

## Amphiphilic antioxidants from “cashew nut shell liquid” (CNSL) waste

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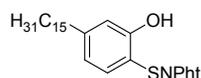
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### Electronic Supplementary Information

#### Synthesis

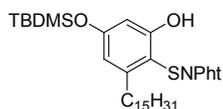
Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. THF, DMF, CHCl<sub>3</sub>, DCM and Et<sub>3</sub>N, were dried following standard procedures. Progress of reaction was monitored by thin-layer chromatography (TLC) on commercially available precoated plates (silica gel 60 F254) 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). <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 400 or 200 and 100 or 50 MHz, respectively. Chemical shifts ( $\delta$ ) are expressed in ppm using residual non-deuterated solvent as an internal standard. Coupling constants ( $J$ ) are given in Hertz (Hz). Mass spectra were obtained with a Shimadzu QP5050. Phthalimidesulfenyl chloride (**4**) was prepared from the corresponding commercially available disulfide (purchased from Chemper s.n.c.). The synthesis of styrene **6** and the protection as TBDMS ethers of resorcinols **2** and **3** were performed as reported elsewhere.<sup>11-15</sup>

**Sulfenylation reactions. General procedure:** To a solution of phenol in dry CHCl<sub>3</sub> (0.5 M) kept at 0 °C, a solution of PhtNSCl (**4**, 1 equiv.) in dry CHCl<sub>3</sub> (0.5 M) was added dropwise. The reaction was stirred at room temperature and monitored by TLC until complete consumption of starting phenol (4-12 h). The mixture was diluted with DCM, washed with saturated NaHCO<sub>3</sub> and water. The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrate *in vacuum* to give the corresponding *ortho*-hydroxy-*N*-thiophthalimides as pale yellow solids used in the cycloaddition step without further manipulation.

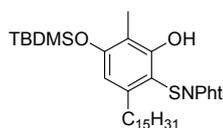


Colourless oil from flash chromatography on silica gel (DCM/petroleum ether 10:1, 82% yield). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.87 (t,  $J$  = 7.0 Hz, 3H), 1.23-1.31 (m, 24H), 1.52-1.58 (m, 2H), 2.53 (t,  $J$  = 7.8

Hz, 2H), 6.69 (dd,  $J = 8.0$  and  $2.0$  Hz, 1H), 6.84 (d,  $J = 2.0$  Hz, 1H), 7.73-7.91 (m, an AA'BB' system plus an aromatic proton, 5H), 8.25 (s, 1H, OH) ppm;  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.1, 22.7, (29.2, 29.3, 29.4, 29.5, 29.6, 29.7 six signals for 10C), 30.9, 31.9, 36.0, 115.4, 116.6, 121.0, 124.1 (2C), 131.9 (2C), 134.8 (2C), 138.2, 151.1, 158.9, 168.5 (2C) ppm.

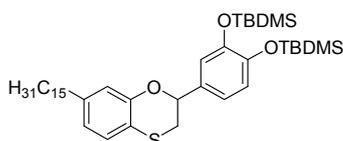


Colourless oil from flash chromatography on silica gel (petroleum ether/DCM 1:1, 76% yield).  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.19 (s, 6H), 0.88 (t,  $J = 6.4$  Hz, 3H), 0.95 (s, 9H), 1.26-1.68 (m, 26H), 3.24 (t,  $J = 7.5$  Hz, 2H), 6.30 (d,  $J = 2.6$  Hz, 1H), 6.35 (d,  $J = 2.6$  Hz, 1H), 7.73-7.91 (m, AA'BB' system, 4H), 8.72 (s, 1H, OH) ppm;  $^{13}\text{C}$ -NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : -4.2 (2C), 14.2, 18.3, 22.8, 25.7 (3C), (29.5, 29.7, 29.8 three signals for 10C), 32.0, 32.5, 34.7, 105.2, 111.0, 113.7, 123.9 (2C), 131.9 (2C), 134.6 (2C), 151.6, 160.7, 161.3, 168.8 (2C) ppm.



