Stereoselective Total Syntheses of the Norlignan Derivatives (±)-Tri-*O*-methylsequirin-B and (±)-Tri-*O*-methylsequirin-C

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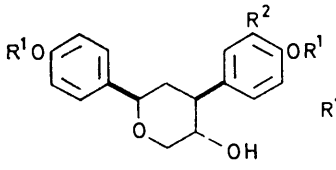
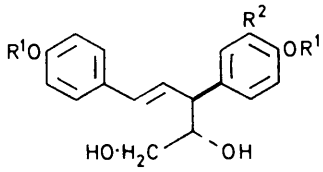
A total synthesis of the trimethyl ether of (±)-sequirin-B (2), a norlignan constituent of *Sequoia sempervirens* (Redwood) is described. 3',4'-Dimethoxyacetophenone was converted into veratroylethylene (9) and thence into 2,2-dimethyl-4-veratroyl-1,3-dioxolan (12) *via* the diol (11). The glycidic acid (16) was obtained from (12) by Darzens condensation with benzyl chloracetate and hydrogenolysis of the resulting ester. Decarboxylation–rearrangement of the glycidic acid was stereoselective, providing the desired diastereoisomer (22) (>80%) of 2-(3,4-dimethoxyphenyl)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (15). Reaction of (22) with *p*-methoxybenzylidenetriphenylphosphorane gave *trans*- and *cis*-(±)-tri-*O*-methylsequirin-C acetonides (24) and (25); the corresponding diols (8) [(±)-tri-*O*-methylsequirin-C] and (27) both cyclised stereospecifically in acid to (2). An alternative route to (8), with improved control over olefin geometry, employed addition of *p*-methoxyphenylacetylene to (12), *trans*-reduction of the acetylenic bond, and removal of the tertiary hydroxy-group by reduction of its hydrogen sulphate ester with lithium aluminium hydride. The differing courses of acid-catalysed cyclisation of (±)-tri-*O*-methylsequirin-C and the related enol acetonide (33) are discussed.

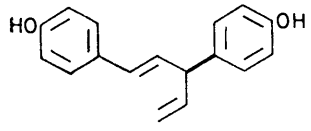
THE heartwood constituents of some members of the *Coniferae* include a small group of phenols, with structures based on a 1,3-diarylpentane skeleton, which



(1) $R^1 = R^2 = H$
(2) $R^1 = H$, $R^2 = OH$
(7) $R^1 = Me$, $R^2 = OMe$



(3) $R^1 = R^2 = H$
(4) $R^1 = H$, $R^2 = OH$
(8) $R^1 = Me$, $R^2 = OMe$



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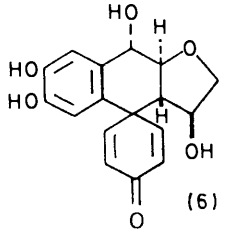
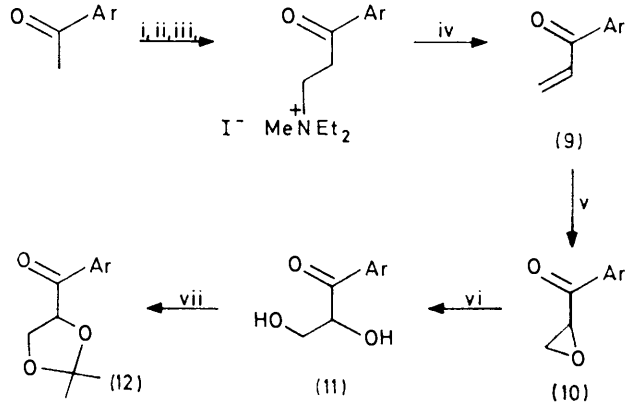


(6)

appear to be biogenetically related to lignans. These norlignans comprise the tetrahydropyrans sequirin-A [1] (sugiresinol [2]) (1) and sequirin-B (2),[1a,b,3] the pent-4-ene-1,2-diols agatharesinol (3) [4] and sequirin-C (4),[1a,b,3] the pentadiene hinokiresinol (5),[4,5] and athrotaxin (6).[6] Study of this group has been so far confined to structure elucidation; we now describe stereoselective total synthesis of (±)-tri-*O*-methylsequirin-B (7) * and (±)-tri-*O*-methylsequirin-C (8).*†

Both syntheses employ the ketone (12), which was prepared from 3',4'-dimethoxyacetophenone. The latter was subjected to a Mannich reaction to provide 3-diethylamino-3',4'-dimethoxypropiophenone. The methiodide of this base decomposed smoothly on shaking with aqueous sodium hydrogen carbonate to yield 3,4-dimethoxyphenyl vinyl ketone (9) (60%). Alkaline hydrogen peroxide converted the vinyl ketone into the αβ-epoxy-ketone (10), which was hydrolysed in dilute acid to the diol (11) [80% from (9)]. The glycol readily formed the acetonide (12) (92%) by acid-catalysed reaction with acetone.



Ar = 3,4-dimethoxyphenyl

Reagents: i, CH_2O, Et_2NH_2Cl; ii, aq. Na_2CO_3; iii, MeI; iv, aq. $NaHCO_3$; v, H_2O_2,NaOH; vi, H_2O,H^+; vii, Me_2CO,H^+

The acetonide (12) (2,2-dimethyl-4-veratroyl-1,3-dioxolan) was then treated with ethyl chloroacetate in a Darzens condensation. With sodium ethoxide as base,

* For preliminary communications see ref. 7. † An alternative synthetic route to sequirin-B has been reported recently.[8]

[1] (*a*) B. Balogh and A. B. Anderson, *Phytochemistry*, 1965, **4**, 569; (*b*) R. Riffer and A. B. Anderson, *ibid.*, 1967, **6**, 1557; (*c*) C. R. Enzell, Y. Hirose, and B. R. Thomas, *Tetrahedron Letters*, 1967, 793.

[2] Y. Kai, *J. Japan Wood Res. Soc.*, 1965, **11**, 23.

[3] N. A. R. Hatam and D. A. Whiting, *Tetrahedron Letters*, 1967, 781; *J. Chem. Soc.* (*C*), 1969, 1921.

