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From catechol-tocopherol to catechol-hydroquinone polyphenolic antioxidant hybrids

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Abstract

Multidefence antioxidants represent a valuable solution for the protection against oxidative stress. From the planned synthesis of a catechol-tocopherol hybrid, we isolated a catechol-hydroquinone hybrid through a BBr_3-mediated benzochromene-fluoren-1-ol transposition. The compound prepared showed a remarkable chain-breaking antioxidant in the catechol portion, while the very sensitive hydroquinone moiety revealed to be an efficient generator of hydroperoxyl radicals.

1 | INTRODUCTION

Polyphenols are probably the most important family of natural and synthetic chain-breaking antioxidants.[1] Flavonoids,[2] as quercetin or catechin and tocopherols,[3] are diffuse in vascular plants where they exert a crucial role in protection against tissue oxidation. At the same time, synthetic phenolic derivatives based on the structure of butyl hydroxy toluene, BHT, or butyl hydroxy anisole, BHA, are typically used for protecting foods, drugs, and polyolefinic polymeric packages from autoxidation.[4] It is well known that either at biological or technological level, the synergistic action of different antioxidants is mandatory in order to achieve an actual protection against oxidative phenomena. Thus, the preparation of molecules able to exert a multidefense action is a valuable field of research.[5] In our group, such goal was accomplished with the synthesis of chalcogen containing catechin-like and tocopherol-like polyphenolic derivatives which showed remarkable antioxidant activities.[6] Despite the introduction of chalcogen atoms in a polyphenolic skeleton could bring interesting additional activities[7] (ie, peroxides quenching and metal chelation), we decided to study the possibility of build-up the compacted catechol-tocopherol hybrid **1** (Figure 1).

In fact, **1** should possess the structural features ensuring a remarkable chain-breaking antioxidant action by the left-side catechin-like structure, with an enhanced planarity due to the fused dialkyl substituted chromane ring,[8] and the right-side chromene skeleton of alpha-tocopherol, the most potent lipophilic phenolic antioxidant known in nature.[3]

Our initial approach to the synthesis of **1** was exploiting the radical arylation of *p*-quinones[9] followed by an oxa-Pictet–Spengler cyclization as depicted in Scheme 1. However, neither by generating the aryl radical under classical method[9] nor by carrying on the reaction using Pd(0) catalysis, as recently reported by Baran,[10] the arylation of 2,3,5-trimethylhydroquinone was observed.

Thus, we decided to follow a different approach for the construction of biphenyl units based on a Pd/norbornene dual catalysis process.[11] As starting materials for this procedure, we prepared bromo derivative **2**, obtained from commercially available 6-bromo-veratraldehyde by addition of MeMgBr, oxidation to the corresponding methyl ketone and a further addition of MeMgBr, and iodo derivatives **3** and **4** as the result of the iodination with I_2/HIO_3 of 2,3-dimethyl- and 2,3,5-trimethyl anisole, respectively (Scheme 2).

We tried then to apply the mentioned procedure,[11] reacting derivative **2** with **3**, or **4**, in the presence of catalytic amounts of $Pd(OAc)_2$, 1.0 equiv of norbornene and dry K_2CO_3 in dry DMF at 105°C. Under this condition, after 24 hours, we were able indeed to isolate derivative **5** (**R**=H) in 64% yield. On the other hand, compound **6** with **R**=Me was not detected in the crude mixture, even forcing

Dedicated to 82nd birthday of Professor Furukawa.

