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A Concise Synthesis of (±)-Antroquinonol with Unusual Scaffold of 4-Hydroxy-2-cyclohexenone

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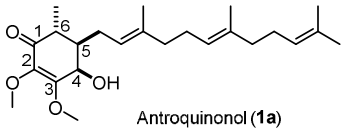
† Electronic supplementary information (ESI) available: Synthetic procedure, compound characterization, ^{1}H, ^{13}C and 2D NMR spectra, as well as crystal data. See DOI:

Abstract.

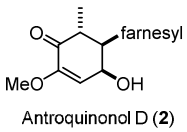
Antroquinonol, first isolated from an endemic mushroom *Antrodia cinnamomea*, is an anticancer compound with a unique core structure of 4-hydroxy-2,3-dimethoxycyclohex-2-enone carrying methyl, farnesyl and hydroxyl substituents in the 4,5-*cis*-5,6-*trans* configuration. A concise synthesis of (±)-antroquinonol is accomplished in 7 steps from 2,3,4-trimethoxyphenol, which is oxidized in methanol to a highly electron-rich substrate of 2,3,4,4-tetramethoxycyclohexadienone for Michael reaction with dimethylcuprate as the strategic key step, followed by alkylation, reduction and epimerization to incorporate the required substituents at three contiguous stereocenters.

Introduction

Antrodia cinnamomea is an indigenous rare mushroom which only parasitizes the camphor tree, *Cinnamomum kanehirai* Hayata that grows in the mountain ranges at high altitude in Taiwan. This fungus is used as a precious traditional Chinese herbal prescription because it contains many bioactive constituents, such as terpenoids, flavonoids, polyphenolics, polysaccharides and benzoquinone derivatives.[1–3] Antroquinonol (**1a**) is first isolated from the cultured mycelia of *A. cinnamomea* in low quantity.[1–3] Unlike ubiquinones, antroquinonol has a sensitive core structure of 4-hydroxycyclohex-2-enone rarely found in nature. Elimination of water molecule or oxidation of this core structure will lead to facile aromatization. The natural analogous compounds of 4-hydroxycyclohexenone type include antroquinonol B[4–6] with modification at the fifteen-carbon substituent, 4-acetylantroquinonol B,[6] and antroquinonol D (**2**)[7] having the structure without a methoxy substituent at the C-3 position. A function of antroquinonol is to block Ras and Rho processing via inhibition of isoprenyltransferases to cause associated cell death.[8] This anticancer agent is currently under clinical evaluation in patients with non-small cell lung cancer.[9, 10]



Antroquinonol (**1a**)



Antroquinonol D (**2**)

The relative 4,5-*cis*-5,6-*trans* configuration of antroquinonol has been determined by spectroscopic methods,[2] and the absolute (4*R*,5*R*,6*R*)-configuration for natural (+)-antroquinonol is recently established by a total synthesis.[11] The core structure of antroquinonol is an electron-rich dimethoxy-substituted cyclohex-2-enone ring that contains methyl, farnesyl and hydroxyl substituents to construct three contiguous stereocenters. As antroquinonol and the related bioactive compounds are only obtained in low quantity from natural source, organic synthesis is an alternative to obtain these materials.

Chen and coworkers have succeeded in a conjugate addition of malonate ion to 4,4-dimethoxycyclohexadienone (**4a**) (Figure 1).[12] However, Chen's synthesis[11] of antroquinonol is conducted by another pathway that requires a long linear synthetic sequence (over 20 steps) because they could not carry out the Michael reaction of 2,3,4,4-tetramethoxy-6-methylcyclohexa-2,5-dienone (**4b**) with various organometallic reagents.[12]

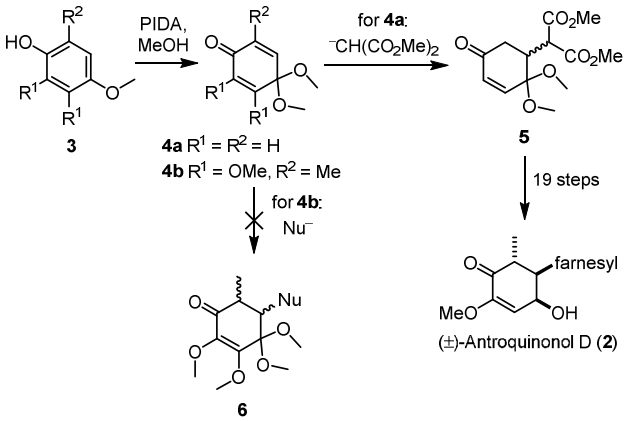


Figure 1. Chen's synthesis[12] of (±)-antroquinonol D via Michael reaction of **4a**. The Michael reactions of cyclohexadienone **4b** fail when nucleophile (Nu^-) is an enolate generated from dimethyl malonate, an organocuprate reagent prepared from ethyl bromoacetate, or a combined reagent of organozinc with $Cu(OTf)_2$. PIDA represents an iodine(III) oxidizing reagent phenyliodine diacetate.

We conceived that realization of the Michael reaction of 2,3,4,4-tetramethoxycyclohexa-2,5-dienone (**9**) with a methylmetal reagent under appropriate conditions would provide a straightforward route to antroquinonol. In our retrosynthetic analysis (Figure 2), the intermediate enolate ion might be trapped by alkylation with farnesyl bromide from the less hindered face to give *trans*-**8** in a stereoselective manner. The carbonyl reduction of *trans*-**8** with an appropriate hydride reagent could occur at the less hindered face to afford **7a**, and the subsequent acid-catalyzed hydrolysis of the dimethyl ketal group would culminate in the target compound **1a**. Compared with benzoquinone analogs, using benzoquinone-monoketal **9** in preparation of the cyclohexene-1,4-dione monoketal **8** is advantageous to prohibit facile aromatization after the Michael reaction and provide a distinct chemical environment for the regioselective transformation. We thus undertook a study of this attractive approach to synthesize antroquinonol in a very short sequence.

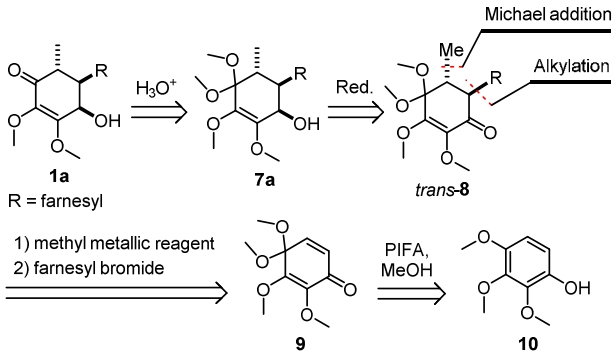


Figure 2. Retrosynthetic analysis of antroquinonol (**1a**). PIFA: phenyliodine bis(trifluoroacetate).

Results and discussion

According to the previously reported procedure,[13] trimethoxybenzaldehyde was subjected to Baeyer–Villiger oxidation with hydrogen peroxide in the presence of sulfuric acid, followed by *in situ* hydrolysis of the formate intermediate, to give trimethoxyphenol **10** in 95% yield. Oxidation of phenol **10** with PIFA in anhydrous MeOH afforded the desired product of benzoquinone-monoketal **9** in 81% yield.[14]

Although Michael additions of 4,4-disubstituted cyclohexadienones with alkylmetal reagents[15–17], dialkylmalonate[12, 18] and acyl-nickel complexes[19] have been reported, there is no precedent for Michael reaction of a highly electron-rich system such as **9** with four electron-donating methoxy groups. In our initial attempt (Table 1, entry 1), the dimethylcuprate reagent was prepared from Grignard reagent MeMgBr (2 equiv) and CuBr•Me_2S (1 equiv) at –78 ^oC in THF solution, and then reacted with compound **9** for 17 h.

