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Synthesis of Methyl 17-(3,5-Dibromo-4-methoxyphenyl)-heptadeca-2,4,6,8,10,12,14,16-octaenoate

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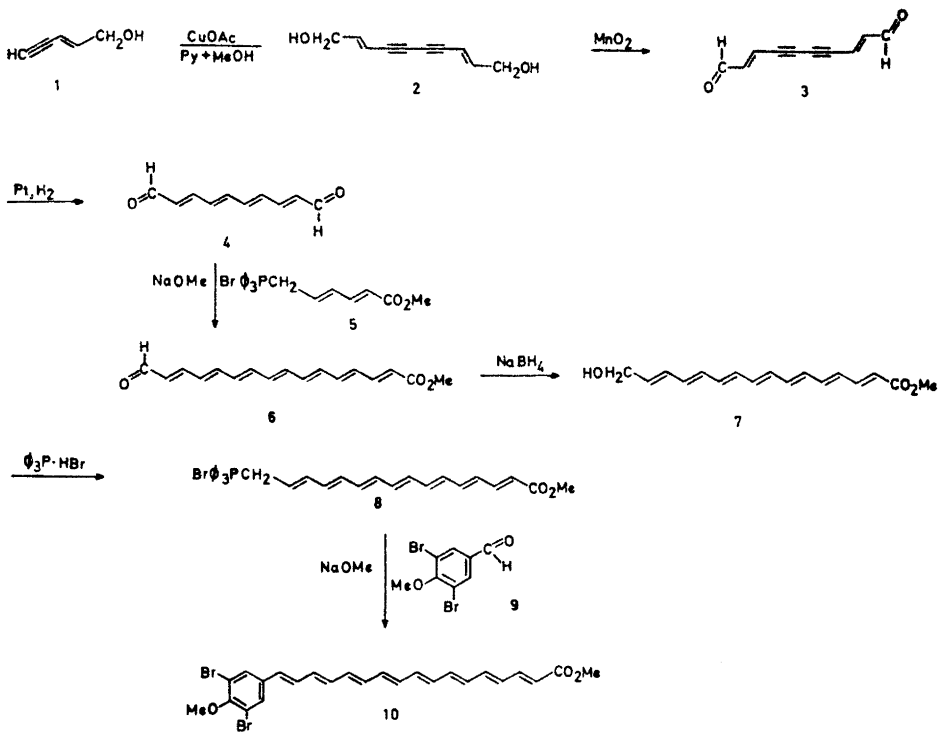
The synthesis of methyl 17-(3,5-dibromo-4-methoxyphenyl)-heptadeca-2,4,6,8,10,12,14,16-octaenoate (*10*) is reported. The pertinent physical data associated with this type of structure is given and includes electronic absorption, infrared and mass spectra.

The intermediates, some of which are new compounds, have been fully characterized.

In the course of the investigations on the pigments of the phytopathogenic bacterium *Xanthomonas juglandis*,[1] one of the structures considered for the main pigment was a conjugated aryl octaene methyl ester in which the aromatic ring was substituted by two bromine atoms and one methoxy group. The substitution pattern on the phenyl ring was not known with certainty but IR data suggested the presence of isolated hydrogens on the ring. From biosynthetic considerations a 3,5-dibromo-4-methoxy substitution pattern was considered plausible. The various physical properties associated with this type of structure could not, on the basis of the available literature, be precisely predicted and necessitated total synthesis in order to compare physical and chemical properties. The synthesis was so designed that alternative substitution patterns on the ring could be achieved with only slight changes in the general scheme. Of particular importance is the intermediate phosphonium salt *8* from which a number of aromatic polyenes can be constructed *via* a one step reaction.

