Synthesis of the Mangostins

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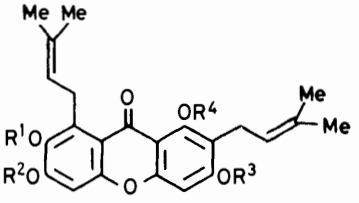
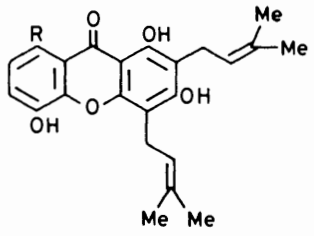
Acylation of 5,7-bisbenzyloxy-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (10c) with 6,8-dimethoxy-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-5-carboxylic acid (9b) in the presence of trifluoroacetic anhydride gave 5,7-dibenzyloxy-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-8-yl, 3,4-dihydro-6,8-dimethoxy-2,2-dimethyl-2*H*-1-benzopyran-5-yl ketone (8c), which was converted, in three steps, into dimethyl-1-isonormangostin (7). Reaction of (7) with boron trichloride resulted in the cleavage of the two terminal pyran rings to give 1,7-bis-(3-chloro-3-methylbutyl)-2,8-dihydroxy-3,6-dimethoxyxanthen-9-one (6a). Selective methylation of (6a) afforded the known 1,7-bis-(3-chloro-3-methylbutyl)-8-hydroxy-2,3,6-trimethoxyxanthen-9-one (6b). Whereas dehydrochlorination of the methoxycarbonyloxy derivative (6c) of (6b) with lithium chloride in dimethylformamide gave a mixture from which dimethylmangostin (1d) and 1,7-bis-(3-methylbut-3-enyl)-8-hydroxy-2,3,6-trimethoxyxanthen-9-one (22c) were isolated by preparative high pressure liquid chromatography, that of (6b) with potassium t-butoxide in dimethyl sulphoxide gave a mixture from which β-mangostin (1b) was obtained, by the same technique.

FROM the yellow colouring matter of the bark, fruit hulls, and dried latex of the mangosteen tree, *Garcinia mangostana* Linn (family Guttiferae), three pigments, *viz.* mangostin, β-mangostin, and γ-mangostin have been isolated; they have been shown to have the xanthone structures (1a—c), respectively.[1-4] Reinvestigation of the hulls of well ripened fruits [5] yielded two more new xanthones, gartanin and 8-deoxygartanin, which were assigned structures (2a) and (2b). We now report the synthesis of dimethylmangostin (1d) [1] and β-mangostin (1b), and hence that of (1a) and (1c) as well, since all three natural mangostins could be prepared from (1d) by stepwise basic demethylation.[4]



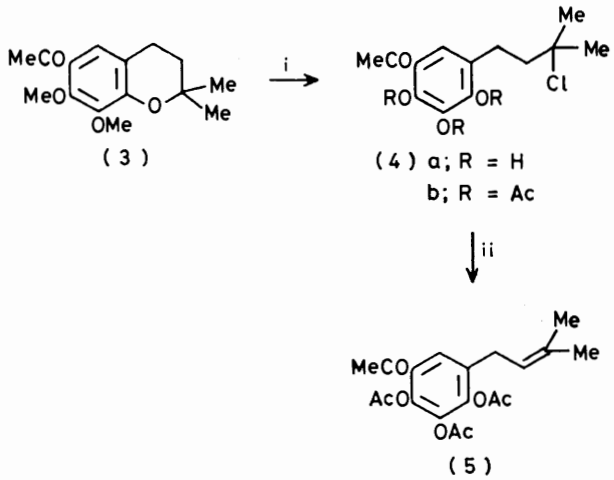
(1) a; R^1 = Me, R^2 = R^3 = R^4 = H
b; R^1 = R^3 = Me, R^2 = R^4 = H
c; R^1 = R^2 = R^3 = R^4 = H
d; R^1 = R^2 = R^3 = Me, R^4 = H
e; R^1 = R^2 = R^3 = Me, R^4 = MeOCO



(2) a; R = OH
b; R = H

Our strategy for the synthesis of (1d) was prompted by the report [6] of successful ring opening of chromans [*e.g.* (3)] with boron trichloride and the subsequent conversion of (4b), derived from the chloro-intermediate (4a), into the corresponding prenyl derivative (5).

A retrosynthetic analysis (⇒) of the target molecule (1d) based on this useful sequence of reactions is outlined in the Scheme. Both precursors (6b) [7] and (7) [1] are known and are readily available from (1d) and (1a), respectively. This greatly reduces the problem associated with structure identity of the relays and provides impetus for the synthetic execution (⟶) of the Scheme.

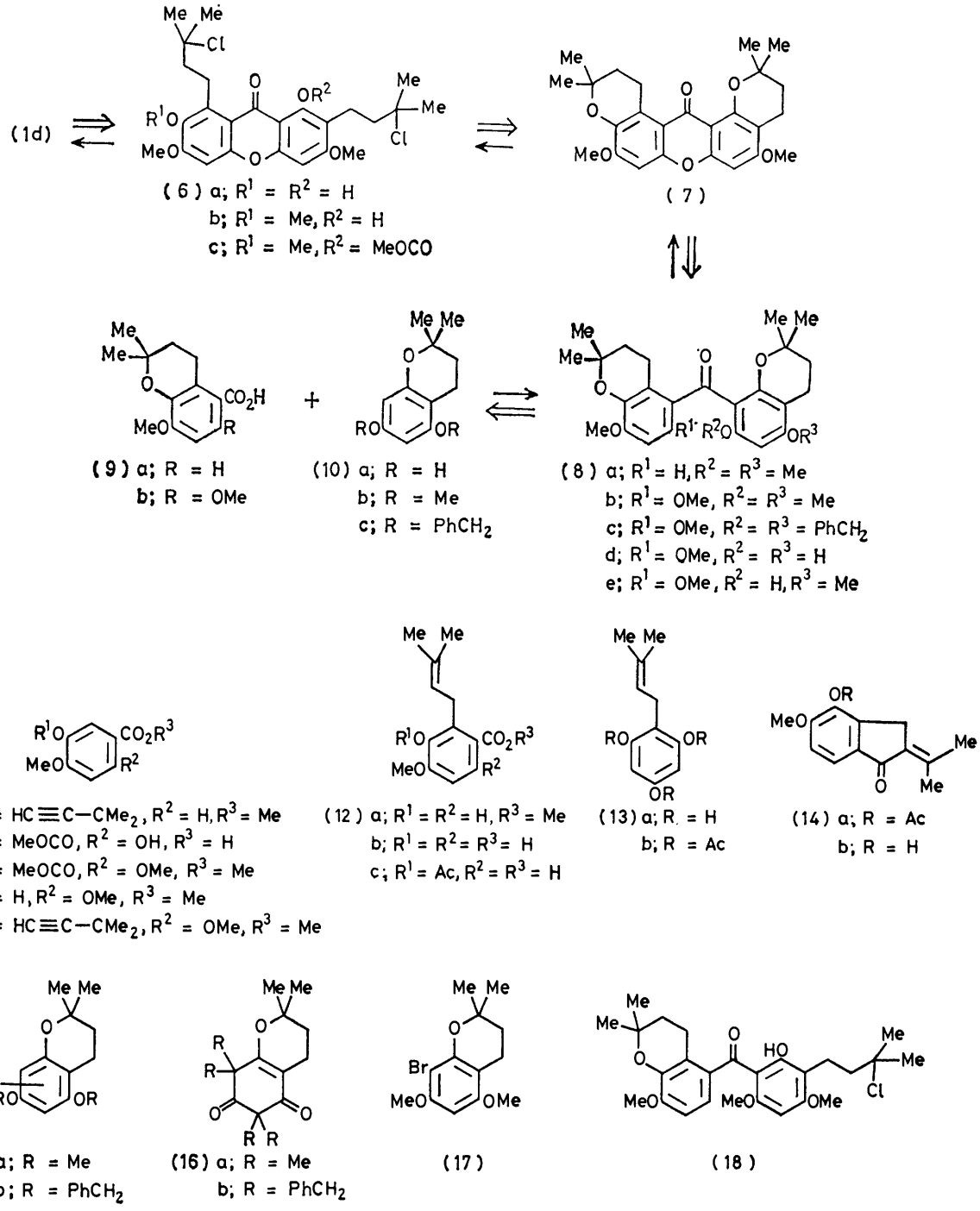


(3) (4) a; R = H
b; R = Ac
(5)

Reagents: i, BCl_3, CH_2Cl_2, 0 °C; ii, LiCl, Me_2NCHO, 100 °C

In a preliminary study, an attempt was made to prepare the open-chain analogue (8a) of benzophenone. Methyl isovanillate was converted by the method of Murray *et al.*[8] into (11a), and thence into (12c). The reaction of (12c) in the presence of trifluoroacetic anhydride with the triacetate (13b) [9] was found to give a ketone which, on the basis of analytical and spectroscopic evidence, is tentatively assigned structure (14a). The apparently ready intramolecular reaction discouraged further work on the preparation of prenylated benzophenones by this method.