[4] C. R. Enzell and B. R. Thomas, *Tetrahedron Letters*, 1966, 2395.

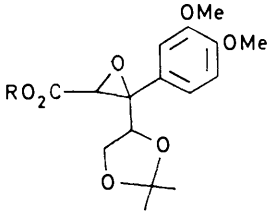
[5] Y. Hirose, N. Oishi, H. Nagaki, and T. Nakatsuka, *Tetrahedron Letters*, 1965, 3665.

[6] P. Daniels, H. Erdtman, K. Nishimura, T. Norin, P. Kierkegaard, and A. M. Pilotti, *J.C.S. Chem. Comm.*, 1972, 246.

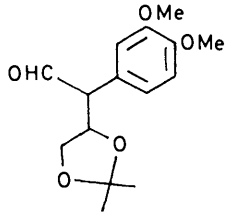
[7] R. V. Davies, N. A. R. Hatam, and D. A. Whiting, *Chem. Comm.*, 1971, 922; R. V. Davies and D. A. Whiting, *Tetrahedron Letters*, 1972, 3849.

[8] Z. Horii, A. Go, T. Momose, and C. Iwata, *Chem. and Pharm. Bull* (*Japan*), 1971, **19**, 2212.

the acetonide was unchanged and ethyl ethoxyacetate was isolated. However potassium t-butoxide (in benzene) catalysed the desired reaction and the glycidic ethyl ester (13) was obtained (62%). This ester was hydrolysed with 1 equiv. of sodium hydroxide to give the sodium salt (14). Efforts to transform this salt into the aldehyde (15), *via* decarboxylation and rearrangement of the acid (16), were unavailing, although various acids were employed to liberate (16), either with one measured equivalent, or with pH control. Although traces of the aldehyde (15) were obtained, the major products were 2-(3,4-dimethoxyphenyl)-4-hydroxybut-2-enal (17) and 3-(3,4-dimethoxyphenyl)furan (18) in



(13) R = Et
(14) R = Na
(16) R = H
(21) R = $PhCH_2$



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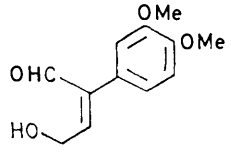

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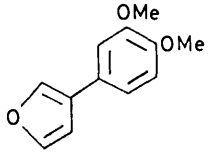
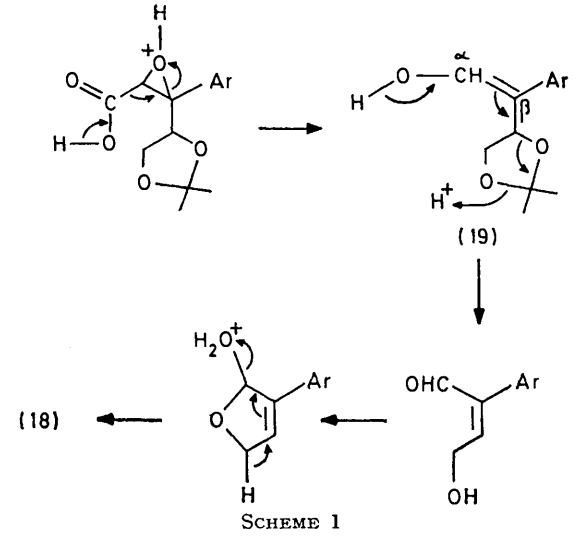


(18)

proportion dependant upon conditions. Thus, a solution of the free acid (16) (see later) in chloroform with a trace of trifluoroacetic acid was transformed completely (15 min at ambient temperature) into the aldehyde (17), whereas a solution in benzene afforded only the furan (18) after 3 days. These reactions are rationalised as shown in Scheme 1. Decarboxylation with epoxide opening gives rise to the enol (19); the normal ketonisation, with β-protonation [to give (15)] is less favoured than ketonisation with loss of acetone, as shown. The formylcinnamyl alcohol (17) then closes to the hemiacetal (20) and dehydration leads to the furan (18). Assignments of structure to the products (17) and (18) are based on spectroscopic evidence (Experimental section); the double bond geometry in (17) is best shown as *Z*, since this configuration would favour cyclisation to the furan.

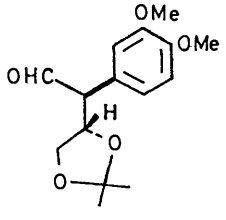
In an alternative approach, the benzyl glycidic ester (62%) was prepared from the ketone (12), using benzyl chloroacetate and potassium t-butoxide; hydrogenolysis of this ester over palladium gave the free glycidic acid (95%), obtained as a crystalline solid. Heating of this acid alone, in water, or alcohols gave only the aldehyde (17) and the furan (18). However, heating the acid in acetone, in a sealed tube at 100°, eventually afforded the requisite aldehydes (22) and (23); the desired (±)-diastereoisomer (22) was predominant (*ca.* 5 : 1 by n.m.r. analysis). Product control in this reaction is not likely



SCHEME 1

to reflect the diastereoisomeric composition of the glycidic acid (certainly a mixture) since the single enol species (19) must mediate. The ratio of aldehydes obtained from ketonisation of (19) with β-protonation will be related to the relative stabilities of the aldehydes. Newman projections (22a) and (23a), showing staggered conformers, suggest that the latter is the less stable because of the gauche aryl–methylene interaction. Thus (22) is the major product. Spectroscopic evidence supporting structure (22) is presented in the Experimental section; the stereochemical assignment depends on the connection with sequirin-B, now to be discussed.

Since the aldehydes (22) and (23) were unstable, attempts at purification were unsuccessful. Therefore,



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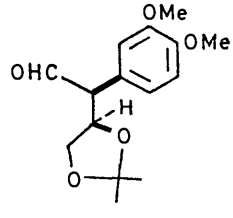

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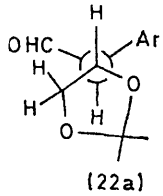
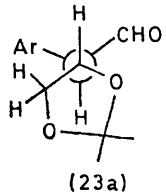


(22a)



(23a)

a batch of the glycidic acid was decarboxylated in acetone as before, and, after removal of solvent, the product was treated with *p*-methoxybenzylidenetriphenylphosphorane, in benzene. The two major products were the *trans*- and *cis*-tri-*O*-methylsequirin-C

acetonides (24) and (25), obtained in *ca.* 9 and 41% yield, respectively (based on the glycidic acid). The two isomers were spectroscopically similar (Experimental section), but the *trans*-form had $J_{1,2}$ 16 Hz, and the *cis*- had $J_{1,2}$ 10 Hz. The *trans*-isomer, m.p. 68—70°, was spectroscopically and chromatographically identical with *trans*-tri-*O*-methylsequirin-C acetonide, m.p. 76—78°, obtained by treatment of the trimethyl ether of natural sequirin C with acetone.

