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CLAISEN REARRANGEMENTS—VI[1]

SYNTHESIS OF THE COUMARINS, SESIBIRICIN AND TODDACULIN

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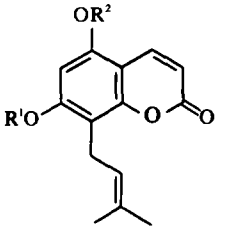
Abstract—The natural coumarins, sesibiricin (1) and toddaculin (28) have been synthesised from 5,7-dihydroxycoumarin, the former by a sequence involving regioselective O-prenylation at C-5 and C-prenylation at C-8. The prenyl ether of 5-hydroxy-7-methoxycoumarin, a key intermediate in the synthesis of toddaculin, has been found to undergo Claisen rearrangement exclusively to the *para* position thereby providing an alternative route to sesibiricin.

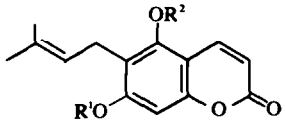
The natural 5,7-dioxygenated coumarin, sesibiricin[2] (1) is unusual in that it possesses two prenyl substituents, one attached to oxygen the other to carbon. In consequence, a projected synthesis of 1 from the readily available 5,7-dihydroxycoumarin (7) would necessitate two regioselective alkylation processes, O-prenylation at C-5 and C-prenylation at C-8.

Previously we have shown[3,4] that pyrolysis of the 1,1- and 3,3-dimethylallyl ethers of 7-hydroxy-5-methoxycoumarin (8) led to an *ortho* Claisen rearrangement in both cases with exclusive migration of the allyl functions to C-8. Thus a suitable synthetic precursor (e.g. 9) of sesibiricin should contain the 7-O-(1,1-dimethylallyl) grouping. However, starting from 7 or the corresponding diacetate (10), selective functionalisation of the oxygen at C-7 would not be anticipated since it is known[4,5] that the oxygen at C-5 is the more readily alkylated. Thus the first step in the synthesis of 9 would necessarily be the protection of the C-5 OH. If this function were protected as its 3,3-dimethylallyl ether, which is the substituent present at this position in sesibiricin, the difficulty would arise of effecting preferential rearrangement of the 1,1-dimethylallyl ether of 9 in the presence of the 3,3-dimethylallyloxy group. Both allyl ethers would be thermally unstable at 190° but the expected relief of steric compression during rearrangement of the former grouping, which was manifested[3] in the rapid rearrangement of 11 to 2 at only 160° led us to anticipate that selective rearrangement of the bis ether (9) should be possible.

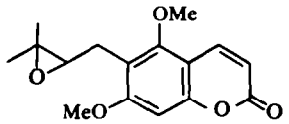
The synthesis of 9 was achieved by two routes. In the more direct sequence, reaction of 7 with 1-bromo-3-methylbut-2-ene and K_2CO_3 in acetone gave, as expected, mainly the bis ether (12; 57%) but fortuitously provided the desired 5-mono ether (13) as the only other major product (23%). That 13 was a 7-hydroxycoumarin followed from its UV spectrum which showed the



1: $R^1 = Me$, $R^2 = CH_2CH{=}CMe_2$
2: $R^1 = H$, $R^2 = Me$
3: $R^1 = R^2 = Me$
4: $R^1 = H$, $R^2 = CH_2CH{=}CMe_2$
5: $R^1 = Me$, $R^2 = H$
6: $R^1 = Me$, $R^2 = COPr$



28: $R^1 = R^2 = Me$
29: $R^1 = Me$, $R^2 = H$



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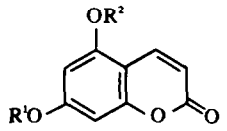


7: $R^1 = R^2 = H$
8: $R^1 = H$, $R^2 = Me$
9: $R^1 = CMe_2CH{=}CH_2$, $R^2 = CH_2CH{=}CMe_2$
10: $R^1 = R^2 = Ac$
11: $R^1 = CMe_2CH{=}CH_2$, $R^2 = Me$
12: $R^1 = R^2 = CH_2CH{=}CMe_2$
13: $R^1 = H$, $R^2 = CH_2CH{=}CMe_2$
14: $R^1 = CH_2CH{=}CMe_2$, $R^2 = H$
15: $R^1 = CMe_2C{\equiv}CH$, $R^2 = CH_2CH{=}CMe_2$
16: $R^1 = Ac$, $R^2 = CH_2CH{=}CMe_2$
17: $R^1 = CH_2CH{=}CMe_2$, $R^2 = Ac$
18: $R^1 = CH_2CH{=}CMe_2$, $R^2 = CMe_2C{\equiv}CH$
19: $R^1 = CMe_2CH_2Me$, $R^2 = CH_2CH{=}CMe_2$
20: $R^1 = Me$, $R^2 = H$
21: $R^1 = Me$, $R^2 = CMe_2CH{=}CH_2$
22: $R^1 = Me$, $R^2 = CH_2CH{=}CMe_2$
23: $R^1 = CH_2CH{=}CMe_2$, $R^2 = Me$
24: $R^1 = Me$, $R^2 = CMe_2C{\equiv}CH$
25: $R^1 = Ac$, $R^2 = CMe_2C{\equiv}CH$
26: $R^1 = H$, $R^2 = CMe_2C{\equiv}CH$
27: $R' = Me$, $R^2 = COPr$

characteristic bathochromic shift on addition of base,[6] and from its subsequent stepwise conversion to **1**. Refluxing a solution of **13** in aqueous acetone with 2-chloro-2-methylbut-3-yne in the presence of K_2CO_3 and KI[3] gave the key intermediate, the dimethylpropargyl ether (**15**).

