

Synthesis of Compounds of the 12-Oxophytodienoic Acid Cascade: OPCs-8 : 0, 6 : 0, 4 : 0, and 2 : 0 (*epi*-Jasmonic Acid)

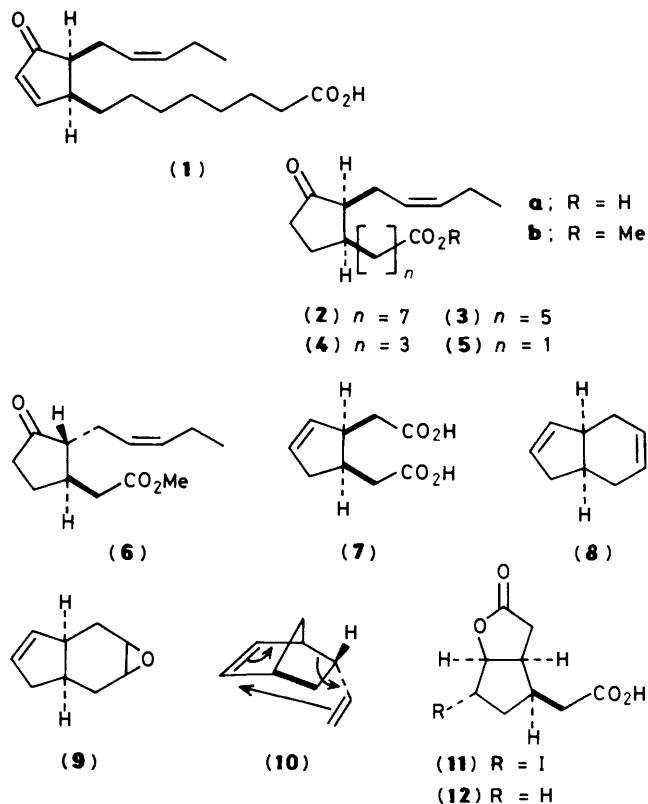
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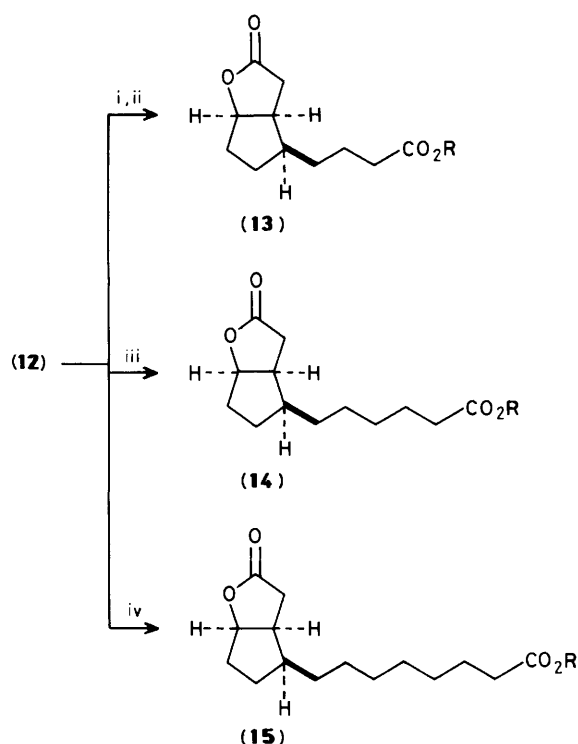
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The β -oxidation compounds of the *cis* series OPC-8 : 0, 6 : 0, 4 : 0, and 2 : 0 (*epi*-jasmonic acid), formed metabolically from dihydro-12-oxophytodienoic acid, are synthesised as their methyl esters; plant regulating functions are associated with the acids of this series.

Enzymic reduction and β -oxidation of 12-oxophytodienoic acid (12-oxoPDA) (1) produces a cascade of products, 3-oxo-2-*cis*-(pent-2*Z*-enyl)cyclopentyl octanoic acid (OPC-8:0) (2), OPC-6:0 (3), OPC-4:0 (4), and *cis*-(*Z*)- or *epi*-jasmonic acid (OPC-2:0) (5).¹ It is believed that this cascade has a significant role in the regulation of processes in plant physiology, beyond what is already known of the activities of jasmonic acid; the latter is found widely distributed in higher plants and fungi and has growth regulating and senescence-inducing properties.² It is of interest that although much synthetic activity has been devoted to methyl *trans*-jasmonate (6) because of its interest to the perfumery industry, recent reports indicate that the odour quality is almost entirely due to methyl (+)-*cis*-(*Z*)-jasmonate.³ We now report syntheses of the OPC series (2b)—(5b) in racemic form.

