Syntheses of Permethylated Derivatives of Pinastric Acid and Gomphidic Acid, Pulvinic Acid Pigments of Lichen and Fungi

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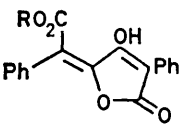
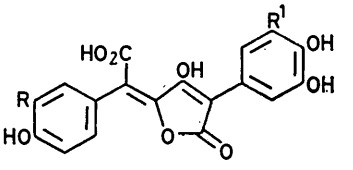
The application of 2-aryl *O*-methyltetronic acids (7) and (20) to the total synthesis of permethylated derivatives of pulvinic acid pigments found in *Lepraria flava* and *Gomphidius glutinosus* is described. Metallation of the tetronic acid (7), followed by treatment with methyl benzoylformate and dehydration of the intermediate carbinol led to *O*-methyl pinastric acid (9), identical with the *O*-methyl derivative of natural pinastric acid from *L. flava*. In a similar manner the tetronic acid (11) and methyl 4-methoxybenzoylformate gave *O*-methylisopinastric acid (12), and condensation between (20) and methyl 4-methoxybenzoylformate led to permethylated gomphidic acid (21). Comparison of ^{1}H n.m.r. shift data for (21) with those reported for gomphidic acid from *G. glutinosus* established structure (2b) for the natural metabolite.

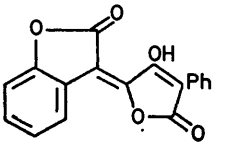
THE group of natural 4-ylidenetetronic acid derivatives (1a) known as pulvinic acids have long been recognised as the pigments responsible for the striking yellow and orange colour of lichens.[1,2] ' Vulpinic acid ' (1b), methyl ester, *e.g.* pinastric acid (4),[10] and amide derivatives of the acid occur naturally. The interesting indole ' cochliodinone ' (5) isolated from cultures of *Chaetomium globosum* and *C. cochliodes*[11] is the only example of a



(1)
a; R = H
b; R = Me



(2)
a; R = OH; R′ = H
b; R = H; R′ = OH
c; R = R^1 = H



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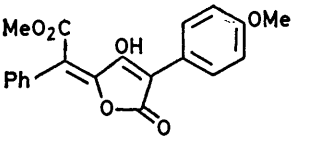

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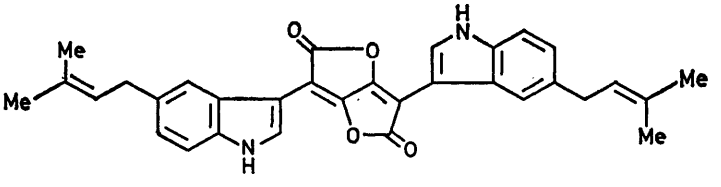
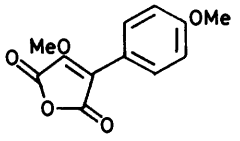


(5)

for example, the methyl ester of pulvinic acid, has been known since 1831, and early Eskimos used lichens containing the acid to poison wolves, a feature which clearly contributed to the trivial naming of the molecule. In more recent years pulvinic acids have been isolated from certain higher fungi belonging to the Boletaceae and Gomphidiaceae;[3-6] their production in lichens is almost certainly associated entirely with the fungal partner. All known natural pulvinic acids show variations which include either hydroxylation or methoxylation of the aryl rings, *e.g.* variegatic acid (2a)[7] and gomphidic acid (2b),[8] or lactonisations involving the carboxy function, *e.g.* calycin (3).[9] In addition, a few natural ' pulvinic acid type ' containing a heterocyclic ring.