RESULTS AND DISCUSSION

Pent-2-en-4-yn-1-ol (*1*) was coupled in a Glaser [2] reaction to give the acetylenic C_{10}-diol *2*, Scheme 1. Attempts to hydrogenate *2* to the corresponding tetraene with Lindlar [3] catalyst met with difficulty, but after MnO_2 oxidation to the dial *3* selective hydrogenation to the dial *4* proceeded smoothly. The conjugated system of *4* was extended by a Wittig reaction with the triphenylphosphonium salt of methyl sorbate (*5*) to give the heptaene *6*. Selective



Scheme 1.

reduction of the aldehyde function with sodium borohydride gave *7* which was converted to the phosphonium salt *8*. Finally, condensation of the phosphoran of *8* with the aromatic aldehyde *9* gave the desired product *10*.

10 melted at 245 – 247°. The *trans*-isomer was extremely insoluble in all common organic solvents and as a result no PMR spectrum was obtained. The same solubility property was noted for dimethylcortisalin (*11*) and *Xanthomonas* pigment *1* (*12*).[1,4]

Synthetic *10* could not be separated from *Xanthomonas 1* (*12*) when chromatographed on silica gel G plates or kieselguhr paper.

The visible absorption spectrum of *10* had λ_{max} 429, 450, and 478 nm in chloroform and 430, 455, and 483.5 nm in pyridine (Fig. 2). Compared to the pigments isolated from *Xanthomonas juglandis*,[1] which have similar proposed structures, the visible spectrum of *10* was hypsochromically displaced by 3 nm in chloroform and showed slightly more fine-structure. These small differences may reflect a difference in the substitution pattern on the phenyl rings. Compared to dimethylcortisalin (*11*),[1,4] which has a chromophore one double bond shorter (Fig. 1), the visible spectrum of *10* displayed much more fine-structure. Some of the increase in fine-structure can be accounted for by the extended chromophore of *10 vs. 11*.[5] However, it is also possible that

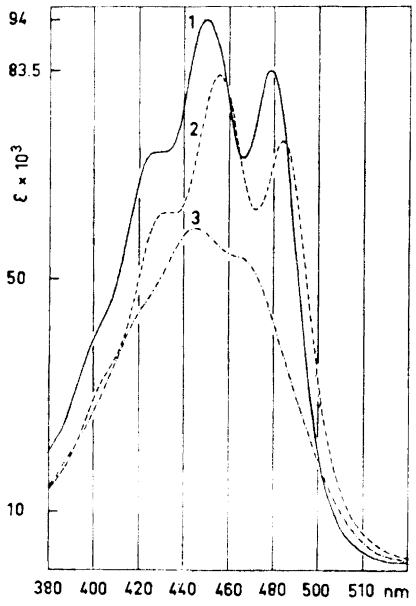
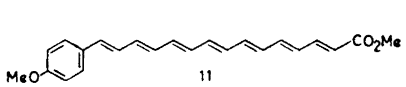


Fig. 1. Absorption spectra in visible light of *10* in $CHCl_3$ (curve 1), *10* in pyridine (curve 2) and *12* in pyridine (curve 3). Extinction values valid only for *10* in $CHCl_3$.

the bromine substituents on the phenyl ring of *10* may influence the fine-structure.



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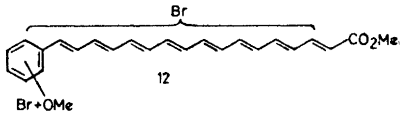

12

The IR-spectrum of *10* is given in Fig. 2. Bands at 1710 and 1010 cm^{-1} assigned to α,β-unsaturated ester [6] and C–H out of plane vibrations of *trans*-disubstituted double bounds are consistent with the same assignments made

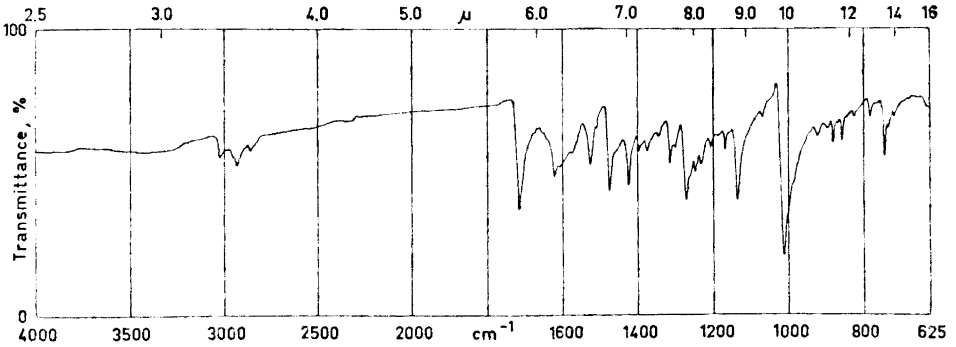

Fig. 2. Infrared spectrum (KBr) of *10*.

