

Maleic Anhydrides in Synthesis. Preparation of Furan-2(5*H*)-one Phosphonate Derivatives and a New Synthesis of Pulvinic Acids and Pulvinone Analogues

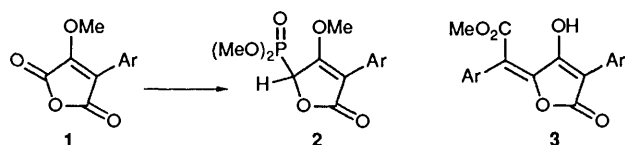
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Reactions between substituted maleic anhydrides, *viz.* **1**, and sodium dimethyl phosphite in refluxing benzene are shown to lead to the corresponding furan-2(5*H*)-one phosphonates **2** and **8**. Wadsworth–Emmons olefination reactions involving **2** and heteroarylaldehydes and arylbenzoyl formates **14** then provides a new synthesis of heterocyclic analogues of pulvinones, *i.e.* **10–13**, and of permethylated pulvinic acids, *e.g.* **16–17** which are found in higher fungi.

Maleic and phthalic anhydrides, and their derivatives, are a rich source of readily available materials which are used extensively in the synthesis of a wide variety of key intermediates employed in the heavy and fine chemicals industries.¹ In previous investigations we have studied the susceptibility of maleic anhydride derivatives towards regio- and stereo-selective attack by hydride and carbon nucleophiles leading to furanone intermediates which were used subsequently in the synthesis of natural pigments produced by higher fungi.² In continuation of these studies, we now describe the facile synthesis of furan-2(5*H*)-one phosphonate derivatives of the type shown by **2** from substituted maleic anhydrides **1**, and the use of these derivatives in the synthesis of natural pulvinic acids, *i.e.* **3**, and a range of heterocyclic substituted analogues, *e.g.* **10**, of pulvinone fungal pigments.

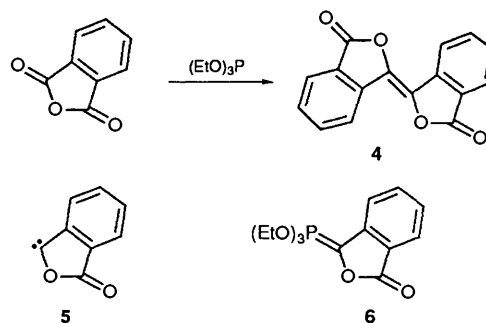


a; Ar = Ph

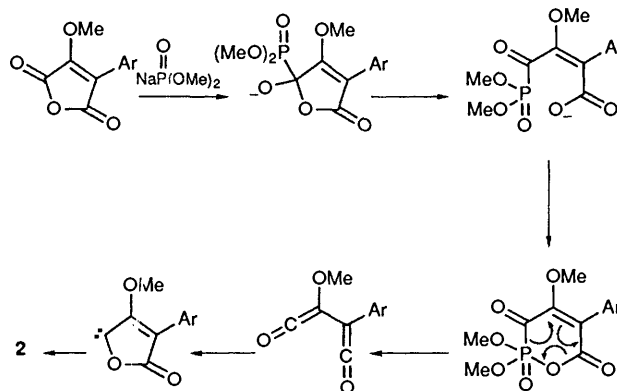
b; Ar = C₆H₂(OMe)_{3-4,5}

The deoxygenative dimerisation of phthalic anhydride in the presence of triethyl phosphite, leading to biphtalyl **4**, was first reported by Ramirez *et al.*³ more than 30 years ago. This unusual reaction has been investigated extensively since this time, and several mechanistic interpretations have been proposed including the most favoured one which suggests that the dimerisation proceeds *via* the phthalide carbene **5** and the corresponding phosphorane **6** intermediates.⁴ Inspired by this work and the work of others,⁵ we undertook a study of the reaction between the 2-aryl-3-methoxy substituted maleic anhydrides **1a** and **1b** and sodium dimethyl phosphite, with a view to the synthesis of phosphonate ester intermediates, *viz.* **2a** and **2b**, of potential use in Wadsworth–Emmons olefination reactions leading to pulvinic acids **3** and pulvinone **10** compounds.

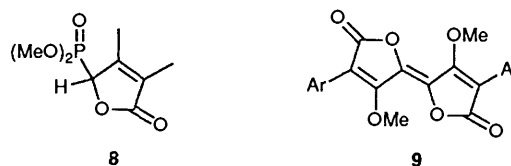
Aryl substituted maleic anhydrides of constitution **1** are easily available in three steps from phenylacetonitriles following: (i) condensation with diethyl oxalate in the presence of base, (ii) hydrolysis and anhydride formation using dilute acid, and (iii) methyl enol ether formation.⁶ When a solution of the phenyl maleic anhydride **1a** in benzene was heated in the presence of 2 equiv. of sodium dimethyl phosphite for 1 h a vigorous reaction ensued, and chromatography led to the phosphonate ester **2a** in 41% yield. In a similar manner, reactions between the 3,4,5-trimethoxyphenylmaleic anhydride **1b** and dimethylmaleic anhydride, and sodium dimethyl phosphite led to the corres-



ponding furan-2(5*H*)-ones **2b** and **8** respectively, albeit in poorer yields (21–35%). We assume that these maleic anhydride-furan-2(5*H*)-one phosphonate conversions proceed *via* the corresponding furan-2(5*H*)-one carbene intermediates, *viz.* **7**, as discussed earlier by other workers (Scheme 1).³⁻⁴ It is interesting that in none of the cases studied were we able to detect the co-formation of 'dimers' of the type **9** from the maleic anhydride-phosphite reactions.



