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# Studies Towards the Total Synthesis of penicillipyrone B via a Biomimetic Approach

Tesi di laurea sperimentale

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# Table of Contents


| | | |
|---|---|---|
| Chapter 1 | | 1 |
| 1.1 | Introduction | 2 |
| 1.2 | Results and Discussion | 5 |
| 1.2.1 | Synthesis of Farnesyl Bromide derivative | 6 |
| 1.2.2 | Synthesis of Iodo-Dioxinone | 6 |
| 1.2.3 | Cross coupling reaction | 7 |
| 1.2.4 | Claisen reaction Keto-Dioxinone Farnesyl derivative. | 8 |
| 1.3 | Unsuccessful Attempt at Pyrone derivative. | 9 |
| Chapter 2 | | 11 |
| 2.1 | Introduction | 12 |
| 2.2 | Result and Discussion | 13 |
| 2.2.1 | Synthesis of Pyrone derivative | 13 |
| 2.2.2 | Synthesis of Epoxyfarnesyl bromide | 13 |
| 2.3 | Attempt couling to Pyrone derivative | 14 |
| 2.4 | Conclusions and perspectives | 14 |
| 3.1 | Experimental Section | 16 |
| 3.2 | Experimental Procedure/Characterization | 17 |
| Appendix | | 28 |
| Bibliography | | 50 |

# Abstract

Pennicillipyrone A and B are two novel meroterpenoids isolated from the marine-derived fungus Penicilliump sp. Although a preliminary toxicity studies demonstrated the bioactivity of penicillipyrone A to be far superior to that of its congener penicillipyrone B, we were intrigued by its structure. Moreover, it appeared as though one could design an efficient total synthesis based on chemistry that was familiar to our laboratory.

The purpose of this project was the study of a new synthesis of Pennicillipyrone B by way of a doubley-biomimetic approach. The intended approach proceeds through a polyene cascade reaction terminated by a nucleophilic pyrone - a reaction not yet known in the literature for the construction of this type of scaffold.

During the course of this study we have learned about the unanticipated reactivity of C2 substituted keto-dioxinones with regard to self-condensation. In addition, four new compounds were synthesized and two synthetic routes to the target molecule are presented.

# Riassunto

Pennicillipyrone A e B sono due nuovi meroterpenoidi isolati dal fungo marino Penicilliump sp. Sebbene studi preliminari di tossicità hanno dimostrato l'attività biologica del penicillipyrone A essere di gran lunga superiore a quella del suo congenere penicillipyrone B, siamo stati colpiti dalla sua struttura. Inoltre, è sembrato che si potesse progettare un efficace sintesi basata sulla chimica già familiare al nostro laboratorio.

Lo scopo di questo progetto è lo studio di una nuova sintesi del Pennicillipyrone B attraverso un approccio doubley-biomimetico. L'intento era sviluppare una reazione non ancora nota in letteratura basata sulla ciclizzazione di polieni con il metodo di Cascade avendo per terminale un gruppo pirone.

Nel corso di questo studio abbiamo scoperto la reattività del sostituente in posizione C2 del cheto-diossinone per quanto riguarda l'auto-condensazione. Inoltre, sono stati sintetizzati quattro nuovi composti e sono mostrate due vie sintetiche per la molecola bersaglio.

# List of Abbreviations

| | |
|---|---|
| α | alpha |
| β | beta |
| μL | micro litres |
| ºC | celcius degree |
| | |
| Ac | acetyl |
| $Ac_2O$ | acetic anyhydride |
| Atm | atmosphere |
| aq | aqueous |
| | |
| bp | boiling point |
| | |
| cm-1 | reciprocal centimeter |
| CSA | camphorsulfonic acid |
| | |
| d | doublet |
| dd | doublet of doublet |
| dddd | doublet of doublet of doublet of doublet |
| DBU | 1,8-Diazabicycloundec-7-ene |
| DCC | N,N'-Dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DIPEA | diisopropylethylamine |
| DMAP | 4-(dimethylamino)pyridine |
| DMF | N,N-dimethylformamide |
| DMSO | dimethylsulfoxide |
| DMP | 2,2-Dimethoxypropane |
| dq | doublet of quartet |
| | |
| ESI | electrospray |
| Et | ethyl |

| | |
|---|---|
| $Et_2O$ | ethyl ether |
| EtOAc | ethyl acetate |
| | |
| h | hour(s) |
| HCl | Hydrochloric Acid |
| HPLC | high performance liquid chromatography |
| Hz | hertz |
| *i*-Pr | isopropyl |
| IR | Infrared spectroscopy |
| | |
| *J* | first order coupling constant |
| | |
| LiHMDS | Lithium 1,1,1,3,3,3-hexamethyldisilazide |
| L | liter |
| | |
| m | multiplet |
| Me | methyl |
| MeOH | methanol |
| min | minute |
| mg | milligram |
| mL | milliliter |
| mmol | millimole |
| mol | mole |
| m.p. | melting point |
| Ms | Methanesulfonyl |
| MS | mass spectroscopy |
| m/z | mass-charge ratio |
| | |
| NaOMe | sodium methoxide |
| *n*-BuLi | n-Butyllithium |
| NIS | N-iodosuccinimide |
| NMR | nuclear magnetic resonance |
| $NEt_3$ | Triethylamine |

| | |
|---|---|
| ppm | parts per million |
| Pr | propyl |
| q | quartet |
| r.t. | (rt) room temperature |
| s | singlet |
| sat. | saturated |
| s.m. | starting material |
| t | triplet |
| t-Bu | tert-Butyl |
| THF | tetrahydrofuran |
| TLC | thin layer chromarography |
| tq | triplet of quartet |

# Chapter 1

## 1.1 Introduction.

The natural products assembled by nature are a rich source of compounds with potential therapeutic application. In fact, natural products, or more often their derivatives, have been exploited for the use of treating human disease for many centuries. The oldest known record dates back to 2400 BC in China where plants were exploited for medicinal purposes. In more recent times the use of modern extraction and screening methods combined with chemical synthesis provide a powerful arsenal for the discovery of new drugs. Of the 1000+ drugs approved for market between 1981 and 2010, approximately 50% were natural product derived.[1]

By definition, natural products constitute any type of chemical compound produced by a living organism. In the context of medicinal chemistry, these compounds are most often secondary metabolites and are thus not directly involved in growth and development.[2]

There are two reasons why secondary metabolites of organisms are such a unique and important source of drug prospects. Firstly, one must understand the role they play in nature. These compound are often used in a species' defense, survival, or regulatory processes. The second important reason has to do with the molecular homology present between different species.

To perform the task for which a molecule has been designed, Nature has encoded very specific information into its chemical structure. This information, for example, can cause an interaction to take place between a specific protein receptor cite to trigger a response. The molecular homology between different species permits this interaction to be transferred to another organism.[3] Thus we may "borrow" the necessary code responsible for a specific interaction between a particular natural product and a protein in an organism. Through the power of chemical synthesis we may perform the necessary structural editing of a natural product to fine tune the interaction and/or other chemical properties needed for drug ability in humans.

One particular class of natural product that could have a potential therapeutic application are the meroterpenoids. Penicillipyrones A and B are two novel meroterpenoids, isolated from the marine derived fungus Penicillium sp.[4] Compound A exhibited significant

induction of quinone reductase (QR) which is a representative detoxification enzyme, and is known to play an important anticancer role through the reduction of electrophilic quinones.[5,6] Therefore, the significant induction of QR by penicillipyrone A may be suggestive of a potential role in cancer prevention.

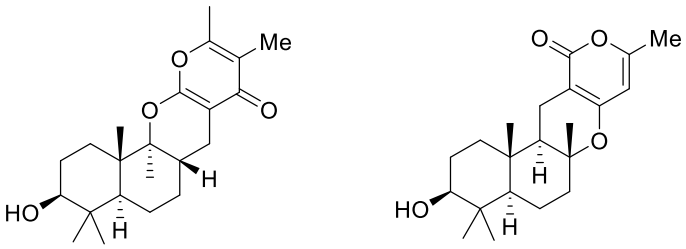



Figure 1. Pennicillipyrone A (1A) and B (1B)

Although a preliminary toxicity studies demonstrated the bioactivity of penicillipyrone A to be far superior to that of its congener penicillipyrone B, we were intrigued by its structure. Moreover, it appeared as though one could design an efficient total synthesis based on chemistry that was familiar to our laboratory.[7]

To the best of our knowledge at the outset of this work were no literature examples of polyene cascade reactions terminated by a nucleophilic pyrone moiety. It was thought that the knowledge gained from this work could be later applied to a synthetic study of penicillipyrone A. Thus, the goal of this thesis was to study the synthesis of penicillipyone B by way of a doubley-biomimetic approach (Figure 2).

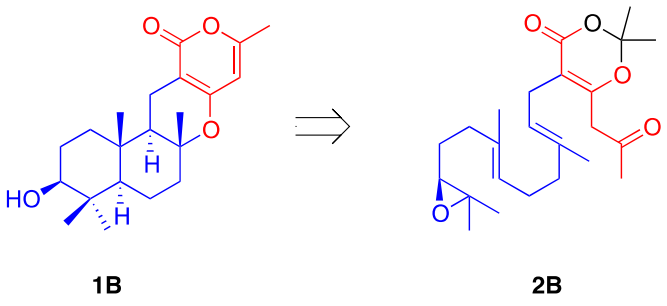



Figure 2. Analysis of Penicillipyrones B (1B)

We envisoned that an appropriately substituted keto-dioxinone derivative would serve as an ideal synthetic precursor to the natural product scaffold (Figure 2). An intramolecular condensation of the keto-dioxinone moiety would give rise to δ-pyrone moiety. This intermediate could then undergo a Lewis acid catalyzed Johnson-Type cyclization,[8] which would furnish the terpenoid framework. Following the principles set forth by Stork and Eschenmoser,[9,10] the geometrically defined olefins in substrate **(2B)** and the well-ordered nature of the transition state would furnish with the desired *trans-anti-trans* relative stereochemistry at each ring junction in *Penicicilliprone B* (Figure 3).

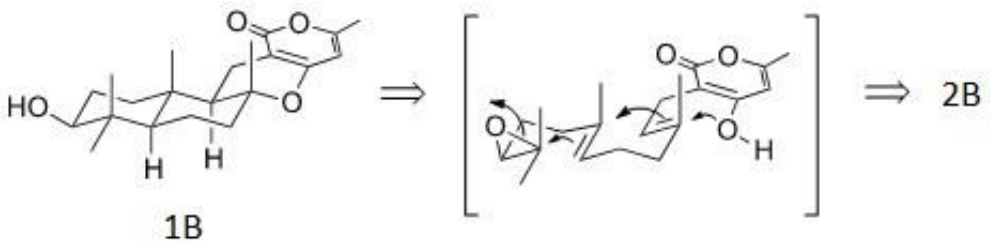



Figure 3. Johnson-Type Cylization

1.2 Results and Discussion.

Our first synthetic route utilized a cross coupling reaction,[11] between two key building blocks – the known iodo-dioxinone **(5)** and the farnesyl derivative **(6)** (Figure 4). After pyrone formation and protecting group removal, conversion of the terminal diol into the epoxide would give the Johnson cyclization precursor.

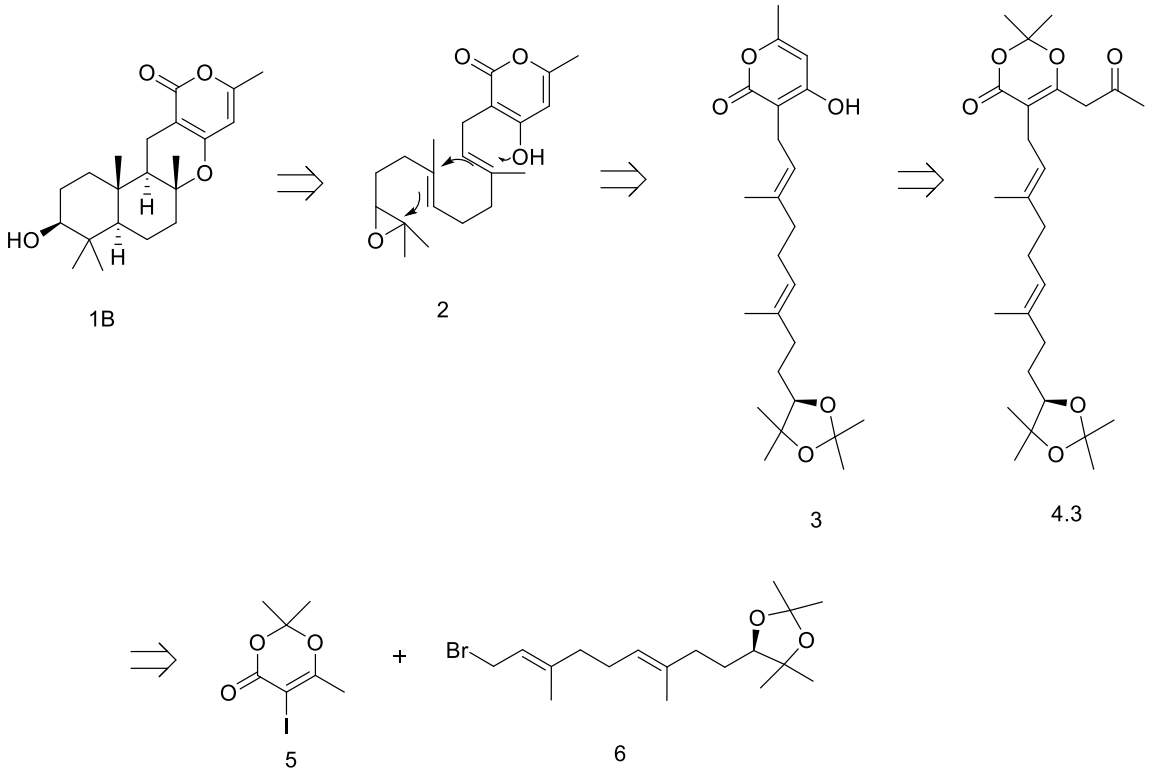
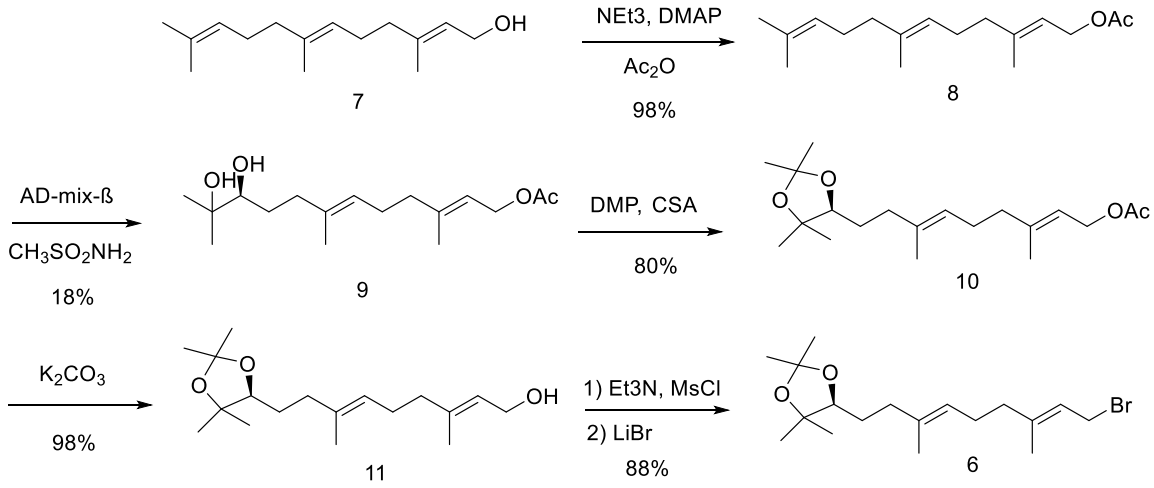



Figure 4. Retrosynthetic Analysis of Penicillipyrones B via Dioxinone

1.2.1 Synthesis of Farnesyl Bromide derivative (**6**).

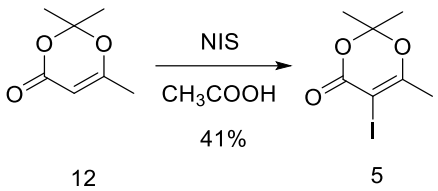
The chiral alkyl halide **(6)** was obtained in 6 steps from commercially available farnesol. Acylation of farnesol **(7)** with acetic anhydride and DMAP gave the corresponding acetate **(8)**.[12] The Sharpless dihydroxylation was used to prepare the 10,11-diol **(9)** in an enantioselective fashion. This product was protected as the corresponding acetonide **(10)** with Dimethoxypropane and a catalytic amount of CSA. After hydrolysis of the acetate **(10→11)** the primary alcohol was converted to the corresponding bromide **(6)** in two additional steps.[13]




Scheme 1. Synthesis of Farnesyl Bromide Derivative

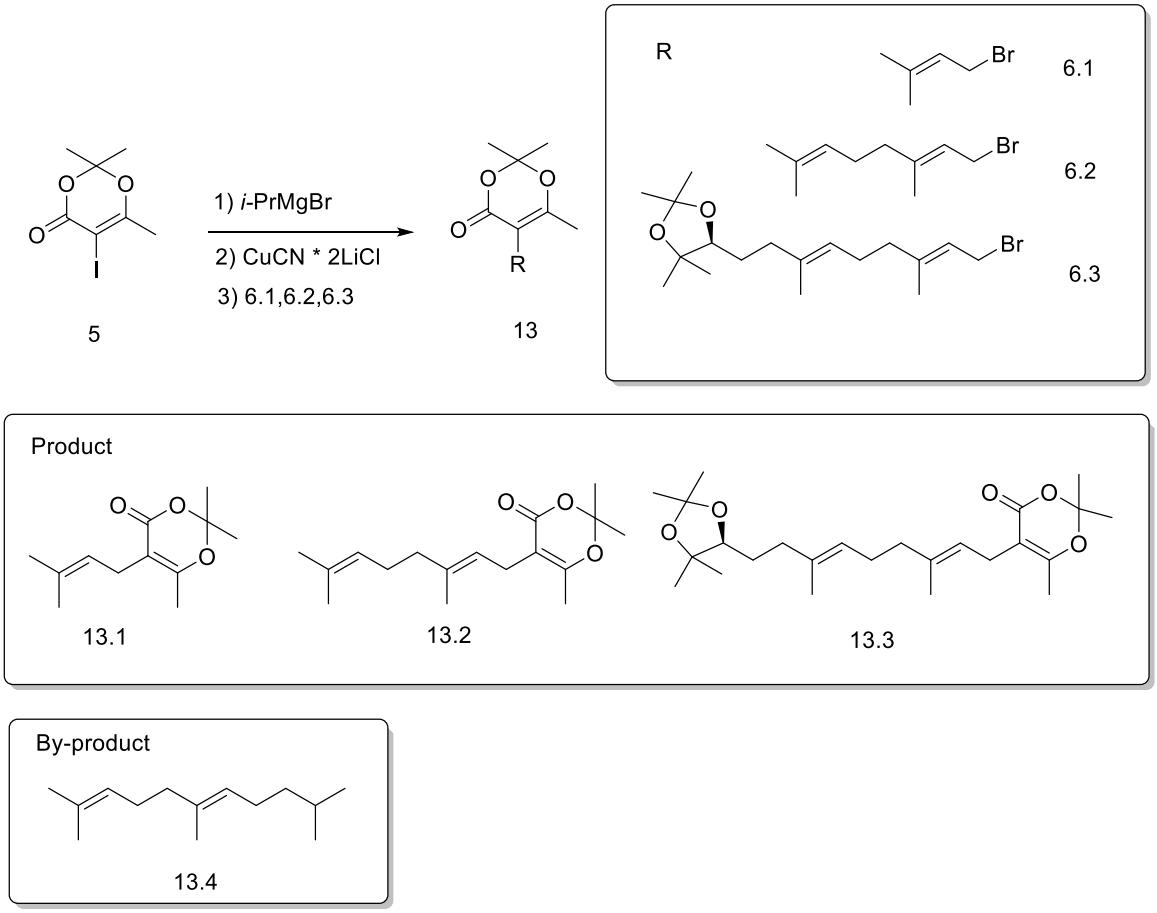
1.2.2 Synthesis of Iodo-Dioxinone (**5**).

