The synthesis of 2-hydroxymethyl derivatives of phenols†

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2-Hydroxymethylphenols have been prepared in good yield by reduction with sodium borohydride of the precursor aldehydes, obtained regiospecifically from reaction of phenols with paraformaldehyde in toluene containing stannic chloride and tri-*n*-butylamine. By contrast, reaction of phenols with either paraformaldehyde under anhydrous conditions or with aqueous formaldehyde results in formation of both the hydroxymethyl and the bishydroxymethyl derivatives. Cyclic acetals of the precursor aldehydes are readily accessible.

Keywords: alkylphenols, 2-hydroxymethylphenols, bishydroxymethylphenols, 2-hydroxylbenzaldehydes, sodium borohydride reduction, cardanol, *t*-nonylphenol [4-(3,5,5-trimethylhexyl)phenol], formaldehyde

We have examined the specific synthesis of 2-hydroxybenzaldehydes and their hydride reduction to give 2-hydroxymethylphenols and found this to be an improvement upon direct hydroxymethylation with paraformaldehyde. Hydroxymethyl derivatives of phenols, notably *o*-compounds, are of interest, as borate complexants[1] in certain cases potentially useful intermediates, for mild oxidation with pyridinium chlorochromate, to form the corresponding aldehydes[1,2] and as model compounds in phenol/formaldehyde polymeric studies.[3]

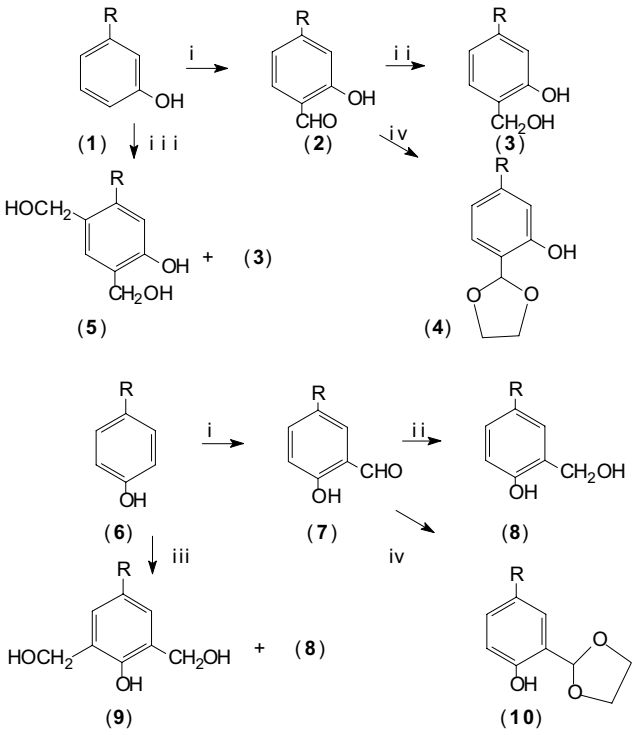
2-Hydroxymethyl derivatives of phenols synthesised by reaction with formaldehyde under acidic conditions tend to polymerise and under base catalysis the reaction is partial requiring a chromatographic separation from the starting material, while under neutral conditions low conversions result, In all cases regiospecificity is absent.[4]

Although some regiospecificity can be achieved, in the reaction of phenol and formaldehyde, by the use of dibutyltin oxide,[5] low conversions resulted. During exploratory work on the synthesis of isoanacardic aldehyde (2-hydroxy-4-pentadecylbenzaldehyde) by mild oxidation of the corresponding hydoxymethyl compound, we found that this could not be obtained regiospecifically from the reaction of 3-pentadecylphenol in alkaline conditions with aqueous formaldehyde.[1] Therefore, we adapted a regiospecific synthesis[2,6] for obtaining the required aldehyde involving the reaction of 3-pentadecylphenoxymagnesium bromide with paraformaldehyde in THF containing hexamethylphosphoric triamide (HMPA).

However, in development studies and to avoid the use of this aprotic solvent, we have modified an alternative approach in which the phenol in toluene containing tri *n*-butylamine and stannicchloride is reacted with paraformaldehye.[7,8] In our work this procedure afforded good yields of 2-hydroxy-4-pentadecylbenzaldehyde and its unsaturated analogues, which are of value as the oximes for the solvent extraction of copper (II).[2] In other cases such aldehyde syntheses afford access to technically and synthetically useful cyclic acetals[7] in protective group applications, enabling phenolic hydroxyl reactions followed by aldehyde group regeneration.

