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RADICAL CYCLISATIONS ONTO 2(5H)-FURANONE AND MALEATE ELECTROPHORES. AN APPROACH TO THE SPIRO- AND LINEAR-FUSED γ-LACTONE RING SYSTEMS FOUND IN THE GINKGOLIDES

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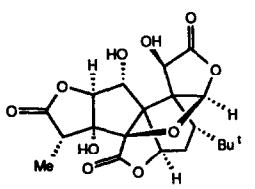
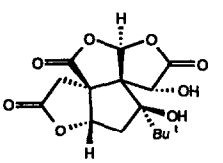
Summary: Intramolecular radical cyclisations involving α-acetal methyl centres, and 2(5H)-furanone and maleate electrophores, allow the facile synthesis of spiro- and linear-fused γ-lactone ring systems e.g. (5), (6), (7) and (8) present in the 'ginkgolides' viz (1) and (2) produced by the ginkgo tree Ginkgo biloba.

The hexa- and tetra-cyclic lactones ginkgolide B (1) and bilobalide (2) obtained from the leaves of Ginkgo biloba ("fossil tree") are amongst the most architecturally complex oxygen-heterocyclic natural products known.[1] Although extracts of the ginkgo tree have been used in Chinese medicine for centuries, the recent realisation that members of the "ginkgolides" are potent and specific antagonists of platelet activating factor (PAF), a fundamental mammalian cell regulator, has stimulated intense medicinal interest in this family of compounds.[2]



(1)



(2)

The ginkgolide molecular framework incorporates an array of carbocyclic, O-heterocyclic, lactonic and hydroxylactonic five-ring systems fused together in a range of linear-, angular-, and spiro-fused combinations. These unique structural features, in combination with their important biological properties, make the ginkgolides and their analogues attractive targets for synthesis.[3] Any approach to the synthesis of ginkgolides however must be based on sound methodology for elaborating the wide array of fused-ring γ-lactone sub-units found within their molecular frameworks. As a contribution to this problem we have examined the scope for intramolecular

radical cyclisations onto 2(5H)-furanone and maleate electrophores as a synthetic entry to some of the spiro- and linear-fused γ-lactone ring systems found in the ginkgolides. In this paper we show how this strategy allows the facile syntheses of the ring-fused lactones (5), (6), (7), and (8) from the easily available precursors (3), (4), (9), and (10) respectively (see Figure 1).[4]

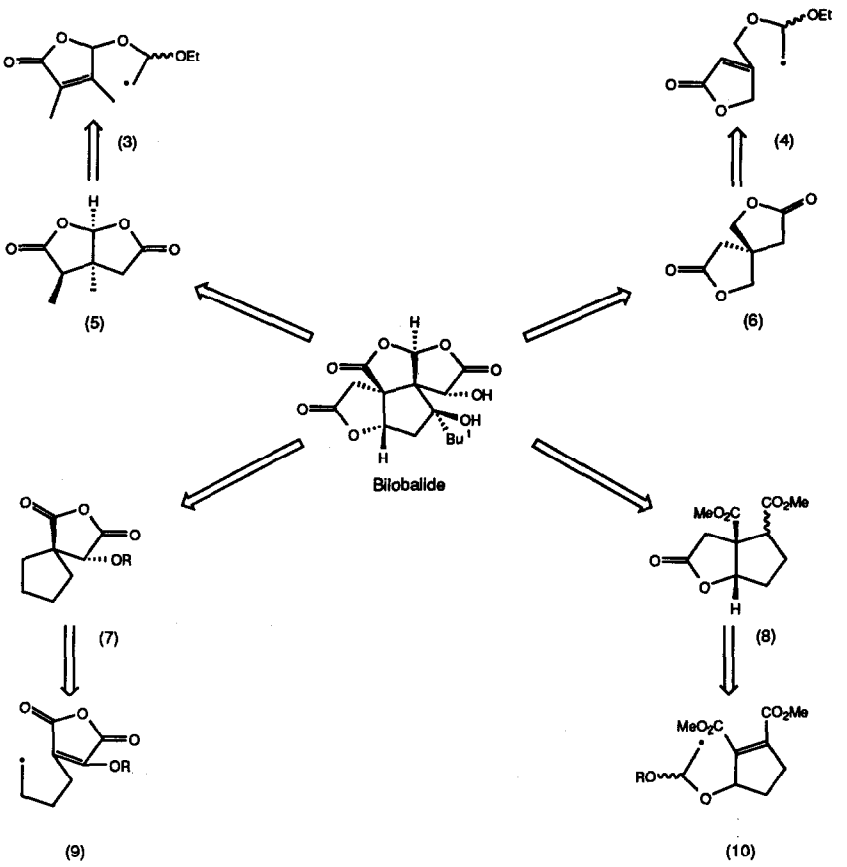
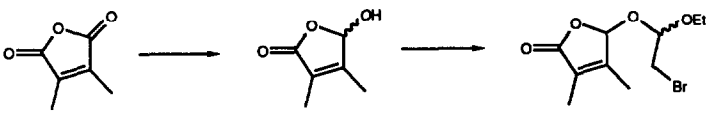


