Synthesis of 12-Oxophytodienoic Acid (12-oxoPDA), Metabolic Parent of OPC-Compounds and *epi*-Jasmonic Acid

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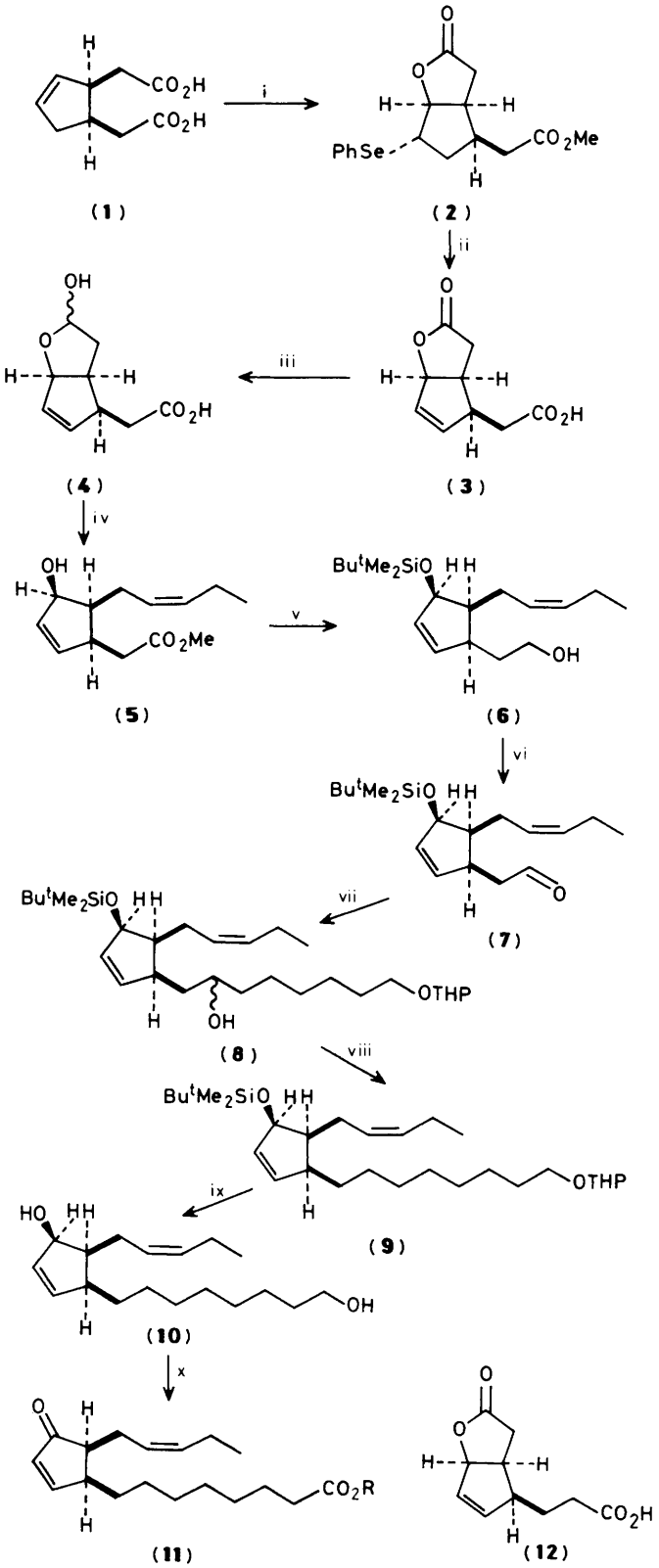
The first synthesis of (±)-12-oxophytodienoic acid, a compound widely distributed in plants, and the metabolic parent of OPC compounds including *epi*-jasmonic acid, is described; whilst structurally resembling prostaglandin PGA_1, it belongs to the *cis*-series not found in mammals.

12-Oxophytodienoic acid (12-oxoPDA) (**11**) is formed by an enzyme with cyclase activity which occurs in flax and other seeds and seedlings and whose substrate is (13*S*)-hydroperoxyoctadeca-(9*Z*),(11*E*),(15*Z*)-trienoic acid.[1] The latter, in its turn, is formed by the action of soya bean lipoxygenase on linolenic acid. 12-OxoPDA is of considerable interest in connection with plant regulatory substances and its reduction and β-oxidation[2] explains the origins of the growth regulating[3] and senescence inducing[4] jasmonic acid. It is also likely to be associated with metabolic pathways leading to jasmone and



