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시클로펜타피론 조제를 위한 고리화 전략

Cyclization Strategy for the Preparation of Cyclopentapyrone

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A Dissertation for the Master of Science

Cyclization Strategy for the Preparation of Cyclopentapyrone

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이 논문을 농학석사학위논문으로 제출함

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Abstract

2-Pyrone is an aromatic heterocycle ubiquitous in natural products and known for its distinct character which exhibits chemical natures of both alkenes and arenes. With such features, 2-pyrone is a valuable precursor for its synthetic application is versatile. Among the derivatives of 2-pyrone, cyclopentapyrone, a pyrone to which cyclopentyl group is fused is a noteworthy scaffold. Not only its structure is at occasional presence in natural compounds, as progress in cycloaddition reactions of 2-pyrone has offered novel ways to synthesis of 6- and 8-membered ring system, employing cyclopentapyrone has shown its potential in rendering fused ring systems (e.g., 5-8 fused ring system). Previous synthetic pathways to cyclopentapyrone are limited to formation of pyrone next to already-existing 5-membered carbocycle not vice versa. While natural products with cyclopentapyrone moiety often features asymmetrically substituted 5-membered carbocycle, the conventional method, however restricts substituent control on the carbocycle, let alone introduction of stereogenic center on the ring. Cyclization from pyrone would resolve such issues that with appropriate substrates and opportune cyclization strategy, manipulation of substituents on the ring is feasible. Two cyclization methods, Nazarov reaction and rhodium-catalyzed hydroacylation, both of which well developed for building substituted 5-membered carbocycle and capable of asymmetric cyclization through which introduction of stereogenic centers are viable were studied for preparation of cyclopentapyrone from 2-pyrone. Attempts with Nazarov cyclization at mild conditions showed no sign of reaction while at harsh conditions, were met with either undesired 1,4-addition or decomposition probably due to electron-deficient nature of 2-pyrone. Upon investigations of rhodium-catalyzed hydroacylation, formation of cyclized ketone was not observed. However, an unexpected cyclized product has been

detected while in use of cationic rhodium catalyst. The product turned out to result from Prins cyclization owing to Lewis acid character of cationic rhodium catalyst. Further optimization on Prins cyclization revealed that combination of protic acid and molecular sieves produces relatively good yield. Although there is room for improvements in respect to yield and substrate scopes, it is anticipated that this method would provide synthetic ways for compounds involving cyclopentapyrone motif. Furthermore, future study employing chiral acid may pave the way for asymmetric cyclization for cyclopentapyrone.

Key words: cyclization, cyclopentapyrone, hydroacylation, Nazarov reaction, Prins reaction, 2-pyrone, rhodium catalysis

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List of Abbreviations

°C	degrees Celsius
^{13}C	carbon-13
^{1}H	proton
Å	Angstrom
Ac	acetyl
Ar	aryl
BAIB	(diacetoxyiodo)benzene
Bu	butyl
calcd	calculated
cm^{-1}	wave number
COSY	H-H correlation spectroscopy
d	day(s); doublet (spectral)
DCE	dichloroethane
dd	doublet of doublets (spectral)
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
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)
LA	Lewis Acid

M	molar
m	multiplet (spectral)
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
NBD	2,5-norbornadiene
NMO	4-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
Ph	phenyl
Pin	pinacol
ppm	parts per million
***p*TSA**	*para*-toluenesulfonic acid
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
t	tert; triplet (spectral)
TBAF	tetrabutylammonium fluoride
TEA	triethylamine
TES	triethylsilyl
THF	tetrahydrofuran
Tf	trifluoromethanesulfonate
TLC	thin layer chromatography
δ	chemical shift

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Introduction

Pyrone is a six-membered heterocycle bearing oxygen and ketone group in the ring. Depending on the relative positions of oxygen and ketone group, pyrone is classified to either 2-pyrone or 4-pyrone (Fig. 1A). 2-pyrone, in particular is well studied as its involvement in biosynthetic pathway intermediates and metabolites is prominent (Goel and Ram, 2009). With such features, its moiety is ubiquitous in animals (Kamano et al., 2002), plants (Deepak et al., 1996; Kupchan and Ognyanov, 1969), marine organisms (Biskupiak and Ireland, 1983; Nagai et al., 2002) and microorganisms (Collins and Halim, 1972; Kong et al., 2005) serving as a valuable precursor for natural compounds (Fig. 1B).

Along with the structural pervasiveness, 2-pyrone is known for unique character which exhibits physical and chemical natures of both alkenes and arenes (Wanninayake, 2016). As aromaticity of 2-pyrone can be shown when drawn in resonance form, 2-pyrone features weak aromaticity which is also distinguished by its chemical shifts (Fig. 2A; Goel and Ram, 2009). In fact, its aromatic potential has been observed as it smoothly undergoes electrophilic substitution such as nitration (W. Pirkle and M. Dines, 1969), sulfonation (Shusherina et al., 1961) and halogenation (W. H. Pirkle and M. B. Dines, 1969) (Fig. 2B). Aliphatic character, on the other hand, has been demonstrated through Diels-Alder (Afarinkia et al., 1992; Delaney et al., 2008; Nelson and Stoltz, 2008) and photocycloaddition reactions functioning as dienes and dienophiles (Takeshita, 1973; West et al., 1993). With such distinctive characters, 2-pyrone is a versatile chemical building block for its synthetic utility is broad. Furthermore, advances in synthetic methodologies for 2-pyrone has contributed to expansion of its applicability (Chaładaj et al., 2012; Hachiya

et al., 2003; Sheibani et al., 2004).

Among 2-pyrone-containing species, cyclopentapyrone, a pyrone to which cyclopentyl groups is fused is a noteworthy scaffold (Fig. 3A). Not only cyclopentapyrone moiety is at occasional presence in natural compounds (Fig. 3B; Jiang et al., 2008; Wang et al., 2017; Ye et al., 2013), as progress in cycloaddition of 2-pyrone has offered novel synthetic methods for 6- and 8-membered ring systems (Nelson and Stoltz, 2008; Zhao and Beaudry, 2014), employing cyclopentapyrone showed its competence in rendering fused ring systems (Khatri and Sieburth, 2015) that are prevalent in natural compounds (Fig. 5B).

Although synthetic pathways to cyclopentapyrone have been developed, they are limited to formation of pyrone next to 5-membered ring system not vice versa (Bonsignore et al., 1989; Güllük et al., 2006; Mandal and Jawalkar, 1989). In fact, introduction of any carbocycle fused to pyrone, from pyrone itself has not been reported to our knowledge. Most of the previous studies for preparation of cyclopentapyrone chose cyclopentanone as a starting material for its manipulation is facile and commercial availability is at advantage (Khatri and Sieburth, 2015; Song et al., 2006).

While natural compounds with cyclopentapyrone motif often exhibit substituents asymmetrically linked to the 5-membered ring system (Fig. 4B), use of cyclopentanone as a starting material, however restricts substituents control on the ring and makes introduction of stereogenic center on the ring challenging which is also an issue with regard to synthesis of natural compounds containing fused ring systems that could be derived from cyclopentapyrone (Fig. 5B).

Cyclization from pyrone, however is anticipated to resolve such

problems that by preparing an appropriate substrate and selecting an opportune cyclization method, introduction of substituents with enantioselectivity on newly formed 5-membered carbocycle could be accomplished. Thus, two cyclization methods a) Nazarov reaction and b) Rhodium catalyzed hydroacylation, both of which well developed for building 5-membered ring system and capable of delivering stereogenic center were explored in attempts to manipulate substituents on cyclopentapyrone.

Nazarov reaction, also known as Nazarov cyclization is one of the most studied and widely used methods to prepare 5-membered carbocycle (Vinogradov et al., 2017). Reported by Nikolaevich Nazarov (1951), it represents a transformation of divinyl ketones into cyclopentenone catalyzed by Brønsted or Lewis acids (Fig. 6A).

As mechanism shown in Fig. 6B, upon activation of cross-conjugated ketone by acid, oxypentadienyl cation intermediate is formed which then undergoes thermally allowed 4π electrocyclization in which stereogenic centers are determined on two bond-forming carbons depending on the direction of the rotation. While one of the two stereogenic centers is removed by subsequent elimination, the other stereocenter is maintained throughout the end of the reaction at which cyclopentenone is formed upon tautomerization. Combination of Lewis acid and chiral ligand (Aggarwal and Belfield, 2003; Cao et al., 2010) or employing chiral Bronsted acid (Rueping et al., 2007) upon Nazarov reaction cyclization has facilitated control of torquoselectivity through which stereoselective rendering of substituents on the ring is realized (Fig. 7).

While pyrone exhibits weak aromaticity, which may hamper participation in Nazarov cyclization, previous studies on reactions involving benzene (Marcus et al., 2008) and other aromatic heterocycles dispelled such

concern (Malona et al., 2006). In introducing stereogenic center through Nazarov cyclization, there may arise a problem during the elimination process at which one of the two stereogenic centers can be removed without selectivity. In case of pyrone, however, we envisioned that aromatic character of pyrone would lead to selective elimination on pyrone due to demand for aromaticity as in cases of previous studies of Nazarov reaction involving arene (Malona et al., 2006; Marcus et al., 2008). Thus, in regard to forming 5-membered carbocycle fused to pyrone, we envisaged that Nazarov cyclization could deliver substituted 5-membered ring system, with chiral environment, in stereoselective way.

Hydroacylation is an addition of a formyl C-H bond across an olefin to generate a ketone (Hartwig, 2010). With ethylene and aldehyde in a chain, intramolecular hydroacylation can serve as a valuable route to carbocycle (Fig. 8A). Due to progress in identification and development of new catalysts, intramolecular hydroacylation reaction has become well-established methods exhibiting wide substrate scopes and synthetic utility (Ghosh et al., 2016).

Hydroacylation can be accomplished using N-heterocyclic carbenes (Janssen-Müller et al., 2015), photocatalysts (Chudasama et al., 2010) or most frequently transition metals including rhodium, cobalt, ruthenium. Among the transition metal catalysts, rhodium is well developed and has proven its synthetic utility (Willis, 2010).

First reported by Sakai and co-workers (1972), catalytic cycle of rhodium catalyzed intramolecular hydroacylation begins with oxidative addition of rhodium(I) into aldehyde C-H bond (Fig. 8B). Formed acyl rhodium hydride intermediate then undergoes coordination with olefin followed by migratory insertion. Reductive elimination finally delivers the ketone product

accompanied by regeneration of rhodium (I). However, a competitive decarbonylative pathway also takes a place from acyl rhodium hydride intermediate which results in irreversible decomposition. This competitive side reaction has been overcome by using cationic rhodium complexes with biphosphine ligand (Fairlie and Bosnich, 1988). Furthermore, use of cationic rhodium in combination with appropriate chiral ligands has provided ways for enantioselective hydroacylation (Barnhart et al., 1997; Barnhart et al., 1994; Kundu et al., 2005). Congruent with our plans to utilize asymmetrically substituted carbocycle, hydroacylation of pyrone in efforts to introduce 5-membered ring system was investigated.

Materials and Methods

General Information

All reactions were carried out under argon, unless otherwise noted. Solvents were distilled before use: tetrahydrofuran from sodium metal, methylene chloride from calcium hydride. Transfer of anhydrous solvents were accomplished 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 as supplied unless otherwise stated. Analytical thin-layer chromatography (TLC) was carried out using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash column chromatography was performed using 40-63 μm Silica gel 60 (Merck). ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz or 600 MHz on Bruker AV VIII 400 or 600 spectrometers and coupling constants (*J*) are reported in Hertz (Hz). FT-IR spectra were obtained on Thermo Scientific Nicolet 6700 and are reported in frequency of the absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on an AB SCIEX Q-TOF 5600 mass spectrometer. Melting points were determined on A. KRÜSS OPTRONIC M3000.

Preparation of Pyrone E (Fig. 10)

4-methoxy-6-methyl-2H-pyran-2-one (45):

To stirred mixture of triacetic acid lactone (10.0 g, 79.3 mmol, 1.00 equiv) and, anhydrous K_2CO_3 (27.4 g, 198 mmol, 2.50 equiv) in acetone (200 mL), dimethyl sulfate (12.0 g, 95.2 mmol, 1.20 equiv) was added. The reaction

mixture was stirred at room temperature for 8 h. It was then filtered to remove remaining base and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc, 2:8) afforded pyrone **45** (9.66 g, 68.9 mmol, 86.9 %) as a white solid. The spectral data were in accordance to the reported one (Clarke and McGlacken, 2015).

(E)-4-methoxy-6-styryl-2H-pyran-2-one (46):

Under argon, oven-dried magnesium turnings (5.14 g, 178 mmol, 2.50 equiv) and methanol (130 mL) in flame-dried two-neck flask equipped with reflux condenser were stirred at room temperature. Catalytic amount of iodine was added to facilitate dissolution of the magnesium. The mixture was stirred until the metal fully dissolved. Pyrone **45** (10.0 g, 71.4 mmol, 1.00 equiv) and benzaldehyde (9.09 g, 85.6 mmol, 1.20 equiv) were then added to the mixture which was heated to 80 °C. After 2h, the reaction mixture was cooled to room temperature to which was added acetic acid (100 mL) and water (400 mL). The mixture was extracted with CH_2Cl_2 (300 mL × 3). The combined organic layers were washed with brine and dried under reduced pressure to afford a yellow solid. Recrystallization from methanol gave pyrone **46** (9.25 g, 40.5 mmol, 56.7%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 – 7.47 (m, 3H), 7.42 – 7.29 (m, 3H), 6.58 (d, J = 16.0 Hz, 1H), 5.95 (d, J = 2.1 Hz, 1H), 5.50 (d, J = 2.2 Hz, 1H), 3.83 (s, 3H).

6-(1,2-dihydroxy-2-phenylethyl)-4-methoxy-2H-pyran-2-one (47):

To a stirring solution of pyrone **46** (9.00 g, 39.4 mmol, 1.00 equiv), NMO (5.56 g, 47.3 mmol, 1.20 equiv) and citric acid monohydrate (16.6 g, 78.8 mmol, 2.00 equiv) in *t*-BuOH/H_2O (200 mL/200 mL) was added $K_2OsO_4 \cdot 2H_2O$ (288 mg,

0.792 mmol, 0.02 equiv). After 2 h, the mixture was diluted with H_2O/brine (150 mL/150 mL) which was then extracted with ethyl acetate (300 mL × 3). The combined organic layers were washed with saturated $Na_2S_2O_3$ aqueous solution (400 mL), dried with brine and Na_2SO_4. The filtrate was then concentrated under reduced pressure to afford a white solid which was used without further purification step.

4-methoxy-2-oxo-2H-pyran-6-carbaldehyde (48):

A mixture of crude pyrone **C** from the previous step and BAIB (14.0 g, 43.4 mmol, 1.10 equiv) in CH_2Cl_2 was stirred vigorously for 2 h. The mixture was then dried under reduced pressure and washed with hexane/ether (8:2) which afforded pyrone **48** (4.23 g, 27.4 mmol, 70.0%, two steps) as a white solid. The spectral data were in accordance to the reported one (Rizzo and Trauner, 2018).

6-(1-hydroxybut-2-en-1-yl)-4-methoxy-2H-pyran-2-one (49):

To a solution of pyrone **48** (1.00 g, 6.49 mmol, 1.00 equiv) in THF (45 mL) at 0 °C was added 1-propenyl magnesium bromide 0.05 M tetrahydrofuran solution (19.5 mL, 9.73 mmol, 1.50 equiv) dropwise using dropping funnel. After the resultant mixture was stirred at 0 °C for 2 h, saturated NH_4Cl aqueous solution (30 mL) was added. The mixture was extracted with CH_2Cl_2 (100 mL × 3). The combined organic phases were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2:EtOAc, 8:2) afforded inseparable mixture of E/Z isomers of pyrone **49** (452 mg, 2.30 mmol, 35.4%) as a yellow oil: R_f 0.36 (CH_2Cl_2:EtOAc, 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.11 (dd, J = 2.3, 1.1 Hz, 1H), 5.92 – 5.73 (m, 1H), 5.60 – 5.43 (m, 1H), 5.40 (p, J = 2.1 Hz, 1H), 5.25 –

4.76 (m, 1H), 3.78 (t, J = 1.7 Hz, 3H), 1.78 – 1.69 (m, 3H).

(E)-6-(but-2-enoyl)-4-methoxy-2H-pyran-2-one (50):

To a solution of E/Z mixtures of pyrone **49** (452 mg, 2.30 mmol, 1.00 equiv) in CH_2Cl_2 (50 mL) was added manganese dioxide (4.00 g, 46.1 mmol, 20.0 equiv) at room temperature. After the resultant mixture was stirred at room temperature for 12 h, manganese dioxide was removed by filtration through a short plug of Celite. The filter cake was thoroughly washed with CH_2Cl_2 (200 mL) and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (hexane:EtOAc, 7:3) afforded pyrone **50** (344 mg, 1.77 mmol, 77.0%) as a yellow solid: R_f 0.25 (hexane:EtOAc, 7:3); mp 154.3-156.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 – 7.18 (m, 1H), 7.01 (ddq, J = 15.4, 3.0, 1.7 Hz, 1H), 6.81 – 6.79 (m, 1H), 5.69 (d, J = 2.3 Hz, 1H), 3.84 (d, J = 1.7 Hz, 3H), 2.00 – 1.95 (m, 3H); HRMS $[M+H]^+$ for $C_{10}H_9O_4^+$ calcd. 195.0652, found: m/z 195.0650

General Procedures for Nazarov Reactions of Pyrone F (Table 1)

To a solution of pyrone **50** (10 mg, 0.05 mmol, 1.00 equiv) in indicated solvent (3 mL) was added Lewis acid (0.05 mmol 1.00 equiv) which was heated to the given temperature. At the completion of the reaction upon monitoring by TLC analysis, the mixture was quenched by saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate (20 mL × 3). The combined organic phases were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure and purified using flash column chromatography.

Preparation of Pyrone 61 (Fig. 11)

3-acetyl-5-bromo-6-ethyl-4-methoxy-2H-pyran-2-one (Pyrone 53):

To a solution of dehydroacetic acid (18.0 g, 107 mmol, 1.00 equiv) in chloroform (300 mL) was added Br_2 (42.8 g, 268 mmol, 2.50 equiv) and I_2 (543 mg, 2.14 mmol, 0.02 equiv) at 0 °C. After the mixture was stirred at 10 °C for 5 days, excess bromine was quenched by the addition of 5% sodium bisulfite aqueous solution (400 mL). The mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The filtrate was then concentrated under reduced pressure. Recrystallization from methanol afforded pyrone **53** (15.7 g, 63.4 mmol, 59.2%) as a white solid. The spectral data were in accordance to the reported one (Harris et al., 1970).

5-bromo-4-hydroxy-6-methyl-2H-pyran-2-one (54):

A stirred mixture of the pyrone **53** (5.00 g, 20.2 mmol) and 90% sulfuric acid (15 g) was heated at 130 °C for 25 min. The mixture was then slowly poured onto ice-water (50 mL) using glass syringe. The formed precipitate was filtered, washed with cold water (200 mL) thoroughly, and dried under vacuum. The crude product **54** was used for the next step without further purification.

