1943

THESIS APPROVAL

GRADUATE SCHOOL, KASETSART UNIVERSITY

Doctor of Philosophy (Organic Chemistry)
DEGREE

Organic Chemistry
FIELD

Chemistry
DEPARTMENT

TITLE: Part I: Synthesis of (±)-Isagarin, (±)-Marticin and (±)-Isomarticin by Palladium(II) Catalysis
Part II: Stereoselective Palladium(0)- Catalyzed Four-Component Cascade synthesis of Pyrrolidinyl isoquinolines

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THESIS

PART I : SYNTHESIS OF (±)-ISAGARIN, (±)-MARTICIN AND (±)-ISOMARTICIN BY PALLADIUM(II) CATALYSIS

PART II: STEREOSELECTIVE PALLADIUM(0)-CATALYZED FOUR-COMPONENT CASCADE SYNTHESIS OF PYRROLIDINYL ISOQUINOLINES

CHATCHAWAN PLOYSUK

A Thesis Submitted in Partial Fulfilment of
the Requirements for the Degree of
Doctor of Philosophy (Organic Chemistry)
Graduate School, Kasetsart University
2007

Chatchawan Ploysuk 2007: Part I: Synthesis of (±)-Isagarin, (±)-Marticin and (±)-Isomarticin by Palladium(II) Catalysis Part II: Stereoselective Palladium(0)- Catalyzed Four-Component Cascade synthesis of Pyrrolidinyl isoquinolines. Doctor of Philosophy (Organic Chemistry), Major Field: Organic Chemistry, Department of Chemistry. Thesis Advisor: Associate Professor Boonsong Kongkathip, Ph.D. 176 pages.

Part I: Pyranonaphthoquinones are known as the important sources of biologically active compounds. Some of these are structurally quite complex such as (-)-isagarin (11), isolated from the roots of *Pentus longiflora*, (+)-marticin (12) and (+)-isomarticin (13), isolated from the culture extraction of fungi. (±)-Isagarin (11) has been synthesized in 5 steps in 24.1% overall yield from 3-allyl-2-bromo-1,4-dimethoxynaphthalene (116). (±)-Marticin (12) and (±)-isomarticin (13) have been synthesized from vanillin in 15 steps with 0.27% overall yield or from hydroquione in 14 steps with 0.36 % overall yield.

The synthesis of (±)-Isagarin (11) started from the 3-allyl-2-bromo-1,4-dimethoxynaphthalene (116) which was prepared from 2-bromo-1,4-naphthoquinone (114). Coupling of 2-bromo-1,4-dimethoxynaphthalene (116) with benzyloxy-acetaldehyde (119) or (tert-butyl-dimethyl-silanyloxy)-acetaldehyde (121) followed by removal of protecting groups (benzyl or silyl) gave olefinic diol (126). Wacker reaction ($PdCl_2$, $CuCl_2$, O_2) of olefinic diol (126) and subsequent oxidation with CAN provided the desired Isagarin (11).

(±)-Marticin (12) and (±)-isomarticin (13) have been successfully synthesized from 1,2,4,5,8-pentamethoxynaphthalene (147). The starting material, 1,2,4,5,8-pentamethoxy naphthalene (147) was prepared from either commercially available vanillin (141) or hydroquinone (154). The key synthesis of (±)-marticin (12) and (±)-isomarticin (13) from 1,2,4,5,8-pentamethoxynaphthalene (147) involved the introduction of a masked acid side chain(132) into the naphthoquinone ring via Friedel-Craft acylation, introduction of an allyl group via radical reaction and the formation of the dioxabicyclic ring by the Wacker reaction.

Part II: Multi-component reactions (MCRs) play an important role in combinatorial chemistry because of its ability to prepare complex molecular architectures from readily available building blocks. Among the advantages of MCRs are yields that higher than almost any sequential synthesis of the same target and a single purification step. Herein, we reported a new type of MCR to synthesize pyrrolidinyl isoquinoline derivatives using a four component-cascade with 2-iodobenzyldehyde to generate azomethine ylides in situ. The azomethine ylides are1,3-dipoles and are immediately trapped with *N*-methyl maleimide (NMM) as the dipolarlophile to form pyrrolidinyl isoquinolines. We also studied the mechanism of this reaction and its stereochemical outcome.

Chatchawan Ploysuk
Student's signature

Thesis Advisor's signature 28 / May / 2007

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor, Associate Professor Boonsong Kongkathip, whose teaching and guidance were a source of great inspiration to me. His valuable helpful suggestions, and assistance were indispensable throughout the course of my graduate study at Kasetsart University.

Thanks are extended to Professor Ronald Grigg for his valuable discussions, suggestions and assistance and also Dr. Sridharan Visuvanathar for his continuous support, advice and discussions while working on my thesis at University of Leeds (MIDAS), England.

I also gratefully acknowledge Associate Professor Ngampong Kongkathip and Associate Professor Apisit Songsasen, my two co-advisors for their suggestions and helpful assistance.

Thanks to Dr. Simon Barret (NMR), Tanya Marinko-Covell (mass spectral data), Martin Huscroft and Ian Blakely (microanalysis), for their professional assistance. Thanks are extended to Associate Professor Sunit Suksamlarn, Department of Chemistry, Faculty of Science, Srinakarin Wiroth University for NMR analyses.

The Thailand Research Fund (TRF) under the Royal Golden Jubilee Program is acknowledged for financial support.

I also express gratitude to the Natural Products and Organic Synthesis Research Unit (NPOS), Department of Chemistry, Faculty of Science, Kasetsart University and the Molecular Innovation, Diversity and Automated Synthesis centre (MIDAS), School of Chemistry, University of Leeds.

Finally, I am thankful to my parents for their understanding, encouragement and warm hospitality and also to the people whose company I have enjoyed.

Chatchawan Ploysuk
April 2007

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LIST OF ABBREVIATIONS

Ac = acetyl
Ar = aromatic
Bn = benzyl
Bu = butyl
br = broad
Bz = benzoyl
CAN = ceric ammonium nitate
Cbz = benzyloxycarbonyl
^{13}C NMR = Carbon nuclear magnetic resonance
CDCl$_3$ = deuterated choloform
CHCl$_3$ = choloform
dba = dibenzylideneacetone
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC = dicyclohexyl carbodiimide
DCM = dichloromethane
dd = doublet of doublet
ddd = doublet of doublet of doublet
DMAP = 4-dimethylaminopyridine
DME = 1,2-dimethoxyethane
DMF = *N*,*N*-dimethylformamide
DMSO = dimethylsulfoxide
ee = enantiomeric excess
EI = electron impact
eq. = equivalent
FTIR = Fourier transform infrared spectroscopy
h = hour
^{1}H NMR = Proton nuclear magnetic resonance
HPLC = high performance liquid chromatography
HRMS = high resolution mass spectroscopy
Hz = Hertz

LIST OF ABBREVIATIONS (cont'd)

ES = electrospray
Et = ethyl
$\mathrm{Et_2O}$ = diethyl ether
EWG = electron withdrawing group
o = ortho
J = coupling constant
m = multiplet
MCRs = multi-component reactions
Me = methyl
MeCN = acetonitrile
min = minute
m.p. = melting point
MS = mass spectroscopy
NMR = nuclear magnetic resonance
NMM = *N*-methyl maleimide
n.O.e = nuclear Overhauser effect
Nu = nucleophile
Ph = phenyl
p = para
q = quartet
r.t. = room temperature
s = singlet
t = triplet
TBDPS = *t*-butyldiphenylsilyl
TBS = *t*-butyldimethylsilyl
TFA = trifluoroacetic acid
TFP = tris(2-furyl)phosphine
THF = tetrahydrofuran

TMS = trimethylsilyl

TMSOTf = trimethylsilyl trifluoromethylsulfonate

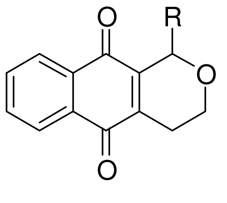
TS = *p*-toluenesulfonyl

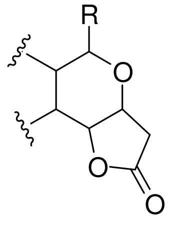
PART I: SYNTHESIS OF (±)-ISAGARIN, (±)-MARTICIN AND (±)-ISOMARTICIN BY PALLADIUM(II) CATALYSIS

INTRODUCTION

Natural products derived from microorganism are very important sources of biologically active compounds especially those systems with a pyranonaphthoquinone skeleton which are isolated from various strains of bacteria and fungi. This class displays activities against a variety of Gram-positive bacteria, pathogenic fungi and yeasts, as well as antiviral activity. In addition, they have been proposed to act as bioreductive alkylating agents (Moore, 1977). Some of the more recently discovered examples are structurally fairly complex and provide significant synthetic challenges.

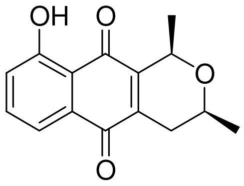
The core skeleton of pyranonaphthoquinone compounds is the naphtho[2,3-c]pyran-5,10-dione ring system (1) and some members of the family containing an additional γ-lactone ring (2) fused to the dihydropyran moiety as the basic subunit.



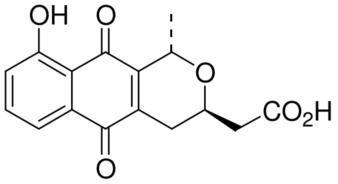


Naphtho[2,3-c]pyran-5,10-dione (1) **γ-lactone ring (2)**

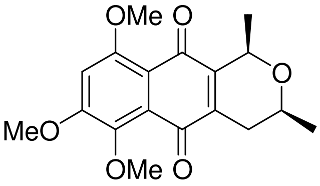
The diversity of chemical structures found within the pyranonaphthoquinone family of antibiotics has prompted syntheses of members of this class, for example: elutherin (3) (Dotz *et al.*, 2000), nanaomycin A (4) (Semmelhack *et al.*, 1985; Decker. *et al.*, 1987; Kreaus et al., 1987) , ventiloquinone E (5) (Giles *et al.*, 1991; Bergeron et al., 1992), ventiloquinone G (6) (Namura. *et al.*, 1987), ventiloquinone J (7) (Giles. *et al.*, 1991), frenolicin B (8) (Kreaus *et al.*, 1993), arizonin C1 (9) (Brimble *et al.*, 1995), granaticin (10) (Namura *et al.*, 1987). Recently, the syntheses of pyranonaphthoquinones were reviewed. (Brimble *et al.*, 2000).



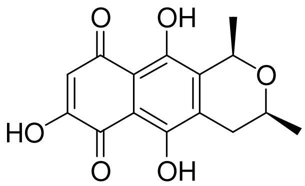
Elutherin (3)



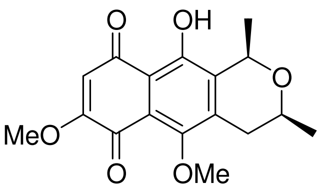
Nanaomycin A (4)



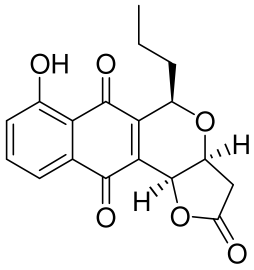
Ventiloquinone E (5)



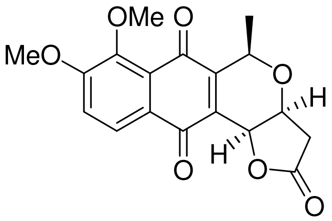
Ventiloquinone G (6)



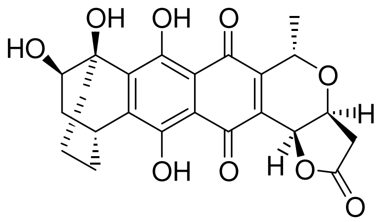
Ventiloquinone J (7)



Frenolicin B (8)

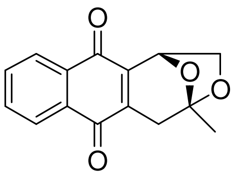


Arizonin C1 (9)

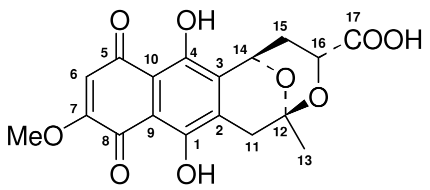


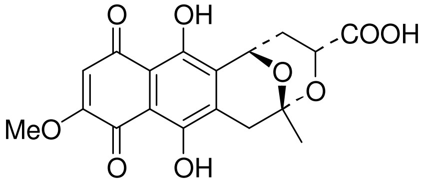
Granaticin (10)

Some members of pyranonaphthoquinone class contain an oxabicyclic moiety connected to naphthoquinone such as (-)-isagarin (11), (+)-marticin (12) and (+)-isomarticin (13) (De Kimpe *et al.*, 1998; Holenstein *et al.*, 1984).



(-)-Isagarin (11)



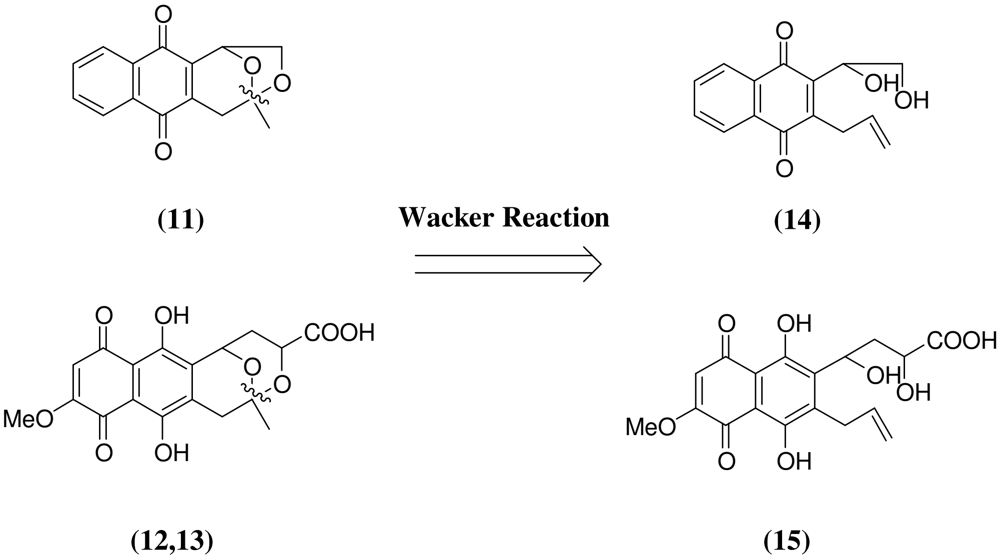


(+)-Marticin (12) **(+)-Isomarticin (13)**

The tetracyclic naphthoquinone (-)-isagarin (11), 1,4-epoxy-4-methyl-1,2,4,5-tetrahydronaphtho[2,3-d]oxepin-6,11-dione, was isolated from the roots of *Pentas longiflora* and subsequently synthesized by De Kimpe *et al.* in 1999.

(±)-Marticin (12) and (±)-isomarticin (13) were isolated from the acid fraction extract of the fungal culture strains: *Fusarium martii, Fusarium. solani* and *Fusarium spp.* (Holenstein *et al.*, 1983; Tatum *et. al.*, 1983). Marticin (12) and isomarticin (13) contain three stereogenic centers (C-12, C-14 and C-16). The stereochemistry at the C-14, C-16 and C-12 position of (±)-marticin (12) was recently revised to be *S*, *S* and *R* whereas the stereochemistry at the C-14, C-16 and C-12 position of (±)-isomarticin (12) was recently revised to be *R*, *R* and *R*, respectively (Holenstein.*et al.* in 1984).

Our group has reported the formation of the dioxabicyclic skeleton of several natural products by palladium-catalysed reactions. For example: the synthesis of brevicomin (Kongkathip *et al.*, 1984), frontalin (Kongkathip *et al.*, 1985) and amberketal (Kongkathip *et al.*, 1999). Isagarin (11), marticin (12) and isomarticin (13) contain a dioxabicyclic ring and might be prepared via Wacker reaction ($PdCl_2/CuCl_2/O_2$) as shown in Scheme 1.



Scheme 1

The objectives of this research are

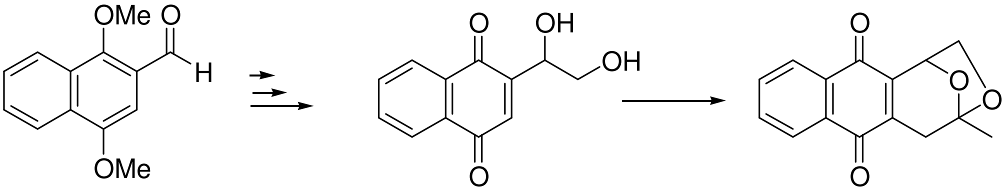
i) to synthesize (±)-isagarin (11)

ii) to synthesize (±)-marticin (12) and (±)-isomarticin (13)

iii) to investigate the intramolecular cyclization reaction by Wacker reaction ($PdCl_2/CuCl_2/O_2$) for the construction of the dioxabicyclic skeleton of these target molecules

LITERATURE REVIEWS

Recently, a new type of tetracyclic naphthoqiunone, named isagarin (11), was isolated from the hexane extract of dried roots of *Pentus longiflora* and subsequently synthesized (Kimpe *et al.* 1999). Kimpe's synthesis relies on the conjugate addition of an acetyl pyridinium ylide, generated *in situ* from *N*-acetylmethyl pyridinium chloride and trimethylamine, to give an unisolated intermediate naphthoquinone containing keto diol functional groups which undergo spontaneous ketalisation to afford isagarin (11).

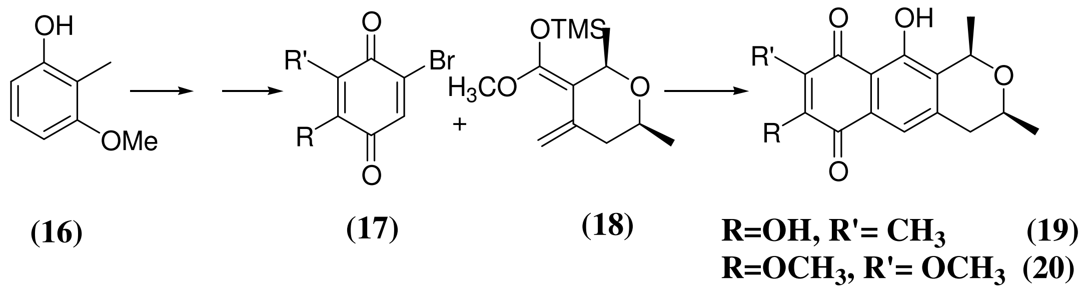


Isagarin (11)

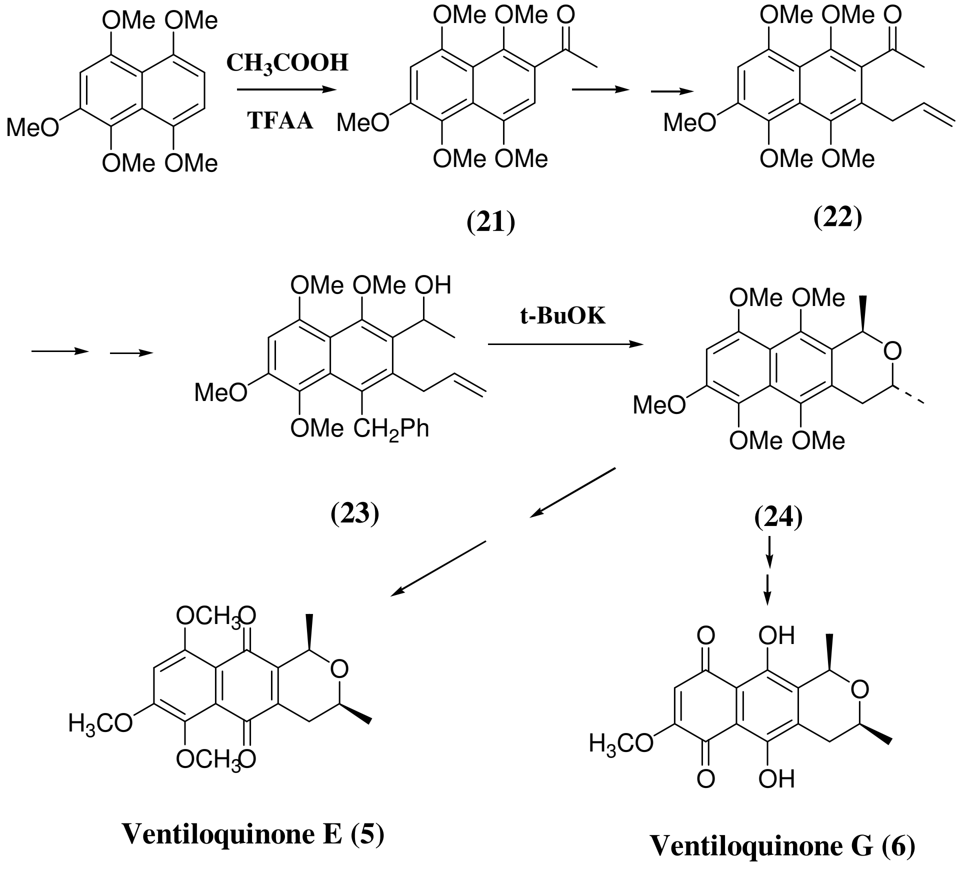
The synthesis of marticin (13) and isomarticin (14) has not been reported. Therefore we proposed syntheses of these form a core naphthoquinone and then building up the cyclic ketal via Wacker reaction.

Ring construction of core pyranonapthoquinone

Many approaches have been proposed for the synthesis of naturally occurring benzoisochroman-5, 10-quinone. In 1990, Brassard succeeded in the synthesis of (+)-ventilagone (19) and ventiloquinone H (20) by Diels-Alder reaction of bromobenzoquinone (17) which was prepared by 3-methoxy-2-methyl phenol (16) and heterocyclic diene (18).

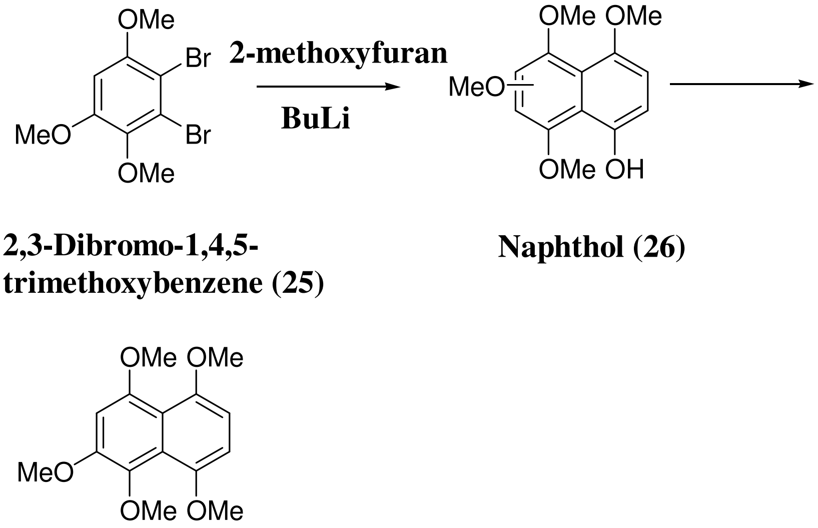


(-)-Ventiloquinone E (5) was synthesized using a different approach (Giles *et al.*, 1991). The ortho acetyl naphthalene (21) precursor was easily prepared from 1,2,4,5,8-pentamethoxynaphthalene. Allylation of (21) followed by reduction and cyclisation afforded the trans-dimethylnaphthopyran (24). Oxidation of (24) with CAN provided ventiloquinone E (5) but when (24) was oxidized using silver(I) oxide and then treated with ethanolic hydrochloric acid ventiloquinone G (6) was formed (Scheme 2).



Scheme 2

The synthesis of 1,2,4,5,8-pentamethoxynaphthalene was achieved from 2,3-dibromo-1,4,5-trimethoxybenzene (25) as starting material (Giles *et al.*, 1988). Reaction of compound (25) with *n*-butyl lithium generated a benzyne intermediate which reacted *in situ* with commercially available 2-methoxyfuran to afford the naphthol (26). Methylation of naphthol (26) using dimethylsulfate and potassium carbonate in acetone gave 1,2,4,5,8-pentamethoxynaphthalene (Scheme 3).



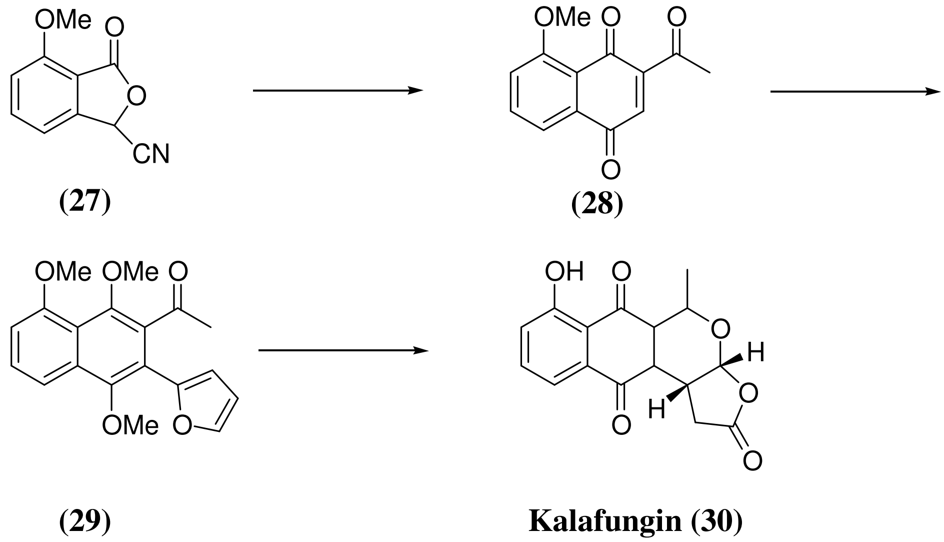
2,3-Dibromo-1,4,5-trimethoxybenzene (25)

Naphthol (26)

1,2,4,5,8-Pentamethoxynaphthalene

Scheme 3

The synthesis of kelafungin (30) described another method to construct the naphthoquinone ring (Kraus *et al.*, 1983). The key step involved 1,4-addition of a phthalide precursor (27) (Scheme 4).



(27) **(28)**

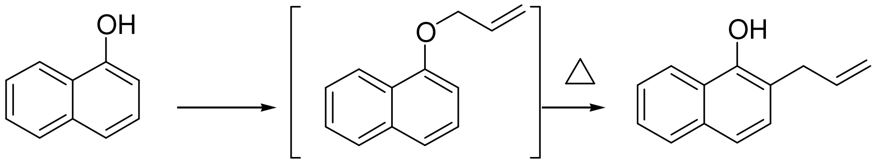
(29) **Kalafungin (30)**

Scheme 4

Introduction of an allyl group onto the naphthalene ring

Generally, C-Allylation can be carried out by Claisen rearrangement of naphthol derivatives or 1,4-addition of an allylmetal reagent to p-naphthoquinone.

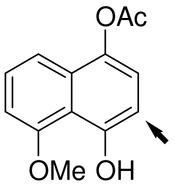
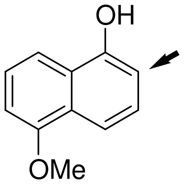
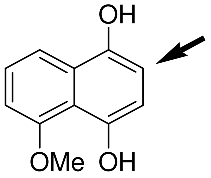
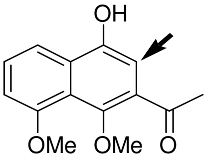
The Claisen rearrangement is a powerful carbon-carbon bond-forming chemical reaction discovered by Rainer Ludwig Claisen in 1912. Heating an allyl vinyl ether (32) initiates a [3,3]-sigmatropic rearrangement to give (33) (Scheme 5**.** Many reports of C-allylation of to naphthalenes via Claisen rearrangement have been published some of which are shown in Table 1.



(31) **(32)** **(33)**

Scheme 5

Table 1 Claisen rearrangement of naphthalene derivatives[a]

Substrates	Conditions	References
 **(34)**	1. Allyl bromide, K_2CO_3, acetone, reflux 2. 200 ^{0}C, 71 %	Kraus *et al.*, 1987.
 **(35)**	1. Allyl bromide, K_2CO_3, acetone, reflux 2. 200 ^{0}C, 81 %	Schmid *et al.*, 1958.
 **(36)**	1. Allyl bromide, K_2CO_3, acetone, reflux 2. Me_2SO_4, K_2CO_3 3. DMF, 140 ^{0}C, 73 %	Masquelin *et al.*, 1995.
 **(37)**	1. Allyl bromide, K_2CO_3, acetone, reflux 2. 220 ^{0}C, 35 min, 75%	Green *et al.*, 1996

[a] Arrows indicated side of allylation

1,4-Addition reaction represents a versatile method to introduce an allyl group into the naphthoquine ring. Normally, the reaction uses but-3-enoic acid or an allylmetal such as allyltin, allylsilane or allylzine as nucleophilic reagents. These methods have been further studied and applied by several groups to synthesize pyranonaphthoquinone class (Table 2).

Table 2 Allylation of naphthoquinone derivatives via 1,4-addition reaction

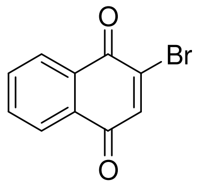
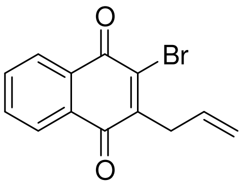
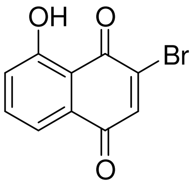
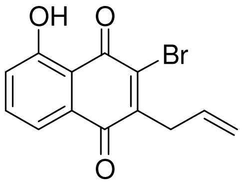
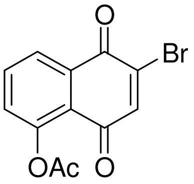
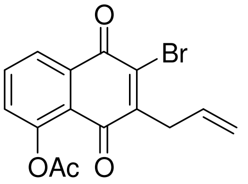
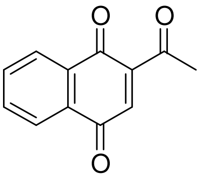
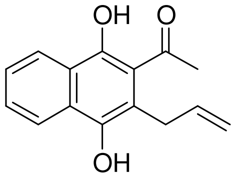
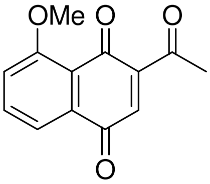
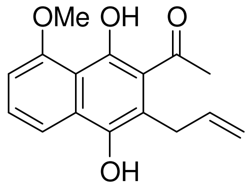
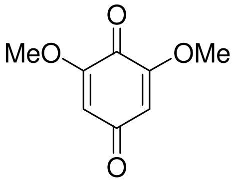
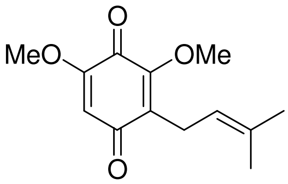
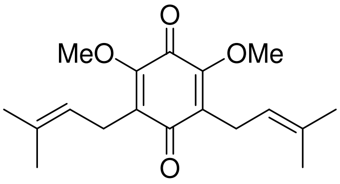
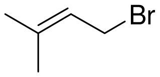
Substrates	Products	Reaction Conditions/ References
 **(38)**	 **(39)**	$AgNO_3$, 3-butenoic acid 70 ^{0}C Ammonium peroxodisulphonate 78 % (Masato *et al.*, 1981)
 **(40)**	 **(41)**	$AgNO_3$, 3-butenoic acid 70 ^{0}C Ammonium peroxodisulphonate 65 % (Kometani *et al.*, 1989)
 **(42)**	 **(43)**	$AgNO_3$, 3-butenoic acid 70 ^{0}C Ammonium peroxodisulphonate 69 % (Masato *et al.*, 1983)

Table 2 (cont'd)

Substrates	Products	Reaction Conditions/ References
 **(44)**	 **(45)**	Allyltrimethyltin, BF$_3$.OEt$_2$, CH$_2$Cl$_2$, -78 ^{0}C , 74 % (Uno *et al.*, 1986)
 **(46)**	 **(47)**	Allyltrimethyltin, BF$_3$.OEt$_2$, CH$_2$Cl$_2$, -78 ^{0}C ,73 % (Uno *et al.*, 1981)
 **(48)**	 **(49)**  **(50)**	Zn, THF, 60 ^{0} C  55 % (Oliveira *et al.*, 1997)

Acylation of naphthalene derivatives

Friedel-Crafts acylation and Fries rearrangement are classical methodology to connect acyl groups onto an aromatic ring to afford aromatic ketones. Normally, the reactions involve an acid chloride or acid anhydride as acylating reagents and a Lewis acid such as $AlCl_3$, $BF_3.OEt_2$, $TiCl_4$ or $SnCl_4$ as catalyst. Some naphthalene examples of Friedel-Crafts acylation and Fries rearrangement are shown in Table 3.

Table 3 Friedel-Crafts acylation and Fries rearrangement of naphthalene derivatives

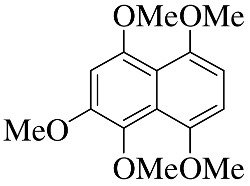
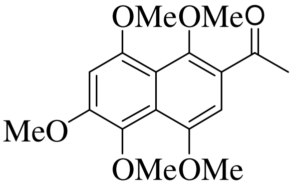
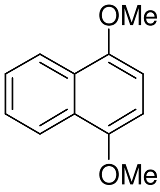
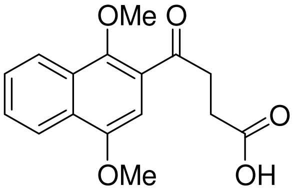
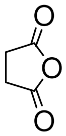
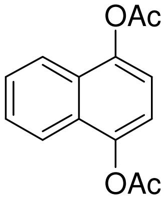
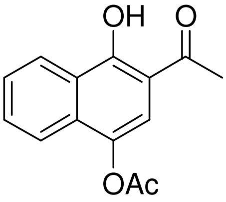
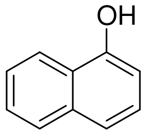
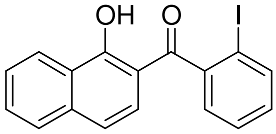
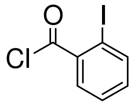
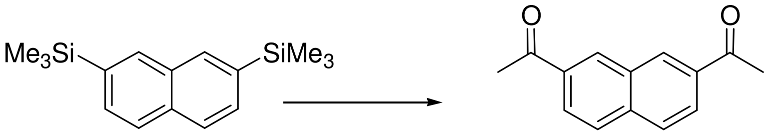
Substrates	Products	Reaction Conditions/ References
 **(51)**	 **(52)**	CH_3COOH, TFAA 12h. 78 % (Giles *et al.*, 1991)
 **(53)**	 **(54)**	$AlCl_3$, nitrobenzene  82 % (Fieser *et al.*, 1963)
 **(55)**	 **(56)**	$BF_3.OAc$ 85 % (Wigle *et al.*, 2000)

Table 3 (Cont'd)

Substrates	Products	Reaction Conditions/ References
 **(57)**	 **(58)**	$TiCl_4$, 120 ^{0}C  **(59)** 87 % (Jones *et al.*, 2000)

A novel coupling approach to acylation of aromatic rings has been achieved by using silylnaphthalene (60), acetyl chloride and aluminum trichloride as a catalyst to give diketone (61) in a good yield (Scheme 6) (Katz *et al.*, 1997).



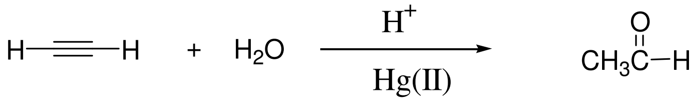
(60) **(61)**

Scheme 6

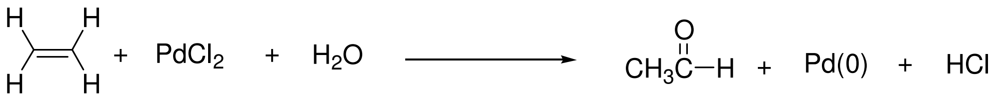
Palladium cyclization by Wacker reaction

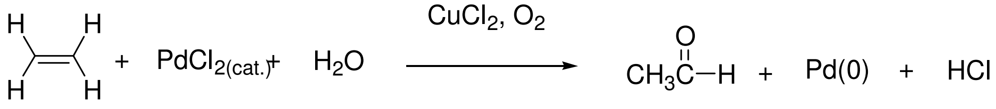
Acetaldehyde was originally prepared from hydration of acetylene. This synthesis is now obsolete because of problems associated with the acetylene. Acetylene is produced by heating a hydrocarbon stream to high temperature, sometimes in the presence of electric arc. All processes for producing acetylene require large amounts of energy. Acetylene is also thermodynamically unstable, it must be handled with extreme care in order to prevent explosion.

The incentive existed to develop production of acetaldehyde from a cheaper and less hazardous starting material. It had long been known that acetaldehyde formed directly from ethylene and water in the presence of a stoichiometric amount of $PdCl_2$ and a commercially feasible process was developed by Smidt that employed Pd in catalytic amounts ($PdCl_2$, $CuCl_2$, O_2).



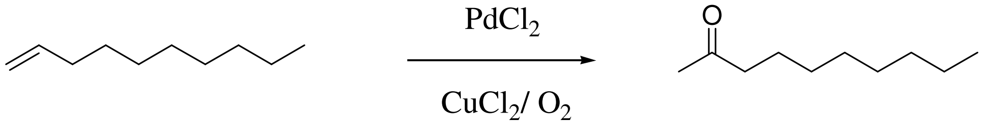
$$H{-}{\equiv}{-}H \quad + \quad H_2O \xrightarrow[Hg(II)]{H^+} CH_3\overset{O}{\overset{\|}{C}}{-}H$$



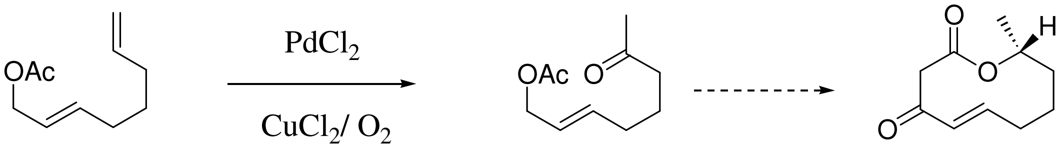


This chemistry was also applied to prepare methyl ketones from terminal olefins. 2-Undecanone (63) was synthesized via palladium catalyst from oxidation of 1-undecene (62) (Miller *et al.*, 1992). In diplodialide synthesis, the diene ester (64) was oxidized to the corresponding methyl ketone (65) a in good yield by the Wacker process (Tsuji, 1979). Only the terminal olefin was oxidized because internal double bonds are much less reactive due to steric hindrance.

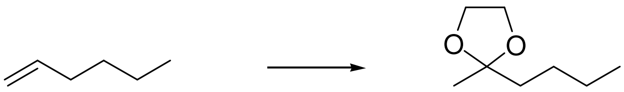
On the basis of mechanism, alcohols could be used as nucleophiles in Wacker reaction to afford ketals. By using dry ethlylene glycol as solvent, ketal (68) was prepared from olefin (67) in a good yield (Hunt *et al.*, 1972).



(62) **(63)**

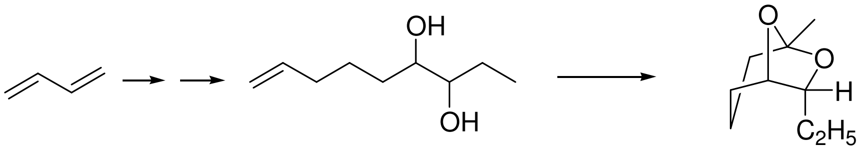


(64) **(65)** **Diplodialide (66)**



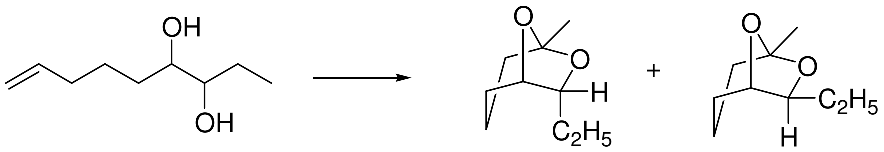
(67) **(68)**

In 1976, Wacker reaction was first modified for intramolecular cyclization reactions. An insect pheromone, endo-brevicomin (70) was simply prepared from the palladium catalyzed cyclization of the olefinic diol (69) by Grigg *et al.*



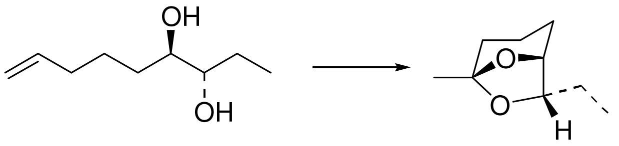
(69) **(70)**

By careful study, it was reported later that the above synthesis route, in fact, provided both endo-and exo-brevicomin (71, 72) in ratio of 1:5 (Grigg *et al.*, 1984).

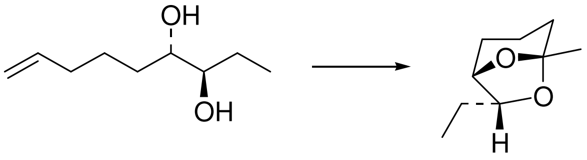


(69) **(71)** **(72)**

In the following year, Mori and Seu (1985) reported the enantioselective synthesis of (1R, 5S, 7S)-(+)-endo-brevicomin (71a) and its (1S, 5S, 7R)-(-)-isomer (71b) from diols 69a and 69b, respectively by using palladium catalyzed cyclization as the key step.

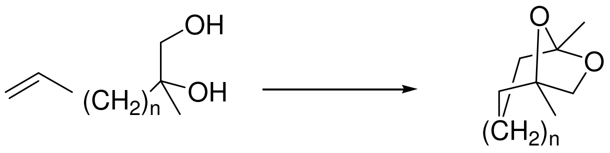


(69a) **(1R,5S,7S)-(+)-endo-brevicomin (71a)**



(69b) **(1S,5R,7R)-(+)-endo-brevicomin (71b)**

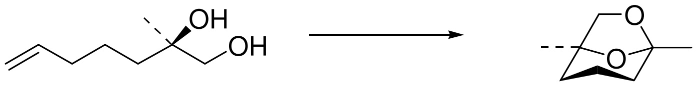
In 1985, Kongkathip *et al.,* applied this reaction to synthesize frontalin (74), an insect pheromone of *Dendroctonus frontalis*, and its analogue (76) from corresponding diols (73) and (75).



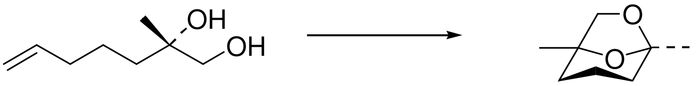
73 : n = 3 **74 : n =1**

75 : n = 4 **76 : n = 2**

During the same period, Hosokawa *et al.* (1985), reported the synthesis of both (S)-(-)-frontalin (78) and unnatural (R)-(+)-frontalin (80) in high enantiomeric excess from olefinic diols (77) and (79), respectively.

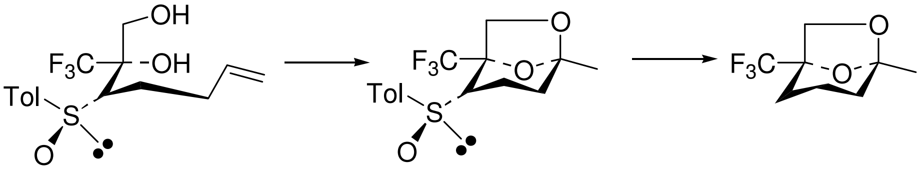


(77) **(78)**



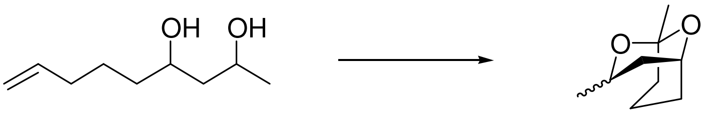
(79) **(80)**

In 1999, Bravo *et al.* developed the synthetic approach of enantiomerically pure (-)-(1S,5S)-1-trifluoromethyl frontalin (83) by using a chiral building block approach.



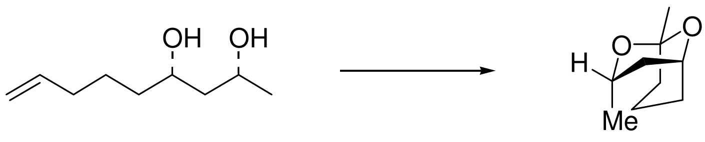
(81) **(82)** **(83)**

The insect attractant, 1,3-dimethyl-2-9 dioxabicyclo [3.3.1] nonane (85) was synthesized from the corresponding 1,3-diol (84) by this method (Kongkathip *et al.*, 1984).

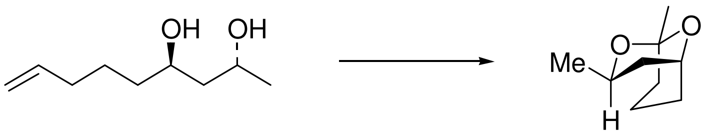


84 **85**

In 1986, Sutherland *el al.*, reported the stereospecific synthesis of exo- and endo-1,3-dimethyl-2,9-[3.3.1] nonane (87 and 89) from 1,3-diols (86) and (88), respectively.

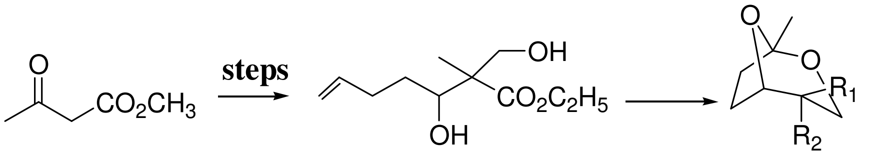


(86) **(87)**



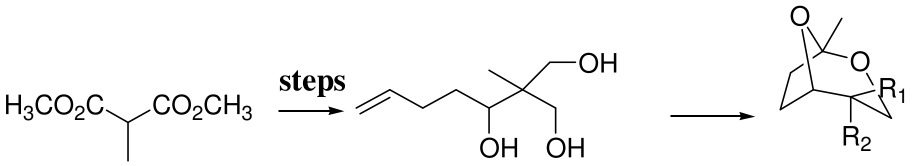
(88) **(89)**

Both diastereoisomers of 2,8-dioxabicyclo [3.2.1] octane derivatives (92, 93), and the 4-hydroxy methyl analogues (96, 97) were synthesized from ethyl acetoacetate (90) and diethyl malonate (94), respectively. The key step of this process involved intramolecular cyclization using palladium chloride as catalyst. (Kongkathip *et al.*, 1999)



(90) **(91)**

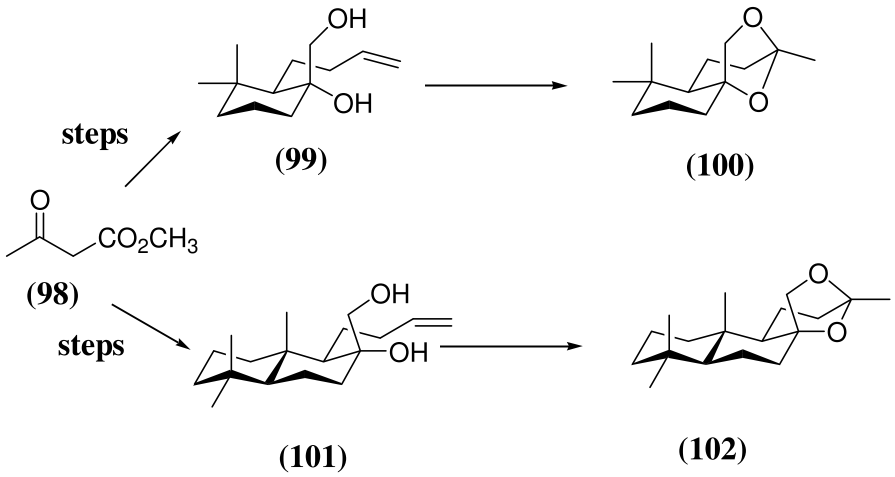
(92) $R_1 = CO_2C_2H_5$; $R_2 = CH_3$
(93) $R_1 = CH_2OH$; $R_2 = CO_2C_2H_5$



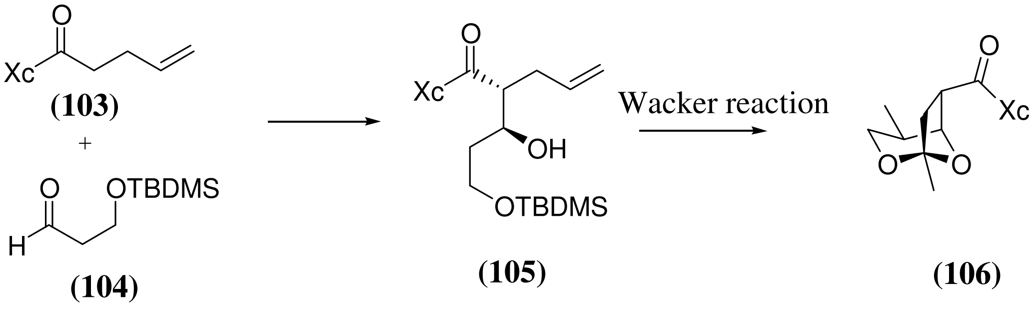
(94) **(95)**

(96) $R_1 = CO_2OH$; $R_2 = CH_3$
(97) $R_1 = CH_3$; $R_2 = CH_2OH$

In the same year, amberketal (100) and acetal homologue (102) were synthesized from a commercially available methyl acetoacetate (98) (Kongkathip *et al.*, 1999).



In 1999, Perlmutter *et al.*, reported a rapid method for enantioselective construction of 2,8-dioxabycyclo[3.2.1]octanes of relevance to zaragozic acid. Asymmetric aldol condensation of (103) with aldehyde (104) provided the partially protected enediol (105) as a single isomer. Direct ring closure of mono silylether (105) proceeded efficiently to (106), obviating the need for desilylation prior to ring closure. Presumably, the HCl generated during the Wacker oxidation is sufficient to promote desilylation of the primary silylether.



MATERIALS AND METHODS

Materials

Instrumentation

The following analytical methods were used throughout this project, unless otherwise indicated.

