Total Synthesis of (±)-Diplodialide-A

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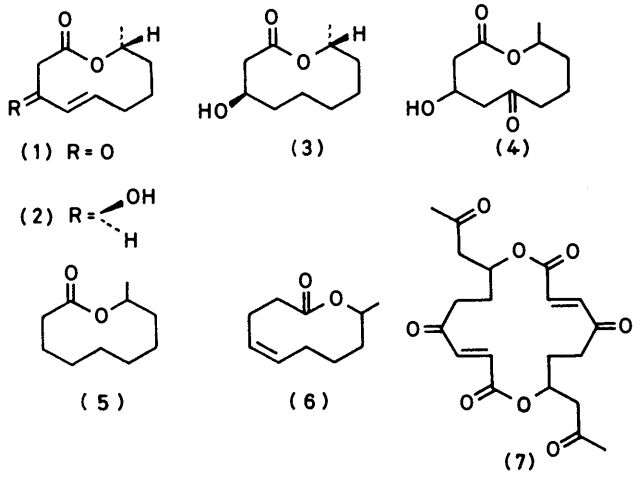
The total synthesis of a ten-membered lactone, diplodialide-A (1) [(*E*)-3-oxodec-4-en-9-olide], is described, involving the lactonization of the seco-acid derivative (22a) and the γ-selenenylation of the dianion of the β-keto lactone (24), followed by selenoxide elimination.

DURING a search for steroid hydroxylase inhibitors of microbial origin, we isolated four new pentaketides from the plant pathogenic fungus *Diplodia pinea*, namely diplodialide-A (a steroid hydroxylase inhibitor) (1), -B



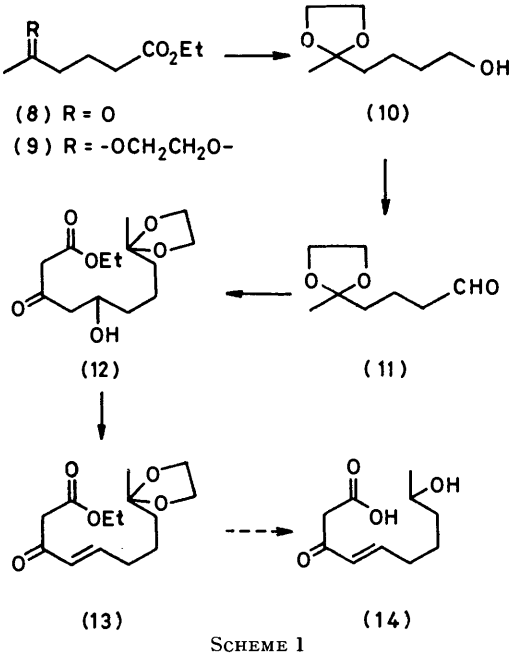
(2), -C (3),[1,†] and -D (4),[2] which are the first members of the ten-membered pentaketide series.[3] Recently, similar ten-membered lactones, decan-9-olide (5) and (*Z*)-dec-4-en-9-olide (6), were isolated from the insect *Phoracanta synonyma*,[4] and a dimeric pentaketide, vermiculine (7), was isolated from the fungus *Penicillium vermiculatum*;[5] compound (7) has been synthesized by Corey *et al.*[6] and White *et al.*[7] We now describe the total synthesis of (±)-diplodialide-A (1).[8]

The construction of macrocyclic lactones is a challenging problem in synthetic organic chemistry [9] and recently several mild and efficient methods for lactonization were developed by Corey [10] and other workers.[9] The yields in the lactonization of ω-hydroxy-acids or their derivatives to give ' medium-size ' lactones (8—11-membered) are not always good, even under high dilution conditions, and the corresponding dilactones are preferentially formed in many cases. However, the yields of the 1 ⟶ 9 lactone of prostaglandin $F_{2\alpha}$(ten-membered) [11] and deisovalerylblastmycin (nine-membered) [12] are fairly good. These facts encouraged us to synthesize diplodialide-A (1) from its seco-acid derivatives.

Our initial plan was to synthesize the seco-acid (14) from the key intermediate (12) (Scheme 1). Compound (12) was synthesized by the reaction of the dianion [13] of ethyl acetoacetate with the aldehyde (11), which was prepared by the following sequential reactions: formation of the ethylenedioxy-derivative of ethyl 5-oxohexanoate (8), lithium aluminium hydride reduction, and oxidation. Unfortunately, dehydration of the aldol (12) resulted in a low yield of the desired αβ-unsaturated ketone (13) even though we examined a wide variety of reaction-conditions to optimize the yield.

We succeeded in accomplishing a total synthesis of (1) by the route in Scheme 2, involving lactonization of the dihydro-seco-acid (21a) and subsequent introduction of the 4,5-double bond. The β-ketoester (19) was synthesized by the γ-alkylation of the dianion of ethyl acetoacetate [14] with the tetrahydropyranyl ether (18) of 6-bromohexan-2-ol in tetrahydrofuran–hexamethylphosphoramide in 78% yield. The bromide (18) was prepared from ethyl 5-oxohexanoate (8) as follows.

