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Synthetic Studies on Isoprenoidquinones. I. A Facile Regio- and Stereocontrolled Synthesis of Protected Hydroquinones with an Omega-Hydroxyprenyl or Omega-Hydroxygeranyl Side Chain

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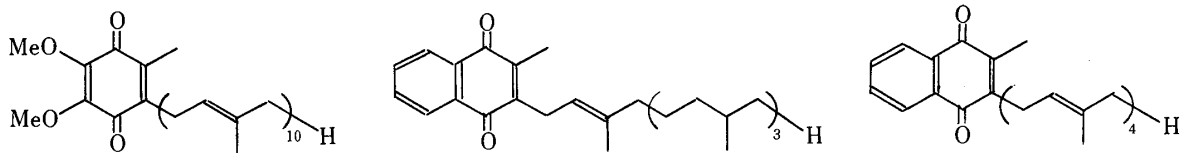
Regio- and stereocontrolled terminal functionalization of protected 2-prenyl- and 2-geranylhydroquinones (**2**) was achieved by way of terminal methallylic sulfides (**4**), which were easily obtained *via* benzenesulfenyl chloride addition followed by dehydrochlorination or *via* allylic chlorination with SO_2Cl_2 followed by sulfenylation, leading to terminal *trans*-allylic alcohols (**5**) which are promising intermediates for the synthesis of polyisoprenoidquinones. In this transformation, interesting steric effects of the hydroquinone nucleus with the adjacent arylic methyl group influencing the site-selectivity in the reactions of the isoprenoid side chain were observed.

Keywords——isoprenoidquinone; *trans*-allylic alcohol; terminal functionalization; benzenesulfenyl chloride addition; allylic chlorination; acyclic steric effect

Various polyprenyl-quinones and -hydroquinones are widely distributed from bacteria to higher plants and animals.[1a] Ubiquinone-10 (coenzyme Q_{10}) (**1a**), phylloquinone (vitamin K_1) (**1b**), and menaquinone-n (vitamin $K_{2(5n)}$) (**1c**) are the representatives of physiological activities and are clinically used as a cardiovascular agent, prothrombogenic vitamin, and antihemorrhagic vitamin, respectively.[1b] Because of the biological and pharmacological importance associated with the all-*trans* geometry of the polyprenyl side chain,[1c] and the occurrence of these compounds in minute quantities in nature, much attention has focused on the stereocontrolled synthesis of such compounds.[2a] During the last four decades, beginning



1a **1b** **1c**

Chart 1

with the independent syntheses of phylloquinone (**1b**) by several groups of workers in 1939,[2b] great efforts have been made to synthesize polyisoprenoidquinones *via* coupling of quinone or hydroquinone derivatives with polyprenols or their derivatives.[2a] In the early stage of synthetic studies, the regio- and stereoselective introduction of the side chain, which is the major requisite in the synthesis of these quinones, had been attained unsatisfactorily. Recently, several new techniques have appeared: activation of the protected hydroquinone by metallation;[3] reactive functionalization of the side chain component by stannylation,[4a] π-allyl metallation,[4b] and phosphorylation;[4c] and formation of hydroquinone-polyprenyl ethers followed by O-to-C rearrangement of the side chain.[5] More recently, another synthetic

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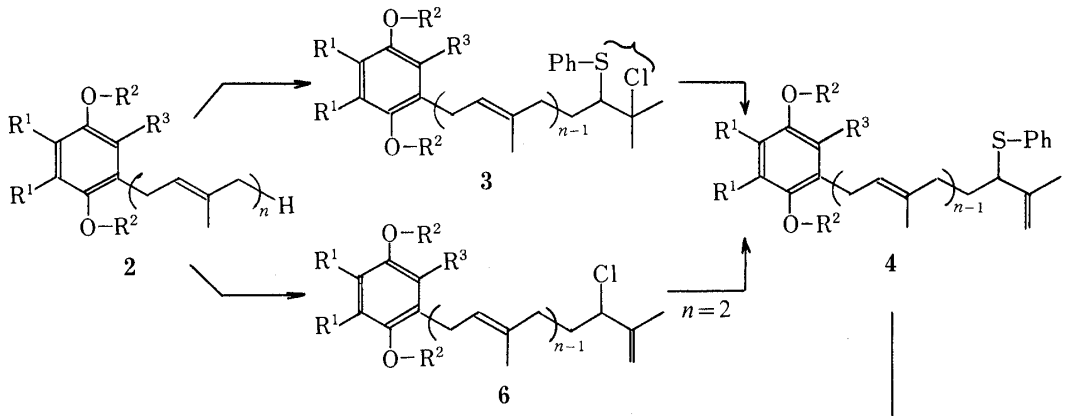
strategy has been reported for these quinones involving elongation of the terminally functionalized side chain of simple isoprenoidhydroquinone derivatives which are prepared by regio- and stereoselective introduction of binary functionalized isoprenoids into quinone components[6a] or by regio- and stereocontrolled modification of 2-prenylhydroquinone derivatives.[6b] The latter method seems to be more attractive from the viewpoint of (a) easy accessibility of the prenyl- and geranylhydroquinone derivatives (**2**) without stereochemical problems concerning the C(2′)-olefinic geometry, particularly for the prenylated ones (**2**, $n=1$) and (b) facility in extension of the side chain to higher homologues by the known methods for C–C bond formation on establishing the general method for regio- and stereoselective terminal functionalization of the side chain in **2**.

