

## Vesicant Principles of Poison Ivy and Related Plants: Synthesis of the Urushiols, 1,2-Dihydroxy-3-[(Z)-pentadec-8-enyl]benzene and 1,2-Dihydroxy-3-pentadecylbenzene

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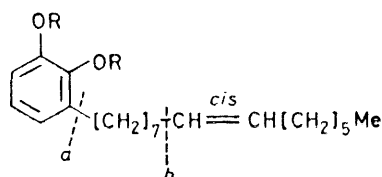
New syntheses of 1,2-dihydroxy-3-[(Z)-pentadec-8-enyl]benzene (1) and 1,2-dihydroxy-3-pentadecylbenzene (4), vesicant principles of Poison Ivy (*Rhus radicans*) and other species of Anacardiaceae, are described starting from 1,2-dimethoxybenzene (7). The lithiation of 1,2-dimethoxybenzene (7) has been re-examined and the yield of the product, 2,3-dimethoxyphenyl-lithium (8), re-determined. The reaction of this aryl-lithium with 1,7-dibromoheptane has been studied by g.l.c., using tributyltin chloride as a quenching reagent. The extracts of two plants of the Anacardiaceae family, *Semecarpus vitiensis* Engl. and *Melanorrhoea beccari* Engl., have been examined for the presence of urushiols. The bark of the latter has been found to contain gallic acid.

1,2-DIHYDROXY-3-[(Z)-PENTADEC-8-ENYL]BENZENE (1) and 1,2-dihydroxy-3-pentadecylbenzene (4) are two of a series of related alkenyl- and alkyl-catechols, also called urushiols,<sup>1</sup> possessing powerful vesicant properties, and found in North American Poison Ivy (*Rhus radicans* Linn.), Poison Oak (*R. toxicodendron* Linn.),<sup>2</sup> Japanese Lac urushiol (*R. verniciflora*),<sup>3</sup> and Manzanillo (*R. striata* Ruiz and Pav.)<sup>4</sup> (family Anacardiaceae). The 'anacardiaceous phenols', as they have been called,<sup>5</sup>

tested equivalent (2), were considered to be composed of three synthons; a catechol unit, a C<sub>7</sub> unit, and a further C<sub>8</sub> unit [see divisions at points *a* and *b* in (1)].

### RESULTS AND DISCUSSION

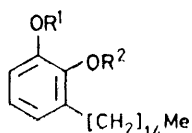
The work of Gilman and his co-workers<sup>14</sup> on lithiation established that 1,2-dimethoxybenzene (7) undergoes lithium-hydrogen exchange with butyl-lithium predominantly at the 3-position, giving 2,3-dimethoxyphenyl-lithium (8). We therefore chose this reaction to initiate our synthesis because it provided an efficient means of functionalising the aromatic nucleus at this position



(1) R = H

(2) R = Me

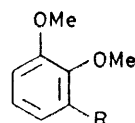
(3) R = SiMe<sub>3</sub>



(4) R<sup>1</sup> = R<sup>2</sup> = H

(5) R<sup>1</sup> = R<sup>2</sup> = Me

(6) R<sup>1</sup> = R<sup>2</sup> = SiMe<sub>3</sub>



(7) R = H

(8) R = Li

(9) R = [CH<sub>2</sub>]<sub>7</sub>Br

(10) R = CO<sub>2</sub>H

(11) R = Me

(12) R = SnBu<sub>3</sub>

(13) R = [CH<sub>2</sub>]<sub>7</sub>C<sub>6</sub>H<sub>3</sub>(OMe)<sub>2</sub>

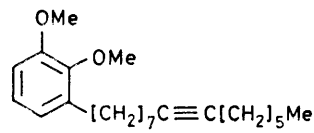
(14) R = Et

(15) R = CHMe<sub>2</sub>

(16) R = CMe<sub>3</sub>

HO<sub>2</sub>C[CH<sub>2</sub>]<sub>7</sub>CO<sub>2</sub>H

(17)



(18)

are also found in species of the genera *Anacardium* (notably the cashew nut tree),<sup>6</sup> *Semecarpus*,<sup>7,8</sup> and *Melanorrhoea*.<sup>9</sup>

Amongst the several syntheses of the urushiols bearing a saturated side-chain (4), the dimethyl ether (5) was first prepared by Backer and Haak<sup>8</sup> in 1938. The more challenging synthesis of the dimethyl ether of the 'unsaturated' urushiol (2) was realised by Wasserman and Dawson,<sup>10</sup> whose group<sup>11</sup> later prepared the parent urushiol (1) in impure form. Later, Japanese workers,<sup>12</sup> utilising a difficultly accessible degradation product of the natural alkenylcatechol (1), achieved a partial synthesis of the protected urushiol (2). Only the synthesis of the urushiol (1) by Tyman and Khor<sup>13</sup> appears to be satisfactory, though even here full experimental details and yields have not been published.

In our synthesis, the target urushiol (1), or its pro-

The assembly of the side-chain in the dimethyl ether (2) commenced with the reaction of equimolar quantities of 2,3-dimethoxyphenyl-lithium (8) and 1,7-dibromoheptane, giving 1-bromo-7-(2,3-dimethoxyphenyl)-heptane (9) in 22% yield. The product (9) was easily separated from the accompanying mixture of starting

materials by distillation, but the recycling of the latter proved to be difficult because the individual components were virtually inseparable by routine methods. 1,7-Dibromoheptane was prepared<sup>15</sup> in high yield from azelaic acid (17) using a modification of the Hunsdiecker reaction.

The final C<sub>8</sub> portion of the carbon skeleton of (2) was attached by reacting the bromoarylheptane (9) with lithio-oct-1-yne<sup>16</sup> to give the intermediate 1,2-dimethoxy-3-(pentadec-8-ynyl)benzene (18) in 70% yield.