As in our synthesis of 12-oxoPDA,⁴ the present approach is based on the dicarboxylic acid (7) prepared from (8) by the selective oxidation reported by Stevens and Hrib who used it in a synthesis of *trans*-jasmonic acid.⁵ Treatment with HOBr [*N*-bromosuccinimide (NBS)—dimethyl sulphoxide (DMSO)—H₂O] gave a mixture of bromohydrins, converted (81% overall) into epoxide (9) by treatment with potassium *t*-butoxide in tetrahydrofuran (THF). Oxidation with chromium trioxide gave the desired *cis*-dicarboxylic acid (7) (30% yield) m.p. 167—169 °C. Since bicyclo[4.3.0]nona-3,8-diene (8) was not commercially available, it was prepared by thermal sigmatropic [3,3] rearrangement of commercial 5-vinyl-norborn-2-ene (*endo*:*exo* 67:33). Only the *endo*-(10) underwent the necessary Cope reaction (~75% yield at 210 °C and 200 psi), the remainder being unchanged or polymer. The





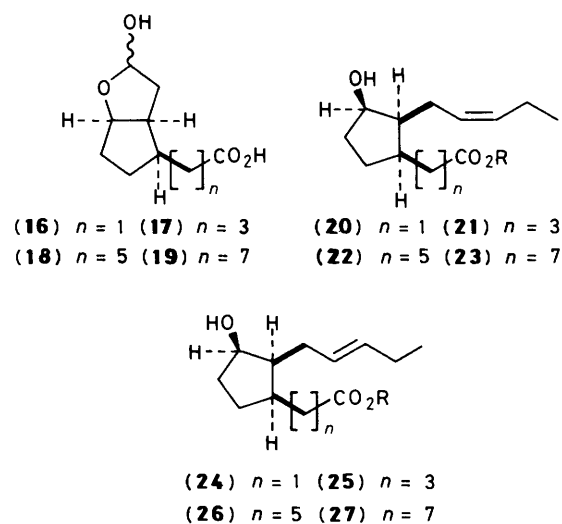
Scheme 1. Reagents: i, (a) COCl_2 , (b) CH_2N_2 , (c) Ag^+ , Et_3N , MeOH , (d) KOH , MeOH ; ii, repeat; iii, Kolbe electrolysis, $\text{HO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{Me}$; iv, Kolbe electrolysis, $\text{HO}_2\text{C}(\text{CH}_2)_6\text{CO}_2\text{Me}$.

diacid (7) was converted into iodolactone (11) with iodine in aqueous potassium iodide containing sodium hydrogen carbonate (80% yield) and then reduced with tributyltin hydride in THF with azoisobutyronitrile present to give deiodinated lactone (12) (78% yield).^{5†}

The lactone (12) was central to the synthetic work (Scheme 1). Kolbe anodic synthesis, coupling with suberic acid monomethyl ester (2.5 mmol) gave (15; $\text{R} = \text{Me}$) (38% yield). Similarly, using adipic acid monomethyl ester, (14; $\text{R} = \text{Me}$) was prepared (25% yield). For the four-carbon side chain series (12) was converted into its acid chloride and transformed into (13; $\text{R} = \text{Me}$) by double Arndt-Eistert synthesis which proceeded quite efficiently (63% overall yield).

After hydrolysis, each of the lactone acids (12), (13)—(15) ($\text{R} = \text{H}$), was reduced to its lactol (16)—(19) by di-isobutyl-aluminium hydride (3.3 equiv. in THF, -73°C). These lactols could be isolated and purified but were usually allowed to react directly with excess of propylidene-triphenyl-phosphorane (5 mol) in DMSO at 70°C , giving (20)—(23) in yields of 45—50%. As in the synthesis of 12-oxoPDA, these Wittig reactions were incompletely stereospecific giving a (*Z*):(*E*) ratio of about 85:15. In each case the unwanted (*E*) materials (24)—(27) were removed by chromatography (15% $\text{AgNO}_3/\text{silica}$) after esterification ($\text{R} = \text{Me}$).

† Converted into the ester with (–)-borneol, it is possible to separate the diastereoisomers from (12) by h.p.l.c., thereby making a chiral version of this synthesis feasible. The unsaturated 12-oxoPDA precursor can be similarly resolved. We thank Dr. W. M. L. Crombie for this information.



Syntheses of (\pm)-OPC-8:0, OPC-6:0, OPC-4:0, and OPC-2:0 (*epi*- or *cis*-jasmonic) esters (2b)—(5b) were completed by oxidation (pyridinium dichromate in dichloromethane) of the purified (*Z*) alcohols (20)—(23) ($\text{R} = \text{Me}$) to their corresponding ketones (72—81% yields). OPC-4:0 was epimerised under acid conditions as a check on its *cis*-stereochemistry and comparison with the other members of the cascade was effected by ^{13}C n.m.r. observation of the 2,3-carbons of the cyclopentanone rings (these lie downfield in the *trans* relative to the *cis* by $\delta \sim 1.4$ and 3.1). The syntheses were designed for late insertion of the olefinic side-chain in order to permit economical deuterium labelling at this site; such deuteriated compounds permit effective search, with identification and quantitation, in plant material by g.l.c.–mass spectroscopic methods.

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