We recently developed a facile method for the preparation of terminal *trans*-allylic alcohols from linear isoprenoids *via* benzenesulfenyl chloride (PhSCl) addition.[7] As an extension of the method to the synthesis of physiologically active compounds, here we report a facile preparation of protected hydroquinone derivatives (**5**) with an omega-hydroxyprenyl or omega-hydroxygeranyl side chain.



	R^1 (R^1-R^1)	R^2	R^3	n
a	H	Me	H	1
b	CH=CH–CH=CH	Me	Me	1
c	CH=CH–CH=CH	CH_2Ph	Me	1
d	OMe	Me	Me	1
e	OMe	CH_2Ph	Me	1
f	CH=CH–CH=CH	Me	Me	2
g	CH=CH–CH=CH	CH_2Ph	Me	2
h	OMe	Me	Me	2

Chart 2

Terminal Functionalization of the Prenyl or Geranyl Side Chain of the Protected Hydroquinones (2): By Way of PhSCl-Addition (Method A)

The starting materials, protected hydroquinones (**2**) with the prenyl or geranyl side chain, were easily prepared according to known methods from the corresponding hydroquinone and quinone derivatives, *p*-methoxyphenol,[8a] 2,3-dimethoxy-5-methyl-1,4-benzoquinone,[6b,8b,c] and 2-methyl-1,4-naphthoquinone.[3a,6b,8c] Dropwise addition of an equivalent amount of PhSCl[9] into a solution of **2a** in CH_2Cl_2 at $-20\,^\circ C$ immediately gave a mixture of a pair of regioisomeric adducts (**3a**), which, without purification, was treated with an excess amount of Et_3N in *N*,*N*-dimethylformamide (DMF) at 60 °C for 40 h to afford the terminal methallylic sulfide (**4a**) in 75% yield after purification by column chromatography on silica gel. The structure of **4a** was characterized by mass (MS) (M^+ 314) and proton nuclear magnetic

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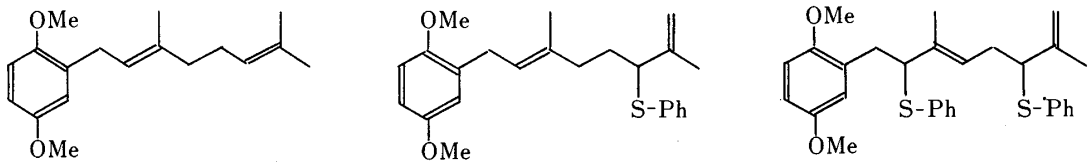
resonance (^{1}H-NMR) spectroscopic methods: the signals of vinylic methyl at δ 1.77 as a singlet and the terminal methylene protons at δ 4.53 and 4.59 as broad singlets were observed. Successive treatments of the allylic sulfide (**4a**) with 30% H_2O_2 in AcOH at room temperature for 20 h and then with trimethyl phosphite [$(MeO)_3P$][10] in MeOH at room temperature for 2 d gave the terminal *trans*-allylic alcohol (**5a**) in 70% yield. The structure and stereohomogeneity of **5a** were confirmed by ^{1}H-NMR analysis: a 3H-singlet at δ 1.67, a 2H-doublet at δ 3.20, two 3H-singlets at δ 3.59 and 3.64, a 2H-singlet at δ 3.81, and a 1H-triplet at δ 5.40 were assignable, respectively, to the vinylic methyl, benzylic methylene, methoxyl, allylic methylene bearing OH, and an olefinic proton, and no signals corresponding to the *cis*-stereoisomer were detected. This type of transformation of **2a** was successfully applied to other prenylated hydroquinones (**2b**—**e**).

