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Michael Addition

Synthesis of (+)-Antroquinonol and Analogues by Using Enantioselective Michael Reactions of Benzoquinone Monoketals

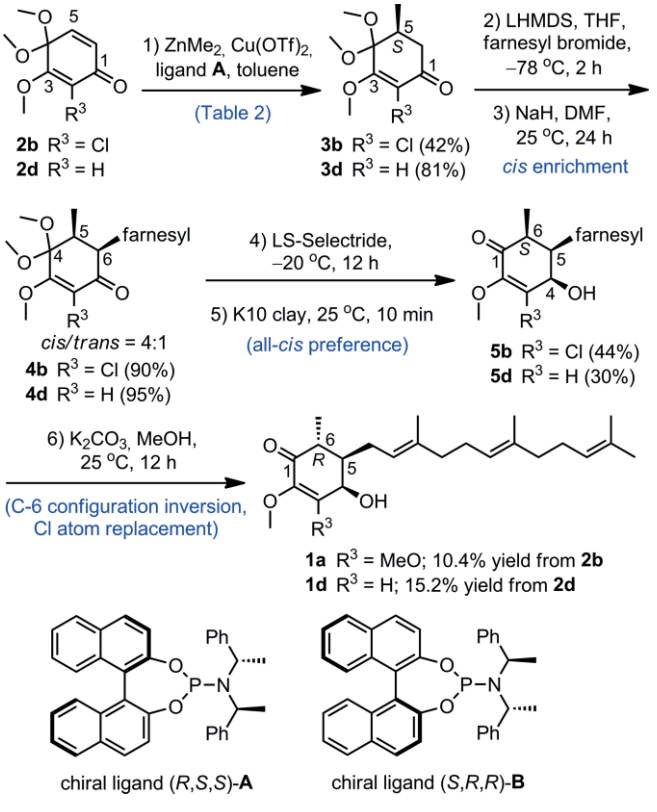
Che-Sheng Hsu[a] and Jim-Min Fang*[a]

Abstract: (+)-Antroquinonol is an anticancer agent that was first isolated from the rare mushroom *Antrodia cinnamomea*, which is indigenous to Taiwan. In this study, (+)-antroquinonol is synthesized from benzoquinone monoketals by using an enantioselective Michael reaction as the strategic step followed by an alkylation, reduction, hydrolysis of a ketal, and inversion of configuration sequence of reactions. Because the enantioselective Michael reaction to the electron-rich 2,3,4,4-tetramethoxycyclohexa-2,5-dien-1-one was problematic, the reaction was facilitated by introducing an electron-withdrawing chloro group to replace the methoxy substituent at the C-2 position. Upon treatment with K_2CO_3 in MeOH in the final step, the chloro substituent was then replaced by the methoxy group concurrently with the inversion of configuration at C-6 to afford (+)-antroquinonol in a one-pot operation. This modular type of synthetic method can also be applied to efficient total syntheses of other antroquinonol analogues that contain the 4-hydroxycyclohex-2-enone core by starting from their corresponding benzoquinone monoketals.

Introduction

The rare mushroom *Antrodia cinnamomea* is indigenous to Taiwan and has been found to contain anticancer constituent (4*R*,5*R*,6*R*)-(+)-antroquinonol (**1a**, Scheme 1),[1] which is currently under clinical evaluation in patients with non-small cell lung cancer[2] and pancreatic cancer.[3] The potency of antroquinonol, however, has been recently questioned.[4] This compound incorporates an electron-rich 2,3-dimethoxycyclohex-2-enone core structure with hydroxyl, farnesyl, and methyl substituents at the C-4, C-5, and C-6 positions. Several related compounds are also found in *A. cinnamomea* including antroquinonol D (**1d**),[5] which has a similar structure to that of antroquinonol but without the methoxy substituent at the C-3 position. Chemists have exercised great efforts to explore viable methods to synthesize antroquinonols with their reduced benzoquinone skeleton.[4,6–8] A key issue of the synthesis involves the formation of the densely substituted six-membered ring with its three contiguous stereocenters. Inhibiting the sensitive 4-hydroxycyclohex-2-enone core structure from facile aromatization through an oxidation or dehydration reaction is another concern.

Chen and co-workers accomplished the first total synthesis of (+)-antroquinonol, which featured an iridium-catalyzed olefin isomerization–Claisen rearrangement reaction of a chiral bis(allyl) ether.[7a] They also developed a second synthesis of (+)-antroquinonol by using D-mannose as a starting material from the chiral pool.[7b] These syntheses, however, require long linear synthetic sequences (over 17 steps). In contrast, our first-gener-



Scheme 1. Synthesis of (+)-antroquinonol (**1a**) and (+)-antroquinonol D (**1d**) through enantioselective Michael reactions (OTf = trifluormethanesulfonate, LHMDS = lithium hexamethyldisilazide, THF = tetrahydrofuran, DMF = *N*,*N*-dimethylformamide, LS-Selectride = lithium trisiamylborohydride).

[a] *Department of Chemistry, National Taiwan University, Taipei 106, Taiwan*
E-mail: jmfang@ntu.edu.tw

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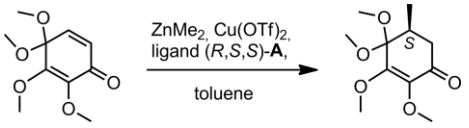
Table 1. Enantioselective Michael reaction of benzoquinone monoketal **2a** (0.48 mmol) under various reaction conditions.[a]



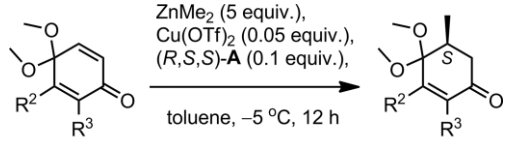
2a **3a**

Entry	$ZnMe_2$ [mmol][b]	$Cu(OTf)_2$ [mmol]	Ligand [mmol]	Solvent [mL]	Temp. [°C]	Time [h]	Conv. [%][c]	Yield [%][d]	% *ee* (*S*)-**3a**[e]
1	0.72	0.024	0.048	THF (1.6)	–50	20	20	–	–
2	0.72	0.024	0.048	PhMe (2.5)	–30	19	9	1.5	99
3	0.72	0.024	0.048	PhMe (2.5)	–10	15	10	1.5	99
4	0.72	0.024	0.048	PhMe (2.5)	–5	15	20	2	99
5	0.72	0.024	0.048	PhMe (2.5)	0	16	20	2	99
6	1.44	0.024	0.048	PhMe (2.5)	–5	18	36	3	99
7	2.40	0.024	0.048	PhMe (2.5)	–5	18	54	3	99
8	2.40	0.024	0.048	PhMe (1.0)	–5	18	100	6	99
9	2.40	0.024	0.048	PhMe (0.5)	–5	18	100	5	99
10	3.36	0.024	0.048	PhMe (2.5)	–5	18	53	4	99
11	2.40	0.048	0.096	PhMe (1.0)	–5	18	100	5	99

[a] Substrate **2a** (0.48 mmol, 1 equiv.) was employed. [b] The nucleophile $ZnMe_2$ was employed as a 1.2 M solution in toluene. [c] The conversion of **2a** was estimated by ^1H NMR spectroscopic analysis of the crude product mixture that contained **3a** (minor) and 2,3,4-trimethoxy-5-methylphenol (major). [d] Isolated yield of **3a** is reported. [e] The enantiomeric excess value of (*S*)-**3a** was determined by HPLC analysis on a Daicel Chiralpak IC column.

ation synthesis of (±)-antroquinonol and (±)-antroquinonol D only requires six steps and uses Michael reactions of the appropriate benzoquinone monoketals with a dimethylcuprate reagent as the strategic key step.[8] In our preliminary study,[8] we indicated that the asymmetric Michael addition[9–12] of 3,4,4-trimethoxycyclohexadienone with a methylmetal reagent could be carried out and that the 1,4-adduct could be elaborated through a similar procedure to give optically active antroquinonol D. Recently, Dhar, Baran, and co-workers examined many routes to synthesize (+)-antroquinonol but found the asymmetric Michael reaction of the appropriate benzoquinone monoketal as the only viable method.[4] Their report has prompted us to disclose our independent research[13] on the enantioselective Michael reactions of benzoquinone monoketals **2a**–**2j** (Tables 1 and 2), which is a continuation of our previous studies[8] and can be applied to the syntheses of (+)-antroquinonol and (+)-antroquinonol D (Scheme 1). Benzoquinone monoketals **2a**–**2j** were readily prepared from the corresponding phenols by oxidation with [bis(trifluoroacetoxy)iodo]benzene (PIFA) in anhydrous methanol.[14]