The ester (8) was reduced with sodium borohydride in methanol at −23 °C to the hydroxy-ester (15). The

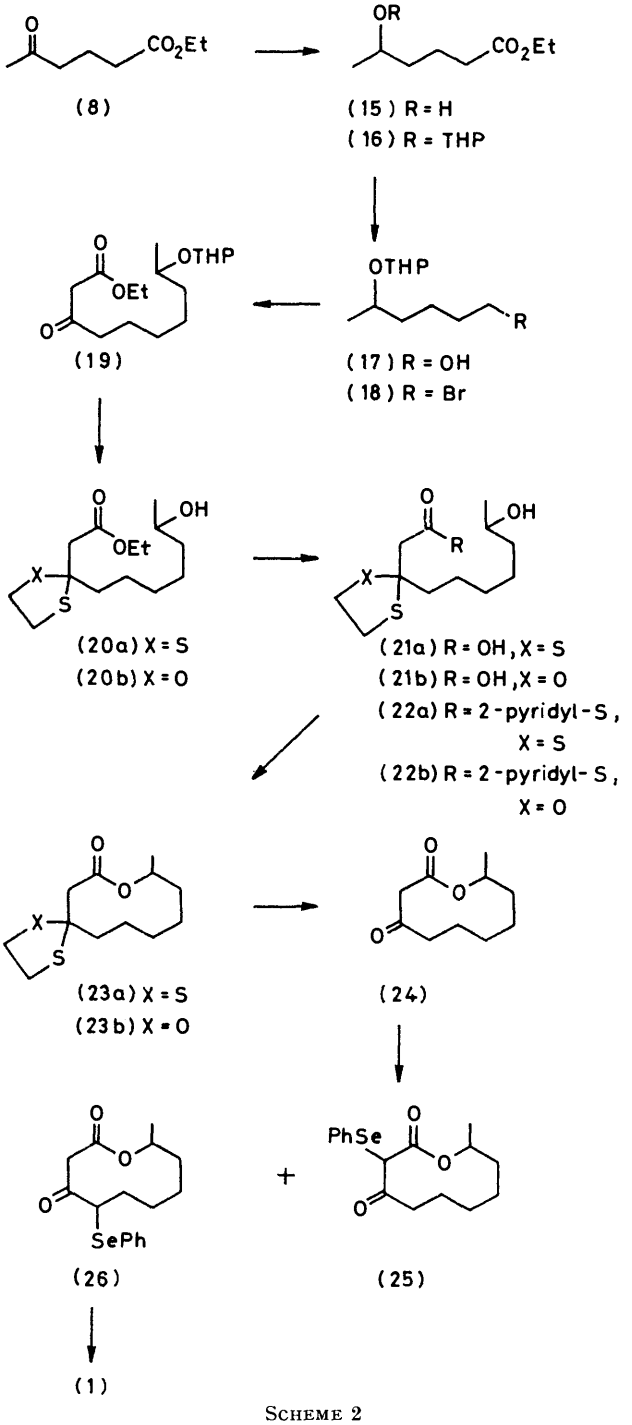


SCHEME 1

alcohol function of (15) was protected by formation of its tetrahydropyranyl ether (16). The ester (16) was reduced with lithium aluminium hydride in ether to give the acid-sensitive alcohol (17). Bromination of (17) by the use of a mild, neutral brominating agent,

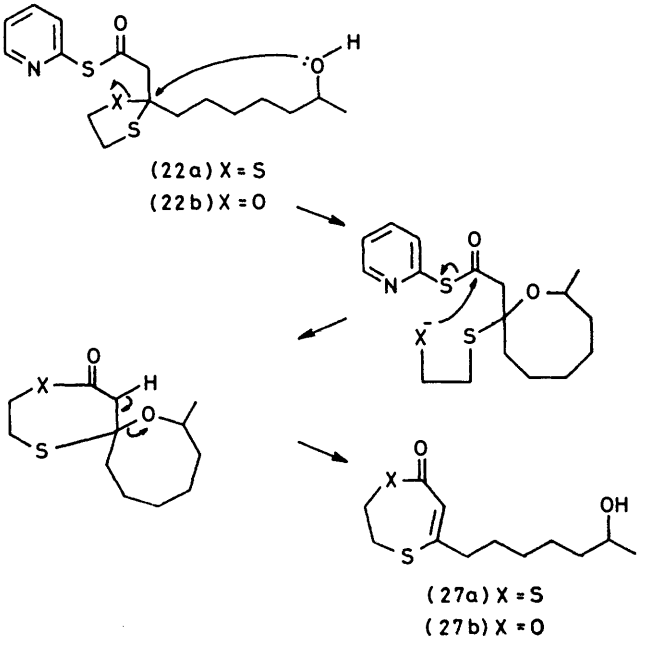
† The absolute stereochemistry at C-3 of (2) was confirmed by ozonolysis of the acetate of (2) which gave (*S*)-malic acid. Since (−)-(2) was converted into (−)-(3) by catalytic hydrogenation, diplodialide-B (2) has the (3*S*,9*R*)-configuration and diplodialide-C (3) the (3*R*,9*R*)-configuration (K. Wada and T. Ishida, *J.C.S. Perkin I*, submitted for publication).