Iodo-dioxinone (**5**) was prepared following a literature description by treatment of Dioxinone with N-Iodosuccinimide (NIS) in acetic acid.[14]




Scheme 2. Synthesis of Iodo-Dioxinone

1.2.3 Cross coupling reaction.




Scheme 3. Cross coupling reaction

With building blocks **5** and **6.3** in hand we decided to investigate the requisite cross coupling reaction. Although the cross coupling reaction among allyl bromide and dioxinone **5** is known, at the time of our study there were no literature examples of more complex allylic substrates.

Before screening the reaction with alkyl bromide **(6.3)** we decided to investigate the conditions with a model compound. Treatment of prenyl bromide **(6.1)** with the cuprate prepared from iodo dioxinone and isopropyl magnesium bromide gave the desired product in fairly modest yield (44%). We speculated that a competitive coupling event between isopropyl magnesium bromide and the allyl halide was taking place. After switching the model compound to the less volatile geranyl bromide we did indeed see compound **(13.4)** as a byproduct in the reaction conditions. Ultimately, we managed to improve the yield of the desired coupling product by increasing the number of equivalents of iodo-dioxinone

from 1 to 1.5 with respect to the alkyl bromide derivative. We saw an increase in yield from 30 to 77 % in the geranyl compound **(13.2)**. Interestingly when we applied our optimized reaction conditions to the real system **(6.3)**, we could only obtain the coupled product **(13.3)** in 43% yield. Increasing the number of sacrificial equivalents of iodo-dioxinone **(5)** did not offer any improvement.

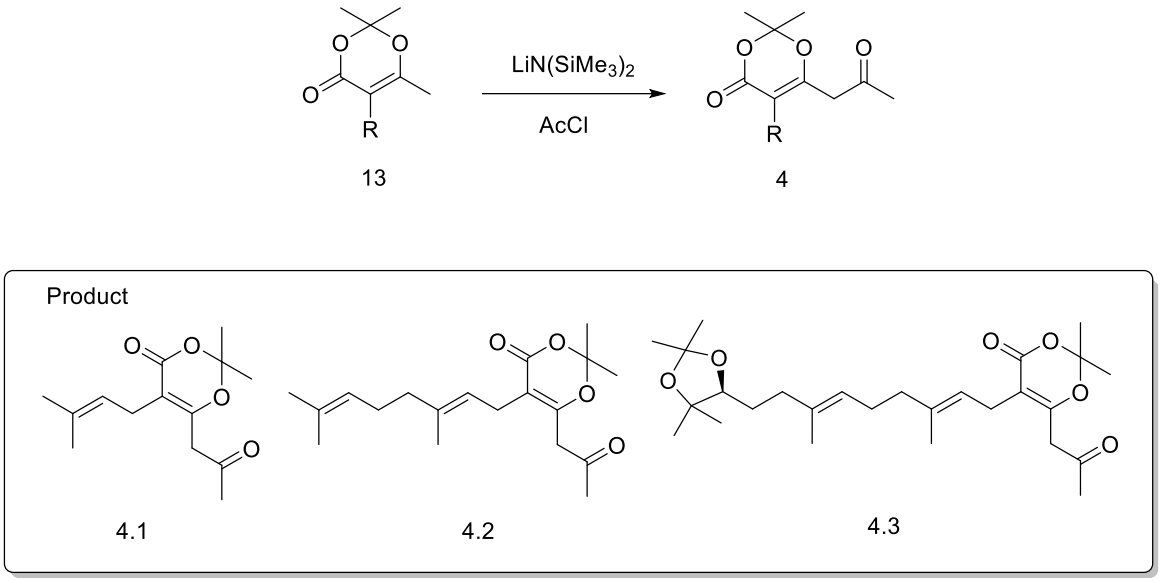
We speculate that chelation of the copper complex to the oxygens of the acetonide protecting group may inhibit coupling.

| *P 5* | *R* | *n. eq. Of i-PrMgBr* | *n. eq. CuCN * 2 LiCl* | *n. eq. Of R* | *n. eq. Of Iodo-Dioxinone* | *Yield %* |
|---|---|---|---|---|---|---|
| *13.1* | *6.1* | *1,1* | *1* | *1,2* | *1* | *44* |
| *13.2* | *6.2* | *1,1* | *1* | *1,2* | *1* | *38* |
| *13.2* | *6.2* | *1,1* | *1* | *1* | *1,5* | *77* |
| *13.3* | *6.3* | *1,1* | *1* | *1* | *1,5* | *43* |

Table 1. Condition and result of Cross Coupling reaction

1.2.4 Claisen reaction Keto-Dioxinone Farnesyl derivative.

Keto-dioxinone **(4)** was synthesized by acylation of the enolate from dioxinone (**13**) with acetyl chloride in THF at -78 °C.[15]




Scheme 4. Claisen reaction

| *Product* | *S.M.* | *n. eq. Of $LiN(SiMe_3)_2$* | *n. eq. AcCl* | *n. eq. 10* | *Yield %* |
|---|---|---|---|---|---|
| *4.1* | *13.1* | *1* | *1* | *1* | *36* |
| *4.2* | *13.2* | *1* | *1* | *1* | *35* |
| *4.3* | *13.3* | *1* | *1* | *1* | *33* |

Table 2. Condition and result of Claisen reaction

## 1.3 Unsuccessful Attempt at Pyrone derivative.

With the desired cross-coupled product in hand, our next task was to construct the pyrone. For this purpose we had two unique options: one could effect intramolecular cyclization to form the pyrone via base catalysis or through ketene trapping. There are a number of examples in the literature that employ these methods in total synthesis.[16]

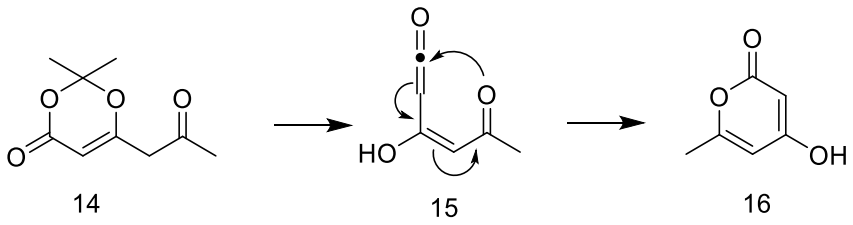
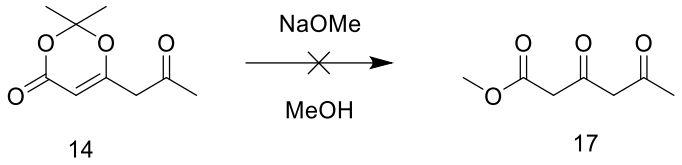



Figure 5. Ketene trapping

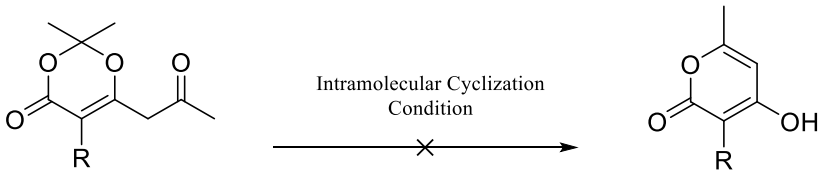
Despite having two possible options to build the pyrone moiety we were ultimately left disappointed as neither method proved effective. When keto-dioxinone **14** was heated to a temperature that would presumably generate ketene **15** via retro-Diels Alder reaction, we only observed substrate decomposition. Addition of DBU did not offer any improvement.

Treatment of keto-dioxinone **(14)** with NaOMe,[17] also led to substrate decomposition; prolonged reaction times gave a mixture of starting material and dioxinone, presumably via a retro Claisen reaction.




Scheme 5. Keto-Dioxinone Methanolysis

While we were left disappointed with this result, we were not entirely surprised. After an extensive literature search, we found that there are no examples of intramolecular cyclization of keto-dioxinones to form pyrones with extended chains at the C-2 position. It is possible that a substituent at the C2 position prevents the reactive ketene intermediate from adopting a conformation, which would allow intramolecular attack. Alternatively ketene formation may be entirely retarded by the C2 substituent. To fully understand the reasons why this reaction failed requires additional experiments and may be a future investigation in the Barrett laboratories.




Scheme 6. Intramolecular Cyclization reaction

| *Staring Material* | *Reaction conditions* | *Result* |
|---|---|---|
| *4.1* | *Toluene, Reflux* | *s.m. recovered* |
| *4.1* | *Methanol, 2 eq. MeONa, 0°C* | *s.m. recovered* |
| *4.2* | *Methanol, 2 eq. MeONa, 0°C to 45°C* | *S.m. and retro Claisen reaction product* |
| *4.2* | *Benzene, 1 eq. DBU, 83°C* | *complex mixture of unidentifiable products* |
| *14* | *Methanol, 2 eq. MeONa, 0°C* | *s.m. recovered* |
| *14* | *Toluene, Reflux* | *% yield product* |

Table 3.Condition and result of Intramolecular reaction

# Chapter 2

2.1 Introduction

To bypass this hurdle, we redesigned our synthetic strategy. We intended to solve the problem of pyrone construction in our second approach by using the diketo ester **17** rather than a keto-dioxinone. The chemoselective alkylation of diketoesters at the C-2 position via the copper acetate complex has been described by Cervello et al.[18] In addition, the literature did contain examples of C-2 substituted pyrones constructed via condensation of keto esters.

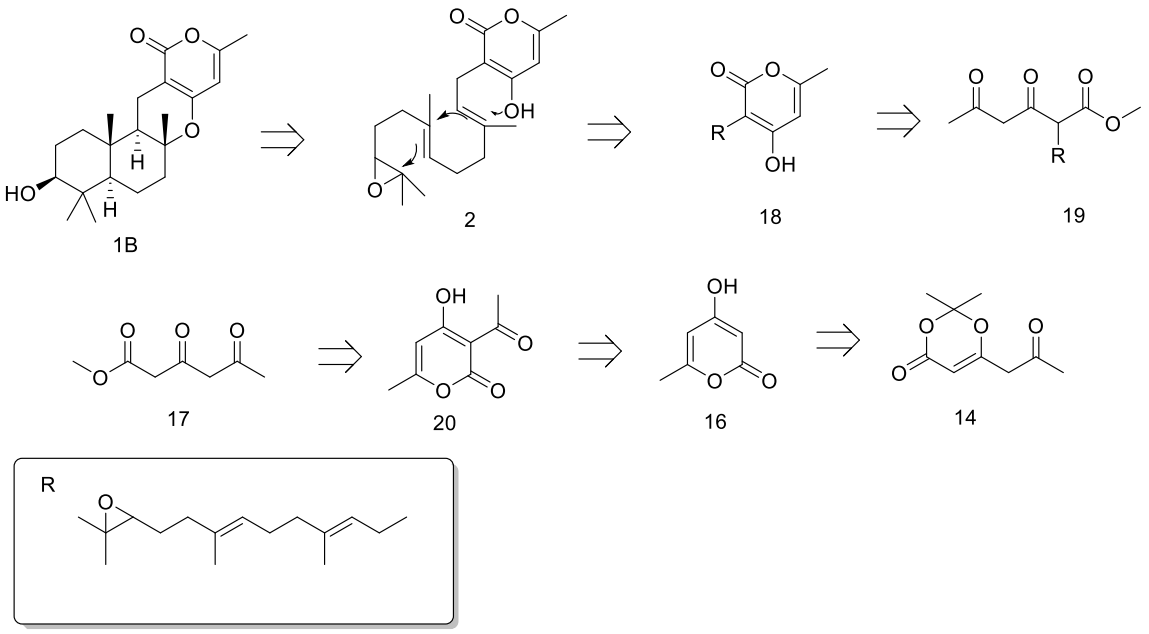
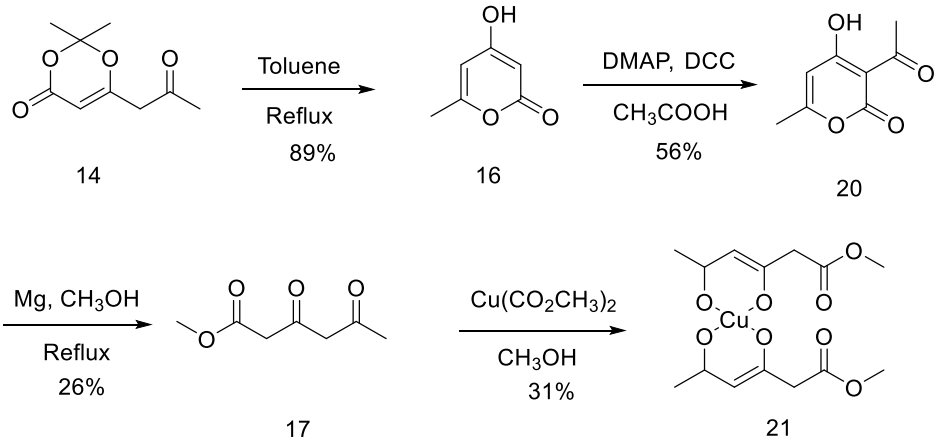



Figure 6. Retrosynthetic Analysis of Penicillipyrones B via Pyrone

2.2 Result and Discussion

2.2.1 Synthesis of Pyrone derivative

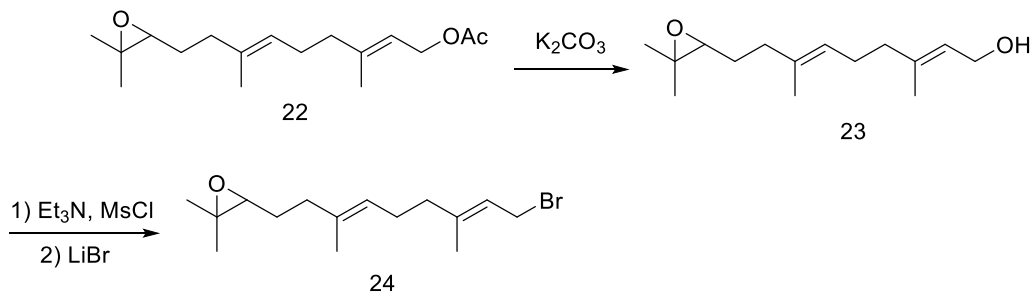
Triacetic acid lactone **(17)** was synthesized from keto-dioxinone **(14)**, a compound we had available in gram quantities in our laboratory. After acylation of the pyrone **(16→20)** we obtained the α-β-diketoester **(17)** by treatment with magnesium powder in methanol. Reaction of the diketoester **(17)** with copper acetate in water/methanol afforded the complex **(21)** (scheme 7), which exhibits a peak at 1734 $cm^{-1}$ in the infrared spectrum.