5-bromo-6-ethyl-4-methoxy-2H-pyran-2-one (55):

To stirred mixture of crude pyrone **54**, anhydrous K_2CO_3 (10.8 g, 78.3 mmol, 5.00 equiv) and butanone (70 mL) heated at 50 °C for 10 minutes, dimethyl sulfate (2.37 g, 18.8 mmol, 1.20 equiv) was added. The resultant mixture was heated at reflux at 80 °C for 8 h. The reaction mixture was cooled to room temperature and filtered to remove the remaining base. The filtrate was then

concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc, 8:2) afforded pyrone **55** (2.30 g, 10.5 mmol, 52.0%, 2 steps) as a white solid. The spectral data were in accordance to the reported one (March et al., 1984).

5-bromo-6-(bromomethyl)-4-methoxy-2H-pyran-2-one (56):

A stirred mixture of pyrone **55** (8.66 g, 39.5 mmol, 1.00 equiv), *N*-bromosuccinimide (9.14 g, 51.4 mmol, 1.30 equiv) and benzoyl peroxide (480 mg, 1.98 mmol, 0.05 equiv) in chloroform (300 mL) was heated at reflux at 70 °C for 24 h. The reaction mixture was cooled to room temperature, filtered to remove excess *N*-bromosuccinimide and then washed with 1 N NaOH aqueous solution (150 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by recrystallization from ethanol afforded pyrone **56** (8.93 g, 30.0 mmol, 75.9%) as a yellow solid. The spectral data were in accordance to the reported one (De March et al., 1985).

5-bromo-6-(hydroxymethyl)-4-methoxy-2H-pyran-2-one (57):

A mixture of pyrone **56** (1.35 g, 4.53 mmol), silica-gel (67 g) and CH_2Cl_2 (100 mL) was evaporated to dryness under reduced pressure. To the mixture was added water (185 mL) and the resultant mixture was stirred vigorously at reflux at 110 °C for 18 h. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (3 × 200 mL) throughly. The combined organic phases were washed with brine (250 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product **57** was used for the next step

without further purification process.

5-bromo-4-methoxy-6-((triethylsilyl)methyl)-2H-pyran-2-one (58):

To stirred mixture of crude pyrone **57**, triethylamine (1.38 g, 13.6 mmol, 3.00 equiv) in CH_2Cl_2 (50 mL) was added chlorotriethylsilane (1.37 g, 9.06 mmol, 1.50 equiv), and the resultant mixture was stirred at room temperature. After 18 h, the aqueous saturated sodium bicarbonate solution (50 mL) was added to the reaction mixture. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane:EtOAc, 5:1) afforded pyrone **58** (1.14 g, 3.26 mmol, 72.0 %) as a white solid: R_f 0.51 (hexane:EtOAc, 7:3); IR (cast film) 3393, 3074, 2954, 2876, 1724, 1562, 1399, 1264, 1038, 1007, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.54 (s, 1H), 4.64 (s, 2H), 3.89 (s, 3H), 1.01 – 0.95 (m, 9H), 0.67 (qd, J = 7.9, 0.7 Hz, 6H); HRMS $[M+H]^+$ for $C_{13}H_{22BrO_4Si^+}$ calcd. 349.0465, found: m/z 349.0464.

6-(hydroxymethyl)-4-methoxy-5-(prop-1-en-2-yl)-2H-pyran-2-one (59):

A solution of pyrone **58** (1.27 g, 3.64 mmol, 1.00 equiv), isopropenylboronic acid pinacol ester (924 mg, 5.50 mmol, 1.20 equiv) in tetrahydrofuran/water (40 mL/1 mL)) was added a solution of $Pd(dppf)Cl_2$ (266 mg, 0.364 mmol, 0.01 mol) in 5 mL of THF and anhydrous potassium carbonate (1.50 g, 10.8 mmol, 3.00 equiv) at room temperature. The resultant mixture was heated at reflux at 70 °C. After 24 h, the reaction mixture was cooled to room temperature and washed with saturated $NaHCO_3$ aqueous solution. The aqueous layer was

extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give black oil. Purification by flash column chromatography (hexane:EtOAc, 5:1) afforded pyrone **59** (882 mg, 2.84 mmol, 78.0%) as a white solid: R_f 0.46 (hexane:EtOAc, 7:3); IR (cast film) 1264, 896, 731, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.51 (s, 1H), 5.26 (p, *J* = 1.6 Hz, 1H), 4.95 (dd, *J* = 2.0, 1.0 Hz, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 1.93 (t, *J* = 1.2 Hz, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 166.58, 162.41, 159.43, 97.33, 89.82, 89.59, 61.74, 61.35, 57.28, 57.16, 6.78, 4.50; HRMS $[M+H]^+$ for $C_{16}H_{27}O_4Si^+$ calcd. 311.1673, found: m/z 311.1670.

6-(hydroxymethyl)-4-methoxy-5-(prop-1-en-2-yl)-2H-pyran-2-one (60):

To stirred mixture of pyrone **59** (944 mg, 3.04 mmol, 1.00 equiv) in tetrahydrofuran (25 mL) was added tetrabutylammonium fluoride 1.0 M tetrahydrofuran solution (3.65 mL, 3.65 mmol, 1.20 equiv) at 0 ℃. The resultant mixture was stirred at room temperature. After 30 min, the aqueous saturated NH_4Cl solution (20 mL) was added to the reaction mixture. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with Brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product **60** was used for the next step without further purification.

4-methoxy-2-oxo-5-(prop-1-en-2-yl)-2H-pyran-6-carbaldehyde (61):

To a solution of pyrone **60** in CH_2Cl_2 (25 mL) was added manganese dioxide (5.29 g, 60.8 mmol, 20.0 equiv) at room temperature. After the resultant mixture

was stirred at room temperature for 80 min, manganese dioxide was removed by filtration through a short plug of Celite. The filter cake was thoroughly washed with CH_2Cl_2 (100 mL) and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexane;EtOAc, 2:1) afforded pyrone **61** (364 mg, 1.87 mmol, 61.7%, 2 steps) as a pale yellow solid: R_f 0.46 (hexane:EtOAc, 7:3); mp 114.1-115.7 °C; IR (cast film) 2964, 2926, 1711, 1683, 1242, 969, 944, 928, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.73 (s, 1H), 5.78 (s, 1H), 5.50 (s, 1H), 5.11 (s, 1H), 3.89 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 181.94, 181.92, 168.22, 160.82, 149.25, 133.65, 128.37, 122.85, 95.03, 56.94, 56.38, 23.60; HRMS $[M+H]^+$ for $C_{10}H_{11}O_4^+$ calcd. 195.0652, found: m/z 195.0650.

General Procedures for Rhodium-Catalyzed Hydroacylation of Pyrone 61 (Table 3)

All solvents were degassed and purged with argon prior to use. To a solution of rhodium catalyst in indicated solvent, (If needed, hydrogen balloon was equipped and purged. Upon hydrogen activation, change in color of the reaction mixture was observed.) pyrone **61** was added and the reaction was monitored by TLC analysis. After completion of the reaction, the mixture was dried under reduced pressure and purified with flash column chromatography.

7-hydroxy-4-methoxy-5-methylene-6,7-dihydrocyclopenta[b]pyran-2(5H)-one (64)

To a solution of pyrone **61** (25.0 mg, 0.129 mmol, 1.00 equiv) and activated 4 Å molecular sieves in CH_2Cl_2 (3 mL) at 0 °C, *p*-toluenesulfonic acid monohydrate (11 g, 0.0645 mmol, 0.50 equiv) was added. The resultant mixture

was stirred at 0° for 45 min. Saturated NH_4Cl aqueous solution (10) was added and the mixture was extracted with ethyl acetate (15 mL × 3), washed with Brine (10 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Purification upon flash column chromatography (hexane:EtOAc, 5:5) afforded Pyrone **64** (13.5 mg, 0.0695 mmol, 54.0%) as a white solid: R_f 0.35 (hexane:EtOAc, 5:5); mp 179.6-181.7 °C; IR (cast film) 3342, 3080, 2956, 2922, 2853, 1692, 1562, 1502, 1266, 1042, 870, 840 cm^{-1}; ^1H NMR (DMSO-d6, 400 MHz): δ 5.68 (s, 1H), 5.44 (td, *J* = 2.2, 1.1 Hz, 1H), 4.92 (q, *J* = 1.7 Hz, 1H), 3.91 (s, 3H), 3.00 (ddt, *J* = 16.6, 7.8, 1.9 Hz, 1H), 2.38 (ddt, *J* = 16.5, 3.4, 2.1 Hz, 1H); ^{13}C NMR (DMSO, 151 MHz) δ 169.29, 168.60, 163.48, 139.79, 112.05, 106.24, 88.38, 68.66, 56.84, 39.03; HRMS $[M+H]^+$ for $C_{10}H_{11}O_4^+$ calcd. 195.0652, found: m/z 195.0650.

Results and Discussion

Preparation of Pyrone 50 (Fig. 10)

In order to prepare appropriate substrates for Nazarov reaction, triacetic acid lactone was chosen as a starting compound for its commercial availability and frequent uses in organic synthesis. Triacetic acid lactone underwent facile methylation with dimethyl sulfate as a methylating agent. Owing to distinct difference between triacetic acid lactone and pyrone **45** in polarity, short column chromatography purification could be carried out even with gram scale. With pyrone **45** in hand, oxidation of methyl group at C-6 was explored. Initial attempts using selenium dioxide and potassium permanganates were accompanied by degradation of the starting compound probably due to oxidative decomposition. We then turned to alternative strategy that would involve condensation followed by oxidative cleavage. Following Rizzo and Trauner's work (2018), pyrone **45** underwent smooth condensation with benzaldehyde to produce pyrone **46**. Subsequent oxidative cleavage using osmium tetroxide and BAIB afforded pyrone **48**. Pyrone **48** was then treated with 2-methylvinyl magnesium bromide which gave an inseparable mixture of E/Z isomers of pyrone **49** in poor yield. Unfortunately, efforts to improve the yield such as increasing Grignard reagent or using 1,4-dioxane as a boosting reagent were met with failure. Upon treatment with manganese dioxide of E/Z mixtures of pyrone **49** for allylic oxidation, exclusively pyrone **50** in E form, probably due to more stable radical intermediate, was obtained negating the need for separation of isomers in the previous step. With pyrone **50** in hand, introducing 5-membered carbocycle next to pyrone using Nazarov cyclization was investigated.

Nazarov Reaction (Table 1)

Our studies on Lewis acid catalyzed Nazarov cyclization of pyrone began by examining the reaction of pyrone **50** with strong Lewis acids such as $AlCl_3$ or $BF_3{\cdot}Et_2O$. Reactions at low temperature or room temperature in dichloromethane resulted in no reaction (entries 1-4). In demand of higher temperature, solvent with higher boiling point was employed. Use of chloroform resulted in either no reaction or decomposition (entries 7-8). Upon treatment with $AlCl_3$ in acetonitrile at 80 ℃, pyrone **50** produced many products but none of which turned out to be the desired product (entry 9). Use of boron $BF_3{\cdot}Et_2O$, on the other hand, yielded 1,4-addition product which was distinguished by absence of vinyl proton next to carbonyl group (entry 10). Most probable nucleophilic source is acetonitrile as its nucleophilicity has been shown (Che et al., 2020; Kumagai et al., 2004). Seeking for solvent that could withstand sufficient thermal condition without nucleophilicity, toluene was selected as its uses in Nazarov cyclization of benzene have been studied (Marcus et al., 2008). Both $AlCl_3$ and $BF_3{\cdot}Et_2O$ resulted in formation of many compounds (entries 11-12). Nonetheless, the formation of the desired carbocycle was not observed. Treating with relatively weak Lewis acid, $Dy(OTf)_3$ which is often in use for other pericyclic reaction, for example Piancatelli rearrangement (Fisher et al., 2014; Palmer and Read de Alaniz, 2013), showed no sign of reaction (entry 13). Use of ferric chloride whose Lewis acidity is in between, delivered 1-4 addition product showing toluene's potential as a Michael donor (entry 14). In need of solvent with weaker nucleophilicity and higher boiling point, chlorobenzene, whose electron withdrawing group would suppress nucleophilic addition, was employed. A combination of $Cu(OTf)_2$ and chlorobenzene, however, produced 1,4-addition

product while use of $AlCl_3$ and $BF_3 \cdot Et_2O$ resulted in decomposition and formation of undistinguishable products respectively (entries 15-17). Uses of 1,2-dichlorobenzene as a solvent for even higher temperature were all met by decomposition (entries 18-19). Upon failure with Lewis acids, conditions with Brønsted acids were examined of which, sulfuric acid and hydrochloric acid turned out to be ineffective (entries 20-22). We reasoned that the result is attributed to electron deficient nature of 2-pyrone (Goel and Ram, 2009) which is in stark contrast to polarized divinyl ketones that underwent smooth Nazarov reaction under milder conditions (He et al., 2003). However, due to difficulty in manipulating pyrone substrate to polarized one, another cyclization method, rhodium-catalyzed hydroacylation was studied as an alternative.

Retrosynthetic Analysis of Pyrone 61 (Fig. 11)

For Rhodium-catalyzed hydroacylation, pyrone **61** was targeted as a key substrate. In preparation for pyrone **61**, we reasoned that oxidation toward aldehyde would best be proceeded at a last stage considering its stability. We then targeted pyrone **60** using Suzuki coupling through which isopropenyl group would be linked to C-5 position. The alcohol **57** was readily accessible from Pyrone **55** (De March et al., 1985). Since bromination of triacetic acid lactone results in 2,5-dibromo compound, in preparation for pyrone **55**, dehydroacetic acid was used instead in which acetyl group in C-5 position prevents unwanted C-2 bromination (Harris et al., 1970).

Preparation of Pyrone 61 (Fig. 12)

Dehydroacetic acid, upon treatment with bromine, underwent facile bromination at C-5 position. Although Harris et al., (1970) proceeded

bromination at 5 ℃ for days, reaction at 10-15 ℃ resulted in improved yield compared to the previous result. Following March et al., (1984), deacetylation under sulfuric acid delivered poor yield of pyrone **54** in irreproducible manner. Reaction time control was critical as decomposition or insufficient conversion would take place within minutes. Therefore, sand bath was not a suitable heating medium due to its low heat conductivity. Though deacetylation in oil bath showed improved reproducibility, efforts to improve the yield were unsuccessful. A dramatic loss was noticed upon recrystallization process compared to the filtered crude product. We then postulated that subsequent methylation reaction without recrystallization would preserve from such loss. Omission of recrystallization process was indeed effective in increasing the overall yield. While two separate steps delivered pyrone **55** with yield close to 20%, methylation of crude pyrone **54** furnished pyrone **55** with overall yield over 50%. However, there was an issue with purification process that though sublimation could be implemented for preparation of pyrone **55** from clean pyrone **54**, as for the case of methylating crude pyrone **54**, column chromatography was essential as sublimation resulted in contaminated product. For decagram scale was not manageable with column chromatography, subsequent radical bromination with the contaminated pyrone **55** was attempted but met with low conversion. We speculated that the low conversion was due to the remaining impurities interfering with the reaction. Pyrone **55** purified with column chromatography smoothly provided brominated pyrone **56** under the identical condition (De March et al., 1985). Upon treatment with silica-gel and water at reflux, bromide **56** was successfully converted to alcohol **57**.

With the alcohol **57** in hand, Suzuki coupling step to introduce isopropenyl group at C-5 position were investigated (Table 2). The reaction was

attempted under various conditions that were effective for coupling to 5-bromopyrone in the previous studies (Afarinkia and Berna-Canovas, 2000; Afarinkia and Vinader, 2004; Palani et al., 2019; Ryu et al., 2004), but resulted in either decomposition of the starting compound or trace amount of desired product. Upon trials of Suzuki coupling with pyrone **55**, relatively higher yield was obtained (entries 7, 8). We then reasoned that presence of hydroxyl group was the cause of the such result and tried to address this issue by changing the reaction sequence in which oxidation of pyrone **57** takes place prior to Suzuki coupling reaction. Allylic oxidation of pyrone **57** using excess manganese dioxide furnished the aldehyde **57a** without any side product. Suzuki coupling to the aldehyde, however, failed to give the desired product (entries 13-16). An alternative strategy to rule out the hydroxyl group in the coupling reaction was to use a protecting group. Triethylsilyl group was considered ideal as an alcohol protecting group for its stability to weak base and facile cleavage (Lalonde and Chan, 1985). Following protection of the alcohol by triethylsilyl group, condition developed by (Palani et al., 2019) finally gave coupled pyrone **59** (entry 20) in good yield. Deprotection of silyl group with tetrabutylammonium fluoride followed by allylic oxidation using manganese dioxide finally delivered the key substrate, pyrone **61**.

Rhodium Catalyzed Hydroacylation (Table 3)

Investigations with rhodium catalyzed hydroacylation of pyrone began with Wilkinson's catalyst as it was the most accessible one. Upon hydrogen activation, treating pyrone **61** with Wilkinson's catalyst yielded pyrone **62** and pyrone **63** (entry 1), both of which were reduced products of pyrone **61** corresponding to the previous studies showing reducing ability of Wilkinson's

catalyst (Daniel et al., 1988; Nelson et al., 2005; Ohta et al., 1999). In attempt to circumvent the undesired hydrogenation, the reaction without hydrogen activation was carried out. Omission of hydrogen activation, however, only resulted in less conversion in reduction (entry 2). Treatment with another rhodium catalyst, $Rh(NBD)_2BF_4$ with dppb as a ligand, surprisingly gave pyrone **64** (entry 4). On tracking course of this unexpected cyclization, we noticed a bond formation between the aldehyde and the olefin in the isopropenyl group. Upon comparison between Wilkinson's catalyst and $Rh(NBD)_2BF_4$, we speculated that cationic character of rhodium in $Rh(NBD)_2BF_4$ could serve as a Lewis acid which may activate aldehyde for the bond formation. To verify whether the reaction was Lewis acid-mediated cyclization, pyrone **61** was exposed to $Sc(OTf)_3$ which delivered the identical product, pyrone **64**. Having confirmed that the cyclization was catalyzed by Lewis acid, we figured that Prins reaction has taken place (Arundale and Mikeska, 1952; Basak and Mal, 2016; Crane and Scheidt, 2010; Han et al., 2013) as similar cases of Prins type cyclization taking place during rhodium catalyzed hydroacylation conditions have been reported (Rastelli et al., 2016; Zhang et al., 2020). The proposed mechanism is shown in Fig. 13. Though rhodium catalyst failed to give hydroacylated ketone, we were pleased with the result as it provided a new way for formation of 5-membered ring system fused to pyrone.

Prins Cyclization (Table 4)

Having established a route to carbocycle next to pyrone, conditions for Lewis acid-catalyzed Prins reaction were investigated. Upon exploring reaction conditions using $Sc(OTf)_3$, precise reaction time control and appropriate selection of reaction temperature turned out to be critical (entries 1-4). TLC

analysis revealed that the formed product underwent decomposition in presence of remaining Lewis acid and the results were often irreproducible probably due to this following decomposition. In attempts to instantly deactivate remaining Lewis acid, various quenching methods were investigated of which, adding ammonium chloride aqueous solution to the reaction mixture proved to be most effective upon monitoring by TLC analysis. Use of other Lewis acids showed that weak Lewis acids could serve its purpose fully and we postulated that employing weaker Lewis acid would alleviate decomposition of the desired product. In fact, when compared to using strong Lewis acids such as $BF_3 \cdot Et_2O$ which gave poor yield (entry 5), relatively weaker Lewis acid, $Dy(OTf)_3$ furnished a moderate yield (entry 8). However, employing Brønsted acid such as *p*TSA monohydrate in presence of molecular sieves showed the best yield with reproducibility (entry 10).

