SYNTHETIC APPLICATIONS

OF

β-KETOTHIOESTERS

A thesis presented by

PETER ROY WOODWARD

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WHIFFEN LABORATORY

DEPARTMENT OF CHEMISTRY

IMPERIAL COLLEGE

LONDON SW7 2AY.

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ABSTRACT

This thesis is divided into two sections. The first section deals with the structures and biological activities of natural products containing the 3-acyltetramic acid unit and goes on to describe and compare the two most widely employed methods for the construction of this unit. These are the 3-acylation of pyrrolidin-2,4-diones and the Dieckmann reaction of N-acylacetyl-α-aminoesters.

The second section is divided into two parts, A and B. In Part A work on the preparation and reactions of ^{t}butyl diethylphosphono-3-oxo-butanthioate and its use in macrolide and diolide synthesis is described.

Part B starts with a review of the various methods of β-ketoamide preparation and continues with a new method developed for their synthesis using β-ketothioesters.

Studies on the fate of stereochemistry at the 5-position of 3-acyltetramic acids during the Dieckmann reaction are reported along with MNDO calculations on the stabilities of the various tautomers of 3-acetyltetramic acid. Part B ends with a description of the application of this new methodology to the syntheses of fuligorubin A and β-lipomycin.

ACKNOWLEDGEMENTS

I would like to thank Professor Steve Ley for his enthusiastic support, expert advice and friendship throughout the course of this work. Thanks also go to my colleagues - both past and present - of the Whiffen and Perkin Labs for providing such a stimulating working environment. In particular I would like to thank Dr. Howard Boughton for numerous helpful discussions and carrying out MNDO calculations and also Dr. Pete Grice for advice and help in using equipment. I am also indebted to Phil, Don, Graham, Subha, and Pete for taking time out from their own research to run NMR spectra. I would also like to acknowledge the contribution that Mike Shipman and Steve Smith have made to this work.

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ABBREVIATIONS

aq	aqueous
Bz	benzyl
BuLi	n-butyl lithium
DCC	dicyclohexylcarbodiimide
deg. C	degrees Celsius
DIBAL	diisobutylaluminium hydride
DMAP	N,N-dimethyl-4-aminopyridine
DMB	2,4-dimethoxybenzyl
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMS	dimethylsulphide
DMSO	dimethylsulphoxide
EEDQ	N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
Et_3N	triethylamine
HOAc	acetic acid
HOBT	1-hydroxybenzo-1,2,3-triazole
HPLC	high performance liquid chromatography
IPA	isopropyl alcohol
KO^tBu	potassium tert-butoxide
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
M	mol dm^{-3}
Meldrum's acid	2,2-dimethyl-1,3-dioxane-4,6-dione
MNDO	minimal neglected differential overlap

NBS	N-bromosuccinimide
NaOMe	sodium methoxide
nOe	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PhH	benzene
PhMe	toluene
PTSA	para-toluenesulphonic acid
Pyr	pyridine
$PyrH^+$	pyridinium
RT	room temperature
sat.	saturated
SEM	(2-trimethylsilylethoxy)methyl
TBAF	tetra-n-butylammonium fluoride
TBDMS	^{t}butyldimethylsilyl
TBDPS	^{t}butyldiphenylsilyl
Tf	trifluoromethanesulphonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
Tos^-	tosylate
Z	benzyloxycarbonyl

TAUTOMERISM

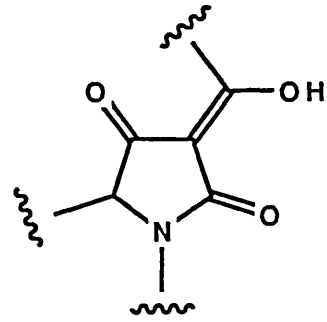
While it is acknowledged that β-ketoesters, β-ketothioesters, β-ketoamides, and 3-acyltetramic acids can exist as a mixture of tautomers, for the sake of simplicity, only one tautomer is shown. In the experimental section the compound is named as the tautomer shown.

INTRODUCTION

3-Acyltetramic Acids

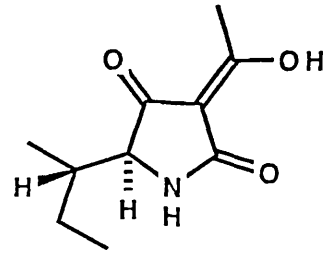
The aim of this review is to outline the structure and biological activities of selected 3-acyltetramic acid natural products, and to describe the development and discuss the methods most widely used for their construction.

INTRODUCTION



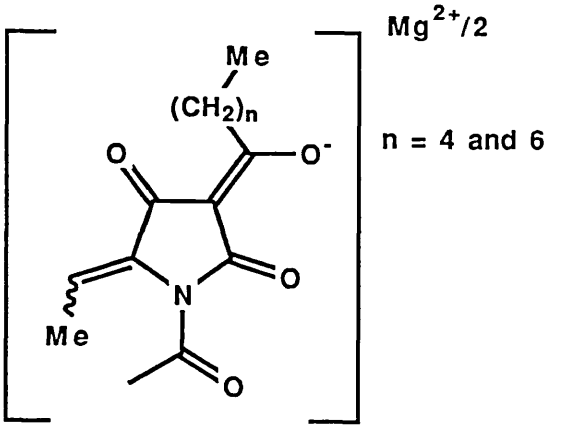
(1)

The 3-acyltetramic acid unit (1) is found in a range of natural products[1], many of which possess significant levels of biological activity. The simplest of these natural products, tenuazonic acid (2)[2/3] isolated from Alternaria tenuis Auct., shows antitumour[4] and antiviral activity[5].



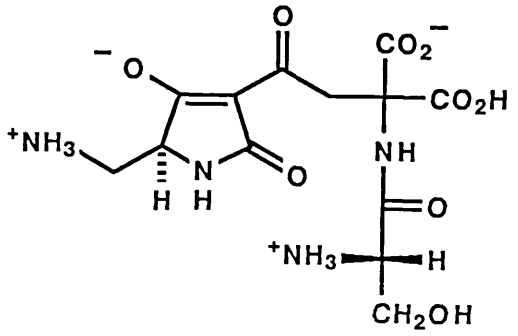
TENUAZONIC ACID (2)

Magnesidin (3)[6], a 1:1 mixture of the magnesium salts of two 3-acyl tetramic acids shows Gram positive antibiotic activity.



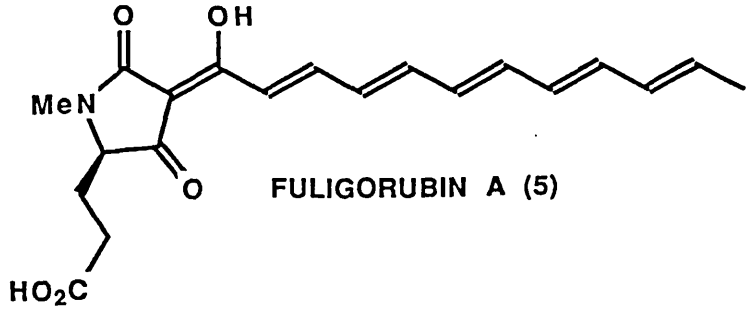
MAGNESIDIN (3)

Malonomicin (K-16) (4)[7] shows antibiotic activity.

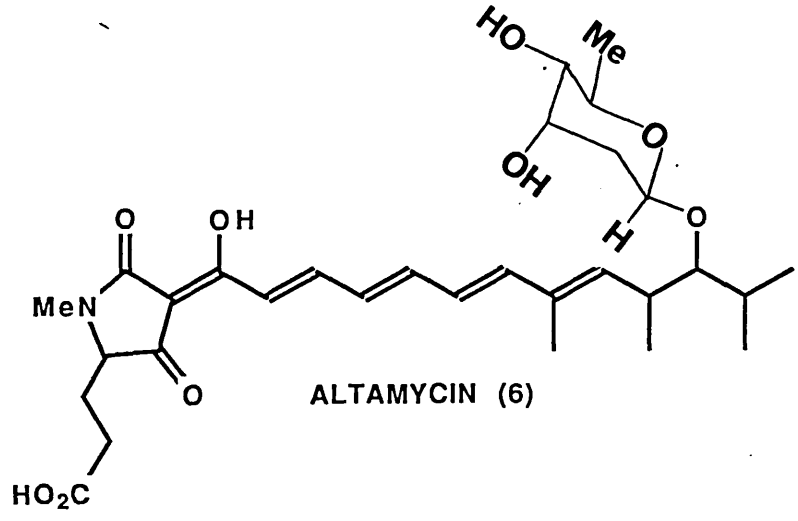


MALONOMICIN (K16) (4)

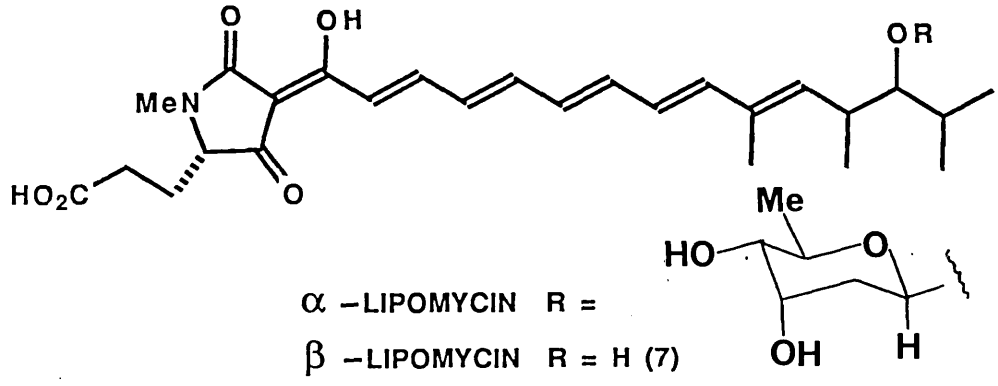
Some 3-acyltetramic acids such as fuligorubin A (5)[8], altamycin (6)[9], the lipomycins (7)[10], oleficin (8)[11] and erythroskyrine (9)[158] contain polyene chains conjugated to the 3-acyl group.



FULIGORUBIN A (5)

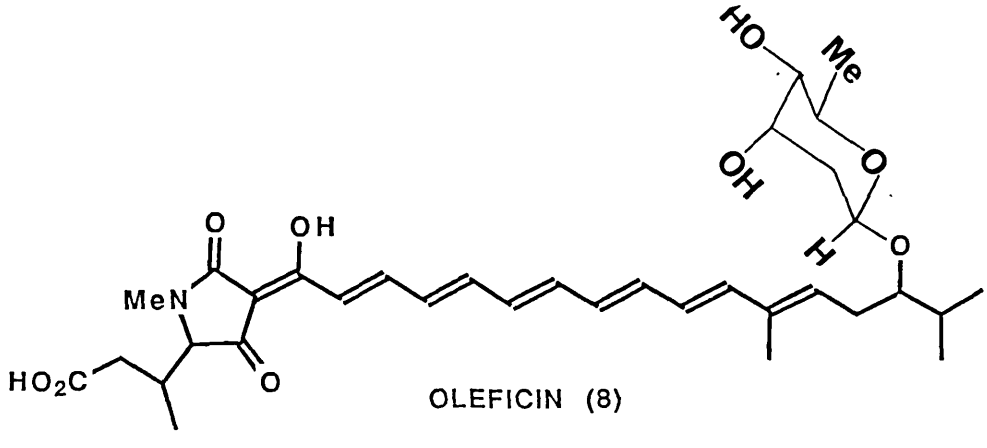


ALTAMYCIN (6)

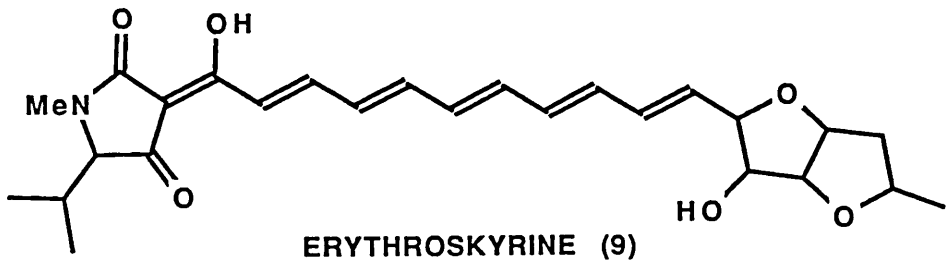


α –LIPOMYCIN R =

β –LIPOMYCIN R = H (7)

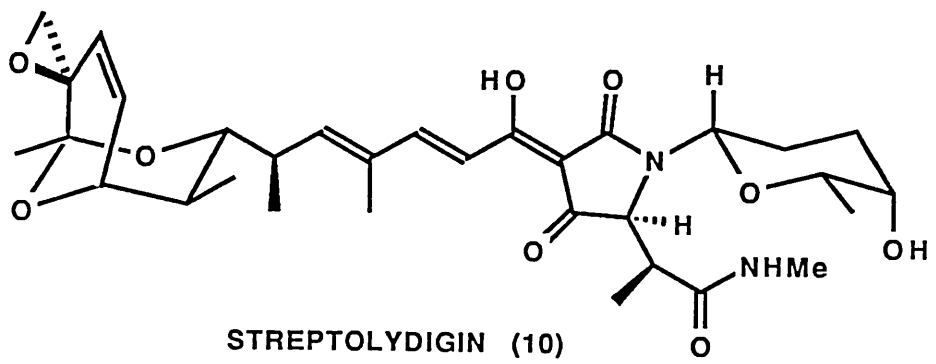


OLEFICIN (8)

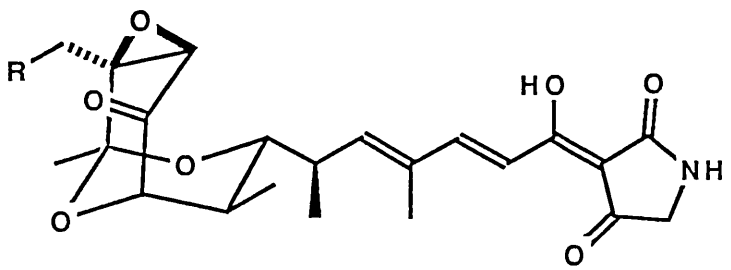


ERYTHROSKYRINE (9)

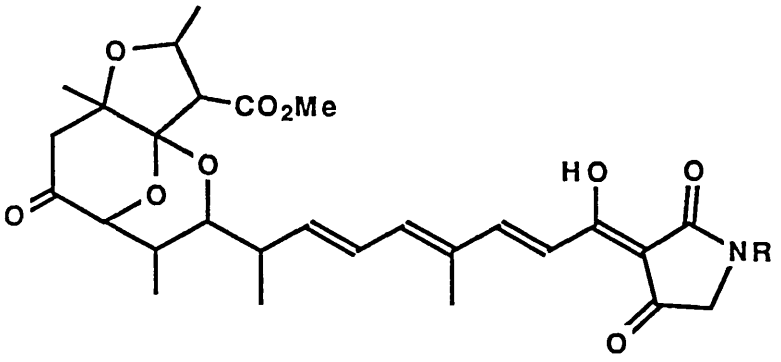
Of these structurally related compounds α-lipomycin (7) and oleficin (8) both show antimicrobial activity.



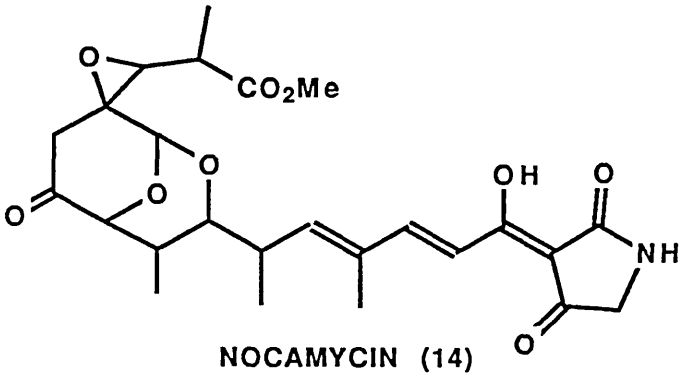
STREPTOLYDIGIN (10)



R = H TIRANDAMYCIN A (11)
R = OH TIRANDAMYCIN B



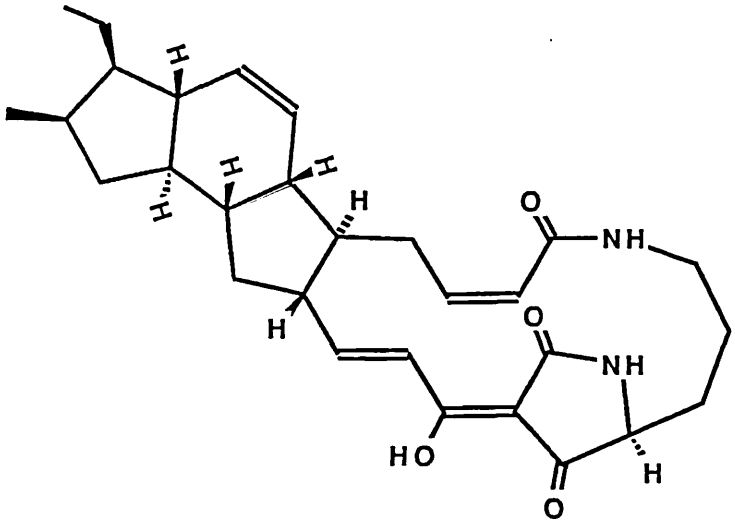
R = Me Bu- 2313A (12)
R = H Bu- 2313B (13)



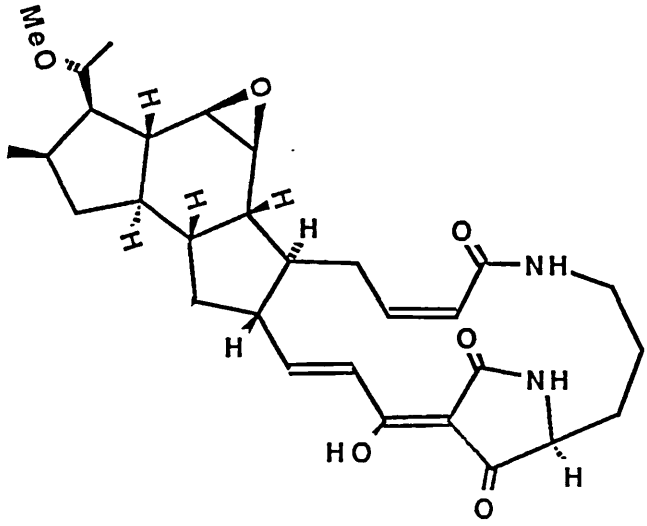
NOCAMYCIN (14)

Streptolydigin (10)[12], tirandamycin A (11)[13], and tirandamycin B[14] show antimicrobial activity and inhibition of bacterial DNA-directed RNA polymerase. Streptolydigin also shows selective inhibition of terminal deoxynucleotidyl transferase from leukaemic cells. Bu-2313A and Bu-2313B[15] (12 and 13 respectively) show antibiotic activity against anaerobes and also show Gram positive antibacterial activity.

Nocamycin (14)[16] is reported to exhibit antitumour and antibiotic activity.



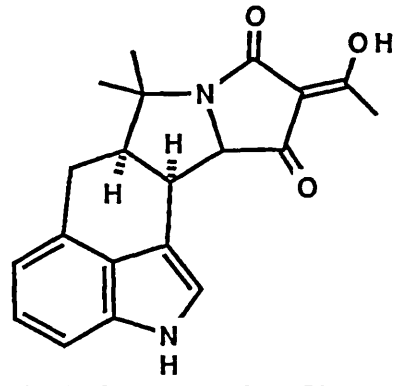
IKARUGAMYCIN (15)



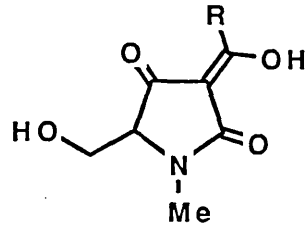
CAPSIMYCIN (16)

Ikarugamycin (15)[17] exhibits antiprotozoal and antibiotic activity. The structurally related capsimycin (16)[18] has also been reported.

Cyclopiazonic acid (17), an indole-containing 3-acetyltetramic acid has been isolated as the toxic principle from a strain of Penicillium cyclopium Westling[19/20].



CYCLOPIAZONIC ACID (17)



EQUISETIN R = $C_{15}H_{23}$

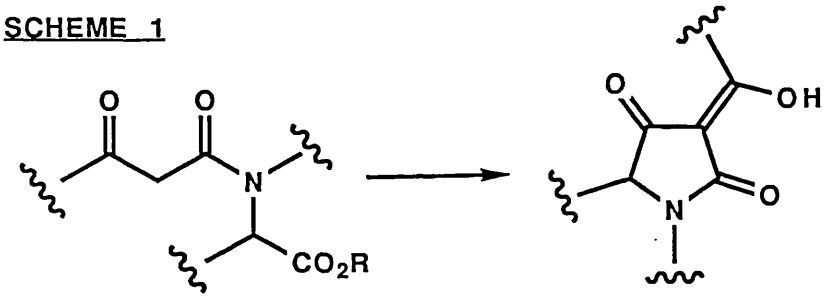
Equisetin, isolated from Fusarium equiseti NRL5537, shows Gram positive antibiotic activity and is more active in vitro than streptomycin and isoniazid against some bacteria[21]. No definite structure is known for this compound. R is a $C_{15}H_{23}$ side chain containing four methyl groups, two double bonds, and two ring formations.

The varied biological activities coupled with the challenging structural features of these compounds has resulted in a great deal of synthetic effort being directed towards not only their total synthesis but also towards the development of methodology for the construction of the 3-acyltetramic acid unit. As a result several ways are now available for introducing the preformed unit or for the in situ construction of the 3-acyltetramic acid.

CONSTRUCTION

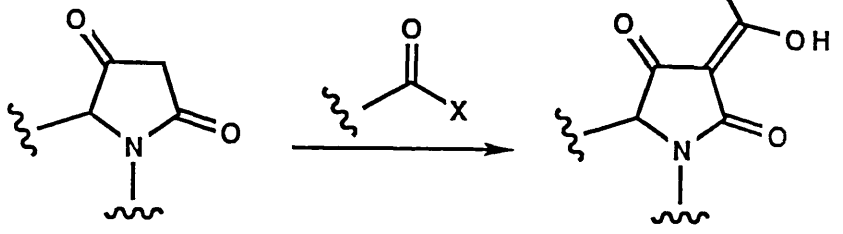
The two most widely used methods of 3-acyltetramic acid synthesis are the Dieckmann reaction of N-acylaceto-α-aminoesters (Scheme 1) and 3-acylation of pyrrolidine-2,4-diones (Scheme 2).

SCHEME 1



R = Alkyl

SCHEME 2



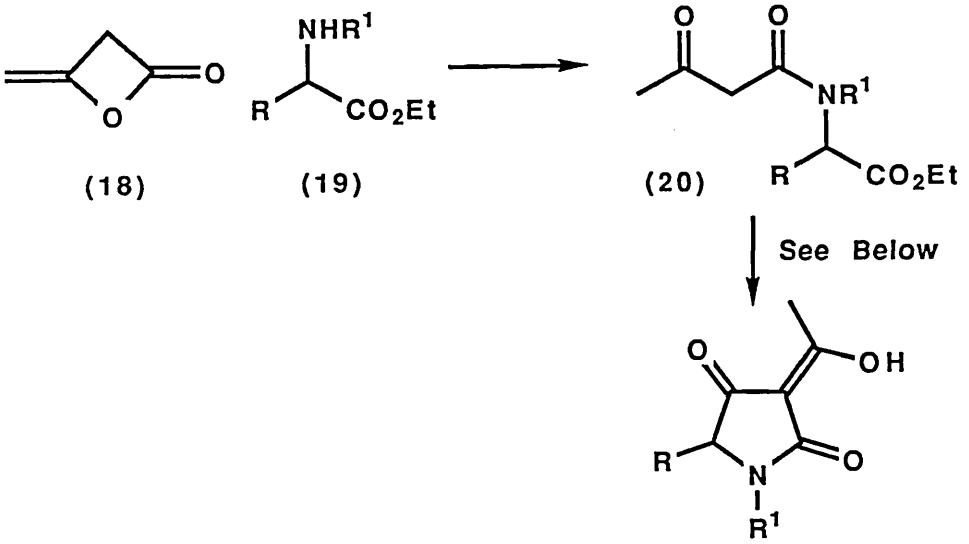
X = Cl , F , OBT

These two approaches are discussed below.

Dieckmann Reaction

Lacey[22] first described the alkoxide mediated Dieckmann reaction to prepare the 3-acetyltetramic acids (21) to (23) in good overall yields from diketene (18) (Scheme 3).

SCHEME 3



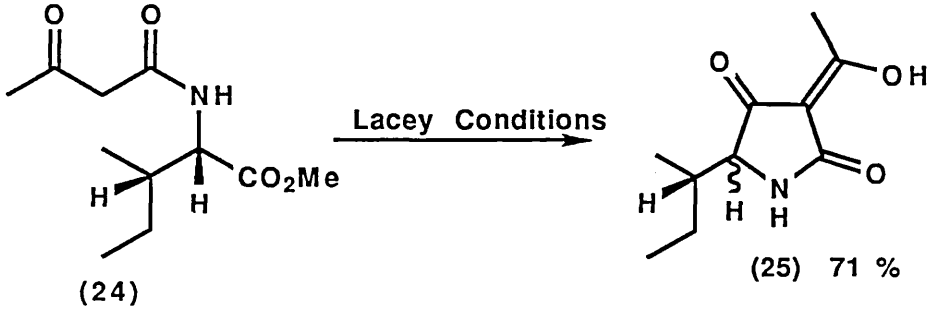
(18) (19) (20)

(21) , (22) , and (23)

	R	R'	CONDITIONS	YIELD/%
(21)	H	Me	NaOMe/MeOH/PhH/3h reflux/stood overnight	66
(22)	Me	H	NaOH/EtOH/PhH/as above	46
(23)	H	Ph	NaOH/EtOH/PhH/5h reflux/stood overnight	85

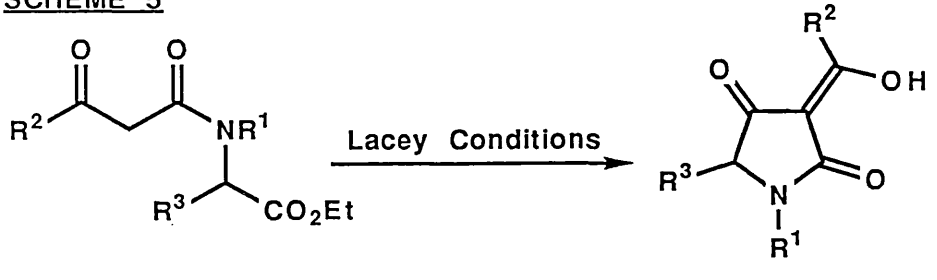
The base mediated Dieckmann reaction has seen wide application for the construction of the 3-acyltetramic acid unit as the following selected examples show (Schemes 4 to 11).