for dimethylcortisalin (*11*) and the pigments isolated from *Xanthomonas juglandis*.[1] The latter band, as previously noted,[1] is shifted to higher frequencies than those associated with conjugated polyenes of the carotenoid type. A band at 1265 cm^{-1} is attributed to a phenolic methoxy group [6] and absorption at 1138 cm^{-1} assigned to the C–O ester stretch.[6] Corresponding assignments have been made for bands noted in the spectra of *11* and Xanthomonas pigment *1*.[1] Absorption arising from C–H out of plane deformations on an aromatic ring occurred at 880 and 855 cm^{-1} in the spectrum of *10*. No bands occurred at 1395 or 1450 cm^{-1} at which positions strong absorption was found in the spectrum of *Xanthomonas* pigment *1* (*12*).[1]

Of particular interest was the mass spectrometric fragmentation pattern for *10* (Fig. 3). Loss of C_6H_6 from the molecular ion probably reflects the thermal

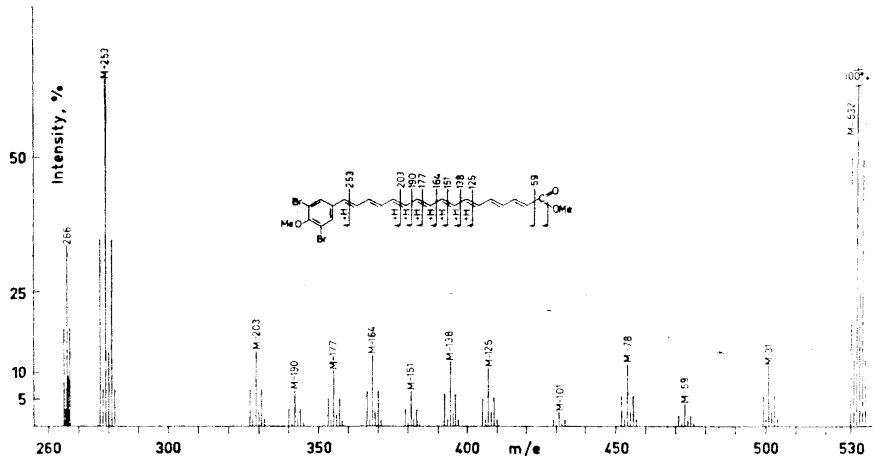

Fig. 3. Mass spectrum of *10*.

expulsion (no metastable ion) of benzene easily envisioned after *trans-cis*-isomerization of the polyene chain, *cf.* Ref. 7. There was no observable loss of HBr or bromine radical from the molecular ion or any fragment ion in the upper region of the spectrum. All prominent ions in the upper mass region were associated with fragmentation of the polyene chain or from the ester function. The fragmentation of *10* is then different from that observed for the Xanthomonas pigment *1* (*12*),[1] which shows a strong ion attributed to loss of HBr from the molecular ion.

In conclusion, comparison of the physical properties of synthetic *10* with pigment *1* isolated from *Xanthomonas juglandis* clearly showed that they are not identical. The difference in structures of *10* and *Xanthomonas* pigment *1* (*12*) probably lies in the substitution pattern on the aromatic ring.

EXPERIMENTAL

General. Solvents were either of analytical grade or distilled before use. All of the reactions involving polyenes were carried out under a blanket of nitrogen and in dim light.

Comparative chromatography was carried out on silica gel HF_{254} plates developed with mixtures of petroleum ether and acetone or Schleicher & Schüll paper No. 287 (kieselguhr paper) developed with benzene.