carbon tetrabromide and triphenylphosphine in pyridine–ether,[15] gave the bromide (18) in good yield. Protection of the keto-group in (19) with ethanedithiol and



SCHEME 2

boron trifluoride–ether in acetic acid was accompanied by simultaneous removal of the tetrahydropyranyl group to afford the dithioacetal ester (20a). Saponification [1.3M KOH in methanol–water (4 : 1)] of (20a) gave the hydroxy-acid (21a). The acid (21a) was treated with di-2-pyridyl disulphide and triphenylphosphine in acetonitrile,[16] and the product was purified by silica gel t.l.c. (developing solvent: 50% ethyl acetate in n-hexane) to yield the pure thiol ester (22a) in 79% yield. A dilute xylene solution of (22a) (5mM) was refluxed for 25 h under argon [10] to give the expected ten-membered lactone (23a) (38% yield) and the dilactone (4.6% yield) accompanied by the unexpected product (27a) (19% yield). In the case of the monothioacetal (22b), prepared by a similar procedure, the undesired compound (27b) was the main product. The structures of compounds (27a) and (27b) were assigned from their physicochemical data. The n.m.r. spectrum of (27a) exhibited two $-SCH_2CH_2S-$ resonances at δ 3.24, but in the spectrum of (27b) the $-SCH_2CH_2O-$ resonance was at lower field (δ 4.72), showing acylation of the hydroxy-group.



SCHEME 3

We believe that (27a) and (27b) are formed by the mechanism in Scheme 3. The above results indicate that the dithioacetal group was more stable than the monothioacetal against attack of the hydroxy group, and the undesired route was suppressed in the case of the lactonization of (22a).

Removal of the dithioacetal group of the lactone (23a) with *N*-bromosuccinimide [17] in aqueous acetone gave the β-ketolactone (24) in 82% yield. The lactone (24) was identical in all respects (i.r., n.m.r., and mass spectra; t.l.c. behaviour) with an authentic sample prepared from naturally occurring (+)-diplodialide-A (1) by catalytic hydrogenation.[1]

The final step in the synthesis of (1) was the introduction of a double bond into (24). We used a new method for the construction of αβ-unsaturated ketones or esters, *via* phenylselenenylation and selenoxide elimination,[18] for this purpose. In a model reaction, the phenylselenenylation of the dianion of ethyl 3-oxodecanoate in tetrahydrofuran–n-hexane, the γ-phenylseleno-β-keto-

ester was preferentially formed in 64% yield. In the case of the β-ketolactone (24), the corresponding dianion was not soluble in tetrahydrofuran–n-hexane, but addition of small amount of hexamethylphosphoramide led to dissolution. Thus, the dianion of (24) in n-hexane–tetrahydrofuran–hexamethylphosphoramide (*ca.* 7 : 4 : 1) was treated with benzeneselenenyl bromide to give the γ-phenylseleno-β-ketolactone (26) in 38% yield.

The n.m.r. spectrum of (26) confirmed the assigned structure: two doublets centred at δ 3.54 (2 H, *J* 15 Hz, $COCH_2CO_2$) and a double doublet at δ 3.84 [1 H, *J* 10 and 5 Hz, CO-C*H*(SePh)-CH_2]. The α-phenylseleno-derivative (25) (28% yield) was also produced, and (25) was readily reconverted into (24) by reduction with Raney nickel in tetrahydrofuran.[19]

Finally, oxidation of the γ-phenylselenolactone (26) with dilute aqueous hydrogen peroxide (3%) in dichloromethane afforded a single product in 60% yield, identical in all respects (i.r., u.v., n.m.r., and mass spectra; t.l.c. and g.l.c. behaviour) with the naturally occurring (+)-diplodialide-A.

Since (+)-diplodialide-A has been converted into (−)-diplodialide-B and (−)-diplodialide-C,[1] the synthesis of (1) constitutes the completion of total syntheses of (±)-diplodialide-B (2) and (±)-diplodialide-C (3).

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were recorded with a JASCO IR-G spectrometer, u.v. spectra with a Hitachi EPS-3T spectrophotometer, ^1H n.m.r. spectra with a JEOL JNM-MH-100 (100 MHz) spectrometer or a JEOL JNM-FX100 (99.6 MHz) Fourier transform spectrometer (tetramethylsilane as internal standard), ^{13}C n.m.r. spectra with a JEOL JNM-FX100 (25.05 MHz) Fourier transform spectrometer (tetramethylsilane as internal standard), and mass spectra (high resolution) with a JEOL JMS-01SG-2 spectrometer. Analytical g.l.c. was performed with a JEOL JGC-1100 gas chromatograph. Kieselgel $60PF_{254}$ (Merck) was used for analytical and preparative t.l.c. Mallincrodt silicic acid was used for column chromatography.

