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Powerful Antioxidative Agents Based on Garcinoic Acid from *Garcinia Kola*

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Abstract—Investigation on the structure–antioxidative activity relationships of derivatives based on garcinoic acid from *Garcinia kola* (Guttiferae) led to discovery of a powerful antioxidative agent.

Introduction

In the previous paper, we reported two new chromanols, garcinoic acid (**1**) and garcinal (**2**), together with δ-tocotrienol (**3**) from the seed of *Garcinia kola* (Guttiferae) collected in Nigeria.[1] The antioxidant activities of those natural products (**1**, **2** and **3**) were around 1.5 times that of *dl*-α-tocopherol by the bleomycin–Fe method reported by Umezawa et al.[1,2] These results indicated that a functional group, the substituent on the chroman skeleton, and/or the double bonds on the side chain, has some influence on the activity. To investigate which features in those structures are important, we have synthesized various types of chroman compounds based on garcinoic acid (**1**), and found a very powerful antioxidative compound (**10a**) showing activity 18.7 times as strong as that of *dl*-α-tocopherol. In this paper, we describe the syntheses of the chroman compounds and the relationships between the structure and antioxidant activity.

Results

General synthetic methods of compounds for antioxidative evaluation

As a typical example, a synthesis of the chroman (**4**) is shown in Scheme 1. Compound **6**, derived easily from *o*-cresol,[3] was treated with *n*-butyl lithium, cuprous iodide and geranylgeranyl bromide to give the 2-alkylated hydroquinone dimethoxymethyl ether (**7d**). Compound **7d** was deprotected with concentrated hydrochloric acid in a mixture of chloroform and methanol as solvent to give an alkylated hydroquinone (**8d**), which was oxidized with manganese oxide in benzene to afford the corresponding quinone (**9d**). Compound **9d** was treated with pyridine under reflux to give a cyclized compound, chromen (**10d**), and then hydrogenated with platinum oxide in ethyl acetate to afford the chroman (**4**) having a saturated side chain. Compound **4** was identical with a compound derived from the natural product **3**. On the other hand, a hydroquinone with a saturated side chain (**12**) was prepared by hydrogenation of **7**, followed by deprotection (Scheme 2).

Other derivatives with a side chain of different lengths were also synthesized, using isoprenyl bromide, geranyl bromide and farnesyl bromide instead of geranylgeranyl bromide, according to similar methods described above.

Involvement in the functional groups on the side chain and benzene ring

Since δ-tocopherol has a very similar structure to that of garcinoic acid, at the beginning of this study, we investigated the participation in the side chain on the antioxidant activity. As shown in Table 1, the terminal functional groups on the side chain such as carboxylic acid (**1**), aldehyde (**2**), methyl (**3**), methoxycarbonyl (**1b**) and hydroxymethyl (**5**) groups had minimal influence on the activity. However, a phenolic hydroxyl group appears to be essential to the activity, because the methyl ether derivatives (**1c** and **1d**) of **1** and **1b** did not show any activity. On the basis of these results, the activities of the compounds having a methyl group at the end of the side chain were investigated in this study.

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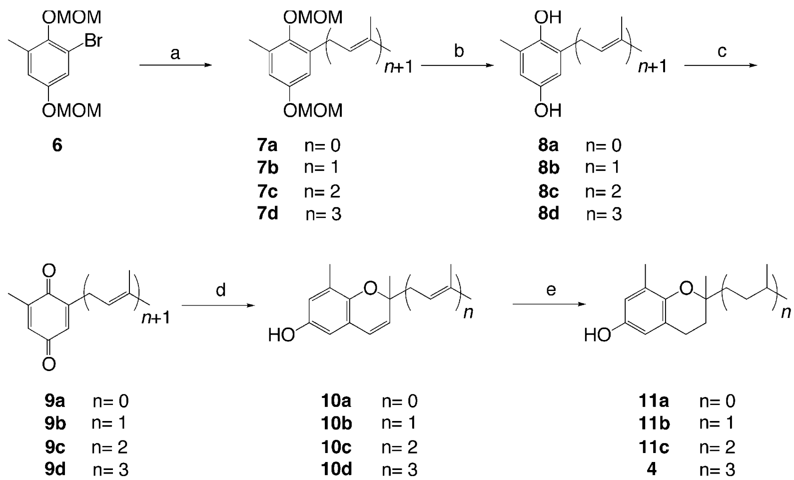
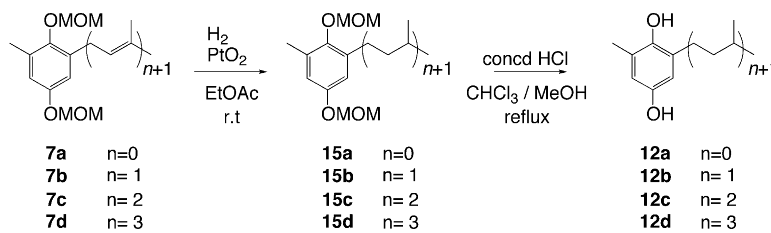


Scheme 1. Synthesis of hydroquinones, chromens and chromans. Reagents: (a) (1) *n*-BuLi, CuI, −78 °C (2), rt: Br$(\;)_{n+1}$ (b) concd HCl, MeOH/$CHCl_3$, reflux; (c) MnO_2: benzene, rt; (d) pyridine, reflux; (e) PtO_2, AcOEt, rt.



Scheme 2. Synthesis of saturated hydroquinones.

Involvement in the length of the side chain

Table 2 shows the relationship between the chain length and antioxidative activity. The results demonstrated that the length of the side chain had significant influence on the activity. The decrease of the number of carbons on the side chain (in the order of R = farnesyl, geranyl, isoprenyl and H) caused an increase of the activity in all cases.

Involvement in the pyran ring

Garcinoic acid and vitamin E exhibit high antioxidant potency, and they all have a pyran ring in their molecule. To ascertain whether the pyran ring is critical for the antioxidative activity, we compared the activities of hydroquinones (**12a–d**), which correspond to the ring-opening compounds of the pyrans (**11a–c** and **4**), with those of pyrans. As the result, it was shown that the activity of the hydroquinones decreased markedly in all cases.

