Pyranonaphthoquinone Antibiotics. Part 1. Syntheses of 9-Demethoxyeleutherins and 9-Deoxynanaomycin A Methyl Ester

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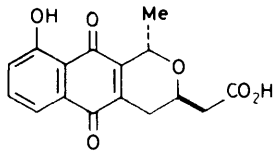
The syntheses of 9-demethoxyeleutherins and 9-deoxynanaomycin A methyl ester starting from indan-1-one derivatives are described. Lemieux–Johnson oxidation of the indene (15) derived from 4,7-dimethoxy-2-methylindan-1-one (14) afforded the diketone (16). The diol (17) obtained by lithium aluminium hydride reduction of (16) was treated with hydrochloric acid to give a *ca.* 1 : 2 mixture of *cis*-5,8-dimethoxy-1,3-dimethylisochroman (18) and the *trans*-isomer (19). Treatment of (16) with hydrogen bromide in acetic acid followed by catalytic reduction gave exclusively the *cis*-isochroman (18). Oxidative demethylation of the isochromans (18) and (19) afforded the quinones (22) and (23), benzannelation of which in two steps yielded 9-demethoxyeleutherin (24) and 9-demethoxyisoeleutherin (25) respectively. The same oxidation of the indene (32) derived from 4,7-dimethoxyindan-1-one (28) afforded the keto-aldehyde (33), which was treated with methoxycarbonylmethylenetriphenylphosphorane to give the conjugated ester (34). Reductive cyclisation of (34) with sodium borohydride afforded a *ca.* 1 : 3.5 mixture of *cis*-5,8-dimethoxy-3-methoxycarbonylmethyl-1-methylisochroman (35) and the *trans*-isomer (36). Oxidative demethylation of (36) followed by benzannelation produced 9-deoxynanomycin A methyl ester (39).

NANAOMYCINS A (1) [1] and D (2),[2] griseusin A (3),[3] and granaticin (4) [4] are representatives of a group of pyranonaphthoquinone antibiotics. These natural products are noteworthy for their biological effects as antimicrobial agents. The nanaomycins, in particular, were reported [1b] to have excellent activities against mycoplasmas. Synthetic efforts in this area have yielded the first total synthesis of racemic nanaomycins A and D in 1978.[5] We have recently embarked on a programme exploring a new synthetic route to nanaomycins, eventually leading to a total synthesis of even more complex molecules such as griseusin A and granaticin.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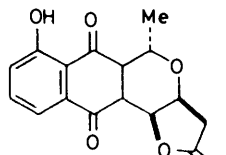
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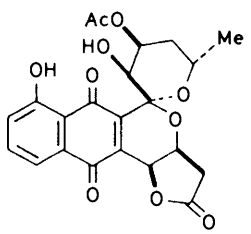
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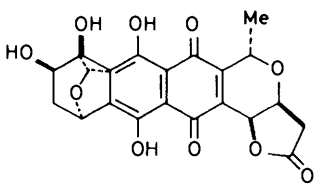
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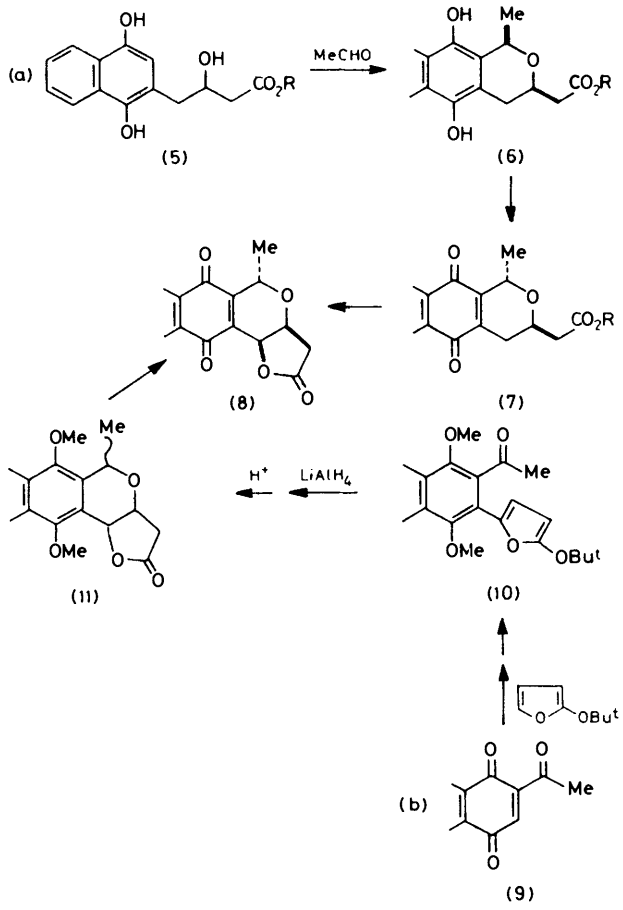
Methods hitherto reported for the construction of the isochroman (or γ-lactoisochroman) ring system could be classified into two categories as illustrated in Scheme 1. The first (a) [5,6] originates from Schmid's method [7] for the synthesis of eleutherin and isoeleutherin.[8] The key step involves condensation of the γ-naphthyl-β-hydroxyester (5) with acetaldehyde giving the isochroman (6), which could be converted into the quinone (7), and further into the γ-lactone (8), by air oxidation. The second approach (b) by Kraus [9] features the Michael addition of a butenolide anion equivalent, 2-t-butoxyfuran, with the acetylnaphthoquinone (9). The condensation product (10) was then reductively cyclised to

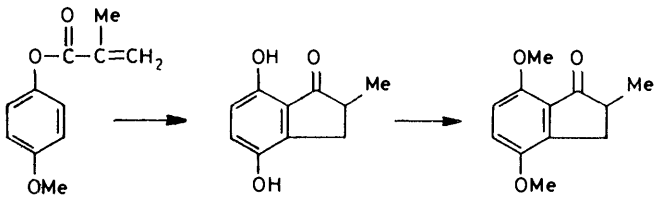


SCHEME 1

give the γ-lactopyran derivatives (11). We have investigated the use of readily accessible indanone derivatives as precursors of the heterocyclic ring system. Results obtained with the synthesis of 9-demethoxyeleutherins performed as a model study and its extension to the synthesis of 9-deoxynanomycin A are now described.