Ethyl 5-Hydroxyhexanoate (15).—To a stirred solution of sodium borohydride (24 g, 632 mmol) in methanol (440 ml) at −23 °C was added dropwise a solution of (8) (20.7 g, 131 mmol) in methanol (50 ml). After 50 min, the mixture was treated with 1M hydrochloric acid to pH 2 and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, and dried (Na_2SO_4). Removal of the solvent gave the *hydroxy-ester* (15) as an oil (19.7 g, 123 mmol); $\nu_{max.}$ (CCl_4) 3 625, 3 475, and 1 735 cm^{-1}; δ($CDCl_3$) 1.22 [3 H, d, *J* 7 Hz, *Me*CH(OH)], 1.28 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 2.34 (1 H, s, exchanges with D_2O), 2.36 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 3.86 [1 H, m, MeC*H*(OH)CH_2], and 4.20 (2 H, q, *J* 7 Hz, CO_2CH_2Me)(Found: $M^+ - H_2O$, 142.099 8. $C_8H_{14}O_2$ requires 142.099 4).

Ethyl 5-(Tetrahydropyran-2-yloxy)hexanoate (16).—To a stirred solution of (15) (10 g, 62.5 mmol) in dry dichloromethane (150 ml) at 0 °C were added dihydropyran (28 ml, 306 mmol) and toluene-*p*-sulphonic acid (110 mg, 0.64 mmol). After 7 h at 0 °C, the solution was washed with saturated aqueous sodium hydrogen carbonate and brine, and dried (Na_2SO_4). Removal of solvent yielded the crude *ether* (16) as an oil (22.7 g), which was used without further purification. Preparative t.l.c. with 10% ethyl acetate in n-hexane of a small sample gave pure (16); $\nu_{max.}$ (CCl_4) 1 735 cm^{-1}; δ($CDCl_3$) two pair of doublets at 1.12 and 1.24 [total 3 H, *J* 7 Hz, MeCH(OTHP)], 1.26 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 2.35 (2 H, t, *J* 7 Hz, $CH_2CH_2CO_2$), 4.16 (2 H, q, *J* 7 Hz, CO_2CH_2Me), and 4.72 [1 H, m, OC*H*(CH_2)O] [Found: $M^+ - C_5H_9O_2$(OTHP), 143.107 9. $C_8H_{15}O_2$ requires 143.107 2] (THP = tetrahydropyran-2-yl).

5-(Tetrahydropyran-2-yloxy)hexan-1-ol (17).—To a stirred suspension of lithium aluminium hydride (4.75 g, 125 mmol) in dry ether (250 ml) at 0 °C was added dropwise crude (16) (22.7 g) in dry ether (30 ml). After 15 min at 0 °C, the mixture was allowed to warm to room temperature and stirred for an additional 2 h. Excess of hydride was decomposed with saturated aqueous sodium sulphate and the resulting white precipitate was filtered off and washed with ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent, followed by column chromatography on silica gel (240 g) (eluting solvent 20% ethyl acetate in n-hexane) afforded the pure alcohol (17) as an oil (7.1 g, 35 mmol); $\nu_{max.}$ (CCl_4) 3 630 and 3 400 cm^{-1}; δ(CCl_4) two pair of doublets at 1.08 and 1.18 [total 3 H, *J* 7 Hz, MeCH(OTHP)] and 2.58 (1 H, m, exchanges with D_2O) [Found: $M^+ - C_5H_9O_2$(OTHP), 101.096 1. $C_6H_{13}O$ requires 101.096 6].

1-Bromo-5-(tetrahydropyran-2-yloxy)hexane (18).—To a stirred solution of the alcohol (17) (5.61 g, 27.8 mmol), carbon tetrabromide (18.4 g, 55.6 mmol), and pyridine (2.24 ml, 27.8 mmol) in dry ether (110 ml) at 0 °C was added dropwise triphenylphosphine (14.6 g, 55.8 mmol) in dry ether (70 ml). The mixture was stirred at 0 °C for 2 h and then at room temperature overnight. Solvent was evaporated off *in vacuo* at 0 °C and the residue was dissolved in n-pentane and filtered. The filtrate was concentrated *in vacuo* at 0 °C to *ca.* 10 ml and chromatographed on a silica gel column (120 g) with 5% ethyl acetate in n-hexane to give the bromide (18) as an oil (4.22 g, 15.9 mmol), no OH i.r. absorption; δ($CDCl_3$) two pair of doublets at 1.12 and 1.23 [total 3 H, *J* 7 Hz, MeCH(OTHP)], and 3.42 (2 H, t, *J* 7 Hz, $BrCH_2CH_2$) (Found: M^+, 264.071 5. $C_{11}H_{21}{}^{79}BrO_2$ requires *M*, 264.072 5).

