Dioxolanones as Synthetic Intermediates. Part 3.† Biomimetic Synthesis of Pulvinic Acids

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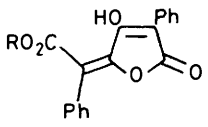
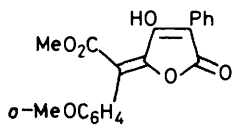
The reaction of the phosphorane (**16**) with methyl arylglyoxylates gives 5-(α-methoxycarbonylarylidene)-2,2-pentamethylene-1,3-dioxolan-4-ones [5′(α-methoxycarbonylarylidene)cyclohexane-spiro-2′-(1′,3′-dioxolan)-4′-ones] which have been treated with the lithium enolates of t-butyl phenylacetic esters to provide a biomimetic synthesis of pulvinic acids. By this method pulvinic acid (**2**), vulpinic acid (**1**), and the unsymmetrically substituted compounds, leprapinic acid (**3**), and xerocomic acid (**4**) have been prepared; the last named was obtained *via* an intermediate (**28**) in which the phenolic groups were protected as benzyl ethers.

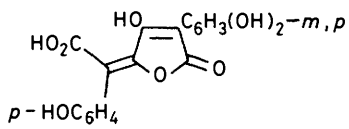
The pulvinic acids[1] have long been known as bright yellow and orange constituents of lichens. Vulpinic acid (**1**) was first isolated in 1831,[2] and although pulvinic acid was not isolated from a natural source until 1952[3] its structure had been proposed by Spiegel in 1882 as a result of degradative studies on vulpinic acid.[4] Other lichenal pulvinic acids, *e.g.* leprapinic acid (**3**), often contain methoxylated aromatic rings. More recently, pulvinic acids have been isolated from higher fungi of the closely related families *Boletaceae* and *Gomphidaceae*. These acids, *e.g.* xerocomic acid (**4**), differ from those of lichenal origin in that they are usually free acids rather than methyl esters, contain hydroxy rather than methoxy substituents, and are isolated in much lower yields.



(**1**) R = Me
(**2**) R = H



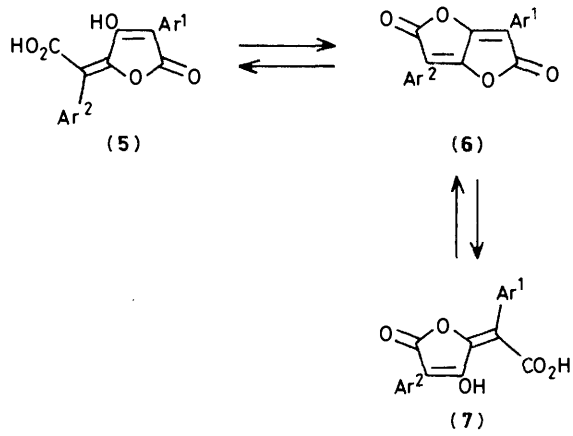
(**3**)



(**4**)

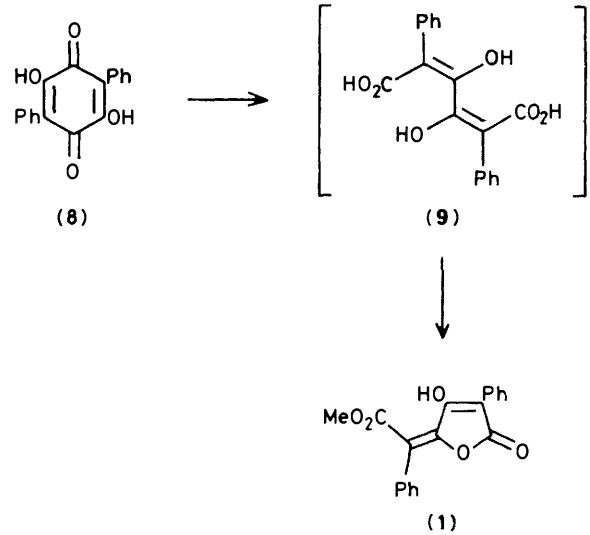
The structure elucidation and synthesis of unsymmetrically substituted pulvinic acids of general type (**5**) have been severely hampered by the rather facile formation of the anhydride (**6**) which can be opened to give (**5**) or the isomeric acid (**7**) (Scheme 1). However, a combination of the degradative method[5] developed by Edwards and Gill, ^{1}H n.m.r. studies by Steglich and co-workers,[6] and the unambiguous synthesis of permethylated pulvinic acids by Pattenden and Knight[7] have been of great value for structure elucidation.

Biosynthetic studies in certain lichens have shown that



(**5**) (**6**) (**7**)

Scheme 1.

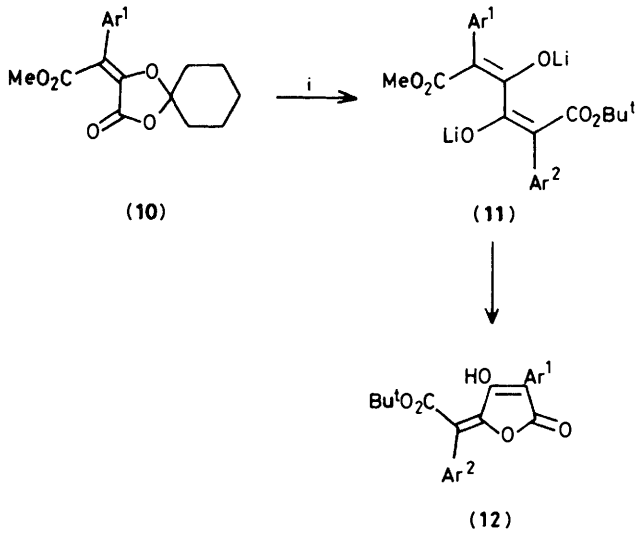


(**8**) (**9**) (**1**)

Scheme 2.

oxidative ring opening of polyporic acid (**8**) leads to vulpinic acid (**1**) *via* the hypothetical intermediate (**9**) (Scheme 2).[1] Indeed this transformation has been effected *in vitro* by lead

† Part 2, preceding paper.