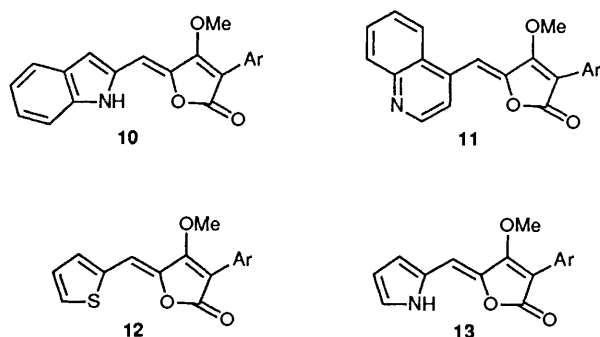
Scheme 1



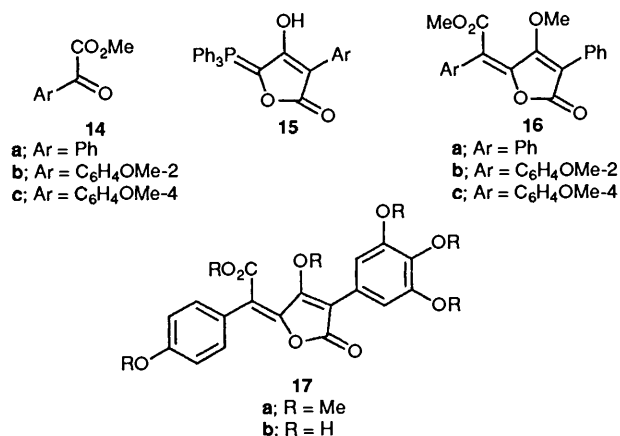
With the novel furan-2(5*H*)-one phosphonate derivatives **2** in hand, we proceeded to investigate their use in the synthesis of heterocyclic analogues of natural pulvinones *e.g.* **10** and in the synthesis of pulvinic acid pigments, *viz.* **3**, produced by fungi.⁷

Thus, when a solution of the phosphonate ester **2a** in benzene

at 0 °C was treated with sodium hydride followed by indole-2-carbaldehyde, chromatography led to a 3:2 mixture of *Z*- and *E*-isomers of the brightly yellow crystalline indolylmethylene-furanone **10** in a satisfying yield of 68%. In a similar manner, the phosphonate ester **2a** underwent Wadsworth–Emmons olefination reactions with quinoline-4-carbaldehyde, thiophene-2-carbaldehyde and pyrrole-2-carbaldehyde leading to the corresponding methylenefuran-2(5*H*)-ones **11**, **12** and **13** respectively in 60–70% yields. Mixtures of *Z*- and *E*-isomers of the methylenefuran-2(5*H*)-ones **10–13** were produced in the aforementioned reactions, and in the cases of **11** and **13** the isomers could be separated cleanly by chromatography. The configurations assigned to the *Z,E* geometric pairs followed from inspection and comparison of chemical shift data in their ¹H NMR and ¹³C NMR spectra.⁸ Thus, in their ¹H NMR spectra, the hydrogen atoms at C-6 in the *E*-isomers of **10–13** are deshielded ($\Delta\delta$ 0.2) by the adjacent ring oxygen atoms, relative to the same signals in the *Z*-isomers. In addition, the carbon atom at C-6 is deshielded ($\Delta\delta$ ca. 7) in the ¹³C NMR of the *E*-isomer relative to the same carbon centre in the *Z*-isomer.



We next turned to the more difficult task of attempting to react the same phosphonate ester **2** with the sterically hindered and electronically deactivated ketone carbonyl group in arylpyruvates, *viz.* **14**. Earlier attempts to achieve this reaction, using the less reactive triphenylphosphorane intermediates **15** had been completely unsuccessful.⁹ To our surprise and satisfaction, we were pleased to discover that the reactions between **2** and **14** in the presence of base proceeded with comparative ease. Thus, condensation between the phosphonate ester **2a** and methyl benzoylformate **14a** at 25 °C in the presence of sodium hydride, produced a 3:1 mixture of *Z*- and *E*-isomers of *O*-methylvulpinic acid **16a** in a combined yield of 66%. The *E*-isomer **16a** could be separated by chromatography, and was shown to be identical with a previously synthesised sample.¹⁰



In a similar manner the anion derived from the furan-2(5*H*)-

one **2a** reacted with both 2-methoxy-**14b** and 4-methoxybenzoylformates **14c**, in refluxing toluene, to produce *Z,E*-mixtures of the corresponding methyl vulpinates **16b** and **16c** respectively in 50–60% preparative yields. Finally, reaction between 4-methoxybenzoylformate **14c** and the anion derived from the 3,4,5-trimethoxyphenyl substituted phosphonate **2b** produced a 3:2 mixture of *Z*- and *E*-isomers of permethylated gomphidic acid **17a**. Photoisomerisation of this mixture in laboratory daylight then gave the *E*-isomer **17a** exclusively which correlated with an authentic sample that we had earlier converted into natural gomphidic acid **18b** by demethylation in the presence of trimethylsilyl iodide.¹¹

Experimental

For general experimental details, see ref. 12. *J* Values are given in Hz throughout.

