behavior is consistent with the high reactivity of $\text{BF}_3\cdot\text{Et}_2\text{O}$, which can induce undesired transformations when thermal control is relaxed.

The consistently low yields are attributed to the use of a large excess of the Lewis acid. $\text{BF}_3\cdot\text{Et}_2\text{O}$ is known to strongly coordinate to oxygen-containing protecting groups, and under these conditions it is likely to promote partial or complete deprotection of the TES group present in the substrate. Deprotection of the TES group would generate more reactive or unstable intermediates, which can undergo further side reactions, thereby reducing the yield of the desired Friedel–Crafts acylation product.

Based on these results, although low temperatures suppress extensive decomposition, the requirement for excess Lewis acid negatively impacts reaction efficiency due to TES deprotection. Conversely, higher temperatures exacerbate side reactions, leading to complex mixtures. Therefore, alternative Lewis acids, milder reaction conditions, or more robust protecting groups may be required to improve the yield and selectivity of this Friedel–Crafts acylation.

Table 3-2. Optimization of Friedel-Crafts acylation



Entry	52 [eq]	Lewis Acid [eq]	Solvent [0.5 M]	Temp. [°C]	Time [h]	Yield 51 [%]
1	5.0	BF ₃ •Et ₂ O [6.0]	DCM	-78	1	30
2	5.0	BF ₃ •Et ₂ O [6.0]	DCM	-78	5	33
3	5.0	BF ₃ •Et ₂ O [6.0]	DCM	-40	1	-

Conclusion of Chapter 3

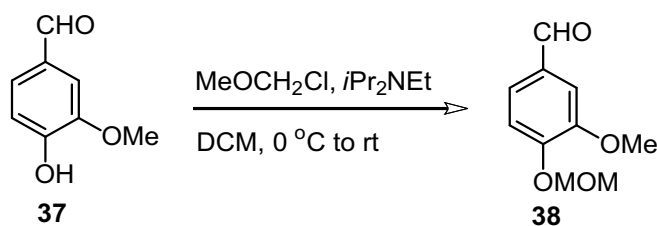
In summary, this study successfully established an efficient synthetic route toward the biologically significant lignan, Alyterinate A, particularly intermediate compound **50**. Beginning with vanillin-derived aldehyde **41** and nitro-olefin **43** precursors, a well-optimized asymmetric Michael addition catalyzed by the Hayashi–Jørgensen catalyst **44** enabled the formation of the key chiral intermediate with moderate yield (87%) and good selectivity (dr : 92:8 ; ee : 96%). Careful control of reaction parameters such as catalyst loading, solvent polarity, temperature, and the presence of *p*-nitrophenol proved crucial in achieving optimal stereochemical outcomes. Subsequent Nef-based cyclization, employing a singlet oxygen strategy, efficiently generated the tetrahydrofuran (THF) core of Alyterinate A, demonstrating the synthetic utility and versatility of this approach. Overall, the developed methodology provides a reliable and scalable pathway for further total synthesis of Alyterinate A, paving the way for the preparation of structural analogs and further biological evaluation of this promising antifungal and anticancer natural product.

References and Notes of Chapter 3

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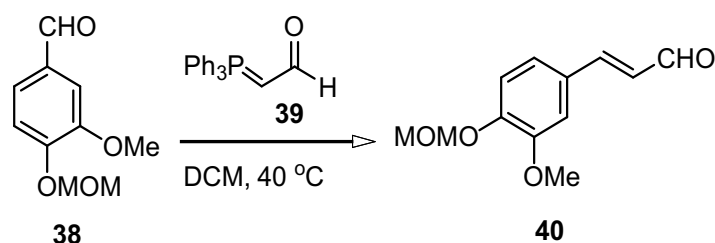
Experimental Section of Chapter 3

Tetrahydrofuran (THF), methanol (CH₃OH), and acetonitrile (CH₃CN) were purchased from Kanto Chemical Co. Inc. Dichloromethane (CH₂Cl₂) and triethylamine (Et₃N) were distilled from CaH₂. All commercially obtained reagents were employed as received. Analytical TLC was carried out using pre-coated silica gel plates (Wako TLC Silicagel 70F₂₅₄, FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan). Wakogel 60N 63-212 μm was used for column chromatography. Optical rotation was measured with a JASCO P2200 polarimeter. ESI-MS were obtained on a JEOL JMS-700TZ (JEOL Ltd., Tokyo, Japan) or BRUKER DALTONICS micro TOF-HS focus spectrometer (Bruker Japan Ltd., Yokohama, Japan). Irradiations of photoreactions were carried out with a blue LED lamp PER-AMR-448, λ_{max} = 448 nm (Techno Sigma Co., Ltd.). The ¹H NMR and ¹³C NMR spectra were recorded using a JNM-ECZR 500 (500 MHz and 126 MHz, respectively) spectrometer (JEOL Ltd., Tokyo, Japan). Chemical shifts were reported in ppm relative to CHCl₃ in CDCl₃ for ¹H NMR (δ = 7.24) and ¹³C NMR (δ = 77.0). Splitting patterns for ¹H NMR were designated as “s, d, t, q, m, dt, dd, and td”. These symbols indicate “singlet, doublet, triplet, quartet, multiplet, doublettriplet, doubletdoublet, and tripletdoublet” respectively.

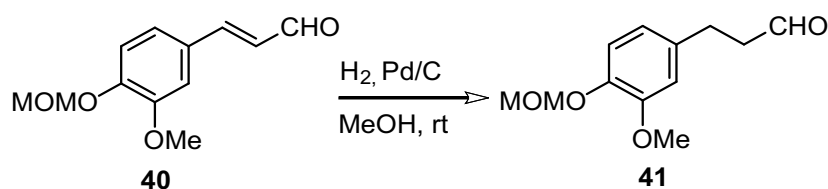


3-methoxy-4-(methoxymethoxy)benzaldehyde (38). To a solution of **37** (250 mg, 1.64 mmol) in CH₂Cl₂ (8.2 mL) was added MOMCl (2.60 mL, 2.47 mmol) and *i*Pr₂NEt (0.56 mL, 2.93 mmol) under Ar atmosphere. The mixture was stirred at 0 °C then room temperature for 17 h. The mixture was quenched with saturated NH₄Cl, extracted with AcOEt, washed with

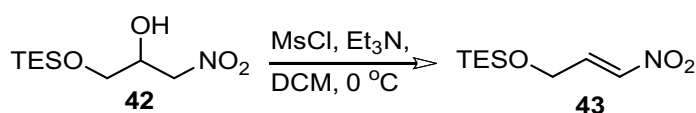
brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane: AcOEt = 90:10, 80:20 then 70:30) to obtain **38** (290 mg, 1.48 mmol, 90%) as a colorless oil: IR (neat) cm⁻¹ 3078, 2958, 2830, 1997, 1685, 1589, 1424, 1265, 1156, 1081, 983, 817, 733, 660; ¹H NMR (CDCl₃, 500 MHz) δ 9.84 (1H, s), 7.41-7.39 (2H, m), 7.25-7.24 (1H, m), 5.30 (2H, s), 3.92 (3H, s), 3.49 (3H, s); ¹³C NMR (CDCl₃, 126 MHz) δ 191.0, 151.9, 150.0, 131.0, 126.4, 114.6, 109.4, 95.0, 56.5, 56.0; HRMS (ESI-TOF) m/z: [M + H]⁺; Calcd for 197.0804; Found 197.0808.



(E)-3-(3-methoxy-4-(methoxymethoxy)phenyl)acrylaldehyde (40). To a solution of **38** (250 mg, 1.27 mmol) in CH₂Cl₂ (4.2 mL) was added **39** (580 mg, 1.91 mmol) under Ar atmosphere. The mixture was stirred for 2 h under reflux conditions. The mixture was evaporated and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane: AcOEt = 85:15 then 65:35) to obtain **40** (228 mg, 1.03 mmol, 81%) as a yellowish oil: IR (neat) cm⁻¹ 2918, 2848, 2743, 1673, 1622, 1596, 1465, 1269, 1128, 1079, 922, 866, 761, 658; ¹H NMR (CDCl₃, 500 MHz) δ 9.83 (1H, s), 8.12 (1H, d, *J* = 9.0 Hz), 7.41-7.45 (2H, m), 7.27-7.24 (1H, m), 6.90 (1H, d, *J* = 9.2 Hz), 5.31 (2H, s), 3.92 (3H, s), 3.50 (3H, s); ¹³C NMR (CDCl₃, 126 MHz) δ 193.6, 152.7, 149.9, 149.4, 128.3, 127.1, 123.1, 115.6, 110.4, 95.1, 56.4, 55.9; HRMS (ESI-TOF) m/z: [M+H]⁺; Calcd for 223.0966; Found 223.0965.

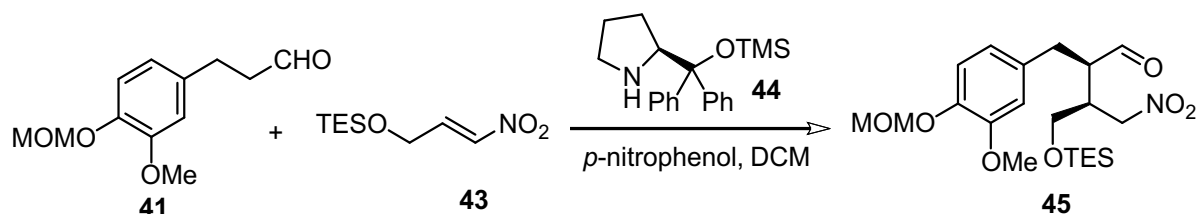


3-(3-methoxy-4-(methoxymethoxy)phenyl)propanal (41). To a solution of **40** (280 mg, 1.26 mmol) in MeOH (2.5 mL) was carefully added 10% Pd/C (14.0 mg, 5% wt) under Ar atmosphere. The solution was purged with H₂ gas stirring was continued under H₂ atmosphere at rt for 17 h. The solution was filtered through celite and then concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane: AcOEt = 65:35) to obtain **41** (231 mg, 1.03 mmol, 82%) as a colorless oil: IR (neat) cm⁻¹ 2953, 2828, 2726, 1724, 1591, 1513, 1465, 1419, 1263, 1155, 1134, 1155, 996, 814, 761, 640; ¹H NMR (CDCl₃, 500 MHz) δ 9.79 (1H, s), 7.01-7.05 (1H, m), 6.72-6.67 (2H, m), 5.17 (2H, s), 3.84 (3H, s), 3.48 (3H, s), 2.89 (2H, t, *J* = 7.5 Hz), 2.75 (2H, t, *J* = 7.4 Hz); ¹³C NMR (CDCl₃, 126 MHz) δ 201.7, 149.7, 144.8, 134.7, 120.2, 116.6, 112.0, 95.5, 56.1, 55.8, 45.4, 27.7; HRMS (ESI-TOF) *m/z*: [M+Na]⁺; Calcd for 247.0947; Found 247.0941.