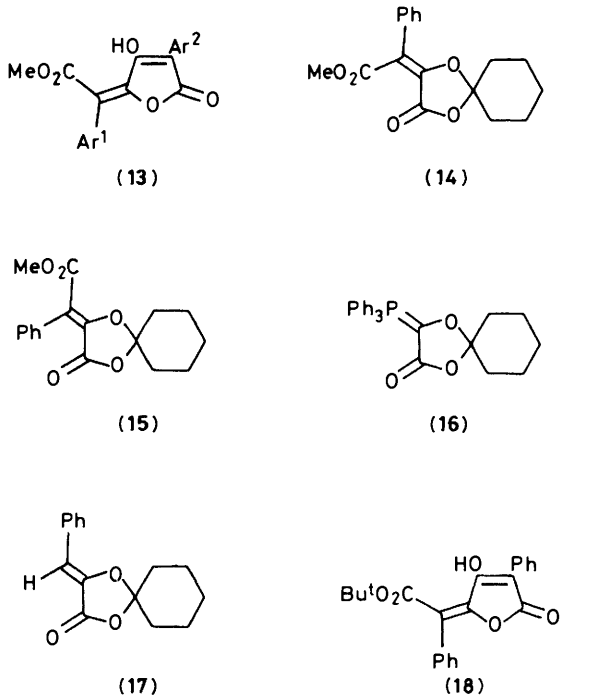


(10) (11) (12)

Scheme 3. *Reagents:* i. $Ar^2CH(Li)CO_2Bu^t$ (2.5 equiv.)

tetra-acetate treatment of polyporic acid (**8**).[8] In order to control the cyclisation of (**9**), where the aryl substituents are not identical, it is necessary to moderate the susceptibility of the two carboxylic functions towards lactonisation. An intermediate which fulfils this requirement is the diester (**11**) in which lactonisation would be expected[9] to occur preferentially at the methoxycarbonyl group. We have attempted to extend our use of dioxolanones as intermediates in the synthesis of tetronic acids to provide a biomimetic synthesis of pulvinic acids by reaction of 5-(α-methoxycarbonylarylidene)dioxolanones (**10**) with the lithium enolates of t-butyl phenylacetic esters (Scheme 3). It was predicted that only the t-butyl ester (**12**) would be formed from cyclisation of expected intermediate (**11**); the alternative cyclisation mode would afford the methyl ester (**13**) and thus the degree of regiospecificity in the cyclisation of (**11**) can be readily discerned by ^1H n.m.r. study of the product.

We first attempted the synthesis of unsubstituted pulvinic acid derivatives (Scheme 3, $Ar^1 = Ar^2 = Ph$) which necessitated the preparation of the dioxolanone (**14**). The reaction between methyl phenylglyoxylate and the phosphorane (**16**)[9] in toluene at 95 °C gave a mixture (*ca.* 6:1) of the (*E*)- and (*Z*)-dioxolanones, (**14**) and (**15**) which were separable by chromatography on silica gel. The double-bond geometries of (**14**) and (**15**) were initially assigned from the u.v. spectra; in the (*E*)-isomer (**14**) the cinnamic acid moiety can exist in the all-planar form, whereas in the (*Z*)-isomer (**15**), steric interactions will cause the phenyl ring to be twisted out of the plane thereby weakening the extended conjugation. Therefore (**15**) would be expected to show a u.v. maximum of smaller extinction coefficient at lower wavelength than (**14**). The major Wittig product had $\lambda_{max.}$ 297 nm (ε 16 400) whereas the minor product had $\lambda_{max.}$ 269 nm (ε 11 000). Consequently the major isomer was assigned the structure of the (*E*)-dioxolanone (**14**), and the u.v. spectrum of this compound was very similar in shape to that of the benzylidenedioxolanone (**17**) ($\lambda_{max.}$ 269 nm, ε 27 200) which had previously been assigned the (*Z*) geometry shown.[9] The structure of the dioxolanone (**14**) was later confirmed by *X*-ray crystallographic analysis which showed the methoxycarbonyl group to be twisted out of the plane of the conjugated system.[10]



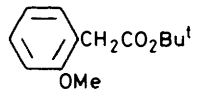
(13) (14) (15) (16) (17) (18)

The reaction between the dioxolanone (**14**) and the lithium enolate of t-butyl phenylacetate in tetrahydrofuran (THF) at −78 °C gave a 92% crude yield of the (*E*)-t-butyl ester (**18**), formed from regiospecific cyclisation of the intermediate (**11**; $Ar^1 = Ar^2 = Ph$). No vulpinic acid (**1**) signals were observed in the ^1H n.m.r. spectrum of the crude tetronic acid product. Treatment of the t-butyl ester (**18**) with 90% trifluoroacetic acid (TFA) gave pulvinic acid (**2**) which showed the same i.r. (solid-state and solution) and u.v. spectra as an authentic sample of pulvinic acid and a similar melting point. The mixed melting point was not depressed. Treatment of the dioxolanone (**14**) with the lithium enolate of methyl phenylacetate gave vulpinic acid (**1**) which showed the same i.r. and u.v. spectra characteristics as an authentic sample. The melting points were also in agreement and the mixed melting point was not depressed.

We then turned to the synthesis of the natural product leprapinic acid (**3**) from the dioxolanone (**14**) and the t-butyl ester (**19**) which was prepared in 60% yield by treatment of 2-methoxyphenylacetic acid with isobutene and concentrated sulphuric acid.

In the synthesis of the t-butyl ester (**18**) the direction of cyclisation of the intermediate (**11**; $Ar^1 = Ar^2 = Ph$) was determined solely by the relative steric influences of the methyl and t-butyl ester groups. Seshadri has shown that the presence of an electron-donating *ortho*- or *para*-substituent on a phenyl ring of a pulvinic anhydride, *e.g.* (**20**), can exert a profound effect on the position of attack by a nucleophile because of the deactivation of one of the lactone carbonyl groups as a result of the resonance form (**21**).[11] By analogy, the contribution of the resonance form (**23**) might render the methyl ester group in the intermediate (**22**) less susceptible to lactonisation and thus give products resulting from cyclisation at the t-butyl ester group.

In the event, reaction of the (*E*)-dioxolanone (**14**) with the lithium enolate of the ester (**19**) gave an almost quantitative yield of a 1:3 mixture of t-butyl esters (**24**) and (**25**) which were separable by chromatography. Using the same conditions the (*Z*)-dioxolanone (**15**) gave a 1:2 mixture (77%) of (**24**) and (**25**). Both these results indicate that the olefinic geometry of the intermediate (**22**) is susceptible to facile stereomutation as a result of extensive resonance delocalisation. Naturally occurring pulvinic acids have always been assigned the (*E*)-stereochemistry at the exocyclic double bond, largely because of their ability to form anhydrides but also because of their capacity for intramolecular hydrogen bonding as shown by i.r. spectroscopy.



