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Chiral Boron Complex-Promoted Asymmetric Diels–Alder Cycloaddition and Its Application in Natural Product Synthesis

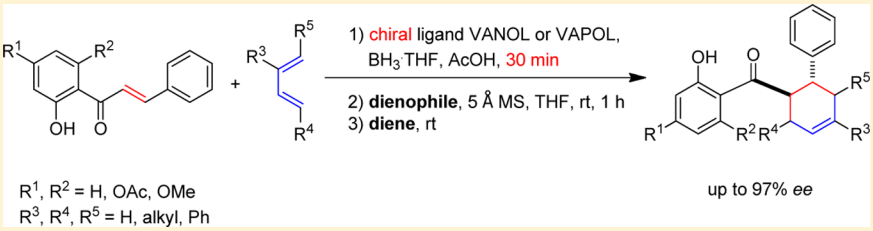
Xia Li,[†,‡] Jianguang Han,[†,‡] Alexander X. Jones,[§] and Xiaoguang Lei*[,‡,§]

[†]School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, 300072, China

[‡]National Institute of Biological Sciences (NIBS), Beijing, 102206, China

[§]Beijing National Laboratory for Molecular Sciences, Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry and Molecular Engineering, Synthetic and Functional Biomolecules Center, and Center for Life Sciences, Peking University, Beijing, 100871, China

Supporting Information



ABSTRACT: An efficient method for the asymmetric Diels–Alder cycloaddition of 2′-hydroxychalcones with acyclic or cyclic dienes has been successfully developed. The Diels–Alder cycloaddition is mediated by a chiral boron complex with VANOL, affording the corresponding products in high yields and with excellent diastereo- and enantioselectivities. This reaction enabled the enantioselective construction of cyclohexene skeletons crucial for the total synthesis of a number of Diels–Alder-type natural products (−)-nicolaioidesin C, (−)-panduratine A, (−)-kuwanon I, (+)-kuwanon J, and (−)-brosimones A and B.

INTRODUCTION

Numerous structurally related Diels–Alder products have been isolated from various *Moraceous* and related plants,[1] such as the chalconoid natural products, nicolaiodesin C (**1**)[2] and panduratin A (**2**);[3] prenylflavonoid Diels–Alder natural products, kuwanon I (**3**)[4] and J (**4**),[5] brosimone A (**5**)[6] and B (**6**);[7] as well as kuwanons G (**7**)[8] and H (**8**)[9] (Figure 1). These molecules all possess a cyclohexene ring derived from Diels–Alder cycloaddition of a 2′-hydroxychalcone-containing dienophile. However, structural variations in the diene and dienophile precursors give rise to natural products which display striking diversity as well as significant biological activities.[10] Accordingly, complex and biologically active Diels–Alder-type natural products have attracted broad attention from the synthetic community over the past decade.[11] Several synthetic methods have been developed to promote Diels–Alder cycloadditions with 2′-hydroxychalcone dienophiles, including thermal promotion,[12] single-electron transfer initiation,[13] as well as silica-supported silver nanoparticle (AgNPs) catalysis.[14] However, all these methods are non-enantioselective. Palomo and co-workers have described the enantioselective total synthesis of (−)-nicolaioidesin C, using a chiral camphor auxiliary.[15] In 2014, our group reported the first direct asymmetric Diels–Alder cycloaddition with 2′-hydroxychalcone dienophiles, using a chiral VANOL-boron Lewis acid complex.[16] We demonstrated the application of our methodology to the synthesis of complex natural products (−)-kuwanon I, (+)-kuwanon J, (−)-brosimone A, and (−)-brosimone B.[16] In this paper, we report a full account of the development and optimization of the chiral boron-Lewis acid-mediated Diels–Alder cycloaddition, a summary of our syntheses of the above natural products, and a report on the syntheses of two related natural products: (−)-nicolaioidesin C and (−)-panduratine A, using this methodology.

Our studies began with the model reaction between 2′-hydroxychalcone **9** as dienophile and diene **10**. Initially, we examined the effect of Brønsted acid catalysts, such as chiral BINOL-derived phosphoric acid (**BA1**),[17] the more strong acidic catalyst *N*-triflyl phosphoramide (**BA2**),[18] (1*S*)-(+)-10-camphorsulfonic acid (**BA3**), and tartaric acid (**BA4**). Unfortunately, all of these attempts failed, including increasing amount of the catalyst (from catalytic to stoichiometric amount), raising complex temperature (from room temperature (rt) to reflux temperature), and extending reaction time, even promoted in microwave conditions, presumably because these Brønsted acids have insufficient efficiency (Table 1). We next turned our attention to chiral Lewis acid catalysts. 2′-Hydroxychalcones have been shown to be resistant to activation by several traditional Lewis acids, and chiral oxazaborolidine (**LA1**) and chiral aluminum Lewis acid complex (**LA2**) failed to catalyze this cycloaddition (Table 1, entries 3 and 4). Inspired by the enantioselective Diels–Alder reactions and chlorinations

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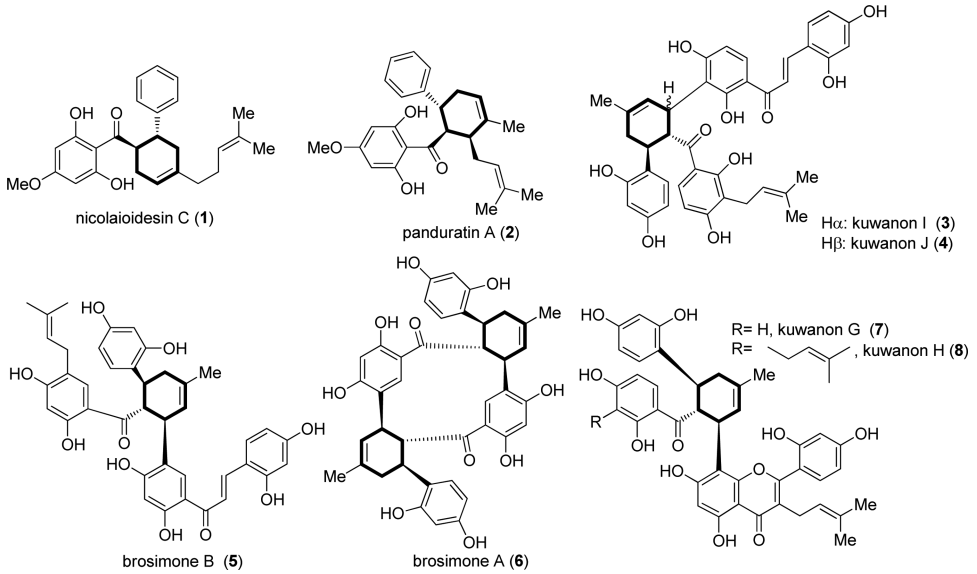
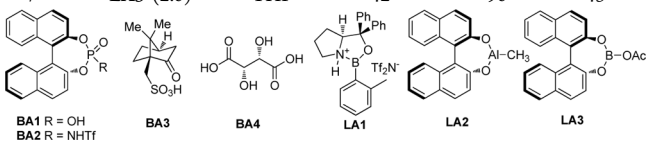


Figure 1. Representative Diels–Alder-Type Natural Products Derived from 2′-Hydroxychalcones.

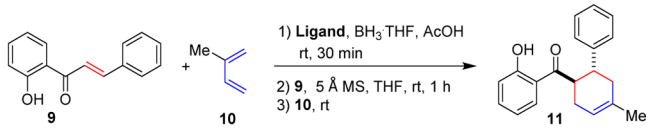
Table 1. Initial Reaction Screening

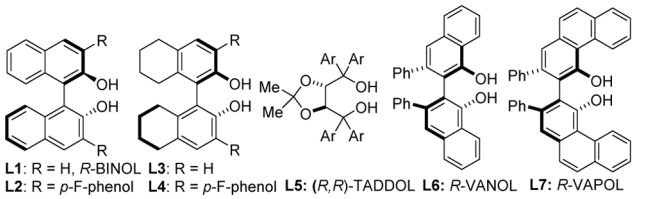
entry	equiv of ligand	solvent	time (h)	yield (%)[a]	ee (%)[b]
1	**BA** (2.0)	DCM	24	N.R.	N.D.
2[c]	**BA** (2.0)	toluene	0.5	N.R.	N.D.
3	**LA1** (2.0)	THF	16	N.R.	N.D.
4	**LA2** (2.0)	DCM	16	trace	N.D.
5	**LA3** (4.0)	THF	16	50	69
6	**LA3** (2.0)	THF	84	30	6
7[d]	**LA3** (2.0)	THF	42	90	43



[a]Conditions: dienophile **9** (1 equiv), diene **10** (20 equiv), rt, isolated yield. [b]Determined by chiral HPLC. [c]80 °C, 100 W. [d]*R*-BINOL, 5 Å MS. THF = tetrahydrofuran, DCM = dichloromethane, N.D. = not detected.

