Metabolites from the Purple Heartwood of Mimosoideae. Part 2.[1] *Acacia carnei* Maiden: Isolation, Synthesis, and Reactions of Crombeone

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The range of natural peltogynoid-type chalcone, flavonol, and dihydroflavonol analogues is extended by the recognition of carnein, β-photomethylquercitin, and (+)-2,3-*trans*-crombeone in the purple heartwood of *Acacia carnei*.

The first synthesis of a 2,3-*trans*-peltogynone, crombeone tetramethyl ether, is effected and its catalytic reduction leads to a 2,3-*trans*-3,4-*cis*-peltogynol analogue. Crombeone itself is subject to a variety of methylene insertion reactions with diazomethane.

CONTINUED extension of our phytochemical survey of Australian and South African *Acacia* species [1,2] includes a more detailed examination of the purple heartwood of *Acacia carnei* Maiden, a phyllodinous tree endemic to Australia. Together with *A. crombei*, *A. peuce*,[1] and *A. fasciculifera* it is differentiated chemically, by the selective occurrence of peltogynol analogues, from several other peltogynoid-containing species previously examined [2-7] in which peltogynol and mopanol analogues coexist.

The deep purple heartwood contains both resorcinol- and phloroglucinol-type analogues of (+)-peltogynol (1a). Significant among the latter group is (+)-2,3-*trans*-crombeone (2a), a 5-hydroxypeltogynone, representing the first dihydroflavonol analogue of (+)-peltogynol with a phloroglucinol A-ring to be correctly identified.[8] Others have subsequently been recognized.[2,7,9] Phenolic metabolites from the heartwood of *A. carnei* also include the peltogynoids (+)-2,3-*trans*-3,4-*trans*- (1a) and (+)-2,3-*trans*-3,4-*cis*-peltogynols (1b), (+)-2,3-*trans*-peltogynone (2b), carnein (3a) (the chalcone analogue of peltogynol), peltogynin (4a) (its flavonol analogue), and β-photomethylquercitin (4b) (the flavonol analogue of crombeone) as well as the flavonoids: fisetin (5a) and the dihydroflavonols, (+)-fustin (6a), (+)-dihydroquercetin (6b), and (+)-3-*O*-methylfustin (6c). All compounds were identified by n.m.r. and mass spectrometry, and the structures confirmed by comparison of their optical rotation and circular dichroism with those of known reference samples.

The absolute configurations of (+)-2,3-*trans*-peltogynone (2b) and (+)-2,3-*trans*-crombeone (2a) were determined as 2*R*,3*R* by c.d. comparison of peltogynone trimethyl ether (2d) (2*R*,3*R*), obtained by oxidative conversion (MnO_2–$CHCl_3$) from tri-*O*-methylpeltogynol (1c) (2*R*,3*S*,4*R*),[3] with its natural counterpart (2d) and with tetra-*O*-methylcrombeone (2c).

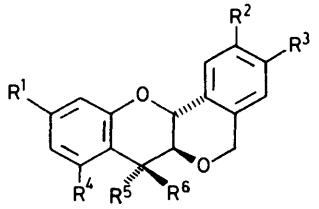
Initial attempts at synthesizing the tetramethyl ether of crombeone (2c) (*cf.* Scheme 1) include steps along lines [(10) ⟶ (13)] developed by Clark-Lewis and Mahandru [10] in the synthesis of 2,3-*cis*-3,4-*cis*-peltogynol trimethyl ether. The chalconecarboxylate (10) used as starting material was prepared from *m*-opianic acid (derived from veratric acid [11]) and 2-hydroxy-4,6-dimethoxyacetophenone (obtained by partial methylation of phloroacetophenone with diazomethane following a Hoesch condensation of phloroglucinol with acetonitrile) *via* an Aldol condensation. Optimum yields were obtained under conditions involving a minimum of ethanol, but contrary to experience with general methods of chalcone synthesis, no spontaneous precipitation occurs. Acidification, however, not only effects the desired precipitation, but is accompanied by isomerization to the phthalide (11) (*cf.* Clark-Lewis and Mahandru [10]) which is apparently reversible with alkali.

The [2]benzopyrano[1]benzopyran (12) is obtained by application of the Algar–Flynn–Oyamada reaction to the phthalide (11). Under the alkaline conditions of this reaction the phthalide (11) most likely undergoes reverse isomerization to the chalcone (10), followed by epoxidation and C-ring cyclization of the latter. The presumed dihydroflavonol-2′-carboxylic acid intermediate leads to the 2,3,8,10-tetramethoxy[2]benzopyrano[4,3-*b*]-[1]benzopyran-5,7-dione (12) *via* oxidation and subsequent D-ring cyclization during acidification. No indication of the dihydro-analogue, as observed by Brown and McBride [12] under similar conditions, was obtained.

Contrary to expectations [13] compound (12) does not undergo the desired reduction to the flavonol analogue (13), but yields a complicated mixture of products under a variety of conditions. Since this unsuccessful step should have lead to the β-photomethylquercetin derivative (15a), this compound was prepared directly from the pentamethyl ether of quercetin (14) by photooxidative cyclization as described by Waiss and Corse.[14,15]

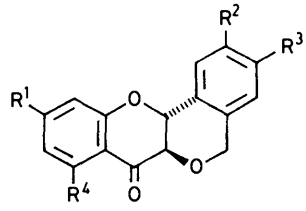
Photolysis of the pentamethyl ether (14) at 350 nm in methanol (with limited access of atmospheric oxygen) for 7 h yields both the tetra-*O*-methyl-β-photomethylquercetin (15a) (43%) and the isomeric mopanol analogue, the tetra-*O*-methyl-α-photomethylquercetin (15b) (20%). The lower proportion of the latter, which appears to be the less stable isomer, may be due to oxidative decomposition, but these much improved yields (*cf.* Waiss and Corse [14,15]) of both products probably result from more favourable reaction conditions. The tetra-*O*-methyl-β-photomethylquercetin (15a) exhibits characteristics (diagnostic sea-green fluorescence

under u.v. light; yellow colouration with formaldehyde–sulphuric acid; R_F 0.06) under t.l.c. conditions [1,2-dichloroethane–acetone (9 : 1)] which are identical to those of the same derivative of a compound observed in the heartwood extracts of both *A. carnei* and *A. crombei*.