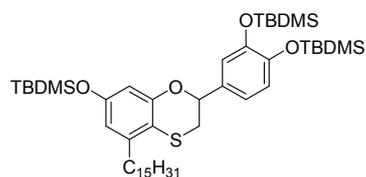
Yellowish oil from flash chromatography on silica gel (petroleum ether/DCM 1:1, 84% yield).  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.21 (s, 6H), 0.88 (t,  $J = 7.0$  Hz, 3H), 1.00 (s, 9H), 1.26-1.49 (m, 24H), 1.56-1.64 (m, 2H), 2.10 (s, 3H), 3.24 (t,  $J = 7.6$  Hz, 2H), 6.28 (s, 1H), 7.73-7.89 (m, AA'BB' system, 4H), 8.78 (s, 1H, OH) ppm;  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : -4.1 (2C), 9.8, 14.1, 18.2, 22.7, 25.7 (3C), (29.3, 29.5, 29.6, 29.66, 29.69, 29.71 six signals for 10C), 31.9, 32.5, 34.4, 110.7, 112.1, 113.8, 124.0 (2C), 132.0 (2C), 134.7 (2C), 147.7, 158.6, 159.4, 169.0 (2C) ppm.

**Cycloaddition reactions. General procedure:** Cycloadditions were carried out heating the *o*-hydroxy-*N*-thiophthalimide derivatives with 1 equiv of  $\text{Et}_3\text{N}$  and 1.5 equiv of styrene **6** in dry chloroform (0.05 M) at  $60^\circ\text{C}$ . After a complete consumption of the *N*-thiophthalimides, monitored by TLC, evaporation of the solvent and flash chromatography on silica gel allowed the isolation of the *O*-silyl protected cycloadducts pale yellow oils. Data are as described below.

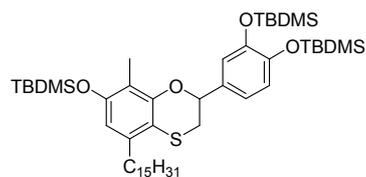


Pale yellow oil from flash chromatography on silica gel (petroleum ether/DCM 6:1, 64%):  $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.20 (s, 6H), 0.21 (s, 6H), 0.89 (t,  $J = 6.4$  Hz, 3H), 1.00 (s, 9H), 1.01 (s, 9H), 1.14-1.41

(m, 24H), 1.44 -1.65 (m, 2H), 2.52 (t,  $J = 7.6$ , Hz, 2H), 3.02 (dd, A part of an ABX system  $J = 13.2$  and 2.2 Hz, 1H), 3.21 (dd, B part of an ABX system  $J = 13.2$  and 9.4 Hz, 1H), 5.07 (dd, X part of an ABX system  $J = 9.4$  and 2.2 Hz, 1H), 6.70-6.77 (m, 2H), 6.85-6.88 (m, 3 H), 7.00 (d,  $J = 8.0$  Hz, 1H) ppm.

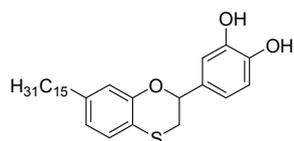


Pale yellow oil from flash chromatography on silica gel (petroleum ether/DCM 6:1, 71%):  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.18 (s, 6H), 0.19 (s, 6H), 0.20 (s, 6H), 0.88 (t,  $J = 6.4$  Hz, 3H), 0.97 (s, 9H), 0.99 (2s, 18H), 1.25-1.48 (m, 24H), 1.55-1.69 (m, 2H), 2.49-2.57 (m, 2H), 2.98-3.19 (m, AB part of an ABX system, 2H), 5.04 (dd, X part of an ABX system  $J = 9.0$  and 2.4 Hz, 1H), 6.33 (as, 2H), 6.84-6.86 (m, 3H) ppm;  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : -4.2 (2C), -3.8 (4C), 14.2, 18.3, 18.6 (2C), 22.8, 25.8 (3C), 26.1 (6C), (29.5, 29.6, 29.7, 29.8, four signals for 10C), 31.9, 32.1, 33.7, 76.3, (107.9, 108.1, 114.6, 118.8, 120.9, 133.6, 140.6, 146.8, 153.0 nine signals for 13C) ppm.

