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A General Synthetic Approach to Hydroquinone Meroterpenoids: Stereoselective Synthesis of (+)-(*S*)-Metachromin V and Alliodorol

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A new general synthetic approach to hydroquinone meroterpenoids is here described. The framework of the aforementioned natural compounds was built up through the Li_2CuCl_4 catalysed cross coupling reaction of the 4-substituted-(*E*)-prenyl acetates **9** with 2,5-bis(benzyloxy)phenyl magnesium bromide **8** as a key step. The latter sp^3-sp^2 coupling affords the products in good chemical yields and in very high stereoisomeric purity. A further key step of the present synthetic method consists of the removal of the benzylic protecting groups by a very mild procedure based on the use of lithium naphthalenide. The latter reagent, in combination with aliphatic dialkylamines, is able to cleave all the benzylic protecting groups leaving unaffected the polyenic moieties. By these means, we devised a new synthesis of the natural hydroquinone geranylhydroquinone, farnesylhydroquinone, metachromin V and alliodorol. In addition, the marine meroterpenoid, (+)-(*S*)-metachromin V, was synthesized for the first time; its chemical structure was confirmed and its absolute configuration was unambiguously assigned.

Keywords: Meroterpenoids, Hydroquinones, Stereoselective synthesis, Cross-coupling, Alliodorol, Metachromin V.

The chemical structure **1** (Figure 1) is common to many natural products. These compounds occur in living beings very different from each other such as higher plants [1,2], sponges [3-8], ascidians [9,10] and mushrooms [11]. Since the latter 1,4-hydroquinones are of a mixed biogenetic origin, the structure of the isoprenic moiety may change considerably depending upon the natural sources of **1**.

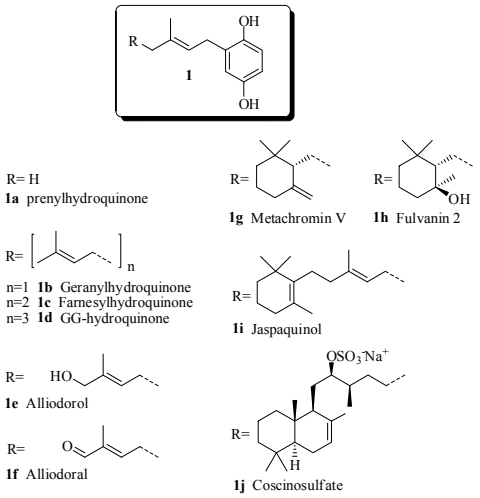

Figure 1: General framework of the 1,4-hydroquinone meroterpenoids **1** and structures of some relevant natural products having the same skeleton.

As a consequence, the biological activity of this class of compounds is quite varied, as demonstrated both by the biological assays on compounds of natural origin and through SAR studies on synthetic derivatives [12,13].

In particular, the prenylated hydroquinones **1a-d** demonstrated high anti-inflammatory activity being able to inhibit both 5-lipoxygenases and tumor necrosis factor α [12]. Otherwise, more complex activities have been ascribed to compounds having a mono or bicylic aliphatic moiety. This is the case with cytotoxic metachromin V [8] (compound **1g**), which inhibits the growth of different human tumor cell lines and of coscinosulfate [6] (compound **1j**) which is a selective inhibitor of CDC25A phosphatase activity.

All these aspects prompted the studies concerning the preparation of different compounds belonging to this class. From a synthetic standpoint, the most obvious approach is based on the preparation of the isoprenic moiety, followed by its coupling with the hydroquinone fragment. Of course, the stereoselective formation of the C-C single bond that links the aromatic ring to the aliphatic chain must proceed without any concomitant double bond isomerization. To overcome this issue, different approaches have been developed (Figure 2).

The simplest synthetic method is based on the electrophilic alkylation of the hydroquinone **2** with the allyl alcohols of type **3** [1, 2]. The process is catalysed by acids and, therefore, suffers from a number of possible side reactions, such as chemical degradation, polymerization and isomerization. Few satisfactory results have been reported, although products having a polyolefinic system or acid-sensitive functional groups can not be prepared by these means. As a consequence, synthetic methods working in basic or neutral conditions are preferred. This is the case with the base catalysed tandem [2,3] and Cope rearrangement of ethers of type **4** [14], which affords hydroquinones **1** in moderate yields. Also for this approach, the harsh experimental conditions, as well as the need of a preliminary preparation of the hydroquinone ether precursors, hamper the general applicability of the method.

