Tetrahedron Vol. 48, No. 6, pp. 1145-1174, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00

Further Reactions of t-Butyl 3-Oxobutanthioate and t-Butyl 4-Diethylphosphono-3-oxobutanthioate : Carbonyl Coupling Reactions, Amination, Use in The Preparation of 3-Acyltetramic Acids and Application to The Total Synthesis of Fuligorubin A.

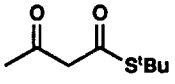
Steven V. Ley,* Stephen C. Smith and Peter R. Woodward.
Department of Chemistry, Imperial College of Science, Technology and Medicine, London, SW7 2AY, UK.

(*Received in UK 28 November* 1991)

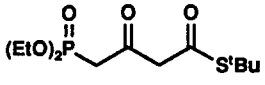
Key words: Acyltetramic acid; Phosphonate; Wadsworth-Emmons; Dieckmann cyclisation; Fuligorubin A.

Abstract: The use of t-butyl-3-oxobutanthioate (1) and t-butyl 4-diethylphosphono-3-oxobutanthioate (2) for the preparation of homologated derivatives suitable for amination in the presence of silver (I) trifluoroacetate to afford the corresponding β-ketoamides is discussed. In particular Wadsworth-Emmons coupling reactions of (2) with various carbonyl compounds gave good yields of *E*-substituted products. Many of the β-ketoamides were shown to be suitable precursors for 3-acyltetramic acids using a Dieckmann cyclisation with tetra-n-butyl ammonium fluoride as the cyclising base. These new reactions were applied to the total synthesis of the polyene 3-acyltetramic acid fuligorubin A.

We have previously reported the preparation and reactions of t-butyl 3-oxobutanthioate (1)[1] and t-butyl 4-diethylphosphono-3-oxobutanthioate (2)[2]. In particular, we have shown their utility in the preparation of a number of 3-acyltetronic acids[3], in β-ketomacrolide and diolide preparation[4] and in various carbonyl coupling reactions.[5]



(1)



(2)

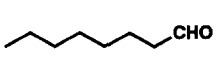
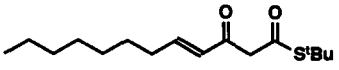
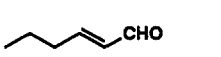
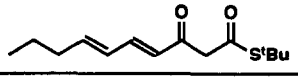
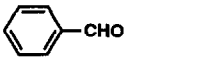
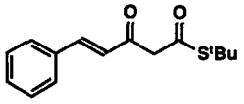
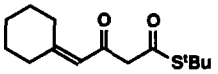
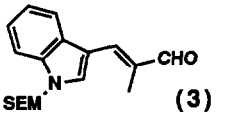
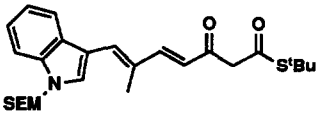
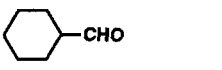
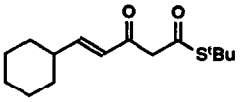
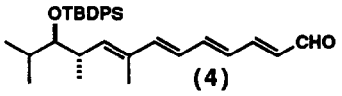
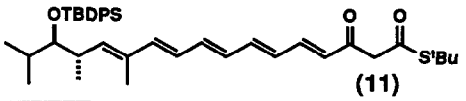
In preliminary studies we have illustrated that these compounds can participate in amination reactions and thus provide precursors for 3-acyltetramic acids. These reactions have been combined in the preparation of fuligorubin A,[6] a novel natural 3-acyltetramic acid. Herein we report in full on aspects of this chemistry.

In view of the current synthetic efforts on various tetramic acids[7] and because of their wide ranging biological activity from antiviral, antitumour, antibiotic, antimicrobial to inhibition of DNA-directed RNA polymerase and terminal deoxynucleotidyl transesterase[8], new routes to these systems are important.

Significant contributions to this area of methodology have already been made by a number of workers of which the recent procedures of Boeckman[7c)d)f)] and Jones[7h)] are especially attractive. In our work we have attempted to combine ease of operation and good yields with mildness of reaction conditions so as to tolerate

other chemically sensitive functional groups. As much of the later chemistry relies on specific conversions of substituted substrates it is appropriate to discuss the Wadsworth-Emmons coupling of the phosphonate (2) with carbonyl compounds as this leads to many alkenyl substituted β-ketothioesters[2]. Owing to the fact that some examples of this process have been reported fully during our macrocyclization studies,[9] these products will be included in the later tables as starting materials.

Table 1 : Wadsworth-Emmons couplings of phosphonate (2)

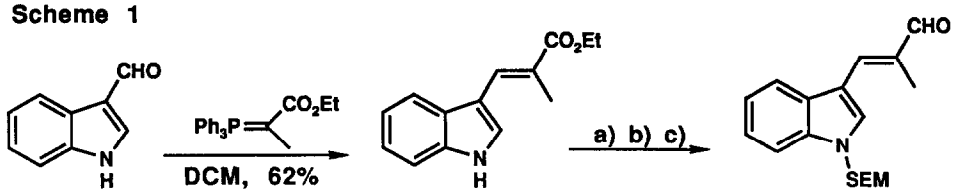
carbonyl compound	product		yield (%)
		(5)	58
		(6)	50
		(7)	55
		(8)	67
 (3)		(9)	99
		(10)	81
 (4)		(11)	62

In a typical reaction the β-ketothiophosphonate ester (2) was reacted with 2 equivalents of sodium hydride in THF at 0°C. After approximately 30 min the carbonyl compound was added, the mixture allowed to warm to room temperature and then worked up in the usual way upon reaction completion. In this manner a number of carbonyl compounds were converted to their corresponding β-ketothioester alkene derivatives, compounds (5) to (11) (Table 1). From the table it should be noticed that both aldehydes and ketones react equally well and that one gets almost exclusively the (*E*)-alkene product.[10] The corresponding use of a triphenylphosphorane derivative of (2) gave low (15-30%) yields and poor selectivity.[11] The precise order of events in the Wadsworth-Emmons coupling reaction undoubtedly follows a complex equilibrium of anions which selectively react with the carbonyl species *via* the γ position (*i.e.* the C4 atom) of (2). For a fuller discussion of putative

species in this pathway one is referred to the work of Schneider who has investigated oxygen analogues of (2) and presented a convincing argument for the various reaction intermediates.[12]

Aldehyde (3) was made by homologation of indole 3-carboxaldehyde (12) (Scheme 1). Reaction with the appropriate phosphorane to give (13), protection of the indole nitrogen with a 2-trimethylsilylethoxymethyl (SEM) group (we have also found this useful in pyrrole chemistry[13]), reduction with diisobutyl aluminium hydride (DIBAL) and oxidation with tetrapropylammonium perruthenate[14] (TPAP) gave the aldehyde in good overall yield.

Scheme 1

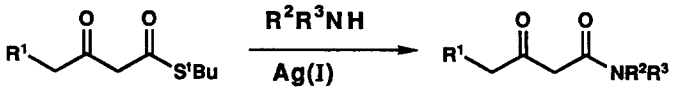


(12) (13) (3)

reagents: a) i) NaH 1.6eq, DMF, 0°C ii) SEMCl, DMF, DMSO, RT, 95%
b) DIBAL 2.5eq, toluene, -78°C, 95% c) TPAP, 4Å sieves, NMO, DCM, 80%

In the next phase of the work we investigated the transformation of the β-ketothioester derivatives to the corresponding β-ketoamides using thiophilic heavy metal salts[15] to promote the amination process similar to that observed in other thioester to amide reactions.[16] In this way we envisaged a new mild procedure for the preparation of β-ketoamides which would be tolerant of many sensitive functional groups (Scheme 2).[17]

Scheme 2



There is a need for such a procedure since the present literature methods are less than satisfactory owing to use of high reaction temperatures, limited substitution patterns in the reactants, multistep processes, masking procedures[18] and the need to make other reactive species such as isocyanates.[19] Furthermore β-ketoamides do show useful biological properties in their own right, such as antimicrobial[20], insect repellant[21] and systemic fungicidal activity.[22] β-Ketoamides also play an important role as synthetic intermediates for a range of heterocyclic ring constructions.[23-28] We find that the β-ketothioesters react rapidly and extremely well under anhydrous conditions[29], with a wide range of amines in the presence of silver (I) trifluoroacetate at room temperature in THF to give good yields of β-ketoamide products (15) to (30) (Table 2)

Table 2 : Preparation of β-ketoamides

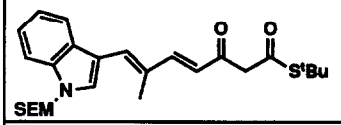
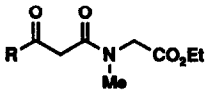
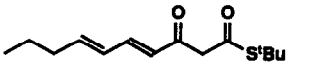
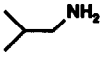
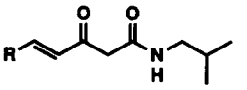
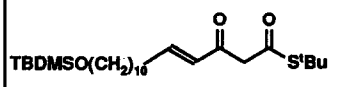
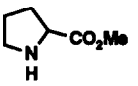
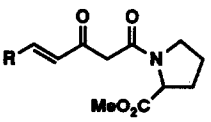
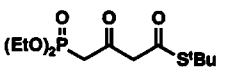
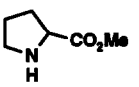
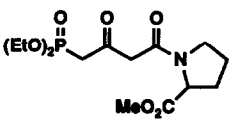
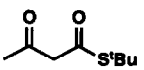
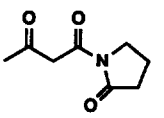
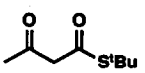
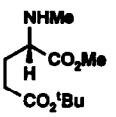
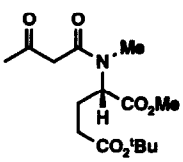
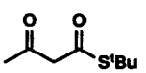
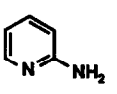
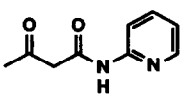
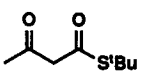
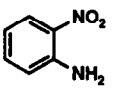
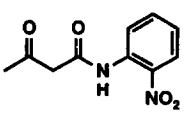
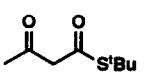
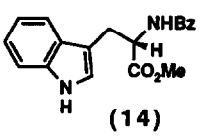
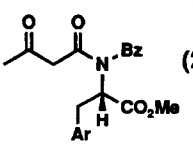
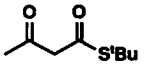
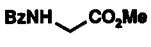
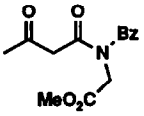
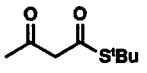
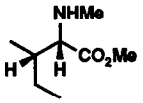
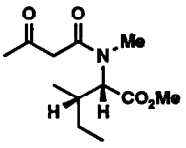
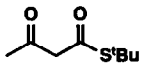
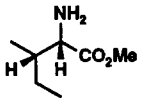
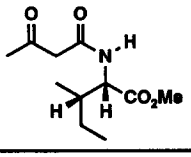
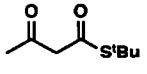
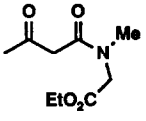
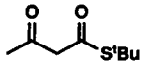
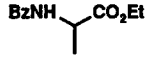
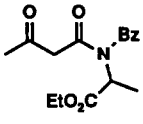
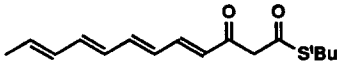
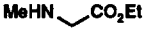
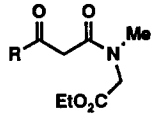
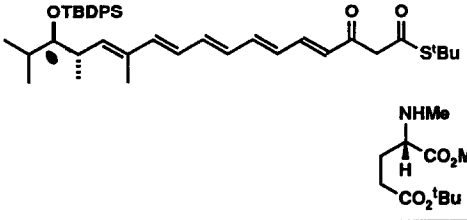
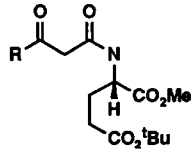
β-ketothioester	amine	product		yield (%)
			(15)	45
			(16)	77
			(17)	65
			(18)	60
			(19)	74
			(20)	64
			(21)	65
			(22)	80
	 (14)		(23)	74

Table 2 contd.

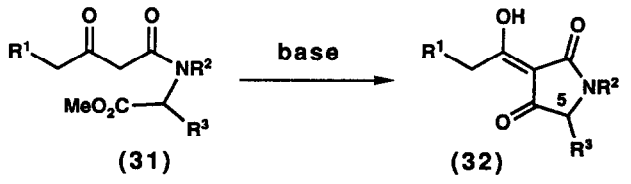
β-ketothioester	amine	product		yield (%)
			(24)	65
			(25)	68
			(26)	64
			(27)	65
			(28)	75
			(29)	45
			(30)	49

In none of these reactions were β-aminocrotonate side products observed which can be a problem in other procedures.[30] Also from table 2 one can see that even electron deficient amines such as 2-aminopyridine,[31] pyrrolidinone and *o*-nitroaniline react well and give good yields of the corresponding products. We have also investigated amination with many amino acid derivatives since these products are required later as the precursors for 3-acyltetramic acids. Importantly, when optically pure amino acid derivatives are used, amination proceeds with full retention of the integrity of the stereogenic centre(s).

When other nitrogen donors are present in the amino acid precursors as in the tryptophan derivative (14) the reaction is highly chemoselective and does not require any separate indole nitrogen protection. Some of the products in these reactions *e.g.*, (30) may find later applications in the synthesis of other 3-acyltetramic acid natural products such as β–lipomycin.[32] Whilst the reactions in the table employ silver (I) trifluoroacetate as the metal promoter for these aminations we have also briefly compared the use of mercury (II) trifluoroacetate and copper (I) trifluoroacetate. However, owing to disposal problems with mercury and stability problems with the copper salt, we believe silver (I) trifluoroacetate to be the superior reagent.

Next we examined the conversion of the amino acid β-ketoamide derivatives (31) to 3-acyltetramic acids (32) (Scheme 3).

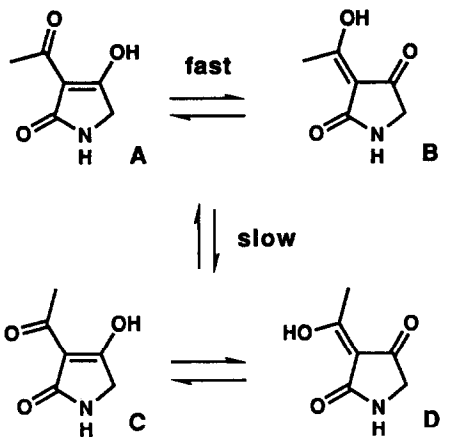
Scheme 3



(31) (32)

While this Dieckmann process for acyltetronic and acyltetramic acid synthesis was first reported by Lacey employing methoxide as the base[33], later improvements have recommended the use of potassium t-butoxide.[34] In our own work we have chosen fluoride ion as a mild and particularly effective base to effect these cyclizations. However, before discussing these reactions it is pertinent to comment on some general problems associated with 3-acyltetramic acid synthesis. Firstly, owing to the configurational lability of the C5 stereogenic centre when R^3 is not equal to hydrogen, conditions have to be mild and appropriate checks for potential racemisation need to be made, especially when using basic reagents. Secondly, the literature indicates that two substituents at C5 are required to give the best results and that when R^3=H the reactions can be poor. Furthermore, the rates of cyclization in the Dieckmann reaction vary considerably depending upon the R^2 substituent. Lastly and most importantly, however, is the existence of the 3-acyltetramic acid in different configurational and tautomeric forms as a result of enolisation. From nmr studies by Steyn and Wessels it has been shown that in $CDCl_3$, 3-acyltetramic acids provide two sets of signals typically in ratios between 5:1 and 8:1 for the four different enolic forms ABC and D grouped together as two sets AB and CD respectively (Figure 1).[35]

Figure 1



The internal equilibrium A⇋B and C⇋D is too fast to measure on the nmr time scale so the signals are due to the time average between the two sets AB⇋CD. By further studies these workers also conclude that form D exists as the major contributor. We have also investigated these equilibria using various computational methods to study the calculated heats of formation.[36] These data agree qualitatively with the observations of Steyn and Wessels that D is energetically preferred to B and that these are preferred to other possible tautomeric forms. In reporting of the nmr data for these compounds, therefore, crude assignment to major and minor conformational isomers is necessary. This picture can become confusing if additional stereogenic centres are present and even more so if racemisation of C5 occurs during synthesis.