Seshadri has shown[5] that methylation of 5,7-diacetoxycoumarin proceeds slightly more rapidly at the 5 position leading, after hydrolysis, to a predominance of 5-methoxy-7-hydroxycoumarin. A more efficient synthesis of **15** was based on this approach. Thus a solution of **10** in dimethoxyethane[7] was refluxed with excess 1-bromo-3-methylbut-2-ene in the presence of K_2CO_3 to give a mixture of the isomeric acetates (**16** and **17**; ~4:1 from NMR) in 58% yield and the bis ether (**12**; 9%). A C-prenylated ether (2%), later shown to be 7-demethylsesibiricin (**4**) was also produced. Separation of the acetates by chromatographic methods proved impossible but fractional crystallisation did provide a sample of the predominant isomer (**16**) the structure of which was, confirmed by mild base hydrolysis to the phenol (**13**). However, dimethylpropargylation of the derived mixture of phenols afforded a readily separable mixture of the required ether (**15**; 72%) and the isomer (**19**; 21%).

Hydrogenation of **15** over Pd–$BaSO_4$ poisoned with quinoline and sulphur afforded the bis ether (**9**; 88%). The regioselective Claisen rearrangement of the 1,1-dimethylallyl ether of **9** was accomplished in high yield by heating at 130° for 1 hr. The sole rearrangement product (**4**), which shows both free OH and intramolecularly bonded OH–π stretching frequencies at 3597 and 3398 cm^{-1} respectively in its solution IR spectrum,[4] was readily converted on methylation to sesibiricin (**1**), completely identical with a sample of natural origin. The structure of the synthetic sesibiricin and hence that of the monoallyl ether (**11**) was verified by conversion of **1** into coumurrayin[3] (**3**) by acid catalysed hydrolysis to **5** and methylation.

Three biogenetically related 5,7-dimethoxycoumarins, toddaculin[8] (**28**) the epoxide aculeatin[9] (**30**) and the corresponding vicinal diol toddalolactone[10] have been isolated from *Toddaculia aculeata*. Since the structure of toaddaculin was established[8] from spectral evidence and from its conversion of racemic aculeatin and toddalolactone, it was of interest to devise an unambiguous synthesis of the parent coumarin.

We envisaged a synthesis of toddaculin from 5,7-dihydroxycoumarin, again employing the *ortho* Claisen rearrangement of a 1,1-dimethylallyl ether for the insertion of the prenyl group at C-6. Since we had shown[3,4] that dimethylallyl ethers of 7-hydroxy-5-alkoxycoumarins underwent regiospecific Claisen rearrangement to C-8, as in the synthesis of **1**, regiospecific migration to C-6 consequently demanded preparation of the 1,1-dimethylallyl ether (**21**) of 5-hydroxy-7-methoxycoumarin (**20**).

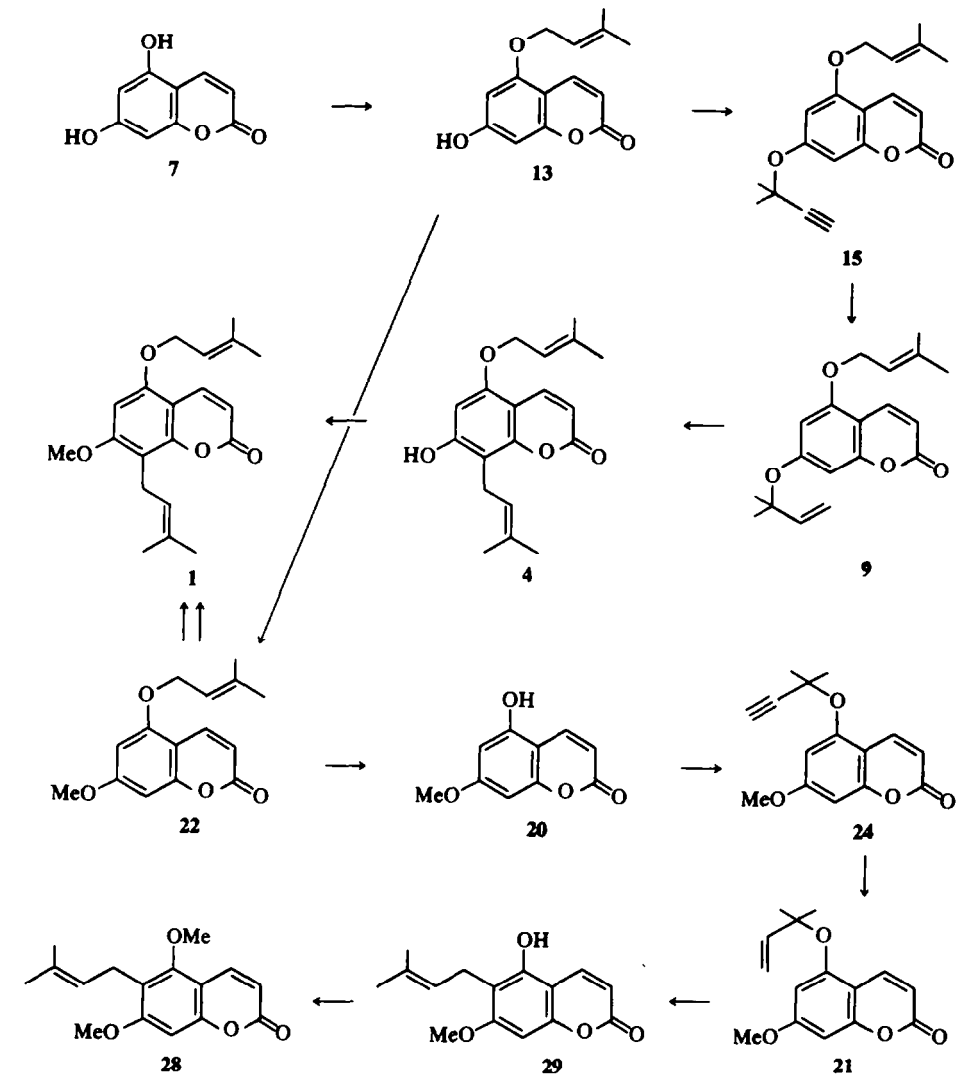
Since partial alkylation of 5,7-diacetoxycoumarin has been found to give predominantly the 5-mono ether, the first step in the conversion of **10** to **21** was necessarily replacement of the 5–OAc by a grouping capable of being replaced by the 1,1-dimethylpropargyl unit after saponification and methylation of the 7–OAc. The acid labile 3,3-dimethylallyl ether was the protecting group of choice and consequently the mixture of isomeric phenols (**13** and **14**), obtained from the dimethylallylation of 5,7-diacetoxycoumarin (*vide supra*), was methylated. Complete TLC separation of the mixture of ethers (**22** and **23**; 4:1 from NMR) was not possible, but partial chromatographic separation followed by fractional crystallisation gave the major isomer (**22**; 61%).