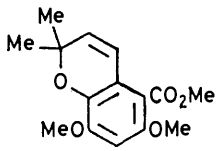
The carboxylic acid (12b) and the phloroglucinol derivative (13a) were then cyclized to the respective chromans (9a) and (10a). Methylation of the latter



SCHEME

with dimethyl sulphate gave, in addition to the known 5,7-dimethoxychroman (10b), a small amount of nuclear-methylated compound (15a). When methylation was conducted with iodomethane, a third compound, assigned structure (16a), was also isolated. The chroman (10b) was brominated with dioxan dibromide [10] to give a mono-bromo-derivative (17). That the bromine is at the 8-position is based on the following experimental evidence. The bromochroman (17) was converted into the corresponding lithio-compound with n-butyl-lithium, and this was then added to the acyl chloride derived from the carboxylic acid (9a) to give the ketone (8a). Reaction of (8a) with a dilute solution of boron trichloride in dichloromethane resulted in the cleavage of one pyran ring to give a compound, $C_{26}H_{33}ClO_6$, the i.r. spectrum of which showed a chelated carboxy absorption at 1 655 cm^{-1}; the n.m.r. spectrum showed signals for a chelated hydroxy at τ −3.05 and three methonyl groups at 6.15 (6 H) and 6.60 (3 H), in agreement with structure (18). Hence (8a) and (17) must have the given structures.

The carboxylic acid (9b) was prepared as follows. The 5-hydroxy group of 2,5-dihydroxy-4-methoxybenzoic acid [1] was protected by formation of its methoxycarbonyloxy derivative (11b), and then methylated to give (11c). Mild alkaline hydrolysis gave (11d), which was cyclized to (19) *via* its dimethylprop-2-ynyl ether (11e). Hydrogenation of (19) followed by saponification afforded (9b). Reaction of the derived acyl chloride with the lithio-derivative of (17) gave the ketone (8b), thus



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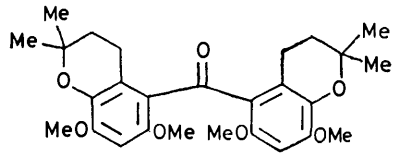

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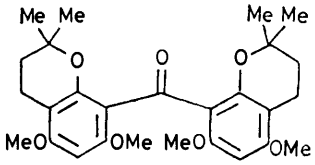

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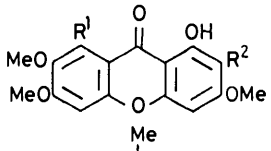

(22) a; $R^1 = CH_2{=}C(Me){-}CH_2CH_2$, $R^2 = Me_2C{=}CHCH_2$

b; $R^1 = Me_2C{=}CHCH_2$, $R^2 = CH_2{=}C(Me){-}CH_2CH_2$

c; $R^1 = R^2 = CH_2{=}C(Me){-}CH_2CH_2$

establishing this reaction as a reliable method for securing the desired benzophenone precursor.

The resistance of the *o*-methoxy-group in benzophenone (8a) to demethylation by boron trichloride was surprising and posed a problem in the planned subsequent cyclization of the intermediate to a xanthone. 5,7-Dihydroxychroman (10a) was therefore converted into the dibenzyl ether (10c). It is of interest that, just as in the methylation of (10a), a nuclear-benzylated product (15b) and a tetra-benzylated ketone (16b) were also isolated, in small quantities. Acylation of the ether (10c) with the carboxylic acid (9b) in the presence of trifluoroacetic anhydride at room temperature for 10 min was found to give the desired benzophenone (8c) (see later). Under more vigorous conditions, however, the only product isolated was (20), probably arising from the reversibility of the acylation, as established by Sundholm [11] in analogous reactions. The alternative structure (21) was ruled out on the basis of the observed chemical shift of the two-proton singlet at τ 3.70 in the ^{1}H n.m.r. spectrum of (20), in comparison with the aromatic proton absorptions of benzophenone (8b) [τ 3.70 (s) and 3.95 (s), the latter attributable to a proton *para* to an ether substituent in a benzene ring [12]].

The protecting benzyl group of (8c) was removed by hydrogenolysis and the product (8d) treated with ethereal diazomethane to give (8e). A minor product (8b) was also isolated and provides strong evidence in favour of structure (8c) as that of the acylation product. Ring closure of (8e), effected with tetramethylammonium hydroxide in refluxing aqueous pyridine, resulted in a xanthone identical with authentic dimethyl-1-isonormangostin (7),[1,7] thus further affirming the assigned structure of the benzophenone (8c).

Initial study of the reaction of (7) with boron trichloride revealed that when the concentration of boron trichloride was $\leqslant$0.25M, only one dihydropyran ring was cleaved, as shown by the downfield shift of only one CMe_2 absorption of (7) from τ 8.55 to 8.33. When more concentrated boron trichloride (*ca.* 1M) solution was used, however, both dihydropyran rings were cleaved to yield the dichloride (6a); however this reacted with diazomethane in dichloromethane only with difficulty. Treatment of (6a) with iodomethane in refluxing acetone solution in the presence of anhydrous potassium carbonate finally afforded the known 3′,3″-dichlorotetrahydrodimethylmangostin (6b).

In view of the results of dehydrochlorination of (4a), it was thought expedient to protect the 8-hydroxy-group of (6b) by formation of the methoxycarbonyloxy derivative (6c) to avoid undesirable dihydropyran ring formation during elimination. The reaction of (6c) with lithium chloride in dimethylformamide at 90—100 °C gave, after 6 h, a product whose ^{1}H n.m.r. resonance spectrum indicated the possibility of it being a mixture containing (1d) and the side-chain double-bond isomers (22a—c). Analytical t.l.c. [four developments in hexane–benzene (2 : 1)], showed three spots, with the most polar corresponding to (1d). Attempts to resolve the mixture by p.l.c. however, were unsuccessful.

The ease with which the protecting methoxycarbonyloxy group was removed was confirmed by the reaction of (1e) with lithium chloride in dimethylformamide, and was also observed in the attempted dehydrochlorination of (6c) with 1,5-diazabicyclo[5.4.0]undec-5-ene. In the latter case, the only product isolated in good yield after 10 h in refluxing benzene solution was (6b). In fact, dehydrochlorination of (6b) occurred readily and without complication in dimethylformamide with lithium chloride to give a mixture shown by ^{1}H n.m.r. to be similar to that obtained from the elimination of (6c) under the same conditions.

Analytical h.p.l.c. of the product from the reaction of (6c), using reverse phase chromatography gave, after three recycles, four incompletely resolved peaks in the approximate area ratios 1 : 2 : 2 : 4. The first peak and the least abundant component had the same retention volume as that of dimethylmangostin (1d). Preparative h.p.l.c. under identical conditions with use of the recycle technique enabled the isolation of products from peak 1

and peak 4 in a pure state, and confirmed that the former was dimethylmangostin (1d). The latter yielded a light yellow solid, $C_{26}H_{30}O_6$, with u.v. absorptions similar to those of (1d). An i.r. peak at 890 cm^{-1} indicates the presence of terminal vinyl group(s) and this is corroborated by the presence of a four-proton n.m.r. doublet at τ 5.21 and 5.29. In addition, multiplet absorptions at τ 6.42—6.58 (2 H), 7.12—7.27 (2 H), and 7.65—7.88 (4 H), attributable to two A_2B_2 systems, and two methyl singlets at τ 8.11 and 8.18 respectively, were observed, and these taken together are consistent with the attachment of two 3-methylbut-3-enyl side-chains in the proposed structure (22c). The mass spectrum of (22c) also showed significant differences from that of (1d).[13] Whereas in (1d), the base peak is the molecular ion at *m/z* 438, in the case of (22c), the base peak is at *m/z* 383 ($M^+ - C_4H_7$) instead, reflecting the ease with which a 2-methylprop-2-enyl fragment is lost as against a dimethylvinyl group. Furthermore, peaks at *m/z* 395 ($M^+ - C_3H_7$) and 339 ($M^+ - C_4H_8 - C_3H_7$) present in the spectrum of (1d) were not observed in that of (22c). These have been rationalized as due to the rearrangement of the 3-methylbut-2-enyl side chain *ortho* to a methoxy substituent and the resultant loss of an isopropyl radical.

