Synthetic Routes to the Piperolides, Fadyenolides, Epoxypiperolides, and Related Compounds

Andrew Pelter, Redha I. H. Al-Bayati, Miqdad T. Ayoub, Wynn Lewis, and Pushpa Pardasani
Department of Chemistry, University College of Swansea, Singleton Park, Swansea SA2 8PP
Rudolf Hansel
Department of Pharmacognosy and Phytochemistry, Free University, Konigin-Luise Str., 2–4, D–1000, Berlin 33

Syntheses of the piperolides, the fadyenolides, epoxypiperolide, and related compounds are described. (±)-Narthogenin is also efficiently produced.

From the Mexican plant *Piper sanctum*[1] we have previously isolated and characterised piperolide (**1**),[1] methylenedioxypiperolide (**2**),[1] (+)-(7*S*,8*S*)-epoxypiperolide (**3**),[2–4] (−)-*erythro*-7,8-dihydro-7,8-dihydroxypiperolide (**4**),[5] as well as a possible photoisomerisation product (5*E*)-piperolide (**5**),[6,7] From *Piper fadyenolii*, indigenous to Jamaica, we have isolated and characterised similar butenolides, the fadyenolides (**6**) and (**7**).[8]

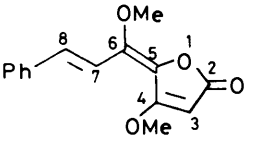
These compounds are of particular interest for two reasons. First they are unique tetronates (derivatives of 4-hydroxybut-3-enolides) derived from higher plants rather than from fungal, microbial, or marine sources.[6,9–12] Secondly some of them, as well as certain of our synthetic products, have strong sedative as well as other most interesting physiological properties.[13]

It is tempting to speculate on a New World mutation in *Piper* species that leads from the usual pyrone derivatives such as kawain (**8a**)[14] and methysticin (**8b**)[14] produced by Old World *Piper* species, to butenolides such as piperolide by an oxidation and rearrangement process similar to that shown in equation (1). It was indeed this speculation that led us to investigate *Piper fadyenolii*[8] and to re-examine *P. sanctum* from which we were able to isolate and characterise the likely precursor (+)-(5*S*,6*S*)-5-acetoxy-6-methoxykawain (**9**),[15,16] as well as the related 4,5-dimethoxy-6-(3′,4′-methylenedioxystyryl)-2-pyrone (**10**).[17] We were able to provide analogies to the postulated biosynthetic processes as instanced in equations (2) and (3).[18,19]

Thus either *cis*- or *trans*-5-hydroxykawain (**11**)[19] yield the same mixture of *erythro*- and *threo*-butenolides (**12**) in low yields, the main product being 6-dimethoxypiperolide (**13**). This ready elimination (*vide infra*) makes rather puzzling the report[20] that compound (**14**), readily available from compound (**12**),[18] can be dehydrogenated in high yield to give piperolide (**1**). The dihydro-5-hydroxykawains (**15**) rearrange similarly to butenolides (**16**) [equation (3)].

Further it seemed possible the epoxypiperolide (**3**) and the related dihydroxypiperolide (**4**) could arise by *in vivo* oxidation of piperolide (**1**). However, *m*-chloroperbenzoic acid (MCPBA) reacts with piperolide to yield only the pyrandione (**17**), which with base rearranges to the butenolide (**18**)[21] (Scheme 1). Osmium tetraoxide reacts with piperolide (**1**) to give a low yield of (±)-*threo*-7,8-dihydro-7,8-dihydroxypiperolide (**19**), which is also furnished by hydrolysis of epoxypiperolide,[5] as well as a small quantity of compound (**4**). Unfortunately, the production of diol (**4**) from epoxypiperolide of known absolute configuration does not suffice to define its absolute configuration, as inversion may occur either at the benzylic C-8 or allylic C-7 atoms.

Of course, these interesting interconversions are all based on kawain or the piperolides and do not serve as the basis for efficient syntheses adapted to providing stereoisomers and analogues of the natural products useful for the exploration of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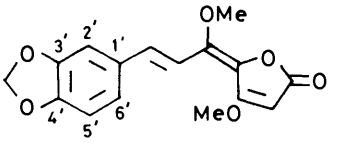
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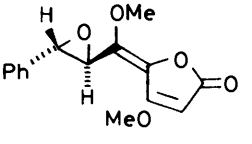
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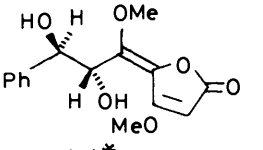
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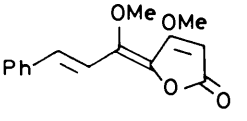
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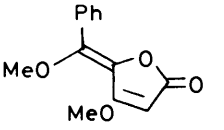
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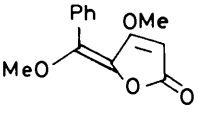
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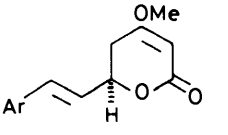
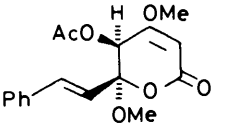
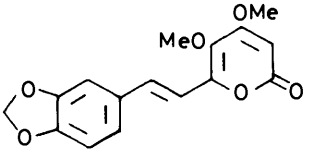

(8) a; Ar = Ph

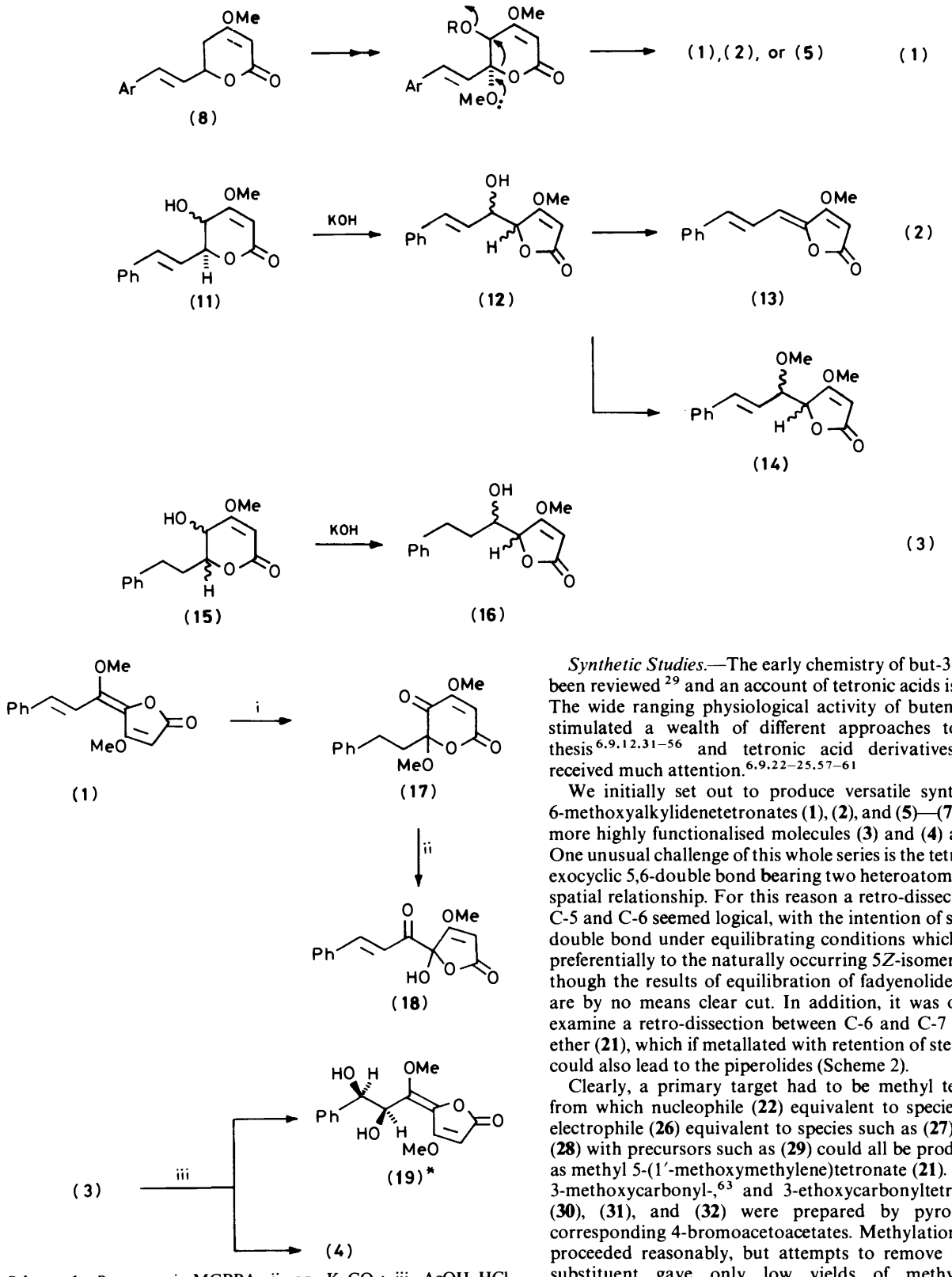
b; Ar =


(9)


(10)

* Relative configuration shown.

structure–activity relationships. Preliminary accounts of our work towards the solution of the synthesis of these small but highly functionalised molecules have appeared[22–25] and during our studies two other groups have carried out a synthesis of piperolide by routes distinct from each other and from our own.[20,26] The first is based on Pollet and Gelin's approach to



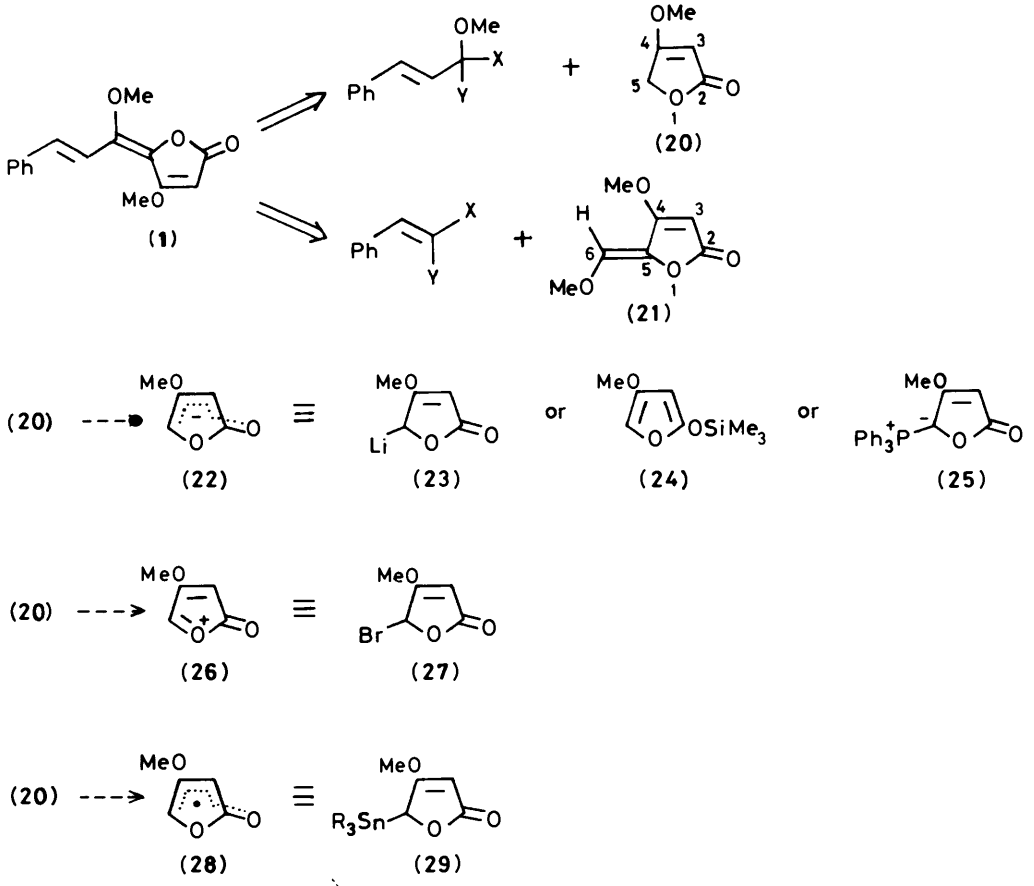
Scheme 1. *Reagents:* i, MCPBA; ii, aq. K_2CO_3; iii, AcOH–HCl. * Relative configuration

tetronates,[27] the final step being a dehydrogenation of 5,6-dihydropiperolide, whilst the other is an adaption of Mulholland's[28] approach, and involves the much safer dehydrogenation of 7,8-dihydropiperolide, though one prior step proceeds in very low yield.

Synthetic Studies.—The early chemistry of but-3-enolides has been reviewed[29] and an account of tetronic acids is available.[30] The wide ranging physiological activity of butenolides[30] has stimulated a wealth of different approaches to their synthesis[6,9,12,31–56] and tetronic acid derivatives have also received much attention.[6,9,22–25,57–61]

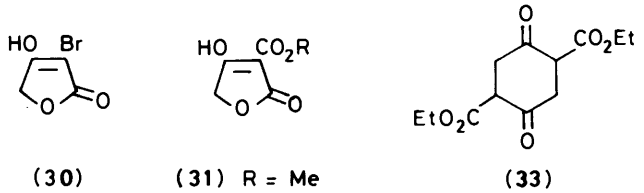
We initially set out to produce versatile syntheses of the 6-methoxyalkylidenetetronates (**1**), (**2**), and (**5**)—(**7**) with the yet more highly functionalised molecules (**3**) and (**4**) also in mind. One unusual challenge of this whole series is the tetrasubstituted exocyclic 5,6-double bond bearing two heteroatoms in a specific spatial relationship. For this reason a retro-dissection between C-5 and C-6 seemed logical, with the intention of setting up the double bond under equilibrating conditions which would lead preferentially to the naturally occurring 5*Z*-isomers (**1**) and (**2**), though the results of equilibration of fadyenolides (**6**) and (**7**) are by no means clear cut. In addition, it was of interest to examine a retro-dissection between C-6 and C-7 to give vinyl ether (**21**), which if metallated with retention of stereochemistry could also lead to the piperolides (Scheme 2).

Clearly, a primary target had to be methyl tetronate (**20**) from which nucleophile (**22**) equivalent to species (**23**)—(**25**), electrophile (**26**) equivalent to species such as (**27**), and radical (**28**) with precursors such as (**29**) could all be produced, as well as methyl 5-(1′-methoxymethylene)tetronate (**21**). 3-Bromo-,[62] 3-methoxycarbonyl-,[63] and 3-ethoxycarbonyltetronic acids[64] (**30**), (**31**), and (**32**) were prepared by pyrolysis of the corresponding 4-bromoacetoacetates. Methylation of acid (**30**) proceeded reasonably, but attempts to remove the 3-bromo substituent gave only low yields of methyl tetronate. Methylation of compounds (**31**) and (**32**) gave mixtures of methylated products, and it was clear that species (**30**)—(**32**) were not suitable for large-scale preparation of methyl tetronate (**20**). The direct pyrolysis of ethyl 4-bromoacetoacetate either alone or in the presence of acid did not yield tetronic acid, presumably due to the predominance of the enol with the hydroxy and ethoxycarbonyl groups *trans* to each other. In the



Scheme 2.

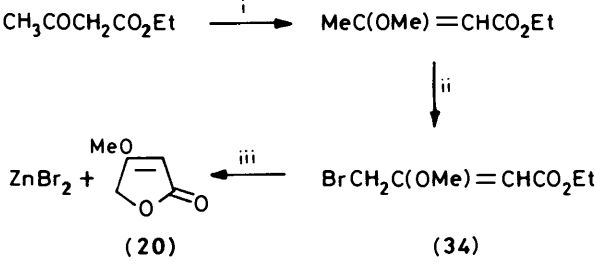
2-substituted acetoacetates the other isomer will predominate. With aqueous potassium carbonate at room temperature in the presence of 18-crown-6 for 20 h, only compound (**33**) was obtained, and in our hands the reported cyclisation of ethyl 4-bromoacetate with potassium hydroxide was unsuitable for large-scale work.



(**30**) (**31**) R = Me (**32**) R = Et (**33**)

However, we found that zinc bromide cyclisation of ethyl 4-bromo-3-methoxybut-2-enoate (**34**),* itself a commercial intermediate used for the production of kawain [63] and available in 95% yield from ethyl acetoacetate, yielded crystalline methyl tetronate (**20**), in 75% isolated yield (Scheme 3). Hence methyl tetronate is a readily available synthon, which can be produced, with ease, on the kilogram scale, and which is suitable for the investigation of the synthesis of substituted tetronates. A very similar methodology has recently been used for the production of 4-alkoxy-3,4-dihydropyrrol-2-ones.[66]

Synthesis of Precursors (**23**)—(**25**), (**27**), *and Related Compounds.*—Methyl tetronate with lithium di-isopropylamide



(**20**) (**34**)

Scheme 3. *Reagents and conditions:* i, $CH(OMe)_3$, H^+; ii, NBS; iii, $ZnBr_2$–xylene, heat

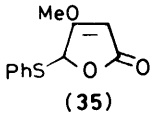
(LDA) in tetrahydrofuran–hexamethylphosphoramide (THF–HMPT) at −78 °C gave a species that we formulated as (**23**), since on quenching with deuterium oxide the product incorporated deuterium at C-5 to the extent of 77%. We used these conditions in our early experiments but later changed to the use of n-butyl-lithium in diethyl ether or THF at −78 °C, which gave almost quantitative incorporation of deuterium at C-5.

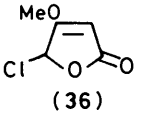
When compound (**23**) is treated with chloro(trimethyl)silane, the water-sensitive furan (**24**) was produced and isolated in 84% yield [from (**20**)] by distillation after an anhydrous work-up. The dimethyl-t-butylsilyl analogue is considerably more water-stable, but was produced in only 16% yield, whilst we were unable to make the methyldiphenylsilyl ether. We therefore utilised compound (**24**) in all subsequent work, despite its lability.

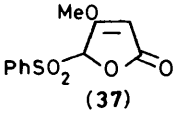
Direct bromination of methyl tetronate (**20**) with NBS in tetrachloromethane with irradiation gave a 94% yield of bromide (**27**) as a rather unstable pale yellow oil, in contrast to

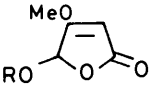
* We thank Klinge Co. Ltd. for gifts of this material.

the previous report[67] that a similar bromination gave only 9% of the 5-bromo derivative, the main product being methyl 3-bromotetronate. A better general method of introducing heteroatoms into the 5-position of compound (**20**) however is by low-temperature reaction of the 5-lithio derivative (**23**). Thus reaction of compound (**23**) with bromine gave a 97% yield of bromide (**27**), with diphenyl disulphide gave a 90% yield of methyl 5-(phenylthio)tetronate (**35**), and with benzenesulphonyl chloride gave the 5-chloro derivative (**36**) in 92% yield. Oxidation of sulphide (**35**) with MCPBA gave methyl 5-(phenylsulphonyl)tetronate (**37**) in 93% yield. Although bromide (**27**) is not particularly stable, it required one week at room temperature in contact with water to yield methyl 5-hydroxytetronate (**38**) in 82% yield. Compound (**38**) has the trivial name of narthogenin and is the aglycone of the antibiotic narthecide.[68,69] The most efficient, quick route to this substance involved hydrolysis with water and neutral silica, which proceeded in 10 h at reflux. Narthogenin was thus available in quantity for biological investigation.[67] A series of alkoxy derivatives (**39**)—(**42**) was prepared from bromide (**27**) by reaction with the corresponding lithium salts. It should be noted that the reaction of the trimethylsilyloxyfuran (**24**) with bromine or *N*-bromosuccinimide (NBS) gave bromide (**27**) in *ca.* 95% yield, and with benzenesulphenyl chloride gave sulphide (**35**) in 83% yield without catalysis. With lead tetra-acetate, compound (**24**) gave the 5-acetoxy derivative (**43**), in an interesting reaction.[9,70,71]

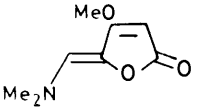

(**35**)

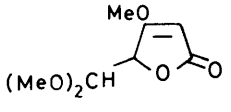

(**36**)

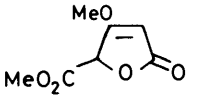

(**37**)



(**38**) R = H (**41**) R = Ph
(**39**) R = Me (**42**) R = $CH_2CH{=}CH_2$
(**40**) R = Bu^n (**43**) R = Ac


(**44**)


(**45**)


(**46**)

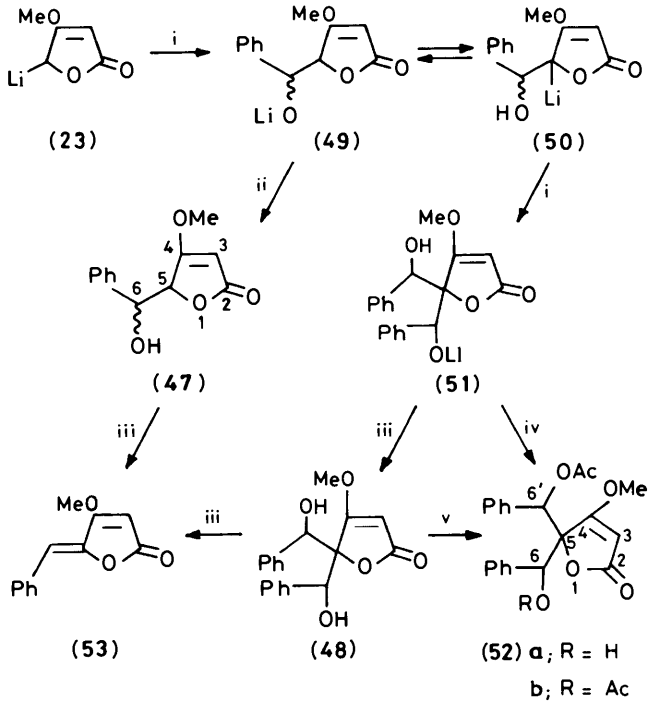
Treatment of bromide (**27**) with triphenylphosphine under a variety of conditions gave rise to only dark oils which, by analogy with literature procedures,[34] should have yielded ylide (**25**) on base treatment. However, no evidence for ylide formation was found on reaction with aldehydes.

Attempts to make compound (**21**) by reaction of compound (**23**) with methyl orthoformate were unsuccessful, as were reactions of methyl tetronate (**20**) with methyl orthoformate activated by titanium tetrachloride and other acids. For this reason we introduced the 'double activation' method[24] in which a solution of methyl 5-lithiotetronate (**23**) was added at −78 °C *via* a cannula to slurries of alkoxy-stabilised carbocations produced by the action of Lewis acids on acetals, ketals, and orthoesters, also at −78 °C. With trimethyl orthoformate, the dimethoxy compound (**45**) was obtained in 85% yield. This is a general method that will be utilised later [see equations (5) and (6)]. In only one simple case did the reaction fail to give the required methoxy compounds, and that was with tetramethyl orthocarbonate, when the ester (**46**) was produced in 81% yield even on anhydrous work-up. Furthermore, zinc bromide-catalysed reaction of compound (**24**) with methyl orthoformate gave acetal (**45**) in 92% yield, and of compound (**24**) with tetramethyl orthocarbonate gave ester (**46**).

Elimination of methanol from acetal (**45**) proved troublesome, but low-temperature reaction with t-butyl-lithium gave compound (**21**) in 82% yield. Use of acid conditions led to extensive degradation. Reaction of methyl tetronate (**20**) directly with bis(dimethylamino)methoxymethane[72] led quantitatively to the enamine (**44**) but conversion of compound (**44**) into the ether (**21**) was not efficient. The most direct and the cheapest method for the production of the vinyl ether (**21**) was the reaction of methyl formate with methyl tetronate (**20**), followed by *in situ* methylation of the intermediate salt. Despite this, our investigation showed that carbon–carbon bonds could be efficiently formed between C-5 of methyl tetronate (**20**) and an electrophile by utilisation either of the salt (**23**) or silyl ether (**24**) as synthons.

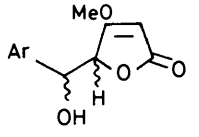
Investigations of Carbon–Carbon Bond Formation involving Compounds (**27**), (**23**), *and* (**24**).—Attempts to form carbon–carbon bonds between methyl tetronate in the cationic form (**27**) were failures, in contrast to the ready reactions of bromide (**27**) with oxyanions and thioanions. Thus reaction with 2-lithio-2-phenethyl-1,3-dithiolane merely gave back, on work-up, the dithiolane plus intractable polymer. Attempts to alkylate the bromide (**27**) with alkyl-lithiums, phenyl-lithium, lithium dimethylcuprate, lithium dibutylcuprate, and ethylmagnesium bromide gave back methyl tetronate (**20**) as the only recognisable product and this approach was abandoned.

