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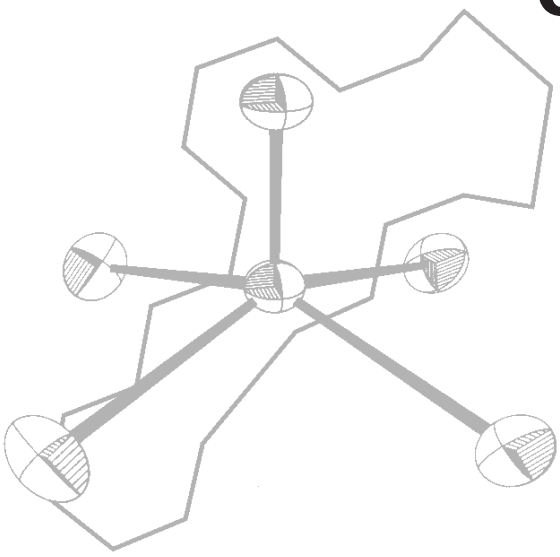

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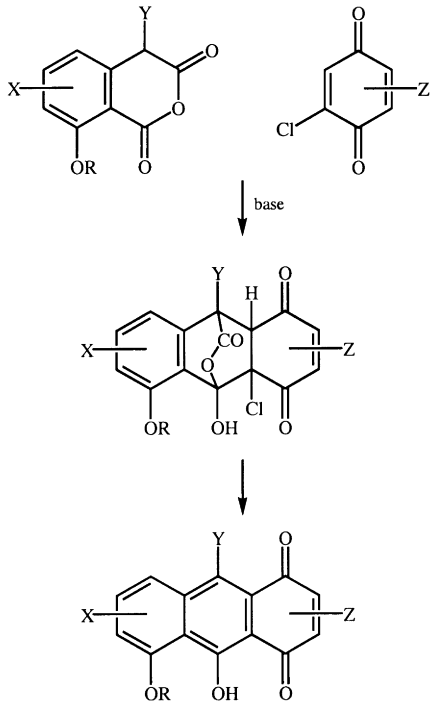
Synthesis of Homophthalates from Allenic Diesters: Conversion into Viocristin and Analogues, and Application to 6-Methylpretetramid*

Ece Caliskan,[A] *Donald W. Cameron*[A,B] *and Peter G. Griffiths*[A]

[A] School of Chemistry, The University of Melbourne, Parkville, Vic. 3052.
[B] Author to whom correspondence should be addressed.

Oxy-substituted homophthalic anhydrides have been synthesized by cycloaddition of di- and tri-oxy butadienes to the allenic diester (1). By base-catalysed cycloaddition to appropriate benzoquinones they have afforded new syntheses of viocristin (19), isoviocristin (20) and analogous 1,4-anthraquinones. Related chemistry has led to the naphthalene (34) and the anhydride (35), intermediates in published syntheses of semivioxanthin and 6-methylpretetramid respectively.

Homophthalic anhydrides undergo regiocontrolled cycloaddition to benzoquinones to form 1,4-anthraquinones (Scheme 1). This is effected by base-catalysed enolization of the anhydride. The derived cycloadduct undergoes aromatization, with loss of carbon dioxide and hydrogen chloride under the reaction conditions. 9-Hydroxy-1,4-anthraquinones so obtained can then react as conventional dienophiles, affording linear tetracyclic systems of biological importance. Tamura's group pioneered this approach in synthesizing anthracyclinones.[1–3] Work here has subsequently used it in synthesizing 6-methylpretetramid.[4]



Scheme 1

Aromatic synthesis of a homophthalic anhydride, substituted as in Scheme 1, typically involves a six-step sequence from an appropriate phenol, proceeding through an indanone that is subsequently ring-opened to a homophthalate.[4] The method is tedious and overall yields are limited, particularly by the indanone formation, which involves concomitant Fries rearrangement and alkylation chemistry.

A potentially simpler approach to the homophthalate system employs allenic diesters (1) as dienophiles. Earlier workers have shown that treating them with simple buta-1,3-dienes[5] or with butadiene equivalents in the form of α-pyrones[6,7] led to homophthalate diesters. For the former case, aromatization of the cycloadduct required a deliberate dehydrogenation step, while α-pyrones required extended heating to 150° to promote addition and decarboxylation. A milder approach along parallel lines was briefly reported by Danishefsky's group,[8] who synthesized the homophthalate diester (2) by treatment of (1) with the reactive 1,1,3-trioxy butadiene (3). The hypothetical cycloadduct (4) was not isolated, rapidly aromatizing with loss of methanol on contact with acid.

This paper extends Danishefsky's chemistry[8] to a wider range of diene and dienophilic systems. Following conversion of the resulting diesters into anhydrides, it then uses Tamura's chemistry[1–3] to synthesize some naturally occurring quinonoid and related products.

The allenic dienophile (1) reacted with the 1,3-dioxy diene (5) in boiling benzene. Aromatization of the crude product with hydrochloric acid in tetrahydrofuran then gave the new homophthalate (6) (92%), whose ^{1}H n.m.r. spectrum

* This paper is dedicated to Professors W. R. Jackson, J. T. Pinhey, R. W. Rickards, S. Sternhell and W. C. Taylor.

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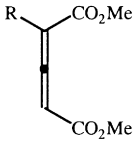
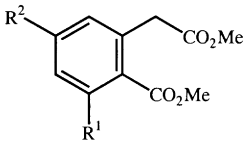
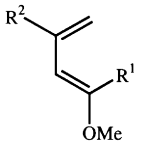


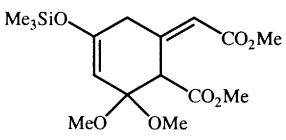
(1) R = H
(36) R = Me



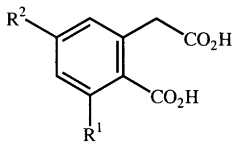
	R^1	R^2
(2)	OMe	OH
(6)	H	OH
(10)	OH	H
(15)	OH	OMe
(31)	OMe	OMe



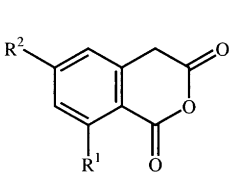
	R^1	R^2
(3)	OMe	$OSiMe_3$
(5)	H	$OSiMe_3$
(9)	$OSiMe_3$	H
(16)	$OSiMe_3$	OMe



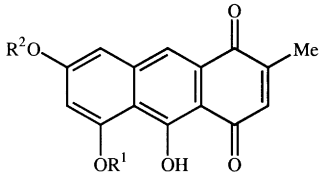
(4)



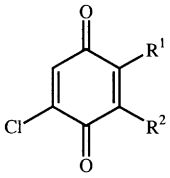
	R^1	R^2
(7)	H	OH
(11)	OH	H
(13)	OMe	OH
(17)	OH	OMe
(32)	OMe	OMe



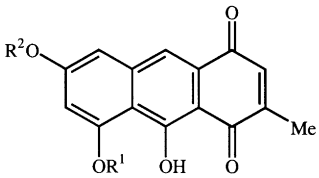
	R^1	R^2
(8)	H	OAc
(12)	OAc	H
(14)	OMe	OAc
(18)	OH	OMe
(33)	OMe	OMe



	R^1	R^2
(19)	Me	H
(20)	H	Me
(21)	H	H
(23)	Me	Ac
(29)	Me	Me



	R^1	R^2
(22)	Me	H
(27)	H	Me



	R^1	R^2
(24)	Me	H
(25)	H	Me
(26)	H	H
(28)	Me	Ac
(30)	Me	Me

was amenable to first-order analysis. Hydrolysis with sodium hydroxide gave the diacid (7) (86%). On being heated in acetyl chloride, this underwent anhydride formation and concomitant acetylation to give (8) (82%). Its ^{1}H n.m.r. spectrum showed acetate and methylene resonances at δ 2.31 and 4.32 respectively, and infrared carbonyl maxima at 1792 and 1739 cm^{-1}.

In the same way, reaction of (1) with the 1,1-dioxy diene (9) successively gave the isomeric aromatized diester (10) (73%), the diacid (11) (74%) and the acetylated anhydride (12) (89%).