We have confirmed the useful syntheses of *o*-substituted benzaldehydes from 2-, 3-, and 4-methylphenol, although the spectral data is new. Scheme 1 shows its further application to 3-ethylphenol (**1**, R = Et), 3-*n*-pentadecylphenol (**1**, R = $C_{15}H_{31}$) and cardanol (**1**, R = $C_{15}H_{31-n}$, n = 0,2,4,6), 4-ethylphenol (**6**, R = Et), 4-*n*-nonylphenol (**6**, R = *n*-C_9J_{19}), and the reduction of the 2-hydroxybenzaldehydes to (**3**) and (**8**).

The hydroxymethylation reaction of 4-*t*-nonylphenol, mainly 4-(3,5,5-trimethylhexyl) phenol, (**6**, R = *t*-C_9H_{19}) with paraformaldehyde under anhydrous and aqueous alkaline conditions (Scheme 1) is described and the formation of the cyclic acetals (**4**, R = Et)) and **10** (R = *n*-C_9H_{19}). It was hoped at the outset of our work that direct hydroxymethylation could be effected regiospecifically, to give access to isoanacardicalcohol (**3**, R = $C_{15}H_{31-n}$) from available cardanol, (**1**, R = $C_{15}H_{31-n}$, n = 0, 2,4,6) a natural resource and of 2-hydroxymethyl-4-(3,5,5-trimethylhexyl)phenol from 4-(3,5,5-trimethylhexyl)phenol (R = C_9H_{19}) available from fossil fuel sources. However, under a variety of experimental conditions, this was not achieved except in unacceptably low yields. Thus, cardanol in aqueous alkaline conditions[1] had, in that work, afforded the required product, isoanacardic alcohol (yield 37.6 %, conversion 71.2 %), together with 4-isomer, the bishydroxymethyl compound and much unchanged starting material, all with chromatographic properties as described.[9] Alternatively, under anhydrous conditions,[1,10] in hydroxymethylations of 4-(3,5,5-trimethylhexyl)phenol



Scheme 1 Synthesis of methylols. Reagents: (i) $SnCl_4$, (n-$C_4H_9)_3N$ $(CH_2O)_n$; (ii) $NaBH_4$; (iii) aq. NaOH, CH_2O anhydr.$(CH_2O)_n$, $(MeOCH_2)_2$, Δ (iv) 4-TSA, $(HOCH_2)_2$.

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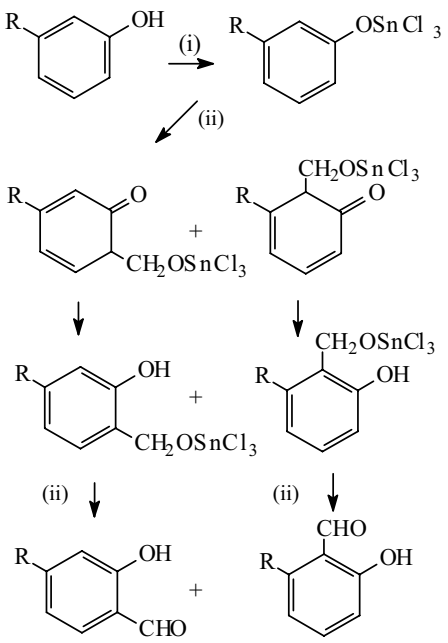

Fig. 1 Formation of *o*-products. Reagents: (i) $SnCl_4$, $(C_4H_9)_3N$, (ii) CH_2O.

with paraformaldehyde, a low yield (14.6 %) of the monomethylol, and under extended reaction, the monohydroxymethyl **3** (31.6 %) and the bishydroxymethyl **9** (9.9 %) resulted. With aqueous formaldehyde, monohydroxymethylation (30.0 %) and bishydroxymethylation (42.4 %) occurred. Such product mixtures required laborious chromatographic separations and accordingly a regiospecific procedure giving a high yield became imperative.

Although it might be anticipated that hydrogen-bonding of the hydroxy group with the C=O in formaldehyde could theoretically aid 2-hydroxymethylation, this appears insufficient and only some form of metallic chelation or interaction of the OH group with a Lewis acid results in regiospecific 2-formylation.

In the stannic chloride procedure with symmetrical *p*-substituted compounds, either of the *o*-positions results in a single product, whereas with unsymmetrical compounds, *e.g.* 3-methylphenol, the minor by-product, 2-hydroxy-6-methylbenzaldehyde is formed as well as the major product, 2-hydroxy-4-methyl benzaldehyde. This is explicable in terms of the two dienones shown (Fig.1) believed to be intermediates, although steric hindrance restricts the formation of the minor product and this effect is magnified with longer chain alkyl groups.