The reactions of compound (**23**) with cinnamaldehyde (and some substituted cinnamaldehydes) were complex, giving rise to a variety of 1,4- as well as 1,2-addition products, and the desired allylic alcohol (**12**) was never isolated pure. Equally, the reactions with cinnamaldehyde equivalents such as 3-phenylthio- and 3-ethoxy-dihydrocinnamaldehyde were extremely complex. The reaction with 1 mol equiv. of benzaldehyde was encouraging, as the desired product (**47**) with a C-5, C-6 linkage was isolated as an *erythro–threo* mixture (Scheme 4). The *threo*-isomer is more polar and crystallises out and its structure was established by *X*-ray analysis.[6] However, compound (**47**) was always accompanied by the disubstituted tetronate (**48**). When benzaldehyde was used in excess, then diol (**48**) was the only product, suggesting that use of a dialdehyde may lead to spiroannelation. No matter in what order the reagents are mixed, compound (**48**) is always produced. *However, when benzaldehyde mixed with* 1 *mol equiv. of water was added to the salt* (**23**), *then only the desired mono-ol* (**47**) *resulted, in excellent yield*! This seemingly paradoxical procedure was suggested by the analysis shown in Scheme 4 in which diol (**48**) comes from the mono-oxyanion (**51**) [readily trapped as the monoacetate (**52a**) by use of acetic anhydride at low temperature], in turn derived from the carbocation (**50**), which is produced in a slow isomerisation from the initial oxyanion (**49**). It is known that the reaction of organometallics with water may be slow compared with their reactions with aldehydes or ketones, though generally this is treated as a nuisance in aqueous work-up of reactions of organometallics.[73] We argued that reaction of the salt (**23**) with benzaldehyde to give the alkoxide (**49**) would be faster than its reaction with water, and that compound (**49**) would be discharged by the water present *prior* to its isomerisation to (**50**) (Scheme 4). The argument is fallible as it depends on the comparison of unknown rate-constants, but *nevertheless it may be useful and general for the control of organometallic reactions.* For many aldehydes it was not necessary to add water (see Experimental section).

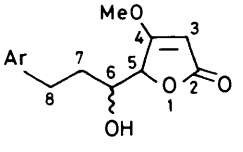


Scheme 4. *Reagents:* i, PhCHO; ii, water; iii, H_2SO_4; iv, Ac_2O; v, Ac_2O–pyridine

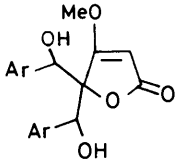
By use of the appropriate aldehydes, compounds (**16**), and (**54**)—(**61**) were made and characterised. The dihydrocinnamaldehydes were made from the corresponding cinnamaldehydes by complete reduction to the saturated alcohol followed by oxidation with chromium trioxide in pyridine–dichloromethane.



(**54**) Ar = 4-MeOC_6H_4
(**55**) Ar = 3,4-$(MeO)_2C_6H_3$
(**56**) Ar = 3,4,5-$(MeO)_3C_6H_2$
(**57**) Ar = 3,4-$(OCH_2O)C_6H_3$

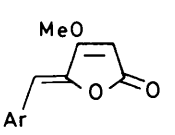


(**16**) Ar = Ph
(**58**) Ar = 4-MeOC_6H_4
(**59**) Ar = 3,4-$(MeO)_2C_6H_3$
(**60**) Ar = 3,4-$(OCH_2O)C_6H_3$

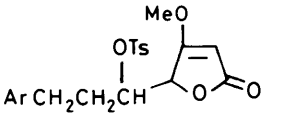


(**61**) Ar = 3,4-$(OCH_2O)C_6H_3$

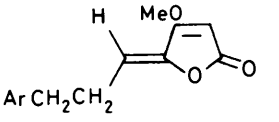
Dehydration of alcohols (**47**) or (**48**) to alkene (**53**) was accomplished with conc. sulphuric acid. This was unsuitable for compounds (**54**)—(**57**) which were converted to their methanesulphonates, which without isolation gave alkenes (**62**)—(**65**) on reaction with aqueous potassium acetate. Compounds (**16**) and (**57**)—(**60**) were converted into their toluene-*p*-sulphonates (**66**)—(**69**), which on reflux with pyridine gave the unsaturated compounds (**70**)—(**73**).



(**62**) Ar = 4-MeOC_6H_4
(**63**) Ar = 3,4-$(MeO)_2C_6H_3$
(**64**) Ar = 3,4,5-$(MeO)_3C_6H_2$
(**65**) Ar = 3,4-$(OCH_2O)C_6H_3$

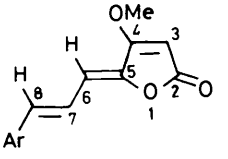


(**66**) Ar = Ph
(**67**) Ar = 4-MeOC_6H_4
(**68**) Ar = 3,4-$(MeO)_2C_6H_3$
(**69**) Ar = 3,4-$(OCH_2O)C_6H_3$



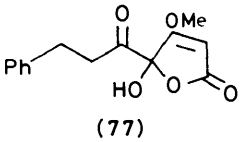
(**70**) Ar = Ph
(**71**) Ar = 4-MeOC_6H_4
(**72**) Ar = 3,4-$(MeO)_2C_6H_3$
(**73**) Ar = 3,4-$(OCH_2O)C_6H_3$

The structure of compound (**62**) was established by *X*-ray crystallography,[9] and a similar stereochemistry was assigned to compounds (**63**)—(**65**) by the similarity of the u.v. spectra and by the n.O.e. effects between the protons of the 4-methoxy group and the ethylidene proton on C-6. Excellent yields of 6-demethoxypiperolide (**13**) and its analogues (**74**)—(**76**) were obtained by reaction of compounds (**70**)—(**73**) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene, the structure of compound (**13**) being established by *X*-ray investigations.[6] No stereoisomers were observed as products of these reactions, nor in any of the condensations of compound (**23**) with aldehydes were any products of addition to C-3 observed.

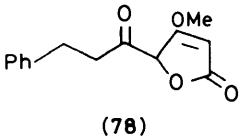


(**13**) Ar = Ph
(**74**) Ar = 4-MeOC_6H_4
(**75**) Ar = 3,4-$(MeO)_2C_6H_3$
(**76**) Ar = 3,4-$(OCH_2O)C_6H_3$

To obtain the piperolides or fadyenolides, compounds of higher oxidation level than the alcohols (**16**) or (**47**) are required. However, mild methods of oxidation of compound (**58**), such as chromium trioxide in pyridine or oxalyl chloride in dimethyl sulphoxide (DMSO), left the alcohol untouched or, as with aluminium t-butoxide–acetone on (**16**), gave alkene (**70**). More vigorous methods such as chromium trioxide in acetic acid yielded ketone (**77**), similar to compound (**18**), plus 3-phenylpropionaldehyde in rather low yields, but none of the required ketone (**78**).

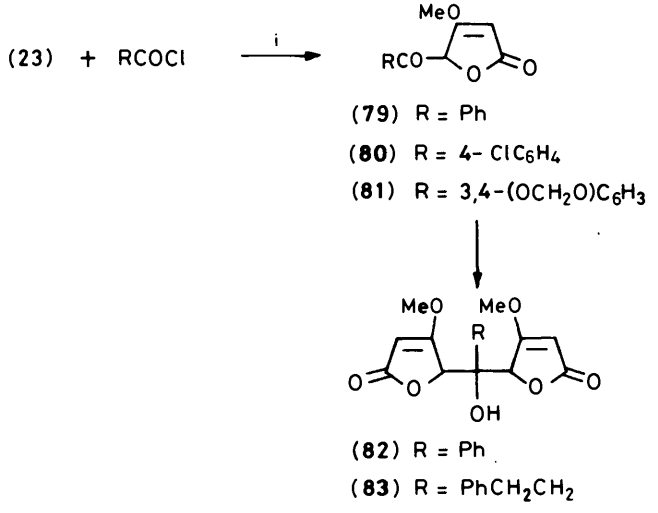


(**77**)



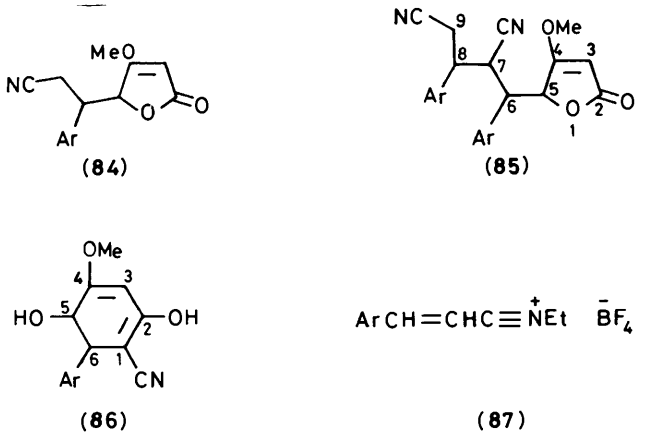
(**78**)

The reactions of acid chlorides with the lithium derivative (**23**) gave either the mono- or di-substituted products (Scheme 5), depending on the stoicheiometry and conditions used. The disubstituted products show very interesting sedative action.[74]



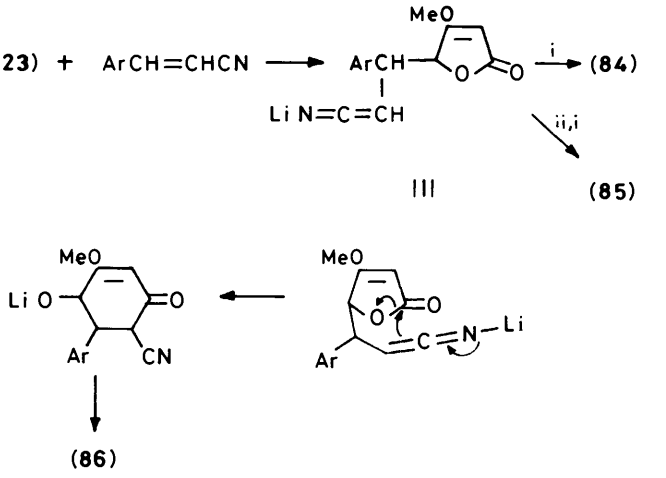
Scheme 5. *Reagents and conditions:* i, THF, −78 °C

Disappointingly, the simple ketone (**78**), an obvious precursor to piperolide, could not be produced in this way, despite repeated attempts. Possibly the ketene is made rapidly under the conditions used and then dimerises rather than condenses with compound (**23**). In the presence of an excess of compound (**23**) a 10% yield of the compound (**83**) was isolated.

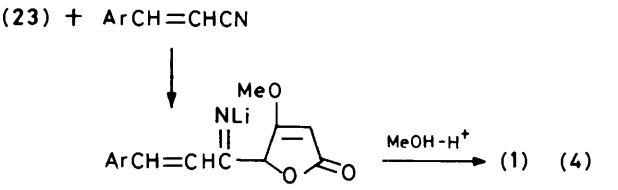


We therefore turned to the condensation of compound (**23**) with nitriles. However, use of either acetonitrile or benzonitrile (or *NN*-dimethylcinnamamide) gave rise to an uncharacterised, possibly polymeric, self-condensation product of compound (**20**). With 4-methoxycinnamonitrile, only 1,4-condensation products (**84**)—(**86**) were observed. Compound (**84**) (as a mixture of *erythro*, *threo* isomers) was the sole isolated product when nitrilium salt (**87**) (produced by the action of triethyloxonium tetrafluoroborate on the nitrile[75]) was treated with compound (**23**). Possible routes to compounds (**84**)—(**86**) are shown in Scheme 6.

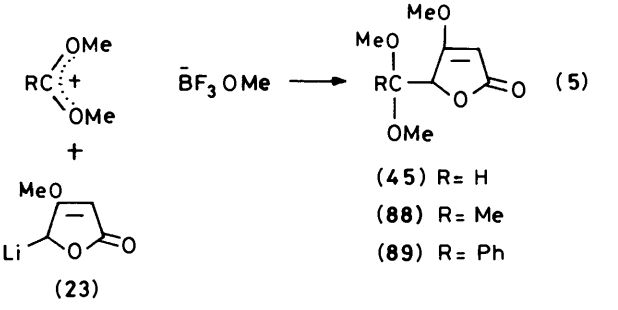
In no case were we able to carry out the projected 1,2-addition process shown in equation (**4**), and we therefore abandoned the approach *via* αβ-unsaturated nitriles.

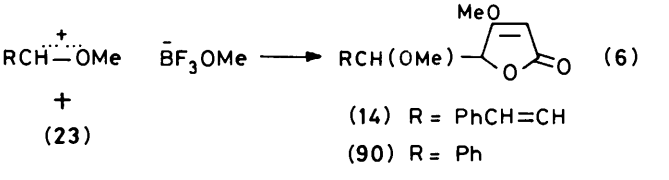


Scheme 6. *Reagents:* i, water; ii, ArCH=CHCN, then water

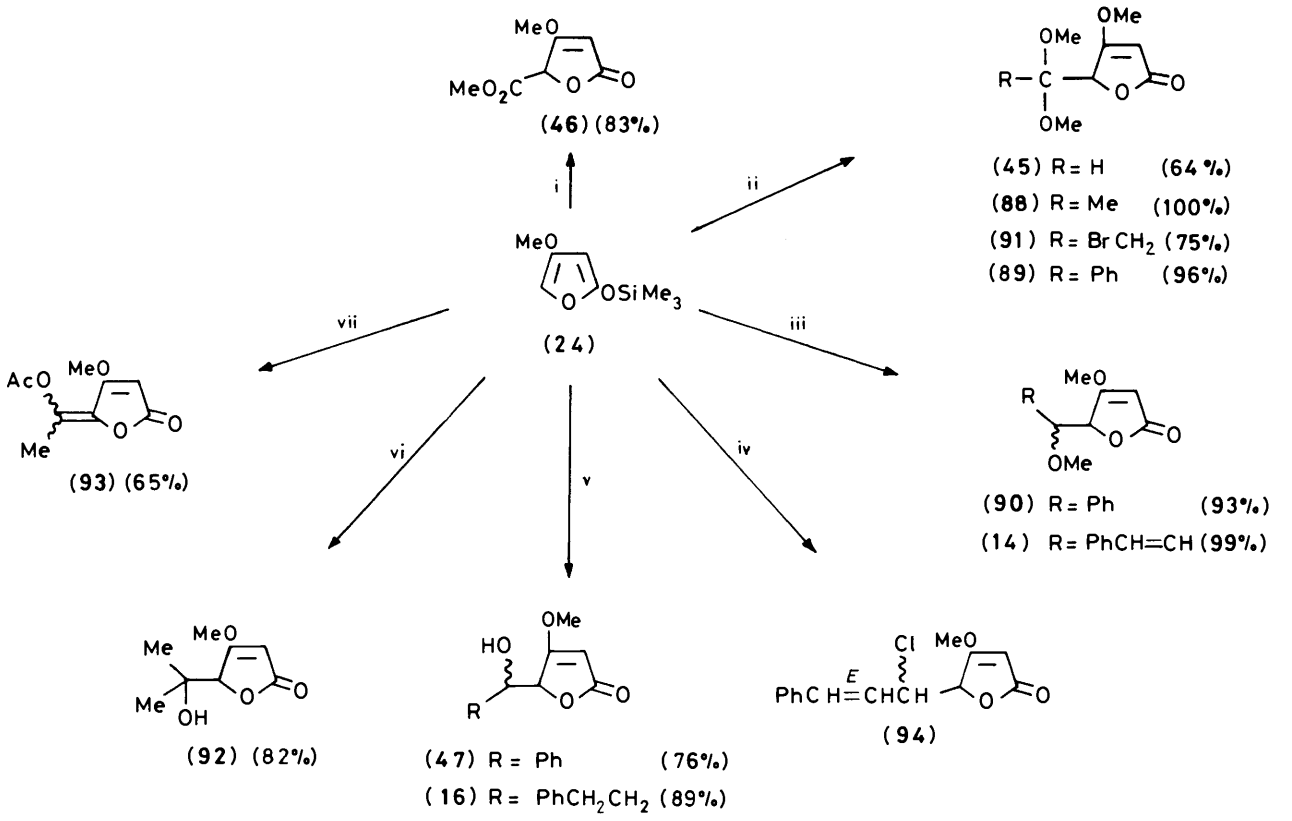


We had already shown that compound (**23**) did not react directly with orthoesters, and further experimentation showed that it was also inert to acetals and ketals. However, we had used 'double activation' [equation (5)] to induce reactions of compound (**23**) with trimethyl orthoformate and tetramethyl orthocarbonate and we therefore further investigated the utility of this method. We were pleased to find that not only was the method of utility with orthoesters [equation (5)] but that it was applicable to acetals as well [equation (6)].





In this way compounds (**45**), (**88**), and (**89**) were made in *ca.* 85% yield and compound (**90**), 5,6-dihydrofadyenolide, was produced as a mixture of *threo* (38%) and *erythro* isomers (41%). It was particularly important that, for the first time, we were able to obtain a 1,2-condensation with a cinnamaldehyde derivative. 5,6-Dihydropiperolide (**14**) resulted directly as an *erythro–threo* mixture in 74% yield from the doubly activated condensation of cinnamaldehyde dimethyl acetal with methyl 5-lithiotetronate (**23**).

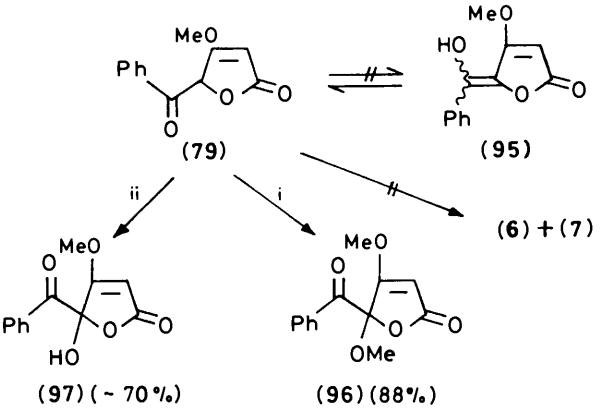


Scheme 7. *Reagents:* i, $C(OMe)_4$; ii, $RC(OMe)_3$; iii, $RCH(OMe)_2$; iv. $PhCH{=}CHCH(OMe)_2$, 2 × $TiCl_4$; v, RCHO; vi, Me_2CO; vii, excess of AcCl

We then turned to the carbon–carbon bond-forming reactions of compound (**24**), which are summarised in Scheme 7. This shows that the Lewis acid-catalysed reactions of compound (**24**)[31,32] with orthocarbonates, orthoesters, acetals, ketones, and aldehydes proceed with great efficiency at low temperatures. Catalytic quantities of titanium tetrachloride or zinc bromide, or stoicheiometric amounts of trifluoroborane–diethyl ether, may be used, but use of tetrabutylammonium fluoride simply led to extensive and rapid decomposion of compound (**24**).

All the reactions with orthoesters proceeded efficiently to give the compounds (**45**), (**88**), (**89**), and (**91**), elimination of methanol from which should allow entry into the natural product series. Reactions with acetals gave the 5,6-dihydro derivatives of some of the natural products. Once more, condensation with cinnamaldehyde dimethyl acetal gave compound (**14**). When 2 mol equiv. of titanium tetrachloride were used, the chloride (**94**) was produced as an *erythro, threo* mixture. Condensation with aldehydes allowed access to the 6-demethoxy series. Condensation with ketones also proceeded well, but the reaction with acetyl chloride was difficult, equimolar proportions of reactants giving rise to polymeric products. Only when compound (**24**) was added to a large excess of acetyl chloride was the ketone trapped as a mixture of the *E*- and *Z*-enol acetates (**93**).

Synthesis of E- *and* Z-*Fadyenolide.*—With methyl 5-benzoyltetronate (**79**) to hand it seemed reasonable to expect its ready conversion into *E*- and *Z*-fadyenolide (**6**) and (**7**), which are merely the methyl enol ethers of compound (**79**). However, spectroscopic examination of the ketone (**79**) gave no indication of the presence of its enol tautomer (**95**), which models showed was sterically inhibited in either the *Z*- or *E*-form. Very many attempts to convert compound (**79**) into the fadyenolides (**6**) and (**7**) failed. In general, methylation was so slow that either there was no reaction, or oxidation to compounds (**96**) or (**97**) intervened (Scheme 8).

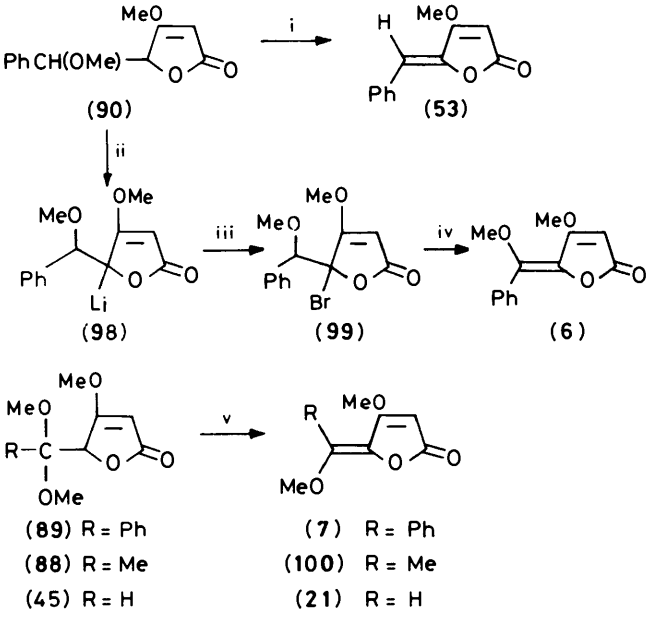


Scheme 8. *Reagents:* i, Me_2SO_4, K_2CO_3; ii, CH_2N_2, BF_3, or $CH(OMe)_3$, MeOH, H^+

We also had compound (**90**) to hand [equation (6) or Scheme 7], but attempted direct dehydrogenation with DDQ gave mainly the olefin (**53**) and only a 1—2% yield of fadyenolides (**6**) and (**7**) (1:1), the thermal elimination of methanol being far easier than dehydrogenation. Use of NBS–*hν*–benzoyl peroxide on compound (**90**) in tetrachloromethane gave essentially the same result [(**6**) and (**7**) *ca.* 5%]. We therefore converted compound (**90**) into the lithium derivative (**98**) at −78 °C and brominated at the same temperature to give compound (**99**), which without isolation was subjected to treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 0 °C. This process

gave *E*- and *Z*-fadyenolide in the ratio 15:1 (Scheme 9) and in 30% yield [allowing for recovered starting material (**90**)].

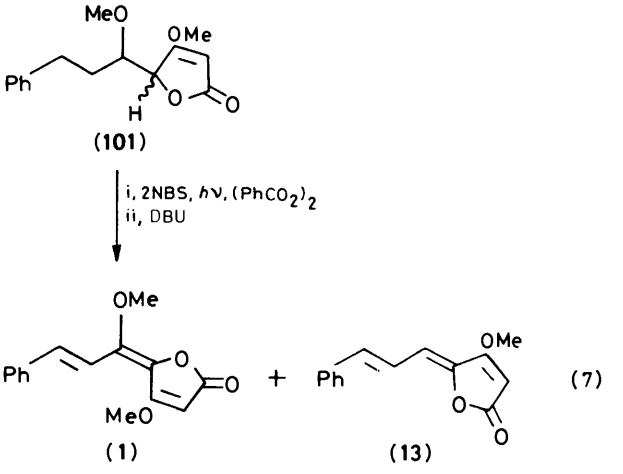
A different approach involved the ketal (**89**), readily available in 70% yield from methyl tetronate [equation (6)] or in 93% yield from the silyl ether (**24**) (Scheme 7). Elimination of methanol from ketal (**89**) should give the fadyenolides, but despite the steric hindrance in compound (**89**) itself it proved difficult to convert it into compound (**6**) and/or (**7**). Thus ketal (**89**) sublimed unchanged and a wide variety of acidic or basic conditions led either to total decomposition or recovery of starting material. However, treatment of compound (**89**) with t-butyl-lithium (but *not* n-butyl-lithium or s-butyl-lithium) gave *E*- and *Z*-fadyenolides in the ratio 1:30, and a yield, after recrystallisation, of 77% of pure *Z*-fadyenolide (**7**). Use of LDA at −78 °C gave 70% of the same isomer from ketal (**89**). The t-butyl-lithium method was also applied successfully to produce analogues of fadyenolide (Scheme 9).