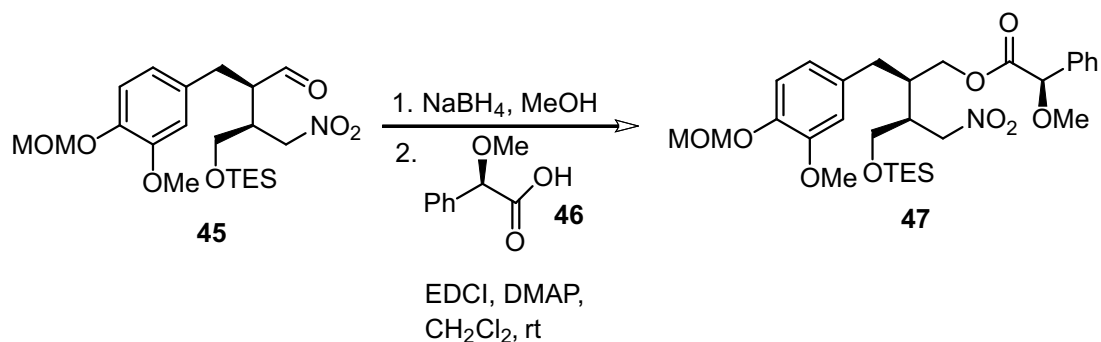
(E)-triethyl((3-nitroallyl)oxy)silane (43). To a solution of **42** (100 mg, 0.425 mmol) in CH₂Cl₂ (1.0 mL) were added NEt₃ (150 μ L, 1.06 mmol) and MsCl (0.068 mL, 0.595 mmol) at 0 °C under Ar atmosphere. After stirring for 5 min, the mixture was quenched with saturated NH₄Cl, extracted with AcOEt, washed with brine, dried over Na₂SO₄, filtered through a short silica gel pad and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (hexane: AcOEt = 95:5, 90:10) to obtain **43** (73.9 mg, 0.340 mmol, 80 %) as

a colorless oil: IR (neat) 3126, 2957, 2912, 2878, 1943, 1716, 1566, 1223, 1140, 1016, 826, 746, 670 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 7.32-7.17 (2H, m), 4.43 (1H, d, $J = 2.1$ Hz), 0.95 (9H, t, $J = 7.8$ Hz), 0.62 (6H, q, $J = 7.8$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) δ 141.7, 139.3, 59.4, 6.6, 4.2.

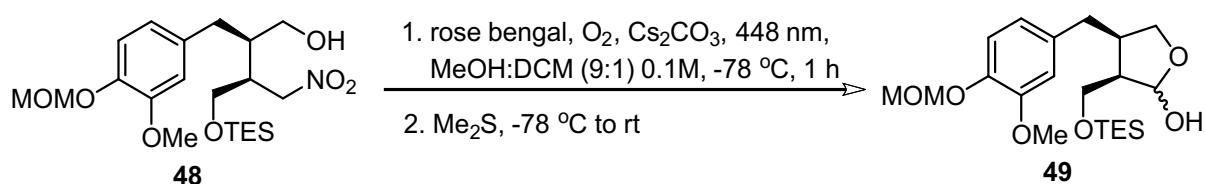


(2R,3S)-2-(3-methoxy-4-(methoxymethoxy)benzyl)-4-nitro-3-(((triethylsilyl)oxy)methyl)butanal (45). To a solution of Hayashi-Jørgensen catalyst (**44**) (6.52 mg, 0.020 mmol) in CH_2Cl_2 (0.20 mL) were added **41** (26.0 mg, 0.120 mmol) in CH_2Cl_2 (50 μL), **43** (22.4 mg, 0.100 mmol) and *p*-nitrophenol (0.27 mg, 0.020 mmol) at 0 $^\circ\text{C}$ under Ar atmosphere. The mixture was stirred for 24 h at 0 $^\circ\text{C}$, evaporated and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane: AcOEt = 95:5, 90:10 then 85:15) to obtain **45** (42.4 mg, 0.096 mmol, 96%, dr >99:1) as a colorless oil: Major diastereomer = IR (neat) cm^{-1} 2955, 2913, 2877, 1723, 1591, 1554, 1514, 1457, 1230, 1134, 1036, 803, 746, 669; ^1H NMR (CDCl_3 , 500 MHz) δ 9.71 (1H, d, $J = 1.3$ Hz), 7.06-7.03 (1H, m), 6.72-6.67 (2H, m), 5.18 (2H, s), 4.53 (1H, dd, $J = 13.0, 8.2$ Hz), 4.43 (1H, dd, $J = 12.8, 4.9$ Hz), 3.84 (3H, s), 3.69-3.65 (2H, m), 3.48 (3H, s), 3.00 (1H, dd, $J = 13.6, 8.0$ Hz), 2.89-2.86 (1H, m), 2.82-2.73 (1H, m), 2.59 (1H, t, $J = 7.8$ Hz), 0.93-0.90 (9H, m), 0.56 (6H, q, $J = 7.9$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) δ 202.4, 149.9, 145.3, 132.2, 121.0, 116.6, 112.4, 95.5, 74.1, 61.4, 56.2, 55.8, 52.9, 40.3, 32.2, 6.8, 6.7, 6.6, 4.3, 4.2, 4.1; HRMS (ESI-TOF) m/z : $[\text{M}+\text{Na}]^+$; Calcd for 464.2085; Found 464.2075.

(2*R*,3*S*)-2-(3-methoxy-4-((methoxymethoxy)benzyl)-4-nitro-3-(((triethylsilyl)oxy)methyl)butan-1-ol (48). To a solution of **45** (120 mg, 0.271 mmol) in MeOH (1.0 mL) was added NaBH₄ (15.0 mg, 0.408 mmol) at 0 °C under Ar atmosphere. After stirring for 15 min, the mixture was quenched with saturated NaHCO₃, extracted with AcOEt, washed with brine, dried over Na₂SO₄, filtered and concentrated. *in vacuo*. The residue was purified by silica gel column chromatography (hexane: AcOEt = 80:20 then 70:30) to obtain **48** (117 mg, 0.252 mmol, 93%) as a colorless oil: IR (neat) cm⁻¹ 3587, 2954, 1734, 1590, 1552, 1514, 1457, 1419, 1264, 1156, 1079, 1004, 923, 811, 745; ¹H NMR (CDCl₃, 500 MHz) ¹H-NMR δ 7.05 (1H, dd, *J* = 8.1, 1.8 Hz), 6.71-6.67 (2H, m), 5.18 (3H, s), 4.61 (1H, dd, *J* = 12.4, 2.5 Hz), 4.49 (1H, dd, *J* = 12.6, 5.0 Hz), 3.85 (3H, s), 3.76 (1H, dd, *J* = 10.7, 5.7 Hz), 3.66-3.62 (1H, m), 3.50 (3H, s), 2.64-2.53 (2H, m), 2.06-2.02 (1H, m), 1.57-1.53 (1H, m), 0.94 (9H, t, *J* = 7.9 Hz), 0.60 (6H, q, *J* = 8.0 Hz); ¹³C NMR (CDCl₃, 126 MHz) δ 149.7, 144.9, 133.7, 121.1, 116.5, 112.5, 95.5, 74.5, 62.4, 62.1, 56.1, 55.8, 44.0, 41.2, 34.8, 6.6, 6.5, 6.3, 4.0, 3.9, 3.8; HRMS (ESI-TOF) *m/z*: [M+H]⁺; Calcd for 444.2414; Found 444.2412.

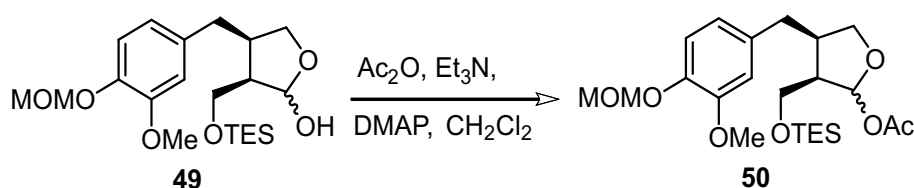


Determination of ee: To a solution of **48** (40.0 mg, 0.120 mmol) in DCM (1.5 mL) was added (*R*)-(-)- α -Methoxyphenylacetic Acid (27.9 mg, 0.168 mmol), EDCI (26.1 mg, 0.168 mmol) and DMAP (0.002 g, 0.012 mmol) at rt under Ar atmosphere. After stirring for 3 h, the mixture was quenched with 1 M HCl extracted with AcOEt, then wash with NaHCO₃ and extracted with AcOEt, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by short silica gel column chromatography (hexane: AcOEt = 60:40) to obtain **47** as a colorless oil. The ee was determined by the ¹H NMR of the ester **47** (ee : 96%) : IR (neat) cm⁻¹ 3662, 3408, 1725, 1691, 1591, 1468, 1349, 1156; ¹H NMR (CDCl₃, 500 MHz) δ 7.44-7.31 (5H, m), 7.00 (1H, dd, *J* = 8.0, 1.6 Hz), 6.54-6.51 (2H, m), 5.16 (2H, s), 4.74 (1H, s), 4.27-4.20 (2H, m), 4.07 (1H, s), 3.77 (3H, s), 3.59 (2H, d, *J* = 4.7 Hz), 3.48 (3H, s), 3.39 (3H, s), 2.63-2.59 (1H, m), 2.45-2.39 (2H, m), 2.14-2.10 (1H, m), 0.91-0.88 (9H, m), 0.53 (6H, dd, *J* = 14.6, 8.0 Hz); ¹³C NMR (CDCl₃, 126 MHz) δ 170.4, 149.8, 145.1, 136.1, 133.1, 129.1, 128.9, 127.1, 121.1, 116.5, 112.4, 95.5, 82.6, 74.5, 64.1, 61.3, 57.4, 56.2, 55.8, 40.6, 39.6, 34.6, 6.7, 4.2; HRMS (ESI-TOF) *m/z*: [M+H]⁺; Calcd for 592.2934; Found 592.2936.