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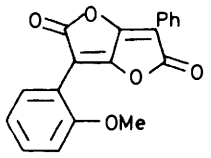

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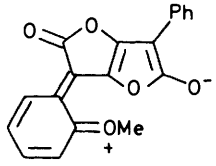

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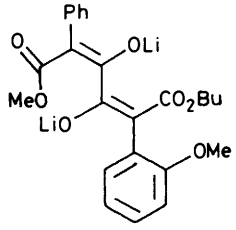

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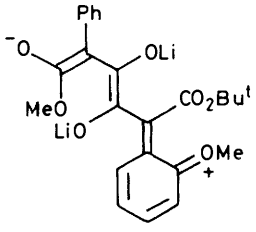

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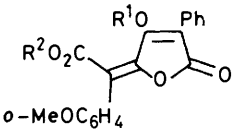
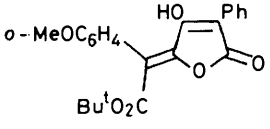


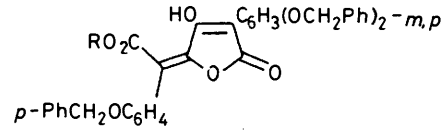
(24) $R^1 = H$; $R^2 = Bu^t$
(26) $R^1 = R^2 = H$
(27) $R^1 = R^2 = Me$



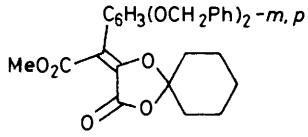
(25)

The solid-state i.r. spectrum of (**24**) showed absorptions at 2 700—2 300 (OH), 1 770 (lactone C=O), and a weak band at 1 675 cm^{-1} (ester C=O). The low frequency and intensity of this latter absorption suggested hydrogen bonding between the ester carbonyl group and the hydroxy group of the tetronic acid nucleus and this was confirmed by the unchanged nature of the solution spectrum. The Nujol mull spectrum of (**25**) showed $\nu_{max.}$ 3 400—2 450 (OH), and carbonyl absorptions at 1 730 (lactone) and 1 705 cm^{-1} (ester) with the latter having the greater intensity. The presence of intermolecular hydrogen bonding in (**25**) between the lactone carbonyl and the hydroxy group of the 5-membered ring was demonstrated by the solution i.r. spectrum which showed $\nu_{max.}$ 3 420 (free OH), 1 770 (lactone C=O), and 1 710 cm^{-1} (ester C=O).

The u.v. irradiation of (**25**) in toluene resulted in quantitative formation of (**24**) which was converted efficiently into the free acid (**26**) using 90% TFA in the presence of anisole. Partial methylation of the acid (**26**) using diazomethane gave leprapinic acid (**3**) in 42% yield after chromatography which was required to remove other methylation products. The synthetic acid (**3**) was identical (^1H n.m.r., i.r., and t.l.c.) with a sample from the synthesis carried out by Chawla and his co-workers[12] and showed all the spectral properties reported for the natural product.[13] Methylation of the acid (**26**) with an excess of diazomethane gave leprapinic acid methyl ether (**27**) which



(28) R = Bu^t
(29) R = H



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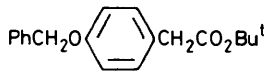

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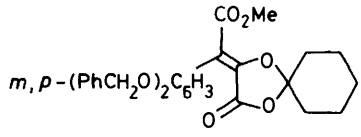

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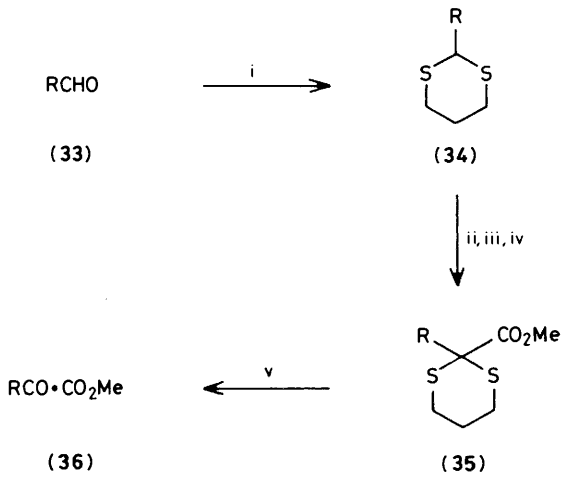


R = $C_6H_3(OCH_2Ph)_2$-*m*,*p*

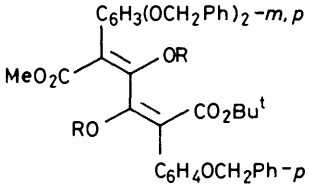
Scheme 4. *Reagents:* i. $HS(CH_2)_3SH$–HCl; ii, n-BuLi; iii, CO_2; iv, CH_2N_2; v, CuO–$CuCl_2$–acetone–H_2O

displayed the spectral behaviour reported.[13] Attention was turned to the synthesis of xerocomic acid (**4**). Our earlier work on pulvinone synthesis[9] had demonstrated the usefulness of benzyl ethers for phenolic protection and it was expected that preparation of the t-butyl ester (**28**), from the dioxolanone (**30**) and t-butyl 4-benzyloxyphenylacetate (**31**), would provide a suitable precursor. The t-butyl ester (**31**) was prepared in 51% yield from 4-benzyloxyphenylacetic acid by the method suggested by Tomita and co-workers.[14]

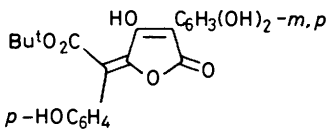
The keto-ester (**36**) was prepared from 3,4-dibenzyloxybenzaldehyde (**33**) by a route (Scheme 4) analogous to that used by Knight and Pattenden for the preparation of methyl 4-methoxyphenylglyoxylate.[7] Treatment of (**36**) with two equivalents of the phosphorane (**16**) for 18 h at 80 °C in toluene gave a high yield of a mixture of dioxolanones (**30**) and (**32**). These were not separable by chromatography but fractional crystallisation gave the major isomer which was assigned the (*E*)-stereochemistry (**30**) from a spectral comparison with the dioxolanone (**14**). The preparation of the t-butyl ester (**28**) was

pursued by reaction of dioxolanone (**30**) with the lithium enolate of t-butyl ester (**31**) in THF. Removal of the solvent and addition of ether and water gave a pale yellow solid which was tentatively assigned the acyclic structure (**37**). The solid-state and solution i.r. spectra showed absorptions at 3 700—2 600 (OH) and *1* 640 cm^{-1}. Treatment with dilute HCl gave a yellow oil, the ^1H n.m.r. spectrum of which showed two methyl ester and two t-butyl ester resonances. Cyclisation of the acyclic intermediate was effected by addition of water to the reaction mixture in THF and reflux until a clear two-phase solution was obtained. Evaporation, followed by addition of water and petroleum gave an orange solid which was precipitated directly from the basic medium. The ^1H n.m.r. spectrum of the crude product showed it to be a single t-butyl ester and (**28**) was obtained in 82% yield after chromatography. The (*E*)-stereochemistry was confirmed by the solid-state and solution i.r. spectra which showed the expected intramolecular hydrogen bonding.