In an attempt to improve the yield of (1d) in the last step, the reaction of (6b) with potassium t-butoxide in dimethyl sulphoxide[14] was investigated. The product obtained, after 6 h at 100—105 °C was shown by analytical t.l.c. to be a complex mixture but containing a strong spot with R_f corresponding to that of β-mangostin (1b). Separation of this component by p.l.c. gave a semi-solid which was found by h.p.l.c. (reverse-phase chromatography) to consist of two incompletely resolved peaks in the approximate area ratio 1 : 3. The second peak after two recycles developed an inflection with higher retention volume. Preparative h.p.l.c. of the mixture under identical conditions (with use of the recycle technique) gave from the first peak a light yellow solid, identical with natural β-mangostin (1b).

EXPERIMENTAL

I.r. and light absorption spectra were measured with a Pye–Unicam SP 1000 and a Perkin-Elmer model 551 spectrophotometer, respectively. Unless otherwise stated, ^1H n.m.r. spectra were determined for solutions in the solvent specified at 90 MHz with a Perkin–Elmer R32 spectrometer and Me_4Si as internal reference. Mass spectra were recorded at 70 eV with an A.E.I. MS30 instrument. Analytical t.l.c. and p.l.c. were performed respectively on Merck pre-coated 0.25 mm and 2 mm Kieselgel 60 F_{254} glass-backed plates; spots were located with iodine vapour or by u.v. illumination. Hexane refers to the fraction of b.p. 64—68°. Elemental analyses were carried out by the Microanalytical Laboratory, National University of Singapore.

Methyl 3-(1,1-*Dimethylprop*-2-*ynyloxy*)-4-*methoxybenzoate* (11a).—A solution of methyl isovanillate (18.2 g, 0.1 mol) and 3-chloro-3-methylbut-1-yne[15] (15.3 g, 0.15 mol) in aqueous acetone (2% v/v; 150 ml) containing potassium iodide (3 g) and anhydrous potassium carbonate (20 g) was stirred and refluxed for 15 h. On cooling, more potassium carbonate (5 g) and 3-chloro-3-methylbut-1-yne (10 g) were added, and refluxing was continued for a further 24 h. The mixture was filtered and the solid washed thoroughly with ether. Acidification of the solid gave isovanillic acid (3 g).

The filtrate was evaporated to dryness, the residue redissolved in ether and extracted with aqueous sodium hydroxide (2%). Acidification of the alkaline solution gave methyl isovanillate (10 g). The ether layer was concentrated and the residue adsorbed onto alumina (Activity III; 120 g). Elution with hexane containing increasing amounts of ether (10—20% v/v) gave the *ester* (11a) (4.5 g), m.p. 54—55° (from aqueous ethanol) (Found: C, 67.7; H, 6.6. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%); $\nu_{max.}$ (KBr) 3 280, 2 120, 1 725, 1 610, and 1 130 cm^{-1}; $\tau(CDCl_3)$ 1.95 (1 H, d, *J* 3 Hz, H-2), 2.25 (1 H, dd, $J_{2,6}$ 3, $J_{5,6}$ 8 Hz, H-6), 3.12 (1 H, d, *J* 8 Hz, H-5), 6.13 (6 H, s, 2 OMe), 3.45 (1 H, s, ≡CH), and 8.33 (6 H, s, CMe_2).

2-(3-*Methylbut*-2-*enyl*)-3-*hydroxy*-4-*methoxybenzoic Acid* (12b).—The ester (11a) (3.75 g, 15.1 mmol) was dissolved in methanol (60 ml) and hydrogenated at room temperature in the presence of 5% Pd–$BaSO_4$ (1.0 g) and quinoline–sulphur poison[16] (10 drops) until uptake of hydrogen was approximately 1 equiv. *Methyl* 3-(1,1-*dimethylprop*-2-*enyloxy*)-4-*methoxybenzoate* (3.65 g) crystallized from aqueous ethanol; m.p. 40—42° (Found: C, 67.0; H, 7.6. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.3%); $\nu_{max.}$ (CCl_4) 1 730, 1 610, 1 135, 1 000, and 925 cm^{-1}.

The preceding ester (3.65 g, 14.6 mmol) dissolved in *N*,*N*-dimethylaniline (50 ml) was heated to reflux under nitrogen for 6 h. The aniline was removed *in vacuo* and the residue dissolved in ether, washed with aqueous hydrochloric acid (0.5N) and water, and dried (Na_2SO_4). *Methyl* 2-(3-*methylbut*-2-*enyl*)-3-*hydroxy*-4-*methoxybenzoate* (12a) had b.p. 120° (bath temp.) at 0.5 mmHg (Found: C, 67.0; H, 7.2. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.3%); $\nu_{max.}$ (CCl_4) 3 580, 1 725, 1 285, and 1 220 cm^{-1}.

The crude rearrangement product (12a) was saponified by refluxing with aqueous sodium hydroxide (10% w/v; 100 ml) under nitrogen (0.5 h). Acidification gave the *acid* (12b) (3.2 g), m.p. 153—154° (from aqueous ethanol) (Found: C, 66.2; H, 6.9. $C_{13}H_{16}O_4$ requires C, 66.0; H, 6.8%); $\nu_{max.}$ (KBr) 3 570, 2 700—2 500, 1 690, 1 615, 1 590, and 1 285 cm^{-1}. The *acetate* (12c), prepared by reaction with acetic anhydride in pyridine, had m.p. 169—170° (Found: C, 64.7; H, 6.6. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%); $\nu_{max.}$ ($CHCl_3$) 2 700—2 500, 1 775, 1 700, 1 610, 1 580, and 1 285 cm^{-1}; $\tau(CDCl_3)$ 1.25 (1 H, br s, CO_2H), 2.00 and 3.15 (1 H each, both d, *J* 9 Hz, H-5 and -6), 4.75—5.05 (1 H, m, =CH), 6.15 (3 H, s, OMe), 6.28 (2 H, d, *J* 6 Hz, $ArCH_2$), 7.69 (3 H, s, MeCO), and 8.25 and 8.33 (6 H, each s, CMe_2).

5,7-*Dihydroxy*-3,4-*dihydro*-2,2-*dimethyl*-2H-1-*benzopyran* (10a).—To a stirred solution of phloroglucinol (5.0 g, 39.7 mmol) in dry dioxan (25 ml) at 40 °C was added boron trifluoride–ether[17] (1.5 ml), followed by 2-methylbut-3-en-2-ol (2.1 ml, 20 mmol), dropwise over 5 min. After a further 1 h at 35—40 °C, the solution was poured into saturated aqueous sodium hydrogen carbonate (250 ml) and the product isolated with ether. The combined ethereal extracts were washed four times with water and once with brine, and dried (Na_2SO_4). Evaporation left a viscous gum which was chromatographed over silica gel (150 g).

Elution with benzene containing increasing amounts of ethyl acetate (5—15% v/v) gave first an unidentified oil (0.56 g), followed by (10a) (0.18 g), colourless needles from chloroform–hexane, m.p. 163—164° (lit.,[18] 163—164°). Elution with benzene–ethyl acetate (5 : 1) gave 2-(3-methylbut-2-enyl) phloroglucinol (13) (2.05 g), needles from chloroform, m.p. 97—98° (lit.,[9] m.p. 97°), triacetate derivative (13b), b.p. 140° at 0.05 mmHg (lit.[9] b.p. 160° at 0.2 mmHg), $\nu_{max.}$ (CCl_4) 1 790, 1 630, 1 600, and 1 200 cm^{-1}; τ($CDCl_3$) 3.20 (2 H, s, ArH), 4.80—5.30 (1 H, m, =CH), 6.84 (2 H, d, *J* 7 Hz, $ArCH_2C$=), 7.77 (9 H, s, 3 MeCO), and 8.32 (6 H, br s, Me_2C). Pure (13) was cyclized to (10a) according to the published procedure.[18]

In another experiment, the viscous gum isolated from the reaction of phloroglucinol (10 g, 79 mmol) with 2-methylbut-3-en-2-ol (4.2 ml, 44 mmol) as described above was heated with aqueous citric acid (5% w/v; 300 ml) on a steam-bath for 15 h and filtered while hot. The filtrate was washed twice with hexane to remove unwanted non-polar material. Isolation with ether gave crude (10a) (4.9 g), which after two recrystallizations from benzene had m.p. and mixed m.p. 163—164°.

