ELSEVIER

Chemistry and Physics of Lipids 120 (2002) 101–108

CPL
CHEMISTRY AND PHYSICS OF LIPIDS

www.elsevier.com/locate/chemphyslip

A synthesis of the phenolic lipid, 3-[(*Z*)-pentadec-8-enyl] catechol, (15:1)-urushiol☆

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Received 22 May 2002; received in revised form 5 August 2002; accepted 6 August 2002

Abstract

A synthesis of (15:1)-urushiol, urushiol monoene, 3-[(*Z*)-pentadec-8-enyl] catechol, 1,2-dihydroxy-3-[(*Z*)-pentadec-8-enyl] benzene, one of the toxic principles of *Rhus toxicodendron* and of *Rhus vernicifera* is described. 6-Chlorohexan-1-ol protected at the OH group with ethyl vinyl ether reacted with 2,3-dimethoxybenzaldehyde in the presence of lithium to give, after removal of the protective group with methanolic 4-toluenesulphonic acid, 1-(2,3-dimethoxyphenyl) heptane-1,7-diol. Catalytic hydrogenolysis in ethanol with palladium–carbon selectively afforded 7-(2,3-dimethoxyphenyl)heptane-1-ol accompanied by a small proportion of the 7-(3-methoxyphenyl)heptane-1-diol, formed by demethoxylation. Reaction of the dimethoxy compound with boron tribromide resulted in both bromination and demethylation to give 7-(2,3-dihydroxyphenyl) heptylbromide. This bromide in tetrahydrofuran (THF) containing hexamethylphosphoric triamide reacted with excess lithium oct-1-yne to give 3-(pentadec-8-enyl)catechol which, by catalytic hydrogenation in ethyl acetate containing quinoline, selectively formed the required *cis* product, 3-[(*Z*)-pentadec-8-enyl]catechol which was identical chromatographically and spectroscopically with urushiol monoene separated from the natural product.

Keywords: Phenolic lipid; Urushiol; 3-Alkenylcatechol; Rhus genus; Synthesis; Alkynes

1. Introduction

Rhus vernicifera, the lacquer tree, indigenous notably in Japan, China, and Korea, is a source of *urushi* and the enzyme laccase, both of which have a current commercial and an historical interest in the economy and culture of those countries (Nagase and Miyakoshi, 1997, 1998) and historically a material of great antiquity (Tyman, 1979; Snyder, 1989). Structurally related substances are also found in the saps of species found in Burma, Taiwan and Vietnam. The related genus, namely poison or ground ivy, (*Rhus toxicodendron*) is found mainly in North America and contains similar phenolic lipids. Early studies (Majima, 1922) indicated the heterogeneous nature of *R. vernicifera* and later chromatographic and structural work (Sunthankar and Dawson, 1954; Symes and Dawson, 1954) on *R. toxicodendron* led to the

☆ Long chain phenols, part 36.

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0009-3084/02/$ - see front matter
PII: S0009-3084(02)00125-1

isolation of the saturated, the 8-monoene, the 8,11-diene and 8,11,14-triene constituents (Fig. 1 a–d) and from *R. vernicifera* a, b, c and e.

The quantitative composition and also the isolation of the 8,11,14-triene from *R. vernicifera* was effected by GC and GC/MS studies (Tyman and Matthews, 1982; Tyman et al., 1993). Other capillary GC analyses of *R. vernicifera* (Du et al., 1984) have indicated greater complexity and in addition to a–e, an 8*Z*, 11*E*-diene, an 8*Z*, 11*E*, 13*Z*-triene and a number of C_{17} constituents have been identified. More recently, capillary GC and supercritical fluid chromatography (Bartus et al., 1994) and pyrolysis GC (Kawanobe, 1996) have been studied.