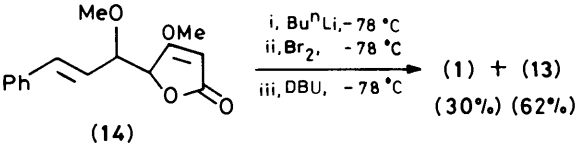
Scheme 9. *Reagents and conditions*: i, DDQ, NBS, *hν*; ii, Bu^{n}Li, −78 °C; iii, Br_2, −78 °C; iv, DBU, room temp.; v, Bu^{t}Li, −78 °C

Thus, both fadyenolides (**6**) and (**7**) were to hand, the synthesis of the *Z*-isomer (**7**) being highly efficient and that of the *E*-isomer (**6**) reasonably so. The process leading to isomer (**6**) seemed readily explicable. The intermediate (**99**) exists as a 3:1 mixture of two forms, but gave a 15:1 mixture of isomers (**6**) and (**7**). This would imply that both *erythro*- and *threo*-(**98**) yield an equilibrated intermediate, which may be a bridged or an unbridged carbocation. Based on CPK atomic models the form yielding the *E*-isomer (**6**) would be expected to be favoured under equilibrating conditions, as was found. The reaction of ketal (**89**) with t-butyl-lithium to give the most hindered isomer (**7**) was more puzzling. The steric consequence of the reaction seems general as ketal (**88**) gave only the *Z*-isomer (**100**) (assignment based on ^{13}C n.m.r. similarities to compounds of known structures),[76] and acetal (**45**) gives compound (**21**). Assuming a concerted *anti*-elimination of methanol, that conformer of ketal (**89**) that would yield *Z*-form (**7**) rather than *E*-form (**6**) does appear marginally less hindered using CPK models. However, the benzene ring of the sterically favoured conformer is orthogonal to the developing π-system, which would be a disadvantage, and the argument is not convincing. A different approach is to consider that a bulkyl lithium alkyl aggregate is attached to both ketal oxygen atoms. This would mean that the effective bulk of the methoxy group remaining is much greater than the phenyl group throughout the whole course of the elimination. Steric factors would then favour the eventual production of *Z*-isomer (**7**).* In any case, synthetic (*Z*)- and (*E*)-fadyenolide are now readily available.

Synthesis of (7*E*)-*Piperolides*.—The methyl ether (**101**), readily available from the alcohol (**16**), was the first substrate tried for the production of the piperolides. Reaction of ether (**101**) under mild conditions with 2 mol equiv. of NBS in the presence of light and benzoyl peroxide, followed by DBU at room temperature, gave the dehydrogenation–elimination product (**13**) in 56% yield, and (5*Z*,7*E*)-piperolide (**1**) in 7% yield [equation (7)]. Analysis of piperolides must be performed as soon as possible after reaction as the 5*Z*- and 5*E*-isomer are in equilibrium in solution. Thus a 1:4 mixture of piperolides (**1**) and (**5**), when kept for one day in chloroform, became a 2:3 mixture. Examination (h.p.l.c.) of a crystalline sample of piperolide isolated from *P. sanctum* showed that it was a mixture of compounds (**1**) and (**5**) in the ratio 4:1. In our original work h.p.l.c. was not available and substance (**5**) might have been missed. Alternatively, the *E*-isomer (**5**) might be produced when *Z*-form (**1**) is kept for any time, though in our hands crystalline isomer (**1**) was stable for long periods in the dark. The production of isomer (**1**) as the only piperolide in the debromination is interesting, but the low yield of the reaction renders the process of little practical value.



Compound (**14**), available to us in very high yields [equation (6) and Scheme 7], has already been reported to give piperolide (**1**) by dehydrogenation. In our hands, however, this process gave the elimination product (**13**) almost entirely. However, lithiation, bromination, and elimination with DBU, all at −78 °C, gave compound (**1**) as the only piperolide isomer in ~30% yield, together with readily separable compound (**13**) (62%) [equation (8)].

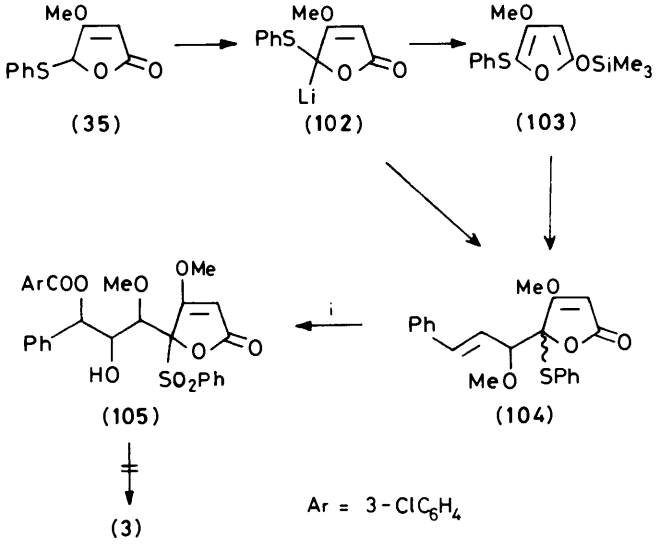


Attempts (*vide infra*) to prepare epoxypiperolide resulted in high-yield syntheses of *all* the piperolides.

* We thank Dr. K. Smith, U.C. Swansea, for proposing this argument.

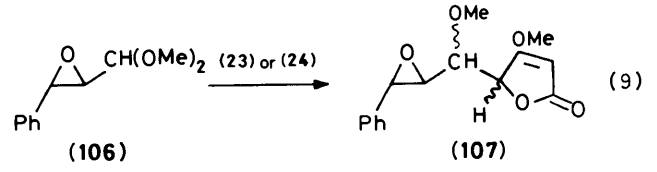
Synthesis of Epoxypiperolides.—Methyl 5-(phenylthio)-tetronate (**35**), on treatment with t-butyl-lithium, was efficiently converted to its 5-lithio derivative (**102**), which either by the double-activation technique or *via* the trimethylsiloxyfuran (**103**) was converted into a mixture of *erythro*- and *threo*-sulphide (**104**) (Scheme 10). Compound (**104**) was inert to sodium metaperiodate, but with excess of MCPBA it gave sulphone (**105**) (75%) as one isomer of unknown stereochemistry.

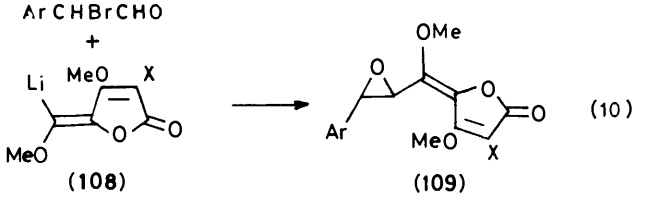
A very large number of experiments, mainly based on thermal- and base (DBU, NEt_3, Pr^i_2NH)-catalysed conversion of sulphone (**105**) into epoxide (**3**) or a derivative of diol (**4**), met with failure. It is by no means clear why the elimination of benzenesulphinic acid from compound (**105**) should be so difficult, and this approach to epoxide (**3**) was not further pursued.



Scheme 10. *Reagent:* i, MCPBA

Although we had made the epoxyacetal (**106**), we were unable to convert it, by any means, into epoxy-5,6-dihydropiperolide (**107**) [equation (9)] nor were we confident that we would be able to dehydrogenate compound (**107**) to the very labile natural product (**3**).

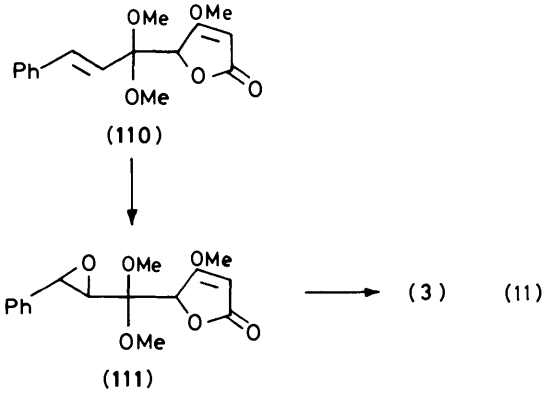




We therefore investigated the lithiation of the vinyl ether (**21**), with a view to carrying out the process shown in equation (**10**).

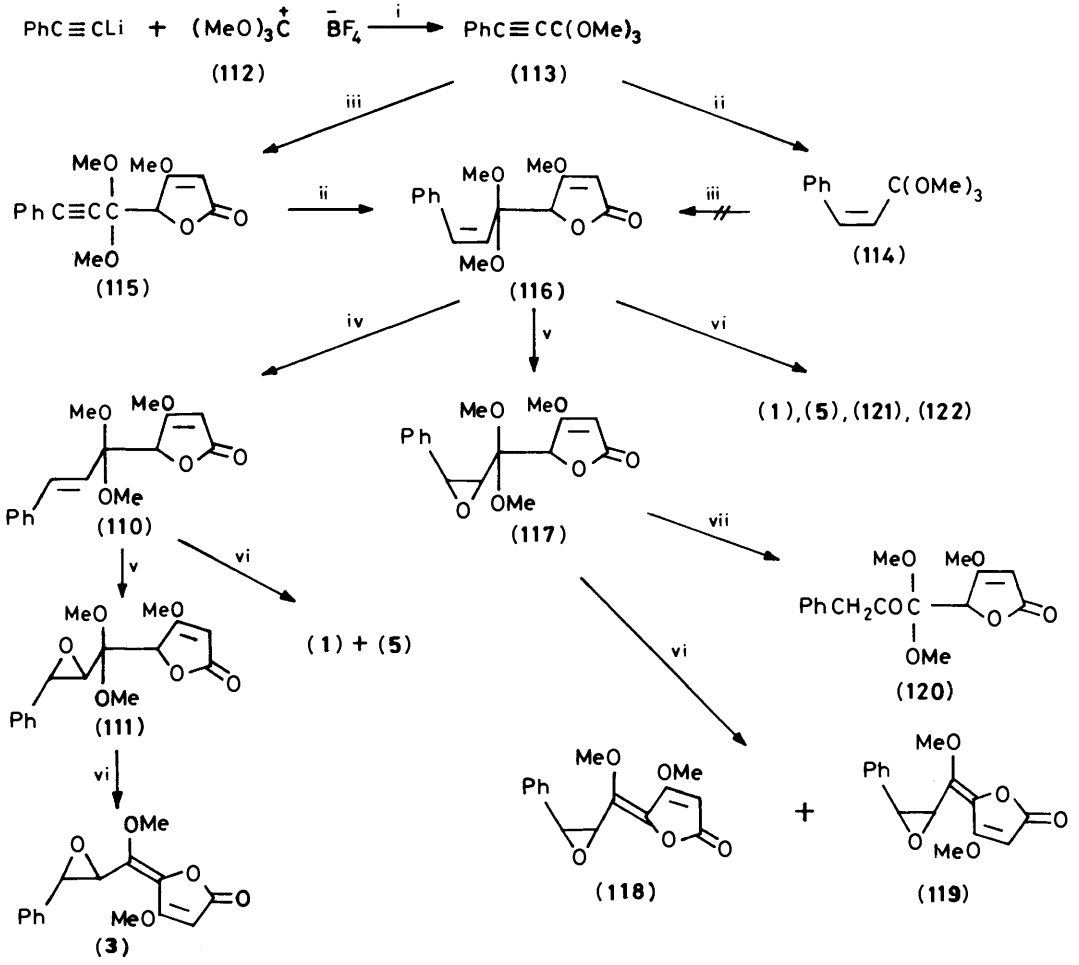
In practice, lithiation of compound (**21**) under all conditions investigated gave rise to the 3-lithio derivative, a finding in line with parallel investigations.[58,60] We did not pursue the approach by use of derivatives (**108**; X = SiR_3, Br, SnR_3) as we felt that removal of the C-3 protecting group in the presence of the labile allylic epoxide group of compound (**109**) would be difficult and tedious.

In view of the difficulty in converting piperolide into epoxypiperolide and of the need to introduce the epoxide group at as late a stage as possible, it seemed that a sequence of the type shown in equation (11) was indicated.[25]



We had already established that elimination of methanol from the alkenyl analogues of compound (**111**) was a ready reaction (Scheme 9) and it was hoped that epoxidation of compound (**110**) would occur without rearrangement. In order to obtain compound (**110**) we envisaged a reaction between trimethyl orthocinnamate and compounds (**24**) or (**23**), having already shown that the silyl ether (**24**) reacts with aryl and alkyl orthoformates as desired and also with cinnamaldehyde dimethyl acetal in a 1,2-fashion [equation (6) and Scheme 7]. Based on this analysis there was a requirement for an efficient route to orthocinnamates, of which there was none in the literature.[77–79] After some preliminary experiments it was decided that the reactions of alkenyl-lithium and alkynyl-lithium compounds with trimethoxycarbonium tetrafluoroborate (**112**)[80] offered the best opportunity for entry to the required series.[81] Compound (**112**) is extremely hygroscopic and though initially it was isolated and manipulated in a dry-box it was found better to produce and use it in excess as an ethereal suspension. The reaction with styryl-lithium is not clean and the matter was not pursued in view of later events. However, reaction of the salt (**112**) with phenylethynyl-lithium gave 90% of orthoester (**113**) (Scheme 11) using a rigidily anhydrous work-up, otherwise methyl phenylethynylcarboxylate resulted. Reduction of alkyne (**113**) to *Z*-alkene (**114**) proceeded quantitatively, though compound (**114**) was labile and somewhat difficult to purify. It was disappointing to find that reaction of alkene (**114**) with compound (**23**), using double activation, was unsuccessful and that Lewis acid-catalysed reaction with compound (**24**) went by 1,4-addition, so that the alkenyl protons disappeared in the ^1H n.m.r. spectrum of the product. Thus, arylalkenyl orthoesters differ from arylalkenyl acetals, which react by 1,2-addition (Scheme 7). For this reason attempts to make *E*-(**114**) were stopped.

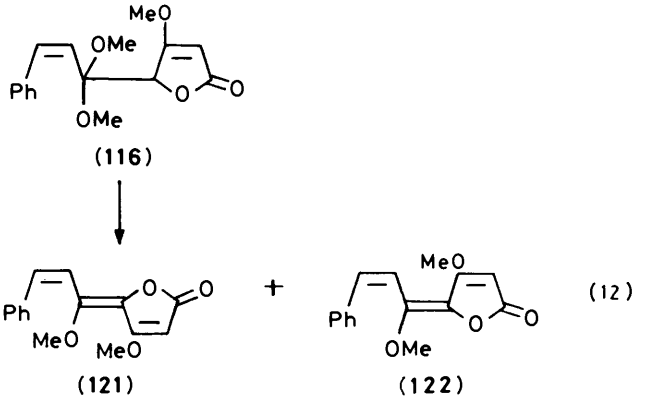
The condensation of the orthoester (**113**) with the silyl ether (**24**) was therefore attempted and though it failed with titanium tetrachloride and gave only low yields with zinc bromide, with trifluoroborane–diethyl ether the alkynyl ketal (**115**) was obtained in 77% yield as a crystalline compound, and was reduced in 86% yield to the alkene (**116**), which is a pivotal intermediate (Scheme 11). Epoxidation of compound (**116**) took 5—6 days but gave epoxide (**117**) as a 1.3:1 mixture of diastereoisomers in 83% yield. The major isomer crystallised out and was used for further reaction, though the mixture would have been usable. Elimination of methanol from the ketal (**117**) to give very interesting unnatural epoxypiperolides by means of



Scheme 11. *Reagents and conditions:* i, Et_2O, −78 °C→0 °C; ii, H_2, Lindlar cat.; iii, $F_3B{\cdot}OEt_2$, (**24**); iv, Amberlyst resin, MeOH; v, MCPBA, CH_2Cl_2; vi, base; vii, $ZnBr_2$

t-butyl-lithium method, which had been so successful for the synthesis of fadyenolides (Scheme 9), in this case gave only a complex mixture. Reaction with lithium bis(trimethylsilyl)amide was equally unsuccessful and reaction with zinc bromide gave rearranged ketone (**120**) in 90% yield. It was finally found that lithium methoxide, of course always produced in the t-butyl-lithium reactions and previously suspected of being an active reagent, when refluxed in toluene with ketal (**117**) gave the vinyl ethers (**119**) and (**118**) in the ratio 1:2 and in 30% overall yield. Although the yield was not as high as was hoped for, the precursor (**117**) is replete with labile functionality [see the rearrangement to compound (**120**)] and it was a relief to obtain the desired products in such a straightforward fashion. Compounds (**118**) and (**119**) were separated by preparative h.p.l.c. and were characterised. This constitutes the first synthesis of any epoxypiperolide.

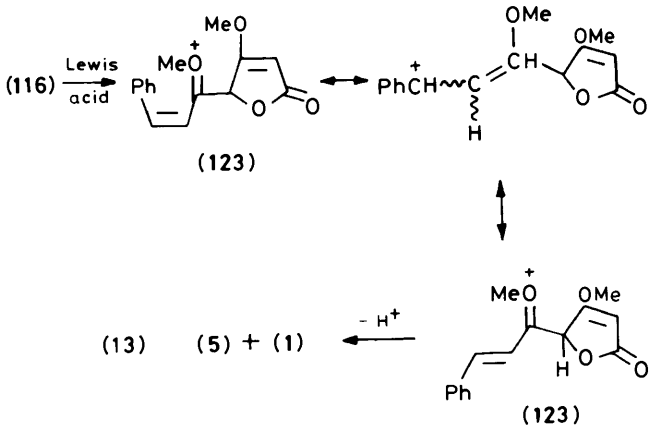
The elimination of methanol from the now readily available ketals (**115**) and (**116**) was of interest and, in particular, the production of (5*Z*,7*Z*)-piperolide (**122**) and (5E, 7*Z*)-piperolide (**121**) [equation (**12**)] would complete the synthesis of all the piperolide isomers. CPK models of compounds (**121**) and (**122**) show that, in these small molecules, the change to a 7*Z*-double bond has a marked effect on the overall shape as compared with 7*E*-isomers (**1**) and (**5**). Thus isomers (**121**) and (**122**) are of particular interest from the viewpoint of structure–activity relationships. Compound (**121**) in particular is so crowded that a stable model is difficult to make.



(12)

We did not succeed in eliminating methanol from the alkynyl ketal (**115**), in line with the finding that alkynyl orthoester (**113**) undergoes 1,2-addition of compound (**24**) whilst alkenyl orthoester (**114**) undergoes 1,4-addition, *i.e.* the alkynyl π-system interacts with the adjacent ketal group less than does the alkenyl π-system.

Lewis acid [$Et_2O{\cdot}BF_3$ or $Ti(OPr^i)_2Cl_2$]-catalysed elimination of methanol from ketal (**116**) gave *only* a mixture of piperolides (**1**) and (**5**) in the ratio 2:3. There had been complete isomerisation of the 7,8-double bond presumably through the equilibrating oxonium ion (**123**) [equation (13)].



Results of the elimination of methanol from ketal (**116**) with either t-butyl-lithium or lithium methoxide are given in Table 1. All four piperolide isomers were formed, their proportions being determined by h.p.l.c., which cleanly separates isomers (**122**) and (**5**) from each other and from a mixture of (**1**) and (**121**), which are in turn estimated by ^{13}C n.m.r. spectroscopy. At −95 °C in the dark almost 80% of the product retains the 7*Z*-stereochemistry and, more surprisingly in view of the strong stereochemical interactions in isomer (**121**), isomers (**121**) and (**122**) are present in almost equal proportions. With the same reagent the ratio of isomer (**121**) formed to (**122**) steadily drops as the temperature is raised to 0 °C with little rise in the total amount of isomers (**1**) and (**5**). Under the reaction conditions there appeared to be a ready thermal isomerisation of compound (**121**) to (**122**), which is not light-catalysed as the reactions were carried out in covered flasks and samples were injected directly into a stainless steel port. Either with catalytic or stoicheiometric quantities of lithium methoxide in refluxing toluene in the light a mixture was obtained that still contained a large amount of 7*Z*-isomers of piperolide.

Experiment 3 was on a preparative scale and gave 97% overall isolated yield of piperolides, and in particular it was easy to separate isomer (**122**) in 68% yield, this being a very efficient route to this piperolide isomer.

It remained to enter the natural 7*E*-series, entry having to be from the 7*Z*-ketal (**116**) due to the failure of the *Z*-orthoester (**114**) to couple with the compound (**24**). Both the photochemical and iodine-induced isomerisations of compound (**116**) to the 7*E*-form (**110**) were unsuccessful. However, when compound (**116**) was dissolved in anhydrous methanol containing Amberlyst resin (H^+ form), compound (**110**) was isolated in 83% yield after recrystallisation. The reaction presumably proceeds *via* oxonium ion (**123**), which is trapped by methanol rather than undergoing elimination. Ketal (**100**) is more labile than its *Z*-isomer (**116**), and decomposes even when kept at 0 °C under nitrogen.

Reaction of ketal (**110**) with t-butyl-lithium gave *ca.* 90% of the natural piperolides (**1**) and (**5**) only, with no trace of 7*Z*-isomers (**121**) and (**122**). Lithium methoxide elimination was slow but gave an 83% isolated yield of piperolides (**1**) and (**5**) in the ratio 2.8:1.

Epoxidation of ketal (**110**) gave compound (**111**) (80%) as a mixture of two isomers, neither of which could be crystallised. The mixture was subjected to the same elimination conditions as were used for its *cis*-isomer (**117**) and this gave epoxypiperolides in 35% yield, comparable with the case with compound (**116**). By h.p.l.c. a main fraction was shown to be compound (**3**), but difficulties of separation on the scale used meant that only 5% of compound (**3**) could be isolated absolutely pure,* and the 5*E*-isomer could not be purified and characterised. The ^1H n.m.r. spectrum of compound (**3**) is unique among those of the epoxypiperolides and that of the synthetic product was identical with the spectrum we had for the natural product. Thus this represents the first synthesis of epoxypiperolide. We have not been able to investigate this reaction further, but see no reason why on a larger scale the yield should not be the same in the 7*E*-series as in the 7*Z*-series.

Table 1. Elimination of methanol from ketal (**115**)

Expt.	Reagent	Temp. (°C)	Proportions (122)	(121)	(1)	(5)
1	Bu^{t}Li[a]	−95	40.3	37.3	7.5	14
2	Bu^{t}Li[a]	−78	56	19.9	15.1	9.0
3	Bu^{t}Li[a]	0	70	15.3	8.6	6.0
			(67.8)[b]	(14.9)	(8.4)	(5.8)
4	LiOMe–toluene[c]	111	45.6	15.6	26.9	12.0
5	LiOMe–toluene[d]	111	47.1	17.4	24.5	10.9

[a] Dark reaction. [b] Figures in parentheses are isolated yields. [c] Catalytic amount of lithium methoxide refluxed for 7 days. [d] Equivalent amount of lithium methoxide refluxed for 2 days.

It should be remarked that all four piperolides and three epoxypiperolides have been prepared and characterised starting from the single precursor (**116**), made in 56% yield from methyl tetronate. From it we obtain compound (**121**) in 39% yield from methyl tetronate, and piperolides (**1**) and (**5**) in 42% yield from methyl tetronate.

Experimental

M.p.s were determined using a hot-stage microscope and were corrected. I.r. (KBr, film or solution) and u.v. (EtOH) spectra were recorded on Pye Unicam SP1050 and Perkin-Elmer 402 spectrometers, respectively. ^1H N.m.r. spectra were obtained from either a Varian HA100 or a Varian XL100 spectrometer. Chemical shifts are given as δ-values and coupling constants in Hz. ^{13}C N.m.r. spectra were obtained from a Varian XL100 instrument and chemical shifts are given as p.p.m. downfield from tetramethylsilane (TMS). N.m.r. samples were run in $CDCl_3$ unless otherwise stated.

Mass spectra were taken on an A.E.I. MS9 double-focussing spectrometer at 250 °C and 70 eV. Preparative layer chromatography (p.l.c.) and t.l.c. were conducted on glass plates coated with Merckogel G.F. 254 silica gel which contained a fluorescent indicator. For h.p.l.c. an Altex pump with a Cecil detector was used.

Nitrogen refers to oxygen-free nitrogen, dried by passage through both conc. sulphuric acid and calcium chloride. THF was distilled under nitrogen over calcium hydride or lithium aluminium hydride and stored under nitrogen. Diethyl ether was purified through an alumina column, distilled over calcium hydride, and stored over sodium wire. Dichloromethane was passed through an alumina column, distilled over calcium hydride, and stored over molecular sieves, type 4A. Benzene was distilled and stored over sodium wire. Pyridine was refluxed over barium oxide, distilled over calcium hydride, and stored over molecular sieves, type 4A. Dimethyl sulphate was distilled and stored under nitrogen. Chloro(trimethyl)silane was distilled and stored under nitrogen. HMPT and di-isopropylamine were dried over molecular sieves, type 4A. All laboratory reagents were purified before use.

Preparation of Methyl Tetronate (**20**).—(a) *Preparation of ethyl 3-methoxybut-2-enoate.* Ethyl acetoacetate (65 g) was

* We thank Dr. R. Pardasani for these experiments.

mixed with redistilled trimethyl orthoformate (53 g) and dry methanol (50 ml), and conc. hydrochloric acid (0.3 ml) was added. The mixture was distilled at once up an efficient fractionating column to give ethyl 3-methoxybut-2-enoate (72 g, 100%), b.p. 190—193 °C (lit.,[63] 188—193 °C).