5,7-Dimethoxy-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran (10b).—To a stirred solution of the dihydroxychroman (10a) (2.0 g, 10.3 mmol) and dimethyl sulphate (3.5 g, 28 mmol) at 30 °C was added aqueous sodium hydroxide (4N; 8 ml), dropwise over 3 h. The mixture was stirred overnight and diluted with water, and the product isolated with ether. Analytical t.l.c. [benzene–hexane (1 : 2); two developments] showed a major spot at R_f 0.44 and a very minor spot at R_f 0.54. The mixture was separated by p.l.c. to give (10a) as the major component (1.6 g), b.p. 116° (bath temp.) at 4 mmHg (lit.,[19] 114° at 1 mmHg); $\nu_{max.}$ (film) 1 620, 1 600, 1 150, and 1 100 cm^{-1}; τ($CDCl_3$) 3.98 (2 H, s, ArH), 6.22 and 6.26 (3 H each, s, 2 OMe), 7.40 (2 H, t, *J* 7 Hz, ring $ArCH_2$), 8.25 (2 H, t, *J* 7 Hz, ring CH_2), and 8.68 (6 H, s, CMe_2). The minor component (0.1 g), 3,4-dihydro-5,7-dimethoxy-2,2,6 (or 8)-trimethyl-2*H*-1-benzopyran (15a) had b.p. 120—125° (bath temp.) at 4 mmHg (Found: C, 71.4; H, 8.6. Calc. for $C_{14}H_{20}O_3$: C, 71.2; H, 8.5%); $\nu_{max.}$ (film) 1 610, 1 165, and 1 130 cm^{-1}; τ($CDCl_3$) 3.92 (1 H, s, ArH), 6.20 (6 H, s, 2 OMe), 7.40 (2 H, t, *J* 7 Hz, ring $ArCH_2$), 7.98 (3 H, s, $ArCH_3$), 8.27 (2 H, t, *J* 7 Hz, ring CH_2), and 8.70 (6 H, s, CMe_2).

When methylation was effected with iodomethane in the presence of aqueous sodium hydroxide, there was isolated by p.l.c. a trace of *2,3,4,8-tetrahydro-2,2,6,6,8,8-hexamethyl-5H-1-benzopyran-5,7(6H)-dione* (16a), R_f 0.12 [benzene–hexane (1 : 2); two developments], which crystallized from aqueous methanol as colourless rods, m.p. 72—73° (Found: C, 72.0; H, 9.0. $C_{15}H_{22}O_3$ requires C, 72.0; H, 8.9%); $\nu_{max.}$ (CCl_4) 1 715, 1 655, 1 620, 1 170, 1 150, and 1 115 cm^{-1}; τ($CDCl_3$) 7.60 (2 H, t, *J* 7 Hz, ring $=C-CH_2$), 8.27 (2 H, t, *J* 7 Hz, ring CH_2), and 8.62 and 8.65 (18 H, s, CMe_2).

Reaction of the Carboxylic Acid (12c) *with 1,3,5-Triacetoxy-2-(3-methylbut-2-enyl)benzene* (13b) *in the Presence of Trifluoroacetic Anhydride*.—Trifluoroacetic anhydride (7 ml) was added to a mixture of the carboxylic acid (12c) (316 mg, 1.14 mmol) and the triacetate (13b) (365 mg, 1.14 mmol) at 0 °C. The solution was stirred at room temperature for 16 h, then concentrated under reduced pressure, and the residue was redissolved in dichloromethane. The dichloromethane solution was washed with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated. The dark residue was adsorbed onto four p.l.c. plates and developed with benzene–ether (6 : 1). A strongly u.v.-active band at R_f 0.31 was taken out and extracted with ethyl acetate, and the product repurified by p.l.c. to give *4-acetoxy-2-isopropylidene-5-methoxyindan-1-one* (14a) (168 mg), which crystallized from aqueous methanol as pale yellow needles, m.p. 163—164° (Found: C, 69.0; H, 6.4. $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.2%); $\nu_{max.}$ (CCl_4) 1 785, 1 705, 1 650, 1 620, 1 285, and 1 190 cm^{-1}; $\lambda_{max.}$ (EtOH) 236br (log ε 4.07) and 302 nm (4.38); τ($CDCl_3$) 8.32 and 7.03 (1 H each, d, *J* 9 Hz, H-6 and -7), 6.10 (3 H, s, OMe), 6.52 (2 H, s, $ArCH_2$), 7.51 and 7.63 (6 H, each s, CMe and MeCO), and 8.03 (3 H, s, CMe).

Alkaline hydrolysis of (14a) gave in poor yield, *4-hydroxy-2-isopropylidene-5-methoxyindan-1-one* 14(b), m.p. 167—168° (from aqueous ethanol) (Found: C, 71.3; H, 6.6. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%); $\nu_{max.}$ (KBr) 3 400—3 100, 1 700, 1 640, 1 615, 1 280, and 1 085 cm^{-1}; τ($CDCl_3$) 2.60 and 3.10 (1 H, each, d, *J* 9 Hz, H-6 and -7), 4.20 (1 H, s, exchangeable, 4-OH), 6.10 (3 H, s, OMe), 6.45 (2 H, s, $ArCH_2$), and 7.56 and 8.00 (3 H each s, CMe_2).

3,4-Dihydro-2,2-dimethyl-8-methoxy-2H-1-benzopyran-5-carboxylic Acid (9a).—(*a*) The ester (12a) (1.0 g, 4 mmol) dissolved in dry benzene (50 ml) containing toluene-*p*-sulphonic acid (0.2 g) was refluxed in a Dean–Stark apparatus for 6 h. The cooled solution was washed with saturated aqueous sodium hydrogen carbonate, dried, (Na_2SO_4) and concentrated. The cyclized product, recrystallized from hexane, had m.p. 73—74° (Found: C, 67.3; H, 7.5. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.3%); $\nu_{max.}$ (KBr) 1 725, 1 610, 1 590, 1 290, and 1 095 cm^{-1}. The crude ester was heated to reflux in methanol (20 ml) containing sodium hydroxide (10%; 10 ml) for 2 h. Acidification afforded the carboxylic acid (9a) (0.72 g), which crystallized from benzene as colourless *needles*, m.p. 172—173° (Found: C, 66.0; H, 7.0. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%); $\nu_{max.}$ (KBr) 2 750—2 500, 1 695, 1 605, 1 585, 1 300, 1 280, and 1 090 cm^{-1}; τ($CDCl_3$) 2.30 and 3.28 (1 H each, d, *J* 9 Hz, H-5 and -6), 6.10 (3 H, s, OMe), 6.81 (2 H, t, *J* 7 Hz, ring $ArCH_2$), 8.20 (2 H, t, *J* 7 Hz, ring CH_2), and 8.61 (6 H, s, CMe_2).

(*b*) The carboxylic acid (12b) (1.5 g) was cyclized similarly to give directly (9a) (1.46 g).

8-Bromo-3,4-dihydro-5,7-dimethoxy-2,2-dimethyl-2H-1-benzopyran (17).—The dihydrobenzopyran (10b) (1.19 g, 5.35 mmol) in dry ether (30 ml) was cooled to between −20 and −25 °C with stirring while an ice-cold solution of dioxan dibromide,[10] prepared from dioxan (0.6 ml, 6.8 mmol) and bromine (0.9 g, 5.6 mmol) in dry ether (15 ml), was added dropwise over 20 min. The solution was allowed to warm to room temperature and washed successively with aqueous sodium hydroxide (10%) and water, dried (Na_2SO_4), and evaporated. The semi-solid residue was recrystallized from hexane to give the *bromo-derivative* (17) (1.4 g), m.p. 83.5—84.5° (Found: C, 51.7; H, 6.0; Br, 26.9. $C_{13}H_{17}O_3Br$ requires C, 51.8; H, 5.7; Br, 26.5%); $\nu_{max.}$ (KBr) 1 610, 1 585, 1 165, and 1 110 cm^{-1}; τ($CDCl_3$) 3.90 (1 H, s, H-6), 6.15 and 6.20 (6 H, each s, 2 OMe), 7.40 (2 H, t, *J* 7 Hz, ring $ArCH_2$), 8.25 (2 H, t, *J* 7 Hz, ring CH_2) and 8.66 (6 H, s, CMe_2).

3,4-Dihydro-2,2-dimethyl-5,7-dimethoxy-2H-1-benzopyran-8-yl 3,4-dihydro-2,2-dimethyl-8-methoxy-2H-1-benzopyran-5-yl Ketone (8a).—The carboxylic acid (9a) (2.10 g, 8.9 mmol) was converted into the acyl chloride with oxalyl chloride (1.2 ml) and dimethylformamide (5 drops) in dry benzene

(30 ml) at room temperature (12 h). After removal of solvent, the residue was redissolved in dry ether and used immediately.