For structure/property studies the usage of pure constituents is advantageous and, since the isolation of these by chromatography of the natural product is laborious and the constituents are subject to degradation, synthesis becomes a viable alternative. Furthermore, recent interest in artificial *urushi* (Ikeda et al., 2001; Nagase and Miyakoshi, 1997) suggests that synthetic analogues could be of significance in structure/property studies. Apart from its polymer technology (Vogl, 2000; Bartus et al., 1994), urushiol has a wood preservative use (Sato and Saito, 1996), medical applications (Wakida, 1992) and anticancer potential (Hong et al., 1999).

A synthesis of urushiol monoene had been described in an earlier preliminary communication (Tyman and Khor, 1974) although no experimental details were given; this present account supplies this information (Scheme 1). In our route, depicted in Scheme 1, *o*-vanillin was converted to 2,3-dimethoxybenzaldehyde (**2**) which, in the presence of lithium, was reacted with 6-chlorohexane-1-ol (protected at the OH group by ethyl vinyl ether) to give, after protective group removal, 7-(2,3-dimethoxyphenyl)heptane-1,7-diol (**3**). Catalytic hydrogenolysis with Pd–C in ethanol afforded 7-(2,3-dimethoxyphenyl)heptan-1-ol (**4**, R = OMe). Bromination and demethylation then smoothly gave 1-bromo-7-(2,3-dihydroxyphenyl)-heptane (**5**), alkylation of which with excess lihthio-oct-1-yne yielded 1,2-dihydroxy-3-(pentadec-8-ynyl)benzene (**6**). Selective catalytic reduction with Pd–C in ethanol containing quinoline afforded, in excellent yield, urushiol monoene, (15:1)-urushiol (**1b**; R = R^1 = OMe), which was spectroscopically and chromatographically identical with the natural product.

Reagents: (i) Me_2SO_4, K_2CO_3, Me_2CO; (ii) Li, THF, $Cl(CH_2)_6OCHMe(OEt)$; EtOH, HCl; (iii) Pd–C, EtOH, H_3O^+; (iv) $CHCl_3$, PBr_3, 0 °C; BBr_3, −80 °C; H_3O^+ (v) $3LiC{\equiv}CC_6H_{13}$, THF, HMPT; (vi) Pd–$BaSO_4$, H_2, EtOAc, quinoline.

2. Experimental procedures

2.1. Extraction of material

R. toxicodendron, poison ivy, in the form of twigs and leaves was kindly supplied by J. Keesing from the Japanese Garden at the Royal Botanic Garden at Kew, Surrey, UK. *R. vernicifera* was obtained through the agency of the Japanese Trade Centre, London, from Dr M. Sato, Industrial Research Institute, Sendai, Japan.

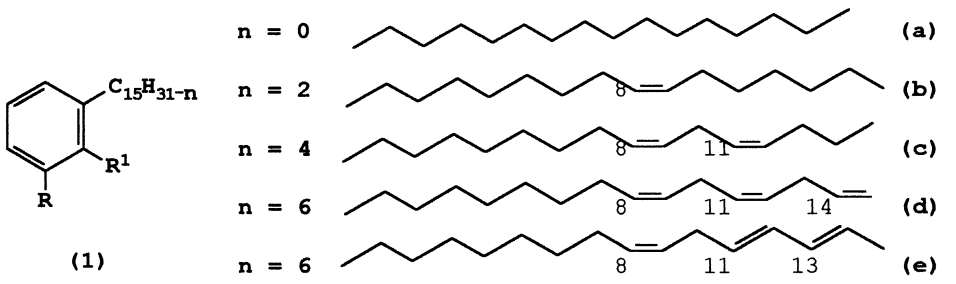
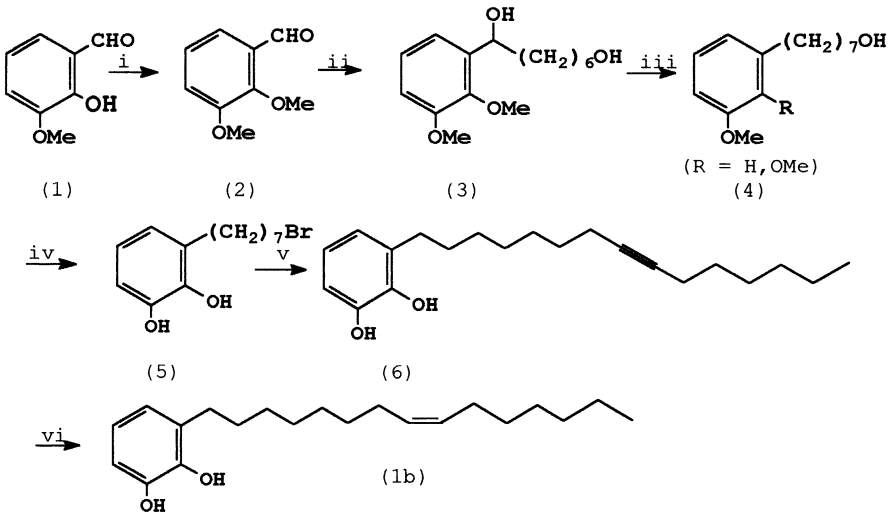