Catalytic semi-hydrogenation of the acetylene (18) was monitored throughout using h.p.l.c., a technique which enabled us to detect reliably the presence of any saturated urushiol derivative (5), formed as a result of overhydrogenation, as well as the desired *Z*-olefin (2), and starting material (18). No simple t.l.c. procedure was found capable of resolving all three compounds.

Catalytic semi-hydrogenation of the intermediate (18) using Lindlar catalyst gave very variable results with some overhydrogenation occurring, but frequently none occurring at all. With the Schneider catalyst (palladium-barium sulphate with pure dry pyridine as solvent)<sup>17</sup> reduction consistently ceased abruptly at the olefin stage giving (2) in quantitative yield as determined by h.p.l.c.

The saturated urushiol derivative (5), used as a reference standard in this work, was prepared in two ways: by complete hydrogenation of the acetylenic intermediate (18), and by a more direct synthesis involving the reaction of 2,3-dimethoxyphenyl-lithium (8) with 1-bromopentadecane, the latter being prepared<sup>15</sup> from palmitic acid by the Hunsdiecker reaction.

The saturated and olefinic urushiol derivatives (5) and (2), respectively, were demethylated in two stages using trimethylsilyl iodide.<sup>18</sup> In both cases, the intermediate bis(trimethylsilyl) derivatives (6) and (3), respectively, were isolated before proceeding with the removal of the silyl protective groups under mild conditions. Both the parent urushiols, 2,3-dihydroxy-3-pentadecylbenzene (4) and 2,3-dihydroxy-3-[(*Z*)-pentadec-8-enyl]benzene (1), were found to be unstable as reported earlier.<sup>2</sup> In contact with air at room temperature they soon darkened giving tarry products. The overall yield from the unsaturated dimethyl ether (2) was depressed slightly by the formation of a high-boiling iodination by-product, produced through the release of free iodine from trimethylsilyl iodide.

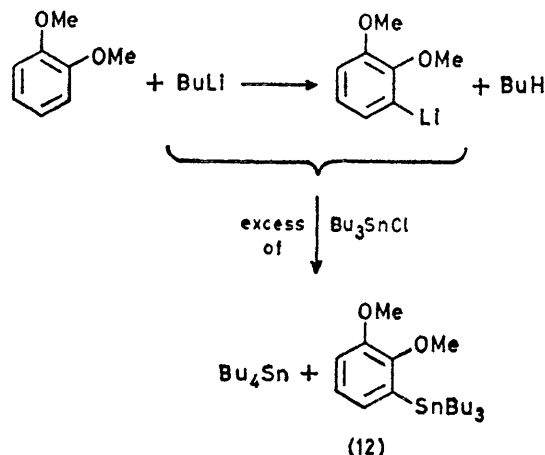
**Lithiation of 1,2-Dimethoxybenzene (7) and Reactions with 1,7-Dibromoheptane.**—In a separate investigation, we re-examined the lithiation of 1,2-dimethoxybenzene (7) and the reaction of the derived aryl-lithium (8) with 1,7-dibromoheptane in order to improve the yield of 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9), which was formed in only 22% yield.

In their preparation of 2,3-dimethoxyphenyl-lithium (8), Gilman and his co-workers<sup>14</sup> unaccountably used *two* molar equivalents of butyl lithium to *one* of 1,2-dimethoxybenzene (7). The site of lithiation and the yield of lithio-product were determined by the standard

carbonation procedure which gave 2,3-dimethoxybenzoic acid (10) in 65% yield.

We repeated the lithiation reaction, but used instead, an equimolar ratio of butyl-lithium to 1,2-dimethoxybenzene (7) in ether. After lithium-hydrogen exchange had taken place, dimethyl sulphate was added, and the products formed identified and estimated by g.l.c. The major product, 2,3-dimethoxytoluene (11) was present in 80% yield, showing that an excess of butyl-lithium is not essential and that the lithiation product (8) is actually formed in higher yield than that reported previously.

We next examined the reaction of 2,3-dimethoxyphenyl-lithium (8) with 1,7-dibromoheptane. In order to monitor the progress of this reaction under various conditions, we evolved the technique of using tributyltin chloride as a quenching reagent: any surplus of butyl-lithium present in the lithiation reactions was detected by its rapid conversion into tetrabutyltin (which is commercially available), while other lithiated species formed were converted into their stable tributyltin derivatives. Tributyltin chloride, tetrabutyltin, and many aryltributyltin derivatives are stable and volatile enough to be analysed directly by g.l.c. The method is reliable because metal halides, such as those of tin(IV), react rapidly and irreversibly with organolithium compounds in the manner shown (Scheme 1), a consequence of the metal being much more electropositive than carbon.<sup>19</sup> In order to detect the presence of tributyl-(2,3-dimethoxyphenyl)tin(IV) (12) (Scheme 1) in the

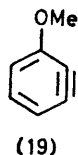


SCHEME 1

quenched reactions, we first prepared it unambiguously from 2,3-dimethoxyphenyl-lithium and tributyltin chloride, and then determined its g.l.c. retention time under standard conditions.