^{1}H and ^{13}C-NMR spectra were recorded on Bruker (300 MHz) spectrometer at Department of Chemistry, Srinakarinwiroth University and on Brucker (400 MHz) Advance DPX-400. Chemical shifts are reported as parts per million (δ) downfield from tetramethylsilane (TMS) as internal standard. Unless otherwise specified deuterochloroform ($CDCl_3$) and deuteracetone (CD_3COCD_3) were used as solvents. Coupling constants (J) are given in Hertz (Hz) and peak multiplicities are reported using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet, dd = double doublet, dt = double triplet.

Mass spectra and accurate masses (HRMS) were obtained on a JEOL JMS-SX102 mass spectrometer, on a GCMS-QP-5050A in electron impact mode at 70 eV and on an Agilent 1100 Series LC/MSSD Trap in chemical ionization.

Infrared (IR) spectra were recorded on a FTIR Perkin-Elmer System 2000 as neat liquid or KBr pellet at Department of Chemistry, Kasetsart University.

Melting points data (mp) were determined on Fisher Johns apparatus at Department of Chemistry, Kasetsart University and are uncorrected.

Chromatographic system

Thin layer chromatography (TLC) was carried out on aluminum sheets coated with 200-300 mesh silica gel with a fluorescent indicator (254 nm) (Merck) for monitoring reaction progress. The chromatograms were visualized under ultraviolet light (254 nm) and/or by spraying with a solution of 3% vanillin in ethanol with 3% sulfuric acid following by heating on a hot plate.

Ultraviolet absorbtion spectra were recorded using a 3D spectra program of HPLC Agilent 1200 series with Eclipe XDB-C18 Pack column [150x406 mm., i.d. 5 μm].

Flash column chromatography was performed as described by Still W.C. employing less than 230 mesh silica gel.

The ratio of enatiomeric mixture of (±)-isagarin (11) was determined by chiral HPLC column (Chiralcel OD column 250 x 4.6 mm).

Chemical reagents

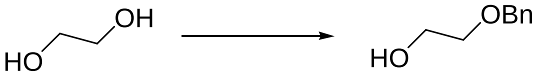
1-Naphthol, p-hydrobenzoquinone, vanillin were purchased from Fluka and Merck.

All other chemicals were obtained from Aldrich, Fluka and Merck Co. and were used without further purification. In the case of anhydrous solvent were dried according to the standard procedure outlined by Vogel (1989) in Vogel' Text Book of Practical Organic Chemistry.

Experimental details of the reactions that failed have not been reported, although they are discussed.

Methods

2-(Benzyloxy)ethanol (118)



(117) (118)

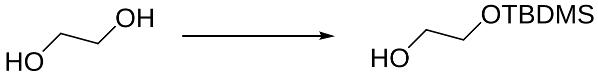
85% KOH (5.6 g, 0.25 mol) was dissolved in ethylene glycol (117) (15.5 mL, 0.25 mol). Benzyl chloride (12.6 mL, 0.1 mol) was added to the solution with stirring, during a period of 2 h and keeping the temperature of the reaction mixture at 90 °C. The temperature was then raised to 130 °C and kept at this point for 2 h. The cooled mixture was diluted with water and then extracted with diethyl ether (3x50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtrate distilled to removethe solvent. The crude product was purified by fractional distillation to give 2-(benzyloxy)ethanol (118) as colorless oil (7.7 g, 51 %) (Marshall, 1988).

FTIR (neat) ν_{max} ; 3400 (OH) , 1630 (C=C), 1455, 1360 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5H, phenyl H), 4.55 (s, 2H, $PhCH_2O$), 3.74 (m, 2H), 3.59 (m, 2H), 2.34 (m, 1H, CH_2OH)

MS (CI), m/z 153.2 (M+1)

(*tert*-Butyldimethylsilyloxy)ethanol (120)



(117) **(120)**

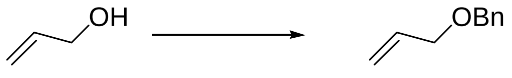
Sodium hydride (0.27 g, 5.6 mmol) was suspended in THF (11 mL) after being washed with ether. Ethylene glycol (117) (0.35 g, 5.6 mmol) was added to the mixture at room temperature and stirred for 45 min during which a large amount of white precipitate formed. *tert*-Butyldimethylsilyl chloride (0.84 g, 5.6 mmol) was then added, and vigorous stirring was continued for 45 min. The mixture was poured into ether (100 mL) and washed with 10% aq. K_2CO_3 (2x30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography (1:9 ; EtOAc : Hexane) to obtain (*tert*-butyldimethylsilyloxy)ethanol (120) as colorless oil (0.7 g, 73%) (Lafontaine, 2003).

FTIR (neat) ν_{max} ; 3403 (OH) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (m, 2H), 3.51 (m, 2H), 1.87 (s, 9H), 0.03 (s, 6H)

MS (CI), m/z 177.3 (M+1)

Allyloxymethyl-benzene (124)



(122) **(123)**

Sodium hydride (0.49 g, 0.017 mmol) was suspended in THF after being washed with ether. Allyl alcohol (1 g, 0.017 mol) was added at room temperature and the mixture was stirred during 45 min during which time a large amount of a white precipitate had formed. The benzyl chloride (0.84 ml, 0.02 mol) was then added, and vigorous stirring was continued for 45 min. The mixture was poured into ether (100 mL) and washed with 10% aq. K_2CO_3 (30 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography to obtain colorless oil (1.2 g , 84%) (Menicagli, 1987).

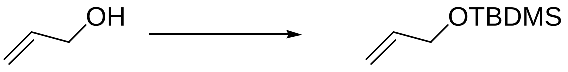
FTIR (neat) ν_{max} ; 1648 (C=C), 1637 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5H), 5.95 (m, 1H), 5.28 (m, 2H), 4.53 (s, 2H), 4.03 (m, 2H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 134.71, 128.3 (2xC), 127.7 (2xC), 127.5, 117.0, 72.1, 71.1

MS (CI), m/z 150.2 (M+1)

Allyloxy-tert-butyl-dimethyl-silane (124)



(122) **(124)**

A stirred solution of allyl alcohol (122) (1 g, 0.017 mol) in CH_2Cl_2 (15 mL) was stirred at room temperature. Then a solution of *tert*-butyldimethylsilyl chloride (3.3 g, 0.022 mol) in DMF (3 mL) was added and stirred overnight. The reaction mixture was poured into ether (100 mL) and washed with 10% aq. K_2CO_3 (30 mL). The organic layer was dried over anhydrous Na_2SO_4, the filtrate filtered and concentrated in vacuo. The residue was purified by flash column chromatography (1:9 ; EtOAc : Hexane) to afford allyloxy-tert-butyl-dimethyl-silane (124) as colorless oil (0.95 g, 73%) (Van de Coevering, 2005).

FTIR (neat) ν_{max} ; 1645 (C=C), 1360 cm^{-1}

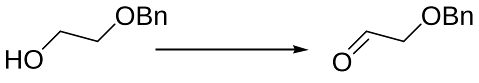
^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.90 (m, 1H), 5.24 (m, 1H), 5.06 (m, 1H), 4.15 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5, 113.9, 64.1, 25.9, 18.4, -4.58

MS (CI), m/z 173.3 (M+1)

(Benzyloxy)acetaldehyde (119)

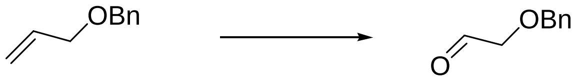
Method 1



(118) **(119)**

A solution of oxalyl chloride (0.6 mL, 6.9 mmol) in dry CH_2Cl_2 (20 mL) was stirred at -78 ^{o}C under nitrogen atmosphere and maintained at that temperature while DMSO (0.98 mL, 13.8 mmol) was added dropwise. After 30 min, a solution of monobenzyl ether (118) (0.7 g, 4.6 mmol) in dry CH_2Cl_2 (1 mL) was added to the reaction mixture, which was stirred at -78 ^{o}C for further 1 h. The mixture was treated dropwise over 10 min with Et_3N (3 mL, 20 mmol). After 30 min, the cold bath was removed and the reaction mixture was filtered through anhydrous Na_2SO_4 pad and the filtrate was concentrated in vacuo. The aldehyde was purified by fractional distillation (110-112 ^{o}C) to give (benzyloxy)acetaldehyde (119) as colorless oil (560 mg, 81%).

Method 2



(123) **(119)**

A solution of allyl ether (123) (500 mg 3.1 mmol) in CH_2Cl_2 (10 mL) was stirred at -78 ^{o}C while air was bubbled through the solution. After 15 min, ozone was bubbled through the solution until the color of solution change from colorless to blue Then, the air was bubbled through the reaction mixture until the solution was colorless. PPh_3 (2.3 g, 8.7 mmol) was then added. The reaction mixture was stirred at room temperature for a further 3 h and concentrated in vacuo. The residue was purified by flash column chromatography (1:9 ; EtOAc : Hexane) to obtain (benzyloxy)acetaldehyde (119) as colorless oil (417 mg, 82%) (Pollex, 2005).

FTIR (neat) ν_{max} ; 1699 (C=O), 1630 (C=C) cm^{-1}

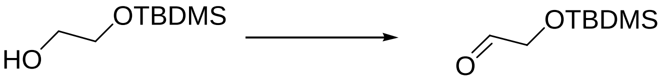
^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.74 (s, 1H), 7.36 (m, 5H), 4.65 (s, 2H), 4.12 (s, 2H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.5, 136.8, 128.6(2xC), 128.3, 127.9(2xC), 75.3, 73.7

MS (CI), m/z 151.1 (M+1)

(*tert*-Butyldimethylsilyloxy)acetaldehyde (121)

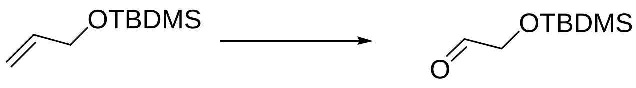
Method 1



(120) **(121)**

A solution of oxalyl chloride (0.6 mL, 6.9 mmol) in dry CH_2Cl_2 (20 mL) was stirred at -78 °C under nitrogen atmosphere and maintained at that temperature while DMSO (0.98 mL, 13.8 mmol) was added dropwise. After 30 min, a solution of silyl ether (120) (0.64 g, 4.6 mmol) in dry CH_2Cl_2 (1 mL) was added to the reaction mixture, which was stirred at -78 °C for further 1 h. The mixture was treated dropwise over 10 min with Et_3N (3 mL, 20 mmol). After 30 min, the cold bath was removed and the reaction mixture was filtered through anhydrous Na_2SO_4 pad and the filtrate was concentrated in vacuo. The residue was purified by fractional distillation to give *tert*-butyldimethylsilyloxy)acetaldehyde (121) as colorless oil (542 mg, 76%) (Lafontaine, 2003).

Method 2



(124) **(121)**

A solution of allyl ether (124) (500 mg 2.9 mmol) in CH_2Cl_2 (10 mL) was stirred at -78 ^oC while air was bubbled through the solution. After 15 min, ozone was bubbled through the solution until the color of solution change from colorless to blue color. Ozone was stopped. Then, the reaction mixture was bubbled with air until the color of the solution change to colorless solution and PPh_3 (2.3 g, 8.7 mmol) was added. The reaction mixture was stirred at room temperature for further 3 h and concentrated in vacuo. The residue was purified by flash column chromatography (1:9 ; EtOAc : Hexane) to obtain (*tert*-butyldimethylsilyloxy) acetaldehyde (121) as colorless oil (385 mg, 76%) (Lafontaine, 2003).

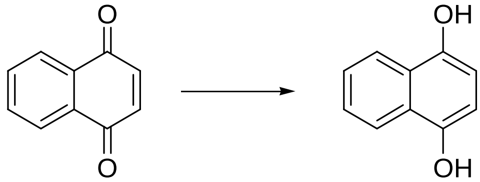
FTIR (neat) ν_{max} ; 1701 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.6 (s, 1H), 4.31 (s, 2H), 0.9 (s, 9H), 0.1 (s, 6H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.1, 75.3, 25.7, -4.1. -4.0

MS (CI), m/z 175.3 (M+1)

p-Hydronaphthoquinone (110)

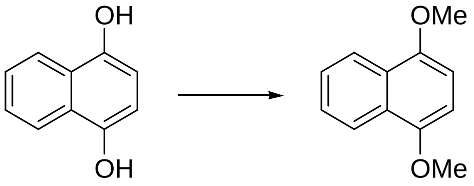


(110)

A solution of *p*-naphthoquinone (10 g, 63.3 mmol) in diethylether (250 mL) and EtOAc (70 mL) was stirred vigorously at room temperature. The solution of $Na_2S_2O_4$ (65 g, 316.5 mmol) in water (50 mL) was added and stirred for 30 min. The organic layer was separated, washed with water (2x100 mL), dried over anhydrous Na_2SO_4 and filtered. The resulting solution was concentrated in vacuo to give *p*-hydronaphthoquinone (110) as a brown crystal in quantitative yield ; mp 191-195 ^{0}C (Oatis *et al.*, 1985, 191-193 ^{o}C).

FTIR (KBr) ν_{max} ; 3260 , 1648 cm^{-1}

1,4-Dimethoxynaphthalene (111)



(110) **(111)**

Method 1

To a stirred suspension of p-hydronaphthoquinone (110) (5 g, 31.25 mmol), anhydrous K_2CO_3 (12.7 g, 92.02 mmol) in dry acetone (100 mL) was added dimethyl sulfate (7.4 mL, 78.11 mmol). The reaction mixtiure was refluxed for 3 h. After cooling to room temperature, the mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by quick column chromatography (hexane-CH_2Cl_2) to obtain the 1,4-dimethoxynaphthalene (111) as a colourless needles (4.32 g, 72 %) ; mp 84-85 ^{0}C (Harvey *et al.*, 2004, 85-86 ^{0}C).

Method 2

To a stirred suspension of *p*-hydronaphthoquinone (110) (5 g, 31.25 mmol), anhydrous K_2CO_3 (12.7 g, 92.02 mmol) in dry acetone (100 mL) was added methyl iodide (9.7 mL, 124 mmol). The reaction mixture was refluxed for 10 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was purified by quick column chromatography (hexane-CH_2Cl_2) to obtain the 1,4-dimethoxynaphthalene (111) as a colourless needles (3.35 g, 57%) ; mp 84-85 ^{0}C (Harvey *et al.*, 2004, 85-86 ^{0}C).

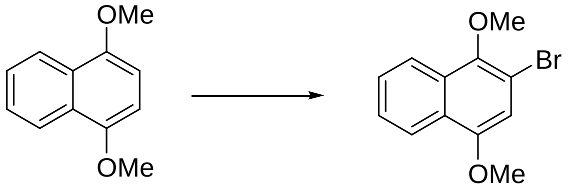
FTIR (KBr), ν_{max} 1593, 1272, 1235 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (m, 2H), 7.50 (m, 2H) , 6.70 (s, 2H), 3.95 (s, 6H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.1 (2xC), 126.9 (2xC), 126.5 (2xC), 122.4 (2xC), 103.8 (2xC), 56.4(2xC)

MS m/e (M^+) (relative intensity) 188 (M^+, 70), 173 (100) , 145 (25)

2-Bromo-1,4-dimethoxynaphthalene (112)



(111) **(112)**

To a solution of 1,4-dimethoxynapthalene (111) (1 g, 4 mmol) in benzene (3 mL) was added bromine (0.25 mL). After being stirred at room temperature for 30 min, the reaction mixture was poured with 10% aq. Na_2CO_3 (10 mL). Benzene layer was separated and dried over anhydrous K_2CO_3 and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (15:85 ; CH_2Cl_2 : Hexane) to give 2-bromo-1,4-dimethoxynaphthalene (112) as colorless oil (982 mg, 92%) (Harvey *et al.*, 2004).

FTIR (KBr), ν_{max} 1581 (C=C), 1105(C-O) cm^{-1}

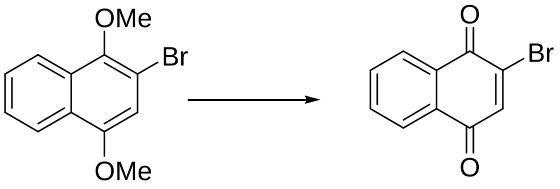
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (m, 1H), 7.97 (m, 1H), 7.45 (m, 2H), 6.79 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.9, 147.4, 129.6, 126.4, 123.2, 122.5, 112.5, 108.6, 62.1(OMe), 56.5(OMe)

MS (CI), m/z 268 (M+1, 60), 266(67), 253(100), 251(95), 129(63)

2-Bromo-1,4-naphthoquinone (114)

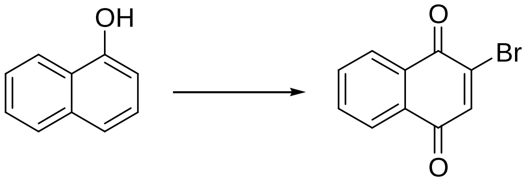
Method 1



(112) (114)

To an ice-cold solution of 2-bromo-1,4-dimethoxynaphthalene (112) (20 mg, 0.1 mmol) in acetonitrile (0.75 mL) was added dropwise a solution of CAN (143 mg, 0.26 mmol) in water (0.5 mL). The reaction mixture was stirred at 0 °C for 15 min, water (10 mL) was added and extracted with EtOAc (3x15 mL). The organic layers were separated and dried over anhydrous Mg_2SO_4 then concentrated under reduced pressure. The residue was purified by flash column chromatography (15: 85; CH_2Cl_2: Hexane) to obtain 2-bromo-1,4-naphthoquinone (114) in quantitative yield as a yellow plates ; mp 131-132 ^{0}C (De Kimpe *et al.*, 2003, 130-132 °C).

Method 2



(113) **(114)**

A solution of 1-naphthol (113) (1 g, 6.94 mmol) in acetic acid (50 mL) was stirred at 45 ^{o}C. Then, a solution of *N*-bromosuccinamide (5 g, 27.8 mmol) in 50% acetic acid solution (150 mL) was added dropwise for 30 min. The resulting solution was stirred at 55-60 ^{o}C for 30 min. Subsequently, water (50 mL) was added to the solution, followed by extraction with CH_2Cl_2 (6x50 mL). The combined organic layers were washed with water (4x100 mL) and saturated $NaHCO_3$ (5x100 mL). The organic phase was dried over anhydrous Mg_2SO_4, filtered and the filtrated concentrated in vacuo. The residue was purified by flash column chromatography (15:85; CH_2Cl_2:Hexane) to provide 2-bromo-1,4-naphthoquinone (114) (1.2 g, 73%) as a yellow plats ; mp 131-132 ^{0}C (De Kimpe *et al*., 2003, 130-132 ^{o}C).

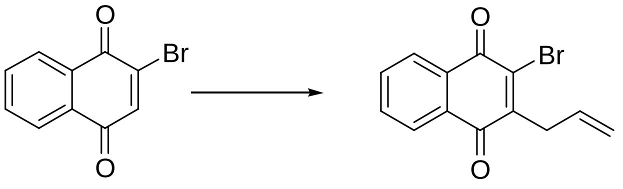
FTIR (KBr) ν_{max} 1679 (C=O), 1657 (C=O), 1590 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (m, 1H), 8.01 (m, 1H), 7.77 (m, 2H), 7.51 (s, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.8, 178.3, 140.8, 140.5, 134.9, 134.6, 132.1, 131.3, 128.2, 127.4

MS (CI), m/z 237.1 (M+1)

2-Allyl-3-bromo-1,4-naphthoquinone (115)



(114) **(115)**

To a stirred suspension of 2-bromo-1,4-naphthoquinone (114) (500 mg, 2.1 mmol), silver nitrate (110 mg, 1.05 mmol), and vinylacetic acid (270 mg, 3.15 mmol) in acetonitrile (50 mL) was added dropwise over 15 min a solution of ammonium persulfate (860 mg, 3.78 mmol) in water (25 mL). The reaction mixture was stirred at 60-70 °C for 8 h. Then, the resulting mixture was poured into cold water (25 mL) and extracted with EtOAc (4x50 mL). The combined organic layers were separated, washed with 10% aq. $NaHCO_3$ (2x50 mL), dried over anhydrous Mg_2SO_4 and filtered. The solution was concentrated in vacuo. The residue was purified by flash column chromatography (5: 95 ; EtOAc: Hexane) to obtain 2-allyl-3-bromo-1,4-naphthoquinone (115) (418 mg, 72%) as a yellow prisms ; mp 70-71 ^{0}C (Maruyama *et al.*, 1986, 72-72 °C).

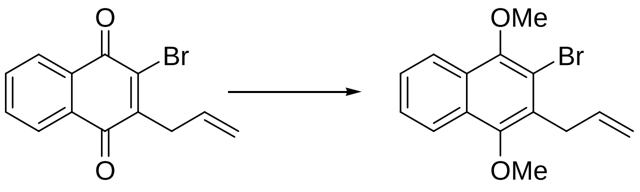
IR (KBr), ν_{max} 1665, 1590 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (2H, m), 7.71 (2H, m), 5.85 (1H, ddt, J=17 Hz, 10 Hz, 6 Hz), 5.25 (1H, dd, J= 17Hz, 1.3 Hz), 5.14 (1H, dd, J=10 Hz, 1.3 Hz), 3.61 (2H, dt, J=6.6 Hz, 1.3 Hz)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.3, 177.7, 148.9, 139.3, 134.2, 133.9, 131.3, 131.1, 127.5, 127.1, 118.2, 35.4

MS (CI), m/z 278.2 (M+1)

2-Allyl-3-bromo-1,4-dimethoxynaphthalene (116)



(115) **(116)**

A solution of 2-allyl-3-bromo-1,4-naphthoquinone (115) (500 mg, 1.8 mmol) in 95% ethanol (20 mL) was added to a solution of tin(II)chloride (1.2 g, 6.34 mmol) in concentrated hydrochloric acid (1.2 mL) at 50 °C. Then, the reaction mixture was stirred for 30 min at the same temperature. After addition of cold water (100 mL), the appearing precipitate was filtered. The precipitate was mixed with dimethyl sulfate (3.42 g, 27 mmol). Then 50% aq. KOH (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 65 °C for 3 h, and then the reaction mixture was poured into cold water (20 mL). The resulting mixture was extracted with diethyl ether (5x50 mL). The combined organic layers were separated, washed with 10% aq. $NaHCO_3$ (2x50 mL), dried over anhydrous Mg_2SO_4 and filtered. The organic extract was concentrated in vacuo. Flash column chromatography of the residue on silica gel (15:85 ; CH_2Cl_2 : Hexane) provided 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116) as colourless (414 mg, 75%) ; mp 56-57 °C (De Kimpe *et al.*, 1999, 57-59 °C).

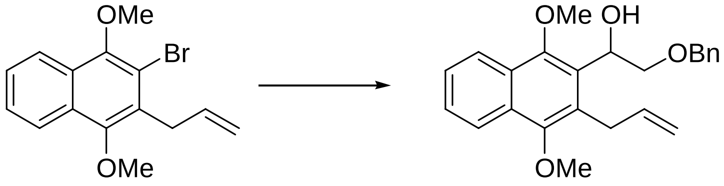
FTIR (KBr) ν_{max} 1612 (C=C), 1593 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (2H, m), 7.51 (2H, m), 6.07 (1H, ddt, J=16.8 Hz, 10.2 Hz, 5.6 Hz), 5.09 (1H, dd, J=10.2 Hz, 1.7 Hz), 5.03 (1H, dd, J=16.8 Hz, 1.7 Hz), 3.97 (3H, s, OMe), 3.91 (3H, s, OMe), 3.79 (2H, dt, J=5.6 Hz, 1.7 Hz)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.9, 150.2, 135.7, 128.2, 127.9, 126.6, 126.5, 122.6, 122.5, 116.7, 115.8, 62.7, 61.34, 34.4

MS (EI), m/z ($M^{+\cdot}$ 5%) 307 (20), 277.1 (100), 257.3 (40), 198.2 (55)

2-Benzyloxy-1-(1,4-dimethoxy-naphthalen-2-yl)-ethanol (125)



(116) **(125)**

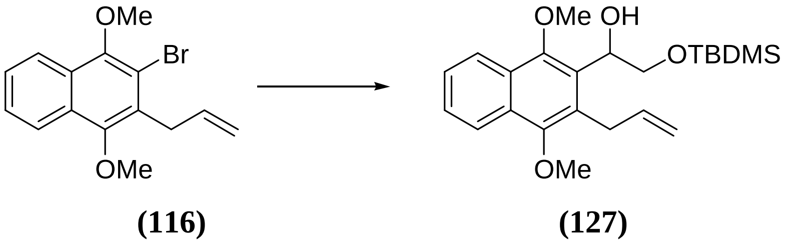
A solution of bromonaphthalene (116) (200 mg, 0.651 mmol) in dry THF (5 mL) was stirred at -78 ^{o}C under N_2 atmosphere. Then, *n*-BuLi (0.5 mL, 0.782 mmol) was added dropwise. Then a solution of (benzyloxy)acetaldehyde (119) (120 mg, 0.782 mmol) in dry THF (1mL) was added dropwise at the same temperature and stirred for an additional 30 min. The resulting mixture was poured into cold water and extracted with diethyl ether (4x30 mL). The combined organic layers were dried over anhydrous Mg_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc: Hexane) to provide 2-benzyloxy-1-(1,4-dimethoxy-naphthalen-2-yl)-ethanol (125) as colorless oil (96 mg, 44%).

FTIR (neat), ν_{max} 3401 (OH) ,1615 (C=C) , 1595 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.0 (m, 2H), 7.45 (m,2H), 7.2 (m, 5H), 6.0 (m, 1H), 5.26 (dd, 1H, J=9, 3.5 Hz), 4.98 (dd, 1H, J= 10, 1.5 Hz), 4.83 (dd, 1H, J=10, 1.5 Hz), 4.55 (dd, 1H, J=12, 15 Hz), 4.2 (t, 2H, J=10 Hz), 3.91 (s, 3H), 3.82 (s, 3H), 3.65 (m,2H), 3.55 (m, 1H)

MS (CI), m/z 379.3 (M+1)

1-(3-Allyl-1,4-dimethoxy-naphthalen-2-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-ethanol (127)



A solution of bromonaphthalene (116) (200 mg, 0.651 mmol) in dry THF (5 mL) was stirred at -78 °C under N_2 atmosphere. Then, *n*-BuLi (0.5 mL, 0.782 mmol) was added dropwise. Then a solution of aldehyde (121) (120 mg, 0.782 mmol) in dry THF (1mL) was added dropwise at the same temperature and stirred for an additional 30 min. The resulting was poured into cold water and extracted with diethyl ether (4x30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to obtain 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-ethanol (127) as colorless oil (184 mg , 70%).

FTIR (neat), ν_{max} 3413 (OH), 1612 (C=C) , 1593 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (m, 2H) , 7.47 (m, 2H) 6.09 (m, 1H), 5.15 (dd, ,J= 4, 9 Hz, 1H), 5.05 (m, 1H), 4.80 (m, 1H), 4.15 (dd, J= 9, 8 Hz, 1H), 4.00 (s, 3H), 3.86 (s, 3H), 3.75 (m, 2H), 3.72 (1H), 0.88 (s, 9H), 0.04 (d, J=12 Hz, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2, 131.2, 129.3, 126.9, 126.5, 123.5, 123.2, 115.4, 71.6, 68.2, 63.5, 62.3, 31.6, 26.3, -5.0, -5.1

MS (CI), m/z 403.4 (M+1)

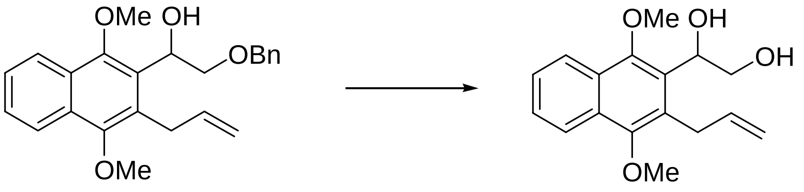
1-(3-Allyl-1,4-dimethoxy-naphthalen-2-yl)-ethane-1,2-diol (126)

Method 1

(127) **(126)**

To a stirred solution of silylether (127) (300 mg, 0.8 mmol) in THF (15 mL) was added TBAF (756 mg, 2.4 mmol). The reaction mixture was stirred at room temperature for 30 min. Then water (50 mL) was added and extracted with diethyl ether (3x40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure. The residue was purified by flash column chromatography (1:3 ; EtOAc : Hexane) to obtain 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-ethane-1,2-diol (126) as colorless oil (200 mg, 87%).

Method 2



(125) **(126)**

To a solution of naphthalene (350 mg, 2.8 mmol) in dry THF (12 mL), was added lithium metal (15 mg, 2.1 mmol) in small pieces. The reaction mixture was stirred at room temperature under N_2 atmosphere until lithium metal was completely dissolved (~3h). The resulting dark green solution of lithium naphthanide was cooled to -78 ^{o}C, followed by addition of a solution of benzyl ether (125) (100 mg, 0.26 mmol) in dry THF (4 mL) dropwise over 5 min. The reaction mixture was stirred at -78 ^{o}C for 30 min. Saturated aqueous ammonium chloride (5 mL) was added to the reaction mixture followed by addition of water (5 mL). The resulting solution was extracted with ether (4x10 mL). The combined extracted was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (4:6 ; EtOAc : Hexane) to obtain 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-ethane-1,2-diol (126) as colorless oil (31 mg, 41%).

FTIR (neat), ν_{max} 3415(OH), 1613(C=C), 1590 (C=C) cm^{-1}

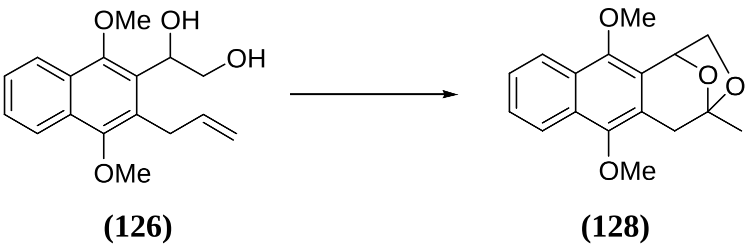
^{1}H NMR (acetone-d_6, 400 MHz) δ 8.00-8.09 (m, 2H), 7.50-7.54 (m, 2H), 6.10 (ddt, 1H, J=17.8 Hz, 7 Hz, 5.5 Hz), 5.31(m, 1H), 4.92-5.00 (m, 2H), 4.1 (dd, 1H, J=9 Hz, 10 Hz), 3.95 (s, 3H), 3.85 (s, 3H) 3.79-3.82 (m, 2H), 3.75 (dd, 1H, J=5 Hz, 10 Hz)

^{13}C NMR (acetone-d_6, 100 MHz) δ 152.3, 151.8, 139.2, 131.3, 129.3, 128.8, 126.9, 126.5, 123.5, 123.2, 115.3, 72.1, 66.9, 63.5, 62.3, 31.6

MS (CI), m/z 288.3 (M+)

Oxabicyclo compound (128)

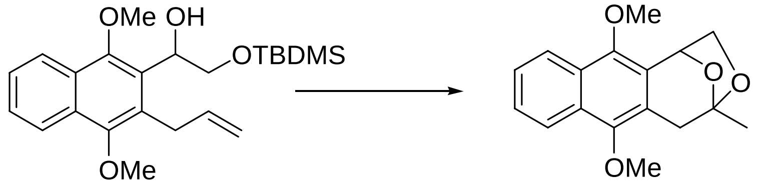
Method 1



(126) **(128)**

A mixture of palladium chloride (4 mg, 0.023 mmol) and anhydrous cupric chloride (47 mg, 0.35 mmol) in dry dimethoxyethane (2 mL) was stirred and heat at 65 °C while oxygen was bubbled through the solution. A solution of diol (126) (100 mg, 0.35 mmol) in dry dimethoxyethane (1 mL) was added dropwise and stirred at 65 °C for further 30 min then cooled to room temperature. The reaction mixture was filtered through a short neutral alumina column and eluted with ether. The resulting solution was concentrated in vacuo. The residue was purified by flash column chromatography (1:4 ; EtOAc : Hexane) to obtain oxabicyclo compound (128) (72 mg, 71%) as colourless plates : mp 71-72 °C.

Method 2



(127) **(128)**

A mixture of palladium chloride (1 mg, 0.0056 mmol) and anhydrous cupric chloride (10 mg, 0.074 mmol) in dry dimethoxyethane (2 mL) was stirred and heat at 65 °C while oxygen was bubbled through the solution. A solution of silyl ether (127) (30 mg, 0.074 mmol) in dry dimethoxyethane (0.5 mL) was added dropwise and the reaction mixture was stirred at 65 °C for further 30 min then cooled to room temperature. The reaction mixture was filtered through a short neutral alumina column and eluted with ether. The resulting solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to obtain oxabicyclo compound (128) (15 mg, 67%) as colourless plates; mp 71-72 °C.

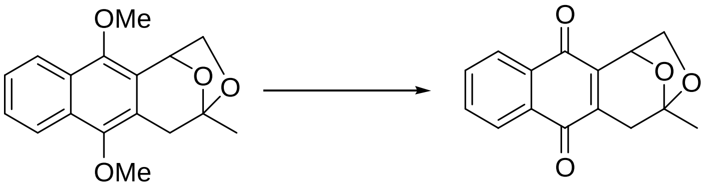
FTIR (KBr), $\nu_{\max}$ 1600 (C=C), 1594 (C=C) cm^{-1}

^{1}H NMR (acetone-d$_6$, 400 MHz) δ 8.04-8.13 (m, 2H), 7.58-7.52 (m, 2H) , 5.79 (d, J=4 Hz, 1H), 3.88-4.01 (m, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.17 (d, J=20, 1H), 3.04 (d, J=20 Hz, 1H), 1.65 (s, 3H)

^{13}C NMR (CDCl$_3$, 100 MHz) δ 150.2, 146.8, 128.3, 127.3, 127.5, 126.1, 125.8, 122.3, 122.1, 121.9, 106.6, 73.4, 71.7, 62.6, 60.9, 36.3, 24.6

HRMS, Found: [M+Na], 309.1101. Calc. for $C_{17}H_{18}O_4$ + Na : 309.1103

(±)-Isagarin (11)



(128) (11)

To an ice-cold solution of oxabicyclo compound (128) (200 mg, 0.70 mmol) in acetonitrile (2 mL) was added dropwise a solution of CAN (30 mg, 0.051 mmol) in water (0.5 ml). After being stirred at at 0 °C for 15 min, the reaction mixture was poured into water (5 mL), extracted with EtOAc (3x10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to obtain (±)-isagarin (11) (170 mg, 95%) as a yellow crystal ; mp 159-160 ^{0}C (De Kimpe *et al.*, 1998, 159-160 °C). The enantiomeric mixture of (11) (ratio 1;1) was separated by chiral HPLC column (Chiralcel OD column 250 x 4.6 mm, hexane: isopropyl alcohol ; 95:5 as eluent, elution rate 1.0 ml/min).

IR (KBr), ν_{max} 1660 (C=O), 1632 (C=C), 1596 (C=C) cm^{-1}

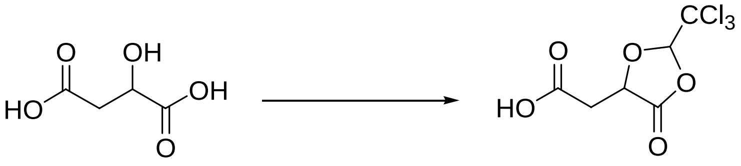
^{1}H NMR ($CDCl_3$, 400 MHz) δ. 8.04-8.13 (m, 2H), 7.70-7.8 (m, 2H), 5.58 (d, J=4 Hz, 1H), 3.93-4.05 (m, 2H), 2.87 (dd, J=1.9, 1.3 Hz, 1H), 2.73 (d, J=19 Hz, 1H), 1.68 (s, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ. 184.1, 182.6, 143.9, 141.7, 133.9, 132.0, 131.6, 133.9, 126.4, 126.3, 106.4, 73.0, 70.2, 36.3, 23.9

HRMS, Found: [M+H$^+$], 257.0818. Calc. for $C_{15}H_{12}O_4 + H^+$: 257.0814

Synthesis of Marticin

(5-Oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetic acid (132)



(131) **(132)**

A solution of *dl*-malic acid (131) (1.2 g, 8.9 mmol) in conc. H_2SO_4 (5 ml, 26 mmol) was stirred at 0 °C and treated with chloral (1.6 g, 12 mmol). The reaction mixture was maintained at 0 °C for 2 h and then at room temperature for another 12 h. After addition of ice water (20g), the precipitate was filtered and washed with water and crystallised from hexane-EtOAc to give (5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetic acid (132) (1.8 g, 79%) as colourless plates ; mp 175-176 °C (Shih *et al*., 1989, 176-178 °C).

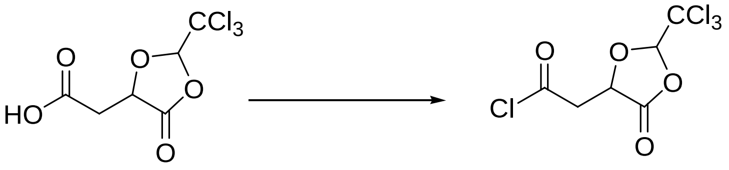
IR (KBr), $\nu_{\max}$ 2973 (OH), 1873 (C=O), 1828 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, DMSO, 400 MHz) ^{1}H NMR δ 5.8 (d, J=1.7 Hz , 1H , CH), 4.72 (m, 1H , CH), 2.91 (dd. J=4 Hz ,18 Hz , 1H , CH), 2.82 (dd, J=4 Hz,18 Hz, 1H , CH)

^{13}C NMR (acetone–d_6, 75 MHz) δ 171.7, 171.4, 106.0(CH), 99.4, 72.9, (CH), 36.4

MS m/e (M^++1) 269.2

(5-Oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl chloride (133)

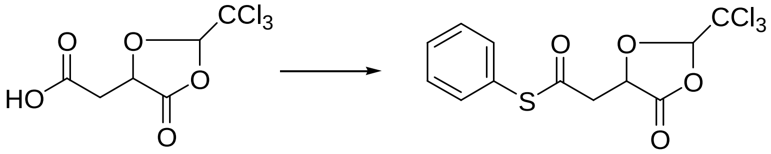


(132) **(133)**

A racemic mixture of protected malic acid (132) (3.4 g, 13 mmol) and thionyl chloride (15 mL, 207 mmol) was refluxed for 50 h. The reaction mixture was concentrated under vacuum to give a pale yellow solid. After washing the solid with dry petroleum ether, the product (133) was obtained as a white solid (3.6 g, 98%); mp 76-77 ^{o}C.

IR (KBr), ν_{max} 1808 (C=O), 1776 (C=O) cm^{-1}

(5-Oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-thioacetic acid S-phenyl ester (134)



(132) **(134)**

Method 1

A mixture of acid (132) (950 mg, 3.61 mmol), DMAP (530 mg, 4.33 mmol) and DCC (900 mg, 4.33 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature. Thiophenol (0.43 ml, 4.33 mmol) was added dropwise. After being stirred for 6 h, the reaction mixture was poured with water (30 mL) and extracted with CH_2Cl_2 (4x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography

(2:8 ; EtOAc : Hexane) to obtain (5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-thioacetic acid S-phenyl ester (134) (730 mg, 79%) as a colourless needles ; mp 78-80 °C.

Method 2

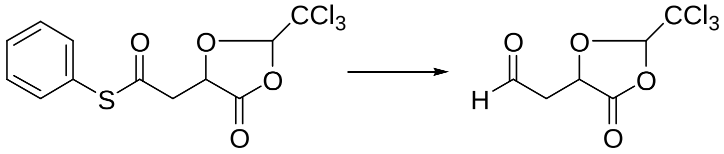
To a stirred solution of acid (132) (950 mg, 3.61 mmol) in benzene (20ml) was added oxalyl chloride (0.8 ml). DMF (2 drops) was added. The reaction mixture was stirred at room temperature for further 1 h and then concentrated under vacuo. The residue was dissolved in CH_2Cl_2 (20 mL). Thiophenol (0.43 ml, 4.33 mmol) and pyridine (0.2 mL) were added. The reaction mixture was stirred for futher 5 h. Then, water (30 mL) was added and extracted with CH_2Cl_2 (4x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography to obtain (5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-thioacetic acid S-phenyl ester (134) a coulourless needles ; mp 78-80 °C (780 mg, 85%).

IR KBr 1737 (C=O) ν_{max} 1699, 1673 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 7.19 (s, 5H), 5.78 (2s, 1H), 4.80-4.47 (m, 1H), 3.35 (dd, 1 H, J= 4.2, 17.8 Hz), 3.25 (dd, 1 H, J= 4.2, 17.8 Hz)

MS m/e (M^++) 356, 281 (33), 207 (61), 110 (100)

(5-Oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetaldehyde (135)



(134) **(135)**

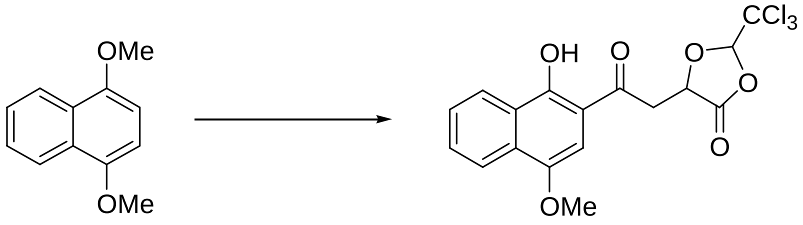
A mixture of thioester (134) (500 mg, 1.4 mmol) and 5% Pd/C (20 mol%, 90 mg) in CH_2Cl_2 (15 mL) was stirred at room temperature. Triethyl silane (4.2 mmol, 0.7 mL) was added dropwise. After stirring for 45 min, the reaction mixture was filtered through a short siliga gel column and eluted with ether. The resulting solution was concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to obtain (5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetaldehyde (135) (410 mg, 85%) as a coulourless needles; mp 91-93 ^{o}C.

IR (KBr), ν_{max} 1737 (C=O), 1699 (C=O), 1673 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.67 (s, 1H), 5.85 (2s, 1H), 4.81-4.79 (m, 1H), 3.25 (dd, 1 H, J= 4.2, 17.7 Hz), 3.05 (dd, 1 H, J= 4.2, 17.7 Hz)

MS m/e (M^{+}+1) 247.6

5-[2-(1-Hydroxy-4-methoxy-naphthalene-2-yl)-2-oxo-ethyl]-2-trichloromethyl-[1,3]dioxolan-4-one (137)



(111) **(137)**

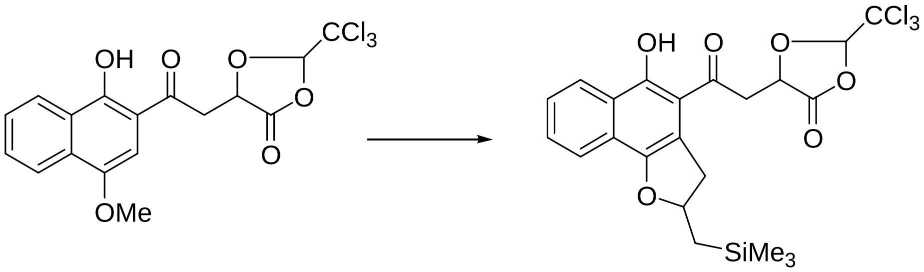
A mixture of 1,4-dimethoxynaphthalene (111) (500 mg, 27 mmol) and acid chloride (56) (2.3 g, 8.1 mmol) in dry CH_2Cl_2 (15 mL) was stirred at 0 °C under N_2 atmosphere. The solution of $AlCl_3$ (710 g, 50.4 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise during 10 min. The reaction mixture was stirred at 0 °C for 12 h. and cool water (30 mL) was added dropwise. The reaction was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were washed with water (2x40 mL), dried over anhydrous $MgSO_4$ and filtered. The resulting solution was concentrated under reduced pressure to give solid residue. The residue was purified by flash column chromatography (20:80 ; CH_2Cl_2 : Hexane) to yield 5-[2-(1-hydroxy-4-methoxy-naphthalene-2-yl)-2-oxo-ethyl]-2-trichloromethyl-[1,3]dioxolan-4-one (137) as a yellow plates (487 mg, 43%); mp 184-186 ^{0}C.

IR (KBr), ν_{max} 1814 (C=O), 1625 (C=O), 1599, (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.05 (s, 1H), 8.39(d, J=8.3 Hz, 1H), 8.13(d, J=8.3 Hz, 1H), 7.63(m, 1H), 7.54(m, 1H), 6.63 (s, 1H) 5.96 (d, J= 1.7 Hz,1H), 4.97 (m, 1H), 3.92 (s, 1H), 3.88 (d, J=4, 1H), 3.83 (d, J=4, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.0 (C=O), 170.9 (C=O), 158.2 (C-O), 147.9 (C-O), 130.4 (CHarom), 127.0 (CHarom), 125.8 (CHarom), 124.6 (CHarom), 122.0 (CHarom), 111.0, 105.2, 98.8, 97.8, 70.8, 55.7, 39.6

5-[2-(5-Hydroxy-2-trimethylsilanylmethyl-2,3-dihydro-naphtho[1,2-b]furan-4-yl)-2-oxo-ethyl]-2-trichloromethyl-[1,3]dioxolan-4-one (139).



(137) **(139)**

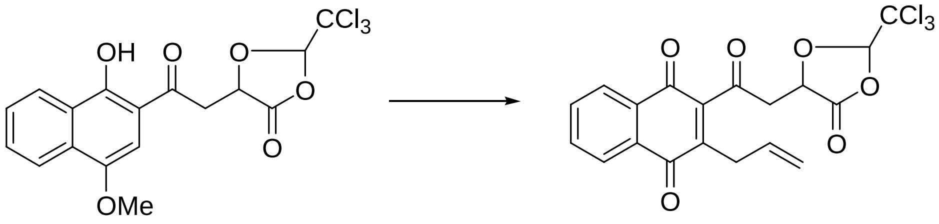
To an ice-cold solution of naphthol (137) (100 mg, 0.24 mmol) in acetonitrile (5 mL) was added dropwise a solution of CAN (390 mg, 0.71 mmol) in water (1.5 mL). The reaction mixture was stirred at 0 °C for 15 min, added water (10 mL) and extracted with EtOAc (3x15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give oil residue. The residue was dissolved with dry CH_2Cl_2 (3 mL) and $SnCl_4$ (0.03 mL, 0.24

mmol) was added dropwise followed by the addition of allyltrimethylsilane (0.06 mL, 0.72 mmol). After being stirred at –78 ^{o}C for 5 h. under N_2 atmosphere, the reaction mixture was poured into water (10 mL), extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were over anhydrous $MgSO_4$, filtered and the filtrate concentrated under reduce pressure to obtain brown oily residue. The residue was purified by flash column chromatography(1:9 ; EtOAc : Hexane) to afford 5-[2-(5-hydroxy-2-trimethylsilanylmethyl-2,3-dihydro-naphtho[1,2-b]furan-4-yl)-2-oxo-ethyl]-2-trichloromethyl-[1,3]dioxolan-4-one (139) as a diastereomeric mixture (71 mg, 56%); mp 51-53 ^{0}C.

IR (KBr), $\nu_{\max}$ 2922, 1824 (C=O) 1716 , 1670 , 1649 cm^{-1}

^{1}H NMR ($CDCl_3$) δ 13.57 (s, 1H), 8.45 (d, J=8.4 Hz, 1H), 7.88 (d, J=6.3 Hz, 1H), 7.67 (t, J=7.6 Hz 1H), 7.54 (t, J=7.6 Hz, 1H), 7.28 (s, 1H), 6.05 (s, 1H), 5.96 (d, J= 1.7 Hz, 1H), 5.14 (m, 1H), 5.01 (s), 4.97 (s, 1H), 3.62 (m, 2H), 3.25 (m 1H), 1.59 (s,1H), 1.41 (m, 1H), 0.19 (s, 9H)

2-Allyl-3-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphtho quinone (140)



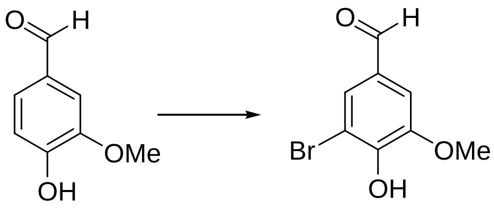
(137) (140)

To an ice-cold solution of naphthol (137) (100 mg, 0.24 mmol) in acetonitrile (5 ml) was added dropwise a solution of CAN (390 mg, 0.71 mmol) in water (1.5 ml). After stirring at 0 ^{o}C for 15 min, the reaction mixture was poured with water (10 ml) and extracted with EtOAc (3x15 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filterd and concentrated under reduced pressure to give a oil residue. The solution of residue in acetonitrile (50 mL) was stirred at room temperature. Silver nitrate (50 mg, 0.5 mmol) and vinylacetic acid (270 mg, 3.15 mmol) were added. Then a solution of ammonium persulfate (860 mg, 3.78 mmol) in water (25 mL) in was added dropwise over 15 min. After being stirred at 60-70 °C for 8 h, the reaction mixture was poured into cold water (25 mL) and extracted with ethyl acetate (4x50 mL). The combined organic layers were washed with 10% aq. $NaHCO_3$ (2x50 mL), dried over anhydrous Mg_2SO_4 and filtered. The organic extract was concentrated in vacuo. The residue was purified by flash column chromatography (2:8 ; EtOAc:Hexane) to obtain 2-allyl-3-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphtho quinone (140) (65 mg, 55 %) as a yellow plates; mp 73-75 ^{0}C.

FTIR (KBr), ν_{max} 1825 (C=O), 1740 (C=O), 1730 (C=O), 1615 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (m, 2H), 7.92 (m, 2H), 6.21 (s, 1H), 5.83 (m, 1H), 5.25-5.12 (m, 2H), 3.88 (dd, J=4, 10 Hz, 1H), 3.52 (dd, J=4, 10 Hz, 1H), 3.25 (m, 2H)

3-Bromo-4-hydroxy-5-methoxy-benzaldehyde (142)



(141) **(142)**

To an ice-cold stirred solution of vanillin (141) (1.5 g, 10 mmol) in acetic acid (3 mL) was added rapidly a solution of Br_2 (0.5 mL, 10 mmol) in acetic acid (2 ml) with stirring for 30 min. After addition of water (20 mL), the appearing precipitate was filtered and washed with water (3x20 mL). The precipitate was purified by quick column chromatography to yield 3-bromo-4-hydroxy-5-methoxy-benzaldehyde (142) (2.18 g, 95%) as a colourless plates; mp 163-164 °C. (Henry *et al.*, 1930, 166-169 °C).