Fig. 1. Formulae of some of the constituents of urushiol from *R. vernicifera* and *R. toxicodendron* (R = R^1 = OH).



Scheme 1. Synthesis of urushiol monoene.

2.2. Chromatography

Analytical TLC was performed on slides (2.5 × 7.5 × 0.25 mm) coated with silica gel GF-254 (Merck) with solvents as indicated and plates were visualised by spraying with 0.1% ethanolic Rhodamine 6G and viewing under long wave UV light.

Argentation TLC was carried out on silica gel G containing 10% silver nitrate with similar visualisation. Argentated preparative and analytical plates were prepared by slurrying silica gel G with aqueous silver nitrate solution containing 10% $AgNO_3$ on the weight of silica gel G used in a volume of water approximately double the weight of silica gel G. Spreading was then carried out as rapidly as possible on slides or preparative plates on described equipment (Tyman and Higdon, 1972). For preparative TLC, plates 20 × 20 cm were used with similar viewing.

Column chromatography was carried out with silica gel MFC (100–200 mesh) (British Drug Houses, Poole, Dorset). GC of all intermediates was carried out with a Pye 104 (model 64) equipped with FID on glass columns (5 × 1/4 in.) containing 3% SE30 on diatomite C (100–120 mesh) with nitrogen (7 psi) as carrier gas at 220 °C. The methyl ethers of synthetic and natural urushiol were analysed on a 2% PEGA column.

2.3. Spectroscopy

Infrared spectra were recorded on a Perkin–Elmer Model 700 as neat liquid films on sodium chloride discs and on a Unicam SP200 instrument. ^{1}H NMR spectra were recorded on a Varian T60 spectrometer with tetramethylsilane as internal standard. Mass spectra were determined on AEI MS9 and Hitachi–Perkin–Elmer RMS4 instruments.

2.4. Synthesis of intermediates and final product

Starting materials were obtained from Aldrich Chemical Co. 6-Chlorohexanol was prepared (Coleman and Bywaters, 1944) from readily available hexane-1,6-diol.

2.4.1. HO-protected 6-chlorohexan-1-ol

To ethyl vinyl ether (37.0 g, 0.50 mol), cooled to 0 °C, containing 4-toluenesulphonic acid (35 mg), 6-chlorohexan-1-ol (3.44 g, 0.025 mol), was added dropwise over 20 min, during which the temperature was kept at 0 °C. The cooling bath was removed and further catalyst (25 mg) added, after

which the mixture was stirred for 1 h. The mixture was then cooled below 5 °C and, after TLC monitoring for completion of reaction, saturated aqueous potassium carbonate (5 ml) was added with vigorous stirring followed by solid K_2CO_3 to remove water. After drying, the mixture was filtered, the solid washed with diethyl ether and the filtrate evaporated to remove solvent and excess ethyl vinyl ether to leave the adduct as a colourless oil (45.7 g, 88%); δ_H (CCl_4) 1.0–1.80 (14H, t, m, 2Me, 4CH_2), 3.10–3.55 (4H, 2t, CH_2O, CH_2Cl), 4.45 (1H, OCHO).

