Synthesis of New Cardanol Derivatives through Combined Iodination/Palladium-Catalysed Cross-Coupling Reactions

Antonio Arcadi,*[a] Orazio. A. Attanasi,[b] Stefano Berretta,[b] Gabriele Bianchi,[a] Paolino Filippone[b]

[a] Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università dell'Aquila, via Vetoio, 67100 L'Aquila, Italy

[b] Centro di Studio delle Sostanze Organiche di Orgine Naturale, Università di Urbino, Via Sasso 75, 61029 Urbino, Italy
Fax +39(0862)433753.; E-mail: arcadi@univaq.it

Received 10 March 2006; revised 21 March 2006

Abstract: A versatile approach to the synthesis of new cardanol derivatives through a combination of aromatic iodination of 3-*n*-pentadecylphenol and palladium-catalysed cross-coupling reactions has been developed. The extent of aromatic iodination is controlled by stoichiometry and affords either the mono-, di- or tri-iodo-cardanol derivatives. Suzuki, Heck and Sonogashira protocols were successfully applied for the vinylation, arylation and alkynylation of the iodo-cardanols. 2,4-Diiodo-5-*n*-pentadecylphenol underwent an unusual sequential regioselective dehalogenation/vinylation reaction. Sequential alkynylation/cyclisation of 2-iodo-3-*n*-pentadecylphenol derivatives were also investigated.

Key words: aromatic substitution, halogenation, palladium, Heck reaction, cross-coupling

Currently, the vast majority of organic chemicals synthesised stem from petroleum feedstocks. Nevertheless, agricultural and biological feedstocks can be excellent alternative, renewable raw materials. At present, it has shown that a host of agricultural products can be transformed into consumer products, however the search for biological sources of alternative feedstocks need not be limited to agricultural products: agricultural waste may also provide important raw materials for the production of consumer compounds. The use of an otherwise unused waste product that would need to be disposed of is very attractive for obvious environmental and economic reasons. In this context the utilisation of cardanol derivatives seems very attractive.

Cardanol[1] is an industrial-grade yellow oil obtained by vacuum distillation of 'Cashew Nut Liquid' (CNSL), the international name for the alkyl phenolic oil contained in the spongy mesocarp of the cashew nut shell (*Anacardium occidentale* L.).

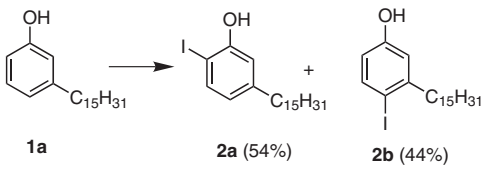
Because of the large demand and high commercial value of the edible kernel, world-wide cashew nut production has shown an increasing trend over the past five to ten years. As a consequence, CNSL now represents a renewable, widely available, and relatively low-cost organic natural material. Distilled cardanol is as a mixture of saturated (3-*n*-pentadecylphenol), mono-olefinic [3-(*n*-pentadeca-8-enyl)phenol], di-olefinic [3-(*n*-pentadeca-8,11-dienyl)phenol] and tri-olefinic [3-(*n*-pentadeca-8,11,14-trienyl)phenol] polyketide long-chain phenols, with an average value of two double bonds per molecule.

Pure saturated 3-*n*-pentadecylphenol of homogeneous chemical composition can be easily obtained by simple hydrogenation of technical-grade distilled cardanol and subsequent purifying distillation and/or crystallisation.

Cardanol derivatives represent a simple entry point for the preparation of additives for lubricants, diesel engine fuels, pour-point depressants, flame retardants, resins, inks, hydrorepellents, and antioxidants.[2] Selective oxidation of cardanol derivatives by methylrhenium trioxide has also been reported.[3] Furthermore, cardanol derivatives of phthalocyanines,[4] porphyrins[5] and fullerenes[6] showed that the introduction of a cardanol moiety in these compounds was important in order to improve their solubility in organic solvents. The corresponding cardanol-based derivatives have also enabled a new class of dyes to be developed that have real prospects not only for photocatalytic processes, but also for other technological applications.[7]

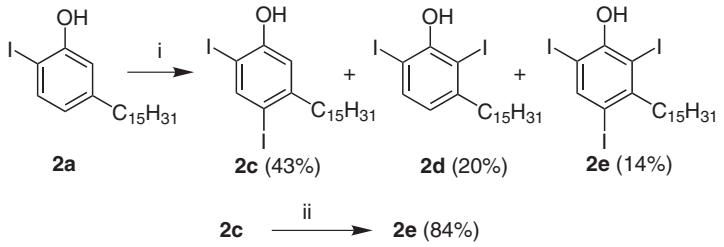
Continuing the investigations on the functionalisation of cardanol, we wish to present our results for the preparation of new cardanol derivatives through a combination of iodination and palladium-catalysed cross coupling reactions.

In recent years, iodophenols[8] have assumed increasing importance in chemistry. This interest can be ascribed to the facile oxidative addition of aryl iodides to low-valent transition metals. The chemistry of the resulting Ar-M-I intermediates has been widely investigated, leading to valuable new syntheses of useful compounds. While aryl bromides/chlorides can often also be used in these reactions, there are cases in which the use of the more reactive aryl iodides has special value. This is particularly true in the case of aryl halides substituted by electron-donating groups such as hydroxyl.



Scheme 1 *Reagents and conditions:* **1a**:NaI:NaOH:NaOCl (1.5:1:1:1), MeOH, 0 °C for 1 h and r.t. for 120 h.

SYNTHESIS 2006, No. 15, pp 2523–2530
Advanced online publication: 26.06.2006
DOI: 10.1055/s-2006-942434; Art ID: Z05006SS

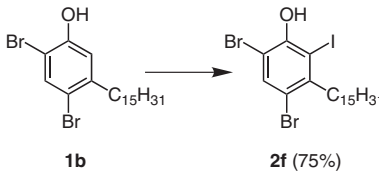


Scheme 2 *Reagents and conditions:* (i) **2a**:NaI:NaOH:NaOCl (1:1:1:1), MeOH, r.t., 3 h; (ii) **2c**:NaI:NaOH:NaOCl (1:1:1:1), MeOH, 50 °C, 2 h.

