Synthesis of the Phytoalexin (±)-Phaseollin: 3-Phenylthiochromans as Masked 2*H*-Chromenes and *o*-Prenyl Phenols

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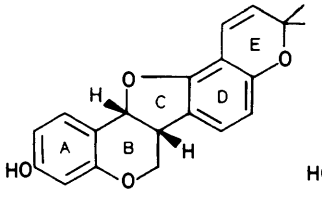
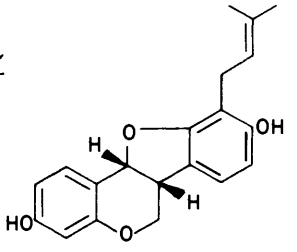
Phenylthiyl radicals are shown to add regiospecifically to 2*H*-chromenes to afford 3-phenylthiochromans (**8**), (**10**), (**13**), (**14**), and (**15**). The sulphide (**15**), as equivalent to a chromene protected against acid and oxidation, has been used in two syntheses of (±)-phaseollin, a major phytoalexin of beans and other legumes, *via* the sequence (**17**)→(**18**)→(**19**)→(**20**)→(**21**)→(±)-(**1**) or (**19**)→(**22**)→(**23**)→(±)-(**1**). Also the 3-phenylthiochromans, on electron transfer from metal naphthalenide or a mercury cathode, open to *o*-prenylphenols, providing a two step route to biogenetically important phenols from chromenes which is tolerant of free phenol and carbonyl functions and trisubstituted double bonds.

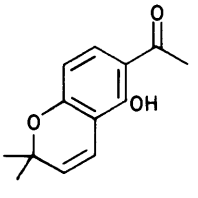
Phytoalexins are metabolites of higher plants whose biosynthesis is stimulated by fungal infection, and which accumulate to contribute to chemical defence against the biological attack. Many phytoalexins, in a diversity of structural type, have now been recognised and the area has been reviewed recently.[1,2] Historically the chromenopterocarpan phaseollin (**1**) was the second such compound to be recognised,[3] in infected bean plants (*Phaseollus vulgare*) and it has since been found in many members of the Leguminosae.[2] Phaseollidin[4a] (**2**), the biosynthetic precursor[4b] of chromene (**1**), frequently co-occurs in detectable concentrations. Phaseollin displays noteworthy antifungal, antibacterial, and antiyeast activities[5] with MIC < 5 μg for various micro-organisms and it is surprising that no synthesis of phaseollin or phaseollidin has yet been reported.



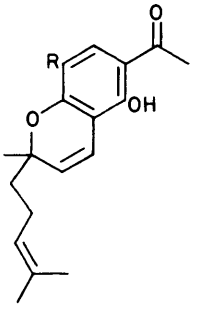
(**1**)



(**2**)



(**3**)



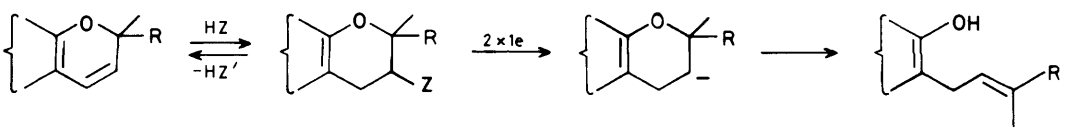
(**4**) R = OH
(**5**) R = H

In planning a synthesis of compound (**1**) it was noted that various methods were available for fusion of a 2,2-dimethyl-2*H*-pyran to phenols, to form the chromene fragment, and that some of these were highly regioselective[6] when applied to suitable phenols, *e.g.* formyl or acyl resorcinols. To take advantage of this the dimethylchromene unit had to be formed early in the synthesis. This requirement made it difficult to form the pterocarpan system either (*a*) through palladium-catalysed annellation using arylmercuric salts[7] since these would have to carry the chromene unit, and a mercurated chromene would presumably react with itself; or (*b*) through isoflavones prepared by way of deoxybenzoins, since the latter are usually formed by the Hoesch reaction, and chromenes do not survive the acid conditions necessary. The third general route to pterocarpans employs isoflavonoids made from chalcones utilising thallium(III) nitrate induced rearrangement.[8] This is efficient in suitable cases; however thallic nitrate reacts with chromene double bonds,[9,10a] leading to ring contraction/alkoxylation, and a chromenochalcone has been converted into a chromenoisoflavone in only few cases[10,11] and in discouraging yields (55, 28, 22, and 7%).

Similar problems arise when assessing routes to phaseollidin (**2**). It was noted in this case that although prenylation of phenols has been widely reported, through direct acid[12] or base[12a,13] catalysed alkylation or by Claisen rearrangement,[14] the majority of such reactions are low yielding: *O*- and di-alkylation and lack of regioselectivity are common problems.

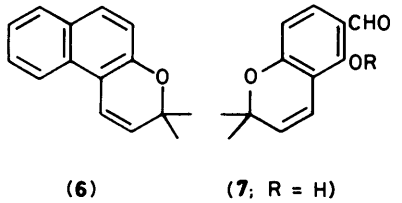
We thus determined to approach the synthesis of phaseollin using the efficient oxidative rearrangement of a chalcone with thallic nitrate, and to develop suitable protection from oxidation for the chromene double bond. It occurred to us that it might be possible to devise an intermediate that could be diverted to an *o*-prenylphenol as well as returned to a chromene, as in the Scheme. We report in this paper that 3-phenylthiochromans fill this role and can be used in the synthesis of (±)-phaseollin and of a variety of *o*-prenylphenols, with regio-control.

In the Scheme, HZ must (*a*) add regioselectivity in an anti-Markownikov fashion, (*b*) be easily modified to permit smooth elimination of HZ′ under neutral conditions, and (*c*) participate in electron transfer. We chose to investigate the radical addition



Scheme.

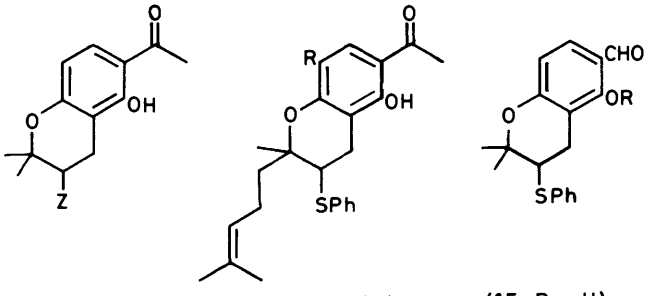
of thiophenol since ionic additions to chromenes can be problematic.[15] The chromenes (**3**)—(**5**) were available from previous work,[6d,f] and the naphthopyran (**6**) was prepared by Claisen rearrangement of 2-methyl-2-(2-naphthyloxy)but-3-yne. The formylchromene (**7**) was prepared by treating 2,4-dihydroxybenzaldehyde with 1,1-dimethoxy-3-methylbutan-3-ol in hot pyridine;[16] a single product was obtained whose chromene orientation follows from the ^{1}H n.m.r. data (see the Experimental section).