5-Dimethoxyphosphoryl-4-methoxy-3-phenylfuran-2(5*H*)-one 2a.—Dimethyl phosphite (440 mm³, 2 equiv.) was added dropwise over 2 min to a stirred suspension of sodium hydride (60% dispersion in oil; 192 mg, 2 equiv.) in dry benzene (25 cm³), under nitrogen at ambient temperature. The mixture was stirred at ambient temperature for 20 min, and then 3-methoxy-4-phenylmaleic anhydride (500 mg, 1 equiv.)⁶ was added portionwise over 5 min. The solution was heated under reflux for 60 min and then quenched by the dropwise addition of water (5 cm³). The organic phase was separated dried and evaporated under reduced pressure. The residue was purified by flash chromatography using ethyl acetate–chloroform (1:4) as eluent to give the phosphonate (293 mg, 41%) as a light yellow oil, λ_{\max}/nm 198.2 (ϵ 22 900), 215.9 (inf) (ϵ 13 100) and 265.6 (ϵ 9900); $\nu_{\max}/\text{cm}^{-1}$ 1765 and 1660; δ_{H} 3.88 (d, *J* 15.3, POCH₃), 3.92 (d, *J* 15.5, POCH₃), 4.02 (OMe), 5.25 (d, *J* 11.0, PCH), 7.40 (m, 3 × ArH) and 7.64 (m, 2 × ArH); δ_{C} 53.6 (d, *J* 7.6) (q), 54.2 (d, *J* 8.0) (q), 58.6 (q), 72.6 (dd, *J* 171.1 and 6.7) (d), 115.9 (d, *J* 9.5) (s), 127.1 (d), 128.0 (d), 138.6 (d), 133.8 (s) and 149.3 (s) (Found: M⁺, 298.0851. C₁₃H₁₅O₆P requires *M*, 298.0606).

5-Dimethoxyphosphoryl-4-methoxy-3-(3,4,5-trimethoxyphenyl)furan-2(5*H*)-one 2b.—Dimethyl phosphite (411 mm³, 2 equiv.) was added dropwise over 5 min to a stirred suspension of sodium hydride (60% dispersion in oil; 179 mg, 2 equiv.) in dry toluene (50 cm³) under nitrogen at ambient temperature. The mixture was stirred at ambient temperature for 20 min, and 3-methoxy-4-(3,4,5-trimethoxyphenyl)maleic anhydride (660 mg, 1 equiv.)⁶ was added portionwise over 5 min. The solution was heated under reflux for 90 min and then quenched by the dropwise addition of water (5 cm³). The organic phase was separated, dried and evaporated under reduced pressure. The residue was purified by flash chromatography using hexane–ethyl acetate (1:4) as eluent to give the phosphonate (180 mg, 21%) as a light yellow gum, λ_{\max}/nm 207.9 (ϵ 35 600), 230.0 (ϵ 15 100) and 284.1 (ϵ 8000); $\nu_{\max}/\text{cm}^{-1}$ 1760 and 1655; δ_{H} 3.86 (OMe), 3.88 (2 × OMe), 3.89 (d, *J* 10.8, OMe), 3.94 (d, *J* 10.9, OMe), 4.07 (OMe), 5.22 (d, *J* 11.1, PCH) and 6.93 (2 × ArH); δ_{C} 54.4 (d, *J* 7.1) (q), 55.1 (d, *J* 6.4) (q), 56.3 (q), 60.7 (q), 60.9 (q), 72.5 (d, *J* 160.7) (d), 105.4 (s), 106.5 (d), 124.2 (s), 138.2 (s), 153.1 (s), 169.8 (s) and 171.3 (s) (Found: M⁺, 388.0895. C₁₆H₂₁O₉P requires *M*, 388.0923).

5-Dimethoxyphosphoryl-3,4-dimethylfuran-2(5*H*)-one 8.—Dimethyl phosphite (1.45 cm³, 2 equiv.) was added dropwise over 2 min to a stirred suspension of sodium hydride (60% dispersion in oil; 634 mg, 2 equiv.) in dry benzene (60 cm³) under nitrogen. The resulting mixture was stirred at ambient temperature for 20 min and then treated portionwise over 5 min with dimethylmaleic anhydride (1 g, 1 equiv.). The solution was