By contrast, with higher aldehydes *p*-substitution occurs[11] but with metallic chelation and more complex aldehydes, *o*-specificity.[11] The hydroxymethyl compound **3**, isoanacardic alcohol (R = $C_{15}H_{31-n}$, n = 0,2,4,6) and **8**, 2-hydroxymethyl-4-(3,5,5-trimethylhexyl)phenol (R = *t*-C_9H_{19}) show excellent chelating properties towards the borate anion[12] and usefulness for its solvent extraction. We have found that *n*-alkyl side chains as in **3** are highly biodegradable in contrast to branched types[13] suggesting that **8** would similarly be immune to biodegradation

Experimental

Materials

Technical cashew nutshell liquid was kindly supplied by 3M Research, Harlow. Chemicals were obtained from Aldrich Chemical Co. All solvents for anhydrous reactions of phenols were dried.

Chromatography

TLC was carried out with silica gel 60A precoated glass plates and visualisations with iodine or under UV light. Column and flash chromatography were carried out on Merck kieselgel 60 (230–400 mesh, ASTM.) and dry flash chromatography on Kieselgel 60H and 60GF.

Spectroscopy

IR spectra were recorded on a Perkin Elmer 1420 instrument as KBr discs or as films for liquids. Proton NMR spectra were performed on a Varian CFT-20 or a Jeol JNM-FX200 in deuterated solvents with tetramethylsilane as internal standard. Mass spectra were recorded on a modified MS 902 AEI instrument and accurate mass measurements by University of Wales, Swansea, Mass Spectroscopy Centre.

Microanalyses were carried out by Butterworth Laboratories Ltd, Teddington and by Medac Ltd., on a Control Equipment Corporation Model 240 XA and Carlo Erba 1106.

Synthesis of 3-, 4-, and 5-methyl 2-hydroxybenzaldehydes

In a general procedure, to a stirred mixture of the respective methylphenol (1.0 m), tri-*n*-butylamine ((0.4 M), and tin tetrachloride (0.1 m) in toluene (250 cm^3), at ambient temperature, paraformaldehyde (2.2 m) was added and after 30 min the yellow solution was heated at 100°C for 5–8 h (TLC monitoring). Then, after cooling the mixture was poured into water acidified with 2 M HCl and ethereally extracted, the ether extract, was washed with sodium chlorides solution, dried and concentrated to give the crude methylsalicylaldehyde.

In this way, from 2-methylphenol (20 g, 185 mmol) 2-hydroxy-3-methylbenzaldehyde was obtained (23.60 g, yield 94 %) and purified by column chromatography (diethyl ether/light petroleum, 40–60°C 1: 1) followed by distillation, b.p., 210–212° (lit.[6] 208°C), R_f 0.78 (diethyl ether, light petroleum, 1: 1); ν_{max} (film, cm^{-1}), 3200 (OH),1650 (CO); δ_H ($CDCl_3$), 11.18 (1H, s, hydrogen–bonded OH), 9.79 (1K, s, CHO), 7.37–6.76 (3H, m, HAr), 2.24 (3H, s, Me) (in broad agreement with Sadtler no.4898); *m/z*, M^+ 136.1. Cald. 136.15.

Similarly, from 3-methylphenol (40 g, 370 mmol) 2-hydroxy-4-methylbenzaldehyde (36.3 g, yield 72 %) was obtained. This was purified by column chromatography, as before, then crystallised (water) to give white needles, m.p. 59–60°C (lit.[6] 60°C); R_f 0.72; ν_{max} (film, cm^{-1}), 3150 (OH), 1660 (CO); δ_H ($CDCl_3$), 10.94 (1H,s, OH), 9.75 (1H, s, CHO), 7.36 (1H, d, J = 8.2 Hz, H-6), 6.90–6.73 (2H, m, H-3 and H-5), 2.35 (3H, s. Me); *m/z*, M^+ 136.1. Cald. 136.15.

From the reaction mixture, 2-hydroxy-6-methylbenzaldehyde was also isolated, m.p. 34–35°C (lit.[14] 31.4–31.9°C) in 6 % yield; ν_{max} (film, cm^{-1}) 3100 (OH), 1655 (CO); δ_H $CDCl_3$) 11.60 (1H,s, OH), 10.10 (1H,s, CHO), 7.30 (1H, q, J = 8 Hz, H-4), 6.80–6.65 (2H,m, H-3 and H-5), 2.60 (3H, s, Me); *m/z*, M^+ 136.1. Reqd. 136.15.