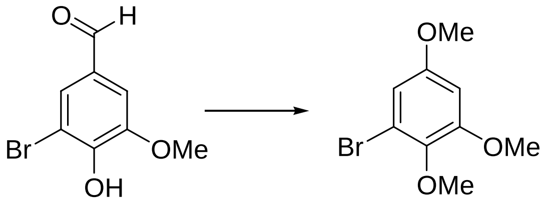
FTIR (KBr), ν_{max} 3291 (O-H) , 1683 (C=O), 1577 (C=C) cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 9.22 (s, 1H), 7.09 (d, J=1.6 Hz, 1H), 6.80 (d, J=1.6 Hz, 1H), 3.14 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.4, 149.3, 148.1, 130.2, 127.9, 114.7, 108.1, 57.2

MS m/e (M^++) 230.8 (M+), 229.0 (M+1)

1-Bromo-2,3,5-trimethoxy-benzene (143)



(142) **(143)**

To a solution of bromovanillin (142) (1g, 4 mmol) in 1N NaOH (10 mL) was added 5% H_2O_2 (20 mL). After being stirred at room temperature for 20 min, the reaction mixture was acidified with 10% HCl and extracted with diethyl ether (3x30 mL). The combined organic layers were dry over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give residue as brown solid. Then the residue was dissolved in dry acetone. K_2CO_3 (1.5g, 10.8 mmol) and dimethyl sulfate (1.3 ml, 13.6 mmol) were added. The reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was filterd and the resulting solution was concentrated under reduce pressure to obtain a black oil residue. The oil residue was purified by flash column chromatography (2:8 ; EtOAc : Hexane) to provide 1-bromo-2,3,5-trimethoxy-benzene (143) as colorless oil (794 mg, 81 %) (Crowther, 1984).

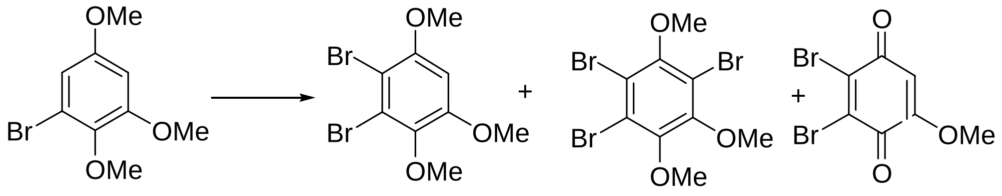
FTIR (KBr), ν_{max} 1570 (C=C) 1577 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.72 (s, 1H), 6.51 (s, 1H), 3.89 (s, 3H), 3.85(s, 3H), 3.74 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.3, 154.1, 140.8, 118.1, 108.0, 100.1, 60.6, 56.1, 55.9

MS m/e (M^++) 246.1, 249.3, 248.1

2,3-Dibromo-1,4,5-trimethoxy-benzene (144)



(143) **(144)** **(148)** **(149)**

To a stirred solution of trimethoxybromobenzene (143) (1 g, 4 mmol) in benzene (3 mL) was added bromine (0.25 mL). After stirring at room temperature for 30 min, the reaction mixture was and was poured with 10% aq. Na_2CO_3 (10 mL). Benzene layer was separated, dried over anhydrous K_2CO_3 and filtered. The filtrate was concentrated under reduce pressure. The residue was purified by flash column chromatography (15:85 ; CH_2Cl_2 : Hexane) to give (144) as a colourless plates (1.05 g, 81%) ; mp 96-98 ^{0}C (Crowther, 1984, 97-99 °C), (148) as a colourless plates (96 mg, 6%) ; mp 91-92 ^{0}C and (149) as yellow oil (58 mg, 5%).

2,3-Dibromo-1,4,5-trimethoxy-benzene (144)

FTIR (KBr), ν_{max} 2943 (C=O), 1634 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.51 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.77 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.8, 153.1, 141.9, 122.1, 105,2, 97.3, 61.1, 57.2, 56.9

MS m/e (M^++) 318.3, 320.3

1,2,4-Tribromo-3,5,6-thimethoxy-benzene (148)

FTIR (KBr), ν_{max} 2974 (C-H), 2940 (C-H), 1561 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.90 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 152.4, 149.3, 121.1, 112.5, 114.0, 61.3(2xC), 61.0

MS m/e (M^++) 401.2(M+)

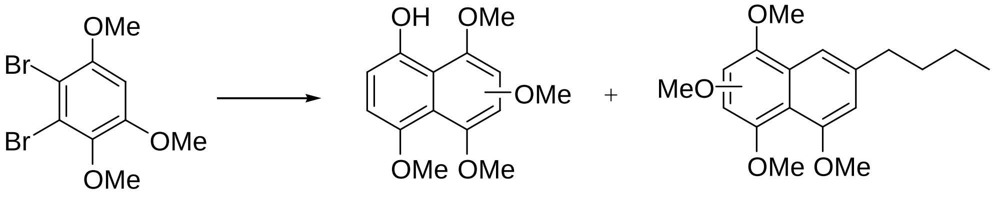
2,3 Dibromo-5-methoxy-[1,4]benzoquinone (149)

FTIR (neat), ν_{max} 1686 (C=O) , 1641 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.80 (s, 1H), 3.88 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.1, 172.5, 158.6, 141.1, 136.5, 106.9, 57.0

Regiomeric naphthol (145)



(144) **(145)** **(146)**

2,3-Dibromo-1,4,5-trimethoxybenzene (144) (150 mg, 0.46 mmol) and 2-methoxyfuran (0.06 mL, 0.5 mmol) were stirred in dry tetrahydrofuran (2 mL) at –78 ^{o}C under nitrogen. *n*-butyl lithium (0.05 mL, 0.41 mmol) was added dropwise at the same temperature during 10 min. The reaction mixture was allowed to warm to room temperature following the addition of water (10 mL) and extracted with ether (3x15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduce pressure. The residue was purified by flash column chromatography (4:6 ; EtOAc : Hexane) to give regioisomeric naphthols (145) as a light brown oil (53 mg, 43%) and byproduct (146) as a light brown oil (37 mg, 27%) (Giles *et al.*, 1988).

Regiomeric naphthol (145)

FTIR (neat), ν_{max} 3290 (0H), 1652 (C=C) cm^{-1}

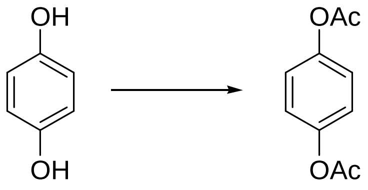
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.63 (s, OH), 6.71 (m, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H), 3.86 (s, 3H)

Byproduct (146)

FTIR (neat), ν_{max} 1661 (C=C), 1630 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, J=2 Hz, 1H), 6.73 (d, J=2 Hz, 1H), 6.64 (s, 1H), 3.98 (s, 6H), 3.96 (s, 3H), 3.84 (s, 3H), 2.71 (t, J=7.7 Hz, 2H), 1.6-1.8 (m, 2H) 1.3-1.5 (m, 2H) and 0.95 (m,3H)

1, 4-Diactoxyphenylester (155)



(154) **(155)**

To a stirred solution of 1,4-dihydrobenzoquinone (10 g, 91 mmol) in acetic anhydride (20 ml) was added dropwise H_2SO_4 (1 drop) at room temperature. Then the reaction mixture was stirred for 30 min. After adding of cold water, the appearing precipitate was filtered and dried to give 1, 4-diactoxyphenylester (155) as a colourless needles (17 g, 100%); mp 121-122 °C (Prichard, 1955, 121-122 °C).

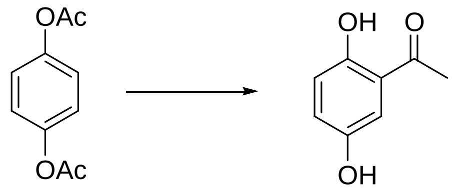
FTIR (KBr), ν_{max} 1740 (C=O), 1615 (C=C) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.0 (s, 4H), 2.22 (s, 6H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1, 150.0, 121.5, 17.2

MS (CI), m/z 195.2 (M+1)

2,5-Dihydroxyacetophenone (156)



(155) **(156)**

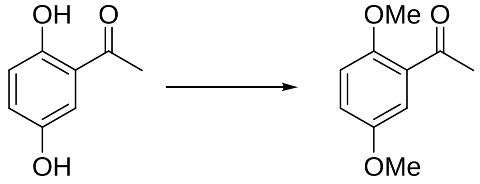
A mixture of dry hydroquinone diacetate (155) (5 g, 0.026 mole) and anhydrous aluminum chloride (0.087 mol, 11.6 g) is finely powdered in a mortar and introduced into a dry 50-mL round-bottom flask fitted with an air condenser protected by a calcium chloride tube and connected to a gas-absorption trap. The flask was placed in an oil bath which was heated slowly from room temperature so that at the end of about 30 minutes the temperature of the oil reaches 110–120°C, at which point the evolution of hydrogen chloride begins. The temperature was then raised slowly to 160–165°C and maintained at that point for about 3 h; at the end of about 2 h the evolution of hydrogen chloride becomes very slow and the mass assumes a green color and becomes pasty in consistency. The reaction flask was removed from the oil bath and allowed to cool to room temperature. The excess aluminum chloride was decomposed by treating the reaction mixture with crushed ice (35 g) followed by concentrated hydrochloric acid (2.5 mL). The solid obtained was collected on a Büchner funnel and washed with two 10-mL portions of cold water. The crude product was purified by flash column chromatography (1:4 ; EtOAc: Hexane) to give 2,5-dihydroxyacetophenone (156) as a yellow needles (3.9 g, 71%) ; mp 201–202 ^{o}C (Amin and Shah, 1955, 201–202 ^{o}C).

FTIR (KBr), $\nu_{\max}$ 3420 (OH), 1690 (C=O)cm^{-1}

^{1}H NMR ($CDCl_3$+DMSO-d6, 400 MHz) δ 11.63 (s, 1H), 7.12 (d, J= 3Hz, 1H), 7.00 (dd, J=3, 9Hz, 1H), 6.75 (d, J=9 Hz, 1H), 2.5 (s, 3H)

MS (CI), m/z 153.1 (M+1)

2,5-Dimethoxyacetophenone (157)



(156) **(157)**

Method 1

A mixture of 2,5-dihydroxyacetophenone (156) (5g, 31.25 mmol), dimethyl sulfate (7.4 ml, 78.11 mmol) and anhydrous K_2CO_3 (12.7g, 92.02 mmol) in dry acetone (100 ml) was refluxed for 5 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by quick column chromatography (hexane:CH_2Cl_2) to obtain 2,5 dimethoxyacetophenone (157) as a yellow oil (4.32 g, 72 %).

Method 2

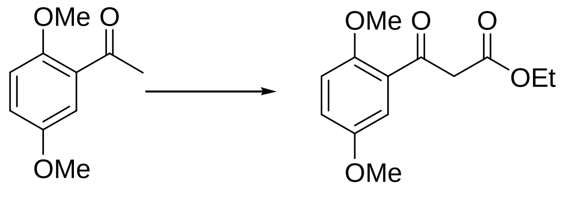
To a mixture of 2,5-dihydroxyacetophenone (156) (50 mg, 0.33 mmol) and tetrabutylammonium iodide (50 mg, 0.13 mmol) in THF (20 ml) was added a solution of 20% aq. KOH (30 mg, 0.43 mmol). After stirring for 5 min, dimethyl sulfate (0.5 mL, 0.1 mmol) was added. The reaction mixture was stirred for 10 h. Then the reaction mixture was extracted with ether (4x50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced presure. The residue was purified by flash column chromatography (2:3 ; EtOAc : Hexane) to obtain 2,5 dimethoxy acetophenone (157) as a yellow oil (71 %, 35 mg) (Amin and Shah, 1955).

FTIR (neat), ν_{max} 1674 (C=O), 1606 (C=C) cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 7.31 (1H, d, J= 3.2 Hz), 7.12 (1H, dd, J= 7.6, 3.2 Hz), 6.91 (1H, d, J= 3.2 Hz), 3.85 (3H, s), 3.79 (3H, s), 2.4 (s, 3H)

MS (CI), m/z 181.2 (M+1)

Ethyl 3-(2,5-dimethoxyphenyl)-3-oxopropanoate (157)



(157) **(158)**

Sodium hydride (2.25 g, 93.5 mmol) was suspended in benzene (100 mL) under a N_2 atmosphere after being washed with ether. A solution of 2,5 dimethoxy acetophenone (157) (7.8 g, 42.6 mmol) and diethylcarbonate (9.75 ml) in benzene (20 mL) was added. The reaction mixture was refluxed at 80 ^{o}C for 4 h. After cooling to room temperature, water (50 mL) was added dropwise. The reaction mixture was extracted with ether (5x50 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (2:8; EtOAc:Hexane) to give ethyl 3-(2,5-dimethoxyphenyl)-3-oxopropanoate (158) as a yellow oil (8.27 g, 77 %) (McPherson *et al.*, 1976).

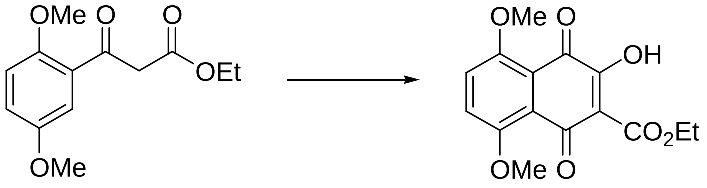
FTIR (neat), ν_{max} 3453 (OH), 1738 (C=O), 1672 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.72 (s, OH), 7.23 (1H, d, J= 3.2 Hz), 7.07 (1H, dd, J= 7.6, 3.2 Hz), 6.91 (1H, d, J= 3.2 Hz), 4.19 (2H, q, J=6.8 Hz), 3.9 (2H, s), 3.86 (3H, s), 3.80 (3H, s), 1.24 (3H, t, J= 6.8 Hz)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.5, 168.0, 153.6, 153.4, 126.2, 121.5, 111.8, 112.5, 113.8, 112.9, 60.7, 55.6, 50.3, 13.9

MS (CI), m/z 253.3 (M+1)

2-Ethoxycarbonyl-3-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (159)



(158) **(159)**

A mixture of keto ester (158) (2.5g, 0.01 mol) and aluminum chloride (4 g, 0.03 mol) was dissolved in dry nitromethane (60 mL) under nitrogen. After stirring for 15 min , a solution of oxalyl chloride (0.82 mL, 0.01 mol) in dry nitromethane (40 mL) was added dropwise. The reaction mixture was heated to 80 ^{o}C for 3 h. After cooling to room temperature, The reaction mixture was poured into 10% aqueous oxalic acid (30 mL), extracted with ether (3x70 mL). The combined extracts were washed with 10% aq. Na_2CO_3 (2x70 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrated was concentrated under reduced pressure. The residue was purified by flash column chromatography (60:30:5 ; EtOAc : CH_2Cl_2 : AcOH) to give 2-ethoxycarbonyl-3-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (159) as a red needles (2 g, 67%); mp 112- 113 °C (Sartori *et al.*, 1993, 112-113 °C).

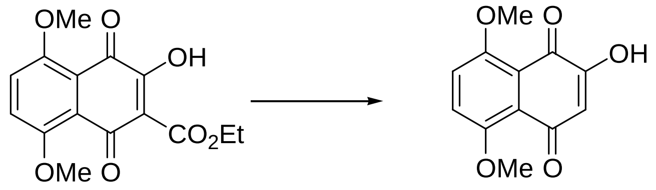
FTIR (KBr), ν_{max} 3430 (OH), 1735 (C=O), 1684 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (1H, d, J=9.6 Hz), 7.26 (1H, d, J=9.6 Hz), 4.46 (2H, q, J=7.1 Hz), 3.98 (3H, s, OMe), 3.95 (3H, s, OMe), 1.42 (3H, t, J=7.1 Hz)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.2, 180.1, 179.3, 176.2, 156.8, 155.4, 154.1, 153.7, 122.7, 121.5, 63.4, 57,3, 56.7, 14.1

MS (CI), m/z 278.9 (M+)

2-Hydroxy-5,8-dimethoxynaphthalene-1,4-dione (160)



(159) **(160)**

A solution of 2-ethoxycarbonyl-3-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (160) (1.3 g, 0.005 mol) in 5% aqueous NaOH (50 mL) was stirred at 60 °C for 8 h. Then a solution of 10% aqueous HCl (50 mL) was added and heating was continued for further 30 min. After cooling to room temperature, the mixture was extracted with ether (4x50 mL), dried over anhydrous Na_2SO_4, filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography with (50:40:5; EtOAc: CH_2Cl_2: AcOH) to give 2-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (160) as a red needles (850 mg, 73%); mp 98-100 °C (Sartori *et al.*, 1993, 102-104 °C).

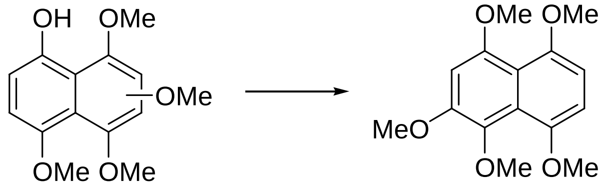
FTIR (KBr), ν_{max} 3405 (OH), 1665 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (1H, d, J=9.0 Hz), 7.26 (1H, d, J=9.0 Hz), 6.22 (1H, s), 4.00 (3H, s, OMe), 3.96 (3H, s, OMe)

MS (CI), m/z 235.1 (M+1)

1,2,4,5,8-Pentamethoxynaphthalene (147)

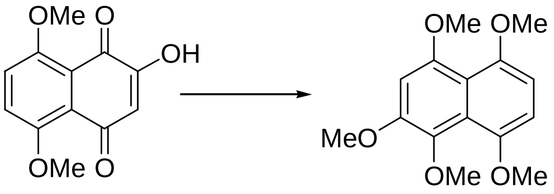
Method 1



(145) **(147)**

A mixture of regiomeric naphthol (145) (100 mg, 0.43 mmol) and tetrabutylammonium bromide (200 mg, 0.83 mmol), 20% aq. KOH (30 mg, 0.43 mmol) in THF (10 mL) was stirred at room temperature. Dimethyl sulfate (0.5 mL, 0.1 mmol) was added. The mixture stirred for 8 h, the reaction mixture was extracted with ether (2x50 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (2:3 ; EtOAc : Hexane) to obtain 1,2,4,5,8-pentamethoxynaphthalene (147) as a yellow needles (70 %, 75 mg) ; mp 101-102 °C (Giles *et al.*, 1988, 102-103 °C) .

Method 2



(160) **(147)**

A mixture of 2-hydroxy-5,8-dimethoxynaphthalene-1,4-dione (160) (10 mg, 0.043 mmol) and tetrabutylammonium bromide (20 mg, 0.083 mmol) in THF (1 mL) was stirred at room temperature. Then 10% aq. $Na_2S_2O_4$ (100 mg, 0.43 mmol) was added. After being stirred for 15 min, 20% aq. KOH (30 mg, 0.43 mmol) was added followed by the addition of dimethyl sulfate (0.5 mL, 0.1 mmol). The reaction mixture was stirred for further10 h. Then the mixture was extracted with ether (2x50 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (2:3 ; EtOAc : Hexane) to obtain 1,2,4,5,8-pentamethoxynaphthalene (147) as a yellow needles (71 %, 7 mg); mp 101-102 °C (Giles *et al*., 1988, 102-103 °C).

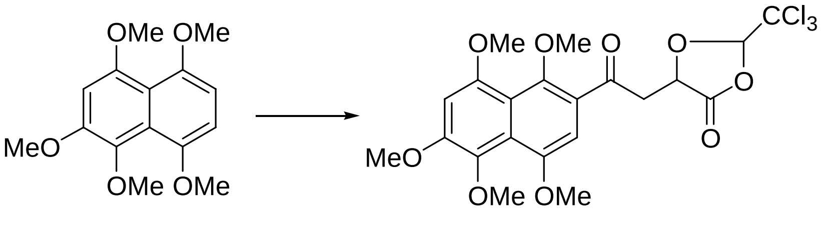
FTIR (KBr), ν_{max} 1601 (C=C) cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 6.72 (1H, d, J= 8.5 Hz), 6.67 (1H, s), 6.58 (1H, d, J= 8.5 Hz), 3.91(3H, s), 3.87(3H, s), 3.84 (3H, s), 3.82, (3H, s), 3.75, (3H, s)

^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.9, 151.5, 150.1, 149.9, 138.1, 124.2, 115.5, 108.9, 105.2, 99.2, 61.9, 57.8, 57.6, 57.4, 57.3

MS (CI), m/z 279.2 (M+1)

5-[2-Oxo-2-(1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-ethyl]-2-trichloromethyl-[1,3] dioxolan-4-one (161)



(147) **(161)**

A mixture of 1,2,4,5,8-pentamethoxy-naphthalene (147) (60 mg, 1.2 mmol) and acid (132) (1.3 g, 5 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C under N_2

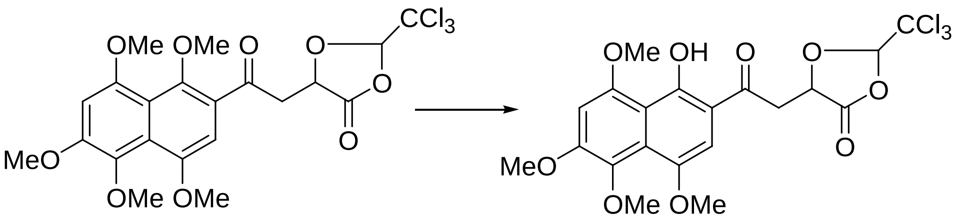
atmosphere. Then, TFAA (0.7 ml, 5 mmol) was added dropwise. The reaction mixture was stirred for further 3 h, then poured into cold water and extracted with CH_2Cl_2 (4x20 mL). The combined organic layers were dried over anh. Na_2SO_4, filtered and the filtrate concentrated in vacuo. The residue was purified by flash column chromatography (3 : ; Hexane : EtOAc) to obtain 5-[2-oxo-2-(1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-ethyl]-2-trichloro methyl-[1,3] dioxolan-4-one (161) as a yellow plates (360 mg, 55%); mp 121-124 °C.

IR (KBr) 1810 ν_{max} (C=O) 1680, 1611 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) δ 7.10 (s, 1H), 6.48 (s, 1H), 5.83 (s,1H), 4.79 (m, 1H) 3.88 (s,3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.69 (s, 3H), 2.98 (dd, J=4.3 Hz, 18 Hz, 1H), 2.89 (dd, J=4.3 Hz, 18 Hz, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.7, 185.3, 153.9, 152.5, 151.5, 137.8, 126.0, 116.2, 105.3, 97.6, 63.3, 61.5, 56.6, 56.6, 56.4, 56.3

5-[2-(1-Hydroxy-4,5,6,8-tetramethoxy-naphthalen-2-yl)-2-oxo-ethyl]-2-trichloro methyl-[1,3]dioxolan-4-one (163)



(161) **(163)**

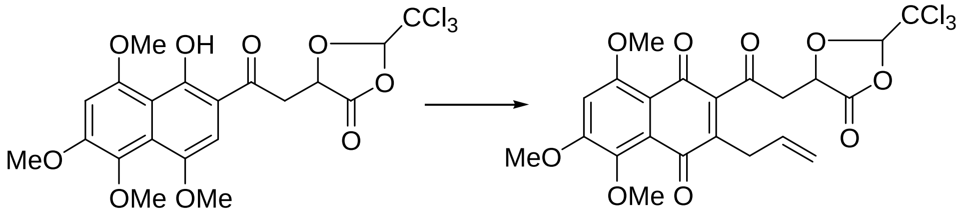
To a solution of naphthalene (161) (150 mg, 0.29 mmol) in dry CH_2Cl_2 (5 mL) at –78 °C under N_2 was added dropwise a solution of BBr_3 in CH_2Cl_2 (1 N, 0.4 ml, 6.6 mmol). After being stirred for 10 min at same temperature, the reaction mixture was quenched with aqueous 10% NH_4Cl (10 mL) and extracted with CH_2Cl_2 (4x30 mL). The combined organic layers were washed with water (2x20 mL), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by flash column chromatography (3 : 2; Hexane : EtOAC) to give 5-[2-(1-hydroxy-4,5,6,8-tetramethoxy-naphthalen-2-yl)-2-oxo-ethyl]-2-trichloro methyl-[1,3]dioxolan-4-one (163) as a brown plates (105 mg, 71%); mp 72-74 ^{0}C.

IR (KBr) 3360 (OH), 2965, 1820 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.01 (s, 1H), 7.24 (s, 1H), 6.41 (s, 1H), 6.23(s, 1H), 4.97 (m, 1H), 3.92 (s, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.52 (dd, J=4 Hz, 18 Hz, 1H), 3.21 (dd, J=4 Hz, 18 Hz, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.2, 185.2, 153.5, 151.2, 151.5, 137.8, 124.1, 116.5, 105.2, 97.4, 60.1, 61.5, 56.2, 56.4, 56.4, 56.4

3-Allyl-5,6,8-trimethoxy-2-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphthoquinone (166)



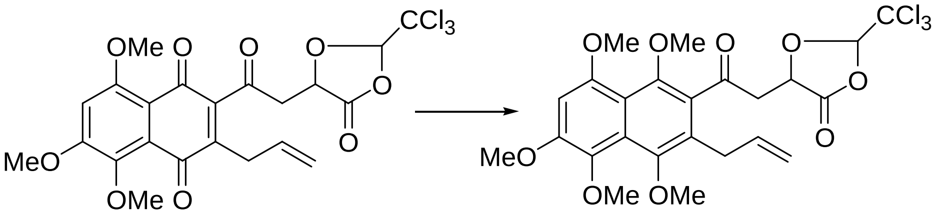
(163) **(166)**

To a stirred ice-cold solution of naphthol (163) (105 mg, 0.24 mmol) in acetonitrile (5 mL) was added dropwise a solution of CAN (390 mg, 0.71 mmol) in water (1.5 mL and stirring was continued for 15 min at 0 ^{o}C, when water (10 mL) was added. The reaction mixture was extracted with EtOAc (3x15 mL), the combined organic layers were dried over anhydrous Mg_2SO_4, filtered and the filtrate concentrated under reduced pressure to give oil residue. The residue was dissolved with acetonitrile (30 ml). Then silver nitrate (45 mg, 0.48 mmol), and vinylacetic acid (135 mg, 1.5 mmol) was added. After 10 min, a solution of ammonium persulfate (430 mg, 1.6 mmol) in water (20 mL) was added dropwise. The reaction mixture was stirred at 60-70 ^{o}C for 8 h. Then, the reaction mixture was poured into cold water (20 mL) and extracted with ethyl acetate (4x 50 mL). The combined organic layers were washed with 10% a solution sodium hydrogen carbonate (2x50 mL), dried over anhydrous $MgSO_4$ and filtered. The organic extract was concentrated in vacuo. The residue was purified by flash column chromatography (95 : 5; Hexane : EtOAC) to obtain 3-allyl-5,6,8-trimethoxy-2-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphthoquinone (166) as a brown needles (61 mg, 50%); mp 81-83 ^{0}C.

IR (neat), ν_{max} 1799, 1675, 1595, 1471 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.24 (s, 1H), 5.92(s, 1H), 5.76 (ddt, J=17, 10.4, 6.7 Hz, 1H) 5.05-5.07 (m, 2H), 4.89 (m, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 3.52 (dd, J=4, 19 Hz, 1H) 3.32 (dd, J=4, 19 Hz, 1H), 3.21 (m, 2H)

5-[2-(3-Allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2-oxo-ethyl]-2-trichloro methyl-[1,3]dioxolan-4-one (167)



(166) **(167)**

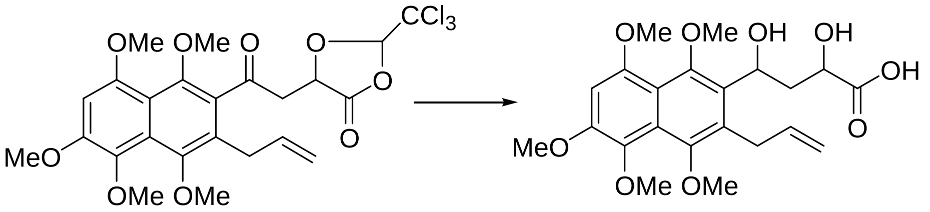
To a stirred solution of quinone (156) (10 mg, 0.019 mmol) in THF (1 ml) was added tetrabutylammonium iodide (20 mg, 0.083 mmol) and a solution of sodium dithionite (100 mg, 0.43 mmol) in water (0.5 mL). After being stirred for15 min at room temperature, K_2CO_3 (60 mg, 0.43 mmol) and dimethyl sulfate (0.5ml, 0.1 mmol) were added. The reaction mixture was stirred overnight. Then the reaction mixture was extracted with ether (4x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (6 : 4; Hexane : EtOAC) to give 5-[2-(3-allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2-oxo-ethyl]-2-

trichloro methyl-[1,3]dioxolan-4-one (167) as a yellow plates (6 mg, 55 %); mp 103-104 ^{0}C.

IR (KBr) ν_{max} 1812 (C=O) 1680, 1611 cm^{-1}

^{1}H NMR (CDCl$_3$, 400 MHz) δ 6.76 (s, 1H), 6.23(m, 1H), 5.81 (s, 1H), 5.14-5.28 (m, 2H), 4.81 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.87(s, 3H), 3.75 (s, 3H), 3.72(s, 3H), 3.32 (m, 2H), 2.87 (dd, J=4, 18 Hz, 1H) 2.64 (dd, J=4, 18 Hz, 1H)

4-(3-Allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2,4-dihydroxy-butyric acid(169)



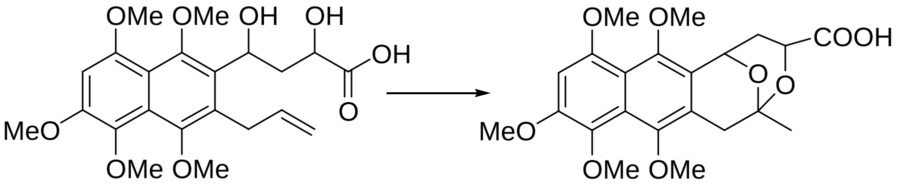
(167) **(169)**

To a stirred solution of naphthalene (157) (100 mg, 0.18 mmol) in EtOH (3 mL) was added a solution of NaBH$_4$ (17 mg, 4.5 mmol) in EtOH (0.25 mL). Stirring was at room temperature for 30 min. Then acetone (1 mL) was added. The reaction mixture was concentrated under reduced pressure. The residue was purified by short column chromatrography to give yellow oil. The oil was dissolved in ethanol (2 mL). A solution of 10% aq.NaOH (1 ml) was added. After being stirred overnight, the reaction mixture was acidified with 20% aq.HCl and extracted with ether (5x20 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (1: 3; EtOH : EtOAC) to give 4-(3-allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2,4-dihydroxy-butyric acid (169) as a yellow oil (48 mg, 62%).

IR (KBr) ν_{max} 3370 (OH), 1731 (C=O) 1682 cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.42 (s, 1H), 6.41 (s, 1H), 6.19 (m, 1H), 5.37 (m, 2H), 4.90 (m, 1H), 4.41 (m, 1H), 4.05 (s, 3H), 4.03 (s, 3H), 3.87(s, 3H), 3.75 (s, 3H), 3.55(s, 3H), 3.43 (m, 2H), 2.94(m, 1H), 2.89 (m, 1H)

Oxabicyclic compound (170)



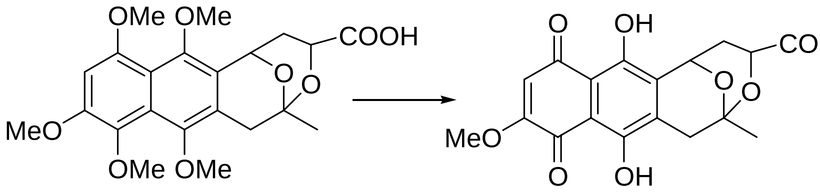
(169) **(170)**

A mixture of palladium chloride (1 mg, 0.0056 mmol) and anhydrous cupric chloride (10 mg, 0.074 mmol) in dry dimethoxyethane (2 mL) was heated at 65 °C while oxygen was bubbled through the solution. A solution of (169) (30 mg, 0.074 mmol) in dry dimethoxyethane (0.5 mL) was added dropwise and the reaction mixture was stirred at 65 °C for further 30 min then cooled to room temperature. The reaction mixture was filtered through a short neutral alumina column and eluted with ether. The resulting solution was concentrated in vacuo. The residue was purified by flash column chromatography (4:1 ; EtOAc : Hexane) to obtain oxabicyclic compound (170) (15 mg, 67%) as a mixture of diasteriomer.

IR (KBr) ν_{max} 3340 (OH), 1736 (C=O) cm^{-1}

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.30(s, 2H), 5.74 (d, j=5 Hz, 1H), 5.31 (d, J=8 Hz, 1H), 4.90 (m, 1H), 4.52 (m, 1H), 4.41 (m, 1H), 4.37 (m, 1H), 4.05 (s, 6H), 4.03 (s, 6H), 3.87(s, 6H),3.51(s,6H), 3.33(s, 6H) 3.0 (d, J=17 Hz, 1H), 2.81(d, J=17 Hz, 1H), 2.63(d, J=17 Hz, 1H), 2.41 (d, J=17 Hz, 1H), 2.21 (m, 2H), 2.05(m, 2H), 1.57(s, 3H), 1.55(s, 3H)

Marticin (12) and its isomer (13)



(170) **(12)** and **(13)**

To stirred ice-cold solution of naphthol (170) (15 mg, 0.12 mmol) in acetonitrile (5 mL) was added a solution of CAN (202 mg, 0.35 mmol) in water (1.5 mL). The reaction mixture was stirred at 0 °C for 15 min and then water (10 mL) was added. The mixture was extracted with EtOAc (3x15 mL). The organic extract was separated and dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give oil residue. The residue was dissolved in dry CH_2Cl_2 (3 ml) at –78 °C under N_2 atmosphere. A solution of BBr_3 in CH_2Cl_2 (1 N, 6 ml, 6.0 mmol) was added dropwise. After being stirred for 10 min at –78 °C, the reaction mixture was quenched with 10% aq.NH_4Cl (5 mL) and extracted with CH_2Cl_2 (4x20 mL). The combined organic layers were washed with water (2x20 mL), dried over anhydrous Na_2SO_4 and filtered and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography (1: 9; Hexane : EtOAC) to give a 1:1.2 mixture of marticin (12) and its isomer (13) in the ration 1: 1.2 (6 mg, 52%).

IR (KBr) ν_{max} 3325 (OH), 1665 (C=O) cm^{-1}

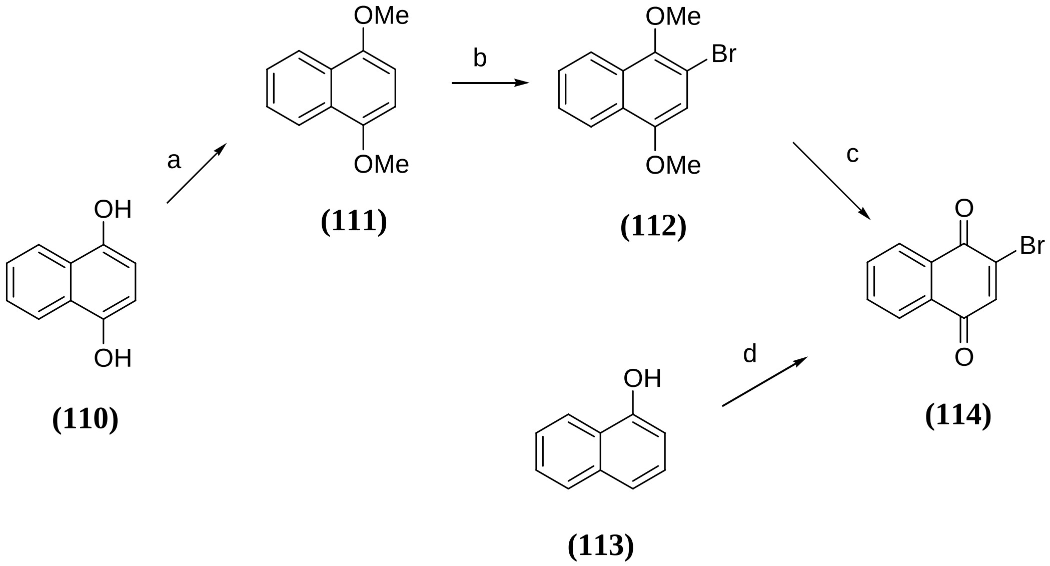
^1H NMR ($CDCl_3$, 400 MHz) δ 12.92 and 12.93 (2s, 2H), 12.42, 12.43(2s, 2H), 6.15, 6.17(2s, 2H), 5.62 (d, j=5 Hz, 1H), 5.39 (d, J=9 Hz, 1H), 4.61 (m, 1H), 4.42(m, 1H), 3.97 (s, 6H), 3.13 (d, J=19 Hz, 1H), 3.09 (d, J=19 Hz, 1H), 2.71(d, J=19 Hz, 1H), 2.62 (d, J=19 Hz, 1H), 2.30(m, 2H), 2.21(m, 2H), 1.60 (s, 3H), 1.56(s, 3H)

RESULTS

Synthesis of (±)-isagarin

Preparation of 2-bromo-1,4-naphthoquinone (114)

The starting material, 2-bromo-1,4-naphthoquinone (114) was prepared from p-hydronaphthoquinone (110) in three steps or from 1-naphthol (113) in one step as shown in Scheme 7.



Scheme 7

Reagents and conditions:

a. dimethyl sulfate, K_2CO_3,dry acetone, reflux,72% 1) or MeI, K_2CO_3, dry acetone, reflux , 57% 1)

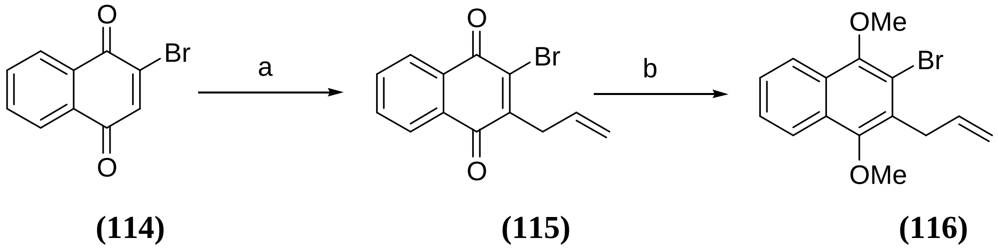
b. Br_2, benzene, 92%1)

c. CAN, MeCN, H_2O, 0 ^{0}C, 100% 1)

d. NBS, acetic acid, 55-60 ^{0}C, 73%1) (Butler *et al*., 1938)

Synthesis of 2-allyl-3-bromo-1,4-naphthoquinone (116)

The 2-allyl-3-bromo-1,4-naphthoquinone (116) was synthesized from (114) in two steps as shown in Scheme 8 (De Kimpe *et al.*, 1999).



Scheme 8

Reagents and conditions:

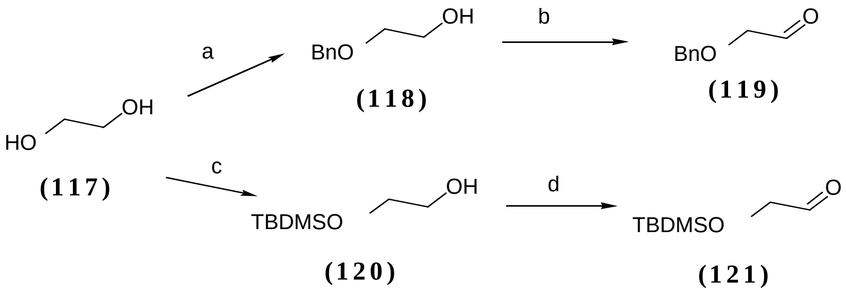
a. vinyl acetic acid, $AgNO_3$, ammonium persulfate, H_2O, MeCN , 60-70 ^{0}C, 72%$^{1)}$

b. $SnCl_2$, HCl, EtOH, 50 ^{0}C then dimethyl sulfate, 50% KOH, 65 ^{0}C, 75%$^{1)}$

Preparation of benzyloxyacetaldehyde (119) and (*tert*-butyldimethylsilyloxy)-acetaldehyde (121)

Benzyloxyacetaldehyde (119) (Kusakabe *et al.*, 1987; Hon *et al.*, 1995) and (*tert*-butyldimethyl silyloxy)acetaldehyde (121) (Enders and Schusseler, 2002; Brown et al., 2000) were synthesized by using two different methods and the synthetic methodologies were described in Scheme 9 and 10.

Method 1

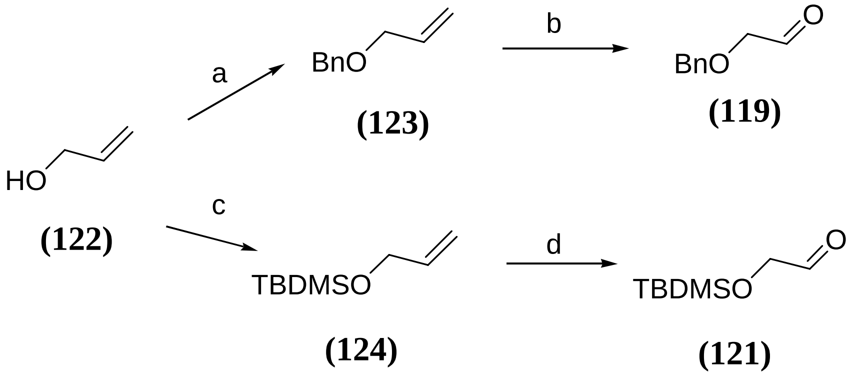


Scheme 9

Reagents and conditions:

a. KOH, Benzyl chloride, 90 ^{0}C, 51%1)
b. oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 ^{0}C, 81%1)
c. NaH, TBDMSCl, THF, rt, 73% 1)
d. Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 ^{0}C, 76%1)

Method 2



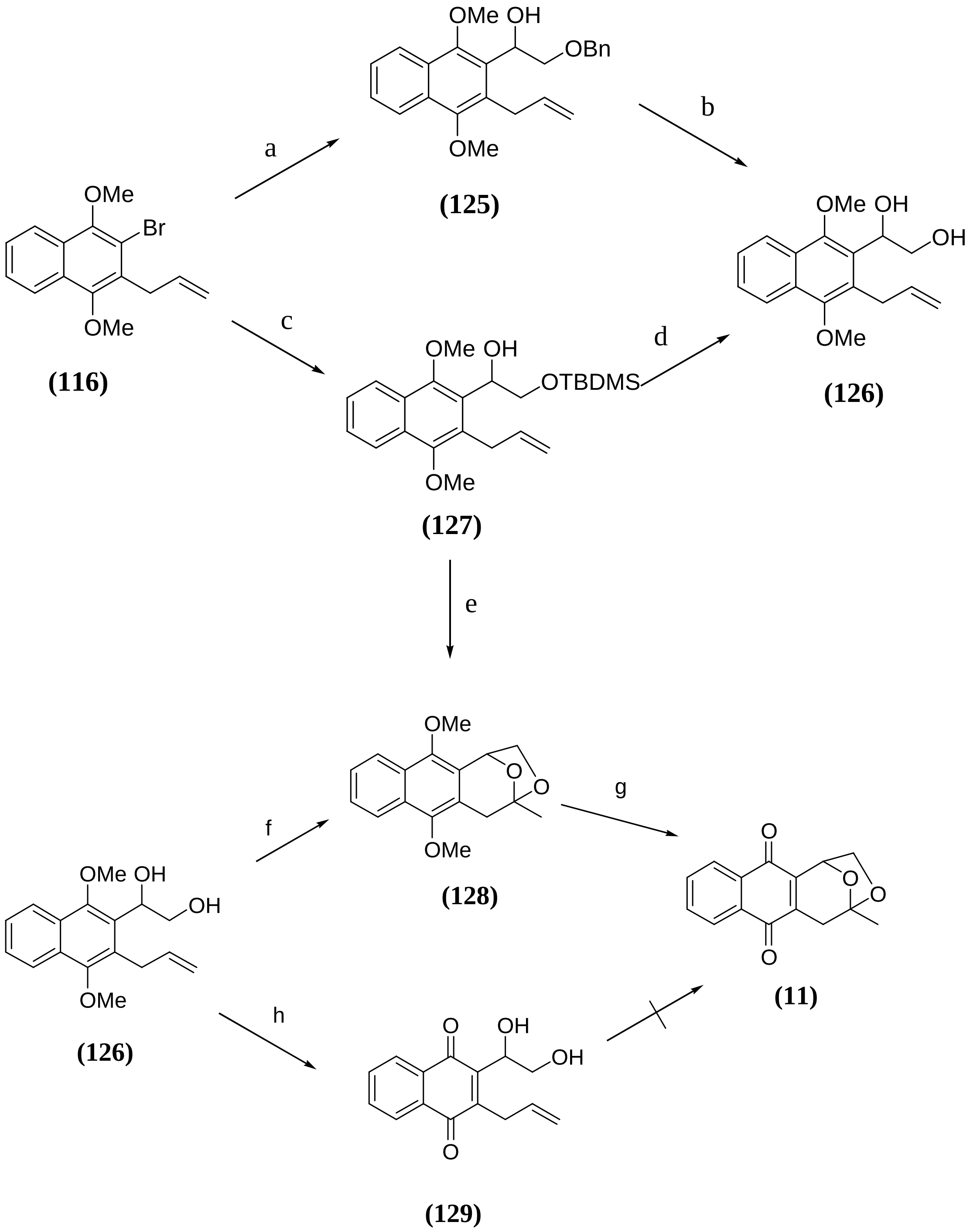
Scheme 10

Reagents and conditions:

a. NaH, BnCl, THF, rt, 84%1)
b. O_3, CH_2Cl_2, -78 ^{0}C then PPh_3, rt, 82%1)
c. TBDMSCl, imidazole, CH_2Cl_2, rt, 73% 1)
d. O_3, CH_2Cl_2, -78 ^{0}C then PPh_3, rt, 76%1)

Synthesis of isagarin (11)

The synthesis of isagarin (11) from 2-allyl-3-bromo-1,4-naphthoquinone (116) is shown in Scheme 11.



Scheme 11

Reagents and conditions:

a. *n*-BuLi, THF then (119), -78 ^{0}C, 44%$^{1)}$

b. Li, naphthalene, THF, -78 ^{0}C, 41%$^{1)}$

c. *n*-BuLi, THF then (121), -78 ^{0}C, 70%$^{1)}$

d. TBAF, THF, rt, 87%$^{1)}$

e. $PdCl_2$, $CuCl_2$, DME, O_2, 65 ^{0}C, 67%$^{1)}$

f. $PdCl_2$, $CuCl_2$, DME, O_2, 65 ^{0}C, 71%, $^{1)}$

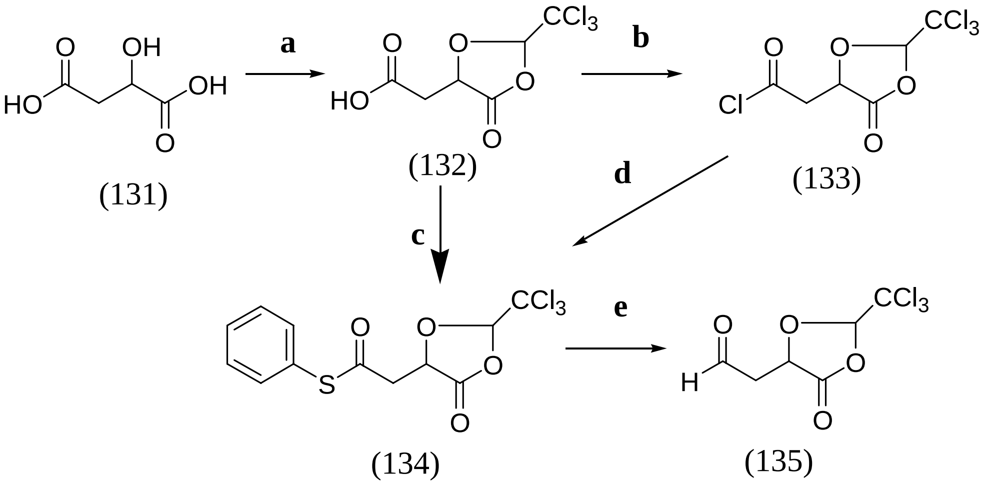
g. CAN, MeCN, H_2O, 0 ^{0}C, 95% $^{1)}$

h. CAN, MeCN, H_2O, 0 ^{0}C, 95% $^{1)}$

Synthesis of (±)-marticin and (±)-isomarticin

Preparation of (5-oxo-2-trichloromethyl-[1,3]dioxalan-4-yl)-acetyl chloride (133).

Acid chloride (133) (Shih *et al.*, 1989) and aldehyde (135) were prepared from *dl*-malic acid (131) in good yield as shown in Scheme 12.