The diester (2), prepared as in the literature,[8] was similarly hydrolysed to the diacid (13) (85%) and thence to the acetylated anhydride (14) (85%). The regioisomeric diester (15) (67%) was next generated by analogous cycloaddition of (1) with the trioxy diene (16). In sequence, it gave the corresponding diacid (17) and the anhydride (18) (88%). This anhydride was isolated without concomitant acetylation of the α-hydroxy group by limiting the time of exposure to acetyl chloride in the final step. Its ^{1}H n.m.r. spectrum showed a chelated hydroxy resonance at δ 10.60.

With access to the anhydrides (8), (12), (14) and (18) thus easily effected, the last two have been applied to new syntheses of the microbial 1,4-anthraquinones viocristin (19), isoviocristin (20) and hydroxyviocristin (21).[9,10] This has involved the general chemistry of Scheme 1. Previous syntheses of these compounds have employed quite different chemistry, proceeding through intermediate 9,10-anthraquinones.[9,11]

Treatment of (14) with sodium hydride at 0° generated the corresponding enolate, which underwent cycloaddition to the chloro quinone (22),[12] forming viocristin acetate (23) (78%) after aromatization. Its ^{1}H n.m.r. spectrum contained a chelated hydroxy resonance at δ 14.89, while the aromatic region showed a pair of *meta*-coupled doublets (δ 6.81, 7.29, *J* 2.2 Hz) and a singlet at δ 7.95. The *C*-methyl and quinonoid protons resonated as an allylically coupled doublet and quartet (δ 2.21, 6.89 respectively, *J* 1.5 Hz), while acetate and methoxy protons were observed as singlets at δ 2.38 and 4.05 respectively. Deacetylation with methanolic sodium hydroxide then gave viocristin (19) (90%). Its physical data were mostly consistent with values reported for natural (19)[9] and wholly so with those reported for a sample of (19) derived by reductive cleavage of the dimeric metabolite asperinine A.[13] For ^{1}H n.m.r. spectra in (D_6)dimethyl sulfoxide, both the synthetic and asperinine-derived materials showed the same discrepancies relative to that reported for natural (19) (Experimental). These seem accountable by reassigning aromatic and quinonoid resonances quoted for the natural material[9] and by association with the chloroform solvent used in the original recrystallization. No such discrepancies were observed for ^{1}H n.m.r. spectra in (D_5)pyridine.

Despite possessing a free hydroxy group, the homophthalic anhydride (18) was similarly convertible into isoviocristin (20). Initially it was assumed that the relevant base-catalysed cycloaddition chemistry would require protection of hydroxy substituents, such as occurred automatically in the acetate formation that generally accompanied anhydride synthesis on heating with acetyl chloride. However, following treatment of (18) with two equivalents of sodium hydride at 0°, the derived enolate pleasingly was found to undergo smooth addition/aromatization with (22) to form isoviocristin (20) (80%) itself. Its spectroscopic data showed good agreement with those reported for the natural material.[9]

These syntheses of viocristin (19) and isoviocristin (20) automatically also constitute a synthesis of hydroxyviocristin (21), Anke and Laatsch having shown that either (19) or (20) was convertible into the latter.[9] Their procedure entailed reductive dealkylation with hydrogen iodide followed by oxidation of the intermediate anthrone. The same overall outcome has now also been effected by direct hydrolysis, involving brief contact of (20) with molten aluminium chloride–sodium chloride. This gave (21) (86%), whose physical data agreed with those reported for the natural compound[9] and that was identical with a sample synthesized here earlier by a different procedure.[11]

To illustrate further the regiocontrol available in the synthesis of the 1,4-anthraquinones (19)–(21), attention then turned to preparing their regioisomers (24)–(26) for the first time. Thus the enolate of (14), on being made to react with the isomeric chloro benzoquinone (27), gave first the acetate (28) (76%) and then, following hydrolysis, the viocristin isomer (24) (88%).

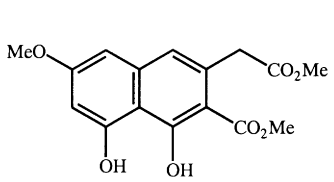
Similarly, the enolate of (18), generated with two equivalents of sodium hydride, reacted with (27) to give the isoviocristin regioisomer (25) (75%). Brief exposure to an aluminium chloride–sodium chloride melt then gave (26) (88%).

The ^{1}H n.m.r. spectra of the new compounds (24)–(26) were very similar to those of their respective regioisomers (19)–(21), as expected. The most notable difference between the two groups was the small but consistent deshielding (0.14–0.27 ppm) of the hydroxy substituent adjacent to the carbonyl group, in the former series. This effect on the chelated hydroxy resonance is qualitatively consistent with those observed on simpler models,[14] for which a still smaller regiochemical difference was considered to be diagnostic. Thus for 5-hydroxy-2-methyl-1,4-naphthoquinone the hydroxy group resonated sharply at δ 11.93, whereas for the 8-hydroxy-2-methyl isomer it was observed at δ 12.01.

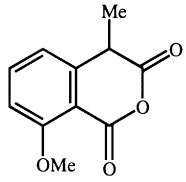
The final pair of 1,4-anthraquinones synthesized were the dimethyl ethers (29) and (30). Treatment of the diester (15) with methyl iodide/silver(I) oxide efficiently gave the appropriate homophthalate (31).[15] As for parallel systems this also efficiently gave the diacid (32)[15] and then the anhydride (33).[16] Enolization of (33) and reaction with (22) afforded the 1,4-anthraquinone (29) (70%). Its ^{1}H n.m.r. spectrum contained a chelated hydroxy resonance (δ 14.92) and two methoxy resonances at δ 3.95 and 4.02. It has been prepared independently by selective methylation of viocristin (19).[9]

The enolate of (33) reacted similarly with the isomeric benzoquinone (27) to give the isomeric 1,4-anthraquinone (30) (72%). Its ^{1}H n.m.r. spectrum was similar to that of (29) except for the expected small deshielding (0.18 ppm) of its chelated hydroxy resonance.

The syntheses so far described have been based on two novel stages proceeding reliably: (i) cycloaddition to the allenic diester (1), necessary for forming the homophthalate system in the first place; and (ii) cycloaddition of derived homophthalic anhydrides as enols. To this point, stage (i) has involved conventional acyclic butadienes and stage (ii) conventional quinonoid dienophiles. The possibility of enolized homophthalic anhydrides themselves functioning as dienes in cycloaddition to (1) was next examined, in order to assess the resulting formation of ring-extended outcomes. A target system (34) was explored, hypothetically derivable by the action of enolized (18) on the diester (1). Compound (34) has been reported as an advanced intermediate in a synthesis[17] of the antifungal agent semivioxanthin. Disappointingly, however, the combination of enolized (18) with (1) under standard conditions could not be made to give (34) in yield greater than 9%. The bulk of the reaction mixture following workup, consisted of diacid (17) deriving from hydrolysis of (18).



(34)



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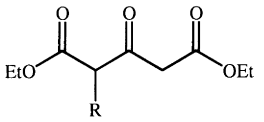
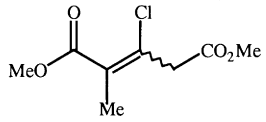


(37) R = H
(38) R = Me



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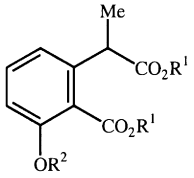

	R^1	R^2
(40)	Me	H
(41)	Me	Me
(42)	H	Me

The ^{1}H n.m.r. spectrum of (34) showed two chelated hydroxy resonances (δ 9.80, 14.26), while the aromatic region appropriately contained a pair of *meta*-coupled doublets (δ 6.55, 6.57, *J* 2.5 Hz) and a singlet at δ 6.95. Its low yield could be attributed to incompatibility of the allenic system (1) with the strongly basic reaction conditions. The published alternative synthesis[17] required six steps, constituting an overall yield of 6%.

The final aspect of this work has sought improved access to the *C*-methyl homophthalic anhydride (35), a key intermediate in our earlier synthesis of 6-methylpretetramid.[4] In that work, compound (35) was derived in six steps from phenol. It was hoped that a better synthesis might result from appropriate cycloaddition to the methyl-substituted allene (36), assuming that such addition might favour the less substituted 3,4-double bond.