In a similar way, 4-methylphenol (40 g, 370 mmol) gave 2-hydroxy-5-methylbenzaldehyde (48.2 g, yield 96 %). This was purified by column chromatography and crystallisation (MeOH) to afford white needles, m.p. 55.3–56.2°C (lit.[6] 55–56°C); R_f 0.70; ν_{max} (film, cm^{-1}) 3200 (OH), 1655 (CO); δ_H ($CDCl_3$) 10.74 ((1H, s, OH), 9.75 (1H s, CHO), 7.32–6.72 (3H, m, HAr), 2.29 (3H. s. Me); *m/z,* M^+ 136.2. Cald. 136.15.

*2-Hydroxy-4- and 5-ethylbenzaldehydes (***2***, and* **7***, R = Et)*

From 3-ethylphenol 45.1 g, 370 mmol) by the general procedure, 2-hydroxy-4-ethylbenzaldehyde was obtained (53.1 g, yield 95%) which was purified by column chromatography as before to afford a yellow oil, R_f 0.80; ν_{max} (film, cm^{-1}), 3200 (OH), 1658 (CO); δ_H ($CDCl_3$) 10.95 (1H, s, OH), 9.75 (1H,s, CHO), 7.39 (1H, d, J = 8.3 Hz, H-6), 6.85–6.75 (2H, m, H-3 and H-5), 2.64 (2H, q, J = 7.6 Hz, CH_2Ar), 1.23 (3H, t, J = 7.7 Hz, *Me* CH_2Ar); *m/z,* M^+ 150.0690. Reqd.for $C_9H_{10}O_2$,150.0688.

With 4-ethylphenol (45.1 g, 370 mmol) by the general method, 2-hydroxy-5-ethylbenzaldehyde (53.5 g, yield 96 %) was obtained and purification by the same procedure gave a yellow oil; R_f 0.78; ν_{max} (film, cm^{-1}) 3200 (OH), 1655 (CO); δ_H ($CDCl_3$), 10.75 (1H, s, OH), 9.77 (1H, s, CHO), 7.37–6.75 (3H, m, HAr), 2.60 (2H, q, J = 7.5 Hz, *CH*$_2$Me), 1.2 (3H, t, J = 7.5, *Me*CH_2Ar); *m/z*, M^+ 150.0686. Reqd, for $C_9H_{10}O_2$ 150.0688.

*2-Hydroxy-5-n-nonylbenzaldehyde (***7***, R = n-*C_9H_{19}*)*

From 4-*n*-nonylphenol (40.0 g, 182 mmol), by the general method, 2-hydroxy-5-*n*-nonylbenzaldehyde (40.2 g yield 89 %) was obtained which was purified by distillation to give a yellow oil, b.p. 100°C/0.5 mmHg, identical with the product obtained[12] by the alternative

method;[6] R_f 0.84; δ_H ($CDCl_3$), 10.77 (1H, s, OH), 9.82 (1H, s, CHO), 7.56–6.82 (3H, m, HAr), 2.60–2.30 (2H, t, J = 7 Hz, CH_2Ar), 1.6–0.66 (17H, m, $(CH_2)_7$ and Me); *m/z*, M^+ 248.3. Reqd. for $C_{16}H_{24}O_2$, 248.2.

*2-Hydroxy-4-n-pentadecylbenzaldehyde (***2**, *R = n-$C_{15}H_{31}$):* With 3-*n*-pentadecylphenol (20.0 g, 65.8 mmol) by the general method 2-hydroxy-4-*n*-pentadecylbenzaldehyde was prepared (18.4 g, yield 84.2 %) and column chromatographed to yield white crystals, m.p. 52–54°C (lit.[2] 50–54°C); R_f 0.86; ν_{max} (KBr disc),cm^{-1} 1655 (CO); δ_H ($CDCl_3$), 10.95 (1H, s, OH), 9.76 (1H, s, CHO), 7.44–6.74 (3H, m, HAr), 2.60 (2H, t, J = 7.7 Hz, CH_2Ar), 1.77–0.79 (29H, $(CH_2)_{13}$Me); *m/z*, M^+ 332.3. Cald. for $C_{22}H_{36}O_2$ 332.4.

