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A short synthesis of (±)-antroquinonol in an unusual scaffold of 4-hydroxy-2-cyclohexenone†

Che-Sheng Hsu, Ho-Hsuan Chou and Jim-Min Fang*

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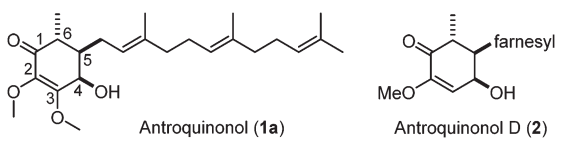
Antroquinonol, which was first isolated from a mushroom, *Antrodia cinnamomea*, found in Taiwan, is an anticancer compound with a unique core structure of 4-hydroxy-2,3-dimethoxycyclohex-2-enone carrying methyl, farnesyl and hydroxyl substituents in the 4,5-*cis*-5,6-*trans* configuration. A short synthesis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

Introduction

Antrodia cinnamomea is an indigenous, rare fungus, 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] A small quantity of antroquinonol (**1a**) is first isolated from the cultured mycelia of *A. cinnamomea*.[1–3] Unlike ubiquinones, antroquinonol has a sensitive core structure of 4-hydroxycyclohex-2-enone rarely found in nature. Elimination of a water molecule or oxidation of this core structure will lead to a simple aromatization. The natural analogous compounds of 4-hydroxycyclohexenone 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 isoprenyl transferases to cause associated cell death.[8] This anticancer agent is currently under clinical evaluation in patients with non-small cell lung cancer.[9,10]



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

†Electronic supplementary information (ESI) available: Synthetic procedure, compound characterization, ^{1}H-, ^{13}C- and 2D-NMR spectra, as well as crystal data. CCDC 1036447–1036450, 1036452 and 1036453. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob00411j

The relative 4,5-*cis*-5,6-*trans* configuration of antroquinonol has been determined previously using spectroscopic methods,[2] and the absolute (4*R*,5*R*,6*R*)-configuration for natural (+)-antroquinonol has recently been established using 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 which are used to construct three contiguous stereocenters. As antroquinonol and the related bioactive compounds are only obtained in small quantities from natural sources, organic synthesis is an alternative to obtain these compounds.

Chen *et al*. have succeeded in making a conjugate addition of dimethyl malonate to 4,4-dimethoxycyclohexadienone (**4a**) (Fig. 1).[12] However, synthesis of antroquinonol by Sulake and

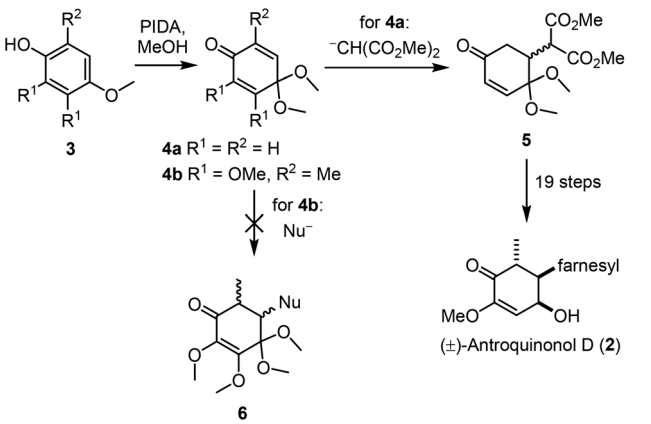


Fig. 1 Synthesis by Chen *et al*.[12] of (±)-antroquinonol D *via* a Michael reaction of **4a**. The Michael reactions of cyclohexadienone **4b** fail when the nucleophile (Nu^-) is an enolate generated from dimethyl malonate, an organocuprate reagent prepared from ethyl bromoacetate, or a combined reagent of organozinc with copper(II) triflate ($Cu(OTf)_2$). PIDA is an iodine(III) oxidizing reagent, phenyliodine diacetate.

