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PREPARATION OF β-KETOMACROLACTONES AND β-KETODIOLIDES USING *S*-t-BUTYL 3-OXOBUTANETHIOATE AND *S*-t-BUTYL 4-DIETHYLPHOSPHONO-3-OXOBUTANETHIOATE

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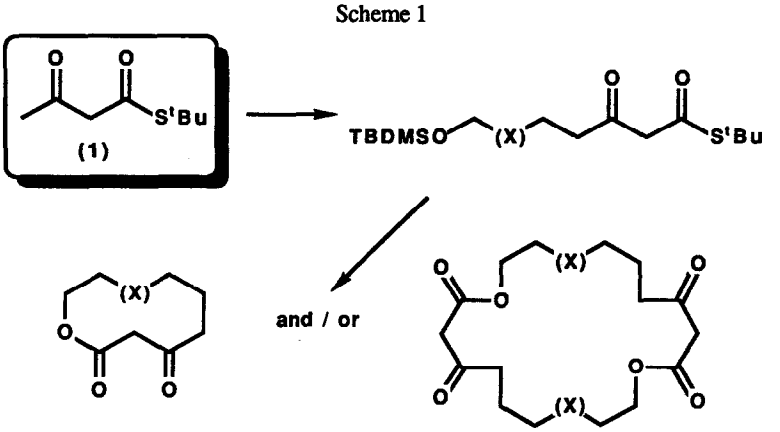
Abstract:- Using *S*-t-butyl 3-oxobutanethioate (1) and *S*-t-butyl 4-diethylphosphono-3-oxobutanethioate (2) various homologation reactions with t-butyldimethylsilyl protected hydroxy-iodides and aldehydes are reported. The products of these reactions after deprotection may be treated with copper (I) trifluoroacetate to afford β-ketomacrolide or β-ketomacrodiolides ranging in ring size from 13 to 32 depending upon the linking carbon atom chains and the reaction conditions. Several of the macrocyclic structures have been studied by X-ray crystallographic methods to determine their solid state conformations.

We have reported on the use of *S*-t-butyl 3-oxobutanethioate[1] (1) and *S*-t-butyl 4-diethylphosphono-3-oxobutanethioate[2] (2) for the preparation of acyltetronic acids[3], novel β-ketoesters[4], β-ketomacrolides and diolides[5] and β-ketoamides[6]. These methods have also been successfully applied in various natural product syntheses[3,7]. Here we describe in full how these very useful synthetic building blocks are effective in the construction of large ring systems containing β-ketolactone units. Many natural products especially macrolide antibiotics[8], contain this group[9] or simple derivatives thereof along with a growing number of other examples[10,11].

In the studies reported below we exploit the use of (1) and (2) for the formation of new carbon-carbon bonds at the γ-position, along with intramolecular trans-esterification of the thioesters (by activation with thiophilic metals[12]) to form macrocyclic systems. In general terms the dianion of (1) is alkylated at the γ-carbon atom with a t-butyldimethylsilyl protected hydroxy-iodide, which after deprotection with hydrofluoric acid (HF) in acetonitrile and treatment with copper (I) trifluoroacetate affords β-ketomacrolide or β-ketomacrodiolides depending upon the ring size and substituents (Scheme 1).

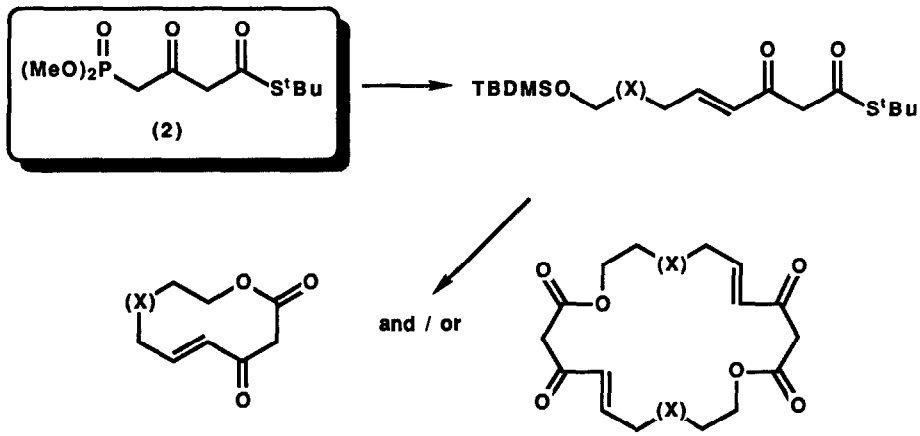
Scheme 1



Alternatively reaction of the ketophosphonate (2) with a similarly protected hydroxy-aldehydes affords *E*-alkenyl-β-ketothioesters. Deprotection and reaction with Cu(I) as above, leads to the corresponding unsaturated macrocyclic structures (Scheme 2).

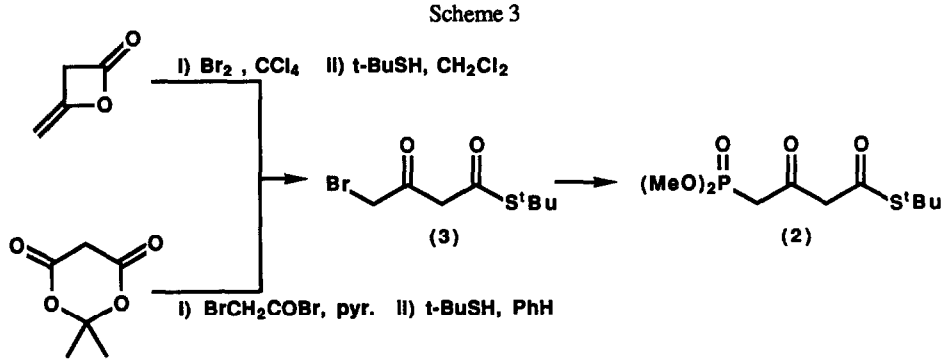
Preparation of (1) has been reported previously[1,13] and is now commercially available. Synthesis of the phosphonate (2) was achieved *via* the γ-bromo-β-ketothioester (3) by reaction with sodium diethylphosphite in 85% yield. Compound (3) was in turn available from diketene by sequential treatment with bromine and t-butylthiol or from Meldrum's acid by acylation with bromoacetyl bromide and reaction with t-butylthiol. (Scheme 3).

Scheme 2



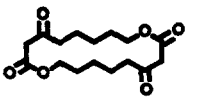
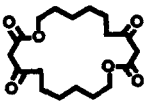
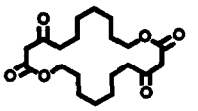
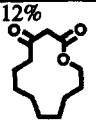
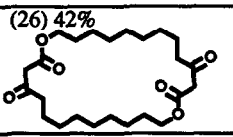
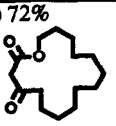
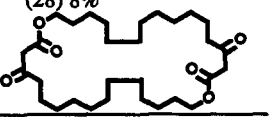
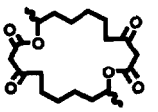
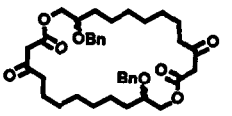
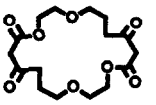
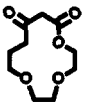
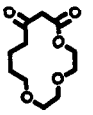
All the protected hydroxy-iodides (4)-(13) used in the first part of this study (Table 1) were obtained by routine and straightforward methodology, the full details of which are not reported here†. Where possible the solid state conformation and constitution of the final products have been determined by X-ray crystallography. These data are important for those interested in using the compounds for macrocyclic stereocontrol studies[14].

Scheme 3



In a typical experiment (1) was deprotonated in dimethoxyethane (DME) by sequential treatment with sodium hydride at -20°C and butyllithium at -40°C to form the dianion. This was quenched with the t-butyldimethylsiloxyalkyl iodides to afford the γ-alkylated products (Table 1). The use of DME in these reactions was essential since only very low yields were obtained in alternative ether solvents. Deprotection with HF in acetonitrile gave the corresponding alcohols in excellent yield. Although we investigated a number of thiophilic metal salts to effect the transesterification of the hydroxy-β-ketothioesters, copper (I) trifluoroacetate was usually superior in producing the macrolides and macrodiolides (Table 1).

These cyclisations proceeded readily at room temperature in methylene chloride solution. Generally we observe that dimeric products are preferred unless the ring size is paricularly large as in entry 5 when the 16-

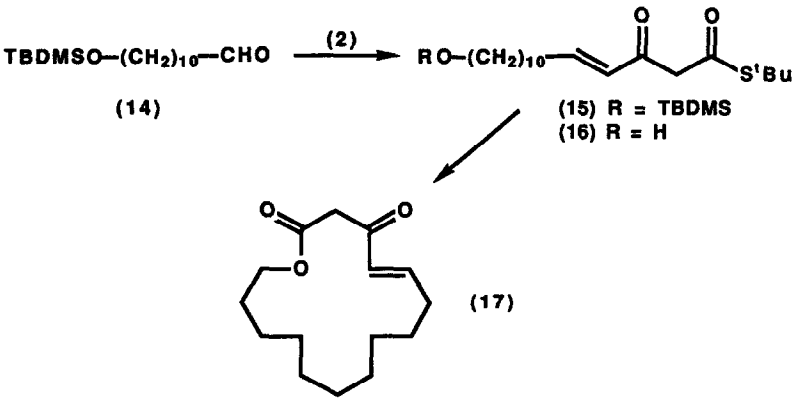
Alkyl halide† (X = I) (Y = TBDMS)	Alkylation (%) (X = $CH_2COCH_2COS^tBu$) (Y = TBDMS)	Deprotection (%) (Y = H)	Product (%)
X–$(CH_2)_4$–OY (4)	67	99	(22) 38% 
X–$(CH_2)_5$–OY (5)	59	90	(23) 49% 
X–$(CH_2)_6$–OY (6)	59	95	(24) 42% 
X–$(CH_2)_8$–OY (7)	39	99	(25) 12%  (26) 42% 
X–$(CH_2)_{11}$–OY (8)	67	90	(27) 72%  (28) 8% 
X–$(CH_2)_4$–CH(OY)–CH_3 (9)	58	98	(29) 49% 
X–$(CH_2)_6$–CH(CH_2OY'')–OCH_2Ph (10) (Y'' = CPh_3)	69	59	(30) 7% 
X–$C_2H_4OC_2H_4$–OY (11)	42	80	(31) 39% 
X–$(CH_2)_2(OC_2H_4)_2$–OY (12)	40	69	(32) 50% 
X–$(CH_2)_3(OC_2H_4)_2$–OY (13)	32	93	(33) 46% 

†Details for the preparations of these trivial iodides are available on request.

membered β-ketomacrolide is the major product (72% yield). However, where further oxygen substituents are present as bridging ethers (entries 8, 9) there is a tendency to form the monomeric β-ketomacrolides.