(b) *Preparation of ethyl 4-bromo-3-methoxybut-2-enoate* (**34**). Ethyl 3-methoxybut-2-enoate (75 g) was heated to 110—115 °C and was vigorously stirred while NBS (75 g) was added in small portions, the temperature during the addition being kept at 100 °C. When addition was complete, the mixture was cooled to 70—80 °C and vigorously stirred while water (125 ml) added. The aqueous layer was separated and the organic layer was washed with water (3 × 35 ml), dried ($MgSO_4$), filtered, and distilled at once to give compound (**34**) (89 g, 95%), b.p. 132—136 °C/25 mmHg (lit.,[63] 134—139 °C/30 mmHg).

(c) *Cyclisation of compound* (**34**) *to give methyl tetronate* (**20**). A mixture of compound (**34**) (100 g), anhydrous zinc bromide (0.5 g), and dry *p*-xylene (100 ml) was heated under reflux for 8 h, and the solvent was removed under reduced pressure. A 2:8 (v:v) mixture of chloroform and diethyl ether (300 ml) was added to the residue, and the mixture was well swirled, decanted, and set aside for 18 h between −20 and 0 °C. Methyl tetronate (**20**), m.p. 64—65 °C (lit.,[82] 67 °C) (20 g), separated as white crystals. The filtrate was evaporated under reduced pressure and the same solvent mixture (*ca.* 75 ml) was added to the residue, and the mixture was set aside as before to give a further crop of methyl tetronate (**20**), m.p. 64—65 °C (17.5 g). The total yield of methyl tetronate was thus 37.5 g (74%) (Found: C, 52.6; H, 5.35. Calc. for $C_5H_6O_3$: C, 52.63; H, 5.26%); $\nu_{max.}$ 1 740 and 1 625 cm^{-1}; $\lambda_{max.}$ 241 nm; δ_H 5.08 (1 H, t, *J* 2 Hz, 3-H), 4.58 (2 H, d, *J* 2 Hz, 5-H), and 5.86 (3 H, s, MeO), δ_C 173.5 (C-2), 88.7 (C-3), 1870.7 (C-4), 67.7 (C-5), and 59.6 (MeO).

Preparation of Methyl 5-(1′-Methoxymethylene)tetronate (**21**).—Sodium hydride (0.42 g, 10 mmol; as a 50% oil dispersion) was weighed into a dry, 250-ml round-bottomed flask fitted with a septum-capped inlet and a magnetic follower. The flask was flushed with nitrogen and the sodium hydride was washed with dry pentane (3 × 2 ml) and then dried *in vacuo*. Nitrogen was admitted, dry diethyl ether (20 ml) was added, and the mixture was stirred and cooled in an ice-bath. A mixture of methyl tetronate (**20**) (1.14 g, 10 mmol) and freshly distilled ethyl formate (50 ml) was added slowly by syringe, and the stirred reaction was kept at room temperature for 15 h. Freshly distilled dimethyl sulphate (0.95 ml, 10 mmol) was then slowly added and the reaction mixture was stirred at room temperature for 2 days, and then filtered. The precipitate was well washed with dry diethyl ether, filtered, and the filtrates were evaporated to give brown crystals. Recrystallisation from methanol gave the *title compound* (**21**) (1.53 g, 98%) as white crystals, m.p. 85—86 °C (Found: C, 53.4; H, 5.1. $C_7H_8O_4$ requires C, 53.2; H, 4.94%); $\nu_{max.}$ 1 760 and 1 610 cm^{-1}; $\lambda_{max.}$(MeOH) 286 nm; δ_H 5 08 (1 H, s, 3-H), 6.25 (1 H, s, 6-H), and 6.12 (6 H, s, 2 × MeO); δ_C 168.5 (C-2), 86.1 (C-3), 171.6 (C-4), 128.3 (C-5), 131.0 (C-6), 61.9 (4-OMe) and 59.1 (6-OMe); *m/z* 156 (100%), 141 (38), 113 (17), 85 (54), 68 (82), and 29 (51).

Preparation of Methyl 5-Lithiotetronate (**23**).—*Procedure A.* n-Butyl-lithium (30.1 ml of a 1.66M-solution in hexane; 50 mmol) was added by syringe to a stirred solution of di-isopropylamine (7 ml, 50 mmol) in dry THF (200 ml) in a septum-capped, three-necked, round-bottomed 500 ml flask under nitrogen at −78 °C. The solution was stirred for 20 min, HMPT (7.5 ml) was added, and the mixture was stirred for the further 15—20 min at −78 °C. A solution of methyl tetronate (5.7 g, 50 mmol) in dry THF (100 ml) in a separate flask was cooled, and added under nitrogen pressure by means of a double-ended needle to the well stirred solution of base held at −78 °C. The mixture was stirred for a further 20 min, after which the solution was used directly in subsequent reactions.

Procedure B. n-Butyl-lithium* (30.1 ml of a 1.66M-solution in hexane; 50 mmol) was introduced into a septum-capped, nitrogen-filled flask by syringe. Dry THF (200 ml) was added, and the solution was cooled to −78 °C and stirred. A solution of methyl tetronate (5.7 g, 50 mmol) in dry THF (100 ml) was precooled and added during 5 min by double-ended needle to the well stirred solution. The solution was stirred for 20 min, then used directly.

Preparation of 4-Methoxy-2-(trimethylsiloxy)furan (**24**).—A solution of chloro(trimethyl)silane (10.8 ml, 85 mmol) in dry THF (10 ml) was cooled to −78 °C and syphoned under nitrogen pressure through a precooled double-ended needle during 3—4 min into a stirred solution of the lithium compound (**23**) (procedure B, 50 mmol) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, then allowed to warm to 20 °C at which temperature it was held for 1 h. The solvent was removed (oil-pump and trap—no moisture!), and dry pentane (90 ml) was added by syringe. The precipitated lithium chloride was removed by filtration under dry nitrogen, the solvent was removed, and the product, b.p. 84 °C/15 mmHg (8.75 g, 94%), was isolated by fractional distillation through an efficient Vigreux column. It must be kept under nitrogen and never exposed to moisture, and owing to its lability it was characterised by spectroscopy and by its reactions: δ_H 4.72 (1 H, d, *J* 2 Hz, 3-H), 6.19 (1 H, d, *J* 2 Hz, 5-H), 3.31 (3 H, s, OMe), and 9.73 (9 H, s, $SiMe_3$); δ_C 151.2 (C-2), 79.4 (C-3), 155.4 (C-4), 113.0 (C-5), 57.2 (OMe), and 0.3 ($SiMe_3$); *m/z* 187 (13%), 186 (89), 143 (44), 114 (4), 113 (3), 89 (10), 75 (8), and 73 (100).

Preparation of 5-Heterosubstituted Derivatives of Methyl Tetronate.—The characteristics of these compounds are given in Tables 2 and 3.

Methyl 5-bromotetronate (**27**). (i) Bromine (0.52 ml, 10 mmol) was added in one portion to a stirred solution of the lithium derivative (**23**) (10 mmol) (procedure B) at −78 °C. The mixture was allowed to warm to *ca.* 20 °C, and was then quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate (3 × 100 ml), and the extract was dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure to give the bromo derivative (**27**) (1.85 g, 97%) as a brown oil.

(ii) A solution of bromine (0.32 g, 2 mmol) in dry dichloromethane (2 ml) was added to a stirred solution of compound (**24**) (0.372 g, 2 mmol) in dry dichloromethane (2 ml) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 30 min, then allowed to warm to room temperature. Evaporation of solvent gave compound (**27**) (0.38 g, 98%) as a pale brown oil.

(iii) A mixture of methyl tetronate (**20**) (1.14 g, 10 mmol), NBS (1.79 g, 10 mmol), and dibenzoyl peroxide (0.05 g) in dry tetrachloromethane (200 ml) was heated to reflux under nitrogen for 6 h whilst being irradiated with u.v. light from a Hanovia 100 W (360 nm) lamp. The mixture was allowed to cool, and was filtered from succinimide, the precipitate being washed with CCl_4 (2 × 10 ml). The combined filtrate and washings were concentrated under reduced pressure to give crude methyl 5-bromotetronate (**27**) as a pale yellow oil (1.81 g, 94%), sufficiently pure for further reaction.

The succinimide was dissolved in 2M-NaOH (1 ml) and the remaining solid was washed with water and collected, dried, and recrystallised from ethyl acetate to give methyl 3-bromotetronate (0.105 g, 5.5%), m.p. 112—114 °C (lit.,[67] 111—114 °C).

* sec-Butyl-lithium and t-butyl-lithium are also satisfactory.

Table 2. Methyl 5-heterosubstituted tetronates*

Compd.	5-Substituent	M.p. (b.p./°C)	$\nu_{max.}$/cm^{-1}	Formula	Analysis[i] Found	Analysis[i] Calc.	δ_H 3-H	δ_H 5-H	δ_H OMe	*m/z*
(**27**)	Br	*a*	1 800, 1 780, 1 640	$C_5H_5BrO_3$			5.08s	4.58s	3.86s	113 (100%), 85 (32), 80 (6), 69 (56)
(**36**)	Cl	*a*	1 795, 1 765, 1 647	$C_5H_5ClO_3$			5.27s	6.37s	4.03s	148 (3%), 113 (100), 85 (22), 69 (41), 36 (6)
(**35**)	SPh	54—55/Et_2O (120/0.1 mmHg)	1 785, 1 760, 1 640	$C_{11}H_{10}O_3S$	59.6 4.7	59.46 4.50	4.90d (*J* 1.5)	5.90d (*J* 1.5)	3.79s	222 (13%), 113 (100), 109 (11), 85 (48), 77 (3), 69 (27)
(**37**)	SO_2Ph	148—149/Et_2O	1 793, 1 750, 1 636, 1 583	$C_{11}H_{10}O_5S$	51.9 4.05	51.97 3.94	5.41s	6.24s	3.91s[b]	113 (100%), 85 (25), 77 (12), 69 (11)
(**38**)	OH	137—138/Et_2O	1 795, 1 755, 1 640	$C_5H_6O_4$	45.9 4.6	46.15 4.61	5.34s	5.87s	3.86d[c,d]	130 (23%), 113 (4), 85 (13), 84 (33), 69 (100)
(**39**)	OMe	74—75/Et_2O	1795, 1 743, 1 650	$C_6H_8O_4$	50.15 5.4	50.0 5.56	5.16s	5.60s	3.92s, 3.52s	144 (18%), 113 (55), 85 (40), 84 (67), 69 (100)
(**40**)	OBu^n	*a*	1 770, 1 740, 1 628	$C_9H_{14}O_4$			5.15s	5.65s	3.91s[e]	113 (100%), 85 (19), 84 (14), 69 (28), 57 (8)
(**41**)	OPh	*a*	1 770, 1 744, 1 630, 1 590	$C_{11}H_{10}O_4$			5.14s	6.06s	3.85s[f]	206 (9%), 113 (100), 85 (23), 84 (5), 77 (2), 69 (12)
(**42**)	$OCH_2CH{=}CH_2$	*a*	1 770, 1 740, 1 625	$C_8H_{10}O_4$			5.21s	5.75s	3.92s[g]	113 (100%), 101 (4), 85 (29), 84 (6), 69 (41), 41 (40)
(**43**)	OAc	91—92/Et_2O	1 800, 1 765, 1 640	$C_7H_8O_5$	48.9 4.8	48.84 4.65	5.25s	6.73s	3.96s[h]	172 (14%), 113 (67), 101 (31), 85 (37), 84 (26), 69 (97), 43 (106)

* In this and all subsequent tables atom designations are made according to the numbering of formulae as given in the text and diagrams.
[a] Oil which decomposed on distillation. [b] $CDCl_3$–[$^2H_6$]Me_2SO (1:5). [c] [$^2H_6$]Me_2SO. [d] OH, 6.93br. [e] OCH_2 3.87—3.53m, $(CH_2)_2$ 1.79—1.21m, Me, 0.93t. [f] ArH, 7.39—6.95m. [g] OCH_2 4.27m, –CH= 6.20—5.68, CH_2=, 5.54—5.16. [h] OAc 2.16s. [i] %C Followed by %H.

Table 3. ^{13}C N.m.r. data of 5-heteroatom substituted derivatives of methyl tetronate*

Compd.	5-Substituent	C-2	C-3	C-4	C-5	OMe
(**36**)	Cl	168.9	83.1	178.9	89.2	60.5
(**35**)	SPh	170.4	83.3	177.5	90.7	59.5
(**37**)	SO_2Ph	169.7	88.6	174.8	91.6	61.0[a]
(**38**)	OH	170.3	89.5	179.0	93.9	59.7[b]
(**39**)	OMe	170.0	90.4	176.5	99.4	59.8, 56.1
(**40**)	OBu^n	170.2	90.6	177.0	99.0	59.8[c]
(**41**)	OPh	169.6	90.5	176.2	96.7	59.9[d]
(**42**)	$OCH_2CH{=}CH_2$	170.4	90.7	176.8	97.8	59.8[e]
(**43**)	OAc	169.5	89.5	176.7	90.5	60.2[f]

* See footnote* in Table 2.
[a] In [$^2H_6$]Me_2SO–$CDCl_3$ (5:1). [b] In [$^2H_6$]Me_2SO. [c] $OCH_2CH_2CH_2$-Me at 69.3, 31.6, 19.1, and 13.7 respectively. [d] PhS at 117.1, 123.8, 129.8, and 156.2. [e] $OCH_2CH{=}CH_2$ at 70.3, 132.7, and 119.0 respectively. [f] OAc at 169.0 and 20.5

Methyl 5-chlorotetronate (**36**). A solution of benzenesulphonyl chloride (0.64 g, 3.65 mmol) in dry THF (4 ml) was added to the lithium salt (**23**) (made by procedure B) (3.33 mmol) stirred at −78 °C under nitrogen. The mixture was then stirred for a further 1 h at −78 °C, allowed to warm to room temperature, quenched with saturated aqueous ammonium sulphate (5 ml), and extracted with ethyl acetate (4 × 25 ml); the extract was dried ($MgSO_4$), filtered, and the solvents were removed. P.l.c. on silica gel with dry diethyl ether as developer gave the title compound (**36**) (0.46 g, 92%) as a yellow oil (see Tables 2 and 3).

Methyl 5-(phenylthio)tetronate (**35**). (i) A solution of diphenyl disulphide 1.09 g, 5 mmol) in dry THF (5 ml) was added to stirred, freshly prepared lithium derivative (**23**) (5 mmol) (procedure B) at −78 °C under nitrogen. The mixture was allowed to warm to room temperature, quenched with saturated aqueous ammonium sulphate (10 ml), and extracted with dichloromethane (3 × 50 ml), and the extract was dried (Na_2SO_4), filtered, and the filtrate was concentrated at water-pump pressure. Fractional distillation gave the title compound (**35**) (0.99 g, 90%) as a yellow oil, b.p. 120 °C/0.1 mmHg.

(ii) A solution of benzenesulphenyl chloride (0.15 g, 1 mmol) in dry dichloromethane (2 ml) was added slowly to a stirred solution of compound (**24**) in dichloromethane (4 ml) at −78 °C under nitrogen. The solution was stirred at room temperature for 24 h, and the crude product (0.23 g) was purified by p.l.c. on silica with toluene as developer, to give the sulphide (**35**) (0.184 g, 83%). The oil crystallised after some time and was recrystallised from diethyl ether (see Tables 2 and 3).

Methyl 5-(phenylsulphonyl)tetronate (**37**). A solution of MCPBA (85% of the peracid) (0.182 g, 0.9 mmol) in dichloromethane (3 ml) was added to a stirred solution of the sulphide (**35**) (0.10 g, 0.45 mmol) in dichloromethane (3 ml) at 0 °C. The mixture was then stirred at 0 °C for a further 1 h, and then for 2 days at room temperature. The mixture was then washed successively with 5% NaOH (3 ml) and water (2 × 3 ml), dried ($MgSO_4$), and filtered. Evaporation gave the sulphone (**37**)

(0.196 g, 93%) as white crystals, m.p. 148—149 °C, which could be recrystallised from diethyl ether (see Tables 2 and 3).

Methyl 5-hydroxytetronate (**38**) (*narthogenin*). (i) Methyl 5-bromotetronate (**27**) (40 mg, 0.208 mmol) was mixed with water (10 ml) and neutral silica (1.0 g). The mixture was heated under reflux for 10 h, then cooled and filtered, and the water was removed under reduced pressure to give narthogenin (**38**), recrystallised from diethyl ether as crystals, m.p. 137—139 °C (20 mg, 74%) (lit.,[67] 137—138.5 °C).

(ii) Water (0.5 ml) was added to the bromide (**27**) (50 mg, 0.26 mmol) in a small sample tube which was well shaken, and was then kept at room temperature for one week. Removal of water gave compound (**38**) (28 mg, 83%), m.p. 137—139 °C.

(iii) A suspension of compound (**27**) (3.0 g, 15.6 mmol) in water (25 ml) was treated with freshly prepared silver oxide (0.2 g, 7.8 mmol) for 20 min at room temperature. The aqueous phase was filtered from silver bromide and the precipitate was thoroughly washed with water (2 × 25 ml). The combined aqueous extracts were taken to dryness under reduced pressure, and the dried product (1.94 g) was recrystallised (Et_2O) to give compound (**38**) (1.2 g, 59%), m.p. 137—139 °C (see Tables 2 and 3).

Methyl 5-methoxytetronate (**39**). Methyl 5-bromotetronate (**27**) (0.96 g, 5 mmol) was dissolved in anhydrous methanol (50 ml) and the solution was heated under reflux in a moisture-protected flask for 10 h, and then cooled to room temperature. Evaporation gave a pale yellow oil (0.99 g), from which crystallisation from diethyl ether gave compound (**39**) (0.67 g, 93%), m.p. 74—75 °C (see Tables 2 and 3).

Methyl 5-butoxytetronate (**40**). The procedure used to prepare compound (**39**) was repeated except that dry butan-1-ol (50 ml) was used to give the crude product (0.905 g). This was purified by column chromatography on silica gel with diethyl ether as eluant to give compound (**40**) (0.805 g, 87%) as a yellow oil (see Tables 2 and 3).

Methyl 5-phenoxytetronate (**41**). The previous procedure (with THF as solvent) may be used but the yield was only 64%. A different preparative procedure was therefore adopted.

A solution of phenol (0.564 g, 6 mmol) in dry THF (30 ml) was treated with n-butyl-lithium (38 ml of a 1.58M-solution in hexane; 6 mmol), and the mixture was stirred overnight at room temperature and then filtered from lithium bromide. The filtrate was concentrated, and the product (0.885 g, 80%) was isolated as a brown oil by rapid elution with diethyl ether from a silica gel column) (see Tables 2 and 3).

Methyl 5-allyloxytetronate (**42**). Lithium allyloxide (1.3 mmol) was prepared by treatment of allyl alcohol (0.09 ml, 1.3 mmol) with n-butyl-lithium (0.84 ml of a 1.54M-solution in hexane; 1.3 mmol) and cooled to −78 °C. A solution of compound (**27**) (0.25 g, 1.3 mmol) in dry THF (5 ml) was then added by syringe during 5 min, and the mixture was stirred for a further 30 min at −78 °C, and then filtered. The yellow precipitate was washed with ethyl acetate (2 × 10 ml) and the solvents were removed to give crude product (0.22 g). Purification by p.l.c. (Et_2O developer) gave compound (**42**) (0.176 g, 80%) as an oil (Tables 2 and 3).

Methyl 5-acetoxytetronate (**43**).[82,83] Compound (**24**) (0.45 g, 2.4 mmol) was added dropwise to a stirred suspension of lead tetra-acetate (1.17 g, 2.64 mmol) in dichloromethane (10 ml) held at −21 °C. After addition was complete the mixture was allowed to warm to room temperature during 1 h. Diethyl ether (30 ml) was added, the precipitate was filtered off, and the filtrate was concentrated. Purification of the residue by p.l.c. on silica with diethyl ether as developer gave the acetate (**43**) (0.35 g, 85%), m.p. 91—92 °C (see Tables 2 and 3).

Reactions of Methyl 5-Lithiotetronate (**23**) *with Aldehydes.*—The general method for the production of compounds (**16**), (**47**), and (**54**)—(**60**), is given below. The yields and physical characteristics of these compounds are given in Table 4. The ^{13}C n.m.r. data are in refs. 5 and 6.

Procedure. A precooled solution of the aldehyde (50 mmol) in dry THF (50 ml) was added during 5 min to a stirred solution of methyl 5-lithiotetronate (**23**) (50 mmol) (prepared by procedure A) at −78 °C by means of nitrogen pressure on a double-ended needle. The mixture was allowed to warm to room temperature, stirred for 2 h, poured onto crushed ice, and brought to pH 6 with dil. hydrochloric acid. The organic layer was separated, the aqueous layer was washed with ethyl acetate (4 × 200 ml), and the combined organic phases were washed with water (4 × 100 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Crystallisation of the residue, from the appropriate solvent mixtures, gave the corresponding *threo*-derivative. The *erythro*-compounds remaining were difficult to obtain free from residual *threo*-compound and were crystallised in the case of (**16**) only. The overall yields of condensation products based on g.l.c. and isolation were generally in excess of 80%, but in Table 4 the yields given are of pure, recrystallised *threo*-isomer only [with the exception of (**16**)]. The procedure given above was modified for (**47**) and (**54**)—(**57**) by the addition of water (50 mmol) to the THF solution of aldehyde prior to addition to the anion.

Preparation of Methyl 5,5-Disubstituted Tetronates from Aldehyde Condensations.—*Methyl 5,5-bis-(α-hydroxybenzyl)-tetronate* (**48**). A solution of methyl 5-lithiotetronate (5 mmol, procedure A) at −78 °C was syphoned under nitrogen pressure into a stirred solution of benzaldehyde (2.65 g, 25 mmol) in dry THF (100 ml) at −78 °C under nitrogen. The mixture was allowed to warm to room temperature, and was then stirred for 2 h, poured onto crushed ice, and brought to pH 6 with dil. hydrochloric acid. The organic layer was separated, the aqueous layer was extracted with ethyl acetate (4 × 50 ml), and the combined organic phases were washed successively with saturated aqueous sodium hydrogensulphite (4 × 25 ml) and water (4 × 25 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Chromatography on silica gel [3:1 chloroform–light petroleum (b.p. 40—60 °C)] gave *diol* (**48**) (1.3 g, 69%), m.p. 189—190 °C (from $CHCl_3$–Et_2O) (Found: C, 70.1; H, 5.3. $C_{19}H_{18}O_5$ requires C, 69.93; H, 5.52%); $\nu_{max.}$(KBr) 1 760 and 1 640 cm^{-1}; δ_H 4.75 (1 H, s, 3-H), 5.05 (2 H, d, *J* 5 Hz, each 6-H), 3.46 (3 H, s, OMe), and 3.95 (2 H, d, *J* 5 Hz, OH); *m/z* 202 (9%), 114 (100), 107 (45), 106 (84), and 105 (82).

Preparation of compound (**52a**). The preparation of compound (**48**) given above was followed exactly but instead of the reaction mixture being poured onto crushed ice, a solution of acetic anhydride (0.51 g, 5 mmol) in THF (5 ml) was added and the mixture was stirred for 2 h. Work-up as for (**48**) gave an oil (3.1 g) which, on crystallisation from chloroform–diethyl ether, gave the monoacetate (**52a**) (0.86 g, 47%), m.p. 209—211 °C (Found: C, 68.25; H, 5.5. $C_{21}H_{20}O_6$ requires C, 68.47; H, 5.43%); $\nu_{max.}$(KBr) 1 760, 1 740, and 1 635 cm^{-1}; δ_H 5.0 (1 H, s, 3-H), 4.85 (1 H, d, *J* 6 Hz, 6-H), 6.15 (1 H, s, 6′-H), 3.60 (3 H, s, OMe), 2.11 (3 H, s, OAc), and 6.2 (1 H, d, *J* 6 Hz, OH); *m/z* 202 (100%), 131 (13), 118 (23), 106 (64), and 105 (62).

