Tetrahedron Vol. 44, No. 16, pp. 5151 to 5160, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + .00

CONSTRUCTION OF 8-OXABICYCLO[5.3.0]DECA-2,9-DIONES: AN APPROACH TO THE PSEUDOGUAIANOLIDES

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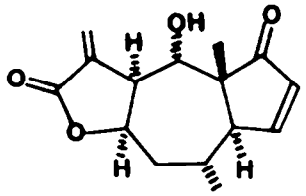
(*Received in UK* 13 *May* 1988)

Abstract An efficient four-step synthesis of 8-oxabicyclo [5.3.0]deca-2,9-diones is described, together with a summary of additional chemistry that provides key intermediates for possible elaboration into pseudoguaianolides.

The pseudoguaianolides are sesquiterpenoids that are mainly confined to the Compositae, but nonetheless comprise a family of at least five hundred structures. Helenalin 1 is a good example of this class - it has a typical pseudoguaianolide structure coupled with a diverse array of biological activities: it exhibits potent anti-inflammatory activity (in rats)[1] at around 2.5 $mg.Kg^{-1}$; and anti-tumour activity[2] at 3.0 $mg.Kg^{-1}$ (increase of lifespan by 200% in rats bearing the P388 leukaemia). Furthermore, it has a long association with folklore,[3,4] for example its use by the Commanche Indians (extracted from sneezeweed - Helenium microcephalum) to induce sneezing following childbirth, with resultant rapid expulsion of the afterbirth.



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Numerous synthetic approaches to the pseudoguaianolides have been explored,[5] but most are complex and involve many stages. Our overall strategy is illustrated in FIGURE ONE, and should allow access to both pseudoguaianolides and guaianolides. In addition it provides opportunities for the assessment of the minimum structures necessary for biological activity. Our initial studies in both areas are the subject of this paper.

We[6] and others[7] have reviewed the chemistry and synthetic potential of oxyallyl carbocations, and for our initial model studies the oxabicycle 2 was employed since this can be easily prepared on the 100 g scale from 2,4-dibromopentan-3-one and furan.[8] Catalytic hydrogenation (10% Pd on charcoal) yielded 3 , and alkylation with methyl bromoethanoate (LDA/THF) yielded

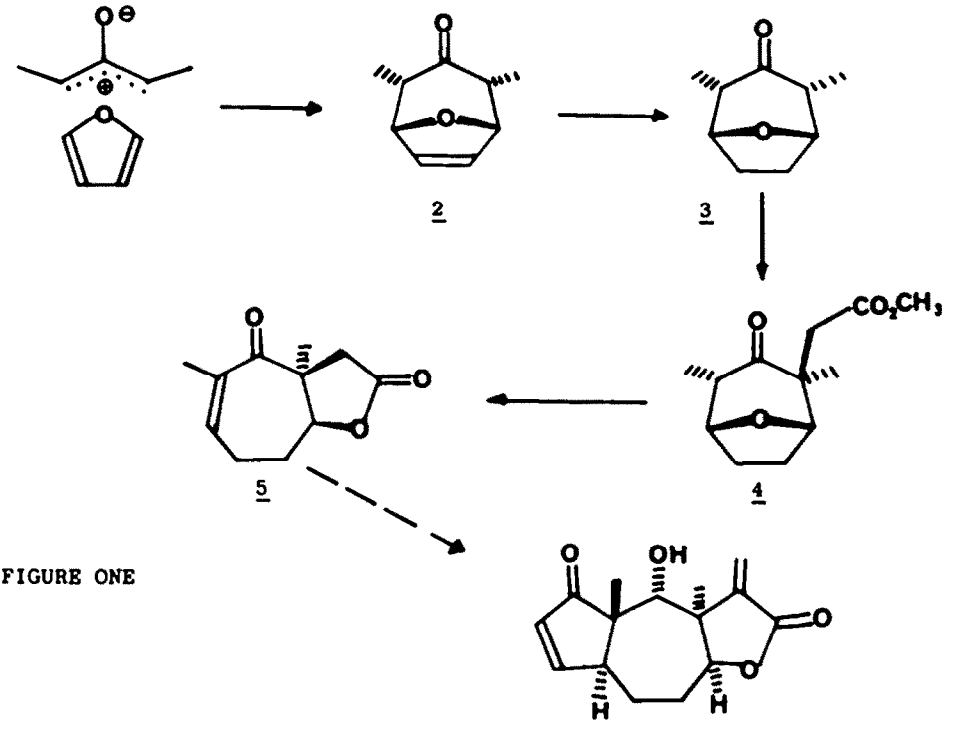


FIGURE ONE

primarily the stereoisomer 4 in good overall yield (96 % from 2). Treatment of this with trimethylsilyl iodide[9] (MeCN,RT), or better with a mixture of $KI/CHCl_3$ and $BF_3.OEt_2$,[10] (followed by addition of DBU for the TMSI method) provided the 8-oxabicyclo[5.3.0]deca-3-en-2,9-dione 5 in good yield (up to 65% from 5 g. of 4). The intermediate 6 could be isolated if the DBU was omitted, and the mechanism shown in FIG. TWO thus seems reasonable for the reaction using TMSI.