*2.4.2. 2,3-Dimethoxybenzaldehyde (**2**)*

2,3-Dimethoxybenzaldehyde was prepared by the methylation of *o*-vanillin (27.2 g) with dimethyl sulphate (27.7 g) in benzene (caution toxic) (150 ml) containing anhydrous potassium carbonate (50 g) and obtained as pale yellow crystals, m.p. 53–55 °C in 98.7% yield; δ_H (CCl_4) 3.95 (6H, s, 2OMe), 6.95–7.40 (3H, m, 3HAr), 13.60 (1H, s, CHO).

*2.4.3. 1-(2,3-Dimethoxyphenyl)heptane-1,7-diol (**3**)*

A solution of 2,3-dimethoxybenzaldehyde (16.6 g, 0.1 mol) and the above adduct (25.02 g, 0.12 mol) in THF (20 ml) was slowly added to lithium as 0.2 mm cubes (1.735 g, 0.23 mol) covered with THF while the temperature was maintained below 10 °C and the mixture then stirred at −20 °C for 16 h. After removal of excess lithium by decanting the mixture through glass wool, the filtrate was diluted with diethyl ether, washed with saturated ammonium chloride solution and the ethereal layer dried ($MgSO_4$) and evaporated to constant weight. The residual oil in ethanol (50 ml), containing cone. HCl (1 ml), was then stirred at 35–40 °C for 5 h, diluted with water and extracted with diethyl ether. The combined extracts were washed with 0.5 M sodium hydroxide, dried ($MgSO_4$) and the ether evaporated to afford the crude product as a pale yellow oil (24 g, 89.5%); the crude diol was purified by vacuum distillation, b.p. 190–210 °C/0.1–0.3 mmHg; δ_H (CCl_4) 1.05–1.80 (10H, m, 5CH_2), 3.05 (2H, s, 2OH, D_2O exch.) 3.45 (2H, t, CH_2OH), 3.75 (6H s, 2OMe), 4.55 (1H, t, CH(OH)), 6.65–7.05 (3H, m, HAr). Repeated preparations gave yields consistently from 86 to 97%. By GC, retention time 4.65 min (SE30, 220 °C).

*2.4.4. 7-(2,3-Dimethoxyphenyl)heptan-1-ol (**4**, R = OMe)*

The purified diol (10.03 g, 0.037 mol) in ethanol (200 ml) containing 10% Pd–C (1.01 g) was hydrogenated at 15 psi in a Parr hydrogenator with agitation over 16 h. Because of slow uptake of hydrogen, further catalyst (0.5 g) and ethanol (5 ml), containing eight drops cone, HCl) were introduced into the hydrogenation flask. Following further agitation and TLC monitoring, the mixture was released to atmospheric pressure under a nitrogen atmosphere, filtered to remove catalyst and the filtrate slightly basified with 5% aqueous sodium bicarbonate, prior to evaporation of the ethanol. The residual oil in diethyl ether was washed with sodium hydroxide solution, with aqueous sodium chloride, dried (Na_2SO_4), filtered and the solvent removed to afford an oil (7.2 g, 76%). The product was further purified, by vacuum distillation under nitrogen, to give five fractions the main fraction being the fourth, (4.7 g, 70%), b.p. 131–136 °C/0.02–0.04 mmHg, or, preferably, by column chromatography on silica gel and elution with chloroform/ethylacetate. Repeated preparations gave crude yields of 76.5–80% and of purified product 50–56%. By TLC, ($CHCl_3$–EtOAc, 70:30), R_f 0.28.

