New Synthesis of Catalpalactone

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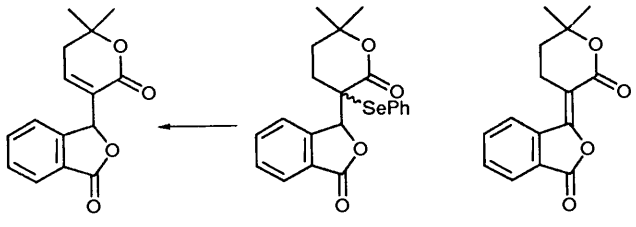
Various alkylidenephthalides (*E*- and *Z*-**5**, **6** and **7**) were prepared by Wittig reaction of phosphoranes **4a**, **4b** and **4c** respectively with phthalic anhydride. The products were then lactonised, using chloro(trimethyl)silane and sodium iodide, to the corresponding dilactones **8** and **3**. Attempts to isomerise the dilactone **3** to catalpalactone **1** failed.

Phthalides **13a**, **13b** and **13c** were prepared by Wittig reaction of phosphoranes **4a**, **4b** and **4c** respectively with phthalaldehydic acid. Lactonisation of **13a** gave the dilactone **15**, while lactonisation of **13b** or **13c** gave dihydrocatalpalactone **9**. Compound **9**, on treatment with NaH and careful acidification with acetic acid, gave acid (*E*) **12**, which on selenolactonisation furnished selenide **2**. Selenide **2** gave catalpalactone **1** on treatment with H_2O_2–AcOH.

Catalpalactone, the dilactone obtained from the heartwood of the ornamental tree *Catalpa ovata* G. Don, has structure **1**.[1] It was reported to be optically inactive and is presumably racemic. Two syntheses of compound **1** have been reported.[2] In both, the selenide **2** is the penultimate intermediate and the double bond is introduced by the standard oxidative elimination method.[3] The double bond is introduced regioselectively endocyclic to the six-membered lactone ring, owing to the propensity of elimination to occur away from the heteroatom.[4]



1 **2** **3**

We considered two new approaches to the synthesis of catalpalactone. In one we sought to obtain dilactone **3** in the first instance and then to isomerise it to compound **1**. In the other, an alternative route to **2**, the intermediate in the reported syntheses, was envisaged. Our experiments on both these approaches are described below.

Results and Discussion

Synthesis of Compound **3** *and Attempted Isomerisation to Catalpalactone.*—In model studies, phthalic anhydride was condensed with the ethoxycarbonylbutenylidenephosphorane **4a**.[5] The Wittig product **5**, $C_{15}H_{14}O_4$ (mixture of *E*- and *Z*-isomer), obtained was separated into its two constituents by flash chromatography. Isomer (*E*)-**5**, which is the less polar, showed, in its NMR spectrum, a signal for 4-H at δ 8.63 (deshielded by the ester carbonyl group) and the methylene protons at δ 3.55; (*Z*)-**5**, on the other hand, had its 4-H signal at higher field, merged with other aromatic proton signals at δ 7.60–8.00, and the methylene protons were shifted downfield at δ 3.62 (deshielded by the benzene ring).

Various methods were tried for the hydrolysis of the ester group of the Wittig product **5**. That with chloro(trimethyl)silane (TMSCl) and sodium iodide in refluxing acetonitrile was found to be the best.[6] When isomers (*E*)-**5** and (*Z*)-**5** were refluxed separately with TMSCl–NaI in acetonitrile, the only product obtained, in 46% yield, was the butanolide **8**, whose NMR spectrum showed a signal for 4-H at δ 9.20, and those for the methylene protons at δ 2.92 and 3.54 as well resolved doublets of doublets. The chemical shift of 4-H indicated that product **8** had the *E* stereochemistry. Since both (*E*)- and (*Z*)-**5** had given only one product, **8**, and because *E*/*Z* isomerisation of a double bond by TMSCl–NaI is possible,[7] then the reaction had presumably given the thermodynamically more stable compound. The stability of compound **8**, despite the steric interaction between the carbonyl oxygen and 4-H, could be due to its expected lower dipole moment. Since both isomers of compound **5** gave only one product, in further experiments the mixture of isomers itself was used to obtain compound **8**.