The quenching experiments using tributyltin chloride showed that virtually no reaction occurs between 2,3-dimethoxyphenyl-lithium (8) and 1,7-dibromoheptane in ether at room temperature: reaction does occur, however, at reflux temperature and is complete after 10 min. The yield of 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9) from this reaction was consistently low, and

large quantities of unreacted 1,2-dimethoxybenzene (7) and 1,7-dibromoheptane accompanied it, as shown by the g.l.c. analyses, suggesting that the reaction was incomplete. There was no evidence that 1,7-di-(2,3-dimethoxyphenyl)heptane (13) was being formed in any significant quantity, so the low yield might be due to the intervention of a side-reaction; one possibility is the elimination of lithium methoxide from 2,3-dimethoxy-



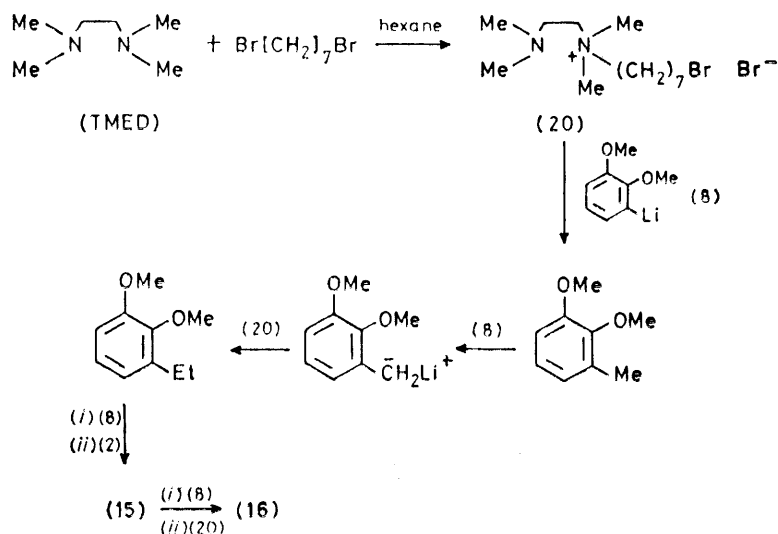
phenyl-lithium to give the aryne (19), and another the dehydrobromination of 1,7-dibromoheptane.

We were doubtful about the first of these explanations because elimination of lithium methoxide at such a low

(11) and (14), were augmented by the higher homologues 2,3-dimethoxyisopropylbenzene (15) and 2,3-dimethoxy-*t*-butylbenzene (16), as shown by g.l.c.-low-resolution mass spectrometry. This curious series of products is presumably formed by a sequence of methylations (Scheme 2), the methyl groups being supplied presumably by the intermediate quaternary ammonium ion (20), an ion in which the methyl groups compete with the more bulky 7-bromoheptyl group for acceptance by the nucleophilic organolithium reagent.

None of these modifications to the procedure was successful in raising the yield of 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9) above 22%.

*Examination of Two Plants of the Anacardiaceae Family for the Presence of Urushiols.*—The chloroform extract of the heartwood of *Semecarpus vitiensis* Engl. was methylated and the fraction likely to contain the urushiols as their methyl ethers carefully examined by



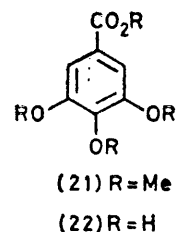
SCHEME 2

temperature as the boiling point of ether seemed unlikely. Evidence collected later suggested that some dehydrobromination was probably occurring.

In order to increase the polarity of the lithium-carbon bond in the intermediate aryl-lithium (8), the bidentate ligand *NNN'*-tetramethylethylenediamine was added to the mixture of 2,3-dimethoxyphenyl-lithium (8) and 1,7-dibromoheptane in ether, and the products of the reaction analysed by g.l.c.-mass spectrometry. 1,7-Dibromoheptane and 1,2-dimethoxybenzene (7) were again found to be major constituents of the reaction mixture, in addition to the desired 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9). Minor g.l.c. peaks, identified by their low-resolution mass spectra only, were attributed to the presence of 7-bromohept-1-ene, 2,3-dimethoxytoluene (11), and 2,3-dimethoxyethylbenzene (14). In later experiments carried out using *NNN'*-tetramethylethylenediamine in hexane, and in hexamethylphosphoric triamide, the latter two products,

h.p.l.c., using the synthesised ethers (2) and (5) as reference standards. Neither compound was found to be present in the extract.

An extract of the bark of *Melanorrhoea beccari* Engl. was similarly methylated and the mixture of methylated



products examined by t.l.c. for the presence of the methylated urushiols (2) and (5). Neither was found, but methyl 3,4,5-trimethoxybenzoate (21) was detected and subsequently isolated. An examination of the

original unmethylated extract of *M. beccari* Engl. showed that gallic acid (22) was the actual natural product present in the bark. The derivative (21) was absent. Gallic acid (22) and its derivatives (e.g. gallo-tannins) are commonly found in species of the family Anacardiaceae.<sup>20</sup>

## EXPERIMENTAL

**1,7-Dibromoheptane.**<sup>15</sup>—Bromine (175 g) in 1,1,2,2-tetrachloroethane (100 ml) was added slowly during 3 h to a well-stirred mixture of azelaic acid (94 g) and red mercuric oxide (110 g) in tetrachloroethane (400 ml) at 80–90 °C. A tetrachloroethane bubbler was connected to the reaction flask and when no further evolution of carbon dioxide was observed, the reaction was assumed to be finished. The tetrachloroethane contained in the bubbler was periodically added to the reaction mixture in order to recycle bromine vapour carried over.

The reaction mixture was filtered and any excess of bromine was removed by passing ethylene gas through the filtrate. The clear filtrate was washed with sodium hydrogencarbonate and then water, and the organic layer dried. After removal of the solvent, the residual oil was found to have a carbonyl band at 1710 cm<sup>-1</sup> in its i.r. spectrum. This contaminant was removed by passing a solution of the oil in light petroleum (b.p. 60–80 °C) through a short column of alumina. The eluate, on removal of the solvent, was distilled under reduced pressure to give 1,7-dibromoheptane (78 g), b.p. 112–114 °C at 1.8 mmHg (lit.,<sup>15b</sup> b.p. 125 °C at 2 mmHg);  $\tau$  (neat liquid) 6.65 (t, 4 H, 2  $\times$  CH<sub>2</sub>Br), 8.19 (m, 4 H, 2  $\times$  CH<sub>2</sub>CH<sub>2</sub>Br, and 8.61 (br s, 6 H, 3  $\times$  CH<sub>2</sub>) [Found:  $M^+$ , 256 (for <sup>79</sup>Br). Calc. for C<sub>7</sub>H<sub>14</sub>Br<sub>2</sub>:  $M$ , 256].

