Chapter 9

Biosynthesis and Biomimetic Synthesis of Flavonoid Diels-Alder Natural Products

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Abstract

This chapter describes the biosynthesis and biomimetic synthesis of naturally occurring flavonoid Diels-Alder adducts found either from the family Moraceae or Zingiberaceae. The main topics addressed are biosynthetic studies by employing *Morus alba L.* cell cultures through feeding experiments of various exogenous substrates and putative precursors, as well as a various biomimetic approach for the chemical syntheses of flavonoid Diels-Alder natural products.

Keywords: biomimetic, flavonoid, Diels-Alder, Cycloaddition, biosynthesis

1. Introduction

The flavonoid Diels-Alder natural products are mainly found from the families of Moraceae and Zingiberaceae. Since the majority of these compounds are discovered from the Moraceae, they are often referred as mulberry Diels-Alder flavonoids or mulberry Diels-Alder type adducts. These secondary metabolites exhibit promising biological activities against hypertension, HIV, tuberculosis, anti-inflammation and cancers [1–7]. Thus far, more than 140 of these Diels-Alder type flavonoids have been discovered from nature (**Figure 1**). The structural complexity and promising bioactivities of these flavonoid Diels-Alder natural products have stimulated research interest into their biosynthesis and chemical synthesis.

The Diels-Alder type flavonoids are considered to be formed through an enzymatic Diels-Alder reaction between a dehydroprenyl diene and a chalcone dienophile (**Scheme 1**) [8]. The diene is usually derived from a flavonoid, such as flavone, flavanone, flavonol, flavanonol, or from a

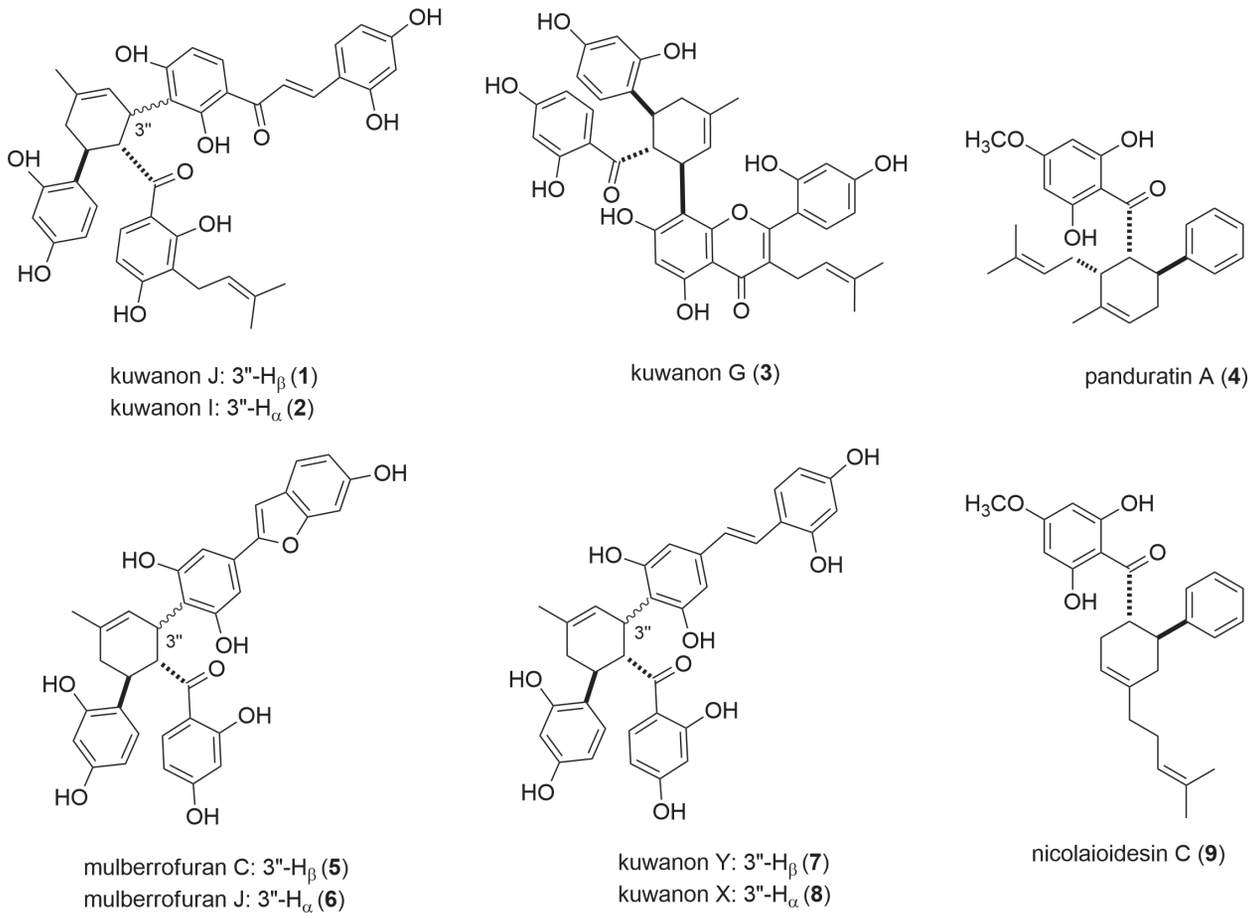
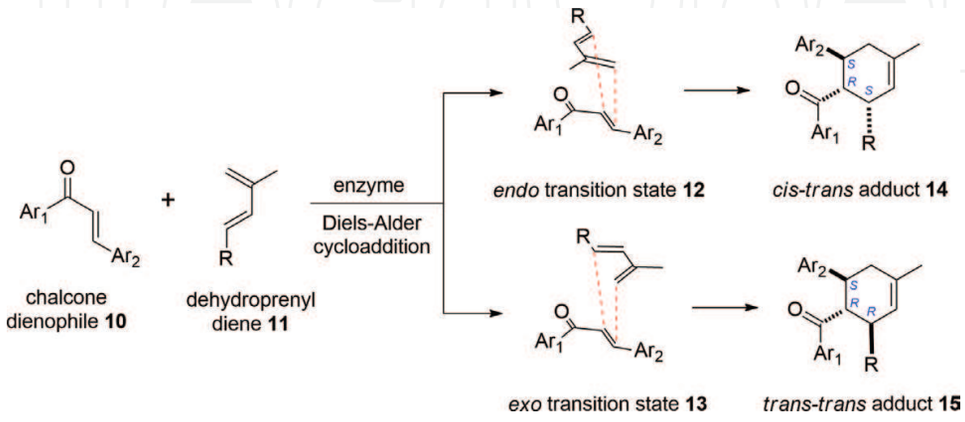


Figure 1. Examples of flavonoid Diels-Alder natural products.

monoterpene, such as myrcene and β-*trans*-ocimene. The dienophile of this class of Diels-Alder compounds is exclusively derived from a chalcone derivative. Subsequent oxidation and cyclization steps of these flavonoid Diels-Alder adducts can result in more complex structures. The Diels-Alder adducts bearing the *cis-trans* stereochemistry on the cyclohexenyl ring would be derived through an *endo* transition state (**12**), whereas the *trans-trans* stereochemistry arises



Scheme 1. Stereochemistry on the cyclohexene ring of flavonoid Diels-Alder natural products.

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from the *exo* transition state (**13**) (**Scheme 1**) [8]. The stereochemistry of these adducts, including the absolute configuration on the cyclohexene ring, has been explicitly confirmed by circular dichroism (CD) spectroscopic evidence [9] and X-ray crystallographic analysis [10, 11]. The unique structural features and diverse activities of these adducts have recently aroused much interest of synthetic and medicinal chemistry. The main topics addressed in this chapter are biosynthesis and biomimetic synthesis of flavonoid Diels-Alder natural products and about 40 references are cited. As the flavonoid Diels-Alder natural products are composed of a diverse family of secondary metabolites, other subclasses where the dienophile is not a chalcone (e.g. mongolicin B, -E, sanggenon B, -R, -S, dimoracin, mulberrofuran H, meroterpene, pauferrol A derivatives, etc) are not covered in this chapter.

2. Biosynthesis of the flavonoid Diels-Alder natural products

Although the biosynthesis of the flavonoid Diels-Alder natural products that derived from a monoterpene is not well-studied [12, 35], it is hypothesized that a Diels-Alder reaction between a chalcone dienophile and a monoterpene (β-*trans*-ocimene or myrcene) would lead to the direct formation of these adducts (**Figure 2**).

The biosynthesis of the mulberry Diels-Alder flavonoids has been intensively studied by Professors Taro Nomura and Shinichi Ueda. The biosynthetic studies of these adducts were carried out in the callus tissues of *Morus alba L* [13]. In their pioneering studies, the callus tissues induced from the leaves or seedlings were cultivated and subjected to selection over a period of 9 years for cell strains with high-pigment productivity [14]. Extraction of these high pigmented cell cultures resulted in isolation of six Diels-Alder adducts, kuwanons J (**1**), Q (**23**), R (**24**), V (**25**), mulberrofuran E (**26**), and chalcomoracin (**27**) along with morachalcone A (**28**), isobavachalcone (**29**), and moracin C (**30**) (**Figure 3**) [15–18].

The structures of metabolites **1**, **23**–**27** suggested that they are either the Diels-Alder adducts from a prenylchalcone and a dehydroprenylchalcone or the Diels-Alder adducts from a prenylchalcone and a dehydroprenyl-2-arylbenzofuran. Nomura and co-workers hypothesized that kuwanon J (**1**) was an adduct of morachalcone A (**28**) and dehydroprenylmorachalcone A. Kuwanon Q (**23**) was an adduct of isobavachalcone (**29**) and dehydroprenylmorachalcone

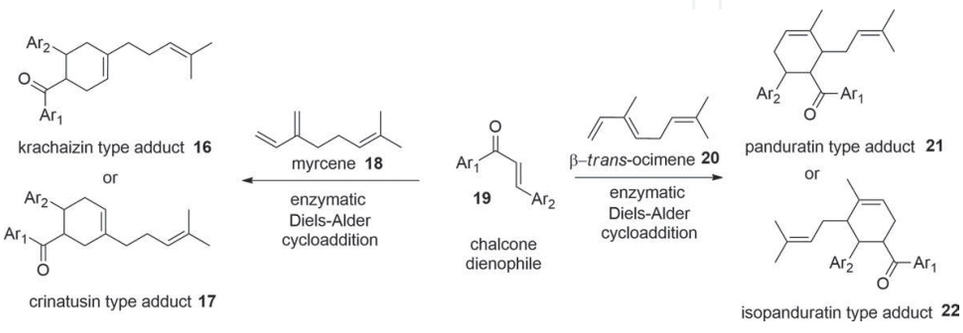

Figure 2. Plausible biosynthesis of flavonoid Diels-Alder natural products that derived from a monoterpene.