Attempted conversion of (**28**) into the free acid (**29**) using 90% TFA gave a mixture of products due to partial debenzylation. The intermediate (**28**) was therefore subjected to hydrogenation (DMF, conc. HCl, 10% Pd-C) to give the t-butyl ester (**38**) which, because of its oxidative instability, was

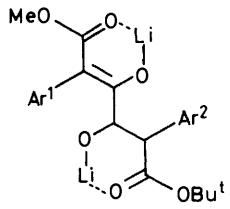


(**37**) R = H
(**39**) R = Li



(**38**)

immediately treated with 90% TFA–anisole to give xerocomic acid (**4**) in 90% yield from (**28**). The product was identical (^1H n.m.r. and t.l.c.) with an authentic sample isolated by Edwards[15] from *Gomphidius rutilus* and showed all the spectral properties reported.[16] The above results describe a versatile route to unsymmetrically substituted pulvinic acids although it appears that a change of substituents on the aromatic rings has a marked effect on the conditions necessary to produce cyclisation of the intermediate dianions of type (**11**). For example, cyclisation of the intermediate (**22**) proceeded easily at room temperature whereas work-up of the reaction involving (**39**) produced an acyclic product. It is possible that, in THF solution, the dianions exist as the chelated species (**40**) which cannot cyclise to pulvinic acids and that addition of water breaks this chelation and allows cyclisation of (**22**) to occur. However the insolubility of (**39**) or its protonated form (**37**) may prevent cyclisation until forcing conditions are used. The insolubility induced by benzyloxy substituents is demonstrated by the fact that the acid (**28**) precipitates directly from basic solution on addition of petroleum.



(**40**)

Experimental

I.r. spectra, calibrated against polystyrene film at 1 603 cm^{-1}, were recorded on a Perkin-Elmer 197 spectrophotometer. 60 MHz ^1H N.m.r. spectra were recorded on Perkin-Elmer R12 and R20A spectrometers, 80 MHz on a Bruker WP80, 90 MHz on a Perkin-Elmer R32, 220 MHz on a Perkin-Elmer R34 and 300 MHz on a Varian SC300 spectrometer; chemical shifts are relative to internal $SiMe_4$ at 0.00 p.p.m. U.v. spectra were recorded on a Varian Cary 118X or Pye Unicam SP8-100 spectrophotometer. Mass spectra were recorded on A.E.I. MS 902 and Kratos MS 45 spectrometers with an ionisation potential of 70 eV. Microanalyses were made on a Perkin-Elmer 240 Elemental Analyser. Melting points were determined on a Buchi 510 or a Kofler hot-stage microscope and are uncorrected as are boiling points. T.l.c. was carried out on silica gel (Fluka GF 254) and examined by u.v. light at 254 and 366 nm or by staining in iodine vapour. Preparative chromatography was performed on silica gel 60 (70—230 mesh ASTM) (Merck). Flash column chromatography was carried out on Kieselgel 60H (Merck). Photochemical irradiation was carried out in an Hanovia 300 ml photochemical reactor. Unless stated otherwise all reactions were carried out at room temperature (18—24 °C). Commercially available solvents were dried by standard procedures and distilled prior to use. Tetrahydrofuran (THF) was distilled from potassium benzophenone ketyl immediately before use. Petroleum refers to the fraction boiling in the range 40—60 °C. Nitrogen was purified by passing it successively through Fieser's solution, saturated aqueous lead(II) acetate, concentrated sulphuric acid, and potassium hydroxide pellets.

General Preparation of Lithium Ester Enolates.—The enolates were prepared in THF as described in the preceding paper.[9]

(E)- *and* (Z)-5′-(α-*Methoxycarbonylbenzylidene*)*cyclohexane-spiro*-2′-(1′,3′-*dioxolan*)-4′-*ones* (**14**) *and* (**15**).—To the phosphorane (**16**) (22 mmol) in toluene (66 ml) at 95 °C under nitrogen was added methyl phenylglyoxylate (3.28 g, 20 mmol) in toluene (20 ml). The mixture was kept at 95 °C for 3 h, allowed to cool, filtered, and evaporated to give a yellow oil. Trituration with ether gave a precipitate of triphenylphosphine oxide which was filtered off. The filtrate was evaporated to give an oily solid (8.79 g). Final traces of triphenylphosphine oxide were removed by chromatography on silica gel (40 g) with chloroform as eluant. The product was purified by m.p.l.c. on silica gel. Elution with ether–petroleum (1:4) gave first (**14**) (4.34 g, 72%), followed by a mixture of (**14**) and (**15**) (0.34 g, 5%) and finally (**15**) (0.75 g, 12%). Both (**14**) and (**15**) were recrystallised from ethyl acetate–petroleum.

(E)-*Isomer* (**14**) had, m.p. 98—100.5 °C (Found: C, 67.7; H, 6.0. $C_{17}H_{18}O_5$ requires C, 67.55; H, 6.0%); $\lambda_{max.}$(EtOH) 297 (ε 16 400) and 309sh nm (12 500); $\nu_{max.}(CH_2Cl_2)$ 1 790s, 1 735s, and 1 645w cm^{-1}; δ_H(80 MHz, $CDCl_3$) 7.35—7.80 (5 H, m), 3.98 (3 H, s, OMe), and 1.39—2.21 (10 H, m); *m/z* 302 (M^+, 6%).

(*Z*)-*Isomer* (**15**) had, m.p. 101.5—105 °C (Found: C, 67.7; H, 5.9. $C_{17}H_{18}O_5$ requires C, 67.55; H, 6.0%); $\lambda_{max.}$(EtOH) 269 nm (ε 11 000); $\nu_{max.}$(CH_2Cl_2) 1 795s, 1 720s, and 1 640w cm^{-1}; δ_H(80-MHz, $CDCl_3$) 7.24—7.55 (5 H, m), 3.81 (3 H, s, OMe), and 1.32—2.22 (10 H, m); *m/z* 302 (M^+, 7%).

(E)-5-(α-*t-Butoxycarbonylbenzylidene*)-3-*phenylfuran*-2,4(3H,5H)-*dione* [(E)-4-(α-*t-Butoxycarbonylbenzylidene*)-2-*phenyltetronic Acid*] (**18**).—To the lithium enolate of t-butyl phenylacetate (9.6 mmol) in THF (40 ml) at −78 °C under nitrogen was added a solution of the (*E*)-dioxolanone (**14**) (0.88 g, 2.93 mmol) in THF (10 ml). The solution was kept at −78 °C for 2 h and at room temperature for 20 h before evaporation of the solvent and partition of the residue between ether and water. The ethereal layer was washed with water and the combined aqueous layers were acidified (pH 1) with dilute HCl. The yellow precipitate was filtered off and dried to give the *t-butyl ester* (**18**) (0.98 g, 92%) which was recrystallised from ethyl acetate–petroleum to give (**18**) (0.79 g, 74%), m.p. 194—202 °C (transition at 130—135 °C) (Found: C, 72.45; H, 5.71. $C_{22}H_{20}O_5$ requires C, 72.5; H, 5.55%); $\lambda_{max.}$(EtOH) 287 (ε 15 850) and 365 nm (11 750); $\nu_{max.}$($CHCl_3$) 2 600w, 1 770s, and 1 670m cm^{-1}; δ_H(220 MHz, $CDCl_3$) 14.11 (1 H, s, exchanges with D_2O), 8.11—8.19 (2 H, d), 7.22—7.51 (8 H, m), and 1.45 (9 H, s, Bu^t); *m/z* 364 (M^+) and 308 ($M^+ - C_4H_8$).