**1-Bromo-7-(2,3-dimethoxyphenyl)heptane** (9).—Butyllithium in hexane (87 ml, 0.2 mol) was added to a stirred solution of 1,2-dimethoxybenzene (27.6 g, 0.2 mol) in dry ether (500 ml) under nitrogen. The mixture was heated under reflux for 4 h, during which time a cream-coloured solid appeared.

The reaction mixture was cooled to -70 °C and 1,7-dibromoheptane (51.6 g, 0.2 mol) in dry peroxide-free tetrahydrofuran (300 ml) was added rapidly. The mixture was allowed to warm to room temperature, then heated under reflux for 4 h, in the course of which the cream solid disappeared. After removal of the solvents, ice, 2M-hydrochloric acid, (10 ml), and light petroleum (b.p. 60–80 °C) (200 ml) were added to the residue and the mixture shaken. The petrol layer was washed with sodium hydrogencarbonate solution and water, and then dried (magnesium sulphate). The yellowish oil obtained after removal of the solvent was distilled under reduced pressure (bulb-to-bulb). The early fractions (b.p. 45–60 °C at 0.005 mmHg) contained 1,2-dimethoxybenzene and 1,7-dibromoheptane (25 g total weight). The fraction of b.p. 95–105 °C at 0.0005 mmHg (14 g, 22%) was found to be 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9);  $\nu_{\max}$  (liquid film) 3 020, 1 605, and 1 590 (aromatic ring), 1 270 and 1 225 (MeO groups), and 750 cm<sup>-1</sup> (CH<sub>2</sub> groups);  $\tau$  (neat liquid) 3.20 (m, 3 H, Ar-H), 6.25 (s, 6 H, 2  $\times$  OMe), 6.70 (t, 2 H, CH<sub>2</sub>Br), 7.43 (t, 2 H, ArCH<sub>2</sub>), and 8.0–8.8 (br s, 10 H, 5  $\times$  CH<sub>2</sub>); <sup>13</sup>C n.m.r. (neat liquid),  $\delta$  p.p.m. from SiMe<sub>4</sub> 152.94 (s), 147.94 (s, 2  $\times$  C-OMe), 136.41 (s, ArC-CH<sub>2</sub>), 123.36 (d), 122.05 (d), 111.08 (d, 3  $\times$  Ar-C-H), 60.18 (q), 55.86 (q, 2  $\times$  OMe), and 28.05–34.38 [m, (CH<sub>2</sub>)<sub>7</sub>Br] [Found:  $M^+$  314.088 5.

C<sub>15</sub>H<sub>23</sub>BrO<sub>2</sub> requires  $M$ , 314.088 1; other measured masses at  $m/e$  234.161 6 (C<sub>15</sub>H<sub>22</sub>O<sub>2</sub>, i.e.  $M$  - HBr) and 151.075 0 (C<sub>9</sub>H<sub>11</sub>O<sub>2</sub>, i.e. C<sub>6</sub>H<sub>3</sub>(OMe)<sub>2</sub>CH<sub>2</sub><sup>+</sup>].

**1,2-Dimethoxy-3-(pentadec-8-ynyl)benzene** (18). Butyllithium in hexane (13 ml, 0.03 mol) was added slowly to a solution of oct-1-yne (3.3 g, 0.03 mol) in dry tetrahydrofuran (150 ml) under nitrogen at 5 °C. 1-Bromo-7-(2,3-dimethoxyphenyl)heptane (9.45 g, 0.03 mol) in hexamethylphosphoric triamide (50 ml) was added slowly, maintaining the temperature below 10 °C. After the addition, the mixture was stirred at room temperature for 24 h. Ice and sodium chloride were added, and the organic materials extracted into ether. After drying (magnesium sulphate), the solvents were removed from the extract under reduced pressure leaving a yellow oil. Bulb-to-bulb distillation of the oil gave (a) a small quantity of 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9), b.p. 120–125 °C at 0.0003 mmHg, and (b) 1,2-dimethoxy-3-(pentadec-8-ynyl)benzene (18) (7.0 g), b.p. 140–145 °C at 0.0003 mmHg (lit.,<sup>10</sup> b.p. 192–192.8 °C at 1.2–1.4 mmHg).

Fraction (b) was further purified by h.p.l.c using a 6-ft reverse-phase column (3 ft  $\times$  2 column,  $\frac{3}{8}$  in, Bondapak C<sub>18</sub>/Porasil-B, 37–75  $\mu$ , elution solvent methanol, 9.9 ml min<sup>-1</sup>) giving the pure acetylene (18);  $\nu_{\max}$  3 020, 1 605, and 1 590 (aromatic ring), and 750 cm<sup>-1</sup> (CH<sub>2</sub> groups);  $\tau$ (CDCl<sub>3</sub>) 3.26 (m, 3 H, Ar-H), 6.19 (s) and 6.22 (s) (6 H, 2  $\times$  MeO), 7.40 (t, 2 H, ArCH<sub>2</sub>), 7.89 (t, 4 H, CH<sub>2</sub>C $\equiv$ CH<sub>2</sub>), 8.65 (br s, 18 H, 9  $\times$  CH<sub>2</sub>), and 9.13 (t, 3 H, Me); <sup>13</sup>C n.m.r. (CCl<sub>4</sub>) ( $\delta$  p.p.m. from SiMe<sub>4</sub>) 152.9 (s) and 147.8 (s) (2  $\times$  ArC-OMe), 136.3 (s, ArC-CH<sub>2</sub>), 123.3 (d), 122.1 (d), 110.6 (d, 3  $\times$  Ar-C-H), 80.0 (s, C $\equiv$ C), 60.0 (q), 55.4 (q, 2  $\times$  OMe), 32.6–29.4 and 22.8–18.9 (12  $\times$  CH<sub>2</sub>), and 14.1q (Me) [Found:  $M^+$ , 344.268 5. Calc. for C<sub>23</sub>H<sub>36</sub>O<sub>2</sub>:  $M$ , 344.271 3].