heated under reflux for 30 min and then quenched by the addition of hydrochloric acid (2 mol dm⁻³; 5 cm³). The organic phase was separated, dried and evaporated under reduced pressure to leave a residue which was purified by flash chromatography using hexane-ethyl acetate (3:7) as eluent to give the *phosphonate* (600 mg, 34%) as a clear gum, λ_{\max}/nm 217.6 (ϵ 12 100); $\nu_{\max}/\text{cm}^{-1}$ 1745 and 1662; δ_{H} 1.86 (br s, CH₃), 2.16 (br s, CH₃), 3.83 (d, *J* 28.1, POCH₃), 3.87 (d, *J* 28.2, POCH₃) and 5.07 (d, *J* 14.3, PCH); δ_{C} 8.5 (q), 12.7 (q), 53.6 (d, *J* 6.8) (q), 54.3 (d, *J* 6.7) (q), 78.2 (d, *J* 164.0) (d), 124.6 (s), 154.3 (s) and 173.4 (s) (Found: M⁺, 220.0461. C₈H₁₃O₅P requires *M*, 220.0500).

5-Indolin-2-ylmethylene-4-methoxy-3-phenylfuran-2(5H)-one 10.—Sodium hydride (60% dispersion in oil; 27 mg, 1.1 equiv.) was added in one portion to a stirred solution of compound **2a** (200 mg, 1 equiv.) in dry benzene (50 cm³), under nitrogen at 0 °C (ice-bath). The solution was stirred at 0 °C for a further 20 min and a solution of indole-2-carbaldehyde (41 mg, 1 equiv.) in dry benzene (2 cm³) was then added dropwise over 2 min. The mixture was stirred for a further 90 min at ambient temperature and then acidified by the addition of hydrochloric acid (2 mol dm⁻³; 5 cm³). The organic phase was separated, dried and evaporated under reduced pressure to leave a residue which was purified by flash chromatography using ethyl acetate-chloroform (9:1) as eluent to give the *furanone* (71 mg, 68%) as an inseparable mixture of (*Z*)- and (*E*)-isomers (3:2), a crystalline yellow solid, m.p. 240–244 °C (from hexane-diethyl ether); λ_{\max}/nm 225.1 (ϵ 29 400), 281.1 (ϵ 16 800), 396.2 (ϵ 26 200); ν_{\max}/nm 3460 and 1740; δ_{H} [(*Z*)-isomer] 3.89 (OMe), 6.73 (CH), 7.25 (m, 2 × ArH), 7.42 (m, 4 × ArH), 7.56 (m, 2 × ArH), 7.82 (m, ArH), 8.07 (d, *J* 2.6, ArH) and 8.87 (NH), [(*E*)-isomer] 3.79 (OMe), 7.05 (CH), 7.26 (m, 2 × ArH), 7.44 (m, 4 × ArH), 7.58 (m, ArH), 7.72 (m, ArH), 7.86 (d, *J* 2.7, ArH) and 8.51 (NH); δ_{C} [(*Z*)-isomer] 60.8 (q), 101.2 (d), 104.2 (s), 109.8 (s), 111.7 (d), 118.4 (d), 120.9 (d), 123.0 (d), 126.7 (s), 128.2 (d), 128.3 (d), 128.4 (d), 129.8 (s), 130.1 (d), 135.7 (s), 139.9 (s), 163.8 (s) and 169.2 (s), [(*E*)-isomer] 60.6 (q), 104.8 (s), 107.0 (d), 108.5 (s), 111.5 (d), 118.4 (d), 121.0 (d), 123.1 (d), 126.7 (s), 127.9 (s), 128.2 (d), 128.3 (d), 128.5 (d), 130.1 (d), 135.6 (s), 140.7 (s), 162.7 (s) and 168.2 (s) (Found: M⁺, 317.1069. C₂₀H₁₅NO₃ requires *M*, 317.1051).

4-Methoxy-3-phenyl-5-(4-quinolyl)methylenefuran-2(5H)-one 11.—Sodium hydride (60% dispersion in oil; 14 mg, 1.1 equiv.) was added in one portion to a stirred solution of compound **2a** (120 mg, 1 equiv.) in dry benzene (50 cm³) under nitrogen at 0 °C (ice-bath). The solution was stirred at 0 °C for a further 20 min, and a solution of quinoline-4-carbaldehyde (63 mg, 1 equiv.) in dry benzene (4 cm³) was then added dropwise over 2 min. The mixture was stirred for a further 90 min at ambient temperature and then acidified by the addition of hydrochloric acid (2 mol dm⁻³; 2 cm³). The organic phase was separated, dried and evaporated under reduced pressure to leave a residue which was purified by flash chromatography using ethyl acetate-chloroform (1:1) as eluent to give: (a) the (*Z*)-isomer of the *furanone* (37 mg, 28%) (eluted first) as a crystalline white solid, m.p. 195–197 °C [from light petroleum (b.p. 40–60 °C)-diethyl ether]; λ_{\max}/nm 272.8 (ϵ 14 200), 316.8 (ϵ 16 000) and 364.4 (ϵ 13 700); $\nu_{\max}/\text{cm}^{-1}$ 1770; δ_{H} 3.92 (OMe), 7.01 (CH), 7.41–7.52 (5 × ArH), 7.62 (ddd, *J* 9.8, 6.9 and 1.4, ArH), 7.75 (ddd, *J* 9.8, 2.6 and 0.9, ArH), 8.10 (d, *J* 4.7, ArH), 8.16 (ddd, *J* 8.2, 2.6 and 0.9, 2 × ArH) and 8.96 (d, *J* 4.7, ArH); δ_{C} 61.2 (q), 100.7 (d), 106.5 (s), 122.2 (d), 123.0 (d), 126.2 (s), 127.1 (d), 128.5 (d), 129.0 (d), 130.4 (d), 130.6 (d), 136.6 (s), 146.3 (s), 148.8 (s), 150.4 (s), 162.9 (s) and 168.4 (s) (Found: M⁺, 329.1035. C₂₁H₁₅NO₃ requires *M*, 329.1054); (b) the (*E*)-isomer of the *furanone* (41 mg, 31%) (eluted second) as a crystalline white

