농학석사학위논문

다 치환 방향족 합성
: Nigerapyrone B의 전합성에 응용

Synthesis of Highly Substituted Arenes
: Application to a Concise Total Synthesis of Nigerapyrone B

2022년 8월

서울대학교 대학원
농생명공학부 응용생명화학전공
김 희 은

A Dissertation for the Master of Science

Synthesis of Highly Substituted Arenes : Application to a Concise Total Synthesis of Nigerapyrone B

August 2022

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이 논문을 농학석사학위논문으로 제출함
2022년 6월

서울대학교 대학원
농생명공학부 응용생명화학전공

김 희 은

김희은의 석사학위논문을 인준함
2022년 7월

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Abstract

Arene, an aromatic hydrocarbon with delocalized π electrons, is a structural precursor of various substances. To date, various aromatic core synthesis methods have been developed, but most have limitations in regioselectivity, efficiency, and reaction conditions. In the previous study, we discovered a novel highly substituted arene synthetic method that has high regioselectivity, high efficiency, and occurs under mild and eco-friendly reaction conditions. With this method which undergoes Claisen rearrangement, sulfoxide elimination, isomerization, 6π electrocyclization, and auto-oxidation, poly-substituted arenes could be synthesized from divinylcarbinol in just two steps. Herein, we applied this base-mediated cascade benzannulation to 4-substituted divinylcarbinols and obtained 4-substituted arenes in high yield. However, unlike the 2- or 3-substituted substrates, cyclohexadienes were found in the trienal synthesis process. We reasoned that appropriate heat and base were required for auto-oxidation and we will try to find out optimal conditions. In addition, even if unsymmetrical divinylcarbinol was used as a starting material, only one kind of regioisomer could be obtained as a trienal synthesis product. This means that Claisen rearrangement is affected by the steric effect. Finally, with the arene synthesized from our novel synthetic method, we attempted to synthesize natural product, Nigerapyrone B. The first method employed the strategy of adding the two starting fragments, which generated unwanted keto enol tautomers instead of desired diketo tautomers. Therefore, by changing the strategy to the reaction method of making a dianion form directly from ethyl 2-methylacetoacetate and adding the arene, it was possible to afford more of desired diketo tautomers. In the end, we could obtain Nigerapyrone B through four steps.

Key words: poly-substituted arene, benzannulation, cyclohexadiene, auto-oxidation, Claisen rearrangement, Nigerapyrone B

***Student Number*: 2020-29438**

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List of Abbreviations

°C	degrees Celsius
^{13}C	carbon-13
^{1}H	proton
calcd	calculated
d	doublet (spectral)
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	dichloroethane
dd	doublet of doublets (spectral)
dq	doublet of quartets (spectral)
DMP	Dess-Martin periodinane
equiv.	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	hertz
J	coupling constant
L	liter(s)
M	molar
m	multiplet (spectral)
mCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)

mmol	millimole(s)
mol	mole(s)
mp	melting point
MTBE	methyl tert-butyl ether
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin layer chromatography
UV	ultraviolet
δ	chemical shift

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Introduction

Arene, from *ar*omatic + -*ene*, is an aromatic hydrocarbon with sigma bonds and delocalized π electrons between atoms forming a ring. The electron delocalization enhances the stability of arenes, which means that arenes lack reactivity compared to general alkenes, and they have unique properties (Janoschek, 1991; Cyrański, 2005; Hess Jr and Schaad, 2003). With such features, arenes and their derivatives are not only important π-ligands in organometallic chemistry, but also structural precursors of various substances such as natural products, pharmaceuticals, and agrochemicals (Hubig et al., 2000; Mortier, 2015). Thus, various aromatic core synthetic methods have been developed and the construction of benzene cores is generally differentiated from two typical methods (van Otterlo and De Koning, 2009; Wu et al., 2020).

One of the methods known so far is to functionalize pre-existing benzene rings to introduce desired substituents (Bunnett and Zahler, 1951; Olah, 1971). This method which includes nucleophilic and electrophilic aromatic substitutions allows us to make predictions about regiochemical outcomes (Swami et al., 2022). In addition, there are also transition metal-mediated coupling reactions which are called arylation (Lafrance and Fagnou, 2006; Kobayashi et al., 2009). These reactions, however, employ pre-functionalized arenes, so there are restrictions on the type and regioselectivity of the substituents. The other is benzannulation which has proven to be an efficient way to directly construct benzene rings. Representatively, there are Masamune-Bergman cyclization, Wulff–Dötz reaction, and Danheiser benzannulation (Bergman, 1973; Dötz, 1975; Waters and Wulff, 2008; Danheiser and Gee, 1984). Others include transition metal-mediated benzannulation (Horning and

Horning, 1947; Moriuchi et al., 2009; Hashmi et al., 2000), acid-, base-catalyzed benzannulation (Asao et al., 2003; Liu et al., 2016; Poudel et al., 2018), benzyne-mediated benzannulation (Ghotekar et al., 2019) and so on.

However, most of the above methods have limited regioselectivity and require harsh reaction conditions. Innovative methods are needed for the efficient elaboration of arene structures. In the previous study, we discovered a novel highly substituted arene synthetic method. Inspired by (Cookson and Gopalan, 1978), in which heating of allyl alkoxy vinyl sulfoxide induces Claisen rearrangement to produce γ,δ-unsaturated aldehyde, followed by base-catalyzed α-sulfoxide elimination to give dienal, it was achieved by accidental discovery of unexpected benzannulation during our trienal **4** synthesis study. Starting with divinylcarbinoxy vinyl sulfoxide **3**, this base-mediated cascade benzannulation undergoes Claisen rearrangement, sulfoxide elimination, isomerization, 6π electrocyclization, and auto-oxidation to finally form arene **6** (Fig. 1). In this method, regioselectivity can be controlled by introducing substituents to the starting material. In addition, since it is a transition metal-free method that requires only base and heat, the reaction condition is mild and eco-friendly. With this synthesis method, we were able to synthesize more than 10 arenes.

We found optimized conditions for the synthesis of trienal **4** and arene **6** from divinylcarbinoxy vinyl sulfoxide **3** (Fig. 2). After synthesizing substances with two or three substituents, we were interested in determining whether 4-substituted divinylcarbinoxy vinyl sulfoxide **3** can also undergo a cascade reaction to from trienal **4** and arene **6**. In addition, we tried to find out if there is any difference when using 4-substituted substrates as starting materials. Thus two 4-substituted divinylcarbinols, **1b** and **1c**, were prepared (Fig. 3). In the

case of divinylcarbinol **1b**, 2-bromo-2-butene, a mixture of cis and trans, was used, and we wanted to demonstrate if two types of isomers obtained from 2-bromo-2-butene affect the yield of synthesized trienal **4b** and arene **6b**. Furthermore, unlike divinylcarbinol **1c**, **1b** is an unsymmetrical divinylcarbinol. Therefore, it was possible to confirm in which direction Claisen rearrangement occurred through the position of the substituent in the trienal product.

Auto-oxidation, which resulted in a benzene ring in this method, does not usually take place in general cyclohexadiene (Lemaire et al., 2001; Tsai et al., 1982). However, under the optimized condition using 1.20 equiv. DBU as a base at 125 ℃, cyclohexadiene **5** was converted to arene **6** (Fig.2). Similarly, according to (Kim et al., 2008), benzene derivative was found upon the reaction of cyclohexene in the presence of 3.00 equiv. DBU in DMF at 130 – 140 °C. This means that DBU leads dehydrogenation at high temperature. Therefore, we tried to identify which factor has the greatest influence on auto-oxidation among the base types, temperature, and so on.

We were interested in synthesizing natural products by applying our new method for arene synthesis. We determined Nigerapyrone B (**11**) as the target product which has a structure containing arene **6a** motif (Fig. 10). Nigerapyrone B, one of the α-pyrone derivatives (Lee, 2015), was extracted from the *Aspergillus niger* MA-132, an endophytic fungus isolated from the marine mangrove plant *Avicennia marina* (Liu et al., 2011). This substance is known to have moderate cytotoxicity against the HepG2 cell line with an IC_{50} of 62 μM (Lee et al., 2013; Wen et al., 2022). Therefore, there is a need to analyze whether it can exhibit bioactivity in other cell lines or can be utilize as a therapeutic agent. However, according to (Liu et al., 2011), only 4mg of Nigerapyrone B can be obtained from 24 L whole fermented cultures through

filtration, extraction, fractionation, and purification. In this study, we attempted to synthesize large amounts of Nigerapyrone B (**11**) more easily through our novel benzannulation reaction.

Materials and Methods

General Information

All reactions were performed in an open-air atmosphere condition using technical grade solvent with magnetic stirring, unless otherwise specified. Anhydrous solvents were dried or distilled under argon prior to use: tetrahydrofuran from sodium/benzophenone, methylene chloride from calcium hydride, and hexane from 4Å Molecular sieves. Transfer of anhydrous solvents and reagents was performed with oven-dried syringes or cannulae. 4Å Molecular sieves and magnesium turnings were stored in oven. All commercially available compounds (Merck (USA), Acros (USA), Aldrich (USA), Alfa Aesar (USA), TCI (Japan)) were used without further purification unless otherwise noted. Thin-layer chromatography (TLC) was carried out using Silica gel 60 F_{254} pre-coated plates (0.25 mm) (Merck). Visualization of the spots on TLC plates was achieved either by UV light or by staining the plates in *p*-anisaldehyde or in potassium permanganate and charring by a heat gun. Flash column chromatography was carried out using Silica gel 60 (0.040-0.063 mm) (Merck). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV VIII 400 or 600 spectrometers. The solvent signals were used as references, and the chemical shifts (δ) were converted to the TMS scale ($CDCl_3$: δ_C = 77.0 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm; $(CD_3)_2CO$: δ_C = 29.84 and 206.26 ppm; residual $(CHD_2)(CD_3)CO$ in $(CD_3)_2CO$: δ_H = 2.05 ppm). Coupling constants (*J*) were reported in Hertz (Hz). High resolution mass spectra (HRMS) were recorded on an AB SCIEX Q-TOF 5600 mass spectrometer.

Preparation of Divinylcarbinols

(E)-2,4-dimethyl-1-phenyl penta-1,4-dien-3-ol (1a):

Under argon, oven-dried magnesium turnings (277.0 mg, 11.39 mmol, 1.60 equiv.) and THF (9.26 mL) were stirred at room temperature in a 25 mL flame-dried two-neck round bottom flask equipped with a reflux condenser. 2-Bromopropene (0.80 mL, 1.12 g, 9.26 mmol, 1.30 equiv.) was added and then the reaction mixture was heated at reflux. After 1 hour, the resulting solution was cooled to room temperature and transferred dropwise to a solution of α-methyl-*trans*-cinnamaldehyde (1.00 mL, 1.04 g, 7.12 mmol, 1.00 equiv.) in THF (24 mL) at 0 °C. The reaction mixture was stirred for 1 hour at 0 °C and then quenched with saturated NH_4Cl aqueous solution (30 mL). After separation of the phases, the aqueous layer was rinsed with MTBE (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (hexane:EtOAc, 9:1) afforded **1a** (1.19 g, 88.7%) as a light yellow oil. The spectral data are consistent with the reported one (Song et al., 2007).

(1*E*,4E)-2,4-dimethyl-1-phenyl-1,4-hexadien-3-ol and (1*E*,4*Z*)-2,4-dimethyl-1-phenyl-1,4-hexadien-3-ol (1b):

The same procedure used for the synthesis of **1a** was applied to make **1b** from Mg turnings (134.1 mg, 5.52 mmol, 1.60 equiv.) and 2-bromo-2-butene, mixture of cis and trans (0.46 mL, 604.9 mg, 4.48 mmol, 1.30 equiv.) in THF (4.5 mL) with α-methyl-*trans*-cinnamaldehyde (0.48 mL, 503.9 mg, 3.45 mmol, 1.00 equiv.) in THF (12 mL). Purification by flash column chromatography (hexane:EtOAc, 9:1) afforded the an inseparable mixture of (1E,4E)/(1E, 4Z)

diastereomers of **1b** (561.9 mg, 80.6%, 1:4 ratio) as a light yellow oil. The spectral data are consistent with the reported one (Sudhakar & Satish, 2015).

(1E,4E)-2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-ol (1c):

(Step 1) To a solution of KOH (716.5 mg, 12.77 mmol, 2.20 equiv.) in H_2O (2 mL) and MeOH (4 mL) was added a mixture of 3-pentanone (0.61 mL, 500.0 mg, 5.81 mmol, 1.00 equiv.) and benzaldehyde (1.30 mL, 1.36 g, 12.77 mmol, 2.20 equiv.) at room temperature. The resulting mixture was heated at reflux for 16 hours. The reaction mixture was cooled to room temperature, neutralized with 1M HCl solution (5 mL), and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure. Subsequent recrystallization with MeOH afforded (1E,4E)-2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-one (315.0 mg, 20.7%) as a white solid. The spectral data are consistent with the reported one (Arnold et al., 2006) and the product was carried to the next step.

(Step 2) To a mixture of (1E,4E)-2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3- 9 one (270.9 mg, 1.03 mmol, 1.00 equiv.) and cerium chloride heptahydrate (442.4 mg, 1.19 mmol, 1.15 equiv.) in MeOH (10 mL) was added slowly sodium borohydride (44.9 mg, 1.19 mmol, 1.15 equiv.) at 0 °C. The resulting mixture was warmed to room temperature. After stirring for 16 hours, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (12 mL). After separation of the phases, the aqueous layer was extracted with MTBE (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (hexane:EtOAc, 9:1) afforded **1c** (221.1 mg, 81.2%) as a colorless oil. The spectral data are consistent with the reported one (Wu et al.,

2021).

Preparation of (Ethynylsulfinyl)benzene

trimethyl((phenylthio)ethynyl)silane (18):

Under argon, to a solution of (trimethylsilyl)acetylene (27.40 mL, 18.90 g, 0.19 mol, 1.40 equiv.) in THF (70 mL) was added a solution of n-butyllithium (1.6 M in hexane, 120 mL, 0.19 mol, 1.40 equiv.) dropwise at -78 °C. After stirring for 1 hours, a solution of diphenyl disulfide (30.00 g, 0.14 mol, 1.00 equiv.) in THF (70 mL) was added dropwise, and then the resulting solution was stirred for 1 hour. The reaction mixture warmed to room temperature. After stirring for 1 hour, the reaction was quenched with H_2O (150 mL). After separation of the phases, the aqueous layer was rinsed with Et_2O (3 × 70 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product **18** was used for the next step without further purification.

ethynyl(phenyl)sulfane (19):

To a stirred solution of crude **18** in MeOH (280 mL) was added 2 M aqueous NaOH (170 mL) at 0 °C. After stirring for 1 hour, the resulting solution was warmed to room temperature. After stirring for 1 hour, the reaction was quenched with H_2O (250 mL). After phase separation, aqueous phase was rinsed with Et_2O (3 × 100 mL). The organic extracts were combined, washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product **19** was used for the next step without further purification.

(ethynylsulfinyl)benzene (2):

To a stirred solution of crude **19** in CH_2Cl_2 (500 mL) was added *m*-chloroperbenzoic acid (36.40 g, 0.21 mol, 1.80 equiv.) at 0 °C. After stirring for 24 hours, the reaction was quenched with saturated $NaHCO_3$ solution (100 mL). After phase separation, aqueous phase was rinsed with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc, 8:2) afforded **2** (19.49 g, 94.4% over three steps) as a brown oil. The spectral data are consistent with the reported one (Debien & Zard, 2013).

Preparation of Divinylcarbinoxy Vinyl Sulfoxides

(((E)-2-(((E)-2,4-dimethyl-1-phenylpenta-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene (3a):

To a stirred solution of (E)-2,4-dimethyl-1-phenylpenta-1,4-dien-3-ol **1a** (1.85 g, 9.83 mmol, 1.00 equiv.) in CH_2Cl_2 (100 mL) was added 4-methylmorpholine (1.62 mL, 1.49 g, 14.74 mmol, 1.50 equiv.) and (ethynylsulfinyl)benzene **2** (2.95 g, 19.66 mmol, 2.00 equiv.) at 0 °C. After stirring for 16 hours, the reaction was quenched with saturated NH_4Cl solution (70 mL). After phase separation, aqueous phase was rinsed with CH_2Cl_2 (3 × 70 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (hexane:EtOAc, 4:1) afforded an inseparable mixture of syn/anti diastereomers of **3a** (2.41 g, 72.5%, 1:1 ratio) as a brown oil. R_f 0.24 (hexane:EtOAc, 7:3); ^{1}H NMR (600 MHz, Chloroform-d) δ 7.63 – 7.58 (m, 4H), 7.52 – 7.40 (m, 6H), 7.39 – 7.31 (m, 4H), 7.33 – 7.22 (m, 6H), 7.22 – 7.18

(m, 2H), 6.60 (s, 1H), 6.56 (s, 1H), 5.89 (d, J = 12.6 Hz, 1H), 5.88 (d, J = 12.7 Hz, 1H), 5.14 (q, J = 0.9 Hz, 1H), 5.13 (q, J = 0.9 Hz, 1H), 5.10 (q, J = 1.4 Hz, 1H), 5.08 (q, J = 1.3 Hz, 1H), 4.74 (s, 1H), 4.74 (s, 1H), 1.78 (d, J = 1.4 Hz, 3H), 1.75 (d, J = 1.4 Hz, 3H), 1.72 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (600 MHz, Chloroform-d) δ 156.37, 156.25, 145.54, 145.47, 140.73, 140.61, 136.78, 136.70, 133.63, 133.53, 130.48, 130.44, 129.55, 129.35, 129.23 (2), 129.14, 129.07, 128.39, 128.36, 127.21, 127.19, 124.54, 124.51, 114.58, 114.43, 114.17, 114.15, 90.64, 90.18, 18.66, 18.51, 13.69, 13.51; HRMS $[M+H]^+$ for $C_{21}H_{23}O_2S^+$ calcd. 339.1413, found: m/z 339.1415.

Mixture of (((E)-2-(((1E,4E)-2,4-dimethyl-1-phenylhexa-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene and (((E)-2-(((1E,4Z)-2,4-dimethyl-1-phenylhexa-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene (3b):

The same procedure used for the synthesis of **3a** was applied to make **3b** from **1b** (648.8 mg, 3.21 mmol, 1.00 equiv.), 4-methylmorpholine (0.53 mL, 486.6 mg, 4.81 mmol, 1.50 equiv.), and **2** (964.3 mg, 6.42 mmol, 2.00 equiv.) in CH_2Cl_2 (32 mL). Purification by flash column chromatography (hexane:EtOAc, 4:1) afforded an inseparable mixture of syn/anti diastereomers of **3b** (789.6 mg, 69.9%, (1E, 4E):(1E, 4Z)=1:4 ratio, syn:anti=1:1 ratio) as a brown oil. R_f 0.11 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.63 – 7.58 (m, 20H), 7.52 – 7.41 (m, 40H), 7.36 – 7.27 (m, 28H), 7.24 – 7.17 (m, 22H), 6.58 (s, 5H), 6.54 (s, 5H), 5.86 (d, J = 12.6, 0.93 Hz, 2H), 5.84 (d, J = 12.6, 0.93 Hz, 8H), 5.63(m, 10H), 5.25 (s, 4H), 5.24 (s, 4H), 4.69 (s, 1H), 4.68 (s, 1H), 1.80 – 1.72 (m, 50H), 1.70 – 1.62 (m, 30H), 1.60 – 1.55 (m, 10H); ^{13}C NMR (600 MHz, Chloroform-d) δ 156.54, 156.49, 156.46, 156.39, 149.00, 145.56, 145.53, 145.51, 137.16, 137.08 (2), 136.98, 134.21, 133.88, 133.74, 133.50, 133.27 (2),

132.22, 132.05, 131.96, 131.88, 131.73, 131.38 (2), 130.42, 130.40, 130.38, 130.36, 129.93, 129.53, 129.19, 129.17, 129.09, 129.05, 128.30, 128.28, 128.26, 127.96, 127.72, 127.55, 126.94, 126.84, 126.55, 126.43, 126.19, 126.12, 125.16, 124.79, 124.49, 124.47, 113.95, 113.83(2), 113.76, 91.92, 91.40, 83.39, 83.04, 17.98, 17.89, 15.06, 14.97, 14.58, 14.40, 13.75, 13.72, 13.49, 13.44, 11.96, 11.74; HRMS $[M+H]^+$ for $C_{22}H_{25}O_2S^+$ calcd. 353.15698, found: m/z 353.15735.