Melting points were determined on an Electrothermal Melting Point Apparatus in sealed evacuated tubes and are uncorrected.

Electronic absorption spectra were recorded on a Coleman Hitachi 124 Spectrometer. IR spectra were obtained from KBr disks or liquid films on a Perkin Elmer 257 instrument and PMR spectra were generally recorded in $CDCl_3$ solutions in a Variant A-60 A instrument. Mass spectra were registered with an AEI MS902 instrument at 70 eV.

Deca-2,8-diene-4,6-diyne-1,10-diol (*2*). Pent-2-en-4-yn-1-ol (15 g) was slowly added over a period of 30 min to a stirred solution of copper(I) acetate (30 g) in pyridine-MeOH (300 ml, 1:1).[8] The mixture was stirred for an additional 2 h after which water was added and the solution extracted with ether. After drying over Na_2SO_4 the organic solvents were removed under vacuum leaving a solid which was recrystallized from methanol and yielded a total of 9.75 g (65 %) of *2*. The diol *2* was kept in the dark under nitrogen since when exposed to light and air *2* rapidly turned dark brown. *2*[8,9] had an m.p. of 160 – 161°, λ_{max} (methanol) 312, 292, 275, and 260 nm; ν_{max} (KBr) 3300 broad (OH), 2120 (C≡C), 1630 (C=C), 1090 (C–O), 950 (CH=CH) and 900 cm^{-1}; τ (deuterated acetone) 7.02 (2 H, O*H*), 5.80 dd (4 H, $J_{1,2}$ = 4 Hz, $J_{1,3}$ = 1.5 Hz, CH_2OH), 4.15 dt (2 H, unresolvable, H-3), 6.5 dt (2 H, $J_{2,3}$ = 16 Hz, $J_{1,2}$ = 4Hz, H-2); *m/e* 162 (M), 144(M – 18), 133(M – 29), 121(M – 41) and 115(M – 18 – 29).

Deca-2,8-diene-4,6-diyne-1,10-dial (3). *2* (9 g) in acetone (50 ml) was cooled to 5° and treated with MnO_2 (4 g) at that temperature with stirring for 1 h. The reaction was monitored by TLC and additional MnO_2 was added as required allowing 1 h between the additions of MnO_2. When the chromatogram showed no starting material, the mixture was filtered and the solvent removed under vacuum. The resulting solid was recrystallized from CH_2Cl_2-acetone solution to give 6.3 g (70 %) of dial *3*; m.p. 144°;[10] λ_{max} (ether) 346, 323, 302, and 277 nm; ν_{max} (KBr) 3000 (=CH), 2118 (C≡C), 1675 (conj. C=O), 1115 (C–O), 2850 (C–H) and 970 (HC=CH) cm^{-1}; τ($CDCl_3$) 3.40 – 3.32 (4 H, olefinic), 0.35 d, 0.43 d (J_{H-H} = 5 Hz, equal quantities of *cis-* and *trans*-isomers, aldehydic H); *m/e* 158 (M), 129(M – 29) and 102(M – 56).

Deca-2,4,6,8-tetraene-1,10-dial (4). *3* (5 g) in 50 ml of acetone-ethyl acetate (1:1) and Lindlar catalyst (0.5 g) was hydrogenated at room temperature in the dark. After the calculated uptake of hydrogen the solution was filtered and the solvent evaporated. The brownish semisolid was dissolved in $CHCl_3$, a trace of I_2 added and the solution refluxed for 2 h to effect isomerization to the *trans*-isomer.[11] After evaporating the solution to dryness the product was crystallized from acetone-CH_2Cl_2 solution to give 2.25 g (45 %) of *4*; m.p. 134°; λ_{max} (methanol) 339, 352, (ethyl ether) 320, 335, 352 nm; ν_{max} (KBr) 3040 (=CH), 2820, 2740 (C–H), 1670 (C=O), 1620 (C=C), 1135 (C–O) and 975 (*trans* CH=CH) cm^{-1}; τ($CDCl_3$) 2.1 – 4.0 (8 H, olefinic, non-resolvable), 0.32 d (J = 8 Hz, aldehydic); *m/e* 162 (M), 129(M – 29) and 121(M – 49).

