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A NEW SYNTHESIS OF PULVINIC ACIDS.

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Summary: Reaction of zinc enolates e.g. (6) derived from arylacetates with 2-aryl-3-methoxymaleic anhydrides e.g. (3) gives intermediates viz (8) which can be dehydrated to Z-and E-isomers of permethylated pulvinic acids; treatment of the latter with trimethylsilyl iodide provides the corresponding pulvinic acids e.g. gomphidic acid (1).

Although known for almost a century, the pulvinic acid group of colouring matter common to several lichens and fungi e.g. gomphidic acid (1) and leprapinic acid (2), have been a difficult class of compound to characterise, due largely to the dearth of synthetic methods to those members having different substitution patterns (i.e. unsymmetrical) in the aryl ring portions of their structures.[1] This synthetic problem has been addressed recently by ourselves[2] and by others.[3] In this Letter we describe a new approach to permethylated pulvinic acids which features a novel Reformatsky-type condensation between arylacetates and arylmethoxymaleic anhydrides. We also demonstrate that treatment of the permethylated pulvinic acids with trimethylsilyl iodide provides an expeditious synthesis of 'free' pulvinic acids

2-Aryl-3-methoxymaleic anhydrides e.g. (3) can be prepared easily and on large scale from the corresponding arylacetonitriles via base-catalysed condensation with diethyl oxalate, followed by sequential hydrolysis, cyclodehydration and methylation.[2]

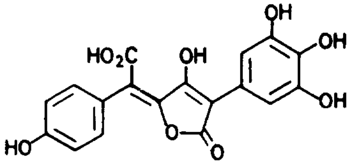
Whereas previous studies have shown that Grignard reagents react with the anhydride (3) leading largely to 2:1 adducts viz (4)[4], and that the phosphorus ylides (5) fail to react at all with (3)[4], the zinc enolate (6) derived from methyl 4-methoxyphenylacetate condenses smoothly with (3) producing the anticipated t-carbinol (8). Thus, deprotonation of methyl 4-methoxyphenylacetate (LDA, Et_2O, -78°C) followed by addition of an ether solution of anhydrous zinc chloride (1 equiv)[5], gave a clear yellow-green solution of (6), which after addition of the anhydride (3) and work-up, produced the *t*-carbinol (8; 40%) as a single diastereoisomer. We assume from the chair-like conformation of the zinc chelate intermediate with the bulkiest groups adopting equatorial orientations that this diastereoisomer has the *anti*-geometry shown (7).

In a similar manner, the Reformatsky-type condensation between the trimethoxyphenyl acetate (9) and the maleic anhydride (10) led to a single diastereoisomer of the β-hydroxy-ester (11). By contrast, the reaction between 2-methoxy-3-phenylmaleic anhydride and the zinc enolate (12) produced a 3:1 mixture of diastereoisomers of (13).

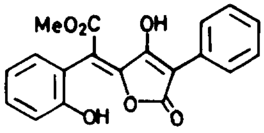
Elimination of the elements of water from the β-hydroxy esters (8), (11) and (13), leading to the corresponding permethylated pulvinic acids, was achieved by treatment with methanesulphonyl chloride followed by diazobicyclononane. Thus, treatment of the hydroxy-ester (8) by this method produced a 5:1 mixture of *Z*-and *E*-isomers of permethylated gomphidic acid (14) which could be separated by chromatography and crystallisation as yellow solids m.p. 94.5-95.5°C and 150-1°C respectively. When solutions of the *Z*-isomer are left in laboratory daylight for periods of days, they rapidly undergo stereomutation leading to the corresponding *E*-isomer (14). In a similar manner to that described for the dehydration of (8), the isomeric β-hydroxy ester (11) produced a mixture of geometrical isomers of permethylated *iso*-gomphidic acid, *viz* (15), and the β-hydroxy-ester (13) gave rise to the *Z*-and *E*-isomers of pulvinate (16). The *E*-pulvinate (16) showed identical spectral features to those described by Seshadri *et al*[6] for the methyl ether of leprapinic acid (2) found in *Lepraria chlorina*.