(E)-5-(α-*Carboxybenzylidene*)-3-*phenylfuran*-2,4(3H,5H)-*dione* [(E)-4-(α-*Carboxybenzylidene*)-2-*phenyltetronic Acid. Pulvinic Acid*] (**2**).—The t-butyl ester (**18**) (0.37 g, 1.0 mmol) was dissolved in 90% TFA (10 ml). After 10 min a yellow solid appeared. The mixture was stirred for 5 h and the solid was filtered off, washed with water, and recrystallised from chloroform to give pulvinic acid (**2**) (0.24 g, 76%), m.p. 202—207 °C (lit.,[17] 216—217 °C); authentic sample 194—206 °C, mixed sample 200—213 °C (Found: C, 70.05; H, 4.0. Calc. for $C_{18}H_{12}O_5$: C, 70.15; H, 3.9%); $\lambda_{max.}$(EtOH) 212 (ε 9 800), 254 (15 150), and 366 nm (9 100); $\nu_{max.}$(dioxane) 3 550w, 2 550w, 1 770s, and 1 675m cm^{-1}; δ_H [220 MHz, $(CD_3)_2SO$] 8.05—8.16 (2 H, d), 7.50—8.60 (2 H, br s), and 7.14—7.48 (8 H, m); *m/z* 308 (M^+) and 290 ($M^+ - H_2O$).

(E)-5(α-*Methoxycarbonylbenzylidene*)-3-*phenylfuran*-2,4-(3H,5H)-*dione* [(E)-4-(α-*Methoxycarbonylbenzylidene*)-2-*phenyltetronic Acid: Vulpinic Acid*] (**1**).—To the lithium enolate of methyl phenylacetate (10 mmol) in THF (40 ml) at −78 °C under nitrogen was added a solution of the (*E*)-dioxolanone (**14**) (0.89 g, 2.94 mmol) in THF (10 ml) over 15 min. The solution was kept at −78 °C for 2 h and at room temperature for 18 h before evaporation of the solvent and partition of the residue between ether and water. The ethereal layer was washed with water and the combined aqueous layers were acidified (pH 1) with dilute HCl. The yellow solid which was precipitated on storage at 0 °C was filtered off and dried (0.81 g, 86%). Recrystallisation of this from methanol gave pure vulpinic acid (**1**) (0.59 g, 62%), m.p. 146—148 °C (lit.,[17] 148—149 °C); authentic sample 146—149 °C, mixed sample 147—150 °C (Found: C, 70.8; H, 4.4. Calc. for $C_{19}H_{14}O_5$: C, 70.8; H, 4.4%); $\lambda_{max.}$(EtOH) 289 (ε 16 200) and 366 nm (8 700); $\nu_{max.}$($CHCl_3$) 2 650m, 1 770s, and 1 675m cm [1]; δ_H(220 MHz, $CDCl_3$) 13.75 (1 H, s, exchanges with D_2O), 8.08—8.22 (2 H, d), 7.22—7.53 (8 H, m), and 3.88 (3 H, s, OMe); *m/z* 322 (M^+) and 290 ($M^+ - CH_3OH$).

t-Butyl 2-Methoxyphenylacetate (**19**).—A mixture of 2-methoxyphenylacetic acid (25 g, 0.15 mol), concentrated H_2SO_4 (1.8 ml), and isobutene (24 g, 0.43 mol) in dry ether (40 ml) was shaken in a sealed flask for 14 h. The flask was cooled, opened, and the mixture was poured into a solution of KOH (24 g) in water (80 ml) with a large amount of ice. The aqueous layer was washed with ether (2 × 30 ml) and the combined ethereal layers were dried (K_2CO_3), filtered, and evaporated under reduced pressure to give a colourless oil (22.5 g) which was distilled through a Vigreux column to give the *t-butyl ester* (**19**) (19.90 g, 60%), b.p. 88—92 °C (0.05 mmHg) (Found: C, 70.3; H, 8.25. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.15%); $\lambda_{max.}$(EtOH) 271 (ε 1 700) and 277 nm (1 600); $\nu_{max.}$(film) 1 735s cm^{-1}; δ_H (220 MHz, $CDCl_3$) 7.15—7.30 (2 H, m), 6.85—6.98 (2 H, m), 3.82 (3 H, s, OMe), 3.54 (2 H, s, CH_2), and 1.43 (9 H, s, Bu^t); *m/z* 222 (M^+, 10%).

(E)- *and* (Z)-5-(2-*Methoxy*-α-*t-butoxycarbonylbenzylidene*)-3-*phenylfuran*-2,4(3H,5H)-*diones* [(E)- *and* (Z)-4-(2-*Methoxy*-α-*t-butoxycarbonylbenzylidene*)-*2-phenyltetronic Acids*] (**24**) *and* (**25**).—To the lithium enolate of t-butyl 2-methoxyphenylacetate (17.5 mmol) in THF (36 ml) at −78 °C was added a solution of the dioxolanones (**14**) and (**15**) (2:1 ratio) (2.11 g, 7 mmol) in THF (14 ml) and the solution was allowed gradually to attain room temperature. Removal of the solvent gave an oil which was partitioned between ether and water. The aqueous layer was acidified (pH 1) and the oily yellow precipitate was extracted with ethyl acetate. The organic layer was dried, filtered, and evaporated to give (**24**) and (**25**) (2.59 g) (5:17 by ^1H n.m.r.). Chromatography on silica gel (70 g) with chloroform as eluant gave the (E)-*t-butyl ester* (**24**) (0.69 g, 25%), followed by a mixture of (**24**) and (**25**) (0.34 g, 12%), and finally the (Z)-*t-butyl ester* (**25**) (1.34 g, 49%).

The (*E*)-isomer (**24**) had m.p. 217—218 °C (transition at 150 °C) (from ethyl acetate–petroleum) (Found: C, 70.1; H, 5.6. $C_{23}H_{22}O_6$ requires C, 70.05; H, 5.6%); $\lambda_{max.}$(EtOH) 274 (ε 19 700) and 370 nm (15 350); $\lambda_{max.}$(EtOH + 1 drop 2M-NaOH) 273 (ε 26 350) and 368 nm (9 250); $\nu_{max.}$(Nujol) 2 550w, 1 770s, and 1 670m cm^{-1}; $\nu_{max.}$($CHCl_3$) 2 550w, 1 770s, and 1 670m cm^{-1}; δ_H (220 MHz, $CDCl_3$) 14.01 (1 H, s, OH), 8.11—8.22 (2 H, m), 7.17—7.55 (5 H, m), 6.88—7.07 (2 H, m), 3.80 (3 H, s, OMe), and 1.40 (9 H, s, Bu^t); *m/z* 394 (M^+).