**Catalytic Hydrogenations.**—*Semi-hydrogenation of 1,2-dimethoxy-3-(pentadec-8-ynyl)benzene* (18) to give 1,2-dimethoxy-3-[(*Z*)-pentadec-8-enyl]benzene (2). 1,2-Dimethoxy-3-(pentadec-8-ynyl)benzene (762 mg) in freshly distilled anhydrous pyridine (10 ml) was hydrogenated in the presence of 5% palladium-barium sulphate (0.25 g). Hydrogen uptake ceased abruptly after the consumption of 1 mol equiv. of hydrogen (ca. 60 ml). After removal of the catalyst, the pyridine was evaporated under reduced pressure leaving the *Z*-olefin which distilled (bulb-to-bulb) with b.p. 170–172 °C at 0.0004 mmHg (760 mg) (lit.,<sup>10</sup> b.p. 196–198 °C at 2 mmHg). H.p.l.c. purity checks were carried out using a reverse-phase  $\mu$ -Bondapak 30-cm column with methanol as the elution solvent. The retention times were: acetylene (18), 2.2 min; olefin (2), 2.4 min; and saturated compound (5), 2.7 min. The *Z*-olefin (2) was the only constituent present from the above semi-hydrogenation;  $\nu_{\max}$  3 020, 1 605, and 1 590 (aromatic ring), and 750 cm<sup>-1</sup> (CH<sub>2</sub> groups);  $\tau$ (CDCl<sub>3</sub>) 3.10 (m, 3 H, Ar-H), 4.60 (t, 2 H, HC=CH), 6.10 (br s, 6 H, 2  $\times$  OMe), 7.35 (t, 2 H, ArCH<sub>2</sub>), 7.95 (t, 4 H, CH<sub>2</sub>C=CH<sub>2</sub>), 8.25–8.65 (br m, 18 H, 9  $\times$  CH<sub>2</sub>), 9.10 (t, 3 H, Me); <sup>13</sup>C n.m.r. (CHCl<sub>3</sub>,  $\delta$  p.p.m. from SiMe<sub>4</sub>) 152.8 (s) and 147.4 (s) (2  $\times$  ArC-OMe), 136.7 (s, ArC-CH<sub>2</sub>), 130.4d (HC=CH), 123.6 (d), 122.1 (d), and 110.2 (d) (3  $\times$  Ar-C-H), 60.4 (q) and 55.6 (q) (2  $\times$  OMe), 32.7–29.7 (m), 22.8 (t, 12  $\times$  CH<sub>2</sub>), and 14.1 (q, Me) [Found:  $M^+$  346.287 0. Calc. for C<sub>23</sub>H<sub>38</sub>O<sub>2</sub>:  $M$ , 346.287 2; other measured mass at  $m/e$  151.074 8 [C<sub>6</sub>H<sub>3</sub>(OMe)<sub>2</sub>CH<sub>2</sub><sup>+</sup>].

**2-Dimethoxy-3-pentadecylbenzene** (5). (a) *By hydrogenation of 1,2-dimethoxy-3-(pentadec-8-ynyl)benzene* (18). Hydrogenation of 1,2-dimethoxy-3-(pentadec-8-ynyl)ben-



zene (0.5 g) in ethyl acetate using 5% palladium-carbon catalyst gave, on work-up, a colourless solid recrystallisation of which from light petroleum (b.p. 40–60 °C) afforded colourless crystals of 1,2-dimethoxy-3-pentadecylbenzene (5) (0.4 g), m.p. 36–37 °C (lit.,<sup>21</sup> m.p. 36–37 °C);  $\nu_{\max}$  3 020, 1 605, and 1 590 (aromatic ring), and 750  $\text{cm}^{-1}$  ( $\text{CH}_2$  groups);  $\tau(\text{CDCl}_3)$  2.9–3.3 (m, 3 H, Ar-H), 6.13 (s), 6.17 (s, 6 H, 2  $\times$  OMe), 7.30 (t, 2 H, Ar- $\text{CH}_2$ ), 8.27 (br s, 2 H,  $\beta$ - $\text{CH}_2$ ), 8.69 (br s, 26 H, 13  $\times$   $\text{CH}_2$ ), and 9.06 (t, (3 H, Me);  $^{13}\text{C}$  n.m.r. ( $\text{CHCl}_3$ ,  $\delta/\text{p.p.m.}$  from  $\text{SiMe}_4$ ) 153.1 (s), 148.2 (s, 2  $\times$  Ar-C-OMe), 136.8 (Ar-C- $\text{CH}_2$ ), 123.5 (d), 122.4 (d), and 111.1 (d) (3  $\times$  Ar-C-H), 60.3 (q) and 55.9 (q) (2  $\times$  OMe), 33.6–28.9 (m), 22.8 (14  $\times$   $\text{CH}_2$ ), and 14.0 (q Me) (Found: C, 79.4; H, 11.7%;  $M^+$ , 348.303 1. Calc. for  $\text{C}_{23}\text{H}_{40}\text{O}_2$ : C, 79.25; H, 11.6%;  $M$ , 348.302 8).

(b) *By direct synthesis.* 1-Bromopentadecane (15.8 g) (b.p. 75 °C at 2 mmHg) (lit.,<sup>22</sup> b.p. 130–131 °C at 6 mmHg) was prepared from palmitic acid (51.6 g), red mercuric oxide (21.8 g), and bromine (32 g) in 1,1,2,2-tetrachloroethane using the Hunsdiecker procedure outlined above for the preparation of 1,7-dibromoheptane.