(**6**) (**7**; R = H) (**25**; R = CH_2OMe) (**8**; Z = SPh) (**9**; Z = SO_2Ph)

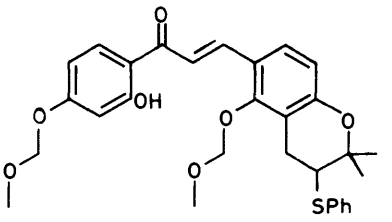
The naphthopyran (**6**), on being heated with thiophenol and azoisobutyronitrile in benzene for 48 h, yielded the 3-phenylthiochroman (**8**) (63%): in the ^{1}H n.m.r. spectrum the olefinic doublets of compound (**6**) were replaced by a 3 H ABC system, and the two methyl groups became non-equivalent, as expected. The regiochemistry of addition follows most clearly from the subsequent chemistry of the product (see below); none of the isomeric 4-phenylthiochroman was detected. Oxidation of the sulphide (**8**) with *m*-chloroperbenzoic acid gave the corresponding sulphone (**9**). A similar addition reaction to the chromene (**3**) also gave a single chroman (**10**) (85%). The same method applied to chromene (**4**) afforded compound (**13**) in only 28% yield, but irradiation of (**4**) with thiophenol and diphenyl disulphide raised the yield of (**13**) to 90%. Chromans (**14**) (56%) and (**15**) (63%) were also obtained by the photo-induced addition to chromenes (**5**) and (**7**). Thus the addition of the phenylthiyl radical is efficient, selective, and tolerant of free phenol and carbonyl functions.

To establish that chromenes could be generated from phenylthiochromans, the sulphide (**10**) was oxidised, with sodium periodate, to the diastereoisomeric sulphoxides (**11**) (70%); a single sulphone (**12**) was obtained using *m*-chloroperbenzoic acid. The sulphoxides (**11**) were not separated but refluxed in toluene for 3 h to form the initial chromene (**3**) (80%), as desired.



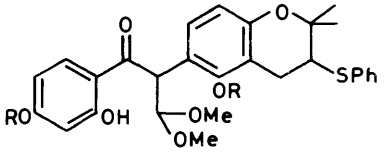
(**10**; Z = SPh) (**11**; Z = SOPh) (**12**; Z = SO_2Ph) (**13**; R = OH) (**14**; R = H) (**15**; R = H) (**16**; R = CH_2OMe)

In pursuance of phaseollin, the methoxymethyl ether (**16**) was condensed, in aqueous ethanolic sodium hydroxide, with the monomethoxymethyl ether of 2′,4′-dihydroxyacetophenone, to provide the chalcone (**17**) (63%). Rearrangement of this chalcone with thallium(III) nitrate in methanol smoothly

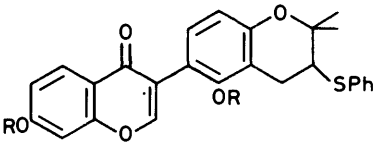


(**17**)

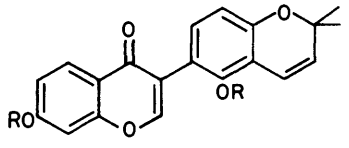
afforded the acetal (**18**) (53%) which was treated with sodium methoxide to induce cyclisation and elimination of methanol to afford the isoflavone (**19**) (83%). Oxidation of this isoflavone was effected with *m*-chloroperbenzoic acid, to give a sulphoxide (37%) which on thermolysis in refluxing toluene yielded the key chromeno isoflavone (**20**) (82%). After brief acid treatment to deprotect the hydroxy functions, the synthesis was completed by reduction with sodium borohydride (1,4- then 1,2-reduction); acid treatment during isolation closed ring C to provide (±)-phaseollin [27% from (**20**), *i.e.* mean 60% yield on the three steps]. Alternatively the isoflavone (**19**) was de-*O*-protected to (**22**), reduced, and cyclised in acid to form the pterocarpan (**23**) [48% from (**19**)] and it was demonstrated in a t.l.c. experiment that pyrolysis of the product of periodiate oxidation of (**23**) also afforded (±)-phaseollin. The identity of the synthetic (±)-phaseollin was established by comparison of u.v., i.r., and ^{1}H n.m.r. spectra data both with literature values[4a] and with data obtained for authentic natural phaseollin (kindly supplied



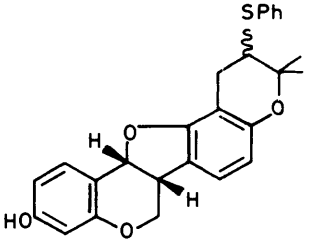
(**18**) R = CH_2OMe



(**19**) R = CH_2OMe
(**22**) R = H

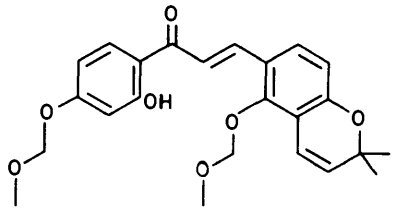


(**20**) R = CH_2OMe
(**21**) R = H

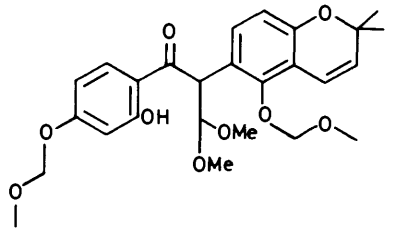


(**23**)

by Dr. P. M. Dewick, Department of Pharmacy). Since phaseollidin (**2**) has been prepared, in unspecified yield, by lithium–ammonia reduction of natural phaseollin,[4b] this work also offers a formal route of (±)-phaseollin. The structures of the synthetic intermediates were authenticated by spectroscopic examination; the data fully support the structural assignments but are otherwise unexceptional, and details are confined to the Experimental section.



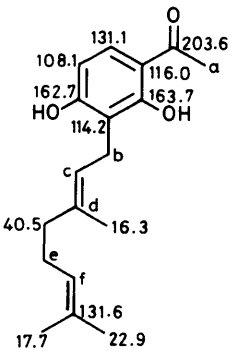
(**24**)



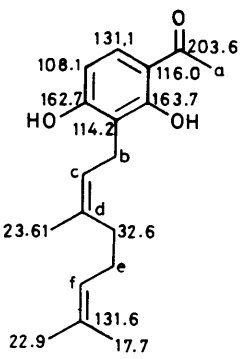
(**26**)

We also prepared the chalcone (**24**) by condensation of monomethoxymethyl resacetophenone with the formyl chromene (**25**), to compare its response to thallium(III) nitrate–methanol oxidation. The reaction necessitated careful monitoring to obtain the chromeno acetal (**26**); the maximum yield (23%) was reached before complete reaction of chalcone (yield 34% on the basis of converted chalcone) suggesting further oxidation of product. Cyclisation (81%) of acetal (**26**) was effected with sodium methoxide and led to the key isoflavone (**20**), thus converging with the first synthetic route.