Scheme 7. Synthesis of Cupper Complex

2.2.2 Synthesis of Epoxyfarnesyl bromide

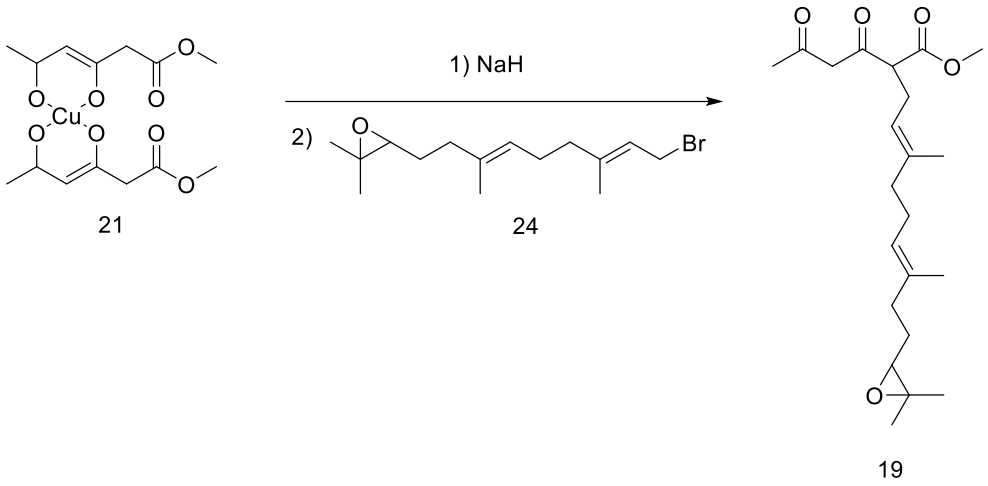
Racemic epoxy farnesyl acetate **(24)** was prepared according to a literature procedure[19] and was available in gram quantities in our laboratory. After deprotection of the ester **(22 →23)** bromide **24** was prepared in two steps from alcohol **23**.




Scheme 8. Synthesis of Epoxyfarnesyl bromide

## 2.3 Attempt coupling to Pyrone derivative

At last we were set up to couple epoxy bromide **24** with copper complex **21**. In the event, treatment of **21** with sodium hydride in THF followed by primary alkylhalide **24** and subsequent hydrolysis gave a mixture of products. Although it appeared as though the desired keto ester **19** was present in the crude reaction mixture, it was impossible to isolate. Due to time constraints the continuation of work on this project ceased at this point.



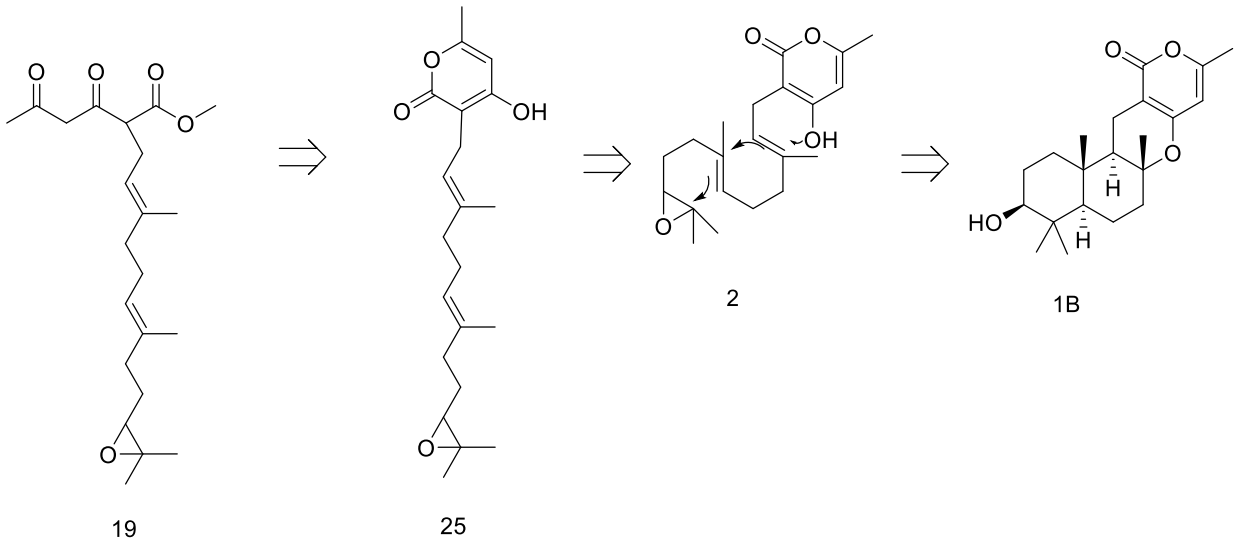

Scheme 9. Synthesis of Ketoester pyrone derivative

## 2.4 Conclusions and perspectives

In conclusion we have developed a straightforward synthesis to compound **4.2** and **4.3**. These compounds are key building blocks for further studies to understand the influence of a side chain on the reactivity C2 substituted keto-dioxinones with regard to pyrone synthesis.

To move forward we plan the construction of the pyrone via the last method herein described.

Once we successfully obtain the beta keto ester with the farnesyl epoxy side chain in position C2 (**25**), we will investigate the cascade reaction, using different Lewis acids, solvents and reaction conditions. The stereochemistry obtained in the ring system of the product, after this key reaction, will be established by means of spectroscopic analyses such as $^{1}$H NMR (e.g. NoE and 2D correlation spectroscopy) and by comparison to the known compound.




Scheme 10. Further studies: the cascade reaction toward compound 1B

This study is ongoing and still under investigation in the Barrett Laboratories.

## 3.1 Experimental Section

### General Information

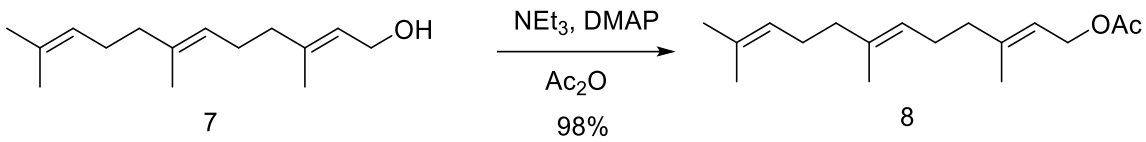
All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. Tetrahydrofuran (THF) was distilled under argon gas. Methanol (MeOH) was distilled from metallic sodium under nitrogen gas.

All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated PE SIL G/UV 250 μm layer polyester-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol, or vanilline, and heat as developing agents.

Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-500 (500 MHz for $^{1}H$ and 126 MHz for $^{13}C$), Varian Inova-400 (400 MHz for $^{1}H$ and 101 MHz for $^{13}C$) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Peak multiplicities are abbreviated: singlet, s; doublet, d; triplet, t; multiplet; m.

Coupling constants are reported in hertz (Hz). Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the Imperial College Universtity.

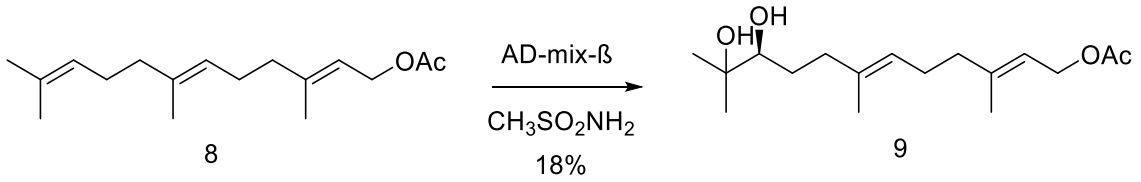
3.2 Experimental Procedure/Characterization




7 8

***(2E,6E)-Farnesyl Acetate (8).*** Acetic anyhydride (44.3 mL, 469 mmol, 3 eq.) was added dropwise to a solution of (2E,6E)-farnesol (34.7 g, 156 mmol, 1 eq.), 4-DMAP (9.56 g, 78.2 mmol, 0.5 eq.), and $Et_3N$ (110 mL, 782 mmol, 5 eq.) in $CH_2Cl_2$ (500 mL) at 0 °C. After stirring for 60 min at 0 °C, the reaction contents were quenched by the addition of water, and the crude product was extracted with $CH_2Cl_2$ (3 × 200mL). The combined organic solution was washed with 1 M HCl (100 mL; back-extracted with 25 mL $CH_2Cl_2$), saturated aqueous $NaHCO_3$ (100mL; back-extracted with 25 mL $CH_2Cl_2$), and brine (100 mL; back-extracted with 25 mL $CH_2Cl_2$). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated. Chromatography through a silica gel plug (20 × 50 mm) with Pentene:EtOAc (15:1 to 5:1) afforded **8** (40.4 g, 98% yield) as a light yellow viscous oil: Rf = 0.53 (silica gel, Pentene:EtOAc, 5:1). [20]

$^1H$ NMR (400 MHz, $CDCl_3$) δ 5.42 – 5.33 (tq, *J* = 7.2, 1.4 Hz, 1H), 5.18 – 5.06 (m, 2H), 4.66 – 4.56 (d, *J* = 7.1 Hz, 2H), 2.24 – 1.92 (m, 11H), 1.75 – 1.69 (dd, *J* = 10.7, 1.3 Hz, 6H), 1.64 – 1.60 (d, *J* = 1.7 Hz, 6H).

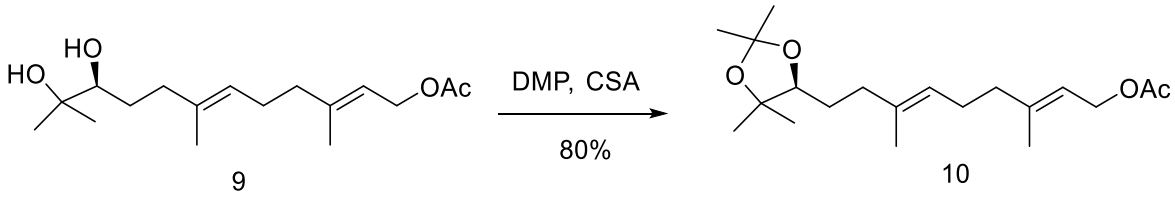



8 9

***(R,2E,6E)-10,11-Dihydroxy-3,7,11-trimethyldodeca-2,6-dienyl Acetate (9).*** To a stirred suspension of AD-mix-β (21.6 g) and $MsNH_2$ (2.76 g, 29.1 mmol, 1.05 eq.) in t-BuOH/water (900 mL, 1:1) was added a solution of farnesyl acetate **8** (7.30 g, 27.7 mmol) in t-BuOH/water (50 mL, 1:1) at 0 °C. The reaction mixture was stirred at that temperature for 17 h before it was quenched with saturated aq. $NaHCO_3$ (80 mL). The resulting mixture was extracted with EtOAc (3 × 150 mL), and the combined organic solution was washed with brine (100 mL) and dried over anhydrous $MgSO_4$. After filtration and removal of the solvent under vacuum, the residue was purified by flash column chromatography with

EtOAc/Pentene (1:2) to give diol **9** (1.53 g, 18 %) as a pale yellow oil: Rf = 0.34 (silica, EtOAc:Pentene 1:1). [21]

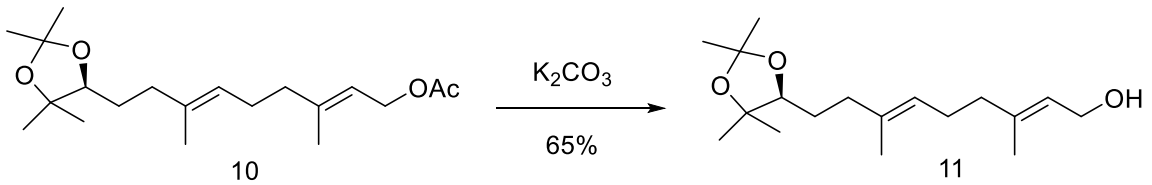
$^1$H NMR (400 MHz, $CDCl_3$) δ 5.35 – 5.24 (tq, *J* = 6.8, 1.4 Hz, 1H), 5.18 – 5.07 (m, 1H), 4.60 – 4.50 (d, *J* = 7.1 Hz, 2H), 3.35 – 3.23 (d, *J* = 10.3 Hz, 1H), 2.58 – 2.50 (d, *J* = 4.1 Hz, 1H), 2.44 – 2.37 (s, 1H), 2.32 – 1.93 (m, 10H), 1.73 – 1.62 (m, 6H), 1.61 – 1.47 (m, 1H), 1.18 – 1.09 (d, *J* = 16.7 Hz, 6H)



9 10

***Acetonide (10).*** To a solution of the known chiral diol **9** (206 mg, 0.67 mmol) in 3.0 mL of dichloromethane were added (±)-10-camphorsulfonic acid (8.0 mg, 33.5 μmol, 0.05 eq.) and 2,2-dimethoxypropane (0.25 mL, 2.01 mmol, 3 eq.) at 0 °C under a argon atmosphere, and the mixture was stirred at room temperature for 1 h. A saturated aqueous solution of sodium bicarbonate (5 mL) was added to the solution, and the aqueous layer was extracted with dichloromethane (5 mL × 3). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was subjected to column chromatography (Pentane/ethyl acetate = 10:1) on 5 g of silica gel to yield acetonide **10** (186 mg, 80% yield) as a colorless oil: Rf = 0.63 (hexane/ethyl acetate = 70:30).

$^1$H NMR (400 MHz, $CDCl_3$) δ 4.65 – 4.54 (d, *J* = 7.0 Hz, 3H), 3.69 – 3.61 (dd, *J* = 9.2, 3.5 Hz, 1H), 2.37 – 1.93 (m, 10H), 1.78 – 1.56 (d, *J* = 1.3 Hz, 3H), 1.51 – 1.37 (s, 6H), 1.37 – 1.27 (d, *J* = 2.8 Hz, 3H), 1.28 – 1.20 (s, 3H), 1.20 – 1.02 (d, *J* = 6.0 Hz, 3H)

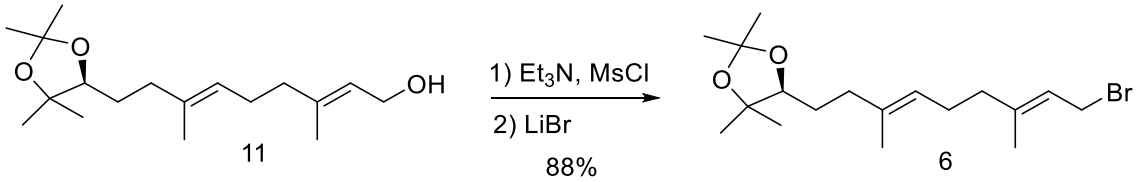


10 11

***Alcohol (11).*** To a solution of acetonide **10** (186 mg, 0.55 mmol, 1 eq.) in 3.30 mL of methanol was added potassium carbonate (570 mg, 4.12 mmol, 7.5 eq), and the mixture was stirred at room temperature for 15 min. Water (20 mL) was added and the aqueous

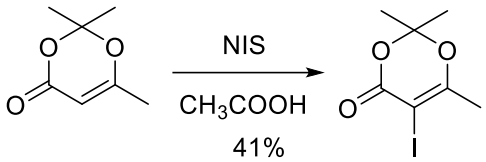
solution was extracted with dichloromethane (20 mL × 3). The combined organic solution was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (Pentene/ethyl acetate = 5:1 to 1:1) on 5 g of silica gel to furnish alcohol **11** (140 mg, 65% yield) as a colorless oil: Rf = 0.31 (hexane/ethyl acetate = 70:30).

$^1$H NMR (400 MHz, $CDCl_3$) δ 5.50 – 5.36 (m, 1H), 5.22 – 5.12 (tt, *J* = 6.6, 1.6 Hz, 1H), 4.21 – 4.12 (t, *J* = 5.9 Hz, 2H), 3.70 – 3.61 (dd, *J* = 9.2, 3.5 Hz, 1H), 2.33 – 1.92 (m, 8H), 1.76 – 1.66 (m, 4H), 1.66 – 1.58 (m, 3H), 1.45 – 1.41 (d, *J* = 2.7 Hz, 3H), 1.35 – 1.29 (s, 3H), 1.29 – 1.21 (s, 3H), 1.17 – 1.06 (m, 3H)




***(10R)-10,11-Isopropylidenedioxy-10,11-dihydrofarnesyl bromide (6).*** To a solution of the allylic alcohol **11** (140 mg, 0.48 mmol, 1 eq.) and $Et_3N$ (0.16 mL, 1.86 mmol, 3.8 eq.) in 3 mL of dry THF was added MsCl (96 µL, 1.24 mmol, 2.5 eq.) at -45 °C under Ar. After the mixture was stirred at this temperature for 45 min and then at 0 °C for 30 min, a solution of LiBr (2M in THF, 1.2 mL, 2.4 mmol, 5 eq.) was added and stirring was continued at 0 °C for 1 h. The reaction mixture was the poured into a mixture of pentene (15 mL) and ice-cooled $NaHCO_3$ (15 mL). The organic solution was separated and the aqueous layer was extracted twice with 15 mL of pentene. The combined organic phase was washed with brine and dried ($MgSO_4$). After removal of the solvent, 54.6 mg (88 %) of allylic bromide **6** was obtained as a colorless oil, which is pure enough for the following reaction. [22]

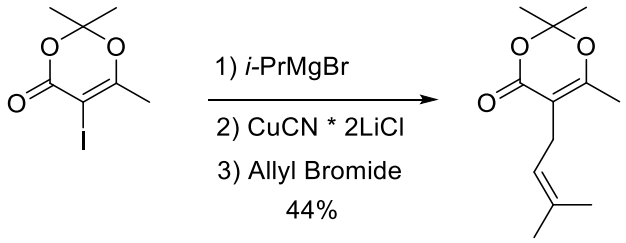
$^1$H NMR (400 MHz, $CDCl_3$) δ 5.55 – 5.42 (tt, *J* = 8.1, 1.2 Hz, 1H), 5.36 – 5.21 (m, 1H), 3.82 – 3.72 (m, 3H), 2.57 – 1.68 (m, 8H), 1.66 – 1.61 (s, 3H), 1.61 – 1.58 (s, 3H), 1.53 – 1.48 (s, 3H), 1.48 – 1.46 (s, 3H), 1.30 – 1.24 (s, 3H), 1.24 – 1.18 (s, 3H)