Although regioselective bromination of cardanol derivatives[9] has been previously studied, the corresponding iodination has thus far remained unexplored. The direct iodination of 3-*n*-pentadecylphenol **1a** may be achieved in aqueous alcohol solvents by the action of a reagent prepared in situ from sodium hypochlorite and sodium iodide.[10] The extent of iodination can be controlled by stoichiometry. Mono iodination of **1a** was carried out with one equivalent of the iodinating agent leading to the formation of 2-iodo-5-*n*-pentadecylphenol (**2a**; 54%) and 4-iodo-3-*n*-pentadecylphenol (**2b**; 44%) in excellent combined yield (Scheme 1).

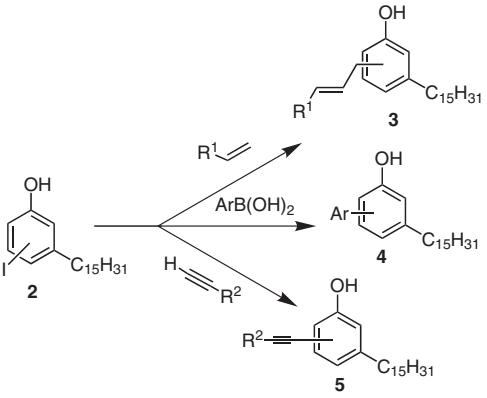
Analogously, the preparation of diiodinated and the triiodinated derivatives (Scheme 2) was effected smoothly, under the same reaction conditions, starting from **2a** and **2c** respectively. The iodinated products reported in this study were isolated by column chromatography over silica gel and characterised by standard analytical means.

Iodination at the 2-position of **1a** was easily accomplished when the 4,6-positions were already occupied. Indeed, the 2-iodo-3-*n*-pentadecyl-4,6-dibromophenol (**2f**) was smoothly prepared in good yield from the 2,4-dibromo-5-*n*-pentadecylphenol (**1b**) (Scheme 3). The bromine on **2f** was considered a potential protecting group since debromination could be achieved both selectively and regioselectively.[11]



Scheme 3 *Reagents and conditions*: **1b**:NaI:NaOH:NaOCl (1:1:1:1), MeOH, r.t., 2 h.

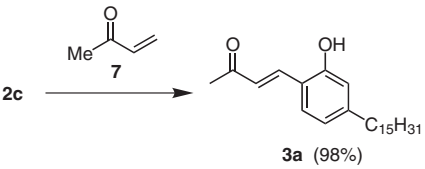
The potential of iodo derivatives **2** as suitable precursors for increasing molecular complexity via palladium-catalysed cross-coupling reactions[12] was then investigated. In particular the aryl iodophenols **2** were exploited as substrates for the synthesis of the corresponding aryl-, vinyl- and alkynyl cardanol derivatives following Suzuki, Heck and Sonogashira protocols, respectively (Scheme 4). It is worth noting that, despite advances in the scope of cross-coupling reactions such as the use of less reactive aryl halides as substrates[13] and the coupling of hindered substrates at very low catalyst loadings and at room temperature,[14] bromo derivatives of 3-*n*-pentadecylphenol (**1a**) proved to be inert to a variety of these reactions conditions.



Scheme 4

Monoiodo derivatives **2a**–**b** underwent palladium-catalysed Heck reaction with both the activated, electron-deficient olefin methyl vinyl ketone and with styrene to afford the corresponding vinyl derivatives **3a**–**c** in good yield (Table 1, entries 1–3).[15] The successful application of the Heck reaction with styrene is significant as this creates a new entry point for the synthesis of powerful antioxidants.[16] In agreement with previous results,[17] **3a**,**c** exhibit antioxidant activity similar to those of other cardanol derivatives and commercial antioxidants.[18]

Surprisingly, the 2,4-diiodo-5-*n*-pentadecylphenol (**2c**) provided **3a** in 98% yield (Scheme 5).



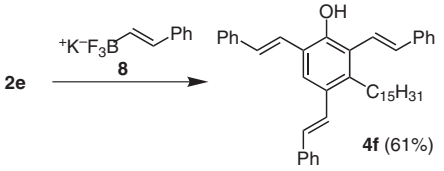
Scheme 5 *Reagents and conditions:* **2c**:**7**:$Pd(OAc)_2$:KOAc (1:6:0.05:3), DMF, 100 °C, 24 h.

The regioselectivity and halogen discrimination in this sequential vinylation/dehalogenation reaction should be considered as two major issues. Reductive dehalogenation of 2,4,6-triiodophenol by sulfite/bisulfate was reported to give only the *para*-deiodinated product 2,6-diiodophenol.[19] Conversely, the *ortho*-iodine was reported to be selectively removed under the influence of tertiary amines/

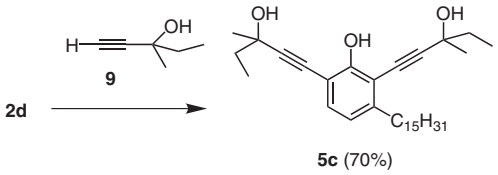
water by a nonreductive deiodination reaction, without affecting *para*-iodine.[20] It is thus very likely that, because of the presence of two iodine atoms which slow down the rate of the Heck reaction, the competitive C-4 reductive dehalogenation of **2c** took place to give **2a** which in turn led to the formation of **3a**. The exact mechanism of the dehalogenation is not yet clearly understood and further exploration is needed.

The palladium-catalysed cross-coupling reaction of aryl halides and organoboron reagents is one of the most widely used synthetic protocols in modern chemistry and in industrial applications. Aryl boronic acids are almost ideal as reagents because they are largely unaffected by the presence of water, tolerate a broad range of functionalities and yield non toxic by-products which can be readily separated from the desired product. We thus examined the palladium-catalysed cross-coupling reaction of **2** with a variety of boronic acids under different reaction conditions. While these reactions have been known for 30 years, there continues to be a significant amount of research devoted to identifying mild reactions conditions that allow the coupling to proceed in the presence of air and use more economic palladium species as catalyst.[23] 'Ligandless' palladium species have been developed that give fast coupling reactions where the phosphine-related side reaction can be suppressed.[24] Considerable improvements are observed when the reactions are carried out in protic solvents, for example, in H_2O[25] or ethanol.[26] Ethanol represented the optimal reaction media for our iodocardanol derivatives. The cross-coupling of **2a**,**b**,**f** with a variety of aryl boronic acids were examined under the optimal reaction conditions [ratio of **2**:aryl boronic acid:$Pd(OAc)_2$:*n*-Bu_4NBr:K_3PO_4 = 1:1.1:0.05:0.05:1 in ethanol at reflux]. The resulting biaryl derivatives **4a–e** were obtained in good yields (Table 1, entries 4–8) showing that the reaction was efficient both with electron-donating and electron-withdrawing substituents on the aryl moiety of the boronic acid derivatives. Under our conditions the results seem to indicate that the reaction outcome is not affected by electronic factors. Although the ability to prepare extremely hindered biaryls via Suzuki–Miyaura coupling reactions has historically proven to be a difficult task, especially with substrates that contain *ortho*,*ortho′*-substituents, the coupling the 2-iodo-3-*n*-pentadecyl-4,6-dibromophenol (**2f**) proceeded as well as that of the less hindered substrates **2a–b**. As expected, chemoselective functionalisation of the C–I bond occurred when both C–I and C–Br groups were present in the phenol moiety. Furthermore, according to recent applications which suggest that alkenyltrifluoroborates[28] are exceptional partners in the Suzuki–Miyaura cross-coupling reaction, providing advantages over other orgaboron substrates, the reaction of the triiododerivative **2g** with potassium β-styryltrifluoro borate (**8**) accomplished the formation of the corresponding 3-pentadecyl-2,4,6-tris[(*E*)-styryl]phenol (**4f**) (Scheme 6).