Hydrolysis of 22 afforded the phenol (**20**) which on treatment with 2-chloro-2-methylbut-3-yne gave the propargyl ether (**24**). Catalytic hydrogenation afforded the 1,1-dimethylallyl ether (**21**) which, like **9**, underwent *ortho* Claisen rearrangement to a small extent during purification on TLC. Pyrolysis of **21** at 114° afforded one major phenolic product, identified as a 5-hydroxycoumarin from its UV spectrum. The NMR spectrum showed the presence of a 3,3-dimethylallyl unit attached to the benzene ring. The product (**29**) exhibits free and OH-π intramolecularly H-bonded OH stretching frequencies at 3606 and 3388 cm^{-1} in its solution IR spectrum, consistent with the introduction of the isoprenoid side chain at C-6 *ortho* to the 5–OH. Methylation afforded toddaculin, completely identical with a natural sample.

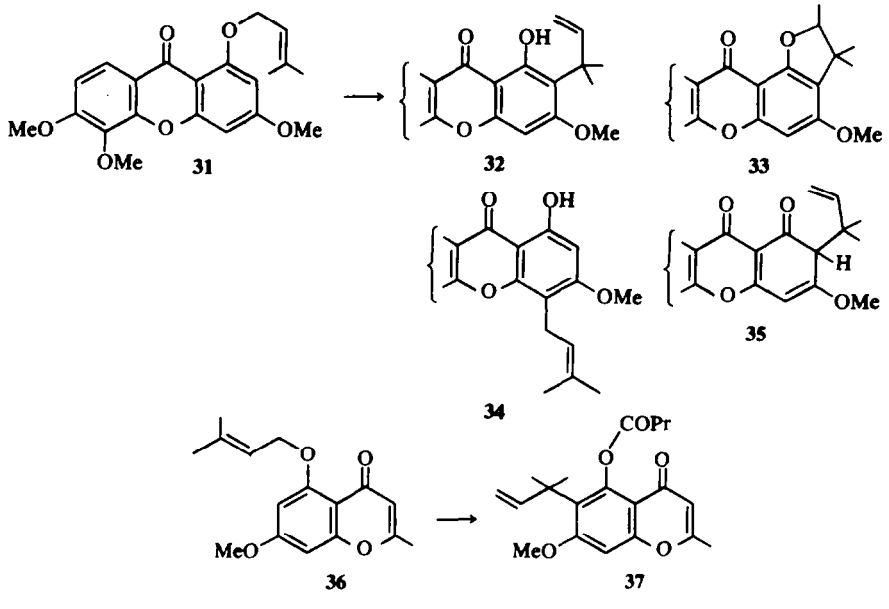
A more direct, though less efficient, route to the key intermediate (**24**) in the toddaculin synthesis was established by direct dimethylpropargylation of 5,7-diacetoxycoumarin (**10**). From the complex mixture of products, the acetoxy ether (**25**) could be isolated. Hydrolysis and methylation gave **24** in 14% yield.

With 5-(3,3-dimethyallyloxy)-7-methoxycoumarin (**22**) available, an alternative synthesis of sesibiricin was envisaged. Thus the ether (**22**) was pyrolysed at 175° in N,N-diethylaniline containing butyric anhydride, conditions which led to its smooth *para* Claisen rearrangement[11] to **6**(86%), the NMR spectrum of which disclosed a 3,3-dimethylallyl group attached to the benzene ring. The butyrate was hydrolysed under mild conditions to a 5-hydroxycoumarin (**5**), the IR spectrum of which showed only a free OH absorption at 3599 cm^{-1}. The absence of intramolecular OH–π H-bonding provided strong evidence that the prenyl substituent was located at C-8 and not at C-6. Treatment of 5 with 1-bromo-3-methylbut-2-ene in the usual manner gave sesibiricin (**1**), the overall yield by this route being 37% from **13**.

The formation of the *para* Claisen rearrangement product (**6**) from the ether (**22**) was anticipated, albeit that it contained a vacant *ortho* position, since it was *meta*-substituted.[12] However, the complete absence of *ortho* rearrangement product was synthetically important but somewhat unexpected. Thus Jefferson and Scheinmann[11,13] found that pyrolysis of the xanthone (**31**) in N,N-diethylaniline gave the phenols (**32** and **34**) and the cyclised *ortho* product (**33**). A predominance of the *para* product (**34**) was interpreted in terms of steric compression in the first formed *ortho*-dienone intermediate (**35**). As a consequence of the cyclic transition state in the rearrangement of **31** to **35**, the 1,1-dimethylallyl substituent will be produced in a pseudo axial orientation. For enolisation to **32** to occur, the *ortho* hydrogen must become pseudo axial a conformation in which steric interaction between the bulky 1,1-dimethylallyl group and the neighbouring OMe is increased. Conversely, free rotation of the 1,1-dimethylallyl group in its first-formed pseudo axial conformation leads to the preferred geometry for a Cope rearrangement to the *para*-dienone and thereby to the *para* product. Remarkably, rearrangement of the chromone ether (**36**) under identical conditions to **22** led exclusively to the *ortho* rearrangement product (**37**). The differing regioselective rearrangements of these structurally very similar ethers (**22** and **36**) must depend on the nature of the attached heterocyclic ring. The *para* rearrangement of **22** can be accounted for



Scheme 1. Synthetic routes to Sesibiricin (1) and Toddaculin (28).