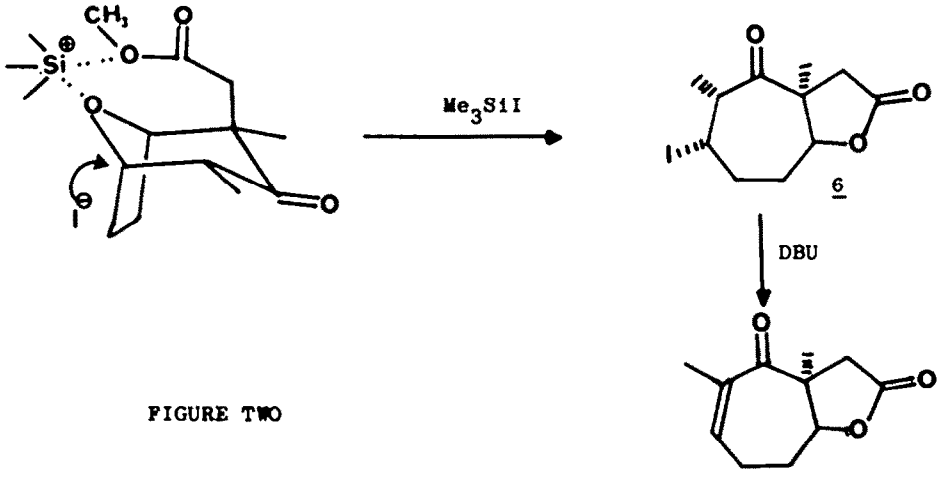


FIGURE TWO

Conversion of 5 into the α-methylene lactone 7 was achieved (albeit in low overall yield) via the sequence methylation (MeI/LDA, 65-70%), phenylselenenylation (PhSeCl/LDA) and oxidative elimination (H_2O_2, HOAc, 0°, 18% for the two steps). In this conversion a mixture of the 5-selenenophenyl species 8 and the desired compound 9 was obtained (ratio ca. 1:4). Upon oxidation, the desired α-methylene lactone was obtained from 9 , and the tertiary