Ethyl 3-Oxo-9-(tetrahydropyran-2-yloxy)decanoate (19).—Dry tetrahydrofuran (80 ml) was directly distilled from lithium aluminium hydride into a 200 ml flask containing sodium hydride (1.18 g; 66% dispersion in oil; 32.4 mmol) and then dry hexamethylphosphoramide (distilled from CaH_2; 8 ml) was added. To the cooled suspension in an ice bath was added dropwise ethyl acetoacetate (3.44 ml, 26.5 mmol) and the resulting solution was stirred at 0 °C for 10 min. To the solution was added dropwise n-butyllithium in n-hexane (1.44M; 20.2 ml, 29.1 mmol) and the resulting orange solution of the dianion was stirred at 0 °C for 10 min. The bromide (18) (3.51 g, 13.2 mmol) in dry tetrahydrofuran (10 ml) was added to the dianion solution, and the mixture was allowed to warm to room temperature. After 1 h, the mixture was treated with saturated aqueous ammonium chloride, acidified to pH 2 with 1M hydrochloric acid and extracted with ether. Removal of the solvent, followed by preparative t.l.c. with 20% ethyl acetate in n-hexane afforded the *γ-alkylated-β-ketoester* (19) as an oil (3.24 g, 10.3 mmol); $\nu_{max.}$ (CCl_4) 1 740 and 1 720 cm^{-1}; δ(CCl_4) two pair of doublets at 1.08 and 1.18 [total 3 H, *J*

7 Hz, MeCH(OTHP)], 1.30 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 2.50 (2 H, t, *J* 7 Hz, CH_2CH_2CO), 3.32 (2 H, s, $COCH_2CO_2$), 4.20 (2 H, q, *J* 7 Hz, $COCH_2Me$), 4.94 (s, small signal due to vinyl hydrogen of the enol form), and 12.24 (s, exchanges with D_2O, small signal due to enolic OH) [Found: M^+, 314.213 6; $M^+ - C_5H_9O_2$(OTHP), 213.152 3. $C_{17}H_{30}O_5$ requires *M*, 314.209 3. $C_{12}H_{21}O_3$ requires 213.149 1].

Ethyl 3,3-(*Ethylenedithio*)-9-*hydroxydecanoate* (20a).—To a stirred solution of the ketoester (19) (2.51 g, 7.98 mmol) and ethanedithiol (3.34 ml, 40 mmol) in acetic acid (8 ml) was added boron trifluoride–diethyl ether (2 ml, 15.8 mmol) at room temperature. After 4 h, the reaction mixture was poured into ice–water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, and dried (Na_2SO_4). Removal of the solvent and preparative t.l.c. with 30% ethyl acetate in n-hexane gave the dithiolan (20a) as an oil (2.03 g, 6.63 mmol); $\nu_{max.}$ (CCl_4) 3 640, 3 450, and 1 740 cm^{-1}; δ(CCl_4) 1.12 [3 H, d, *J* 6 Hz, *Me*CH(OH)], 1.27 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 2.54 (1 H, s, exchanges with D_2O), 2.90 (2 H, s, CH_2CO_2), 3.22 (4 H, s, $S[CH_2]_2S$), 3.64 [1 H, m, $MeCH(OH)CH_2$], and 4.06 (2 H, q, *J* 7 Hz, CO_2CH_2Me) (Found: M^+, 306.133 9. $C_{14}H_{26}O_3S_2$ requires *M*, 306.132 3).

3,3-(*Ethylenedithio*)-9-*hydroxydecanoic Acid* (21a).—A solution of the ester (20a) (2.03 g, 6.63 mmol) in 1.3M potassium hydroxide in methanol–water (4 : 1) (28 ml) was stirred at room temperature overnight. The mixture was acidified to pH 1 with hydrochloric acid, saturated with sodium chloride, and extracted with ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4). Removal of the solvent and preparative t.l.c. with 50% ethyl acetate in n-hexane gave the *hydroxy-acid* (21a) as an oil (1.60 g, 5.75 mmol); $\nu_{max.}$ (CH_2Cl_2) 3 600, 3 400, and 1 713 cm^{-1}; δ($CDCl_3$) 1.19 [3 H, d, *J* 6 Hz, *Me*CH(OH)], 3.04 (2 H, s, CH_2CO_2), 3.29 (4 H, s, $S[CH_2]_2S$), 3.80 [1 H, m, $MeCH(OH)CH_2$], and 6.1br (2 H, exchanges with D_2O) (Found: M^+, 278.101 6. $C_{12}H_{22}O_3S_2$ requires *M*, 278.101 0).

S-2-*Pyridyl* 3,3-([*Ethylenedithio*)-9-*hydroxydecanethioate* (22a).—To a stirred solution of the hydroxy-acid (21a) (566 mg, 2.04 mmol) in dry acetonitrile (6 ml) was added triphenylphosphine (1 066 mg, 4.07 mmol) and di-2-pyridyl disulphide (895 mg, 4.07 mmol). The mixture was stirred at room temperature for 4 h. Removal of the solvent and preparative t.l.c. with 50% ethyl acetate in n-hexane gave the *ester* (22a) as an oil (595 mg, 1.60 mmol); $\nu_{max.}$ (CCl_4) 3 625, 3 400, 3 100, 1 710, and 1 573 cm^{-1}; δ(CCl_4) 1.08 [3 H, d, *J* 6 Hz, *Me*CH(OH)], 3.32 (4 H, s, $S[CH_2]_2S$), 3.30 (2 H, s, CH_2CO-pyridyl), 3.60 [1 H, m, $MeCH(OH)CH_2$], 7.1 (1 H, m), 7.5 (2 H, m), and 8.4 (1 H, m) (Found: $M^+ - C_5H_5NS$ (pyridine-2-thiol), 260.088 7. $C_{12}H_{20}O_2S_2$ requires 260.090 5).