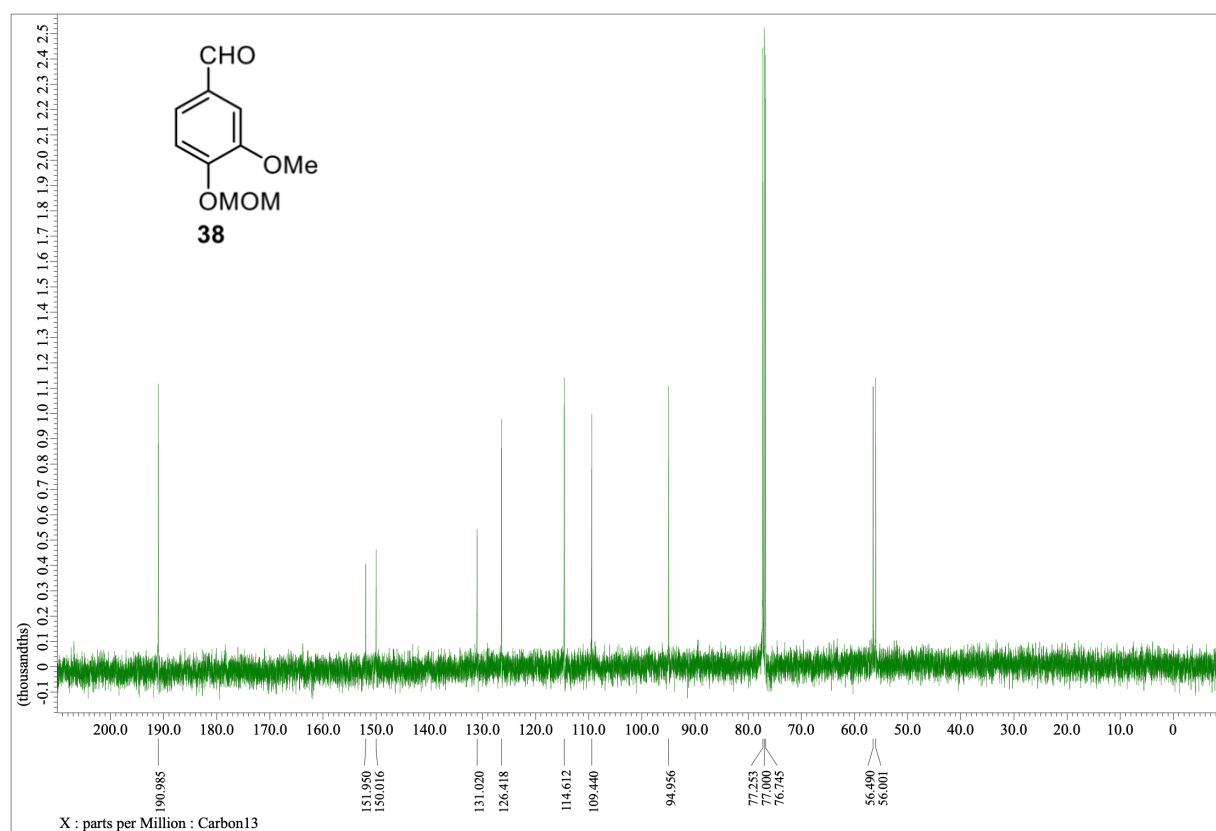
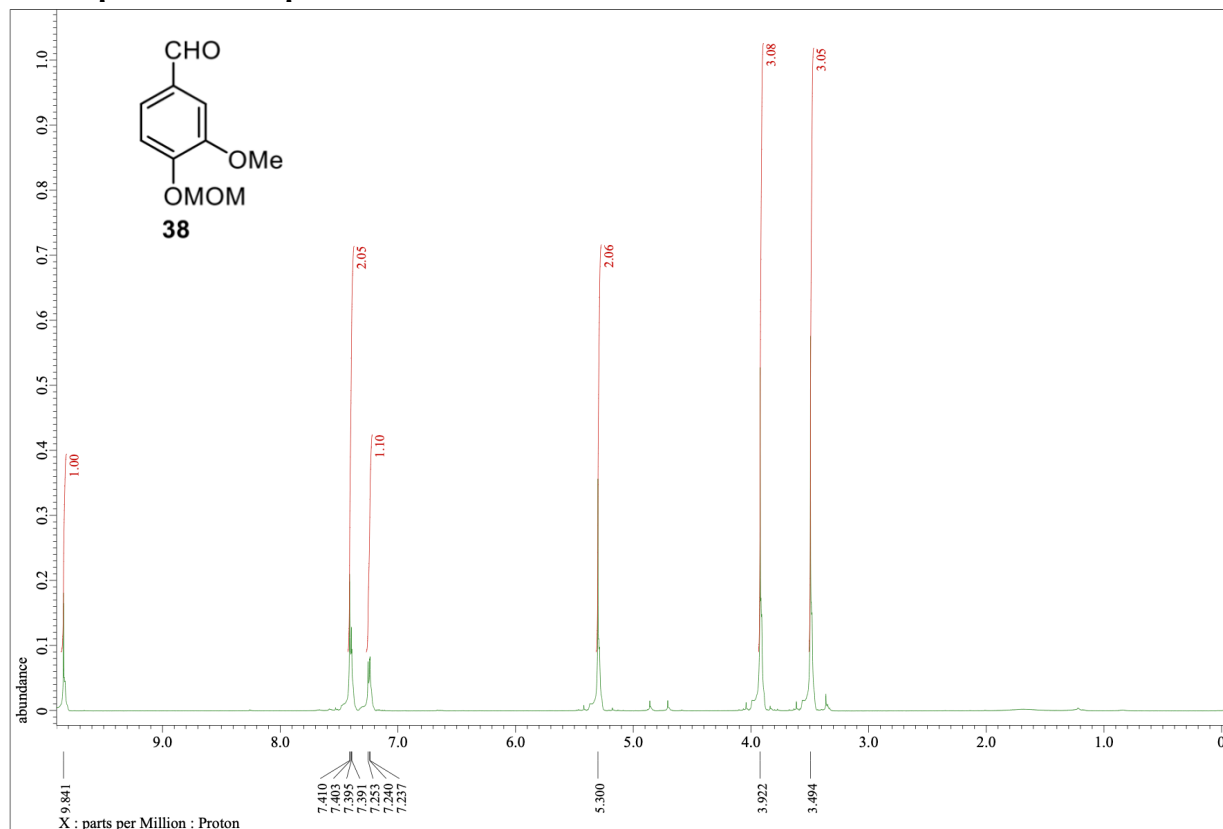
(3*R*,4*R*)-4-(3-methoxy-4-(methoxymethoxy)benzyl)-3-(((triethylsilyl)oxy)methyl)tetrahydrofuran-2-ol (49**).** A two-neck glass vessel was charged with a solution of **48** (441 mg, 0.996 mmol) in MeOH-CH₂Cl₂ (10 mL, 9:1 v/v), Cs₂CO₃ (486 mg, 1.49 mmol), rose bengal (0.051 g, 0.0498 mmol). The mixture was stirred and bubbled with O₂ gas at 0 °C for 1 min, cooled to at -78 °C, irradiated LED light (λ_{max} = 448 nm, 680 mW) directly in the solution

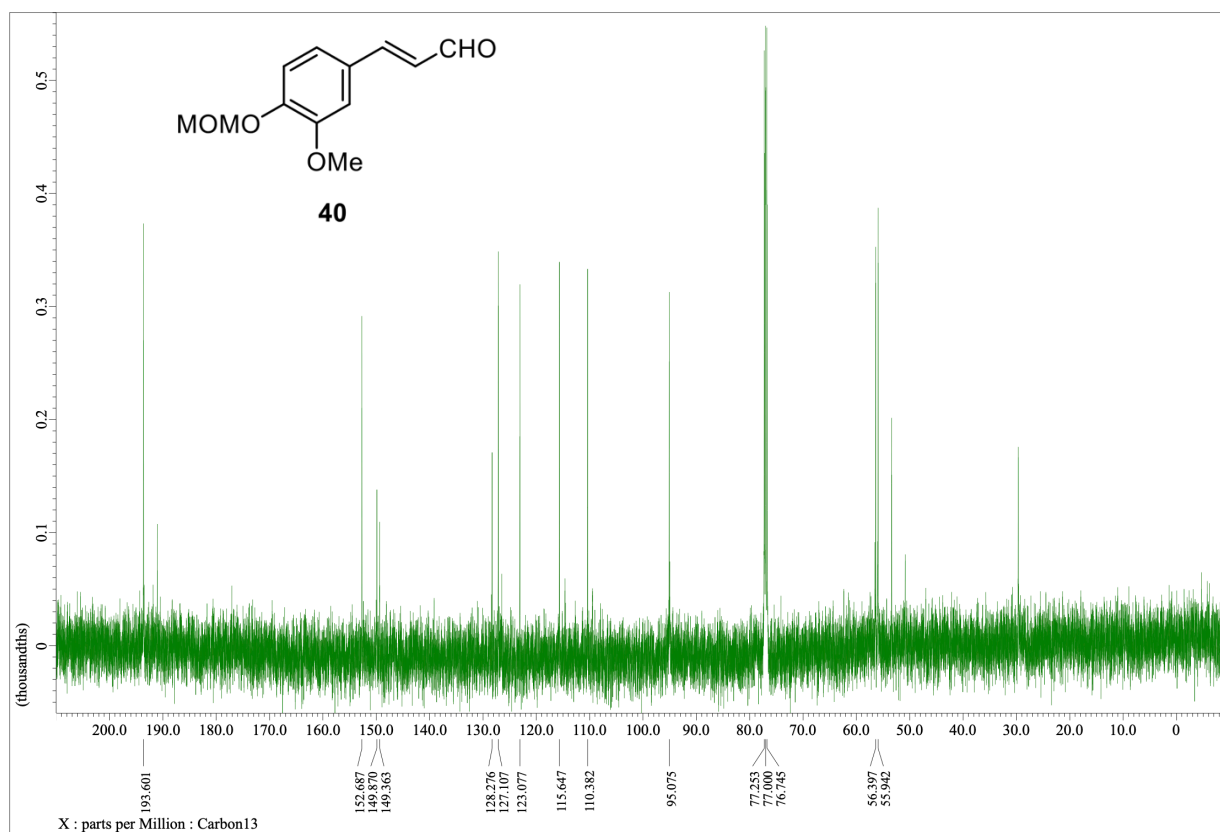
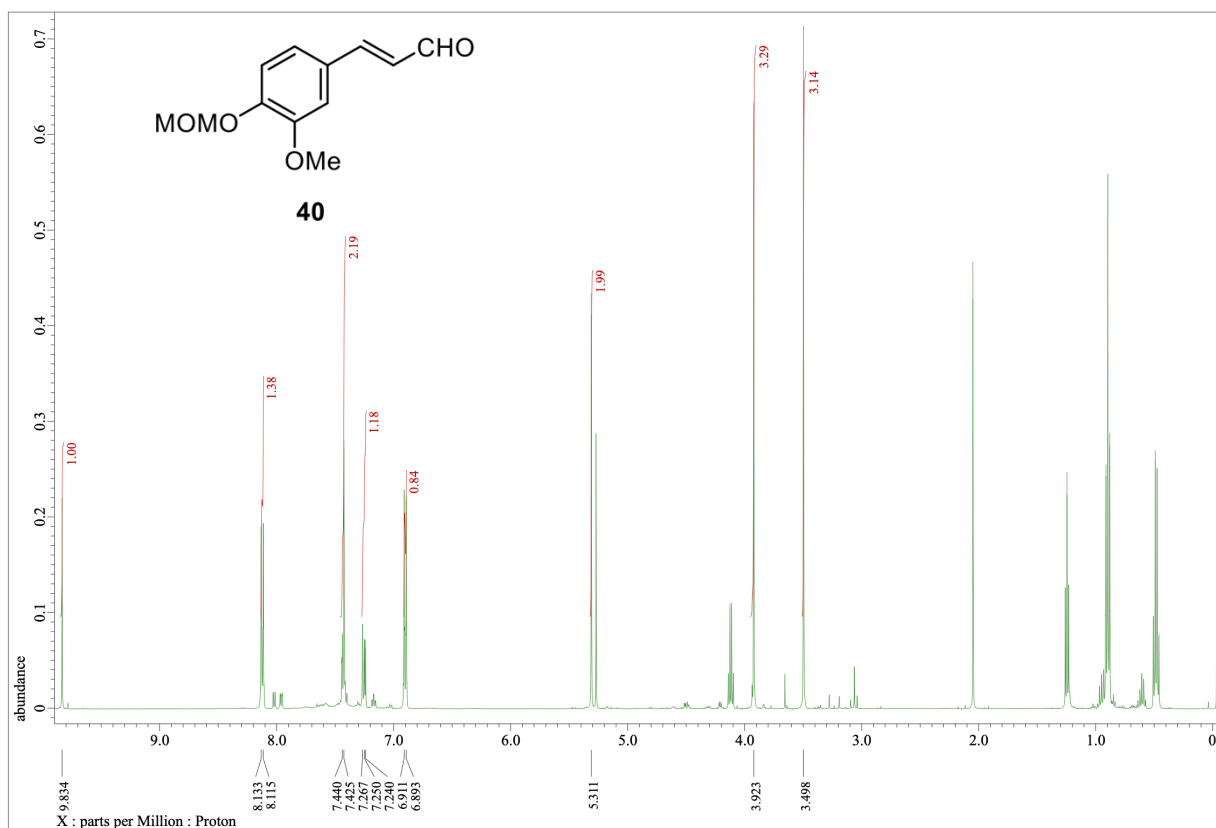
under O₂ atmosphere with stirring at -78 °C. After 1 h, Me₂S (0.222 mL, 2.99 mmol) was added to the mixture, and stirred for 15 min at room temperature. The mixture was then filtered through a short path silica gel pad and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane: AcOEt = 85:15, 80:20 then 77:23) to obtain **49** (234 g, 0.568 mmol, 57%) as a colorless oil. The following data were collected from a mixture of diastereomers (dr = 3:1); IR (neat) cm⁻¹ 3587, 2954, 1734, 1590, 1552, 1514, 1457, 1419, 1264, 1156, 1079, 1004, 923, 811, 745; ¹H NMR (CDCl₃, 500 MHz) δ 7.04 (1H, dd, *J* = 8.1, 2.8 Hz), 6.68-6.66 (2H, m), 5.47 (2/3 x 1H, t, *J* = 4.9 Hz), 5.34 (1/3 x 1H, s), 5.18 (2H, d, *J* = 1.4 Hz), 4.11-4.06 (1H, m), 3.94-3.91 (1H, m), 3.84 (3H, s), 3.80-3.76 (2/3 x 1H, m), 3.70 (1/3 x 1H, q, *J* = 5.3 Hz), 3.57 (1H, d, *J* = 8.6, 6.6 Hz), 3.49 (3H, s), 2.89 (2/3 x 1H, t, *J* = 7.5 Hz, 1H), 2.81 (1/3 x 1H, t, *J* = 6.9 Hz), 2.77-2.73 (2/3 x 1H, m), 2.68 (1/3 x 1H, dd, *J* = 13.7, 8.6 Hz), 2.22-2.18 (1H, m), 2.02-1.99 (1H, m), 0.94-0.91 (9H, m), 0.52-0.63 (6H, m); ¹³C NMR (CDCl₃, 126 MHz) δ 3.9, 4.1, 6.5, 6.5, 38.6, 39.0, 39.5, 42.5, 45.2, 50.5, 54.7, 55.6, 55.6, 55.9, 62.6, 71.6, 71.9, 95.4, 99.9, 101.3, 111.9, 112.0, 116.3, 116.5, 120.0, 120.4, 120.5, 134.6; HRMS (ESI-TOF) *m/z*: [M-OH]⁺; Calcd for 395.2228; Found 295.2248.