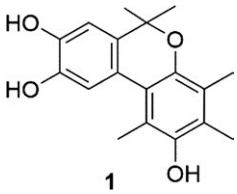
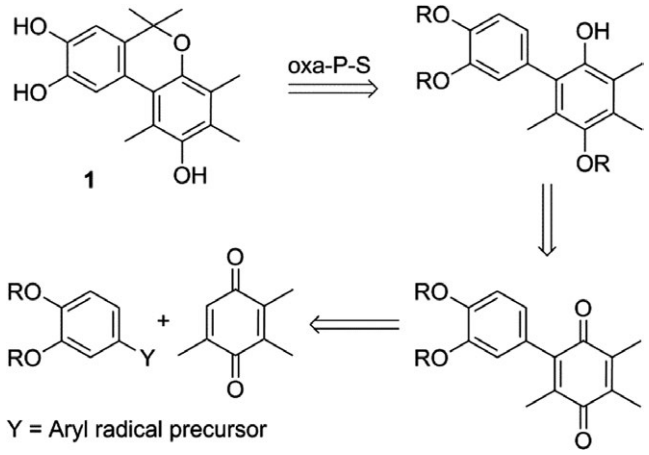
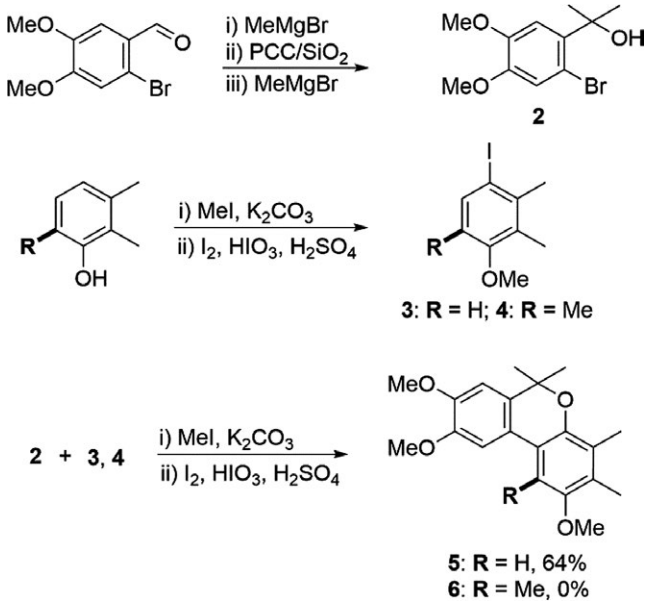


FIGURE 1 Structure of envisaged compact catechol-tocopherol hybrid **1**



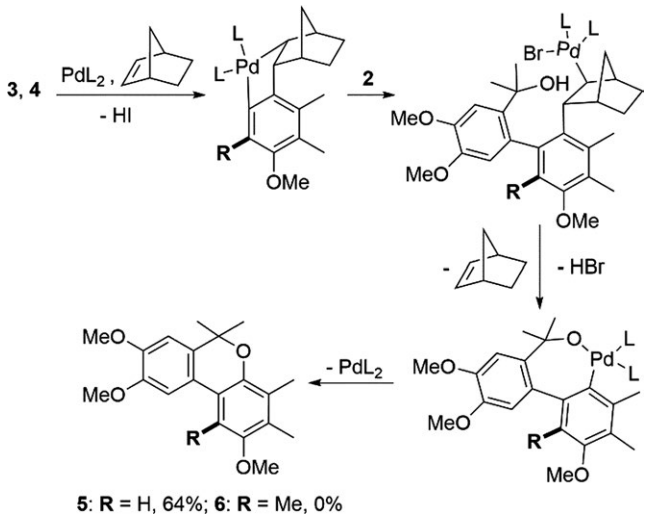
SCHEME 1 Retrosynthetic analysis for catechol-tocopherol hybrid **1**



SCHEME 2 Synthesis of benzochromene derivative **5**

the reaction condition in terms of stoichiometry (up to 0.2 equiv $Pd(OAc)_2$, temperature (up to 150°C), and times (up to 100 h).