12 5

***5-iodo-1,3-dioxin-4-one (5).*** A solution of 2,2,6-trimethyl-1,3-dioxin-4-one **12** (142 mg; 1 mmol, 1 eq.) and N-iodosuccinimide (NIS) (310 mg; 1.3 mmol, 1.3 eq.) in acetic acid (2.5 mL) was stirred for 19 h at room temperature in the dark. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic solution was washed with water (20 mL) and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was chromatographed on silica gel (Pentene–AcOEt 10:1) to give the 2,2,6-trimethyl-5-iodo-1,3-dioxin-4-one **5** as pale yellow prisms (118 mg; 41%). [23]

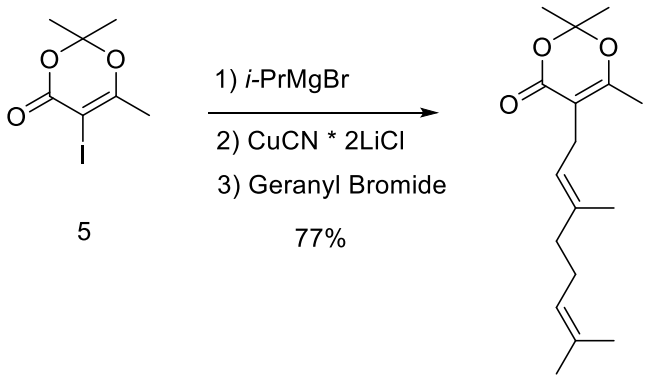
$^1$H NMR (400 MHz, $CDCl_3$) δ 2.34 – 2.27 (s, 3H), 1.74 – 1.66 (s, 6H)




5 13.1

***5-Prenyl-2,2,6-trimethyl-[1,3]dioxin-4-one (13.1).*** A solution of *i*-PrMgBr (1.74 mL, 1.1 mmol, 1.1 eq.) in THF (0.63 M) was added dropwise over 5 min to a stirred solution of the 5-iodo-1,3-dioxin-4-one **5** (268 mg, 1.0 mmol, 1.0 eq.) in THF (1.35 mL) at -30 °C under Argon. After 1 h a solution of Copper (I) cyanide di (Lithium Chloride) complex (0.18 mL, 1.1 mmol, 1.1 eq.) was added dropwise. The resulting solution was then stirred for 30 min and Prenyl Bromide (0.15 mL, 1.2 mmol, 1.2 eq.) was added. The reaction mixture was allowed to warm to room temperature, brine was added and the reaction mixture was worked up as usual. The crude residue was purified by column chromatography on silica to give **13.1** (93.6 mg, 44 %) as a colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$) δ 5.13 – 4.98 (tp, *J* = 4.6, 1.8 Hz, 1H), 2.99 – 2.90 (d, *J* = 6.8 Hz, 2H), 2.00 – 1.92 (s, 3H), 1.72 – 1.67 (m, 6H), 1.67 – 1.60 (s, 6H)

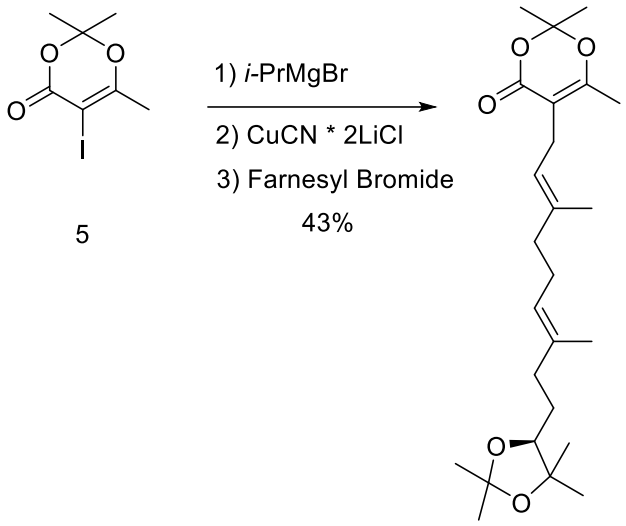



5

13.2

***5-Geranyl-2,2,6-trimethyl-[1,3]dioxin-4-one (13.2).*** A solution of *i*-PrMgBr (2.90 mL, 1.65 mmol, 1.1 eq.) in THF (0.56 M) was added dropwise over 5 min to a stirred solution of the 5-iodo-1,3-dioxin-4-one **(5)** (402 mg, 1.5 mmol, 1.5 eq) in THF (1.35 mL) at -30 °C under Argon. After 1 h a solution of Copper(I) cyanide di(Lithium Chloride) complex (0.26 mL, 1.5 mmol, 1.1 eq.) was added dropwise. The resulting solution was then stirred for 30 min and Geranyl Bromide (0.38 mL, 1.95 mmol, 1.0 eq.) was added. The reaction mixture was allowed to warm to room temperature, brine was added and the reaction mixture was worked up as usual. The crude residue was purified by column chromatography on silica to give **13.2** (281 mg, 77 %) as a colorless oil.

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 5.11 – 4.94 (m, 2H), 3.05 – 2.85 (d, J = 6.8 Hz, 2H), 2.16 – 1.91 (m, 7H), 1.70 – 1.63 (m, 12H), 1.60 – 1.58 (s, 3H). $^{13}$C NMR (126 MHz, CDCl3) δ 163.4, 162.2, 135.8, 131.4, 124.1, 121.5, 105.0, 104.7, 39.6, 26.5, 25.7, 25.0, 23.7, 17.7, 17.4, 16.1. IR (film): ν = 2973, 2919, 2852, 1721, 1645, 1390 $cm^{-1}$ HRMS [ES+] calc for $C_{17}H_{27}O_3$ $[M+H]^+$ 279.1960, found 279.1958.

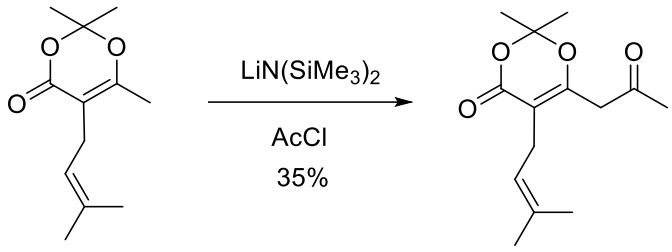



5

13.3

***5-[10,11-Isopropylidenedioxy-10,11-dihydrofarnesyl]-2,2,6-trimethyl-[1,3]dioxin-4-one (13.3).*** A solution of i-PrMgBr (0.76 mL, 0.36 mmol, 1.1 eq.) in THF (0.43 M) was added dropwise over 5 min to a stirred solution of the 5-iodo-1,3-dioxin-4-one **(5)** (101 mg, 0.38 mmol, 1.5 eq) in THF (1.35 mL) at -30 °C under Argon. After 1 h a solution of Copper(I) cyanide di(Lithium Chloride) complex (62 µL, 0.36 mmol, 1.1 eq.) was added dropwise. The resulting solution was then stirred for 30 min and Farnesyl Bromide **(7)** (100 mg, 0.27 mmol, 1.0 eq.) was added. The reaction mixture was allowed to warm to room temperature, brine was added and the reaction mixture was worked up as usual. The crude residue was purified by column chromatography on silica to give **13.3** (50.2 mg, 43 %) as a colorless oil.

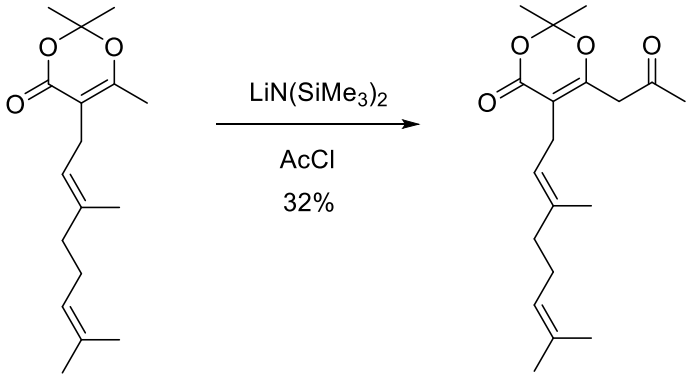
$^{1}$H NMR (400 MHz, $CDCl_3$) δ 5.19 – 5.01 (dt, *J* = 25.3, 6.9 Hz, 2H), 3.73 – 3.58 (dd, *J* = 9.3, 3.5 Hz, 1H), 3.02 – 2.92 (d, *J* = 6.8 Hz, 2H), 2.25 – 1.98 (m, 8H), 1.98 – 1.94 (s, 3H), 1.71 – 1.67 (s, 3H), 1.66 – 1.63 (s, 6H), 1.62 – 1.59 (s, 3H), 1.44 – 1.41 (s, 3H), 1.34 – 1.30 (s, 3H), 1.27 – 1.21 (s, 3H), 1.11 – 1.07 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.4, 162.2, 135.8, 134.4, 124.5, 121.5, 106.4, 104.9, 104.8, 82.8, 80.1, 39.6, 36.7, 29.7, 28.6, 27.7, 26.9, 26.6, 26.1, 25.0, 23.7, 22.9, 17.4, 16.2, 16.00. IR (film): ν = 2983, 2920, 2850, 1727, 1646, 1236 $cm^{-1}$ HRMS [ES+] calc for $C_{25}H_{40}O_5Na$ $[M+Na]^+$ 443.2773, found 443.2773




13.1 4.1

***5-Prenyl-2,2-trimethyl-6-(1-methyl-2-oxopropyl)-1,3-Dioxin-4-one (4.1).*** $LiN(SiMe_3)_2$ in THF (1 M; 0.22 mL, 0.22 mmol, 1 eq.) was added dropwise with stirring to **13.1** (46.8 mg, 0.22 mmol, 1 eq.) in THF (1 mL) and the resulting pale yellow solution stirred at –70 °C for 50 min, when AcCl (15 µL, 0.22 mmol, 1 eq.) was added. The reaction temperature was maintained at –70 °C for 45 min after which time the solution was poured onto aqueous HCl (1 M; 1 mL) and $Et_2O$ (2 mL) was added. The organic phase was washed with brine (3 × 5 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography ($Et_2O$ : Pentene 1:10 to 1:5) gave product **(4.1)** (18.1 mg, 35%) as a colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$) δ 5.08 - 4.95 (m, 1H), 3.42 - 3.34 (s, 2H), 2.98 - 2.87 (d, J = 6.8 Hz, 2H), 2.24 - 2.19 (s, 3H), 1.71 - 1.63 (s, 12H)

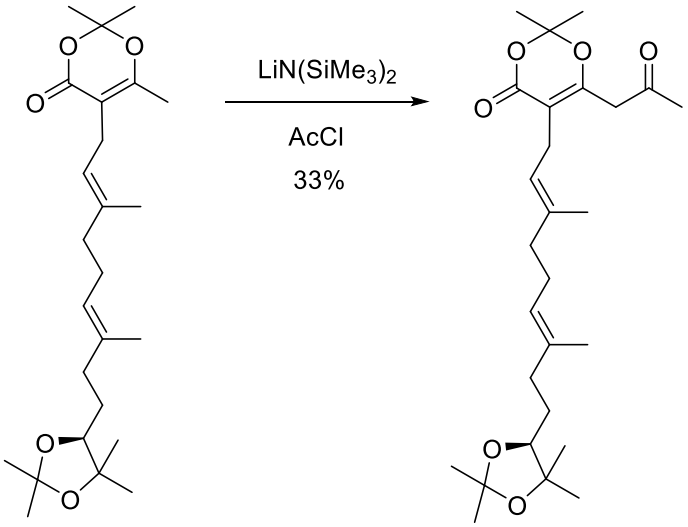



13.2 4.2

***5-Geranyl-2,2-trimethyl-6-(1-methyl-2-oxopropyl)-1,3-Dioxin-4-one (4.2).*** $LiN(SiMe_3)_2$ in THF (1 M; 0.72 mL, 0.72 mmol, 1 eq.) was added dropwise with stirring to **13.2** (200 mg, 0.72 mmol, 1 eq.) in THF (2.7 mL) and the resulting pale yellow solution stirred at –70 °C for 1 h, when AcCl (51 µL, 0.72 mmol, 1 eq.) was added. The reaction temperature was maintained at –70 °C for 90 min after which time the solution was poured onto aqueous

HCl (1 M; 1 mL) and $Et_2O$ (2 mL) was added. The organic phase was washed with brine (3 × 5 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography ($Et_2O$ : Pentene 1 : 10 to 1 : 5) gave keto-dioxinone **(4.2)** (18.1 mg, 32%) as a colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$) δ 5.10 – 4.99 (dddd, J = 9.6, 6.6, 4.7, 3.3 Hz, 2H), 3.43 – 3.34 (s, 2H), 2.99 – 2.91 (d, J = 6.8 Hz, 2H), 2.24 – 2.19 (s, 3H), 2.12 – 1.90 (m, 4H), 1.74 – 1.63 (d, J = 6.2 Hz, 12H), 1.57 – 1.53 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 201.3, 162.0, 159.3, 136.4, 131.5, 124.0, 121.1, 107.7, 105.6, 45.7, 39.5, 30.1, 29.7, 26.5, 25.7, 25.1, 23.6, 17.7, 16.2. IR (film): ν = 2921, 2852, 1725, 1646, 1369 cm$^{-1}$ HRMS [ES+] calc for $C_{19}H_{29}O_4$ $[M+H]^+$ 321.2066, found 321.2063

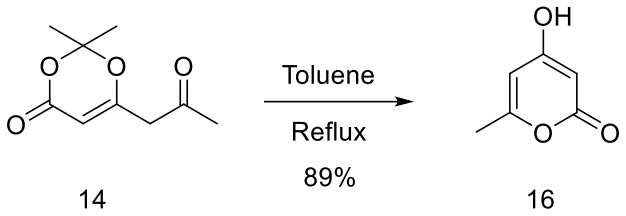



13.3 4.3

***5-[10,11-Isopropylidenedioxy-10,11-dihydrofarnesyl]-2,2-trimethyl-6-(1-methyl-2-oxopropyl)-1,3-Dioxin-4-one (4.3).*** $LiN(SiMe_3)_2$ in THF (1 M; 0.12 mL, 0.12 mmol, 1 eq.) was added dropwise with stirring to **13.3** (50.2 g, 0.12 mmol, 1 eq.) in THF (1 mL) and the resulting pale yellow solution stirred at –70 °C for 50 min, when AcCl (8 µL, 0.12 mmol, 1 eq.) was added. The reaction temperature was maintained at –70 °C for 45 min after which time the solution was poured onto aqueous HCl (1 M; 1 mL) and $Et_2O$ (2 mL) was added. The organic phase was washed with brine (3 × 5 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography ($Et_2O$ : Pentene 1:10 to 1:5) gave product **(4.3)** (18.1 mg, 33%) as a colorless oil.

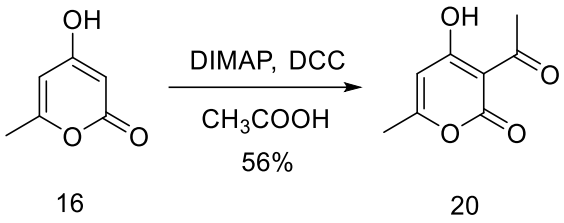
$^1$H NMR (400 MHz, $CDCl_3$) δ 5.19 – 4.96 (m, 2H), 3.72 – 3.59 (dd, *J* = 9.3, 3.5 Hz, 1H), 3.43 – 3.33 (s, 2H), 3.00 – 2.90 (d, *J* = 6.7 Hz, 2H), 2.25 – 2.20 (s, 3H), 2.18 – 1.93 (m, 8H), 1.72 – 1.66 (d, *J* = 4.4 Hz, 9H), 1.63 – 1.59 (s, 3H), 1.45 – 1.40 (d, *J* = 2.2 Hz, 3H),

1.35 – 1.30 (s, 3H), 1.27 – 1.22 (d, *J* = 3.3 Hz, 3H), 1.11 – 1.07 (s, 3H). IR (film): ν = 2922, 2852, 1729, 1373 $cm^{-1}$ HRMS [ES+] calc for $C_{27}H_{42}O_6Na$ $[M+Na]^+$ 485.2879, found 485.2880



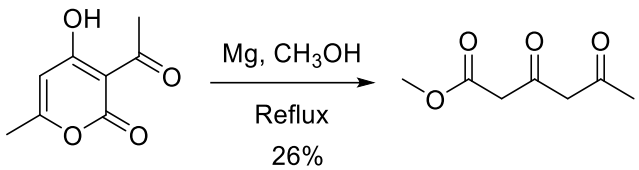

***4-Hydroxy-6-methylpyran-2-one (16).*** A solution of Keto-dioxinone **(14)** (7 g, 38.8 mmol) in toluene (50 mL) was stirred at reflux for 2 h. The reaction mixture was allowed to warm to room temperature. The resulting precipitate formed was filtered off and washed with cold water, leading to the isolation of 4-hydroxy-6-methylpyran-2-one **(16)** as a white solid in 89% yield. [24]

$^1$H NMR (400 MHz, $CDCl_3$) δ 5.91 – 5.84 (d, *J* = 2.1 Hz, 1H), 5.52 – 5.43 (d, *J* = 2.0 Hz, 1H), 2.30 – 2.21 (s, 3H)