Table 2. Screening the Chiral Ligand





entry	ligand	time (h)	yield (%)[a]	ee (%)[b]
1	**L1**	42	90	43
2	**L2**	43	80	47
3	**L3**	30	95	43
4	**L4**	22	95	37
5	**L5**	31	90	13
6	**L6**	12	99	95
7[c]	**L6**	12	95	95
8[d]	**L6**	12	95	95
9[e]	**L6**	12	95	94
10	**L7**	12	99	92

[a]Conditions: Chiral ligand (2 equiv), BH_3·THF (2 equiv), AcOH (2 equiv), dienophile **9** (1 equiv), diene **10** (20 equiv), 5 Å MS, isolated yield. [b]Determined by chiral HPLC. [c]**L6** (1.2 equiv). [d]With recycled ligand, one cycle, 99% recovery **L6**. [e]With recycled ligand, two cycles, 97% recovery **L6**.

on the juglone systems,[19] we selected the optically active BINOL-boron complex (**LA3**) to promote the asymmetric Diels–Alder cycloaddition. To our delight, the chiral boron Lewis acid complex could effectively promote the cycloaddition of dienophile **9** and diene **10** to afford Diels–Alder adduct **11** (Table 1, entry 5). In this asymmetric Diels–Alder reaction, a superstoichiometric amount of the chiral boron complex was needed. When we reduced the amount of the chiral Lewis acid, yield and enantioselectivity of the cycloaddition adduct decreased (Table 1, entries 5 and 6). We suspected that the chiral ligand–dienophile intermediate may hydrolyze in the presence of water or open to the air, and indeed higher yields and moderate ee value could be regained at lower complex loading by addition of activated 5 Å molecular sieves (Table 1, entry 7).

Employing the same Diels–Alder reaction conditions as in Table 1, entry 7, we screened a number of different chiral ligands in order to optimize enantioselectivity (Table 2). We first considered whether sterically large BINOL substituent groups may improve enantioselectivity, but found that both the highly bulky chiral binaphthol ligand (**L2**),[19a,c] the chiral reduced-type binaphthol ligand (**L3** and **L4**),[20] and (*R*,*R*)-TADDOL ligand (**L5**) result in relatively low enantioselectivity in our model reaction. Employing the vaulted 2,2′-binaphthol (VANOL, **L6**) and 3,3′-biphenanthrol (VAPOL, **L7**),[21] developed by William D. Wulff and co-workers, 1.2 equiv complex loading was found to give the desired adducts with excellent yield and ee value. Although a stoichiometric amount of the chiral boron complex

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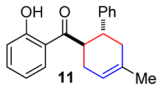
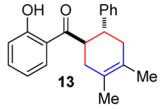
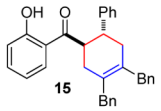
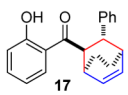
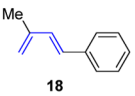
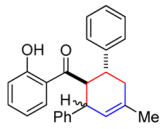
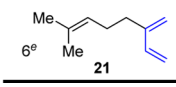
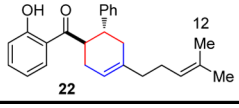
is still required, the chiral ligands can be recycled repeatedly; both yield and ee value are retained after one and two recycles using the recovered chiral ligand VANOL in the asymmetric Diels–Alder reaction (Table 2, entries 7–9).

To determine the substrate generality and limitations of this strategy, several dienes were subjected to asymmetric Diels–Alder reaction under the optimized conditions (Table 3). All the

Table 3. Diels–Alder of Dienophile 9 and Dienes

Entry	Diene	Product	Time (h)	Yield (%)[a]	*ee* (%)[b]
1	 **10**	 **11**	6	90	95
2	 **12**	 **13**	4	99	92/96[c]
3	 **14**	 **15**	12	94	96
4[d]	 **16**	 **17**	68	90	90
5	 **18**	 Hα: **19** *endo*, Hβ: **20** *exo* *endo*:*exo* = 5.4:1	9	99	91 (*endo*) 38 (*exo*)
6[e]	 **21**	 **22**	12	99	94

[a]*R*-VANOL (1.2 equiv), BH_3·THF (1.2 equiv), AcOH (1.2 equiv), dienophile **9** (1 equiv), dienes (20 equiv, unless specified otherwise), diene **14** and **18** (5 equiv), 5 Å MS, yield of isolated product. [b]Determined by chiral HPLC. [c]*R*-VAPOL (1.2 equiv). [d]Single *endo* isomer. [e]Single regioisomer isomer.

substituted dienes were converted to the corresponding adducts in satisfactory yield with high ee value. Single regioisomers were observed for unsymmetrical 2-substituted and 1,3-disubstituted dienes, and the *endo*/*exo* diastereoselectivity for diene **18** was 5.4:1 (Table 3, entries 1, 5, and 6).

To explain the excellent enantioselectivity observed in the [4 + 2]-Diels–Alder cycloaddition, we propose an assembly involving 2′-hydroxychalcone and a chiral boron-VANOL complex (Figure 2). A calculated model by Chem3D indicates that upon activation of the ketone moiety by the boron Lewis acid, the chiral VANOL ligand is probably forms a $\pi-\pi$ stacking interaction with the chalcone dienophile, which shields the α-face and dictates the stereofacial approach of the diene from the less hindered β-face.

Encouraged by the effective asymmetric Diels–Alder reaction with a wide variety of substrates, we decided to apply our strategy to the total syntheses of (−)-nicolaiodesin C and (−)-panduratin A. Chalcone **23** and myrcene were mixed under the optimal reaction conditions, and then the acetyl group was removed to afford (−)-nicolaiodesin C (**1**) with 96% ee. (−)-Panduratin A was obtained from the same reaction sequence, starting from Diels–Alder cycloaddition of 1:3 *E*:*Z* ocimene (*E*,*Z*)-ocimene[22] with chalcone **23** to give the target molecule in 56% yield and 87% ee (Scheme 1). When pure *Z*-ocimene reacted with the dienophile, no Diels–Alder adduct was isolated.[12c] The lower yield of the Diels–Alder step was probably due to the fact that the requisite *E*-ocimene has been found to undergo olefin isomerization and polymerization under acid conditions.[23]

Encouraged by the successful total syntheses of (−)-nicolaiodesin C and (−)-panduratin A, we then sought to explore the total syntheses of the more complex natural products, (−)-kuwanon I and (+)-J, (−)-brosimone A and B. We strived to access all of the four natural products from the common intermediate **24**, which can undergo sigmatropic rearrangement to form *ortho*-prenylated chalcone **25**, a synthetic precursor for kuwanons I and J, or *para*-prenylated chalcone **26** for brosimones A and B (Scheme 2).

The important research work reported by Nomura and co-workers showing the chalcone (**M-1**) was transformed to the methylated kuwanon J (**M-3**) upon treatment with the *Morus alba* cell cultures (Scheme 3).[24] The findings indicated that kuwanon J might be biosynthesized by dehydrogenase and Diels–Alderase. Inspired by this elegant biosynthesis study, we envisioned a synthetic route which could effectively mimic the required transformations catalyzed by dehydrogenase and Diels–Alderase in nature.

Our synthetic approach to kuwanons I and J began with preparation of the dienophile. Initially, prenylation of readily available chalcone **27** under standard conditions afforded *O*-prenyl chalcone **24**, which was subjected to a montmorillonite K-10-catalyzed sigmatropic rearrangement to afford the desired chalcone **25** (37%) for kuwanons I and J, [1,5]-sigmatropic rearrangement product **26** (27%) for brosimones A and B, along with deprenylated chalcone **27** (36%) (Scheme 4). In order to increase the reactivity of dienophile, we converted the MOM protecting groups into the more electron-withdrawing acetyl groups (35%, 2 steps).

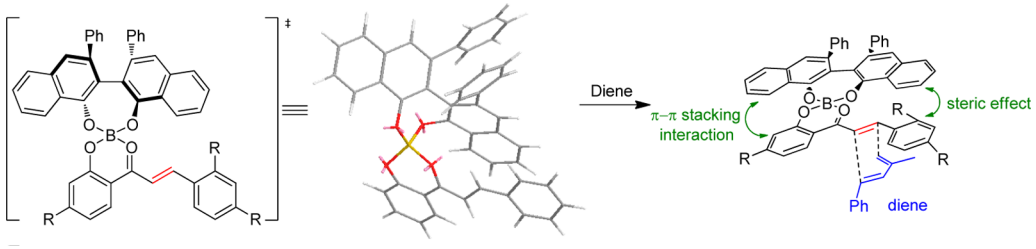


Figure 2. Proposed mechanism for the enantioselective Diels–Alder reaction and structure of the chiral VANOL-boron Lewis acid–dienophile complex.