5-Carbomethoxy-2,4-pentadienyl-triphenylphosphonium bromide (*5*). Methyl sorbate (50 g), *N*-bromosuccinimide (70 g) and benzoyl peroxide (0.2 g) were mixed with CCl_4 (25 ml) in a 3-necked round bottom flask fitted with a condenser. The mixture was heated while stirring and the CCl_4 allowed to distill off until the temperature of the reaction mixture rose to 111°. Stirring was stopped and the reaction mixture held at 111 – 115° while the mixture turned orange in color. After 15 min a small aliquot (0.05 ml) was withdrawn which showed no activity when tested against KI in dilute H_2SO_4. The reaction mixture was cooled and worked-up in the normal manner. Double distillation gave methyl ε-bromosorbate (19 g, 15 %); b.p. 81 – 84°/0.75 Torr.[12,13]

Methyl ε-bromosorbate (10 g) and triphenylphosphine (20 g) were refluxed in benzene (50 ml) for 20 h. The salt *5* crystallized from solution as it was formed but later could not be recrystallized after a number of attempts and was used without further purification; yield 15 g (64 %); τ($CDCl_3$) 6.32 (3 H, OCH_3, 4.98 dd (2 H, J_{H-P} = 17 Hz, J_{H-H} = 8 Hz, CH_2 – 1), 4.4 – 3.6 (4 H, olefinic) and 2.4 – 2.1 (15 H, aromatic).

Methyl 16-oxo-hexadeca-2,4,6,8,10,12,14-heptaenoate (6). Sodium methoxide was slowly added to a stirred methanolic solution of *5* (3 g) under a blanket of nitrogen until the phosphonium salt was totally converted to the corresponding phosphoran. Two-fold excess of *4* (2 g) in methanol was rapidly added and the solution allowed to stir at room temperature for 1 h and then for an additional 1 h at 50 °. Water was added and the mixture extracted with $CHCl_3$, the organic phase dried over NaCl and evaporated under vacuum. The solid residue was chromatographed on an Al_2O_3 (1 % H_2O) column developed with benzene from which *6* (1 g, 58 %) was isolated; crystallized from ether *6* melted at 154°; λ_{max} ($CHCl_3$) 405, 423, 450, (ethyl ether) 392, 409, 433 and (acetone) 395, 414, 439 nm; ν_{max} (KBr) 2930 – 3020 (CH), 1720 (conj. ester), 1665 (conj. aldehyde), 1620, 1590 (C=C), 1140 (C – O) and 1010 (CH=CH) cm^{-1}; τ ($CHCl_3$) 6.23 (3 H, OCH_3), 2.9 – 4.1 (14 H, olefinic), 0.35 d (1 H, $J = 7$ Hz, aldehydic H); *m/e* 270(M), 255(M – 15), 239(M – 31) and 211(M – 59).

Methyl 16-hydroxy-hexadeca-2,4,6,8,10,12,14-heptaenoate (7). A methanolic solution of *6* (1 g) cooled to 0° was treated with $NaBH_4$ until TLC analysis showed complete conversion to the mono-ol *7*. The solution was worked up in the normal manner and *7* (0.9 g, 89 %) isolated and purified on a deactivated Al_2O_3 (2 % H_2O) column developed with benzene-5 % ether; λ_{max} (ether) 375, 389, 407, ($CHCl_3$) 380, 397, 416 nm; ν_{max} (KBr) 3260 (OH), 2960 – 3030 (CH), 1715 (conj. ester), 1620 (C=C),1335 (C – O), 1140 (C – O) and 1010 (CH=CH) cm^{-1}; τ ($CDCl_3$) 6.25 (3 H, OCH_3), 5.75 d (2 H, $J = 6$ Hz, $CH_2 - 1$), 3.0 – 4.3 (14 H, olefinic); *m/e* 272(M), 257(M – 15), 241(M – 31), 213(M – 59), and 196 (M – 78).