SCHEME 4 [23]



(24) (25) 71 %

SCHEME 5 [24]



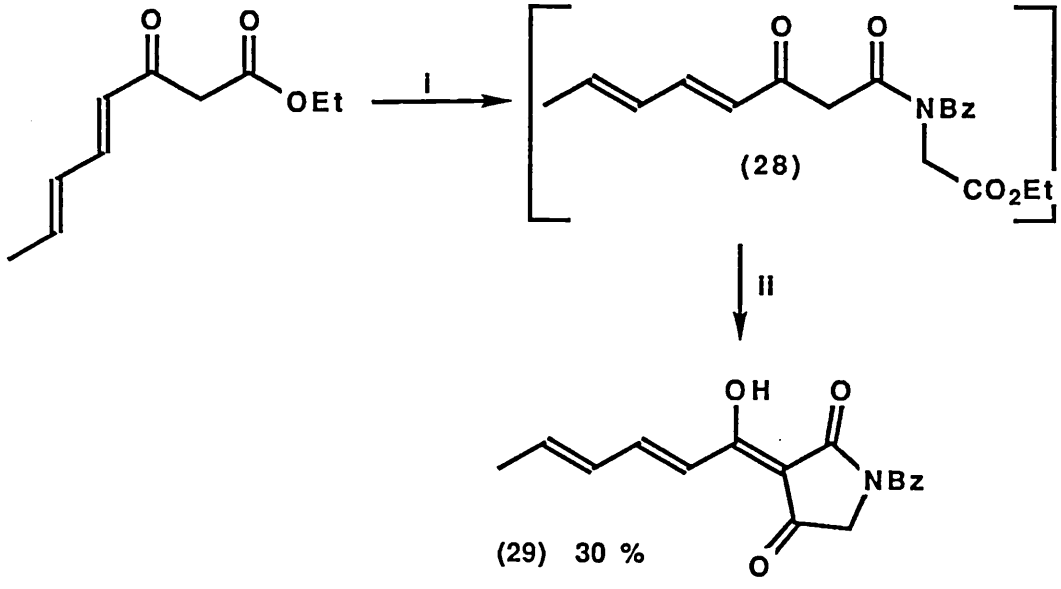
(26) (27) 13 - 53 %

R^1 = Me, Bz

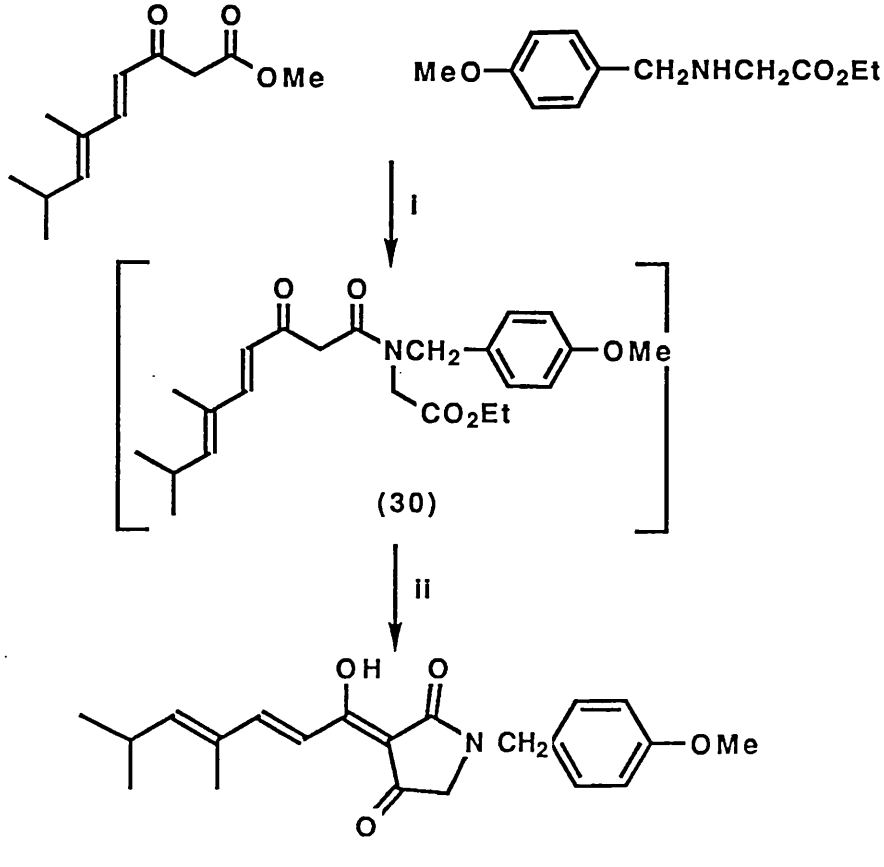
R^2 = H , Alkyl, Alkenyl

R^3 = H , Me, Ph

SCHEME 6 [25]



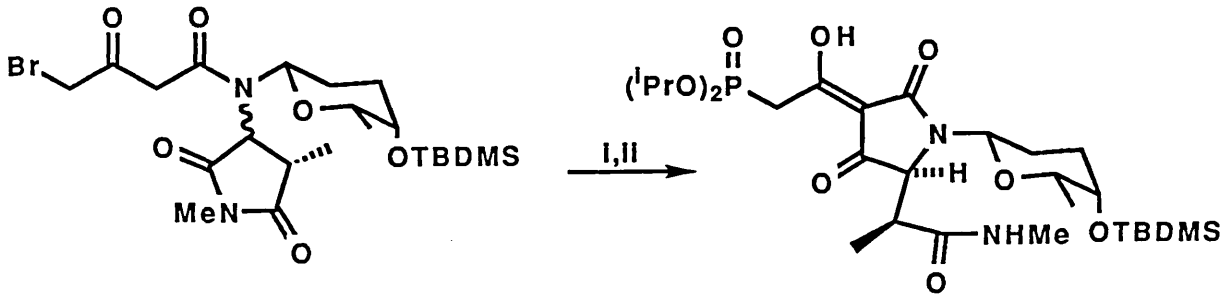
Reagents : I, $BzNHCH_2CO_2Et$, Xylene, 120-125 deg.C, 6h ; II, Lacey Conditions



(31) 35 %

Reagents : I, Xylene,125-130 deg.C, 8h ; II, Lacey Conditions

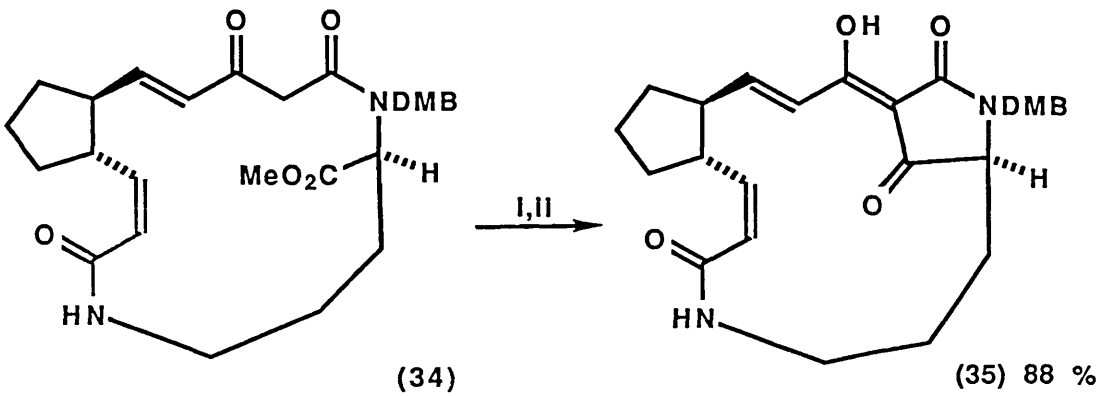
SCHEME 7 [26]



(32) (33) 90 %

Reagents : i, KP(O)(^{i}PrO)$_2$, THF, 0 deg.C ; ii, H^+

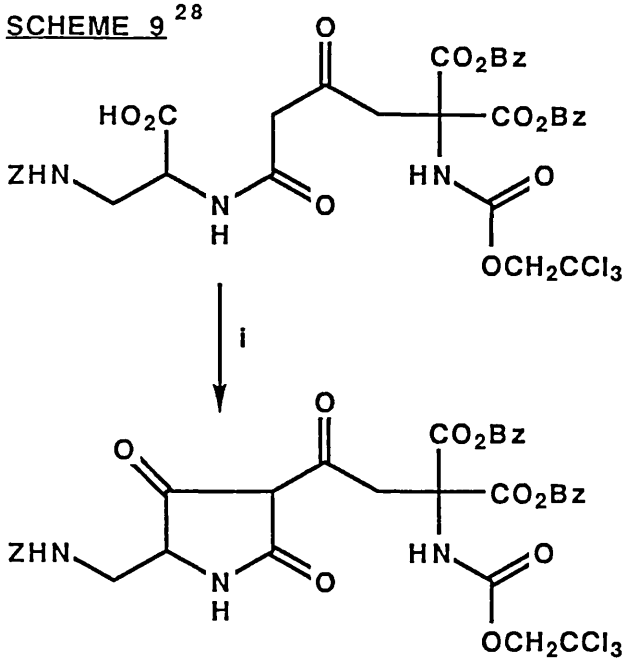
SCHEME 8 [27]



(34) (35) 88 %

Reagents : i, KO^{t}Bu, THF ; ii, H^+

SCHEME 9 [28]

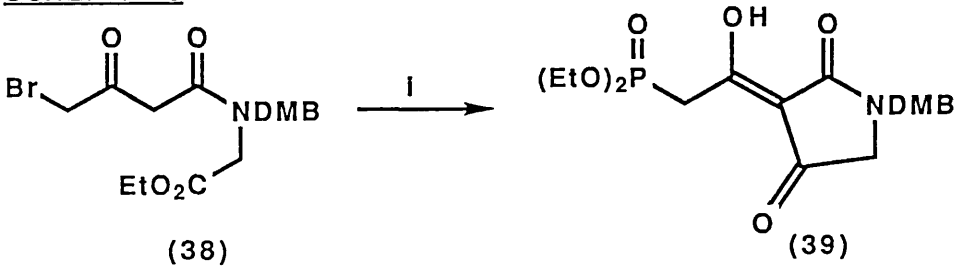


(36)

(37)

Reagents : i, HOBT, DCC, Et_3N, THF, 0 deg.C

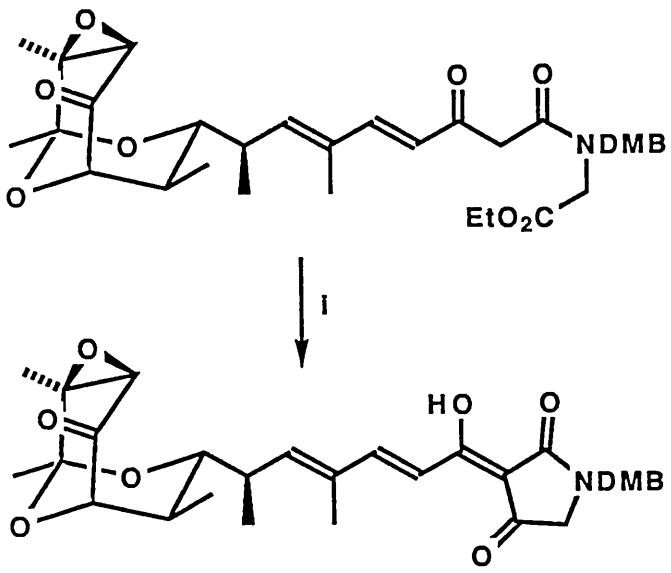
SCHEME 10 [29]



(38) (39)

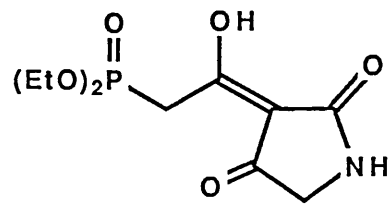
Reagents : i, $KP(O)(EtO)_2$, THF, 22 deg.C, 12h

SCHEME 11 [30]



Reagents : I, KO^{t}Bu, THF, room temperature

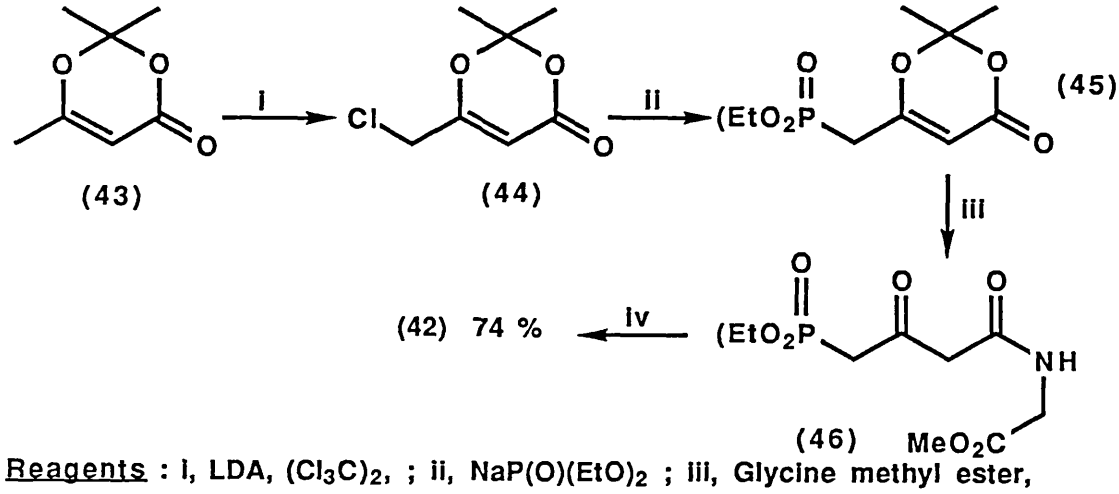
The product (39) of Scheme 10 has seen extensive application in the synthesis of tirandamycin A (11). The original reagent developed for this purpose, described first by Boeckman[31] and subsequently by DeShong[32], was the phosphonate (42), unsubstituted on N-1.



(42)

Boeckman prepared (42) from the acetone-diketene adduct (43) (Scheme 12).

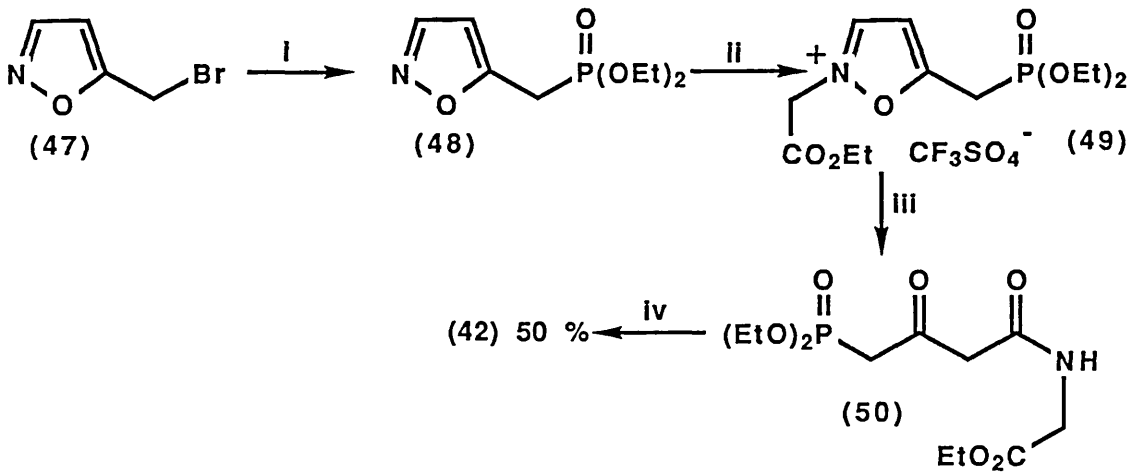
SCHEME 12



Reagents : i, LDA, $(Cl_3C)_2$, ; ii, $NaP(O)(EtO)_2$; iii, Glycine methyl ester, PhH, reflux ; iv, NaOMe, MeOH

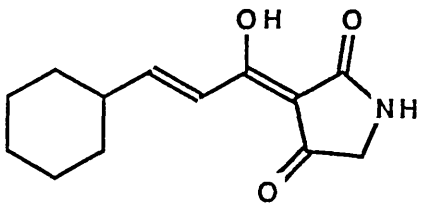
DeShong prepared (42) by a somewhat esoteric route using the base-induced fragmentation of the isoxazolium salt (49) to construct the β-ketoamide intermediate (50, Scheme 13).

SCHEME 13

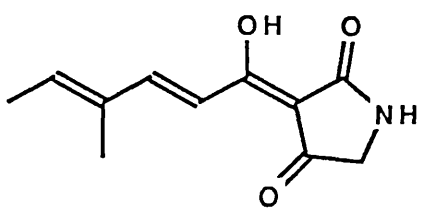


Reagents : i, $(EtO)_3P$; ii, $CF_3SO_3OCH_2CO_2Me$; iii, $NaHCO_3$; iv, NaOEt, EtOH

Boeckman reported reactions of the phosphonate dianion with cyclohexanecarboxaldehyde and tiglaldehyde to give the 3-enoyl products (51) and (52) in 72% and 64% yields respectively.



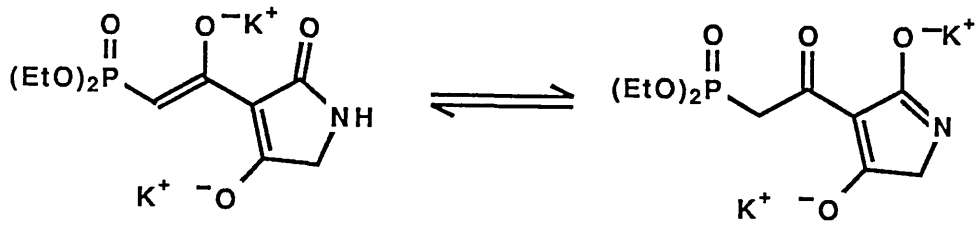
(51)



(52)

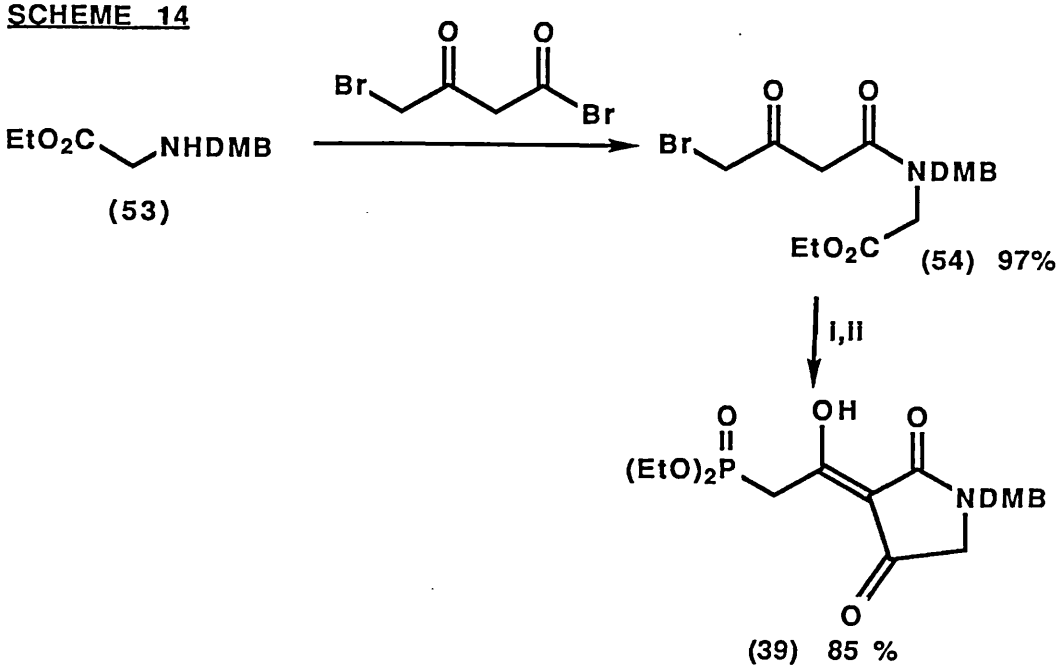
DeShong[32] stated that he found the phosphonate (42) reacted with aldehydes but gave no details of these reactions.

Schlessinger[29] however found that (42) reacted poorly with unsaturated aldehydes, requiring forcing conditions. He attributed this reluctance to react to the lack of regio-definition of the dianion formed from (42).



The reduced reactivity due to the lack of regio-definition was overcome by introducing the acid labile 2,4-dimethoxybenzyl group (DMB) onto N-1 of the phosphonate to give (39). Phosphonate (39) was prepared as shown (Scheme 14).

SCHEME 14

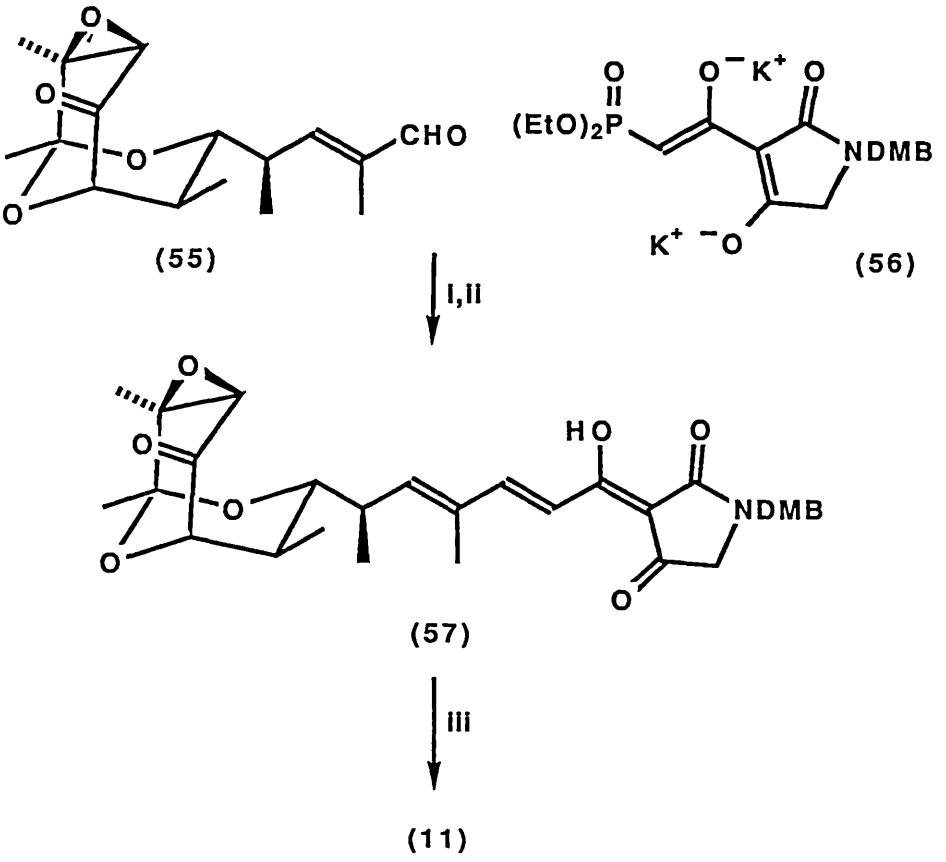


Reagents : I, 2 x $KP(O)(EtO)_2$; II, H^+

Treatment of (54) with two equivalents of the potassium salt of diethyl phosphite resulted in cyclisation and bromide displacement to give (39). The N-DMB phosphonate (39) was found to be a very effective reagent for the introduction of the preformed 3-acyltetramic acid unit. It reacted with a range of saturated, and more importantly, from a tirandamycin A total synthesis perspective, unsaturated aldehydes to give the 3-enoyl products in good yields (80% to 99%). The DMB group could be readily removed with neat trifluoroacetic acid (60% to 85%).

Phosphonate (39) was subsequently used by Schlessinger[33], Boeckman[34], and DeShong[35] in their syntheses of tirandamycin A. Reaction of the presumed dianion intermediate (56) with the aldehyde (55) gave (57) which on treatment with trifluoroacetic acid gave tirandamycin A (11, Scheme 15).

SCHEME 15

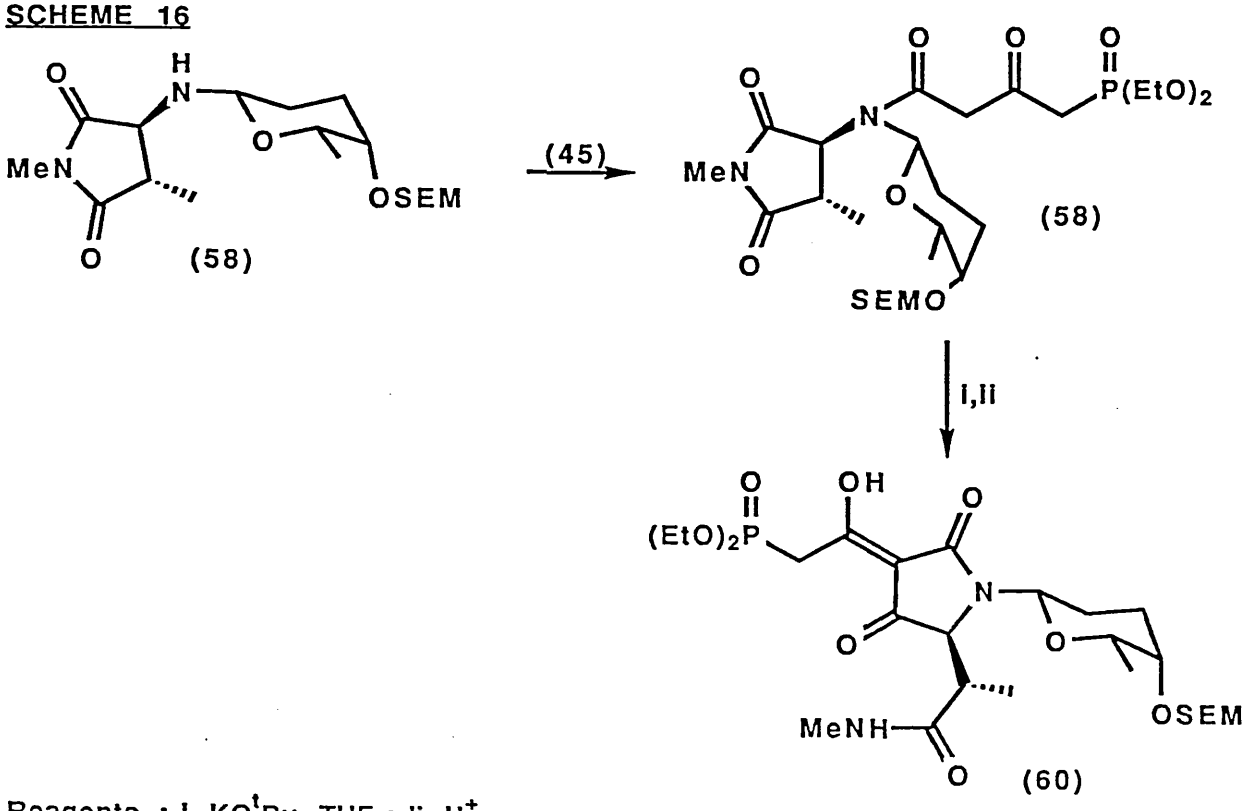


Reagents : I, THF ; II, H^+ ; III, TFA

The reaction depicted in Scheme 11 is the penultimate step in Bartlett's total synthesis of tirandamycin A[30] and is unique in that it is the only total synthesis of tirandamycin A to include a Dieckmann reaction on a compound with an intact bicyclic ketal unit.

In a more recent publication, Boeckman[36] described the synthesis of the phosphonate (60) required for the introduction of the 3-acyltetramic acid unit of streptolydigin (10) by the route outlined below (Scheme 16).

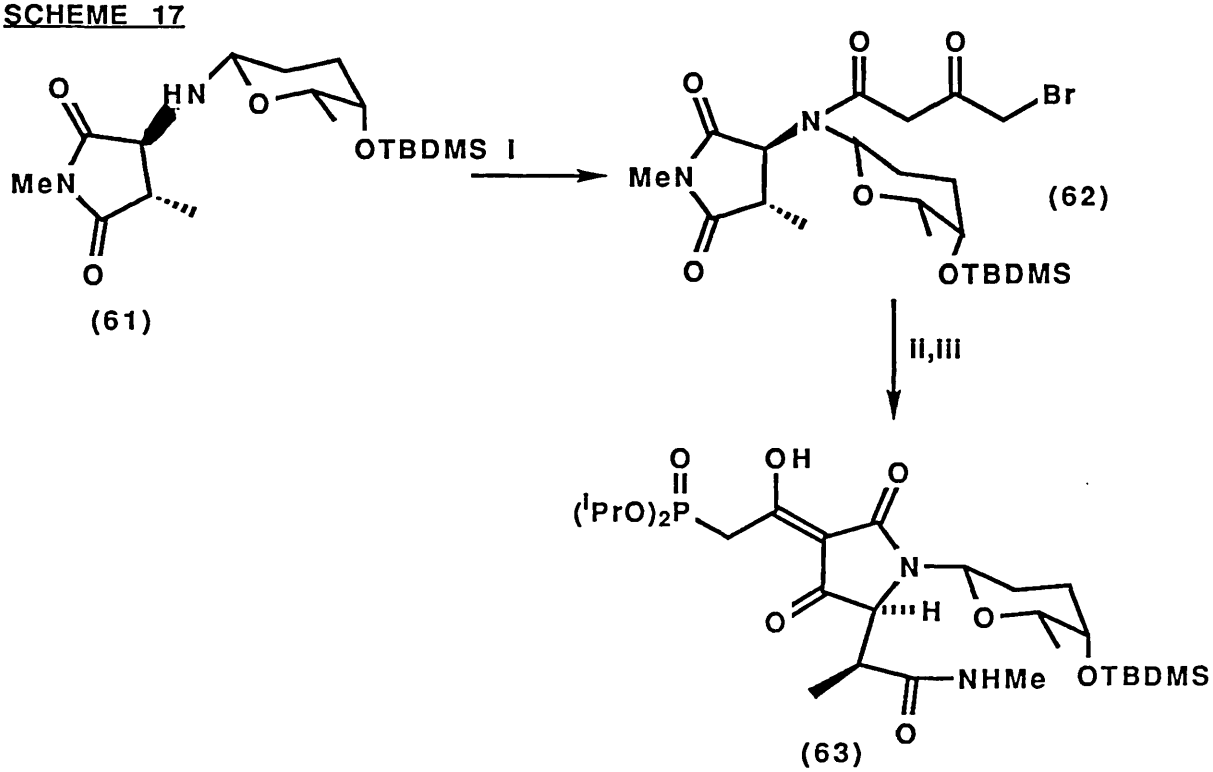
SCHEME 16



Reagents : I, KO^{t}Bu, THF ; II, H^+

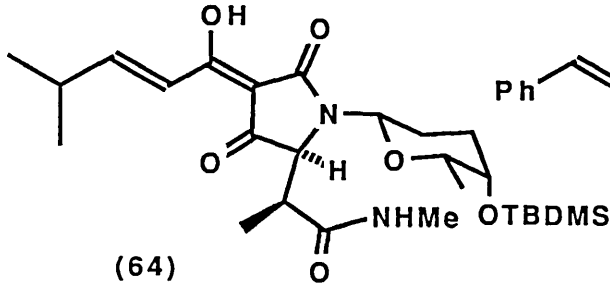
No reactions of (60) were reported by Boeckman. Schlessinger has subsequently reported the synthesis of the similar phosphonate (63) by the route shown below (Scheme 17)[26].

SCHEME 17

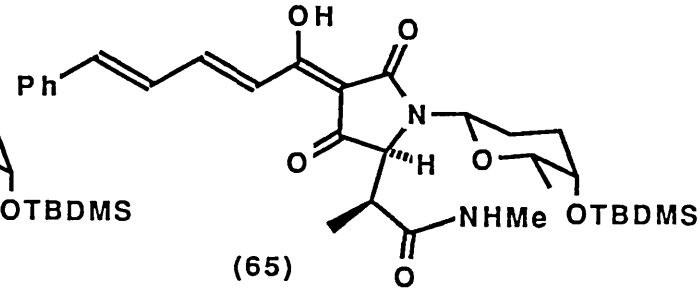


Reagents : i, $BrCH_2COCH_2COBr$; ii, 2 x $KP(O)(^iPrO)_2$; iii, H^+

Schlessinger found that treatment of the mono-sodium salt of (63) with either LDA or KO^tBu and reaction of the presumed dianion with iso-butyraldehyde gave (64) in 70% yield, and reaction with trans-cinnamaldehyde gave (65) in 55% yield.

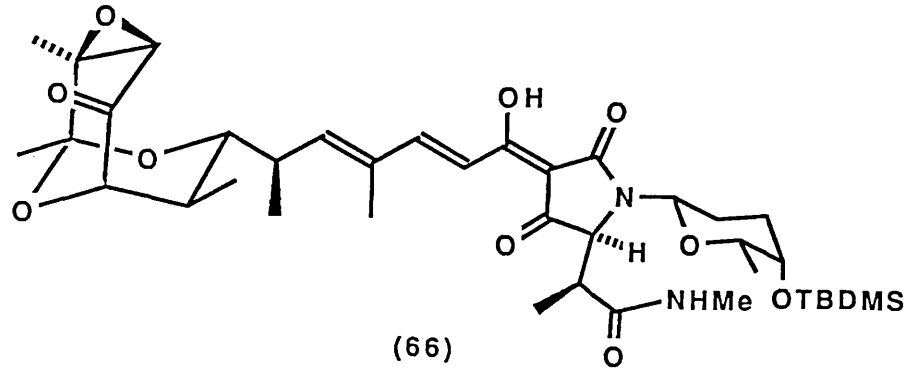


(64)



(65)

Reaction with trans-2-hexenal failed to give the desired olefination product, but reaction with the unsaturated aldehyde derived from tirandamycin A degradation gave a 20% yield of (66) which portends well for the total synthesis of streptolydigin (10).

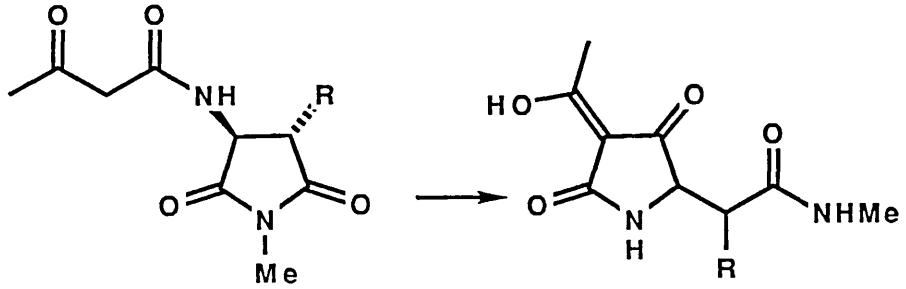


(66)

Two of the Dieckmann reactions shown have involved cyclisation into an aspartimide unit instead of an ester (Schemes 7 and 16). This modification has been used by these groups to prepare the 3-acyltetramic acid unit similar to, or the same as that found in streptolydigin (10)[26/37].