Synthesis of 9-Demethoxyeleutherin (24) *and 9-Demethoxyisoeleutherin* (25).—For the synthesis of the starting indan-1-ones, we have used the Fries rearrangement and subsequent Friedel–Crafts reaction [10] of appropriate aryl esters of unsaturated acids. Careful heating of the methacrylate (12) with aluminium chloride–sodium chloride (90 °C for 40 min, 120 °C for 50 min, and then 180 °C for 10 min) afforded 4,7-dihydroxy-2-methylindan-1-one (13), which was treated with sodium hydroxide–dimethyl sulphate to give 4,7-dimethoxy-2-methylindan-1-one (14) (Scheme 2).

Reaction of the indanone (14) with methylmagnesium iodide yielded an unstable Grignard product, which, when shaken in ether with dilute hydrochloric acid, was transformed to 4,7-dimethoxy-2,3-dimethylindene (15) in 72% yield. Oxidative cleavage of the double bond of

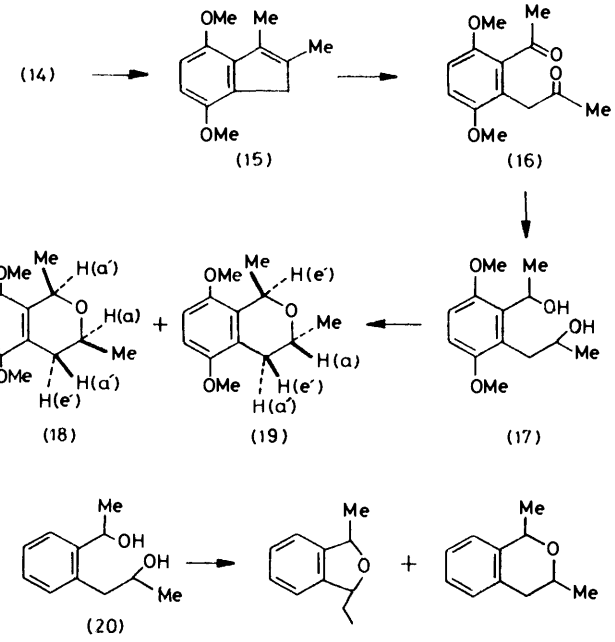


(12) (13) (14)

SCHEME 2

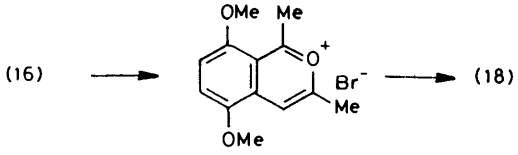
the indene (15) by the Lemieux–Johnson method produced an oily diketone (16) in 72% yield. The crude (16) was reduced, without further purification, with lithium aluminium hydride to give the diol (17). The diol was then subjected to an acid-catalysed cyclisation.

Benkeser and Johnston [11] reported that the cyclisation of an analogous diol (20) with toluene-*p*-sulphonic acid in acetic acid at 100 °C gave two products, the major being an isobenzofuran and the minor an isochroman derivative. When we attempted to cyclise the diol (17) under milder conditions [stirring an ethereal solution of (17) with hydrochloric acid], it was dehydrated readily to give only 1,3-dimethylisochroman as a *ca.* 1 : 2 mixture of the stereoisomers (18) and (19) (by g.l.c.), which could be separated by silica gel chromatography. It should be noted that no isobenzofuran derivative was detected. The isochroman structures of (18) and (19) were supported by their n.m.r. spectra, each showing two 3-Me and 1-Me doublets at δ 1.34 and 1.54 (each *J* 7 Hz) for (18) and at 1.31 and 1.49 (each *J* 7 Hz) for (19). The stereochemistry of the isomers was assigned by comparing long-range coupling constants ($J_{1,4}$). The minor product (18) which exhibited larger coupling constants ($J_{1a',4a'}$ 2 Hz; $J_{1a',4e'}$ 1 Hz) was assigned the *cis*-structure, and the major ($J_{1,4}$ <1 Hz) the *trans*-isomer. This stereochemical assignment was supported by an acid-catalysed equilibration experiment: the *cis*-isomer (18) could be epimerised in methanesulphonic acid to the thermodynamically more stable *trans*-isomer giving a *ca.* 1 : 4 mixture of (18) and (19) (Scheme 3).



SCHEME 3

The *cis*-isomer was most conveniently obtained from the diketone (16) by the two-step procedure in Scheme 4. Treatment of (16) with hydrogen bromide in acetic acid produced the deeply coloured oxonium salt (21), which was characterised by two downfield singlets at δ 2.07 and 2.94 corresponding to the C-1 and C-3 methyl groups. Catalytic hydrogenation of the salt over platinum gave exclusively the *cis*-isochroman (18) in an overall yield of 40% from (16), only a trace amount of the *trans*-isomer (19) being detected by g.l.c.



