SYNTHESIS OF THE MAIN CARBON SKELETON OF SOOTEPENSEONE AND ITS DERIVATIVES

APIWAT CHOMPOOSOR

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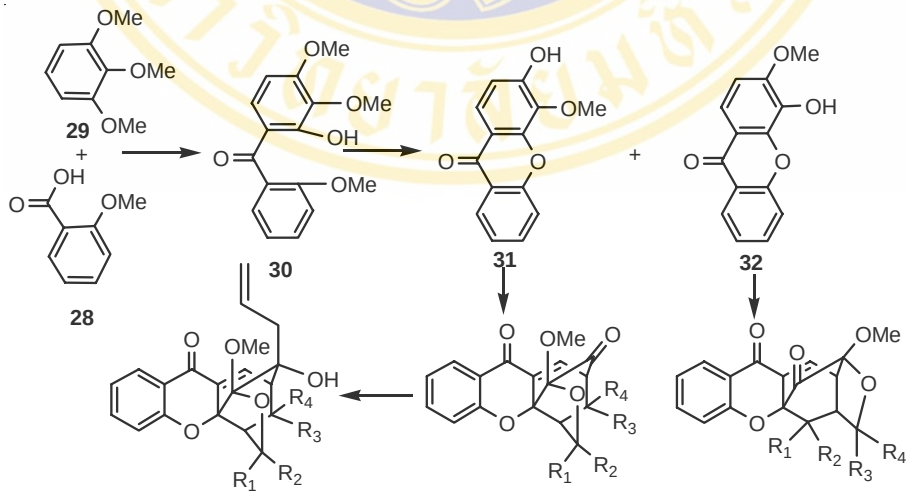
ABSTRACT

A convergent synthetic approach to the main carbon skeleton of the sootepenseone was investigated, utilizing an oxidative allylation, followed by an intramolecular Diels-Alder cyclization strategy of the constant tricyclic core.

The synthesis starts from commercially available 2-methoxybenzoic acid (**28**) and 1,2,3-trimethoxybenzene (**29**). The synthetic strategy involves formation of benzophenone **30**, cyclization to xanthone system followed by demethylation to yield xanthones **31** and **32**. Treatment of the xanthones **31** and **32** with phenyliodonium(III) bistrifluoroacetate (PIFA) in the presence of various allyl alcohols yielded the corresponding tricyclic products **107**, **108**, **110**, **114**, **115**, **116**, **117** and **118**. Compounds **110** and **108** contain the basic carbon skeleton present in naturally occuring sootepenseone (**9**) and 1-*O*-methylneobractatin (**7**), respectively. Attempts to promote allylation reaction at the ketal carbon, however, were not successful, leading to the undesired compounds **119**, **120** and **121** in low yields.



KEY WORDS: SOOTEPENSEONE, MASKED *o*-BENZOQUINONE
92 P. ISBN 974-04-6392-4

การศึกษาการสังเคราะห์โครงสร้างหลักของซูทีเพนซีโอนและอนุพันธ์ (SYNTHESIS OF THE MAIN CARBON SKELETON OF SOOTEPENSEONE AND ITS DERIVATIVES)

อภิวัฒน์ ชมภูสอ 4536971 SCOC/M

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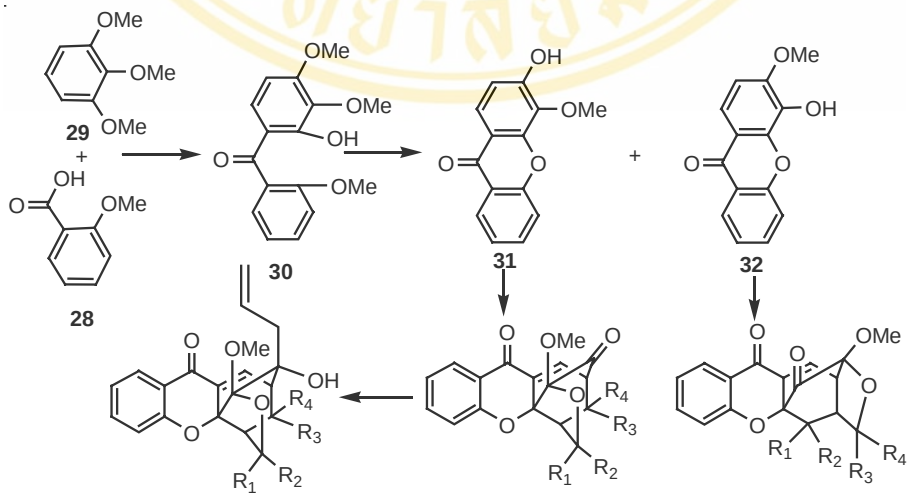
บทคัดย่อ

จากการศึกษาการสังเคราะห์โครงสร้างหลักของสารจำพวกซูทีเพนซีโอนและอนุพันธ์ พบว่าสามารถทำได้จากปฏิกิริยาออกซิเดชัน แล้วตามด้วยการปิดวงแบบ intramolecular Diels-Alder ในการสังเคราะห์เราใช้ 2-methoxybenzoic acid (**28**) และ 1,2,3-trimethoxybenzene (**29**) เป็นสารตั้งต้น ในปฏิกิริยานี้ผลิตภัณฑ์ที่ได้คือ เบนโซฟีโนน **30** ซึ่งจะเกิดปฏิกิริยาปิดวงได้แซนโทน ตามด้วยปฏิกิริยาการเสียหมู่เมธิลให้ผลิตภัณฑ์เป็นแซนโทน **31** และ **32** เมื่อนำเอาแซนโทน **31** และ **32** ที่ได้ไปทำปฏิกิริยากับไฮเปอร์เวเลนซ์ไอโอดีนในแอลลิลแอลกอฮอล์แบบต่างๆ จะได้สารประกอบ **107**, **108**, **110**, **114**, **115**, **116**, **117** และ **118** โดยพบว่าสาร **110** และ **108** ที่สังเคราะห์ได้เป็นโครงสร้างหลักของสารที่พบได้ในธรรมชาติจำพวก sootepenseone (**9**) และ 1-*O*-methylneobractatin (**7**) ตามลำดับ หลังจากนั้นได้นำสารประกอบ **107**, **110** และ**114** ที่ได้ไปทำปฏิกิริยาแอลลิเลชัน โดยที่ปฏิกิริยาเกิดขึ้นที่คาร์บอนิลคาร์บอนแทนที่จะเกิดที่คีทาลคาร์บอน ดังนั้นจึงได้สารประกอบ **119**, **120** และ **121** ในเปอร์เซ็นผลได้ที่ต่ำ



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CONTENTS

LIST OF ABBREVIATIONS

Ar	aromatic
b.p.	boiling point
br	broad
brs	broad singlet
calcd.	calculated
$CDCl_3$	deuterochloroform
conc.	concentration
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
DMF	*N*,*N*-dimethylformamide
DMSO-d_6	hexadeuterodimethylsulfoxide
equiv	equivalent
EtOAc	ethyl acetate
g	gram
h	hour (s)
Hz	hertz
HRMS	high resolution mass spectrometry
IR	infrared
J	coupling constant
Lit.	literature

LIST OF ABBREVIATIONS (Cont.)

m	multiplet
M	molar
Me	methyl
MHz	megahertz
min	minute (s)
mg	milligram
mL	milliliter
mmol	millimole
m/z	a value of mass divided by charge
M^+	molecular ion
m.p.	melting point
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
Ph	phenyl
ppm	part per million
q	quartet
ref.	reference
rt	room temperature
s	singlet
SiO_2	silica gel
t	triplet
THF	tetrahydrofuran

LIST OF ABBREVIATIONS (Cont.)

TMS	tetramethylsilane
TLC	thin-layer chromatography
δ	chemical shift
ν_{max}	maximum absorption frequencies
°C	degree Celsius
%	percentage

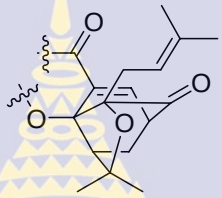
THE RELEVANCE OF THE RESEARCH WORK TO THAILAND

The research work is part of the basic research on the utilization of Thai plant for pharmaceutical purposes. The target compound for the synthetic endeavor was isolated from Thai plant, *Dasymaschalon sootepense*, and has been demonstrated to have antitumor activity. The research work will further the goal of developing this compound or its analogues into therapeutic agents. It also provides an opportunity to use the plant itself for curing the disease. This research effort is an example of an attempt to utilize the natural resource of the country for the well-being of its people with a help of science and technology.

CHAPTER I
INTRODUCTION

1. Naturally occuring compounds containing the 4-oxatricyclo[4.3.1.0]decan-2-one skeleton

An intriguing 4-oxatricyclo[4.3.1.0]decan-2-one ring system **1** was found in a growing class of biologically active natural products.[1, 2]



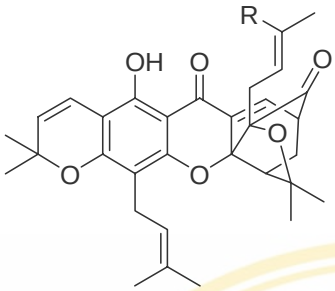
1

Among them, morellin (**2**) produced by *Garcinia morella* was first discovered as a xanthonoid natural product containing this 4-oxatricyclic system.[3] The genus *Garcinia* were well known to be rich in xanthones with enormous diversity in both structure and biological activities. Many xanthones were reported to have interesting biological activities such as cytotoxic, antitumor, antiinflammatory, antimicrobial, antifungal and monoxanthine oxidase activities.[4] Since the initial disclosure of morellin structure, many other natural products sharing the same caged skeleton have been isolated, namely morellic acid (**3**) and forbesione (**4**) (isolated from *Garcinia forbesii*). A class of prenylated xanthones structurally related to morellin, such as bractatin (**5**), 1-*O*-methylbractatin (**6**) and 1-*O*-methylneobractatin (**7**), were reported to be isolated from *G. morella, G. hanburyi, G. forbesii, G. gaudichaudii and G. lateriflora*.[2, 4]

Ollis *et al*. reported the isolation of a complex prenylated xanthone, gambogic acid (**8**), from the resin of *G. hanburyi* collected in Thailand.[5] Its structural assignments were based on the analysis of NMR spectral data in comparison with those of morellin.[6] Gambogic acid (**8**), which was found in appreciable quantity from the resin of various plants in the Guttiferae family, was reported to have been used as natural pigment.

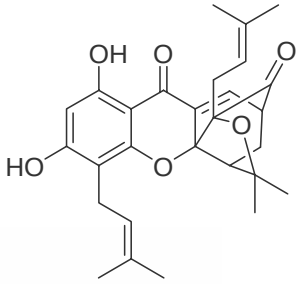
Tada and co-workers isolated phloroglucinol derivatives from the Guttiferae family and reported that the crude resin of *G. hanburyi* was found to exhibit potent cytotoxicity.[7] In addition to the known gambogic acid (**8**) as a major active constituent, the resin was also found to contain several gambogic acid derivatives.

Recently, Reutrakul *et al*. isolated a caged xanthone, namely sootepenseone (**9**) from *Dasymaschalon sootepense*.[8] This discovery represents the first isolation of a "caged" xanthone from plant belonging to the Annonaceae family. The methanol extract which exhibited cytotoxic activity against L 1210 cell lines, was partitioned with *n*-hexane and ethyl acetate, respectively. After exhaustive chromatographic purification, compound **9** was isolated from the ethyl acetate fraction.

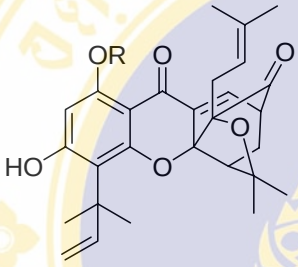


2: R = CHO : morellin

3: R = CO_2H : morellic acid

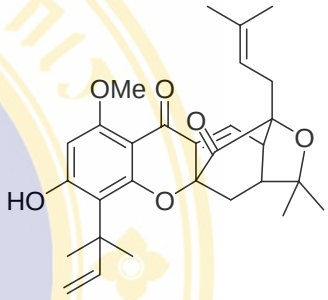


4: forbesione

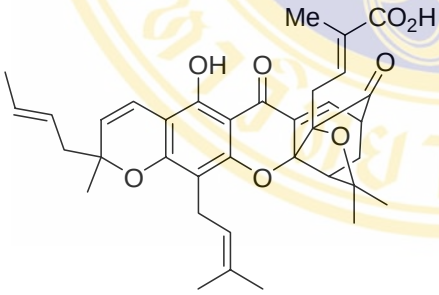


5: R = H : bractatin

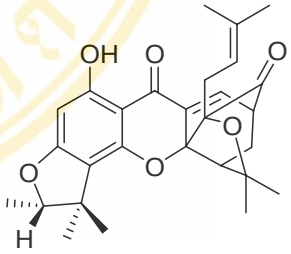
6: R = Me :1-*O*-methylbractatin



7: 1-*O*-methylneobractatin



8: gambogic acid



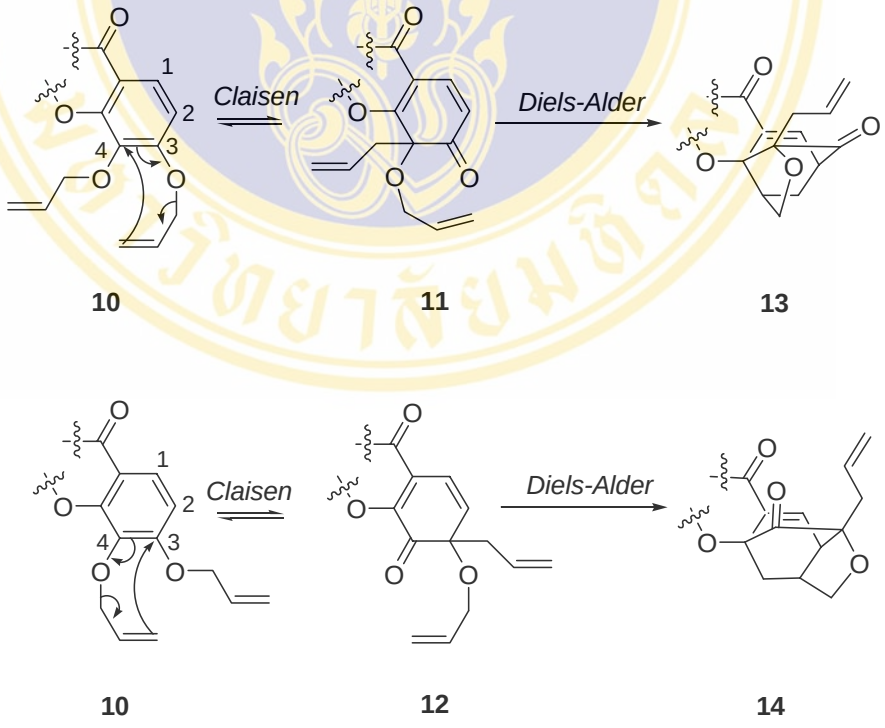
9: sootepenseone

Scheme 1

In addition to their striking structural architecture, most of these compounds exhibit interesting antibacterial and cytotoxic activities.[9a, 9b] Their biological activities were proposed partially, if not exclusively, due to the presence of the 4-oxatricyclo [4.3.1.0]decan-2-one moiety since a simple planar xanthones alone did not show any marked biological profiles.[10]

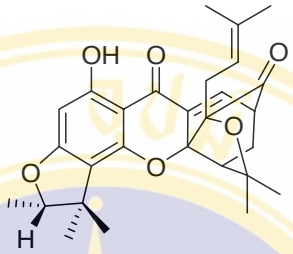
From the biosynthetic standpoint, these natural products were presumed to derive from a common benzophenone intermediate of a mixed shikimate-acetate pathway that had undergone plant-specific prenylation, rearrangement and oxidation reaction.[11, 12]

An elegant proposal for the biosynthesis of gambogic acid had been put forward in the early 1970s by Quillinan *et al.*[10, 12] The caged scaffold of the molecule was proposed to naturally arise from a tandem Claisen/Diels-Alder rearrangement. As a result of this postulate, compound **10** was prepared and was subjected to the conditions for tandem Claisen/Diels-Alder rearrangement. As shown in Scheme 2, an initial non-regioselective Claisen rearrangement involving migration of the allyloxy group at C-3 to the *ortho* position led to an intermediate **11** which underwent Diels-Alder cyclization to give compound **13**. An alternative pathway may be taken place in which the Claisen rearrangement involved the allyloxy group at C-4, leading to an intermediate **12** which underwent Diels-Alder cyclization to yield compound **14.**



Scheme 2

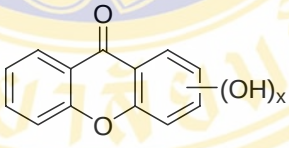
Sootepenseone (**9**) is a caged xanthone that was found to have an antitumor activity. Its intricate molecular structure and important biological activity attract us to initiate a synthetic approach to synthesize the compound and its analogues in an adequate amount for further biological evaluations.



9: sootepenseone

2. Syntheses of the xanthone core

Traditionally, xanthones syntheses involve the connection of two aryl fragments to form the internal pyranone ring **15**. There are numerous other routes, but none is of general application and some require uncommon starting materials or involve a number of steps.[13] The approaches to the synthesis of compound of this type are summarized in Scheme 3.



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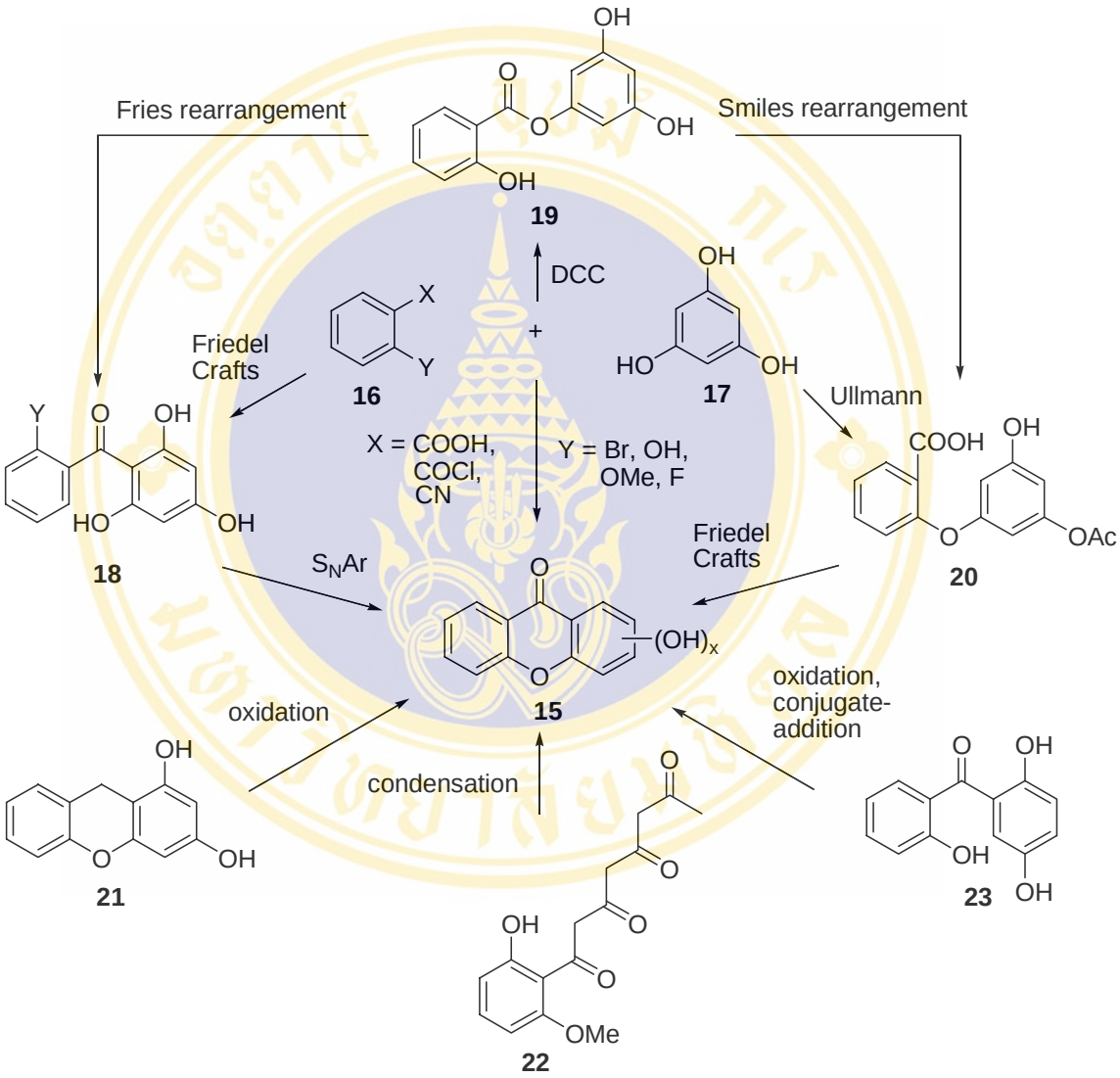
The carbonyl connection can be formed by three reaction types: (i) Friedel-Crafts acylation of compounds **16** and **17** to give benzophenone **18**,[14] (ii) biaryl ester migration, such as the Fries rearrangement of compound **19**;[15] or (iii) aryl anion addition to a benzoyl chloride.[16] The ether linkage can be formed intermolecularly by the Ullmann method,[17] or intramolecularly by an S_NAr mechanism[18] or Smiles rearrangement.[19] The xanthone skeleton can also be formed from two aryl components in one step by either a combined Friedel-Crafts/aryl condensation,[18] or by aryl anion addition to salicylaldehyde followed by reduction to the xanthene **21** and eventual oxidation to the xanthone **15** (Tanase's

method).[20] Some less conventional methods for xanthone synthesis are also known, e.g. conversions of compound **22** or **23** to compound **15**.[21]

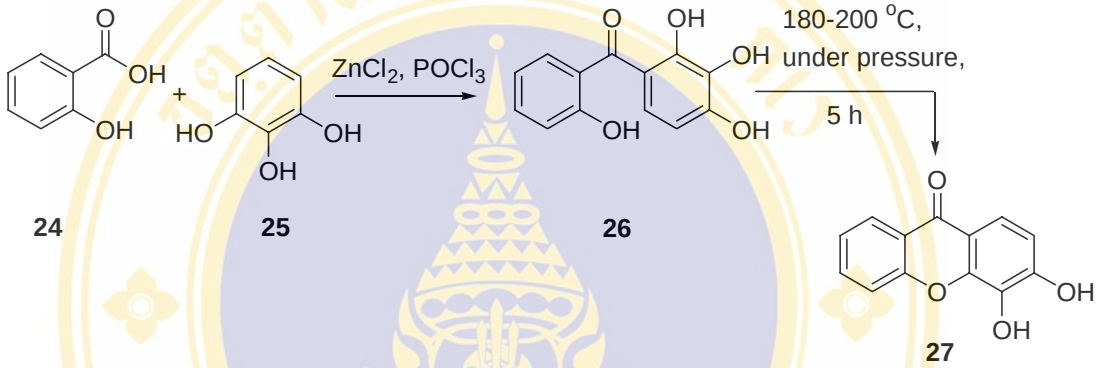


Scheme 3

A number of highly oxygenated xanthones have been obtained through the corresponding benzophenone intermediates synthesized under the Friedel-Crafts reaction conditions. The alkoxybenzophenone intermediates thus obtained are cyclized under a

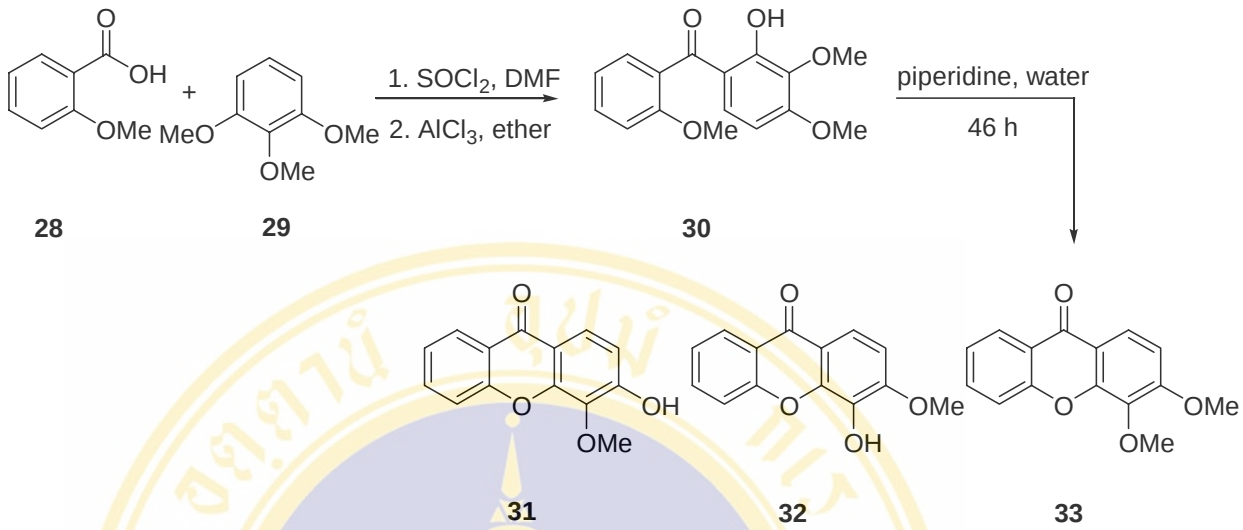
variety of reaction conditions, involving the use of aqueous alkali hydroxides, for example, sodium hydroxide, potassium hydroxide and aqueous piperidine.[22]

Although the method described by Grover *et al.* had serious limitations, it has been used extensively for the synthesis of phytoxanthones.[23] The synthesis comprised condensation of an *o*-hydroxybenzoic acid (**24**) with phenol **25** in the presence of zinc chloride and phosphorus oxytrichloride, leading to benzophenone **26** followed by thermolysis of **26** under pressure to give xanthone **27** (Scheme 4).