The new allene (36) was synthesized by conventional chemistry.[18] Diethyl acetone-1,3-dicarboxylate (37) was mono-*C*-methylated to give (38).[19,20] Treatment with phosphorus pentachloride followed by boiling in methanolic acid afforded the chloro diester (39) (85%). It was formed appar-

ently as a single geometrical isomer, whose configuration was not established. Its ^{1}H n.m.r. spectrum showed *C*-methyl, two methoxy and methylene resonances at δ 2.05, 3.67, 3.70 and 3.90 respectively. On treatment with trimethylamine at 0° it gave the desired allene (36) (88%).

The ^{1}H n.m.r. spectrum of (36) contained a doublet methyl resonance (δ 1.96, *J* 2.9 Hz) coupling to the olefinic proton, which was observed as a corresponding quartet (δ 5.89). Significant long-range coupling has analogously been observed for other allenic systems.[21,22] There was also an infrared absorption maximum at 1957 cm^{-1} consistent with the allenic group.[22]

Cycloaddition of diene (9) to the allene (36) proceeded in boiling benzene followed by aromatization with acid. The anticipated product (40) was not purified but was directly *O*-methylated with methyl iodide/silver(I) oxide to give the methoxy diester (41) (75%). As a dienophile, the allene (36) was only marginally less reactive than its unsubstituted counterpart (1) and it pleasingly underwent addition with selectivity completely favouring the less substituted of its two ene components, within the limits of detection.

The ^{1}H n.m.r. spectrum of (41) showed resonances consistent with the three aromatic protons, together with complementary doublet and quartet resonances (δ 1.47, 3.72 respectively, *J* 7.1 Hz) corresponding to the ethylidene group, and a non-ester methoxy singlet at δ 3.65. Its mass spectrum showed an appropriate molecular ion at *m/z* 252. On hydrolysis it gave the diacid (42)[23] (88%), which underwent dehydration in boiling acetyl chloride to afford the target anhydride (35)[23] (76%). Its spectroscopic and other physical data were indistinguishable from those for this compound, independently obtained in our previous work.[4] In that latter synthesis the yield of (35) from phenol was 17% overall, in six steps. The new approach afforded the same anhydride in yield of 32% based on the acetonedicarboxylate (38); or of 50% based on the allenic diester (36). To this can be added considerable qualitative advantage in its mildness, convenience and relative simplicity.

Experimental

General

Melting points were determined on a Kofler hot-stage and are uncorrected. Microanalyses were carried out by National Analytical Laboratories, Melbourne, or Chemical and Microanalytical Services, Geelong. Electronic spectra were recorded in chloroform unless otherwise stated, by using a Varian Super Scan 3 spectrophotometer. Infrared spectra were recorded with a Perkin–Elmer 983G Grating spectrophotometer. Solids were recorded as potassium bromide disks and liquids as films between sodium chloride plates. Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded with a JEOL JNM-GX400 spectrometer or a Varian Unity 300 spectrometer. The solvent was (D)chloroform unless otherwise stated. High- and low-resolution mass spectra were recorded by using a V.G. Micromass 7070F or a JEOL JSM-AX505H instrument at 70 eV. The mass of each ion is given followed by its relative intensity. In general, only peaks greater than 20% are quoted. Analytical and preparative thin-layer chromatography (t.l.c.) were carried out on glass coated with a layer of silica gel [Merck Kieselgel 60 GF254 or Merck Kieselgel 60 GF254 containing 2% oxalic acid (oxalated silica)]. The separated components were extracted from the silica with ethyl acetate or dichloromethane. Oxalic acid was removed by washing the extracts with water and then drying over magnesium sulfate prior to evaporation. Flash chromatography was carried out using Merck Kieselgel No. 9385. In instances where the silica had been acidified with oxalic acid (2% w/w), the separated fractions were washed with water before drying and evaporation. All solvents were of A.R. grade or were redistilled prior to use. Petrol refers to the fraction boiling in the range 60–80° and light petrol refers to the fraction boiling in the range 40–60°. Organic extracts were generally dried over magnesium sulfate before evaporation at reduced pressure.

Methyl (5-Hydroxy-2-methoxycarbonylphenyl)acetate (6)

A solution of (5)[24] (2.6 g) and allene (1)[18] (2 g) in benzene (20 cm^3) was heated at reflux for 20 h. The solvent was evaporated and the residue was dissolved in a solution of tetrahydrofuran (10 cm^3) and concentrated hydrochloric acid (3 drops). The solution was stirred at room temperature for 20 min and the resulting suspension was filtered to give the *diester* (6) as a white solid (2.6 g, 92%). Recrystallization from diethyl ether/light petrol afforded colourless needles, m.p. 110–112° (Found: C, 58.7; H, 5.4. $C_{11}H_{12}O_5$ requires C, 58.9; H, 5.4%). ν_{max} 3319, 1710, 1608 cm^{-1}. δ 3.75, 3.83, s, s, 2×OMe; 3.95, s, CH_2; 6.24, s, OH; 6.61, d, *J* 2.6 Hz, H 6; 6.67, dd, *J* 8.6, 2.6 Hz, H 4; 7.92, d, *J* 8.6 Hz, H 3. *m/z* 224 (M, 15%), 193 (39), 192 (80), 165 (84), 164 (100), 149 (76), 135 (31).

(2-Carboxy-5-hydroxyphenyl)acetic Acid (7)

The diester (6) (1 g) was dissolved in 10% aqueous sodium hydroxide (20 cm^3) solution and heated to 80° for 30 min. The cooled solution was acidified with concentrated hydrochloric acid to pH 1–2, diluted with water (20 cm^3) and extracted with diethyl ether (4×50 cm^3). The ethereal phase was dried and concentrated to yield the *diacid* (7) as a white solid (750 mg, 86%), m.p. 194–197° (Found: $M^{+\bullet}$, 196.0365. $C_9H_8O_5$ requires $M^{+\bullet}$, 196.0372). ν_{max} 3341, 1689, 1656 cm^{-1}. δ [(D$_6$)acetone] 3.99, s, CH_2; 6.82, m, H 4, H 6; 7.96, d, *J* 9.3 Hz, H 3; 9.09, s, OH. *m/z* 196 (M, 5%), 178 (30), 152 (61), 150 (33), 135 (28), 134 (100), 121 (25), 106 (49), 105 (24), 78 (26), 77 (32).

*6-Acetoxy-1*H*-2-benzopyran-1,3(4*H*)-dione (8)*

Diacid (7) (200 mg) was dissolved in a mixture of acetone (5 cm^3) and acetyl chloride (15 cm^3) and the solution was heated at reflux for 2 h. The solvent was removed by evaporation to give the anhydride (8),[5] as a white solid (190 mg, 82%). Recrystallization from acetone/petrol gave colourless needles, m.p. 155–157° (Found: C, 60.2; H, 3.7. Calc. for $C_{11}H_8O_5$: C, 60.0; H, 3.6%). ν_{max} 1792, 1739 cm^{-1}. δ [(D$_6$)acetone] 2.31, s, OAc; 4.32, s, CH_2; 7.27, d, *J* 2.2 Hz, H 5; 7.30, dd, *J* 8.4, 2.2 Hz, H 7; 8.15, d, *J* 8.4 Hz, H 8. *m/z* 220 (M, 23%), 178 (30), 134 (100), 106 (43), 77 (20).

Methyl (3-Hydroxy-2-methoxycarbonylphenyl)acetate (10)

Diene (9)[25] (3 g) and allene (1) (1.8 g) were made to react as for the formation of (6). The acidified solution was stirred at room temperature for 20 min before being diluted with water (20 cm^3) and extracted into diethyl ether (2×50 cm^3). The combined extracts were washed with water, dried and concentrated. The oily residue was subjected to flash chromatography, with diethyl ether/petrol (1 : 4) as eluent, and the major band gave the diester (10) (1.9 g, 73%) as a white solid. Recrystallization from diethyl ether/light petrol gave colourless plates, m.p. 54–56° (lit.[26] 53–55°). δ 3.69, 3.90, s, s, 2×OMe; 3.89, s, CH_2; 6.72, d, *J* 8 Hz, H 4; 6.97, d, *J* 8 Hz, H 6; 7.37, t, *J* 8 Hz, H 5; 11.21, s, OH.

(2-Carboxy-3-hydroxyphenyl)acetic Acid (11)

The diester (10) (500 mg) was hydrolysed as for the formation of (7) to give the diacid (11) (320 mg, 74%) as a white solid, m.p. 160–162° (lit.[26] 161–163°) which was used in the next step without further purification. δ [(D$_6$)acetone] 4.01, s, CH_2; 6.83, d, *J* 8 Hz, H 4; 6.89, d, *J* 8 Hz, H 6; 7.40, t, *J* 8 Hz, H 5.