The bromide (17) (2.68 g, 8.9 mmol) was dissolved in dry ether (35 ml) and n-butyl-lithium (4.4 ml; 2.04 mmol ml^{-1}) was added at −70 °C. The mixture was stirred at room temperature for 2 h, then added dropwise over 1 h to the acyl chloride solution at 0 °C. After stirring overnight at room temperature, the mixture was poured into ice-cold aqueous hydrochloric acid (0.5N; 30 ml) and the product filtered off, washed with ether, then water, and dried. Recrystallization from benzene–hexane gave the *ketone* (8a) (2.23 g), m.p. 202.5—203.5° (Found: C, 70.9; H, 7.1%; M^+, 440.2162. $C_{26}H_{32}O_6$ requires C, 70.9; H, 7.3%; *M*, 440.2200), $\nu_{max.}$ (KBr) 1 670, 1 605, 1 590, and 1 120 cm^{-1}; τ($CDCl_3$) 2.95 (1 H, d, *J* 9 Hz, H-6), 3.38 (1 H, d, *J* 9 Hz, H-7), 3.85 (1 H, s, H-6), 6.15 (6 H, s, 2 OMe), 6.25 (3 H, s, OMe), 6.75 and 7.40 (2 H each, t, *J* 7 Hz, ring $ArCH_2$), 8.00—8.50 (4 H, m, ring CH_2), 8.60 and 8.95 (6 H each, s, 2 CMe_2); *m/z* 440 (10%), 410, (11), 409 (40), 354 (13), 353 (60), 249 (3), 219 (16), 218 (100), 203 (17), 193 (44), 175 (9), 167 (9), and 163 (6).

Reaction of the Ketone (8a) *with Boron Trichloride*.—The ketone (8a) (0.63 g, 1.4 mmol) was dissolved in dry dichloromethane (30 ml) and boron trichloride in dichloromethane (*ca.* 1M; 13 ml) was added at 0 °C. After a further 4 h at room temperature, the solution was cooled to 0 °C, and water (20 ml) was cautiously added. The mixture was diluted with dichloromethane (50 ml) and stirred for 15 min, and the organic layer was separated and washed successively with water and saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated. The residue was extracted with boiling hexane (4 × 30 ml); concentration of the extracts afforded pale yellow needles of 3-(3-*chloro*-3-*methylbutyl*)-4,6-*dimethoxy*-2-*hydroxyphenyl* 3,4-*dihydro*-2,2-*dimethyl*-8-*methoxy*-2H-1-*benzopyran*-5-*yl* *ketone* (18) (0.48 g), m.p. 148—149° (Found: C, 65.6; H, 7.0; Cl, 7.3%; M^+ 476.1950. $C_{26}H_{33}ClO_6$ requires C, 65.5; H, 7.0; Cl, 7.4%; *M*, 476.1967); $\nu_{max.}$ (KBr) 1 655sh, 1 630, 1 600, 1 290, and 1 100 cm^{-1}; τ($CDCl_3$) −3.05 (1 H, s, exchangeable, chelated OH), 3.35, (2 H, s, ArH), 4.15, (1 H, s, ArH), 6.15 (6 H, s, 2 OMe), 6.60 (3 H, s, OMe), 7.00—7.50 (4 H, m, $ArCH_2$), 7.80—8.30 (4 H, m, CCH_2), and 8.33 and 8.62 (6 H each s, 2 CMe_2); *m/z* 476 (4%), 441 (5), 440 (16), 409 (10), 385 (8), 353 (19), 218 (20), and 191 (100).

2-*Hydroxy*-4-*methoxy*-5-*methoxycarbonyloxybenzoic Acid* (11b).—Methyl chloroformate (2.42 ml, 32 mmol) was added, dropwise over 10 min, to a stirred solution of 2,5-dihydroxy-4-methoxybenzoic acid [1] (5.52 g, 30 mmol) in water (100 ml) containing sodium hydroxide (2.52 g, 63 mmol) at 0—5 °C. After a further 1 h at the same temperature, the solution was acidified (N-HCl) and the precipitate collected, washed, and recrystallized. The pure product (6.29 g) was obtained from aqueous methanol as feathery *needles*, m.p. 195—196° (Found: C, 49.7; H, 4.3. $C_{10}H_{10}O_7$ requires C, 49.6; H, 4.2%); $\nu_{max.}$ (KBr) 1 775 and 1 680 cm^{-1}.

Methyl 2,4-*Dimethoxy*-5-*methoxycarbonyloxybenzoate* (11c).—The acid (11b) (7.58 g, 31.3 mmol) in acetone (100 ml) containing anhydrous potassium carbonate (10.5 g) and dimethyl sulphate (9 g) was refluxed for 6.5 h. Evaporation of the filtered solution and recrystallization of the solid residue from benzene–hexane gave the pure methyl ester (11c) as colourless *needles* (7.8 g), m.p. 108—110° (Found: C, 53.3; H, 5.2. $C_{12}H_{14}O_7$ requires C, 53.3; H, 5.2%); $\nu_{max.}$ (KBr) 1 780 and 1 725 cm^{-1}.

Methyl 5-*Hydroxy*-2,4-*dimethoxybenzoate*.—The ester (11c) (7.77 g, 28.4 mmol) in tetrahydrofuran (60 ml) was hydrolysed with sodium hydroxide (0.5N; 30 ml) at 0—5 °C. After 0.5 h, more 0.5N-sodium hydroxide (30 ml) was added and the solution stirred at room temperature until reaction was complete (t.l.c., 1 h). Solvent was removed *in vacuo* and the residue acidified (N-HCl). The product was recrystallized from benzene–hexane to give *methyl* 5-*hydroxy*-2,4-*dimethoxybenzoate* (11d) (5.65 g), m.p. 123—124° (Found: C, 56.5; H, 5.7. $C_{10}H_{12}O_5$ requires C, 56.6; H, 5.7%); $\nu_{max.}$ (KBr) 3 380 and 1 700 cm^{-1}; τ($CDCl_3$) 2.53 and 3.46 (1 H each, s, H-6 and -3), 4.75 (1 H, s, exchangeable, 5-OH), and 6.04, 6.11, and 6.13 (9 H, all s, 3 OMe).

Methyl 5-(1,1-*Dimethylprop*-2-*ynyloxy*)-2,4-*dimethoxybenzoate* (11e).—A mixture of the ester (11d) (10 g, 47 mmol), potassium carbonate (13 g), potassium iodide (1.3 g) and 3-chloro-3-methylbut-1-yne (9.6 g) in aqueous acetone (1.5% v/v; 200 ml) was heated under reflux and stirred for 48 h with further addition of 3-chloro-3-methylbut-1-yne (10 g) and potassium carbonate (13 g) after 24 h. The mixture was filtered and the filtrate concentrated to dryness. The residue was chromatographed over silica gel (200 g). Elution with benzene gave a coloured oil, followed by the ester (11e) (2.95 g) which crystallized from cyclohexane as colourless *needles*, m.p. 93.5—94.5° (Found: C, 64.8; H, 6.6. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%); $\nu_{max.}$ (KBr) 3 250, 2 100, and 1 730 cm^{-1}; τ($CDCl_3$) 2.13 and 3.52 (1 H each, s, H-6 and H-3), 6.13 and 6.16 (9 H each, s, 3 OMe), 7.51 (1 H, s, H−C≡C), and 8.41 (6 H, s, CMe_2). Further elution with benzene containing increasing amounts of ether (5—20% v/v) gave unchanged ester (11d) (3.2 g).

Methyl 6,8-*Dimethoxy*-2,2-*dimethyl*-2H-1-*benzopyran*-5-*carboxylate* (19).—A solution of the ester (11e) (2.0 g) in *N*,*N*-diethylaniline (100 ml) was heated to reflux under nitrogen for 7.5 h, and the product was worked up as described for preparation of (12a). The crude product, after three recrystallizations from aqueous ethanol, afforded (19) as colourless *prisms* (1.8 g), m.p. 122—123° (Found: C, 64.8; H, 6.6. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%); $\nu_{max.}$ (KBr) 1 715 and 1 590 cm^{-1}; τ($CDCl_3$) 3.58 (1 H, s, H-7), 3.63 and 4.33 (1 H each, d, *J* 10 Hz, ring =CH), 6.16 (6 H, s, 2 OMe), 6.24 (3 H, s, OMe) and 8.60 (6 H, s, CMe_2).