Scheme 4

Unfortunately, many natural xanthones are not readily accessible by the existing methods and an alternative approach was required. Synthetic considerations largely concern orientation control and selective methylation and demethylation. The synthesis described by Grover *et al*. starting from salicylic acid and phenol derivatives does not always give the required xanthones, and the reaction may be accompanied by unwanted demethylations. The procedure may also lead to benzophenone formation or a multiplicity of products. The alternative now described is an efficient general synthesis, and involves formation of 2-hydroxy-2'-methoxybenzophenones (**30**), followed by the quantitative elimination of methanol in the presence of alkali to give xanthones (Scheme 5).[24]

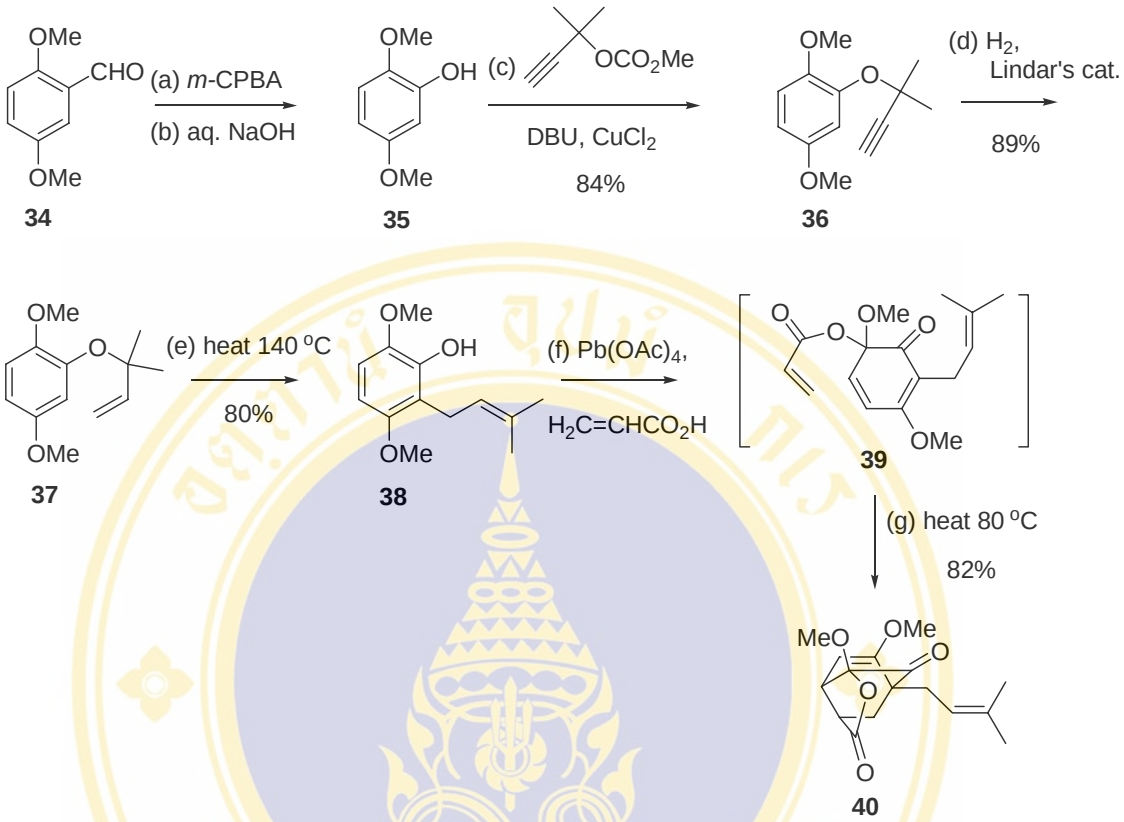


Scheme 5

3. Synthetic approaches to the 4-oxatricyclo[4.3.1.0]decan-2-one core

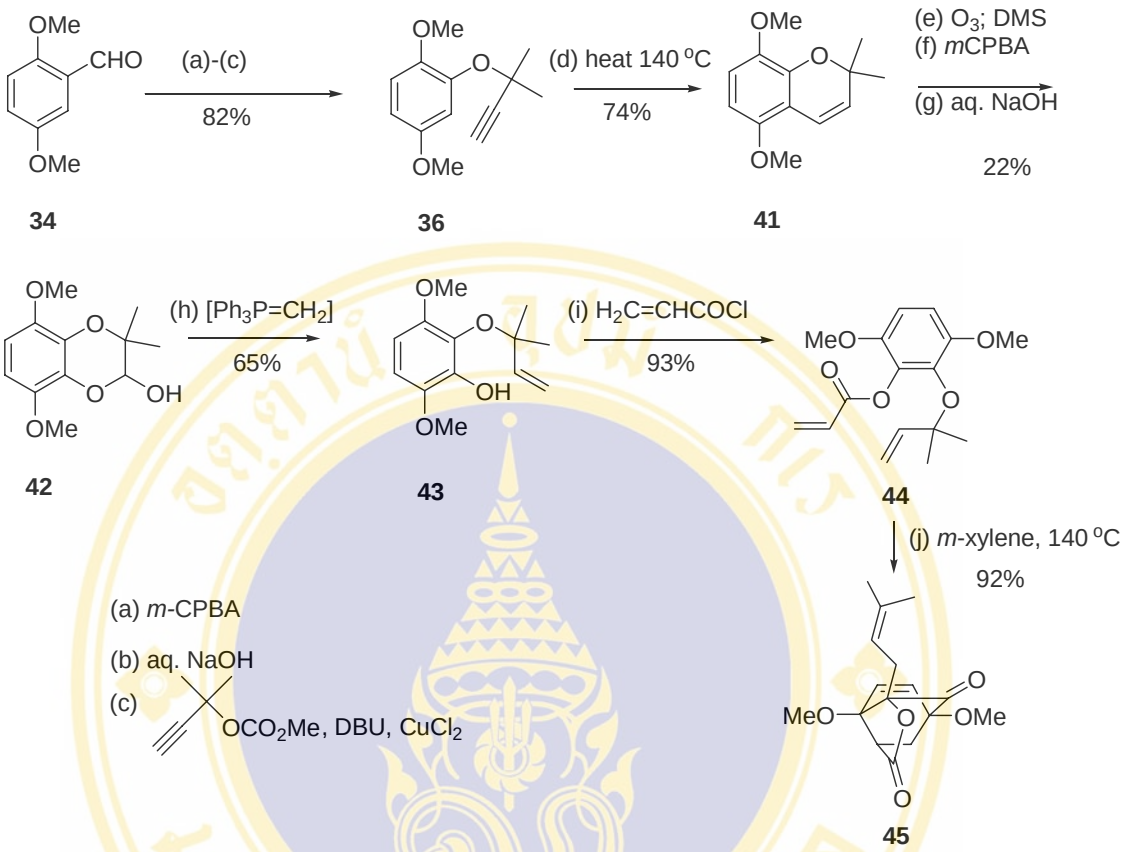
Theodorakis and co-workers described two different routes to synthesize the polycyclic scaffold encountered in many of the *Garcinia* derived natural products.[10]

The first approach employed a Wessely oxidation/Diels-Alder reaction shown in Scheme 6 starting from 2,5-dimethoxybenzaldehyde **34**. Compound **34** was converted to compound **38** in five steps and Wessely oxidation of **38** by treatment with $Pb(OAc)_4$ in acrylic acid produced unstable intermediate **39** which subsequently underwent intramolecular Diels-Alder cycloaddition to give tricyclic lactone **40**.



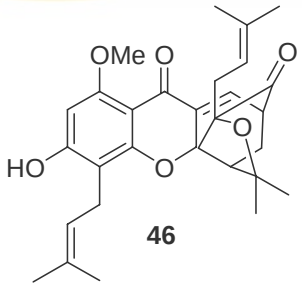
Scheme 6

The second approach was based on a tandem Claisen/Diels-Alder rearrangement which could produce the desired tricyclic compound **45** in 10 steps starting from commercially available 2,5-dimethoxybenzaldehyde (**34**) as shown in Scheme 7. Intramolecular Diels-Alder cyclization of **44** under refluxing *m*-xylene afforded the tricyclic compound **45**.



Scheme 7

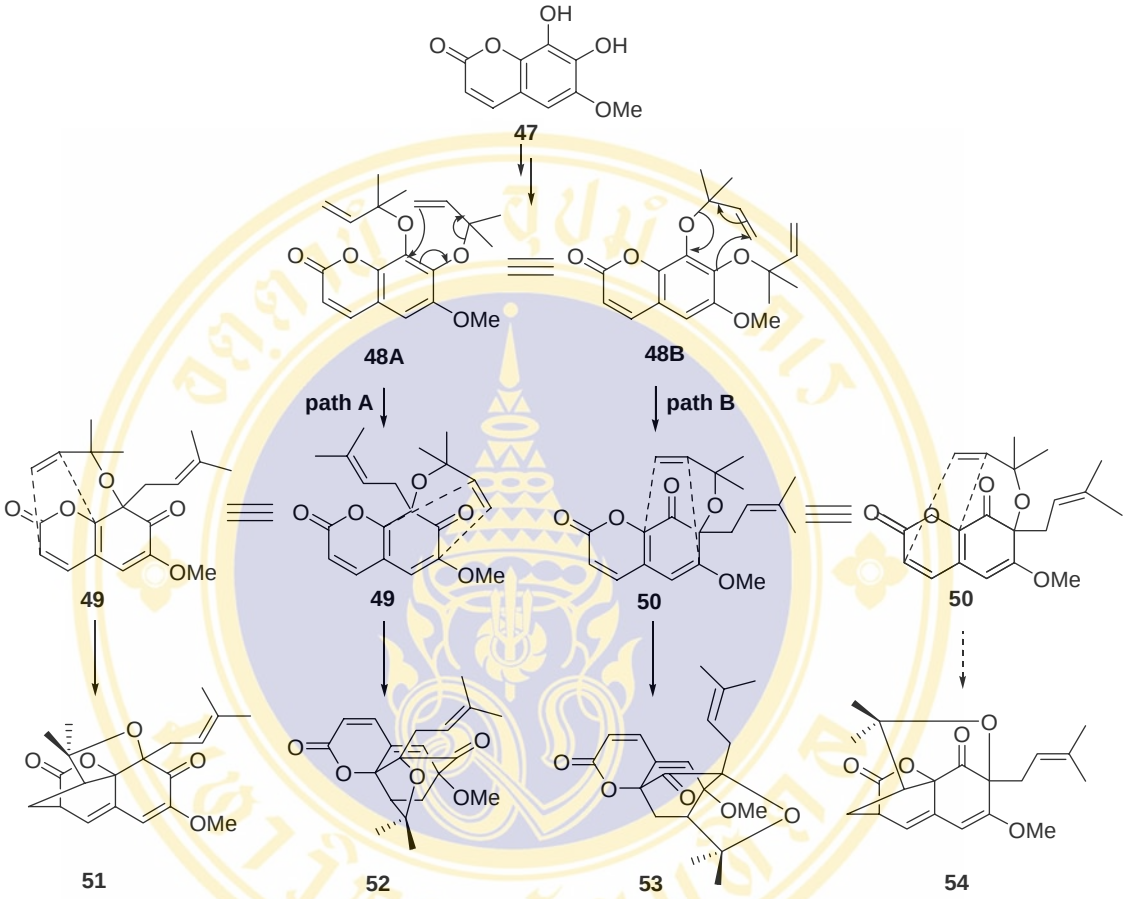
In 2001, Nicolaou *et al*. reported a development of Claisen rearrangement followed by intramolecular Diels-Alder cycloaddition as a useful tool for construction of compound **46** containing a highly substituted polycyclic system.[1]



46

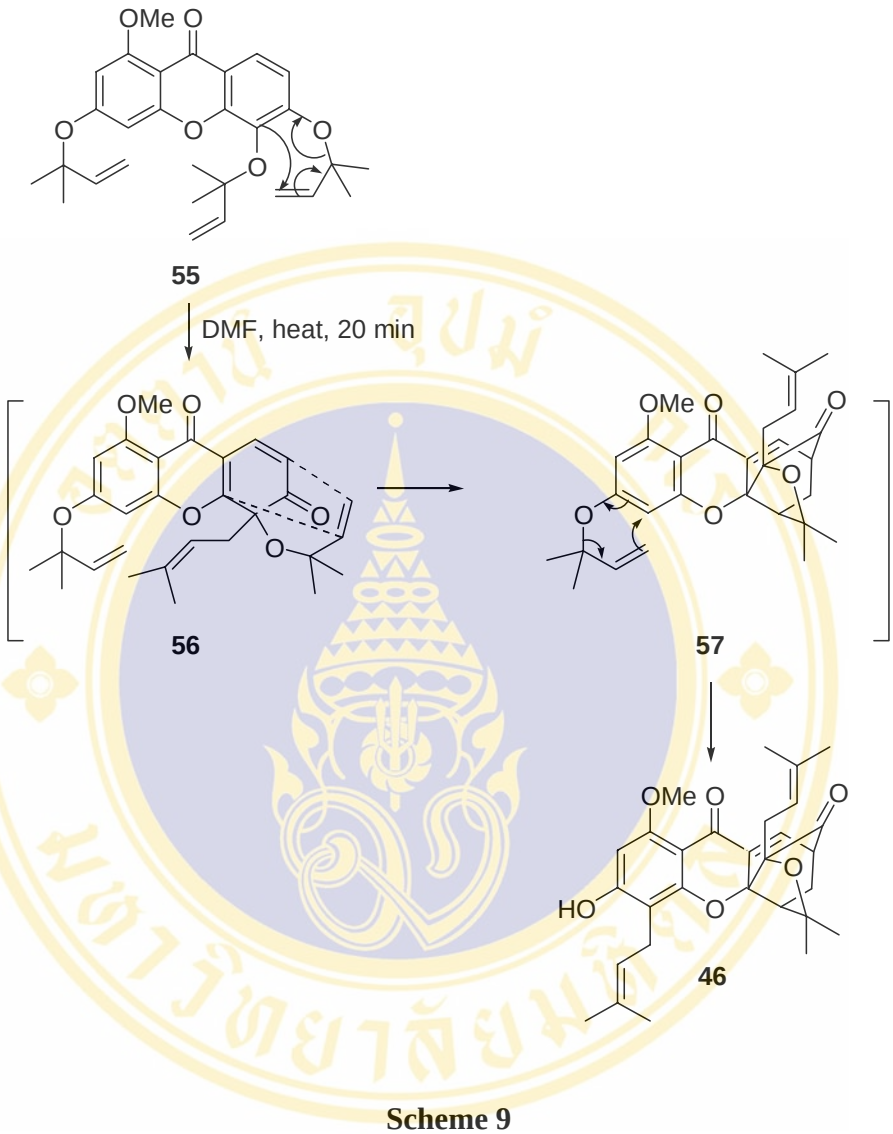
The precursor **48** synthesized from coumarin (**47**) could engage in two possible Claisen rearrangement pathways (paths **A** and **B**) to furnish intermediates **49** and **50**. Each intermediate could undergo two different intramolecular Diels-Alder reactions

leading to compounds **51** (43%), **52** (18%) and **53** (30%) (Scheme 8). Compound **54** was not formed because of its highly strained structure.



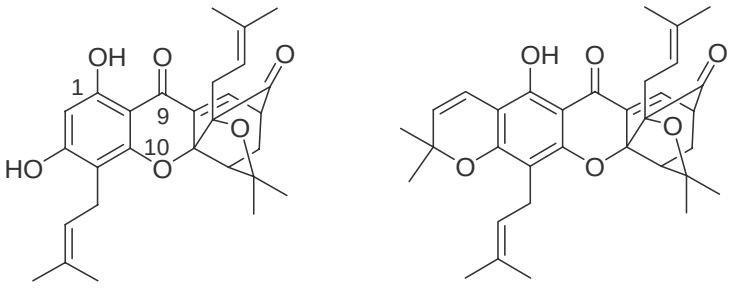
Scheme 8

The usefulness of the above synthetic methodology was demonstrated in an expedition synthesis of 1-*O*-methylforbesione (**46**). Upon heating prenylated xanthone **55** in DMF at 120 ^{o}C, the desired 1-*O*-methylforbesione (**46**) was indeed obtained as a major product in 63% yield, presumably *via* an anticipated Claisen rearrangement followed by an intramolecular Diels-Alder reaction, as shown in Scheme 9.



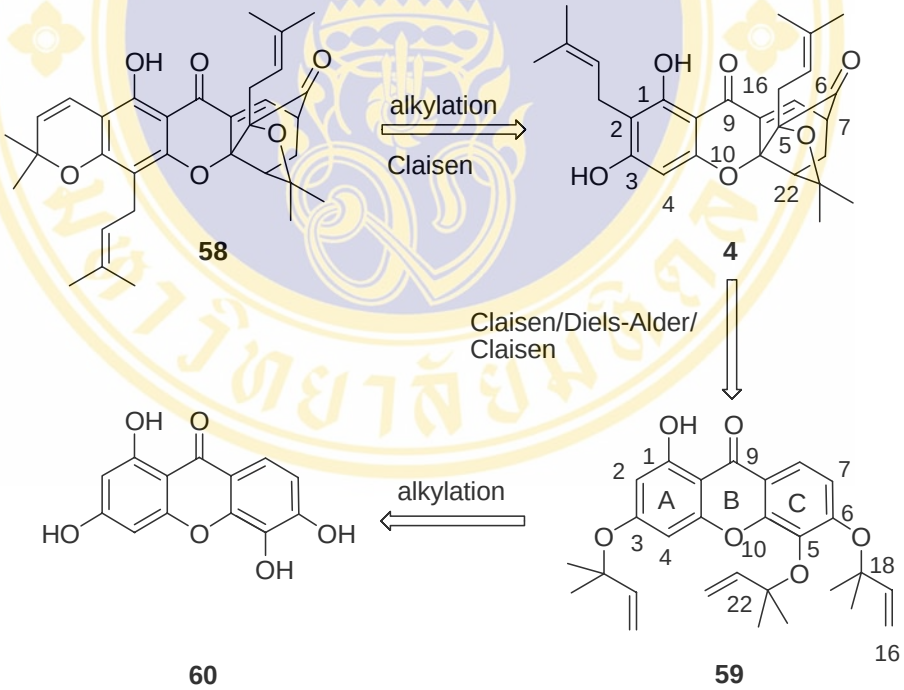
Scheme 9

In 2003, Tisdale *et al.* demonstrated the synthesis of forbesione (**4**) and deoxymorellin (**58**) by utilizing a tandem Claisen/Diels-Alder/Claisen rearrangement.[25]



Central to the strategy is a biomimetic Claisen/Diels-Alder/Claisen reaction cascade that proceeds in a regioselective manner and produces the desired scaffold exclusively. The observed regioselectivity and product distribution of the Claisen/Diels-Alder/Claisen reaction are attributed to the electronic effects of the xanthone oxygen (O10), the C-9 carbonyl group and the nature of the C-1 functionality.

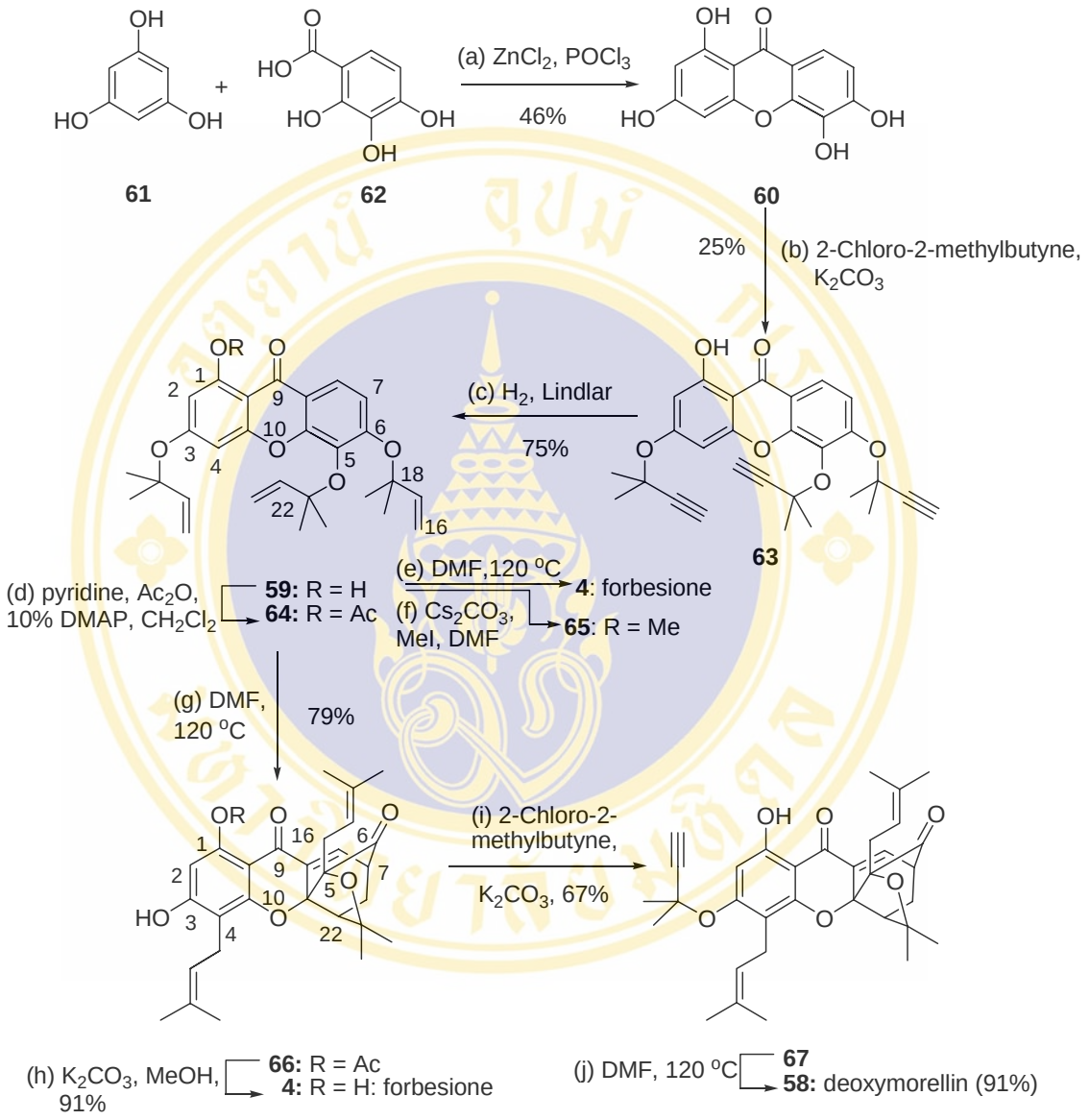
The retrosynthesis approach toward **4** and **58** is shown in Scheme 10. Disconnection of deoxymorellin (**58**) across the pyran ring suggests a synthetic entry to this natural product from forbesione (**4**) via propargylation of the C3 hydroxy group and subsequent Claisen cyclization. Inspired by the proposed biosynthetic scenario, compound **4** could be arisen from rearrangement of tris-allyloxy precursor **59**, the fused ring system of which can be tracted to xanthone **60**.



Scheme 10

Successful implementation of such a strategy would require control over the regioselectivity of both the A-ring Claisen rearrangement, *i.e.* prenylation at C4 over C2,

and formation of the desired caged motif during the C-ring Claisen/Diels–Alder reaction. Reduction of this plan to practice is illustrated in Scheme 11.



61 62 60 63

59: R = H
64: R = Ac
4: forbesione
65: R = Me
66: R = Ac
4: R = H: forbesione
67
58: deoxymorellin (91%)

Scheme 11

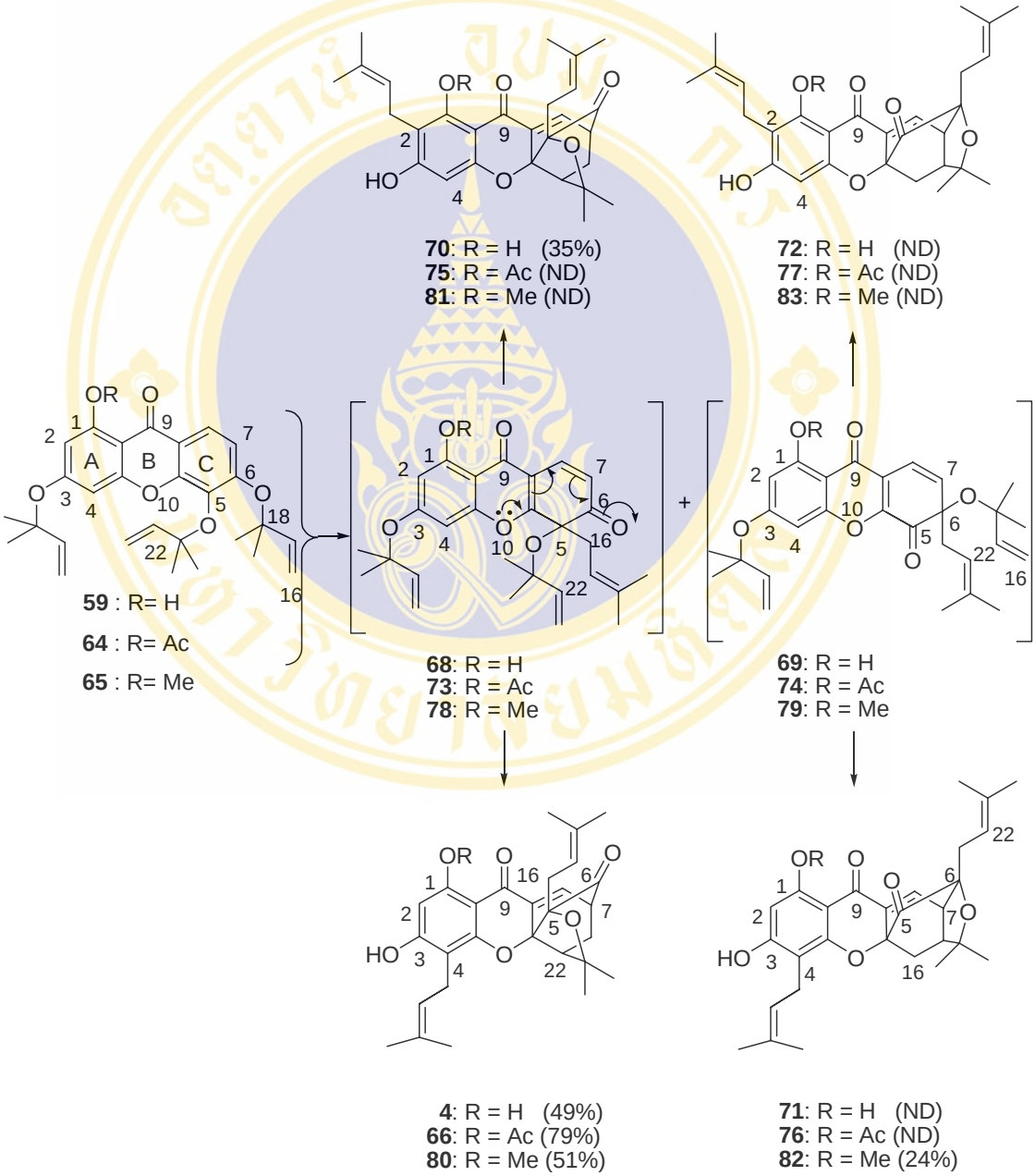
In principle, precursor **59** can open its rearrangement cascade by delivering a prenyl group to either the C5 or C6 center, forming intermediates **68** and **69**, respectively

(Scheme 12). Intermediate **68** is responsible for the desired caged structure and could lead, after Claisen rearrangement of the C3 allyloxy unit, to forbesione (**4**) and/or isoforbesione (**70**). In a similar manner, intermediate **69** could lead to an isomeric caged structure, the so-called neo skeleton, ultimately forming neoforbesione (**71**) and/or isomer **72**. Similar structures are expected with precursors **64** and **65**.