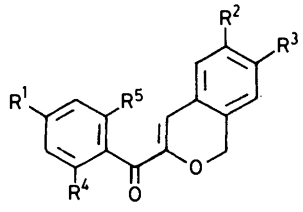
(1)

a; $R^1 = R^2 = R^3 = R^5 = OH$; $R^4 = R^6 = H$
b; $R^1 = R^2 = R^3 = R^6 = OH$; $R^4 = R^5 = H$
c; $R^1 = R^2 = R^3 = OMe$; $R^4 = R^6 = H$; $R^5 = OH$
d; $R^1 = R^2 = R^3 = OMe$; $R^4 = R^5 = H$; $R^6 = OH$
e; $R^1 = R^2 = R^3 = R^4 = R^6 = OH$; $R^5 = H$
f; $R^1 = R^2 = R^3 = R^4 = OMe$; $R^6 = OH$; $R^5 = H$



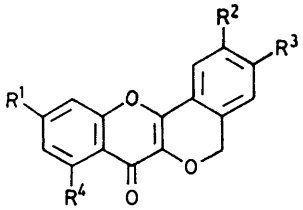
(2)

a; $R^1 = R^2 = R^3 = R^4 = OH$
b; $R^1 = R^2 = R^3 = OH$; $R^4 = H$
c; $R^1 = R^2 = R^3 = R^4 = OMe$
d; $R^1 = R^2 = R^3 = OMe$; $R^4 = H$
e; $R^1 = R^2 = R^3 = OMe$; $R^4 = OH$



(3)

a; $R^1 = R^2 = R^3 = R^5 = OH$; $R^4 = H$
b; $R^1 = R^2 = R^3 = R^4 = R^5 = OH$
c; $R^1 = R^2 = R^3 = R^5 = OMe$; $R^4 = H$



(4)

a; $R^1 = R^2 = R^3 = OH$; $R^4 = H$
b; $R^1 = R^2 = R^3 = R^4 = OH$
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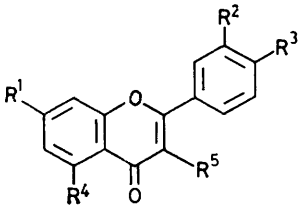
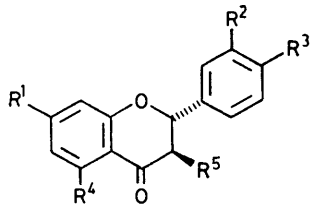
d; $R^1 = R^2 = R^3 = R^4 = OMe$



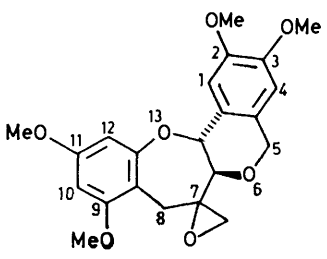
(5)

a; $R^1 = R^2 = R^3 = R^5 = OH$; $R^4 = H$
b; $R^1 = R^2 = R^3 = R^5 = OMe$; $R^4 = H$
c; $R^1 = R^2 = R^3 = R^4 = R^5 = OH$

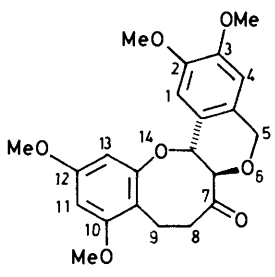


(6)

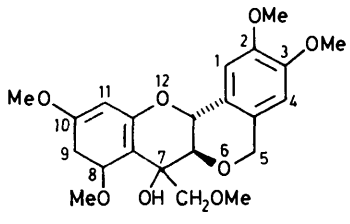
a; $R^1 = R^2 = R^3 = R^5 = OH$; $R^4 = H$
b; $R^1 = R^2 = R^3 = R^4 = R^5 = OH$
c; $R^1 = R^2 = R^3 = OH$; $R^4 = H$; $R^5 = OMe$
d; $R^1 = R^2 = R^3 = R^5 = OMe$; $R^4 = H$
e; $R^1 = R^2 = R^3 = OMe$; $R^4 = H$; $R^5 = OH$
f; $R^1 = R^2 = R^3 = R^4 = OMe$; $R^5 = OH$



(7)



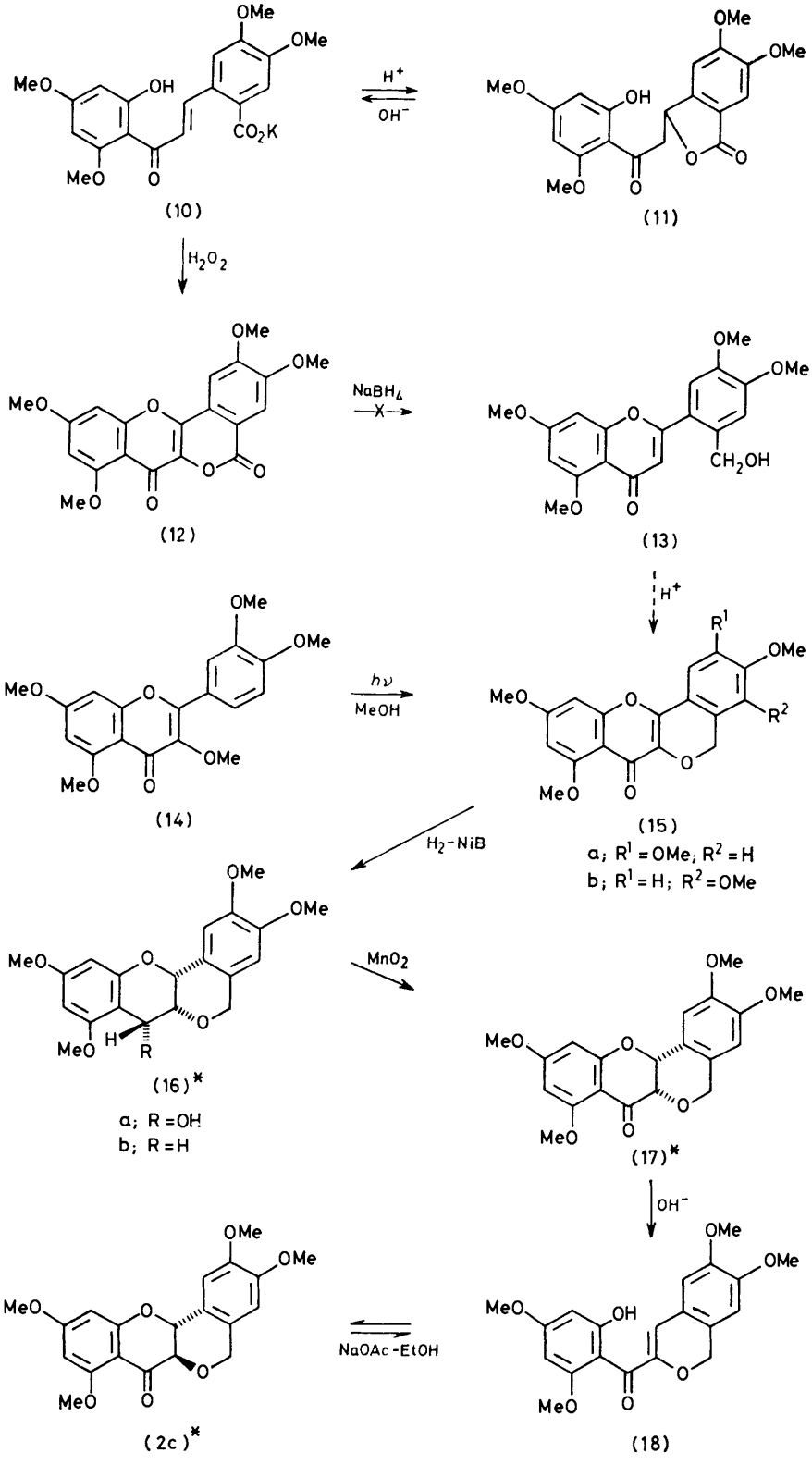
(8)