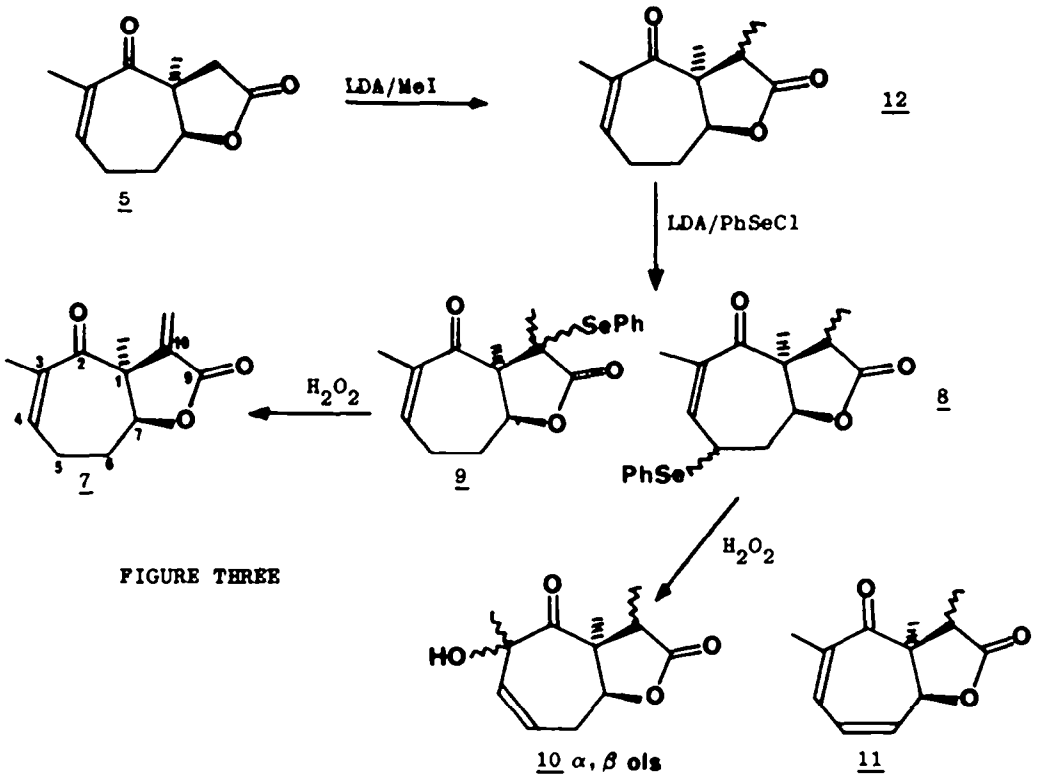


FIGURE THREE

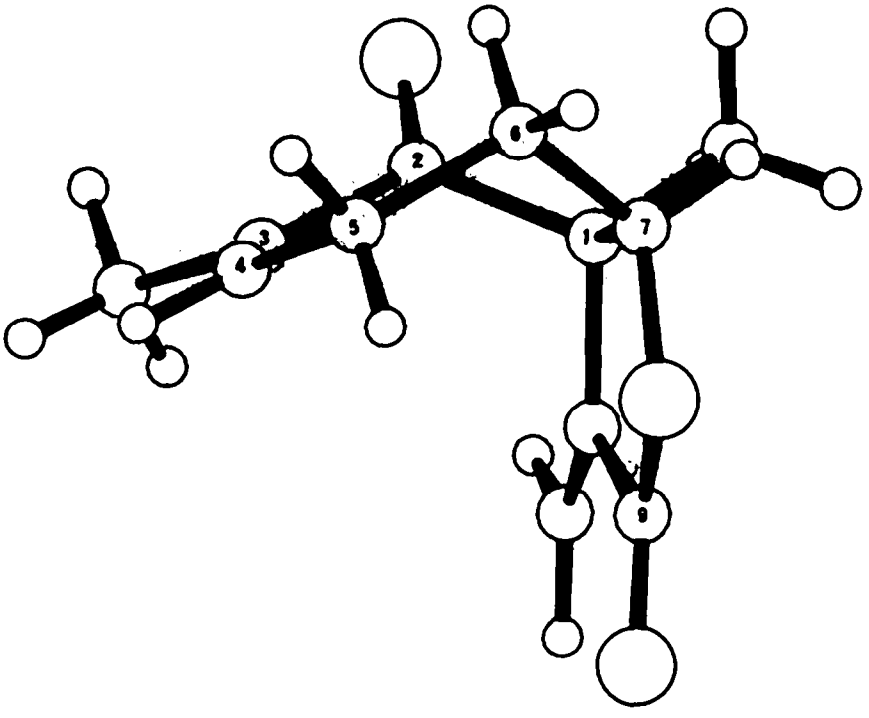


FIGURE FOUR

alcohol 10 (rearrangement and hydrolysis 19% yield) and diene (11) (<5% yield) from 8 . This whole sequence is illustrated in FIG. THREE. An X-ray crystallographic analysis was carried out on 7 , and the ORTEP plot is shown in FIG. FOUR. Interestingly, this α-methylene lactone had modest cytotoxic activity in vitro against the LI210 tumour line, whilst the 10-methyl compound 12 was devoid of activity.

Another α-methylene lactone 13 was prepared via the sequence shown in FIG. FIVE. Reduction of compound 4 with sodium borohydride in ethanol yielded lactone 14 and alcohol 15 in a ratio of 1:4, and the lactone 14 was then converted into 13 via the method described previously. This compound exhibited no significant anti-tumour activity.

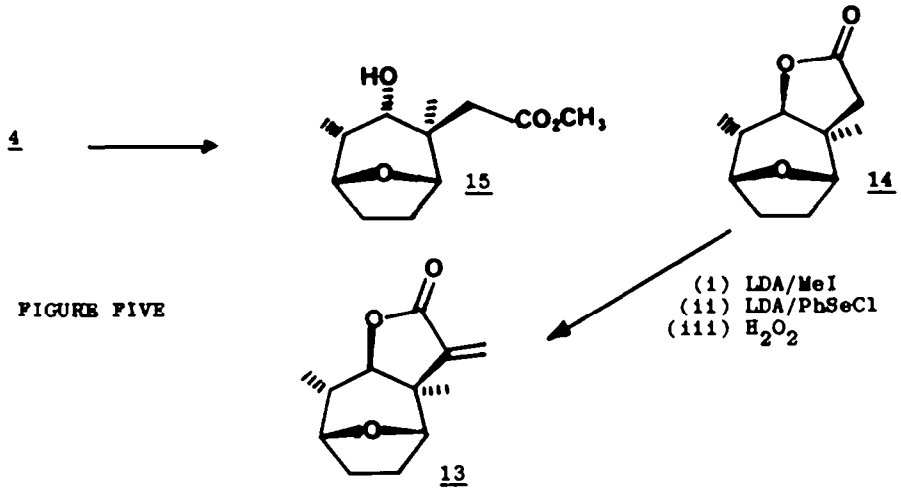
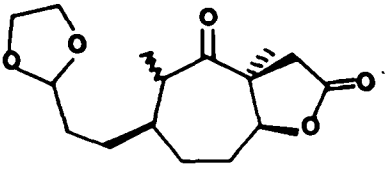


FIGURE FIVE

Finally, in an attempt to prepare the final cyclopentenone ring, lactone 5 was treated (in the presence of $CuBr.Me_2S$) with the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxolane to produce a mixture of acetals 16 (88%). These could be converted into the aldehydes 17 and 18 (ratio 2:1) using weak acid, but all attempts to effect ring closure via acid- or base-catalysed Aldol reactions were unsuccessful, with recovery of the aldehydes 17 and 18. Presumably the retro-Aldol reaction is more favoured; and alternative successful attempts to complete the synthesis will be described elsewhere.