For the cyclization studies we found that the amino acid β-ketoamides prepared in table 2 undergo a smooth Dieckmann reaction using 2-2.5 equivalents of tetra-n-butylammonium fluoride (TBAF) in THF at room temperature for a few minutes to give the acyltetramic acids (33) to (39) generally in good yields (Table 3). For reactions involving free NH groups the rate of cyclization was noticeably slower requiring reflux conditions for 24 hours with a large excess of TBAF as the base. For (15) the substrate contains a fluoride labile protecting group on the indole nitrogen atom and consequently cyclization was achieved by treatment with potassium t-butoxide which gave the corresponding 3-acyltetramic acid (33) in 84% yield. In order to assess the extent of racemisation, or otherwise during cyclization the N-methylisoleucine derivative (35) (Table 3) acts as an excellent probe since it contains a second fixed and known asymmetric carbon atom.[37] Table 4 provides the results of this study whereby the enantiomerically pure ester (25) was treated with various cyclizing conditions, including our TBAF procedure, the original Lacey conditions of extended methoxide treatment[33], the modified Bloomer and Kappler t-butoxide procedure[34] and new conditions where we have reduced the temperature and time of these alkoxide based reactions (Table 4).

Table 3 : Cyclisation of β-ketoamides to tetramic acids

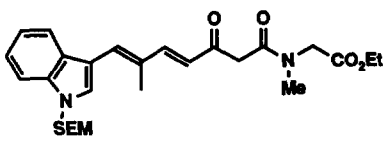
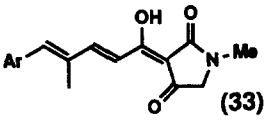
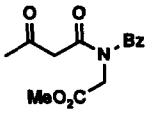
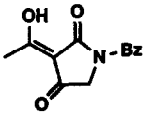
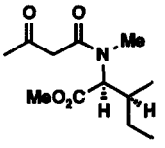
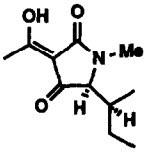
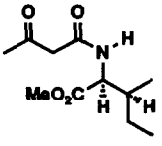
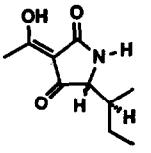
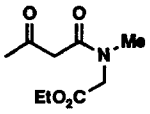
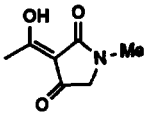
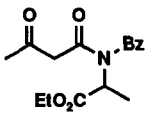
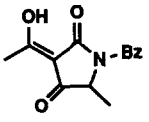
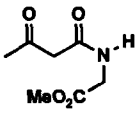
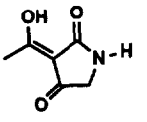
β-ketoamide	tetramic acid product		yield (%)
		(33)	84
		(34)	78
		(35)	85
		(36)	55
		(37)	70
		(38)	92
		(39)	35

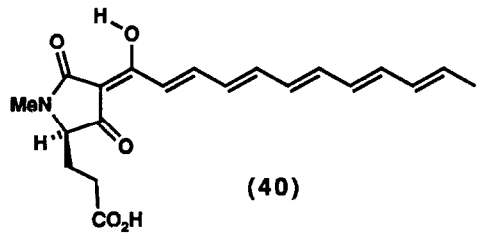
Table 4 : Effect of conditions on C5 racemisation rates in the cyclisation of (25)

entry	reagents and conditions	optical rotation	yield %
a)	TBAF, THF, 5min, RT	-36	85
b)	NaOMe, MeOH, benzene, 3hr reflux, stand overnight	+15	74
c)	NaOMe, MeOH, 5min, RT	-36	78
d)	NaOMe, MeOH, 24hr, RT	-31	75
e)	KO^{t}Bu, ^{t}BuOH, 2hr, reflux	-25	88
f)	KO^{t}Bu, ^{t}BuOH, 5min, RT	-36	90

By examining the rotation of the product one can see immediately that TBAF, methoxide or t-butoxide at room temperature for short periods of time (5 min) cause no detectable racemisation of the C5 centre (entries a, c and f of Table 4). Whereas higher temperatures and longer reaction times are detrimental particularly if methoxide is used as the base under Lacey conditions. The fact that potassium t-butoxide is acceptable without causing racemisation at room temperature becomes important during our later studies of the total synthesis of the natural product fuligorubin A.[6]

The cyclization reactions of the parent isoleucine ester (26) are of considerable interest since the product of this reaction is also a natural product, namely tenuazonic acid (36).[38] Syntheses of this material have already been reported in the literature.[39] Indeed the work by Harris using the Dieckmann reaction under the original Lacey conditions gave a compound with a rotation of -76.5. Following four recrystallisations *via* the corresponding copper (II) salt this rotation could be raised to the optically pure value of -124. Measurement of the rotation of the product using 10 equiv. of TBAF at reflux for 24 h as in table 3 gave a rotation of +5.1. This result, together with nmr studies, showed that complete racemisation at C5 had occurred and once again confirms that long reaction times and high temperatures should be avoided if enantiomerically pure 3-acyl-tetramic acids are required.

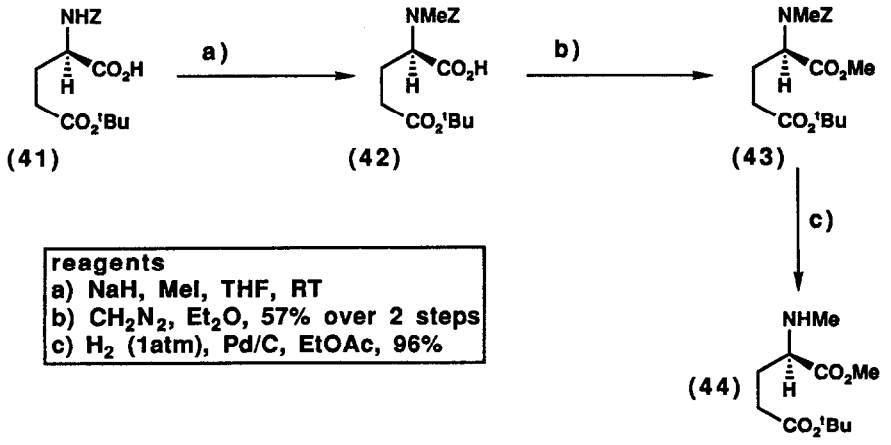
In the work described above we have developed new methodology and reactions of β-keto t-butylthioesters (1) and (2) and their derivatives. This has also led to the use of (2) in reactions with carbonyl compounds to give unsaturated thioester derivatives which have been subsequently used in amination reactions with amines in the presence of silver (I) salts. The products of some of these reactions were useful precursors for the preparation of 3-acyltetramic acids. It was reasonable, therefore, to harness these procedures in the total synthesis of fuligorubin A (40).[6]



(40)

Fuligorubin A (40) is a recently isolated, novel polyene acyltetramic acid pigment from the yellow slime mould *Fuligo septica* (L) Wiggers.[40] This compound is thought to be involved in photoreceptor and energy conversion processes during the life cycle of this interesting species. Fuligorubin A contains the unusual D-configured glutamic acid residue and had not been previously synthesised.[6] For the preparation of (40) we first had to construct the appropriately substituted amino acid residue (44). This was achieved using conventional chemistry from the commercially available protected (*R*)-glutamic acid derivative (41) involving N-methylation with sodium hydride and methyl iodide,[41] esterification with diazomethane followed by removal of the benzyloxycarbonyl protective group by hydrogenolysis using palladium on charcoal catalyst (Scheme 4).

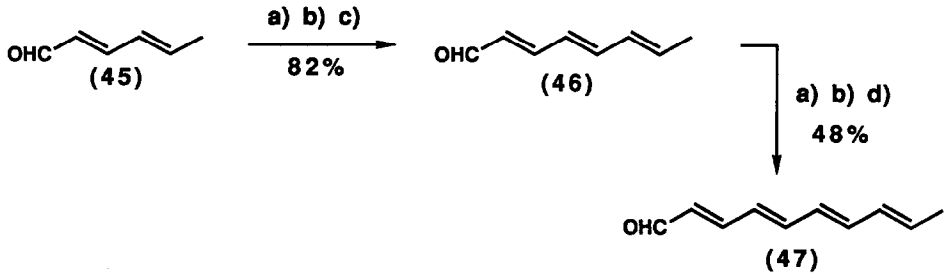
Scheme 4



For the next stage of the synthesis the polyene aldehyde (47)[42] was required. While we initially investigated convergent routes to (47) we found these to be unsatisfactory especially in the purity of the required all (*E*)-geometry of the polyene. We therefore utilised an iterative approach from (*E*,*E*)-hexadienal (45) which required homologation with triethylphosphonoacetate, DIBAL reduction and oxidation of the intermediate allylic alcohol to the aldehyde (46) with manganese dioxide. Further treatment with triethylphosphonoacetate, DIBAL reduction and oxidation with barium manganate[43] gave the geometrically pure polyene aldehyde (47) (Scheme 5). Since our preliminary communication, we have repeated this synthesis on a larger scale and found that the volume of solvent required to carry out these allylic oxidations was inhibitory. This problem could be overcome

by the use of catalytic TPAP[14] and 4-methylmorpholine-N-oxide (NMO) in acetonitrile with a yield of 70% obtained for (46) and 75% for (47) from their respective alcohols.

Scheme 5



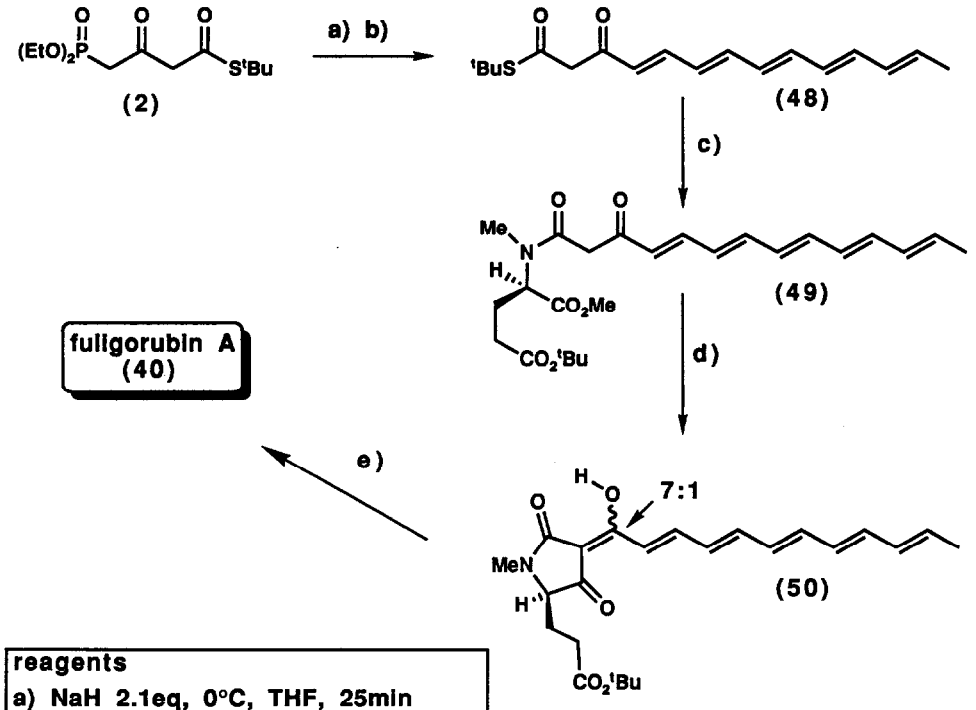
reagents
a) $(EtO)_2P(O)CH_2CO_2Et$ 1.1eq, NaH 1.1eq, THF, 0°C, 5min.
b) DIBAL 3eq, toluene, -78°C, 15min.
c) MnO_2 12eq, DCM, RT, 90min.
d) $BaMnO_4$ 7.5eq, DCM, RT, 3hr.

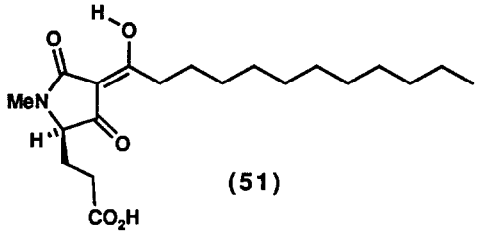
For the final stages of the synthesis we were able to employ the previously established methods. Reaction of (47) with t-butyl 4-diethylphosphono-3-oxobutanethioate (2) gave the β-ketothioester (48) in excellent yield (Scheme 6). Coupling of (48) with the protected D-glutamic acid derivative (44) in the presence of silver (I) trifluoroacetate gave the corresponding β-ketoamide (49). The rate of this reaction was dramatically increased by the use of 4Å molecular sieves and we also found that reduced quantities of both the amine (44) and silver (I) trifluoroacetate were needed when using this modification. Finally (49) was converted to the acyltetramic acid derivative (50) by rapid treatment (30min) with freshly sublimed potassium t-butoxide in t-butanol. This compound was found to exist in a 7:1 tautomeric ratio. Deprotection to fuligorubin A (40) was achieved using neat formic acid[44] at room temperature (Scheme 6). The synthetic material was identical in all respects to that reported for the natural product.[40]

To confirm that no racemisation had occurred at the C2 stereogenic centre during the later stages of the synthesis, (40) was hydrogenated according to the procedure described by Steglich[40] to the decahydro derivative (51), which was again identical to the reported data including the optical rotation.

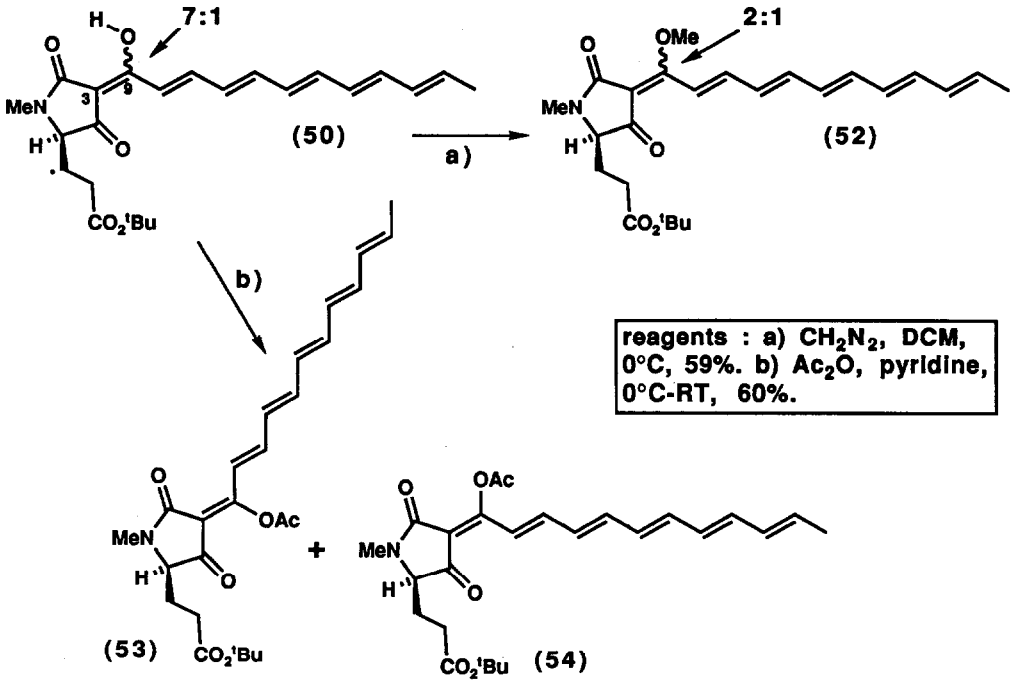
In order to simplify the nmr spectra of the tautomeric polyenes and check the stereochemical integrity of the double bonds, attempts were made to trap out the tautomers of (50) (Scheme 7). Methylation using diazomethane gave an inseparable 2:1 mixture of C3-C9 double bond isomers (52). Acetylation[45] gave two separable compounds (53) and (54) in a 3:2 ratio. The relative stereochemistry was not determined but it was clear that the polyene of each was 100% *E*.

Scheme 6


(2)
a) b)
(48)
c)
(49)
d)
7:1
(50)
e)
fuligorubin A
(40)
reagents
a) NaH 2.1eq, 0°C, THF, 25min
b) (47), 0°C, THF, 75%
c) AgOCOCF3 1.5eq, Na2HPO4,
(44) 1.5eq, THF, RT, 30min, 67%
d) tBuOK 2eq, tBuOH, RT, 30min,
75%. e) HCOOH, neat, RT, 1hr 100%


(51)

Scheme 7



In summary we have extended further the chemistry of the dicarbonyl synthons (1) and (2) and used these precursors in the preparation of a number of 3-acyltetramic acids.