The Sonogashira coupling[28] of the monoiodides **2a–b** with 3-methyl-1-pentyn-3-ol (**9**) afforded the corresponding alkynyl derivatives **5a–b** (Table 1, entries 9–10). Analogously, the diiodo derivative **2d** gave **5c** (Scheme 7).

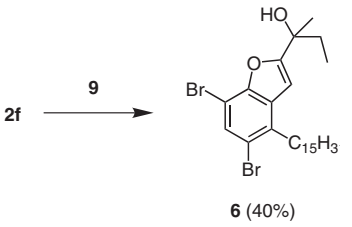


Scheme 6 *Reagents and conditions*: **2e**:**8**:K_3PO_4:$Pd(OAc)_2$:*n*-Bu_4NBr (1:3.6:6:0.05:0.005), EtOH, 80 °C, 24 h.



Scheme 7 *Reagents and conditions*: **2d**:**9**:Et_3N:$PdCl_2(PPh_3)_2$:CuI (1:2.6:2.6:0.02:0.04), THF, 60 °C, 4 h.

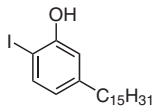
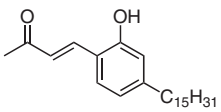
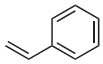
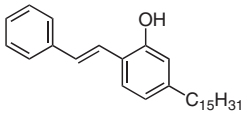
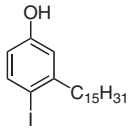
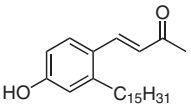
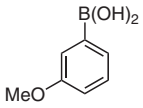
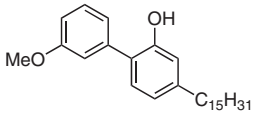
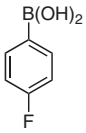
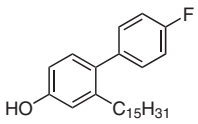
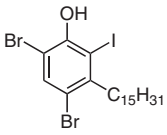
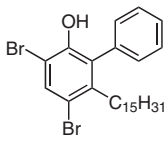
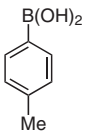
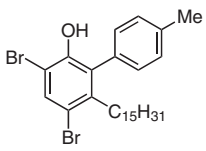
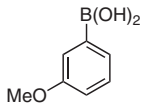
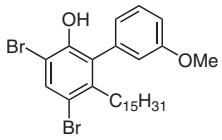
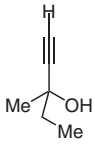
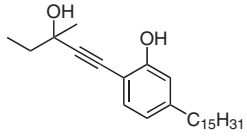
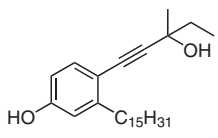
It is worth noting that, in contrast to the usual outcome of the palladium-catalysed reactions of *ortho*-iodophenol derivatives with 1-alkynes,[29] the product derived by the sequential alkynylation/cyclisation reaction was observed only in trace amounts. The formation of this latter derivative should be favoured in the presence of electron-withdrawing substituents in the aromatic moiety of **2** and, indeed, the palladium-catalysed reaction of 4,6-dibromo-2-iodo-3-pentadecylphenol (**2f**)with 3-methyl-1-pentyn-3-ol (**9**) afforded 2-(5,7-dibromo-4-pentadecylbenzofuran-2-yl)butan-2-ol (**6**) as the major product (Scheme 8).



Scheme 8 *Reagents and conditions*: **2f**:**9**:Et_3N:$PdCl_2(PPh_3)_2$:CuI (1:1.3:1.3:0.02:0.04), THF, 60 °C, 24 h.

In summary, we have developed a versatile route for the synthesis of new cardanol derivatives through a combined aromatic iodination/palladium-catalysed cross-coupling process. The extent of aromatic iodination is controlled by stoichiometry. 2-Iodo- and 2,4-diiodo-5-*n*-pentadecylphenol, and 2,6-diiodo-, 4-iodo-, 2,4,6-triiodo-, and 2-iodo-4,6-dibromo-3-*n*-pentadecylphenol derivatives have been synthesised. Suzuki, Heck and Sonogashira protocols were found to be useful tools for the vinylation, arylation and alkynylation of these iodo cardanol derivatives. 2,4-Diiodo-5-*n*-pentadecylphenol undergoes an unusual sequential regioselective dehalogenation/vinylation reaction. Sequential alkynylation/cyclisation of 2-iodo-3-*n*-pentadecylphenol derivatives promises an easy entry point to polysubstituted benzo[*b*]furans.

Table 1 Palladium-Catalysed Cross-Coupling Reactions of Iodo-3-*n*-pentadecylphenol Derivatives **2a**,**b**,**f**

Entry	Iodo-cardanol derivatives	Cross-coupling reagents	Reaction conditions[b]	Products	Yield[a] (%)
1	 **2a**	 **7**	A	 **3a**	60
2	**2a**		A	 **3b**	55
3	 **2b**	**7**	A	 **3c**	86
4	**2a**		B	 **4a**	85
5	**2b**		B	 **4b**	80
6	 **2f**		B	 **4c**	78
7	**2f**		B	 **4d**	80
8	**2f**		B	 **4e**	56
9	**2a**	 **9**	C	 **5a**	40
10	**2b**	**9**	C	 **5b**	72

[a] Isolated yield after flash chromatography.