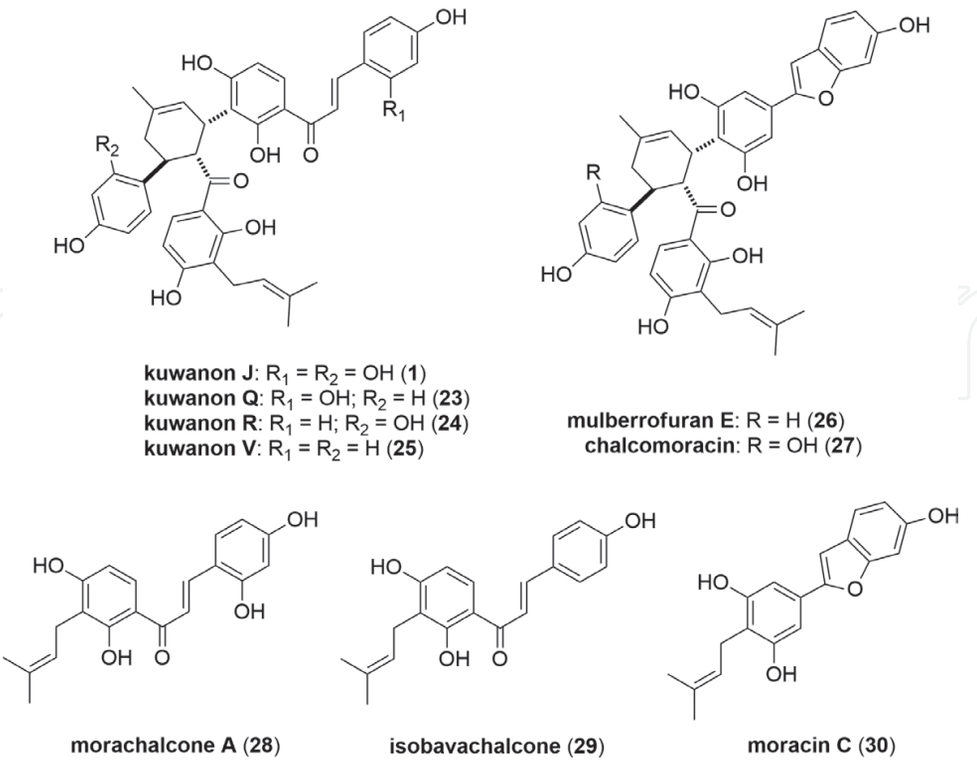

Figure 3. Metabolites isolated from the *Morus alba* cell cultures [15–18].

A. Kuwanon R (**24**) was an adduct of morachalcone A (**28**) and dehydroprenylisobavachalcone. Kuwanon V (**25**) was an adduct of isobavachalcone (**29**) and dehydroprenylisobavachalcone. Chalcomoracin (**27**) was an adduct of morachalcone A (**28**) and dehydroprenylmoracin C. Mulberrofuran E (**26**) was an adduct of isobavachalcone (**29**) and dehydroprenylmoracin C. It is interesting that these Diels-Alder metabolites and their monomeric precursors (morachalcone A, isobavachalcone and moracin C) were isolated from *M. alba* cell cultures. In addition, the callus tissue can produce 100 times more mulberrofuran E and chalcomoracin than the intact plant [15–17]. The biosynthetic studies of these Diels-Alder adducts were further examined through feeding experiments of various exogenous substrates and putative precursors to the *M. alba* cell cultures.

2.1. Feeding experiments with ^{13}C-labeled acetate to the *Morus alba* cell cultures

Acetate is an important carbon source for biosynthesis studies in *M. alba* cell cultures. Feeding experiments of [1–^{13}C]-, [2–^{13}C]-, or [1, 2–$^{13}C_2$]-acetates to the *M. alba* cell cultures resulted in the highly ^{13}C-enriched aromatic carbons of chalcomoracin (**27**) and kuwanon J (**1**), indicating that both **27** and **1** are derived from two molecules of cinnamoylpolyketide precursors (**Figure 4**) [19]. From the labeling patterns, the chalcone moiety (**34**) of both chalcomoracin (**27**) and kuwanon J (**1**) is hypothesized to be derived via deoxygenation at C-5 of the cinnamoylpolyketide precursor **31**, followed by Claisen condensation and aromatization (**Figure 5**) [20]. The 2-arylbenzofuran moiety (**36**) of **27** and **1** is hypothesized to be derived by the Aldol condensation at C-3 and C-8 of the cinnamoylpolyketide precursor **32**, followed by decarboxylation and aromatization (**Figure 5**) [19].

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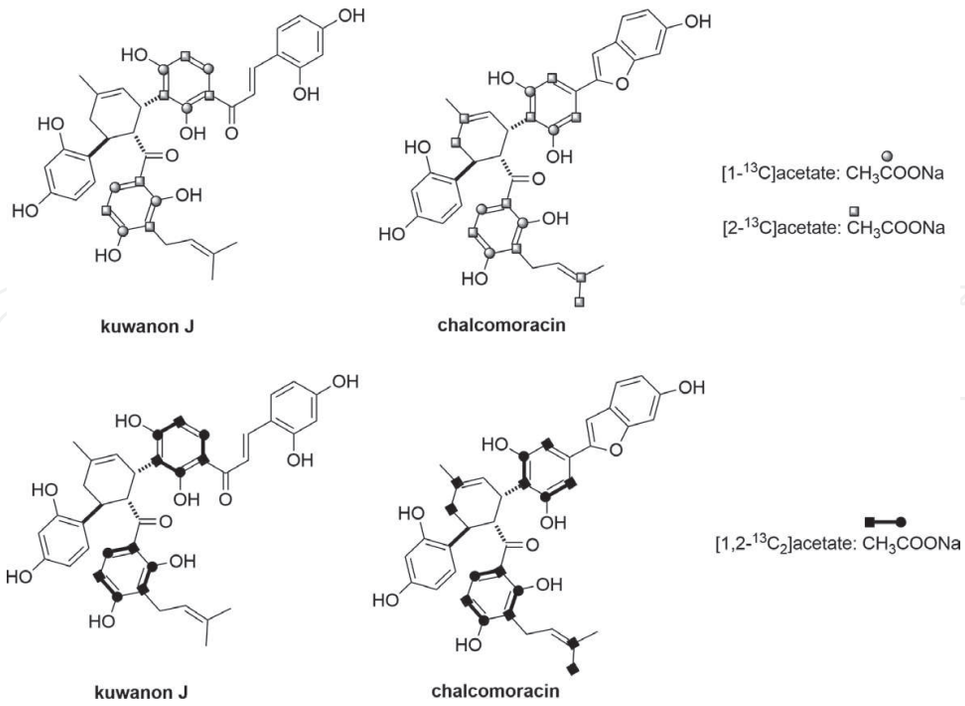

Figure 4. ^{13}C-labeling patterns of Kuwanon J and chalcomoracin from [1-^{13}C]-, [2-^{13}C]-, or [1, 2-$^{13}C_2$]acetate [19].

However, unlike the aromatic carbons, the isoprene units of chalcomoracin were marginally labeled (~0.4% enrichment) [19]. On the basis of ^{13}C–^{13}C spin coupling in the ^{13}C-NMR spectrum, the labeling of [2–^{13}C] acetate was incorporated into the starter acetate carbons in the biosynthesis of the isoprene unit of chalcomoracin (**27**). On the contrary, the [1–^{13}C] acetate was not incorporated in the isoprene unit of chalcomoracin (**27**) [19]. These findings suggested that a tricarboxylic acid (TCA) cycle was involved in the biosynthesis of the isoprenyl unit of chalcomoracin [8]. The rational of this hypothesis was derived from the ^{13}C-labeling experiments. In the experiment with [2–^{13}C] acetate, the contiguous ^{13}C labels can be derived from the methyl groups of the intact acetate administered by way of at least two passages through the TCA cycle

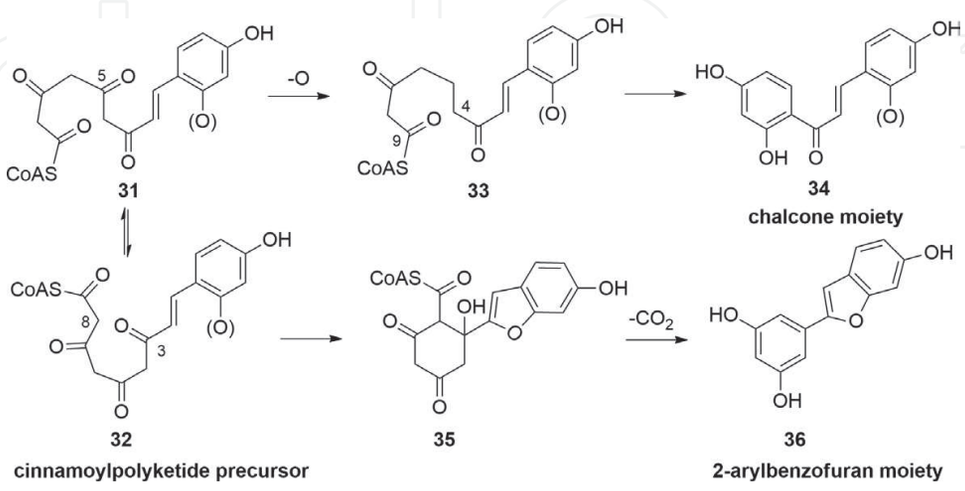

Figure 5. Hypothesized conversion of the chalcone and 2-arylbenzofuran moieties from cinnamoylpolyketide precursor [19].