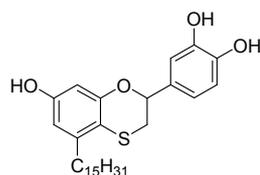


Pale yellow oil from flash chromatography on silica gel (petroleum ether/DCM 6:1, 66%):  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.20 (s, 12H), 0.21 (s, 6H), 0.88 (t,  $J = 6.6$  Hz, 3H), 0.98 (s, 9H), 1.00 (s, 9H), 1.01 (s, 9H), 1.20-1.42 (m, 24H), 1.45-1.53 (m, 2H), 2.06 (s, 3H), 2.48-2.56 (m, 2H), 3.06-3.09 (m, AB part of an ABX system, 2H), 5.07 (at, X part of an ABX system,  $J = 5.7$  Hz, 1H), 6.32 (s, 1H), 6.83-6.94 (m, 3H) ppm;  $^{13}\text{C-NMR}$  (50 MHz,  $\text{CDCl}_3$ )  $\delta$ : -3.9 (6C), 9.5 14.2, 18.4, 18.6 (2C), 22.8, 25.9 (3C), 26.1 (6C), (29.5, 29.6, 29.8, three signals for 10C), 31.9, 32.0, 33.4, 76.1, (107.9, 113.1, 115.9, 118.5, 120.7, 134.0, 136.6, 146.5, 146.8, 151.0 ten signals for 13C) ppm.

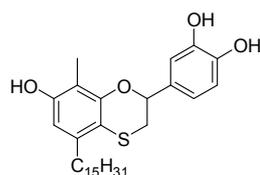
**Desilylation Reactions. General Procedure:** To a solution of O-silyl protected cycloadducts, in dry THF (0.04 M) at  $-10\text{ }^\circ\text{C}$ , a solution of TBAF $\cdot$ 3H $_2$ O in DCM (1 equiv for each TBDMSO group) was added and the reaction monitored by TLC till the disappearance of silylated starting product. The crude mixture was diluted with ethyl acetate, washed with saturated  $\text{NH}_4\text{Cl}$  and water. The organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated to dryness. Purification of the residue from filtration over a short path of silica gel afforded the required products **8-10**. Spectroscopic data are as follows:



**8:** Glassy white solid from filtration over a short path of silica gel (petroleum ether/DCM 3:1, 98%):  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.88 (t,  $J = 6.8$  Hz, 3H), 1.24-1.42 (m, 24H), 1.53-1.62 (m, 2H), 2.50 (t,  $J = 7.8$ , Hz, 2H), 3.02 (dd,  $J = 13.2$  and 2.0 Hz, 1H), 3.21 (dd,  $J = 13.2$  and 9.6 Hz, 1H), 5.06 (dd,  $J = 9.6$  and 2.0 Hz, 1H), 5.34 (bs, 2H, OH), 6.72 (dd,  $J = 8.0$  and 2.0 Hz, 1H), 6.75 (d,  $J = 2.0$  Hz, 1H), 6.86-6.89 (m, 2 H), 6.93 (d,  $J = 2.0$  Hz, 1H), 7.00 (d,  $J = 8.0$  Hz, 1H) ppm;  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 14.1, 22.7, (29.2, 29.3, 29.5, 29.6, 29.7 five signals for 10C), 31.2, 31.8, 32.0, 35.4, 76.4, (113.3, 113.6, 115.5, 118.5, 119.0, 122.0, 124.8, 126.9, 133.5, 141.0, 143.7, 152.1 twelve signal for 13C) ppm. MS  $m/z$  (int. rel. %): 470 ( $\text{M}^+$ , 57), 336 (RDA, 13), 136 (97), 43 (100). Analysis for  $\text{C}_{29}\text{H}_{42}\text{O}_3\text{S}$ . Calcd: C, 74.00; H, 8.99. Found: C, 73.88; H, 9.07.