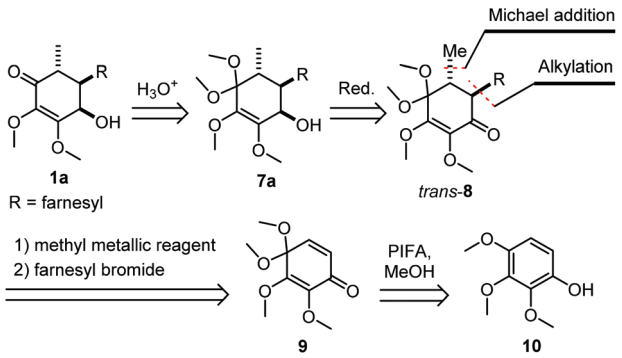


Fig. 2 Retrosynthetic analysis of antroquinonol (**1a**). PIFA: phenyliodine bis(trifluoroacetate).

Chen[11] was conducted using another pathway that required 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]

It was thought the Michael reaction of 2,3,4,4-tetramethoxycyclohexa-2,5-dienone (**9**) with a methyl metal reagent under appropriate conditions would provide a straightforward route to antroquinonol. In our retrosynthetic analysis (Fig. 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 give **7a**, and the subsequent acid catalyzed hydrolysis of the dimethyl ketal group would result in the target compound **1a**. Compared with benzoquinone analogs, using benzoquinone monoketal **9** in the preparation of the cyclohexene-1,4-dione monoketal **8** is advantageous as it prevents the easy aromatization after the Michael reaction and provides a distinct chemical environment for the regioselective transformation. Thus, a study of this attractive approach to synthesizing antroquinonol using a very short sequence of reactions was undertaken.

Results and discussion

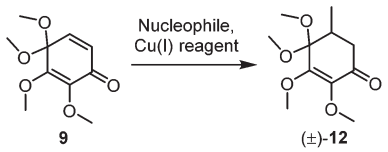
According to the previously reported procedure,[13] trimethoxybenzaldehyde was subjected to the Baeyer–Villiger oxidation with hydrogen peroxide (H_2O_2) in the presence of sulfuric acid (H_2SO_4), followed by *in situ* hydrolysis of the formate intermediate, to give trimethoxyphenol **10** with a yield of 95%. Oxidation of trimethoxyphenol **10** with PIFA in anhydrous methanol (MeOH) gave the desired product of benzoquinone-monoketal **9** with a yield of 81%.[14]

Although Michael additions of 4,4-disubstituted cyclohexadienones with alkyl metal reagents,[15–17] dialkylmalonate[12,18] and acyl-nickel complexes[19] have been reported, there is no precedent for a Michael reaction of a highly electron-rich system such as **9** with four electron-donating methoxy groups. In the initial attempt (Table 1, entry 1), the dimethylcuprate reagent was prepared from Grignard reagent methyl magnesium bromide (MeMgBr, 2 equiv.) and copper(I) bromide dimethylsulfide complex ($CuBr{\cdot}Me_2S$, 1 equiv.) at −78 °C in tetrahydrofuran (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** (Fig. 3). Formation of **10** might involve electron transfer (eT) of the cuprate reagent to reduce the cyclohexenedione **9**,[20] followed by elimination of a molecule of MeOH to give the aromaticity. Raising the reaction temperature to −60 °C (Table 1, entry 2), the desired 1,4-adduct **12** was obtained in low yield (13%) together with significant amounts of **10** and **11**.

