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A Straightforward Hetero-Diels–Alder Approach to (2-*ambo*,4′*R*,8′*R*)-α/β/γ/δ-4-Thiatocopherol

Stefano Menichetti,*[a] Riccardo Amorati,[b] Maria Grazia Bartolozzi,[a] Gian Franco Pedulli,[b] Antonella Salvini,[a] and Caterina Viglianisi[a]

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A simple and original inverse electron demand hetero-Diels–Alder reaction has been successfully applied to the synthesis of (2-*ambo*,4′*R*,8′*R*)-α/β/γ/δ-4-thiatocopherol. Commercially available methyl hydroquinones and (2*E*,7*R*,11*R*)-(+)-phytol were exploited for the preparation of the *ortho*-thioquinones, acting as electron-poor dienes, and of the proper 1,3-diene used as dienophile, respectively. The benzoxathiine cycloadducts, with the required tocopherol-like skeleton, were obtained with complete control of regio and chemoselectivity. The antioxidant activity of 4-thiatocopherols was measured and rationalized in comparison with that of the corresponding natural components of Vitamin E.

Introduction

Vitamin E (Vit. E) is a mixture of eight compounds, namely α-, β-, γ- and δ-tocopherol **1a**–**d** and tocotrienol **2a**–**d** (Figure 1), with α-tocopherol (α-TOH, **1a**) being the main and more bio-available component. Actually, after more than 80 years from the discovery that this dietary supplement is indispensable for reproduction in rats,[1] the mechanism of action of Vit. E remains unclear.[2] Nevertheless, the major part of investigations indicate that the biological importance of Vit. E is connected to its antioxidant activity.[2b] Actually, α-TOH has been demonstrated, above all by the huge work done by K. U. Ingold and co-workers, to be the more efficient natural lipophilic chain breaking antioxidant.[3]

While the study of the antioxidant activity of natural compounds, including polyphenols, represents a wide field of research, the preparation of synthetic antioxidants, with optimized activity, solubility, bioavailability and lack of toxicity, is much less developed. For example, to the best of our knowledge, only three examples of compounds with the α-TOH structure but different hetero atoms in the chromane skeleton have been reported in the literature.

In particular, *all-rac*-α-thiotocopherol[4] (**3a**) and α-selenotocopherol[5] (**3b**) have been prepared in order to check the effect of different chalcogen atoms. Derivative **4** (2-*ambo*,4′*R*,8′*R*)-pyridinol[6] was synthesized to exploit the high radical scavenging activity and good stability achieved by introducing nitrogen atoms both in the saturated and in the aromatic ring[7] (Figure 2). However, the procedures to prepare derivatives **3a**, **3b** and **4** are complex, require many steps and lead to low overall yields, and thus have not been tested for the synthesis of β-, γ- and δ-analogues.

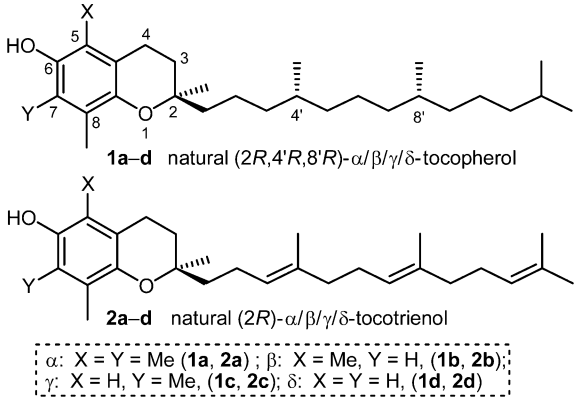

Figure 1. Vitamin E components.

In this paper we report an original approach for the synthesis of (2-*ambo*,4′*R*,8′*R*)-α/β/γ/δ-4-thiatocopherols **5a**–**d** (Figure 2) based on an inverse electron demand hetero-Diels–Alder reaction (HDAR) of electron-poor *ortho*-thioquinones (*o*-TQs), used as dienes, with a 1,3-diene acting as dienophile. As a validation of the synthetic methodology, the antioxidant profile of derivatives **5a**–**d**, obtained by determining the Bond Dissociation Enthalpies (*BDE*) of the phenolic OH bond and the rate constants (k_{inh}) for the reaction with peroxyl radicals, is also reported and rationalized in comparison with the activities of the natural analogues.

[a] Dipartimento di Chimica "U. Schiff" Polo Scientifico e Tecnologico Università di Firenze,
Via della Lastruccia 13, 50019 Sesto Fiorentino, Italy
Fax: +39-055-4573531
E-mail: stefano.menichetti@unifi.it
[b] Dipartimento di Chimica Organica "A. Mangini" Università di Bologna,
Via S. Giacomo 11, 40126 Bologna, Italy
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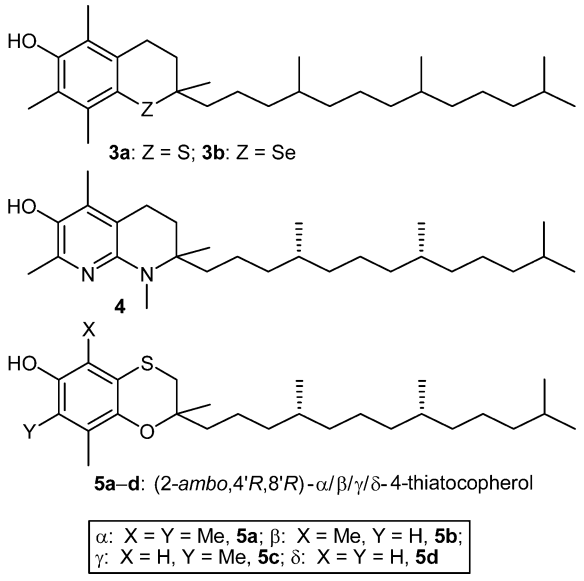
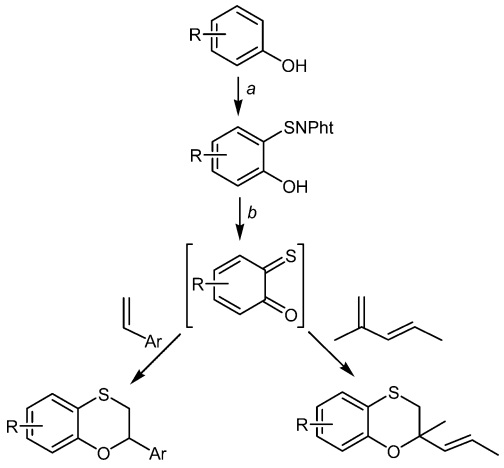


Figure 2. Literature-available hetero analogues **3a**, **3b**, **4** of α-tocopherol, and 4-thiatocopherols **5a**–**d** reported in this paper.