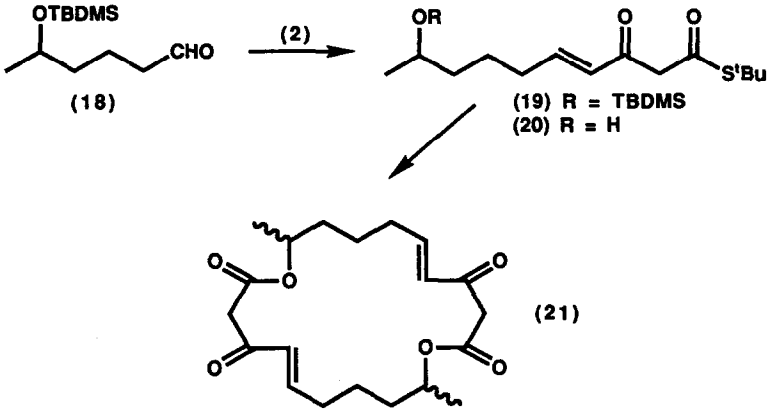
Where possible we have also determined the structures by X-ray crystallographic methods. These data were important at least to describe the solid state conformations within these novel systems. What is apparent from these determinations is that where possible the hydrocarbon linking chains adopt extended gauche arrangements with some degree of lipophilic interaction. The β-ketolactone unit prefers to be involved with the turn of the ring systems and most noticably adopts a conformation where the β-keto unit is not coplanar, thus disfavouring the enolic tautomer. The structures for which X-ray crystalllographic data could be obtaind are depicted in figures 1, 2, 3, 4 and 5.

In the second series of experiments designed to study the effect of an olefinic linkage within the macrocyclic structure two compounds have been prepared using the *S*-t-butyl 4-diethylphosphono-3-oxobutanethioate (2) to set up an *E*-double bond[15,16] within the rings. Compound (2) was reacted with 11-(t-butyldimethylsilyloxy)undecanal (14) to give an 84% yield of the coupled β-keto-alkene (15). Following deprotection with HF in acetonitrile the alcohol (16) was cyclised with copper (I) trifluoroacetate to give the unsaturated β-ketomacrolide (17) in 35% yield.



Once again the structure and solid state conformation of (17) was determined by X-ray crystallography (Figure 4).

In a similar fashion the thioester phosphonate (2) was reacted with the aldehyde (18) to give an excellent yield of the *E*-coupled product (19). Deprotection of (19) to give the free hydroxyl derivative (20) required tetra-n-butylammonium fluoride in tetrahydrofuran. Dimerisation of (20) to the diolide (21) was then achieved using



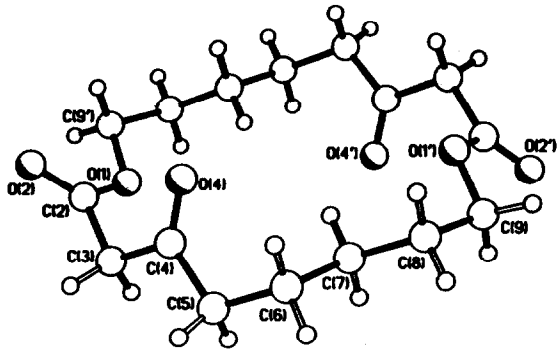


Fig. 1, the molecular structure of (22) with crystallographic numbering. The sequence of torsion angles within the asymmetric portion starting with that about the O(1)-C(2) bond is; *a*, *g*+, *a*, *a*, *g*-, *a*, *a*, *g*+, *a*.

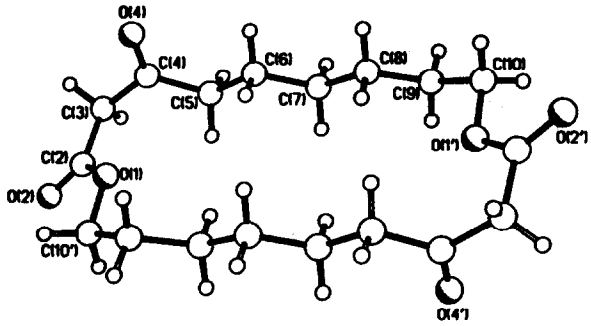


Fig. 2, the molecular structure of (23) with crystallographic numbering. The sequence of torsion angles within the asymmetric portion starting with that about the O(1)-C(2) bond is; *a*, 1, *g*+, *a*, *a*, *a*, *a*, *g*+, *a*.

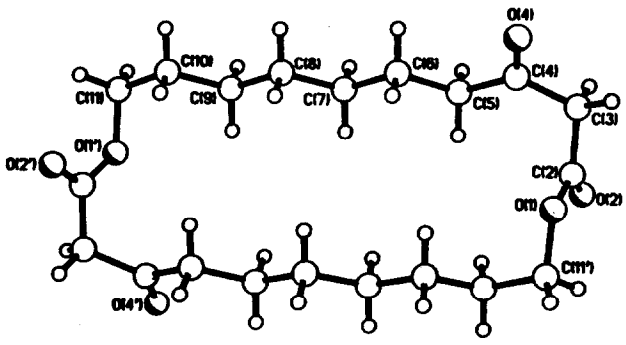


Fig. 3, the molecular structure of (24) with crystallographic numbering. The sequence of torsion angles within the asymmetric portion starting with that about the O(1)-C(2) bond is; *a*, *g*-, *g*-, *a*, *a*, *a*, *a*, *a*, *a*, *g*+, *g*+

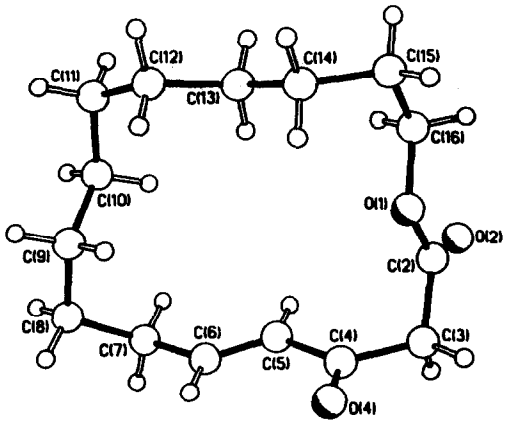


Fig. 4, the molecular structure of (17) with crystallographic numbering. The sequence of torsion angles within the macrolide starting with that about the O(1)-C(2) bond is; *a*, *g*+, *g*+, *a*, *a*, (-136), *g*+, *g*+, *a*, *g*+, *g*+, *a*, *a*, *g*-, *g*-, *a* .

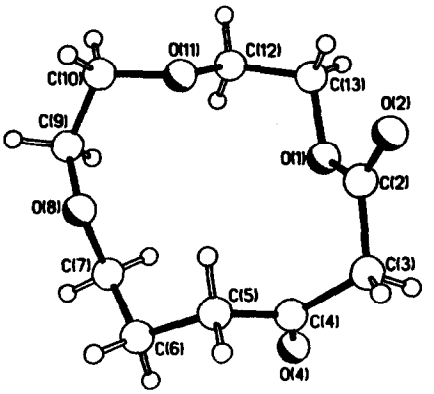


Fig. 5, the molecular structure of (32) with crystallographic numbering. The sequence of torsion angles within the macrolide starting with that about the O(1)-C(2) bond is; *a*, *g*-, *g*-, *a*, *g*-, *g*-, *a*, (-133), *g*+, *g*+, *a*, *g*+, (-126).

copper (I) trifluoroacetate as in previous examples. Various unsuccessful attempts were made to alter these reaction conditions to selectively afford the corresponding monomeric macrolide of (20), since this would have constituted a synthesis of the natural product diplodiolide[17].

The polyoxygenated compounds reported in the above studies are now being evaluated as potential metal speciation materials. We are also exploring the chemistry of the unusual β-dicarbonyl arrangement and developing routes to related amidic systems.

We acknowledge SERC, (Grant No. GR/D2502.6), (postdoctoral fellowship M.J.F.) for financial support.

Experimental.

^{1}H nmr spectra were recorded in $CDCl_3$ using a Joel FX 90Q or a Bruker WM250 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 983G spectrometer. Mass spectra were obtained using VG-7070B, VG 12-253 and VG ZAB-E instruments; microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Column chromatography was performed on Merck Kiesegel 60 (230-400 mesh) unless otherwise stated. Diethyl ether, dimethoxyethane and tetrahydrofuran were distilled from sodium-benzophenone ketyl; dichloromethane from phosphorous pentoxide; toluene from sodium; and acetonitrile from calcium hydride before use. Petroluem ether b.p. 40-60°C was distilled before use. Other solvents and reagents were purified by standard procedures as necessary. Analytical thin layer chromatography was performed using pre-coated glass backed plates (Merck Kieselgel 60 F_{254}) and visualised by ultra-violet, acidic ammonium molybdate (IV) or iodine as appropriate.