Rinehart[37] originally reported the reaction involving the treatment of (67) and (68) with NaOMe to give the 3-acetyltetramic acids (69) and (70) respectively in good yields (Scheme 18).

SCHEME 18



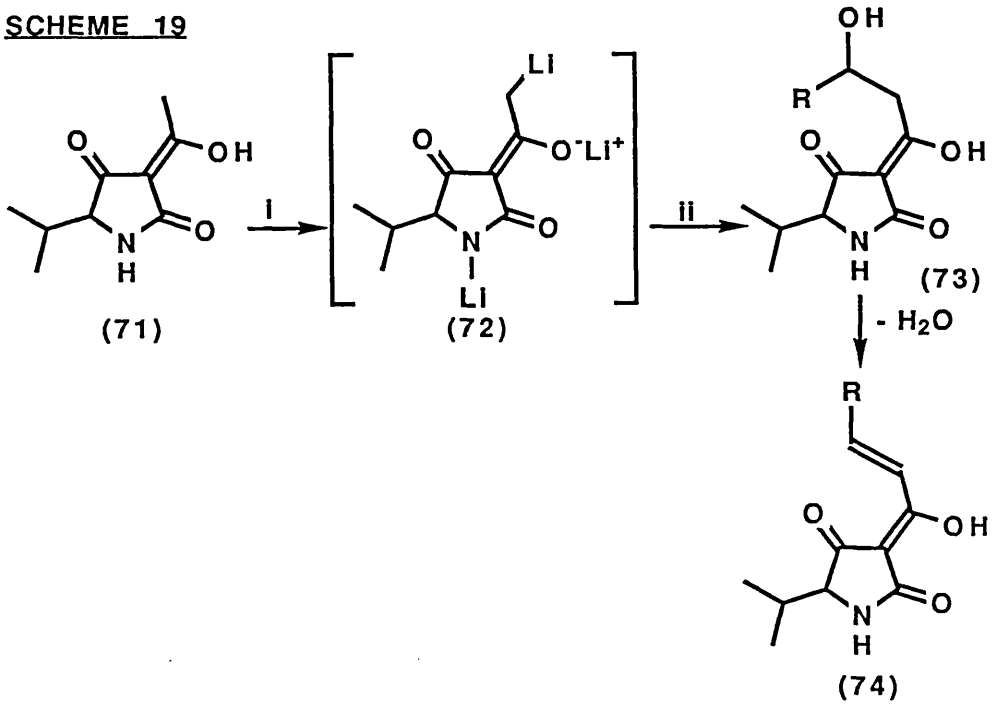
R = H (67) (69) 71 %

R = Me (68) (70) 75 %

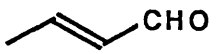
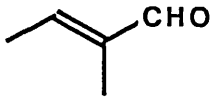
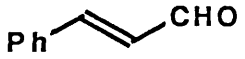
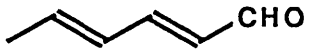
The fate of the C-5 stereochemistry was not commented on. Boeckman and Schlessinger both used this modification to prepare the phosphonates (60) and (63) previously mentioned (Schemes 16 and 17 respectively).

Jones[38] has recently reported an alternative procedure for introducing the intact 3-acyltetramic acid unit. This involves the reaction of the presumed tri-lithio derivative (72) with unsaturated aldehydes to give, in quantitative yield, the adducts (73). Elimination (HCl/CH_2Cl_2, or $POCl_3/CHCl_3$, or $BF_3.Et_2O$) gives the desired unsaturated products (74, Scheme 19).

SCHEME 19

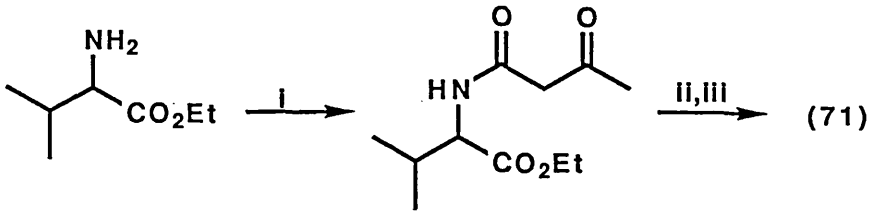


Reagents : i, 3BuLi, THF ; ii, RCHO

RCHO	OVERALL YIELD / %
	54
	49
	45
	73

The 3-acetyltetramic acid (71) was readily available in high yield by the following route (Scheme 20).

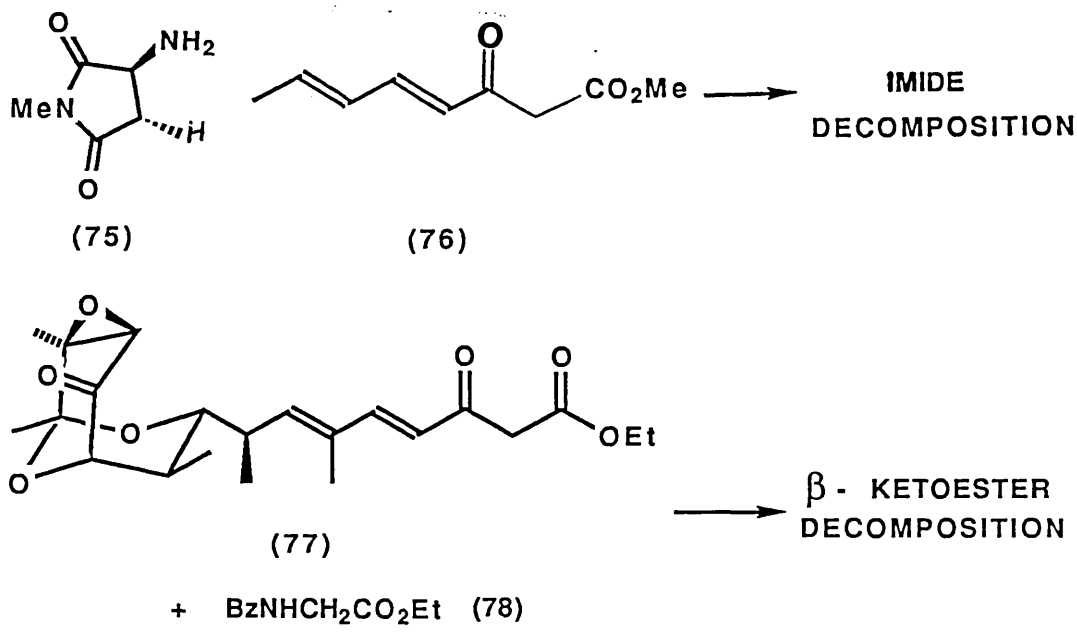
SCHEME 20



Reagents : i, Diketene, EtOH ; ii, NaOEt, EtOH ; iii, H^+

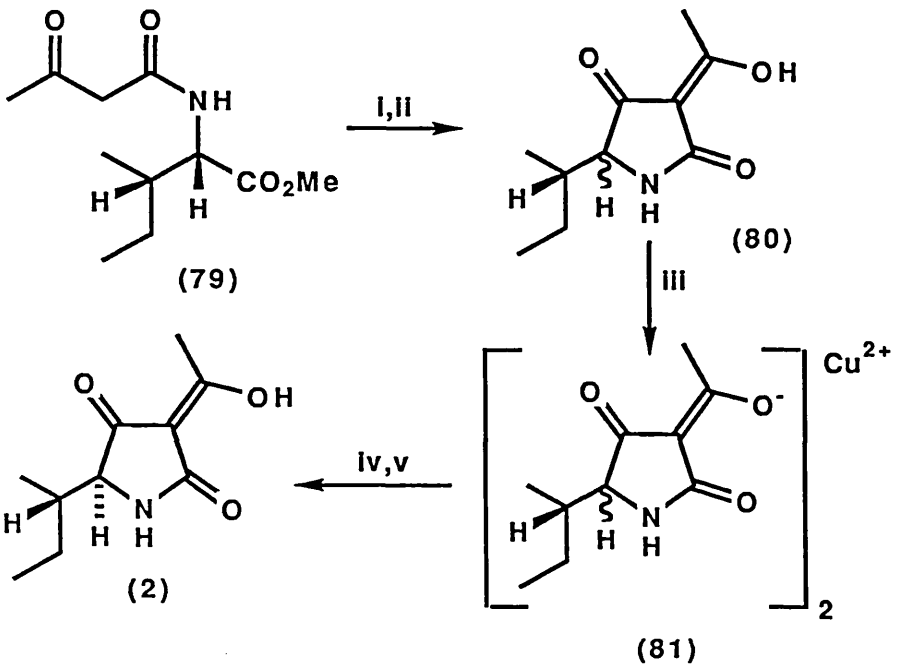
The Dieckmann approach to 3-acyltetramic acids is not without its attendant problems. Major difficulties preparing the β-ketoamide esters from β-ketoesters have been reported by Rinehart[25/37] (Scheme 21). Under the harsh conditions required for reaction, extensive decomposition of (75)[37] and (77)[25] was observed.

SCHEME 21



In their preparation of tenuazonic acid (2) Harris et al[23], using the cyclisation conditions described by Lacey (Scheme 3), observed epimerisation at the 5-position of the 3-acetyltetramic acid. The required enantiomer was obtained by converting compound (80) to its Cu(II) derivative (81) and recrystallising four times followed by conversion back to the free 3-acetyltetramic acid (2, Scheme 22).

SCHEME 22



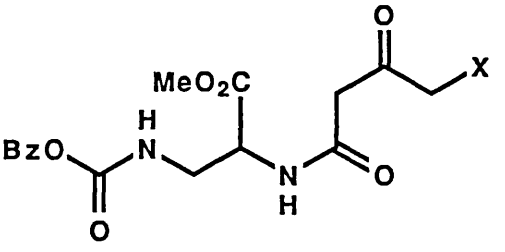
Reagents : I, NaOMe, MeOH ; II, H^+ ; III, Cu(II)OAc ;

IV, 4 recrystallisations ; V, H_2S

$[\alpha]_{546}$ Cu(II) salt $-76.5^0 \rightarrow -122^0$

This racemisation problem at C-5 appears to be associated mainly with the preparation of 3-acyltetramic acids with a hydrogen on N-1. Possible reasons for this are discussed in the next section.

In his malonomicin (4) studies van der Baan reports[28] problems with the cyclisation of the substrates (82) and (83).



X = OCH_2Ph (82)

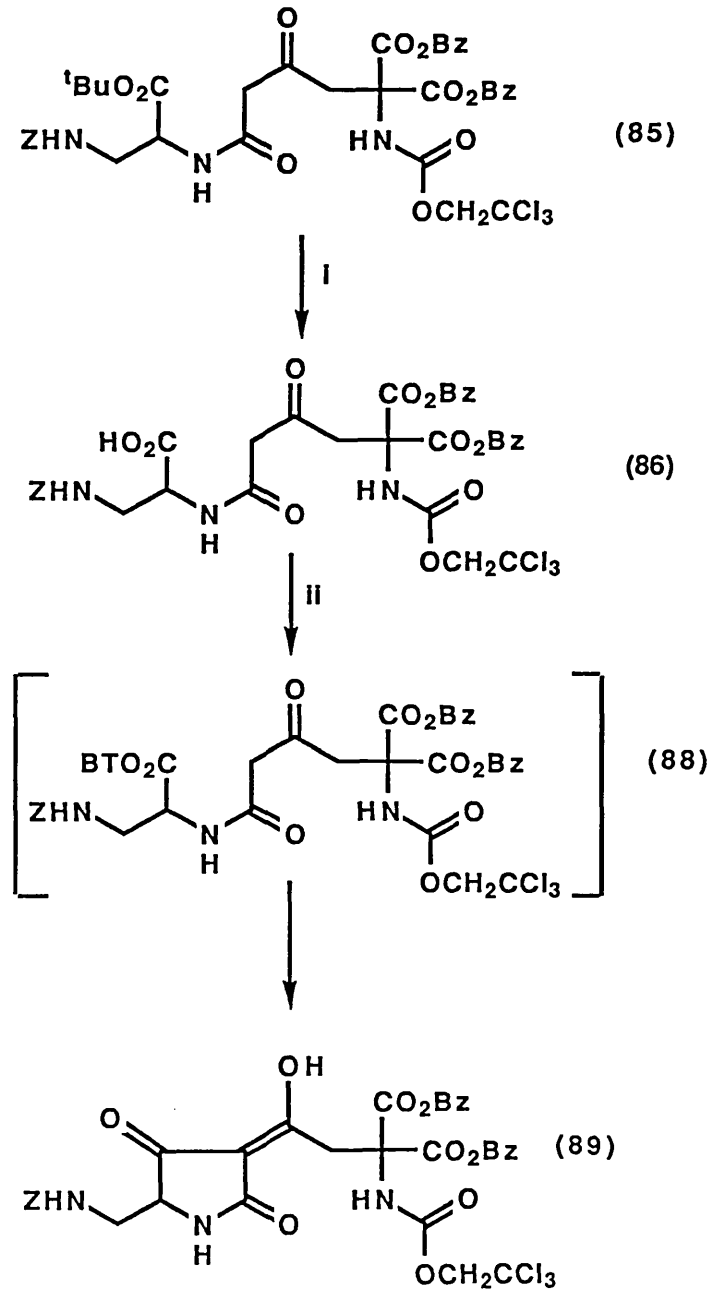
O^tBu (83)

^tBu (84)

This failure to cyclise is attributed to electronic rather than steric reasons since (84) cyclised without any problem (NaOMe, MeOH, PhH, reflux, 73%).

Van der Baan also experienced cyclisation problems with the more advanced malonomicin intermediate (85). This problem was overcome by hydrolysis of (85) to the acid (86), conversion to the 1-benzotriazole ester (88) and <u>in situ</u> cyclisation (Scheme 23).

SCHEME 23



Reagents : i, PTSA, HOAc ; ii, HOBT, DCC, Et_3N, THF

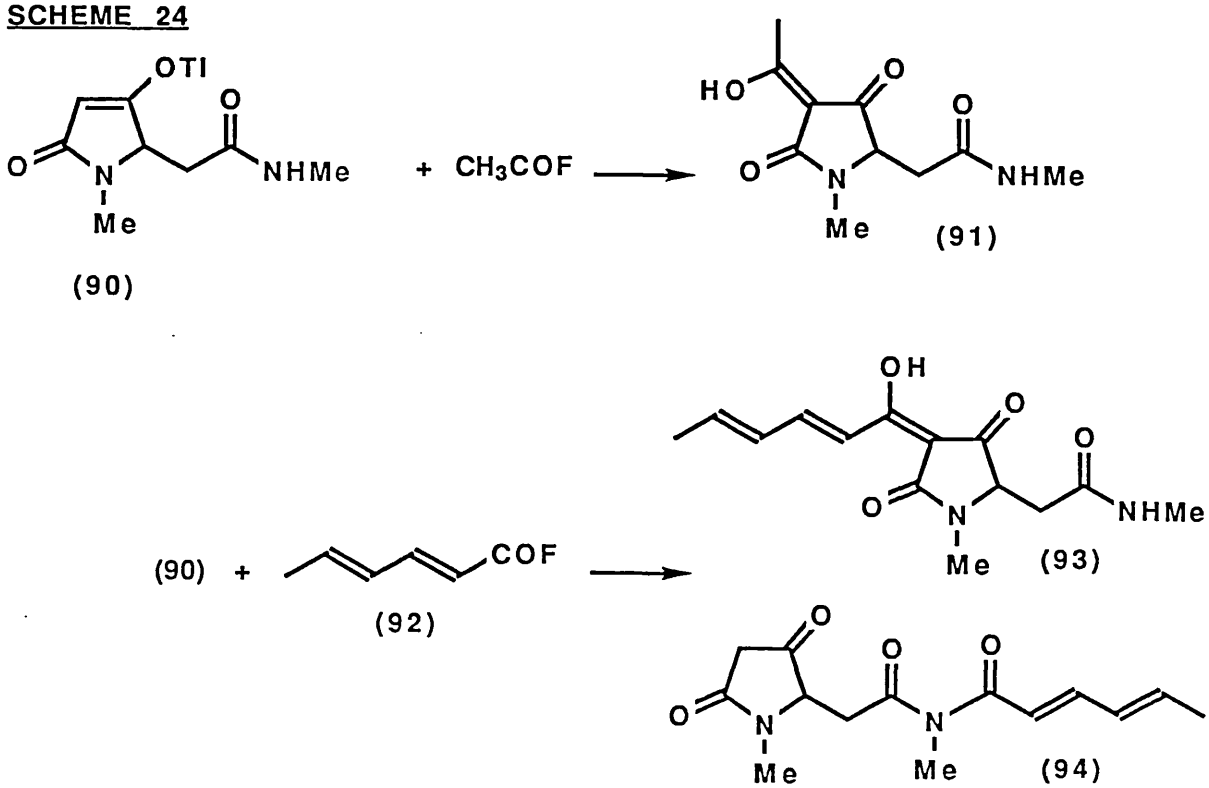
Direct Acylation of Tetramic Acid

This approach, shown in general in Scheme 2, is perhaps the more attractive method for *in situ* construction of the 3-acyltetramic acid unit and has consequently received much attention.

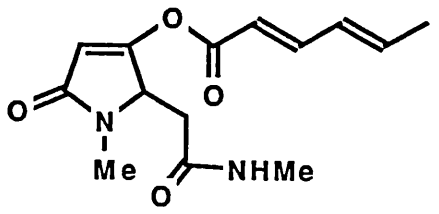
However, work on the direct introduction of an unsaturated side chain by this route has met with considerable problems. In his streptolydigin studies Rinehart[25] used conditions known to favour the *C*-acylation over *O*-acylation of β-diketones developed by McKillop[39].

Although acetyl fluoride acylated the 3-position of the thallium salt (90) to give the desired product (91) in 57% yield (Scheme 24), with sorbyl fluoride (92) a mixture of *C*-acylated (93) and *N*-acylated (94) products were obtained in 4% and 43% yields respectively.

SCHEME 24



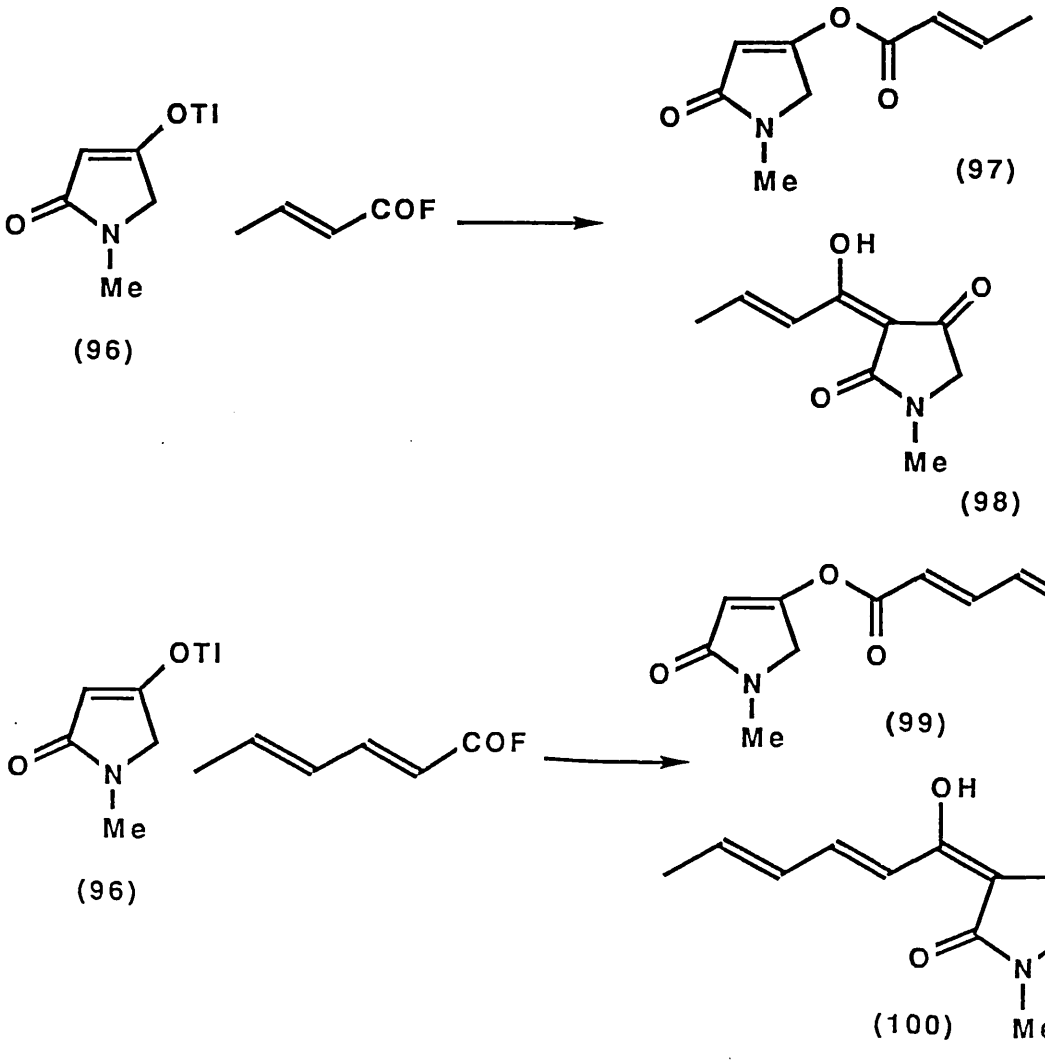
The use of the corresponding dienoyl chloride gave the O-acylated compound (95) as did the use of other metal salts (Na, EtOMg, Li).



(95)

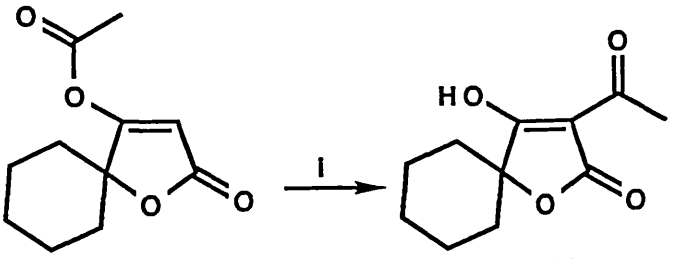
Rinehart also investigated this approach in his tirandamycin A studies[25]. Using sorbyl and crotonyl fluorides and the thallium tetramate (96), only low yields (6% and 3%) of the desired 3-acylated products (100) and (98) were obtained, the major products being the O-acyl compounds (97) and (99) (32% and 24% yield respectively, Scheme 25).

SCHEME 25



A recent paper in the related 3-acyltetronic acid area reports the rearrangement of the O-acylation product (101) into the 3-acyltetronic acid (102, Scheme 26)[40]. This methodology might also work with the tetramic acid O-acylated products.

SCHEME 26



(101) (102)

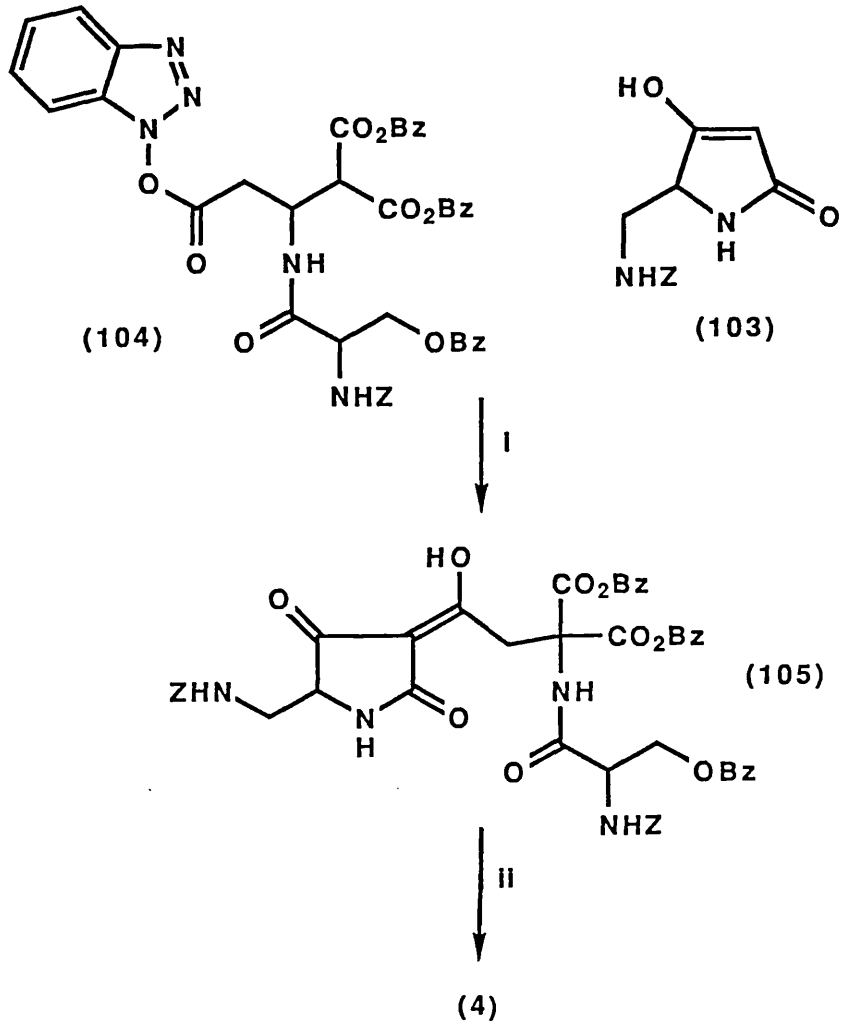
Reagents : I, Et_3N, DMAP, CH_2Cl_2, room temperature

Also reported is the one-pot formation of 3-acyltetronic acids from a variety of tetronic acids under mild conditions in good yields. The reactions involve treating a mixture of the tetronic acid, Et_3N, and DMAP with either the acid anhydride or the carboxylic acid and DCC at room temperature in CH_2Cl_2. No acylations with α,β-unsaturated carboxylic acids or anhydrides were reported and the reaction failed with benzoyl and trimethylacetyl, stopping at the O-acyl stage, presumably because of steric hindrance in the O to C migration.

This methodology could in principle be applied to the synthesis of 3-acyltetramic acids. Indeed something similar has been reported by van der Baan in his malonomicin studies[28].

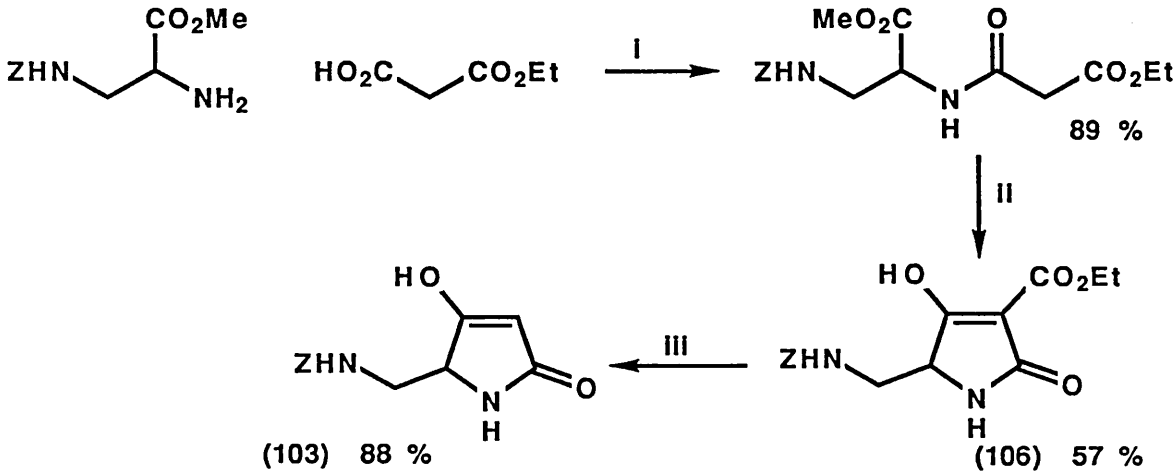
These authors employed base induced 3-acylation of the tetramate (103) using the active ester (104) prepared *in situ* as the penultimate step in their total synthesis of malonomicin to give (105) in 40% yield. Hydrogenation over Pd-C subsequently gave malonomicin (4) in 86% yield (Scheme 27).

SCHEME 27



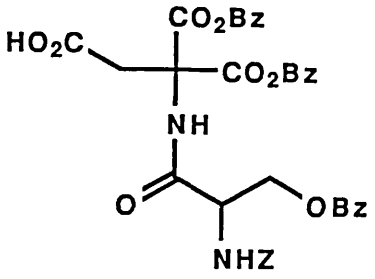
The tetramic acid (103) was synthesised from (106) by boiling in nitromethane or acetonitrile with a trace of water present. Compound (106) was readily available by the route shown (Scheme 28).

SCHEME 28

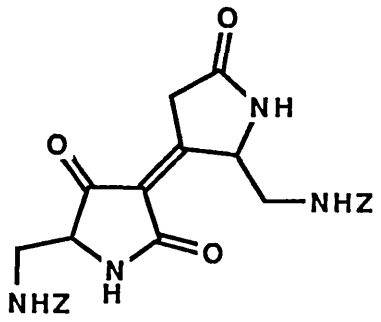


Reagents : I, EEDQ, Et_3N, CH_2Cl_2, 0 deg.C ; ii, NaOMe, MeOH, PhH ; iii, CH_3NO_2, H_2O, reflux, 30 min

Acylation was initially attempted by van der Baan using the acid (107). Under the basic conditions used the reaction failed, the dimer (108) being formed. Acylation under Lewis acid catalysis ($TiCl_4$ or BF_3) also failed.

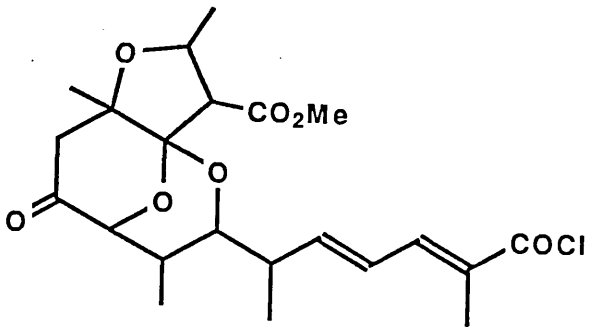


(107)

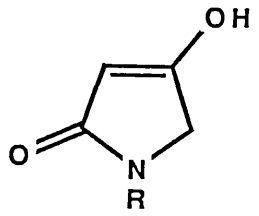


(108)

In their relay synthesis of Bu-2313A and Bu-2313B (12,13) Toda et al[15] experienced difficulty in coupling the acid chloride (109), obtained from a degradation product, with the tetramic acids (110).