*2-Hydroxy-4-mixed isoaacardic aldehyde (***2**, *R = $C_{15}H_{31-n}$):* By the general procedure, mixed cardanol, (1, R = $C_{15}H_{31-n}$,*n* = 0,2,4,6) (20 g, 65.8 mmol) afforded 2-hydroxy-4-mixed isoanacardic aldehyde as a mixture of saturated, monoene, diene and triene constituents comprising a pale brown oil; R_f 0.85; ν_{max} (film, cm^{-1}) 1655 (CO); δ_H ($CDCl_3$), 10.95 (1H, s, OH), 9.75 (1H, s, CHO), 7.38 (1H, d, J = 8.1 Hz, H-6), 6.81–6.70(2H, m, H-3 and H-5), 5.64–4.94 (5H, m CH_2 =CH, CH=CH), 2.83–2.65 [2H, m, CH_2(CH=CH)$_2$], 2.55 (2H, m, CH_2CH=CH), 1.59–1.20 [m, $CH_2)_n$], 1,00–0.80 (3H, t- Me); *m/z*, M^+ 332.3, 330.3, 328.3, 326.3. Reqd. for C_6H_3(OH)(CHO)($C_{15}H_{31-n}$), *n* = 0,2,4,6, 332.4, 330.4, 328.4, 326.4 respectively.

*Synthesis of cyclic acetals (***4**, *R = C_2H_5 and* **10**, *R = n-C_9H_{19}):* 2-Hydroxy-4-ethylbenzaldehyde (7.7 g, 51 mmol), and 1,2-dihydroxyethane (60 cm^3, 971 mmol), in dry benzene (150 cm^3) containing 4-toluene sulfonic acid (0.6 g) were refluxed with water removal in a Dean-Stark apparatus for 24 h under nitrogen. After cooling the mixture was washed with 10 % potassium carbonate solution, the benzene layer was dried and concentrated to give the crude acetal (7.70 g, 77 %) which was purified by column chromatography (diethyl ether and light petroleum with gradient elution) to give an oil; R_f 0.36 (diethyl ether/light petroleum, 1: 1); δ_H ($CDCl_3$) 7.59 (1H, s, OH), 7.20–6.63 (3H, m, HAr), 5.85 (1H, s, CHAr), 4.06 [4H, s, $(CH_2)_2$], 2.57 (2H, q, J = 7.3 Hz, CH_2Ar), 1.19 (3H t, J = 7.5 Hz, *Me*CH_2). *m/z*, M^+ found 194.0944. $C_{11}H_{14}O_3$ requires 194.0943.

2-Hydroxy-4-*n*-nonylbenzaldehyde (2.0 g, 8 mmol), and 1,2-dihydroxyethane (9.5 cm^3, 153 mmol) in dry benzene 70 cm^3) containing 4-toluene sulfonic acid (0.08 g), were refluxed with water removal for 24 h under nitrogen. The cooled mixture was then washed with 10 % potassium carbonate solution, the benzene layer was dried and concentrated to afford the acetal (1.8 g, 76 %) which was purified as before, to give an oil; R_f 0.19; (diethyl ether/light petroleum, 1: 3; (Found: C, 73.81; H, 9.80. $C_{18}H_{28}O_3$ requires, C, 73.94; H, 9.64 %); δ_H ($CDCl_3$), 7.47 (1H, s, OH), 7.23–6.72 (3H, m, HAr), 5.87 (1H s, CHAr), 4.07 [4H, s. $(CH_2)_2$], 1.72–0.46 [19H, m., $(CH_2)_8$Me]; *m/z*, M^+, found: 292.2042. $C_{18}H_{28}O_3$ requires 292.2038.

Reduction of alkyl o-hydroxybenzaldehydes: To a stirred ice-cooled solution of the hydroxyaldehyde in methanol–water (1: 1) sodium borohydride was added until the yellow colour was discharged. The solution was saturated with ammonium chloride and extracted with diethyl ether, washed wth ammonium chloride, dried and the solvent evaporated in *vacuo* to afford the methylol.which was purified by column chromatography or distillation, as indicated.

2-Hydroxymethyl-4-methylphenol (3.65 g, 72 %), (**8**, R = Me) was obtained from 2-hydroxy-5-methylbenzaldehyde (5 g). It was purified by distillation b.p. 180°C/10^{-3}mm.Hg as a solid, (lit.[14] 104°C); R_f 0.10 (EtOAc–$CHCl_3$, 1: 9); ν_{max} (film, cm^{-1}) 3350 (OH); δ_H ($CDCl_3$), 7.40 (1H, s, ArOH), 7.06–6.72 (3H, m, HAr), 4.84(2H, s, CH_2Ar), 3.40 (1H, s, OH), 2.49 (3H, s, MeAr); *m/z*, M^+ 138.2. Cald. for $C_8H_{10}O_2$ 138.1.