Lactonization of (22a) *to* 3,3-(*Ethylenedithio*)*decan*-9-*olide* (23a).—A solution (5mM) of the ester (22a) (595 mg, 1.60 mmol) in dry xylene (320 ml) was heated under reflux with stirring under argon for 25 h. Solvent was evaporated off *in vacuo* to give a dark red oil, preparative t.l.c. of which (10% ethyl acetate) afforded the lactone (23a) (158 mg, 0.608 mmol; R_F 0.53) and the corresponding dilactone (19 mg, 0.036 5 mmol; R_F 0.23). Further preparative t.l.c. of the more polar fraction (311 mg; R_F 0—0.13) with 50% ethyl acetate in n-hexane afforded the dithiepin (27a) (78 mg, 0.30 mmol; R_F 0.43). 3,3-(*Ethylenedithio*)*decan*-9-*olide* (23a) was an oil; $\nu_{max.}$ (CCl_4) 1 740 cm^{-1}; δ(CCl_4) 1.24 [3 H, d, *J* 6 Hz, MeCH(OR)], 2.84 (1 H, d, *J* 12 Hz) and 3.04 (1 H, d, *J* 12 Hz) (CH_2CO_2), 3.28 (4 H, s, $S[CH_2]_2S$), and 4.92 (1 H, m, $OCHMeCH_2$) (Found: M^+, 260.089 9. $C_{12}H_{20}O_2S_2$ requires *M*, 260.090 5). The corresponding dilactone formed needles, m.p. 153—155 °C (from acetone); $\nu_{max.}$ (CCl_4) 1 735 cm^{-1}; δ(CCl_4) 1.20 (6 H, d, *J* 6 Hz, 2 × *Me*CH), 2.92 (4 H, s, 2 × CH_2CO_2), 3.22 (8 H, s, 2 × $S[CH_2]_2S$), and 4.90 (2 H, m, 2 × $OCHMeCH_2$) (Found: M^+, 520.180 3. $C_{24}H_{40}O_4S_4$ requires *M*, 520.180 9). 2,3-*Dihydro*-5-(6-*hydroxyheptyl*)-1,4-*dithiepin*-7-*one* (27a) was an oil; $\nu_{max.}$ (CCl_4) 3 625, 3 400, and 1 657 cm^{-1}; $\lambda_{max.}$ (MeOH) 226 (ε 5.47 × 10^3), 237 (4.65 × 10^3), 262 (2.73 × 10^3), and 312 nm (2.52 × 10^3); δ($CDCl_3$) 1.18 [3 H, d, *J* 6 Hz, *Me*CH(OH)], 1.74 (1 H, s, exchanges with D_2O), 2.38 (2 H, t, *J* 7 Hz, $C{=}CCH_2CH_2$), 3.24 (4 H, m, $S[CH_2]_2S$), 3.80 [1 H, m, $CH_2CH(OH)Me$], and 6.28 (1 H, s, COC=C); ^{13}C n.m.r. δ($CDCl_3$) 23.51 (q) 25.40 (t), 28.51 (t), 28.93 (t), 31.67 (t), 35.0 (t), 38.98 (t), 41.60 (t), 67.61 (d), 130.87 (d), 141.14 (s), and 197.90 (s) (Found: M^+, 260.094 1. $C_{12}H_{20}O_2S_2$ requires *M*, 260.090 5).

Ethyl 3,3-(*Ethyleneoxythio*)-9-*hydroxydecanoate* (20b).—To a solution of the ketoester (19) (107 mg, 0.34 mmol) in dry tetrahydrofuran (1 ml) at 0 °C was added mercaptoethanol (0.17 ml, 2.4 mmol), freshly fused zinc chloride (224 mg, 1.65 mmol), and anhydrous sodium sulphate (255 mg, 1.80 mmol). After 10 min at 0 °C, the mixture was allowed to warm to room temperature and stirred for an additional 4 h. After dilution with water, the solution was extracted with ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent and preparative t.l.c. with 10% ethyl acetate in dichloromethane gave the oxathiolan (20b) as an oil (90 mg, 0.31 mmol); $\nu_{max.}$ (CCl_4) 3 640, 3 500, and 1 740 cm^{-1}; δ(CCl_4) 1.12 (3 H, d, *J* 6 Hz, *Me*CH), 1.26 (3 H, t, *J* 7 Hz, CO_2CH_2Me), 1.82 (1 H, s, exchanges with D_2O), 2.72 (1 H, d, *J* 14 Hz) and 2.76 (1 H, d, *J* 14 Hz) (CH_2CO_2), 2.96 (2 H, t, *J* 6 Hz, SCH_2CH_2O), 3.66 [1 H, m, $MeCH(OH)CH_2$], and 4.08 (4 H, q and t overlapped, *J* 7 and 6 Hz, respectively, CO_2CH_2Me and SCH_2CH_2O) (Found: M^+, 290.154 1. $C_{14}H_{26}O_4S$ requires *M*, 290.155 1).