(109)



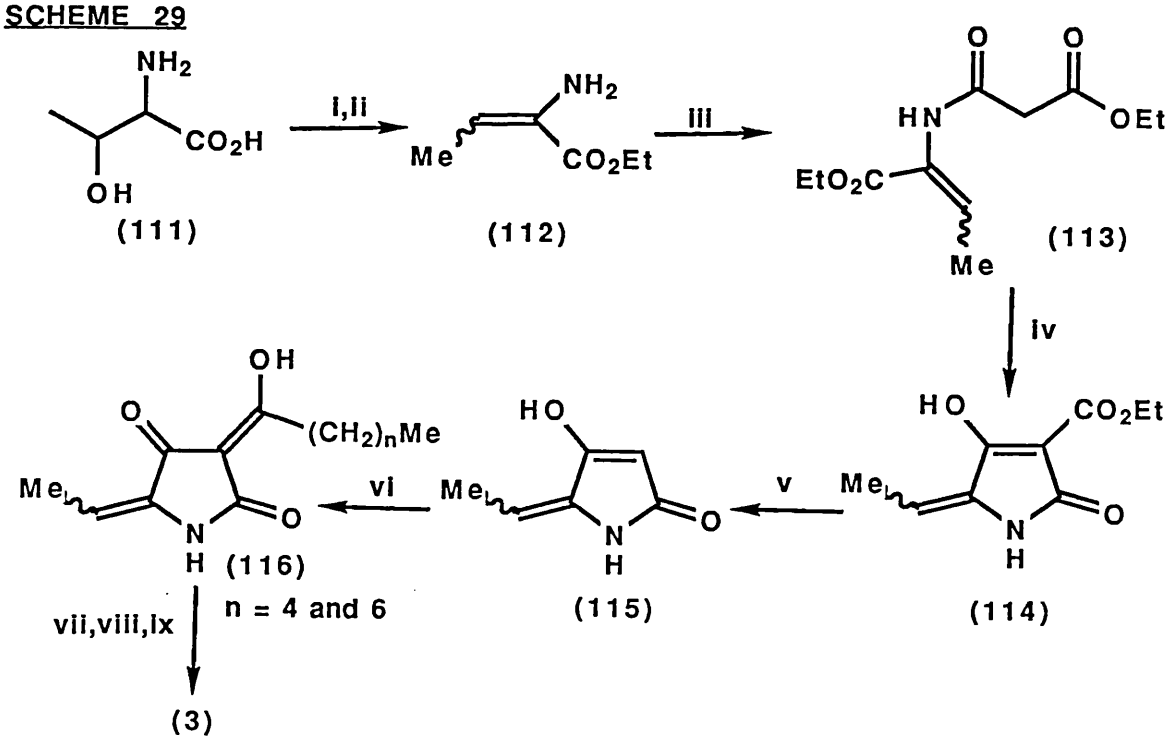
(110)

R = H or Me

Using the reported literature methods ($BF_3.Et_2O$, Et_3N) neither of the natural products were obtained. However, the use of stronger bases (KO^tBu or NaH in DMF) led to low yields of Bu-2313A (12).

However, largely due to work by Bhat and Jones, this direct method of 3-acyltetramic acid synthesis now seems to be a viable process. Bhat[6] reported the total synthesis of magnesidin (3) using a $BF_3.Et_2O$ mediated 3-acylation of the tetramic acid (115) with hexanoyl and octanoyl chlorides. The total synthesis is shown below (Scheme 29).

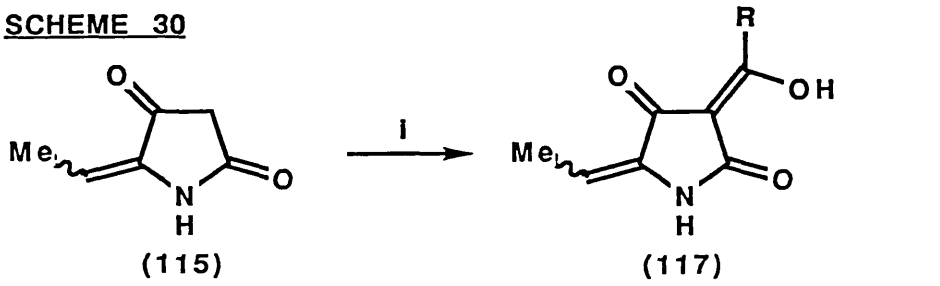
SCHEME 29



Reagents : i, Ac_2O, HOAc ; ii, HCl, EtOH ; iii, $ClCOCH_2CO_2Et$; iv, NaOEt ; v, EtOAc, H_2O ; vi, $BF_3.Et_2O$, $CH_3(CH_2)_nCOCl$; vii, 0.1N NaOH ; viii, $MgCl_2$; ix, Ac_2O, HOAc

In another communication Bhat[41] describes the synthesis of a series of 3-acyltetramic acids (117) using the same method in yields of around 50% (Scheme 30).

SCHEME 30



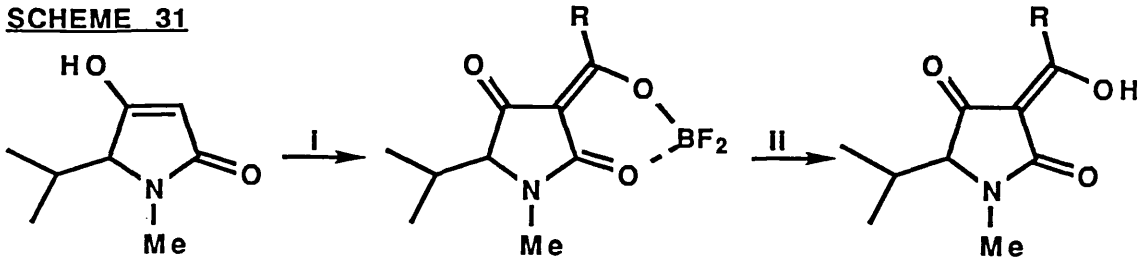
(115) (117)

R = C_3H_7 , C_5H_{11} , C_7H_{15} , C_9H_{19}

Reagents : I, RCOCl, $BF_3.Et_2O$

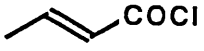
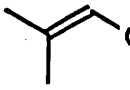
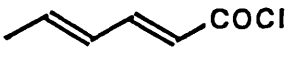
Jones[42] has also reported the successful Lewis acid mediated 3-acylation of the tetramic acid (118) using $BF_3.Et_2O$ and acid chlorides (Scheme 31).

SCHEME 31



(118) (119) (120) to (125)

Reagents : I, RCOCl, $BF_3.Et_2O$; II, MeOH

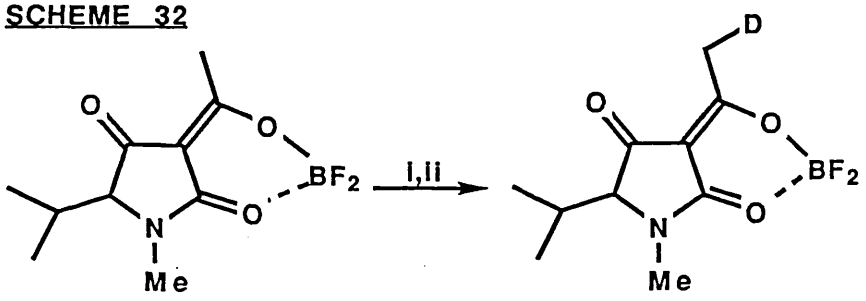
RCOCl	BF_2 COMPLEX YIELD / %	ACID YIELD / %
CH_3COCl	71	93 (120)
$CH_3(CH_2)_4COCl$	71	94 (121)
	78	86 (122)
	67	92 (123)
	51	80 (124)
PhCOCl	50	80 (125)

Jones was able to prepare several 3-acyltetramic acids containing double bonds conjugated to the 3-acyl group (122 to 124). These are of considerable relevance to the synthesis of tirandamycin, streptolydigin and the other 3-polyenoyl tetramic acid natural products.

The products were isolated as the boron difluoride complexes (119). These were found to be easily handleable compounds and could be conveniently purified before conversion into the free 3-acyltetramic acid by treatment with methanol.

The chemistry of these boron complexes was also investigated and it was found that mono-deprotonation occurred on the 3-acetyl group (Scheme 32).

SCHEME 32

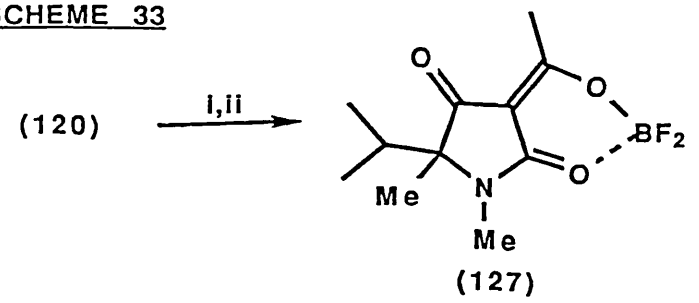


(120) (126)

Reagents : I, LDA ; II, D_2O

Double deprotonation and quenching with methyl iodide gave (127), methylation occurring at the 5-position (Scheme 33).

SCHEME 33

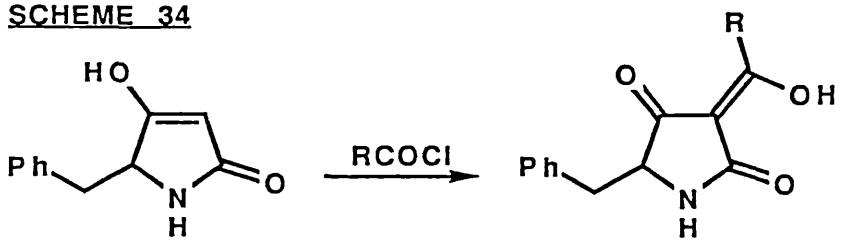


(127)

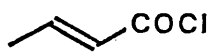
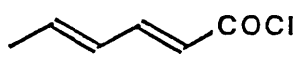
Reagents : i, 2LDA ; ii, MeI

These results represent an improvement on the procedure reported in a previous paper[43] describing the acylation of the tetramic acid (128) using a combination of different Lewis acids and solvents (Scheme 34).

SCHEME 34

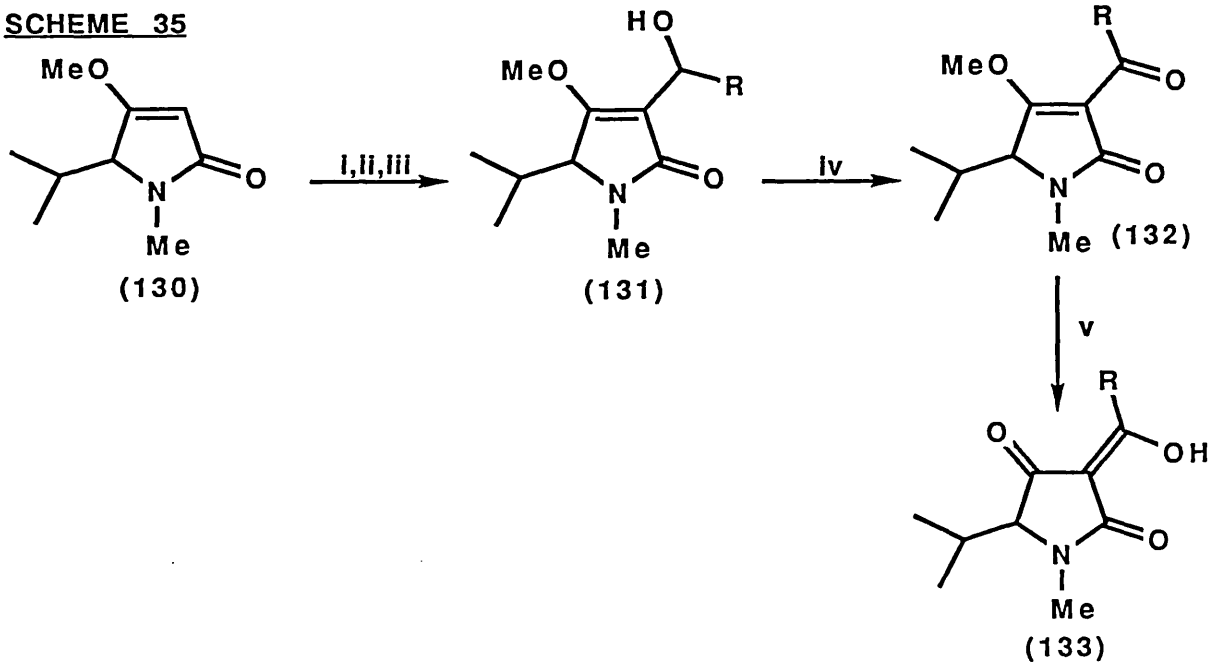


(128) (129)

RCOCl	LEWIS ACID	YIELD / %
CH_3COCl	$BF_3.Et_2O$	55
$CH_3(CH_2)_4COCl$	$BF_3.Et_2O$	63
	$BF_3.Et_2O$	0
	$SnCl_4$	0
	$TiCl_4, CH_3NO_2$	52
	$BF_3.Et_2O$	20
	$TiCl_4, CH_3NO_2$	33

Problems were experienced with acylations using unsaturated acid chlorides as the last two entries in Scheme 34 indicate. Another paper by Jones[44] reports a complementary method of 3-acylation under basic conditions involving the directed metallation of the methyl tetramate (130) followed by reaction with aldehydes to give the hydroxy products (131). These are then converted to the 3-acyltetramic acids (133) by oxidation to the methyl 3-acyltetramate (132) followed by hydrolysis (Scheme 35).

SCHEME 35



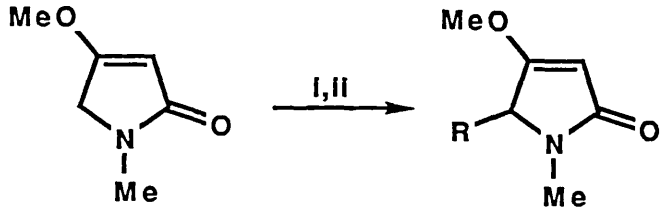
Reagents : i, ^{n}BuLi ; ii, RCHO ; iii, H^{+} ; iv, MnO_2, CH_2Cl_2 ; v, NaOH, H_2O

RCHO	ALCOHOL YIELD / % (131)	KETONE YIELD / % (132)	ACID / % (133)
$CH_3(CH_2)_4$ CHO	57	64	83
	54	63	91
	58	87	80
PhCHO	70	90	85

In another publication Jones[45] has reported a more flexible method of synthesising the tetramic acids required for the acylation reactions, involving elaboration of the preformed heterocycle.

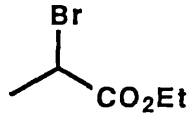
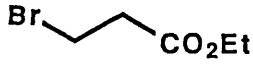
It was found that the methyl tetramate (134) could be lithiated at C-5 and the resulting anion reacted with alkyl halides (Scheme 36).

SCHEME 36



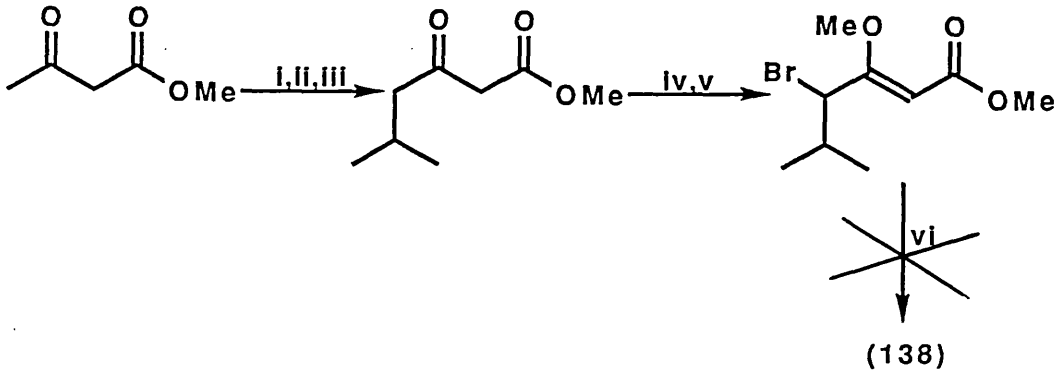
(134) (135) to (138)

Reagents : I, 1.2 ^{n}BuLi ; II, RX

RX	YIELD / %
MeI	82 (135)
	94 (136)
	90 (137)
$(CH_3)_2CHI$	50 (138)

A previous attempt to prepare (138) from methyl acetoacetate had failed at the final step (Scheme 37).

SCHEME 37

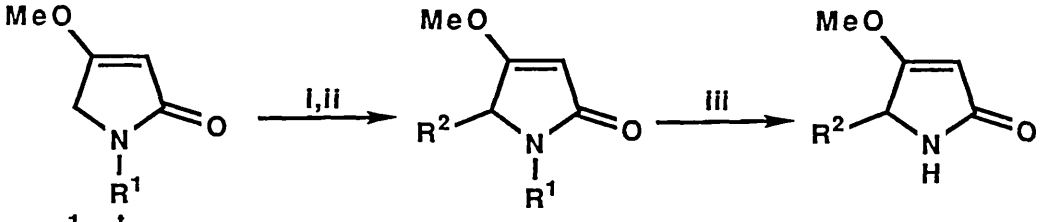


(138)

Reagents : I, 2LDA ; II, $(CH_3)_2CHI$; III, H^+ ; IV, $(MeO)_3CH$, H^+ ; V, NBS ; VI, $MeNH_2$

The successful alkylation of N-unsubstituted tetramic acids was found to require N-protection as the silyl derivative (139 and 140). Deprotection was effected with 40% aqueous hydrofluoric acid (Scheme 38).

SCHEME 38



$R^1 = {}^tBuMe_2Si$ (139)

$= {}^iPr_3Si$ (140)

(141)

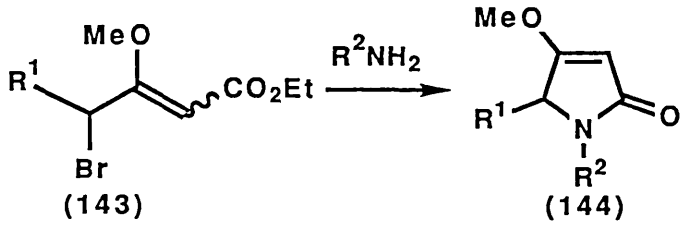
(142)

Reagents : i, BuLi ; ii, R_2X ; iii, HF, H_2O

R^2X	YIELD / %
MeI	not reported
$BrCH_2CO_2Et$	46

Also described was an improved procedure for introducing a variety of N-substituents. These had previously been introduced by reacting alkylamines with the bromoester (143, Scheme 39).

SCHEME 39

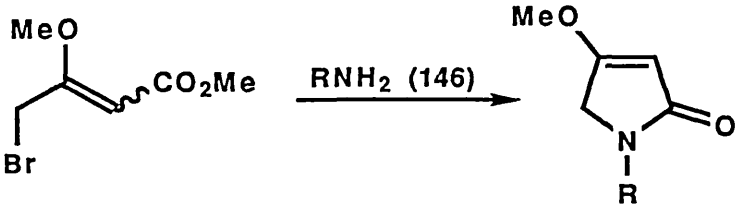


(143) (144)

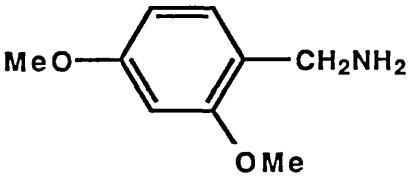
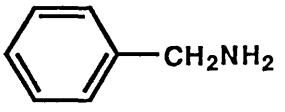
R^1 = Alkyl, R^2 = H, Me

This method uses a large excess of the amine in aqueous solution in which the bromoesters (143) are not generally soluble. The improved procedure involved using a stoichiometric amount of the amine (146) in ethanol containing Et_3N (Scheme 40).

SCHEME 40



(145) (147)

RNH2 (146)	YIELD / %
	60
	40
$CH_3(CH_2)_7NH_2$	45

In a complementary approach the N-1 position of the tetramic acid (148) was elaborated *via* either the N-1 lithio derivative or more efficiently using solid-liquid phase transfer conditions (Scheme 41).

SCHEME 41



(148) (149)

Reagents : i, KOH, Bu_4HSO_4, RX, THF

RX	YIELD / %
MeI	55
$PhCH_2Br$	60
$CH_3(CH_2)_7I$	43

SUMMARY

The main two approaches used for the preparation of 3-acyltetramic acids are the Dieckmann reaction and the 3-acylation of tetramic acids. These are essentially complementary since Dieckmann reactions are carried out under basic conditions whilst the acylations are generally carried out under Lewis acid mediated conditions. The Dieckmann approach has seen wider application to the synthesis of 3-acyltetramic acids.

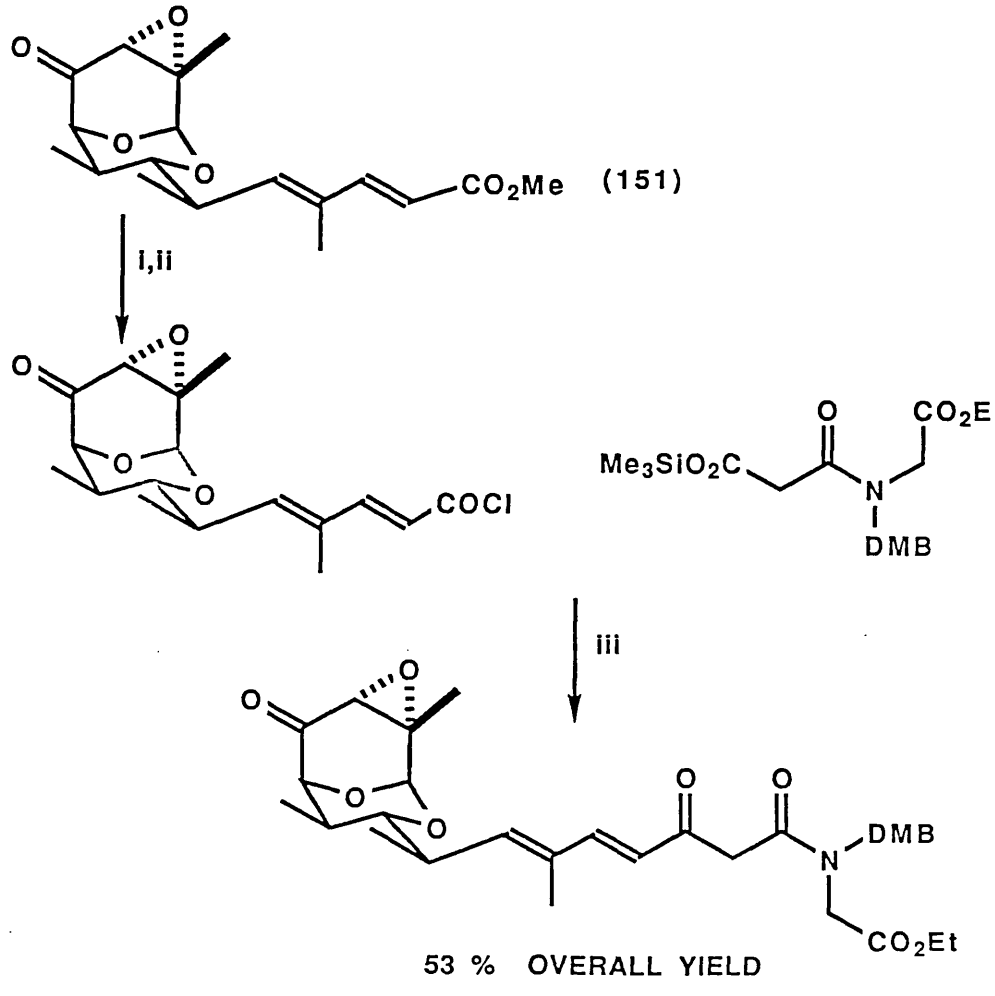
The Dieckmann reaction can be carried out under quite mild conditions enabling, as Bartlett has shown (Scheme 11), complex substrates such as the bicyclic ketal of tirandamycin A, which is known to be unstable to strong bases, to be tolerated. The cyclisation problems experienced by van der Baan (82, 83, and Scheme 23) seem to be restricted to his malonomicin studies.

Racemisation at the C-5 position can also be a problem, but only seems to occur with β-ketoamide esters with a proton on nitrogen. Possible explanations for this phenomenon are discussed in detail in the following section. This could of course be overcome by the introduction of a removeable substituent on N-1, but would add extra steps to the overall synthetic sequence.

A major problem with the Dieckmann approach can be the synthesis of the required β-ketoamide esters required for the cyclisation. This is especially true if this involves the direct conversion of the appropriate β-ketoester to the β-ketoamide. This process requires prolonged heating at high temperatures in order to effect reaction. Other methods currently available for β-ketoamide synthesis are discussed in the next section.

However, as Bartlett[30] has again shown in his tirandamycin A synthesis, alternative milder methods of β-ketoamide preparation are available which are compatible with complex sensitive substrates such as (151) in Scheme 42.

SCHEME 42

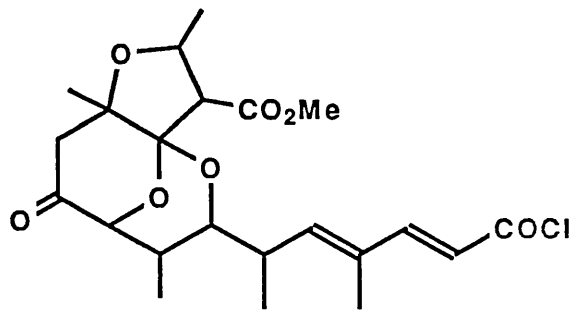


Reagents : i, NaOH, H_2O, ^tBuOH, RT, 30 min ; ii, ClCOCOCl, PhH, 30 min RT ; iii, KO^tBu, THF, -78 deg.C

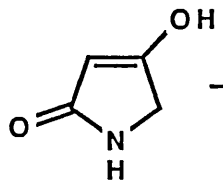
By contrast, the reagents required for the 3-acylation of tetramic acids are readily available, with a variety of substituent patterns on the tetramic acid being easily accessible. Now that the initial problems of O vs C acylation regioselectivity seem to have been overcome this route would seem quite an attractive route to 3-acyltetramic acids.

However, a real problem is the sensitivity of some substrates to the conditions used for the acylation. The problems met by Toda et al in their Bu-2313A and Bu-2313B relay syntheses have already been mentioned. They found that the acid chloride (109) was unstable to $BF_3.Et_2O$, but that the acylation could be effected, albeit in low yield, under basic conditions (Scheme 43)[15].

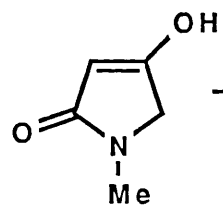
SCHEME 43



(109)



(109) —i→ Bu - 2313B (13) 11 %



(109) —ii→ Bu - 2313A (12) 6 %

Reagents : i, KO^{t}Bu, DMF ; ii, NaH, DMF

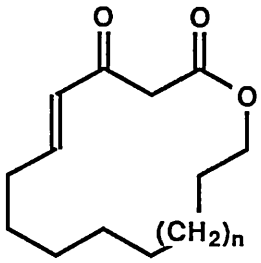
To date, no studies have been carried out into the question of whether any racemisation occurs at the C-5 position when this approach is used.

As mentioned earlier, the active ester acylation used by van der Baan might prove to be a good general method for 3-acylation under mild conditions, and if this were so, would certainly see wide application in the synthesis of 3-acyltetramic acids.

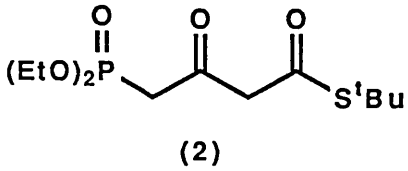
RESULTS AND DISCUSSION

INTRODUCTION

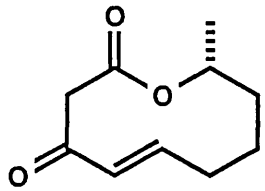
This section is divided into two Parts A and B. In Part A work on constructing unsaturated β-ketomacrolides such as (1) using the thioester phosphonate (2) is described[46]. The application of this methodology to the synthesis of natural products, in particular diplodialide A(3)[47] is discussed.



(1)



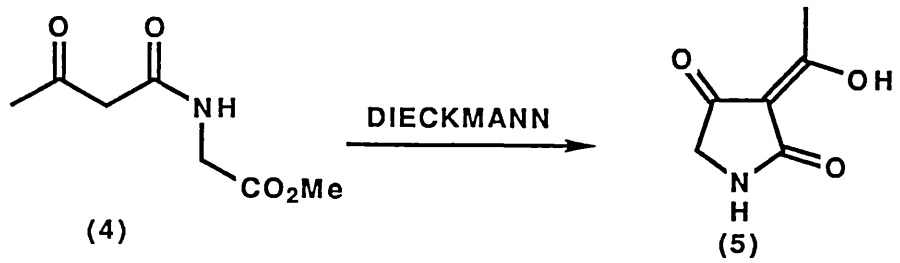
(2)



(3)

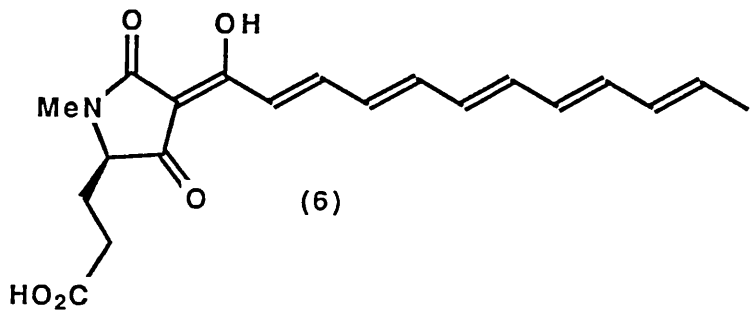
In Part B the conversion of β-ketothioesters into β-ketoamides[48] is discussed together with studies on the Dieckmann reaction of β-ketoamide esters such as (4) to give 3-acyltetramic acids (5, Scheme 1).

SCHEME 1

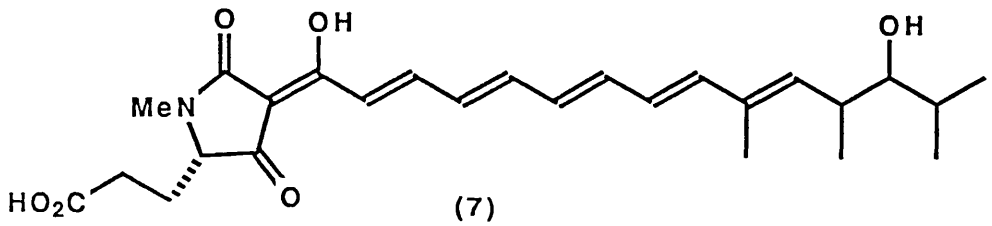


(4) (5)

The application of this methodology to the synthesis of the 3-acyltetramic acid natural products fuligorubin A(6)[8] and β-lipomycin (7)[10] is described.