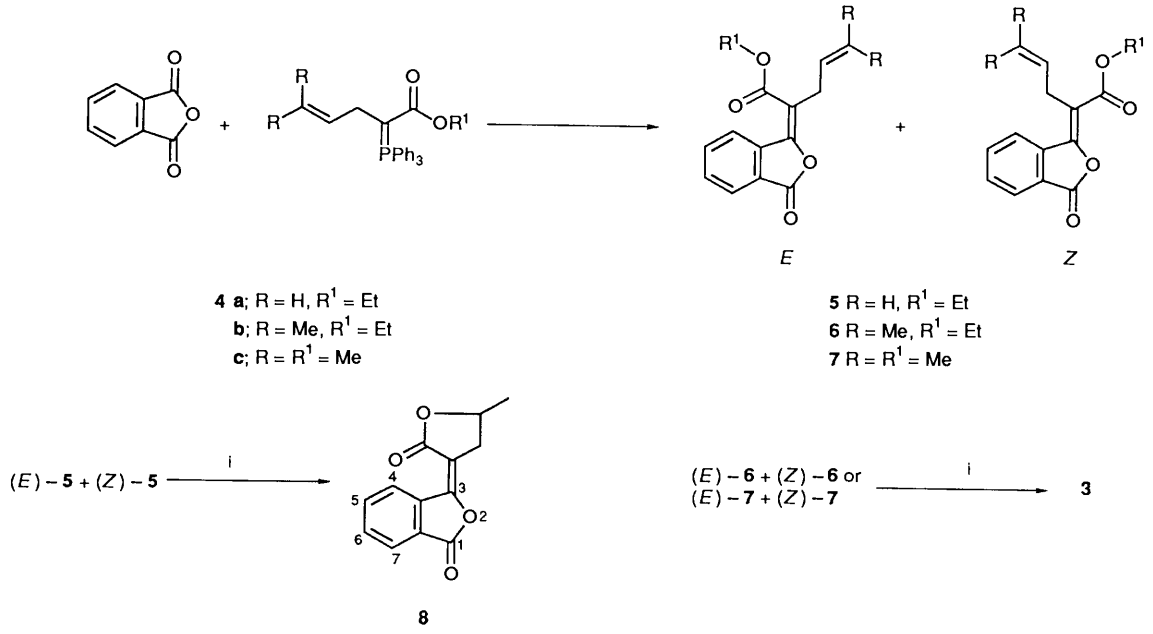
To build the carbon skeleton of catalpalactone, the above reaction sequence was carried out with phthalic anhydride and the phosphorane **4b**. The Wittig product **6**, $C_{17}H_{18}O_4$, obtained as a mixture of its *E*- and *Z*-isomer, was separated into its constituents and characterised. For the hydrolysis, however, the mixture itself was employed, when, with TMSCl–NaI in refluxing acetonitrile, the six-membered lactone **3** was obtained as a single compound in 54% yield. When phosphorane **4c** (methyl esters are known to be more cleanly hydrolysed by TMSCl–NaI) was used in the above reaction, compound **3** was obtained in 70% overall yield (Scheme 1).

Attempts to isomerise the exocyclic double bond in compound **3** to give the endocyclic product catalpalactone **1** by using bases such as Bu^{t}OK, lithium diisopropylamide (LDA), NaH–diethyl ether or NaH–tetrahydrofuran (THF) led to unidentified products. Use of toluene-*p*-sulphonic acid (pTSA) in refluxing benzene resulted in quantitative recovery of the starting compound **3**.

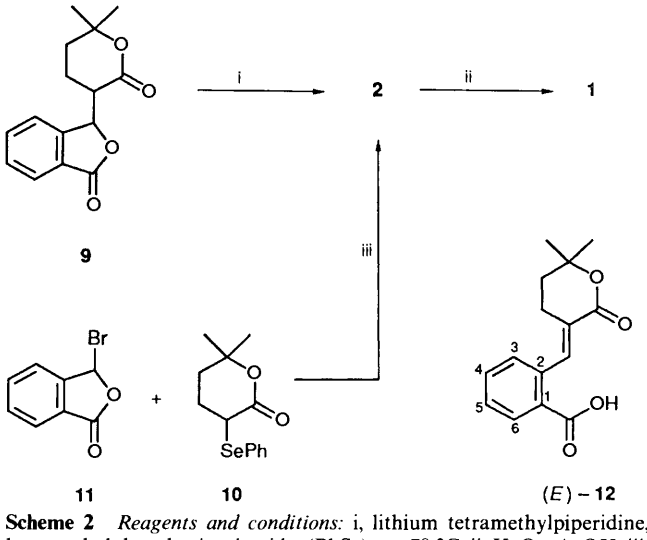
New Synthesis of Intermediate **2** *and its Conversion into Catalpalactone* **1**.—Two syntheses of selenide **2** (diastereoisomeric mixture) are known. One is by base-catalysed selenation of dihydrocatalpalactone **9**,[2a] where the yield is poor (15%). The other is alkylation of the seleno lactone **10** with 3-bromophthalide **11**,[2b] where the yield is 47%. Selenide **2** has been separated into its diastereoisomers and each has been converted into catalpalactone **1** (Scheme 2).

We planned to obtain compound **2** by selenolactonisation[8] of the unsaturated lactone acid (*E*)-**12**. This procedure was particularly attractive, since asymmetric selenolactonisation could be possible [eqn. (1)].

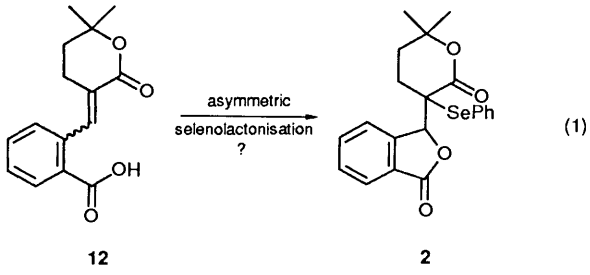
Acid (*E*)-**12** could be obtained by Wittig reaction of the

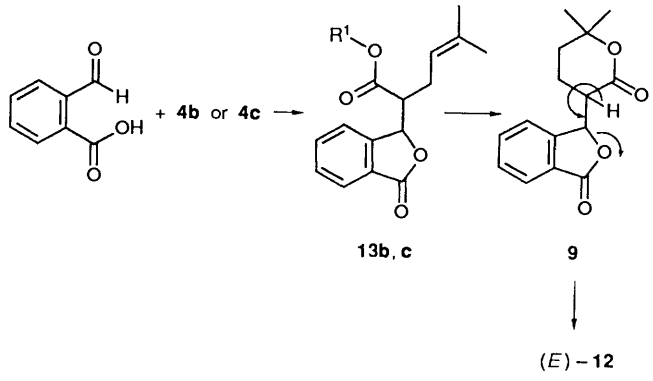


Scheme 1 *Reagents:* i, TMSCl, NaI, MeCN, reflux



Scheme 2 *Reagents and conditions:* i, lithium tetramethylpiperidine, hexamethylphosphoric triamide, $(PhSe)_2$, −78 °C; ii, H_2O_2, AcOH; iii, LDA, −78 °C