Why is the Claisen/Diels–Alder reaction regioselective? The answer may lie in the electronic effects of both the xanthone oxygen (O10) and the C9 carbonyl group. The C9 carbonyl group of precursor **59** is *para* to the C6 allyloxy unit and thus, it can accept electron density from the C6 oxygen. This contributes to a weakening of the ether bond to the C18 alkyl fragment facilitating its rupture. In addition, as shown in structure **68** (Scheme 12) the xanthone oxygen (O10) is *meta* to the C6 carbonyl group thereby stabilizing it by resonance. Such a stabilization effect cannot be achieved at the C5 carbonyl group of intermediate **69**. In precursor **59**, the combination of such effects leads to the exclusive formation of **68** over **69** and ultimately, the desired caged scaffold (combined isolated yield for **4** and **70**: 84%). Similar effects are operative in the rearrangement of 1-*O*-acetylated precursor **64** (R = Ac) and lead to the isolation of **66** in 79% yield. In these two cases, any products having the neo structure were not isolated. However, when the 1-*O*-methylated precursor **65** was subjected to similar reaction conditions, it produced 1-*O*-methylforbesione (**80**) (51% yield) together with 1-*O*-methylneoforbesione (**82**) (24% yield). The results with **65** (R = Me) parallel the observations made by Nicolaou and Li[1] and provide further evidence of the role played by the C9 carbonyl group. In compound **65**, the withdrawing effect of the carbonyl is attenuated by the presence of the C1 methyl ether (vinylogous ester structure). This reduces the inclination of the O–C18 bond to rupture which leads to intermediates **78** and **79** and thus, the formation of isomers **80** and **82**.

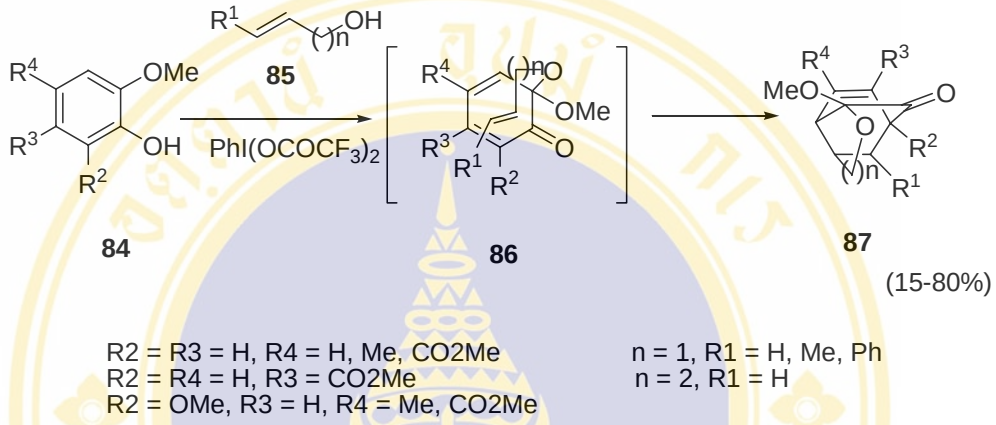
The outcome of the tandem Claisen/Diels–Alder/Claisen rearrangement of **59**, **64** and **65** and its dependency on the nature of the C1 functionality is in agreement with the structures that constitute the family of caged *Garcinia* natural products. These naturally occurring compounds share a common caged structure exemplified by the simplest among them, forbesione (**4**). The only exception to this trend is provided by the structure of 1-*O*-methylneobractatin (**7**), which contains the alternative, neo scaffold (Scheme 1). This

compound was isolated from extracts of the dried and powdered leaves of *Garcinia bracteata* as a minor constituent along with 1-*O*-methylbractatin (**6**). The presence of the seemingly innocuous 1-*O*-methyl group seems to explain the concomitant formation of both **7** and **6** from **65**. This suggests that the 1-*O*-methyl group was incorporated by nature prior to the tandem Claisen/Diels–Alder/Claisen rearrangement.



Scheme 12

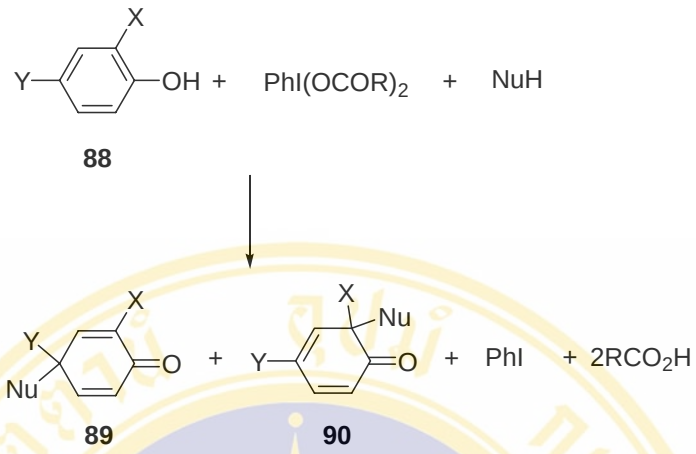
Liao and coworkers reported the oxidation of commercially available 2-methoxyphenols (**84**) in the presence of alkenols **85** to afford masked *o*-benzoquinone (MOBs) bearing alkene moiety **86**.[26] The MOBs could undergo intramolecular Diels-Alder reaction to furnish tricyclic system **87** (Scheme 13).



Scheme 13

4. The chemistry of masked *o*-benzoquinones

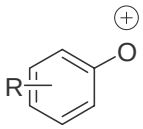
Recently, hypervalent iodine compounds have become widely used and are of important synthetic reagents.[27] In particular, phenyliodonium(III) diacetate (PIDA) and phenyliodonium(III) bistrifluoroacetate (PIFA) are efficient reagents for the preparation of *ortho*- or *para*-quinones,[28] dialkoxycyclohexadienones (quinone ketals), alkoxyalkyldienones[29] and 4-hydroxy-4-alkylcyclohexadienones from phenols (Scheme 14).[30]



Scheme 14

Cyclohexadienones are important synthetic intermediates and the mechanism for their formation is therefore of interest. One-electron oxidation of phenols is generally assumed to be a favored mode of biochemical oxidation, particularly for a large scale production of lignin as well as for that of lignans, tannins, plant and insect pigments, some antibiotics, and many alkaloids. One-electron oxidation involving a wide variety of metal ions has long been known and widely used.[31] Electrochemical methods have also been used to study one-electron phenolic oxidations.

Two-electron oxidation of phenols to give phenyloxenium ions (ArO^+) **91**, is less well explored.[32] Phenyloxenium ions **91** were proposed as intermediates in phenol oxidation promoted by thallium(III), copper(II) or iodine(III). Some of them could be generated and characterized electrochemically, while some are stable enough to be isolated.

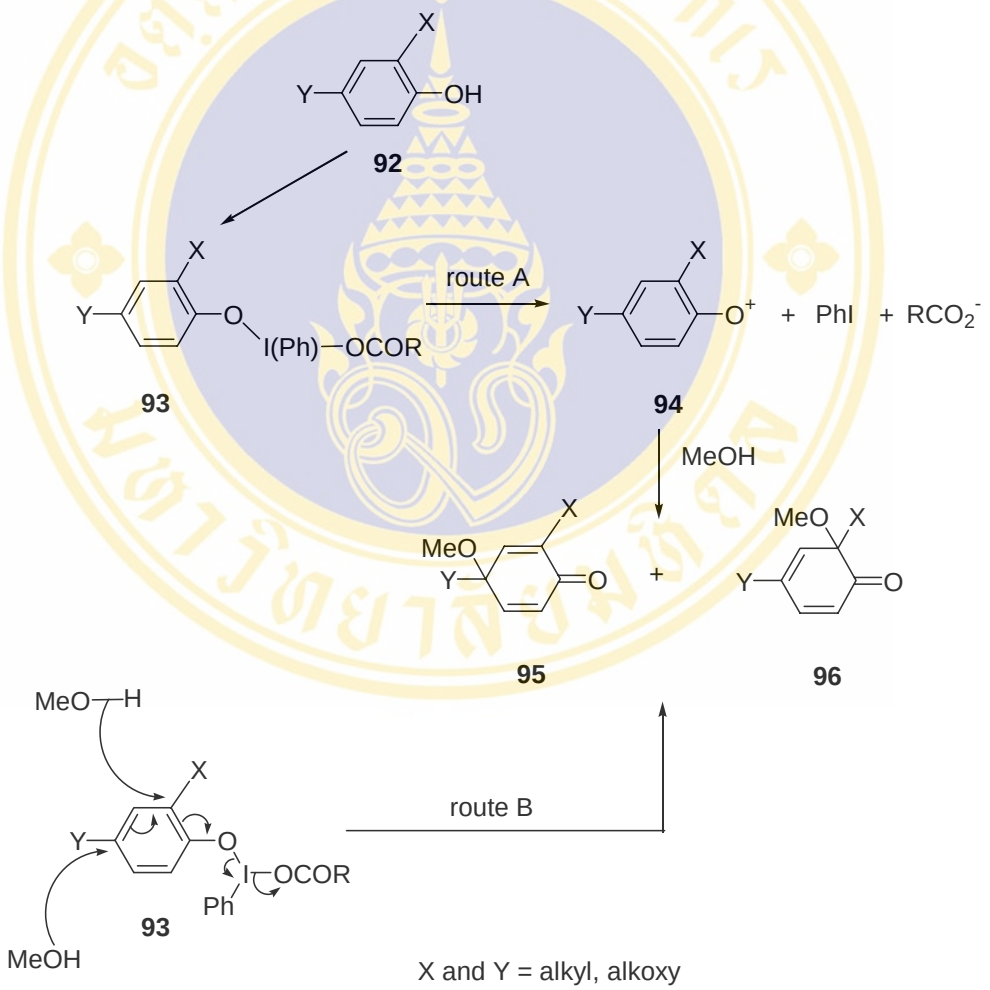


91

Figure 1

Pelter *et al*. proposed the mechanism for the formation of intermediates **91** and their reactions involving inter- and intramolecular nucleophilic attack.[32] There are two main

possibilities for phenolic oxidation pathway performed by $PhI(OCOR)_2$ as shown in Scheme 15. The first point to be noted was that the by-products were simply acetic acid or trifluoroacetic acid and iodobenzene, the latter being readily recycled. In route A, the intermediate **93**, common to both pathways, dissociated to give solvated phenoxenium ion **94** as intermediate which further reacted with methanol to give **95** and/or **96**. In route B, there was no dissociation. The products **95** and **96** arose from a concerted mechanism involving the direct attack of methanol on intermediate **93**.



Scheme 15

Benzoquinones and their derivatives have a vast synthetic potential as useful intermediates to create compounds possessing molecular complexity. Complex molecules with defined stereochemistry could be constructed from readily available starting materials.[33] Simple *o*-benzoquinones are unstable and usually undergo notorious reactions in addition to dimerization. On the other hand, masked *o*-benzoquinones (MOBs) protected at one of the carbonyl functionalities, are relatively stable compared to the corresponding unprotected *o*-benzoquinones (Figure 2).[34]

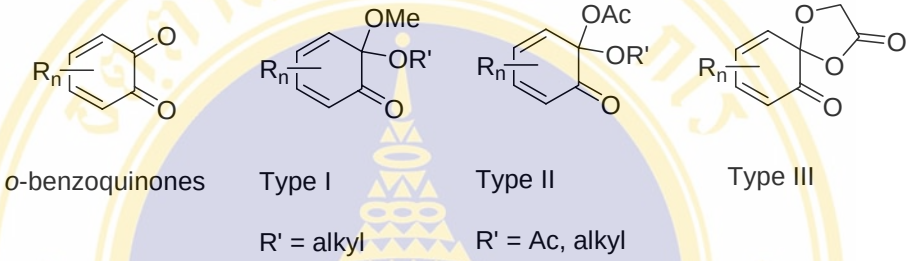
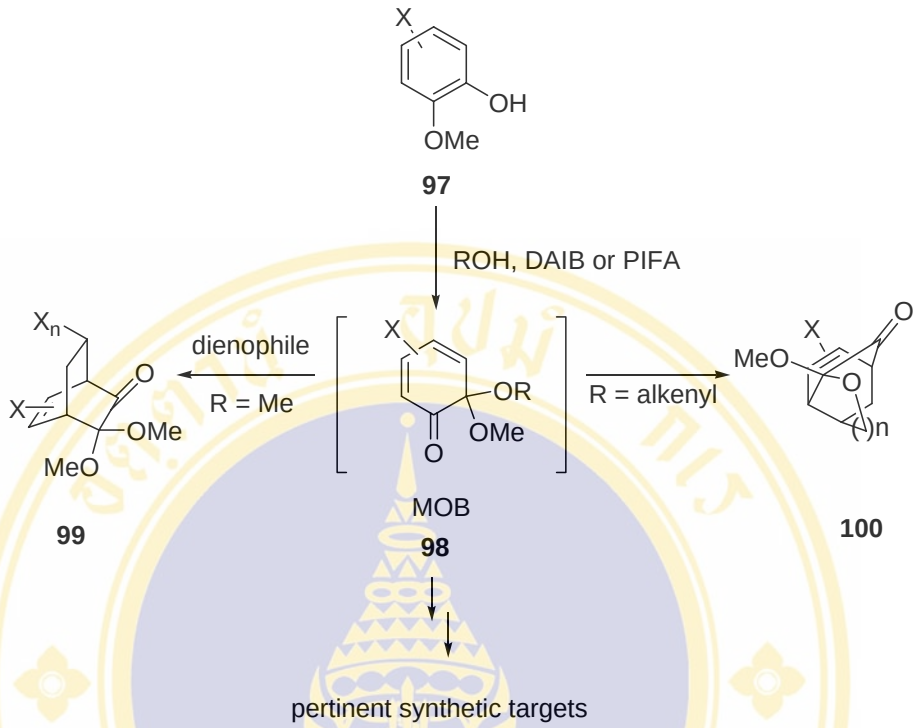


Figure 2

The MOBs which are linearly conjugated cyclohexadienones can potentially participate in cycloaddition and nucleophilic addition reactions. The double bonds of the diene moiety being positioned between a carbonyl and an acetal functions are electronically differentiated and can be elaborated regioselectively as monoprotection for the vicinal carbonyl system.

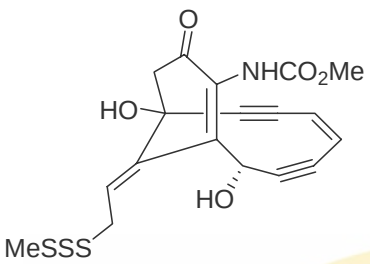
Liao and coworkers found that the oxidation of 2-methoxyphenols (**97**) can be effected by hypervalent iodines, such as phenyliodonium(III) diacetate (PIDA) or phenyliodonium(III) bistrifluoroacetate (PIFA), in the presence of an alcohol.[35] Under the oxidative reaction conditions, the *in situ* generated masked *o*-benzoquinones (MOBs) **98** readily underwent a facile intermolecular Diels-Alder reaction in a regio- and stereocontrolled manner with electron-deficient dienophiles to produce the corresponding bicyclo[2.2.2]octenone derivatives **99**.

When the oxidation of 2-methoxyphenols (**97**) was carried out in the presence of an alkenol, MOBs **98** underwent a facile intramolecular Diels-Alder cycloaddition *via* a tandem oxidative acetalization, following by an intramolecular cycloaddition process to furnish tricyclic ring systems **100** as shown in Scheme 16.[33]

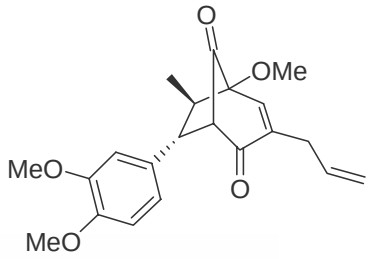


Scheme 16

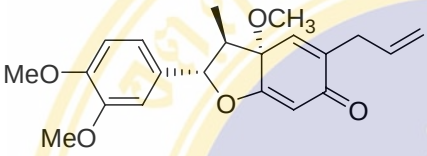
Remarkably, the adducts obtained from the MOBs/Diels-Alder strategy have been utilized in the syntheses of several natural products. The inter- and intramolecular Diels-Alder reactions of MOBs had already been utilized as a key step in the total syntheses of calicheamicinone (**101**),[36] (±)-liliflol B (**102**), (±)-kadsurenone (**103**), denudatin B (**104**),[37] xestoquinone (**105**),[38] and halenoquinone (**106**) (Scheme 17).[39]



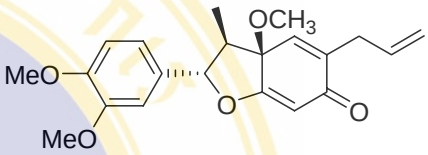
101: (±)-calicheamicinone



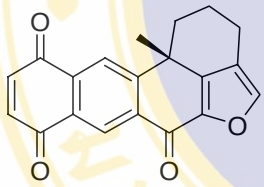
102: liliflol B



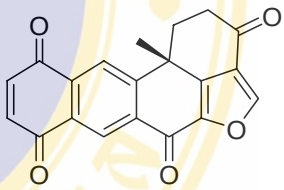
103: kadsurenone



104: denudatin B



105: xestoquinone

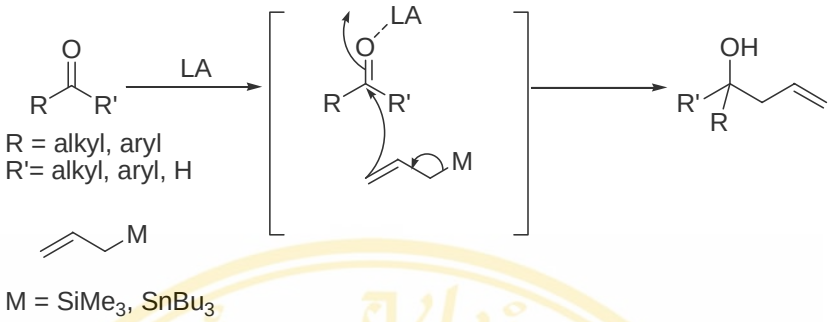


106: halenaquinone

Scheme 17

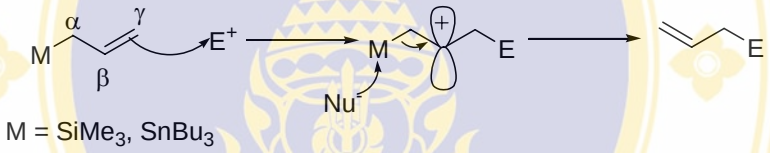
5. Allylation reaction of caged xanthone

The allylation reaction is one of the most useful carbon-carbon bond-forming reactions in organic synthesis.[40] Allylstannanes and allylsilanes have been widely used for the efficient conversion of aldehydes and ketones to useful homoallylic alcohols. Although a number of Lewis acids have been found to promote this reaction, some Lewis acids (e.g. $AlCl_3$ and $TiCl_4$) are very sensitive to moisture and difficult to handle in large scale processes. The mechanism for the allylation is shown in Scheme 18.



Scheme 18

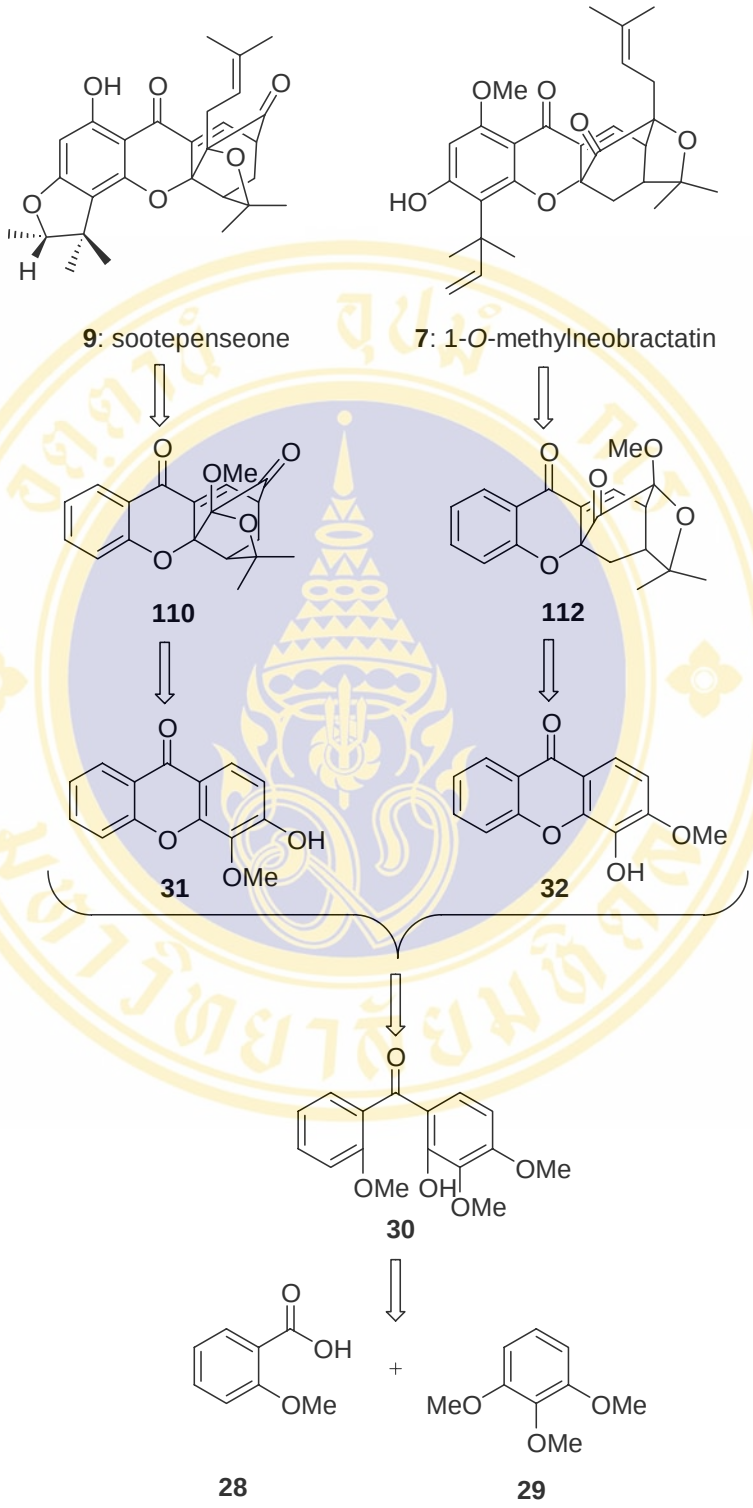
Additionally, their regioselective reactions with electrophiles can be explained by the intermediate formation of carbonium ion intermediates, which are hyperconjugatively stabilized by the carbon-silicon or carbon-tin bond in the beta position (Scheme 19).



Scheme 19

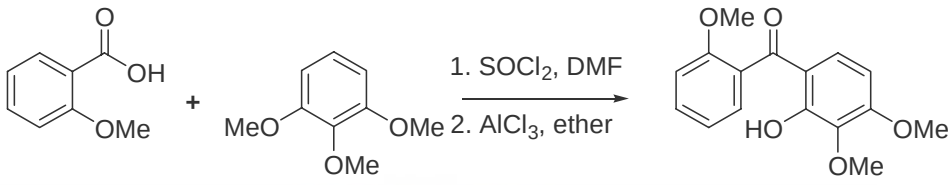
CHAPTER II
RESULTS AND DISCUSSION

Our retrosynthetic plan is shown in Scheme 20. Compounds **110** and **112** were anticipated to be obtained from intramolecular Diels-Alder cycloaddition reaction of 3-hydroxy-4-methoxyxanthen-9-one (**31**) and 4-hydroxy-3-methoxyxanthen-9-one (**32**), respectively. The xanthones **31** and **32** were derived from cyclization reaction followed by selective demethylation of 2-hydroxy-2',3,4-trimethoxybenzophenone (**30**) which in turn could be obtained from 2-methoxybenzoic acid (**28**) and 1,2,3-trimethoxybenzene (**29**).[24]



Scheme 20

1. Preparation of 2-hydroxy-2',3,4-methoxybenzophenone (30).[24]



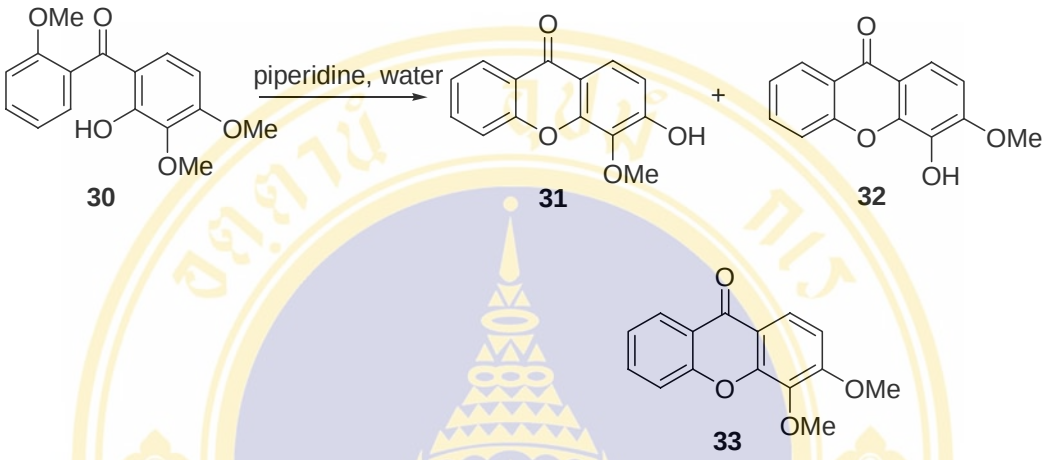
28 **29** **30**

Scheme 21

2-Hydroxy-2',3,4-trimethoxybenzophenone (**30**) was prepared by Friedel-Crafts acylation reaction. Treatment of 2-methoxybenzoic acid (**28**) with thionyl chloride in the presence of dimethylformamide as catalytic agent gave 2-methoxybenzoyl chloride. In the next step, a mixture of 2-methoxybenzoyl chloride, 1,2,3-trimethoxybenzene (**29**), and aluminium trichloride in ether solution was stirred at room temperature for 20 h. Compound **30** formed was poured into water, washed with saturated aqueous sodium hydrogencarbonate and dried. The analytically pure compound was obtained by crystallization from methanol. It is important to perform this reaction under anhydrous conditions because aluminium trichloride was very sensitive to moisture. During work up, the reaction mixture had to be slowly poured into water because the remaining aluminium trichloride reacted severely with water. The 2-hydroxy-2',3,4-trimethoxy benzophenone (**30**) was isolated in 78% yield.