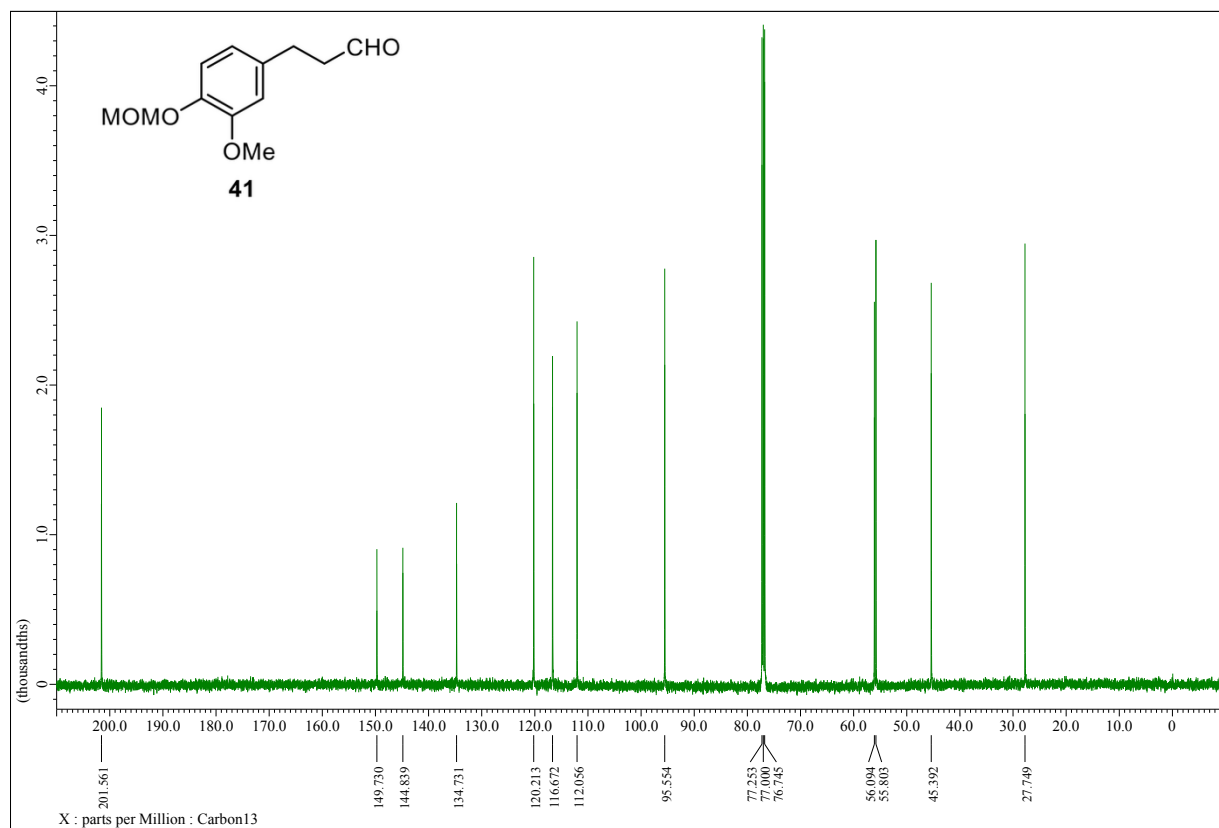
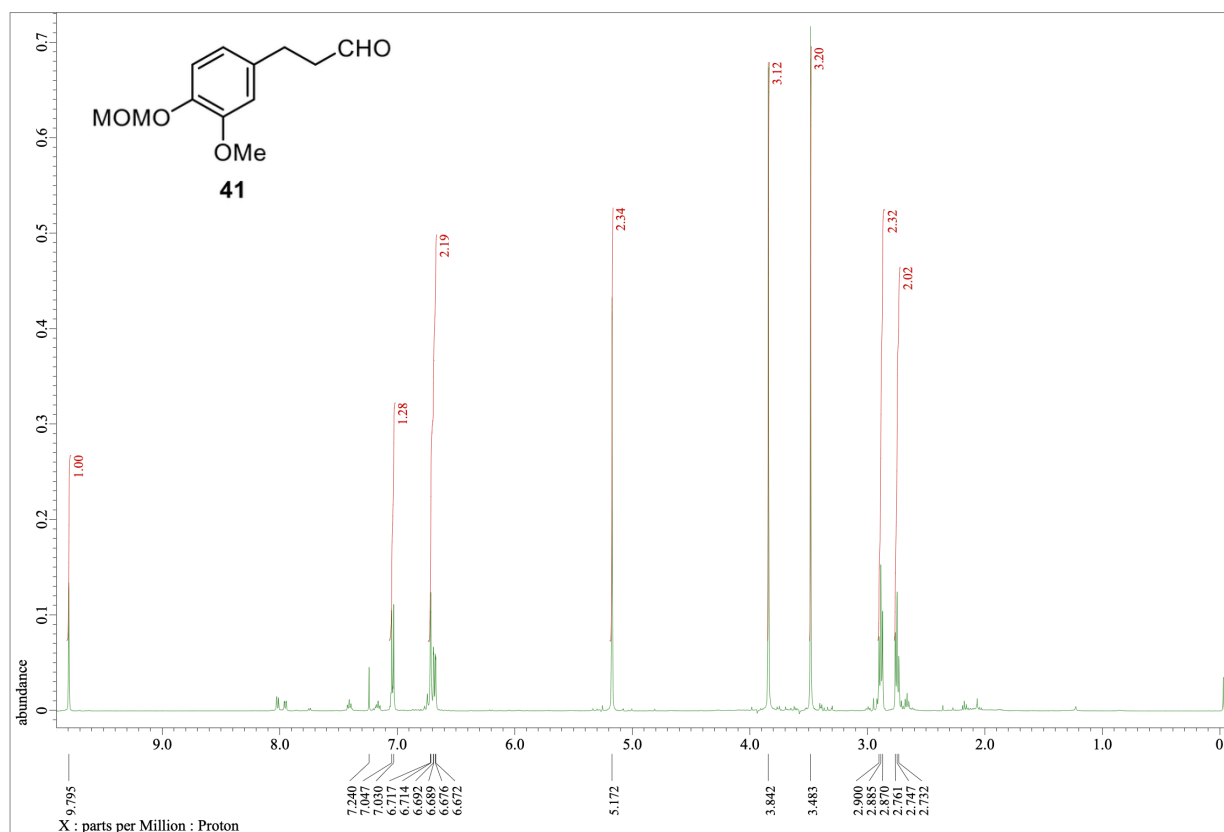