(9)

High-pressure (100—110 atm) catalytic hydrogenation at 90—100 °C of the synthetic tetra-*O*-methyl-β-photomethylquercetin (15a), using freshly prepared nickel boride catalyst,[16] gives two products. The required (±)-2,3-*cis*-3,4-*cis*-tetra-*O*-methylcrombeol (16a) ($J_{2,3}$ *ca.* 1.0, $J_{3,4}$ 5.6 Hz; *cf.* 4′,5′,7-tri-*O*-methyl-2,3-*cis*-3,4-*cis*-peltogynol,[1] $J_{2,3}$ *ca.* 1.0, $J_{3,4}$ 4.4 Hz) and its 4-deoxy-analogue, 4′,5′,7-tri-*O*-methyl-5-methoxypeltogynan (16b), were obtained as crystalline compounds in yields of 8.4 and 31%, respectively. Control of this reaction is obviously difficult due to concomitant hydrogenolysis of the sensitive 4-benzyl function.

As expected the synthetic (±)-2,3-*cis*-3,4-*cis*-crombeol tetramethyl ether (16a) is oxidized almost quantitatively with MnO_2 in $CHCl_3$ to the 4-oxo-analogue, 2,3-*cis*-crombeone tetramethyl ether (17). This compound and its 2,3-*trans*-isomer derived from natural sources,[8]



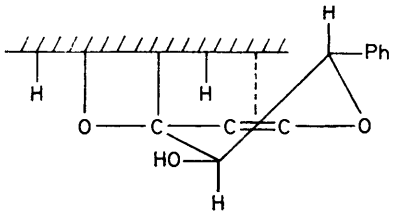
Racemates : (2*R*)-enantiomer indicated

SCHEME 1

exhibit similar n.m.r. spectra, except for differences in their 2,3-spin-spin coupling constants ($J_{2,3}$ 5.8 and 12.0 Hz respectively), corresponding to ' twisted boat ' and ' sofa ' conformations for the C- and D-rings, respectively, of the former, and ' sofa ' and ' half-chair ' conformations (C- and D-rings, respectively) for the latter.

(±)-2,3-*cis*-Crombeone tetramethyl ether (17) is amenable to C-ring opening in alkaline medium to give a peltogynoid-type chalcone, 3-(2-hydroxy-4,6-dimethoxybenzoyl)-6,7-dimethoxyisochromene (18), identical to that prepared by a similar conversion from natural (+)-2,3-*trans*-crombeone tetramethyl ether (2c). Under optimum conditions (NaOAc in 50% EtOH under reflux for 8 h) established for β-cyclization,[17] the above chalcone (18) furnishes relatively low (15%) yields of the desired crystalline (±)-2,3-*trans*-crombeone tetramethyl ether (2c).

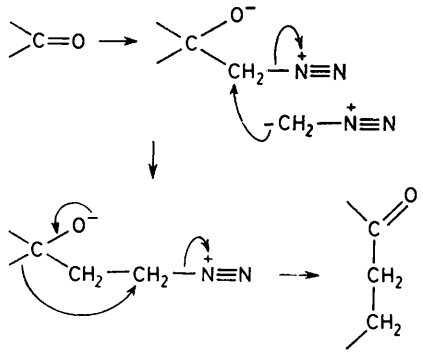
Additional proofs of the structure of the natural (+)-2,3-*trans*-crombeone are its conversions into the chalcone (3b), into the spirocoumaranone crombenin,[18] and into β-photomethylquercetin (4b), as well as 2,3-*trans*-3,4-*cis*-crombeol (1e) by simple catalytic hydrogenation (PtO_2, 1 atm, 25 °C). The former group will be detailed elsewhere, while the latter represents an interesting case in that hydrogenation of the tetramethyl ether (2c) pro-



bably proceeds from the least hindered ' upper ' side of the sofa conformation *via* a π-carbonyl system as shown to form the expected [19] 2,3-*trans*-3,4-*trans*-isomer. However, spontaneous C-4 epimerization results from the ease with which fission of the 4-C–OH bond occurs, due to effective delocalization of the incipient carbocation. Re-addition of the OH group at C-4 occurs from the less hindered axial direction, yielding the thermodynamically more stable 2,3-*trans*-3,4-*cis*-crombeol tetramethyl ether (1f). The stereochemistry of the derivative follows from its coupling constants ($J_{2,3}$ 9.6, $J_{3,4}$ 3.6 Hz) corresponding to ' half-chair ' and ' sofa ' arrangements for the heterocyclic C- and D-rings, respectively.

Reaction of crombeone with diazomethane results in a range of products, recognized as originating from nucleophilic addition of this reagent to the 4-carbonyl group, followed by solvolysis or by varying degrees of repetitive methylene ring-insertion reactions.[8] These compounds comprise a predominant crystalline dibenzopyrano-[3,2-*b*]oxepinspiro-oxiran derivative (7), an amorphous dibenzopyrano[3,2-*b*]oxocinone derivative (8), and 4-methoxymethyl-3′,4′,5,7-tetra-*O*-methylcrombeol (9). All structures are consistent with mass and n.m.r. spectral data and exhibit a common *trans*-diaxial AB quartet (H-2 and H-3) with coupling constants dependent on ring size ($J_{2,3}$ decreasing with increasing ring size): $J_{2,3}$ 12.0 (2c), 10.0 (9), 9.5 (7), and 9.5 Hz (8). Having determined the absolute configuration (2*R*,3*R*) of crombeone (2a), that of (8) is accordingly known, while (7) and (9) have known absolute configuration at C-2 and C-3, but with arrangements at C-4 in each instance as yet undefined. The dibenzopyrano[3,2-*b*]oxepin-spiro-oxiran (7) and 4-methoxymethylcrombe-4-ol derivatives (9) are the expected products from known methylene addition to or across the carbonyl group and methylene insertion on either side of the carbonyl group [20] but formation of the dibenzopyrano[3,2-*b*]oxocinone derivative (8) is apparently unusual. This compound, which is isomeric with (7), exhibits carbonyl absorption at 1 710 cm^{-1} indicating absence of conjugation with the phenolic A-ring. Considering that the AB system of the 2 and 3 protons is intact, and the mutual coupling of the inserted methylene functions, the enlarged eight-membered ring plausibly arises from successive methylene additions prior to a concerted 1,3-migration by the A-ring (*cf.* Scheme 2).