The crude product (4.0 g) in chloroform (4.0 g) was chromatographed on silica gel (MFC, 180 g) and eluted with 6 × 250 ml of chloroform(C)–ethylacetate(E) of compositions, 100C, 80C–120E, 75C–25E, 3 × 70C–30E, to give six fractions, respectively, the 4th of which contained the product (1.80 g, 45%) also present in small amount in the 3rd and 5th fractions; δ_H (CCl_4), 1.35 (10H, s, 5CH_2), 2.55 (2H, t, CH_2Ar), 2.65 (1H, s, OH, exch. D_2O), 3.45 (2H, t, CH_2OH), 3.75 (6H. s, 2MeO), 6.50–6.95 (3H, m, HAr); ν_{max} (cm^{-1}, NaCl disc), 3350 (OH), 2930, 2850 (CH_2), 1590, 1580, 1470, 1420, 1265, 1220, 1170, 1080, 1060, 1010, 745; *m/z* 252 (M^+), 122 (base peak). By GC, retention time 4.05 min (SE30, 220 °C).

An earlier fraction in the vacuum distillation of the main product and also a band with higher R_f in

prep TLC, was concluded, from spectroscopic evidence, to be a 2-demethoxylation product, namely 7-(3-methoxyphenyl)heptan-1-ol (**4**, R = H); *m/z* 222 (M^+) 220, 192, 147, 135, 122 (base peak), 121, 91, 78, 7741, 39, 28, 18. By GC, retention time 3.15 min (SE30, 220 °C).

*2.4.5. 7-(2,3-Dihydroxyphenyl)heptyl bromide (**5**)*

7-(2,3-Dimethoxyphenyl)heptan-1-ol (l.79 g, 0.0071 mol) in dry chloroform (50 ml) was treated with phosphorus tribromide (2.36 g, 0.0087 mol) in chloroform (10 ml) and the temperature of the stirred mixture kept at 0 °C. Then, after 4 h at ambient temperature with TLC monitoring, formation of the bromide, 7-(2,3-dimethoxyphenyl)heptyl bromide was complete. To the mixture, boron tribromide (4.7 g) was added and after 7 days, during which the progress of demethylation was followed by TLC and GC, the mixture was carefully diluted with ice/water, and the chloroform solution washed with water until neutral, dried (Na_2SO_4) and the chloroform removed in vacuo to leave a faintly pink coloured oil (1.58 g, 77.5%) which was purified by prep TLC (ethyl acetate–chloroform, 20:80); δ_H (CCl_4) 1.40 (10H, s, $5CH_2$), 2.60 (2H, t, CH_2Ar), 3.37 (2H, t, CH_2Br), 5.60 (2H, bs, OH, exch. D_2O), 6.65 (3H, s, HAr). The bromide (1.55 g) was also prepared also from the heptanol (1.70 g) in dichloromethane (17 ml) directly with boron tribromide (5.08 g) in dichloromethane (7.5 ml) in 80% yield. Repeated preparations gave yields of 80%, and above. By TLC, ($CHCl_3$–EtOAc, 80:20), R_f 0.61. By GC, retention time 4.75 min (SE30, 220 °C).