Scheme 1. *Reagents and conditions*: i, (a) PhSeCl, THF, −78 °C→20 °C, (b) CH_2N_2; ii, (a) H_2O_2, THF, (b) KOH, MeOH; iii, DIBAL (3.3 mol), −45 °C; iv, (a) Ph_3P=CHEt, DMSO, 70 °C, (b) CH_2N_2; v, (a) Bu^tMe_2SiCl, DMF, imidazole, (b) DIBAL, THF, −78 °C; vi, PDC, CH_2Cl_2; vii, $BrMg[CH_2]_6OTHP$, THF: viii, (a) $MeSO_2Cl$, pyridine, (b) $LiAlH_4$, Et_2O, reflux; ix, (a), $Bu_4N^+F^-$, THF, 45 °C, (b) PPTS, EtOH, 50 °C; x, for R = H: PDC, DMF, 20 °C; for R = Me: CH_2N_2.

other jasmonoids, the pyrethrins ketols,[5] and natural products from *Chromolaena* spp.[6] 12-OxoPDA is widely distributed in higher plants[7] and its structure (**11**) clearly resembles the mammalian prostaglandins (PGA_1), yet there are major differences. Thus, all of the latter have a *trans*-attachment of side chains, whilst 12-oxoPDA and its degradation cascade have *cis*-attachments. An even more marked contrast is the apparently differing modes of biosynthesis.[8,9] We now report the first synthesis of (±)-12-oxoPDA.

In selecting a suitable starting point attention was turned to the *cis*-cyclopentenediacetic acid (**1**),[10] which had earlier been employed in a synthesis of *trans*(*Z*)-jasmone.[11] Treatment with benzeneselenenyl chloride gave a selenolactonic acid (75% yield), m.p. 130—131 °C, which was esterified to form the methyl ester (**2**), m.p. 68—69 °C, in almost quantitative yield. Oxidative elimination followed by hydrolysis gave the unsaturated lactone acid (**3**), m.p. 114—115 °C, in 92% yield overall. The lactone (**3**) was reduced to the lactol (**4**) by di-isobutylaluminium hydride (DIBAL) in tetrahydrofuran (THF), but the lactol was not purified but treated directly with excess of propylidenetriphenylphosphorane in dimethyl sulphoxide (DMSO) and then esterified with diazomethane to give (**5**). The Wittig reaction was not fully stereospecific, giving an 85 : 15 mixture of (*Z*) : (*E*) alkenes (51% yield over three steps). After conversion into the t-butyldimethylsilyl derivative (99%), the (*Z*)/(*E*) mixture was separated by chromatography over 15% silver nitrate impregnated silica [eluant : ethyl acetate–benzene (1 : 10)]. The synthesis was then continued with the pure t-butyldimethylsilyl-(*Z*)-ester which was reduced to alcohol (**6**) (94%) by di-isobutylaluminium hydride.

A number of attempts were made to extend the length of the saturated side chain† and the method eventually selected was oxidation of alcohol (**6**) to aldehyde (**7**) (78%) using pyridinium dichromate (PDC) and treatment of (**7**) with a refluxing solution of $BrMg[CH_2]_6OTHP$ (THP = tetrahydropyran-2-yl) in THF for 1 h. This gave, in 92% yield, a pair of (±)-diastereoisomers (**8**) which were chromatographically separable. Each diastereoisomer was mesylated in almost theoretical yield, and then reductively demesylated by refluxing with lithium aluminium hydride in ether. Both gave the same product (**9**), one in 75%, the other in almost 100% yield. The cyclopentene (**9**) was stripped of its protecting groups, first removing the silyl protection with tetrabutylammonium fluoride (~100%), and then the tetrahydropyran-2-yl group (56% yield) by pyridinium toluene-*p*-sulphonate (PPTS). Oxidation of both the secondary and primary alcohol functions in (**10**), using pyridinium dichromate in DMF, followed by esterification, gave (±)-12-oxoPDA as its methyl ester (20% yield). The compound was identical (^1H n.m.r. and t.l.c. comparisons), with a specimen of authentic 12-oxoPDA made in our laboratory[9] enzymically using flax enzyme.[1] It was epimerised at C-13 by acid to give the *trans*-isomer which was spectroscopically and chromatographically (g.l.c.) distinct from the natural *cis*-isomer.

During the synthesis checks on *cis*-stereochemistry were made using nuclear Overhauser effects on the set of *cis*-disposed ring methine protons: the validity of this correlation was checked by an *X*-ray structure determination of (**12**).

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† For example, Kolbe anodic synthesis at an earlier stage employing (**3**), and successfully used in the cyclopentanone OPC series, gave low yields. Similarly, employment of an Arndt–Eistert homologated precursor (**12**) gave unsatisfactory yields.

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