We then turned our attention to the formation of *o*-prenylphenols from 3-phenylthiochromans. In a very few cases[16] (as with phaseollidin, above) direct reduction of a 2*H*-chromene with lithium–ammonia has been reported, but this method seemed to us incompatible with sensitive functions, *e.g.* benzylic carbonyl groups. We examined instead reductive ring opening following the Scheme, using electron transfer to the sulphur function to initiate C–S bond fission and a subsequent formal $E2_{CB}$ process. Using the naphthyldihydropyran (**8**), three methods for electron transfer reduction were tried, (*i*) lithium naphthalenide in tetrahydrofuran, (*ii*) potassium naphthalenide in tetrahydrofuran, and (*iii*) electrolysis using a mercury cathode, and acetonitrile–tetraethylammonium bromide electrolyte. In each case the naphthol (**27**) was obtained (in 63, 60, and 53% yields respectively), and the same product resulted (70%) from treatment of the sulphone (**9**) with potassium naphthalenide. The structure of (**27**) rests securely on ^{1}H n.m.r. spectroscopic measurements (see the Experimental section). Similar reactions were carried out with the phenylthiochromans (**10**), (**13**), and (**14**), and reductive ring opening proceeded satisfactorily in each case, without carbonyl reduction or interference by free hydroxy functions. In this way the phenol (**28**)[17] was obtained [59% and 49% from methods (*ii*) and (*iii*)] from the chroman (**10**), and also from the corresponding sulphone (**12**) [method (*ii*); 25%]. Reduction of the sulphide (**13**) gave the geranylphenol (**29**) (49%), as a 1:1 mixture of *E* and *Z*



(**29a**)

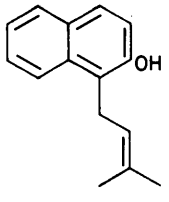


(**29b**)

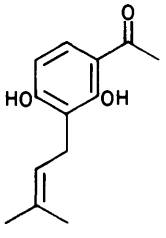
a 25.8, 25.9
b 22.1, 22.0
c 123.8, 123.2
d 135.5, 135.2
e 27.4, 26.1
f 125.5, 125.2

isomers, ^{13}C n.m.r. data for these are summarised in the Figure. Finally, the trihydric geranylacetophenone (**30**) was obtained, as an unstable oil.

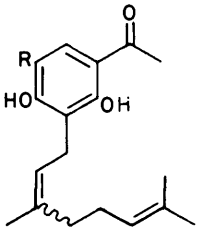
Thus *o*-prenylphenols can be readily obtained from 2*H*-chromenes in a process which tolerates the common functional groups found in natural *O*-heterocycles of this type. In total synthesis this route may offer useful regioselectivity, and a number of natural product interconversions are made possible. Since *o*-prenylphenols are believed, in biogenetic theory, to be the initial product of prenyl pyrophosphate–phenol condensation,[18] accessibility to them is required for biosynthetic studies.



(**27**)



(**28**)



(**29**) R = H
(**30**) R = OH

Experimental

Light petroleum refers to the fraction b.p. 40—60 °C.

2-*Methyl*-2-(2-*naphthyloxy*)*but*-3-*yne*.—3-Chloro-3-methylbut-1-yne (3.8 g), 2-naphthol (2.75 g), anhydrous potassium carbonate (6.0 g), and potassium iodide (2.7 g) were refluxed in dry acetone (40 cm^3) for 19 h. The mixture was diluted with brine (200 cm^3) and extracted with ether. The extracts were washed with aqueous sodium hydroxide, and were dried and evaporated. The residue was distilled to give the *title compound*

(72%), as a yellow oil, b.p. 118—120 °C (0.05 mmHg) (Found: M^+ 210.105. $C_{15}H_{14}O$ requires M, 210.104); $\lambda_{max.}$ 242 (4.61), 261 (4.58), 303 (4.51), and 315 nm (4.50); δ($CDCl_3$) 8.0—7.0 (7 H, m, ArH), 1.66 (1 H, s, C≡CH), and 1.46 (6 H, s, 2 × Me).

3,3-*Dimethyl*-3H-*naphtho*[2,1-b)*pyran* (**6**).—2-Methyl-2-(2-naphthyloxy)but-3-yne (5 g) and *N*,*N*-diethylaniline (25 cm^3) were refluxed for 30 min. The cooled mixture was diluted with ether, washed with dilute hydrochloric acid, and evaporated. The residue was distilled to yield the *title compound* (3.87 g, 76%) as a viscous oil, b.p. 126 °C (0.05 mmHg) (Found: C, 86.1; H, 7.05%; M^+, 210.105. $C_{15}H_{14}O$ requires C, 85.7; H, 6.7%; M, 210.104); $\lambda_{max.}$ 243 nm (4.61); δ 7.8—6.8 (6 H, m, ArH), 6.76 (1 H, d, J 9, 1-H), 5.42 (1 H, d, J 9, 2-H), and 1.37 (6 H, s, 2 × Me).

3,3-*Dimethyl*-2-*phenylthio*-2,3-*dihydro*-1H-*naphtho*[2,1-b]-*pyran* (**8**)—3,3-Dimethyl-3*H*-naphtho[2,1-*b*]pyran (15 g), thiophenol (17.18 g), and azoisobutyronitrile (0.5 g) were refluxed in dry benzene (150 cm^3) for 48 h. The solution was diluted with ether and washed with aqueous sodium hydroxide, water, and brine. Evaporation of the solvents gave a solid residue which was crystallised from ethyl acetate–light petroleum to give the *title compound* (14.5 g, 63%), m.p. 78—80 °C (Found: C, 78.5; H, 6.3%; M^+, 320.124. $C_{21}H_{20}SO$ requires C, 78.75; H, 6.25%; M, 320.123); $\lambda_{max.}$ 256 (4.59), 2.75 (4.55), and 288 nm (4.54); δ 2.36—3.18 (11 H, m, ArH), 6.44—7.00 (3 H, m, $CHCH_2$), and 8.40 and 8.60 (each 3 H, s, Me).