Oxidation of *gem*-dimethyl olefins with *tert*-BuOOH in the presence of SeO_2 is a useful method for direct conversion to terminal *trans*-allylic alcohols.[11] Examination of the efficiency of the method (*tert*-BuOOH/cat. SeO_2/CH_2Cl_2/20 °C/4 d) on a prenylated hydroquinone (**2d**), however, gave a poor yield (40%) of the terminal *trans*-allylic alcohol (**5d**) after treatment of the crude mixture with $NaBH_4$ in EtOH and a tedious chromatographic separation. An analogous low yield production of a *trans*-allylic aldehyde corresponding to **5a** from **2a** by SeO_2 oxidation was reported by Manners.[8a] He reported also that an application of our method[7] for terminal functionalization to 2-geranyl-1,4-hydroquinone dimethyl ether (i) gave the desired terminal methallylic sulfide (ii) and the bis-methallylic sulfide (iii) as a by-



i ii iii

Chart 3

product in a ratio of 2 : 1.[8a] The result seems to be consistent with our previous observation in higher polyisoprenoids,[7b] in which steric and electronic factors influenced on the site-selectivity of PhSCl addition. Thus, we were very curious to investigate how much the adjacent arylic methyl group blocks the internal olefinic site in PhSCl addition in the 2-geranyl-3-methyl-1,4-hydroquinone system. Thus, the geranylated naphthohydroquinone (**2f**) was subjected to PhSCl addition at −20 °C in CH_2Cl_2 using an equivalent amount of PhSCl. The crude adduct (**3f**) was warmed with Et_3N in DMF at 60 °C in this case for 20 h. The product was purified by column chromatography to give in 77% yield the desired terminal methallylic sulfide (**4f**) whose structure was verified by spectral analysis: the parent peak was observed at *m/e* 446 in the MS and ^{1}H-NMR gave a reasonable spectrum which showed two vinylic methyl singlets at δ 1.70 and 1.80, one proton triplet assignable to the allylic proton attached to the carbon bearing the S-Ph group at δ 3.44, the benzylic methylene as a doublet at δ 3.51, the terminal methylene protons as broad singlets at δ 4.42 and 4.58, and the olefinic proton as a broad triplet at δ 5.15. A small amount (less than 10%) of by-products which might be derived from the bis-adduct was obtained, but structural determination was not carried out exactly. The above result revealed that the adjacent arylic methyl group in the quinoid system with the geranyl side chain enhanced the site-selectivity at the terminal olefin in PhSCl addition. The other geranylated hydroquinones (**2g, h**) also afforded terminal allylic sulfides (**4g, h**) in good yields by the same procedure. Transformation of these terminal allylic sulfides (**4f**—**h**) to the terminal *trans*-allylic alcohols (**5f**—**h**) proceeded smoothly. The results are summarized in Table I.

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TABLE I. Terminal Functionalization of Protected 2-Prenyl- and 2-Geranyl-Hydroquinones (**2**) Providing Terminal Methallylic Sulfides (**4**) and Terminal *trans*-Allylic Alcohols (**5**)

Isoprenoidhydroquinone (**2**)	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
Sulfide (**4**)	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
% yield (method A)[a]	75	80	81	83	88	77	72	71
(method B)[a]	19	—	—	—	—	72	70	75
Alcohol (**5**)	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**
% yield	70	71	70	73	73	73	67	72

a) For procedures, see the experimental section.

By Way of Terminal Allylic Chlorination and Sulfenylation (Method B)