(6)

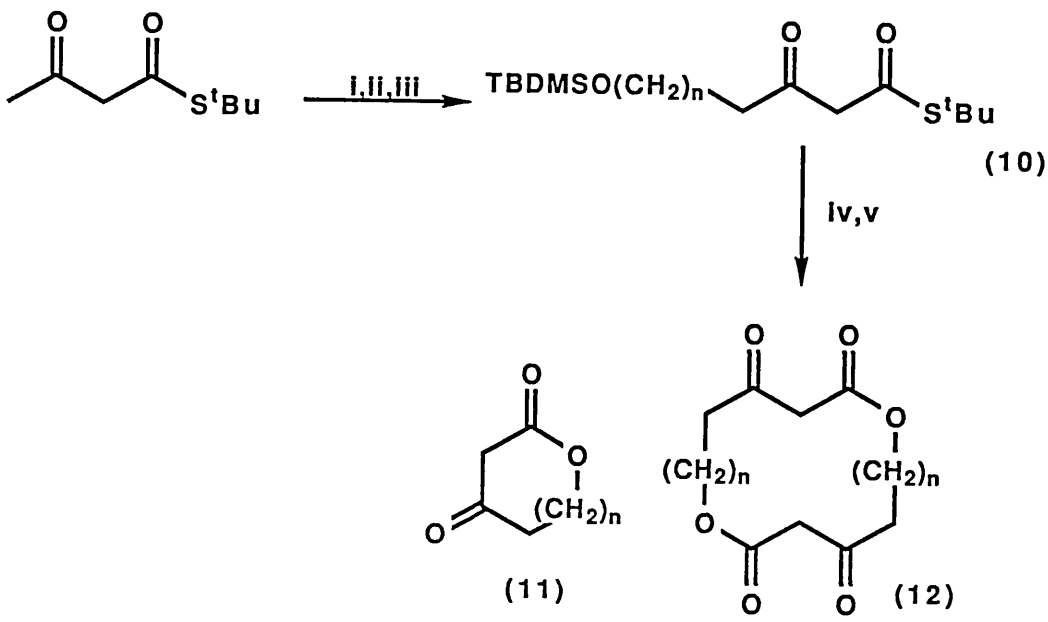


(7)

PART A: THE SYNTHESIS OF MACROLIDES AND DIOLIDES

Previous work[49] has established methodology for the conversion of β-ketothioester alcohols into monolides (11) and diolides (12) (Scheme 2).

SCHEME 2



Reagents : i, NaH, DME ; ii, ^{n}BuLI ; iii, I(CH$_2$)$_n$OTBDMS (9); iv, HF, H$_2$O, MeCN ; v, Cu(1)OCOCF$_3$, CH$_2$Cl$_2$, Na$_2$HPO$_4$

TABLE I

Entry	n	Monomer (11) % yield [ring size]	Dimer (12) % yield [ring size]
1	4	- [9]	38 [18]
2	5	- [10]	49 [20]
3	6	- [11]	42 [22]
4	8	12 [13]	42 [26]
5	11	72 [16]	8[a] [32]
6	11	62 [16]	16[b] [32]

a) Addition of thioester as 0.06M solution in CH_2Cl_2.

b) Addition of thioester as 0.19M solution in CH_2Cl_2.

Alkylation of the dianion of ^{t}butyl acetothioacetate (8) with the protected iodoalcohols (9) gave the substituted β-ketothioesters (10). Deprotection of the alcohols with HF[50] and treatment with copper(I) trifluoroacetate in CH_2Cl_2 afforded mixtures of monolide and diolide.

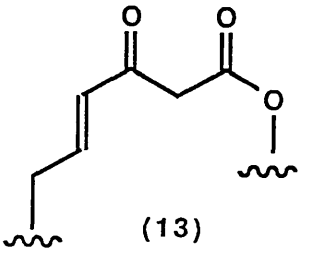
The exact ratio of the products (11) and (12) depended on the dilution and more markedly on the length of the carbon chain of the thioester alcohol (Table I).

It can be seen from the table that as the chain length of the thioester alcohol increases monomer formation becomes more favourable.

When n = 11 (entry 5) the major product becomes the monolide due to the ease of formation of 16-membered lactones.

The dependence of ring size on reaction conditions is demonstrated in entry 6 where conditions favouring dimer formation are used with a resulting decrease in the monolide-diolide ratio. All experiments were carried out by adding a solution of the thioester alcohol in CH_2Cl_2 (0.06M or 0.19M) to a buffered 0.1M solution of copper(I)trifluoro-acetate (5 equivalents) in CH_2Cl_2.

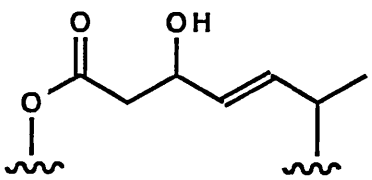
This work has now been extended to the preparation of monolides and diolides containing unsaturation in the 4 position (13)[46].



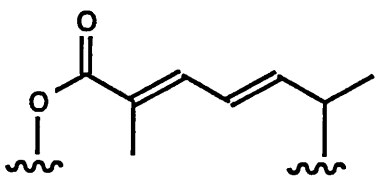
(13)

There is a large number of natural products[51] containing functionality which could in principle be readily derived from this structural arrangement. The relevant partial structures of a few of these compounds are shown diagramatically in Scheme 3.

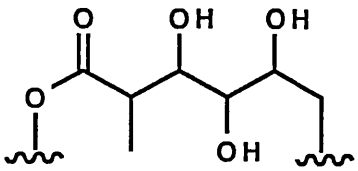
SCHEME 3



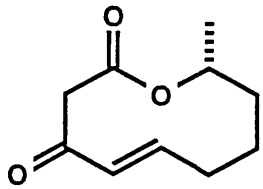
Scopafungins



Azalomycins



Erythromicins

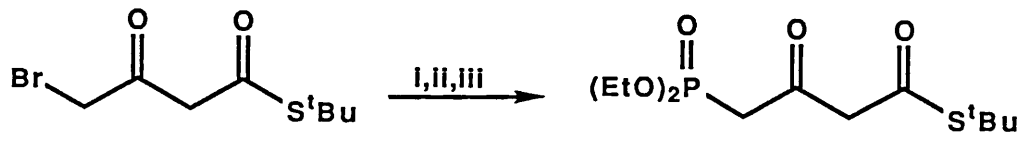


(3)

Diplodialide A (3), one of a family of related natural products[52], contains this precise structural arrangement. Although entry (2) in Table I shows only diolide formation, it was thought that by using conditions strongly favouring monolide formation the desired 10-membered lactone would result.

The unsaturation in (13) was generated using the thioester phosphonate (2). This was prepared by reaction of the sodium salt of diethyl phosphite (15)[53] with the monoanion of the thioester bromide (14, Scheme 4).

SCHEME 4

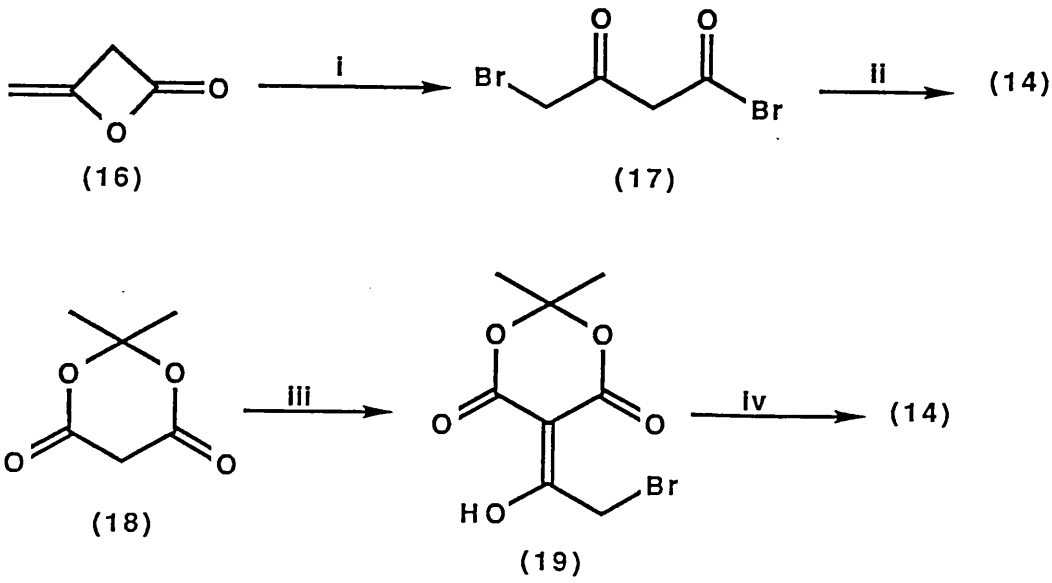


(14) (2)

Reagents : i, NaH, THF ; ii, $NaP(O)(OEt)_2$ (15) ; iii, H^+

Thioester bromide (14) was synthesised by two routes (Scheme 5): the first using diketene (16)[54], the second from Meldrum's acid (18)[55].

SCHEME 5



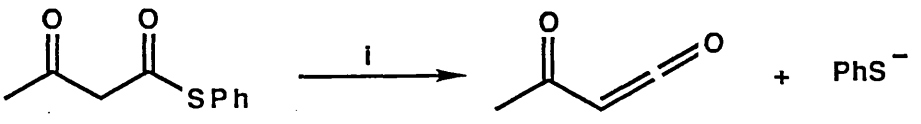
(16) (17) (18) (19)

Reagents : i, Br_2, CCl_4 ; ii, ^{t}BuSH, CH_2Cl_2 ; iii, $BrCH_2COBr$, Pyr, CH_2Cl_2 ; iv, ^{t}BuSH, PhH, reflux

In the first route the bromoacetylacyl bromide (17) was not isolated but treated directly with a solution of 2-methylpropan-2-thiol in CH_2Cl_2 to give the desired bromide (14) in 73% overall yield. Acyl bromides have not previously been used in the preparation of thioesters. Masamune has used acyl chlorides but these require the use of the thallium (I) salt of the thiol to give good yields of the thioesters[56]. The generality of this reaction has not been investigated.

The second route to the thioester bromide (14) involved the novel thiol ring opening of the acylated Meldrum's acid derivative (19) in an overall yield of 75% from Meldrum's acid (18).

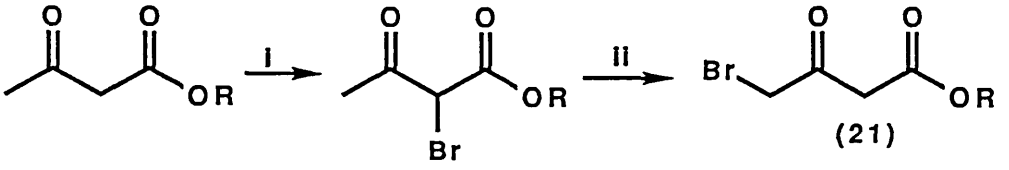
The use of 2-methylpropan-2-thiol as the thioester thiol group was based on previous β-ketothioester experience where it was found that phenylthioesters underwent facile elimination upon anion formation at the 2-position. Similar problems occurred with SMe and SEt.



Reagents : i, NaH, DME

Several other routes to the bromide (14) were also investigated but were found to be unsuccessful. It has been shown that β-ketoesters may be brominated at the α-position (20) and the product rearranged by passing air through a solution of (20) affording the γ-bromoketoester (21, Scheme 6)[57].

SCHEME 6



(20) (21)

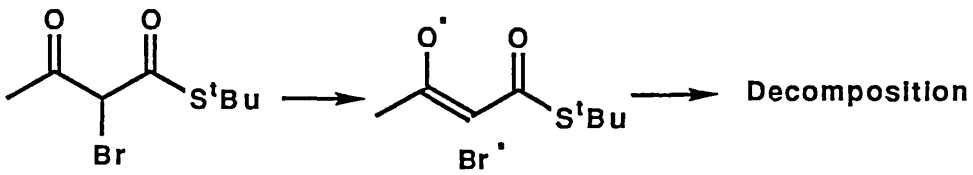
R = alkyl

Reagents : I, Br_2, $CHCl_3$; II, air blown through reaction

By analogy the α-bromothioester (22, Scheme 7) was prepared by adding bromine to a cooled solution of the β-ketothioester in CH_2Cl_2. However, despite extensive effort the bromide (22) would not rearrange to the desired compound either under the conditions described above or by the addition of radical promotors (AIBN or dibenzoyl peroxide) followed by irradiation with light. All attempts to effect the α to γ bromine migration resulted in complete decomposition of the compound. None of the γ-bromothioester (14) was isolated from the resultant complex reaction mixtures.

It is possible that the rearrangement occurs by a free radical mechanism and the failure of the reaction may be due to the bromine radical preferentially migrating to the halophilic sulphur atom of the thioester thereby promoting a decomposition process (Scheme 7).

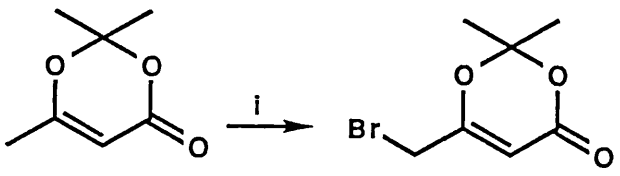
SCHEME 7



(22) (23)

The only product that could be isolated in reasonable amounts was ^{t}butyl disulphide. Another approach centred on the bromide (25)[31] which was available from the acetone-diketene adduct (24, Scheme 8)[58].

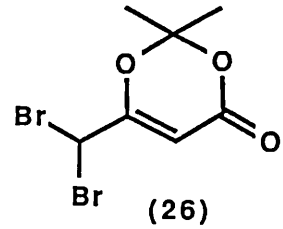
SCHEME 8



(24) (25)

Reagents : i, NBS, CCl_4, Benzoyl Peroxide

Allylic bromination with N-bromosuccinimide of the adduct (24) afforded a mixture of products comprising of starting material (24), the desired bromide (25), and some dibromide (26).

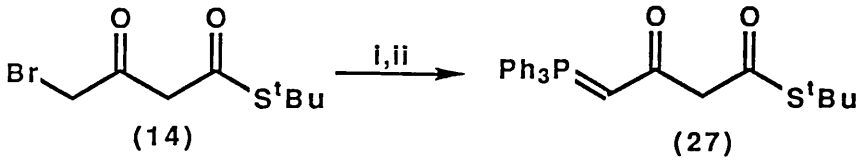


(26)

Unfortunately the best isolated yield of (25) was 35% and the opening of (25) with ^{t}butyl thiol proved troublesome. Therefore this approach was abandoned.

With two viable routes to the required bromothioester (14) now available attention was initially focused on the preparation of the phosphorane (27)[59] (Scheme 9).

SCHEME 9

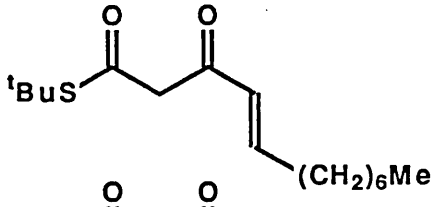
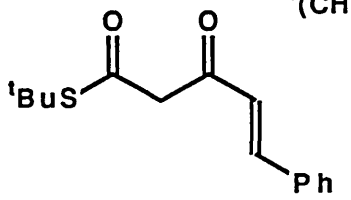


(14) (27)

Reagents : i, Ph_3P, PhH ; ii, $NaHCO_3$, H_2O

The phosphorane (27) was found to react slowly with aldehydes and required forcing conditions to effect olefination (Table II).

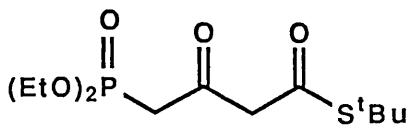
TABLE II

ENTRY	ALDEHYDE	PRODUCT	YIELD/%
1	$CH_3(CH_2)_6CHO$		35
2	PhCHO		15
3	$^tBuMe_2SiO(CH_2)_{10}CHO$	NO PRODUCT ISOLATED	

The products from entries 1 and 2 were found to have exclusively E double bond geometry (J 15.6 and 17.5 Hz respectively).

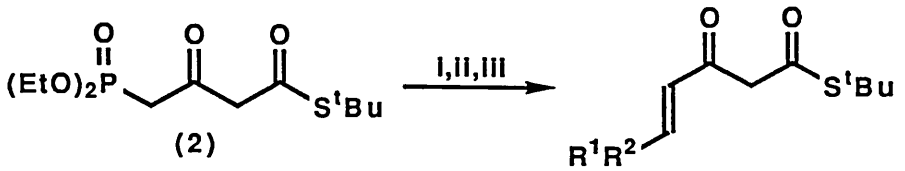
Prolonged heating of the reactants in benzene (48h) was necessary to effect reaction and under these conditions substantial decomposition of the phosphorane occurred.

Attention was therefore transferred to the potentially more reactive phosphonate (2)[60], which was found to react smoothly and in good yield with a variety of aldehydes and ketones (Table III).



(2)

TABLE III : THIOESTER PHOSPHONATE REACTIONS



Reagents : I, 2NaH, THF ; II, Aldehyde or Ketone (R^1R^2CO) ; III, H^+

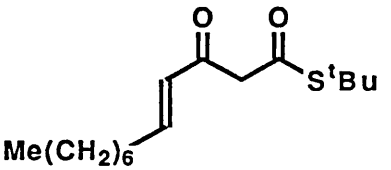
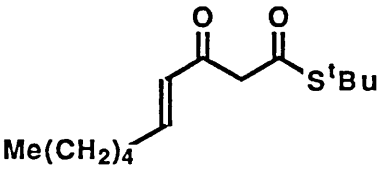
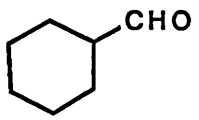
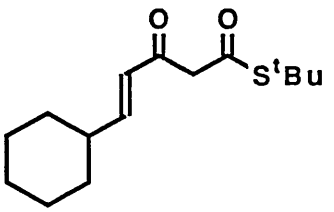
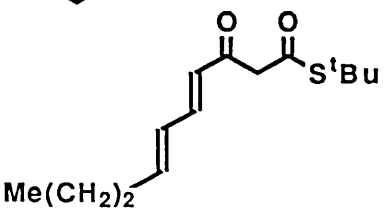
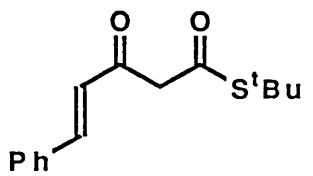
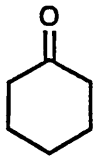
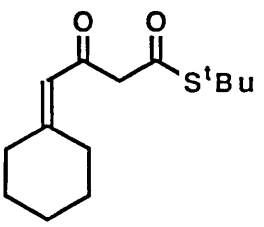
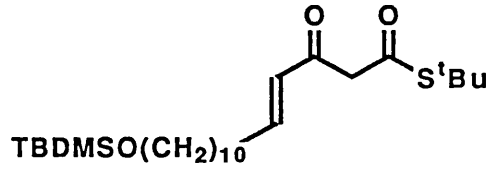
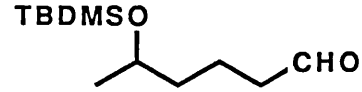
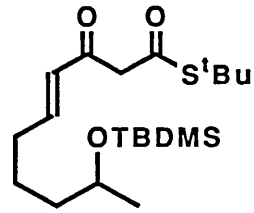
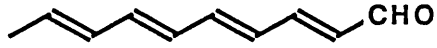
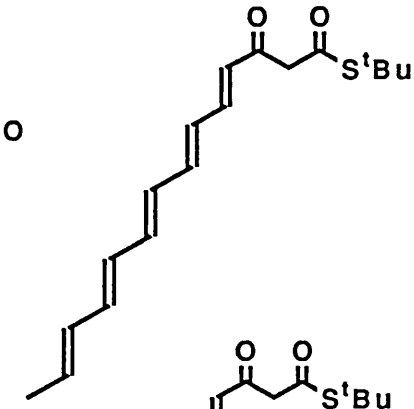
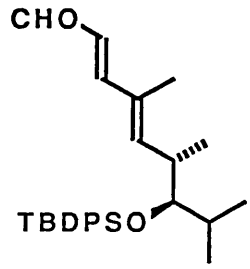
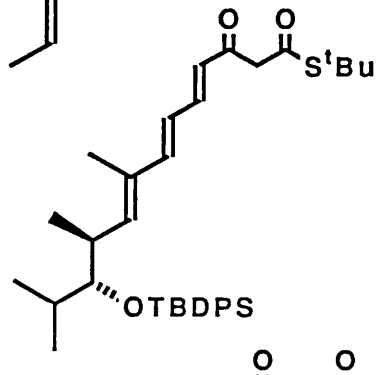
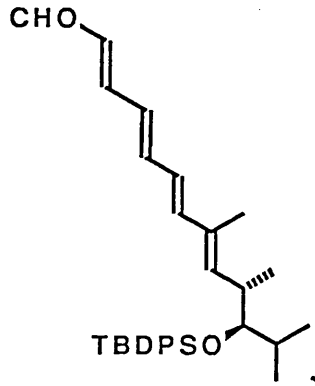
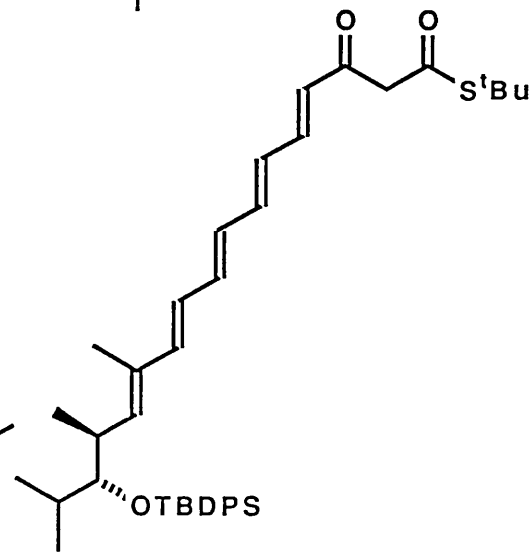
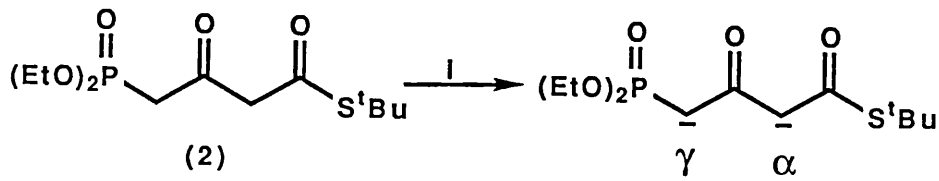
Entry	Aldehyde/Ketone	Product	Yield/%
1	$CH_3(CH_2)_6CHO$		58
2	$CH_3(CH_2)_4CHO$		68
3			81
4			50
5	PhCHO		55
6			68

TABLE III : continued

Entry	Aldehyde/Ketone	Product	Yield/%
7	$TBDMSO(CH_2)_{10}CHO$		84
8			84
9			61
10			77
11			62

Although in deuteriochloroform solution these compounds existed as a mixture of keto and enol tautomers, the geometry of the new double-bond could be unambiguously assigned as E from the olefinic coupling constants of between 15.5 and 18.0Hz.

It is worth commenting on the exact sequence of events occurring in the reaction. Experimentally the reaction involved the addition of a solution of the thioester phosphonate (2) in THF to a suspension of two equivalents of sodium hydride in THF at 0^0C. When the resulting hydrogen evolution had finished, generally after 15 to 20 minutes, the aldehyde or ketone was added. It has been generally assumed[61/62] that sodium hydride doubly deprotonates the phosphonate giving the α,γ-dianion (28).

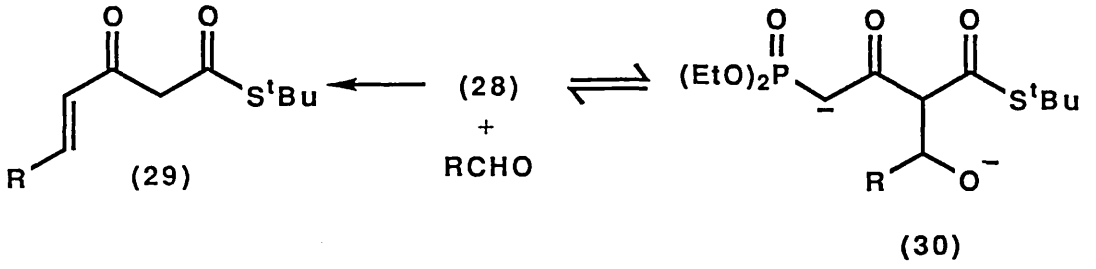


(2) (28)

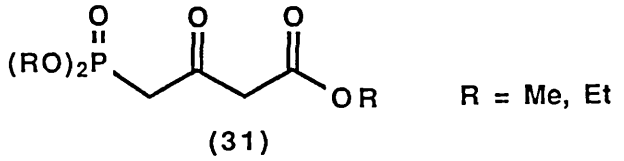
Reagents : I, 2NaH

The dianion (28) subsequently either undergoes an irreversible Emmons-Wadsworth reaction[60] with the carbonyl compound *via* the γ-position to give the desired unsaturated product (29) or reacts through the α position in a reversible aldol reaction (30) as shown in Scheme 10.

SCHEME 10

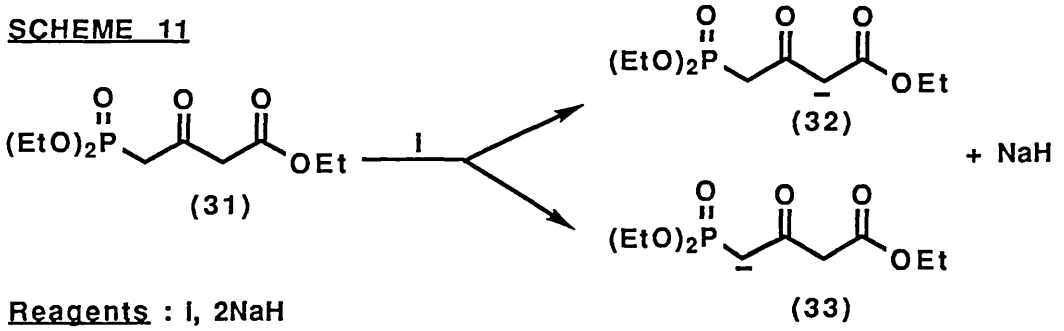


However it was noticed that when the carbonyl compound was added, the evolution of hydrogen soon recommenced. This has also been observed in the reactions of the oxygen analogue (31) of the thioester phosphonate and an explanation for this observation has been recently proposed by Schneider *et al*[63].



It was suggested that rather than double deprotonation occurring to give the dianion, single deprotonation occurs to give an equilibrium mixture of α and γ monoanions (32) and (33) respectively (Scheme 11).

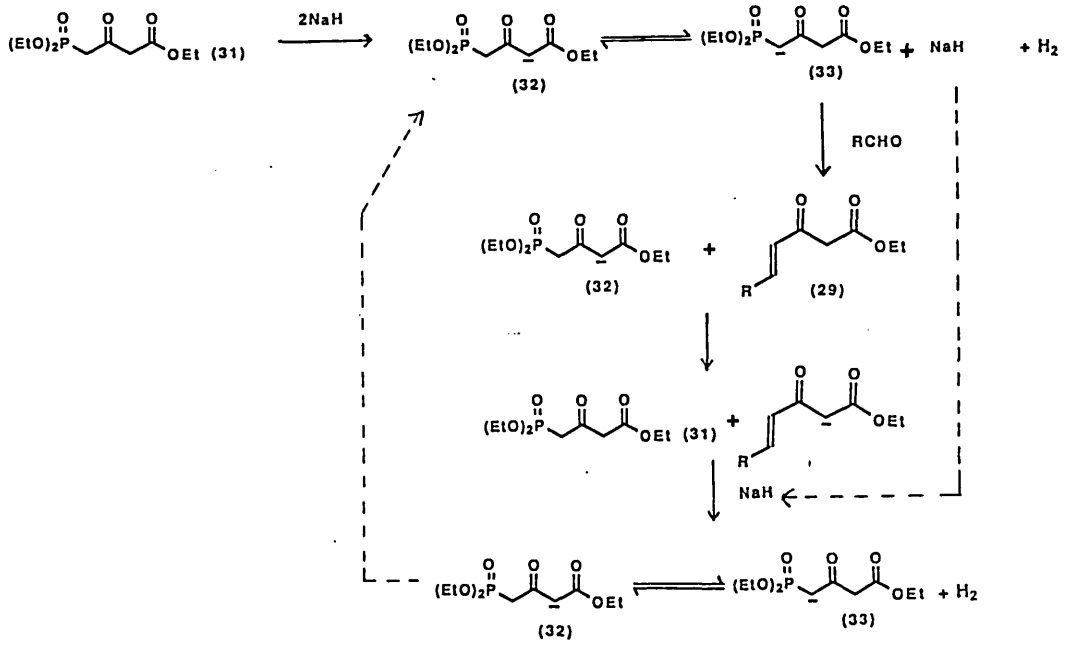
SCHEME 11



Reagents : I, 2NaH

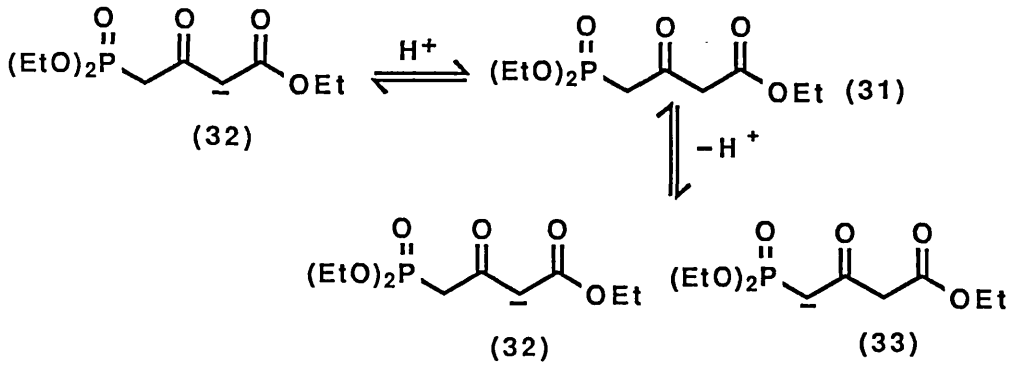
On the addition of the aldehyde the γ-anion (33) reacts more rapidly to give the expected unsaturated product. It is suggested by Schneider that the α-anion (32) deprotonates the unsaturated product and that the remaining equivalent of sodium hydride present then reacts with the now reprotonated phosphonate (i.e. 31) at the α or γ positions and the reaction cycle begins again. It is this second deprotonation which results in the evolution of hydrogen observed after the aldehyde has been added. The final reaction mixture will contain the deprotonated unsaturated product as shown diagramatically in Scheme 12.

