Long Chain Phenols. Part 17.[1] The Synthesis of 5-[(Z)-Pentadec-8-enyl]resorcinol, ' Cardol monoene,' and of 5-[(ZZ)-Pentadec-8,11-dienyl]-resorcinol Dimethyl Ether, ' Cardol diene ' Dimethyl Ether†

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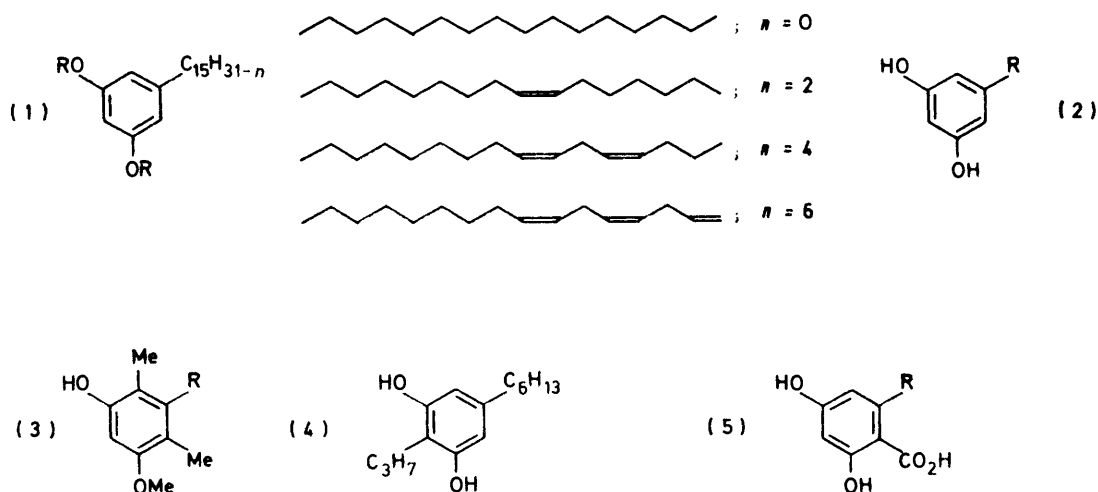
Two unsaturated compounds in the ' cardol ' series, an important component phenol from *Anacardium occidentale*, have been synthesised. 3,5-Dimethoxybenzaldehyde interacted with OH-protected 6-chlorohexan-1-ol in the presence of lithium to give, after acidic treatment, 1-(3,5-dimethoxyphenyl)heptane-1,7-diol which was hydrogenolysed selectively to 7-(3,5-dimethoxyphenyl)heptan-1-ol. Conversion into the bromide and alkylation of lithio-oct-1-yne gave 5-(pentadec-8-ynyl)resorcinol dimethyl ether which was selectively converted into the 8-(Z)-alkene. Demethylation with lithium iodide gave 5-[(Z)-pentadec-8-enyl]resorcinol which was identical to ' cardol monoene'. Reaction of 7-(3,5-dimethoxyphenyl)heptyl bromide with the lithium derivative of OH-protected propargyl alcohol, gave after acidic treatment 10-(3,5-dimethoxyphenyl)dec-2-yn-1-ol, the bromide of which with pent-1-ynylmagnesium bromide afforded 5-pentadec-8,11-diynylresorcinol dimethyl ether. Selective hydrogenation yielded 5-[(ZZ)-pentadeca-8,11-dienyl]resorcinol dimethyl ether identical with the dimethyl ether of ' cardol diene.'

PLANT sources of long-chain resorcinols are numerous comprising ' cardol ' (1; R = H, $n = 0, 2, 4, 6$), the major dihydric phenolic mixture in natural and technical cashew nut-shell liquid from *Anacardium occidentale*,[2a,2b] persoonol,[2c] 5-[(Z)-undec-3-enyl]resorcinol (2; R = $C_{11}H_{21}$) from *Persoonia elliptica*, grevillol[2d] (2; R = $C_{13}H_{27}$) from *Grevillea robusta* A. Cunn., 5-pentadec-10-enylresorcinol[2e] from *Grevillea pyramidalis*, bilobol[2f,g] (1; R = H, $n = 2$) from *Ginkgo biloba*, and

general methods for the synthesis of this group of compounds. A phenolic monoene and the dimethyl ether of a phenolic diene have been prepared.

RESULTS AND DISCUSSION

The several approaches investigated for the synthesis of 7-(3,5-dimethoxyphenyl)heptan-1-ol (6) are summarised in Scheme 1. It was advantageous to attempt the use of 3,5-dimethoxybenzoic acid rather than the less avail-

unsaturated and saturated compounds of different chain lengths from the algal source *Cystophora torulosa*.[2h] Saturated phenols (2) of plant origin[2i] and others (3; R = C_{15}, C_{17})[2j,k] and (4)[2l] of non-plant origin have been described. Both groups probably arise from orsellinic acids[1] (5) by way of long-chain alkyl tetraketide precursors. No syntheses of unsaturated resorcinols have previously been described and the present work, communicated in part,[3] has been concerned with finding

able aldehyde as an ArC, together with a C_6 synthon. Alternative combinations such as ArC₂ (3,5-dimethoxy-acetophenone) with a C_5 synthon, ArC₃ (3,5-dimethoxy-cinnamic acid) with C_4, or Ar (3,5-dimethoxyfluoro-benzene) in an aryne route[1] with a C_7 component were all less attractive.

Model experiments between lithium 3-methoxy-benzoate and n-butyl-lithium led to di-n-butyl-(3-methoxyphenyl)ethanol[4] as well as 3-methoxyvalero-phenone, and the successful use of 3,5-dimethoxybenzoic acid seemed unpromising.

Attention was turned next to ethyl 3,5-dimethoxy-benzoate [Scheme 1(a)]. Ambiguity in the hydrolysis of an alkylated β-keto-ester led to the use of ylides derived from dimethyl sulphoxide.[5] The model compounds α-(methylsulphinyl)acetophenone[6] and α-(methylsulphinyl)-3,5-dimethoxyacetophenone (7) were prepared from the respective esters and the carbanion of dimethyl sulphoxide but the latter (as the carbanion) could not be alkylated with n-propyl iodide to yield (8).

was synthesised by standard procedures from n-butyl-magnesium bromide and 3,5-dimethoxybenzaldehyde and oxidation of the resultant alcohol with chromium trioxide–pyridine. 3,5-Dimethoxybenzoyl chloride re-acted with the ' lithium dialkylcuprate ' from OH-pro-tected 6-chlorohexan-1-ol and removal of the protective group gave 3,5-dimethoxyphenyl 7-hydroxyhexyl ketone (9) accompanied however by some dodecane-1,2-diol and some other minor impurities. Both a low temper-
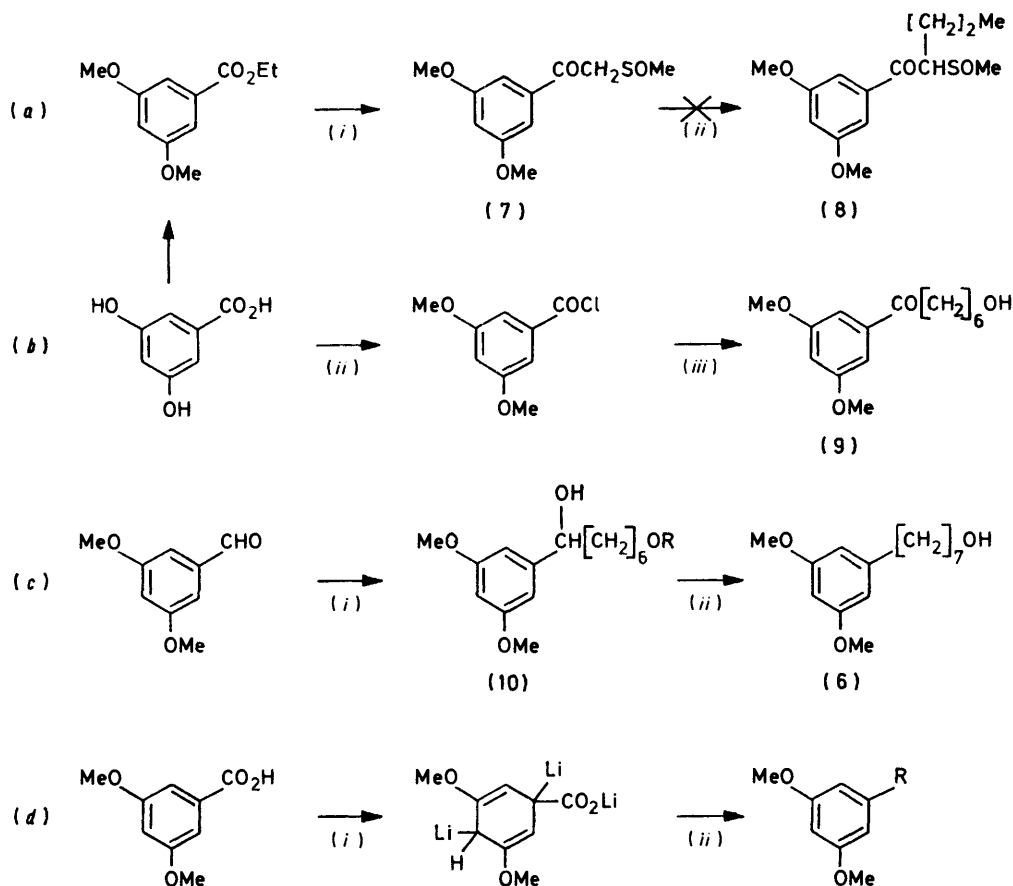

SCHEME 1   (a) (i) NaH, DMSO; (ii) DMSO, NaH, I[CH₂]₂Me: (b) (i) CH₂=CHOEt, HO[CH₂]₆Cl, toluene-p-sulphonic acid; (ii) H⁺, EtOH, CCl₄, Me₂SO₄, K₂CO₃–Me₂CO, OH⁻, H⁺, PCl₅; (iii) Li (RO[CH₂]₆)₂Cu {from RO[CH₂]₆Cl —Li→ —CuI→ Li (RO[CH₂]₆)₂Cu}, −80 °C, H⁺, MeOH: (c) (i) Li, Cl[CH₂]₆OR [R = CH(Me)OEt]; (ii) (1) H⁺, MeOH, toluene-p-sulphonic acid, EtOH, OH⁻, H⁺, H₂, Pd–C; (2) Mg, Cl[CH₂]₆OR (R = tetrahydropyran-2-yl); (d) (i) Li–NH₃, EtOH; (ii) RBr, H⁺, Pb(OAc)₄, Cu²⁺

It was therefore unlikely that the dimethoxy-compound would interact with the required OH-protected 5-iodopentanol to furnish, by way of reductive cleavage to (9), a route to (6). The failure of alkylation with the 3,5-dimethoxy-compound can probably be ascribed to electronic inactivation.