[19]. In the experiment with [1–^{13}C] acetate, the ^{13}C label was not found in the isoprenyl unit, presumably due to the removal of carbon dioxide during passage through the TCA cycle (**Figure 6**).

This hypothesis was reinforced by the feeding experiment with [2–^{13}C] acetate in a pulsed manner (three times, every 12 h) to the *M. alba* cell cultures [21]. The result from this experiment enabled the identification of the satellite peaks based on the ^{13}C–^{13}C spin coupling between carbons at C-25'' and C23'', C-7'' and C-1'', C-23'' and C-24'' as well as C-6'' and C-1'' of chalcomoracin. The ^{13}C-enrichment at C-7'' and C-25'' occurred after the first and third [2–^{13}C] acetate administrations but not at the second administration suggested the isomerization between the 3,3-dimethylallyl and 3-methylbutadienyl groups (**Figure 7**) [8]. The coupling patterns of the central carbons (C-1'' and C-23'') appeared as doublet signal instead of the doublet of doublet signal indicated that these central carbons are independently coupled with the adjacent methyl carbons. Nomura *et al.* hypothesized that the independent ^{13}C-labeling pattern at the isoprenyl unit might due to the transfer of ^{13}C-labeling from *cis*-methyl to *trans*-methyl through the diene formation (**Figure 7**) [8, 21]. Taken together, these findings gave conclusive evidence on the diene formation from the isoprenyl moiety for the Diels-Alder cycloaddition reaction. Thus, the feeding experiment with ^{13}C-labeled acetate revealed that the Diels-Alder adducts chalcomoracin and kuwanon J are biosynthesized through the [4 + 2] cycloaddition reaction between two cinnamoylpolyketide-derived molecules [8].

2.2. Feeding experiments with methoxychalcone and prenylated flavone precursors

Based on the fact that methoxychalcone or methoxy-substituted Diels-Alder adducts have not been found in the *M. alba* cell cultures, therefore involvement of these precursors in the construction of the Diels-Alder adducts would be an important evidence for the enzymatic intermolecular Diels-Alder reaction in *M. alba* cell cultures.

Indeed, feeding methoxychalcone **37** to the cell cultures yielded prenylchalcone **38** and Diels-Alder adducts **40**–**43** (**Figure 8**) [22]. The formation of the prenylchalcone **38** from methoxychalcone **37** in the cell cultures indicated that isoprenylation occurs after the formation of chalcone skeleton from cinnamoylpolyketide precursor.

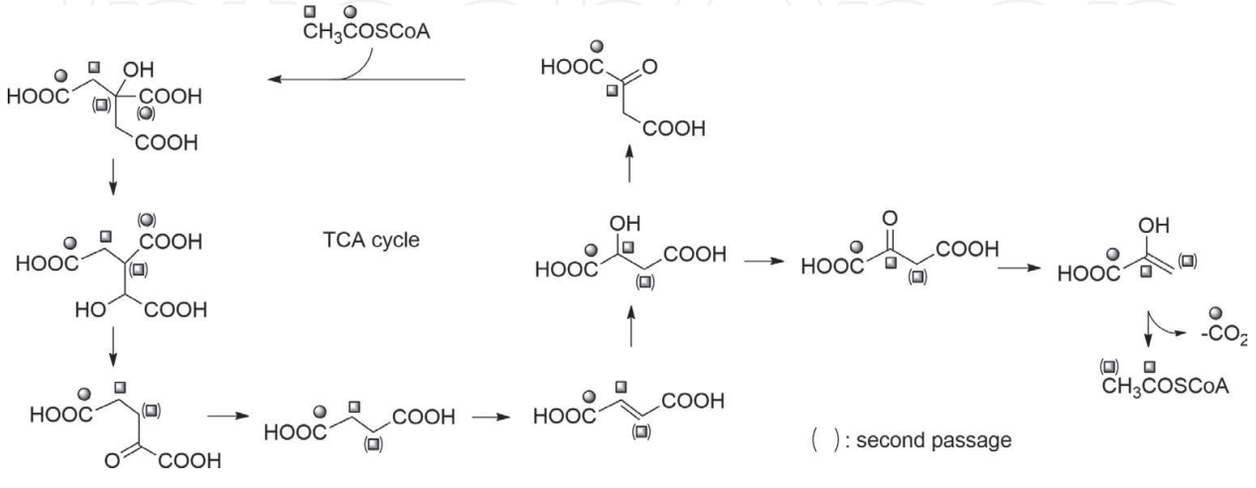

Figure 6. Formation of reorganized [1, 2-$^{13}C_2$]acetate through the TCA cycle [19].

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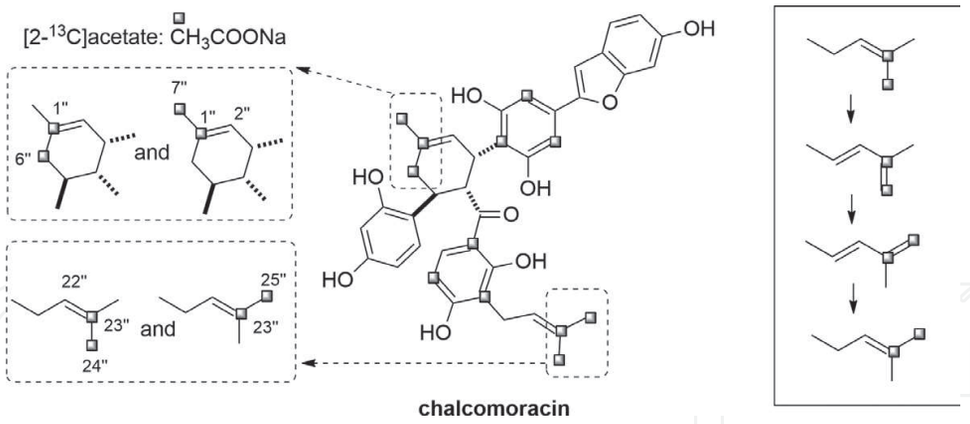

Figure 7. Two independent ^{13}C-labeling patterns at the isoprenyl units of chalcomoracin and the transfer of the ^{13}C-labeling from *cis*-methyl carbon to *trans*-methyl carbon through the diene formation [8, 19].

The metabolites **40**–**43** revealed that the methoxychalcone **37** was incorporated into the Diels-Alder adducts. Interestingly, when the synthetic prenylchalcone **38** was fed to the cell cultures, the same Diels-Alder metabolites **40**–**43** were isolated. Similarly, the feeding experiment of trimethoxychalcone **39** afforded the Diels-Alder metabolite **44** [22]. Taken together, these results suggested that both the requisite diene and dienophile can be derived from the same chalcone precursor. For example, dehydrogenation of the prenyl unit of chalcone **38**, followed by

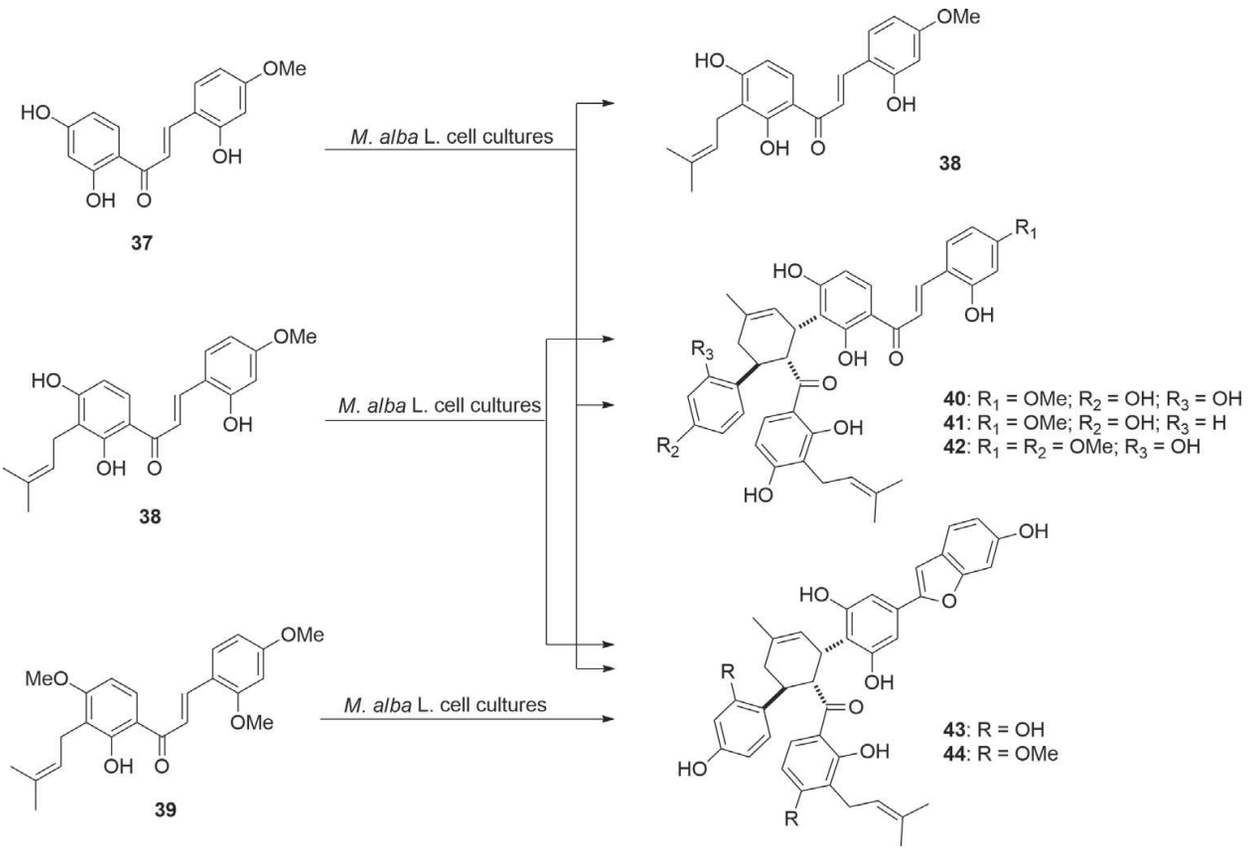

Figure 8. Feeding experiments of methoxychalcone derivatives to the *M. alba* cell cultures [22].

intermolecular [4 + 2] cycloaddition reaction with the α, β-double bond of another chalcone **38** leads to the formation of the Diels-Alder adduct **42** (**Figure 8**).