3,3-(*Ethyleneoxythio*)-9-*hydroxydecanoic Acid* (21b).—A solution of the ester (20b) (75 mg, 0.26 mmol) in 1.3M potassium hydroxide in methanol–water (4 : 1) (1 ml) was stirred at room temperature overnight. The mixture was acidified with 1M hydrochloric acid, saturated with sodium chloride, and extracted with ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4). Removal of the solvent and preparative t.l.c. with 10% methanol in dichloromethane gave the *hydroxy-acid* (21b) as an oil (35 mg, 0.13 mmol); $\nu_{max.}$ (CH_2Cl_2) 3 600, 3 450, and 1 710 cm^{-1}; δ($CDCl_3$) 1.19 (3 H, d, *J* 6 Hz, *Me*CH), 2.94 (2 H, s, CH_2CO_2H), 3.07 (2 H, t, *J* 6 Hz, SCH_2CH_2O), 3.77 [1 H, m, $MeCH(OH)$], 4.20 (2 H, t, *J* 6 Hz, SCH_2CH_2O), and 5.62br (2 H, exchanges with D_2O) (Found: M^+, 262.124 3. $C_{12}H_{22}O_4S$ requires *M*, 262.123 8).

Lactonization of (22b) *to* 3,3-(*Ethyleneoxythio*)*decan*-9-*olide* (3b).—To a solution of the hydroxy-acid (21b) (123 mg, 0.47 mmol) in dry xylene (1 ml) was added triphenylphosphine (273 mg, 1.04 mmol) and di-2-pyridyl disulphide (226 mg, 1.03 mmol), and the mixture was stirred at room temperature for 3 h. The mixture was diluted with dry xylene (10 ml) and the solution was added dropwise during 4 h to refluxing dry xylene (100 ml) under argon. Reflux was continued for an additional 68 h. Solvent was evaporated off *in vacuo* to give yellow oil, which was chromato-

graphed on preparative t.l.c. with 20% ethyl acetate in n-hexane to afford a trace of a diastereoisomeric mixture of the desired lactone (23b) (*ca.* 1 : 1; R_F 0.44 and 0.48). Further t.l.c. of the more polar fraction (422 mg, R_F 0—0.26) with 70% ethyl acetate in n-hexane afforded the unexpected product (27b) (43 mg, 0.18 mmol). 3,3-(Ethyleneoxythio)-decan-9-olide (23b) was an oil (Found: M^+, 244.113 8. $C_{12}H_{20}O_2S$ requires M, 244.113 3), identical in mass spectra with authentic (23b) prepared from natural (+)-diplodialide-A (1) *via* (24). Their identity was also shown by t.l.c. and g.l.c.; coinjection with authentic (23b) on 5% OV-210 at 130 °C showed no peak separation. 2,3-Dihydro-5-(6-hydroxyheptyl)-1,4-oxathiepin-7-one was an oil; $\nu_{max.}$ (CCl_4) 3 625, 3 500, and 1 620 cm^{-1}; $\lambda_{max.}$ (MeOH) 257 nm (ε 1.08 × 10^4); δ($CDCl_3$) 1.18 [3 H, d, *J* 6 Hz, MeCH(OH)], 1.72 (1 H, s, exchanges with D_2O), 2.20 (2 H, t, *J* 7 Hz, C=CH_2CH$_2$), 3.18 (2 H, m, SCH_2CH$_2$O), 3.80 [1 H, m, MeC*H*(OH)], 4.72 (2 H, m, SCH$_2$CH_2O), and 5.43 (1 H, s, COCH=C); ^{13}C n.m.r. δ($CDCl_3$) 23.51 (q), 25.34 (t), 27.53 (t), 28.87 (t), 29.36 (t), 37.28 (t), 38.98 (t), 67.86 (d), 74.68 (t), 106.84 (d), 167.56 (s), and 192.85 (s) (Found: M^+, 244.112 8. $C_{12}H_{20}O_3S$ requires M, 244.113 3).

3-*Oxodecan*-9-*olide* (24).—To a stirred solution of *N*-bromosuccinimide (1.954 g, 11 mmol) in acetone–water (9 : 1) (21 ml) at −5 °C was added a solution of the dithiolan (23a) (316 mg, 1.22 mmol) in acetone (9 ml). After 15 min at −5 °C, the mixture was poured into saturated aqueous sodium sulphite, and extracted with ether. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine and dried (Na_2SO_4). Removal of solvent and preparative t.l.c. with 20% ethyl acetate in n-hexane gave the β-ketolactone (24) as an oil (183 mg, 0.995 mmol); $\nu_{max.}$ (CCl_4) 1 745 and 1 715 cm^{-1}; δ(CCl_4) 1.26 (3 H, d, *J* 6 Hz, *Me*CH), 3.36 (2 H, s, COCH$_2$-CO$_2$), and 5.08 (1 H, m, OC*H*MeCH$_2$) (Found: M^+, 184.109 1. $C_{10}H_{16}O_3$ requires M, 184.109 9), identical (i.r., n.m.r., and mass spectra and t.l.c.) with authentic (24) prepared from natural (+)-diplodialide-A (1) by catalytic hydrogenation (10% Pd–C in ethyl acetate).