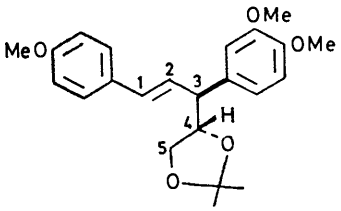
Several other products were isolated from this Wittig reaction in very small quantities, including 4,4'-dimethoxystilbene, *p*-methoxytoluene, and the pentadienol (26). The stilbene probably arose by oxidation [9] of the phosphorane to anisaldehyde, which would then react with more phosphorane. *p*-Methoxytoluene must have arisen *via* hydrolysis of the phosphorane, and the diene (26) (possibly a mixture of stereoisomers, although it could not be resolved by t.l.c.) was probably formed through reaction of the ylide with the aldehyde (17). Traces of stereoisomers of (24) and (25) were not purified.

Both acetonides (24) and (25) were readily and quantitatively hydrolysed to the corresponding diols (8) and (27), m.p. 118 and 133°. The synthetic *trans*-diol (8) had u.v., i.r., and n.m.r. spectra almost identical with those of the trimethyl ether of natural (optically active) sequirin-C, m.p. 121°. The diacetyl derivatives of both synthetic and natural materials were also chromatographically and spectroscopically identical. A different synthesis, providing only the 1,2-*trans*-isomer rather than *cis*–*trans* mixtures, is described later.

Both the *trans*- and *cis*-isomers (8) and (27) cyclised to (±)-tri-*O*-methylsequirin-B (7) (90%) on refluxing with methanolic hydrogen chloride for 2—3 days. The synthetic product, m.p. 121—123°, could not be distinguished by chromatography, or by u.v., i.r., and n.m.r. spectroscopy, from the trimethyl ether, m.p. 136°, of natural (—)-sequirin-B; the monoacetates of the synthetic and natural compounds (m.p.s 154 and 134°, respectively) were otherwise identical apart from chiroptical properties.

The cyclisation of the diols (8) and (27) involves protonation at C-2, and intramolecular trapping of the C-1 carbonium ion centre by the C-5 hydroxy-group. This reaction proceeds with high stereospecifity, presumably through a transition state reflecting the stability of the product (7) in which all the substituents on the tetrahydropyran ring are equatorial.[3] In conjunction with the selectivity of formation of the aldehyde (22), a good degree of overall stereoselectivity was achieved in the synthesis of (±)-tri-*O*-methylsequirin-B. However, since rather poor yields of (±)-trimethylsequirin-C were obtained, a modified route to this compound was sought, with improved control over double-bond geometry.

Accordingly, the keto-acetonide (12) was condensed with *p*-methoxyphenylacetylene in sodamide–liquid ammonia, giving the acetylenic alcohol (28) as a mixture (58%) of diastereoisomers; separation of these was deferred to a later stage. Reduction with lithium aluminium hydride gave the corresponding *trans*-olefinic alcohol (29) (99%), $J_{1,2}$ 16 Hz. The hydrogen sulphate ester (30) was then formed, by reaction with sulphur



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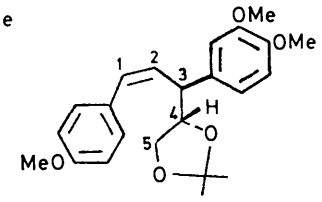

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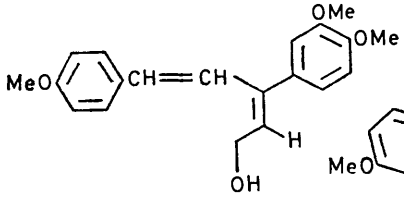

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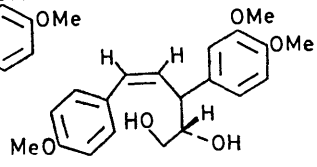

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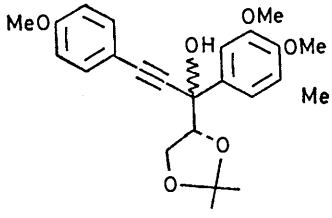

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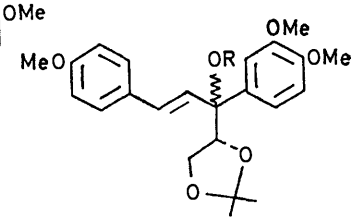
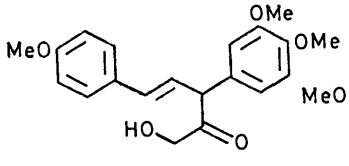


(29) R = H
(30) R = SO_3H



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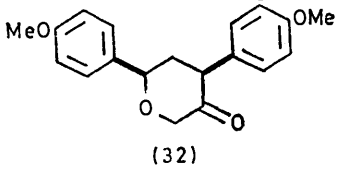

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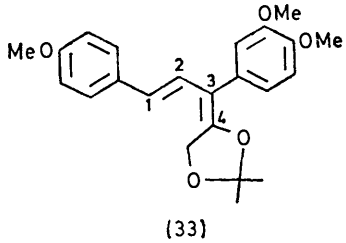


(33)

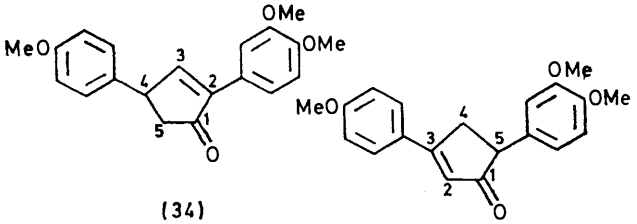
trioxide–pyridine,[10] and reduced (without further purification) with lithium aluminium hydride to (±)-tri-*O*-methylsequirin-C acetonide, and a diastereoisomer. The

[9] H. Bestmann, *Angew. Chem.*, 1960, **72**, 34.
[10] E. J. Corey and K. Achiwa, *J. Org. Chem.*, 1969, **34**, 3668.

former (24) was isolated by p.l.c. [33% from (29)] and was identical with the sample already described. (±)-Tri-*O*-methylsequirin-C was obtained on hydrolysis.