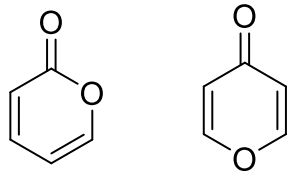
Future Direction

Although elaboration of cyclopentapyrone from pyrone has been reached via Prins reaction, there is much room for improvement in respect to yield and substrate scopes. Efforts will be made on further optimization to increase yield and to expand substrate scopes. With regard to introducing a stereogenic center to the carbocycle, Asymmetric cyclization employing chiral acids could be attempted (Liu et al., 2016; Liu et al., 2015; Tsui et al., 2015).

Figure and Table

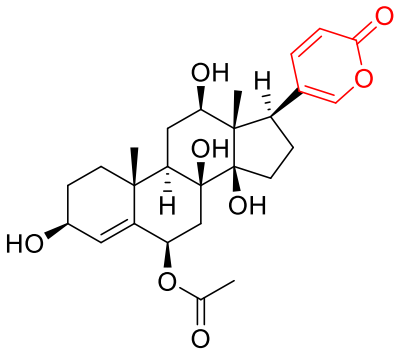
Figure 1. Pyrones and Examples of Natural Compounds with 2-pyrone Functionality

A. Different pyrone ring systems

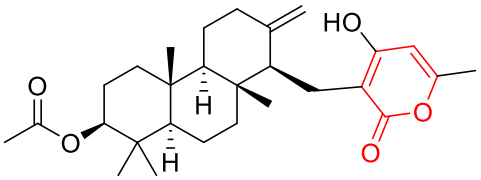


2-pyrone (**1**) 4-pyrone (**2**)

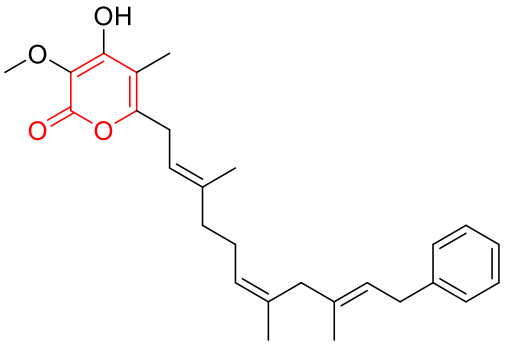
B. 2-Pyrone as a component of natural products



12β-Hydroxyscillirosidin (**3**)



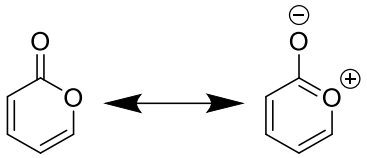
Aszonapyrone A (**4**)



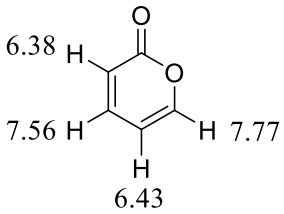
Lehualide A (**5**)

Figure 2. Aromatic and Aliphatic Characters of Pyrone

A. Aromatic Features of 2-Pyrone

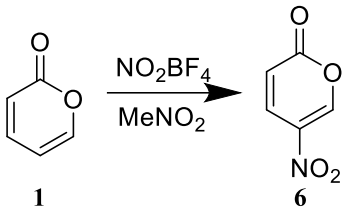


Resonance Form of 2-Pyrone

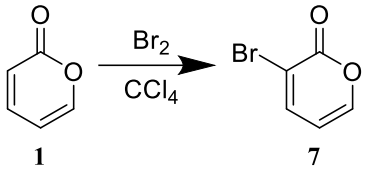


Chemical Shifts of 2-Pyrone

B. Reactions Exhibiting Aromatic Potentials of 2-Pyrone

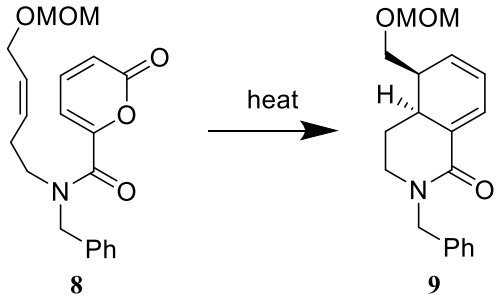


Nitration

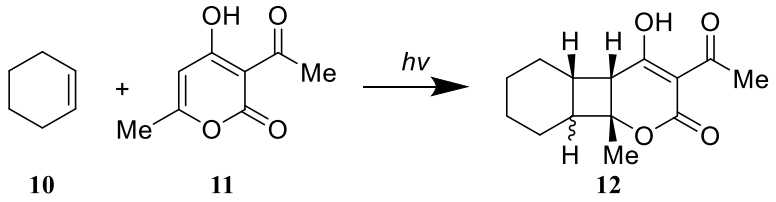


Halogenation

C. Reactions Exhibiting Aliphatic Characters of 2-Pyrone



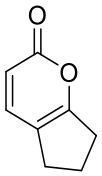
Diels-Alder Reaction



Photocycloaddition

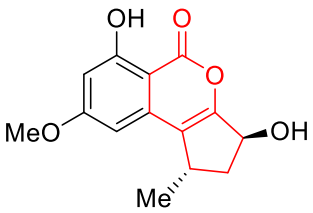
Figure 3. Cyclopentapyrone and Its Structures in Natural Products

A. Cyclopentapyrone

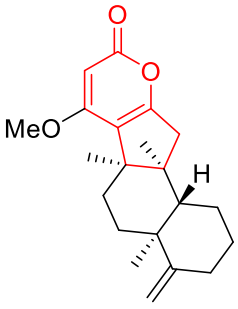


13

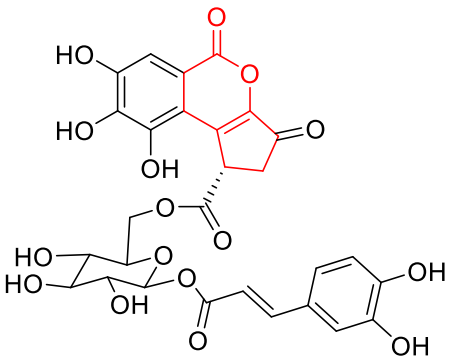
B. Natural Products Containing Cyclopentapyrone Moiety



Phialophoriol (**14**)



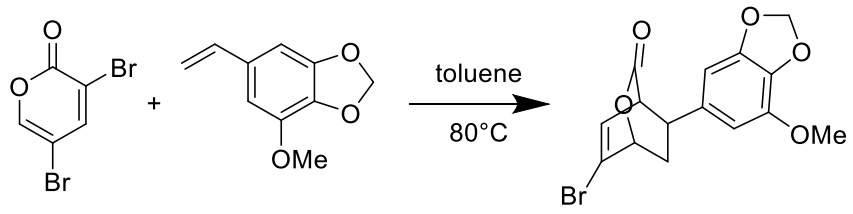
Hyrtiolactone A (**15**)



Balanophotannin D (**16**)

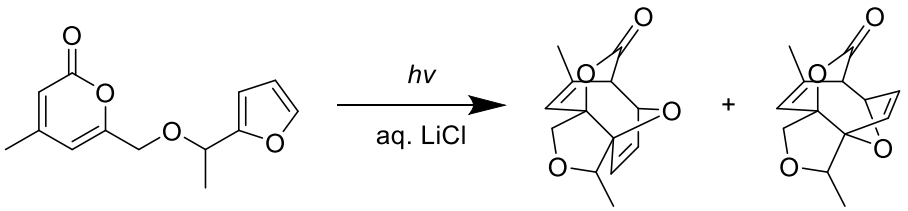
Figure 4. Examples of Cycloaddition of 2-pyrone and Its Application in Formation of Fused Ring System

A) An example of Cycloaddition for 6-membered Ring System



17 **18** **19**

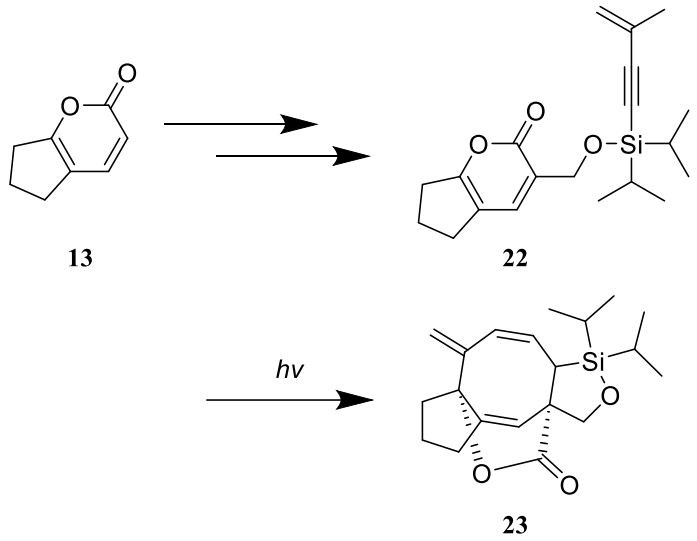
B) An example of Cycloaddition for 8-membered Ring System



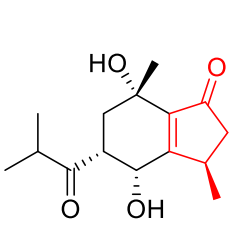
20 **21a** **21b**

Figure 5. Applications of Cyclopentapyrone in Formation of Fused Ring System

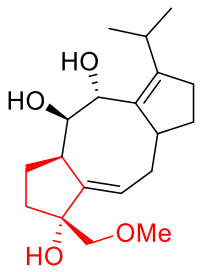
A) Formation of 8-5 Fused Ring System Using 4+4 Photocycloaddition



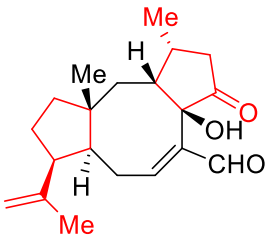
B) Natural Products Exhibiting Stereocenter on Five-membered Carbocycle Fused to 6- and 8-membered Ring



Nardochinone B (**24**)



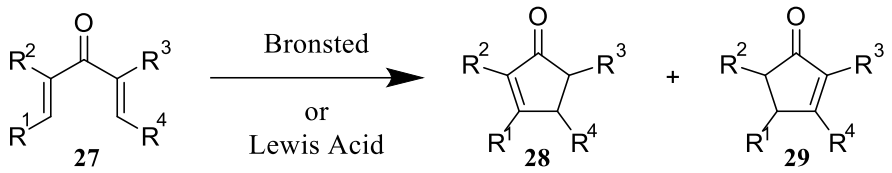
Cotylenin A (**25**)



Traversianal (**26**)

Figure 6. Nazarov Cyclization

A. Scheme



B.Mechanism

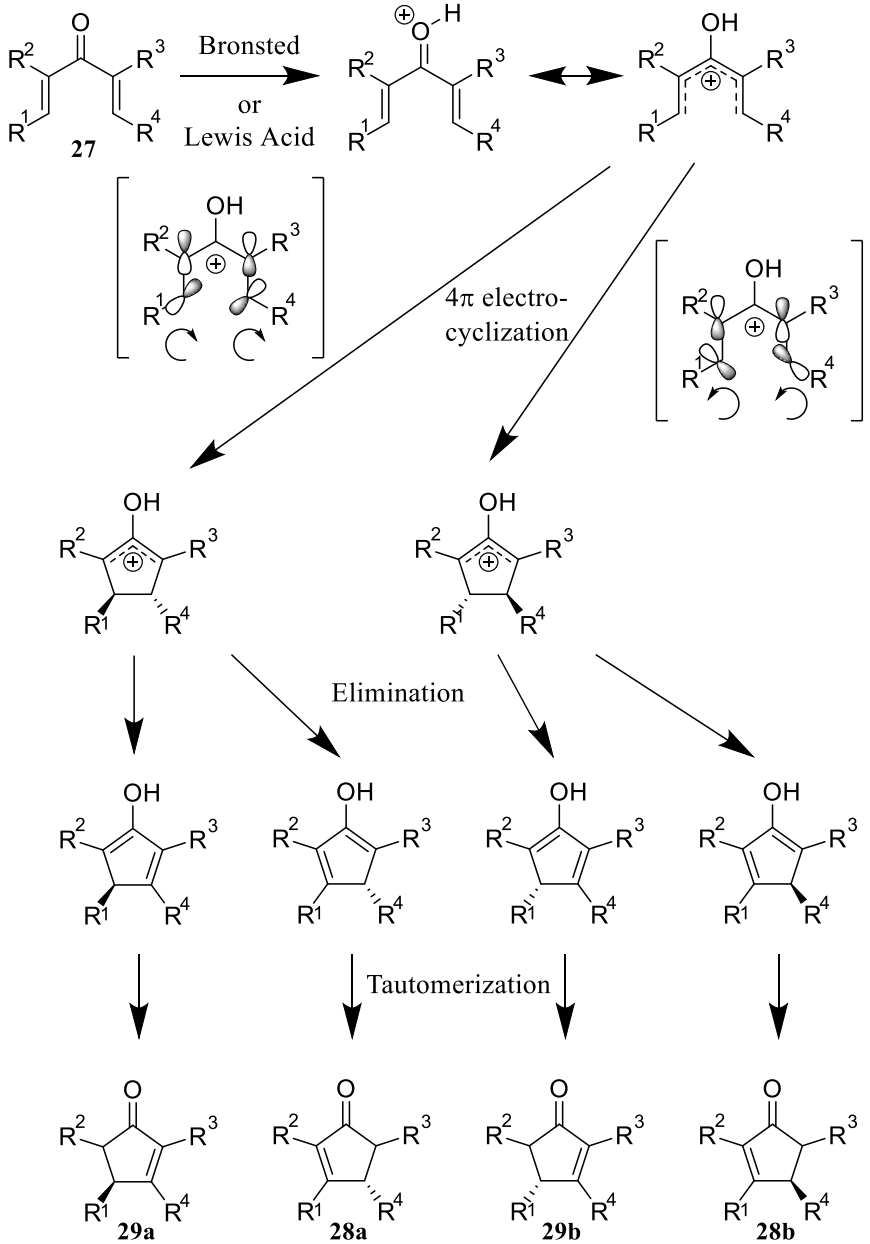
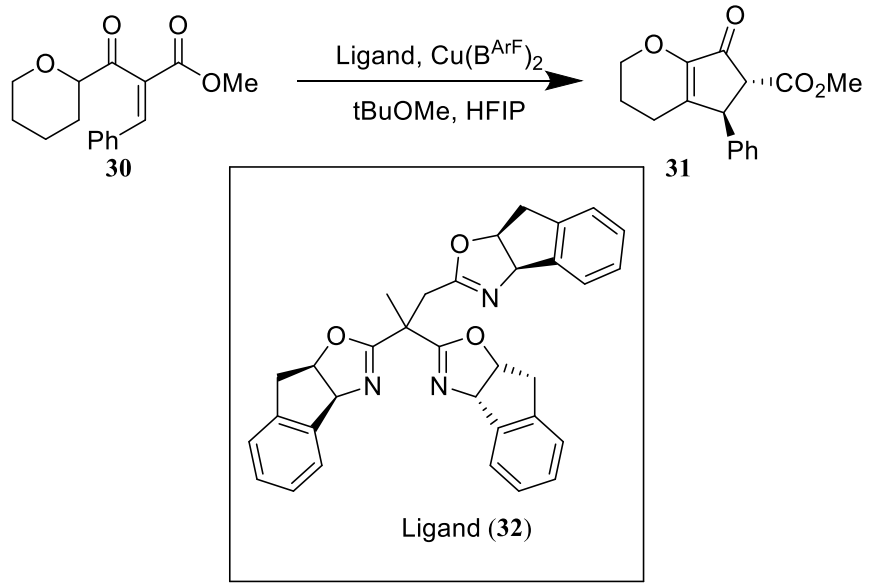


Figure 7. Asymmetric Nazarov Cyclization



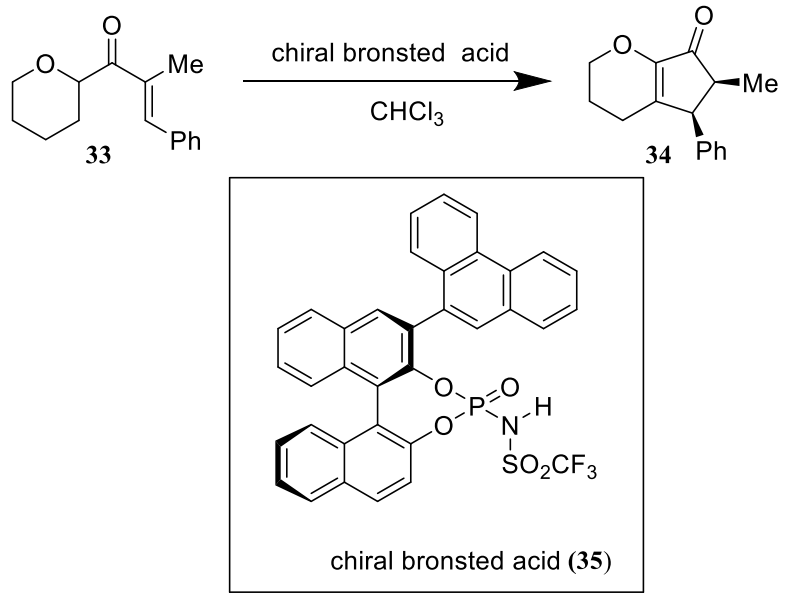
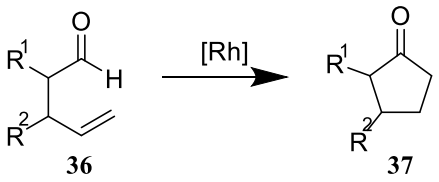


