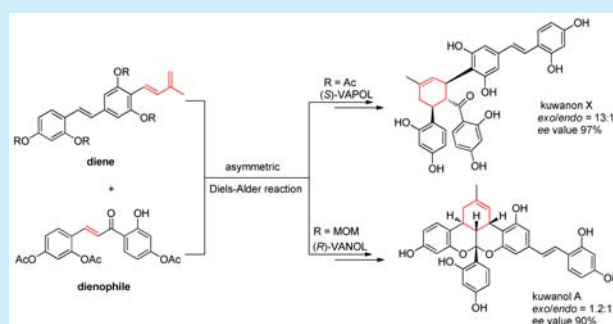


Enantioselective Total Syntheses of Kuwanon X, Kuwanon Y, and Kuwanol A

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Supporting Information

ABSTRACT: The first enantioselective total syntheses of (–)-kuwanon X, (+)-kuwanon Y, and (+)-kuwanol A have been accomplished by using asymmetric Diels–Alder cycloaddition promoted by chiral VANOL or VAPOL/boron Lewis acid. The biosynthesis-inspired asymmetric Diels–Alder cycloaddition shows high *exo* selectivity (*exo/endo* = 13/1), which was unprecedented in the previous total syntheses of related prenylflavonoid Diels–Alder natural products. An acid catalyzed intramolecular ketalization process enabled a biomimetic transformation to construct the polycyclic skeleton of kuwanol A efficiently.



About 50 kinds of optically active Diels–Alder type natural products have been isolated from the moraceous plant whose root bark has been used as a traditional Chinese medicine for antiphlogistic, expectorant, antipyretic, and diuretic purposes.¹ Some of them, as bioactive plant constituents, showed promising biological activities such as antibacterial, hypotensive, antiphlogistic activities, etc.² Structurally, these molecules share the same chalcone dienophile moiety but differ in the dehydroprenyl diene moiety. Based on the structure of diene, the Diels–Alder type adducts from the moraceous plant can be divided into five structural categories.^{1b,3,4} Due to their promising biological activities and striking chemical structures, the Diels–Alder type natural products represent very attractive synthetic targets, and efforts have been made toward the total syntheses of three categories of the adducts.⁴

Representative Diels–Alder type adducts of a chalcone and a dehydroprenylstilbene, one group of adducts from the moraceous plant, are shown in Figure 1: kuwanon X (1),⁵ kuwanon Y (2),⁶ kuwanol E (3),⁷ and the related ketalized adducts kuwanol A (4)⁸ and sorocein I (5).⁹ To date no total syntheses of this type of natural products have been reported, although some of them have shown promising biological activities.¹⁰ For example, the kuwanol E is one of the most potent natural compound inhibitors of *Mycobacterium tuberculosis* protein tyrosine phosphatase B ($K_i = 1.6 \pm 0.1 \mu\text{M}$) discovered by far.^{10c}

Although many methods¹¹ have been developed to synthesize Diels–Alder type adducts or their derivatives, the enantioselective total syntheses of these natural products are very limited. Recently, an asymmetric Diels–Alder cycloaddition, catalyzed by chiral VANOL or VAPOL-boron Lewis acid, has been reported

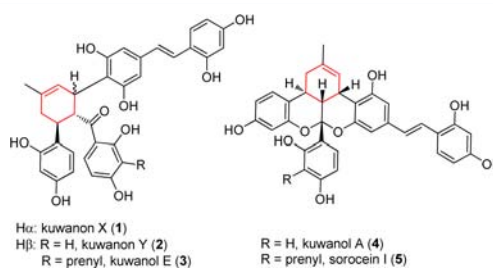


Figure 1. Representative Diels–Alder type adducts of a chalcone and a dehydroprenylstilbene.

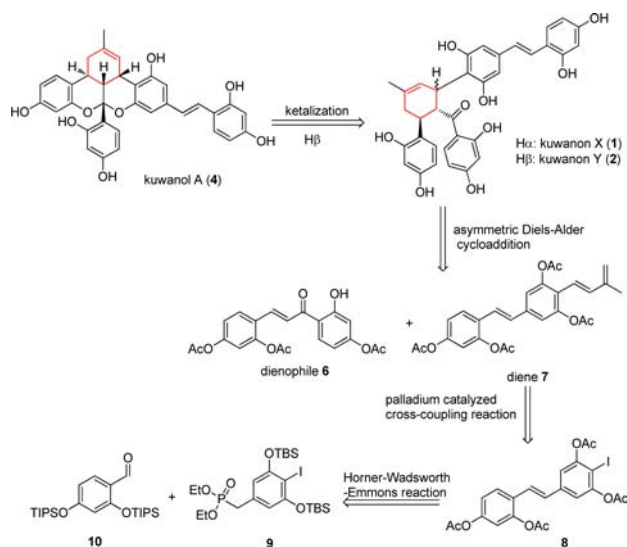
to construct the desired cyclohexene skeleton by our group.^{12a,b} In our continuous efforts to synthesize the different Diels–Alder type adducts from different categories, herein we would like to report the first enantioselective total syntheses of kuwanons X and Y, and kuwanol A.