1-Bromopentadecane (15.8 g) in dry tetrahydrofuran (100 ml) was added to a slurry of 2,3-dimethoxyphenyllithium [prepared from 1,2-dimethoxybenzene (8.14 g) and butyl-lithium in hexane (40 ml, 1.45M-solution)]. The mixture was heated under reflux for 40 h, the progress of the reaction being monitored by t.l.c. After addition of ice and water, the organic layer was dried and the solvents removed to yield an oil, which was partially purified by distillation under reduced pressure (b.p. 150–180 °C at 0.000 5 mmHg) prior to further purification on an alumina (type H) column. Light petroleum (b.p. 40–60 °C) eluted a fraction which was again distilled to give 1,2-dimethoxy-3-pentadecylbenzene (5) as an oil (2.7 g), b.p. 181 °C at 0.000 5 mmHg, which rapidly solidified, m.p. 36–37 °C, identical with the product prepared in (a) above.

#### Demethylation Reactions with Trimethylsilyl Iodide.<sup>18</sup>—

(i) 1,2-Bis(trimethylsilyloxy)-3-[(Z)-pentadec-8-enyl]benzene (3). A solution of the dimethoxypentadecenylbenzene (2) (420 mg) in  $\text{CDCl}_3$  (2 ml) was placed in an n.m.r. tube (masked with aluminium foil to exclude light) and trimethylsilyl iodide (0.35 ml) was added. The reaction was monitored daily by examination of the  $^1\text{H}$  n.m.r. spectrum. After 3 days at room temperature some demethylation had occurred as a partial loss of the OMe signals at  $\tau$  6.35 was noted together with the appearance of new signals at  $\tau$  8.05 (MeI) and 9.85 (Ar-O-SiMe<sub>3</sub>). The reaction temperature was raised thereafter to 50 °C and after 8 days a further portion of trimethylsilyl iodide (0.2 ml) was added (the reagent gives a  $^1\text{H}$  signal at  $\tau$  9.28). The reaction was complete after 17 days.

After removing all volatile constituents, including some free iodine, under reduced pressure at room temperature, the product was isolated by distillation (bulb-to-bulb). 1,2-Bis(trimethylsilyloxy)-3-[(Z)-pentadec-8-enyl]benzene (3) was obtained as an almost colourless oil, b.p. 115–120 °C at 0.000 3 mmHg (350 mg);  $\nu_{\max}$  1 585  $\text{cm}^{-1}$  (aromatic ring);  $\tau(\text{CDCl}_3)$  3.28 (m, 3 H, Ar-H), 4.66 (t, 2 H,  $\text{HC}=\text{CH}$ ), 7.49 (t, 2 H, Ar- $\text{CH}_2$ ), 8.00 (br m, 4 H,  $\text{CH}_2\text{CH}=\text{CHCH}_2$ ), 8.68 (br s, 18 H, 9  $\times$   $\text{CH}_2$ ), 9.17 (t, 3 H, Me), and 9.72 (s) and 9.79 (s) (18 H, 2  $\times$  OSiMe<sub>3</sub>) [Found:  $M^+$ , 462.334 7.  $\text{C}_{27}\text{H}_{50}\text{O}_2\text{Si}_2$  requires  $M$ , 462.334 7; other measured masses at  $m/e$  267.123 5  $\text{C}_6\text{H}_3(\text{OSiMe}_3)_2\text{CH}_2^+$  and 179.052 2 ( $\text{C}_6\text{H}_3\text{O}_2\text{SiMe}_2\text{CH}_2^+$ ). A small quantity of non-volatile material remained whose n.m.r. spectrum lacked the ole-

finic proton signal at  $\tau$  4.66, this being replaced by a new signal at  $\tau$  5.95 indicative of the CH-I system.

(ii) 1,2-Bis(trimethylsilyloxy)-3-pentadecylbenzene (6). A solution of 1,2-dimethoxy-3-pentadecylbenzene (5) (0.5 g) and trimethylsilyl iodide (0.6 ml) in  $\text{CDCl}_3$  (3 ml, containing  $\text{SiMe}_4$ ) was heated at 50 °C for 4 days in an n.m.r. tube, after which time examination of the reaction mixture by  $^1\text{H}$  n.m.r. spectroscopy showed that no methoxy-signals remained. The mixture was worked up as in (i) above by bulb-to-bulb distillation to give 1,2-bis(trimethylsilyloxy)-3-pentadecylbenzene (6) as a colourless oil (0.57 g), b.p. 120–125 °C at 0.000 3 mmHg;  $\nu_{\max}$  1 585  $\text{cm}^{-1}$  (aromatic ring);  $\tau(\text{CDCl}_3)$  3.21 (m, 3 H, Ar-H), 7.45 (t, 2 H, Ar- $\text{CH}_2$ ), 8.68 (br s, 26 H, 13  $\times$   $\text{CH}_2$ ), 9.12 (t, 3 H, Me), 9.70 (s) and 9.76 (s) (18 H, 2  $\times$  OSiMe<sub>3</sub>) [Found:  $M^+$  464.350 3.  $\text{C}_{27}\text{H}_{52}\text{O}_2\text{Si}_2$  requires  $M$ , 464.350 4; other measured mass at  $m/e$  179.052 9 ( $\text{C}_6\text{H}_3\text{O}_2\text{SiMe}_2\text{CH}_2^+$ ).