In addition, all these Diels-Alder metabolites derived from the methoxychalcone precursors were optically active and have the same stereochemistry as that of chalcomoracin (**27**) and kuwanon J (**1**). The results based on the feeding experiments of methoxychalcone derivatives revealed that the [4 + 2] cycloaddition reaction in the *M. alba* cell cultures is an enzymatic process.

Nomura *et al.* further attempted the synthesis of Diels-Alder natural product, artonin I (**46**) by using *M. alba* cell cultures (**Figure 9**) [23]. Although it is theoretically possible that artonin I could be derived from a chalcone dienophile (morachalcone A **28**) and a prenylflavone diene (**45**), but precursor of **45** (artocarpesin **47**) has not been found in *M. alba* cell cultures. Indeed, feeding **47** to the *M. alba* cell cultures resulted in the isolation of artonin I (**46**) through dehydrogenation of the prenyl group of **47** followed by the enzymatic [4 + 2] cycloaddition reaction with an endogenously generated morachalcone A **28**. This is the first example of a natural product's structure elucidation through enzymatic synthesis by using *M. alba* cell cultures [8].

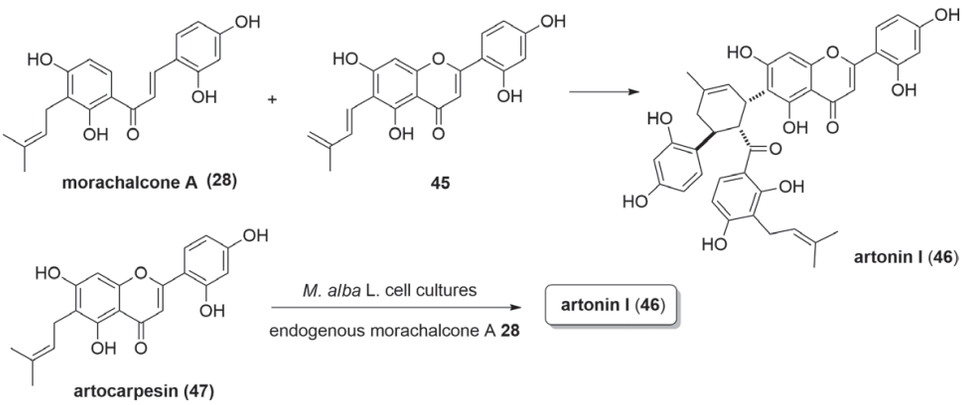

Figure 9. Biosynthesis of artonin I by administration of artocarpesin to the *M. alba* cell cultures [23].

3. Biomimetic synthesis of the flavonoid Diels-Alder natural products

The Diels-Alder cycloaddition reaction which named after Otto Paul Hermann (1876–1954) and Kurt Alder (1902–1958) was discovered during their studies on the reaction of benzoquinone and cyclopentadiene in 1928. Today, this cycloaddition reaction is a well-known method that is widely used to synthesize a six-membered cyclic compound in a regio- and stereocontrolled way. The following section discusses the use of this powerful synthetic methodology to prepare flavonoid Diels-Alder natural products based on the biosynthesis models.

3.1. Thermal conditions

During the early studies of the Diels-Alder cycloaddition reaction, the reaction was essentially carried out under thermal conditions owing to the simplicity of the experimental setup

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and the efficiency of the thermal process. Today, thermal promoted Diels-Alder cycloaddition reaction remains the first line approach for the construction of a six-membered cyclic compound, including that of flavonoid Diels-Alder natural products [24–30].

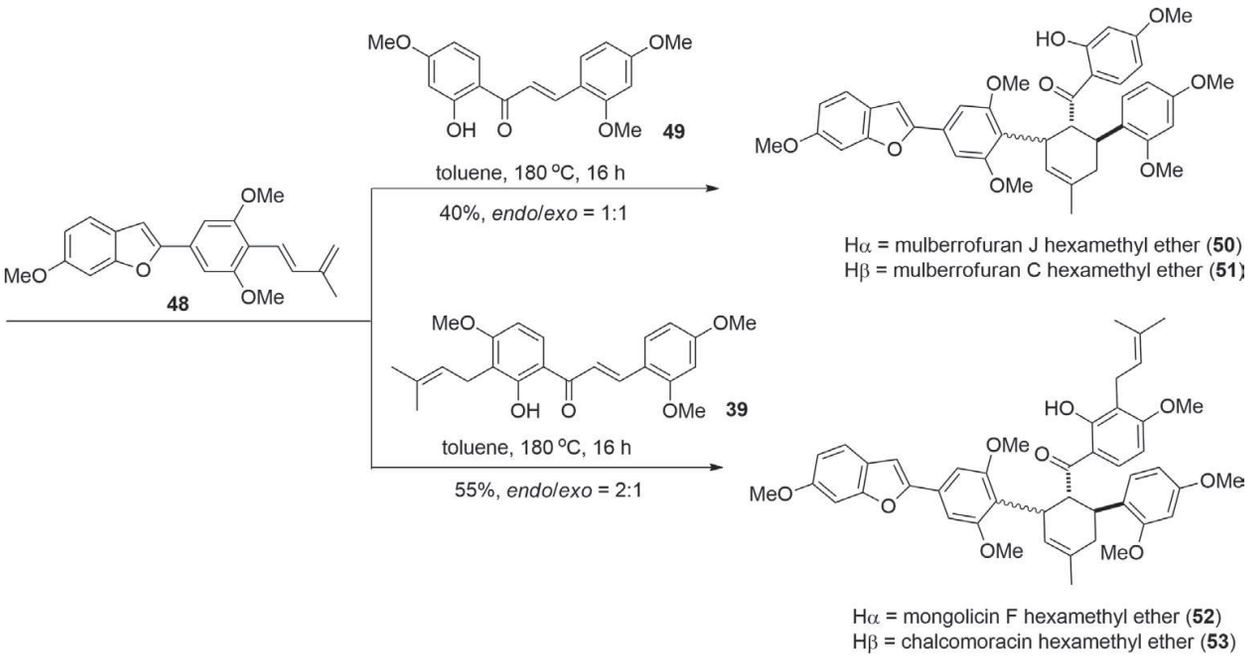
In 2010, Rizzacasa and co-workers reported the synthesis of racemic methyl ether derivatives of chalcomoracin, mongolicin F, mulberrofurans C and J *via* thermal Diels-Alder reaction (180°C in toluene) between chalcone dienophiles (**39** and **49**) and a dehydroprenyl-2-arylbenzofuran diene (**48**) (**Scheme 2**). The thermal Diels-Alder reaction resulted in a mixture of *endo*- and *exo*-diastereomers in almost equal quantity [24].

Rizzacasa and co-workers also reported a similar strategy for the synthesis of (±)-kuwanon I and J hexamethyl ethers. They hypothesized that the presence of an *ortho*-phenol group in the chalcone dienophile was essential for the Diels-Alder cycloaddition reaction. However, attempts to deprotect the methyl ethers of these Diels-Alder adducts using various demethylating agents were unsuccessful [25].

Rahman and co-workers utilized the thermal-promoted Diels-Alder reaction to synthesize (±)-dorsterone, (±)-kuwanon V and (±)-morusalbanol A pentamethyl ethers based on the biosynthesis models [27, 29, 30].

3.2. High pressure conditions

Although the thermal-promoted Diels-Alder reaction provides a rapid entry to flavonoid Diels-Alder adducts, this method may not be successful due to the instability of the diene or dienophile under a high-temperature condition. This limitation can be overcame using a high-pressure system for the Diels-Alder reaction.



Scheme 2. Synthesis of (±)-mulberrofuran J (**50**), (±)-mulberrofuran C (**51**), (±)-mongolicin F (**52**), and (±)-chalcomoracin (**53**) hexamethyl ethers by thermal Diels-Alder reaction [24].

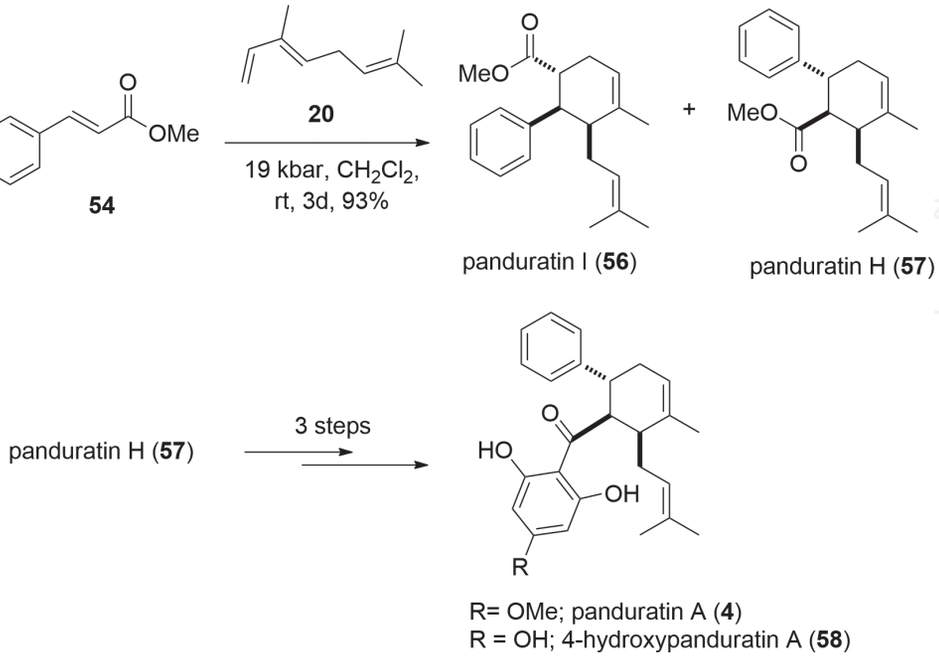
In 2013, Mcleod and co-workers utilized this strategy to synthesize (±)-panduratin A (**4**) and (±)-4-hydroxypanduratin A (**58**) [31]. Instead of late-stage Diels-Alder cycloaddition to synthesize the cyclohexenyl core of **4** and **58**, they initiated the biomimetic Diels-Alder reaction in an early stage by using methyl cinnamate (**54**) and β-*trans*-ocimene (**20**) (**Scheme 3**). High-pressure Diels-Alder reaction between **54** and **20** in dichloromethane at 19 kbar at room temperature gave a mixture of (±)-panduratin I (**56**) and (±)-panduratin H (**57**) in 1:2.9 ratio in 93% yield after 3 days. Subsequent transformations of panduratin H **57** afforded the natural products (±)-panduratin A and (±)-4-hydroxypanduratin A in three more further steps.