The cyclisation of tri-*O*-methylsequirin-C (8) to tri-*O*-methylsequirin-B (7) in acid proceeds in high yield, as already noted. It was hoped that the cyclisation of the ketol (31) might follow a similar course to provide the ketone (32), which is not readily obtained by oxidation of the equatorial alcohol (7). The enol acetonide (33) of the ketol (31) could be readily prepared by dehydration of the alcohol (29) with pyridine–toluene-*p*-sulphonyl chloride; both the (1*E*,3*Z*)- (33) and (1*E*,3*E*)-isomers were obtained, and the former (major) form was purified. The 3*Z*-stereochemistry was assigned after consideration of the products obtained on cyclisation.

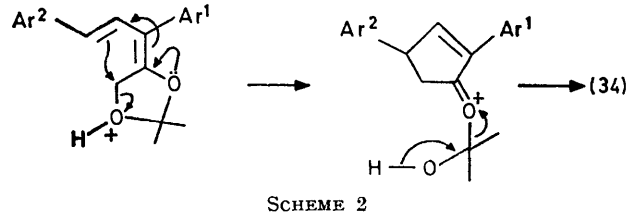
The enol acetonide (33) was treated with acid under various conditions [acetone–5M-hydrochloric acid (5 : 1 at 50°; methanol–0·25M-hydrochloric acid (2 : 1) at reflux; benzene–ethylene glycol–toluene-*p*-sulphonic acid (1%) at reflux]. All the experiments gave complex mixtures with certain common components. None of the major products could be identified as the tetrahydropyranone (32), or as the ketol (31). Instead, two arylcyclopentenones were isolated. The first, $C_{20}H_{20}O_4$,



(34)

(35)

was given structure (34); it had $\nu_{max.}$ 1700 cm^{-1} (cyclopentenone) and $\lambda_{max.}$ 285 nm. N.m.r. signals were observed at τ 2·32 (*J* 3 Hz, olefinic-H β to CO), 5·93 (*J* 1, 3 and 7 Hz, 4-H), 6·91 (q, *J* 7 and 18 Hz, 5-H_a) and 7·57 (q, *J* 3 and 18 Hz, 5-H_b), as well as aromatic and methoxy-resonances. The isomer (35), $C_{20}H_{20}O_4$, had in comparison more conjugation [$\lambda_{max.}$ 317 nm (log ε 4·00), $\nu_{max.}$ 1685 cm^{-1}], and the n.m.r. showed τ 3·46 (s, olefinic H, α to C=O) and 6·1—6·9 (m, $-CH_2-CH<$). The cyclisation of (33) in acid is rationalised in Scheme 2; it appears that the enol acetonide cyclises, after protonation at the 5-oxygen atom, as shown, more readily than it opens to the ketol (31); alternatively, the latter is



SCHEME 2

formed but cyclises through its enolic form to the cyclopentenone (34) by a mechanism similar to that in Scheme 2, rather than to the ketone (32) *via* a C-1 carbonium ion. The cyclopentenone (34) presumably equilibrates with the more conjugated ketone (35) by prototropic shift.

EXPERIMENTAL

Except where otherwise stated, the following generalisations apply. I.r. spectra were recorded for solutions in chloroform or carbon tetrachloride. U.v. measurements (Unicam SP700) were made for solutions in ethanol; log ε follows $\lambda_{max.}$ in parentheses. N.m.r. spectra were recorded for solutions in deuteriochloroform using tetramethylsilane as internal standard; observed line separations are quoted, rather than derived coupling constants. Sodium 3-trimethylsilylpropane-1-sulphonate was used as reference for solutions in deuterium oxide. T.l.c. chromatography was carried out with Silica Gel G (Merck, nach Stahl); spots were developed with iodine vapour. In preparative work, 1 × 450 × 450 mm or 0·8 × 200 × 200 mm layers of Silica Gel HF254 were employed. Organic solutions were dried with anhydrous sodium sulphate and evaporated under reduced pressure.

3-Diethylamino-3′,4′-dimethoxypropiophenone Methiodide.—3′,4′-Dimethoxyacetophenone (45 g), paraformaldehyde (10 g), and diethylammonium hydrochloride (36 g) were dissolved in ethanol (40 cm^3), and the solution was diluted with acetone (800 cm^3). When precipitation of the Mannich salt commenced, the mixture was filtered free of starting materials. Addition of ether (200 cm^3) induced crystallisation of *3-diethylamino-3′,4′-dimethoxypropiophenone hydrochloride* (64 g, 85%), m.p. 129—130° (Found: C, 59·75; H, 8·15; N, 4·70. $C_{15}H_{24}ClNO_3$ requires C, 59·7; H, 8·0; N, 4·65%). The free base was obtained from an aqueous solution of the hydrochloride after basification with aqueous sodium carbonate, and treated with methyl iodide (1 mol. equiv.) in ether at ambient temperature for 48 h to give the *methiodide* (8), m.p. 161—163° (Found: C, 47·25; H, 6·05; N, 3·2. $C_{16}H_{26}INO_3$ requires C, 47·17; H, 6·35; N, 3·45%).

Veratroylethylene.—The foregoing methiodide (8) (20 g) was mixed with water (150 cm^3) containing anhydrous sodium hydrogen carbonate (40 g), and the slurry was shaken with ether (200 cm^3) for 10 h; all the methiodide had then disappeared. After separation of the ether layer, the aqueous fraction was extracted with ether. The combined extracts were washed with water, dried, and evaporated to yield veratroylethylene (9) (5·7 g, 60%), as an unstable liquid.