3,4-*Dihydro*-6,8-*dimethoxy*-2,2-*dimethyl*-2H-1-*benzopyran*-5-*carboxylic Acid* (9b).—The benzopyran (19) (1.39 g) in ethanol (70 ml) was hydrogenated over 10% palladium–carbon (360 mg) at 1 atm. *Methyl* 3,4-*dihydro*-6,8-*dimethoxy*-2,2-*dimethyl*-2H-1-*benzopyran*-5-*carboxylate* crystallized from aqueous ethanol as colourless plates (1.28 g), m.p. 108—109.5° (Found: C, 64.2; H, 7.0. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.2%); $\nu_{max.}$ (KBr) 1 735 and 1 610 cm^{-1}.

The above ester was saponified by heating in methanol containing sodium hydroxide (0.5N) for 2 h. The pure carboxylic acid (9b) crystallized from aqueous methanol as colourless *needles*, m.p. 173.5—175° (Found: C, 63.3; H, 7.0. $C_{14}H_{18}O_5$ requires C, 63.1; H, 6.8%); $\nu_{max.}$ (KBr) 3 360, 1 740, and 1 605 cm^{-1}; τ($CDCl_3$) 3.55 (1 H, s, H-7), 6.08 and 6.13 (3 H each, s, OMe), 6.90 and 8.25 (2 H each, t, *J* 7 Hz, ring CH_2), 8.68 (6 H, s, CMe_2).

3,4-*Dihydro*-5,7-*dimethoxy*-2,2-*dimethyl*-2H-1-*benzopyran*-8-*yl* 3,4-*dihydro*-6,8-*dimethoxy*-2,2-*dimethyl*-2H-1-*benzopyran*-5-*yl Ketone* (8b).—The bromide (17) (2.07 g, 6.9 mmol) was converted into the lithio-derivative, which was added

to the acyl chloride of carboxylic acid (9b) (1.85 g, 6.9 mmol) as described in the preparation of the ketone (8a). The product gave, after recrystallization from benzene–hexane, the ketone (8b) (1.2 g) as colourless *rods*, m.p. 191—193° (Found: C, 69.0; H, 7.2. $C_{27}H_{34}O_7$ requires C, 68.9; H, 7.3%); $\nu_{max.}$ (KBr) 1 670, 1 600, and 1 120 cm^{-1}; $\tau(CDCl_3)$ 3.70 and 3.95 (1 H each, s, ArH), 6.18, 6.25, and 6.55 (3 H each, s, 3 OMe), 7.15 and 7.46 (2 H each, t, *J* 7 Hz, ring $ArCH_2$), 8.00—8.45 (4 H, m, ring CH_2), and 8.65 and 9.03 (6 H each, s, 2 CMe_2).

5,7-*Bisbenzyloxy*-3,4-*dihydro*-2,2-*dimethyl*-2H-1-*benzopyran* (10c).—The dihydroxychroman (10a) (5.85 g, 30 mmol) in acetone (100 ml) containing anhydrous potassium carbonate (12.5 g) and benzyl bromide (13.4 g) was heated under reflux with stirring for 24 h. The filtered solution was distilled *in vacuo* to remove solvent and unchanged benzyl bromide, and the residue, dissolved in benzene–hexane (1 : 1 v/v) was filtered through alumina (50 g). Evaporation left an oil which partially crystallized. Trituration with hexane followed by recrystallization from ethanol afforded pure product (10c) (6.8 g), m.p. 121—121.5° (Found: C, 80.1; H, 7.0. $C_{25}H_{26}O_3$ requires C, 80.2; H, 7.0%); $\nu_{max.}$ (KBr) 1 615 and 1 590 cm^{-1}; $\tau(CDCl_3)$ 2.63 (10 H, br s, Ph), 3.81 and 3.89 (1 H each, d, *J* 3 Hz, H-6 and -8), 4.99 and 5.02 (4 H, each s, $ArCH_2O$), 7.34 and 8.24 (2 H each, t, *J* 7 Hz, H-3 and -4), and 8.68 (6 H, s, CMe_2). The residue from concentration of the hexane filtrate was chromatographed over silica gel (30 g). Elution with benzene–hexane (1 : 2) gave 6(or 8)-benzyl-5,7-bisbenzyloxy-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (15b) (1.1 g), m.p. 92—94° (from methanol) (Found: C, 82.5; H, 7.0. Calc. for $C_{31}H_{32}O_3$: C, 82.3; H, 7.1%); $\nu_{max.}$ 1 615 and 1 590 cm^{-1}; $\tau(CDCl_3)$ 2.67, 2.78, and 2.84 (5 H each, s, Ph), 3.71 (1 H, s, H-6 or -8), 5.05 and 5.28 (2 H each, s, $ArCH_2O$), 5.98 (2 H, s, $ArCH_2$), 7.30 and 8.25 (2 H each, t, *J* 7 Hz, ring CH_2), and 8.67 (6 H, s, CMe_2).

In a separate experiment, the dihydroxychroman (10a) (952 mg, 4.9 mmol) in acetone (20 ml) containing sodium iodide (77 mg), benzyl chloride (1.65 g) and anhydrous potassium carbonate (3.8 g) gave, after refluxing for 24 h, a mixture separated by chromatography over silica gel, of the dibenzyl ether (10c) (324 mg) and 6,6,8,8-*tetrabenzyl*-2,3,4,8-*tetrahydro*-2,2-*dimethyl*-5H-1-*benzopyran*-5,7(6H)-*dione* (16b) (270 mg), m.p. 139—140° (from benzene) (Found: C, 84.1; H, 7.2. $C_{39}H_{38}O_3$ requires C, 84.4; H, 6.9%); $\nu_{max.}$ (CCl_4) 1 710, 1 655, and 1 610 cm^{-1}; $\tau(CDCl_3)$ 2.80—3.20 (20 H, m, Ph), 7.10 and 7.44 (4 H, q, *J* 14 Hz, $ArCH_2$), 7.18 and 7.50 (4 H, q, *J* 14 Hz, $ArCH_2$), 7.76 and 8.62 (2 H each, t, *J* 8 Hz, ring CH_2), and 9.02 (6 H, s, CMe_2).

5,7-*Bisbenzyloxy*-3,4-*dihydro*-2,2-*dimethyl*-2H-1-*benzopyran*-8-*yl* 3,4-*Dihydro*-6,8-*dimethoxy*-2H-1-*benzopyran*-5-*yl Ketone* (8c).—To a stirred solution of the dibenzyl ether (10c) (2.0 g, 5.3 mmol) and the carboxylic acid (9b) (800 mg, 3.0 mmol) in dry methylene chloride (25 ml) at 30 °C was added trifluoroacetic anhydride (3 ml). After 10 min, the solution was concentrated *in vacuo* to dryness and the residue, redissolved in benzene, was chromatographed over silica gel (50 g). Elution with benzene gave the unchanged dibenzyl ether (10c) (480 mg). Elution with benzene containing ether (5—10% v/v) gave the ketone (8c) (1.31 g), which crystallized from ethanol as colourless *plates*, m.p. 174—175° (Found: C, 75.5; H, 6.8. $C_{39}H_{42}O_7$ requires C, 75.2; H, 6.8%); $\nu_{max.}$ (KBr) 1 665 and 1 605 cm^{-1}; $\tau(CDCl_3)$ 2.65 and 2.75 (5 H each, s, Ph), 3.69 and 3.88 (1 H each, s, H-7 and -6), 4.99 and 5.03 (2 H each, s, $ArCH_2O$), 6.15 and 6.59 (3 H each, s, OMe), 7.20 and 7.40 (2 H each, t, *J* 8 Hz, ring CH_2), 8.33 and 8.42 (2 H each, t, *J* 8 Hz, ring CH_2), and 8.68 and 8.96 (6 H each, s, CMe_2).

In another experiment, when a solution of the dibenzyl ether (10c) (1.06 g, 2.83 mmol) and the carboxylic acid (9b) (400 mg, 1.5 mmol) in dry methylene chloride (15 ml) containing trifluoroacetic anhydride (2 ml) was stirred at 29 °C for 5 h and then heated to reflux for 45 min, the only product isolated from column chromatography over silica gel was *bis*-(3,4-*dihydro*-6,8-*dimethoxy*-2,2-*dimethyl*-2H-1-*benzopyran*-5-*yl*) *ketone* (20), m.p. 205—207° (from aqueous ethanol) (Found: C, 69.0; H, 7.5. $C_{27}H_{34}O_7$ requires C, 68.9; H, 7.3%); $\nu_{max.}$ (KBr) 1 670 and 1 605 cm^{-1}; $\tau(CDCl_3)$ 3.70 (2 H, s, ArH), 6.17 and 6.60 (6 H each, s, 4 OMe), 7.13 and 8.23 (4 H each, t, ring CH_2), and 8.62 (12 H, s, 2 CMe_2).