3,3-*Dimethyl*-2-*phenylsulphonyl*-2,3-*dihydro*-1H-*naphtho*-[2,1-b]*pyran* (**9**).—The sulphide (**8**) (104 mg) in dichloromethane (15 cm^3) was cooled to 0 °C and treated with *m*-chloroperbenzoic acid (123 mg) in dichloromethane (5 cm^3). The solution was allowed to warm to room temperature and set aside for 20 h. The solution was washed with aqueous sodium metabisulphite, dried, and evaporated. The residue was recrystallised from ethanol to yield the *title sulphone* (114 mg, 99%), m.p. 188—190 °C (Found: C, 71.65; H, 5.58%; M^+, 352.114. $C_{21}H_{20}O_3S$ requires C, 71.59; H, 5.68%; M, 352.113); $\lambda_{max.}$ 288 (4.54), 317 (4.49), and 332 nm (4.97); δ 8.00—6.84 (11 H, m, ArH), 3.68—2.84 (3 H, m, 1-H_2, 2-H), and 1.84 and 1.56 (each 3 H, s, Me).

1-(3-*Methylbut*-2-*enyl*)-2-*naphthol* (**27**).—(*a*) Lithium metal (0.36 g) was added in small pieces to a stirred solution of naphthalene (2.2 g) in dry tetrahydrofuran (70 cm^3) under argon, at room temperature. A dark green solution was formed over 1.5 h, which was cooled to −42 °C; to this was added 3,3-dimethyl-2-phenylthio-3*H*-naphtho[2,1-*b*]dihydropyran (3 g) in tetrahydrofuran (10 cm^3), and the solution was stirred at −32 °C for 0.5 h when acetic acid (5 cm^3) was added. The mixture was diluted with water and extracted with ether. The extracts were washed with aqueous sodium hydrogen carbonate and brine, dried, and evaporated. The residue was chromatographed on silica (chloroform elution), to yield the *title naphthol* (1.26 g, 64%) as an unstable oil which solidified when allowed to stand, m.p. 44—46 °C (Found: C, 84.4; H, 7.75%; M^+, 212.119. $C_{15}H_{16}O$ requires C, 84.87; H, 7.60%; M, 212.120); δ 8.05—7.05 (6 H, m, ArH), 5.5 (1 H, s, OH), 5.33 (1 H, t, J 7, C*H*=CMe_2), 3.80 (2 H, d, J 7 Hz, $ArCH_2$), and 1.91 and 1.75 (both 3 H, s, Me); this naphthol formed an oily *acetate* (Found: M^+, 254.129. $C_{17}H_{18}O_2$ requires M, 254.131); δ 8.10—7.15 (6 H, m, ArH), 5.20 (1 H, t, J 8, C*H*=CMe_2), 3.70 (1 H, d, J 8, $ArCH_2$), 2.35 (3 H, s, COMe), and 1.85 and 1.67 (both 3 H, s, Me).

(*b*) To a solution of naphthalene (4.2 g, 32.8 mmol) in tetrahydrofuran (dried over $LiAlH_4$; 30 ml) were added chips of potassium metal (1.1 g, 28.1 mmol). A dark green colour was observed within 60 seconds and the flask was stirred for a further 2 h, to ensure complete reaction of the potassium, to give a 0.94M solution of potassium naphthalenide. The preformed potassium naphthalenide (0.5 cm^3, 0.5 mmol) was transferred by syringe to a solution of 3,3-dimethyl-2-phenylsulphonyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]dihydropyran (26.5 mg) in dry tetrahydrofuran (2 cm^3). The solution was kept at room temperature for 1 h, and it was then diluted with aqueous hydrochloric acid. The mixture was extracted with ether. The extracts were evaporated to dryness and the residue was chromatographed on silica ether–hexane (1:3) to yield the *title naphthol* (11 mg, 70%), m.p. 44—46 °C, with ^1H n.m.r. data indistinguishable from those above.

(*c*) A divided electrolysis cell was set up with dimethylformamide saturated with tetraethylammonium bromide in both anode and cathode compartments, with a stirred mercury cathode. 3,3-Dimethyl-2-phenylthio-2,3-dihydro-1*H*-naphtho-[2,1-*b*]dihydropyran (277 mg) was introduced into the cathode compartment and a current of 22 mA was passed at 20 V for 4.5 h, (*i.e.* 4 F mol^{-1}).

The contents of the cathode cell were collected in ether. The ether solution was washed with water, dried, and evaporated. The residue was chromatographed on silica, eluting with ethyl acetate–light petroleum (1:9) to yield the *title compound* (97 mg, 53%), with ^1H n.m.r. data virtually identical with those above.

6-*Acetyl*-2,2-*dimethyl*-3-*phenylthiochroman*-5-*ol* (**10**).—6-Acetyl-2,2-dimethyl-2*H*-chromen-5-ol (**3**) (472 mg), thiophenol (594 mg), and azoisobutyronitrile (100 mg) were refluxed in dry benzene (20 cm^3) for 72 h. The cooled solution was diluted with ether, washed with aqueous sodium hydroxide, dried, and evaporated. The residue was recrystallised from ethanol to yield the *title compound* (625 mg, 88%), m.p. 86—88 °C from ethanol (Found: C, 69.8; H, 6.35%; M^+ 328.112. $C_{19}H_{20}O_3S$ requires C, 69.51; H, 6.10%; M, 328.113); δ 7.12 (5 H, s, Ar*H*), 7.02 (1 H, d, J 9 Hz, 7-H), 5.94 (1 H, d, J 9 Hz, 8-H), 3.20—2.40 (3 H, m, 3-H, 4-H_2), 2.32 (3 H, s, COMe), and 1.40 and 1.34 (each 3 H, s, Me).

6-*Acetyl*-2,2-*dimethyl*-3-*phenylsulphinyl*-*chroman*-5-*ol* (**11**).—6-Acetyl-2,2-dimethyl-3-thiophenoxychroman-5-ol (110 mg, 0.338 mmol) and sodium periodiate (101 mg 0.472 mmol) were refluxed together in methanol (20 cm^3) for 24 h. The solution was then evaporated and chromatography of the residue on silica [eluting with ether–hexane (1:3)] gave the starting sulphide (36%) followed by the title sulphoxide (52 mg, 45%) as a mixture of diastereoisomers, m.p. 127—132 °C (decomp.) [Found: m/z 328.114. $C_{19}H_{20}O_3S$ (M − O) requires 328.113].

Pyrolysis of the Sulphoxide (**11**).—The sulphoxide (**11**) (7.1 mg) was refluxed in toluene (15 cm^3) under nitrogen for 3 h. Evaporation and chromatography gave 6-acetyl-2,2-dimethyl-2*H*-chromen-5-ol (3.8 mg, 80%), identified by ^1H n.m.r. spectroscopic comparison with an authentic sample.