The applicability of the lithium dialkylcuprate synthesis[7] [Scheme 1 (b)] was now investigated via the model reactions of lithium di-n-butylcuprate with benzoyl chloride, 3-methoxybenzoyl chloride, and 3,5-dimethoxy-benzoyl chloride, respectively in which valerophenone (62%), 3-methoxyvalerophenone (79%), and 3,5-dime-thoxyvalerophenone (92%) were obtained. The latter

ature (−78 °C) and a three-fold proportion (effectively a six-fold ratio) of alkylating agent appear essential since higher temperatures and lower proportions led to lower yield and unreacted acid chloride, respectively, at the methanolic quenching stage, resulting in undesir-able methyl ester formation. The formulation of the reaction according to equation (1) may be an over-simplification. A route requiring a more economical pro-portion of the protected 6-chlorohexan-1-ol was sought.

$$Li\ (R)_2Cu + 2ArCOCl \longrightarrow 2RCOAr + LiCl + CuCl \quad (1)$$
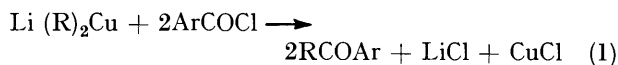
In the original procedure for the synthesis of (6),

3,5-dimethoxybenzaldehyde had been treated with the Grignard reagent from the tetrahydropyranyl derivative of 6-chlorohexan-1-ol, but the pronounced formation of dodecane-1,12-diol by Wurtz coupling, as well as the required diol (10; R = H), and the requirement for a base hydrolysis treatment in order to effect the following hydrogenolysis stage,* made it desirable to improve the whole procedure. This objective was later attained by the reaction of 6-chlorohexan-1-ol (OH-protected through ethyl vinyl ether) with 3,5-dimethoxybenzaldehyde and lithium [Scheme 1 (c)]. Formation of dodecane-1,12-diol was prevented by the addition of a mixture

with phosphorus tribromide, since chloroform and ether as solvents gave poorer results. The pathway of the reaction has been discussed.[10]

Major by-products were the phosphite esters $(HO)_2$-P(OR), and $HOP(OR)_2$ formed by hydrolysis of bromo-alkoxyphosphorus analogues, and $P(OR)_3$, evident from both t.l.c. analysis, and from the [1]H n.m.r. signal at δ 4.00 (CH_2-P) and the i.r. absorption at 2 400 cm^{-1} (P-H). The two latter phosphites were with difficulty hydrolysable to the original alcohol; some trialkyl-phosphite appeared to be lost through the Arbuzov[11] reaction leading to a dialkyl alkyl phosphonate. The
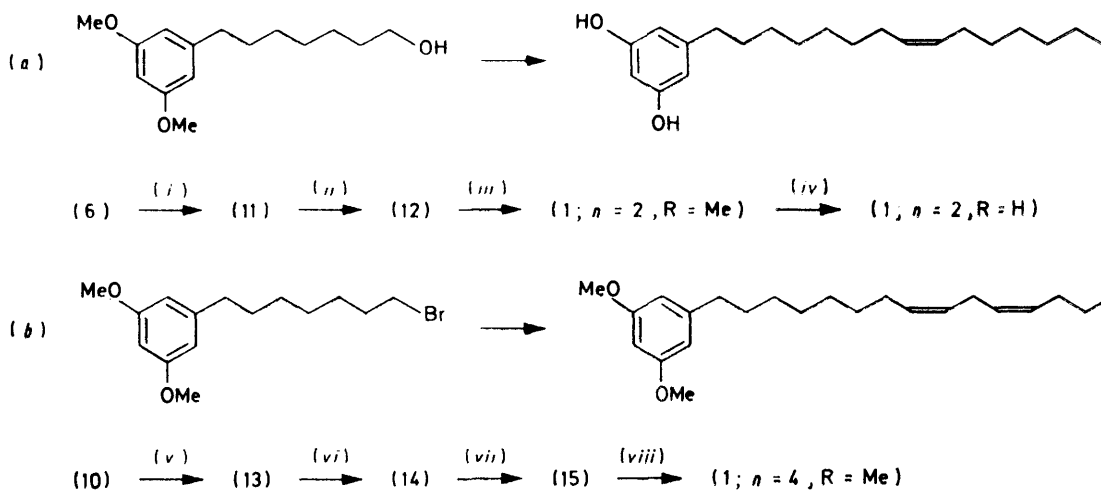
Scheme 2   (a) (i) PBr₃; (ii) (1) BuⁿLi, HC≡CC₆H₁₃, HMPT; (2) LiNH₂, HC≡CC₆H₁₃, HMPT; (iii) H₂, Pd–BaSO₄, quinoline; (iv) LiI, collidine; (b) (v) HC≡CCH₂OH, H₂C=CHOEt, toluene-p-sulphonic acid, LiNH₂, HMPT, HCl, MeOH; (vi) PBr₃, pyridine, Et₂O; (vii) EtMgBr, HC≡CC₃H₇, CHCl₃, NH₄Cl; (viii) H₂, Pd–BaSO₄, quinoline

of the chloro-compound and the aldehyde at low temperature to the lithium, thus enabling the alkyl-lithium to be reacted as soon as formed, and by maintaining a low concentration of the chloro-compound through slow addition. Methanolic hydrochloric acid in catalytic amounts enabled the resultant diol (10) to be hydrogenolysed in high yield without the need for acidification of the reaction medium. Although base hydrolysis proved much less imperative it was still used as a routine step.

Model experiments [8] on the alkylation of the Birch reduction [9] product from the more available 3,5-dimethoxy-benzoic acid followed by oxidative decarboxylation as typified by Scheme 1 (d) were promising although as yet incomplete, and would avoid the hydrogenolysis stage.

The reactions used for the monoene (1; $n = 2$, R = H) and the diene dimethyl ether (1; $n = 4$, R = Me) are given in Scheme 2.

7-(3,5-Dimethoxyphenyl)heptyl bromide (11) was best obtained from the alcohol (6) by reaction in benzene

* The slow hydrogenolysis was believed to be caused by 4-toluenesulphonic esters, arising from the protecting group removal, acting as catalyst poisons.

effectiveness of benzene as a solvent may be attributable to increased HBr attack on the soluble bromoalkoxy-phosphorus compounds giving the alkyl bromide (11) rather than on insoluble phosphites. Both hydrobromic acid and hydrobromic acid–concentrated sulphuric acid gave very moderate yields of (11) accompanied by demethylation products.

7-(3,5-Dimethoxyphenyl)heptyl bromide interacted with lithio-oct-1-yne, from n-butyl-lithium or lithamide and excess of oct-1-yne, in tetrahydrofuran containing hexamethylphosphoric triamide.[12] The product, 5-pentadec-8-ynylresorcinol dimethyl ether (12) was smoothly hydrogenated to 5-[(Z)-pentadec-8-enyl]resorcinol dimethyl ether (1; $n = 2$, R = Me) with palladium–barium sulphate in methanol containing quinoline. Model experiments with tetradec-7-yne were necessary since excess of quinoline entirely inhibited hydrogenation, and an insufficiency led to tetradecane. Synthetic (14), identical by t.l.c. and g.l.c., and spectroscopic comparison (i.r. and [1]H n.m.r.) with the dimethyl ether of cardol monoene, was slowly but smoothly demethylated by way of the half methyl ether when refluxed with lithium iodide in collidine,[13] following unsuccessful attempts with pyridine hydrochloride or boron tribro-

mide. The synthetic monoene (1; R = H, n = 2) was identical chromatographically (including argentation t.l.c.) and spectroscopically with the natural product.