*8-Acetoxy-1*H-*2-benzopyran-1,3(4*H*)-dione (12)*

The diacid (11) (100 mg) was dissolved in a mixture of acetone (5 cm^3) and acetyl chloride (10 cm^3), and the solution was heated at reflux for 2 h. Concentration of the mixture afforded the anhydride (12) (100 mg, 89%) as a white solid. Recrystallization from acetone/petrol gave colourless needles, m.p. 151–154° (Found: C, 60.0; H, 3.7. $C_{11}H_8O_5$ requires C, 60.0; H, 3.6%). ν_{max} 1780, 1745, 1605 cm^{-1}. δ [(D_6)acetone] 2.31, s, Ac; 4.37, s, CH_2; 7.22, d, *J* 8 Hz, H 7; 7.42, d, *J* 8 Hz, H 5; 7.78, t, *J* 8 Hz, H 6. *m/z* 220 (M, 2%), 178 (100), 160 (35), 150 (63), 134 (28).

Methyl (5-Hydroxy-3-methoxy-2-methoxycarbonylphenyl)acetate (2)

Diene (3)[27] (2.2 g) and allene (1) (1.4 g) were made to react as for the formation of (10). The crude product was subjected to flash chromatography, with diethyl ether as eluent, to give the diester (2) (1.7 g, 76%) as a white solid. Recrystallization from diethyl ether/petrol gave colourless needles, m.p. 82–84° (lit.[8] 70–72°) (Found: C, 56.7; H, 5.6. Calc. for $C_{12}H_{14}O_6$: C, 56.7; H, 5.6%). ν_{max} 3283, 1724, 1690 cm^{-1}. δ 3.62, s, CH_2; 3.70, 3.76, 3.85, s, s, s, 3×OMe; 5.86, br s, OH; 6.30, br s, 2×ArH. *m/z* 254 (M, 40%), 223 (48), 222 (31), 195 (84), 194 (100), 191 (23), 179 (82), 165 (20), 69 (21).

(2-Carboxy-5-hydroxy-3-methoxyphenyl)acetic Acid (13)

Diester (2) (240 mg) was heated to 60–70° in 10% aqueous sodium hydroxide solution (20 cm^3) for 1 h. The cooled solution was acidified to pH 1–2 with concentrated hydrochloric acid, diluted with water (25 cm^3) and extracted with ethyl acetate (4×20 cm^3). The combined extracts were dried and concentrated to give the *diacid* (13) (183 mg, 85%) as a white solid, m.p. 184–185° (Found: $M^{+\bullet}$, 226.0488. $C_{10}H_{10}O_6$ requires $M^{+\bullet}$, 226.0477). ν_{max} 3083, 1712, 1665, 1604 cm^{-1}. δ [(D_6)acetone] 3.71, s, CH_2; 3.84, s, OMe; 6.45, d, *J* 2.2 Hz, H 4 or H 6; 6.49, d, *J* 2.2 Hz, H 4 or H 6; 9.00, br s, OH. *m/z* 226 (M, 8%), 208 (M − H_2O, 14), 182 (100), 180 (20), 164 (65), 138 (20), 137 (83), 121 (22), 107 (23), 69 (23), 64 (21), 58 (37).

*6-Acetoxy-8-methoxy-1*H-*2-benzopyran-1,3(4*H*)-dione (14)*

To a solution of the diacid (13) (100 mg) in acetone (4 cm^3) was added acetyl chloride (10 cm^3) and the mixture was heated at reflux for 10 h. The cooled solution was concentrated to give the *anhydride* (14) (88 mg, 85%) as a white solid. Recrystallization from acetone/petrol afforded colourless needles, m.p. 134–136° (Found: C, 57.2; H, 3.8. $C_{12}H_{10}O_6$ requires C, 57.6; H, 4.0%). ν_{max} 1786, 1750 cm^{-1}. δ [(D_6)acetone] 2.29, s, Ac; 3.94, s, OMe; 4.22, s, CH_2; 6.81, d, *J* 2 Hz, H 7; 6.95, d, *J* 2 Hz, H 5. *m/z* 250 (M, 10%), 208 (32), 164 (100), 121 (15), 106 (13).

Methyl (3-Hydroxy-5-methoxy-2-methoxycarbonylphenyl)acetate (15)

Diene (16)[28] (920 mg) and allene (1) (600 mg) were made to react as for the formation of (10). The crude product was subjected to flash chromatography, with diethyl ether/petrol (1 : 1) as eluent, and the major band afforded the *diester* (15) (650 mg, 67%) as a white solid. Recrystallization from diethyl ether/light petrol gave colourless needles, m.p. 79–81° (Found: C, 56.7; H, 5.7. $C_{12}H_{14}O_6$ requires C, 56.7; H, 5.6%). ν_{max} 3441, 1728, 1686 cm^{-1}. δ 3.69, 3.82, 3.86, s, s, s, 3×OMe; 3.83, s, CH_2; 6.29, d, *J* 2.5 Hz, H 4; 6.43, d, *J* 2.5 Hz, H 6; 11.66, s, OH. *m/z* 254 (M, 44%), 223 (23), 222 (55), 195 (46), 194 (99), 190 (34), 179 (100), 135 (40).

(2-Carboxy-3-hydroxy-5-methoxyphenyl)acetic Acid (17)

The diester (15) (220 mg) was hydrolysed as for the formation of (7) to give the *diacid* (17) (190 mg, 97%). Recrystallization from dichloromethane/petrol gave colourless microneedles, m.p. 160–163° (Found: C, 53.0; H, 4.7. $C_{10}H_{10}O_6$ requires C, 53.1; H, 4.5%). ν_{max} 2988, 1683 cm^{-1}. δ [(D_6)acetone] 3.84, s, OMe; 3.95, s, CH_2; 6.40, d, *J* 2.5 Hz, H 4 or H 6; 6.43, d, *J* 2.5 Hz, H 4 or H 6; 10.60, s, OH. *m/z* 226 (M, 13%), 208 (72), 190 (34), 183 (91), 180 (100), 164 (36), 151 (27), 137 (78), 107 (24), 69 (25).

*8-Hydroxy-6-methoxy-1*H-*2-benzopyran-1,3(4*H*)-dione (18)*

The diacid (17) (76 mg) was dissolved in a solution of acetyl chloride (10 cm^3) and acetone (1 cm^3) and the mixture was heated at reflux for 1 h. Concentration of the solution afforded the *anhydride* (18) (62 mg, 88%) as a white solid. Recrystallization from acetone/petrol gave colourless needles, m.p. 173–177° (Found: C, 57.9; H, 3.9. $C_{10}H_8O_5$ requires C, 57.7; H, 3.9%). ν_{max} 1784, 1696 cm^{-1}. δ [(D_6)acetone] 4.25, s, CH_2; 6.48, d, *J* 2.5 Hz, H 5 or H 7; 6.55, d, *J* 2.5 Hz, H 5 or H 7; 10.60, s, OH. *m/z* 208 (M, 10%), 207 (83), 189 (32), 180 (100), 164 (34), 151 (28), 78 (20), 69 (21).

7-Acetoxy-10-hydroxy-5 methoxy-2-methyl-1,4-anthraquinone (23)

To a stirred suspension of sodium hydride (22 mg, 60% in paraffin oil) in tetrahydrofuran (5 cm^3) at 0° was added the anhydride (14) (57 mg). The mixture was stirred for 20 min before being added dropwise to a solution of the benzoquinone (22)[12] (42 mg) in tetrahydrofuran (5 cm^3). The resulting purple solution was stirred for a further 10 min at 0° and warmed to room temperature over 30 min. The mixture was quenched with saturated ammonium chloride solution (10 cm^3) and extracted with ethyl acetate (2×70 cm^3). The combined organic extracts were washed with water, dried and concentrated to a dark red residue which was subjected to preparative t.l.c., with toluene/ethyl acetate (7 : 3) as eluent. Removal of the leading red band afforded the anthraquinone (23) (68 mg, 78%) and recrystallization from dichloromethane/petrol gave red needles, m.p. dec. >208° (lit.[9] dec. 210°). δ 2.21, d, *J* 1.5 Hz, Me; 2.38, s, Ac; 4.05, s, OMe; 6.81, d, *J* 2.2 Hz, H 6; 6.89, q, *J* 1.5 Hz, H 3; 7.29, d, *J* 2.2 Hz, H 8; 7.95, s, H 9; 14.89, s, OH.