Compound **30** was obtained as a needle yellow solid and was characterized. The IR spectrum showed υ_{max} signals at 3312-3541 cm^{-1} for O-H stretching of phenol and at 1599 cm^{-1} for C=O stretching. The ^{1}H NMR (500 MHz) spectrum exhibited three singlet signals at δ 3.78, 3.91 and 3.94 ppm assigned for three methoxy groups and a singlet signal at δ 12.50 ppm assigned for a phenolic hydroxyl group. Molecular formula of compound **30** was confirmed by mass spectrometry ($[M^{+}]$ = m/z 288).

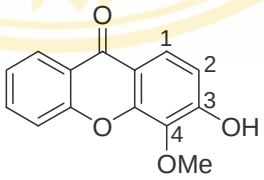
2. Preparation of 3-hydroxy-4-methoxyxanthen-9-one (31), 4-hydroxy-3-methoxy xanthen-9-one (32) and 3,4-dimethoxyxanthen-9-one (33).[24]



30 **31** **32** **33**

Scheme 22

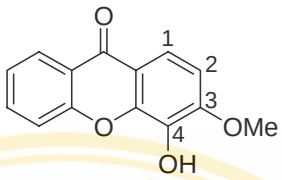
When a suspension of 2-hydroxy-2',3,4-trimethoxybenzophenone (**30**) in piperidine containing water was heated at 100-110 ^{o}C for 46 h, 3-hydroxy-4-methoxyxanthen-9-one (**31**), 4-hydroxy-3-methoxyxanthen-9-one (**32**) and 3,4-dimethoxyxanthen-9-one (**33**) were obtained in 38%, 45% and 5%, respectively.



31

The 3-hydroxy-4-methoxyxanthen-9-one (**31**) was obtained as a white solid.[43] Its IR absorption peak showed signals of O-H stretching at υ_{max} 3208 cm^{-1} and C=O stretching at υ_{max} 1643 cm^{-1}. The ^{1}H NMR (300 MHz) spectrum exhibited a singlet signal at δ 4.09 ppm belonging to a methoxy group. The NOESY spectrum of **31** had no NOE correlation between the methoxy protons and H-2. It confirms that the methoxy group is *meta* to the

H-2 of phenyl ring. Molecular ion ([M^+]) of **31** at m/z 242 was confirmed by mass spectrometric analysis.



32

The 4-hydroxy-3-methoxyxanthen-9-one (**32**) was obtained as a white solid.[43] The IR spectrum showed signals of O-H stretching at υ_{max} 3240 cm^{-1} and C=O stretching at υ_{max} 1644 cm^{-1}. The ^{1}H NMR (300 MHz) spectrum exhibited a singlet signal at δ 4.05 ppm assigned for a methoxy group. The NOESY spectrum of **32** showed NOE correlations between the methoxy proton and H-2. This correlation confirms that the methoxy group is *ortho* to the H-2 of phenyl ring. Mass spectrometric analysis of **32** gave a molecular ion ([M^+]) at m/z 242.

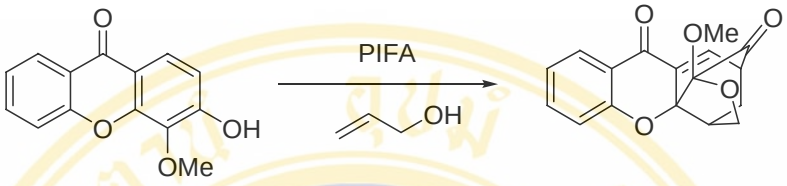
The 3,4-dimethoxyxanthen-9-one (**33**) was obtained as a white solid.[43] Its IR spectrum showed υ_{max} signals at 2850-2930 cm^{-1} for C-H stretching of alkyl group and 1663 cm^{-1} for C=O stretching. The ^{1}H NMR (300 MHz) spectrum exhibited two singlet signals at δ 4.02 and 4.05 ppm, indicating the presence of two methoxy groups. Mass spectrum analysis of **33** gave molecular ion ([M^+]) at m/z 256.

Compounds **31**, **32** and **33** were previously synthesized by Gnerre and co-workers.[43] It should be noted that compound **31** is a naturally occurring substance isolated from *Calophyllum* and *Mesua ferrea* (Guttiferae).[42] Sultanbawa and co-workers conducted a structural elucidation of **31** to have ^{1}H NMR (100 MHz) spectrum possessing two doublets of aromatic protons (^3J = 8.0 Hz) at δ 8.14 (1H) and 7.65 (1H) and two triplets of aromatic protons (^3J = 8 Hz) at δ 7.81 (1H) and 7.43 (1H). This indicates that one of the xanthone ring is unsubstituted. The presence of a singlet signal at 3.92 (3H) indicated that the compound contained a single methoxy group.[44, 45]

In this work, compounds **31** and **32** were synthesized in a 2-steps reaction resulting in a more efficient synthesis comparing to our previous work. [41]

3. Reaction of 3-hydroxy-4-methoxyxanthen-9-one (31) and 4-hydroxy-3-methoxy xanthen-9-one (32) with allyl alcohol.[46]

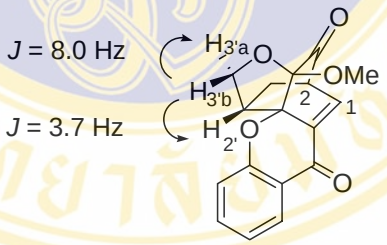
3.1 Reaction of 3-hydroxy-4-methoxyxanthen-9-one (31) with 2-propen-1-ol.



31 **107**

Scheme 23

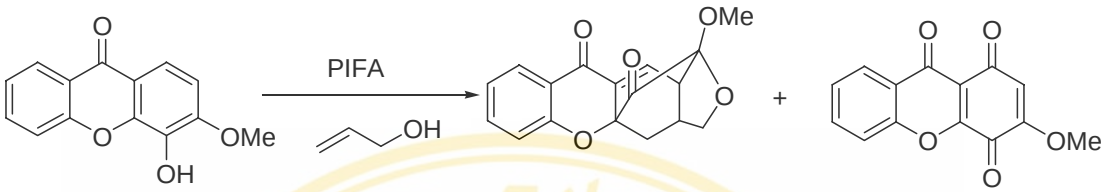
Compound **107** was prepared from the intramolecular Diels-Alder reactions of the unstable masked *o*-benzophenone in 45% yield by a slow addition of 3-hydroxy-4-methoxyxanthen-9-one (**31**) in THF solution to a THF solution of phenyliodonium(III) bistrifluoroacetate (PIFA, 1.5 equiv) and allyl alcohol (10 equiv). Compound **107** was obtained as a pale yellow solid and was characterized. The IR spectrum showed signals of C=O stretching at υ_{max} 1615 and 1740 cm^{-1} and C=C stretching at υ_{max} 1450 cm^{-1}.



107

The structure and relative stereochemistry of **107** were clearly established by analysis of its ^{1}H NMR spectrum. The ^{1}H NMR (500 MHz) spectrum exhibited signal at δ 4.65 ppm for H-3'b with $J_{H3'b,H3'a}$ = 8.0 Hz and $J_{H3'b,H2'}$ = 3.7 Hz, indicating that H-3'b was *syn* to the H-2'. The intramolecular Diels-Alder cycloaddition was evidenced by a coupling constant (J = 7.1 Hz) between H-1 at δ 7.35 ppm and H-2 at δ 3.35-3.40 ppm. The chemical shifts and J values shown supported that compound **107** has structure as indicated. Mass spectrum of **107** exhibited a molecular ion ([M^+]) peak at m/z 298.

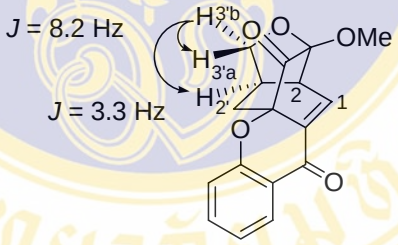
3.2 Reaction of 3-hydroxy-4-methoxyxanthen-9-one (32) with 2-propen-1-ol.



32 **108** **109**

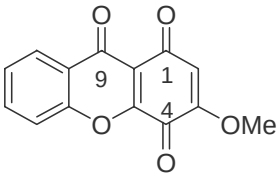
Scheme 24

When 4-hydroxy-3-methoxyxanthen-9-one (**32**) was used as a starting material, compound **108** was produced in 10% yield. Evidently, **108** was obtained in low yields due to the easy oxidation of **32** to 3-methoxyxanthene-1,4,9-trione (**109**) (40% yield). The adduct **108** was obtained as a pale yellow solid and was characterized. The IR spectrum showed signals of C=O stretching at υ_{max} 1660 and 1770 cm^{-1} and C=C stretching at υ_{max} 1450 cm^{-1}.



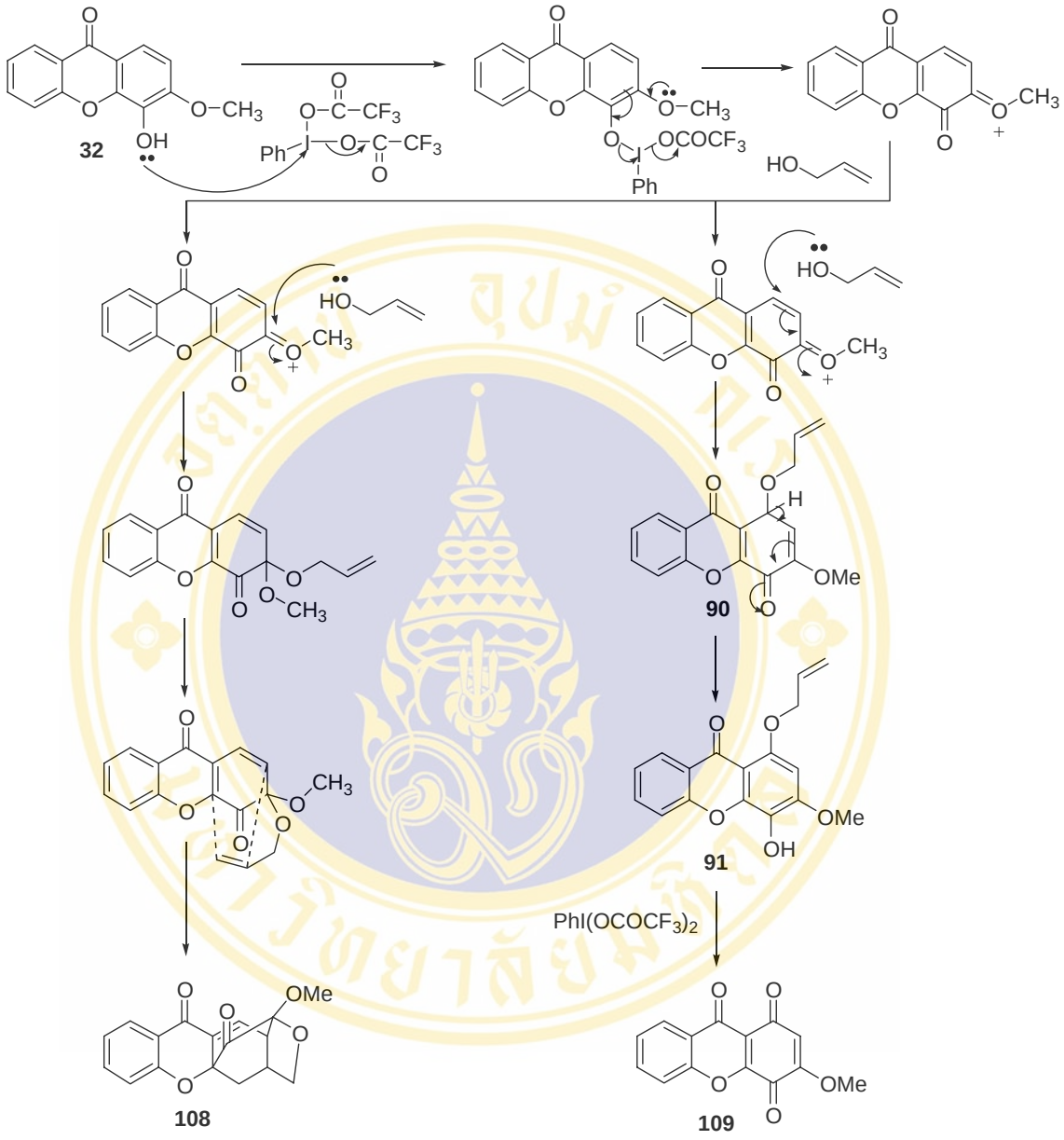
108

The structure and relative stereochemistry of **108** was clearly established by analysis of its ^{1}H NMR spectrum. The ^{1}H NMR (500 MHz) spectrum exhibited signal at δ 4.16 ppm for H-3'b with $J_{H3'b,H3'a}$ = 8.2 Hz and $J_{H3'b,H2'}$ = 3.3 Hz, indicating that H-3'b was *syn* to the H-2'. The intramolecular Diels-Alder cycloaddition was evidenced by a coupling constant (J = 7.0 Hz) between H-1 at δ 7.22 ppm and H-2 at 3.60 ppm. The chemical shift and J values shown supported that compound **108** has structure as indicated. Mass spectrum of **108** exhibited a molecular ion ([M^+]) peak at m/z 298.



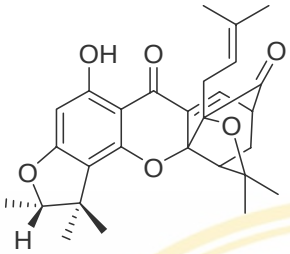
109

Compound **109** was obtained as a yellow solid and was characterized. The IR spectrum showed signals of C=O stretching at υ_{max} 1628-1700 cm^{-1} and C=C stretching at υ_{max} 1450-1600 cm^{-1}. The ^{1}H NMR (500 MHz) spectrum exhibited a singlet signal at δ 6.12 ppm for the proton at the *β*-olefinic carbon. The ^{13}C NMR spectrum (125 MHz) exhibited signals at δ 174.16, 175.69 and 182.48 ppm, indicating that **109** contained three carbonyl carbons assigned to C-9, C-1 and C-4, respectively. Mass spectrum of **109** gave a molecular ion peak at m/z 256. Compound **109** could be derived by the mechanism as proposed in Scheme 25.[47]

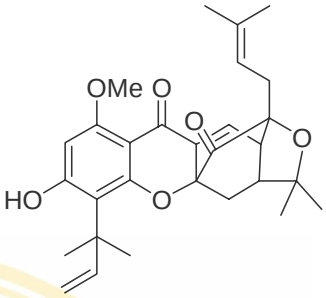


Scheme 25

It should be emphasized that compound of type **109** was previously synthesized by the oxidation of 1,4-dihydroxyxanthone using Ag(I) oxide.[48]

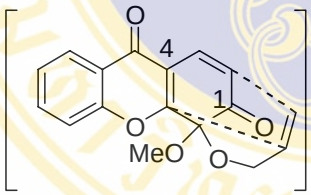


9: sootepenseone

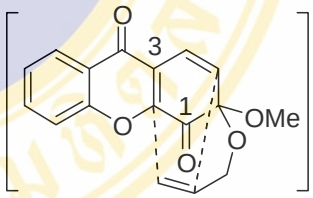


7: 1-*O*-methylneobractatin

It should be noted that the presence of a suitable substituent on the cyclohexadienone moiety of the unstable intermediates **107A** and **108A** is of importance for the cycloaddition to proceed with high efficiency.[49] The intermediate **107A** has electron withdrawing carbonyl substituent on C-4 of the 2,4-cyclohexadienone moiety, leading to an increase in the cycloaddition efficiency. In contrast, the intermediate **108A** has a carbonyl group on C-3 of the 2,4-cyclohexadienone moiety, causing a decrease in the reaction efficiency.



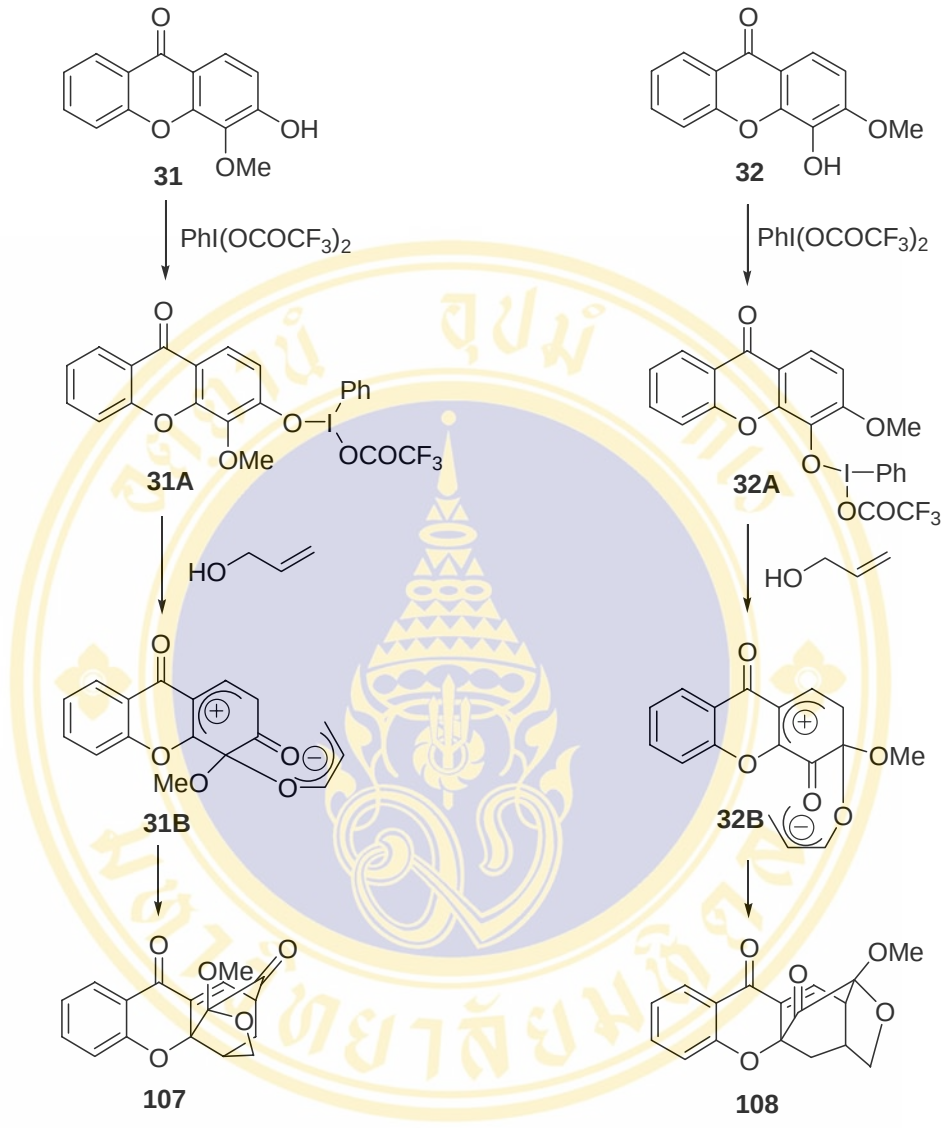
107A



108A

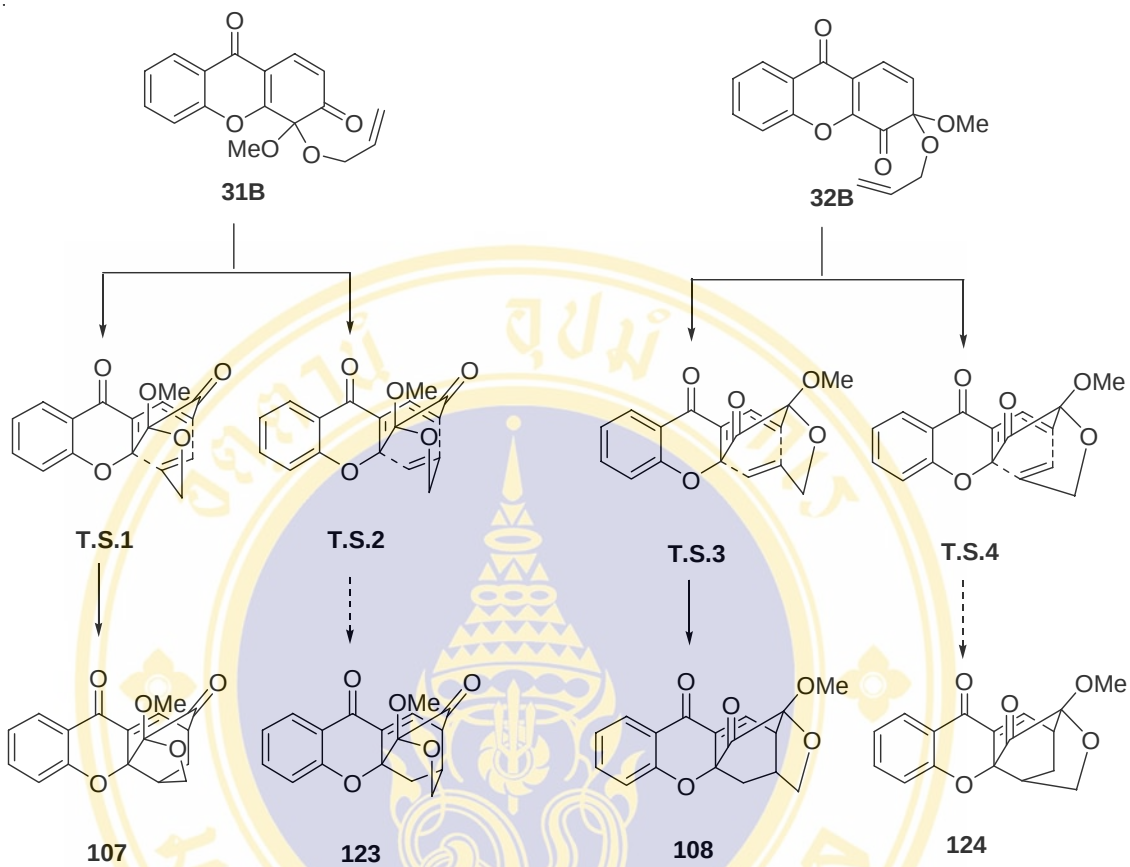
Scheme 26

The formation of compounds **107** and **108** in the one-pot reaction could be rationalized by the mechanism as proposed in Scheme 27. Initially, the oxygen atom of allyl alcohol acted as nucleophilic to attack at the C-4 and C-3 carbon atom of the intermediates **31A** and **32A**, respectively, giving zwitterionic intermidiates **31B** and **32B**.[50] Subsequent intramolecular cyclization of these intermediates finally gave cycloadducts **107** and **108**, respectively.



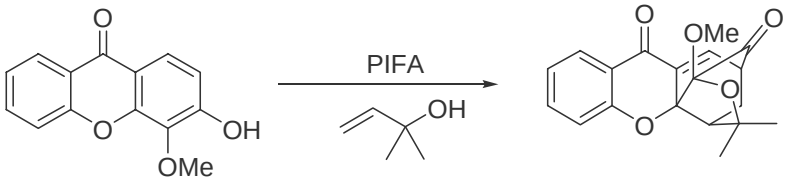
Scheme 27

Moreover, each of the cycloaddition reaction on intermediates **31B** and **32B** can take place along two stereoisomeric reactive channels corresponding to the relative stereochemistry around the alkene double bond. The more favored **T.S.1** led to the formation of compound **107** and the **T.S. 3** gave compound **108**, Scheme 28.



Scheme 28

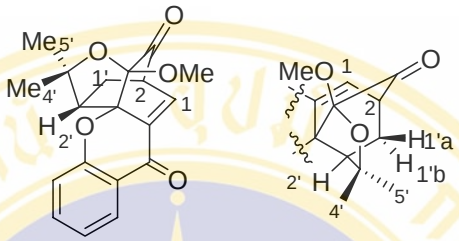
3.3 Reaction of 3-hydroxy-4-methoxyxanthen-9-one (31) with 2-methyl-3-buten-2-ol.



Scheme 29

Compound **110** was prepared from the intramolecular Diels-Alder reactions of the unstable masked *o*-benzophenone derived from compound **31** and 2-methyl-3-buten-2-ol in 28% yield. The reaction was performed by a slow addition of 3-hydroxy-4-

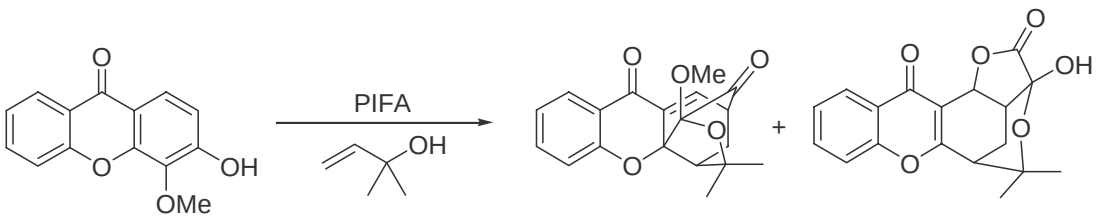
methoxyxanthen-9-one (**31**) in THF solution to a THF solution of phenyliodonium(III) bistrifluoroacetate (PIFA, 1.5 equiv) and 2-methyl-3-buten-2-ol (10 equiv). Compound **110** was obtained as a pale yellow solid and was characterized. The IR spectrum showed signals of C=O stretching at υ_{max} 1667 and 1744 cm^{-1}.



110

The structure and relative stereochemistry of **110** were clearly established by analysis of its ^{1}H NMR spectrum. The ^{1}H NMR (500 MHz) spectrum exhibited signal at δ 2.52 ppm for H-2' as a doublet with $J_{H2',H1'b}$ = 9.6 Hz, indicating that H-2' was *syn* to the H-1'b. The intramolecular Diels-Alder cycloaddition was evidenced by a coupling constant (*J* = 7.0 Hz) between H-1 at δ 7.59 ppm and H-2 at δ 3.44-3.46 ppm. The two geminal methyl groups appear as singlet at δ 1.32 ppm and δ 1.82 ppm. The chemical shifts and *J* values shown supported that compound **110** has structure as indicated. Mass spectrum of **110** exhibited a molecular ion ([M^+]) peak at m/z 326.

3.4 Reaction of 3-hydroxy-4-methoxyxanthen-9-one (31) with 2-methyl-3-buten-2-ol.

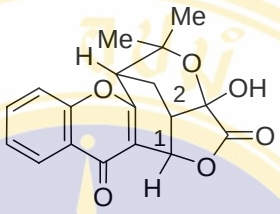


31 **110** **111**

Scheme 30

Compound **111** (20%yield) was obtained as an unexpected product when PIFA was used in excess. The reaction was carried out by a slow addition of 3-hydroxy-4-methoxyxanthen-9-one (**31**) in THF solution to a THF solution of phenyliodonium(III)

bistrifluoroacetate (PIFA, 4.0 equiv) and 2-methyl-3-buten-2-ol (10 equiv). Compound **111** was obtained as a white solid and was characterized. The IR spectrum showed signals of O-H stretching at υ_{max} 3414 cm^{-1}, C=O stretching at υ_{max} 1651 and 1775 cm^{-1} and C=C stretching at υ_{max} 1627 cm^{-1}.