Instead of the desired Michael addition, the reaction tended to give an aromatic compound **10** and a 1,2-addition product, which was hydrolyzed on silica gel column to yield **11** (Figure 3). Formation of **10** might involve electron-transfer of the cuprate reagent to reduce the cyclohexenedione **9**,[20] followed by elimination of a molecule of MeOH to assume aromaticity. Raising the reaction temperature to –60 ^{o}C (Table 1, entry 2), the desired 1,4-adduct **12** was obtained in low yield (13%) along with significant amounts of **10** and **11**.

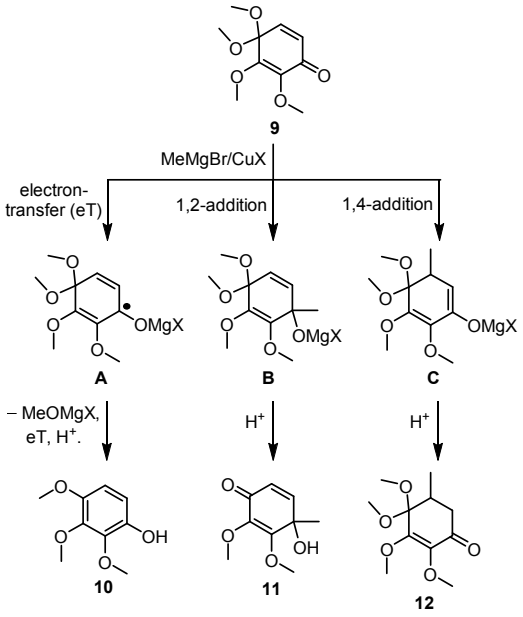
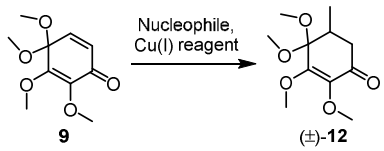


Figure 3. Three reaction modes of cyclohexadienone **9** with organocuprate reagent MeMgBr/CuX. The electron-transfer pathway led to phenol **10**, which can be recycled to compound **9** by oxidation with PIFA in methanol. The 1,2-addition at carbonyl led to the product **11** due to hydrolysis on silica gel chromatography. The 1,4-addition at β-carbon gave the Michael adduct **12**.

We then investigated the effects of reaction temperature, solvents and various methyl metallic reagents in the Michael reaction of compound **9**. The yield of 1,4-adduct **12** increased to 30% as the reaction temperature increased from –60 ^{o}C to –50 ^{o}C (Table 1, entry 3). No 1,2-adduct was observed, presumably the kinetic 1,2-addition product might be reverted to the thermodynamically favored 1,4-adduct at –50 ^{o}C.[21] However, the yields of 1,4-adduct **12** at a reaction temperature higher than –50 ^{o}C also decreased (Table 1, entries 4 and 5), presumably due to the instability of the cuprate reagent. When MeMgBr was replaced by MeLi, MeMgCl or MeMgI for preparation of cuprate reagent, the yield of 1,4-adduct **12** deteriorated (Table 1, entries 6–8). No reaction occurred by using Me_2Zn/CuBr•Me_2S or Me_3Al/CuBr•Me_2S as the nucleophilic agent (Table 1, entries 9 and 10). Less 1,4-adduct **12** was obtained when the reaction was performed in *t*-BuOMe, Et_2O or toluene instead of THF solution (Table 1, entries 11–13). After screening various copper(I) salts (Table 1, entries 14–20), CuCl was found to be the best choice for preparation of cuprate reagent with MeMgBr to achieve the conjugate addition of compound **9** (THF, –50 ^{o}C, 7 h), giving the desired product **12** in 50% yield (Table 1, entry 14). Under such reaction conditions, exclusive regioselectivity for 1,4-addition was realized without formation of 1,2-adduct. Though the electron-transfer process could not be avoided, the side product of trimethoxyphenol **10** could be oxidized with PIFA in methanol to regenerate the starting material of benzoquinone-monoketal **9**.

Table 1. Michael reaction of cyclohexadienone **9** with methyl metallic reagent, giving cyclohexenone **12**.



entry	nucleophile (2 equiv)	Cu(I) reagent (1 equiv)	solvent	temp. (°C)	time (h)	yield of **12** (%)
1	MeMgBr	CuBr•Me_2S	THF	–78	17	0[a,b]
2	MeMgBr	CuBr•Me_2S	THF	–60	7	13[a,b]
3	MeMgBr	CuBr•Me_2S	THF	–50	7	30[b]
4	MeMgBr	CuBr•Me_2S	THF	–30	7	18
5	MeMgBr	CuBr•Me_2S	THF	–20	15	5
6	MeLi	CuBr•Me_2S	THF	–50	12	0[b]
7	MeMgCl	CuBr•Me_2S	THF	–50	12	10[b]
8	MeMgI	CuBr•Me_2S	THF	–50	15	2[b]
9	Me_2Zn	CuBr•Me_2S	THF	–50	50	NR[c]
10	Me_3Al	CuBr•Me_2S	THF	–50	43	NR[c]
11	MeMgBr	CuBr•Me_2S	*t*-BuOMe	–50	25	10
12	MeMgBr	CuBr•Me_2S	Et_2O	–50	30	18

13	MeMgBr	CuBr•Me_2S	PhMe	–50	38	8
14	**MeMgBr**	**CuCl**	**THF**	**–50**	**7**	**50**[b]
15	MeMgBr	CuBr	THF	–50	12	10[b]
16	MeMgBr	CuI	THF	–50	15	20[b]
17	MeMgBr	CuOAc	THF	–50	8	23[b]
18	MeMgBr	CuSPh	THF	–50	18	20[b]
19	MeMgBr	CuTC[d]	THF	–50	20	28[b]
20	MeMgBr	CuCN	THF	–50	21	25[b]

[a] Compound **11** was obtained in 18–25% yields as the 1,2-addition product hydrolyzed on silica gel column chromatography.

[b] The major product was phenol **10** (50–80% yields) derived from an electron-transfer pathway.

[c] No reaction occurred, and the starting material **9** was recovered.

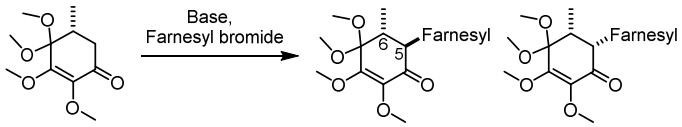
[d] CuTC represents copper(I) thiophene-2-carboxylate.