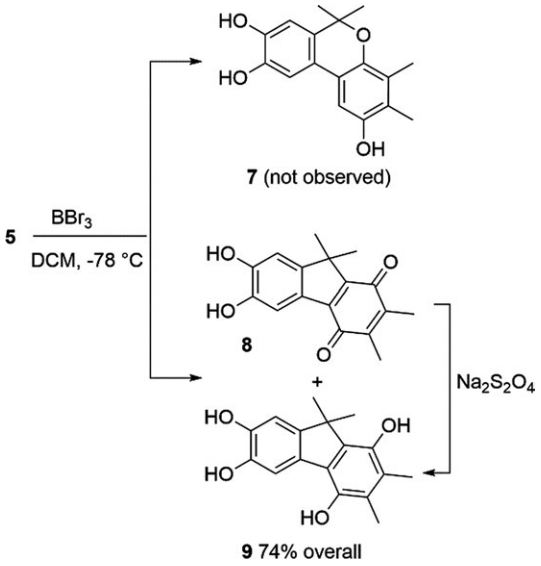
Taking in consideration the mechanism proposed for such transformation (Scheme 3), it is reasonable to consider that a penta substituted iodo derivative, like **4**, could suffer



SCHEME 3 Proposed mechanism for benzochromene **5** formation

of a certain steric hindrance when **R**≠H at the palladacycle intermediate level, preventing the formation of the benzochromene system.

When we imagined the synthesis of a compact polyphenolic antioxidant like **1**, formally deriving from demethylation of methoxy groups in **6**, we selected the skeleton of alpha-tocopherol with three methyl groups on the chromene moiety that ensure an optimal chain-breaking antioxidant activity. However, demethylation of methoxy groups of compound **5** should allow the preparation of derivative **7**, bearing the skeleton of beta-tocopherol that ensure a good antioxidant activity as well. Thus, we studied the demethylation of methoxy groups of **5** using BBr_3 in DCM at −78°C as depicted in Scheme 4. The analysis of the deep purple crude reaction mixture, obtained after a work-up at low temperature, pointed out the presence of two derivatives, **8** and **9**, with a very similar R_f on TLC, none corresponding to the expected phenolic species **7**. In fact, the ^{13}C NMR spectrum (d6 acetone) of the crude mixture indicated two signals at 183.6 and 186.5 supportive of the conjugated carbonyls of quinone **8**. The analysis of the ^{1}H NMR spectrum (d6 acetone) of the mixture was less supportive yet indicating the presence of two different compounds in roughly 1:3 ratio (**8**:**9**) with a total amount of phenolic OH not compatible with the triphenolic compound **7**. Thus, we imagined that the reaction of **5** with BBr_3, despite carried out at −78°C, caused the demethylation of the methoxy groups and the contemporary opening of the chromene ring. This causes the formation of tertiary carbocation able to undergo an intramolecular electrophilic alkylation with formation of the dimethylfluorene skeleton. Additionally, p-hydroquinone portion of **9** undergoes a facile oxidation, even under the reaction condition used for demethylation, to quinone **8**. As a



SCHEME 4 BBr_3 methoxy groups demethylation and access to fluoren -1-ol **9**

matter of fact, refluxing the crude mixture obtained after work-up with an excess of $Na_2S_2O_4$ in a 1:2 Et_2O/H_2O mixture, we observed the complete reduction of **8** to **9** that was isolated in 74% after a fast column chromatography (Scheme 4).

In fact, despite **9** could be completely characterized and its antioxidant activity measured (*vide infra*), it spontaneously reacted with atmospheric oxygen with partial formation of **8**. On the other hand, the possibility of completely convert hydroquinone **9** into quinone **8** failed since any attempt led to extensive decomposition, probably due to the contemporary oxidation of the catecholic moiety. The chromane-indene acid catalyzed transposition is a well-known procedure;[12] however, very rare are the examples of its use for the synthesis of polyphenolic fluorene derivatives[13] such as the catechol-hydroquinone hybrid prepared in this study. Several attempts to obtain **7** under basic conditions using EtSNa, avoiding the chromane-fluorene transposition, gave only random monodemethylation of the methoxy groups.