The effects of reaction temperature, solvents and various methyl metallic reagents in the Michael reaction of compound **9** were then investigated. The yield of the 1,4-adduct **12** increased to 30% as the reaction temperature increased from −60 °C to −50 °C (Table 1, entry 3). No 1,2-adduct was observed, and it was presumed that the kinetic 1,2-addition product had reverted to the thermodynamically favored 1,4-adduct at −50 °C.[21] However, the yields of the 1,4-adduct **12** at a reaction temperature higher than −50 °C also decreased (Table 1, entries 4 and 5), presumably because of the instability of the cuprate reagent. When MeMgBr was replaced by methyllithium (MeLi), methylmagnesium chloride (MeMgCl) or methylmagnesium iodide (MeMgI) for preparation of the cuprate reagent, the yield of 1,4-adduct **12** deteriorated (Table 1, entries 6–8). No reaction occurred when dimethyl zinc (Me_2Zn)/$CuBr{\cdot}Me_2S$ or trimethylaluminium (Me_3Al)/$CuBr{\cdot}Me_2S$ were used as the nucleophilic agent (Table 1, entries 9 and 10). Less 1,4-adduct **12** was obtained when the reaction was performed in methyl *t*-butyl ether (*t*-BuOMe), diethyl ether (Et_2O) or toluene (PhMe) instead of THF solution (Table 1, entries 11–13). After screening various copper(I) salts (Table 1, entries 14–20), copper(I) chloride (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 °C, 7 h), giving the desired product **12** with a yield of 50% (Table 1, entry 14). Under such reaction conditions, exclusive regioselectivity for 1,4-addition was realized without formation of the 1,2-adduct. Although the electron-transfer process could not be avoided, the side product of trimethoxyphenol **10** could be oxidized with PIFA in MeOH to regenerate the benzoquinone-monoketal **9** starting material.

In our original design (Fig. 2), the alkylation reaction was 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 °C to give exclusively, a *trans*-**8** product (Table 2, entry 1), albeit at 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 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[d]	THF	−50	15	20[b]
17	MeMgBr	CuOAc[e]	THF	−50	8	23[b]
18	MeMgBr	CuSPh[f]	THF	−50	18	20[b]
19	MeMgBr	CuTC[g]	THF	−50	20	28[b]
20	MeMgBr	CuCN[h]	THF	−50	21	25[b]

[a] Compound **11** was obtained in yields of 18–25% as the 1,2-addition product hydrolyzed with silica gel column chromatography. [b] The major product was phenol **10** (yields of 50–80%) derived from an electron-transfer pathway. [c] No reaction (NR) occurred, and the starting material **9** was recovered. [d] CuI is copper(I) iodide. [e] CuOAc is copper(I) acetate. [f] CuSPh is copper(I) phenolthiolate. [g] CuTC is copper(I) thiophene-2-carboxylate. [h] CuCN is copper(I) cyanide.

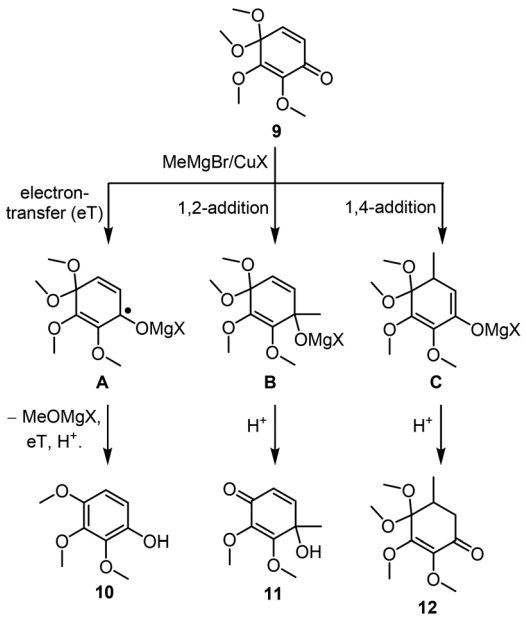
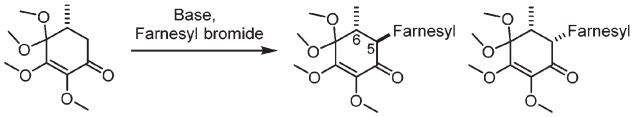


Fig. 3 Three reaction modes of cyclohexadienone **9** with organocuprate reagent MeMgBr/CuX. The electron transfer pathway led to phenol **10**, which can be recycled to compound **9** by oxidation with PIFA in MeOH. The 1,2-addition at the carbonyl led to product **11** because of the hydrolysis using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