((1E,4E)-2,4-dimethyl-3-(((E)-2-(phenylsulfinyl)vinyl)oxy)penta-1,4-diene-1,5-diyl)dibenzene (3c):

The same procedure used for the synthesis of **3a** was applied to make **3c** from **1c** (665.3 mg, 2.52 mmol, 1.00 equiv.), 4-methylmorpholine (0.42 mL, 381.8 mg, 3.77 mmol, 1.50 equiv.), and **2** (755.5 mg, 5.03 mmol, 2.00 equiv.) in CH_2Cl_2 (25 mL). Purification by flash column chromatography (hexane:EtOAc:Et_3N, 77:20:3) afforded an inseparable mixture of syn/anti diastereomers of **3c** (590.7 mg, 56.5%, 1:1 ratio) as a brown oil. R_f 0.10 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.62 – 7.59 (m, 2H), 7.46 – 7.43 (m, 3H), 7.38 – 7.27 (m, 9H), 7.24 – 7.21 (m, 2H), 6.67 (s, 1H), 6.63 (s, 1H), 5.93 (d, J = 12.6 Hz, 1H), 5.30 (s, 1H), 4.86 (s, 1H), 1.85 (d, J = 1.4 Hz, 3H), 1.82 (d, J = 1.3 Hz, 3H); ^{13}C NMR (600 MHz, Chloroform-d) δ 156.15, 136.88, 136.78, 133.66, 133.55, 130.47, 129.25, 129.20, 129.18, 129.12, 128.98, 128.41, 128.38, 127.19, 124.55, 114.46, 91.69, 14.32, 14.13; HRMS $[M+H]^+$ for $C_{27}H_{27}O_2S^+$ calcd. 415.1726, found: m/z 415.1731.

Synthesis of Trienal, Cyclohexadiene, and Arene

(2E,4E,6E)-4,6-dimethyl-7-phenylhepta-2,4,6-trienal (4a):

To a solution of (((E)-2-(((E)-2,4-dimethyl-1-phenylpenta-1,4- dien-3-yl)oxy)vinyl)sulfinyl)benzene **3a** (483.0 mg, 1.43 mmol, 1.00 equiv.) in DCE (8 mL) was added sodium carbonate (60.1 mg, 0.57 mmol, 0.40 equiv.). The resulting mixture was heated at reflux (85 °C) for 48 hours. The reaction mixture was cooled to room temperature and filtered through a filter paper to remove the remaining base. The filtrate was then concentrated under reduced pressure. Purification by flash column chromatography (hexane:MTBE, 24:1) gave **4a** (183 mg, 60.4%) as a yellow oil: R_f 0.53 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 9.62 (d, J = 7.8 Hz, 1H), 7.42 – 7.27 (m, 5H), 7.21 (d, J = 15.3 Hz, 1H), 6.64 (s, 1H), 6.54 (s, 1H), 6.22 (dd, J = 15.5, 7.8 Hz, 1H), 2.14 (d, J = 1.4 Hz, 3H), 2.10 (d, J = 1.4 Hz, 3H); ^{13}C NMR (600 MHz, Methylene Chloride-d2) δ 194.01, 158.75, 146.02, 137.55, 135.26, 135.08, 133.71, 129.68, 128.64, 128.17, 127.59, 18.79, 14.41; HRMS $[M+H]^+$ for $C_{15}H_{17}O^+$ calcd. 213.1274, found: m/z 213.1269.

(2E,4E,6Z)-4,6-dimethyl-7-phenylhepta-2,4,6-trienal (4a'):

Purification by flash column chromatography (hexane:MTBE, 24:1) gave minor isomer **4a'** (36.1 mg, 12.0%) as a yellow oil: R_f 0.57 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 9.59 (d, J = 7.7 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.26 – 7.20 (m, 3H), 7.18 (d, J = 15.5 Hz, 1H), 6.66 (s, 1H), 6.56 (s, 1H), 6.15 (dd, J = 15.5, 7.8 Hz, 1H), 2.12 (d, J = 1.2 Hz, 3H), 1.79 (d, J = 1.2 Hz, 3H); ^{13}C NMR (600 MHz, Chloroform-d) δ 194.11, 157.85, 141.46, 137.58, 134.73, 133.89, 132.70, 129.01, 128.42, 127.95, 127.23, 24.62, 14.34; HRMS $[M+H]^+$ for $C_{15}H_{17}O^+$ calcd. 213.1274, found: m/z 213.1268.

(2E,4E,6E)-3,4,6-trimethyl-7-phenylhepta-2,4,6-trienal (4b):

The same procedure used for the synthesis of **4a** was applied to make **4b** from **3b** (96.9 mg, 0.27 mmol, 1.00 equiv.) and sodium carbonate (11.7 mg, 0.11 mmol, 0.40 equiv.) in DCE (13 mL). Purification by flash column chromatography (hexane:MTBE, 24:1) gave **4b** (29.0 mg, 44.2%) as a yellow oil: R_f 0.49 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.19 (d, J = 7.8 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.28 – 7.24 (m, 1H), 6.64 (s, 1H), 6.50 (s, 1H), 6.19 (dq, J = 7.9, 1.2 Hz, 1H), 2.39 (d, J = 1.2 Hz, 3H), 2.09 (d, J = 1.2 Hz, 3H), 2.08 (d, J = 1.2 Hz, 3H); ^{13}C NMR (400 MHz, Chloroform-d) δ 192.18, 158.51, 137.72, 137.40, 136.14, 134.97, 132.60, 129.28, 128.38, 127.10, 126.76, 19.14, 15.91, 14.66; HRMS $[M+H]^+$ for $C_{16}H_{19}O^+$ calcd. 227.14304, found: m/z 227.14258.

(2E,4E,6Z)- 3,4,6-trimethyl-7-phenylhepta-2,4,6-trienal (4b'):

Purification by flash column chromatography (hexane:MTBE, 24:1) gave minor isomer **4b'** (8.6 mg, 16.3%) as a yellow oil: R_f 0.52 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 10.17 (d, J = 7.9 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.28 – 7.24 (m, 1H), 6.73 (s, 1H), 6.48 (s, 1H), 6.10 (dq, J = 7.9zz, 1.2 Hz, 1H), 2.35 (d, J = 1.2 Hz, 3H), 2.05 (d, J = 1.2 Hz, 3H), 1.74 (d, J = 1.2 Hz, 3H); HRMS $[M+H]^+$ for $C_{16}H_{19}O^+$ calcd. 227.14304, found: m/z 227.14258.

3,4,6-trimethyl-1,2-dihydro-[1,1'-biphenyl]-2-carbaldehyde (5b):

Purification by flash column chromatography (hexane:MTBE, 49:1) gave mixture of **5b** (11.5 mg, 18.5%) and **6b** (1.4 mg, 2.3%) as a colorless oil: For **5b**, R_f 0.72 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 9.52 (dd, J = 1.6, 0.8 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.21 (m, 2H), 7.17 – 7.15 (m, 1H), 5.72 (d, 1.7 Hz, 1H), 3.58 (s, 1H), 2.82 (s, 1H), 1.84 (d, 0.8 Hz, 3H),

1.77 (s, 3H), 1.70 (s, 3H); HRMS $[M+H]^+$ for $C_{16}H_{19}O^+$ calcd. 227.14304, found: m/z 227.14625.

* Yields of each product were calculated by the integration ratio on NMR spectra

(2Z,4E,6E)-4,6-dimethyl-3,7-diphenylhepta-2,4,6-trienal (4c), (2Z,4E,6Z)-4,6-dimethyl-3,7-diphenylhepta-2,4,6-trienal (4c'):

The same procedure used for the synthesis of **4a** was applied to make **4c** from **3c** (30.4 mg, 0.07 mmol, 1.00 equiv.) and sodium carbonate (3.1 mg, 0.03 mmol, 0.40 equiv.) in DCE (3.5 mL). Purification by flash column chromatography (hexane:MTBE, 24:1) gave mixture of **4c** (3.0 mg, 14.0%) and **4c'** (1.1 mg, 5.4%) as a yellow oil: For **4c**, R_f 0.59 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 9.32 (d, J = 8.0 Hz, 1H), 7.45 – 7.27 (m, 10H), 6.43 (s, 1H), 6.30 (d, J = 8.0 Hz, 1H), 6.13 (s, 1H), 2.20 (d, J = 1.1 Hz, 3H), 1.99 (s, 3H); For **4c',** R_f 0.59 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 9.30 (d, J = 8.0 Hz, 1H), 7.45 – 7.27 (m, 10H), 6.41 (s, 1H), 6.21 (d, J = 8.0 Hz, 1H), 6.21 (s, 1H), 1.99 (s, 3H), 1.84 (d, J = 1.1 Hz, 3H); HRMS $[M+H]^+$ for $C_{21}H_{21}O^+$ calcd. 289.15869, found: m/z 289.15839.

* Yields of each isomer were calculated by the integration ratio on NMR spectra

4',6'-dimethyl-1',2'-dihydro-[1,1':3',1''-terphenyl]-2'-carbaldehyde (5c):

Purification by flash column chromatography (hexane:MTBE, 49:1) gave **5c** (12.8 mg, 60.5%) as a colorless oil: R_f 0.72 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 9.58 (d, J = 0.9 Hz, 1H), 7.35 – 7.26 (m, 5H), 7.25 – 7.16 (m, 3H), 7.00 – 6.95 (m, 2H), 5.92 (q, 1.6 Hz, 1H), 3.78 (d, 1.3 Hz, 1H), 3.32 (q, 1.2 Hz, 1H), 1.90 (s, 3H), 1.81 (d, 1.6 Hz, 3H); ^{13}C NMR (600 MHz,

Chloroform-d) δ 190.43, 140.96, 140.25, 137.63, 131.93, 128.91, 128.85, 128.35, 127.85, 127.18, 126.88, 125.70, 122.49, 61.77, 44.66, 21.99, 19.14; HRMS $[M+H]^+$ for $C_{21}H_{21}O^+$ calcd. 289.15869, found: m/z 289.15866.

Synthesis of Arene

4,6-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (6a):

To a solution of (((E)-2-(((E)-2,4-dimethyl-1-phenylpenta-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene **3a** (2.41 g, 7.12 mmol, 1.00 equiv.) in toluene (120 mL) was added 1,8-diazabicyclo(5.4.0)undec-7-ene (1.27 mL, 1.30 g, 8.54 mmol, 1.20 equiv.). The resulting mixture was heated at reflux for 48 hours. After cooling to room temperature, the reaction was quenched with saturated NH_4Cl solution (50 mL). After phase separation, aqueous phase was rinsed with MTBE (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (hexane:MTBE, 49:1) gave **6a** (1.35 g, 90.2%) as a colorless oil: R_f 0.68 (hexane:EtOAc, 4:1); ^{1}H NMR (600 MHz, Chloroform-d) δ 9.67 (s, 1H), 7.67 (s, 1H), 7.47 – 7.39 (m, 3H), 7.35 – 7.32 (m, 1H), 7.24 – 7.20 (m, 2H), 2.42 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (600 MHz, Chloroform-d) δ 193.14, 143.05, 137.58, 137.27, 136.93, 136.48, 134.45, 130.24, 128.45, 127.80, 125.00, 21.13, 20.06; HRMS $[M+H]^+$ for $C_{15}H_{15}O^+$ calcd. 211.1117, found: m/z 211.1118.

3,4,6-trimethyl-[1,1'-biphenyl]-2-carbaldehyde (6b)

The same procedure used for the synthesis of **6a** was applied to make **6b** from **3b** (91.4 mg, 0.26 mmol, 1.00 equiv.) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.05 mL, 47.4 mg, 0.31 mmol, 1.20 equiv.) in toluene (13 mL). Purification by

flash column chromatography (hexane:MTBE, 49:1) gave **6b** (40.0 mg, 68.8%) as a pale yellow oil: R_f 0.79 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d) δ 9.78 (s, 1H), 7.46 – 7.15 (m, 6H), 2.49 (s, 3H), 2.35 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (600 MHz, Chloroform-d) δ 195.99, 143.87, 138.25, 137.28, 135.84, 135.17, 134.04, 133.88, 130.10, 128.49, 127.58, 20.36, 19.79, 15.94; HRMS $[M+H]^+$ for $C_{16}H_{17}O^+$ calcd. 225.12735, found: m/z 225.12727.

4',6'-dimethyl-[1,1':3',1''-terphenyl]-2'-carbaldehyde (6c)

The same procedure used for the synthesis of **6a** was applied to make **6c** from **3c** (74.7 mg, 0.18 mmol, 1.00 equiv.) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.03 mL, 32.9 mg, 0.22 mmol, 1.20 equiv.) in toluene (9 mL). Purification by flash column chromatography (hexane:MTBE, 49:1) gave **6c** (46.2 mg, 89.5%) as a white solid: R_f 0.28 (hexane:EtOAc, 24:1); mp 150.3-153.1 °C; ^{1}H NMR (400 MHz, Chloroform-d) δ 9.66 (s, 1H), 7.45 – 7.35 (m, 7H), 7.22 – 7.17 (m, 4H), 2.11 (s, 6H); 13C NMR (600 MHz, Chloroform-d) δ 194.12z, 141.01, 138.87, 136.48, 135.63, 134.14, 129.56, 128.38, 127.30, 20.19; HRMS $[M+H]^+$ for $C_{21}H_{19}O^+$ calcd. 287.1430, found: m/z 287.1428.

Preparation of 4-Ethoxy-2,2,5,8,8-pentamethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene

Ethyl 2-methyl-3-((trimethylsilyl)oxy)but-2-enoate (20):

Under argon, to a solution of ethyl 2-methylacetoacetate (3.60 mL, 3.60 g, 24.97 mmol, 1.00 equiv.) and triethylamine (4.52 mL, 3.28 g, 32.46 mmol, 1.30 equiv.) in hexane (40 mL) was added trimethylsilyl chloride (3.80 mL, 3.26 g, 29.96 mmol, 1.20 equiv.) dropwise at room temperature. The resulting solution was stirred for 24 hours. The resulting colorless precipitate was filtrated and

washed with dry hexane. The combined liquid phases were concentrated under reduced pressure to give **20** as a colorless oil. The crude product **20** was used for the next step without further purification.

4-Ethoxy-2,2,5,8,8-pentamethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene (7):

Under argon, to a solution of diisopropylamine (4.20 mL, 3.03 g, 29.96 mmol, 1.20 equiv.) in THF (75 mL) was added a solution of n-butyllithium (2.5 M in hexane, 29.96 mmol, 12.00 mL, 1.20 equiv.) dropwise at 0 °C. After stirring for 30 minutes, the reaction mixture was cooled to –78 °C and crude **20** was added dropwise. After stirring for 30 minutes, trimethylsilyl chloride (4.12 mL, 3.53 g, 32.46 mmol, 1.30 eq) was added dropwise and the resulting mixture was stirred for 1 hour. The reaction mixture was warmed to 0 °C. After stirring for 15 hours, the volatile compounds of reaction mixture were evaporated under reduced pressure at 25 °C. The resulting precipitated colorless precipitate was filtrated and washed with hexane. The combined liquid phases were concentrated under reduced pressure at 25 °C to give **7** (4.12 g, 57.2% over two steps) as a colorless oil. The spectral data are consistent with the reported one (Burkhardt & Dickschat, 2018).

Synthesis of Nigerapyrone B

ethyl 5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopentanoate (8) - method 1:

Under argon, to a solution of starting aldehyde **6a** (732.8 mg, 3.48 mmol, 1.00 equiv.) in CH_2Cl_2 (50 mL) was added titanium chloride (1 M in CH_2Cl_2, 3.48 mL, 3.48 mmol, 1.00 equiv.) dropwise at -78 °C. After 10 minutes, 4-ethoxy-

2,2,5,8,8-pentamethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene **7** (2.01 g, 6.97 mmol, 2.00 equiv.) was added dropwise and the resulting mixture was stirred at -78 °C for 3 hours. The reaction mixture was warmed to 0 °C and stirred for 15 hours. After warming to room temperature, the reaction was quenched with water (50 mL). After phase separation, aqueous phase was rinsed with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc, 4:1) afforded an inseparable mixture of syn/anti diastereomers of **8** (trace amounts, 1:3 ratio) as a yellow oil. R_f 0.31 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d): δ 7.44 – 7.32 (m, 3H), 7.31 – 7.28 (m, 1H), 7.21 – 7.17 (m, 1H), 7.08 – 7.02 (m, 2H), 4.92 (m, 1H), 4.13 (m, 2H), 3.34 (m, 3H), 2.74 (m, 2H), 2.38 (s, 3H), 1.97 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.22 (d, J = 7.2 Hz, 3H); ^{13}C NMR (600 MHz, Chloroform-d): δ 206.49, 206.43, 170.12, 170.10, 140.36, 140.32, 139.52, 139.48, 137.59, 137.58, 136.96, 136.93, 136.41, 136.37, 130.09, 130.07, 129.64 (2), 129.40, 129.37, 129.02, 128.97, 128.51, 128.48, 127.24, 123.62, 67.02, 66.88, 61.59, 61.57, 53.40, 53.29, 49.34, 49.27, 21.42, 20.84, 14.20, 12.62; HRMS $[M-H_2O+H]^+$ for $C_{22}H_{25}O_3^+$ calcd. 337.17982, found: m/z 337.17904.

ethyl (Z)-5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-3,5-dihydroxy-2-methylpent-2-enoate (12):

Purification by flash column chromatography on silica gel (hexane:EtOAc, 4:1) gave unwanted **12** (489.1 mg, 1.38 mmol, 39.6%) as a yellow oil. R_f 0.26 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d): δ 7.43 – 7.35 (m, 3H), 7.29 – 7.27 (m, 1H), 7.16 – 7.11 (m, 2H), 7.08 – 7.04 (m, 1H), 5.14 (dd, J

= 14.4, 3.4 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.76 (dd, *J* = 16.9, 14.4 Hz, 1H), 2.42 (s, 3H), 2.38 (dd, *J* = 16.9, 3.4 Hz, 1H), 1.99 (s, 3H), 1.61 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H)

5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopentanoic acid (13):

Purification by flash column chromatography on silica gel (hexane:EtOAc, 4:1) gave unwanted **13** (217.2 mg, 0.66 mmol, 19.1%) as a white solid. R_f 0.12 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d): δ 7.46 – 7.37 (m, 3H), 7.30 – 7.28 (m, 1H), 7.23 – 7.19 (m, 1H), 7.13 – 7.10 (m, 1H), 7.08 – 7.05 (m, 1H), 5.44 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.38 (q, *J* = 6.6 Hz, 2H), 2.68 (m, 2H), 2.39 (s, 3H), 1.99 (s, 3H), 1.30 (t, *J* = 6.6 Hz, 3H)

ethyl (E)-5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-2-methyl-3-oxopent-4-enoate (16):

Under argon, to a stirred suspension of $NaHCO_3$ (287.0 mg, 34.2 mmol, 10.00 equiv.) and **12** (121.1 mg, 0.34 mmol, 1.00 equiv.) in CH_2Cl_2 (11 mL) was added Dess-Martin periodinane (434.7 mg, 1.02 mmol, 3.00 equiv.) at room temperature. After stirring for 18 hours, the reaction mixture was quenched with saturated $Na_2S_2O_3$ aqueous solution (10 mL). After phase separation, aqueous phase was rinsed with CH_2Cl_2 (10 mL × 3). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc, 4:1) afforded unwanted **16** (15.1 mg, 0.04 mmol, 13.2%) as a yellow oil. R_f 0.55 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d): δ 7.45 – 7.37 (m, 5H), 7.34 (d, *J* = 16.0 Hz, 1H), 7.17 – 7.15 (m, 1H), 7.13 –

7.11 (m, 1H), 6.64 (d, J = 16.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.61 (q, J = 7.2 Hz, 1H), 2.39 (s, 3H), 2.06 (s, 3H), 1.29 (d, J = 7.2 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); HRMS $[M+H]^+$ for $C_{22}H_{25}O_3^+$ calcd. 337.17982, found: m/z 337.18049.

ethyl 5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopentanoate (8) - method 2:

Under argon, to a solution of diisopropylamine (1.23 mL, 891.6 g, 8.81 mmol, 12.00 equiv.) in THF (32 mL) was added a solution of n-butyllithium (1.6 M in hexane, 8.81 mmol, 5.51 mL, 12.00 equiv.) dropwise at -78 °C. After stirring for 10 minutes, ethyl 2-methylacetoacetate (0.42 mL, 423.4 mg, 2.94 mmol, 4.00 equiv.) was added dropwise and the resulting solution was warmed to 0 °C. After stirring for 2 hours, the solution of arene **6a** (154.4 mg, 0.73 mmol, 1.00 equiv.) in THF (4 mL) was added to the reaction mixture at -78 °C. The reaction mixture was stirred for 18 hours and then quenched with saturated NH_4Cl aqueous solution (30 mL). After separation of the phases, the aqueous layer was rinsed with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc, 4:1) afforded an inseparable mixture of syn/anti diastereomers of **8** (213.5 mg, 0.60 mmol, 82.0%, 1:3 ratio) as a yellow oil.

ethyl (Z)-5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopent-4-enoate (9):

Under argon, to a stirred suspension of $NaHCO_3$ (171.6 mg, 2.04 mmol, 10.00 equiv.) and **8** (72.4 mg, 0.20 mmol, 1.00 equiv.) in CH_2Cl_2 (20 mL) was added

Dess-Martin periodinane (346.5 mg, 0.82 mmol, 4.00 equiv.) at room temperature. After stirring for 18 hours, the reaction mixture was quenched with saturated $Na_2S_2O_3$ aqueous solution (20 mL). After phase separation, aqueous phase was rinsed with CH_2Cl_2 (15 mL × 3). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc, 4:1) afforded **9** (51.7 mg, 71.8%) as a yellow oil: R_f 0.56 (hexane:EtOAc, 4:1); ^{1}H NMR (400 MHz, Chloroform-d): δ 7.38 – 7.31 (m, 4H), 7.22 – 7.19 (m, 1H), 7.19 – 7.15 (m, 2H), 5.24 (s, 1H), 4.10 (qd, J = 7.2, 2.2 Hz, 2H), 3.12 (q, J = 7.2 Hz, 1H), 2.39 (s, 3H), 2.11 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, Chloroform-d): δ 192.14, 186.68, 170.77, 139.70, 137.65, 137.25, 137.03, 135.96, 133.68, 129.76, 128.37, 127.27, 126.86, 101.14, 61.33, 49.51, 21.09, 20.82, 14.19, 14.12; HRMS $[M+H]^+$ for $C_{22}H_{25}O_4^+$ calcd. 353.17474, found: m/z 353.17495.