solid, m.p. 159–161 °C (from hexane-diethyl ether); λ_{\max}/nm 317.1 (ϵ 21 600); $\nu_{\max}/\text{cm}^{-1}$ 1760; δ_{H} 3.39 (OMe), 7.14 (CH), 7.37–7.52 (m, 6 × ArH), 7.62 (ddd, *J* 9.6, 6.9 and 1.3, ArH), 7.77 (ddd, *J* 9.5, 6.9 and 1.5, ArH), 7.99 (dd, *J* 8.3 and 1.0, ArH), 8.02 (d, *J* 7.8, ArH) and 8.92 (d, *J* 7.8, ArH); δ_{C} 59.5 (q), 107.6 (d), 109.2 (s), 121.1 (d), 123.6 (d), 127.3 (d), 127.5 (s), 128.0 (d), 128.8 (s), 129.0 (d), 129.1 (d), 135.5 (s), 144.4 (s), 147.1 (s), 148.5 (d), 161.2 (s) and 166.7 (s) (Found: M⁺, 329.0983. C₂₁H₁₅NO₃ requires *M*, 329.1054).

4-Methoxy-3-phenyl-5-(2-thenylidene)furan-2(5H)-one 12.—Sodium hydride (60% dispersion in oil; 14 mg, 1.1 equiv.) was added in one portion to a stirred solution of compound **2a** (200 mg, 1 equiv.) in dry benzene (50 cm³), under nitrogen at 0 °C (ice-bath). The solution was stirred at 0 °C for a further 20 min and thiophene-2-carbaldehyde (31 mm³, 1 equiv.) was then added dropwise over 2 min. The mixture was stirred for a further 90 min at ambient temperature and then acidified by the addition of hydrochloric acid (2 mol dm⁻³; 2 cm³). The organic phase was separated, dried and evaporated under reduced pressure to leave a residue which was purified by flash chromatography using light petroleum (b.p. 40–60 °C)-diethyl ether (1:1) as eluent to give the *furanone* (74 mg, 70%) as an inseparable mixture of (*Z*)- and (*E*)-isomers (3:2), a crystalline yellow solid, m.p. 89–91 °C [from light petroleum (b.p. 40–60 °C)-diethyl ether]; λ_{\max}/nm 358.4 (ϵ 26 900); $\nu_{\max}/\text{cm}^{-1}$ 1750; δ_{H} [(*Z*)-isomer] 3.83 (OMe), 6.57 (CH), 7.07 (dd, *J* 5.1 and 3.7, ArH), 7.33–7.46 (m, 4 × ArH), 7.47 (dm, *J* 5.1, ArH) and 7.49–7.53 (m, 2 × ArH); [(*E*)-isomer] 3.85 (OMe), 6.91 (CH), 7.04 (dd, *J* 5.2 and 3.7, ArH), 7.31 (dm, *J* 5.1, ArH), 7.33–7.46 (m, 4 × ArH) and 7.49–7.53 (m, 2 × ArH); δ_{C} [(*Z*)-isomer] 60.8 (q), 102.0 (d), 106.0 (s), 127.7 (d), 128.3 (d), 128.5 (d), 129.2 (s), 129.8 (s), 130.1 (d), 135.8 (s), 140.8 (s), 163.2 (s), 168.2 (s), [(*E*)-isomer] 60.3 (q), 108.7 (s), 109.0 (d), 127.4 (d), 128.3 (d), 128.5 (d), 129.2 (s), 129.9 (d), 130.1 (d), 133.6 (d), 134.8 (s), 141.2 (s), 161.8 (s) and 168.0 (s) (Found: M⁺, 284.0504. C₁₆H₁₂O₃S requires *M*, 284.0507).