3.3. Single electron transfer initiated Diels-Alder reaction

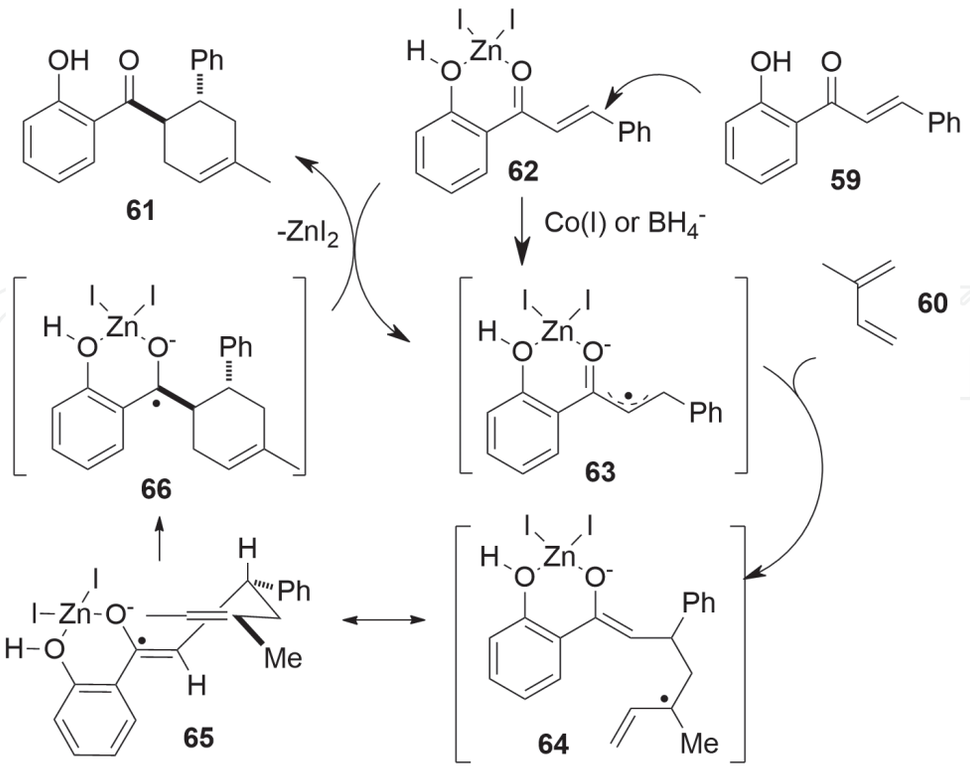
In 1960 when Yates and Eaton first reported the acceleration of the Diels-Alder reaction by Lewis acid catalysts, a variety of Lewis acid catalysts have been developed to accelerate the reaction [32].

Porco and co-workers developed a Lewis acid catalyst system that composed of multiple components (CoI_2/*o*-phenanthroline/ZnI_2/Bu_4NBH_4) for the [4 + 2]-cycloaddition reaction between 2′-hydroxychalcone dienophiles and various simple dienes [33]. They hypothesized that the mechanism of this catalytic system was a single electron transfer initiated process (**Scheme 4**).

According to their report, the role of $CoI_2$and $Bu_4NBH_4$was hypothesized to be an electron donor [33]. As outlined in **Scheme 4**, coordination of ZnI_2 activated the carbonyl of 2′-hydroxychalcone **59** to form complex **62**. In the presence of electron donors, complex **62** may undergo metal-ion-promoted single electron transfer to generate a chalcone radical anion **63**. The regioselective addition of **63** to the diene should generate a stabilized, allylic radical **64** which may undergo ring-closing cyclization to produce ketyl intermediate **65**. Loss of ZnI_2 from **65** and subsequent single electron transfer to another complex **62** may



Scheme 3. Biomimetic synthesis of (±)-panduratin A and (±)-4-hydroxypanduratin A by using high pressure conditions [31].

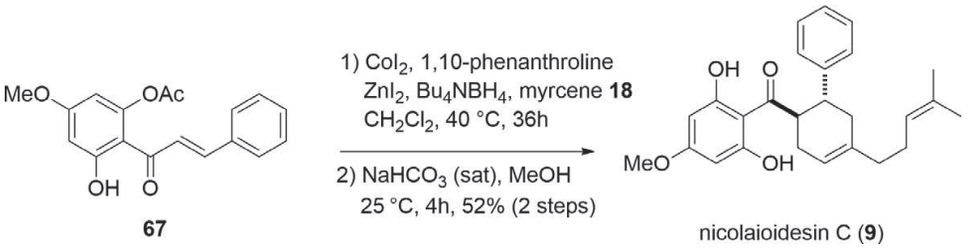


Scheme 4. Proposed mechanism for an electron transfer-initiated Diels-Alder cycloaddition reaction [33].

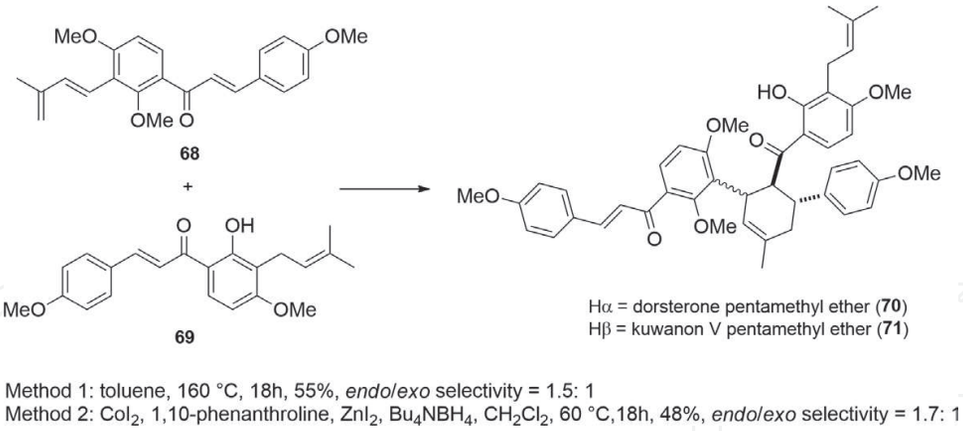
afford cycloadduct **61**, thereby restarting the catalytic cycle [33]. Following this mechanistic studies, Porco *et al*. further established the total synthesis of (±)-nicolaioidesin C (**9**) by using myrcene as a diene (**Scheme 5**) [33].

Rahman and co-workers used the thermal-promoted as well as single-electron-transfer-initiated Diels-Alder reaction to compare the efficiency of the biomimetic synthesis of (±)-kuwanon V (**71**) and (±)-doresterone (**70**) methyl ethers [27]. Thermal Diels-Alder cycloaddition between dienophile **69** and diene **68** in a pressure tube at 160°C for 18 h afforded **70** (*exo*-adduct) and **71** (*endo*-adduct) in 55% yield in a 1.5:1 ratio (**Scheme 6**). A comparable result (48% yield, 1.7:1 ratio) was obtained by using the single electron transfer initiated Diels-Alder reaction (ZnI_2, Bu_4NBH_4, CoI_2, 1, 10-phenanthroline in 60:10:10:10 mol%).

Recently, Valentina *et al.* reported the synthesis of (±)-kuwanol E and the heptamethyl ether derivative of (±)-kuwanol Y by using a combination of thermal conditions and Lewis acid



Scheme 5. Biomimetic synthesis of (±)-nicolaioidesin C (**9**) [33].

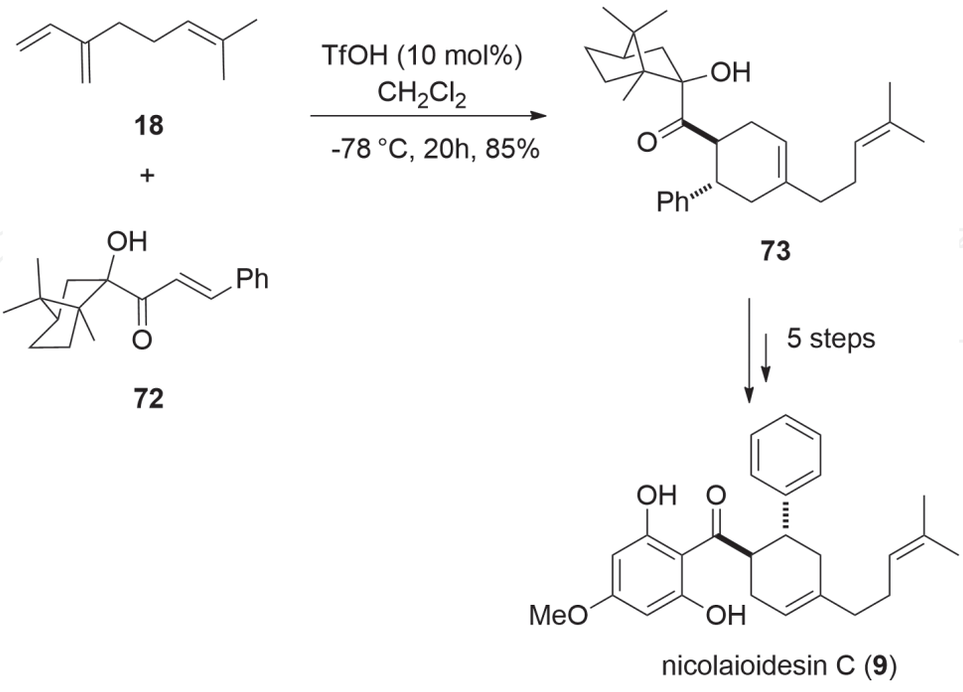


Scheme 6. Biomimetic synthesis of (±)-dorsterone and (±)-kuwanon V pentamethyl ethers [27].

catalyst [34]. The key synthetic step involved a borane tetrahydrofuran mediated biomimetic intermolecular Diels-Alder cycloaddition reaction. It is noteworthy that the *endo*/*exo* diastereoselectivity of the reaction was proven to be temperature-controlled.