(Table 2, entries 2–6), which reacted smoothly with farnesyl bromide at a 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 the *cis*-**8** isomer appeared at a relatively high field of δ_H 0.78 (d, J = 7.0 Hz) presumably because of the shielding effect of the adjacent farnesyl substituent. The two methine protons exhibited 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 sodium hydride (NaH) or potassium *t*-butoxide (*t*-BuOK) as the base (Table 2, entries 7 and 8) only produced *cis*-**8** isomer in low yields (<35%). Unlike cyclohexanones, the 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, it was assumed that epimerization of **8** occurring at room temperature might favor the *cis* isomer. When a mixture of *trans*-**8** and *cis*-**8** isomers (1 : 1) was treated with NaH (0.1 equiv.) in dimethylformamide (DMF) solution at room temperature for a period of 24 h, *cis*-**8** actually became the predominant isomer (75%) compared to the *trans*-**8** (25%). This result supports the theory that *cis*-**8** is indeed the thermodynamically favored isomer.

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[b]	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 using ^{1}H-NMR spectral analysis. [b] *t*-BuOH is *t*-butyl alcohol.

It is an attractive strategy to perform a three-component coupling reaction in a one-pot method.[22,23] As shown in our original design (Fig. 2), the 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 give compound **8**. Unfortunately, all the attempts at the consecutive α-alkylation failed presumably because of the instability of the enolate ion.

In general, the trajectory of the approach of the H^- in the reduction of the 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, it was thought that the carbonyl reduction of *trans*-**8** would occur by H^- attack from the less hindered face to give **7a** in the 4,5-*cis* configuration (Fig. 4). In contrast to this prediction, the reduction of *trans*-**8** with lithium aluminium hydride ($LiAlH_4$) in THF at −78 °C gave exclusively the all-*trans* product **7b** (Fig. 4), which was then subjected to an acid catalyzed hydrolysis to give **1b** and **13b** with yields of 18% and 73%, respectively (Table 3, entry 1). Compound **1b** which had 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 give the 1,3-trans-positional isomer **13b** which had the carbonyl group adjacent to the hydroxyl substituent. The C-3 hydrolysis was a preferable pathway, presumably because of the facilitation by the stereoelectronic effect and participation of the adjacent hydroxyl group,[12,24] although the real reaction mechanism would be discovered after advanced computations and experimental evidence.

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** (Fig. 4). In comparison, the axial attack of H^- (from $LiAlH_4$) onto the *trans*-**8** compound, giving **7b** in an all-*trans* configuration, was favored because the equatorial approach of the H^- would exert a torsional strain between farnesyl and the emerging hydroxyl group (Fig. 4). In contrast, the axial attack of H^- onto *cis*-**8** compound, giving **7d** in the 4,5-*trans* configuration, was not favored because of the steric hindrance of the methyl substituent on the axial orientation.

It was disappointing that this two-step process did not yield the desired antroquinonol (**1a**) as was predicted by the retrosynthetic analysis (Fig. 2). To render the reduction of *trans*-**8** by H^- attack from the equatorial direction to obtain **7a** in the 4,5-*cis* configuration, other reducing agents including i-Bu_2AlH, $Li(Ot\text{-}Bu)_3AlH$, $NaBH_4/CeCl_3$, $LiEt_3BH$, $Li(s\text{-}Bu)_3BH$ and $Li(siamyl)_3$-BH were examined (Table 3, entries 3–9). From these, only the bulky reducing agents $Li(Ot\text{-}Bu)_3AlH$ and $Li(s\text{-}Bu)_3BH$ could deliver H^- to *trans*-**8** from the equatorial direction to give **7a** (Table 3, entries 4 and 7). However, the subsequent treatment of **7a** with oxalic acid only proceeded with C-3 hydrolysis to give **13a** without formation of antroquinonol (**1a**). Because the axial attack of H^- to *trans*-**8** was a favorable process for obtaining **1b** in an all-*trans* configuration, performing a Mitsunobu reaction[25,26] on **1b** for the stereochemical inversion of its hydroxyl group was considered. The desired Mitsunobu reaction of **1b** did not work, and this was presumably because of the steric congestion of this molecule.