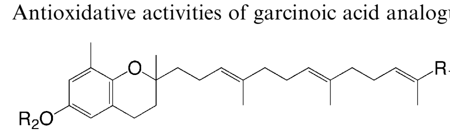
Involvement in the unsaturated bond

The remaining points to be investigated were the unsaturated bonds on the side chain and the pyran ring. First, the contribution of the unsaturated bonds on the side chain to the antioxidative activity was investigated using δ-tocotrienol and δ-tocopherol (**4**). This comparison revealed that unsaturation or saturation of the side-chain did not have any influence practically on the activity. Moreover, as shown in Table 2, the activities of compounds which possess unsaturated bonds on the pyran ring and side chain were 1.5–2.0 times as strong as those of compounds with a dihydropyran ring as well as a saturated side chain.

Discussion

We synthesized various types of analogues which are structurally related to garcinoic acid (**1**) for the structure–antioxidative activity relationships, and their

Table 1. Antioxidative activities of garcinoic acid analogues



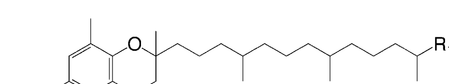
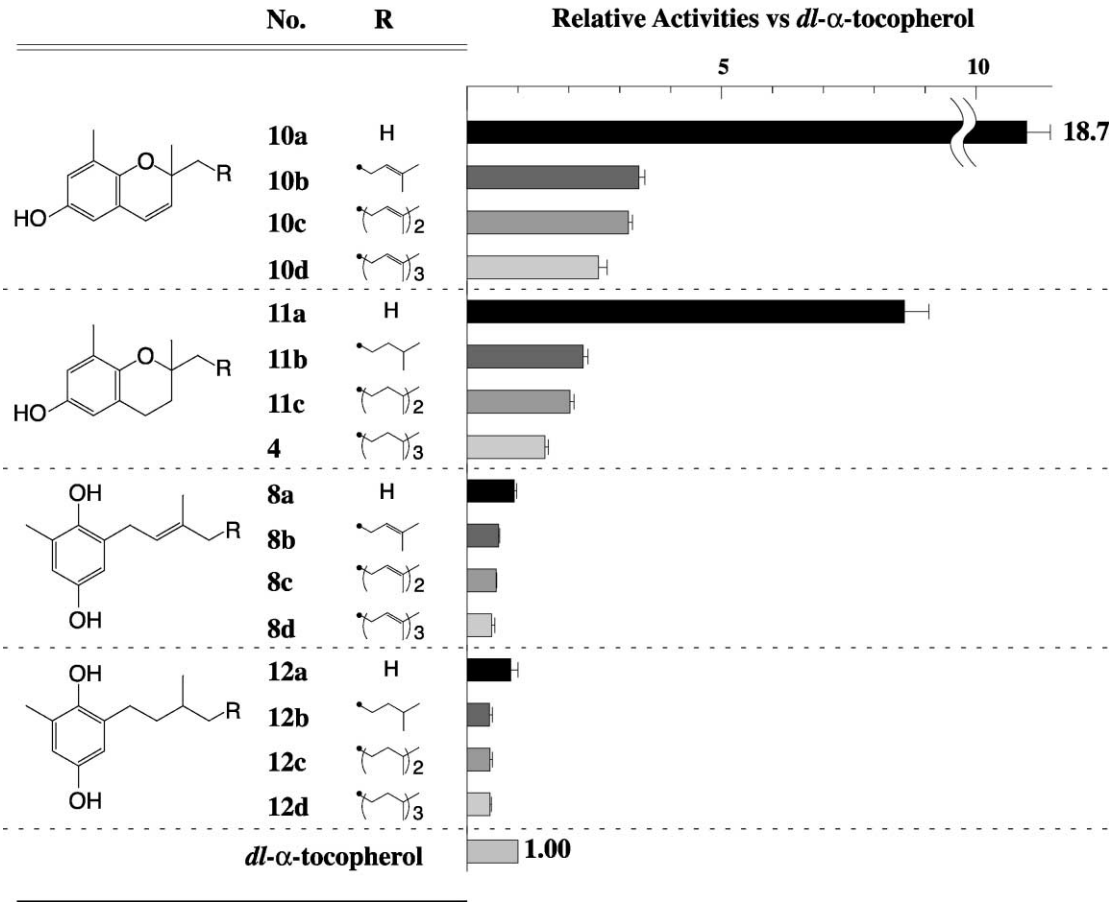
Entry	R_1	R_2	Antioxidant activity
δ-Tocotrienol (**3**)	CH_3	H	1.47±0.03
(**5**)	CH_2OH	H	1.52±0.05
Garcinal (**2**)	CHO	H	1.52±0.01
Garcinoic acid (1)	COOH	H	1.53±0.05
(**1b**)	$COOCH_3$	H	1.51±0.04
(**1c**)	COOH	CH_3	0
(**1d**)	$COOCH_3$	CH_3	0
			
δ-Tocepherol (**4**)	CH_3	H	1.53±0.09
(**4b**)	COOH	H	1.53±0.02
(**4c**)	$COOCH_3$	H	1.51±0.01

Table 2. Relative antioxidative activities versus *dl*-α-tocopherol



antioxidative activities were investigated. As the result, we found a very powerful antioxidative compound (**10a**) which is 18.7 times stronger than *dl*-α-tocopherol. The activity was consequently found to be affected significantly by structural features.

The activity does not depend on the oxidative state of the terminal of the side chain, but on its length. That is to say, the shorter the side chain, the higher the potency. The mono prenylated analogues showed the most powerful activity. Especially in the case of pyran-type compounds, the decrease of the isoprenyl unit dramatically strengthened the activities [1.53 (**4**) to 8.11 (**11a**), and 2.58 (**10d**) to 18.7 (**10a**)]. Furthermore, chromen-type compounds showed stronger activity than chroman-type compounds, though both of them are significantly superior to hydroquinone-type compounds which were obtained as the synthetic intermediates. Consequently, to exhibit the strongest antioxidative activity, as observed in compound **10a**, such simple structural characteristics possessing a phenolic hydroxyl group, a chromen moiety and a shorter side chain were revealed to be critical.

The mechanism to show antioxidative activity of vitamin E suggested that a phenoxyl radical, which is formed via the phenolic hydroxyl group at the 4′-position, inhibits the autoxidation of lipids.[4] This hypothesis was proved by the evidence that the methylated compound at the 4′-position of δ-tocotrienol did not show the activity. However, the participation of the shorter side chain and the pyran ring was not studied in detail. On the basis of the results mentioned above, the mechanism will be revealed, and it will be discussed elsewhere.