[b] Reaction conditions: (A) DMF, 24 h at 100 °C, molar ratios **2**:alkene:$Pd(OAc)_2$:AcOK = 1:3:0.05:3; (B) EtOH, 24 h at 80 °C, molar ratios **2**:boric acid:$Pd(OAc)_2$:K_3PO_4:*n*-Bu_4NBr = 1:1.2:0.05:2:0.05; (C) THF, 24 h at 60 °C, molar ratios **2**:**9**:$PdCl_2(PPh_3)_2$:CuI:Et_3N = 1:1.3:0.02:0.04:1.3.

All starting materials were commercially available and were used as purchased without further purification, unless otherwise stated. The products, after conventional workup, were purified by flash chromatography on silica gel, eluting with *n*-hexane–ethyl acetate mixtures. ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra were recorded on a Bruker AC 200 spectrometer in $CDCl_3$. EI and ESI mass spectra were recorded respectively on a ThermoFinnigan Trace DSQ-GC equipped with direct exposition probe and on a ThermoFinnigan LCQ DecaXP equipped with an orthogonal ESI source. IR spectra were recorded in KBr pellets or neat in NaCl disks using a Perkin-Elmer 683 spectrometer. 3-*n*-Pentadecylphenol (1a) was kindly supplied by Oltremare SpA (Bologna, Italy) and 2,4-dibromo-5-*n*-pentadecylphenol (1b) was prepared according to the literature.[9]

Iodination; General Procedure

3-*n*-Pentadecylphenol derivative (6.6 mmol of **1a** or 4.4 mmol of **1b**) was dissolved in MeOH (50 mL) and NaI (0.660 g, 4.4 mmol) followed by NaOH (0.176 g, 4.4 mmol) were added, and the solution was cooled to 0 °C. Sodium hypochlorite aq (0.326 g, 4.0% NaOCl) was added dropwise over 30 min at 0 °C and the mixture was stirred for 1 h at 0 °C then at r.t. until the starting 3-pentadecylphenol derivative was completely consumed (monitored by TLC). After completion the mixture was adjusted to pH 7 using aq HCl (5%). EtOAc (100 mL) was added, and the organic layer taken, dried (Na_2SO_4) and the solvent was evaporated. Column chromatographic purification on silica gel (230-400 mesh), eluting with *n*-hexane–EtOAc mixtures afforded the corresponding pure 3-*n*-pentadecylphenol iodo derivative.

2-Iodo-5-pentadecylphenol (2a)

Purified by column chromatography (*n*-hexane–EtOAc, 98:2).

White solid; yield: 1.021 g (54%).

IR (KBr): 3330, 1410, 600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.25–129 (m, 24 H), 1.55–1.60 (m, 2 H), 2.52 (t, *J* = 5.2 Hz, 2 H), 5.24 (s, 1 H), 6.51 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.82 (d, *J* = 2.0 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.2, 29.4, 29.5, 29.6, 29.7, 30.0, 30.1, 31.1, 31.9, 35.4, 81.8, 115.1, 122.9, 137.7, 145.8, 154.6.

ESI-MS: *m*/*z* (%) = 431.5 (6) [M + 1]$^+$, 107.2 (100).

Anal. Calcd for $C_{21}H_{35}IO$: C, 58.60; H, 8.20. Found: C, 58.50; H, 8.15.

4-Iodo-3-pentadecylphenol (2b)

Purified by column chromatography (*n*-hexane–EtOAc, 95:5).

White solid; yield: 0.8322 g (44%).

IR (KBr): 3330, 1460, 610 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H), 1.25 (br s, 24 H), 1.47–1.54 (m, 2 H), 2.60 (t, *J* = 7.3 Hz, 2 H), 6.41 (dd, *J* = 8.5, 3.0 Hz, 1 H), 5.25 (br s, 1 H), 6.70 (d, *J* = 3.0 Hz, 1 H), 7.60 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 28.0, 29.3, 29.4, 29.6, 29.7, 30.1, 31.9, 33.6, 40.8, 89.1, 115.0, 116.5, 139.9, 146.8, 155.7.

ESI-MS: *m*/*z* (%) = 429.8 (52) [M$^+$], 233.7 (100), 106.9 (59).

Anal. Calcd for $C_{21}H_{35}IO$: C, 58.60; H, 8.20. Found: C, 58.33; H, 8.25.

2,4-Diiodo-5-pentadecylphenol (2c)

Purified by column chromatography (*n*-hexane–EtOAc, 99:1).

White solid; yield: 1.052 g (43%).

IR (KBr): 3320, 1470, 640 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 5.9 Hz, 3 H), 1.54–1.25 (m, 26 H), 2.59 (t, *J* = 7.2 Hz, 2 H), 5.25 (s, 1 H), 6.86 (s, 1 H), 8.00 (s, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.2, 29.3, 29.4, 29.5, 29.7, 29.9, 31.9, 40.3, 83.1, 93.2 115.6, 146.4, 147.7, 155.1.

ESI-MS: *m*/*z* (%) = 555.1 (100) [M – 1]$^-$.

Anal. Calcd for $C_{21}H_{34}I_2O$: C, 45.34; H, 6.16. Found: C, 45.50; H, 6.25.

2,6-Diiodo-3-pentadecylphenol (2d)

Purified by column chromatography (*n*-hexane–EtOAc, 99:1).

White solid; yield: 0.489 g (20%).

IR (KBr): 3330, 1460, 640 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.0 Hz, 3 H), 1.25 (br s, 24 H), 1.53–1.60 (m, 2 H), 2.66 (t, *J* = 7.3 Hz, 2 H), 6.00 (br s, 1 H), 6.56 (d, *J* = 8.1 Hz, 1 H), 7.50 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 27.9, 29.3, 29.4, 29.5, 29.7, 29.9, 31.9, 33.6, 119.3, 121.6, 123.4, 136.5, 141.9, 150.7.

ESI-MS: *m*/*z* (%) = 557.62 (10) [M + 1]$^+$, 268.02 (80), 141 (100).

Anal. Calcd for $C_{21}H_{34}I_2O$: C, 45.34; H, 6.16. Found: C, 45.20; H, 6.01.

2,4,6-Triiodo-3-pentadecylphenol (2e)

Purified by column chromatography (*n*-hexane–EtOAc, 99:1).