Scheme 2.

on steric grounds and while similar steric arguments apply to the *ortho*-dienone from **36**, the driving force for enolisation of this dienone to be preferred to a further sigmatropic rearrangement must be attributed to the strong chelation resulting from aromatisation to the 5-hydroxychromone.

EXPERIMENTAL

M.ps were determined with a Kofler hot stage apparatus. IR spectra of $CHCl_3$ solns were recorded on a Perkin–Elmer 225 spectrophotometer. NMR spectra of solns in $CDCl_3$ with TMS as internal standard were recorded by Mr. J. Gall on a Varian T-60 or a Varian HA-100 spectrometer. Mass spectra were recorded by Mr. A. Ritchie with an AEI-GEC MS12 mass spectrometer. UV spectra were recorded on a Unicam SP800 spectrometer and refer to EtOH solns; λ_{max} (in base) refers to EtOH solns to which 2 drops of 4N NaOH were added. Microanalyses were performed by Mr. J. M. L. Cameron and his staff. Kieselgel G (Merck) was used for preparative TLC. Light petroleum refers to the fraction of b.p. 40–60°.

Dimethylallylation of 5,7-dihydroxycoumarin. K_2CO_3 (1·4 g) was added to a soln of **7** (1·5 g) in acetone (100 ml) and the mixture refluxed for 1 hr. 1-Bromo-3-methylbut-2-ene (3·7 g) was then added and the mixture refluxed for 3·5 hr. After filtration and evaporation, the residue was extracted into EtOAc, washed with NaOH aq (0·8%w/v), with brine to neutrality and dried. Evaporation and crystallisation from ether-light petroleum afforded 5,7 - *di*(3 - *methylbut* - 2 - *enyl*)*oxycoumarin* (**12**) as colourless needles (1·46 g, 55%), m.p. 79–81° (Found: C, 72·8; H, 7·15. $C_{19}H_{22}O_4$ requires: C, 72·6; H, 7·05%); mass spectral peaks at *m/e* 314 (2%, M^+), 178 (59) and 69 (100); NMR signals at τ8·20 (12H, bs), 5·43 (4H, bd, J = 6·5 Hz), 4·50 (2H, bt, J = 6·5 Hz), 3·90 (1H, d, J = 9·5 Hz), 3·70 (1H, d, J = 2 Hz), 3·60 (1H, d, J = 2 Hz) and 2·04 (1H, d, J = 9·5 Hz). The neutralised washings were extracted with EtOAc and the organic layer washed with brine, dried and evaporated. The residual solid (0·7 g) was separated by TLC [3 × EtOAc-light petroleum (3 : 17)] into (i) 5 - (3 - *methylbut* - 2 - *enyl*)*oxy* - 7 - *hydroxy* - 8 - (3 - *methylbut* - 2 - *enyl*)*coumarin* (**4**; 55 mg, 2%), needles, m.p. 196–198° (from acetone) (Found: C, 72·5; H, 6·85. $C_{19}H_{22}O_4$ requires: C, 72·6, H, 7·05%); ν_{max} 3597 and 3398 cm^{-1} (ε 64 and 77); λ_{max} 226(sh), 258(sh), 264 and 337 nm (log ε 4·18, 3·98, 4·00 and 4·14), λ_{max} (in base) 249(sh), 280 and 396 nm (log ε 3·93, 4·00 and 4·25); mass spectral peaks at *m/e* 314(M^+, 6%), 246(83), 191(100) and 69(98); NMR signals (d_6–DMSO) at τ8·35(3H, s), 8·22(9H, s), 6·73(2H, bd, J = 6·5 Hz), 5·43(2H, bd, J = 6·5 Hz), 4·85(1H, bt, J = 6·5 Hz), 4·56 (1H, bt, J=6·5 Hz), 3·96(1H, d, J = 9·5 Hz), 3·60(1H, s) and 2·10(1H, d, J = 9·5 Hz).

(ii) 5 - (3 - *Methylbut* - 2 - *enyl*)*oxy* - 7 - *hydroxycoumarin* (**13**). Plates (460 mg, 23%), m.p. 143·5–145° (from ether) (Found: C, 68·0; H, 5·6. $C_{14}H_{14}O_4$ requires: C, 68·3; H, 5·75%); ν_{max} 3585 and 3287 cm^{-1} (ε 100 and 120); λ_{max} 249, 258 and 333 nm (log ε 3·83, 3·81 and 4·13), λ_{max} (in base) 239, 274 and 386 nm (log ε 3·79, 3·74 and 4·25); mass spectral peaks at *m/e* 246 (M^+, 8%), 191 (15), 178(89), 150(36) and 69(100); NMR signals at τ8·27(3H, s), 8·22(3H, s), 5·45(2H, bd, J = 6·5 Hz), 4·53(1H, bt, J = 6·5 Hz), 3·88(1H, d, J = 9·5 Hz), 3·65 (1H, d, J = 2 Hz), 3·39(1H, d, J = 2 Hz), 1·97(1H, d, J = 9·5 Hz) and 1·50(1H, bs).