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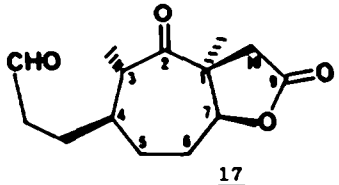

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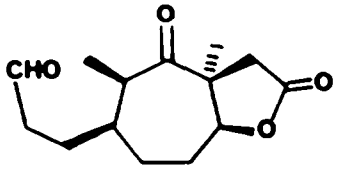

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Experimental

I.r. spectra were recorded with a Perkin-Elmer 157 double beam grating spectrophotometer (all samples were dissolved in CH_2Cl_2): n.m.r. spectra were recorded with a Perkin-Elmer R34 (220MHz) instrument, or with a Bruker WM400 (400MHz) instrument (University of Warwick) using tetramethylsilane as internal standard; flash chromatography was performed using Merck silica gel (250-400 mesh); solvents were distilled from calcium hydride when required anhydrous; and pet. ether means the fraction boiling between 40 and 60°C. The cycloadduct 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one, 2, was prepared as described in ref. 8.

2,4-Dimethyl-8-oxabicyclo[3.2.1]octan-3-one, 2

A solution of 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-one (9.8g, 64.5 mmol) in A.R. ethyl acetate (200 cm^3) was placed in a 500 cm^3 Parr bottle, followed by a slurry of 10% Pd/C catalyst (900 mg) in ethyl acetate (20 cm^3). This was subsequently hydrogenated for 18h at 3 atm pressure using a Parr hydrogenator. Catalyst was then filtered off through Celite, and the mother liquor concentrated to 9.9g (100%) of a clear oil, R_f 0.33 (light petroleum-diethyl ether 2:3). No further purification was necessary.

ν_{max} 1707 (C=O), 1381, 1159, 1047, and 951 cm^{-1}.

δ ($CDCl_3$), 0.95 (6H,d,J7Hz,2xCH_3), 1.7-1.9 (4H,m,CH_2-6 and CH_2-7), 2.6-3.0 (2H,m,H-2 and H-4), 4.5(2H,m,H-1 and H-5).

m/e (%) M^+ = 154(15), 98(20), 69(40), 56(100), 41(40).

2,4-Dimethyl-2-(methyl-2'-ethanoate)-8-oxabicyclo[3.2.1]octan-3-one, 3.

Lithium diisopropylamide (20.2mmol) was prepared from diisopropylamine (2.85 cm^3, 2.06g, 20.2 mmol) and n-butyl lithium (12.65 cm^3, 8.65g, 20.2 mmol) in dry THF (40 cm^3) at 0°C under nitrogen in 20 minutes. To this was added 2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (1.90g, 12.3 mmol) in dry THF (40 cm^3) at -78°C. The resultant mixture was stirred at -78°C for 90 minutes under nitrogen. To the enolate anion thus formed was added methyl bromoacetate (2.60 cm^3, 4.20g, 30.75 mmol), and the mixture allowed to warm to room temperature, then allowed to stir for a further 24 hours. The reaction was quenched by addition of water (60 cm^3) and the product extracted into ethyl acetate (4x50 cm^3), before washing with brine (2x50 cm^3), and drying over $MgSO_4$. Concentration under reduced pressure yielded a yellow oil. Any remaining traces of methyl bromoacetate were removed on a high vacuum pump. After flash chromatography (light petroleum:diethyl ether - 2:3) 2.69g (96%) of a pale yellow oil was obtained. Found: C 63.77%, H 8.07%; $C_{12}H_{18}O_4$ requires C 63.69%, H 8.01%.

ν_{max} 1738 (ester C=O), 1705 (ketone C=O), 1155, 1055, 1028, 953, 930, 902 cm^{-1}.

δ ($CDCl_3$) 0.95 (3H,d,J7Hz,CH_3-4), 1.03 (3H,s,CH_3-2), 1.70-1.90 (4H,m,CH_2-6 and CH_2-7), 2.57 (1H,d,J14Hz,H-2'a), 3.20 (1H,d,J14.5Hz,H-2'b), 3.00-3.30 (1H,m,H-4), 3.65 (3H,s,OCH_3), 4.20-4.40 (1H,m,H-1), 4.42-4.60 (1H,m,H-5).

m/e (%) 226.1195 (18), 195(19), 158(44), 128(88), 126(100), 100(59), 86(19), 59(19), 57(15), 55(44), $C_{12}H_{18}O_4$ requires 226.1205.