The chain-breaking antioxidant activity of **9** was determined by studying the inhibition of the thermally initiated autoxidation of styrene, used as reference hydrocarbon, under controlled conditions. Autoxidation of styrene is a radical chain reaction (see Equations 1-6) carried on mainly by alkylperoxyl radicals ($ROO^{\cdot}$) which are representative of the reactive oxygen species responsible for the oxidation of natural lipids and man-made materials under air.[14] The initiator is represented by azobis(isobutyronitrile) (AIBN), whose decomposition at 30°C originates a constant flux of free radicals (initiation rate, R_i).

$$\mathrm{In} \rightarrow R^{\bullet} \quad (1)$$

$$R^{\bullet} + O_2 \rightarrow ROO^{\bullet} \quad (2)$$

$$ROO^{\bullet} + PhCHCH_2 \rightarrow PhC^{\bullet}HCH_2OOR(=ROO^{\bullet}) \quad (3)$$

$$2ROO^{\bullet} \rightarrow \text{nonradical products} \quad (4)$$

$$ROO^{\bullet} + AH_2 \rightarrow ROOH + AH^{\bullet} \quad (5)$$

$$AH^{\bullet} + ROO^{\bullet} \rightarrow ROOH + A \quad (6)$$

The reaction was followed by measuring the oxygen consumption by an automatic oxygen uptake recording apparatus, build in our laboratory, based on a differential pressure transducer.[15] In the absence of antioxidants, the O_2 consumption is linear (see Figure 2A, trace a), whereas in the presence of an antioxidant, the O_2 consumption is retarded or completely inhibited for a period that depends on its concentration (Figure 2A, trace b).

The number of radicals trapped by each antioxidant molecule (n) is related to the length of the inhibited period τ through Equation (7), in which the initiation rate R_i can be determined by using a reference antioxidant.[14] The rate

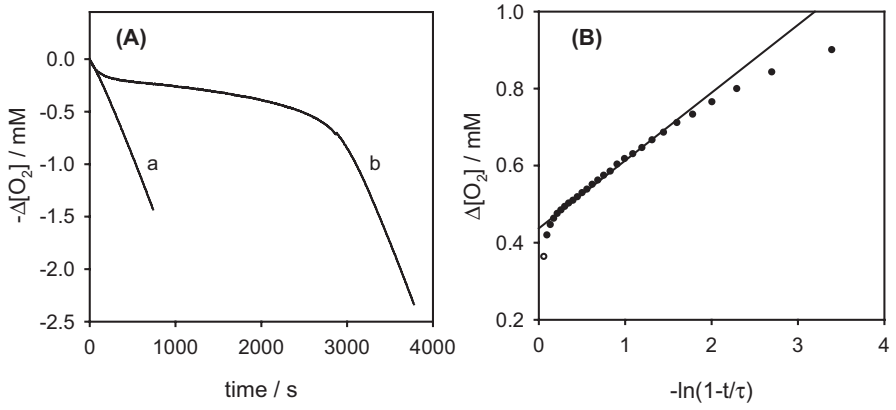


FIGURE 2 (A) Oxygen consumption observed during the autoxidation of styrene (4.3 mol L^{-1}) in chlorobenzene initiated by AIBN (0.05 mol L^{-1}) at 30°C without antioxidants (a) or in the presence of **9** (10 μmol L^{-1}). (B) Analysis of trace (b) by Equation 8

constant of the reaction of the antioxidant with ROO· radicals (k_{inh}, see Equation 5) was calculated by using Equation (8): A plot of $\Delta[O_2]t$ *vs* $\ln(1\text{-}t/\tau)$ gives a straight line of slope k_p [styrene]/k_{inh} from which k_{inh} is obtained by using the known k_p value at 30°C of styrene, that is, 41 M^{-1} s^{-1}.[14,15]