Scheme 12

Reagents and conditions:

a. *dl*-Malic acid, $H_2SO_{4,}$ CCl_3CHO, 79%$^{3)}$

b. $SOCl_2$, reflux, 2 days, 98%^{2}

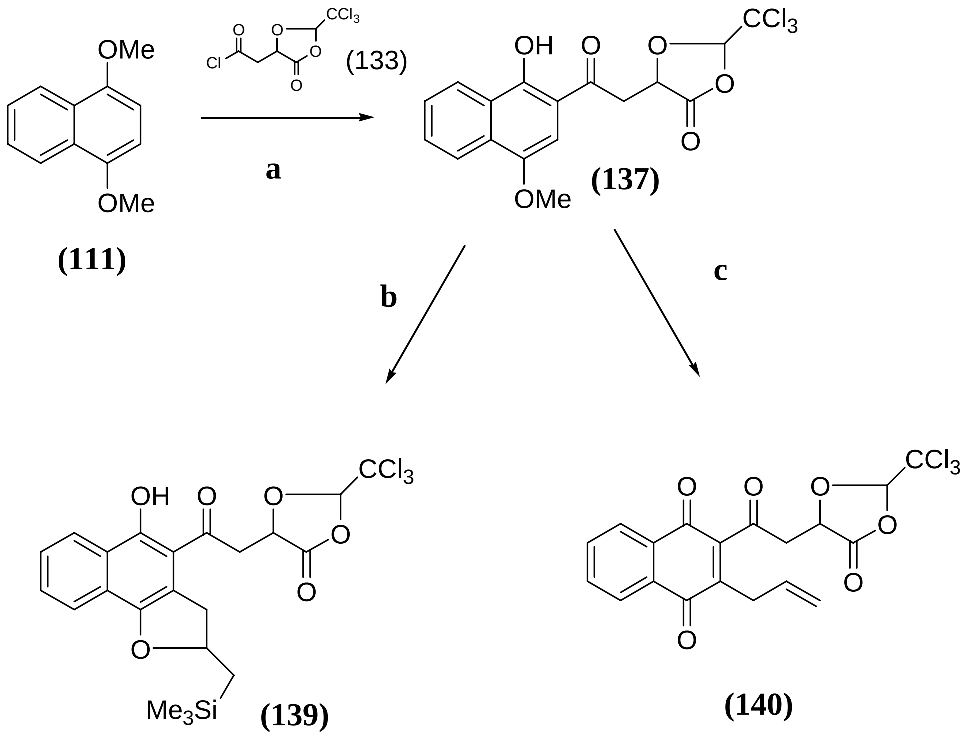
c. DCC, CH_2Cl_2, DMAP, thiophenol, 79%$^{1)}$

d. thiophenol, pyridine, rt, 85%$^{1)}$

e. Et$_3$SiH, Pd/C, rt, 98%1)

Model synthesis of marticin

The synthesis of 2-allyl-3-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphthoquinone (140) from 1,4-methoxynaphthalene (111) was shown in Scheme 13.



Scheme 13

Reagents and conditions:

a. (133), AlCl$_3$, CH$_2$Cl$_2$, rt, 0 ^{0}C , 43%1)

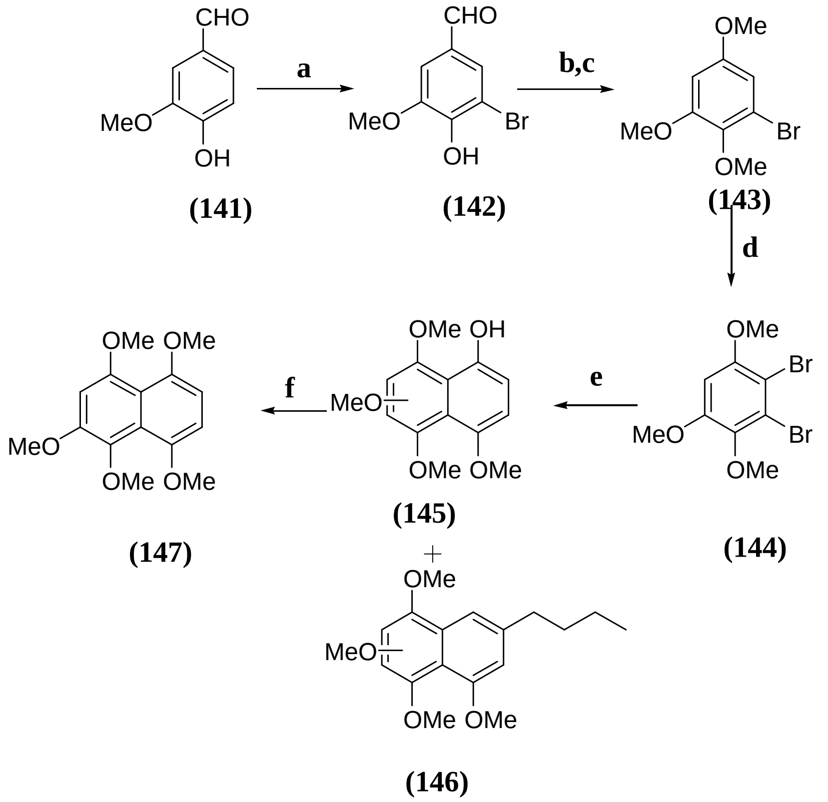
b. CAN, MeCN, H$_2$O; allyl trimethylsilane, SnCl$_4$, dry CH$_2$Cl$_2$, 78 ^{0}C, N$_2$, 56% over two steps 1)

c. CAN, MeCN, H$_2$O; vinyl acetic acid, AgNO$_3$, ammonium persulfate, H$_2$O, MeCN, 60-70 ^{0}C, 55% yield 1)

Synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147)

The synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147) using two different methods were shown in Scheme 14 (Giles *et al.*, 1988) and 15.

Method 1



Scheme 14

Reagents and conditions:

a. Br_2, acetic acid, 0 ^{0}C, 95%$^{1)}$

b. H_2O_2, NaOH, 0 ^{0}C

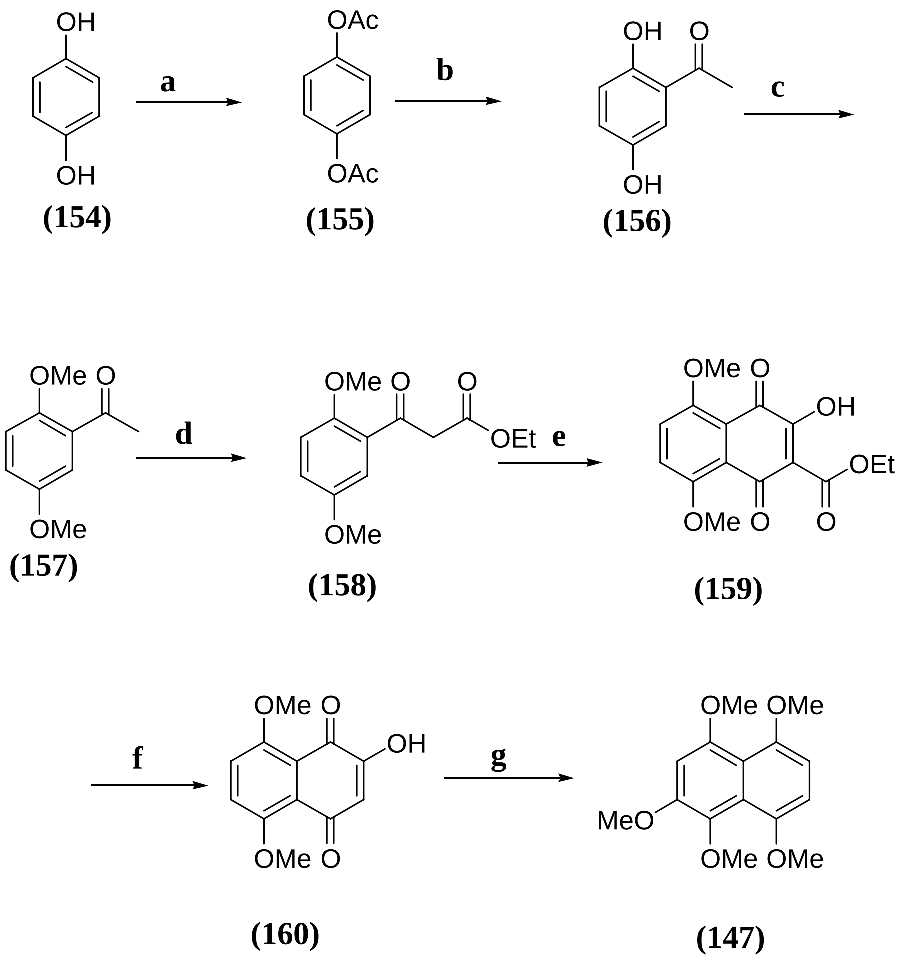
c. Dimethyl sulfate, K_2CO_3, dry acetone, reflux, 81% yield over two steps$^{1)}$

d. Br_2, benzene, 81%$^{1)}$

e. 2-Methoxyfuran, *n*-BuLi, dry THF, -78 ^{0}C, (145) (43%) and (146) (27%))$^{1)}$

f. Dimethyl sulfate, K_2CO_3, dry acetone, reflux, 70%$^{1)}$

Method 2



Scheme 15

Reagents and conditions:

a. Ac_2O, H_2SO_4, 100%$^{1)}$

b. $AlCl_3$, 165 ^{0}C, 71%

c. dimethyl sulfate, K_2CO_3, dry acetone, reflux, 72% $^{1)}$ or dimethyl sulfate, KOH, TBAI, H_20, THF, rt, 71%$^{1)}$

d. diethyl carbonate, NaH, benzene, reflux, 77%$^{1)}$

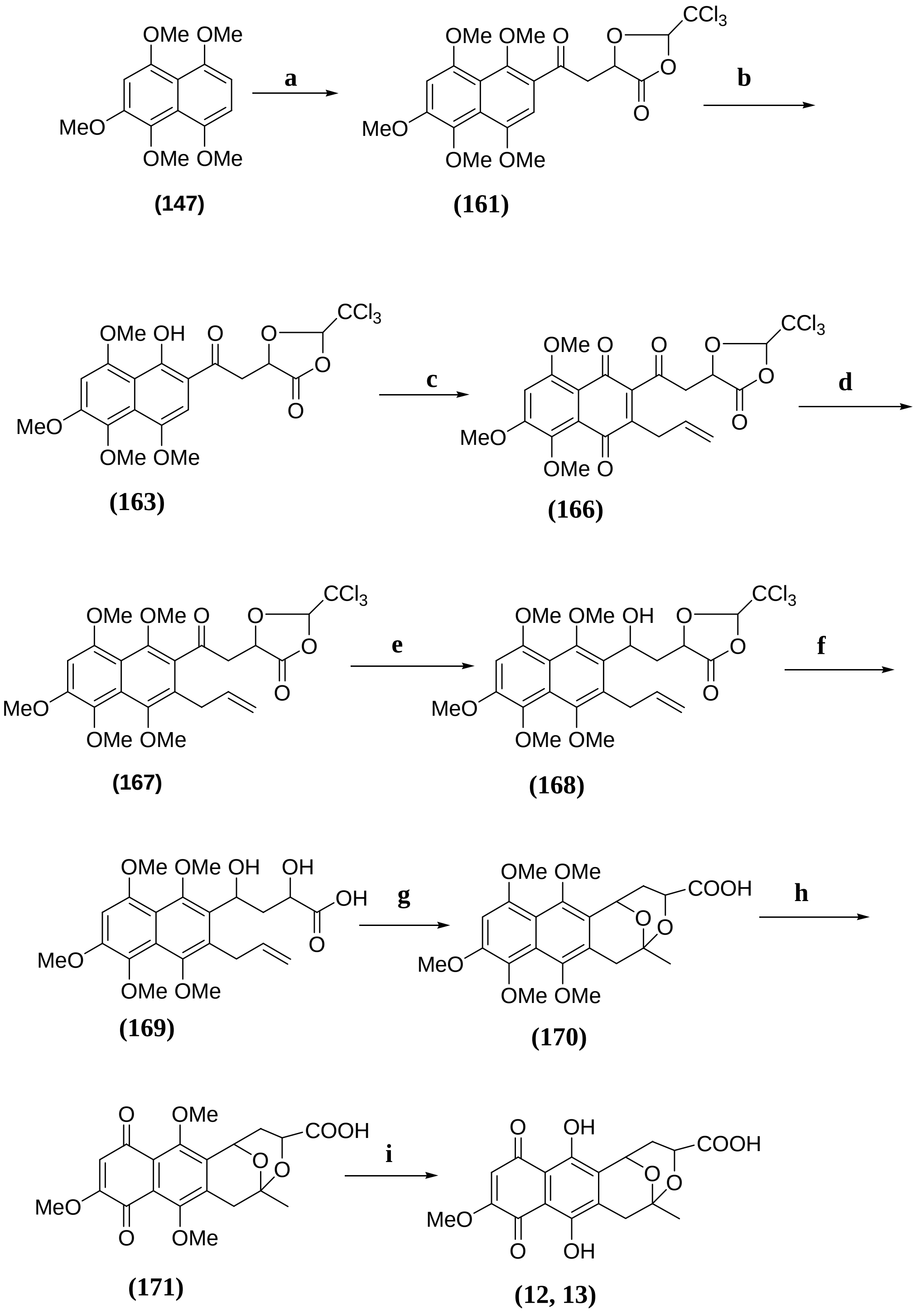
e. oxalyl chloride, $AlCl_3$, $MeNO_2$, reflux, 67%$^{1)}$

f. 5% KOH 65 ^{0}C then 10% HCl, 65 ^{0}C, 73%$^{1)}$

g. dimethyl sulfate, $Na_2S_2O_4$, KOH, TBAI, H_20, THF, rt, 71%$^{1)}$

Marticin (12)

The synthesis of (±)-marticin (12) from 1,2,4,5,8-pentamethoxynaphthalene (147) is shown in Scheme 16.



Scheme 16

Reagents and conditions:

a. TFAA, CH_2Cl_2, 0 ^{0}C, 55%$^{1)}$

b. BBr_3, CH_2Cl_2, -78 0 ^{0}C, 71%$^{1)}$

c. CAN/ MeCN/ H_2O, 0 ^{0}C; vinyl acetic acid, $AgNO_3$, ammonium persulfate, H_2O, MeCN , 60-70 ^{0}C, 50% $^{1)}$

d. Dimethyl sulfate, $Na_2S_2O_4$, K_2CO_3, TBAI, H_20, THF, rt, 55%$^{1)}$

e. $NaBH_4$, EtOH, 0 ^{0}C

f. NaOH, EtOH, 62% over two steps$^{1)}$

g. $PdCl_2$, $CuCl_2$, DME, O_2, 65 ^{0}C, 67% $^{1)}$

h. CAN/ MeCN/ H_2O, 0 ^{0}C

i. BBr_3, CH_2Cl_2, -78 0 ^{0}C, 52 % over two steps $^{1)}$

1) yield refers to chromatographic product

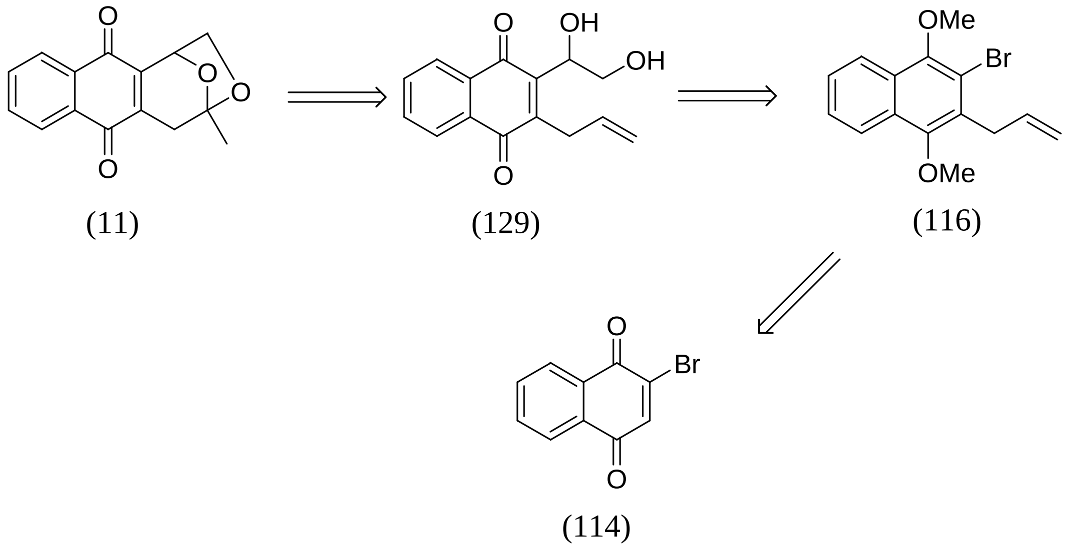
2) yield refers to crude product

3) yield refers to crystallized product

DISCUSSION

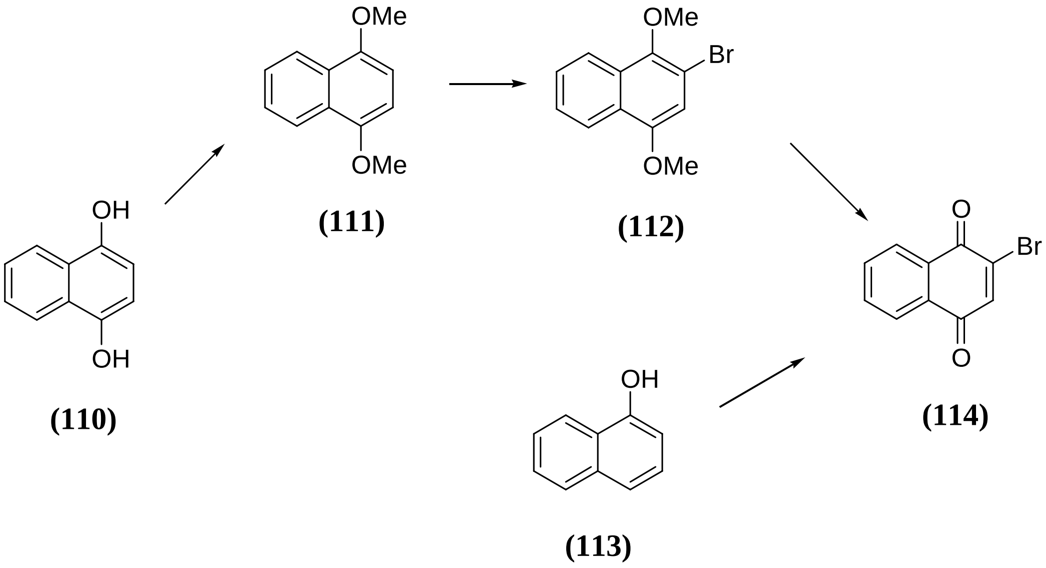
Isagarin

Pentas longiflora Oliv. (Rubiaceae) is woody herb which is reputed to possess medicinal properties. In Rwanda, where it is known as the traditional medicine under the name “Isagara”, the powdered roots of *P. longiflora* are used to treat the skin disease *Pityriasis versicolor*. The tetracyclic naphthoqiunone isagarin (11), 1,4-epoxy-4-methyl-1,2,4,5-tetrahydronaphtho [2,3-d]oxepin-6,11-dione was isolated from the roots of *P. longiflora* and subsequently synthesized by Kimpe *et al.* in 1999. We have shown that bicyclic ketals of this type can be obtained by palladium catalysed cyclization of the corresponding diol onto a proximal terminal alkene. Our new synthetic approach of isagarin (11) involving the Wacker ($PdCl_2$, $CuCl_2$, O_2) cyclization of (129) to (11), was demonstrated by the retrosynthetic sequence outlined in Scheme 17.

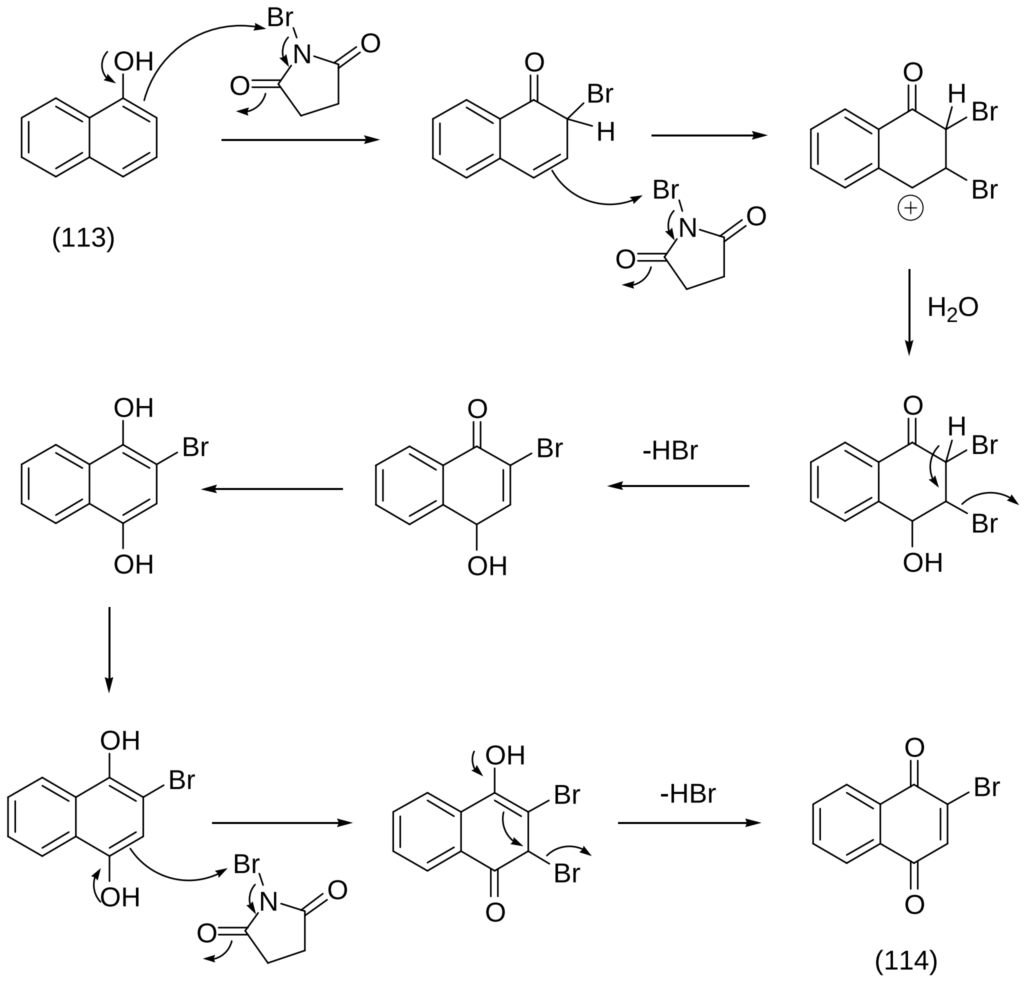


Scheme 17

2-Bromo-1,4-naphthoquinone (114) was prepared from p-hydro naphthoquinone (110) in three steps. Methylation of p-hydronaphthoquinone (110) has been studied under two reaction conditions. Dimethylsulfate, K_2CO_3 in acetone gave 1,4-dimethoxy-naphthalene (111) in 72% yield whilst MeI and K_2CO_3, in acetone afforded the methylated product in 57% yield. The results indicated that dimethylsulfate is a better methylating agent than MeI. Bromination of (111) gave 1,4-dimethoxy-2-bromo-naphthalene (112) which was oxidized to 2-bromo-1,4-naphthoquinone (114) by ceric(IV) ammonium nitrate (CAN) (Scheme 18). Alternatively, (114) can be prepared from 1-naphthol (113) by oxidative bromination according to the procedure of Butler *et al.* (Scheme 19).



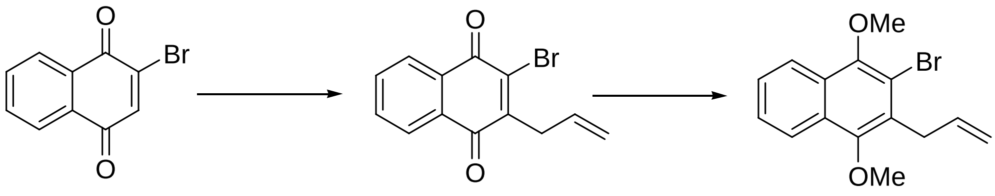
Scheme 18



Scheme 19

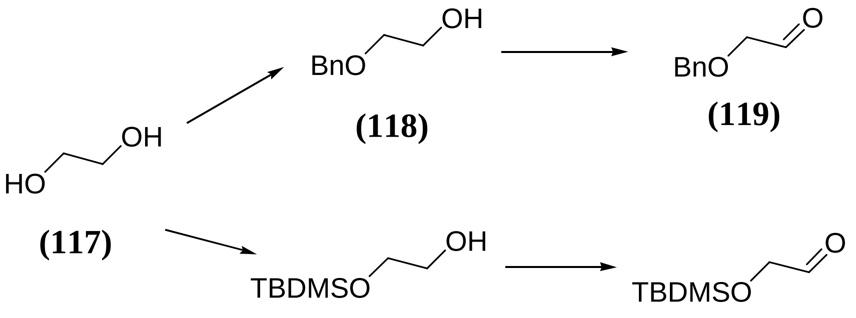
Radical allylation of naphthoquinone (114) with vinyl acetic acid, using ammonium persulfate and silver nitrate in aqueous acetonitrile, allowed the introduction of an allyl side chain at C(**3**) to give allylnaphthoquinone (115) in 72% yield. Reductive methylation of (115) by means of tin (II) chloride and dimethyl sulfate afforded 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116) in 75% yield. The IR spectrum of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116) showed intense absorption bands at 1612 (C=C) and 1593 (C=C) cm^{-1}.The ^1H NMR spectrum ($CDCl_3$) with two-proton multiplets at δ 8.06 (Ar-H) and δ 7.51 (Ar-H) indicated the presence of a naphthalene moiety. The ^1H NMR data also showed the presence of the allyl moiety: three olefenic protons at δ 6.07 (ddt, J= 16.8 Hz, 10.2 Hz and 5.6 Hz), 5.09 (dd, J=10.2 Hz and1.7 Hz) and 5.03 (dd, J=16.8 Hz and 1.7 Hz) and methylene protons (at δ 3.79, showing double of doublet with J=5.6 Hz and 1.7 Hz). The ^1H

NMR spectrum with two singlet signals δ at 3.97 and 3.91 was identified as the two methoxy proton.



(114) **(115)** **(116)**

Benzyloxy-acetaldehyde (119) and (tert-butyl-dimethyl-silanyloxy)-acetaldehyde (121), the intermediates for coupling with 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116), were synthesized by two approaches (Schemes 20, 21). Selective protection of ethylene glycol (117) with benzyl chloride or tert-butyl-dimethylsilyl chloride gave 2-benzyloxy-ethanol (118) and 2-(tert-butyl-dimethyl-silanyloxy)-ethanol (120) in 51% and 73% yield, respectively. Oxidation of 2-benzyloxy-ethanol (118) was investigated by several different methods as summarized in Table 4.



(117) **(118)** **(119)** **(120)** **(121)**

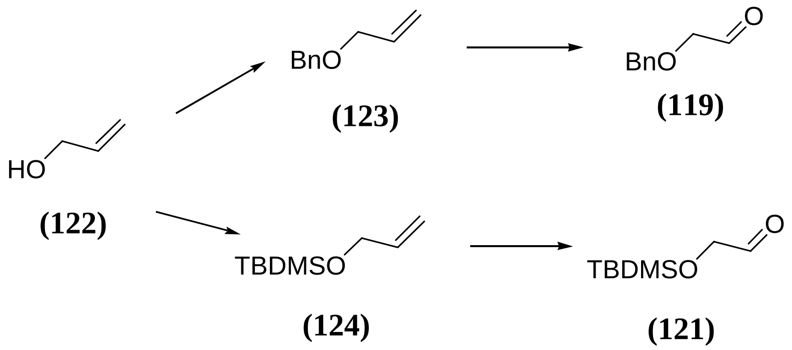
Scheme 20

Due to the instability of benzyloxy-acetaldehyde (119), oxidation of 2-benzyloxy-ethanol (118) with IBX, PCC, PDC or P_2O_5,/DMSO provided complex mixtures or trace amounts of benzyloxy-acetaldehyde (119). Therefore Swern oxidation (oxalyl chloride, DMSO, Et_3N), a mild oxidation method was used to oxidize 2-benzyloxy-ethanol (118) to benzyloxy-acetaldehyde (119) in 81% yield. 2-(tert-Butyl-dimethyl-silanyloxy)-ethanol (120) was also subjected to Swern reaction to obtain (tert-butyl-dimethyl-silanyloxy)-acetaldehyde (121) in 76% yield.

Table 4 Reaction conditions for oxidation of 2-(benzyloxy)ethanol (118)

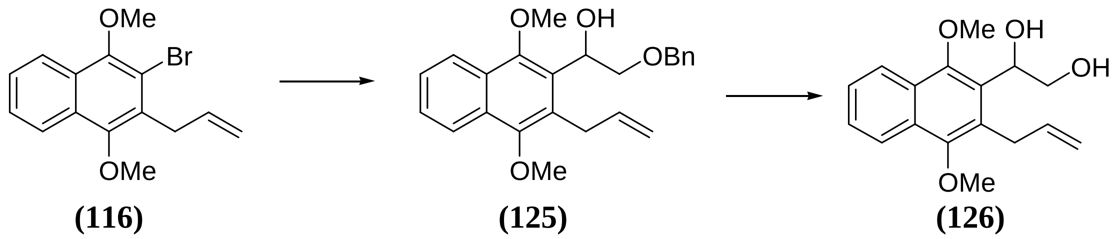
Reaction Conditions	Results
IBX /DMSO, RT	complex mixture
PCC/ CH_2Cl_2, RT	complex mixture
PDC/ CH_2Cl_2	complex mixture
P_2O_5, DMSO, CH_2Cl_2	trace amount of aldehyde (119)
Oxalyl chloride, DMSO, Et_3N (Swern Oxidation)	aldehyde (119) (76%)

Alternatively, (119) or (121) were easily prepared from protection of allyl alcohol (122) via (123) or (124 by ozonolysis in good yield (Scheme 21).

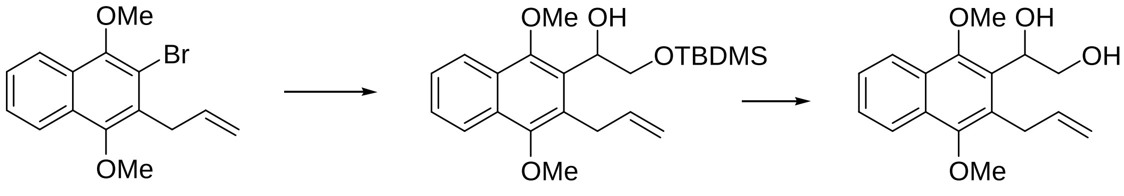


Scheme 21

With aldehyde (119) in hand, bromide-lithium exchange of (116) with *n*-butyllithium at low temperature gave the corresponding lithium salt, which was immediately trapped with (119) affording (125) as a racemic mixture in 70% yield.Radical debenzylation of (125) with lithium naphthalenide furnished the desired diol (126) in poor yield because of the difficulty of controlling the mol amount of lithium naphthalinide generated *in situ*. The structure of (126) was elucidated from spectroscopic data. The IR spectrum with absorptions at 1613 cm^{-1} (C=C) and 1590 cm^{-1} and the ^{1}H NMR spectrum (CDCl$_3$) with two-proton multiplets at δ 8.00-8.09 and 7.50-7.54 (m, 2H) indicated the presence of a naphthalene moiety. The characteristic peaks of the allyl moiety appeared at δ 6.10 (ddt, 1H, J=17.8 Hz, 7 Hz, 5.5 Hz), δ 4.92-5.00 (m, 2H and δ 3.79-3.82 (m, 2H). The one proton multiplt at δ 5.31 is indicative of a CH-OH unit. The two-proton signals of CH$_2$OH unit occurred at δ 4.1 (dd, 1H, J=9 Hz, 10 Hz) and 3.75 (dd, , J=5 Hz, 10 Hz).

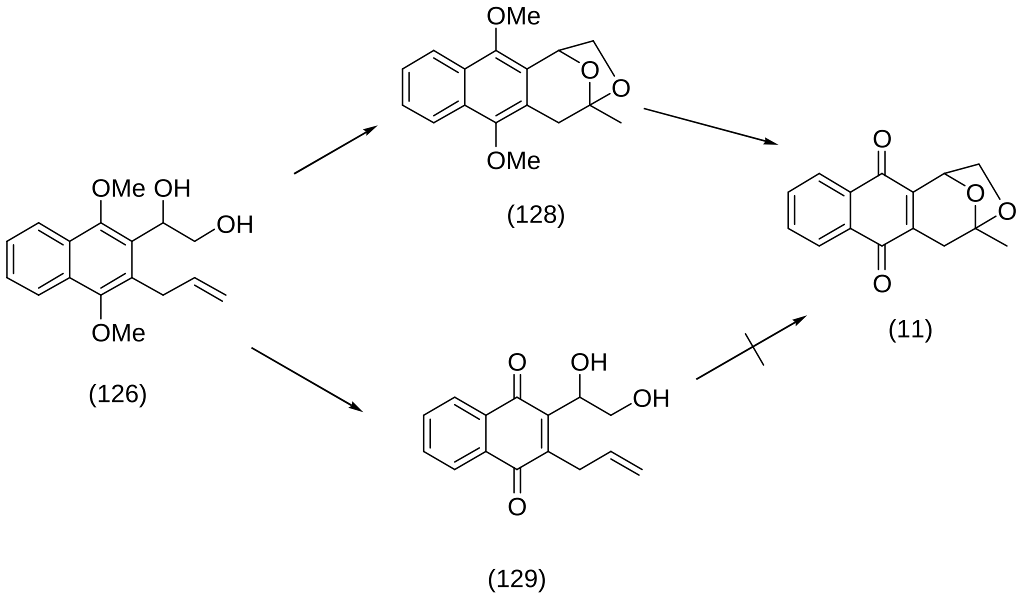


Debenzylation of diol (126) gave an unsatisfactory yield. The silyl group (TBDMS) was considered since it is stable in basis condition and easy to remove with fluoride ion. Coupling of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116) with aldehyde (121) using *n*-BuLi provided silyl ether (127) in 70% yield. Desilylation of (127) using TBAF gave the key intermediate (126) as colorless oil in 87% yield after chromatographic purification.



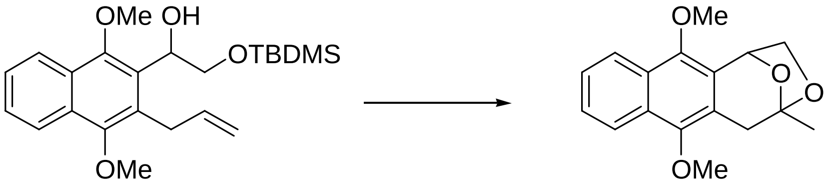
(116) **(127)** **(126)**

The Pd(II) promoted cyclization of (126) proceeded at 65^{o}C in anhydrous dimethoxyethane in the presence of 0.02 mol equivalent of Pd chloride, cupric chloride (4.0 mol. eq) and air bubbling to afford racemic (128) in 71%. Finally, oxidative demethylation of (128) with ceric(IV) ammonium nitrate (CAN) gave the desired isagarin (11) as a racemic mixture in 95% yield (Scheme 22). isagarin (11) was identified on the basis of its spectral properties. The IR spectrum with absorptions at 1596 cm^{-1} (C=C) and 1632, 1661 cm^{-1} (C=O) and the ^{1}H NMR spectrum ($CDCl_3$) with two-proton multiplets at δ 7.70-7.8 (Ar-H) and δ 8.04-8.13 (Ar-H) indicated the presence of a naphthoquinone moiety. The ^{1}H NMR data also showed the presence of a singlet signal of a methyl group (δ 1.68, 3H) and a methylene group (δ 2.73 and 2.87, d), the with a geminal coupling constant of 19.6 Hz. The one proton doublet at δ 5.58 with J = 4.0 Hz, is indicative for a CH-O unit substituted at the carbon adjacent to one of the carbonyl groups of the naphthoquinone nucleus. This oxygenated methine group holds a position adjacent to a CH_2O unit, which shows a degenerate spin system at δ 3.93-4.05.



Scheme 22

It was found that direct ring closure of mono silylether (127) proceeded as efficiently as that of (126), obviating the need for desilylation prior to ring closure (Scheme 23). Presumably the HCl generated during the Wacker oxidation is sufficient to promote desilylation of the primary silylether.

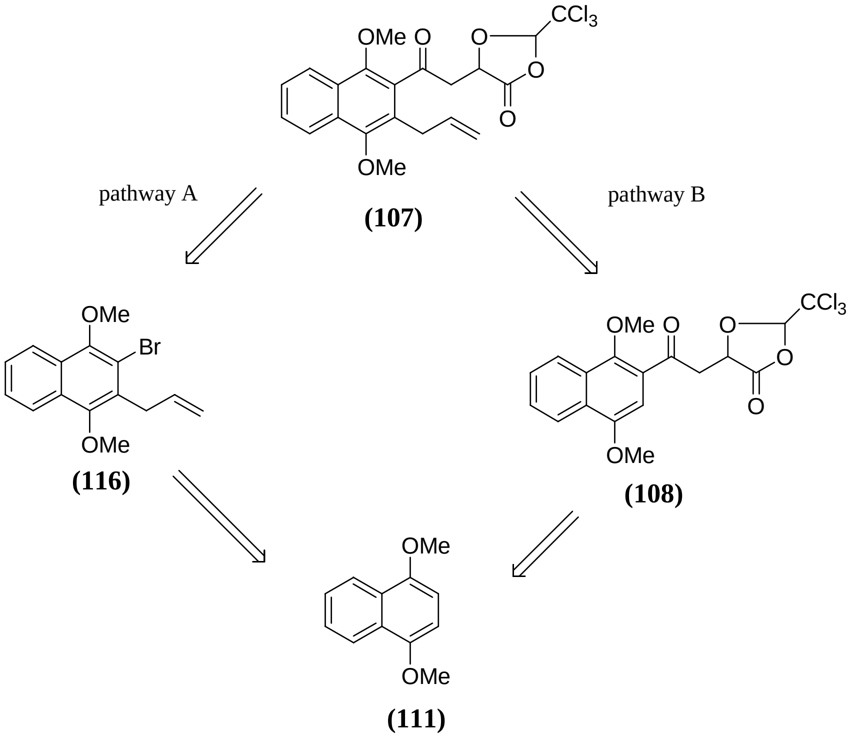


(127) **(11)**

Our synthetic methodology for (±)-isagarin (11) starting from 2-bromo-1,4-naphthoquinone (6) has been achieved in 5 steps with 24.1% overall yield whereas synthesis of (±)-isagarin (11) by De Kimpe *et al.* which started from 1,4-dimethoxynaphthaldehyde was accomplished in 4 steps with 64.6% overall yield.

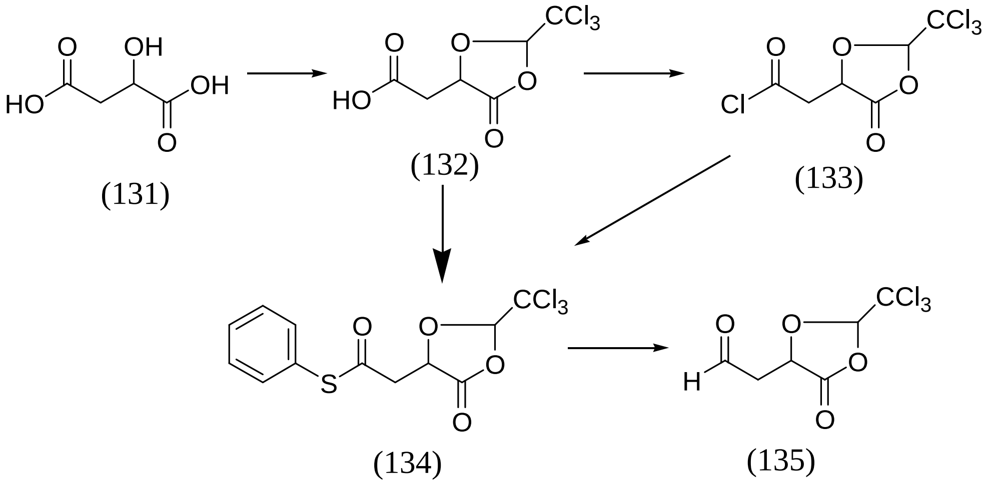
(±)-Marticin (12) and (±)- isomarticin (13)

We investigated the introduction allyl and acyl side chains onto the aromatic ring via the synthesis of model compound (107). The synthetic plan of (107) was divided into two pathways and is illustrated by the retrosynthetic sequence outlined in Scheme 24.



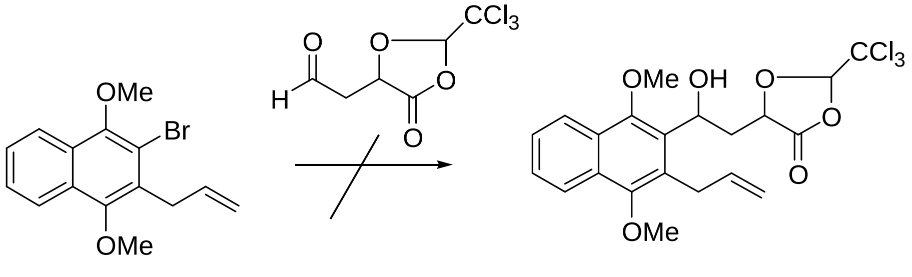
Scheme 24

Acid chloride (133) required for the acyl side chain was prepared from *dl*-malic acid (131) according to the procedure of Eggerer (1964). Aldehyde (135), another reagent for introduction of a side chain, was also prepared from (132) via thio ester (134), then hydrogenation using triethylsilane in the presence of 5% Pd/C to provide (135) in high yield (Scheme 25).



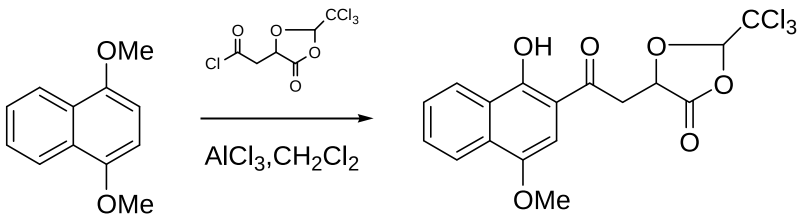
Scheme 25

In our plan, allyl side chain will be introduced onto naphthalene (111) followed by the introduction of the acyl side chain. With allyl naphthalene (116) in hand, an attempt to couple aldehyde (135) using *n*-BuLi was unsuccessful due to the instability of aldehyde (135) to the basis condition.



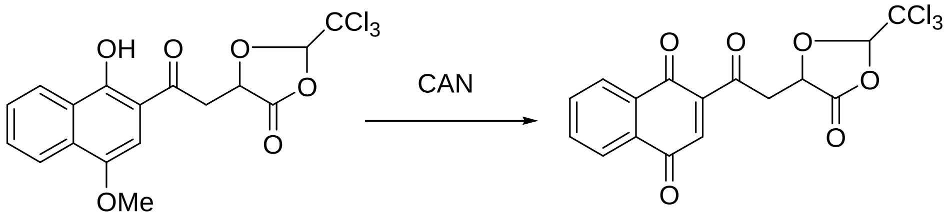
(116) **(136)**

We next attempted the introduction of the acyl side chain via Fridel-Craft acylation using acid chloride (133) in the presence of 3 mol of $AlCl_3$ in CH_2Cl_2 which afforded product (137) in 43% yield.



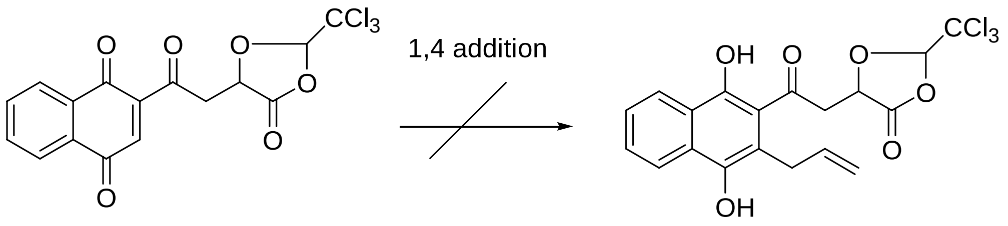
(111) **(137)**

Oxidation of the naphthol (137) by CAN provided unstable quinone (138) after chromatographic separation therefore the crude product was used in the next reaction without further purification.



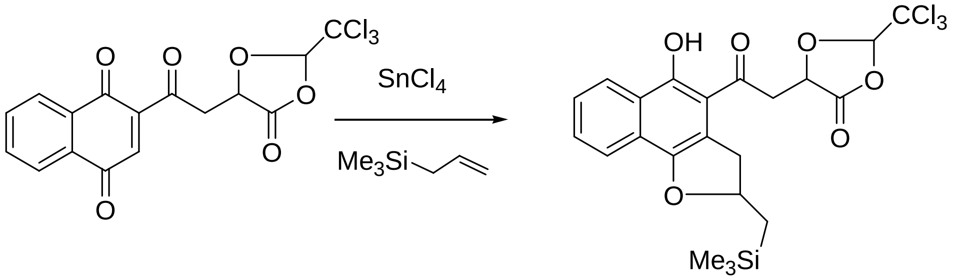
(137) **(138)**

Several attempts to introduce allyl group onto the unpurified quinone (138) by 1,4-addition an allyl cuprate complex failed. Probably, because this reaction still contained the oxidizing agent (CAN) from the previous step.



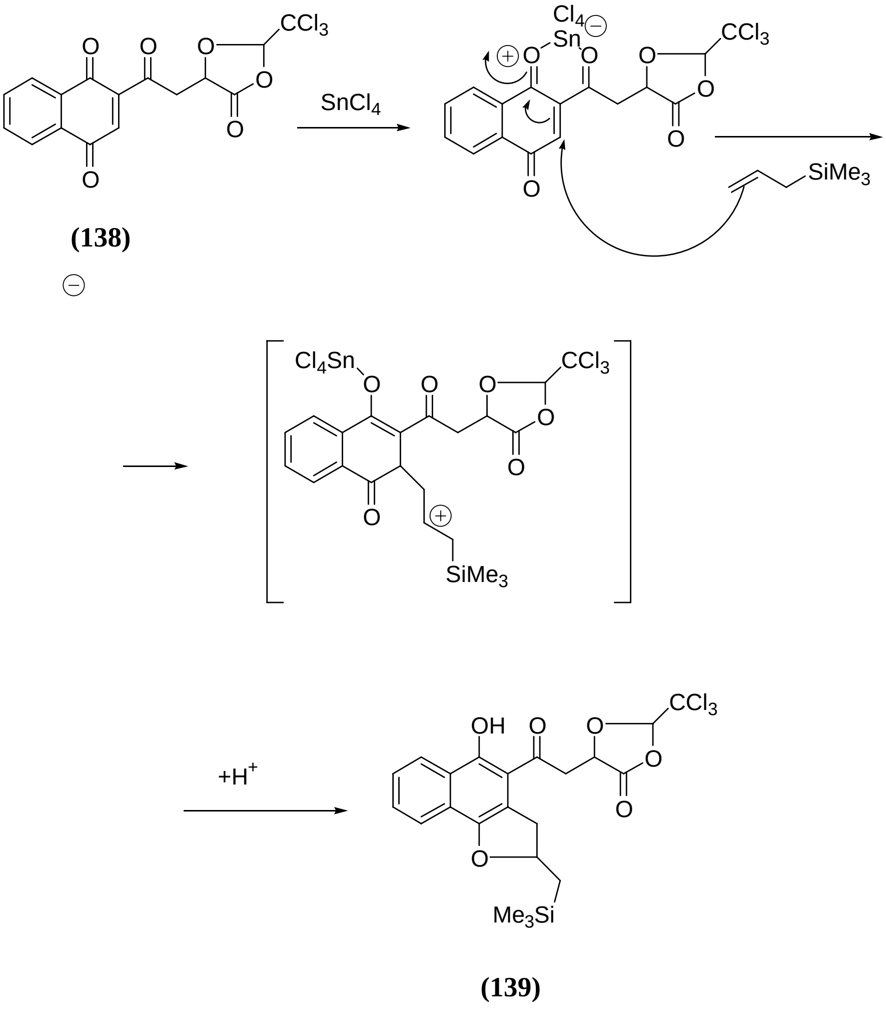
(138)

The1,4-addition to naphthoquinone (138) using allyl silane and $SnCl_4$ as catalyst, was all also investigated. Surprisingly, the reaction did not give the allyl quinone product (140); the furan naphthol (139) was obtained instead.



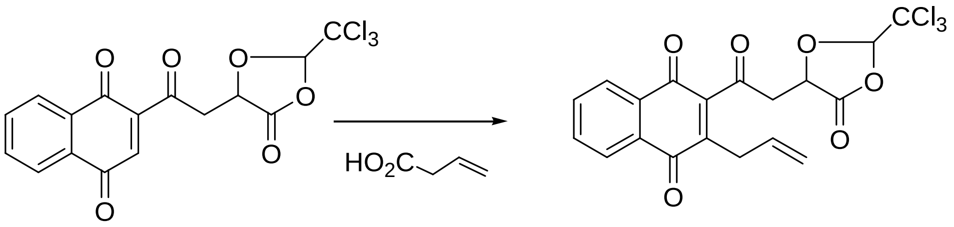
(138) **(139)**

The plausible mechanism for the above reaction is illustrated in Scheme 26.



Scheme 26

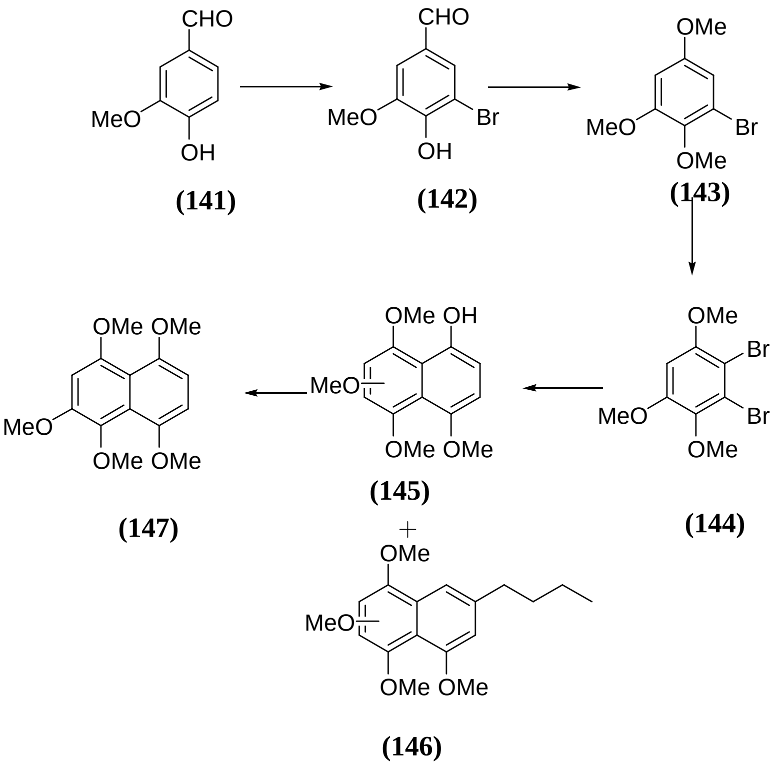
However, radical allylation of naphthoquinone (138) with vinyl acetic acid, using ammonium persulfate and silver nitrate in acetonitrile, allowed the introduction of the allyl side chain at C(**3**). The product (140) was obtained in 72% yield (2 steps). The IR spectrum with absorptions at 1730 cm^{-1} (C=O) and 1615 (C=C) cm^{-1} indicated the naphthoquinone moiety and the characteristic peaks of naphthoquinone moiety appeared at δ 8.15 (m, 2H) and 7.92 (m, 2H). ^{1}H NMR signals of (140) at δ 5.83 (m, 1H), 5.25-5.12 (m, 2H) and 3.25 (m, 2H) support the 1,4- addition of the allyl group onto the naphthoquinone ring.