Recently, several methods for the allylic chlorination of terminal *gem*-dimethyl olefins using chlorine,[12a] aqueous HOCl,[12b] *tert*-BuOCl,[12c] arylselenide with NCS,[12d] and by an electrochemical approach[12e] have been reported. We also reported an allylic chlorination using SO_2Cl_2 in the preparation of a terminal methallylic sulfide from citronelic acid.[13] This sequence of transformation intrigued us to apply to the quinoid system. Treatment of the prenylhydroquinone (**2a**) with an equivalent amount of SO_2Cl_2 in CH_2Cl_2 at 0 °C for 1 h gave chlorinated products which proved to consist mainly of the desired allylic chloride (**6a**) on the basis of ^{1}H-NMR analysis: the vinylic methyl singlet at δ 1.82, the allylic proton attached to the carbon bearing Cl at δ 4.58 as a triplet, and two terminal methylene protons at δ 4.70 and 4.80 as broad singlets were detected. The crude chloride was subjected to sulfenylation (NaSPh/DMF/0 °C/1 h) as used for the conversion of terminal methallylic chlorides to the corresponding sulfide without involvement of the S_N2' mode,[13] but was recovered unchanged. Sulfenylation of the chloride (**6a**) turned out to proceed very sluggishly and even on prolonged treatment with NaSPh at 20 °C for 24 h, a poor yield (19%) of the desired sulfide (**4a**) was attained. Attempts to use the sequence of chlorination and sulfenylation, aiming at the allylic sulfides (**4b, d, e**), on the other prenylated hydroquinones (**2b, d, e**) with the adjacent arylic methyl group were unsuccessful, although allylic chlorination took place.

In contrast, smooth sulfenylation occured of the allylic chlorides derived from the geranylated hydroquinones (**2f—h**). Thus, chlorination of **2f** was carried out by treatment with an equivalent amount of SO_2Cl_2 at −20 °C for 1 h to produce also in this case the monochlorinated product (**6f**) with a small amount of by-products. The crude chloride was directly subjected to sulfenylation at 0—20 °C for 1.5 h. Purification of the product gave the desired allylic sulfide (**4f**) in 72% yield. The other terminal allylic sulfides (**4g, h**) were also obtained in 70—75% yields from **2g** and **2h** in the same manner. In this transformation (chlorination and sulfenylation), the protected hydroquinone nucleus again proved to exert a steric effect on the reaction of the side chain.

Now we have versatile and flexible building blocks for the synthesis of a variety of biologically important polyisoprenoidquinones in hand. Utilization of these terminal *trans*-allylic alcohols (**5**) in the synthesis of physiologically active quinones (**1a—c**) will be reported in the following paper.[14]

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-1 spectrometer in $CHCl_3$ solution and characteristic bands (ν_{max}) are reported in cm^{-1}. ^{1}H-NMR spectra were recorded on a Hitachi R-20B spectrometer (60 MHz) in CCl_4 solution with

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tetramethylsilane (TMS) as an internal standard; chemical shifts are reported in δ (ppm) relative to TMS and coupling constants (J) in hertz (Hz). MS were obtained on a JMS-D300 instrument at an ionizing potential of 70 eV and peaks are represented in m/e values with relative intensities. Thin layer chromatography was performed on Wakogel B-5F silica gel with a hexane–Et_2O solvent system. Column chromatography was accomplished on Wakogel C-200 (100—200 mesh) silica gel with a hexane–Et_2O elution system.

Materials——Protected 2-prenyl- and 2-geranyl-1,4-hydroquinones were prepared according to the literature: 2-prenyl-1,4-dimethoxybenzene (**2a**) from 4-methoxy-phenol,[8a] 2-prenyl-3-methyl-1,4-dimethoxynaphthalene (**2b**) and 2-geranyl-3-methyl-1,4-dimethoxynaphthalene (**2f**) from 2-methyl-1,4-naphthoquinone,[3a,8c] 1-prenyl-2-methyl-3,4,5,6-tetramethoxybenzene (**2d**), 1-prenyl-2-methyl-3,6-dibenzyloxy-4,5-dimethoxybenzene (**2e**), and 1-geranyl-2-methyl-3,4,5,6-tetramethoxybenzene (**2h**) from 2,3-dimethoxy-5-methyl-1,4-benzoquinone.[6b,8c] 2-Prenyl-3-methyl-1,4-dibenzyloxynaphthalene (**2c**) and 2-geranyl-3-methyl-1,4-dibenzyloxynaphthalene (**2g**) were synthesized by the reported method[8c] from 2-methyl-1,4-naphthoquinone *via* 2-bromo-3-methyl-1,4-naphthohydroquinone: protection of the hydroquinone functionality by benzylation followed by C–C coupling with prenyl bromide or geranyl bromide. ^{1}H-NMR data for **2c** and **2g** are as follows:

2c: 1.70, 1.81 (each 3H, br s, 2 × $=CCH_3$), 2.32 (3H, s, Ar–CH_3), 3.50 (2H, d, J=7.0, Ar–CH_2), 3.82 (6H, s, 2 × OCH_3), 5.07 (1H, br t, J=7.0, =CH), 7.21—7.47, 7.83—8.05 (each 2H, m, arom-H).