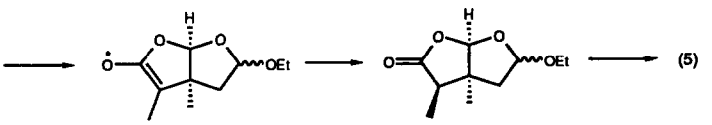
Figure 1

The synthesis of the extremely unusual linear fused acetal bis-lactone (5) can be achieved starting from dimethylmaleic anhydride. Thus, controlled reduction of 2,3-dimethylmaleic anhydride, using lithium tri-t-butoxyaluminium hydride in glyme at -20°C, first led to the 4-hydroxy-2-butenolide (11),[5] which was obtained as colourless crystals in 72% yield. Treatment of (11) with 1,2-dibromoethyl ethyl ether, generated in situ from bromine and ethyl vinyl ether,[6] in the presence of triethylamine in

cold dichloromethane, next led to a 1:1 mixture of diastereoisomers of the air and moisture sensitive bromo-acetal (12, 60%). Treatment of (12) with tri-n-butyltin hydride and catalytic 2,2'- azobis-(2-methylpropionitrile) (AIBN) in refluxing benzene afforded a mixture of diastereoisomers of the linear-fused lactone-acetal (14) resulting from facile 5-exo-trigonal cyclisation, in 80% yield. Finally, oxidation of (14) using one equivalent of m-chloroperbenzoic acid in dry dichloromethane containing a catalytic amount of boron trifluoride etherate[7] led to the acetal bis-lactone (5) which was produced as colourless needles. The anti-relationship between the two methyl groups in the bicyclic molecule (5) was established by n.O.e. difference spectroscopy; thus irradiation at δ 1.43 (angular methyl) in the p.m.r. spectrum enhanced the -CH(Me) signal at δ 2.7 by 2.4%, and irradiation at δ 1.27 enhanced the signal at δ 5.7 (OCHO) by 1.6%. The anti-relationship between the two methyl groups in (5) is anticipated, following quenching of the product radical centre (13) from cyclisation of (12), from the least hindered, convex face of the molecule.

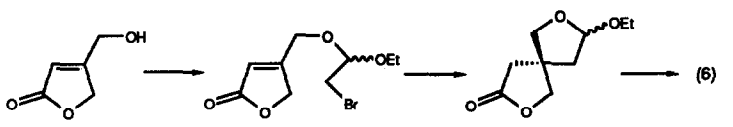


(11) (12)



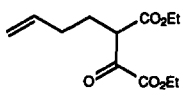
(13) (14)

The synthesis of the spiro-fused bis-lactone (6) was achieved via radical cyclisation onto the 2(5H)-furanone double bond in the intermediate (16). Thus, treatment of the known natural product 3-hydroxymethyl 2-butenolide (15)[8] with a mixture of bromine in ethyl vinyl ether in the presence of triethylamine at -78°C, first afforded the bromo-acetal (16). Reaction between (16) and tri-n-butyltin hydride-AIBN then led to the spiro system (17, 88%), which upon oxidation using Jones reagent at 0°C gave the extremely polar and partially water soluble spiro bis-lactone (6)[9] as colourless rectangular crystals.

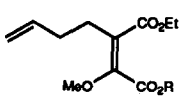


(15) (16) (17)

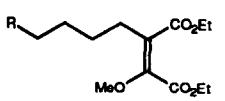
To explore the use of other 'acrylate' electrophores in radical cyclisations leading to the spiro-fused oxyanhydride (7) we synthesised the substituted methoxymaleic anhydride (22) together with the substituted maleate (20b). Thus, a Claisen condensation between ethyl hex-5-enoate and diethyl oxalate followed by methylation of the resulting keto-ester (18), using alkaline dimethyl sulphate, first gave the methyl ether (19a). Hydroboration-oxidation of (19a) next led to the carbinol (20a), which was then converted into the bromide (20b). Saponification of the substituted



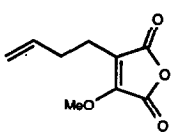
(18)



(19)
a R = Et
b R = H



(20)
a R = OH
b R = Br



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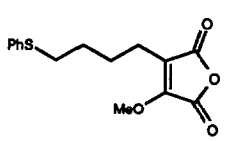
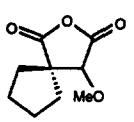
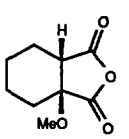


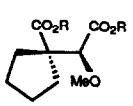
(22)



(7)



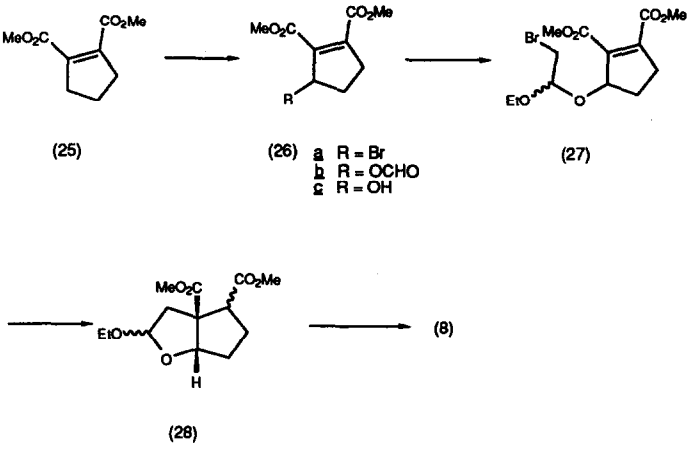
(23)



(24)
a R = Et
b R = H

maleate (19a) in the presence of aqueous methanolic potassium hydroxide followed by treatment with thionyl chloride provided the corresponding maleic anhydride (21), which upon treatment with thiophenol in the presence of AIBN at 80°C led to the crystalline phenylsulphide (22). All attempts to cyclise (22) to the spiro-anhydride (7) [or to (23)], under a diverse range of radical initiation conditions met with failure; either (22) was recovered unchanged or decomposition of the starting material occurred. By contrast, cyclisation of the bromide (20b) proceeded smoothly in the presence of tri-n-butyltin hydride and AIBN to give the spiro bis-ester (24a) in 91% yield; none of the product resulting from 6-endo trigonal cyclisation was detected. Saponification of (24a) in the presence of methanolic potassium hydroxide, followed by cyclodehydration of the resulting succinic acid (24b), using hot thionyl chloride, finally provided the desired oxyanhydride (7).