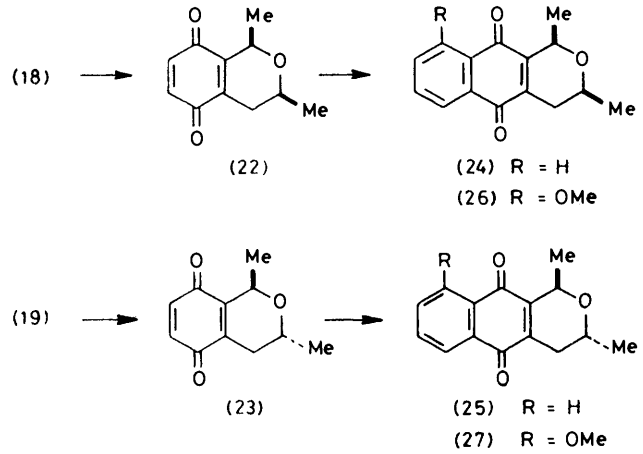
SCHEME 4

Oxidative demethylation of the isochromans (18) and (19) was then carried out with cerium(IV) ammonium nitrate in aqueous acetonitrile to produce the corresponding quinones (22) and (23) in the same yield (85%). The difference between the long-range coupling constants for 1-H and 4-H for the quinone isomers was quite distinctive, as found for eleutherin (26) and isoeleutherin (27): [12] 4.0 and 2.8 Hz for (22); 2.0 and <1.0 Hz for (23).

The final benzannelation was performed in two steps in excellent yields. Treatment of (22) with 1-acetoxy-

buta-1,3-diene in toluene at room temperature afforded a cycloaddition product, presumably as a mixture of two regioisomers. The crude adduct was then stirred with sodium carbonate in aqueous ethanol to afford 9-demethoxyeleutherin (24) in 89% yield. 9-Demethoxyisoeleutherin (25) was also obtained by the same procedure from (23) in 91% yield (Scheme 5).

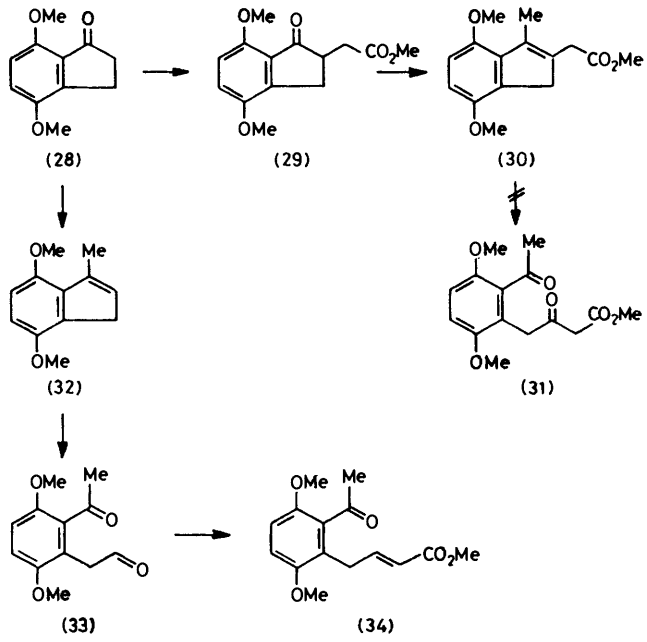
Synthesis of 9-Deoxynanaomycin A Methyl Ester (39).—We first attempted to synthesise the β-keto-ester (31) starting with the indanone (29) *via* the indene (30) by employing essentially the same procedure as just described. However, Lemieux–Johnson oxidation of the indene (30) did not lead to any identifiable product. Therefore, we investigated an alternative route, the key intermediate of which was the conjugated ester (34).



SCHEME 5

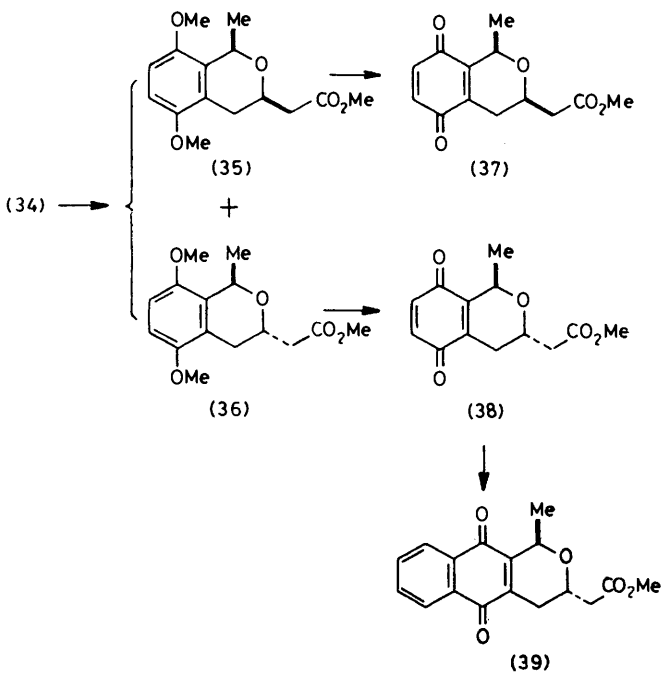
4,7-Dimethoxyindan-1-one (28) obtained by Buck's method [13] was treated with methylmagnesium iodide and the product was briefly treated with hydrochloric acid to give 4,7-dimethoxy-3-methylindene (32) in 85% yield. The double bond of the indene (32) was then subjected to oxidative cleavage by the Lemieux–Johnson method. The resulting unstable keto-aldehyde (33) was immediately treated with a slight excess of methoxycarbonylmethylenetriphenylphosphorane in benzene at room temperature to yield the conjugated ester (34), shown to be the stereochemically homogeneous *E*-isomer by n.m.r. analysis (J_{vic} 16 Hz) (Scheme 6).