Dimethylallylation of 5,7-diacetoxycoumarin. (a) K_2CO_3 (2·43 g) was added to a soln of **10**(1·35 g) in 1,2-dimethoxyethane (25 ml) and the mixture stirred for 1 hr. 1 - Bromo - 3 - methylbut - 2 - ene (2·76 g) was then added and the mixture refluxed for 21 hr. More K_2CO_3 (0·5 g) and 1 - bromo - 3 - methylbut - 2 - ene (1 g) were added and refluxing continued for a further 21 hr. Work up gave an oily solid which was separated by TLC [EtOAc-light petroleum (3 : 7)] into (i) the bis ether (**12**; 165 mg, 9%); (ii) the hydroxy ether (**4**; 43 mg, 2%); (iii) a mixture of the isomeric acetates (**16** and **17**; ~4 : 1 from NMR) (974 mg, 58%). The major isomer, 5 - (3 - *methylbut* - 2 - *enyl*)*oxy* - 7 - *acetoxycoumarin* (**16**) was isolated by fractional crystallisation from ether-acetone as needles, m.p. 127–129° (Found: C, 66·9; H, 5·6. $C_{16}H_{16}O_5$ requires: C, 66·65; H, 5·6%), $\nu_{max}^{CCl_4}$ 1773 and 1749 cm^{-1}; λ_{max} 211, 240, 248 and 303 nm (log ε 4·44, 3·79, 3·76 and 4·18); mass spectral peaks at *m/e* 288 (M^+, 3%), 220(20), 178(34), 150(36) and 69(100); NMR signals at τ8·24 (3H, s), 8·17(3H, s), 7·68(3H, s), 5·42(2H, bd, J = 6·5 Hz), 4·35(1H, bt, J = 6·5 Hz), 3·79(1H, d, J = 9·5 Hz), 3·52(1H, d, J = 2 Hz) 3·35(1H, d, J = 2 Hz) and 2·13 (1H, d, J = 9·5 Hz). The acetate (32 mg) in MeOH (2 ml) was refluxed with $NaHCO_3$ aq (0·1 ml, 1% w/v) for 0·5 hr. The cooled soln was carefully neutralised with dil HCl (1% w/v) and after evaporation of most of the solvent, the residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated to give **13** (23 mg, 81%) identical (mixed m.p., IR and NMR) with an authentic sample.

(b) The experiment was repeated using a shorter reflux time (27 hr), conditions which gave **12** (2%), no C-alkylated ether (**4**) and the mixture of isomeric acetates (**16** and **17**; 60%). When the isomeric acetates (900 mg) were dissolved in MeOH (12 ml) and $NaHCO_3$ aq (0·3 ml, 1% w/v) added, a bright orange fluorescence appeared. The soln was then refluxed for 0·7 hr and worked up as above to give, after purification on TLC [EtOAc-light petroleum (3 : 7)] a mixture of **13** and **14** (4 : 1 from NMR) as plates (640 mg, 77%) from ether.

(c) Repeating the experiment with acetone as solvent gave **12** (6%), **4** (2%), the mixture of **16** and **17** (3 : 1 from NMR; 41%) and unreacted 5,7-diacetoxycoumarin (30%).

Dimethylpropargylation. K_2CO_3 (0·42 g) was added to a soln **13** and **14** (0·3 g) in aqueous acetone (3% v/v; 25 ml) and the mixture stirred for 0·5 hr. 2 - Chloro - 2 - methylbut - 3 - yne (2 g) and KI (0·16 g) were added and the mixture refluxed for 12 hr. More K_2CO_3 (0·25 g) and 2 - chloro - 2 - methylbut - 3 - yne (1·1 g) were added and refluxing continued for a further 6 hr. After filtration and evaporation, the residue was dissolved in a mixture of EtOAc and brine. The organic layer was washed with brine, dried and evaporated. The residual oil (0·53 g) was separated by TLC [2 × EtOAc-light petroleum (3 : 17)] into (i) 5 - (3 - *methylbut* - 2 - *enyl*)*oxy* - 7 - (1,1 - *dimethylpropargyl*)*oxycoumarin* (**15**; 262 mg, 72%) needles, m.p. 114–116° (from ether-light petroleum) (Found: C, 71·05, H, 6·6. $C_{19}H_{20}O_4 . \frac{1}{2}H_2O$ requires: C, 71·0; H, 6·6%); ν_{max} 3295 and 1725 cm^{-1}; λ_{max} 219(sh), 246, 254 and 320 nm (log ε 3·99, 3·59, 3·57 and 3·93); mass spectral peaks at *m/e* 312 (M^+, 6%), 244(14), 229(16), 178(87), 150(27), 69(87) and 41(100); NMR signals at τ8·09(12H, m), 7·34(1H, s), 5·43(2H, bd, J = 6·5 Hz), 4·54(1H, bt, J = 6·5 Hz), 3·86(1H, d, J = 9·5 Hz), 3·51(1H, d, J = 2 Hz), 3·08(1H, d, J = 2 Hz) and 2·02(1H, d, J = 9·5 Hz), and (ii) 5 - (1,1 - *dimethylpropargyl*)*oxy* - 7 - (3 - *methylbut* - 2 - *enyl*)*oxycoumarin* (**19**; 73 mg, 21%) plates, m.p. 84–86° (from ether-light petroleum) (Found: C, 71·45; H, 6·3); ν_{max} 3296 and 1720 cm^{-1}; λ_{max} 219, 246, 254 and 323 nm (log ε 4·12, 3·79; 3·73 and 4·12); mass spectral peaks at *m/e* 312 (M^+, 6%), 244(12), 229(22), 178(80), 150(30), 69(86) and 41(100); NMR signals at τ8·25 (12H, m), 7·35(1H, s), 5·46(2H, bd, J = 6·5 Hz), 4·51(1H, bt, J = 6·5 Hz), 3·86(1H, d, J = 9·5 Hz), 3·52(1H, d, J = 2 Hz), 3·04(1H, d, J = 2 Hz) and 2·10(1H, d, J = 9·5 Hz).

Reduction. A mixture of sulphur (1 g) and quinoline (6 g) was heated at 160° for 6 hr. The cooled mixture was diluted to 70 ml with xylene and stored at −5°. Immediately prior to use, 0·7 ml of this soln was diluted to 70 ml with EtOAc.

Pd–$BaSO_4$ (5% w/w; 96 mg) was added to a soln of **15** (200 mg) in EtOAc (25 ml) and 0·95 ml of the quinoline-sulphur poison added. Hydrogen (1 mole) was adsorbed after 1·5 hr. After removal of catalyst and solvent, the residue (209 mg) was separated on TLC [2 × EtOAc-light petroleum (3 : 17)] into (i) **9** as an impure oil (176 mg, 88%); NMR signals at τ8·45(6H, s), 8·23(3H, s), 8·18(3H, s), 5·45(2H, bd, J = 6·5 Hz), 4·77(1H, d, J = 18 Hz), 4·71 (1H, d, J = 10 Hz), 4·50(1H, bt, J = 6·5 Hz), 3·88(1H, d, J = 9·5 Hz), 3·84(1H, dd, J = 18 and 10 Hz), 3·66(1H, d, J = 2 Hz), 3·42(1H, d, J = 2 Hz) and 2·02(1H, d, J = 9·5 Hz); (ii) **4** (5 mg, 2%) identified by m.p., TLC, IR and UV, and (iii) **13** (4 mg, 2%).