6-*Acetyl*-3-*phenylsulphonyl*-2,2-*dimethylchroman*-5-*ol* (**12**).—The phenylthiochroman (**10**) (123 mg) in dichloromethane (15 cm^3) was treated with *m*-chloroperbenzoic acid (164 mg). After 48 h more peracid (106 mg) was added and the reaction was allowed to continue for a further 24 h. The mixture was treated with aqueous sodium hydrogen sulphite and extracted with ether. The organic layers, when dried and evaporated, gave a residue which was chromatographed [diethyl ether–hexane (1:2)] to yield the *title sulphone* (134 mg, 94%), m.p. 161.5—162.5 °C (Found: C, 63.1; H, 5.8%; M^+, 360.101. $C_{19}H_{20}O_5S$ requires C, 63.31; H, 5.79%; M, 360.103).

2′,4′-Dihydroxy-3′-(3-methylbut-2-enyl)acetophenone (**28**).—(*a*) Potassium naphthalenide (0.94M; 5 cm^3) in tetrahydrofuran was added to 6-acetyl-3-phenylthio-2,2-dimethylchroman-5-ol (253 mg) in dry tetrahydrofuran (15 cm^3), at ambient temperature. After 80 min, water (2 cm^3) was added. The product was poured into dilute hydrochloric acid and the mixture was extracted with ether. The ether extracts were washed with water and evaporated. The residue was chromatographed on silica [ether–hexane (1:3)] to provide the *title resorcinol* (100 mg, 59%), m.p. 149—151 °C from benzene–light petroleum (Found: C, 71.15; H, 7.4%; M^+, 220.112. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%; *M*, 220.110); δ(CD_3COCD_3) 13.17 (1 H, s, OH), 9.2 (1 H, br s, OH), 7.65 (1 H, d, *J* 9 Hz, 6-H), 6.51 (1 H, d, *J* 9 Hz, 5-H), 5.29 (1 H, t, *J* 8, C*H*=Me_2), 3.35 (2 H, d, *J* 8, CH_2), 2.53 (3 H, s, COMe), and 1.80 and 1.66 (each 3 H, s, Me).

(*b*) A similar experiment was carried out using lithium naphthalenide at −32 °C for 30 min, to yield the same product, 38%, m.p. 149—151 °C.

(*c*) Experiment (*a*) was repeated, but using the sulphone (**12**) (42 mg) with potassium naphthalenide (0.77M; 2 cm^3) for 2 h. Product isolation as before gave the title resorcinol (6.5 mg, 25%), m.p. 146—148 °C, with i.r. and ^1H n.m.r. spectra closely similar to those of the above specimen.

(*d*) 6-Acetyl-3-phenylthio-2,2-dimethylchroman-5-ol (119 mg) was introduced into the cathode compartment of a divided electrolytic cell containing dimethylformamide saturated with tetraethylammonium bromide. A current of 20 mA was passed at 25 V for 87 min (total 3 F mol^{-1}). The cathode compartment contents were taken up in ether and washed with dilute hydrochloric acid. The ether layer was evaporated and the residue was chromatographed as in (*a*) to yield the title compound (39 mg, 49%), m.p. 148—149 °C, with ^1H n.m.r. spectroscopic data identical to those of the first sample above.

6-Acetyl-2-methyl-2-(4-methylpent-3-enyl)-3-phenylthiochroman-5-ol (**14**).—Diphenyl disulphide (0.40 g) and thiophenol (1.29 g) were dissolved in benzene (13 cm^3) with 6-acetyl-2-methyl-2-(4-methylpent-3-enyl)-2*H*-chromen-5-ol (463 mg). The solution was degassed and irradiated with a medium pressure mercury lamp (450 W), through a Pyrex filter, for four days. The solution was evaporated to dryness. The residue was chromatographed on silica [ethyl acetate–light petroleum (1:40)→(1:20)] to yield both diastereoisomers of the *title sulphide* as an oil (350 mg, 56%) (Found: 72.85; H, 7.0%; M^+, 396.173. $C_{24}H_{28}O_3S$ requires C, 72.69; H, 7.12%; *M*, 396.176); δ 13.18 and 13.10 (both 1 H, s, OH), 7.6—7.2 (6 H, m, 7-H, SPh), 6.5—6.3 (1 H, 2 d, *J* 9 Hz, 8-H), 5.15 (1 H, m, C*H*=CMe_2), 3.5—2.8 (3 H, m, 3-H, 4-H_2), 2.55 (3 H, s, COMe), 2.0 (4 H, m, CH_2CH_2), and 1.70, 1.60, and 1.53 (each 3 H, s, Me).

(2E,6Z)-3′-(3,7-Dimethylocta-2,6-dienyl)-2′,4′-dihydroxyacetophenone (**29**).—The phenylthiochroman (**14**) (176 mg), in dry tetrahydrofuran (10 cm^3) at −78 °C, was treated with potassium naphthalenide (0.64M; 3 cm^3). The mixture was allowed to warm to −30 °C, and was kept at this temperature for 1 h. Water (2 cm^3) was added, and the mixture was then diluted with brine and acidified. The organic products were collected in ether, and separated by chromatography on silica [diethyl ether–hexane (1:3)→(1:1)] to give the *title phenol* (62 mg, 48%), m.p. 93—96 °C from hexane (Found: C, 74.9; H, 8.66%; M^+, 288.171. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%; *M*, 288.173); δ 13.17 (1 H, s, OH), 7.63 (1 H d, *J* 9 Hz, 6-H), 6.53 (1 H, d, *J* 9 Hz, 5-H), 5.30 (2 H, br t, 2 × CH=C), 3.39 (2 H, d, *J* 8 Hz, ArCH_2), 2.55 (3 H, s, COMe), and 2.24—1.50 (br, 2 × CH_2, 3 × Me).

6-Acetyl-2-methyl-2-(4-methylpent-3-enyl)-3-phenylthiochroman-5,8-diol (**13**).—6-Acetyl-2-methyl-2-(4-methylpent-3-enyl)-2*H*-chromene-5,8-diol (1.05 g, 3.48 mmol), diphenyl disulphide (1.55 g, 7.11 mmol) and thiophenol (6.42 g, 58 mmol) were dissolved in dry degassed benzene (30 cm^3) and irradiated through Pyrex for 72 h, using a 450 W medium pressure mercury lamp. The residue obtained after evaporation was chromatographed on silica [ether–hexane, (1:2)→(1:1)] to yield the *title chroman* (1.3 g, 90%), m.p. 79.5—80.5 °C from ether–hexane (Found: C, 69.5; H, 6.85%; M^+, 412.171. $C_{24}H_{28}O_4S$ requires C, 69.87; H, 6.84%; *M*, 412.171); δ 13.20 (1 H, s, 5-OH), 7.78—7.66 (2 H, m, 2 × ArH), 7.48—7.32 (3 H, m, 3 × ArH), 7.16 (1 H, s, 7-H), 5.36 (1 H, br t, C=CH), 3.38—3.60 (3 H, m, 3-H, 4-H_2), 2.51 (3 H, s, COMe), 2.0—1.55 (4 H, m, 2 × CH_2), and 1.50, 1.24, and 1.20 (each 3 H, s, Me).