1,3-Dimethyl-8-oxabicyclo-[5.3.0]-dec-3-en-2,9-dione, 5, and 1,3-Dimethyl-4-iodo-8-oxabicyclo-[5.3.0]-decan-2,9-dione, 6.

To ester 4 (6.674g, 29.5 mmol) dissolved in benzene (30ml) was added iodotrimethylsilane (9.5ml, 66.5 mmol). The mixture was then stirred for 4 hours at a temperature of 50→60°C under N_2 and in the absence of light. The products were isolated by the addition of $Na_2S_2O_3$ (50ml of a 0.5M solution) and extraction with CH_2Cl_2 (x3). The organic extracts were combined and then washed with brine

before drying over $MgSO_4$ and evaporating down to a pale yellow solid. This represents impure 6 from which an analytical sample could be obtained by flash chromatography (eluent ethyl acetate:ether 1:1). However normally 6 was not isolated but carried through to 5. Thus the pale yellow solid was taken up in THF (20 ml), DBU (4.6 ml, 31 mmol) added and the mixture stirred for 10 minutes at room temperature. The solvent was removed under pressure and the residue purified by flash chromatography (eluent ether) to give 5 4.501g as a clear oil, pure by t.l.c. (ether R_f 0.38) analysis. Yield 79%.

ν_{max} 1790 (C=O, lactone), 1682 (C=O, conjugated ketone), 1381, 1352, 1210, 1200, 1185, 1130, 1040, 1030, 978, and 952 cm^{-1}.

δ (100MHz, $CDCl_3$), 1.42 (3H,s,CH_3-1), 1.9 (3H,m,CH_3-3), 1.8→2.55 (4H,m,CH_2-5 and CH_2-6) and superimposed 2.3 (1H,d,J18Hz, H-10a), 3.35 (1H,d,J18Hz,H-10b), 4.4 (1H,dd,J10 and 3 5Hz,H-7), 6.2 (1H,m,H-4);

m/e (%) 194.0940 (M^+, 83), 150(22), 111(35), 108(30), 99(16), 98(36), 96(18), 95(100), 82(99), 71(17), 67(50), 54(25), 53(26); $C_{11}H_{14}O_3$ requires 194.0943.

Physical and spectroscopic details for 6; white crystalline solid decomp. pt. 114°→6°C; found C 67.87%, H 7.37%; $C_{11}H_{14}O_3$ requires C 68.02%, H 7.26%.

ν_{max} 1800 (C=O, lactone), 1707 (C=O, ketone), 1351, 1300, 1226, 1199, 1182, 1021, and 1011 cm^{-1}.

δ (100MHz, $CDCl_3$), 1.13 (3H,d, J7Hz, CH_3-3), 1.43 (3H,s,CH_3-1), 1.8→2.5 (4H,m, CH_2-5 and CH_2-6), 2.36 (1H,d,J18Hz,H-10a), 2.46 (1H,dq,J7 and 3.5Hz,H-3), 3.18 (1H,d,J18Hz,H-10b), 4.45→4.6 (2H,m,H-7 and H-4).

m/e (%), 195.1019 $C_{11}H_{15}O_3$ (M^+- I, 100), 177(51), 153(20), 113(24),107(18), 71(16), 69(38), 55(65); $C_{11}H_{15}O_3$ requires 195.1017.

Preparation of 5 using Boron Trifluoride and Potassium Iodide

To a stirred solution of ester 4 (1.78g, 8.0 mmol) and potassium iodide (4.27g, 25.4 mmol) in dry chloroform (30 cm^3) under nitrogen at 0°C, was added distilled boron trifluoride etherate (3.2 cm^3, 3.7g, 25.3 mmol) dropwise. The reaction was then heated to 55°C and stirred for three days, when all the starting material had disappeared (t.l.c. analysis).

The reaction was worked-up by quenching with saturated sodium hydrogen carbonate (20 cm^3) and extracting into diethyl ether (3x15 cm^3). The organic extracts were then washed with aqueous sodium thiosulphate (20 cm^3) and water (20 cm^3), followed by drying over magnesium sulphate. Concentration gave a red/orange oil which was subsequently purified by flash column chromatography (2:1/diethyl ether:petroleum ether). Purification gave 1.01g (65%) of 5 at R_f=0.29 and a return of 0.59 (33%) of starting material at R_f = 0.54.

1,3,10-Trimethyl-8-oxabicyclo-[5.3.0]-dec-3-en-2,9-dione, 12.