General procedure for the preparation of thioesters.

S-t-butyl 3-oxobutanethioate (1) (1 equiv.) in dry DME was added dropwise to a suspension of sodium hydride (1.1 equiv.) in dry DME at -20°C under argon. After stirring for 5min, the colourless solution was cooled to -40°C and n-butyllithium (1.1 equiv.) was added to generate the dianion. The yellow solution was allowed to warm to -20°C, stirred for 5min and recooled to -40°C. The iodide (1.1 equiv.) in DME was added dropwise and the reaction mixture allowed to warm to 0°C over 1h. The solution was poured into saturated aqueous ammonium chloride solution and extracted with ether. The organic phase was washed with water (1x)

and brine (1x) and the aqueous washes re-extracted with ether (1x). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. Chromatography gave the pure thioester.

S-t-Butyl 8-(t-butyldimethylsilyloxy)-3-oxooctanethioate.
The dianion, from *S*-t-butyl 3-oxobutanethioate (1g, 5.7mmol), sodium hydride (190mg, 80% disp., 6.3mmol) and n-butyllithium (4.2ml, 1.5M in hexanes, 6.3mmol), was alkylated with 4-(t-butyldimethylsilyloxy)butyl iodide (1.98g, 6.3mmol) according to the method described in the general procedure above. Work-up followed by chromatography (5% ether-light petroleum b.p. 40-60°C) gave the title compound (1.4g, 67%) as a pale red oil; δ (250MHz, $CDCl_3$) (46% enol) 0.04 (6H, s), 0.90 (9H, s), 1.31-1.71 (15H, m), 2.16 and 2.58 (2H, 2t, J 7.5 Hz), 3.59 (1.1H, s), 3.64 (2H, t, J 7.5 Hz), 5.26 (0.45H, s), 10.18 (0.45H, s); ν_{max} (film) 2933, 1722, 1677, 1616, 1254, 1100, 836, 776 cm^{-1}; mass spectrum m/z 303 (M^+-^{t}Bu), 247, 213, 131, 75, 57; analysis found : C, 59.85; H, 10.16; S, 8.97; $C_{18}H_{36}O_3SSi$ requires : C, 59.95; H, 10.06; S, 8.89%.

S-t-Butyl 9-(t-butyldimethylsilyloxy)-3-oxononanethioate.
The dianion from *S*-t-butyl 3-oxobutanethioate (4g, 22.9mmol), sodium hydride (1g, 60% disp., 25.3mmol) and n-butyllithium (16.4ml, 1.54M in hexanes, 25.3mmol), was alkylated with 5-(t-butyldimethylsilyloxy)pentyl iodide (8.3g, 25.3mmol) according to the method described in the general procedure above. Work-up followed by chromatography (5% ether-light petroleum b.p. 40-60°C) gave the desired compound (5.1g, 59%) as a pale red oil; δ (250MHz, $CDCl_3$) (35% enol) 0.02 (6H, s), 0.86 (9H, s), 1.23-1.36 and 1.39-1.64 (17H, m), 2.09 and 2.51 (2H, 2t, J 7.3 Hz), 3.53 (1.3H, s), 3.56 (2H, t, J 6.4 Hz), 5.29 (0.35H, s); ν_{max} (film) 2931, 1721, 1676, 1615, 1254, 1099, 837, 775 cm^{-1}; mass spectrum m/z 317 (M^+-^{t}Bu), 261, 227, 201, 185, 75, 57; analysis found : C, 61.10; H, 10.38; $C_{19}H_{38}O_3SSi$ requires : C, 60.91; H, 10.22%.

S-t-Butyl 9-(t-butyldimethylsilyloxy)-3-oxodecanethioate.
The dianion from *S*-t-butyl 3-oxobutanethioate (1g, 5.7mmol), sodium hydride (0.3g, 50% disp., 6.3mmol) and n-butyllithium (4.5ml, 1.4M in hexanes, 6.3mmol), was alkylated with 5-(t-butyldimethylsilyloxy)hexyl iodide (2.16g, 6.3mmol) according to the method described in the general procedure above. Work-up followed by chromatography (5% ether-light petroleum b.p. 40-60°C) afforded the above product (1.37g, 58%) as a pale red oil; δ (250MHz, $CDCl_3$) (40% enol) 0.05 (6H, s), 0.88 (9H, s),1.0 and 1.1 (3H, 2s), 1.27-1.67 (27H, m), 2.13 and 2.53 (2H, 2t, J 7.0 Hz), 3.56 (1.2H, s, keto), 3.75 (1H, m), 5.32 (0.4H, s,), 12.9 (0.4H, s); ν_{max} (film) 2932, 1725, 1677, 1615, 1364, 1081, 836 cm^{-1}; mass spectrum m/z 331 (M^+-^{t}Bu), 241, 215, 159, 75, 57; analysis found : C, 62.05; H, 10.54; S, 8.08; $C_{20}H_{40}O_3SSi$ requires : C, 61.80; H, 10.37; S, 8.25%.

S-t-Butyl 10-(t-butyldimethylsilyloxy)-3-oxodecanethioate.
The dianion from *S*-t-butyl 3-oxobutanethioate (2g, 11.5mmol), sodium hydride (0.5g, 60% disp., 12.6mmol) and n-butyllithium (8.4ml, 1.5M in hexanes, 12.6mmol), was alkylated with 6-(t-butyldimethylsilyloxy)hexyl iodide (4.3g, 12.6mmol) according to the method described in the general procedure above. Work-up followed by chromatography (5% ether-light petroleum b.p. 40-60°C) gave the title compound (2.63g, 59%) as a pale red oil; δ (250MHz, $CDCl_3$) (66% enol) 0.05 (6H, s), 0.89 (9H, s), 1.25-1.66 (19H, m), 2.14 and 2.56 (2H, 2t, J 7.5 Hz), 3.58 (0.66H, s), 3.64 (2H, t, J 7.5 Hz), 5.36 (0.66H, s); ν_{max} (film) 2930, 1724, 1676, 1614, 1255, 1100, 836, 775 cm^{-1}; mass spectrum m/z 331 (M^+-^{t}Bu), 275, 241, 199, 190, 75, 57; analysis found : C, 61.73; H, 10.66; $C_{20}H_{40}O_3SSi$ requires : C, 61.80; H, 10.37%.

S-t-Butyl 12-(t-butyldimethylsilyloxy)-3-oxododecanethioate.
The dianion from *S*-t-butyl 3-oxobutanethioate (2g, 11.5mmol), sodium hydride (0.5g, 60% disp., 12.6mmol) and n-butyllithium (8.2ml, 1.54M in hexanes, 12.6mmol), was alkylated with 8-(t-butyldimethylsilyloxy)octyl iodide (4.7g, 12.6mmol) according to the method described in the general procedure above. Work-up followed by chromatography (5% ether-light petroleum b.p. 40-60°C) afforded the desired compound (1.87g, 39%) as a pale red oil; δ (250MHz, $CDCl_3$) (35% enol) 0.04 (6H, s), 0.87 (9H, s), 1.23-1.33 and 1.43-1.61 (23H, m), 2.11 and 2.52 (2H, 2t, J 7.5 Hz), 3.54 (1.3H, s), 3.58 (2H, t, J 6.6 Hz), 5.31 (0.35H, s); ν_{max} (film) 2929, 1723, 1675, 1613, 1254, 1098, 836, 775 cm^{-1}; mass spectrum m/z 359 (M^+-^{t}Bu), 303, 269, 227, 185, 75, 57; analysis found : C, 63.32; H, 10.64; $C_{22}H_{44}O_3SSi$ requires : C, 63.34; H, 10.64%.

S-t-Butyl 15-(t-butyldimethylsilyloxy)-3-oxopentadecanethioate.

The dianion from *S*-t-butyl 3-oxobutanethioate (5g, 29.0mmol), sodium hydride (1.2g, 60% disp., 29.0mmol) and n-butyllithium (18.5ml, 1.55M in hexanes, 29.0mmol), was alkylated with 11-(t-butyldimethylsilyloxy)undecyl iodide (6.0g, 14.5mmol) according to the method described in the general procedure above. Work-up followed by chromatography (5% ether-light petroleum b.p. 40-60°C) gave the above product (4.5g, 67%) as a pale red oil; δ (250MHz, $CDCl_3$) (55% enol) 0.03 (6H, s), 0.87 (9H, s), 1.25-1.60 (29H, m), 2.12 and 2.53 (2H, 2t, J 7.5 Hz), 3.56 (1.3H, s), 3.61 (2H, t, J 6.7 Hz), 5.35 (0.55H, s), 9.88 (0.55H, s); ν_{max} (film) 2927, 1723, 1675, 1613, 1254, 1099, 836, 775 cm^{-1}; mass spectrum m/z 401 (M^+-^{t}Bu), 345, 312, 285, 227, 261, 90, 75, 57; analysis found : C, 65.34; H, 11.12, S, 7.25; $C_{25}H_{50}O_3SSi$ requires : C, 65.45; H, 10.98, S, 6.99%.

S-t-Butyl 6-(2-(t-butyldimethylsilyloxy)ethoxy)-3-oxohexanethioate.