6-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-4-hydroxy-3-methyl-2H-pyran-2-one (10):

Under argon, to a solution of **9** (51.7 mg, 0.15 mmol, 1.00 equiv.) in benzene (15 mL), 1,8-diazabicyclo(5.4.0)undec-7-ene (0.11 mL, 111.6 mg, 0.73 mmol, 5.00 equiv.) was added. The resulting mixture was heated at reflux (85 °C) for 18 hours. The reaction mixture was cooled to room temperature and then quenched with 1 M HCl solution (10 mL). After phase separation, aqueous phase was rinsed with EtOAc (10 mL × 3). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc, 5:5) afforded **10** (38.2 mg, 85.1%) as a white solid: R_f 0.35

(hexane:EtOAc, 5:5); ^{1}H NMR (400 MHz, Acetone-d_6): δ 7.40 – 7.35 (m, 2H), 7.33 – 7.28 (m, 2H), 7.26 – 7.23 (m, 1H), 7.17 – 7.13 (m, 2H), 5.75 (s, 1H), 2.90 (s, 3H), 2.39 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (600 MHz, Acetone-d_6): δ 165.30, 164.28, 159.77, 140.31, 138.61, 137.93, 137.67, 133.42, 133.22, 130.38, 129.13, 127.91, 127.82, 103.45, 99.06, 20.94, 20.87, 8.59; HRMS $[M+H]^+$ for $C_{20}H_{19}O_3^+$ calcd. 307.13287, found: m/z 307.13283.

Nigerapyrone B (11):

To a solution of **10** (38.2 mg, 0.12 mmol, 1.00 equiv.) in acetone (12 mL), potassium carbonate (86.2 mg, 0.62 mmol, 5.00 equiv.) was added at room temperature. After 10 min, dimethyl sulfate (0.06 mL, 78.6 mg, 0.62 mmol, 5.00 equiv.) was added and the resulting mixture was heated at reflux (70 °C) for 2 hours. The reaction mixture was cooled to room temperature and then quenched with saturated NH_4Cl aqueous solution (10 mL). After phase separation, aqueous phase was rinsed with EtOAc (10 mL × 3). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc, 5:5) afforded Nigerapyrone B (**11**) (36.5 mg, 91.4%) as a yellow solid: R_f 0.79 (hexane:EtOAc, 5:5); ^{1}H NMR (600 MHz, Acetone-d_6): δ 7.46 – 7.42 (m, 2H), 7.41 (br, 1H), 7.38 – 7.34 (m, 1H), 7.28 (br, 1H), 7.23 – 7.21 (m, 1H), 7.21 – 7.20 (m, 1H), 5.88 (s, 1H), 3.51 (s, 3H), 2.41 (s, 3H), 2.08 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (600 MHz, Acetone-d_6): δ 165.92, 164.80, 160.08, 140.75, 138.61, 138.10, 137.79, 133.44, 133.04, 130.53, 129.45, 128.10, 127.66, 101.08, 99.14, 56.64, 20.97, 20.93, 8.63; HRMS $[M+H]^+$ for $C_{21}H_{21}O_3^+$ calcd. 321.14852, found: m/z 321.14848.

Results and Discussion

Preparation of Divinylcarbinoxy Vinyl Sulfoxide (Fig. 5)

The first thing to do for synthesizing divinylcarbinoxy vinyl sulfoxide **3** was to prepare three types of divinylcarbinol **1** (Fig. 3C). Divinylcarbinols **1a** and **1b** were prepared by adding vinyl Grignard reagent to α-methyl-*trans*-cinnamaldehyde (Fig. 3A). Divinylcarbinol **1c** was resulted in through condensation and reduction of 3-pentanone and benzaldehyde (Fig. 3B). To prepare Grignard reagent for divinylcarbinol **1b**, a mixture of cis and trans of 2-bromo-2-butene was used. As a result, (1E, 4E) and (1E, 4Z)-2,4-dimethyl-1-phenyl-1,4-hexadien-3-ols of **1b** were synthesized as an inseparable mixture in a ratio of 1:4.

Another fragment, (ethynylsulfinyl)benzene **2**, was prepared in three steps from (trimethylsilyl)acetylene and diphenyl disulfide as starting materials (Fig. 4). In the second and third steps, the reaction proceeded with crude trimethyl((phenylthio)ethynyl)silane **18** and ethynyl(phenyl)sulfane **19**, respectively, and only the last step was purified.

The desired divinylcarbinoxy vinyl sulfoxide **3** was synthesized by reacting divinylcarbinol **1** with (ethynylsulfinyl)benzene **2** in the presence of 4-methylmorpholine (Fig. 5). However, it was observed that divinylcarbinol **1** did not completely disappear on TLC, even though 1.50 equiv. (ethynylsulfinyl)benzene **2** was added. Reported by (Petit et al., 2014; Ramachandran et al., 2005), self-condensation can occur when a substance with an acetylene moiety participates in a base-catalyzed reaction. Therefore, the reaction proceeded at a low temperature of 0 ℃, which is more likely to avoid dimerization. In addition, at least 2.00 equiv. (ethynylsulfinyl)benzene **2** had to

be added in preparation for dimerization.

Synthesis of Trienal (Fig. 6)

The trienal **4** synthesis was carried out under the optimized reaction condition in the previous study (Fig. 2). In case of divinylcarbinoxy vinyl sulfoxide **3a**, the desired trienal **4a** was obtained with good yield when heated at reflux using 0.40 equiv. Na_2CO_3 as a base in DCE. A separable minor isomer of trienal **4a'** was also formed. Divinylcarbinoxy vinyl sulfoxides **3b** and **3c** were also reacted under the same condition. Similarly, major isomers **4b**, **4c** and minor isomers **4b'**, **4c'** could be obtained, but they were not separated yet. Therefore, the yields of each isomer were calculated by the integration ratio on NMR spectra (Fig. S18, S20 and S21).

Divinylcarbinoxy vinyl sulfoxide **3b** produced only one type of regioisomer **4b** and **4b'**. This was reasoned by the vinylic proton peaks in the ^{1}H NMR spectrum and their predicted coupling constant values (Fig. S16, S18, and Fig. 7). If trienal **4b''** exists, the H_A peak should exhibit a quartet corresponding to ^3J 4~10 Hz. However, a quartet with a coupling constant in this range was not found. Instead, a singlet was observed at 6.64 ppm, which corresponds to the H_A of trienal **4b**. In addition, we could discover ^4J 1.2 Hz in the H_B peak, which corresponds to trienal **4b**. Reported by (Ziegler, 1988), Claisen rearrangement of olefin with larger substituents is inhibited by the steric effect. When there are two types of olefins that can participate in Claisen rearrangement, the olefin with the smaller substituents is preferred for the reaction. In other words, the size of the substituents attached to the olefin determines the regioselectivity, which explains why only trienal **4b** was synthesized instead of **4b''**.

Interestingly, in both cases **3b** and **3c**, we were able to discover new

substances with an aldehyde moiety. We assigned them as cyclohexadiene intermediates **5** in the trienal to arene reaction (Fig. 8). Trace amounts of arenes **6b**, **6c** were also obtained as well as trienals **4b**, **4c** and cyclohexadienes **5b**, **5c**. When looking at the trienal **4** formed through Claisen rearrangement and sulfoxide elimination, the substituent R^4 is very adjacent to the carbonyl group. It is reasoned that the bulky substituent R^4 promoted isomerization to reduce steric hindrance between the R^4 group and the carbonyl group. The isomerized trienal **4** could readily undergo 6π electrocyclization, so unexpected cyclohexadiene **5** and arene **6** were obtained together. These results were observed more prominently in divinylcarbinoxy vinyl sulfoxide **3c** with a bulkier phenyl group in the substituent R^4. In addition, after 6π electrocyclization, not all cyclohexadienes **5** underwent auto-oxidation even though arenes **6** are more stable substances. Benzene is a two-dimensional aromatic molecule and all atoms in the benzene ring are in the same plane (Feixas et al., 2007). Benzene derivatives with bulky groups in the ortho positions tend to exhibit significant distortion of the ring and this distortion causes the loss of aromaticity of the benzene ring (Endo et al., 2005; Feixas et al., 2008). In the case of cyclohexadiene **5**, in which the two substituent pairs are ortho-positioned to the carbonyl group, it is considered that the temperature was not high enough for dehydrogenation to give arene **6** with a distorted benzene ring.

Synthesis of Arene (Fig. 9)

In a previous study, we observed that arene **6** was formed as a by-product during trienal **4** synthesis from divinylcarbinoxy vinyl sulfoxide **3**. There are studies that 6π electrocyclization cause ring closure from a conjugated trienal, and an

oxidant such as DDQ should be added or the leaving group should be removed to give a benzene ring for subsequent oxidation (Dell'Erba et al., 2001; Daniels et al., 2009). It is known that flavin coenzyme acts as a hydride donor or acceptor and forms α, β-unsaturated carbonyl groups by E1cB elimination of H_2 (Soderberg, 2012). Inspired by dehydrogenases, we reasoned that DBU was responsible for a similar effect (Ikeda et al., 1997; Mies et al., 2020). The aldehyde, an electron withdrawing group in cyclohexadiene **5**, will facilitate this E1cB dehydrogenation.

As a result of analyzing previous studies and experimental results, we proposed that arene **6** was synthesized through cascade reactions of isomerization, 6π electrocyclization, and auto-oxidation from trienal **4** formed through Claisen rearrangement and sulfoxide elimination of divinylcarbinoxy vinyl sulfoxide **3**. We were able to produce the desired arene **6** with high yield by performing arene synthesis under the condition optimized in the previous study (Fig 2).

Synthesis of Nigerapyrone B

We applied this base-mediated cascade benzannulation to the synthesis of natural products. As the target material, Nigerapyrone B **11** including the structure in which two benzene rings are directly connected was selected (Fig. 10). Following the research on Nictriapyrone synthesis (Burkhardt and Dickschat, 2018), we reasoned that Nigerapyrone B **11** could be synthesized using arene **6a** as a starting material.

We tried to synthesize another starting material 4-ethoxy-2,2,5,8,8-pentamethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene **7**, which leads to bonding with arene **6a** and assembling the pyrone ring (Fig 11). Following

(Burkhardt and Dickschat, 2018), we could synthesize **7** through two steps.

The next step was to make ethyl 5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopentanoate **8** by adding the two synthesized fragments, **6a** and **7**. However, this addition reaction yielded a trace amount of the desired **8**, and accompanied the unwanted products **12** in 40% and **13** in 19% (Fig. 12). The hydrolyzed product **13** was reasoned to be generated by addition of water during quenching after the reaction was completed. Reported by (Pérez and Toro-Labbé, 2000; Monajjemi et al., 2010), keto tautomers are generally thermodynamically more stable than enol counterparts by approximately 20 kcal/mol, so keto tautomers predominantly present in most substances. However, if an extra intramolecular stabilization exists, enol tautomers are more favored (Raczyńska et al., 2005; Ferrari et al., 2011). Therefore, the β-keto enol form **12**, which can stabilize molecules by forming a strong intramolecular H-bond, is more stable product and formed more than the β-diketo form **8**.

Since this keto form **8** should be converted to the enol form when the pyrone ring is formed (Fig. 15), we just proceeded with the oxidation of **12** using DMP (Fig 13). However, the desired oxidized product **14** was not formed and only the unwanted dehydrated product **16** was observed. In the case of DMP oxidation, two molecules of acetic acid are formed during the reaction (Dess and Martin, 1983). Therefore, acid-sensitive substances should be buffered with pyridine or sodium bicarbonate before adding DMP (Oguma et al., 2018; Davison et al., 2021; Meyer and Schreiber, 1994). However, even if more than 10.00 equiv. sodium bicarbonate was added, dehydration could not be prevented. We reasoned that this dehydrated product **16** can build a very stable conjugated system (Hissler et al., 2003). This was the same when using pyridine

as a base. Swern oxidation and manganese dioxide oxidation were also tried, but the oxidized product **14** was not observed.

We thought that dehydration could be prevented by changing the reaction order, so we determined to carry out oxidation after cyclization (Fig. 14). Cyclization of the β-keto enol tautomer **12** was attempted using KOH as a base referring to (Iqbal et al., 2018). However, the cyclization product dihydropyrone **17** was not observed. Instead, we could discover the formation of the β-diketo tautomer **8**. Reported by (Novak et al., 2000; Jiménez-Cruz et al., 2015; Yamabe et al., 2004), the keto-enol equilibrium varies depending on the substituent, temperature, and solvent effect. This equilibrium is shifted to the more polar diketo tautomer as the solvent polarity increases and the reaction temperature rises. The aqueous KOH solution was used for cyclization, and it seems that the polar H_2O solvent shifted the equilibrium to the diketo form. Rather, (Ferrari et al., 2011) said that the tautomeric equilibrium shifts to the keto enol form when the pH increases due to the base. In this cyclization reaction, only the keto enol form existed, so it seems that the diketo form was slightly formed due to the equilibrium in spite of adding the base. In fact, it could be observed that only a small amount of the keto enol tautomer was converted to the diketo tautomer. Since the β-diketo tautomer **8** with ester moiety can be hydrolyzed when water is added in the presence of $TiCl_4$, it is necessary to control the equilibrium between the diketo form **8** and the keto enol form **12** using an appropriate polar solvent (Fig. 12).

Since the amount of the desired product **8** was different depending on the reaction conditions, and it was difficult to make **8** with high yield with the TMS group attached **7**, we tried to make the β-diketo tautomer **8** using another method. Ethyl 2-methylacetoacetate was treated with lithium diisopropylamide

to make a dianion, and arene **6a** was added. The desired product **8** was obtained with a yield of 82.0% with a very small amount of side product, and with this, the next oxidation step was carried out.

With this β-diketo form **8**, we went back to the previously planned method and proceeded with oxidation (Fig. 16). As a result, the desired oxidized product **9** could be obtained. After that, pyrone **10** was formed through DBU-mediated ketoester lactonization, which was then finally synthesized Nigerapyrone B (**11**) through O-methylation.

Conclusion

We developed a novel method for arene synthesis in two steps through cascade reaction of Claisen rearrangement, sulfoxide elimination, isomerization, 6π electrocyclization, and auto-oxidation. The substrate scope could be extended to substrates with four substituents. Through the separation of cyclohexadiene during trienal synthesis, it was found that sufficient heat and base were required to synthesize arene by dehydrogenation. We employed arene **6a** to natural product synthesis and could obtain Nigerapyrone B (**11**) through four steps. It is the first total synthesis of Nigerapyrone B which was completed by applying our novel method for arene synthesis.

Future Direction

In many cases of auto-oxidation, the reaction takes place when a metal catalyst is used. However, in cyclehexadiene **5** with a cyclohexa-2,4-diene-1-carbaldehyde moiety, auto-oxidation occurred completely by raising the temperature to 125 ℃ in the presence of DBU and toluene. On the other hand, in milder condition, when sodium carbonate was used at 85 ℃ on 4-substituted substrates in DCE, only small amounts of arenes were formed. To elucidate the

exact mechanism of auto-oxidation, we will proceed with the reaction by changing the conditions such as base, temperature, and solvent (Fig 16). Anaerobic condition can also be judged.

Figure and Table

Figure 1. A New Cascade Reaction for the Highly Substituted Arene

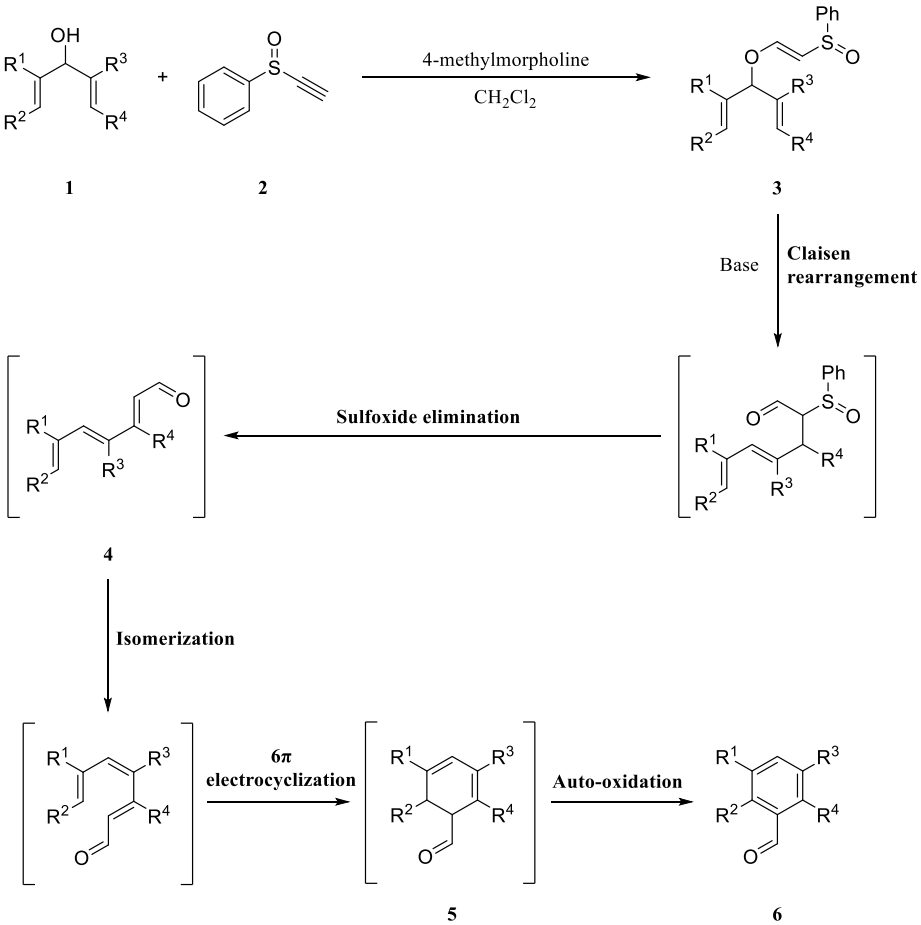


Figure 2. Optimization Conditions for Cascade Reactions

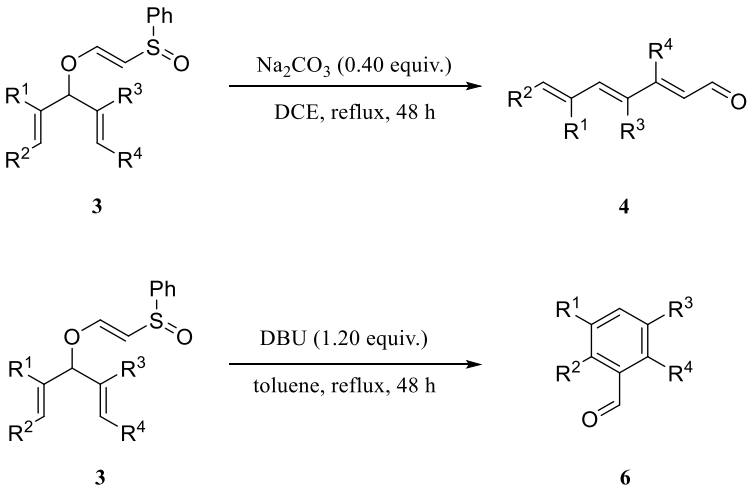
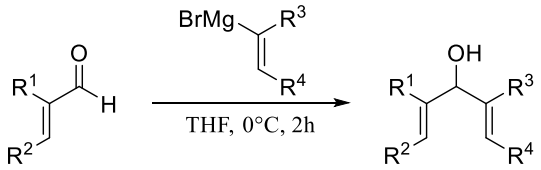