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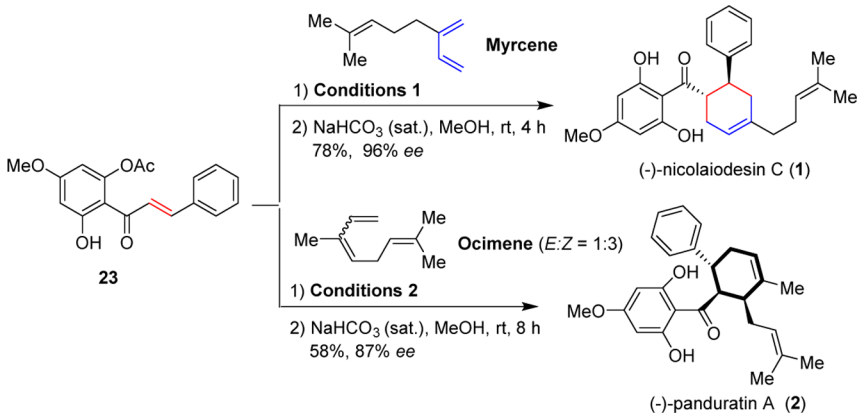
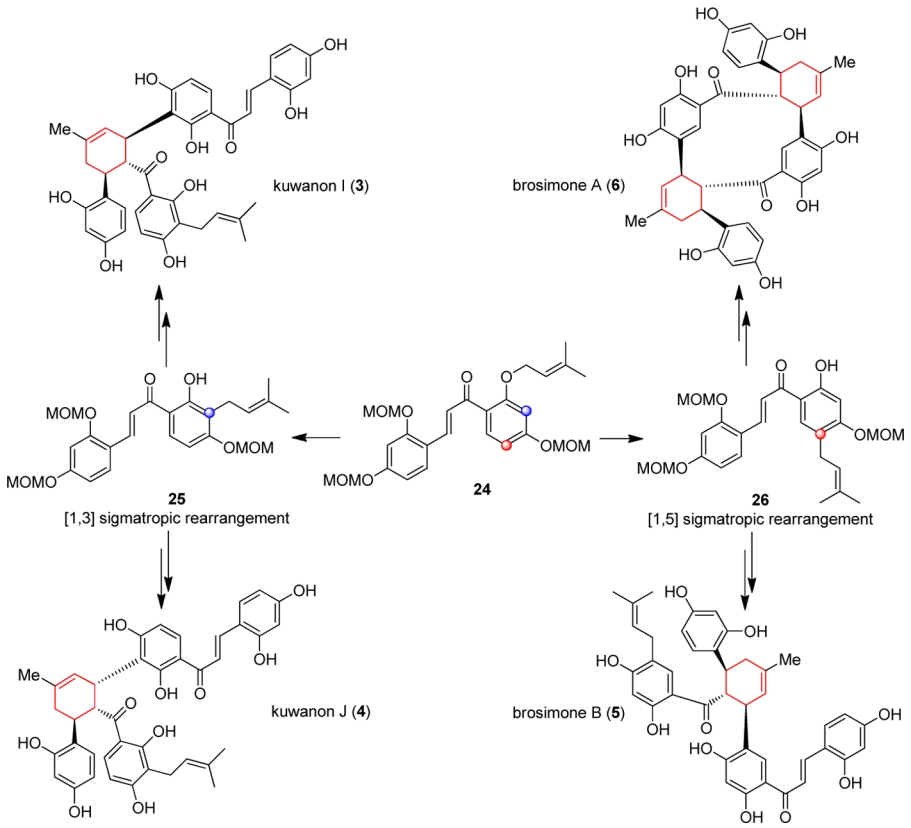
Scheme 1. Total Syntheses of (−)-Nicolaiodesin C and (−)-Panduratin A[a]



[a]Reagents and conditions: (1) (a) *R*-VANOL (1.2 equiv), AcOH (1.2 equiv), BH_3·THF (1.2 equiv); (b) Dienophile **23**, 5 Å MS, THF, rt, 1 h; (c) Myrcene, rt, 16 h, 88%. (2) (a) *S*-VANOL (2.0 equiv), AcOH (2.0 equiv), BH_3·THF (2.0 equiv). (b) Dienophile **23**, 5 Å MS, THF, rt, 1 h. (c) Ocimene (*E*:*Z* = 1:3), rt, 68 h, 57%.

Scheme 2. Synthetic Plan for Kuwanons I and J and Brosimones A and B



A permethylated *ortho*-prenylated chalcone **29** was selected as the synthetic precursor of diene **32** in order to increase the Diels−Alder reactivity of the diene. The key biomimetic dehydrogenation to generate **32** involved a regioselective Schenck ene reaction[25] of chalcone **29** and reduction and dehydration of tertiary allylic alcohol **31** to give the desired diene (Scheme 5).

With both dienophile **28** and diene **32** in hand, we began to evaluate the chiral boron complex-catalyzed Diels−Alder cycloaddition (Scheme 6). We were pleased to find that the [4 + 2] cycloaddition between dienophile **28** and diene **32** proceeded smoothly under the optimal conditions to afford *endo*/*exo* diastereomers (**34** and **33**, respectively) in 75% yield with a 1.2:1 ratio. The completion of the syntheses of kuwanons I and J required only removal of the acetyl and methyl protection groups. Hydrolysis of the products **33** and **34** under basic conditions afforded the compound **35** and **36**. Unfortunately, many attempts at methyl group deprotection of either **35** or **36** led only to decomposition. We attempted to use other electron-donating protecting groups of the diene, such as MOM, MTM, and TIPS groups. Unfortunately, the late-stage global deprotection only led to incomplete deprotection or decomposition. This issue was resolved by converting the phenolic hydroxyl group to acetyl esters. Ultimately, the usage of

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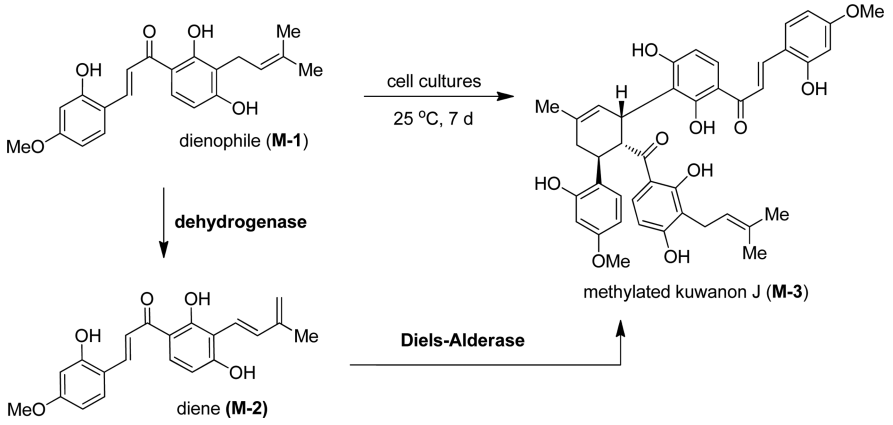
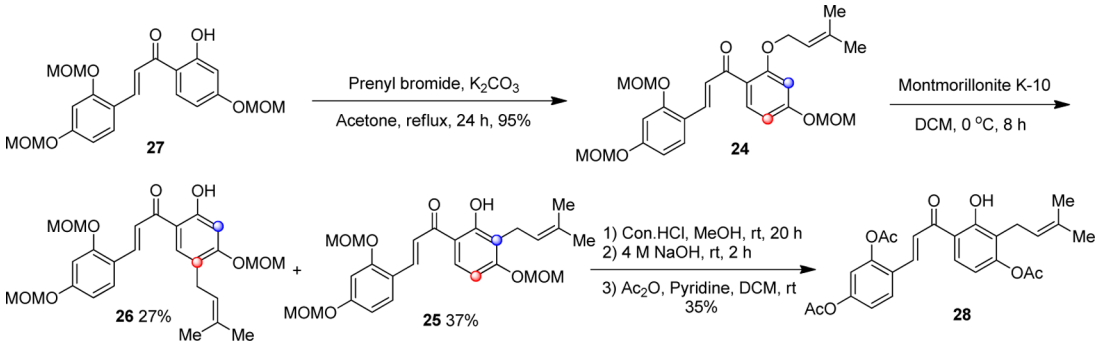
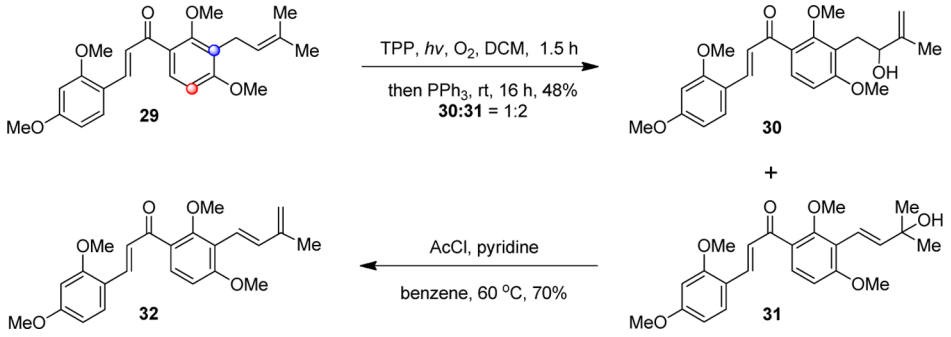
Scheme 3. Biosynthesis of Methylated Kuwanon J



Scheme 4. Synthesis of Dieneophile 28



Scheme 5. Synthesis of Diene 32



acetyl protecting groups was an essential factor in completing total syntheses of kuwanons I and J and brosimones A and B (vide infra).