In view of the absence of methylene insertions during the methylation of peltogynone (2b) with diazomethane, as opposed to the relative susceptibility of crombeone and dihydroquercetin to such reactions, the extent of the competing reactions in the case of crombeone could depend on the concurrence of a number of possible factors: (*i*) the phloroglucinol A-ring acting as a stronger



SCHEME 2

electron-releasing moiety than the resorcinol A-ring (peltogynone), thus promoting aryl migration; (*ii*) the strong hydrogen bond (4-CO to 5-OH) delays methylation of 5-OH, thus partly preserving the nucleophilic character of the phloroglucinol-type A-ring during methylation; and (*iii*) added strain in the C-ring through the presence of the heterocyclic D-ring promoting 1,2 and 1,3 migrations. In practice compounds, *e.g.* crombeone and dihydroquercetin, which are susceptible to secondary reactions with diazomethane are successfully methylated by dimethyl sulphate in acetone under completely anhydrous conditions.

The existence of a novel peltogynoid chalcone, carnein (3a), indicates that D-ring cyclization of a hypothetical α-methoxychalcone [21] occurs prior to C-ring

cyclization in peltogynoid synthesis, the possible intermediacy of such a peltogynoid chalcone being apparently supported by the coexistence of the first optically active 3-*O*-methyldihydroflavonol analogue, 2,3-*trans*-3-*O*-methylfustin (6c). On this assumption the energy requirements for subsequent C-ring cyclization of the chalcone (3a) would be increased due to enhanced ring strain in the resultant dihydroflavonol, peltogynone (2b) resulting in an unfavourable peltogynoid-type chalcone ⇌ dihydroflavonol equilibrium.[21] No chemical analogies exist for the alternative (*i.e.* D-ring cyclization following upon initial C-ring cyclization) leading to 3-*O*-methylfustin (6c), nor for D-ring cyclization of an α-methoxychalcone, although photochemical analogies for the former exist in the case of 3-*O*-methylflavonols.[14,15] However, natural occurrence of crombenin, a peltogynoid spirocoumaranone in *A. crombei* [18] and *A. peuce* [1] (*cf.* ref. 22) lends support to the postulate of initial D-ring cyclization.

EXPERIMENTAL

Authentic samples of the cross-section of the stem of *A. carnei* were collected 8 km north-west of ' Hewart Downes Homestead ' and 60 km west of Tibooburra (December 1971), 3 km north of Byrnedale Station and 46 km north of Menindee (September 1971), and 117.5 km west of Wanaaring on the road to Milparinka (September 1971). Collections were organised and the samples kindly supplied by Dr. Mary D. Tindale, Royal Botanic Gardens and National Herbarium, Sydney, Australia.

Other experimental details are as defined for *A. peuce*.[1]

Extraction and Preliminary Fractionation of Compounds from A. carnei.—Drillings (496 g) from the heartwood of *A. carnei* were dewaxed with n-hexane (3 × 1.5 l) for 36 h. The dry wax-free drillings were extracted with ethyl acetate (6 × 1.5 l) for 72 h at ambient temperatures, giving a purple powder (55 g) on removal of the solvent. Continued extraction with MeOH (4 × 1.5 l) for 48 h gave a further 26.3 g extractive, containing considerable proportions of oxidized phenolics (two-dimensional paper chromatography).

Enrichment of the low proportion of high-R_F components was effected by column chromatography (3.5 × 70 cm) of the crude ethyl acetate extract (6 × 7.5 g) on Whatman CF 1 cellulose powder. Following development (flow rate 2 ml min^{-1}) with 2% (v/v) AcOH and 80% (v/v) MeOH successively, extraction of the respective eluants with ethyl acetate yields two distinct fractions, A (6.4 g, high-R_F components) and B (31.1 g, low-R_F components) on evaporation of the solvent.

The high-R_F compounds (A, 6.4 g) were re-fractionated by preparative paper chromatography (p.p.c.) by upward migration with 20% aqueous AcOH. Two bands in the high-R_F region were eluted, producing fractions A_1 (R_F 0.71, 2.8 g) and A_2 (R_F 0.52, 0.99 g). Low-R_F extractives (B, 31.1 g) were similarly treated to give four sub-fractions B_1—B_4 [R_F 0.47 (0.3 g), 0.38 (12.1 g), 0.18 (7.94 g), and 0.06 (1.4 g), respectively].

Fraction A_1 (2.5 g) was methylated with diazomethane and purified of oxidized material by column chromatography (' Merck ' silica gel, 70—325 mesh; 2 × 33 cm; flow rate 1 ml min^{-1}), using benzene-acetone (1 : 1) as eluant, to give 1.13 g of methylated product. This was further separated into three sub-fractions A_{1a}—A_{1c} [R_F 0.64 (45 mg), 0.54 (93 mg), and 0.41 (107 mg), respectively] by t.l.c. [benzene–acetone (7 : 3)].

(±)-3,3′,4′,7-*Tetra*-O-*methyl*-2,3-trans-*fustin* [(+)-trans-3,3′,4′,7-*Tetramethoxyflavanone*] (6d).—This crystallized from fraction A_{1a} [using cyclohexane–acetone (8 : 2)] as *colourless needles* (22 mg), m.p. 149 °C (lit.,[4] 143 °C: racemate) (Found: M^+, 344.125. Calc. for $C_{19}H_{20}O_6$: M, 344.126); $[\alpha]_D^{30}$ +43° (*c* 0.6 in $CHCl_3$) (lit.,[4] racemate); n.m.r. identical to that in the literature.[4]

(±)-3′,4′,7-*Tri*-O-*methyl*-2,3-trans-*fustin* [(±)-trans-3-*Hydroxy*-3′,4′,7-*trimethoxyflavanone*] (6e).—The contents of fraction A_{1b} were purified by t.l.c. in 1,2-dichloroethane–acetone (9 : 1) giving a band (R_F 0.37) which crystallized from EtOH as colourless needles (38 mg), m.p. 141 °C (lit.,[23] 138—140 °C: racemate); M^+, 330; $[\alpha]_D^{24}$ −7° (*c* 0.66 in $CHCl_3$) (lit.,[23] −44°); n.m.r. identical to that of an authentic sample.

(+)-3′,4′,5,7-*Tetra*-O-*methyl*-2,3-trans-*dihydroquercetin* [(+)-trans-3-*Hydroxy*-3′,4′,5,7-*tetramethoxyflavanone*] (6f).—The compound from fraction A_{1c} crystallized from EtOH as *colourless needles* (50 mg), m.p. 189 °C (lit.,[24] 198 °C: racemate); M^+, 360; $[\alpha]_D^{25}$ −9° (*c* 0.58 in $CHCl_3$); n.m.r. identical to that of the methyl ether of an authentic sample.