In our original design (Figure 2), the alkylation reaction is anticipated to occur in a stereoselective manner to give **8** in the *trans*-configuration. Indeed, ketone **12** was treated with lithium diisopropylamide (LDA) in THF solution to generate the lithium enolate, which reacted with farnesyl bromide at –78 ^{o}C to afford *trans*-**8** product exclusively (Table 2, entry

1), albeit in a low conversion (30%). Alternatively, compound **12** was treated with lithium hexamethyldisilazide (LHMDS), sodium hexamethyldisilazide (NHMDS) or potassium hexamethyldisilazide (KHMDS) to generate the enolate ion (Table 2, entries 2–6), which reacted smoothly with farnesyl bromide in high conversion (60–95%) to give the alkylation product **8** (as a mixture of *trans* and *cis* isomers) after a prolonged reaction time (12 h). The *trans*-**8** isomer showed the proton signal of 6-methyl at δ_H 0.94 (d, J = 6.5 Hz) and two methine protons on the cyclohexene ring at δ_H 2.69–2.51 (m). In comparison, the 6-methyl of *cis*-**8** isomer appeared at a relatively high field of δ_H 0.78 (d, J = 7.0 Hz) presumably due to the shielding effect of the adjacent farnesyl substituent. The two methine protons exhibited as distinct signals at δ_H 2.40 (H-6,qd, J = 7.0, 4.4 Hz) and 2.80 (H-5, dt, J = 9.7, 4.4 Hz). The alkylation reaction utilizing NaH or *t*-BuOK as the base (Table 2, entries 7 and 8) only produced *cis*-**8** isomer in low yields (< 35%). Unlike cyclohexanones, stereochemical outcome of the alkylation reactions in the cyclohex-2-en-1-one system appeared to be less predictive. From the data shown in Table 2, we assumed that epimerization of **8** might occur at room temperature to favor the *cis* isomer. When a mixture of *trans*-**8** and *cis*-**8** isomers (1:1) was treated with NaH (0.1 equiv) in DMF solution at room temperature for a period of 24 h, *cis*-**8** actually became the predominant isomer (75%) over *trans*-**8** (25%). This result supports that *cis*-**8** is indeed the thermodynamically favored isomer.

It is an attractive strategy to perform three-component coupling reaction in a one-pot operation.[22, 23] As shown in our original design (Figure 2), Michael addition of a methyl metallic reagent to cyclohexadienone **9** would generate an enolate ion, which could be trapped *in situ* by farnesyl bromide to afford compound **8**. Unfortunately, all our attempts for the consecutive α-alkylation failed presumably due to the instability of the enolate ion.

Table 2. Alkylation of ketone **12** with farnesyl bromide, giving compound **8**.[a]



(±)-**12** (±)-*trans*-**8** (±)-*cis*-**8**

entry	base	solvent	temp. (°C)	time (h)	conversion (%) of **12**	*trans*/*cis* ratio of **8**
1	LDA	THF	–78→25	5	30	1:0
2	**LHMDS**	**THF**	**–78→25**	**12**	**95**	**1:1**
3	LHMDS	PhMe	–78→25	12	67	1:1
4	LHMDS	Et_2O	–78→25	12	75	1:2
5	NHMDS	THF	–78→25	12	60	1:1
6	KHMDS	THF	–78→25	12	65	1:1
7	NaH	THF	0→25	12	20	0:1
8	*t*-BuOK	*t*-BuOH	0→25	12	34	0:1

[a] Ketone **12** was treated with a base (2 equiv) at –78 °C (entries 1–6) or 0 °C (entries 7 and 8) for 2 h to generate the corresponding enolate ion. After addition of farnesyl bromide (2 equiv), the mixture was stirred at the indicated temperature for a period of 5–12 h. The ratio of *trans*-**8** to *cis*-**8** was estimated by the ^{1}H NMR spectral analysis.

In general, the trajectory of H^- approach in reduction of carbonyl should determine the orientation of the resulting hydroxyl group. The delicate selection between axial and equatorial approaches to cyclohexenone **8** might be related to the torsional effect and 1,3-diaxial interactions. At the first glance, we thought the carbonyl reduction of *trans*-**8** would occur by H^- attack from the less hindered face to afford **7a** in the 4,5-*cis* configuration (Figure 4). In contrast to our prediction, the reduction of *trans*-**8** with $LiAlH_4$ in THF at –78 °C gave exclusively the all-*trans* product **7b** (Figure 4), which was subjected to an acid-catalyzed hydrolysis to afford **1b** and **13b** in 18% and 73% yields, respectively (Table 3, entry 1). Compound **1b** having the hydroxyl substituent at the C-4 position was derived from a direct hydrolysis (C-1 hydrolysis) of the dimethylketal group in **7b**, whereas the C-3 hydrolysis proceeded with the participation of a C-3 methoxy group to yield the 1,3-transpositional isomer **13b** having the carbonyl group adjacent to the hydroxyl substituent. The C-3 hydrolysis was a preferable pathway, presumably due to facilitation by the stereoelectronic effect and participation of the adjacent hydroxyl group,[12, 24] though the real

reaction mechanism would be accounted on advanced computations and experimental evidence.

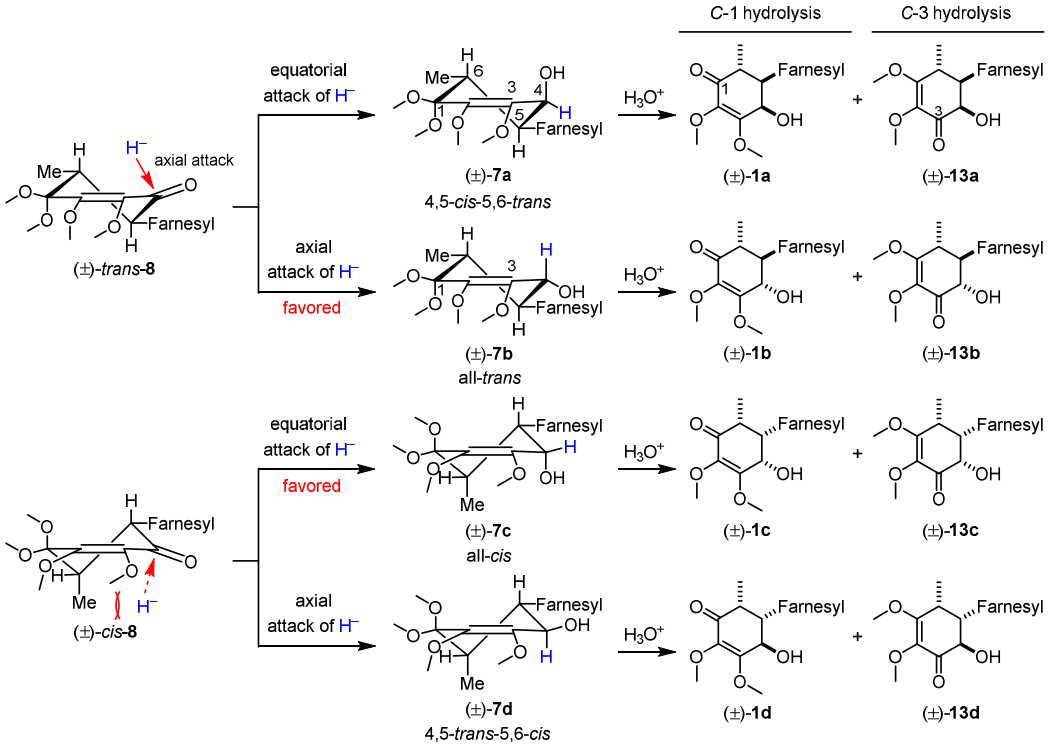
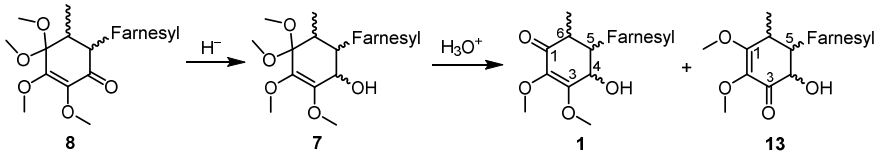


Figure 4. Stereo- and regiochemistry in reduction of ketone **8**. Subsequent hydrolysis of the reduction product **7** gave compound **1** and the 1,3-transpositional isomer **13**.