In order to complete the total synthesis of these natural products, we turned our attention to synthesis of acetyl group protected diene (Scheme 7). Initial *ortho*-prenylated chalcone **28** was subjected to the standard Schenck ene reaction conditions, followed by subsequent reduction with PPh_3 to afford the tertiary allylic alcohol **38** and secondary allylic alcohol **37** in 71% combined yield with a 2:1 ratio. The diene **39** was further prepared by dehydration of the tertiary allylic alcohol **38** in 75% yield. Unfortunately, several attempts for the dehydration of secondary allylic alcohol **37** failed due to low reactivity. Considering the fact that tertiary alcohols are typically better substrates for dehydration, we screened commonly used photosensitizers and solvents to improve the selectivity for the tertiary alcohol. We observed that a visible light-mediated[26] regioselective Schenck ene reaction using $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as photosensitizer and MeOH as solvent significantly improved the ratio for tertiary alcohol (from 2:1 to 8:1). To the best of our knowledge, this biomimetic transformation represents the first $Ru(bpy)_3Cl_2{\cdot}6H_2O$-mediated regioselective Schenck ene reaction.

We next turned our attention to synthesis of the *para*-prenylated chalcone diene, which was the synthetic precursor for brosimones A and B. It was found that a relatively good regioselectivity for the Schenck ene-reduction of chalcone **40** was obtained by using tetraphenylporphyrin (TPP) as photosensitizer and MeOH as solvent. The tertiary allylic alcohol **42** and secondary allylic alcohol **41** were afforded in 63% combined yield with 3.2:1 ratio, respectively. The diene **43** was further prepared by dehydration of the tertiary allylic alcohol **42** in 68% yield (Scheme 7).

With both dienophile **28** and diene **39** in hand, we began to evaluate the key Diels–Alder cycloaddition catalyzed by chiral boron complex in total syntheses of kuwanons I and J (Scheme

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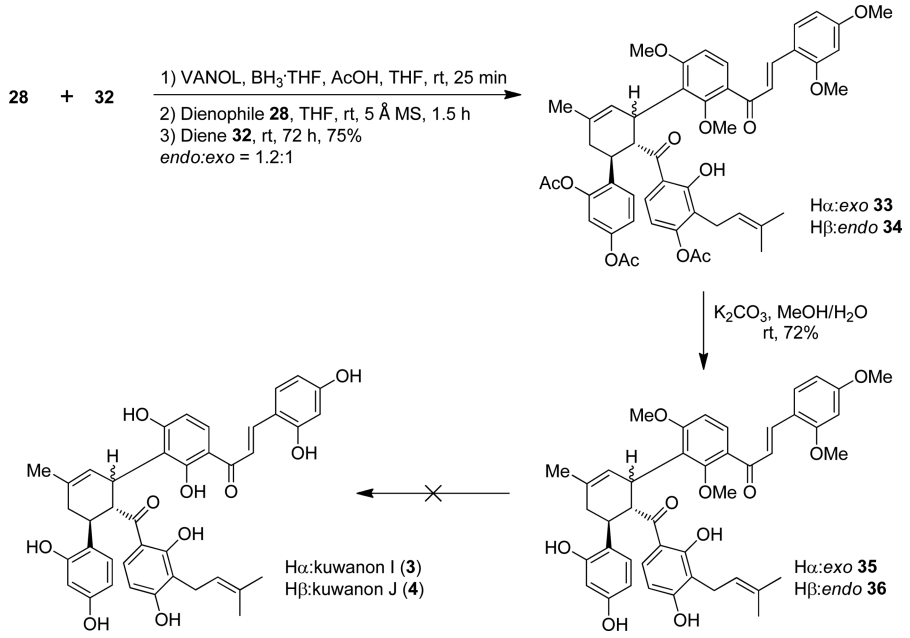
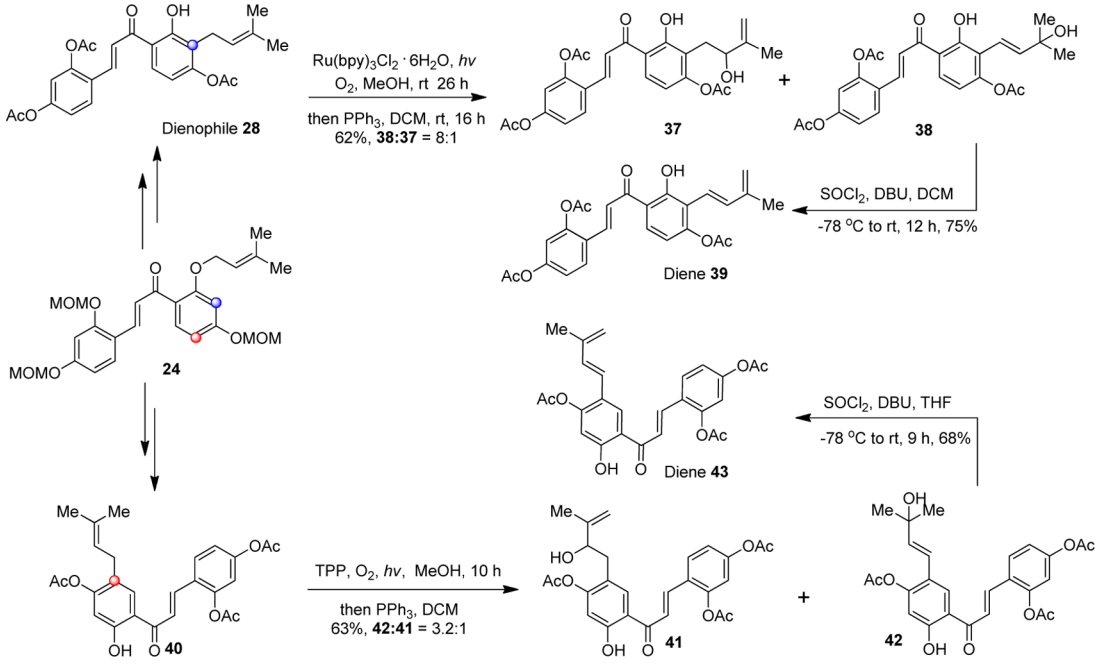
Scheme 6. Attempted Synthetic Route for Kuwanons I and J



Scheme 7. Biomimetic Synthetic Design for Dienes



8).We envisaged several challenges in the Diels–Alder step, due to the electron deficiency of acetyl protected diene **39** and the large steric size of both substrates. However, we were delighted to find that under the optimized reaction conditions, the Diels–Alder cycloaddition proceeded smoothly to afford *endo*/*exo* diastereomers (**45**:**44** = 1.2:1) in moderate yield and moderate enantiomeric excess (58% ee for **45**, 51% ee for **44**).[27] The non-enantioselective reaction, using only BH_3·THF and AcOH yielded 12% of the Diels–Alder cycloadducts in the same reaction time. Therefore, we increased the ligand loading in order to reduce background reaction.[28] Increasing the equivalents of ligand from 1.2 to 2.5 resulted in an obvious improvement in enantioselectivity (97% ee for **45**, 60% ee for **44**). The best results for *exo*-product were obtained when *S*-8,8′-dimethyl-VANOL (**L8**) was used as a chiral ligand. Finally, global deprotection of the Diels–Alder cycloadducts *exo*-**44** and *endo*-**45** under mild basic conditions efficiently furnished the desired natural products kuwanons I (**1**) and J (**2**), both in 70% yield. The ^1H and ^{13}C NMR spectra of the synthetic kuwanons I and J were consistent with those reported for the natural products.[4,5]

The *para*-prenylated chalcone **40** and diene **43** were utilized in the total synthesis of brosimone B (Scheme 9). To our surprise, both VANOL and VAPOL ligands can afford *endo* and *exo* diastereomers in good yields and excellent enantiomeric excess for both *endo* and *exo* products (with *S*-VANOL as ligand, 98% ee for *endo* **46**, 93% ee for *exo* **47**). The structure of *endo*-diastereomer **46** was confirmed by 2D-NMR. Final deprotection

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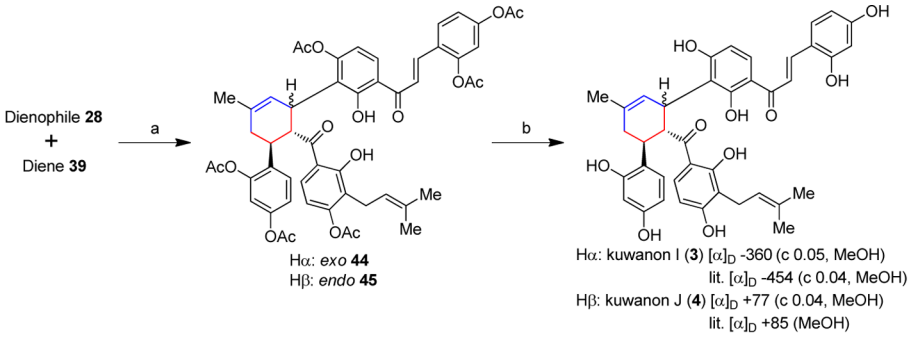
Scheme 8. Syntheses of (−)-Kuwanon I and (+)-Kuwanon J