On the contrary, the direct sp^2-sp^3 palladium catalyzed coupling of the tributyltin derivative **5** with either halides **6** [13] or carbonates **7** [15] affords **1** in higher yields and milder conditions. According to this approach jaspaquinol (**1i**) and fulvanin 2 (**1h**) were successfully

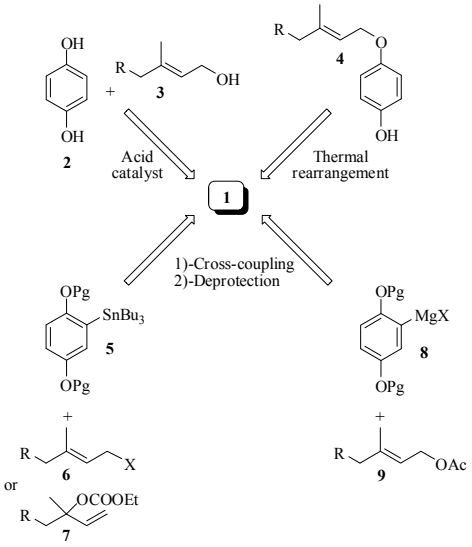

Figure 2: Synthetic approaches to 1,4-hydroquinone meroterpenoids.

prepared. It is worth noting that the cross coupling reaction with carbonate of type **7** does not allow complete stereocontrol, affording compounds of type **1** along with their corresponding (*Z*)-isomers, which are not easily separable. In addition, the organometallic reagents of type **5** require a somewhat demanding preparation.

In order to find a reliable synthetic access to the hydroquinone derivatives of type **1**, we improved the aforementioned cross coupling based approach, overcoming its main drawbacks. More specifically, we envisaged that the organotin derivatives **5** and the halides **6** could be replaced with Grignard reagent **8** and 4-substituted-(*E*)-prenyl acetates **9**, respectively. It has already been demonstrated that allyl acetates react with Grignard reagents in the presence of catalytic Li_2CuCl_4 to give, stereospecifically, the corresponding S_N2 cross-coupling derivatives [16-18], but this specific method has not been applied to the preparation of compounds of type **1** before.

Thus, we prepared 2,5-bis(benzyloxy)phenylmagnesium bromide, starting from bromide **10** (Figure 3), which was in turn synthesized by bromination of hydroquinone **2** followed by benzylation [15]. As first substrates we selected geranyl acetate (**9b**) and farnesyl acetate (**9c**), which were prepared by acetylation of the corresponding commercially available alcohols. The reaction of the aforementioned acetates with an excess of Grignard reagent (**8**) (1.5 eq.) in the presence of catalytic Li_2CuCl_4, at –20°C, afforded coupling products **11b** and **11c** in good yield and with almost complete stereoselectivity.

More specifically, lithium naphthalenide [19, 20] proved to be very effective in accomplishing this deprotection step. Unfortunately, when the starting substrate contains a polyunsaturated system, we observed the formation of side products with a concomitant drop in the overall yields, even at low temperature (–78°C). Most likely this effect is due to the reaction of the formed alkyl lithium derivatives which react with either substrates or products before quenching. Hence, we slightly modified the original procedure, introducing an excess of dialkylamine (diethyl or diisopropyl, more than 2 eq.) directly into the reaction mixture. The aforementioned amines do not react with lithium naphthalenide, but are able to quench alkyl lithium derivatives as soon as they are formed.

According to our thinking, our improved deprotection procedure turned out to be effective and reliable when applied to the synthesis

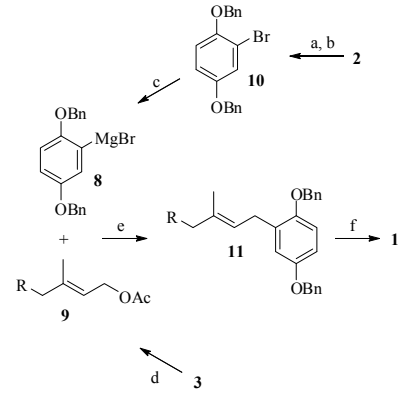

Figure 3: The stereoselective synthesis of **1** based on the copper catalyzed cross-coupling of Grignard reagent **8** with acetates **9**. Reagents and conditions: a) Br_2, *t*BuOMe, 0°C; b) BnBr, K_2CO_3, acetone, reflux 12 h; c) Mg turnings, THF, reflux; d) Ac_2O, Py; e) **9**, Li_2CuCl_4 cat., **8**, 1.5 eq.**,** THF, –20°C, 2 h, then rt 2-4 h; f) Lithium naphthalenide, 8 eq., THF/Et_2NH, –78°C, 2-6 h.

of all the compounds reported in this paper. By these means, compounds **1b** and **1c** were prepared in good overall yields and their spectral data were in good agreement with those reported for the natural products [1, 2, 10].

Taking advantage of the acquired experience, we decided to achieve the synthesis of further natural products of type **1**. As we have recently developed the enantiospecific preparation of (*S*)-γ-monocyclofarnesol (**3g**) (Figure 4) by a chemo-enzymatic approach [21, 22], we selected metachromin V [8] (compound **1g**) as an ideal synthetic target. In effect, the isoprenic moiety of the latter meroterpene matches entirely with the chemical structure of **3g**. In addition, metachromin V was isolated in racemic form and its chemical structure was assigned only on the basis of its spectral data. Therefore, both its absolute configuration and its structure still remain to be assigned unambiguously. Moreover, the biological properties of **1g** were investigated only on a racemic specimen. Hence, the preparation of its enantiomeric forms could give more information about the bioactivity of the meroterpene itself.