Viocristin (7,10-Dihydroxy-5-methoxy-2-methyl-1,4-anthraquinone) (19)

The anthraquinone (23) (24 mg) was dissolved in a solution of sodium hydroxide in methanol (15 cm^3, 0.1 M) and the dark mixture was stirred at room temperature for 30 min. The solution was acidified to pH 1–2 with concentrated hydrochloric acid, diluted with water (10 cm^3) and extracted with ethyl acetate (3×40 cm^3). The combined extracts were washed with water, dried and concentrated. The purple residue was subjected to preparative t.l.c., with toluene/ethyl acetate (7 : 3) as eluent. Removal of the leading purple band gave viocristin (19) (29 mg, 90%). Sublimation (210°/10^{-4} mbar) gave violet microcrystals which decomposed without melting below 300° (Found: $M^{+\bullet}$, 284.0693. $C_{16}H_{12}O_5$ requires $M^{+\bullet}$, 284.0685). λ_{max} (log ε) (EtOH) 249, 280sh, 337, 495, 524, 564sh nm (4.20, 4.65, 3.68, 3.81, 3.85, 3.61). ν_{max} 3392, 1662, 1617, 1589, 1511, 1440, 1407, 1362, 1213, 1168, 1108 cm^{-1}. δ [(D_6)dimethyl sulfoxide] 2.08, br s, Me; 3.89, s, OMe; 6.70, br s, H 6; 6.96, br s, H 3; 6.98, br s, H 8; 7.74, s, H 9; 10.73, s, 7-OH; 14.89, s, 10-OH. δ [(D_5)pyridine] 2.07, d, *J* 1.5 Hz, Me; 3.92, s, OMe; 6.87, q, *J* 1.5 Hz, H 3; 7.01, d, *J* 2 Hz, H 6; 7.26, d, *J* 2 Hz, H 8; 8.10, s, H 9. *m/z* 284 (100%), 266 (18), 255 (23), 238 (35), 210 (16).

For naturally derived viocristin (19),[9] m.p. dec. >300°. λ_{max} (log ε) (EtOH) 253, 280sh, 340, 497, 517, 527 nm (4.59, 4.62, 3.74, 3.91, 3.91, 3.90). ν_{max} 1667, 1639, 1590, 1510, 1437, 1399, 1366, 1210, 1163, 1107, 1048 cm^{-1}. δ [(D_6)dimethyl sulfoxide] 2.10, d, *J* 1 Hz, 2-Me; 3.94, s, OMe; 6.70, m, H 3; 6.96, 7.26, (br s, br s, H 6, H 8); 7.72, s, H 9; 14.89, s, 10-OH. δ [(D_5)pyridine] 2.08, s, Me; 4.00, s, OMe; 6.87, 7.00, br s, br s H 3, H 6; 8.08, s, H 9. *m/z* 284 (M, 100%), 266 (20, M − H_2O), 255 (25, M − CHO), 238 (30). Comparison with parallel data cited for natural isoviocristin (20)[9] and for the related 1,4-anthraquinones synthesized herein suggests that, for the original spectrum[9] [in (D_6)dimethyl sulfoxide], the cited δ values for H 3 and H 6 should be interchanged. At 300 MHz the former resonance nearly overlaps that for H 8; in the original spectrum, run at 100 MHz, the cited δ value for H 8 (7.26) may possibly derive from chloroform solvent used in the original recrystallization.

For (19) derived from reductive cleavage of asperinine A,[13] m.p. >300°. λ_{max} (log ε) (EtOH) 253, 281sh, 340, 487, 417 (*sic*), 530 nm. ν_{max} 3400, 1665, 1635, 1615, 1590, 1518 cm^{-1}. δ [(D_6)dimethyl sulfoxide] 2.08, d, *J* 1.5 Hz, Me; 3.91, s, OMe; 6.70, d, *J* 2 Hz, H 6; 6.97, m, H 3; 6.98, d, *J* 2 Hz, H 8; 7.74, s, H 9; 10.75, s, 7-OH; 14.90, s, 10-OH. *m/z* 284 (M), 266, 255, 238, 210.

Isoviocristin (5,10-Dihydroxy-7-methoxy-2-methyl-1,4-anthraquinone) (20)

To a suspension of sodium hydride (15 mg, 60% in paraffin oil) in tetrahydrofuran (7 cm^3) was added the anhydride (18) (30 mg) and the mixture was stirred at 0° for 15 min before being added dropwise to a solution of the benzoquinone (22)[12] (22 mg) in tetrahydrofuran. Stirring was continued for 10 min at 0° and the mixture was warmed to room temperature over 40 min before being quenched with saturated ammonium chloride solution (30 cm^3). The suspension was extracted with dichloromethane (3×50 cm^3), and the extract was washed with water, dried and concentrated. The dark residue was subjected to preparative t.l.c., with toluene/ethyl acetate (7 : 3) as eluent, and removal of the leading purple band afforded isoviocristin (20) as a dark solid (36 mg, 80%). Recrystallization from dichloromethane/petrol gave microcrystals which decomposed without melting below 199°. λ_{max} (log ε) 256, 282, 293, 306sh, 339, 506, 535, 572 nm (4.77, 3.94, 3.94, 3.77, 3.68, 3.94, 3.96, 3.77). ν_{max} 3403, 1658, 1618, 1577, 1502, 1460, 1425, 1374, 1359, 1293, 1226, 1154, 1085, 1032, 1002, 893, 839, 701 cm^{-1}. δ 2.20, d, *J* 1.4 Hz, Me; 3.92, s, OMe; 6.65, d, *J* 2.2 Hz, H 6; 6.84, d, *J* 2.2 Hz, H 8; 6.90, q, *J* 1.4 Hz, H 3; 7.85, s, H 9; 10.28, s, 5-OH; 15.98, s, 10-OH. *m/z* 284 (M, 100%), 227 (27), 213 (41), 188 (24), 185 (24), 139 (59), 127 (32), 117 (20), 102 (25), 99 (22), 89 (37), 88 (21), 87 (22), 77 (23), 75 (27), 74 (21), 69 (21), 62 (39), 61 (22), 56 (28), 53 (32).

For naturally derived isoviocristin (20),[9] m.p. 198°. λ_{max} (log ε) 258, 282, 294, 306sh, 341, 507, 535, 572sh nm (4.77, 4.00, 3.99, 3.84, 3.73, 3.99, 4.02, 3.79). ν_{max} 1667, 1623, 1582, 1504, 1464, 1429, 1376, 1359, 1292, 1227, 1156, 1086, 1034, 999, 891, 840, 700 cm^{-1}. δ 2.21, d, *J* 1.5 Hz, Me; 3.95, s, OMe; 6.67, 6.86, (d, d, *J* 2.3, 2.3 Hz, H 6, H 8); 6.91, q, *J* 1.5 Hz, H 3; 7.86, s, H 9; 10.32, s, 5-OH; 16.02, s, 10-OH.

Hydroxyviocristin (5,7,10-Trihydroxy-2-methyl-1,4-anthraquinone) (21)

The anthraquinone (20) (20 mg) was added to a melt of anhydrous aluminium trichloride (2 g) and sodium chloride (0.5 g) at 140°. The mixture was quickly heated to 180°, stirred for 2 min, cooled for 1 min, and then poured into ice (200 cm^3) containing concentrated hydrochloric acid (10 cm^3). The purple mixture was stirred for 1 h with gentle heating before being extracted with dichloromethane (3×30 cm^3). The combined organic extracts were washed with water (2×20 cm^3), dried and concentrated to give a dark residue which was subjected to preparative t.l.c., with toluene/ethyl acetate (9 : 1) as eluent. The leading purple band was removed to afford hydroxyviocristin (21) (16 mg, 86%) as a sparingly soluble dark solid which decomposed without melting below 250°. Attempted recrystallization or sublimation resulted in decomposition. It was indistinguishable from authentic material[11] in chromatographic behaviour, and electronic, i.r., and n.m.r. spectra. λ_{max} [MeOH containing Me_2SO (5%) and HCO_2H (1%)] (log ε) 288sh, 338, 503sh, 530, 572sh nm (3.97, 3.78, 3.81, 3.83, 3.67). ν_{max} 1647, 1610, 1588, 1443, 1400, 1369, 1155, 1087, 878, 669 cm^{-1}. δ [(D_6)acetone] 2.16, d, *J* 1.2 Hz, Me; 6.60, d, *J* 2.2 Hz, H 6; 6.99, d, *J* 2.2 Hz, H 8; 7.03, br s, H 3; 7.78, s, H 9; 9.71, br s, 7-OH; 10.40, s, 5-OH; 16.19, s, 10-OH. *m/z* 270 (M, 100%), 255 (9), 242 (15), 241 (8), 227 (5), 155 (5), 109 (10), 97 (6), 83 (10).