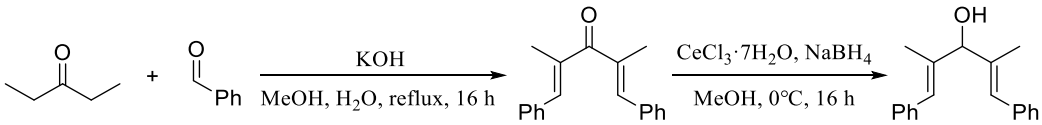
Figure 3. Preparation of Divinylcarbinols 1

A. Scheme for Divinylcarbinols 1a – 1b



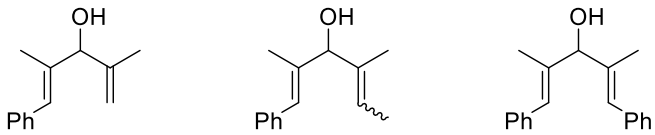
1

B. Scheme for Divinylcarbinol 1c



1c

C. Substrates



1a **1b** **1c**

Figure 4. Preparation of (Ethynylsulfinyl)benzene 2

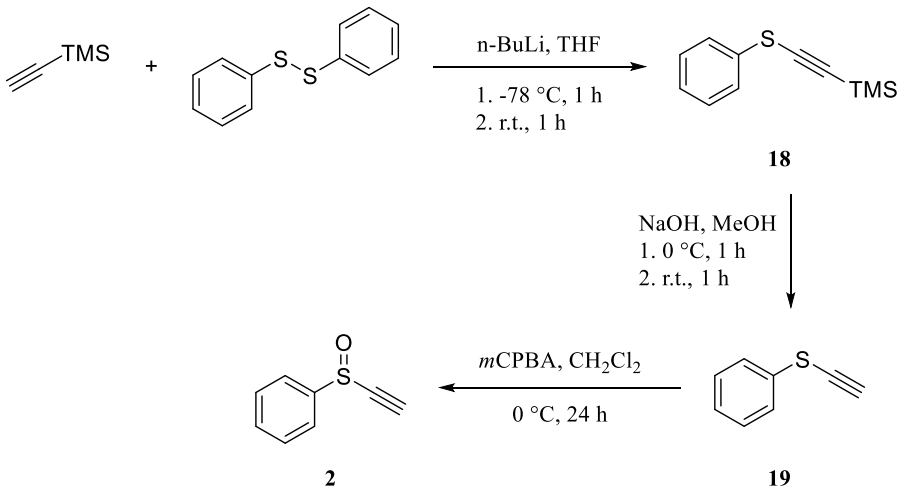
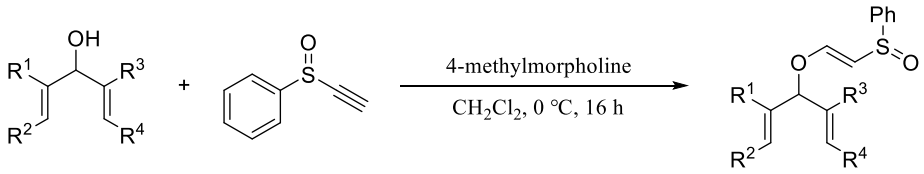


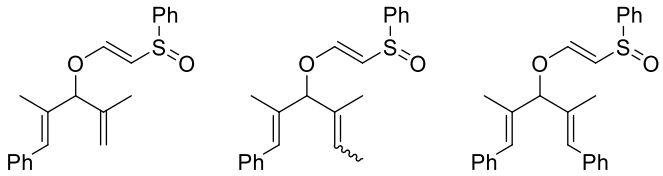
Figure 5. Synthesis of Divinylcarbinoxy Vinyl Sulfoxides 3

A. Scheme



1 **2** **3**

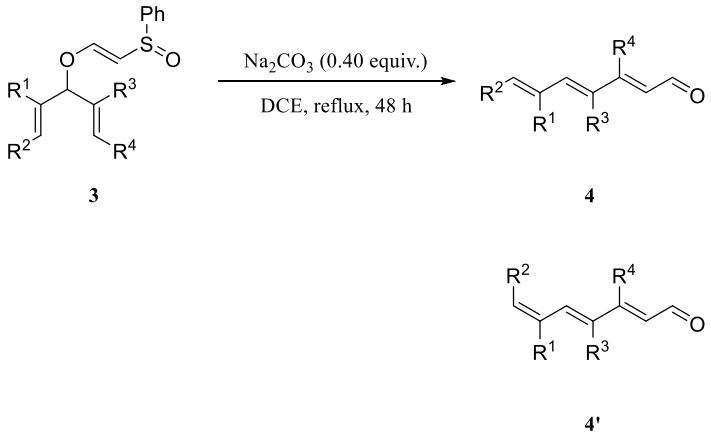
B. Substrates



3a **3b** **3c**

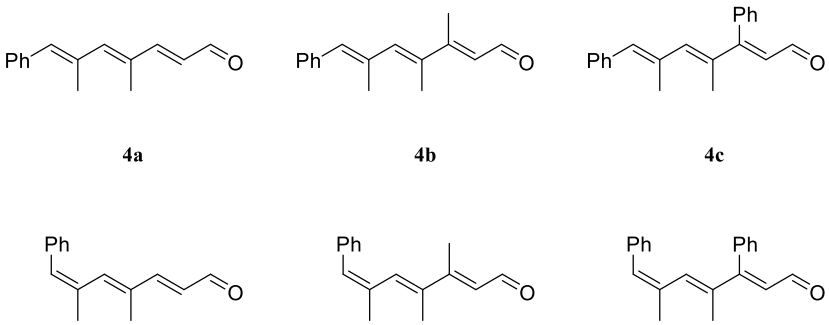
Figure 6. Synthesis of Trienals 4

A. Scheme



3 **4** **4'**

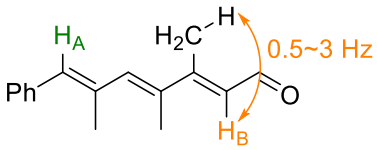
B. Substrates



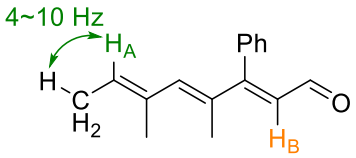
4a **4b** **4c**

4a' **4b'** **4c'**

Figure 7. Predicted Coupling Constant of Trienals 4b and 4b''



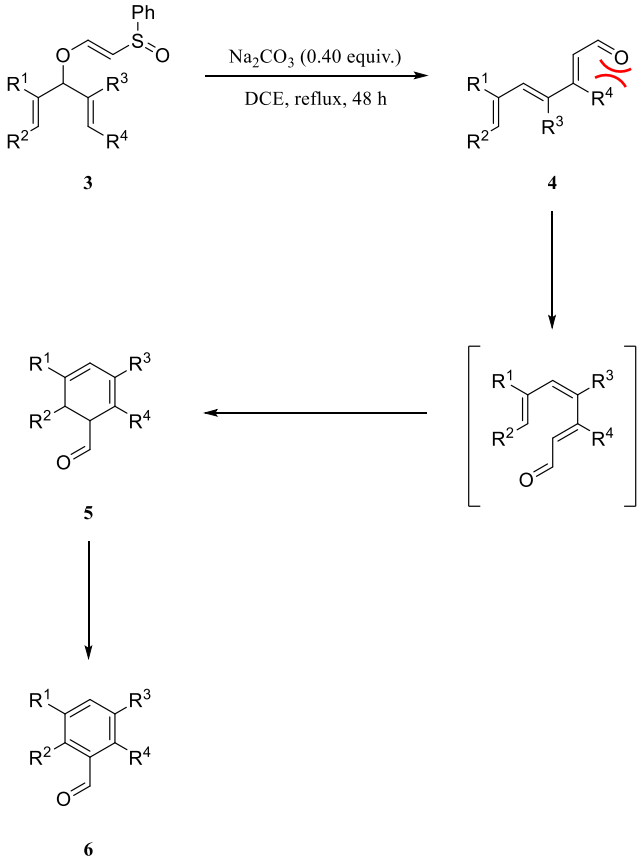
4b



4b''

Figure 8. Unexpected Synthesis of Cyclohexadienes 5 During Synthesis of Trienals 4

A. Scheme

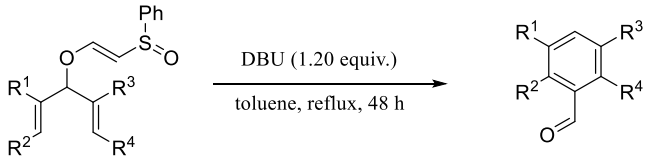


B. Substrates

5b **5c**

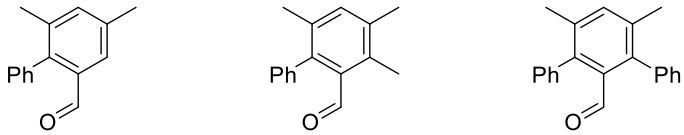
Figure 9. Synthesis of Arenes 6

A. Scheme



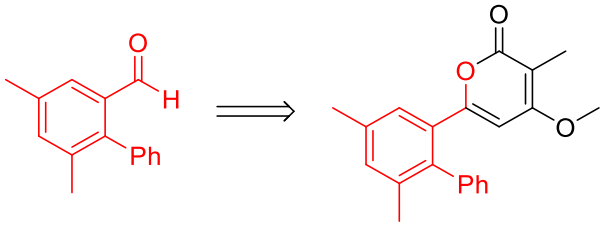
3 **6**

B. Substrates



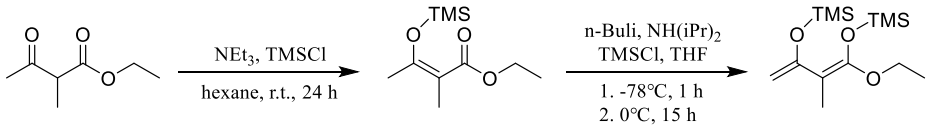
6b **6b** **6c**

Figure 10. Target Natural Product Nigerapyrone B for Total Synthesis



6a **Nigerapyrone B (11)**

Figure 11. Preparation of 4-Ethoxy-2,2,5,8,8-pentamethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene 7



20 **7**

Figure 12. Addition of arene 6a and 4-Ethoxy-2,2,5,8,8-pentamethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene 7

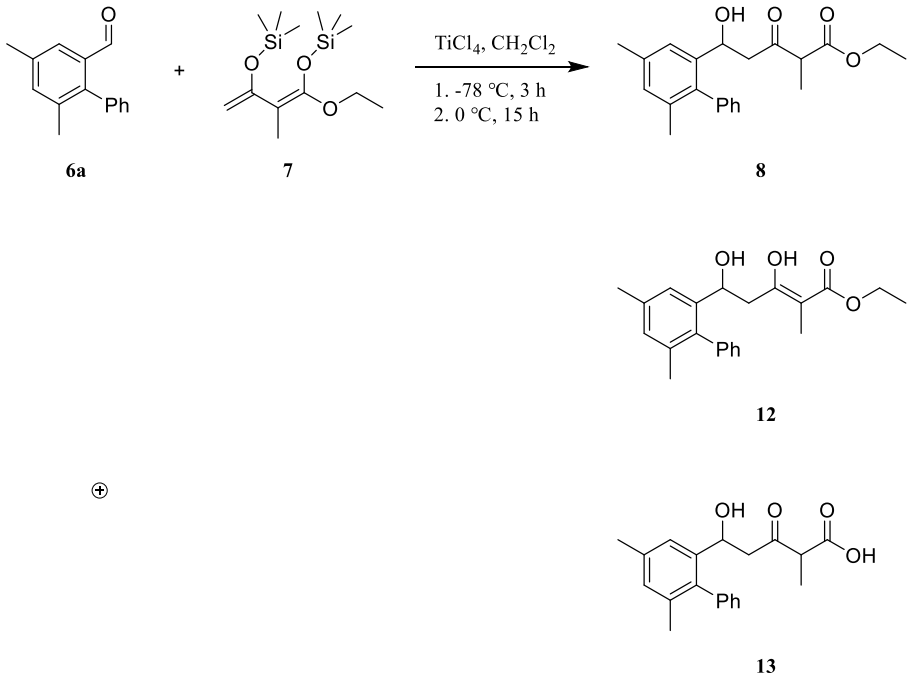
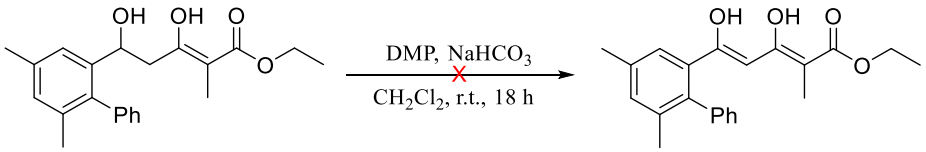


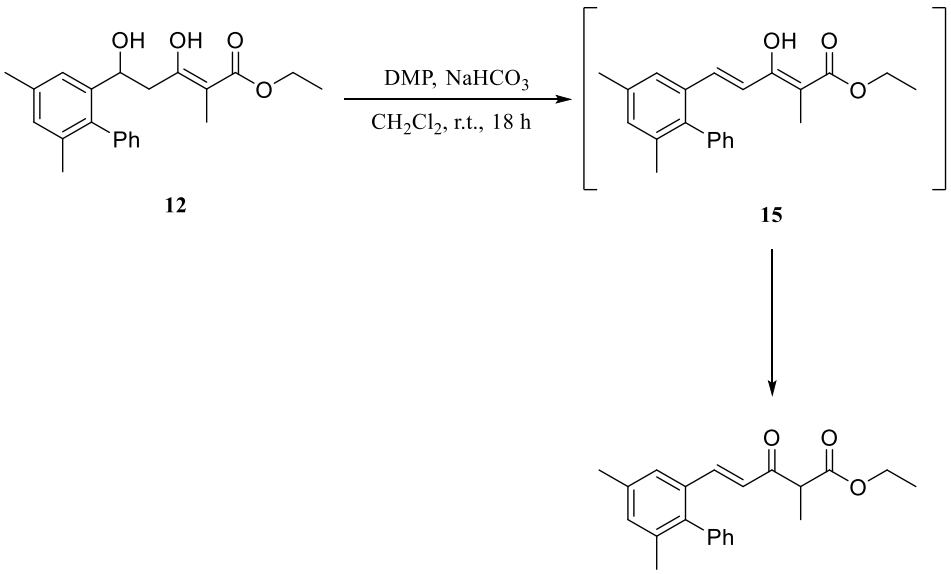
Figure 13. DMP Oxidation of Ethyl (Z)-5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-3,5-dihydroxy-2-methylpent-2-enoate 12

A. Expected Oxidation



12 **14**

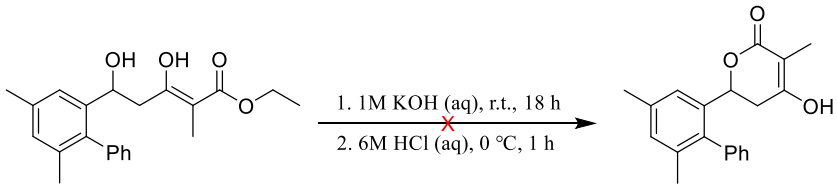
B. Unexpected Dehydration



12 **15** **16**

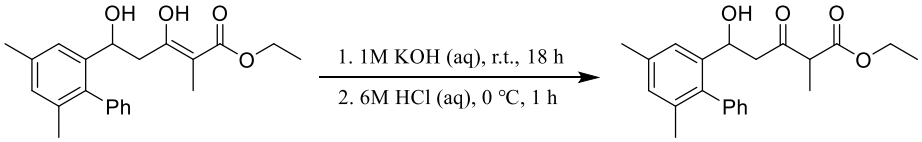
Figure 14. Change the Order of Reactions

A. Expected Cyclization



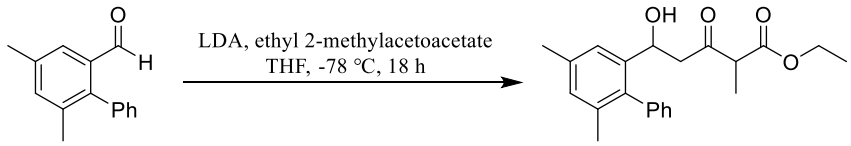
12 **17**

B. Unexpected Tautomerization



12 **8**

Figure 15. Synthesis of Ethyl 5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopentanoate 8



6a **8**

Figure 16. Synthesis of Nigerapyrone B (11)

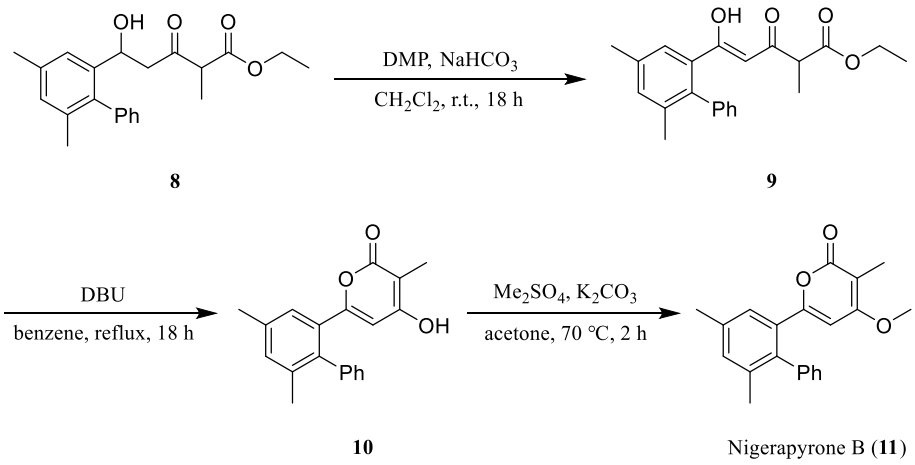
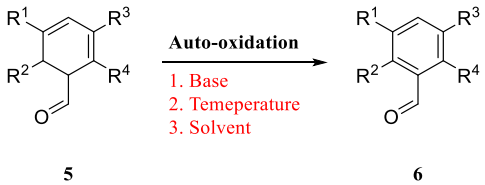


Figure 17. Future Plan for Identification of Auto-oxidation Mechanism



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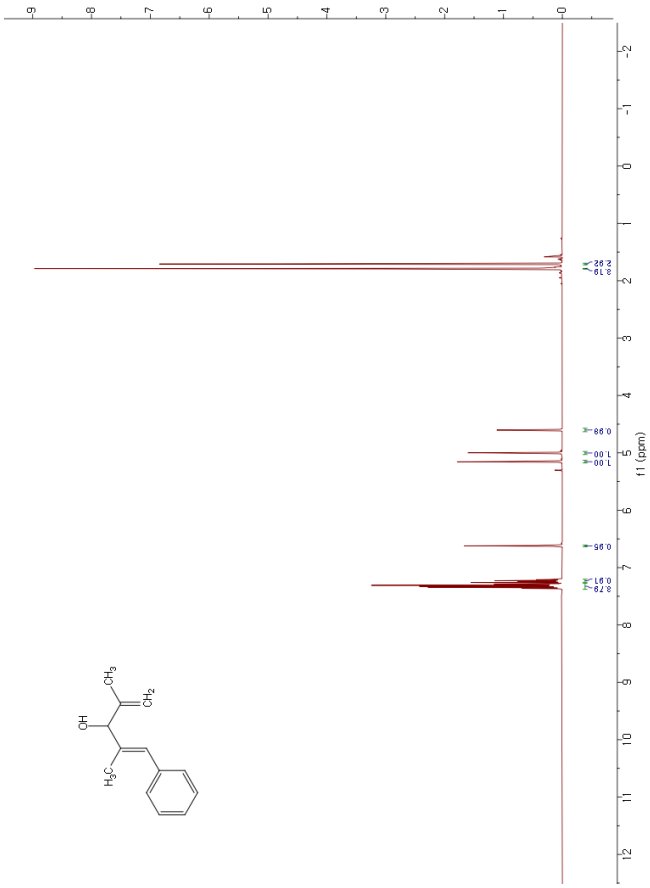
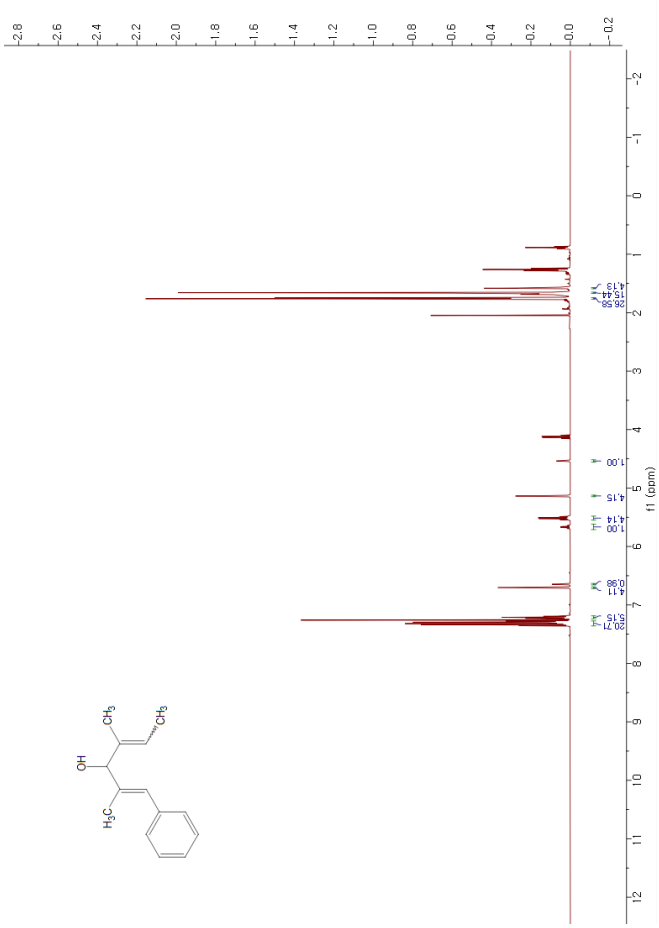
Supplementary Materials