The (*Z*)-isomer (**25**) had m.p. 132—134 °C (ether–petroleum) (Found: C, 69.7; H, 5.6. $C_{23}H_{22}O_6$ requires C, 70.05; H, 5.6%); $\lambda_{max.}$(EtOH) 271 (ε 20 050) and 344 nm (12 550); $\lambda_{max.}$(EtOH + 1 drop 2M-NaOH) 273 (ε 26 000) and 379 nm (8 200); $\nu_{max.}$(Nujol) 3 400—2 450w, 1 730s, and 1 705s cm^{-1}; $\nu_{max.}$($CHCl_3$) 3 420m, 1 770s, and 1 710s cm^{-1}; δ_H (80 MHz, $CDCl_3$) 7.85—8.03 (2 H, m), 6.95—7.65 (7 H, m), 5.90 (1 H, s, OH), 3.85 (3 H, s, OMe), and 1.49 (9 H, s, Bu^t); *m/z* 338 ($M^+ - C_4H_8$, 8%).

Irradiation of (Z)-*t-Butyl Ester* (**25**).—A solution of the ester (**25**) (0.40 g, 1.02 mmol) in toluene (200 ml) under nitrogen was irradiated with u.v. light from a 125-W medium-pressure mercury vapour arc tube for 3 h. The solvent was evaporated under reduced pressure and the residue chromatographed on silica gel to remove a trace of polar impurity. Elution with chloroform gave the (*E*)-t-butyl ester (**24**) (0.39 g, 97%).

(E)-5-(α-*Carboxy*-2-*methoxybenzylidene*)-3-*phenylfuran*-2,4(3H, 5H)-*dione* [(E)-4-(α-*Carboxy*-2-*methoxybenzylidene*)-2-*phenyltetronic Acid: 2′-Methoxypulvinic Acid*] (**26**).—The (*E*)-t-butyl ester (**24**) (0.385 g, 0.98 mmol) was dissolved in 90% TFA (15 ml) with anisole (1.03 g, 9.44 mmol). A yellow precipitate began to appear almost immediately and after 16 h the solvent was evaporated under reduced pressure. Recrystallisation of the residue from dichloromethane gave the acid (**26**) (0.175 g, 53%). Recrystallisation of the mother liquors from dichloromethane–petroleum gave a second crop (0.108 g, 33%), m.p. 221—222 °C (lit.,[18] 213—214 °C) (Found: C, 67.4; H, 4.3. Calc. for $C_{19}H_{14}O_6$: C, 67.45; H, 4.15%); $\lambda_{max.}$(EtOH) 267 (ε 25 300) and 363 nm (11 300); $\lambda_{max.}$(EtOH + 1 drop 2M-NaOH) 276 (ε

25 300) and 351 nm (10 350); $\nu_{max.}$(Nujol) 3 400—2 800m, 2 450w, 1 755s, and 1 680w cm^{-1}; $\nu_{max.}$($CHCl_3$) 3 400—2 100m, 1 770s, and 1 680m cm^{-1}; δ_H (80 MHz, $CDCl_3$) 13.41 (1 H, s, OH), 8.07—8.21 (2 H, m), 6.88—7.62 (7 H, m), and 3.81 (3 H, s, OMe); *m/z* 338 (M^+, 16%) and 320 ($M^+ - H_2O$, 78%).

(E)-5-(2-*Methoxy-α-methoxycarbonylbenzylidene*)-3-*phenylfuran*-2,4(3H,5H)-*dione* [(E)-4-(2-*Methoxy-α-methoxycarbonylbenzylidene*)-2-*phenyltetronic Acid: Leprapinic Acid*] (**3**).—2′-Methoxypulvinic acid (**26**) (0.2 g, 0.59 mmol) was dissolved in methanol and an ethereal solution of diazomethane was added in small portions until t.l.c. showed complete consumption of acid (**26**). The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (100 g). Elution with chloroform gave leprapinic acid (**3**) (86 mg, 42%), leprapinic acid methyl ether (**27**) (28 mg, 11%), and finally (**27**) contaminated with two minor impurities. The title compound had m.p. 160—164 °C (MeOH) (lit.,[13] 164—165 °C) (Found: C, 68.0; H, 4.5. Calc. for $C_{20}H_{16}O_6$: C, 68.20; H, 4.60%); $\lambda_{max.}$(EtOH) 273 (ε 19 100) and 370 nm (12 500); $\lambda_{max.}$(EtOH + 1 drop 2M-NaOH) 270 (ε 21 600) and 371 nm (9 000); $\nu_{max.}$(Nujol) 2 500w, 1 770s, and 1 680m cm^{-1}; $\nu_{max.}$($CHCl_3$) 2 625w, 1 775s, and 1 680m cm^{-1}; δ_H (80 MHz, $CDCl_3$) 13.67 (1 H, s, OH), 8.05—8.25 (2 H, m), 6.85—7.57 (7 H, m), 3.81 (3 H, s, OMe), and 3.77 (3 H, s, OMe); *m/z* 352 (M^+, 20%).

(E)-5-(2-*Methoxy-α-methoxycarbonylbenzylidene*)-4-*methoxy*-3-*phenylfuran*-2(5H)-*one* [*Methyl* (E)-4-(2-Methoxy-*α-methoxycarbonylbenzylidene*)-2-*phenyltetronate: Leprapinic Acid Methyl Ether*] (**27**).—To 2′-methoxypulvinic acid (**26**) (86 mg, 0.25 mmol) was added an excess of ethereal diazomethane. After 1 h the solvent was evaporated under reduced pressure and the residue was recrystallised from methanol to give the ether (**27**), m.p. 151—152 °C (lit.,[13] 150—152 °C); $\lambda_{max.}$(MeOH) 230 (ε 12 600), 260 (9 400), and 332 nm (18 500); $\nu_{max.}$($CHCl_3$) 1 770s and 1 730s cm^{-1}; δ_H (80 MHz, $CDCl_3$) 6.82—7.60 (9 H, m), 3.81 (6 H, s, 2 × OMe), and 3.75 (3 H, s, OMe); *m/z* 366 (M^+, 100%).

t-Butyl 4-*Benzyloxyphenylacetate* (**31**).—Phosphoryl chloride (11.2 ml) was added over 1 h to a stirred solution of 4-benzyloxyphenylacetic acid (24 g, 99 mmol) in pyridine (128 ml) and t-butyl alcohol (200 ml) cooled to −10 °C. After 0.5 h at −10° C the mixture was stirred at room temperature for 2 h and evaporated under reduced pressure. To the residue were added ether (600 ml) and water (200 ml). The ethereal layer was washed with 2% citric acid (3 × 100 ml), 2% NH_4OH (2 × 100 ml), and water (2 × 100 ml), dried (K_2CO_3), filtered, and evaporated to give a yellow oil which was chromatographed on silica gel (150 g) with chloroform as eluant. The product was distilled from K_2CO_3 through a short Vigreux column to give the t-butyl ester (**31**) which solidified with time (14.92 g, 51%), b.p. 160 °C (0.06 mmHg) (Found: C, 76.8; H, 7.7. Calc. for $C_{19}H_{22}O_3$: C, 76.5; H, 7.4%); $\lambda_{max.}$(EtOH) 224 (ε 14 300), 275 (1 700), and 282 nm (1 500); $\nu_{max.}$($CHCl_3$) 1 725s cm^{-1}; δ_H (220 MHz, $CDCl_3$) 7.31—7.47 (5 H, m), 7.18 (2 H, d, *J* 8 Hz), 6.94 (2 H, d, *J* 8 Hz), 5.05 (2 H, s, OCH_2Ph), 3.45 (2 H, s, CH_2), and 1.41 (9 H, s, Bu^t); *m/z* 298 (M^+, 12%).