Acknowledgements: We thank the SERC and ICI Agrochemicals (for a scholarship to SCS) for funding. We are grateful to Dr Jim Anderson for performing the allylic oxidations using TPAP.

Experimental

^1H and ^{13}C nmr spectra were recorded in $CDCl_3$ unless otherwise stated, using a Jeol FX 90Q, Bruker WM 250 or AM-500 nmr spectrometer, using residual protic solvent $C\underline{H}Cl_3$ (δ_H =7.26 ppm) or $\underline{C}DCl_3$ (δ_C=77.0 ppm, t) as internal reference. Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer. Mass spectra were recorded using VG-7070B, VG 12-253 and VG ZAB-E instruments in the Imperial College Chemistry Department Mass Spectroscopy laboratory and the SERC Mass Spectrometry Service in Swansea. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory and by MEDAC Ltd at the University of Brunel. Melting points were determined on a Reichert hot stage apparatus. Optical rotations were measured using an Optical Activity AA-1000 polarimeter. Molecular modelling was performed using the MACROMODEL package,[46] on an Evans and Sutherland PS-390 graphics terminal. All experiments were carried out in oven dried glassware under an argon atmosphere unless otherwise stated. Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh) unless otherwise stated. Florisil refers to 200-300 U.S. mesh Florisil as supplied by BDH Ltd. Diethyl ether, tetrahydrofuran and dimethoxyethane solvents were distilled from sodium benzophenone ketyl; dichloromethane from phosphorous pentoxide; toluene

from sodium; acetonitrile and dimethyl sulphoxide from calcium hydride; methanol from magnesium; triethylamine and diisopropylamine from potassium hydroxide. Petrol refers to petroleum ether b.pt. 40-60°C which was distilled prior to use as was ethyl acetate. 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 acidic ammonium molybdate (IV). Known esters of amino-acids for use in thioester coupling reactions were made using standard chemistry. Diazomethane solutions were prepared from Diazald® under a flow of argon. Numbering for ^1H nmr assignments follows the systematic (IUPAC) nomenclature. Coupling constants are measured in Hertz.

Preparation of Ethyl (2*E*) 3-(3-indolyl)-2-methylprop-2-enoate (13). A mixture of indole-3-carboxaldehyde (1.45g, 10mmol) and carboethoxyethylidenetriphenylphosphorane (5.44g, 15mmol) in anhydrous DCM (120ml) was stirred at room temperature for 24hr, during which time it turned orange/brown. The solvent was removed *in vacuo* and the residual brown oil purified by flash chromatography (gradient elution, 50-60% ether/petrol) to give the unsaturated ester (13) (1.43g, 62%) as colourless crystals; m.pt. 145-146°C; υ_{max} (film) 3237, 2968, 1675, 1603, 1266, 1252, 1111 and 731 cm^{-1}; ^1H δ (500MHz, $CDCl_3$) 1.36 (3H, t, J 7.0, $CH_2C\underline{H}_3$), 2.17 (3H, d, J 1.2, allylic Me), 4.28 (2H, q, J 7.0, $C\underline{H}_2CH_3$), 7.18-7.29 (2H, m, H-6' and H-7'), 7.41 (1H, dd, J 1.7, 6.8, H-5'), 7.49 (1H, d, J 2.7, H-2'), 7.81 (1H, dd, J 7.0, 0.4, H-8'), 8.03 (1H, s, H-3) and 8.52 (1H, br s, NH); m/z (EI) 229 (M^+), 200 (M^+-C_2H_5), 184 (M^+-C_2H_5-H_2O), 155, 130, 117 (indole); Found C 73.12; H 6.50; N 6.09%. $C_{14}H_{15}NO_2$ requires C 73.34; H 6.59; N 6.11%.

Preparation of Ethyl (2*E*) 2-methyl-3-[3-(N-trimethylsilylethyloxymethyl)indolyl]prop-2-enoate. To a stirred suspension of sodium hydride (280mg of a 60% oil dispersion, 7.0mmol) in DMF (12.5ml) at 0°C was added a solution of the ester (13) (1.00g, 4.35mmol) in DMSO (2.5ml) dropwise. The mixture turned yellow and was allowed to warm to room temperature over 25min, resulting in a cloudy, bright yellow mixture. This was cooled back to 0°C and SEMCl (1.15ml, 6.55mmol) was added in one go, causing the colour to discharge. The reaction was stirred for 40min, poured into water (200ml) and extracted with ether (4x100ml). The combined ether layers were washed with water (100ml), brine (100ml), dried (Na_2SO_4) and evaporated to a pale yellow oil. Flash chromatography (20% ether/petrol) gave the N-SEM protected indole (1.48g, 95%) as a colourless oil; υ_{max} (film) 2952, 1695, 1622, 1527, 1465, 1363, 1320, 1247, 1106, 835 and 742 cm^{-1}; ^1H δ (500MHz, $CDCl_3$) -0.06 (9H, s, $Si\underline{Me}_3$), 0.90 (2H, t, J 8.2, $C\underline{H}_2Si$), 1.38 (3H, t, J 7.1, $CH_2C\underline{H}_3$), 2.19 (3H, d, J 1.2, allylic Me), 3.51 (2H, t, J 8.1, $OC\underline{H}_2CH_2Si$), 4.30 (2H, q, J 7.1, $C\underline{H}_2CH_3$), 5.54 (2H, s, $NC\underline{H}_2O$), 7.26 (1H, dt, J 0.9, 7.0, H-6'), 7.32 (1H, dt, J 1.0, 7.0, H-7'), 7.45 (1H, s, H-3), 7.51 (1H, d, J 8.2, H-5'), 7.81 (1H, d, J 7.85, H-8') and 8.02 (1H, s, H-2'); m/z (EI) 359 (M^+), 329, 314, 301, 243, 229, 183, 168, 154, 103, 73; Found C 66.93; H 8.22; 4.09%. $C_{20}H_{29}NO_3Si$ requires C 66.81; H 8.13; N 3.89%.

Preparation of (2*E*) 2-Methyl-3-[3-(N-trimethylsilylethyloxymethyl)indolyl]prop-2-en-1-ol. DIBAL (6.48ml of a 1.5M solution in toluene, 9.73mmol, 2.5equiv) was added dropwise to a solution of the ester (1.40g, 3.89mmol) in anhydrous toluene (60ml) at -78°C. The solution turned yellow. After 10min at -78°C, water (4ml) was added dropwise (care) and the mixture allowed to warm to room temperature, during which time the yellow colour discharged and the reaction became gelatinous. The gel was poured into a stirred suspension of $MgSO_4$ (5g) and $NaHCO_3$ (5g) in ethyl acetate (400ml). Filtration followed by evaporation of the solvent *in vacuo* gave a pale yellow oil. Purification by flash chromatography (80% ether/petrol) gave the allylic

alcohol (1.17g, 3.69mmol) as a colourless oil which slowly crystallised; m.pt. 64-65°C; υ_{max} (film) 3390, 3050, 2950, 1610, 1534, 1465, 1377, 1355, 1248, 1234, 1073, 1014, 859, 835, 741, 690 and 663 cm^{-1}; ^1H δ (500MHz, $CDCl_3$) -0.06 (9H, s, $SiMe_3$), 0.89 (2H, t, J 8.2, CH_2Si), 1.47 (1H, br t, OH), 1.99 (3H, d, J 1.0, allylic Me), 3.49 (2H, t, J 8.1, OCH_2CH_2Si), 4.27 (2H, d, J 3.25, H-1), 5.50 (2H, s, NCH_2O), 6.69 (1H, t, J 1.1, H-3), 7.18 (1H, dt, J 1.0, 7.5, H-6'), 7.23 (1H, s, H-2'), 7.27 (1H, dt, J 1.1, 7.6, H-7'), 7.48 (1H, d, J 8.2, H-5') and 7.68 (1H, d, J 7.9, H-8'); m/z (EI) 317 (M^+), 301, 287, 259, 242, 230, 218, 200, 189, 168, 130, 103 and 73; Found C 67.95; H 8.69; N 4.39%. $C_{18}H_{27}NO_2Si$ requires C 68.09; H 8.57; N 4.41%.

Preparation of (2*E*) 2-Methyl-3-[3-(N-trimethylsilylethyloxymethyl)indolyl]prop-2-enal (3). A mixture of the allylic alcohol prepared above (940mg, 2.96mmol), NMO (800mg, 5.92mmol, 2equiv) and powdered 4Å sieves (500mg) in anhydrous DCM (40ml) was stirred at room temperature for 10min. TPAP (50mg, catalytic) was added and the mixture stirred for 8hr, during which time the colour changed to dark brown. The solid was filtered over a pad of celite, the filtrate evaporated *in vacuo* and the residue purified by flash chromatography (20% ether/petrol) to give the aldehyde (3) (747mg, 80%) as an orange oil; υ_{max} (film) 3316w, 3050, 2951, 2892, 1741, 1662, 1617, 1521, 1466, 1375, 1353, 1322, 1238, 1130, 1084, 1042, 1002, 859, 837, 744, 693, 663 and 612 cm^{-1}; ^1H δ (500MHz, $CDCl_3$) -0.05 (9H, s, $SiMe_3$), 0.91 (2H, t, J 8.1, CH_2Si), 2.10 (3H, d, J 1.0, allylic Me), 3.53 (2H, t, J 8.0, OCH_2CH_2Si), 5.57 (2H, s, NCH_2O), 7.31 (1H, t, J 7.0, H-7'), 7.36 (1H, t, J 7.05, H-6'), 7.55 (1H, d, J 8.1, H-5'), 7.59 (1H, s, H-3), 7.62 (1H, s, H-2'), 7.83 (1H, d, J 7.8, H-8') and 9.62 (1H, s, H-1); m/z (EI) 315 (M^+), 285, 257, 242, 229, 198, 189, 168, 154, 128, 103 and 73; Found C 68.80; H 8.05%. $C_{18}H_{25}NO_2Si$ requires C 68.53; H 7.99%.

Preparation of (2*S*) N-Benzyloxycarbonyl-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester.[46] DCC (0.37g, 1.79mmol) was added to a stirred solution of the acid (0.571g, 1.63mmol), DMAP (20mg, 0.164mmol), and methanol (72ml, 1.78mmol) in DCM (10ml) at RT under argon. The reaction was stirred for 10 min, filtered, and the filtrate washed with water (3 x 10ml), 5% HOAc (3 x 60 ml), and water (1 x 10ml). The DCM solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography (20% ether/petrol) gave (2*S*) N-benzyloxycarbonyl-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (0.502g, 85%) as a colourless, viscious oil; $[\alpha]_D^{25}$ -26.6 (c1.9, $CHCl_3$) ; υ_{max} (film) 2977, 1741, 1717, 1704, 1451, and 1154cm^{-1}; m/z (EI) 365 (M^+), 323 309, 250, 206, and 91; ^1H δ (90MHz, $CDCl_3$) (rotamer mixture) 1.40 (9H, s, ^{t}Bu), 1.80 to 2.40 (4H, m, 2 x H-3, 2 x H-4), 2.88 (3H, s, N-Me), 3.62, 3.69 (3H, 2s, CO_2Me), 4.70 (1H, m, H-2), 5.10 (2H, s, OCH_2 Ph), and 7.32 (5H, s, aromatics); Found: C 62.4; H 7.70; N 3.88. $C_{19}H_{27}NO_6$ requires C 62.5; H 7.45; N 3.83%.

Preparation of (2*S*) N-Methylglutamic Acid α-methyl ester γ-^{t}butyl ester. A stirred suspension of 10% palladium on carbon (30mg) and diester (0.200g, 0.547mmol) in ethyl acetate (10ml) was hydrogenated at room temperature and pressure for 16hr, filtered and the volatile material was removed under reduced pressure. Flash chromatography (40% ether/petrol) gave (2*S*) N-methylglutamic acid α-methyl γ-^{t}butyl diester (119mg, 94%) as a colourless oil; $[\alpha]_D^{25}$ - 0.9 (c 5.2, $CHCl_3$); υ_{max} (film) 3340, 2977, 1732, and 1154cm^{-1}; ^1H δ (90MHz, $CDCl_3$) 1.40 (9H, s, ^{t}Bu), 1.85 to 2.25 (5H, m, 2 x H-3, 2 x H-4, NH), 2.35 (3H, s, N-Me), 2.94 (1H, m, H-2), and 3.70 (3H, s, CO_2Me); m/z (EI) 231 (M^+), 175, 158, and 116; Found: C 57.3; H 9.42; N 5.92. $C_{11}H_{21}NO_4$ requires C 57.1; H 9.15; N 6.06%.

General Procedure for the Preparation of Unsaturated β-Ketoamides from Ketones or Aldehydes. ^{t}Butyl 4-diethylphosphono-3-oxobutanthioate (2) (1.2 equiv) was added to a stirred suspension of

sodium hydride (from a 60% oil dispersion pre-washed twice with sodium dried petrol, 2.2 equiv with respect to the phosphonate) in anhydrous THF (0.2M solution of phosphonate) at 0°C under argon. The suspension was stirred for 1hr, during which time it turned bright orange then dark brown. The aldehyde or ketone (1equiv) in a small volume of THF was then added *via* cannula at 0°C. The reaction was allowed to warm to room temperature and followed by tlc. Most reactions were complete within minutes although it was possible to leave overnight. The reactions were worked up by pouring into sat NH_4Cl (aq) (twice the volume of THF). The organic phase was separated and the aqueous phase re-extracted with ether (x2). The combined ether layers were washed with water (x2), brine, dried ($MgSO_4$) and evaporated *in vacuo*. Crude products were purified by column chromatography. All showed some degree of enol/keto tautomerism by nmr.

Preparation of ^{t}Butyl (4*E*) 3-oxododec-4-enthioate (5). The thioester-phosphonate (2) (3.04g, 9.8mmol) was reacted with sodium hydride (826mg of a 60% oil dispersion, 21.6mmol) and then octanal (1.05g, 8.19mmol) to give after work up and flash chromatography (20% DCM/petrol) ^{t}butyl (4*E*) 3-oxododec-4-enthioate (5) (1.35g, 58%) as a pale yellow oil; υ_{max} (film) 3386, 2925, 2855, 1653, 1584 and 1077 cm^{-1}; ^1H δ (250MHz, $CDCl_3$) (70% enol form) 0.88 (3H, t, J 8.8, H-12), 1.28 (10H, br s, 2xH-7 to H-11 inclusive), 1.47 (2.7H, s, ^{t}BuS, keto), 1.51 (6.3H, s, ^{t}BuS, enol), 2.21 (2H, m, 2xH-6), 3.71 (0.6H, s, H-2, keto), 5.31 (0.7H, s, H-2, enol), 5.67 (0.7H, dq, J, 15.9, 1.5, H-4, enol), 6.16 (0.3H, dt, J 15.9, 1.5, H-4, keto), 6.70 (0.7H, dt, J 15.9, 6.8, H-5, enol), 6.91 (0.3H, dt, J 15.9, 6.8, H-5, keto) and 10.14 (0.7H, br s, enol OH); m/z (EI) 284 (M^+) 228, 195, 168, 153 and 57; Found C 67.5, H 10.1%. $C_{16}H_{28}O_2S$ requires C 67.6, H 9.93%.

Preparation of ^{t}Butyl (4*E*,6*E*) 3-oxo-4,6-decadienthioate (6). The thioester-phosphonate (2) (1.01g, 3.25mmol) was reacted with (*E*) 2-hexenal (0.255g, 2.30mmol) under the standard conditions and worked up as normal. Flash chromatography (1% ether/petrol) gave ^{t}butyl (4*E*,6*E*) 3-oxo-4,6-decadienthioate (6) (0.296g, 50%) as a pale yellow oil; υ_{max} (film) 3209, 2960, 2925, 1627, 1566, and 1076cm^{-1}; ^1H δ (250MHz, $CDCl_3$) (30% keto form) 0.91 (2.1H, t, J 7.0, 3 x H-10 enol), 0.92 (0.9H,t, J 7.0, 3 x H-10 keto), 1.47 (2.7H, s, ^{t}BuS keto), 1.51 (6.3H, s, ^{t}BuS enol), 1.44 (2H, m, 2 x H-9), 2.13 (2H, m, 2 x H-8), 3.70 (0.6H, s, H-2 keto), 5.34 (0.7H, s, H-2 enol), 5.78 (0.7H, d, J 15.8, H-4 enol), 6.10 (2.3H, br m, H-4 keto, H-6 and H-7), 7.07 (0.7H, dd, J 15.8, 10.5, H-5 enol), 7.20 (0.3H, dd, J 15.8, 10.5, H-5 keto), and 12.58 (0.7H, br s, OH enol); m/z (EI) 254 (M^+), 198, 165, 123, and 57. Found: C 66.1; H,8.81. $C_{14}H_{22}O_2S$ requires C 66.1; H 8.72%.