Structural elucidation amongst members of the natural pulvinic acids, has invariably presented immense problems, particularly in those cases where the aryl rings have been unsymmetrically substituted. During a period covering almost a decade, Seshadri and his co-workers[10] for example examined the structure of pinastric acid, and even today formulation (4) is not without doubt. The problem of assigning structures to these molecules has received recent attention by Edwards and Gill,[3] who have developed a useful and unambiguous degradation procedure, and also by Steglich *et al.*[12] who

have demonstrated that comparative shift data in the ^1H n.m.r. of isomeric pulvinic acids can provide strong clues to the structure of unsymmetrical derivatives. In



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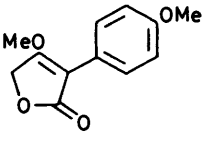

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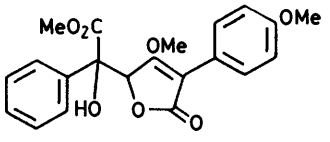

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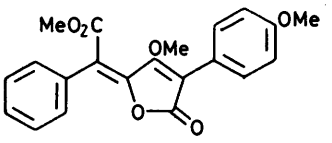
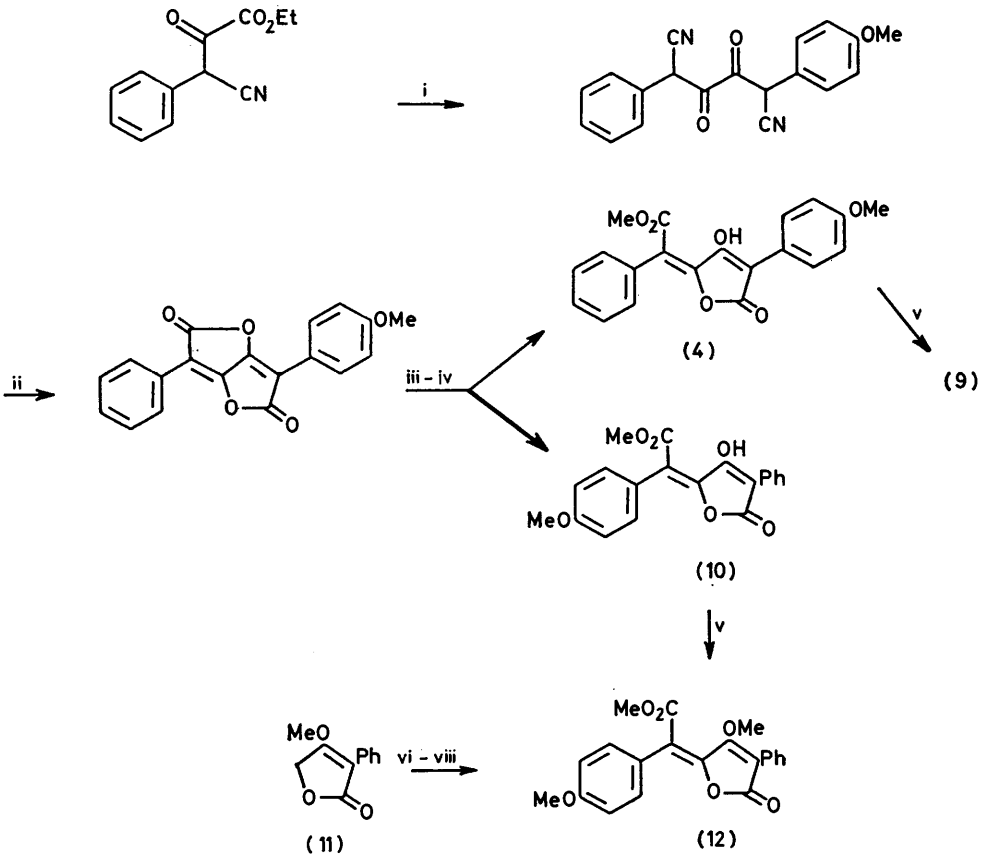


(9)

our studies of the synthesis of natural 4-ylidenebutenolides and 4-ylidenetetronic acids, we have developed unambiguous syntheses of the closely related 'pulvinone' group of natural pigments, based on the the first unambiguous synthesis of unsymmetrical pulvinic acids as exemplified by gomphidic acid (2b) from *Gomphidius glutinosus*, and pinastric acid (4) from *Lepraria flava* and other lichens.[14]