As a corollary to the above studies, we also prepared the linear-fused lactone bis-ester (8) starting from the cyclopentene diester (25)[10] following: allylic bromination to (26a), displacement by formate and hydrolysis to (26c), conversion to the bromo-acetal (27) and finally radical cyclisation (Bu_3SnH - AIBN) to (28) and Jones oxidation. This sequence resulted in the formation of a 1:1 mixture of α- and β- sec-ester epimers of the desired bicyclic lactone (8) in good overall yield.



The present studies have demonstrated beyond doubt the potential for the 2(5H) furanone and maleate electrophores in intramolecular free-radical cyclisations leading to complex ring-fused lactone systems containing a

plethora of quaternary carbon centres. It now remains to be established how generally useful these radical cyclisations are when using advanced, more elaborately substituted intermediates en route to the ginkgolides; this work is in progress.

EXPERIMENTAL

For general experimental details see ref. 11.

5-Hydroxy-3,4-dimethylfuran-2(5H)-one (11)[5]. - A solution of dry t-butanol (0.99 ml; 3.3 equiv.) in dry glyme (3 ml) was added dropwise during 5-10 min. to a cooled (water bath) suspension of lithium aluminium hydride (132 mg; 1.1 equiv.) in dry glyme (5 ml). The resulting suspension of lithium tri-t-butoxy aluminium hydride was added dropwise during 10 min. to a stirred solution of 2,3-dimethylmaleic anhydride (400 mg; 1.0 equiv.) in dry glyme (4 ml) which had been cooled to -15°C (dry ice-CCl_4). The mixture was stirred at -15°C for 1 hr. and then at 25°C for 16 h. The mixture was cooled to 0°C and acidified by the addition of 2M sulphuric acid. The organic layer was separated, and the aqueous layer was then extracted with ether (3 x 20 ml). The combined organic extracts were dried and evaporated in vacuo, and the residue was then purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (4:1, then pure ether) as eluant to give the hydroxy-butenolide (293 mg; 72%) as a crystalline white solid, m.p. 81-82°C [petroleum ether (b.p. 80-100°C)-ether], ν_{max} ($CHCl_3$) 3310 (OH), 1750, 1690, 980 $cm.^{-1}$, δ_H 6.0 (OC<u>H</u>O), 5.7 (O<u>H</u>), 2.05 (C<u>H</u>$_3$), 1.85 (C<u>H</u>$_3$), (Found: C, 56.1; H, 6.4; m/z 128.021; Calc. for $C_6H_8O_3$: C, 56.2; H, 6.3%; <u>M</u> 128.0368.

5-(1-Ethoxy-2-bromoethoxy)-3,4-dimethylfuran-2(5H)-one (12). - A solution of bromine (242 µl; 2.0 equiv.) in dry methylene chloride (10 ml) was cooled to -78°C and titrated with ethyl vinyl ether (~450 µl) until a pale-yellow solution resulted. Dry triethylamine (818 µl; 2.5 equiv.) was added, followed by a solution of 5-hydroxy-3,4-dimethylfuran-2(5<u>H</u>)-one (300 mg; 1.0 equiv.) in dry methylene chloride (2 ml). The mixture was allowed to warm to room temperature, where it was stirred for 18 h. The solution was evaporated to dryness in vacuo, and the residue was then purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (7:1, then 1:1) as eluant to give 1:1 mixture of diastereoisomers of the bromo-acetal (390 mg; 60%) as a

colourless oil, ν_{max} ($CHCl_3$) 1765, 1695 and 970 $cm.^{-1}$, δ_H (faster moving diastereoisomer) 5.87 [C(O)OCHO], 5.0 (t, J 5.5 Hz, CHOEt), 3.8-3.5 (m, CH_3CH_2O), 3.45 (d, J 5.5 Hz, CH_2Br), 2.0 (CH_3), 1.8 CH_3), 1.25 (t, J 7Hz, CH_3CH_2O), δ_H (slower moving diastereoisomer) 5.83 [C(O)OCHO], 5.0 (t, J 5.5 Hz, CHOEt), 3.8-3.5 (m, CH_3CH_2O), 3.4 (d, J 5.5 Hz, CH_2Br), 1.98 (CH_3), 1.84 (CH_3), 1.30 (t, J 7Hz, CH_3CH_2O), (Found: m/z 111.0436; $C_6H_7O_2$ (M-OCH(OEt)CH_2Br) requires: 111.0437).

3α,3aβ-Dimethyl-5-ethoxy-3a,4,5,6aβ-tetrahydro-furo[2,3-b]furan2(3H)-one (14). - Tri-n-butyltin hydride (465 µl; 2.0 equiv.) was added to a degassed (N_2) solution of the bromo-acetal (12) (240 mg; 1.0 equiv.) and AIBN (28 mg; 0.2 equiv.) in dry benzene (43 ml), and the mixture was then heated under reflux for 2 h. The solution was cooled to room temperature, and the solvent was then evaporated in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (6:1 then 1:1) as eluant to give a mixture of diastereoisomers of the cyclic acetal (380 mg; 80%) as a colourless oil, ν_{max} ($CHCl_3$) 1775 $cm.^{-1}$, δ_H 5.63, 5.61 (OCHO), 5.3-5.2 (m, CHOEt), 3.9-3.2 (m, CH_3CH_2O), 2.6-2.2 (2xq, J~7 Hz, $CH_3CHC(O)$), 2.07-1.7 (m, CH_2CHOEt), 1.37 (CH_3), 1.4-1.1 (2xt, J 7 Hz, CH_3CH_2O), 1.22, 1.14 (d, J 7Hz, CH_3CH); (Found: m/z 199.0912; $C_{10}H_{16}O_4$ (M-1) requires: 199.0854).