Realizing that *trans*-**8** was not a suitable precursor for the synthesis of antroquinonol, we switched to *cis*-**8** as an alternative substrate. In this study, it was learned that *cis*-**8** was actually the thermodynamically favored isomer instead of *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* com-

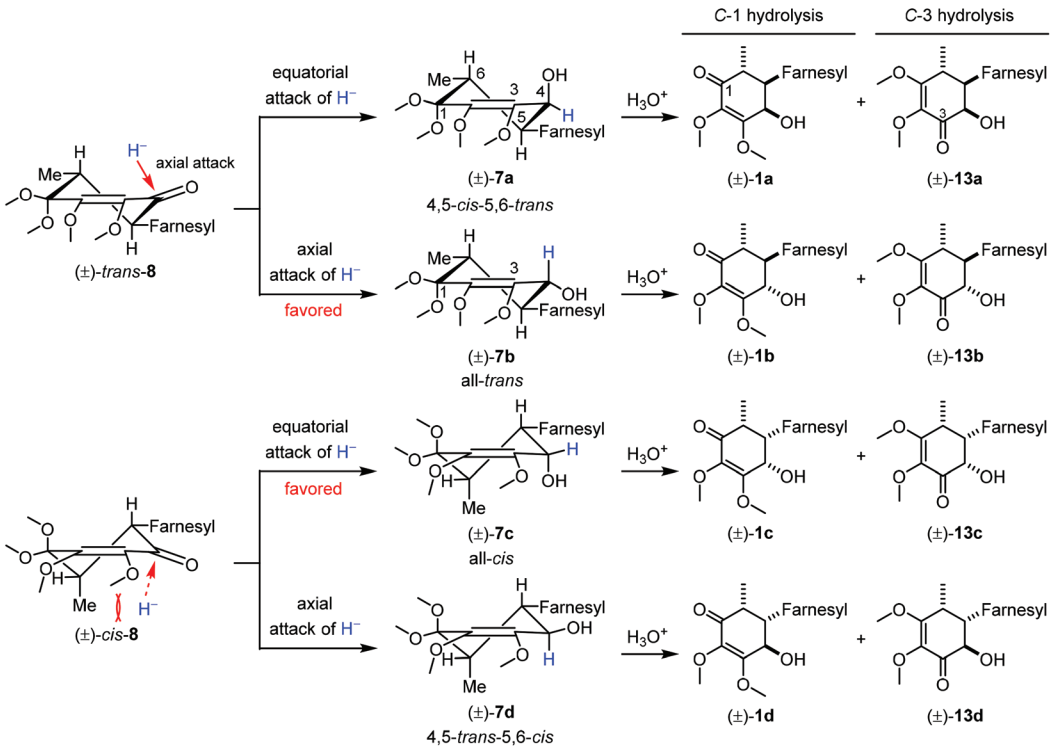
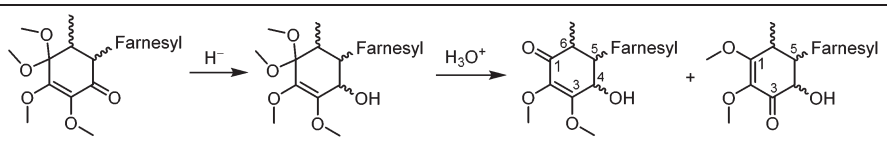


Fig. 4 Stereo- and regiochemistry in the reduction of ketone **8**. Subsequent hydrolysis of the reduction product **7** gave compound **1** and the 1,3-transpositional isomer **13**.