SCHEME 12



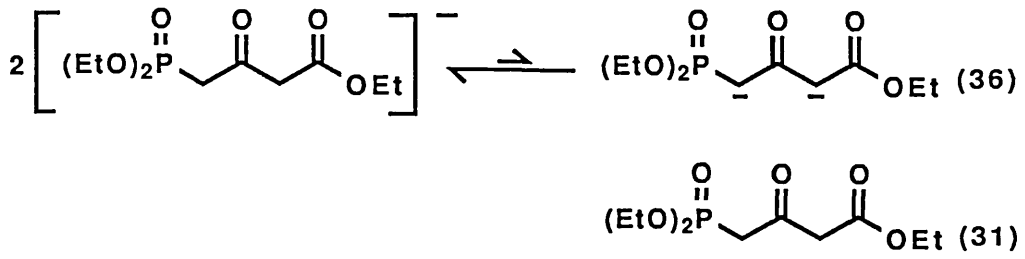
For an equilibrium to exist between the α and γ-anions some kind of proton donor must be present to enable this process to occur (Scheme 13).

SCHEME 13



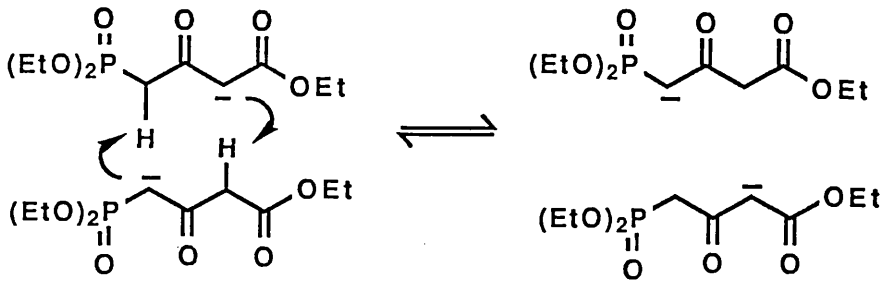
Proton donation could occur <u>via</u> the intermediacy of the phosphonate dianion (36) which would only have to be present in very low concentrations (Scheme 14).

SCHEME 14

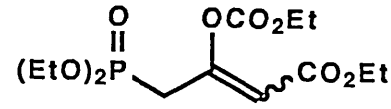


Another possibility is that proton transfer could occur by a bimolecular process as in Scheme 15.

SCHEME 15



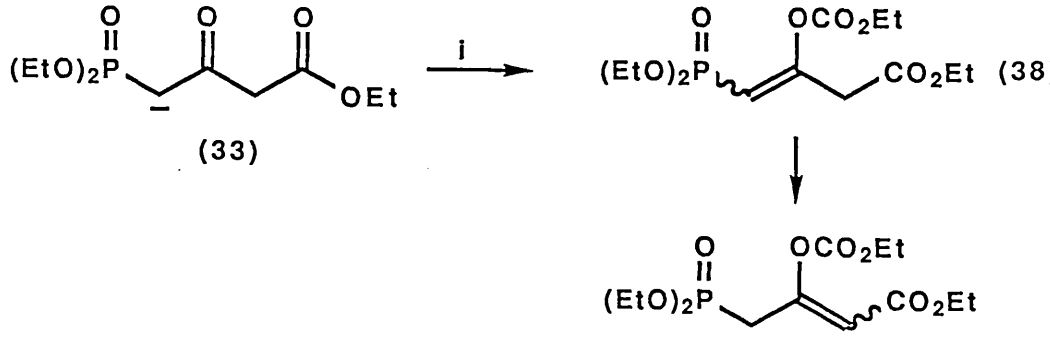
Unfortunately the existence of this α to γ monoanion equilibrium was not demonstrated particularly well by Schneider. It was found that quenching a mixture of the monoanions with ethyl chloroformate gave a product (37) that could possibly have resulted from the α-monoanion only.



(37)

It is possible that this product was actually derived from a mixture of the α and γ monoanions and that double bond isomerisation occurred in the product of the γ-anion (Scheme 16).

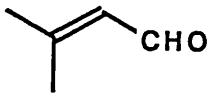
SCHEME 16



(33) (38) (37)

Reagents : i, $ClCO_2Et$

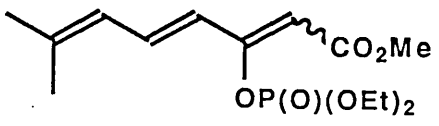
Along with the second evolution of hydrogen, the best evidence for this mechanism comes from the observation that the yields of the reaction are considerably higher when 2 equivs. of sodium hydride are used instead of 1, as the following example illustrates.



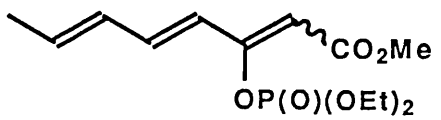
	1 Equiv	2 Equiv
	21 %	53 %

Using one equivalent of sodium hydride will result in incomplete reaction since the recycled phosphonate will not be re-deprotonated.

The presence of deprotonated, unsaturated product was demonstrated by quenching the 3-methylbut-2-enal and crotonaldehyde reaction mixtures with diethyl chlorophosphate to give the products (39) and (40) respectively.



(39)

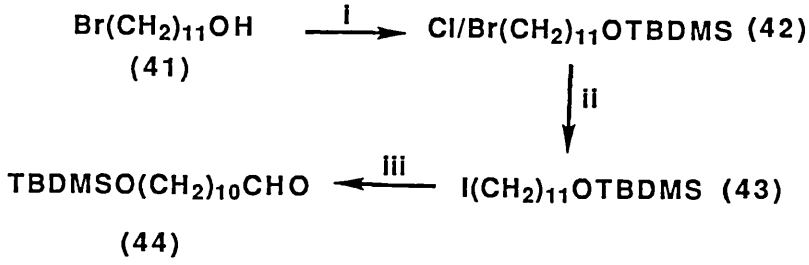


(40)

Schneider found it necessary to use one equivalent of sodium hydride followed by one equivalent of ^{n}BuLi in order to generate the dianion.

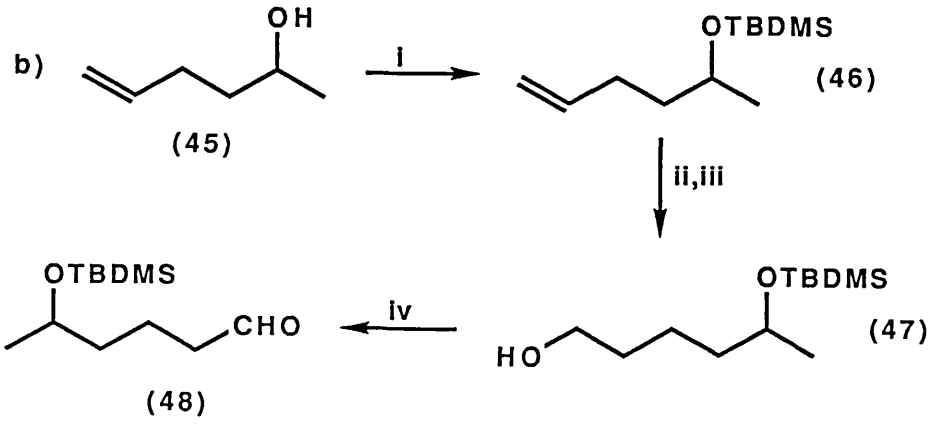
Aldehydes (44) and (48) {entries (7) and (8) in Table III} were prepared as outlined (Schemes 17 and 18 respectively).

SCHEME 17



Reagents : i, TBDMSCl, DMF, Imidazole ; ii, NaI, Acetone ; iii, DMSO, $NaHCO_3$

SCHEME 18



Reagents : i, TBDMSCl, DMF, Imidazole ; ii, BH_3.DMS, THF ; iii, H_2O_2 then NaOH, H_2O ; iv, PCC, CH_2Cl_2

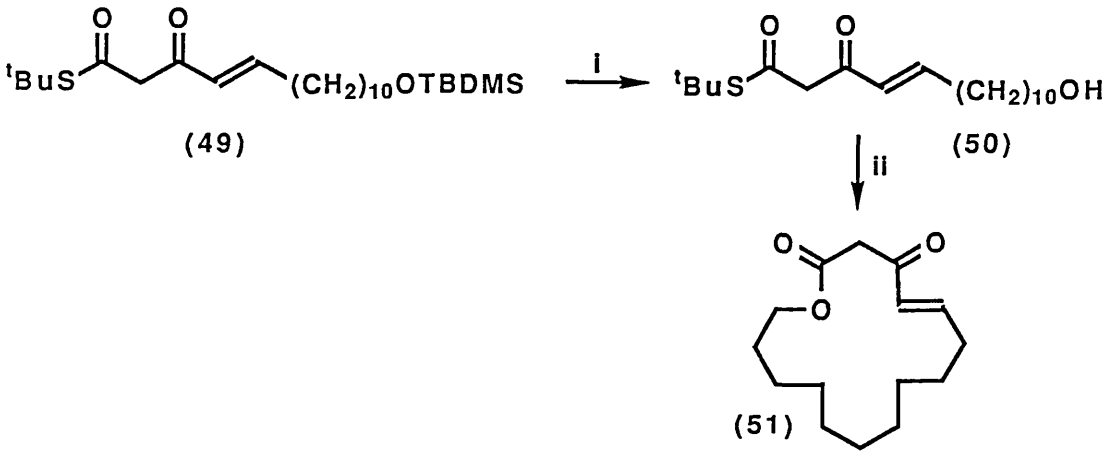
In Scheme 17 ^{t}butyldimethylsilyl protection[64] of the commercially available alcohol (41) caused some trans-halogenation of the bromide to give a 3:2 mixture of the bromide and chloride (42). This mixture was converted to the iodide (43, 87% overall) under Finkelstein conditions[65]. Kornblum reaction[66] of the iodide gave the desired aldehyde (44).

In Scheme 18 the commercially available alkene alcohol (45) was protected and then subjected to hydroboration with borane-dimethyl sulphide complex followed by oxidative workup[67] to give the terminal alcohol (47). Oxidation of (49) with PCC[68] gave the required aldehyde (48).

The preparation of the aldehydes and the significance of the products of entries 9, 10, and 11 in Table III will be described and discussed later in Part B.

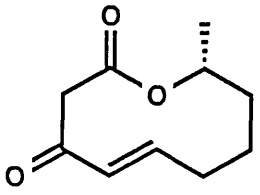
The product of entry 7 in Table III (49) was deprotected with HF[50] to give the alcohol (50) which on treatment with five equivalents of freshly prepared copper(I) trifluoroacetate gave the 16-membered monolide (51) in 35% yield (Scheme 19).

SCHEME 19

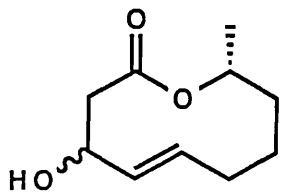


Reagents : i, HF, H_2O, MeCN ; ii, $Cu(I)OCOCF_3$, CH_2Cl_2, Na_2HPO_4

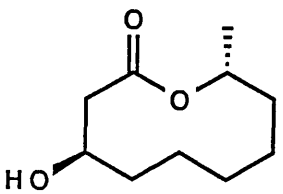
An X-ray crystallographic structure of (51) is shown on page (80). The product from entry 8 in Table III (55) on deprotection and lactonisation would give the racemate of the natural product diplodialide A (3) which is one of four 10-membered lactones (3, 52 to 54) isolated from Diplodia pinea by Wada[47/52].



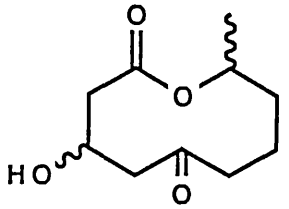
(3)
DIPLODIALIDE A



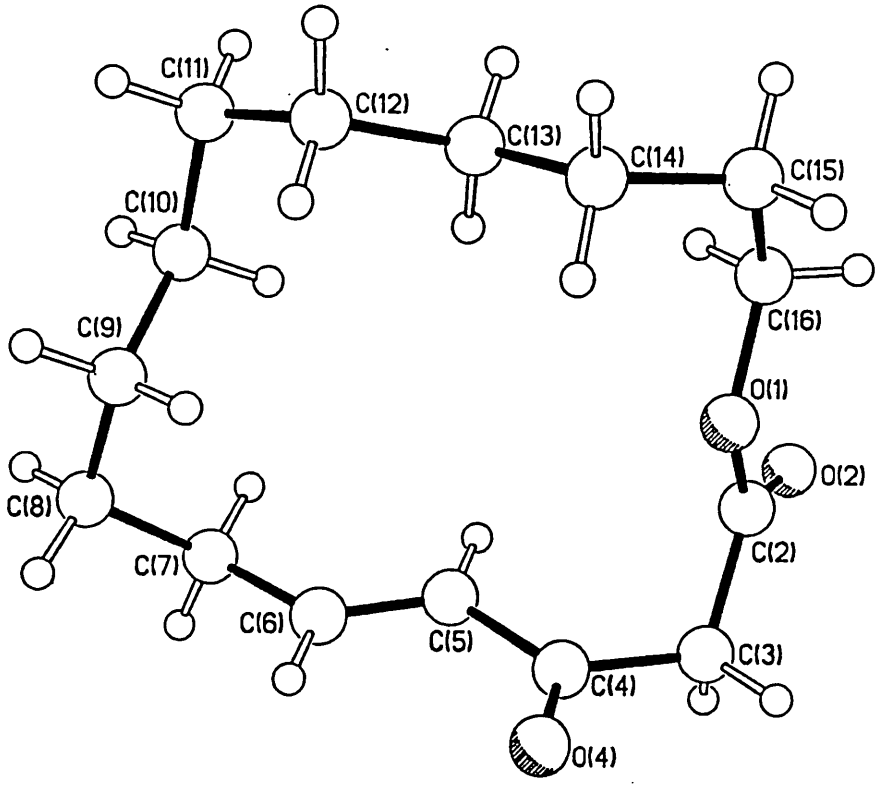
(52)
DIPLODIALIDE B



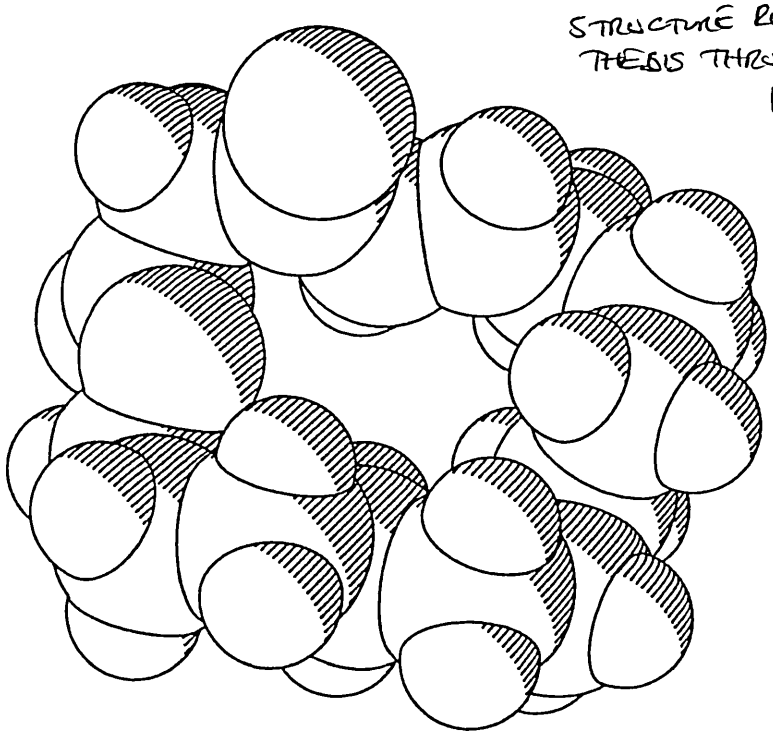
(53)
DIPLODIALIDE C



(54)
DIPLODIALIDE D



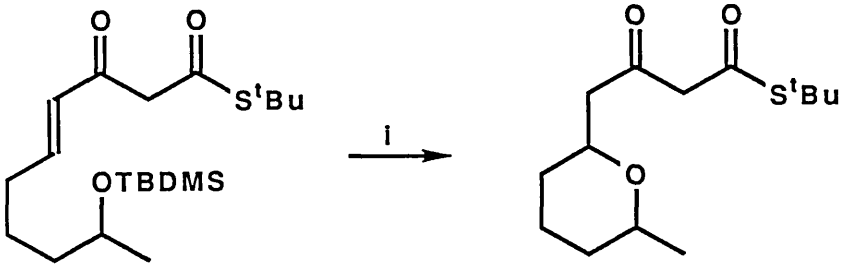
TO VIEW AS ABOVE STRUCTURE ROTATE THESIS THROUGH 180°.



Deprotection of (55) and cyclisation would constitute a short, concise synthesis of diplodialide A and would be a considerable improvement on the reported syntheses (see later).

Deprotection of (55) was initially attempted using HF but this gave the tetrahydropyran (56) as a mixture of diastereoisomers. Clearly these products resulted from deprotection of the silyl ether and subsequent Michael addition of the alcohol to the conjugated double bond (Scheme 20).

SCHEME 20

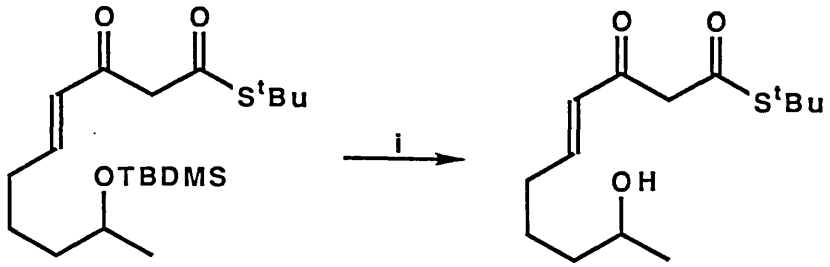


(55) (56)

Reagents : i, HF, H_2O, MeCN

However the use of two or more equivalents of tetra-n-butylammonium fluoride (TBAF)[69/70] solved the problem and gave the desired product (57) in 85% yield (Scheme 21).

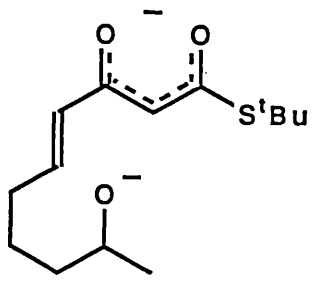
SCHEME 21



(55) (57)

Reagents : i, TBAF, THF

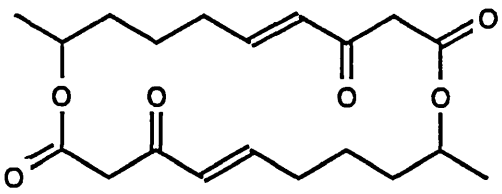
Under these basic conditions, deprotection and loss of the α-proton may occur with the delocalisation of the resulting negative charge formed by α-proton removal effectively removing the double bond from conjugation (58).



(58)

However all attempts to cyclise the thioester alcohol (57) failed to produce any of the desired monomeric product even though a range of thiophilic metals were tried [copper(I), silver(I), mercury(II), and nickel(II)] under a number of dilution conditions.

Treatment of (57) with freshly prepared copper(I) trifluoroacetate in dry degassed CH_2Cl_2 in the presence of Na_2HPO_4 buffer led to the rapid consumption of starting material and the formation of one major, more polar product by TLC. Work-up with saturated ammonium chloride solution containing ammonia (to remove Cu(II) species) followed by chromatography gave a colourless oil. The ^1H n.m.r. spectrum of the product was similar to that reported for diplodialide A except that it indicated the presence of diastereoisomers (which of course could not be present in the monolide structures) and mass spectral evidence confirmed that the product was in fact the diolide (59).



(59)

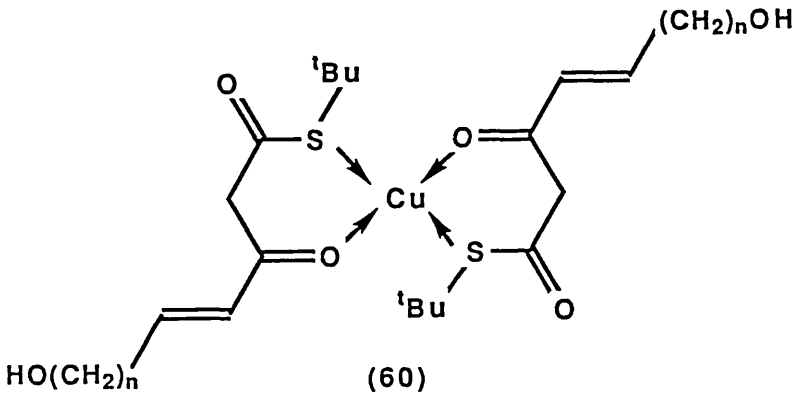
Even under conditions designed to strongly favour monolide formation [a highly dilute solution of thioester alcohol (0.18mmol dm^{-3}, 50mg dm^{-3}) in CH_2Cl_2 added very slowly (over six hours) to a stirred solution of a large excess of copper(I) trifluoroacetate (100 equivalents in 10ml of CH_2Cl_2)] none of the monolide was isolated.

Use of other thiophilic metals {Ag(I), Hg(II), or Ni(II)} afforded none of the dimer, only the pyran (56) or polymeric material resulted.

The failure of the lactonisation reaction to give any of the monomeric product was probably a consequence of the lack of the necessary conformational freedom in the thioester alcohol to allow intramolecular reaction to occur. The use of the Cu(I) mediated macrolactonisation has also been shown to favour diolide formation using shorter chain thioester alcohols[49].

A molecular model of the keto tautomer of the thioester alcohol showed that although the necessary intramolecular approach of the alcohol to the thioester could theoretically occur, it would require extensive conformational reorganisation.

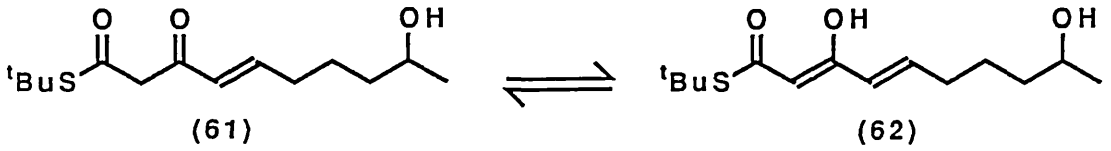
The copper(I) trifluoroacetate system seems to be unique among the thiophilic metals used in promoting diolide formation with β-ketothioester alcohols and a possible mechanistic explanation of this diolide preference could be the initial formation of a Cu(I) complex involving two molecules of the β-ketothioester alcohol (60).



(60)

The Cu(I) ion has a coordination sphere of 4 and is thus capable of accepting these two bidendate ligands. If there is insufficient length in the alcohol chain of the coordinated thioester alcohol, formation of the monolide becomes difficult, making intermolecular reaction between the two coordinated ligands a more favourable process yielding the diolide. When Cu(I) is used for these cyclisations very little of the higher order lactones (triolides, tetralides, etc.) are formed, monolides and/or diolides being the major products.

Intramolecular cyclisation would be expected to occur more favourable <u>via</u> the keto tautomer because of the greater conformational flexibility associated with it. The ^{1}H n.m.r. spectrum of the initial thioester alcohol showed it to exist as a 1:1 mixture of the two keto-enol tautomers (61 and 62 respectively).



(61) (62)

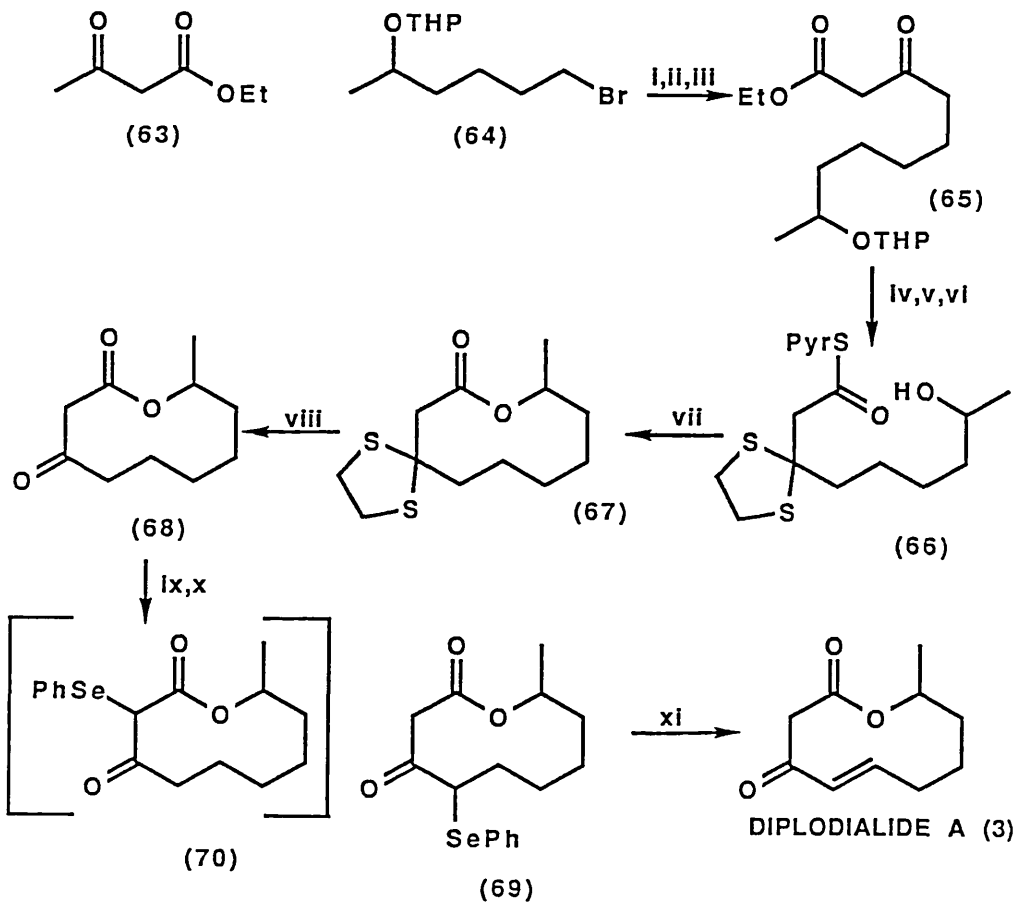
However the presence of some of the thioester alcohol as the enol tautomer is unlikely to have any effect on the lactonisation process since the rate of proton transfer and thus keto-enol tautomer interconversion would be considerably faster than the transesterification reaction.

It is instructive at this point to examine the two diplodialide A syntheses which used a lactonisation process as the ring forming reaction and to comment on the methods used to effect this cyclisation.

These syntheses of diplodialides using 2-pyridylthioesters have been published by Wada[52] and Gerlach[71] (Schemes 22 and 23 respectively).

SCHEME 22

Wada and Ishida [52]



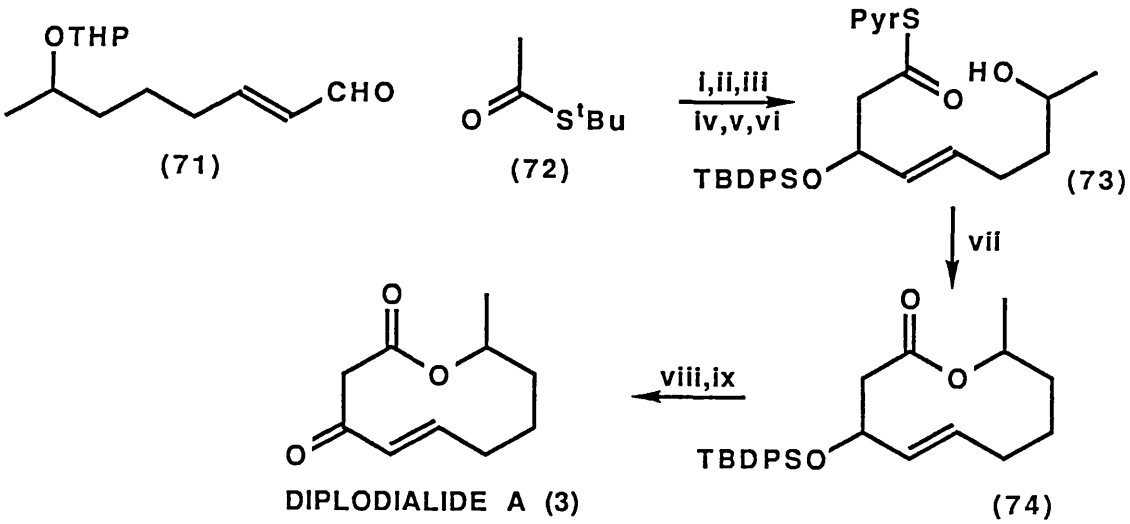
Reagents : i, NaH, HMPA ; ii, ^{n}BuLi then (64) ; iii, H^{+} ; iv, $(HSCH_2)_2$, $BF_3.Et_2O$; v,KOH, MeOH, H_2O ; vi, 2,2'-Dipyridyl disulphide, Ph_3P, MeCN ; vii, Heat, Xylene ; viii, NBS, Acetone, H_2O ; ix, LDA, HMPA, PhSeBr, THF ; x, H^{+} ; xi, 3% H_2O_2, CH_2Cl_2, O deg.C.

Alkylation of the dianion of ethyl acetoacetate (63) with the THP protected bromide (64) gave the β-ketoester (65). Protection of the ketone as the dithiolane, hydrolysis of the ester, conversion to the 2-pyridyl thioester followed by THP removal gave (66).

Thermal cyclisation of (66) afforded the lactone (67) in 38% yield which on treatment with NBS/acetone gave dihydrodiplodialide (68). Treatment of the dianion of (68) with phenylselenyl bromide gave a separable mixture of the selenides (69) and (70) in a 4:3 ratio respectively. Finally, oxidation of the selenide (69) to the selenoxide and syn elimination afforded diplodialide A (3).