Table 2. Enantioselective Michael reactions of benzoquinone monoketals **2a**–**2j**.[a]



2a–**2j** **3a**–**3j**

Entry	Compd.	R^2	R^3	Product	Yield [%][b]	% *ee* (*S*)-**3**
1	**2a**	MeO	MeO	**3a**	6[c]	99[d]
2	**2b**	MeO	Cl	**3b**	42[e]	99[d]
3	**2c**	Cl	Cl	**3c**	71	93[f]
4	**2d**	MeO	H	**3d**	81	98[d]
5	**2e**	Me	Me	**3e**	37	99[f]
6	**2f**	Me	H	**3f**	44	99[d]
7	**2g**	Ph	H	**3g**	40	97[d]
8	**2h**	Cl	H	**3h**	77	93[f]
9	**2i**	Br	H	**3i**	74	87[f]
10	**2j**	I	H	**3j**	70	94[f]

[a] Substrate **2a**–**2j** (1 equiv.), Me_2Zn (5 equiv.), $Cu(OTf)_2$ (0.05 equiv.) and ligand (*R*,*S*,*S*)-**A** (0.1 equiv.) in toluene were stirred at –5 °C for 12 h. [b] Isolated yield is reported. The absolute configuration of the major enantiomer was determined by comparison to the structure of (*S*)-**3g**, which was unambiguously determined by X-ray diffraction and NMR analyses. [c] The major product was 2,3,4-trimethoxy-5-methylphenol (>70 % yield). [d] The enantiomeric excess value of the 1,4-adduct was determined by HPLC analysis on a Daicel Chiralpak IC column. [e] The reaction was performed at 0 °C, and approximately 15 % of starting material **2b** was recovered. [f] The *ee* value of the 1,4-adduct was determined by HPLC analysis on a Daicel Chiralpak IF column.

Results and Discussion

In the final step of our synthetic strategy, a base-catalyzed epimerization is utilized to establish the (*R*) configuration at the C-6 position. Thus, the (*R*)-binaphthol-derived phosphoramidite chiral ligand (*R*,*S*,*S*)-**A**, based on Feringa's protocol,[15] was chosen for the enantioselective Michael reaction. In our previous study,[8] MeMgBr–CuCl was determined as the best nucleophilic reagent for the conjugate addition to benzoquinone monoketal **2a** in tetrahydrofuran (THF). However, this relatively active reagent could not be applied to the enantioselective Michael addition of **2a**, even in the presence of the chiral ligand, under the optimized conditions because of competition from a 1,2-addition reaction and facile aromatization to give 2,3,4-trimethoxy-5-methylphenol. Although we were able to repeat the previously reported Michael reaction of 4,4-dimethoxycyclohexa-2,5-dien-1-one by using Me_2Zn, $Cu(OTf)_2$, and chiral ligand (*S*,*R*,*R*)-**B**[15] to obtain the desired conjugate addition product

(*R*)-3-methyl-4,4-dimethoxycyclohex-2-en-1-one in 72 % yield with 99 % *ee*, the enantioselective Michael reaction of **2a** was problematic, because the four electron-donating methoxy substituents make **2a** a poor Michael acceptor toward a nucleophilic reagent.[8] The similar problem of reluctant Michael reactions of highly electron-rich system has also been encountered by the Baran and Chen groups.[4,6]

After screening various reaction conditions (Table 1) such as the solvent, reaction temperature, reaction time, concentration of substrate **2a**, and quantities of Me_2Zn, $Cu(OTf)_2$, and the (*R*,*S*,*S*)-**A** ligand, we finally obtained the desired conjugate addition product (*S*)-**3a** in a low yield (6 %) with excellent enantioselectivity (>99 % *ee*; Table 1, Entry 8 and Table 2, Entry 1). The major product 2,3,4-trimethoxy-5-methylphenol (>70 % yield) was presumably derived by elimination of methanol from (*S*)-**3a** under the reaction conditions. In contrast, the asymmetric Michael reaction of **2d** was performed with Me_2Zn (5 equiv.) in the presence of $Cu(OTf)_2$ (0.05 equiv.) and (*R*,*S*,*S*)-**A** (0.1 equiv.) in toluene at –5 °C to give the conjugate addition product (*S*)-**3d** in high yield (81 %) with high enantioselectivity (98 % *ee*; Table 2, Entry 4).

As the substituent of **2a** (R^3 = MeO) versus that of **2d** (R^3 = H) seemed to influence the outcome of the reaction, we then investigated the asymmetric Michael reactions of benzoquinone monoketals that contain various R^2 and R^3 substituents (Table 2). Interestingly, the substrates (i.e., **2b**, **2c**, and **2h**) that contain the electron-withdrawing chloro substituent at the C-2 and/or C-3 positions tended to provide higher yields of the conjugate addition product than those afforded by substrates (**2a**, **2e**, and **2f**) that contain electron-donating substituents. The *ee* values of the 1,4-adducts were determined by chiral HPLC analysis, and the major product **3g** (Table 2, Entry 7) was shown to have the (*S*) configuration according to X-ray diffraction analysis (Supporting Information, Figure S58). Assuming the asymmetric Michael reactions of **2a**–**2j** proceeded with the same enantiomeric preference, all conjugate addition products **3a**–**3j** should favor the (*S*) enantiomers. This reasoning is also supported by the conversion of (*S*)-**3b** and (*S*)-**3d** into (+)-antroquinonol and (+)-antroquinonol D, respectively, as described herein.

With the optically active **3b** and **3d** in hand, the subsequent alkylation and reduction reactions were smoothly carried out by using our previous experimental protocols[8] that suggest the appropriate reducing agent and reaction conditions to attain the desired stereochemical outcome. For the synthesis of (+)-antroquinonol, the conjugate addition product (*S*)-**3b** was treated with lithium hexamethyldisilazide and farnesyl bromide to give the alkylation product, which was then subjected to a base-catalyzed isomerization to afford **4b** predominating in the *cis* configuration. Compound **4b** was then reduced with LS-Selectride® at –20 °C followed by hydrolysis of the ketal group in the presence of mild acidic K10 clay[16] to give **5b**. The all-*cis* configuration in **5b** was supported by its ROESY spectrum, which shows the correlation between the H-4 (at δ = 4.48 ppm) and H-6 (at δ = 2.58 ppm) signals as well as that between 6-CH_3 (at δ = 1.25 ppm) and the farnesyl CH_2 (at δ = 2.38 ppm) signals. Compound **5b** was then treated with K_2CO_3 in methanol to undergo an inversion of configuration at C-6 along with the substitution of the chlorine atom at C-3 with a methoxy group through an addition–elimination mechanism. Thus, (+)-antroquinonol (**1a**) was synthesized in 10.4 % overall yield from **2b** by employing a six-step sequence. The synthetic sample of **1a** exhibits the same physical and spectroscopic properties (i.e., [α], MS, ^{1}H NMR, and ^{13}C NMR) as that of natural (+)-antroquinonol.

(+)-Antroquinonol D (**1d**) was then synthesized from (*S*)-**3d** by using a similar procedure, which includes alkylation with farnesyl bromide, reduction with LS-Selectride®, ketal hydrolysis, and inversion of the configuration at C-6. This modular synthetic method can be applied to the preparation of analogous compounds by varying the benzoquinone monoketal, the organometal, and the alkylating agent.

Conclusions

We have successfully carried out the enantioselective Michael reactions of 4,4-dimethoxycyclohexa-2,5-dienones **2a**–**2j** with dimethylzinc in the presence of $Cu(OTf)_2$ as the catalyst and the (*R*)-binaphthol-derived phosphoramidite chiral ligand (*R*,*S*,*S*)-**A** under the optimized reaction conditions to afford conjugate addition products **3a**–**3j** with high enantioselectivity (Table 2). Electron-withdrawing substituents, such as a chloro group, at the C-2 and/or C-3 positions of the substrate promoted the Michael reaction (Table 2, Entries 2, 3, and 8 vs. 1, 5, and 6) to give higher yields of the conjugate addition products.