E,Z-3-(3,7-Dimethylocta-2,6-dienyl)-2,4,5-trihydroxyacetophenone (**30**).—To a stirred solution of 6-acetyl-2-methyl-2-(4-methylpent-3-enyl)-3-phenylthiochroman-5,8-diol (161 mg) in tetrahydrofuran (15 cm^3) was added potassium naphthalenide (0.94M; 2 cm^3). After 2 h at ambient temperature water and dilute hydrochloric acid were added. The organic products were isolated through ether extraction and purified by column chromatography [silica; ether–hexane (1:3)] to yield the *title phenol* as an unstable oil (13 mg, 11%) (Found: M^+, 304.167. $C_{18}H_{24}O_4$ requires *M*, 304.167); δ 12.65 (1 H, s, OH), 7.20 (1 H, s, 6′-H), 5.20 (2 H, br, C=CH), 3.40 (2 H, d, *J* 8 Hz, ArCH_2), 2.48 (3 H, s, COMe), and 2.2—1.6 (13 H, br).

6-Formyl-2,2-dimethylchromen-5-ol (**7**).—2,4-Dihydroxybenzaldehyde (2.0 g), 1,1-dimethoxy-3-methylbutan-3-ol (3.95 g) and dry pyridine (1.25 g) were heated to reflux, under nitrogen, for 40 h. The products were dissolved in ether, washed with dilute hydrochloric acid, and evaporated. The residue was chromatographed on silica [ethyl acetate–light petroleum (1:9)] to give the title chromenol (1.13 g, 38%), m.p. 65—67 °C, (lit.,[19] m.p. 69—69.5 °C) (Found: C, 70.65; H, 6.1%; M^+, 204.079. Calc. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%; *M*, 204.079). This phenol formed a *methoxymethyl derivative* (**25**) (an oil), on treatment with chloromethyl methyl ether in dry acetone over anhydrous potassium carbonate (Found: C, 67.3; H, 6.85%; M^+, 248.107. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.50%; *M*, 248.105); δ 10.28 (1 H, s, CHO), 7.75 (1 H, d, *J* 7 Hz, 7-H), 6.73 (1 H, d, *J* 7 Hz, 8-H), 6.66 (1 H, d, *J* 10, 4-H), 5.74 (1 H, d, *J* 10 Hz, 3-H), 5.50 (2 H, s, OCH_2O), 3.64 (3 H, s, OMe), and 1.22 (6 H, s, 2 × Me).

3-(5-Methoxymethoxy-2,2-dimethyl-2H-benzo[b]pyran-6-yl)-1-(2-hydroxy-4-methoxymethoxyphenyl)prop-2-en-1-one.—(**24**) 2′-Hydroxy-4′-methoxyacetophenone [prepared (78%) from 2′,4′-dihydroxyacetophenone and chloromethyl methyl ether in dry acetone over anhydrous potassium carbonate for 80 min, b.p. 128 °C, 1.5 mmHg (lit.,[20] b.p. 118—122 °C, 0.2 mmHg] (1.1 g) and 6-formyl-5-methoxymethoxy-2,2-dimethyl-2*H*-chromene (1.4 g) in anhydrous methanol (3 cm^3) were treated with sodium hydroxide (500 mg) and just enough water to form a homogeneous solution. The mixture was stirred at ambient temperature for 10 h, when it was diluted with brine and extracted with ether. Evaporation of the extracts and recrystallisation of the residue gave the *title compound* (645 mg, 27%), m.p. 92.5—94.5 °C (from methanol) (Found: C, 67.6; H, 6.44%; M^+, 426.171. $C_{24}H_{26}O_7$ requires C, 67.60; H, 6.15%; *M* 426.168); $\nu_{max.}$($CHCl_3$) 1 640, 1 600, 1 040, and 970 cm^{-1}; δ 13.50 (1 H, s, OH), 8.20 (1 H, d, *J* 16 Hz, C*H*=CHCO), 7.86 (1 H, d, *J* 9 Hz), 7.51 (1 H, d, *J* 16 Hz, CH=C*H*CO), 7.55 (1 H, d, *J* 9 Hz), 6.55 (4 H, m, 4 × ArH), 5.70 (1 H, d, *J* 9 Hz, ArCH=C*H*), 5.06 (2 H, s, OCH_2O), 5.03 (2 H, s, OCH_2O), 3.65 (3 H, s, OMe), 3.50 (3 H, s, OMe), and 1.46 (6 H, s, 2 × Me).

1,1-*Dimethoxy*-2-(5-*methoxymethoxy*-2,2-*dimethyl*-2H-*benzo*[b]*pyran*-6-*yl*)-3-(2-*hydroxy*-4-*methoxymethoxyphenyl*) *propane*-3-*one* (**26**).—The chalcone (**24**) (690 mg) was suspended with stirring in dry methanol (100 cm^3), and thallium(III) nitrate trihydrate (755 mg) was added. The mixture was stirred for 85 min, when sodium metabisulphite (6.6 g) was added and the stirring was continued for 100 min. The yellow solution was decanted, diluted with water (200 cm^3), and extracted with chloroform. The extracts, after washing with aqueous sodium hydrogen carbonate, were dried and evaporated. The residue was chromatographed on silica [ethyl acetate–light petroleum (1:8)→(1:6)]. The starting chalcone (164 mg, 24%) was eluted first, followed by the *title compound* (199 mg, 25%), as a viscous oil (Found: M^+, 488.206. $C_{26}H_{32}O_9$ requires M, 488.205); $\nu_{max.}$($CHCl_3$) 1 630 cm^{-1}; δ 12.70 (1 H, s, OH), 7.98 (1 H, d, J 9 Hz, ArH), 7.23 (1 H, d, J 9 Hz, ArH), 6.6—6.26 (3 H, m, 3 × ArH), 6.68 (1 H, d, J 10, ArC*H*=CH), 5.60 (1 H, d, J 10 Hz, ArCH=C*H*), 5.26—4.96 (6 H, 1- and 2-H, 2 × OCH_2O), 3.66, 3.46, 3.40, and 3.26 (each 3 H, s, OMe), and 1.40 and 1.37 (each 3 H, s, Me).