(138) **(140)**

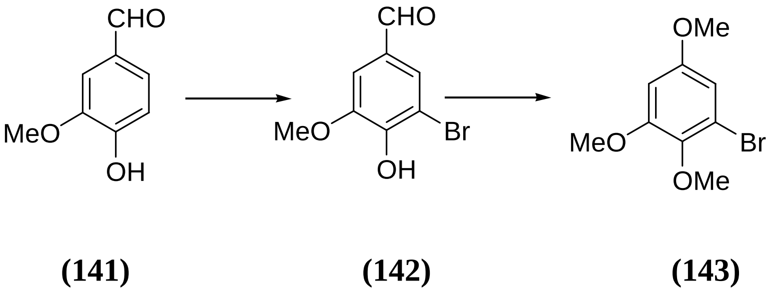
Synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147)

After the successful synthesis of model compound (140), we next studied on the synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147) via two pathways. In the first pathway, the synthetic plan started from vanillin (141) (Scheme 27).



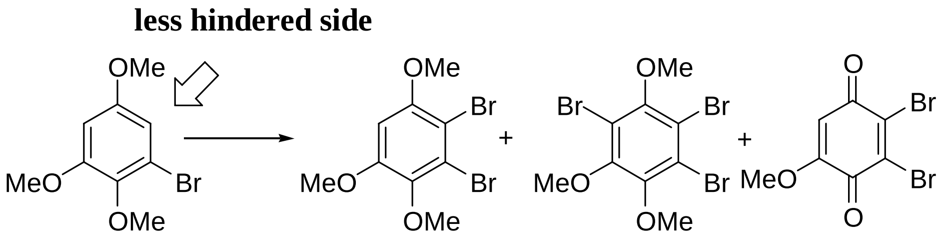
Scheme 27

Bromination of commercially available vanillin (141) provided bromovanillin (142) in 95% yield. Bayer-Villiger oxidation and methylation of bromovanillin (142) provided 3-bromo-1,2,5-trimethoxybenzene (143) in 81% yield.



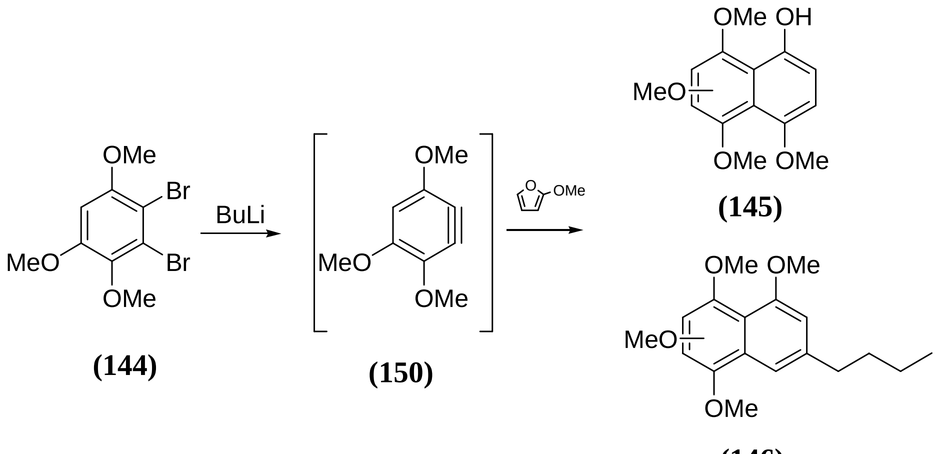
Bromination of 3-bromo-1,2,5-trimethoxybenzene (143) by treatment with Br_2 in benzene resulted in a mixture of 2,3-dibromo-1,4,5-trimethoxy-benzene (144) (81%), 1,2,4-tribromo-3,5,6-trimethoxy-benzene (148) (6%) and 2,3-dibromo-5-

methoxy-[1,4]benzoquinone (149) (5%). Bromination occurred mainly at the less hindered site of 3-bromo-1,2,5-trimethoxybenzene (143) affording (144) as the major product. Some oxadative demethylation of (144) occurred under the reaction conditions.



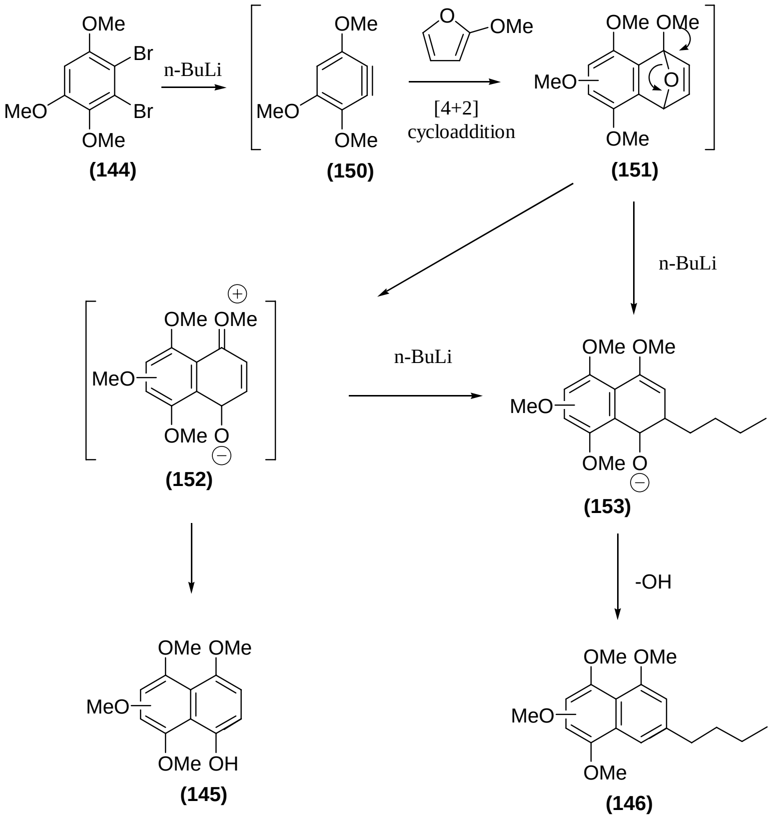
(143) **(144)** **(148)** **(149)**

Naphthol (145) was synthesized from 3,4-dibromo-1,2,5-trimethoxybenzene (144). In this reaction, benzyne (150) was generated in situ and immediately trapped with commercially available 2-methoxyfuran to afford regiomeric naphthol (145) (33%) as a mixture of regioisomers and undesired byproduct (146) (21%).



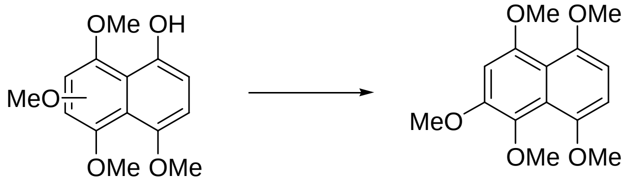
(144) **(150)** **(145)** **(146)**

A plausible mechanism for formation of (145) and (146) have been proposed involves [4+2] cycloaddition of benzyne (150) and 2-methoxyfuran to give intermediate (151) which subsequently undergoes furan ring opening to give regioisomeric naphthols (145). The ^{1}H NMR spectrum of (145) showed butyl group at δ 0.95 (m,3H), 1.3-1.5 (m, 2H), 1.6-1.8 (m, 2H) and 2.71 (t, J=7.7 Hz, 2H). This proton signals supported attract of butyl anion onto aromatic ring. The byproduct can be rationalized by attack of the butyl carbanion on the adduct (151) or (152), which would lead to ring opening to afford intermediate (153), and this could protonate oxygen and dehydrate **(**Scheme 28) (Giles *et al.*, 1988).



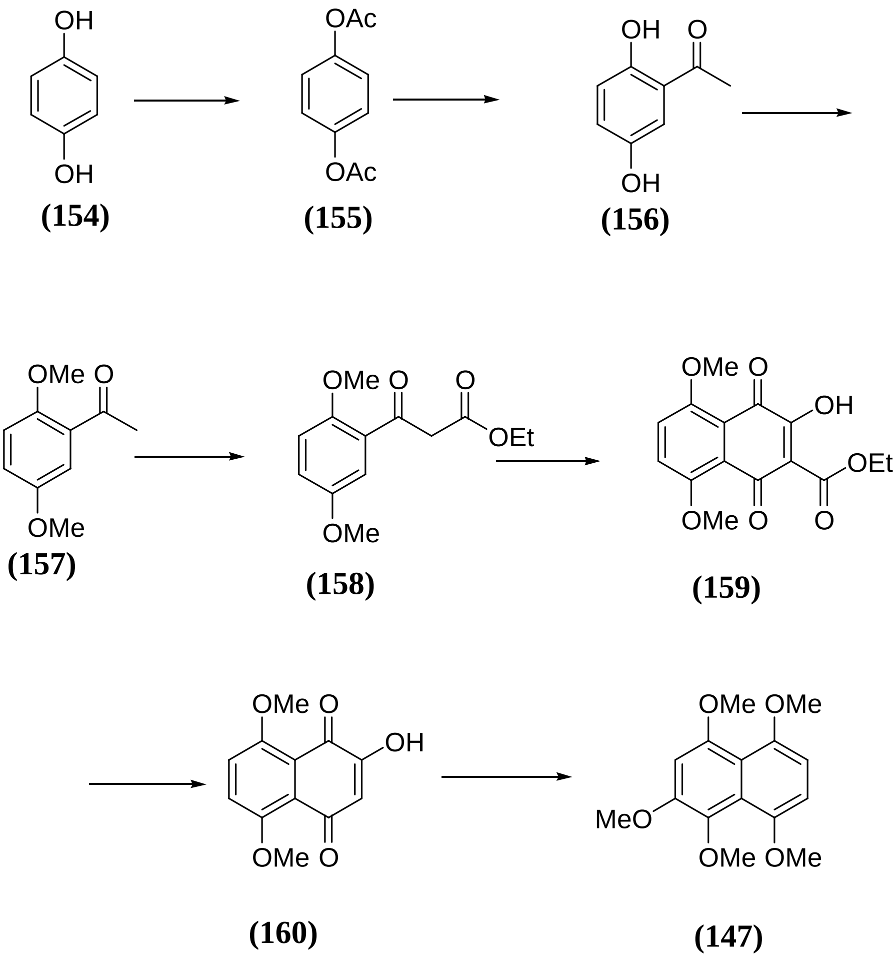
Scheme 28

Finally, methylation of the regioisomeric mixture of naphthols (145) using Me_2SO_4 gave 1,2,4,5,8-pentamethoxynaphthalene (147) in 43% yield.



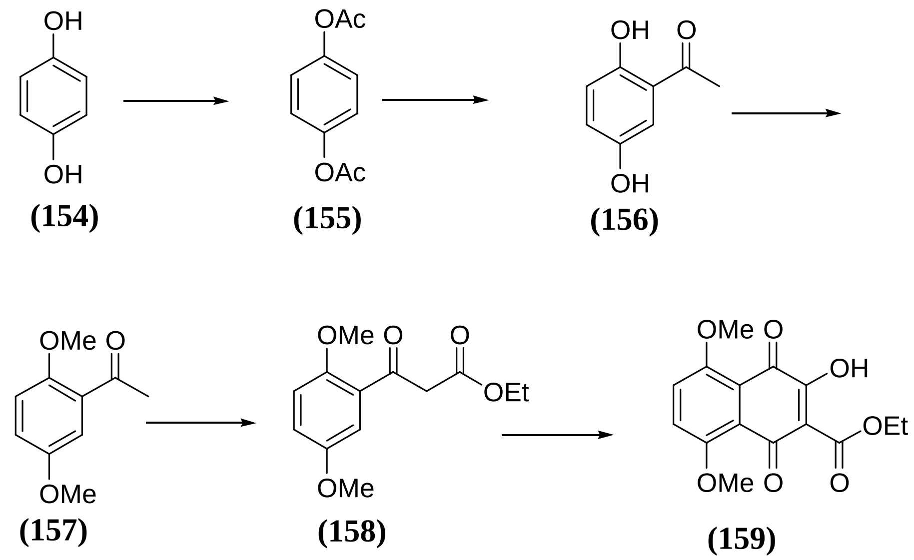
(145) **(147)**

The second synthesis of 1,2,4,5,8-pentamethoxynaphthalene (147) started from hydroquinone (154) as shown in Scheme 29.

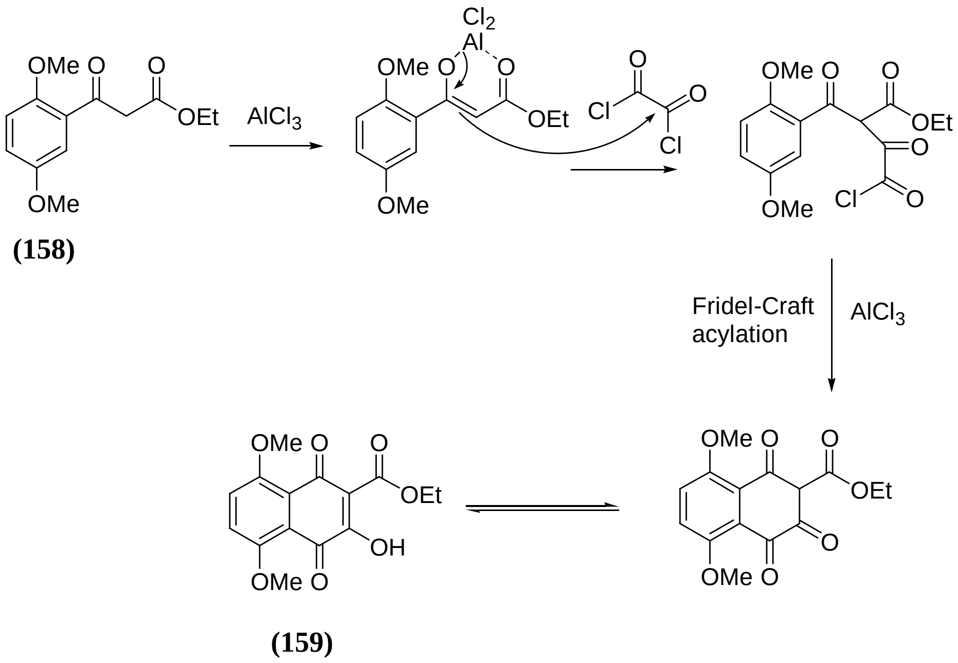


Scheme 29

Acetylation of p-hydrobenzoquinone (154) using acetic anhydride in H_2SO_4 provided diacetate (155) in quantitative yield. Fried rearrangement of (155) was carried out at 165 ^{o}C using $AlCl_3$ to give 2,5-dihydroxyacrtophenone (156) in 71%. Methylation of (156) using dimethyl sulfate, K_2CO_3, in actone afforded 2,5-dimethoxy acetophenone (157) in 71% yield over two steps. Alternatively, the conversion of (156) to (157) has been accomplished in 71 yield% by using dimethyl sulfate, TBAI, KOH, H_2O. Treatment of (157) with NaH and diethyl carbonate furnished (2,5-dimethoxyphenyl)-3-oxopropanoate (158) in 81% yield.

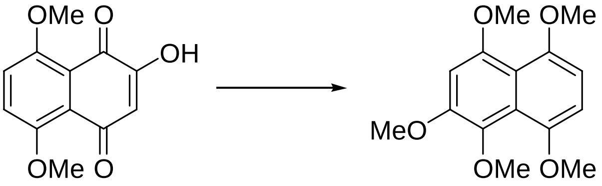


The next step of the reaction sequence was to construct the naphthoquinone ring via intramolecular Fridel-Craft acylation. Treatment of 158 with oxalyl chloride and $AlCl_3$, in refluxing $MeNO_2$ provided naphthoquinone (159) in 74% yield. This conversion is rationalized in Scheme 30.



Scheme 30

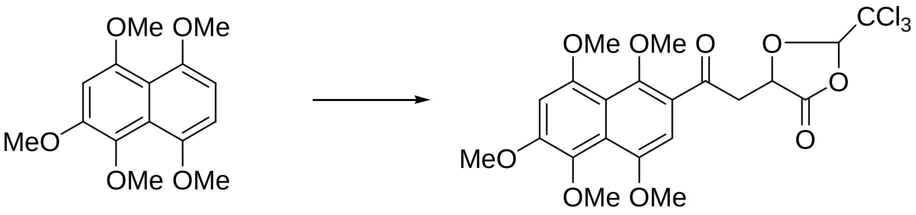
Finally, reductive methylation of 159 using dimethyl sulfate, $Na_2S_2O_4$, KOH, and TBAI, in THF, H_20 provided the desired 1,2,4,5,8-pentamethoxynaphthalene in 43% yield.



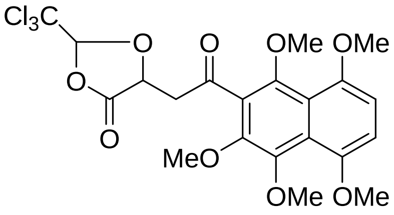
(160) **(147)**

Synthesis of (±)-marticin (12) and (±)-isomarticin (13)

With 1,2,4,5,8-pentamethoxynaphthalene(147) and side chains (132 or 133) in hand, we next investigated the connection of both compounds via Fridel-Craft acylation. Unfortunately, Fridel-Craft acylation of (147) using 2 mol of acid chloride (133) in the presence of 3 mol of $AlCl_3$ in CH_2Cl_2 provided 1:1 mixture of (161) and (162) as a inseparable product. (161) arises from acylation at the less hindered position (right hand side) whilst (162) arises from acylation at the more hindered and more electron rich position (left hand side). The mixture of (161) and (162) was characterized on the basis of ^1H NMR spectra. ^1H NMR spectrum ($CDCl_3$) exhibited two-proton doublets (J= 7.5 Hz) at δ 6.57 (Ar-H) and δ 6.45 (Ar-H) which indicated the presence of the naphthalene moiety of (162) whilst the signals of the naphthalene moiety of (162) appeared at 7.10 (d, J= 2.4 Hz) and 6.47 (d, J= 2.4 Hz).

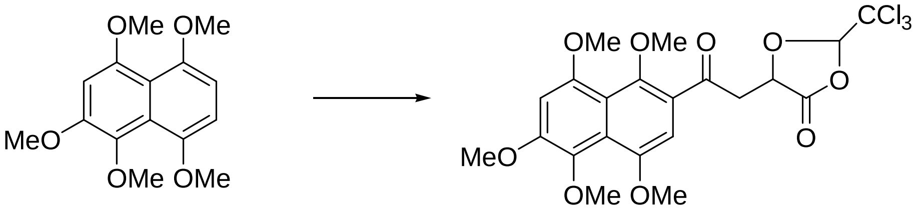


(147) **(161)**



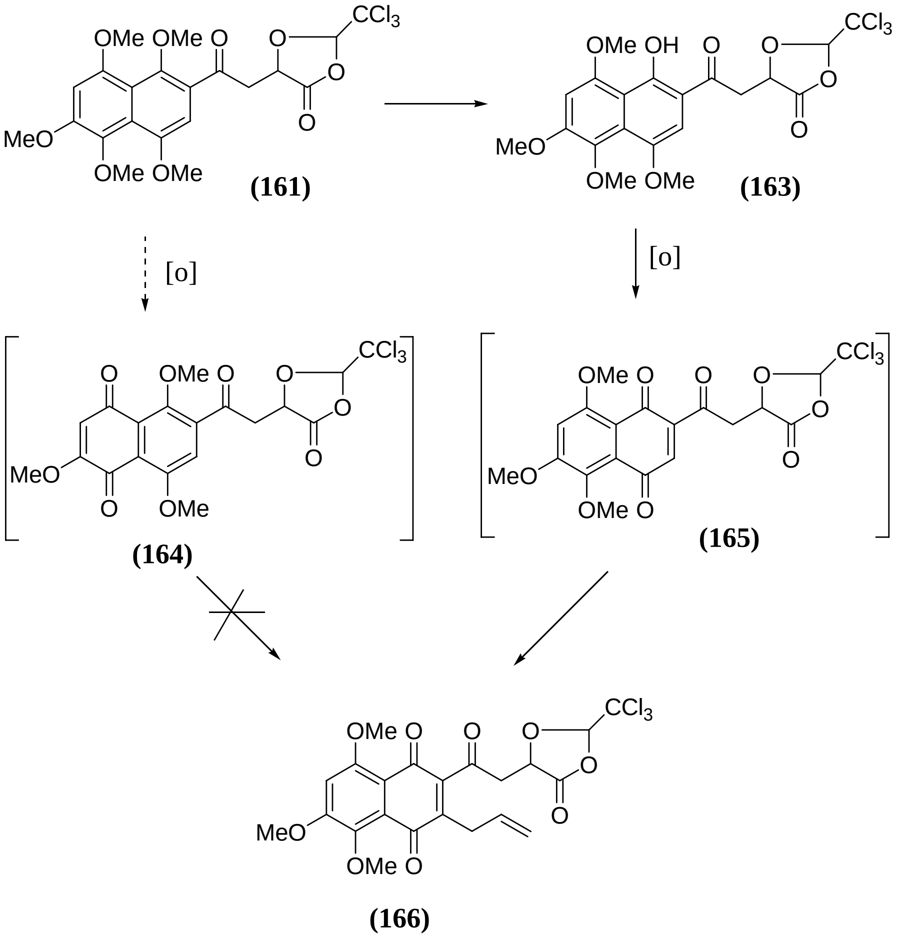
(162)

Possibly, byproduct (162) occur form the use of too active an acylating agent. To overcome the problem, a less active acylating agent was used without a Lewis acid catalyst. Treatment of acid (132) in TFAA generated acid anhydride *in situ* which was subsequently reacted with (147) to give only the desired (161) in 55% yield.



(147) **(161)**

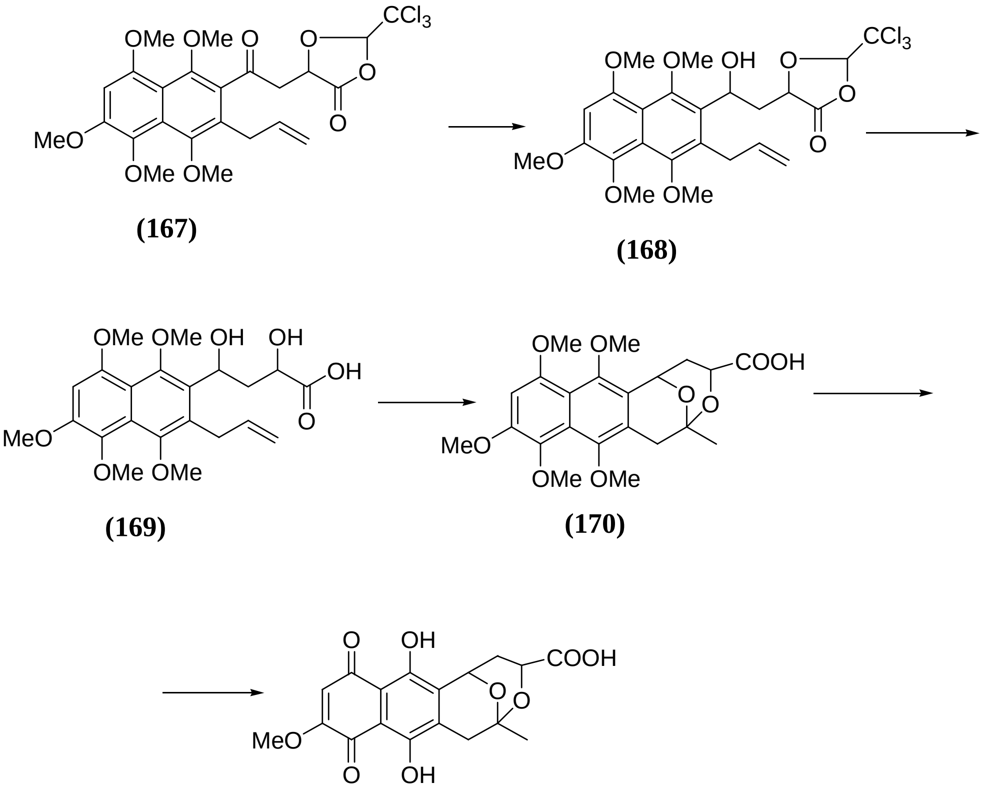
In the next step of the reaction sequence, we planned to introduce an allyl group onto (161) via radical allylation. From Giles's report (1988), oxidation of 1,2,4,5,8-pentamethoxynaphthalene derivatives using CAN led to the oxidation at the ring that has most electron density (left hand side of naphthalene ring). If (161) is oxidized with CAN, unwanted naphthoquinone (164) will be formed. This problem was solved by making the right side of naphthalene ring more electron rich by selective demethylation of (161) using BBr$_3$ which gave (163) in 71% yield. Oxidation of (163) with CAN then provided (165) which was used in the next step without further purification. Radical allylation of naphthoquinone (165) with vinyl acetic acid, using ammonium persulfate and silver nitrate in acetonitrile, furnished allylnaphthoquinone (166) in Scheme 31.



Scheme 31

Several attempts to reductivly methylate (166) using dimethyl sulfate, Na$_2$S$_2$O$_4$, KOH, TBAI, in THF, $H_2$0 were unsuccessful. This is probably because KOH could removes the side chain protecting group. By using K$_2$CO$_3$ as a milder base KOH, (167) was obtained in 55% yield.

Reduction of (167) using $NaBH_4$ gave alcohol (168) as a distereomeric mixture which was used in the next step without further purification. Deprotection of unpurifiled (168) with KOH furnished (169). The Pd(II) promoted cyclization of (159) proceeded at 65°C in anhydrous dimethoxyethane with 0.02 mol equivalent of Pd chloride, cupric chloride (4.0 mol. eq) and air bubbling into the reaction to afford (170) as a diastereomer in 67% yield. Finally, oxidation of (170) using CAN followed by demethylation using BBr_3 gave the desired marticin (12) and isomarticin (13) as a 1 :1.2 mixture in 52% yield (Scheme 32). The ratio of products was confirmed by ^1H NMR and HPLC.



(167) **(168)** **(169)** **(170)** **(12, 13)**

Scheme 32

The ^1H NMR of both products (12), (13) were compared with reference spectra as shown in Table 5.

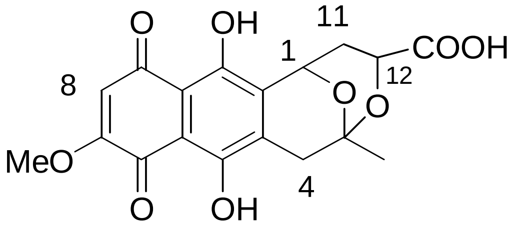


Table 5 ^{1}H NMR data of marticin (12) and isomarticin (13)

position	Marticin	Isomaticin	Marticin (Holenstein *et al.* in 1984)	Isomaticin (Holenstein *et al.* in 1984)
OH	12.93 (S)	12.92 (S)	12.93 (S)	12.91 (S)
OH	12.43 (S)	12.42 (S)	12.53 (S)	12.51 (S)
CH-8	6.15 (S)	6.17 (S)	6.18 (S)	6.20 (S)
CH-1 (eq)	4.61 (m)	4.42(m)	4.58 (m)	4.31(dd) (J=12, 3 Hz)
OMe	3.97 (S)	3.97 (S)	3.94 (S)	3.97 (S)
CH-12 (ax)	5.39 (d, J=9 Hz)	5.62 (d, J=5 Hz)	5.42 (d, J=9 Hz)	5.62 (d, J=5 Hz)
CH-11 (ax)	2.30 (m)	2.30 (m)	2.30 (m)	2.30 (m)
CH-11(eq)	2.21 (m)	2.21 (m)	2.22 (m)	2.21 (m)

CH-4 (eq)	3.09 (d, J=19 Hz)	3.13 (d, J=19 Hz)	3.02 (d, J=19 Hz)	3.13 (d, J=19 Hz)
CH-4 (ax)	2.71 (d, J=19 Hz)	2.62 (d, J=19 Hz)	2.73 (d, J=19 Hz)	2.67 (d, J=19 Hz)
Me	1.56 (S)	1.60 (S)	1.68(S)	1.70 (S)

CONCLUSION

The application of the Wacker reaction for the synthesis of natural products which containing oxabicyclic moieties has been demonstrated by our group. Herein, we reported the synthesis of some pyrannonaphthoquinones ((±)-isagarin (11), (±)-marticin (12, (±)-isomarticin (13)) via Wacker process as the key step.

The synthesis of (±)-isagarin (11) starting from 2-bromo-1,4-naphthoquinone (6) has been achieved in 5 steps with 24.1% overall yield. (±)-Marticin (12) and (±)-isomarticin (13) have been successfully synthesized from a commercially available vanillin (141) or *p*-hydrobenzoquinone (154). (±)-Marticin (12) and (±)-isomarticin (13) has been successfully synthesized from either vanillin (141) in 15 steps in 0.27% overall yields or *p*-hydrobenzoquinone (154) in 14 steps in 0.36 % overall yields.

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PART II: STEREOSELECTIVE PALLADIUM(0)-CATALYZED FOUR-COMPONENT CASCADE SYNTHESIS OF PYRROLIDINYL ISOQUINOLINES

INTRODUCTION

Multi-component reactions (MCRs) play an important role in combinatorial chemistry because of there ability to prepare complex molecular architectures from readily available building blocks (Grigg *et al*., 1999; Ugi *et al*., 2000; Montgomery *et al*., 2000). Among the advantages of MCRs are yields that higher than almost any sequential synthesis of the same target, a single purification step and easy to adaptation to combinatorial synthesis. A MCR is defined as three or more different starting materials that react to form product, where most, if not all the atoms are incorporated in the final product.

We have demonstrated a series of novel palladium catalyzed cascade reaction which involved the synthesis of bis(2-allyl)tertiary amines. 1,2,3,4-tettrahydroisoquinolines, isoindolinones, 4-methyllene-3,4-dihydro-1(2H)-isoindolinones and triazole analogues (Grigg *et al*., 2000; Grigg *et al*., 2003). The development of these reactions involves the use of allenes as “relay switches” in palladium cascade reactions and is a very creative and significant idea for the construction of complex nitrogen heterocycles. We focus on the combination of palladium cascade reactions with other significant atom economic reactions to develop novel synthesis of complex bioactive nitrogen heterocycles. In 1999, Fruhaul *et al*. demonstrated imines can be used as nucleophiles in palladium catalyzed allene reactions to afford iminium species. As part our on going interest in the design of palladium-catalyzed allylation processes in the tactical combination with core reactions, we have explored combinations that have 1,3-dipolar cycloaddition processes as the key step in the synthesis of heterocycles (Grigg *et al*., 2001; Grigg *et al*., 2003). To our knowledge, this palladium-catalyzed four component cascade process is the first reported case which combines palladium catalyzed allene reaction with a 1,3-dipolar cycloaddition reaction in one pot.

The objective was to prepare pyrrolidinyl isoquinoline derivatives using a four component cascade with 2-iodobenzyldehyde that generates azomethine ylids *in situ* which are trapped with *N*-methyl maleimide (NMM) as the dipolarlophile.

LITERATURE REVIEW

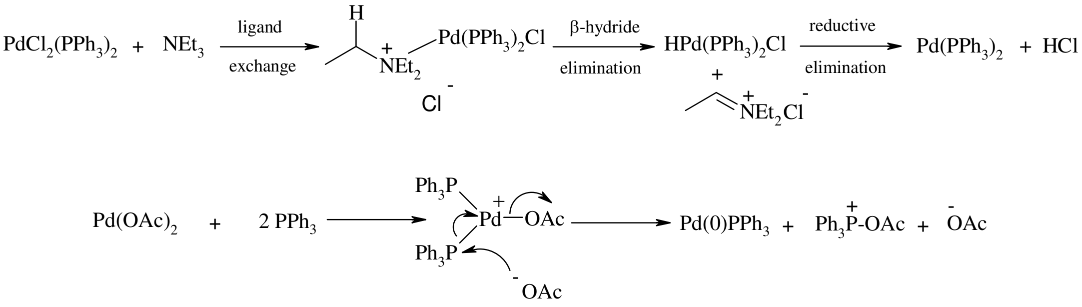
Palladium-catalyzed reactions of allenes

Over the last few decades, palladium-catalyzed reactions have assumed a key role in organic synthesis because they exhibit a high level of chemo-, regio-, and stereoselectivity in a wide range of transformation (de Meijere and Meyer, 1994; Mueller and Beller, 1998). Palladium catalysed reaction of allenes with carbon and heteroatom nucleophiles leading to the formation of carbon-carbon and carbon-heteroatom bonds generally proceed with the involvement of a π-allylpalladium intermediate. This combination is playing an increasing role in organic synthesis (Hiroi and Kato, 1996; Yamamoto and Radhakrishnan, 1999).

Palladium

There are several features that make reactions involving the most important transition metal, palladium, particularly useful and versatile. Palladium catalysts are the most widely used both in industrial and academic laboratories on both small and large scale because they offer many possibilities for carbon-carbon, carbon-hetroatom bond formation. The tolerance of Pd reagents to many functional groups such as carbonyl and hydroxyl groups is a further important feature. Pd-catalyzed reactions can be carried out without protection of many functional groups. Additionally the chemo- and regioselectivity of Pd catalysts has fostered an ever-increasing amount of research.

Both palladium(0) complexes and palladium(II) salts are used in organic synthesis. Palladium(0) complexes are used as catalysts and palladium(II) salts either as stoichiometric reagents or as catalysts. Tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$, and tris(dibenzylideneacetone)dipalladium(0), $Pd_2(dba)_3$, or the chloroform complex, $Pd_2(dba)_3$-$CHCl_3$, which is air-stable, are the most common sources of palladium(0). Palladium(II) salts such as $PdCl_2$ and $Pd(OAc)_2$ are commercially available, widely used and more stable. They can be used in two important ways: as unique stoichiometric oxidizing agents, and as precursors of Pd(0) complexes (Tsuji, 1995). The reduction of palladium(II) to palladium(0) can be achieved with amines, phosphines, alkenes and organometallic reagents such as DIBAL-H, butyl lithium or trialkyl aluminium. For example, $PdCl_2(PPh_3)_2$ was reduced to palladium(0) *in situ* in the presence of phosphine ligands (Scheme 1).



Scheme 1

Allenes

The allene or 1,2-dienes serve as potential precursors of highly complex and strained target molecules of biological and industrial importance. Their unique reactivity has been successfully applied to pharmaceuticals, dyes, polymers, etc (Zimmer *et al.*, 2000). Allenes comprise two adjacent double bonds with their π–orbitals perpendicular to each other, with the central atom (*sp*-hybridised) joined to two terminal (sp^2-hybridised) carbon atoms. As a consequence, allenes are chiral if both the 1- and 3- carbon centres are unsymmetrically substituted (Figure 1).

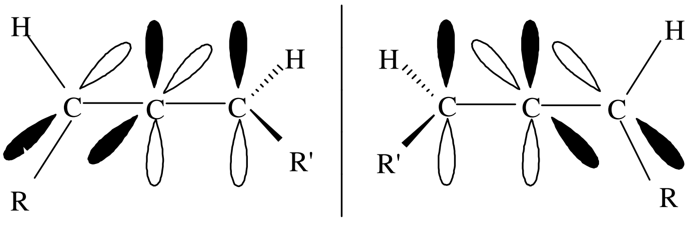


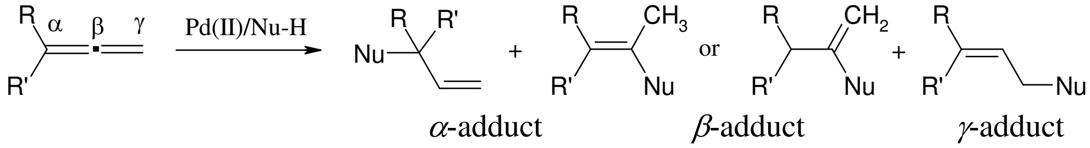
Figure 1 allene

The allene was first prepared in 1887 by Burton and von Pechmann, (1887) but the structure was not confirmed until 1954 (Jones *et al.*, 1954). Up to the 1950's, allenes were considered highly unstable and difficult to prepare, (Celmer and Solomons, 1952) but recently a variety of methodologies have been developed for their synthesis (Grigg and Sridharan, 1998; Lautens *et al.*, 1998). Research on the catalytic reactions of allenes started in the 1960's and since then publications, particularly those involving iron (Shiabata *et al.*, 1995), cobalt (Owada *et al.*, 1997) nickel (Satyanarayana *et al.*, 1990), ruthenium (Yamaguchi *et al.*, 1995), rhodium (Yamaguchi *et al.*, 1994) and palladium (Grigg and Sridharan, 1999) have flourished.

Cascade reactions

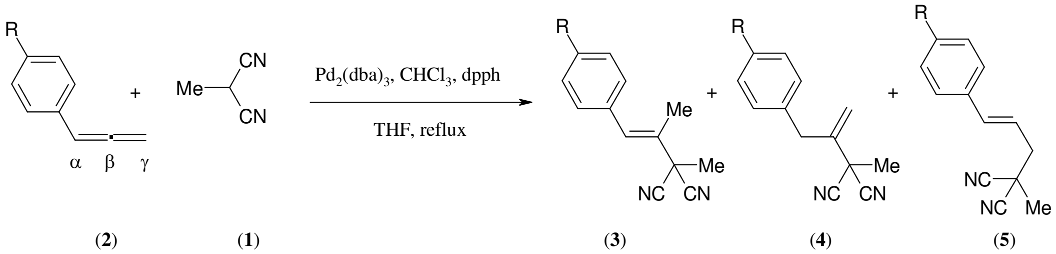
Organic synthesis is concerned with developing viable processes to useful materials by methods that minimize waste, maximize molecular complexity and are highly selective (regio-, stereo-, chiro- and chemo-specific). Cascade processes aspire to meet these criteria. A cascade reaction is a multi-step process where the functionality created in the first step allows the second step to proceed and so forth until the desired product is generated. Compared to a conventional synthesis, a cascade reaction generates a significant increase in molecular complexity much more effectively. The need for only one work-up and purification also minimises waste, making cascades environmentally friendly. Palladium has recently played a prominent role in cascade reactions due to its outstanding catalytic properties (Grigg and Sridharan, 1999).

Palladium catalysed reactions of allenes involving π–allylpalladium species, were reported in 1964 by Schultz, and recently a growing number of applications in cascade reactions have been reported (Zimmer *et al.*, 2000). Nucleophilic addition to allenes coordinated by Pd(II) can give rise to three possible regioisomers depending upon the substituents on the terminal carbon atoms (Scheme 2).



Scheme 2

Yamamoto *et al.* (1999) investigated the regioselectivity of the reaction of arylallenes having different *para*-subsituents. The reaction of activated methylene and methine reactants (1) with (2) is catalysed by $Pd_2(dba)_3$/dppb in THF under reflux. When an electron withdrawing group (e.g., Br, CF_3, OCF_3) was present at the *para*-position, attack occurs at the *β*-position of the allene affording mixture of (3) and (4). Whereas carbon-carbon bond formation at the γ-position (5) was observed in the presence of para electron-donating groups (e.g., Me, OMe) (Scheme 3).



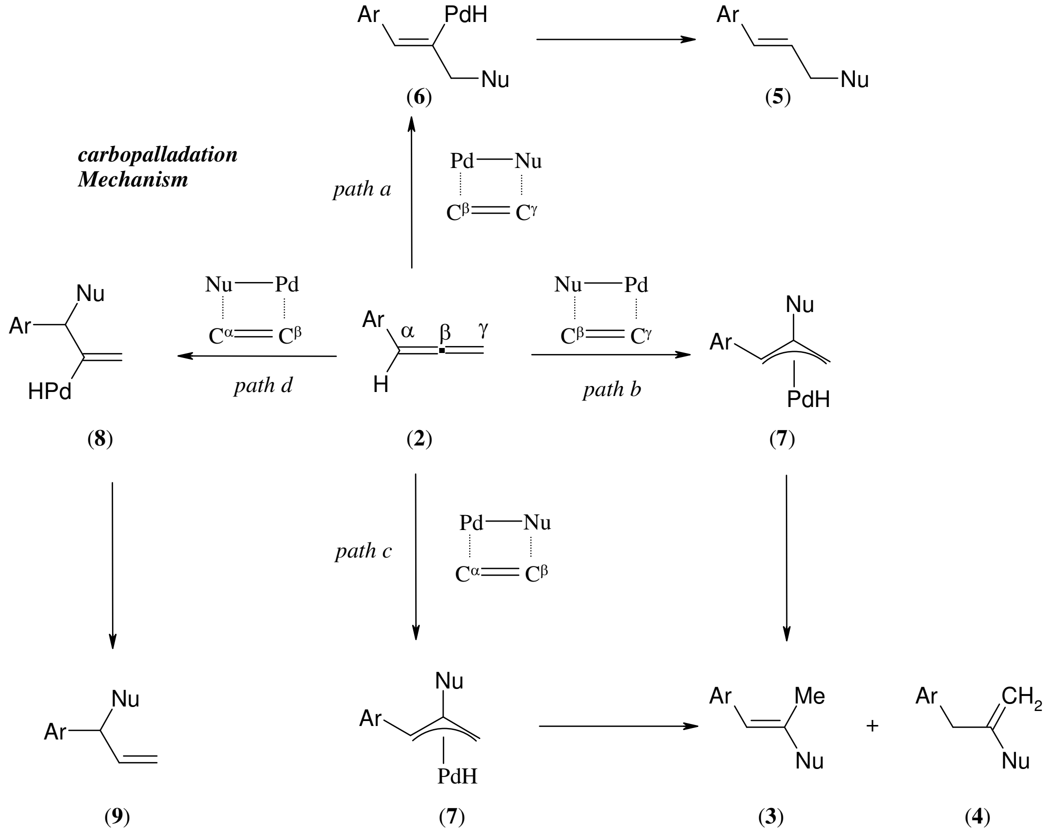
Scheme 3

Table 1 Regioselectivity of the reaction of activated methylene (1) and arylallene (2)

R	3 (%)	4 (%)	5 (%)
Br	46	14	-
CF_3	47	20	-
OCF_3	68	16	-
OMe	-	-	85

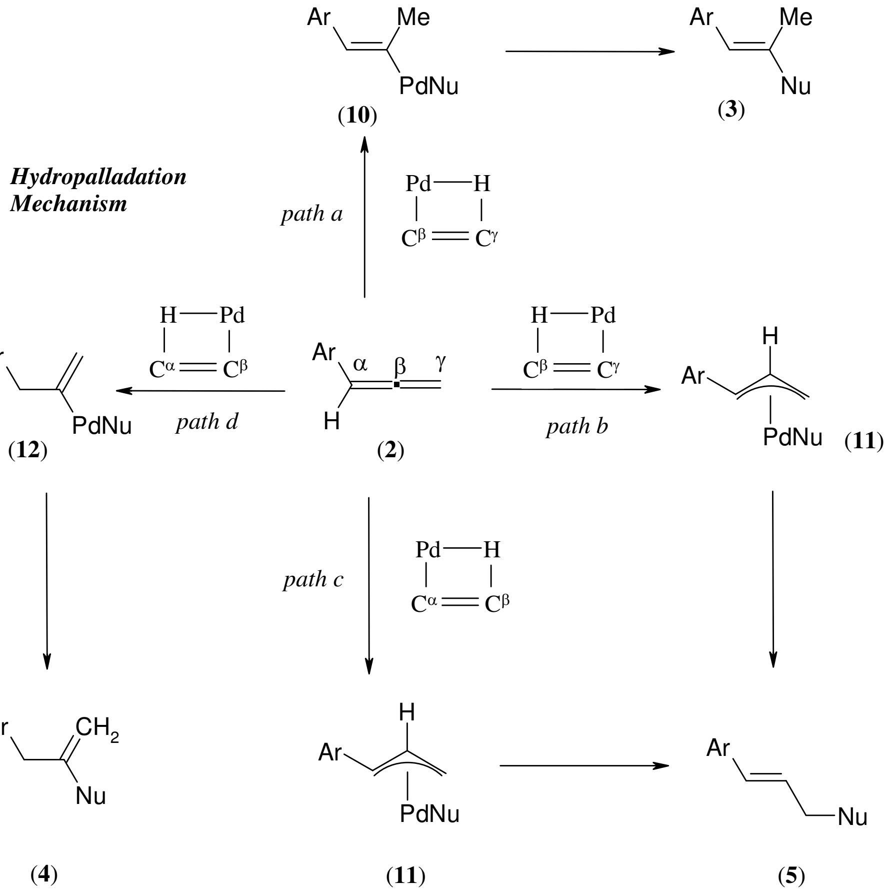
Product formation can be expained either by a carbopalladation (Scheme 4) or or by a hydropalladation mechanism (Scheme 5). Carbopalladation of the C^{γ}=C^{β} bond of (2) Scheme 4, (path a) give (6), which was transformed into (5).

Carbopalladation of the C^{β}=C^{γ} bond (path b) and C^{β}=C^{α} bond (path c) produce the π-allypalladium intermediate (7) leading to the β-adducts (3) and (4). Carbopalladation of the C^{α}=C^{β} bond (path d) is a difficult pathway due to the steric hindrance at the C^{α} atom.



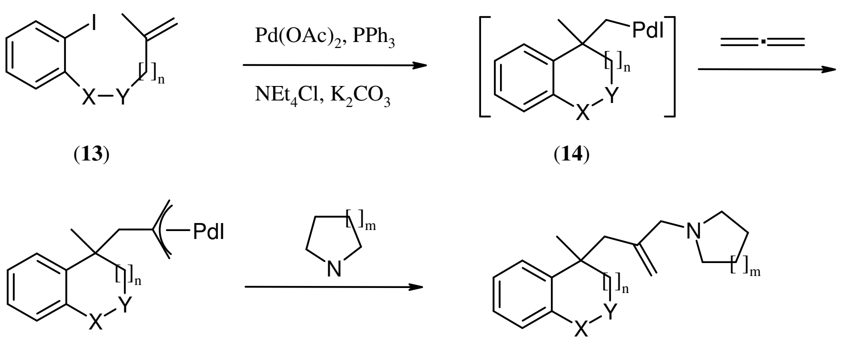
Scheme 4

Hydropalladation of the C^{γ}=C^{β} bond of (2) (Scheme 5 path a) gives (10), which affords β-adduct (3) *via* reductive elimination. Hydropalladation of C^{β}=C^{γ} bond (path b) and C^{β}=C^{α} bond (path c) produce the π-allypalladium intermediate (11). Attack of a nucleophile at the centre carbon atom of the π-allypalladium intermediate is not common. Therefore, compound 11 is unlikely to give β-adducts, but instead affords the γ-adduct (5). Hydropalladation of C^{α}=C^{β} bond (path d) provides (12), which is transformed into (4).



Scheme 5

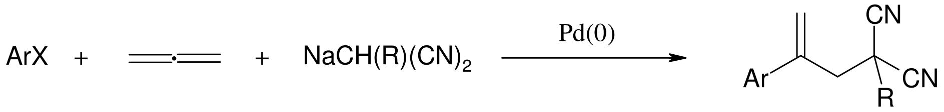
In the mid-1990s, Grigg developed an extremely useful palladium-catalysed cyclization-anion capture methodology employing a 'zipper' starter species. The presence of a methallyl or similar moiety in the side chain of the aryl halides (13) prevents *β*-hydride elimination in intermediate (14), which permits allene insertion forming the *π*–allylpalladium species (15). Nucleophile attack on (15) gives heterocycles (16) (Scheme 6) (Grigg, 1994). Recently this palladium-catalysed cyclization-anion capture process has been substantially extended (Grigg and Sridharan, 1999).



(13) (14) (15) (16)

Scheme 6

Malononitrile could be sequentially alkylated by conventional and/or less traditional methods to afford dialkylated products (Diez-Barra *et al.*, 1991). There are many non-traditional ways of accessing dialkylated malononitriles. A typical example was shown in (Scheme 7) which employs the Pd catalysed reactions of allenes.



(17) (18) (19) (20)

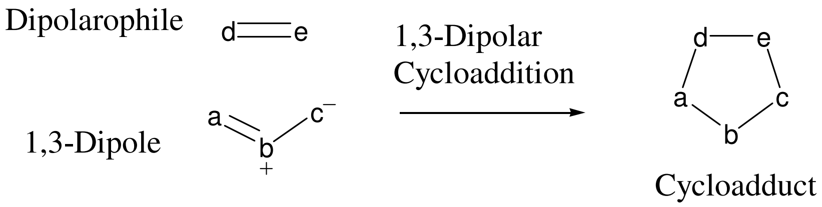
Scheme 7

1,3-dipolar cycloaddition reactions

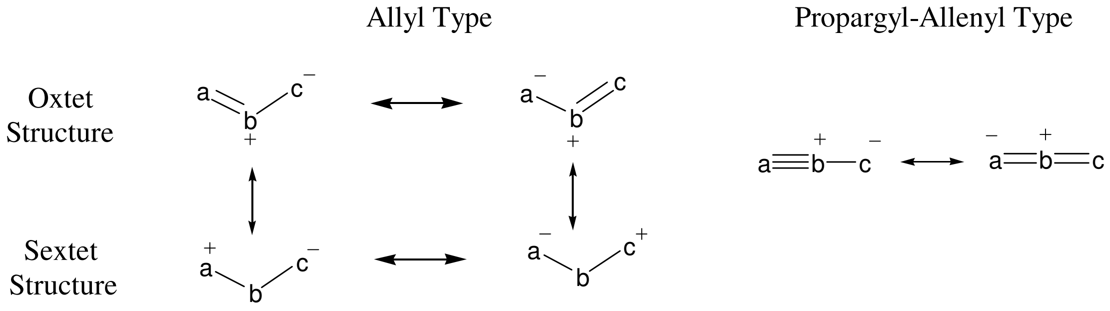
1,3-Dipolar cycloadditions, known as the Huisgen reaction, play a very important role in the synthesis of heterocycles (Kurt *et al.*, 1998). They are the reaction between a 1,3-dipole and a dipolarophile, most of which are substituted alkenes, to form a five-membered ring. Rolf Huisgen (1963) first discovered the prospects of varying the 1,3-dipole and its high value for synthesis of 5-membered heterocycles. The history of 1,3-dipole was started in 1883 by Curtius, who discovered diazoacetic ester. Five years later, Buchner studied the reaction of diazoacetic ester with α,β-unsaturated ester and described the first 1,3-dipolar cycloaddition reaction.