The dianion from *S*-t-butyl 3-oxobutanethioate (6g, 34.5mmol), sodium hydride (1.5g, 60% disp., 37.9mmol) and n-butyllithium (24.5ml, 1.55M in hexanes, 37.9mmol), was alkylated with 2-(2-(t-butyldimethylsilyloxy)ethoxy)ethyl iodide (5.7g, 17.3mmol) according to the method described in the general procedure above. Work-up followed by chromatography (5% ether-light petroleum b.p. 40-60°C) afforded the title compound (2.8g, 42%) as a pale red oil; δ (250MHz, $CDCl_3$) (33% enol) 0.02 (6H, s), 0.85 (9H, s), 1.42 and 1.46 (9H, 2s), 1.81 (2H, qi, J 7.1 Hz) 2.18 (0.66H, dd, J 8.8, 7.0 Hz), 2.59 (1.34H, t, J 7.1 Hz) 3.43 (4H, m), 3.52 (1.34H, s), 3.68 (2H, m), 5.29 (0.33H, s); ν_{max} (film) 2929, 1723, 1675, 1615, 1254, 1105, 836 cm^{-1}; mass spectrum m/z 377 (MH^+), 319, 287, 201, 111, 85, 57; analysis found : C, 57.68; H, 9.92; S, 8.39; $C_{18}H_{36}O_4SSi$ requires : C, 57.40; H, 9.63; S, 8.51%.

S-t-butyl-6-(2-(2-(t-butyldimethylsilyloxy)ethoxy)ethoxy)-3-oxohexanethioate.

A stirred suspension of sodium hydride (267mg, 60% disp., 6.6mmol) in dry DME (20ml) was cooled to -30°C and treated dropwise with 2-methyl-2-propanethiol (750μl, 0.60g, 6.66mmol). The mixture was allowed to warm to 0°C over 15min then recooled to -30°C and treated dropwise with diketene (560μl, 0.60g, 7.14mmol). The mixture was stirred for 1h then warmed to 0°C and stirred a further 15min. The clear yellow solution was then cooled to -35°C and treated dropwise with n-butyllithium (2.5M in hexane, 2.0ml, 5mmol). The resulting dark red solution was stirred for 15min then treated dropwise with a solution of 2-(2-(t-butyldimethylsilyloxy)ethoxy)ethoxyethyl iodide (1.87g, 5mmol) in dry DME (5ml). The mixture was stirred at -35°C for 1h and then allowed to warm to ambient temperature (28°C). After stirring for 1h at this temperature the mixture was cooled to 0°C and quenched with aqueous ammonium chloride solution (40ml). The aqueous phase was extracted with ether (3 x 100ml) and the combined organic extracts were washed with brine (50ml), dried (Na_2SO_4) and evaporated to give, after chromatography (gradient elution 10% ether-light petroleum b.p. 40-60°C to 50% ether-light petroleum b.p. 40-60°C), the desired product as a clear oil (840mg, 40%) ν_{max} (film) 2954, 2927, 1723, 1675, 1614, 1362, 1253, 939, 836 and 777 cm^{-1}; δ (60MHz, $CDCl_3$) 0.10 (6H, s), 0.95 (9H, s), 1.50 (9H, s), 1.9 (2H, m), 2.65 (2H, t, J 6 Hz), 3.3-3.9 (12H, m), 5.31 (0.1H, s); mass spectrum m/z 363 (M^+-^{t}Bu), 331, 57; accurate mass measurement found : 363.1656; $C_{16}H_{31}O_5SSi$ requires : 363.1661 amu; analysis found : C, 57.2; H, 9.75%; $C_{20}H_{40}O_5SSi$ requires : C, 57.1; H, 9.58%.

S-t-butyl-7-(2-(2-(t-butyldimethylsilyloxy)ethoxy)ethoxy)-3-oxoheptanethioate.

A stirred suspension of sodium hydride (400 mg, 60% disp., 10mmol) in dry DME (30 ml) was cooled to -30°C and treated dropwise with 2-methyl-2-propanethiol (1.15ml, 0.90g, 10mmol). The mixture was allowed to warm to 0°C over 15min then recooled to -30°C and treated dropwise with diketene (800μl, 0.84g, 10mmol). The mixture was stirred for 1h then warmed to 0°C and stirred a further 15min. The clear yellow solution was then cooled to -35°C and treated dropwise with n-butyllithium (2.5M in hexane, 4.0ml, 10mmol). The resulting dark red solution was stirred for 15min then treated dropwise with a solution of 2-(2-(t-butyldimethylsilyloxy)ethoxy)ethoxypropyl iodide (2.0g, 5.56mmol) in dry DME (5 ml). The mixture was stirred at -35°C for 1h and then allowed to warm to ambient temperature (28°C). After stirring for 1h at this temperature the mixture was cooled to 0°C and quenched with aqueous ammonium chloride solution (40ml). The aqueous phase was extracted with ether (3 x 100ml) and the combined organic extracts were washed with brine (50ml), dried (Na_2SO_4) and evaporated to give, after chromatography (gradient elution 10% ether-light petroleum b.p. 40-60°C to 50% ether-light petroleum b.p. 40-60°C), the title compound as a clear oil (780mg, 32%) ν_{max} (film) 2954, 1722, 1675, 1617, 1363, 1254, 1107, 835 and 778 cm^{-1}; δ (250MHz, $CDCl_3$) 0.05 (6H, s), 0.88 (9H, s),1.47 and 1.50 (9H, 2s), 1.55-1.70 (4H, m), 2.56 (2H, t, J 7 Hz), 3.44 (2H, m), 3.55 (6H, m), 3.62 (2H, m), 3.77 (2H, t, J 5 Hz), 5.32 (0.1H, s); mass spectrum m/z 377 (M^+-^{t}Bu), 277, 235, 216, 84; accurate mass measurement found : 377.1805; $C_{17}H_{33}O_5SSi$ requires : 377.1818 amu.

S-t-butyl-12-triphenylmethyloxy-11-benzyloxy-3-oxododecanethioate

A stirred suspension of sodium hydride (2.66g, 60% disp., 67mmol) in dry DME (200ml) was cooled to -30°C and treated dropwise with 2-methyl-2-propanethiol (7.5ml, 6g, 67mmol). The mixture was allowed to warm to 0°C over 15min then recooled to -30°C and treated dropwise with diketene (5.22ml, 5.6g, 67mmol). The mixture was stirred for 1h then warmed to 0°C and stirred a further 15min. The clear yellow solution was then cooled to -35°C and treated dropwise with n-butyllithium (2.5M in hexane, 2.66ml, 6.66mmol). The resulting dark red solution was stirred for 15min then treated dropwise with a solution of 8-triphenylmethyloxy-7-benzyloxyoctyl iodide (20.1g, 33.3mmol) in dry DME (100ml). The mixture was stirred at -35°C for 1h and then allowed to warm to ambient temperature (28°C). After stirring for 1h at this temperature the mixture was cooled to 0°C and quenched with aqueous ammonium chloride solution (200ml). The aqueous phase was extracted with ether (3 x 300ml) and the combined organic extracts were washed with brine (100ml), dried (Na_2SO_4) and evaporated to give, after chromatography (gradient elution light petroleum b.p. 40-60°C to 10% ether-light petroleum b.p. 40-60°C), the above product (15g, 69%) ν_{max} (film) 2928, 2859, 1721, 1674, 1614, 1364, 1080 and 706 cm^{-1}; δ (60MHz, $CDCl_3$) 1.0-1.7 (21H, m), 2.5 (2H, t, J 7.1 Hz), 3.2-3.5 (5H, m), 4.6 (2H, qa, J 7 Hz), 7.1-7.6 (20H, m); mass spectrum m/z 291 (MH^+-CPh_3-^tBuSCO), 243; accurate mass measurement found : 291.1956; $C_{18}H_{27}O_3$ requires : 291.1960 amu.

General procedure for the preparation of the hydroxy thioesters.

A solution of 40% aqueous hydrogen fluoride in acetonitrile (1M solution, 3 equiv.) was added to the thioester (1 equiv.) at ambient temperature. After stirring for 15min the solution was poured into water and extracted with dichloromethane. The organic phase was dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography gave the pure alcohol.

S-t-Butyl 8-Hydroxy-3-oxooctanethioate.

S-t-Butyl 8-(t-butyldimethylsilyloxy)-3-oxooctanethioate (500mg, 1.39mmol) was converted to the alcohol as described in the general procedure above. Chromatography (70% ether-light petroleum b.p. 40-60°) gave the product (340mg, 99%) as a pale yellow oil; δ (250MHz, $CDCl_3$) (22% enol) 1.24-1.71 (15H, m), 2.18 and 2.60 (2H, 2t, J 7.5 Hz), 2.29 (1H, br s), 3.60 (1.6H, s), 3.65 (2H, t, J 7.5 Hz), 5.38 (0.2H, s); ν_{max} (film) 3398, 2933, 1721, 1674, 1614, 1365, 1083 cm^{-1}; mass spectrum m/z 172 (M^+-^tBu-H_2O), 139, 97, 57; analysis found : C, 58.34; H, 9.03; S, 13.05; $C_{12}H_{22}O_3S$ requires : C, 58.50; H, 9.00; S, 13.01%.

S-t-Butyl 9-Hydroxy-3-oxononanethioate.

S-t-Butyl 9-(t-butyldimethylsilyloxy)-3-oxononanethioate (4g, 10.7mmol) was converted to the alcohol as described in the general procedure above. Chromatography (50% ether-light petroleum b.p. 40-60°) afforded the alcohol (2.5g, 90%) as a colourless oil; δ (250MHz, $CDCl_3$) (11% enol) 1.17-1.36 and 1.40-1.60 (17H, m), 1.97 (1H, br s), 2.06 and 2.47 (2H, 2t, J 7.2 Hz), 3.49 (1.8H, s), 3.54 (2H, t, J 6.5 Hz), 5.25 (0.1H, s); ν_{max} (film) 3386, 2931, 1718, 1675, 1613, 1364, 1079 cm^{-1}; mass spectrum m/z 243 (MH^+-H_2O), 204, 171, 144, 129, 111, 57; analysis found : C, 60.11; H, 9.44; S, 12.04; $C_{13}H_{24}O_3S$ requires : C, 59.97; H, 9.29; S, 12.31%.