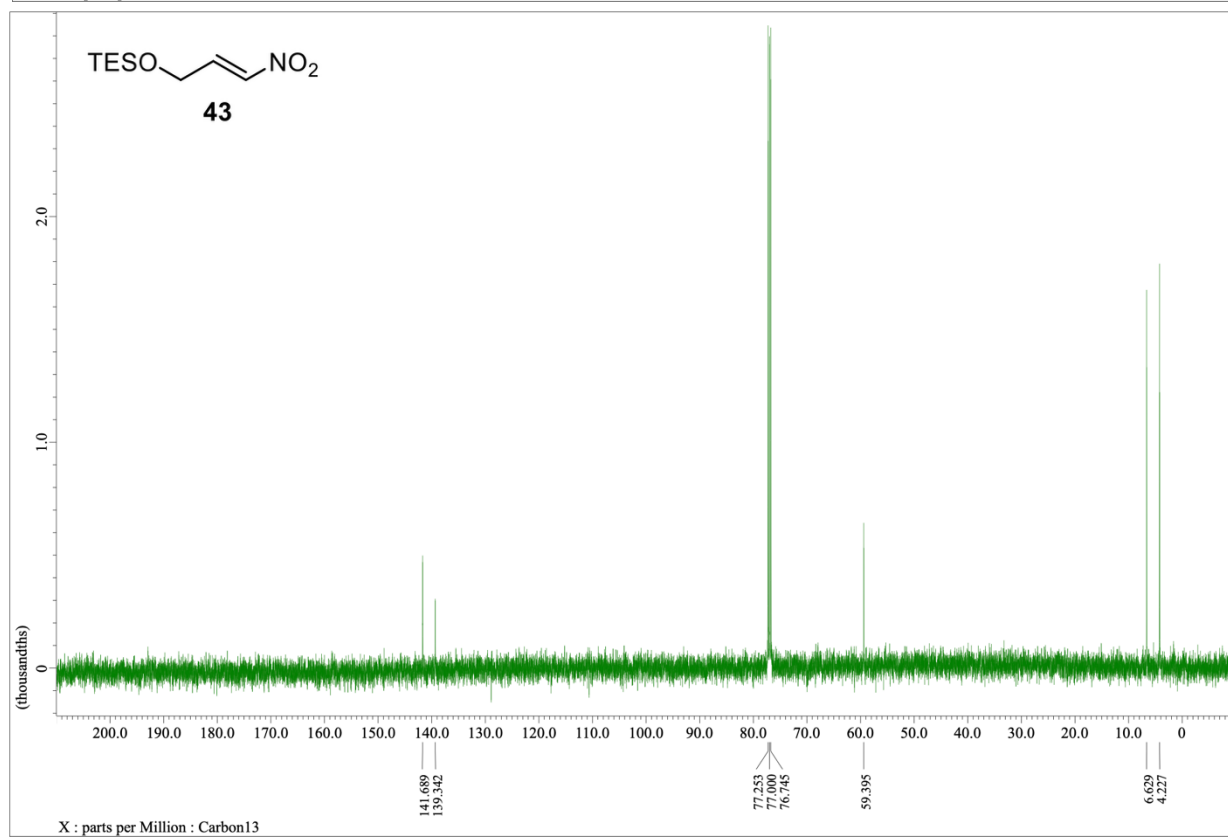
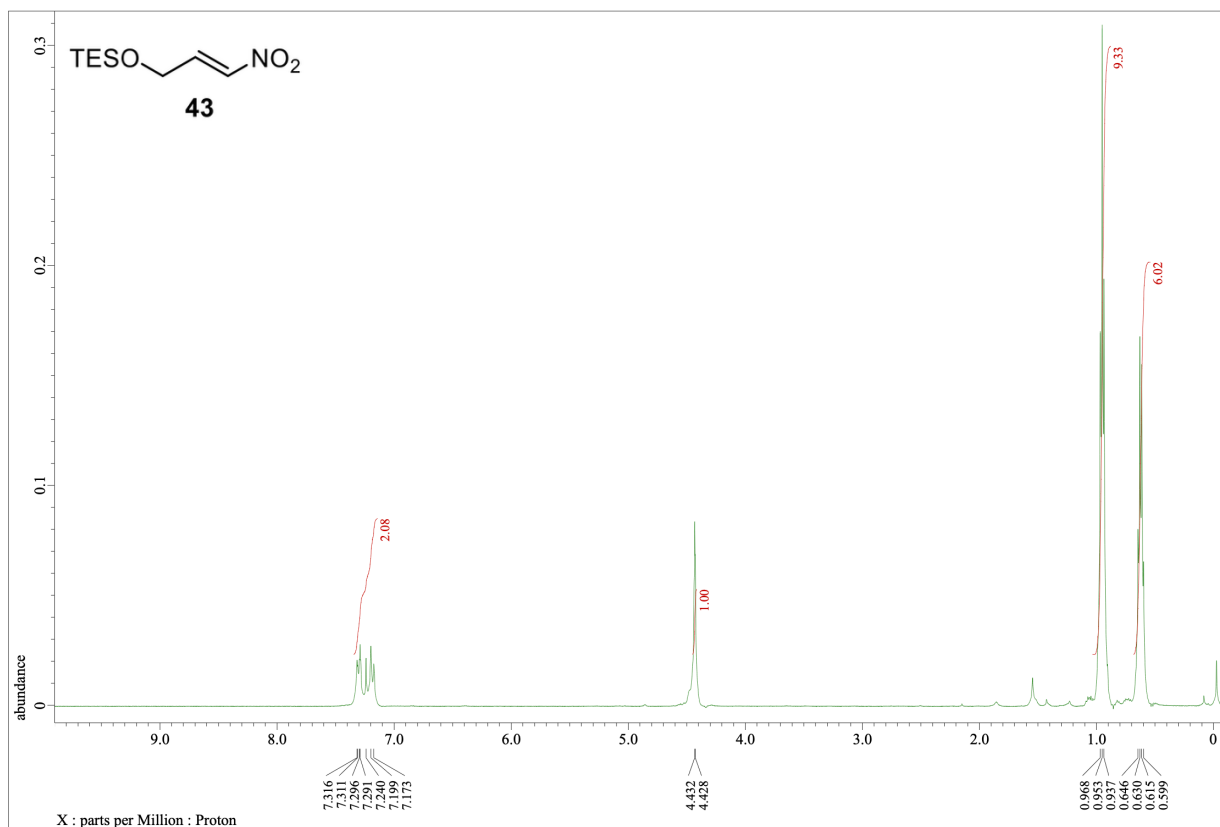
Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane: AcOEt = 80:20 then 75:25) to obtain **50** (84.7 mg, 0.186 mmol, 77%) as a colorless oil. The following data were collected from a mixture of diastereomers (dr = 3:1); IR (neat) cm⁻¹ 2954, 1734, 1590, 1552, 1514, 1457, 1419, 1264, 1156, 1079, 1004, 923, 811, 745; ¹H-NMR (CDCl₃, 500 MHz) δ 7.05 (1H, d, *J* = 7.7 Hz), 6.66 (2H, s), 6.32 (1/3x1H, d, *J* = 4.6 Hz), 6.11 (2/3x1H, d, *J* = 1.9 Hz), 5.18 (2H, s), 4.12-4.09 (1H, m), 4.05-4.02 (2/3x1 H, m), 3.95 (1/3x1H, dd, *J* = 11.2, 7.9 Hz), 3.86 (3H, s), 3.76 (1H, t, *J* = 8.5 Hz, 1H), 3.70-3.67 (1H, m), 3.49 (3H, s), 3.35 (d, *J* = 7.0 Hz, 0H), 3.28 (d, *J* = 7.2 Hz, 0H), 2.88-2.81 (2H, m), 2.70 (1H, dd, *J* = 13.7, 8.4 Hz), 2.56 (1H, dd, *J* = 13.7, 8.9 Hz), 2.08 (1/3x3H, s), 2.01 (2/3x3H, s), 0.95 (9H, td, *J* = 7.9, 2.6 Hz), 0.63-0.55 (6H, m); ¹³C NMR (CDCl₃, 126 MHz) δ 4.1, 4.3, 6.7, 6.7, 14.1, 27.8, 38.8, 39.2, 39.7, 42.7, 45.4, 50.7, 54.9, 55.8, 55.8, 56.1, 60.8, 62.8, 71.8, 72.1, 95.6, 100.1, 101.5, 112.1, 112.2, 116.5, 116.7, 120.2, 120.6, 120.7, 134.4, 134.8.

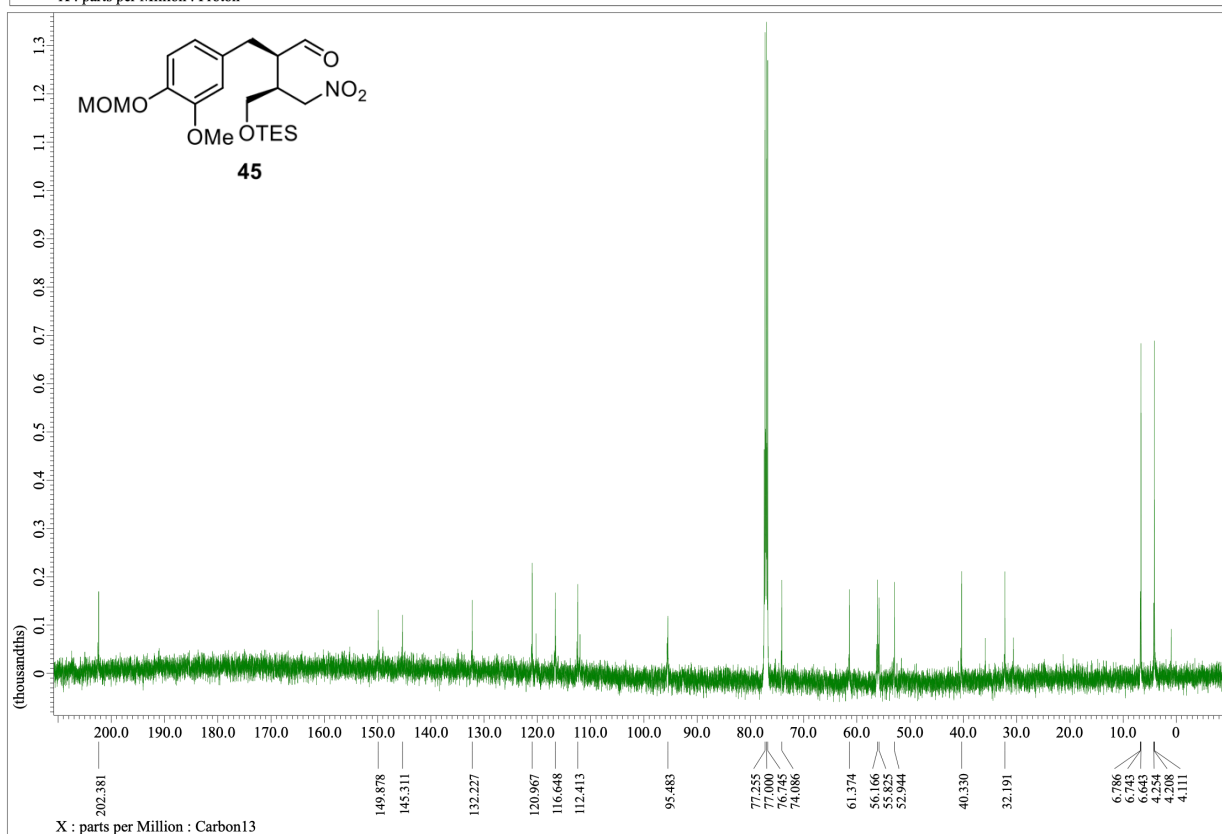
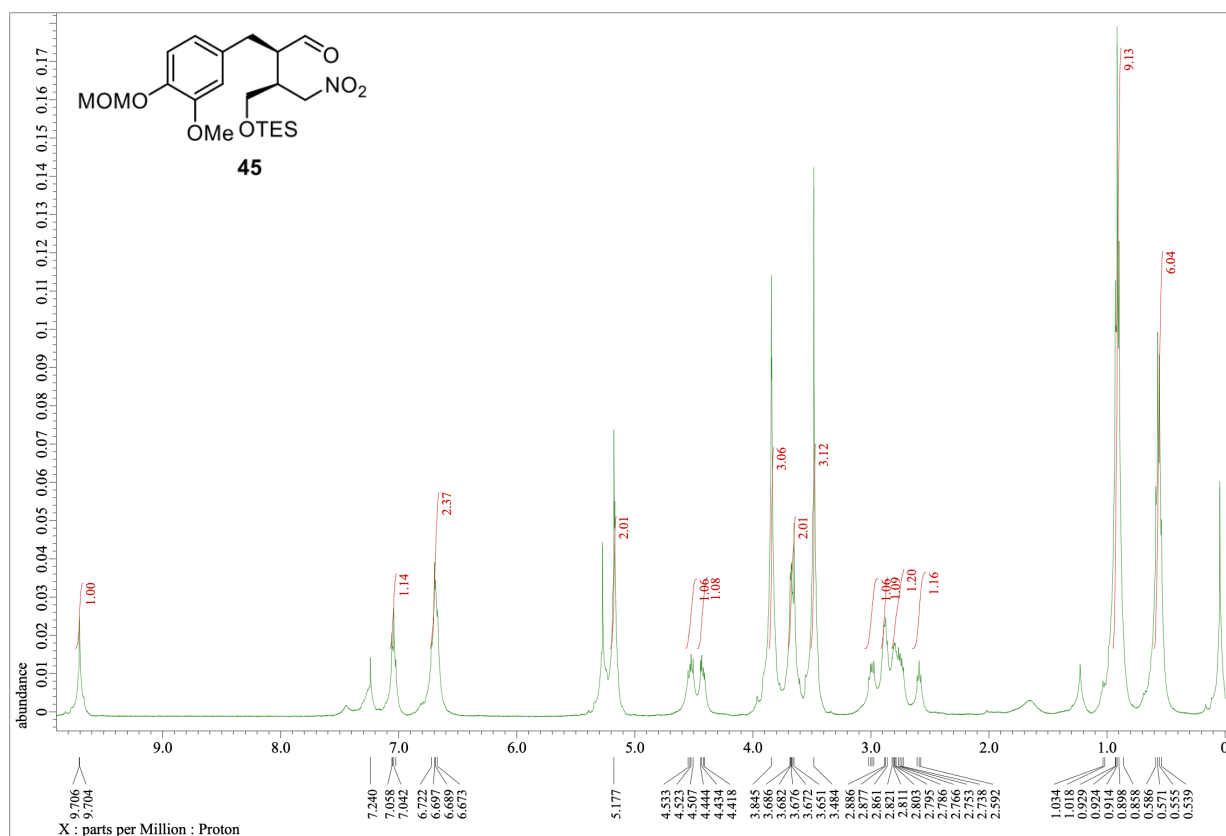
NMR spectra of Chapter 3