Basic aspects

A 1,3-dipole is delineated as a '**a-b-c**' structure, containing a formal positive and negative charge, which undergoes [3+2] cycloaddition with dipolarophile '**d-e**' to form a five-member ring system in which the 1,3-dipole provides three atoms and the dipolarophile provides two atoms.

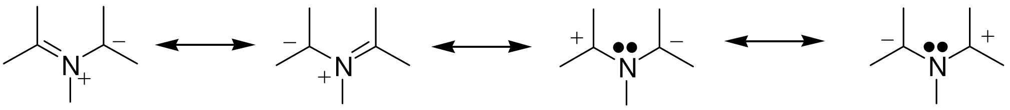


Basically, 1,3-dipoles can be classified into different types: the allyl and propargyl/allenyl type depending on nature and resonance structure of parent skeletons. In the allyl type 1,3-dipole has four-electron π-system orthogonal to the dipolar plane and can be represented by four canonical forms. Two are octet structures in which all three atoms have a complete octet and other two are sextet structures in which terminal atoms **a** and **c** both have six electrons. The central atom b can be nitrogen, oxygen or sulphur. Whilst the propargyl/allenyl type is linear and possesses extra π-orbital located in the a-b-c plane. This π-orbital is not directly involved in both of resonance structure and reaction of dipole. The central atom **b** is limit to nitrogen.



Azomethine ylides

Azomethine ylides are one of the most important class of 1,3 dipoles. They comprise a central nitrogen atom together with sp2 terminal carbon atoms. This ylide, which contains four electrons in its three p-orbitats, may be represented using a canonical form.



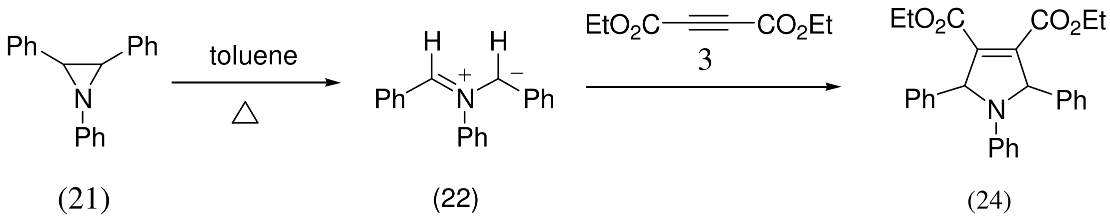
This ylide can be classified as non-stabilized, stabilized or stable. Non-stabilized type has no electron withdrawing groups at one or both of the ylide termini. Stabilized type has one or more electron withdrawing groups at the ylide termini. Both of these types are very common and generated *in situ*. In the case of stable type, it is stable and isolable but it is rare.

Non-stabilized azomethine ylides

Many approaches were used for the generation of non-stabilized azomethine ylides.

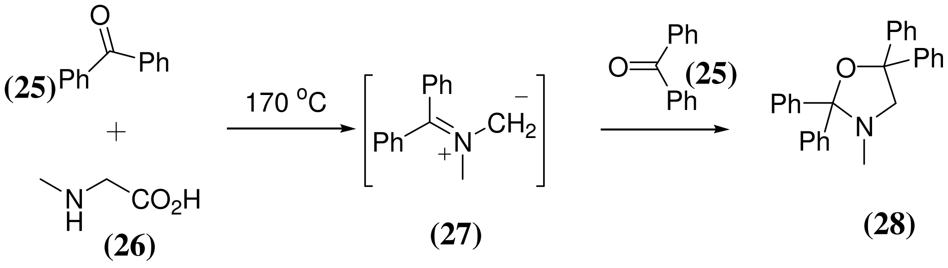
Aziridine pathway

In 1965, Heine and Peavy demonstrated the frist example of the ring opening of an aziridine to generate an azomethine ylide. 1,2,3-Triphenylaziridine (21) was refluxed in tolulene in the presence of diethyl acetylenedicarboxyrate (23). Azomethine ylide (22) was generated *in situ* and subsequently trapped by acetylene (23) to give a quantitative yield of cycloadduct (24). Later studies, Padwa and Huisgen (1965) obtained similar results independently.

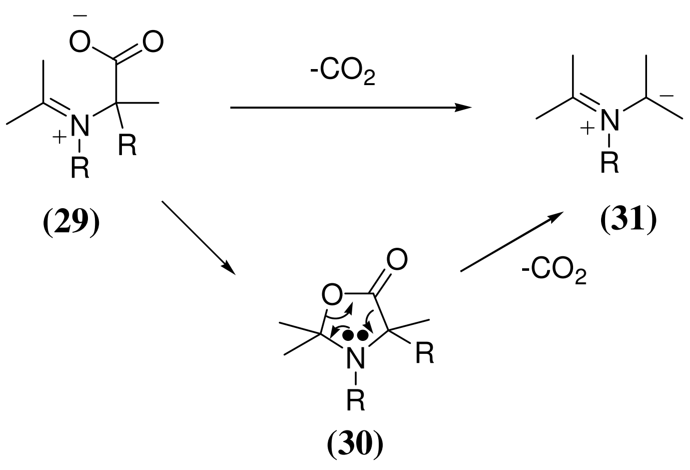


Decarboxylation pathway

The first example of decarboxylative route which involved heating sarcorsine (6) at 170 °C to give azomethine ylide **27** *in situ* was reported by Rizzi *et al.* in 1970. The ylide **27** was trapped with diphenylketone (25) to give cycloadduct (28).



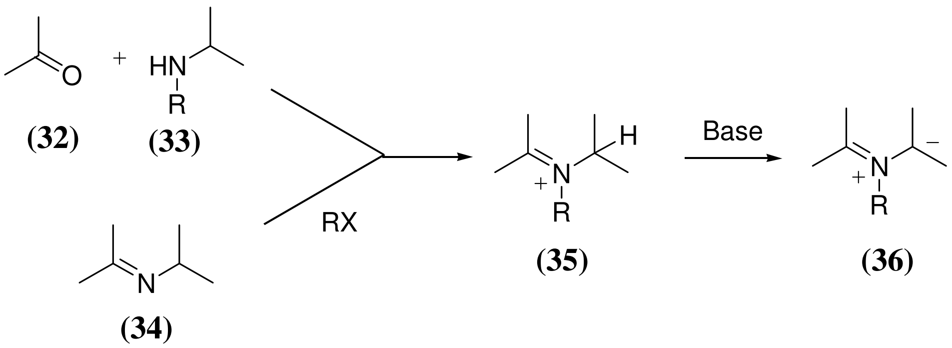
α-Amino acids were used to generate N-unsubstituted (or N-substituted) azomethine ylides (31). The formation of azomethine ylides (31) were simply explained by either direct decarboxylation of the zwitterions (29) or by cyclisation to **30** and subsequent retrocycloaddition (Joucla *et al.*, 1985).



(29) (30) (31)

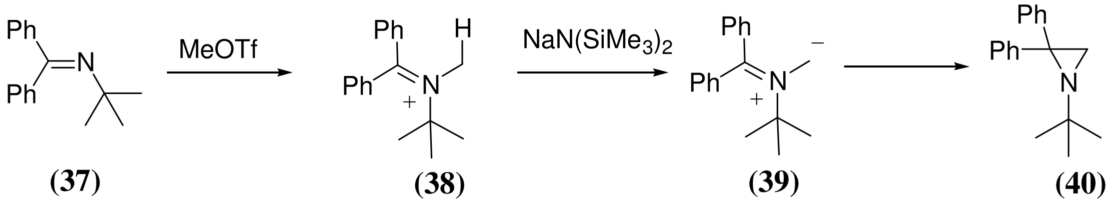
Deprotonation of iminium ions

Normally, iminium ions are prepared by condensation of carbonyl compound (32) with secondary amimes (33) or *N*-alkylation of imines (34) followed by α-deprotronation of (35) to afford (36) (Tsuge *et al.*, 1989).



(32) (33) (34) (35) (36)

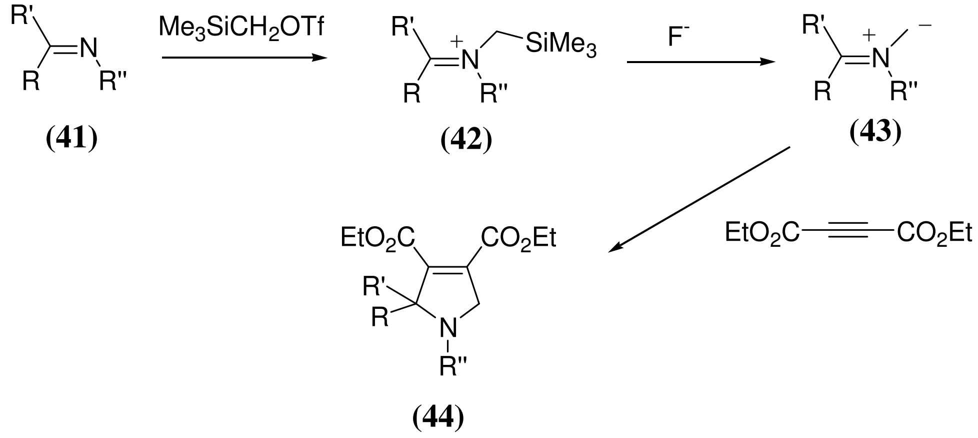
In 1975, Deyrup *et at.* reported the use of MeOTf for *N*-alkylation of imime (17) to from iminium salt (18). α-Deprotronation of (38) generated the non-stabilized azomethine ylide (39) and subsequent ring closure to give aziridine (40) in a quantitative yield.



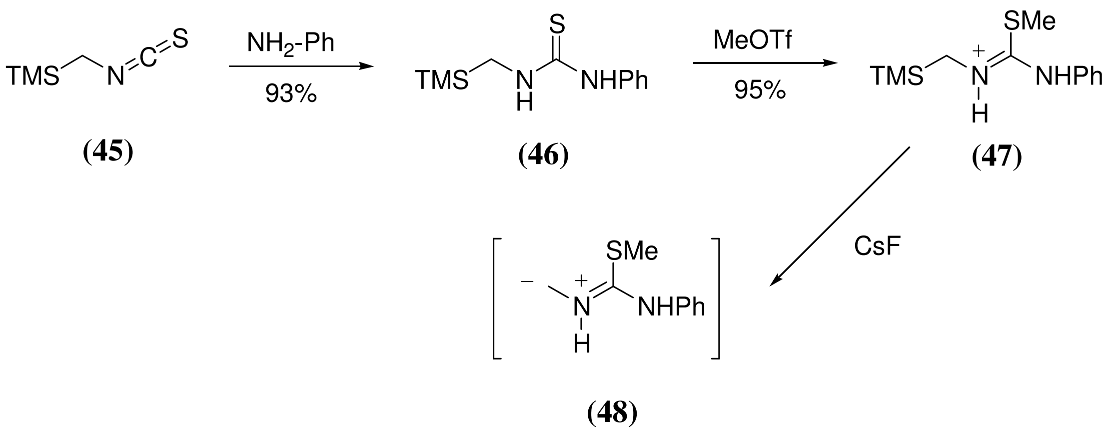
(37) (38) (39) (40)

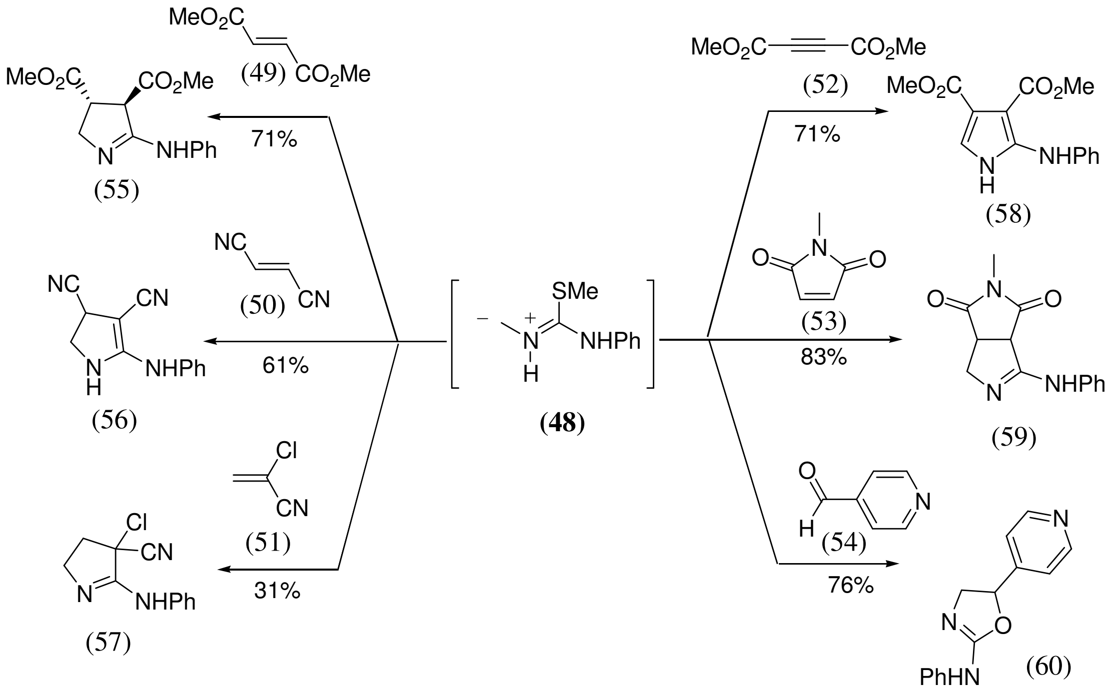
Desilylation pathway

This approach is fairly common for generation of non-stabilized azomethine ylides. In 1979, Vedejs and Martines reported the modified iminium iron route which involved alkylation of imine (41) by using trimethylsilylmethyl trifate to form the iminium salt (42). Desilylation of (42) by F$^-$ ion gave non-stabilized azomethine ylide (43) which was trapped by dimethyl acetylenedicarboxylate (Vedejs *et al.*, 1986).



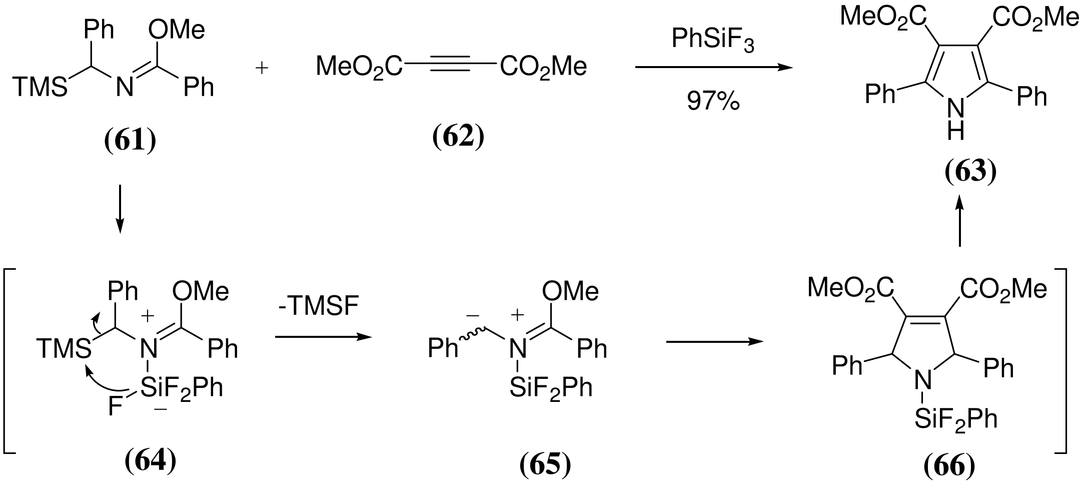
Tsuge *et al.* (1984) reported the generation of azomethine ylide (48) from isothiocyanate (45) (Scheme 10). Treatment of azomethine ylide (48) *in situ* with electron-deficient olefins (49), (50), (51), (52), (53) and (54) gave cycloadduct (55), (56), (57), (58), (59) and (50), respectively, after elimination of methylthio group (Scheme 8) (Tsuge *et al.*, 2000).



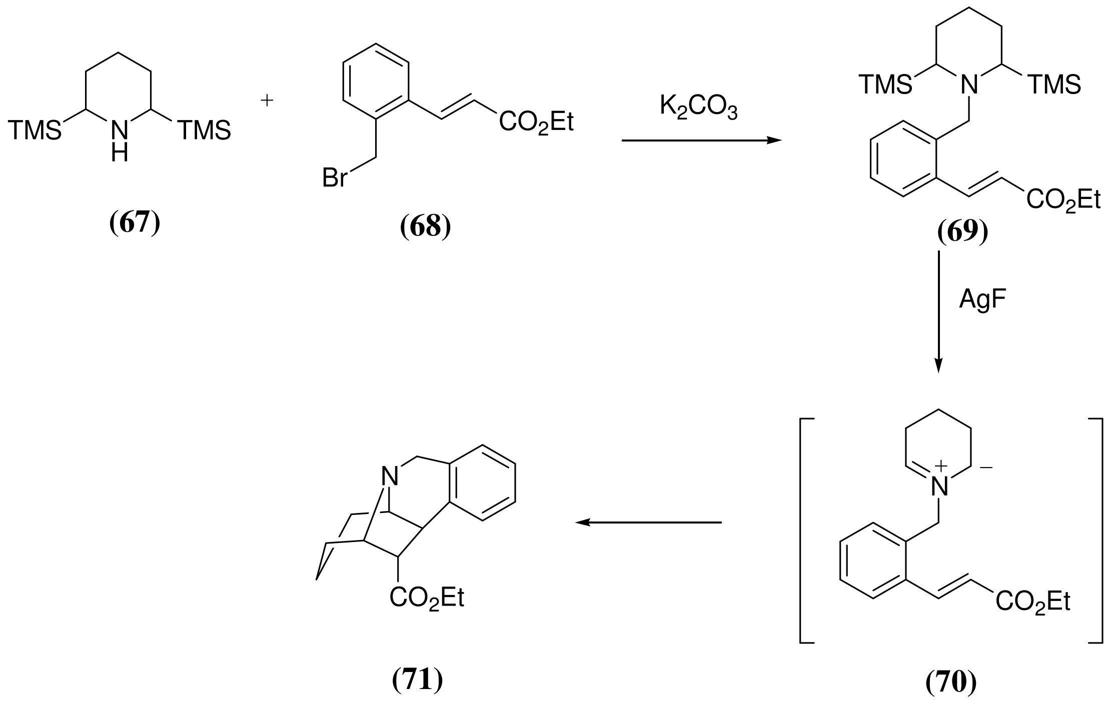


Scheme 8

The related N-silylated azomethine ylide (65) was obtained by treatment of α-silylimidate (61) with trifluorophenylsilane under relatively mild conditions. This azomethine ylide reacted with acetylenic (62) (or olefinic dipolarophiles) to give pyrroline (66) which then underwent aromatization to provide the N-unsubstitued pyrroles (63) (Damrauer *et al.*, 1986).



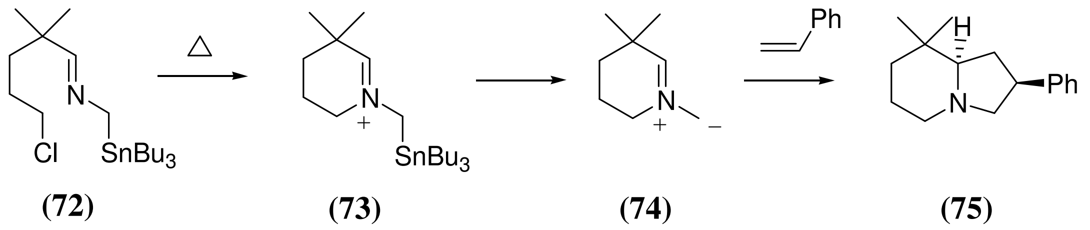
Nitrogen bridge-heterocycle (71) was prepared in a regio- and stereospecific route via the intramolecular 1,3-dipolar cycloaddition of nonstabilized cyclic azomethine ylide (70), which is generated by the sequential double desilyation of N-alkyl α,α'-bis(trimethylsilyl)cyclic amines (69) using AgF as a one electron oxidant. A typical example was shown in Scheme 9, whereby cycloadduct (71) was obtained regio- and stereospecifically in a good yield (Pandey *et al.*, 2000).



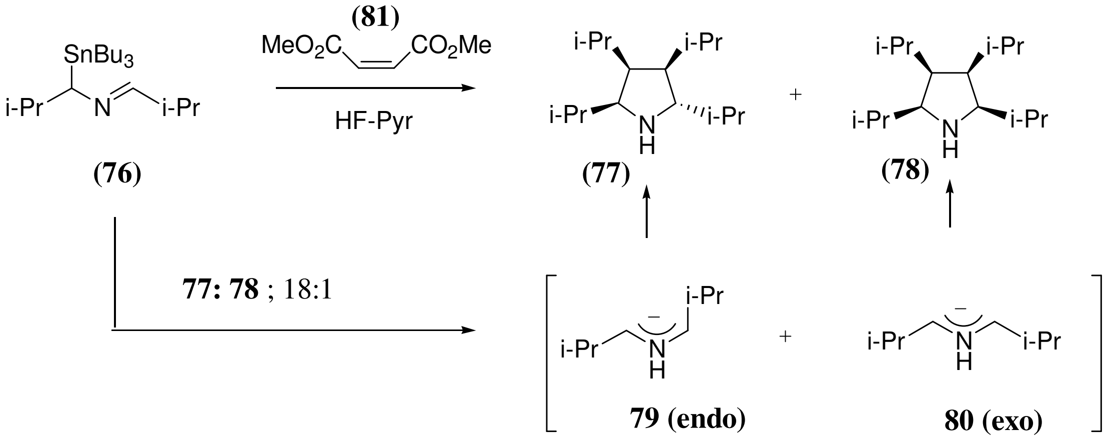
Scheme 9

Destannylation pathway

The destannylation pathway is fairly similar to desilylation pathway and showed in below. Intramolecular cyclisation of (72) furnished (73) and subsequent destannylation generated non-stabilized azomethine ylide (74) which underwent cycloaddition to form (75) as a single diastereomer (Katrizky *et al.*, 1998).

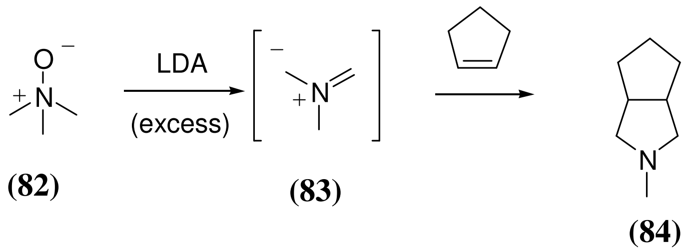


The generation of non-stabilized azomethine ylides by protodestannyllation of (2-azaallyl)stannanes (76) is interesting in that cycloaddition with electron-poor alkene (81) gave trans-2,5-dialkypyrrolidine (77) as the major product with high stereoselectivity (**77** **:** **78** ; 18 : 1) in 68 % yield. The major product structures implicated dipole (**79**) with endo-transition states (Pearson *et al.*, 1999).

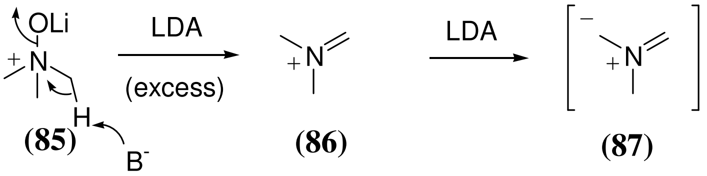


N-oxide pathway

In 1983, Roussi first reported the use of trimethylamine N-Oxide (82) with a large excess of lithium diisopropylamide (LDA) to generate the non-stabilized azomethine ylide (83).



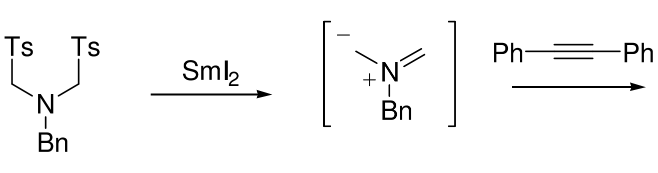
The plausible mechanism was illustrated. O-lithiation of tertiary amine N-oxide (85) followed by α-deprotonation gave an iminium intermediate (86) which was underwent α-deprotonation again to give non-stabilized azomethine ylide (87) (Roussi *et al.*, 1988).



(85) **(86)** **(87)**

SmI$_2$ reduction pathway

The final approach was first reported by Roussi *et al.* The azomethine ylide (89) was generated by treatment of (88) with SmI$_2$ in THF/HMPA at rt for 18 h in the presence of diphenylacetylene to obtain the dihydropyrrole (90).



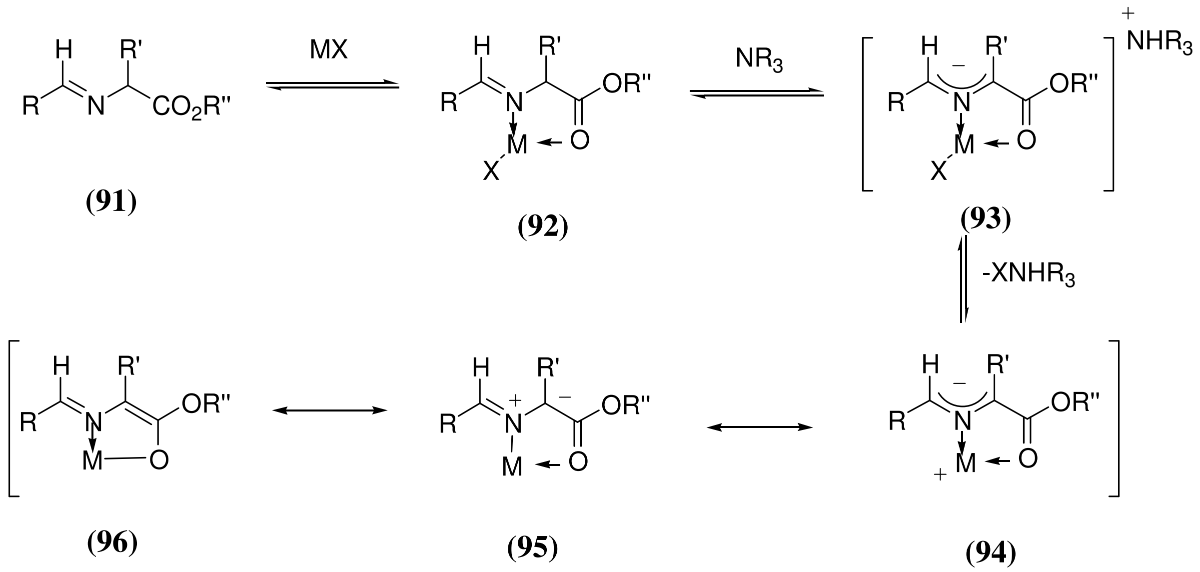
(88) **(89)** **(90)**

Stablised azomethine ylides

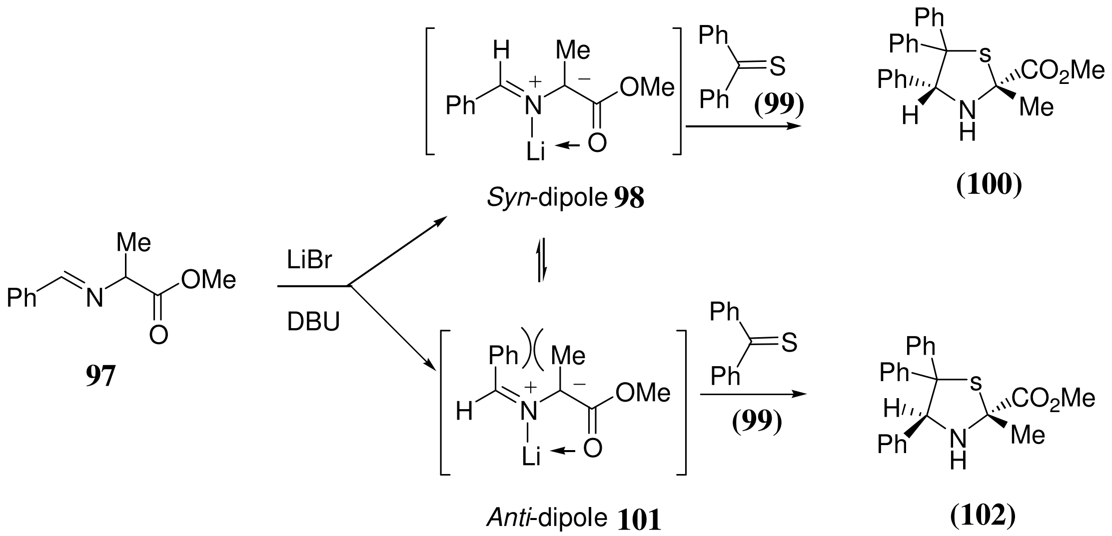
Stablised azomethine ylides can be generated by the same methods of non-stabilized azomethine ylides. The additional methods include the following:

N-metallation pathway

Coordination of an appropriate metal ion to the imine (91) afforded complexes (92) which undergoes deprotonation by base to form the (E,E)-metallo-azomethine ylide (93) It is unclear whether (93) loses the metal counter ion X to afford (94) and R$_3$NHX. The three canonical forms ((94), (95) and (96)) represent the relative degrees of coordination by the nitrogen and oxygen atoms. A wide range of metal salts and bases have been employed in this process. However, LiBr or AgOAc are the most used metal salts, whereas DBU or triethylamine are most frequently used bases (Grigg *et al.*, 1995)

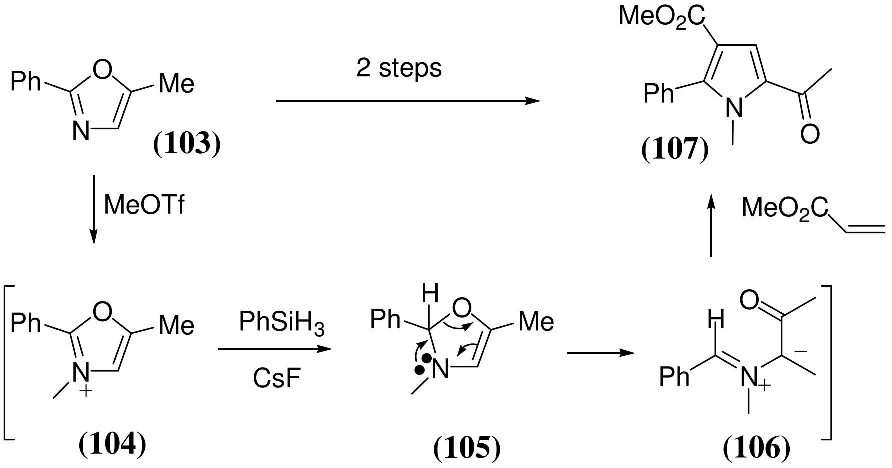


1,3-Dipolar cycloaddition of N-benzylidenalamine methyl ester (97) with thiobenzophenone (99) as a dipolarophile in the presence of LiBr and DBU gave a 4:1 mixture of diasteromers (100) and (102) in good yield. The product was formed regioselectively to generate *in situ* lithio-azomethine ylide syn-dipole (98) and anti-dipole (101), respectively (Heimgartner *et al.*, 2001).



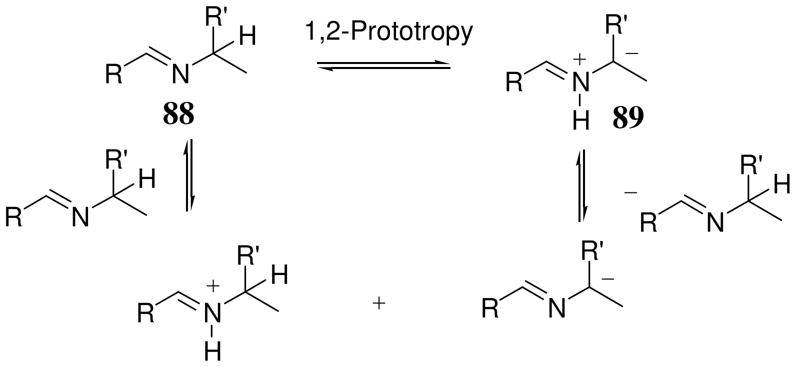
Oxazolidione pathway

In 1986, Vedejs developed the methodology to generate azomethine ylide via reduction oxazolium salt. Treatment of oxazole (103) with methyl triflate provided the oxazonium salt (104) followed by reduction by hydride transfer from $PhSiH_3/CsF$ to afford the oxazoline (105) which was spontaneously open the ring to give azomethine ylide (106). The ylide was trapped with methyl acrylate to give a single diastereoisomer (107) in good yield.



Formal 1,2-prototropy in imines

The formal 1,2-prototropy of imines of α-amino acid esters was first discovered by Grigg *et al.* in 1978, who has contributed extensively in this area to both mechanism and the application (Grigg *et al.*,1980; Grigg *et al.*, 1987). The formation of (109) is a bimolecular process involving two molecules of (108) since a concerted 1,2-shift, a four-electron process, contravenes the Woodward-Hoffman rules. The pKa of the proton and the basicity of the nitrogen atom control the process with are, in turn, dependent on the activating group R and R' group respectively.



Stable azomethine ylides

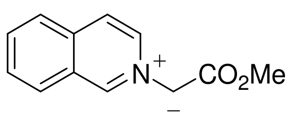
Stable azomethine ylides are comparatively rare and can be classified into three types;

(i) One C-N bond of the azomethine ylide is located within a heteroaromatic structure (Surpateanu *et al.*, 1984).

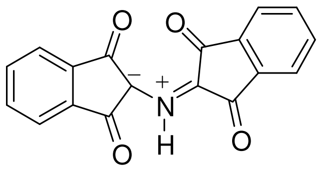
(ii) Neither C-N bond of azomethine ylide is located within a heteroaromatic structure (Grigg *et al.*, 1989).

(iii) The azomethine ylide is locade within a mesoionic ring system (Huisgen *et al.*, 1964).

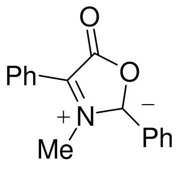
The example of each type is shown in below.



110 (i)



111 (ii)



112 (iii)

MATERIAL AND METHODS

Materials

Instrumentation

The following analytical methods were used throughout this work, unless otherwise indicated.

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba MOD 1106 Elemental Analyser. Mass spectra (EI and FAB) were obtained using a VG-Autospec operating at 70 eV. Electrospray (ES) mass spectra were obtained on a LCT Micromass (TOF). Accurate molecular masses were determined at Leeds using perfluorotributylamine or polyethylenimine as an internal standard or obtained from the EPSRC Swansea Mass Spctroscopy Service. IR spectra were recorded on a Nicolet Magna FT-IR 560 spectrometer. To prepare samples for IR, a small amount of sample was dissolved in dichloromethane, transferred onto a germanium plate and left to dry. Optical rotation was recorded on a AA100 polarimeter.

Nuclear magnetic resonance spectra were recorded at 250 MHz on a Bruker AC 250 instrument or at 500 MHz on a Bruker DRX 500 instrument. Deuterochloroform was used as the solvent with tetramethylsilane (TMS) as internal standard. Chemical shifts are given in part per million (δ) downfield from tetramethylsilane (TMS) and coupling constants are given in Hertz (Hz). Enantioselectivities were determine by HPLC using chiral stationary phase (Daicel Chiralcel OD column, 250 x 4.6 nm) with 1 ml/min flow rate (solvent system hexane/IPA; 80/20), and monitored by UV fluorescence at 230 nm.

Chromatographic system

Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the chromatograms were visualized under a 254 nm UV lamp and/or by spraying with a solution of vanillin (3% in ethanol with 3% sulfuric acid) followed by heating.

Flash column chromatography was performed according to the method of Still and co-workers (1978) using silica gel 60 (Merck 9385, 230-400 mesh).

Column chromatography was performed on silica gel 60 (70-230 mesh, Merck) and the column was packed by slurry method.

Chemical reagents

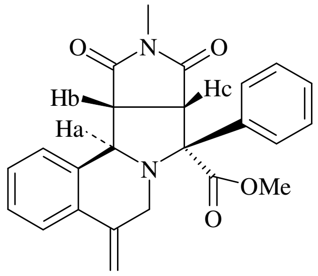
Solvents and reagents used for synthesis were obtained from commercial sources and used directly without purification unless noted. All reagents and solvents were purified according to literature procedures. The term ether refers to diethyl ether and petroleum ether is the fraction with boiling point 40-60 °C. Dry tetrahydrofuran (THF) was freshly distilled under N_2 from sodium with benzophenone ketyl as an indicator.

Experimental details of the reactions that failed have not been reported, although they are discussed.

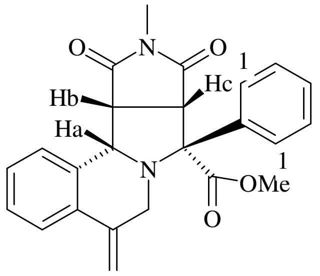
Methods

Amino acid methyl ester hydrochloride (1.2 mmol) was mixed with 2-iodobenzadehyde (232 mg, 1.0 mmol), *N*-methylmalemide (155 mg, 1.4 mmol), Pd_2dba_3 (23 mg, 2.5 mol%), TFP (23 mg, 10 mol%) and Cs_2CO_3 (4 mmol, 1.4g,) in toluene (15 ml) in a Schlenk tube. The mixture was solidified (liq. N_2) and degassed (two freeze, pump, and thaw cycles) before addition of allene (1 bar). It was then heated at 100 °C for 24 h. The mixture was allowed to cool to room temperature and excess allene vented. Then the reaction mixture was filtered through celite, the solvent was evaporated under vacuum and the resulting crude product was purified by flash column chromatography.

Methyl (8S,8aS,11R,11bR)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a, 9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (126) and methyl (8S,8aS,11R,11bS)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (127)



(126)



(127)

According to the general procedure, phenyl glycine methyl ester hydrochloride (125) (242 mg, 1.2 mmol) was employed to give crude product. Purification by flash column chromatography eluting with ether afforded the product (126) (125 mg, 31%) and the product (127) (136 mg, 34%).

126 obtained as colourless needles, m.p. 244-246 °C

FTIR ν_{max}(film), 2951, 1773, 1701, 1485, 1434, 1380, 1280 cm^{-1}

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.00 (d, 1H, *J* 7.7 Hz, ArH), 7.80 (d, 1H, *J* 7.6 Hz, ArH), 7.63 (d, 2 x 1H, *J* 7.5 Hz, ArH), 7.33-7.46 (m, 5H, ArH), 5.73 and 5.05 (s, 2 x 1H, =CH$_2$), 4.28 (d, 1H, *J* 7.9 Hz, Ha), 3.81 (d, 1H, *J* 13.2 Hz, NC$\underline{H}$H), 3.75 (s, 3H, OMe), 3.50 (dd, 1H, *J* 10.2 and 7.9Hz, Hb), 3.43 (d, 1H, *J* 10.2 Hz, Hc), 3.14 (s, 3H, NMe), 3.11 (d, 1H, *J* 13.2 Hz, NC$\underline{H}$H)

^{13}C NMR (75 MHz, CDCl$_3$) δ 176.6 (C=O), 175.9 (C=O), 169.1 (C=O), 132.2 (Cq), 138.9 (Cq), 137.1 (2 x Cq), 128.6 (2xCH), 128.0 (CH), 127.3 (CH), 127.1 (CH), 126.5 (2xCH), 123.6 (CH), 108.3 (CH$_2$), 63.0 (CH), 56.6 (CH), 52.2 (CH$_2$), 51.9 (CH$_3$), 49.8 (CH), 25.2 (CH$_3$)

m/z (ES, %) : 402.9 (M+1, 100).

Found; C, 71.60; H, 5.30; N, 7.10 $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96%

n.O.e	Enhancement (%)		
Irradiated proton	Ha	Hb	Hc
Ha	-	-	-
Hb	2.68	-	6.98
Hc	-	4.28	3.22

127obtained as colourless needles, m.p. 220-221 °C.

FTIR ν_{max}(film) 3016, 2951, 2796, 1776, 1745, 1703, cm^{-1}

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.52 (t, 2H, *J* 7.3 Hz, ArH), 7.37 (t, 2H, *J* 7.3 Hz, ArH), 7.29 (t, 1H, *J* 7.3 Hz, ArH), 7.22 (d, 2H, J 7.7 Hz, ArH, H1), 7.12 (t, 1H, *J*

7.3 ArH), 7.06 (t, 1H, *J* 7.7 Hz, ArH), 5.56 and 5.01 (s, 2 x 1H, =CH_2), 4.24 (t, 1H, *J* 7.7 Hz, Hb), 4.16 (d, 1H, *J* 7.7 Hz, Ha), 4.10 (d, 1H, *J* 12.0 Hz, C$\underline{H}$HN), 3.92 (d, 1H, *J* 8.1 Hz, Hc), 3.73 (s, 3H, OMe), 2.73 (s, 3H, NMe) 2.46 (d, 1H, *J* 12.0 C$\underline{H}$HN Hz, C$\underline{H}$HN).

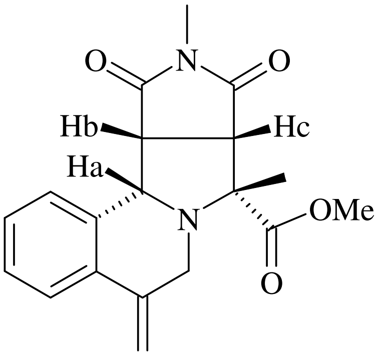
^{13}C NMR (75 MHz, acetone-d_6) δ 176.9 (C=O), 175.7 (C=O), 171.9 (C=O), 141.2 (Cq), 134.2 (Cq), 133.9 (Cq), 133.4 (Cq), 130.6 (CH), 129.4 (2 x CH), 129.3 (2 x CH), 129.1 (2 x CH), 127.9 (CH), 124.8 (CH), 108.9 (CH_2), 76.4 (Cq), 62.8 (CH), 53.0 (CH_3), 52.8 (CH_2), 52.6 (CH), 46.8 (CH), 25.5 (CH_3).

m/z (ES, %) : 402.9 (M+1, 100).

Found; C,71.55; H, 5.60; N, 7.00 $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96%

n.O.e	Enhancement (%)			
Irradiated proton	Ha	Hb	Hc	ArH(1)
Ha	-	9.22	2.3	1.1
Hb	3.21	-	10.91	7.25
ArH(1)	8.7	3.3	3.22	-

<u>Methyl (8S,8aS,11R,11bS)-8,10-dimethyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (139)</u>



(139)

According to the general procedure, alanine methyl ester hydrochloride (129) (167.5 mg, 1.2 mmol) was employed and the reaction was carried out at 110 °C for 24 h to give crude product. Purification by flash column chromatography eluting with ether afforded the product (139) (227 mg, 67%) as colourless needles, m.p. 214-215 °C.

FTIR ν_{max}(film) 2991, 2950, 1739, 1700, 1435, 1383, 1248 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 1H, *J* 7.7 Hz, ArH), 7.57 (d, 1H, *J* 7.7 Hz, ArH), 7.35-7.21 (m, 2H, ArH), 5.60 and 5.00 (s, 2 x 1H, $=CH_2$), 4.40 (d, 1H, *J* 7.2 Hz, Ha), 3.77 (s, 3H, OMe), 3.71 (t, 1H, *J* 7.2 Hz, Hb), 3.52 (d, 1H, *J* 11.8 Hz, $C\underline{H}HN$), 3.22 (m, 2H, Hc and $C\underline{H}HN$), 2.82 (s, 3H, NMe) 1.48 (s, 3H, Me).

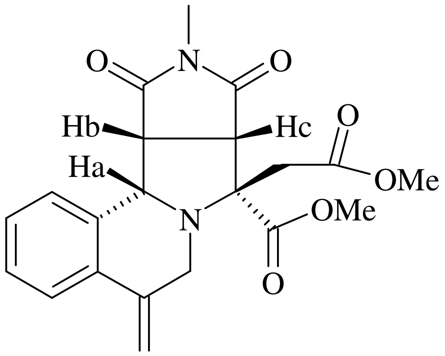
^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0 (C=O), 175.0 (C=O), 172.1 (C=O), 139.1 (Cq), 132.6 (Cq), 132.5 (Cq), 128.8 (CH), 127.5 (CH), 127.3 (CH), 124.4 (CH), 109.1 (CH_2), 70.4 (C), 62.4 (CH), 54.8 (CH), 53.1 (CH), 51.1 (CH_3), 45.9 (CH_2), 25.6 (CH_3), 15.0 (CH_3).

m/z (ES; %): 340.8 (M+1, 100).

Found; C, 67.10; H, 5.96; N, 8.35 $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23%.

n.O.e	Enhancement (%)			
Irradiated proton	Ha	Hb	Hc	Me
Ha	-	9.4	4.1	6.4
Hb	8.4	-	11.2	2.1
Me	5.1	1.1	6.4	-

Methyl (8S,8aS,11R,11bS)-8-(2-methoxy-2-oxoethyl)-10-methyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*] isoquinoline -8-carboxylate (140)



(140)

According to the general procedure, aspartic acid methyl ester hydrochloride (130) (237 mg, 1.2 mmol) was employed to give crude product. Purification by flash column chromatography eluting with ether afforded the product (140) (227 mg, 57%) as pale yellow needles, m.p. 95-96 °C.

FTIR ν_{max}(film) 2952, 1776, 1735, 1703, 1436, cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): 7.64 (d, 1H, *J* 6.7 Hz, ArH), 7.54 (d, 1H, *J* 7.2 Hz, ArH), 7.36-7.22 (m, 2H, ArH), 5.57 and 5.01 (s, 2 x 1H, =CH_2), 4.45 (d, 1H, *J* 7.7 Hz, Ha), 3.88 (d, 1H, *J* 8.19 Hz, C$\underline{H}$HN), 3.80 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.70 (m, 2H, Hb and C$\underline{H}$HN), 3.18 (d, 1H, *J* 12.3 Hz, Hc), 2.93 and 2.84 (d, 2 x 1H, *J* 15.8 Hz, CH_2), 2.82 (s, 3H, NMe).

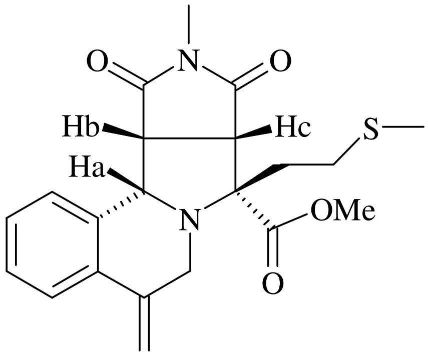
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (2 x C=O), 169.8 (C=O), 166.9 (C=O), 133.9 (Cq), 127.4 (Cq), 127.3 (Cq), 123.6 (CH), 122.6 (CH), 122.0 (CH), 119.1 (CH), 103.8 (CH_2), 65.2 (Cq), 57.2 (CH), 49.5 (2x CH_3), 47.9 (CH_2), 45.9 (CH), 40.7 (CH), 20.4 (CH3), 9.8 (CH_2).

m/z (ES, %): 398.8 (M+1, 100).

Found; C, 63.35; H, 5.60; N, 7.10 $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03%.

n.O.e	Enhancement (%)			
Irradiated proton	Ha	Hb	Hc	C$\underline{H}_2$ CO_2Me
Ha	-	10.0	3.4	8.6
Hc	4.9	26.7	-	0.3
C$\underline{H}_2$ CO_2Me	6.6	2.1	2.0	-

Methyl (8S,8aS,11R,11bS)-10-methyl-5-methylene-8-[(methylthio)methyl]-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (141)



(141)

According to the general procedure, methionine methyl ester hydrochloride (131) (240 mg, 1.2 mmol) was employed and the reaction was carried out at 100 °C for 24 h to give crude product. Purification by flash column chromatography eluting with ether afforded the product (141) (216 mg, 56%) as yellow plates, m.p. 84-85 °C.

FTIR ν_{max}(film) 3056, 2951, 1775, 1732, 1702, 1603, 1435, 1382 cm^{-1}

^1H NMR (300 MHz, acetone-d_6) δ 7.67 (d, 1H, *J* 7.2 Hz, ArH), 7.55 (d, 1H, *J* 7.7 Hz, ArH), 7.29- 7.20 (m, 2H, ArH), 5.56 and 4.96 (s, 2 x 1H, =CH_2), 4.61 (d, 1H, *J* 6.7 Hz, Ha), 3.96 (t, 1H, *J* 6.7, Hb), 3.67 (s, 3H, OMe), 3.51(d, 1H, *J* 6.7 Hz, Hc), 3.42 (d, 1H, *J* 12 Hz, C$\underline{H}$HN), 2.91 (m, 2H, CH_2S), 2.69 (s, 3H, NMe), 2.38 (m, 1H, C$\underline{H}$HN), 2.2-2.05 (m, 2H, C$\underline{H}_2$$CH_2S$), 2.16 (s, 3H, SMe).