3a,6aβ-Dihydro-3α,3ab-dimethyl-furo[2,3-b]furan-2,5(3H,4H)-dione (5). - m-Chloroperbenzoic acid (85 mg; 85%, remainder m-chlorobenzoic acid, 1.0 equiv.) was added to a solution of the acetal (14) (76 mg; 1.0 equiv.) in dry methylene chloride (2 ml) containing boron trifluoride etherate (1 drop, catalytic), and the clear solution was then stirred at room temperature for 24 h. (during which time a thick, white precipitate formed). The mixture was diluted with ether (30 ml), and then washed successively with saturated sodium bicarbonate solution (2 x 5 ml) and brine (1 x 5 ml). After drying and evaporation of the solvent in vacuo, the residue was purified by chromatography using light petroleum (b.p.40°-60°C)- ether (1:2) as eluant to give the bis-"lactone-acetal" (43 mg; 66%) as colourless needles, m.p. 116.5-117°C [petroleum ether (b.p. 80-100°C)-ether], ν_{max} 1800 and 1000 $cm.^{-1}$, δ_H 5.87 (OCHO), 2.74-2.65 [q, J 7.2Hz, $CH_3CHC(O)$], 2.61, 2.32 [dd of AB system, J 18Hz, $CH_2C(O)$], 1.43 (CH_3), 1.28, 1.26 (d, J 7.2Hz, CH_3CH). Irradiation at δ1.43 gave an n.O.e. enhancement at δ2.74/2.65, δ2.32 and δ5.87 of 2.4%, 1.8% and 1.5% respectively, and irradiation at δ1.28/1.26 gave an enhancement at δ2.74-2.65 of 7.5%; δ_C 174, 173, 106(d), 47, 44(d), 35(t), 22(q), 9(q); (Found: C, 56.6; H, 6.1%; m/z 126.0681; $C_8H_{10}O_4$ requires: C, 56.5; H, 5.9%; ($M-CO_2$) 126.0681).

Ethyl 3,3-Diacetoxymethylacrylate[8]. - A solution of triethylphosphonoacetate (10.32 g; 1.0 equiv.) in dry tetrahydrofuran (29 ml) was added dropwise during 20 min. to a suspension of sodium hydride (60% dispersion in mineral oil; 1.93 g; 1.05 equiv.) in dry tetrahydrofuran (86 ml), and the clear brown solution was then stirred at room temperature for 1 h. A solution of diacetoxyacetone (8.0 g; 1.0 equiv.) in dry tetrahydrofuran (23 ml) was added dropwise during 20 min., and the resulting brown gummy solution was stirred at room temperature for 0.5 h. and then heated under reflux for 0.5 h. The mixture was allowed to cool to room temperature, after which time it was poured into water (500 ml) and extracted with ether (5 x 75 ml). The combined ethereal extracts were washed with brine (1 x 100 ml) and then dried. The solvent was evaporated in vacuo and the residue was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (3:1) as eluant to give the tri-ester (5.77 g; 49%) as a colourless oil, ν_{max} (film) 1745, 1720, 1375, 1225, 885 $cm.^{-1}$, δ_H 6.0 (m, =C<u>H</u>), 5.25 (C<u>H</u>$_2$OAc), 4.75 (C<u>H</u>$_2$OAc), 4.2 (q, <u>J</u> 7Hz, C<u>H</u>$_2$CH$_3$), 2.1 (C<u>H</u>$_3$CO), 2.07 (C<u>H</u>$_3$CO), 1.3 (t, <u>J</u> 7Hz, C<u>H</u>$_3$CH$_2$O); (Found: C, 53.9; H, 6.5; Calc. for $C_{11}H_{16}O_6$: C, 54.1; H, 6.6%).

4-Hydroxymethylfuran-2(5H)-one (15). - A solution of the tri-ester (5.5 g; 1.0 equiv.) in a mixture of methanol (5.5 ml) and dilute sulphuric acid (10% solution; 5.5 ml) was heated under reflux for 2 h. The mixture was cooled to room temperature, and then neutralised by the addition of solid sodium bicarbonate. Excess solid was removed by filtration, and the residue was then washed thoroughly with ethyl acetate. The filtrate was extracted with ethyl acetate (10 x 10 ml) and the combined organic extracts were then dried ($MgSO_4$) and evaporated in vacuo to leave the butenolide (2.01 g; 83%) as a white, crystalline solid, m.p. 50-51°C (ether) (Lit.[8] m.p. 51-3°C), ν_{max} ($CHCl_3$), 3420 (OH), 1790, 1650, 1140 $cm.^{-1}$, δ_H 6.0 (t, <u>J</u> 1.8Hz, :C<u>H</u>), 4.88 (d, <u>J</u> 1.8Hz, C<u>H</u>$_2$OCO), 4.56 (C<u>H</u>$_2$OH), 3.66 (OH); (Found: C, 52.5; H, 5.2; m/z 114.0315; Calc. for $C_5H_6O_3$: C, 52.7; H, 5.3%; <u>M</u> 114.0315).

4-(2-Bromo-1-ethoxy)ethoxymethyl-furan-2(5H)one (16). - A solution of bromine (425 µl; 2.0 equiv.) in dry methylene chloride (18 ml) was cooled to -78°C and titrated with ethyl vinyl ether (850 µl) until a colourless solution resulted. A solution of the hydroxy butenolide (15) (500 mg; 1.0 equiv.) and dry triethylamine (1.53 ml; 2.5 equiv.) in dry methylene chloride (2 ml) was added, and the mixture was then allowed to warm to room temperature. The mixture was stirred at room temperature for 7 h, and then poured into 1<u>M</u> hydrochloric acid solution (20 ml). The layers were separated, and the aqueous phase was then extracted with ethyl acetate (3 x 15 ml). The

combined organic phases were dried, and evaporated in vacuo to leave a residue which was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (1:1) as eluant to give the bromo-acetal (630 mg; 78%) as a pale-yellow oil, ν_{max} ($CHCl_3$) 1785, 1755, 1655, 1135 cm.$^{-1}$, δ_H 6.0 (t, J 1.75Hz, :CH), 4.88 (d, J 1.75Hz, CH_2OCO), 4.78 (t, J 5.3Hz, OCHOEt), 4.55 (CH_2O), 3.8-3.54 (dq, J~5.3Hz, OCH_2CH_3), 3.4 (CH_2Br), 1.24 (t, J 5.3Hz, CH_3CH_2O); (Found: m/z 220.9681. $C_7H_8BrO_3$ (M-EtO) requires: 220.9725).