For naturally derived hydroxyviocristin (21),[9] m.p. 250°. λ_{max} ($CHCl_3$/MeOH) (log ε) 257, 282, 295, 307sh, 342, 515sh, 535, 572 nm (4.70, 4.01, 3.98, 3.81, 3.64, 4.00, 4.03, 3.84). ν_{max} 1664, 1630, 1597, 1445, 1383, 1367, 1227, 1159, 1089, 1028, 990, 887, 833, 728, 699 cm^{-1}. δ [(D)chloroform/(D_6)acetone] 2.22, d, *J* 1.5 Hz, Me; 6.68, d, *J* 2.5 Hz, H 6; 6.92, d, *J* 2.5 Hz, H 8; 6.94, m, H 3; 7.84, s, H 9; 9.04, 10.46, 16.16, s, s, s, 3×OH. *m/z* 270 (M, 98%), 255 (23), 242 (10), 241 (12), 227 (38), 155 (27), 109 (31), 97 (45), 95 (40), 83 (51), 81 (54), 42 (100), 41 (85).

For a sample of (21) independently derived from previous work here:[11] m.p. dec. 280°. λ_{max} [MeOH containing Me_2SO (5%) and HCO_2H (1%)] (log ε) 279sh, 338, 503sh, 530, 577sh nm (4.00, 3.98, 3.69, 3.93, 3.69). ν_{max} 3360br, 1655sh, 1620, 1585, 1510sh cm^{-1}. δ [(D_6)acetone] 2.16, br s, Me; 6.60, d, *J* 2.2 Hz, H 6; 6.99, d, *J* 2.2 Hz, H 8; 7.03, br s, H 3; 7.78, s, H 9; 9.72, br s, 7-OH; 10.40, s, 5-OH; 16.18, s, 10-OH.

6-Acetoxy-9-hydroxy-8-methoxy-2-methyl-1,4-anthraquinone (28)

To a suspension of sodium hydride (13 mg, 60% in paraffin oil) in tetrahydrofuran (5 cm^3) was added the anhydride (14) (44 mg) and the mixture was stirred for 15 min at 0° before being added dropwise to a solution of the benzoquinone (27)[29] (35 mg) in tetrahydrofuran (5 cm^3). Stirring was continued at 0° for 10 min and the mixture was warmed to room temperature over 30 min before being quenched with saturated ammonium chloride solution (20 cm^3). It was then extracted with ethyl acetate (3×50 cm^3), and the extract was washed with water, dried and concentrated. The dark residue was subjected to preparative t.l.c., with chloroform as eluent, and the leading red band was removed to afford the *anthraquinone* (28) (53 mg, 76%) as a red solid. Recrystallization from dichloromethane/petrol gave red needles, m.p. dec. >215° (Found: $M^{+\bullet}$, 326.0781. $C_{18}H_{14}O_6$ requires $M^{+\bullet}$, 326.0790). λ_{max} (log ε) 263sh, 325, 347sh, 485, 508, 548sh nm (4.11, 3.71, 3.46, 4.05, 4.07, 3.78). ν_{max} 3450, 1750, 1656, 1610 cm^{-1}. δ 2.24, d, *J* 1.6 Hz, Me; 2.38, s, OAc; 4.05, s, OMe; 6.81, d, *J* 2 Hz, H 7; 6.84, q, *J* 1.6 Hz, H 3; 7.91, s, H 10; 15.06, s, OH. (The signal for H 5 was evidently obscured by a residual chloroform peak at δ 7.26.) δ (C_6D_6) 1.63, d, *J* 1.5 Hz, Me; 1.78, s, OAc; 3.32, s, OMe; 6.30, q, *J* 1.5 Hz, H 3; 6.51, d, *J* 2 Hz, H 7; 6.97, d, *J* 2 Hz, H 5; 7.97, s, H 10; 15.34, s, OH. *m/z* 326 (M, 53%), 284 (100), 83 (28), 81 (42), 71 (21), 69 (85), 56 (39), 54 (40).

6,9-Dihydroxy-8-methoxy-2-methyl-1,4-anthraquinone (24)

The anthraquinone (28) (17 mg) was hydrolysed and the crude product chromatographed, as for the formation of (19), to afford the *dihydroxy anthraquinone* (24) (15 mg, 88%) as a dark solid. Sublimation (210°/10^{-4} mbar) gave violet microcrystals, m.p. dec. >238° (Found: $M^{+\bullet}$, 284.0673. $C_{16}H_{12}O_5$ requires $M^{+\bullet}$, 284.0685). λ_{max} (log ε) (EtOH) 252, 288sh, 301sh, 339, 490, 521, 563sh nm (4.64, 3.81, 3.66, 3.64, 3.79, 3.87, 3.67). ν_{max} 3420, 1629, 1596 cm^{-1}. δ [(D_6)dimethyl sulfoxide] 2.13, br s, Me; 3.90, s, OMe; 6.69, d, *J* 1.9 Hz, H 7; 6.90, br s, H 3; 6.96, d, *J* 1.9 Hz, H 5; 7.70, s, H 10; 10.78, br s, 6-OH; 15.06, s, 9-OH. *m/z* 284 (M, 26%), 266 (M − H_2O, 6), 149 (47), 97 (28), 85 (29), 83 (41), 71 (46), 69 (49), 56 (100).

8,9-Dihydroxy-6-methoxy-2-methyl-1,4-anthraquinone (25)

To a suspension of sodium hydride (29 mg, 60% in paraffin oil) in tetrahydrofuran (10 cm^3) was added the anhydride (18) (77 mg) and the whole was stirred at 0° for 20 min before being added dropwise to a solution of the benzoquinone (27) (57 mg) in tetrahydrofuran (10 cm^3). The mixture was stirred at 0° for 10 min and warmed to room temperature over 40 min. The dark suspension was quenched with saturated ammonium chloride solution (15 cm^3) and extracted with chloroform (3×50 cm^3). The combined organic extracts were washed with water (2×20 cm^3), dried and concentrated. The purple residue was subjected to flash chromatography (on silica containing 2% oxalic acid), with toluene/ethyl acetate (7 : 3) as eluent. Removal of the leading purple band afforded the *anthraquinone* (25) as a dark solid (78 mg, 75%). Recrystallization from dichloromethane/petrol gave microcrystals which decomposed without melting below 215° (Found: C, 67.8; H, 4.2. $C_{16}H_{12}O_5$ requires C, 67.5; H, 4.5%). λ_{max} (log ε) 256, 280, 290, 304sh, 334, 497, 527, 567sh nm (4.86, 4.11, 4.11, 3.92, 3.75, 4.07, 4.13, 3.94). ν_{max} 3377, 1695, 1648 cm^{-1}. δ 2.24, br s, Me; 3.93, s, OMe; 6.67, d, *J* 2.3 Hz, H 7; 6.79, br s, H 3; 6.86, d, *J* 2.3 Hz, H 5; 7.84, s, H 10; 10.16, s, 8-OH; 16.25, s, 9-OH. *m/z* 284 (M, 100%), 188 (20), 139 (20), 266 (21), 255 (30), 238 (40), 149 (42).