Methyl 5,5-bis-(α-acetoxybenzyl)tetronate (**52b**). Acetic anhydride (0.273 g, 2.01 mmol) was added to a solution of compound (**48**) (0.22 g, 0.67 mmol) in pyridine (10 ml) and the mixture was stirred at room temperature for 48 h, and was then poured onto crushed ice (*ca.* 30 g) and extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed successively with water (2 × 100 ml), 5% aqueous HCl (2 × 100 ml), and 5% aqueous sodium hydrogencarbonate (2 × 100 ml), dried ($MgSO_4$), filtered, evaporated at water-pump pressure, and then at 2 mmHg pressure overnight. Recrystallisation from diethyl ether–light petroleum gave the

Table 4. Some physical and chemical properties of compounds (**16**), (**47**),[a] and (**54**)—(**60**)[a]*

Compd.	Side group	Yield (%)[b]	M.p. (°C)	Crystallisation solvent	$\nu_{max.}$ (KBr) cm^{-1}	Formula	Analysis[c] Found	Calc.	δ_H[a] 3-H	5-H	6-H	7-H	8-H	4-OMe	OH[e]
(**47**)	PhCHOH	69	147—148	$CHCl_3$–Et_2O	1 750, 1 725, 3 370	$C_{12}H_{12}O_4$	65.6 5.4	65.45 5.45	5.28s	5.0m	5.14m			3.8s	5.65 (*J* 7)
(**54**)	4-$MeOC_6H_4$-CHOH	70	128—129	$CHCl_3$–Et_2O	1 750, 1 720, 3 370	$C_{13}H_{14}O_5$	62.2 5.35	62.40 5.60	5.36s	5.05m	5.1m			3.9s	5.65d[f] (*J* 7)
(**55**)	VerCHOH[g]	66	179—181	MeOH–Et_2O	1 760, 1 750, 3 500	$C_{14}H_{16}O_6$	60.3 6.0	60.00 5.71	5.12s	4.9m	4.9m			3.76s	5.8d[h] (*J*8)
(**56**)	3,4,5-$(MeO)_3$-C_6H_2	51	167—169	MeOH–Et_2O	1 740, 3 380	$C_{15}H_{18}O_7$	58.4 5.6	58.06 5.80	5.35s	5.12m	4.9m			3.9s	5.72[i] (*J* 8)
(**57**)	PipCHOH[j]	73	163—165	MeOH–THF	1 720, 3 300	$C_{13}H_{12}O_6$	59.35 4.3	59.09 4.54	5.35s	5.0m	4.85m			3.9s	5.35d[k] (*J* 7)
(**16a**)[l]	Ph$[CH_2]_2$-CHOH	89 49	180—181	MeOH–Et_2O	1 740, 3 420	$C_{14}H_{16}O_4$	67.8 6.7	67.74 6.45	5.26s	4.77d (*J* 2)	3.65m	1.8m	2.65m	3.78s	4.95d (*J*8)
(**16b**)[m]		40	84—85	Et_2O–C_6H_{14}	1 740, 3 435	$C_{14}H_{16}O_4$	67.7 6.6	67.74 6.45	5.27s	4.72d (*J* 3)	3.76m	1.7m	2.6m	3.76s	4.7d (*J* 8)
(**58**)	4-$MeOC_6H_4$-$[CH_2]_2$CHOH	53	174—177	EtOAc–C_6H_{14}	1 730, 3 350	$C_{15}H_{18}O_5$	64.9 6.5	64.80 6.53	5.26s	4.76 br s	3.7m	1.8m	2.6m	3.78s	4.85br[n]
(**59**)	Ver$[CH_2]_2$-CHOH	50	165—168	MeOH–Et_2O	1 730, 3 340	$C_{16}H_{20}O_6$	62.0 6.6	62.33 6.49	5.25s	4.76 br s	3.7m	1.8m	2.55m	3.78s	4.16d[o] (*J* 8)
(**60**)	Pip$[CH_2]_2$-CHOH	40	130—133	MeOH–Et_2O	1 740, 3 410	$C_{15}H_{16}O_6$	61.5 5.5	61.64 5.47	5.25s	4.75d (*J* 1)	3.65m	1.76m	2.58m	3.78s	4.89d[p] (*J*8)

* See footnote * in Table 2.

[a] Properties are of *threo*-isomers. [b] Isolated recrystallised yield of *threo*-isomer, with the exception of (**16**). [c] %C then %H. [d] All spectra run in $[^2H_6]Me_2SO$. [e] Exchanges with D_2O. [f] ArO*Me* 3.78s. [g] Ver = 3,4-dimethoxyphenyl. [h] Ar$(OMe)_2$ 3.72s (6 H). [i] Ar$(OMe)_3$ 3.8s (6 H) and 3.7s (3 H). [j] Pip = 3,4-methylenedioxyphenyl. [k] OCH_2O 6.0s. [l] *threo*-(**16**). [m] *erythro*-(**16**). [n] ArO*Me* 3.65s. [o] Ar$(OMe)_2$ 3.68 and 3.64. [p] OCH_2O 5.88.

diacetate (**52b**) (0.192 g, 70%), m.p. 198—199 °C (Found: C, 67.25; H, 5.75. $C_{23}H_{22}O_7$ requires C, 67.31; H, 5.36%); $\nu_{max.}$(KBr) 1 770, 1 760, and 1 645 cm^{-1}; δ_H 4.68 (1 H, s, 3-H), 6.15 (2 H, s, each 6-H), 3.62 (3 H, s, OMe), and 2.11 (6 H, s, OAc); *m/z* 305 (0.2%), 304 (3.1), 203 (42), 202 (100), 107 (12), and 105 (8).

Preparation of compound (**61**). The procedure followed was exactly that for compound (**48**), except that piperonal (3.75 g, 25 mmol) was substituted for benzaldehyde. *Compound* (**61**) (1.45 g, 70%) was obtained as white crystals, m.p. 241—243 °C (from MeOH–Et_2O) (Found: C, 61.0; H, 4.45. $C_{21}H_{18}O_9$ requires C, 60.86; H, 4.34%); δ_H 4.88 (1 H, s, 3-H), 4.95 (2 H, d, *J* 6 Hz, each 6-H), 3.55 (3 H, s, OMe), 6.05 (1 H, d, *J* 5 Hz, OH), and 6.05 (2 H, s, OCH_2O); $\nu_{max.}$(KBr) 1 750 and 1 635 cm^{-1}; *m/z* 248 (0.4%), 246 (28), 151 (15), 150 (100), 149 (100), 131 (39), 119 (11), and 114 (29).

Elimination Reactions of Compounds (**47**) *and* (**54**)—(**57**).—*Methyl 5-benzylidenetetronate* (**53**). The alcohol (**47**) (2 g) was added to stirred, conc. sulphuric acid at room temperature. After 10 min, the black solution was added carefully to crushed ice and the product was extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed successively with water (100 ml), 5% aqueous sodium hydrogen carbonate (10 ml), and saturated aqueous sodium chloride (100 ml). After the extracts had been dried, filtered, and evaporated, the crude product was recrystallised from methanol to give compound (**53**) (1.55 g, 85%), m.p. 138—140 °C. Most physical characteristics are given in Table 5, the ^{13}C n.m.r. data are reported in ref. 76.

Preparation of Methyl 5-Arylidenetetronates (**62**)—(**65**).—*General procedure.* A solution of the alcohol (**54**)—(**57**) (10 mmol) in dry pyridine (30 ml) was cooled to 0 °C, stirred, and treated with redistilled methanesulphonyl chloride (15 mmol). The mixture was allowed to warm to room temperature and was stirred in a stoppered flask for 20 h. A 20% aqueous solution of potassium acetate (100 ml) was added and the mixture was heated (80—90 °C) on a water-bath. The grey precipitate was filtered off and recrystallised. Physical data, yields, analyses, and recrystallisation solvents are given in Table 5. The ^{13}C n.m.r. spectra have been reported in ref. 76.

*Preparation of Toluene-*p*-sulphonates* (**66**)—(**69**).—*General procedure.* A solution of the alcohol (**16**) or (**58**)—(**60**) (10 mmol) in dry pyridine (10 ml) in a 100-ml glass-stoppered Erlenmeyer flask was cooled to 0 °C and treated with toluene-*p*-sulphonyl chloride (20 mmol). When solution was complete, the flask was placed in a refrigerator for 30 h. The mixture was poured into ice–water (300 g) and extracted with chloroform (3 × 100 ml). The combined extracts were washed successively with 5% hydrochloric acid (2 × 50 ml) and saturated aqueous cadmium chloride (100 ml) to remove last traces of pyridine. The organic layer was dried (Na_2SO_4), filtered, and evaporated at water-pump pressure. The tosyl esters (**66**)—(**69**) were purified by recrystallisation, relevant data being shown in Table 6.

*Conversion of Toluene-*p*-sulphonates* (**66**)—(**69**) *into Dihydrocinnamylidene Derivatives* (**70**)—(**73**).—The tosyl ester (**66**)—(**69**) (10 mmol) was placed in a 50 ml round-bottomed flask fitted with condenser and drying tube, and dry pyridine (25 ml) was added. The mixture was heated under reflux for 5 h, cooled, poured into stirred ice–water (100 g), and extracted with chloroform (3 × 100 ml). The combined extracts were washed successively with 5% hydrochloric acid (100 ml), saturated aqueous cadmium chloride (100 ml), and water (100 ml). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed. The product was placed on a silica column, eluted with a mixture light petroleum–chloroform (1:1), and recrystallised. The relevant data for compounds (**70**)—(**73**) are in Table 5. The ^{13}C n.m.r. data have been reported in ref. 76.

Preparation of Methyl Cinnamylidenetetronates (**13**) *and* (**74**)—(**76**).—(i) *General procedure.* A mixture of a methyl 5-

Table 5. Data relating to methyl 5-arylidenetetronates and 5-arylalkylidenetetronates*

Compd.	Group on C-6	Yield (%)[a]	M.p. (°C)	Crystallisation solvent	$\nu_{max.}$(KBr) cm^{-1}	Formula	Analysis[b] Found	Analysis[b] Calc.	δ_H 3-H	6-H	7-H	8-H	4-OMe
(**53**)	Ph	85	138—140	MeOH	1 780, 1 760, 1 610	$C_{12}H_{10}O_3$	71.1 5.1	71.28 4.95	5.70s[c]	6.29s			3.92s
(**62**)	4-$MeOC_6H_4$	75	98—100	MeOH	1 780, 1 760, 1 615, 1 600	$C_{13}H_{12}O_4$	67.3 5.3	67.24 5.17	5.62s[c]	6.22s			3.92s[d]
(**63**)	3,4-$(MeO)_2C_6H_3$	78	142—144	THF–Et_2O	1 790, 1 760, 1 610, 1 600	$C_{14}H_{14}O_5$	64.1 5.4	64.12 5.34	5.70s[c]	6.30s			4.05[e]
(**64**)	3,4,5-$(MeO)_3C_6H_2$	84	184—185	THF	1 770, 1 750, 1 600, 1 580	$C_{15}H_{16}O_6$	61.5 5.4	61.64 5.47	5.48s[c]	6.10s			3.86s[f]
(**65**)	3,4-$(OCH_2O)C_6H_3$	75	166—168	THF–Et_2O	1 780, 1 750, 1 600	$C_{13}H_{10}O_5$	63.8 4.4	63.41 4.06	5.63s[c]	6.2s			3.92s[g]
(**70**)	$Ph[CH_2]_2$	69	Oil		1 780, 1 620, 1 615	$C_{14}H_{14}O_3$	73.15 6.3	73.04 6.08	5.10s	5.38t	2.68m	2.68m	3.75s
(**71**)	4-$MeOC_6H_4[CH_2]_2$	77	Oil		1 780, 1 620	$C_{15}H_{16}O_4$	69.1 6.4	69.23 6.15	5.10s	5.37t	2.62m	2.62m	3.79s[h]
(**72**)	3,4-$(MeO)_2C_6H_3[CH_2]_2$	64	78—80	EtOH	1 750, 1 610	$C_{16}H_{18}O_5$	66.2 6.2	66.20 6.20	5.18s	5.42t	2.70m	2.70m	3.80s[i]
(**73**)	3,4-$(OCH_2O)C_6H_3$	90	Oil		1 750, 1 610	$C_{15}H_{14}O_5$	65.7 5.0	65.69 5.10	5.12s	5.35t	2.59m	2.59m	3.78s[j]

* See footnote * in Table 2.
[a] All yields of purified, isolated product. [b] %C, %H. [c] Run in [$^2H_6$]Me_2SO. [d] OMe 3.74s. [e] 2 × OMe 3.82s. [f] 2 × OMe 3.78, OMe 3.6s. [g] OCH_2O 6.0s. [h] OMe 3.7s. [i] OMe 3.6s and 3.4s. [j] OCH_2O 5.8s.

Table 6. Data relating to compounds (**66**)—(**69**)*

Compd.	6-Substituent	Yield (%)[a]	M.p. (°C)	Crystallisation solvent	$\nu_{max.}$ (KBr) cm^{-1}	Formula	Analysis[b] Found	Analysis[b] Calc.	δ_H 3-H	5-H	6-H	7-H	8-H	4-OMe
(**66**)	$Ph[CH_2]_2$	75	128—130	$CHCl_3$–Et_2O	1 750, 1 630	$C_{21}H_{22}O_6S$	62.5 5.7	62.68 5.47	5.05	4.76br	4.9m	2.05m	2.59m	3.7s
(**67**)	4-$MeOC_6H_4[CH_2]_2$	64	121—123	MeOH–Et_2O	1 760, 1 630	$C_{22}H_{24}O_7S$	61.4 5.5	61.11 5.55	4.98s	4.74br	4.85dd (*J* 2, 1)	2.05m	2.48m	3.69s[c]
(**68**)	3,4-$(MeO)_2C_6H_3[CH_2]_2$	60	123—125	$CHCl_3$–C_6H_{14}	1 750, 1 635	$C_{23}H_{26}O_8S$	59.8 5.6	59.74 5.62	5.0s	4.78br	4.78br	2.1m	2.60m	3.7s[d]
(**69**)	3,4-$(OCH_2O)C_6H_3$	65	124—126	$CHCl_3$–Et_2O	1 750, 1 640	$C_{22}H_{22}O_8S$	59.1 4.8	59.19 4.93	5.0s	4.76br	4.85dd (*J* 2, 1)	2.0m	2.47m	3.7s[e]

* See footnote * in Table 2.
[a] All yields are of recrystallised product. [b] %C, %H. [c] MeO 3.69s. [d] 2 × OMe 3.7s. [e] OCH_2O 6.0s.

(2′,3′-dihydrocinnamylidene)tetronate (**70**)—(**73**), DDQ (0.229 g, 1.5 mmol), and dry benzene (30 ml) was heated under reflux in an inert atmosphere until there was no trace of starting material [24 h for (**70**)—(**72**) and 48 h for (**70**)]. As the reaction proceeded there was precipitation of the hydroquinone and the intense red colour of the solution faded. The mixture was cooled, then filtered, and the insoluble hydroquinone was well washed with benzene (2 × 5 ml). The combined filtrate and washings were concentrated under reduced pressure, the residue was placed on an alumina column, and the product was eluted with benzene. Concentration of the solvent was followed by crystallisation to give the required methyl cinnamylidenetetronate. The physical characteristics of these compounds are reported in Table 7; the ^{13}C n.m.r. data have been given in ref. 76.

(ii) *Preparation of compound* (**13**) *from the chloride* (**94**) (vide infra). A solution of compound (**94**) (mixture of *erythro* and *threo* isomers, 130 mg, 0.49 mmol) in dry benzene (5 ml) was stirred with DBU (0.1 ml, 0.5 mmol) at room temperature for one week. The mixture was filtered, the filtrate was concentrated, and the resulting black oil (0.143 g) was purified by p.l.c. on silica gel with diethyl ether as developer. This gave compound (**13**) (0.105 g, 94%) as yellow crystals, m.p. 128—130 °C.

Preparation of Ketone (**77**).—The alcohol (**16**) (0.15 g, 0.6 mmol) was dissolved in AnalaR glacial acetic acid (6 ml), and a solution of chromium trioxide (0.08 g, 0.8 mmol) in a mixture of water (0.1 ml) and glacial acetic acid (0.3 ml) was added. The mixture was stirred overnight, and diluted with water (50 ml), and dichloromethane (10 ml) was added. The resulting emulsion was broken by addition of 3% aqueous ammonia, the dichloromethane layer was separated, and the aqueous extract was washed with dichloromethane (4 × 20 ml). The combined extracts were washed successively with saturated aqueous

Table 7. Data relevant to compounds (13) and (74)—(76)*

Compd.	8-Aryl group	Yield (%)[a]	M.p. (°C)	Crystallisation solvent	$\nu_{max.}$ (KBr) cm^{-1}	Formula	Analysis[b] Found	Analysis[b] Calc.	δ_H 3-H	6-H	7-H	8-H	4-OMe
(13)	Ph	77	128—130	$CHCl_3$–Et_2O	1 770, 1 755, 1 600	$C_{14}H_{13}O_3$	73.6 5.3	73.68 5.26	5.18s	6.05d (*J* 11)	7.1dd (*J* 11, 16)	6.7d (*J* 16)	3.82s
(74)	4-$MeOC_6H_4$	87	125—127	$CHCl_3$–Et_2O	1 770, 1 750, 1 600	$C_{15}H_{14}O_4$	69.6 5.4	69.76 5.42	5.14s	6.05d (*J* 11)	7.05m	6.65d (*J* 16)	3.82s[c]
(75)	3,4-$(MeO)_2C_6H_3$	78	145—149	$CHCl_2$–Et_2O	1 770, 1 750, 1 600	$C_{16}H_{16}O_5$	67.0 5.15	66.66 5.55	5.18s	6.05d (*J* 11)	6.8m	6.60d (*J* 16)	3.82s[d]
(76)	3,4-$(OCH_2O)C_6H_3$	85	195—199	C_6H_6–Et_2O	1 760, 1 740, 1 600	$C_{15}H_{12}O_5$	66.3 4.8	66.17 4.41	5.16s	6.02d (*J* 11)	6.8m	6.60d (*J* 16)	3.83s[e]

* See footnote * in Table 2.
[a] All yields are of crystallised product. [b] %C %H. [c] MeO 3.72s. [d] 2 × OMe 3.86s. [e] OCH_2O 5.86s.

Table 8. Physical and spectroscopic properties of compounds (79)—(83)*

Compd.	Yield (%)[a]	M.p. (°C)	$\nu_{max.}$ (KBr) cm^{-1}	Formula	Analysis[b] Found	Analysis[b] Calc.	δ_H 3-H	5-H	OMe
(79)	67	128—130[c]	1 780, 1 750, 1 680, 1 630	$C_{12}H_{10}O_4$	66.15 4.2	66.05 4.58	5.25s	6.12s	3.9s
(80)	50	161—164[c]	1 770, 1 740, 1 670, 1 630	$C_{12}H_9ClO_4$	57.1 3.65	57.14 3.37	5.24s	6.02s	3.92s
(81)	51	150—152[c]	1 780, 1 750, 1 680, 1 630	$C_{13}H_{10}O_6$	59.25 3.9	59.54 3.81	5.6s	6.8s	3.9s
(82)	45	240—245[d]	1 790, 1 750, 1 730, 3 250	$C_{17}H_{16}O_7$	61.3 4.65	61.44 4.81	5.28s 5.2s	5.57s 5.0s	3.57s[e,f] 3.5s
(83)	45	227—229[d]	1 750, 3 380	$C_{19}H_{20}O_7$	63.0 5.6	63.33 5.55	5.4s	5.02s	3.82s[e,g]

* See footnote * in Table 2.
[a] Yields are of purified crystallised product. [b] %C, then %H. [c] Recrystallised from $CHCl_3$–EtO. [d] Recrystallised from MeOH–Et_2O. [e] Run in $[^2H_6]Me_2SO$. [f] OH 6.14s. [g] 7-H 1.75m, 8-H 2.6m.

sodium hydrogencarbonate (2 × 10 ml) and water (2 × 10 ml), and dried ($MgSO_4$). Filtration, and evaporation of the solvent, gave a clear oil (97.5 mg). From this, p.l.c. [silica; CH_2Cl_2–EtOAc (9:1)] gave a middle band, which was separated and extracted with methanol. Filtration and evaporation gave the acyloin (77) (47 mg), identical in all respects with an authentic sample (given by J. Schulz, Berlin); *m/z* 150 (13%), 134 (14), 133 (21), 129 (22), 105 (48), 104 (17), 92 (26), and 91 (100); $\nu_{max.}$(film) 3 400, 1 775, and 1 740 cm^{-1}; δ_C 170.3 (C-2), 91.0 (C-3), 177.0 (C-4), 139.9 (C-5), 201.2 (C-6), 37.1 (C-7), and 29.1 (C-8); δ_H 5.14 (1 H, s, 3-H), 2.86 (4 H, br, 7- and 8-H_2), 3.72 (3 H, s, OMe), 4.9—5.6 (1 H, br, OH), and 6.9—7.4 (5 H, m, Ph). Starting alcohol (20 mg) was also recovered from the front band (R_F *ca.* 0.8) of the preparative plate.

Preparation of Ketones (79)—(81) *and Alcohols* (82) *and* (83) *from Compound* (23) *and Acid Chlorides.*—A solution of the acid chloride (5 or 10 mmol) in THF (10 ml) was cooled to −78 °C and added by nitrogen pressure through a cannula to a solution of lithium compound (23) (procedure A) in THF also held at −78 °C. The mixture was allowed to warm to room temperature, and was then stirred for 2 h, poured onto crushed ice, and brought to pH 6 with dil. HCl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (4 × 200 ml). The combined organic phases were washed with water (4 × 100 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Crystallisation from the appropriate solvents yielded the corresponding product.

For benzoyl and dihydrocinnamoyl chlorides, equivalent quantities gave mainly the alcohols (82) and (83), whereas either 1 or 2 equiv. of 4-chlorobenzoyl chloride or piperonyloyl chloride gave mainly the ketones (80) and (81). Surprisingly, use of 2 equiv. of benzoyl chloride gave mainly (67%) the ketone (79). The yields, characterisations, and some physical properties of compounds (79)—(83) are in Table 8. The ^{13}C n.m.r. data of compounds (79)—(81) are reported in ref. 76. Compound (82) has δ_C 171.6, 171.3 (C-2), 90.3, 90.7 (C-3), 179.8, 180.7 (C-4), 79.5, 80.6 (C-5), and 76.7 (C-6).

Preparation of Compounds (84)—(86) *by Condensation of* (E)-p-*Methoxycinnamonitrile with Methyl* 5-*Lithiotetronate* (23).—*Preparation of methyl* 5-[2-*cyano*-1-(p-*methoxyphenyl*) *ethyl*]-*tetronate* (84). (*E*)-*p*-Methoxycinnamonitrile (1.5 g, 10 mmol) and triethyloxonium tetrafluoroborate (1.9 g, 10 mmol) were stirred together in THF for 3 h at room temperature. The solution was then slowly siphoned through a cannula into a stirred solution of methyl 5-lithiotetronate (23) (method A) (10 mmol) at −78 °C under nitrogen pressure, and the mixture was allowed to warm to room temperature and was then stirred for a further 2 h before being poured over crushed ice and brought to pH 6 with dil. hydrochloric acid and the organic layer separated. The aqueous phase was extracted with ethyl acetate (4 × 200 ml), and the organic phases were combined and extracted with water (4 × 100 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a pale yellow oil (4.4 g). The oil was placed on a column of silica gel, from which elution with a 1:1 mixture of chloroform–light petroleum gave *compound* (84) (1.5 g, 55%) as white needles, m.p. 121—124 °C (Found: C, 65.7;

H, 5.7; N, 5.0%; $M^{+\bullet}$, 273.1000. $C_{15}H_{15}NO_4$ requires C, 65.93; H, 5.49; N, 5.12%; $M^{+\bullet}$, 273.1000); $\nu_{max.}$ 2 260 and 1 755 cm^{-1}; δ_H 4.7 (1 H, s, 3-H), 5.0 (1 H, m, 5-H), 3.4 (1 H, m, 6-H), 2.8 (2 H, m, 7-H), and 3.64 (6 H, s, OMe); δ_C 171.4, 171.2 (C-2), 90.1, 89.9 (C-3), 180.5 (C-4), 79.5, 78.9 (C-5), 42.2, 42.0 (C-6), 19.9, 17.4 (C-7), 126.4 (C-1'), 129.4, 128.9 (C-2'), 118.8, 113.6 (C-3'), 158.4 (C-4'), 59.9, 59.6 (OMe, butenolide), and 54.9 (ArO*Me*).

Preparation of methyl 5-[2',4'-*dicyano*-1',3'-*bis*-(p-*methoxyphenyl*)*butyl*]*tetronate* (**85**). A solution of (*E*)-p-methoxycinnamonitrile (1.59 g, 10 mmol) in THF (15 ml) was cooled to −78 °C and added to a stirred solution of methyl 5-lithiotetronate (**23**) (10 mmol, procedure A) in THF, also at −78 °C. The mixture was allowed to warm to 0 °C, and was then stirred for 1 h. A saturated solution of hydrogen chloride in dry methanol (10 ml) was added, and the mixture was stirred for a further 2 h at room temperature. Work-up as in the previous experiment gave a yellow oil (3.0 g). Silica gel chromatography with a 1:1 mixture of light petroleum and chloroform gave *compound* (**85**) (1.09 g, 25%), m.p. 108—110 °C (from $CHCl_3$) (Found: C, 69.15; H, 5.5; N, 5.8. $C_{25}H_{24}N_2O_5$ requires C, 69.44; H, 5.55; N, 6.48%); $M^{+\bullet}$, 432; $\nu_{max.}$(KBr) 2 260, 1 750, 1 640, and 1 620 cm^{-1}; δ_H 4.68 (1 H, d, 3-H), 5.24 (1 H, m, 5-H), 3.5 (2 H, m, 6- and 8-H), 2.8 (3 H, m, 7- and 9-H), 3.7 (6 H, s, 2 × ArO*Me*), 3.62 (3 H, s, butenolide OMe), and 2.8—3.3 (*ca.* 10 H, m, ArH); δ_C 171.3 (C-2), 90.3 (C-3), 179.7 (C-4), 78.4 (C-5), 41.6 (C-6), 39.3 (C-7), 46.9 (C-8), 18.9 (C-9), 118.2, 117.5 (2 × CN), 59.4 (butenolide OMe), 55.3 (2 × ArO*Me*), 130.5, 123.1 (C-1', C-1''), 129.8, 127.9 (C-2', C-2''), 114.8 (C-3', C-3''), and 160.1, 159.8 (C-4', C-4'').