Pyrolysis of **9**. The ether **9** (120 mg) was heated at 130° for 1·5 hr under reduced pressure. The residue was separated by TLC [EtOAc-light petroleum (3 : 17), then $CHCl_3$] into (i) 5 - (3 - *methylbut* - 2 - *enyl*)*oxy* - 7 - (1,1 - *dimethylpropyl*)*oxycoumarin* (**19**) as a colourless oil (11 mg, 8%), b.p. 145°/0·02 mm (Found: C, 72·45; H, 7·45. $C_{19}H_{24}O_4$ requires: C, 72·1; H, 7·65%); mass spectral peaks at *m/e* 316(M^+, 6%), 248(23), 178(100), 149(39) and

69(90); NMR signals at τ9·03(3H, t, $J = 6$ Hz), 8·62(6H, s), 8·23(3H, s), 8·22(2H, q, $J = 6$ Hz), 8·18(3H, s), 5·43(2H, bd, $J = 6·5$ Hz), 4·52(1H, bt, $J = 6·5$ Hz), 3·85(1H, d, $J = 9·5$ Hz), 3·71(1H, d, $J = 2$ Hz), 3·45(1H, d, $J = 2$ Hz) and 2·05(1H, d, $J = 9·5$ Hz); and (ii) **4** (91 mg, 77%), m.p. 196–198°, identical (mixed m.p., TLC, IR, UV, NMR and mass spectrum) with the sample obtained by alkylation of **7**.

Sesibiricin. K_2CO_3 (0·5 g) was added to a soln of **4** (46 mg) in acetone (5 ml) and the mixture stirred for 1 hr. MeI (1 ml) was added and the mixture refluxed for 4 hr. Work up gave a residue which was purified by TLC [EtOAc-light petroleum (3:17), then $CHCl_3$] to yield sesibiricin (**1**; 39 mg, 81%) needles, m.p. 121–122° (lit.[2] 120–122°) from ether-light petroleum) (Found: C, 73·2; H, 7·2. Calc. for $C_{20}H_{24}O_4$: C, 73·15; H, 7·35%); ν_{max} 1720, 1617 and 1603 cm^{-1}; λ_{max} 225(sh), 255, 261 and 329 nm (log ε 3·18, 3·07, 3·10 and 3·15); mass spectral peaks at *m/e* 328 (M^+, 6%), 260(26), 245(64), 220(23), 191(22) and 69(100); NMR signals at τ8·33(3H, s), 8·17(9H, s), 6·56(2H, bd, $J = 6·5$ Hz), 6·07(3H, s), 5·40(2H, bd, $J = 6·5$ Hz), 4·78(1H, bt, $J = 6·5$ Hz), 4·52(1H, bt, $J = 6·5$ Hz), 3·93(1H, d, $J = 9·5$ Hz), 3·69(1H, s) and 2·05(1H, d, $J = 9·5$ Hz), identical (mixed m.p., IR and TLC) with an authentic sample.

Coumurrayin. A soln of **1** (20 mg) in MeOH (1 ml) and conc. HCl (5 drops) was refluxed for 1·5 hr. The cooled soln was neutralised with NaOH aq and most of the solvent evaporated. After dilution with water and extraction into EtOAc, the organic layer was washed with brine, dried and evaporated. The phenol **5** (11 mg) was treated with MeI and K_2CO_3 (10 mg) in refluxing acetone (1 ml) for 2 hr to give a yellow oil which was distilled at 160°/0·04 mm. On standing, the distillate (6 mg) solidified, m.p. 155–157°. The physical properties (m.p., mixed m.p., IR, UV and TLC) of this compound were identical with those of **3**.[3]

Methylation of **13** *and* **14**. A mixture **13** and **14** (600 mg) was methylated using K_2CO_3 (709 mg), MeI (1 ml) and acetone (25 ml). After refluxing for 2 hr, work up gave a mixture of **22** and **23** (4:1 from NMR) as an oil which was separated by TLC [2 × EtOAc-light petroleum (3:17)] into (i) **22**, needles (139 mg, 23%), m.p. 91–94° (lit.[14] 90–92°); NMR signals at τ8·22(3H, s), 8·17(3H, s), 6·14(3H, s), 5·42(2H, bd, $J = 6·5$ Hz), 4·50(1H, bt, $J = 6·5$ Hz), 3·89(1H, d, $J = 9·5$ Hz), 3·71(1H, d, $J = 2$ Hz), 3·60(1H, d, $J = 2$ Hz) and 2·41(1H, d, $J = 9·5$ Hz); (ii) a mixture **22** and **23** (345 mg, 57%) which on crystallisation from ether-light petroleum gave **22** (248 mg). On trituration of the evaporated mother liquors with ether, the isomer **23** was obtained as plates (15 mg), m.p. 99–102° (lit.[4] 101–102°).

Hydrolysis of **22**. A soln of **22** (64 mg) in MeOH (1 ml) and conc. HCl (6 drops) was refluxed for 2 hr. The cooled soln was neutralised with Na_2CO_3 aq (0·5% w/v) and most of the solvent evaporated. The residue was diluted with water (10 ml) and extracted with EtOAc. Drying and evaporation gave **8** as a yellow solid (47 mg, 87%), m.p. 224–228° (lit.[15] 228–229°); λ_{max} 249, 257 and 327 nm (log ε 3·71, 3·73 and 4·09), λ_{max} (in base) 237(sh), 270, 325 and 388 nm (log ε 3·80, 3·89, 3·81 and 3·79).