For the diene, 7-(3,5-dimethoxyphenyl)heptyl bromide was interacted with the lithium derivative of OH-protected propargyl alcohol (with ethyl vinyl ether) [12] (from lithamide and the acetylenic compound), in tetra-hydrofuran containing hexamethylphosphoric triamide to give in high yield, after careful acidic methanolysis, 10-(3,5-dimethoxyphenyl)dec-2-yn-1-ol (13). Correct conditions for the use of lithamide with the protected acetylenic compound were established by alkylations with 1-bromoheptane to give finally dec-2-ynol.* 10-(3,5-Dimethoxyphenyl)dec-2-ynyl bromide (14) was smoothly formed in ethereal solution at -30 °C from the acetylenic alcohol with phosphorus tribromide containing a trace of pyridine. Interaction of the acetylenic bromide (14) with pent-1-ynylmagnesium bromide in tetrahydrofuran containing cuprous chloride gave a 91% yield of the diyne (15), 5-(pentadec-8,11-diynyl)resorcinol dimethyl ether. To find the best conditions for the preceding reaction, oct-1-ynyl-magnesium bromide and allyl bromide were reacted in tetrahydrofuran containing cuprous chloride to give hendec-4-yn-1-ene in 77% yield.[14] The diyne (15), an unstable material requiring t.l.c. purification in a nitrogen atmosphere, was selectively and smoothly catalytically hydrogenated with palladium–barium sul-phate in methanol containing quinoline by way of the 8-(Z)-en-11-yne and the 11-(Z)-en-8-yne (g.l.c. monitor-ing to the required diene, 5-[(Z)Z]-pentadeca-8,11-dienyl]resorcinol dimethyl ether. The product was purified by argentation t.l.c. (E-isomers with higher R_F values were not observed) and the purified synthetic diene (1; R = Me, n = 4) was chromatographically and spectroscopically identical with the diene constituent of natural cardol (1; n = 0, 2, 4, 6) separated by argent-ation t.l.c. and methylated or $vice$ $versa$. Demethylation of the synthetic diene dimethyl ether with lithium iodide in collidine afforded a number of products including cardol diene, not formed, however, in practicable yield.
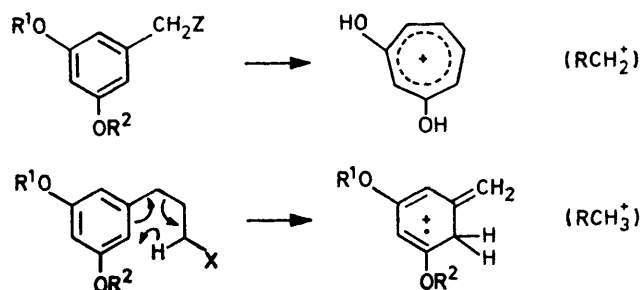
The constituents of cardol, their methyl ethers, and the intermediates obtained in this work exhibited characteristic mass spectra with prominent molecular ions and a favoured resonance-stabilised base peak due to β-cleavage of the side-chain with hydrogen transfer rather than direct β-cleavage. The ratio of these peaks

($i.e.$ RCH_3^+ : RCH_2^+) was usually between 3.5 and 5, characteristic of long-chain phenols having a long chain $meta$ to one or more hydroxy-groups.[15] For compounds of the cardol series (R^1 = R^2 = H; Z and X, C_{14} and C_{12} chains), RCH_3^+ : RCH_2^+ was 124 : 123. For the dimethyl ether series (R^1 = R^2 = Me; Z and X various chains), RCH_3^+ : RCH_2^+ was 152 : 151 and for the mono-methyl derivative of cardol monoene it was 138 : 137.

EXPERIMENTAL

Thin layer chromatography (t.l.c.): Analytical t.l.c. was carried out on laboratory coated (0.25 cm) microscope slides with silica gel G (Merck) Type 60 or with foil-backed plates (60, F254). Preparative t.l.c. plates with silica gel G (20 cm × 20 cm × 0.2 cm) were prepared or obtained ready for use (60, F254). Bands were visualised with 0.1% ethanolic Rhodamine 6G and u.v. irradiated or (type F254) simply irradiated. Silver nitrate (15%) impregnated t.l.c. plates were prepared and visualised by spraying with 50% aqueous sulphuric acid and charring (150 °C), or preparative plates by spraying with 0.1% ethanolic 2,7-dichloro-fluorescein. The solvents used in t.l.c. were: A, chloro-form; B, ethyl acetate–chloroform (1 : 1); C, diethyl ether; D, ethyl acetate–chloroform (1 : 9); F, ethyl acetate–chloroform (3 : 2); G, benzene–chloroform (1 : 1); H, light petroleum (b.p. 60°—80°); J, ethyl acetate-chloroform (1 : 99); and K, ethyl acetate–chloroform (1 : 3). For substances liable to autoxidation, application of samples to t.l.c. plates was carried out in a nitrogen box, also used after development to remove solvent.

Gas–liquid chromatography (g.l.c.): Analytical g.l.c. was conducted using a Pye 104 or 105 chromatograph with a flame-ionisation detector. The carrier gas was nitrogen at 45 cm³ min⁻¹ ($ca.$ lb in⁻²). The stationary phases, all on Diatomite C, were A (3% SE30), B (3% SE52), C (5% APL), and D (2% PEGA); data is presented as type of column, temperature (°C), and retention time (min).

I.r. spectra were recorded on a Perkin-Elmer 700 or a Pye Unicam SP200 spectrometer (liquids as films and solids as discs). ¹H N.m.r. spectra were determined with a Varian T60 at 60 mHz with tetramethylsilane as internal standard. Mass spectra were determined on an MS50 (PCMU), MS902A (Mr. D. Carter, School of Pharmacy, University of London), and MS902 and RMS4 (Brunel). Accurate mass measurements (PCMU) were made by a mass marker and by computer (VGZAB).

All reactions with alkyl-lithium compounds and acetyl-enic reagents were carried out under argon and nitrogen, respectively, in the evacuable apparatus described.[15]

Dry benzene and ether were stored over sodium wire. Elemental analyses were carried out by BMAC Ltd, Teddington, Middlesex.

2-(6-$Chlorohexanyloxy)tetrahydropyran$.— 6-Chlorohexan-1-ol, b.p. 108 °C at 12 mmHg (lit.,[16] 114—117 °C at 20 mmHg); δ(CCl₄) 3.4—3.7 (4 H, 2 × t, CH_2Cl, CH_2OH), 3.3 (1 H, s, OH, exchangeable with D₂O), and 1.5 (8 H, m [CH_2]₄); g.l.c. (A, 130, 8.8). To 6-chlorohexan-1-ol (13.65 g,

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* It has been found useful in nucleophilic substitutions with lithium derivatives of the protected propargyl alcohol (and of oct-1-yne) to use excess of the acetylene, to avoid unreacted lithamide. This could occur with an equimolecular proportion and was particularly undesirable in the case of lithium derivatives formed by way of n-butyl-lithium on account of the risk of nuclear lithiation of methoxyphenyl compounds.

0.1 mol) and 2,3-dihydropyran (9.25 g, 0.11 mol) cooled in an ice-bath, phosphorus oxychloride (0.03 cm³) was added and the mixture stirred overnight. After basification, ethereal extraction, washing (sodium chloride solution), and drying (K₂CO₃), the recovered organic material (16 g) was distilled to give 2-(6-*chlorohexanyloxy*)*tetrahydropyran* as a colourless oil (14.5 g, 67%) (Found: C, 59.85; H, 9.6. C₁₁H₂₁ClO₂ requires C, 59.8; H, 9.52%); δ(CCl₄) 4.5 (1 H, t, OCH), 3.0—4.0 (6 H, 3 × t, CH₂Cl, CH₂O, and CH₂O), and 1.5 (14 H, m, [CH₂]₇); ν_{max.} (film) 740ω (C–Cl), 1 040—1 080s (C–O–C), 1 455m (C–H), and 2 950s cm⁻¹ (C–H stretch).

To ethyl vinyl ether (20 g, 0.278 mol) cooled to 0 °C (solid CO₂–acetone) toluene-*p*-sulphonic acid (20 mg) and then 6-chlorohexan-1-ol (1.84 g) were added. After the commencement of an exothermic reaction the mixture was again cooled to keep the temperature below 10 °C, and the remainder of the 6-chlorohexan-1-ol (18.4g) added with stirring at 0—10 °C (45 min). After the addition the temperature was kept below 20 °C (1 h), further toluene-*p*-sulphonic acid added (14 mg) and stirring continued at 15 °C (1 h). To the cooled solution (5—10 °C) a solution of potassium carbonate (3 cm³) was added, and then powdered K₂CO₃ to remove the water. The mixture was filtered, the solid washed, and a stream of ammonia passed into the filtrate (traces of acid on the glassware caused acetal decomposition). After removal of ether and ethyl vinyl ether, the required acetaldehyde ethyl 6-chlorohexyl acetal was obtained as a colourless sweet-smelling liquid (28.3 g, 98%); δ(CCl₄) 4.50 (1 H, q, CH), 3.20—3.70 (6 H, m, 2 × CH₂O, CH₂Cl), 0.8—2.20 (14 H, m, [CH₂]₄, 2 × Me); ν_{max.} (film) 1 085, 1 100, 1 140 (s, O–C–O–C), 2 980 (s, CH₂), and 2 960 cm⁻¹ (Me).

1-(3,5-*Dimethoxyphenyl*)*heptane*-1,7-*diol*.—(*i*) To dry magnesium (0.73 g) and tetrahydrofuran (8 cm³) containing a crystal of iodine, 2-(6-chlorohexyloxy)tetrahydropyran (6.64 g) in tetrahydrofuran (25 cm³) was gradually added (30 min). After the stirred mixture had been gently warmed (30 min) and refluxed (4 h), the reaction flask was cooled (ice-bath) and a solution of 3,5-dimethoxybenzaldehyde (4.5 g) in tetrahydrofuran (25 cm³) added during 30 min. After stirring at ambient temperature overnight, the mixture was refluxed for 2 h, cooled, decomposed with ammonium chloride solution, ethereally extracted, dried (K₂CO₃), and the product recovered as a brown oil (9.22 g, 76%), the tetrahydropyranyl derivative of the diol, 2-[7-hydroxy-7-(3,5-dimethoxyphenyl)heptyloxy]tetrahydropyran; δ(CCl₄) 1.42 (16 H, m, [CH₂]₈), 3.5 (4 H, m, 2 × CH₂O), 3.75 (6 H, s, 2 × OMe), 4.5 [2 H, m, Ar-C*H* and OC*H*(R)O], 6.35 (2 H, m, Ar-H), and 6.95 (1 H, d, Ar-H); ν_{max.} (film) 850 (Ar–H), 1 040—1 070 (s, C–O–C), 2 950 (s, C–H), and 3 500 (m, OH).