By a similar procedure, a 1:1 mixture of *trans*-**8** and *cis*-**8** was reduced with $LiAlH_4$ (Table 3, entry 2), followed by consecutive hydrolysis, to give **1b** (9%), **13b** (37%), **1c** (7%), **13c** (18%), **1d** (18%) and **13d** (2%). The all-*cis* products (**1c** and **13c**) were derived from **7c**, and the 4,5-*trans*-5,6-*cis* products (**1d** and **13d**) were derived from **7d** (Figure 4). In comparison, the axial attack of H^- (from $LiAlH_4$) onto *trans*-**8** compound, giving **7b** in

all-*trans* configuration, was favored because the equatorial approach of H^- would exert a torsional strain between farnesyl and the emerging hydroxyl group (Figure 4). In contrast, the axial attack of H^- onto *cis*-**8** compound, giving **7d** in the 4,5-*trans* configuration, was disfavored due to the steric hindrance of the methyl substituent on the axial orientation.

Table 3. Reduction of ketone **8** to alcohol **7**, followed by hydrolysis in acidic conditions, gives compounds **1** and **13**.



entry	**8**	reduction			ratio of hydrolysis products[a]							
	trans/*cis*	reagent	solvent	temp.	from **7a**		from **7b**		from **7c**		from **7d**	
				(°C)	**1a**	**13a**	**1b**	**13b**	**1c**	**13c**	**1d**	**13d**
					4,5-*cis*-5,6-*trans*		all-*trans*		all-*cis*		4,5-*trans*-5,6-*cis*	
1	1:0	$LiAlH_4$	THF	–78	0	0	1	4	0	0	0	0
2	1:1	$LiAlH_4$	THF	–78	0	0	5	20	4	10	10	1
3	1:1	*i*-Bu_2AlH	CH_2Cl_2	–78	0	0	7	18	3	11	10	1
4	1:1	$Li(Ot\text{-}Bu)_3AlH$	THF	0	0	10	3	12	4	11	7	3
5	1:1	$NaBH_4$, $CeCl_3$	MeOH	0	0	0	2	8	1	2	5	2

6	1:1	$LiEt_3BH$[b]	THF	–78	0	0	1	3	1	2	1	0
7	1:1	Li(*s*-Bu)$_3$BH[b]	THF	–40	0	1	1	3	2	3	0	0
8	1:1	Li(siamyl)$_3$BH[b]	THF	–40	0	0	1	4	2	3	0	0
9	**1:3**	**Li(siamyl)$_3$BH[b]**	**THF**	**–40**	**0**	**0**	**1**	**4**	**6**	**9**	**0**	**0**

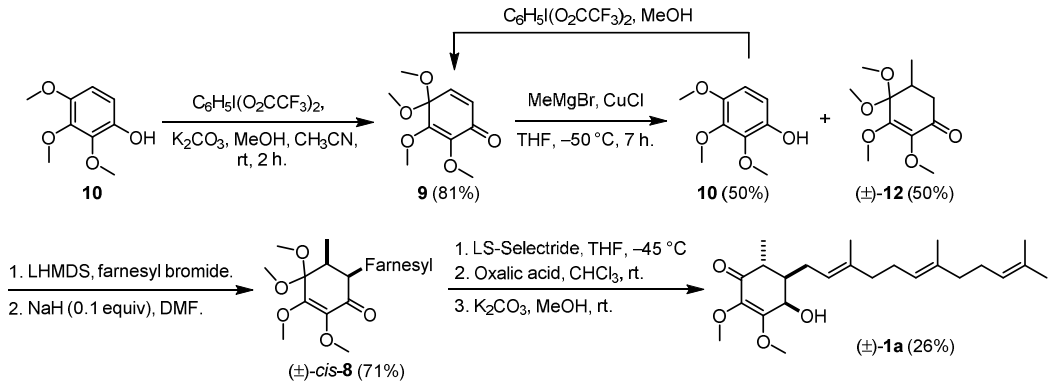
[a] The ratio was determined by the weights of isolated products.

[b] These commercially available reagents have the trade names Super-Hydride ($LiEt_3BH$), L-Selectride [Li(*s*-Bu)$_3$BH] and LS-Selectride [Li(siamyl)$_3$BH].

To our disappointment, this two-step process did not yield the desired antroquinonol (**1a**) as that predicted in the retrosynthetic analysis (Figure 2). To render the reduction of *trans*-**8** by H^- attack from the equatorial direction to obtain **7a** in the 4,5-*cis* configuration, we examined other reducing agents including *i*-Bu_2AlH, Li(O*t*-Bu)$_3$AlH, $NaBH_4/CeCl_3$, $LiEt_3BH$, Li(*s*-Bu)$_3$BH and Li(siamyl)$_3$BH (Table 3, entries 3–9). Among them, only the bulky reducing agents Li(O*t*-Bu)$_3$AlH and Li(*s*-Bu)$_3$BH could deliver H^- to *trans*-**8** from the equatorial direction to furnish **7a** (Table 3, entries 4 and 7). However, the subsequent treatment of **7a** with oxalic acid only proceeded with the C-3 hydrolysis to afford **13a** without formation of antroquinonol (**1a**). Since the axial attack of H^- to *trans*-**8** was a favorable process to obtain **1b** in all-*trans* configuration, we considered performing Mitsunobu reaction[25, 26] of **1b** for the

stereochemical inversion of its hydroxyl group. The desired Mitsunobu reaction of **1b** did not work, presumably due to the steric congestion of this molecule.

Realizing that *trans*-**8** was not a suitable precursor for the synthesis of antroquinonol, we switched to utilize *cis*-**8** as an alternative substrate. In this study, we learned that *cis*-**8** was actually the thermodynamically favored isomer over *trans*-**8**. Reduction of *cis*-**8** with $Li(siamyl)_3BH$ was the best way to obtain **7c** (Table 3, entries 8 and 9). Finally, the all-*cis* compound **1c** was obtained from **7c** by the acid-catalyzed C-1 hydrolysis. The subsequent treatment of **1c** with a base K_2CO_3 in MeOH solution rendered epimerization at the C-6 position to yield (±)-antroquinonol (Scheme 1). The ^1H and ^{13}C NMR spectra of the synthetic (±)-**1a** were in full agreement with that of natural (+)-antroquinonol (Figures S1 and S2 in Supplementary Information (ESI)).



Scheme 1. Synthesis of (±)-antroquinonol

In summary, our synthesis of (±)-antroquinonol (Scheme 1) started with a Michael reaction of cyclohexadienone **9** to give cyclohexenone **12** (50%). The other product **10** (50%), derived from an electron-transfer process, could be effectively reverted to the starting material **9** by oxidation with PIFA in methanol (80%). Upon treatment of **12** with LHMDS (Table 2, entry 2), the enolate ion was generated and subjected to α-alkylation with farnesyl bromide to afford **8** as a mixture of the *trans* and *cis* isomers, which proceeded with a base-catalyzed epimerization to end up with *cis*-**8** in 71% overall yield. The all-*cis* isomer **1c**, obtained from reduction of *cis*-**8** with Li(siamyl)$_3$BH and the subsequent C-1 hydrolysis (Table 3, entry 8), underwent a base-catalyzed epimerization to give (±)-antroquinonol in the 4,5-*cis*-5,6-*trans* configuration. We thus accomplished a concise synthesis of (±)-antroquinonol from trimethoxyphenol **10** by a 7-step sequence in 7.4% overall yield.