We first of all examined synthetic routes to the *O*-methyl derivative (9) of pinastric acid (4), a molecule whose structure has been the subject of considerable investigation.[10] The maleic anhydride derivative (6) is readily available,[13] and *O*-methyl tetronic acid (7) can be obtained from (6) by regioselective reduction using metal hydride reagents. The metallation of (7) with lithium *N*-cyclohexyl-*N*-isopropylamide at −78 °C followed by reaction with methyl benzoylformate was largely regioselective and produced the tertiary alcohol (8). A number of reagents were investigated to effect the dehydration of (8) to (9), and ultimately this was accomplished using a hot suspension of phosphorus pentaoxide in dry benzene.

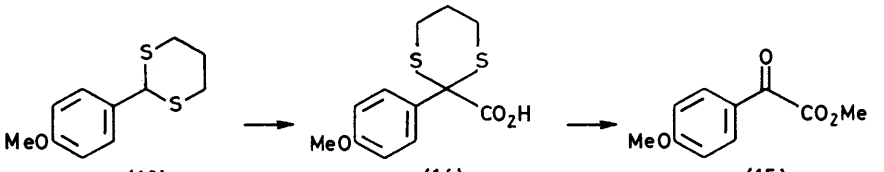
Chromatography then led to the *O*-methylpulvinate (9), pale yellow-coloured needles, which was identical (mixed m.p. and spectral data) with the *O*-methyl derivative of a 'synthetic' pinastric acid [*viz.* (4)]



SCHEME 1 *Reagents:* i, NaH–4-$MeOC_6H_4CH_2CN$; ii, HOAc–H_2SO_4; iii, KOH–MeOH; iv, fractional crystallisation; v, CH_2N_2; vi, LCPA; vii, 4-$MeOC_6H_4CO{\cdot}CO_2Me$; viii, P_2O_5–C_6H_6

utilisation of 3-aryl-2-methoxymaleic anhydrides [*e.g.* (6)] and *O*-methyl 2-aryltetronic acids [*e.g.* (7)] as key intermediates (see preceding paper).[13] Here we report the development of the general methodology leading to separated by fractional crystallisation of the mixture of pinastric acids (4) and (10) prepared according to Scheme 1; this sample has been correlated previously with the natural metabolite from *L. flava*.[10]

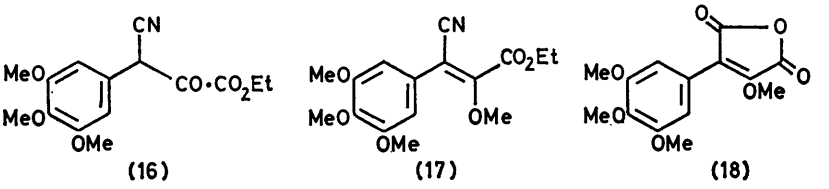
The *O*-methyl derivative (12) of 'isopinastric acid' (10) was synthesised in a similar unambiguous manner, from the *O*-methyl tetronic acid (11) and methyl 4-methoxybenzoylformate. The isomer (12) showed spectral data almost superimposable with the pulvinate obtained from isopinastric acid (10), prepared as outlined in Scheme 1. It is worth mentioning that during these studies we found that the most practical route to the otherwise difficultly accessible benzoylformate (15) first prepared from 3,4,5-trimethoxyphenylacetonitrile by the methods outlined previously.[13] Thus, condensation between the phenylacetonitrile and diethyl oxalate gave ethyl 3-cyano-3-(3,4,5-trimethoxy)pyruvate (16) which was converted into the cinnamate (17). Treatment of the cinnamate with acid [under conditions controlled to avoid demethylation of the 4-OMe group to give (19) [15]] then led to the anhydride (18) which by reduction with lithium aluminium hydride gave the