The strong antioxidative compounds described in this paper will be lead compounds of drugs which prevent oxidative stress diseases such as aging, inflammation, carcinogenesis, arteriosclerosis and so on.

Experimental

General

IR spectra were recorded on JASCO FT/IR-5000 spectrometer. ^{1}H NMR spectra were recorded on JEOL A-400 spectrometer using chloroform-*d* as solvent. Chemical shifts for ^{1}H NMR are given in parts per million (δ) relative to solvent signal (chloroform-*d*: δ_H 7.24) as internal standards. EI-MS was obtained with Hitachi M-80 and JEOL MS-700 spectrometers, and FABMS was obtained with JEOL HX-110 spectrometer using *m*-nitrobenzyl alcohol as a matrix. Analytical and preparative TLC were performed on silica gel 60 F254

(Merck) with the thickness 0.25 and 0.5 mm, respectively. Column chromatography was carried out on silica gel BW-820MH (Fuji Silysia Chemicals, Co., Ltd.).

Antioxidant activity assay[2]

A mixture of 0.2 M Tris–HCl buffer (pH 7.4), 8 mM sodium arachidonate, a mathanolic solution of an antioxidant, 1 mM bleomycin and 1.08 mM $FeSO_4$ (each 1 mL) was incubated at 37 °C for 5 min, followed by addition of 0.2 M HCl (10 μL). After addition of 0.5% thiobarbituric acid (0.2 mL), the solution was incubated at 37 °C for 30 min. Then, H_2O (0.4 mL) and *n*-BuOH (1 mL) were added, and the mixture was vigorously shaken and centrifuged at 3000 rpm for 10 min. The absorbance of the *n*-BuOH layer at 532 nm was measured by spectrophotometry. The concentration of *dl*-α-tocopherol, used as the positive control, and samples was controlled to 0.15 mM. The abosorbance of methanol only instead of samples were served as a blank. The relative antioxidative activity was defined as a ratio of the value of sample to that of *dl*-α-tocopherol.

Isolation of garcinoic acid (1) and garcinal (2)

Garcinoic acid (**1**) and garcinal (**2**) were isolated from the seed of *Garcinia kora* described in ref 1.

Preparation of methyl garcinoate (1b). Garcinoic acid (**1**) (442 mg, 1.04 mmol) in 10 mL of diethylether was treated with a ethereal solution of diazomethane at −78 °C for 5 min. After evaporation of the solvent, the residue was subjected to column chromatography using SiO_2 [hexane–acetone (4:1)] to give a methyl ester (**1b**) (367 mg, 80%) as a colorless oil.

Data of **1b**: IR ν_{max} (film) 3410, 1696, 1646 cm^{-1}; ^1H NMR δ 1.24 (3H, s), 1.57 (2H, m), 1.57 (3H, s), 1.61 (3H, s), 1.74 (2H, m), 1.81 (3H, d, $J=1.5$ Hz), 1.95 (2H, t, $J=7.4$ Hz), 2.02–2.07 (6H, m), 2.10 (3H, s), 2.21 (2H, dt, $J=7.3$, 7.7 Hz), 2.67 (2H, t, $J=6.6$ Hz), 3.71 (3H, s), 4.53 (1H, s, D_2O exchangeable), 5.09 (2H, br t, $J=7.6$ Hz), 6.36 (1H, d, $J=2.9$ Hz), 6.46 (1H, d, $J=2.9$ Hz), 6.72 (1H, dt, $J=1.5$, 7.3 Hz); EI-MS *m/z* 440 $[M]^+$; EI-HRMS *m/z* 440.2947 $[M^+]$ ($C_{28}H_{40}O_4$ requires 440.2927).

Preparation of methyl garcinoate 4′-methyl ether (1d). A mixture of methyl garcinoate (**1b**) (88 mg, 20 mmol), methyl iodide (57 mg, 40 mmol) and potassium carbonate (55 mg, 40 mmol) in acetone (15 mL) was stirred at room temperature for 12 h. The reaction mixture was successively washed with water and brine, and dried over anhydrous sodium sulfate. Crude product was purified using SiO_2 column and chloroform as eluent to afford the methyl ether (**1d**) (66 mg, 72%) as a colorless oil.

Data of **1d**: IR ν_{max} (film) 1717, 1653 cm^{-1} ^1H NMR δ 1.24 (3H, s), 1.54 (2H, m), 1.54 (3H, s), 1.57 (3H, s), 1.74 (2H, m), 1.80 (3H, s), 1.96 (2H, t, $J=7.4$ Hz), 2.02–2.13 (6H, m), 2.13 (3H, s), 2.23 (2H, dt, $J=7.3$, 7.6 Hz), 2.71 (2H, br t, $J=6.6$ Hz), 3.71 (6H, s), 5.11 (2H, br t, $J=7.0$ Hz), 6.42 (1H, d, $J=3.0$ Hz), 6.54 (1H, d, $J=3.0$ Hz), 6.72 (1H, qt, $J=1.5$, 7.3 Hz); EI-MS *m/z* 454 $[M]^+$; EI-HRMS *m/z* 454.3079 $[M^+]$ ($C_{29}H_{42}O_4$ requires 454.3083).

Preparation of garcinoic acid 4′-methyl ether (1c). Compound **1d** (40 mg, 0.09 mmol) in 5 mL of 0.35 M potassium hydroxide–methanol solution was refuxed for 3 h. The reaction mixture was neutralized with concentrated HCl and extracted with ethyl acetate. The ethyl acetate layer was washed successively with water and brine, and dried over anhydrous sodium sulfate. Purification by column chromatography on SiO_2 [hexane–ethyl acetate (3:1)] afforded **1c** (24 mg, 64%) as a yellow oil.