(*ii*) To a stirred mixture of lithium wire (3 g) and tetrahydrofuran (50 cm³) in an argon atmosphere at −20° (solid CO₂–CCl₄), a small portion of a solution of 3,5-dimethoxybenzaldehyde (9.95 g, 0.06 mol) and acetaldehyde ethyl 6-chlorohexyl acetal, (14.92 g, 0.072 mol) in tetrahydrofuran (29 cm³) was added and the cooling bath removed. After reaction had commenced (shown by the lithium becoming brighter) the remainder of the solution was added dropwise (6 h). When the reaction temperature had risen to ambient (1 h), excess of lithium was removed by filtration (glass wool) and the filtrate decomposed by stirring vigorously with saturated ammonium chloride solution (50 cm³). The aqueous layer was extracted with ether (2 450

cm³) and the combined organic phases washed with water (30 cm³), dried (MgSO₄·H₂O), and concentrated to yield a sweet-smelling ⁷ yellow oil, ethoxy-[1-(3,5-dimethoxyphenyl)heptyloxy]methane (19.8 g, 97%), R_F (D) 0.14; δ(CCl₄) 0.80—1.80 (13 H, m, [CH₂]₅ and Me), 2.35 (1 H, br s, OH, D₂O exchangeable), 3.10—3.55 (4 H, m, 2 × CH₂O), 3.60 (6 H, s, 2 × OMe), 4.4—4.6 [2 H, m, C*H*Ar, C*H*(OR)₂], 6.03 (1 H, t, Ar-H, *J_m* 2 Hz), and 6.21 (2 H, d, Ar-H *J_m* 2 Hz); ν_{max.} (film) 1 170 (C–O), 1 610 (C=C), and 3 480 cm⁻¹ (s, OH); g.l.c. (A, 220, 21.0).

The crude product (19.0 g) in methanol (250 cm³) containing concentrated hydrochloric acid (5 cm³) was stirred for 30 min (t.l.c. monitoring); the reaction was then neutralised with 3M aqueous sodium hydroxide, most of the methanol removed, and the residue in ether washed with water (2 × 50 cm³), dried, and concentrated to a light brown oil (14.98 g, 100%) which slowly solidified to give upon recrystallisation (benzene) colourless prisms of 1-(3,5-*dimethoxyphenyl*)*heptane*-1,7-*diol*, m.p. 60—62 °C; R_F (F) 0.30. The preparation, carried out seven times, gave crude yields of 86—100% (Found: C, 67.3; H, 9.05. C₁₅H₂₄O₄ requires C, 67.16; H, 9.05%); g.l.c. (A, 200, 22.93; 220, 15.2; C, 200, 53.4, 28.0).

7-(3,5-*Dimethoxyphenyl*)*heptan*-1-*ol*.— 1-(3,5-Dimethoxyphenyl)heptane-1,7-diol (8.0 g; crude material) was heated at 60—70 °C (45 min) with 10% ethanolic potassium hydroxide (100 cm³), cooled, and neutralised with dilute hydrochloric acid. After removal of the ethanol, the diol was extracted with ether, washed with sodium chloride solution (2 × 30 cm³), and concentrated to give a brown oil which hydrogenolysed readily.

The purified diol (2.88 g, 0.017 5 mol) in ethanol (75 cm³) containing 5% Pd–C (0.2 g) was shaken with hydrogen at atmospheric pressure. Absorption ceased when 235 cm³ hydrogen had been taken up (t.l.c. monitoring), and after filtration and concentration of the filtrate, crude 7-(3,5-*dimethoxyphenyl*)*heptan*-1-*ol* was obtained as a light amber oil (2.14 g, 92%). After preparative t.l.c. (solvent D) it was obtained pure, R_F (D) 0.42, b.p. 220 °C at 1.5 mmHg. Five preparations gave crude yields of 92%—100% (Found: C, 71.45, 71.25; H, 9.85, 9.6. C₁₅H₂₄O₃ requires C, 71.43; H, 9.53%); δ(CCl₄) 1.10—1.90 (11 H, m, [CH₂]₅, and OH exchangeable with D₂O), 2.57 (2 H, t, C*H₂*Ar, *J* 7 Hz) 3.62 (2 H, t, CH₂OH), 3.75 (s, 6 H, 2 × OMe), and 6.21—6.42 (3 H, m, Ar-H); ν_{max.} (film) 1 060s (C–OH), 2 860s (CH₂), and 3 380 cm⁻¹ (s, O–H). G.l.c. (A, 220, 9.05; C, 200).

7-(3,5-*Dimethoxyphenyl*)*heptyl* *Bromide*.—(*i*) 7-(3,5-Dimethoxyphenyl)heptan-1-ol (1.65 g, 0.006 5 mol) in dry benzene (3 cm³) at 0 °C was treated with phosphorus tribromide (0.591 g, 0.002 2 mol) in dry benzene (1.5 cm³) and after 1.25 h, further phosphorus tribromide (0.591 g, 0.002 2 mol) in benzene (1.5 cm³) added (t.l.c. and g.l.c. had indicated incomplete reaction). After warming to 60 °C (1.5 h) reaction (t.l.c.) was complete and the mixture treated with sodium chloride solution (20 cm³), then extracted with ether (2 × 20 cm³), washed with 10% sodium carbonate solution (3 × 20 cm³), dried, and concentrated to yield a brown oil (0.84 g, 41%). Preparative t.l.c. (solvent D) gave a pale yellow oil, 7-(3,5-*dimethoxyphenyl*)*heptyl* *bromide* (0.343 g, 26%), R_F (D) 0.83 (Found: C, 57.65; H, 7.55; Br, 24.25. C₁₅H₂₃BrO₂ requires C, 57.12; H, 7.31; Br, 25.16%); δ(CCl₄) 1.06—2.11 (10 H,m, [CH₂]₅), 2.48 (2 H, t, C*H₂*Ar, *J* 8 Hz), 3.32 (2 H, t, CH₂Br, *J* 7 Hz), 3.71 (s, 6 H, 2 OMe), and 6.20 (3 H, m, Ar-H);

$\nu_{max.}$ (film) 1 600m (C=C) and 2 950 cm^{-1} (s, CH$_2$); g.l.c. (A, 220, 11.6). From the aqueous layer after acidification, ethereal extraction, drying, and recovery, a thick red-brown oil (0.60 g) was obtained, representing mono- and di-phosphite esters, δ(CCl$_4$) 4.00 (CH$_2$-P).

The phosphorus tribromide method was used to obtain the crude bromide (12.4 g) which was column chromatographed on silica gel (60, 35—70 mesh, Merck, 500 g) and eluted with chloroform (4 000 cm^3) to give, after recovery, the pure bromide (9.98 g, 81%). The phosphite esters produced (6.47 g) were hydrolysed by refluxing (24 h) with 6M sodium hydroxide (50 cm^3). Recovery of the organic material gave a brown oil (2.32 g) which was the starting alcohol (t.l.c.). With this recovery the yield of the bromide was 46%.

Phosphorus tribromide in dry ether containing 1% pyridine gave a yield of 29% of the bromide from the alcohol.

(ii) Crude 7-(3,5-dimethoxyphenyl)heptan-1-ol (1.00 g, 3.97 mmol) was added to 48% hydrobromic acid (1.6 cm^3) and concentrated sulphuric acid (0.22 cm^3) and the mixture kept on the steam-bath (6 h), when t.l.c. indicated no further change. The bromide was worked up as before to yield a brown oil (0.885 g, 76%) which upon t.l.c. purification (solvent D) gave the pure product as a pale yellow oil. From the alkaline extraction what appeared (t.l.c.) to be the phenolic bromide was obtained as a viscous brown oil (0.170 g, 17% of starting weight) by acidification.

5-(*Pentadec-8-ynyl*)*resorcinol Dimethyl Ether*.—Reactions were monitored by t.l.c. and by g.l.c. (*i*) To a stirred solution of oct-1-yne (0.615 4 g) in dry tetrahydrofuran (2 cm^3) at −20 °C, a 23% hexane solution of n-butyl-lithium (2 cm^3) was added (by syringe through a septum). When the temperature reached 0 °C, hexamethylphosphoric triamide (1.5 cm^3) was added followed by 7-(3,5-dimethoxyphenyl)heptyl bromide (0.767 g) in tetrahydrofuran (2 cm^3), after which the reaction mixture was stirred at 0 °C (3 h) and finally at ambient temperature (16 h). Addition of sodium chloride solution followed by ethereal extraction and recovery gave a light brown oil (0.722 g, 86%) which by preparative t.l.c. [chloroform–light petroleum (3 : 7)] gave 5-(*pentadec-8-ynyl*)*resorcinol dimethyl ether*, and after further purification, a colourless solid, m.p. 56—57 °C; (Found: C, 79.2; H, 10.5. C$_{23}$H$_{36}$O$_2$ requires C, 79.8; H, 10.2%); δ(CCl$_4$) 0.9 (3 H, t, Me), 1.35 (20 H, m, [CH$_2$]$_{10}$), 2.3 (4 H, mt, CH$_2$C≡C), 3.8 (6 H, s, 2 × OMe), and 6.2 (3 H, m, Ar–H); $\nu_{max.}$ (film) 840s (Ar–H), 1 065s (C–O·C), 1 440—1 470 (C–H def.), 1 600 (C=C conj.), 2 250w (C≡C), and 2 950 cm^{-1} (C–H str.); g.l.c., (A, 220, 42.9).