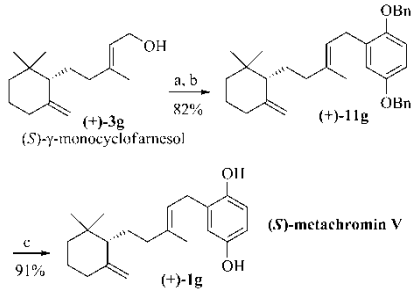

Figure 4: Synthesis of (*S*)-(+)-metachromin (**1g**) starting from (*S*)-γ- monocyclofarnesol (**3g**). Reagents and conditions: a) Ac_2O, Py; b) Li_2CuCl_4 cat., **8**, 1.5 eq.**,** THF, –20°C 2 h, then rt 2 h; c) Lithium naphthalenide, 8 eq., THF/Et_2NH, –78°C, 4 h.

According to our synthetic approach, an (*S*)-**3g** sample having high stereoisomeric purity (98% isomeric purity and 96% ee) was acetylated and the acetate was treated with Grignard reagent **8** in the presence of catalytic Li_2CuCl_4, at –20°C. The coupling product (+)-**11g** was obtained in good yield and with almost complete stereocontrol. The following cleavage of the two benzyl ether groups was efficiently performed at –78°C, using lithium naphthalenide in the presence of Et_2NH. The obtained (+)-(*S*)-metachromin V (**1g**) showed spectroscopic data consistent with those recorded for the natural product [8], thus allowing us to confirm unambiguously the chemical structure assigned to the meroterpene extracted from the marine sponge *Thorecta reticulata*.

As a final point, we would also check the applicability of our procedure to the synthesis of compounds having allyl hydroxy groups (or their derivatives) in their chemical scaffold. Actually, the presence of this kind of functional groups might imply some problem of regioselectivity both in the cross coupling step and in the deprotection reaction. To this end we selected alliodorol **1e** (Figure 5) as a suitable target to be stereoselectively prepared in order to substantiate the reliability of our method. The aforementioned meroterpene is a natural compound isolated from the heartwood of *Cordia alliodora* [1] and possesses a prenol group with (*E*)-configuration.

According to our approach, the most logical precursor of alliodorol **1e** is compound **9e**, which is easily preparable by oxidation of geraniol acetate (**9b**) [23]. Hence, the latter ester was treated with *tert*-butyl hydroperoxide in the presence of a catalytic amount of SeO_2 to afford, regioselectively, alcohol **9e** contaminated with the corresponding aldehyde. The protection of the hydroxyl group as TBDPS ether gave compound **12**, and the following cross-coupling reaction with Grignard reagent **8** afforded compound **13** as a single isomer. The removal of the protecting groups was performed stepwise. Since compound **13** contains two different kinds of allyl ether, the direct reaction with lithium naphthalenide should be avoided so as not to run into problems of regioselectivity. Therefore, the silyl ether was first hydrolysed by means of TBAF in THF and the obtained alcohol **11e** was treated with LDA at low temperature (–78°C). Through this means, the obtained lithium alcolate acquires a negative charge on the oxygen atom and, therefore, should be unreactive toward the dissolving metal reagents. Our experiments confirmed that the latter lithium salt was actually unaffected by lithium naphthalenide.

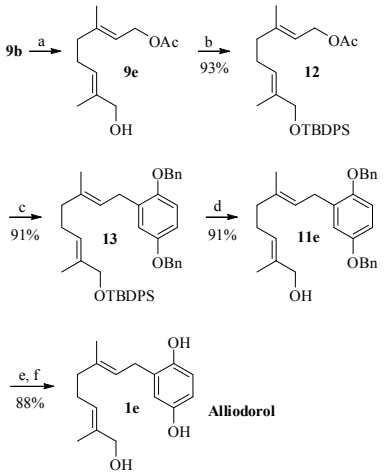

Figure 5: Synthesis of the 1,4-hydroquinone meroterpenoid alliodorol (**1e**) starting from geranyl acetate (**9b**). Reagents and conditions: a) 1.2 eq. of *t*BuOOH aq., 0.02 eq. of SeO_2, 0.1 eq. of salicylic acid, CH_2Cl_2, rt, 24 h; b) TBDPSiCl, imidazole, DMAP cat., DMF, rt 4 h; c) Li_2CuCl_4 cat., **8**, 1.5 eq., THF, –20°C, 2 h, then rt 3 h; d) TBAF, 1.2 eq., THF, rt 2 h; e) LDA, 1.1 eq., THF, –78°C 10 min.; f) Lithium naphthalenide, 8 eq., THF/iPr_2NH, –78 °C, 5 h.