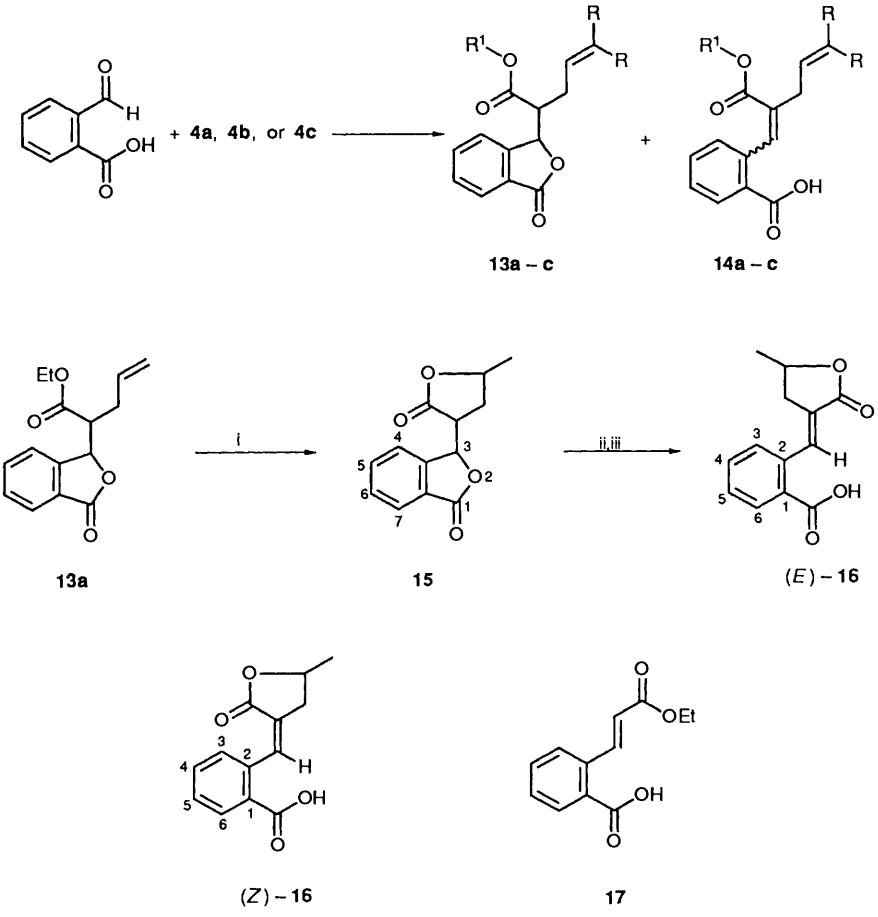
Scheme 3

phosphorane **4b** or **4c** with phthalaldehydic acid, followed by hydrolytic lactonisation and then retro-Michael opening of the phthalide ring (Scheme 3).

In model studies, phthalaldehydic acid was condensed with the phosphorane **4a** in refluxing chloroform. The product was separated into acidic and neutral fractions. The acid fraction was a mixture of the *E* and *Z* isomers of ester acid **14a**. This was sensitive to cyclisation and was characterised only by NMR spectroscopy. The mixture showed, in its NMR spectrum, two sets of signals for the $MeCH_2O$ and =CH–C*H*$_2$–C= groups. The olefinic and aromatic protons appeared as groups of complex signals. The neutral fraction was also a mixture of diastereoisomers of the phthalide **13a**, $C_{15}H_{16}O_4$, and showed, in its NMR spectrum, two sets of signals for the $MeCH_2O$ group. The remaining protons appeared as groups of complex signals. The mixture of *E* and *Z* isomers of compound **14a**, on treatment with ethereal HCl, gave the phthalide **13a**, $C_{15}H_{16}O_4$, (diastereoisomeric mixture) in 80% yield.

When compound **13a** (mixture of diastereoisomers) was treated with TMSCl–NaI in refluxing acetonitrile the dilactone **15**, $C_{13}H_{12}O_4$ (mixture of diastereoisomers), was obtained in 55% yield. Compound **15** on treatment with NaH in THF at room temperature, followed by careful acidification with acetic acid, gave the unsaturated lactone acid **16**, $C_{13}H_{12}O_4$, as a single compound.

Two structures are possible for the lactone acid **16**, *viz.* (*E*)-**16** and (*Z*)-**16**. A choice between the two could not be made on the basis of the NMR spectrum, as the two-proton multiplet at δ 8.25 could be attributed to any two of the three protons at C-6 (deshielded by the *ortho* carboxy group), C-3 (deshielded by lactone carbonyl group) and the β-olefinic proton of (*Z*)-**16** or the 6-H and β-olefinic protons of (*E*)-**16**. However, the UV spectrum of the compound [λ_{max} 276 (ε/dm^3 mol^{-1} cm^{-1} 4100) and 219 nm (ε 3580)] was very similar to that of *E*-ethyl *o*-carboxycinnamate **17** [λ_{max} 278 (ε 2890) and 219 nm (ε 2570)], indicating that the compound had the *E* geometry as represented by structure (*E*)-**16** (Scheme 4).