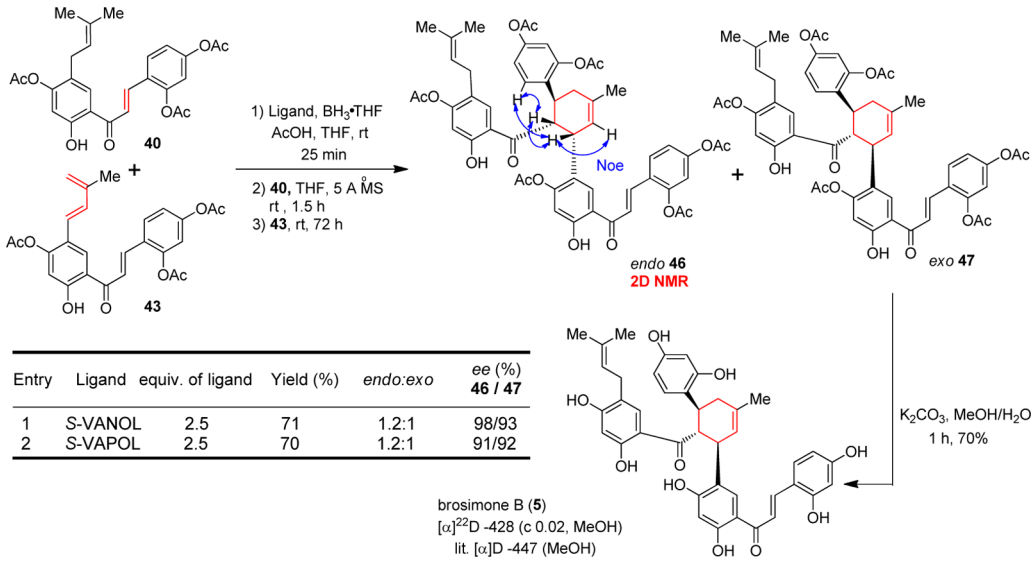


(a) Ligand, BH_3·THF, AcOH, 5 Å MS, THF, rt, 72 h; (b) K_2CO_3, MeOH/H_2O (10:1), rt, 1 h, 70%.

Entry	Ligand[a]	Equiv of Ligand	Yield (%)[b]	*endo:exo*	*ee* (%)[c] *endo/exo*
1	*S*-VANOL	1.2	72	1.2:1	58/51
2	*R*-VANOL	2.5	80	1.1:1	97/60
3	*S*-VAPOL	2.5	19	1.1:2	40/25
4	L8	2.5	54	1:1.2	86/84

(a) Ligand, BH_3·THF, AcOH, 5 Å MS, THF, rt, 72 h; (b) K_2CO_3, MeOH/H_2O (10:1), rt, 1 h, 70%.

Scheme 9. Synthesis of (−)-Brosimone B



Entry	Ligand	equiv. of ligand	Yield (%)	*endo:exo*	*ee* (%) **46 / 47**
1	S-VANOL	2.5	71	1.2:1	98/93
2	S-VAPOL	2.5	70	1.2:1	91/92

of the acetyl groups of *exo*-diastereomer **47** afforded brosimone B (**5**) in 70% yield.

The dimeric natural product, brosimone A, is a structurally complex compound derived through the homodimerization of **43**, presumably via a remarkable tandem inter/intramolecular asymmetric Diels–Alder cycloaddition process. To our knowledge, the sequential one-pot inter- and intramolecular Diels–Alder cycloaddition cascade was rarely described before.[29] Fortunately, when chiral boron complex was used, all three expected products were obtained, namely *endo–endo* **48** in 28% yield with 98% ee, *exo–endo* **49** in 20% yield (see below for ee value determination), and *exo–exo* **50** in 13% yield with 95% ee (entry 1). Finally, global deprotection of the *exo–exo* product **50** under mild basic conditions (K_2CO_3, MeOH) efficiently afforded brosimone A (**6**) in 70% yield. The ^1H and ^{13}C NMR spectra of the synthetic brosimone A were in agreement with those reported for the natural product[6] (Scheme 10).

The structures of the two natural products analogues *endo–endo* **48** and *exo–endo* **49** were confirmed by different methods (Scheme 11). Sequentially deacetylation and methylation of *endo–endo* **48**, the permethylation product **51** was obtained in 56% yield over 2 steps. The structure of the *endo–endo* **51** was unambiguously determined by X-ray crystallographic analysis. However, it proved not possible to directly measure the ee value of *exo–endo* **49** due to the presence of a mixture of conformational isomers in the chiral HPLC chromatogram. An indirect method was therefore devised, whereby **49** was converted to the known permethylated analogue **53**, previously reported by the Porco group.[14c] Deprotection of the acetyl groups and methylation of *exo–endo* **49** afforded **53** in 49% yield

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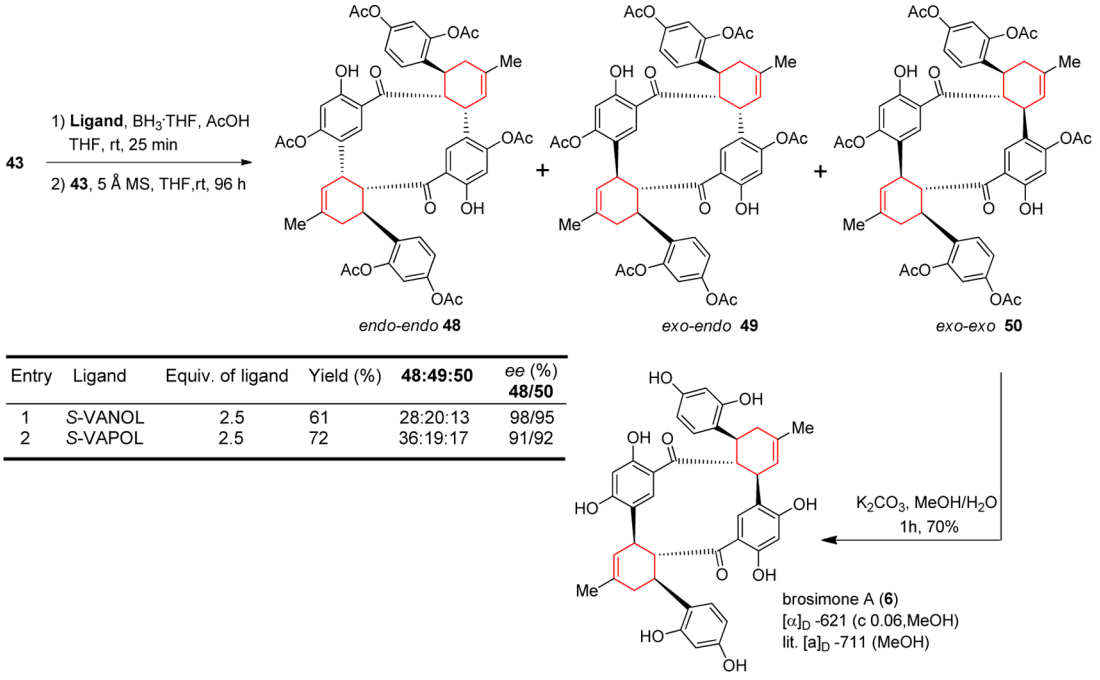
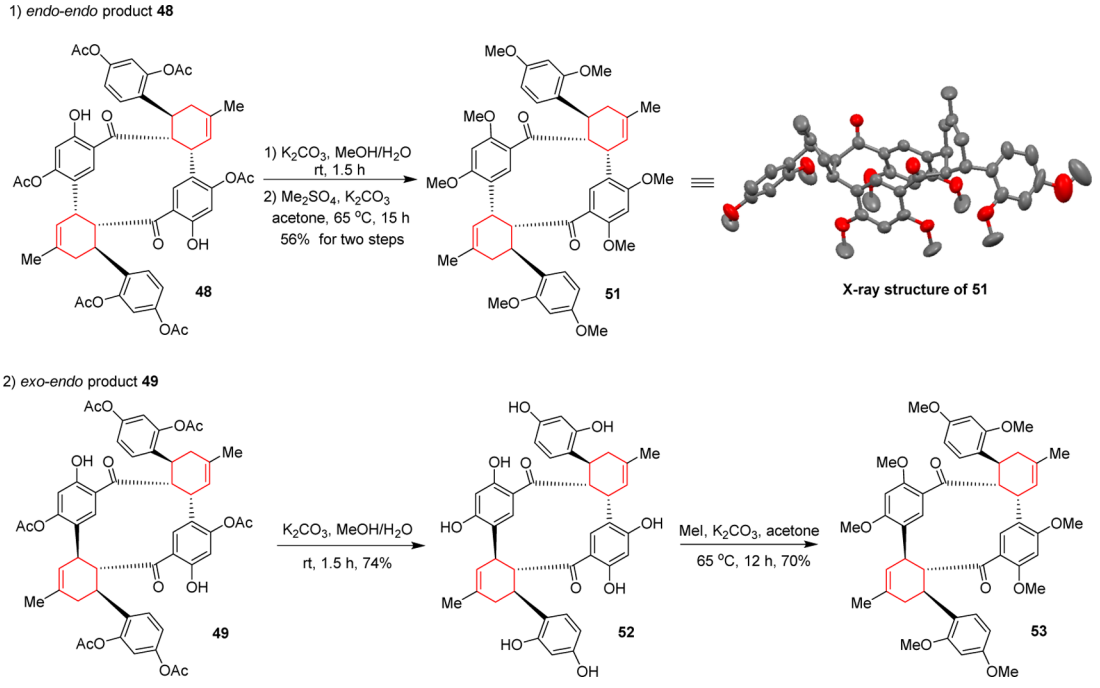
Scheme 10. Synthesis of (−)-Brosimone A