Data of **1c**: IR ν_{max} (film) 3450 (br), 1688 cm^{-1}; ^1H NMR δ 1.24 (3H, s), 1.57 (2H, m), 1.57 (3H, s), 1.58 (3H, s), 1.73 (2H, m), 1.81 (3H, s), 1.96 (2H, t, $J=7.0$ Hz), 2.02–2.13 (6H, m), 2.13 (3H, s), 2.26 (2H, dt, $J=7.3$, 7.6 Hz), 2.71 (2H, br t, $J=7.0$ Hz), 3.71 (3H, s), 5.11 (2H, br t, $J=7.3$ Hz), 6.42 (1H, d, $J=3.0$ Hz), 6.85 (1H, d, $J=3.0$ Hz), 6.85 (1H, qt, $J=1.5$, 7.3 Hz); EI-MS *m/z* 440 $[M]^+$; EI-HRMS *m/z* 440.2940 $[M^+]$ ($C_{28}H_{40}O_4$ requires 440.2927).

Hydrogenation of garcinoic acid to form saturated garcinoic acid (4b). Garcinoic acid (**1**) (17 mg, 0.04 mmol) and platinum oxide (5 mg) in ethyl acetate (5 mL) were stirred under hydrogen atmosphere at room temperature for 2 h. The mixture was filtered through Celite afforded a saturated garcinoic acid (**4b**) (17 mg, 100%) as a yellow oil.

Data of **4b**: IR ν_{max} (film) 3330 (br) cm^{-1}; ^1H NMR δ 0.80–1.80 (32H, m), 2.09 (3H, s), 2.43 (2H, dt, $J=7.3$, 7.3 Hz), 2.65 (2H, t, $J=7.0$ Hz), 6.36 (1H, d, $J=2.2$ Hz), 6.46 (1H, d, $J=2.2$ Hz); EI-MS *m/z* 432 $[M]^+$; EI-HRMS *m/z* 432.3216 $[M^+]$ ($C_{27}H_{44}O_4$ requires 432.3240).

Hydrogenation of methyl garcinoate to form saturated methyl garcinoate (4c). Methyl garcinoate (**1b**) (11 mg, 0.01 mmol) and platinum oxide (5 mg) in ethyl acetate (5 mL) were stirred under hydrogen atmosphere at room temperature for 2 h. The mixture was filtered through celite afforded a saturated garcinoic acid (**4c**) (11 mg, 99%) as a yellow oil.

Data of **4c**: IR ν_{max} (film) 1740 cm^{-1}; ^1H NMR δ 0.80–1.81 (36H, m), 2.10 (3H, s), 2.44 (2H, dt, $J=7.3$, 7.6 Hz), 2.70 (2H, br t, $J=7.0$ Hz), 3.71 (3H, s), 6.42 (1H, d, $J=2.7$ Hz), 6.54 (1H, d, $J=2.7$ Hz); EI-MS *m/z* 446 $[M]^+$; EI-HRMS *m/z* 446.3390 $[M^+]$ ($C_{28}H_{46}O_4$ requires 446.3396).

Reduction of garcinoic acid to form primary alcohol (5). A mixture of methyl garcinoate (**1b**) (448 mg, 1.02 mmol), *N*,*N*-diisopropylethylamine (526 mg, 4.08 mmol) and methoxymethyl chloride (328 mg, 4.08 mmol) in dichloromethane (60 mL) was stirred at room temperature for 12 h. The reaction mixture was extracted

with chloroform and the organic layer was washed successively with water and brine, and dried over anhydrous sodium sulfate. Purification by column chromatography on SiO_2 (chloroform as eluent) afforded MOM ether (**13**) (382 mg, 77%) as a colorless oil.

MOM ether (**13**) (349 mg, 0.72 mmol) in 40 mL of THF was treated with lithium aluminum hydride (110 mg, 2.90 mmol) at room temperature for 12 h. After addition of methanol (35 mL), the mixture was filtered through celite. The filtrate was extracted with ethyl acetate, and then successively washed with water and brine, and dried over anhydrous sodium sulfate. By column chromatography, using SiO_2 [hexane–ethyl acetate (5:1)] afforded a primary alcohol (**14**) (222 mg, 70%) as a colorless oil.

The alcohol (**14**) (40 mg, 0.09 mmol) in a mixed solvent of chloroform and methanol (1:1) (1.5 mL) was treated with concentrated HCl (50 μL) under reflux for 1 h. The mixture was extracted with chloroform and then washed successively with water and brine, and dried over anhydrous sodium sulfate. The crude product was purified by preparative TLC on SiO_2 [hexane–ethyl acetate (5:1)] afforded a reduced garcinoic acid (**5**) (29 mg, 81%) as a colorless oil.

Data of **13**: IR ν_{max} (film) 3372 (br) cm^{-1}; ^1H NMR δ 1.24 (3H, s), 1.58 (2H, m), 1.58 (6H, s), 1.74 (2H, m), 1.81 (3H, d, $J=1.5$ Hz), 1.95 (2H, t, $J=7.4$ Hz), 2.04–2.11 (6H, m), 2.13 (3H, s), 2.24 (2H, dt, $J=7.3$, 7.7 Hz), 2.70 (2H, t, $J=6.6$ Hz), 3.46 (3H, s), 3.71 (3H, s), 5.05 (2H, s), 5.11 (2H, qt, $J=1.5$, 7.6 Hz), 6.58 (1H, d, $J=2.9$ Hz), 6.66 (1H, d, $J=2.9$ Hz), 6.72 (1H, qt, $J=1.5$, 7.3 Hz); EI-MS m/z 484 $[M]^+$; EI-HRMS m/z 484.3214 $[M^+]$ ($C_{30}H_{44}O_5$ requires 484.3189).

Data of **14**: IR ν_{max} (film) 3372 (br) cm^{-1}; ^1H NMR δ 1.24 (3H, s), 1.55 (2H, m), 1.55 (3H, s), 1.56 (3H, s), 1.64 (3H, s), 1.75 (2H, m), 1.93–2.11 (10H, m), 2.12 (3H, s), 2.70 (2H, t, $J=7.0$ Hz), 3.46 (3H, s), 3.97 (2H, s), 5.05 (2H, s), 5.09 (2H, qt, $J=1.5$, 7.3 Hz), 5.11 (1H, qt, $J=1.5$, 7.3 Hz), 5.36 (1H, dt, $J=1.5$, 7.3 Hz), 6.58 (1H, d, $J=2.9$ Hz), 6.62 (1H, d, $J=2.9$ Hz); EI-MS m/z 456 $[M]^+$; EI-HRMS m/z 456.3249 $[M^+]$ ($C_{29}H_{44}O_4$ requires 456.3240).