2-(3,4-*Dibenzyloxyphenyl*)-1,3-*dithiane* (**34**).—A solution of 3,4-dibenzyloxybenzaldehyde (**33**)[9] (23.1 g, 75 mmol) and propane-1,3-dithiol (8.1 g, 75 mmol) in chloroform (150 ml) was stirred for 1 h and cooled to −20 °C. Dry HCl was bubbled through the solution for 10 min after which the mixture was allowed to attain room temperature and then stirred for 1 h. The solution was washed with water (3 × 25 ml), 10% KOH (3 × 25 ml), and water (3 × 25 ml), dried (K_2CO_3), filtered, and evaporated to leave an off-white solid which was recrystallised from ethyl acetate–petroleum to afford the dithiane (26.4 g, 86%), m.p. 107—107.5 °C (Found: C, 70.6; H, 6.0; S, 15.7. $C_{24}H_{24}O_2S_2$ requires C, 70.55; H, 5.9; S, 15.7%); $\lambda_{max.}$(EtOH) 230 (ε 19 000) and 279 nm (4 900); $\nu_{max.}$(Nujol) 1 600w, 1 580w, and 1 510m cm^{-1}; δ_H (80 MHz, $CDCl_3$) 6.80—7.55 (13 H, m), 5.15 (2 H, s, OCH_2Ph), 5.13 (2 H, s, OCH_2Ph), 5.08 (1 H, s, CH), 2.70—3.25 (4 H, m, 2 × CH_2), and 1.65—2.30 (2 H, m, CH_2); *m/z* 408 (M^+, 18%).

2-(3,4-*Dibenzyloxyphenyl*)-2-*methoxycarbonyl*-1,3-*dithiane* (**35**).—To a solution of the dithiane (**34**) (20.4 g, 50 mmol) in THF (300 ml) at −78 °C was added a solution of n-butyllithium (2M; 26.5 ml, 53 mmol) in hexane. The mixture was kept at −78 °C for 1 h, and then poured onto freshly chopped solid carbon dioxide and stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue partitioned between ether and water. The aqueous layer was cooled and acidified with concentrated HCl to give a white precipitate which almost immediately became an oil. This was extracted with ethyl acetate and the dried extracts were evaporated and immediately treated with ethereal diazomethane until no further evolution of nitrogen was observed. Evaporation gave the crude product (19 g) which was chromatographed on silica gel (400 g) with chloroform as eluant. The product was recrystallised from cyclohexane–petroleum to give the *methyl ester* (**35**) (11.68 g, 50%). Chromatography and recrystallisation of the mother-liquors gave a further crop (1.2 g, 7%), m.p. 90.5—92 °C (MeOH–water) (Found: C, 67.1; H, 5.8; S, 13.4. $C_{26}H_{26}O_4S_2$ requires C, 66.9; H, 5.6; S, 13.7%); $\lambda_{max.}$(EtOH) 245 (ε 7 400) and 281 nm (3 100); $\nu_{max.}$($CHCl_3$) 1 730s cm^{-1}; δ_H (80 MHz, $CDCl_3$) 6.78—7.80 (13 H, m), 5.15 (2 H, s, OCH_2Ph), 5.13 (2 H, s, OCH_2Ph), 3.64 (3 H, s, OMe), 2.44—3.32 (4 H, m, 2 × CH_2), and 1.69—2.24 (2 H, m, CH_2); *m/z* 466 (M^+, 8%).

Methyl 3,4-*Dibenzyloxyphenylglyoxylate* (**36**).—A mixture of the methyl ester (**35**) (6.97 g, 15 mmol), CuO (5.96 g, 75 mmol), and $CuCl_2$ (5.05 g, 37.5 mmol) in acetone (150 ml) and water (1.5 ml) was heated at reflux point for 3.5 h. The solvent was evaporated and the residual black mass was triturated with chloroform and filtered. Evaporation of the filtrate gave a pale yellow solid (4.67 g) which was chromatographed on silica gel (200 g) with chloroform as eluant to give the *glyoxylate* (**36**) (3.26 g, 58%), m.p. 94—95 °C (MeOH–water) (Found: C, 73.4; H, 5.3. $C_{23}H_{20}O_5$ requires C, 73.4; H, 5.35%); $\lambda_{max.}$(EtOH) 233 (ε 14 500), 284 (10 600), and 310 nm (9 600); $\nu_{max.}$($CHCl_3$) 1 740s, 1 675s, and 1 595s cm^{-1}; δ_H (80 MHz, $CDCl_3$) 6.85—7.68 (13 H, m), 5.25 (2 H, s, OCH_2Ph), 5.18 (2 H, s, OCH_2Ph), and 3.90 (3 H, s, OMe); *m/z* 376 (M^+, 5%).

(E)-5′-[*α-Methoxycarbonyl*-(3,4-*dibenzyloxybenzylidene*)]*cyclohexanespiro*-2′-(1′,3′-*dioxolan*)-4′-*one* (**30**).—To the phosphorane (**16**) (13 mmol) in toluene (26 ml) at 80 °C under nitrogen was added a solution of the glyoxylate (**36**) (2.54 g, 6.5 mmol) in toluene (35 ml). The mixture was stirred for 18 h, filtered, and evaporated to give the crude product (8.07 g) which contained a mixture of (**30**) and (**32**) (*ca.* 6:1 by ^1H n.m.r. spectroscopy). The mixture was chromatographed on silica gel with chloroform as eluant. The product (3.67 g) was recrystallised from ethanol to give a white solid which was almost entirely the (E)-*dioxolanone* (**30**) (2.72 g, 81%), m.p. 127.5—128.5 °C (Found: C, 72.4; H, 5.9. $C_{31}H_{30}O_7$ requires C, 72.35; H, 5.9%); $\lambda_{max.}$(EtOH) 238 (ε 11 000) and 328 nm (18 200); $\nu_{max.}$($CHCl_3$) 1 785s, 1 735s, and 1 650w cm^{-1}; δ_H (80 MHz, $CDCl_3$) 6.82—7.67 (13 H, m), 5.20 (2 H, s, OCH_2Ph), 5.18 (2 H, s, OCH_2Ph), 3.87 (3 H, s, OMe), and 1.25—2.07 (10 H, m); *m/z* 514 (M^+, 11%). The mother-liquors contained a mixture (0.44 g, 13%) of (**30**) and (**32**) (7:10 by ^1H n.m.r.).