On the contrary, the latter reagent cleaved efficiently the benzyl protecting groups to afford alliodorol (**1e**) in good yield, without any detectable isomeric impurity and showing spectroscopic data consistent with those recorded for natural alliodorol (**1e**) [1].

In conclusion, we have developed a simple and reliable synthetic path to meroterpenes of type **1**. The method consists of a high stereoselective cross-coupling between 2,5-bis(benzyloxy)phenyl-magnesium bromide and 4-substituted-(*E*)-prenyl acetates **9** catalysed by Li_2CuCl_4.

The obtained compounds of type **11** are effectively debenzylated using lithium naphthalenide in the presence of diethylamine to give the title meroterpenes in good overall yields and with complete stereoselectivity. By these means, we synthesized the natural hydroquinones geranylhydroquinone (**1b**), farnesylhydroquinone (**1c**), metachromin V (**1g**) and alliodorol (**1e**). It is worth noting that the marine meroterpenoid (+)-(*S*)-metachromin V (**1g**) was synthesized for the first time; its chemical structure was confirmed and its absolute configuration was unambiguously assigned.

Experimental

General: All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All reagents were of commercial quality. TLC: Merck silica gel 60 F_{254} plates. CC: silica gel. GC-MS analyses: HP-6890 gas chromatograph equipped with a 5973 mass detector, using a HP-5MS column (30 m × 0.25 mm, 0.25 μm firm thickness; Hewlett Packard) with the following temp. program: 60° (1 min) – 6°/min – 150° (1 min)– 12°/min – 280° (5 min); carrier gas, He; constant flow 1mL/min; split ratio, 1/30; t_R given in min: t_R(**1b**) 25.52, t_R(**1g**) 29.42, t_R(**10**) 30.66; mass spectra: *m/z* (rel.%). Mass spectrum of compounds **1c**, **1g**, **1e**, **11b**, **11c**, **11e**, **12**, and **13** were recorded on a Bruker ESQUIRE 3000 PLUS spectrometer (ESI detector). Optical rotations: Jasco-DIP-181 digital polarimeter, measured at 20°C. Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected. ^1H and ^{13}C spectra and DEPT experiments: $CDCl_3$ solns. at rt; Bruker-AC-400 spectrometer at 400, 100 and 100 MHz, respectively; chemical shifts in ppm relative to internal $SiMe_4$ (=0 ppm), *J* values in Hz.

2-Bromo-1,4-bis(benzyloxy)benzene (**10)**: Bromine (54 g, 338 mmol) was added dropwise to a vigorously stirred solution of hydroquinone (40 g, 363 mmol) in *t*BuOMe (400 mL) keeping the temperature below 0°C by external cooling (ice/NaCl bath). The mixture was allowed to reach rt in the course of 1 h and then was stirred for a further 4 h. The solvent was removed under reduced pressure and the residue was roughly purified by chromatography using *n*-hexane/ethyl acetate (4:1–1:1) as eluent. The obtained monobromo derivative (48.2 g, 256 mmol) was dissolved in acetone (300 mL) and was treated with K_2CO_3 (80 g, 579 mmol) and benzyl bromide (100 g, 585 mmol) stirring at reflux for 12 h. The reaction was then cooled, diluted with cold water and extracted with diethyl ether (2 x 250 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed using *n*-hexane/diethyl ether (95:5–9:1) as eluent to afford pure **10** (62.7 g, 170 mmol, 47% yield overall) as a colorless oil which crystallised on standing.
MP: 54-55ºC (*n*-hexane). Lit. [24] MP: 47-49ºC
^1H NMR (400 MHz, $CDCl_3$): 4.99 (2H, s), 5.03 (2H, s), 6.81-6.89 (2H, m), 7.23 (1H, d, *J* = 2.5 Hz), 7.28-7.49 (10H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 70.8 (CH_2), 71.8 (CH_2), 113.1 (C), 114.6 (CH), 115.4 (CH), 120.1 (CH), 127.2 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 136.6 (C), 136.8 (C), 149.6 (C), 153.5 (C).
GC-MS (EI): *m/z* (%) = 370 [M^++1] (6), 368 [M^+–1] (6), 288 (<1), 211 (1), 197 (1), 169 (1), 141 (1), 115 (1), 91 (100).

(*S*)-γ-Monocyclofarnesol (+)-**3g**: 98% chemical purity, 96% ee, γ/α isomeric ratio 98:2; $[\alpha]_D$: +10.3 (*c* 2, $CHCl_3$) was obtained according to our previously reported procedure [21].

Geranyl acetate (**9b)** was prepared by acetylation of commercial geraniol using pyridine and acetic anhydride followed by aqueous work-up and distillation of the resulting ester at reduced pressure.