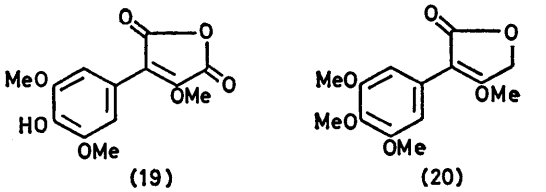


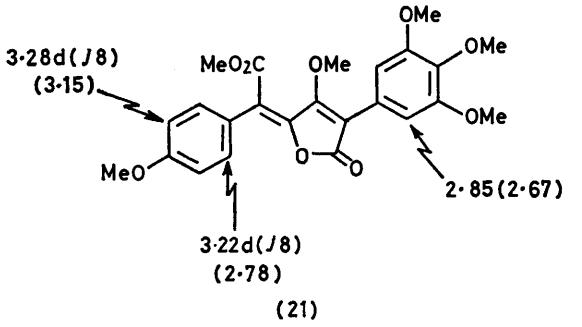
(the corresponding 2-methoxy-derivative was also prepared) was from 4-methoxybenzaldehyde following conversion into the dithian (13), metallation and carboxylation to (14), esterification, and finally removal of the dithian protecting group with Cu^{II} salts in acetone–water.

We next turned to the application of *O*-methyltetronic acid (20) as precursor for the aldol-type synthesis of permethylated gomphidic acid (21). The tetrahydroxy-substituted pulvinic acid, gomphidic acid (2b) co-occurs with the related xerocomic acid (2c) in the fungus *Gomphidius glutinosus*.[8] Constitution (2b) has been given to the metabolite, largely on the basis of comparative ^1H n.m.r. shift data with model compounds.[12] The maleic anhydride derivative (18) was *O*-methyltetronic acid (20), accompanied by the 4-hydroxy-derivative.

In a manner similar to that described for pulvinates (9) and (12), the *O*-methyltetronic acid (20) with methyl 4-methoxybenzoylformate gave permethylated gomphidic acid (21), as orange crystals, m.p. 66—70 °C, which displayed spectral features similar to those reported for the naturally occurring gomphidic acid and its tetra-acetate. In addition, comparison between the







^1H n.m.r. shift data of the permethylated derivative with those reported for gomphidic acid from *G. glutinosus*,[12] summarised on formula (21) (data for gomphidic acid in parentheses) endorses the structure (2b) assigned to the natural metabolite.

EXPERIMENTAL

For general experimental details see preceding paper.

2-(4-Methoxyphenyl)-1,3-dithian-2-carboxylic Acid (14).—A solution of n-butyl-lithium (2.2M) in hexane (23 ml) was added to a stirred solution of 2-(4-methoxyphenyl)-1,3-dithian [16] (11.3 g) in dry tetrahydrofuran (150 ml) at −50 °C under nitrogen. The mixture was stirred at −50 °C for 0.75 h, and then poured onto a slurry of solid carbon dioxide in ether, and left at room temperature for 3 h. The mixture was extracted with 2N-aqueous potassium hydroxide, and the aqueous layer was then separated, washed with ethyl acetate, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. Evaporation of the ethyl acetate extracts and crystallisation of the residue from ethyl acetate gave the *acid* (10.5 g, 78%) as colourless plates, m.p. 155—156 °C, $\nu_{max.}$(KBr) 3 130, 1 727, and 1 609 cm^{-1}; τ[$(CD_3)_2CO$] −0.2 (CO_2H), 2.36 (d, *J* 8.5, 2 H), 3.13 (d, *J* 8.5, 2 H), 6.23 (OMe), 6.8—7.5 (m, 4 H), and 7.9—8.28 (m, 2 H) (Found: C, 53.0; H, 5.4. $C_{12}H_{14}O_3S_2$ requires C, 53.3; H, 5.2%).