(+)-4′,5′,7-*Tri*-O-*methyl*-2,3-trans-3,4-cis-*peltogynol* {(+)-6a,7-cis-6a,12a-trans-2,3,10-*Trimethoxy*-6a,12a-*dihydro*-5H,7H-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7-*ol*} (1d).—Fraction B_1 (300 mg) was methylated with dimethyl sulphate, and peltogynidin (4c), which developed as an impurity, was removed by column chromatography [' Merck ' silica gel, 70—325 mesh; 1 × 15 cm; flow rate 1 ml min^{-1}; benzene–acetone (1 : 1)] to give 210 mg of product. This was purified twice by t.l.c. with benzene–acetone (8 : 2) (R_F 0.41) and 1,2-dichloroethane–acetone (9 : 1) (R_F 0.40), respectively, to yield the compound (1d) which crystallized from EtOH as colourless needles (72 mg), m.p. 141 °C (lit.,[7] 140 °C); $[\alpha]_D^{29}$ +242° (*c* 0.4 in $CHCl_3$) (lit.,[25] +270°); n.m.r. identical to that in the literature.[3]

(+)-4′,5′,7-*Tri*-O-*methyl*-2,3-trans-3,4-trans-*peltogynol* {(+)-6a,7-trans-6a,12a-trans-2,3,10-*Trimethoxy*-6a,12a-*dihydro*-5H,7H-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7-*ol*} (1c).—A portion (500 mg) of fraction B_2 was methylated with dimethyl sulphate and the product (187 mg) purified in two stages by t.l.c. (R_F 0.40, 0.35) as indicated for the *trans-cis*-isomer (1d). The contents of the band of R_F 0.35 from the second system yielded colourless needles (107 mg) from EtOH, m.p. 199 °C (lit.,[3] 200 °C); $[\alpha]_D^{24}$ +257° (*c* 0.48 in $CHCl_3$) (lit.,[25] + 250°); n.m.r. identical to that in the literature.[3]

(±)-2,3-trans-3,4-trans-*Peltogynol* {(+)-6a,7-trans-6a,-12a-trans-6a,12a-*Dihydro*-5H,7H-[2]*benzopyrano*[4,3-b][1]*benzopyran*-2,3,7,10-*tetraol*} (1a).—The remainder of fraction B_2 was purified according to the method of Robinson and Robinson,[9] yielding the product (1a), which readily crystallized from the minimum volume of water as dark blue platelets (9.8 g), m.p. 236 °C (lit.,[26] 240 °C); $[\alpha]_D^{25}$ +265° (*c* 0.57 in EtOAc) (lit.,[26] +273°).

Secondary Fractionations.—A portion (1.5 g) of fraction B_3 was methylated with dimethyl sulphate and the product (1.64 g) freed from peltogynols by column chromatography (' Merck ' silica gel, 70—325 mesh; 2 × 52 cm; flow rate 0.5 ml min^{-1}) with benzene–acetone (6 : 4) as eluant. Yellow fluorescent (350 nm) fractions (low R_F) were combined, giving a peltogynol-free product (159 mg). This

was subjected to t.l.c. separation in 1,2-dichloroethane–acetone (9 : 1), yielding fractions B_{3a} (R_F 0.64, 80 mg) and B_{3b} (R_F 0.55, 61 mg).

However, due to difficulties encountered during the isolation of low-concentration compounds from fraction B_3, a second portion (3.5 g) was fractionated by p.p.c., using downward migration in water-saturated butan-2-ol. From this a product (292 mg) was obtained (R_F 0.67) which was then methylated with diazomethane and separated into five sub-fractions B_{3c}—B_{3g} [R_F 0.53 (64 mg), 0.47 (49 mg), 0.39 (33 mg), 0.24 (15 mg), and 0.06 (22 mg)], by t.l.c. with 1,2-dichloroethane–acetone (9 : 1).

(+)-4′,5′,5,7-*Tetra*-O-*methyl*-2,3-trans-*crombeone* {(+)-6a,12a-trans-2,3,8,10-*Tetramethoxy*-6a,12a-*dihydro*-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7(5H)-*one*} (2c).—The contents of fraction B_{3a} crystallizes as colourless *needles* (74 mg) from EtOH, m.p. 192 °C (Found: C, 64.5; H, 5.4. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%); M^+, 372; $[\alpha]_D^{24}$ +259° (*c* 0.29 in $CHCl_3$); c.d. (*c* 0.044 in MeOH) $[\theta]_{350}$ 1.31 × 10^4, $[\theta]_{314}$ 5.75 × 10^4, $[\theta]_{284}$ 0.74 × 10^4, $[\theta]_{266}$ 1.81 × 10^4, $[\theta]_{245}$ 1.15 × 10^4, $[\theta]_{235}$ 6.23 × 10^4; δ($CDCl_3$) 7.17 (s, 6′-H), 6.57 (s, 3′-H), 6.25 (d, *J* 2.5 Hz, 6-H), 6.14 (d, *J* 2.5 Hz, 8-H), 5.24 (br d, *J* 12.0 Hz, 2-H), 4.94 (br s, CH_2), 4.25 (d, *J* 12.0 Hz, 3-H), 3.97 (s, OMe), and 3.90 (s, 3 × OMe).

(+)-4′,5′,5,7-*Tetra*-O-*methyl*-2,3-trans-3,4-cis-*crombeol* {(+)-6a,7-cis-6a,12a-trans-2,3,8,10-*Tetramethoxy*-6a,12a-*dihydro*-5H,7H-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7-*ol*} (1f).—Catalytic hydrogenation (activated PtO_2, 100 mg) of *trans*-crombeone tetramethyl ether (2c) (40 mg) in dioxan (15 ml) for 3 h at atmospheric pressure yields compound (1f). Following purification by t.l.c. [benzene–acetone (7 : 3)], the product (R_F 0.47) crystallizes from cyclohexane–acetone (minimum acetone) as colourless *needles* (16.7 mg), m.p. 166 °C (Found: C, 64.0; H, 6.0. $C_{20}H_{22}O_7$ requires C, 64.1; H, 5.9%); M^+ 374; δ([$^2H_6$]acetone) 7.24 (s, H-6′), 6.73 (s, H-3′), 6.20 (d, *J* 2.4 Hz, H-6), 6.15 (d, *J* 2.4 Hz, H-8), 5.24 (d, *J* 9.6 Hz, H-2), 5.02 (d, *J* 3.6 Hz, H-4), 4.84 (br s, CH_2), 3.86, 3.84, 3.80, and 3.77 (s, 4 × OMe), 3.58 (q, *J* 9.6 and 3.6 Hz, H-3), and 2.74 (br s, 4-OH).

(+)-4′,5′,7-*Tri*-O-*methyl*-2,3-trans-*crombeone* {(+)-6a,12a-trans-8-*Hydroxy*-2,3,10-*trimethoxy*-6a,12a-*dihydro*-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7(5H)-*one* (2e).—Fraction B_{3b} yielded *colourless needles* (54 mg) from acetone, m.p. 209 °C; M^+, 358; $[\alpha]_D^{28}$ +255° (*c* 0.35 in pyridine); $\nu_{max.}$ 1 660 and 3 400 cm^{-1}; δ($CDCl_3$) 3.87 (s, 5-OH), 7.25 (s, 6′-H), 6.55 (s, 3′-H), 6.23 (d, *J* 2.3 Hz, 6-H), 6.13 (d, *J* 2.3 Hz, 8-H), 5.23 (br d, *J* 12.0 Hz, 2-H), 4.95 (br s, CH_2), 4.23 (d, *J* 12.0 Hz, 3-H), 3.89 (s, 2 × OMe), and 3.86 (s, OMe).