Through our present synthetic method, all possible isomers **1a**–**1d** and **13a**–**13d** differing in regio- or stereochemistry were obtained. Their structures were determined by the MS and NMR (^{1}H, ^{13}C, COSY, NOESY, and HSQC) analyses. Table 4 lists the chemical shifts and coupling constants of characteristic proton and carbon resonances. The carbonyl signals of **1a**–**1d** from C-1 hydrolysis consistently occurred at lower fields (δ_C 197–199) than their C-3 hydrolysis products **13a**–**13d** (at δ_C 194–196), whereas the difference in proton signals was less diagnostic.

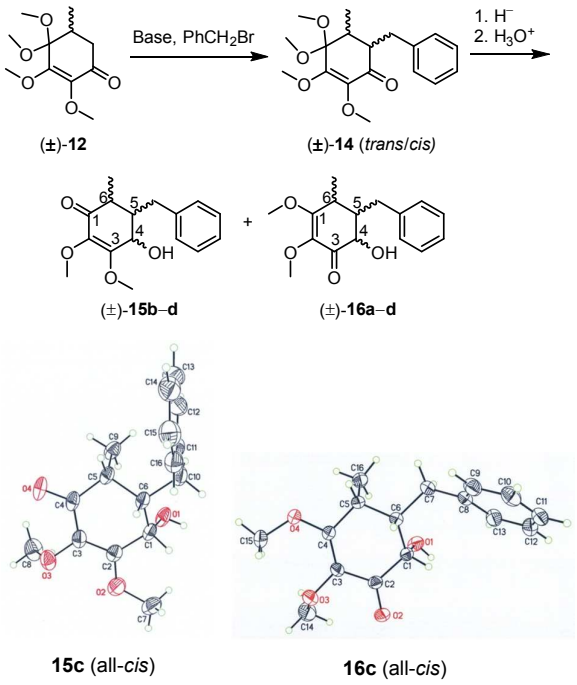
Table 4. Selected ^{1}H and ^{13}C NMR spectral data.[a]

compound	H-4	H-6	Me-6	C-1	C-4	C-6	$\underline{C}H_3$-6
1a	4.34 (d, 3.1)	2.52 (qd, 6.7, 11.0)	1.16 (d, 6.7)	197.1	68.0	40.3	12.3
1b	4.25 (d, 8.5)	2.24–2.17 (m)	1.19 (d, 6.7)	197.1	69.2	42.0	13.1
1c	4.40 (br s)	2.46 (qd, 7.3, 4.3)	1.23 (d, 7.3)	199.2	69.7	44.1	14.8
1d	4.29 (d, 4.4)	2.88 (qd, 6.8, 3.8)	1.08 (d, 6.8)	197.6	69.6	40.2	11.8
13a	4.42 (d, 5.5)	2.61 (qd, 7.3, 1.6)	1.29 (d, 7.3)	194.9	70.8	34.6	16.0
13b	3.84 (d, 12.5)	2.56–2.40 (m)	1.19 (d, 7.0)	196.2	72.2	35.3	15.4
13c	4.12 (d, 2.0)	2.86 (qd, 7.0, 4.5)	1.20 (d, 7.0)	195.5	75.3	37.1	15.0
13d	3.91 (d, 12.2)	2.62–2.57 (m)	1.11 (d, 7.3)	195.7	71.6	34.4	11.9

[a] Chemical shifts (δ) are given in parts per million (ppm) relative to δ_H 7.24 and δ_C 77.0 (central line of triplet) for $CHCl_3$ and $CDCl_3$, respectively. Data in parenthesis are coupling constants (*J*) given in Hz.

To further support the structural assignments, we also carried out the alkylation reactions of **12** with benzyl bromide to give *trans*-**14** and *cis*-**14**, which were subsequently reduced and hydrolyzed to afford compounds **15b**–**15d** and **16a**–**16d** (Scheme 2), by the procedures similar to that for transformation of *trans*-**8**/*cis*-**8** to **1b**–**1d** and **13a**–**13d**. A base-promoted

epimerization of the all-*cis* compound **15c** yielded **15a**, which is related to antroquinonol (**1a**) in the 4,5-*cis*-5,6-*trans* configuration.



Scheme 2. Synthesis of benzyl analogs **15a**–**d** and the 1,3-transpositional isomers **16a**–**d**. The X-ray crystal structures of all-*cis* isomers (±)-**15c** and (±)-**16c** are shown. The structural assignments of their counterparts (±)-**1c** and (±)-**13c** bearing farnesyl substituent, in lieu of the benzyl group, are supported by the crystal structures of (±)-**15c** and (±)-**16c** in combination with the detailed NMR analyses (^{1}H, ^{13}C, COSY, NOESY, HSQC) and mechanistic rationale.

Attempts to obtain the single crystal of antroquinonol have not been realized, presumably due to high flexibility of the farnesyl substituent. Fortunately, **15b**, **15c**, **15d**, **16b** and **16c** were crystalline compounds suitable to the X-ray diffraction analyses for rigorous structural elucidation (see SI). The pairs of the farnesylated and benzylated compounds (**1a**/**15a**, **1b**/**15b**, **1c**/**15c**, **1d**/**15d**, **13a**/**16a**, **13b**/**16b**, **13c**/**16c** and **13d**/**16d**) all exhibited good correlations in the ^{1}H and ^{13}C NMR spectra (see SI). The stereochemical relationship was supported by their NOESY spectra (see SI). For example, H-6 (at δ_H 2.52) in antroquinonol (**1a**) displayed an NOE correlation with the methylene protons (at δ_H 2.22) of farnesyl substituent, indicating their orientation on the same face of cyclohexene ring. In a similar manner, H-5 (at δ_H 2.00) of **15a** showed an NOE correlation with Me-6 at δ_H 1.25, consistent with the 5,6-*trans* configuration. Furthermore, isomers in each series of **1a**–**d**, **13a**–**d**, **15a**–**d** and **16a**–**d** exhibited the same eluting order on silica-gel thin-layer chromatography. Accordingly, the least polar **b**-isomers were eluted out first, followed by **a**-, **d**- and **c**-isomers.

Conclusion

In our present study, we completed a concise synthesis of (±)-antroquinonol (**1a**) in 7 steps from the readily available starting material of 2,3,4-trimethoxyphenol, which was oxidized in methanol to give 2,3,4,4-tetramethoxycyclohexadienone (**9**). Michael reaction of **9** along with the subsequent alkylation and reduction reactions were applied to establish three

contiguous stereocenters on the skeleton of benzoquinone-monoketal. This study demonstrates the first example for Michael reaction of **9** which is a highly electron-rich cyclohexadienone carrying four electron-donating methoxy substituents. Besides **1a**–**d**, their transpositional isomers **2a**–**d** were obtained as a new chemical entity for potential evaluation of bioactivities.[27] We also prepared the analogous compounds **15a**–**d** and **16a**–**d** having benzyl substituent at the C-5 position. Their structures were rigorously established by meticulous NMR analyses with the assistance of X-ray diffractions of some crystalline compounds. By comparison of ^{1}H and ^{13}C NMR spectra, the structures of **1a**–**d** and **13a**–**d** were also unambiguously elucidated by correlation with their counterpart **15a**–**d** and **16a**–**d**. These structural correlations were in agreement with mechanistic rationale of the reaction consequences. Therefore, natural (+)-antroquinonol was confirmed to the structure of **1a** having the 4,5-*cis*-5,6-*trans* configuration. It is still worthy to investigate asymmetry Michael additions[28–31] of **9** and its analogs using chiral catalysis or auxiliaries. Along this line, our preliminary result indicated that asymmetric Michael reaction of 3,4,4-trimethoxycyclohexadienone with methylmetal reagent could be carried out, and the 1,4-adduct could be elaborated to an optically active antroquinonol D by a procedure similar to that delineated in Scheme 1. The asymmetric Michael reactions of other cyclohexadienone derivatives for the synthesis of optically active antroquinonol and its analogs are currently under investigation.