2-Methoxycarbonyl-2-(4-methoxyphenyl)-1,3-dithian.— A solution of 2-(4-methoxyphenyl)-1,3-dithian-2-carboxylic acid (7 g) in methanol (300 ml) containing concentrated sulphuric acid (1 ml) was heated under reflux for 48 h, then evaporated to 100 ml, diluted with water (1 l), and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts and crystallisation of the residue from cyclohexane gave the ester (7.2 g, 97%) as colourless needles, m.p. 61—62 °C, $\nu_{max.}$($CHCl_3$) 1 724 and 1 612 cm^{-1}; τ 2.5 (d, *J* 8.5, 2 H), 3.24 (d, *J* 8.5, 2 H), 6.33 (2 × OMe), 6.87—7.58 (m, 4 H), and 7.8—8.4 (m, 2 H) (Found: C, 54.8; H, 5.7. $C_{13}H_{16}O_3S_2$ requires C, 54.9; H, 5.6%).

Methyl 4-Methoxybenzoylformate (15).—A mixture of 2-methoxycarbonyl-2-(4-methoxyphenyl)-1,3-dithian (5.7 g), copper(II) chloride (6 g), and copper(II) oxide (7.2 g) in acetone (200 ml) containing water (2 ml) was heated under reflux for 1 h, then cooled, and filtered. The residue was dissolved in warm ether and the mixture was again filtered. Evaporation of the ether extracts and crystallisation of the residue from n-hexane gave the formate (3.1 g, 79%) as colourless needles, m.p. 50—50.5 °C (lit.,[17] m.p. 54 °C), $\nu_{max.}$(KBr) 1 726, 1 668, and 1 601 cm^{-1}; τ 2.09 (d, *J* 8.5, 2 H), 3.13 (d, *J* 8.5, 2 H), 6.1 (OMe), and 6.18 (OMe).

Methyl 2-Methoxybenzoylformate.—The formate was prepared from 2-(2-methoxyphenyl)-1,3-dithian [16] in a similar manner to that described for methyl 4-methoxybenzoylformate. Carboxylation of the anion produced from the dithian gave (80%) 2-(2-methoxyphenyl)-1,3-dithian-2-carboxylic acid as colourless prisms, m.p. 207—209 °C (decomp.) (from acetone), $\nu_{max.}$(KBr) 3 200, 1 721, and 1 600 cm^{-1} (Found: C, 53.0; H, 5.2. $C_{12}H_{14}O_3S_2$ requires C, 53.3; H, 5.2%) which was esterified in ether–10% methanol with diazomethane to produce the corresponding methyl ester (96%) as needles, m.p. 155—156 °C (from cyclohexane), $\nu_{max.}$ 1 722 cm^{-1}; τ 2.1 (dd, *J* 8.5 and 2, 1 H), 2.7 (dd, *J* 8.5 and 2, 1 H), 2.8—3.2 (m, 2 H), 6.21 (OMe), 6.31 (OMe), 6.4—6.9 (m, 2 H), 7.1—7.52 (m, 2 H), and 7.8—8.1 (m, 2 H).

Treatment of the ester with copper(II) chloride and copper(II) oxide, afforded the formate (88%) as a colourless oil, $\nu_{max.}$ (film) 1 736 and 1 668 cm^{-1}; τ 2.0—2.55 (m, 2 H), 2.76—3.07 (m, 2 H), 6.09 (OMe), and 6.12 (OMe); *m/e* 194; $C_{10}H_{10}O_4$ *M* 194.