Further elution of the column with chloroform yielded a compound (1.67 g), m.p. 187—190 °C, of unknown structure.

Preparation of 2,5-*Dihydroxy*-4-*methoxy*-6-(p-*methoxyphenyl*) *cyclohexa*-1,3-*diene*-1-*carbonitrile* (**86**). A solution of (*E*)-cinnamonitrile (1.59 g, 10 mmol) in dry THF (15 ml) was added to a solution of methyl 5-lithiotetronate (**23**) (10 mmol) in THF (procedure A) at −78 °C. The solution was allowed to warm to room temperature and was then worked up as in the previous two experiments to give a yellow oil (2.2 g). Column chromatography first gave compound (**84**) (0.5 g, 20%) as white needles, m.p. 121—125 °C (from Et_2O), eluted with light petroleum–chloroform (1:1). Further elution with neat chloroform gave the *title compound* (**86**) (0.38 g, 14%) as white needles, m.p. 167—170 °C (from $CHCl_3$) (Found: C, 65.6; H, 5.3; N, 5.2%; $M^{+\bullet}$, 273.100. $C_{15}H_{15}NO_4$ requires C, 65.93; H, 5.49; N, 5.12%; *M*, 273.100); $\nu_{max.}$ 3 450, 2 275, 1 675, and 1 610 cm^{-1}; δ_H[$(CD_3)_2SO$] 5.45 (1 H, s, 3-H), 4.45 (1 H, d, *J* 10 Hz, 5-H), 3.25 (1 H, d, *J* 10 Hz, 6-H), and 7.1 (4 H, d, *J* 12 Hz, ArH).

Preparation of Compounds (**14**), (**45**), *and* (**88**)—(**90**) *by the 'Double Activation' Technique.—General procedure.* A solution of the acetal or orthoester (2.5 mmol)* in dry diethyl ether (10 ml) was added dropwise to efficiently stirred freshly distilled trifluoroborane–diethyl ether (0.31 ml, 2.5 mmol*) at −78 °C under nitrogen. The mixture was stirred for a further 20 min, and an ethereal solution of methyl 5-lithiotetronate (**23**) [prepared as in procedure B for (**23**), but with dry diethyl ether replacing the THF used] (2.5 mmol*) was then added through a double-ended needle during 5 min to the well stirred slurry by means of nitrogen pressure. The reaction mixture was allowed to warm to room temperature during 2 h, and was then diluted with diethyl ether (25 ml), washed successively with saturated aqueous sodium hydrogencarbonate (15 ml) and water (2 × 15 ml), dried ($MgSO_4$), filtered, and evaporated. Crystallisation of the residue from the appropriate solvent often yielded product directly, but column chromatography prior to crystallisation was needed in some cases.

Preparation of methyl 5-(*dimethoxymethyl*)*tetronate* (**45**). The general procedure outlined above was used, starting with lithium compound (**23**) (10 mmol), trimethyl orthoformate (4.24 g, 40 mmol), and trifluoroborane–diethyl ether (10 mmol), with a diethyl ether:THF mixture (10:1) as solvent. Work-up as in the general procedure gave compound (**45**) (1.32 g, 85%). For characterisation and physical characteristics see Tables 9 and 10.

Methyl 5-(1,1-*dimethoxyethyl*)*tetronate* (**88**). Anion (**23**) (5 mmol), trimethyl orthoacetate[84] (1.2 g, 10 mmol), and trifluoroborane–diethyl ether (10 mmol) were allowed to react according to the general procedure, with Et_2O–THF (10:1) as solvent. The usual work-up gave an oil (1.5 g), which was purified by elution [dichloromethane, then dichloromethane–ethyl acetate (9:1)] from a silica gel column. Methyl tetronate (**20**) (0.12 g) was recovered from the first fractions, and then compound (**88**) (0.65 g, 81%), m.p. 78.5 °C (from Et_2O). Characterisation and physical data for compound (**88**) are given in Tables 9 and 10.

Methyl 5-(1',1'-*dimethoxybenzyl*)*tetronate* (**89**). The general procedure given was applied to trimethyl orthobenzoate[85] to give compound (**89**) (82%), m.p. 102 °C (from Et_2O) (based on consumed methyl tetronate), plus recovered methyl tetronate (**20**) (0.15 g, 53%). It was noticed that reverse addition to that given in the general procedure lowered the yield by *ca.* 30%. Characterisation and physical data for compound (**89**) are given in Tables 9 and 10.

Preparation of methyl 5-(*methoxycarbonyl*)*tetronate* (**46**). This compound was prepared by the general procedure from compound (**23**) (2.5 mmol), tetramethyl orthocarbonate (0.7 g, 5 mmol), and trifluoroborane–diethyl ether (2.5 mmol) at −78 °C. Work-up as usual gave compound (**46**) (0.35 g, 81%), m.p. 79 °C (from Et_2O). Analytical and some physical properties are in Table 9. ^{13}C N.m.r. data are in Table 10. The mass spectrum had peaks at *m/z* 172 (6%), 113 (100), 85 (31), 69 (16), and 59 (17).

Preparation of 5,6-*dihydropiperolide* (**14**). Compound (**14**) was prepared according to the general procedure, starting with compound (**23**) (procedure B) (1 mmol), trifluoroborane–diethyl ether (1 mmol), and the dimethyl acetal of cinnamaldehyde[86] (0.18 g, 1 mmol). Work-up as in the general procedure gave an oil, purified by p.l.c. on silica gel developed with chloroform. This yielded compound (**14**) (0.193 g, 74%) as a mixture of *threo* and *erythro* isomers. Physical data are in Tables 9 and 10. The mass spectrum of the mixture had peaks at *m/z* 228 (1.3%), 147 (100), 115 (37), 113 (3), 91 (14), and 77 (9).

Preparation of methyl 5-(1-*methoxybenzyl*)*tetronate* (5,6-*dihydrofadyenolide*) (**90**). Compound (**90**) was prepared by application of the general procedure, starting with compound (**23**) (procedure B) (2.5 mmol), benzaldehyde dimethyl acetal (0.76 g, 5 mmol), and trifluoroborane–diethyl ether (5 mmol). After the usual work-up the *threo*-isomer (**90a**) crystallised from methanol as white crystals, m.p. 75—76 °C (0.22 g, 37.6%), and by concentration of the mother liquor the *erythro*-isomer (**90b**), m.p. 96—97 °C (0.24 g, 41%), was also isolated. Physical data and analyses for isomers (**90a**) and (**90b**) are given in Tables 9 and 10. Compound (**90a**) had peaks in the mass spectrum at *m/z* 202 (25%), 121 (100), 118 (8), 113 (1), 90 (8), 77 (15), 69 (36), and 41 (2); and isomer (**90b**) had *m/z* 234 (0.6%), 202 (18), 121 (100), 118 (3), 113 (3), 90 (3), 77 (23), 69 (24), and 41 (31).

The Reactions of 4-*Methoxy*-2-(*trimethylsiloxy*)*furan* (**24**) *with Carbon Electrophiles.—General procedures. A.* 4-Methoxy-2-(trimethylsiloxy)furan (**24**) (0.93 g, 5 mmol) was added by syringe during 1 min to a well stirred mixture of compound (X) (5 mmol) and powdered anhydrous zinc bromide (50 mg) in dry dichloromethane (20 ml) at −95 °C under nitrogen. The syringe

* Unless otherwise stated.

Table 9. Characterisation and some physical properties of ketals (**45**), (**88**), (**89**), and (**91**), ethers (**14**) and (**90**), and ester (**46**)*

Compd.	Yield (%)[a]	M.p. (°C)	$\nu_{max.}$/cm^{-1}	Formula	Analysis[b] Found	Calc.	δ_H 3-H	5-H	6-H	7-H	8-H	4-OMe	6-OMe
(**45**)	85	Oil	1 765, 1 640	$C_8H_{12}O_5$	50.9 6.7	51.06 6.38	5.12d (*J* 2)	4.8dd (*J* 2, 6)	4.53d (*J* 6)			3.90s	3.40s, 3.32s
(**88**)	81	78.5[c]	1 770, 1 645	$C_9H_{14}O_5$	53.4 7.1	53.46 6.93	5.15d (*J* 2)	4.88d (*J* 2)		1.17s		3.92s	3.29s
(**89**)	82	102[c]	1 758, 1 745, 1 640	$C_{14}H_{16}O_4$	63.7 5.8	63.64 6.08	5.09d (*J* 2)	4.61d (*J* 2)				3.72s	3.40s, 3.32s
(**91**)	75	Oil	1 765, 1 675	$C_9H_{13}BrO_3$	38.7 4.85	38.43 4.64	5.10d (*J* 2)	5.16		3.51s		3.94s	3.38s
(**14a**)[d]	74	Oil	1 800, 1 760,				5.1d (*J* 2)	4.92d (*J* 2)	4.11dd (*J* 2, 8)	6.11d (*J* 16, 8)	6.66d (*J* 16)	3.84s	3.26s
(**14b**)[d]		Oil	1 638	$C_{15}H_{16}O_4$	*e*		5.04d (*J* 2)	4.76d (*J* 2)	4.02dd (*J* 2, 8)	6.06dd (*J* 16, 8)	6.60d (*J* 16)	3.81s	3.32s
(**90a**)[f]	38	75—76[h]	1 758, 1 645, 1 610	$C_{13}H_{14}O_4$	66.5[i] 6.25	66.66 5.98	5.0d (*J* 2)	4.88dd (*J* 2, 4)	3.51d (*J* 4)			3.84s	3.28s
(**90b**)[g]	41	96—97[h]	1 778, 1 767, 1 646 1 610				4.80d (*J* 2)	5.12dd (*J* 2, 4)	3.57d (*J* 4)			3.6s	3.30s
(**46**)	81	79[c]	1 800, 1 765, 1 640	$C_7H_8O_5$	49.0 4.8	48.84 4.65	5.23s	5.23s				3.95d	3.73s

* See footnote * in Table 2.
[a] Yield of isolated, purified material. [b] %C, %H. [c] From Et_2O. [d] Isolated as mixture of (**14a**) *threo*, and (**14b**) *erythro*, isomers. [e] Known compound (ref. 18). [f] *threo*-Isomer. [g] *erythro*-Isomer. [h] From MeOH. [i] Analysis on mixture of *erythro* and *threo* isomers.

Table 10. ^{13}C N.m.r. data (δ_C) for compounds (**14**), (**45**), and (**88**)—(**91**)*

Compd.	Heterocyclic carbons C-2	C-3	C-4	C-5	Aliphatic carbons C-6	C-7	C-8	4-OMe	6-OMe	Aromatic carbons C-1′	C-2′	C-3′	C-4′
(**45**)	172.1	90.1	179.5	78.9	102.9			59.8	56.2, 55.9				
(**88**)	172.0	90.2	180.5	78.9	100.4	16.9		60.0	49.0, 48.7				
(**89**)	171.5	90.5	179.7	78.4	102.6			59.4	49.7, 49.4	134.8	128.1	127.5	128.8
(**91**)	171.5	90.6	179.9	77.9	99.6	29.2		59.8	49.9				
(**14a**)	172.5	90.0	179.8	80.8	79.9	124.3	135.2	59.6	57.1	135.8	126.8	128.7	128.7
(**14b**)	172.5	90.3	179.6	81.4	80.8	122.6	135.2	59.7	56.9	135.8	126.8	128.7	128.5
(**90a**)	172.1	90.2	179.4	80.5	81.2			59.4	57.5	136.1	128.4[a]	127.5	128.5[b]
(**90b**)	172.0	90.3	179.6	80.8	82.7			59.6	57.5	134.4	128.2[a]	127.8	128.6[b]
(**46**)	171.5	89.1	177.3	76.4	165.7			60.3	53.4				

* See footnote * in Table 2.
[a,b] These assignments are interchangeable.

was washed with dichloromethane (2 ml), which was then added to the mixture. The mixture was stirred for 1 h at −95 °C, allowed to warm to room temperature, and stirred for a further 2 days. Dry diethyl ether (50 ml) and dry dichloromethane (30 ml) were added, and zinc bromide was filtered off with strict exclusion of air and moisture. The solvent was evaporated off under reduced pressure to yield the desired product.

B. A solution of compound (**24**) (0.372 g, 2 mmol) in dry dichloromethane (2 ml) was added to a stirred mixture of compound (X) (2 mmol) and titanium tetrachloride (0.22 ml, 2 mmol) in dry dichloromethane (3 ml) under nitrogen at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, allowed to warm to room temperature, diluted with dichloromethane (20 ml), and washed successively with saturated aqueous sodium hydrogencarbonate (2 × 5 ml) and water (5 ml), dried ($MgSO_4$), and the solvent was removed to give product, which was further purified as appropriate.

Reactions of Compound (**24**) *with Orthoesters.—Synthesis of methyl* 5-(*methoxycarbonyl*)*tetronate* (**46**). Compound (**46**) was prepared by addition of titanium tetrachloride (0.18 ml, 1.61 mmol) to a stirred mixture of tetramethyl orthocarbonate (0.22 g, 1.61 mmol) and compound (**24**) (0.30 g, 1.61 mmol) in dichloromethane (15 ml) at −78 °C under nitrogen. The reaction mixture was allowed to warm to room temperature, then worked up as in procedure B above. Removal of the solvent gave compound (**46**) (0.23 g, 83%) as white crystals, m.p. 79 °C, identical in all respects with the sample prepared by 'double activation' and characterised in Tables 9 and 10.

Methyl 5-(*dimethoxymethyl*)*tetronate* (**45**). Trimethyl orthoformate (0.53 g, 5 mmol) and compound (**24**) were treated according to procedure A to give compound (**45**) (0.88 g, 93%), characterisation of which is given in Tables 9 and 10.

Methyl 5-(1′,1′-*dimethoxyethyl*)*tetronate* (**88**). Trimethyl orthoacetate[84] (1.8 g, 15 mmol) and compound (**24**) (5 mmol) were treated according to procedure A to give compound (**88**) (1.01 g, 100%), characterised in Tables 9 and 10.

Methyl 5-(2′-*bromo*-1′,1′-*dimethoxyethyl*)*tetronate* (**91**). 2-Bromo-1,1,1-trimethoxyethane[87] (0.6 g, 3 mmol), compound (**24**) (0.37 g, 2 mmol), and zinc bromide (50 mg) were treated

according to method A to give compound (**91**) (0.42 g, 75%) as an oil. Analysis and characterisation are given in Tables 9 and 10.

Methyl 5-(1′,1′-*dimethoxybenzyl*)*tetronate* (**89**). Trimethyl orthobenzoate (0.93 g, 5 mmol), compound (**24**) (0.93 g, 5 mmol), and powdered, anhydrous zinc bromide (50 mg) were reacted according to method A, to give compound (**89**), (1.26 g, 95.5%) as white crystals, m.p. 102 °C, identical in all respects with the product of the 'double activation' method, and characterised in Tables 9 and 10.

Methyl 5-(1′-*methoxybenzyl*)*tetronate* (**90**). Method A was applied to benzaldehyde dimethyl acetal (0.76 g, 5 mmol) and compound (**24**) (0.93 g, 5 mmol) to give compound (**90**) (1.09 g, 93%) as a mixture of *threo* and *erythro* isomers. See Tables 9 and 10 for characterisation of the product from the 'double activation' reaction, with which this product was identical.

Methyl 5-(1′-*methoxycinnamyl*)*tetronate* (5,6-*dihydropiperolide*) (**14**). Cinnamaldehyde dimethyl acetal (0.18 g, 1 mmol), compound (**24**) (0.186 g, 1 mmol), and titanium tetrachloride (0.11 ml, 1 mmol) were treated as in procedure B. P.l.c. on silica gel developed with toluene gave compound (**14**) (0.25 g, 96%) as a mixture of two diastereoisomers, characterised in Tables 9 and 10.

Methyl 5-(1′-*chlorocinnamyl*)*tetronate* (**94**). Cinnamaldehyde dimethyl acetal (0.45 g, 2.5 mmol), compound (**24**) (0.47 g, 2.5 mmol), and titanium tetrachloride (0.55 ml, 5 mmol) were treated as in procedure B to give a brown oil (1.05 g). Crystallisation from chloroform gave *threo*-(**94**) (0.28 g, 42.4%) as white crystals, m.p. 133—134 °C. From the mother liquor was isolated a mixture of *threo* and *erythro* isomers. For *threo*-(**94**) (Found: C, 63.4; H, 5.0. $C_{14}H_{13}ClO_3$ requires C, 63.64; H, 4.92%); $\nu_{max.}$(KBr) 1 754 and 1 638 cm^{-1}; δ_H 5.19 (1 H, d, *J* 1 Hz, 3-H), 4.94 (1 H, dd, *J* 1 and 2 Hz, 5-H), 4.84 (1 H, dd, *J* 2 and 8 Hz, 6-H), 6.35 (1 H, dd, *J* 8 and 16 Hz, 7-H), 6.74 (1 H, d, *J* 16 Hz, 8-H), and 3.88 (3 H, s, OMe); δ_C 171.6 (C-2), 90.9 (C-3), 178.5 (C-4), 80.0 (C-5), 59.4 (C-6), 124.5 (C-7), 134.7 (C-8), 135.3 (C-1′), 127.0 (C-2′), and 128.7 (C-3′ and -4′).

Methyl 5-(1′-*hydroxybenzyl*)*tetronate* (**47**). Benzaldehyde (0.2 ml, 2 mmol), compound (**24**) (0.37 g, 2 mmol), and titanium tetrachloride (0.22 ml, 2 mmol) were treated together according to procedure B to give *threo*-(**47**) (0.335 g, 76%) as white crystals, m.p. 147—149 °C, identical in all respects with an authentic sample. The physical properties of compound (**47**) are given in Table 4.

Methyl 5-(1′-*hydroxy*-3′-*phenylpropyl*)*tetronate* (**16**). Alcohol (**16**) was prepared as a mixture of diastereoisomers (**16a**) and (**16b**) (Table 4) by use of procedures A and B on dihydrocinnamaldehyde (0.27 g, 2 mmol) and compound (**24**) (0.372 g, 2 mmol) in 89 and 85% yield respectively. Physical constants for isomers (**16a**) and (**16b**) are given in Table 4.

Methyl 5-(1′-*hydroxy*-1′-*methylethyl*)*tetronate* (**92**). Acetone (0.15 g, 2.5 mmol), compound (**24**) (0.372 g, 2 mmol), and titanium tetrachloride (0.22 ml, 2 mmol) at −78 °C were treated together according to procedure B. Work-up yielded *compound* (**92**) (0.28 g, 82%), m.p. 71—72 °C (from Et_2O) (Found: C, 55.75; H, 7.2. $C_8H_{12}O_4$ requires C, 55.81; H, 6.98%); $\nu_{max.}$(KBr) 3 540, 1 753, and 1 632 cm^{-1}; δ_H 5.20 (1 H, s, 3-H), 4.62 (1 H, s, 5-H), 1.17, 1.15 (6 H, 2 × CMe), 3.92 (3 H, s, OMe), and 3.51 (1 H, s, OH); δ_C 172.9 (C-2), 90.0 (C-3), 181.2 (C-4), 71.3 (C-5), 59.4 (C-6), 25.4, 24.8 (2 × C*Me*), and 59.9 (OMe); *m/z* 114 (100%), 113 (4), 59 (97), 58 (2), and 43 (48).

Methyl 5-(1′-*acetoxyethylidene*)*tetronate* (**93**). Compound (**24**) (0.19 g, 1 mmol) was added to a stirred mixture of acetyl chloride (1 ml) and titanium tetrachloride (0.11 ml, 1 mmol) held at −80 °C under nitrogen. The reaction mixture was stirred at −80 °C for 30 min, then allowed to warm to room temperature overnight.

The mixture was added to water (5 ml), diluted with diethyl ether (40 ml), and washed successively with saturated aqueous sodium hydrogencarbonate (2 × 15 ml), water (2 × 15 ml), dried ($MgSO_4$), and filtered, and the solvent was evaporated off to yield a pale brown crystalline solid (131 mg). This was purified by t.l.c. on silica gel developed with diethyl ether. The second band (R_F ~0.5) was recovered with methanol to give *compound* (**93**) (73 mg, 65%), m.p. 138—140 °C, as a mixture of *Z*- and *E*-enol acetates (60:40 or 40:60) (Found: C, 54.1; H, 5.1. $C_9H_{10}O_5$ requires C, 54.54; H, 5.48%). The compound showed $\nu_{max.}$(KBr) 1 770, 1 735, 1 715, 1 638, and 1 608 cm^{-1}; δ_H 2.19 (3 H, s, OAc), 2.11, 2.17 (3 H, s, C=CMe), 3.86, 3.92 (3 H, s, O*Me*), and 5.21, 5.24 (1 H, s, 3-H) (peaks due to major isomer given first); δ_C 15.9, 16.7 (C-7), 20.5, 20.6 (OCO*CH*$_3$), 59.6, 59.7 (OMe), 90.0, 90.1 (C-3), 133.4, 135.8 and 134.9, 137.1 (C-5 and -6), 166.8, 167.3 (C-2), 168.8, 169.7 (*CH*$_3$*CO*$_2$), and 168.7, 170.5 (C-4).

Experiments Directed to the Synthesis of the Fadyenolides.—*Preparation of methyl* 5-*benzoyl*-5-*methoxytetronate* (**96**). Potassium carbonate (1.0 g) (dried at 100 °C) was placed in a 100 ml, two-necked, round-bottomed flask fitted with a condenser, drying tube, gas inlet, and a septum cap. The flask was flushed with nitrogen and then a solution of methyl 5-benzoyltetronate (**79**) (0.49 g, 2.25 mmol) in dry acetone (5 ml) was added. The resulting mixture was heated under reflux for 4 h, and then dimethyl sulphate (1.1 ml, 11.25 mmol) was added during 30 min. The reaction mixture was heated under reflux for 16 h, cooled, filtered, and then poured into water (10 ml). The mixture was kept for 1 h, and then extracted with chloroform (4 × 20 ml); the combined extracts were dried ($MgSO_4$), filtered, and concentrated to give an oil (0.68 g). This was purified by t.l.c. on silica gel developed with chloroform to give *compound* (**96**) as a yellow oil (0.49 g, 87.5%) (Found: C, 62.7; H, 5.05. $C_{13}H_{12}O_5$ requires H, 62.90; H, 4.84%); $\nu_{max.}$(film) 1 783, 1 700, 1 650, and 1 600 cm^{-1}; δ_H 5.34 (1 H, s, 3-H), 3.98 (3 H, s, 4-OMe), and 3.44 (3 H, s, 5-OMe); δ_C 168.7 (C-2), 92.6 (C-3), 176.3 (C-4), 105.4 (C-5), 189.7 (C-6), 133.1 (C-1′), 130.6 (C-2′), 128.3 (C-3′), 133.9 (C-4′), 60.0 (4-OMe), and 51.7 (5-OMe).

Preparation of methyl 5-*benzoyl*-5-*hydroxytetronate* (**97**). A solution of compound (**79**) (0.181 g, 0.83 mmol) in a 1:1 mixture of methanol and trimethyl orthoformate (5 ml) plus one drop of conc. hydrochloric acid was stirred at room temperature for 48 h. Evaporation gave a brown oil (0.15 g) which, by p.l.c. on silica gel developed with ethyl acetate, furnished *compound* (**97**) (0.13 g, 67%) (Found: C, 61.15; H, 4.8. $C_{12}H_{10}O_5$ requires C, 61.54; H, 4.3%); $\nu_{max.}$(film) 3 370, 1 780, 1 698, and 1 600 cm^{-1}; δ_H 5.28 (1 H, s, 3-H), 3.85 (3 H, s, OMe), and 6.47 (1 H, br, OH); δ_C 170.8 (C-2), 90.4 (C-3), 178.9 (C-4), 100.7 (C-5), 190.7 (C-6), 132.5 (C-1′), 129.8, 128.8 (C-2′ and -3′), 134.5 (C-4′), and 60.4 (OMe).