A soln of **8** (24 mg) and n-butyric anhydride (0·25 ml) in dry pyridine (0·5 ml) was stirred for 2 hr, then poured into iced water and left for 2 hr before extraction with EtOAc. The organic layer was washed repeatedly with brine, dried and evaporated and traces of pyridine in the residue removed as an azeotrope with benzene to give the *butyrate* **27** (29 mg, 86%) plates, m.p. 108–109° (from ether) (Found: C, 64·1; H, 5·3. $C_{14}H_{14}O_5$ requires: C, 64·1; H, 5·4%); ν_{max} 1760, 1728 and 1620 cm^{-1}; λ_{max} 216(sh), 243, 253 and 320 nm (log ε 4·40, 3·77, 3·69 and 4·23); mass spectral peaks at *m/e* 262 (M^+, 14%), 192(100), 164(34) and 71(52); NMR signals at τ8·93(3H, t, $J = 7$ Hz), 8·17(2H, sextet.. $J = 7$ Hz), 7·36(2H, t, $J = 7$ Hz), 6·14(3H, s), 3·75(1H, d, $J = 9·5$ Hz), 3·34(2H, s) and 2·41(1H, d, $J = 9·5$ Hz).

Pyrolysis of **22**. A suspension of **22** (70 mg) in N,N-diethylaniline (0·5 ml) and n-butyric anhydride (0·2 ml) was shaken at 175° until the first formed melt had dissolved, then maintained at 175° for 2 hr. The cooled mixture was diluted with iced water (20 ml), kept for 2 hr and extracted with EtOAc. The organic layer was washed with dil HCl (1% w/v) to pH 2, K_2CO_3 aq (5% w/v) to pH 11, brine to neutrality, dried and evaporated. The residue was separated by TLC [EtOAc-light petroleum (1:4)] into (i) the *butyrate* (**6**), needles (76 mg, 86%), m.p. 98–100° (from ether) (Found: C, 68·9; H, 6·8. $C_{19}H_{22}O_5$ requires: C, 69·05; H, 6·7%); ν_{max} 1763, 1740(sh), 1728 and 1614 cm^{-1}; λ_{max} 218, 250 and 320 nm (log ε 4·06, 3·72 and 4·03); mass spectral peaks at *m/e* 330 (M^+, 18%), 260(84), 245(62), 189(18), 71(38) and 43(100); NMR signals at τ8·92(3H, t, $J = 7$ Hz), 8·32(3H, s), 8·18(2H, sextet, $J = 7$ Hz), 8·17(3H, s), 7·35(2H, t, $J = 7$ Hz), 6·50(2H, d, $J = 6·5$ Hz), 6·08(3H, s), 4·78(1H, bt, $J = 6·5$ Hz), 3·77(1H, d, $J = 9·5$ Hz), 3·35(1H, s), and 2·40(1H, d, $J = 9·5$ Hz); and (ii) the butyrate (**27**; 12 mg, 2%).

A soln of **6** (37 mg) in MeOH (3 ml) and NaOH aq (1% w/v, 1 ml) was refluxed for 15 min. The cooled soln was neutralised with dil HCl (1% w/v) and most of the solvent evaporated. The residue was diluted with water (25 ml) and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. After TLC purification ($CHCl_3$), crystallisation from MeOH afforded 5 - *hydroxy* - 7 - *methoxy* - 8 - (3 - *methylbut* - 2 - *enyl*)*coumarin* (**5**) as needles (25 mg, 86%), m.p. 195–197° (Found: C, 69·15; H, 6·3. $C_{15}H_{16}O_4$ requires: C, 69·2; H, 6·2%); ν_{max} 3599 (ε 161), 1730, 1719 and 1616 cm^{-1}; λ_{max} 223(sh), 258(sh), 263 and 324 nm (log ε 4·15, 4·08, 4·12 and 4·14), λ_{max} (in base) 224, 238, 276, 324 and 399 nm (log ε 4·35, 4·10, 4·18, 3·89 and 3·85); mass spectral peaks at *m/e* 260 (M^+, 66%), 245(96), 217(100), 205(72) and 189(56); NMR signals (d_6-acetone) at τ8·32 (3H, s), 8·17(3H, s), 6·76(1H, bs), 6·60(2H, d, $J = 6·5$ Hz), 6·12(3H, s), 4·80(2H, bt, $J = 6·5$ Hz), 3·94(1H, d, $J = 9·5$ Hz), 3·52(1H, s), and 1·98(1H, d, $J = 9·5$ Hz).

The phenol **5** was converted into **1** in the usual manner using K_2CO_3, dimethylallyl bromide and acetone, the product being identical (mixed m.p., NMR and IR) with sesibiricin.

Toddaculin. K_2CO_3 (0·71 g) was added to a soln of 5 - hydroxy - 7 - methoxycoumarin (0·34 g) in aqueous acetone (3% v/v; 25 ml) and the mixture stirred for 1 hr. 2 - Chloro - 2 - methylbut - 3 - yne (3·28 g) and KI (0·22 g) were added and the mixture refluxed for 14 hr. Work up gave an oil which was purified by TLC [2 × EtOAc-light petroleum (3:17)] to give 5-(1,1-*dimethylpropargyl*)*oxy* - 7 - *methoxycoumarin* (**24**), yellow plates (0·31 g, 69%), m.p. 89–91° (from ether) (Found: C, 69·6; H, 5·45. $C_{15}H_{14}O_4$ requires: C, 69·75; H, 5·45%); $\nu_{max}^{CCl_4}$ 3304, 1746 and 1609 cm^{-1}; λ_{max} 220(sh), 246, 255 and 324 nm (log ε 3·91, 3·61, 3·57 and 3·84); mass spectral peaks at *m/e* 258 (M^+, 16%), 244(58), 193(94), 164(100), 149(31) and 68(66); NMR signals at τ8·23(6H, s), 7·32(1H, s), 6·16(3H, s) 3·89(1H, d, $J = 9·5$ Hz), 3·55(1H, d, $J = 2$ Hz), 3·05(1H, d, $J = 2$ Hz) and 2·13(1H, d, $J = 9·5$ Hz).