1,2-Dihydroxy-3-[(Z)-pentadec-8-enyl]benzene (1). 1,2-Bis(trimethylsilyloxy)-3-[(Z)-pentadec-8-enyl]benzene (3) (250 mg) in tetrahydrofuran (5 ml) and water (3 drops) was treated with trifluoroacetic acid (3 drops) and the mixture left in an n.m.r. tube at room temperature. Reaction was observed to be complete after 20 min by a shift in the trimethylsilyloxy-signals to a new higher-field position close to that of  $\text{SiMe}_4$ . Volatile constituents were removed at 60 °C and 0.000 3 mmHg leaving 1,2-dihydroxy-3-[(Z)-pentadec-8-enyl]benzene as a clear oil (150 mg). Attempted distillation of a portion of this oil under high vacuum (0.000 3 mmHg) produced extensive decomposition at temperatures  $>150$  °C. The phenol was too susceptible to aerial oxidation to purify it by column chromatography or t.l.c.;  $\nu_{\max}$  (liquid film) 3 440 (OH), and 1 620 and 1 595  $\text{cm}^{-1}$  (aromatic ring);  $\tau(\text{CDCl}_3)$  3.34 (br s, 3 H, Ar-H), 4.70 (br t, 4 H,  $\text{HC}=\text{CH}$  and 2  $\times$  OH; the triplet became sharper and equivalent to 2 H on addition of  $\text{D}_2\text{O}$ ), 7.43 (t, 2 H, Ar- $\text{CH}_2$ ), 8.07 (t, 4 H,  $\text{CH}_2\text{CH}=\text{CHCH}_2$ ), 8.75 (br s, 18 H, 9  $\times$   $\text{CH}_2$ ), and 9.13 (t, 3 H, Me) (Found:  $M^+$ , 318.255 6.  $\text{C}_{21}\text{H}_{34}\text{O}_2$  requires  $M$ , 318.255 7).

1,2-Dihydroxy-3-pentadecylbenzene (4). 1,2-Bis(trimethylsilyloxy)-3-pentadecylbenzene (6) (450 mg) was desilylated and worked up as described above. The product, 1,2-dihydroxy-3-pentadecylbenzene (300 mg) appeared as a colourless solid, m.p. 58–59 °C (lit.,<sup>7</sup> m.p. 57–58 °C);  $\nu_{\max}$  (Nujol) 3 380 (OH), and 1 620 and 1 595  $\text{cm}^{-1}$  (aromatic ring);  $\tau(\text{CDCl}_3)$  3.31 (br s, 3 H, Ar-H), 4.61 (br s, 2 H, 2  $\times$  OH, disappears on addition of  $\text{D}_2\text{O}$ ), 7.42 (t, 2, Ar- $\text{CH}_2$ ), 8.40 (2 H,  $\beta$ - $\text{CH}_2$ ), 8.74 (br s, 24 H, 12  $\times$   $\text{CH}_2$ ), and 9.12 (t, 3 H, Me) (Found:  $M^+$ , 320.271 4.  $\text{C}_{21}\text{H}_{36}\text{O}_2$  requires  $M$ , 320.271 3).

*Reactions of 2,3-Dimethoxyphenyl-lithium (8).—*(a) *With dimethyl sulphate to give 2,3-dimethoxytoluene (11).* Equimolar quantities (0.05 mol) of butyl-lithium in hexane and 1,2-dimethoxybenzene in ether were allowed to react under reflux for 4 h in a nitrogen atmosphere. An excess of distilled dimethyl sulphate was added and, after the reaction was complete, the volatile constituents were removed under reduced pressure leaving an oil. Dilute hydrochloric acid was added to the oil and the mixture extracted with light petroleum (b.p. 60–80 °C). After washing the extract with aqueous sodium hydrogencarbonate solution it was dried and the solvent evaporated. The oil remaining was distilled under reduced pressure (1 mmHg) and the distillate examined by g.l.c. [Pye 104, 9-ft glass column, 30% OV-17 on Chromosorb W (100–120 mesh), 200 °C, flame-ionisation detector]. The results confirmed that

only two components were present, these being 1,2-dimethoxybenzene (7) and 2,3-dimethoxytoluene (11) (both identified by peak enhancement using authentic standards). The area contained under the peaks (determined by weight and by use of a planimeter) indicated a yield of 80% of 2,3-dimethoxytoluene (11).

(b) *With tributyltin chloride to give tributyl-(2,3-dimethoxyphenyl)tin.* 2,3-Dimethoxyphenyl-lithium in ether, prepared as in (a), was treated with an excess of tributyltin chloride. After heating the mixture under reflux for 1 h, it was left overnight at room temperature and then water was added. The organic layer was washed successively with dilute hydrochloric acid, water, aqueous sodium hydrogencarbonate, and finally water. Solvents were removed from the dried extract and the oil remaining distilled under reduced pressure (bulb-to-bulb) to give tributyl-(2,3-dimethoxyphenyl)tin (12) as a colourless liquid, b.p. 125 °C at 0.000 3 mmHg, in almost quantitative yield;  $\nu_{\text{max}}$  (liquid film) 3 050 and 1 580 (aromatic ring), and 1 260  $\text{cm}^{-1}$  (Ar-OMe);  $\tau$  (neat liquid) 3.15 (m, 3 H, Ar-H), 6.24 (s) and 6.38 (s) (6 H,  $2 \times \text{OMe}$ ), 8.60–8.85 (m, 18 H,  $9 \times \text{CH}_3$ ), and 9.08 (t, 9 H,  $3 \times \text{Me}$ );  $M^+$  not present, first major peak at  $m/e$  371 ( $M^+ - \text{C}_4\text{H}_9$ ) (Found: C, 56.60; H, 8.68.  $\text{C}_{20}\text{H}_{36}\text{O}_2\text{Sn}$  requires C, 56.23; H, 8.49%).

(c) *Quenching reactions with tributyltin chloride.* The retention times of 1,2-dimethoxybenzene (1.4 min), 1,7-dibromoheptane (1.8 min), tetrabutyltin (1.9 min), tributyltin chloride (2.4 min), tributyl-(2,3-dimethoxyphenyl)tin (12) (8.4 min), and 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9) (9.8 min) were determined separately and mixed together using the g.l.c. column conditions described in (a) but at a temperature of 240 °C.