2g: 1.56, 1.62, 1.80 (each 3H, s, 3 × $=CCH_3$), 1.90—2.20 (4H, br, CH_2CH_2), 2.32 (3H, s, Ar–CH_3), 3.50 (2H, d, J=7.0, Ar–CH_2), 3.77, 3.80 (each 3H, s, 2 × OCH_3), 4.90—5.10 (1H, br, =CH), 5.10 (1H, br t, J=7.0, =C<u>H</u>CH_2Ar), 7.23—7.50, 7.80—8.10 (each 2H, m, arom-H).

General Procedure for the Transformation of 2-Prenyl- or 2-Geranyl-hydroquinone Ethers (2) to Terminal Methallylic Sulfides (4)——Method A: To a solution of 2-prenyl-1,4-dimethoxybenzene (**2a**) (206 mg, 1.0 mmol) in CH_2Cl_2 (2.0 ml) was added dropwise a solution of PhSCl (145 mg, 1.0 mmol) in CH_2Cl_2 (0.5 ml) over a period of 5 min under stirring at −20 °C. After 10 min stirring, the mixture was concentrated *in vacuo* to give the crude adduct (**3a**) (350 mg) as an oil, which was directly warmed in DMF (4.0 ml) with Et_3N (0.5 ml) at 60 °C for 40 h. The mixture was extracted with Et_2O, washed with water, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give the crude product (310 mg). Purification of the product by column chromatography afforded pure allylic sulfide, 2-(3′-methyl-2′-phenylthio-3′-butenyl)-1,4-dimethoxybenzene (**4a**) (236 mg, 75%) as an oil.

For 2-geranylated hydroquinones (**2**, n=2) a period of 20 h of warming of the PhSCl-adducts (**3**, n=2) was enough to obtain the allylic sulfides (**4**, n=2).

Method B: To a mixture of 2-geranyl-3-methyl-1,4-dimethoxynaphthalene (**2f**) (340 mg, 1.0 mmol) and pyridine (90 μl) in CH_2Cl_2 (3.0 ml) was added dropwise a solution of SO_2Cl_2 (135 mg, 1.0 mmol) in CH_2Cl_2 (0.5 ml) at −20 °C over a period of 5 min. Stirring was continued for 1 h at the same temperature and then the reaction was quenched by addition of 5% aq. $NaHCO_3$. The mixture was extracted with Et_2O, washed with water, dried over anhyd. $MgSO_4$, and concentrated *in vacuo* to give the crude allylic chloride (**6f**) (445 mg). ^{1}H-NMR: 1.75, 1.80 (each 3H, s, 2 × $=CCH_3$), 2.30 (3H, s, Ar–CH_3), 3.48 (2H, d, J=7.0, Ar–CH_2), 4.03—4.30 (1H, m, CH(Cl)), 4.72, 4.81 (each 1H, br s, $=CH_2$), 5.11 (1H, br t, J=7.0, =CH), 7.20—7.43, 7.73—8.00 (each 2H, m, arom-H). The chloride (**6f**) was, without further purification, dissolved in DMF (4.0 ml), and PhSNa (172 mg, 1.3 mmol) was added in portions to the stirred solution at 0 °C. Stirring was continued for 1 h at the same temperature and then at room temperature for 30 min. The mixture was extracted with Et_2O, washed with water, dried, and concentrated to give a crude product, which was purified by column chromatography to yield the terminal methallylic sulfide (**4f**) (320 mg, 72%) as an oil.

For 2-prenylated hydroquinones (**2**, n=1), however, this method was not effective because sulfenylation of the terminal methallylic chlorides (**6**, n=1), which were easily obtained by the same treatment with SO_2Cl_2, proceeded very sluggishly even at room temperature for 20 h. For example, **2a** gave **4a** in 19% overall yield *via* **6a**. ^{1}H-NMR of **4a**: 1.82 (3H, s, $=CCH_3$), 2.90—3.07 (2H, m, Ar–CH_2), 3.60, 3.67 (each 3H, s, 2 × OCH_3), 4.58 (1H, t, J=7.5, CH(Cl)), 4.70, 4.80 (each 1H, br s, $=CH_2$), 6.52 (3H, s, arom-H).