Scheme 4 *Reagents:* i, TMSCl, NaI, MeCN, reflux; ii, NaH, THF; iii, AcOH

To obtain dihydrocatalpalactone **9**, the above sequence of reactions was carried with the phosphorane **4b** and phthalaldehydic acid. The product was separated into acidic and neutral fractions. The acidic fraction **14b** (mixture of *E* and *Z* isomers) was again sensitive to cyclisation and was characterised only by NMR spectroscopy. The neutral fraction was the phthalide **13b**, $C_{17}H_{20}O_4$ (mixture of diastereoisomers). Compound **13b** on treatment with TMSCl–NaI in refluxing acetonitrile gave dihydrocatalpalactone **9**, $C_{15}H_{16}O_4$ (mixture of diastereoisomers) in 57% yield. The mixture was separated into diastereoisomeric racemates **9A** and **9B**. The major isomer had m.p. 151–152 °C and its NMR data were in agreement with those previously reported.[1] The minor isomer had m.p. 118–119 °C and is not reported in the literature. Dihydrocatalpalactone **9** (mixture of diastereoisomers) was obtained in better yield (72%) when the phosphosphorane **4c** (*i.e.*, methyl ester) was used in the above reaction sequence.

The acid (*E*)-**12**, needed for the preparation of compound **2** by selenolactonisation, was obtained by the reaction of dihydrocatalpalactone **9** (mixture of diastereoisomers) with NaH in THF, followed by careful acidification with acetic acid. The acid had structure (*E*)-**12** only, as indicated by its UV spectrum [λ_{max} 278 (ε 4000) and 219 nm (ε 3690)].

The acid (*E*)-**12** obtained above had NMR data [δ 1.11 (6 H, s, 2 × Me), 1.48–1.58 (2 H, m, CCH_2CH_2), 2.25–2.52 (2 H, m, $=CCH_2CH_2$), 7.25–7.82 (3 H, m, ArH), 8.14 (1 H, d, 6-H) and 8.20 (1 H, s, COC=CH)] different from those reported previously for this compound.[2b]

The selenolactonisation was carried out on acid (*E*)-**12** by reaction with benzeneselenenyl chloride and pyridine in dichloromethane. The selenide **2**, $C_{21}H_{20}O_4Se$ (mixture of diastereoisomers), obtained in 50% yield, was separated into the diastereoisomers **2A** and **2B**. Both isomers showed NMR spectral data in agreement with those for the reported isomers.[2b]

The selenide **2** (mixture of diastereoisomers) on treatment with H_2O_2 and a trace of acetic acid gave racemic catalpalactone **1** in quantitative yield.

Experimental

Capillary m.p.s were determined on a Gallenkamp m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 337 instrument, and ^1H NMR spectra for solutions in deuteriochloroform on a JEOL FX 90Q instrument. Tetramethylsilane was the internal standard, and coupling constants (*J*) are given in Hz. Elemental analyses were performed on a Hosli C,H analyser. Mass spectra were recorded on a Finnigan MAT 1020 GC/MS instrument. Solvents were dried and purified according to standard procedures. All extracts obtained were washed thoroughly with water and dried over sodium sulphate (anhydrous). All reactions were monitored by TLC (silica gel GF 254). Flash chromatography was performed on an EF-10 instrument using silica gel (finer than 200 mesh). Preparative HPLC was performed on a Jobin Yvon miniprep LC instrument using silica gel (TLC grade).

1-Ethoxycarbonylbut-3-enylidene(triphenyl)phosphorane **4a**.—A mixture of ethoxycarbonylmethylene(triphenyl)phosphorane (3.48 g, 10 mmol) and allyl bromide (3.02 g, 25 mmol) in dry chloroform (20 cm^3) was refluxed on an oil-bath for 6 h. Excess of solvent was distilled off and the residue was thoroughly dried *in vacuo*. To the dry, foamy residue was added water (100 cm^3), the mixture was extracted with benzene (2 × 25 cm^3). and the organic layer was separated and

discarded. The aqueous layer was made biphasic by addition of benzene (50 cm^3). To this mixture were added 2 drops of phenolphthaline. The mixture was basified with 2 mol dm^{-3} NaOH as indicated by the pink colour of the aq. layer. The organic layer was separated and the aq. layer was extracted with benzene (2 × 25 cm^3). The combined organic layers were washed with water, dried and concentrated under reduced pressure to give a thick syrupy residue (3.25 g, 84%) of compound **4a**, which was used without further purification.

1-*Ethoxycarbonyl*-4-*methylpent*-3-*enylidene*(*triphenyl*)-*phosphorane* **4b**.—Using the above procedure, ethoxycarbonylmethylene(triphenyl)phosphorane (3.48 g, 10 mmol) and 3,3-dimethylallyl bromide (3.72 g, 25 mmol) gave a thick syrupy residue (3.55 g, 85%) of compound **4b**, which was used without further purification.

1-*Methoxycarbonyl*-4-*methylpent*-3-*enylidene*(*triphenyl*)-*phosphorane* **4c**.—Using the above procedure, methoxycarbonylmethylene(triphenyl)phosphorane (3.34 g, 10 mmol) and 3,3-dimethylallyl bromide (3.72 g, 25 mmol) gave a thick syrupy residue (3.13 g, 78%) of compound **4c**, which was used without further purification.