3-(2,2-*Dimethyl*-5-*methoxymethoxy*-2H-*benzo*[b]*pyran*-6-*yl*)-7-*methoxymethoxy*-4H-*benzo*[b]*pyran*-4-*one* (**20**).—The acetal (**26**) (103 mg), was refluxed in 0.1M-sodium methoxide in methanol (25 cm^3) for 60 min. Water (100 cm^3) was added, and the solution was extracted with ether. The extracts were washed with aqueous sodium hydroxide, dried, and evaporated to yield the *title compound* (74 mg, 81%) as a yellowish oil which showed one spot on t.l.c. [silica; ethyl acetate–light petroleum (1:5)] (Found: M^+, 424.153. $C_{24}H_{24}O_7$ requires M, 424.153); $\nu_{max.}$($CHCl_3$) 1 640 cm^{-1}; δ 8.27 (1 H, d, J 10, 5-H), 7.94 (1 H, s, 2-H), 7.15 (3 H, m, 3 × ArH), 6.57 (2 H, d, J ArC*H*=CH), 5.67 (1 H, d, J 10 Hz, ArCH=C*H*), 5.28, 4.83 (each 2 H, s, OCH_2O), 3.52, 3.31 (each 3 H, s, OMe), and 1.44 (6 H, s, 2 × Me).

6-*Formyl*-5-*hydroxy*-2,2-*dimethyl*-3-*phenylthiochroman* (**15**).—The formylchromene (**7**) (425 mg), diphenyl disulphide (158 mg), and thiophenol (3 cm^3), in benzene (13 cm^3) were irradiated, using a 450 W medium pressure mercury lamp (Pyrex filter), for 6 days. After evaporation of the solvent the major product was isolated by chromatography on silica [ethyl acetate–light petroleum (1:19)→(1:9)], as the *title sulphide* (0.41 g, 63%), an oil (Found: C, 68.7; H, 6.0; M^+, 314.097. $C_{18}H_{18}O_3S$ requires C, 68.76; H, 5.77%; M^+, 314.0976); δ (250 MHz) 11.75 (1 H, s, ArOH), 9.65 (1 H, s, ArCHO), 7.48—7.43 (2 H, m, 2 × ArH), 7.34—7.25 (4 H, m, 3 × ArH, 7-H), 6.43 (1 H, d, J 8.5 Hz, 8-H), 3.37 (1 H, dd, J 6, 10 Hz, 3-H), 3.13 (1 H, dd, J 6 and 17 Hz, 4-H_{eq}), 2.74 (1 H, dd, J 10 and 17 Hz, 4-$H_{ax.}$), 1.55 (3 H, s, Me), and 1.40 (3 H, s, Me).

This compound formed an oily *methoxymethyl ether* (**16**) on treatment with chloromethyl methyl ether at room temperature for 1.5 h (Found: C, 67.1; H, 6.0; M^+, 358.123. $C_{20}H_{22}O_4S$ requires C, 67.3; H, 6.18%; M, 358.124); δ 10.12 (1 H, s, ArCHO), 7.70 (1 H, d, J 9 Hz, 7-H), 7.55—7.30 (5 H, m, Ph), 6.75 (1 H, d, J 9 Hz, 8-H), 5.06 (2 H, s, OCH_2O), 3.50 (3 H, s, OMe), 3.5—2.65 (3 H, m, 3-H and 4-H_2), and 1.56 and 1.41 (each 3 H, s, Me).

3-(5-*Methoxymethoxy*-2,2-*dimethyl*-3-*phenylthiochroman*-6-*yl*)-1-(2-*hydroxy*-4-*methoxymethoxyphenyl*)*prop*-2-*en*-1-*one* (**17**).—2′-Hydroxy-4′-methoxymethoxyacetophenone (0.4 g) and the formylchroman (**16**) (0.75 g), were dissolved in dry methanol (1.8 cm^3). Sodium hydroxide (225 mg) was added followed by the minimum amount of water required to form a homogeneous solution. The mixture was stirred at room temperature for 17 h, and then heated at 50 °C for 24 h, when it was diluted with water. The mixture was extracted with ether and the extracts were evaporated and chromatographed on silica [ether–hexane (1:4)] to yield the *title chalcone* (686 mg, 63%) as a yellow oil (Found: M^+ 536.185. $C_{30}H_{32}O_7S$ requires M^+, 536.187); δ 11.5 (1 H, s, ArOH), 8.15 (1 H, d, J 16 Hz, COCH=C*H*), 7.87 (1 H, d, J 9 Hz, ArH), 7.62—7.28 (7 H, m, Ph, 2 × ArH), 6.78—6.52 (3 H, m, 3 × ArH), 5.22 and 5.00 (each 2 H, s, OCH_2O), 3.52 and 3.49 (each 3 H, s, OMe), 3.37—2.67 (3 H, m, CH_2CH), and 1.54 and 1.41 (each 3 H, s, Me).

3-(2-*Hydroxy*-4-*methoxymethoxyphenyl*)-1,1-*dimethoxy*-2-(5-*methoxymethoxy*-2,2-*dimethyl*-3-*phenylthiochroman*-6-*yl*)-*propan*-3-*one* (**18**)—Thallium nitrate trihydrate (766 mg; 94% by titration) was added to the above chalcone (**17**) (807 mg) in dry methanol (40 cm^3) and chloroform (3 cm^3). Precipitation of thallous nitrate was observed after 35 min and was complete after 130 min, when sodium metabisulphite (0.5 g) was added. The mixture was stirred for a further 30 min before the solution was decanted and diluted with water. The organic products were collected by chloroform extraction and purified by column chromatography [hexane–ether (4:1)]. Unchanged starting chalcone (64 mg, 8%) was eluted first, followed by the *title acetal* (444 mg, 49%; 53% based on chalcone utilised) as a non-crystalline mixture of diastereoisomers (Found: M^+, 598.220. $C_{32}H_{38}O_9S$ requires M, 598.224); δ 7.99 (1 H, d, J 9 Hz, ArH), 7.55—6.33 (6 H, ArH), 6.65—6.50 (3 H, ArH), 5.25—5.10 (6 H, 2 × OCH_2O, 1- and 2-H), 3.60, 3.50, 3.46, and 3.29 (12 H, 4 × OMe), 3.35—2.70 (3 H, pyran, 3-H, 4-H_2), and 1.53, 1.51, 1.36, and 1.30 (12 H, 4 × Me); $\nu_{max.}$ 1 620 cm^{-1}.

3-(5-*Methoxymethoxy*-2,2-*dimethyl*-3-*phenylthiochroman*-6-*yl*)-7-*methoxymethoxy*-4H-*benzo*[b]*pyran*-4-*one* (**19**).—The above acetal (**18**) (437 mg) was dissolved in 0.1M-sodium methoxide in methanol and the solution was refluxed for 30 min under nitrogen, when it was diluted with water. The organic products were isolated through ether extraction to yield the *title isoflavone* (371 mg) as an amorphous glassy solid, which showed one spot on t.l.c. [silica; ethyl acetate–light petroleum (1:5)] (Found: C, 67.55; H, 5.8%; M^+, 534.171. $C_{30}H_{30}O_7S$ requires C, 67.40; H, 5.65%; M, 534.171); δ 8.26 (1 H, d, J 9 Hz, 5-H), 7.97 (1 H, s, 2-H), 7.60—7.07 (8 H, m, 3 × ArH, SPh), 6.72 (1 H, d, J 9 Hz, ArH), 5.30 and 4.78 (each 2 H, s, OCH_2O), 3.53 and 3.24 (each 3 H, s, OMe), 3.40—2.60 (3 H, pyran, 3-H, 4-H_2), and 1.57 and 1.40 (each 3 H, s, Me).