S-t-Butyl 9-Hydroxy-3-oxodecanethioate.

S-t-Butyl 9-(t-butyldimethylsilyloxy)-3-oxodecanethioate (1.3g, 3.36mmol) was converted to the alcohol as described in the general procedure above. Chromatography (50% ether-light petroleum b.p. 40-60°) gave the title compound (0.9g, 98%) as a pale yellow oil; δ (250MHz, $CDCl_3$) (45% enol) 1.17 and 1.18 (3H, 2s), 1.22-1.66 (17H, m,), 2.13 and 2.54 (2H, 2t, J 7 Hz), 3.57 (1.1H, s), 3.78 (1H, m), 5.33 (0.45H, s); ν_{max} (film) 3413, 1721, 1677, 1615, 1365, 1081, 733 cm^{-1}; mass spectrum m/z 217 (M^+-^tBu), 185, 167, 125, 82, 57; analysis found : C, 61.27; H, 9.78; S, 11.92; $C_{14}H_{26}O_3S$ requires : C, 61.28; H, 9.55; S, 11.68%.

S-t-Butyl 10-Hydroxy-3-oxodecanethioate.

S-t-Butyl 10-(t-butyldimethylsilyloxy)-3-oxodecanethioate (2.5g, 6.4mmol) was converted to the alcohol as described in the general procedure above. Chromatography (70% ether-light petroleum b.p. 40-60°) afforded the desired product (1.67g, 95%) as a colourless oil; δ (250MHz, $CDCl_3$) (40% enol) 1.24-1.66 (19H, m), 2.10 (1H, br s), 2.14 and 2.55 (2H, 2t, J 7.5 Hz), 3.56 (1.2H, s), 3.65 (2H, t, J 7.5 Hz), 5.33 (0.4H, s); ν_{max} (film) 3365, 2931, 1720, 1674, 1614, 1364, 1079 cm^{-1}; mass spectrum m/z 185 (M^+-S^tBu), 167, 158, 143, 125, 83, 57; accurate mass measurement found : 185.1181; $C_{10}H_{17}O_3$ requires : 185.1178 amu.

S-t-Butyl 12-Hydroxy-3-oxododecanethioate.

S-t-Butyl 12-(t-butyldimethylsilyloxy)-3-oxododecanethioate (1.8g, 4.3mmol) was converted to the alcohol as described in the general procedure above. Chromatography (50% ether-light petroleum b.p. 40-60°) gave the desired alcohol (1.3g, 99%) as a pale yellow oil; δ (250MHz, $CDCl_3$) (25% enol) 1.18-1.32 and 1.38-1.57 (23H, m), 1.97 (1H, br s), 2.06 and 2.47 (2H, m), 3.50 (1.5H, s), 3.56 (2H, t, J 6.6 Hz), 5.27 (0.25H, s); ν_{max} (film) 3378, 2928, 1720, 1676, 1613, 1364, 1161 cm^{-1}; mass spectrum m/z 213 (M^+-S^{t}Bu), 186, 153, 110, 57; analysis found : C, 63.35; H, 10.20; $C_{16}H_{30}O_3S$ requires : C, 63.54; H, 9.99%.

S-t-Butyl 15-Hydroxy-3-oxopentadecanethioate.

S-t-Butyl 15-(t-butyldimethylsilyloxy)-3-oxopentadecanethioate (4g, 8.7mmol) was converted to the alcohol as described in the general procedure above. Chromatography (50% ether-light petroleum b.p. 40-60°) gave the title compound (2.7g, 90%) as a colourless oil which solidified on cooling; δ (250MHz, $CDCl_3$) (12% enol) 1.18-1.60 (29H, m), 2.10 and 2.49 (2H, 2t, J 7.3 Hz), 3.52 (1.8H, s), 3.60 (2H, t, J 6.6 Hz), 5.29 (0.1H, s); ν_{max} (film) 3366, 2926, 1720, 1675, 1612, 1364, 1180 cm^{-1}; mass spectrum m/z 255 (M^+-S^{t}Bu), 237, 228, 195, 152, 57; analysis found : C, 66.17; H, 10.75; S, 9.47; $C_{19}H_{36}O_3S$ requires : C, 66.23; H, 10.53; S, 9.30%.

S-t-Butyl 6-(2-Hydroxyethoxy)-3-oxohexanethioate.

S-t-Butyl 6-(2-(t-butyldimethylsilyloxy)ethoexy)-3-oxohexanethioate (2g, 5.3mmol) was converted to the alcohol as described in the general procedure above. Chromatography (70% ether-light petroleum b.p. 40-60°) afforded the above product (1.1g, 80%) as a pale yellow oil; δ (250MHz, $CDCl_3$) (15% enol) 1.42 and 1.46 (9H, 2s), 1.85 (2H, qi, J 6.3 Hz) 2.19 (0.3H, dd, J 7.5, 6.3 Hz), 2.23 (1H, br s), 2.59 (1.7H, t, J 6.9 Hz), 3.45 (4H, m), 3.55 (1.7H, s), 3.66 (2H, m), 5.31 (0.15H, s); ν_{max} (film) 3426, 2961, 1717, 1672, 1615, 1364, 1122 cm^{-1}; mass spectrum m/z 205 (M^+-^{t}Bu), 200, 173, 146, 111, 87, 57; analysis found : C, 54.69; H, 8.67; S, 12.12; $C_{12}H_{22}O_4S$ requires : C, 54.94; H, 8.45; S, 12.22%.

S-t-butyl-6-(2-(2-hydroxyethoxy)ethoxy)-3-oxohexanethioate.

A stirred solution of *S*-t-butyl-6-(2-(2-(t-butyldimethylsilyloxy)ethoxy)ethoxy)-3-oxohexanethioate (830mg, 1.9mmol) in dry acetonitrile (20ml) was treated with aqueous hydrogen fluoride (150μl, 40%) and stirred for 2h at ambient temperature. The reaction mixture was poured into ether (50ml) and saturated aqueous sodium bicarbonate (20ml) and separated. The aqueous phase was extracted with ether (2 x 20ml) and the combined organic extracts were washed with brine (20ml), dried (Na_2SO_4), evaporated and chromatographed (ether) to give the title compound as a clear oil (0.45g, 69%) ν_{max} (film) 3446, 2866, 1716, 1670, 1615, 1364, 1083 and 989 cm^{-1}; δ (60MHz, $CDCl_3$) 1.46 (9H, s), 1.83 (2H, qi, J 7 Hz), 2.58 (2H, t, J 7 Hz), 3.3-3.9 (13H, m), 5.30 (0.1H, s); mass spectrum m/z 307 (MH^+), 217, 111; analysis found : C, 54.8; H, 8.73; $C_{14}H_{26}O_5S$ requires : C, 54.9; H, 8.55%.

S-t-butylthio-7-(2-(2-hydroxyethoxy)ethoxy)-3-oxoheptanethioate.

A stirred solution of *S*-t-butyl-7-(2-(2-(t-butyldimethylsilyloxy)ethoxy)ethoxy)-3-oxoheptanoate (750mg, 1.76mmol) in dry acetonitrile (20ml) was treated with aqueous hydrogen fluoride (150μl, 40%) and stirred for 2h at ambient temperature. The reaction mixture was poured into ether (50ml) and saturated aqueous sodium bicarbonate (20ml) and separated. The aqueous phase was extracted with ether (2 x 20ml) and the combined organic extracts were washed with brine (20ml), dried (Na_2SO_4), evaporated and chromatographed (ether) to give the desired product as a clear oil (0.49g, 81%) ν_{max} (film) 3428, 2867, 1717, 1675, 1611, 1454, 1403, 1364 and 1117 cm^{-1}; δ (250MHz, $CDCl_3$) 1.47 and 1.50 (9H, 2s), 1.53-1.70 (4H, m), 1.70-2.00 (1H, br s), 2.58 (2H, t, J 7 Hz), 3.46 (2H, t, J 6 Hz), 3.54-3.8 (10H, m), 5.32 (0.1H, s); mass spectrum m/z 231 (M^+-S^{t}Bu), 125, 99, 57; accurate mass measurement found : 231.1219; $C_{11}H_{19}O_5$ requires : 231.1232 amu.

S-t-Butyl 12-hydroxy-11-benzyloxy-3-oxododecanethioate.

A stirred solution of *S*-t-butyl-12-triphenylmethyloxy-11-benzyloxy-3-oxododecanethioate (9g, 13.8mmol) in anhydrous methanol (1380ml) was treated with Amerlyst IR 15® acid resin (4.5g) at 0°C. After stirring for 1h the mixture was allowed to warm slowly to ambient temperature and stirred overnight. The mixture was filtered and the filtrate evaporated to give a yellow oil. This was dissolved in a small quantity of benzene and chromatographed (gradient elution 25% ether-light petroleum b.p. 40-60°C to ether) to give the alcohol as a clear oil (3.33g, 59%) ν_{max} (film) 3430, 2920, 1720, 1676, 1613, 1434, 1384, 1101 cm^{-1}; δ (90MHz, $CDCl_3$) 1.2 - 1.8 (21H, m), 2.1 and 2.5 (3H, 2br t, J 6 Hz), 3.4-3.8 (4.6H, m), 4.6 (2H, s), 5.3 (0.2H, s), 7.4 (5H, s);

mass spectrum m/z 391 (MH^+-H_2O), 333, 225, 211, 91; accurate mass measurement found : 391.2311; $C_{23}H_{35}SO_3$ requires : 391.2307 amu.