$$R_i = n[ArOH]/\tau \quad (7)$$

$$\Delta[O_2] = (k_p k_{inh})[styrene] \ln(1 - t/\tau) \quad (8)$$

The results reported in Table 1 show that the k_{inh} of **9** is relevant, being only three times lower than that of the best lipophilic natural antioxidant α-tocopherol, and higher than that of related catechols and polyphenols. On the other hand, the number of radical trapped by **9** is unexpectedly small. The presence of both hydroquinone and catechol moieties would imply a n factor of 4, whereas experimentally n is 1.5. The reason for this result can be understood by considering the magnitudes of n factors of substituted hydroquinones reported in Table 1. While hydroquinone can trap two ROO· radicals, the addition of two or three methyl groups lowers the n factor to 0.6 and 0.1, respectively. This decrease in the efficiency of radical trapping is due to the reversible reaction of the semiquinone with O_2, which causes the production of HOO· which propagates the oxidative chain (Scheme 5).[18,19] The rate constant of this reaction appears to be proportional to the number of electron-donating groups on the aromatic ring of the hydroquinone portion of compound **9**, and it can be expected that a hydroquinone having four alkyl substituents has a n factor of 0, that is, every ROO· trapped is converted into HOO·.

It can be therefore concluded that the low n factor of **9** is due to quantitative HOO· production by its hydroquinone moiety, whereas in the case of the catechol portion of the molecule, this effect is small (see Scheme 5).

In conclusion, in this paper, we described the serendipitous synthesis of a catechol-hydroquinone polyphenolic antioxidant hybrid based on a rare benzo[*b*]chromene fluoren-1-ol BBr_3-mediated transposition. Studying the chain-breaking antioxidant ability of derivative **9** we pointed out a very fast reaction with peroxyl radicals ROO· ($k_{inh} \approx 1x10^6$ M^{-1} s^{-1}) due to the catechol moiety, but a very short inhibition time and consumption of radical units ($n \approx 1.5$) caused by the concomitant generation of hydroxyl radical HOO· due to the hydroquinone portion. Further insight on the synthesis and activity of multipotent hybrid polyphenolic antioxidants are in due course in our laboratories.

2 | EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded with Varian Mercury Plus 400, using $CDCl_3$ as solvent when not differently indicated. Residual $CHCl_3$ at 7.26 ppm and central line of $CDCl_3$ at 77.00 ppm were used as the reference of ^1H-NMR and ^{13}C-NMR spectra, respectively. FT-IR spectra were recorded with Spectrum Two FT-IR Spectrometer. GC-MS spectra were recorded with a QMD 100 Carlo Erba. ESI-MS spectra were recorded with a JEOL MStation JMS700. Melting points were measured with Stuart SMP50 Automatic Melting Point Apparatus. All the reactions were monitored by TLC on commercially available precoated plates (silica gel 60 F 254), and the products were visualized with acidic vanillin solution. Silica gel 60 (230–400 mesh) was used for column chromatography. Dry solvents were obtained by The PureSolv Micro Solvent Purification System.

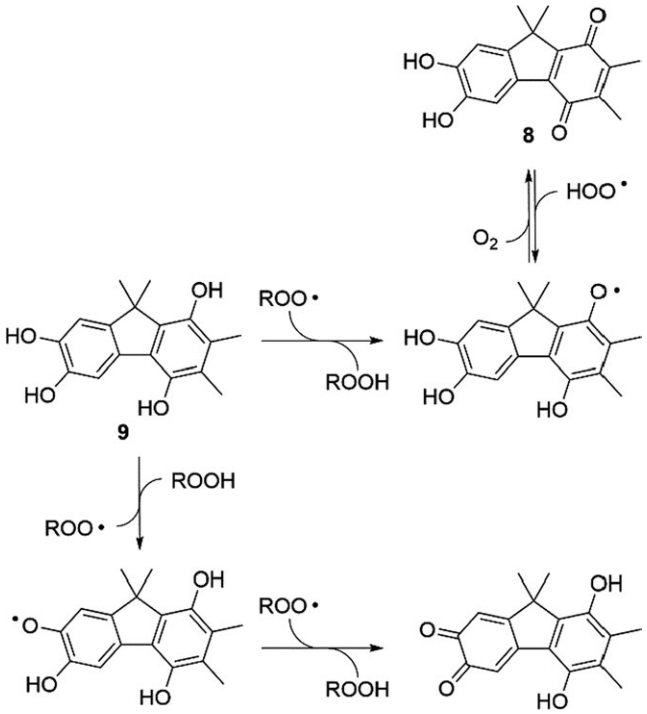
2.1 | 1-(2-Bromo-4,5-dimethoxyphenyl) ethanol