Preparation of ^{t}Butyl (4*E*) 3-oxo-5-phenyl-4-pententhioate (7). The thioester-phosphonate (2) (0.296g 0.954mmol) was reacted with benzaldehyde (84.4mg, 0.795mmol) under the standard conditions and worked up as normal. Flash chromatography (5% ether/petrol) gave ^{t}butyl (4*E*) 3-oxo-5-phenyl-4-pententhioate (7) (0.115g, 55%) as a pale yellow solid ; m.pt. 60-62°C; υ_{max} (film) 3300, 3058, 3025, 2996, 1636, 1585, 1569, and 1077cm^{-1}; ^1H δ (250MHz, $CDCl_3$) (30% keto form) 1.48 (2.7H, s, ^{t}BuS keto), 1.52 (6.3H, s, ^{t}BuS enol), 3.82 (0.6H, s, H-2 keto), 5.48 (0.7H, s, H-2 enol) 6.32 (0.7H, dd, J 17.1, 1.9, H-4 enol), 6.82 (0.3H, d, J 17.1, H-4 keto), 6.50 (6H, br m, H-5 and aromatics), and 12.70 (0.7H, br d, J 1.9, OH enol); m/z (EI) 262 (M^+), 206, 173, 131, and 57; Found: C 68.4; H 6.94. $C_{15}H_{18}O_2S$ requires C 68.7; H 6.92%.

Preparation of ^{t}Butyl 4-cyclohexylidenyl-3-oxo-butanthioate (8). The thioester-phosphonate (2) (0.964g 3.11mmol) was reacted with cyclohexanone (0.203g, 2.07mmol) under the standard conditions and worked up as normal. Flash chromatography (1% ether/petrol) gave ^{t}butyl 4-cyclohexylidenyl-3-oxobutanthioate (8) (0.353g, 67%) as a pale yellow solid ; m.pt. 33-35°C; υ_{max} (film) 2929, 2856, 1671, 1645, 1613, 1574, and 1081cm^{-1}; ^1H δ (250MHz, $CDCl_3$) (30% enol form) 1.47 (6.3H, s, ^{t}BuS keto), 1.52 (2.7H, s, ^{t}BuS enol),

1.66 (6H, br m, 2 x H-3', 4' and 5' cyclohexyl), 2.20, 2.75, 2.83 (2H, t, J 7.6; 0.6H, m; 1.4H, m, 2 x H-2' and 2 x H-6' cyclohexyl), 3.58 (1.4H, s, H-2 keto), 5.29 (0.3H, s, H-2 enol), 5.39 (0.3H, s, H-4 enol), 6.04 (0.7H, s, H-4 keto), and 13.06 (0.3H, br s, OH enol); m/z (EI) 254 (M^+), 198, 165, 123, and 57; Found: C 65.8; H 8.78. $C_{14}H_{22}O_2S$ requires C 66.1; H 8.72%.

Preparation of (4*E*, 6*E*) ^{t}Butyl-6-methyl-7-[3-(N-trimethylsilylethyloxymethyl)indolyl]-3-oxohepta-4,6-dienthioate (9). The thioester-phosphonate (2) (1.43g, 4.60mmol) was added dropwise to a suspension of sodium hydride in THF (70ml) at 0°C. After 20min, the effervescence had ceased and the colour had changed to dark brown. The aldehyde (3) (737mg, 2.34mmol) in THF (10ml) was added *via* cannula. The mixture was stirred for 15min and worked up as usual. The residue was purified by flash chromatography (20% ether/petrol) to give the polyene (9) (1.17g, 99%) as an orange/brown oil; υ_{max} (film) 3389, 2952, 2922, 1623, 1566, 1521, 1465, 1377, 1325, 1299, 1248, 1234, 1121, 1077, 944, 868, 836, 741 and 663 cm^{-1}; ^1H δ (500MHz, $CDCl_3$) (70% enol form) -0.06 (9H, 2s, $SiMe_3$, enol and keto form), 0.90 (2H, 2t, J 8.2, CH_2Si, enol and keto form), 1.49 (2.7H, s, ^{t}Bu, keto form), 1.546.3H, s, ^{t}Bu, enol form), 2.11 (2.1H, s, allylic Me, enol form), 2.36 (0.9H, s, allylic Me, keto form), 3.51 (2H, 2t, J 8.1, OCH_2CH_2Si, enol and keto form), 3.80 (0.6H, s, H-2, keto form), 5.52, 5.53 (2H, 2s, NCH_2O, enol and keto form), 5.82 (0.7H, d, J 15.4, H-5, enol form), 6.30 (0.3H, d, J 15.5, H-4, keto form), 7.04 (0.7H, s, H-2, enol form), 7.18-7.31 (2.7H, m, H-6', H-7' enol and keto forms and H-4 enol form), 7.38, 7.43 (1H, 2s, H-2 enol and keto form respectively), 7.45-7.50 (2H, 2d, J 4.9 and 8.3, H-5' and H-8'), 7.59 (0.3H, d, J 15.4, H-5 keto form), 7.71 (1H, d, J 7.95, H-7, enol and keto form) and 9.75 (0.7H, d, J 1.5, OH, enol form); m/z (EI) 471 (M^+), 381, 354, 340, 296, 279, 274, 264, 254, 247, 236, 194, 149 and 90; Found C 66.13; H 8.01; N 3.16%. $C_{26}H_{37}NO_3SSi$ requires C 66.21; H 7.91; N 2.97%.

Preparation of ^{t}Butyl (4*E*) 5-cyclohexyl-3-oxo-4-pententhioate (10). The thioester-phosphonate (2) (0.130g, 0.420mmol) was reacted with cyclohexanecarboxaldehyde (48mg, 0.43mmol) under the standard conditions and worked up as normal. Flash chromatography (30% DCM/petrol) gave ^{t}butyl (4*E*) 5-cyclohexyl-3-oxo-4-pententhioate (10) (93.2mg, 81%) as a pale yellow oil; υ_{max} (film) 2925, 2852, 1650, 1583, and 1076cm^{-1}; ^1H δ (250MHz, $CDCl_3$) (50% enol form) 1.20, 1.70 (10H, 2m, $(CH_2)_5$ cyclohexyl), 1.46, 1.51 (9H, 2s, ^{t}BuS keto and enol) 2.15 (1H, m, H-6), 3.69 (1H, s, 2 x H-2 keto), 5.31 (0.5H, s, H-2 enol) 5.62 (0.5H, dm, J 17.9, H-4), 6.09 (0.5H, dm, J 17.9, H-4) 6.64 (O.5H, dd, J 17.9, 2.5, H-5), 6.83 (0.5H, dd, J 17.9, 2.5, H-5), and 12.62 (0.5H, br s, OH enol); m/z (EI) 268 (M^+), 212, 179, and 57; Found: C 67.1; H 9.20. $C_{15}H_{24}O_2S$ requires C 67.1; H 9.01%.

Preparation of ^{t}Butyl (4*E*, 6*E*, 8*E*, 10*E*, 12*E*) (14*S, 15*R**) 15-^{t}butyldiphenylsilyloxy-12,14,16-trimethyl-3-oxo-4,6,8,10,12-heptadecapentaenthioate (11).** The thioester-phosphonate (2) (89.2mg, 0.287mmol) was added to a stirred suspension of sodium hydride (25.2mg, 60% oil dispersion, 0.632mmol) in THF (10ml) at 0°C. The reaction was stirred for 1hr and then the aldehyde (4) (67.6mg, 0.139mmol) was added. The reaction was allowed to warm to room temperature, stirred for 16hr and worked up as usual. Flash chromatography (1% ether/petrol) gave the coupled product (11) (55.5mg, 62%) as an orange foam; υ_{max} (film) 3330, 2963, 1665, 1640, 1615, 1566, 1426, 1108, and 1075cm^{-1}; ^1H δ (500MHz,$CDCl_3$) (80% enol form) 0.81 (6H,m), 0.88 (3H, d, J 6.7, 14-Me, 16-Me, 3 x H-17, 1.06 (9H, s, ^{t}BuSi), 1.56 (1.8H, s, ^{t}BuS keto), 1.58 (7.2H, s, ^{t}BuS enol), 1.60 (3H, s, 12-Me), 1.78 (1H, m, H-16), 2.64 (1H, m, H-14), 3.50 (1H, m, H-15), 3.72 (0.4H, m, 2 x H-2 keto), 5.37 (0.8H, s, H-2 enol), 5.74 (2H, m), 6.15 (1H, m), 6.27

(3H, m), 6.43 (1H, m), 6.55 (1H, m, H-4, H-6 to H-11, H-13), 7.16 (1H, dd, J 15.0, 11.4, H-5), and 7.39, 7.69 (10H, 2m, 2 x Ph) (OH enol not detected); m/z (EI) 526, 495, 469, 339, 311 and 216.

General Procedure for the Preparation of β-Ketoamides from β-Ketothioesters. Silver (I) trifluoroacetate (1.1equiv) was added to a stirred solution of the amine (1equiv) and the β-ketothioester (1.1equiv) in THF (10% dilution of reactants) at room temperature under argon. We now also recommend the addition of powdered 4Å molecular sieves. If the thioester was the more valuable reagent, the amine could be used in excess (1.1 equiv). The reactions were followed by tlc until complete. The reactions were best left stirring even after tlc indicated completion until precipitation of the silver salt was evident as this greatly facilitated the work up procedure. The reactions were worked up by removing the solvent *in vacuo*, resuspending the solid in ether, filtering, and collecting the filtrate. This precipitation/filtration procedure was repeated until most of the silver residues were removed (once or twice more). The solvent was removed *in vacuo* and the residue purified by column chromatography. The silver salts may elute slowly from the column if present.

Preparation of Ethyl 2-[N-methyl (4*E*, 6*E*) N-(6-methyl-3-oxo-7-(3-(N-trimethylsilylethyloxymethyl)indolyl)hepta-4,6-dienoyl)]ethanoate (15). To a mixture of the thioester (9) (597mg, 1.27mmol), Na_2HPO_4 (750mg) and sarcosine ethyl ester (freshly obtained by $NaHCO_3$ (aq) neutralisation of 850mg of the corresponding hydrochloride salt - approx. 4equiv - and extracting with DCM) in anhydrous THF (50ml) at room temperature was added silver (I) trifluoroacetate (350mg, 1.58mmol, 1.25equiv). After 5hr, the mixture was filtered through a pad of celite. The solvent was evaporated *in vacuo* and the residue taken up in ether and refiltered. Evaporation and flash chromatography on florisil (20% MeOH/DCM) gave the amide (15) (287mg, 45%) as an unstable dark orange oil; υ_{max} (film) 2951, 1743, 1629, 1579, 1484, 1375, 1234, 1199, 1121, 1081, 965, 836 and 743 cm^{-1}; ^1H δ (500MHz, $CDCl_3$) (80% enol form, ~3:1 rotameric mixture, major form assigned) -0.06 (9H, s, $SiMe_3$), 0.90 (2H, t, J 8.1, CH_2Si), 1.28 (3H, t, J 6.9, CH_2CH_3), 2.13 (3H, s, allylic Me), 3.10 (3H, s, NMe), 3.41 (2H, t, J 8.1, OCH_2CH_2Si), 4.16-4.26 (4H, m, NCH_2CO_2Et and CH_2CH_3), 5.51 (2H, s, NCH_2O), 5.97 (1H, d, J 15.1, H-4'), 7.01 (1H, s, H-2') and 7.16-7.75 (7H, m, H-2", H-5"-H-8", H-5' and including 7.37, s, H-7'); m/z (EI) 498 (M^+), 480, 452, 427, 380, 355, 334, 263, 247, 194 and 117; Found (M^+) 498.2550. $C_{27}H_{38}N_2O_5Si$ requires 498.2543.

Preparation of (4*E*,6*E*) N-isobutyl-3-oxo-4,6-decadienamide (16). Silver (I) trifluoroacetate (0.351g, 1.59mmol) was added to a stirred solution of thioester (6) (0.367g, 1.45mmol) and 2-methylpropylamine (0.201ml, 1.73mmol) in THF (6ml) at room temperature. The reaction was stirred for 30min and worked up as usual. Flash chromatography (35% ether/petrol) gave (4*E*,6*E*) N-isobutyl-3-oxo-4,6-decadienamide (16) (0.264g, 77%) as a colourless oil; υ_{max} (film) 3310, 2959, 1637, 1587, 1412, and 1117cm^{-1}; ^1H δ (500MHz, $CDCl_3$) 0.92 (6H, d, J 6.7, CH_3CHCH_3), 0.94 (3H, t, J 6.0, 3 x H-10), 1.48 (2H, h, J 6.0, 2 x H-9), 1.79 (1H, s, J 6.7, CH_3CHCH_3), 2.18 (2H, q, J 6.0, 2 x H-8), 3.10 (2H, dd, J 6.7, 6.0, NCH_2CHR), 3.53 (2H, s, 2 x H-2), 6.11 (1H, d, J 17, H-4), 6.24 (2H, m, H-5 and H-6), 7.19 (1H, br s, NH), and 7.26 (1H, dd, J 10, 17Hz, H-5); m/z (EI) 237 (M^+), 194, 165, 142, and 95. Found: C 70.7; H 9.93; N 5.84. $C_{14}H_{23}NO_2$ requires C 70.9; H 9.77; N 5.90%.

Preparation of (±) N-[(4*E*) 15-^{t}Butyldimethylsilyloxy-3-oxo-4-pentadecenoyl]proline methyl ester (17). Silver (I) trifluoroacetate (162mg, 0.733mmol) was added to a stirred solution of the corresponding thioester (0.318g, 0.696mmol) and methyl (±)-prolinate (86mg, 0.666mmol) in THF (5ml). The reaction was stirred for 16hr and worked up as usual. Flash chromatography (30% ether/petrol) gave (±)-N-[(4*E*)-15-

^{t}butyldimethylsilyloxy-3-oxo-4-pentadecenoyl]proline methyl ester (17) (0.214g, 65%) as a colourless oil; υ_{max} (film) 2928, 2855, 1747, 1657, and 1596cm^{-1}; ^{1}H δ (250MHz, $CDCl_3$) 70% enol form, 4:1 rotamer mixture) 0.01 (6H, Me_2Si), 0.86 (9H, s ^{t}BuSi), 1.24 (14H, br s, 2 x H-7 to H-13), 1.45 (4H, br m, 2 x H-6, H-14), 1.98, 2.17 (4H, 2 br m, 2 x H-3, H-4 proline), 3.47 (2H, br m, N CH_2 proline), 3.56 (2H, t, J 5.7, 2 x H-15), 3.60 (0.6H, 2s, 2 x H-2 keto), 3.70 to 3.72 (3H, 4s, CH_3O_2C keto, enol, both rotamers), 4.34 (0.3H, m, NCHCO$_2$Me keto), 4.50 (0.7H, m, NCHCO$_2$Me enol), 4.75 (0.14H, s, H-2 enol rotamer), 5.00 (0.56H, s, H-2 enol rotamer), 5.72 (0.14H, d, J 15.2, H-4 enol rotamer), 5.77 (0.56H, d, J 15.2, H-4 enol rotamer), 6.15 (0.06H, d, J 17.0, H-4 keto rotamer), 6.19 (0.24H, d, J 17.0, H-4 keto rotamer), 6.50 (0.7H, dt, J 15.2, 6.8, H-5 enol), 6.96 (0.3H, dt, J 17.0, 6.8, H-5 keto), 13.92 (0.56H, br s, OH enol rotamer), and 14.21 (0.14H, br s, OH enol rotamer); m/z (EI) 495 (M^+), 480 and 438; Found (M^+-^{t}Bu) 438.2683. $C_{23}H_{40}NO_5Si$ requires 438.2676.