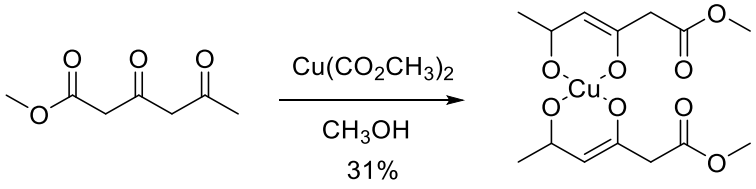

***3-Acetyl-4-hydroxy-6-methyl-2-pyrone (20).*** To a solution of 3-Acetyl-4-hydroxy-6-methyl-2-pyrone **(16)** (4.39 g, 34.8 mmol, 1 eq.) in toluene (85.0 mL), DMAP (0.85 g, 6.97 mmol, 0.2 eq.), acetic acid (2 mL, 34.8 mmol), DCC (7.19 g, 34.8 mmol, 1 eq.) were added. The reaction mixture was stirred at 100 °C for 2 h, then the organic solution was evaporated. The crude product was purified by using column chromatography (Pentene:EtOAc 2:1) to afford 3.33 g of product **20** as light yellow solid. Yield: 56%. 3-Methylcarbonyl-4-hydroxy-6-methyl-2-pyrone **(20)**. [25]

$^1$H NMR (400 MHz, $CDCl_3$) δ 5.99 – 5.89 (s, 1H), 2.72 – 2.63 (s, 3H), 2.31 – 2.24 (s, 3H)



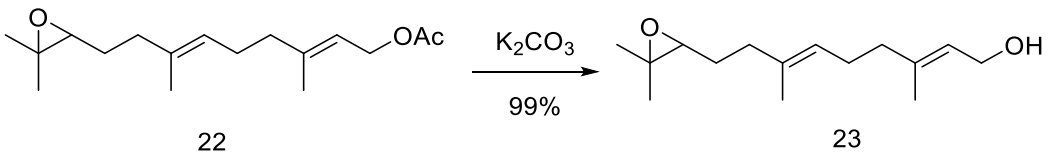

20 17

***Methyl 3,5-diozohexanoate (17).*** To a magnetically stirred solution of magnesium methylate [prepared from Mg turnings (484 mg, 19.9 mmol) and MeOH (30.0 mL)] were added 3-Acetyl-4-hydroxy-6-methyl-2-pyrone **(20)** (1.11 g, 6.60 mmol, 3 eq.) and MeOH (30 mL). The reaction mixture was heated under reflux for 15 h and the solvent evaporated under reduced pressure. The residue was dissolved in AcOEt and acidified with 1N HCl (10 mL). After extracting with AcOEt (5 x 20 mL), the combined organic solution was washed with brine, dried ($MgSO_4$) and evaporated. Chromatography (EtOAc : Pentene 1:2 to 2:1) gave Methyl 3,5-diozohexanoate **(17)** (272 mg, 26%) as a colorless liquid.
$^1$H NMR ($CDCI_3$, 200 MHz) : enol form: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.62 – 5.59 (s, 1H), 3.76 – 3.72 (d, *J* = 3.0 Hz, 3H), 3.36 – 3.31 (s, 2H), 2.11 – 2.06 (s, 3H)




17 21

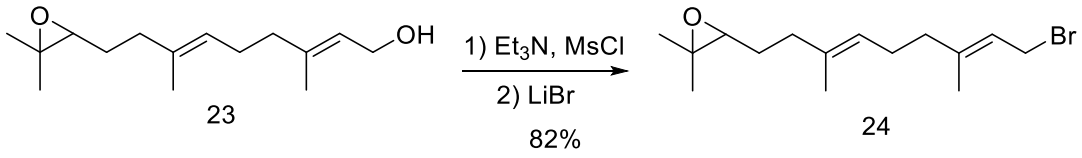
***Bis-(Methy1 3,5-dioxohexanoate)-copper(II) (21).*** A solution of copper (II) acetate monohydrate (171 mg, 0.94 mmol) in water (2.7 mL) was added into a stirred solution of Methyl 3,5-diozohexanoate **(17)** (272 mg, 1.72 mmol, 1.8 eq.) in methanol (0.3 mL). The immediately formed precipitate was filtered, sequentially washed with water and with cold acetone and dried under vacum to afford 120 mg (31%) of Bis(Methy1 3,5-dioxohexanoate)copper(II) **(21)**. IR (thin film): 1731, 1631 $cm^{-1}$.




22 23

***10,11-Epoxyfarnesol (23).*** To a solution of 10,11-Epoxyfarnesyl acetate (500 mg, 1.78 mmol) in 10 mL of methanol was added potassium carbonate (1.85 g, 13.4 mmol, 7.5 eq.), and the mixture was stirred at room temperature for 15 min. Water (20 mL) was added to the reaction mixture, and the aqueous layer was extracted with dichloromethane (20 mL × 3). The organic solution was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The Epoxyfarnesol **(23)** (443 mg, 99% yield) was pure enough to use in the next step. [26]

$^1$H NMR (400 MHz, $CDCl_3$) δ 5.49 – 5.35 (tt, *J* = 5.9, 1.4 Hz, 1H), 5.22 – 5.11 (tt, *J* = 5.4, 1.6 Hz, 1H), 4.22 – 4.06 (dd, *J* = 6.9, 3.8 Hz, 2H), 2.76 – 2.63 (t, *J* = 6.1 Hz, 1H), 2.28 – 1.95 (m, 8H), 1.74 – 1.50 (m, 6H), 1.37 – 1.28 (s, 3H), 1.28 – 1.23 (s, 3H)



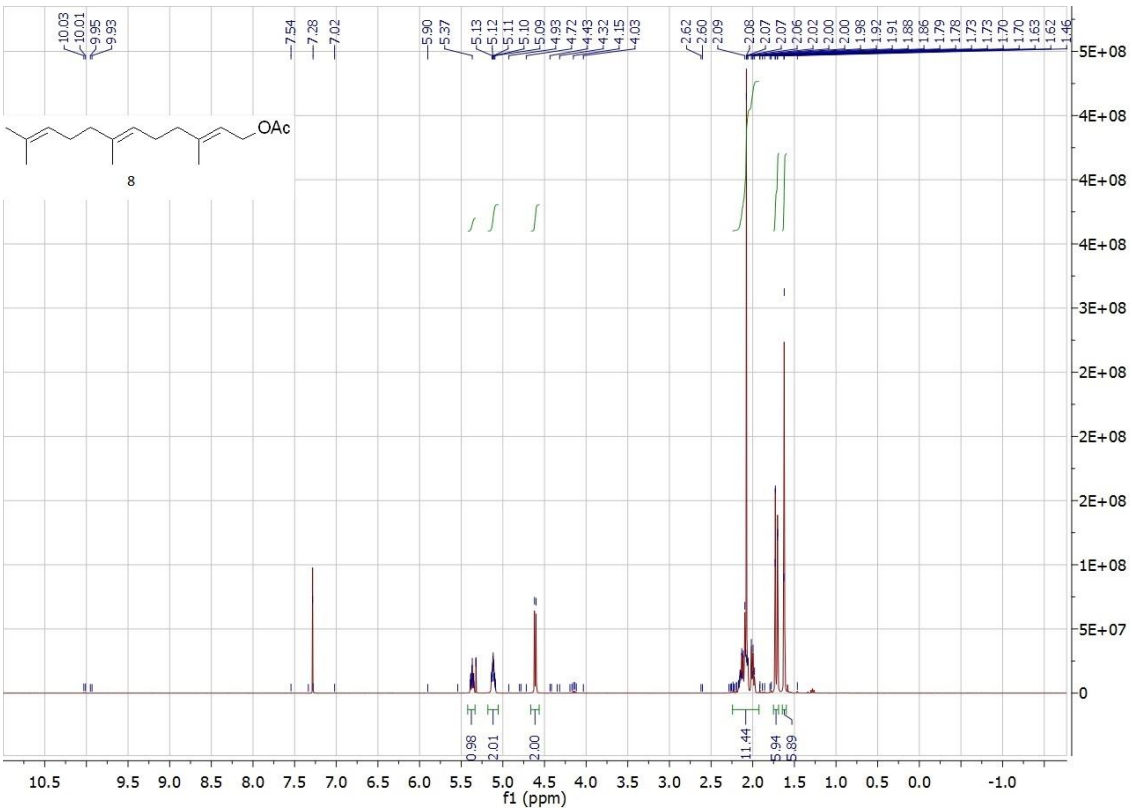

23 24

***10,11-Epoxyfarnesyl bromide (24).*** To a solution of the allylic alcohol **(23)** (443 mg, 1.86 mmol) and $Et_3N$ (0.52 mL, 3.72 mmol, 2 eq.) in 11 mL of dry THF, was added MsCl (0.19 mL, 2.4 mmol, 1.3 eq) at -45 °C under Ar. After the mixture was stirred at this temperature for 45 min and then at 0 °C for 30 min, a solution of LiBr (2 M in THF, 4.7 mL, 9.3 mmol, 5 eq.) was added and stirring was continued at 0°C for 1 h. The reaction mixture was the poured into a mixture of pentene (15 mL) and ice-cooled $NaHCO_3$ (15 mL). The organic solution was separated and the aqueous layer was extracted twice with 15 mL of pentene. The combined organic phase was washed with brine and dried ($MgSO_4$). After removal of the solvent, 461 mg (82%) of allylic bromide **(24)** was obtained as a colorless oil, which is pure enough for the following reaction.

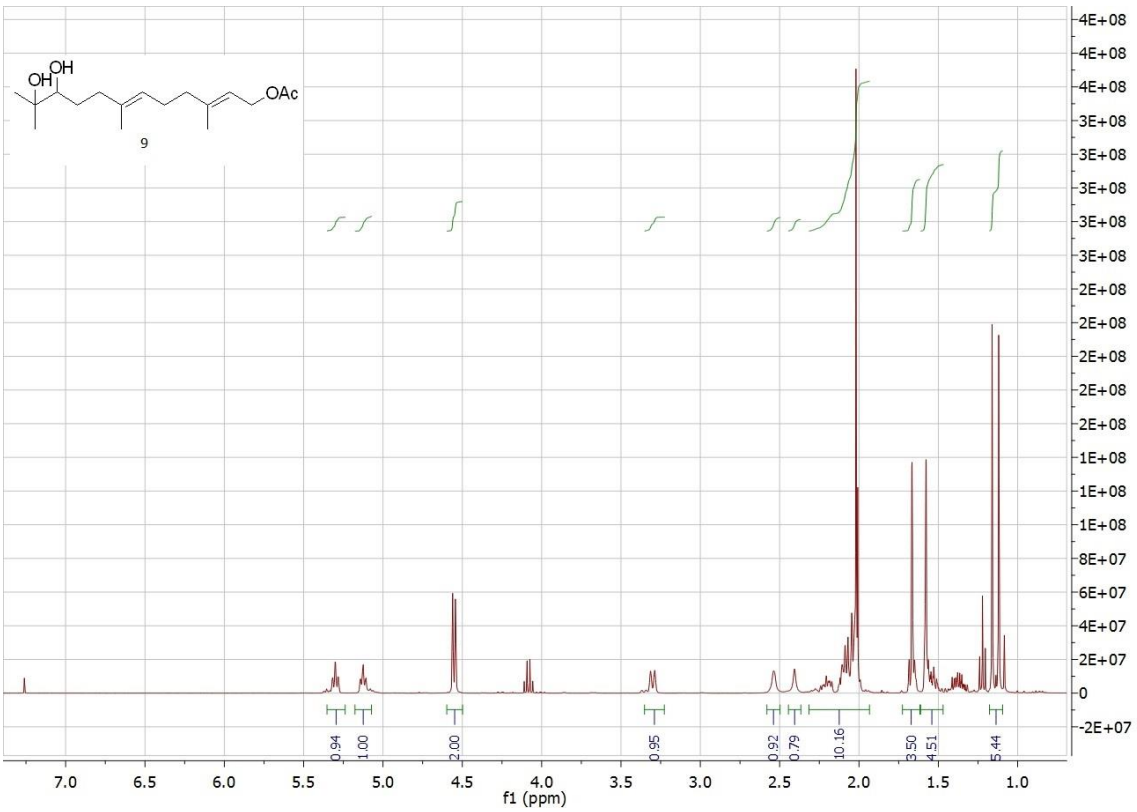
$^1$H NMR (400 MHz, $CDCl_3$) δ 5.62 – 5.45 (t, *J* = 8.5 Hz, 1H), 5.20 – 5.07 (t, *J* = 6.3 Hz, 1H), 4.07 – 3.96 (d, *J* = 8.5 Hz, 2H), 2.77 – 2.65 (t, *J* = 6.1 Hz, 1H), 2.27 – 1.96 (dtt, *J* = 15.8, 9.8, 5.6 Hz, 8H), 1.76 – 1.70 (s, 3H), 1.67 – 1.53 (m, 3H), 1.35 – 1.28 (s, 3H), 1.28 – 1.23 (s, 3H)

# APPENDIX

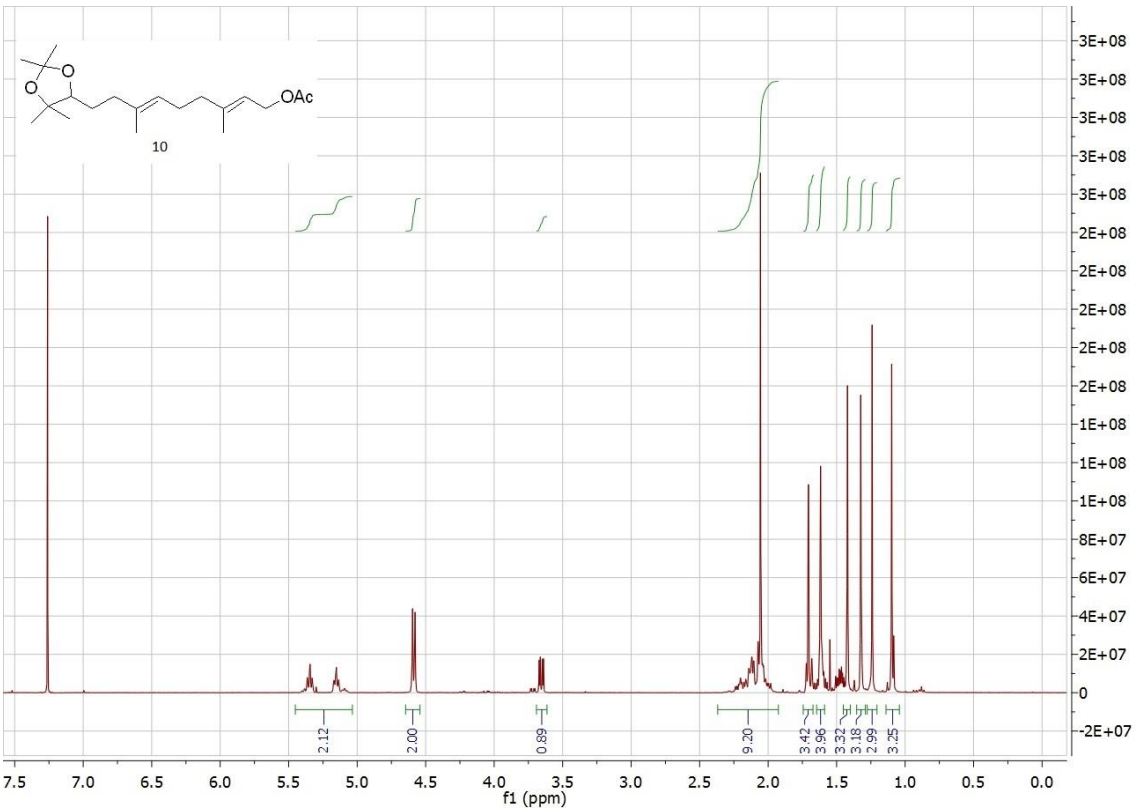
***(2E,6E)-Farnesyl Acetate (8) $^{1}H$ NMR***



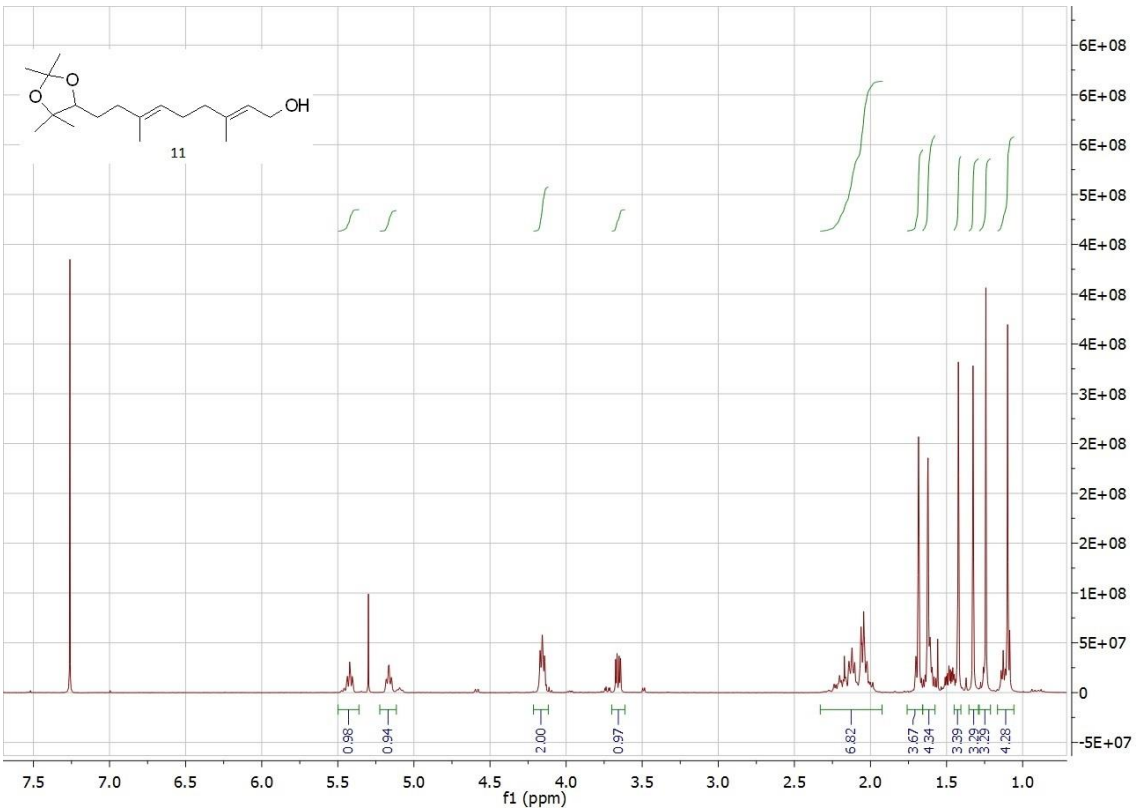
***(R,2E,6E)-10,11-Dihydroxy-3,7,11-trimethyldodeca-2,6-dienyl Acetate (9) $^{1}H$ NMR***