3,4-*Dihydro*-5,7-*dihydroxy*-2,2-*dimethyl*-2H-1-*benzopyran*-8-*yl* 3,4-*Dihydro*-6,8-*dimethoxy*-2,2-*dimethyl*-2H-1-*benzopyran*-5-*yl Ketone* (8d).—A solution of the ketone (8c) (1.05 g, 1.69 mmol) in ethyl acetate (80 ml) containing palladium–carbon (10% w/w; 380 mg) was hydrogenated at atmospheric pressure to give the debenzylated ketone (8d) (670 mg), which crystallized from aqueous ethanol as yellow *needles*, m.p. 231—233° (Found: C, 67.9; H, 7.1. $C_{25}H_{30}O_7$ requires C, 67.9; H, 6.8%); $\nu_{max.}$ (KBr) 3 400 and 1 630br cm^{-1}; $\tau[(CD_3)_2CO]$ −3.67 (2 H, s, exchangeable, 2 OH), 3.44 and 4.02 (1 H each, s, H-7 and -6), 6.19 and 6.36 (3 H each, s, OMe), 7.50 (4 H, t, *J* 8 Hz, ring $ArCH_2$), 8.28 and 8.40 (2 H each, t, *J* 8 Hz, ring CH_2), and 8.70 and 9.12 (6 H each, s, 2 CMe_2).

3,4-*Dihydro*-7-*hydroxy*-5-*methoxy*-2,2-*dimethyl*-2H-1-*benzopyran*-8-*yl* 3,4-*dihydro*-6,8-*dimethoxy*-2,2-*dimethyl*-2H-1-*benzopyran*-5-*yl Ketone* (8e).—Ethereal diazomethane was added to a solution of the ketone (8d) (260 mg) in methanol (5 ml) at 0—5 °C and the solution was left at room temperature overnight. The solvent was then removed and the residue was applied to two p.l.c. plates and developed twice in benzene–ether (3 : 1). The larger band at R_f 3.9 was eluted with ethyl acetate and gave the monomethylated ketone (8e) (175 mg), which crystallized from aqueous ethanol as light yellow *needles*, m.p. 156—158° (Found: C, 68.3; H, 7.3. $C_{26}H_{32}O_7$ requires C, 68.4; H, 7.1%); $\nu_{max.}$ ($CHCl_3$) 1 620 cm^{-1}; $\tau[(CD_3)_2CO]$ −3.76 (1 H, s, exchangeable, OH), 3.43 and 3.92 (1 H each, s, H-7 and -6), 6.12, 6.18, and 6.36 (3 H each, s, OMe), 7.46 and 7.53 (4 H, each t, *J* 8 Hz, ring $ArCH_2$), 8.28 and 8.40 (4 H, each t, *J* 8 Hz, ring CH_2), and 8.70 and 9.12 (6 H each, s, 2 CMe_2). A minor band at R_f 0.21 gave the ketone (8b) (45 mg), m.p. and mixed m.p. 191—192°.

3,4,9,12,13,14-*Hexahydro*-5,9-*dimethoxy*-2,2,11,11-*tetramethyl*-2H-*dipyrano*[2,3-a : 2′,3′-j]*xanthen*-14-*one* (*Dimethyl*-1-*isonormangostin* [1,7]) (7).—A solution of the ketone (8e) (250 mg) in pyridine (15 ml) containing water (15 ml) and tetramethylammonium hydroxide [20] (2.5 ml; 25% w/v solution in water) was heated under reflux for 40 h, cooled, acidified (HCl), and extracted with dichloromethane. T.l.c. of the residue obtained after removal of solvent showed it to be a mixture of the unchanged ketone (8e) and the expected xanthone (7). The mixture was applied to two p.l.c. plates which were developed in hexane–ethyl acetate (2 : 1). The more polar band, eluted with ethyl acetate, gave dimethyl-1-isonormangostin (7) (55 mg), identified by m.p. and mixed m.p. (214—215°; lit.,[1] 213.9—215.2°), and i.r. and ^1H n.m.r. spectra [$\nu_{max.}$ (CCl_4) 1 660, 1 625, and 1 610 cm^{-1}; $\tau(CDCl_3)$ 3.34 and 3.69 (1 H each, s, H-8 and -6), 6.08 and 6.12 (3 H each, s, 2 OMe), 6.42 (2 H, t, *J* 8 Hz,

13-H_2), 7.35 (2 H, t, *J* 8 Hz, 4-H_2), 8.20 (4 H, t, *J* 8 Hz, 3- and 12-H_2), and 8.55 and 8.63 (6 H each, s, CMe_2)].

Reaction of Dimethyl-1-isonormangostin (7) *with Boron Trichloride*.—Boron trichloride in dichloromethane (*ca.* 1M; 3 ml) was added to a stirred solution of dimethyl-1-isonormangostin (7) (400 mg, 0.94 mmol) in dichloromethane (1 ml) at 0—5 °C, and after 3 h at 0—5 °C the solution was allowed to warm to room temperature (1 h) and poured into ice–water. After addition of more dichloromethane (50 ml), the mixture was stirred for 0.5 h, and worked up as described for (18). Removal of solvent left an orange-brown solid which was extracted with boiling hexane (6 × 30 ml). Concentration of the hexane solution gave 1,7-*bis*-(3-*chloro*-3-*methylbutyl*)-2,8-*dihydroxy*-3,6-*dimethoxyxanthen*-9-*one* (6a) (85 mg) as pale yellow needles, which after recrystallizations from the same solvent had m.p. 176—178° (Found: C, 60.5; H, 6.1; Cl, 14.3. $C_{25}H_{30}Cl_2O_6$ requires C, 60.4; H, 6.1; Cl, 14.3%), $\nu_{max.}$ (KBr) 3 570, 1 660, and 1 615 cm^{-1}; τ($CDCl_3$) −3.60, (1 H, s, exchangeable, 8-OH), 3.32 and 3.75 (1 H each, s, H-5 and -4), 4.42 (1 H, s, exchangeable, 2-OH), 6.02 and 6.12 (3 H each, s, 2 OMe), 6.30—6.60 (2 H, m, 1-$ArCH_2$), 7.00—7.30 (2 H, m, 7-$ArCH_2$), 7.80—8.20 (4 H, m, 2 $ClCCH_2$), and 8.28 and 8.34 (6 H each, s, CMe_2).

1,7-*Bis*-(3-*chloro*-3-*methylbutyl*)-8-*hydroxy*-2,3,6-*trimethoxyxanthen*-9-*one* (3′,3″-*Dichlorotetrahydrodimethylmangostin* [7]) (6b).—The dichloroxanthone (6a) (72 mg) in acetone (5 ml) containing iodomethane (20 μl) and anhydrous potassium carbonate (60 mg) was stirred and heated under reflux for 1 h, with more iodomethane (6 μl) being added after 0.5 h. Filtration and removal of solvent gave 3′,3″-dichlorotetrahydrodimethylmangostin (6b), which crystallized from hexane as light yellow needles, identified by m.p., mixed m.p. (155—157° lit.,[13] 156.5—157.5°), and i.r. and ^{1}H n.m.r. spectra [$\nu_{max.}$ (KBr) 1 660 and 1 610 cm^{-1}; τ −3.43 (1 H, s, exchangeable, 8-OH), and 3.81 (1 H each, s, H-5 and -4), 6.08, 6.16, and 6.18 (9 H, each s, 3 OMe), 6.35—6.66 (2 H, m, 1-$ArCH_2$), 7.04—7.39 (2 H, m, 7-$ArCH_2$), 7.84—8.18 (4 H, m, 2 $ClCCH_2$), and 8.30 and 8.38 (6 H each, s, CMe_2).