8-Ethoxy-2,7-dioxaspiro[4.4]nonane-3-one (17). - Tri-n-butyltin hydride (1.26 ml; 2.0 equiv.) was added to a degassed (N_2) solution of the bromo-acetal (16) (620 mg; 1.0 equiv.) and AIBN (77 mg; 0.2 equiv.) in dry benzene (117 ml), and the solution was then heated under reflux for 2 h. The solution was cooled to room temperature, and the benzene was then evaporated in vacuo. The residue was dissolved in acetonitrile (30 ml) and washed with pentane (3 x 15 ml), and the acetonitrile layer was then evaporated in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (4:1, then 1:1, then 1:2) as eluant to give the bicyclic acetal (372 mg; 85%) as a colourless oil, ν_{max} ($CHCl_3$) 1780, 1380, 1350 cm.$^{-1}$, δ_H 5.1 (m, OCHOEt), 4.15 (AB quartet, J 9.2Hz, CH_2O), 3.8-3.3 (complex m, CH_3CH_2O), 3.85 (CH_3O), 2.6 (m, CH_2CO), 2.0 (m, CH_2CH), 1.2 (t, J 7, CH_3CH_2); (Found: m/z 186.0896. $C_9H_{14}O_4$ requires M 186.0901).

2,7-Dioxaspiro[4.4]nonane-3,8-dione (6). - A solution of the bicyclic acetal (17) (250 mg) in acetone (1 ml) was titrated with Jones reagent to a permanent red end-point. The mixture was evaporated to dryness in vacuo, and the residue was then purified by chromatography using ethyl acetate as eluant to give the bis-lactone (144 mg; 68%) as colourless rectangular crystals, m.p. 211-213°C (ethyl acetate) (Lit.[9] m.p. 206-208°C), ν_{max} ($CHCl_3$) 1785 cm.$^{-1}$, δ_H (acetone D_6) 4.40 [2 x $CH_2OC(O)$], 2.82, 2.80 (2 x dd, J 17.8Hz, CH_2CO). δ_C (acetone D_6) 206, 76(t), 45, 39(t); (Found: C, 53.8; H, 5.2; m/z 156.0425); Calc. for $C_7H_8O_4$: C, 53.8; H, 5.2%; M 156.0429).

Ethyl 3-Carbethoxy-2-oxo-hept-6-enoate (18). - Finely chopped sodium metal (690 mg; 1.1 equiv.) was added during 0.75 h. to a solution of ethyl hex-5-enoate (3.5 g; 1.0 equiv.), diethyl oxalate (4.1 ml; 1.1 equiv.) and dry ethanol (3.5 ml; 2.2 equiv.) in dry benzene (30 ml), and the mixture was then heated at 50°C for 19 h. The resulting brown solution was cooled to 0°C, and then acidified by the addition of 2M hydrochloric acid. The layers were separated, and the aqueous phase was then extracted with ether (3 x 20 ml). The combined organic phases were washed with brine (2 x 30 ml), dried

and evaporated in vacuo to leave a brown oily residue, which was purified by chromatography using light petroleum (b.p. 40°-60°C)ether (7:1) as eluant to give the keto di-ester (3.16 g; 53%) as a pale-yellow oil, ν_{max} (film) 3480(w), 1730, 1645, 920 cm.$^{-1}$, δ_H 12.6 [:C(OH)], 5.7 (m, :CH), 5.0 (m, CH_2), 4.4-4.0 (m, 2 x OCH_2CH_3), 2.1-2.0 (m, $-CH_2CH_2-$), 1.5-1.2 (m, 2 x CH_2CH_2), (Found: m/z 242.1175; $C_{12}H_{18}O_5$ requires M 242.1197).

Ethyl 3-Carboethoxy-2-methoxyhept-2,6-dienoate (19a). - Dry dimethyl sulphate (220 µl; 1.1 equiv.) was added dropwise during 12 min. to a refluxing solution of the keto di-ester (18) (500 mg; 1.0 equiv.) in dry acetone (15 ml) containing potassium carbonate (428 mg; 1.5 equiv.). The mixture was heated under reflux for a further 2 h., and then cooled to room temperature and poured into water (40 ml). The aqueous solution was extracted with ether (3 x 20 ml) and the combined ether extracts were then washed with water (1 x 20 ml) and brine (1 x 20 ml). Evaporation of the dried extracts left a residue which was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (6:1, then 4:1) as eluant to give the methyl enol ether (350 mg; 66%) as a colourless oil, ν_{max} (film) 1735, 1705, 1630, 1300 cm.$^{-1}$, δ_H 5.85-5.67 (m, :CH), 5.1-4.9 (m, :CH_2), 3.7 (OCH_3), 2.5-2.1 (m, $-CH_2CH_2-$), 1.5-1.2 (m, 2 x OCH_2CH_3), (Found: m/z 256.1301; $C_{13}H_{20}O_5$ requires: M 256.1350).