Yields and physicochemical properties for the terminal methallylic sulfides (**4**) obtained are listed in Table I and indicated as follows:

4a: MS: 314 (M^+, 54%), 205 (100%), 163 (69%). IR: 2810, 1640, 1604, 1580, 1490, 1460, 1430, 1365. NMR: 1.77 (3H, s, $=CCH_3$), 2.80—2.98 (2H, m, Ar–CH_2), 3.57, 3.60 (each 3H, s, 2 × OCH_3), 3.80—4.07 (1H, dd, J=9.5, 7.0, CH(SPh)), 4.53, 4.59 (each 1H, br s, $=CH_2$), 6.49—6.63 (3H, m, arom-H), 6.96—7.35 (5H, m, S–Ph). *Anal.* Calcd for $C_{19}H_{22}O_2S$: C, 72.59; H, 7.05. Found: C, 72.30; H, 7.04.

4b: mp 145—146 °C (Et_2O–hexane). MS: 378 (M^+, 21%), 269 (30%), 215 (100%). IR: 2830, 1640, 1583, 1480, 1450, 1440, 1350. NMR: 1.85 (3H, s, $=CCH_3$), 2.47 (3H, s, Ar–CH_3), 3.12 (2H, d, J=8.0, Ar–CH_2), 3.76 (6H, s, 2 × OCH_3), 4.07 (1H, t, J=8.0, CH(SPh)), 4.57, 4.60 (each 1H, br s, $=CH_2$), 7.00—7.50 (7H, m, arom-H), 7.80—8.05 (2H, m, arom-H). *Anal.* Calcd for $C_{24}H_{26}O_2S$: C, 76.15; H, 6.92. Found: C, 76.30; H, 6.98.

4c: mp 102—103 °C (Et_2O–hexane). IR: 1640, 1585, 1495, 1470, 1450, 1435, 1380, 1365, 1340. NMR: 1.80 (3H, s, $=CCH_3$), 2.38 (3H, s, Ar–CH_3), 3.13 (2H, d, J=8.0, Ar–CH_2), 4.10 (1H, t, J=8.0, CH(SPh)), 4.50, 4.58 (each 1H, br s, $=CH_2$), 4.89, 4.92 (each 2H, s, 2 × OCH_2Ph), 6.94—7.65 (17H, m, arom-H), 7.90—8.10 (2H, m, arom-H). *Anal.* Calcd for $C_{36}H_{34}O_2S$: C, 81.47; H, 6.46. Found: C, 81.51; H, 6.37.

4d: MS: 388 (M^+, 6%), 280 (31%), 225 (100%). IR: 1640, 1580, 1465, 1405, 1370, 1350. NMR: 1.83 (3H, s,

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$=CCH_3$), 2.12 (3H, s, Ar–CH_3), 2.90 (2H, d, $J=8.0$, Ar–CH_2), 3.69, 3.73, 3.76, 3.80 (each 3H, s, $4\times OCH_3$), 3.83 (1H, t, $J=8.0$, CH(SPh)), 4.61 (2H, br s, $=CH_2$), 7.00—7.35 (5H, m, S–Ph). *Anal.* Calcd for $C_{22}H_{28}O_4S$: C, 68.01; H, 7.26. Found: C, 67.80; H, 7.29.

4e: IR: 1640, 1583, 1460, 1420, 1365, 1340. NMR: 1.75 (3H, s, $=CCH_3$), 2.12 (3H, s, Ar–CH_3), 2.90 (2H, d, $J=8.0$, Ar–CH_2), 3.85, 3.88 (each 3H, s, $2\times OCH_3$), 4.50, 4.58 (each 1H, br s, $=CH_2$), 4.89, 4.97 (each 2H, s, $2\times OCH_2Ph$), 7.00—7.50 (15H, m, arom-H). *Anal.* Calcd for $C_{34}H_{36}O_4S$: C, 75.52; H, 6.71. Found: C, 75.36; H, 6.68.

4f: MS: 446 (M^+, 69%), 237 (44%), 215 (100%). IR: 1640, 1590, 1480, 1450, 1440, 1370, 1350. NMR: 1.70, 1.80 (each 3H, s, $2\times =CCH_3$), 1.70—2.15 (4H, m, CH_2CH_2), 2.30 (3H, s, Ar–CH_3), 3.44 (1H, t, $J=7.0$, CH(SPh)), 3.51 (2H, d, $J=7.0$, Ar–CH_2), 3.76, 3.79 (each 3H, s, $2\times OCH_3$), 4.42, 4.58 (each 1H, br s, $=CH_2$), 5.15 (1H, br t, $J=7.0$, $=CH$), 6.90—7.50 (7H, m, arom-H), 7.80—8.05 (2H, m, arom-H). *Anal.* Calcd for $C_{29}H_{34}O_2S$: C, 77.98; H, 7.67. Found: C, 78.15; H, 7.87.