2-Hydroxymethyl-5-methylphenol (**3**, R = Me) (3.6 g, 71 %) was produced from 2-hydroxy-4-methylbenzaldehyde (5.0 g) and purified by distillation b.p. 160°C/10^{-3}mm.Hg (lit.[15]160°C/10^{-3}mm.); R_f 0.12; ν_{max} (film, cm^{-1}) 3355 (OH); δ_H $(CD_3)_2CO$) 7.15 (1H, d, J = 7.2 Hz, H-3), 6.90–6.70 (2H, m, HAr, H-4, H-6), 4.92 (2H, s, CH_2Ar), 3.55 (2H, bs, 2OH), 2.22 (3H, s, MeAr); *m/z*, M^+ 138.2.Cald. for $C_8H_{10}O_2$ 138.1.

2-Hydroxymethyl-6-methylphenol (3.9 g, 77 %) was obtained from 2-hydroxy-3-methylbenzaldehyde (5.0 g) and purified column chromatography with diethyl ether/light petroleum and gradient elution followed by crystallisation (light petroleum) to give white prisms, m.p. 32–33°C, (lit. [15] 32°C); ν_{max} (KBr disc, cm^{-1}) 3360 (OH); δ_H $(CD_3)_2CO$) 6.94–6.44 (3H, m, HAr), 4.88 (2H, bs, 2OH), 4.78 (2H, s, CH_2Ar), 2.22 (3H, s, MeAr); *m/z*, M^+ 138.1. Cald. for $C_8H_{10}O_2$ 138.0681.

2-Hydroxymethyl-4-ethylphenol (**8**, R = Et), (3.7 g, 73 %) was obtained from 2-hydroxy-5-ethylbenzaldehyde (5 g) and purified by column chromatography with diethyl ether/light petroleum 40–60°C with gradient elution; to give an oil, R_f 0.12; ν_{max} (film cm^{-1}) 3350 (OH); δ_H $(CD_3)_2CO$) 7.25 (1H, s, OH), 7.19–6.67 (3H, m, HAr), 4.82 (2H, s, CH_2Ar), 2.55 (2H, q, J = 7.5 Hz, CH_2Me), 1.18, (3H, t, J = 8.4 Hz, *Me*CH_2); *m/z*, M^+ 152.1. Cald.for $C_9H_{12}O_2$ 152.0837.

2-Hydroxymethyl-5-ethylphenol (**3**, R = Et), (3.2 g, 63 %) was produced from 2-hydroxy-4-ethylbenzaldehyde (5.0 g) and purified by column chromatography with gradient elution; to g oil, R_f 0.12; ν_{max} (film, cm^{-1}) 3350 (OH); δ_H $(CD_3)_2CO$, 7.25 (1H, s, HOAr), 7.15 (1H, d, J = 8.0 Hz, H-3), 6.70 (2H, m, H-4 and H-6), 4.67 (2H, s, CH_2Ar), 2.54 (2H, 2H, q, J = 7.1 Hz, CH_2Me), 1.17 (3H, t, J = 7.3, MeCH_2); *m/z*, M^+152.1. Reqd.for $C_9H_{12}O_2$ 152.0837.

2-Hydroxymethyl-5-*n*-pentadecylphenol (**3**, R = $C_{15}H_{31}$), (1.95 g, 65 %) was obtained from 2-hydroxy-4-pentadecylbenzaldehyde (3.0 g) in ice-cold diethyl ether, by reduction with lithium aluminium hydride (0.69 g, 18.3 mmol) over 1 h. The reaction mixture was allowed to warm to ambient temperature, and was diluted with water. Then acidified with 2 M sulfuric acid and extracted with diethyl ether, The dried extract was concentrated and purified by column chromatography with diethyl ether/light petroleum 40–60°C and gradient elution, m.p. 96–97°C; (lit.[1] 96–97°C); R_f 0.37 (chloroform-ethyl acetate, 90: 10). Found: C, 78.76; H, 11.58. Cald. for $C_{22}H_{38}O_2$ C, 78.99; H, 11.45$; ν_{max} (KBr disc, cm^{-1} 3355; δ_H ($CDCl_3$) 6.89 (1H, d, J = 7,7 Hz, H-3), 6.75–6.60 (2H, m, H-4 and H-6), 4.78 (2H, s, $ArCH_2OH$), 2.52 (2H, t, J = 7.2, Hz, CH_2Ar), 1.42–0.90 [26H, m, $(CH_2)_{13}$], 0.87 (3H, t, J = 7.2, Me]; *m/z*, M^+(%), 334.6 (34.9). Reqd. for $C_{22}H_{38}O_2$ 334.3, M^+ + 1, 335.3 (8.4).