4-Methoxy-3-phenyl-5-pyrrol-2-methylenefuran-2(5H)-one 13.—Sodium hydride (60% dispersion in oil; 27 mg, 1.1 equiv.) was added in one portion to a stirred solution of compound **2a** (200 mg, 1 equiv.) in dry benzene (50 cm³) under nitrogen at 0 °C (ice-bath). The solution was stirred at 0 °C for a further 20 min and a solution of pyrrole-2-carbaldehyde (31 mg, 1 equiv.) in dry benzene (2 cm³) was then added dropwise over 2 min. The mixture was stirred for a further 90 min at ambient temperature and then acidified by the addition of hydrochloric acid (2 mol dm⁻³; 2 cm³). The organic phase was separated, dried and evaporated under reduced pressure to leave a residue which was purified by flash chromatography using light petroleum (b.p. 40–60 °C)-diethyl ether (9:1) as eluent to give: (a) the (*Z*)-isomer of *furanone* (17 mg, 20%) (eluted first) as a crystalline yellow solid, m.p. 158–159 °C [from light petroleum (b.p. 40–60 °C)-diethyl ether]; λ_{\max}/nm 391 (ϵ 29 400); $\nu_{\max}/\text{cm}^{-1}$ 1745; δ_{H} 3.85 (OMe), 6.28 (CH), 6.49 (m, ArH), 7.02 (m, ArH), 7.36–7.46 (m, 3 × ArH), 7.51–7.55 (m, 2 × ArH) and 9.52 (NH); δ_{C} 60.9 (q), 100.2 (d), 105.1 (s), 110.4 (d), 115.3 (d), 123.4 (d), 126.4 (d), 128.4 (d), 129.5 (s), 130.1 (d), 138.0 (s), 163.7 (s) and 168.4 (s) (Found: M⁺, 267.0895. C₁₆H₁₅NO₃ requires *M*, 267.0895); (b) the (*E*)-isomer of the *furanone* (36 mg, 42%) (eluted second) as a crystalline yellow solid, m.p. 137–139 °C [from light petroleum (b.p. 40–60 °C)-diethyl ether]; λ_{\max}/nm 395.2 (ϵ 23 700); $\nu_{\max}/\text{cm}^{-1}$ 1735; δ_{H} 3.94 (OMe), 6.29 (m, ArH), 6.52 (m, ArH), 6.65 (CH), 6.97 (m, ArH), 7.36–7.50 (m, 3 × ArH) and 7.52 (m, 2 × ArH); δ_{C} 61.8 (q), 106.1 (s), 106.9 (d), 111.0 (d), 118.1 (d), 122.8 (d), 125.0 (s), 128.2 (d), 128.4 (d), 130.0 (d), 130.6 (s), 138.0 (s), 162.2 (s) and 167.8 (s) (Found: M⁺, 267.0888. C₁₆H₁₅NO₃ requires *M*, 267.0895).

Methyl α -(3-Methoxy-5-oxo-4-phenyl-2,5-dihydrofuran-2-ylidene)phenylacetate (O-Methylvulpinic Acid) 16a.—Sodium hydride (60% dispersion in oil; 15 mg, 1.1 equiv.) was added in one portion to a stirred solution of compound **2a** (100 mg, 1 equiv.) in dry benzene (10 cm³), under nitrogen at 0 °C (ice-bath). The solution was stirred at 0 °C for 20 min and methyl benzoylformate (53 mm³; 1.1 equiv.) was then added dropwise over 1 min. The mixture was stirred at 0 °C for a further 1 h and then acidified by the addition of hydrochloric acid (2 mol dm⁻³; 2 cm³). The organic phase was separated, dried and evaporated under reduced pressure to leave a residue which was purified by flash chromatography using hexane–diethyl ether (1:1) as eluent to give: (a) the (*Z*)-isomer of *O*-methylvulpinic acid (16 mg, 26%) (eluted first) as a crystalline white solid, m.p. 90–92 °C [from light petroleum (b.p. 80–100 °C)–diethyl ether]; λ_{\max}/nm 313.6 (ϵ 12 600); $\nu_{\max}/\text{cm}^{-1}$ 1770 and 1730; δ_{H} 3.34 (OMe), 3.85 (CO₂Me), 7.38 (m, 8 \times ArH) and 7.53 (m, 2 \times ArH); δ_{C} 52.5 (q), 60.2 (q), 110.7 (s), 116.6 (s), 127.5 (d), 128.1 (s), 128.4 (d), 128.7 (2 \times d), 129.4 (2 \times d), 131.2 (s), 144.1 (s), 162.7 (s), 166.5 (s) and 166.7 (s) (Found: M⁺, 336.1000. Calc. for C₂₀H₁₆O₅: M, 336.0996); (b) recovered starting material (45 mg, 45%). When the reaction was repeated under identical conditions at ambient temperature and the crude residue was purified using hexane–diethyl ether (1:1) as eluent *O*-methylvulpinic acid (75 mg, 66%) was obtained as a mixture of (*Z*)- and (*E*)-isomers (3:1). High pressure liquid chromatography using hexane–diethyl ether (4:1) as eluent then gave: (a) the (*Z*)-isomer of *O*-methylvulpinic acid (eluted first) which showed spectral data identical to those described above; (b) the (*E*)-isomer of *O*-methylvulpinic acid **16** (eluted second) as a crystalline white solid, m.p. 141–142 °C (from hexane–diethyl ether) (lit.,^{10b} m.p. 142–143 °C); λ_{\max}/nm 227.8 (ϵ 13 200) and 329.1 (ϵ 24 200); $\nu_{\max}/\text{cm}^{-1}$ 1760 and 1720; δ_{H} 3.80 (OMe), 3.91 (CO₂Me), 7.31–7.56 (m, 8 \times ArH) and 7.65–7.81 (m, 2 \times ArH); δ_{C} 52.5 (q), 61.0 (q), 107.9 (s), 116.0 (s), 128.0 (d), 128.1 (d), 128.4 (d), 128.7 (s), 128.9 (d), 129.0 (d), 129.6 (d), 130.7 (s), 141.4 (s), 162.3 (s), 166.7 (s) and 167.4 (s) (Found: M⁺, 336.1002. Calc. for C₂₀H₁₆O₅: M, 336.0996); a proportion of the mixture (40 mg, 36%) remained unseparated.