*2.4.6. 3-(Pentadec-8-ynyl)catechol (**6**)*

To 7-(2,3-dihydroxyphenyl)heptyl bromide (0.5176 g, 0.00194 mol) in THF (1.5 ml), containing HMPT (1 ml), a solution of lithio oct-1-yne in THF (10 ml) prepared from 1-octyne (1.365 g, 0.0124 mol) and 1 M *n*-butyl lithium in hexanes (0.572 g, 0.0105 mol) was added under nitrogen at −50 °C and the stirred mixture maintained at that temperature, before TLC monitoring and completion of the reaction at ambient temperature. The mixture was diluted with water, neutralised and extracted with ether. The combined extracts were washed with aqueous sodium chloride, dried (Na_2SO_4) and the ether removed in vacuo to leave a pale oil; δ_H (60 MHz, CCl_4) 0.80–0.98 (3H, t, Me), 1.32 (18H, s, $(CH_2)_9$, 1.92–2.32 (4H, m, $2CH_2CH=$), 2.44–2.66 (2H, t, CH_2Ar), 6.48–6.68 (3H, m, HAr); ν_{max} (cm^{-1}, NaCl disc) 3450 (OH), 2800, 2650 (CH_2), 2000 (C≡C), 1475 (C–H, def.), 830 (C–H, arom.). By TLC, ($CHCl_3$–EtOAc, 95:5) R_f 0.53. By GC, retention time 20.4 min. (SE30, 220 °C).

*2.4.7. 3-[(8Z)-Pentadecenyl]catechol (**1b**)*

3-(Pentadec-8-ynyl)catechol (0.155 g, 0.0049 mol) in ethyl acetate (3 ml) containing 5% Pd–$BaSO_4$ (0.16 g) and quinoline (one drop) in methanol (1.5 ml) was hydrogenated at ambient pressure and temperature until the required uptake of hydrogen (11 ml) had been consumed. The mixture was filtered, the catalyst was washed with diethyl ether and the filtrate then washed with dilute HCl, followed by sodium chloride solution, dried and the ether evaporated to give an oil; δ_H (60 mHz, CCl_4), 0.08–0.98 (3H, t, Me), 1.32 (18H, m, $(CH_2)_9$, 1.80–2.20 (4H, m, $2CH_2CH=$), 2.44–2.72 (2H, t, CH_2Ar), 5.00–5.40 (2H, bs, OH, exch. D_2O), 5.23–5.40 (2H, t, CH=CH, *J*, 5.5, Hz), 6.43 (3H, s, HAr); ν_{max} (cm^{-1}, NaCl disc) 3400 (bs, OH), 2900, 2840 (CH_2), 1595 (C–O), 1475 (C–H, def.), 835 (C–H, arom.); the product was chromatographically (TLC and GC) and spectroscopically (IR and NMR) identical with natural (15:1)-urushiol; by TLC on silica gel G ($CHCl_3$–EtOAc, 90:10), R_f 0.56 for both synthetic and natural urushiol; on silica gel G containing 10% $AgNO_3$ ($CHCl_3$–EtOAc, 80:20), R_f 0.69 for both the natural and synthetic monoene. By GC, retention time, 17.3 min, natural mixture monoene, diene, triene 17.5 min (SE30, 220 °C).

The dimethyl ether (**1b**; $R = R^1 = OMe$) was also obtained on an analytical scale from 7-(2,3-dimethoxyphenyl)heptyl bromide derived from **4** with phosphorus tribromide by reaction with lithio-1-octyne and catalytic hydrogenation of the resultant alkyne. The bromide prepared from the heptanol with phosphorus tribromide was reacted in HMPT with excess lithio oct-1-yne and the product purified by TLC, and catalytically hydrogenated as for the catechol analogue to give 3-[8(*Z*)-pentadecenyl]veratrole, which was chroma-

tographically (GC and TLC) identical to the methylated monoene in methylated natural urushiol.

2.4.8. Extraction of urushiol from Rhus toxicodendron

Dried crushed twigs cut in 0.5–0 75 in. lengths (7.30 g) were extracted in a Soxhlet apparatus during 3 h with ethanol (300 ml), secondly with (200 ml) and finally with (100 ml) until the final ethanol extract was only faintly coloured. The first two extracts afforded upon evaporation, 0.0608 and 0.1022 g, respectively, of crude urushiol which was dissolved in diethyl ether to give a green–brown solution. Prep TLC (chloroform–ethyl acetate, 90:10) gave a main band with R_f 0.67 of mixed urushiol. Elution with 10% methanol in ether and recovery afforded a product (0.0712 g) having, by TLC comparison with the synthetic product, an identical R_f of 0.69. Argentation TLC (chloroform–ethyl acetate, 80:20) separated the monoene (R_f 0.69), diene (R_f 0.63) and triene (R_f 0.57) constituents.