SCHEME 23

GERLACH et al [71]

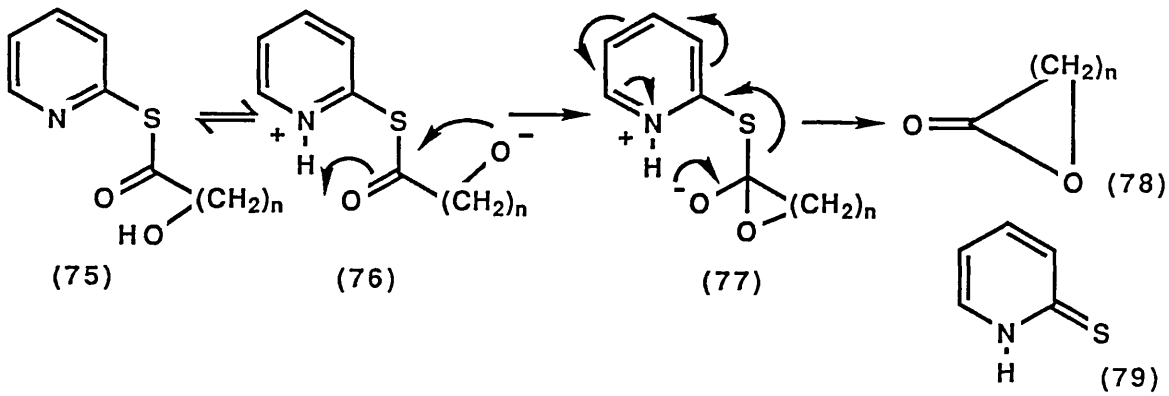


Reagents : i, LDA ; ii, H^+ ; iii, TBDPSCl, Imidazole, DMF ; iv, TsOH, MeOH ; v, $AgNO_3$, H_2O ; vi, 2,2'-Dipyridyl disulphide, Ph_3P ; vii, $AgClO_4$, Dioxane, H_2O ; viii, TBAF, THF ; ix, MnO_2

In the second synthesis of diplodialide A (Scheme 23) aldol reaction between the ^{t}butylthioester (72) and unsaturated aldehyde (71) followed by protection of the generated alcohol, thioester hydrolysis, conversion to the 2-pyridyl thioester and deprotection of the other alcohol gave (73). In this case lactonisation to (74) was achieved in 67% yield using the milder $AgClO_4$ mediated cyclisation. Deprotection and oxidation gave diplodialide A (3).

Although a thioester lactonisation, the mechanism of the 2-pyridylthioester cyclisation is significantly different from that involving ^{t}butylthioesters. Corey[72] has tentatively proposed a mechanism involving a double activation process (Scheme 24).

SCHEME 24



Both the carboxyl and hydroxyl group are activated by proton transfer from hydroxyl to carboxylic oxygen. This process is clearly more favoured in the 2-pyridylthioester than ordinary thioesters due to the greater stability of the dipolar intermediate (76), which can then undergo a facile, electrostatically driven cyclisation to (77) yielding the lactone (78) by elimination of 2-pyridinethione (79). Kinetic studies conducted later by Wollenberg[73] have substantiated this mechanism. The modification used by Gerlach of adding $AgClO_4$ to the reaction medium accelerates the reaction due to the metal-sulphur co-ordination which occurs leading to a more electrophilic carbonyl centre. Even with this "double activation" approach the reactions still needed to be carried out at high dilution.

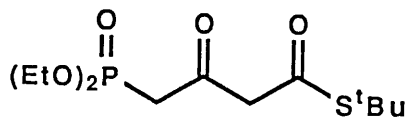
In the light of the proposed mechanism for Cu(I) mediated thioester alcohol lactonisation and the two syntheses described above, the most likely steps that could have been taken to ensure intramolecular reaction would have been removal of the 3-keto functionality in the thioester alcohol and conversion of the ^{t}butylthioester into a 2-pyridylthioester.

Removing the 3-keto functionality of the thioester alcohol and replacing this with e.g. 3-OTHP would have resulted in a molecule which would have chelated less readily with the Cu(I). However these modifications would detrimentally add to the length of the overall synthesis.

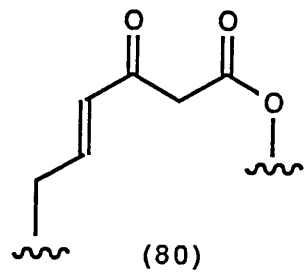
In summary it has been shown that the thioester phosphonate (2) is a highly satisfactory reagent for use in the construction of monolides and diolides containing the functionality below (80) and was found to react with a variety of aldehydes and a ketone to give double bonds of exclusively (E) geometry in good yield. In the appropriate cases these can be transformed into monolides and diolides.

The failure of the diplodialide A synthesis was due to the unsuitability of the thioester alcohol (57) for the Cu(I) mediated intramolecular lact onisation procedure.

NO SPACE



(2)

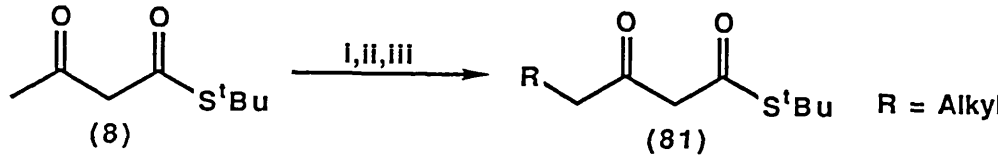


(80)

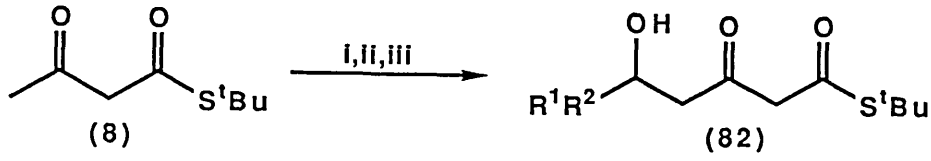
PART B: β-KETOAMIDES AND 3-ACYLTETRAMIC ACIDS

β-Ketothioesters[46/48/49/74-76] have been shown to be important derivatives of the more well known and synthetically useful β-ketoesters[57/77-81]. Similar to β-ketoesters the dianions obtained from β-ketothioesters (8) may be regiospecifically reacted with alkyl halides to give the γ-alkylated products (81) and reacted with aldehydes and ketones to give alcohols (82, Scheme 25).

SCHEME 25



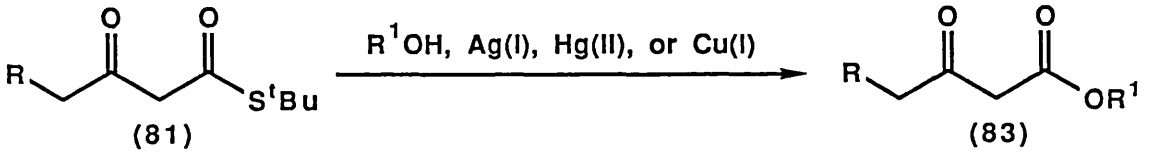
Reagents : i, NaH, DME ; ii, ^{n}BuLi ; iii, RX



R^1 = Alkyl, Aryl
R^2 = H, Alkyl, Aryl
Reagents : i, NaH, DME ; ii, ^{n}BuLi ; iii, R^1COR^2

β-Ketothioesters may be transesterified in the presence of thiophilic metals under mild conditions to give β-ketoesters (83, Scheme 26). Thus β-ketoesters containing R^1 groups with functionality incompatible with the dianion reaction conditions may be readily synthesised.

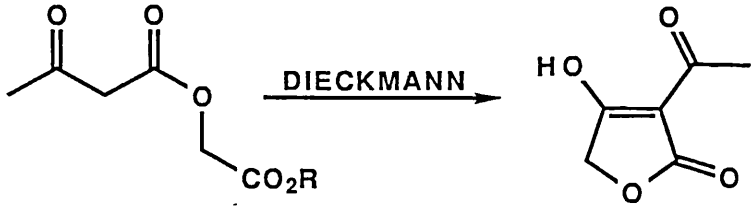
SCHEME 26



R,R^1 = Alkyl

In previous work[74/75] β-ketoesters such as (84) (R = alkyl) were converted by base mediated Dieckmann reaction into 3-acyltetronic acids (85, Scheme 27).

SCHEME 27

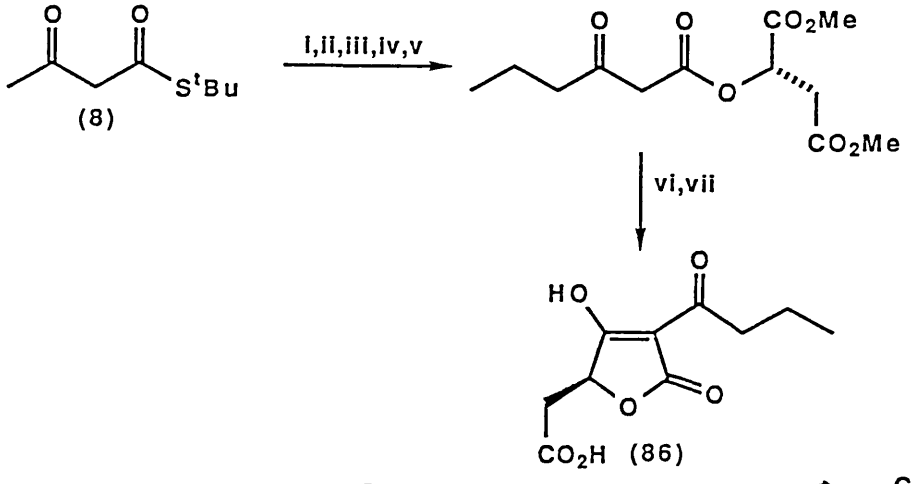


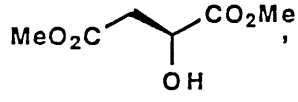
(84) (85)

This methodology was used in the synthesis of the tetronic acid natural products (-) carlosic acid (86), carolic acid (87), and (-) carlic acid (88) as outlined below (Scheme 28)[75].

SCHEME 28

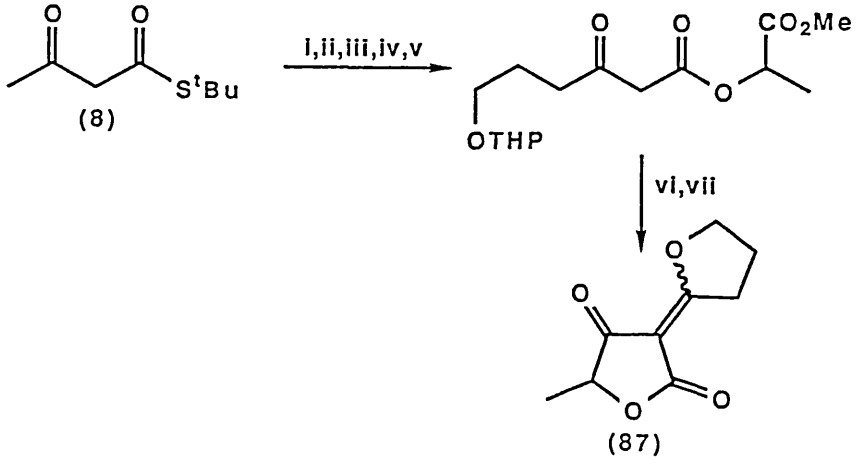
(-) Carlosic Acid :-

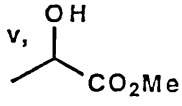


Reagents : I, NaH, DME ; ii, ^{n}BuLi ; iii, EtI ; iv, H^{+} ; v, 

$Ag(I)OCOCF_3$, THF ; vi, TBAF, THF ; vii, 1N HCl

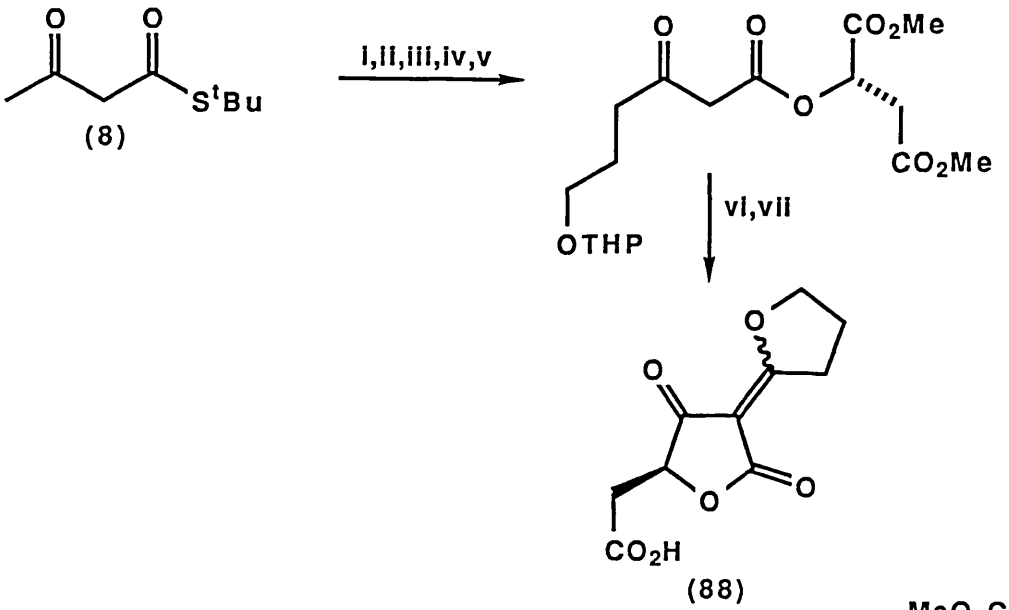
Carolic Acid :-



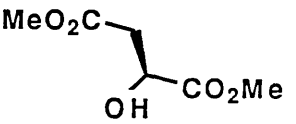
Reagents : I, NaH, DME ; ii, ^{n}BuLI ; iii, $I(CH_2)_3OTHP$; iv, H^{+}; v, 

$Ag(I)OCOCF_3$, THF ; vi, TBAF, THF ; vii, H^{+}

(-) Carlic Acid:-

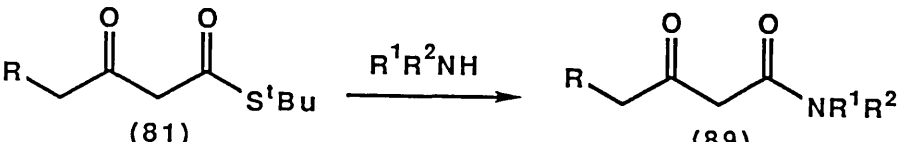


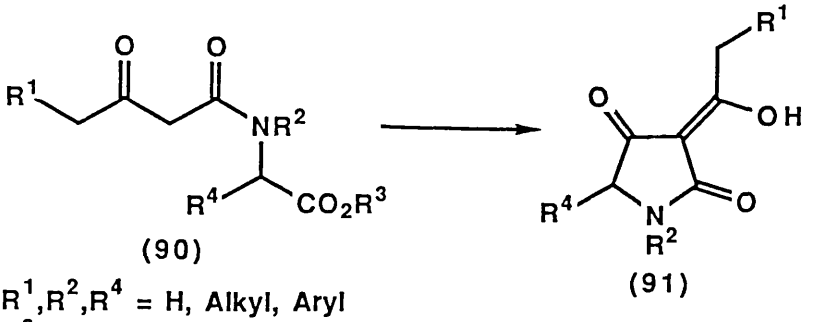
Reagents : i, NaH, DME ; ii, ^{n}BuLi ; iii, $I(CH_2)_3OTHP$; iv, H^+ ; v, $Ag(I)OCOCF_3$, THF ; vi, TBAF, THF ; vii, 1N HCl



A potentially useful extension of this methodology would therefore be the conversion of the β-ketothioesters (81) into β-ketoamides (89) and in the appropriate cases, such as (90), cyclisation into 3-acyltetramic acids (91) as shown in Scheme 29.

SCHEME 29

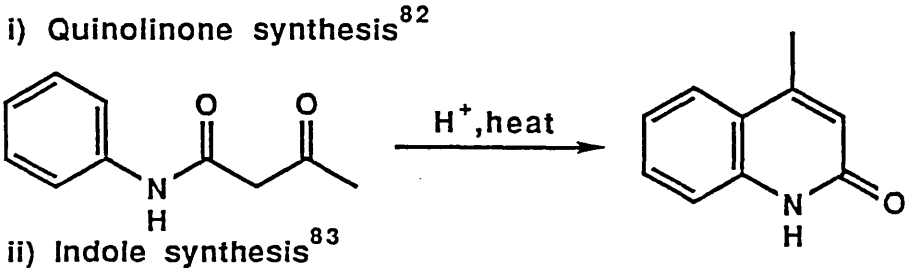




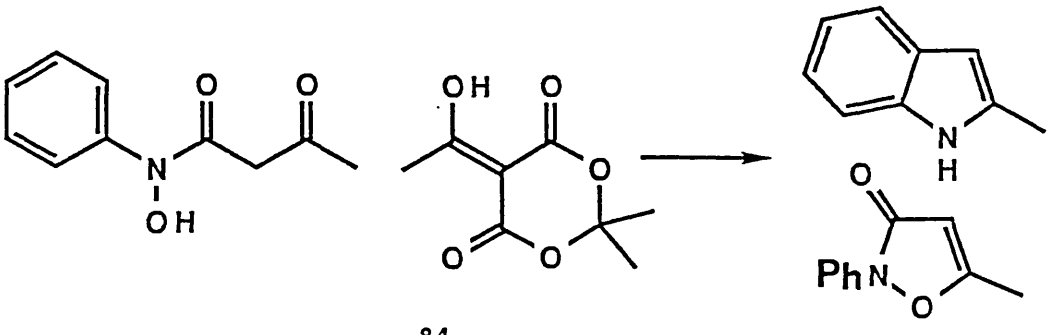
β-Ketoamides are not only important synthetic intermediates for 3-acyltetramic acid preparation but they also find use in a range of heterocyclic syntheses as the following examples show (Scheme 30).

SCHEME 30

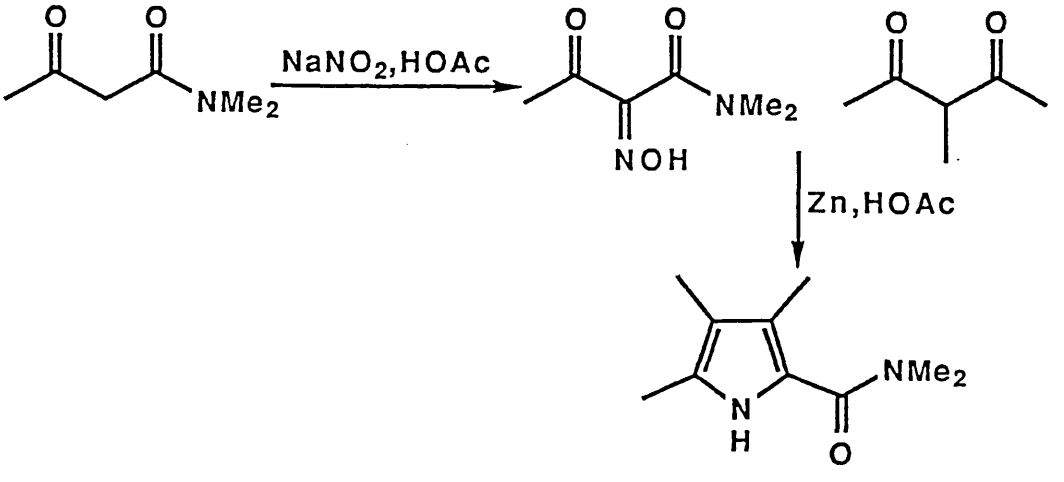
i) Quinolinone synthesis[82]



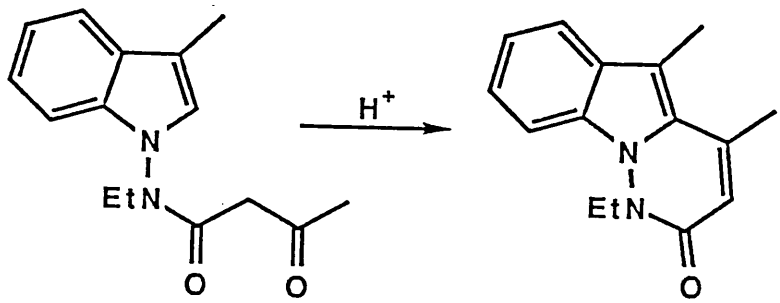
ii) Indole synthesis[83]



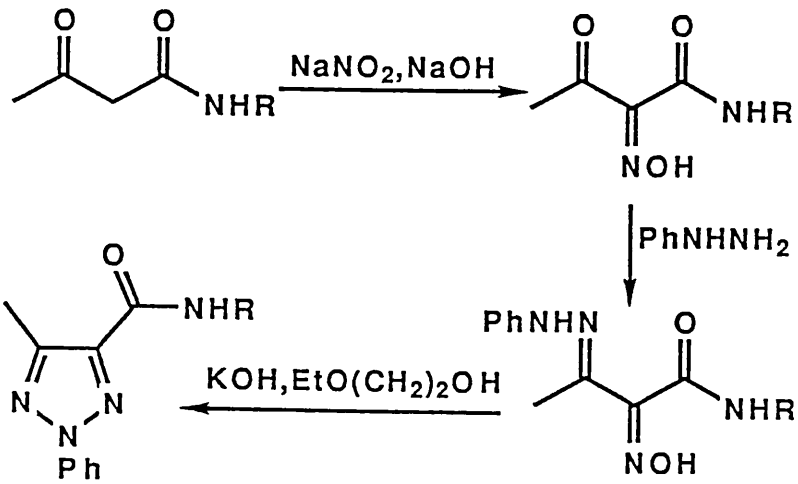
iii) 2-Pyrrolecarboxamides[84]



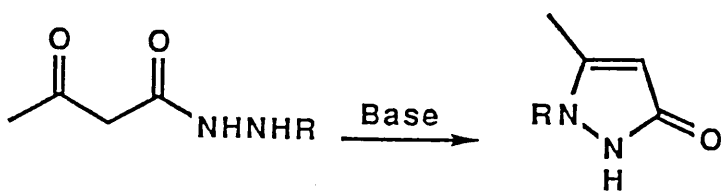
iv) Dihydropyridazinoindoles[85]



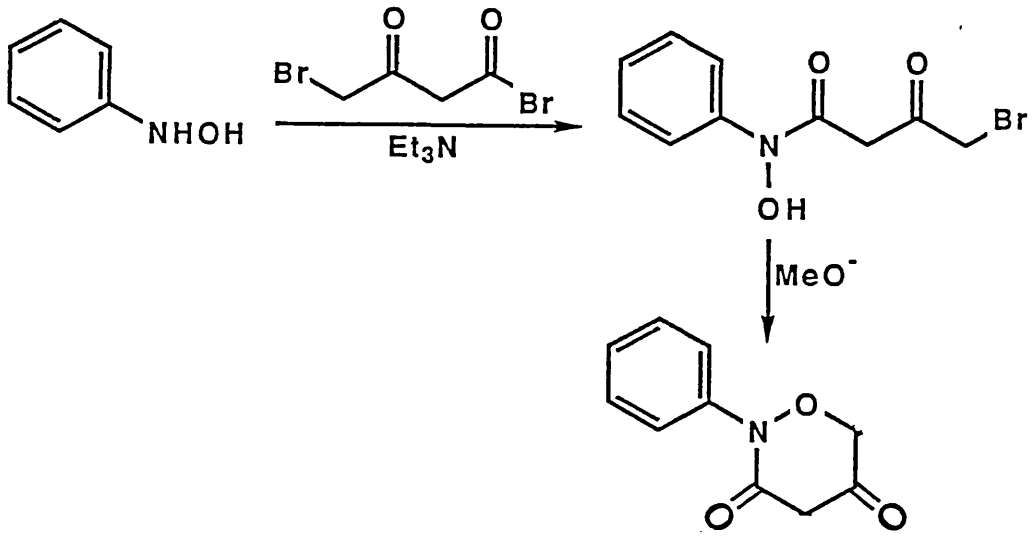
v) *vic*-Triazoles[86]



vi) Pyrazolines[87]



vii) 1,2-Oxazines[88]



β-Ketoamides themselves are of interest because of the antimicrobial[89], insect repellent[90], and systemic fungicidal[91] activity they exhibit. They may be prepared by a number of different routes, the most widely used of which are listed and discussed under the following headings:

1) Diketene or diketene derivatives

2) Claisen Condensation

3) β-Ketoesters

4) β-Ketoamides

5) Acylated Meldrum's acid derivatives

6) Base mediated fragmentation of isoxazolium salts

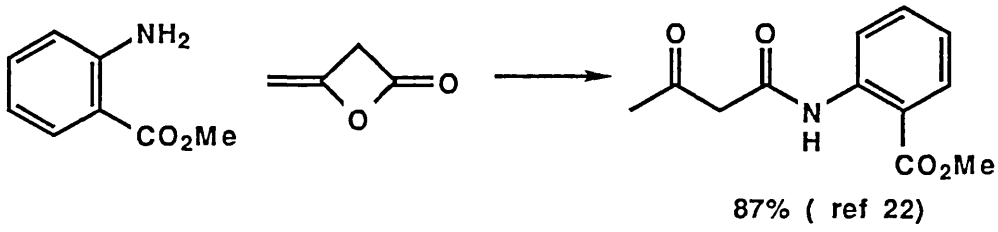
7) From isocyanates

Each of these seven routes will be discussed in turn.

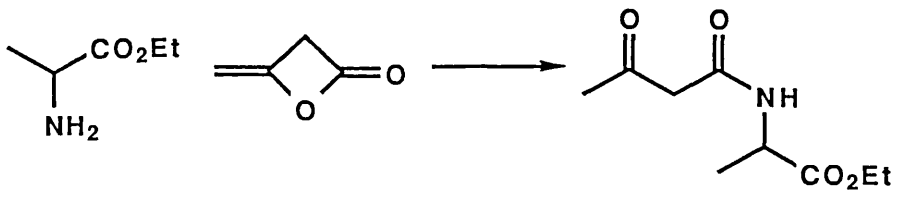
1) Diketene or Diketene derivatives

The reaction of diketene with amines gives good yields of β-ketoamides[54/92] (Scheme 31). This method has seen wide application, mainly due to the great interest in 3-acetyltetramic acid synthesis (vide infra)[22-24].

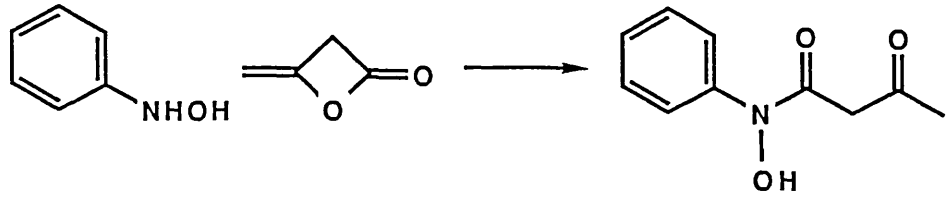
SCHEME 31



87% (ref 22)



86% (ref 22)

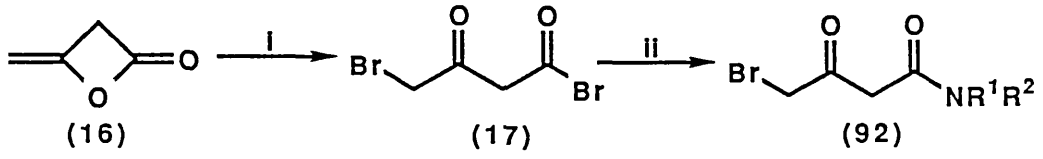


40% (ref 92)

An obvious shortcoming of this approach is that it cannot be used for the synthesis of β-ketoamides bearing functionality on the butanamide chain since substituted diketenes are not readily available.

By derivatising the diketene first it is possible to extend the utility of this approach. For example, reaction of diketene (16) with bromine gives the bromoacetyl bromide (17, Scheme 32)[54].

SCHEME 32

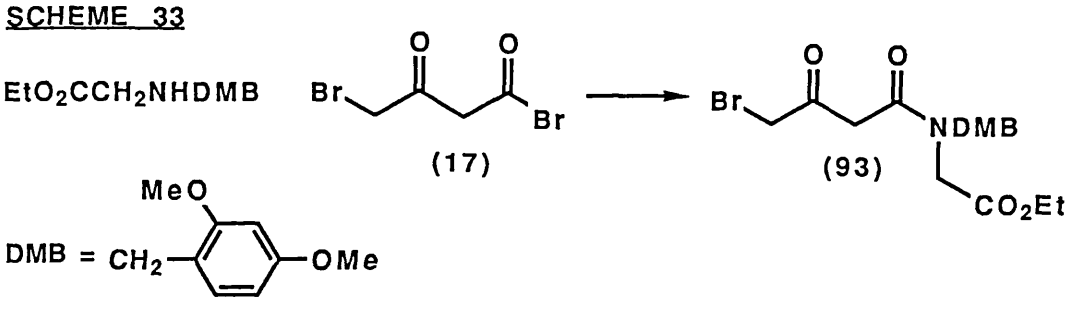


(16) (17) (92)

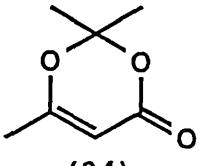
Reagents : i, Br_2, CCl_4 ; ii, R^1R^2NH

This bromide reacts with amines to give the 4-bromo-3-oxobutanamides (92). This particular reaction sequence was used by Schlessinger to prepared the bromide (93, Scheme 33)[29] used in the total synthesis of tirandamycin A[33].

SCHEME 33



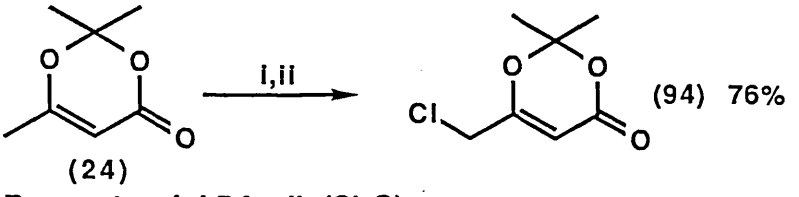
Reaction of diketene and acetone gives the adduct (24)[58]. As described in Part A (24) can be readily functionalised at the allylic methyl position.



(24)

In addition to the allylic bromination discussed previously the adduct can be chlorinated by first deprotonating with LDA and reacting the resulting anion with hexachloroethane (Scheme 34).