Methyl α -(3-Methoxy-5-oxo-4-phenyl-2,5-dihydrofuran-2-ylidene)(2-methoxyphenyl)acetate (O-Methylleprapinic Acid) 16b.—Sodium hydride (60% dispersion in oil; 43 mg, 1.1 equiv.) was added in one portion to a stirred solution of compound **2a** (200 mg, 1 equiv.) in dry toluene (20 cm³) under nitrogen at 0 °C (ice-bath). The solution was stirred at 0 °C for 20 min and a solution of methyl 2-methoxybenzoylformate (118 mg; 1.1 equiv.) in dry toluene (2 cm³) was then added dropwise over 2 min. The mixture was heated under reflux for 20 min and then acidified by the addition of hydrochloric acid (2 mol dm⁻³; 2 cm³). The organic phase was separated, dried and evaporated under reduced pressure to leave a residue which was purified by flash chromatography using hexane–diethyl ether (1:1) as eluent to give *O*-methylleprapinic acid (110 mg, 45%) as a mixture of (*Z*)- and (*E*)-isomers (3:2). High pressure liquid chromatography using hexane–diethyl ether (3:2) as eluent then gave: (a) the (*Z*)-isomer of *O*-methylleprapinic acid (eluted first) as a crystalline white solid, m.p. 95–96 °C (from hexane–diethyl ether) (lit.,¹¹ m.p. 96–97 °C); λ_{\max}/nm 198.8 (ϵ 35 900), 274.6 (ϵ 10 400), 323.6 (ϵ 12 500); $\nu_{\max}/\text{cm}^{-1}$ 1760 and 1720; δ_{H} 3.33 (OMe), 3.83 (OMe), 3.84 (CO₂Me), 6.90–7.01 (m, 2 \times ArH), 7.30–7.42 (m, 5 \times ArH) and 7.52–7.58 (m, 2 \times ArH); δ_{C} 52.5 (q), 55.6 (q), 60.4 (q), 110.4 (d), 111.1 (s), 114.3 (s), 120.8 (d), 121.4 (s), 128.3 (d), 128.4 (s), 128.9 (d), 129.6 (d), 130.3 (d), 132.0 (d), 145.8 (s), 157.6 (s), 162.4 (s), 165.7 (s) and 166.9 (s) (Found: M⁺, 366.1116. Calc. for C₂₁H₁₈O₆: M, 366.1103); (b) the (*E*)-isomer of *O*-methylleprapinic acid **16b** (eluted second) as a crystalline white solid, m.p. 141–142 °C (from hexane–

diethyl ether) (lit.,¹¹ m.p. 148–149 °C); λ_{\max}/nm 262.8 (ϵ 8300), 331.2 (ϵ 15 900); $\nu_{\max}/\text{cm}^{-1}$ 1760 and 1720; δ_{H} 3.85 (OMe), 3.89 (OMe), 3.90 (CO₂Me), 6.97–7.10 (m, 2 \times ArH) and 7.39–7.62 (m, 7 \times ArH); δ_{C} 52.4 (q), 55.8 (q), 61.1 (q), 109.0 (s), 111.3 (s), 114.3 (s), 119.9 (d), 121.0 (s), 128.3 (d), 128.4 (s), 128.8 (d), 129.9 (d), 130.8 (d), 132.1 (d), 143.7 (s), 157.6 (s), 163.4 (s), 166.9 (s) and 167.5 (s) (Found: M⁺, 366.1071. Calc. for C₂₁H₁₈O₆: M, 366.1103); a proportion of the mixture (60 mg, 23%) remained unseparated.