111

The structure and relative stereochemistry of **111** were clearly established by analysis of its ^{1}H NMR spectrum and X-ray crystallographic data. The ^{1}H NMR (500 MHz) spectrum exhibited signal at δ 5.67 ppm with $J_{H1,H2}$ = 7.8 Hz. Relative stereochemistry was also confirmed the by X-ray diffraction analysis. The X-ray ORTEP diagram is as shown in Figure 3, indicating that H-1 was *syn* to the H-2. The chemical shifts and *J* values along with X-ray crystallographic data shown supported that compound **111** has structure as indicated. Mass spectrum of **111** exhibited a molecular ion ([M^+]) peak at m/z 328.

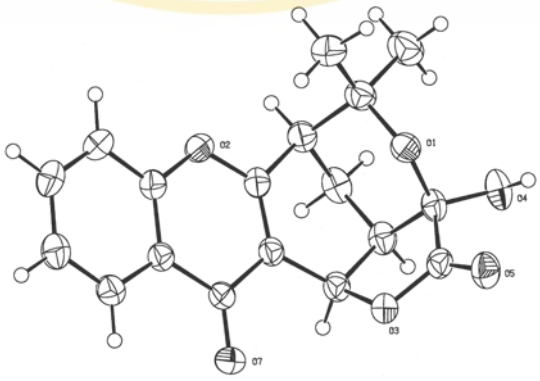
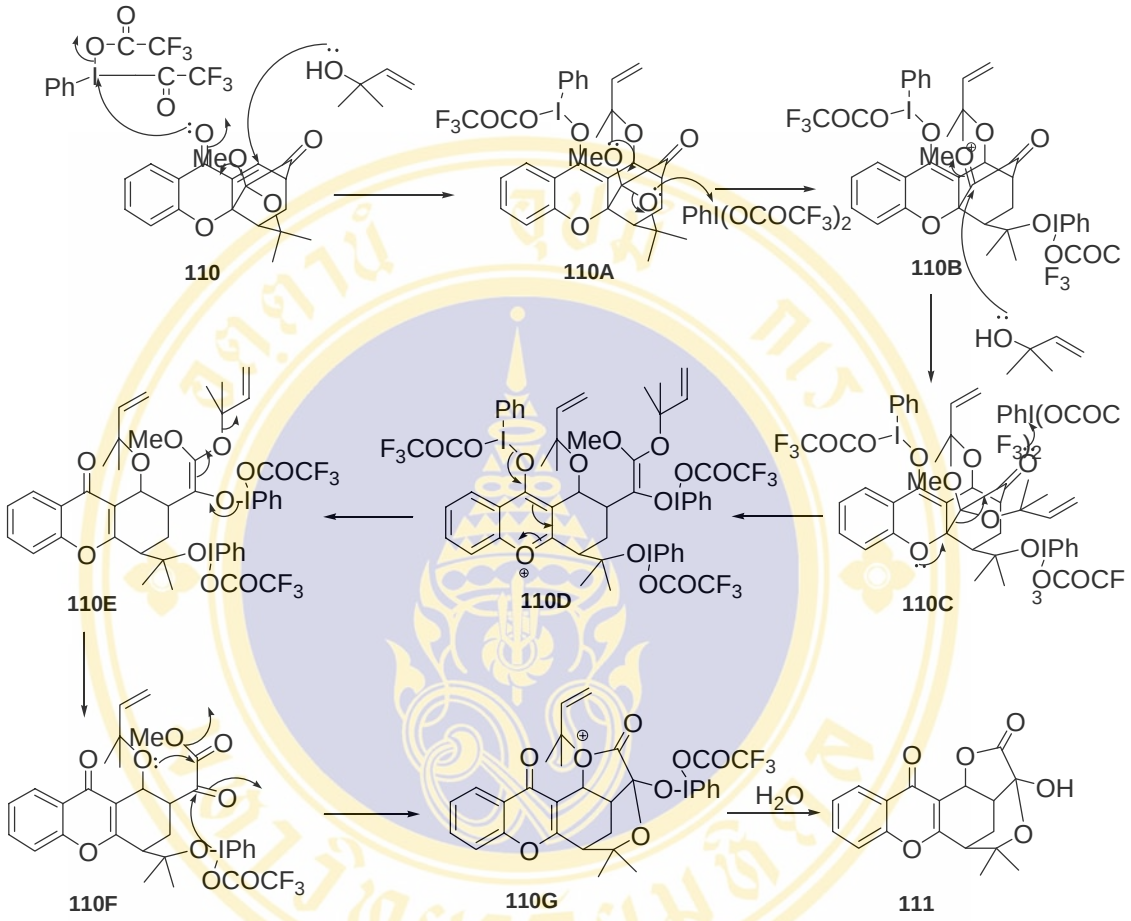


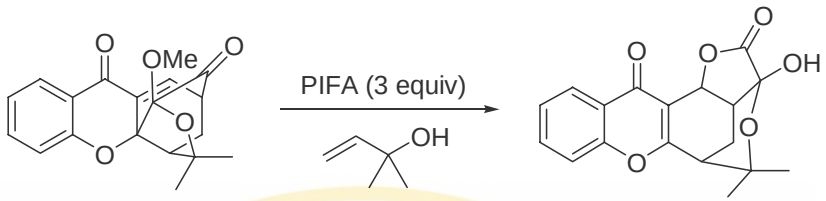
Figure 3

The rearranged product **111** could be derived by the mechanism as proposed in Scheme 31.



Scheme 31

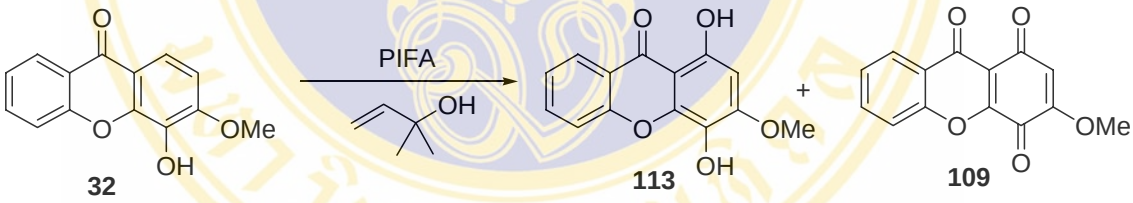
3.5 Reaction of compound 110 with 2-methyl-3-buten-2-ol.



110 **111**

Compound **111** (17%yield) was obtained when compound **110** was exposed to PIFA (3 equiv). The reaction was carried out by adding a solution of compound **110** in THF to a THF solution of phenyliodonium(III) bistrifluoroacetate (PIFA, 3.0 equiv) and 2-methyl-3-buten-2-ol (10 equiv). Compound **111** was obtained as a white solid. The result implied that compound **111** should have been formed via **110**.

3.6 Reaction of 3-hydroxy-4-methoxyxanthen-9-one (32) with 2-methyl-3-buten-2-ol.



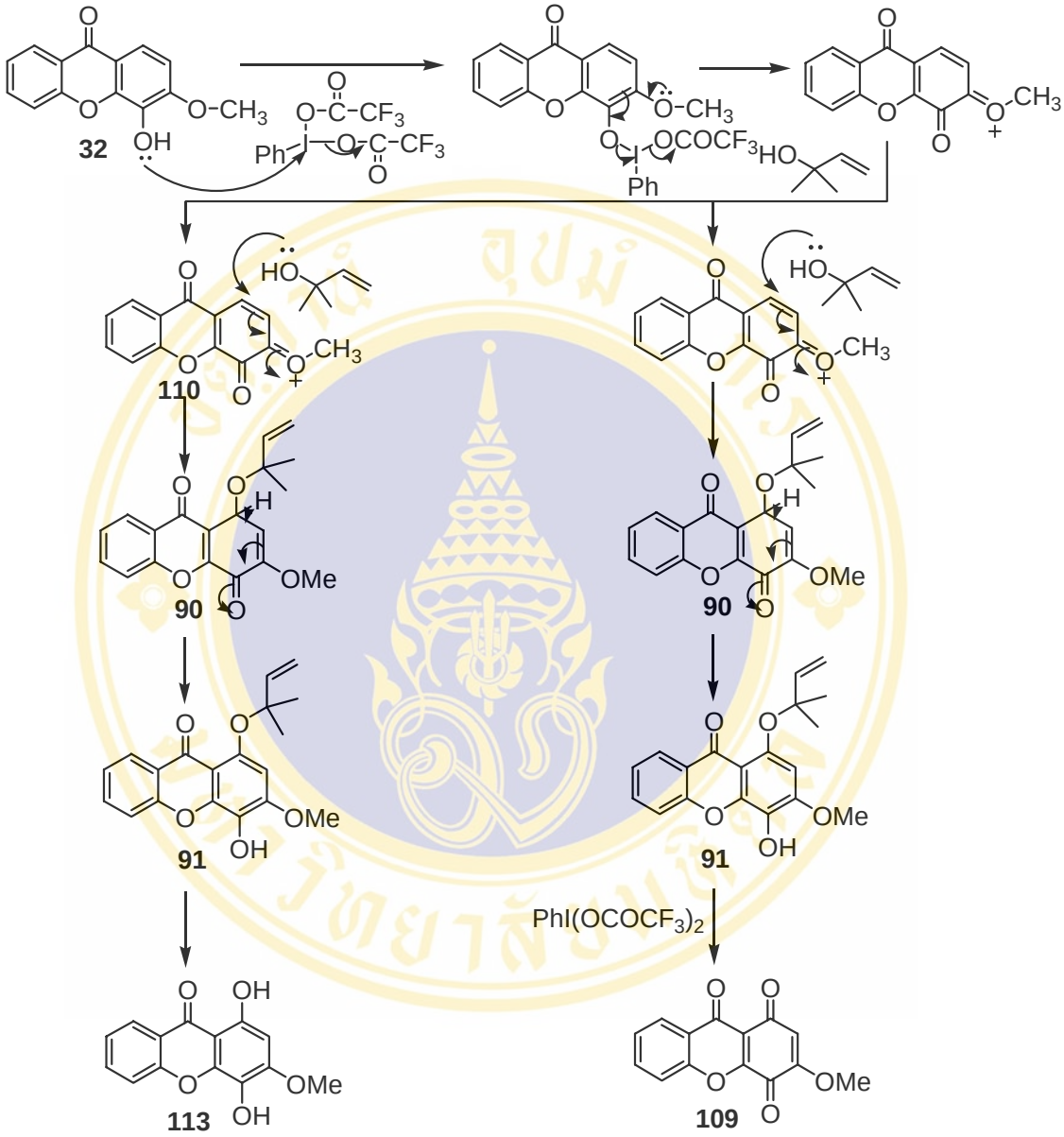
32 **113** **109**

Scheme 32

When 4-hydroxy-3-methoxyxanthen-9-one (**32**) was used as a starting material, no caged structure was formed. The isolated compounds were identified to be xanthone **113** (10% yield) and compound **109** (40% yield).

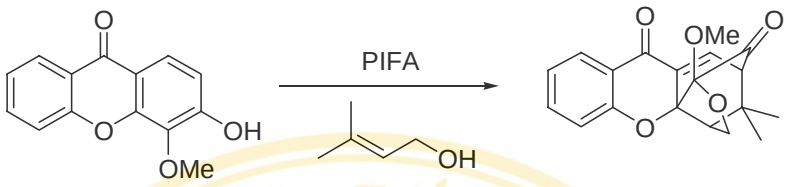
Compound **113** was obtained as a yellow solid and was characterized. The IR spectrum showed signals O-H stretching at υ_{max} 3410 cm^{-1}, C=O stretching at υ_{max} 1661 cm^{-1}. The ^{1}H NMR (500 MHz) spectrum exhibited a singlet signal at δ 3.92 ppm of a methoxy group and two singlet signals at δ 8.91 and 12.40 ppm, indicating the presence of two phenolic hydroxy groups with the latter being chelated to the C-9 carbonyl oxygen. The ^{13}C NMR spectrum (125 MHz) exhibited signals at δ 180.60 ppm, indicating that **113** contained a carbonyl carbons assigned to C-9. Mass spectrum of **113** gave a molecular ion peak at m/z 258.

The compound **113** could be derived by the mechanism as proposed in Scheme 33.



Scheme 33

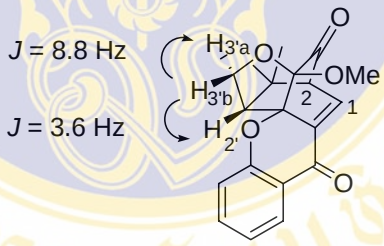
3.7 Reaction of 3-hydroxy-4-methoxyxanthen-9-one (31) with 3-methyl-2-buten-1-ol.



31 **114**

Scheme 34

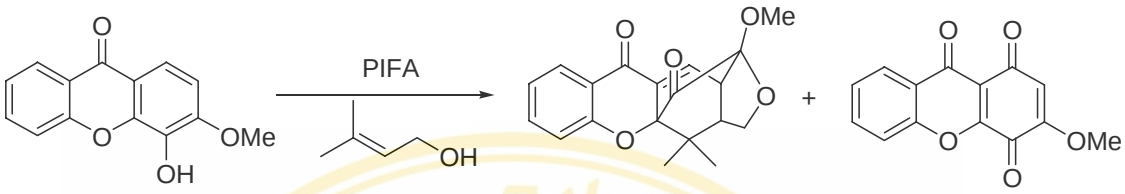
Compound **114** was prepared from the intramolecular Diels-Alder reactions of the unstable masked *o*-benzophenone in 53% yield by a slow addition of 3-hydroxy-4-methoxyxanthen-9-one (**31**) in THF solution to a THF solution of phenyliodonium(III) bistrifluoroacetate (PIFA, 1.5 equiv) and 3-methyl-2-buten-1-ol (10 equiv). Compound **114** was obtained as a pale yellow solid and was characterized. The IR spectrum showed signals of C=O stretching at υ_{max} 1673 and 1751 cm^{-1}.



114

The structure and relative stereochemistry of **114** were clearly established by analysis of its ^{1}H NMR spectrum. The ^{1}H NMR (500 MHz) spectrum exhibited signal at δ 4.04 ppm for H-3'b with $J_{H3'b,H3'a}$ = 8.8 Hz and $J_{H3'b,H2'}$ = 3.6 Hz, indicating that H-3'b was *syn* to the H-2'. The intramolecular Diels-Alder cycloaddition was evidenced by a coupling constant (J = 7.1 Hz) between H-1 at δ 7.41 ppm and H-2 at δ 3.07 ppm. The geminal methyl groups appear at δ 0.99 ppm and δ 1.22 ppm. The chemical shifts and J values shown supported that compound **114** has structure as indicated. Mass spectrum of **114** exhibited a molecular ion ([M^+]) peak at m/z 326.

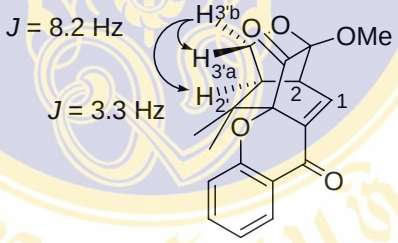
3.8 Reaction of 3-hydroxy-4-methoxyxanthen-9-one (32) with 3-methyl-2-buten-1-ol.



32 **115** **109**

Scheme 35

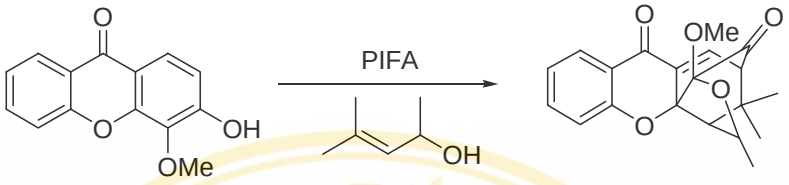
When 4-hydroxy-3-methoxyxanthen-9-one (**32**) was used as a starting material, compound **115** was produced in 25% yield. Evidently, **115** was obtained in low yields due to the easy oxidation of **32** to 3-methoxyxanthene-1,4,9-trione (**109**) (40% yield). The adduct **115** was obtained as a pale yellow solid and was characterized. The IR spectrum showed signals C=O stretching at υ_{max} 1667 and 1760 cm^{-1}.



115

The structure and relative stereochemistry of **115** was clearly established by analysis of its ^{1}H NMR spectrum. The ^{1}H NMR (300 MHz) spectrum exhibited signal at δ 3.72 ppm for methylene H-3'. The intramolecular Diels-Alder cycloaddition was evidenced by a coupling constant (J = 7.0 Hz) between H-1 at δ 7.43 ppm and H-2 at 3.72 ppm. The two geminal methyl groups exhibit at δ 0.91 ppm and δ 1.32 ppm. The chemical shift and J values shown supported that compound **115** has structure as indicated. Mass spectrum of **115** exhibited a molecular ion ($[M^{+}]$) peak at m/z 326.

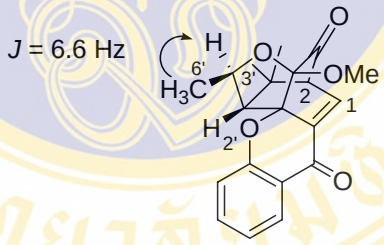
3.9 Reaction of 3-hydroxy-4-methoxyxanthen-9-one (31) with 4-methyl-3-penten-2-ol.



31 **116**

Scheme 36

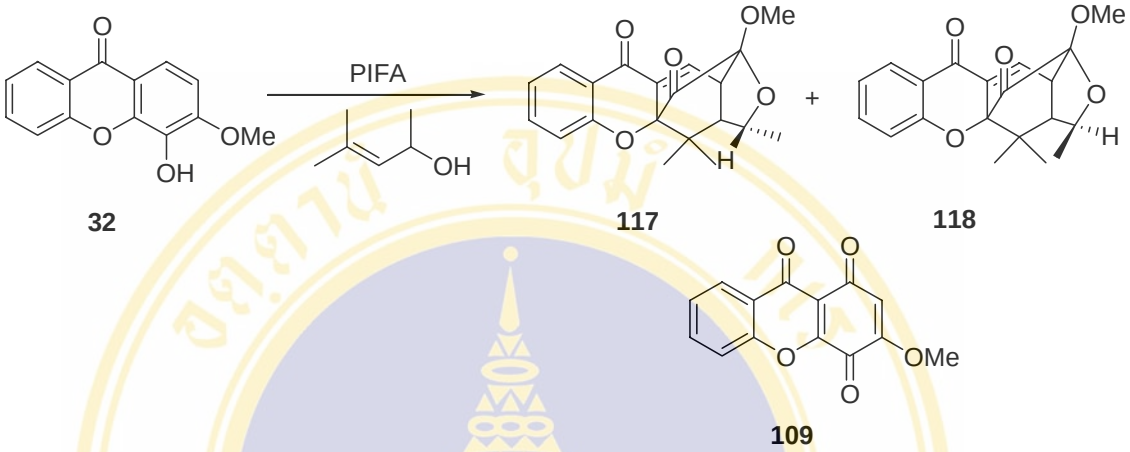
Compound **116** (15% yield) was prepared from the intramolecular Diels-Alder reactions of the unstable masked *o*-benzophenone derived from **31**. The reaction was carried out by treatment of 3-hydroxy-4-methoxyxanthen-9-one (**31**) with phenyliodonium(III) bistrifluoroacetate (PIFA, 1.5 equiv) and 4-methyl-3-penten-2-ol (10 equiv). Compound **116** was obtained as a pale yellow solid and was characterized. The IR spectrum showed signals of C=O stretching at υ_{max} 1672 and 1734 cm^{-1}.



116

The structure and relative stereochemistry of **116** were clearly established by analysis of its ^{1}H NMR spectrum. The ^{1}H NMR (500 MHz) spectrum exhibited a signal at δ 4.37 ppm as a quartet for H-3' with $J_{H3',H6'}$ = 6.6 Hz, indicating that H-3' was *anti* to the H-2'. The intramolecular Diels-Alder cycloaddition was evidenced by a coupling constant (J = 7.0 Hz) between H-1 at δ 7.34 ppm and H-2 at δ 2.98 ppm. The two geminal methyl exhibit at δ 0.86 ppm and 1.11 ppm. The chemical shifts and J values shown supported that compound **116** has structure as indicated. Mass spectrum of **116** exhibited a molecular ion ([M^+]) peak at m/z 340.

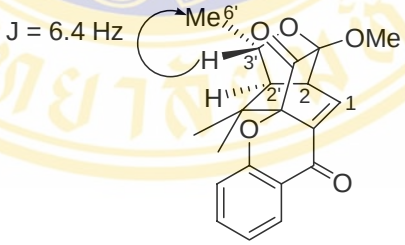
3.10 Reaction of 3-hydroxy-4-methoxyxanthen-9-one (32) with 4-methyl-3-penten-2-ol.



32 **117** **118** **109**

Scheme 37

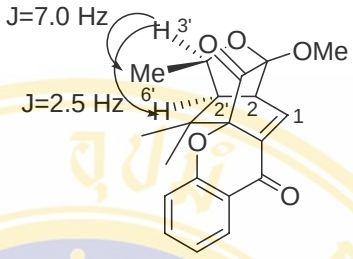
When 4-hydroxy-3-methoxyxanthen-9-one (**32**) was used as a starting material, compound **117** was produced in 15% yield along with its isomeric compound **118** (5% yield). Evidently, **117** was obtained in low yields due to the easy oxidation of **32** to 3-methoxyxanthene-1,4,9-trione (**109**) (40% yield).



117

The adduct **117** was obtained as a pale yellow solid and was characterized. The IR spectrum showed signals C=O stretching at υ_{max} 1673 and 1736 cm^{-1}. The structure and relative stereochemistry of **117** was clearly established by analysis of its ^1H NMR spectrum. The ^1H NMR (500 MHz) spectrum exhibited a signal at δ 4.46 ppm for H-3' as a quartet with $J_{H3',H6'}$ = 6.4 Hz, indicating that H-3' was *anti* to the H-2'. The intramolecular Diels-Alder cycloaddition was evidenced by a coupling constant (J = 7.0 Hz) between H-1 at δ 7.43 ppm and H-2 at δ 3.88 ppm. The chemical shift and J values

shown supported that compound **117** has structure as indicated. Mass spectrum of **117** exhibited a molecular ion ([M^+]) peak at m/z 340.



118

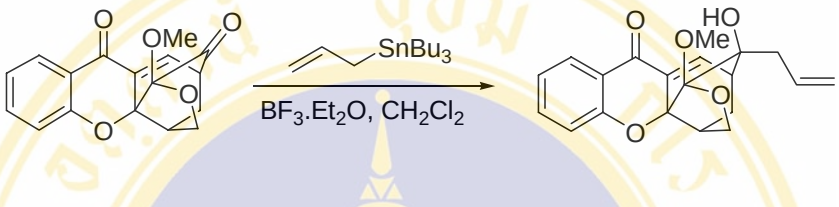
The adduct **118** was obtained as a pale yellow solid and was characterized. The IR spectrum showed signals C=O stretching at υ_{max} 1673 and 1736 cm^{-1}. The structure and relative stereochemistry of **118** was clearly established by analysis of its ^1H NMR spectrum. The ^1H NMR (500 MHz) spectrum exhibited a signal at δ 4.58 ppm for H-3' as a quartet of doublets with $J_{H3',H6'}$ = 7.0 Hz and $J_{H3',H2'}$ = 2.5 Hz, indicating that H-3' was *syn* to the H-2'. The intramolecular Diels-Alder cycloaddition was evidenced by a coupling constant (J = 7.0 Hz) between H-1 at δ 7.43 ppm and H-2 at δ 3.88 ppm. The chemical shift and J values shown supported that compound **118** has structure as indicated. Mass spectrum of **118** exhibited a molecular ion ([M^+]) peak at m/z 340.

In the oxidative addition reaction followed by the intramolecular Diels-Alder reaction, the yield of reaction is influenced by two factors:

The first factor is a type of allyl alcohol employed. The primary allylic alcohol reacts with masked *o*-benzoquinones more effectively than the secondary and the tertiary allylic alcohols, respectively. The second factor is a steric effect in the intramolecular Diels-Alder step. The more substituted allylic alcohols gave higher yield, eventhough longer reaction time was required.

4. Reaction of the caged xanthone with allyltributylstannane in the presence of boron trifluoride etherate as a Lewis acid.

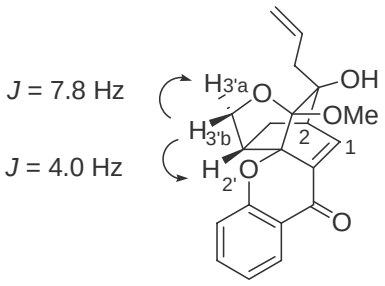
4.1 Reaction of the caged xanthone 107 with allyltributylstannane in the presence of boron trifluoride etherate as a Lewis acid.



107 **119**

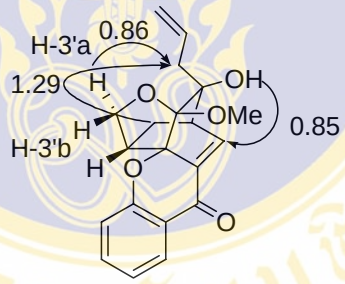
Scheme 38

Compound **107** was treated with allyltributylstannane to provide compound **119** in 29% yield. The reaction was carried out by a slow addition of a solution of allyltributylstannane (1.2 equiv) in CH_2Cl_2 to a -78 ^oC CH_2Cl_2 solution of a mixture of a caged xanthone **107** (1.0 equiv) and boron trifluoride etherate (3.0 equiv). Subsequently, the temperature was raised to room temperature. Unfortunately, the expected product derived from the addition of the allyl group to the ketal carbon was not formed. The only product observed was compound **119**. The compound **119** was characterized by means of spectroscopic techniques. The IR spectrum showed signals of O-H stretching at υ_{max} 3506 cm^{-1}, C=O stretching at υ_{max} 1735 cm^{-1} and C=C stretching at υ_{max} 1610 cm^{-1}.