Preparation of (±) N-(4-Diethylphosphono-3-oxobutanoyl)-proline methyl ester (18). Silver (I) trifluoroacetate (0.288g, 13.0mmol) was added to a stirred solution of the thioester-phosphonate (2) (0.386g, 12.5mmol) and methyl (±)-prolinate (0.153g, 11.9mmol) in THF (8ml). The mixture was stirred for 16hr and worked up by the usual procedure. Flash chromatography (10% isopropyl alcohol/DCM) gave (±)-N-(4-diethylphosphono-3-oxobutanoyl)-proline methyl ester (18) (0.248g, 60%) as a colorless oil; υ_{max} (film) 3466, 2982, 1743, 1639, 1599, 1252, and 1025cm^{-1}; ^{1}H δ (250MHz, $CDCl_3$) 35% enol form, 4:1 rotamer mixture) 1.24 (6H, t, J 7.0, $(CH_3CH_2O)_2P$), 1.90, 2.24 (4H, 2m, 2 x H-3, 2 x H-4 proline), 2.67 (0.14H, d, J 21.3, PCH_2CO enol rotamer), 2.70 (0.56H, d, J 21.3, PCH_2CO enol rotamer, 3.23 (1.3H, d, J 21.3, PCH_2CO keto), 3.40 (1.3H, s, H-2 keto), 3.50 (2H, m, CH_2N), 3.63 (0.4H, s, CH_3O_2C keto rotamer), 3.65 (1.6H, s, CH_3O_2C keto rotamer), 3.67 (0.2H, s, CH_3O_2C enol rotamer), 3.69 (0.8H, s, CH_3O_2C enol rotamer), 4.04 (4H, 2q, J 7.0, $(CH_3CH_2O_2)P$), 4.40 (1H, m, NCHCO$_2$Me), 4.90 (0.07H, d, J 3.0, H-2 enol rotamer), 5.60 (0.28H, d, J 3.0, H-2 enol rotamer), 14.40 (0.28H, br s, OH enol rotamer), and 14.70 (0.07H, br s, OH enol rotamer); m/z (EI) 349 (M^+), 221, 179, and 151; Found (M^+) 349.1299. $C_{14}H_{24}NO_7P$ requires 349.1290.

Preparation of N-Acetoacetylpyrrolidin-2-one (19). Silver (I) trifluoroacetate (1.46g, 6.61mmol) was added to a stirred solution of 2-pyrrolidinone (0.56g, 6.58mmol) and ^{t}butyl 3-oxobutanthioate (1) (1.15g, 6.60mmol) in THF (20ml). The reaction was stirred for 3hr and worked up by the usual procedure. Flash chromatography (75% ether/petrol) gave N-acetoacetyl-pyrrolidin-2-one (19) (0.823g, 74%) as a colourless oil; υ_{max} (film) 2937, 1735, 1689, 1628, 1364, 1326, and 1190cm^{-1}; ^{1}H δ (90MHz, $CDCl_3$) 2.00 (2H, m, 2 x H-4 pyrrolidinone), 2.17 (3H, s, 3 x H-4), 2.48 (2H, td, J 7.7, 0.9, 2 x H-3 pyrrolidinone), 3.75 (2H, t, J 7.0, 2 x H-5 pyrrolidinone), and 3.89 (2H, s, 2 x H-2); ^{13}C, δ (22.5Hz, $CDCl_3$, decoupled) 16.70 (C4 pyrrolidinone), 29.88 (C3 pyrrolidinone), 32.94 (C4), 44.90 (C5 pyrrolidinone), 52.04 (C2), 166.72 (C2 pyrrolidinone), 175.44 (C1), and 201.08 (C3); Found: C 56.9; H 6.59; N 8.27. $C_8H_{11}NO_3$ requires C 56.8; H 6.55; N 8.28%.

Preparation of (2*S*) N-Acetoacetyl-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (20). Silver (I) trifluoroacetate (0.110g, 0.498 mmol) was added to a stirred solution of glutamate (0.105g, 0.452 mmol) and ^{t}butyl 3-oxobutanthioate (1) (86.6 mg, 0.497 mmol) in THF (5ml) at room temperature. The reaction was stirred for 2hr and worked up as usual. Flash chromatography (60% ether/petrol) gave (2S)-N-acetoacetyl-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (20) (91.4mg, 64%) as a colourless oil; $[\alpha]_D^{20}$ -29.2 (c 2.6, $CHCl_3$); υ_{max} (film) 3430, 2978, 1724, 1647, and 1154cm^{-1} ; ^{1}H δ (90MHz, $CDCl_3$) (rotamer and tautomer mixture) 1.44 (9H, s, ^{t}Bu), 1.95 (2H, m, 2 x H-3), 2.24 (5H, m, 2 x $CH_2CO_2{}^t$Bu including 3 x H-4),

2.82, 2.89, 2.91 (3H, 3s N-Me), 3.56 (2H, s, 2 x H-2), 3.70, 3.72 (3H, s, CO_2Me), and 5.12 (1H, m, $CHCO_2Me$); m/z (EI) 315, (M^+), 259, 205, 158, and 116. Found (M^+) 315.1688. $C_{15}H_{25}NO_6$ (M^+) requires 315.1682.

Preparation of N-(2-Pyridyl)-3-oxobutanamide (21). Silver (I) trifluoroacetate (0.434g, 1.97mmol) was added to a stirred solution of 2-aminopyridine (0.168g, 1.78mmol) and ^{t}butyl 3-oxobutanthioate (1) (0.327g, 1.88mmol) in THF (5ml). The reaction was stirred for 5min and worked up by the usual procedure. Flash chromatography (gradient elution, 40-80% ether/petrol) gave N-(2-pyridyl)-3-oxobutanamide (21) (0.205g, 65%) as a pale orange amorphous solid; m.pt. 109-110°C (lit.[31] 113-114°C); υ_{max} (KBr disc) 3242, 3058, 1718, 1666, 1576, 1542, and 1434cm^{-1}; ^{1}H δ (60MHz, $CDCl_3$) (15% enol form) 1.9 (0.45H, s, CH_3 enol), 2.3 (2.55H, s, CH_3 keto), 3.6 (1.7H, s, H-3 keto), 5.1 (0.15H, s, H-3 enol), 7.0 to 8.5 (3H, 3m, pyridyl H-3, 4, and 5), and 10.0 (1H, m, H-6 pyridyl); λ_{max} (95% EtOH/H_2O) 232 and 276nm (ε_{max} 11000 and 9500dm^3 mol^{-1} cm^{-1}); m/z (EI) 178 (M^+), 163, and 94; Found: C 60.5; H 5.67; N 15.5. $C_9H_{10}N_2O_2$ requires C 60.7; H 5.66; N 15.7%.

Preparation of N-(2-Nitrophenyl)-3-oxobutanamide (22). Silver (I) trifluoroacetate (0.512g, 2.32mmol) was added to a solution of o-nitroaniline (0.291g, 2.11mmol) and ^{t}butyl 3-oxo-butanthioate (1) (0.386g, 2.21mmol) in THF (6ml) and stirred for 3hr followed by the usual work up. Flash chromatography (gradient elution, 20-40% ether/petrol) gave N-(2-nitrophenyl)-3-oxobutanamide (22) (0.376g, 80%) as a pale yellow solid; m.pt. 64°C (lit.[47] m.pt. 66-67°C); υ_{max} ($CHCl_3$) 3515, 3398, 1624, 1572, 1511, and 1346cm^{-1}; ^{1}H δ (60MHz, $CDCl_3$) 20% enol form) 2.0 (0.6H, s, H-4 enol), 2.3 (2.4H, s, H-4 keto), 3.6 (1.6H, s, H-2 keto), 5.0 (0.2H, s, H-2 enol), 7.1 and 7.5 (2H, 2m, H-4 and H-5 aryl), 8.1 and 8.7 (2H, 2m, H-3 and H-6 aryl), 11.0 (1H, br s, NH), and 13.0 (0.2H, br s, OH enol); m/z (EI) 222 (M^+), 176, and 138; Found: C 54.2; H 4.52; N 12.5. $C_{10}H_{10}N_2O_4$ requires C 54.1; H 4.54; N 12.6%.

Preparation of (2*S*) N-α-acetoacetyl-N-α-benzylytryptophan methyl ester (23). Silver (I) trifluoroacetate (64mg, 0.29mmol) was added to a stirred solution of aminoester (74mg, 0.24mmol) and ^{t}butyl 3-oxobutanthioate (1) (45mg, 0.27mmol) in THF (4ml) at RT under argon. The reaction mixture was stirred for 30 minutes and worked up by the usual procedure. Flash chromatography (ether/petrol) gave (2*S*)-N-α-acetoacetyl-N-α-benzylytryptophan methyl ester (23) (70mg, 74%) as colourless needles; m.pt. 94-100°C; υ_{max} (nujol mull) 3380, 2995, 2940, 1725, 1630, 1440, and 1350cm^{-1}; ^{1}H δ (250MHz, $CDCl_3$) (mixture of rotamers and tautomers) 1.60-2.25 (3H, several s, CH_3CO tautomers and rotamers) 3.42 and 3.47 (3H, 2s, CO_2CH_3 two rotamers or tautomers), 3.31-3.60 (2H, m, CH_2CH), 3.61 and 3.67 (1.5H, 2s, $COCH_2CO$, two rotamers), 3.84-4.44 (2H, two sets of 2d, NCH_2Ph), 4.49-4.80 (1H, m, CH_2CH), 5.05 (0.25H, s, $COCH_2CO$ enol), 7.00-7.60 (10H, m, aromatics), and 8.12 (1H, br, s, NH indole) (OH enol not detected); m/z (EI) 392 (M^+), 308, 249, 201, 130, and 91; Found: C 70.2; H 6.18; N 7.11. $C_{23}H_{24}N_2O_4$ requires C 70.4; H 6.17; N 7.14%.

Preparation of N-Acetoacetyl-N-benzylglycine methyl ester (24). Silver (I) trifluoroacetate (1.03g, 4.67mmol) was added to a stirred solution of N-benzylglycine methyl ester (0.76g, 4.24mmol) and ^{t}butyl 3-oxobutanthioate (1) (0.81g, 4.67mmol) in THF (40ml). The reaction was stirred for 16hr and worked up by the usual procedure. Flash chromatography (75% ether/petrol) gave N-acetoacetyl-N-benzylglycine methyl ester (24) (0.76g, 65%) as a colourless oil; υ_{max} (film) 3400, 2936, 1747, 1647, 1492, and 1203cm^{-1}; ^{1}H δ (90MHz, $CDCl_3$) (30% enol form, 2:1 rotamer mixture) 2.02 (0.9H, s, 3 x H-4 enol rotamers), 2.39 (2.1H, s, 3 x H-4 keto rotamers), 3.60 (0.47H, s, 2 x H-2 minor keto rotamer), 3.70 (0.93H, s, 2 x H-2 major keto rotamer), 3.80 (3H, s, CO_2Me), 4.05 (0.67H, s, 2 x NCH_2CO_2Me minor rotamer), 4.15 (1.33H, s, CH_2CO_2Me major

rotamer), 4.55, 4.59, 4.65 (2H, 3s, NCH_2CO_2Me), 5.35 (0.3H, s, 1 x H-2 enol rotamers), 7.40 (5H, m, aromatics), and 13.90 (0.3H, br s, enol OH); m/z (EI) 263 (M^+), 178, 120 and 91; Found: C 63.9; H 6.55; N 5.29. $C_{14}H_{17}NO_4$ requires C 63.9; H 6.51; N 5.32%.

Preparation of (2*S*,3*S*) N-Acetoacetyl-N-methylisoleucine methyl ester (25). Silver (I) trifluoracetate (61.6mg, 0.279mmol) was added to a stirred solution of aminoester (50.4mg, 0.254mmol) and ^{t}butyl 3-oxobutanthioate (1) (50.0mg, 0.287mmol) in THF (5ml). The reaction was stirred for 20hr and worked up as usual. Flash chromatography (15% ether/petrol) gave (2*S*,3*S*) N-acetoacetyl-N-methylisoleucine methyl ester (25) (42.1mg, 68%) as a colourless oil; $[\alpha]_D^{25}$ - 131 (c 2.4, $CDCl_3$); b.pt. 178-180°C/0.04mmHg; υ_{max} (film) 3400, 1737, 1647, and 1201cm^{-1}; ^{1}H δ (500MHz, $CDCl_3$) (30% enol form, 4:1 rotamer mixture) 0.92 (6H, m, $CH_3CH_2CHCH_3$), 1.20 (1H, m, 1 x $CH_3CH_2CHCH_3$), 1.42 (1H, m, 1 x $CH_3CH_2CHCH_3$), 2.0 (1H, m $CH_3CH_2CHCH_3$), 1.95 (0.9H, s, 3 x H-4 enol), 2.25 (2.1H, s, 3 x H-4 keto), 2.92 (0.18H, s, N-Me enol minor rotamer), 2.94 (0.42H, s, N-Me keto minor rotamer), 2.95 (2.4H, s, N-Me enol and keto major rotamers), 3.59 (1.12H, d, J 3, H-2 keto major rotamer), 3.61 (0.2H, d, J 3, H-2 keto minor rotamer), 3.71 (2.1H, s, CO_2Me keto), 3.74 (0.9H, s, CO_2Me enol), 5.00, 5.02 (1H, 2d, J 10, $CHCO_2Me$ 5.14 (0.24H, s, H-2 enol major rotamer) 5.22 (0.06H, s, H-2 enol minor rotamer), 14.52 (0.24H, br s, enol OH major rotamer), and 14.54 (0.06H, br s, enol OH minor rotamer); m/z (EI) 243 (M^+), 225, 212, 184, and 100; Found: C 59.5; H 8.95; N 5.73. $C_{12}H_{21}NO_4$ requires C 59.2; H 8.70; N 5.76%.

Preparation of (2*S*,3*S*) N-Acetoacetylisoleucine methyl ester (26). Silver (I) trifluoroacetate (0.478g, 2.16mmol) was added to a stirred solution of methyl (2*S*,3*S*)-isoleucinate (0.227g, 1.73mmol) and ^{t}butyl 3-oxobutanthioate (1) (0.332g, 1.90mol) in THF (15ml). The reaction was stirred for 3hr and worked up by the usual procedure. Flash chromatography (ether) gave (2*S*,3*S*) N-acetoacetylisoleucine methyl ester (26) (0.253g, 60%) as a colourless oil; $[\alpha]_D^{25}$ -22.0 (c 2.0 MeOH); υ_{max} (film) 3315, 2966, 2879, 1735, 1712, 1648, 1512, and 1301cm^{-1}; ^{1}H δ (90MHz, $CDCl_3$) 0.90 (6H, m, $CH_3CH_2CHCH_3$), 1.30 (2H, m $CH_3CH_2CHCH_3$), 1.90 (1H, m $CH_3CH_2CHCH_3$), 2.26 (3H, s, CH_3CO), 3.43 (2H, s, $COCH_2CON$), 3.72 (3H, s, CH_3O), 4.56 (1H, dd, J 8.2, 4.6, $CHCO_2Me$), and 7.35 (1H, br d, NH); ^{13}C δ (22.5MHz, $CDCl_3$, decoupled) 11.45 ($CH_3CH_2CHCH_3$), 15.42 ($CH_3CH_2CHCH_3$), 25.06 ($CH_3CH_2CHCH_3$), 30.80 (CH_3CO), 37.57 ($CH_3CH_2CHCH_3$), 49.54 ($COCH_2CON$), 51.98 (CH_3O_2C), 56.55 ($NHCHCO_2Me$), 165.37, 171.96 (CH_2CONH, CO_2Me), and 203.94 (CH_3COCH_2).