Data of **5**: IR ν_{max} (film) 3330 (br) cm^{-1}; ^1H NMR δ 1.24 (3H, s), 1.55 (2H, m), 1.55 (3H, s), 1.57 (3H, s), 1.64 (3H, s), 1.75 (2H, m), 1.93–2.11 (10H, m), 2.11 (3H, s), 2.67 (2H, br t, $J=7.0$ Hz), 3.98 (2H, s), 5.07 (2H, br t, $J=6.8$ Hz), 5.36 (1H, dt, $J=1.5$, 7.3 Hz), 6.35 (1H, d, $J=3.0$ Hz), 6.45 (1H, d, $J=3.0$ Hz); EI-MS m/z 412 $[M]^+$; EI-HRMS m/z 412.2960 $[M^+]$ ($C_{27}H_{40}O_3$ requires 412.2977).

Preparation of hydroquinone (8). To a solution of the protected hydroquinone (**6**)[3] (462 mg, 1.59 mmol) in THF (30 mL) was added *n*-BuLi (152 mg, 2.38 mmol) at −78 °C. The mixture was kept at −78 °C for 30 min followed by addition of copper iodide(I) (456 mg, 2.38 mmol), and stirred for 2 h. A solution of geranylgeranyl bromide (731 mg, 2.07 mmol) in THF (5 mL) was added dropwise, and then the mixture was warmed to room temperature for 1.5 h. The mixture was extracted with ethyl acetate and then washed successively with 5% $NaHCO_3$ aqueous solution, water and brine, and dried over anhydrous sodium sulfate. Purification by flash chromatography on SiO_2 [hexane–chloroform (1:1)] afforded a geranylgeranyl protected hydroquinone (**7d**) (252 mg, 33%) as a yellow oil. In the same manner, **7a–c** were prepared using isopentenyl bromide, geranyl bromide and farnesyl bromde instead of geranylgeranyl bromide, respectively.

To the MOM ether (**7d**) (120 mg, 0.25 mmol) in a mixed solvent of chloroform and methanol (1:1) (5 mL) was added with concentrated hydrochloric acid (30 μL), and the mixture was refluxed for 1 h. The mixture was extracted with chloroform (20 mL) and then the resulted organic layer was washed successively with water and brine, and dried over anhydrous sodium sulfate. Purification by column chromatography on SiO_2 [chloroform–ethyl acetate (20:1)] afforded a hydroquinone (**8d**) (96 mg, 98%) as a yellow oil. In the same manner, **8a–c** were prepared.

Data of **7a**: ^1H NMR δ 1.68 (3H, s), 1.72 (3H, d, $J=1.4$ Hz), 2.26 (3H, s), 3.32 (2H, d, $J=7.3$ Hz), 3.45 (3H, s), 3.58 (3H, s), 4.89 (2H, s), 5.09 (2H, s), 5.25 (1H, qt, $J=1.4$, 7.3 Hz), 6.66 (1H, d, $J=2.9$ Hz), 6.70 (1H, d, $J=2.9$ Hz); EI-MS m/z 280 $[M^+]$, 203 (base); EI-HRMS m/z 280.1683 $[M^+]$ ($C_{16}H_{24}O_4$ requires 280.1675).

Data of **7b**: ^1H NMR δ 1.58 (3H, s), 1.66 (3H, s), 1.68 (3H, s), 2.09 (4H, d, $J=7.7$ Hz), 2.26 (3H, s), 3.34 (2H, d, $J=7.3$ Hz), 3.45 (3H, s), 3.58 (3H, s), 4.89 (2H, s), 5.08 (2H, s), 5.08 (1H, t, $J=7.7$ Hz), 5.28 (1H, t, $J=7.3$ Hz), 6.67 (1H, d, $J=2.9$ Hz), 6.70 (1H, d, $J=2.9$ Hz); EI-MS m/z 348 $[M^+]$, 69 (base); EI-HRMS m/z 348.2476 $[M^+]$ ($C_{21}H_{32}O_4$ requires 348.2301).

Data of **7c**: ^1H NMR δ 1.53 (3H, s), 1.58 (6H, s), 1.66 (3H, s), 1.95–2.15 (8H, m), 2.26 (3H, s), 3.33 (2H, d, $J=7.4$ Hz), 3.45 (3H, s), 3.58 (3H, s), 5.08 (2H, s), 5.09 (2H, s), 5.10 (2H, t, $J=7.4$ Hz), 5.28 (1H, t, $J=7.0$ Hz), 6.66 (1H, d, $J=2.4$ Hz), 6.70 (1H, d, $J=2.4$ Hz); EI-MS m/z 416 $[M^+]$, 149 (base); EI-HRMS m/z 416.2941 $[M^+]$ ($C_{26}H_{40}O_4$ requires 416.2927).

Data of **7d**: ^1H NMR, δ 1.53 (3H, s), 1.66 (6H, s), 1.68 (6H, s), 1.90–2.09 (12H, m), 2.26 (3H, s), 3.33 (2H, d, $J=7.0$ Hz), 3.45 (3H, s), 3.58 (3H, s), 4.89 (2H, s), 5.08 (2H, s), 5.09 (3H, t, $J=7.3$ Hz), 5.26 (1H, t, $J=7.3$ Hz), 6.66 (1H, d, $J=2.9$ Hz), 6.70 (1H, d, $J=2.9$ Hz); EI-MS m/z 484 $[M^+]$, 149 (base); EI-HRMS m/z 484.3560 $[M^+]$ ($C_{31}H_{48}O_4$ requires 484.3553).

Data of **8a**: IR ν_{max} (film) 3400 (br) cm^{-1}; ^1H NMR, δ 1.73 (3H, s), 1.75 (3H, s), 2.17 (3H, s), 3.26 (2H, d, $J=7.3$ Hz), 4.34 (1H, s, –OH), 4.72 (1H, s, –OH), 5.26 (1H, t, $J=7.3$ Hz), 6.43 (1H, d, $J=3.2$ Hz), 6.48 (1H, t, $J=3.2$ Hz); EI-MS m/z 192 $[M^+]$, 175 (base); EI-HRMS m/z 192.1159 $[M^+]$ ($C_{12}H_{16}O_2$ requires 192.1150).