General procedure for the macrolactonization of the hydroxy-thioesters

The thioester (1 equiv.) in dry degassed dichloromethane (DCM) was added, under an argon atmosphere, to copper (I) trifluoroacetate (5 equiv.) in dry degassed DCM (0.1M solution) containing disodium hydrogen phosphate buffer (10 equiv.) to give a final concentration of 0.02M with respect to the thioester. A black precipitate was formed immediately on addition of the thioester and the mixture was stirred at ambient temperature until no starting material remained by tlc analysis. The solution was poured into DCM (50mlmmol^{-1}) and saturated aqueous ammonium chloride solution (50mlmmol^{-1}) containing aqueous ammonia solution (S.G. 0.880, 1mlmmol^{-1}) and stirred vigorously in the presence of air for 20min. The mixture was filtered through a plug of glass wool, the layers separated and the aqueous phase re-extracted with DCM (2 x). The combined organics were dried (Na_2SO_4) and the solvent removed *in vacuo*. Chromatography afforded the pure product(s).

3-Oxo-octan-8-diolide (22).

S-t-Butyl 8-hydroxy-3-oxooctanethioate (150mg, 0.61mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method described in the general procedure, chromatography on silica in 1% ether-DCM gave the diolide (36mg, 38%) as a white solid. Recrystallisation (ether-DCM) afforded colourless needles, m.p. 115-116°C; δ (250MHz, $CDCl_3$) 1.34-1.45 and 1.56-1.74 (12H, 2m), 2.61 (4H, t, J 6.3 Hz), 3.42 (4H, s), 4.18 (4H, t, J 5.8 Hz); ν_{max} (KBr disc) 2943, 1741, 1702, 1398, 1265 cm^{-1} ; mass spectrum m/z 313 (MH^+), 294, 211, 157, 139 , 97; analysis found : C, 61.66; H, 7.85; $C_{16}H_{24}O_6$ requires : C, 61.52; H, 7.74%.

3-Oxo-nonan-9-diolide (23).

S-t-Butyl 9-hydroxy-3-oxononanethioate (1g, 3.8mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method described in the general procedure, chromatography on silica in 1% ether-DCM furnished the title compound (320mg, 49%) as a white solid. Recrystallisation (ether-DCM) gave colourless needles, m.p. 115-117°C; δ (250MHz, $CDCl_3$) 1.29-1.44 and 1.55-1.71 (16H, 2m), 2.54 (4H, t, J 5.8 Hz), 3.43 (4H, s), 4.16 (4H, t, J 5.8 Hz); ν_{max} (film) 2935, 1742, 1708, 1464, 1405, 1257, 978 cm^{-1}; mass spectrum m/z 340 (M^+) 255, 239, 171, 153, 111, 83, 69; analysis found : C, 63.43; H, 8.41; $C_{18}H_{28}O_6$ requires : C, 63.51; H, 8.29%.

3-Oxo-decan-9-diolide (29).

S-t-Butyl 9-hydroxy-3-oxodecanethioate (1g, 3.8mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method described in the general procedure, chromatography on silica in 50% ether-light petroleum b.p. 40-60°C gave the diolide (320mg, 49%) as a white solid. Recrystallisation (ether-DCM) afforded colourless needles, m.p. 85-87°C (not suitable for X-ray chrystallograhpy); δ (250MHz, $CDCl_3$) 1.24 (6H, d, J 6.8 Hz), 1.17-1.40 and 1.47-1.68 (16H, 2m), 2.41-2.65 (4H, m), 3.41, 3.36 and 3.45 (4H, s and 2d, J 14.9 Hz meso and dl), 4.98 (4H, m); ν_{max} (film) 2937, 1720, 1709, 1259, 1043 cm^{-1}; mass spectrum m/z 368 (M^+) 267, 185, 167, 125, 55; analysis found : C, 64.90; H, 8.78; $C_{20}H_{32}O_6$ requires : C, 65.19; H, 8.75%.

3-Oxo-decan-10-diolide (24).

S-t-Butyl 10-hydroxy-3-oxodecanethioate (100mg, 0.36mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method described in the general procedure, chromatography on silica in 5% ether-DCM afforded the diolide (26mg, 40%) as a white solid. Recrystallisation (ether-DCM) furnished colourless needles, m.p. 105-107°C; δ (250MHz, $CDCl_3$) 1.23-1.44 and 1.52-1.70 (20H, 2m), 2.55 (4H, t, J 7.3 Hz), 3.39 (4H, s), 4.14 (4H, t, J 6.0 Hz); ν_{max} (KBr disc) 2926, 1739, 1707, 1296, 1184, 1086 cm^{-1}; mass spectrum m/z 368 (M^+), 350, 269, 227, 185, 166, 125, 82; analysis found : C, 65.26; H, 8.68; $C_{20}H_{32}O_6$ requires : C, 65.19; H, 8.75%.

3-Oxo-dodecan-12-diolide (26) and 3-oxododecan-12-olide (25).

S-t-Butyl 12-hydroxy-3-oxododecanethioate (1.1g, 3.6mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method described in the general procedure, chromatography on silica (gradient elution 3% to 5% ether-DCM) gave firstly 3-oxo-dodecan-12-olide

(96mg, 12%) as a colourless oil which solidified on standing; δ (250MHz, $CDCl_3$) 1.25-1.44 and 1.59-1.72 (14H, 2m), 2.61 (2H, t, J 6.5 Hz), 3.42 (2H, s), 4.18 (2H, dd, J 6.3, 5.3 Hz); ν_{max} (film) 2936, 1737, 1700, 1460, 1261, 1137, 985 cm^{-1}; mass spectrum m/z 212 (M^+), 194, 152, 110, 82, 69; accurate mass measurement found : 212.1415; $C_{12}H_{20}O_3$ requires : 212.1412 amu; and secondly, 3-oxododecan-12-diolide (321 mg, 42%), as a white solid. Recrystallisation from ether-DCM afforded white needles m.p. 110-112°C; δ (250MHz, $CDCl_3$) 1.22-1.38 and 1.57-1.65 (28H, 2m), 2.55 (4H, t, J 7.1 Hz), 3.41 (4H, s), 4.15 (4H, t, J 6.0 Hz); ν_{max} (KBr disc) 2922, 1741, 1707, 1292, 1181, 1089 cm^{-1}; mass spectrum m/z 424 (M^+), 406, 297, 213, 195, 153, 110; analysis found : C, 67.75; H, 9.58; $C_{24}H_{40}O_6$ requires : C, 67.89; H, 9.50%.

3-Oxo-pentadecan-15-diolide (28) and 3-oxopentadecan-15-olide (27).

S-t-Butyl 15-hydroxy-3-oxopentadecanethioate (200mg, 0.58mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method described in the general procedure, chromatography on silica (gradient elution DCM to 3% ether-DCM) gave firstly 3-Oxopentadecan-15-olide (106mg, 72%) as a colourless oil which solidified on standing; δ (250MHz, $CDCl_3$) 1.21-1.37 and 1.54-1.66 (20H, 2m), 2.49 (2H, t, J 7.1 Hz), 3.39 (2H, s), 4.12 (2H, dd, J 6.5, 5.1 Hz); ν_{max} (film) 2926, 1739, 1710, 1305, 1264 cm^{-1}; mass spectrum m/z 254 (M^+), 236, 152, 103, 82, 55; accurate mass measurement found : 254.1875; $C_{12}H_{20}O_3$ requires : 254.1882 amu; and secondly, 3-oxopentadecan-15-diolide (12 mg, 8%) as a white solid. Recrystallisation from ether-DCM furnished white needles m.p. 130-131°C; δ (250MHz, $CDCl_3$) 1.20-1.38 and 1.52-1.68 (40H, 2m), 2.51 (4H, t, J 7.2 Hz), 3.40 (4H, s), 4.12 (4H, t, J 6.0 Hz); ν_{max} (KBr disc) 2919, 1747, 1708, 1465, 1232, 723 cm^{-1}; mass spectrum m/z 508 (M^+), 490, 339, 255, 236, 152, 103, 55; analysis found : C, 70.86; H, 10.51; $C_{30}H_{52}O_6$ requires : C, 70.83; H, 10.30%.

11-Benzyloxy-3-oxo-dodecan-12-diolide (30).

S-t-Butyl 12-hydroxy-11-benzyloxy-3-oxododecanethioate (3.3mg, 7.8mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method described in the general procedure, chromatography on silica (gradient elution DCM to 3% ether-DCM) afforded the diolide (370mg, 7%) as a colourless oil which solidified on standing; δ (90MHz, $CDCl_3$) 1.0-1.65 (42H, m), 2.50 (4H, t, J 7.2 Hz), 3.40-3.65 (4H, m), 4.20 (4H, d, J 4 Hz), 4.48 (2H, d, J 12 Hz), 4.65 (2H, d, J 12 Hz); ν_{max} (film) 2929, 2855, 1741, 1709, 1605, 1452 cm^{-1}; mass spectrum m/z 545 (M^+-$PhCH_2$), 439, 421, 377, 354, 281, 261, 256, 244, 229, 211, 194, 169, 155, 116, 104, 91; accurate mass measurement found : 545.3066; $C_{31}H_{45}O_8$ requires : 545.2997 amu.

7-Oxa-3-oxononan-9-diolide (31).