15-Carbomethoxypentadeca-2,4,6,8,10,12,14-heptenyl-triphenylphosphonium bromide (8). *7* (0.9 g) in $CHCl_3$ (5 ml), was stirred with triphenylphosphine hydrobromide (2.5 g) at 20° in the dark for 15 h. The solvent was evaporated and the residue triturated with ethyl ether from which the Wittig salt *8* (0.75 g, 38 %) was collected as a finely divided solid. No attempt was made to further purify the product.

3,5-Dibromo-4-methoxybenzaldehyde (9). *p*-Hydroxybenzaldehyde (15 g) was brominated according to the procedure described by Brink [14] to obtain 3,5-dibromo-4-hydroxybenzaldehyde, m.p. 182 – 183° from MeOH – H_2O; λ_{max} (MeOH) 273 nm; ν_{max} (KBr) 3140, 1665, 1595, 1570, 1550, 1300, 1230, 1040, 900 and 830 cm^{-1}; τ($CDCl_3$) 4.67 (1 H, O*H*), 1.92 (2 H, aromatic), 0.13 (1 H, aldehydic); *m/e* 278, 280, 282 (1:2:1, M). 3,5-Dibromo-4-hydroxybenzaldehyde was converted into the sodium salt and thence to the methoxy derivative *9* using the procedure described by Lindemann;[15] m.p. 85 – 87° from petroleum ether, λ_{max} (MeOH) 271 nm; ν_{max} (KBr) 1680, 1550, 1470, 1260, 1205, 1185, 980, and 875 cm^{-1}; τ ($CDCl_3$) 6.04 (3 H, OCH_3), 1.97 (2 H, aromatic), 0.15 (1 H, aldehydic); *m/e* 292, 294, 296 (1:2:1, M).

Methyl 17-(3,5-dibromo-4-methoxyphenyl)-heptadeca-2,4,6,8,10,12,14,16-octaen-1-oate (10). Sodium methoxide was slowly added to a stirred solution of *8* (200 mg) and *9* (200 mg) and the mixture allowed to stir for 1 h at 20° and then 2 h at 50°. Water was added and the solution was filtered to remove *10* some of which had precipitated. The solution was extracted with $CHCl_3$ and the extract combined with the solid product isolated from the filtration. The product was chromatographed on silica gel G from which all *trans-10* was isolated and crystallized; m.p. 245 – 247° from MeOH-$CHCl_3$. The crystalline product was slightly soluble in $CHCl_3$, CH_2Cl_2, pyridine, DMSO, and acetone; insoluble in petroleum ether, MeOH, ethyl ether, CCl_4, and dioxane. The visible absorption spectrum had λ_{max} ($CHCl_3$) 429, 450 ($\varepsilon = 94\,000$), and 478 nm ($\varepsilon = 83\,500$), (pyridine) 430, 455, and 483.5 nm; ν_{max} (KBr) 3050 – 2900 (CH), 1710 (conj. ester), 1620 (C=C), 1265 (OMe), 1038 (C – O), 1010 (HC=CH), 880 (isolated aromatic CH), 855 and 745 cm^{-1} (aromatic, CH); *m/e* 530, 532, 534 (1:2:1, M, for fragmentation pattern see structure *10*), 499, 501, 503 (M – 31), 471, 473, 475 (M – 59), 452, 454, 456 (M – 78), 405, 407, 409 (M – 125), 392, 394, 396 (M – 138), 379, 381, 383 (M – 151), 366, 368, 370 (M – 164), 353, 355, 357 (M – 177), 340, 342, 344 (M – 190), 327, 329, 331 (M – 203), 277, 279, 281 (M – 253), 265, 266, 267 (doubly charged ion).

Synthetic *10* could not be separated from *Xanthomonas 1* (*12*) when co-chromatographed on S & S kieselguhr paper developed with benzene ($R_F = 0.78$) or on silica gel G plates developed with petroleum ether-acetone, 80:20 ($R_F = 0.80$).

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