Lithium diisopropylamide (37.6 mmol) was prepared from diisopropylamine (5.30 ml, 37.6 mmol) and n BuLi (22.1 ml of a 1.7M solution, 37.6 mmol) in dry THF, with stirring at -78°C under N_2 for 20 minutes. To this was added 5 (6.076 g, 31 mmol) in THF (20 ml) and the mixture was stirred at -78° under N_2 for 1 hour. To the enolate was added methyl iodide (3.0 ml, 48 mmol) and the mixture was then allowed to warm up from -78°C to room temperature, while stirring under N_2. The reaction was quenched by the addition of H_2O (≈ 50ml) and the product isolated by extraction of the aqueous phase with ether (x3). The organic extracts were combined, then washed with brine (x1) before drying over $MgSO_4$ and concentrating to an oil. Product purification was carried out by flash chromatography (eluent ether) to give 4.37 g of 12 as a white crystalline solid (67%). Physical and spectroscopic properties of 12; white crystalline solid

m.pt. 81→83°C; ν_{max} 1775 (C=O, lactone), 1676 (C=O, conjugated ketone), 1350, 1221, 1199, 1180, 1136, 1028, 1008, and 970 cm^{-1}; δ (100MHz, CDCl), 1.2 (3H,d,J 7Hz, CH_3-10), 1.25 (3H,s,CH_3-1), 1.85→2.1 (5H,m,CH_3-3 and CH_2-6), 2.3→2.5 (2H,m,CH_2-5), 2.28 (1H,q,J 7Hz,H-10), 4.25 (1H, dd, J 7 and 5Hz, H-7), 6.1 (1H,m,H-4); ^{m}/e (%), 208.1101 (M^+, 2.13), 125(34), 122(21), 108(48), 97(22), 96(20), 95(66), 84(19), 83(79), 82(100), 68(18), 67(33), 55(37), 54(24), 53(27); $C_{12}H_{16}O_3$ requires 208.1099.

1,3-Dimethyl-10-methylene-8-oxabicyclo[5.3.0]-dec-3-en-2,9-dione 7 and the isomeric 1,3,10-trimethyl-8-oxabicyclo[5.3.0]-dec-4-en-3-ol-2,9-dione 10

Lithium diisopropylamide (14.3 mmol) was prepared from diisopropylamine (2 ml, 14.3 mmol) and n BuLi (8.5 of a 1.7M solution, 14.4 mmol) in dry THF stirring at -78°C under N_2 for 20 minutes. To this was added 12 2.00g, 9.6 mmol) in THF (11 ml) and the mixture stirred at -78°C under N_2 for 50 minutes. To the thus formed enolate was added dropwise phenylselenenyl chloride (2.769 g, 14.5 mmol) in dry THF (12 ml). The reaction was then allowed to warm up from -78°C to room temperature over 3 hours while stirring under N_2. The reaction was quenched by the addition of HCl (50 ml of a 0.5M solution) and the products extracted with ether (x3). The organic extracts were then combined and washed with brine before drying over $MgSO_4$ and the removal of the solvent to give an oil. The t.l.c. (ether:pet. ether 40-60° 3:2) analysis of this oil showed the presence of phenylselenenyl chloride, two major product components (R_f's 0.48 and 0.39), and one minor product component (R_f 0.30). The use of flash chromatography (eluent ether:pet. ether 40→60° 3:2) yielded these product components in the following quantities: 0.308g (R_f 0.48), 1.489g (R_f 0.39) and 0.300g (R_f 0.30). Each product component was then submitted to oxidation with hydrogen peroxide. Thus for example the product component with R_f 0.39 (1.489g) was dissolved in THF (15 ml) and acetic acid (0.6 ml), cooling to 0°C. To the solution was added hydrogen peroxide (2.9 ml of a 30% ^{w}/v solution) and the mixture was stirred for 1 hour at 0°C. The reaction was quenched with saturated $NaHCO_3$ solution and the product extracted with CH_2Cl_2 (x3). The organic extracts were combined and washed with brine (x1) before drying over $MgSO_4$ and concentrating to an oil. Product purification by flash chromatography (eluent ether:pet. ether 40→60° 7:3) gave 359 mg of 7 (18%) and 300 mg of 10α (14%).

Physical and spectroscopic details for 7; white crystalline solid m.pt. 110→112°C; ν_{max} 1760 (C=O, conjugated lactone), 1682 (C=O, conjugated ketone), 1278, 1203, 1152, 1039, 1018, 970 and 959 cm^{-1}; δ (100MHz, CDCl), 1.46 (3H, s, CH_3-1), 1.85 (3H, m, CH_3-3), 1.9→2.5 (4H, m, CH_2-5 and CH_2-6), 4.48 (1H, dd, J 9 and 3Hz, H-7), 5.48 (1H, s, exo =C-H), 6.05 (1H, m, H-4), 6.3 (1H, s, exo =C-H); ^{m}/e (%), 206.0945 (M^+, 33), 163(45), 136(100), 126(71), 124(20), 110(21), 95(59), 83(26), 82(63), 81(73), 80(23), 79(37), 68(25), 67(47), 55(27), 54(40), 53(67); $C_{12}H_{14}O_3$ requires 206.0942.