4g: IR: 1640, 1590, 1495, 1475, 1450, 1440, 1380, 1365, 1340. NMR: 1.68 (6H, s, $2\times =CCH_3$), 1.70—2.15 (4H, m, CH_2CH_2), 2.30 (3H, s, Ar–CH_3), 3.45 (1H, t, $J=7.5$, CH(SPh)), 3.52 (2H, d, $J=7.5$, Ar–CH_2), 4.43, 4.57 (each 1H, br s, $=CH_2$), 4.89 (4H, br s, $2\times OCH_2Ph$), 5.15 (1H, br t, $J=7.5$, $=CH$), 6.90—7.60 (17H, m, arom-H), 7.90—8.15 (2H, m, arom-H). *Anal.* Calcd for $C_{41}H_{42}O_2S$: C, 82.23; H, 7.07. Found: C, 82.08; H, 7.21.

4h: MS: 456 (M^+, 14%), 347 (17%), 225 (100%). IR: 1640, 1580, 1460, 1415, 1400, 1370, 1345. NMR: 1.72 (6H, s, $2\times =CCH_3$), 1.60—2.20 (4H, m, CH_2CH_2), 2.07 (3H, s, Ar–CH_3), 3.23 (2H, d, $J=7.0$, Ar–CH_2), 3.47 (1H, t, $J=7.0$, CH(SPh)), 3.71, 3.80 (each 6H, s, $4\times OCH_3$), 4.45, 4.60 (each 1H, br s, $=CH_2$), 5.05 (1H, br t, $J=7.0$, $=CH$), 7.00—7.30 (5H, m, S–Ph). *Anal.* Calcd for $C_{27}H_{36}O_4S$: C, 71.02; H, 7.94. Found: C, 71.25; H, 7.95.

Preparation of 2-(4′-Hydroxy-3′-methyl-2′-(*E*)-butenyl)-1,4-dimethoxybenzene (5a). General Procedure for the Transformation of Terminal Methallylic Sulfides (4) to Terminal *trans*-Allylic Alcohols (5)——A solution of **4a** (315 mg, 1.0 mmol) in AcOH (4.0 ml) was treated dropwise with 30% H_2O_2 (120 μl) at room temperature and the mixture was stirred for 16 h at room temperature. The mixture was diluted with CH_2Cl_2, washed successively with water, 5% aq. $NaHCO_3$, and water again, dried over anhyd. $MgSO_4$, and concentrated to give the crude sulfoxide (310 mg). The crude sulfoxide was stirred in MeOH (5.0 ml) with $(MeO)_3P$ (250 mg, 2.0 mmol) for 2 d at room temperature. The reaction mixture was concentrated *in vacuo* and the residue was extracted with Et_2O, washed with saturated brine, dried, and solvent was evaporated off to leave a crude product, which was purified by column chromatography to provide the pure alcohol (**5a**) (155 mg, 70%).

Yields and physicochemical properties of the terminal *trans*-allylic alcohols (**5**) obtained are listed in Table I and indicated as follows:

5a: MS: 222 (M^+, 100%), 191 (73%), 173 (40%), 121 (47%). IR: 3550, 3380, 2810, 1604, 1585, 1490, 1460, 1430, 1370. NMR: 1.67 (3H, s, $=CCH_3$), 2.50 (1H, s, OH), 3.20 (2H, d, $J=7.5$, Ar–CH_2), 3.59, 3.64 (each 3H, s, $2\times OCH_3$), 3.81 (2H, s, $=CC\underline{H}_2OH$), 5.40 (1H, br t, $J=7.5$, $=CH$), 6.46—6.60 (3H, m, arom-H). *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.98; H, 8.07.

5b: mp 84 °C (Et_2O–hexane). MS: 286 (M^+, 100%), 271 (17), 253 (22%). IR: 3560, 3420, 1590, 1450, 1375, 1350. NMR: 1.80 (3H, s, $=CCH_3$), 2.30 (3H, s, Ar–CH_3), 3.51 (2H, d, $J=7.5$, Ar–CH_2), 3.78 (6H, s, $2\times OCH_3$), 3.85 (2H, s, $=CC\underline{H}_2OH$), 5.32 (1H, br t, $J=7.5$, $=CH$), 7.25—7.45, 7.85—8.08 (each 2H, m, arom-H). *Anal.* Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.34; H, 7.90.