Reaction of 2,3-dimethoxyphenyl-lithium (8) with 1,7-dibromoheptane was allowed to take place initially at  $-80$  °C and then room temperature. Samples were withdrawn from the reaction at appropriate intervals, quenched with an excess of tributyltin chloride, and the mixture of products examined by g.l.c. These results showed the presence of 1,2-dimethoxybenzene (7), 1,7-dibromoheptane, and the aryltributyltin (12), but no 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9).

The same reaction mixture was heated under reflux for 10 min and a sample withdrawn and quenched as before with an excess of tributyltin chloride. G.l.c. examination showed an increase in the quantity of 1,2-dimethoxybenzene (7), a decrease in the quantity of 1,7-dibromoheptane, and the appearance for the first time of 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9). The aryltributyltin (12) was absent.

After heating for 30 and then 60 min, respectively, under reflux, the reaction mixture was again examined by the use of the quenching technique followed by g.l.c. analysis. No further change in the product composition could be detected in either case.

(d) *Reactions of 2,3-dimethoxyphenyl-lithium (8) in the presence of NNN'-tetramethylethylenediamine.* 2,3-Dimethoxyphenyl-lithium (8) was generated as in (a) using hexane (150 ml) in place of ether, and with the addition of NNN'-tetramethylethylenediamine (10 ml). 1,7-Dibromoheptane (0.05 mol) was added at  $-80$  °C and the mixture then warmed and heated under reflux for 15 h. Worked up as in (a), the product was distilled under high vacuum to give two fractions, (i) b.p. 50–60 °C at 0.000 5 mmHg, and (ii) b.p. 95–105 °C at 0.000 5 mmHg. Both fractions

were analysed by g.l.c.–mass spectroscopy: fraction (i) consisted mainly of 1,2-dimethoxybenzene (7) and 1,7-dibromoheptane, in addition to some minor constituents identified as shown in the Table.

Fraction (ii) contained mainly 1-bromo-7-(2,3-dimethoxyphenyl)heptane (9) (23%).

*Extraction of Two Species of Anacardiaceae.*—(a) *Semecarpus vitiensis Engl.* Shavings (258 g) from the heartwood of the tree collected in Fiji were Soxhlet-extracted with chloroform for 24 h. Removal of the solvent under reduced pressure yielded a brown sticky residue (3.37 g). Methylation of this extract with an excess of dimethyl sulphate, and anhydrous potassium carbonate, in acetone under nitrogen during 24 h gave a crude mixture of methylated products (6.3 g). Column chromatography enriched the

G.l.c.–mass spectrometry data \* for minor peaks in fraction (i)

Peak	Retention time/min	$M^+$	Possible formula	Possible structure
1	11.4	194	$\text{C}_{12}\text{H}_{18}\text{O}_2$	(16)
2	13.2	166	$\text{C}_{10}\text{H}_{14}\text{O}_2$	(14)
3	13.7	180	$\text{C}_{11}\text{H}_{16}\text{O}_2$	(15)
4	17.4	138	$\text{C}_8\text{H}_{10}\text{O}_2$	(7)
5	19.7	152	$\text{C}_9\text{H}_{12}\text{O}_2$	(11)

\* A.E.I. MS902 linked to a Pye 104 g.l.c. containing an 18-ft glass column packed with 3% SE30 on Chromosorb W(100–120 mesh); carrier gas helium, temperature programme 140–200 °C at 6 °C  $\text{min}^{-1}$ .

fraction in which methylated urushiols were expected (light petroleum, b.p. 40–60 °C, on silica gel) to be found if present. H.p.l.c. analysis of this fraction using a 250  $\times$  4 mm stainless-steel Porasil-10 column [eluted with iso-octane–chloroform (90:10), 5  $\mu\text{l}$  sample, u.v. detector] failed to reveal any methylated urushiols.

Under these conditions the acetylene (18), the olefin (2), and the saturated methyl urushiol (4) had the following retention times; 34.4 min, 12.7 min, and 17.2 min, respectively.

(b) *Melanorrhoea beccari Engl.* The dried bark of the tree collected in Borneo was ground to a powder (970 g) and Soxhlet-extracted with (i) light petroleum (b.p. 40–60 °C) to give a thick yellow oil (24.5 g, 2.5%) and then (ii) with methanol to give a dark brown gum (37.7 g, 3.9%). The methanol extract (37.7 g), anhydrous potassium carbonate (55 g), and acetone (300 ml) were heated under reflux whilst dimethyl sulphate (31.5 g) was added dropwise during 1 h. After heating for 24 h, the mixture was worked up by separating the inorganic materials prior to removal of the solvent from the filtrate.

*Isolation of Methyl 3,4,5-Trimethoxybenzoate (21).*—The methylated extract (3 g) was chromatographed over silica gel. The fractions eluted from the column were monitored by t.l.c. using the dimethylurushiols (2) and (5) as reference standards. None of the components in the mixture corresponded with the standards. The most abundant fraction, eluted with light petroleum (b.p. 60–80 °C)–chloroform (1:1) (1.24 g) was further purified by column chromatography and preparative t.l.c. [silica gel chloroform–ethyl acetate (95:5),  $R_F$  0.16, dark blue under u.v. light] to give methyl 3,4,5-trimethoxybenzoate (21) identical (i.r.,  $^1\text{H}$  n.m.r., and m.p.) with an authentic sample prepared from gallic acid (22) (Found:  $M^+$ , 226.084 3. Calc. for  $\text{C}_{11}\text{H}_{14}\text{O}_5$ :  $M$ , 226.084 1).

*Isolation of Gallic Acid* (22).<sup>23</sup>—The crude methanol extract from the bark (25 g) was Soxhlet-extracted with ether, and this extract worked up by chromatography over silica gel. Elution with ether gave a fraction which on trituration with benzene left an insoluble fraction (1.5 g). Preparative t.l.c. [silica gel, ethyl acetate–acetic acid (99 : 1)  $R_F$  0.7] gave gallic acid (22) (30 mg), identical with an authentic sample (mixed m.p. and i.r. spectra).

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