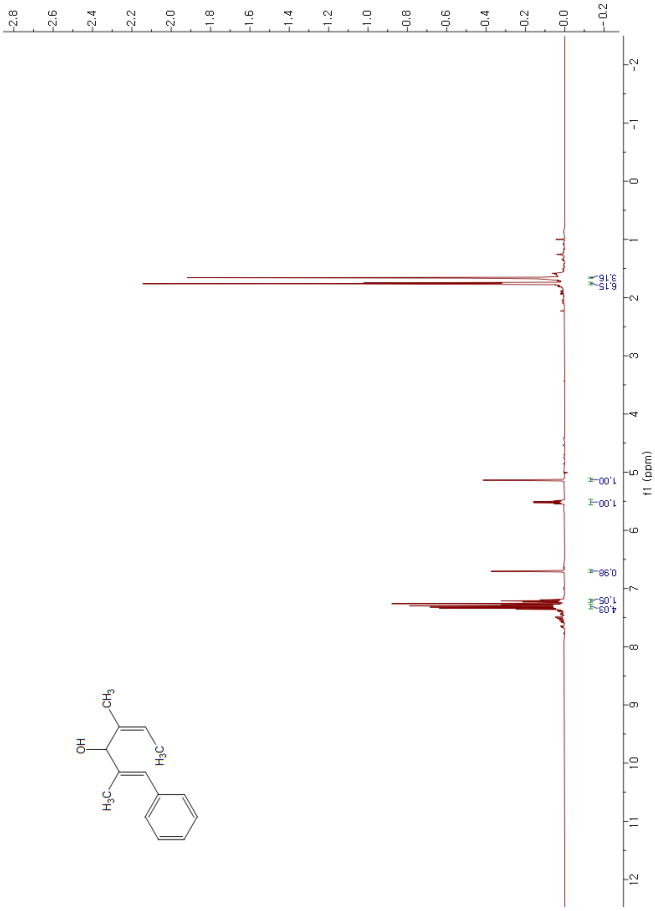
S1. ^{1}H NMR Data of (E)-2,4-dimethyl-1-phenylpenta-1,4-dien-3-ol (1a)



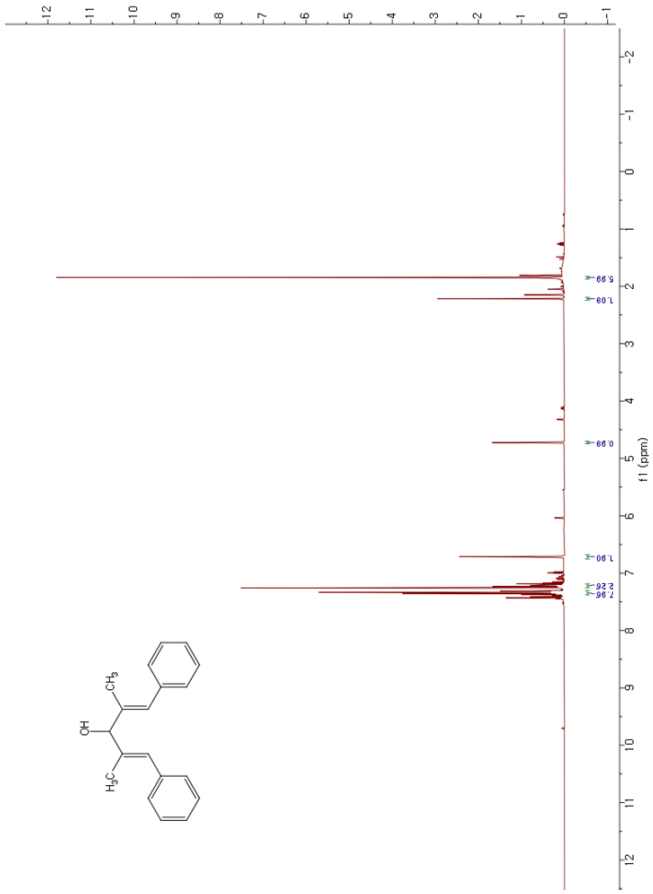
S2. ^{1}H NMR Data of (1*E*,4E)-2,4-dimethyl-1-phenyl-1,4-hexadien-3-ol and (1*E*,4*Z*)-2,4-dimethyl-1-phenyl-1,4-hexadien-3-ol (1b)



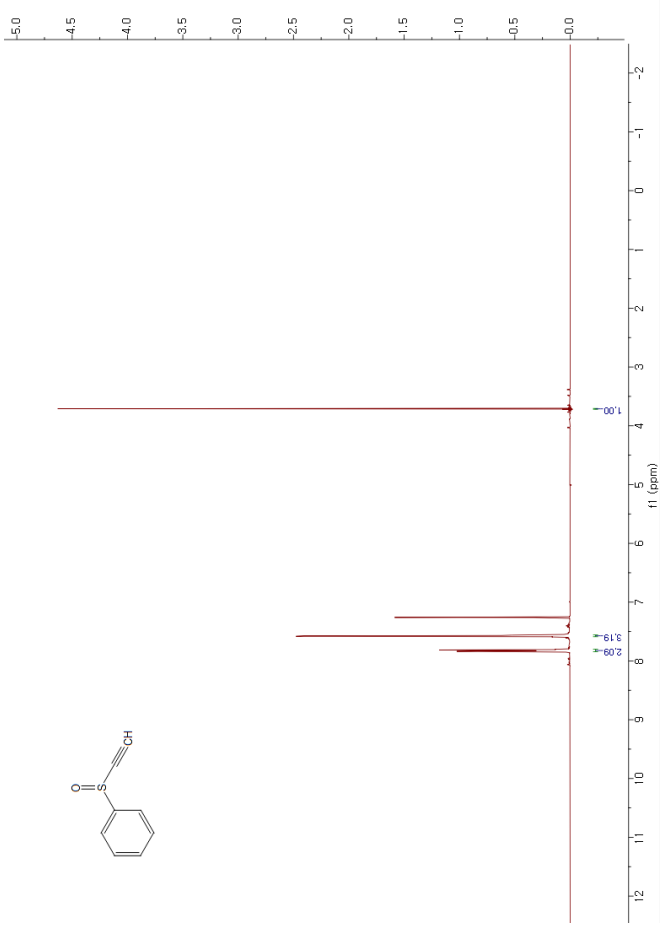
S3. ^{1}H NMR Data of (1*E*,4*Z*)-2,4-dimethyl-1-phenyl-1,4-hexadien-3-ol (1b)



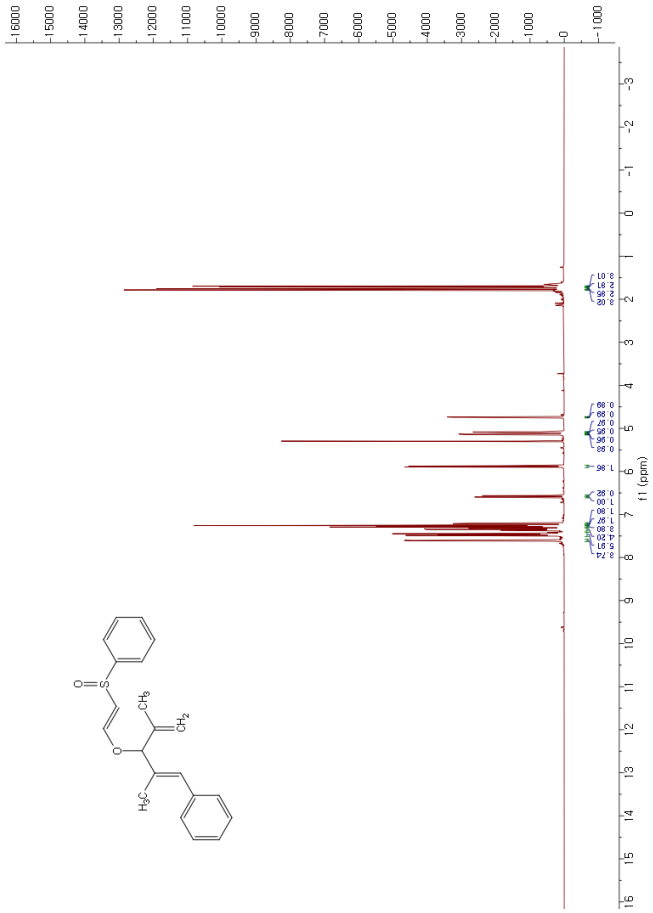
S4. ^{1}H NMR Data of (1E,4E)-2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-ol (1c)



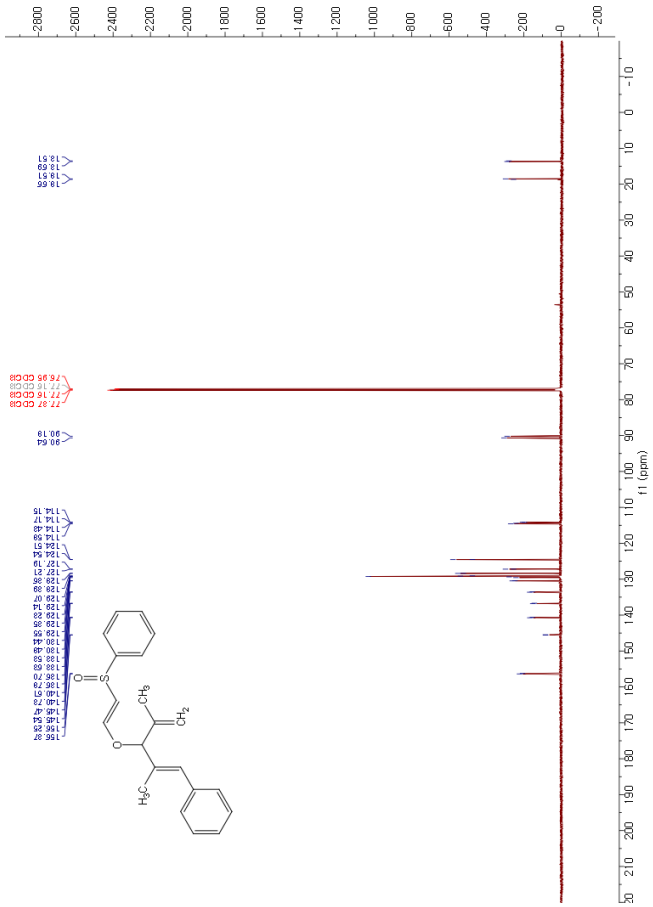
S5. ^{1}H NMR Data of (ethynylsulfinyl)benzene (2)



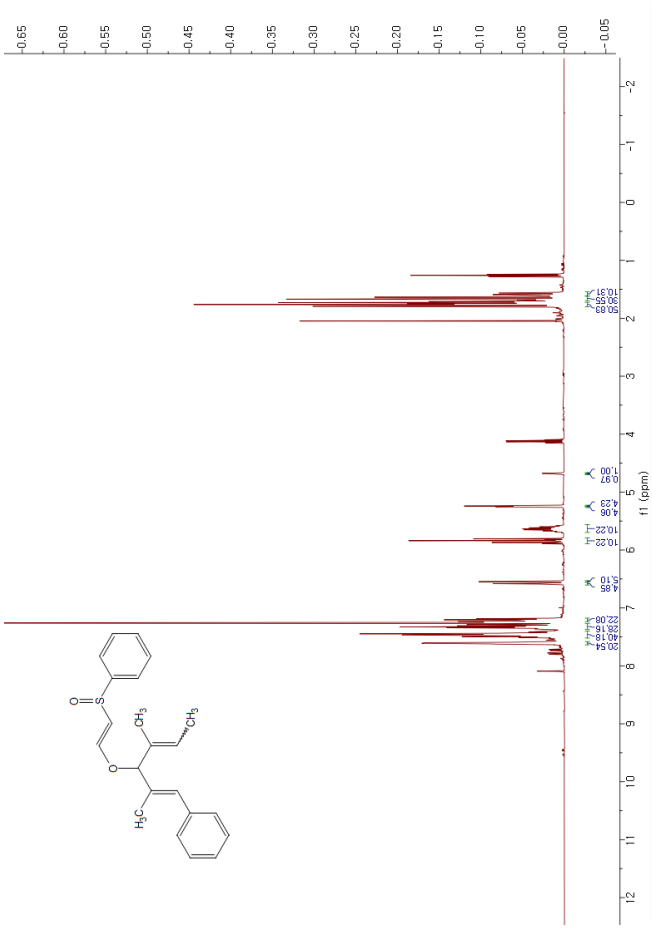
S6. ^{1}H NMR Data of (((E)-2-(((E)-2,4-dimethyl-1-phenylpenta-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene (3a)



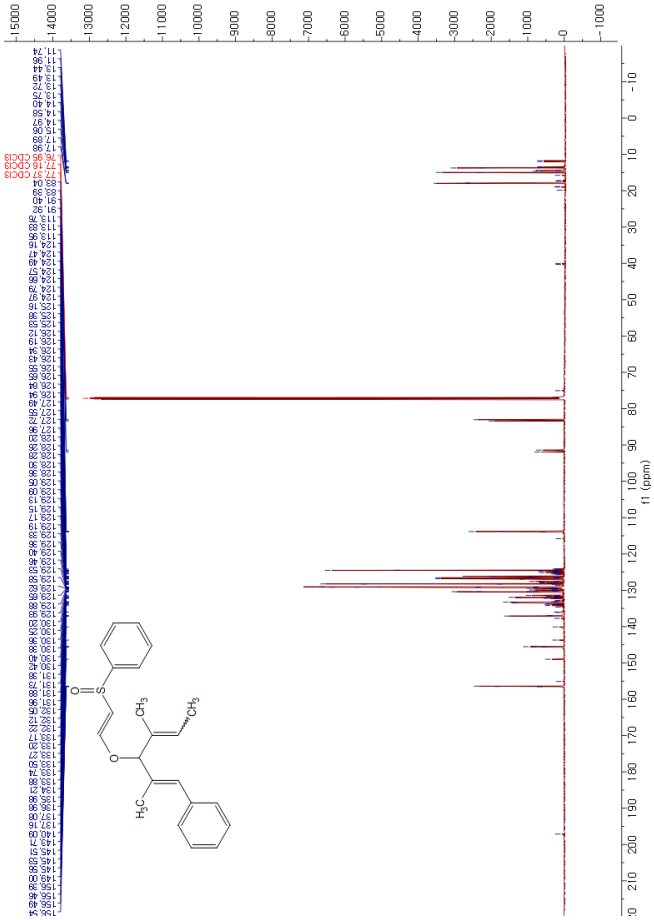
S7. ^{13}C NMR Data of (((E)-2-(((E)-2,4-dimethyl-1-phenylpenta-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene (3a)



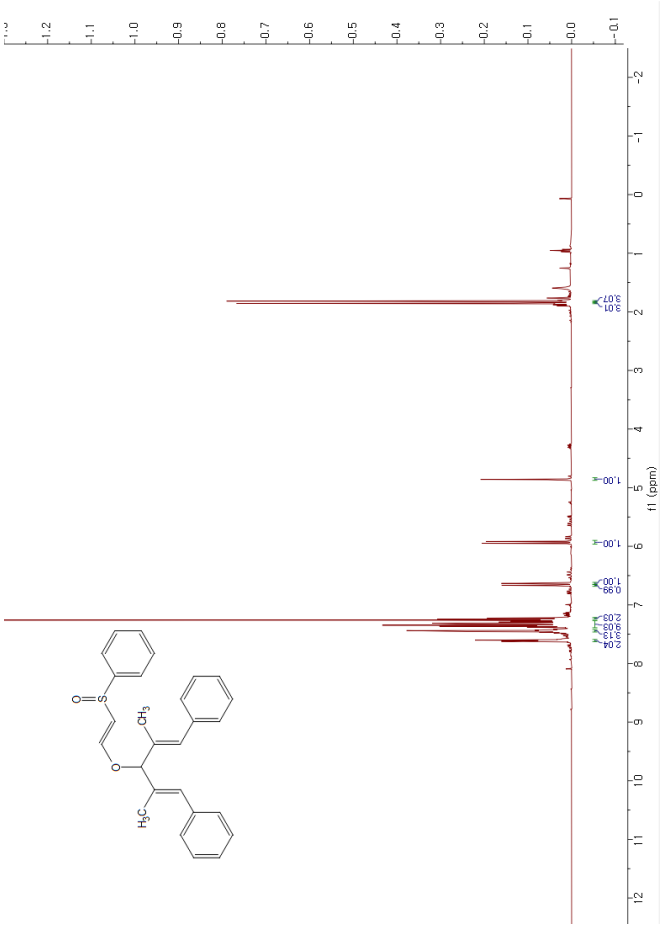
S8. ^{1}H NMR Data of (((E)-2-(((1E,4E)-2,4-dimethyl-1-phenylhexa-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene and (((E)-2-(((1E,4Z)-2,4-dimethyl-1-phenylhexa-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene (3b)



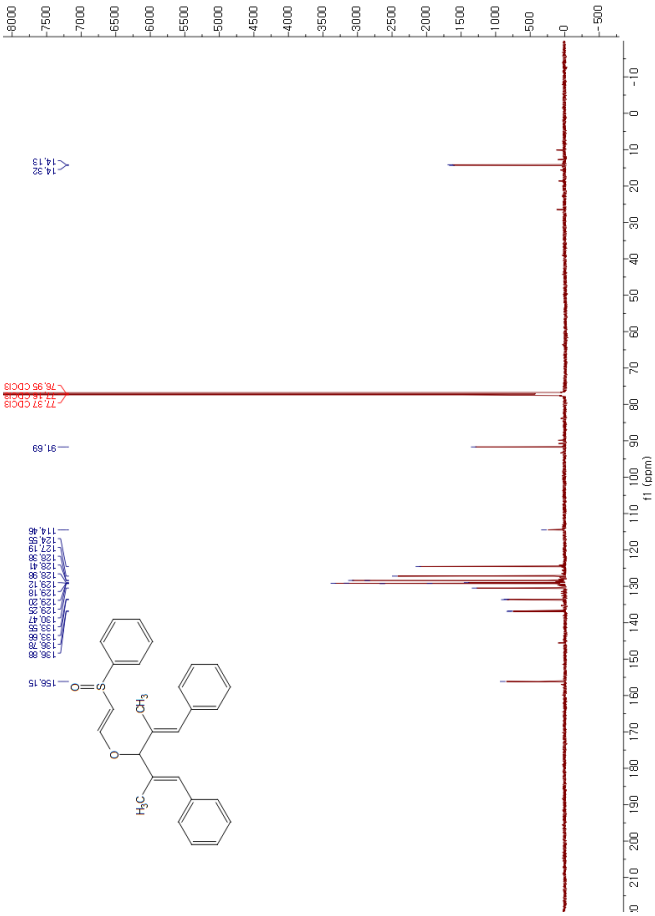
S9. ^{13}C NMR Data of (((E)-2-(((1E,4E)-2,4-dimethyl-1-phenylhexa-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene and (((E)-2-(((1E,4Z)-2,4-dimethyl-1-phenylhexa-1,4-dien-3-yl)oxy)vinyl)sulfinyl)benzene (3b)