Methyl 4'-Methoxypulvinate Methyl Ether [O-*Methyl Pinastric Acid*; *4-Methoxy-5-(α-methoxycarbonyl-p-methoxybenzylidene)-3-p-methoxyphenylfuran-2(5H)-one* (9).—A solution of the but-2-en-4-olide [4-methoxy-3-*p*-methoxyphenylfuran-2(5*H*)-one] (7) (0.44 g) in dry tetrahydrofuran (8 ml) was added to a stirred solution of lithium *N*-cyclohexyl-*N*-isopropylamide [prepared from *N*-cyclohexyl-*N*-isopropylamine (0.28 g) and n-butyl-lithium (2M) in hexane (1 ml)] in tetrahydrofuran (3 ml) at −70 °C under argon. A solution of methyl benzoylformate (0.33 g) in tetrahydrofuran (2 ml) was added immediately, and the resulting mixture was stirred at −70 °C for 0.5 h, and then set aside to warm to room temperature during 3 h. The mixture was poured into water and extracted with ether. The combined ether extracts were washed with dilute hydrochloric acid and water and then dried and evaporated to leave the crude tertiary alcohol intermediate as a yellow gum. A vigorously stirred solution of the crude tertiary alcohol (0.45 g) in dry benzene (80 ml) was heated at 60 °C in the presence of phosphorus pentaoxide (10 g) for 6 h, and then cooled. The mixture was diluted with water (1 l) and thoroughly extracted with ether. Evaporation of the washed and dried ether extracts left a residue which was chromatographed in chloroform on silica gel to give *O*-methylpinastric acid (0.1 g) which crystallised from chloroform–cyclohexane (5 : 95) as pale yellow needles, m.p. 140—141 °C, $\lambda_{max.}$(EtOH) 340 nm (ε 13 020); $\nu_{max.}$(KBr) 1 772, 1 722, 1 630, and 1 601 cm^{-1}; τ 2.3—2.43 (m, 2 H), 2.52 (d, *J* 9, 2 H), 2.6—2.71 (m, 3 H), 3.08 (d, *J* 9, 2 H), 6.13 (OMe), 6.19 (OMe), and 6.24 (OMe); *m/e* 366.110 4; $C_{21}H_{18}O_6$ *M* 366.110 3; starting butenolide (0.2 g) was also recovered by chromatography. The *O*-methylpinastric acid was identical (mixed m.p. 139—141 °C, identical i.r. and ^{1}H n.m.r.) with a sample prepared by methylation (CH_2N_2) of the ' pinastric acid ', m.p. 201—203 °C (lit.,[10] m.p. 202—204 °C) obtained by fractional crystallisation of the isomer mixture produced from saponification (KOH–MeOH) of 4-methoxypulvinic dilactone.

Methyl 4-Methoxypulvinate Methyl Ether [O-*Methyl Isopinastric Acid*; *4-Methoxy-5-(α-methoxycarbonyl-p-methoxybenzylidene)-3-phenylfuran-2(5H)-one* (12)].—The pulvinate (0.09 g) was prepared from 3-methoxy-2-phenylbut-2-en-4-olide [4-methoxy-3-phenylfuran-2(5*H*)-one] (0.38 g) and methyl 4-methoxybenzoylformate (0.39 g) in an identical manner to that described for the isomeric pulvinate. It crystallised from chloroform–cyclohexane (5 : 95) as pale yellow prisms, m.p. 171—172 °C, $\lambda_{max.}$ 353 nm (ε 21 000); $\nu_{max.}$ 1 760, 1 724, 1 635, and 1 602 cm^{-1}; τ 2.3 (d, *J* 9, 2 H), 2.37—2.61 (m, 5 H), 3.04 (d, *J* 9, 2 H), 6.09 (OMe), 6.16 (OMe), and 6.24 (OMe); *m/e* 366.109 9; starting butenolide (0.18 g) was also recovered by chromatography. The *O*-methylisopinastric acid was identical (mixed m.p. 171—173 °C, identical i.r. and ^{1}H n.m.r.) with a sample, m.p. 173—174 °C, prepared by methylation (CH_2N_2) of the ' pinastric acid ', m.p. 129—130 °C (lit.,[10] m.p. 127—129 °C) obtained by fractional crystallisation of the isomer mixture produced from saponification (KOH–MeOH) of 4-methoxypulvinic dilactone.