3-*Oxo*-4-*phenylselenodecan*-9-*olide* (26) *and* 3-*Oxo*-2-*phenylselenodecan*-9-*olide* (25).—A flame dried flask was flushed with argon and cooled to 0 °C.

To the flask were added 1M lithium di-isopropylamide (0.82 ml, 0.82 mmol) and dry hexamethylphosphoramide (0.1 ml), followed by addition of the β-ketolactone (24) (58.0 mg, 0.315 mmol) in dry tetrahydrofuran (0.2 ml). The resulting yellow solution of the dianion was stirred at 0 °C for 25 min. To this solution was added benzeneselenenyl bromide solution in tetrahydrofuran (0.55 ml, 0.41 mmol). After 5 min at 0 °C, the reaction was quenched with 0.5M hydrochloric acid and the mixture was extracted with ether. The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent and preparative t.l.c. with 3% ethyl acetate in benzene afforded the *γ-phenylseleno-β-ketolactone* (26) (24 mg, 0.071 mmol; R_F 0.38), the *α-phenylseleno-β-ketolactone* (25) (18 mg, 0.053 mmol; R_F 0.45), and the starting material (24) (24 mg; R_F 0.26). The γ-phenylseleno-β-ketolactone (26) was an oil; $\nu_{max.}$ (CCl_4) 3 070, 1 740, and 1 700 cm^{-1}; δ(CCl_4) 1.28 (3 H, d, *J* 7 Hz, *Me*CH), 3.16 (1 H, d, *J* 15 Hz) and 3.92 (1 H, d, *J* 15 Hz) (COCH$_2$CO$_2$), 3.84 [1 H, dd, *J* 10 and 5 Hz, COC*H*(SePh)CH$_2$], 5.02 (1 H, m, O−C*H*MeCH$_2$), and 7.0—7.6 (5 H, ArH) (Found: M^+, 340.057 3. $C_{16}H_{20}O_3{}^{80}Se$ requires M, 340.057 8). The α-phenylseleno-β-ketolactone (25) was an oil; $\nu_{max.}$ (CCl_4) 3 070, 1 740, and 1 710 cm^{-1}; δ(CCl_4) 1.20 and 1.28 (3 H, d, *J* 7 Hz, *Me*CH), 4.44 and 4.49 [1 H, s, COCH(SePh)CO$_2$], and 5.04 (1 H, m, O-C*H*Me) (Found: M^+, 340.063 2. $C_{10}H_{20}O_3{}^{80}Se$ requires M, 340.057 8).

Preparation of the β-*Ketolactone* (24) *from* α-*Phenylseleno*-β-*ketolactone* (25).—Reduction of (25) (31 mg, 0.091 mmol) with a catalytic amount of Raney nickel (W-1) in tetrahydrofuran (2 ml) was complete in 2 h at room temperature. After removal of the catalyst and solvent, the residue was purified by preparative t.l.c. with 5% ethyl acetate in benzene to give the β-ketolactone (24) as an oil (12 mg, 0.065 mmol).

(E)-3-*Oxodec*-4-*en*-9-*olide* [(±)-*Diplodialide*-*A*] (1).—To a stirred solution of the selenide (26) (25 mg, 0.074 mmol) in dichloromethane (1 ml) at 0 °C was added dropwise 3% aqueous hydrogen peroxide (0.21 ml, 0.184 mmol). After 10 min at 0 °C, the mixture was warmed to room temperature and stirred for an additional 50 min. The mixture was poured into water and extracted with dichloromethane. The organic layer was washed with 2% aqueous sodium hydrogen carbonate and brine and dried (Na_2SO_4). Removal of solvent and preparative t.l.c. with 30% ethyl acetate in n-hexane yielded (±)-diplodialide-A (1) as an oil (8.0 mg, 0.044 mmol); $\nu_{max.}$ (CCl_4) 1 740, 1 700, and 1 645 cm^{-1}; $\lambda_{max.}$ (MeOH) 232 (ε 7 190) and 310 nm (109); δ($CDCl_3$) 1.28 (3 H, d, *J* 7 Hz, *Me*CH), 3.34 (1 H, d, *J* 14 Hz) and 3.78 (1 H, d, *J* 14 Hz) (COCH$_2$CO$_2$), 5.16 (1 H, m, O-C*H*Me), 5.88 (1 H, d, *J* 16 Hz, COC*H*=CH), and 6.72 (1 H, m, COCH=C*H*CH$_2$) (Found: M^+, 182.091 6. $C_{10}H_{14}$-O_3 requires M, 182.094 3), identical (i.r., u.v., n.m.r., and mass spectra) with naturally occurring (±)-diplodialide-A. Their identity was also shown by t.l.c. and g.l.c.; coinjection with authentic material on 1.5% OV-1 at 90 °C showed no peak separation.

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