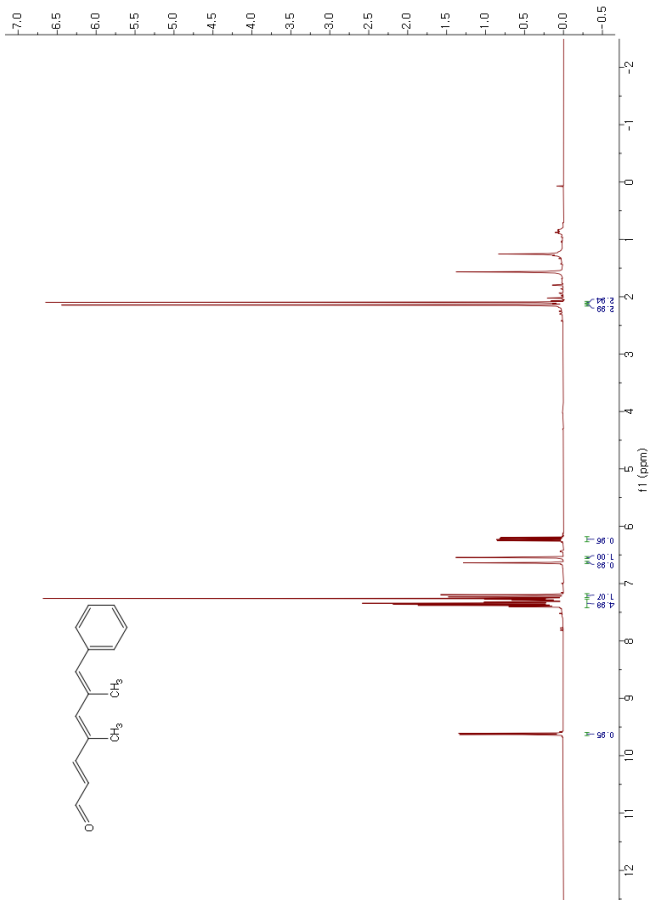
S10. ^{1}H NMR Data of ((1E,4E)-2,4-dimethyl-3-(((E)-2-(phenylsulfinyl)vinyl)oxy)penta-1,4-diene-1,5-diyl)dibenzene (3c)



S11. ^{13}C NMR Data of ((1E,4E)-2,4-dimethyl-3-(((E)-2-(phenylsulfinyl)vinyl)oxy)penta-1,4-diene-1,5-diyl)dibenzene (3c)



S12. ^{1}H NMR Data of (2E,4E,6E)-4,6-dimethyl-7-phenylhepta-2,4,6-trienal (4a)



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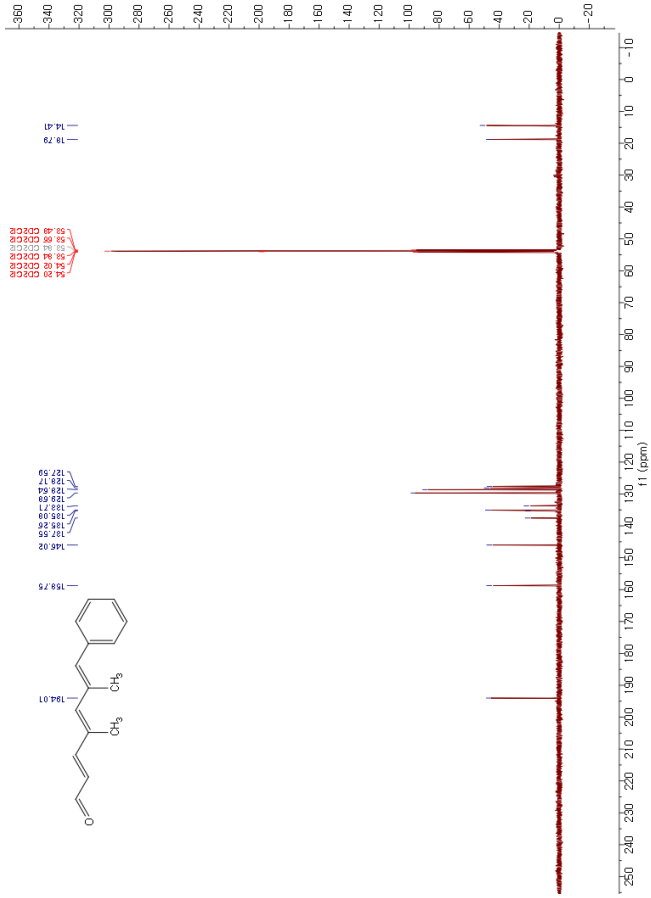
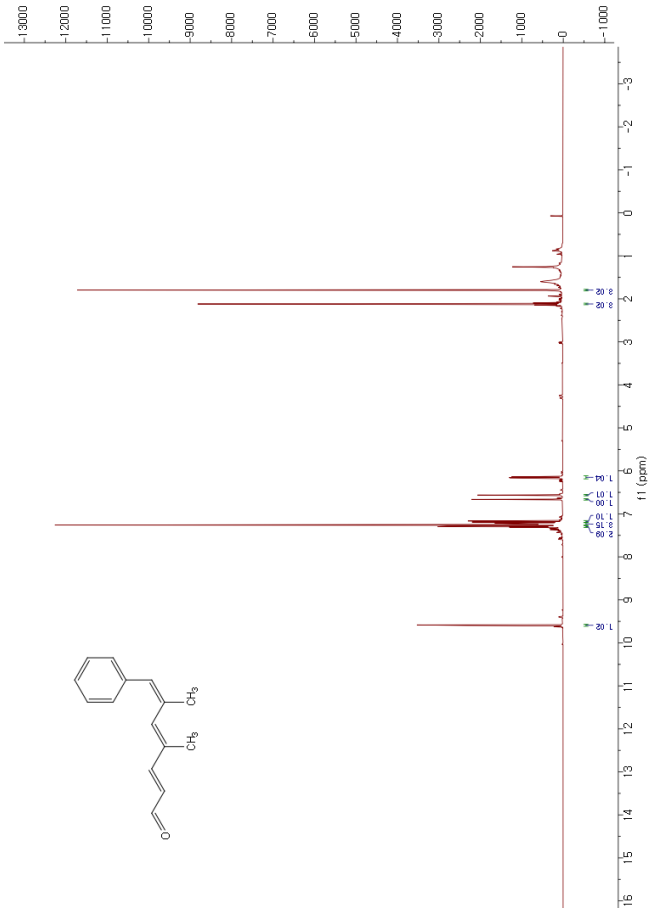
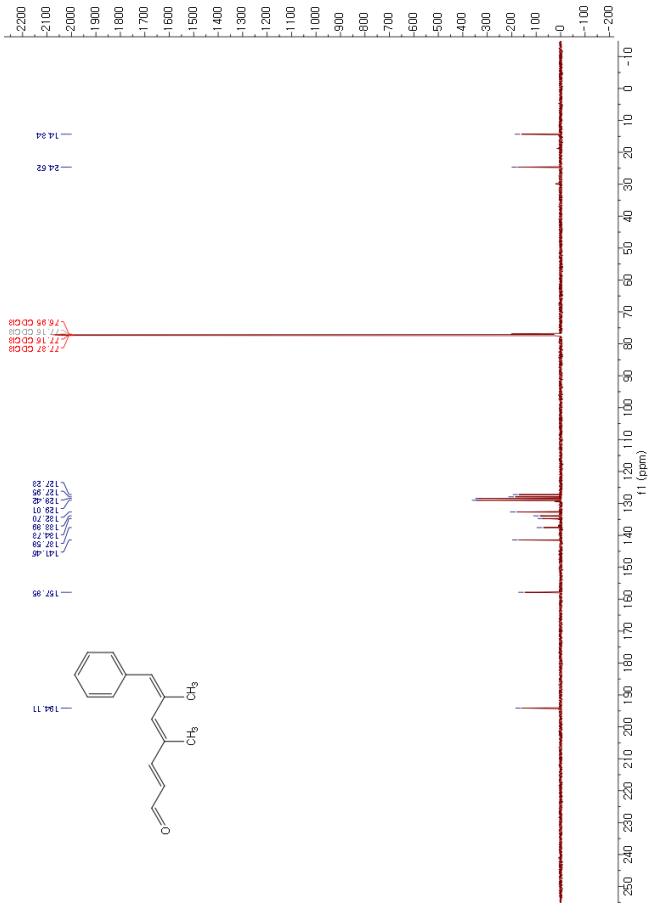


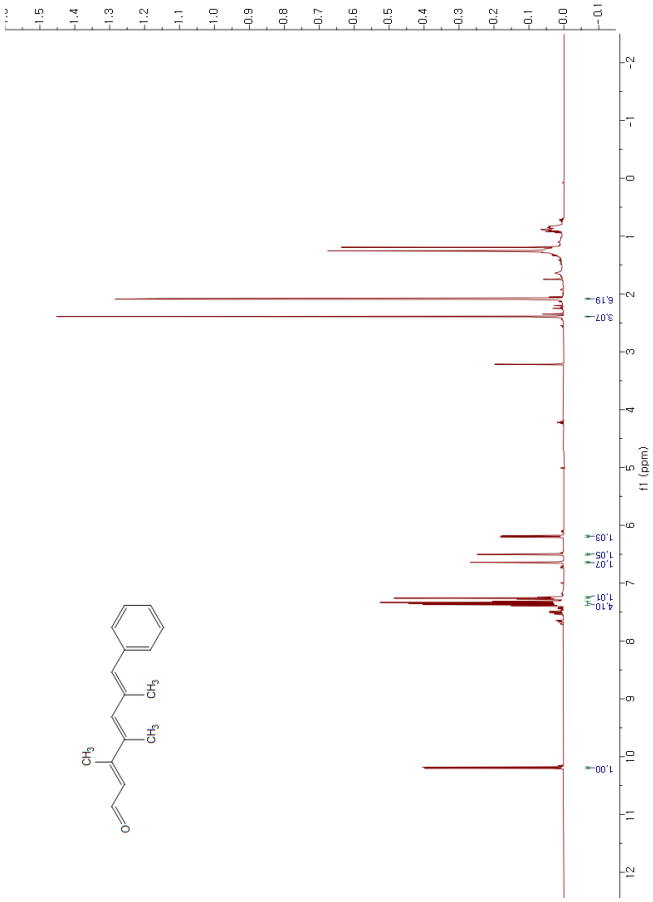
S14. ^{1}H NMR Data of (2E,4E,6Z)-4,6-dimethyl-7-phenylhepta-2,4,6-trienal (4a')



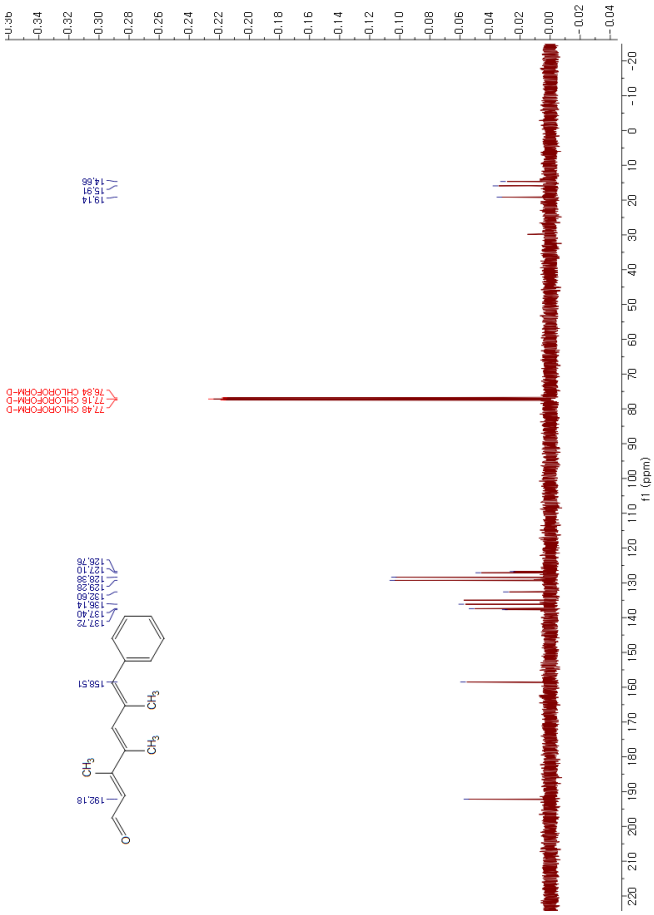
S15. ^{13}C NMR Data of (2E,4E,6Z)-4,6-dimethyl-7-phenylhepta-2,4,6-trienal (4a')



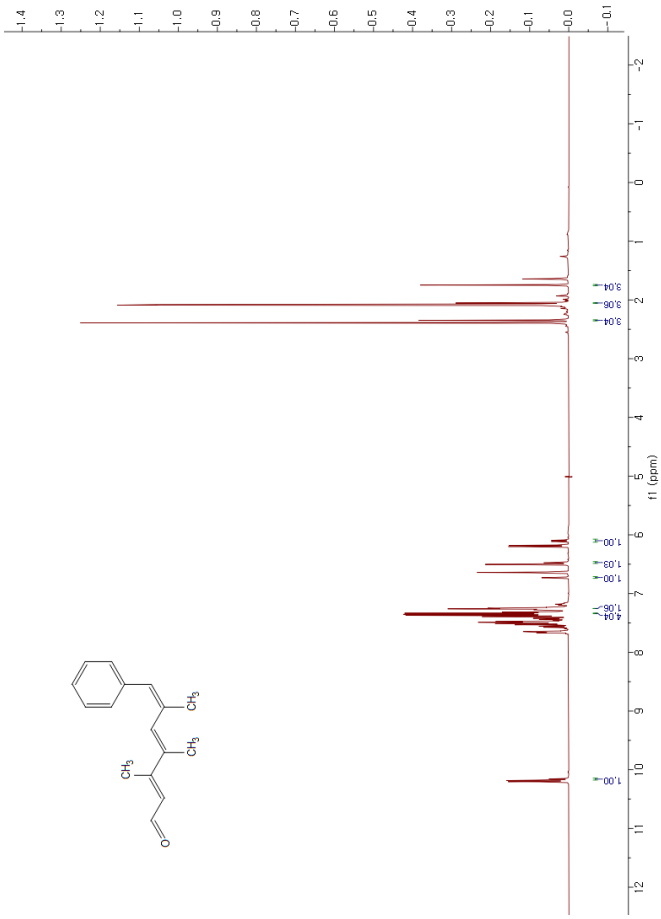
S16. ^{1}H NMR Data of (2E,4E,6E)-3,4,6-trimethyl-7-phenylhepta-2,4,6-trienal (4b)



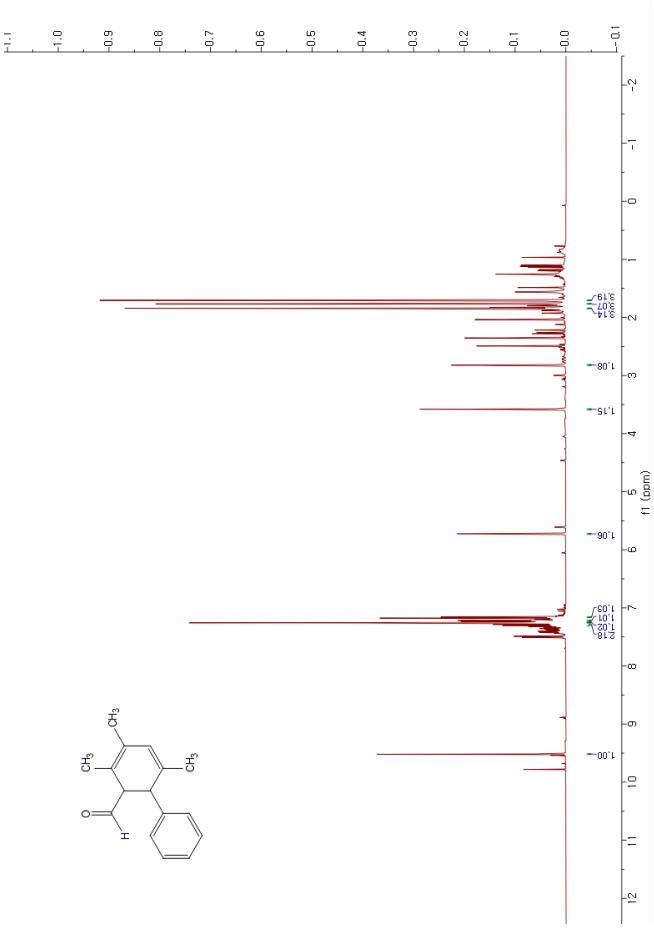
S17. ^{13}C NMR Data of (2E,4E,6E)-3,4,6-trimethyl-7-phenylhepta-2,4,6-trienal (4b)



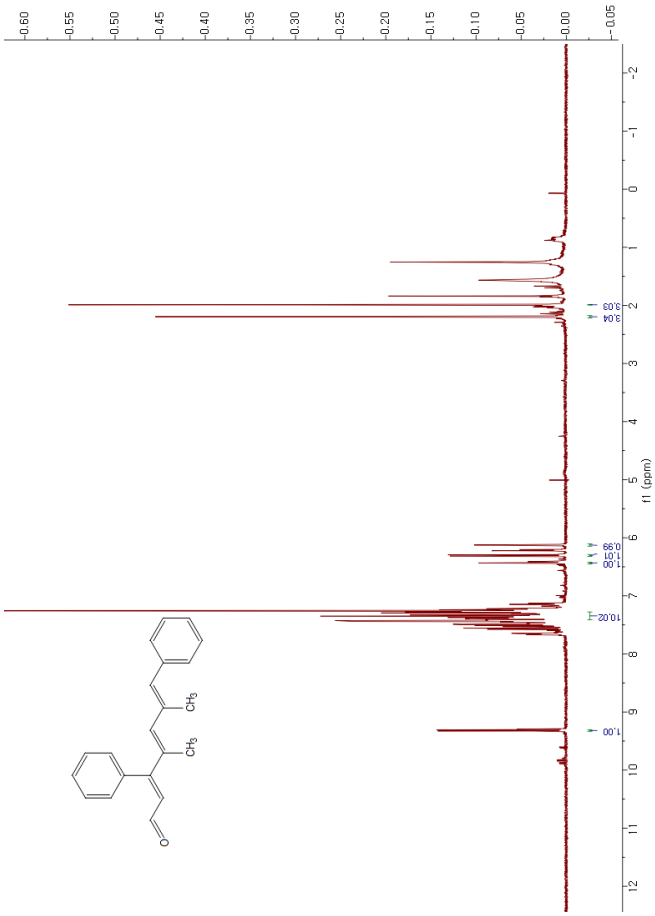
S18. ^{1}H NMR Data of (2E,4E,6Z)- 3,4,6-trimethyl-7-phenylhepta-2,4,6-trienal (4b')



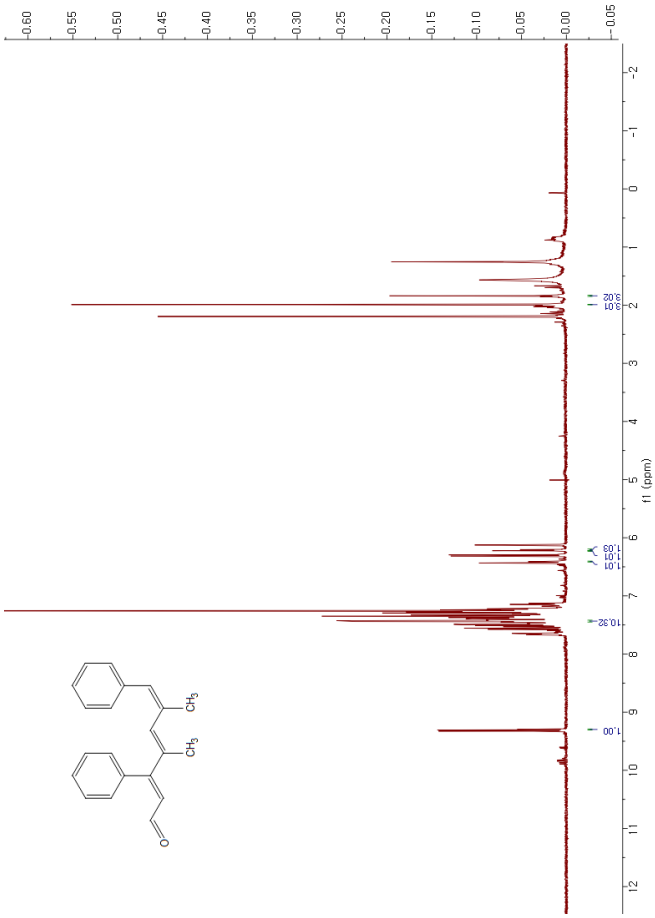
S19. ^{1}H NMR Data of 3,4,6-trimethyl-1,2-dihydro-[1,1'-biphenyl]-2-carbaldehyde (5b)