Experimental

General

Melting points were recorded on in open capillaries and are not corrected. Nuclear magnetic resonance (NMR) spectra were obtained on (400 MHz) or (500 MHz) spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to δ_H 7.24 / δ_C 77.0 (central line of t) for $CHCl_3/CDCl_3$. 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. Distorsionless enhancement polarization transfer (DEPT) spectra were taken to determine the types of carbon signals. The ESI–MS experiments were conducted on a high-resolution mass spectrometer.

All the reagents and solvents were reagent grade and were used without further purification unless otherwise specified. All solvents were anhydrous grade unless indicated otherwise. CH_2Cl_2 was distilled from CaH_2. All non-aqueous 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 using aqueous *p*-anisaldehyde as visualizing agent. Silica gel (0.040–0.063 mm particle size) was used for column chromatography. Flash chromatography was performed on silica gel of

60–200 μm particle size. Molecular sieves were activated under high vacuum at 220 ^{o}C over 6 hours.

Representative procedure for Michael reactions (Table 1, entry 14)

Under an atmosphere of nitrogen, a solution of CuCl (99 mg, 1.0 mmol) in THF (4 mL) was cooled to –50 °C, and MeMgBr (2.0 mmol, 2.0 mL of 1.0 M solution in THF) was added. The mixture was stirred at –50 °C for 1 h, and a solution of cyclohexadienone **9** (214 mg, 1.0 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at –50 °C for 7 h, quenched with saturated aqueous NH_4Cl (5.0 mL), and then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 0.5 M NaOH (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with elution of EtOAc/hexane (15:85) to yield a Michael addition product **12** (115 mg, 50% yield).

Representative procedure for alkylation reactions (Table 2, entry 2)

Under an atmosphere of nitrogen, lithium hexamethyldisilazide (LHMDS, 4.34 mmol, 4.3 mL of 1.0 M solution in THF) was added to a solution of cyclohexenone **12** (0.5 g, 2.17 mmol) in THF (5.0 mL) at –78 °C. The mixture was stirred for 2 h, and a solution of farnesyl bromide (1.2 g, 4.34 mmol) in THF (3.0 mL) was added at –78 ^{o}C. The dry-ice cooling bath was removed, and the mixture was allowed to warm to room temperature over a period of 5–12 h, quenched with water (5.0 mL), and then extracted with EtOAc (3 × 20 mL). The organic

phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on aluminum oxide with elution of EtOAc/ hexane (8:92) to yield the alkylation product **8** (890 mg, 95% yield) as a mixture of *trans* and *cis* isomers (1:1).

A sample of **8** (900 mg, 2.07 mmol) containing *trans* and *cis* isomers (1:1) was subjected to epimerization by treatment with NaH (8.0 mg, 0.21 mmol) in DMF (5.0 mL) at 25 °C for 24 h, giving the *trans* and *cis* isomers in a ratio of 1:3.

Representative procedures for reduction and hydrolysis (Table 3, entry 7)

Under an atmosphere of nitrogen, a solution of cyclohexenone **8** (0.9 g, 2.07 mmol) containing *trans* and *cis* isomers (1:1) in THF (5.0 mL) was stirred at –40 °C for 15 min, and L-Selectride (4.14 mmol, 4.2 mL of 1.0 M solution in THF) was added dropwise. The mixture was stirred at –40 °C for 5 h, quenched with water (5.0 mL), and then extracted with EtOAc (3 × 20 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure to give alcohol **7** as a mixture of diastereomers.

The above-prepared sample of **7**, without further purification, was dissolved in $CHCl_3$ (5.0 mL), and oxalic acid (0.2 g, 2.17 mmol) was added at room temperature. The mixture was stirred for 10 min, quenched with water (5.0 mL), and then extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel

with elution of EtOAc/hexane (15:85) to yield compounds **1b (**71 mg, 9% yield), **1c** (142 mg, 18% yield), **13a** (75 mg, 9% yield), **13b** (226 mg, 27% yield) and **13c** (214 mg, 27% yield).

Representative procedure for epimerization

Ketone **1c** (30 mg, 0.077 mmol) in the 4,5-*cis*-5,6-*cis* configuration was dissolved in MeOH (4.0 mL), and K_2CO_3 (32 mg, 0.23 mmol) was added. The mixture was stirred at room temperature for 12 h, quenched with water (5.0 mL), and then extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with elution of EtOAc/CH_2Cl_2 (5:95) to yield the isomer **1a** (antroquinonol, 25 mg, 83% yield) in the 4,5-*cis*-5,6-*trans* configuration.

2,3,4-Trimethoxyphenol (10).[13] A solution of 2,3,4-trimethoxybenzaldehyde (5.0 g, 36.7 mmol) and H_2O_2 (5.3 g of 31% aqueous solution, 48 mmol) in MeOH (50 mL) was added concentrated H_2SO_4 (0.5 mL) at room temperature. The mixture was stirred for 24 h, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with elution of EtOAc/hexane (15:85) to yield phenol **10** (6.3 g, 95% yield). $C_9H_{12}O_4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (1 H, d, J = 8.0 Hz), 6.50 (1 H, d, J = 8.0 Hz), 3.87 (3 H, br s), 3.83 (3 H, br s), 3.74 (3 H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 143.3, 142.2, 140.5, 108.7, 107.6, 61.0, 60.7, 56.4. HRMS (negative mode)

calcd for $C_9H_{11}O_4$: 183.0657, found: *m*/*z* 183.0661 $[M - H]^-$.

2,3,4,4-Tetramethoxycyclohexa-2,5-dien-1-one (9).[14] To a stirred solution containing 2,3,4-trimethoxyphenol (**7**, 2.0 g, 10.9 mmol) and powdered K_2CO_3 (3.0 g, 21.7 mmol) in anhydrous MeOH (45 mL) was added a solution of iodobenzene di(trifluoroacetate) (PIFA, 4.7 g, 10.9 mmol) in CH_3CN (22 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C to room temperature, diluted with water, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with elution of EtOAc/hexane (20:80) to yield cyclohexadienone **9** (1.9 g, 81% yield). $C_{10}H_{14}O_5$; IR ν_{max} (neat) 2994 2948, 2834, 1672, 1607, 1313, 1210, 1076, 951, 833, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.48 (1 H, d, *J* = 10.4 Hz), 6.25 (1 H, d, *J* = 10.4 Hz), 4.16 (3 H, s), 3.74 (3 H, s), 3.31 (6 H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 155.1, 140.0, 138.4, 129.9, 96.8, 60.9, 60.2, 51.1 (2 ×). HRMS calcd for $C_{10}H_{15}O_5$: 215.0919, found: *m*/*z* 215.0913 $[M + H]^+$.