White solid; yield: 2.520 g (84%).

IR (KBr): 3410, 1460, 710 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 5.4 Hz, 3 H), 1.44–1.25 (m, 26 H), 2.87 (t, *J* = 7.2 Hz, 2 H), 5.25 (s, 1 H), 8.09 (s, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 28.0, 29.2, 29.4, 29.5, 29.7, 31.9, 47.1, 78.9, 87.4, 88.5, 145.6, 147.3, 154.1.

ESI-MS: *m*/*z* (%) = 681.0 (40) [M – 1]$^-$, 589.2 (100).

Anal. Calcd for $C_{21}H_{33}I_3O$: C, 36.97; H, 4.88. Found: C, 36.50; H, 4.90.

4,6-Dibromo-2-iodo-3-pentadecylphenol (2f)

Purified by column chromatography (*n*-hexane–EtOAc, 99:1).

White solid; yield: 1.940 g (75%).

IR (KBr): 3420, 1420, 650 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.25 (br s, 24 H), 1.36 (br s, 2 H), 2.98 (t, *J* = 6.4 Hz, 2 H), 5.98 (s, 1 H) 7.67 (s, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 27.9, 29.3, 29.4, 29.6, 29.7, 31.9, 42.2, 46.9, 90.6, 105.4, 113.4, 135.2, 145.0, 151.1.

ESI-MS: *m*/*z* (%) = 590.5 (6) [M + 1]$^+$, 588.6 (13) [M + 1]$^+$, 586.6 (8) [M + 1]$^+$, 392.9 (22), 390.97 (48), 388.9 (25), 266.9 (48), 264.93 (100), 262.9 (58).

Anal. Calcd for $C_{21}H_{33}Br_2IO$: C, 42.88; H, 5.65. Found: C, 42.69; H, 5.50.

Palladium-Catalysed Cross-Coupling of Iodo Derivatives 2a,b with Alkenes; General Procedure

A round-bottom flask was charged with a solution of $Pd(OAc)_2$ (11 mg, 0.05 mmol), the iododerivative **2** (1.0 mmol), the appropriate alkene (2.0 mmol) and AcOK (0.294 g, 3.0 mmol) in DMF (2 mL). The reaction mixture was stirred for 24 h at 100 °C then diluted with EtOAc (100 mL). The organic layer was washed with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL) and dried

(Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with *n*-hexane–EtOAc mixtures to give corresponding pure product **3**.

(*E*)-4-(2-Hydroxy-4-pentadecylphenyl)but-3-en-2-one (3a)
Purified by column chromatography (*n*-hexane–EtOAc, 95:5).

Yellowish solid; yield: 0.223 g (60%).

IR (KBr): 3310, 1730, 710 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H), 1.25 (m, 24 H), 1.50–1.75 (m, 2 H), 2.41 (s, 3 H), 2.53 (t, *J* = 8.4 Hz, 2 H), 6.25 (s, 1 H), 6.66–6.75 (m, 2 H), 6.99 (d, *J* = 16.4 Hz, 1 H), 7.37 (d, *J* = 8.5 Hz, 1 H), 7.84 (d, *J* = 16.4 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 26.7, 29.4, 29.5, 29.7, 31.04, 31.9, 35.9, 116.5, 119.0, 120.8, 126.6, 129.5, 141.0, 148.0, 156.4, 200.9.

ESI-MS: *m*/*z* (%) = 371.5 (100) $[M - 1]^-$.

Anal. Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82. Found: C, 80.64; H, 10.60.

5-Pentadecyl-2-[(*E*)-styryl]phenol (3b)
Purified by column chromatography (*n*-hexane–EtOAc, 98:2).

Yellowish solid; yield: 0.224 g (55%).

IR (KBr): 3580, 830 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 5.8 Hz, 3 H), 1.25 (br s, 24 H), 1.37–1.57 (m, 2 H), 2.53 (t, *J* = 7.8 Hz, 2 H), 5.18 (s, 1 H), 6.62 (d, *J* = 8.1 Hz, 1 H), 6.76 (d, *J* = 7.8 Hz, 1 H), 7.07 (d, *J* = 16.5 Hz, 1 H), 7.23–7.26 (m, 2 H), 7.34 (d, *J* = 16.5 Hz, 1 H), 7.38–7.44 (m, 3 H), 7.50 (d, *J* = 7.4 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.4, 29.6, 29.7, 31.2, 31.3, 31.9, 34.4, 35.6, 35.8, 115.9, 120.9, 121.4, 122.0, 126.4, 126.9, 127.4, 128.6, 129.4, 137.8, 144.2, 152.8.

ESI-MS: *m*/*z* (%) = 405.6 (100) $[M - 1]^-$.

Anal. Calcd for $C_{29}H_{42}O$: C, 80.66; H, 10.41. Found: C, 80.59; H, 10.35.

(*E*)-4-(4-Hydroxy-2-pentadecylphenyl)but-3-en-2-one (3c)
Purified by column chromatography (*n*-hexane–EtOAc, 95:5).

White solid; yield: 0.320 g (86%).

IR (KBr): 3310, 1730, 710 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.7 Hz, 3 H), 1.26 (br s, 24 H), 1.53–1.57 (m, 2 H), 2.36 (s, 3 H), 2.71 (t, *J* = 8.0 Hz, 2 H), 6.56 (d, *J* = 15.9 Hz, 1 H), 6.73–677 (m, 2 H), 7.52 (d, *J* = 15.9 Hz, 1 H), 7.81 (d, *J* = 15.9 Hz, 1 H), 8.42 (br s, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.8, 27.5, 29.3, 29.4, 29.6, 29.8, 30.1, 30.5, 30.9, 31.7, 32.0, 33.4, 114.1, 116.9, 124.4, 125.3, 128.4, 140.9 145.4, 159.3, 198.4.

ESI-MS: *m*/*z* (%) = 373.3 (100) $[M + 1]^+$.

Anal. Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82. Found: C, 80.70; H, 10.50.

Palladium-Catalysed Cross-Coupling of Iodo Derivatives 2a,b,f with Organoboron Compounds; General Procedure
A round-bottom flask was charged with a solution of $Pd(OAc)_2$ (5 mg, 0.02 mmol), the iodo derivative **2** (1.0 mmol), the appropriate boronic acid (1.3 mmol), K_3PO_4 (0.424 g, 2.0 mmol), *n*-Bu_4NBr (0.016 g, 0.05 mmol) in EtOH (2 mL). The reaction mixture was stirred for 24 h at 80 °C then the mixture was diluted with EtOAc (100 mL). The organic layer was washed with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with *n*-hexane–EtOAc mixtures to give corresponding pure product **4**.