To a cold (-10°C) solution of 6-bromo-veratraldehyde (500 mg, 2.04 mmol) in dry THF (20 mL), a solution of 3M MeMgBr in Et_2O (1.36 mL, 4.08 mmol) is added. The reaction mixture is stirred under a positive nitrogen atmosphere, at −10°C for 1 hour and then at rt for 20 hours. It is then poured into a saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (3 × 40 mL). The combined organic layers are dried over Na_2SO_4, filtered, and concentrated in vacuum to yield the desired product as a pale-yellow oil (555 mg, quantitative yield) used without further purification in the next step. ^1H-NMR, 400 MHz: 7.11 (s, 1H); 6.97 (s,

TABLE 1 Rate constants of reaction with ROO· radicals and stoichiometric coefficient for **9** and other relevant phenolic antioxidants[a]

Antioxidant	k_{inh} (M^{-1} s^{-1})	n	Ref.
9	$(1.0 \pm 0.1) \times 10^6$	1.5	This work
alpha-tocopherol	3.2×10^6	2	[14]
4-methylcatechol	4.2×10^5	1.9	[16]
caffeic acid phenethyl ester	6.8×10^5	1.5	[17]
hydroquinone	5.5×10^6	2.0	[18]
2,5-dimethylhydroquinone	1.2×10^6	≈0.6	[19]
2,3,5-trimethylhydroquinone	2.3×10^6	≈0.1	[19]

[a]In chlorobenzene at 30°C.



SCHEME 5 Mechanism of the reaction of **9** with ROO˙ radicals and generation of chain-propagating HOO˙ radicals from hydroquinone portion

1H); 5.18 (q, $J = 6.8$ Hz, 1H); 3.90 (s, 3H); 3.86 (s, 3H); 1.45 (d, $J = 6.8$ Hz, 3H) ppm.

2.2 | 1-(2-bromo-4,5-dimethoxyphenyl) ethanone

To a solution of 1-(2-Bromo-4,5-dimethoxyphenyl)ethanol (500 mg, 1.91 mmol) in dry DCM (20 mL), a homogeneous mixture of PCC (1.235 g, 5.73 mmol) and silica gel (6 g) is added. The resulted reaction mixture is stirred at rt for 6 hours. The solvent is then evaporated, and the resulting crude product is filtered through a short silica gel column and eluted with DCM and then EtOAc to yield the desired product as a yellowish solid (421 mg, 81%) used without further purification in the next step. ^{1}H-NMR, 400 MHz, CDCl3: 7.14 (s, 1H); 7.04 (s, 1H); 3.91 (s, 3H); 3.89 (s, 3H); 2.67 (s, 3H) ppm.

2.3 | 2-(2-bromo-4,5-dimethoxyphenyl) propan-2-ol (2)

To a cold (−10°C) solution of 1-(2-bromo-4,5-dimethoxyphenyl) ethanone (421 mg, 1.54 mmol) in dry THF (15 mL), a solution of 3M MeMgBr in Et_2O (1.50 mL, 3.08 mmol) is added. The reaction mixture is stirred under a nitrogen atmosphere at −10°C for 1 hour and then at rt for 10 hour. It is then diluted with DCM (40 mL), poured into a saturated aqueous NH_4Cl solution (20 mL), and extracted with DCM (2 × 40 mL). The combined organic layers are dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product is purified by column chromatography (eluent DCM/EtOAc = 3/1) to yield the desired product as an orange oil (365 mg, 81%) used without further purification in the next step.[20] ^{1}H-NMR, 400 MHz: 7.27 (s, 1H); 7.02(s, 1H); 3.86 (s, 3H); 3.85 (s, 3H); 1.72 (s, 6H) ppm.