Preparation and Pyrolysis of 3-(5-*Methoxymethoxy*-2,2-*dimethyl*-3-*phenylsulphinylchroman*-6-*yl*)-7-*methoxymethoxy*-4H-*benzo*[b]*pyran*-4-one (**19**; *S*-oxide).—*m*-Chloroperbenzoic acid (38.5 mg, 0.223 mmol) was added to a solution of the above isoflavone (**19**) (109 mg, 0.204 mmol) in dry dichloromethane (50 cm^3); the mixture was stirred for 25 h at ambient temperature when sodium metabisulphite (800 mg) was added and stirring was continued for 30 min. The mixture was diluted with water and the organic products were collected into ether and the acidic material washed out with aqueous sodium hydrogen carbonate. Chromatography on silica (ether–0→5% ethyl acetate) of the residue obtained after solvent evaporation gave the title isoflavone (41 mg, 37%) (Found: C, 65.95; H, 6.0%; M^+ − PhSOH, 424.150. $C_{30}H_{30}O_8S$ requires C, 65.45; H, 5.45%; M − PhSOH 424.152); $\nu_{max.}$($CHCl_3$) 1 640, 1 610, and 1.570 cm^{-1}; δ 8.25 (1 H, d, J 9 Hz, 5-H), 7.95 (1 H, s, 2-H), 7.70—7.55 (5 H, SPh), 7.20—7.07 (3 H, m, ArH), 6.73 (1 H, d, J 9 Hz, ArH), 5.32 (2 H, s, OCH_2O), 5.27 (2 H, AB system, OCH_2O), 3.55 and 3.27 (each 3 H, s, OMe), 3.10—2.39 (3 H, pyran 3-H, 4-H_2), and 1.88 and 1.48 (each 3 H, s, Me).

This isoflavone (38 mg) was refluxed in toluene (25 cm^3) under nitrogen for 30 min. The solution was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. Chromatography of the residue on silica [hexane–(25→100%) ether] gave 3-(5-methoxymethoxy-2,2-dimethyl-2*H*-benzo[*b*]-

pyran-6-yl)-7-methoxymethoxy-4*H*-benzopyran-4-one (24 mg, 82%), with ^{1}H n.m.r. data indistinguishable from those of the specimen previously described.

5,7-*Dihydroxy*-3-(2,2-*dimethyl*-3-*phenylthiobenzo*[b]-*pyran*-6-*yl*)-4H-*benzo*[b]*pyran*-4-*one* (**22**).—3-(5-Methoxymethoxy-2,2-dimethyl-3-phenylthiobenzo[*b*]pyran-6-yl)-7-methoxymethoxy-4*H*-benzo[*b*]pyran-4-one (**19**) (106 mg), was refluxed in methanol (15 cm^3) and 2M-hydrochloric acid (15 cm^3) under nitrogen for 30 min. After dilution with water the product was collected through ether extraction as the solid *title isoflavone* (88 mg, 99%) (Found: M^+, 446.117. $C_{26}H_{22}O_5S$ requires M, 446.118); δ(CD_3COCD_3) 8.32 (1 H, s, 2-H), 8.15 (1 H, d, *J* 9 Hz, 5-H), 7.65—7.50 (2 H, m, ArH), 7.40—7.30 (3 H, m, ArH), 7.15—7.0 (2 H, m, ArH), 6.40 (1 H, d, *J* 9 Hz, ArH), 3.70—2.80 (3 H, m, pyran 3-H, 4-H_2).

Preparation of the Pterocarpan (**23**).—The above isoflavone (**22**) (48 mg) was dissolved in methanol (35 cm^3). Sodium borohydride (300 mg) was added and the mixture was stirred for 135 min at room temperature, when 2M-hydrochloric acid (100 cm^3) was added. The reaction was stirred for a further 30 min when the organic products were collected through ether extraction and purified on a silica column [ether–hexane (1:1)] to yield the *title compound* (27 mg, 49%) as a mixture (*ca.* 1:1) of diastereoisomers, m.p. 88—90 °C (Found: M^+, 432.132. $C_{26}H_{24}O_4S$ requires M, 432.129).

(±)-*Phaseollin* (**1**).—The isoflavone (**20**) (74 mg) was dissolved in methanol (12.5 cm^3) and 3M-hydrochloric acid (12.5 cm^3), and the solution was refluxed for 25 min. The solution was diluted with brine (80 cm^3) and extracted with ether. The extracts were washed with brine and evaporated. The residue crystallised on trituration with chloroform. The crystalline product was dissolved in methanol (30 cm^3) with 2M-sodium hydroxide (1 cm^3). Sodium borohydride (100 mg) was added and the reactants were stirred for 48 h under nitrogen. The mixture was acidified with excess 2M-hydrochloric acid and set aside for 2 h. The organic products were collected in chloroform and purified on a silica column (light petroleum–11% ethyl acetate) to yield (±)-*phaseollin* (12 mg) (Found: M^+, 322.122. $C_{20}H_{18}O_4$ requires M, 322.121); δ($CDCl_3$) (250 MHz) 7.41 (1 H, d, *J* 8 Hz, 1-H), 6.95 (1 H, d, *J* 8 Hz, 7-H), 6.56 (1 H, dd, *J* 2 and 8 Hz, 2-H), 6.50 (1 H, d, *J* 10 Hz, 12-H), 6.42 (1 H, d, *J* 2 Hz, 4-H), 6.34 (1 H, d, *J* 8 Hz, 8-H), 5.58 (1 H, d, *J* 10 Hz, 13-H), 5.48 (1 H, d, *J* 6.5 Hz, 11a-H), 4.21 (1 H, m, 6-H_{eq}), 3.59 (1 H, 6-H_{ax}), 3.47 (1 H, m, 6a-H), and 1.42 and 1.39 (each 3 H, s, Me); $\nu_{max.}$($CHCl_3$) 3 600, 2 880, 1 620, 1 590, 1 470, 1 450, 1 120, and 1 050 cm^{-1}; $\lambda_{max.}$(EtOH) 205 (4.45), 231 (4.25), 271infl (3.68), 281 (3.79), 286infl. (3.74), and 317 nm (3.16).

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