As depicted in Scheme 1, the kuwanol A (4) could be derived from the *endo*-kuwanon Y (2) through a biomimetic acid catalyzed ketalization.⁶ The kuwanons X (1) and Y (2) could be generated through asymmetric Diels–Alder cycloadditions from the known dienophile 6¹³ and diene 7. For the synthesis of diene 7, the dehydroprenyl group could be introduced by palladium catalyzed cross-coupling reaction from iodide 8 in which C–C double bond could be constructed by Horner–Wadsworth–Emmons reaction from phosphonate 9 and aldehyde 10.

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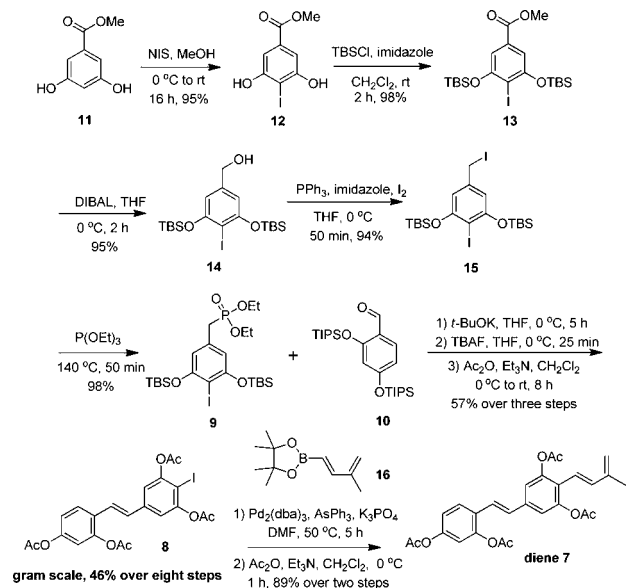
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Scheme 1. Retrosynthetic Analysis of Kuwanon X, Kuwanon Y, and Kuwanol A



As shown in Scheme 2, the synthesis of diene 7 commenced with iodination of methyl 3,5-dihydroxybenzoate **11** to give

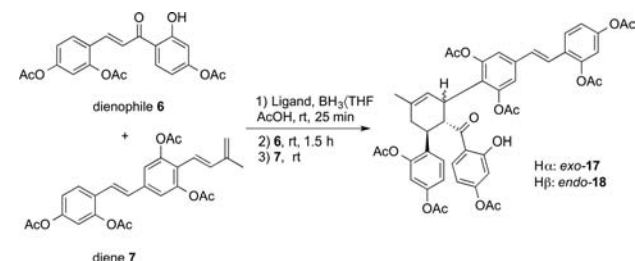
Scheme 2. Synthesis of the Diene 7



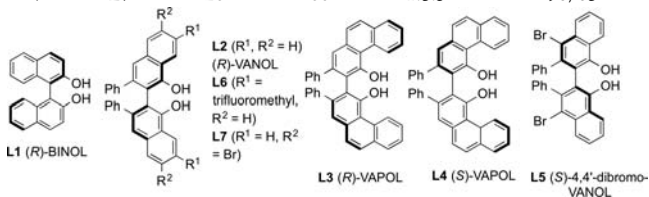
iodide **12** in 95% yield. Compound **12** was protected with TBS group to give **13**, then reduced by DIBAL to afford alcohol **14**, iodinated to give iodide **15** and followed by reacting with triethyl phosphite to afford **9** in high yield over four steps. Iodide **8** was obtained in 57% yield over three steps by Horner–Wadsworth–Emmons reaction followed by deprotection of the silyl protecting groups and reprotection with acetyl groups. With iodide **8** in hand, first we tried to prepare diene **7** by Heck reaction with 2-methylbut-3-en-2-ol and dehydration^{11f} (not shown). Unfortunately, only a mixture was obtained. Alternatively, Suzuki reaction was used to synthesize diene **7**.^{11c,14} Diene **7** could not be obtained in satisfying yield by Suzuki reaction in one step, though acetyl reprotection of the crude mixture gave diene **7** in 89% yield.