3.4. Chiral ligand-Brønsted acid catalysis

The first asymmetric synthesis of flavonoid Diels-Alder natural products was reported by Palomo and co-workers in 2010 (**Scheme 7**). They employed a recoverable chiral auxiliary ((1 *R*)-(+)-camphor) in the asymmetric synthesis of nicolaioidesin C (**9**) [35]. First, the biomimetic Diels-Alder reaction between myrcene **18** and α'-hydroxy enone dienophile **72** was



Scheme 7. Asymmetric biomimetic synthesis of (-)-nicolaioidesin C (**9**) [35].

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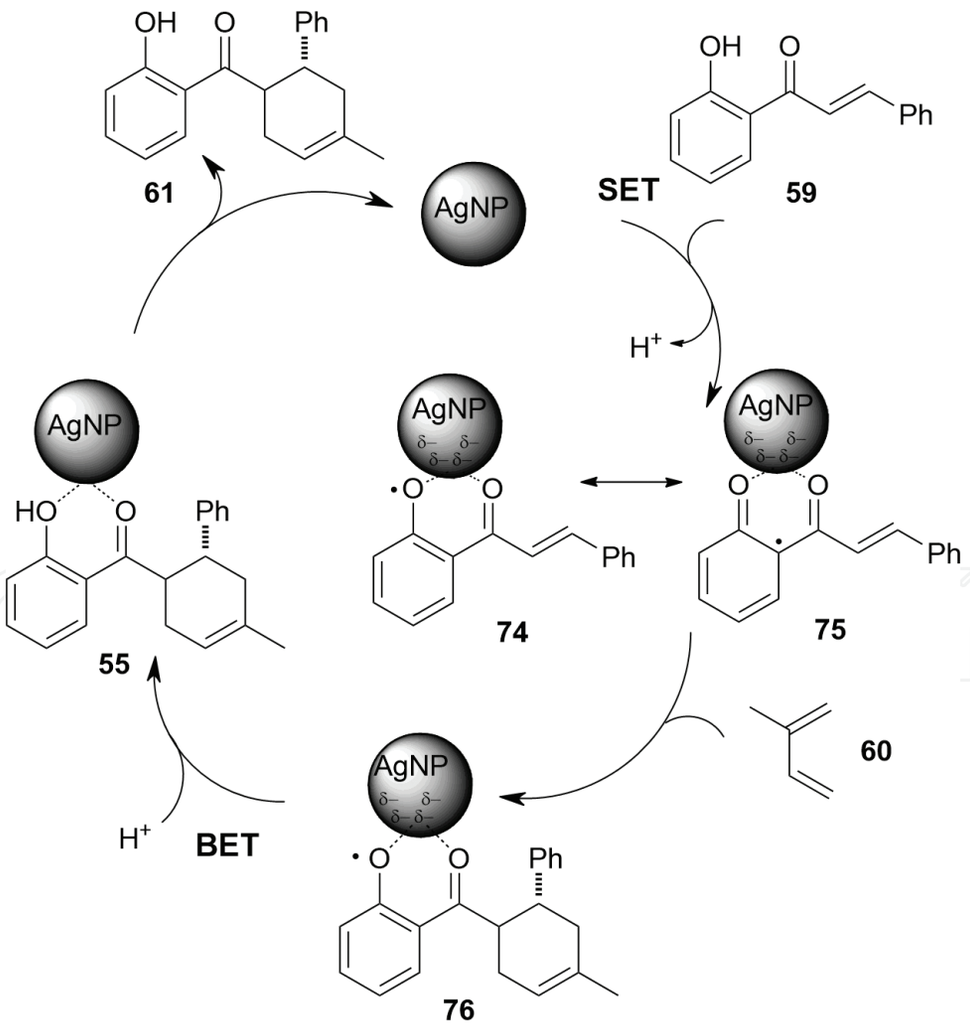
catalyzed by triflic acid at -78°C in dichloromethane to afford an enantiomeric enriched intermediate **73** in 85% yield. Subsequent transformation of the intermediate **73** in five further steps afforded (-)-nicolaioidesin C (**9**).

3.5. Silver nanoparticles catalyzed dehydrogenative Diels-Alder reaction

In 2010, Porco and co-workers discovered that silver (0) nanoparticles (AgNp) could effectively catalyze the Diels-Alder cycloaddition reaction [36]. The AgNP was prepared from a 3:1 molar ratio of $AgBF_4/Bu_4NBH_4$ in CH_2Cl_2 and then coated with silica gel. The solid product was filtered and then calcinated at 220°C to give AgNP. A proposed catalytic cycle was showed in **Scheme 8** [36]. It was hypothesized that proton removal and single electron transfer from the absorbed chalcone **59** to the silver nanoparticles may generate the AgNP-stabilized phenoxyl radical intermediate **74** which is in resonance with the radical **75**. A proposed concerted Diels-Alder reaction between the radical intermediate **74**/**75** and diene **60** provides **76** which generates **55** via back electron transfer (BET) and protonation [36]. A final desorption step gave the Diels-Alder adduct **61**. Porco and co-workers hypothesized that this silver



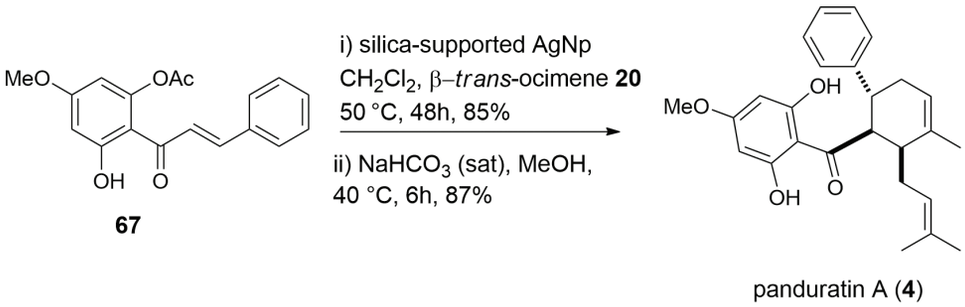
Scheme 8. Proposed mechanism for the silver nanoparticles-catalyzed Diels-Alder reaction [36].

nanoparticle (AgNp) may serve as 'electron shuttle' catalysts by accepting and returning a single electron from and to the substrate [36].

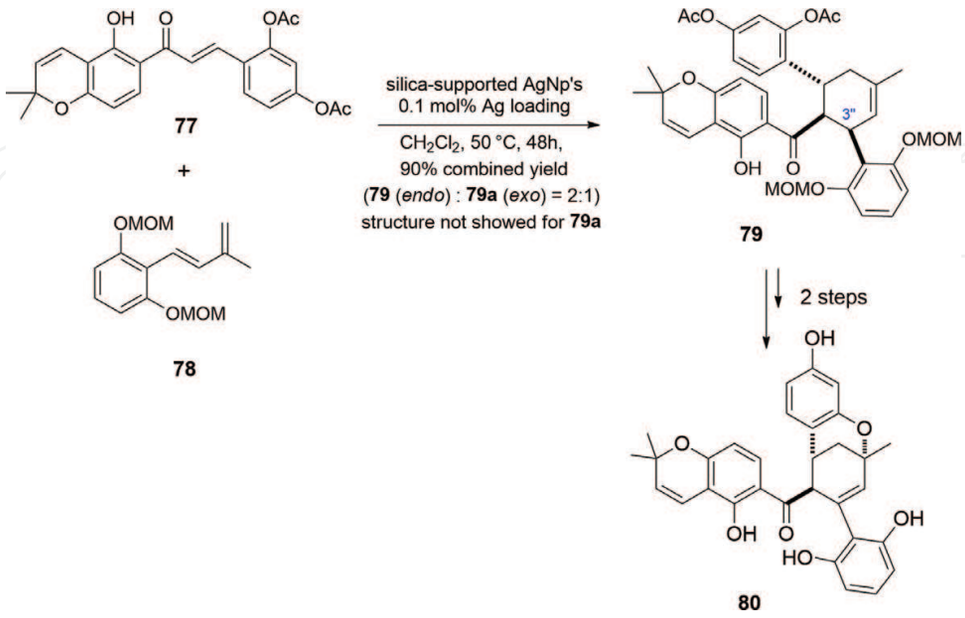
Following the mechanistic studies, Porco *et al.* utilized AgNP for the biomimetic syntheses of (±)-panduratin A (**Scheme 9**) [36] and (±)-sorocenol B (**Scheme 10**) [37]. Inspired by the aforementioned biosynthesis studies, Porco and co-workers found that the AgNP can also be used to promote dehydrogenation of the prenyl group of a flavonoid to form the requisite diene for the Diels-Alder reaction with a 2′-hydroxychalcone dienophile. Such tandem reactions were successfully employed for the synthesis of (±)-brosimone A and (±)-brosimone B (**Scheme 11**) [38].

3.6. Chiral ligand-Lewis acid complex mediated Diels-Alder reaction

In 2014, Lei and Wulff *et al.* reported the first enantioselective total synthesis of (-)-kuwanon I (**2**), (+)-kuwanon J (**1**), (-)-brosimone A (**86**) and (-)-brosimone B (**84**) by using chiral ligand-Lewis



Scheme 9. Synthesis of (±)-panduratin A (**4**) [36].



Scheme 10. Biomimetic synthesis of (±)-sorocenol B [37].