Entry	Ligand	Equiv. of ligand	Yield (%)	**48:49:50**	*ee* (%) **48/50**
1	*S*-VANOL	2.5	61	28:20:13	98/95
2	*S*-VAPOL	2.5	72	36:19:17	91/92

Scheme 11. Structural Confirmation of *endo*−*endo* 48 and *exo*−*endo* 49



over 2 steps. The NMR data for synthetic **53** fully matched with the compound obtained by permethylation of *exo*−*endo* hexamethyl ether. Unfortunately, the ee value of the *exo*−*endo* octamethyl ether **53** was only 31%.

CONCLUSIONS

An efficient method for the enantioselective Diels−Alder of 2′-hydroxychalcone and its derivatives has been developed, promoted by a chiral VANOL-boron Lewis acid complex. The cycloaddition proceeds smoothly at room temperature to provide the desired products in high yield and enantioselectivity. This methodology was applied to the enantioselective total syntheses of the prenylflavonoid Diels−Alder-type natural products (−)-nicolaioidesin C, (−)-panduratine A, (−)-kuwanon I, (+)-kuwanon J, (−)-brosimone A, and (−)-brosimone B. Key elements of the syntheses include the biosynthesis-inspired asymmetric Diels−Alder cycloaddition as well as a biomimetic dehydrogenation reaction sequence for generation of the required diene precursor, involving regioselective Schenck ene reaction reduction and dehydration. Furthermore, a remarkable tandem inter/intramolecular asymmetric Diels−Alder cycloaddition process was applied for the synthesis of brosimone A. Advances in the enantioselective synthesis of other related

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complex natural products with important biological activities and further mechanistic studies are in progress.

EXPERIMENTAL SECTION

General Procedure for the Asymmetric Diels−Alder Reaction.[19a,c] Chiral ligand (1.2 equiv) was dissolved in anhydrous THF, then the solution was treated sequentially with BH_3·THF (1.2 equiv) and glacial AcOH (1.2 equiv). The resulting mixture was stirred at rt for 30 min, concentrated to dryness, and further dried under high vacuum at rt for 30 min. The colorless residue was dissolved in THF, then added the preactivated 5 Å molecular sieve (20 weight equiv) and dienophile (1.0 equiv). The resulting dark-red solution was stirred at rt for 1 h before the diene (5.0−20 equiv) was added to the reaction mixture. The reaction was stirred at rt and monitored by TLC. Once completed, the mixture was quenched by addition of H_2O (15.0 equiv), filtered through the Celite, and further washed with EtOAc, and the organic filtrates were collected and concentrated in vacuo. The residue was purified by flash column chromatography to afford the desired Diels−Alder cycloadducts and recovered chiral ligand, unless otherwise stated. The racemate Diels−Alder cycloadduct was prepared using the general procedure, employing the racemate BINOL or VANOL as the ligand.

Chalcone (9). To a stirred solution of 2′-hydroxyacetophenone (1.2 mL, 10 mmol) in MeOH (50 mL) was added benzaldehyde (1.0 mL, 10 mmol), followed by slow addition of a KOH aqueous solution (20 mol/L, 23 mL). The resulting orange solution was stirred at 40 °C for 3 days. The reaction mixture was diluted with saturated aqueous NH_4Cl, adjusted to pH 4 by adding 1 M HCl, extracted with EtOAc (50 mL × 2), washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate:petroleum ether = 1:5) to afford the compound **9** (2.0 g, 90%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.83 (s, 1H), 7.95−7.91 (m, 2H), 7.69−7.65 (m, 3H), 7.53−7.49 (m, 1H), 7.49−7.43 (m, 3H),7.05−7.03 (m, 1H), 6.98−6.93 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 163.6, 145.5, 136.4, 134.6, 130.9, 129.6, 129.0, 128.6, 120.1, 120.0, 118.8, 118.6. The spectroscopic data for this compound were identical to those reported in the literature.[30]

Chalcone (23). Diels−Alder cycloadducts (**11**/**13**/**15**/**17**/**19**/**20**/**22**/**1**). These known compounds were prepared according to the reference.[13]

Compound (24/25/26/27/28/37/38/39/40/41/42/43). These known compounds were prepared according to the reference.[16] Diels−Alder cycloadducts (**44**/**45**/**46**/**47**/**48**/**49**/**50**/**51**/**52**/**53**). For detailed information on these known compounds see ref 16.

Diels−Alder Adduct (11). The general procedure was followed by employing *R*-VANOL (0.026 mmol, 1.2 equiv), dienophile chalcone **9** (5 mg, 0.022 mmol, 1 equiv), and diene **10** (45 μL, 20 equiv). The desired compound **11** (6.0 mg, 90%) was isolated as a light-yellow solid and as a single regioisomer. 95.0% ee (isopropanol:hexane = 2:98), retention time 6.0 and 6.8 min; $[\alpha]_D^{24}$ +20.6 (*c* 0.91, DCM).

Diels−Alder Adduct (13). The general procedure was followed by employing *R*-VANOL (25.8 mg, 0.0588 mmol, 1.2 equiv), dienophile chalcone **9** (11 mg, 0.049 mmol, 1 equiv), and diene **10** (131 μL, 20 equiv). The desired compound **13** (15 mg, 99%) was isolated as a light-yellow oil. 95.9% ee (isopropanol:hexane =2:98), retention time 4.9 and 5.3 min; $[\alpha]_D^{23}$ +39.6 (*c* 0.84, DCM).

Diels−Alder Adduct (15). The general procedure was followed by employing *R*-VANOL (0.073 mmol, 1.2 equiv), dienophile chalcone **9** (0.06 mmol, 1 equiv), and diene **14** (71 mg, 5 equiv). The desired compound **15** (25.0 mg, 94%) was isolated as a light-yellow solid. 96.5% ee (isopropanol:hexane = 2:98), retention time 7.3 and 8.6 min; $[\alpha]_D^{18}$ 16.1 (*c* 0.86, DCM).

Diels−Alder Adduct (17). The general procedure was followed by employing *R*-VANOL (0.25 mmol, 1.2 equiv), dienophile chalcone **9** (47 mg, 1 equiv), and diene **16** (0.4 mL, 20 equiv). The desired compound **17** (57.3 mg, 90%) was isolated as a light-yellow solid and as a single *endo*-isomer. 90.2% ee (isopropanol:hexane = 2:98), retention time 7.1 and 8.9 min; $[\alpha]_D^{18}$ 153 (*c* 0.23, DCM).

Diels−Alder Adduct (19) and (20). The general procedure was followed by employing *R*-VANOL (0.105 mmol, 1.2 equiv), dienophile chalcone **9** (0.087 mmol, 1 equiv), and diene **18** (63 mg, 5 equiv). The desired *endo* Diels−Alder adduct **19** and *exo* Diels−Alder adduct **20** (31.08 mg, 99%) were isolated as white solid. The ratio of *exo*- to *endo*-isomer is 1:5.4. *endo* Diels−Alder adduct **19**: 90.7% ee (isopropanol:hexane = 1:99), retention time 5.2 and 5.7 min; $[\alpha]_D^{22}$ +170.3 (*c* 0.96, DCM). *exo* Diels−Alder adduct **20**: 37.6% ee (isopropanol:hexane = 2:98), retention time 4.7 and 5.3 min; $[\alpha]_D^{23}$ −10.63 (*c* 0.36, DCM).

Diels−Alder Adduct (22). The general procedure was followed by employing *R*-VANOL (12 mg, 1.2 equiv), dienophile chalcone **9** (0.022 mmol, 1 equiv), and diene **21** (76 μL, 20 equiv). The desired compound **22** (8.0 mg, 99%) was isolated as a light-yellow oil and as a single regioisomer. 94.3% ee (isopropanol:hexane = 2:98), retention time 4.4 and 5.1 min; $[\alpha]_D^{22}$ + 16.38 (*c* 0.47, DCM).