With diene **7** and dienophile **6** in hand, attention was turned to the asymmetric Diels–Alder cycloaddition. As shown in Table 1,

Table 1. Screening of Chiral Ligands for the Asymmetric Diels–Alder Cycloaddition



entry	ligands	time (h)	yield (%)	endo/exo ^a	ee (%) ^b endo/exo
1	L1	23	95	1:4.2	70/13
2	L2	24	70	1:5.3	94/81
3	L3	21	69	1:11.4	50/96
4	L4	21	79	1:13.0	53/97
5	L5	22	60	1:3.1	0/1
6	L6	20	42	1:7.0	81/63
7	L7	28	80	1:3.5	96/63



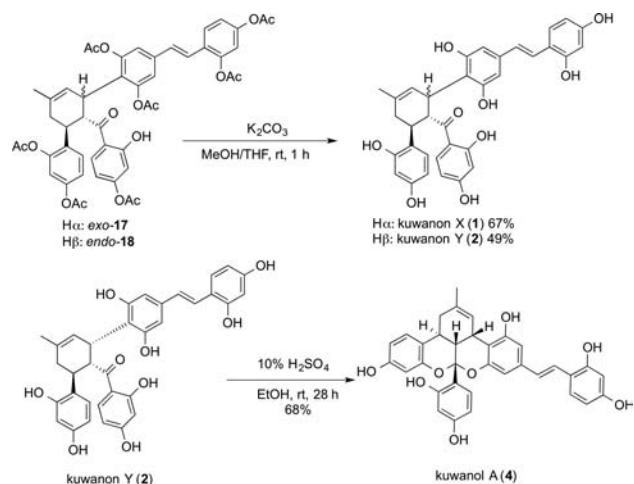
^aBased on ¹H NMR analysis. ^bDetermined by chiral HPLC analysis.

(*R*)-BINOL (**L1**), (*R*)-VANOL (**L2**), and (*R*) and (*S*)-VAPOL (**L3** and **L4**) were initially used to catalyze the reaction. All of these chiral boron complexes showed unexpected *exo* selectivity¹⁵ (entries 1–4). Among them, **L4** effectively catalyzed the Diels–Alder cycloaddition with very high *exo* selectivity (*exo/endo* = 13/1) and *ee* value (97%), which could be used directly for the enantioselective total synthesis of **1** (entry 4). For the enantioselective synthesis of **2**, using **L2** as chiral ligand gave a satisfying *ee* value but not a good *endo*-selectivity (entry 2). Then several VANOL derivatives were used to improve the *endo*-selectivity (entries 5–7). The (*S*)-4,4'-dibromo-VANOL (**L5**) had the biggest negative impact on the enantioselectivity, which was consistent with the previous results.^{12a,16} (entry 5). Compared with **L2**, the (*R*)-7,7'-difluoromethyl-VANOL (**L6**) gave worse *endo*-selectivity and enantioselectivity (entry 6), while (*R*)-6,6'-dibromo-VANOL (**L7**) exhibited satisfying enantioselectivity and improved *endo*-selectivity (entry 7). A proposed transition state to explain the Diels–Alder selectivity has been reported by our previous study^{12b} and is also included in the Supporting Information.

The corresponding *exo*-**17** and *endo*-**18** were treated with K₂CO₃ in the mixture of THF and MeOH to give **1** and **2** in yields of 67% and 49%, respectively, as shown in Scheme 3. The spectroscopic data for synthetic **1** and **2** were in agreement with those reported for the natural products. With **1** and **2** in hand, sulfuric acid was employed to catalyze the biomimetic intramolecular ketalization of *exo*-**1** and *endo*-**2**, but only *endo*-**2** formed a ketalized product (see Supporting Information for detailed mechanism), which was confirmed as kuwanol A (**4**).