1,7-*Bis*-(3-*chloro*-3-*methylbutyl*)-2,3,6-*trimethoxy*-8-*methoxycarbonyloxyxanthen*-9-*one* (6c).—Dichlorotetrahydrodimethylmangostin (6b) (250 mg, 0.49 mmol) in acetone (30 ml) containing methyl chloroformate (0.5 ml) and anhydrous potassium carbonate (1.0 g) was heated under reflux for 24 h with more methyl chloroformate (0.3 ml) and anhydrous potassium carbonate (0.7 g) being added after 16 h. Filtration and evaporation gave a light brown solid, which was redissolved in benzene and filtered through silica gel (5 g). Pure (6c) (150 mg) crystallized from cyclohexane as colourless *needles*, m.p. 177—178° (Found: C, 59.1; H, 6.0; Cl, 12.4. $C_{28}H_{34}Cl_2O_8$ requires C, 59.1; H, 6.0; Cl, 12.4%); $\nu_{max.}$ ($CHCl_3$) 1 775, 1 655, 1 630, and 1 610 cm^{-1}; τ($CDCl_3$) 3.30 and 3.33 (2 H, each s, H-4 and -5), 6.05 (6 H, s, 2 OMe), 6.17 (3 H, s, OMe), 6.33—6.68 (2 H, m, 1-$ArCH_2$), 7.02—7.33 (2 H, m, 7-$ArCH_2$), 7.80—8.16 (4 H, m, 2 $ClCCH_2$), and 8.26 and 8.38 (6 H each, s, CMe_2).

2,3,6-*Trimethoxy*-8-*methoxycarbonyloxy*-1,7-*bis*-(3-*methylbut*-2-*enyl*)*xanthen*-9-*one* (1e).—Dimethylmangostin (1d) (200 mg, 0.46 mmol) in acetone (15 ml) containing methyl chloroformate (1 ml) and anhydrous potassium carbonate (1.5 g) was heated under reflux for 24 h. Filtration and evaporation left the 8-methoxycarbonyloxy derivative (1e) (160 mg) which crystallized from aqueous ethanol as colourless short *needles*, m.p. 128—129° (Found: C, 67.9; H, 6.7. $C_{28}H_{32}O_8$ requires C, 67.8; H, 6.5%); $\nu_{max.}$ ($CHCl_3$) 1 775, 1 660, 1 630, and 1 610 cm^{-1}; τ($CDCl_3$) 3.33 and 3.36 (2 H, each s, H-4 and -5), 4.60—5.02 (2 H, m, 2 =CH), 5.90 (2 H, d, *J* 7 Hz, 1-$ArCH_2$), 6.07, 6.09 and 6.23 (9 H, each s, 3 OMe), 6.65 (2 H, d, *J* 7 Hz, 7-$ArCH_2$), and 8.18, 8.25, and 8.35 (12 H, each s, 2 Me_2C).

Reaction of 1,7-*Bis*-(3-*chloro*-3-*methylbutyl*)-8-*methoxycarbonyloxy*-2,3,6-*trimethoxyxanthen*-9-*one* (6c) *with Lithium Chloride in Dimethylformamide*.—A solution of the dichloride (6e) (835 mg, 1.47 mmol) in dry dimethylformamide (20 ml) containing anhydrous lithium chloride (3.5 g) was stirred and heated at 95—105 °C under nitrogen for 6 h. The solvent was removed *in vacuo* and the residue was diluted with water and extracted with dichloromethane (4 × 40 ml). The combined extracts were washed successively with water and saturated aqueous sodium hydrogen carbonate, then filtered through silica gel, and concentrated to give a yellow semi-solid (520 mg). Analytical t.l.c. of the product after four developments with hexane–benzene (2 : 1) showed three spots at R_f 0.31, 0.36 and 0.41 respectively, with the first spot corresponding to dimethylmangostin (1d). Analytical h.p.l.c. of sample (20 μl) in tetrahydrofuran solution (30 mg ml^{-1}) using a Radial Pak A (C_{18}) column and acetonitrile–tetrahydrofuran–water (2 : 1 : 2) as eluant at a flow rate of 6.0 ml min^{-1} gave, after three recycles, four incompletely resolved peaks of approximately area ratio 1 : 2 : 2 : 4. The first peak had the same retention time as authentic dimethylmangostin (1d). Preparative h.p.l.c. (30 injections) under identical conditions gave from the first peak, pale yellow needles identified as dimethylmangostin (1d) (1.5 mg) by m.p., mixed m.p., and i.r. spectrum. From the last peak was obtained 8-*hydroxy*-1,7-*bis*-(3-*methylbut*-3-*enyl*)-2,3,6-*trimethoxyxanthen*-9-*one* (22c) (6.5 mg), which crystallized from aqueous ethanol as pale yellow needles, m.p. 137—138° (Found: M^+, 438.2011. $C_{26}H_{30}O_6$ requires *M*, 438.2042), $\nu_{max.}$ (CCl_4) 1 650, 1 600, 1 220, 1 125, and 890 cm^{-1}; $\lambda_{max.}$ (EtOH) 244 (log ε 4.48), 261 (4.50), 311 (4.34), and 350 nm (3.82); τ(JEOL FX-100 spectrometer; $CDCl_3$) −3.67 (1 H, s, 8–OH), 3.27 and 3.70 (1 H each, s, H-5 and -4), 5.21 and 5.29 (4 H, d, $=CH_2$), 6.03, 6.21, and 6.17 (3 H each, s, OMe), 6.42—6.58 (2 H, m, 1-$ArCH_2$), 7.12—7.27 (2 H, m, 7-$ArCH_2$), 7.65—7.88 (4 H, m, 2 $=CCH_2$), and 8.11 and 8.18 (3 H each, s, =CMe); *m/z* 438 (17%), 384 (25), 383 (100), 367 (4), 327 (10), 313 (4), and 297 (2).

When a solution of the dichloride (6b) (794 mg, 1.55 mmol) and lithium chloride (2.0 g) in dimethylformamide (25 ml) was heated for 5.5 h and worked up as described above, a yellow semi-solid product (519 mg) was obtained. T.l.c. and ^{1}H n.m.r. indicated the product to be a mixture similar to that isolated from (6c).

Reaction of 2,3,6-*Trimethoxy*-8-*methoxycarbonyloxy*-1,7-*bis*-(3-*methylbut*-2-*enyl*)*xanthen*-9-*one* (1e) *with Lithium Chloride in Dimethylformamide*.—The xanthone (1e) (117 mg, 0.24 mmol) in dimethylformamide (4 ml) containing lithium chloride (450 mg) was heated at 95—100° for 5 h. The product was worked up as for (6c), then dissolved in benzene–hexane (1 : 1) and filtered through neutral alumina (0.5 g), affording dimethylmangostin (1d) (88 mg), identified by m.p., mixed m.p., and i.r. spectrum.

Reaction of 1,7-*Bis*-(3-*chloro*-3-*methylbutyl*)-2,3,6-*trimethoxy*-8-*methoxycarbonyloxyxanthen*-9-*one* (6c) *with* 1,5-*Diazabicyclo*[5.4.0]*undec*-5-*ene*.—A solution of the dichloride (6c) (1.26 g, 2.21 mmol) in dry benzene (15 ml) containing 1,5-diazabicyclo[5.4.0]undec-5-ene (1.0 ml) was heated

under reflux for 10 h, cooled, and filtered through buffered silica gel (pH 7) (20 g) (Merck Kieselgel 60 (70–230 mesh ASTM) was washed with pH 7 phosphate buffer and dried overnight at 150 °C). The combined washings (75 ml) were concentrated and the residue after two recrystallizations from cyclohexane was identified as (6b) (980 mg) by m.p., mixed m.p., and i.r. spectrum.

Reaction of 1,7-*Bis*-(3-*chloro*-3-*methylbutyl*)-8-*hydroxy*-2,3,6-*trimethoxyxanthen*-9-*one* (6b) *with Potassium t-Butoxide*.—A solution of the dichloride (6b) (147 mg, 0.29 mmol) in dimethyl sulphoxide (2.5 ml) containing potassium t-butoxide (530 mg, 4.73 mmol) was heated to 100—105° for 6 h, cooled, acidified (2N-H_2SO_4; 10 ml) and extracted with ethyl acetate. The ethyl acetate solution was washed several times with water, then with brine, dried (Na_2SO_4), and concentrated. Analytical t.l.c. of the residue developed in benzene–ethyl acetate (17 : 3) showed a faint spot at R_f 0.58 corresponding to (1d), but an intense spot at R_f 0.41 corresponding to (1b), besides other more polar material. P.l.c. of the mixture using benzene–hexane (1 : 1), gave, after three developments, a major yellow band at R_f 0.28, which was collected and extracted with ethyl acetate. Analytical h.p.l.c. of the semi-solid product (37 mg) on a Radial Pak A (C_{18}) column using acetonitrile–water (containing 1% acetic acid) (7 : 3) as eluant, at a flow rate of 2 ml min^{-1}, showed two incompletely resolved peaks with retention times 25.6 and 27.6 min in the approximate area ratio 1 : 3. The second peak after two recycles showed an inflection of higher retention volume. Preparative h.p.l.c. under identical conditions with use of the recycle technique gave, from the first peak, β-mangostin (1b), identified by m.p., mixed m.p., and i.r. spectrum.

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