Farnesyl acetate (**9c**) **and** (***S***)**-γ-monocyclofarnesol acetate** (**9g**) were prepared according to the following procedure described for farnesol:

Farnesol **3c** (*trans*, *trans* isomer, 1 g, 4.5 mmol) was dissolved in pyridine (3 mL) and acetic anhydride (3 mL). The obtained mixture was set aside for 3 h. The reaction was concentrated in a rotary evaporator and then dried for 1 h further in high vacuum. The residue (1.12 g. 94% yield) consisted of almost pure farnesol acetate (**9c**).

(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dienyl acetate 9e: 96% chemical purity (by GC), was prepared through the stereoselective oxidation of geraniol acetate (**9b**) by means of *t*BuOOH, salicylic acid and catalytic SeO_2 [23].

(2*E*,6*E*)-8-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethylocta-2,6-dienyl acetate (**12**): A solution of acetate **9e** (2.5 g, 11.8 mmol), imidazole (0.9 g, 13.2 mmol) and DMAP (0.1 g, 0.8 mmol) in dry DMF (15 mL) was treated with *tert*-butylchlorodiphenyl silane (3.6 g, 13.1 mmol) stirring at rt for 3 h. The reaction was then quenched by the addition of a saturated solution of $NaHCO_3$ (100 mL) and was extracted with diethyl ether (2 x 100 mL). The combined organic phases were dried and concentrated under reduced pressure. The residue was chromatographed using *n*-hexane/diethyl ether (95:5–9:1) as eluent to afford pure **12** (4.95 g, 93% yield) .
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.06 (9H, s), 1.60 (3H, s), 1.71 (3H, s), 2.02 (3H, s), 2.04-2.11 (2H, m), 2.12-2.21 (2H, m), 4.04 (2H, s), 4.58 (2H, d, *J* = 7.1 Hz), 5.36 (1H, t, *J* = 7.1 Hz), 5.42 (1H, t, *J* = 7.1 Hz), 7.32-7.44 (6H, m), 7.65-7.71 (4H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 13.5 (Me), 16.4 (Me), 19.3 (C), 21.0 (Me), 25.6 (CH_2), 26.8 (Me), 39.2 (CH_2), 61.3 (CH_2), 68.8 (CH_2), 118.4 (CH), 123.5 (CH), 127.5 (CH), 129.5 (CH), 133.9 (C), 134.3 (C), 135.5 (CH), 142.0 (C), 171.0 (C).
MS (ESI): 473.5 (M^++Na)

General procedure for cross-coupling of the Grignard reagent 8 with allyl acetates 9: A solution of bromide **10** (3.69 g, 10 mmol) in dry THF (5 mL) was added dropwise, under a static atmosphere of nitrogen, to a vigorously stirred suspension of activated magnesium turnings in dry THF (15 mL). After the exothermic reaction had settled down, the mixture was stirred at 50°C for a further 2 h. The obtained Grignard reagent **8** was added dropwise, under a static atmosphere of nitrogen, to a cooled (–20°C) mixture of the acetate **9** (5 mmol) in dry THF (20 mL) to which had been previously added Li_2CuCl_4 (0.5 mL of a 0.5 M solution in THF). After stirring for 2 h, the reaction was slowly allowed to reach rt, stirred at this temperature for a further 2 h and then poured into an ice cooled mixture of diethyl ether (100 mL) and saturated aqueous NH_4Cl (100 mL).The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue consisted of a mixture of compound **11** and 1,4-bis(benzyloxy)benzene, which arose from quenching of **8**. The crude product was purified by chromatography using *n*-hexane/diethyl ether (95:5–9:1) as eluent to afford **11**, often containing some residual 1,4-bis(benzyloxy)benzene, which has an Rf very similar to those of the coupling products.

The purity of the obtained compounds **11** was measured by NMR analysis. The yields were calculated by weighing the purified products and taking into account the purity measurements.

(*E*)-2-(3,7-Dimethylocta-2,6-dienyl)-1,4-bis(benzyloxy)benzene 11b: According to the above described procedure, geranyl acetate (**9b**) was converted into hydroquinone derivative **11b** (79% yield).
Amorphous white solid
^{1}H NMR (400 MHz, $CDCl_3$): 1.59 (3H, s), 1.64 (3H, s), 1.66 (3H, s), 1.99-2.15 (4H, m), 3.37 (2H, d, *J* = 7.3 Hz), 4.98 (2H, s), 5.00 (2H, s), 5.11 (1H, br t, *J* = 6.5 Hz), 5.32 (1H, t, *J* = 7.3 Hz), 6.71 (1H, dd, *J* = 8.7, 2.7 Hz), 6.79 (1H, d, *J* = 8.7 Hz), 6.83 (1H, d, *J* = 2.7 Hz), 7.24-7.49 (10H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 16.1 (Me), 17.7 (Me), 25.6 (Me), 26.7 (CH_2), 28.5 (CH_2), 39.7 (CH_2), 70.6 (CH_2), 70.8 (CH_2), 111.8 (CH), 112.8 (CH), 117.0 (CH), 122.1 (CH), 124.3 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 128.4 (CH), 131.3 (C), 132.0 (C), 136.4 (C), 137.5 (C), 137.7 (C), 151.0 (C), 153.1 (C).
MS (ESI): 449.6 (M^++Na)