Figure 8. Rhodium Catalyzed Hydroacylation

A. Scheme



36 **37**

B. Mechanism

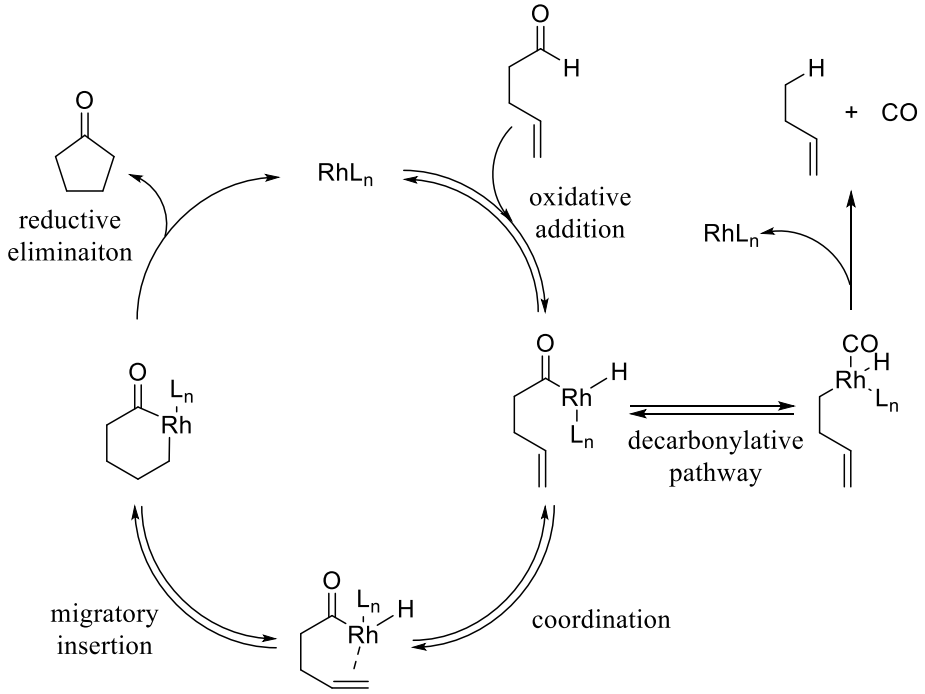


Figure 9. Asymmetric Rhodium-Catalyzed Hydroacylation

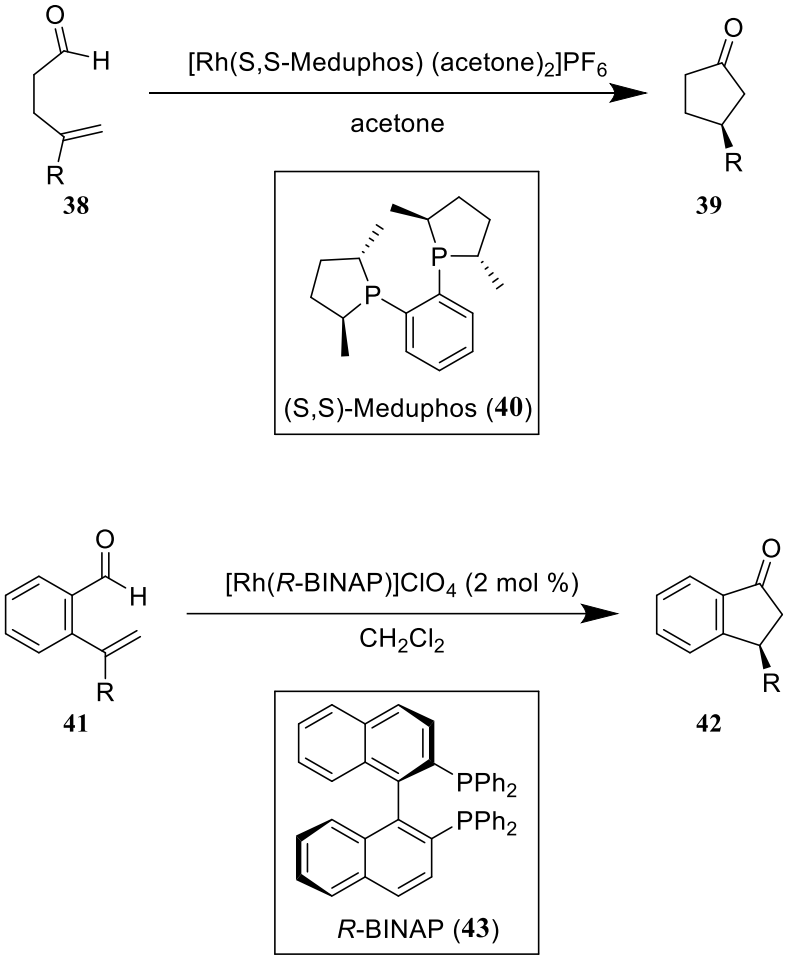


Figure 10. Preparation of Pyrone 50

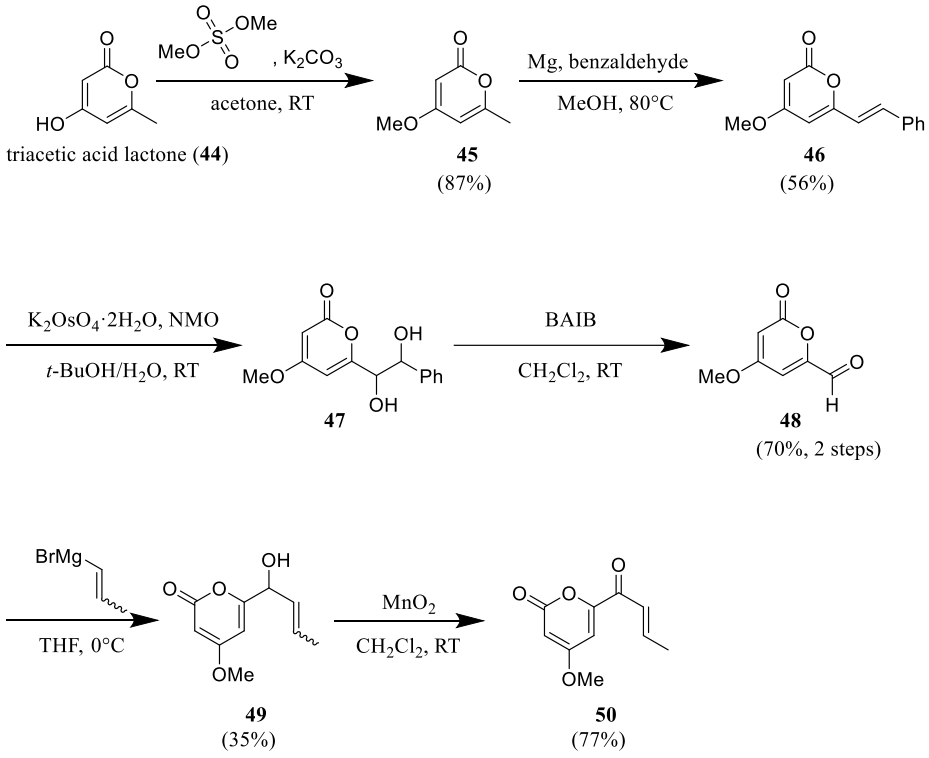
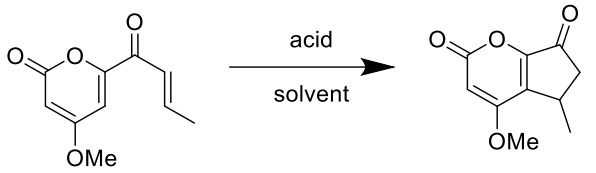


Table 1. Nazarov Cyclization of Pyrone



50 **51**

Entry	Acid	Solvent	Temp	Time	Results
1	$AlCl_3$	CH_2Cl_2	0 °C	8 h	no reaction
2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0 °C	8 h	no reaction
3	$AlCl_3$	CH_2Cl_2	RT	8 h	no reaction
4	$BF_3{\cdot}OEt_2$	CH_2Cl_2	RT	8 h	no reaction
5	$Cu(OTf)_2$	1,2-dichloroethane	60 °C	8 h	decomposition
6	$BF_3{\cdot}OEt_2$	1,2-dichloroethane	60 °C	8 h	no reaction
7	$AlCl_3$	CH_3Cl	70 °C	8 h	no reaction
8	$BF_3{\cdot}OEt_2$	CH_3Cl	70 °C	8 h	decomposition
9	$AlCl_3$	CH_3CN	80 °C	8 h	messy
10	$BF_3{\cdot}OEt_2$	CH_3CN	80 °C	8 h	1,4 addition
11	$AlCl_3$	toluene	110 °C	8 h	messy
12	$BF_3{\cdot}OEt_2$	toluene	110 °C	8 h	messy
13	$Dy(OTf)_3$	toluene	110 °C	8 h	no reaction
14	$FeCl_3$	toluene	110 °C	8 h	1,4 addition
15	$AlCl_3$	chlorobenzene	130 °C	8 h	decomposition
16	$BF_3{\cdot}OEt_2$	chlorobenzene	130 °C	8 h	messy
17	$Cu(OTf)_2$	chlorobenzene	130 °C	8 h	1,4 addition
18	$AlCl_3$	1,2-dichlorobenzene	160 °C	8 h	decomposition
19	$BF_3{\cdot}OEt_2$	1,2-dichlorobenzene	160 °C	8 h	decomposition
20	HCl	1,4-dioxane	110 °C	8 h	no reaction
21	H_2SO_4	1,4-dioxane	110 °C	8 h	no reaction
22	H_2SO_4	water	110 °C	2 h	messy

Figure 11. Retrosynthetic Analysis for Pyrone 61

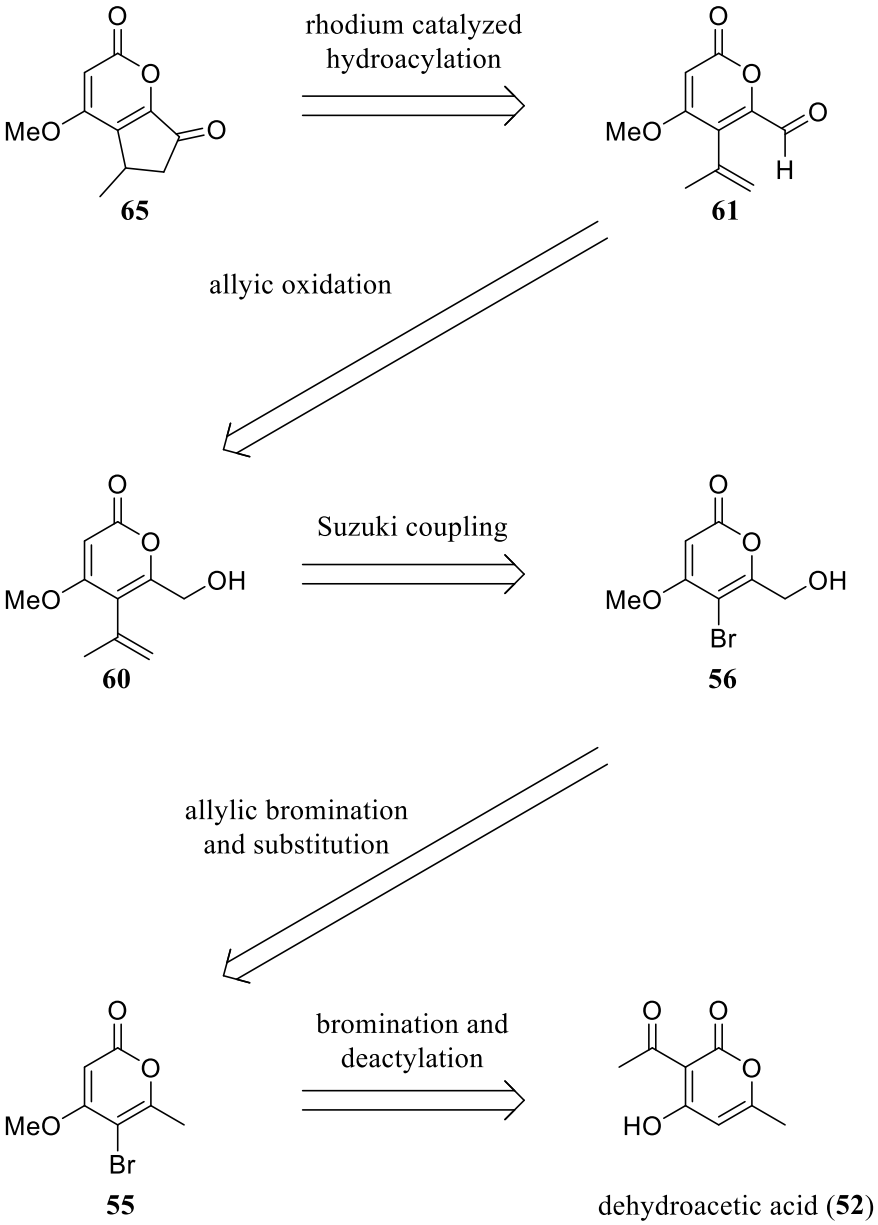


Figure 12. Preparation of Pyrone 61

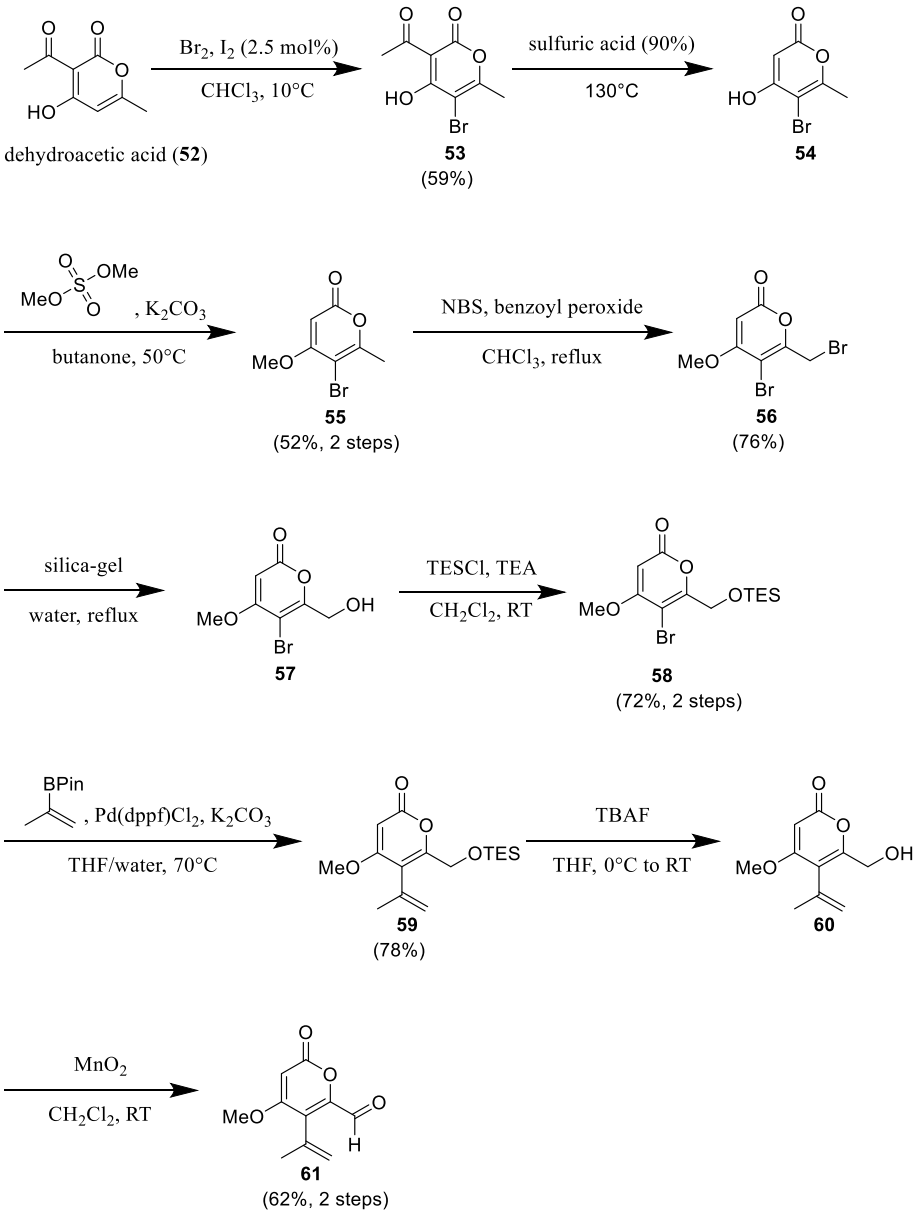
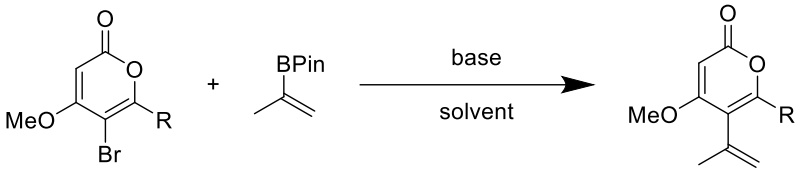


Table 2. Optimization of Suzuki Coupling to Pyrone

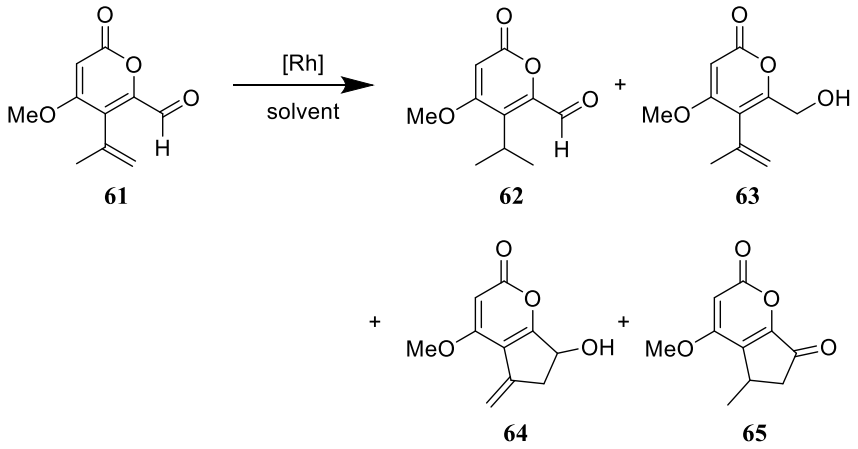


57 R = CH_2OH
55 R = CH_3
57a R = CHO
58 R = CH_2OTES

Entry	Substrate	Catalyst	Base	Solvent	Temp	Time	Yield
1	**57**	$Pd(PPh_3)_4$	Na_2CO_3	1,4-dioxane	RT	8 h	no reaction
2	**57**	$Pd(PPh_3)_4$	Na_2CO_3	1,4-dioxane	100 °C	48 h	messy
3	**57**	$Pd(PPh_3)_4$	$NaHCO_3$	Toluene/H_2O	70 °C	24 h	trace amount
4[a]	**55**	$Pd(PPh_3)_4$	Na_2CO_3	DMF	50 °C	30 h	14%
5[a]	**57**	$Pd(PPh_3)_4$	Na_2CO_3	DMF	50 °C	2 h	no reaction
6[a]	**57**	$Pd(PPh_3)_4$	Na_2CO_3	DMF	100 °C	4 h	decomposition
7	**55**	$Pd(PPh_3)_4$	Cs_2CO_3	1,4-dioxane	90 °C	5 h	42%
8[a]	**55**	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	90 °C	2.5 h	43%
9[a]	**57**	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	90 °C	4 h	decomposition
10[a]	**57**	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	70 °C	2 h	6%
11[a]	**57**	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	40 °C	84 h	18%
12[a,b]	**57**	$Pd(PPh_3)_4$	Cs_2CO_3	THF/H_2O	70 °C	16 h	decomposition
13[a]	**61**	$Pd(PPh_3)_4$	Cs_2CO_3	1,4-dioxane	RT	6 h	decomposition
14[a]	**61**	$Pd(PPh_3)_4$	Cs_2CO_3	acetone	RT	6 h	decomposition
15[a]	**61**	$Pd(PPh_3)_4$	Na_2CO_3	DMF	RT	6 h	decomposition
16[a]	**61**	$Pd(dppf)Cl_2$	Cs_2CO_3	DMF	RT	6 h	decomposition
17[a]	**58**	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	50 °C	24 h	9%
18[a]	**58**	$Pd(PPh_3)_4$	Na_2CO_3	DMF	50 °C	168 h	15%
19[b]	**58**	$Pd(dppf)Cl_2$	Cs_2CO_3	toluene/H_2O	50 °C	48 h	8%
20	**58**	$Pd(dppf)Cl_2$	K_2CO_3	THF/H_2O	70 °C	24 h	78%

[a] 1.50 equiv of CuI added. [b] Potassium isopropenyltrifluoroborate used.