3′-Methoxy-4-pentadecylbiphenyl-2-ol (4a)
Purified by column chromatography (*n*-hexane–EtOAc, 90:10).

White solid; yield: 0.349 g (85%).

IR (neat): 3450, 690 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.5 Hz, 3 H), 1.26 (br s, 24 H), 1.50–1.55 (m, 2 H), 2.59 (t, *J* = 7.7 Hz, 2 H), 3.83 (s, 3 H), 5.36 (br s, 1 H), 6.78–7.04 (m, 5 H), 7.15 (d, *J* = 8.2 Hz, 1 H), 7.37 (t, *J* = 8.2 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.4, 29.5, 29.3, 29.7, 31.3, 31.9, 35.7, 55.3, 113.4, 114.5, 115.6, 120.9, 121.1, 129.7, 130.3, 138.5, 144.6, 150.1, 160.3.

ESI-MS: *m*/*z* (%) = 411.3 (30) $[M + 1]^+$, 214.9 (100).

Anal. Calcd for $C_{28}H_{42}O_2$: C, 81.90; H, 10.31. Found: C, 81.50; H, 10.20.

4′-Fluoro-2-pentadecylbiphenyl-4-ol (4b)
Purified by column chromatography (*n*-hexane–EtOAc, 95:5).

White solid; yield: 0.318 g (80%).

IR (neat): 3350, 800 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H), 1.14–1.25 (m, 24 H), 1.45–1.70 (m, 2 H), 2.41–2.56 (m, 2 H), 5.52 (br s, 1 H), 6.72–6.76 (m, 3 H), 6.99–7.11 (m, 2 H), 7.12–7.18 (m, 1 H), 7.20 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.9, 31.3, 31.9, 33.0, 33.7, 35.8, 112.6, 114.6, 115.2 (d, J_{C-F} = 17.6 Hz), 130.8, 131.1 (d, J_{C-F} = 12.5 Hz), 133.7, 142.3, 143.0, 154.6, 161.9 (d, J_{C-F} = 251.2 Hz).

ESI-MS: *m*/*z* (%) = 399.3 (25) $[M + 1]^+$, 202.0 (60), 107.99 (100).

Anal. Calcd for $C_{27}H_{39}FO$: C, 81.36; H, 9.86. Found: C, 81.45; H, 9.50.

3,5-Dibromo-6-pentadecylbiphenyl-2-ol (4c)
Purified by column chromatography (*n*-hexane–EtOAc, 95:5).

White solid; yield: 0.419 g (78%).

IR (neat): 3520, 860 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.0 Hz, 3 H), 1.04–1.34 (br s, 26 H), 2.37–2.45 (m, 2 H), 5.18 (s, 1 H), 7.18–7.23 (m, 2 H), 7.41–7.48 (m, 3 H), 7.68 (s, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.2, 22.7, 28.9, 29.2, 29.4, 29.5, 29.6, 29.7, 31.9, 33.7, 107.3, 115.4, 128.1, 128.4, 129.0, 130.4, 134.7, 135.3, 141.3, 149.3.

ESI-MS: *m*/*z* (%) = 540.4 (12) $[M + 1]^+$, 536.2 (22) $[M + 1]^+$, 182.2 (82), 181.0 (100).

Anal. Calcd for $C_{27}H_{38}Br_2O$: C, 60.23; H, 7.11. Found: C, 60.30; H, 7.13.

3,5-Dibromo-4′-methyl-6-pentadecylbiphenyl-2-ol (4d)
Purified by column chromatography (*n*-hexane–EtOAc, 95:5).

White solid; yield: 0.442 g (80%).

IR (neat): 3540, 1310, 810 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H), 1.14–1.30 (br s, 26 H), 2.37 (m, 5 H), 5.16 (s, 1 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.3 (d, *J* = 8.0 Hz, 2 H), 7.67 (s, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 21.3, 22.7, 28.9, 29.2, 29.3, 29.4, 29.7, 31.9, 33.6, 107.1, 115.3, 128.7, 129.6, 129.8, 131.9, 134.6, 138.4, 141.4, 149.4.

ESI-MS: *m*/*z* (%) = 551.4 (100) $[M - 1]^-$.

Anal. Calcd for $C_{28}H_{40}Br_2O$: C, 58.07; H, 7.58. Found: C, 58.10; H, 7.65.

3,5-Dibromo-3′-methoxy-6-pentadecylbiphenyl-2-ol (4e)
Purified by column chromatography (*n*-hexane–EtOAc, 95:5).

White solid; yield: 0.318 g (56%).

IR (KBr): 3490, 1430, 570 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 6.0 Hz, 3 H), 1.17 (m, 26 H), 2.30–2.38 (m, 2 H), 3.74 (s, 3 H), 5.08 (s, 1 H), 6.67–6.73 (m, 2 H), 6.86–6.92 (m, 1 H), 7.32 (t, *J* = 7.9 Hz, 1 H), 7.60 (s, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.2, 22.7, 28.9, 29.4, 29.7, 31.9, 33.7, 55.3, 107.2, 114.3, 115.1, 115.4, 122.0, 130.2, 134.6, 134.8, 136.4, 141.2, 149.2, 160.0.

ESI-MS: *m*/*z* (%) = 570.5 (12) $[M + 1]^+$, 568.5 (24) $[M + 1]^+$, 556.6 (24) $[M + 1]^+$, 212.1 (58), 211.0 (100).

Anal. Calcd for $C_{28}H_{40}Br_2O_2$: C, 59.16; H, 7.09. Found: C, 59.25; H, 7.30.

3-Pentadecyl-2,4,6-tris[(*E*)-styryl]phenol (4f)
A round-bottom flask was charged with a solution of $Pd(OAc)_2$ (10 mg, 0.04 mmol), 2,4,6-triiodo-3-pentadecylphenol (**2e**; 0.296 g, 0.43 mmol), potassium β-styryltrifluoroborate (**8**; 0.327 g, 1.56 mmol), K_3PO_4 (0.551 g, 2.598 mmol) and *n*-Bu_4NBr (0.012 g, 0.04 mmol) in EtOH (2 mL). The reaction mixture was stirred at 80 °C until the iododerivative **2e** was completely consumed (monitored by TLC). The mixture was diluted with EtOAc (100 mL), the organic layer was washed with H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 99:1) to give pure **4f** (0.160 g, 61%) as a yellowish solid.