Although Michael reactions of unsubstituted benzoquinone monoketals have previously been explored,[9–12,14,17] the conjugate addition reaction of highly electron-rich Michael acceptors, in particular benzoquinone monoketal **2a**, is a long-standing problem.[4,6] Baran and co-workers solved this matter by searching for the appropriate ketal protecting group.[4] We independently found that **2b**, which contains the electron-withdrawing chloro group as a surrogate for the methoxy substituent at C-2, could undergo a facilitated enantioselective Michael addition reaction. The treatment of **5b** with K_2CO_3/MeOH in the final step of the synthesis allowed the chlorine atom to be replaced by a methoxy group along with the inversion of the configuration at C-6 in a one-pot operation, thus affording a short and efficient total synthesis of (+)-antroquinonol.

We also demonstrated a practical method for enantioselective Michael reactions of substituted benzoquinone monoketals that have various R^2 and R^3 substituents (Table 2). The transformation of the conjugate addition products into a series of antroquinonol analogues that contain the unusual 4-hydroxycyclohex-2-enone core structure would be feasible by subsequent alkylation, reduction, and ketal hydrolysis reactions. For example, the oxidation of 3,4-dimethoxyphenol by treatment with PIFA in methanol gave 3,4,4-trimethoxycyclohexa-2,5-dien-1-one (**2d**), which proceeded in an enantioselective Michael reaction to give (*S*)-**3d** in 81 % yield with 98 % *ee*. Thus, the total synthesis of antroquinonol D was accomplished in a reasonable overall yield (>15 %) by using a five-step reaction sequence from (*S*)-**3d** (Scheme 1).

Experimental Section

General Methods: Melting points were recorded in open capillary tubes on a Yanaco or Electrothermal MEL-TEMP 1101D apparatus. Optical rotations were measured on a Japan JASCO Co. DIP-1000 digital polarimeter. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on Nicolet Magna 550-II or Thermo Nicolet 380 FTIR spectrometers. The NMR spectroscopic data were recorded with a Bruker Advance-400 (400 MHz), a Bruker AVIII (500 MHz), or a Varian Unity Plus (400 MHz) spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to δ_H = 7.24 ppm/δ_C = 77.0 ppm (central line of triplet) for $CHCl_3$/$CDCl_3$ and δ_H = 7.20 ppm/δ_C = 128.0 ppm for C_6D_5H/C_6D_6. The splitting patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double of doublets), and br. (broad). Coupling constants (*J*) are given in Hz. DEPT spectra were recorded to determine the types of carbon signals. The ESI–MS experiments were conducted on a Bruker Daltonics BioTOF III high resolution mass spectrometer. The MALDI–MS measurements were performed on a Bruker Daltonics Ultraflez II MALDI–TOF/TOF 2000 mass spectrometer. The 2,5-dihydroxybenzoic acid (DHB), as the MALDI matrix, was photoionized at different irradiances of a UV laser with λ_{max} at 337 and 355 nm. The *ee* values were determined by HPLC analysis using a chiral column (Chiralpak IC or Chiralpak IF, 0.46 cm ID × 25 cm, particle size: 5 μm) and eluting with either 2-propanol/hexane or EtOH/hexane. The flow rate of the indicated elution solvent was maintained at 1 mL min^{-1}, and the retention time of a compound is recorded accordingly. The HPLC instrument was equipped with an ultraviolet detector. All the reagents and solvents were reagent grade and used without further purification, unless otherwise specified. All solvents were anhydrous grade, unless indicated otherwise. CH_2Cl_2 was distilled from CaH_2. All nonaqueous reactions were carried out in oven-dried glassware under a slight positive pressure of argon, unless otherwise noted. Reactions were magnetically stirred and monitored by thin layer chromatography on silica gel, and aqueous *p*-anisaldehyde was used as a visualizing agent. Silica gel (0.040–0.063 mm particle sizes) was used for column chromatography. Flash chromatography was performed on silica gel (60–200 μm particle size). Molecular sieves were activated under high vacuum at 220 °C over 6 h.

Representative Procedure A. Synthesis of Benzoquinone Monoketals: A stirred solution that contained 2,3,4-trimethoxyphenol (2.0 g, 11 mmol) and powdered K_2CO_3 (3.0 g, 22 mmol) in anhydrous MeOH (45 mL) was cooled in an ice bath. A solution of PIFA (4.7 g, 11 mmol) in CH_3CN (22 mL) was added at 0 °C. The ice bath was removed, and the mixture was stirred at 0–25 °C for 10 min. Water was added, and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to yield cyclohexadienone **2a** (1.9 g, 81 % yield).

Representative Procedure B. Asymmetric Michael Reactions: Under argon, a solution of $Cu(OTf)_2$ (8.7 mg, 0.024 mmol) and the (*R*)-binaphthol-derived phosphoramidite chiral ligand (*R*,*S*,*S*)-**A** (0.048 mmol) in toluene (1.0 mL) was stirred at room temperature for 1 h. The colorless solution was cooled to −5 °C. Cyclohexadienone **2d** (88 mg, 0.48 mmol) and Me_2Zn (1.2 M solution in toluene, 2.0 mL, 2.4 mmol) were added. The mixture was stirred at −5 °C for 12 h and then poured into an ice-cold saturated aqueous solution of NH_4Cl (5 mL). The resulting mixture was then extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with NaOH (1.0 M solution, 30 mL) and brine (30 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 15:85) to yield (*S*)-**3d** (77.8 mg, 81 % yield). The reaction afforded the product with 98 % *ee*, as determined by HPLC [Daicel Chiralpak IC column; hexane/*i*PrOH, 90:10; flow rate: 1.0 mL min^{-1}; UV detection at 254 nm; column temperature: 25 °C]: t_R = 17.6 min (*S* isomer) and 19.4 min (*R* isomer). When the (*S*)-binaphthol-derived phosphoramidite chiral ligand (*S*,*R*,*R*)-**B** was used in the conjugate addition reaction, (*R*)-**3d** was obtained by a similar procedure.

Representative Procedure C. Preparation of Racemic Mixture of 3a–3j for HPLC Analysis: The racemic mixtures of **3a**–**3j** were prepared by the Michael reactions of **2a**–**2j**, respectively, using the MeMgBr–CuCl reagent according to our previously reported procedure.[8] For example, a solution of CuCl (99 mg, 1.0 mmol) in THF (4 mL) was cooled to −50 °C, and MeMgBr (1.0 M in THF, 2.0 mL, 2.0 mmol) was added under nitrogen. The mixture was stirred at −50 °C for 1 h, and a solution of cyclohexadienone **2a** (214 mg, 1.0 mmol) in THF (1 mL) was added dropwise. The reaction was stirred at −50 °C for 7 h and quenched with saturated aqueous NH_4Cl (5.0 mL). The resulting mixture was then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with NaOH (0.5 M solution, 30 mL) and brine (30 mL), and the organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 15:85) to yield the conjugate addition product (±)-**3a** (115 mg, 50 % yield).

2,3,4,4-Tetramethoxycyclohexa-2,5-dien-1-one (2a):[8] $C_{10}H_{14}O_5$ (yellow oil). R_f = 0.24 (EtOAc/hexane, 40:60). IR (neat): $\tilde{\nu}_{max}$ = 2994, 2948, 2834, 1672, 1607, 1313, 1210, 1076, 951, 833, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (s, 6 H), 3.74 (s, 3 H), 4.16 (s, 3 H), 6.25 (d, *J* = 10.4 Hz, 1 H), 6.48 (d, *J* = 10.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.2, 155.4, 140.2, 138.8, 130.2, 97.2, 61.2, 60.5, 51.4 ppm. HRMS: calcd. for $C_{10}H_{15}O_5$ $[M + H]^+$ 215.0919; found 215.0913.