Table 3. Rhodium-Catalyzed Hydroacylation of Pyrone



61 **62** **63** **64** **65**

Entry	Catalyst	Ligand	Solvent	H_2 Activation	Temp	Time	Yield
1	$Rh(PPh_3)_3Cl$	-	CH_2Cl_2	O	RT	3 d	22 (**62**), 32 (**63**)
2	$Rh(PPh_3)_3Cl$	-	CH_2Cl_2	X	RT	3 d	17 (**63**)
3	$Rh(PPh_3)_3Cl$	-	1,2-DCE	X	RT	1 d	Trace amount (**63**)
4	$Rh(NBD)_2BF_4$	dppb	1,2-DCE	O	50 °C	2 h	30 (**64**)

Figure 13. Proposed Mechanism of Prins Cyclization of Pyrone

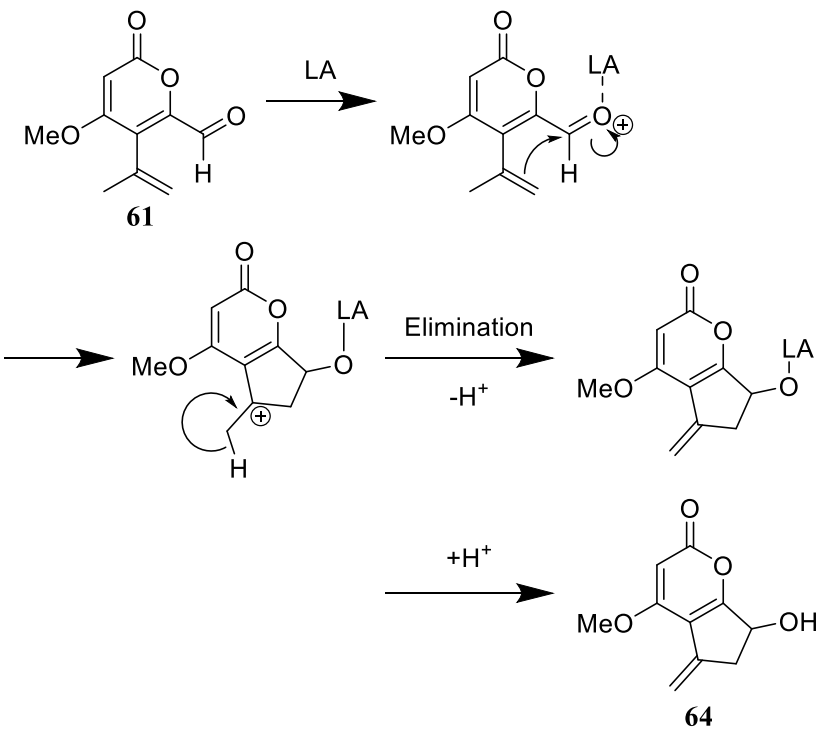
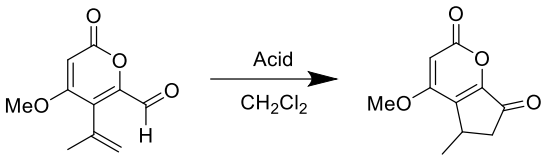


Table 4. Optimization for Prins Cyclization of Pyrone



61 **64**

Entry	Acid (equiv)	Temp	Time	Quenched with	Yield
1	$Sc(OTf)_2$ (0.5)	-78 °C	2 h	water	no reaction
2	$Sc(OTf)_2$ (0.5)	0 °C	30 min	water	21%
3	$Sc(OTf)_2$ (0.5)	-10 °C	30 min	celite	37%
4	$Sc(OTf)_2$ (0.5)	-41 °C	6 h	celite	5%
5	$BF_3{\cdot}OEt_2$ (2.5)	-78 °C	10 min	NH_4Cl (sat.)	12%
6	$Cu(OTf)_2$ (0.5)	0 °C	4 h	NH_4Cl (sat.)	trace amount
7	$Cu(OTf)_2$ (0.5)	-20 °C to 0 °C	1 h	NH_4Cl (sat.)	44%
8	$Dy(OTf)_2$ (0.5)	0 °C to RT	45 min	NH_4Cl (sat.)	48%
9	$AlCl_3$ (0.5)	-78 °C to 0 °C	30 min	NH_4Cl (sat.)	25%
10[a]	*p*TSA (0.5)	0 °C	45 min	NH_4Cl (sat.)	54%
11	*p*TSA (0.5)	0 °C	45 min	NH_4Cl (sat.)	22%

[a] Molecular sieves (4Å) were added.

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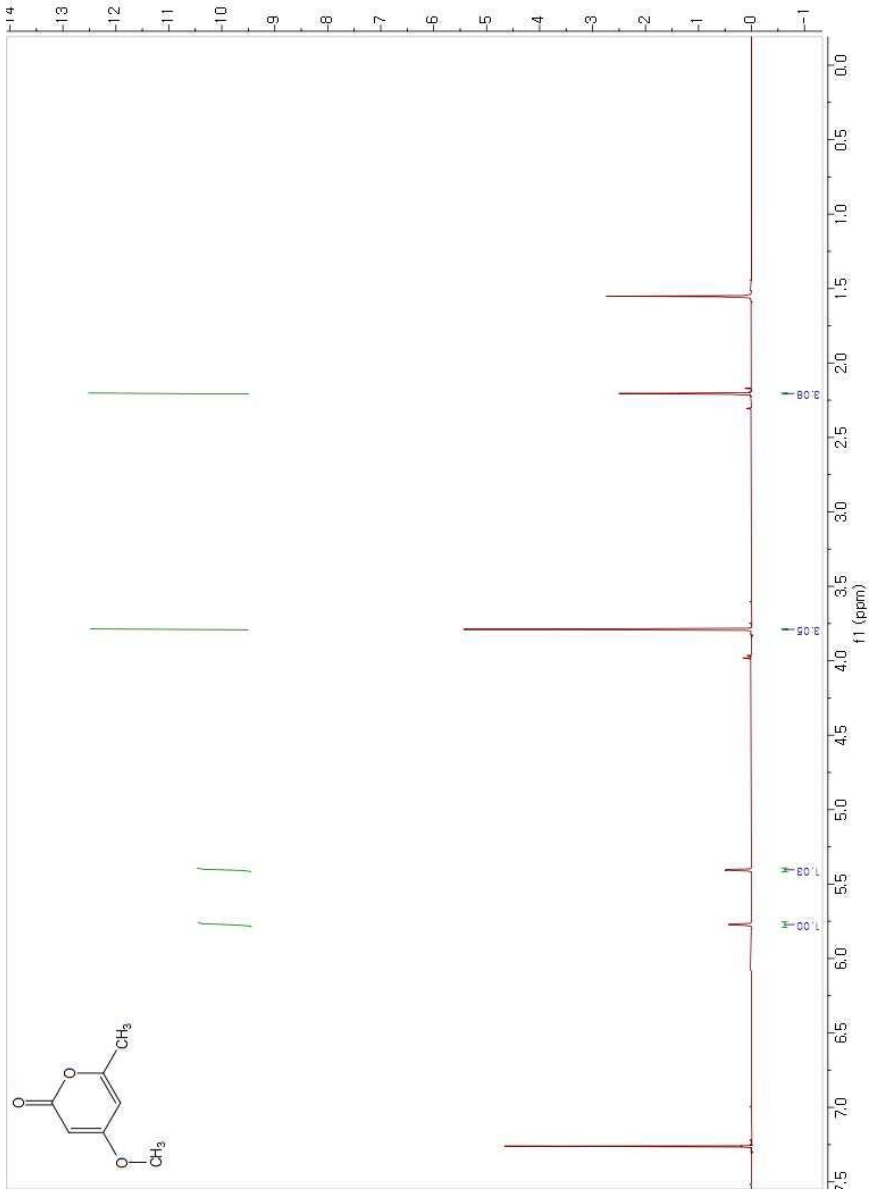
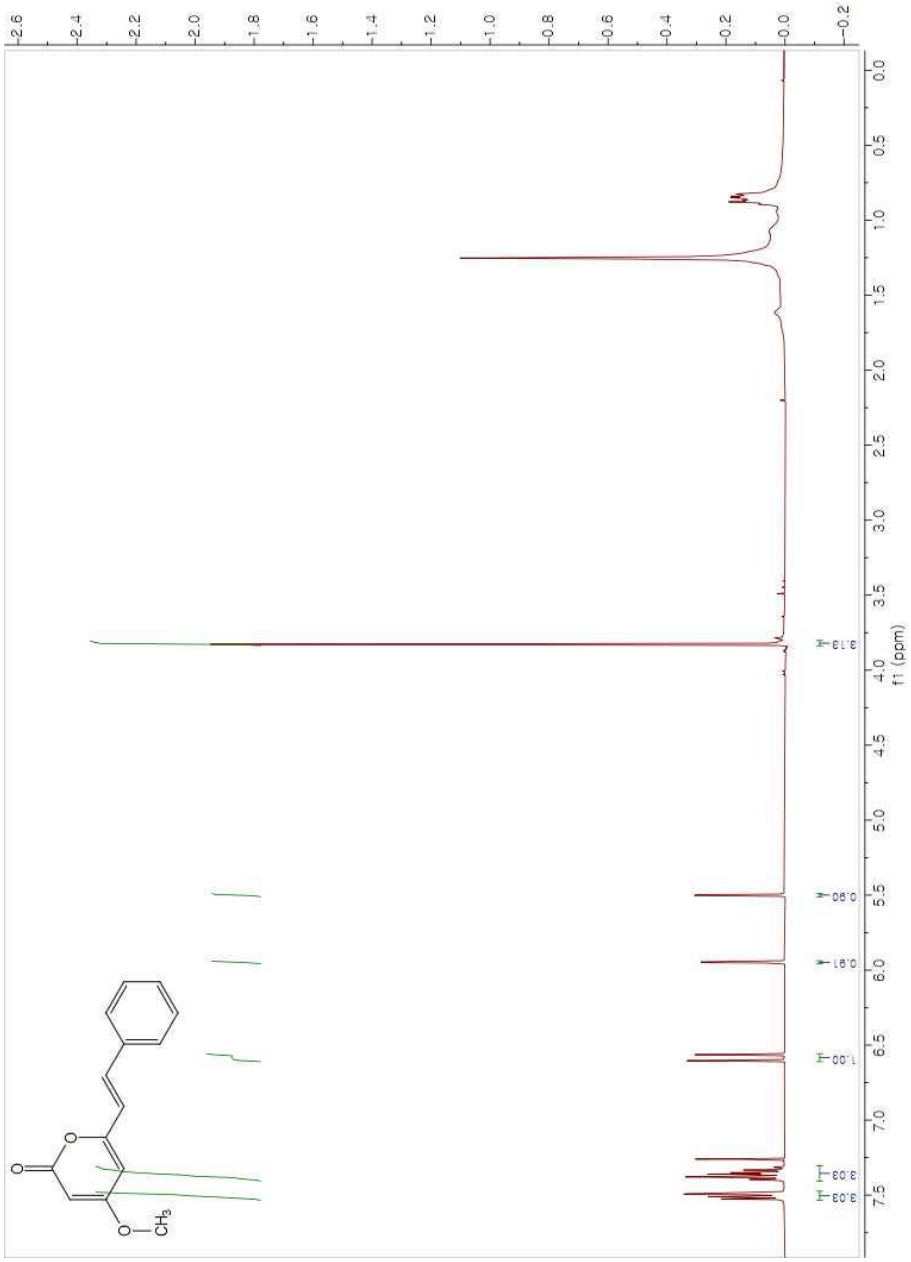
Supplementary Materials

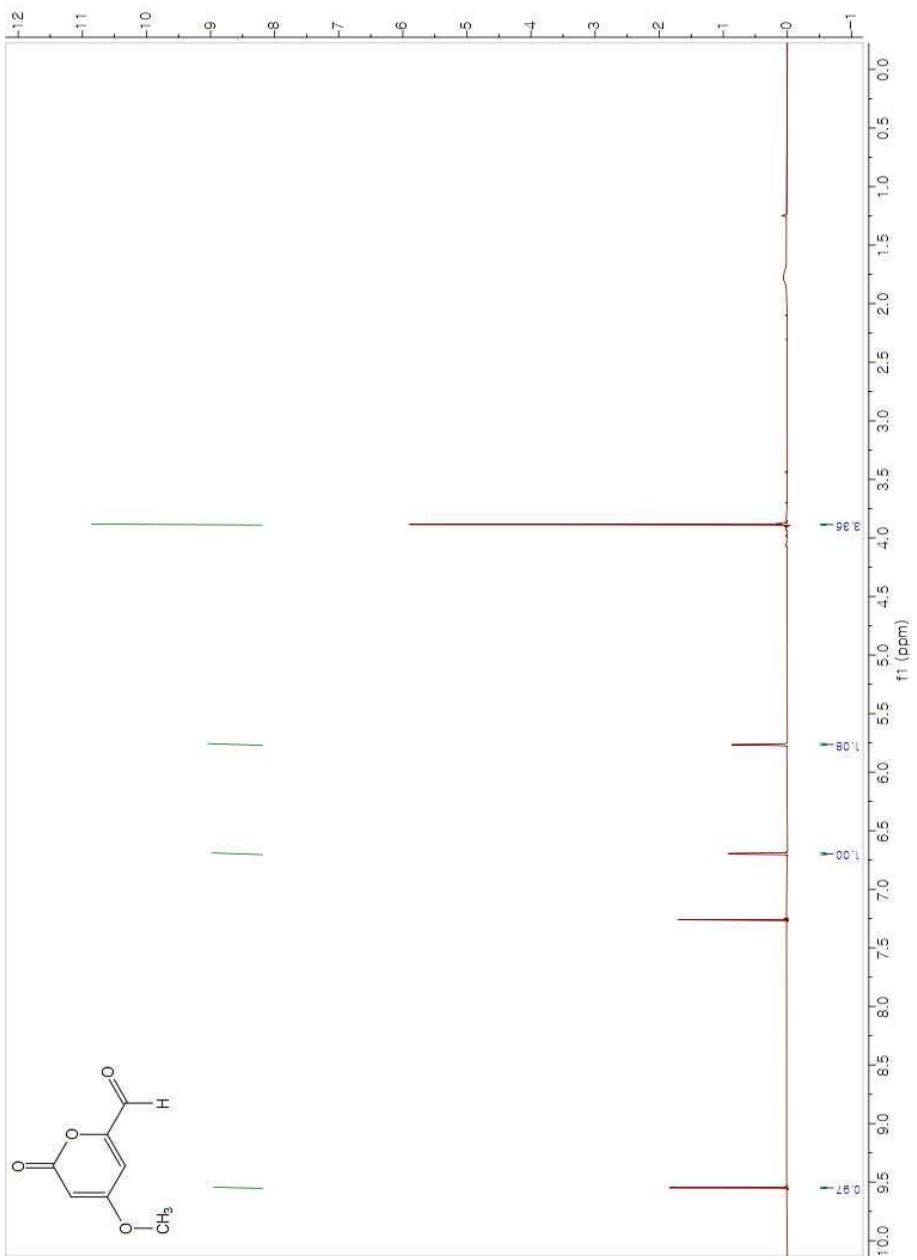
S1. ^{1}H NMR Data of 4-methoxy-6-methyl-2H-pyran-2-one (Pyrone 45)



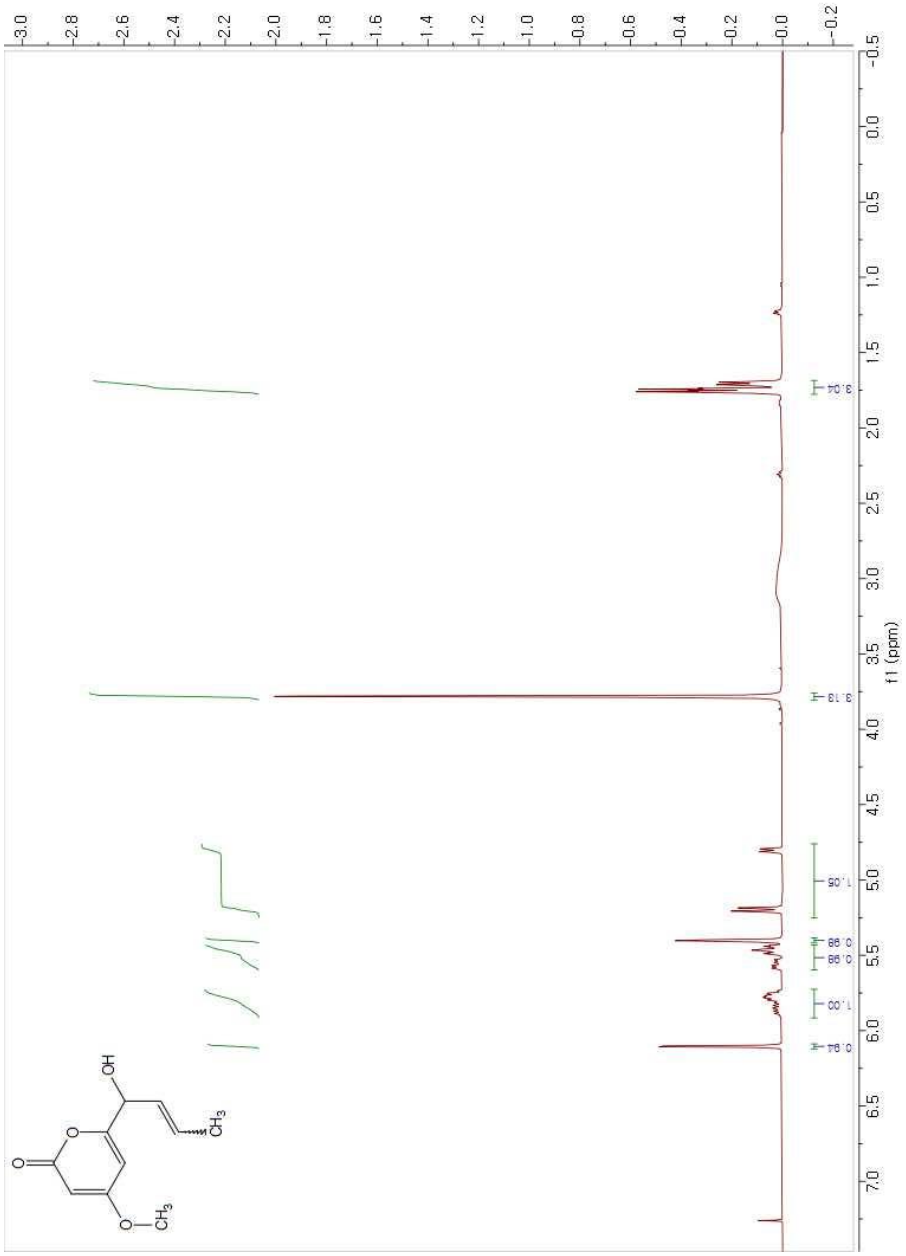
S2. ^{1}H NMR Data of (E)-4-methoxy-6-styryl-2H-pyran-2-one (Pyrone 46)