Results and Discussion

In recent years the HDAR of *o*-TQs with properly substituted styrenes, used as dienophiles, allowed us to prepare several hydroxy and methoxy substituted 2-aryl benzoxathiines (Scheme 1).

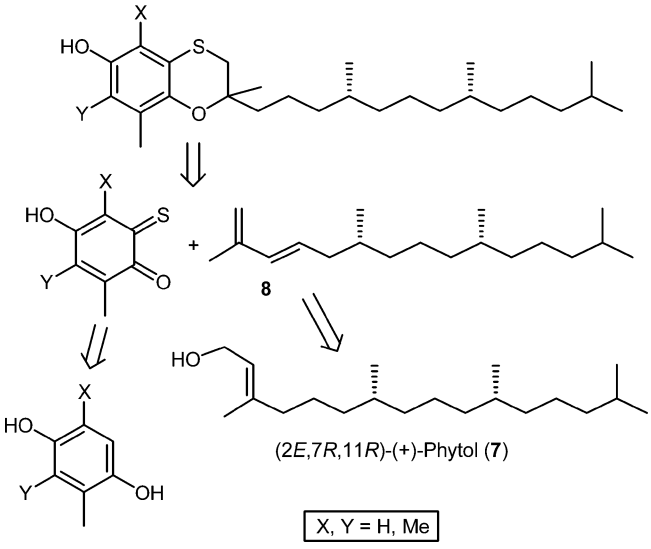


Scheme 1. Generation and reactivity of *o*-TQ as electron-poor dienes. Reagents and conditions: *a*) PhtNSCl (**6**), $CHCl_3$, room temp.; *b*) Et_3N, $CHCl_3$, 65 °C.

We have shown that these heterocycles, for their ability to act as radical scavengers, metal chelators and hydroperoxide quenchers, can be considered multi-defense antioxidants, resembling flavonoids, such as catechin, and tocopherols, the two more important families of natural polyphenolic antioxidants.[8–12]

o-TQs were generated in situ by base-mediated elimination of phthalimide from *ortho*-hydroxy-*N*-thiophthalimides which, in turn, are the products of the S_EAr of phenols with the phthalimidesulfenyl chloride **6**, PhtNSCl (Pht = phthaloyl), as reported in Scheme 1.[9,12,13] During the study of *o*-TQs cycloaddition reactions, we discovered that they can react as electron-poor dienes with 1,3-dienes that behave as electron-rich dienophiles. This distinctive Diels–Alder process occurs in any case with cyclic dienes and under thermodynamic control with acyclic derivatives.[14] In all the examples studied we observed a complete control of regio- and chemoselectivity, thus, for example, the cycloaddition of *o*-TQs with 2-methylpenta-1,3-diene affords a single benzoxathiine product, deriving from the exclusive participation of the 1,3-diene terminal double bond as dienophile, and bearing the oxygen atom in the allylic position (Scheme 1).[12,14]

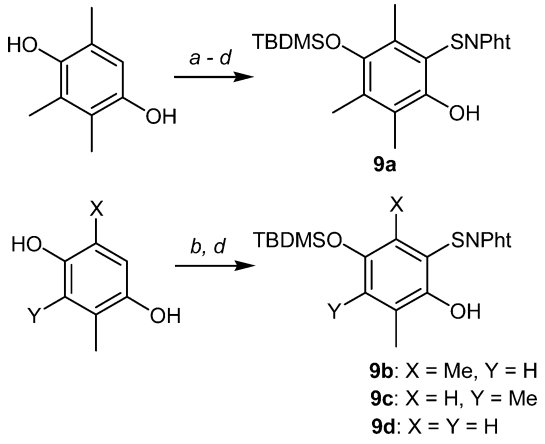
This result prompted us to prepare the α-, β-, γ- and δ-4-thiatocopherols with a common strategy following the disconnection reported in Scheme 2.



Scheme 2. Disconnection for the HDAR-based synthesis of 4-thiatocopherols.

Methylhydroquinones were envisaged as starting materials for the dienic *o*-TQs, while (2*E*,7*R*,11*R*)-phytol (**7**) was chosen as a suitable precursor of the 1,3-diene **8** required as dienophile (Scheme 2).

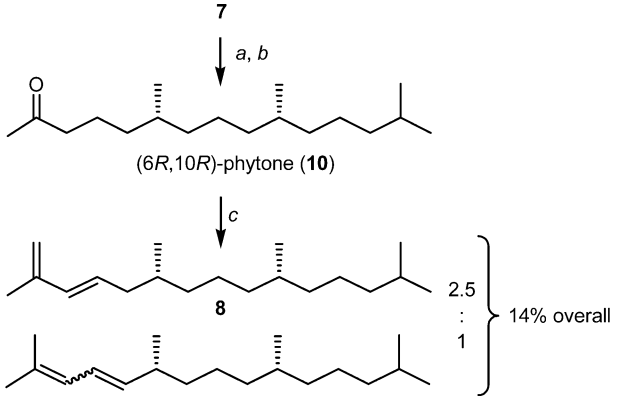
Indeed, the *ortho*-hydroxy-*N*-thiophthalimides **9a**–**d**, i.e. the precursors of the proper *o*-TQs, were prepared as reported in Scheme 3 from commercially available 2,3,5-trimethyl-, 2,3-dimethyl- and 2-methylhydroquinone, while 2,5-dimethylhydroquinone was easily obtained by reduction of the corresponding commercial quinone. The more hindered phenolic OH of trimethylhydroquinone was protected as the TBDMS ether by a known method[12] while the other hydroquinones were directly monoprotected using TBDMSCl and imidazole (IMI) in dry DMF. In this way, the subsequent sulfenylations with **6** occurred regiospecifically *ortho* to the free OH group affording the expected *N*-thiophthalimides **9a**–**d** as single, pure crystalline, indefinitely stable derivatives (Scheme 3, see Exp. Sect. and Supporting Information).