Preparation of N-Acetoacetyl-N-methylglycine ethyl ester (27). Silver (I) trifluoroacetate (1.40g, 6.34mmol) was added to a stirred solution of ^{t}butyl 3-oxobutanthioate (1) (1.10g, 6.31mmol) and ethyl sarcosinate (0.67g, 5.72mmol) in THF (12ml). The reaction was stirred for 16hr and worked up by the usual procedure. Flash chromatography (ether) gave N-acetoacetyl-N-methylglycine ethyl ester (27) (0.748g, 65%) as a colourless oil; ^{1}H δ (90MHz, $CDCl_3$) (87% keto form, 3:1 rotamer mixture) 1.30 (3H, 2q, J 7.1, $CH_3CH_2O_2C$), 1.95 (0.65H, s, H-4 minor keto rotamer), 2.26, 2.30 (2.35H, 2s, H-4 enol major and minor rotamer, major keto rotamer), 3.00 (0.65H, s, N-Me minor keto rotamer), 3.07 (0.29H, s, N-Me major enol rotamer), 3.09 (2.06H, s, N-Me major keto, minor enol rotamer), 3.50 (0.44H, s, 2 x H-2 minor keto rotamer), 3.60 (1.30H, s, 2 x H-2 major keto rotamer), 3.90 (2H, br s, 2 x CH_2CO_2Et), 4.20 (2H, br q, J 7.1, CH_3CH_2O), 5.20 (0.13H, br s, H-2 enol), and 13.9 (0.13H, br s, OH enol); m/z (EI) 201 (M^+), 183, 155 and 128.

Preparation of (±) N-Acetoacetyl-N-benzylalanine Ethyl Ester (28). Silver (I) trifluoroacetate (0.527g, 2.39mmol) was added to a stirred solution of ^{t}butyl 3-oxobutanthioate (1) (0.416g, 2.39mmol) and

(±)-N-benzylalanine ethyl ester (0.45g, 2.17mmol) in THF (25ml). The reaction was stirred for 16hr and worked up by the usual procedure. Flash chromatography (40% ether/petrol) gave (±)-N-acetoacetyl-N-benzylalanine ethyl ester (28) (0.474g, 75%) as a colourless oil; υ_{max} (film) 3200, 2985, 1738, 1633, 1589, 1479, and 1026cm^{-1}; ^{1}H δ (60MHz, $CDCl_3$) (75% enol form) 1.20 (3H, t, J 7.5, CH_3CH_2O), 1.40 (3H, d, J 6.0, 3 x H-3), 1.85 (2.25H, s, CH_3CO enol), 2.20 (0.75H, s, CH_3CO keto), 3.40 (0.5H, s, $COCH_2CONH$ keto), 4.10 (3H, m, CH_3CH_2O, H-2), 4.50 (2H, m, NCH_2Ph), 5.0 (0.75H, s, H-2 enol), 7.25 (5H, s, aromatics), and 14.20 (0.75H, br s, enol OH).

Preparation of Ethyl 2-[N-methyl (4*E*, 6*E*, 8*E*, 10*E*, 12*E*) N-(3-oxo-4,6,8,10,12-tetradecapentaenoyl)]ethanoate (29). Using the general procedure, the thioester (48) (200mg, 0.657mmol) in THF (20ml) was reacted with sarcosine ethyl ester (370mg, 4.8equiv) in the presence of silver (I) trifluoroacetate (232mg, 1.05mmol, 1.6equiv) and Na_2HPO_4 for 5.5hr. Flash chromatography (10% ether/petrol) gave the amide (29) (97mg, 45%) as a bright yellow solid; m.pt. 155-160°C; υ_{max} (film) 3440, 3350, 2929, 1745, 1624, 1587, 1208 and 1006 cm^{-1}; ^{1}H δ (250MHz, $CDCl_3$) (85% enol form, ~3:1 rotameric mixture, major form assigned) 1.26 (3H, t, J 4.5, CH_2CH_3), 1.82 (3H, d, J 6.8, H-14'), 3.80 (3H, s, NMe), 4.10-4.28 (4H, m, CH_2CO_2Et and CH_2CH_3), 5.28 (1H, br s, H-2'), 5.7-6.6 (9H, m, H-4' and H-6'-H-13' inclusive) and 7.10 (1H, dd, J 14.9, 11.3, H-5'); m/z (EI) 331 (M^+), 285, 258 (M^+-CO_2Et), 214 (M^+-$C_5H_{12}NO_2$), 199, 172, 145 and 118; Found (M^+) 331.1784. $C_{19}H_{25}NO_4$ requires 331.1784.

Preparation of (2*S*) N-(4*E*,6*E*,8*E*,10*E*,12*E*) (14*S, 15*R**) 15-^{t}Butyldiphenylsilyloxy-12,14,16-trimethyl-3-oxo-4,6,8,10,12-heptadecapentaenoyl]-N-methylglutamic Acid α-Methyl Ester γ-^{t}Butyl Ester (30).** Silver (I) trifluoroacetate (26.9mg, 0.122mmol) was added to a stirred solution of thioester (11) (52.3mg, 81.3mmol) and aminodiester (56.4mg, 0.244mmol) in THF (5ml). The reaction was stirred for 15 min and the volatile material thoroughly removed *in vacuo*. The residue was preadsorbed onto silica (3g) and flash chromatography (gradient elution, 20-40% ether/petrol) gave (2*S*) N-[(4*E*,6*E*,8*E*,10*E*,12*E*) (14*S**,15*R**)-15-^{t}butyldiphenylsilyloxy-12,14,16-trimethyl-3-oxo-4,6,8,10,12-heptadecapenta-enoyl]-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (30) (31.3mg, 49%); υ_{max} (film) 3400, 2960, 1735, 1628, 1586, 1481, 1152, and 1110cm^{-1}; ^{1}H δ (500MHz, $CDCl_3$) (70% enol form, mixture of rotamers and diastereoisomers) 0.82 (6H, m), 0.87 (3H, d J 6.7, 14-Me, 16-Me, 3 x H-17), 1.06 (9H, s, ^{t}BuSi), 1.42 (9H, s, ^{t}BuO_2C), 1.58 (3H, s, 12-Me), 1.78 (1H, m, H-16), 2.00, 2.28 (4H, 2m, $CH_2CH_2CO_2$ ^{t}Bu), 2.65 (1H, m, H-14), 2.90, 2.93, 2.96 (3H, 3s, N-Me), 3.50 (1H, m, H-15), 3.70 (0.6H, s, 2 x H-2 keto), 3.72, 3.74 (3H, 2s, CO_2Me), 5.22 (1.7H, m, including 0.7H, s, H-2 enol, H-2), 5.72 (1H, m), 5.93 (1H, m), 6.16 (1H, m), 6.28 (3H, m), 6.41 (1H, m), 6.43 (1H, m, H-4, H-6 to H-11 inclusively, H-13), 7.14 (1H, dd, J 14.7, 10.7, H-5), and 7.40, 7.70 (10H, 2m, 2 x Ph) (OH enol not detected); m/z (EI) 726 (M^+-^{t}butyl), 495, 311, 199, and 135; Found (M^+-^{t}Bu) 726.3840. $C_{43}H_{56}NO_7Si$ requires 726.3826.

Preparation of (3*Z*) 3-[(2*E*, 4*E*) 1-(1-Hydroxy-4-methyl-5-(3-(N-trimethylsilyl-ethyloxymethyl)indolyl)penta-2,4-dienylidene)]-N-methyl-2,4-pyrrolidinedione (33). Freshly sublimed KO^{t}Bu (130mg, 1.16mmol, 2equiv) was added portionwise to a stirred solution of the amide (15) (289mg, 0.58mmol) in anhydrous ^{t}BuOH (25ml) and stirring continued until tlc showed consumption of starting material (~30min). The mixture was poured into water (100ml), citric acid (25ml of a 10% aqueous solution) was added and the resulting orange/red precipitate was extracted with ether (4x50ml). The combined extracts were washed with water (50ml), brine (50ml), dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give an orange red solid. This was precipitated from ether/petrol to give the pure tetramic acid (33) (220mg, 84%) as an

amorphous orange solid; Rf 0.56 (AcOH:EtOAc:DCM 1:9:10); υ_{max} (film) 3381, 2922, 1618, 1563, 1515, 1485, 1465, 1403, 1235, 1217, 1043 and 663 cm^{-1}; ^1H δ ($CDCl_3$) (5:1 tautomeric forms, major form assigned) -0.05 (9H, s, $SiMe_3$), 0.91 (2H, t, J 8.1, OCH_2CH_2Si), 2.24 (3H, s, allylic Me), 3.05 (3H, s, NMe), 3.52 (2H, t, J 8.1, OCH_2CH_2Si), 3.75 (2H, s, H-5), 5.55 (2H, s, NCH_2O), 7.23-7.28 (4H, m, H-2', H-5", H-6" and H-7" inclusive), 7.51 (1H, s, H-5') 7.53 (1H, s, H-2"), 7.75 (1H, d, J 7.8, H-8") and 7.83 (1H, d, J 15.4, H-3'); m/z (EI) 452 (M^+), 334, 254, 194, 167, 140, 113 and 73; Found C 66.12; H 7.18; N 6.11%. $C_{25}H_{32}N_2O_4Si$ requires C 66.34; H 7.13; N 6.19%.

General Procedure for TBAF Cyclisation of β-Ketoamides to Tetramic Acids. TBAF (1M solution in THF, 2 equiv) was added to a solution of the amide in THF at RT under argon and stirred until tlc indicated consumption of starting material. The solvent was then removed under reduced pressure and water added to the residue. This was acidified to pH 1 with 4M H_2SO_4 (aq). The aqueous suspension was extracted with ether (x 3), the combined organic extracts dried ($MgSO_4$), the solvent evaporated *in vacuo* and the residue purified as appropriate.

Preparation of 1-Benzyl-3-[(*Z*) 1-hydroxyethylidene]-2,4-pyrrolidinedione (34). TBAF (1.90 ml, 1M solution in THF, 1.90mmol) was added to a stirred solution of amide (24) (0.249g, 0.944mmol) in THF (5ml) at RT under argon. The reaction was stirred for 30min and worked up as usual. Recrystallisation gave 1-benzyl-3-[(*Z*)-1-hydroxyethylidene]-2,4-pyrrolidinedione (34) (0.171g, 78%) as needles; m.pt. 78°C (from petrol) (lit.[30] 74-76°C); υ_{max} ($CHCl_3$) 2919, 2800 (v.br.), 1712, 1617, 1496, and 1232 cm^{-1}; ^1H δ (90 MHz, $CDCl_3$) (4:1 ratio of tautomers) 2.48 (2.4H, s, CH_3 3-acetyl major tautomer), 2.59 (0.6H, s, CH_3 3-acetyl minor tautomer), 3.64 (1.6H, s, H-5 major tautomer), 3.75 (0.4H, s, H-5 minor tautomer), 4.65 (2H, s, NCH_2Ph), 7.32 (5H, m, aromatics), and 10.5 (1H, br s, OH); ^{13}C δ (22.5 MHz, $CDCl_3$) (two tautomers) 19.39, 19.75 (CH_3 3-acetyl), 45.33 ($PhCH_2N$), 51.92, 54.97 (C5), 102.21, (C3), 128.08, 128.88, 135.22, 136.14 (aryl carbons), 166.59, 172.94 (C2), 183.68, 187.40 ($CH_3C(OH)$=), and 191.31, 197.54 (C4); m/z (EI) 231 (M^+), 106, and 91; Found: C 67.7; H 5.73; N 6.00. $C_{13}H_{13}NO_3$ requires C 67.5: H 5.67; N 6.06%.

Preparation of (5*S*) 3-[(*Z*) 1-Hydroxyethylidene]-1-methyl-5-[(*S*) 1-methylpropyl]-2,4-pyrrolidinedione (35). TBAF (5.7ml, 1M solution in THF, 5.7mmol) was added to a stirred solution of amidoester (25) (0.690g, 2.84 mmol) in THF (7ml) at RT under argon. The reaction was stirred for 45 min and worked up as usual. The residue was distilled to give (5*S*) 3-[(*Z*)-1-hydroxyethylidene]-1-methyl-5-[(*S*)-1-methylpropyl]-2,4-pyrrolidinedione (35) (0.508g, 85%) as a pale yellow viscous oil; b.pt. 150°C, 0.01 mmHg; $[\alpha]_D^{20}$ -36 (c 3.7, $CHCl_3$); υ_{max} (film) 3000 (v.br.), 2964, 1708, 1637, 1457, and 1168 cm^{-1}; ^1H δ (90 MHz, $CDCl_3$) 4:1 tautomer ratio) 0.83 (3H, t, J 7.2, $CH_3CH_2CHCH_3$), 0.97 (3H, d, J 6.4, $CH_3CH_2CHCH_3$), 1.52 (2H, m, $CH_3CH_2CHCH_3$), 1.90 (1H, m, $CH_3CH_2CHCH_3$), 2.38 (2.4H, s,Me 3-acetyl minor tautomer), 2.90 (0.6H, s, N-Me minor tautomer), 2.93 (2.4H, s, N-Me major tautomer), 3.59 (0.8H, d, J 2.6, H-5 major tautomer), 3.75 (0.2H, d, J 3.1, H-5 minor tautomer) (OH not detected); ^{13}C δ (125.8 MHz, D_6 acetone, 9:1 tautomer ratio, decoupled spectrum) 11.95 ($CH_3CH_2CHCH_3$), 13.38 ($CH_3CH_2CHCH_3$), 18.80 (Me 3-acetyl) 24.40, 24.64 ($CH_3CH_2CHCH_3$), 26.85 (NMe), 34.49, 34.78 ($CH_3CH_2CHCH_3$), 69.37 (C5), 102.27 (C3), 172.45 (C2), 181.70 ($CH_3C(OH)$=), and 194.05 (C4); m/z (EI) 211 (M^+) and 155; Found (M^+) 211.1209. $C_{11}H_{19}NO_3$ requires 211.1208.

Preparation of (5*RS*) 3-[(*Z*) 1-Hydroxyethylidene]-5-[(*S*)-1-methyl Propyl]-2,4-pyrrolidinedione (36). A solution of amidoester (26) (1.15g, 5.02mmol) in TBAF/THF solution (50ml, 1M

solution, 50.0mmol) was heated under reflux for 24hr. The usual work up followed by distillation of the residue gave (5*RS*)-3-[(*Z*)-1- hydroxyethylidene]-5-[(*S*)-1-methylpropyl]-2,4-pyrrolidinedione (36) (0.543g, 55%) as a pale yellow viscous oil; b.pt. 200°C, 0.03mmHg; $[\alpha]_D^{25}$ 5.1 (c 3.2, $CHCl_3$); υ_{max} (film) 3300, 2965, 1707, 1653, and 1220cm^{-1}; ^{1}H δ (90MHz, $CDCl_3$) (7:3 tautomer ratio, approximately 1:1 diastereoisomer ratio) 0.90 (6H, m, $CH_3CH_2CHCH_3$), 1.30 (2H, m, $CH_3CH_2CHCH_3$), 1.96 (1H, m, $CH_3CH_2CHCH_3$), 2.41 (2.1H, s, Me 3-acetyl major tautomer), 2.48 (0.9H, s, Me 3-acetyl minor tautomer, 3.75, 3.84, 3.91 (1H, m, H-5), and 7.22 (1H, br s, NH) (OH not detected); λ_{max} (EtOH) 243 and 277nm (ε_{max} 8100 and 14300dm^3 mol^{-1} cm^{-1}); Found: C 60.9; H 7.66; N 6.99. $C_{10}H_{15}NO_3$ requires C 60.9; H 7.72; N 7.10%.

Preparation of 3-[(*Z*) 1-Hydroxyethylidene]-1-methyl-2,4-pyrrolidinedione (37). TBAF (1.6ml, 1M solution in THF, 1.6mmol) was added to a stirred solution of amide (27) (0.210g, 1.05mmol) in THF (5ml) at RT under argon. After 30min stirring followed by the usual work up, the residue was sublimed (0.01 mmHg) giving 3-[(*Z*)-1-hydroxyethylidene]-1-methyl-2,4-pyrrolidinedione (37) (0.113g, 70%) as a white amorphous solid; m.pt. 50-51°C; υ_{max} ($CHCl_3$) 3400, 2962, 1709, 1637, and 1251 cm^{-1}; ^{1}H δ (90MHz, $CDCl_3$) (9:1 ratio of tautomers) 2.40 (2.7H, s, CH_3 3-acetyl major tautomer), 2.50 (0.3H, s, CH_3 3-acetyl minor tautomer), 2.98 (3H, 2s, N-Me both tautomers), 3.69 (1.8H, s, H-5 major tautomer), 3.82 (0.2H, s, H-5 minor tautomer), and 9.7 (1H, br s, OH); ^{1}H δ (90MHz, D_6 acetone) (single tautomer) 2.58 (3H s, CH_3 3-acetyl), 3.19 (3H, s, N-Me), and 4.03 (2H, s, H-5) (OH not detected); λ_{max} (EtOH) 233 (sh), 245, and 281nm (ε_{max} 7500, 9000, and 12500dm^3 mol^{-1} cm^{-1}); m/z (EI) 155 (M^+), 140, 84, and 44; Found: C 54.1; H 5.80; N 8.98. $C_7H_9NO_3$ requires C 54.2; H 5.85; N 9.03%.