IR (KBr): 3520, 1460, 680 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 5.5 Hz, 3 H), 1.25 (br s, 26 H) 2.80–2.95 (m, 2 H), 5.95 (s, 1 H), 6.64 (d, *J* = 17.9 Hz, 1 H), 6.95 (d, *J* = 14.9 Hz, 1 H), 7.21–7.44 (m, 19 H), 7.53 (s, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1, 22.7, 29.4, 29.7, 30.6, 31.9, 122.4, 122.7, 122.9, 123.1, 123.7, 125.6, 126.1, 126.5, 126.6, 127.3, 127.6, 127.9, 128.1, 128.6, 128.9, 129.2, 129.8, 130.0, 130.1, 135.8, 136.9, 138.1.

ESI-MS: *m*/*z* (%) = 609.5 (45) $[M - 1]^-$.

Anal. Calcd for $C_{45}H_{54}O$: C, 80.94; H, 11.07. Found: C, 80.87; H, 10.88.

Palladium-Catalysed Cross-Coupling of Iodo Derivatives 2a,b with 3-Methyl-1-pentyn-3-ol (9); General Procedure
A round-bottom flask was charged with a solution of $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (0.08 g, 0.04 mmol), the iodo derivative **2** (1.0 mmol), 3-methyl-1-pentyn-3-ol (**9**; 0.128 g, 1.3 mmol) and Et_3N (0.131 g, 1.3 mmol) in THF (2 mL). The reaction mixture was stirred for 24 h at 60 °C then the mixture was diluted with EtOAc (100 mL). The organic layer was washed with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL) and dried (Na_2SO_4). After removal of the solvent, the residue was purified by column chromatography on silica gel eluting with *n*-hexane–EtOAc mixtures to give corresponding pure product **5**.

2-(3-Hydroxy-3-methylpent-1-ynyl)-5-pentadecylphenol (5a)
Purified by column chromatography (*n*-hexane–EtOAc, 90:10).

Oil; yield: 0.160 g (40%).

IR (neat): 3420, 1470, 810 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.2 Hz, 3 H), 1.10 (t, *J* = 7.3 Hz, 3 H), 1.25 (br s, 26 H), 1.58 (s, 3 H), 1.79 (q, *J* = 7.3 Hz, 2 H), 2.67 (t, *J* = 8.0 Hz, 2 H), 6.10 (s, 1 H), 6.67 (dd, *J* = 7.9, 1.6 Hz, 1 H), 6.77 (d, *J* = 1.6 Hz, 1 H), 7.19 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 9.2, 14.1, 22.7, 27.8, 29.0, 29.2, 29.4, 29.5, 29.6, 29.7, 31.0, 31.9, 35.9, 36.6, 69.5, 78.0, 99.0, 106.2, 114.7, 120.6, 131.4, 146.2, 156.6.

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.47; H, 8.91. Found: C, 80.67; H, 8.98.

4-(3-Hydroxy-3-methylpent-1-ynyl)-3-pentadecylphenol (5b)
Purified by column chromatography (*n*-hexane–EtOAc, 90:10).

Oil; yield: 0.160 g (72%).

IR (neat): 3330, 1450, 900 cm^{-1}

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.1 Hz, 3 H), 1.10 (t, *J* = 7.5 Hz, 3 H), 1.25 (br s, 26 H), 1.57 (s, 3 H), 1.74 (q, *J* = 7.5 Hz, 2 H), 2.67 (t, *J* = 8.0 Hz, 2 H), 5.62 (s, 1 H), 6.57 (dd, *J* = 8.2, 2.6 Hz, 1 H), 6.65 (d, *J* = 2.6 Hz, 1 H), 7.25 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 9.1, 14.1, 22.7, 27.8, 29.0, 29.3, 29.5, 29.6, 29.7, 30.6, 31.9, 34.8, 36.7, 69.5, 78.1, 94.4, 112.8, 114.2, 115.7, 133.8, 147.1, 155.8.

ESI-MS: *m*/*z* (%) = 383.56 (90) $[M - H_2O]^+$.

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.87; H, 10.88.

2,6-Bis(3-hydroxy-3-methyl-1-pent-1-ynyl)-3-pentadecylphenol (5c)
A round-bottom flask was charged with a solution of $PdCl_2(PPh_3)_2$ (3 mg, 0.004 mmol), CuI (0.002 g, 0.008 mmol), 2,4-diiodo-3-pentadecylphenol (**2d**; 0.117 g, 0.2 mmol), 3-methyl-1-pentyn-3-ol (**9**; 0.053 g, 0.55 mmol) and Et_3N (0.051 g, 0.55 mmol) in THF (2 mL). The reaction mixture was stirred for 4 h at 60 °C then diluted with EtOAc (100 mL). The organic layer was washed with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 90:10) to give pure **5c** (0.073 g, 70%) as an oil.

IR (neat): 3420, 1450, 700 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.7 Hz, 3 H), 1.09 (t, *J* = 7.8 Hz, 6 H), 1.26 (br s, 27 H), 1.58 (s, 6 H), 1.99 (q, *J* = 7.8 Hz, 4 H), 2.69 (t, *J* = 7.8 Hz, 2 H), 6.72 (d, *J* = 7.9 Hz, 1 H), 7.14 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 8.3, 14.0, 24.4, 27.2, 29.5, 29.7, 30.5, 31.9, 32.9, 33.3, 66.6, 72.9, 81.9, 87.9, 101.9, 118.6, 124.8, 127.4, 128.4, 132.0, 136.4, 162.7.

ESI-MS: *m*/*z* (%) = 497.39 (5) $[M^+]$, 441.44 (15), 405.25 (100).

Anal. Calcd for $C_{33}H_{52}O_3$: C, 79.79; H, 10.55. Found: C, 79.80; H, 10.54.

2-(5,7-Dibromo-4-pentadecylbenzofuran-2-yl)butan-2-ol (6)
A round-bottom flask was charged with a solution of $PdCl_2(PPh_3)_2$ (0.003 g, 0.004 mmol), CuI (0.002 g, 0.008 mmol), 4,6-dibromo-2-iodo-3-pentadecylphenol (**2f**; 0.118 g, 0.2 mmol), 3-methyl-1-pentyn-3-ol (**9**; 0.026 g, 0.26 mmol) and Et_3N (0.026 g, 0.26 mmol) in THF (2 mL). The reaction mixture was stirred for 24 h at 60 °C then the mixture was diluted with EtOAc (100 mL). The organic layer

was washed with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and the solvent was removed. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 85:15) to give pure **6** (0.044 g, 40%) as a white solid.