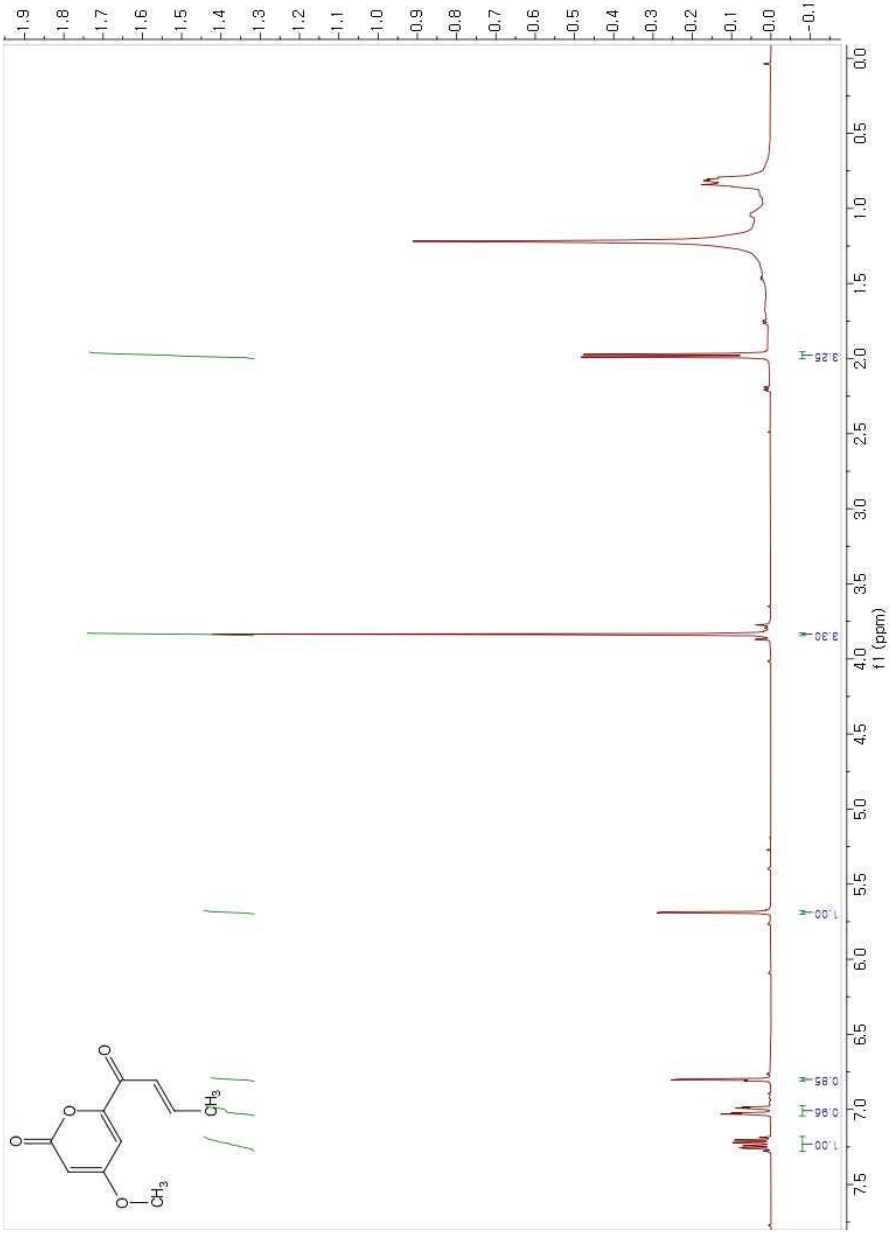
S3. ^{1}H NMR Data of 4-methoxy-2-oxo-2H-pyran-6-carbaldehyde (Pyrone 48)



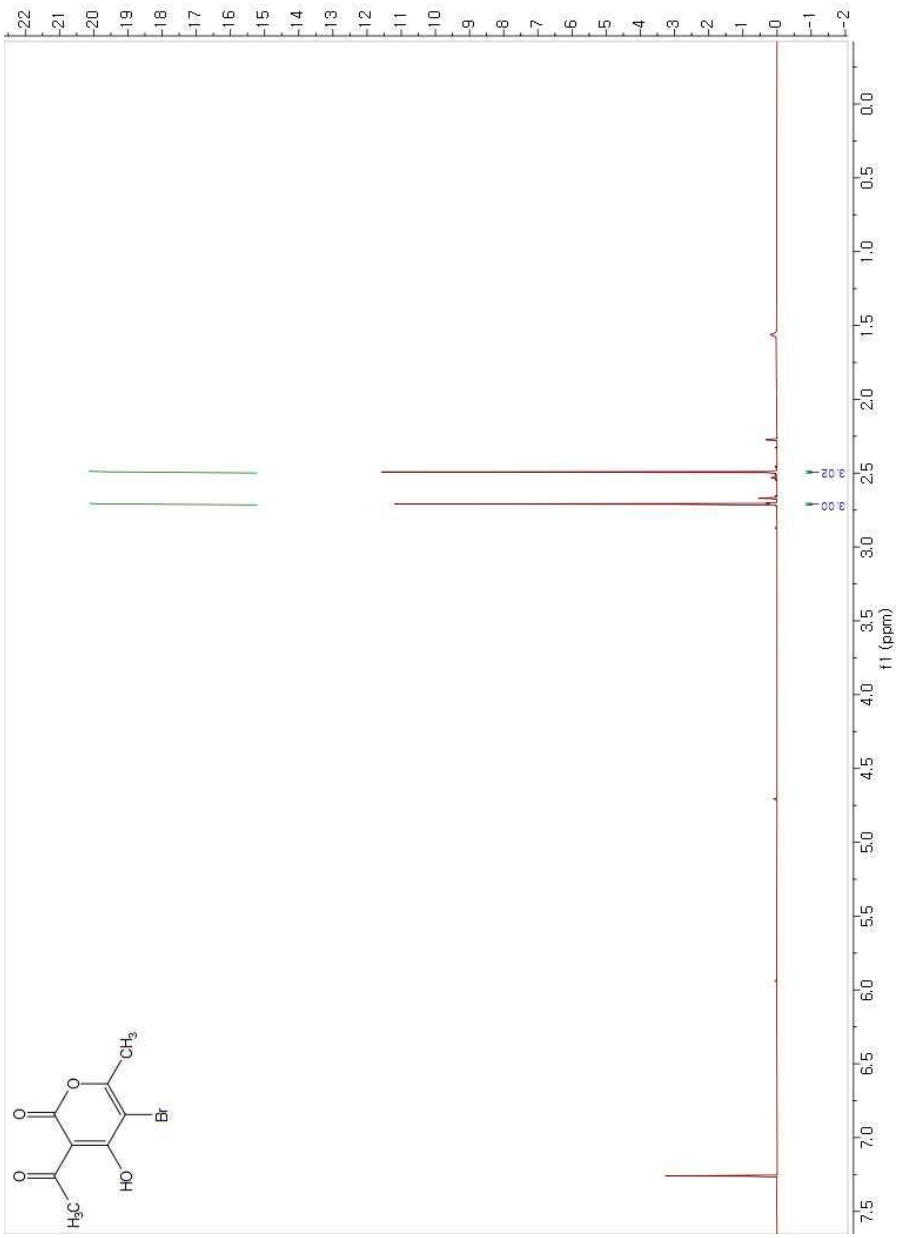
S4. ^{1}H NMR Data of 6-(1-hydroxybut-2-en-1-yl)-4-methoxy-2H-pyran-2-one (Pyrone 49)



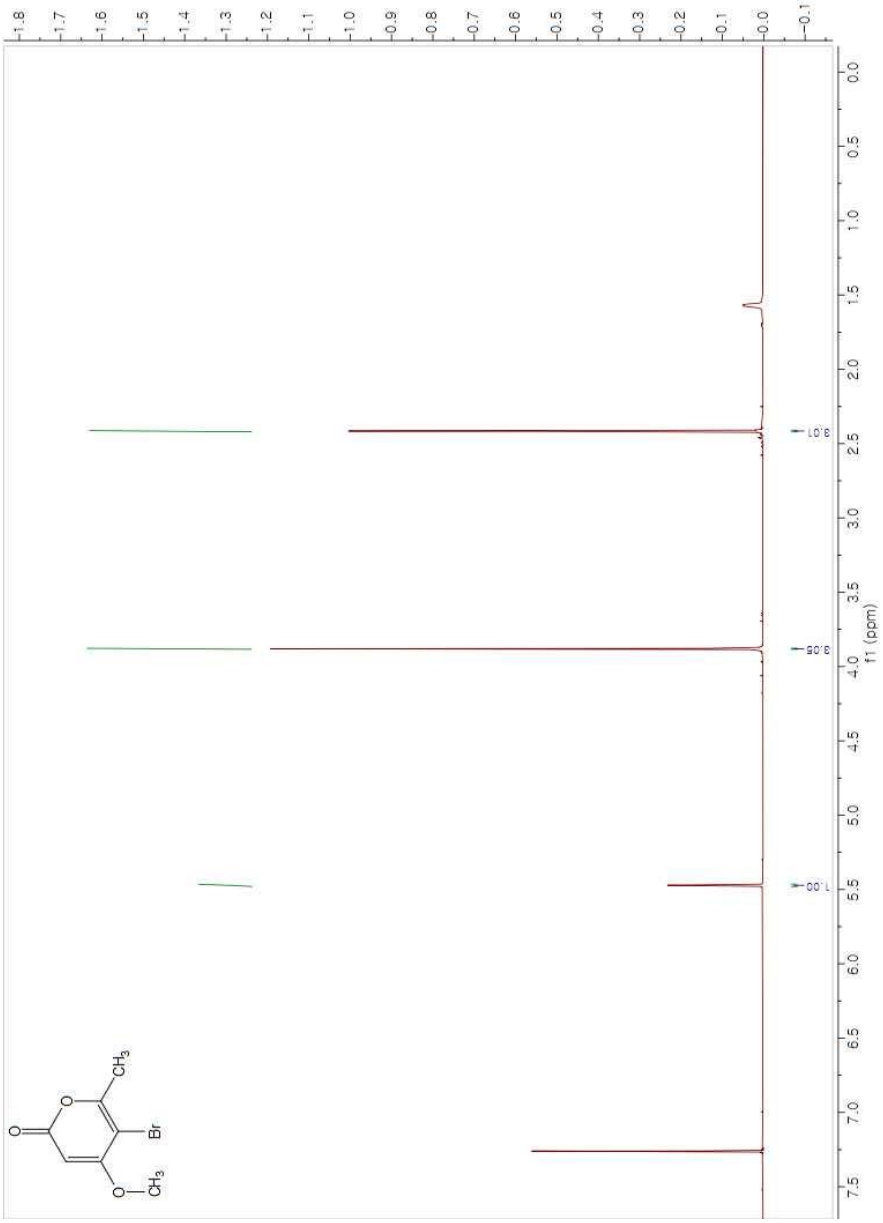
S5. ^{1}H NMR Data of (E)-6-(but-2-enoyl)-4-methoxy-2H-pyran-2-one (Pyrone 50)



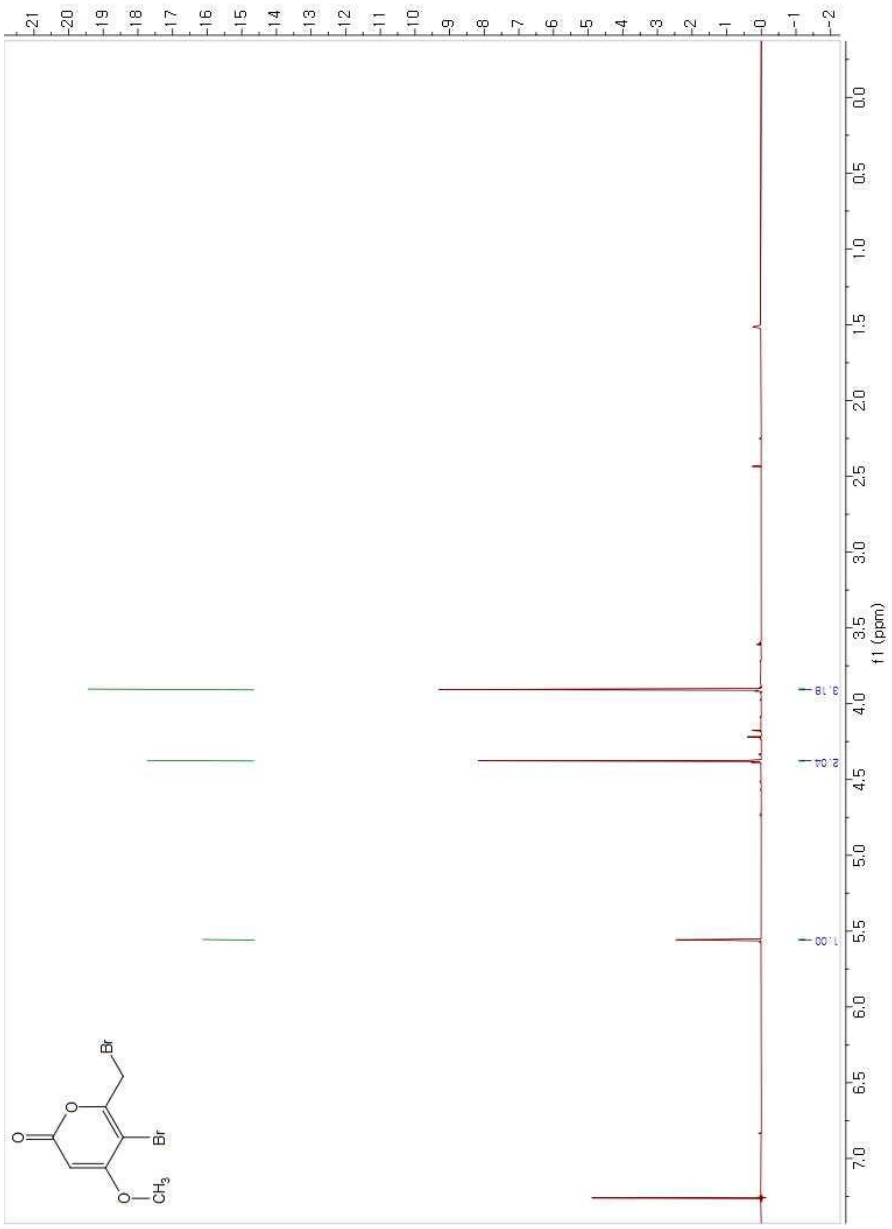
S6. ^{1}H NMR Data of 3-acetyl-5-bromo-6-ethyl-4-methoxy-2H-pyran-2-one (Pyrone 53)



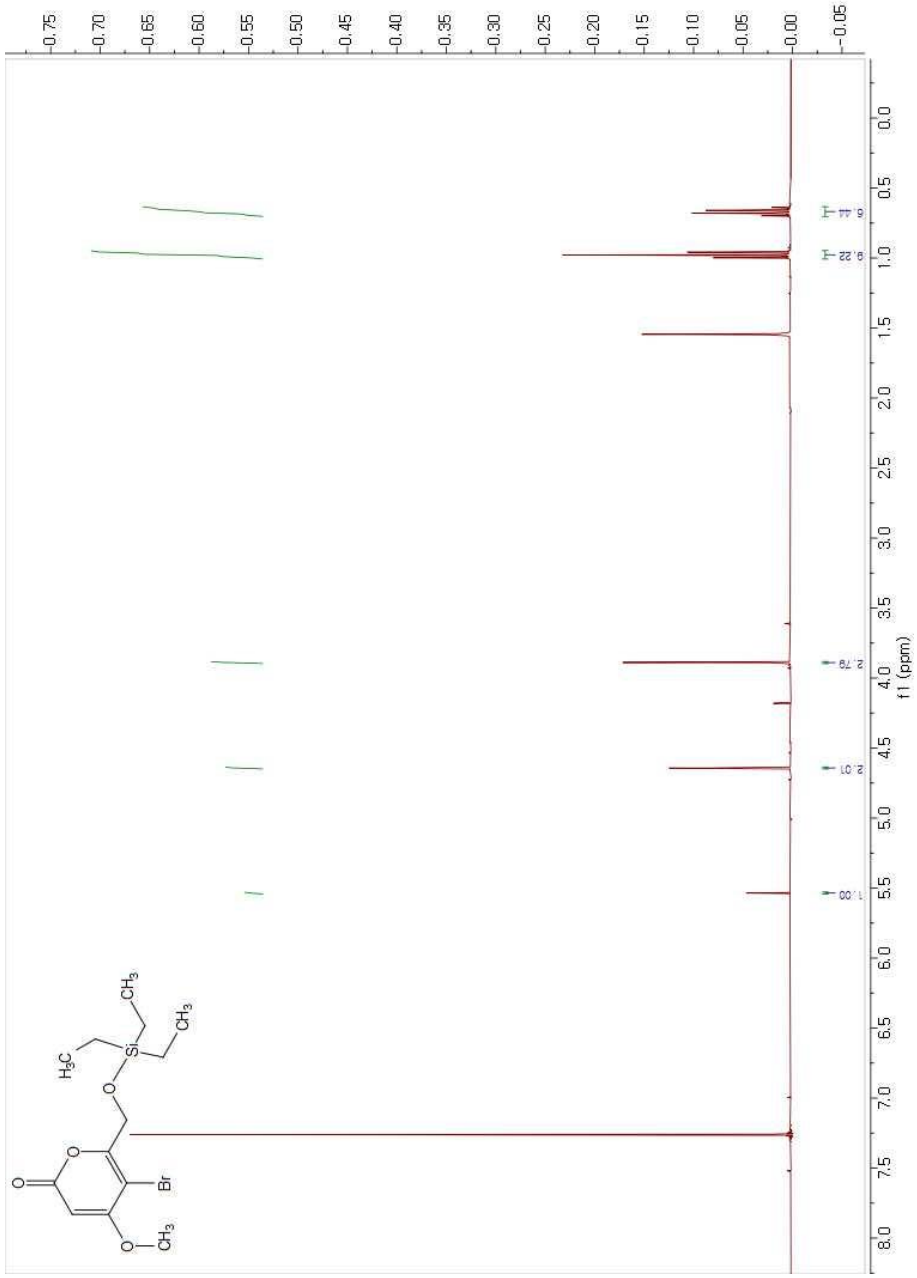
S7. ^{1}H NMR Data of 5-bromo-6-ethyl-4-methoxy-2H-pyran-2-one (Pyrone 55)