2-Chloro-3,4,4-trimethoxycyclohexa-2,5-dien-1-one (2b): According to representative procedure A, 2-chloro-3-methoxyphenol (0.8 g, 5 mmol) and PIFA (4.3 g, 10 mmol) in anhydrous MeOH (45 mL) were stirred at 0–25 °C for 10 min to give cyclohexadienone **2b** ($C_9H_{11}ClO_4$, 709 mg, 65 % yield) as a yellow oil; R_f = 0.26 (EtOAc/hexane, 20:80). IR (neat): $\tilde{\nu}_{max}$ = 2957, 2838, 1673, 1588, 1457, 1293, 1082, 1063, 920, 824 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (d, *J* = 12 Hz, 1 H), 6.37 (d, *J* = 12 Hz, 1 H), 4.23 (s, 3 H), 3.29 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.3, 161.8, 139.8, 130.3, 115.1, 97.5, 60.0, 51.5 (2×) ppm. HRMS: calcd. for $C_9H_{12}ClO_4$ $[M + H]^+$ 219.0424; found 219.0432

2,3-Dichloro-4,4-dimethoxycyclohexa-2,5-dien-1-one (2c): According to representative procedure A, 2,3-dichlorophenol (0.5 g, 3 mmol) and PIFA (3.5 g, 8 mmol) in anhydrous MeOH (45 mL) were stirred at 0–25 °C for 10 min to give cyclohexadienone **2c** ($C_8H_8Cl_2O_3$, 497 mg, 75 % yield) as an orange oil; R_f = 0.44 (EtOAc/hexane, 20:80). IR (neat): $\tilde{\nu}_{max}$ = 2948, 2829, 1667, 1305, 1215, 1077, 952, 833, 742 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (d, *J* = 10.0 Hz, 1 H), 6.56 (d, *J* = 10.0 Hz, 1 H), 3.29 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2, 148.8, 143.9, 134.4, 130.4, 96.3, 51.6 (2×) ppm. HRMS: calcd. for $C_8H_9Cl_2O_3$ $[M + H]^+$ 222.9929; found 222.9930.

3,4,4-Trimethoxycyclohexa-2,5-dien-1-one (2d):[8] According to representative procedure A, 3,4-dimethoxyphenol (2.0 g, 13 mmol), K_2CO_3 (3.4 g, 26 mmol), and PIFA (5.6 g, 13 mmol) in anhydrous MeOH (52 mL)/CH_3CN (26 mL) were stirred at 0–25 °C for 10 min to give cyclohexadienone **2d** ($C_9H_{12}O_3$, 1.9 g, 95 % yield) as a colorless oil; R_f = 0.28 (EtOAc/hexane, 25:75). IR (neat): $\tilde{\nu}_{max}$ = 2950, 2832,

1672, 1313, 1210, 1075, 951, 833, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.55 (J = 8.0 Hz, 1 H), 6.27 (d, J = 8.0 Hz, 1 H), 5.60 (d, J = 2.5 Hz, 1 H), 3.80 (s, 3 H), 3.31 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.1, 169.1, 140.2, 131.2, 104.2, 94.1, 56.0, 51.4 (2×) ppm. HRMS: calcd. for $C_9H_{13}O_4$ 185.0814 $[M + H]^+$; found 185.0818.

4,4-Dimethoxy-2,3-dimethylcyclohexa-2,5-dien-1-one (2e): According to representative procedure A, 2,3-dimethylphenol (0.5 g, 4 mmol), K_2CO_3 (1.7 g, 12 mmol), and PIFA (3.5 g, 8 mmol) in anhydrous MeOH (45 mL)/CH_3CN (22 mL) were stirred at 0–25 °C for 10 min to give cyclohexadienone **2e** ($C_{10}H_{14}O_3$, 373 mg, 50 % yield) as a brown oil; R_f = 0.52 (EtOAc/hexane, 20:80). IR (neat): $\tilde{\nu}_{max}$ = 2942, 2833, 1672, 1305, 1215, 1075, 950, 833, 676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.68 (d, J = 10.0 Hz, 1 H), 6.40 (d, J = 10.0 Hz, 1 H), 3.16 (s, 6 H), 1.88 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.7, 149.3, 143.3, 135.4, 132.2, 95.7, 50.9 (2×), 13.1, 10.8 ppm. HRMS: calcd. for $C_{10}H_{15}O_3$ $[M + H]^+$ 183.1021; found 183.1023.

4,4-Dimethoxy-3-methylcyclohexa-2,5-dien-1-one (2f): According to representative procedure A, 3-methyphenol (0.5 g, 5 mmol) and PIFA (4.3 g, 10 mmol) in anhydrous MeOH (20 mL) were stirred at 0–25 °C for 10 min to give cyclohexadienone **2f** ($C_9H_{12}O_3$, 420 mg, 50 % yield) as a yellow oil; R_f = 0.24 (EtOAc/hexane, 10:90). IR (neat): $\tilde{\nu}_{max}$ = 2939, 2830, 1674, 1305, 1215, 1077, 952, 833, 676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, J = 10.5 Hz, 1 H), 6.38 (d, J = 10.5 Hz, 1 H), 6.21 (s, 1 H), 3.21 (s, 6 H), 1.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.9, 155.9, 143.8, 132.3, 129.8, 95.4, 50.9 (2×), 16.6 ppm. HRMS: calcd. for $C_9H_{13}O_3$ $[M + H]^+$ 169.0865; found 169.0869.

4,4-Dimethoxy-3-phenylcyclohexa-2,5-dien-1-one (2g): According to representative procedure A, 3-phenylphenol (0.5 g, 3 mmol) and PIFA (3.4 g, 6 mmol) in anhydrous MeOH (12 mL) were stirred at 0–25 °C for 10 min to give cyclohexadienone **2g** ($C_{14}H_{14}O_3$, 300 mg, 45 % yield) as a yellow oil; R_f = 0.33 (EtOAc/hexane, 15:85). IR (neat): $\tilde{\nu}_{max}$ = 2997, 2829, 1667, 1632, 1213, 1077, 965, 898, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, J = 7.5, 2.0 Hz, 2 H), 7.45–7.35 (m, 3 H), 6.74 (d, J = 10.0 Hz, 1 H), 6.69 (d, J = 2.0 Hz, 1 H), 6.48 (dd, J = 10.0, 2.0 Hz, 1 H), 3.22 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.6, 153.4, 144.8, 134.7, 130.1, 129.0, 128.5 (2×), 128.1 (2×), 97.3, 51.1 (2×) ppm. HRMS: calcd. for $C_{14}H_{15}O_3$ $[M + H]^+$ 231.1021; found 231.1024.

3-Chloro-4,4-dimethoxycyclohexa-2,5-dien-1-one (2h): According to representative procedure A, 3-chlorophenol (0.5 g, 4 mmol) and PIFA (3.4 g, 8 mmol) in anhydrous MeOH (45 mL) were stirred at 0–25 °C for 10 min to give cyclohexadienone **2h** ($C_8H_9ClO_3$, 602 mg, 80 % yield) as a yellow oil; R_f = 0.51 (EtOAc/hexane, 20:80). IR (neat): $\tilde{\nu}_{max}$ = 2948, 2829, 1667, 1305, 1215, 1077, 952, 833, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, J = 10.5 Hz, 1 H), 6.60 (s, 1 H), 6.44 (d, J = 10.5 Hz, 1 H), 3.30 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.2, 152.7, 143.8, 131.6, 131.3, 94.8, 51.4 (2×) ppm. HRMS: calcd. for $[M + H]^+$ $C_8H_{10}ClO_3$ 189.0318; found 189.0319.

3-Bromo-4,4-dimethoxycyclohexa-2,5-dien-1-one (2i): According to representative procedure A, 3-bromophenol (0.5 g, 3 mmol) and PIFA (2.6 g, 6 mmol) in anhydrous MeOH (12 mL) were stirred at 0–25 °C for 10 min to give cyclohexadienone **2i** ($C_8H_9BrO_3$, 540 mg, 78 % yield) as a yellow oil; R_f = 0.47 (EtOAc/hexane, 20:80). IR (neat): $\tilde{\nu}_{max}$ = 2951, 2831, 1670, 1310, 1215, 1077, 951, 833, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.88–6.82 (m, 2 H), 6.46 (d, J = 10.0 Hz, 1 H), 3.28 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.6, 146.6, 143.9, 135.7, 131.7, 118.8, 94.9, 51.4 (2×) ppm. HRMS: calcd. for $[M + H]^+$ $C_8H_{10}BrO_3$ 232.9813; found 232.9815.

3-Iodo-4,4-dimethoxycyclohexa-2,5-dien-1-one (2j): According to representative procedure A, 3-iodophenol (0.50 g, 2.3 mmol) and PIFA (2.0 g, 4.6 mmol) in anhydrous MeOH (9 mL) were stirred at 0–25 °C for 10 min to give cyclohexadienone **2j** ($C_8H_9IO_3$, 322 mg, 50 % yield) as a yellow oil; R_f = 0.33 (EtOAc/hexane, 10:90). IR (neat): $\tilde{\nu}_{max}$ = 2951, 2834, 1669, 1630, 1215, 1077, 951, 833, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 2.0 Hz, 1 H), 6.94 (d, J = 10.0 Hz, 1 H), 6.51 (dd, J = 10.3, 2.0 Hz, 1 H), 3.25 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.6, 143.4, 142.9, 132.0, 129.3, 94.5, 51.1 (2×) ppm. HRMS: calcd. for $C_8H_{10}IO_3$ $[M + H]^+$ 280.9625; found 280.9628.