2.4.9. Methylation of synthetic monoene and of natural urushiol from Rhus toxicodendron

The synthetic monoene (0.010 g) in benzene (0.50 ml) containing dimethyl sulphate (0.05 ml) and potassium carbonate (0.20 g) was refluxed during 2.5 h under nitrogen. The cooled mixture was diluted with water, and after the addition of diethyl ether, the upper solvent layer was separated, dried and concentrated to give the dimethyl ether as an oil. Methylation proceeds (TLC monitoring) by way of the monomethyl ether (**1b**; R = OMe, R^1 = OH) (Tyman and Matthews, 1977) which has properties reminiscent of the 'hindered' phenols.

In a similar way, the natural material (0.0016 g) in benzene (0.20 ml) containing dimethyl sulphate (002 ml) and potassium carbonate (0.10 g) was methylated and worked up as before. By GC, the retention time of the methylated synthetic monoene was 9.45 min (2% PEGA, 200 °C) in agreement with the methyl ether of the monoene in the fully methylated natural product, for the constituents of which the per cent composition and retention times were, saturated (4.8%, 8.8 min), monoene (31.8%, 9.5 min), diene (47.5%, 11.6 min) and triene (15.8%, 14.0 min).

3. Results and discussion

There have been a number of attempts to synthesise urushiol constituents, commencing with the saturated member (**1a**) and subsequently the (15:1)-monoene. The dimethyl ether of the *cis*-monoene (**1b**, R = R^1 = OMe) was prepared (Wasserman and Dawson, 1943) although not the parent catechol; but its synthesis was claimed from the debenzylation of a 1,8-diene intermediate of **1** (Loev and Dawson, 1959) although the product was not characterised chromatographicaly or spectroscopically. Subsequently, the 2,3-dibenzyl ether of urushiol itself (**1**, R = R^1 = OBn) was separated on alumina into the dibenzylmonoene, diene and triene each of which was debenzylated by the same procedure in hot butanol with sodium (Markiewitz and Dawson, 1965) a procedure likely to cause some conjugation of the unsaturation. By the use of 8-(2,3-dimethoxyphenyl)octanal, obtained from urushiol dimethyl ether by ozonisation, a partial synthesis of the dimethyl ether of the monoene, and later of the diene and triene, was effected (Sato, 1973) through a Wittig reaction, but without stereochemical characterisation. The alkene group(s) can be formed by either a Wittig reaction or by way of an alkyne precursor and examples of both approaches have been given (Tyman, 1979, 1996). Although the relative proportion of *cis*/*trans* isomers is predictable by operating under kinetic or thermodynamic control, the alkyne/alkene route generally seems to be more specific. An acetylenic route afforded the monoene but in low overall yield (Halim et al., 1980). In this approach, 2,3-dimethoxyphenyl lithium was reacted with 1,7-dibromoheptane to give 1-bromo-7-(2,3-dimethoxyphenyl)heptane in low yield[1]. Alkylation of this bromo derivative

[1] Halim et al. (1980) very kindly acknowledged (p. 2331) that only the synthesis by Tyman and Khor appears to be satisfactory but it is unfortunate that these experimental details and yields have not been reported until now.

with lithio oct-1-yne afforded 1,2-dimethoxy-3-(pentadec-8-ynyl)benzene, which was catalytically hydrogenated to the corresponding alkene. Demethylation by way of trimethylsilyl iodide afforded, by way of the bis trimethylsilyl derivative, the required product (15:1)-urushiol, (**1b**) in very low overall yield. More recently the 8*Z*, 11*Z*, 14 and 8*Z*, 11*E*, 13*E*-trienes have been synthesised (Miyakoshi et al., 1991) by a Wittig reaction of 8-(2,3-diacetoxyphenyl)octanal with a C_7 unsaturated phosphoran which in the case of the 8*Z*, 11*Z*, 14-triene gave a 42% yield compared with yields of 65–90% generally found in the alkyne–alkene route. The Wittig sequence described involves the conversion of a terminal ω-bromo to an ω-iodooctyl group and then to the oxo group in 8-(2,3-diacetoxyphenyl)octanal, with some loss of yield.