(+)-4′,5′,7-*Tri*-O-*methyl*-2,3-trans-*peltogynone* {(+)-6a,12a-trans-2,3,10-*Trimethoxy*-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7(5H)-*one*} (2d).—The contents of fraction B_{3c} crystallized from EtOH as *colourless needles* (48 mg), m.p. 214 °C (lit.,[25] 213 °C: synthetic racemate) (Found: M^+, 342.110. Calc. for $C_{19}H_{18}O_6$: *M*, 342.110); $[\alpha]_D^{25}$ +276° (*c* 0.9 in $CHCl_3$) (lit.,[26] +279°); c.d. (*c* 0.045 in MeOH) $[\theta]_{350}$ 1.00 × 10^4, $[\theta]_{326}$ 5.78 × 10^4, $[\theta]_{306}$ 0, $[\theta]_{284}$ −2.42 × 10^4, $[\theta]_{277}$ 0, $[\theta]_{267}$ 2.50 × 10^4, $[\theta]_{253}$ 0.81 × 10^4, $[\theta]_{235}$ 6.23 × 10^4; δ($CDCl_3$) 7.96 (d, *J* 9.5 Hz, 5-H), 7.17 (s, 6′-H), 6.61 (dd, *J* 9.5 and 2.2 Hz, 6-H), 6.58 (d, *J* 2.2 Hz, 8-H), 6.43 (br s, 3′-H), 5.24 (br d, *J* 12.0 Hz, 2-H), 4.87 (s, CH_2), 4.27 (d, *J* 12.0 Hz, 3-H), and 3.86, 3.75, and 3.70 (s, 3 × OMe).

2′,4,4′,5-*Tetra*-O-*methylcarnein* {3-(2,4-*Dimethoxybenzoyl*)-5,7-*dimethoxy*-1H-[2]*benzopyran*} (3c).—Crystallization of fraction B_{3d} from acetone produced *colourless needles* (35 mg), m.p. 124 °C (Found: M^+, 356.126. Calc. for $C_{20}H_{20}O_6$: *M*, 356.126); δ[$CDCl_3$–C_6D_6 (3 : 1)] 7.35 (d, *J* 9.0 Hz, 6′-H), 6.58 (s, 5-H), 6.48 (dd, *J* 9.0 and 2.4 Hz, 5-H), 6.46 (d, *J* 2.4 Hz, 3′-H), 6.13 (s, 4-H), 5.13 (s, CH_2), 3.71 (s, 2 × OMe), and 3.65, 3.62, (s, 2 × OMe).

3,3′,4′,7-*Tetra*-O-*methylfisetin* [3,3′,4′,7-*Tetramethoxyflavone*] (5b).—Fraction B_{3e} crystallized from EtOAc as colourless needles (21 mg), m.p. 178 °C (lit.,[27] 180 °C); M^+, 342; n.m.r. identical to that of an authentic sample.

4′,5′,7-*Tri*-O-*methylpeltogynin* {2,3.10-*Trimethoxy*-[2]-*benzopyrano*[4,3-b][1]*benzopyran*-7(5H)-*one*} (4c).—Fraction B_{3f} crystallized from EtOH as yellow needles (7 mg), m.p. 259 °C (lit.,[5] 260 °C), mixed m.p. with authentic sample 259 °C; $\nu_{max.}$ 1 716 cm^{-1} (i.r. spectrum identical to authentic sample).

5-*Methoxy*-4′,5′,7-*Tri*-O-*methylpeltogynin* {2,3,8,10-*Tetramethoxy*-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7(5H)-*one*} (4d).—The compound present in fraction B_{3g} could not be isolated in sufficient quantity for characterization, but is qualitatively identical (sea-green fluorescence under u.v.; yellow colouration with spray-reagent; R_F 0.06) with 4′,5,5′,7-tetra-*O*-methyl-β-photomethylquercetin obtained by photolysis of quercetin pentamethyl ether (see later).

Methylene Insertions.—A phenolic crombeone-enriched fraction (R_F 0.49, 410 mg) was obtained from a portion of fraction B_3 (3.5 g) by p.p.c., employing downward migration in water-saturated butan-2-ol (see above). This was methylated by diazomethane (excess, 48 h) and yielded tri-*O*-methylcrombeone (2e) (72.9 mg, R_F 0.20), accompanied by three artefacts, compounds (7)—(9) [70.8 mg (R_F 0.74), 40.9 mg (R_F 0.67), and 63.9 mg (R_F 0.34), respectively], following separation by t.l.c. [benzene–acetone (7 : 3)].

trans-2,3,9,11-*Tetramethoxy*-6a,7,8,13a-*tetrahydro*-5H-*dibenzo*[c,g]*pyrano*[3,2-b]*oxepin*-7-*spiro*-*oxiran* (7).—This crystallizes from EtOH as *white needles* (66 mg), m.p. 156 °C (Found: C, 65.9; H, 6.0. $C_{22}H_{24}O_7$ requires C, 66.0; H, 6.0%); *m/e* 400 (100%, M^+), 370 (27), 369 (89), 342 (9.0), 341 (44), 203 (27), 192 (23), 191 (50), 179 (9.3), 178 (4.1), 167 (37), 166 (4.0), and 165 (4.8); c.d. (MeOH) $[\theta]_{300}$ 0, $[\theta]_{292}$ −2.4 × 10^3, $[\theta]_{284}$ 0, $[\theta]_{276}$ 3.1 × 10^3, $[\theta]_{250}$ 0.6 × 10^3; δ(C_6D_6) 7.38 (s, H-1), 6.09 (s, H-4), 6.59 (d, *J* 2.5 Hz, H-10), 6.20 (d, *J* 2.5 Hz, H-12), 4.96 (d, *J* 9.5 Hz, H-13a), 4.50 (br s, 5-H_2), 3.85 (d, *J* 9.5 Hz, H-6a), 3.52, 3.40, 3.35, and 3.29 (s, 4 × OMe), 3.31 and 2.49 (2 × d, *J* 6.5 Hz, oxiran-CH_2), 3.21 and 2.88 (2 × d, *J* 15.0 Hz, 8-H_2).

trans-2,3,10,12-*Tetramethoxy*-6a,8,9,14a-*tetrahydrodibenzo*[c,g]*pyrano*[3,2-b]*oxocin*-7(5H)-*one* (8).—Purification by t.l.c. [benzene–acetone (9 : 1), ×2] yielded a light yellow amorphous compound (R_F 0.47, 19 mg), m.p. 137 °C (Found: C, 65.8; H, 6.0%; M^+, 400.152. Calc. for $C_{22}H_{24}O_7$: C, 66.0; H, 6.0%; *M*, 400.152); *m/e* 400 (M^+); ν_{CO} 1 705 cm^{-1}; c.d. (MeOH) $[\theta]_{340}$ 0, $[\theta]_{300}$ −5.7 × 10^3, $[\theta]_{287}$ 0, $[\theta]_{281}$ 5.1 × 10^3, $[\theta]_{250}$ 1.3 × 10^3; δ($CDCl_3$) 7.37 (s, H-1), 6.55 (s, H-4), 6.34 (s, H-11 and H-13), 4.87 (br s, 5-H_2), 4.77 (d, *J* 11.5 Hz, H-6a and H-14a), 3.97, 3.88, 3.82, and 3.81 (s, 4 × OMe), and 3.5—2.55 (m, 8-H_2 and 9-H_2).