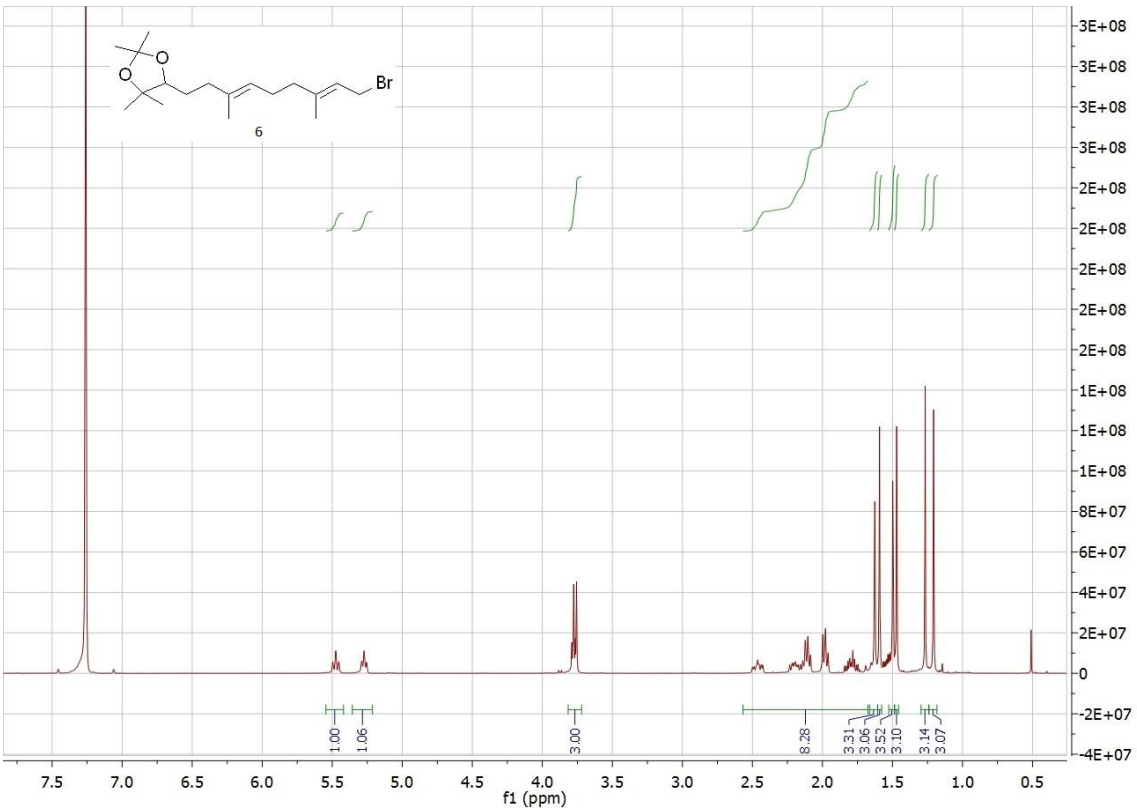
***Acetonide (10) $^{1}H$ NMR***



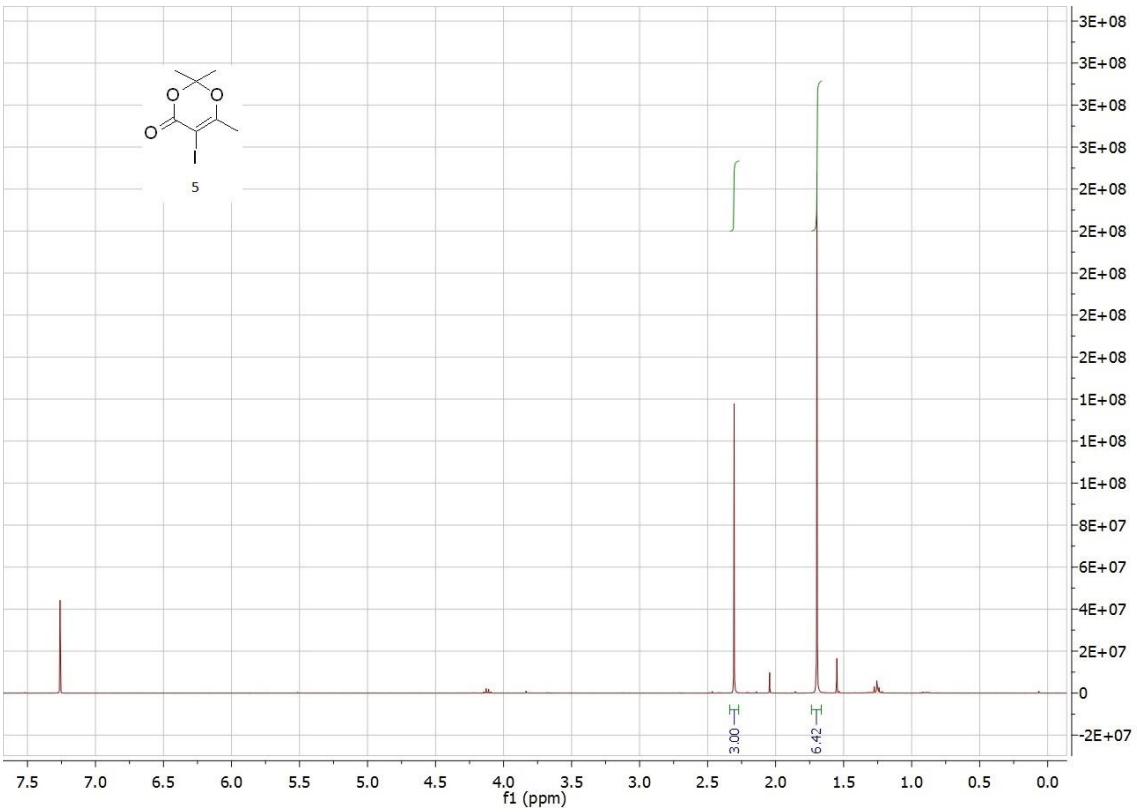
***Alcohol (11) $^{1}H$ NMR***



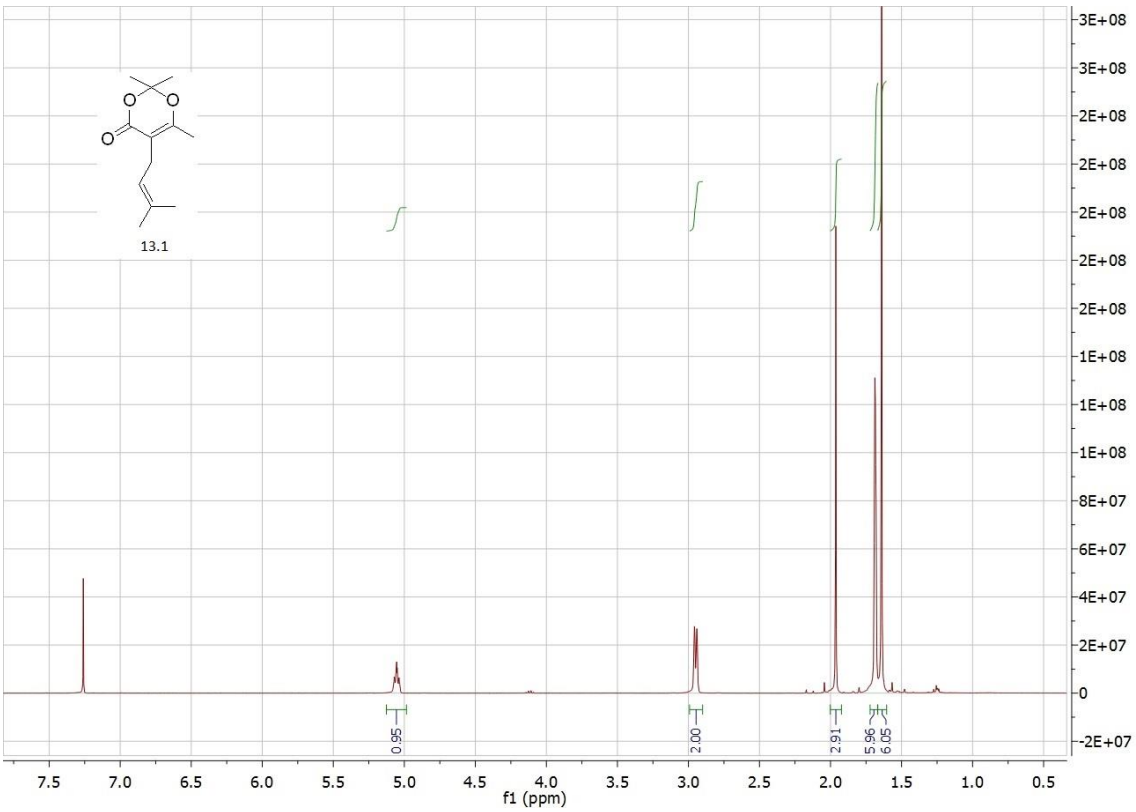
***(10R)-10,11-Isopropylidenedioxy-10,11-dihydrofarnesyl bromide (6) $^{1}$H NMR***



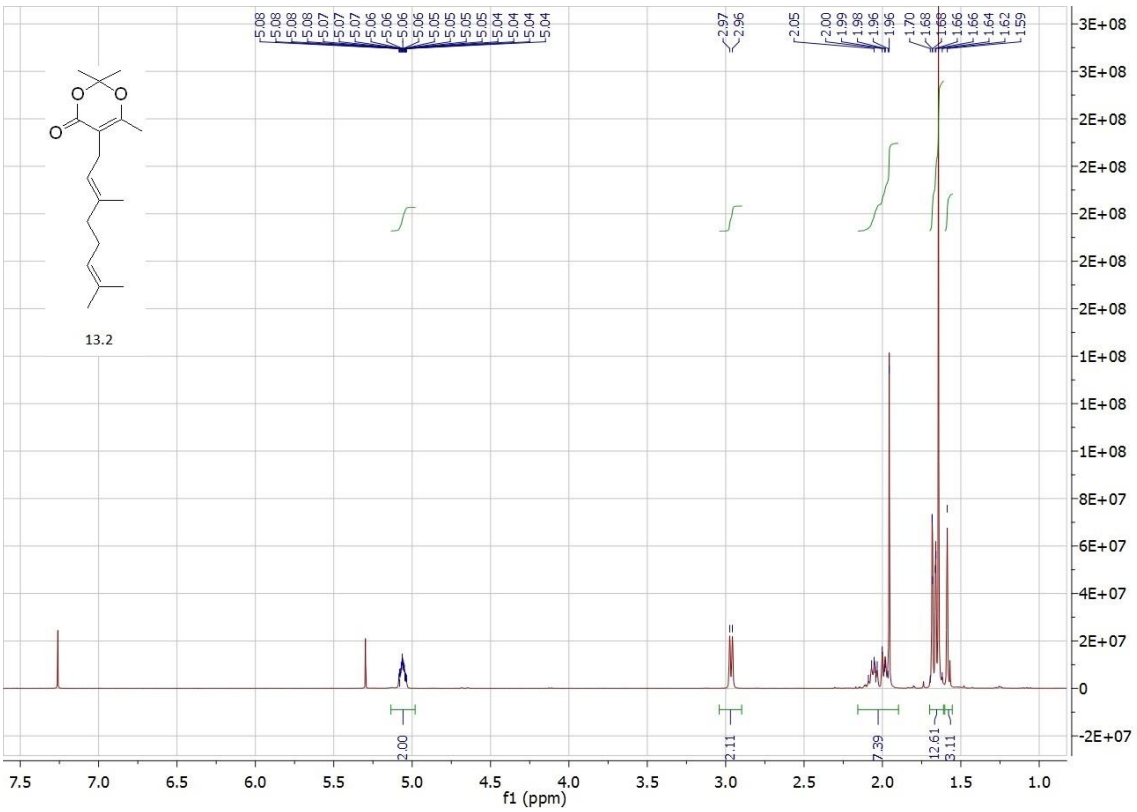
***5-iodo-1,3-dioxin-4-one (5) $^{1}H$ NMR***



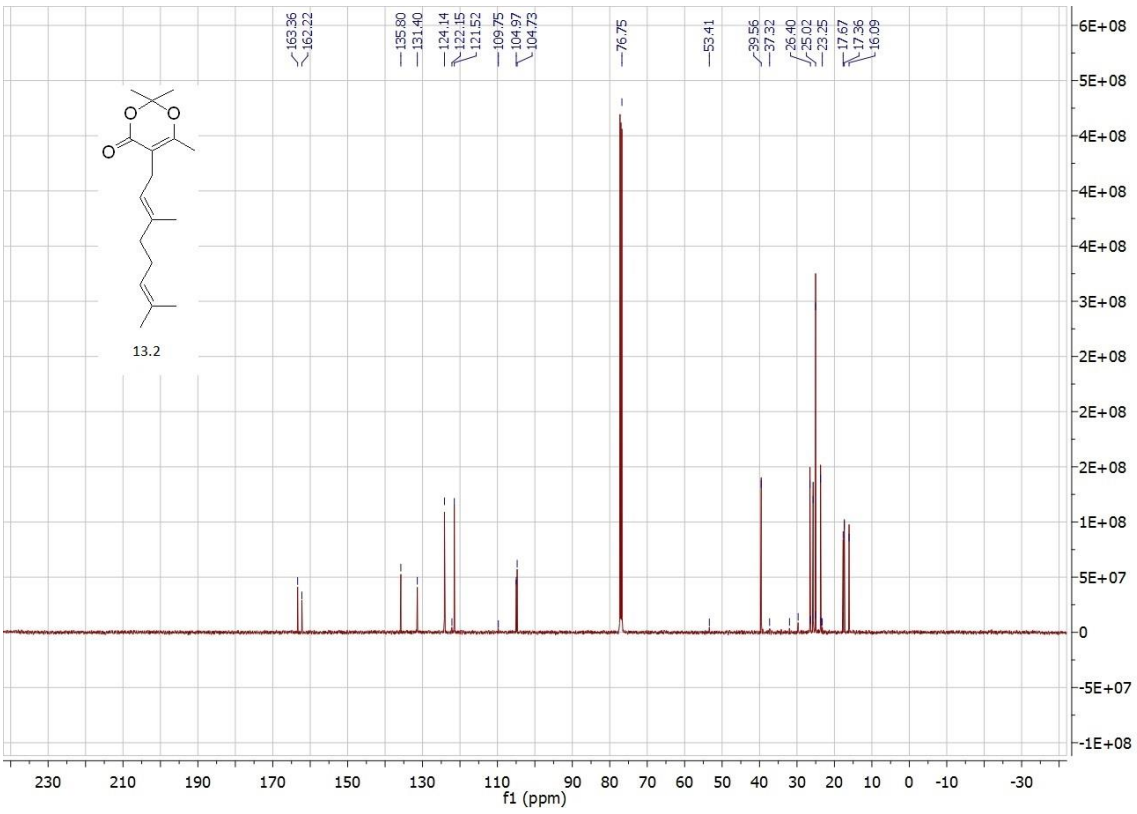
***5-Prenyl-2,2,6-trimethyl-[1,3]dioxin-4-one (13.1) $^{1}H$ NMR***



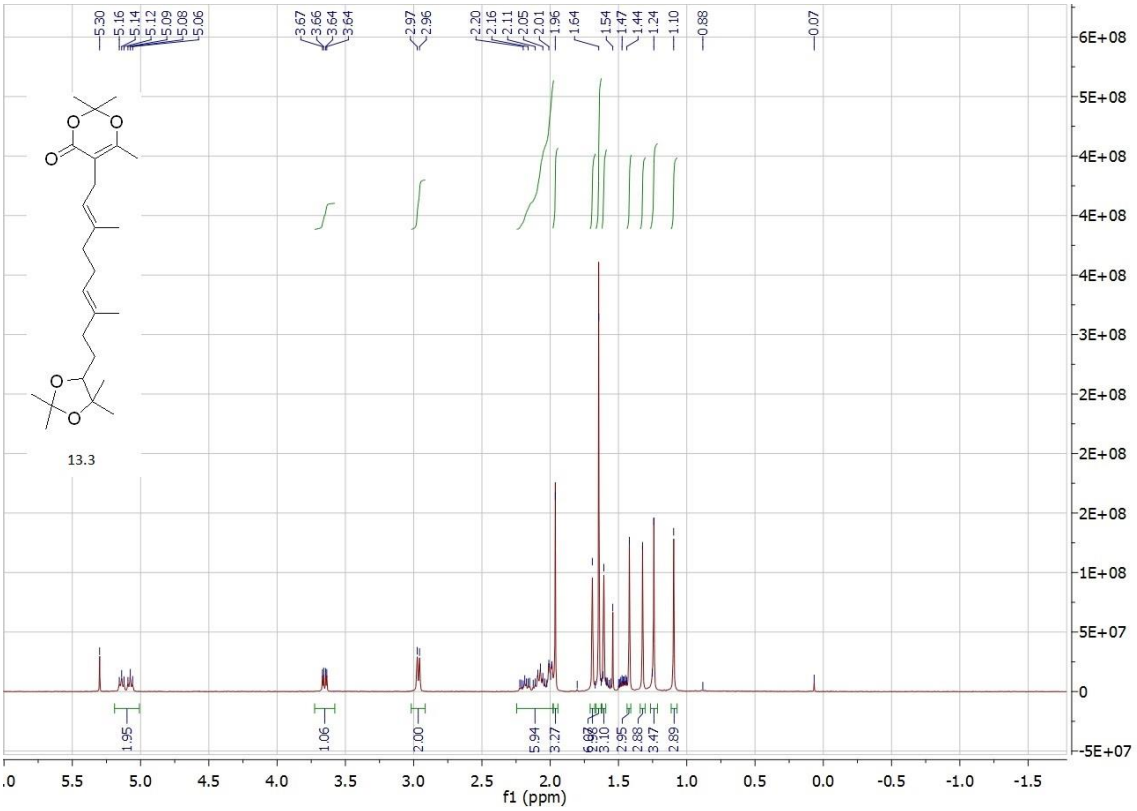
***5-Geranyl-2,2,6-trimethyl-[1,3]dioxin-4-one (13.2) $^{1}H$ NMR***