Ethyl 3-Carboethoxy-7-hydroxy-2-methoxyhept-2-enoate (20a). - Boranedimethyl sulphide complex (10.0M liquid; 58 µl; 0.72 equiv.) was added to a stirred solution of the alkene (19a) (200 mg; 1.0 equiv.) in dry tetrahydrofuran (5 ml) and the colourless solution was then stirred at room temperature for 15 min. The mixture was cooled to 10°C, then 3M sodium hydroxide solution (400 µl; 1.5 equiv.) was added cautiously, followed by the dropwise addition of 30% aqueous hydrogen peroxide solution. The mixture was stirred at room temperature for 30 min. (during which time a white, gummy precipitate formed), then poured into water (15 ml) and the aqueous solution was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine (1 x 15 ml), then dried and the solvent was evaporated in vacuo to leave the alcohol (160 mg; 75%) as a colourless oil which was used without further purification, ν_{max} (film) 3440, 1730, 1715, 1630 cm.$^{-1}$, δ_H 4.4-4.0 (m, 2 x OCH_2CH_3 and -OH), 3.71 (OCH_3), 3.62 (t, J 5.9 Hz, CH_2OH), 2.35 (t, J 6.8 Hz, CH_2C:), 1.5-1.34 (m, $-CH_2CH_2-$), 1.29-1.18 (m, 2 x OCH_2CH_3), (Found: m/z 274.1463. $C_{13}H_{22}O_6$ requires: M 274.1509).

Ethyl 7-Bromo-3-carboethoxy-2-methoxyhept-2-enoate (20b). - A solution of 1,2-dibromotetrachloroethane (117 mg; 1.1 equiv.) in dry ether (2 ml) was added dropwise during 2 min. to a cooled (0°C) solution of the alcohol (20a) (90 mg; 1.0 equiv.) and triphenylphosphine (129 mg; 1.5 equiv.) in dry ether (5 ml), and the mixture was then stirred at 0°C for 10 min., (during which time a thick, white precipitate formed). The mixture was absorbed onto silica and purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (6:1 then 1:1) as eluant to give the bromide (84 mg; 76%) as a colourless oil, ν_{max} (film) 1730, 1715, 1630 cm.$^{-1}$, δ_H 4.45-4.05 (2 x q, J 7.0 Hz, $OC\underline{H}_2CH_3$), 3.71 ($OC\underline{H}_3$), 3.47-3.32 (t, J 6.3 Hz, $C\underline{H}_2Br$), 2.43-2.27 (t, J 7.0 Hz, $C\underline{H}_2C$:), 2.01-1.57 (m, $C\underline{H}_2C\underline{H}_2$), 1.42-1.18 (2 x t, J 7.0 Hz, $OCH_2C\underline{H}_3$), (Found: m/z 337.0578; $C_{13}H_{21}BrO_5$ requires: M 337.0566).

3-Carbeothoxy-2-methoxyhept-2,6-dienoic acid (19b). - Solid potassium hydroxide (168 mg; 2.2 equiv.) was added to a solution of the di-ester (19a) (350 mg; 1.0 equiv.) in a mixture of methanol (3 ml) and water (1 ml), and the translucent yellow solution was then stirred at room temperature for 7 h. The mixture was acidified at 0°C by the addition of 2M hydrochloric acid, and the aqueous solution was then extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine (1 x 20 ml) and then dried. The solvent was evaporated in vacuo to leave the mono-acid (250 mg; 80%) as a pale-yellow oil which was used without further purification, ν_{max} (film) 3640-2340 (br, OH), 1730-1700, 1630 cm.$^{-1}$, δ_H 10.2 ($CO_2\underline{H}$), 5.97-5.67 (m, :C$\underline{H}$), 5.1-4.9 (m, $-C\underline{H}_2C\underline{H}_2-$), 1.3 (t, J 7.2 Hz, $OCH_2C\underline{H}_3$); (Found: m/z 187.0619. $C_8H_{11}O_5$ ($M-C_3H_5$) requires: 187.0632).

2-(3-Buten-1-yl)-3-methoxymaleic anhydride (21). - A solution of the mono acid (19b), (213 mg; 1.0 equiv.) in freshly distilled thionyl chloride (1.1 ml; 16.0 equiv.) was heated under reflux in an atmosphere of nitrogen for 0.75 h. The mixture was cooled to room temperature, and the excess thionyl chloride was then removed by distillation at reduced pressure. The brown oily residue was purified by chromatography using light petroleum (b.p. 40°C-60°C)- ether (5:1) as eluant to afford the sensitive anhydride (112 mg; 66%) as a colourless oil, ν_{max} (film) 1840, 1770, 1670, 1460, 750 cm.$^{-1}$, δ_H 5.8-5.7 (m, :C$\underline{H}$), 5.09-5.0 (m, :C$\underline{H}_2$), 4.25 ($OC\underline{H}_3$), 2.54-2.50 (m, $-C\underline{H}_2-$), 2.36-2.31 (m, $-C\underline{H}_2-$), δ_C 164.3, 160.5, 153.5(d), 135.5(d), 135.9(d), 117.8, 116.2(t), 59.85, 31.4(t), 21.6(t); (Found: m/z 182.0560. $C_9H_{10}O_4$ requires: M 182.0543).

2-(4-Phenylthio-but-1-yl)-3-methoxymaleic anhydride (22). - A solution of the anhydride (21) (110 mg; 1.0 equiv.) and AIBN (41 mg; 0.41 equiv.) in freshly distilled thiophenol (0.5 ml) was heated at 80°C under an argon atmosphere for 1 h. The mixture was cooled to room temperature, and excess thiophenol was then removed by distillation at reduced pressure. The residual yellow oil was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (5:1, then 1:1) as eluant to give the sulphide (140 mg; 80%) as a crystalline white solid, m.p. 44-45°C [petroleum ether (b.p. 80-100°C)-ether], ν_{max} (film) 1845, 1770, 1670, 925, 750 $cm.^{-1}$, δ_H 7.32-7.15 (m, aromatics), 4.2 ($OC\underline{H}_3$), 2.92 (t, J 6.7 Hz, $C\underline{H}_2SPh$), 2.39 (t, J 7.2 Hz, $:CC\underline{H}_2$), 1.73-1.62 (m, $-C\underline{H}_2C\underline{H}_2-$), δ_C 164.4, 160.4, 153.3(d), 136.0, 129.1(d), 128.7(d), 125.8(d), 118.1, 59.7, 32.9(t), 28.3(t), 26.5(t), 21.6(t); (Found: C, 61.5; H, 5.4; S, 11.0; $C_{15}H_{16}SO_4$ requires: C, 61.6; H, 5.5; S, 11.0%).