Wittig Reaction of the Phosphorane **4a** *with Phthalic Anhydride*.—A mixture of phthalic anhydride (0.74 g, 5 mmol) and the phosphorane **4a** (1.95 g, 5 mmol) in dry benzene (10 cm^3) was refluxed for 5 h. The reaction mixture showed two spots on TLC (hexane–ethyl acetate, 90:10), R_f 0.4 and 0.5. Evaporation of solvent and flash chromatography of the residue with hexane–ethyl acetate (95:5) as eluent gave, from the initial fractions, *compound* (*E*)-**5** (0.58 g, 48%) as a thick, transparent syrup (Found: C, 69.6; H, 5.4. $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.46%); ν_{max}(Nujol)/cm^{-1} 1720 and 1790; δ_H 1.40 (3 H, t, *J* 8, CH_2Me), 3.55 (2 H, br d, *J* 7, =CHCH_2C), 4.43 (2 H, q, *J* 8, OCH_2Me), 5.05–5.47 (2 H, m, CH=CH_2), 5.74–6.32 (1 H, m, C*H*=CH_2), 7.60–8.21 (3 H, m, ArH) and 8.63 (1 H, dd, *J* 8 and 2, 4-H); and from later fractions, *compound* (*Z*)-**5** (0.3 g, 30%) as flakes, m.p. 75–76 °C (from ethyl acetate–hexane) (Found: C, 69.5; H, 5.3%); ν_{max}(Nujol)/cm^{-1} 1635, 1710 and 1780; δ_H 1.40 (3 H, t, *J* 8, CH_2*Me*), 3.62 (2 H, br d, *J* 5, =CCHCH_2), 4.40 (2 H, q, *J* 7, OCH_2Me), 5.08–5.42 (2 H, m, CH=CH_2), 5.77–6.30 (1 H, m, CH_2C*H*=CH_2), 7.60–8.00 (3 H, m, ArH) and 8.10 (1 H, dd, *J* 7 and 2, 7-H).

Wittig Reaction of the Phosphorane **4b** *with Phthalic Anhydride*.—From phthalic anhydride (0.74 g, 5 mmol) and the phosphorane **4b** (2.08 g, 5 mmol) was obtained *compound* (*E*)-**6** (0.60 g, 42%) as a solid, m.p. 61 °C (from ethyl acetate–hexane) (Found: C, 71.5; H, 6.8. $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34%); ν_{max}(Nujol)/cm^{-1} 1620, 1720 and 1790; δ_H 1.38 (3 H, t, *J* 8, CH_2*Me*), 1.60 (6 H, s, =CMe_2), 3.45 (2 H, d, *J* 7, =CCH_2CH), 4.40 (2 H, q, *J* 8, OCH_2Me), 5.13–5.38 (1 H, br t, *J* 7, =C*H*CH_2), 7.57–8.14 (3 H, m, ArH) and 8.50 (1 H, d, *J* 8, 4-H), as well as *compound* (*Z*)-**6** (0.50 g, 35%) as a solid, m.p. 91–92 °C (from ethyl acetate–hexane) (Found: C, 70.9; H, 6.4%); ν_{max}(Nujol)/cm^{-1} 1615, 1710 and 1780; δ_H 1.39 (3 H, t, *J* 8, CH_2*Me*), 1.74 (3 H, s, =CMe), 1.80 (3 H, s, =CMe), 3.54 (2 H, br d, *J* 7, =CHCH_2C=), 4.40 (2 H, q, *J* 8, OCH_2Me), 5.03–5.30 (1 H, br t, *J* 7, C*H*=CMe), 7.59–8.00 (3 H, m, ArH) and 8.08 (1 H, dd, *J* 8 and 2, 7-H).

Wittig Reaction of the Phosphorane **4c** *with Phthalic Anhydride*.—From phthalic anhydride (0.74 g, 5 mmol) and the phosphorane **4c** (2.01 g, 5 mmol) was obtained compound (*E*)-7 (0.68 g, 50%) as a solid, m.p. 91–92 °C (from ethyl acetate–hexane) (Found: C, 70.7; H, 5.8. $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92%); ν_{max}(Nujol)/cm^{-1} 1630, 1720 and 1800; δ_H 1.70 (3 H, s, =CMe), 1.76 (3 H, s, =CMe), 3.46 (2 H, d, *J* 7, CHCH_2C), 3.93 (3 H, s, OMe), 5.06–5.35 (1 H, br t, *J* 7, =CHCH_2), 7.55–8.16 (3 H, m, ArH) and 8.50 (1 H, d, *J* 8, 4-H); *m*/*z* 272 (M^+) and its *isomer* (*Z*)-7 (0.35 g, 26%) as needles, m.p. 112 °C (from ethyl acetate–hexane) (Found: C, 70.65; H, 6.0%); ν_{max}(Nujol)/cm^{-1} 1634, 1720 and 1790; δ_H 1.74 (3 H, s, =CMe), 1.80 (3 H, s, =CMe), 3.54 (2 H, br d, *J* 7, =CCH_2CH), 3.94 (3 H, s, OMe), 5.05–5.30 (1 H, br t, *J* 7, =C*H*CH_2), 7.60–8.00 (3 H, m, ArH) and 8.10 (1 H, dd, *J* 7 and 1, 7-H); *m*/*z* 272 (M^+).

Lactonisation of the Mixture (E)-**5** *and* (Z)-**5**.—The mixture of compounds (*E*)-**5** and (*Z*)-**5** (0.258 g, 1 mmol) was added to a solution of anhydrous sodium iodide (0.30 g, 2 mmol) and chloro(trimethyl)silane (0.25 cm^3, 2 mmol) in dry acetonitrile (5 cm^3) and the mixture was refluxed for 18 h. Solvent was removed under reduced pressure. Water (15 cm^3) was added to the dark residue and the mixture was extracted with diethyl ether (3 × 10 cm^3). The combined extract was washed successively with saturated aq. sodium thiosulphate (2 × 10 cm^3) and then with water and was then dried. Removal of solvent gave a crude solid, which was crystallised from chloroform–diethyl ether to give *compound* **8** (0.105 g, 46%) as pale yellow plates, m.p. 174 °C (Found: C, 67.7; H, 4.3. $C_{13}H_{10}O_4$ requires C, 67.80; H, 4.38%); ν_{max}(Nujol)/cm^{-1} 1685, 1770 and 1790; δ_H 1.53 (3 H, d, *J* 8, CH*Me*), 2.92 and 3.54 [(1 H, dd, *J* 14 and 6) and (1 H, dd, *J* 14 and 8), respectively, CHCH_2C=], 4.68–5.10 (1 H, m, OC*H*Me), 7.51–8.12 (3 H, m, ArH) and 9.20 (1 H, d, *J* 8, 4-H).