Ethyl 3-Cyano-2-methoxy-3-(3,4,5-trimethoxyphenyl)acrylate (17).—Ethyl 3-cyano-3-(3,4,5-trimethoxyphenyl)-pyruvate (16) was first prepared (88%) from 3,4,5-trimethoxyphenylacetonitrile [18] and diethyl oxalate, according to the general procedure outlined in the preceding paper.[13] Methylation of the pyruvate (33 g) with dimethyl sulphate (11 ml) in dry acetone (900 ml) containing anhydrous potassium carbonate (18 g), in the usual manner gave the acrylate (33.4 g, 97%) which crystallised from chloroform–

n-pentane as colourless needles, m.p. 61—62 °C, $\lambda_{max.}$ 309 nm, $\nu_{max.}$(KBr) 2 240, 1 735, and 1 598 cm^{-1}; τ 3.1 (2 H), 5.58 (q, *J* 7, CH_2CH_3), 6.15 (4 × OMe), and 8.56 (t, *J* 7, CH_2CH_3) (Found: C, 59.4; H, 6.0; N, 4.2. $C_{16}H_{19}NO_6$ requires C, 59.8; H, 5.9; N, 4.3%).

2-Methoxy-3-(3,4,5-trimethoxyphenyl)maleic Anhydride [*3-Methoxy-4-(3,4,5-trimethoxyphenyl)furan-2,5-dione*] (18).—Ethyl 3-cyano-2-methoxy-3-(3,4,5-trimethoxyphenyl)acrylate (17 g) in acetic acid (160 ml) and water (90 ml) was treated portionwise with concentrated sulphuric acid (140 ml) at such a rate that the temperature did not exceed 110 °C. The mixture was cooled, then poured onto iced water and extracted with ether. The ether extracts were washed with water, and then with 2N-potassium hydroxide. The aqueous layer was acidified with dilute hydrochloric acid, and then extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts, left a residue which crystallised from methanol to give the *anhydride* (7 g, 48%) as yellow needles, m.p. 151—152 °C, $\lambda_{max.}$($CHCl_3$) 384 nm; $\nu_{max.}$($CHCl_3$) 1 819, 1 758, 1 648, and 1 580 cm^{-1}; τ 2.63 (2 H), 5.56 (OMe), and 6.06 (3 × OMe) (Found: C, 56.9; H, 5.0. $C_{14}H_{14}O_7$ requires C, 57.1; H, 4.8%).

When a mixture of the acrylate (17) and acetic acid in water and concentrated sulphuric acid was heated under reflux for 1 h, the usual work-up afforded a 1 : 1 mixture of the anhydrides (18) and (19). *2-(4-Hydroxy-3,5-dimethoxy-3-methoxymaleic anhydride* [*3-(4-hydroxy-3,5-dimethoxyphenyl)-4-methoxyfuran-2,5-dione*] (19) crystallised from acetone as orange-red plates, m.p. 188—189 °C, $\lambda_{max.}$($CHCl_3$) 409 nm; $\nu_{max.}$(KBr) 3 420, 1 816, 1 741, 1 636, and 1 600 cm^{-1}; τ[$(CD_3)_2CO$] 2.66 (2 H), 5.58 (OMe), and 6.1 (2 × OMe) (Found: C, 55.9; H, 4.3. $C_{13}H_{12}O_7$ requires C, 55.7; H, 4.3%).