(*S*)-2,3,4,4-Tetramethoxy-5-methylcyclohex-2-en-1-one (3a): According to representative procedure B, cyclohexadienone **2a** (100 mg, 0.48 mmol) and Me_2Zn (1.2 M in toluene, 2.0 mL, 2.4 mmol) were treated with $Cu(OTf)_2$ (8.7 mg, 0.024 mmol) and the ligand (*R*,*S*,*S*)-**A** (25.9 mg, 0.048 mmol) at −5 °C for 12 h to give (*S*)-**3a** ($C_{11}H_{18}O_5$, 6.6 mg, 6 % yield) as a yellow oil. The reaction afforded the product with 99 % *ee*, as determined by HPLC [Daicel Chiralpak IC column; hexane/EtOH, 90:10; flow rate: 1.0 mL min^{-1}; UV detection at 254 nm; column temperature: 25 °C]: t_R = 12.8 min (*S* isomer). R_f = 0.24 (30 % EtOAc/hexane). $[\alpha]_D^{25}$ = +65.0 (c = 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.09 (s, 3 H), 3.64 (s, 3 H), 3.28 (s, 3 H), 3.26 (s, 3 H), 2.72 (dd, J = 16.8, 4.3 Hz, 1 H), 2.47 (td, J = 7.0, 4.3 Hz, 1 H), 2.27 (dd, J = 16.8, 3.8 Hz, 1 H), 0.97 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 158.9, 138.3, 101.1, 60.9, 60.4, 51.0, 48.2, 41.1, 33.9, 14.5 ppm. HRMS: calcd. for $C_{11}H_{19}O_5$ $[M + H]^+$ 231.1232; found 231.1234.

(*S*)-2-Chloro-5-methyl-3,4,4-trimethoxycyclohex-2-en-1-one (3b): According to representative procedure B, cyclohexadienone **2b** (100 mg, 0.46 mmol) and Me_2Zn (1.2 M in toluene, 1.9 mL, 2.3 mmol) were treated with $Cu(OTf)_2$ (8.3 mg, 0.023 mmol) and the ligand (*R*,*S*,*S*)-**A** (24.8 mg, 0.046 mmol) at 0 °C for 12 h to give (*S*)-**3e** ($C_{10}H_{15}ClO_4$, 45.2 mg, 42 % yield) as a yellow oil. The reaction afforded the product with 99 % *ee*, as determined by HPLC [Daicel Chiralpak IC column; hexane/*i*PrOH, 98:2; flow rate: 0.5 mL min^{-1}; UV detection at 254 nm; column temperature: 25 °C]: t_R = 46.1 min (*S* isomer). R_f = 0.55 (EtOAc/hexane, 25:75). $[\alpha]_D^{25}$ = +52.9 (c = 3.5, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2943, 2837, 1689, 1590, 1459, 1213, 1052, 1033, 805 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.11 (s, 3 H), 3.31 (s, 3 H), 3.28 (s, 3 H), 2.88 (dd, J = 17.1, 4.3 Hz, 1 H), 2.55 (m, 1 H), 2.45 (dd, J = 17.1, 3.7 Hz, 1 H), 0.99 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.2, 167.3, 118.0, 101.8, 61.3, 51.4, 48.3, 41.5, 34.1, 14.4 ppm. HRMS: calcd. for $C_{10}H_{15}ClNaO_4$ $[M + Na]^+$ 257.0557; found 257.0552.

(*S*)-2,3-Dichloro-4,4-dimethoxy-5-methylcyclohex-2-en-1-one (3c): According to representative procedure B, cyclohexadienone **2c** (100 mg, 0.45 mmol) and Me_2Zn (1.2 M in toluene, 1.9 mL, 2.2 mmol) were treated with $Cu(OTf)_2$ (8.1 mg, 0.023 mmol) and the ligand (*R*,*S*,*S*)-**A** (24.3 mg, 0.045 mmol) at −5 °C for 12 h to give (*S*)-**3c** ($C_9H_{12}Cl_2O_3$, 76.3 mg, 71 % yield) as a brown oil. The reaction afforded the product with 93 % *ee*, as determined by HPLC [Daicel Chiralpak IF column; hexane/*i*PrOH, 95:5; flow rate: 0.6 mL min^{-1}; UV detection at 254 nm; column temperature: 25 °C]: t_R = 10.5 min (*S* isomer) and 12.1 min (*R* isomer). R_f = 0.44 (EtOAc/hexane, 10:90). $[\alpha]_D^{25}$ = −0.9 (c = 1.23, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2969, 2942, 2841, 1701, 1577, 1458, 1240, 1052, 947, 784 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.33 (s, 3 H), 3.31 (s, 3 H), 2.96 (dd, J = 17.4, 4.6 Hz, 1 H), 2.70–2.62 (m, 1 H), 2.52 (dd, J = 17.4, 4.0 Hz, 1 H), 0.97 (d, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.2, 151.2, 133.9, 100.1, 51.3, 48.6, 41.4, 35.3, 14.4 ppm. HRMS: calcd. for $C_9H_{13}Cl_2O_3$ $[M + H]^+$ 239.0242; found 239.0246.

(*S*)-3,4,4-Trimethoxy-5-methylcyclohex-2-en-1-one (3d): The employment of representative procedure B afforded (*S*)-**3d** ($C_{10}H_{16}O_4$) as a colorless oil. The reaction afforded the product with 98 % *ee*, as determined by HPLC [Daicel Chiralpak IC column; hexane/*i*PrOH, 90:10; flow rate: 1.0 mL min^{-1}; UV detection at 254 nm; column temperature: 25 °C]: t_R = 17.6 min (*S* isomer) and 19.4 min (*R* isomer). R_f = 0.25 (EtOAc/hexane, 30:70). $[\alpha]_D^{24}$ = +13.8 (*c* = 2.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2972, 2941, 2837, 1659, 1608, 1458, 1223, 1074, 1028, 772 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34 (s, 1 H), 3.73 (s, 3 H), 3.31 (s, 3 H), 3.26–3.20 (m, 3 H), 2.78 (dd, *J* = 17.1, 5.0 Hz, 1 H), 2.63–2.52 (m, 1 H), 2.24 (dd, *J* = 17.1, 3.0 Hz, 1 H), 0.98 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 171.3, 103.3, 99.9, 55.9, 48.1, 41.7, 34.8, 14.6 ppm. HRMS: calcd. for $C_{10}H_{17}O_4$ [M + H]$^+$ 201.1127; found 201.1137.

(*S*)-4,4-Dimethoxy-2,3,5-trimethylcyclohex-2-en-1-one (3e): According to representative procedure B, cyclohexadienone **2e** (100 mg, 0.55 mmol) and Me_2Zn (1.2 M in toluene, 2.3 mL, 2.7 mmol) were treated with $Cu(OTf)_2$ (10.8 mg, 0.03 mmol) and the ligand (*R*,*S*,*S*)-**A** (32.3 mg, 0.06 mmol) at −5 °C for 12 h to give (*S*)-**3e** ($C_{11}H_{18}O_3$, 40.3 mg, 37 % yield) as a brown oil. The reaction afforded the product with 99 % *ee*, as determined by HPLC [Daicel Chiralpak IF column; hexane/EtOH, 98:2; flow rate: 0.5 mL min^{-1}; UV detection at 220 nm; column temperature: 25 °C]: t_R = 14.5 min (*S* isomer). R_f = 0.39 (EtOAc/hexane, 10:90). $[\alpha]_D^{25}$ = +8.2 (*c* = 1.25, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2965, 2940, 2831, 1672, 1455, 1378, 1261, 1143, 1096, 1056, 960, 925 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD): δ = 3.28 (s, 3 H), 3.16 (s, 3 H), 2.83 (dd, *J* = 17.7, 5.5 Hz, 1 H), 2.66–2.58 (m, 1 H), 2.21 (dd, *J* = 17.7, 2.4 Hz, 1 H), 2.01 (s, 3 H), 1.78 (s, 3 H), 0.88 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 199.9, 154.0, 134.7, 101.7, 51.0, 47.8, 42.6, 35.7, 17.1, 15.3, 11.4 ppm. HRMS: calcd. for $C_{11}H_{19}O_3$ [M + H]$^+$ 199.1334; found 199.1335.