(*ii*) As a model experiment, tetradec-7-yne was prepared. To lithamide [from lithium (0.107 g) and liquid ammonia (100 cm^3) in the usual way] oct-1-yne (3.3 g) was added (30 min) and after stirring (1 h) at 0 °C, hexamethylphosphoric triamide (3 cm^3) followed by 1-bromohexane (4.1 g) in tetrahydrofuran (10 cm^3). The reaction mixture was stirred at ambient temperature (16 h), warmed (2 h) at 40 °C, worked up by addition of water, and ethereally extracted to give tetradec-7-yne as a pale brown oil (3.47 g, 72%) with a single g.l.c. peak; δ(CCl$_4$) 0.92 (6 H, t, 2 × Me), 1.35 (16 H, m, [CH$_2$]$_8$), and 2.1 (4 H, t, CH$_2$C≡C); $\nu_{max.}$ (film) 1 475 (C–H def.) and 2 940s cm^{-1} (CH, CH$_2$).

To lithamide from lithium (0.22 g) and liquid ammonia (80 cm^3) oct-1-yne (0.3 g) was added (30 min) and after stirring (2 h), hexamethylphosphoric triamide (8 cm^3) was added followed by 7-(3,5-dimethoxyphenyl)heptyl

bromide (0.16 g) in tetrahydrofuran (20 cm^3). After stirring (16 h) at ambient temperature and then warming at 40° (7 h) (g.l.c. indicated the formation of the penta-decynyl compound in over 80% yield), the mixture was treated with water and the organic material recovered to give a brown oil (0.52 g). Preparative t.l.c. [chloroform–light petroleum (3 : 7)] gave a pale yellow oil, 5-[pentadec-8-ynyl]resorcinol dimethyl ether (0.118 g, 68%).

5-[(*Z*)-*Pentadec-8-enyl*]*resorcinol Dimethyl Ether*.—The best conditions for the hydrogenation of the previous (pentade-cynyl) compound were found with tetradec-7-yne as a model compound. To Pd–BaSO$_4$ (0.091 g), 0.5 cm^3 of a solution of quinoline (2 drops) in methanol (4 cm^3) was added, the mixture shaken in a hydrogen atmosphere, tetradec-7-yne (0.173 g) in ethyl acetate (2 cm^3) introduced through a rubber septum and the mixture again shaken at atmospheric pressure with hydrogen until the theoretical volume had been absorbed. Filtration, acidic washing of the filtrate, and recovery in the usual way gave a light brown oil, tetradec-7-ene (0.15 g), which was characterised by g.l.c. and argentation t.l.c.

To Pd–BaSO$_4$ (0.1 g), 0.5 cm^3 of a solution of quinoline (1 drop) in methanol (4 cm^3) was added and the catalyst suspension shaken in an atmosphere of hydrogen (30 min). 5-(Pentadec-8-ynyl)resorcinol dimethyl ether (0.073 g) in ethyl acetate (1.5 cm^3) was added and the mixture shaken again until the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate in ether solution was washed with 0.1M sulphuric acid solution and water, dried, and concentrated to a yellow oil (0.08 g), preparative t.l.c. of which (solvent D) gave 5-[(*Z*)-*pentadec-8-enyl*]*resorcinol dimethyl ether* identical chromatographically (t.l.c. and g.l.c.) and spectroscopically with the dimethyl ether of the natural product. For the synthetic and natural material, δ(CCl$_4$) 0.9 (3 H, t, Me), 1.35 (18 H, m, [CH$_2$]$_9$), 1.95 (4 H, t, CH$_2$C=), 2.4 (2 H, t, C*H$_2$*Ar), 3.75 (6 H, s, 2 × OMe), 5.3 (2 H, t, CH=CH, J_{cis} 5 Hz), and 6.2 (3 H, m, Ar–H); $\nu_{max.}$ 2 945, 2 870 (CH$_2$), 1 735w, 1 610 (C=C), 1 068 (COC), 940, and 840 cm^{-1} (Found: M^+, 346.286 1. C$_{23}$H$_{38}$O$_2$ requires M, 346.287 1); g.l.c. (A, 220, 38.7).

5-[(*Z*)-*Pentadec-8-enyl*]*resorcinol*.—The progress of the reaction was followed by t.l.c. and g.l.c. 5-[(*Z*)-Pentadec-8-enyl)resorcinol dimethyl ether (0.042 5 g) was refluxed (18 h) with lithium iodide (0.168 3 g) in *sym*-collidine (1 cm^3) under nitrogen. T.l.c. (solvent D) showed the presence of the dimethyl ether, the monomethyl ether, and the dihydric phenol. G.l.c. monitoring (220 °C, 3% SE30) showed three peaks corresponding to these three compounds. After further heating (48 h), the dimethyl ether had nearly all reacted and after the addition of more lithium iodide (0.065 3 g), followed by refluxing (16 h), the amount of monomethyl ether had been considerably reduced. The cooled mixture was ethereally extracted (all soluble) and after acidic washing the recovered material from the ether was purified by preparative t.l.c. (solvent D). The lower band was identical (R_F) with ' cardol monoene ' and the upper band was the monomethyl ether. The recovered product, 5-[(*Z*)-*pentadec-8-enyl*]*resorcinol* was identical by t.l.c. (ordinary plates) and AgNO$_3$-t.l.c. (R_F 0.71), by g.l.c. (A, 220, 67.2), and spectroscopically (^{1}H n.m.r. and i.r., superimposable spectra), with ' cardol monoene ' separated from the natural product or technical cashew nutshell liquid; δ(CCl$_4$), 0.9 (3 H, t, Me), 1.35 (18 H, m, [CH$_2$]$_9$), 2.00 (4 H, t, CH$_2$C=), 2.45 (2 H, t, C*H$_2$*Ar), 5.40

(2 H, t, CH=CH, J_{cis} 5 Hz), 5.20—5.40 (2 H, br s, 2 × OH, D_2O exchangeable), and 6.2 (3 H, m, Ar-H); $\nu_{max.}$ (film) 870, 1 005, 1 160 (C-O-C), 1 470, 1 605 (C=C), 2 860, 2 940 (CH_2), and 3 380 cm^{-1} (OH) (Found: M^+, 318. $C_{21}H_{34}O_2$ requires M, 318); base peak at m/e 124, peak height (124 : 123) 4 : 1. For cardol monomethyl ether: M^+ 332. $C_{22}H_{36}O_2$ requires M, 332; base peak at m/e 138, peak height (138 : 137) ratio 3 : 1; g.l.c., [A, 220, 53.6; (15 : 0)-cardol dimethyl ether, 41.1].

Acetaldehyde Ethyl Prop-2-ynyl Acetal.—To freshly distilled ethyl vinyl ether (7.7 h, 0.107 mol) at 0 °C containing toluene-p-sulphonic acid (0.0075 g) propargyl alchol (3.002 g, 53.6 mmol) was added portionwise. Cooling was removed, and restored before the reaction temperature reached 10 °C; the remainder of the propargyl alcohol was added during 20 min while the temperature was kept between 0 and 10 °C. The cooling bath was then removed and the temperature not allowed to exceed 20 °C. After the addition of further toluene-p-sulphonic acid (0.005 g) stirring was continued (1 h) at 15 °C. The mixture was then cooled, and worked up as for the adduct of 6-chlorohexan-1-ol, giving a pale yellow sweet-smelling liquid (6.315 g, 92%). Distillation gave a colourless product, acetaldehyde ethyl prop-2-ynyl acetal, b.p. 32 °C at 0.1 mmHg (5.50 g, 80%); $\delta(CCl_4)$ 1.00—1.40 (6 H, m, 2 × Me), 2.32 (1 H, t, HC≡, J 2 Hz), 3.15—3.82 (m, 2 H, OCH_2), 4.19 (2 H, d, OCH_2, J 2 Hz), and 4.80 (1 H, q, O-CH-O); $\delta[CS_2$-Eu(DPM)$_3$, 100% w/w] 1.78; $\nu_{max.}$ (film) 1 130 (C-O str), 2 120 (m, C≡C), and 3 340w cm^{-1} (≡C-H str).

Dec-2-ynol.—This was prepared as a model for the subsequent reaction of 7-(3,5-dimethoxyphenyl)heptyl bromide. To a lithamide suspension [prepared from lithium (0.30 g, 0.043 5 mol) and liquid ammonia in the usual way] acetaldehyde ethyl prop-2-ynyl acetal (5.57 g, 0.043 5 mol) in dry tetrahydrofuran (10 cm^3) was added followed by hexamethylphosphoric triamide (5 cm^3) and tetrahydrofuran (15 cm^3). The mixture was stirred (20 min), 1-bromoheptane (2.49 g, 0.014 mole) was added and, after 24 h, sodium chloride solution (200 cm^3). Ethereal recovery gave acetaldehyde ethyl dec-2-ynyl acetal as a brown liquid (t.l.c.); methanolysis (1 h) of this (6.22 g) with methanol (50 cm^3) containing concentrated hydrochloric acid (1 cm^3), neutralisation with 3M sodium hydroxide solution, removal of the methanol, ethereal extraction, and concentration gave crude dec-2-ynol, R_F (G) 0.58; $\delta(CCl_4)$ 0.70—1.80 (13 H, m, [CH_2]$_5$Me), 2.00—2.42 (2 H, t, CH_2C≡, J 2 Hz), 2.48 (1 H, m, OH, exchangeable with D_2O), and 4.12 (2 H, m, ≡C-CH_2O); $\nu_{max.}$ (film) 2 330w (C≡C str) 2 860s (C-H str), 2 930 (s, C-H), and 3 360s cm^{-1} (OH).