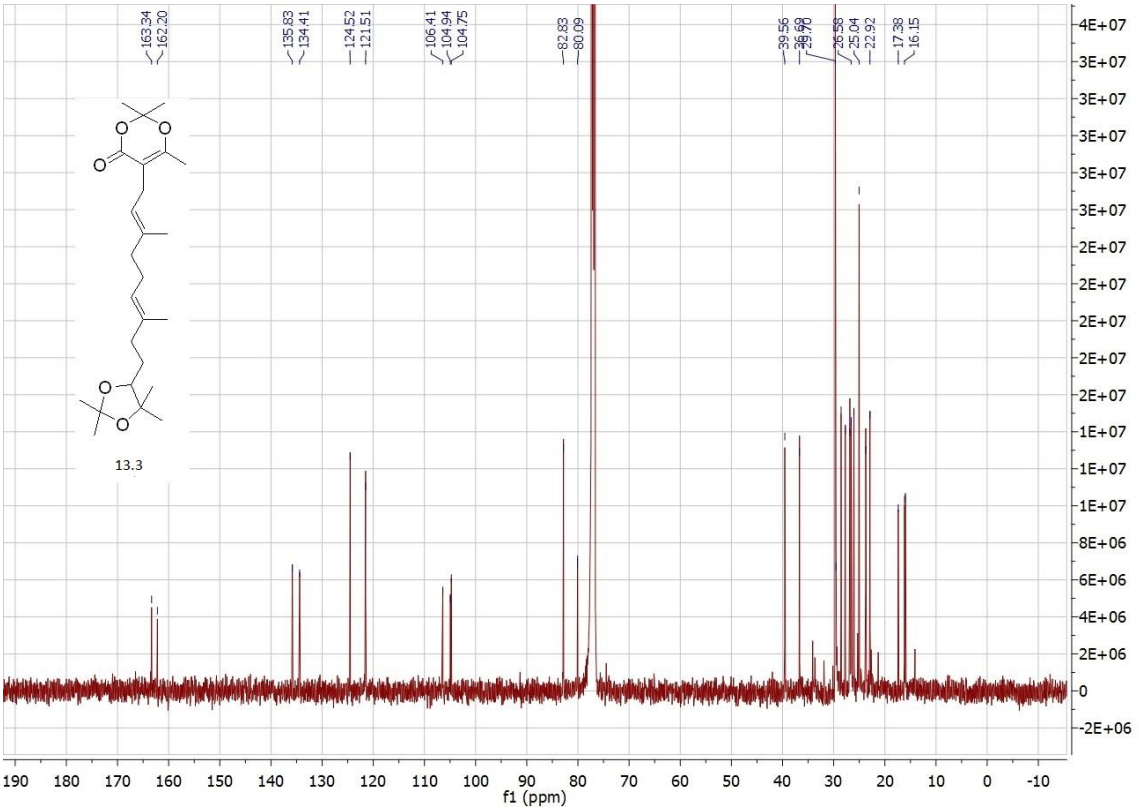
***5-Geranyl-2,2,6-trimethyl-[1,3]dioxin-4-one (13.2) $^{13}C$ NMR***



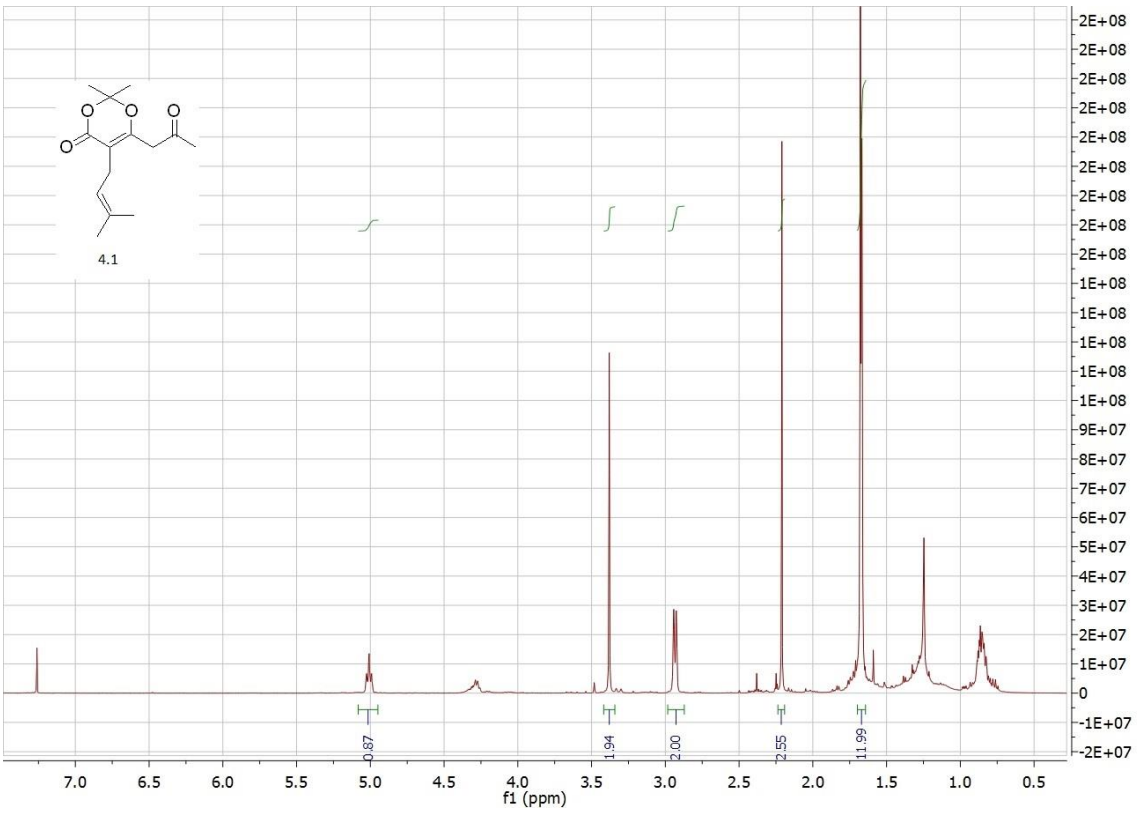
***5-[10,11-Isopropylidenedioxy-10,11-dihydrofarnesyl]-2,2,6-trimethyl-[1,3]dioxin-4-one (13.3) $^{1}$H NMR***



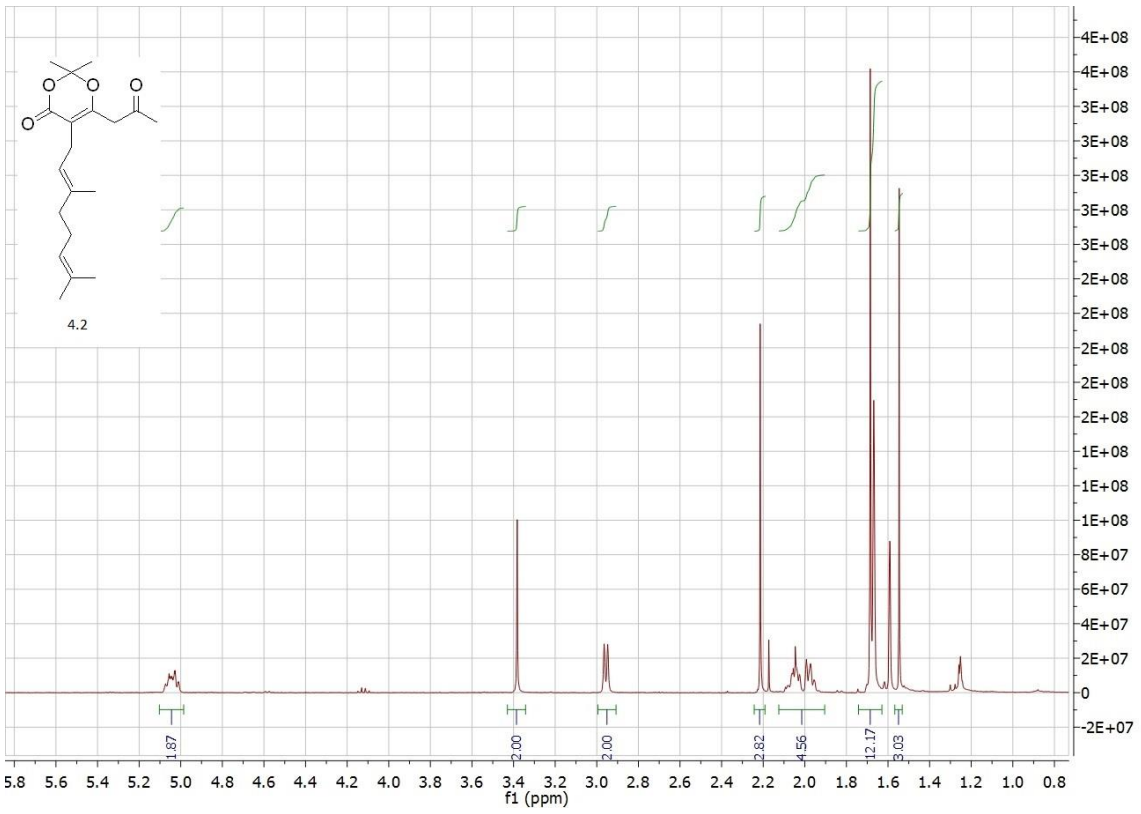
***5-[10,11-Isopropylidenedioxy-10,11-dihydrofarnesyl]-2,2,6-trimethyl-[1,3]dioxin-4-one (13.3) $^{13}C$ NMR***



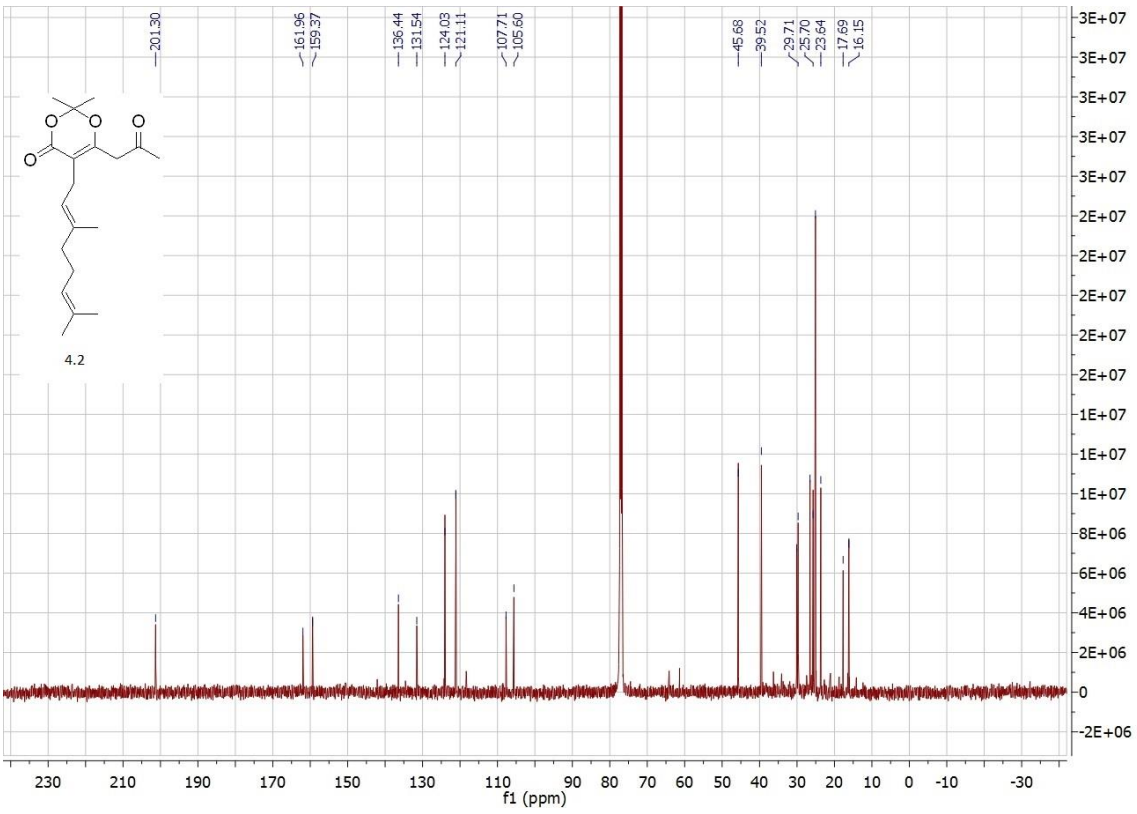
***5-Prenyl-2,2-trimethyl-6-(1-methyl-2-oxopropyl)-1,3-Dioxin-4-one (4.1) $^{1}$H NMR***



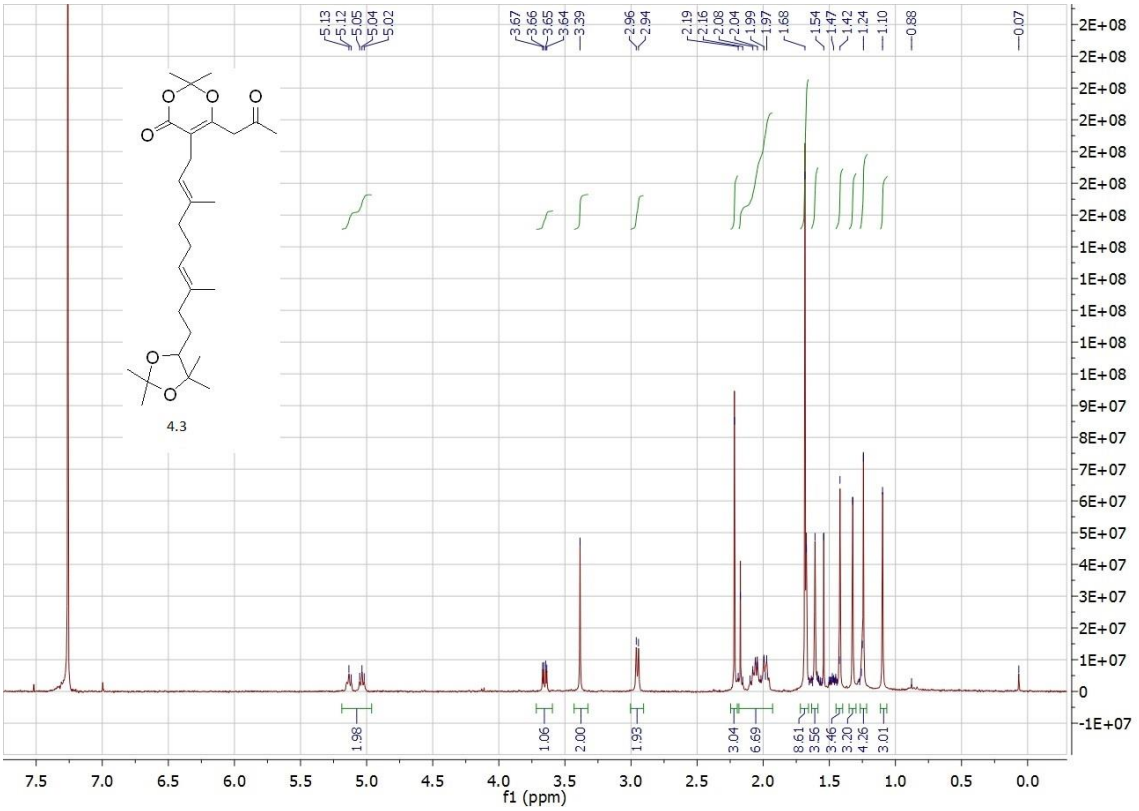
***5-Geranyl-2,2-trimethyl-6-(1-methyl-2-oxopropyl)-1,3-Dioxin-4-one (4.2) $^{1}$H NMR***