S-t-Butyl 6-(2-hydroxyethoxy)-3-oxohexanthioate (500mg, 1.9mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method described in the general procedure, chromatography on silica in 30% ether-DCM gave the title compound (130mg, 39%) as a colourless oil which solidified on cooling m.p. 56-59°C; δ (250MHz, $CDCl_3$) 1.88 (4H, qi, J 6.6 Hz), 2.64 (4H, t, J 6.6 Hz), 3.47 (4H, t, J 6.6 Hz), 3.53 (4H, s), 3.58 (4H, m), 4.26 (4H, m); ν_{max} (film) 2870, 1741, 1710, 1260, 1128 cm^{-1} ; mass spectrum m/z 344 (M^+) 326, 301, 217, 173, 111, 86; accurate mass measurement found : 344.1471; $C_{16}H_{24}O_8$ requires : 344.1471 amu.

7,10-Dioxa-3-oxo-tridecan-13-olide.(32).

S-t-butyl-6-(2-(2-hydroxyethoxy)ethoxy)-3-oxohexanethioate (400mg, 1.3mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method described in the general procedure, chromatography on silica (ether), afforded the desired product (140mg, 50%) as a clear oil which crystallised on standing to give needles m.p. 38-40°C; δ (250MHz, $CDCl_3$) 1.88 (2H, qi, J 5.7 Hz), 2.85 (2H, t, J 5.7 Hz), 3.44 (2H, s), 3.47-3.62 (6H, m), 3.69 (2H, m), 4.34 (2H, m); ν_{max} (film) 2867, 1743, 1710, 1260, 1119 cm^{-1}; mass spectrum m/z 216 (M^+), 173, 128, 110, 86; accurate mass measurement found : 216.0994; $C_{10}H_{16}O_5$ requires : 216.0998 amu; analysis found : C, 55.7; H, 7.45; $C_{10}H_{16}O_5$ requires : C, 55.6; H, 7.46%.

8,11-Dioxa-3-oxo-tetradecan-14-olide (33).

S-t-butyl-7-(2-(2-hydroxyethoxy)ethoxy)-3-oxoheptanethioate (450mg, 1.3mmol) was treated with copper (1) trifluoroacetate as described in the general procedure above. After work-up according to the method

described in the general procedure, chromatography on silica (ether), afforded the title compound (100mg, 32%) as a clear oil which crystallised on standing to give needles m.p. 32-34 °C; δ (250MHz, $CDCl_3$) 1.58-1.69 (2H, m), 1.70-1.82 (2H, m), 2.87 (2H, t, J 7.5 Hz), 3.40 (2H, s), 3.48-3.64 (6H, m), 3.67-3.74 (2H, m), 4.34-4.50 (2H, m) ; ν_{max} (film) 2866, 1741, 1709, 1255, 1123 cm^{-1}; mass spectrum m/z 230 (M^+), 187, 124, 96, 86; accurate mass measurement found : 230.1153; $C_{10}H_{16}O_5$ requires : 230.1154 amu.

S-t-Butyl 4-Bromo-3-oxobutanethioate (3).

Bromine (0.88ml 17mmol) was added dropwise to a stirred sollution of diketene (1.35ml 17mmol) in carbon tetrachloride (50ml) at -10°C under an atmosphere of argon. The pale orange colour of the mixture was allowed to decolourise after each addition. The resulting pale yellow clear solution was stirred at -10°C for a further 15min after the bromine addition had been completed. This solution was then added *via* a cannula into a stirred solution of t-butylthiol (9.7ml, 86mmol) in dry dichloromethane (100ml) at -10°C under an atmosphere of argon. The resulting solution was stirred for a further 30min, allowed to warm to room temperature and poured into water (200 ml). The organic phase was washed with water (2 x 100ml), saturated aqueous sodium bicarbonate solution (100ml) and brine (100ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Chromatiography (40% dichloromethane-light petroleum b.p. 40-60°C) gave *S*-t-butyl 4-bromo-3-oxobutanthioate (3.14g, 73%) as a pale yellow oil; δ (60MHz, $CDCl_3$) (35% enol) 1.45 and 1.50 (9H, 2s), 3.75 and 3.85 (2H, 2s), 4.10 (1.3H, s), 5.55 (0.35H, s); ν_{max} (film) 2963, 1723, 1670, 1622, 1364, 1072 cm^{-1}; m/z 254 and 252 (M^+), 198, 173, 165, 163, 57; analysis found : C, 38.23; H, 5.31; $C_8H_{13}O_2BrS$ requires : C, 37.95; H, 5.18%.

S-t-Butyl 4-diethylphosphino-3-oxobutanethioate (2).

Diethyl phosphite (6.61ml, 51.3mmol) was added dropwise to a stirred suspension of sodium (2.36g, 103mmol) in tetrahydrofuran (THF) (100ml) at room temperature under argon. After the addition was complete the suspension was boiled for 90min and then cooled to -10°C to give a solution of sodium diethyl phosphite which was used crude without characterisation. *S*-t-Butyl 4-bromo-3-oxobutanethioate (11.8g, 46.6mmol) was added dropwise to a stirred suspension of sodium hydride (2.05g, 60% disp., 51.3mmol) in THF (120ml) at -10°C under argon. The resulting solution was stirred at -10°C for a further 30min, and the solution of sodium diethyl phosphite added dropwise *via* a cannula. The mixture was stirred for a further 1h at -10°C and then allowed to warm to room tmperature overnight, poured into saturated aqueous ammonium chloride (200ml) and diethyl ether (400ml). The organic phase was separated, the aqueous layer re-extracted with ether (2 x 100ml), and the combined organic phases washed with water (2 x 100ml) and brine (100ml), dried ($MgSO_4$) and evaporated to give the title compound as an orange oil (12.3g, 85%) requiring no further purification; δ (250 MHz, $CDCl_3$) (28% enol) 1.33 (6H, t, J 6.8 Hz), 1.44 and 1.50 (9H, 2s), 2.69 and 3.23 (4H, 2d, J 24 Hz), 3.78 (1.4H, s), 4.14 (4H, m), and 5.45 (0.3H, d, J 2.7 Hz); ν_{max} (film) 2964, 2926, 1723, 1674, 1617, 1456, 1262 cm^{-1}; m/z 310 (M^+), 253, 221, 194, 179, 57; analysis found : C, 46.44; H, 7.47; $C_{12}H_{23}O_5PS$ requires : C, 46.44; H, 7.47%.

S-t-Butyl 15-(t-butyldimethylsilyloxy)-3-oxo-4*E*-pentadecenethioate (15).

S-t-butyl 4-diethylphosphino-3-oxobutanthioate (0.49g, 1.58mmol) was added to a stirred suspension of sodium hydride (0.126g, 60% disp., 3.16mmol) in THF (40ml) at 0°C under argon. The suspension was stirred at 0°C for 1h and 11-(t-butyldimethylsilyloxy)undecanal (0.316g, 1.05mmol) added. The mixture was allowed to warm to room temperature and stirred for a further 6h. The resulting clear solution was poured into saturated aqueous ammonium chloride (50ml) and ether (50ml). The layers were separated, the aqueous phase re-extracted with ether (2 x 50ml) and the combined organic phases washed with water (2 x 50ml) and brine (50ml), dried ($MgSO_4$) and evaporated. Chromatography (25% DCM-light petroleum b.p. 40-60°C) afforded the desired product as a pale yellow oil (0.4g, 84%); δ (250 MHz, $CDCl_3$) (50% enol) 0.02 (6H, s), 0.84 (9H, s), 1.23 (16H, br s), 1.42 and 1.46 (9H, 2s), 2.17 (2H, m), 3.54 (2H, t, J 6.5 Hz), 3.67 (1H, s), 5.27 (0.5H, s) 5.63 and 6.10 (1H, 2dt, J 15.5, 1.5 Hz), 6.65 and 6.86 (0.5H, dt, J 15.5, 7 Hz), 12.57 (0.5H, s); ν_{max} (film) 2927, 2854, 1653, 1585, 1254, 1078, 836 cm^{-1}; m/z 399 (M^+-^{t}Bu), 385, 367, 343, 57; analysis found : C, 65.90; H, 10.81; $C_{25}H_{48}O_3SSi$ requires : C, 65.73; H, 10.59%.

S-t-Butyl 9-(t-butyldimethylsilyloxy)-3-oxo-4*E*-decenethioate (19).

S-t-butyl 4-diethylphosphino-3-oxobutanthioate (0.118g, 0.38mmol) was added to a stirred suspension of sodium hydride (37mg, 60% disp., 0.925mmol) in THF (12ml) at 0°C under argon. The suspension was stirred at 0°C for 1h and 5-(t-butyldimethylsilyloxy)hexanal (70mg, 0.303mmol) added. The mixture was allowed to warm to room temperature and stirred for a further 16h. The resulting clear solution was poured into

saturated aqueous ammonium chloride (40ml) and ether (40ml). The layers were separated, the aqueous phase re-extracted with ether (2 x 40ml) and the combined organic phases washed with water (2 x 40ml) and brine (40ml), dried ($MgSO_4$) and evaporated. Chromatography (2% ether-light petroleum b.p. 40-60°C) gave the title compound as a pale yellow oil (98.7mg, 84%); δ (250 MHz, $CDCl_3$) (50% enol) 0.05 (6H, s), 0.89 (9H, s), 1.02 (3H, d, J 8 Hz), 1.36 (2.7H, s), 1.38 (4H, m), 1.42 (6.3H, s), 2.20 (2H, m), 3.71 (0.6H, s), 3.80 (1H, m), 5.30 (0.7H, s), 5.68 (0.7H, dt, J 15, 1.6 Hz), 6.16 (0.3H, dt, J 15, 1.6 Hz), 6.69 (0.7H, dt, J 15, 6.9 Hz), 6.90 (0.3H, dt, J 15, 6.9 Hz), 12.61 (0.7H, br s); ν_{max} (film) 2957, 2928, 1653, 1585, 1077, 835 cm^{-1}; m/z 386 (M^+), 329 (M^+-^{t}Bu), 273, 165, 111, 57; analysis found : C, 62.3; H, 10.2; $C_{20}H_{38}O_3SSi$ requires : C, 62.1; H, 9.91%.