6,8,9-Trihydroxy-2-methyl-1,4-anthraquinone (26)

The anthraquinone (25) (12 mg) was added to a melt of anhydrous aluminium trichloride (1 g) and sodium chloride (0.3 g) at 140°. The mixture was quickly heated to 180°, stirred for 2 min, air-cooled for 1 min, then poured into ice (100 cm^3) containing concentrated hydrochloric acid (5 cm^3). The purple suspension was stirred with gentle heating for 70 min before being extracted with dichloromethane (3×20 cm^3). The combined organic extracts were washed with water, dried and concentrated to leave a dark residue which was subjected to preparative t.l.c., with toluene/ethyl acetate (9 : 1) as eluent. The major purple band

was removed to afford the *trihydroxy anthraquinone* (26) as a dark solid (6.3 mg, 88%), m.p. dec. >290° (Found: $M^{+\bullet}$, 270.0530. $C_{15}H_{10}O_5$ requires $M^{+\bullet}$, 270.0528). λ_{max} [MeOH containing Me_2SO (5%) and HCO_2H (1%)] (log ε) 290, 335, 494sh, 525, 565sh nm (3.80, 3.67, 3.77, 3.86, 3.68). ν_{max} 3374, 1695, 1647, 1610 cm^{-1}. δ [(D_6)acetone] 2.20, d, *J* 1.7 Hz, Me; 6.61, d, *J* 2 Hz, H 7; 6.85, m, H 3; 7.00, d, *J* 2 Hz, H 5; 7.73, s, H 10; 9.65, br s, 6-OH; 10.17, s, 8-OH; 16.33, s, 9-OH. *m/z* 271 (M+1, 23%), 270 (M, 100), 242 (11), 213 (7), 174 (12), 97 (14), 56 (29).

Methyl (3,5-Dimethoxy-2-methoxycarbonylphenyl)acetate (31)

To a solution of diester (15) (250 mg) in dichloromethane (20 cm^3) was added silver(I) oxide (2.5 g) and methyl iodide (1 cm^3). The mixture was stirred at room temperature in the absence of light for 24 h. The suspension was filtered and the solid was washed with dichloromethane (2×10 cm^3). The filtrate and washings were concentrated to give a pale yellow solid which was recrystallized from diethyl ether/petrol to give the diester (31)[15] (250 mg, 95%) as colourless needles, m.p. 50–52° (Found: C, 58.4; H, 6.1. Calc. for $C_{13}H_{16}O_6$: C, 58.2; H, 6.0%). ν_{max} 1727, 1699 cm^{-1}. δ 3.67, s, CH_2; 3.68, 3.82, 3.83, 3.86, s, s, s, s, 4×OMe; 6.40, d, *J* 2.3 Hz, H 4 or H 6; 6.41, d, *J* 2.3 Hz, H 4 or H 6. *m/z* 268 (M, 37%), 237 (41), 236 (24), 209 (74), 208 (100), 193 (86).

(2-Carboxy-3,5-dimethoxyphenyl)acetic Acid (32)

The diester (31) (103 mg) was dissolved in 10% aqueous sodium hydroxide solution (20 cm^3) and heated to 80° for 30 min. The cooled solution was acidified to pH 1–2 with concentrated hydrochloric acid, diluted with water (30 cm^3) and extracted with ethyl acetate (4×50 cm^3). The combined extracts were dried and concentrated to give diacid (32) (76 mg, 83%) as a white solid. Recrystallization from acetone/petrol gave colourless cubes, m.p. 175–178° (lit.[15] 172–173°). δ [(D_6)acetone] 3.77, s, CH_2; 3.84, 3.87, s, s, 2×OMe; 6.55, d, *J* 2.5 Hz, H 4 or H 6; 6.58, d, *J* 2.5 Hz, H 4 or H 6.

*6,8-Dimethoxy-1*H*-2-benzopyran-1,3(4*H*)-dione (33)*

A solution of diacid (32) (200 mg) in acetyl chloride (10 cm^3) was heated at reflux for 30 min. The cooled solution was concentrated to give the anhydride (33) (161 mg, 87%) as a pale yellow solid. Recrystallization from acetone/petrol afforded colourless microneedles, m.p. 166–167° (lit.[16] 167–168°). δ [(D_6)acetone] 3.92, 3.93, s, s, 2×OMe; 4.15, s, CH_2; 6.60, d, *J* 2.4 Hz, H 5 or H 7; 6.63, d, *J* 2.4 Hz, H 5 or H 7.

10-Hydroxy-5,7-dimethoxy-2-methyl-1,4-anthraquinone (29)

To a suspension of sodium hydride (10 mg, 60% in paraffin oil) in tetrahydrofuran (10 cm^3) was added anhydride (33) (28 mg) and the mixture was stirred at 0° for 10 min before being added dropwise to a solution of the benzoquinone (22) (20 mg) in tetrahydrofuran (7 cm^3). Stirring was continued at 0° for 30 min and the mixture was warmed to room temperature over 20 min. The suspension was then quenched with saturated ammonium chloride solution (20 cm^3) and extracted with dichloromethane (2×20 cm^3). The combined extracts were washed with water, dried and concentrated to give a red residue which was subjected to flash chromatography (on silica containing 2% oxalic acid), with toluene/ethyl acetate (7 : 3) as eluent. The leading red band was removed to afford the anthraquinone (29) (26 mg, 70%) as a dark red solid. Recrystallization from dichloromethane/petrol gave red microneedles, m.p. dec. >225° (lit.[9] 224°). δ 2.19, d, *J* 2 Hz, Me; 3.95, 4.02, s, s, 2×OMe; 6.63, d, *J* 2.2 Hz, H 6; 6.84, br s, H 3 and H 8; 7.87, s, H 9; 14.92, s, OH.

9-Hydroxy-6,8-dimethoxy-2-methyl-1,4-anthraquinone (30)

Sodium hydride (19 mg, 60% in paraffin oil), anhydride (33) (70 mg) and the benzoquinone (27) (49 mg) were made to react as for the formation of (29). After chromatography the major red band was removed to give the *anthraquinone* (30) (67 mg, 72%) as a red solid. Recrystallization from dichloromethane/petrol afforded microneedles, m.p. dec. >208° (Found: $M^{+\bullet}$, 298.0838. $C_{17}H_{14}O_5$ requires $M^{+\bullet}$, 298.0841). λ_{max} (log ε) 286, 300, 331, 488, 516, 552sh nm (3.98, 3.99, 3.92, 4.07, 4.12, 3.90). ν_{max} 1690, 1678 cm^{-1}. δ 2.23, br s, Me; 3.95, 4.03, s, s, 2×OMe; 6.64, d, *J* 2 Hz, H 7; 6.80, br s, H 3; 6.86, d, *J* 2 Hz, H 5; 7.85, s, H 10; 15.10, s, OH. *m/z* 298 (M, 100%), 280 (22), 269 (20), 252 (25), 180 (21).

Methyl (4,5-Dihydroxy-7-methoxy-3-methoxycarbonylnaphthalen-2-yl)acetate (34)

To a suspension of sodium hydride (24 mg, 60% in paraffin oil) in tetrahydrofuran (10 cm^3) was added anhydride (18) (60 mg) and the mixture was stirred at 0° for 10 min. The suspension was added to a solution of the allene (1) (54 mg) in tetrahydrofuran (5 cm^3) and the whole was stirred at 0° for 20 min and at room temperature for 2 h. A solution of 10% aqueous hydrochloric acid (2 cm^3) was added and stirring was continued for 30 min before the mixture was diluted with water (20 cm^3) and extracted with dichloromethane (2×20 cm^3). The combined organic extracts were dried and concentrated to give an oily residue which was subjected to preparative t.l.c., with diethyl ether as eluent. Isolation of the major band (R_F 0.8) afforded the diester (34) (8 mg, 9%) as colourless needles, m.p. 161–163° (lit.[17] 162.0–162.5°). δ 3.70, 3.88, 3.92, s, s, s, 3×OMe; 3.91, s, CH_2; 6.55, d, *J* 2.5 Hz, H 6 or H 8; 6.57, d, *J* 2.5 Hz, H 6 or H 8; 6.95, s, H 1; 9.80, s, 5-OH; 14.26, s, 4-OH. *m/z* 320 (M, 20%), 288 (32), 256 (100), 229 (10), 200 (10).

Diethyl 3-Oxopentanedioate Magnesium Complex[19]

To a solution of diethyl acetone-1,3-dicarboxylate (37) (20 g) and triethylamine (10 g) in dry benzene (80 cm^3) was added anhydrous magnesium dichloride (4.8 g) and the mixture was heated at reflux for 90 min. The cooled suspension was concentrated and the residue was dissolved in dry diethyl ether (50 cm^3). The resulting precipitate was filtered off and the solid was washed with diethyl ether. The filtrate and washings were concentrated to give the magnesium complex[19] (20 g, 95%) as a pale yellow viscous oil. δ 1.21, t, *J* 7 Hz, 2×CH_2**Me**; 3.10, s, C**H**$_2CO_2$Et; 4.08, q, *J* 7 Hz, 2×C**H**$_2$Me; 4.72, s, CH.