2-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyl)-1,4-bis(benzyloxy)benzene 11c: According to the above described procedure, farnesyl acetate (**9c**) was converted into hydroquinone derivative **11c** (75% yield).
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.58 (6H, s), 1.64 (3H, s), 1.66 (3H, s), 1.93-2.00 (2H, m), 2.00-2.15 (6H, m), 3.37 (2H, d, *J* = 7.3 Hz), 4.98 (2H, s), 5.01 (2H, s), 5.08 (1H, t, *J* = 6.7 Hz), 5.13 (1H, t, *J* = 6.7 Hz), 5.32 (1H, t, *J* = 7.3 Hz), 6.71 (1H, dd, *J* = 8.5, 3.0 Hz), 6.79 (1H, d, *J* = 8.5 Hz), 6.84 (1H, d, *J* = 3.0 Hz), 7.26-7.45 (10H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 16.0 (Me), 16.1 (Me), 17.6 (Me), 25.7 (Me), 26.6 (CH_2), 26.7 (CH_2), 28.5 (CH_2), 39.7 (CH_2), 39.8 (CH_2), 70.5 (CH_2), 70.7 (CH_2), 111.7 (CH), 112.7 (CH), 116.9 (CH), 122.0 (CH), 124.2 (CH), 124.4 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 131.2 (C), 131.9 (C), 135.0 (C), 136.5 (C), 137.4 (C), 137.6 (C), 150.9 (C), 153.0 (C).
MS (ESI): 517.7 (M^++Na)

(2*E*,6*E*)-8-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethylocta-2,6-dienyl-1,4-bis(benzyloxy)benzene 13: According to the above described procedure, acetate **12** was converted into hydroquinone derivative **13** (91% yield).
Colorless thick oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.05 (9H, s), 1.59 (3H, s), 1.65 (3H, s), 2.01-2.09 (2H, m), 2.09-2.20 (2H, m), 3.36 (2H, d, *J* = 7.1 Hz), 4.04 (2H, s), 4.96 (2H, s), 4.99 (2H, s), 5.33 (1H, t, *J* = 7.1 Hz), 5.43 (1H, t, *J* = 7.1 Hz),), 6.70 (1H, dd, *J* = 8.6, 3.0 Hz), 6.78 (1H, d, *J* = 8.6 Hz), 6.82 (1H, d, *J* = 3.0 Hz), 7.24-7.46 (16H, m), 7.64-7.71 (4H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 13.5 (Me), 16.1 (Me), 19.3 (C), 26.3 (CH_2), 26.9 (Me), 28.6 (CH_2), 39.5 (CH_2), 69.1 (CH_2), 70.6 (CH_2), 70.8 (CH_2), 111.9 (CH), 112.9 (CH), 117.0 (CH), 122.3 (CH), 124.4 (CH), 127.2 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 129.5 (CH), 132.0 (C), 134.0 (C), 134.0 (C), 135.6 (CH), 136.3 (C), 137.5 (C), 137.7 (C), 151.0 (C), 153.1 (C).
MS (ESI): 703.7 (M^++Na)

(*S*)-(*E*)-2-(5-(2,2-Dimethyl-6-methylenecyclohexyl)-3-methylpent-2-enyl)-1,4-bis(benzyloxy)benzene 11g: According to the above described procedure, alcohol **3g** was acetylated and then converted into hydroquinone derivative **11g** (82% overall yield).
Colorless oil
$[\alpha]_D$: +6.1 (*c* 4, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$): 0.82 (3H, s), 0.90 (3H, s), 1-14-1.22 (1H, m), 1.38-1.60 (5H, m), 1.63 (3H, s), 1.70 (1H, dd, *J* = 11.3, 3.0 Hz), 1.73-1.84 (1H, m), 1.91-2.10 (3H, m), 3.36 (2H, d, *J* = 7.3 Hz), 4.53 (1H, s), 4.74 (1H, s), 4.99 (2H, s), 5.01 (2H, s), 5.30 (1H, t,

J = 7.3 Hz), 6.72 (1H, dd, *J* = 8.8, 3.0 Hz), 6.80 (1H, d, *J* = 8.8 Hz), 6.84 (1H, d, *J* = 3.0 Hz), 7.27-7.45 (10H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 16.2 (Me), 23.7 (CH_2), 24.7 (CH_2), 26.3 (Me), 28.4 (Me), 28.5 (CH_2), 32.5 (CH_2), 34.9 (C), 36.3 (CH_2), 38.3 (CH_2), 53.6 (CH), 70.5 (CH_2), 70.7 (CH_2), 108.8 (CH_2), 111.7 (CH), 112.7 (CH), 116.9 (CH), 121.8 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 132.0 (C), 137.1 (C), 137.4 (C), 137.6 (C), 149.3 (C), 150.9 (C), 153.0 (C).