5c: mp 108—109 °C (Et_2O–hexane). IR: 3550, 1585, 1490, 1445, 1380, 1340. NMR: 1.05 (1H, s, OH), 1.72 (3H, s, $=CCH_3$), 2.32 (3H, s, Ar–CH_3), 3.55 (2H, d, $J=8.0$, Ar–CH_2), 3.86 (2H, s, $=CC\underline{H}_2OH$), 4.93 (4H, s, $2\times OCH_2Ph$), 5.33 (1H, br t, $J=8.0$, $=CH$), 7.23—7.60 (12H, m, arom-H), 7.85—8.15 (2H, m, arom-H). *Anal.* Calcd for $C_{30}H_{30}O_3$: C, 82.16; H, 6.90. Found: C, 82.01; H, 6.97.

5d: MS: 296 (M^+, 100%), 265 (25%), 247 (27%), 189 (37%). IR: 3400, 1580, 1460, 1410, 1350. NMR: 1.75 (3H, s, $=CCH_3$), 2.06 (3H, s, Ar–CH_3), 2.40 (1H, s, OH), 3.25 (2H, d, $J=7.0$, Ar–CH_2), 3.70, 3.79 (each 6H, s, $4\times OCH_3$), 3.82 (2H, s, $=CC\underline{H}_2OH$), 5.22 (1H, br t, $J=7.0$, $=CH$). *Anal.* Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.62; H, 8.28.

5e: IR: 3560, 1580, 1460, 1420, 1365, 1340. NMR: 1.61 (3H, s, $=CCH_3$), 1.91 (1H, s, OH), 2.03 (3H, s, Ar–CH_3), 3.24 (2H, d, $J=7.0$, Ar–CH_2), 3.75 (2H, s, $=CC\underline{H}_2OH$), 3.84 (6H, s, $2\times OCH_3$), 4.86, 4.89 (each 2H, s, $2\times OCH_2Ph$), 5.13 (1H, br t, $J=7.0$, $=CH$), 7.10—7.50 (10H, m, arom-H). *Anal.* Calcd for $C_{28}H_{32}O_5$: C, 74.97; H, 7.19. Found: C, 74.77; H, 7.32.

5f: MS: 354 (M^+, 100%), 237 (45%). IR: 3380, 1590, 1450, 1375, 1350. NMR: 1.55, 1.79 (each 3H, s, $2\times =CCH_3$), 1.65 (1H, s, OH), 1.85—2.20 (4H, m, CH_2CH_2), 2.30 (3H, s, Ar–CH_3), 3.48 (2H, d, $J=7.0$, Ar–CH_2), 3.80 (8H, s, $2\times OCH_3$ and $=CC\underline{H}_2OH$), 5.06 (1H, br t, $J=7.0$, $=CH$), 5.20 (1H, br, $=CH$), 7.23—7.50, 7.80—8.10 (each 2H, m, arom-H). *Anal.* Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.06; H, 8.74.

5g: IR: 3550, 3400, 1585, 1490, 1450, 1380, 1340. NMR: 1.52, 1.68 (each 3H, s, $2\times =CCH_3$), 1.71 (1H, s, OH), 1.90—2.20 (4H, m, CH_2CH_2), 2.30 (3H, s, Ar–CH_3), 3.50 (2H, d, $J=7.0$, Ar–CH_2), 3.71 (2H, s, $=CC\underline{H}_2OH$), 4.90 (4H, s, $2\times OCH_2Ph$), 5.10 (1H, br t, $J=7.0$, $=CH$), 5.20 (1H, br, $=CH$), 7.20—7.60 (12H, m, arom-H), 7.90—8.10 (2H, m, arom-H). *Anal.* Calcd for $C_{35}H_{38}O_3$: C, 82.97; H, 7.56. Found: C, 82.69; H, 7.53.

5h: MS: 364 (M^+, 100%), 225 (98%). IR: 3400, 1465, 1405, 1350. NMR: 1.58, 1.74 (each 3H, s, $2\times =CCH_3$), 1.73 (1H, s, OH), 1.95—2.25 (4H, m, CH_2CH_2), 2.05 (3H, s, Ar–CH_3), 3.21 (2H, d, $J=7.0$, Ar–CH_2), 3.70, 3.79 (each

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6H, s, $4\times OCH_3$), 3.80 (2H, s, $=CC\underline{H}_2OH$), 4.98 (1H, br t, $J=7.0$, $=CH$), 5.22 (1H, br, $=CH$). *Anal.* Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.09; H, 8.95.

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