**9:** Glassy white solid from filtration over a short path of silica gel (petroleum ether/EtOAc 2:1, 84%):  $^1\text{H-NMR}$  (400 MHz,  $\text{C}_2\text{D}_6\text{CO}$ )  $\delta$ : 0.88 (t,  $J = 6.8$  Hz, 3H), 1.23-1.42 (m, 24H), 1.57-1.64 (m, 2H), 2.46-2.59 (m, 2H), 3.08-3.15 (m, AB part of an ABX system 2H), 5.01 (at, X part of an ABX system  $J = 5.2$  Hz, 1H), 6.28 (d,  $J = 2.8$  Hz, 1H), 6.39 (d,  $J = 2.8$  Hz, 1H), 6.79 (dd,  $J = 8.0$  and 2.0 Hz, 1H), 6.85 (d,  $J = 8.0$ , 1H), 6.95 (d,  $J = 2.0$  Hz, 1H), 7.95 (s, 2H, OH), 8.09 (s, 1H, OH) ppm;  $^{13}\text{C-NMR}$  (100 MHz,  $\text{C}_2\text{D}_6\text{CO}$ )  $\delta$ : 14.4, 23.3, (30.1, 30.2, 30.3, 30.4 four signals for 10C), 30.6, 32.1, 32.6, 34.2, 77.6, (104.1, 107.0, 110.9, 114.2, 116.0, 118.7, 133.6, 141.5, 146.0, 154.4, 155.9 eleven signals for 13C) ppm. MS  $m/z$  (int. rel. %): 350 (RDA, 11), 156 (29), 124 (100), 43 (53). Analysis for  $\text{C}_{29}\text{H}_{42}\text{O}_4\text{S}$ . Calcd: C, 71.56; H, 8.70. Found: C, 71.28; H, 8.66.



**10:** Glassy pale yellow solid from filtration over a short path of silica gel (petroleum ether/EtOAc 2:1, 80%):  $^1\text{H-NMR}$  (400 MHz,  $\text{C}_2\text{D}_6\text{CO}$ )  $\delta$ : 0.89 (t,  $J = 6.8$  Hz, 3H), 1.26-1.43 (m, 24H), 1.56-1.64 (m, 2H), 2.10 (s, 3H), 2.44-2.57 (m, 2H), 3.08 (dd,  $J = 13.2$  and 9.6 Hz, 1H), 3.17 (dd,  $J = 13.2$  and 2.4 Hz, 1H),

5.05 (dd,  $J = 9.6$  and  $2.4$  Hz, 1H), 6.43 (s, 1H), 6.84-6.90 (m, 2H), 7.01 (d,  $J = 1.6$  Hz, 1H), 7.89 (s, 1H, OH), 7.94 (s, 1H, OH), 8.0 (s, 1H, OH) ppm;  $^{13}\text{C}$ -NMR (100 MHz,  $\text{C}_2\text{D}_6\text{CO}$ )  $\delta$ : 8.8, 14.4, 23.3, (30.1, 30.2, 30.3, 30.4 four signals for 10C), 30.6, 32.1, 32.6, 34.0, 77.5, (107.1, 110.2, 112.1, 114.0, 116.0, 118.4, 133.8, 137.6, 145.9, 146.0, 152.3, 153.6 twelve signals for 13C) ppm. MS  $m/z$  (int. rel. %): 364 (RDA, 16), 169 (35), 137 (92), 43 (100). Analysis for  $\text{C}_{30}\text{H}_{44}\text{O}_4\text{S}$ . Calcd: C, 71.96; H, 8.86. Found: C, 71.81; H, 8.80.

**Autoxidations.** Kinetic measurements with peroxy radicals were performed by studying the inhibited autoxidation of styrene in chlorobenzene or in water at  $30\text{ }^\circ\text{C}$ , initiated by AIBN (0.05 M), in the presence of variable amounts of the investigated compounds or 2,2,5,7,8-pentamethyl-6-chromanol (PMHC) as reference antioxidants (figure ESI-1). The autoxidation was followed by monitoring the oxygen consumption in an oxygen uptake apparatus built in our laboratory and based on a Validyne DP15 differential pressure transducer.<sup>10</sup> The rate of initiation  $R_i$  was measured in a preliminary set of experiments from the length of the inhibition period  $\tau_{inh}$ , using PMHC as a reference antioxidant:  $R_i = 2 [\text{PMHC}] / \tau_{inh}$ .