trans-2,3,8,10-*Tetramethoxy*-7-*methoxymethyl*-6a,12a-*dihydro*-5H,7H-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7-*ol* (9).—Purification by t.l.c. [benzene–acetone (1 : 1)] gave a white amorphous wax (R_F 0.59, 17.2 mg), m.p. 51—56 °C (Found: C, 62.8; H, 6.1%; M^+, 418.162. Calc. for $C_{22}H_{26}O_8$: C, 63.1; H, 6.3%; *M*, 418.163); δ(C_6D_6) 7.37 (s, H-1), 6.45 (d, *J* 2.4 Hz, H-9), 6.17 (s, H-4), 6.11 (d, *J* 2.4

Hz, H-11), 5.68 (d, *J* 10.4 Hz, H-12a), 4.74 (br s, 5-H_2), 4.65 (br s, CH_2OMe), 4.28 (d, *J* 10.4 Hz, H-6a), 3.55, 3.45, 3.39, and 3.35 (s, 4 × OMe), and 3.20 (s, CH_2OMe).

Tannins.—Fractions A_1 and especially A_2 contain high concentrations of tannins. An anthocyanidin test on the latter gives peltogynidin and an unknown anthocyanidin [R_F 0.64 and 0.75, respectively in formic acid–3N HCl (1 : 1)] with similar colours in u.v. light (350 nm) and daylight. The tannins could not be purified due to the complexity of the mixture.

Attempted Synthesis of [2]*Benzopyrano*[4,3-b][1]*benzopyran*.— *2′-Hydroxy-4′,4,5,6′-tetramethoxy*-trans-*chalcone*-2-*carboxylic acid* (10). 2-Hydroxy-4,6-dimethoxyacetophenone [28] (m.p. 87 °C, 750 mg) was condensed with *m*-opianic acid [29] (m.p. 188 °C) (700 mg) dissolved in a minimum of 96% EtOH, by addition of 60% aqueous KOH (6 ml) and dilution with water to the extent that any precipitate just re-dissolved. Acidifying with 3N HCl after 60 h at 25 °C does, however, not yield the expected chalcone (10), but the isomeric (±)-tetramethoxybenzoylphthalide (11), which crystallized from pyridine as *colourless needles* (997 mg), m.p. 207 °C (Found: M^+, 388.116. $C_{20}H_{20}O_8$ requires *M*, 388.116); δ([$^2H_5$]pyridine) 7.53 (s, 7-H), 7.29 (s, 4-H), 6.38 (d, *J* 2.0 Hz, 5′-H), 6.27 (t, *J* 5.4 Hz, 3-H), 6.13 (d, *J* 2.0 Hz, 3′-H), 5.10 (br s, 2′-OH), 3.87, 3.84, 3.77, and 3.70 (s, 4 × OMe), and 4.00—3.60 (m, α-CH_2).

(±)-3-(2-*Acetoxy*-4,6-*dimethoxybenzoyl*)-5,6-*dimethoxyphthalide*.—(±)-Tetra-*O*-methoxybenzoylphthalide (100 mg) was acetylated with Ac_2O–pyridine giving the acetate as *colourless needles* (96 mg) from $CHCl_3$ containing *ca.* 5% EtOH, m.p. 178 °C; δ([$^2H_5$]pyridine) 7.51 (s, 7-H), 7.22 (s, 4-H), 6.64 (d, *J* 2.4 Hz, 5′-H), 6.55 (d, *J* 2.4 Hz, 3′-H), 6.88 (t, *J* 6.0 Hz, 3-H), 3.90, 3.84, 3.76, and 3.72 (s, 4 × OMe), 4.00—3.57 (m, α-CH_2), and 2.36 (s, OAc).

2,3,8,10-*Tetramethoxy*[2]*benzopyrano*[4,3-b][1]*benzopyran*-5,7-*dione* (12).— (±)-Tetra-*O*-methoxybenzoylphthalide (500 mg) was dissolved in 4% aqueous KOH (5 ml) at 96 °C and diluted with water (15 ml). 6% (v/v) Aqueous H_2O_2 (6 ml) was added at 14 °C during 30 min with continuous agitation, and the mixture stirred for 3.5 h at the same temperature (14 °C). After cooling to 7 °C, excess of H_2O_2 was destroyed with 6% aqueous $NaHSO_3$ (2.5 ml) and 2N HCl (3.5 ml) was added to obtain a precipitate which was centrifuged and washed with $CHCl_3$ (2 × 5 ml) and warm 80% EtOH (4 × 5 ml). The residue crystallized from MeOH–$CHCl_3$ (2 : 3) as colourless needles (276 mg), m.p. 319 °C (lit.,[15] 322—324 °C); M^+ 384; δ($CDCl_3$) 7.70 (s, 8′-H), 7.43 (s, 5′-H), 6.23 (d, *J* 2.4 Hz, 6-H), 6.14 (d, *J* 2.4 Hz, 8-H), and 4.04, 3.97, 3.93, and 3.85 (s, 4 × OMe).

Several attempts, involving a variety of methods,[30-32] to reduce compound (12) to the desired 2′-hydroxymethyl-4′,5,5′,7-tetramethoxyflavanone (13) proved unsatisfactory due to a complex mixture of products.

Synthesis of (±)-4′,5,5′,7-*Tetra*-O-*methyl*-2,3-trans-*crombeone* {(±)-trans-2,3,8,10-*Tetramethoxy*-6a,12a-*dihydro*-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7(5H)-*one*}.— *4′,5′,5,7-Tetra*-O-*methyl*-β-*photomethylquercetin* (15a) {2,3,8,10-*Tetramethoxy*-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7(5H)-*one*}. Quercetin pentamethyl ether (4 × 500 mg) (14), prepared by methylation of commercial quercetin with dimethyl sulphate, was dissolved in MeOH (4 × 500 ml) and irradiated (350 nm, 384 W) in a Rayonet photochemical reactor (Southern New England Ultra-Violet Co., Middletown, Connecticutt, New Jersey) under nitrogen in quartz glass for 7 h. Evaporation of the solvent and purification by t.l.c. [1,2-dichloroethane–acetone (9 : 1)] yielded the products (R_F 0.06 and 0.14), the former crystallizing from MeOH–$CHCl_3$ (1 : 1) as yellow needles (860 mg), m.p. 207 °C (lit.,[15] 209—210 °C) (Found: M^+, 370.105. Calc. for $C_{20}H_{18}O_7$: *M*, 370.105); n.m.r. identical to that in the literature.[15]