Reduction of (34) with sodium borohydride in methanol produced two products in a ratio of 1 : 3.5 (by g.l.c.). Both compounds, isolated by preparative t.l.c., were shown by spectral data (n.m.r. and m.s.) to possess an isochroman structure. The major, more polar product which showed smaller values of $J_{1,4}$ (<1 Hz) was tentatively assigned the *trans*-isochroman structure (36) and the other ($J_{1a',4a'} = J_{1a',4e'} = 1.5$ Hz) the *cis*-structure (35). The isochromans (35) and (36) were oxidatively demethylated with cerium(IV) ammonium nitrate in aqueous acetonitrile to afford the corresponding quinones (37) and (38) respectively. The values of the long-range coupling constants $J_{1,4}$ for (37) (3.7 and 2.5 Hz) and (38) (2.2 and <1 Hz) were compatible with the foregoing relative configurations. Compound (38) was converted into (39) by the procedure just described: Diels–Alder reaction of the quinone (38) with 1-acetoxy-



SCHEME 6

buta-1,3-diene followed by treatment with sodium carbonate formed deoxynanaomycin A methyl ester (39) in 78% yield (Scheme 6). The structure of (39) was fully confirmed by its m.p. (185—187 °C; lit.,[6] 185—187 °C) and spectral data (n.m.r., i.r., and m.s.).



SCHEME 7

EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro melting point apparatus. I.r. spectra were taken on a Hitachi 215 spectrometer and n.m.r. spectra on a JEOL MH-100 spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a Hitachi RMU-6MG or a JEOL D-300 spectrometer. T.l.c. was performed on Merck silica gel 60 F_{254} plates and preparative t.l.c. was carried out on Merck silica gel 60 $PF_{254+366}$. Merck silica gel 60 (70—230 mesh) was used for column chromatography. G.l.c. analyses were performed on a Yanagimoto G-1800 apparatus.

4,7-Dihydroxy-2-methylindan-1-one (13).—A mixture of 4-methoxyphenol (10 g, 0.08 mol) and methacryl chloride (9.3 g, 0.089 mol) was heated at 70 °C for 30 min and then at 100 °C for 20 min. The mixture was added to ether (100 ml), the ethereal solution washed with 2M-sodium hydroxide solution and dried ($MgSO_4$), and the solvent removed under reduced pressure to yield *4-methoxyphenyl methacrylate* (12) (13.3 g, 86%) as an off-white solid, $\nu_{max.}$ (Nujol) 1 720 cm^{-1}, δ($CDCl_3$) 2.00 (3 H, s, C-Me), 3.72 (3 H, s, OMe), 5.64br (1 H, s, olefinic H), 6.24br (1 H, s, olefinic H), and 6.72—7.04 (4 H, m, Ar-H), *m/e* 192 (M^+), 164 ($M^+ - CO$), and 124 ($C_7H_8O_2^+$, 100%). A mixture of the methacrylate (12) (13.3 g, 0.069 mol), aluminium chloride (66 g, 0.5 mol), and sodium chloride (26.5 g, 0.45 mol) was heated at 90 °C for 40 min, at 120 °C for 50 min, and then at 180 °C for 10 min under nitrogen. The mixture was added to water, the resulting suspension extracted with ethyl acetate, the organic layer washed with 10%-hydrochloric acid and dried ($MgSO_4$), and the solvent evaporated off to yield a solid. Crystallisation from chloroform afforded *4,7-dihydroxy-2-methylindan-1-one* (13) (5.7 g, 46%), m.p. 160—163 °C; $\nu_{max.}$ (KBr) 3 230 and 1 645 cm^{-1}; *m/e* 178 (M^+, 100%) and 163 ($M^+ - Me$) (Found: C, 67.2; H, 5.9. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%).

4,7-Dimethoxy-2-methylindan-1-one (14).—To a solution of the indanone (13) (10 g, 0.056 mol) in 2M-sodium hydroxide solution (60 ml) dimethyl sulphate was added dropwise (20 g, 0.16 mol) over 30 min and the mixture was stirred at room temperature for 30 min and then heated at 70 °C for 10 min. The resulting mixture was extracted with ethyl acetate, the extract washed with 10% sodium hydroxide solution and water, and dried ($MgSO_4$). The solvent was evaporated off under reduced pressure to give a solid. Repeated crystallisation from ethyl acetate–ether afforded *4,7-dimethoxy-2-methylindan-1-one* (14) (8.6 g, 75%), m.p. 79.5—82.5 °C; $\nu_{max.}$ (KBr) 1 705 cm^{-1}; δ($CDCl_3$) 1.25 (3 H, d, *J* 7 Hz, 2-Me), 2.40—3.40 (3 H, m, 2- and 3-H), 3.79 and 3.83 (each 3 H, s, 4- and 7-OMe), 6.64 (1 H, d, *J* 8 Hz, Ar-H), and 6.90 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 206 (M^+, 100%), 191 ($M^+ - Me$), and 177 ($C_{10}H_9O_3^+$) (Found: C, 69.6; H, 6.6. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.8%).

4,7-Dimethoxy-2,3-dimethylindene (15).—An ethereal solution of methylmagnesium iodide (2M-solution; 10 ml, 0.02 mol) was added dropwise, over 5 min, to a solution of the indanone (14) (2.0 g, 9.7 mmol) in ether (150 ml) at 0 °C and the mixture was stirred at room temperature for 50 min, poured into saturated ammonium chloride solution, and extracted with ether. The ethereal extract was vigorously shaken with 10% hydrochloric acid for 2 min, washed with dilute sodium hydrogen carbonate solution, dried ($MgSO_4$), and the solvent removed under reduced pressure. Column chromatography on silica gel, with benzene as eluant, afforded *4,7-dimethoxy-2,3-dimethylindene* (15) (1.78 g, 72%), m.p. 53—55 °C (from Et_2O–hexane); δ($CDCl_3$) 1.96 and 2.14 (each 3 H, s, 2- and 3-Me), 3.12br (2 H, s, CH_2), 3.72 and 3.76 (each 3 H, s, 4- and 7-OMe), 6.45 (1 H, d, *J* 8 Hz, Ar-H), and 6.63 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 204 (M^+, 100%) and 189 ($M^+ - Me$) (Found: C, 76.2; H, 7.8. $C_{18}H_{16}O_2$ requires C, 76.4; H, 7.9%).