Veratroylethylene Oxide (10).—Veratroylethylene (7·5 g) in methanol (100 cm^3) was treated with 30% hydrogen peroxide (15 cm^3) with stirring, with the temperature kept below 25°. 3N-Sodium hydroxide (10 cm^3) was added during 1 h at 15°. After being stirred for 18 h at ambient temperature, the mixture was diluted with water (600 cm^3) and extracted with chloroform. The extracts, after washing, drying, and evaporation, yielded a gum. Chromatography on silica gel (elution with benzene–chloroform, 2 : 1) gave the *aroylethylene oxide* (10) (6·5 g, 80%), m.p. 56—58° (from methanol) (Found: C, 63·6; H, 5·7. $C_{11}H_{12}O_4$ requires C, 63·45; H, 5·8%), $\nu_{max.}$ (Nujol) 1685, 1600, and 1590 cm^{-1}, τ 2·19 (1H, d, *J* 2 Hz), 2·39 (1H, dd), 3·08 (1H, d, *J* 9 Hz), 5·79 (1H, dd, *J* 3 and 5 Hz), 6·07 (3H, s), 6·10 (3H, s), and 7·00 (2H, m, *J* 3,5, and 6 Hz).

Veratroylethylene Glycol (11).—The epoxide (10) (3 g) was refluxed for 48 h in acetone (150 cm^3) with water (30 cm^3) and 4N-sulphuric acid (5 cm^3). After evaporation of

acetone (*ca.* 80 cm³) the product was diluted with water (400 cm³) and extracted with chloroform. The extracts, after washing, drying, and evaporation, afforded the *glycol* (11), m.p. 82—84 or 101—102° (dimorphic) (Found: C, 58·35; H, 6·15. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·25%), $\nu_{max.}$ (Nujol) 3500 and 1695 cm⁻¹, τ 2·45 (2H, m), 3·12 (1H, d, *J* 9 Hz), 4·81 (1H, dd, *J* 3 and 4 Hz), 5·85 (2H, s, 2 × OH), 6·08 (6H, s), and 5·6—6·5 (2H).

2,2-*Dimethyl*-4-*veratroyl*-1,3-*dioxolan*.—The glycol (11) (4 g) was dissolved in dry acetone (1 dm³) and hydrochloric acid (0·25 cm³); anhydrous sodium sulphate (4 g) was added, and the mixture was stirred for 96 h. Anhydrous sodium hydrogen carbonate (4 g) was then added, and after 4 h more the mixture was filtered. The filtrate was evaporated to produce the *dioxolan* (12) (4·2 g, 92%), m.p. 82—83° (from acetone–ether) (Found: C, 63·2; H, 6·6. $C_{14}H_{18}O_5$ requires C, 63·15; H, 6·8%), τ 2·30 (2H), 3·08 (1H), 4·74 (1H, t, *J* 6 Hz), 5·70 (2H, d, *J* 6 Hz), 6·04 (6H, s), and 8·51 (6H, s, CMe_2).

Ethyl 3-(3,4-*Dimethoxyphenyl*)-3-(2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*)-2,3-*epoxypropionate* (13).—The dioxolan (12) (2·66 g) was added with stirring to benzene (30 cm³) containing dry potassium t-butoxide (25 g); the mixture was kept under nitrogen and at 0° during the addition. Ethyl chloroacetate (2·5 g) was added during 5 min, still at 0°. The mixture was then stirred for 15 h at room temperature, mixed with water, and extracted with ether. The extracts were washed, dried, and evaporated. The residue was chromatographed on silica gel; the fraction eluted by benzene–ethyl acetate (4 : 1) was further purified by p.l.c. The band eluted with benzene–ethyl acetate (3 : 1) afforded an oil which crystallised from light petroleum (b.p. 40—60°) at −20°, to yield the *epoxy-ester* (13) (2·11 g, 62%), m.p. 47·5—49·5° (Found: C, 61·65; H, 6·9. $C_{18}H_{24}O_7$ requires C, 61·4; H, 6·8%), $\lambda_{max.}$ 203 (4·62), 235 (3·94), and 280 nm (3·45), $\nu_{max.}$ 1760 and 1730 cm⁻¹ (*cf.* ref. 11), τ (CCl_4) 3·17 (3H, m, ArH), 5·42 (1H, t, *J* 7 Hz), 5·95—6·35 (5H, m), 6·24 (6H, s, 2 × OMe), 8·68 (6H, s, CMe_2), and 9·07 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), *m/e* 352 ($M^{+\cdot}$) and 165 (100%). By a similar method, but using t-butyl chloroacetate, the corresponding *t-butyl ester*, m.p. 78—80° (71%), was prepared (Found: C, 63·05; H, 7·5. $C_{20}H_{28}O_7$ requires C, 63·1; H, 7·35%). Pyrolysis of this ester, after the method of Büchi,[12] failed to produce the aldehyde (15).

Sodium 3-(3,4-*Dimethoxyphenyl*)-3-(2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*)-2,3-*epoxypropionate* (14) *and its Acid-catalysed Decomposition*.—The epoxy-ester (13) (7·8 g) in ethanol (30 cm³) and water (0·4 cm³) was added to sodium ethoxide [from sodium (0·51 g) in ethanol (20 cm³)]; the solution was stirred for 16 h, then evaporated. The residue was dissolved in water and washed with ether. The aqueous solution was evaporated and the residue crystallised from aqueous acetone to yield the sodium salt (14), m.p. 360°, τ (D_2O) 2·75—2·90 (3H, m, ArH), 5·44 (1H, t, *J* 7 Hz), 5·85 (1H, s), 5·70—6·25 (2H, m), 6·15 (3H, s) and 6·21 (3H, s) (2 × OMe), and 8·58 (3H, s) and 8·68 (3H, s) (2 × Me).