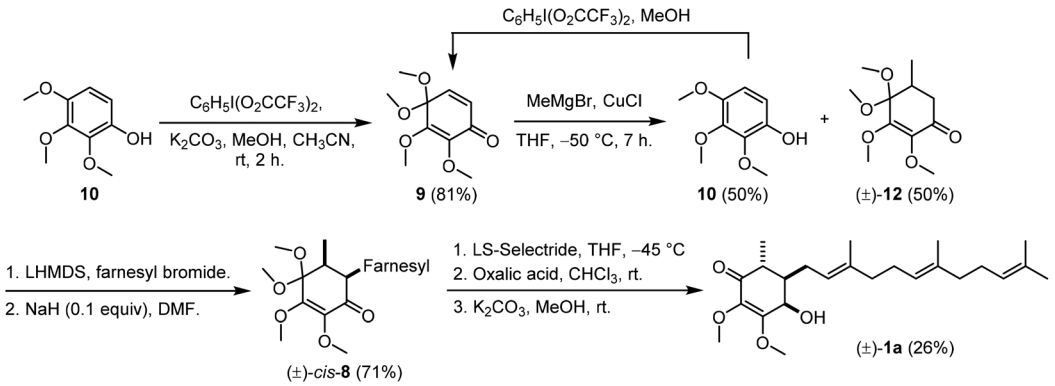
Table 3 Reduction of ketone **8** to alcohol **7**, followed by hydrolysis in acidic conditions, to give compounds **1** and **13**



					Ratio of hydrolysis products[a]							
					From **7a**		From **7b**		From **7c**		From **7d**	
	8	Reduction			**1a**	**13a**	**1b**	**13b**	**1c**	**13c**	**1d**	**13d**
Entry	*trans*/*cis*	Reagent	Solvent	Temp. (°C)	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[b]	CH_2Cl_2	−78	0	0	7	18	3	11	10	1
4	1 : 1	$Li(Ot\text{-}Bu)_3AlH$[c]	THF	0	0	10	3	12	4	11	7	3
5	1 : 1	$NaBH_4$[d]/$CeCl_3$[e]	MeOH	0	0	0	2	8	1	2	5	2
6	1 : 1	$LiEt_3BH$[f]	THF	−78	0	0	1	3	1	2	1	0
7	1 : 1	$Li(s\text{-}Bu)_3BH$[f]	THF	−40	0	1	1	3	2	3	0	0
8	1 : 1	$Li(siamyl)_3BH$[f]	THF	−40	0	0	1	4	2	3	0	0
9	**1 : 3**	**$Li(siamyl)_3BH$[f]**	**THF**	**−40**	**0**	**0**	**1**	**4**	**6**	**9**	**0**	**0**

[a] The ratio was determined by the weights of the isolated products. [b] i-Bu_2AlH is diisobutylaluminium hydride. [c] $Li(Ot\text{-}Bu)_3AlH$ is lithium tri-*tert*-butoxyaluminium hydride. [d] $NaBH_4$ is sodium borohydride. [e] $CeCl_3$ is cerium(III) chloride. [f] These commercially available reagents have the trade names Super-Hydride (lithium triethylborohydride, $LiEt_3BH$), L-Selectride [lithium tri-*sec*-butylborohydride, $Li(s\text{-}Bu)_3BH$] and LS-Selectride [lithium trisamylborohydride, $Li(siamyl)_3BH$].

pound **1c** was obtained from **7c** by the acid catalyzed C-1 hydrolysis. The subsequent treatment of **1c** with a base (potassium carbonate, K_2CO_3) in MeOH solution caused epimerization at the C-6 position to yield (±)-antroquinonol (Scheme 1). The proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13-NMR (^{13}C NMR) spectra of the synthetic (±)-**1a**



Scheme 1 Synthesis of (±)-antroquinonol. CH_3CN: acetonitrile, $CHCl_3$: chloroform.

agreed well with those of natural (+)-antroquinonol [Fig. S1 and S2 in the ESI†].