5-Methyl-2,3,4,4-tetramethoxycyclohex-2-en-1-one (12). $C_{11}H_{18}O_5$; IR ν_{max} (neat) 2940, 2833, 1675, 1609, 1306, 1227, 1066, 994 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.09 (3 H, s), 3.64 (3 H, s), 3.28 (3 H, s), 3.26 (3 H, s), 2.72 (1 H, dd, *J* = 16.8, 4.3 Hz), 2.47 (1 H, td, *J* = 7.0, 4.3 Hz), 2.27 (1 H, dd, *J* = 16.8, 3.8 Hz), 0.97 (3 H, d, *J* = 7.0 Hz). ^{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. HRMS calcd for $C_{11}H_{19}O_5$: 231.1232, found: *m*/*z* 231.1234 $[M + H]^+$.

6-Farnesyl-5-methyl-2,3,4,4-tetramethoxycyclohex-2-en-1-one (8). The alkylation reaction of **12** with farnesyl bromide according to the representative procedure afforded compound **8** as a mixture of *trans* and *cis* isomers (1:1), which were inseparable on silica gel column. $C_{26}H_{42}O_5$; IR ν_{max} (neat) 2965, 2927, 2853, 1673, 1615, 1450, 1265, 1087, 1025, 970, 873, 833 cm^{-1}. ^1H NMR (1:1 isomers, 400 MHz, $CDCl_3$) δ 5.05 (6 H, d, J = 6.0 Hz, olefinic protons), 4.09 (3 H, s, *trans*), 4.05 (3 H, s, *cis*), 3.63 (6 H, s), 3.28 (3 H, s, *cis*), 3.27 (3 H, s, *trans*), 3.24 (3 H, s, *trans*), 3.22 (3 H, s, *cis*), 2.80 (1 H, dt, J = 9.7, 4.4 Hz, *cis*), 2.69–2.51 (2 H, m), 2.40 (1 H, qd, J = 7.0, 4.4 Hz, *cis*), 2.35–2.23 (3 H, m, *trans*), 2.09–1.88 (17 H, m), 1.63 (6 H, s), 1.60 (6 H, s) 1.55 (12 H, s), 0.94 (3 H, d, J = 6.5 Hz, *trans*), 0.78 (3 H, d, J = 7.0 Hz, *cis*). ^{13}C NMR (1:1 isomers, 100 MHz, $CDCl_3$) δ 196.4, 196.2, 158.8, 157.3, 145.0, 138.4, 137.2, 136.9, 135.0, 134.9, 131.2, 131.1, 124.4, 124.3, 124.2, 124.1, 124.0, 121.5, 121.4, 101.2, 101.1, 60.8, 60.7, 60.3, 60.2, 51.0, 50.9, 50.7, 49.2, 47.5, 47.0, 42.0, 39.9, 39.8, 39.7 (2 ×), 37.5, 35.7, 28.9, 26.7, 26.6, 26.5, 25.6 (2 ×), 24.5, 17.6 (2 ×), 16.1, 16.0, 15.9, 14.6, 9.4. HRMS calcd for $C_{26}H_{43}O_5$: 435.3110, found: m/z 435.3104 $[M + H]^+$.

5-Farnesyl-4-hydroxy-6-methyl-2,3-dimethoxycyclohex-2-en-1-one (1a–1d):

(4,5-*Cis*-5,6-*trans*)-isomer **1a** (antroquinonol)[2,11]: $C_{24}H_{38}O_4$; ^1H NMR (500 MHz, $CDCl_3$) δ 5.14 (1 H, t, J = 7.3 Hz), 5.07 (2 H, t, J = 6.7 Hz), 4.34 (1 H, d, J = 3.1 Hz), 4.05 (3 H, s), 3.65 (3 H, s), 2.52 (1 H, qd, J = 6.7, 11.0 Hz), 2.22 (2 H, t, J = 7.3 Hz), 2.12–1.92 (8 H, m), 1.74 (1 H, dtd, J = 10.9, 7.5, 3.4 Hz), 1.66 (3 H, s), 1.64 (3 H, s), 1.58 (6 H, s), 1.16 (3 H, d, J

= 6.7 Hz). ^{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. HRMS calcd for $C_{24}H_{38}O_4$: 391.2848, found: *m*/*z* 391.2854 $[M + H]^+$.

(4,5-*Trans*-5,6-*trans*)-isomer **1b**: $C_{24}H_{38}O_4$; IR ν_{max} (neat) 3439, 2967, 2851, 1666, 1614, 1450, 1280, 1073, 994, 791, 747 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (1 H, t, *J* = 7.3 Hz), 5.05 (2 H, t, *J* = 6.4 Hz), 4.25 (1 H, d, *J* = 8.5 Hz), 4.10 (3 H, s), 3.64 (3 H, s), 2.60 (1 H, br s), 2.58–2.51 (1 H, m), 2.24–2.17 (1 H, m), 2.17–1.89 (9 H, m), 1.84–1.77 (1 H, m), 1.65 (6 H, s), 1.57 (6 H, s), 1.19 (3 H, d, *J* = 6.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 160.3, 138.7, 135.2, 135.2, 131.3, 124.3, 124.0, 118.8, 69.2, 60.7, 60.3, 45.9, 42.0, 40.0, 39.7, 26.7, 26.5, 26.3, 25.7, 17.7, 16.3, 16.0, 13.1. HRMS calcd for $C_{24}H_{39}O_4$: 391.2848, found: *m*/*z* 391.2854 $[M + H]^+$.

(4,5-*Cis*-5,6-*cis*)-isomer **1c**: $C_{24}H_{38}O_4$; IR ν_{max} (neat) 3424, 2922, 2850, 1737, 1612, 1450, 1231, 1043, 1012, 773 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15–5.03 (3 H, m), 4.40 (1 H, br s), 4.07 (3 H, s), 3.65 (3 H, s), 2.46 (1 H, qd, *J* = 7.3, 4.3 Hz), 2.38–2.28 (1 H, m), 2.15–1.91 (11 H, m), 1.65 (3 H, s), 1.63 (3 H, s), 1.57 (6 H, s), 1.23 (3 H, d, *J* = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 160.6, 137.4, 135.3, 135.2, 131.3, 124.3, 123.9, 121.5, 69.7, 60.5, 59.6, 44.1, 40.3, 39.8, 39.7, 26.8, 26.5, 25.7, 25.6, 17.7, 16.2, 16.0, 14.8. HRMS calcd for $C_{24}H_{38}O_4$: 391.2848, found: *m*/*z* 391.2854 $[M + H]^+$.

(4,5-*Trans*-5,6-*cis*)-isomer **1d**: $C_{24}H_{38}O_4$; IR ν_{max} (neat) 3431, 2976, 2919, 2849, 1667,

1614, 1451, 1234, 1039, 969, 781, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.13–5.02 (3 H, m), 4.29 (1 H, d, J = 4.4 Hz), 4.05 (3 H, s), 3.65 (3 H, s), 2.88 (1 H, qd, J = 6.8, 3.8 Hz), 2.38 (1 H, br s), 2.13–1.90 (11 H, m), 1.65 (3 H, s), 1.57 (6 H, s), 1.54 (3 H, s), 1.08 (3 H, d, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 158.9, 137.8, 135.5, 135.2, 131.3, 124.3, 123.9, 121.2, 69.6, 60.6, 59.5, 44.8, 40.2, 39.8, 39.7, 26.7, 26.5, 25.7, 25.5, 17.7, 16.1, 16.0, 11.8. HRMS calcd for $C_{24}H_{38}O_4$: 391.2848, found: m/z 391.2854 $[M + H]^+$.