Ethyl 2-(1-Carbeothoxycyclopent-1-yl)-2-methoxyethanoate (24a). - Tri-n-butyltin hydride (96 µl; 2.0 equiv.) was added to a degassed (N_2) solution of the bromide (20b) (60 mg; 1.0 equiv.) and AIBN (6 mg; 0.2 equiv.) in dry benzene (9 ml), and the mixture was then heated under reflux for 1 h. The mixture was cooled to room temperature, and the solvent was then removed in vacuo. The residue was purified by chromatography using light petroleum (b.p.40°C-60°C)-ether (19:1 then 4:1) as eluant to give the spiro bis-ester (42 mg; 91%) as a colourless oil, ν_{max} (film) 1730, 1030 $cm.^{-1}$, δ_H 4.34-4.12 (m, 2 x $OC\underline{H}_2CH_3$), 4.12 ($C\underline{H}OMe$), 3.43 ($OC\underline{H}_3$), 2.09-1.58 (8H, methylene envelope), 1.30-1.25 (m, 2 x $OCH_2C\underline{H}_3$); δ_C 175.3, 170.9, 83.9(d), 60.9(t), 60.8(t), 59.2(q), 57.2, 33.2(t), 31.3(t), 25.9(t), 25.8(t), 14.2(q), 14.1(q); (Found: m/z 258.1451; $C_{13}H_{22}O_5$ requires: M 258.1451).

2-(1-Carboxycyclopent-1-yl)-2-methoxyethanoic acid (24b). - A solution of the di-ester (24b) (36 mg; 1.0 equiv.) and solid potassium hydroxide (46 mg; 5.9 equiv.) in a mixture of methanol (0.8 ml) and water (0.2 ml) was heated under reflux for 8 h. The mixture was cooled to room temperature, and then acidified by the addition of 2M hydrochloric acid. Brine (5 ml) was added, and the aqueous solution was then extracted with ethyl acetate (3 x 5 ml). The combined ethyl acetate extracts were dried, and then evaporated in vacuo to leave the di-acid (28 mg; 88%) as an oil which crystallised on standing, m.p. 127°-127.5°C [petroleum ether (b.p.80°-100°C)-ether], ν_{max} ($CHCl_3$) 3600-2300 (br,-OH), 1710 $cm.^{-1}$, δ_H 7.8 (br 2 x $CO_2\underline{H}$), 3.91 ($C\underline{H}OCH_3$), 3.28 ($OC\underline{H}_3$), 2.0-1.4 (8H, m); (Found: C, 53.6, H, 7.1; $C_9H_{14}O_5$ requires: C, 53.4, H, 7.0%).

2-Methoxy-3-spirocyclopentylmaleic anhydride (7). - A solution of the di-acid (24b) (25 mg; 1.0 equiv.) in freshly distilled thionyl chloride (0.4 ml) was heated under reflux in an atmosphere of nitrogen for 2.5 h. Excess thionyl chloride was removed by distillation at reduced pressure, and the residue was then purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (2:1, then pure ether) as eluant to give the anhydride (18 mg; 79%) as a colourless oil, ν_{max} ($CHCl_3$), 1860, 1780 $cm.^{-1}$, δ_H 4.0 ($C\underline{H}OCH_3$), 3.68 ($OC\underline{H}_3$), 2.2-1.8 (8H, m); (Found: m/z 112.0855. $C_7H_{12}O$ ($M-C_2O_3$) requires: 112.0823).

Dimethyl 3-bromocyclopentene-1,2-dicarboxylate (26a). - A solution of dimethylcyclopentene-1,2-dicarboxylate (200 mg; 1.0 equiv.)[10] and N-bromosuccinimide (203 mg; 1.05 equiv.) in chloroform (10 ml) was irradiated with a 300W sun lamp for 15 min. while maintaining a gentle reflux. The mixture was cooled to room temperature, and the solvent was then evaporated in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40°-60°C)- ether (4:1) as eluant to give the bromide (211 mg; 74%) as a colourless oil, ν_{max} (film) 1725, 1640, 1000 $cm.^{-1}$, δ_H 5.2 (m, C<u>H</u>Br), 3.82 (2 x $OC\underline{H}_3$), 2.7-2.5 (m, methylene envelope); (Found: m/z 183.0639. $C_9H_{11}O_4$ ($M-CO_2$) requires: 183.0622).

Dimethyl 3-formyloxycyclopentene-1,2-dicarboxylate (26b). - A solution of the bromide (26a) (200 mg; 1.0 equiv.) in dioxan (2 ml) was added to a solution of sodium formate (78 mg; 1.5 equiv.) in formic acid (98%; 1 ml), and the mixture was heated at 60°C for 16 h. The mixture was cooled to room temperature, water (10 ml) was added and the separated aqueous phase was then extracted with ether (3 x 10 ml). The combined organic extracts were neutralised by the addition of solid sodium bicarbonate, and then washed successively with saturated sodium bicarbonate solution (1 x 15 ml), water (1 x 15 ml) and brine (1 x 15 ml). Evaporation of the dried extracts, followed by purification of the residue by chromatography using light petroleum (b.p. 40°-60°C)-ether (4:1) as eluant gave the formate (92 mg; 53%) as a colourless oil, ν_{max} ($CHCl_3$) 1720, 1650 $cm.^{-1}$, δ_H 8.0 ($OC\underline{H}O$), 6.14 (m, C<u>H</u>OCHO), 3.82 ($OC\underline{H}_3$), 3.78 ($OC\underline{H}_3$), 2.7-2.3 (m, methylene envelope); (Found: m/z 228.9631; $C_{10}H_{12}O_6$ requires: <u>M</u> 228.0630).