Scheme 3. Synthesis of the *o*-TQ precursors **9a**–**d**. Reagents and condition: *a*) PivCl, Py, DCM, room temp.; *b*) TBDMSCl, IMI, DMF, room temp.; *c*) KOH, MeOH/DMF, room temp.; *d*) **6**, $CHCl_3$, room temp. (–10 °C for **9a**).

The preparation of (6*R*,10*R*)-2,6,10,14-tetramethylpentadeca-1,3-diene (**8**) using enantiopure phytol **7** as starting material was more synthetically demanding.

Our initial strategy, foresaw the transformation of **7** into (6*R*,10*R*)-6,10,14-trimethylpentadeca-2-one (**10**), known as phytone,[15] followed by the one-pot conversion of the latter into diene **8** as recently reported in the literature.[16] The synthesis of enantiopure ketone **10** was easily achieved, in two steps and very good yield, by OsO_4/NMO mediated dihydroxylation followed by a $Pb(OAc)_4$ oxidation (Scheme 4).[17]

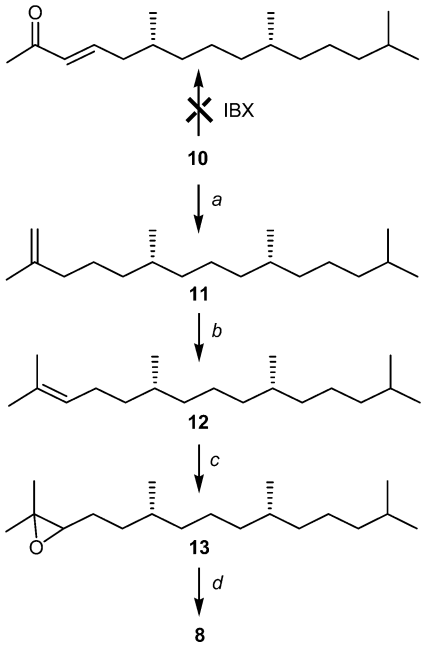


Scheme 4. Transformation of (2*E*,7*R*,11*R*)-(+)-phytol (**7**) in (6*R*,10*R*)-phytone (**10**) and one-pot synthesis of 1,3-diene **8**. Reagents and conditions: *a*) OsO_4 (0.2 mol-%), NMO (2 equiv.), *t*BuOH/THF/H_2O, room temp., 48 h; 98%; *b*) $Pb(OAc)_4$, (3 equiv.), toluene, room temp., 2 h; 98%; *c*) Me_2SO_2, *t*BuOK, DMAC, 90 °C.

Then, the one-pot transformation of ketone **10** into diene **8** using dimethyl sulfone and *t*BuOK in dimethylacetamide was carefully investigated.[16]

Unfortunately, we were unable to obtain reasonable yield of **8** and, more disappointingly, even stopping the reaction far from the complete consumption of the starting ketone, the target 1,3-diene was always isolated together with variable amounts of the corresponding internal isomers, that became the unique products under harsher reaction conditions. The best result, in terms of yield and purity of diene **8**, i.e. with the lower amount of internal isomers, is reported in Scheme 4.

Another simple transformation of phytone (**10**) into diene **8** we considered was the oxidation of **10**, using *o*-iodoxybenzoic acid (IBX) as described by Nicolaou et al., to the corresponding α,β-unsaturated ketone, followed by a Wittig olefination to introduce the required extra carbon and the 1,3-diene function (Scheme 5).



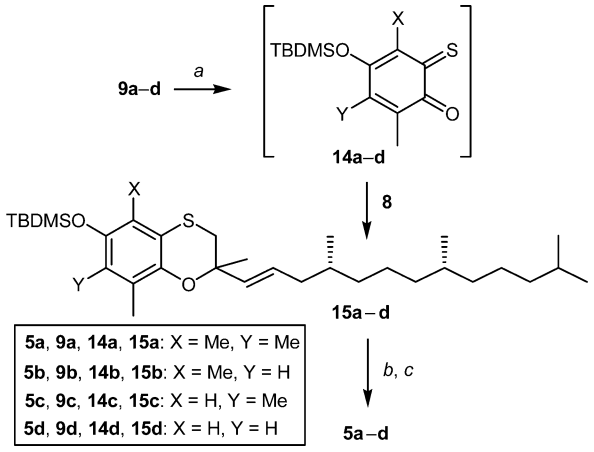
Scheme 5. IBX (failed) and POP paths for the synthesis of 1,3-diene **8**. Reagents and conditions: *a*) Ph_3PCH_3Br, $(Me_3Si)_2NLi$, THF, –78 °C, 1 h, 92%; *b*) TsOH (0.3 equiv.), toluene, 90 °C, 23 h, 91%; *c*) *m*-CPBA (2 equiv.), DCM, room temp., 40 min, 98%; d) Ph_3PO/Tf_2O (POP, 2 equiv.), TEA (5 equiv.), K_2CO_3 (5 equiv.), DCE, 90 °C, 2 h, 40%.

Regrettably, we failed in the α,β-oxidation of **10**, either using the commercial available IBX or a freshly prepared sample obtained with both the oxone[18] and the $KBrO_3$ preparative methodologies.[19] We tried without success the oxidation of **10** with IBX under the original reaction conditions[20] as well as using many of the successive reported adjustments[21] (Scheme 5).

Despite these disappointing initial results, we were able to prepare diene **8** in satisfactory yields using phytone **10** as starting material as depicted in Scheme 5. An initial Wittig olefination allowed us to prepare the terminal alkene **11** which was converted into the thermodynamic internal isomer **12** with 0.3 equiv. of TsOH in toluene at 90 C°. The alkene **12** was oxidized with *m*-CPBA to the corresponding epoxide **13**. These three steps occurred with very good yields and can be carried out without purification of the intermediates. Eventually, epoxide **13** reacted with freshly prepared Hendrickson reagent (or POP)[22] to give the expected 1,3-diene **8** isolated in 40% yield (Scheme 5). This methodology required more steps than those initially envisaged and the yield of the last step was not brilliant. How-

ever, its simplicity and reproducibility allowed the preparation of diene **8**, isolated as single regio- and stereoisomer, in practical amount for the following steps of the sequence leading to the four target thiatocopherols.