119

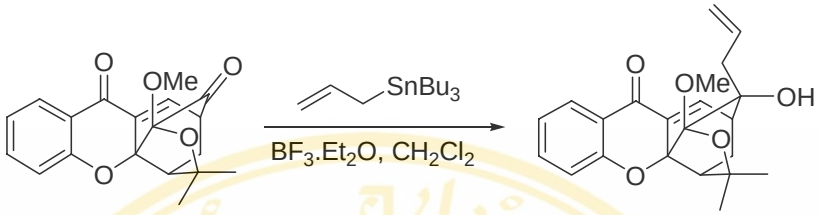
The structure and relative stereochemistry of **119** were clearly established by analysis of its ^{1}H NMR spectrum. The ^{1}H NMR (500 MHz) spectrum exhibited signal at δ 4.57 ppm assigned for H-3'b with $J_{H3'b,H3'a}$ = 7.8 Hz and $J_{3'b,H2'}$ = 4.0 Hz, indicating that H-3'b was *syn* to the H-2'. The signal at δ 5.10-5.14 ppm and δ 5.88-5.97 ppm belong to three vinylic protons of the allyl group. Regioselectivity and stereoselectivity in allylation reaction were confirmed by NOE experiments (Figure 4). Irradiation of the signal at δ 1.62 ppm (H-1') enhanced the signal at δ 2.20 ppm and δ 2.56 ppm (H-10) by 1.3%. Irradiation of the signal at δ 3.76 ppm (H-3'a) enhanced the signal at δ 2.20 ppm and δ 2.56 ppm (H-10) by 0.9%. In addition, irradiation of the signal at δ 2.88 ppm (OH) gave the enhancement to the signal at δ 7.56 ppm (H-1) by 0.9%. Mass spectrum of **119** exhibited a molecular ion ([M^{+}]) peak at m/z 340. The spectroscopic data supported that compound **119** has structure as indicated.



119

Figure 4

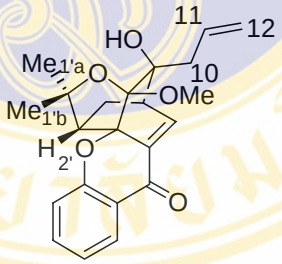
4.2 Reaction of the caged xanthone 110 with allyltributylstannane in the presence of boron trifluoride etherate as a Lewis acid.



110 **120**

Scheme 39

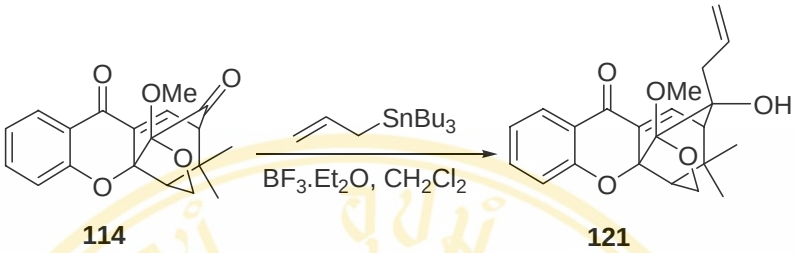
Treatment of compound **110** with allyltributylstannane provided compound **120** in 25% yield. The reaction was performed by a slow addition of a solution of allyltributylstannane (1.2 equiv) in CH_2Cl_2 to a CH_2Cl_2 solution of a mixture of a caged xanthone **110** (1.0 equiv) and boron trifluoride etherate (3.0 equiv). Again, no desired product was observed. Compound **120** formed was obtained as a white solid and was characterized. The IR spectrum showed signals of O-H stretching at υ_{max} 3481 cm^{-1}, C=O stretching at υ_{max} 1670 cm^{-1} and C=C stretching at υ_{max} 1622 cm^{-1}.



120

The structure and relative stereochemistry of **120** were clearly established by analysis of its ^1H NMR spectrum. The ^1H NMR (300 MHz) spectrum exhibited signal at δ 5.02-5.10 and 5.85-5.99 ppm assigned for three vinylic protons at C-11 and C-12. The spectroscopic data supported that compound **120** has structure as indicated. Mass spectrum of **120** exhibited a molecular ion ($[M^+]$) peak at m/z 360.

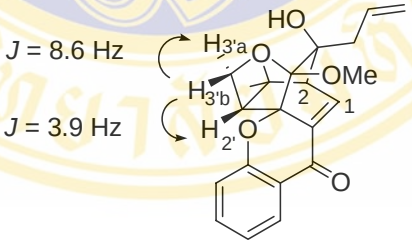
4.3 Reaction of the caged xanthone 114 with allyltributylstannane in the presence of boron trifluoride etherate as a Lewis acid.



114 **121**

Scheme 40

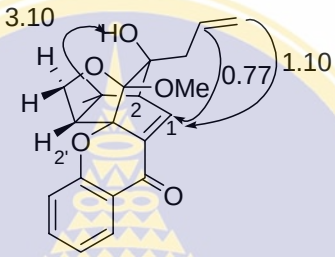
When compound **114** was treated with allyltributylstannane, compound **121** was obtained in 28% yield. The reaction was performed by a slow addition of a solution of allyltributyl stannane (1.2 equiv) in CH_2Cl_2 to a CH_2Cl_2 solution of a mixture of a caged xanthone **114** (1.0 equiv) and boron trifluoride etherate (3.0 equiv). Similar results were observed. Compound **121** derived from the addition of allyltributylstannane to the carbonyl carbon, was obtained as a white solid. Its IR spectrum showed signals of O-H stretching at υ_{max} 3452 cm^{-1}, C=O stretching at υ_{max} 1692 cm^{-1} and C=C stretching at υ_{max} 1608 cm^{-1}.



121

The structure and relative stereochemistry of **121** were clearly established by analysis of its ^1H NMR spectrum. The ^1H NMR (500 MHz) spectrum exhibited signal at δ 4.63 ppm as doublet of doublets for H-3'b with $J_{H3'b,H3'a}$ = 8.6 Hz and $J_{H3'b,H2'}$ = 3.9 Hz, indicating that H-3'b was *syn* to the H-2. The signal at δ 5.03-5.13 ppm and δ 5.93-6.01 ppm belong to three vinylic protons of the allyl group. Regioselectivity and stereoselectivity in allylation reaction were confirmed by NOE experiments (Figure 5).

Irradiation of the signal at δ 1.34 ppm (CH_3-5') enhanced the signal at δ 3.64 ppm (OH) by 3.1%. Irradiation of the signal at δ 5.96 ppm (H-11) enhanced the signal at δ 7.63 ppm (H-1) by 0.8%. In addition, irradiation of the signal at δ 5.09 ppm (H-12) gave the enhancement to the signal at δ 7.63 ppm (H-1) by 1.1%. Mass spectrum of **121** exhibited a molecular ion ([M^+]) peak at m/z 360. The spectroscopic data supported that compound **121** has structure as indicated

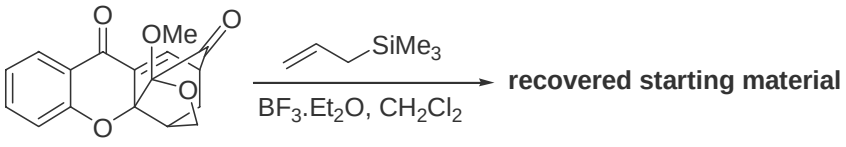


121

Figure 5

5. Reaction of the caged xanthone 107 with allyltrimethylsilane in the presence of various Lewis acid.

5.1 Reaction of the caged xanthone 107 with allyltrimethylsilane in the presence of boron trifluoride etherate.



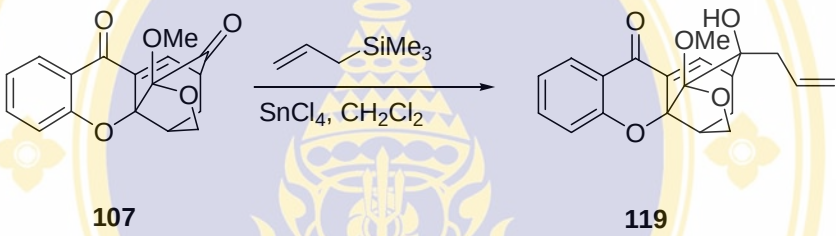
107

Scheme 41

With the unsuccessful and discouraging results, allylation by other allylating reagents was sought.

When compound **107** was treated with allyltrimethylsilane by adding a CH_2Cl_2 solution of allyltrimethylsilane (1.2 equiv) to a CH_2Cl_2 solution of a mixture of a caged xanthone **107** (1.0 equiv) and boron trifluoride etherate (3.0 equiv), no reaction took place. Compound **107** was recovered (84%). The results implied that, under the same conditions, allyltrimethylsilane is not so reactive as allyltributylstannane.

5.2 Reaction of the caged xanthone 107 with allyltrimethylsilane in the presence of tin tetrachloride.



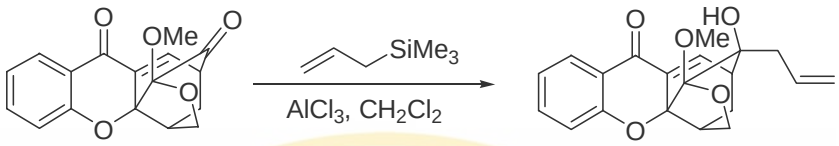
107 **119**

Scheme 42

Therefore, the allylation reaction mediated by allyltrimethylsilane was optimized by varying type of Lewis acid employed.

When compound **107** was treated with allyltrimethylsilane (1.2 equiv) in the presence of tin tetrachloride (3.0 equiv), compound **119** was obtained in 28% yield. The reaction followed that observed when **107** was exposed to allylation using allyltributylstannane in the presence of boron trifluoride etherate.

5.3 Reaction of the caged xanthone 107 with allyltrimethylsilane in the presence of aluminium trichloride.

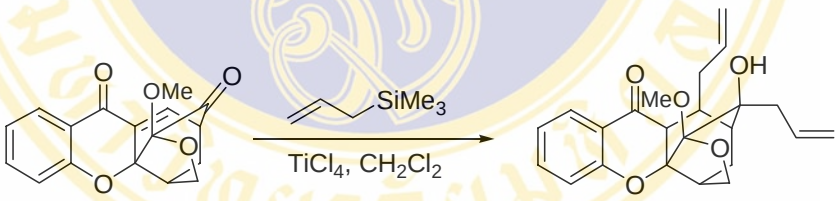


107 **119**

Scheme 43

A variation of Lewis acid was briefly studied. When compound **107** was treated with allyltrimethylsilane (1.2 equiv) and aluminium trichloride (3.0 equiv), compound **119** was obtained in 35% yield. No significant improvement in chemical yield of compound **119** was observed.

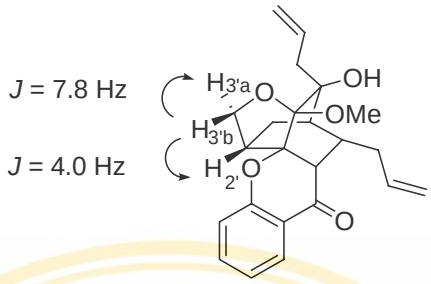
5.4 Reaction of the caged xanthone 107 with allyltrimethylsilane in the presence of titanium tetrachloride.



107 **122**

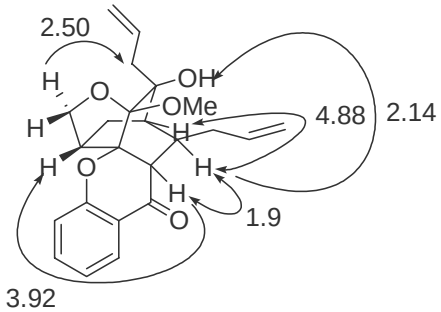
Scheme 44

A strong Lewis acid such as $TiCl_4$ was also investigated. Compound **107** was treated with allyltrimethylsilane (1.2 equiv) and titanium tetrachloride (3.0 equiv) to provide compound **122** in 28% yield. Compound **122** was obtained as a clear gel and was characterized. The IR spectrum showed signals of O-H stretching at υ_{max} 3522 cm^{-1}, C=O stretching at υ_{max} 1691 cm^{-1} and C=C stretching at υ_{max} 1607 cm^{-1}.



122

The structure and relative stereochemistry of **122** were clearly established by analysis of its ^{1}H NMR spectrum. The ^{1}H NMR (500 MHz) spectrum exhibited signal at δ 4.58 ppm for H-3' with $J_{H3'b,H3'a}$ = 7.1 Hz and $J_{H3'b,H2'}$ = 3.1 Hz, indicating that H-3'b was *syn* to the H-2'. The signal at δ 5.05-5.15 ppm and δ 5.86-5.98 ppm belong to three vinylic protons of the allyl group. Regioselectivity and stereoselectivity in allylation reaction were confirmed by NOE experiments (Figure 6). Irradiation of the signal at δ 1.79 ppm (H-2) enhanced the signal at δ 3.50-3.55 ppm (H-1) by 4.9%. Irradiation of the signal at δ 2.51 ppm (H-2') enhanced the signal at δ 2.74 ppm (H-8b) by 3.92%. Irradiation of the signal at δ 3.52 ppm (H-1) enhanced the signal at δ 2.93 ppm (OH) by 2.1% and enhanced the signal at δ 2.74 ppm (H-8b) by 1.9 %. In addition, irradiation of the signal at δ 3.66 ppm (H-3'a) gave the enhancement to the signal at δ 2.14 ppm (H-10) by 2.5%. Mass spectrum of **122** exhibited a molecular ion ([M^{+}]) peak at m/z 382. The spectroscopic data supported that compound **122** has structure as indicated.

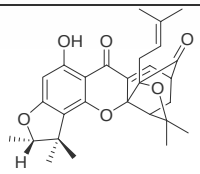


122

Figure 6

All the synthesized caged compounds **107**, **108**, **110**, **111**, **114**, **115**, **116**, **117** and **118**, **119**, **120**, **121** and **122** as well as simple xanthone derivatives (**31** and **32**) and compound **109** were tested for their *in vitro* activity against a variety of cancer cell lines and the results are summarized in Table 2. As can be seen from the Table, compounds **110**, **114** and **116** displayed interesting cytotoxic activity against P-388, KB, MCF-7, LU-1 and ASK cell lines (Table 2, entries 4, 5 and 6). It should be emphasized that compounds **110**, **114** and **116** contain only basic carbon skeleton of sootepenseone (**9**). For the neo-caged xanthones, a mixture of compounds **117** and **118** containing basic skeleton of 1-*O*-methylneobractatin (**7**) (Table 2, entry 9) exhibited interesting activity against P-388, KB, COL-2, MCF-7, LU-1 and ASK cell lines. Compounds **117**+**118** contain only basic carbon skeleton of 1-*O*-methylneobractatin **7**. In some cases, monoallylation product shows better activity (Table 2, entries 11, 12 and 13) while diallylation product (compound **122**) did not cytotoxic profile (Table 2, entry 14). This implied that the carbon-carbon double bond of the α,β–unsaturated ketone is, to some extent, crucial for the biological activity. It should be noted that these results are similar to those observed by Zang and co-workers.[51]

Table 1 Cytotoxic assay of sootepenseone.[8a]

Compound	Cell line, (ED_{50} μg/ mL)			
	KB	L1210	SK-OV-3	LNCAP
 **9**	1.74	1.74	1.74	1.74

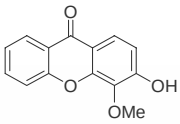
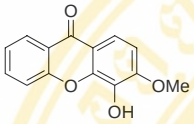
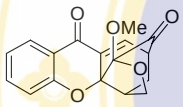
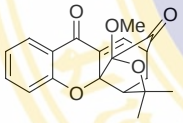
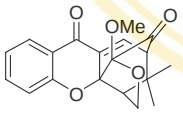
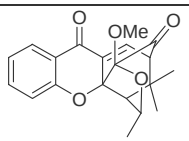
KB: epidermal carcinoma of the oral carvity

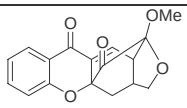
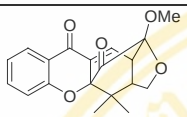
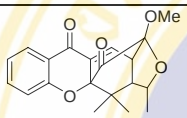
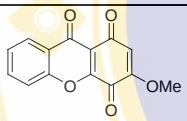
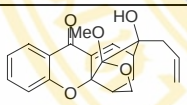
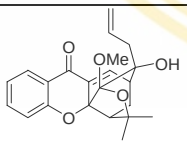
L1210: mice lymphatic leukemia

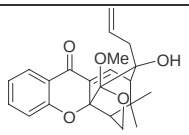
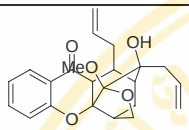
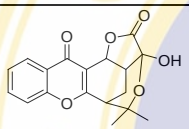
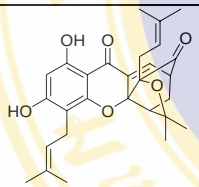
LNCAP: lymphoma metastasis of prostate carcinoma

SK-OV-3: human ovarian carcinoma

Table 2 Results from *in vitro* cytotoxicity assay (S. Sophasan, MU).

entry	Compounds		Cell lines					
			P-388	KB	COL-2	MCF-7	LU-1	ASK
1	 **31**	ED_{50}	-*	-*	-*	-*	-*	-*
2	 **32**	ED_{50}	1.002	-*	-*	-*	-*	-*
3	 **107**	ED_{50}	9.20	10.87	10.89	4.81	10.27	10.97
4	 **110**	ED_{50}	0.67	2.09	9.33	2.91	0.45	2.19
5	 **114**	ED_{50}	0.16	0.80	15.91	0.99	11.49	9.76
6	 **116**	ED_{50}	0.28	0.67	2.19	1.04	2.29	1.86

entry	Compounds		Cell lines					
			P-388	KB	COL-2	MCF-7	LU-1	ASK
7	 **108**	ED_{50}	3.45	3.63	-*	6.60	3.08	10.16
8	 **115**	ED_{50}	4.91	10.12	-*	8.16	15.33	-*
9	 **117**+**118**	ED_{50}	<0.16	0.54	1.76	0.63	2.08	1.52
10	 **109**	ED_{50}	-*	9.60	9.06	8.63	-*	-*
11	 **119**	ED_{50}	<0.16	0.58	11.41	0.81	9.09	3.27
12	 **120**	ED_{50}	7.32	8.62	12.84	7.32	10.79	13.86

entry	Compounds		Cell lines					
			P-388	KB	COL-2	MCF-7	LU-1	ASK
13	 **121**	ED_{50}	<0.16	0.37	0.38	0.36	0.41	0.46
14	 **122**	ED_{50}	-*	-*	-*	-*	-*	-*
15	 **111**	ED_{50}	1.41	8.99	11.32	7.51	10.76	13.32
16	 **4**	ED_{50}	0.40	2.17	2.47	1.98	7.40	2.82

-* = negative test

CHAPTER III
CONCLUSIONS

In conclusion, we have demonstrated a one pot two-step process, oxidative allylation followed by intramolecular Diels-Alder reaction, as a powerful tool for a rapid construction of highly substituted polycyclic carbon skeletons. The synthesis of **110** (3 steps, 8.89% yield) and **108** (3 steps, 3.51% yield) starting from commercially available 2-methoxybenzoic acid (**28**) and 1,2,3-trimethoxybenzene (**29**) was satisfactorily accomplished.

Compound **110** was found to exhibit interesting activity against P-388, KB, MCF-7, LU-1and ASK cancer cell lines. It should be noted that compounds **110** and **108**, obtained from compounds **31** and **32**, respectively, are the main carbon skeleton of several natural products, such as sootepenseone (**9**) and 1-*O*-methylneobractatin (**7**).

A variety of allylic alcohols were employed in the step of oxidative allylation followed by intramolecular Diels-Alder reaction, derived from compounds **31** and **32**, to provide a number of caged xanthone analogs. Attempts to perform allylation at the ketal carbon were not successful. Under all conditions investigated, allylation primarily took place at the ketone carbonyl carbon.

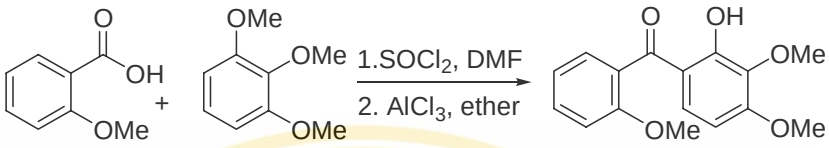
CHAPTER IV
EXPERIMENTAL

General Methods

^{1}H spectra were recorded on a Bruker DPX-300 (300 MHz), Bruker AVANCE 500 (500 MHz) spectrometer. Chemical shifts (δ) were measured in parts per million (ppm) with tetramethylsilane (δ=0) as an internal standard. ^{13}C NMR spectra were recorded on a Bruker Advance-300 (75 MHz) or a Bruker AVANCE 500 (125 MHz) spectrometer with residual non-deuterated solvent peak as an internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. Mass spectromeric analyses were recorded on a Bruker Esquire or Thermo Finnigan Polaris Q mass spectrometer. High resolution mass spectra for formula confirmation were recorded on Quadrupole-Time of Fligh Tandem Mass Spectrometer at Department of Chemistry, Faculty of Science, Chiangmai University. Low resolution mass spectra (EIMS) were recorded at Mahidol University on a Finnigan MAT INCOS 50 mass spectrometer. Melting points were determined on an Electrothermal IA 9000 series apparatus and are uncorrected.

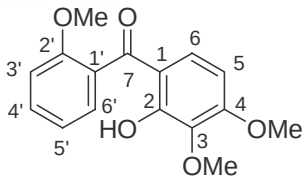
Solvents and reagents were purified as follows: tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl; dichloromethane (CH_2Cl_2) and acetone were distilled from phosphorus pentoxide (P_2O_5) and were stored over activated molecular sieves (4Å). Radial chromatography on a Chromatotron was performed with Merck silica gel 60 F_{254} (Art. 7749). Silica gel 60 (Art. 7734) at atmospheric pressure and Merck silica gel 60 (Art. 7736) for medium pressure. Preparatory layer chromatography (PLC) was performed using Merck silica gel 60 F_{254} (Art. 7747). Analytical TLC was performed with Merck TLC aluminium sheet silica gel 60 F_{254} (Art. 5554) with 0.2 mm. thickness. Unless otherwise noted, all reactions were performed under positive argon atmosphere in oven-dried glassware cooled in a dessicator before use. All chemicals were purchased from Fluka AG or Aldrich chemical company and were used without prior purification.

1. Preparation of 2-hydroxy-2',3,4-trimethoxybenzophenone (30).[24]



28 **29** **30**

A mixture of 2-methoxybenzoic acid (**28**) (1.0 g, 6.5 mmol), thionyl chloride (5.0 mL, 65.0 mmol) and a catalytic amount of dimethyl formamide (0.1 mL, 1.3 mmol) was heated under reflux at 80 ^{o}C for 2 h. The reaction mixture was cooled and evaporated to remove the excess of thionyl chloride. The residue was transfered to a solution 1,2,3-trimethoxybenzene (**29**) (1.3 g, 7.8 mmol) in sodium-dried ether (50 mL), and anhydrous powdered aluminium chloride (3.5 g, 0.026 mol) was subsequently added. The resulting two-phase, deep red mixture was stirred at room temperature for 20 h. The solvent was evaporated off under reduced pressure and the viscous residue was poured into water. The aqueous suspension was acidified with 10% HCl (10 mL) and was extracted with ethyl acetate (3x25 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated (aspirator) to give a crude oil. 2-Hydroxy-2',3,4-trimethoxybenzophenone (**30**) (1.46g, 78%) was obtained as a yellow solid after crystallization from methanol.



30

Compound **30**

A yellow solid (methanol), mp 121.0-123.5 °C; R_f 0.5 (50% EtOAc/hexane).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 3.78 (s, 3H, OCH_3-2'), 3.91 (s, 3H, OCH_3-4), 3.94 (s, 3H, OCH_3-3), 6.40 (d, *J* = 9.1 Hz, 1H, H-5), 7.01 (d, *J* = 8.4 Hz, 1H, H-3′), 7.05 (td, *J*

= 7.8, 0.9 Hz, 1H, H-5'), 7.10 (d, *J* = 9.1 Hz, 1H, H-6), 7.27 (dd, *J* = 8.0, 1.7 Hz, 1H, H-6′), 7.47 (td, *J* = 8.5, 1.7 Hz, 1H, H-4′), 12.50 (s, 1H, OH-2).

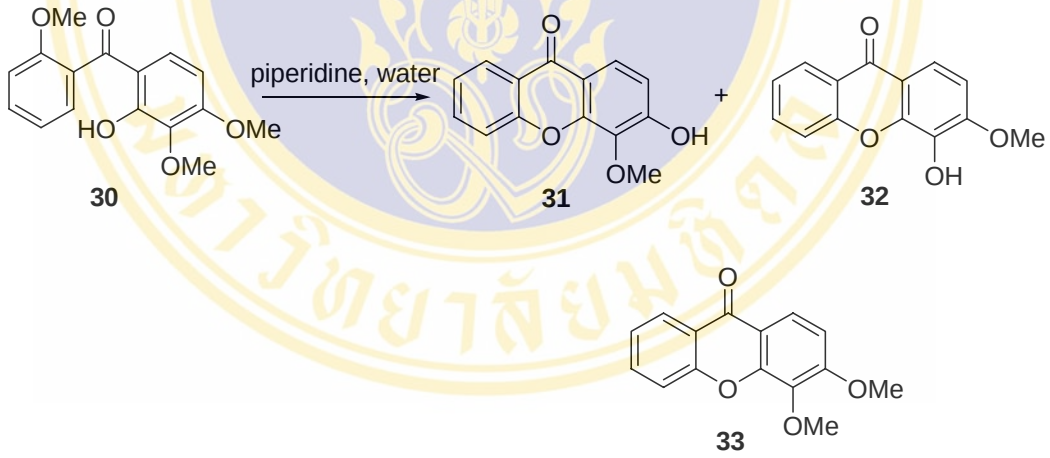
^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 55.67, 56.06, 60.65, 102.76, 111.43, 115.73, 120.38, 127.92, 128.71, 130.24, 131.56, 136.32, 156.39, 157.46, 158.66, 200.67.

IR (nujol, cm^{-1}): 3412 (O-H), 1599 (C=O), 1499, 1454, 1421 1343, 1285.

MS: m/z (% relative intensity) 289 (M^++H, 7), 288 (M^+, 40), 257 (100), 180 (32), 152 (50), 135 (30).

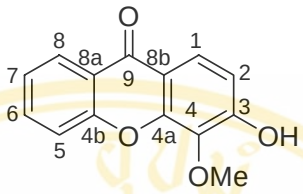
HRMS: Molecular ion (M+Na) calcd for $C_{16}H_{16}O_5Na$: 311.0895; found (ESI positive) m/z = 311.0894, error = 0.3 ppm.

2. Preparation of 3-hydroxy-4-methoxyxanthen-9-one (31), 4-hydroxy-3-methoxy xanthen-9-one (32) and 3,4-dimethoxyxanthen-9-one(33).[24]



A mixture of 2-hydroxy-2',3,4-trimethoxybenzophenone (**30**) (2.5 g, 8.6 mmol) and piperidine (30 mL) containing water (25 mL) was heated under reflux for 46 h. The cooled mixture was poured into a 4 N hydrochloric acid (150 mL). The mixture was extracted by dichloromethane (3x25 mL) and the dried ($MgSO_4$) extract was evaporated to a granular solid which was further purified by a chromatographic method. After purified, 3-hydroxy-4-methoxyxanthen-9-one (**31**) (0.79, 38%), 4-hydroxy-3-methoxy

xanthen-9-one (**32**) (0.93 g, 45%), and 3,4-dimethoxyxanthen-9-one (**33**) (0.11 g, 5%), were obtained.