Data of **8b**: IR ν_{max} (film) 3450 (br) cm^{-1}; ^1H NMR δ 1.53 (3H, s), 1.67 (3H, s), 1.75 (3H, s), 2.04 (2H, m), 2.16 (2H, m), 2.16 (3H, s), 3.27 (2H, d, $J=7.4$ Hz), 4.60 (1H, s, –OH), 4.77 (1H, s, –OH), 5.03 (1H, t, $J=7.4$ Hz), 5.25 (1H, t, $J=7.4$ Hz), 6.44 (1H, d, $J=2.7$ Hz), 6.48 (1H, d, $J=2.7$ Hz); EI-MS m/z 260 [M^+], 149 (base); EI-HRMS m/z 260.1782 [M^+] ($C_{17}H_{24}O_2$ requires 260.1776).

Data of **8c**: IR ν_{max} (film) 3450 (br) cm^{-1}; ^1H NMR δ 1.55 (3H, s), 1.57 (6H, s), 1.75 (3H, s), 1.95–2.16 (8H, m), 2.03 (3H, s), 3.27 (2H, d, $J=7.3$ Hz), 5.27 (2H, t, $J=7.3$ Hz), 5.28 (1H, t, $J=7.3$ Hz), 6.43 (1H, d, $J=2.7$ Hz), 6.48 (1H, d, $J=2.7$ Hz); EI-MS m/z 328 [M^+], 149 (base); EI-HRMS m/z 328.2408 [M^+] ($C_{22}H_{32}O_2$ requires 328.2402).

Data of **8d**: IR ν_{max} (film) 3450 (br) cm^{-1}; ^1H NMR δ 1.53 (3H, s), 1.58 (6H, s), 1.66 (6H, s), 1.91–2.10 (12H, m), 2.26 (3H, s), 3.33 (2H, d, $J=7.4$ Hz), 5.09 (3H, t, $J=7.4$ Hz), 5.11 (1H, t, $J=7.1$ Hz), 6.66 (1H, d, $J=2.7$ Hz), 6.70 (1H, d, $J=2.7$ Hz); FABMS m/z 397 $[M+H]^+$; FABHRMS m/z 397.3088 $[M+H]^+$ ($C_{27}H_{40}O_2$ requires 397.3107).

Preparation of chromen-type compounds (10). A solution of the hydroquinone (**8d**) (96 mg, 0.24 mmol) in benzene (8 mL) was treated with manganese dioxide (42 mg, 0.48 mmol) at room temperature for 30 min. The mixture was filtered through celite. The fitrate was concentrated in vacuo, and the resulted residue was subjected to flash chromatography on SiO_2 [hexane–ethyl acetate (30:1)] to afford a quinone (**9d**) (72 mg, 76%) as a yellow oil.

A solution of the quinone (**9d**) (37 mg, 0.09 mmol) was refluxed in pyridine (5 mL) under reflux for 4 h. After removal of pyridine by evaporation, the residue was purified by preparative TLC on SiO_2 [hexane–ethyl acetate (15:1)] to afford a chromen (**10d**) (22 mg, 61%) as a yellow oil. Compound **10a**–**c** were prepared in the same manner described above.

Data of **9a**: IR ν_{max} (film) 1655 cm^{-1}; ^1H NMR δ 1.61 (3H, s), 1.73 (3H, d, $J=1.3$ Hz), 2.03 (3H, d, $J=1.3$ Hz), 3.09 (2H, dd, $J=3.0$, 7.3 Hz), 5.19 (1H, qt, $J=1.3$, 7.3 Hz), 6.45 (1H, dt, $J=2.4$, 3.0 Hz), 6.53 (1H, qd, $J=1.3$, 2.4 Hz); EI-MS m/z 190 [M^+], 175 (base); EI-HRMS m/z 190.1005 [M^+] ($C_{12}H_{14}O_2$ requires 190.0994).

Data of **9b**: IR ν_{max} (film) 1650 cm^{-1}; ^1H NMR δ 1.55 (3H, s), 1.58 (3H, s), 1.60 (3H, s), 2.03 (2H, m), 2.04 (3H, s), 2.08 (2H, t, $J=6.6$ Hz), 3.10 (2H, d, $J=7.4$ Hz), 5.05 (1H, t, $J=7.4$ Hz), 5.13 (1H, t, $J=7.4$ Hz), 6.44 (1H, d, $J=2.5$ Hz), 6.53 (1H, d, $J=2.5$ Hz); EI-MS m/z 258 [M^+], 149 (base); EI-HRMS m/z 258.1634 [M^+] ($C_{17}H_{22}O_2$ requires 258.1620).

Data of **9c**: IR ν_{max} (film) 1650 cm^{-1}; ^1H NMR δ 1.55 (3H, s), 1.60 (6H, d, $J=1.0$ Hz), 1.61 (3H, s), 1.98 - 2.12 (8H, m), 2.03 (3H, s), 3.10 (2H, d, $J=7.4$ Hz), 5.07 (2H, t, $J=7.4$ Hz), 5.14 (1H, qt, $J=1.0$, 7.0 Hz), 6.44 (1H, d, $J=2.4$ Hz), 6.53 (1H, qt, $J=1.3$, 2.4 Hz); EI-MS m/z 326 [M^+], 228 (base); EI-HRMS m/z 326.2249 [M^+] ($C_{22}H_{30}O_2$ requires 326.2246).

Data of **9d**: IR ν_{max} (film) 1650 cm^{-1}; ^1H NMR δ 1.55 (3H, s), 1.58 (6H, s), 1.60 (3H, s), 1.65 (3H, s), 1.92–2.03 (8H, m), 2.04 (3H, s), 2.08 (2H, t, $J=6.6$ Hz), 3.10 (2H, d, $J=7.4$ Hz), 5.05 (3H, t, $J=7.4$ Hz), 5.13 (1H, t, $J=7.4$ Hz), 6.44 (1H, d, $J=2.5$ Hz), 6.53 (1H, d, $J=2.5$ Hz); EI-MS m/z 394 [M^+], 175 (base); EI-HRMS m/z 394.2845 [M^+] ($C_{27}H_{38}O_2$ requires 394.2872).