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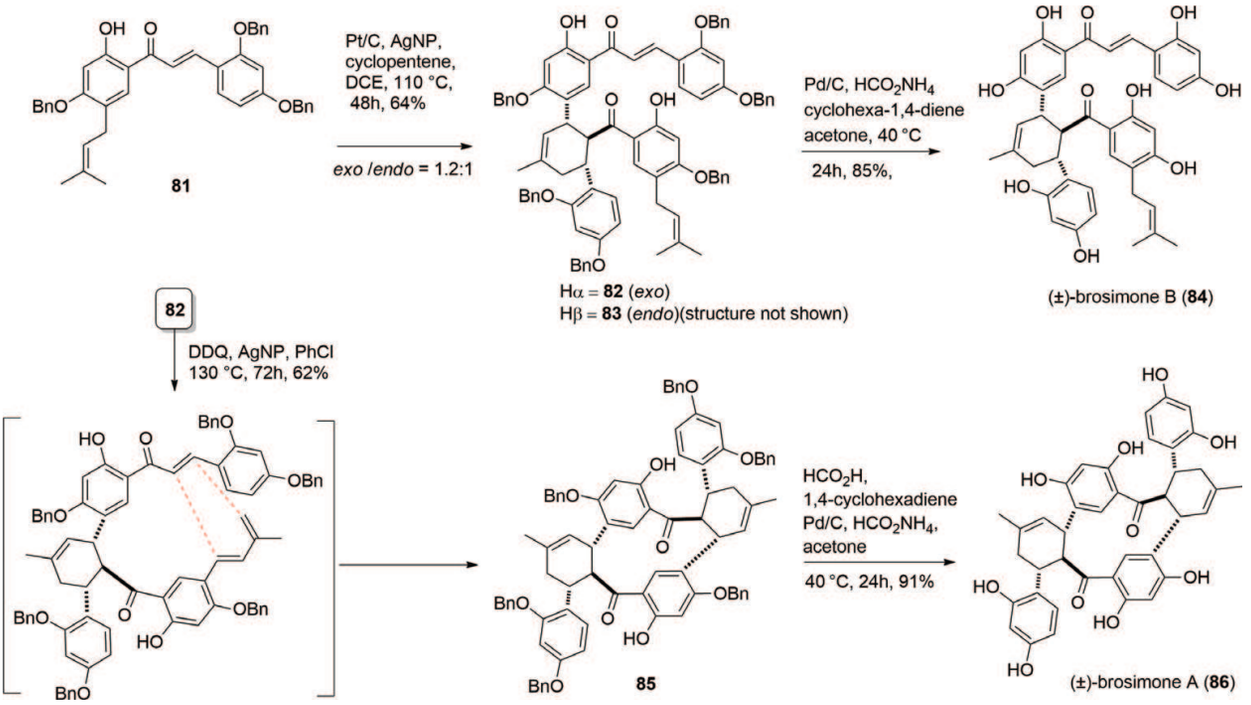


Scheme 11. Biomimetic synthesis of (±)-brosimone A and (±)-brosimone B [38].

acid complex. This complex was prepared by coordination of an axially chiral ligand such as VANOL or VAPOL to borane [39].

Scheme 12 shows the mechanism proposed by Lei and co-workers for the enantioselective Diels-Alder reaction [39]. The mechanism was proposed to proceed through the formation of a chiral boron complex **88**, followed by formation of a tetracoordinate boron complex **89** with 2′-hydroxychalcone dienophile. Subsequently, Diels-Alder reaction between the chiral complex **89** and a diene afforded a mixture of *endo*/*exo* diastereomers in high enantiomeric excess. Lei and co-workers proposed that the enantioselective Diels-Alder reaction may be induced by the following factors [39, 40].

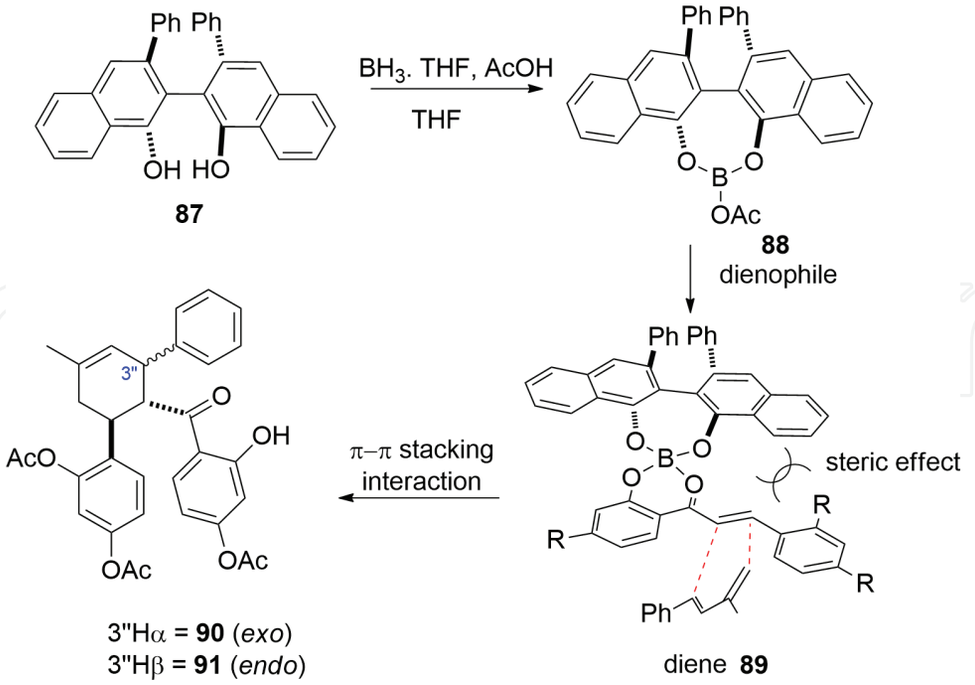
(a) The coordination bond between boron and dienophile which may lower the energy of LUMO.

(b) The mobility of dienophile may be reduced upon complexation.

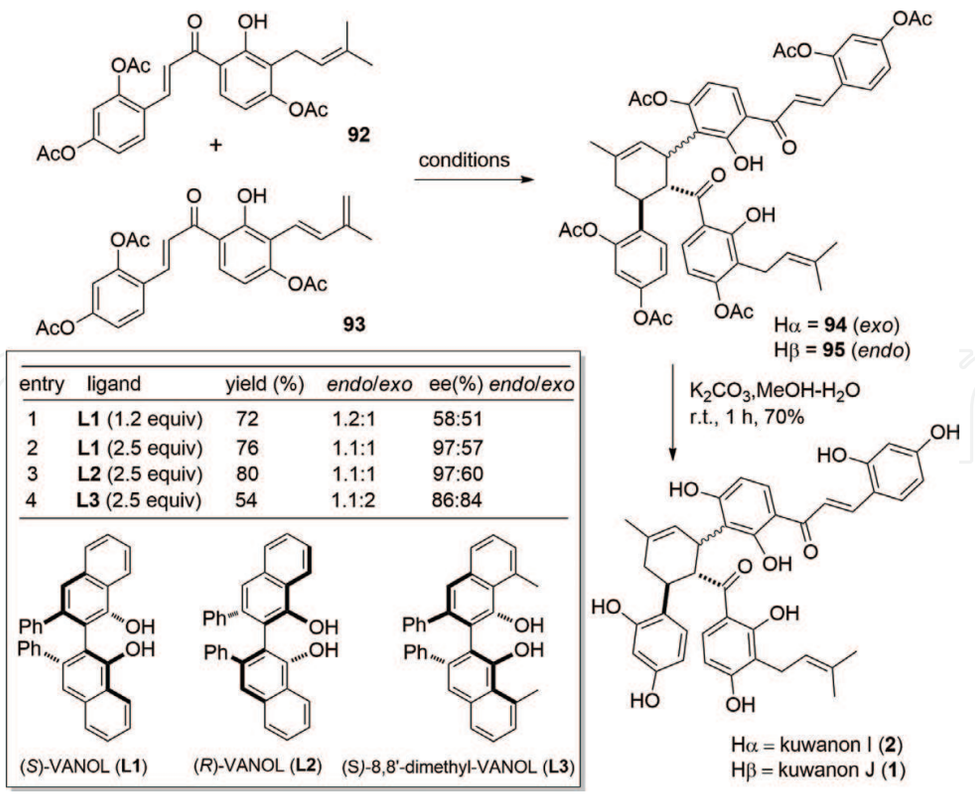
(c) The π-π stacking between the chiral ligand and dienophile shielding one face of the chalcone dienophile from attack by the diene.

Following the mechanistic studies, the (*S*)-VANOL-borane complex was efficiently used to mediate the synthesis of (-)-kuwanon I (**2**), (+)-kuwanon J (**1**), (-)-brosimone A (**84**) and (-)-brosimone B (**85**) [39]. Asymmetric Diels Alder reaction for these molecules was summarized in **Schemes 13–15**.

Based on the reported results, the chiral ligand strongly influences the enantioselectivity of the cycloaddition reaction. A 2.5 equivalent of (*R*)-VANOL is required for the optimal formation of



Scheme 12. Proposed mechanism for the chiral ligand-Lewis acid complex mediated enantioselective Diels-Alder reaction [39, 40].



entry	ligand	yield (%)	*endo*/*exo*	ee(%) *endo*/*exo*
1	**L1** (1.2 equiv)	72	1.2:1	58:51
2	**L1** (2.5 equiv)	76	1.1:1	97:57
3	**L2** (2.5 equiv)	80	1.1:1	97:60
4	**L3** (2.5 equiv)	54	1.1:2	86:84

Scheme 13. Chiral ligand-Lewis acid complex mediated enantioselective synthesis of (–)-kuwanon I (**2**) and (+)-kuwanon J (**1**) [39].