Lactonisation of the Mixture (E)-**6** *and* (Z)-**6**.—Lactonisation of the mixture of compounds (*E*)-**6** and (*Z*)-**6** (0.286 g, 1 mmol) gave *compound* **3** (0.139 g, 54%) as needles, m.p. 128 °C (from ethyl acetate–hexane) (Found: C, 70.0; H, 5.5. $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.46%); ν_{max}(Nujol)/cm^{-1} 1605, 1700 and 1795; δ_H 1.44 (6 H, s, CMe_2), 1.92 (2 H, t, *J* 7, $Me_2CCH_2CH_2$), 3.02 (2 H, t, *J* 7, CH_2CH_2C=), 7.57–8.10 (3 H, m, ArH) and 9.05 (1 H, d, *J* 8, 4-H); *m*/*z* 258 (M^+).

Lactonisation of the Mixture (E)-7 *and* (Z)-7.—Lactonisation of the mixture (*E*)-7 and (*Z*)-7 (0.272 g, 1 mmol) gave compound **3** (0.180 g, 70%), identical with the compound obtained earlier.

Wittig Reaction of Compound **4a** *with Phthalaldehydic Acid*.—Phthalaldehydic acid (0.75 g, 5 mmol) was added to a solution of the phosphorane **4a** (1.94 g, 5 mmol) in dry $CHCl_3$ (15 cm^3). The mixture was refluxed for 4 h. The solvent was removed under reduced pressure, the thick residue was dissolved in ethyl acetate and the solution washed thoroughly and successively with saturated aq. sodium hydrogencarbonate (3 × 20 cm^3) and with water. Concentration of the solution then gave a thick syrup, which on flash chromatography (hexane–ethyl acetate, 90:10) gave *compound* **13a** (0.78 g, 68%) as a thick, transparent liquid (Found: C, 69.0; H, 6.20. $C_{15}H_{16}O_4$ requires C, 69.21; H, 6.20%); ν_{max}(Nujol)/cm^{-1} 1730 and 1780; δ_H 1.11 (3 H, t, *J* 8, CH_2*Me*), 1.25 (3 H, t, *J* 8, CH_2Me), 2.28–3.25 (6 H, m, $COCHCH_2$), 4.08 (2 H, q, *J* 8, OCH_2Me), 4.24 (2 H, q, *J* 8, OCH_2Me), 4.95–5.28 (4 H, m, =CH_2), 5.77 (2 H, br d, *J* 5, OC*H*Ar), 5.60–6.11 (2 H, m, C*H*=CH_2), 7.31–7.88 (6 H, m, ArH) and 8.00 (2 H, br d, *J* 7, 7-H).

The combined aq. basic extract was acidified with dil. HCl and extracted with diethyl ether (3 × 20 cm^3) and the extract was washed with water and dried. Removal of solvent gave compound **14a** (0.260 g, 20%) as a thick syrup; δ_H 0.83 (3 H, t, *J* 8, CH_2*Me*), 1.28 (3 H, t, *J* 8, CH_2*Me*), 3.01 (2 H, br d, *J* 5, CH_2CH=), 3.15 (2 H, br d, *J* 6, CH_2CH=), 3.39 (2 H, q, *J* 8, OCH_2Me), 4.28 (2 H, q, *J* 8, OCH_2Me), 4.82 (4 H, m, CH_2C*H*=CH_2 and CO_2H, exchangeable with D_2O), 5.52–6.04

(4 H, m, $CH_2CH{=}CH_2$), 7.15–7.71 (8 H, m, ArH) and 8.05–8.30 (2 H, m, 6-H).

Conversion of Acid **14a** *into Lactone* **13a**.—The acid **14a** was converted into the lactone **13a** in quantitative yield by treatment with saturated ethereal HCl at room temperature for 24 h, or by loading onto silica gel and elution with hexane–ethyl acetate (95:5).

Wittig Reaction of Compound **4b** *with Phthalaldehydic Acid.*—Reaction of phthalaldehydic acid (0.75 g, 5 mmol) and the phosphorane **4b** (2.08 g, 5 mmol) gave, from the neutral extract after flash chromatography, *compound* **13b** (0.94 g, 65%) as a thick, transparent syrup (Found: C, 71.0; H, 6.8. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99%); ν_{max}(Nujol)/cm^{-1} 1604, 1735 and 1780; δ_H 1.10 (3 H, t, *J* 8, CH_2Me), 1.24 (3 H, t, *J* 8, CH_2Me), 1.51 (3 H, s, =CMe), 1.55 (3 H, s, =CMe), 1.64 (6 H, s, 2 × Me), 2.20–3.12 (6 H, m, $COCHCH_2$), 4.02 (2 H, q, *J* 8, OCH_2Me), 4.17 (2 H, q, *J* 8, OCH_2Me), 4.92–5.20 (2 H, m, CH=), 5.66 (2 H, t, OC*H*Ar), 7.33–7.75 (6 H, m, ArH) and 7.88 (2 H, dd, *J* 7 and 2, 7-H); and, from the aq. basic extract, compound **14b** (0.28 g, 20%) as a thick syrup; δ_H 0.88 (3 H, t, *J* 8, CH_2Me), 1.31 (3 H, t, *J* 8, CH_2Me), 1.43 (3 H, br s, =CMe), 1.62 (3 H, br s, =CMe), 1.68 (3 H, br s, =CMe), 1.74 (3 H, br s, =CMe), 2.78 (4 H, d, *J* 6, $CHCH_2$), 3.82 (2 H, q, *J* 8, OCH_2Me), 4.30 (2 H, q, *J* 8, OCH_2Me), 4.85–5.40 (2 H, m, $=CHCMe_2$), 7.10–7.70 (8 H, m, ArH), 7.91–8.15 (2 H, m, 6-H) and 9.00 (2 H, br s, exchangeable with D_2O, CO_2H).