cis- (18) *and trans-* (19) *Dimethoxy-1,3-dimethylisochroman*.—(a) A solution of the indene (15) (1.78 g, 9.7 mmol) and osmium tetraoxide (25—50 mg, 0.1—0.2 mmol) in dioxan (60 ml) and water (20 ml) was stirred at room temperature for 5 min and then sodium metaperiodate (3.91 g, 0.018 mol) was added, in portions, to the solution over 30 min. The mixture was stirred for 3 days, diluted with water, and extracted with ether. The ethereal extract was washed with water and dried ($MgSO_4$), and the solvent evaporated off under reduced pressure to give *3-acetonyl-2-acetyl-1,4-dimethoxybenzene* (16) (1.48 g, 72%); $\nu_{max.}$ 1 720 and 1 700 cm^{-1}; δ($CDCl_3$) 2.02 and 2.32 (each 3 H, s, 2 × COMe), 3.45 (2 H, s, CH_2), 3.52 and 3.56 (each 3 H, s, 1- and 4-OMe), and 6.45 (2 H, s, Ar-H); *m/e* 236 (M^+), 221 ($M^+ - Me$), 194 ($M^+ - CH_2{:}C{:}O$), and 179 ($C_{10}H_{11}O_3^+$, 100%). A mixture of this crude diketone (16) (0.2 g, 0.85 mmol) and lithium aluminium hydride (0.3 g, 7.9 mmol) in ether (20 ml) was refluxed for 3 h. Saturated Rochelle salt (potassium sodium tartrate) solution was added and the product was extracted with chloroform. Evaporation of the dried ($MgSO_4$) organic layer left *2-(1-hydroxyethyl)-3-(2-hydroxypropyl)-1,4-dimethoxybenzene* (17) (0.172 g, 85%) as an oil; $\nu_{max.}$ (neat) 3 400 cm^{-1}. A solution of the crude diol (17) (0.172 g, 0.72 mmol) in ether (20 ml) was stirred with concentrated hydrochloric acid (2 ml) at 0 °C for 1 h, washed with water and dilute sodium hydrogencarbonate solution, and dried ($MgSO_4$). The solvent was evaporated off and the residual oil distilled under reduced pressure to afford the 1,3-dimethylisochromans (0.115 g, 73%), b.p. 90—100 °C at 1 Torr, showing two spots on t.l.c. owing to the presence of two diastereoisomers, R_F 0.85 and 0.80 (SiO_2; benzene–ethyl acetate, 5 : 1). The individual isomers were obtained by preparative t.l.c. (SiO_2; benzene–ethyl acetate, 9 : 1) as pale yellow oils. The less polar compound was cis-*5,8-dimethoxy-1,3-dimethylisochroman* (18) (26 mg, 16%); δ($CDCl_3$) 1.34 (3 H, d, *J* 7 Hz, 3-Me), 1.54 (3 H, d, *J* 7 Hz, 1-Me), 2.34 (1 H, ddd, *J* 17, 11, and 2 Hz, 4a′-H), 2.84 (1 H, ddd, *J* 17, 2.5, and 1 Hz, 4e′-H), 3.50—3.80 (1 H, m, 3-H), 3.84 (6 H, s, 5- and 8-OMe), 5.10br (1 H, q, *J* 7 Hz, 1-H), and 6.80 (2 H, s, Ar-H); *m/e* 222 (M^+) and 207 ($M^+ - Me$, 100%) (Found: M^+, 222.124 8. $C_{13}H_{18}O_3$ requires *M*, 222.125 7). The more polar compound was trans-*5,8-dimethoxy-1,3-dimethylisochroman* (19) (57 mg, 36%); δ($CDCl_3$) 1.31 (3 H, d, *J* 6 Hz, 3-Me), 1.49 (3 H, d, *J* 6 Hz, 1-Me), 2.28 (1 H, dd, *J* 17 and 11 Hz, 4a′-H), 2.78 (1 H, dd, *J* 17 and 3 Hz, 4e′-H), 3.76 (6 H, s, 5- and 8-OMe), 3.90—4.20 (1 H, m, 3-H), 5.10 (1 H, q, *J* 6 Hz, 1-H), and 6.64 (2 H, s, Ar-H); *m/e* 222 (M^+) and 207 ($M^+ - Me$, 100%) (Found: M^+, 222.129 2. $C_{13}H_{18}O_3$ requires *M*, 222.125 7). The ratio of *cis-* to *trans*-isomers obtained here was determined by g.l.c. to be 1 : 2 (t_R 4.7 and 5.7 min; 20% SE-30 on Shimalite W at 160 °C). The *cis–trans* ratios obtained by using other catalysts at room temperature for 10 min were as follows: 1 : 3 with 1% H_2SO_4 in AcOH (80% yield); 1 : 4 with $MeSO_3H$ (70% yield).

(b) A solution of hydrogen bromide in acetic acid (26%; 3 ml) was added to a solution of the diketone (16) (0.714 g,

3 mmol) in acetic acid (2 ml). After a few minutes, ethyl acetate (50 ml) was added to the mixture and filtration of the resulting reddish precipitate gave 5,8-*dimethoxy*-1,3-*dimethylisochromenylium bromide* (21) (0.578 g, 64%); $\nu_{max.}$ (KBr) 1 640, 1 600, 1 560, and 1 490 cm^{-1}, $\delta(CD_3CO_2D)$ 2.07 and 2.94 (each 3 H, s, 1- and 3-Me), 4.17 and 4.29 (each 3 H, s, 5- and 8-OMe), 7.64 (1 H, s, *J* 8 Hz, Ar-H), 8.16 (1 H, d, *J* 8 Hz, Ar-H), and 8.36 (1 H, s, 4-H); *m/e* 219 (M^+ − Br), 218 (M^+ − HBr), and 213 (M^+ − HBr − Me, 100%). The oxonium salt (21) (0.2 g, 0.7 mmol) was catalytically hydrogenated in acetic acid (6 ml) over PtO_2 (0.1 g) under atmospheric pressure for 24 h. After the catalyst and the solvent were removed, the residual oil was dissolved in ether, washed with dilute sodium hydrogencarbonate solution and water, dried ($MgSO_4$), and the solvent removed under reduced pressure to afford an oil (91 mg, 60%), which was identical (n.m.r. spectrum) with *cis*-5,8-dimethoxy-1,3-dimethylisochroman (18).