*2-Hydroxymethyl-5-mixed isoanacardic alcohol (***3**, *R = $C_{15}H_{31-n}$):* 2-Hydroxymethyl-5-mixed unsaturated isoanacardic alcohol (1.8 g, 60 %) was obtained from 2-hydroxy-4-mixed unsaturated isoanacardic aldehyde (**3**, R = C_{15} H_{31-n}), (3.0 g) in dry diethyl ether which was reduced with lithium aluminium hydride (0.69 g, 18.3 mmol) as for the saturated compound. After work up, as before, the product was purified by column chromatography to give a pale brown oil, R_f 0.37; ν_{max} (film, cm^1); δ_H ($CDCl_3$) 10.95 (1H,s, OH), 9.75 (1H,s, CHO), 7.38 (1H, d, J = 8.1 Hz, H-6), 6.81–6.70 (2H, m, H-3 and H-5), 5.64–4.94 (5H, m, CH_2 =CH, CH=CH), 2.83–2.65 [2H, m, CH_2-(CH=CH)$_2$], 2.55 (2H, t, J = 7.8, CH_2Ar), 2.25–1.85 (2H, m, CH_2CH=CH),1.59–1.20 [m, $CH_2)_n$], 1.00–0.80 (3H, m, Me); *m/z*, M^+-H_2O, 316..1, 314.1, 312.1, 310,1. Cald. for C_6H_3(OH)(CH_2OH)($C_{15}H_{31-n}$), *n* = 0,2,4,6 334.3, 332.3, 330.3,328.3 respectively.

2-Hydroxymethyl-4-(3,5,5-trimethylhexyl)phenol (**8**, *R = t-C_9H_{19}) and 2,6-dihydroxymethyl-4-(3,5,5-trimethylhexyl)phenol* (**9**, *R = t-C_9H_{19}*): Anhydrous method: Initial attempts by the described method[10] afforded 14.6% yield although with modifications slightly improved yields were obtained. *t*-Nonylphenol (10 g, 0.045 mol, paraformaldehyde (20.70 g, 0.45 mol) xylene (90 cm^3).and dimethoxyethane (9.4 cm^3, 0.09 mol) in a closed glass reactor were stirred and heated at 135°C for 100 h (TLC monitoring indicated two bands at R_f 0.28 and 0.13, chloroform-ethyl acetate, 90: 10). The cooled mixture was filtered to remove paraformaldehyde, then concentrated in vacuo. Purification by column chromatography with chlorofom-light petroleum 40–60°C and gradient elution gave firstly **8**, as a pale yellow oil (3.59 g, 31.6%), R_f 0.28 and secondly, the bis **9**, a yellow oil, (1.26 g, 9.9%), R_f 0.13. For **8**, ν_{max} (film, cm^{-1}) 3340 (OH),1610 (benzene ring), 1370 (HOAr) 1000 (HOR); δ_H ($CDCl_3$) 7.20–8.17 (1H, bs, OH, D_2O exch.), 6.47–7.03 (3H, m, HAr), 4.63 (2H, s, $HOCH_2Ar$), 2.23–2.97 (1H, bs, D_2O exch., $HOCH_2Ar$), 0.43–1.77 (19H, m, $C_9H_{19}Ar$); m/z, M^+, found, 250.1934. Reqd. for $C_{16}H_{26}O_2$,250.1933.

For **9**, obtained as the final fraction by gradient elution, ν_{max} (film, cm^1), 3350 (OH), 1610 (benzene ring), 1380 (C-O, HOAr), 1250 (HOR), 1190, 1020 (OH, phenol and primary alc.); δ_H ($CDCl_3$), 7.60–8.0 (1H, bs, HOAr, D_2O exch.), 6.72 (2H, s, HAr), 4.60 [4H, s, ($CH_2OH)_2Ar$], 2.67–1.17 [2H, bs, D_2O exch.($HOCH_2)_2Ar$], 0.51–1.80 (19H,m, $C_9H_{19}Ar$); *m/z*, M^+ 280.2, M^+ + 1 (281.2). $C_{16}H_{26}O_3$ requires 280.28. A variety of attempts to improve the yield of **8** were not successful and 31.6 % remained the best.