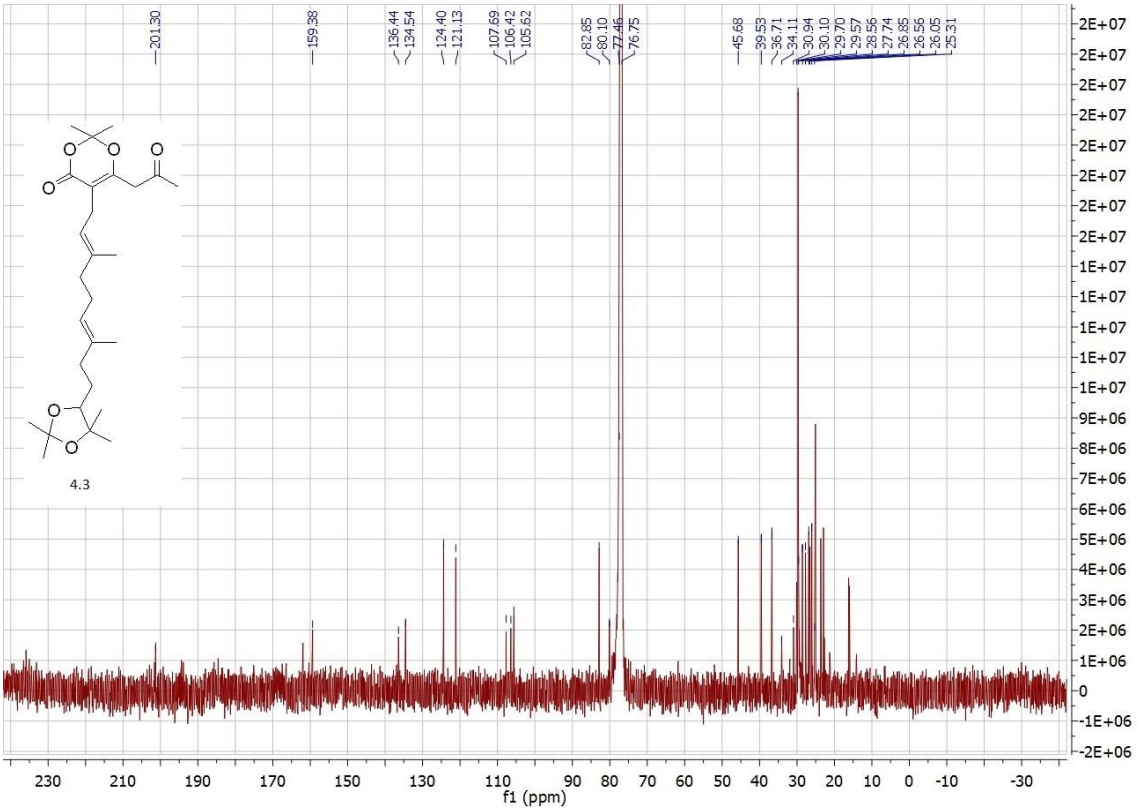
***5-Geranyl-2,2-trimethyl-6-(1-methyl-2-oxopropyl)-1,3-Dioxin-4-one (4.2) $^{13}C$ NMR***



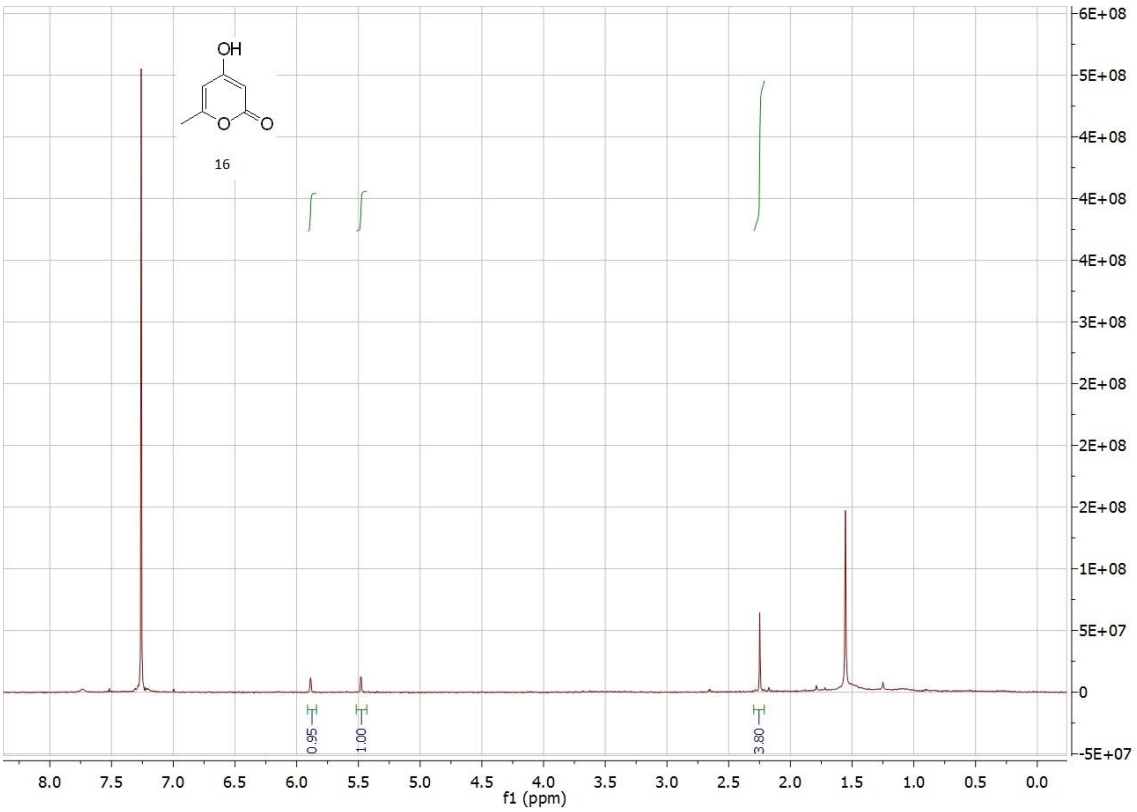
***5-[10,11-Isopropylidenedioxy-10,11-dihydrofarnesyl]-2,2-trimethyl-6-(1-methyl-2-oxopropyl)-1,3-Dioxin-4-one (4.3) $^{1}$H NMR***



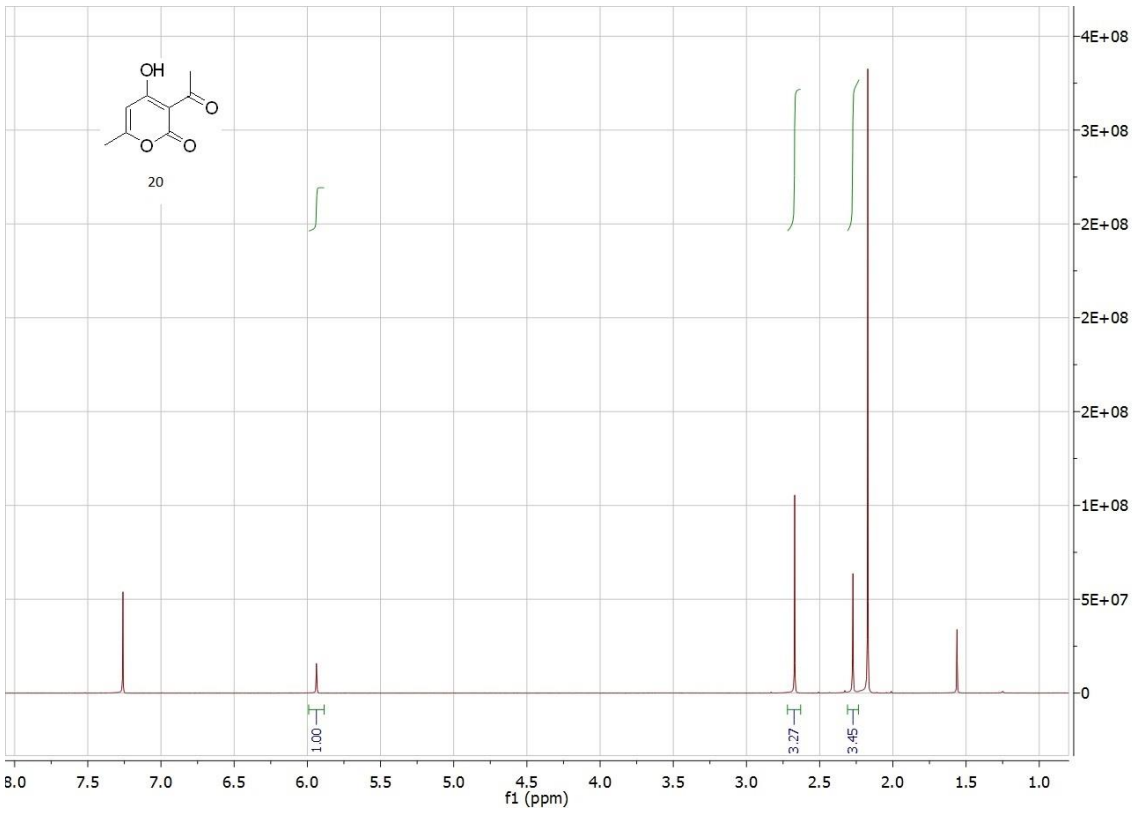
***5-[10,11-Isopropylidenedioxy-10,11-dihydrofarnesyl]-2,2-trimethyl-6-(1-methyl-2-oxopropyl)-1,3-Dioxin-4-one (4.3) $^{13}C$ NMR***



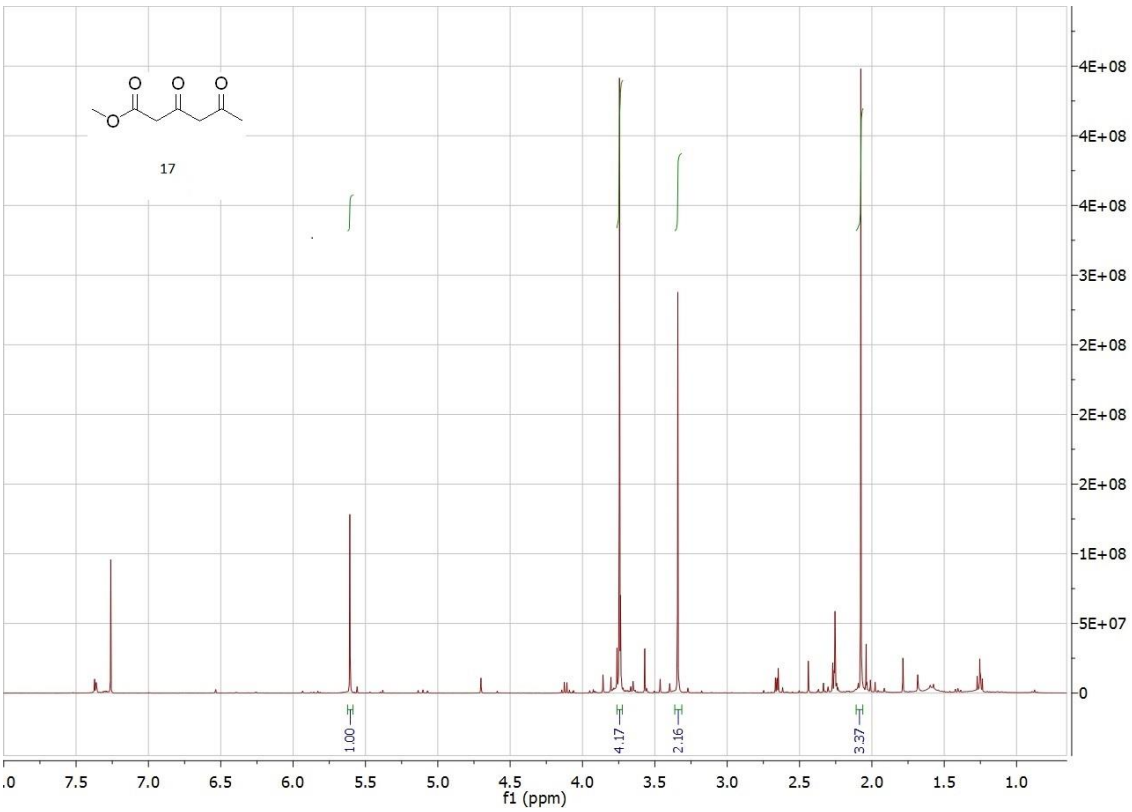
***4-Hydroxy-6-methylpyran-2-one (16) $^{1}H$ NMR***



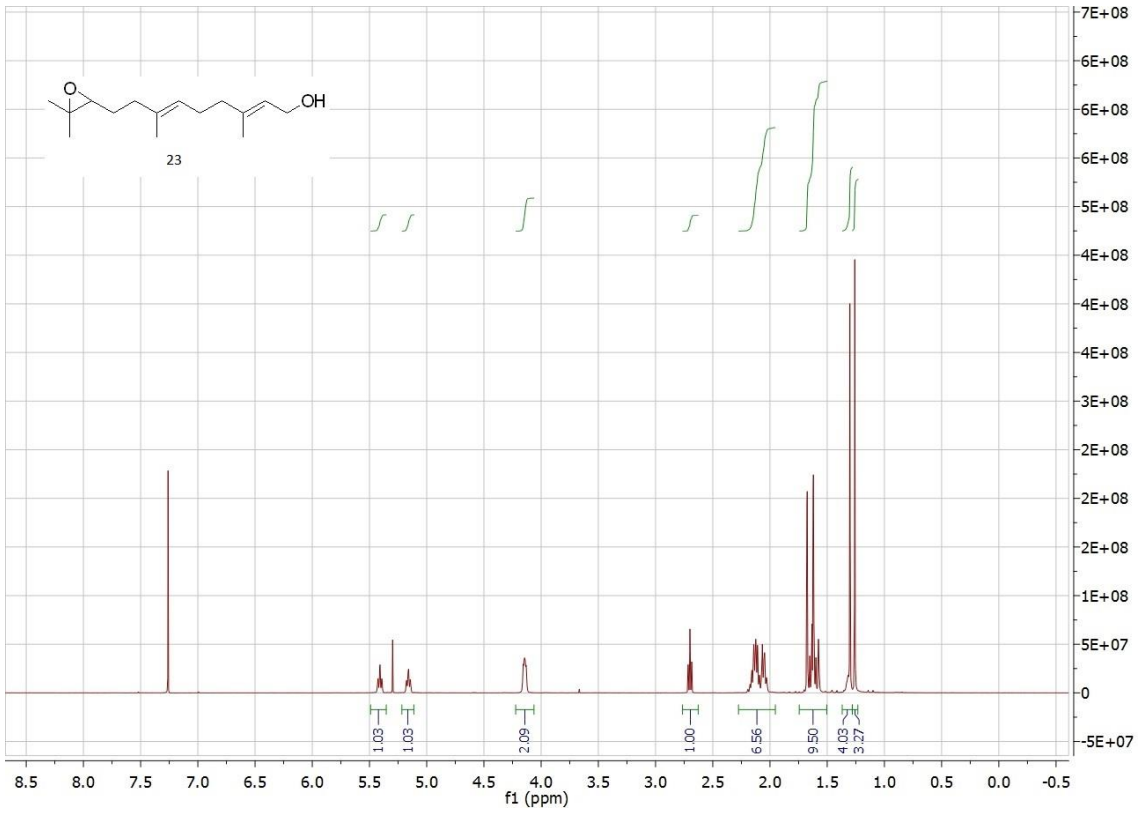
***3-Acetyl-4-hydroxy-6-methyl-2-pyrone (20) $^{1}H$ NMR***



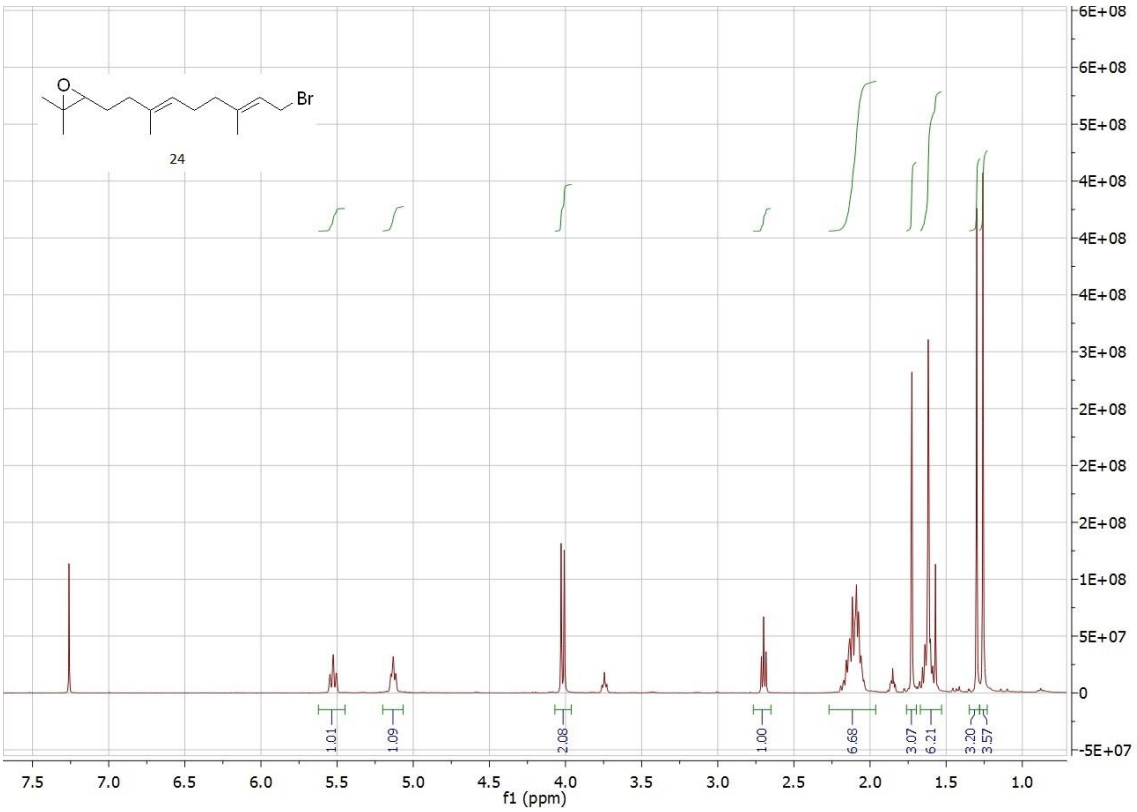
***Methyl 3,5-diozohexanoate (17) $^{1}H$ NMR***



## *10,11-Epoxyfarnesol (23) $^{1}H$ NMR*



***10,11-Epoxyfarnesyl bromide (24) $^{1}$H NMR***



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