10-(3,5-Dimethoxyphenyl)dec-2-yn-1-ol.—To a lithamide suspension in liquid ammonia (50 cm^3), prepared from lithium (0.107 g, 0.155 mol), acetaldehyde ethyl prop-2-ynyl acetal (1.99 g, 0.015 5 mol) in dry tetrahydrofuran (3.6 cm^3) followed by hexamethylphosphoric triamide (1.8 cm^3) and tetrahydrofuran (5.4 cm^3) were added. The reaction mixture was stirred (20 min), 7-(3,5-dimethoxyphenyl)-heptyl bromide (1.58 g, 0.005 mol) introduced gradually (18 min) and after stirring (16 h) the organic material was recovered in the usual way to give acetaldehyde 10-(3,5-dimethoxyphenyl)dec-2-ynyl ethyl acetal as a brown oil (2.51 g, 106%), R_F (G) 0.64. Methanolysis with methanol (25 cm^3) containing hydrochloric acid (0.5 cm^3) was complete after 15 min. (t.l.c.) and the product was isolated (after removal of methanol) by ethereal extraction to give

a brown oil (1.438 g, 99%). Preparative t.l.c. purification (solvent D) gave 10-(3,5-*dimethoxyphenyl*)*dec-2-yn-1-ol* as a pale yellow oil (90%), R_F (D) 0.46. Repetition gave a crude yield of 100% (Found: C, 74.45; H, 9.05. $C_{18}H_{26}O_3$ requires C, 74.48; H, 8.97%); $\delta(CCl_4)$, 0.97—1.72 (10 H, m, [CH_2]$_5$), 1.84 (1 H, s, OH, exchangeable with D_2O), 2.00—2.35 (2 H, m, CH_2-C≡), 2.51 (2 H, t, CH_2Ar, J 7 Hz), 3.72 (6 H, s, 2 × OMe), 4.09 (2 H, t, ≡C-CH_2OH, J 2 Hz) and 6.18 (3 H, m, Ar-H); $\nu_{max.}$ (film) 1 600 (aromatic C=C), 2 250w (C≡C str), and 2 850 and 2 930s cm^{-1} (s, CH_2, CH_3O) (Found M^+ 290.187 7. $C_{18}H_{26}O_3$ requires M, 290.187 7); other major peaks (70 eV) at m/e 151 and 152 (base peak); peak height (152 : 151) ratio 3.8 : 1; g.l.c. (B, 220, 16.54).

10-(3,5-Dimethoxyphenyl)-1-bromodec-2-yne.— 10-(3,5-Dimethoxyphenyl)dec-2-yn-1-ol (2.90 g, 0.01 mol) in dry ether (2.78 cm^3) containing pyridine (0.056 cm^3) was stirred and cooled to −30 °C in a nitrogen atmosphere during the addition (45 min) of phosphorus tribromide (0.965 g, 3.56 mmol). The temperature was maintained at −30 °C (2 h) and then allowed to rise to ambient (3 h); the mixture was then warmed to 40 °C (30 min), extracted with ether (30 cm^3), washed successively with sodium chloride solution (10 cm^3), 5% sodium carbonate solution (2 × 15 cm^3), and water (10 cm^3), dried, and the ether evaporated to give the crude bromide (2.809 g, 81%) as a red-brown oil. Repetition gave a 67% yield. The combined aqueous layers were acidified and ethereally extracted to give a viscous brown oil (0.33 g) which was a mixture of phosphite esters (^{1}H n.m.r.). The crude bromide was purified by preparative t.l.c. (solvent G) to give 10-(3,5-dimethoxyphenyl)-1-bromodec-2-yne as a pale yellow oil; R_F (G) 0.75; (Found: C, 62.05; H, 7.4; Br, 22.05. $C_{18}H_{25}BrO_2$ requires C, 61.19; H, 7.08; Br, 22.66%). This material was unstable and darkened upon standing (*cf.* propargyl bromide); $\delta(CCl_4)$ 1.08—1.83 (10 H, m, [CH_2]$_5$), 2.01—2.39 (2 H, m, CH_2C≡), 2.52 (2 H, t, CH_2Ar, J 7 Hz), 3.77 (6 H, s, 2 × OMe), 3.87 (2 H, t, ≡CCH$_2$Br, J 2 Hz), and 6.22 (3 H, m, Ar-H); $\nu_{max.}$ (film) 1 600 (Ar C=C), 2 245w (C≡C), 2 850, and 2 945m (C-H str); (Found: M^+, 352.104. $C_{18}H_{25}{}^{79}BrO_2$ requires M, 352.103 8); major peaks (70 eV) at m/e 151 and 152 (base peak); peak height rates (152 : 151) 3.2 : 1.

Undec-1-en-4-yne.—As a model for the conditions of preparation of the diyne the following preparation was carried out. Ethylmagnesium bromide solution was prepared from magnesium (2.432 g, 0.1 mol), dry ether (18.5 cm^3), and ethyl bromide (10.9 g, 0.1 mol) in dry tetrahydrofuran (24 cm^3). To stirred oct-1-yne (2.12 g, 0.019 mol) in dry tetrahydrofuran (5 cm^3) under nitrogen, ethylmagnesium bromide (0.02 mol) in dry tetrahydrofuran (9 cm^3) was added followed by cuprous iodide (0.1 g). To the mixture after 5 min, allyl bromide (2.78 g, 0.023 mol) in tetrahydrofuran (5 cm^3) was added. After warming to 48 °C, the mixture became lime green in colour and (argentation t.l.c.) reaction was complete in 1 h. The cooled mixture was acidified with 0.5M hydrochloric acid (5 cm^3), ethereally extracted (2 × 10 cm^3), the ethereal extracts washed with sodium chloride solution, dried, and undec-1-en-4-yne recovered as a brown oil (2.066 g, 77%), R_F (AgNO$_3$-t.l.c.) solvent H, 0.69; oct-1-yne, R_F 0.80; $\delta(CCl_4)$ 0.67—1.15 (3 H, m, Me), 1.15—1.62 (8 H, m, [CH_2]$_4$), 2.00—2.20 (2 H, m, ≡C-CH_2), 2.73—3.00 (2 H, m, ≡C-CH_2-CH=), 4.84—5.44 (2 H, m =CH_2), and 5.44—6.14 (1 H, m, CH≡); $\nu_{max.}$ 2 240 (C≡C), 2 870, 2 940 (s, C-H str), and 3 095m cm^{-1} (=CH_2 str).

5-(*Pentadeca*-8,11-*diynyl*)*resorcinol Dimethyl Ether*.—To pent-1-yne (0.68 g, 0.01 mol) in dry tetrahydrofuran (2.66 cm³) under nitrogen, ethylmagnesium bromide (0.01 mol) in dry tetrahydrofuran (4.65 cm³) was added and the mixture warmed to 40 °C (15 min) to complete formation of pent-1-ynylmagnesium bromide. An aliquot of the solution (4.83 cm³, 6.03 mmol) of pent-1-ynylmagnesium bromide was added under nitrogen to a solution of 10-(3,5-dimethoxyphenyl)-1-bromodec-2-yne (0.71 g, 2.01 mmol) in dry tetrahydrofuran (0.8 cm³). Anhydrous cuprous chloride (0.016 g) was introduced, the stirred mixture was warmed to 45 °C, and after 2 h (reaction monitored by t.l.c. and g.l.c.) poured into saturated ammonium chloride solution, extracted with ether (2 × 10 cm³), and the combined extracts washed with water (1 × 5 cm³). After drying, the ethereal solution yielded an amber oil (0.600 g, 91%), which was purified by argentation t.l.c. (solvent *J*, nitrogen box) to give 1-(3,5-*dimethoxyphenyl*)*pentadeca*-8,11-*diyne* as a yellow unstable oil (45%). The product was kept under nitrogen at 0 °C in the dark. A repetition with the bromide (0.68 g) gave a crude yield of 91%; R_F (solvent J, AgNO₃-t.l.c.) 0.57; g.l.c. (D, 220, 82.2) (Found: δ. 80.95; H, 9.6. $C_{23}H_{32}O_2$ requires C, 81.18; H, 9.41%); $CCCl_4$) 0.78—1.85 (15 H, m, $[CH_2]_5$, CH_2Me), 2.10 (4 H, m, 2 × ≡C–CH₂), 2.52 (2 H, t, CH_2Ar), 3.02 (2 H, m, ≡C–CH₂–C≡), 3.74 (6 H, s, 2 × OMe), and 6.23 (3 H, m, Ar-H); $v_{max.}$ (film), 1 600 (ArC=C), 2 230w (C≡C), 2 850, and 2 940s cm⁻¹ (CH₂, CH₃) (Found: M^+, 340.239 9. $C_{23}H_{32}O_2$ requires M, 340.240 2); other major peaks (at 70 eV) 151 and 152 (base peak); peak height (152 : 151) ratio 3.2 : 1.