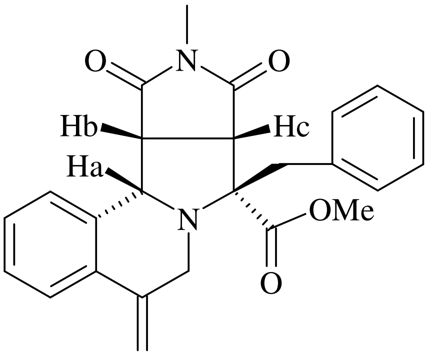
^{13}C NMR (75 MHz, acetone-d_6): 177.0 (C=O), 176.0 (C=O), 172.3 (C=O), 141.2 (Cq), 134.7 (Cq), 133.5 (Cq), 130.3 (CH), 128.0 (CH), 127.8 (CH), 125.0 (CH), 108.4 (CH_2), 74.0 (CH), 62.9 (CH), 61.0 (Cq), 53.3 (CH_3), 52.9 (CH), 52.1 (CH_2), 47.4 (CH_2), 31.8 (CH_2), 29.4 (CH_3), 25.4 (CH_3).

m/z (ES, %): 400.8 (M+1, 100).

Found; C, 62.80; H, 6.10; N, 6.83 $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99%

n.O.e	Enhancement (%)		
Irradiated proton	Ha	Hb	CH_2S
Ha	-	8.4	7.3
Hb	7.5	-	6.5
CH_2S	2.4	3.7	-

Methyl (8S,8aS,11R,11bS)-8-benzyl-10-methyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (142)



(142)

According to the general procedure, phenyl alanine methyl ester hydrochloride (132) (259 mg, 1.2 mmol) was employed and the reaction mixture was carried out at 100 °C for 24 h to give crude product. Purification by flash column chromatography eluting with ether afforded the product **142** (230 mg, 55%) as pale yellow plates, m.p. 173-174.2 °C.

FTIR ν_{max}(film) 3062, 3027, 2951, 1775, 1736, 1703, 1602, 1495, 1435, 1287 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, 1H, *J* 8.2 Hz, ArH), 7.55 (d, 1H, *J* 7.9 Hz, ArH), 7.35-7.20 (m, 7H, ArH), 5.45 and 4.90 (s, 2 x 1H, $=CH_2$), 4.7 (d, 1H, *J* 7.7 Hz, Ha), 3.84 (s, 3H, OMe), 3.62 (t, 1H, *J* 7.7 Hz, Hb), 3.52 (d, 1H, *J* 12.2 Hz, $C\underline{H}HN$), 3.38 (s, 2H, CH_2Ph), 3.37 (d, 1H, *J* 7.7 Hz, Hc), 3.15 (d, 1H, *J* 12.2 Hz, $C\underline{H}HN$), 2.77 (s, 3H, NMe).

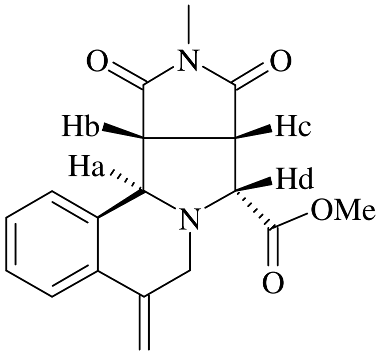
^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2 (C=O), 175.1 (C=O), 172.2 (C=O), 139.5 (Cq), 137.6 (Cq), 133.2 (Cq), 132.5 (Cq), 131.0 (CH), 130.0 (CH), 129.3 (CH), 129.2 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 124.7 (CH), 108.7 (CH_2), 73.8 (C), 62.5 (CH), 53.1 (CH_2), 53.1 (CH), 51.2 (CH_3), 46.5 (CH_2), 37.4 (CH), 25.7 (CH_3).

m/z (ES, %): 416.9 (M+1, 100).

Found; C, 71.90; H, 5.96; N, 6.51 $C_{25}H_{24}N_2O_4$: C, 72.10; H,5.81; N, 6.73%

n.O.e	Enhancement (%)		
Irradiated proton	Ha	Hb	Hc and CH_2Ph
Ha	-	11.0	7.1
Hb	8.2	-	8.5
Hc and CH_2Ph	3.90	4.7	-

Methyl (8S,8aS,11R,11bR)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (143)



(143)

According to the general procedure, glycine methyl ester hydrochloride (138) (150 mg, 1.2 mmol) was employed and the reaction was carried out at 110 °C for 48 h to give crude product. Purification by flash column chromatography eluting with 1:3 v/v hexane: ether afforded the inseparable 3:1 mixture product (88 mg, 27%) of (143) and (144) as a colourless gum.

FTIR ν_{max}(film) 3041, 2952, 2854, 1778, 1750, 1700, 1481

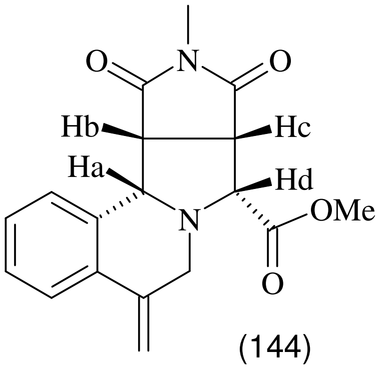
^{1}H NMR (300 MHz, $CDCl_3$: a major product **143**): 7.64 (d, 1H, *J* 7.8 Hz, ArH), 7.52 (d, 1H, *J* 7.6 Hz, ArH), 7.34-7.22 (m, 2H, ArH), 5.56 and 4.98 (s, 2 x 1H, =CH_2), 4.61 (d, 1H, *J* 7.5 Hz, Ha), 4.24 (bs, 1H, Hd), 3.80 (dd, 1H, *J* 9.7 and 7.5 Hz, Hb), 3.78 (s, 3H, OMe), 3.66 (d, 1H, *J* 12.5 Hz, C$\underline{H}$HN), 3.62(d, 1H, *J* 9.7 Hz, Hc), 3.46 (d, 1H, *J* 12.5 Hz, C$\underline{H}$HN), 2.84 (s, 3H, NMe).

m/z (ES, %): 326.9 (M+1, 100).

HRMS (ES+) Found MH$^+$, 327.1338 $C_{18}H_{19}N_2O_4$ requires MH$^+$, 327.1345.

n.O.e	Enhancement (%)			
Irradiated proton	Ha	Hb	Hc	Hd
Ha	-	15.7	-	-
Hc	-	7.4	-	3.21
Hd	-	3.4	2.59	-

<u>Methyl (8S,8aS,11R,11bS)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (144)</u>



(144)

According to the general procedure, glycine methyl ester hydrochloride (138) (150 mg, 1.2 mmol) was employed and the reaction was carried out at 100 °C for 12 h to give crude product. Purification by flash column chromatography eluting with 1:3 v/v hexane: ether afforded the product **144** (222 mg, 68%) as colourless needles, m.p. 175-176 °C.

FTIR ν_{max}(film) 3056, 2952, 2854, 1778, 1751, 1703, 1481, 1436, 1385 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, 1H, *J* 7.8 Hz, ArH), 7.38-7.26 (m, 3H, ArH), 5.70 (s, 1H, C=C<u>H</u>H), 5.60 (bs, 1H, Hd), 5.0 (s, 1H, C=C<u>H</u>H), 3.88-3.84 (m, 2H, Ha and C<u>H</u>HN), 3.84 (s, 3H, OMe), 36.7(d, 1H, *J* 7.2 Hz , Hb), 3.48 (m, 2H, *J* 4.6 Hz, Hc and C<u>H</u>HN), 3.05 (s, 3H, NMe).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6 (C=O), 176.4 (C=O), 170.1 (C=O), 135.2 (Cq), 134.1 (Cq), 133.1 (Cq), 129.7 (CH), 127.8 (CH), 124.4 (2 x CH), 112.6 (CH_2), 66.1 (CH), 62.3 (CH), 52.8 (CH_3), 51.6 (2x CH), 47.5 (CH_2), 26.0 (CH_3).

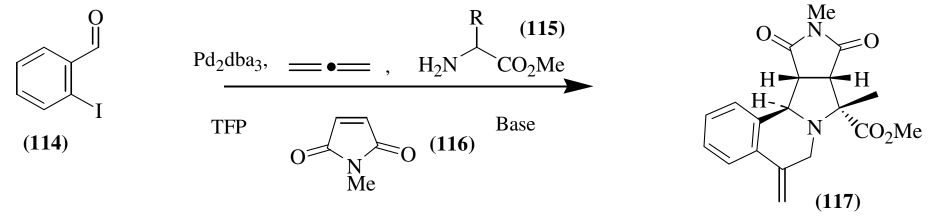
m/z (ES, %): 326.9 (M^+ 1, 100).

Found; C, 66.14; H, 5.62; N, 8.6 $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58%.

n.O.e	Enhancement (%)			
Irradiated proton	Ha	Hb	Hc	Hd
Ha	-	15.7	1.1	1.4
Hb	31.7	-	-	8.6
Hc	1.2	1.0	-	3.21
Hd	0.4	3.4	2.59	-

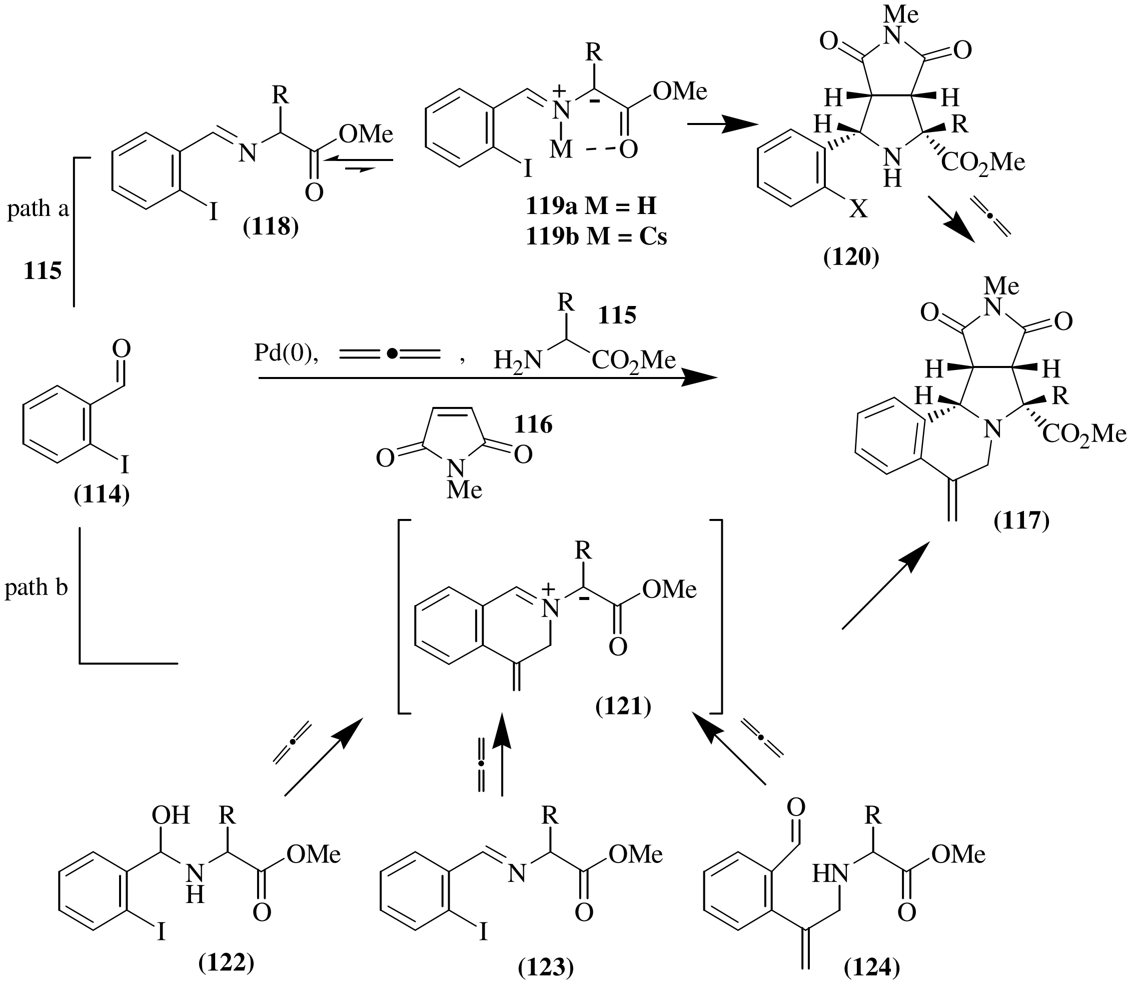
RESULTS AND DISCUSSION

The main purpose of this research was to study the palladium-catalyzed four-component cascade reaction of 2-iodobenzyl aldehyde (114), amino acid methyl ester (115), allene and NNM (116) in the presence of $Pd_2(dba)_3$ (2.5 mol%) and tris(2-furyl)phosphane (TFP) (10 mol%)) (Scheme 10).



Scheme 10

Two plausible mechanisms might be involved in the reaction (Scheme 11). 2-iodobenzyl aldehyde (114) was reacted with allene, amino acid methyl ester (115), and *N*-methyl maleimide (96) in the presence of Pd(0) to afford (117) via path a or path b. Path a involves formation of imine (118), which undergoes 1,3-dipolar cycloaddition via the azomethine ylide (119a) or (119b) (endo transition state) to give (120). Successive palladium catalyzed allene/nucleophile incorporations then afford (117). In path b, palladium catalyzed allenylation / nucleophile incorporation generated azomethine ylide (121) which undergoes a 1,3-dipolar cycloaddition to afford 97. Azomethine ylide (121) could arise via the precursors (122), (123) or (124).



Scheme 11

The four-component cascade reaction of 2-iodobenzaldehyde (114) (1 mmol) was investigated by reacting with allene (1 bar), phenyl glycine methyl ester hydrochloride (125) (1.2 mmol), *N*-methyl maleimide (116) (1 mmol), Pd_2dba_3 (2.5 mol%), TFP(10 mol%) and K_2CO_3 (4 mol eq) in toluene 10 ml at 100°C for 48 h. The product (126) was obtained in low yield (15%) (Table 2, Entry 1).

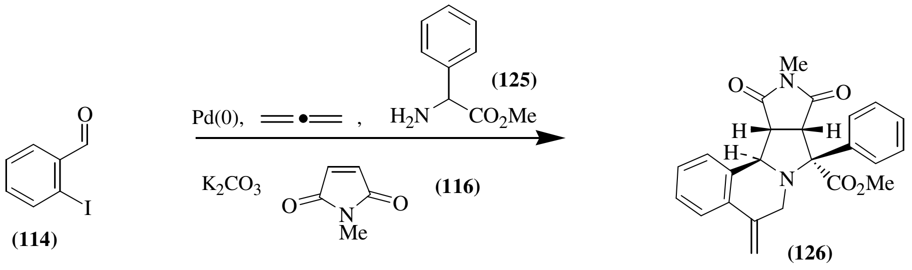
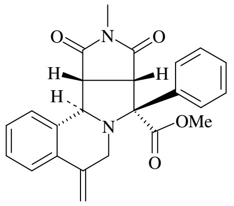
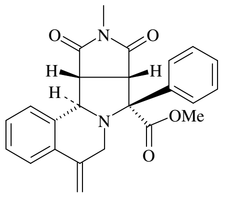
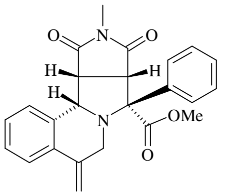


Table 2 Reaction optimization of phenyl glycine methyl ester hydrochloride (125)

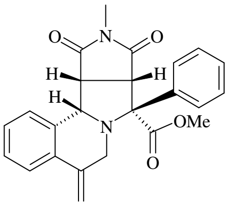
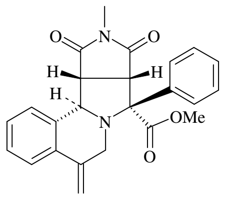
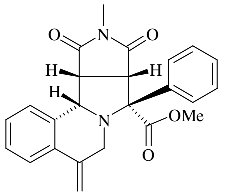
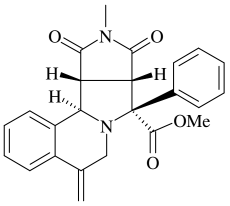
Entry	Base (4 mol eq.)	Time (h)	Results
1	K_2CO_3	48	 **126** (15%)
2	DBU	48	Complex mixture
3	Cs_2CO_3	48	 **126**(31%)  **127**(34%)

To increase the yield of (126), the reaction was optimized by changing base. In the case of organic base DBU, only a complex mixture (Table 2, entry 2) was observed. Explanation of this unsuccessful result (Table 2, entry 2) is still not clear since DBU is employed in normal 1,3-dipole cycloaadition reactions to afford cycloadducts in a good yield (Grigg *et al.*, 1995). DBU might interfere in palladium-catalyzed allenylation step. An inorganic base Cs_2CO_3, was also employed in cascade reaction to afford a mixture of diastereomer (126) (31%) and (127) (34%) (Table 2, entry 3). This result was indicated that Cs_2CO_3 is a more active base than K_2CO_3 and lead to the satisfactory yield but gives a mixture of diastereomers (126) and (127). The configuration of (126) and (127) were established by n.O.e. studies.

The reaction time of cascade reaction was also optimized (Table 3). Interestingly, decreasing the reaction time to 12 h led to only kinetic product (127) in

59% yield (Table 3, entry 1) whilst increasing the reaction time to 72 h afforded only thermodynamic product (126) in 31% (Table 3, entry 3). This suggested that (126) might arise via the epimerization of (127) or alternatively (127) underwent a retro 1,3-dipolar cycloaddition reaction to generate syn azomethine ylide which then underwent stereo mutation to generate anti azomethine ylide followed by 1,3-dipolar cycloaddition reaction.

Table 3 Reaction time optimization of phenyl glycine methyl ester hydrochloride (125)

Entry	Base (4 mol eq.)	Time (h)	Results
1	Cs_2CO_3	12	 126(59%)
2	Cs_2CO_3	24	 126(13%)  127(45%)
3	Cs_2CO_3	72	 126(31%)

We also used a range of amino acid methyl esters in the four-component cascade reaction. Amino acid methyl esters were employed in cascade reaction by using 2-iodo-benzyldehyde (114), *N*-methyl maleimide (116) (1 mmol), Pd_2dba_3 (2.5 mol%), TFP(10 mol%) and Cs_2CO_3 (4 mol eq) in toluene 10 ml at 100ºC for 24 h (Table 4).

Table 4 Four-component cascade reaction of amino acid methyl esters

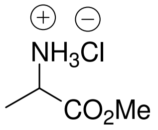
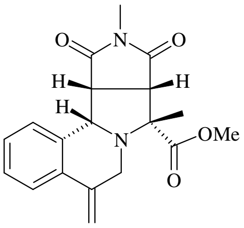
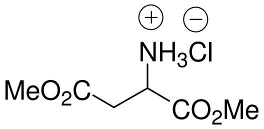
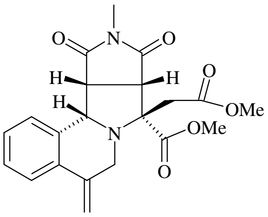
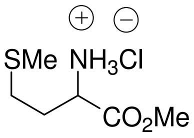
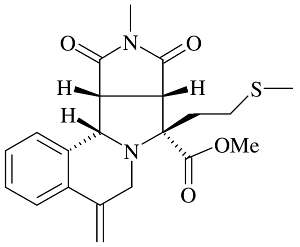
Entry	Amino acid methyl esters (1.2 mol eq.)	Results
1	 Alanine methyl ester (129)	 **139**(67%)
2	 Aspartic methyl ester (130)	 **140**(57%)
3	 Methionine methyl ester (131)	 **141**(56 %)

Table 4 (Cont'd)

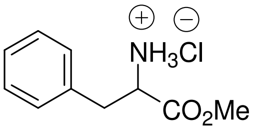
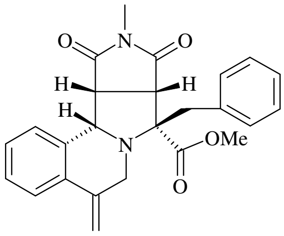
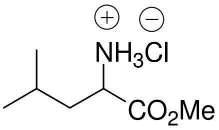
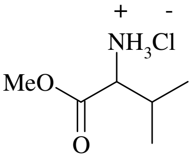
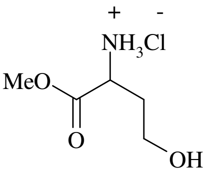
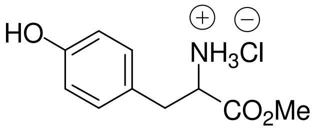
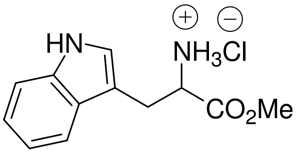
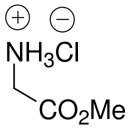
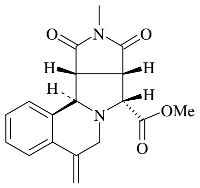
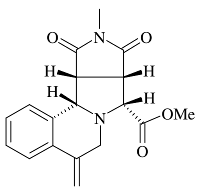
Entry	Amino acid methyl esters (1.2 mol eq.)	Results
4	 Phenyl alanine methyl ester (132)	 **142**(55%)
5	 Leucine methyl ester(133)	Complex mixture
6	 Valine methyl ester (134)	Complex mixture
7	 Serine methyl ester (135)	Complex mixture
8	 Tyrosine methyl ester (136)	Complex mixture

Table 4 (Cont'd)

Entry	Amino acid methyl esters (1.2 mol eq.)	Results
9	 Tryptophan methyl ester (137)	Complex mixture
10	 Glycine methyl ester (138)	  (143) (144) 1 :1 inseparable mixture (53%)

In the case of leucine methyl ester (133), valine methyl ester (134), serine methyl ester (135), tyrosine methyl ester (136) and tryptophan methyl ester (137) (Table 4, entry 5-9), the four-component cascade reactions did not provide the expected products but gave only complex mixture. The possible explanations of these unsuccessful results (Table 4, entry 5-9) are steric hindrance of amino methyl esters (Table 4, entry 5-6) or that the amino methyl esters are unstable under the reaction condition (Table 4, entry 7-9) or the reaction times are too long and cycloadducts decompose.

However, alanine methyl ester (129), aspartic acid methyl ester (130), methionine methyl ester (131) and phenylalanine methyl ester (132) were successfully employed in the cascade reaction (Table 4, entry 1-4) to give (139)-(142) in 54-67% yield.

Interestingly, glycine methyl ester (138) was employed under the above cascade under essentially same conditions to afford a 1:1 mixture of inseparable diassteromer (143) and (144) in 53% yield. The ratio of diastereomers (143) and (144) was determined by the integration of ^{1}H NMR spectra (Table 1, entry 6). It was found that decreasing the reaction time of the cascade reaction to 12 h led to only kinetic product (144) in 68% yield.

The four-component cascade reaction of a range of amino acid methyl esters led to the kinetic products via 1,3-dipolar cycloaddition of azomethine ylide (endo transition state) with NMM (116). Therefore, the mechanism of four-component cascade reaction is more likely to proceed via path a than path b.

CONCLUSION

We have demonstrated a novel four-component palladium catalysed 1,3-dipolarcycloaddition / allene insertion / nucleophile incorporation cascade for the synthesis of pyrroldinyl isoquinolines. A plausible mechanism for the four-component cascade involved the generation of intermediate azomethine ylides which undergo cycloaddition through an endo transition state prior to incorporation of the allene. The four-component cascades result in a substantial increase in molecular complexity with construction of five new bonds, two rings and four stereocenters.

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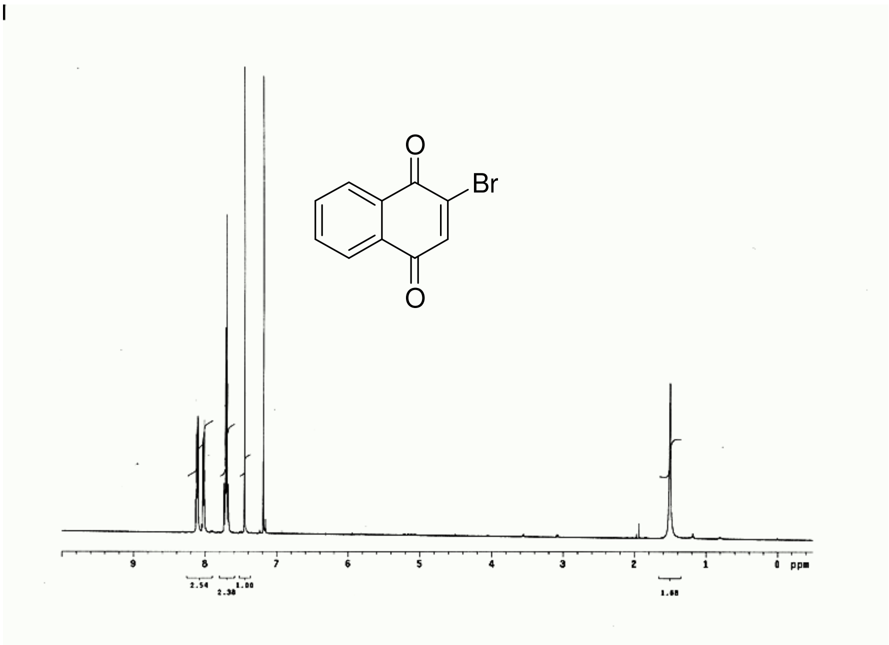
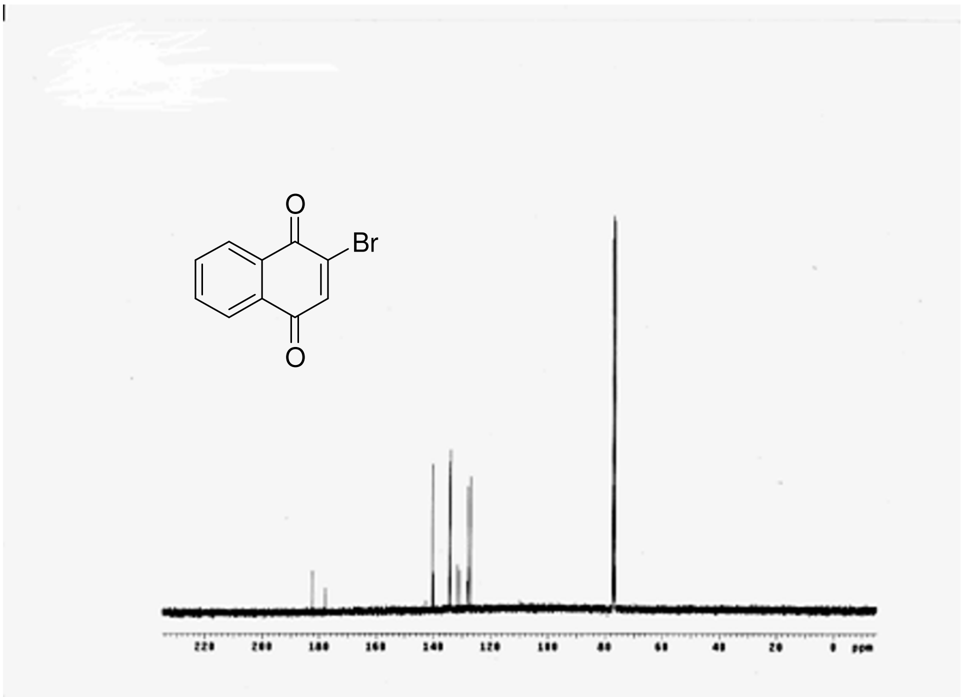
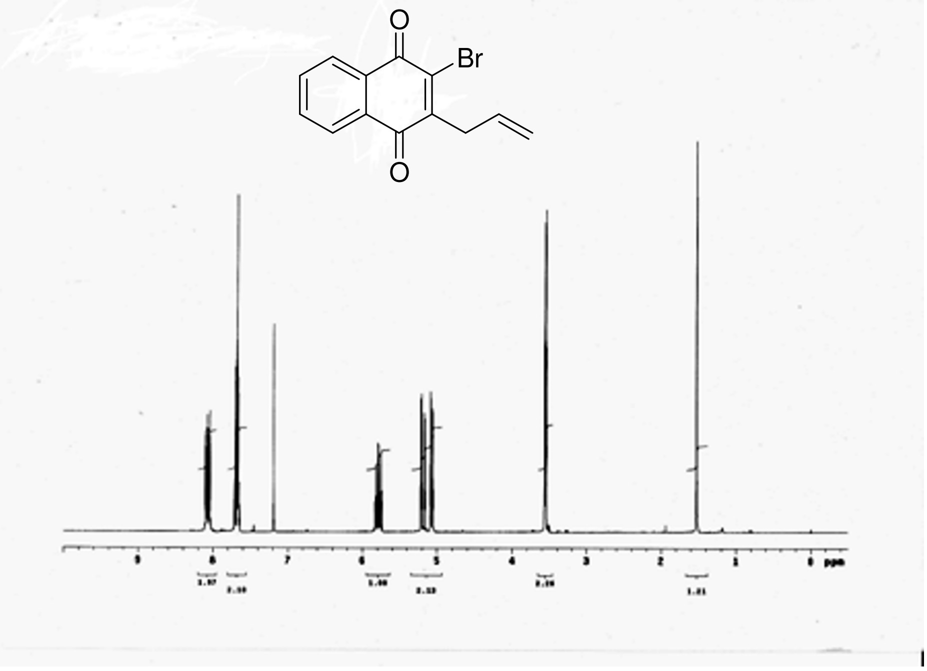
APPENDIX



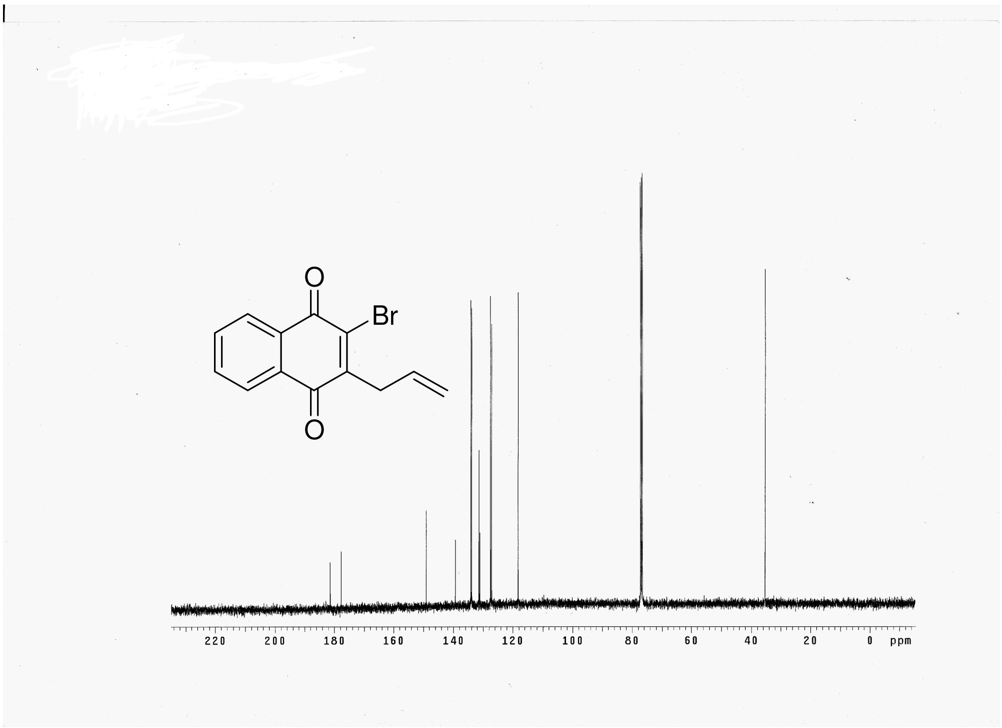
Appendix Figure 1 400 MHz ^{1}H NMR spectrum of 2-bromo-1,4-naphthoquinone (114)



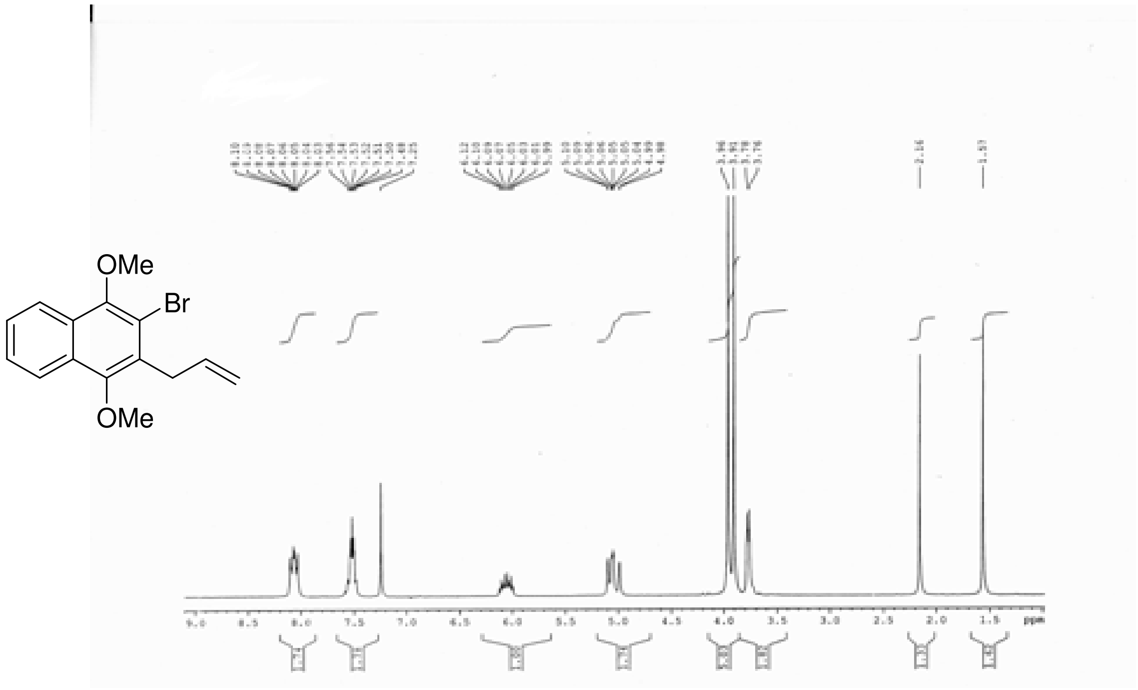
Appendix Figure 2 400 MHz ^{1}H NMR spectrum of 2-bromo-1,4-naphthoquinone (114)



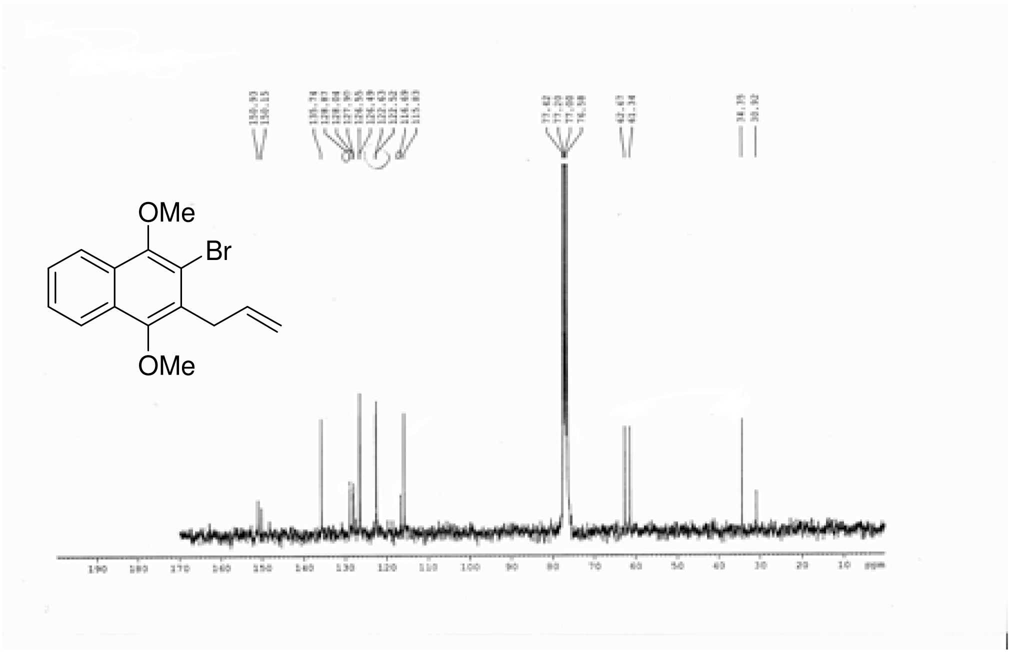
Appendix Figure 3 400 MHz ^{1}H NMR spectrum of 2-allyl-3-bromo-1,4-naphthoquinone (115)



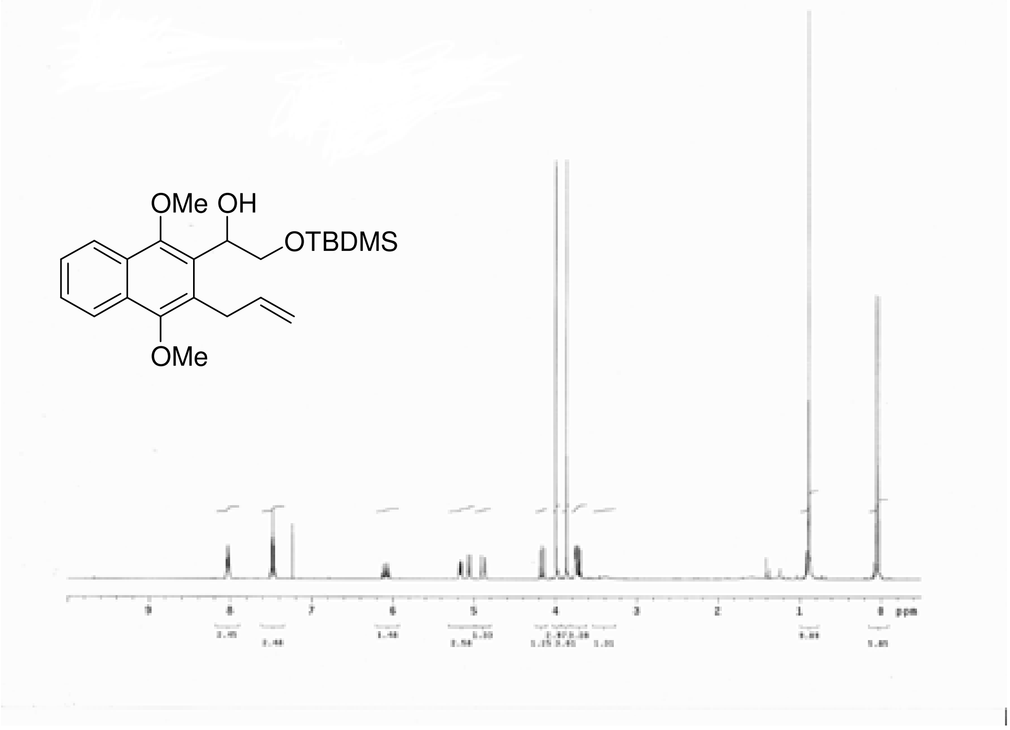
Appendix Figure 4 100MHz ^{13}C NMR spectrum of 2-allyl-3-bromo-1,4-naphthoquinone (115)



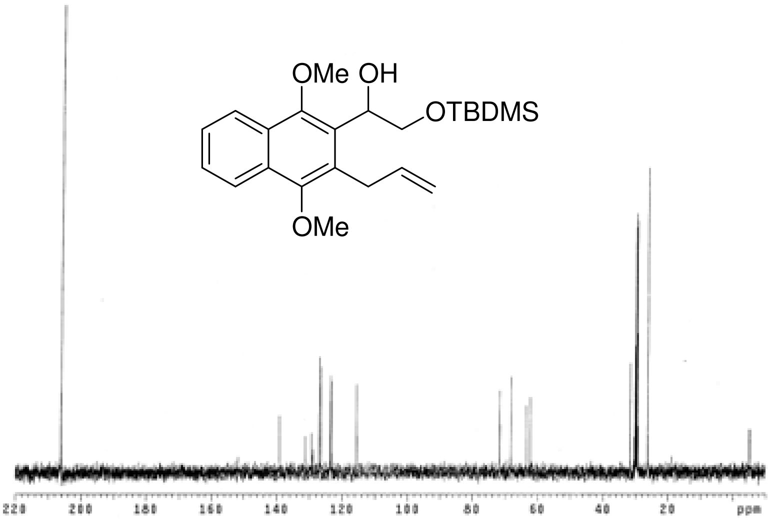
Appendix Figure 5 300 MHz ^{1}H NMR spectrum of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116)



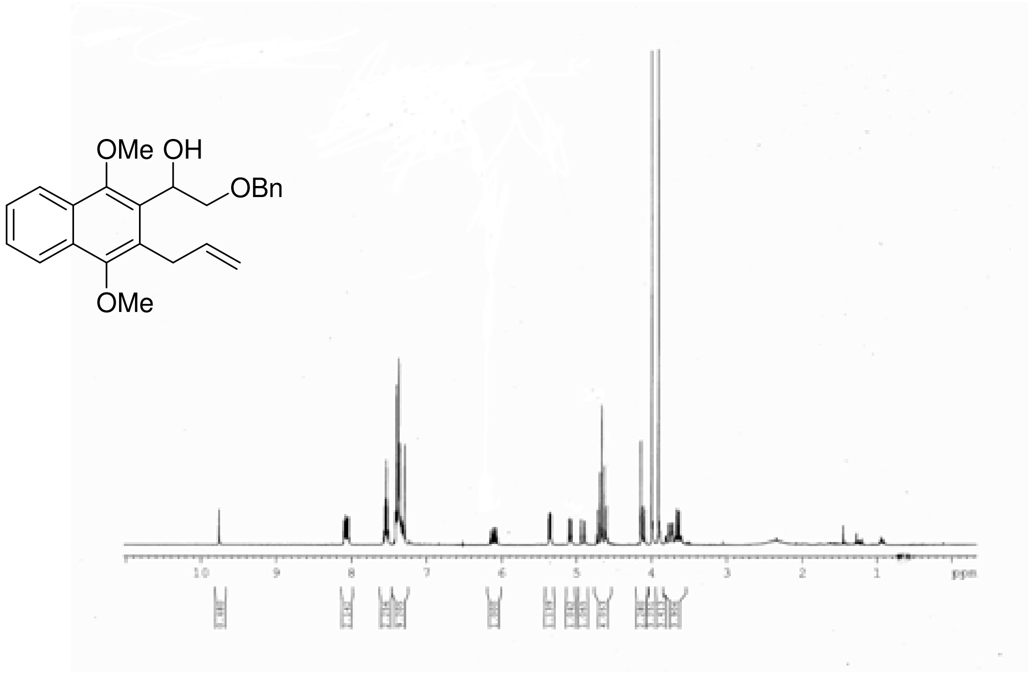
Appendix Figure 6 100 MHz ^{1}C NMR spectrum of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (116)



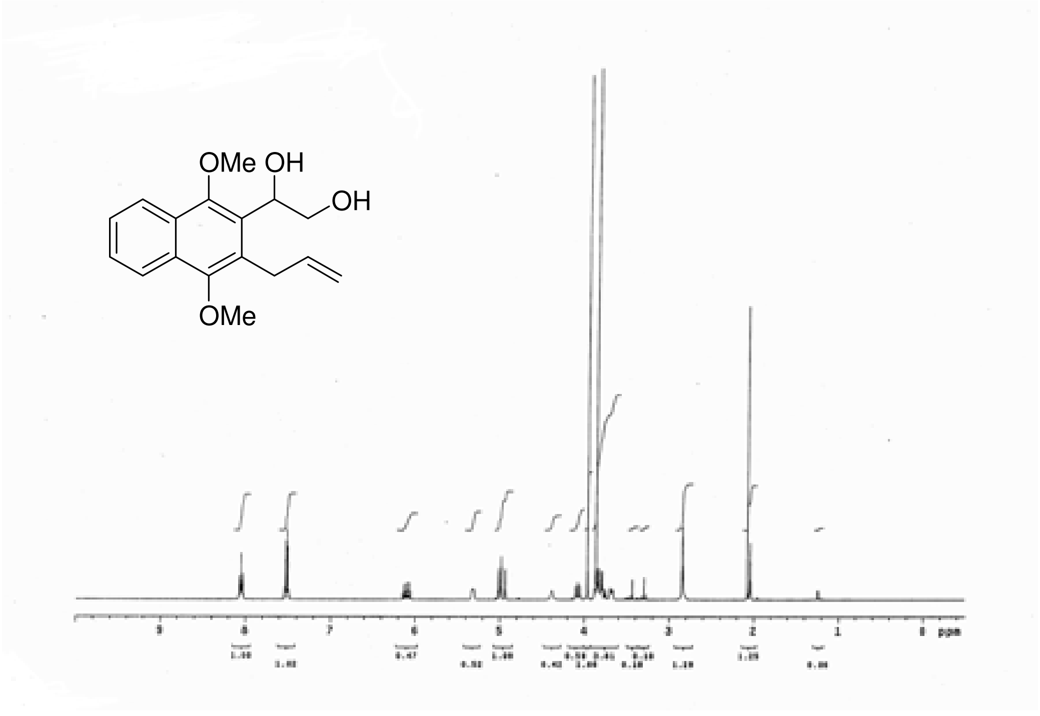
Appendix Figure 7 400 MHz ^{1}H NMR spectrum of 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-ethanol (127)



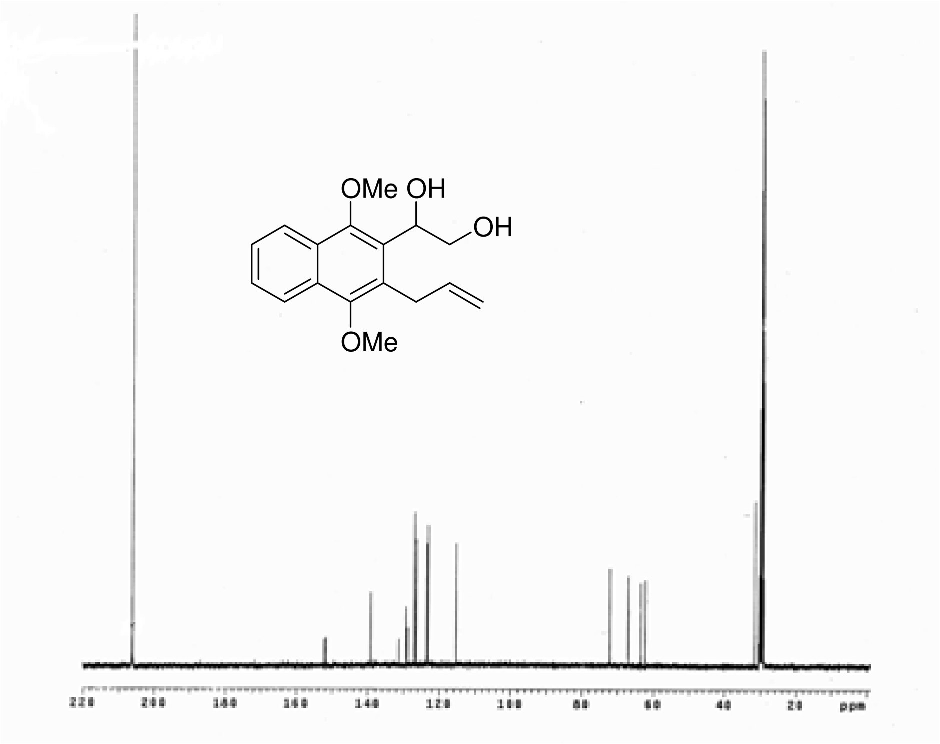
Appendix Figure 8 100 MHz ^{13}C NMR spectrum of 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-ethanol (127)



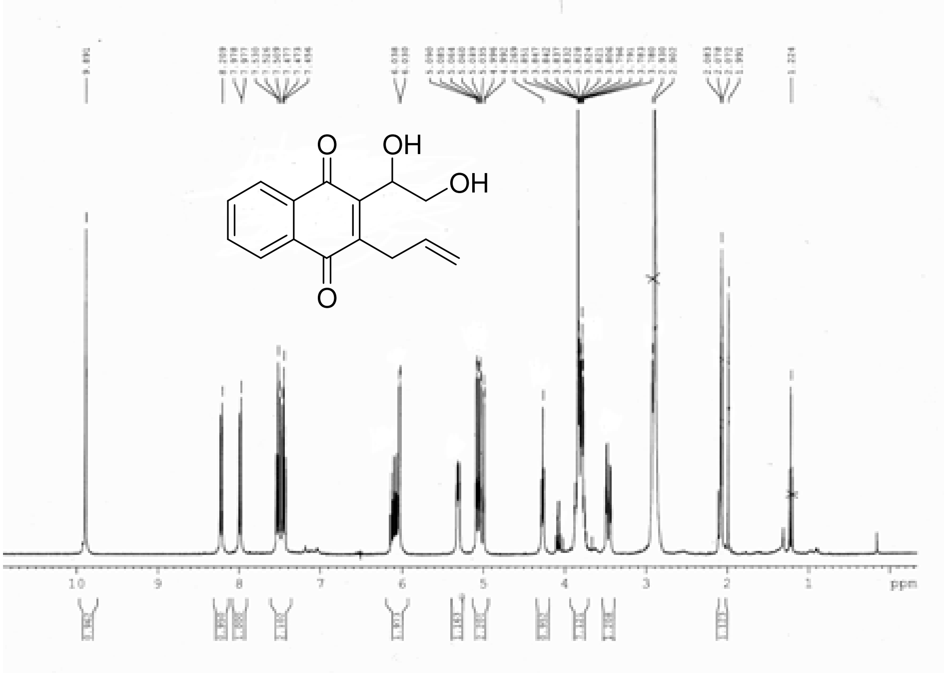
Appendix Figure 9 400 MHz ^{1}H NMR spectrum of 2-benzyloxy-1-(1,4-dimethoxy-naphthalen-2-yl)-ethanol (125)