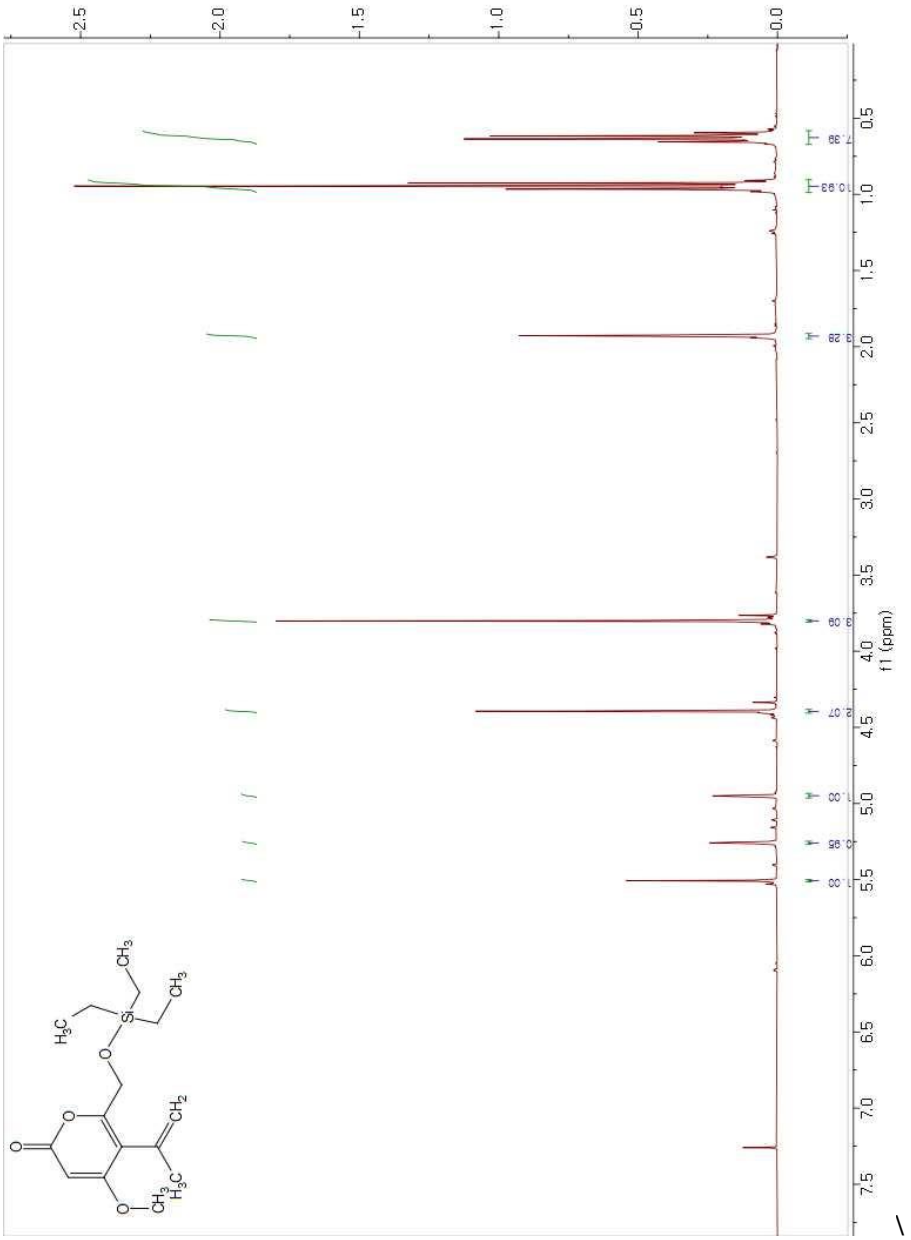
S8. ^{1}H NMR Data of 5-bromo-6-(bromomethyl)-4-methoxy-2H-pyran-2-one (Pyrone 56)



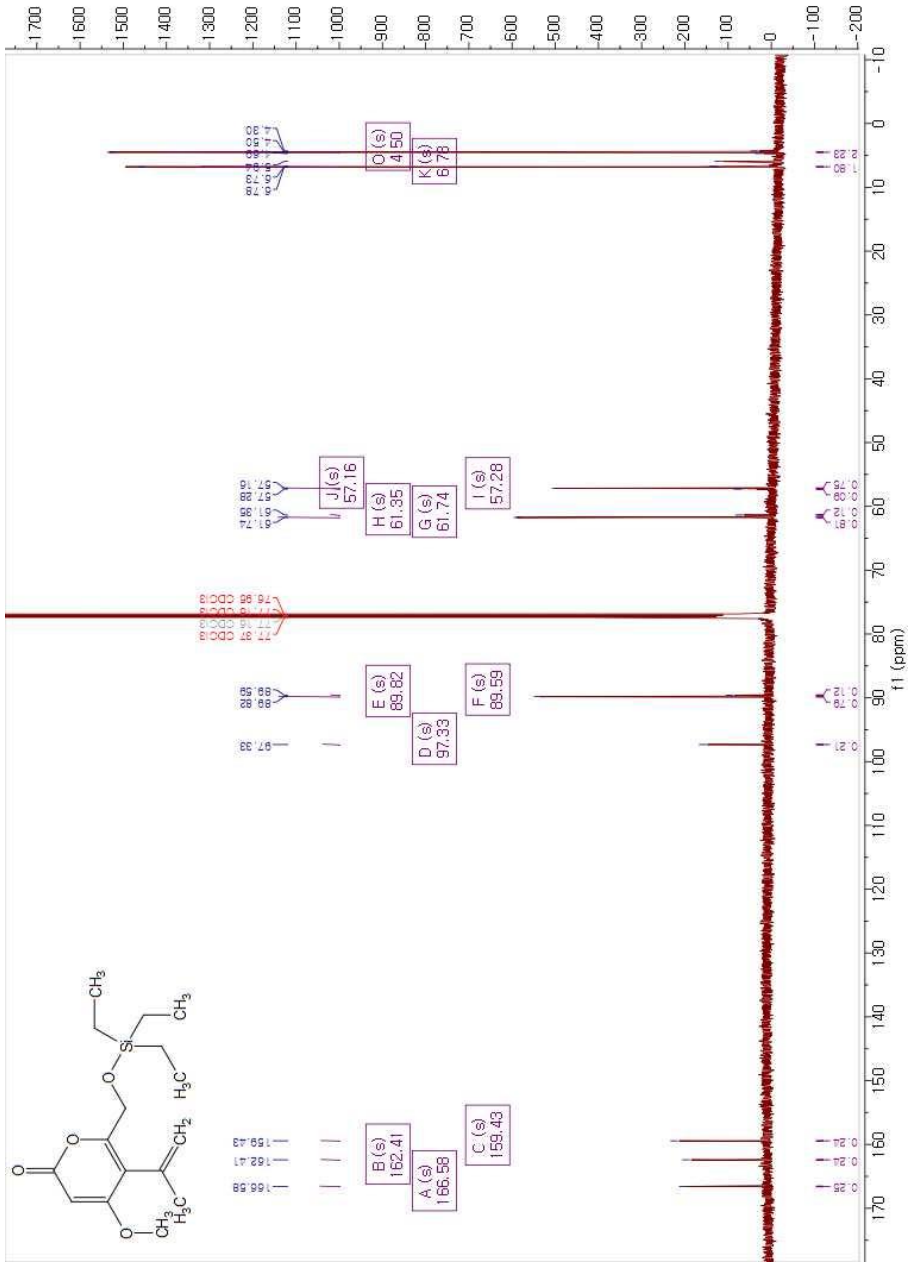
S9. ^{1}H NMR Data of 5-bromo-4-methoxy-6-((triethylsilyl)methyl)-2H-pyran-2-one (Pyrone 58)



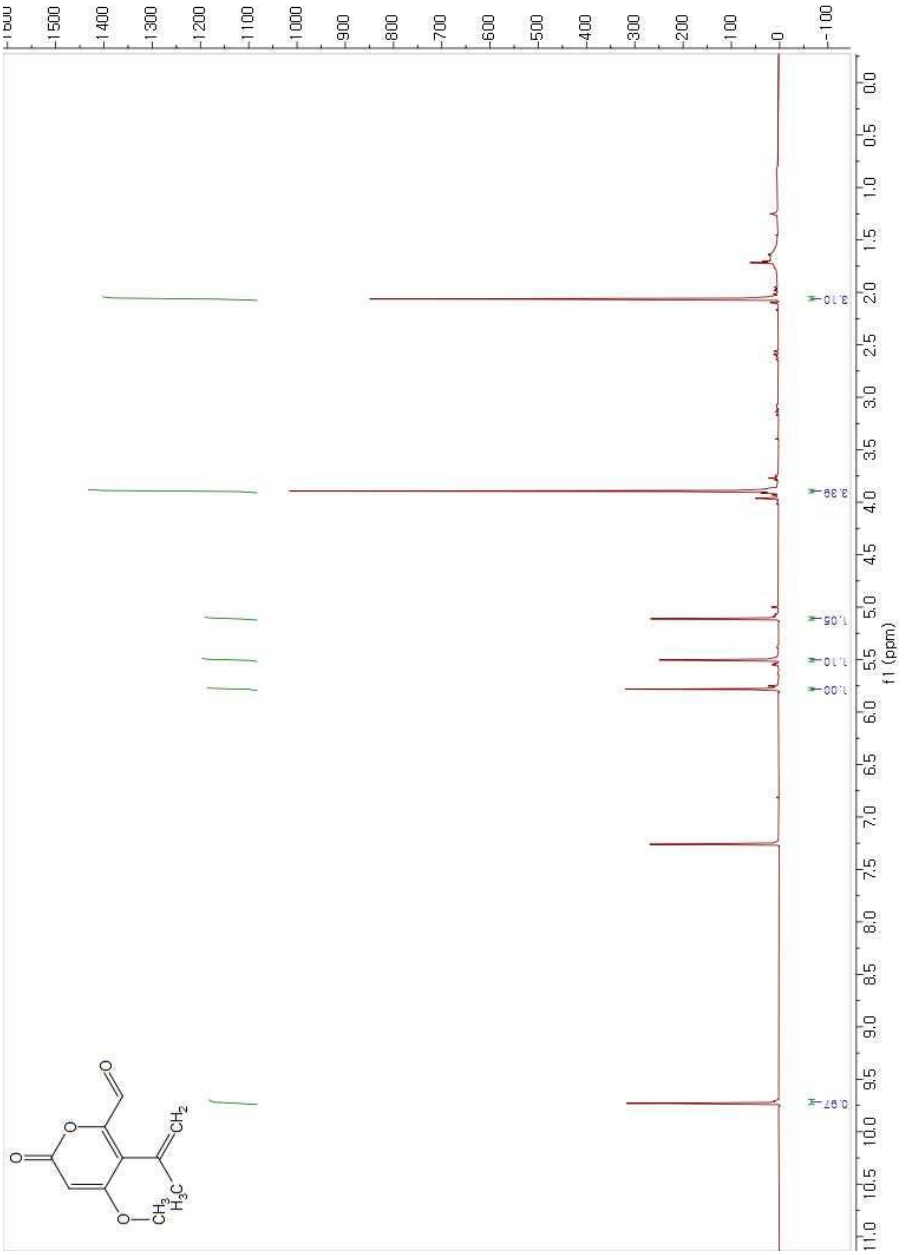
S10. ^{1}H NMR Data of 4-methoxy-5-(prop-1-en-2-yl)-6-(((triethylsilyl)oxy) methyl)-2H-pyran-2-one (Pyrone 59)



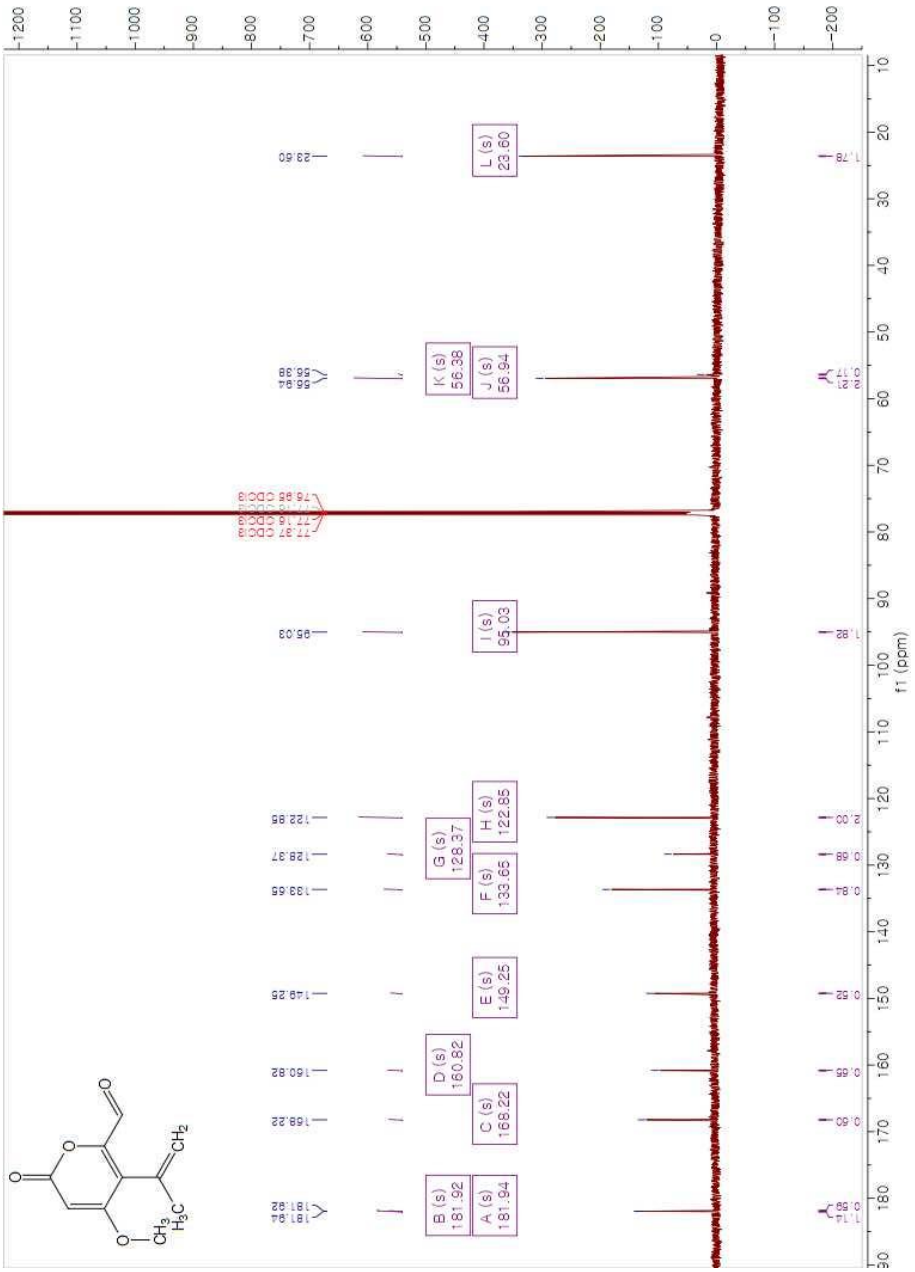
S11. ^{13}C NMR Data of 4-methoxy-5-(prop-1-en-2-yl)-6-(((triethylsilyl)oxy) methyl)-2H-pyran-2-one (Pyrone 59)



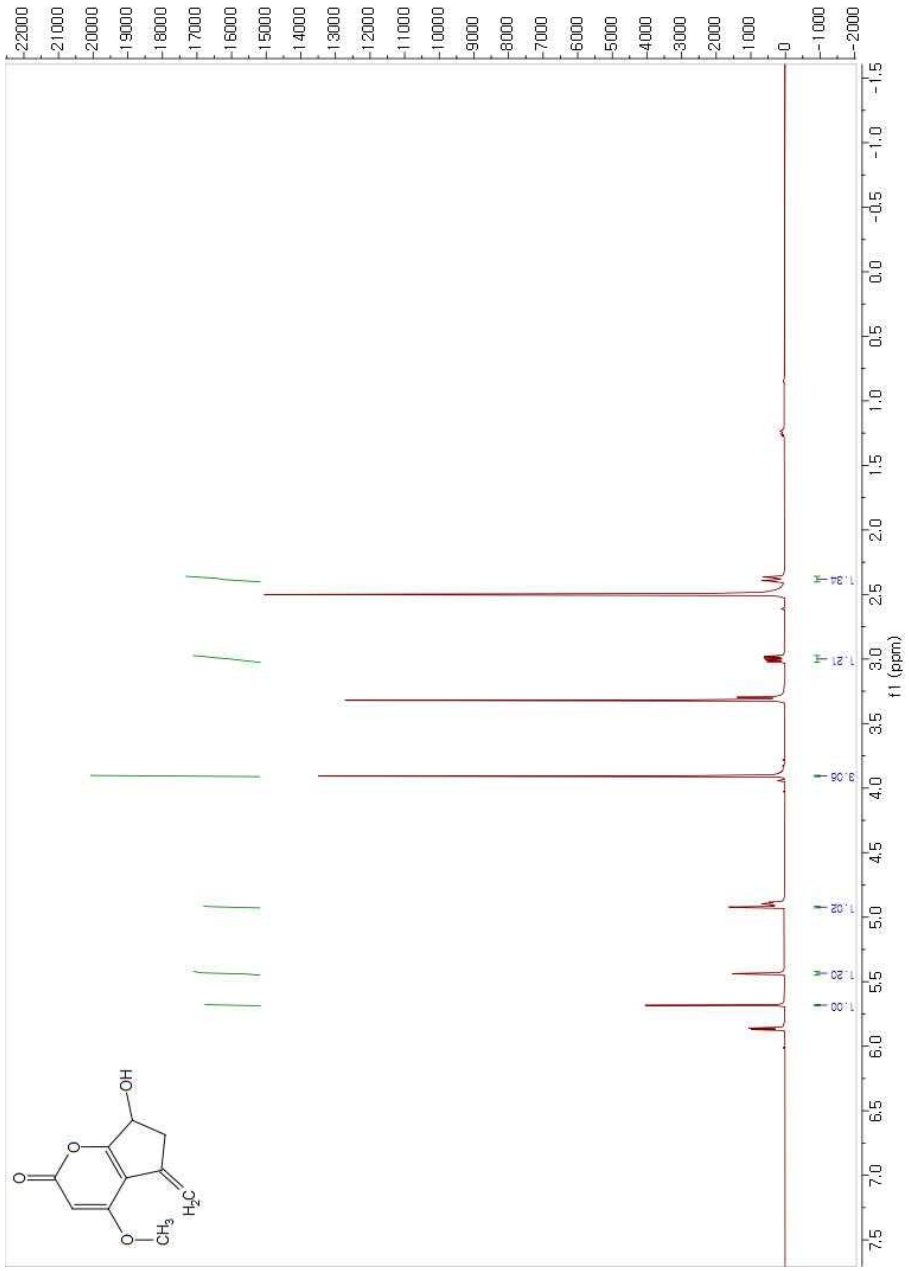
S12. ^{1}H NMR Data of 4-methoxy-2-oxo-5-(prop-1-en-2-yl)-2H-pyran-6-carbaldehyde (Pyrone 61)