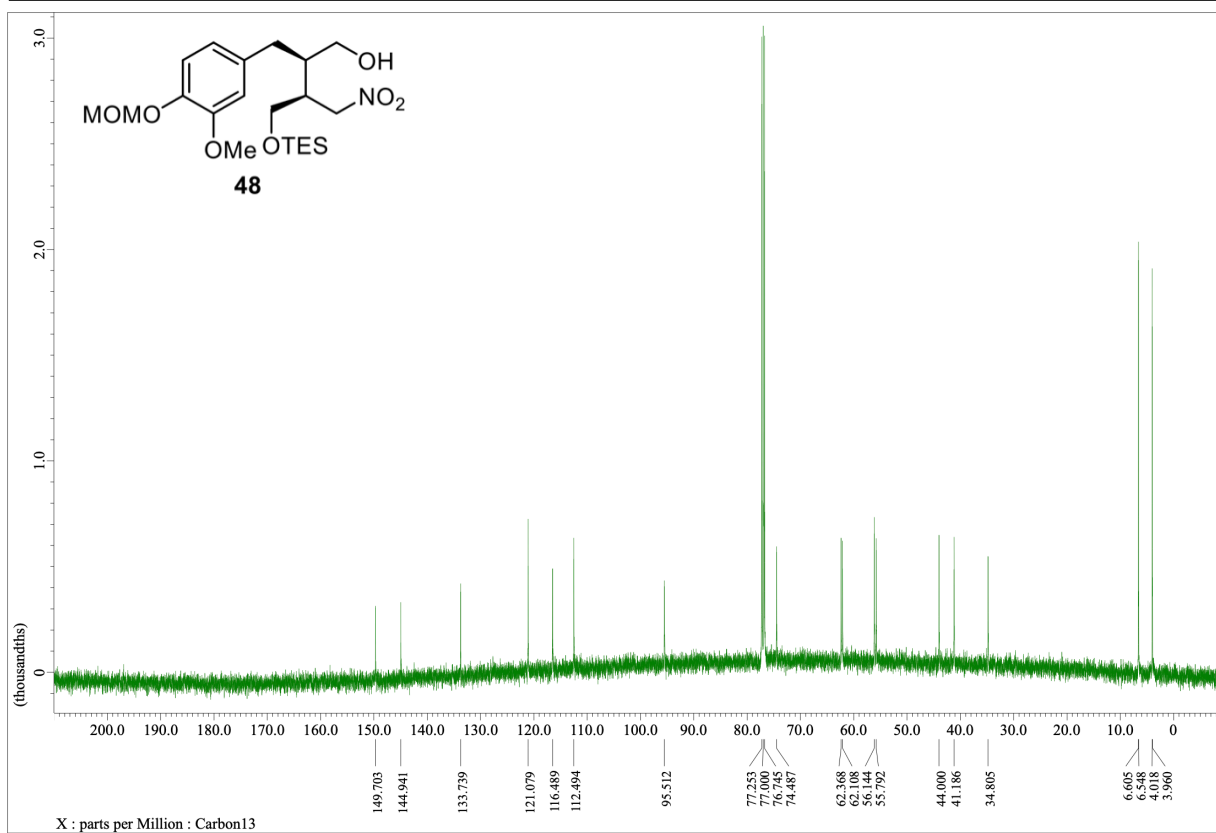
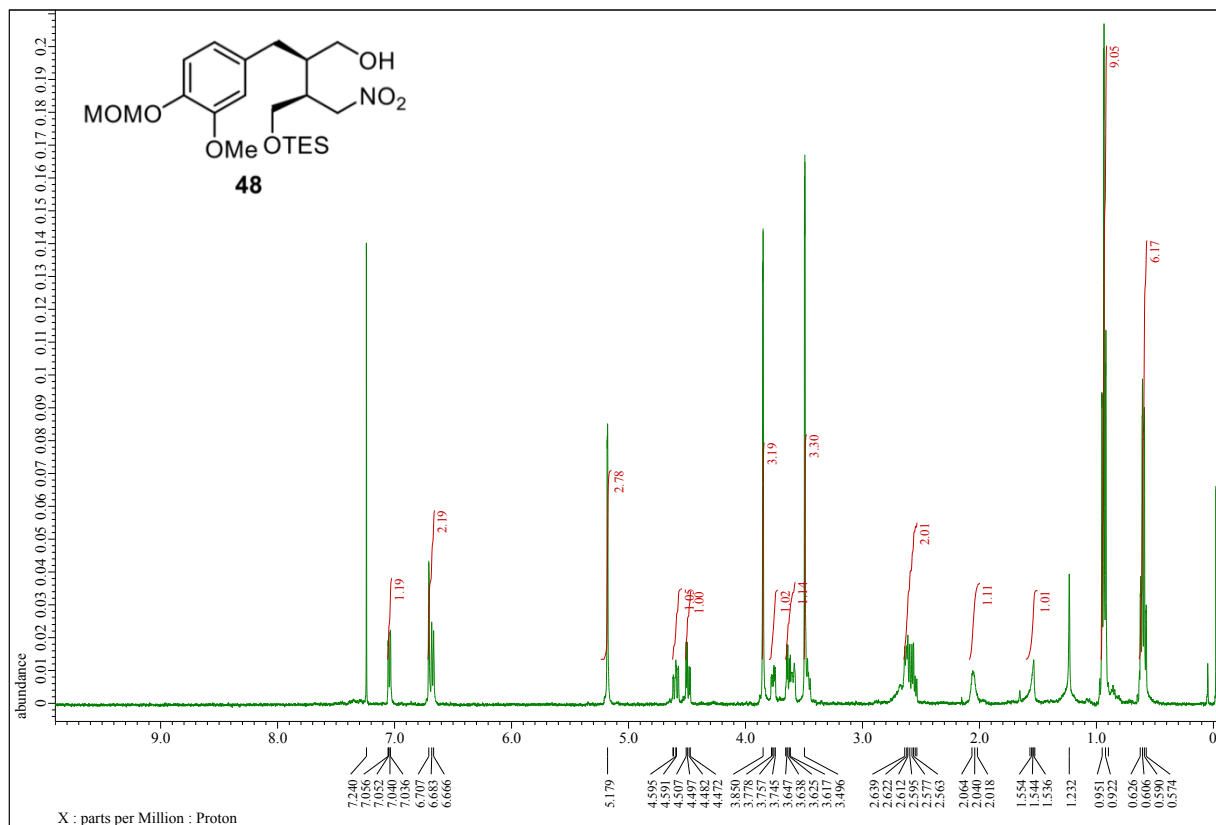