Conversion of Acid **14b** *into Lactone* **13b**.—Compound **14b** was converted into compound **13b** quantitatively on chromatography over silica gel (finer than 200 mesh) with hexane–ethyl acetate (95:5) as eluent.

Wittig Reaction of Compound **4c** *with Phthalaldehydic Acid.*—Reaction of phthalaldehydic acid (0.75 g, 5 mmol) and the phosphorane **4c** (2.01 g, 5 mmol) gave, from the neutral organic extract, *compound* **13c** (0.76 g, 55%) as a thick, transparent syrup (Found: C, 69.8; H, 6.4. $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.61%); ν_{max}(Nujol)/cm^{-1} 1740 and 1780; δ_H 1.54 (6 H, s, 2 × CMe), 1.65 (6 H, s, 2 × Me), 2.25–3.17 (6 H, m, $COCHCH_2$), 3.64 (3 H, s, OMe), 3.80 (3 H, s, OMe), 4.95–5.25 (2 H, br t, $=CHCH_2$), 5.78 (2 H, br d, OC*H*Ar), 7.35–7.88 (6 H, m, ArH) and 7.95 (2 H, d, 7-H); and, from the basic aq. extract, compound **14c** (0.410 g, 30%) as a thick syrup; ν_{max}/cm^{-1} 2500–3600; δ_H 1.41 (3 H, s, =CMe), 1.66 (3 H, s, =CMe), 1.70 (3 H, s, =CMe), 1.77 (3 H, s, =CMe), 2.95 (2 H, d, *J* 7, $CHCH_2C{=}$), 3.15 (2 H, d, *J* 7, $CHCH_2C{=}$), 3.40 (3 H, s, OMe), 3.80 (3 H, s, OMe), 5.08 (1 H, br t, *J* 7, =CH), 5.25 (1 H, br t, *J* 7, =CH), 7.05–7.80 (8 H, m, ArH), 7.90–8.15 (2 H, m, 2-H) and 7.80–8.60 (2 H, br, exchangeable with D_2O, CO_2H).

Conversion of Acid **14c** *into Lactone* **13c**.—Compound **14c** was converted into **13c** quantitatively on chromatography (silica gel finer than 200 mesh, and elution with hexane–ethyl acetate, 95:5).

Lactonisation of Ester Lactone **13a**.—Lactonisation of compound **13a** (0.26 g, 1 mmol) gave a crude solid, which on crystallisation from chloroform–diethyl ether gave *dilactone* **15** (0.128 g, 55%) as a solid, m.p. 116–117 °C (Found: C, 66.9; H, 5.0. $C_{13}H_{12}O_4$ requires C, 67.23; H, 5.21%); ν_{max}(Nujol)/cm^{-1} 1775; δ_H 1.40 (3 H, t, *J* 6.5, $CHMe$), 1.50–2.57 (2 H, m, $CHCH_2CH$), 3.12–3.48 (1 H, m, $COCHCH_2$), 4.47–4.92 (1 H, m, OC*H*Me), 6.02 (1 H, d, *J* 3.5, OC*H*Ar) and 7.48–8.15 (4 H, m, ArH).

Lactonisation of Ester Lactone **13b**.—Lactonisation of compound **13b** (0.288 g, 1 mmol) gave a crude product, which was separated by HPLC on silica gel (TLC-grade) and elution with hexane–ethyl acetate (80:20). First fractions gave the major isomer **9A** (0.11 g, 42%) as a solid m.p. 151–152 °C (from $CHCl_3$–Et_2O) (lit.,[1] 153–154 °C); ν_{max}(Nujol)/cm^{-1} 1600, 1715 and 1765; δ_H 1.46 (6 H, s, CMe_2), 1.30–1.85 (4 H, m, CCH_2CH_2CH), 2.85–3.15 (1 H, m, $COCHCH_2$), 6.34 (1 H, d, *J* 3.5, ArC*H*O) and 7.40–8.00 (4 H, m, ArH). Later fractions gave *compound* **9B** (0.040 g, 15%) as needles, m.p. 118–119 °C (from $CHCl_3$–Et_2O) (Found: C, 69.3; H, 6.1. $C_{15}H_{16}O_4$ requires C, 69.21; H, 6.20%); ν_{max}(Nujol)/cm^{-1} 1600, 1700 and 1760; δ_H 1.15 (3 H, s, CMe), 1.43 (3 H, s, CMe), 1.50–2.00 (4 H, m, $CHCH_2CH_2C$), 3.25–3.55 (1 H, m, $COCHCH_2$), 6.32 (1 H, d, *J* 4, ArC*H*O), 7.33–7.88 (3 H, m, ArH) and 7.98 (1 H, dd, *J* 7 and 2, 7-H); *m/z* 260 (M^+).

Lactonisation of Ester Lactone **13c**.—Lactonisation of compound **13c** (0.274 g, 1 mmol) gave a crude compound, which on chromatography over silica gel with hexane–ethyl acetate (70:30) gave a solid (0.182 g, 70%) which, in its NMR spectrum, showed all the signals of isomers **9A** and **9B** mentioned above. The compound was used without further purification.