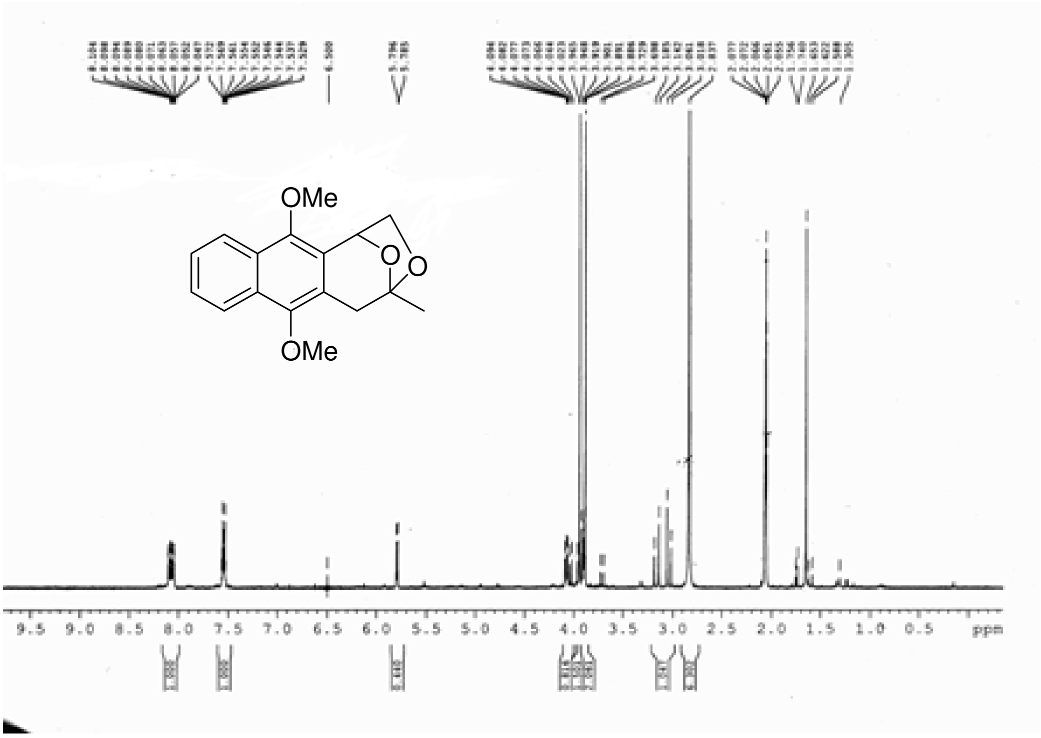
Appendix Figure 10 400 MHz ^{1}H NMR spectrum of 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-ethane-1,2-diol (126)



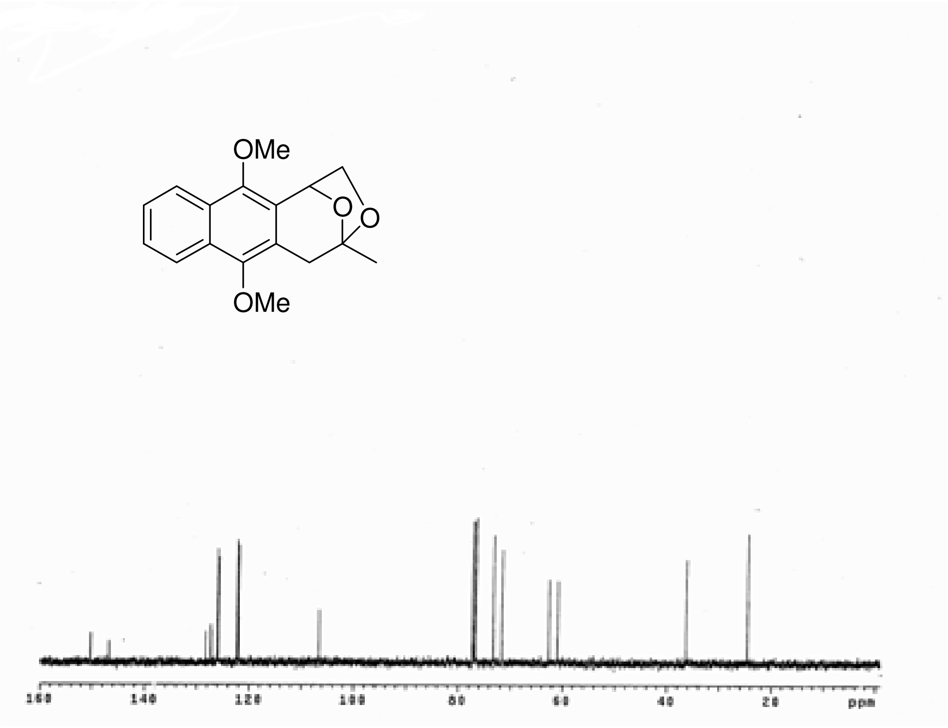
Appendix Figure 11 100 MHz ^{13}C NMR spectrum of 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-ethane-1,2-diol (126)



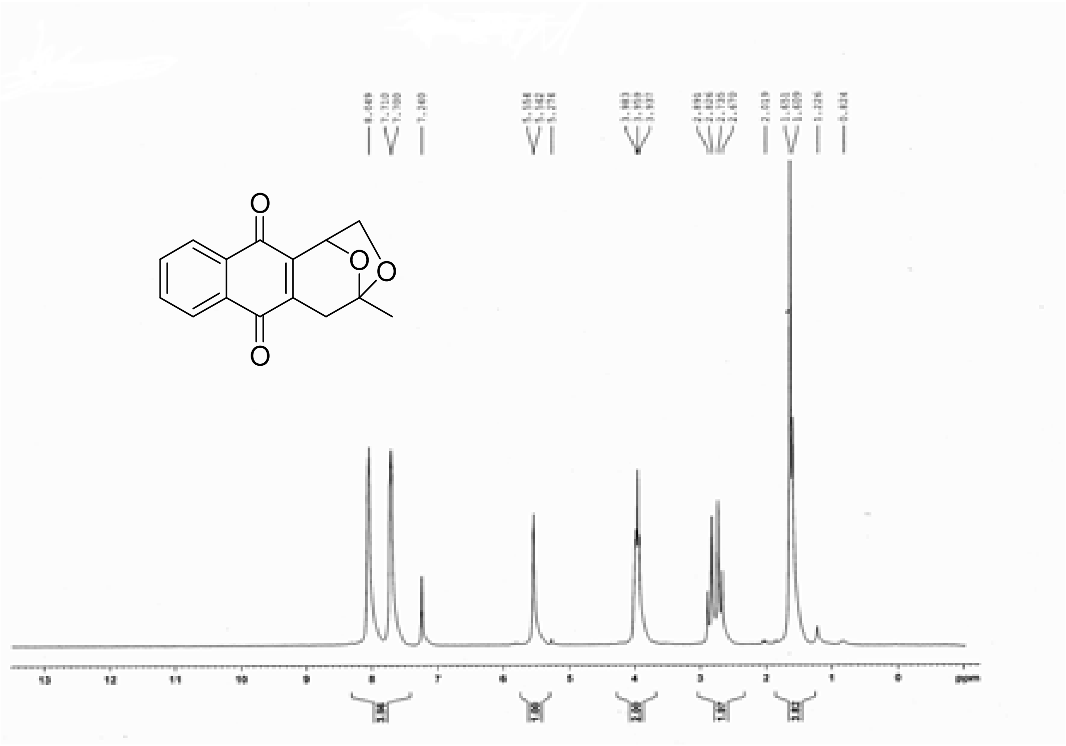
Appendix Figure 12 400 MHz ^{1}H NMR spectrum of 1-(3-allyl-1,4-dimethoxy-naphthalen-2-yl)-ethane-1,2-diol (126)



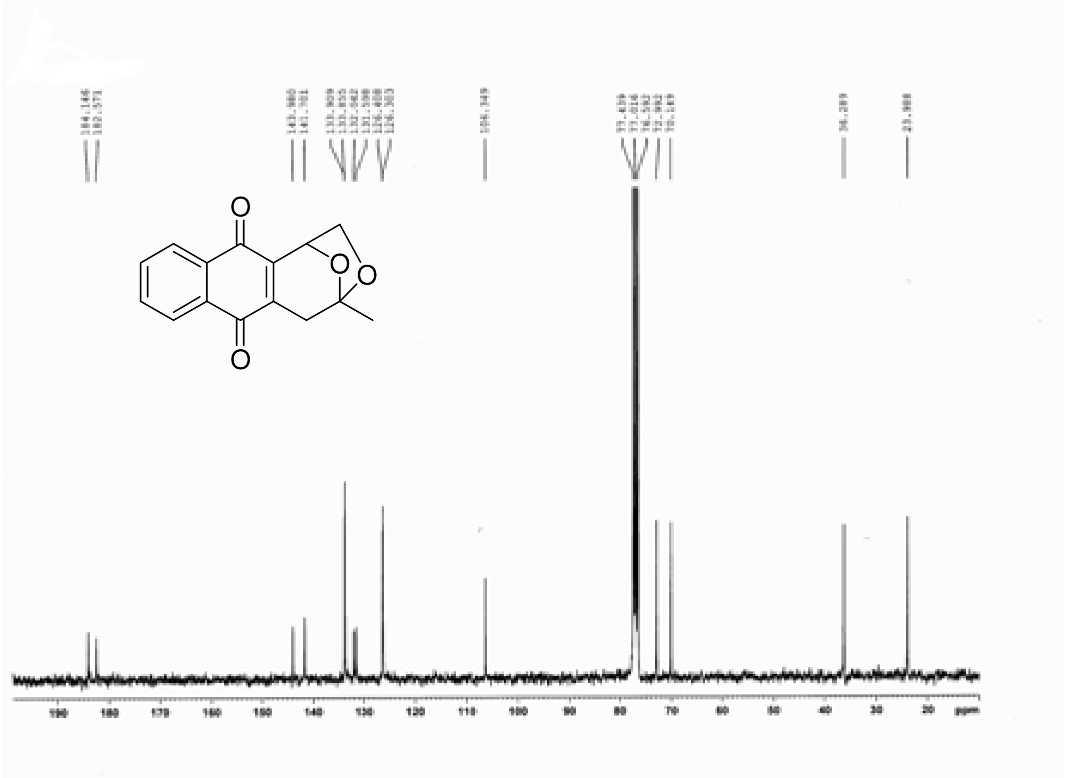
Appendix Figure 13 400 MHz ^{1}H NMR spectrum of oxabicyclic compound (128)



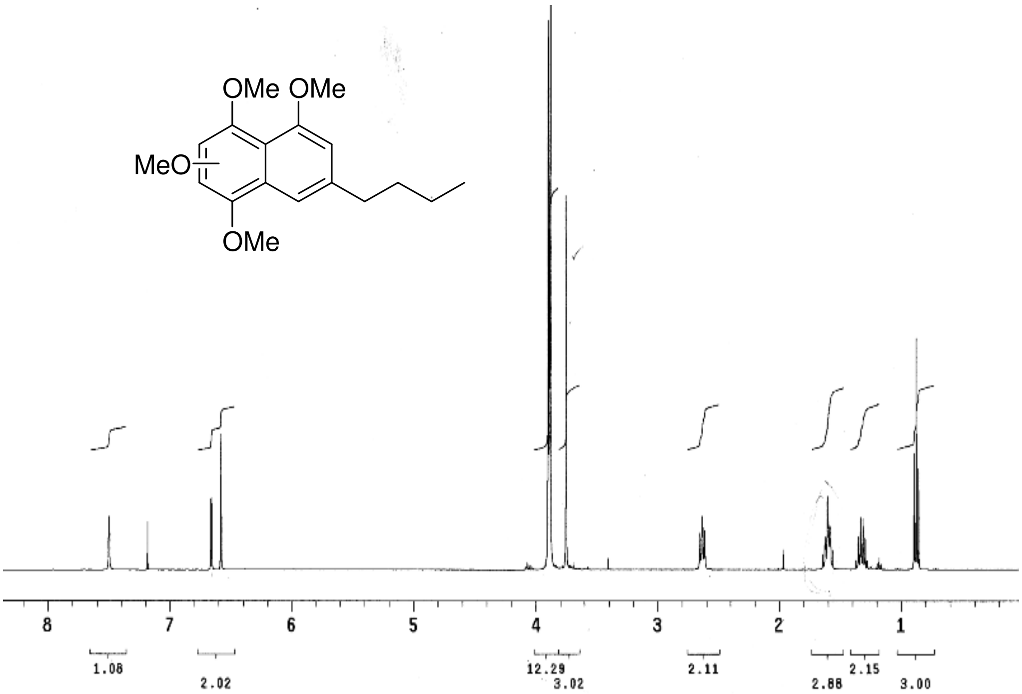
Appendix Figure 14 100 MHz ^{13}C NMR spectrum of oxabicyclic compound (128)



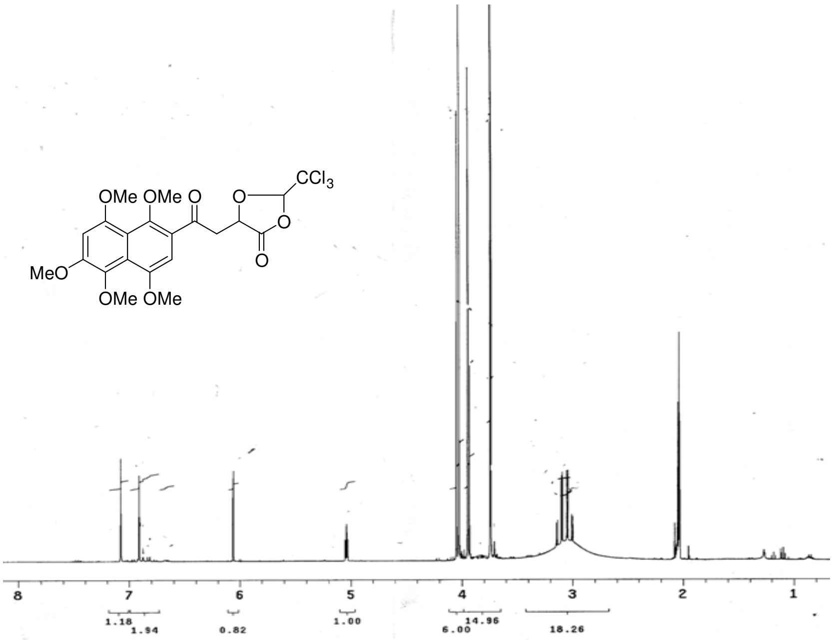
Appendix Figure 15 300 MHz ^{1}H NMR spectrum of Isagarin (11)



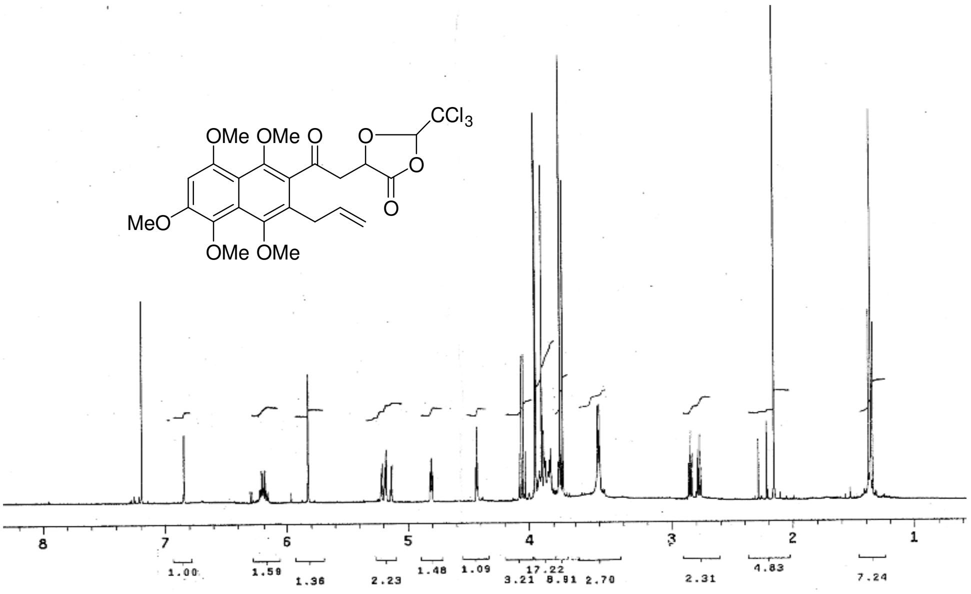
Appendix Figure 16 100 MHz ^{13}C NMR spectrum of Isagarin (11)



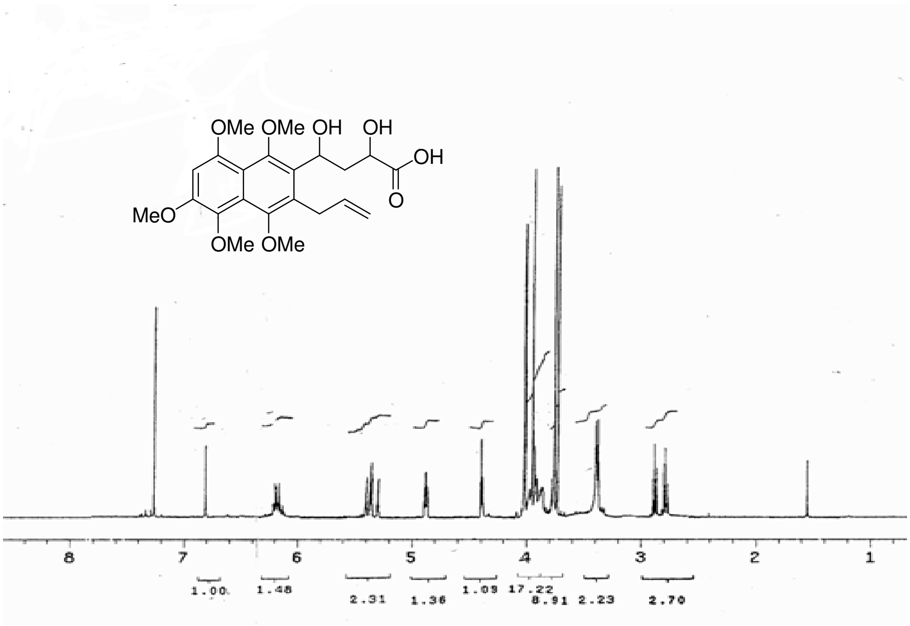
Appendix Figure 17 400 MHz ^{1}H NMR spectrum of byproduct (146)



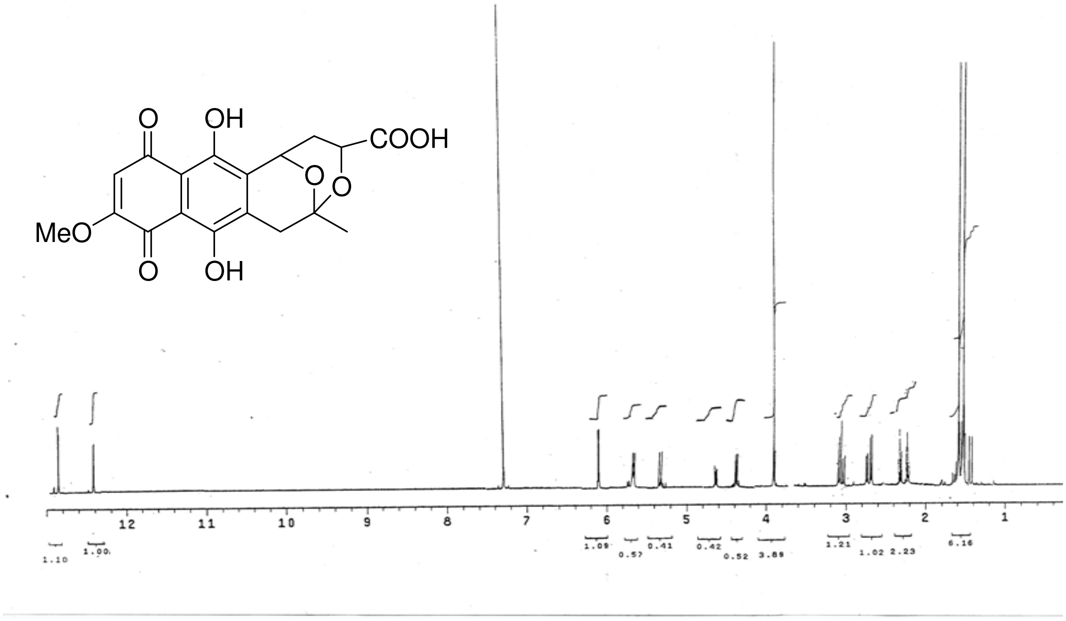
Appendix Figure 18 400 MHz ^{1}H NMR spectrum of 5-[2-oxo-2-(1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-ethyl]-2-trichloromethyl-[1,3] dioxolan-4-one (154)



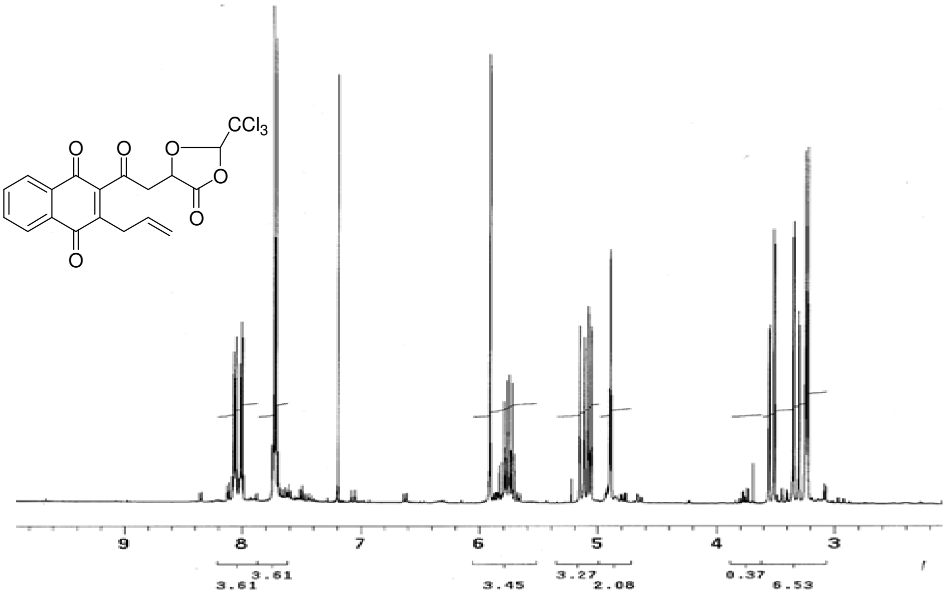
<u>Appendix Figure 19</u> 400 MHz ^{1}H NMR spectrum of 5-[2-(3-allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2-oxo-ethyl]-2-trichloro methyl-[1,3]dioxolan-4-one (157)



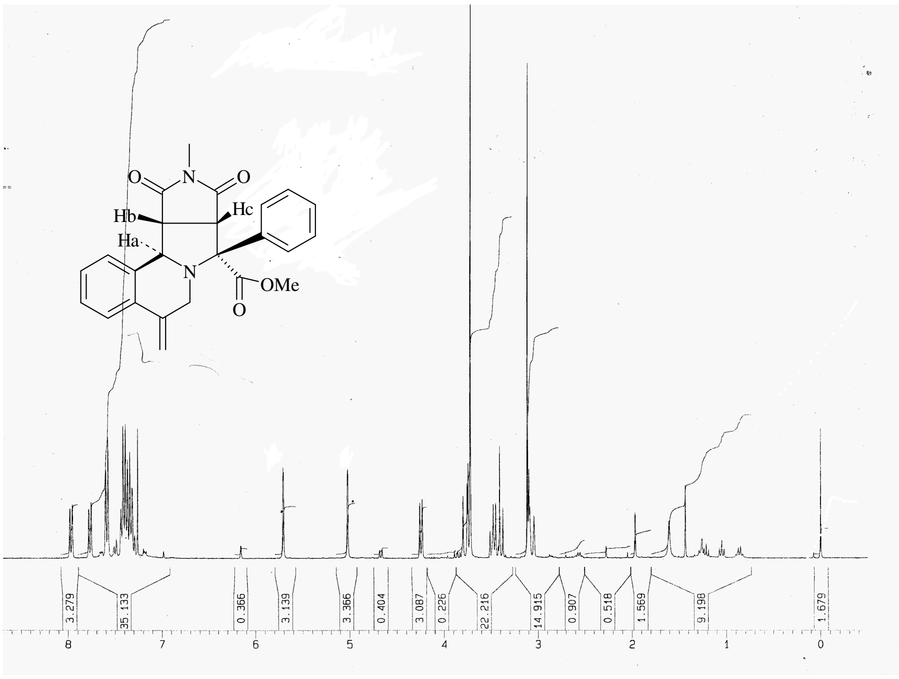
<u>Appendix Figure 20</u> 400 MHz ^{1}H NMR spectrum of 4-(3-allyl-1,4,5,6,8-pentamethoxy-naphthalen-2-yl)-2,4-dihydroxy-butyric acid (159)



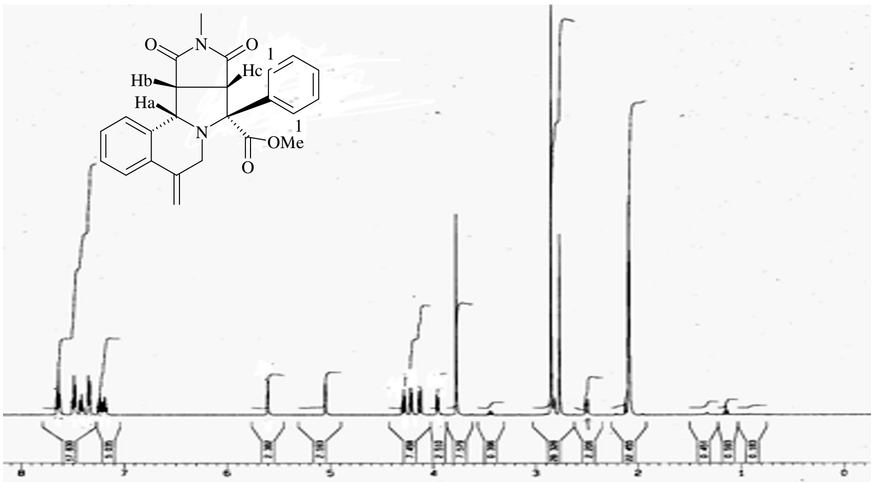
Appendix Figure 21 400 MHz ^{1}H NMR spectrum of marticin (12) and isomarticin (13)



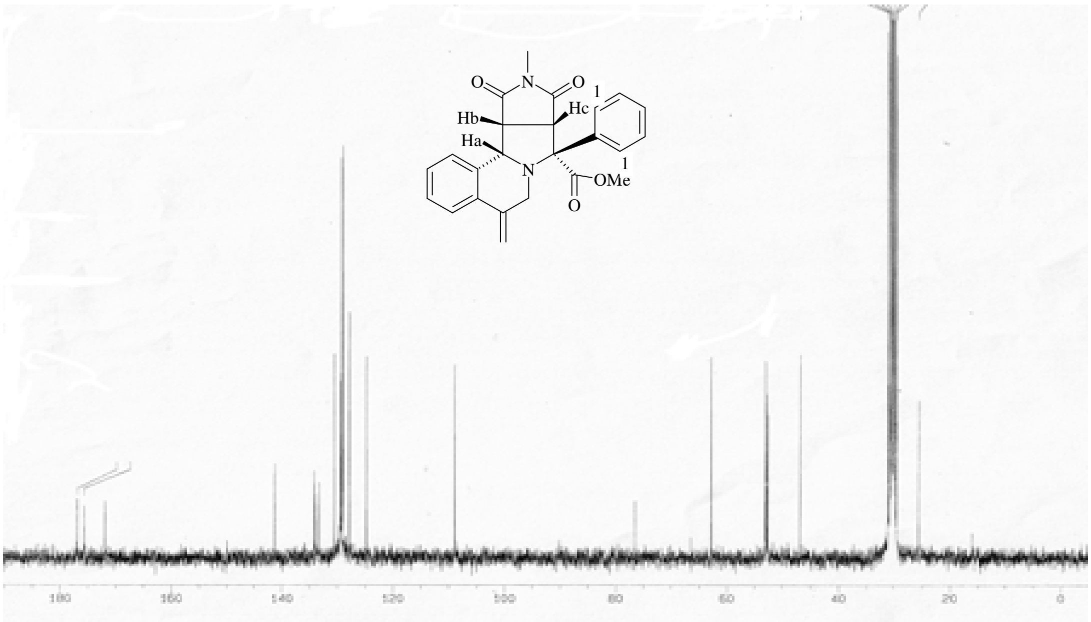
Appendix Figure 22 400 MHz ^{1}H NMR spectrum of 2-allyl-3-[2-(5-oxo-2-trichloromethyl-[1,3]dioxolan-4-yl)-acetyl]-[1,4]naphtho quinone (140)



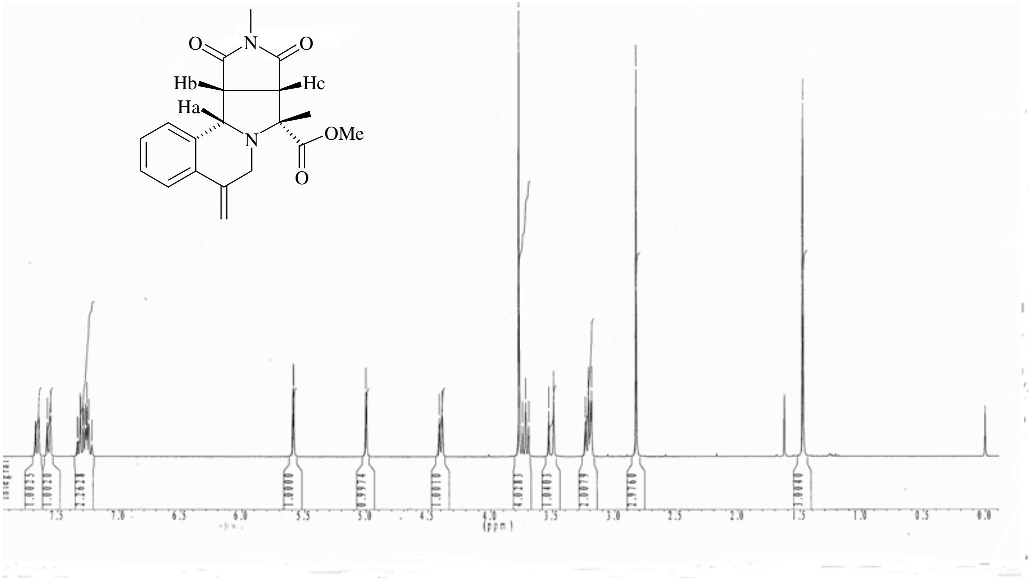
Appendix Figure 23 400 MHz ^{1}H NMR spectrum of methyl (8S,8aS,11R,11bR)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a, 9, 10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (126)



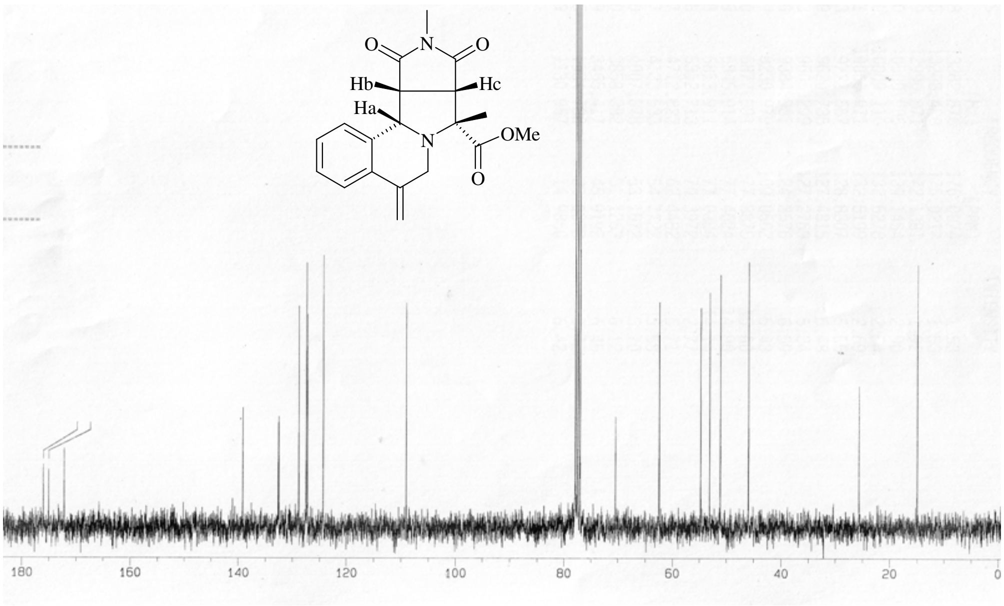
Appendix Figure 24 400 MHz ^{1}H NMR spectrum of methyl (8S,8aS,11R,11bS)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a, 9, 10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (127)



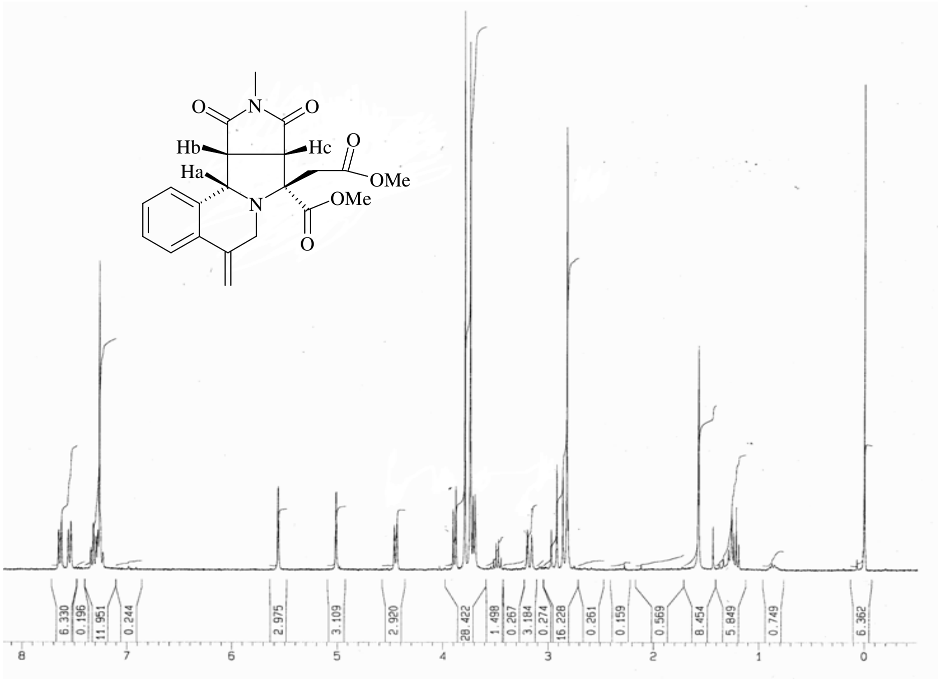
Appendix Figure 25 100 MHz ^{13}C NMR spectrum of methyl (8S,8aS,11R,11bS)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a, 9, 10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (127)



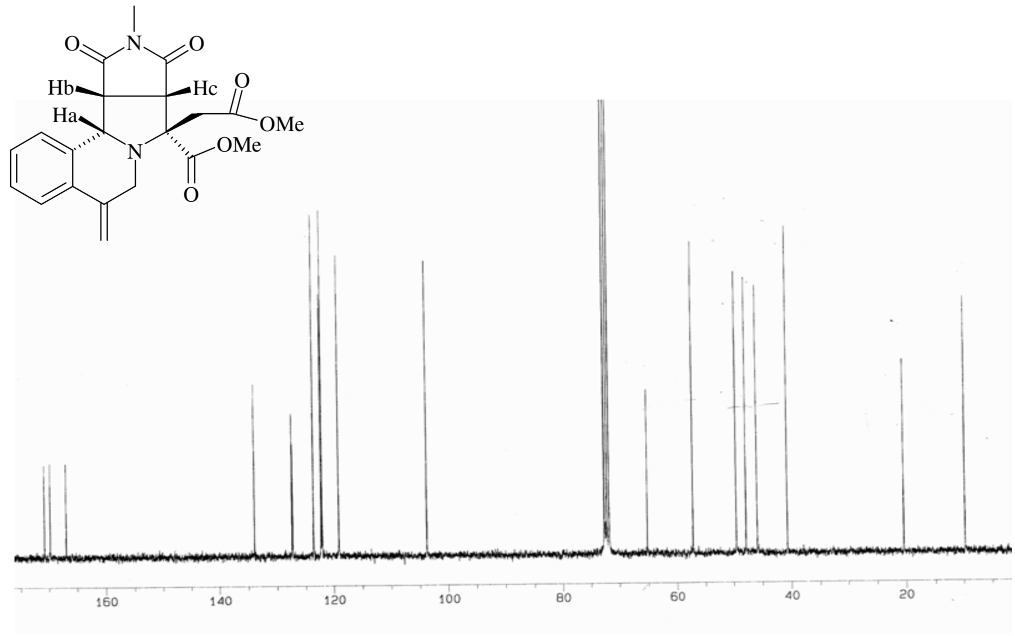
Appendix Figure 26 400 MHz ^{1}H NMR spectrum of methyl (8S,8aS,11R,11bS)-8,10-dimethyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11, 11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (139)



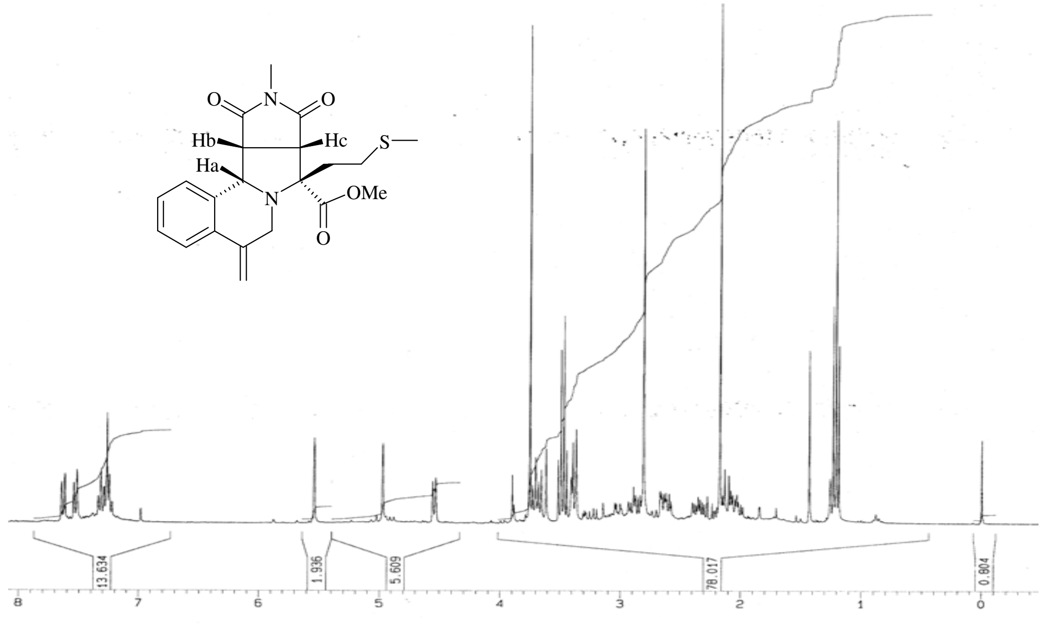
Appendix Figure 27 100 MHz ^{13}C NMR spectrum of methyl (8S,8aS,11R,11bS)-8,10-dimethyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11, 11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (139)



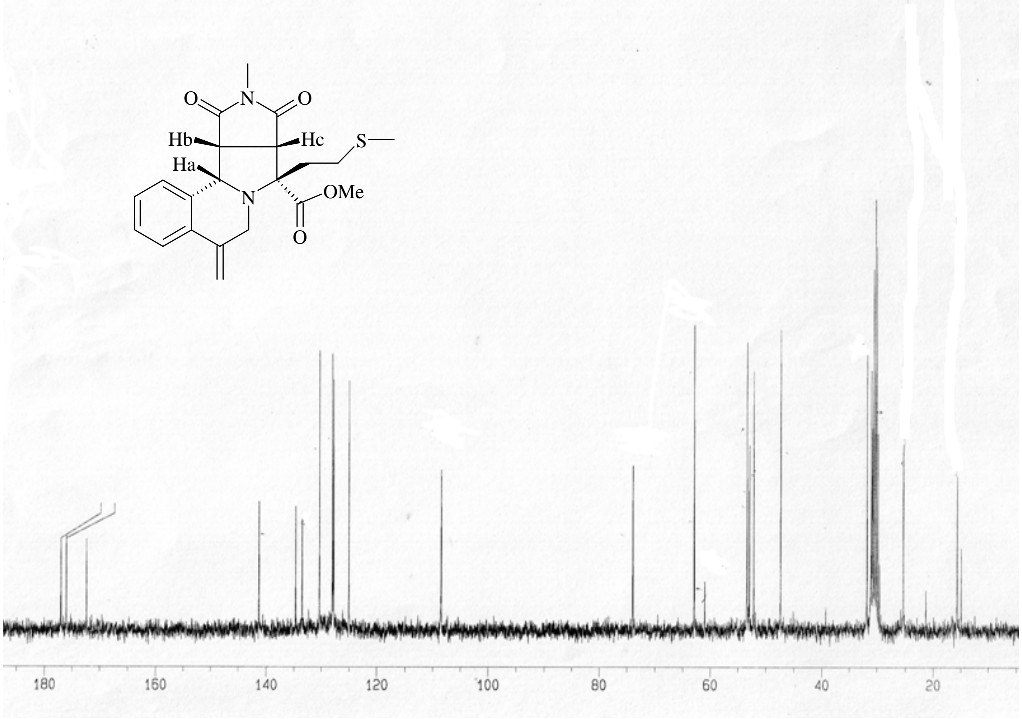
Appendix Figure 28 400 MHz ^{1}H NMR spectrum of methyl (8S,8aS,11R,11bS)-8-(2-methoxy-2-oxoethyl)-10-methyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4] pyrrolo[2,1-*a*] isoquinoline -8-carboxylate (140)



Appendix Figure 29 100 MHz ^{13}C NMR spectrum of methyl (8S,8aS,11R,11bS)-8-(2-methoxy-2-oxoethyl)-10-methyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4] pyrrolo[2,1-*a*] isoquinoline -8-carboxylate (140)

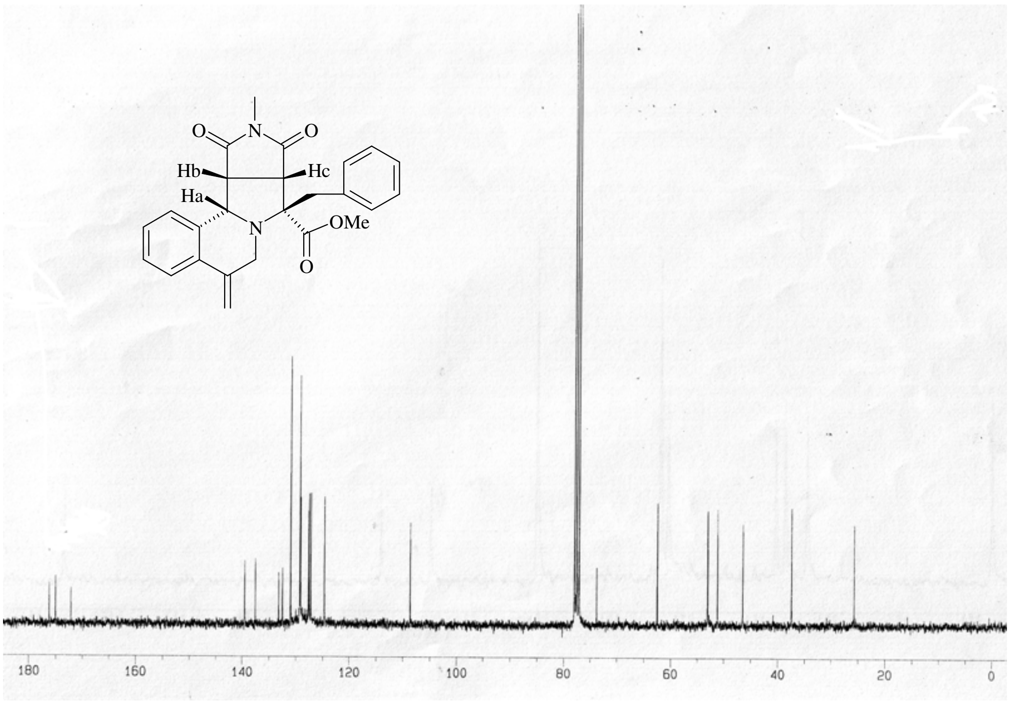


Appendix Figure 30 400 MHz ^{1}H NMR spectrum of methyl (8S,8aS,11R,11bS)-10-methyl-5-methylene-8-[(methylthio)methyl]-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4] pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (141)

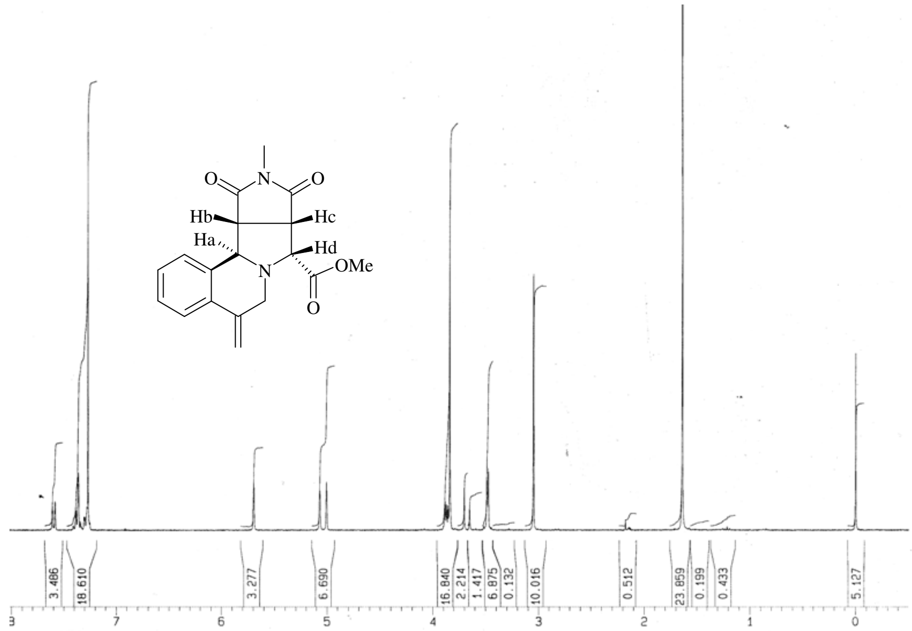


Appendix Figure 31 100 MHz ^{13}C NMR spectrum of methyl (8S,8aS,11R,11bS)-10-methyl-5-methylene-8-[(methylthio)methyl]-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (141)

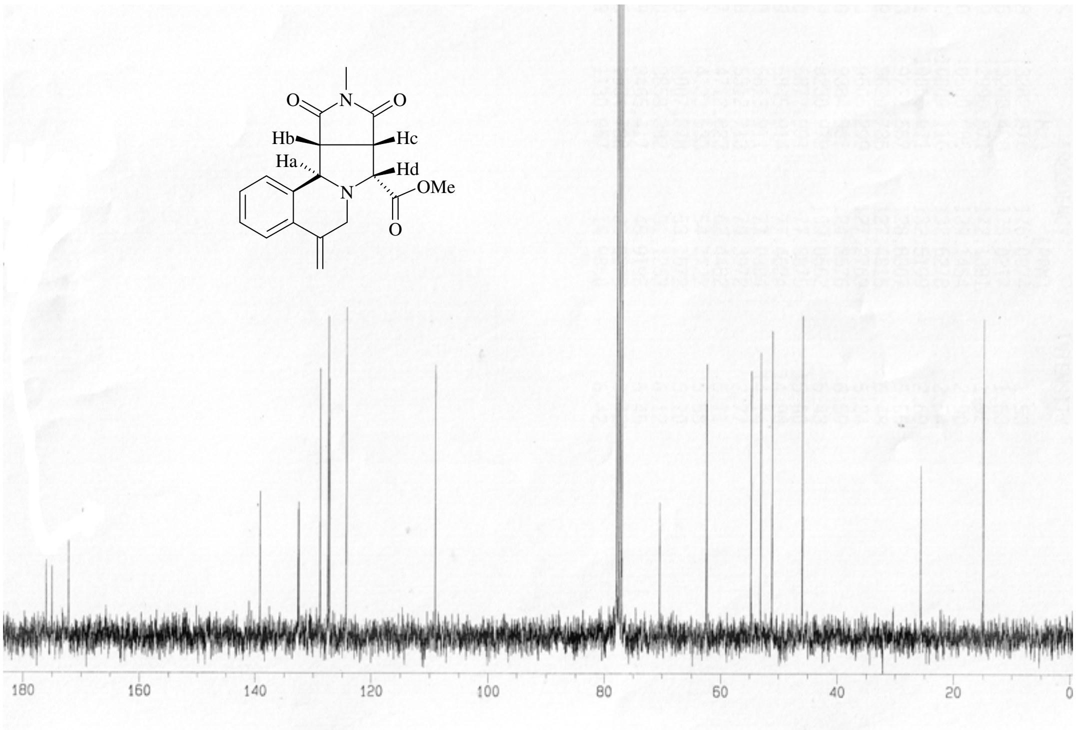
Appendix Figure 32 400 MHz ^{1}H NMR spectrum of methyl (8S,8aS,11R,11bS)-8-benzyl-10-methyl-5-methylene-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (142)



Appendix Figure 33 100 MHz ^{13}C NMR spectrum of methyl (8S,8aS,11R,11bS)-8-benzyl-10-methyl-5-methylene-9,11-dioxo-5,8,8a, 9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (142)



Appendix Figure 34 400 MHz ^{1}H NMR spectrum of methyl (8S,8aS,11R,11bR)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a,9, 10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (143)



Appendix Figure 35 100 MHz ^{13}C NMR spectrum of methyl (8S,8aS,11R,11bR)-10-methyl-5-methylene-9,11-dioxo-8-phenyl-5,8,8a,9,10,11,11a,11b-octahydro-6H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (143)

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2. **Chatchawan Ploysuk**, Boonsong Kongkathip, Ngampong Kongkathip. Synthesis of Isagarin, a Tetracyclic Naphthoquinone via a Palladium-Catalyzed Cyclization. **Syn. Comm**. 2007, 37(9), 1463-1471.