Attempted preparation of fadyenolide by dehydrogenation of 5,6-*dihydrofadyenolide* (**90**). A 25-ml, round-bottomed flask was fitted with a condenser and a drying tube, and was charged with compound (**90**) (50 mg) (mixture of *threo* and *erythro* isomers), DDQ (50 mg), and dry benzene (10 ml). The mixture was heated under reflux for 10 h, cooled, and filtered, and the solvent was removed to give crude product (105 mg). H.p.l.c. on silica (1% propan-2-ol–cyclohexane) showed only *ca.* 1—2% of (*Z*)- and (*E*)-fadyenolide (1:1) (**7**) and (**6**). Crystallisation from methanol yielded compound (**53**) (41 mg, 96.7%), m.p. 137—140 °C, identical in all respects with an authentic sample (Table 5).

Preparation of (E)-*fadyenolide* (**6**). n-Butyl-lithium (3.95 ml of a 1.32M-solution in hexane, 5.21 mmol) was added to a stirred solution of HMPT (0.75 ml) in THF (20 ml) at −78 °C under nitrogen. A solution of compound (**90**) (1.17 g, 5 mmol) in dry THF (15 ml) was added and the mixture was stirred at −78 °C for 15 min. Bromine (0.27 ml, 5.21 mmol) was added in one portion and the mixture was stirred at −78 °C for 90 min. DBU (0.8 ml, 5.21 mmol) was added in one portion and the mixture

was stirred at −78 °C for 3 h, then allowed to warm for *ca.* 16 h to room temperature. The mixture was filtered, the precipitate was washed with dry benzene (3 × 20 ml), and the combined filtrates were evaporated under reduced pressure to give a black oil (1.82 g). Column chromatography with chloroform as eluant gave the bromide (**99**) (3:1 mixture of isomers by h.p.l.c.) (0.55 g, 72.5%) and starting material (0.65 g).

The unstable 5-bromotetronate (0.55 g, 1.76 mmol) was dissolved in dry glyme ($MeOCH_2CH_2OMe$) (50 ml) cooled to −78 °C, and to the stirred solution was added a solution of DBU (0.27 g, 1.76 mmol) in glyme (10 ml), and the mixture was stirred for 2 h at −78 °C, then allowed to come to room temperature, and filtered, and the precipitate was washed with benzene (3 × 20 ml). The combined filtrates were concentrated under reduced pressure to give a brown oil (0.62 g). Column chromatography on silica with diethyl ether as eluant gave compound (**53**) and fadyenolide (*E*:*Z* 15:1). P.l.c. (toluene) yielded compound (**53**) (0.075 g) and (*E*)-fadyenolide (**6**) (0.162 g, 39.7%). The overall yield from compound (**90**) was 29.5%. The product was completely identical with the naturally occurring material (Found: C, 66.8; H, 5.48. Calc. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.17%); $\lambda_{max.}$ 231 (ε 16 070) and 307 nm (37 240); $\nu_{max.}$(KBr) 1 780, 1 740, 1 673, and 1 594 cm^{-1}; δ_H 5.25 (1 H, s, 3-H), 3.97 (3 H, s, 4-OMe), and 3.62 (3 H, s, 6-OMe); δ_C 168.1 (C-2), 88.9 (C-3), 171.7 (C-4), 144.6 (C-5), 135.0 (C-6), 131.2 (C-1′), 129.0, 128.6 (C-2′ and -3′), 130.0 (C-4′), 60.6 (4-OMe), and 59.6 (6-OMe).

Preparation of (*Z*)-*fadyenolide* (**7**). A solution of acetal (**89**) (0.3 g, 1.14 mmol) in dry THF (5 ml) was added to a stirred solution of t-butyl-lithium (0.7 ml of a 1.65M-solution in hexane, 1.14 mmol) in THF (10 ml) at −78 °C during 4 min. The mixture was allowed to warm to room temperature for 16 h, then poured onto saturated aqueous ammonium chloride (5 ml). The product was taken up into ethyl acetate (3 × 15 ml), and the combined extracts were dried ($MgSO_4$), filtered, and concentrated to yield a brown oil (0.34 g). Crystallisation from diethyl ether–light petroleum gave (*Z*)-fadyenolide (**7**) (0.202 g, 76.5%), m.p. 128—131 °C, identical in all respects with the natural product (Found: C, 67.5; H, 5.3. Calc. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.17%); $\lambda_{max.}$(MeOH) 234 (8 210) and 307 nm (27 090); $\nu_{max.}$(KBr) 1 773, 1 743, 1 665, and 1 588 cm^{-1}; δ_H 5.12 (1 H, s, 3-H), 3.73 (3 H, s, 4-OMe), and 3.61 (3 H, s, 6-OMe); δ_C 167.8 (C-2), 87.5 (C-3), 170.9 (C-4), 144.0 (C-5), 130.5 (C-6), 130.7 (C-1′), 128.0, 130.1 (C-2′ and -3′), 129.1 (C-4′), and 58.9 , 58.8 (4- and 6-OMe).

Use of LDA instead of t-butyl-lithium gave a 69.7% yield of (*Z*)-fadyenolide.

Synthesis of Piperolide (**1**).—(1) *Preparation of methyl* 5-(1′-*methoxy*-3′-*phenylpropyl*)*tetronate* (**101**). The alcohol (**16a**) (0.248 g, 1 mmol) (Table 4) was dissolved, under nitrogen, in the minimum quantity of a 5:1 mixture of glyme and HMPT. The solution was cooled to −78 °C under nitrogen, and n-butyl-lithium (0.5 ml of 2M-solution, 1 mmol) was added. The mixture was stirred for 30 min at −78 °C, iodomethane (2 mmol) was added, and the reaction mixture was allowed to come to room temperature, and was then stirred for 2 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 ml), and extracted with ethyl acetate (3 × 10 ml), and the extracts were dried ($MgSO_4$), and concentrated under reduced pressure to give a mixture (*ca.* 1:1) of *threo*- and *erythro*-(**101**) (49%). The *threo*-ether (**101a**) was separated by crystallisation from chloroform–diethyl ether as needles, m.p. 101—102 °C. The *erythro*-isomer, as usual, was present in the mother liquors. For *threo*-(**101a**) (Found: C, 68.85; H, 7.05. $C_{15}H_{18}O_4$ requires C, 68.70; H, 6.87%); $\nu_{max.}$(KBr) 1 750 and 1 640 cm^{-1}; δ_H[$(CD_3)_2SO$] 5.32 (1 H, s, 3-H), 4.94 (1 H, d, *J* 5 Hz, 5-H), 3.38 (1 H, m, 6-H), 1.85 (2 H, m, 7-H), 2.65 (2 H, m, 8-H), 3.8 (3 H, s, 4-OMe), and 3.18 (3 H, s, 6-OMe); for *erythro*-(**101a**) $\nu_{max.}$ 1 750 and 1 642 cm^{-1}; δ_H 5.32 (1 H, s, 3-H), 5.12 (1 H, d, *J* 8 Hz, 5-H), 3.35 (1 H, m, 6-H), 1.65 (2 H, m, 7-H), and 2.62 (2 H, m, 8-H). The ^{13}C n.m.r. data were reported in ref. 76.

Bromination–dehydrobromination of compound (**101a**). Compound (**101a**) (1.31 g, 5 mmol) was dissolved in tetrachloromethane (450 ml), and NBS (1.79 g, 10 mmol) and benzoyl peroxide (0.05 g) were added. The mixture was stirred at 20 °C for 7 h whilst being irradiated with light from an Hanovia 100 W 360 nm lamp. Succinimide was filtered off and the solvent was removed at 25 °C under reduced pressure. Dry benzene (100 ml) was added, followed by DBU (3.04 g, 10 mmol), on which the reaction mixture turned black. The mixture was stirred for 20 h, filtered, and concentrated to give a black oil (1.4 g), purified on a neutralised silica column (200 mesh) by elution with a chloroform gradient in light petroleum. This gave a pale yellow oil (0.82 g), which on crystallisation from diethyl ether gave compound (**13**) (Table 7) (0.52 g) as pale yellow needles, m.p. 128—130 °C. The residue was subjected to p.l.c. with benzene to give piperolide (**1**) (R_F 0.27) (90 mg, 7%), m.p. 110—111 °C (lit.,[1] 110—112 °C), identical in all respects (^1H n.m.r., ^{13}C n.m.r., m.p., mixed m.p., $\lambda_{max.}$, m.s., $\nu_{max.}$, h.p.l.c.) with an authentic sample. A further crop of compound (**13**) (0.12 g) was also obtained (R_F 0.68), to give a total yield of 0.64 g (56%).

(2) *From ether* (**14**). A mixture of *threo*- and *erythro*-(**14**) (100 mg, 0.385 mmol) in dry THF (5 ml) was added to a stirred solution of n-butyl-lithium (0.28 ml of a 1.4M-solution in hexane, 0.385 mmol) in THF (5 ml) under nitrogen at −78 °C. After the mixture had been stirred for 15 min at −78 °C, a standard solution (0.2 ml of Br_2 diluted to 10 ml by dry THF) of bromine in THF (1 ml, 0.385 mmol) was added. The mixture was stirred at −78 °C for a further 45 min, and this was followed by addition of a standard solution (1 ml, 0.385 mmol) of DBU in THF (0.6 ml of DBU diluted to 10 ml by dry THF). After being stirred for a further 2 h, the reaction mixture was allowed to warm to room temperature overnight, and was then filtered, and the solvent was removed to give a black oil (0.43 g). H.p.l.c. analysis (Hypersil No. 5, dichloromethane) showed the presence of mainly compound (**13**), plus compounds (**1**) and (**5**) in a 9:1 ratio. Purification by p.l.c. on silica (diethyl ether) gave compound (**13**) (54 mg, 61.5%) and piperolide (**1**) (30 mg, 31%), m.p. 110—111 °C, identical with a sample isolated from natural sources.

Experiments Directed to the Synthesis of Epoxypiperolide (**3**).—*Preparation of methyl* 5-(1′-*methoxycinnamyl*)-5-(*phenylthio*)*tetronate* (**104**). *A*. A solution of methyl 5-(phenylthio)tetronate (**35**) (0.45 g, 2 mmol) in dry THF (9 ml) was added to a stirred solution of t-butyl-lithium (2.65 mmol) in THF (15 ml) at −95 °C under nitrogen. In a separate flask, a solution of cinnamaldehyde dimethyl acetal (1.78 g, 10 mmol) in diethyl ether (40 ml) was added dropwise to trifluoroborane–diethyl ether (1.24 ml, 10 mmol) at −78 °C, and the mixture was stirred for 20 min under nitrogen. The slurry was cooled to −95 °C, well stirred, and the solution of methyl 5-lithio-5-(phenylthio)tetronate (**102**), at −95 °C, was added dropwise by use of nitrogen pressure on a cooled, double-ended needle. The reaction mixture was allowed to warm to room temperature during 2 h, and was then diluted with diethyl ether (25 ml), washed successively with saturated aqueous sodium hydrogencarbonate (15 ml) and water (2 × 15 ml), dried ($MgSO_4$), filtered, and evaporated to give a pale yellow oil (3.25 g). This was purified by column chromatography with benzene on silica gel to give cinnamaldehyde (0.72 g) and a mixture of the required sulphide (**104**) and cinnamaldehyde. Further column chromatography [benzene–chloroform (9:1)] gave *sulphide* (**104**) as a (1:1) mixture of *threo* and *erythro* isomers (1.32 g,

72%) (Found: C, 68.55; H, 5.55. $C_{21}H_{20}O_4S$ requires C, 68.48; H, 5.70%); $\nu_{max.}$ 1 770 and 1 640 cm^{-1}; *threo*-(**104**), δ_H 4.68 (1 H, s, 3-H), 4.18 (1 H, d, *J* 8 Hz, 6-H), 6.22 (1 H, dd, *J* 8 and 16 Hz, 7-H), 6.73 (1 H, d, *J* 16 Hz, 8-H), 3.68 (3 H, s, 4-OMe), and 3.28 (3 H, s, 6-OMe); *erythro*-(**104**), δ_H 4.64 (1 H, s, 3-H), 4.23 (1 H, d, *J* 8 Hz, 6-H), 6.09 (1 H, dd, *J* 8 and 16 Hz, 7-H), 6.62 (1 H, d, *J* 16 Hz, 8-H), 3.66 (3 H, s, 4-OMe), and 3.39 (3 H, s, 6-OMe). The mixture showed *m/z* 228 (2%), 227 (10), 147 (100), 115 (14), 113 (23), and 69 (8).

B. 3-Methoxy-2-phenylthio-5-(trimethylsiloxy)furan (**103**). To a stirred solution of the lithium salt (**102**) (5 mmol), prepared as in A, was syphoned during 3 min a solution of chlorotrimethylsilane (1.1 ml, 8.5 mmol) in dry THF (4 ml) at −95 °C under nitrogen *via* a cooled, double-ended needle. The mixture was stirred for a further 1 h at −95 °C, then allowed to warm to room temperature. Dry pentane (10 ml) was added, the mixture was filtered under nitrogen, and the filtrate was evaporated to give a crude product which was fractionally distilled to give the sulphide (**103**) (1.32 g) as an oil, b.p. 140 °C/0.5 mmHg. This labile product was not completely pure by ^1H n.m.r. spectroscopy, and was used immediately.

Preparation of sulphide (**104**). Distilled, but slightly impure, compound (**103**) (0.735 g, 2.5 mmol), cinnamaldehyde dimethyl acetal (0.89 g, 5 mmol), and zinc bromide (50 mg, 2.5 mmol) were treated according to procedure A as used for 4-methoxy-2-(trimethylsiloxy)furan (**24**) (see p. 734). After the reaction mixture had been stirred at room temperature for one week, the usual work-up gave a crude product (1.39 g), purified by column chromatography on silica gel with benzene–dichloromethane (9:1) as eluant. This gave compound (**104**) (0.71 g, 77%) as a mixture of two isomers (1:4).

Oxidation of sulphide (**104**) *to sulphone* (**105**). To a solution of sulphide (**104**) (0.28 g, 0.76 mmol) in dry dichloromethane (5 ml) at 0 °C was added dropwise a solution of MCPBA (0.462 g, 2.28 mmol of 85% peracid) in dichloromethane (5 ml). The reaction mixture was stirred at 0 °C for 1.5 h, washed with 10% aqueous sodium hydrogencarbonate (2 × 5 ml), dried ($MgSO_4$), and filtered, and the solvents were removed under reduced pressure. This gave compound (**105**) (0.322 g) as a single isomer, m.p. 116—117 °C; $\nu_{max.}$(KBr) 1 795, 1 648, 1 638, and 1 590 cm^{-1}; δ_H 3.86 (1 H, s, 3-H), 4.02 (1 H, d, *J* 2 Hz, 6-H), 3.45 (1 H, m, 7-H), 4.49 (1 H, d, *J* 4 Hz, 8-H), 3.87 (3 H, s, 4-OMe), 3.53 (3 H, s, 6-OMe), and 2.02—2.94 (14 H, m, ArH); δ_C 168.2 (C-2), 92.2 (C-3), 176.1 (C-4), 98.5 (C-5), 62.0 (C-6), 54.7 (C-7), 76.0 (C-8), 60.4 (4-OMe), 59.7 (6-OMe), 168.2 (CO), and 136.2, 135.1, 134.0, 130.3, 130.1, 129.0, 128.7, 128.5, 128.3, 126.0, and 125.8 (aromatic C).

Trimethyl phenylorthopropiolate (**113**). (i) *Preparation of trimethoxycarbonium tetrafluoroborate* (**112**).[80] A 500 ml, three-necked, round-bottomed flask fitted with magnetic bar, pressure equalising funnel, tap adaptor, and septa was evacuated, and then filled with dry argon. Tetramethyl orthocarbonate (13.3 ml, 100 mmol) and dry diethyl ether (80 ml) were added and the flask was cooled to 0 °C. Trifluoroborane–diethyl ether (16.5 ml, 150 mmol) and dry diethyl ether (20 ml) were added to the funnel by syringe through the septum cap, and the solution was added dropwise to the well stirred solution of tetramethyl orthocarbonate. There was an immediate precipitation of the tetrafluoroborate (**112**). The reaction mixture was stirred at 0 °C for 20 min, the temperature was allowed to rise to ambient, and the mixture was stirred for a further 3 h. A mixture of diethyl ether and pentane (2:1) (200 ml) was added, the salt was allowed to settle, and the solvent was removed with a double-ended needle. This process was repeated four times, and then diethyl ether (200 ml) was introduced as the solvent for further reaction.

(ii) A 250 ml, round-bottomed flask was fitted with magnetic stirrer bar, septum-capped pressure-equalising funnel, and septum-capped tap adaptor, and was flushed with argon. Phenylacetylene (5.5 ml, 50 mmol) and light petroleum (b.p. 40—60 °C) (30 ml) were added, and the mixture was cooled to 0 °C. A hexane solution of n-butyl-lithium (33.1 ml of 1.51M-solution, 50 mmol) was introduced into the funnel and was added dropwise to the stirred solution of phenylacetylene at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and then at room temperature for 30 min. Diethyl ether (40 ml) was added to dissolve the lithium phenylacetylide.

This solution was then slowly added, by use of argon pressure, to the well stirred suspension of previously prepared tetrafluoroborate (**112**) cooled to −78 °C. After the addition the temperature was allowed to rise to −10 °C (1.5 h), when the fluffy precipitate of salt (**112**) began to change to a thick precipitate. This was accentuated when the cooling bath was removed and the mixture stirred at room temperature for 30 min. The colour of the supernatant liquid changed from colourless to yellow-brown, and the liquid was at once transferred to another flask fitted with magnetic bar and septum-capped tap adaptor. (Leaving the reaction for long periods causes strong darkening and a diminution of yield.)

Solvent was removed from the supernatant liquid under reduced pressure, and cyclohexane was added to precipitate inorganic salts, which were rapidly filtered off through a dried Celite pad under argon pressure. Removal of cyclohexane under reduced pressure gave crude orthopropiolate (**113**) (9.3 g), with an ^1H n.m.r. spectrum almost identical with that of a pure sample. The crude product was fractionally distilled to give compound (**113**) (7.6 g, 84%), b.p. 86 °C/0.1 mmHg, which was stored under dry argon (Found: C, 69.05; H, 6.7. $C_{12}H_{14}O_3$ requires C, 69.8; H, 6.07%);* $\nu_{max.}$ 2 238 cm^{-1}; δ_H 5.50 (9 H, s, 3 × OMe) and 7.2—7.65 (5 H, m, Ph); δ_C 110.8 (C-1), 82.2 (C-2), 84.6 (C-3), 121.3 (C-1′), 132.1 (C-2′), 128.7 (C-3′), 129.2 (C-4′), and 50.8 (OMe); *m/z* 191 (2%), 175 (100), 160 (4), 130 (5), 129 (59), 115 (6), 102 (10), and 101 (3).

Preparation of trimethyl cis-*orthocinnamate* (**114**). A dry hydrogenation flask was charged with the orthopropiolate (**113**) (3.19 g, 15 mmol) in dry hexane (50 ml) containing Lindlar catalyst (0.275 g). The flask was attached to a hydrogenation apparatus and shaken at room temperature for 15 min (a longer time leads to overhydrogenation). Filtration and evaporation gave a crude product, which by n.m.r. spectroscopy was *ca.* 90% pure, but which contained some methyl *cis*-cinnamate and a little overhydrogenation product. Compound (**114**) was very labile and decomposed on attempted distillation and also on chromatography. It was therefore used as such. Compound (**114**) showed $\nu_{max.}$(film) 1 645 and 2 845 cm^{-1}; δ_H 5.42 (1 H, d, *J* 13 Hz, 2-H), 6.59 (1 H, d, *J* 13 Hz, 3-H), 3.15 (9 H, s, 3 × OMe), and 7.12—7.42 (5 H, m, Ph); δ_C 49.4 (OMe), 114.1 (C-1), and 125.7, 127.9, 128.0, 130.2, 135.2s, and 135.4d (alkenyl and aromatic carbons).

Preparation of methyl 5-(1′,1′-dimethoxy-3′-phenylprop-2′-ynyl)tetronate (**115**). A two-necked, round-bottomed flask was fitted with magnetic bar, tap-adapter, and septa, and was filled with argon. Orthoester (**113**) (5.7 g, 28 mmol) was added, followed by dry diethyl ether (150 ml) *via* a double-ended needle. The flask was cooled to −78 °C, the contents were stirred, and trifluoroborane–diethyl ether (3.1 ml, 25 mmol) was added dropwise from a syringe. A pale yellow, fluffy precipitate formed and the reaction mixture was left to stir at −78 °C for 2 h.

In another 500 ml, round-bottomed flask a solution of the (trimethylsiloxy)furan (**24**) (5.1 g, 27 mmol) in diethyl ether (10 ml) was prepared under argon, cooled to −78 °C, and transferred to the stirred suspension in the first flask at −78 °C by means of argon pressure on a double-ended needle. The reaction mixture was stirred for 1 h at −78 °C, allowed to warm

* Analysis here was difficult due to rapid hydrolysis of the orthoester to ester.

slowly to room temperature, and then stirred for a further 16 h.

The brown reaction mixture was diluted with dry diethyl ether (200 ml), washed successively with saturated aqueous sodium hydrogen carbonate (3 × 25 ml) and water (3 × 50 ml) and dried ($MgSO_4$). Filtration was followed by removal of solvent to give crude product (7.3 g, almost pure by ^1H n.m.r. spectroscopy). This was purified by rapid elution (10—30% chloroform in hexane) on a chromatotron. The middle band (of three) was collected, and concentrated to give a pale yellow solid, which was crystallised from THF–hexane to give the ketal (**115**) as white, lustrous crystals (5.6 g, 77%), m.p. 106 °C (Found: C, 66.75; H, 5.55. $C_{16}H_{16}O_5$ requires C, 66.65; H, 5.59%); $\nu_{max.}$(Nujol) 2 238, 1 790, 1 758, 1 725, 1 630, and 1 615 cm^{-1}; δ_H 5.14 (1 H, d, *J* 1 Hz, 3-H), 4.94 (1 H, d, *J* 1 Hz, 5-H), 3.85 (3 H, s, 4-OMe), 3.47 (6 H, s, 2 × 6-OMe), and 7.22—7.50 (5 H, m, Ph); δ_C 171.8 (C-2), 90.7 (C-3), 179.4 (C-4), 79.8 (C-5), 99.3 (C-6), 80.5 (C-7), 88.8 (C-8), 121.1 (C-1′), 128.4, 132.1 (C-2′ and -3′), and 129.4 (C-4′). The mass spectrum had no molecular ion, but showed peaks at *m/z* 175.075 89 ($C_{11}H_{11}O_2$, *M* − tetronate, 100%), 256.075 34 ($C_{15}H_{12}O$, *M* − MeOH, 4), 155.034 22 ($C_7H_7O_4$, 6), 129.034 03 (C_9H_5O, PhC≡CCO, 35), and 101.039 12 (C_8H_5, PhC≡C, 3).

Preparation of methyl 5-[1′,1′-*dimethoxy*-3′-*phenylprop*-2′-(Z)-*enyl*]*tetronate* (**116**). A 100 ml, long-necked hydrogenation flask was charged with the alkyne (**115**) (0.76 g) and Lindlar catalyst (0.16 g, ~20% w/w), and dry THF (15 ml) and hexane (10 ml) were added. The flask was attached to a hydrogenation apparatus, flushed with hydrogen, and then shaken for 25 min at room temperature and pressure.

The catalyst was filtered off and the solvent was removed. Recrystallisation of the residue from THF–hexane gave *compound* (**116**) (0.65 g, 85%), m.p. 96—97 °C (Found: C, 65.9; H, 6.05. $C_{16}H_{18}O_5$ requires C, 65.74; H, 6.21%); $\nu_{max.}$(KBr) 1 795, 1 760, 1 750, and 1 630 cm^{-1}; δ_H 5.01 and 5.08 (1 H each, d, *J* 1 Hz, 3- and 5-H), 5.27 (1 H, d, *J* 13 Hz, 7-H), 6.71 (1 H, d, *J* 13 Hz, 8-H), 3.77 (3 H, s, 4-OMe), 3.27, 3.30 (2 × 3 H, s, 2 × 6-OMe), 7.17—7.4 (3 H, m, ArH), and 7.4—7.64 (2 H, m, ArH); δ_C 171.8 (C-2), 90.48 (C-3), 179.9 (C-4), 79.43 (C-5), 101.8 (C-6), 135.8 (C-7), 136.5 (C-8), 127.5, 127.7 (C-1′ and -2′), 129.8 (C-3′), and 125.5 (C-4′); *m/z* 258.089 19 ($C_{15}H_{14}O_4$, 16%), 215 (10), 213 (6), 187.0606 ($C_8H_{11}O_5$, 9), 179 (7), 178 (12), 177.0915 ($C_{11}H_{13}O_2$, 100), 155.0344 ($C_7H_7O_4$, 14), 131.0497 (C_9H_7O, 60), 128 (7), 127 (8), 121 (5), 115 (21), 113.0239 ($C_5H_5O_3$, 2), 105 (10), 103.0548 (C_8H_7, 61), 102 (13), 91 (20), 77 (54), and 69 (35).