Epimerisation of cis-5,8-*Dimethoxy*-1,3-*dimethylisochroman* (18).—A solution of the *cis*-isochroman (18) (10 mg, 0.045 mmol) in methanesulphonic acid (1 ml) was stirred at room temperature for 10 min. The resulting mixture was diluted with water, extracted with ethyl acetate, the extract dried ($MgSO_4$), and the solvent removed under reduced pressure to give an oil (8 mg, 80%), which was a *ca.* 1 : 4 mixture of the starting *cis*-isochroman (18) and the *trans*-isomer (19) (by g.l.c.).

cis- (22) *and* trans- (23) 1,3-*Dimethylisochroman*-5,8-*dione*.—A solution of cerium(IV) ammonium nitrate (0.532 g, 0.97 mmol) in water (0.8 ml) was added dropwise, over 5 min, to a stirred solution of the *cis*-isochroman (18) (72 mg, 0.324 mmol) in acetonitrile (0.8 ml) at room temperature and the mixture was stirred for 30 min, diluted with water, and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and the solvent evaporated off. The residual oil was distilled under reduced pressure to afford cis-1,3-*dimethylisochroman*-5,8-*dione* (22) (53 mg, 85%) as a yellow oil, b.p. 100—110 °C at 1 Torr; $\nu_{max.}$ (neat) 1 655 cm^{-1}; $\delta(CDCl_3)$ 1.32 (3 H, d, *J* 6 Hz, 3-Me), 1.44 (3 H, d, *J* 6 Hz, 1-Me), 2.08 (1 H, ddd, *J* 18, 11, and 4 Hz, 4-H), 2.59 (1 H, dt, *J* 18 and 2.8 Hz, 4-H), 3.40—3.60 (1 H, m, 3-H), 4.45—4.65 (1 H, m, 1-H), and 6.62 (2 H, s, Ar-H); *m/e* 192 (M^+) and 177 (M^+ − Me, 100%) (Found: C, 68.5; H, 6.1. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%).

Similarly, the *trans*-isochroman (19) (56 mg, 0.25 mmol) was converted into the *trans-isomer* (23) (41 mg, 85%), m.p. 102.5—105.5 °C (from EtOH); $\nu_{max.}$ (KBr) 1 660 cm^{-1}; $\delta(CDCl_3)$ 1.33 (3 H, d, *J* 6 Hz, 3-Me), 1.45 (3 H, d, *J* 6 Hz, 1-Me), 2.08 (1 H, ddd, *J* 19, 10, and 2 Hz, 4-H), 2.56 (1 H, dd, *J* 19 and 4 Hz, 4-H), 3.70—4.10 (1 H, m, 3-H), 4.80br (1 H, q, *J* 6 Hz, 1-H), and 6.66 (2 H, s, Ar-H); *m/e* 192 (M^+) and 177 (M^+ − Me, 100%) (Found: C, 69.0; H, 6.2%).

cis- (22) *and* trans- (IV)(22) 1,3-*Dimethyl*-3,4-*dihydro*-1H-*naphtho*[2,3-c]*pyran*-5,10-*dione*.—A solution of the *cis*-quinone (22) (50 mg, 0.26 mmol) and 1-acetoxybutadiene (0.1 g, 0.89 mmol) in toluene (1 ml) was set aside at room temperature for 3 days. The mixture was evaporated to dryness under reduced pressure and the residual oil was dissolved in ethanol (5 ml). To the solution was added 1% sodium carbonate solution (0.5 ml) and the mixture was stirred at room temperature for 5 h, diluted with ethyl acetate, and washed with water. Evaporation of the dried ($MgSO_4$) organic layer left a yellow solid, which was recrystallised from ethanol to afford cis-1,3-*dimethyl*-3,4-*dihydro*-1H-*naphtho*[2,3-c]*pyran*-5,10-*dione* (24) (56 mg, 89%), m.p. 122—125 °C; $\nu_{max.}$ (KBr) 1 660 cm^{-1}; $\delta(CDCl_3)$ 1.39 (3 H, d, *J* 6 Hz, 3-Me), 1.56 (3 H, d, *J* 6 Hz, 1-Me), 2.24 (1 H, ddd, *J* 18, 11, and 3.8 Hz, 4-H), 2.80 (1 H, dt, *J* 18 and 2.7 Hz, 4-H), 3.50—3.80 (1 H, m, 3-H), 4.70—5.00 (1 H, m, 1-H), 7.60—7.80 (2 H, m, Ar-H), and 7.95—8.20 (2 H, m, Ar-H); *m/e* 242 (M^+, 100%) and 227 (M^+ − Me) (Found: C, 74.55; H, 5.7. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%).

Similarly, the *trans*-quinone (23) (56 mg, 0.25 mmol) was converted into the trans-*isomer* (25) (55 mg, 91%), m.p. 146—148 °C (from EtOH); $\nu_{max.}$ (KBr) 1 660 cm^{-1}; $\delta(CDCl_3)$ 1.40 (3 H, d, *J* 6 Hz, 3-Me), 1.57 (3 H, d, *J* 6 Hz, 1-Me), 2.18 (1 H, ddd, *J* 18, 10, and 2 Hz, 4-H), 2.80 (1 H, dd, *J* 18 and 3.2 Hz, 4-H), 3.90—4.20 (1 H, m, 3-H), 5.60br (1 H, q, *J* 6 Hz, 1-H), 7.70—7.90 (2 H, m, Ar-H), and 8.05—8.25 (2 H, m, Ar-H); *m/e* 242 (M^+, 100%) and 227 (M^+ − Me) (Found: C, 74.2; H, 5.8%).