Having in hand the *N*-thiophthalimide precursors of the dienic *o*-TQs required for the formation of α-, β-, γ- and δ-4-thiachromane aromatic ring, and the proper dienophile for the introduction of the phythyl aliphatic tail, we performed the cycloaddition reactions to produce the bicyclic skeleton. *N*-thiophthalimides **9a**–**d** were treated with TEA in $CHCl_3$ at 65 °C to generate *o*-TQs **14a**–**d** in the presence of 1,3-diene **8** as reported in Scheme 6. To our satisfaction, the benzoxathiines **15a**–**d**, possessing the expected tocopherol-like skeleton, were isolated as single regioisomers in reasonable to good yields (Scheme 6).



Scheme 6. HDAR based synthesis of α-, β-, γ- and δ-4-thiatocopherol **5a**–**d**. Reagents and conditions: *a*) TEA (1 equiv.), **8** (1.2 equiv.), $CHCl_3$, 65 °C; 16 h, 64–72%; *b*) H_2 (10 atm), Pd/C 10%, toluene, 60 °C; *c*) TBAF·$3H_2O$ (1 equiv.), THF, room temp., 3 h, 56–70% over two steps.

The reduction of the C1′–C2′ double bond by catalytic hydrogenation with Pd/C, followed[23] by desilylation of phenolic TBDMS ethers with TBAF hydrate in dry THF, afforded the target α-, β-, γ- and δ-4-thiatocopherol **5a**–**d** as described in Scheme 6. The formation, during cycloaddition, of the new stereogenic center on C2, occurred without control of the absolute stereochemistry. In fact, benzoxathiines **15a**–**d**, and, 4-thiatocopherols **5a**–**d**, were obtained and isolated as near 1:1 mixtures of diastereoisomers (i.e. 2-*ambo*,4′R,8′R). Diastereoisomeric ratios were obtained by ^{1}H NMR spectra that showed two almost coincident and equivalent signals for the AB systems corresponding to the S-CH2 groups (see experimental).[24] All the attempts of separation, at every step of the synthetic sequence, were, disappointingly but not surprisingly, unsuccessful.

The antioxidant activity of 4-thiatocopherols **5a**–**d** was evaluated by measuring the rate constant (k_{inh}) for their reaction with peroxyl radicals and the dissociation enthalpy of the phenolic O–H bond (*BDE*).

Kinetic measurements with peroxyl radicals were performed by studying the inhibited autoxidation of styrene at 303 K in chlorobenzene, initiated by azobisisobutyronitrile (AIBN), in the presence of **5a**–**d**, using 2,2,5,7,8-pentamethyl-6-chromanol (PMHC) as reference antioxidant.[3a,27] The autoxidations were followed by monitoring the oxygen consumption in an oxygen uptake apparatus based on a differential pressure transducer, which has been described previously.[28] The observed kinetics are in agreement with Equations (1), (2), (3), (4), (5) and (6).[27]

$$\text{Initiator} \xrightarrow{R_i} R^\bullet \quad (1)$$

$$R^\bullet + O_2 \longrightarrow ROO^\bullet \quad (2)$$

$$ROO^\bullet + RH \xrightarrow{k_p} ROOH + R^\bullet \quad (3)$$

$$ROO^\bullet + ROO^\bullet \xrightarrow{2k_t} \text{non-radical products} \quad (4)$$

$$ROO^\bullet + ArOH \xrightarrow{k_{inh}} ROOH + ArO^\bullet \quad (5)$$

$$ROO^\bullet + ArO^\bullet \longrightarrow \text{non-radical products} \quad (6)$$

With the exception of **5d**, the investigated compounds show a neat inhibition period in styrene (see Figure 3), the length (τ) of which provides the stoichiometric coefficient, i.e., the number of peroxyl radicals trapped by one molecule of antioxidant: $n = R_i\,\tau/[AH]$, where R_i is the initiation rate, measured in a preliminary set of experiments, and [AH] is the concentration of antioxidants. The coefficients *n* for **5a**–**c** are in the range 1.9 ± 0.2, typical of phenolic antioxidants acting via reactions 5 and 6.[3a]

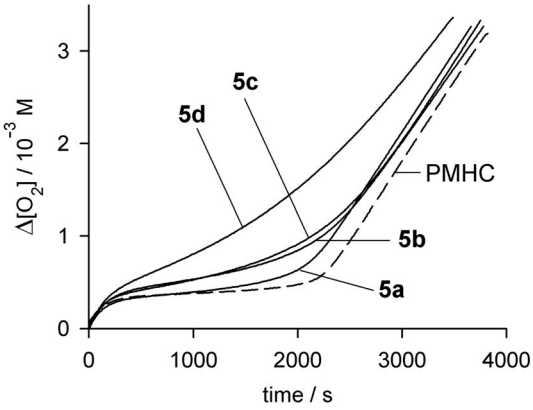


Figure 3. Oxygen consumption recorded during the AIBN (0.05 M) initiated styrene (4.3 M) autoxidation in chlorobenzene at 303 K in the presence of the investigated thiatocopherols and PMHC used as a reference antioxidant (all 6.3×10^{-6} M).

The rates of reaction with peroxyl radicals k_{inh}, reported in Table 1, were obtained by using Equation (7),[3a] where k_p is the rate constant of propagation of styrene (41 $M^{-1}\,s^{-1}$).[29]

Table 1. *BDE*(O–H) and k_{inh} of 4-thiatocopherols **5a**–**d**, natural tocopherols**1a**–**d**, BHT and BHA.