(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dienyl-1,4-bis(benzyloxy)benzene 11e: TBAF (1.25 g of the trihydrate salt, 4 mmol) was added portionwise at rt to a stirred solution of ether **13** (2.5 g, 85% purity, 3.1 mmol) in dry THF (30 mL). When the silyl ether was completely cleaved (4 h), the reaction was diluted with diethyl ether (100 mL) and quenched with water (100 mL). The aqueous phase was then extracted with further ether (100 mL) and the combined organic phases were washed with brine, dried and concentrated *in vacuo*. The residue was purified by chromatography eluting with *n*-hexane-diethyl ether (95:5 – 8:2) as eluent to afford pure **11e** (1.25 g, 91% yield).
Colorless thick oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.37 (1H, br s), 1.63 (3H, s), 1.64 (3H, s), 2.03-2.12 (2H, m), 2.12-2.21 (2H, m), 3.36 (2H, d, *J* = 7.2 Hz), 3.93 (2H, s), 4.99 (2H, s), 5.01 (2H, s), 5.32 (1H, t, *J* = 7.2 Hz), 5.38 (1H, t, *J* = 7.2 Hz), 6.71 (1H, dd, *J* = 8.7, 3.0 Hz), 6.80 (1H, d, *J* = 8.7 Hz), 6.82 (1H, d, *J* = 3.0 Hz), 7.26-7.48 (10H, m).
^{13}C NMR (100 MHz, $CDCl_3$): 13.6 (Me), 16.0 (Me), 26.0 (CH_2), 28.4 (CH_2), 39.3 (CH_2), 68.8 (CH_2), 70.6 (CH_2), 70.9 (CH_2), 111.6 (CH), 112.8 (CH), 117.2 (CH), 122.5 (CH), 125.7 (CH), 127.2 (CH), 127.5 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 128.5 (CH), 132.0 (C), 134.9 (C), 136.0 (C), 137.4 (C), 137.6 (C), 151.0 (C), 153.0 (C).
MS (ESI): 465.6 (M^++Na)

General procedure for debenzylation of compounds 11: Lithium naphthalenide (14 mL of a 0.6 M solution in THF) was added dropwise, under a static atmosphere of nitrogen, to a stirred solution of **11** (1 mmol) and Et_2NH (2 mL) in dry THF (20 mL) at −78°C. After complete cleavage of the benzyl ethers (2-6 h, TLC analysis) the reaction was poured into a mixture of diethyl ether (100 mL) and saturated aqueous NH_4Cl (100 mL). The organic phase was separated and the aqueous phase was extracted with further ether (2 x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed using *n*-hexane/ethyl acetate as eluent to afford pure **1**.

(*E*)-2-(3,7-Dimethylocta-2,6-dienyl)benzene-1,4-diol (1b): According to the above described procedure, compound **11b** was converted into geranyl hydroquinone **1b** (85% yield).
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.60 (3H, s), 1.68 (3H, s), 1.74 (3H, s), 2.02-2.16 (4H, m), 3.29 (2H, d, *J* = 7.3 Hz), 4.68 (1H, br s), 4.81 (1H, br s), 5.04-5.10 (1H, m), 5.29 (1H, t, *J* = 7.3 Hz), 6.56 (1H, dd, *J* = 8.5, 2.9 Hz), 6.60 (1H, d, *J* = 2.9 Hz), 6.67 (1H, d, *J* = 8.5 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): 16.1 (Me), 17.7 (Me), 25.6 (Me), 26.5 (CH_2), 29.6 (CH_2), 39.6 (CH_2), 113.7 (CH), 116.6 (CH), 116.6 (CH), 121.4 (CH), 123.9 (CH), 128.3 (C), 131.9 (C), 138.5 (C), 148.2 (C), 149.4 (C).
GC-MS (EI): *m/z* (%) = 246 [M^+] (50), 231 (1), 203 (8), 190 (4), 177 (18), 161 (41), 149 (22), 135 (16), 123 (100), 107 (21), 81 (16), 69 (49), 55 (11).