(E)-3-(3,4-*Dibenzyloxyphenyl*)-5-(α-*t-butoxycarbonyl*-4-*benzyloxybenzylidene*)-*furan*-2,4(3H,5H)-*dione* [(E)-2-(3,4-*Dibenzyloxyphenyl*)-4-(α-*t-butoxycarbonyl*-4-*benzyloxybenzylidene*)*tetronic Acid*] (**28**).—To the lithium enolate of t-butyl 4-benzyloxyphenylacetate (2.5 mmol) in THF (9 ml) at −78 °C under nitrogen was added a solution of the (*E*)-dioxolanone (**30**) (0.515 g, 1.0 mmol) in THF (10 ml). The reaction mixture was allowed gradually to attain room temperature and was then stirred overnight. To the clear orange solution was added water (2 ml) whereupon a milky white precipitate appeared. The mixture was heated to reflux until a clear, two-phase solution was obtained (25 min), after which the solvent was evaporated to leave an oil. Water (25 ml) and petroleum (200 ml) were added and the mixture was stirred. The orange precipitate was filtered off and washed thoroughly with petroleum to give the crude product (0.63 g) which was shown by ^{1}H n.m.r. spectroscopy to be (**28**) together with a trace of t-butyl 4-benzyloxyphenylacetate. Chromatography on silica gel (45 g) with chloroform–petroleum (1:1) as eluant gave the *t-butyl ester* (**28**) (0.56 g, 82%), m.p. 139—141 °C (ethyl acetate–petroleum) (Found: C, 75.9; H, 5.6. $C_{43}H_{38}O_8$ requires C, 75.65; H, 5.6%); $\lambda_{max.}$(EtOH) 307 (ε 18 500) and 382 nm (8 200); $\nu_{max.}$(Nujol) 2 600m, 1 775s, and 1 670m cm^{-1}; $\nu_{max.}$($CHCl_3$) 2 500w, 1 770s, and 1 670m cm^{-1}; δ_H [80 MHz, $(CD_3)_2CO$] 14.05 (1 H, s), 7.99 (1 H, d, *J* 2 Hz), 7.81 (1 H, dd, *J* 8, 2 Hz), 7.05—7.70 (20 H, m), 5.30 (2 H, s, OCH_2Ph), 5.27 (2 H, s, OCH_2Ph), 5.24 (2 H, s, OCH_2Ph), and 1.58 (9 H, s, Bu^t).

(E)-3-(3,4-*Dihydroxyphenyl*)-5-(4-*hydroxy*-α-*carboxybenzylidene*)*furan*-2,4(3H,5H)*dione* [(E)-2-(3,4-*Dihydroxyphenyl*)-4-(4-*hydroxy*-α-*carboxybenzylidene*)*tetronic Acid: Xerocomic Acid*] (**4**).—To a solution of the t-butyl ester (**28**) (346 mg, 0.51 mmol) in DMF (20 ml) was added 10% Pd-C (120 mg) and concentrated HCl (3 drops). The mixture was stirred under hydrogen for 3.5 h. The catalyst was removed by filtration and the solvent was evaporated to give the t-butyl ester (**38**) as a red oil which was stirred with 90% TFA (8 ml) and anisole (0.548 g, 5.1 mmol) for 16 h. The solvent was evaporated and the residue was chromatographed on silica gel (50 g) with benzene–ethyl acetate–formic acid (13:5:1) as eluant to give xerocomic acid (**4**) [161 mg, 90% from the t-butyl ester (**28**)], m.p. 294—298 °C (formic acid) (lit.,[16] 295 °C) (Found: C, 60.4; H, 3.2. Calc. for $C_{18}H_{12}O_8$: C, 60.7; H, 3.4%); $\lambda_{max.}$(EtOH) 257 (ε 26 050) and 395 nm (12 550); $\lambda_{max.}$(EtOH + 1 drop 2M-NaOH) 243 (ε 16 100) and 383 nm (25 100); $\nu_{max.}$(Nujol) 3 175s, 2 500w, 1 735s, and 1 680m cm^{-1}; $\nu_{max.}$(dioxane) 3 300s, 1 780s, 1 675m, and 1 600s cm^{-1}; δ_H (80 MHz, $(CD_3)_2CO$] 7.78 (1 H, d, *J* 2 Hz), 7.64 (1 H, dd, *J* 8, 2 Hz), 7.35 (2 H, d, *J* 8 Hz), and 6.95 (3 H, d, *J* 8 Hz); *m/z* 356 (M^+, 10%), 338 ($M^+ - H_2O$, 100%). The synthetic sample was identical (^{1}H n.m.r. and t.l.c.) with an authentic natural sample from *Gomphidius rutilus*.[15]

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References

1 For a review on 4-ylidenetetronic acids see G. Pattenden, *Fortschr. Chem. Org. Naturst.*, 1978, **35**, 133.
2 W. Brieger, 'Handbuch der biologischen Arbeitsmethoden, Abteilung 1: Chemische Methoden,' (E. Aberhalden, ed.), Urban and Schwarzenberg, Berlin and Vienna, 1923, Teil 10, pp. 340—346.
3 J. Murray, *J. Chem. Soc.*, 1952, 1345.
4 A. Spiegel, *Chem. Ber.*, 1882, **15**, 1546.
5 R. L. Edwards and M. Gill, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1538.
6 W. Steglich, H. Besl, and K. Zipfel, *Z. Naturforsch., Teil B*, 1974, **29**, 96.
7 D. W. Knight and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1979, 84.
8 R. L. Frank, G. R. Clark, and J. N. Coker, *J. Am. Chem. Soc.*, 1950, **72**, 1824.
9 R. Ramage, G. J. Griffiths, F. E. Shutt, and J. N. A. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1531; and preceding paper.
10 B. Beagley and R. Pritchard, personal communication.
11 S. C. Agarwal and T. R. Seshadri, *Tetrahedron*, 1964, **20**, 17.
12 H. M. Chawla, S. S. Chibber, and S. Niwas, *Tetrahedron Lett.*, 1980, 2089.
13 S. C. Agarwal and T. R. Seshadri, *Tetrahedron*, 1965, **21**, 3205.
14 M. Tomita, K. Fujitani, and Y. Aoyagi, *Tetrahedron Lett.*, 1967, 1201.
15 P. C. Beaumont and R. L. Edwards, *J. Chem. Soc. C*, 1971, 2582.
16 W. Steglich, W. Furtner, and A. Prox, *Z. Naturforsch., Teil B*, 1968, **23**, 1044.
17 W. Zopf, *Ann. Chem.*, 1895, **284**, 107.
18 O. P. Mittal and T. R. Seshadri, *J. Chem. Soc.*, 1955, 3053.

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