2.4 | 1-iodo-4-methoxy-2,3-dimethylbenzene (3)

To a solution of 2,3-dimethylanisole (1.326 g, 9.74 mmol) in acetic acid (31 mL) and water (3.5 mL), H_2SO_4 (0.39 mL), I_2 (0.989 g, 3.896 mmol), and HIO_3 (0.342 g, 1.948 mmol) were added in sequence. The reaction mixture is heated at 50°C for 4 days. It is then decolorized with aqueous sodium hydrogen sulfite (10% w/v), diluted with water (200 mL), and extracted with petroleum ether (3 × 100 mL). The combined organic extracts are washed with water (100 mL), a saturated aqueous $NaHCO_3$ solution (2 × 100 mL), water (100 mL), and brine (100 mL). The organic layer is then dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude is purified by column chromatography (eluent: petroleum ether (EP)] to yield the desired product as a white solid (1.433 g, 56%).[21] ^{1}H-NMR, 200 MHz, $CDCl_3$: 7.63 (d, $J = 4.0$ Hz, 1H); 6.48(d, $J = 4.0$ Hz, 1H); 3.79 (s, 3H); 2.42 (s, 3H); 2.23 (s, 3H) ppm.

2.5 | 1-iodo-4-methoxy-2,3,5-trimethylbenzene (4)

To a solution of 2,3,5-trimethylanisole (1.683 g, 11.21 mmol) in acetic acid (36 mL) and water (4 mL), H_2SO_4 (0.45 mL), I_2 (1.138 g, 4.484 mmol), and HIO_3 (0.394 g, 2.242 mmol) were added in sequence. The reaction mixture is heated at 50°C for 5 days. It is then decolorized with aqueous sodium hydrogen sulfite (10% w/v), diluted with water (200 mL), and extracted with petroleum ether (3 × 100 mL). The combined organic extracts are washed with water (100 mL), a saturated aqueous $NaHCO_3$ solution (2 × 100 mL), water (100 mL), and brine (100 mL). The organic layer is then dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude is purified by column chromatography (eluent: EP/EtOAc=12/1) to yield the desired product as a colorless oil (1550 mg, 50%).[22] ^{1}H-NMR, 400 MHz, CDCl3: 7.50 (s, 1H); 3.81 (s, 3H); 2.44 (s, 3H); 2.33 (s, 3H), 2.23 (s, 3H) ppm.

2.6 | 2,8,9-trimethoxy-3,4,6,6-tetramethyl-6H-benzo[c]chromene (5)

To a Schlenk-type flask, containing $Pd(OAc)_2$ (4.27 mg, 0.02 mmol) and K_2CO_3 (131 mg, 0.95 mmol), a solution of iodo derivative **3** (100 mg, 0.38 mmol), bromo

derivative **2** (100 mg, 0.36 mmol), and norbornene (36 mg, 0.38 mmol) in dry DMF is added. The reaction mixture is stirred under nitrogen at 105°C for 24 hours. After cooling to rt, the organic layer is diluted with EtOAc (10 mL), washed with water (2 × 10 mL), and dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude is purified by column chromatography (eluent: EP/EtOAc=8/1) to yield the desired product as a yellow solid (75 mg, 64%). Mp = 115-116 °C. ^{1}H-NMR, 400 MHz: 7.14 (s, 1H); 6.96 (s, 1H); 6.74 (s, 1H); 3.98 (s, 3H); 3.92 (s, 1H); 3.88 (s, 3H); 2.20 (s, 3H); 2.19 (s, 3H); 1.60 (s, 6H) ppm. ^{13}C-NMR, 100 MHz: 152.2; 148.6; 148.4; 144.3; 132.6; 127.0; 126.2; 122.5; 119.5; 106.6; 105.5; 102.1; 77.3; 56.4; 56.1; 56.0; 27.3; 12.1; 11.9 ppm. Elemental Analysis for $C_{20}H_{24}O_4$, Calcd: C, 73.15; H, 7.37. Found: C, 73.46; H, 7.38.