(*S*)-4,4-Dimethoxy-3,5-dimethylcyclohex-2-en-1-one (3f): According to representative procedure B, cyclohexadienone **2f** (100 mg, 0.60 mmol) and Me_2Zn (1.2 M in toluene, 2.5 mL, 3.0 mmol) were treated with $Cu(OTf)_2$ (10.8 mg, 0.03 mmol) and the ligand (*R*,*S*,*S*)-**A** (32.3 mg, 0.06 mmol) at −5 °C for 12 h to give (*S*)-**3f** ($C_{10}H_{16}O_3$, 48.6 mg, 44 % yield) as a brown oil. The reaction afforded the product with 99 % *ee*, as determined by HPLC [Daicel Chiralpak IC column; hexane/*i*PrOH, 98:2; flow rate: 0.5 mL min^{-1}; UV detection at 220 nm; column temperature: 25 °C]: t_R = 37.5 min (*S* isomer) and 39.7 min (*R* isomer). R_f = 0.35 (EtOAc/hexane, 10:90). $[\alpha]_D^{25}$ = −2.0 (*c* = 1.43, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2965, 1677, 1457, 1437, 1256, 1123, 1075, 1053, 946 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.88 (s, 1 H), 3.25 (s, 3 H), 3.21 (s, 3 H), 2.85 (dd, *J* = 17.7, 4.9 Hz, 1 H), 2.59 (m, 1 H), 2.21 (d, *J* = 17.7 Hz, 1 H), 2.00 (d, *J* = 1.8 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.6, 158.4, 128.7, 100.5, 50.6, 47.4, 42.1, 35.2, 21.0, 14.9 ppm. HRMS: calcd. for $C_{10}H_{16}O_3Na$ [M + Na]$^+$ 207.0991; found 207.0998.

(*S*)-4,4-Dimethoxy-5-methyl-3-phenylcyclohex-2-en-1-one (3g): According to representative procedure B, cyclohexadienone **2g** (100 mg, 0.43 mmol) and Me_2Zn (1.2 M in toluene, 1.8 mL, 2.2 mmol) were treated with $Cu(OTf)_2$ (7.8 mg, 0.02 mmol) and the ligand (*R*,*S*,*S*)-**A** (21.6 mg, 0.04 mmol) at −5 °C for 12 h to give (*S*)-**3g** ($C_{15}H_{17}O_3$, 42.3 mg, 40 % yield) as as a colorless solid. The reaction afforded the product with 97 % *ee*, as determined by HPLC [Daicel Chiralpak IC column; hexane/*i*PrOH, 98:2; flow rate: 0.5 mL min^{-1}; UV detection at 254 nm; column temperature: 25 °C]: t_R = 41.5 min (*R* isomer) and 48.5 min (*S* isomer). The colorless solid was recrystallized from Et_2O/hexane (3:7); m.p. 99.5–101.2 °C. R_f = 0.39 (EtOAc/hexane, 10:90). $[\alpha]_D^{26}$ = +246.8 (*c* = 0.63, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2936, 2835, 1660, 1597, 1476, 1306, 1203, 1124, 1051, 758, 698 cm^{-1}. ^{1}H NMR (500 MHz, C_6D_6): δ = 7.36 (dd, *J* = 7.3, 1.8 Hz, 2 H), 7.15–7.07 (m, 3 H), 6.13 (s, 1 H), 3.06 (dd, *J* = 17.4, 5.2 Hz, 1 H), 2.89 (s, 3 H), 2.88 (s, 3 H), 2.40–2.33 (m, 1 H), 2.30 (d, *J* = 17.4 Hz, 1 H), 0.86 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 196.9, 157.4, 139.5, 131.2, 129.4, 128.4, 128.3, 128.1, 127.9, 101.6, 50.8, 46.9, 42.1, 35.2, 15.0 ppm. HRMS: calcd. for $C_{15}H_{19}O_3$ [M + H]$^+$ 247.1334; found 247.1336.

(*S*)-3-Chloro-4,4-dimethoxy-5-methylcyclohex-2-en-1-one (3h): According to representative procedure B, cyclohexadienone **2h** (100 mg, 0.46 mmol) and Me_2Zn (1.2 M in toluene, 1.9 mL, 2.3 mmol) were treated with $Cu(OTf)_2$ (8.3 mg, 0.023 mmol) and the ligand (*R*,*S*,*S*)-**A** (24.8 mg, 0.046 mmol) at 0 °C for 12 h to give (*S*)-**3h** ($C_9H_{13}ClO_3$, 72.3 mg, 77 % yield) as a yellow oil. The reaction afforded the product with 93 % *ee*, as determined by HPLC [Daicel Chiralpak IF column; hexane/*i*PrOH, 95:5; flow rate: 0.6 mL min^{-1}; UV detection at 254 nm; column temperature: 25 °C]: t_R = 13.6 min (*R* isomer) and 16.3 min (*S* isomer). R_f = 0.53 (EtOAc/hexane, 10:90). $[\alpha]_D^{25}$ = +52.9 (*c* = 3.5, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2943, 2837, 1689, 1590, 1459, 1213, 1052, 1033, 805 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.11 (s, 3 H), 3.31 (s, 3 H), 3.28 (s, 3 H), 2.88 (dd, *J* = 17.1, 4.3 Hz, 1 H), 2.55 (m, 1 H), 2.45 (dd, *J* = 17.1, 3.7 Hz, 1 H), 0.99 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.2, 167.3, 118.0, 101.8, 61.3, 51.4, 48.3, 41.5, 34.1, 14.4 ppm. HRMS: calcd. for $C_9H_{13}ClNaO_3$ 227.0451 [M + Na]$^+$; found 227.0452.

(*S*)-3-Bromo-4,4-dimethoxy-5-methylcyclohex-2-en-1-one (3i): According to representative procedure B, cyclohexadienone **2i** (100 mg, 0.43 mmol) and Me_2Zn (1.2 M in toluene, 1.8 mL, 2.1 mmol) were treated with $Cu(OTf)_2$ (7.8 mg, 0.022 mmol) and the ligand (*R*,*S*,*S*)-**A** (0.043 mmol) at −5 °C for 12 h to give (*S*)-**3i** ($C_9H_{13}BrO_3$, 79.2 mg, 74 % yield) as a yellow oil. The reaction afforded the product with 87 % *ee*, as determined by HPLC [Daicel Chiralpak IF column; hexane/*i*PrOH, 95:5; flow rate: 0.6 mL min^{-1}; UV detection at 254 nm; column temperature: 25 °C]: t_R = 13.0 min (*R* isomer) and 14.4 min (*S* isomer). R_f = 0.68 (EtOAc/hexane, 20:80). $[\alpha]_D^{25}$ = +0.9 (*c* = 3.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2967, 2941, 2835, 1690, 1604, 1248, 1129, 1054, 934, 772 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.58 (s, 1 H), 3.38 (s, 3 H), 3.33 (s, 3 H), 2.87 (dd, *J* = 17.1, 4.9 Hz, 1 H), 2.70–2.63 (m, 1 H), 2.33 (dd, *J* = 17.1, 3.1 Hz, 1 H), 0.98 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.7, 148.6, 134.6, 98.7, 51.2, 48.4, 41.9, 35.7, 14.7 ppm. HRMS calcd. for $C_9H_{14}BrO_3$ [M + H]$^+$ 249.0126; found 249.0129.