Diethyl 2-Methyl-3-oxopentanedioate (38)

To a solution of the foregoing magnesium complex (21.4 g) in tetrahydrofuran (50 cm^3) at 0° was added sodium hydride (4.2 g, 60% in paraffin oil) and the suspension was stirred at room temperature for 30 min. A solution of methyl iodide (6.6 cm^3) in tetrahydrofuran (10 cm^3) was added dropwise to the suspension and stirring was continued for 22 h in the absence of light. The mixture was quenched slowly with 5% aqueous hydrochloric acid (40 cm^3) and then acidified to pH 1–2 with concentrated hydrochloric acid. The suspension was extracted with diethyl ether (3×50 cm^3) and the combined organic extracts were washed with water (100 cm^3), dried and concentrated. Distillation yielded the diester (38) (19.5 g, 90%) as a colourless oil, b.p. 100°/0.05 mmHg (lit.[20] 108–110°/1 mmHg). δ 1.23, t, *J* 7 Hz, 2×CH_2**Me**; 1.32, d, *J* 7 Hz, 2-Me; 3.53, 3.60, ABq, *J* 16 Hz, 4CH_AH_B; 3.68, q, *J* 7 Hz, H 2; 4.15, q, *J* 7 Hz, 2×C**H**$_2$Me.

Dimethyl 3-Chloro-2-methylpent-2-enedioate (39)

To a stirred solution of the diester (38) (19.3 g), under nitrogen, was added slowly, over 30 min, ground phosphorus pentachloride (20.6 g) and the mixture was warmed to 40° and stirred for a further 30 min. The red solution was cooled, poured onto ice (100 cm^3) and stirred for 15 min. The suspension was extracted with dichloromethane (3×50 cm^3) and the combined organic extracts were dried and concentrated. The residue was dissolved in a solution of anhydrous methanol (100 cm^3) and concentrated sulfuric acid (7 cm^3) and the mixture was heated at reflux for 18 h. The excess methanol was distilled off and the yellow residue was cooled to room temperature before being extracted with diethyl ether (5×40 cm^3). The combined extracts were washed successively with aqueous saturated sodium hydrogen carbonate solution (50 cm^3) and saturated sodium chloride solution (50 cm^3), then dried and concentrated. Distillation yielded the *methyl diester* (39) (15.7 g, 85%) as a colourless oil, b.p. 60–70°/0.05 mmHg (Found: C, 46.8; H, 5.5. $C_8H_{11}ClO_4$ requires C, 46.5; H, 5.4%). ν_{max} 1742, 1712 cm^{-1}. δ 2.05, s, 2-Me; 3.67, 3.70, s, s, 2×OMe; 3.90, s, CH_2. *m/z* 208 (M[^{37}Cl], 20%), 206 (M[^{35}Cl], 50), 174 (25), 144 (25), 146 (75), 59 (100).

Dimethyl 2-Methylpenta-2,3-dienedioate (36)

To a stirred solution of the foregoing ester (39) (4.2 g) in tetrahydrofuran (20 cm^3) at 0° was added dropwise triethylamine (3.2 cm^3) and the mixture was stirred at 0–5° for 18 h. The resulting suspension was filtered and washed with anhydrous diethyl ether (3×20 cm^3). The combined filtrate and washings were washed with aqueous hydrochloric acid (3×15 cm^3, 0.1 M) and saturated sodium chloride solution (20 cm^3). The ethereal layer was dried and concentrated to give an oily residue which was distilled to yield the *pentadienedioate* (36) (3 g, 88%) as a colourless oil, b.p. 60–63°/0.1 mmHg (Found: C, 56.6; H, 6.1. $C_8H_{10}O_4$ requires C, 56.5; H, 5.9%). ν_{max} 1957, 1727, 1630 cm^{-1}. δ 1.96, d, *J* 2.9 Hz, 2-Me; 3.75, s, 2×OMe; 5.89, q, *J* 2.9 Hz, H 4. *m/z* 170 (M, 24%), 156 (20), 142 (32), 83 (55), 58 (100), 51 (24), 50 (20).

Methyl 2-(3′-Methoxy-2′-methoxycarbonylphenyl)propanoate (41)

To a solution of the allene (36) (400 mg) in benzene (2 cm^3) was added diene (9) (670 mg) and the mixture was heated at reflux for 20 h. The cooled solution was concentrated and the residue was dissolved in tetrahydrofuran (1 cm^3). Concentrated hydrochloric acid (2 drops) was added and the solution was stirred at room temperature for 20 min before being extracted with diethyl ether (2×20 cm^3). The ethereal layer was washed with water, dried and concentrated to give an oily residue which was dissolved in dichloromethane (5 cm^3). Silver(I) oxide (2 g) and methyl iodide (1 cm^3) were added to the solution and the whole was stirred for 20 h in the absence of light. The suspension was filtered and the solid was washed with dichloromethane (2×20 cm^3). The filtrate and washings were concentrated and the residue was subjected to preparative t.l.c., with diethyl ether as eluent. The leading band was removed to afford the *diester* (41) (443 mg, 75%) as a white solid, m.p. 35–36° (Found: C, 62.0; H, 6.3. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.4%). ν_{max} 1727 cm^{-1}. δ 1.47, d, *J* 7.1 Hz, CMe; 3.65, s, OMe; 3.72, q, *J* 7.1 Hz, H 2; 3.82, 3.92, s, s, 2×CO_2Me; 6.84, d, *J* 8.1 Hz, H 6′ or H 4′; 6.95, d, *J* 8.1 Hz, H 6′ or H 4′; 7.34, t, *J* 8.1 Hz, H 5′. *m/z* 252 (M, 73%), 177 (21), 161 (20), 91 (20), 69 (22), 57 (100), 56 (20).

2-(2′-Carboxy-3′-methoxyphenyl)propanoic Acid (42)

A solution of diester (41) (100 mg) in aqueous sodium hydroxide solution (20 cm^3, 0.1 M) was heated at 80° for 1 h. The cooled solution was acidified with concentrated hydrochloric acid to pH 1–2 and diluted with water (20 cm^3) before being extracted with diethyl ether (100 cm^3). The ethereal phase was filtered while hot (charcoal), dried and concentrated to yield the diacid (42) (75 mg, 88%) as a white solid, m.p. 178–180° (lit.[23] 180–182°). It was undepressed in admixture with authentic material[4] and was indistinguishable from it in chromatographic behaviour. δ [(D_6)acetone] 1.41, d, *J* 7.1 Hz, CMe; 3.83, s, OMe; 3.86, q, *J* 7.1 Hz, H 2; 6.97, d, *J* 8 Hz, H 4′ or H 6′; 6.99, d, *J* 8 Hz, H 4′ or H 6′; 7.37, t, *J* 8 Hz, H 5′.

*8-Methoxy-4-methyl-1*H*-2-benzopyran-1,3(4*H*)-dione (35)*

The diacid (42) (100 mg) in a sublimation apparatus was dissolved in acetyl chloride (5 cm^3) and acetone (1 cm^3) with heating. Heating was continued until all the solvent evaporated to leave a viscous residue. Sublimation (100°/0.01 mmHg) afforded the anhydride (35) (70 mg, 76%) as white microneedles, m.p. 90–92° (lit.[23] 90–92°). ν_{max} 1785, 1745, 1600, 1480 cm^{-1}. δ [(D_6)acetone] 1.66, d, *J* 7 Hz, CMe; 3.96, s, OMe; 4.21, q, *J* 7 Hz, C**H**Me; 7.12, d, *J* 8 Hz, H 5 or H 7; 7.16, d, *J* 8 Hz, H 5 or H 7; 7.70, t, *J* 8 Hz, H 6.

For (35) derived from phenol:[4] m.p. 90–92°. ν_{max} 1787, 1743, 1594, 1478 cm^{-1}. δ [(D_6)acetone] 1.66, d, *J* 7 Hz, Me; 3.96, s, OMe; 4.21, q, *J* 7 Hz, C**H**Me; 7.16, apparent t, *J* 7 Hz, 2×ArH; 7.73, apparent t, *J* 7.7 Hz, 1×ArH.

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