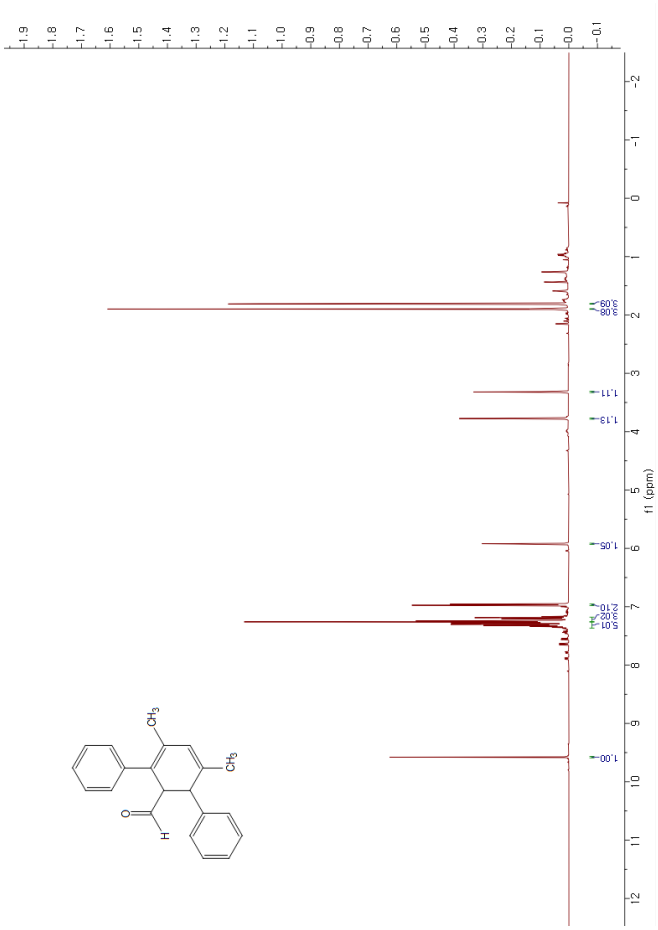
S20. ^{1}H NMR Data of (2Z,4E,6E)-4,6-dimethyl-3,7-diphenylhepta-2,4,6-trienal (4c)



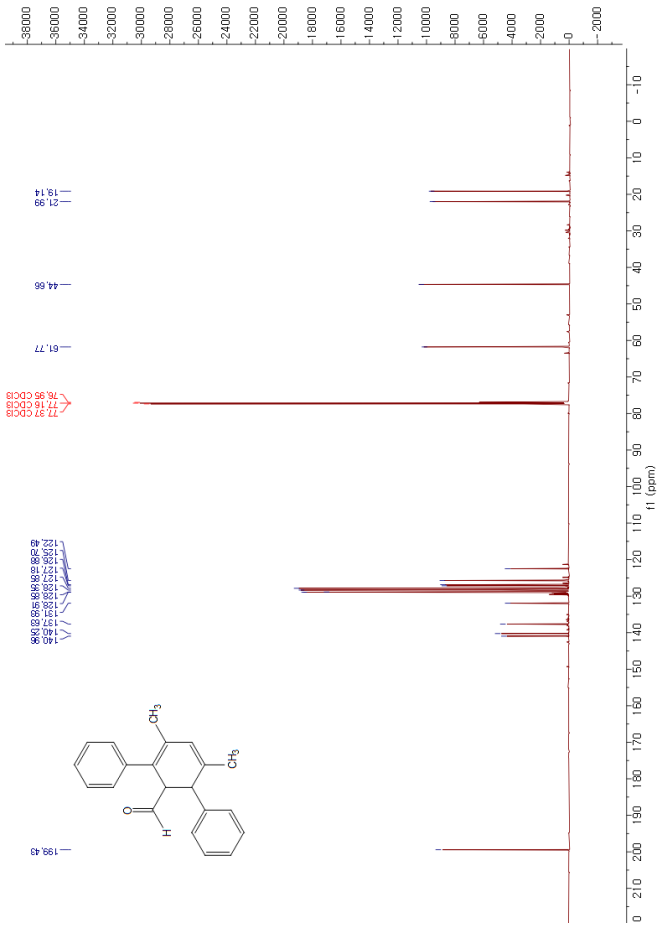
S21. ^{1}H NMR Data of (2Z,4E,6Z)-4,6-dimethyl-3,7-diphenylhepta-2,4,6-trienal (4c')



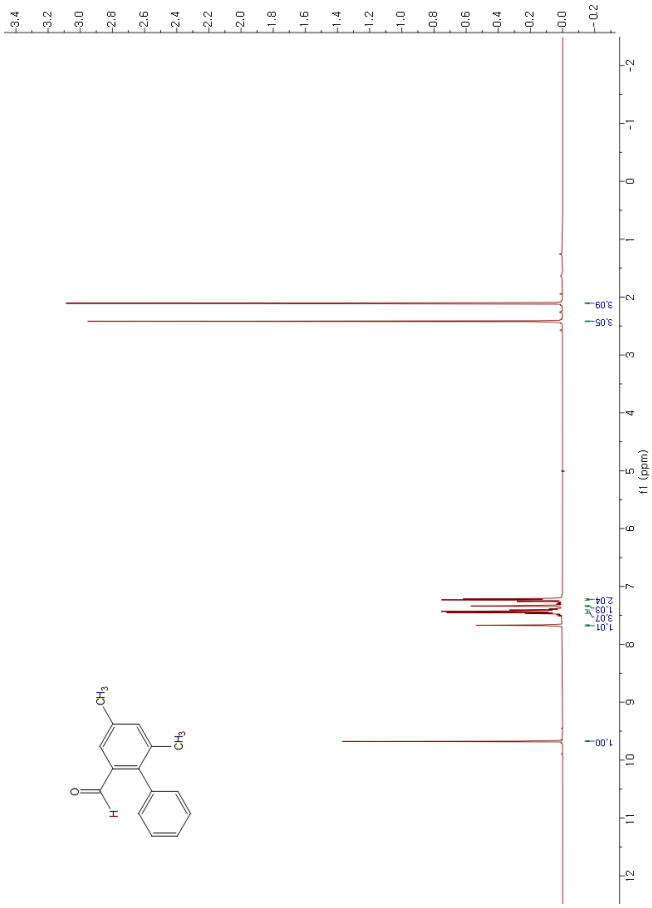
S22. ^{1}H NMR Data of 4',6'-dimethyl-1',2'-dihydro-[1,1':3',1''-terphenyl]-2'-carbaldehyde (5c)



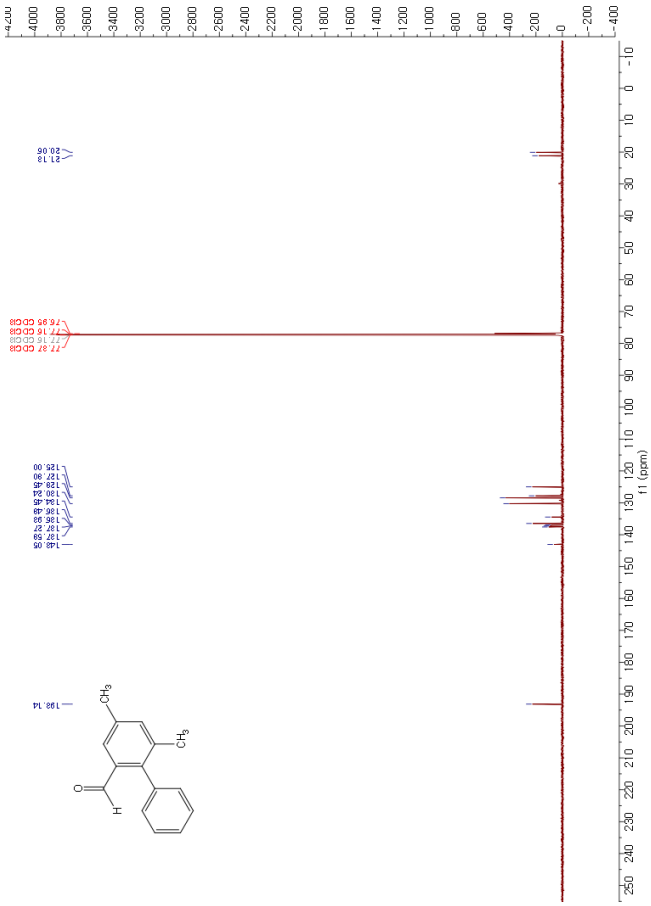
S23. ^{13}C NMR Data of 4',6'-dimethyl-1',2'-dihydro-[1,1':3',1''-terphenyl]-2'-carbaldehyde (5c)



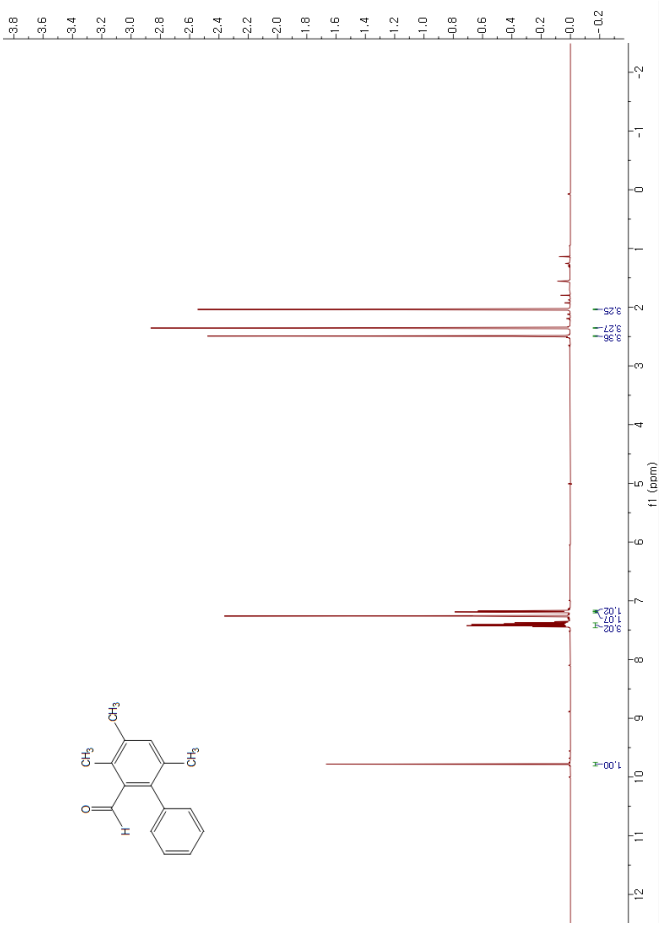
S24. ^{1}H NMR Data of 4,6-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (6a)



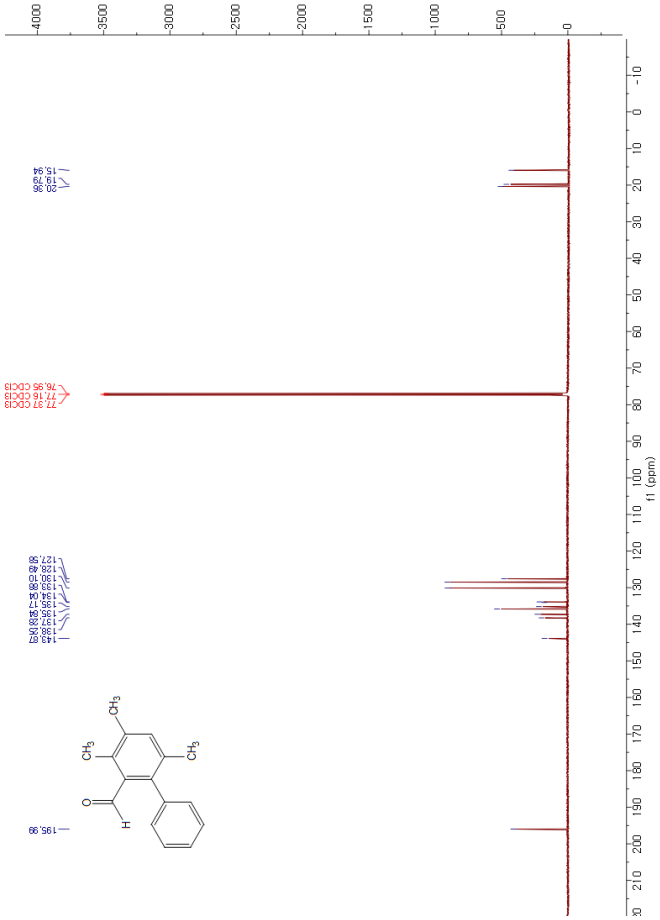
S25. ^{13}C NMR Data of 4,6-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (6a)



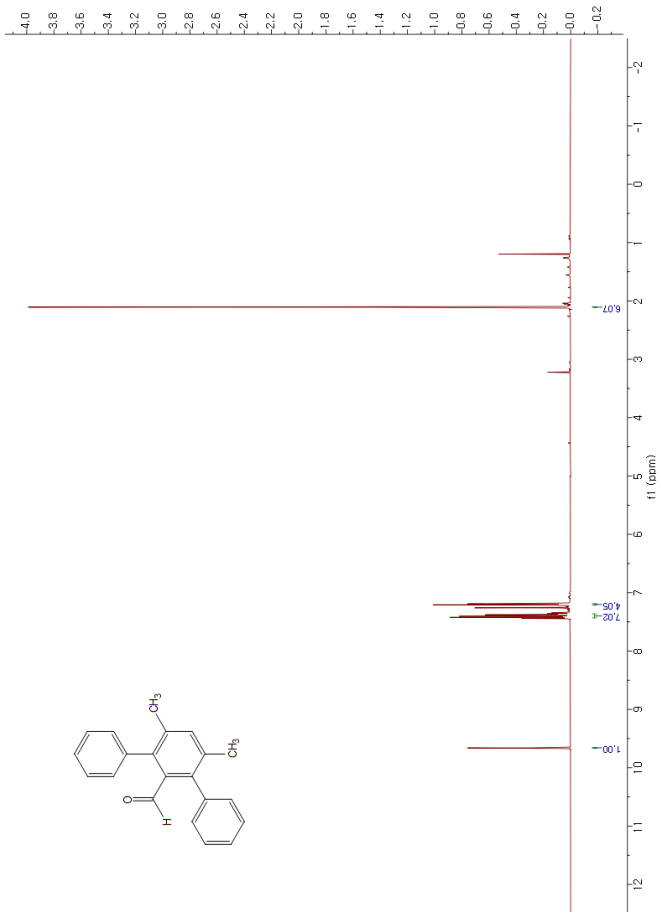
S26. ^{1}H NMR Data of 3,4,6-trimethyl-[1,1'-biphenyl]-2-carbaldehyde (6b)



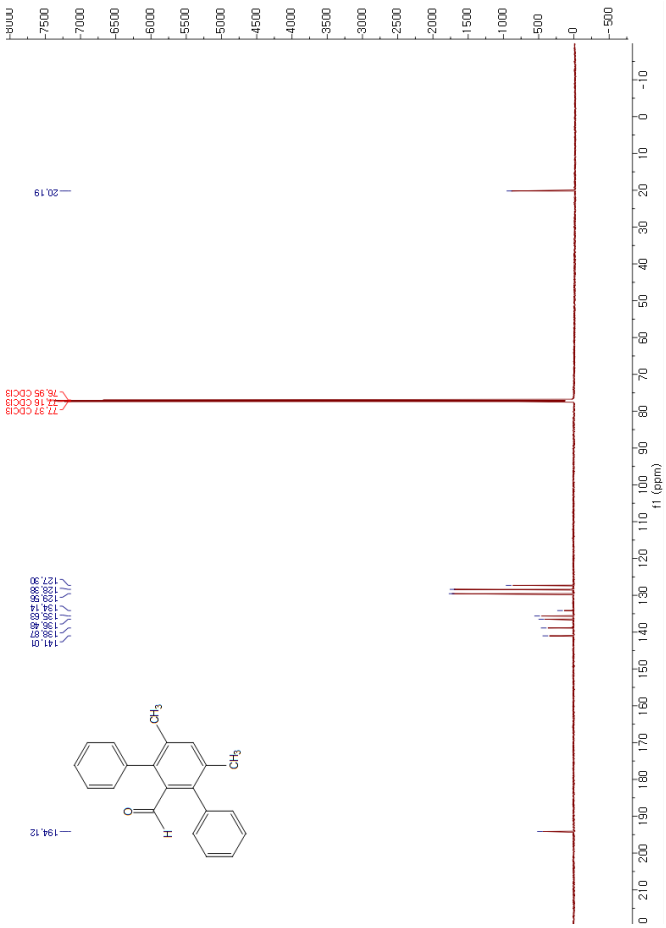
S27. ^{13}C NMR Data of 3,4,6-trimethyl-[1,1'-biphenyl]-2-carbaldehyde (6b)



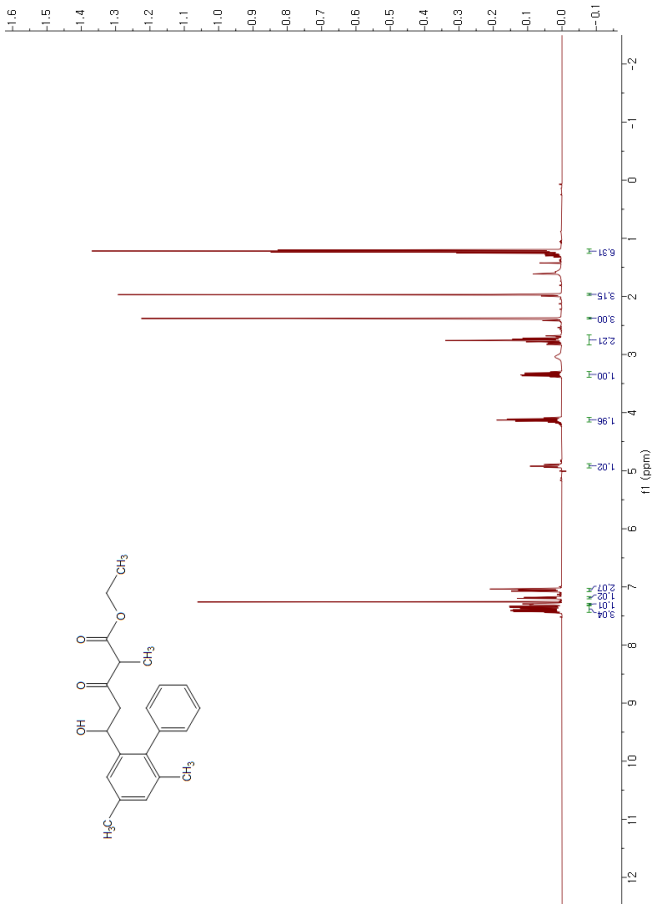
S28. ^{1}H NMR Data of 4',6'-dimethyl-[1,1':3',1''-terphenyl]-2'-carbaldehyde (6c)



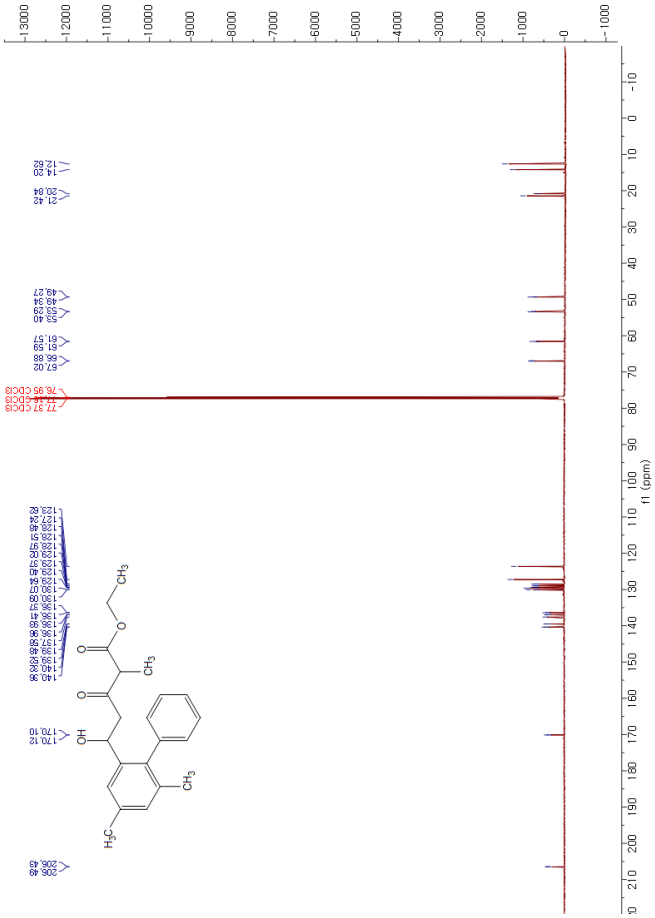
S29. ^{13}C NMR Data of 4',6'-dimethyl-[1,1':3',1''-terphenyl]-2'-carbaldehyde (6c)



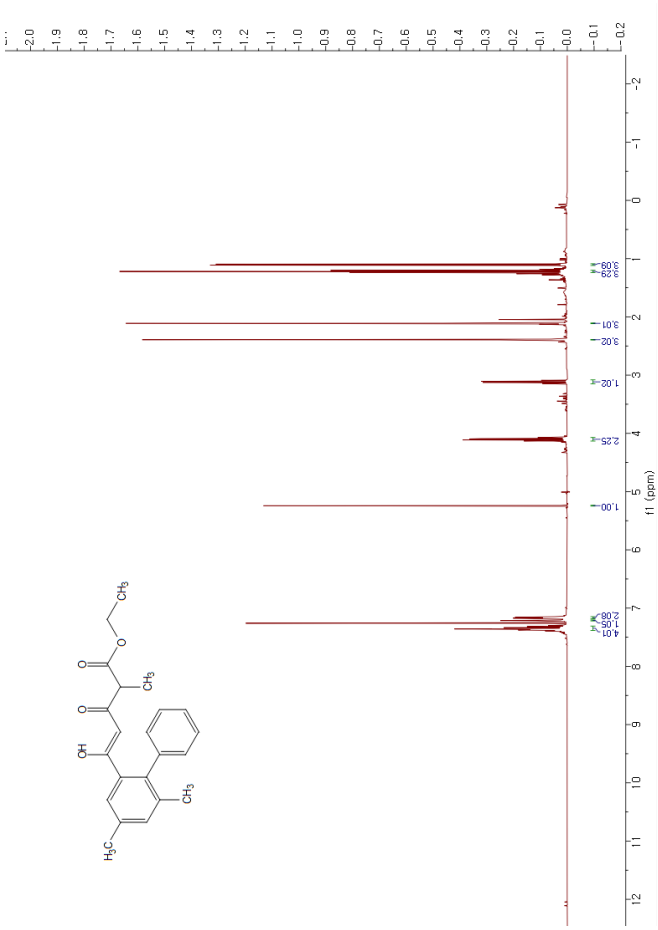
S30. ^{1}H NMR Data of ethyl 5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopentanoate (8)