5-Farnesyl-4-hydroxy-6-methyl-1,2-dimethoxycyclohex-1-en-3-one (13a–13d):

(4,5-*Cis*-5,6-*trans*)-isomer **13a**: $C_{24}H_{38}O_4$; IR ν_{max} (neat) 3468, 2961, 2920, 1666, 1610, 1456, 1280, 1044, 994, 800, 790 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.10–4.99 (3 H, m), 4.42 (1 H, d, J = 5.5 Hz), 4.01 (3 H, s), 3.65 (3 H, s), 3.57 (1 H, s), 2.61 (1 H, qd, J = 7.3, 1.6 Hz), 2.25–2.19 (1 H, m), 2.11–1.90 (9 H, m), 1.79–1.69 (1 H, m), 1.66 (3 H, s), 1.57 (6 H, s), 1.50 (3 H, s), 1.29 (3 H, d, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 166.7, 138.0, 135.1, 133.5, 131.3, 124.3, 123.9, 121.9, 70.8, 60.6, 59.2, 44.9, 39.8, 39.7, 34.6, 26.7, 26.5, 25.7, 24.0, 17.7, 17.6, 16.1, 16.0. HRMS calcd for $C_{24}H_{38}O_4$: 391.2848, found: m/z 391.2854 $[M + H]^+$.

(4,5-*Trans*-5,6-*trans*)-isomer **13b**: $C_{24}H_{38}O_4$; IR ν_{max} (neat) 3470, 2961, 2927, 1666, 1601, 1454, 1301, 1201, 1046, 984, 963, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (1 H, t, J = 7.5 Hz), 5.05 (2 H, t, J = 6.3 Hz), 4.04 (3 H, s), 3.84 (1 H, d, J = 12.5 Hz), 3.72 (1 H, s), 3.63 (3 H, s), 2.56–2.40 (2 H, m), 2.37–2.25 (1 H, m), 2.13–1.88 (8 H, m), 1.66 (3 H, s), 1.65 (3 H,

s), 1.63–1.60 (1 H, m), 1.59 (3 H, s), 1.57 (3 H, s), 1.19 (3 H, d, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 167.4, 138.4, 135.1, 133.5, 131.3, 124.3, 124.1, 118.7, 72.2, 60.6, 60.6, 46.1, 40.1, 39.8, 35.3, 26.8, 26.4, 25.7, 25.2, 17.7, 16.3, 16.0, 15.4. HRMS calcd for $C_{24}H_{38}O_4$: 391.2848, found: m/z 391.2854 $[M + H]^+$.

(4,5-*Cis*-5,6-*cis*)-isomer **13c**: $C_{24}H_{38}O_4$; IR ν_{max} (neat) 3458, 2966, 2921, 2852, 1665, 1597, 1451, 1309, 1027, 975, 935, 775 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14–5.01 (3 H, m), 4.12 (1 H, d, J = 2.0 Hz), 4.07 (3 H, s), 3.64 (3 H, s), 3.54 (1 H, br s), 2.86 (1 H, qd, J = 7.0, 4.5 Hz), 2.25 (1 H, m), 2.10–1.89 (10 H, m), 1.66 (3 H, s), 1.58 (3 H, s), 1.56 (3 H, s), 1.55 (3 H, s), 1.20 (3 H, d, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 166.8, 135.4, 135.0, 134.3, 131.2, 124.4, 124.1, 123.5, 75.3, 60.7, 60.4, 45.1, 39.8, 39.7, 37.1, 26.7, 26.5, 25.7, 22.1, 17.7, 16.0, 16.0, 15.0. HRMS calcd for $C_{24}H_{38}O_4$: 391.2848, found: m/z 391.2854 $[M + H]^+$.

(4,5-*Trans*-5,6-*cis*)-isomer **13d**: $C_{24}H_{38}O_4$; IR ν_{max} (neat) 3450, 2967, 2920, 1666, 1600, 1450, 1280, 1073, 994, 791, 770 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08–5.05 (3 H, m), 4.05 (3 H, s), 3.91 (1 H, d, J = 12.2 Hz), 3.65 (3 H, s), 2.62–2.57 (2 H, m), 2.13–1.88 (10 H, m), 1.66 (3 H, s), 1.64 (3 H, s), 1.58 (6 H, br s), 1.11 (3 H, d, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.7, 170.2, 137.5, 135.2, 133.6, 131.3, 124.4, 123.9, 120.3, 71.6, 60.8, 59.5, 43.4, 39.8, 39.7, 34.4, 26.8, 26.4 (2 ×), 25.7, 17.7, 16.3, 16.0, 11.9. HRMS calcd for $C_{24}H_{38}O_4$: 391.2848, found: m/z 391.2854 $[M + H]^+$.

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Legends for Figures, Schemes and Tables:

Figure 1. Chen's synthesis[12] of (±)-antroquinonol D via Michael reaction of **4a**. The Michael reactions of cyclohexadienone **4b** fail when nucleophile (Nu^-) is an enolate generated from dimethyl malonate, an organocuprate reagent prepared from ethyl bromoacetate, or a combined reagent of organozinc with $Cu(OTf)_2$. PIDA represents an iodine(III) oxidizing reagent phenyliodine diacetate.

Figure 2. Retrosynthetic analysis of antroquinonol (**1a**). PIFA: phenyliodine bis(trifluoroacetate).

Figure 3. Three reaction modes of cyclohexadienone **9** with organocuprate reagent MeMgBr/CuX. The electron-transfer pathway led to phenol **10**, which can be recycled to compound **9** by oxidation with PIFA in methanol. The 1,2-addition at carbonyl led to the product **11** due to hydrolysis on silica gel chromatography. The 1,4-addition at β-carbon gave the Michael adduct **12**.

Figure 4. Stereo- and regiochemistry in reduction of ketone **8**. Subsequent hydrolysis of the reduction product **7** gave compound **1** and the 1,3-transpositional isomer **13**.

Scheme 1. Synthesis of (±)-antroquinonol

Scheme 2. Synthesis of benzyl analogs **15a**–**d** and the 1,3-transpositional isomers **16a**–**d**. The X-ray crystal structures of all-*cis* isomers (±)-**15c** and (±)-**16c** are shown. The structural assignments of their counterparts (±)-**1c** and (±)-**13c** bearing farnesyl substituent, in lieu of

the benzyl group, are supported by the crystal structures of (±)-**15c** and (±)-**16c** in combination with the detailed NMR analyses (^{1}H, ^{13}C, COSY, NOESY, HSQC) and mechanistic rationale.

Table 1. Michael reaction of cyclohexadienone **9** with methyl metallic reagent, giving cyclohexenone **12**.

Table 2. Alkylation of ketone **12** with farnesyl bromide, giving compound **8**.[a]

Table 3 Reduction of ketone **8** to alcohol **7**, followed by hydrolysis in acidic conditions, gives compounds **1** and **13**.

Table 4. Selected ^{1}H and ^{13}C NMR spectral data.[a]

Table of Contents (Graphic Abstract)