In summary, the synthesis of (±)-antroquinonol (Scheme 1) started with a Michael reaction of cyclohexadienone **9** to give cyclohexenone **12** (50%). The other product **10** (50%), was derived from an electron transfer process, which could be effectively reverted to the starting material **9** by oxidation with PIFA in MeOH (80%). Upon treatment of **12** with LHMDS (Table 2, entry 2), the enolate ion was generated and then subjected to α-alkylation with farnesyl bromide to give **8** as a mixture of the *trans* and *cis* isomers, which proceeded after a base catalyzed epimerization to give *cis*-**8** with an overall yield of 71%. The all-*cis* isomer **1c**, obtained from reduction of *cis*-**8** with $Li(siamyl)_3BH$ 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. Thus, a short synthesis of (±)-antroquinonol from trimethoxyphenol **10** by a 7-step sequence with an overall yield of 7.4% was accomplished.

Using the present synthetic method, all possible isomers **1a–1d** and **13a–13d** differing in regio- or stereochemistry were obtained. Their structures were determined using mass spectroscopy (MS) and NMR [^{1}H, ^{13}C, correlation spectroscopy (COSY), nuclear Overhauser effect spectroscopy (NOESY), and heteronuclear single quantum coherence (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.

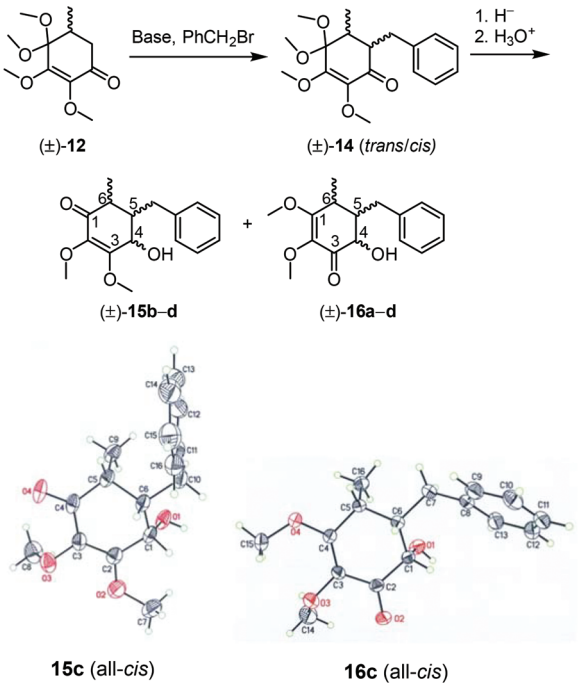
To further support the structural assignments, the alkylation reactions of **12** with benzyl bromide ($PhCH_2Br$) were also carried out to give *trans*-**14** and *cis*-**14**, which were subsequently reduced and hydrolyzed to give compounds **15b–15d** and **16a–16d** (Scheme 2), by the procedures 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** gave **15a**, which is related to antroquinonol (**1a**) in the 4,5-*cis*-5,6-*trans* configuration.

Attempts to obtain a single crystal of antroquinonol did not succeed, presumably because of the high flexibility of the farnesyl substituent. Fortunately, **15b**, **15c**, **15d**, **16b** and **16c** were crystalline compounds suitable for the X-ray diffraction analyses for rigorous structural elucidation (see ESI†). 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-NMR and ^{13}C-NMR spectra (see ESI†). The stereochemical relationship was supported by their NOESY spectra (see ESI†). 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 the farnesyl substi-

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

Compound	H-4	H-6	Me-6	C-1	C-4	C-6	*C*H3-6
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 deuterated chloroform ($CDCl_3$), respectively. Data in parentheses are coupling constants (J) given in Hz.



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

tuent, indicating their orientation on the same face of the 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, which was 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 (TLC). Accordingly, the least polar **b**-isomers were eluted first, followed by the **a**-, **d**- and **c**-isomers.