	BDE[a]	k_{inh}[b]		*BDE*[a]	k_{inh}[b]
5a	78.8	1.3×10^6	**1a**	77.1[c]	3.2×10^6 [d]
5b	80.6	7.6×10^5	**1b**	–[e]	1.3×10^6 [d]
5c	80.7	5.8×10^5	**1c**	–[e]	1.4×10^6 [d]
5d	81.8	3.0×10^5	**1d**	–[e]	4.4×10^5 [d]
BHA	77.2[c]	1.1×10^5 [d]			
BHT	79.9[c]	1.4×10^4 [d]			

[a] Solvent benzene, kcal mol^{-1}, error ±0.3 kcal mol^{-1}. [b] Solvent styrene/chlorobenzene, M^{-1} s^{-1}, error ±10%. [c] From refs.[30,31] [d] From ref.[27] [e] Not available.

$$-\Delta[O_2]_t = k_p\,[\text{styrene}]\,k_{inh}^{-1}\ln(1 - t/\tau) \quad (7)$$

In Table 1, the k_{inh} values for natural tocopherols **1a**–**d**, and for two synthetic antioxidants, 2,6-di-*tert*-butyl-4-methylphenol (or butyl hydroxy toluene, BHT) and 2,6-di-*tert*-butyl-4-methoxyphenol (or butyl hydroxy anisole, BHA), are also reported.[3a,27]

The O–H bond-dissociation enthalpies (*BDE*) in phenols **5a**–**d** were determined by measuring, by means of EPR spectroscopy, the equilibrium constant, K_8, for the hydrogen-atom transfer reaction between the investigated molecule (ArOH), a reference phenol (Ar′OH) and the corresponding phenoxyl radicals generated under continuous photolysis; see Equation (8) and Figure 4.[30]

$$\text{ArOH} + \text{Ar'O}^\bullet \underset{}{\overset{K_8}{\rightleftharpoons}} \text{ArO}^\bullet + \text{Ar'OH} \quad (8)$$

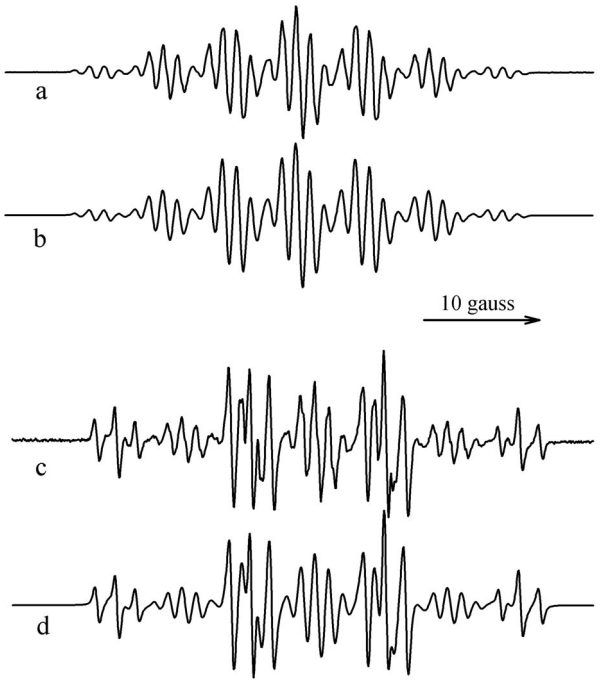


Figure 4. Experimental (a, c) and simulated (b, d) EPR spectra obtained irradiating a benzene solution of **5a** (a, b) and a mixture of **5a** and BHT (c, d) in concentration ratio 1:1.7.

The *BDE* values reported in Table 1 were calculated from the known *BDE*(O–H) value of the reference species Ar′OH by means of Equation (9) with the assumption that the entropic term can be neglected.[30] In this study, the reference phenol was BHT, the revised *BDE*(O–H) of which is 79.9 kcal mol^{-1}.[30,31]

$$BDE(\text{ArO–H}) = BDE(\text{Ar'O–H}) - RT\ln K_8 \quad (9)$$

To check the reliability of the results, $\log(k_{inh})$ values for **5a**–**d** were plotted against their *BDE*(O–H), in comparison to reference phenols characterized by different substituents in *ortho* position to the phenolic OH (Figure 5). The logarithms of the rate constants for H-atom abstraction are known to be inversely proportional to the *BDE*(O–H)s. The slope and the *y*-intercept of these plots are dependent on the nature of the abstracting radicals and on the steric crowding around the phenolic OH group, respectively.[30,32,33] In Figure 5 it is shown that **5b**–**d** are on the same line of unhindered phenols, this being consistent with the presence, in *ortho* position to the OH group, of only one methyl group in **5b**,**c** and with the absence of any substituent in **5d**. Compound **5a** is near to the line of 2,6-dimethylphenols, as expected from its structure.

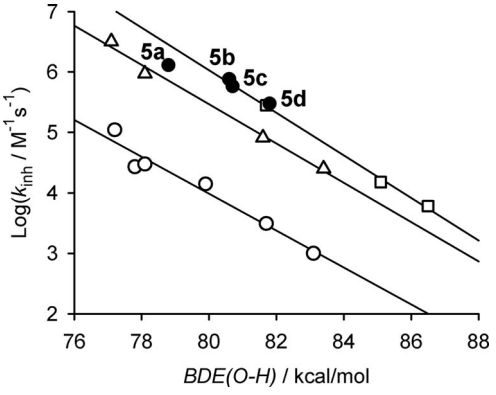


Figure 5. Plot of BDE(O–H) and $\log k_{inh}$ values for the investigated compounds (black dots) and for some reference phenols: (o) 2,6-*t*Bu-4-XPhOH; (Δ) 2,6-Me-4-XPhOH; (□) 4-XPhOH.[33]

Similarly to natural derivatives, the antioxidant activity of 4-thiatocopherols increases with the number of methyl groups on the aromatic ring. α-4-Thiatocopherol **5a** has the lowest *BDE*(O–H) and is the most active antioxidant (highest k_{inh}) of the compounds prepared (Table 1). The k_{inh} value of this compound indicate that it is a much better inhibitor of the autoxidation reaction than, for example, BHT and BHA, two synthetic antioxidants commonly used as stabilizers and preservatives (Figure 6).