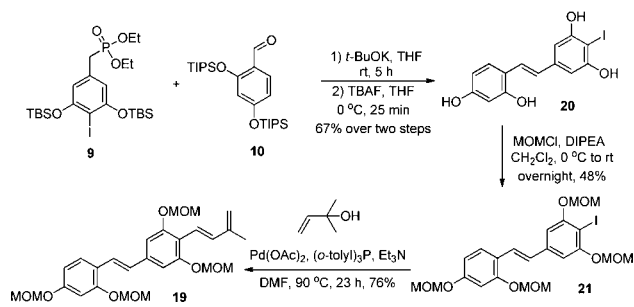
Although the enantioselective total synthesis of the ketalized compound **4** was accessible by using *R*-VANOL as a chiral ligand,

Scheme 3. Syntheses of Kuwanon X, Kuwanon Y, and Kuwanol A



the total yield from dienophile **6** was very low (3.7% over three steps) due to the low *endo*-selectivity and moderate yield in the subsequent two steps. As previously reported,^{11c,f,g} when the two phenolic hydroxyl groups in the *ortho* position of the dehydroprenyl group were protected by MOM or Me group instead of acetyl group, no obvious *exo/endo* stereoselectivity was observed in the Diels–Alder cycloaddition. This inspired us to further investigate whether the two acetyl groups near the dehydroprenyl group played a key role in the *exo*-selectivity. MOM-protected diene **19** was synthesized from phosphonate **9** and aldehyde **10** as shown in Scheme 4. Iodide **21** was obtained

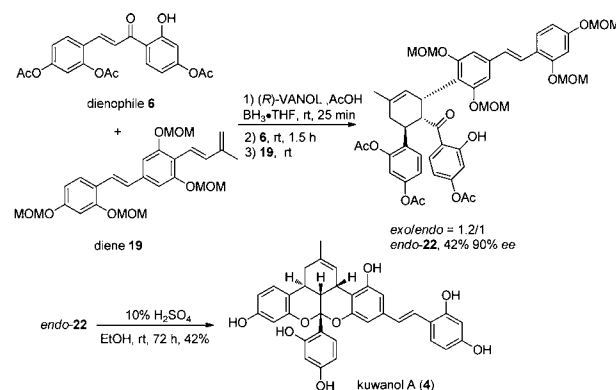
Scheme 4. Syntheses of the MOM Protected Diene



from precursors **9** and **10** after three steps. With iodide **21** in hand, commercially available 2-methyl-but-3-en-2-ol was again tested to synthesize diene **19** by Heck reaction and dehydration.¹⁷ After screening several conditions, diene **19** could be obtained in 76% yield directly from 2-methylbut-3-en-2-ol.

With MOM protected diene **19** in hand, the asymmetric Diels–Alder cycloaddition promoted by (*R*)-VANOL (**L2**)/boron Lewis acid was achieved as shown in Scheme 5. Compared with the acetyl protected diene **7** (Table 1, entry 2), when diene **19** was used, the *endo/exo* stereoselectivity was changed from 1/5.3 to 1/1.2 without losing the enantioselectivity (from 94% to 90%). This indicates that different substitution in diene may contribute to different stereoselectivity in the asymmetric Diels–Alder cycloaddition.^{15k,18} With the raised HOMO in diene **19**, the cycloaddition transition state occurs earlier in the reaction pathway; hence, there is less steric demand one would need to overcome for the *endo* transition state in comparison to the *exo*

Scheme 5. Synthesis of Kuwanol A from MOM Protected Diene 19



transition state, and so the subtle improvement to 1.2/1 was possible.¹⁹

In the next step, several acidic conditions such as 0.8 M HCl in THF/*i*-PrOH and 0.8 M sulfuric acid in EtOH were evaluated for one-pot deprotection and ketalization of *endo*-**22** but all failed. Ultimately we found deprotection/ketalization of **22** could be achieved in one step to afford **4** by using 10% sulfuric acid/EtOH. By changing the protecting group in the diene moiety, the total yield of kuwanol A (**4**) increased from 3.6% to 17.6% from the same dienophile **6** with one step shorter and no significant change in enantioselectivity.

In summary, the first enantioselective total syntheses of kuwanons X and Y and kuwanol A have been accomplished by employing a chiral ligand/boron Lewis acid promoted asymmetric Diels–Alder cycloaddition in 12 and 11 steps, respectively. The asymmetric Diels–Alder reaction featured high *exo*-selectivity. The synthesis also featured a biomimetic acid-catalyzed intramolecular ketalization process to furnish the striking polycyclic framework of kuwanol A in one step. Demonstrated by total syntheses of kuwanons X and Y and kuwanol A, the chiral ligand/boron Lewis acid catalyzed asymmetric Diels–Alder cycloaddition will have a broad application in the total syntheses of other related complex natural products isolated from moraceous plants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03285.

Experimental procedures, product characterizations, and ¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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