Conclusion

In this present study, a short synthesis of (±)-antroquinonol (**1a**) was completed in seven steps from the readily available starting material of 2,3,4-trimethoxyphenol, which was oxidized in MeOH to give 2,3,4,4-tetramethoxycyclohexadienone (**9**). A Michael reaction of **9** together 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 of a 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 their bioactivities.[27] The analogous compounds **15a–d** and **16a–d** having a benzyl substituent at the C-5 position were also prepared. Their structures were rigorously established by meticulous NMR analyses with the assistance of X-ray diffraction measurements of some of the crystalline compounds. By comparison of ^{1}H-NMR and ^{13}C-NMR spectra, the structures of **1a–d** and **13a–d** were also unambiguously elucidated by correlation with their counterparts, **15a–d** and **16a–d**. These structural correlations were in agreement with the mechanistic rationale of the reactions. Therefore, the structure of natural (+)-antroquinonol was confirmed to be that of **1a** having the 4,5-*cis*-5,6-*trans* configuration. It is still worth investigating the asymmetric Michael additions[28–31] of **9** and its analogs using chiral catalysis or auxiliary methods. Our preliminary results indicated that asymmetric Michael reaction of 3,4,4-trimethoxycyclohexadienone with a methyl metal 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 shown 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 in open capillaries and are not corrected. NMR spectra were obtained on a 400 MHz or a 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 spectra were taken to determine the types of carbon signals. The electrospray ionisation–MS experiments were conducted using high-resolution mass spectrometry (HRMS).

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. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. 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 TLC on silica gel using aqueous *p*-anisaldehyde as a 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 °C over six 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 ammonium chloride (5.0 mL), and then extracted with ethyl acetate (EtOAc, 3 × 20 mL). The combined organic layers were washed with 0.5 M sodium hydroxide (30 mL) and brine (30 mL). The organic phase was dried over magnesium sulfate ($MgSO_4$), and concentrated under reduced pressure. The residue was purified using column chromatography on silica gel with EtOAc/hexane (15 : 85) as eluent to give a Michael addition product **12** (115 mg, yield of 50%).

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 in a dry ice cooling bath, and a solution of farnesyl bromide (1.2 g, 4.34 mmol) in THF (3.0 mL) was added at −78 °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 EtOAc/hexane (8 : 92) as eluent to yield the alkylation product **8** (890 mg, yield of 95%) 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 previously 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 EtOAc/hexane (15 : 85) as eluent to yield compounds **1b** (71 mg, yield of 9%), **1c** (142 mg, yield of 18%), **13a** (75 mg, yield of 9%), **13b** (226 mg, yield of 27%) and **13c** (214 mg, yield of 27%).

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 EtOAc/CH_2Cl_2 (5 : 95) as eluent to yield the isomer **1a** (antroquinonol, 25 mg, yield of 83%) 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 to 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 EtOAc/hexane (15 : 85) as eluent to yield phenol **10** (6.3 g, yield of 95%). $C_9H_{12}O_4$; ^{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) calculated 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 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 EtOAc/hexane (20 : 80) as eluent, to yield cyclohexadienone **9** (1.9 g, yield of 81%). $C_{10}H_{14}O_5$; IR ν_{max} (neat) 2994, 2948, 2834, 1672, 1607, 1313, 1210, 1076, 951, 833, 740 cm^{-1}. ^{1}H-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 calculated 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}. ^{1}H-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 calculated 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 procedure discussed earlier gave compound **8**

as a mixture of *trans* and *cis* isomers (1 : 1), which were inseparable on a 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}. ^{1}H-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 calculated 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] $C_{24}H_{38}O_4$; ^{1}H-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 calculated 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 calculated 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 calculated 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}. ^{1}H-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 calculated 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}. ^{1}H-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 calculated 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}. ^{1}H-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 calculated 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 calculated 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 calculated for $C_{24}H_{38}O_4$: 391.2848, found: m/z 391.2854 $[M + H]^+$.

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