In agreement with our previous studies on the antioxidant activity of benzoxathiines,[12] 4-thiatocopherols are slightly poorer radical scavengers than the corresponding tocopherols (Table 1), because the volume of the sulfur atom and the length of the carbon–sulfur bonds induce conformational modifications in the saturated fused ring which decrease the stability of 4-thiatocopheroxyl radicals.[12] X-ray analyses of structurally related benzoxathiines showed that in these compounds C3 lays almost on the

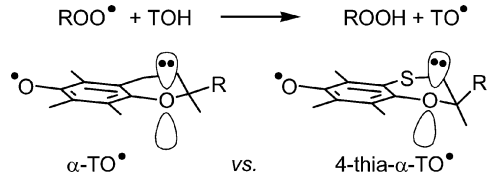


Figure 6. Schematic reaction of tocopherols with peroxyl radicals and conformational effects on the stability of α-tocopheroxyl and 4-thia-α-tocopheroxyl radicals.

plane containing the aromatic ring, O1 and S4.[34] This pushes C2 out of this plane more than in natural tocopherols (Figure 6).[27,35] As a consequence, the lone pair orbital on O1, responsible for the stabilization of 4-thia-α-TO˙, is more twisted and, hence, less conjugated with the aromatic π-system than in tocopheroxyl radical α-TO˙ (Figure 3).

Conclusions

We have shown a practical HDAR approach for the synthesis of (2-*ambo*,4′*R*,8′*R*)-α/β/γ/δ-4-thiatocopherol. This novel access to the tocopherol skeleton exploits the ability of *o*-TQs to react with 1,3-dienes with complete control of the regio and chemoselectivity. The activity of these very efficient multi-defence antioxidants has been measured and rationalized using natural tocopherols as model compounds.

The possibility of application of such HDAR for the preparation of other hetero-modified tocopherols is under investigation in this laboratory.

Experimental Section

General: Unless noted otherwise, materials were purchased from commercial suppliers and used without further purification. THF, DMF, $CHCl_3$, DCM and Et_3N, were dried following standard procedures. Progress of reaction was monitored by thin-layer chromatography (TLC) on commercially available precoated plates (silica gel 60 F_{254}) and the products were visualized with acid vanillin solution. Purification of the products was performed by flash column chromatography using silica gel 60 (230–400 mesh). Melting points were determined in a capillary tube using a Büchi 510 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recoded at 400 or 200 and 100 or 50 MHz, respectively. Chemical shifts (δ) are expressed in ppm using residual nondeuterated solvent as an internal standard. Coupling constants (*J*) are given in Hertz (Hz). Mass spectra were obtained with a Shimadzu QP5050. Optical rotations were measured in $CHCl_3$. Phthalimidesulfenyl chloride (**6**) was prepared from the corresponding commercially available disulfide (purchased from Chemper s.n.c.) as reported elsewhere.[12] Protection as TBDMS ethers and sulfenylation of methyl hydroquinones have been carried out as previously reported.[12] Preparation and isolation of *N*-thiophthalimides **9a**–**d** as well as spectroscopic details of cycloadducts **15a**–**d** are available as Supporting Information.

(7*R*,11*R*)-3,7,11,15-Tetramethyl-1,2,3-hexadecanetriol: To a solution of (2*E*,7*R*,11*R*)-phytol (**7**) (purchased from Molecular Biosciences, 4.50 g, 15.20 mmol) in *t*BuOH/THF/H_2O (10:6:1 84 mL) was added 4-methylmorpholine *N*-oxide (NMO) (3.17 g, 27.00 mmol) and OsO_4 (2.5% in *t*ButOH, 220 μL, 0.017 mmol). The solution was stirred at room temperature and checked by TLC. After 24 h additional NMO (1.10 g, 9.40 mmol) and OsO_4 (220 μL, 0.017 mmol) were added and stirring continued for further 24 h, then saturated aqueous Na_2SO_3 solution was added and the mixture stirred for 30 min, diluted with AcOEt, washed with aqueous HCl (7%), water and brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo to give the desired triol that was used without further purification (4.92 g, 14.90 mmol, 98% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.82–0.86 (m, 12 H), 0.97–1.56 (m, 24 H), 3.47–3.50 (m, 1 H), 3.62–3.73 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = (21 signals for 40 nonequivalent C) 19.6, 19.7, 21.0, 22.1, 22.6, 22.7, 24.5, 24.7, 27.9, 31.1, 32.76, 32.81, 37.2, 37.4, 37.5, 37.6, 39.3, 39.5, 63.2, 74.5, 75.8 ppm.

(6*R*,10*R*)-6,10,14-Trimethylpentadecan-2-one (10): To a solution of the triol (4.92 g, 14.90 mmol) in toluene (170 mL) $Pb(OAc)_4$ 95% (19.85 g, 42.56 mmol) was added at room temperature and the solution stirred for 2 h. After this time, the mixture was diluted with Et_2O and washed with a $NaHCO_3$ saturated aqueous solution, water and brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo to give ketone **10** as a colourless oil (3.94 g, 14.60 mmol, 98% yield). Spectroscopic data were in agreement with those available in literature.[15] ^1H NMR (400 MHz, $CDCl_3$): δ = 0.81–0.85 (m, 12 H), 0.96–1.64 (m, 19 H), 2.10 (s, 3 H), 2.37 (t, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 19.7, 21.4, 22.5, 22.6, 24.4, 24.7, 27.9, 29.7, 32.6, 32.7, 36.4, 37.17, 37.23, 37.3, 39.3, 44.1, 209.2 ppm.

(6*R*,10*R*)-2,6,10,14-Tetramethylpentadec-1-ene (11): A solution of LiHMDS 1.0 M in THF (48 mL, 48.00 mmol) was added to a suspension of CH_3PPh_3Br (17.15 g, 48.00 mmol) in dry THF (120 mL) kept at –20 °C under nitrogen. The resulting mixture was warmed to room temperature and the orange solution was stirred for 1 h, then cooled to –78 °C and phytone (**10**) (1.61 g, 6.00 mmol) in dry THF (15 mL) was added. The mixture was warmed to room temperature and stirred for additional 1 h. The reaction was quenched at –78 °C with a saturated aqueous solution of NH_4Cl and extracted with DCM. The combined organic phases were washed with water and brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was filtered through a short pad of silica gel using petroleum ether as eluent to give **11** as a colourless oil (1.47 g, 5.52 mmol, 92% yield). $[\alpha]_D^{23}$ = +1.87 (*c* = 0.2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 12 H), 1.02–1.58 (m, 19 H), 1.72 (s, 3 H), 1.99 (t, *J* = 7.2 Hz, 2 H), 4.67–4.69 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.74, 19.75, 22.4, 22.6, 22.7, 24.5, 24.8, 25.1, 28.0, 32.7, 32.8, 36.7, 37.3, 37.40, 37.44, 38.1, 39.4, 109.5, 146.3 ppm.