Methyl α -(3-Methoxy-5-oxo-4-phenyl-2,5-dihydrofuran-2-ylidene)(4-methoxyphenyl)acetate (O-Methylisopinastric Acid) 16c.—Sodium hydride (60% dispersion in oil; 43 mg, 1.1 equiv.) was added in one portion to a stirred solution of compound **2** (200 mg; 1 equiv.) in dry toluene (20 cm³) under nitrogen at 0 °C (ice-bath). The solution was stirred at 0 °C for 20 min and then a solution of methyl 4-methoxybenzoylformate (118 mg, 1.1 equiv.) in dry toluene (2 cm³) was added dropwise over 2 min. The mixture was heated under reflux for 20 min and then acidified by the addition of hydrochloric acid (2 mol dm⁻³; 2 cm³). The organic phase was separated, dried and evaporated under reduced pressure to leave a residue which was purified by flash chromatography using hexane–diethyl ether (1:2) as eluent to give *O*-methylisopinastric acid (140 mg, 57%), a crystalline orange solid, as an inseparable mixture of (*Z*)- and (*E*)-isomers (2:1), m.p. 126–129 °C (from hexane–diethyl ether); λ_{\max}/nm 194.5 (ϵ 12 900) and 349.6 (ϵ 19 000); $\nu_{\max}/\text{cm}^{-1}$ 1720 and 1755; δ_{H} [(*Z*)-isomer] 3.36 (OMe), 3.81 (OMe), 3.81 (CO₂Me), 6.90 (d, *J* 8.7, 2 \times ArH), 7.26–7.50 (m, 5 \times ArH) and 7.54 (d, *J* 8.9, 2 \times ArH), [*E*-isomer] 3.76 (OMe), 3.84 (OMe), 3.89 (CO₂Me), 6.92 (d, *J* 8.9, 2 \times ArH), 7.40–7.60 (m, 5 \times ArH) and 7.65 (d, *J* 9.0, 2 \times ArH); δ_{C} [(*Z*)-isomer] 52.5 (q), 55.0 (q), 60.3 (q), 110.7 (s), 113.1 (d), 117.1 (s), 123.2 (s), 127.9 (d), 128.0 (s), 128.5 (d), 129.2 (d), 130.7 (d), 143.4 (s), 159.8 (s), 162.8 (s), 165.9 (s) and 167.0 (s), [*E*-isomer] 52.5 (q), 55.0 (q), 60.9 (q), 107.4 (s), 114.0 (d), 116.0 (s), 123.3 (s), 127.9 (d), 128.0 (s), 128.4 (d), 129.4 (d), 130.3 (d), 139.7 (s), 160.2 (s), 162.5 (s), 166.6 (s) and 167.6 (s) (Found: M⁺, 366.1110. Calc. for C₂₁H₁₈O₆: M, 366.1103). A pure sample of the *E*-isomer of *O*-methyl isopinastric acid **16c** was obtained by photoisomerism (laboratory daylight) of the mixture in chloroform, as a crystalline yellow solid, m.p. 172–173 °C (from hexane–diethyl ether) (lit.,¹¹ m.p. 174–175 °C); λ_{\max}/nm 353.3 (ϵ 26 700), 319.5 (ϵ 19 500), 284.0 (ϵ 17 300) and 235.6 (ϵ 25 900); $\nu_{\max}/\text{cm}^{-1}$ 1755 and 1725; δ_{H} identical with above; δ_{C} identical with above (Found: M⁺, 366.1063. Calc. for C₂₁H₁₈O₆: M, 366.1103).

Methyl α -[3-Methoxy-5-oxo-4-(3,4,5-trimethoxyphenyl)-2,5-dihydrofuran-2-ylidene](4-methoxyphenyl)acetone (Permethyated Gomphidic Acid) 17a.—Sodium hydride (60% dispersion in oil; 10 mg, 1.1 equiv.) was added in one portion to a stirred solution of compound **2b** (50 mg, 1 equiv.) in dry toluene (10 cm³), under nitrogen at 0 °C (ice-bath). The mixture was stirred at 0 °C for 20 min and a solution of methyl 4-methoxybenzoylformate (27 mg, 1.1 equiv.) in dry toluene (2 cm³) was then added dropwise over 2 min. The mixture was heated under reflux for 36 h and then acidified by the addition of hydrochloric acid (2 mol dm⁻³; 2 cm³). The organic phase was separated, dried and evaporated under reduced pressure to give a crude residue which was purified by flash chromatography using light petroleum (b.p. 40–60 °C)–diethyl ether (2:3) as eluent to give permethylated gomphidic acid (12 mg, 21%), a crystalline yellow solid, as a mixture of (*Z*)- and (*E*)-isomers (3:2), which on photoisomerisation (laboratory daylight) in chloroform gave exclusively the *E*-isomer, m.p. 153–154 °C (from methanol) (lit.,¹¹ m.p. 150–151 °C) (Found: C, 62.9; H, 5.4. Calc. for C₂₄H₂₄O₉: C, 63.2; H, 5.4%); λ_{\max}/nm 360.8 (ϵ 17 600); $\nu_{\max}/\text{cm}^{-1}$ 1750 and 1725; δ_{H} 3.82 (OMe), 3.84 (OMe), 3.88 (CO₂Me),

3.89 (OMe), 6.76 ($2 \times \text{ArH}$), 6.94 (d, J_{AB} 9.0, $2 \times \text{ArH}$) and 7.65 (d, J_{AB} 9.0, $2 \times \text{ArH}$); δ_{C} 52.7 (q), 55.3 (q), 56.2 (q), 60.8 (q), 61.0 (d), 107.0 (d), 108.0 (d), 114.3 (d), 116.3 (s), 123.3 (s), 123.6 (s), 130.7 (d), 138.5 (s), 139.8 (s), 153.1 (s), 160.4 (s), 162.5 (s), 167.2 (s) and 167.7 (s); (Found: M^+ , 456.1426. Calc. for $\text{C}_{23}\text{H}_{24}\text{O}_9$: M , 456.1419).

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