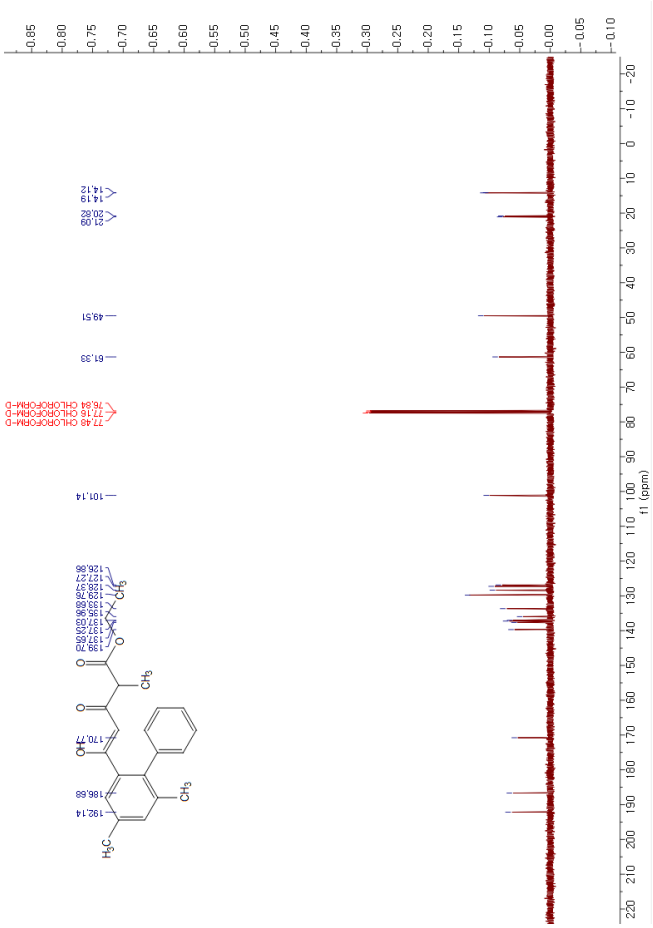
S31. ^{13}C NMR Data of ethyl 5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopentanoate (8)



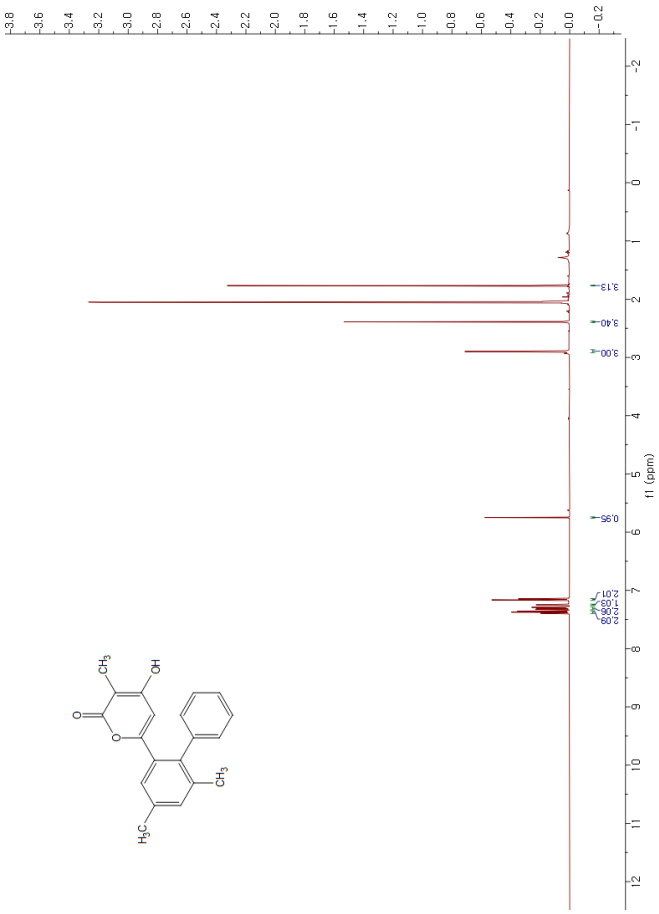
S32. ^{1}H NMR Data of ethyl (Z)-5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopent-4-enoate (9)



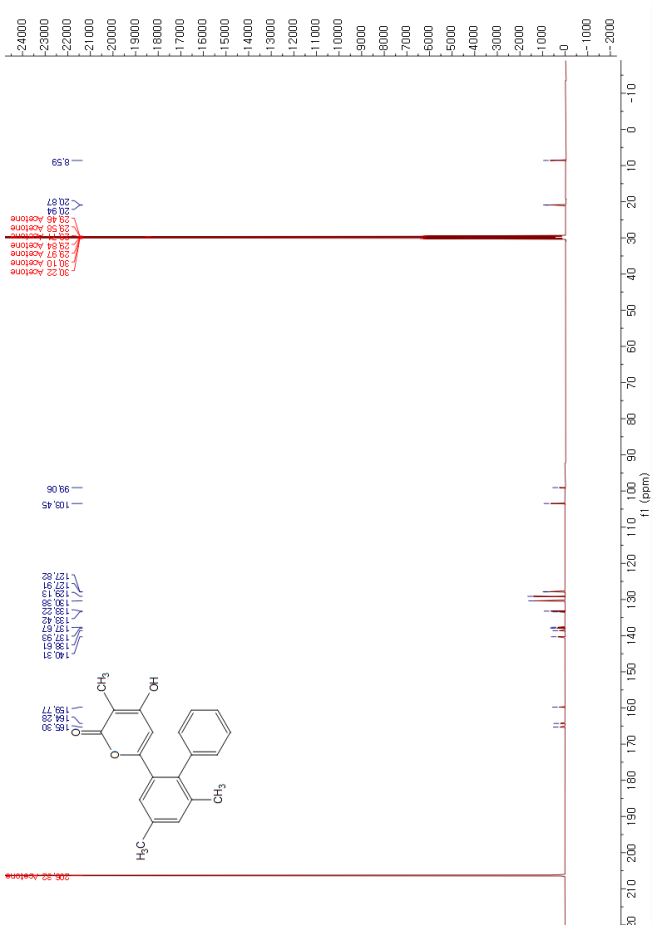
S33. ^{13}C NMR Data of ethyl (Z)-5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopent-4-enoate (9)



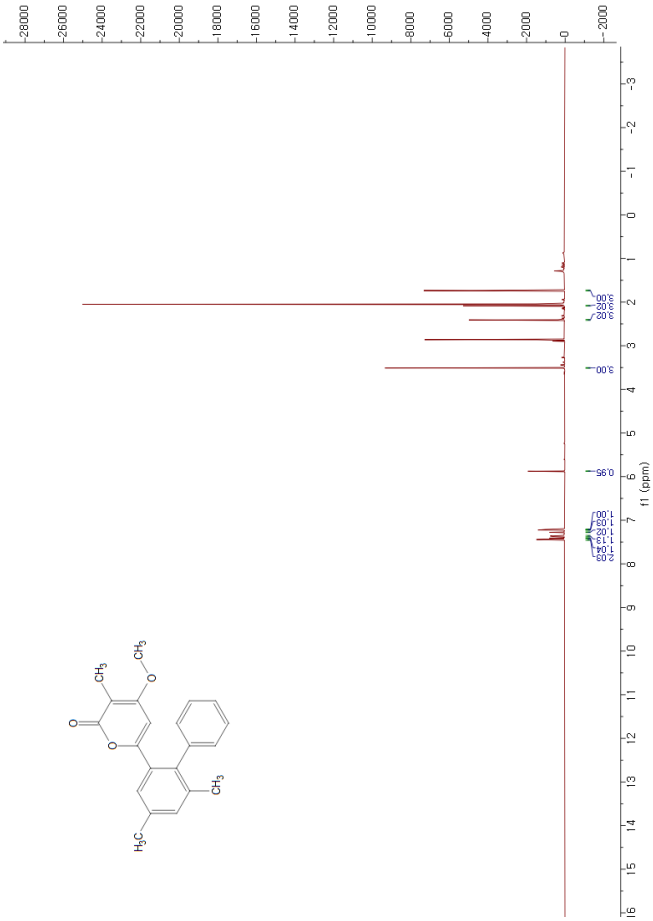
S34. ^{1}H NMR Data of 6-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-4-hydroxy-3-methyl-2H-pyran-2-one (10)



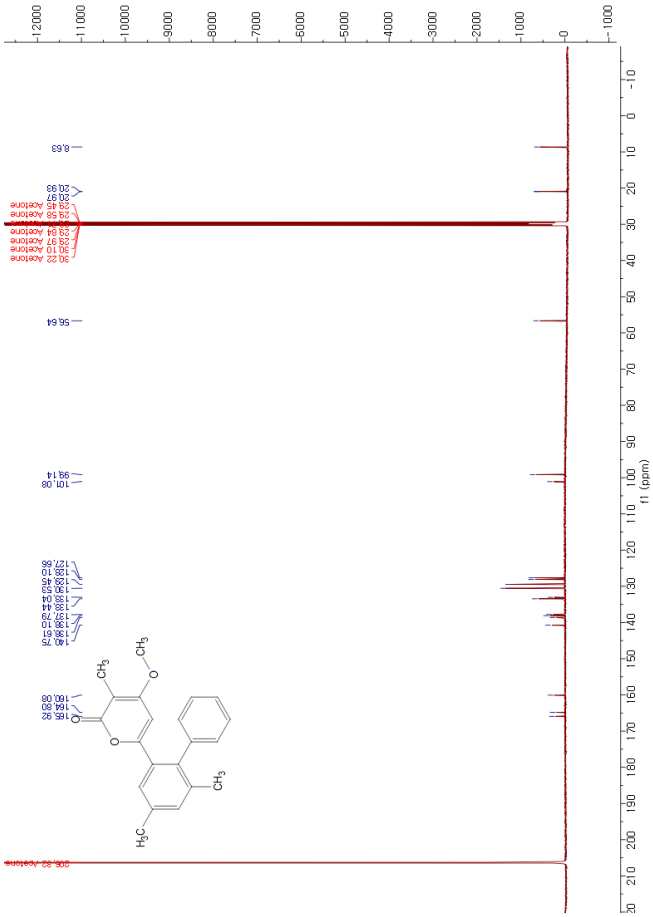
S35. ^{13}C NMR Data of 6-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-4-hydroxy-3-methyl-2H-pyran-2-one (10)



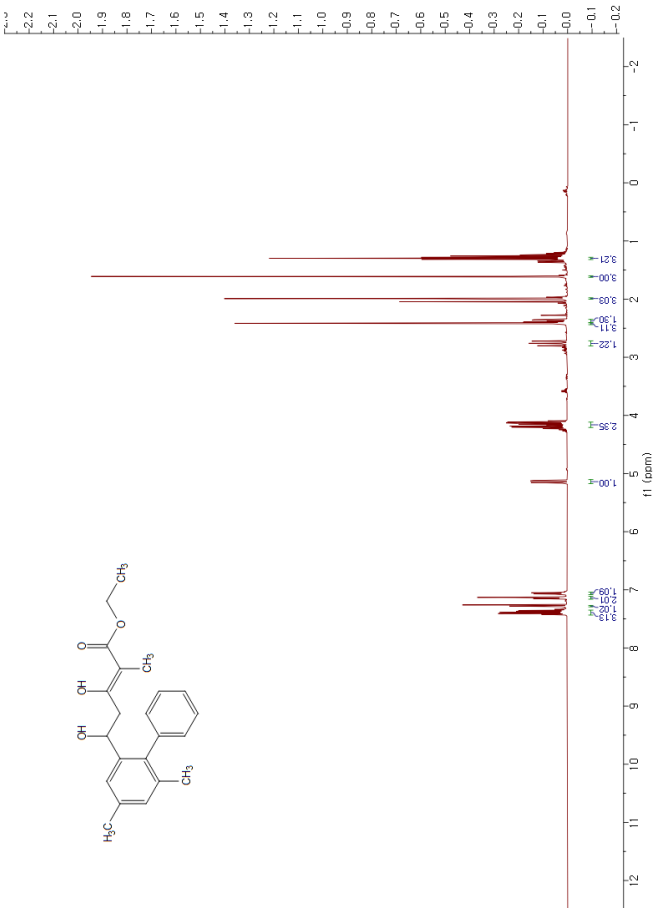
S36. ^{1}H NMR Data of Nigerapyrone B (11)



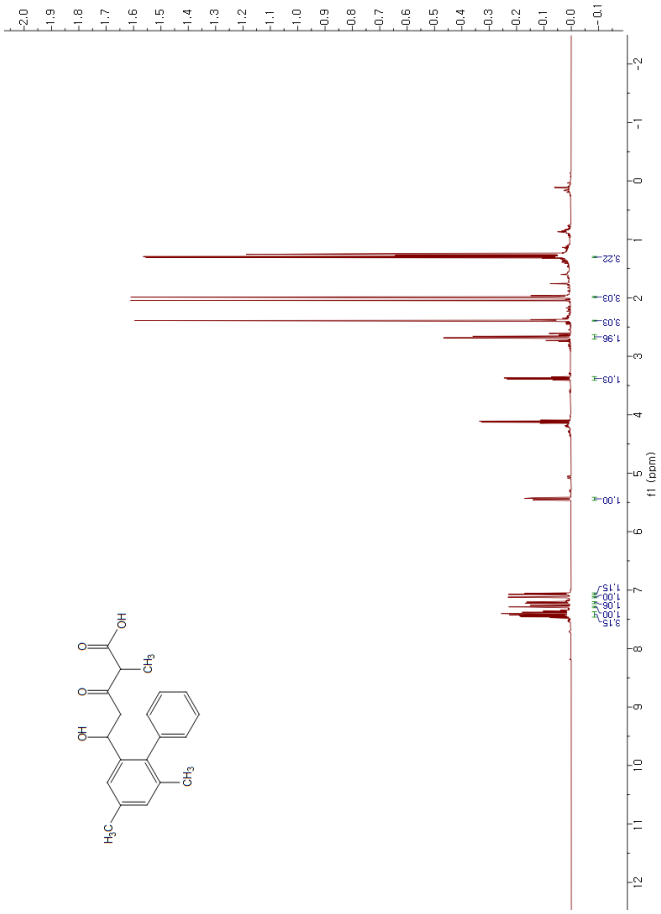
S37. ^{13}C NMR Data of Nigerapyrone B (11)



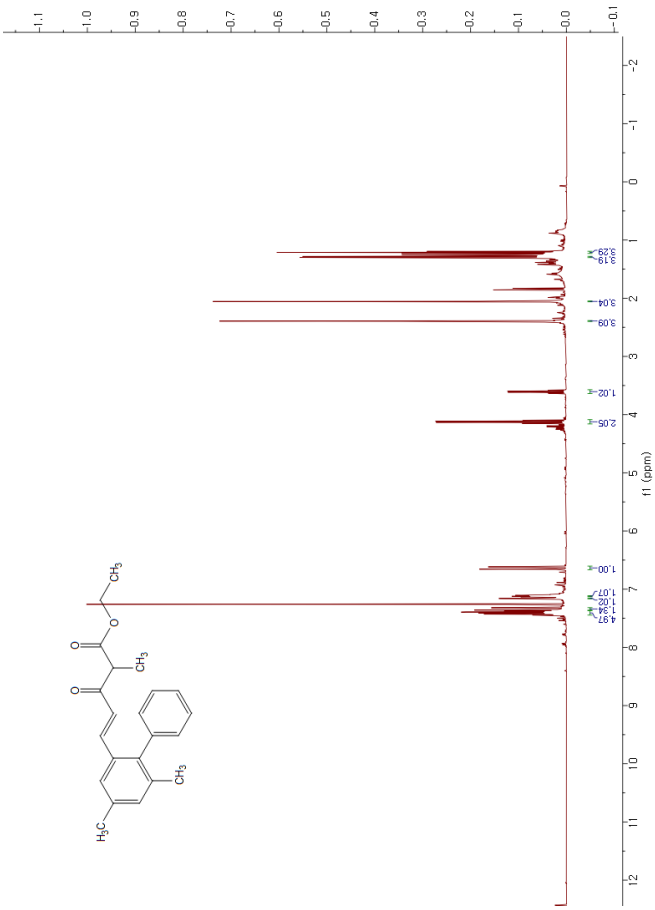
S38. ^{1}H NMR Data of ethyl (Z)-5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-3,5-dihydroxy-2-methylpent-2-enoate (12)



S39. ^{1}H NMR Data of 5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-5-hydroxy-2-methyl-3-oxopentanoic acid (13)



S40. ^{1}H NMR Data of ethyl (E)-5-(4,6-dimethyl-[1,1'-biphenyl]-2-yl)-2-methyl-3-oxopent-4-enoate (16)



초 록

비편재화된 π 전자를 가진 방향족 탄화수소인 아린은 다양한 물질의 구조적 전구체이다. 현재까지 다양한 방향족 합성법이 개발되었지만, 대부분이 위치선택성, 효율, 반응 조건에 한계가 있다. 이전 연구에서 우리는 위치 선택성과 효율이 높으며 온화하고 친환경적인 반응 조건에서 일어나는 고도로 치환된 아린 합성 방법을 새롭게 발견했다. 클라이젠 재배열, 설폭사이드 제거, 이성질화, 6π 전자고리화, 그리고 자기산화를 거치는 이 방법을 사용하면 단 2단계로 다이비닐카비놀로부터 다치환된 아린을 합성할 수 있다. 본 연구에서 이러한 염기를 매개로 한 연쇄 벤젠고리화 반응을 4개의 치환기를 가진 다이비닐카비놀에 적용하여 4개의 치환기를 가진 아린을 높은 수율로 얻을 수 있었다. 그러나 2개 또는 3개의 치환기를 가진 기질과 달리 트라이에날 합성 과정에서 사이클로헥사다이엔이 발견되었다. 자기산화를 위해서는 적절한 열과 염기가 필요하다고 판단하여 최적의 조건을 찾기 위해 노력할 것이다. 또한, 비대칭 디이비닐카비놀을 시작 물질로 사용하더라도 트라이에날 합성 산물로 한 종류의 위치이성질체만 얻을 수 있었다. 이것은 클라이젠 재배열이 입체 효과의 영향을 받는다는 것을 의미한다. 마지막으로, 우리의 새로운 합성법으로 합성된 아린으로 천연물인 Nigerapyrone B 합성을 시도했다. 첫 번째 방법으로 두 시작 물질을 더하는 전략을 사용하였고, 이 과정에서 원하는 다이키토 호변체 대신 원하지 않은 키토 이놀 호변체가 더 많이 생성되었다. 따라서 에틸 2-메틸아세토아세테이트로부터 직접 2 음이온 형태를 만들고 아린을 첨가하는 반응 방법으로 전략을 변경함으로써, 원하는 다이키토 호변이성질체를 더 많이 얻을 수 있었다. 최종적으로 총 4단계를 거쳐 Nigerapyrone B를 얻을 수 있었다.

주요어: poly-substituted arene, benzannulation, cyclohexadiene, auto-

oxidation, Claisen rearrangement, Nigerapyrone B

학 번: 2020-29438

Acknowledgment

벌써 2년이라는 시간이 지나 석사 과정을 마치게 되었습니다. 석사 생활을 하는 동안 저를 지지해주고 응원해주신 제 주위의 많은 분께 감사합니다.

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그리고 좋은 자극을 주며 일상에 생기를 불어넣어 주는 오랜 친구들 나연이, 선주, 우정이, 유정이, 은영이에게 고맙습니다.

마지막으로 저의 안식처, 사랑하는 우리 가족, 항상 따뜻한 격려를 해주시는 할머님, 언제나 제 선택을 존중해주시는 부모님, 누구보다 누나를 생각하는 마음이 큰 도현이에게도 감사 인사를 드립니다.

2년을 돌이켜보았을 때 주위 분들이 있어 많이 배웠고 석사 생활을 하는 데 있어 정말 큰 도움이 되었습니다. 이 은혜를 잊지 않고 밝은 에너지로 보답하겠습니다. 감사합니다.