(6*R*,10*R*)-2,6,10,14-Tetramethylpentadec-2-ene (12): To a solution of alkene **11** (651 mg, 2.45 mmol) in toluene (25 mL) *p*-toluenesulfonic acid (270 mg, 1.40 mmol) was added and the mixture was heating at 90 °C for 23 h. The solution was cooled to room temperature, diluted with hexane and washed with saturated aqueous solution of $NaHCO_3$, water and brine, dried with Na_2SO_4 anhydrous and concentrated in vacuo to give **12** as a coulorless oil used without further purification (less than 4% of residual terminal isomer **11** was detected) (590 mg, 2.22 mmol, 91% yield). $[\alpha]_D^{23}$ = +1.68 (*c* = 0.2). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 12 H), 1.02–1.58 (m, 17 H), 1.61 (s, 3 H), 1.69 (s, 3 H), 1.88–2.06 (m, 2 H), 5.11 (t, *J* = 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 19.6, 19.7, 22.6, 22.7, 24.4, 24.8, 25.6, 25.7, 28.0, 32.4, 32.8, 37.1, 37.30, 37.32, 37.4, 39.4, 125.1, 130.9 ppm.

2,2-Dimethyl-3-[(3*R*,7*R*)-3,7,11-trimethyldodecyl]oxirane (13): To a solution of **12** (1.23 g, 4.76 mmol) in DCM (40 mL) at 0 °C, *m*-

CPBA (2.34 g, 9.52 mmol) was added. The reaction mixture was stirred at room temperature for 40 min, then a 10% aqueous solution of Na_2SO_3 was added and stirred for additional 30 min. The mixture was extracted with DCM, the organic phase was washed with 6% aqueous solution of $NaHCO_3$ and water, dried with anhydrous Na_2SO_4 and concentrated in vacuo to give **13** as a colorless oil used without furter purification (1.32 g, 4.68 mmol, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.88 (m, 12 H), 1.01–1.62 (m, 25 H), 2.69 (t, J = 6.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = (29 signals for 38 nonequivalent C) 18.6, 18.7, 19.57, 19.62, 19.7, 22.6, 22.7, 24.3, 24.4, 24.8, 24.9, 26.4, 26.5, 27.9, 32.6, 32.7, 32.8, 33.47, 33.51, 37.1, 37.26, 37.27, 37.33, 37.4, 39.3, 58.2, 58.3, 64.7, 64.8 ppm.

(6*R*,10*R*)-2,6,10,14-Tetramethylpentadeca-1,3-diene (8): Under a nitrogen atmosphere, to a stirred solution of triphenylphosphane oxide (661 mg, 2.33 mmol) kept at 0 °C in dry 1,2-dichloroethane (3.4 mL), a 0.5 M solution of triflic anhydride (1.73 mmol) in dichloroethane was added dropwise and stirred at 0 °C for 10 min, while a white precipitate of POP is formed. To this suspension dry K_2CO_3 (812 mg, 5.88 mmol) was added, followed by a solution of epoxide **13** (391 mg, 1.13 mmol) in 1,2-dichloroethane (1 mL) and Et_3N (800 μL, 5.78 mmol). The precipitate of POP dissolves quickly. The solution was heated to reflux and stirred for 2 h. After this time the solution was diluted with H_2O and extracted with DCM, the organic phase was dried with anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column flash chromatography on silica gel using hexane/DCM, 10:1 as eluent allowed the isolation of diene **8** as a colorless oil (118 mg, 40% yield). $[\alpha]_D^{23}$ = +0.68 (c = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.88 (m, 12 H), 1.02–1.56 (m, 15 H), 1.84 (br. s, 3 H), 1.87–1.97 (m, 1 H), 2.07–2.16 (m, 1 H), 4.86 (s, 2 H), 5.64 (dt, J = 15.2 and 7.6 Hz, 1 H), 6.12 (d, J = 15.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 19.7, 22.6, 22.7, 24.5, 24.8, 28.0, 29.7, 31.9, 32.7, 37.0, 37.2, 37.3, 39.4, 40.4, 114.0, 129.7, 133.8, 142, 2 ppm. MS: m/z (%) = 264 (8) [M$^{+\cdot}$], 149 (8), 109 (36), 57 (100). $C_{19}H_{36}$ (264.49): calcd. C 86.28, H 13.72; found C 86.58, H 13.32.

Cycloaddition Reactions. General Procedure: The cycloaddition reactions were carried out heating the *o*-hydroxy-*N*-thiophthalimide derivatives **9a**–**d** with 1 equiv. of Et_3N and 1.2 equiv. of diene **8** in dry chloroform (0.05 M) at 65 °C. After 16 h, a complete consumption of the thiophthalimides was monitored by TLC, evaporation of the solvent and flash chromatography on silica gel allowed the isolation of the cycloadducts **15a**–**d**, spectroscopic details are available as Supporting Information

Hydrogenation Reactions. General Procedure: In a glass vial placed in a stainless-steel autoclave, a solution of compounds **15a**–**d** in toluene (0.04 M) and 5% Pd/C (10 mol-%) were introduced. The autoclave was then pressurized at room temperature with 10 atm H_2, placed in a thermostatic oil bath at 60 °C (± 1 °C) and rocked overnigth. At the end of the reaction, the autoclave was cooled to room temperature and the gaseous contents were vented off. Filtration through a Celite pad and evaporation of the solvent gave the reduced cycloadducts as yellow oils, used without further purification in the next step.

Desilylation Reactions. General Procedure: A solution of TBAF·3H_2O (1 equiv.) in dry THF (0.05 M) was added dropwise to a solution of TBDMS ethers, in dry THF (0.05 M) kept at room temperature. The reactions were monitored by TLC untill the disappearance of silylated starting product (roughly 3 h). The solutions were diluted with DCM, washed with saturated aqueous NH_4Cl solution and H_2O, dried with anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography on silica gel using DCM as eluent afforded 4-thiatocopherols **5a**–**d** isolated as pale yellow oils.