Aqueous method

To 4-(3,5,5-trimethylhexyl)phenol) 11.44 g, 0.052 mol), at 60°C containing 3M sodium hydroxide (1 cm^3) 37 % aqueous formaldehyde solution (5.4 cm^3, 0.066 mol) was added and the mixture reacted for a further 24 h. The cooled mixture was then extracted with diethyl ether, the extract was washed with dilute hydrochloric acid, saturated aqueous sodium chloride (3×100 cm^3), dried and concentrated to afford an oil. This was purified by dry-column flash chromatography

with diethyl ether/light petroleum, 40–60°C and gradient elution to give **8** (3.90 g, 30.0 %), R_f 0.29 and **9** (6.18 g, 42.4 %), R_f 0.13. For **8**, ν_{max} (film, cm^{-1}) 3350, 1620, 1390, 1260, 1180, 1020; δ_H (CCl_4) 6.33–6.90 (4H, m, HAr and OH, D_2O exch.), 4.50 (2H, s, HO*CH*$_2$Ar), 3.10–3.87 (1H, bs, *HO*CH_2Ar, D_2O exch.), 0.37–1.57 (19H, C_9H_{19}Ar); *m/z*, M^+ 250.4 (19.4%), M^+ + 1 251.4,(3.2%). Found: 250.1932; cald, for $C_{16}H_{26}O_2$, 250.1933.

For **9**, ν_{max} (film, cm^{-1}), 3400, 1620, 1390, 1260, 1190,1020; δ_H (CCl_4), 7.67–8.20 (1H, bs, HOAr, D_2O exch.), 6.67 (2H, s, HAr), 3.83–4.53 [6H, s. on bs, $(HOCH_2)_2$Ar, D_2O exch.), 0.40–1.63 (19H, C_9H_{19}Ar); *m/z*, M^+ 280.5 (11.1%). Found, 280.2032. Cald. for $C_{17}H_{28}O_3$, 280.2038.

To optimise the yield for **9**, experiments with 4-(3,5,5-trimethylhexyl)phenol (10 mmol each) and aqueous formaldehyde (22, 50 and 100 mmol) in the presence of 3M sodium hydroxide, gave yields of **8**, (16 %, 5 % and 0 %) and of **9**, (62 %, 85 % and 98 %) respectively. **9** Proved to be a more efficient borate extractant than **8** in studies[12] which will be described elsewhere.

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References

1 J.H.P. Tyman and S.K. Mehet, *Chem. Phys. of Lipids*, 2003, 126, 177.
2 J.H.P. Tyman and S.J.A. Iddenten, *J. Chem. Tech. Biotech*, 2005, **80**, 1319; UK Patent Application GB 2152925A.
3 E.R.H. Jones and I.K.M. Robson, BP Patent specification 634960, (Dec. 23, 1947).
4 A. Knop and W. Scheib, *Chemistry and Application of Phenolic Resins*, Springer-Verlag, Berlin, 1979, 35.
5 A. Ninagawa, Y. Ohnishi, H. Takeuchi and H. Matsuda*, Makromol. Chem. Rapid Commun*., 1985, **6**, 793.
6 G Casiraghi, G. Casnati, M. Cornia, A. Pochini, A. Puglia, G. Sartori and G. Ungaro, *J. Chem. Soc., Perkin Trans*., 1978, 318; J,H.P. Tyman, (unpublished work).
7 P. Payne, *Ph.D. Thesis*, Brunel Univ., 1992.
8 G. Casiraghi, G. Casnati, G. Puglia, G. Sartori and G. Terenghi, *J. Chem. Soc., Perkin Trans*., 1980, 1862.
9 N.H. Isaiah and J.S. Aggarwal, *J. Chromatogr.*, 1971, **62**, 473; J.H.P. Tyman, *Phenols, Aromatic carboxylic acids and Indoles*, Ch.25, p,899, Handbook of Thin Layer Chromatography, (Eds. J. Sherma and B. Fried), M Dekker, 2nd edn. 1996.
10 G. Casiraghi, G. Casnati, G. Puglia and G. Sartori, *Synthesis*, 1980, **10**, 124.
11 J.H.P. Tyman, *Synthetic and Natural Phenols*, Elsevier, Amsterdam, 1996, Chap.6, p157.
12 S.K. Mehet, Ph.D. Thesis, Brunel Univ., 1988; J.H.P. Tyman, UK Patent Application, GB 2407813 (16 May, 2003).
13 J.H.P. Tyman and I.E. Bruce, *J. Surfactants Detergents,* 2004, **7**, 169-173.
14 P. Marchand and J.B. Grenet, Fr. 1328945, (June 7th 1963).
15 I.M. Heilbron and H.M. Bunbury, *Dictionary of Organic Compounds*, Eyre and Spotiswoode, London, 1953.