5-[(*ZZ*)-*Pentadeca*-8,11-*dienyl*)]*resorcinol Dimethyl Ether*.—1-(3,5-Dimethoxyphenyl)pentadeca-8,11-diyne was hydrogenated on palladium–barium sulphate, in ethyl acetate containing quinoline. The following table shows the effect of the proportion of quinoline on the time of hydrogenation (to the diene).

Diyne g	Pd–BASO₄ g	Drops of quinoline /g catalyst	(100% conversion)
0.100	0.085	4.00	>72 h
0.340	0.160	1.04	55 min
0.320	0.320	2.08	65 min

The diyne (0.320 g, 0.94 mol), purified by argentation t.l.c. in ethyl acetate (11 cm³) containing quinoline (= 0.67 drop), and Pd–BaSO₄ (0.320 g) was shaken at ambient pressure and temperature until hydrogen absorption reached the theoretical volume and had become slow (42 cm³, 1 g). The filtered mixture was washed with 0.01M hydrochloric acid (3 × 50 cm³) and the combined aqueous washings extracted with ether (2 × 10 cm³). After drying (MgSO₄·H₂O) and recovery, the crude product as a yellow oil (0.277 g, 86%) was purified by preparative AgNO₃-t.l.c. (solvent D) to give as a pale yellow oil (42%), 5-[(*ZZ*)-pentadeca-8,11-dienyl]resorcinol dimethyl ether, R_F (D) (AgNO₃-t.l.c.) 0.83, identical with that of methylated natural cardol diene; g.l.c. (D, 200, 29). A second preparation gave an 85% yield of the crude diene. The hydrogenation progress was monitored by g.l.c. on column D, during which the formation of the two isomeric 8,11-enynes was observed; g.l.c. (D, 220, 49.4) (Found: C, 80.2; H, 10.65. $C_{23}H_{36}O_2$ requires C, 80.23; H, 10.47%); δ(C₆D₆, 100 MHz) 0.87 (3 H, t, Me) 1.18—1.48 (10 H, m, $[CH_2]_5$), 1.48—1.70 (2 H, m, CH_2Me), 1.97—2.18 (4 H, m,

CH₂C=), 2.51 (2 H, t, CH_2Ar), 2.88 (2 H, t, =C–CH₂–C=), 3.37 (6 H, s, 2 × OMe), 5.47 (2 H, m, Ar-H), and 6.48 (1 H, m, Ar-H); $v_{max.}$ (film) (SP 200) 694m (=CH *cis*, out-of-plane def), 1 593 (aromatic C=C), 1 605s (C=C str), 2 725s, 2 955m (CH₂ and CH₃ str), and 3 005m (=C–H str) (an extremely small band at 970 cm⁻¹ possibly indicated a trace of *trans* =C–H) (Found: M^+, 344.270 9. $C_{23}H_{36}O_2$ requires M, 344.271 5); m/e (70 ev) at 151 and 152 (base peak); peak height ratio (152 : 151) 5.7 : 1. Attempted demethylation of the dimethyl ether with lithium iodide in collidine gave a small yield of dihydric phenol (1; $n=4$, R = Me) but more was polymerised. G.l.c. (A, 200, 660).

Separation of Natural Cardol.—Cardol containing the three unsaturated constituents was obtained from the t.l.c. or column separation of technical cashew nut-shell liquid (CNSL) or from natural CNSL from the filtrate after the separation of anacardic acid.[17] The monoene, diene, and triene constituents were separated by argentation t.l.c. of the dihydric phenol [ethyl acetate–chloroform (1 : 1)] followed by methylation or *vice versa* with cardol methyl ether (solvent D). Cardol (1.47 g) in chloroform (5 cm³) was separated [chloroform–ethyl acetate (1 : 1)] on six AgNO₃-t.l.c. plates and cardol monoene, 0.225 g (R_F 0.71), cardol diene, 0.165 g (R_F 0.47), and cardol triene, 0.520 g (R_F 0.24) were obtained. Re-purification of each separated band after elution [ether–methanol (90 : 10)], evaporation and recovery was effected on ordinary t.l.c. plates with solvent D. For the *monoene*, Found: C, 79.1; H, 10.35. $C_{21}H_{34}O_2$ requires C, 79.24; H, 10.69%. For the *diene*, Found: C, 79.4; H, 10.55. $C_{21}H_{32}O_2$ requires C, 79.75; H, 10.10%. For the *triene*, Found: C, 80.4; H, 9.8. $C_{21}H_{30}O_2$ requires C, 80.26; H, 9.52%. All were golden oils at ambient temperature but solidified at −20 °C. They were unstable through autoxidation, and darkened upon keeping.

¹H n.m.r. Monoene, δ(CCl₄), see earlier experimental details. Diene, δ(CCl₄) 0.72—1.07 (3 H, t, OMe), 1.17—1.77 (12 H, m, $[CH_2]_6$), 1.87—2.12 (4 H, m, –CH₂–C=), 2.12—2.43 (2 H, t, CH_2Ar), 2.63—2.87 (2 H, m, =C–CH₂–C=), 5.23—5.40 (4 H, 't', CH=CH, J 5 Hz), 6.03—6.27 (3 H, m, Ar-H), and 6.73—7.17 (2 H, br s, Ar-OH, D₂O exchangeable). Triene, δ(CCl₄) 0.97—1.63 (10 H, m, $[CH_2]_5$), 1.77—2.10 (2 H, m, CH₂C=), 2.10—2.43 (2 H, t, CH_2Ar), 2.52—2.90 (4 H, m, =C–CH₂–C=), 4.73—5.10 (2 H, m, =CH₂), 5.13—5.47 (5 H, m, CH=CH, J 5 Hz), 5.97—6.23 (3 H, m, Ar-H), and 6.27—6.93 (2 H, br s, Ar-OH, D₂O exchangeable); g.l.c. [A, 220; (triene) 74.5; (diene), 69.8; (monoene) 67.2].

Methylation of Cardol.—Natural cardol, from natural CNSL (0.262 g, 0.76 mmol) and dimethyl sulphate (1.58 g, 12.5 mmol) in benzene (48 cm³) containing anhydrous potassium carbonate (12 g) were refluxed (16 h) under nitrogen. Water (50 cm³) was added to the cooled mixture and the organic material, extracted into ether after copious water washing, was recovered as a brown oil (0.263 g, 92%). Argentation t.l.c. (solvent D) showed three bands due to cardol monoene dimethyl ether (R_F 0.97), cardol diene dimethyl ether (R_F 0.83), and cardol triene dimethyl ether (R_F 0.36).

Cardol Monoene Dimethyl Ether.—Cardol monoene, separated by AgNO₃-t.l.c. of cardol (0.061 g), in benzene (6 cm³) containing dimethyl sulphate (0.2 cm³) and anhydrous potassium carbonate (2.0 g) was refluxed (30 h), when t.l.c. showed 95% conversion into the dimethyl ether. The cooled reaction mixture was diluted with water and

extracted with ether; the ethereal extract was washed, dried, and evaporated to give a yellow oil (0.074 g) having ^{1}H n.m.r. and i.r. spectra identical with (and superimposable on) those of the synthetic monoene dimethyl ether; g.l.c. (A, 220, 38.7).

In a similar way cardol diene and triene were methylated with the additional precaution that the reaction was effected under nitrogen. The crude products were purified on ordinary plates with solvent J. Diene dimethyl ether, g.l.c. (D, 200, 29). The three methyl ethers had the following spectroscopic properties: monoene dimethyl ether: see earlier experimental details: cardol triene dimethyl ether; δ(CCl$_4$) 1.12—1.53 (10 H, m, [CH$_2$]$_5$), 1.80—2.20 (2 H, m, CH$_2$–C=), 2.37—2.66 (2 H, t, CH_2Ar), 2.60—2.90 (4 H, m, $2 \times$ =C–CH$_2$–C=), 3.70 (6 H, s, 2 × OMe), 4.77—5.10 (3 H, m, CH=CH$_2$), 5.17—5.43 (6 H, m, CH=CH, J 4 Hz), and 6.17 (3 H, m, Ar-H): cardol diene dimethyl ether; δ(CCl$_4$) 0.17—1.03 (3 H, t, Me), 1.03—1.52 (10 H, m, [CH$_2$]$_5$), 1.80—2.06 (4 H, m, 2 × CH$_2$–C=), 2.32—2.66 (2 H, t, CH_2Ar), 2.50—2.90 (2 H, m, 2 × C–CH$_2$–C=), 3.60 (3 H, s) OMe), 5.10—5.37 (4 H, m, CH=CH), and 6.10 (3 H, m, Ar-H). For the phenols: the triene, found: M^+, 314.224 5. C$_{21}$H$_{30}$O$_2$ requires M, 314.223 8; for the diene, found: M^+ 316.2400. C$_{21}$H$_{32}$O$_2$ requires 316.2394; for the monoene, found M^+, 318.255 0. C$_{21}$H$_{34}$O$_2$ requires M, 318.255 0. The base peak in all the constituents was at m/e 124 and the peak height ratio (124 : 123) was ca. 4 : 1 in all cases (see Results and Discussion section). Cardol monoene (PCMU): major peaks at m/e 318 (5.5), 124 (100), and 123 (16.6). Cardol diene (PCMU): m/e 316 (11.2), 124 (100), and 123 (25.7). Cardol triene (PCMU): m/e 314 (15.9, 124 (100), 123 (42.7). Cardol triene dimethyl ether, the diene dimethyl ether, and the monoene dimethyl ether had molecular ions at m/e 342, 344, and 346, respectively. The base peak was at m/e 152 in each case and the peak height ratio (152 : 151) was 3.6 to 5 in all cases. Cardol monoene dimethyl ether (PCMU): m/e 346 (2.6), 152 (100), and 151 (13.8). Cardol diene dimethyl ether (MS-902): m/e 344, 152 (base peak), and 151. Cardol triene dimethyl ether (MS902): m/e 342, 152 (base peak), and 151. Cardol monoene methyl ether (RMS4): m/e 332, 138 (base peak), and 137. I.r. spectra: cardol diene; $\nu_{max.}$ (film), 3 400s (OH), 2 940, 2 870s (CH$_2$), 1 700vw, 1 605s (C=C), 1 472s, 1 385w, 1 348w, 1 356w, 1 308w, 1 158s, 1 105w, 1 008vw, 930vw, 855m, and 702 cm^{-1}: cardol triene; $\nu_{max.}$ (film), 3 370s (OH), 2 930, 2 860s (CH$_2$), 1 703w, 1 600s (C=C), 1 468m, 1 350w, 1 308w, 1 270w, 1 160s, 1 155s, 1 004w, 925vw, 852 m, and 700 cm^{-1}.