(−)-Nicolaioidesin C (1). The general procedure was followed by employing *R*-VANOL (79 mg, 1.2 equiv), dienophile chalcone **23** (47 mg, 0.18 mmol, 1 equiv), 5 Å MS (20 weight equiv to dienophile), and myrcene (0.52 mL, 20 equiv). The reaction was stirred at rt for 16 h, quenched by addition of H_2O (15.0 equiv), filtered through the Celite, and further washed with EtOAc. The organic filtrates were collected and concentrated in vacuo. The residue was purified by flash chromatography to afford the desired Diels−Alder cycloadducts acetylated nicolaioidesin C (59.4 mg, 88%) and recovered chiral ligand (75 mg, 95%). To the resulting light-yellow residue were added 2 mL of MeOH and 2 mL of saturated $NaHCO_3$ solution. The resulting pale-yellow suspension was stirred at rt for 4 h, and the reaction mixture was adjusted to pH 4 by adding 1 M HCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (hexane: EtOAc = 4:1), and further separation was achieved by preparative TLC (hexane: EtOAc = 3:2) to afford the nicolaioidesin C (78%). 95.8% ee (isopropanol:hexane =10:90), retention time 8.8 and 10.4 min; $[\alpha]_D^{26}$ −31 (*c* 0.91, MeOH), while $[\alpha]_D^{25}$ = −25 (*c* 1.0, MeOH) for (−)-nicolaioidesin C reported in literature.[15]

(−)-Panduratin A (2). The general procedure was followed by employing *S*-VANOL (58 mg, 2.0 equiv), dienophile chalcone **23** (20 mg, 1 equiv), and ocimene (600 mg, 20 equiv). The reaction was stirred at rt for 68 h, quenched by addition of H_2O (15.0 equiv), filtered through the Celite, and further washed with EtOAc, and the organic filtrates were collected and concentrated in vacuo. The residue was purified by flash chromatography to afford the desired Diels−Alder adduct acetylated panduratin A (14.8 mg, 51%, 57% brsm) as a light-yellow oil. The resulting light-yellow residue was dissolved in MeOH (1 mL), and then 1 mL of saturated $NaHCO_3$ solution was added. The resulting pale-yellow suspension was stirred at rt for 8 h. The reaction mixture was adjusted to pH 4 by adding 1 M HCl, extracted with EtOAc (10 mL), and washed with brine (10 mL). The resulting aqueous layer was extracted with EtOAc (10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification on preparative TLC (15% EtOAc in hexane) afforded (−)-panduratin A (7.8 mg, 58%) as a light-yellow solid. The spectroscopic data for this compound were identical to those reported in the literature.[10d] 86% ee (isopropanol:hexane = 10:90), retention time 4.9 and 6.6 min; HRMS (ESI) *m*/*z* calculated for $C_{26}H_{30}O_4$ (M + H^+): 407.2222, found: 407.2218; $[\alpha]_D^{23}$ −43 (*c* 0.39, EtOH), while $[\alpha]_D^{23}$ = −25 (*c* 0.07, MeOH) for natural (−)-panduratin A.

Chalcone (29). To a stirred solution of chalcone **25** (217.0 mg, 0.46 mmol) in MeOH (4.5 mL) was slowly added concentrated HCl (330 μL) at rt. The resulting orange solution was stirred at rt for 20 h, and then to the resulting orange solution was slowly added 4 M NaOH (3 mL) at 0 °C. The reaction was stirred at rt for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl, adjusted to pH 4 by adding 1 M HCl, and extracted with EtOAc. The organic layer was successively washed with water, brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in DMF (20 mL), and K_2CO_3 (95 mg, 0.69 mmol) and MeI (37 μL, 0.60 mmol) were added to the resulting orange solution. The reaction mixture was kept at rt for 24 h, quenched by addition of H_2O (1 mL),

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and extracted with EtOAc. The organic layer was successively washed with water, brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude residue was purified by flash chromatography (hexane:EtOAc = 4:1) to afford **29** (54.0 mg, 30%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 16.0 Hz, 1H), 7.59 (d, J = 2.8 Hz, 1H), 7.56 (d, J = 2.8 Hz, 1H), 7.48 (d, J = 16.0 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.52 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 5.23−5.15 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.75(s, 3H), 3.40 (d, J = 6.7 Hz, 2H), 1.79 (s, 3H),1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 162.8, 161.1, 160.1, 158.7, 138.6, 131.5, 130.1, 129.9, 126.6, 124.4, 123.7, 122.8, 117.3, 106.1, 105.3, 98.3, 63.0, 55.8, 55.5, 25.8, 22.8, 17.8; IR (neat) ν_{max} 2936, 2838, 1652, 1593, 1463, 1333, 1271, 1212, 1092, 1031 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{24}H_{29}O_5$: 397.2010, found: 397.2013.

Compound (31). Dried air was bubbled through a CH_2Cl_2 (40 mL) solution of chalcone **29** (1.9 g, 4.8 mmol) and tetraphenylporphine (10 mg, 0.024 mmol) as the photosensitizer. The reaction mixture was stirred at rt and irradiated with a halogen lamp (150 W) for 1.5 h. Then triphenylphosphine (1.4 g, 5.3 mmol) was added, and the solution was stirred 16 h at rt before concentrated. The residue was purified by column chromatography (hexane:EtOAc = 3:1) to afford **31** (623 mg, 32%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 16.0 Hz, 1H), 7.56 (t, J = 8.4 Hz, 2H), 7.44 (d, J = 16.0 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.8 Hz, 1H), 6.51 (dd, J = 8.4, 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.69 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ192.5, 162.9, 160.9, 160.1, 158.7, 142.9, 138.9, 130.9, 130.0, 127.2, 124.6, 119.3, 117.2, 116.1, 106.6, 105.4, 98.4, 71.5, 62.1, 55.8, 55.5, 55.5, 29.9, 29.7; IR (neat) ν_{max} 3451, 2970, 1584, 1504, 1458, 1266, 1212, 1097 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{24}H_{29}O_6$: 413.1959, found: 413.1963.

Compound (30). The secondary allylic alcohol **30** was also isolated in 16% yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 16.0 Hz, 1H), 7.57 (t, J = 8.8 Hz, 2H), 7.42 (d, J = 16.0 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 6.51 (dd, J = 8.6, 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 5.0 (s, 1H), 4.84(s, 1H), 4.29 (d, J = 8.4 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H), 3.06 (dd, J = 13.5, 3.6 Hz, 1H), 2.89 (dd, J = 13.5, 9.0 Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 162.9, 161.0, 160.2, 158.9, 147.6, 139.4, 130.3, 130.2, 126.5, 124.2, 120.6, 117.1, 110.0, 106.3, 105.4, 98.4, 75.8, 62.8, 55.9, 55.5, 55.4, 30.4, 18.1; IR (neat) ν_{max} 3455, 2941, 2838, 1650, 1593, 1462, 1334, 1271, 1211, 1100 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{24}H_{29}O_6$: 413.1959, found: 413.1953.

Diene (32). A mixture of chalcone **31** (160 mg, 0.39 mmol), acetyl chloride (36 μL, 0.5 mmol), and pyridine (41 μL, 0.5 mmol) in benzene (3 mL) was heated to 60 °C for 8 h, and then 15 mL of 5% aqueous $NaHCO_3$ was poured into the reaction mixture. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by column chromatography (hexane:EtOAc = 9:1) to afford diene **32** (107 mg, 70% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 16.0 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 16.0 Hz, 1H), 7.35 (d, J = 16.4 Hz, 1H), 6.78 (d, J = 14.4 Hz, 1H), 6.75 (d, J = 6.8 Hz, 1H), 6.51 (dd, J = 8.8, 2.4 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 5.11 (d, J = 11.2 Hz, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.71 (s, 3H) 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 162.9, 160.9, 160.1, 158.7, 143.2, 138.9, 136.8, 130.1, 129.9, 127.2, 124.5, 119.8, 119.2, 117.3, 117.2, 106.6, 105.3, 98.3, 62.3, 55.9, 55.5, 55.4, 18.3; IR (neat) ν_{max} 2939, 1651, 1588, 1464, 1334, 1270, 1212, 1099 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{24}H_{27}O_5$: 395.1853, found: 395.1857.