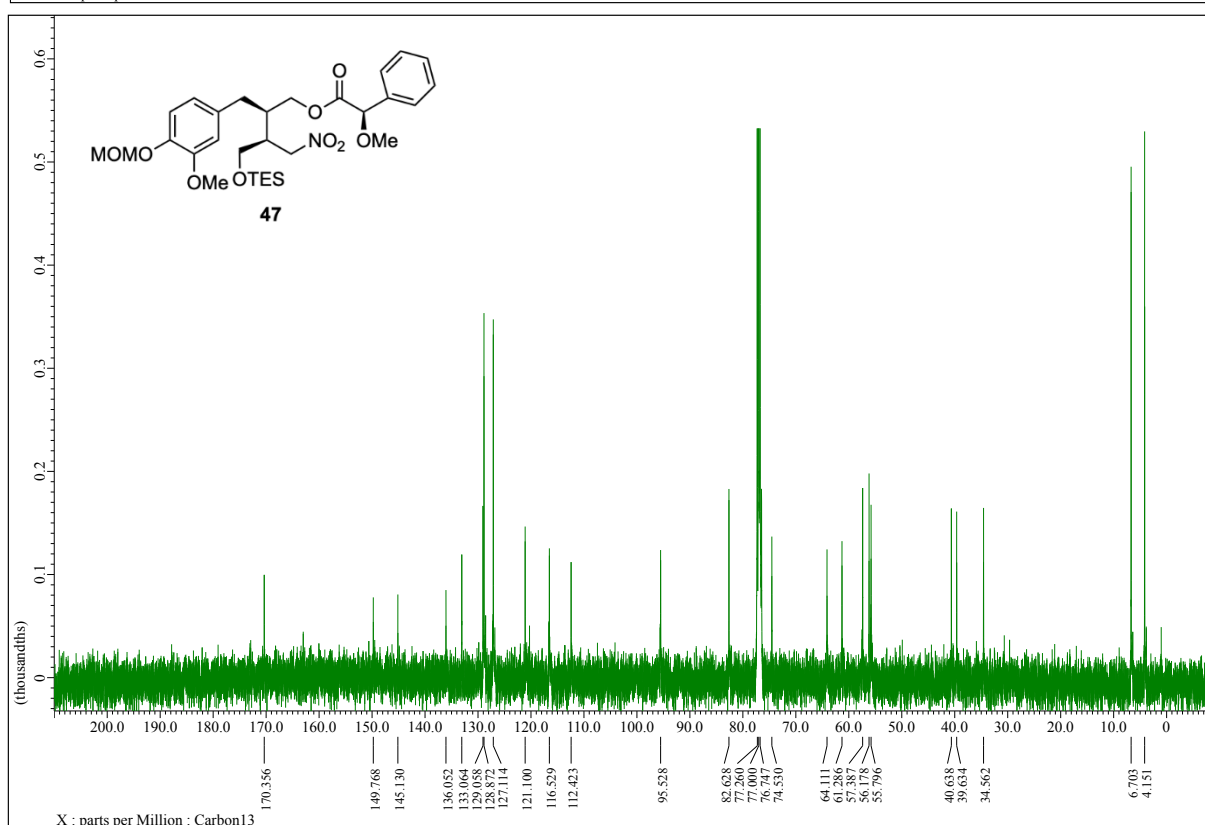
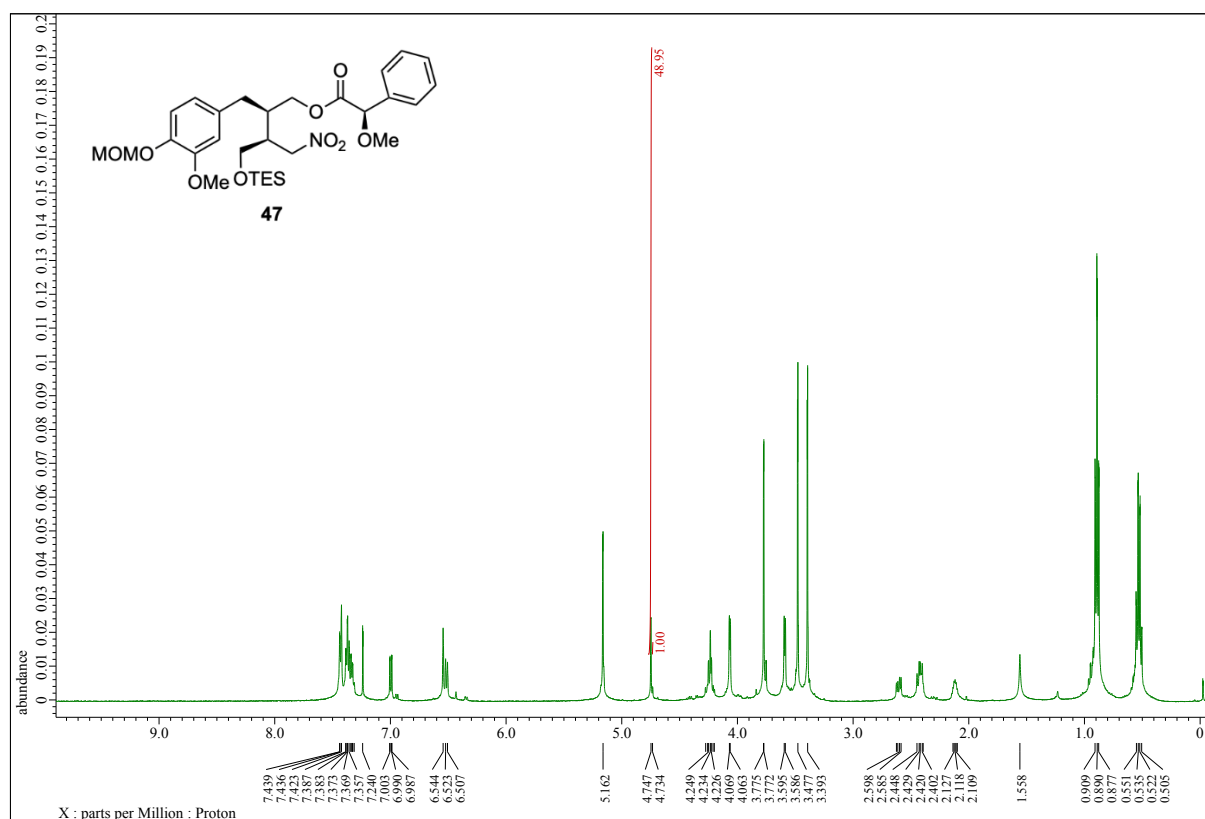


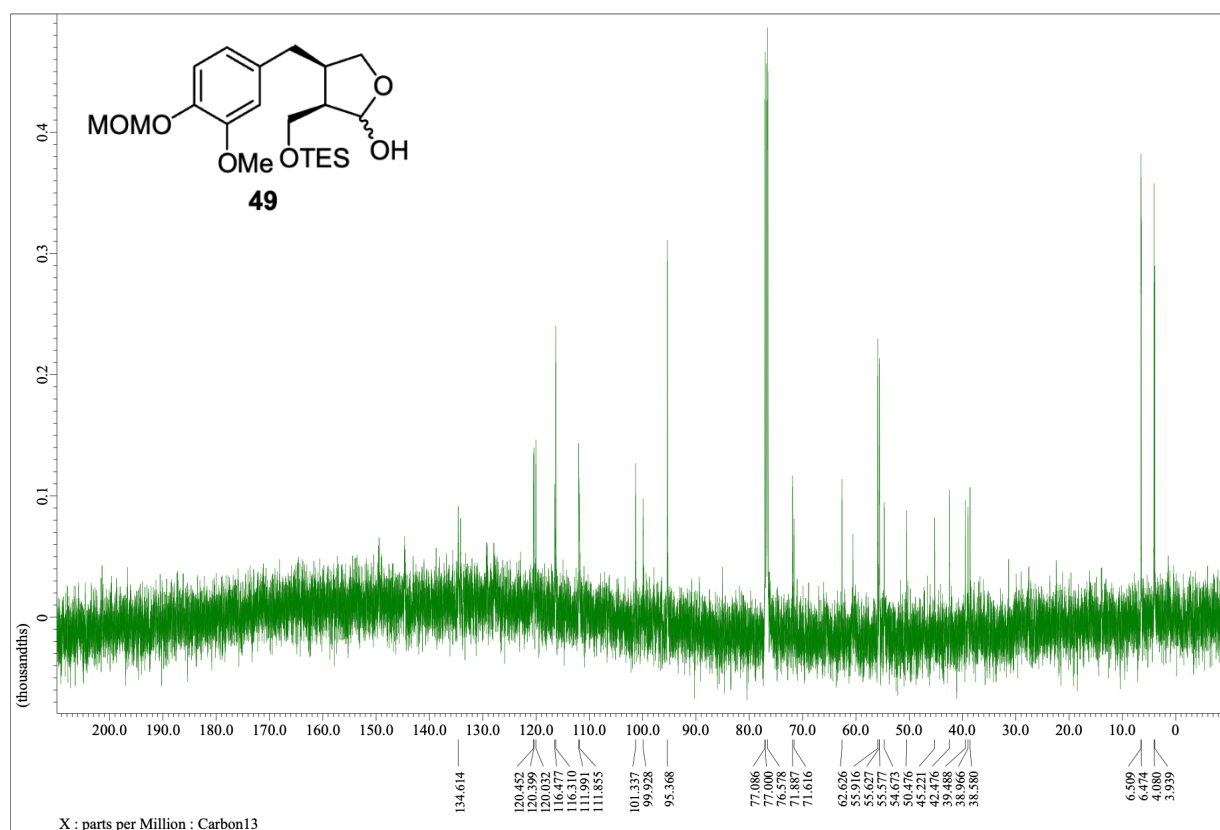
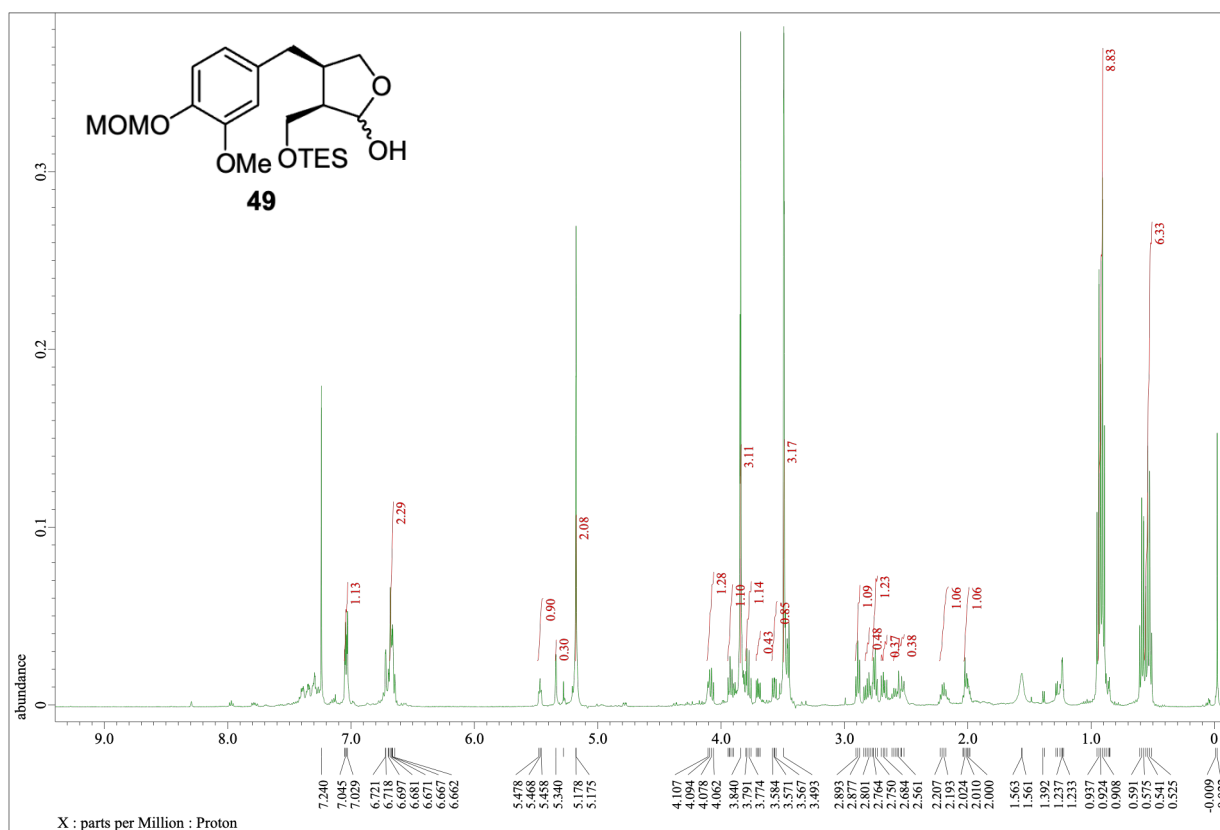