Dimethyl 3-hydroxycyclopentene-1,2-dicarboxylate (26c). - A solution of sodium carbonate (115 mg; 2.7 equiv.) in water (1 ml) was added to a solution of the formate (26b) (92 mg; 1.0 equiv.) in methanol (1 ml), and the mixture was stirred at room temperature for 5 min. Water (5 ml) was

added, and the aqueous solution was then extracted with ether (3 x 5 ml). The ethereal extracts were combined, then washed with brine (1 x 10 ml), dried and evaporated in vacuo. Purification of the residue by chromatography using light petroleum (b.p. 40°-60°C)-ether (3:1) as eluant gave the alcohol (50 mg; 63%) as a colourless oil, ν_{max} 3450 (OH), 1720, 1650 cm.$^{-1}$, δ_H 5.1 (t, J 7 Hz, CHOH), 3.75 (2 x OCH_3), 2.8-1.8 (m, methylene envelope); (Found: m/z 200.0670. $C_9H_{12}O_5$ requires: M 200.0680).

Dimethyl 3-(1-Ethoxy-2-bromoethoxy)cyclopentene-1,2-dicarboxylate (27). - A solution of bromine (477 µl; 2.0 equiv.) in dry methylene chloride (30 ml) maintained at -78°C was titrated with ethyl vinyl ether (~860 µl) until a colourless solution resulted. A solution of the alcohol (26c) (900 mg; 1.0 equiv.) in dry triethylamine (1.45 ml; 2.5 equiv.) was added, and the mixture was then allowed to warm to room temperature where it was stirred for 5 h. The brown solution was poured into 1M hydrochloric acid (30 ml), the phases were separated, and the aqueous phase was then extracted with ether (3 x 15 ml). The combined organic phases were dried and evaporated in vacuo, and the residue was then purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (4:1 then 1:1) as eluant to give a mixture of diastereoisomers of the bromo-acetal (1.23 g; 78%) as a pale-yellow oil, ν_{max} ($CHCl_3$) 1720, 1650, 915 cm.$^{-1}$, δ_H 5.1 (m, CHO), 4.8 (m, OCHO), 3.79 (2 x OCH_3), 3.65-3.5 (m, CH_3CH_2O), 3.3 (m, CH_2Br), 2.7-2.1 (m, methylene envelope), 1.3-1.1 (2xt, J 7Hz, CH_3CH_2O); (Found: m/z 305.0018. $C_{11}H_{14}BrO_5$ (M-EtO) requires: 305.0016).

5,6-Dicarbomethoxy-3-ethoxy-2-oxabicyclo[3.3.0]octane (28). - Tri-n-butyltin hydride (26 µl; 2.0 equiv.) was added to a degassed (N_2) solution of the bromo-acetal (27) (170 mg; 1.0 equiv.) and AIBN (16 mg; 0.2 equiv.) in dry benzene (24 ml) and the solution was then heated under reflux for 1 h. The solution was cooled to room temperature and the solvent was then evaporated in vacuo. The residue was purified by chromatography using light petroleum (b.p. 40°-60°C)-ether (9:1 then 1:1) as eluant to give a mixture of diastereoisomers of the cyclic acetal (119 mg; 90%) as a colourless oil, ν_{max} (film) 1735, 1435 cm.$^{-1}$, δ_H 5.3-5.05 (m, OCHO), 4.9-4.5 (m, CH-O), 3.75 (OCH_3), 3.66, 3.65 (OCH_3), 3.7-3.32 (m, OCH_2CH_3), 2.8-1.2 (m, OCH_2CH_3), 2.8-1.2 (7H, m), 1.3-1.1 (2xt, OCH_2CH_3); (Found: m/z 272.1246. $C_{13}H_{20}O_6$ requires: M 272.1254).

5,6-Dicarbomethoxy-2-oxabicyclo[3.3.0]octan-3-one (8). - A solution of the cyclic acetal (28) (70 mg; 1.0 equiv.) in acetone (0.3 ml) was titrated with Jones reagent to a permanent red end-point. The mixture was stirred at room temperature for 15 min, then brine (2 ml) was added and the aqueous solution was extracted with ether (3 x 5 ml). The combined ethereal extracts were washed successively with saturated sodium bicarbonate solution (2 x 5 ml) and brine (1 x 5 ml), dried and the solvent was then evaporated in vacuo to leave a light-brown oily residue. Chromatography using light petroleum (b.p. 40°-60°C)-ether (3:1) as eluant gave a 1:1 mixture of diastereoisomers of the bicyclic lactone (40 mg; 64%) as a colourless oil, ν_{max} ($CHCl_3$) 1780, 1735 $cm.^{-1}$, δ_H 5.1 (dd, J 6.5 and 2.3 Hz, CHOC(O)-), 4.97 (d, J 5.6 Hz, CHOC(O)-), 3.83 (OCH_3), 3.74 (OCH_3), 3.71 (OCH_3), 3.70 (OCH_3), 3.50 (dd, J 11.7 and 6.6 Hz, ($CHCO_2Me$), 3.00 (dd, J 7.7 and 7.7 Hz, $CHCO_2Me$), 3.33, 2.58 (dd, J 19.2 Hz CH_2CO_2), 3.25 2.85 (dd, J 18.7 Hz, CH_2CO_2), 2.42-1.94 (m, CH_2CH_2-), δ_C 174.6, 174.0, 173.0, 172.2, 171.7, 171.5, 87.7(d), 87.4(d), 59.0, 57.3, 53.5(d), 51.8(d), 53.4(q), 52.9(q), 52.2(q), 39.13(t), 33.93(t), 32.52(t), 31.40(t), 27.55(t), 26.57(t); (m/z 242.0812. $C_{11}H_{14}O_6$ requires: M 242.0835).

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