4,7-*Dimethoxy*-3-*methylindene* (32).—An ethereal solution of methylmagnesium iodide (2M-solution; 1 ml, 2 mmol) was added dropwise, over 5 min, to a stirred solution of 4,7-dimethoxyindan-1-one [13] (28) (0.2 g, 1.04 mmol) in ether (15 ml) at 0 °C and the mixture was stirred at room temperature for 1 h, poured into saturated ammonium chloride solution, and extracted with ether. The ethereal extract was vigorously shaken with 10% hydrochloric acid for 2 min, washed with dilute sodium hydrogencarbonate solution and dried ($MgSO_4$), and the solvent removed under reduced pressure. Column chromatography on silica gel, with benzene as eluant, afforded 4,7-*dimethoxy*-3-*methylindene* (32) (0.158 g, 80%) as a pale yellow solid, m.p. 50—55 °C; $\delta(CDCl_3)$ 2.26 (3 H, q, *J* 2 Hz, 3-Me), 3.14 (2 H, quintet, *J* 2 Hz, CH_2), 3.72 and 3.75 (each 3 H, s, 4- and 7-OMe), 5.93 (1 H, sextet, *J* 2 Hz, 2-H), and 6.44—6.70 (2 H, m, Ar-H); *m/e* 190 (M^+, 100%) and 175 (M^+ − Me).

2-*Acetyl*-3-(3-*methoxycarbonylprop*-2-*enyl*)-1,4-*dimethoxybenzene* (34).—A solution of the indene (32) (0.3 g, 1.58 mmol) and osmium tetraoxide (25—50 mg, 0.1—0.2 mmol) in dimethoxyethane (6 ml) and water (2 ml) was stirred at room temperature for 5 min and then sodium metaperiodate (0.705 g, 3.3 mmol) was added, in portions, to the solution over 30 min. The mixture was stirred for 4 h, diluted with water, and extracted with ether. The ethereal extract was washed with water and dried ($MgSO_4$), and the solvent evaporated off under reduced pressure to give 2-*acetyl*-3-*formylmethyl*-1,4-*dimethoxybenzene* (33) (0.278 g, 79%) as a pale yellow oil; $\nu_{max.}$ (neat) 2 720, 1 725, and 1 690 cm^{-1}; $\delta(CDCl_3)$ 2.44 (3 H, s, Ac), 3.62 (2 H, d, *J* 1 Hz, CH_2), 3.72 and 3.75 (each 3 H, s, 1- and 4-OMe), 6.77 (2 H, s, Ar-H), and 9.56 (1 H, t, *J* 1 Hz, CHO); *m/e* 222 (M^+), 194 (M^+ − CO), and 179 (M^+ − CO − Me, 100%). A solution of this crude keto-aldehyde (33) (0.278 g, 1.25 mmol) and methoxycarbonylmethylenetriphenylphosphorane (0.5 g, 1.5 mmol) in benzene (12 ml) was stirred at room temperature for 24 h. The resulting solution was concentrated under reduced pressure and the residue was chromatographed on silica gel, with benzene as eluant, to yield 2-*acetyl*-3-(3-*methoxycarbonylprop*-2-*enyl*)-1,4-*dimethoxybenzene* (34) (0.115 g, 45%) as an oil, b.p. 160—170 °C at 1 Torr; $\delta(CDCl_3)$ 2.38 (3 H, s, Ac), 3.40 (2 H, dd, *J* 7 and 1.5 Hz, CH_2), 3.64 (3 H, s, OMe), 3.80 (6 H, s, 2 × OMe), 5.60 (1 H, dt, *J* 16 and 1.5 Hz, C:C*H*·CO_2Me), 6.75 (2 H, s, Ar-H), and 6.90 (1 H, dt, *J* 16 and 7 Hz, C*H*:CH·CO_2Me); *m/e* 278 (M^+), 263 ($C_{13}H_{16}O_4^+$), 205

($C_{12}H_{13}O_3^+$, 100%), and 204 ($C_{12}H_{13}O_3^+$) (Found: C, 64.8; H, 6.3. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%).

cis- (35) *and* trans- (36) *Methyl* 5,8-*Dimethoxy*-1-*methylisochroman*-3-*ylacetate*.—Sodium borohydride (0.5 g, 0.013 mol) was added at 0 °C, in portions, to a stirred solution of the conjugated ester (34) (0.15 g, 0.54 mmol) in methanol (10 ml) over 30 min and the mixture was stirred at room temperature for 24 h, poured into water, and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and the solvent evaporated off under reduced pressure to give isochromans (0.138 g, 92%) as a pale yellow oil showing two spots on t.l.c. owing to the presence of two diastereoisomers, R_F 0.55 and 0.50 (SiO_2; benzene–ethyl acetate, 10 : 1). The individual isomers were obtained by preparative t.l.c. (SiO_2; benzene–ethyl acetate, 9 : 1) as pale yellow oils. The less polar compound was *methyl* cis-5,8-*dimethoxy*-1-*methylisochroman*-3-*ylacetate* (35) (26 mg, 17%); $\nu_{max.}$ (neat) 1 735 cm^{-1}; δ($CDCl_3$) 1.46 (3 H, d, *J* 6 Hz, 1-Me), 2.18 (1 H, ddd, *J* 17, 11, and 1.5 Hz, 4-H), 2.62 (2 H, d, *J* 6 Hz, $CH_2{\cdot}CO_2Me$), 2.80 (1 H, ddd, *J* 17, 2.7, and 1.5 Hz, 4-H), 3.63 (3 H, s, OMe), 3.60 (6 H, s, two OMe), 3.70—4.00 (1 H, m, 3-H), 4.91 (1 H, q, *J* 6 Hz, 1-H), and 6.52 (2 H, s, Ar-H); *m/e* 280 (M^+, 100%), 265 ($M^+ - Me$), and 262 ($M^+ - H_2O$) (Found: M^+, 280.131 5. $C_{15}H_{20}O_5$ requires *M*, 280.131 2). The more polar compound was the trans-*isomer* (36) (60 mg, 40%); $\nu_{max.}$ (neat) 1 740 cm^{-1}; δ($CDCl_3$) 1.45 (3 H, d, *J* 6 Hz, 1-Me), 2.27 (1 H, dd, *J* 17 and 11 Hz, 4-H), 2.53 (2 H, d, *J* 6 Hz, $CH_2{\cdot}CO_2Me$), 2.73 (1 H, dd, *J* 17 and 3.5 Hz, 4-H), 3.63 (3 H, s, OMe), 3.65 (6 H, s, two OMe), 4.10—4.40 (1 H, m, 3-Me), 4.90 (1 H, q, *J* 6 Hz, 1-H), and 6.49 (2 H, s, Ar-H); *m/e* 280 (M^+, 100%), 265 ($M^+ - Me$), and 262 ($M^+ - H_2O$) (Found: M^+, 280.132 8). The *cis*- to *trans*-isomer ratio was determined by g.l.c. to be 1 : 3.5 (t_R 2.7 and 3.3 min; 20% SE-30 on Shimalite W at 220 °C).