31

Compound **31**[41]

A white solid (EtOAc/hexane), mp 212.0-213.0 °C; R_f 0.3 (20% EtOAc/hexane, 2 elutions).

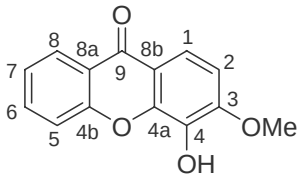
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.09 (s, 3H, OCH_3), 6.36 (s, 1H, OH), 6.95 (d, *J* = 8.8 Hz, 1H, H-2), 7.32 (t, *J* = 7.2 Hz, 1H, H-7), 7.48 (d, *J* = 8.1 Hz, 1H, H-5), 7.65 (ddd, *J* = 8.1, 7.2, 1.6 Hz, 1H, H-6), 7.98 (d, *J* = 8.8, 1H, H-1), 8.28 (dd, *J* = 7.9, 1.6 Hz, 1H, H-8).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 61.94 (OCH_3), 112.43 (C-2), 116.49 (C-8b), 117.76 (C-5), 121.68 (C-8a), 122.84 (C-1), 124.21 (C-7), 126.82 (C-8), 133.80 (C-4), 134.46 (C-6), 149.88 (C-4a), 154.22 (C-3), 155.77 (C-4b), 176.18 (C-9).

IR (nujol, cm^{-1}): 3207 (O-H), 1643 (C=O), 1229 (C-CO-C), 1200 (C-O, O-H), 1154 (C-O-C).

MS: m/z (% relative intensity) 242 (M^+, 100), 227 (80), 199 (26), 121 (3), 76 (3).

HRMS: Molecular ion (M^+) calcd for $C_{14}H_{10}O_4$: 242.0579; found (EI) m/z = 242.0579, error = 4 ppm; base peak = 242 amu.



32

Compound **32**[41]

A white solid (EtOAc/hexane), mp 194.5-194.7 °C; R_f 0.2 (20% EtOAc/hexane, 2 elutions).

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.05 (s, 3H, OCH_3), 5.90 (s, 1H, OH), 7.01 (d, *J* = 8.8 Hz, 1H, H-2), 7.38 (t, *J* = 7.1 Hz, 1H, H-7), 7.58 (d, *J* = 8.7 Hz, 1H, H-5), 7.71 (ddd, *J* = 8.7, 7.1, 1.5 Hz, 1H, H-6), 7.92 (d, *J* = 8.8 Hz, 1H, H-1), 8.34 (dd, *J* = 8.0, 1.5 Hz, 1H, H-8).

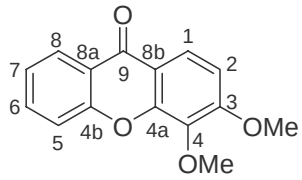
^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 56.59 (OCH_3), 107.50 (C-2), 116.81 (C-8b), 117.93 (C-5), 118.05 (C-1), 121.53 (C-8a), 123.92 (C-7), 126.74 (C-8), 133.28 (C-4), 134.57 (C-6), 144.8 (C-4a), 150.90 (C-3), 156.14 (C-4b), 176.60 (C-9).

IR (nujol, cm^{-1}): 3240 (O-H), 1643 (C=O), 1225 (C-CO-C), 1199 (C-O, O-H), 1154 (C-O-C).

MS: m/z (% relative intensity) 242 (M^+, 100), 227 (28), 199 (17), 121 (3), 76 (3).

LCMS: Molecular ion (M+Na) calcd for $C_{14}H_{10}O_4Na$: 265.0; found m/z = 265.0.

HRMS: Molecular ion (M^+) calcd for $C_{14}H_{10}O_4$: 242.0579; found (EI) m/z = 242.0586, error = 3 ppm; base peak = 242 amu.



33

Compound **33**[41]

A white solid (EtOAc/hexane), mp 156.0-157.0 °C; R_f 0.5 (20% EtOAc/hexane, 2 elutions).

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 4.02 (s, 3H, OCH_3-3), 4.05 (s, 3H, OCH_3-4), 7.15 (d, *J* = 8.9 Hz, 1H, H-2), 7.38 (ddd, *J* = 7.8, 7.7, 0.9 Hz, 1H, H-7), 7.59 (d, *J* = 8.2 Hz, 1H, H-5), 7.72 (ddd, *J* = 8.2, 7.8, 1.1, 1H, H-6), 8.10 (d, *J* = 9.0 Hz, 1H, H-1), 8.34 (dd, *J* = 7.7, 1.1 Hz, 1H, H-8).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 55.77 (OCH_3-3), 60.93 (OCH_3-4), 108.62 (C-2), 116.80 (C-8b), 118.04 (C-5), 121.54 (C-8a), 122.43 (C-1), 123.95 (C-7), 126.64 (C-8), 134.52 (C-6), 136.40 (C-4), 150.61 (C-4a), 156.16 (C-4b), 157.57 (C-3), 176.54 (C-9).

IR (nujol, cm^{-1}): 1643 (C=O), 1229 (C-CO-C), 1154 (C-O-C).

MS: m/z (% relative intensity) 257 (M+H, 15), 256 (M^+, 100), 241 (44), 213 (27).

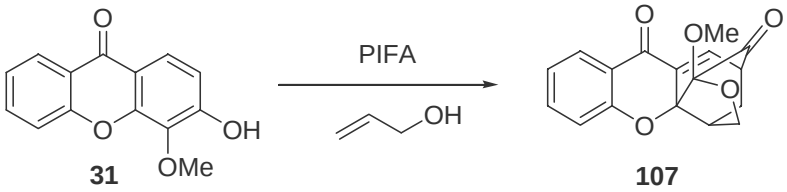
LCMS: Molecular ion (M+Na) calcd for $C_{15}H_{12}O_4Na$: 279.063; found m/z = 279.1.

HRMS: Molecular ion (M^+) calcd for $C_{15}H_{12}O_4$: 256.0136; found (EI) m/z = 256.0140, error = 2 ppm; base peak = 256 amu.

3. Reaction of 3-hydroxy-4-methoxyxanthen-9-one (31) and 4-hydroxymethoxy xanthen xanthen-9-one (32) with allyl alcohol in the presence of hypervalent iodine.

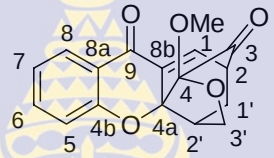
General Procedure I[51]

To a stirred solution of allyl alcohol (10 equiv) in THF (ca. 4 M) was added phenyliodonium(III) bistrifluoroacetate (PIFA) (1.5 equiv). To this solution mixture at rt a solution of xanthone (1 equiv) in dry THF (ca. 0.4 M) was added dropwise over 10 min *via* a syringe pump (2 mL/ min). After 6 h at rt solid $NaHCO_3$ (3 equiv) was added and the mixture was stirred at rt for 10 min before diluted with water (25 mL). The aqueous layer was separated and extracted with EtOAc (3x25 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated (aspirator). The residue was purified by radial chromatography on silica gel.



31 **107**

3.1 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.3 g, 0.6 mmol), allyl alcohol (0.3 mL, 4.1 mmol) and 3-hydroxy-4-methoxyxanthen-9-one (**31**) (0.1 g, 0.4 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to yield compound **107** (0.05 g, 45%).



107

Compound **107**[41]

A pale yellow solid (EtOAc/hexane), mp 102.0-102.5 °C; R_f 0.7 (1:4 EtOAc/hexane, 3 elutions).

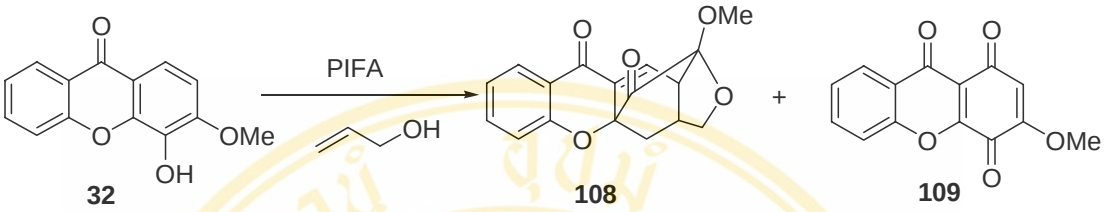
^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.75-1.78 (m, 1H, H-1′a), 1.85-1.87 (m, 1H, H-1′b), 2.63 (ddd, *J* = 10.2, 3.6, 1.6 Hz, 1H, H-2′), 3.35-3.40 (m, 1H, H-2), 3.50 (s, 3H, O-CH_3), 3.81 (d, *J* = 8.0 Hz, 1H, H-3′a), 4.65 (dd, *J* = 8.0, 3.7 Hz, 1H, H-3′b), 6.95-7.05 (m, 2H, H-5, H-7), 7.35 (d, *J* = 7.1 Hz, 1H, H-1), 7.45 (ddd, *J* = 8.0, 7.5, 1.8 Hz, 1H, H-6), 7.85 (dd, *J* = 7.8, 1.8 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 28.33 (C-1′), 41.22 (C-2′), 46.24 (C-2), 54.08 (OCH_3), 73.30 (C-3′), 87.46 (C-4a), 97.81 (C-4), 118.00 (C-7), 119.27 (C-8a), 122.20 (C-5), 127.47 (C-8), 133.94 (C-8b), 134.27 (C-1), 136.66 (C-6), 159.75 (C-4b), 176.54 (C-9), 198.67 (C-3).

IR (nujol, cm^{-1}): 1735 (C=O), 1228 (C-CO-C), 1043 (C-O-C).

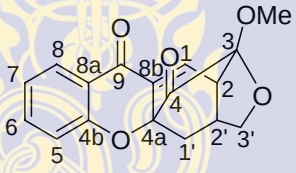
MS: m/z (% relative intensity) 299 (24), 269 (19), 211 (100).

ESITOF: Molecular ion (M+H) calcd for $C_{17}H_{15}O_5$: 299.0919; found (EI) m/z = 299.0941, error = 7 ppm; base peak = 299 amu.



32 **108** **109**

3.2 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.4 g, 1.2 mmol), allyl alcohol (0.6 mL, 8.3 mmol) and 4-hydroxy-3-methoxyxanthen-9-one (**32**) (0.2 g, 0.8 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent), to yield compound **108** (0.03 g, 10%) and 3-methoxyxanthene-1,4,9-trione (**109**) (0.09 g, 40%).



108

Compound **108**[41]

A pale yellow solid (EtOAc/hexane), mp 102.0-102.5 °C; R_f 0.7 (1:4 EtOAc/hexane, 3 elutions).

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.15 (d, *J* = 2.89 Hz, 2H, H-1′), 2.42-2.51 (m, 1H, H-2′), 3.42 (s, 3H, OCH_3), 3.60 (dd, *J* = 7.0, 4.4 Hz, 1H, H-2), 3.88 (d, *J* = 8.2 Hz, 1H, H-3′a), 4.16 (dd, *J* = 8.2, 3.3 Hz, 1H, H-3′b), 6.96 (ddd, *J* = 7.8, 7.6, 1.1 Hz, 1H, H-7), 7.07 (d, *J* = 8.8 Hz, 1H, H-5), 7.22 (d, *J* = 7.0 Hz, 1H, H-1), 7.45 (ddd, *J* = 8.8, 7.8, 1.8 Hz, 1H, H-6), 7.80 (dd, *J* = 7.8, 1.8 Hz, 1H, H-8).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 33.51 (C-2′), 36.91 (C-1′), 43.42 (C-2), 51.57 (OCH_3), 74.34 (C-3′), 83.79 (C-4a), 97.14 (C-3), 118.19 (C-5), 119.10 (C-8a), 122.10 (C-

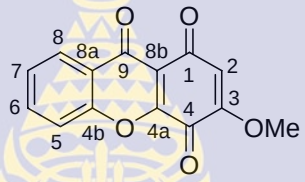
7), 126.88 (C-8), 134.27 (C-1), 135.14 (C-8b), 136.55 (C-6), 160.03 (C-4b), 175.19 (C-9), 195.29 (C-4).

IR (nujol, cm^{-1}): 1760 (C=O), 1668 (C=O), 1230 (C-CO-C), 1206 (C-O, O-H), 1147 (C-O-C).

MS: m/z (% relative intensity) 316 (26), 299 (100), 271 (58), 211 (14).

HRMS: Molecular ion (M+H) calcd for $C_{17}H_{15}O_5$: 299.0919; found (EI) m/z = 299.0924, error = 2 ppm; base peak = 299 amu.

HRMS: Molecular ion ($M+NH_4$) calcd for $C_{17}H_{18}NO_5$: 316.1185; found (CI, NH_3) m/z = 316.1187, error = 0.6 ppm; base peak 299 amu.



109

Compound **109**[41]

A yellow solid (EtOAc/hexane), mp 201.0-202.5 °C; R_f 0.7 (1:2 EtOAc/hexane, 2 elutions).

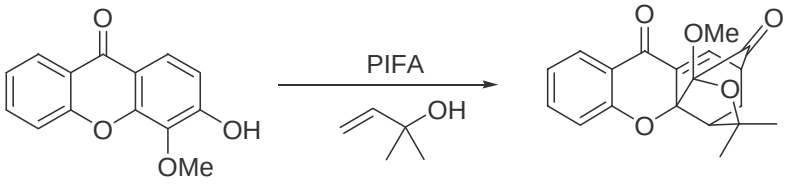
^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 3.98 (s, 3H, OCH_3), 6.12 (s, 1H, H-2), 7.51 (ddd, *J* = 8.0, 7.6, 1.0 Hz, 1H, H-7), 7.70 (d, *J* = 8.5 Hz, 1H, H-5), 7.79 (ddd, *J* = 8.5, 7.6, 1.6 Hz, 1H, H-6), 8.30 (dd, *J* = 8.0, 1.6 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 56.70 (OCH_3), 109.40 (C-2), 113.92 (C-8b), 119.10 (C-5), 126.45 (C-8a), 126.78 (C-7), 126.91 (C-8), 135.31 (C-6), 154.50 (C-4b), 155.19 (C-4a), 157.0 (C-3), 174.16 (C-9), 175.69 (C-1), 182.48 (C-4).

IR (nujol, cm^{-1}): 1701 (C=O), 1678 (C=O), 1089 (C-O-C).

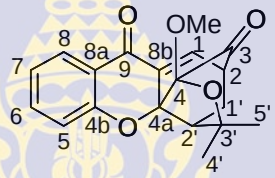
MS: m/z (% relative intensity) 256 (31), 255 (100), 241 (8), 213(53).

ESITOF: Molecular ion (M+K) calcd for $C_{14}H_8O_5K$: 279.0060; found (EI) m/z = 279.0052, error = 3 ppm; base peak = 280 amu.



31 **110**

3.3 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.26 g, 0.6 mmol), 2-methyl-3-buten-2-ol (0.43 mL, 0.35 mol) and 3-hydroxy-4-methoxyxanthen-9-one (**31**) (0.1 g, 0.4 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to afford compound **110** (0.04 g, 30%).



110

Compound **110**

A pale yellow solid (EtOAc/hexane), mp 149.0-149.5 °C; R_f 0.3 (20% EtOAc/hexane, 2 elutions).

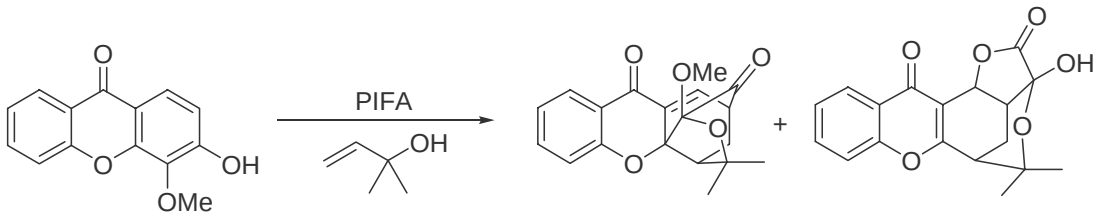
^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.32 (s, 3H, CH_3), 1.39 (ddd, *J* = 13.6, 9.6, 1.1 Hz, 1H, H-1′), 1.82 (s, 3H, CH_3), 2.32 (dd, *J* = 13.7, 4.5 Hz, 1H, H-1), 2.52 (d, *J* = 9.6 Hz,1H, H-2’), 3.44-3.46 (m, 1H, H-2), 3.57 (s, 3H, O-CH_3), 7.08-7.10 (m, 2H, H-5, H-7), 7.54-7.56 (m, 1H, H-6), 7.59 (d, *J* = 7.0 Hz, 1H, H-1), 7.97 (dd, *J* = 8.1, 1.7 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 24.62 (C-1′), 28.75 (CH_3), 30.07 (CH_3), 47.03 (C-2), 47.60 (C-2’), 53.96 (OCH_3), 81.61 (C-3’), 89.43 (C-4a), 97.60 (C-4), 118.02, 122.05 (C-5 or C-7), 119.16 (C-8a), 127.36 (C-8), 134.47 (C-8b), 136.21 (C-1), 136.51 (C-6), 159.87 (C-4b), 176.90 (C-9), 201.12 (C-3)

IR (nujol, cm^{-1}): 1744 (C=O), 1667 (C=O), 1607, 1577, 1463, 1340, 1308, 1232.

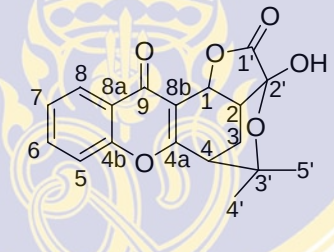
MS: m/z (% relative intensity) 326 (M^+, 1), 239 (98), 229 (50), 197 (100).

HRMS: Molecular ion (M+Na) calcd for $C_{19}H_{18}O_5Na$: 349.1051; found (ESI positive) m/z = 349.1052, error = 0.3 ppm.



31 **110** **111**

3.4 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.7 g, 1.6 mmol), 2-methyl-3-buten-2-ol (0.4 mL, 0.35 mol) and 3-hydroxy-4-methoxyxanthen-9-one (**31**) (0.1 g, 0.4 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) affording compound **110** (6.7 mg, 5%) and compound **111** (0.03 g, 20%).



111

Compound **111**

A white solid (EtOAc/hexane), mp 177.0-179.8 °C; R_f 0.3 (50% EtOAc/hexane, 3 elutions).

^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 1.08 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.02 (dt, *J* = 14.0, 3.1 Hz, 1H, H-3), 2.48-2.52 (m, 1H, H-3), 2.83 (t, *J* = 2.6 Hz, 1H, H-4), 2.87-2.90 (m, 1H, H-2), 5.67 (d, *J* = 7.8 Hz, 1H, H-1), 7.51 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H, H-7), 7.63 (d, *J* = 8.1 Hz, 1H, H-5), 7.82 (ddd, *J* = 8.7, 7.1, 1.2 Hz, 1H, H-6), 8.07 (dd, *J* = 8.0, 1.6 Hz, 1H, H-8).

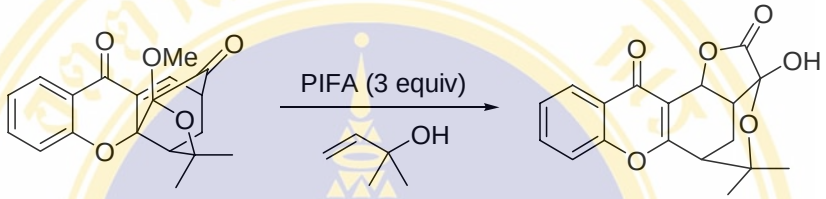
^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 20.45 (C-3), 26.87 (CH_3), 28.68 (CH_3), 35.78 (C-2), 41.24 (C-4), 71.60 (C-1), 74.11 (C-3'), 93.30 (C-2'), 116.68 (C-8b), 118.26 (C-5),

123.18 (C-8a), 124.98 (C-8), 125.80 (C-7), 134.49 (C-6), 155.01 (C-4b), 169.08 (C-1'), 172.42 (C-4a), 175.27 (C-9).

IR (nujol, cm^{-1}): 3414 (O-H), 1775 (C=O), 1651 (C=O), 1463, 1133, 1125.

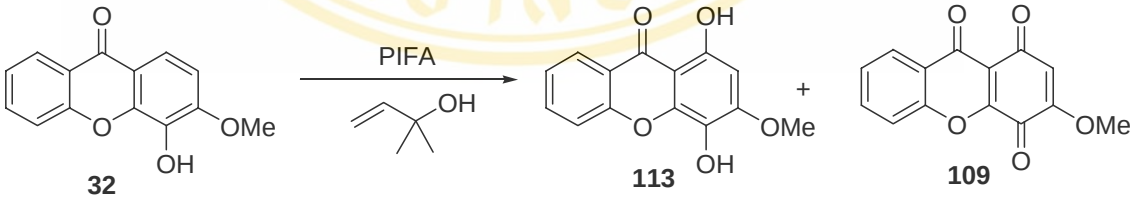
MS: m/z (% relative intensity) 328 (100), 261 (11), 197 (17).

HRMS: Molecular ion (M+Na) calcd for $C_{18}H_{16}O_6Na$: 351.0844; found (ESI positive) m/z = 351.0844, error = 0 ppm.



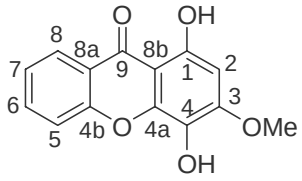
110 **111**

3.5 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.11 g, 0.27 mmol), 2-methyl-3-buten-2-ol (0.08 mL, 0.9 mmol) and compound **110** (0.03 g, 0.09 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:1 EtOAc/hexane eluent) affording compound **111** (0.005 g, 17%).



32 **113** **109**

3.6 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.4 g, 1.2 mmol), 2-methyl-3-buten-2-ol (0.6 mL, 8.3 mmol) and 4-hydroxy-3-methoxyxanthen-9-one (**32**) (0.2 g, 0.9 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent), affording 1,4-dihydroxy-3-methoxyxanthene-9-one (**113**) (0.03 g, 10%), 3-methoxyxanthene-1,4,9-trione (**109**) (0.09 g, 40%).



113

Compound **113**

A yellow solid (EtOAc/hexane); R_f 0.4 (50% EtOAc/hexane).

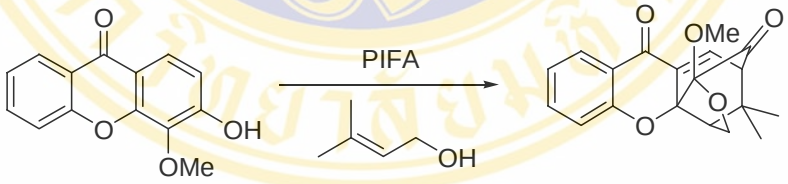
^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 3.92 (s, 3H, OCH_3), 6.57 (s, 1H, H-2), 7.46 (t, *J* = 7.5 Hz, 1H, H-7), 7.62 (d, *J* = 8.2 Hz, 1H, H-5), 7.86 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H, H-6), 8.14 (dd, *J* = 7.9, 1.6 Hz, 1H, H-8), 8.91 (s, 1H, OH-4), 12.40 (s, 1H, OH-1).

^{13}C NMR (125 MHz, DMSO-d_6, ppm): δ 56.41, 94.72, 102.49, 117.85, 119.57, 124.23, 125.35, 126.00, 135.91, 154.77, 154.77, 155.64, 155.88, 180.62.

IR (nujol, cm^{-1}): 3410 (O-H), 1661 (C=O), 1605, 1466.

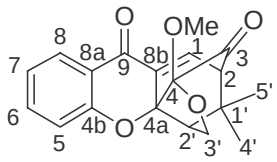
MS: m/z (% relative intensity) 258 (M^+, 8), 197 (30), 149 (49), 135(100).

HRMS: Molecular ion (M+H) calcd for $C_{14}H_9O_5$: 259.0528; found (ESI positive) m/z = 259.0607, error = 3 ppm.



31 **114**

3.7 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.26 g, 0.6 mmol), 3-methyl-2-buten-1-ol (0.43 mL, 0.35 mol) and 3-hydroxy-4-methoxyxanthen-9-one (**31**) (0.1 g, 0.4 mmol) were employed. The reaction was carried out for 16 h to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to afford compound **114** (0.07 g, 53%).



114

Compound **114**

A pale yellow solid (EtOAc/hexane), mp 155.5-156 °C; R_f 0.4 (20% EtOAc/hexane, 2 elutions).

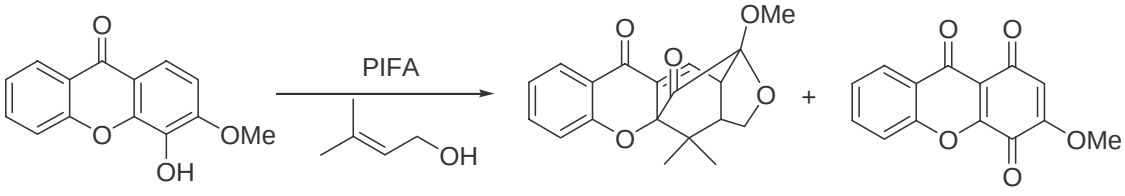
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.99 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 2.16 (d, *J* = 3.6 Hz, 1H, H-2′), 3.07 (d, *J* = 7.1 Hz,1H, H-2), 3.58 (s, 3H, O-CH_3), 4.09 (d, *J* = 8.8 Hz, 1H, H-3′a), 4.65 (dd, *J* = 8.8, 3.7 Hz, 1H, H-3′b), 7.04-7.11 (m, 2H, H-5, H-7), 7.41 (d, *J* = 7.1 Hz, 1H, H-1), 7.55 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1H, H-6), 7.98 (dd, *J* = 7.9, 1.6 Hz, 1H, H-8).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 24.76, 28.23, 33.70, 52.26, 53.97, 59.93, 67.93, 87.77, 96.49, 118.00, 119.17, 122.15, 127.42, 133.02, 133.97, 136.66, 159.89, 176.58, 198.70.

IR (nujol, cm^{-1}): 1751 (C=O), 1673 (C=O), 1610, 1465, 1319.

MS: m/z (% relative intensity) 299 (24), 269 (19), 211 (100).

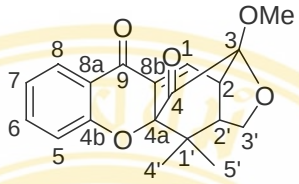
HRMS: Molecular ion (M+Na) calcd for $C_{19}H_{18}O_5Na$: 349.1051; found (ESI positive) m/z = 349.1053, error = 0.5 ppm.



32 **115** **109**

3.8 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.4 g, 1.2 mmol), 3-methyl-2-buten-1-ol (0.6 mL, 8.3 mmol) and 4-hydroxy-3-

methoxyxanthen-9-one (**32**) (0.2 g, 0.8 mmol) were employed. The reaction was carried out for 16 h to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent), to afford compound **115** (0.06 g, 25%) and 3-methoxyxanthene-1,4,9-trione (**109**) (0.09 g, 40%).