The low yield (22%) in the first stage lithium reaction by Halim et al. (1980) with 1,7-dibromoheptane leading to 1-bromo-7-(2,3-dimethoxyphenyl)heptane is probably attributable to Wurtz side reactions and contrasts with that of 84% reported by Miyakoshi et al. for the homologous 1,8-dibromooctane, but may indicate the unpredictable character of this reaction. Wurtz side reaction also occurs in Grignard reactions resulting in the persistent by-product, dodecane-1,12-diol, which was difficult to remove.

In our own work, this deviation was avoided by using nucleophilic addition of 2,3-dimethoxybenzaldehyde to HO-protected 6-chlorohexan-1-ol in the presence of lithium. This sequence had proved highly effective for routes in the synthesis of the monoenes of the phenolic lipid analogues cardanol and cardol (Tyman, 1996) by way of the respective 3-methoxy or 3,6-dimethoxyphenylheptane-1,7-diols.

Selective catalytic hydrogenolysis of the secondary OH group in (**3**) with Pd–C proceeded in high yield and thus it was unexpected to encounter demethoxylation of the 2-methoxy group, albeit in low yield, in the present work to give by-product, 7-(3-methoxyphenyl)heptane-1-ol (Tyman, 1975); the consumption of hydrogen, allowing for some adsorption by the catalyst, was found to be nearly the theoretical volume. This minor by-product was easily removable either by distillation, chromatography or preparative TLC. Initially 7-(2,3-dimethoxyphenyl)heptyl bromide (**5**) was prepared with phosphorus tribromide but a further advantage in the present route was the reaction of the dimethoxy compound (**4**) with boron tribromide alone at low temperature to effect both demethylation and bromide formation to give (**5**). Although the resulting dihydroxyphenyl compound consumed 3 mol of lithio oct-1-yne at the next stage, the 2,3-dithio salt of 7-(2,3-dihydroxyphenyl)heptyl bromide was soluble in the reaction mixture and formation of the pentadecynyl product (**6**) proceeded in excellent yield. By contrast, the demethylation stage in the synthesis the Halim et al. (1980) required two additional steps while in the route adopted by Miyakoshi et al. (1991) the catechol system was acetylated prior to Wittig reaction and finally deacetylaion effected with $LiAlH_4$ in only moderate yield. We had in earlier work found catalytic reduction with Lindlar's catalyst to be very slow and hence adopted the method using Pd–C poisoned with quinoline which was found to be capable of careful regulation in selectively affording the *cis*-alkene without reduction to the alkane. The derivation of a satisfactory route to (**5**) also provides a method towards the diene (**1c**) and triene (**1d**), by formation of 10-(2,3-dihydroxyphenyl)dec-2-yn-1-ol and reaction of the derived bromide with magnesio bromo derivatives of 1-pentyne and of pent-1-yn-4-ene, followed by selective reduction, work which will be described elsewhere. The same procedure in the present synthesis with *p*-vanillin, in place of the *o*-isomer, might be employed for the 4-alkenylcatechols of the thitsiol series, the saturated constituent of which, 1,2-dihydroxy-4-pentadecylbenzene, has been synthesised (Tyman, 1973).

Phenolic lipids are a significant group in the general family of lipids although their syntheses have generally received little attention (Gunstone, 1999). Thus it is believed that the methodology described in the present communication and developed over the past two decades gives access to range of intermediates and procedures for the synthesis of structural isomers and C_{17} analogues.

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