2.7 | 2,3,9,9-tetramethyl-9H-fluorene-1,4,6,7-tetraol (9)

To a solution of derivative **5** (55 mg, 0.17 mmol) in DCM dry (3.5 mL) cooled at -78°C, a solution of BBr_3, 1M in DCM (770 µL, 0.77 mmol) is added. The mixture is then warmed to rt and stirred for 4 hours, then poured slowly into ice, and extracted with DCM (4 × 30 mL). The combined organic layers are dried over Na_2SO_4, filtered and concentrated in vacuum to give a mixture of derivatives **8** and **9** as a purple solid. The crude is poured in Et_2O (2 mL), H_2O (1 mL), phosphate buffer 0.1 mol L^{-1} pH = 7.5 (1 mL), and 1.5 mol L^{-1} aqueous $Na_2S_2O_4$ (1 mL) and refluxed for 1 hour. A discoloration of the reaction mixture from purple to yellow is observed, and the mixture is cooled to rt, diluted with Et_2O (20 mL), and washed with 10% HCl (2 × 20 mL). The organic layer is dried over Na_2SO_4, filtered, and concentrated in vacuum to yield the desired product **9** (36 mg, 74%, mp = 162-165°C) as dark yellow solid turning purple standing over atmospheric oxygen. ^{1}H-NMR, 400 MHz, $(CD_3)_2CO$: 7.65 (s, OH); 7.63 (s, 1H); 7.59 (s, OH); 6.89 (s, OH); 6.88 (s, 1H); 6.59 (s, OH); 2.21 (s, 3H); 2.19 (s, 3H); 1.51 (s, 6H) ppm. ^{13}C-NMR, 100 MHz,$(CD_3)_2CO$: 146.1; 145.1; 143.8; 143.5; 137.2; 131.0; 126.4; 122.9; 122.0; 110.5; 108.7; 46.7; 24.7; 12.0; 11.9 ppm. IR, KBr: 3521 (OH stret.); 3435-3262 (OH stretc.) cm^{-1}. ESI-MS *m/z* negative mode: 285.23 [M-H] $^-$; 570.87 [2M-H]$^-$. Elemental Analysis for $C_{17}H_{18}O_4$, Calcd: C, 71.31; H, 6.34. Found: C,71.45; H, 6.63.

3 | AUTOXIDATION EXPERIMENTS

Autoxidation experiments were performed in a two-channel oxygen uptake apparatus, based on a Validyne DP 15 differential pressure transducer built in our laboratory.[15] The chain-breaking antioxidant activity of **9** was evaluated by studying the inhibition of the thermally initiated autoxidation of styrene (4.3 mol L^{-1}) in chlorobenzene. In a typical experiment, an air-saturated mixture of the oxidizable substrate and the solvent, 1:1 (v/v), containing AIBN (0.05 mol L^{-1}) as an initiator was equilibrated with an identical reference solution containing an excess of 2,2,5,7,8-pentamethyl-6-chromanol (PMHC). After equilibration, and when a constant O_2 consumption was reached, a concentrated solution of the antioxidant (final concentration = 5–10 µmol L^{-1}) was injected in the sample flask. The oxygen consumption in the sample was measured after the calibration of the apparatus from the differential pressure recorded with time between the two channels. Initiation rates, R_i, were determined by the inhibitor method using PMHC as a reference antioxidant: $R_i = 2[PMHC]/\tau]$, where τ is the length of the induction period (R_i = 5-7 × 10^{-9} M s^{-1})[14].

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