Preparation of (±) 1-Benzyl-3-[(*Z*) 1-hydroxyethylidene]-5-methyl-2,4-pyrrolidinedione (38) TBAF (0.73ml, 1 M solution in THF, 0.73mmol) was added to a stirred solution of (28) (0.170g, 0.584mmol) in THF (3ml) at RT under argon. The reaction was stirred for 5 min and worked up as usual. The residue was distilled (Kugelrohr) to give (±) 1-benzyl-3-[(*Z*) 1-hydroxyethylidene]-5-methyl-2,4-pyrrolidinedione (38) (0.124g, 92%) as a pale yellow viscous oil; υ_{max} (film) 3400, 1709, 1629, 1237 and 929 cm^{-1}; ^{1}H δ (250MHz, $CDCl_3$) (85:15 tautomer ratio) 1.28 (2.55H, d, J 6.1, CH_3CH major tautomer). 1.38 (0.45H, d, J 6.1, CH_3CH minor tautomer), 2.43 (2.55H, s, CH_3 3-acetyl major tautomer), 2.55 (0.45H, s, CH_3 3-acetyl minor tautomer), 3.60 (0.85H, q, J 6.1, H-5 major tautomer), 3.75 (0.15H, q, J 6.1, H-5 minor tautomer), 4.05 (0.15 H, d, J, 14.5, 1 x CH_2Ph minor tautomer), 4.10 (0.85 H, d, J 14.5, 1 x CH_2Ph major tautomer) 5.10 (0.85 H, d, J 14.5, 1 x CH_2Ph major tautomer), 5.16 (0.15 H, d, J 14.5, 1 x CH_2Ph minor tautomer), and 7.27 (5H, m, aromatics) (OH not detected); ^{1}H δ (90 MHz, D_6 acetone) single tautomer) 1.23 (3H, d, J 6.5, CH_3CH), 2.39 (3H, s, CH_3 3-acetyl), 3.70 (1H, q, J 6.5, H-5), 4.32 (1H, d, J 14.6, 1 x CH_2Ph), 4.99 (1H, d, J 14.6, 1 x CH_2Ph), and 7.32 (5H, s, aromatics) (OH not detected); ^{13}C δ (22.5 MHz, D_6 acetone) 15.16 (CH_3CH), 19.06 ($CH_3CHC(OH)$=) 43.54 (NCH_2Ph), 61.36 (C-5), 101.70 (C-3), 128.31, 128.74, 129.41, 137.34 (6 phenyl carbons), 173.29 (C-2), 183.85 (CH3C(OH)=), and 194.95 (C-4); m/z (EI) 245 (M^+), 106, and 91; Found (M^+) 245.1057. $C_{14}H_{15}NO_3$ requires 245.1052; Found: C 67.9; H 6.24; N 5.63. $C_{14}H_{15}NO_3$ requires C 68.6; H 6.17; N 5.71%.

Preparation of 3-[(*Z*) 1-Hydroxyethylidene]-2,4-pyrrolidinedione (39). A solution of amidoester (0.52g, 3.00mmol) in TBAF/THF solution (30 ml, 1M solution, 30.0mmol) was heated under reflux for 24h and worked up as usual. Recrystallisation of the residue from ethyl acetate gave 3-[(*Z*) 1-hydroxyethylidene]-2,4-pyrrolidinedione (39) (0.148g, 35%) as colourless microneedles; m.pt. 154-155°C; (lit.[22] 155°C); ^{1}H δ (90 MHz, $CDCl_3$) (3:1 tautomer ratio) 2.46 (2.25H, s, Me 3-acetyl major tautomer), 2.51 (0.75H, s, Me 3-acetyl

minor tautomer, 3.80 (1.5H, s, 2 x H-5 major tautomer), 3.93 (0.5H, s, 2 x H-5 minor tautomer), 6.65 (1H, br s, N-H), and 12.70 (1H, br s, OH); ^{1}H δ (90MHz, D_6 acetone) (single tautomer) 2.37 (3H, s, Me 3-acetyl), 3.76 (2H, s, 2 x H-5), and 7.60 (1H, br s, NH) (OH not detected).

Preparation of (2*R*) N-Benzyloxycarbonyl-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (43). Sodium hydride (3.28g of a 60% oil dispersion, 81.9mmol) was added portionwise to a stirred solution of the glutamic acid derivative (41) (9.20g, 27.3mmol) and iodomethane (13.6ml, 0.218mmol) in THF at 0°C. The reaction was allowed to warm to room temperature and stirred for 24hr. Ethyl acetate (100ml) was added to remove residual NaOH, followed by careful addition of water (5ml) to destroy the excess sodium hydride. The mixture was evaporated to a yellow foam which was partitioned between ether (500ml) and water (300ml). The ether layers were washed with sat. $NaHCO_3$ (aq) (2x200ml). The combined aqueous layers were acidified to pH3 with aqueous citric acid and then extracted with ethyl acetate (3x200ml). The combined ethyl acetate layers were dried ($MgSO_4$) and evaporated *in vacuo*. The residue (42) was redissolved in ether and treated with diazomethane at room temperature. Evaporation of the solvent *in vacuo* and purification of the residue by flash chromatography (gradient elution, 40-60% ether/petrol) gave the diester (43) (5.64g, 57% over two steps) as a colourless oil; identical spectroscopically to the corresponding 2*S* enantiomer; $[\alpha]_D^{25}$ +28.9 (c=1.67, $CHCl_3$); Found C 62.41, H 7.50, N 3.72. $C_{19}H_{27}NO_6$ requires C 62.45, H 7.45, N 3.83%.

Preparation of (2*R*) N-Methylglutamic Acid α-methyl ester γ-^{t}butyl ester (44). A stirred suspension of 10% palladium on carbon (600mg) and diester (43) (5.50g, 15.1mmol) in ethyl acetate (250ml) was hydrogenated at RT and pressure for 4hr, filtered and the volatile material was removed under reduced pressure. Flash chromatography (80% ether-petrol) gave (2*R*)-N-methylglutamic acid α-methyl γ-^{t}butyl diester (44) (3.35g, 96%) as a colourless oil; identical spectroscopically to the corresponding 2*S* enantiomer; $[\alpha]_D^{25}$ -0.15 (c=5.33, $CHCl_3$); Found C 55.07, H 9.11, N 5.62. $C_{11}H_{21}NO_4.1/2H_2O$ requires C 54.98, H 9.23, N 5.62%.

Preparation of Ethyl (2*E*, 4*E*, 6*E*) 2,4,6-octatrienoate. Triethylphosphonoacetate (34.05ml, 0.171mol) was added dropwise to a stirred suspension of sodium hydride (6.87g, 60% oil dispersion, 0.173mol) in THF (300ml) at 0°C. The mixture was stirred for 1hr, during which time it cleared. (2*E*, 4*E*) 2,4-hexadienal (17.22ml, 0.156mol) was added dropwise. The colour changed immediately to red/brown and a thick mass began to form. The reaction was allowed to warm to room temperature and stirred overnight. It was quenched by pouring into sat. NH_4Cl (aq) (750ml) and extracting with ether (3x750ml). The combined ether extracts were washed with water (2x150ml), brine (4x150ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by flash chromatography (2% ether/petrol) to give the ester (22.9g, 88%) as a colourless solid; m.pt. 30°C; υ_{max} (film) 2989, 1704, 1617, 1587, 1444, 1365, 1340, 1296, 1135, 1036, 1005 and 974 cm^{-1}; ^{1}H δ (250MHz, $CDCl_3$) 1.28 (3H, t, J 7.1, $CH_2\underline{CH_3}$), 1.82 (3H, d, J 5.7, H-8), 4.20 (2H, q, J 7.1, $\underline{CH_2}CH_3$), 5.70-6.80 (5H, m, H-2, H-4, H-5, H-6 and H-7) and 7.28 (1H, dd, J 15.5, 10.7, H-3); m/z (EI) 166 (M^+), 137, 121 and 93.

Preparation of (2*E*, 4*E*, 6*E*) 2,4,6-Octatrienal (46). DIBAL (27.5ml, 1.5M solution in toluene, 41.3mmol) was added dropwise to a stirred solution of the trieneester (prepared above) (2.28g, 13.7mmol) in toluene (100ml) at -78°C The solution was stirred at -78°C for 15min. Water (15ml) was added carefully and the mixture allowed to warm to room temperature, whereupon it formed a gelatinous mixture. This was poured into a stirred suspension of $NaHCO_3$ (50g) and $MgSO_4$ (50g) in ethyl acetate (500ml). The suspension was filtered off under suction and the filtrate evaporated *in vacuo* to give the allylic alcohol (1.685g, quantitative) as a colourless

solid. This solid was taken up in DCM (500ml) and MnO_2 (14.9g, 171mmol) was added. After stirring vigorously for 90min, the solid was filtered off (washing with copious quantities of ethyl acetate) and the filtrate evaporated *in vacuo* to give the aldehyde (46) (1.56g, 93% from the ester) as a pale yellow waxy solid; υ_{max} (film) 3021, 2816, 1672, 1604, 1163, 1116, 1018 and 995 cm^{-1}; ^1H δ (250MHz, $CDCl_3$) 2.11 (3H, d, J 5.3, H-8), 6.10-7.20 (5H, m, H-2, H-4, H-5, H-6 and H-7), 7.40 (1H, dd, J 15.1, 10.5, H-3) and 9.80 (1H, d, J 7.9, H-1).

Larger scale procedure for preparation of (46): A mixture of the allylic alcohol (13.1g, 119mmol, prepared as above), NMO (16.7g, 143mmol, 1.2equiv) and powdered 4Å molecular sieves (5g) in acetonitrile (250ml) was stirred at room temperature for 10min whereupon TPAP (837mg, 2.38mmol, 2mol%) was added in one portion. The reaction became warm and was then stirred at room temperature for 16hr. Further sieves (1g), NMO (2.8g, 0.2equiv) and TPAP (418mg, 1mol%) were added and stirring continued for 12hr whereupon a final quantity of TPAP (418mg, 1mol%) was added. After 16hr (44hr in total), the mixture was filtered through celite, the solvent evaporated *in vacuo* and the residue purified by flash chromatography (15% ethyl acetate/petrol) to give the aldehyde (46) (10.22g, 70% from ester) identical to that obtained previously.

Preparation of Ethyl (2*E*, 4*E*, 6*E*, 8*E*) 2,4,6,8-Decatetraenoate. The triene aldehyde (46) (1.54g, 12.6mmol) was reacted with triethylphosphonoacetate (3.15g, 14.1mmol) and sodium hydride (562mg of a 60% oil dispersion,14.1mmol) in THF (50ml) in an analogous procedure to that used previously. The residue was recrystallised from ether at -78°C to give the geometrically pure tetraene ester (1.67g, 69%) as fine colourless needles which started to turn pale yellow rapidly if left open to light and air; υ_{max} (film) 2989, 1699, 1618, 1596, 1303, 1248, 1155 and 1006 cm^{-1}; ^1H δ (500MHz, $CDCl_3$) 1.29 (3H, t, J 7.2, $CH_2\underline{CH_3}$), 1.81 (3H, d, J 6.8, H-10), 4.20 (2H, q, J 7.2, $\underline{CH_2}CH_3$), 5.84 (1H, d, J 15.3, H-2), 5.85 (1H, dq, J 15.0, 6.8, H-9), 6.14 (1H, dd, J 15.0, 10.8, H-8), 6.18 (1H, dd, J 14.9, 11.0, H-6), 6.28 (1H, dd, J 14.8, 11.5, H-4), 6.37 (1H, dd, J 14.9, 10.8, H-7), 6.56 (1H, dd, J 14.8, 11.0, H-5) and 7.31 (1H, dd, J 15.3, 11.5, H-3); m/z (EI) 192 (M^+), 163, 147, 119 and 91.

Preparation of (2*E*, 4*E*, 6*E*, 8*E*) 2,4,6,8-Decatetraenal (47).[42] DIBAL (17.4ml, 1.5M solution in toluene, 26.09mmol) was used to reduce the tetraene ester (1.67g, 8.70mmol) to the allylic alcohol in toluene (150ml) in an analogous procedure to that used previously. The colourless solid allylic alcohol was taken up in DCM (200ml) and barium manganate (17.4g, 68.1mmol) was added. After 3hr, the solid was filtered off under suction (washing with copious quantities of ethyl acetate) and the filtrate was evaporated *in vacuo*. Purification of the residue by flash chromatography (preadsorbtion on silica, 2% ether/petrol) gave the tetraene aldehyde (47) (906mg, 70% from the ester) as an unstable pale yellow solid which was used rapidly in the next step; υ_{max} (film) 1668, 1588, 1017 cm^{-1}; ^1H δ (500MHz, $CDCl_3$) 2.09 (3H, d, J 5.9, H-10), 6.0-7.25 (7H, m, H-2, H-4 to H-9 inclusive), 7.40 (1H, dd, J 15.1, 10.5, H-3) and 9.81 (1H, d, J 7.9, H-1).

Larger scale procedure for preparation of (47): A mixture of the allylic alcohol (8.40g, 51.9mmol, prepared as above), NMO (7.30g, 62.3mmol, 1.2equiv) and powdered 4Å molecular sieves (3g) in acetonitrile (400ml) was stirred at room temperature for 10min whereupon TPAP (182mg, 51.9μmol, 1mol%) was added in one portion. The reaction became warm and was then stirred at room temperature for 10min. Further NMO (1.52g, 0.25equiv) and TPAP (418mg, 1mol%) were added and stirring continued for 80min. The mixture was then filtered through celite, the solvent evaporated *in vacuo* and the residue purified by flash chromatography (gradient elution, 10-15% ethyl acetate/petrol) to give the aldehyde (47) (5.80g, 75% from ester) identical to that obtained previously.

Preparation of ^{t}Butyl (4*E*, 6*E*, 8*E*, 10*E*, 12*E*) 3-oxo-4,6,8,10,12-tetradecapentaenethioate (48). ^{t}Butyl 4-diethylphosphono-3-oxobutanthioate (3.71g, 12.0mmol) was added to a stirred suspension of sodium hydride (0.961g of a 60% oil dispersion, washed with petrol) in THF (350ml) at 0°C. The suspension was stirred for 30min whereupon the aldehyde (47) (900mg, 6.07mmol) in THF (30ml) was added *via* cannula. The reaction was allowed to warm to room temperature and stirred overnight. The dark brown mixture was then poured into sat. NH_4Cl (aq) (350ml), the organic phase was separated and the aqueous re-extracted with ether (3x200ml). The combined organic phases were washed with water (100ml), brine (200ml), dried ($MgSO_4$), evaporated *in vacuo* and the residue purified by flash chromatography (2% ether/petrol) to give the pentaeneketothioester (48) (1.38g, 75%) as a golden orange waxy solid; υ_{max} (film) 2966, 1617, 1582, 1410, 1360, 1307, 1256, 1218, 1179, 1068, 1003, 948, 858, 826 and 763 cm^{-1}; ^1H δ (500MHz, $CDCl_3$) (85% enol form) 1.50 (1.35H, s, ^{t}Bu, keto form), 1.55 (7.65H, s, ^{t}Bu enol form), 1.80 (3H, d, J 5.9, H-14), 3.70 (0.3H, s, 2xH-2 keto form), 5.40 (0.85H, H-2 enol form), 5.60-6.50 (9H, m, H-4, H-6 to H-13 inclusive), 7.17 (1H, dd, J 14.8, 10.8, H-5) and 12.56 (0.85, d, J 1.3, enol OH); m/z 304 (M^+), 248, 111, 90 and 57; Found (M^+) 304.1496. $C_{18}H_{24}O_2S$ requires 304.1497.