Physical and spectroscopic details for 10α; white crystalline solid m.pt. 51→56°C; ν_{max} 3470 (OH), 1780 (C=O, lactone), 1705 (C=O, ketone), 1350, 1139, 1102, 1030, and 1007 cm^{-1}; δ (100 MHz, $CDCl_3$), 1.3 (3H, d, J 7Hz, CH_3-10), 1.42 (3H, s, CH_3-1), 1.58 (3H, s, CH_3-3), 2.35→2.5 (2H, m, CH_2-6), 3.45 (1H, q, J 7Hz, H-10), 4.2 (1H, s, D_2O exchanges, OH), 4.5 (1H, dd, J 8 and 5Hz, H-7), 5.7 (2H, m, H-4 and H-5); ^{m}/e (%), 196 (M^+ -CO, 1.79), 112(18), 85(4), 84(100), 83(9), 69(43), 55(9).

Product component with R_f 0.48 on oxidation and product purification gave rise to 101 mg of a 10β (5%) as a white crystalline solid m.pt. 108-112°;

ν_{max} 3480 (OH), 1780 (C=O, lactone), 1704 (C=O, ketone), 1348, 1200, 1138, 1101, 1006, and 730 cm^{-1}; δ (100 MHz, CDCl), 1.26 (3H,d,J 7Hz, CH_3-10), 1.48 (3H,s, CH_3-1), 1.52 (3H,s,CH_3-3), 2.2-2.6(2H,m,CH_2-6), 3.3 (1H,q,J 7Hz,H-10), 3.4(1H,br.s,D_2O exchanges,OH), 4.85(1H,dd,J 9.5 and 5Hz), 5.8 (2H,m,H-4 and H-5); ^{m}/e (%), 196 (M^+ -CO, 1.2), 112 (17), 85 (17), 84 (100), 83 (6), 69 (37), 55 (10).

2,7-Dimethyl-5,11-dioxatricyclo-[6.2.1.$0^{2,6}$]-undecan-4-one, 14, and and 2,4-dimethyl-2-(carbomethoxymethyl)-8-oxabicyclo-[3.2.1]-octan-3-ol. 15

To ketone 4 (5.510g, 24.4 mmol) dissolved in isopropanol (25 ml) at 50-55°C was added $NaBH_4$ (0.98g, 35.0 mmol) stirring at 50-55°C for 3 hours. Products were isolated by removing the isopropanol under reduced pressure, adding NH_4Cl solution (5% soln. 50 ml) to the residue and extracting with ethyl acetate (x4). Products were purified by flash chromatography (eluent CH_2Cl_2: ether 4:1) to give 1.072g of 14, 1.888g of 15, 0.860g of the isopropyl ester analogue of 15 and 0.200g of a mixture of products in yields of 22%, 34% and 14% respectively.

Physical and spectral properties of 14; white crystalline solid m.pt. 84-86°C; ν_{max} 1770 (lactone C=O), 1160, 1041, 1032, 997, and 926 cm^{-1}; δ(220MHz, $CDCl_3$), 1.0(3H, d, J 7Hz, CH_3-7), 1.08 (3H, s, CH_3-2), 1.6-2.0 (5H, m, CH_2-9, CH_2-10, and H-7), 2.08 (1H, d, J 17Hz, H-3a), 3.13 (1H, m, H-1), 4.2 (1H, m, H-8); ^{m}/e (%), 196 (M^+) (17), 128(11), 98(33), 81(17), 80(18), 71(100), 70(32), 69(33), 68(15), 67(29), 55(31); $C_{11}H_{16}O_3$ requires C 67.32, H 8.22; found C 67.11 and H 8.26%.

Physical and spectral properties of 15; white crystalline solid m.pt. 73-74°C; ν_{max} 3450 (-OH), 1730 (ester C=O), 1241, 1207, 1190, 1145, 1040, 1009, 989, and 964 cm^{-1}; δ (100 MHz, $CDCl_3$), 0.92(3H,d,J 7Hz,CH_3-4), 1.05(3H,s, CH_3-2), 2.46(1H,d,J 14Hz,CH_2CO_2), 2.63(1H,d,J 14Hz,CH_2CO_2), 3.9(1H,d,J 7Hz,H-1), 4.05(1H,dd,J 7 and 4Hz,H-5); ^{m}/e, 228 (M^+).