Preparation of methyl 5-(cis-2′,3′-*epoxy*-1′,1′-*dimethoxy*-3′-*phenylpropyl*)*tetronate* (**117**). Compound (**116**) (2.3 g, 7.5 mmol) was dissolved in dry dichloromethane (50 ml), and MCPBA (6.9 g, 37.5 mmol of 85% pure peracid) was added. The mixture was stirred for 48 h under argon at room temperature until there was no starting material left, as shown by h.p.l.c.

The mixture was filtered, the precipitate was washed with dichloromethane (3 × 15 ml), and the combined organic filtrates were stirred with saturated aqueous sodium hydrogensulphite (100 ml) for 20 min. The organic layer was separated, washed successively with saturated aqueous sodium hydrogencarbonate (3 × 100 ml) and water (2 × 50 ml), and dried ($MgSO_4$). Filtration and evaporation gave crude product (4.0 g). This was purified by elution off a 4 mm silica plate (2 g portions) on a chromatotron, first with light petroleum–chloroform (1:1) and then with chloroform. The first fraction was MCPBA and the second was a mixture of diastereoisomers of the required epoxide (**117**) (2.0 g, 83%) as a thick oil. The ratio of the two isomers was 1.3:1 (^{13}C n.m.r.). Treatment with THF–hexane at 0 °C gave the major isomer as a crystalline solid, m.p. 117 °C (1.0 g). The mother liquor still contained some of this isomer, but was rich in the other isomer. The *epoxide* of m.p.117 °C showed the following data (Found: C, 62.95; H, 5.80. $C_{16}H_{18}O_6$ requires C, 62.73; H, 5.92%); δ_H 5.18 (1 H, d, *J* 1 Hz, 3-H), 4.60 (1 H, d, *J* 1 Hz, 5-H), 3.32 (1 H, d, *J* 4 Hz, 7-H), 3.98 (1 H, d, *J* 4 Hz, 8-H), 3.68 (3 H, s, 4-OMe), 3.31, 3.41 (2 × 3 H, s, 2 × 6-OMe), and 7.22—7.52 (5 H, m, Ph); δ_C 171.7 (C-2), 90.5 (C-3), 178.9 (C-4), 80.3 (C-5), 98.5 (C-6), 55.9 (C-7), 59.9 (C-8), 59.6 (4-OMe), and 50.0, 50.5 (6-OMe); *m/z* 245 (2%), 193.0865 ($C_{11}H_{13}O_3$, 52), 187.0606 ($C_8H_{11}O_5$, 18), 169 (6), 121 (36), 118 (6), 113.0239 ($C_5H_5O_3$), 105 (8), 104 (10), 103 (100), 91 (22), 77 (12), and 75 (11).

The non-crystalline isomer had δ_C 171.6 (C-2), 90.3 (C-3), 179.7 (C-4), 79.2 (C-5), 99.4 (C-6), 56.2 (C-7), 59.5 (C-8), 58.9 (4-OMe), and 50.2, 49.8 (2 × 6-OMe).

Preparation of piperolides from compound (**116**). A 25 ml, round-bottomed flask was fitted with a septum-capped tap adapter, magnetic bar, and septum-capped pressure-equalising dropping funnel. After the flask had been flushed with nitrogen, t-butyl-lithium (1 mmol, 0.6 ml of 1.8M-solution in hexane) and THF (2 ml) were added, and the solution was cooled to 0 °C. The whole apparatus was wrapped in a black bag and the dropping funnel was charged with a solution of compound (**116**) (300 mg, 1.03 mmol) in THF (4 ml). This solution was then added dropwise to the stirred solution of t-butyl-lithium, and the reaction mixture was stirred for 1 h at 0 °C, then allowed to rise to ambient temperature, at which the solution became yellow. The reaction was allowed to proceed for 30 h (h.p.l.c. sampling), when it was quenched with water (5 ml), and extracted with dichloromethane (2 × 25 ml). The combined organic extracts were washed with water (3 × 10 ml), dried ($MgSO_4$), filtered, and concentrated to give a yellow solid (250 mg, 97%). The mixture of isomers was separated by repeated injection preparative h.p.l.c. on a 9—10 mm Hypersil column eluted with 0.1% methanol in dichloromethane. Peak 1 (15 mg, 5.8%) was a thick oil which solidified after some time. The last peak was (5*Z*,7*Z*)-piperolide (**122**) (175 mg, 66%), whilst the middle peak was a mixture of natural piperolide (**1**) (9%) and the 5*E*,7*Z*-isomer (**121**) (15%). [*Note.* When the reaction was carried out at −95 °C and quenched at −95 °C, then isomer (**121**) was present as 37% of the mixture.] The spectra of compound (**121**) were determined by difference. Compound (**122**) showed *m/z* 258 (10%), 243 (2), 213 (5), 186 (7), 185 (6), 157 (13), 155 (5), 147 (5), 143 (6), 131 (100), 129 (10), 115 (14), 111 (18), 107 (15), 103 (34), 97 (16), 95 (12), 91 (3), 85 (16), 83 (17), 81 (11), and 77 (38). The ^1H and ^{13}C n.m.r. spectra of all the piperolides are given in Table 1.

Preparation of epoxypiperolides (**118**) *and* (**119**). A 50 ml, three-necked, round-bottomed flask was fitted with magnetic bar, two septum-capped tap-adapters, and a reflux condenser leading *via* a bubbler to an argon line. A freshly made solution of lithium methoxide (2.2 ml of a 0.068M-solution, 0.15 mmol) in methanol was added and the methanol was removed under reduced pressure. Dry benzene (2 ml) was added and the solvent was again removed (oil-pump), to leave a white solid. Toluene (10 ml) was injected onto the product, and then a solution of compound (**117**) (46 mg, 0.15 mmol) in toluene (5 ml) was dripped in *via* a double-ended needle. The mixture was then heated under reflux for 48 h under argon, being regularly monitored by h.p.l.c.

The reaction mixture was cooled, washed with water (2 × 10 ml), dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure to give the product as a yellow oil (41 mg, 100%). H.p.l.c. showed no starting material, but two new peaks were seen (R_t 7.35, 8.40 min; Hypersil with 0.2% MeOH–CH_2Cl_2). Semi-preparative h.p.l.c. allowed both isomers to be collected (16 mg, 39%), and further h.p.l.c. on analytical columns gave the 5*E*-isomer (**118**) (4 mg) and the 5*Z*-isomer (**119**) (9 mg) [Found: (mixture) C, 66.1; H, 4.9. $C_{15}H_{14}O_5$ requires C, 65.68; H, 5.15%). Epoxide (**118**) had *m/z* 274.0841 ($C_{15}H_{14}O_5$ requires *m/z* 274.0841), with peaks at *m/z* 274 (7%), 246 (13), 245 (47), 228 (8), 213 (13), 139 (47), 131 (11), 125 (25),

Table 11. ^1H and ^{13}C n.m.r. data for the piperolides *

	δ_H						δ_C								
	3-H	7-H	8-H	ArH	4-OMe	6-OMe	C-2	C-3	C-4	C-5	C-6	C-7	C-8	4-OMe	6-OMe
(1)	5.17s	←	7.12—7.54	→	399s	3.92s	167.2	87.9	171.0	142.7	131.9	119.3	134.2	61.4	59.6
(5)	5.25s	←	7.20—7.60	→	3.95s	3.79s	167.5	89.6	170.2	144.7	135.8	118.2	*a*	62.9	60.3
(122)	5.13s	6.33d (*J* 13)	6.77d (*J* 13)	7.14—7.44m	3.84s	3.54s	168.0	87.8	170.9	141.3	130.8	117.9	137.5	59.5[b]	58.8[b]
(121)	5.24s	6.30d (*J* 13)	6.78d (*J* 13)	7.12—7.60m	3.89s	3.23s	170.7	89.3	177	143.5	*a*	117.0	*a*	59.6[b]	59.4[b]

* See footnote * in Table 2.
[a] Signals coincide with those of aromatic carbons and are not definitely assignable. [b] Signals may be interchanged.

121 (21), 105 (48), 103 (12), 91 (21), 84 (19), 77 (35), and 69 (100); $\nu_{max.}$($CHCl_3$) 1 765 and 1 605 cm^{-1}; δ_H 5.50 (1 H, s, 3-H), 4.18 and 4.38 (each 1 H, d, *J* 2 Hz, 7- and 8-H), and 7.18—7.61 (5 H, m, Ph); δ_C 167.4 (C-2), 88.7 (C-3), 169.9 (C-4), 140.6 (C-5), 59.1, 59.2 (C-7 and -8), 54.9 (6-OMe), and 60.4 (4-OMe).

Epoxide (**119**) had *m/z* 274.0841 ($C_{15}H_{14}O_5$, 8%), 246 (18), 245 (74), 228 (9), 215 (10), 213 (16), 139 (63), 131 (19), 125 (28), 121 (34), 105 (61), 103 (11), 91 (31), 84 (27), 77 (41), and 69 (100); δ_H 5.03 (1 H, s, 3-H), 4.20 and 4.28 (each 1 H, d, *J* 4 Hz, 7- and 8-H), 3.90, 3.94 (each 3 H, s, OMe), and 7.20—7.60 (5 H, m, Ph); δ_C 167.3 (C-2), 86.8 (C-3), 170.9 (C-4), 138.3 (C-5), and 59.1, 59.2 (C-7 and -8).

Preparation of methyl 5-(1′,1′-*dimethoxy*-3′-*phenylacetonyl*)-*tetronate* (**120**). A 25 ml, three-necked, round-bottomed flask fitted with tap adapter, bent side-tube, two septa, and magnetic bar was charged with epoxide (**117**) (51 mg) and filled with argon. Dichloromethane (3 ml) was injected into the flask, and the reaction mixture was stirred and held at −78 °C. Zinc bromide (27 mg) was added by rotating the side-tube, and the mixture was stirred for 10 min at −78 °C, and then allowed to warm to ambient temperature. After 6 h the reaction mixture was diluted with dichloromethane (3 ml), stirred overnight, and filtered rapidly through dry Celite, and the solvent was removed to give a colourless oil (45 mg). The product was almost pure by h.p.l.c. on Hypersil, and was purified further by elution from a chromatotron plate (SiO_2; CH_2Cl_2) and shown to be essentially pure by h.p.l.c. [0.1% MeOH in CH_2Cl_2; Hypersil; $\lambda_{max.}$(MeOH) 237 nm]. The product showed $\nu_{max.}$(film) **1** 780, 1 755, and 1 640 cm^{-1}; $\lambda_{max.}$(MeOH) 227 nm; δ_H 5.06 (2 H, s, 3- and 5-H), 3.95 (2 H, d, *J* 1 Hz, 8-H), 3.85 (3 H, s, 4-OMe), 3.2, 3.5 (each 3 H, s, 2 × 6-OMe), and 7.1—7.5 (5 H, m, Ph); δ_C 171.1 (C-2), 90.1 (C-3), 179.8 (C-4), 78.0 (C-5), 102.8 (C-6), 203.8 (C-7), 46.9 (C-8), 133.2 (C-1′), 128.4, 129.9 (C-2′ and -3′), 133.2 (C-4′) and 50.2, 51.1 (2 × 6-OMe), and 59.8 (4-OMe); *m/z* 193 (7%), 187 (100), 177 (11), 159 (14), 139 (12), 131 (11), 121 (89), 119 (6), 113 (15), 105 (24), 103 (14), 91 (41), 77 (21), and 75 (25).

Isomerisation of Z-*ketal* (**116**) *to* E-*ketal* (**110**). A warm 50 ml, round-bottomed flask with magnetic bar was charged with compound (**116**) (1.2 g) and oven-dried Amberlyst resin (H^+ form; 0.64 g), and the flask was cooled under nitrogen. Freshly dried methanol (12 ml) and methyl orthoformate (4 ml) were injected, and the mixture was stirred at room temperature for 48 h. The supernatant liquid was removed under nitrogen with a double-ended needle, the resin was washed with dry methanol (4 ml), and the washings were added to the supernatant liquid. Methanol was removed under reduced pressure to give a pale yellow solid, which was recrystallised at once from THF–hexane as white crystals of the *E*-isomer (**110**) (1.0 g, 83%), m.p. 43—44 °C. Compound (**110**) was far less stable than its *Z*-isomer (**116**), and even at 0 °C under nitrogen it broke down to several compounds. It must be therefore used at once. By h.p.l.c. (Hypersil; 0.2% MeOH–CH_2Cl_2) it was >97% pure as originally prepared. It ran considerably faster (R_t 7.69 min.) than its *Z*-isomer (R_t 13.37 min.), and showed $\nu_{max.}$(Nujol) 1 790, 1 748, and 1 630 cm^{-1}; δ_H 4.98 (2 H, m, 3- and 5-H), 5.80 (1 H, d, *J* 16 Hz, 7-H), 6.82 (1 H, d, *J* 16 Hz, 8-H), 3.82 (3 H, s, 4-OMe), 3.32 (6 H, s, 2 × 6-OMe), and 7.1—7.5 (5 H, m, Ph); δ_C 172.1 (C-2), 90.7 (C-3), 180.3 (C-4), 78.9 (C-5), 101.0 (C-6), 123.0 (C-7), and 136.1 (C-8); *m/z* 258 (99%), 215 (30), 213 (13), 187 (15), 183 (11), 181 (18), 177 (14), 175 (19), 171 (11), 155 (25), 144 (11), 131 (100), 129 (16), 115 (21), 105 (31), 103 (76), 102 (12), 91 (15), and 77 (66).

Preparation of natural piperolides (**1**) *and* (**5**) *from compound* (**110**). The procedure used was exactly as for the elimination of methanol from the epoxide (**117**) to give the epoxypiperolides (**118**) and (**119**). Thus, compound (**110**) (41 mg, 0.14 mmol), lithium methoxide (2.05 ml of a freshly prepared 0.068M-solution, 0.14 mmol), and toluene (15 ml) were heated under reflux for 240 h. The mixture was washed with water (3 × 10 ml), dried ($MgSO_4$), and filtered, and the solvent was removed to give a yellow solid (30 mg, 82.4%). H.p.l.c. (monitoring at 237 nm) showed no starting material and (335 nm) only the readily separable natural piperolides (**1**) and (**5**) in the ratio 2.8:1. The ^1H n.m.r. spectra were identical in all respects with those of the natural products. (*n.b.* Use of Bu^tLi at room temperature for 2 days gave >90% of the natural piperolides by ^1H n.m.r. spectroscopy.)

Preparation of trans-*epoxide* (**111**). A 25 ml, round-bottomed flask equipped with magnetic bar and flushed with nitrogen was charged with alkene (**110**) (190 mg, 0.65 mmol), MCPBA (430 mg, 3-fold excess of 75% pure peracid), and dry dichloromethane (6 ml). The resultant solution was stirred at room temperature for 120 h. After 7 h a white precipitate began to appear. Saturated aqueous sodium sulphite (10 ml) was added and the mixture was stirred for 15 min. Dichloromethane (10 ml) was then added, and the organic layer was separated, washed successively with saturated aqueous $NaHCO_3$ (3 × 10 ml) and water (2 × 10 ml), dried ($MgSO_4$), filtered, and concentrated to give a colourless oil (162 mg, 80%) as a mixture (2.5:1) of two isomers. Although they were readily separable by h.p.l.c., attempts to purify them by crystallisation or by chromatotron were unsuccessful, and they were used as such for the preparation of epoxypiperolide (**3**). The mixture had $\delta_D(C_6D_6)$ 4.53, 4.68 (1 H each, s 3- and 5-H), 2.9 (1 H, d, *J* 3 Hz, 7-H), 3.98, 4.07 (1 H, d, *J* 3 Hz, 8-H), 3.29, 3.09, 3.01 (3 × OMe); δ_H ($CDCl_3$) 4.92—5.02 (2 H, m, 3-and 5-H), 2.88, 2.91 (1 H, d, *J* 2 Hz, 7-H), 3.82, 3.92 (1 H, d, *J* 2 Hz, 8-H), 3.82, 3.75 (3 H, s, 4-OMe), 3.34, 3.32, 3.43, 3.44 (6 H, s, 2 × 6-OMe), and 7.0—7.4 (5 H, m, Ph); δ_C 171.3, 171.6 (C-2), 90.6, 90.4 (C-3), 179.5, 179.1 (C-4), 79.0, 78.0 (C-5), 98.1, 97.5 (C-6), 59.9, 60.1 (C-7 and -8), 53.5, 53.3 (4-OMe), and 50.6, 50.4, 50.3, and 49.5 (2 × 6-OMe); *m/z* 193 (74%), 187 (38), 177 (5), 175 (5), 169 (10), 159 (8), 139 (5), 131 (6), 121 (44), 118 (6), 113 (13), 103 (100), 91 (30), 77 (20), and 75 (18).

Preparation of epoxypiperolide (**3**). A three-necked, 100 ml, round-bottomed flask was fitted with a septum-capped tap

adapter, a Soxhlet apparatus with lithium aluminium hydride under glass wool in the cup, and a magnetic stirring bar. The apparatus was flushed with nitrogen and a freshly prepared methanolic solution of lithium methoxide (7.3 ml of a 0.06M-solution, 0.44 mmol) was introduced. The methanol was removed under reduced pressure, dry benzene (2 ml) was added, the mixture was stirred, and the solvent was removed (oil-pump). The remaining white solid was taken up into xylene (20 ml) and the apparatus was filled with nitrogen. A solution of epoxide (**111**) (135 mg, 0.44 mmol) in xylene (7 ml) was added *via* nitrogen pressure on a double-ended needle, and was washed in with more xylene (4 ml). The total volume of xylene was made up to 60 ml, and the mixture was heated under reflux for 21 h, then poured into water (25 ml), and the organic layer was dried ($MgSO_4$) and filtered. This solution was passed down a neutral alumina column (50 g; 0.5 inch diameter) from which elution with chloroform gave crude product (42 mg, 35%). This was subjected to repeated injection h.p.l.c. (0.2% MeOH in CH_2Cl_2) on Hypersil. The third fraction was an oil (6 mg, 5%), which had an observed molecular ion at *m/z* 274.0845 ($C_{15}H_{14}O_5$), and a ^1H n.m.r. spectrum identical in all respects with the unique spectrum for natural 5*Z*-7,8-*trans*-epoxypiperolide (**3**).[2-4] We could not fully characterise the other two fractions, but the ^1H n.m.r. spectrum of one of them (3 mg) indicated that it was 5*E*-7-8-*trans*-epoxypiperolide, whilst the other (6 mg) could be the compound resulting from loss of methanol from the isomerised ketone (**120**).

Miscellaneous Experiments.—Preparation of methyl 5-(*dimethylaminomethylene*)*tetronate* (**44**). A solution of methyl tetronate (**20**) (5.0 g, 43.86 mmol) in dimethylamino-(dimethoxy)methane (25 ml) was made up in a 50 ml, round-bottomed flask equipped for distillation. The mixture was heated in an oil-bath at 110—120 °C (temperature not in excess of 120 °C) with slow, continuous distillation of methanol. After 3 h the mixture was cooled to room temperature, and the excess of solvent–reagent was removed under reduced pressure to leave a yellow oil, which slowly crystallised. Recrystallisation from chloroform gave *compound* (**44**) (7.31 g, 99%) as orange needles, m.p. 57—58 °C (Found: C, 56.9; H, 6.6; N, 8.25. $C_8H_{11}NO_3$ requires C, 56.80; H, 6.50; N, 8.20%); $\nu_{max.}$ 1 730 and 1 673 cm^{-1}; δ_H 4.84 (1 H, s, 3-H), 6.04 (1 H, s, 6-H), 3.82 (3 H, s, OMe), and 3.07 (6 H, s, NMe_2); δ_C 169.8 (C-2), 80.3 (C-3), 171.5 (C-4), 120.2 (C-5), 122.9 (C-6), 59.5 (OMe), and 42.4 (NMe_2); *m/z* 169 ($M^{+\cdot}$ 100%), 154 (7), 126 (27), 98 (46), 85 (6), 69 (27), and 42 (52).

Preparation of 2-(*Dimethyl-t-butylsiloxy*)-4-*methoxyfuran.*—A solution of methyl tetronate (**20**) (5.7 g, 50 mmol) in anhydrous THF (80 ml) was added by double-ended needle to a solution of n-butyl-lithium (50 mmol, 30.1 ml of a 1.66M-solution in hexane) in THF (180 ml) stirred at −78 °C under nitrogen. The solution of compound (**23**) was stirred at −78 °C for 10 min, then allowed to warm to room temperature during *ca.* 2 h, and then a THF solution (17.6 ml) of chlorodimethyl-t-butylsilane (0.728 g ml^{-1}) (12.835 g, 85 mmol) was added by nitrogen pressure on a double-ended needle. The mixture was held at −78 °C for 15 min, and was then allowed to warm to room temperature during *ca.* 2 h. The solvent was removed on an oil-pump, and dry hexane (90 ml) was added. Filtration under nitrogen, and removal of solvent, gave a red oil which, on distillation at 80—82 °C (5 mmHg), gave the *title compound* (2.22 g, 16%) (Found: C, 57.95; H, 9.2. $C_{11}H_{20}O_3Si$ requires C, 57.86; H, 8.83%); δ_H 4.88 (1 H, d, *J* 2 Hz, 3-H), 6.44 (1 H, d, *J* 2 Hz, 5-H), 0.14 (6 H, s, $SiMe_2$), and 0.86 (9 H, s, CMe_3); δ_C 150.7 (C-2), 79.2 (C-3), 155.2 (C-4), 112.5 (C-5), 57.1 (OMe), 18.1 ($SiCMe_3$), 25.5 ($SiCMe_3$), and −4.8 ($SiMe_2$); *m/z* 228 (26%), 150 (7), 147 (16), 143 (14), 114 (7), 98 (27), 94 (7), 93 (90), 89 (32), 85 (5), 77 (13), 75 (65), 74 (12), and 73 (100).

Preparation of 1,2-*Epoxy*-3,3-*dimethoxy*-1-*phenylpropane* (**106**).—MCPBA (12.29 g of 70% peracid, 50 mmol) was added to a solution of cinnamaldehyde dimethyl acetal (8.9 g, 50 mmol) in a mixture of dichloromethane (300 ml) and 0.5M-aqueous $NAHCO_3$ (150 ml). The mixture was stirred for 42 h at room temperature, and the organic layer was separated, washed successively with 1M-NaOH (150 ml) and water (150 ml), and dried ($MgSO_4$). Filtration followed by removal of solvent gave the crude product (8.5 g) as a pale yellow oil. Distillation through a Vigreux column yielded the *title compound* (**106**) (5.23 g), b.p. 86 °C/0.45 mmHg (Found: C, 68.35; H, 7.5. $C_{11}H_{14}O_3$ requires C, 68.01; H, 7.28%); δ_H 4.39 (1 H, d, *J* 3 Hz, 3-H), 3.08 (1 H, q, *J* 2 and 3 Hz, 2-H), 3.88 (1 H, d, *J* 2 Hz, 1-H), 3.38 (6 H, s, 2 × OMe), and 7.26 (5 H, m, Ph); δ_C 61.3 (C-1), 55.0 (C-2), 102.3 (C-3), 53.6, 54.4 (OMe), 136.6 (C-1′), 128.3, 128.5 (C-2′ and -4′), and 125.8 (C-3′); *m/z* 162 (21%), 131 (12), 121 (60), 105 (10), 91 (26), and 75 (100).

Preparation of Diethyl 2,5-*Dioxocyclohexane*-1,4-*dicarboxylate* (**33**).—A solution of ethyl 4-bromoacetate (30 ml) in diethyl ether (100 ml) was added to a stirred solution of 20% aqueous potassium carbonate (100 ml) and 18-crown-6 (0.2 g). The biphasic mixture was stirred for 24 h at room temperature, and the solid product at the interface was filtered off. The ether layer was separated and washed twice with water (100 ml), dried (Na_2SO_4), and filtered, and the solvent was removed to yield a brown oil (4 g), with a complex ^1H n.m.r. spectrum. The combined aqueous extracts were neutralised with 5M-HCl, and the solid product was collected, washed with water (3 × 10 ml), and dried *in vacuo*. The dry product (9 g) was recrystallised from ethyl acetate (50 ml) to give the diester (**33**) (8 g, 22%), m.p. 125—126 °C (lit.,[88] 125—125.5 °C); $\delta_H(C_5D_5N)$ 1.15 (6 H, t, *J* 7 Hz, OCH_2Me), 4.13 (4 H, q, *J* 7 Hz, OCH_2Me), 3.11 (4 H, s, CH_2), and 12.45 (*ca.* 2 H, br, OH); $\nu_{max.}$(KBr) 1 680 and 1 640 cm^{-1}.

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