Conversion of Dilactone **15** *into Acid Lactone* (E)-**16**.—A solution of compound **15** (0.232 g, 1 mmol) in dry THF (5 cm^3) was treated with NaH (0.027 g, 1.2 mmol). The mixture was stirred at room temperature for 1 h. THF was removed under reduced pressure. To the residue was added ethyl acetate (10 cm^3), followed by dil. acetic acid until the aq. layer became acidic. The organic layer was separated and the aq. layer was extracted with ethyl acetate (2 × 5 cm^3). The combined organic layers were washed and dried. Evaporation of the solvent gave a thick syrup, which on crystallisation gave *compound* (E)-**16** (0.22 g, 95%) as crystals; m.p. 134 °C (from $CHCl_3$–MeOH) (Found: C, 67.4; H, 5.25. $C_{13}H_{12}O_4$ requires C, 67.23; H, 5.21%); ν_{max}(Nujol)/cm^{-1} 1700, 1750 and 2500–3600; δ_H 1.45 (3 H, d, *J* 7, $CHMe$), 2.64 (1 H, ddd, *J* 18, 7 and 4, $=CCH_2$), 3.28 (1 H, ddd, *J* 18, 8 and 2.5, $CHCH_2C{=}$), 4.58–4.90 (1 H, m, OC*H*Me), 7.38–7.86 (3 H, m, ArH) and 8.25 (2 H, m, 6-H and CH=CCO).

Conversion of Mixture **9A** *and* **9B** *into Acid* (E)-**12**.—A THF solution of the mixture of dilactones **9A** and **9B** (0.26 g, 1 mmol; in 5 cm^3) was treated with NaH (0.027 g, 1.2 mmol) and stirred at room temperature for 1 h. The mixture was acidified with acetic acid to give compound (*E*)-**12** (0.248 g, 95%) as needles, m.p. 155 °C (from $CHCl_3$–MeOH) (Found: C, 69.6; H, 6.45. Calc. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20%); ν_{max}(Nujol)/cm^{-1} 1700, 1720 and 2500–3600; δ_H 1.11 (6 H, s, CMe_2), 1.48–1.58 (2 H, m, CCH_2CH_2), 2.25–2.52 (2 H, m, $CH_2CH_2C{=}$), 7.25–7.82 (3 H, m, ArH), 8.14 (1 H, d, *J* 8, 6-H) and 8.20 (1 H, s, COC=C*H*Ar); *m/z* 260 (M^+).

Selenolactonisation of Acid (E)-**12**.—A solution of the acid (*E*)-**12** (0.260 g, 1 mmol) and pyridine (0.25 cm^3) in dry CH_2Cl_2 (10 cm^3) was treated with benzeneselenenyl chloride (0.192 g, 1 mmol) and the mixture was stirred at room temperature for 18 h. Dil. HCl was added to the mixture to remove pyridine. The organic layer was separated, washed and dried. On evaporation, an oily residue was obtained, which on preparative HPLC (silica gel, TLC-grade) with hexane–ethyl acetate (80:20) as eluent gave, in the initial fractions, benzeneselenenyl chloride (0.090 g recovery) and then compound **2A** (0.156 g, 37%) as a solid, m.p. 190–192 °C (from $CHCl_3$–Et_2O) (lit.,[2b] 192–195 °C); ν_{max}(Nujol)/cm^{-1} 1600, 1710 and 1780; δ_H 1.35 (3 H, s, CMe), 1.45 (3 H, s, CMe), 1.40–2.50 (4 H, m, $COCH_2CH_2C$), 6.10 (1 H, s, C*H*Ar), 7.20–8.00 (8 H, m, ArH) and 8.45 (1 H, d, *J* 7, 7-H), and finally compound **2B** (0.055 g, 13%) as a solid, m.p. 165–167 °C (from $CHCl_3$–Et_2O) (lit.,[2b] 168–172 °C);

ν_{max}(Nujol)/cm^{-1} 1600, 1700 and 1770; δ_H 1.00 (3 H, s, CMe), 1.42 (3 H, s, CMe), 1.35–2.40 (4 H, m, $COCH_2CH_2C$), 5.92 (1 H, s, COC*H*Ar) and 7.36–8.00 (9 H, m, ArH); *m/z* 416 (M^+).

Oxidation of Selenides **2A** *and* **2B** *to Catalpalactone.*—The diastereoisomeric mixture of selenides **2A** and **2B** (0.208 g, 0.5 mmol) was dissolved in CH_2Cl_2 (5 cm^3) and the solution was cooled to 0 °C. To the mixture were added acetic acid (one drop) and aq. 30% H_2O_2 (1 cm^3). The mixture was stirred for 1 h, water was added to the mixture, the organic layer was separated and the aq. layer was extracted with CH_2Cl_2 (2 × 5 cm^3). The combined organic phases were washed and dried. Evaporation of solvent gave a thick semi-solid, which on chromatography (silica gel) with hexane–ethyl acetate (80:20) gave catalpalactone **1** (0.116 g, 90%), m.p. 105–106 °C (from MeOH) (lit.,[1] 106–107 °C); ν_{max}(Nujol)/cm^{-1} 1600, 1720 and 1770; δ_H 1.30 (3 H, s, CMe), 1.43 (3 H, s, CMe), 2.45 (2 H, m, $=CHCH_2CMe_2$), 6.38 (1 H, br s, COOC*H*Ar), 6.65 (1 H, t, *J* 5, $CH_2CH{=}$), 7.40–7.90 (3 H, m, ArH) and 8.00 (1 H, br d, *J* 7, 7-H); *m/z* 258 (M^+).

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