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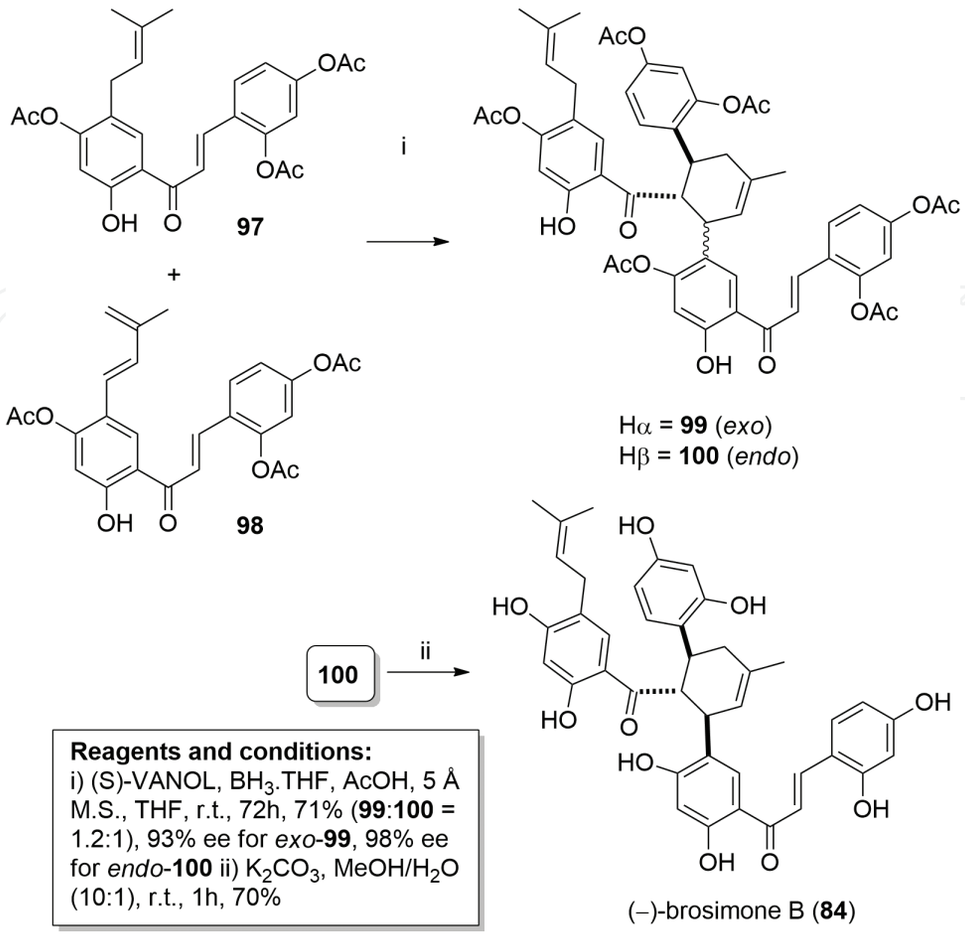


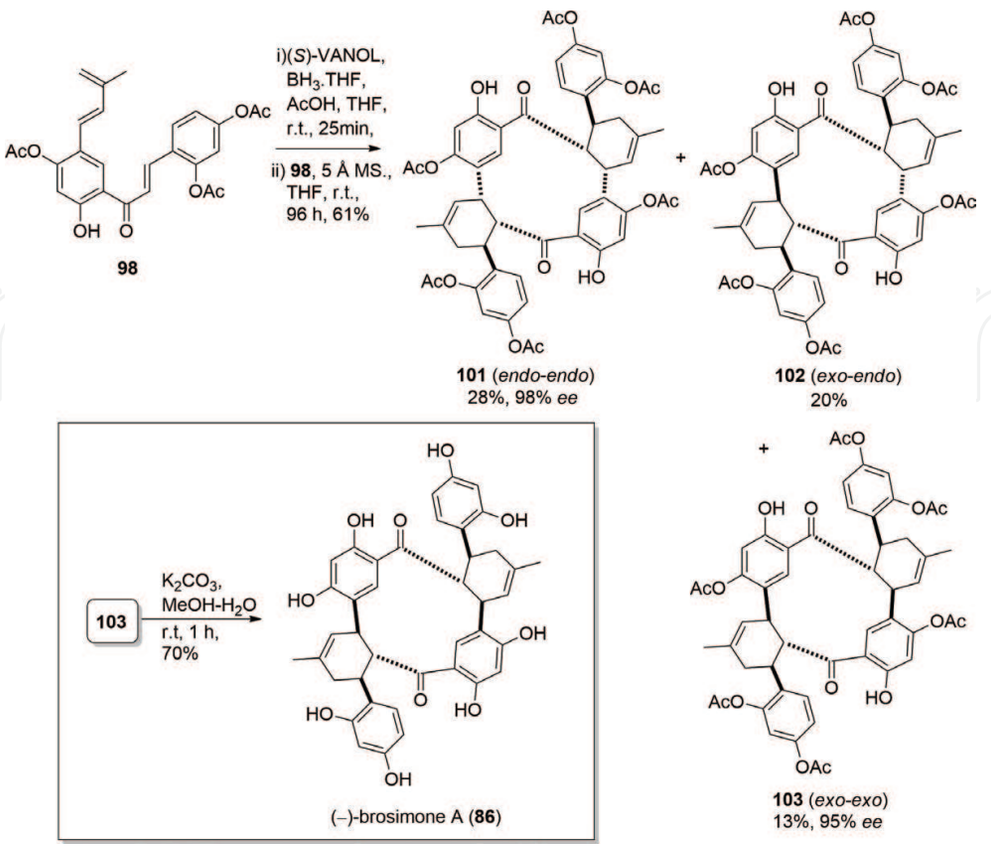
Scheme 14. Enantioselective synthesis of (–)-brosimone B [39].

kuwanon J precursor *endo*-**95** (97% ee, 1.1:1 *endo*/*exo*), whereas similar amount of (*S*)-8, 8′-dimethyl-VANOL is required for the optimal formation of kuwanon I precursor *exo*-**94** (84% ee, 1.2:1 *exo*/*endo*). Finall, deprotection of the acetate group of *endo*-**95** and *exo*-**94** furnished the desired natural products (-)-kuwanon J (**1**) and (+)-kuwanon I (**2**), respectively (**Scheme 13**) [39].

The synthetic routes for (–)-brosimone B (**84**) and (–)-brosimone A (**86**) were showed in **Schemes 14** and **15**, respectively. For (–)-brosimone B (**84**), cycloaddition reaction between dienophile **97** and diene **98** using (*S*)-VANOL gave a mixture of diastereomers **99** and **100** in 71% yield in a 1.2:1 ratio. Remarkably, excellent enantiomeric excess (*ee*) values for both compounds were obtained (98% *ee* for **100**, 93% *ee* for **99**). Deprotection of the acetyl groups of **100** gave (-)-brosimone B in 70% yield (**Scheme 14**) [39, 40].

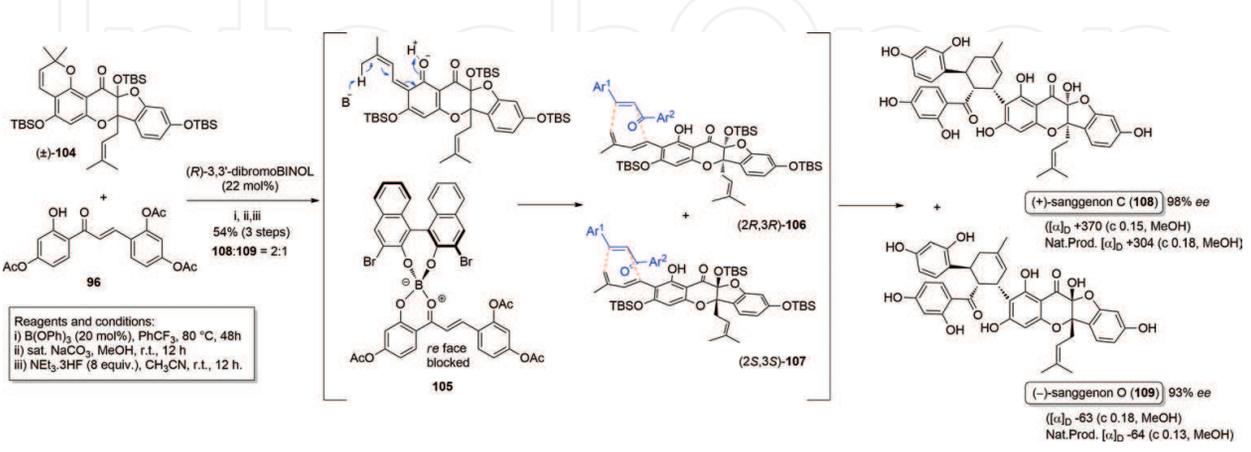
The diene **98** was also used in the synthesis of brosimone A (**86**) in a one-pot inter-/intramolecular Diels-Alder cycloaddition cascade strategy (**Scheme 15**). The (*S*)-VANOL-borane complex efficiently mediated the cycloaddition reaction to give a mixture of three diastereomers **101**–**103** (**Scheme 15**). Deprotection of the adduct **103** gave (-)-brosimone A (**86**) in 70% yield [39, 40].

In 2016, Porco and co-workers reported the syntheses of the flavonoid Diels-Alder natural products sanggenon C (**108**) and sanggenon O (**109**) by using a combination of silver nanoparticles (AgNP) and a BINOL-borate catalyst (**Scheme 16**) [41].



Scheme 15. Enantioselective synthesis of (–)-brosimone A [39].

A catalytic amount of triphenylborate ($B(OPh)_3$) and (*R*)-3,3′-dibromoBINOL was used to mediate the asymmetric Diels-Alder reaction between diene precursor **104** and dienophile **105** (**Scheme 16**). In the first step, the diene precursor **104** underwent a retro 6π-electrocyclisation followed by a formal 1,7 hydrogen shift process to afford the requisite diene functionality. Reaction of this diene with dienophile **105** in the present of a catalytic amount of chiral



Scheme 16. Asymmetric synthesis of sanggenons C (**108**) and O (**109**) [41].

BINOL-borate complex ((*S*)-3,3′-dibromoBINOL/triphenylborate) afforded a mixture of cycloadducts, which after deprotection gave sanggenon C (**108**) and sanggenon O (**109**) in 2:1 ratio of 98 and 93% ee, respectively. The use of AgNP gave a racemic mixture of **108** and **109**.

In conclusion, this chapter has provided an overview of biosynthesis and biomimetic synthesis of flavonoid Diels-Alder natural products. Intensive biosynthesis studies led by Nomura *et al*. have provided important information for the enzymatic formation of these natural products. In particular, information from the diene formation and the feeding experiments have paved the way for an exploration of chemical synthesis of these natural products. Finally, with the innovative chemical strategies, enantiomerically pure flavonoid Diels-Alder natural products were made possible for further biological activities evaluation.

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