Diels−Alder Adduct (34). Racemic VANOL (117.3 mg, 0.27 mmol) was dissolved in THF (10 mL) and treated sequentially with BH_3·THF (270 μL, 0.27 mmol) and glacial AcOH (15.5 μL, 0.27 mmol). The resultant mixture was stirred at rt for 25 min, and then was concentrated to dryness and further dried under high vacuum at rt for 15 min. The colorless residue was dissolved in THF (12 mL), and the chalcone **28** (104 mg, 0.22 mmol) and 5 Å MS were added. The resulting dark-red solution was stirred at rt for 1.5 h, followed by addition of diene **32** (220 mg, 0.56 mmol). The reaction mixture was stirred at rt for 72 h before filtered through Celite. The organic layers were collected and concentrated. The residue was purified by column chromatography (hexane:EtOAc = 4:1) to afford a mixture of **34** and other Diels−Alder adduct **33**. The mixture was separated by preparative TLC (hexane:EtOAc = 3:2, silica gel) to afford Diels−Alder adduct **34** (78 mg, 41% yield) as a yellow amorphous solid and another Diels−Alder adduct **33** (65 mg, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 1H), 7.88 (d, J = 16.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.07 (d, J = 12.8 Hz, 1 H), 6.82−6.90 (m, 3H), 6.53 (dd, J = 1.2, 8.4 Hz, 1H), 6.46 (s, 1H), 6.32−6.42(m, 3 H), 5.49 (s, 1H), 5.00 (t, J = 6.4, 13.2 Hz, 1H), 4.65 (s, 1H), 4.35 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.51 (s, 3H), 3.17 (d, J = 6.4 Hz, 5H), 2.35−2.45(m, 1H), 2.29 (s, 3H), 2.20 (s, 3H), 2.14−2.16 (m, 1H), 2.08 (s, 3H), 1.81 (s, 3H), 1.67 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 192.1, 169.4, 168.8, 168.6, 162.9, 161.9, 160.4, 158.9, 153.8, 148.7, 135.4, 133.0, 132.0, 131.9, 131.4, 130.3, 127.9, 127.2, 126.1, 125.0, 122.4, 122.1, 119.3, 119.1, 118.1, 117.3, 117.0, 116.0, 112.6, 105.4, 105.2, 104.1, 98.2, 97.9, 62.6, 55,4, 55.4, 55.3, 54.7, 53.4, 35.0, 29.6, 25.6, 23.4, 22.5, 21.0, 20.9, 20.5, 17.7; IR (neat) ν_{max} 2967, 2923, 2850, 1766, 1632, 1590, 1414, 1263, 2298 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{50}H_{53}O_{13}$: 861.3481, found: 861.3473.

Diels−Alder Adduct (33). Using the same purification procedure, another Diels−Alder adduct **33** (65 mg, 34% yield) was also obtained as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.79 (s, 1H), 12.72 (s, 1H), 7.98 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.42 (d, 9.2 Hz, 1H), 7.36 (d, 15.6 Hz, 1H), 6.85 (d, J = 5.6 Hz, 2H), 6.75−6.37 (m, 3H), 6.37−6.18 (m, 1H), 6.11 (d, J = 8.8 Hz, 1H), 5.33 (d, J = 14.4 Hz, 1H), 4.96 (d, J = 6.4 Hz, 1H), 4.75−4.22 (m, 3H), 3.94 (s, 1H), 3.89−3.73 (m, 7H), 3.70 (s, 1H), 3.59−3.38 (m, 3H), 3.21−2.86 (m, 3H), 2.50−2.33 (m, 3H), 2.24 (m, 4H), 2.21−2.09 (m, 5H), 1.76 (s, 3H), 1.66 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 193.1, 169.1, 168.8, 168.3, 163.1, 161.6, 160.2, 160.0, 159.5, 153.9, 148.9, 148.6, 139.4, 131.9, 131.3, 130.6, 130.4, 130.1, 128.1, 127.6, 126.7, 124.6, 123.9, 121.7, 121.2, 121.1, 119.2, 118.4, 112.1, 105.5, 105.3, 98.5, 98.3, 63.5, 62.7, 56.1, 55.5, 39.1, 38.5, 31.2, 29.7, 25.6, 25.4, 23.0, 22.5, 22.3, 21.1, 20.8, 17.7; IR (neat) ν_{max} 2936, 1773, 1654, 1593, 1505, 1438, 1371, 1215, 1093 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{50}H_{53}O_{13}$: 861.3481, found: 861.3473.

Diels−Alder Adduct (35). Compound **33** (15 mg, 0.017 mmol) and K_2CO_3 (7.9 mg, 0.058 mmol) were dissolved in a MeOH/water (10:1, 1 mL) solution. The reaction mixture was stirred at rt for 1 h, quenched by addition of formic acid (42 μL) at 0 °C, and then stirred at rt for an additional 10 min. The reaction mixture was diluted with water and extracted with EtOAc (10 mL × 3), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 2:1) to afford the *exo* Diels−Alder adduct **35** (13 mg, 72%), as a yellow amorphous powder. ^{1}H NMR (400 MHz, acetone) δ 13.15 (s, 1H), 13.05 (s, 1H), 7.99 (d, J = 16.0 Hz, 2H), 7.86 (d, J = 16.0 Hz, 2H), 7.76 (m, 3H), 7.64−7.53 (m, 4H), 7.32 (m, 5H), 7.07 (d, J = 8.0 Hz, 3H), 6.79 (dd, J = 19.6, 11.2 Hz, 2H), 6.73−6.65 (m, 3H), 6.63−6.56 (m, 2H), 6.51 (dd, J = 14.4, 8.8 Hz, 3H), 6.43−6.32 (m, 5H), 6.31- 6.18 (m, 4H), 5.33 (m, 4H), 4.99 (m, 6H), 4.52−4.40 (m, 4H), 4.11−4.02 (m, 6H), 4.01 (d, J = 7.2 Hz, 3H), 3.91 (d, J = 8.2 Hz, 6H), 3.86 (d, J = 5.6 Hz, 10H), 3.78 (d, J = 7.2 Hz, 7H), 3.68 (m, 6H), 3.53 (m, 3H), 3.07 (m, 5H), 2.91−2.77 (m, 2H), 2.24−2.09 (m, 4H), 1.99−1.95 (m, 3H), 1.77 (d, J = 10.8 Hz, 5H), 1.75 (s, 3H), 1.68−1.60 (m, 5H), 1.56 (m, 3H), 1.52 (d, J = 9.6 Hz, 4H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, acetone) δ 209.1, 208.6, 190.7, 190.5, 163.2, 163.1, 162.7, 162.6, 162.0, 161.3, 161.1, 160.5, 160.4, 160.2, 160.2, 158.5, 156.4, 155.7, 137.8, 137.0, 132.2, 131.9, 130.7, 130.3, 130.0, 129.7, 129.7, 127.2, 126.6, 125.0, 124.5, 124.4, 123.9, 123.8, 122.4, 122.3, 116.7, 114.8, 114.7, 114.2, 114.0, 107.2, 106.6, 106.3, 106.1, 106.0, 105.9, 103.0, 98.3, 98.1, 62.7, 62.7, 55.5, 55.3, 55.2, 55.1, 54.9, 39.2, 38.7, 26.9, 24.9, 24.8, 22.6, 22.5, 22.4, 21.2, 16.9; IR (neat) ν_{max} 3372, 2923, 2860, 1602, 1461, 1283, 11649, 993 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{44}H_{47}O_{10}$: 735.3164, found: 735.3170.

Diels−Alder Adduct (36). Compound **34** (48.0 mg, 0.06 mmol) and K_2CO_3 (25.8 mg, 0.19 mmol) were dissolved in a MeOH/water

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(10:1, 3 mL) solution. The reaction mixture was stirred at rt for 1 h, quenched by addition of formic acid (42 μL) at 0 °C, and then stirred at rt for an additional 10 min. The reaction mixture was diluted with water and extracted with EtOAc (10 mL × 3), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 2:1) to afford the *endo* Diels–Alder adduct **36** (29 mg, 72%), as a yellow amorphous powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (s, 1H), 8.02 (d, J = 16.0 Hz, 1H), 7.68 (d, J = 9.2 Hz, 1H), 7.48 (m, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.56 (dd, J = 8.8, 2.4 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.36 (dd, J = 8.4, 4.4 Hz, 3H), 6.29 (s, 1H), 5.41 (s, 1H), 5.05 (s, 1H), 4.68 (s, 1H), 4.29 (s, 1H), 4.15 (dd, J = 11.2, 8.0 Hz, 1H), 3.85 (s, 12H), 3.80 (d, J = 7.2 Hz, 1H), 3.49 (s, 3H), 3.21 (s, 3H), 2.54–2.13 (m, 2H), 1.80 (s, 3H), 1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 198.1, 163.6, 163.0, 162.5, 160.3, 155.2, 154.8, 135.5, 133.6, 130.8, 130.6, 130.2, 127.7, 124.9, 124.1, 121.8, 121.0, 117.2, 116.6, 113.9, 113.5, 108.4, 107.5, 105.6, 105.4, 104.9, 98.3, 63.0, 60.4, 55.5, 55.1, 52.3, 37.1, 35.5, 29.9, 29.7, 25.7, 23.6, 21.5, 21.0, 17.8; IR (neat) max 3359, 2962, 2923, 2850, 1589, 1504, 1461, 1267, 1161, 1093 cm^{-1}; HRMS (ESI) $[M + H]^+$ calculated for $C_{44}H_{47}O_{10}$: 735.3164, found: 735.3156.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02248.

Copies of NMR spectra and chiral HPLC chromatography for selected compounds (PDF)

X-ray crystallographic data for compound **51** (CIF file)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xglei@pku.edu.cn.

Notes

The authors declare no competing financial interest.

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