3-Methoxy-2-(3,4,5-trimethoxyphenyl)but-2-en-4-olide [*4-Methoxy-3-(3,4,5-trimethoxyphenyl)furan-2(5H)-one*] (20).—A suspension of lithium aluminium hydride (0.19 g) in dry tetrahydrofuran (4 ml) was added dropwise to a stirred solution of 2-methoxy-3-(3,4,5-trimethoxyphenyl)maleic anhydride (18) (2.94 g) in tetrahydrofuran (35 ml) at −70 °C under argon. The mixture was stirred between −40 and 0 °C for 2 h, and then diluted with water, acidified with dilute hydrochloric acid, and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts left a residue which was chromatographed in chloroform–methanol (94 : 6) on silica gel to give: (*a*) the *butenolide* (0.5 g) (eluted first), which crystallised from methanol as colourless prisms, m.p. 136—137 °C, $\lambda_{max.}$(EtOH) 275 nm; $\nu_{max.}$(KBr) 1 732 and 1 636 cm^{-1}; τ 2.76 (2 H), 5.19 (CH_2), 6.01 (OMe), and 6.09 (3 × OMe) (Found: C, 60.0; H, 6.1. $C_{14}H_{16}O_6$ requires C, 60.0; H, 5.7%); and (*b*) 4-hydroxy-3-methoxy-2-(3,4,5-trimethoxyphenyl)but-2-en-4-olide [5-hydroxy-4-methoxy-3-(3,4,5-trimethoxyphenyl)furan-2(5*H*)-one] (0.6 g) (eluted second), which crystallised from methanol as colourless needles, m.p. 178—179 °C, $\lambda_{max.}$(EtOH) 284 nm; $\nu_{max.}$(KBr) 3 410, 1 763, and 1 661 cm^{-1}; τ[$(CD_3)_2CO$] 2.74 (2 H), 3.0 (O*H*), 3.69 (d, *J* *ca.* 8, C*H*OH), 5.79 (OMe), 6.21 (2 × OMe), and 6.28 (OMe) (Found: C, 56.5; H, 5.8. $C_{14}H_{16}O_7$ requires C, 56.7; H, 5.4%).

In a similar manner, reduction of 2-(4-hydroxy-3,5-dimethoxy)-3-methoxymaleic anhydride (19) with lithium aluminium hydride gave a mixture of 2-(4-hydroxy-3,5-dimethoxyphenyl)-3-methoxybut-2-en-4-olide [3-(4-hydroxy-3,5-dimethoxyphenyl)-4-methoxyfuran-2(5*H*)-one], colourless needles, m.p. 156.5—157.5 °C (from methanol), $\lambda_{max.}$(EtOH) 284 nm; $\nu_{max.}$(KBr) 3 480, 1 742, and 1 642 cm^{-1}; τ[$(CD_3)_2CO$] 2.62 (2 H), 2.84 (O*H*), 4.97 (CH_2), 5.88 (OMe), and 6.14 (2 × OMe) (Found: C, 58.4; H, 5.5. $C_{13}H_{14}O_6$ requires C, 58.6; H, 5.3%) and 4-hydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)-3-methoxybut-2-enolide [5-hydroxy-3-(4-hydroxy-3,5-dimethoxyphenyl)-4-methoxyfuran-2(5*H*)-one], m.p. 172—174 °C (from methanol), $\nu_{max.}$(KBr) 3 450, 1 730, and 1 640 cm^{-1}; *m/e* 282.072 7, $C_{13}H_{14}O_7$ requires *M* 282.073 9.

Methyl 3′,4,4′,5′-Tetramethoxypulvinate Methyl Ether [*Permethyl Gomphidic Acid* (21)].—The pulvinate was prepared from 3-methoxy-2-(3,4,5-trimethoxyphenyl)but-2-en-4-olide (0.47 g) and methyl 4-methoxybenzoylformate (0.38 g) in an identical manner to that described for *O*-methylpinastric acid. Repetitive chromatography in chloroform on silica gel gave the pulvinate (0.045 g) as orange crystals, m.p. 66—70 °C (from chloroform), $\lambda_{max.}$(EtOH) 352 and 279 nm; $\nu_{max.}$(KBr) 1 765, 1 730, 1 665, 1 632, and 1 605 cm^{-1}, τ 2.85 (2 H), 3.22 (d, *J* 8, 2 H), 3.28 (d, *J* 8, 2 H), 6.1—6.3 (6 × OMe); *m/e* 456.144 9, $C_{24}H_{24}O_9$ requires *M* 456.142 0; starting butenolide (0.15 g) was recovered by chromatography.*

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* *Note added in proof.* The stereochemistry of natural gomphidic acid (2b) is not known, but *X*-ray measurements on synthetic (9) have now established that natural pinastric acid has the *E* geometry shown in (4). Our recent work suggests that synthetic (21) probably has *Z* geometry (M. J. Begley, D. R. Gedge, and G. Pattenden, unpublished results).

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