115

Compound **115**

A pale yellow solid (EtOAc/hexane), mp 147.0-148.0 °C; R_f 0.5 (50% EtOAc/hexane, 2 elutions).

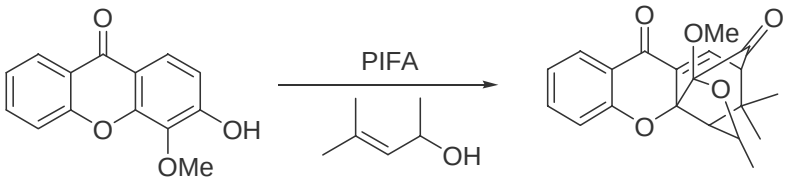
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.91 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 2.07 (t, *J* = 3.7 Hz, 1H, H-2'), 3.54 (s, 3H, OCH_3), 3.72 (dd, *J* = 6.9, 4.4 Hz, 1H, H-2), 4.07-4.18 (m, 2H, H-3'), 7.07 (t, *J* = 7.3 Hz, 1H, H-7), 7.24 (d, *J* = 8.4 Hz, 1H, H-5), 7.43 (d, *J* = 7.0 Hz, 1H, H-1), 7.56 (ddd, *J* = 8.3, 7.8, 1.6 Hz, 1H, H-6), 7.92 (dd, *J* = 7.9, 1.5 Hz, 1H, H-8).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 20.44, 24.33, 40.11, 43.37, 45.74, 51.77, 69.79, 89.67, 96.67, 118.31, 118.71, 122.16, 127.17, 133.61, 133.91, 136.71, 161.16, 175.82, 195.87.

IR (nujol, cm^{-1}): 1760 (C=O), 1668 (C=O), 1608, 1464, 1318.

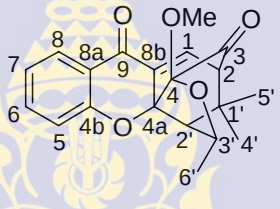
MS: m/z (% relative intensity) 327 (M^+, 5), 298 (25), 239 (100), 197 (36).

HRMS: Molecular ion (M+Na) calcd for $C_{19}H_{18}O_5Na$: 349.1051; found (ESI positive) m/z = 349.1052, error = 0.3 ppm.



31 **116**

3.9 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.26 g, 0.6 mmol), 4-methyl-3-penten-2-ol (0.43 mL, 0.35 mol) and 3-hydroxy-4-methoxyxanthen-9-one (**31**) (0.1 g, 0.4 mmol) were employed. The reaction was carried out for 16 h to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to afford compound **116** (0.02 g, 15%).



116

Compound **116**

A pale yellow solid (EtOAc/hexane), mp 185.5-186.0 °C; R_f 0.5 (20% EtOAc/hexane, 2 elutions).

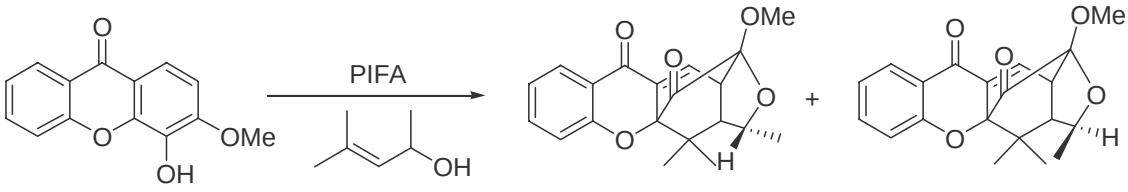
^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 0.86 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.64 (d, *J* = 6.6 Hz, 3H, CH_3-6'), 1.87 (s, 1H, H-2'), 2.98 (d, *J* = 6.2 Hz, 1H, H-2), 3.49 (s, 3H, O-CH_3), 4.37 (q, *J* = 6.6 Hz, 1H, H-3'), 6.97-7.03 (m, 2H, H-5, H-7), 7.34 (d, *J* = 7.0 Hz, 1H, H-1), 7.48 (ddd, *J* = 7.2, 6.8, 1.8 Hz, 1H, H-6), 7.91 (dd, *J* = 8.0, 1.8 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 22.15, 25.60, 28.10, 35.36, 54.00, 56.16, 60.55, 75.23, 88.31, 97.01, 117.96, 119.16, 122.08, 127.38, 133.65, 134.16, 136.59, 159.87, 176.72, 200.14.

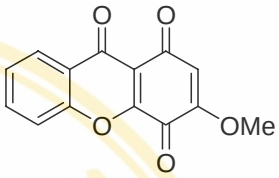
IR (nujol, cm^{-1}): 1734 (C=O), 1672 (C=O), 1644, 1615, 1465, 1314.

MS: m/z (% relative intensity) 341 (M^++H, 13), 312 (37), 297 (30), 253 (100), 225 (40).

HRMS: Molecular ion (M+Na) calcd for $C_{20}H_{20}O_5Na$: 363.1208; found (ESI positive) m/z = 363.1208, error = 0 ppm.

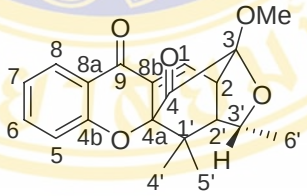


32 **117** **118**



109

3.10 According to the general procedure I, phenyliodonium(III) bistrifluoroacetate (PIFA) (0.4 g, 1.2 mmol), 4-methyl-3-penten-2-ol (0.6 mL, 8.3 mmol) and 4-hydroxy-3-methoxyxanthen-9-one (**32**) (0.2 g, 0.8 mmol) were employed. The reaction was carried out for 16 h to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent), to afford an inseparable 3:1 stereomeric mixture of compound **117** (0.042 g, 15%, calculated from ^{1}H NMR integral) and compound **118** (0.013 g, 5%, calculated from ^{1}H NMR integral) together with 3-methoxyxanthene-1,4,9-trione (**109**) (0.09 g, 40%).



117

Compound **117** (a major isomer in an inseparable mixture of **117**+**118**)

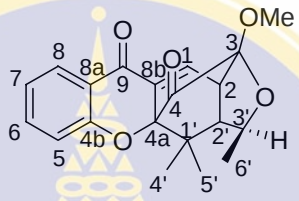
A pale yellow solid (EtOAc/hexane), R_f 0.4 (20% EtOAc/hexane, 2 elutions).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 0.89 (s, 3H, CH_3-5'), 1.32 (s, 3H, CH_3-4'), 1.41 (d, *J* = 6.4 Hz, 3H, CH_3-6'), 1.77 (d, *J* = 4.7 Hz, 1H, H-2'), 3.51 (s, 3H, O-CH_3), 3.88 (dd, *J* = 7.0, 4.7 Hz, 1H, H-2), 4.46 (q, *J* = 6.4 Hz, 1H, H-3'), 7.07 (t, *J* = 7.7 Hz, 1H, H-7), 7.24 (d, *J* = 8.5 Hz, 1H, H-5), 7.43 (d, *J* = 7.0 Hz, 1H, H-1), 7.56 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1H, H-6), 7.92 (dd, *J* = 7.9, 1.5 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 20.86 (CH_3), 21.89 (CH_3-6′), 24.45 (CH_3), 39.69 (C-2), 41.21 (C-1′), 50.26 (O-CH_3), 50.26 (C-2’), 75.25 (C-3’), 90.02 (C-4a), 96.67 (C-3), 118.30 (C-5), 118.70 (C-8a), 122.11 (C-7), 127.10 (C-8), 133.60 (C-1), 134.20 (C-8b), 136.70 (C-6), 161.10 (C-4b), 175.80 (C-9), 196.20 (C-4).

IR (nujol, cm^{-1}): 1736 (C=O), 1673 (C=O), 1613, 1466, 1316.

MS: m/z (% relative intensity): 341 (M^++H, 7), 253 (100), 225 (75), 211 (49).



118

Compound **118** (a minor isomer in an inseparable mixture of **117**+**118**)

A pale yellow solid (EtOAc/hexane), R_f 0.4 (20% EtOAc/hexane, 2 elutions).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 0.87 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.56 (d, *J* = 7.0 Hz, 3H, CH_3-6’), 1.93 (dd, *J* = 3.8, 2.7 Hz, 1H, H-2’), 3.55 (s, 3H, O-CH_3), 3.78 (dd, *J* = 7.0, 4.0 Hz, 1H, H-2), 4.58 (qd, *J* = 7.0, 2.5 Hz, 1H, H-3’), 7.07 (t, *J* = 7.7 Hz, 1H, H-7), 7.24 (d, *J* = 8.5 Hz, 1H, H-5), 7.43 (d, *J* = 7.0 Hz, 1H, H-1), 7.56 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1H, H-6), 7.92 (dd, *J* = 7.9, 1.5 Hz, 1H, H-8).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 17.71 (CH_3-6’), 21.90 (CH_3), 25.42 (CH_3), 42.01 (C-1′), 46.10 (C-2), 49.34 (C-2’), 51.17 (O-CH_3), 79.88 (C-3’), 90.02 (C-4a), 96.38 (C-3), 118.31 (C-5), 118.70 (C-8a), 122.11 (C-7), 127.09 (C-8), 134.01 (C-1), 133.79 (C-8b), 136.67 (C-6), 161.12 (C-4b), 175.84 (C-9), 196.20 (C-4).

IR (nujol, cm^{-1}): 1736 (C=O), 1673 (C=O), 1613, 1466, 1316.

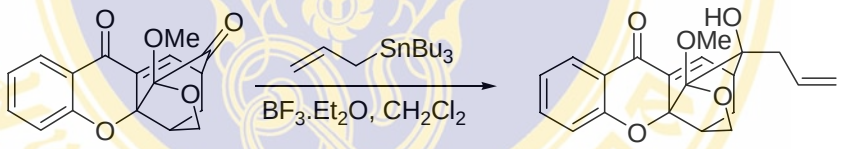
MS: m/z (% relative intensity): 341 (M^++H, 7), 253 (100), 225 (75), 211 (49).

HRMS: Molecular ion (M+Na) calcd for $C_{20}H_{20}O_5Na$: 363.1208; found (ESI positive) m/z = 363.1211, error = 0.8 ppm.

4. Reaction of the caged xanthone with allyltributylstannane in the presence of boron trifluoride etherate as Lewis acid.

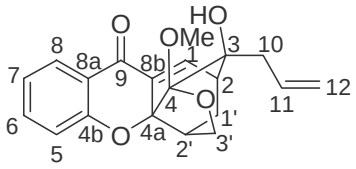
General Procedure II [40]

To the round-bottomed flask charged with a solid caged xanthone, was added dry dichloromethane (1 mL). The solution was cooled to -78 ^{o}C and boron trifluoride etherate was added dropwise. Subsequently, a 0.4 M allyltributylstannane solution in CH_2Cl_2 was added dropwise over a 30-min period. Following the completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature for 1.5 h. The reaction mixture was treated with 10% hydrochloric acid (5 mL) and was allowed to stand for 5 min. The aqueous phase was extracted with dichloromethane (3x10 mL). The combined organic layers were washed with water (3x10 mL) and brine (3x10 mL), dried (Anh. $MgSO_4$) and concentrated (aspirator). The residue was purified by radial chromatography.



107 **119**

4.1 According to the general procedure II, compound **107** (0.05 g, 0.16 mmol), boron trifluoride etherate (0.06 mL, 0.48 mmol) and allyltributylstannane (0.06 mL, 0.20 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to give compound **119** (0.015 g, 29%).



119

Compound **119**

A white solid (EtOAc/hexane), mp 150.5-151.5 °C; R_f 0.4 (20% EtOAc/hexane, 2 elutions).

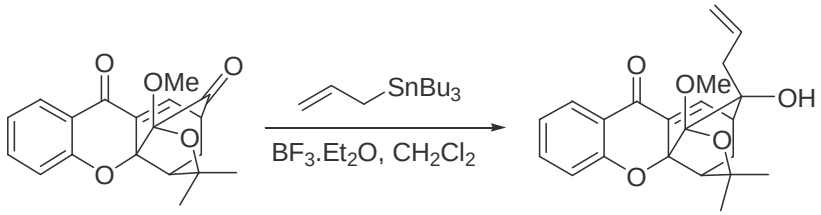
^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.58-1.62 (m, 2H, H-1′), 2.20 (dd, *J* = 14.1, 9.1 Hz, 1H, H-10), 2.28 (ddd, *J* = 10.0, 3.8, 2.2 Hz, 1H, H-2′), 2.56 (ddt, *J* = 14.1, 5.3, 1.5 Hz, 1H, H-10), 2.88 (s, 1H, OH), 3.03 (dt, *J* = 7.0, 2.9 Hz, 1H, H-2), 3.48 (s, 3H, O-CH_3), 3.76 (d, *J* = 7.8 Hz, 1H, H-3′a), 4.57 (dd, *J* = 7.8, 4.0 Hz, 1H, H-3′b), 5.10-5.14 (m, 2H, H-12), 5.88-5.97 (m, 1H, H-11), 6.96 (dd, *J* = 8.5, 0.9 Hz, 1H, H-5), 7.04 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H, H-7), 7.48 (ddd, *J* = 8.5, 7.0, 1.7 Hz, 1H, H-6), 7.56 (d, *J* = 6.9 Hz, 1H, H-1), 7.98 (dd, *J* = 7.9, 1.8 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 28.55 (C-1′), 41.22 (C-2′), 46.24 (C-2), 54.08 (OCH_3), 73.30 (C-3′), 87.46 (C-4a), 97.81 (C-4), 118.00 (C-7), 119.27 (C-8a), 122.20 (C-5), 127.47 (C-8), 133.94 (C-8b), 134.27 (C-1), 136.66 (C-6), 159.75 (C-4b), 176.54 (C-9), 198.67 (C-3).

IR (nujol, cm^{-1}): 3506 (O-H),1735 (C=O), 1610, 1461, 1315.

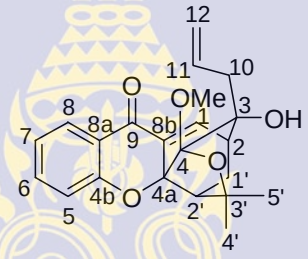
EI-MS: m/z (% relative intensity) 341 (M^++H, 1), 211 (100), 197 (46), 184 (25).

HRMS: Molecular ion (M+Na) calcd for $C_{20}H_{20}O_5Na$: 363.1208; found (ESI positive) m/z = 363.1209, error = 0.3 ppm.



110 **120**

4.2 According to the general procedure II, compound **110** (0.05 g, 0.15 mmol), boron trifluoride etherate (0.05 mL, 0.45 mmol) and allyltributylstannane (0.05 mL, 0.18 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to afford compound **120** (0.015 g, 25%).



120

Compound **120**

A white solid (EtOAc/hexane), mp 135.7-136.5 °C; R_f 0.5 (20% EtOAc/hexane, 2 elutions).

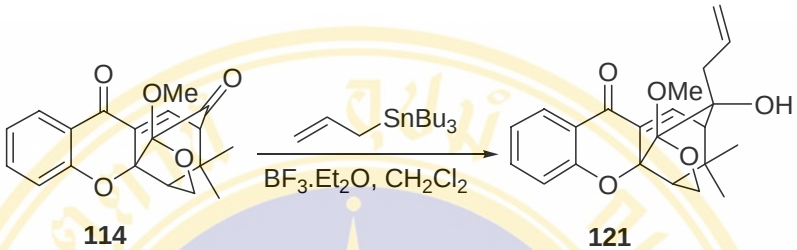
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.14-1.25 (m, 1H, H-1'), 1.58 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 1.88-1.95 (m, 1H, H-10), 2.14 (d, *J* = 10.6 Hz, 1H, H-2′), 2.22-2.34 (m, 2H, H-3', H-10), 2.84-2.87 (m, 1H, H-2), 3.49 (s, 3H, O-CH_3), 3.53 (s, 1H, OH), 5.02-5.10 (m, 2H, H-12), 5.85-5.99 (m, 1H, H-11), 7.02 (d, *J* = 8.3 Hz, 1H, H-5) 7.07 (t, *J* = 7.6 Hz, 1H, H-7), 7.52 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1H, H-6), 7.68 (d, *J* = 7.2 Hz, 1H, H-1), 7.99 (dd, *J* = 7.8, 1.4 Hz, 1H, H-8).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 23.82 (C-1′), 28.06 (CH_3), 29.69 (CH_3), 40.51 (C-2), 42.00 (C-10), 48.71 (C-2'), 53.13 (OCH_3), 79.03 (C-3), 82.60 (C-3'), 91.87 (C-4a), 107.34 (C-4), 117.49 (C-12), 117.61 (C-5), 119.19 (C-8a), 121.72 (C-7), 127.31 (C-8), 131.44 (C-8b), 134.91 (C-11), 135.92 (C-6), 143.51 (C-1), 159.51 (C-4b), 177.53 (C-9).

IR (nujol, cm^{-1}): 3481 (O-H),1670 (C=O), 1622, 1464.

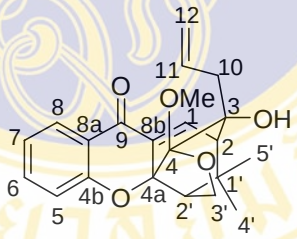
EI-MS: m/z (% relative intensity) 369 (M^++H, 4), 240 (19), 239 (34), 197 (100).

HRMS: Molecular ion (M+Na) calcd for $C_{22}H_{24}O_5Na$: 391.1521; found (ESI positive) m/z = 391.1522, error = 0.3 ppm.



114 **121**

4.3 According to the general procedure II, compound **114** (0.05g, 0.15 mmol), boron trifluoride etherate (0.05 mL, 0.45 mmol) and allyltributylstannane (0.05 mL, 0.18 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to afford compound **121** (0.016 g, 28%).



121

Compound **121**

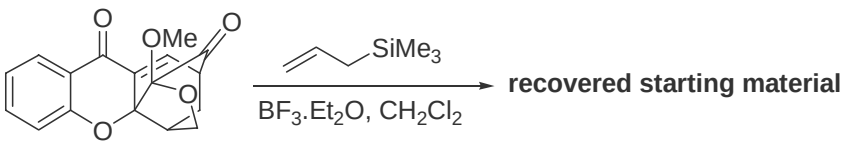
A white solid (EtOAc/hexane), mp 140.0-142 °C; R_f 0.5 (20% EtOAc/hexane, 2 elutions). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 0.85 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.95 (d, *J* = 3.9 Hz, 1H, H-2'), 2.00 (dd, *J* = 14.7, 9.6 Hz, 1H, H-10), 2.23 (ddt, *J* = 14.6, 5.9, 1.7 Hz, 1H, H-10), 2.56 (d, *J* = 7.3 Hz, 1H, H-2), 3.47 (s, 3H, O-CH_3), 3.64 (s, 1H, OH), 4.17 (d, *J* = 8.6 Hz, 1H, H-3'a)), 4.63 (dd, *J* = 8.6, 3.9 Hz, 1H, H-3'b), 5.05-5.13 (m, 2H, H-12), 5.93-6.01 (m, 1H, H-11), 7.02 (dd, *J* = 8.2, 0.5 Hz, 1H, H-5), 7.09 (ddd, *J* = 7.8, 7.4, 0.9 Hz, 1H, H-7), 7.54 (ddd, *J* = 8.5, 7.0, 1.6 Hz 1H, H-6), 7.63 (d, *J* = 7.2 Hz, 1H, H-1), 8.02 (dd, *J* = 7.9, 1.8 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 26.65 (CH_3), 33.54 (CH_3), 37.59 (C-1'), 43.66 (C-10), 52.90 (C-2), 53.48 (C-2'), 54.10 (OCH_3), 68.81 (C-3'), 81.96 (C-3), 90.00 (C-4a), 106.69 (C-4), 118.47 (C-12), 118.64 (C-5), 120.35 (C-8a), 122.66 (C-7), 128.36 (C-8), 130.42 (C-8b), 135.78 (C-11), 136.95 (C-6), 144.61 (C-1), 160.85 (C-4b), 178.30 (C-9).
IR (nujol, cm^{-1}): 3453 (O-H), 1692 (C=O), 1608, 1460, 1292.
EI-MS: m/z (% relative intensity) 369 (M^++H, 10), 368 (M^+, 18), 353 (100), 309 (53), 251 (31), 239 (49), 211 (73), 197 (48).
HRMS: Molecular ion (M+H) calcd for $C_{22}H_{25}O_5$: 369.1702; found (ESI positive) m/z = 369.1702, error = 0 ppm.

5. Reaction of the caged xanthone 107 with allyltrimethylsilane in the presence of various Lewis acid.

General Procedure III [40]

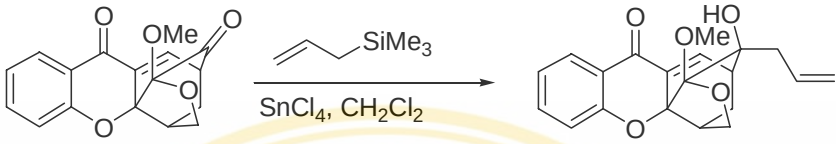
To the round-bottomed flask charged with a solid caged xanthone **107**, was added dry dichloromethane (1 mL). The solution was cooled to -78 ^oC and Lewis acid was added dropwise. Subsequently, a 0.4 M allyltrimethylsilane solution in CH_2Cl_2 was added dropwise over a 30-min period. Following the completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to temperature for 1.5 h. The reaction mixture was treated with 10% hydrochloric acid (5 mL), and was allowed to stand for 5 min. The aqueous phase was extracted with dichloromethane (3x10 mL). The combined organic layers were washed with water (3x10 mL) and brine (3x10 mL), dried (Anh. $MgSO_4$) and concentrated (aspirator). The residue was purified by radial chromatography.



107

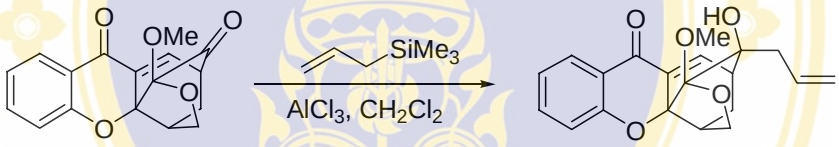
5.1 According to the general procedure II, compound **107** (0.5 g, 0.16 mmol), boron trifluoride etherated (0.06 mL, 0.48 mmol) and allyltrimethylsilane (0.03 mL, 0.20

mmol) were employed. No reaction took place and compound **107** was recovered (0.42 g, 84%).



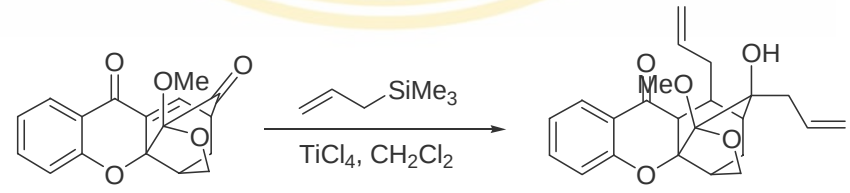
107 **119**

5.2 According to the general procedure II, compound **107** (0.5 g, 0.16 mmol), tin tetrachloride (0.05 mL, 0.48 mmol) and allyltrimethylsilane (0.03 mL, 0.20 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to yield compound **119** (0.015 g, 28%).



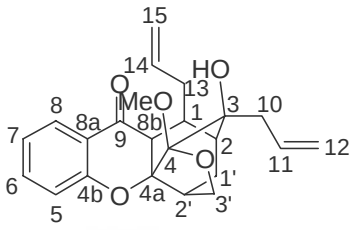
107 **119**

5.3 According to the general procedure II, compound **107** (0.5 g, 0.16 mmol), aluminium trichloride (0.0638 g, 0.48 mmol) and allyltrimethylsilane (0.03 mL, 0.20 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to yield compound **119** (0.019 g, 35%).



107 **122**

5.4 According to the general procedure II, compound **107** (0.5 g, 0.16 mmol), titanium tetrachloride (0.05 mL, 0.48 mmol) and allyltrimethylsilane (0.03 mL, 0.20 mmol) were employed to produce a crude residue that was purified by radial chromatography (SiO_2, 1:4 EtOAc/hexane eluent) to afford compound **122** (0.014 g, 25%).



122

Compound **122**

A white solid (EtOAc/hexane), mp 73.5-74.0 °C; R_f 0.6 (20% EtOAc/hexane, 2 elutions).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 1.53-1.57 (m, 1H, H-1'), 1.79 (q, *J* = 2.9 Hz, 1H, H-2), 2.14 (dd, *J* = 13.7, 9.1 Hz, 1H, H-10), 2.25 (t, *J* = 7.5 Hz, 1H, H-13), 2.38 (ddd, *J* = 14.0, 10.9, 2.9 Hz, 1H, H-1'), 2.51 (dt, *J* = 11.2, 2.4 Hz, 1H, H-2'), 2.62-2.65 (m, 1H, H-10), 2.74 (d, *J* = 4.5 Hz, 1H, H-8b), 2.93 (s, 1H, OH), 3.04 (s, 3H, O-CH_3), 3.50-3.55 (m, 1H, H-1), 3.66 (d, *J* = 7.1 Hz, 1H, H-3′a), 4.58 (dd, *J* = 7.1, 3.1 Hz, 1H, H-3′b), 5.05-5.15 (m, 4H, H-12, H-15), 5.86-5.98 (m, 2H, H-11, H-14), 6.98 (dd, *J* = 8.3, 0.6 Hz, 1H, H-5), 7.04 (ddd, *J* = 7.8, 7.2, 0.7 Hz, 1H, H-7), 7.50 (ddd, *J* = 8.4, 7.0, 1.8 Hz, 1H, H-6), 7.89 (dd, *J* = 7.8, 1.8 Hz, 1H, H-8).

^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 25.91 (C-1′), 28.44 (C-1), 36.83 (C-2), 39.57 (C-13), 40.21 (C-10), 41.36 (C-2'), 47.34 (C-8b), 51.01 (OCH_3), 73.15 (C-3'), 79.18 (C-3), 85.78 (C-4a), 105.30 (C-4), 116.24 (C-15), 116.95 (C-5), 118.01 (C-12), 120.70 (C-7, C-8a), 126.47 (C-8), 134.32 (C-11), 135.06 (C-6), 136.59 (C-14), 159.27 (C-4b), 191.09 (C-9).

IR (nujol, cm^{-1}): 3522 (O-H), 1691 (C=O), 1607, 1462, 1326.

EI-MS: m/z (% relative intensity) 383 (M^++H, 40), 382 (M^+, 44), 365 (75), 341 (69), 309 (64), 261 (98), 241 (58), 211 (38), 121 (100).

HRMS: Molecular ion (M+Na) calcd for $C_{23}H_{26}O_5Na$: 405.1677; found (ESI positive) m/z = 405.1678, error = 0.2 ppm.

.

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