Valerophenone.—(*i*) α-(Methylsulphinyl)acetophenone was prepared in a purer state than previously to give colourless prisms, m.p. 83—84 °C (lit.,[6] 77—78 °C) (Found: C, 59.2; H, 5.5; S, 18.4. Calc. for C$_9$H$_{10}$O$_2$S: C, 59.35; H, 5.49; S, 17.58%); R_F (E) 0.09. Upon keeping the chloroform solution (24 h), 60% decomposition took place to give four substances, apparently not observed previously, (t.l.c.), none of which were tautomers; only CHCl$_3$ caused this. To α-(methylsulphinyl)acetophenone (0.91 g) in dimethyl sulphoxide (9.2 cm^3) sodium hydride (0.50 g) was added and upon carbanion formation, n-propyl iodide (0.85 g). After 30 min, work-up in the usual way gave a light brown oil (0.86 g, 77%); R_F (A) 0.57. The crude material (0.476 g) was reduced in THF–water (9 : 1) with aluminium amalgam (0.54 g) during 15 min. The mixture was filtered, the solid washed (n-pentane–benzene) and the filtrate washed with water and concentrated to give valero-

phenone as a pale brown oil (0.34 g), R_F (A) 0.74 (single spot), identical with a reference sample.

(*ii*) Benzoyl chloride in dry ether was added to n-butyl-lithium in dry ether at −78 °C containing cuprous iodide, and after 15 min the reaction mixture was treated with methanol at −78 °C; this gave, after work-up, valero-phenone (62%), R_F (A) 0.80; g.l.c. (A, 130, 8.4). Temperatures of −10 and −20 °C and acid chloride–lithium dialkylcuprate molar ratios of 1 : 1 and 1 : 2 instead of 1 : 3 were ineffective, and yields were drastically lowered.

3-Methoxyvalerophenone.—(*i*) To lithium 3-methoxybenzoate [from lithium hydride (0.278 g) in 1,2-dimethoxyethane (20 cm^3) reacted with 3-methoxybenzoic acid (4.56 g) in dimethoxyethane (20 cm^3) by refluxing (2.5 h) followed by cooling (to 10 °C)] n-butyl-lithium (2.175 g) in hexane (16 cm^3) was added (30 min) and the mixture stirred (2 h). Dilution with water, acidification, separation of the acidic (2.5 g) from the neutral material (1.0 g) and spectroscopic examination (^{1}H n.m.r. and i.r.) showed the latter to contain 3-methoxyvalerophenone and dibutyl-(3-methoxyphenyl)-methanol.

(*ii*) 3-Methoxybenzoyl chloride (1.070 g, 6.3 mmol) in dry ether was introduced into prepared n-butyl-lithium (3.82 g, 4.2 mmol) in ether (20 cm^3) at −78 °C, previously added to cuprous iodide (3.82 g, 21 mmol) at 0 °C. After stirring (15 min) at −78 °C methanol (80 cm^3) was added and the mixture allowed to reach ambient temperature. Work-up in the usual way by ethereal extraction, alkaline and water washing, drying, and recovery gave a pale brown fragrant oil (1.02 g, 79%) which was 3-methoxy-valerophenone, b.p. 105—108 °C at 1 mmHg (lit.,[18] 196 °C at 30 mmHg); R_F (A) 0.58; δ(CCl$_4$) 0.70—1.90 (7 H, m, [CH$_2$]$_2$ and CH$_3$), 2.80 (2 H, t, CH$_2$CO), 3.73 (6 H, s, 2 × OMe), and 6.70—7.40 (4 H, m, Ar-H).

3,5-Dimethoxyvalerophenone.—(*i*) To ethereal n-butylmagnesium bromide (one tenth aliquot) [prepared from n-butyl bromide (13.7 g) in dry ether (12 cm^3) with magnesium (2.43 g)] 3,5-dimethoxybenzaldehyde (1.0 g) in dry ether (6 cm^3) was added and the mixture refluxed (6 h) to give complete reaction (t.l.c.). Work-up gave n-butyl-(3,5-dimethoxyphenyl)methanol, R_F (A) 0.17; $\nu_{max.}$ (film) 2 940 and 3 400 cm^{-1}. The alcohol (0.5 g) in pyridine (3 cm^3) was oxidised (2 h) at 0 °C (t.l.c. monitoring) with chromium trioxide–pyridine to give, after work-up by ethereal extraction and alkaline washing, 3,5-dimethoxy-valerophenone (0.41 g, 84%), b.p. (microbulb) 150 °C at 0.3 mmHg, m.p. 34—36 °C, R_F (A) 0.43.

(*ii*) 3,5-Dimethoxybenzoyl chloride [prepared by Scheme 1(*b*) from 3,5-dihydroxybenzoic acid to the ethyl ester (92%), ethyl 3,5-dimethoxybenzoate (63%), 3,5-dimethoxybenzoic acid (80%), and finally 3,5-dimethoxybenzoyl chloride (88%)] was treated with n-butyl-lithium (3 mol) prepared by the same procedure as for 3-methoxy-valerophenone, to give a 92% yield, m.p. 34—35 °C; R_F (A) 0.45. In the use of aged n-butyl-lithium (Alfa Inorganics Ltd), the formation of only n-butyl 3,5-dimethoxybenzoate was observed. Products from oxidative decomposition of Bu^{n}Li have not previously been commented upon (2BuLi + O$_2$→2BuOLi) and only hydrolysis (to BuH) and carbonation products previously noted; δ(CCl$_4$) 0.80—1.90 (7 H, m, [CH$_2$]$_2$ and CH$_3$), 2.79 (2 H, t, CH$_2$CO), 3.75 (6 H, s, 2 % OMe), 6.46 (1 H, m, Ar-H, J 2 Hz), and 6.94 (2 H, m, Ar-H, J 2 Hz).

(*iii*) The sodium salt of dimethyl sulphoxide [from DMSO (10.7 cm^3) and sodium hydride (0.50 g)] in tetra-

hydrofuran was interacted with ethyl 3,5-dimethoxy-benzoate (1.47 g) in the usual way to give colourless prisms of *α-methylsulphinyl-3,5-dimethoxyacetophenone* (1.41 g, 77%), m.p. 87—87 °C; R_F (A) 0.09 (Found: C, 55.65; H, 5.85; S, 14.35. $C_{11}H_{24}O_4$ requires C, 54.70; H, 5.78; S, 13.32%). Attempts to alkylate the sodium salt of the compound with n-propyl iodide were not successful.

3,5-Dimethoxyphenyl 7-Hydroxyhexyl Ketone.—To stirred lithium chips (0.330 g, 46 mmol) in dry ether (5 cm³), acetaldehyde ethyl 6-chlorohexyl acetal (4.83 g, 23.2 mmol) in dry ether (5 cm³) was added (6 h) at 0 °C. The unreacted lithium was removed and cuprous iodide (1.54 g, 8.1 mmol) was added to give a green-black colouration and after the stirred mixture had been cooled (−78 °C), 3,5-dimethoxybenzoyl chloride (0.54 g, 2.7 mmol) in dry ether (5 cm³) was added in one portion. After 15 min, methanol (40 cm³) was added (at −78 °C) and the mixture worked up as previously to give a brown oil (3.01 g) which, after interaction with ethanol (25 cm³) containing concentrated hydrochloric acid (0.5 cm³), followed by work-up by neutralisation, extraction, washing, and drying, gave a pale brown semi-solid (0.65 g, 90%) which was purified by preparative t.l.c. (solvent D) to give 3,5-dimethoxyphenyl) 7-hydroxyhexyl ketone, R_F (D) 0.20, still containing some minor impurities; g.l.c. (A, 160, 8.4); δ(CCl₄) 0.6—2.00 (9 H, m, [CH₂]₄ and OH [D₂O exchangeable), 2.88 (2 H, t, CH₂CO, J 6 Hz), 3.59 (2 H, t, CH₂O, J 6 Hz), 3.78 (6 H, s, 2 OMe), 6.47 (1 H, 't', Ar-H, J 2 Hz), 6.93 (2 H, 'd', Ar-H, J 2 Hz); $ν_{max.}$ (film) 1 160 cm⁻¹ (C—OH str), 1 600 (s, aromatic C=C), 1 680 (C=O str), 1 720 (C=O ester), and 3 400 (OH str).

The 3-methoxy-analogue gave upon Wolff–Kishner reduction in DMSO with potassium t-butoxide and hydrazine the theoretical yield of 7-(3-methoxyphenyl)-heptan-1-ol.

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