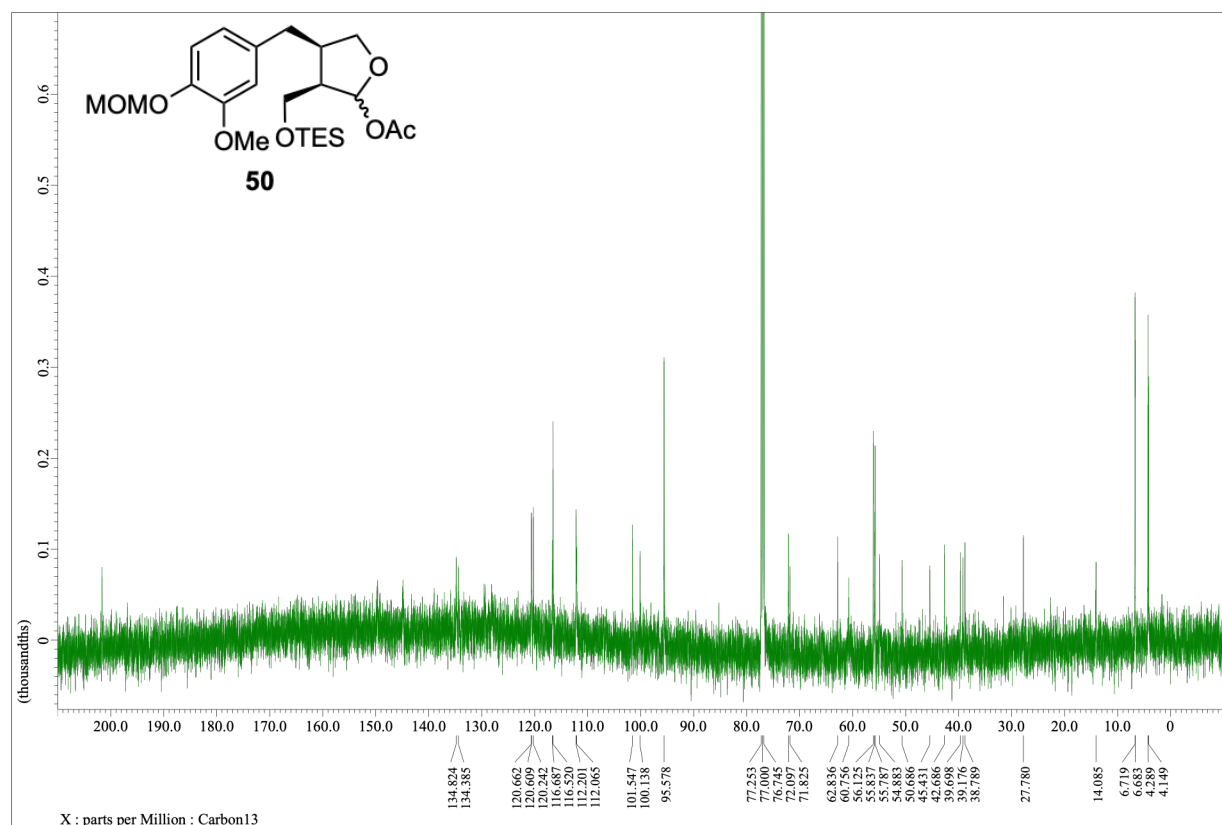
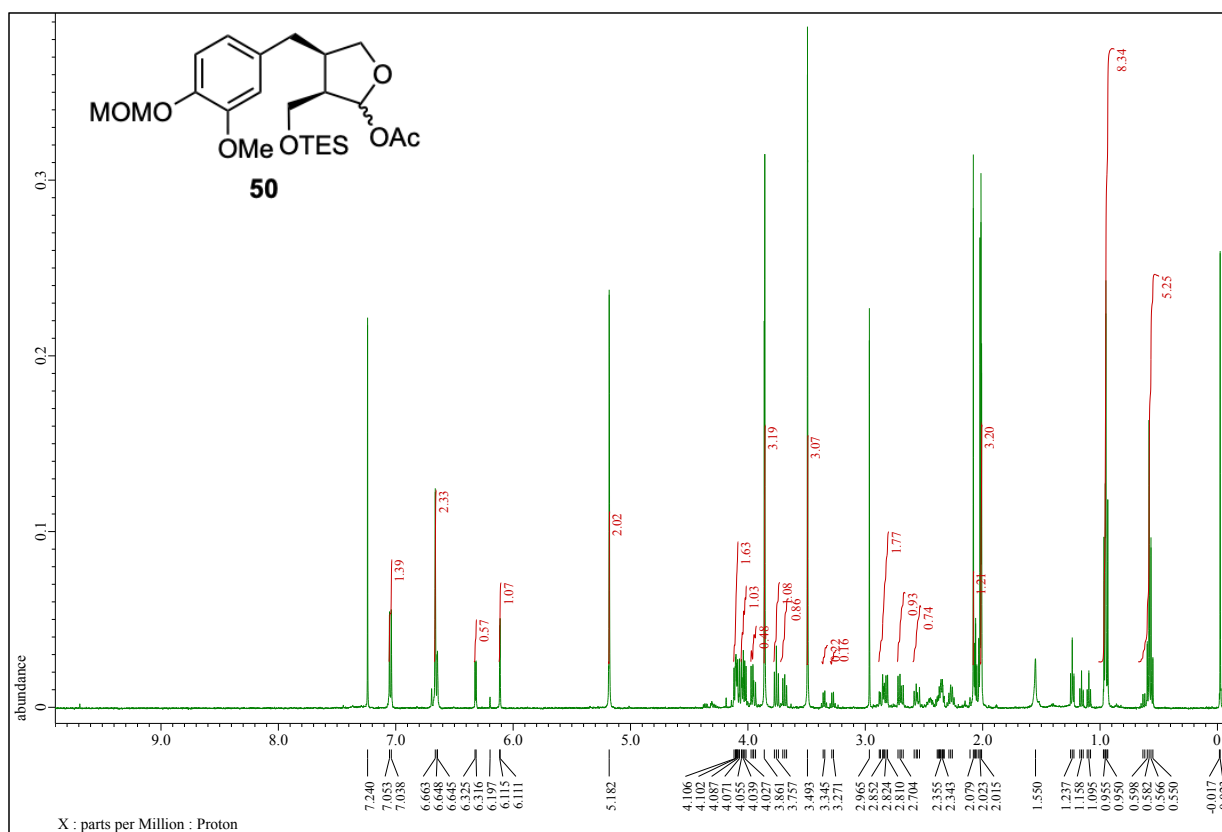












General Summary and Future Perspective

This study has explored the synthetic potential of the nitro group as a versatile functional group in modern organic synthesis, with particular focus on its transformation into aldehydes via the Nef reaction. Nitroalkanes, due to their dual electrophilic and nucleophilic character and facile generation of nitronate intermediates, serve as highly valuable intermediates for constructing complex molecular architectures. While classical applications often use nitro groups transiently, their transformation into carbonyl compounds, especially aldehydes, remains a significant challenge. Limitations of classical aldehyde-forming Nef reactions include harsh reaction conditions, limited functional group tolerance, aldehyde instability, epimerization, and competing side reactions such as Henry condensations.

To overcome these challenges, in Chapter 2, this work developed a visible-light-mediated, singlet oxygen-driven Nef protocol for aldehyde formation. Using Rose Bengal under blue LED irradiation ($\lambda_{\text{max}} = 448 \text{ nm}$) with Cs_2CO_3 , nitronate intermediates were converted efficiently into aldehydes. Mechanistic investigations revealed the critical role of peroxide intermediates and demonstrated that reductants such as dimethyl sulfide enable selective cleavage of these species, favoring the desired ionic pathway and suppressing side reactions. Ion chromatography and model studies provided detailed insight into the reaction mechanism, establishing the centrality of peroxide intermediates and the selective control required for high aldehyde yield and stability.

The optimized photochemical Nef methodology exhibited broad substrate scope and functional group tolerance. Acid- and base-sensitive protecting groups, sterically hindered nitroalkanes, and aromatic derivatives were all efficiently converted into aldehydes under mild conditions. The reaction also enabled intramolecular cyclizations to cyclic acetals and was further extended into a one-pot NaBH_4 -mediated transformation to hydroxymethyl derivatives, providing access to alcohol intermediates without the need for multi-step oxidation–reduction

sequences. Overall, yields were significantly improved and reaction times shortened from days to hours compared with classical protocols, demonstrating a practical and scalable approach.

The broader utility of this methodology, in Chapter 3, the application of Nef-based methodology was explored through the total synthesis of Alyterinate A. Alyterinate A is a structurally complex lignan ester with pronounced antifungal activity against *Pythium insidiosum* and cytotoxicity against P388 murine leukemia and HeLa cervical cancer cells. Lignans, as β - β -linked diphenolic secondary metabolites, are widely recognized for their pharmacological potential, including antibacterial, antiviral, antioxidant, and cytotoxic activities. Natural sources of Alyterinate A are limited, making an efficient synthetic route critical for further biological evaluation.

The synthetic strategy began with retrosynthetic analysis aimed at constructing the hydroxy-functionalized tetrahydrofuran (THF) core via a Nef-based cyclization. Aldehyde **41** was synthesized from vanillin using MOM protection, Wittig olefination, and selective hydrogenation, while nitro-olefin **43** was prepared from a secondary nitro alcohol via mesylation and elimination. The key asymmetric Michael addition, catalyzed by the Hayashi-Jørgensen catalyst (**44**) in dichloromethane with *p*-nitrophenol, afforded high selectivity (dr = 92:8, ee 96%) and 87% yield. Subsequent reduction with NaBH₄ produced alcohol **46** in 93% yield, which underwent the singlet oxygen-mediated Nef cyclization to yield cyclic acetal **47** (57% yield, dr 3:1). Next, acetylation furnished the target compound **48** (87% yield, dr = 3:1, ee : 96%). Finally, compound **51** could be obtained through a Friedel-Crafts acylation reaction with a 33% yield.

Collectively, this work demonstrates that strategic reaction design, coupled with modern photochemical techniques, can overcome longstanding challenges in classical functional group interconversions. The singlet oxygen-mediated Nef reaction provides a versatile and general approach to aldehyde synthesis, enabling the construction of sensitive and structurally complex

frameworks. Its successful application to the synthesis of Alyterinate A intermediate underscores its potential for broader applications in the synthesis of lignan derivatives and pharmaceutically relevant molecules.

Looking forward, the principles established here provide a foundation for further exploration of nitro group chemistry under mild, sustainable, and photochemically mediated conditions. Future studies may extend this methodology to other nitro-containing substrates, explore additional reductive and trapping strategies, and integrate these transformations into multi-step syntheses of complex natural products and pharmaceuticals.

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