(*S*)-3-Iodo-4,4-dimethoxy-5-methylcyclohex-2-en-1-one (3j): According to representative procedure B, cyclohexadienone **2j** (100 mg, 0.36 mmol) and Me_2Zn (1.2 M in toluene, 1.5 mL, 1.8 mmol) were treated with $Cu(OTf)_2$ (6.5 mg, 0.018 mmol) and the ligand (*R*,*S*,*S*)-**A** (19.4 mg, 0.036 mmol) at 0 °C for 12 h to give (*S*)-**3j** ($C_9H_{12}IO_3$, 74.6 mg, 70 % yield) as a yellow oil. The reaction afforded the product with 94 % *ee*, as determined by HPLC [Daicel Chiralpak IF column; hexane/*i*PrOH, 95:5; flow rate: 0.6 mL min^{-1}; UV detection at 254 nm; column temperature: 25 °C]: t_R = 18.4 min (*R* isomer) and 19.7 min (*S* isomer). R_f = 0.42 (EtOAc/hexane, 10:90). $[\alpha]_D^{26}$ = −18.9 (*c* = 1.7, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2965, 2939, 2835, 1683, 1588, 1460, 1243, 1121, 1073, 1052, 932, 876, 775 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (s, 1 H), 3.42 (s, 3 H), 3.31 (s, 3 H), 2.88 (dd, *J* = 17.6, 5.0 Hz, 1 H), 2.72–2.58 (m, 1 H), 2.31 (dd, *J* = 17.6, 2.5 Hz, 1 H), 0.96 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.2, 142.3, 129.2, 97.5, 50.8, 48.6, 41.6, 34.9, 14.9 ppm. HRMS: calcd. for $C_9H_{14}IO_3$ [M + H]$^+$ 296.9988; found 296.9990.

(5*S*,6*RS*)-2-Chloro-6-farnesyl-3,4,4-trimethoxy-5-methylcyclohex-2-en-1-one (4b): Under nitrogen, LHMDS (1.0 M in THF, 0.9 mL, 0.9 mmol) was added to a solution of (*S*)-**3b** (100 mg, 0.43 mmol) in THF (2.0 mL) at −78 °C. After the mixture was stirred at −78 °C

for 2 h, a solution of farnesyl bromide (245 mg, 0.86 mmol) in THF (1.0 mL) was added at –78 °C. The dry ice cooling bath was removed, and the mixture was warmed to room temperature over a period of 2 h and quenched with water (5.0 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on aluminum oxide (EtOAc/hexane, 5:95) to yield the alkylation product (5*S*)-**4b** ($C_{25}H_{39}ClO_4$, 170 mg, 90 % yield) as a mixture of *trans* and *cis* isomers (1:1). The sample (170 mg, 0.39 mmol) that contained the *trans* and *cis* isomers (1:1) was subjected to epimerization by treatment with NaH (2.0 mg, 0.04 mmol) in DMF (3.0 mL) at 25 °C for 24 h to give the mixture of the *trans* and *cis* isomers (1:4) as a yellow oil; R_f = 0.53 (*cis*) and 0.49 (*trans*, EtOAc/hexane, 10:90). IR (neat): $\tilde{\nu}_{max}$ = 2966, 2936, 2855, 1695, 1601, 1457, 1379, 1210, 1071, 1053, 967, 808, 774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 1:4 mixture of isomers): δ = 5.15–4.98 (m, 6 H, olefinic protons), 4.14 (s, *trans*, MeO-3), 4.05 (s, *cis*, MeO-3), 3.32–3.29 (s, 4 H), 3.27 (s, *cis*, MeO-4), 3.25 (s, *trans*, MeO-4), 2.95 (dt, *J* = 9.4, 4.0 Hz, CH, *cis*), 2.70 (CH, m, *cis*), 2.63–2.56 (CH, m, *trans*), 2.47 (qd, *J* = 7.0, 4.0 Hz, 5-H, *cis*), 2.43–2.30 (CH_2, m, *trans*), 2.16–1.87 (m, 16 H), 1.65 (s, 5 H), 1.62 (s, 4 H), 1.57 (s, 10 H), 0.96 (d, *J* = 6.5 Hz, Me-5, *trans*), 0.79 (d, *J* = 7.0 Hz, Me-5, *cis*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 1:4 mixture of isomers): δ = 193.0, 165.9, 137.3, 135.1, 131.3, 124.3, 124.0, 121.1, 102.0, 61.2, 51.4, 48.1, 47.6, 39.9, 39.8, 39.7, 37.8, 26.8, 26.6, 25.7, 25.1, 17.7, 16.2, 16.0, 9.4 ppm. HRMS: calcd. for $C_{25}H_{39}NaClO_4$ $[M + Na]^+$ 461.2435; found 461.2437.

(5*S*,6*RS*)-6-Farnesyl-3,4,4-trimethoxy-5-methylcyclohex-2-en-1-one (4d):[8] Under nitrogen, lithium hexamethyldisilazide (1.0 M in THF, 1.0 mL, 1.0 mmol) was added to a solution of (*S*)-**3d** (100 mg, 0.5 mmol) in THF (2.0 mL) at –78 °C. After the mixture was stirred at –78 °C for 2 h, a solution of farnesyl bromide (285 mg, 1.0 mmol) in THF (1.0 mL) was added at –78 °C. The dry ice cooling bath was removed, and the mixture was warmed to room temperature over a period of 2 h and quenched with water (5 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on aluminum oxide (EtOAc/hexane, 10:90) to yield the alkylation product (5*S*)-**4d** ($C_{25}H_{40}O_4$, 192 mg, 95 % yield) as a mixture of *trans* and *cis* isomers (1:1). This sample (192 mg, 0.48 mmol) that contained *trans* and *cis* isomers (1:1) was subjected to epimerization by treatment with NaH (2.0 mg, 0.05 mmol) in DMF (3.0 mL) at 25 °C for 24 h to give the mixture of the *trans* and *cis* isomers (1:4) as a yellow oil. R_f = 0.50 (*cis*) and 0.51 (*trans*, EtOAc/hexane, 20:80). IR (neat): $\tilde{\nu}_{max}$ = 2966, 2925, 2854, 1663, 1616, 1457, 1364, 1210, 1069, 1052 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 1:4 mixture of isomers): δ = 5.36 (s, *trans*, 2-H), 5.32 (s, *cis*, 2-H), 5.12–5.02 (m, 6 H, olefinic protons), 3.73 (s, *trans*, MeO-3), 3.71 (s, *cis*, MeO-3), 3.28 (s, 4 H), 3.25 (s, *cis*, MeO-4), 3.21 (s, *trans*, MeO-4), 2.94–2.83 (CH, m, *cis*), 2.71–2.61 (CH, m, *cis*), 2.59–2.54 (CH, m, *trans*), 2.53–2.45 (m, *cis*, 5-H), 2.45–2.35 (CH, m, *trans*), 2.35–2.23 (CH, m, *trans*), 2.12–1.89 (m, 12 H), 1.65 (s, 4 H), 1.62 (s, 3 H), 1.57 (s, 7 H), 0.96 (d, *J* = 7.0 Hz, Me-5, *trans*), 0.79 (d, *J* = 7.0 Hz, Me-5, *cis*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 1:4 mixture of isomers): δ = 199.6, 170.1, 136.8, 135.0, 131.2, 124.3, 124.1, 121.6, 103.3, 100.6, 55.9, 51.1, 47.7, 47.6, 39.9, 39.8, 38.2, 26.8, 26.6, 25.6, 24.5, 17.6, 16.2, 16.0, 9.4 ppm. HRMS: calcd. for $C_{25}H_{41}O_4$ $[M + H]^+$ 405.3005; found 405.3004.

(4*R*,5*R*,6*S*)-3-Chloro-5-farnesyl-4-hydroxy-2-methoxy-6-methylcyclohex-2-en-1-one (5b): Under nitrogen, a solution of (5*S*)-**4b** (100 mg, 0.23 mmol, mixture of *trans* and *cis* isomers, 1:4) in THF (3.0 mL) was stirred at –20 °C for 15 min, and LS-Selectride (1.0 M in THF, 0.5 mL, 0.5 mmol) was added dropwise. The mixture was stirred at –20 °C for 12 h and quenched with water (5.0 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (30 mL), dried with $MgSO_4$, and concentrated under reduced pressure to give the crude alcohol product as a mixture of diastereomers. Without further purification, this sample was dissolved in CH_2Cl_2 (5 mL). Montmorillonite K10 (acidic clay, 200 mg, 2.2 mmol) was added, and the mixture was stirred at room temperature for 10 min and then filtered. The filtrate was concentrated under reduced pressure to give a residue. Purification by column chromatography on silica gel (EtOAc/hexane, 10:90) gave (4*R*,5*R*,6*S*)-**5b** ($C_{23}H_{35}ClO_3$, 40 mg, 44 % yield for two steps) as a colorless oil. R_f = 0.18 (EtOAc/hexane, 10:90). $[\alpha]_D^{25}$ = +25.1 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3491, 2972, 2938, 2852, 1694, 1683, 1380, 1223, 1010, 771 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.14–5.03 (m, 3 H), 4.48 (d, *J* = 4.3 Hz, 1 H), 3.78 (s, 3 H), 2.58 (qd, *J* = 7.3, 4.3 Hz, 1 H), 2.38 (dt, *J* = 15.0, 7.3 Hz, 1 H), 2.30–2.22 (m, 1 H), 2.16–1.93 (m, 10 H), 1.66 (s, 3 H), 1.64 (s, 3 H), 1.58 (s, 6 H), 1.25 (d, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.6, 148.2, 140.6, 138.0, 135.4, 131.3, 124.3, 123.8, 121.1, 72.4, 59.9, 45.2, 41.7, 39.8, 39.7, 26.7, 26.4, 25.8, 25.7, 17.7, 16.2, 16.0, 14.2 ppm. HRMS: calcd. for $C_{23}H_{35}NaClO_3$ $[M + Na]^+$ 417.2167; found 417.2160.