3′,4′,5,7-*Tetra*-O-*methyl*-α-*photomethylquercetin* {3,4,8,10-*Tetramethoxy*-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7(5H)-*one*} (15b). The product (R_F 0.14) from the above irradiation of quercetin pentamethyl ether yielded yellow needles (421 mg) from MeOH–$CHCl_3$ (1 : 1), m.p. 203 °C (lit.,[15] 202—203 °C) (Found: M^+, 370.105. Calc. for $C_{20}H_{18}O_7$: *M*, 370.105); n.m.r. identical to that in the literature.[15]

(±)-4′,5,5′,7-*Tetra*-O-*methyl*-2,3-cis-3,4-cis-*crombeol* {(±)-6a,12a-cis-6a,7-cis-2,3,8,10-*Tetramethoxy*-6a,12a-*dihydro*-5H,7H-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7-*ol*} (16a). Tetra-*O*-methyl-β-photomethylquercetin (15a) (855 mg) was dissolved in 96% EtOH (50 ml) and hydrogenated (100—110 atm) for 24 h at 90—100 °C with freshly prepared nickel boride [from nickel acetate (2 g) and $NaBH_4$ (1 g)] [33] as catalyst. Following filtration and evaporation of the solvent the product was purified by t.l.c. [benzene–acetone (7 : 3)]. The contents of the band of R_F 0.22 crystallized from EtOH as *colourless needles* (84 mg), m.p. 193 °C (Found: M^+, 374.136. $C_{20}H_{22}O_7$ requires *M*, 374.136); δ($CDCl_3$) 6.97 (s, 6′-H), 6.66 (s, 3′-H), 6.18 (d, *J* 2.2 Hz, 6-H), 6.12 (d, *J* 2.2 Hz, 8-H), 5.35 (d, *J* 5.6 Hz, 4-H), 5.04 (br s, CH_2), 4.79 (br s, 2-H), 4.19 (d, *J* 5.6 Hz, 3-H), 3.95 (s, OMe), 3.93 (s, 2 × OMe), 3.83 (br s, 4-OH), and 3.74 (s, OMe).

4′,5′,7-*Tri*-O-*methyl*-5-*methoxypeltogynan* {6a,12a-cis-2,3,-8,10-*Tetramethoxy*-6a,12a-*dihydro*-5H-[2]*benzopyrano*[4,3-b][1]*benzopyran*} (16b). Compound (16b) was obtained as the major product from the hydrogenolysis of β-photomethylquercetin pentamethyl ether (15a) (855 mg) followed by t.l.c. separation (R_F 0.67) as indicated above, and crystallized from EtOH as *colourless needles* (237 mg), m.p. 189 °C (Found: M^+, 358.141. $C_{20}H_{22}O_6$ requires *M*, 358.141); δ($CDCl_3$) 7.00 (s, H-6′), 6.62 (s, H-3′), 6.13 (s, H-6 and H-8), 4.93 (br s, OCH_2), 4.73 (d, *J* *ca.* 1.0 Hz, H-2), 4.20—3.68 (m, H-3), 3.95, 3.89, 3.82, and 3.74 (s, 4 × OMe), and 3.09—2.89 (m, 4-CH_2).

(±)-4′,5,5′,7-*Tetra*-O-*methyl*-2,3-cis-*crombeone* (17) {(±)-6a,12a-cis-2,3,8,10-*Tetramethoxy*-6a,12a-*dihydro*-[2]*benzopyrano*[4,3-b][1]*benzopyran*-7(5H)-*one*}. (±)-*cis*,*cis*-Tetra-*O*-methylcrombeol (16a) (78 mg) was oxidized by stirring with MnO_2 (1.1 g) in $CHCl_3$ (15 ml) for 4 h. The product crystallized from EtOH as *colourless needles* (74 mg), m.p. 195 °C (Found: M^+, 372.121. $C_{20}H_{20}O_7$ requires *M*, 372.120); δ($CDCl_3$) 6.95 (s, 6′-H), 6.65 (s, 3′-H), 6.17 (d, *J* 2.4 Hz, 6-H), 6.10 (d, *J* 2.4 Hz, 8-H), 5.34 (d, *J* 5.8 Hz, 2-H), 5.03 (br s, OCH_2), 4.17 (d, *J* 5.8 Hz, 3-H), 3.95 (s, OMe), 3.90 (s, 2 × OMe), and 3.74 (s, OMe).

3-(2-*Hydroxy*-4,6-*dimethoxybenzoyl*)-6,7-*dimethoxy*-1H-2-*benzopyran* (18). c-Ring fission of *cis*-tetra-*O*-methylcrombeone (17) to the analogous chalcone (18) was accomplished by heating the former (69 mg) with 10% aqueous KOH (15 ml) on a water-bath for 75 min with constant agitation. Filtration of the orange solution followed by acidification with 2N HCl (pH *ca.* 2) produced a yellow precipitate which was centrifuged, and crystallized from EtOH as *yellow needles* (60 mg), m.p. 93 °C, mixed m.p. with the chalcone prepared from natural *trans*-tetra-*O*-methylcrombeone, 93 °C (Found: M^+, 372.120. $C_{20}H_{20}O_7$ requires *M*, 372.120); δ($CDCl_3$) 10.45 (br s, 2′-OH), 6.74 (s, 5-H), 6.65 (s, 8-H), 6.57 (s, 4-H), 6.17 (d, *J* 2.2 Hz,

5′-H), 6.04 (d, J 2.2 Hz, 3′-H), 5.18 (br s, CH_2), 3.90 (s, 2 × OMe), and 3.85 and 3.80 (s, 2 × OMe).

(±)-4′,5,5′,7-*Tetra*-O-*methyl*-2,3-trans-*crombeone* (2c). The chalcone (**18**) (55 mg), dissolved in EtOH (5 ml), was refluxed with sodium acetate (240 mg) for 48 h. Extraction of the mixture with EtOAc (5 × 20 ml) following dilution with water (40 ml) yielded a product which was purified by t.l.c. in benzene–acetone (8 : 2). The contents of the band of R_F 0.32 crystallized from EtOH as *colourless needles* (8.7 mg), m.p. 184 °C (Found: M^+, 372.121. $C_{20}H_{20}O_7$ requires M, 372.121) (m.s. identical to that of the corresponding derivative of the natural product, m.p. 192 °C); δ($CDCl_3$) 7.17 (s, 6′-H), 6.57 (s, 3′-H), 6.25 (d, J 2.5 Hz, 6-H), 6.14 (d, J 2.5 Hz, 8-H), 5.24 (br d, J 12.0 Hz, 2-H), 4.94 (br s, CH_2), 4.25 (d, J 12.0 Hz, 3-H), 3.97 (s, OMe), and 3.90 (s, 3 × OMe) (identical to the corresponding derivative of the natural product).

We thank Dr. Mary D. Tindale, Royal Botanic Gardens and National Herbarium, Sydney, N.S.W. 2000, for the collection and authentication of sections of *A. carnei*, and the South African Council of Scientific and Industrial Research, Pretoria, and Sentrale Navorsingsfonds of this University for financial support.

[0/866 *Received*, 9*th June*, 1980]

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