2-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienyl)benzene-1,4-diol 1c: According to the above described procedure, compound **11c** was converted into farnesyl hydroquinone **1c** (90% yield).
Colorless oil
^{1}H NMR (400 MHz, $CDCl_3$): 1.59 (6H, s), 1.67 (3H, s), 1.75 (3H, s), 1.94-2.02 (2H, m), 2.02-2.17 (6H, m), 3.29 (2H, d, *J* = 7.1 Hz), 4.63 (1H, br s), 4.79 (1H, br s), 5.05-5.13 (2H, m), 5.30 (1H, t, *J* = 7.1 Hz), 6.56 (1H, dd, *J* = 8.6, 3.0 Hz), 6.60 (1H, d, *J* = 3.0 Hz), 6.66 (1H, d, *J* = 8.6 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): 16.0 (Me), 16.2 (Me), 17.6 (Me), 25.6 (Me), 26.4 (CH_2), 26.7 (CH_2), 29.6 (CH_2), 39.7 (CH_2), 39.7 (CH_2), 113.7 (CH), 116.5 (CH), 116.6 (CH), 121.3 (CH), 123.7 (CH), 124.4 (CH), 128.3 (C), 131.3 (C), 135.5 (C), 138.6 (C), 148.2 (C), 149.4 (C).
MS (ESI): 337.4 (M^++Na)

(*S*)-(*E*)-2-(5-(2,2-Dimethyl-6-methylenecyclohexyl)-3-methylpent-2-enyl)benzene-1,4-diol (+)-1g: According to the above described procedure, compound **11g** was converted into (+)-(*S*)-metachromin V **1g** (91% yield).
Colorless thick oil
$[\alpha]_D$: +8.2 (*c* 1.8, $CHCl_3$). Lit. [8] $[\alpha]_D$: 0 (*c* 0.1, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$): 0.83 (3H, s), 0.91 (3H, s), 1.17-1.28 (1H, m), 1.39-1.64 (5H, m), 1.69 (1H, dd, *J* = 11.2, 3.4 Hz), 1.75 (3H, s), 1.77-1.88 (1H, m), 1.93-2.12 (3H, m), 3.30 (2H, d, *J* = 7.3 Hz), 4.52 (1H, d, *J* = 2.4 Hz), 4.75 (1H, br s), 5.08 (2H, br s), 5.28 (1H, t, *J* = 7.3 Hz), 6.57 (1H, dd, *J* = 8.5, 2.9 Hz), 6.61 (1H, d, *J* = 2.9 Hz), 6.67 (1H, d, *J* = 8.5 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): 16.3 (Me), 23.7 (CH_2), 24.7 (CH_2), 26.2 (Me), 28.4 (Me), 29.5 (CH_2), 32.5 (CH_2), 34.8 (C), 36.3 (CH_2), 38.3 (CH_2), 53.7 (CH), 108.9 (CH_2), 113.7 (CH), 116.4 (CH), 116.7 (CH), 121.0 (CH), 128.4 (C), 139.0 (C), 148.0 (C), 149.2 (C), 149.4 (C).
GC-MS (EI): *m/z* (%) = 314 [M^+] (27), 299 (5), 281 (3), 207 (8), 191 (19), 175 (34), 161 (48), 149 (18), 135 (18), 123 (100), 107 (19), 95 (23), 81 (25), 69 (19), 55 (14).
MS (ESI): 337.5 (M^++Na) and 313.3 (M^-).

2-((2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dienyl)benzene-1,4-diol 1e: A stirred solution of **11e** (0.44 g, 1 mmol) and *i*Pr_2NH (2 mL) in dry THF (15 mL) was treated under nitrogen with freshly prepared LDA (1.9 mL of a 0.55 M solution in THF) at −78°C. After 15 min., lithium naphthalenide (14 mL of a 0.6 M solution in THF) was added dropwise, and stirring was prolonged at the same temperature until complete cleavage of the benzyl ethers (5 h, TLC analysis). The reaction was then poured into a mixture of diethyl ether (100 mL) and saturated aqueous NH_4Cl (100 mL) and the organic phase was separated. The aqueous phase was extracted with further ether (2 x 100 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed using *n*-hexane/ethyl acetate (4:1–1:1) as eluent to afford pure **1e** (0.23 g, 88 % yield).
Colorless thick oil.
^{1}H NMR (400 MHz, $CDCl_3$): 1.64 (3H, s), 1.66 (3H, s), 2.16-2.29 (4H, m), 2.45 (1H, br s), 3.28 (2H, d, *J* = 7.4 Hz), 4.04 (2H, s), 5.00 (2H, br s), 5.29 (1H, t, *J* = 7.4 Hz), 5.40 (1H, t, *J* = 6.6 Hz), 6.54 (1H, dd, *J* = 8.6, 3.0 Hz), 6.62 (1H, d, *J* = 3.0 Hz), 6.63 (1H, d, *J* = 8.6 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): 13.6 (Me), 15.4 (Me), 24.9 (CH_2), 28.5 (CH_2), 39.1 (CH_2), 68.4 (CH_2), 113.5 (CH), 116.1 (CH), 116.3 (CH), 122.3 (CH), 125.1 (CH), 128.2 (C), 134.8 (C), 137.3 (C), 147.4 (C), 150.1 (C).
MS (ESI): 285.4 (M^++Na)

Supplementary data: Copies of the ^{1}H NMR and ^{13}C NMR spectra of metachromin V (**1g**) and alliodorol (**1e**) are available.

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