(4*R*,5*R*,6*S*)-5-Farnesyl-4-hydroxy-2-methoxy-6-methylcyclohex-2-en-1-one (5d):[8] Under nitrogen, a solution of (5*S*)-**4d** (100 mg, 0.25 mmol, mixture of *trans* and *cis* isomers, 1:4) in THF (3.0 mL) was stirred at –20 °C for 15 min, and LS-Selectride (1.0 M in THF, 0.5 mL, 0.5 mmol) was added dropwise. The mixture was stirred at –20 °C for 12 h and quenched with water (5 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL), and the combined extracts were washed with brine (30 mL), dried with $MgSO_4$, and concentrated under reduced pressure to give the crude alcohol (*S*)-**5d** as a mixture of diastereomers. Without further purification, this sample was dissolved in CH_2Cl_2 (5 mL). Montmorillonite K10 (acidic clay, 200 mg, 2.17 mmol) was added, and the mixture was stirred at room temperature for 10 min and then filtered. The filtrate was concentrated under reduced pressure to give a residue. Purification by column chromatography on silica gel (EtOAc/hexane, 10:90) gave (4*R*,5*R*,6*S*)-**5d** ($C_{23}H_{36}O_3$, 27 mg, 30 % yield for two steps) as a colorless oil. R_f = 0.28 (EtOAc/hexane, 30:70). $[\alpha]_D^{25}$ = +21.7 (*c* = 0.525, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3474, 2972, 2926, 2855, 1687, 1631, 1451, 1378, 1220, 1080, 772 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.68 (d, *J* = 3.7 Hz, 1 H), 5.17 (br. s, 1 H.), 5.06 (d, *J* = 6.7 Hz, 2 H), 4.68–4.76 (m, 1 H), 3.62 (s, 3 H), 2.59 (dd, *J* = 7.3, 3.7 Hz, 1 H), 2.29 (d, *J* = 4.3 Hz, 2 H), 2.10–1.91 (m, 10 H), 1.66 (s, 3 H), 1.61 (s, 3 H), 1.58 (s, 6 H), 1.22 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.7, 150.6, 137.5, 135.4, 131.3, 124.3, 123.8, 122.5, 115.2, 69.5, 55.1, 45.4, 39.7, 39.6, 29.7, 26.7, 26.4, 25.7, 24.1, 17.7, 16.2, 16.0, 13.8 ppm. HRMS: calcd. for $C_{23}H_{36}NaO_3$ $[M + Na]^+$ 383.2557; found 383.2556.

(4*R*,5*R*,6*R*)-5-Farnesyl-4-hydroxy-2,3-dimethoxy-6-methylcyclohex-2-en-1-one [1a, (+)-Antroquinonol]:[1] A mixture of (4*R*,5*R*,6*S*)-**5b** (40 mg, 0.1 mmol) and K_2CO_3 (41 mg, 0.3 mmol) in MeOH (2.0 mL) was stirred at room temperature for 12 h for the inversion of the configuration at C-6 and substitution of the chloro group with a methoxy group. The mixture was quenched with saturated aqueous NH_4Cl (5 mL) and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/CH_2Cl_2, 2:98) to give (+)-antroquinonol ($C_{24}H_{38}O_4$, 31 mg, 80 % yield) as a yellow oil. R_f = 0.56 (EtOAc/hexane, 25:75). $[\alpha]_D^{25}$ = +45.0 (*c* = 0.48, $CHCl_3$); ref.[1] $[\alpha]_D^{18}$ = +72.7 (*c* = 0.28, $CHCl_3$); ref.[4] $[\alpha]_D^{20}$ = +52.0 (*c* = 0.364, MeOH); ref.[6] $[\alpha]_D^{25}$ = +44.6 (*c* = 1.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.14 (t, *J* = 7.3 Hz, 1 H), 5.07 (t, *J* =

6.7 Hz, 2 H), 4.34 (d, *J* = 3.1 Hz, 1 H), 4.05 (s, 3 H), 3.65 (s, 3 H), 2.52 (qd, *J* = 6.7, 11.0 Hz, 1 H), 2.22 (t, *J* = 7.3 Hz, 2 H), 2.12–1.92 (m, 8 H), 1.74 (dtd, *J* = 10.9, 7.5, 3.4 Hz, 1 H), 1.66 (s, 3 H), 1.64 (s, 3 H), 1.58 (s, 6 H), 1.16 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.1, 160.4, 138.1, 135.9, 135.4, 131.1, 124.3, 123.9, 121.0, 68.0, 60.6, 59.2, 43.4, 40.3, 39.8, 39.7, 27.0, 26.8, 26.4, 25.7, 17.7, 16.1, 16.0, 12.3 ppm. HRMS: calcd. for $C_{24}H_{38}O_4$ $[M + H]^+$ 391.2848; found 391.2854.

(4*R*,5*R*,6*R*)-5-Farnesyl-4-hydroxy-2-methoxy-6-methylcyclohex-2-en-1-one [1d, (+)-Antroquinonol D]:[5] A mixture of (4*R*,5*R*,6*S*)-**5d** (36 mg, 0.1 mmol) and K_2CO_3 (41 mg, 0.3 mmol) in MeOH (2.0 mL) was stirred at room temperature for 12 h for the inversion of the configuration at C-6. The mixture was purified by column chromatography on silica gel (EtOAc/CH_2Cl_2, 5:95) to give (+)-antroquinonol D ($C_{23}H_{36}O_3$, 30 mg, 82 % yield) as a yellow oil. R_f = 0.36 (EtOAc/hexane, 30:70). $[\alpha]_D^{24}$ = +50.0 (*c* = 0.25, $CHCl_3$); ref.[5] $[\alpha]_D^{23}$ = +52.2 (*c* = 0.5, MeOH); ref.[7a] $[\alpha]_D^{24}$ = +48.6 (*c* = 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ = 5.91 (d, *J* = 6.1 Hz, 1 H), 5.21 (t, *J* = 7.0 Hz, 1 H), 5.13–5.04 (m, 2 H), 4.54–4.45 (m, 1 H), 3.59 (s, 3 H), 2.73–2.61 (m, 1 H), 2.32–2.21 (m, 1 H), 2.21–2.00 (m, 8 H), 2.00–1.91 (m, 2 H), 1.85–1.76 (m, 1 H), 1.66 (s, 3 H), 1.62 (s, 3 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.16 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 198.8, 152.1, 138.1, 136.0, 132.1, 125.5, 125.4, 123.3, 116.7, 65.1, 55.3, 47.5, 43.4, 40.9, 40.8, 28.1, 27.8, 27.4, 25.9, 17.8, 16.2, 16.1, 13.1 ppm. HRMS: calcd. for $C_{23}H_{36}NaO_3$ $[M + Na]^+$ 383.2562; found 383.2556.

CCDC 1456966 (for **3g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Keywords: Asymmetric synthesis · Natural products · Enantioselectivity · Michael addition · Quinones

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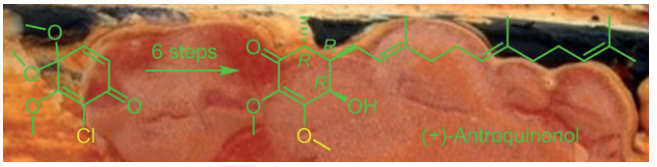
Michael Addition



The electron-withdrawing chloro group has been employed as a surrogate of a methoxy substituent to facilitate the enantioselective Michael reaction, which is the key strategic step in the short and efficient synthesis of (+)-antroquinonol.

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