(2-*ambo*,4′*R*,8′*R*)-α-4-Thiatocopherol (5a): 56% Yield over two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.87 (m, 12 H), 1.00–1.75 (m, 21 H), 1.36 (s, 3 H), 2.11 (s, 3 H), 2.14 (s, 3 H), 2.17 (s, 3 H), 2.86 (two almost coincident AB systems, J = 12.8 Hz, 2 H, CH_2-S), 4.26 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = (32 signals for 56 nonequivalent C) 12.0, 12.2, 19.6, 19.66, 19.73, 21.0, 21.1, 22.6, 22.7, 23.9, 24.4, 24.8, 28.0, 32.63, 32.64, 32.8, 34.70, 34.75, 37.28, 37.33, 37.37, 37.44, 39.4, 39.8, 39.9, 72.8, 114.5, 116.5, 119.5, 124.6, 142.2, 145.2 ppm. MS: m/z (%) = 448 (35) [M$^{+\cdot}$], 195 (23), 184 (100), 57 (40). $C_{28}H_{48}O_2S$ (448.75): calcd. C 74.94, H 10.78; found C 74.88, H 10.53.

(2-*ambo*,4′*R*,8′*R*)-β-4-Thiatocopherol (5b): 61% Yield over two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.87 (m, 12 H), 1.00–1.74 (m, 21 H), 1.35 (s, 3 H), 2.11 (s, 3 H), 2.13 (s, 3 H), 2.87 (two almost coincident AB systems, J = 12.8 Hz, 2 H, CH_2-S), 4.28 (br. s, 1 H, OH), 6.39 (s, 1 H, H7) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = (31 signals for 54 nonequivalent C) 11.8, 16.1, 19.61, 19.65, 19.7, 21.00, 21.02, 22.6, 22.7, 23.9, 24.4, 24.8, 28.0, 32.6, 32.8, 34.50, 34.54, 37.28, 37.30, 37.38, 37.43, 39.4, 39.76, 39.81, 72.4, 113.8, 117.3, 117.7, 125.8, 142.6, 146.2 ppm. MS: m/z (%) = 434 (37) [M$^{+\cdot}$], 181 (34), 170 (100), 57 (48), 43 (78). $C_{27}H_{46}O_2S$ (434.72): calcd. C 74.60, H 10.67; found C 74.41, H 10.76.

(2-*ambo*,4′*R*,8′*R*)-γ-4-Thiatocopherol (5c): 70% Yield over two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 12 H), 1.01–1.76 (m, 21 H), 1.37 (s, 3 H), 2.11 (s, 3 H), 2.12 (s, 3 H), 2.85 (two almost coincident AB systems, J = 12.8 Hz, 2 H, CH_2-S), 4.34 (s, 1 H, OH), 6.39 (s, 1 H, H5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = (32 signals for 54 nonequivalent C) 11.9, 12.1, 19.61, 19.64, 19.7, 20.99, 21.03, 22.6, 22.7, 24.1, 24.4, 24.8, 28.0, 32.60, 32.62, 32.8, 34.4, 34.5, 37.27, 37.31, 37.37, 37.43, 39.4, 39.8, 39.9, 73.4, 109.7, 113.7, 120.6, 127.9, 142.3, 147.0 ppm. MS: m/z (%) = 434 (18) [M$^{+\cdot}$], 181 (14), 170 (75), 167 (21), 57 (44), 43 (100). $C_{27}H_{46}O_2S$ (434.72): calcd. C 74.60, H 10.67; found C 75.01, H 11.03.

(2-*ambo*,4′*R*,8′*R*)-δ-4-Thiatocopherol (5d): 64% Yield over two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.87 (m, 12 H), 1.01–1.75 (m, 21 H), 1.36 (s, 3 H), 2.12 (s, 3 H), 2.85 (two almost coincident AB system, J = 12.8 Hz, 2 H), 4.32 (s, 1 H, OH), 6.40 (two almost coincident AB systems, J = 3.2 Hz, 2 H, H5, H7) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = (29 signals for 52 nonequivalent C) 16.3, 19.61, 19.63, 19.7, 20.9, 22.6, 22.7, 24.1, 24.4, 24.8, 28.0, 32.6, 32.8, 34.48, 34.51, 37.27, 37.32, 37.37, 37.43, 39.4, 39.8, 39.8, 73.3, 110.2, 114.6, 117.1, 129.3, 142.6, 148.3 ppm. MS: m/z (%) = 420 (26) [M$^{+\cdot}$], 167 (21), 156 (86), 57 (53), 43 (100). $C_{26}H_{44}O_2S$ (420.69): calcd. C 74.23, H 10.54; found C 74.49, H 10.73.

Kinetic Experiments: The rate constants for the reaction with peroxyl radicals, k_{inh}, were measured by following the oxygen consumption during the autoxidation of styrene (4.3 M) in chlorobenzene at 30 °C using AIBN (0.05 M) as radical initiator, in the presence of compounds **5a**–**5d** and in concentrations ranging from 3 to 9×10^{-6} M. The reaction was performed in an oxygen uptake apparatus built in our laboratory[28] using a procedure previously described.[12] The rate of initiation R_i was determined in preliminary experiments using PMHC as reference antioxidant, whose n = 2.[3a]

Thermochemical Measurements: The *BDE*(O-H) values were determined by using the EPR equilibration technique, which consists in photolyzing concentrated (0.05 M) benzene solutions of the investigated compound and a reference phenol (BHT) in the presence of di-*tert*-butyl peroxide (5% v/v).[30] As the consumption of the reacting phenols is negligible, the equilibrium constant can be calcu-

lated from the molar ratio of the two equilibrating radicals, obtained by computer simulation from the EPR spectra.[30] Different concentration ratios of starting phenols were used in order to check if the equilibrium was reached. Experimental EPR spectra and hyperfine splitting constants of the investigated phenols are reported in the Supporting Information.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and characterization of *N*-thiophthalimides **9a**–**d** and cycloadducts **15a**–**d**, the one-pot synthesis of diene **8** from phytone **10** as well as the EPR experiments on thiatocopherols **5a**–**d**.

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