The sodium salt (2 g) in water (50 cm³) was treated dropwise with 0·1N-hydrochloric acid (55 cm³, 1 mol. equiv.). The mixture was extracted with chloroform. The extracts, after washing, drying, and evaporation, afforded a gum containing three main components. These were separated by column chromatography on silica [elution with benzene–acetonitrile (4 : 1)]. The product of lowest R_F (0·4) was crystallised from ether (yield 0·95 g, 74%; m.p. 105—106°) and proved to be 2-(3,4-*dimethoxyphenyl*)-4-*hydroxybut*-2-*enal* (17) (Found: C, 64·7; H, 6·45. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%), $\lambda_{max.}$ 224sh (4·18) and 284 nm (3·53), $\nu_{max.}$ 3500, 2750, 1680, and 1610 cm⁻¹, τ 0·34 (1H, s), 3·07 (1H, d, *J* 9 Hz), 3·24 (1H, t, *J* 7 Hz), 3·28 (1H, s), 3·32 (1H, d, *J* 9 Hz), 5·52 (2H, d, *J* 7 Hz), 6·12 (3H, s) and 6·15 (3H, s) (2 × OMe), and 7·62 (1H, s, OH), *m/e* 222 ($M^{+\cdot}$, 100%).

The compound of intermediate R_F (0·75) was identified as the aldehyde (15) (180 mg, 11%) (see below). The third compound (R_F 0·85) was 3-(3,4-*dimethoxyphenyl*)*furan* (18) (35 mg, 3%), obtained as needles, m.p. 72—74° [from light petroleum (b.p. 40—60°)] (Found: C, 70·4; H, 5·75. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·85%), $\lambda_{max.}$ 207 (4·50), 257 (4·02), and 290 nm (3·48), τ 2·36 (1H, m), 2·58 (1H, m), 2·86—3·26 (3H, m), 3·36 (1H, m), and 6·15 (6H, s); *m/e* 204 ($M^{+\cdot}$, 100%).

Benzyl 3-(3,4-*Dimethoxyphenyl*)-3-(2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*)-2,3-*epoxypropionate* (21).—The dioxolan (12) (6·3 g) was added, under nitrogen and at 0°, to a stirred suspension of potassium t-butoxide (6 g) in benzene (60 cm³). Benzyl chloroacetate [13] (7·2 g) was added dropwise, and the mixture was stirred for 15 h at room temperature, under nitrogen. Water was then added and the organic layer separated. The aqueous layer was extracted with ether, and the combined organic extracts were washed, dried, and evaporated. The residue was purified by column chromatography on silica. The fraction eluted with light petroleum (b.p. 40—60°)–ethyl acetate (5 : 1) crystallised from ether to afford the *benzyl ester* (21) (6 g, 61%), m.p. 87—89° (Found: C, 67·0; H, 6·5. $C_{23}H_{26}O_7$ requires 66·75; H, 6·3%), $\nu_{max.}$ 1750 and 1720 cm⁻¹, $\lambda_{max.}$ 234 (3·90) and 279 nm (3·43), τ 2·70—3·25 (8H, m, ArH), 5·1 (2H, s), 5·40 (1H, t, *J* 7 Hz), 5·93 (1H, s), 6·11 (2H, d, *J* 7 Hz), 6·17 (3H, s), 6·28 (3H, s), and 8·62 (6H, s, CMe_2); *m/e* 414 ($M^{+\cdot}$) and 91 (100%).

3-(3,4-*Dimethoxyphenyl*)-3-(2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*)-2,3-*epoxypropionic Acid* (16).—The benzyl ester (21) (3·1 g) in ethanol (150 cm³) was hydrogenated over palladium–carbon (0·2 g) (uptake 1 mol. equiv.). Filtration, evaporation, and crystallisation from n-hexane–acetone (5 : 1) gave the αβ-*epoxy-acid* (16) (2·3 g, 95%), m.p. 68—78° (decomp.) (Found: C, 59·4; H, 6·15. $C_{16}H_{20}O$ requires C, 59·3; H, 6·2%), $\nu_{max.}$ 1705 cm⁻¹, $\lambda_{max.}$ 235 (3·92) and 276 nm (3·46), *m/e* 324 ($M^{+\cdot}$), and 180 (100%). A solution of this acid in benzene decomposed during 4 days to yield 3-(3,4-dimethoxyphenyl)furan, m.p. 72—74°, identical with the foregoing specimen.

2-(3,4-*Dimethoxyphenyl*)-2-(2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*)*acetaldehyde* (15).—Equal parts of a solution of the epoxy-acid (16) (1·25 g) in acetone (reagent grade; 11 cm³) were sealed in five glass tubes (10 × 1 cm) and heated in steam at 100° for 3 h; >80% conversion into the aldehyde (15) was estimated by n.m.r. Evaporation left a residue which was used directly in preparative work. A sample was purified by chromatography on silica gel [benzene–acetonitrile (4 : 1)] to yield a mixture of stereoisomers which failed to crystallise; $\nu_{max.}$ 2720 and 1720 cm⁻¹, τ 0·18 (1H, *J* 2 Hz, CHO), 0·29 (1H, *J* 2 Hz, CHO, major stereoisomer), 3·10—3·35 (3H, m, ArH), 5·37 [1H, dd, *J* 7 and 7 Hz, $CH(O){\cdot}CH_2{\cdot}O$], 5·78 (1H, dd, *J* 7 and 8 Hz, $CH{\cdot}CH_aH_b{\cdot}O$), 6·00—6·40 (1H, $CH{\cdot}CH_aH_b{\cdot}O$), 6·14 (6H, s,

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2 × OMe), 6·38 (1H, dd, *J* 1 and 7 Hz, C*H*·CHO), and 8·68 (6H, s, CMe_2).