IR (neat): 400, 1450, 920 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.85–0.95 (m, 6 H), 1.25 (br s, 27 H), 1.59 (s, 3 H), 1.95–2.00 (m, 2 H), 2.86 (t, *J* = 7.9 Hz, 2 H), 6.66 (s, 1 H), 7.61 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.2, 14.1, 22.7, 26.3, 29.1, 29.3, 29.4, 29.7, 30.0, 31.9, 33.1, 34.2, 72.4, 101.3, 117.3, 127.5, 129.9, 134.4, 134.8, 163.9.

ESI-MS: *m/z* (%) = 561.74 (6) $[M + 1]^+$, 559.61 (15) $[M + 1]^+$, 558.72 (27) $[M + 1]^+$, 557.80 (35) $[M + 1]^+$, 529.60 (100).

Anal. Calcd for $C_{27}H_{42}Br_2O_2$: C, 58.07; H, 7.58. Found: C, 58.10; H, 7.65.

Acknowledgment

Work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, and by the University of L'Aquila and the University of Urbino (Italy).

References

(1) Tyman, J. H. P. *Synthetic and Natural Phenols*; Elsevier: Amsterdam, **1996**.
(2) (a) Attanasi, O. A.; Filippone, P. *Chim. Ind. (Milan)* **2003**, *85*, 11; and references therein. (b) Amorati, R.; Attanasi, O. A.; Ali, B. E.; Filippone, P.; Mele, G.; Spadavecchia, J.; Vasapollo, G. *Synthesis* **2002**, 2749.
(3) (a) Saladino, R.; Mincione, E.; Attanasi, O. A.; Filippone, P. *Pure Appl. Chem.* **2003**, *75*, 265. (b) Saladino, R.; Neri, V.; Mincione, E.; Filippone, P. *Tetrahedron* **2002**, *58*, 8493. (c) Saladino, R.; Neri, V.; Mincione, E.; Marini, S.; Coletta, M.; Fiorucci, C.; Filippone, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 581.
(4) Attanasi, O. A.; Ciccarella, G.; Filippone, P.; Mele, G.; Spadavecchia, J.; Vasapollo, G. *J. Porphyrins Phthalocyanines* **2003**, *7*, 52.
(5) (a) Tagliatesta, P.; Crestini, C.; Saladino, R.; Neri, V.; Filippone, P.; Fiorucci, C. *J. Porphyrins Phthalocyanines* **2002**, *6*, 12. (b) Attanasi, O. A.; Del Sole, R.; Filippone, P.; Mazzetto, S. E.; Mele, G.; Vasapollo, G. *J. Porphyrins Phthalocyanines* **2004**, *8*, 1276.
(6) Attanasi, O. A.; Del Sole, R.; Filippone, P.; Ianne, R.; Mazzetto, S. E.; Mele, G.; Vasapollo, G. *Synlett* **2004**, 799.
(7) Mele, G.; Del Sole, R.; Vasapollo, G.; Garcia-Lòpez, E.; Palmisano, L.; Mazzetto, S. E.; Attanasi, O. A.; Filippone, P. *Green Chem.* **2004**, *6*, 604.
(8) Adimurthy, S.; Ramachandraiah, G.; Ghosh, P. K.; Bedekar, A. V. *Tetrahedron Lett.* **2003**, *44*, 5099 and references therein..
(9) Attanasi, O. A.; Buratti, S.; Filippone, P. *Org. Prep. Proced. Int.* **1995**, *6*, 645.
(10) Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287.
(11) (a) Effenberg, F. *Angew. Chem. Int. Ed.* **2002**, *41*, 1699. (b) Choi, H. Y.; Chi, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 9202.
(12) For a recent review on the palladium-catalysed cross-coupling reactions, see: Nicolaou, K. C.; Bulger, P. C.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
(13) Little, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.
(14) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.
(15) Arcadi, A.; Cacchi, S.; Marinelli, F.; Morera, E.; Ortar, G. *Tetrahedron* **1990**, *46*, 7151.
(16) Guiso, M.; Marra, C.; Farina, A. *Tetrahedron Lett.* **2002**, *43*, 597.
(17) Amorati, R.; Pedulli, G. F.; Valgimigli, L.; Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Saladino, R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2142.
(18) The antioxidant properties of **3a**,**c** were determined by kinetic measurements (inhibition rate constants K_{inh} $M^{-1}s^{-1}$); The inhibition rate constants for **3a**,**c** are 6.2×10^{-3} $M^{-1}s^{-1}$ and 6.5×10^{-3} $M^{-1}s^{-1}$, respectively. For comparison, the inhibition rate constant of the commercial antioxidant 2,6-di-*tert*-butyl-4-methylphenol (BHT) is 2.6×10^{-4} $M^{-1}s^{-1}$.
(19) Adimurthy, S.; Ramachandraiah, G. *Tetrahedron Lett.* **2004**, *45*, 5251.
(20) Talekar, R. S.; Chen, G. S.; Lai, S.-Y.; Chern, J.-W. *J. Org. Chem.* **2005**, *70*, 8590.
(21) Suzuki, A. *Chem. Commun.* **2005**, 4759.
(22) (a) Christmann, U.; Vilar, R. *Angew. Chem. Int. Ed.* **2005**, *44*, 366. (b) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527. (c) Miura, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2201.
(23) Shaughnessy, K. H.; DeVasher, R. B. *Curr. Org. Chem.* **2005**, *9*, 585.
(24) Moreno-Mannas, M.; Pajuclo, F.; Pleixatas, R. *J. Org. Chem.* **1995**, *60*, 2396.
(25) Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* **2003**, 4080.
(26) Deng, Y.; Gong, L.; Mi, A.; Liu, H.; Jiang, Y. *Synthesis* **2003**, 337.
(27) Molander, G. A.; Figureoa, R.; Vagelos, R.; Vagelos, D. *Aldrichimica Acta* **2005**, *38*, 49.
(28) (a) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409. (b) Lindström, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291.
(29) (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Synthesis* **1986**, 749. (b) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabbrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **2000**, 1432. (d) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, 453.