2,7-Dimethyl-3-methylene-5,11-dioxatricyclo-[6.2.1.$0^{2,6}$]undecan-4-one 13

This was prepared as described for compound 7, and had the following physical and spectral properties: white crystalline product m.pt. 130-132°C; ν_{max} 1755 (lactone C=O), 1668 (C=C), 1381, 1296, 1111, 995, and 945 cm^{-1}; δ (220 MHz, $CDCl_3$), 1.02(3H,d,J 7Hz,CH_3-7), 1.12(3H,s,CH_3-2), 1.65-2.1(5H,m, CH_2-9,CH_2-10 and H-7), 3.86(1H,d,J 9Hz,H-6), 4.15(1H,m,H-8), 4.45(1H,m,H-1), 5.53(1H,s,C=C-H) and 6.33(1H,s,C=C-H); ^{m}/e, (%), 208.1097 (M^+, 0.52), 111(11), 116(100), 98(6), 80(5), 71(41), 55(6), 54(5), 53(5). $C_{12}H_{16}O_3$ requires 208.1099.

1,3-dimethyl-4-formylethyl-8-oxabicyclo[5.3.0]deca-2,9-diones 17 and 18

Dry magnesium turnings (0.54g, 23 mmol) were placed in a three-neck R.B. flask with dry THF (40 cm^3) and a crystal of iodine. A condenser and solids addition tube containing dimethyl sulphide-copper bromide complex (1.12g, 5.4 mmol) were attached and the system placed under nitrogen. One tenth of a solution of 2-(2-bromoethyl)-1,3-dioxolane (2.40 cm^3, 3.71g, 21 mmol) in dry THF (20 cm^3) was added to the magnesium turnings, and the flask placed in a hot water bath to initiate the reaction. Once started (10 mins.) the remainder of the bromoacetal was added dropwise, and the reaction allowed to stir for 1 hour.

The flask was subsequently cooled to -78°C and the $Me_2S.CuBr$ complex added. The mixture was then placed in a -24°C bath (CCl_4/dry ice), and stirred for

10 minutes. During this period a grey-green colour developed. The ketone (5) (0.83g, 4.2 mmol) in dry THF (20 cm^3) was added slowly and the reaction mixture allowed to warm to 0°C over a period of 90 minutes, whereupon the reaction was adjudged complete.

Work-up was performed by quenching with saturated ammonium chloride (30 cm^3) and the product extracted into diethyl ether (3x30 cm^3). After washing with brine, the organic extracts were dried over $MgSO_4$ and concentrated to a yellow oil. Purification by flash column chromatography (ether:petrol/4:1) gave a mixture of two stereoisomers 16 (approx. 2:1) in a total yield of 88% (1.10g).

This mixture of the stereoisomers (400 mg., 1.35 mmol) was placed in a R.B. flask with A.R. acetone (15 cm^3) and 2M HCl (2 cm^3), and the mixture stirred at room temperature for 18 hours. Analysis by t.l.c. revealed a slower-running product (Rf 0.23 cf. 0.33; ether). The reaction was worked up after 36 hours by addition of saturated sodium bicarbonate solution (30 cm^3), before extraction of products into ether (3x20 cm^3). The combined organic extracts were washed with brine before drying and concentrated to give a yellow oil. Purification by flash column chromatography (ether:petrol/4:1) produced a co-chromatographing mixture of two aldehydes 17 and 18 in a ratio of 2:1 respectively. Yield was 76% (258 mg.).

ν_{max}(neat) 2940, 1780, 1710, 1670, 1455, 1380, 1200, 1015 and 955 cm^{-1};
For compound 17: δ ($CDCl_3$, 400 MHz) 1.15(d,J 7Hz,3H,3-Me), 1.32 (s, 3H,1-Me), 1.50-1.65 (m,2H,4-H and 5-H), 1.65-1.85 (m, 2H,6-H and 1'-H),1.85-2.0(m,2H,5-H and 6-H), 2.40 (m,2H,2'-H_2), 2.52 (d,J 18.5Hz,1H,10-H), 2.70 (d, J 18.5Hz,1H, 10-H), 2.83 (m,1H,3-H), 4.50 (m,1H,7-H), 9.23 (t,1H,CHO) ppm;

For compound 18: δ ($CDCl_3$, 400MHz), 1.1-1.2 (m,1H,1'-H), 1.14 (d, J 6.8Hz, 3H, 3-Me), 1.39 (s,3H,1-Me), 1.50-1.60 (m,1H,6-H), 1.68-1.78 (m,2H,4-H and 5-H), 1.78-1.80 (m, 1H, 5-H), 1.80-1.95 (m,2H,6-H and 1'-H), 2.27 (d,J 18.2Hz,1H,10-H), 2.35-2.50 (m,2H,2'-H_2), 3.00 (m,1H,3-H), 3.10 (d,J 18.2Hz,1H,10-H), 4.38 (dd, J 2.1 and 11.4Hz, 1H,7-H), 9.85 (t,1H,CHO), ppm;
for the mixture of 17 and 18: found C 66.6%, H 7.9%;
$C_{14}H_{20}O_4$ requires: C 66.63%; H 7.99%.

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Acknowledgements

We thank the S.E.R.C. for the Ph.D. studentships awarded to W.J.C. and A.J.M.