Preparation of (2*R*) N-Methyl-N-[(4*E*, 6*E*, 8*E*, 10*E*, 12*E*) 3-oxo-4,6,8,10,12-tetradecapentaenoyl]-glutamic acid α-methyl ester γ-^{t}butyl ester (49). A mixture of the glutamic acid derivative (44) (3.20g, 13.8mmol), Na_2HPO_4 (5.0g) and 4Å powdered sieves (5.0g) in THF (60ml) was stirred at room temperature for 10mins whereupon the pentaeneketothioester (48) (2.78g, 9.13mmol) was added in THF (30ml) *via* cannula. Silver (I) trifluoroacetate (3.05g, 13.8mmol) was added in one portion and the mixture stirred at room temperature in the dark for 30min. The solid was filtered off over celite, washing with ether. Evaporation of the solvent *in vacuo* and purification of the residue by flash chromatography (gradient elution, 40-60% ether/petrol) gave the ketoamide (49) (2.74g, 67%) as a bright yellow solid, m.pt. 130-135°; $[\alpha]_D^{25}$ +64.1 (c=0.32, $CHCl_3$); υ_{max} (film) 3610, 2926, 1725, 1677, 1620, 1583, 1153 and 1005cm^{-1}; ^1H δ (500MHz, $CDCl_3$) (95% enol form, ~5:1 rotamer mixture, assignment for major enol rotamer) 1.43 (9H, s, ^{t}Bu), 1.80 (3H, d, J 6.5, 3xH-14'), 1.95-2.03 (1H, m, H-3), 2.18-2.34 (3H, m, H-3 and 2xH-4), 2.92 (3H, s, NMe), 3.72 (3H, s, CO_2Me), 5.20 (1H, dd, J 10.4, 4.9, H-1), 5.21 (1H, s, H-2'), 5.81 (1H, dq, J 14.8, 6.8, H-13'), 5.90 (1H, d, J 15.0, H-4'), 6.09-6.19 (2H, m, H-10' and H-12'), 6.24-6.39 (3H, m, H-8', H-9' and H-11'), 6.51 (1H, dd, J 14.7, 10.9, H-7') and 7.11 (1H, dd, J 15.0, 11.6, H-5'); m/z (EI), 445 (M^+), 389 (MH^+-^{t}Bu), 357, 244, 215, 186, 172, 158 and 116; Found (M^+) 445.2466. $C_{25}H_{35}NO_6$ requires 445.2464.

Preparation of Fuligorubin A ^{t}butyl ester (50). KO^{t}Bu (1.01g, 8.98mmol) was added portionwise over 10min to a stirred mixture of the ketoamide (49) (2.00g, 4.49mmol) in ^{t}BuOH (60ml) at room temperature. Residual solid dissolved and the colour darkened from yellow to orange/brown as the mixture was stirred for a further 1hr at room temperature. Water (30ml) and sat. aqueous citric acid (2ml) were added, resulting in an immediate vivid red precipitate. This was extracted with ether (4x100ml) and the combined extracts were washed with water (3x50ml), dried (Na_2SO_4) and evaporated *in vacuo*. Trituration of the resulting solid with ether gave the tetramic acid (50) (1.40g, 75%) as an orange/red amorphous powder (7:1 tautomeric mixture); υ_{max} (film) 2977, 2930, 1726, 1685, 1616, 1577, 1559, 1442, 1405, 1367, 1147 and 1005cm^{-1}; ^1H δ (500MHz, $CDCl_3$) (major tautomer) 1.41 (9H, s, tBu), 1.80 (3H, d, J 6.8, 3xH-20), 1.99-2.05 (1H, m, H-6), 2.13-2.25 (3H, m, H-6 and 2xH-7), 2.97 (3H, s, NMe), 3.72-3.73 (1H, m, H-5), 5.83 (1H, dq, J 14.0, 7.1, H-19), 6.11-6.16 (1H, m, H-18), 6.19 (1H, dd, J 14.8, 11.0, H-16), 6.32 (1H, dd, J 14.6, 11.1, H-14), 6.34 (1H, dd, J 14.8, 10.5, H-17), 6.44 (1H, dd, J 14.6, 11.8, H-12), 6.47 (1H, dd, J 14.6, 11.1, H-15), 6.69 (1H, dd, J 14.5,

11.2, H-13), 7.13 (1H, d, J 15.1, H-10) and 7.50 (1H, dd, J 15.0, 8.4, H-11); ^{13}C δ ($CDCl_3$) (major tautomer) 18.5 (C20), 23.6 (C6), 26.6 (NMe), 28.0 (OC<u>Me</u>$_3$), 29.0 (C7), 65.3 (C5), 80.7 (O<u>C</u>Me$_3$), 100.1 (C3), 120.5, 130.0, 130.5, 131.3, 131.8, 132.9, 136.9, 139.1, 143.5, 144.6 (polyene carbons), 171.8 (C8), 172.8, 173.6 (C2 and C9) and 193.7 (C4); ^{13}C δ ($CDCl_3$) (minor tautomer) 18.5 (C20), 23.7 (C6), 26.8 (NMe), 28.0 (OC<u>Me</u>$_3$), 29.0 (C7), 63.1 (C5), 80.7 (O<u>C</u>Me$_3$), 103.7 (C3), 119.7, 130.0, 130.8, 131.3, 131.8, 133.0, 137.1, 139.5, 143.7, 145.5 (polyene carbons), 171.8 (C8), 172.8, 173.6 (C2 and C9) and 193.7 (C4); m/z (EI) 413 (M^+), 357 (MH^+-^{t}Bu), 340, 310, 212, 194, 131, 98 and 57; Found (M^+) 413.2202. $C_{24}H_{31}NO_5$ requires 413.2202; Found C 67.73; H 7.36; N 3.24. $C_{24}H_{31}NO_5.1/2H_2O$ requires C 68.22; H 7.63; N 3.32%.

Preparation of 9-O-Methylfuligorubin A ^{t}butyl ester (52). A solution of diazomethane in DCM was added dropwise to a solution of the tetramic acid (50) (46.1mg, 0.112mmol) in DCM at 0°C until tlc showed disappearance of starting material. The solution was evaporated *in vacuo* and the residue purified by flash cromatography (gradient elution, 60-80% ether/petrol) to give the methylated tetramic acid (52) (28.1mg, 59%) as a bright red gum (a co-running 2:1 mixture of C3-C9 double bond isomers); υ_{max} (film) 2929, 1723, 1661, 1595, 1548, 1518, 1440, 1387, 1151, 1053 and 1006cm^{-1}; ^1H δ (500MHz, $CDCl_3$) (major isomer) 1.41 (9H, s, ^{t}Bu), 1.81 (3H, d, J 6.9, 3xH-20), 1.99-2.06 (1H, m, H-6), 2.15-2.22 (3H, m, H-6 and 2xH-7), 2.98 (3H, s, NMe), 3.69-3.72 (1H, m, H-5), 4.14 (3H, s, OMe), 5.83 (1H, dq, J 7.3, 14.9, H-19), 6.14 (1H, ddd, J 14.8, 10.8, 1.6, H-18), 6.18-6.22 (1H, dd, J 14.9, 11.1, H-16), 6.30-6.36 (2H, m, H-14 and H-17), 6.43-6.52 (2H, m, H-12 and H-15), 6.67 (1H, dd, J 14.5, 11.1, H-13), 7.38 (1H, dd, J 14.8, 11.2, H-11) and 7.56 (1H, d, J 14.9, H-10); ^1H δ (500MHz, $CDCl_3$) (minor isomer) as for major isomer, except 2.95 (3H, s, NMe), 4.25 (3H, s, OMe), 6.68 (1H, dd, J 14.6, 11.2, H-13), 7.35 (1H, d, J 14.7, H-10) and 7.40 (1H, dd, J 14.8, 10.5, H-11); ^{13}C δ ($CDCl_3$) (major isomer) 18.5 (C20), 27.3 (NMe), 24.1 (C6), 28.0 (OC<u>Me</u>$_3$), 29.2 (C7), 63.7 (C5), 64.4 (OMe), 80.6 (O<u>C</u>Me$_3$), 106.2 (C3), 124.1, 130.1, 131.2, 131.6, 131.8, 132.7, 136.6, 138.7, 142.5, 144.7 (polyene carbons), 168.6, 171.9, 173.3 (C2, C8 and C9) and 194.0 (C4); ^{13}C δ ($CDCl_3$) (minor isomer) 18.5 (C20), 24.4 (C6), 27.4 (NMe), 28.0 (OC<u>Me</u>$_3$), 29.2 (C7), 64.8 (OMe), 65.0 (C5), 80.6 (O<u>C</u>Me$_3$), 106.3 (C3), 124.5, 130.1, 131.6, 131.6, 131.8, 132.8, 136.8, 138.8, 142.9, 145.0 (polyene carbons), 166.9, 171.9, 174.2 (C2, C8 and C9) and 197.5 (C4); m/z (ACE, CI, NH_3) 428 (MH^+), 427 (M^+), 372, 298, 242, 228, 186 and 132; Found (MH^+) 428.2437. $C_{25}H_{34}NO_5$ requires 428.2437.

Preparation of 9-O-Acetylfuligorubin A ^{t}butyl ester (53) and (54). Acetic anhydride (175μl, 1.86mmol) was added *via* syringe to a stirred solution of the tetramic acid (50) (77.0mg, 0.186mmol) in pyridine (5ml) at 0°C. After stirring at 0°C for 1hr, the solution was allowed to warm to room temperature and stirred for a further 2hr. Ether (30ml) was added and the mixture was washed with sat. $CuSO_4$ (aq) (3x30ml), water (2x20ml), dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Purification of the residue by flash chromatography (gradient elution, 50-80% ether/petrol) gave in order of elution the major C9-acetate (30.6mg, 36%) as an unstable red/purple gum; υ_{max} (film) 2938, 1775, 1736, 1698, 1671, 1654, 1637, 1597, 1563, 1540, 1457, 1396, 1150 and 1008cm^{-1}; ^1H δ (500MHz, $CDCl_3$) 1.41 (9H, s, ^{t}Bu), 1.81 (3H, d, J 6.9, 3xH-20), 1.97-2.02 (1H, m, H-6), 2.13-2.20 (3H, m, H-6 and 2xH-7), 2.40 (3H, s, OAc), 3.00 (3H, s, NMe), 3.71-3.72 (1H, m, H-5), 5.86 (1H, dq, J 14.8, 7.1, H-19), 6.12-6.17 (1H, m, H-18), 6.20 (1H, dd, J 14.8, 11.2, H-16), 6.29-6.39 (2H, m, H-14 and H-17), 6.48 (1H, dd, J 14.4, 11.1, H-15), 6.52 (1H, dd, J 14.5, 11.5, H-12), 6.69 (1H, dd, J 14.5, 11.3, H-13), 7.18 (1H, dd, J 14.9, 11.5, H-11) and 7.79 (1H, d, J 14.9, H-10); m/z (EI) 455 (MH^+), 413 (MH^+-OAc), 357, 340, 279, 211, 194 and 98; Found (M^+) 455.2308. $C_{26}H_{33}NO_6$ requires 455.2308; and the minor C9-acetate (20.2mg, 24%) as an unstable red/purple gum; υ_{max}

(film) 2976, 1774, 1729, 1702, 1680, 1633, 1597, 1580, 1541, 1391, 1156 and 1009cm^{-1}; ^{1}H δ ($CDCl_3$) 1.41 (9H, s, ^{t}Bu), 1.82 (3H, d, J 6.9, 3xH-20), 1.98-2.03 (1H, m, H-6), 2.18-2.24 (3H, m, H-6 and 2xH-7), 2.42 (3H, s, OMe), 2.96 (3H, s, NMe), 3.75-3.77 (1H, m, H-5), 5.85 (1H, dq, J 14.9, 7.1, H-19), 6.15 (1H, ddd, J 14.6, 10.7, 1.4, H-18), 6.21 (1H, dd, J 14.8, 11.1, H-16), 6.34 (1H, dd, J 14.4, 11.0, H-14), 6.37 (1H, dd, J 14.7, 11.3, H-17), 6.49 (2H, dd, J 14.5, 11.6, H-12 and H-15), 6.71 (1H, dd, J 14.5, 11.2, H-13), 7.22 (1H, dd, J 14.8, 11.6, H-11) and 7.57 (1H, d, J 14.9, H-10); m/z (EI) 455 (MH^+), 413 (MH^+-OAc), 357, 340, 279, 211, 194 and 98; Found (M^+) 455.2308. $C_{26}H_{33}NO_6$ requires 455.2308.

Preparation of Fuligorubin A (40). A solution of fuligorubin A ^{t}butyl ester (50) (1.40g, 3.39mmol) in 98% formic acid (50ml) was stirred at room temperature for 80min. The solvent was evaporated *in vacuo* and the residue azeotroped with dry toluene (3x50ml) to give fuligorubin A (1.25g, quantitative) as an analytically pure brick red powder; m.pt. >230°C (dec) [lit. 150°C (dec) for dihydrate[40]]; υ_{max} (KBr disc) 3500-2500 (br), 2924, 1704, 1613, 1445, 1405, 1259, 1009, 940 and 822cm^{-1}; ^{1}H δ (500MHz, D_6 acetone)[48] 1.76 (3H, d, J 6.8, H-20), 2.14-2.23 (2H, m, 2xH-6), 2.23-2.34 (2H, m, 2xH-7), 2.97 (3H, s, NMe), 5.60 (1H, br s, H-5), 5.85 (1H, dq, J 14.9, 6.9, H-19), 6.18 (1H, ddd, J 14.8, 10.7, 1.6, H-18), 6.29 (1H, dd, J 14.9, 11.0, H-16), 6.42 (1H, dd, J 14.8, 11.2, H-14), 6.46 (1H, dd, J 14.7, 11.6, H-12), 6.59 (1H, dd, J 14.8, 10.9, H-15), 6.89 (1H, dd, J 14.6, 11.3, H-13), 7.12 (1H, br d, J 14.8, H-10) and 7.50 (1H, dd, J 15.0, 11.7, H-11); ^{13}C δ (D_6 acetone) 18.5 (C20), 24.5 (C6), 26.8 (NMe), 28.3 (C7), 66.1 (C5), 101.0 (C3), 121.1, 131.2, 131.5, 132.5, 132.9, 133.2, 137.7, 140.0, 144.4, 144.8 (polyene carbons), 172.4 (C8), 173.8 (C9), 174.2 (C2) and 194.5 (C4); m/z (EI) 357 (M^+), 309, 284, 264, 190 and 136; Found (M^+) 357.1577. $C_{20}H_{23}NO_5$ requires 357.1576; Found C 65.56; H 6.31; N 3.63. $C_{20}H_{25}NO_5$. $1/2H_2O$ requires C 65.56; H 6.60; 3.82%. Data identical to that reported for the natural product.[40]

Preparation of 10,11,12,13,14,15,16,17,18,19-decahydrofuligorubin A (51). A solution of fuligorubin A (215mg, 0.602mmol) in methanol (30ml) containing 50mg of 10% Pd/C catalyst was hydrogenated at atmospheric pressure and room temperature for 16hr. The catalyst was filtered off over celite and the solvent evaporated to give the decahydro derivative (51) (201mg, 91%) as an orange oil; $[\alpha]_D^{25}$ +18 (c=0.39, MeOH) [lit +14 (c=0.05, MeOH)]; υ_{max} (film) 3500-2500 (br), 2923, 2851, 1706, 1610, 1459 and 1256cm^{-1}; ^{1}H δ (250MHz, $CDCl_3$) 0.89 (3H, br s, 3xH-20), 1.30 (18H, m, H-11 to H-19), 2.08 (1H, m, H-6), 2.21 (3H, m, 2xH-7 and H-6), 2.82 (2H, m, H-10), 2.94 (3H, s, NMe) and 3.82 (1H, m, H-5); ^{13}C δ ($CDCl_3$) 14.5 (C20), 24.8 (C6), 26.9 (NMe), 28.8 (C7), 23.7, 27.1, 30.3, 30.4, 30.4, 30.5, 30.6, 30.7, 33.0, 34.7 (C10-C19), 66.0 (C5), 103.2 (C3), 123.6, 126.2, 126.5 (C2, C8 and C9) and 196.7 (C4); m/z (ACE, NH_3, CI) 367 (M^+), 349 (M^+-H_2O), 322 (M^+-CO_2H), 308, 240, 227, 209, 181, 116 and 98; Found (M^+) 367.2359. $C_{20}H_{33}NO_5$ requires 367.2359; Found C 62.11; H 8.94; N 3.40. $C_{20}H_{33}NO_5.H_2O$ requires C 62.31; H 9.15; N 3.63%. Data identical to reported literature data.[40]

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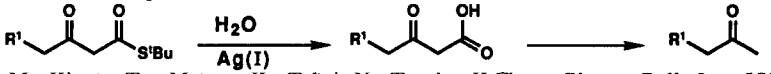

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