Pd–$BaSO_4$ (5% w/w; 35 mg) and the quinoline-sulphur poison (0·33 ml) were added to a soln of **24** (60 mg) in EtOAc (25 ml) and the mixture hydrogenated for 2·5 hr when the uptake of hydrogen was approximately 1 mole. After filtration and evaporation, the residue was separated by TLC [2 × EtOAc-light petroleum (3:17)] into (i) **21** as a yellow oil (49 mg, 84%) showing NMR signals at τ8·43(3H, s), 6·20(3H, s), 4·76(1H, d, $J = 18$ Hz), 4·75(1H, d, $J = 10$ Hz), 3·88(1H, dd, $J = 18$ and 10 Hz) 3·85(1H, d, $J = 9·5$ Hz), 3·60(1H, d, $J = 2$ Hz), 3·45(1H, d, $J = 2$ Hz) and 2·05(1H, d, $J = 9·5$ Hz); and (ii) 5 - hydroxy - 7 - methoxycoumarin (2 mg).

The ether **21** (35 mg) was heated for 2 hr at 114° under reduced pressure and the residue purified by TLC ($CHCl_3$) to give 5-*demethyltoddaculin* (**29**), plates (24 mg, 70%); m.p. 150–153° (from ether-acetone) (Found: C, 69·0; H, 6·05. $C_{13}H_{10}O_4$ requires: C, 69·2; H, 6·2%); ν_{max} 3606, 3388(br) and 1719 cm^{-1} (ε 154; 346 and 724); λ_{max} 230, 255 and 328 nm (log ε 4·33, 3·78 and 4·23); λ_{max} (in base) 226, 273, 336 and 396 nm (log ε 4·45, 4·05, 4·10 and 3·76); mass spectral peaks at *m/e* 260 (M^+ 52%), 245(14), 205(100), and 177(62); NMR signals (d_6-acetone) at τ8·35 (3H, s), 8·25(3H, s), 6·60(2H, d, $J = 6·5$ Hz); 6·07(3H, s), 6·02(1H, m), 4·82(1H, bt, $J = 6·5$ Hz), 3·90(1H, d, $J = 9·5$ Hz), 3·48(1H, s) and 1·85(1H, d, $J = 9·5$ Hz).

The phenol **29** (20 mg) was converted into the methyl ether using K_2CO_3 (40 mg), MeI (0·5 ml) and acetone (5 ml) at reflux for 2 hr. Work up gave **28** (22 mg) crystallised from ether as plates, m.p. 93–94° (lit.[5] 95°); ν_{max} 1743, 1609 and 1378 cm^{-1}; λ_{max} 226, 244, 254 and 328 nm (log ε 4·29, 3·79, 3·68 and 4·19); mass spectral peaks at *m/e* 274 (M^+, 88%), 259(100), 244(45), 219(38), 216(32) and 188(29); NMR signals at τ8·32(3H, s), 8·22(3H, s), 6·64(2H, d, $J = 6·5$ Hz), 6·18(3H, s), 6·14(3H, s), 4·84(1H, bt, $J = 6·5$ Hz), 3·70(1H, d, $J = 9·5$ Hz), 3·38(1H, s) and 2·15(1H, d, $J = 9·5$ Hz), identical (mixed m.p. TLC and IR) with a natural sample.

Direct dimethylpropargylation of **10**. K_2CO_3 (213 mg) was added to a warm soln of **10** (211 mg) in aqueous acetone (4% v/v; 15 ml). After stirring for 1 hr, 2 - chloro - 2 - methylbut - 3 - yne (2·24 g) and KI (78 mg) were added and the mixture refluxed for 24 hr. Work up gave an oil which was purified by TLC [2 × EtOAc-light petroleum (3:17)] to give 5 - (1,1 - *dimethylpropargyl)oxy* - 7 - *acetoxycoumarin* (**25**) as needles (38 mg, 14%), m.p. 104–106° (from ether-light petroleum) (Found: C, 67·0; H, 5·05. $C_{16}H_{14}O_5$ requires: C, 67·1; H, 4·95%); $\nu_{max}^{CCl_4}$ 3309, 1751 and 1621 cm^{-1}; λ_{max} 238, 248 and 300 nm (log ϵ 3·77, 3·69 and 4·16); mass spectral peaks at *m/e* 286 (M^+, 14%), 271(14), 243(13), 229(100) and 178(55); NMR signals at τ8·21(6H, s), 7·65(3H, s), 7·32(1H, s), 3·72(1H, d, J = 9·5 Hz), 3·23(1H, s), 2·84(1H, s) and 2·04(1H, d, J = 9·5 Hz).

A soln of **25** (30 mg) in MeOH (5 ml) and $NaHCO_3$ aq (1% w/v; 0·1 ml) was refluxed for 30 min. The cooled soln was neutralised with dil HCl (1% w/v) and most of the solvent evaporated. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated to give 5 - (1,1 - *dimethylpropargyl)oxy* - 7 - *hydroxycoumarin* (**26**) as a yellow solid (27 mg, 95%), m.p. 190–200°; ν_{max} 3586, 3300 and 1727 cm^{-1}; λ_{max} 221(sh), 249, 258 and 327 nm (log ϵ 4·09, 3·70, 3·60 and 4·09); λ_{max} (in base) 225, 235, 273 and 380 nm (log ϵ 4·29, 4·00, 3·76 and 4·25); mass spectral peaks at *m/e* 244 (M^+, 18%), 229(46), 178(100), 150(92) and 68(98%); NMR signals (d_6-acetone) at τ8·23 (6H, s), 6·73(1H, s), 3·90(1H, d, J = 9·5 Hz), 3·54(1H, d, J = 2 Hz), 2·95(1H, d, J = 2 Hz) and 2·00(1H, d, J = 9·5 Hz).

The phenol **26** (15 mg) was methylated using MeI (0·3 ml), K_2CO_3 (20 mg) and acetone (3 ml) to yield 5 - (1,1 - dimethylpropargyl)oxy - 7 - methoxycoumarin (24; 19 mg).

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