Although demethylation of permethylated pulvinic acids to the corresponding 'free' acids has proved difficult in the past[7], we have now found that trimethylsilyl iodide[8] is a particularly efficient reagent for the conversion. The reactions are conveniently carried out in deuteriochloroform solutions in p.m.r. tubes sealed under nitrogen and warmed to 55°C. After approximately three days (p.m.r. monitoring) the resulting persilylated pulvinic acids were hydrolysed with methanol to give the free pulvinic acids.

In this manner, both the *Z*-and *E*-geometrical isomers of permethylated gomphidic acid e.g. (14) produced the same *E*-gomphidic acid (1), red powder m.p. 205-215°C(decomp.), λ_{max}(EtOH) 260 (13,800), 398 (6,500) nm., δ6.86 (d, *J*8.3, 2 x :C*H*), 7.17 (d, *J*8.3, 2 x :C*H*), 7.35 (2 x :C*H*) which was identical with a sample isolated by Steglich *et al*[9], from *Gomphidius glutinosus*. By contrast, the permethylated *iso*-gomphidic acid (15) led to *iso*-gomphidic acid (17), orange-red needles, m.p. 220-8°C (decomp.), λ_{max} (EtOH) 263 (20,100), 397 (7,800)nm., δ6.41 (2 x :C*H*), 6.9 (d, *J*8.5, 2 x :C*H*), 8.05 (d, *J*8.5, 2 x :C*H*).[10, 11]



(1)



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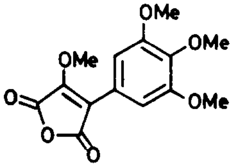

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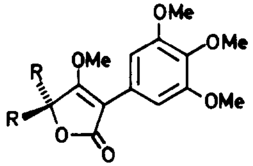

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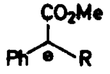
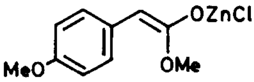
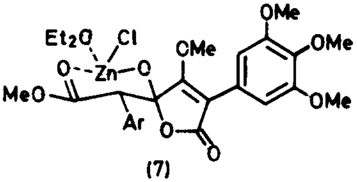


$R = \overset{+}{P}Ph_3$ or $PO(OEt)_2$

(5)

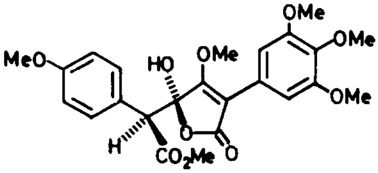


(6)

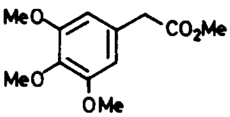


(7)

Ar = 4-OMeC$_6$H$_4$



(8)



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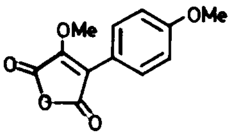
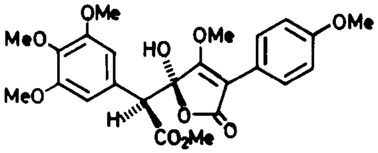


(10)



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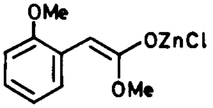

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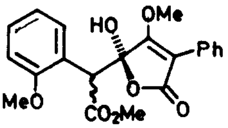

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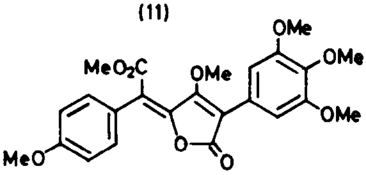
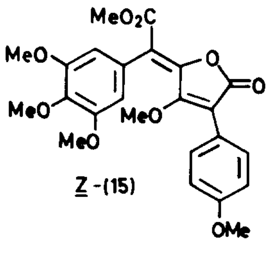
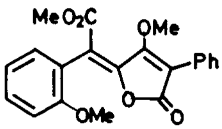


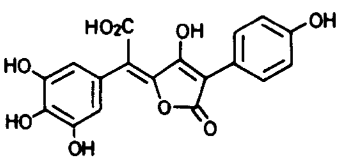
E-(14)



Z-(15)



(16)



(17)

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10. Comparative t.l.c. and spectral data confirmed that the previously reported synthesis of permethylated gomphidic acid[2] produced largely the *Z*-geometrical isomer.

11. All new compounds showed satisfactory i.r., uv, visible absorption and n.m.r. data, in addition to microanalytical or mass spectroscopic data.

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