cis- *and* trans-*Tri*-O-*methylsequirin-C Acetonide* [(25) *and* (24)].—The aldehydes (22) and (23), prepared from the glycidic acid (16) (2·5 g), were dissolved in dry benzene. Under nitrogen, a solution of *p*-methoxybenzylidenetriphenylphosphorane [from *p*-methoxybenzyltriphenylphosphonium chloride (4·06 g) in benzene (20 cm^3) with butyllithium in n-hexane (7·68 cm^3; 1·12M)] was added slowly, until the red colour of the ylide persisted. The mixture was stirred for 15 min, and water (200 cm^3) was added. The benzene layer was separated and the aqueous layer extracted with ether. The combined organic extracts were washed, dried, and evaporated to a gum, which was separated by p.l.c. [benzene–acetonitrile (3 : 1)]. Among the products isolated were *p*-methoxytoluene (150 mg), 4,4′-dimethoxystilbene, m.p. 213—214°, and 3-(3,4-dimethoxyphenyl)-furan, all identified by comparison with authentic specimens. The major product was a mixture (1·48 g, 50% from the glycidic acid) of *cis*- and *trans*-tri-*O*-methylsequirin. C acetonide; the isomers were separated by p.l.c. [four elutions with light petroleum (b.p. 40—60°)–ethyl acetate (4 : 1)]. The trans-*acetonide* (24) (290 mg, 10%) had m.p. 68—70° (from n-hexane) (Found: C, 71·8; H, 7·45, $C_{23}H_{28}O_5$ requires C, 71·8; H, 7·25%), $\lambda_{max.}$ 265 (4·43) nm, τ 2·64 and 3·13 (4H, m, *J* 1 and 8 Hz, ArH), 3·09 (3H, s, ArH), 3·46 (1H, d, *J* 16 Hz, CH=C*H*Ar), 3·81 (1H, dd, *J* 7 and 16 Hz, C*H*=CHAr), 5·50 [1H, m, *J* 6, 7, and 7 Hz, –C*H*(O)–], 5·89 (1H, dd, *J* 6 and 8 Hz, O·CH_aH_b), 6·10 (3H, s), 6·13 (3H, s), and 6·21 (3H, s) (3 × OMe), 6·21 (1H, O·CH_aH_b), 6·44 (1H, t, *J* 7 Hz, C*H*–CH=CH), and 8·59 (3H, s) and 8·64 (3H, s) (CMe_2); *m/e* 384 ($M^{+\cdot}$) and 283 (100%). The cis-*acetonide* (25) (1·15 g) was non-crystalline (single spot on t.l.c.) (Found: C, 71·8; H, 7·45%), τ 2·74 (2H, d), 3·30 (2H, d), 3·30 (3H, s) 3·68 (1H, d, *J* 10 Hz), 4·11 (1H-q, *J* 7 and 10 Hz), 5·81 (1H, q, *J* 7 Hz), 6·00—6·50 (2H, m), 6·24 (3H, s), 6·30 (6H, s), 6·64 (1H, t, *J* 7 Hz), 8·60 (3H, s), and 8·68 (3H, s).

A final product, also non-crystalline, was probably 3-(3,4-dimethoxyphenyl)-5-(4-methoxyphenyl)penta-3,5-dien-1-ol (26), τ 2·60—3·80 (9H, ArH and CH=CH), 4·11 (1H, t, *J* 7 Hz, C=C*H*·CH_2), 5·77 (2H, d, *J* 7 Hz, CH_2·OH), 6·21, 6·27, 6·31 (each 3H, s, OMe), and 7·95 (1H, s, OH).

(±)-*Tri*-O-*methylsequirin*-C (8).—The *trans*-acetonide (24) (290 mg) was stirred in methanol (50 cm^3) and water (1 cm^3) with concentrated hydrochloric acid (0·25 cm^3) for 30 min. Saturated aqueous sodium hydrogen carbonate (5 cm^3) and water (200 cm^3) were added, and the mixture was extracted with ether. The dried extracts were evaporated to yield (±)-*tri*-O-*methylsequirin-C* (260 mg, 99%), m.p. 117—119° (from ether–n-hexane) (Found: C, 69·7; H, 7·2. $C_{20}H_{24}O_5$ requires C, 69·7; H, 7·0%). It was spectroscopically closely similar to the trimethyl ether, m.p. 121—122°, of natural sequirin-C. Acetylation with pyridine–acetic anhydride at room temperature yielded the non-crystalline (±)-*tri*-O-*methylsequirin-C diacetate* (Found: C, 67·1; H, 6·3. $C_{24}H_{28}O_7$ requires C, 67·3; H, 6·5%), $\nu_{max.}$ 1735 cm^{-1}.

(±)-cis-*Tri*-O-*methylsequirin-C*.—The *cis*-acetonide (25) (500 mg) was hydrolysed in a similar fashion to the *trans*-isomer, to yield cis-*tri*-O-*methylsequirin-C* (430 mg, 96%), m.p. 132—134° (from ether) (Found: C, 69·9; H, 7·05%), $\lambda_{max.}$ 264 nm (4·40), *m/e* 344 (M^+) and 283 (100%). It formed a non-crystalline *diacetate* (Found: C, 67·2; H, 6·5%).

(±)-*Tri*-O-*methylsequirin-B*.—Synthetic tri-*O*-methylsequirin-C (*cis* or *trans*; 150 mg) was refluxed in methanol (20 cm^3) with concentrated hydrochloric acid (0·25 cm^3) for 90 h. The mixture was poured into water and extracted with ether; the dried extracts, on evaporation, yielded (±)-*tri*-O-*methylsequirin-B* (134 mg, 90%), m.p. 121—123° (from methanol) (Found: C, 69·75; H, 7·15%), with i.r., u.v., and n.m.r. spectra identical with those of the trimethyl ether of natural sequirin-B. It formed a (±)-*monoacetate*, m.p. 133—135°, on treatment with acetic anhydride–pyridine (Found: C, 68·65; H, 6·7. $C_{22}H_{26}O_6$ requires C, 68·45; H, 6·75%), $\nu_{max.}$ 1720 cm^{-1}, spectroscopically and chromatographically identical with the corresponding derivative of the natural phenol.