Data of **10a**: IR ν_{max} (film) 3400 (br) cm^{-1}; ^1H NMR δ 1.38 (6H, s), 2.11 (3H, s), 5.60 (1H, d, $J=9.5$ Hz), 6.20 (1H, d, $J=9.5$ Hz), 6.31 (1H, d, $J=2.9$ Hz), 6.46 (1H, d, $J=2.9$ Hz); EI-MS m/z 190 [M^+], 158 (base); EI-HRMS m/z 190.1016 [M^+] ($C_{12}H_{14}O_2$ requires 190.0994).

Data of **10b**: IR ν_{max} (film) 3350 (br) cm^{-1}; ^1H NMR δ 1.34 (3H, s), 1.56 (3H, s), 1.64 (3H, s), 1.66 (2H, m), 2.11 (2H, m), 2.12 (3H, s), 4.40 (1H, s, –OH), 5.08 (1H, t, $J=7.0$ Hz), 5.56 (1H, d, $J=9.8$ Hz), 6.23 (1H, d, $J=9.8$ Hz), 6.30 (1H, d, $J=3.0$ Hz), 6.45 (1H, d, $J=3.0$ Hz); EI-MS m/z 258 [M^+], 175 (base); EI-HRMS m/z 258.1649 [M^+] ($C_{17}H_{22}O_2$ requires 258.1620).

Data of **10c**: IR ν_{max} (film) 3350 (br) cm^{-1}; ^1H NMR δ 1.34 (3H, s), 1.56 (3H, s), 1.65 (3H, d, $J=1.8$ Hz), 1.66 (2H, m), 1.92–2.03 (6H, m), 2.11 (3H, s), 5.06 (1H, qt, $J=1.3$, 7.0 Hz), 5.09 (1H, qt, $J=1.3$, 7.0 Hz), 5.57 (1H, d, $J=9.8$ Hz), 6.23 (1H, d, $J=9.8$ Hz), 6.30 (1H, d, $J=3.0$ Hz), 6.45 (1H, d, $J=3.0$ Hz); EI-MS m/z 326 [M^+], 175 (base); EI-HRMS m/z 326.2238 [M^+] ($C_{22}H_{30}O_2$ requires 326.2246).

Data of **10d**: IR ν_{max} (film) 3350 (br) cm^{-1}; ^1H NMR δ 1.34 (3H, s), 1.56 (3H, s), 1.58 (3H, s), 1.66 (6H, d, $J=1.8$ Hz), 1.66 (2H, m), 1.80–2.11 (10H, m), 2.12 (3H, s), 4.41 (1H, s, –OH), 5.06 (2H, br. t, $J=7.0$ Hz), 5.08 (1H, t, $J=7.0$ Hz), 5.56 (1H, d, $J=9.8$ Hz), 6.23 (1H, d, $J=9.8$ Hz), 6.30 (1H, d, $J=3.0$ Hz), 6.46 (1H, d, $J=3.0$ Hz); EI-MS m/z 394 [M^+], 175 (base); EI-HRMS m/z 394.2841 [M^+] ($C_{27}H_{38}O_2$ requires 394.2872).

Hydrogenation of prenylated chromens to form chroman-type compounds (11). A mixture of the chromen (**10d**) (12 mg, 0.03 mmol) and platinum oxide (5 mg) in ethyl acetate (5 mL) was stirred under hydrogen atmosphere at room temperature for 2 h. The mixture was filtered through celite. After evaporation of the filtrate, the residue was purified by preparative TLC on SiO_2 [hexane–acetone (15:1)] afforded a δ-tocopherol (**4**) (9.3 mg, 74%) as a yellow oil. Compounds **11a**–**c** were also prepared in the same manner from **10a**–**c**.

Data of **11a**: IR ν_{max} (film) 3355 (br) cm^{-1}; ^1H NMR δ 1.30 (6H, s), 1.76 (2H, t, $J=6.8$ Hz), 2.12 (3H, s), 2.70 (2H, t, $J=6.8$ Hz), 6.39 (1H, d, $J=2.9$ Hz), 6.48 (1H, d, $J=2.9$ Hz); EI-MS m/z 192 [M^+], 95 (base); EI-HRMS m/z 192.1141 [M^+] ($C_{12}H_{16}O_2$ requires 192.1150).

Data of **11b**: IR ν_{max} (film) 3375 (br) cm^{-1}; ^1H NMR δ 0.84 (6H, d, $J=8.0$ Hz), 0.86 (3H, s), 1.20–1.70 (9H, m), 1.34 (3H, s), 2.10 (3H, s), 2.67 (2H, t, $J=7.0$ Hz), 6.36

(1H, d, $J=2.8$ Hz), 6.46 (1H, d, $J=2.8$ Hz); EI-MS m/z 262 [M^+], 149 (base); EI-HRMS m/z 262.1939 [M^+] ($C_{17}H_{26}O_2$ requires 262.1933).

Data of **11c**: IR ν_{max} (film) 3375 (br) cm^{-1}; ^1H NMR δ 0.84 (6H, d, $J=7.4$ Hz), 0.86 (3H, d, $J=7.4$ Hz), 1.20–1.60 (18H, m), 1.24 (3H, s), 2.18 (3H, s), 2.46 (1H, td, 5.0, 11.0 Hz), 2.56 (1H, td, $J=5.8$, 11.0 Hz), 6.39 (1H, d, $J=2.8$ Hz), 6.45 (1H, d, $J=2.8$ Hz); EI-MS m/z 332 [M^+], 137 (base); EI-HRMS m/z 332.2898 [M^+] ($C_{22}H_{36}O_2$ requires 332.2715).

Data of **4**: IR ν_{max} (film) 3375 (br) cm^{-1}; ^1H NMR δ 0.83 (6H, d, $J=7.0$ Hz), 0.84 (3H, d, $J=7.4$ Hz), 0.86 (3H, d, $J=7.4$ Hz), 1.20–1.79 (23H, m), 1.23 (3H, s), 2.11 (3H, s), 2.68 (2H, t, 7.0 Hz), 6.37 (1H, d, $J=2.8$ Hz), 6.47 (1H, d, $J=2.8$ Hz); EI-MS m/z 402 $[M]^+$; EI-HRMS m/z 402.3489 [M^+] ($C_{27}H_{46}O_2$ requires 402.3498).