cis- (37) *and* trans- (38) *Methyl* 1-*Methyl*-5,8-*dioxo*-5,8-*dihydroisochroman*-3-*ylacetate*.—A solution of cerium(IV) ammonium nitrate (0.49 g, 0.9 mmol) in water (1 ml) was added dropwise, over 5 min, to a stirred solution of the *cis*-isochroman (35) (85 mg, 0.3 mmol) in acetonitrile (1 ml) at room temperature. The mixture was stirred for 30 min, diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and the solvent evaporated off. The resulting oil was chromatographed on silica gel, with benzene as eluant, afforded *methyl* cis-1-*methyl*-5,8-*dioxo*-5,8-*dihydroisochroman*-3-*ylacetate* (37) (65 mg, 86%) as a dark yellow oil; $\nu_{max.}$ (neat, 1 740 and 1 660 cm^{-1}; δ($CDCl_3$) 1.44 (3 H, d, *J* 7 Hz, 1-Me), 2.17 (1 H, ddd, *J* 18, 11, and 3.7 Hz, 4-H), 2.62 (2 H, dd) *J* 6 and 2.9 Hz, $CH_2{\cdot}CO_2Me$), 2.66 (1 H, dt, *J* 18 and 2.5 Hz, 4-H), 3.68 (3 H, s, CO_2Me), 3.70—4.00 (1 H, m, 3-H), 4.50—4.80 (1 H, m, 1-H), and 6.67 (2 H, s, Ar-H); *m/e* 250 (M^+), 235 ($M^+ - Me$), 218 ($M^+ - MeOH$), 177 ($C_{10}H_9O_3^+$), and 176 ($C_{10}H_8O_3^+$).

Similarly, the *trans*-isochroman (36) (0.139 g, 0.5 mmol) was converted into the trans-*isomer* (38) (95 mg, 77%), m.p. 99—100.5 °C (from MeOH); $\nu_{max.}$ (neat) 1 740 and 1 660 cm^{-1}; δ($CDCl_3$) 1.47 (3 H, d, *J* 7 Hz, 1-Me), 2.16 (1 H, ddd, *J* 19, 11, and 2.2 Hz, 4-H), 2.61 (2 H, d, *J* 6 Hz, $CH_2{\cdot}CO_2Me$), 2.68 (1 H, dd, *J* 19 and 3.5 Hz, 4-H), 3.73 (3 H, s, CO_2Me), 4.20—4.40 (1 H, m, 3-H), 4.84 (1 H, q, *J* 7 Hz, 1-H), and 6.75 (2 H, s, Ar-H); *m/e* 250 (M^+), 235 ($M^+ - Me$), 218 ($M^+ - MeOH$), 177 ($C_{10}H_9O_3^+$, 100%), and 176 ($C_{10}H_8O_3^+$) (Found: C, 62.4; H, 5.6. $C_{13}H_{14}O_5$ requires C, 62.4; H, 5.6%).

Methyl trans-1-*Methyl*-5,10-*dioxo*-3,4,5,10-*tetrahydro*-1H-*naphtho*[2,3-c]*pyran*-3-*ylacetate* (39).—A solution of the *trans*-quinone (38) (30 mg, 0.12 mmol) and 1-acetoxybutadiene (60 mg, 0.54 mmol) in toluene (0.7 ml) was set aside at room temperature for 2 days. The mixture was evaporated to dryness under reduced pressure and the residual oil was dissolved in ethanol (3 ml). To the solution was added 1% sodium carbonate solution (0.3 ml) and the mixture was stirred at room temperature for 5 h, diluted with ethyl acetate, and washed with water. Evaporation of the dried ($MgSO_4$) organic layer left a yellow solid, which was recrystallised from methanol to afford methyl *trans*-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-3-ylacetate (39) (28 mg, 78%) as yellow needles, m.p. 185—187 °C (lit.,[6] m.p. 185—187 °C); $\nu_{max.}$ (KBr) 1 735 and 1 660 cm^{-1}, the n.m.r. data of which were completely identical with those reported by Pyrek,[6] *m/e* 300 (M^+), 268 ($M^+ - MeOH$), 227 ($C_{14}H_{11}O_3^+$), and 226 ($C_{14}H_{10}O_3^+$, 100%) (Found: C, 67.8; H, 5.4. Calc. for $C_{17}H_{16}O_5$: H, 68.0; H, 5.4%).

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