S-t-Butyl 15-hydroxy-3-oxo-4*E*-pentadecenethioate (16).

To a stirred solution of *S*-t-Butyl 15-(t-butyldimethylsilyloxy)-3-oxo-4*E*-pentadecenethioate (0.445g, 0.974mmol) in acetonitrile (10ml) at room temperature was added HF (0.5ml, 40% aq.) After 15min the solution was poured into water (50ml) and extracted with DCM (3 x 50ml). The combined organic phases were washed with water (2 x 50ml), brine (1 x 50ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Chromatography (50% ether-light petroleum b.p. 40-60°C) afforded the desaired product (0.327g, 98%) as a pale yellow oil; δ (250 MHz, $CDCl_3$) (30% enol) 1.30 (15H, br s), 1.45 and 1.51 (9H, 2s), 1.50 (2H, m), 3.63 (2H, t, J 6.5 Hz), 3.70 (1.4H, s), 5.30 (0.3H, s), 5.36 (0.7H, d, J 16 Hz), 6.14 (0.3H, t, J 16 Hz), 6.69 (0.7H, dt, J 16, 7 Hz), 6.91 (0.3H, dt, J 16, 7 Hz), 12.61 (0.3H, br s); ν_{max} (film) 3347, 2925, 2853, 1652, 1584, 1077 cm^{-1}; m/z 342 (M^+), 286, 253, 57; analysis found : C, 66.4; H, 10.1; $C_{19}H_{34}O_3S$ requires : C, 66.6; H, 10.0%.

S-t-Butyl 9-hydroxy-3-oxo-4*E*-decenethioate (20).

Tetra-n-butyl ammonium fluoride (3ml, 1M in THF, 3mmol) was added to a stirred solution of *S*-t-Butyl 9-hydroxy-3-oxo-4*E*-decenethioate (0.191g, 0.494mmol) in THF (5ml) at room temperature. The solution was stirred for 4h, poured into pH7 buffer solution (20ml) and ether (20ml), the layers separated, and the aqueous layer re-extracted with ether (2 x 20ml). The combined ether layers were washed with brine (50ml), dried ($MgSO_4$), and evaporated. Chromatography (30% ether-light petroleum b.p. 40-60°C) gave the title compound (0.114g, 85%) as a colourless oil; δ (250 MHz, $CDCl_3$) (50% enol) 1.19 and 1.21 (3H, 2d, J 8 Hz), 1.40 (5H, br s), 1.45 and 1.50 (9H, 2s), 2.22 (2H, m), 3.69 (1H, s), 3.79 (1H, m), 5.29 (0.5H, s), 5.67 (0.5H, d, J 15.7 Hz), 6.15 (0.5H, dt, J 15.7, 1.7 Hz), 6.66 (0.5H, dt, J 15.7, 6.6 Hz), 6.90 (0.5H, dt, J 15.7, 6.6 Hz), 12.60 (0.5H, br s); ν_{max} (film) 3383, 2961, 2926, 2863, 1652, 1584, 1078 cm^{-1}; m/z 272 (M^+), 215 (M^+-^{t}Bu), 183, 165, 99, 57; analysis found : C, 61.5; H, 9.16; $C_{14}H_{24}O_3S$ requires : C, 61.7; H, 8.88%.

3-Oxo-4*E*-pentadecen-15-olide (17).

A solution of *S*-t-Butyl 15-hydroxy-3-oxo-4*E*-pentadecenethioate (0.118g, 0.345mmol) in dry degassed DCM (150ml) was added to copper (I) trifluoroacetate (1.22g, 6.91mmol) and disodium hydrogen phosphate (1.91g, 13.5mmol) in dry degassed DCM (100ml) and the reaction mixture stirred for 10min at room temperature. The solution was poured into DCM (200ml) and saturated aqueous ammonium chloride (200ml) containing ammonia (1ml, S.G. 0.88) and stirred vigorously for 20min.. The mixture was filtered through a plug of glass wool, the layers separated, and the aqueous phase re-extracted with DCM (2 x 100ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. Chromatography (DCM) gave the macrolide (30.5mg, 35%) as a white solid. Recrystallisation (light petroluem b.p. 40-60°C) afforded colourless prisms, m.p. 54°C; δ (250 MHz, $CDCl_3$) 1.26 and 1.57 (16H, 2m), 2.26 (2H, m), 3.50 (2H, s), 4.14 (2H, t, J 6.5 Hz) 6.21 (1H, dt, J 15, 1.5 Hz), 6.90 (1H, dt, J 15, 7.6 Hz); ν_{max} (film) 2930, 2856, 1736, 1691, 1674, 1623, 1458, 1256 cm^{-1}; m/z 252 (M^+), 234, 224, 150, 95, 81; analysis found : C, 71.7; H, 9.71; $C_{15}H_{24}O_3$ requires : C, 71.4; H, 9.59%.

3-Oxo-4*E*-decen-9-diolide (21).

A solution of *S*-t-Butyl 9-hydroxy-3-oxo-4*E*-decenethioate (0.856g, 3.14mmol) in dry degassed DCM (100ml) was added over 60min to copper (I) trifluoroacetate (5.54g, 31.4mmol) and disodium hydrogen phosphate (8.92g, 62.8mmol) in dry degassed DCM (200ml) and the reaction mixture stirred for 2h at room temperature. The solution was poured into saturated aqueous ammonium chloride (500ml) containing ammonia (5ml, S.G. 0.88) and stirred vigorously for 20min. The mixture was filtered through a plug of glass wool, the layers separated, and the aqueous phase re-extracted with DCM (2 x 200ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. Chromatography (40% ether-light petroleum b.p. 40-60°C)

gave the diolide (0.4g, 35%) as a colourless, viscous oil; δ (250 MHz, $CDCl_3$) 1.23 (6H, m), 1.55 (8H, br s), 2.20 (4H, m), 3.58 (4H, br s), 4.96 (2H, m), 6.14 (2H, br d, J 16.8 Hz), 6.86 (2H, m); ν_{max} (film) 2980, 2938, 2865, 1726, 1670, 1625, 1257, 1229 cm^{-1}; m/z 364 (M^+), 292, 182, 164, 139, 123, 81; analysis found : C, 65.7; H, 7.77; $C_{20}H_{28}O_6$ requires : C, 65.9; H, 7.75%.

Crystal data.

Compound (17): $C_{15}H_{24}O_3$, M = 252.4, monoclinic, a = 9.885(3), b = 8.627(3), c = 17.403(7)Å, β = 98.55(3)°, V = 1468Å^3, space group $P2_1/a$, Z = 4, D_c = 1.14gcm^{-3}, μ = 6cm^{-1}.

Compound (22): $C_{16}H_{24}O_6$, M = 312.4, monoclinic, a = 10.486(4), b = 5.000(1), c = 16.630(4)Å, β = 102.12(3)°, V = 852Å^3, space group $P2_1/n$, Z = 2 (the molecule is disposed about a centre of symmetry), D_c = 1.22gcm^{-3}, μ = 7cm^{-1}.

Compound (23): $C_{18}H_{28}O_6$, M = 340.4, monoclinic, a = 4.671(2), b = 24.095(9), c = 8.344(3)Å, β = 103.78(3)°, V = 912Å^3, space group $P2_1/c$, Z = 2 (the molecule is disposed about a centre of symmetry), D_c = 1.24gcm^{-3}, μ = 7cm^{-1}.

Compound (24): $C_{20}H_{32}O_6$, M = 368.5, triclinic, a = 5.521(1), b = 8.249(2), c = 11.822(3)Å, α = 95.55(2), β = 101.63(2), γ = 106.21(21)°, V = 500Å^3, space group $P1$, Z = 1 (the molecule is disposed about a centre of symmetry), D_c = 1.22gcm^{-3}, μ = 7cm^{-1}.

Compound (32): $C_{10}H_{16}O_5$, M = 216.2, monoclinic, a = 15.154(9), b = 5.041(2), c = 15.759(7)Å, β = 113.21(4)°, V = 1106Å^3, space group $P2_1/n$, Z = 4, D_c = 1.30gcm^{-3}, μ = 8cm^{-1}.

Data collection and processing.

Compound (17): 1503 independent measured reflections, 1411 observed [$|F_o| > 3\sigma(|F_o|)$, $2\theta \leq 100°$].

Compound (22): 1153 independent measured reflections, 1112 observed ($2\theta \leq 116°$).

Compound (23): 944 independent measured reflections, 859 observed ($2\theta \leq 100°$).

Compound (24): 1329 independent measured reflections, 1199 observed ($2\theta \leq 116°$).

Compound (32): 1130 independent measured reflections, 930 observed ($2\theta \leq 100°$).

All data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromater) using GKomega-scans. The data were corrected for Lorentz and polarisation factors; no absorption corrections were applied.

Structure analysis and refinement.

All structures were solved by direct methods. The non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were idealised, C-H = 0.96Å, assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon atoms. Refinement was by block-cascade full-matrix least-squares to give for;

(17), R = 0.041, R_w = 0.051, [$w^{-1} = \sigma^2(F)+0.00031F^2$],

(22), R = 0.050, R_w = 0.073, [$w^{-1} = \sigma^2(F)+0.00028F^2$],

(23), R = 0.051, R_w = 0.057, [$w^{-1} = \sigma^2(F)+0.00123F^2$],

(24), R = 0.040, R_w = 0.051, [$w^{-1} = \sigma^2(F)+0.00039F^2$],

(32), R = 0.065, R_w = 0.068, [$w^{-1} = \sigma^2(F)+0.00014F^2$].

Computations were carried out on an Eclipse S140 computer using the SHELXTL[18] program system.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See notice to authors, issue no.1.

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