Preparation of hydroquinone possessing saturated side chain (12). A mixture of the protected hydroquinone (**7d**) (15 mg, 0.03 mmol) and platinum oxide (5 mg) in ethyl acetate (5 mL) was stirred at room temperature for 2 h. The mixture was filtered through celite. After evaporation of the filtrate, the residue was purified by preparative TLC on SiO_2 [hexane–acetone (15:1)] afforded a MOM ether having a saturated side-chain (**15d**) (14 mg, 89%) as a yellow oil.

The MOM ether (**15d**) (11 mg, 0.02 mmol) in a mixed solvent of chloroform and methanol (1:1) (5 mL) was refluxed with concentrated hydrochloric acid (30 μL) for 1 h. The mixture was extracted with chloroform (20 mL) and the organic layer was successively washed with water and brine, and dried over anhydrous sodium sulfate. Purification by column chromatography on SiO_2 [chloroform–ethyl acetate (20:1)] afforded compound **12d** (6.3 mg, 77%) as a yellow oil. Compounds **12a**–**c** were also prepared in the same manner.

Data of **15a**: ^1H NMR, δ 0.84 (6H, d, $J=7.4$ Hz), 1.06 (1H, tq, $J=5.5$, 7.4 Hz), 1.26 (2H, dt, $J=5.5$, 7.4 Hz), 2.17 (3H, s), 2.64 (2H, t, $J=7.4$ Hz), 3.45 (3H, s), 3.58 (3H, s), 4.88 (2H, s), 5.10 (2H, s), 6.36 (1H, d, $J=2.6$ Hz), 6.46 (1H, d, $J=2.6$ Hz); EI-MS m/z 282 [M^+], 209 (base); EI-HRMS m/z 282.1861 [M^+] ($C_{12}H_{16}O_2$ requires 282.1831).

Data of **15b**: ^1H NMR δ 0.83 (6H, d, $J=8.0$ Hz), 0.85 (3H, d, $J=7.3$ Hz), 1.10 - 1.60 (10H, m), 2.15 (3H, s), 2.46 (1H, td, $J=5.4$, 11.0 Hz), 2.52 (1H, td, $J=5.9$, 11.0 Hz), 3.45 (3H, s), 3.58 (3H, s), 4.88 (2H, s), 5.08 (2H, s), 6.68 (2H, s); EI-MS m/z 352 [M^+] (base); EI-HRMS m/z 352.2568 [M^+] ($C_{21}H_{36}O_4$ requires 352.2614).

Data of **15c**: ^1H NMR δ 0.83 (6H, d, $J=8.0$), 0.85 (3H, d, $J=8.0$), 0.92 (3H, d, $J=8.0$), 1.20–1.80 (17H, m), 2.25 (3H, s), 2.53 (1H, td, 5.4, 11.0 Hz), 2.63 (1H, td, $J=5.9$, 11.0 Hz), 3.46 (3H, s), 3.58 (3H, s), 4.88 (2H, s), 5.09 (2H, s), 6.68 (2H, s); EI-MS m/z 422 [M^+] (base); EI-HRMS m/z 422.3399 [M^+] ($C_{26}H_{40}O_4$ requires 422.3396).

Data of **15d**: ^1H NMR δ 0.82 (6H, d, $J=8.0$ Hz), 0.85 (6H, d, $J=8.0$ Hz), 0.93 (3H, d, $J=8.0$ Hz), 1.20–1.80 (24H, m), 2.25 (3H, s), 2.45 (1H, td, $J=5.4$, 11.0 Hz), 2.53 (1H, td, $J=5.9$, 11.0 Hz), 3.45 (3H, s), 3.58 (3H, s), 4.88 (2H, s), 5.09 (2H, s), 6.67 (2H, s); FABMS m/z 493 $[M+H]^+$; FABHRMS m/z 493.4252 $[M+H]^+$ ($C_{31}H_{56}O_4$ requires 493.4257).

Data of **12a**: IR ν_{max} (film) 3400 (br) cm^{-1}; ^1H NMR δ 0.84 (6H, d, $J=7.4$ Hz), 1.08 (1H, tq, $J=5.5$, 7.4 Hz), 1.26 (2H, dt, $J=5.5$, 7.4 Hz), 2.17 (3H, s), 2.67 (2H, t, $J=7.4$ Hz), 6.36 (1H, d, $J=2.6$ Hz), 6.46 (1H, d, $J=2.6$ Hz); EI-MS m/z 194 [M^+], 165 (base); EI-HRMS m/z 194.1329 [M^+] ($C_{12}H_{16}O_2$ requires 194.1306).

Data of **12b**: IR ν_{max} (film) 3400 (br) cm^{-1}; ^1H NMR δ 0.84 (6H, d, $J=7.4$ Hz), 0.86 (3H, d, $J=7.3$ Hz), 1.10–1.60 (10H, m), 2.18 (3H, s), 2.47 (1H, td, $J=5.9$, 10.2 Hz), 2.55 (1H, td, $J=5.1$, 10.2 Hz), 6.45 (2H, s); EI-MS m/z 264 [M^+] (base); EI-HRMS m/z 264.2048 [M^+] ($C_{21}H_{36}O_4$ requires 264.2089).

Data of **12c**: IR ν_{max} (film) 3400 (br) cm^{-1}; ^1H NMR δ 0.82 (6H, d, $J=8.0$ Hz), 0.83 (3H, d, $J=8.0$ Hz), 0.92 (3H, d, $J=8.0$ Hz), 1.20–1.60 (17H, m), 2.25 (3H, s), 2.47 (1H, td, 5.4, 11.0 Hz), 2.53 (1H, td, $J=5.9$, 11.0 Hz), 6.69 (2H, s); EI-MS m/z 334 [M^+], 175 (base); EI-HRMS m/z 334.2885 [M^+] ($C_{22}H_{38}O_2$ requires 334.2872).

Data of **12d**: IR ν_{max} (film) 3400 (br) cm^{-1}; ^1H NMR δ 0.82 (6H, d, $J=8.0$ Hz), 0.84 (6H, d, $J=8.0$ Hz), 0.93 (3H, d, $J=8.0$ Hz), 1.20–1.80 (24H, m), 2.25 (3H, s), 2.47 (1H, td, $J=5.4$, 11.0 Hz), 2.53 (1H, td, $J=5.9$, 11.0 Hz), 6.46 (2H, s); FABMS m/z 405 $[M+H]^+$; FABHRMS m/z 405.3726 $[M+H]^+$ ($C_{27}H_{48}O_2$ requires 405.3732).

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