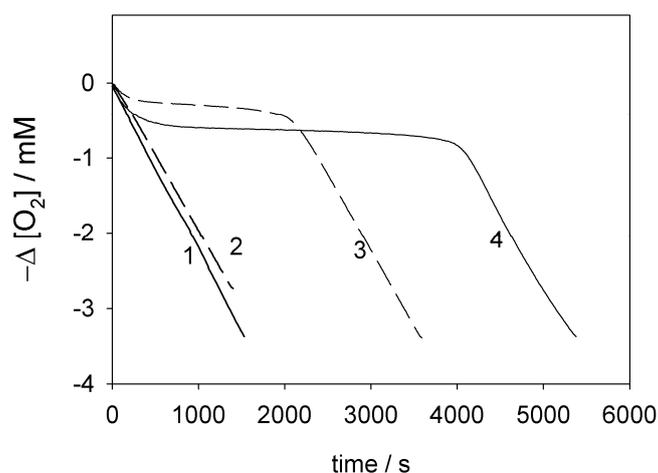


Figure ESI-1. Oxygen consumption observed during the autoxidation of styrene (4.3 M) initiated by AIBN (0.05 M) at  $30\text{ }^\circ\text{C}$  without inhibitor (1 and 2) and inhibited by **11** (trace 3:  $6.3\text{ }\mu\text{M}$ , trace 4:  $12\text{ }\mu\text{M}$ ), in homogeneous solution (dashed lines) and in the two-phases system (solid lines).

Inhibition constants ( $k_{inh}$ ) were determined using equation 8, where  $R_0$  and  $R_{inh}$  are the  $\text{O}_2$  consumption rates in the absence and in the presence of the antioxidant, respectively (see Figure ESI 2).

$$\frac{R_0}{R_{inh}} - \frac{R_{inh}}{R_0} = \frac{nk_{inh}[\text{AH}]}{(2k_tR_i)^{1/2}} \quad (8)$$

In the case of compounds **9** and **10**, the inhibition period was longer than that of equal amounts of **8**, because of the presence of an additional phenolic moiety in the molecule. In the case shown in Figure ESI-2, the  $k_{\text{inh}}$  value for the second OH group was estimated from the slope of the oxygen consumption after about 3000 sec.

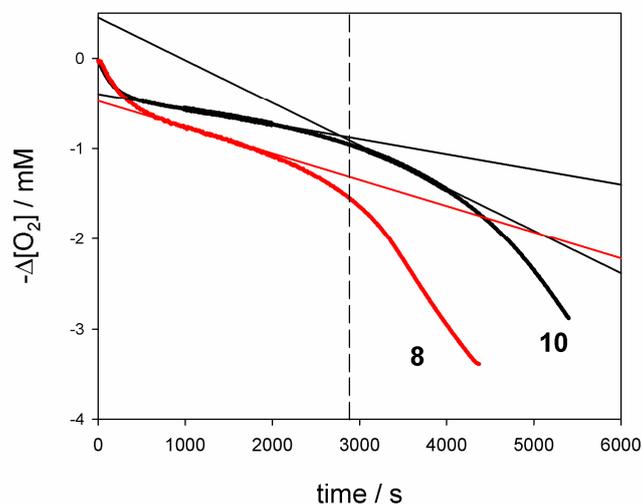


Figure ESI-2. Oxygen consumption observed during the autoxidation of styrene (4.3 M) in chlorobenzene initiated by AIBN (0.05 M) at 30 °C inhibited by **8** and **10** (8.3 μM).

**Styrene / water partitioning.** Solutions of **12** and **13** ( $1-5 \times 10^{-4}$  M) in H<sub>2</sub>O and were vigorously mixed with an equal volume of styrene and their concentration was determined by measuring the absorbance of the H<sub>2</sub>O layer by UV-vis spectroscopy.