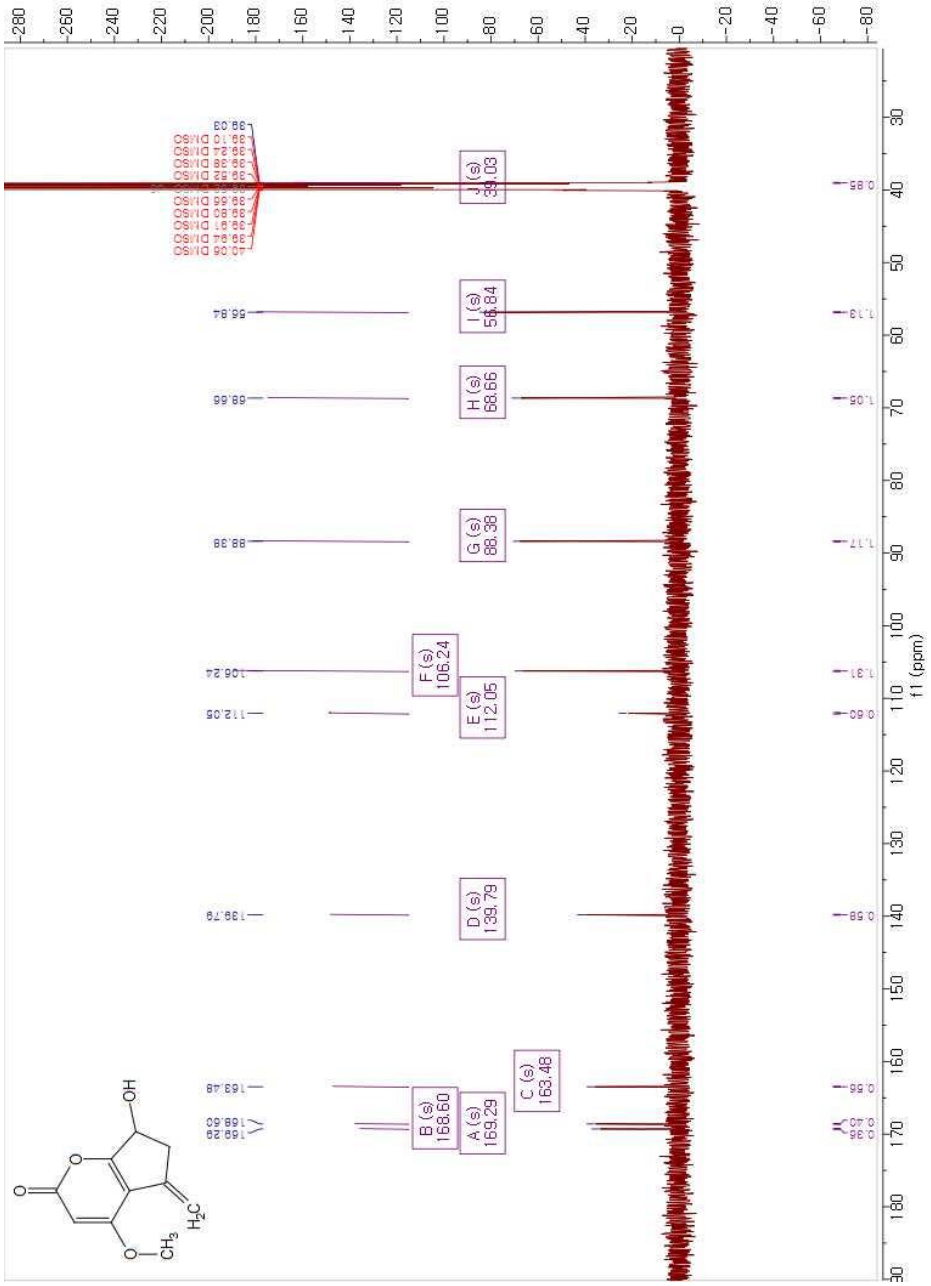
S13. ^{13}C NMR Data of 4-methoxy-2-oxo-5-(prop-1-en-2-yl)-2H-pyran-6-carbaldehyde (Pyrone 61)



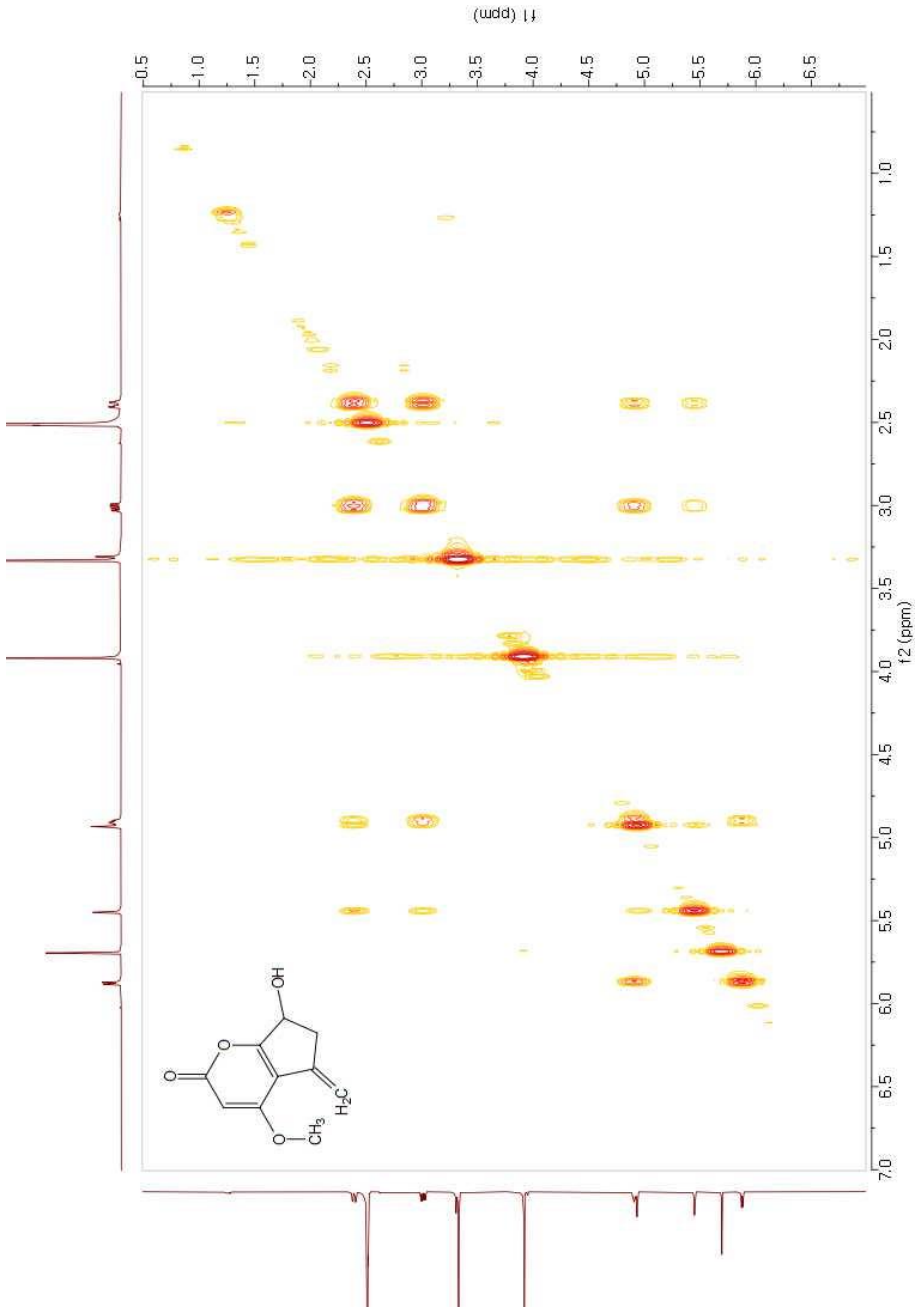
S14. ^{1}H NMR Data of 7-hydroxy-4-methoxy-5-methylene-6,7-dihydrocyclopenta[b]pyran-2(5H)-one (Pyrone 64)



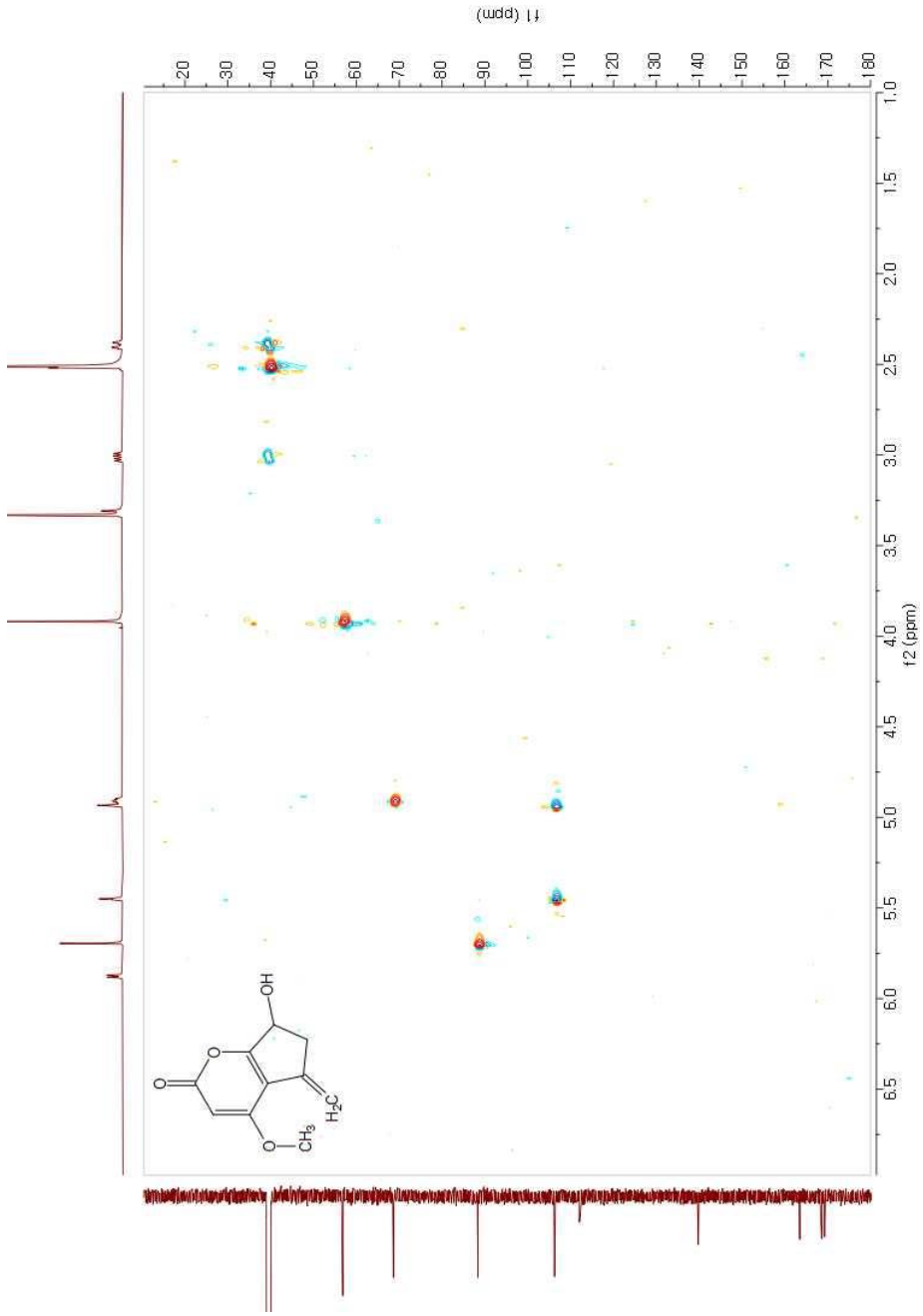
S15. ^{13}C NMR Data of 7-hydroxy-4-methoxy-5-methylene-6,7-dihydrocyclopenta[b]pyran-2(5H)-one (Pyrone 64)



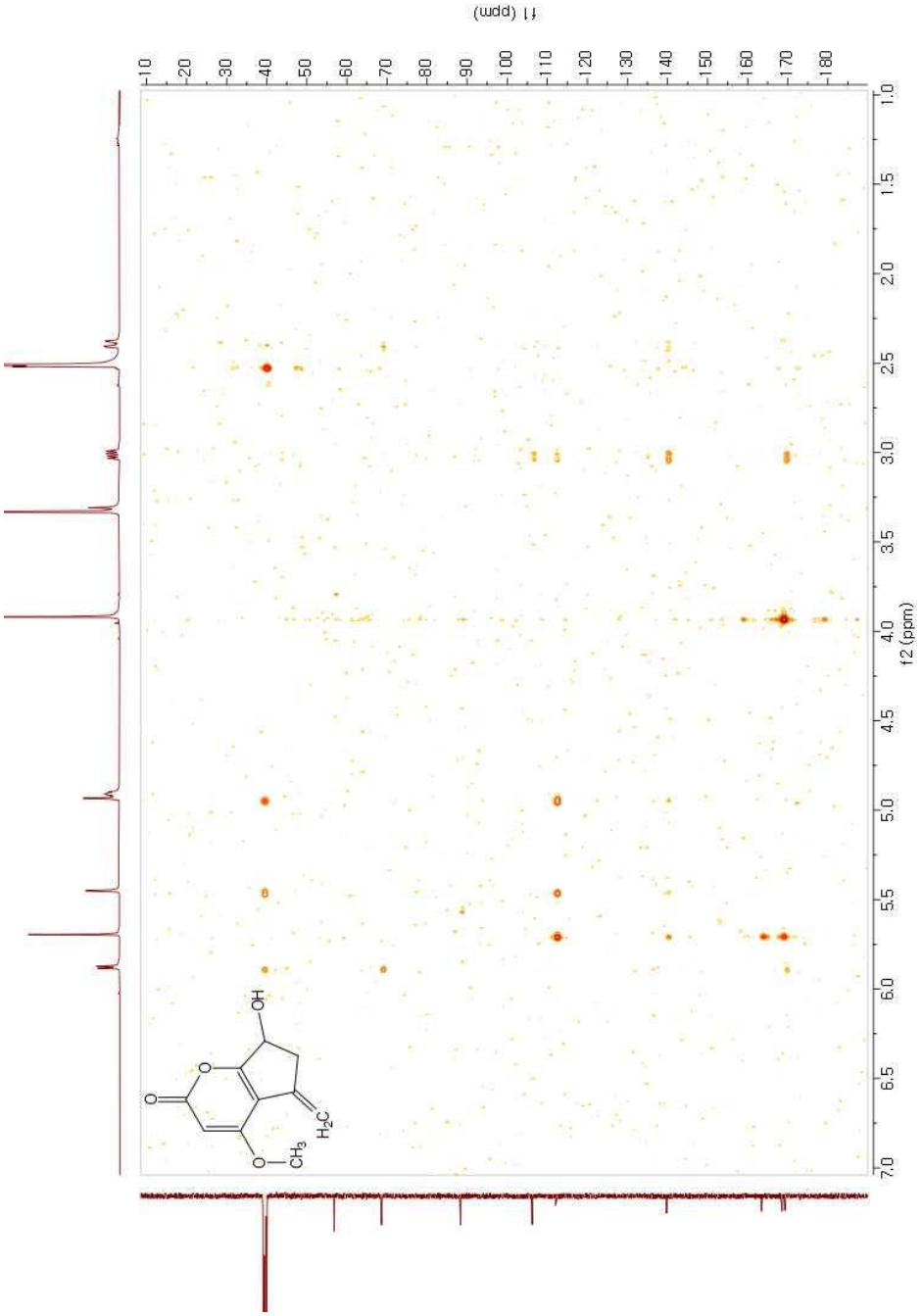
S16. COSY NMR Data of 7-hydroxy-4-methoxy-5-methylene-6,7-dihydrocyclopenta[b]pyran-2(5H)-one (Pyrone 64)



S17. HSQC NMR Data of 7-hydroxy-4-methoxy-5-methylene-6,7-dihydrocyclopenta[b]pyran-2(5H)-one (Pyrone 64)



S18. HMBC NMR Data of 7-hydroxy-4-methoxy-5-methylene-6,7-dihydrocyclopenta[b]pyran-2(5H)-one (Pyrone 64)



초 록

2-피론은 방향족 고리활물로 자연계에서 많이 발견될 뿐 아니라 알켄과 아렌의 두가지 화학적 특성을 공유하고 있으므로 유기합성에 활용도가 높은 전구체이다. 2-피론의 구조를 포함하는 화합물 중에서 시클로펜타피론은 피론에 오각고리가 붙어있는 물질로 주목할 만한 물질이다. 이 구조가 천연물에 종종 나타날 뿐 아니라 2-피론이 고리화첨가 반응을 통해 육각, 팔각 고리화합물을 합성하는 방법이 개발됨에 따라 시클로펜타피론을 시료로 이용하면 5-8 고리구조와 같은 축합고리구조를 합성하는데 기여할 수 있기 때문이다. 기존에 존재하는 시클로펜타피론은 오각고리에서 피론을 합성하는 방법은 알려져 있지만 피론으로부터 오각고리를 붙이는 방법은 알려져 있지 않다. 자연계에 존재하는 시클로펜타피론 구조 혹은 5-8 축합고리계에서 오각 고리에 비대칭적으로 연결되어 있는 치환기가 있는 데 반면 기존의 시클로펜타피론 합성법은 치환기를 오각 고리 내에 원하는 곳에 도입시키기 쉽지 않을 뿐 아니라 비대칭성을 구현하기 어렵다는 단점이 있다. 한 편, 2-피론으로부터 고리화 반응을 통하여 시클로펜타피론을 합성을 할 경우 시작물질의 형태를 조절하고 적절한 고리화 반응을 적용한다면 오각 고리에 치환기를 도입할 수 있음은 물론 비대칭적 고리화 반응을 시도해 볼 수 있다. 본 연구에서는 오각 탄소 고리를 합성하는데 잘 알려진 나자로프 고리화 반응과 로듐을 촉매로 이용하는 하이드로아실화 반응을 이용하여 피론으로부터 시클로펜타피론을 합성하고자 하였다. 나자로프 반응 시도 결과 다양한 조건에도 불구하고 분해되거나 원치 않던 1,4-첨가반응이 일어났다. 이는 2-피론의 전자가 결핍되어있는 특성으로 기인한 것으로 판단된다. 로듐을 촉매로 하는 분자내 하이드로아실화 반응을 탐구한 결과, 기대했던 케톤 화합물이 나오지 않았으나 예상치 못했던 형태의 오각 고리가 형성되었는데 이는 로듐 촉매가 루이스 산으로 작용하여 프린스 고리화 반응이 일어난 것으로 나타났다. 이 결과를 바탕으로 연구하여 브론스티드 산과 분자 여과기를

사용하였을 때, 프린스 고리화 반응의 수득률이 비교적 높게 나오는 것을 밝혀내었다. 본 연구를 바탕으로 다양한 치환체를 가진 시클로펜타피론 합성이 가능할 것으로 판단되며 비대칭성인 산을 이용하는 추후 연구를 통해 입체이성질체의 시클로펜타피론 합성하는데 기여할 수 있을 것으로 기대된다.

주요어: cyclization, cyclopentapyrone, hydroacylation, Nazarov reaction, Prins reaction, 2-pyrone, rhodium catalysis

학 번: 2019-24776

Acknowledgment

길다면 길고 짧다면 짧은 2년이 지나고 석사 과정을 마치게 되었습니다. 지금 돌이켜보면 이렇게 석사 생활을 하였다는 것이 행운이라는 생각이 들 정도로 주변의 정말 많은 분들로부터 도움을 받고 또 값진 경험을 한 것 같습니다.

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마지막으로 저를 믿고 뒤에서 아낌 없이 응원해주신 어머님, 저의 멘토 역할을 해주시며 방향을 알려주신 큰 고모께 감사 인사를 드립니다.

너무 과분하게 많은 도움을 받은 것 같습니다. 받은 은혜 잊지 않고 선한 영향력으로 보답할 수 있도록 최선을 다하겠습니다. 감사합니다.