1-(3,4-*Dimethoxyphenyl*)-1-(2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*)-3-(4-*methoxyphenyl*)-*prop*-2-*yn*-1-*ol* (28).—A solution of the dioxolan (12) (8 g) in dry tetrahydrofuran (10 cm^3) was added slowly to sodium *p*-methoxyphenylacetylide in liquid ammonia [from *p*-methoxyphenylacetylene (5·24 g) and sodium (1 g) in the usual way], and the mixture was stirred for 12 h. Solid ammonium chloride (4 g) was added, and the ammonia was evaporated off. The mixture was partitioned between water (200 cm^3) and ether (200 cm^3), and the aqueous layer was further extracted with ether. The organic extracts were dried and evaporated. Column chromatography on silica gel separated starting materials, and the products were separated by p.l.c. [benzene–ethyl acetate (4 : 1)]. The major product was the *acetylenic-alcohol* (28) (6·9 g, 58%), which crystallised from n-hexane as a mixture of diastereoisomers, m.p. 93—95° (Found: C, 69·15; H, 6·7. $C_{23}H_{26}O_6$ requires C, 69·3; H, 6·55%), $\lambda_{max.}$ 255 (4·44), 282infl (3·77), and 293 nm (3·12), $\nu_{max.}$ (KBr) 3460 and 2270 cm^{-1}, τ (CCl_4) 2·15 and 3·25 (both 2H, d, 4-MeO·C$_6H_4$), 2·77 and 3·38 [3H, m, $(MeO)_2C_6H_3$], 5·78 (1H, t, *J* 7 Hz), 5·99 (1H, d, *J* 9 Hz), 6·10—6·30 (1H, m). 6·22 (3H, s) and 6·25 (6H, s) (2 × OMe), and 8·55 and 8·68 (each 3H, s, CMe); *m/e* 398 ($M^{+\cdot}$) and 297 (100%). A second product (R_F 0·65; 86 mg) crystallised from light petroleum (b.p. 40—60°) with m.p. 91—93°, and proved to be 4-(3,4-*dimethoxyphenyl*)-2-*methylbut*-3-*yn*-2-*ol* (Found: C, 70·85 H, 7·20. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%), identical with an authentic specimen formed from addition of *p*-methoxyphenylacetylene to acetone.

1-(3,4-*Dimethoxyphenyl*)-1-(2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*)-3-(4-*methoxyphenyl*)*prop*-2-*en*-1-*ol* (29).—The alkynyl alcohol (28) (1 g) in dry tetrahydrofuran (5 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (0·2 g) in dry tetrahydrofuran; the mixture was kept at 0° during the addition. After 10 h at room temperature, the excess of metal hydride was destroyed and an excess of water was added. The altered product was extracted with ether, and the extracts were washed, dried, and evaporated, to yield the *alcohol* (29) (990 mg, 99%), as a non-crystalline mixture of diastereoisomers (Found: C, 69·35; H, 7·25. $C_{23}H_{28}O_6$ requires C, 69·1; H, 7·05%), τ (CCl_4) 2·83—3·61 (7H, m, ArH), 3·36 (1H, d, *J* 16 Hz), 4·00 (1H, d, *J* 16 Hz), 5·63 (1H, t, *J* 7 Hz), 6·24 (2H, d, *J* 7 Hz), 6·39, 6·42, and 6·44 (each 3H, s), and 8·79 (6H, s, CMe_2).

(±)-*Tri*-O-*methylsequirin-C Acetonide* (24).—The alcohol (29) (0·4 g) was dissolved in dry tetrahydrofuran (6 cm^3). Pyridine–sulphur trioxide complex (0·35 g, 2 mol. equiv.) [prepared by adding chlorosulphonic acid to pyridine in carbon tetrachloride] was added, at 0°, and the mixture was kept at 0° for 18 h. Lithium aluminium hydride

(0·228 g, 6 mol. equiv.) in dry tetrahydrofuran (6 cm³) was added at 0°. The mixture was stirred for 1 h at 0°, and for 8 h at room temperature. After addition of water, the mixture was extracted with ether, and the extracts were washed, dried, and evaporated. The residue was separated by p.l.c. [elution with benzene–acetonitrile (3 : 1)]. The band with R_F 0·8 gave, on extraction, (±)-tri-*O*-methylsequirin-C acetonide (125 mg, 33%), m.p. 69—70° (from n-hexane), identical with the foregoing synthetic product.

Dehydration of the Alcohol (29).—The alcohol (29) (0·95 g) in dry pyridine (40 cm³) was refluxed with toluene-*p*-sulphonyl chloride (0·55 g) for 2·5 h. After dilution with water the mixture was extracted with ether. The extracts, after washing, drying, and evaporation, gave a gum containing two stereoisomers (5 : 1) of the diene (33). The more abundant (1E,3Z)-*isomer* (33) crystallised from aqueous methanol with m.p. 125—127° (Found: C, 72·05; H, 6·6. $C_{23}H_{26}O_5$ requires C, 72·25; H, 6·8%), $\lambda_{max.}$ 228sh (4·25) and 308 nm (4·49), τ 2·70 (1H, d, *J* 16 Hz), 2·66 (1H, d) and 3·18 (1H, d) (both *J* 9 Hz, MeO·C_6H_4), 3·06—3·26 [3H, $(MeO)_2C_6H_3$], 4·01 (1H, d, *J* 16 Hz), 5·57 (2H, s), 6·10, 6·15, and 6·23 (each 3H, s, 3 × OMe), and 8·44 (6H, s, CMe_2); *m/e* 382 ($M^{+\cdot}$), and 265 (100%).

Cyclisation of the Acetonide (33) *in Acid.*—(*a*) The acetonide (33) (240 mg) in benzene (25 cm³) and ethylene glycol (5 cm³) was refluxed with toluene-*p*-sulphonic acid (250 mg) for 12 h. The product was washed with water, dried, and evaporated. Three products, R_F 0·2, 0·4, and 0·75 [benzene–acetone (8 : 1)] were indicated by t.l.c. The major component, R_F 0·4, isolated by p.l.c., was 5-(3,4-*dimethoxyphenyl*)-3-(4-*methoxyphenyl*)*cyclopent*-2-*enone* (35) (150 mg), m.p. 159—161° (from ethanol) (Found: C, 74·55; H, 6·3. $C_{20}H_{20}O_4$ requires C, 74·15; H, 6·15%), *m/e* 324 ($M^{+\cdot}$). The component of R_F 0·2 was isolated only in small quantity (5 mg); the other product (R_F 0·75) was chromatographically the same as the cyclopentenone (34) [see (*b*)].

(*b*) The acetonide (200 mg) was refluxed for 12 h in water (5 cm³), methanol (20 cm³), and 4N-hydrochloric acid (4 cm³). The mixture was poured into aqueous sodium hydrogen carbonate and extracted with ether. The extracts, on washing, drying, and evaporation gave a gum, purified by p.l.c. The major component (R_F 0·75) was identified as 2-(3,4-*dimethoxyphenyl*)-4-(4-*methoxyphenyl*)-*cyclopent*-2-*enone* (34) (Found: C, 74·35; H, 6·25%).

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