SCHEME 34

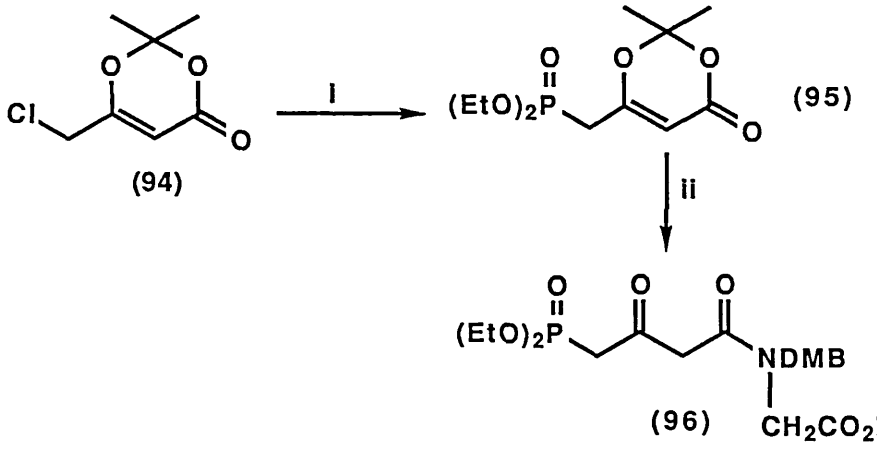


(24)

Reagents : i, LDA ; ii, $(Cl_3C)_2$

Treatment of (94) with the sodium salt of diethyl phosphite (15) readily gives the phosphonate (95) upon acidic work up. Heating the phosphonate (95) in THF with the glycine ester (97) under acid catalysis produces the β-ketoamide phosphonate (96, Scheme 35) in good yield.

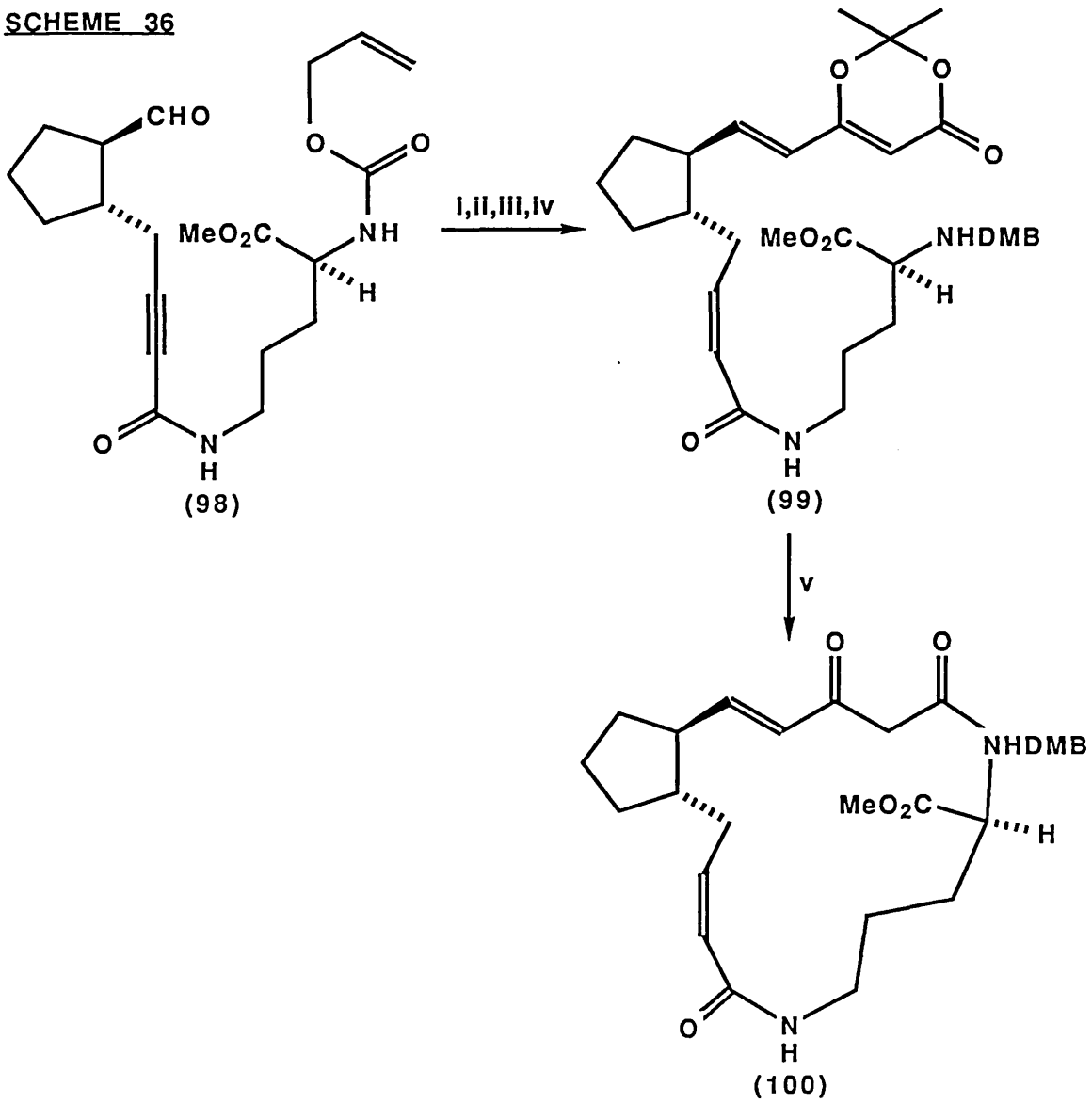
SCHEME 35



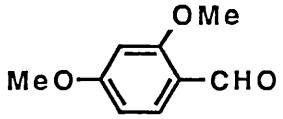
Reagents : i, $NaP(O)(OEt)_2$ (15) ; ii, $DMBNHCH_2CO_2Me$ (97), $PyrH^+$ Tos^-

The phosphonate (96) was an intermediate used by Boeckman in the synthesis of tirandamycin A[34]. An interesting intramolecular variant of this approach to β-ketoamides was used later by Boeckman in studies towards the macrocyclic subunit of ikarugamycin (99 to 100, Scheme 36)[27].

SCHEME 36



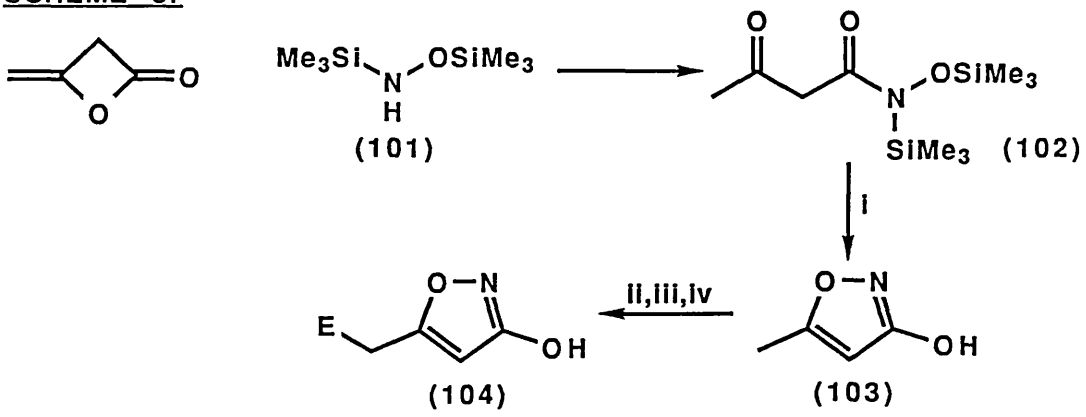
Reagents : i, (95), KO^{t}Bu ; ii, $(Ph_3P)_4Pd$, Ph_3P, HOAc ; iii, H_2, $Pd/BaSO_4$;

iv, 

, $NaCNBH_3$; v, PhMe, heat

Another approach involves the reaction of diketene with the silylated hydroxylamine derivative (101) affording the β-ketoamide (102) which, on treatment with HCl, produces the isoxazole derivative (103, Scheme 37).

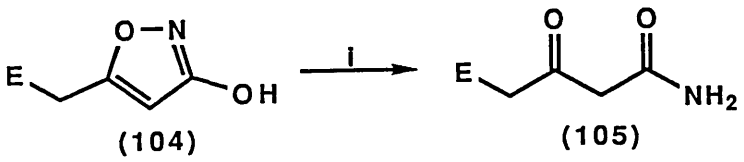
SCHEME 37



Reagents : i, HCl ; ii, 2LDA ; iii, E^+ (electrophile) ; iv, H^+

Treatment of (103) with two equivalents of LDA and reaction with a variety of electrophiles gave (104). Hydrogenation of the substituted derivatives (104) also leads to β-ketoamides (105, Scheme 38)[93].

SCHEME 38



(104) (105)

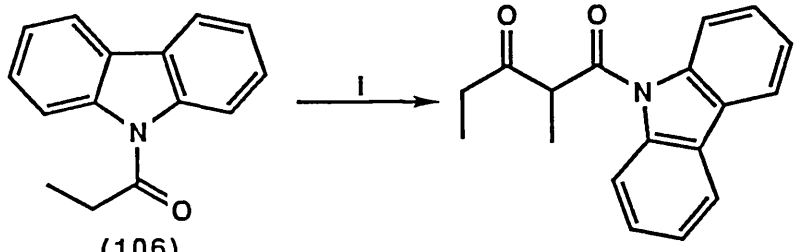
Reagents : i, H_2

This approach however is limited to the preparation of primary amides.

2) Claisen Condensation

The Claisen condensation has also been briefly investigated as a route to β-ketoamides. Both the self-condensation of N,N-disubstituted carboxamides (106 to 107, Scheme 39)[94] and the condensation of the anion from (108) with acyl carbonates (109, Scheme 40)[90] have been reported.

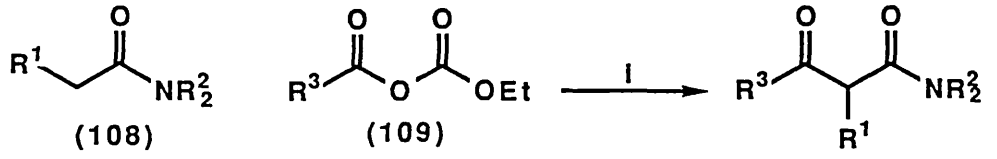
SCHEME 39



(106) (107)

Reagents : i, ^{n}BuMgBr

SCHEME 40



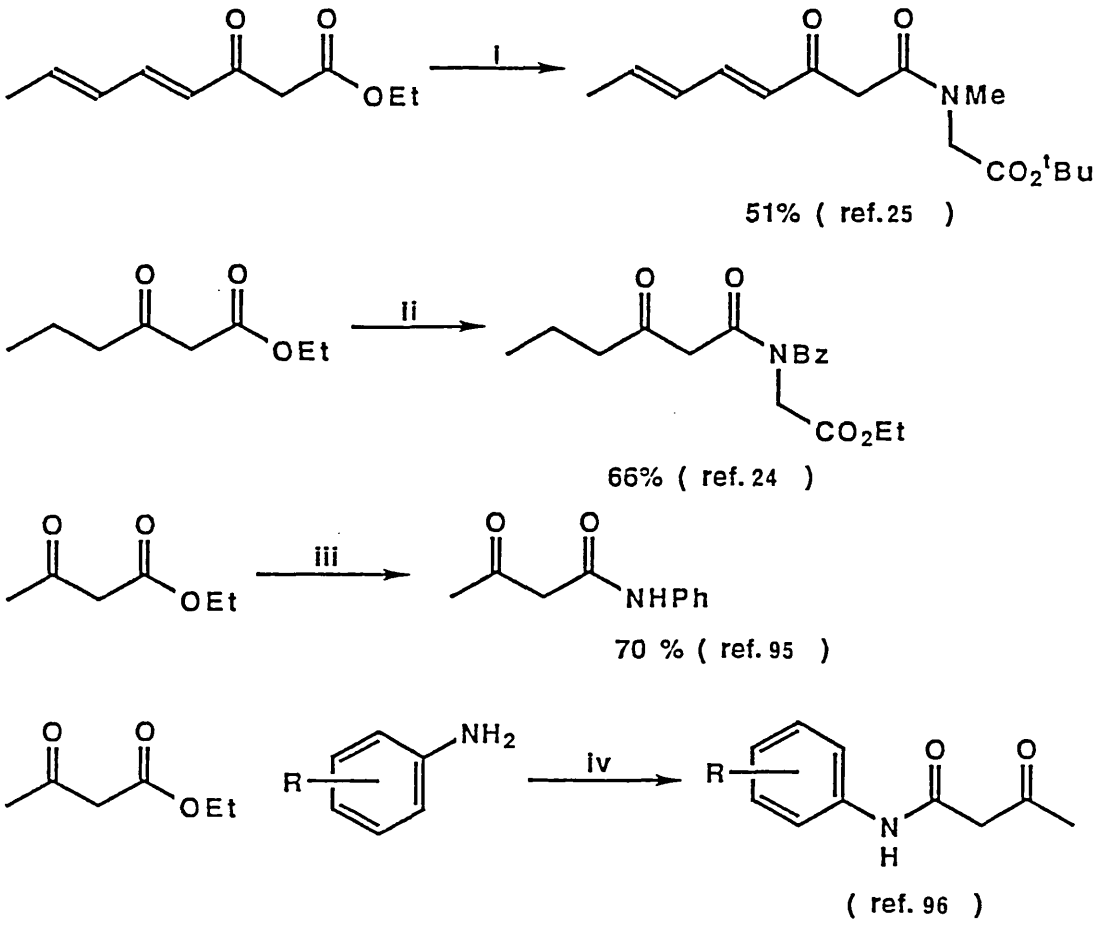
Reagents : I, LDA

R^1 = H,Me
R^2 = Me,Et
R^3 = $^{n}C_3H_7$,$^{c}C_6H_{11}$,C_6H_5,$CH_3CH{=}CH$

3) β-Ketoesters

The most direct method of preparing β-ketoamides would make use of β-ketoesters as precursors. Importantly this route would enable the versatile dianion chemistry of the β-ketoesters to be exploited. However, as the following examples show (Scheme 41) the reaction requires forcing conditions, typically prolonged heating.

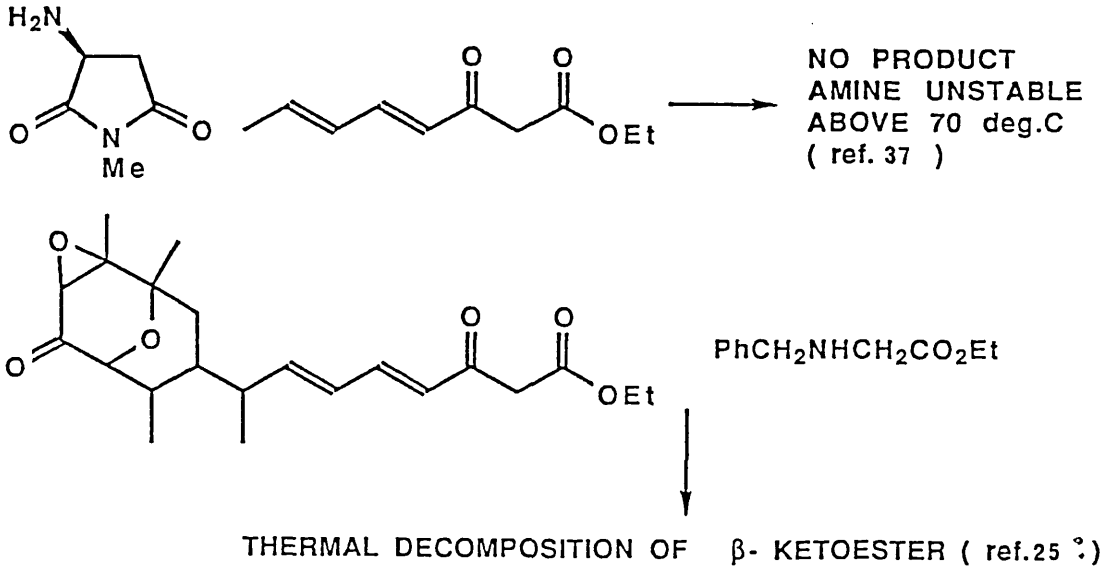
SCHEME 41



Reagents and Conditions : i, $MeNHCH_2CO_2{}^tBu$, Xylene, 110 deg.C ; ii, $PhCH_2NHCH_2CO_2Et$, Xylene, 125-130 deg.C, 20.5 h ; iii, $PhNH_2$, Xylene, catalytic Pyr, 135 deg.C, 5 h ; iv, 150 deg.C, 5h

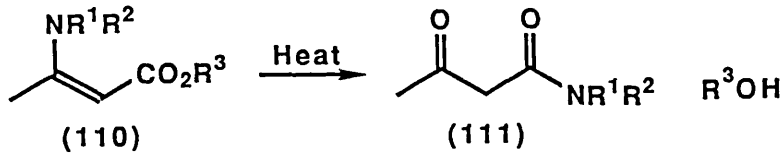
As the following two examples show, these vigorous conditions can cause severe problems in more complex examples (Scheme 42).

SCHEME 42



The use of prolonged high temperatures is necessary to convert the initially formed β-aminocrotonate (110) into the β-ketoamide (111, Scheme 43).

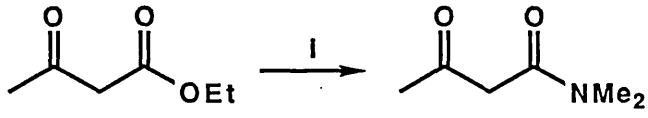
SCHEME 43



(110) (111)

One example of the preparation of a β-ketoamide from a β-ketoester involving a tin(IV) amide has been reported (Scheme 44)[98].

SCHEME 44



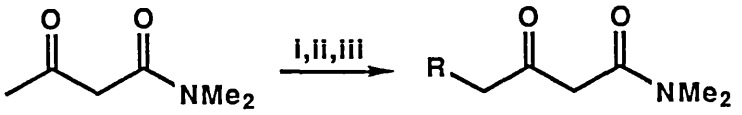
Reagents : I, $^{n}Bu_3SnNMe_2$, Et_2O

However the general applicability of this reaction to β-ketoamide preparation was not investigated.

4) β-Ketoamides

In some limited examples it has been shown that β-ketoamides may be further elaborated via their corresponding dianions in a manner similar to β-ketoesters (Scheme 45)[99].

SCHEME 45



Reagents : i, NaH ; ii, BuLi ; iii, RX

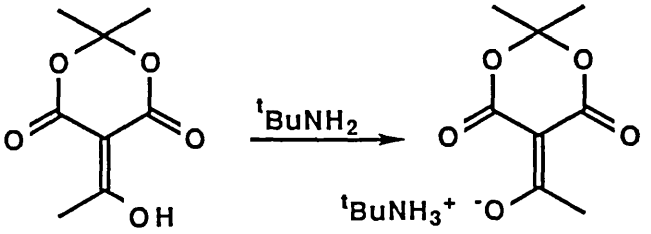
RX = $C_6H_5CH_2Cl$
$(C_6H_5)_2COCl$
CH_3CO_2Et
$C_6H_5CO_2Et$
$CH_3COCH(Na)CO_2Me$
$C_6H_5COCH(Na)CO_2Et$

However this approach is not applicable to β-ketoamides containing easily racemiseable centres or functionality which will not withstand the conditions used for the generation of the dianion.

5) Acylated Meldrum's acid derivatives

Acylated Meldrum's acid derivatives can be reacted with alcohols[55] and thiols[46] to give β-ketoesters and β-ketothioesters respectively. Opening with amines to form β-ketoamides might be expected to be less straightforward due to deprotonation by the amine to form the salt of the acylated adduct. In fact this was the only product formed when (112) was reacted with ^{t}butylamine (Scheme 46).

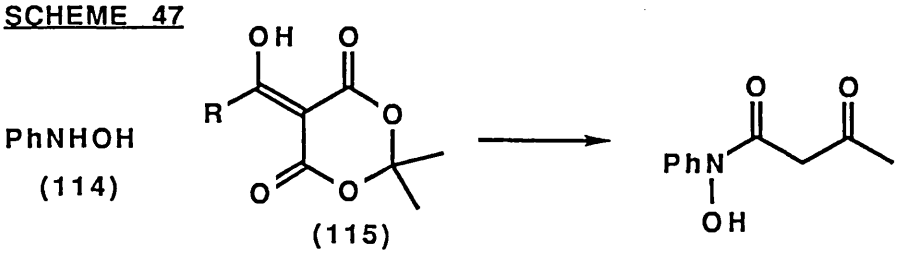
SCHEME 46



(112) (113)

However the successful opening of the acylated adducts (115) with N-hydroxyaniline (114) in boiling acetonitrile has been reported (Scheme 47)[100].

SCHEME 47

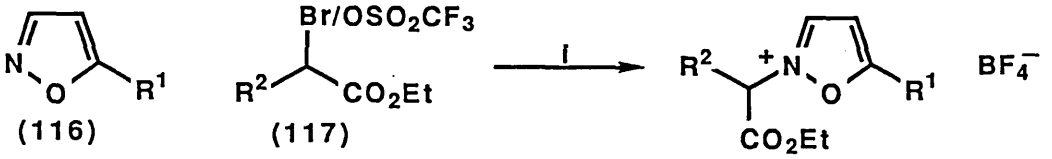


R = Alkyl,Phenyl,Benzyl

6) Base mediated fragmentation of isoxazolium salts

In 1966 Woodward[101] reported that isoxazolium salts (118) could be hydrolysed in dilute base solution to β-ketoamides in good yield. This approach has been used more recently to prepare β-ketoamides in connection with 3-acyltetramic acid studies by DeShong[32/35]. The isoxazolium salts (118) were prepared by treatment of the isoxazoles (116) with the bromoesters or in some cases triflates (117, Scheme 48).

SCHEME 48



(116) (117) (118)

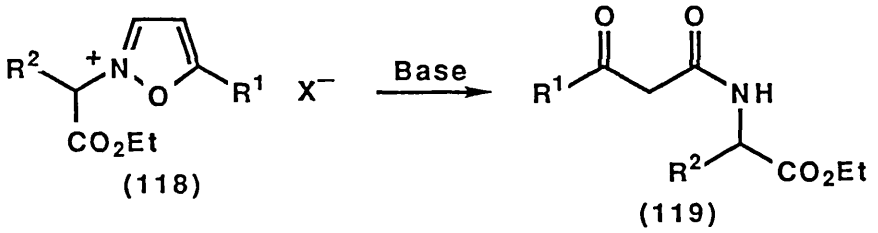
Reagents : I, $AgBF_4$

R^1 = Me,Ph,CH_2Ph,$CH_2P(O)(OEt)_2$

R^2 = H,Me

Hydrolysis of the isoxazolium salts (118) was achieved with a variety of bases to produce β-ketoamides (119, Scheme 49).

SCHEME 49



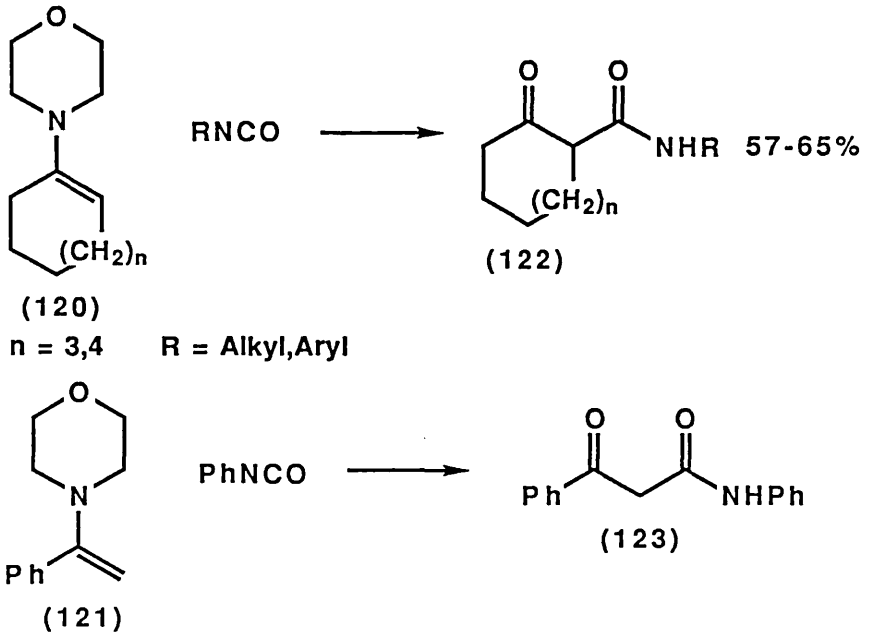
(118) (119)

7) From Isocyanates

A number of methods for synthesising β-ketoamides by reacting various carbon nucleophiles with isocyanates have been recently published.

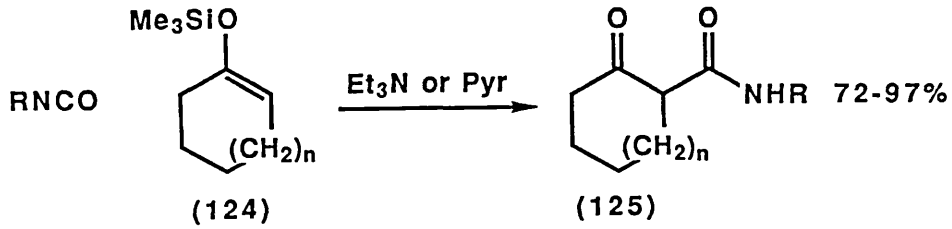
Enamines (120, 121) react with alkyl and arylisocyanates to give β-ketoamides in reasonable yields[102] (122, 123, Scheme 50).

SCHEME 50



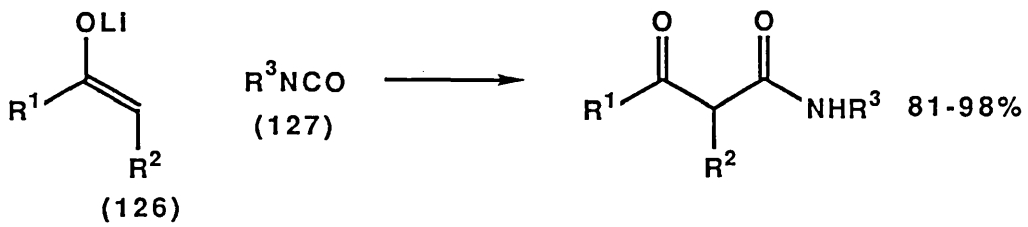
Ojima[103] has reported the reaction of silyl enol (124) ethers with phenyl and α-naphthylisocyanate in the presence of catalytic triethylamine or pyridine isocyanates to give the products (125, Scheme 51).

SCHEME 51



Wolfe[104] has recently reported the direct reaction of lithium enolates (126) with isocyanates (127) as shown in Scheme 52 as a route to β-ketoamides.

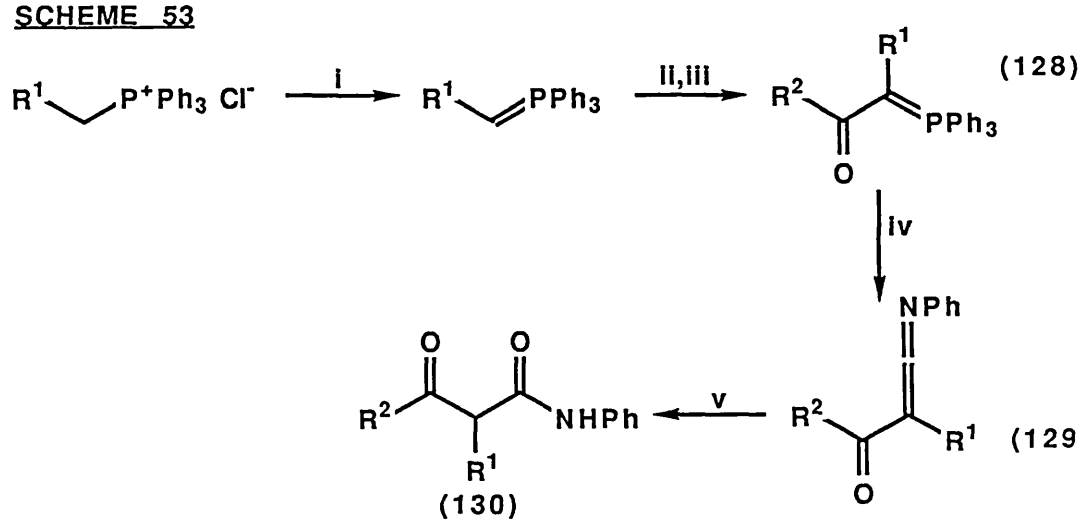
SCHEME 52



R^1 = Ph,^{t}Bu
R^2 = H,Me
R^3 = Aryl,Cyclohexyl

An interesting variation on this route has also been recently reported by Bestmann[105]. This involves <u>in situ</u> generation of the acylphosphoranes (128) and reaction with phenylisocyanate to give the α-acylketenimines (129) which are subsequently hydrolysed to the β-ketoamides (130, Scheme 53).

<u>SCHEME 53</u>



<u>Reagents</u> : i, $NaN(SiMe_3)_2$; ii, R^2COCl ; iii, Base ; iv, PhNCO ; v, H^+/H_2O

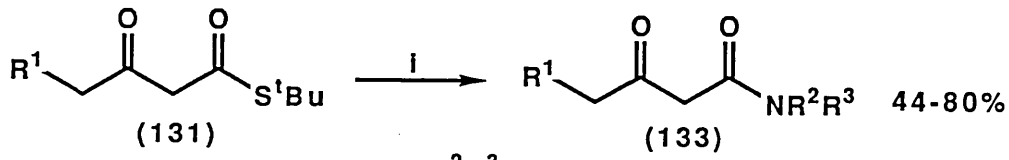
Another method of β-ketoamide synthesis, of particular relevance to 3-acyltetramic acid synthesis is that used by Bartlett in the synthesis of tirandamycin A[30]. This was described in the introduction (Scheme 42).

With the considerable current interest in 3-acyltetramic acid synthesis, new, more flexible routes for the construction of the β-ketoamide precursors are of interest.

Earlier, in the introduction to this section a mild transesterification of β-ketothioesters with alcohols to give substituted β-ketoesters was described.

We have now found that the treatment of a mixture of a β-ketothioester (131) and an amine (132) in THF at room temperature with either silver(I) trifluoroacetate or mercury(II) trifluoroacetate leads to the rapid formation of β-ketoamides (133, Scheme 54) usually in good yield[48].

SCHEME 54



(131) (133)

Reagents and Conditions: i, R^2R^3NH (132), Ag(I) or $Hg(II)OCOCF_3$, THF, RT

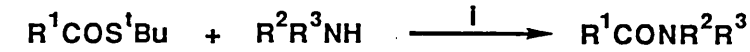
R^1 = H,Alkyl,Alkenyl,Polyenyl
R^2 = H,Alkyl
R^3 = Alkyl,Aryl

In contrast to β-ketoesters, β-aminocrotonates were never detected. Table IV lists a number of examples of this transformation.

TABLE IV : THIOESTER TO AMIDE CONVERSIONS

For convenience the structures of the numbered thioesters are shown at the end of the table.

General Scheme



Reagents and Conditions : I, $Ag(I)OCOCF_3$, THF, room temperature

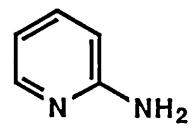
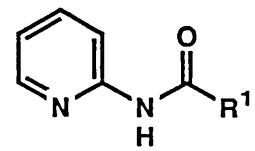
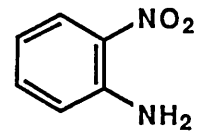
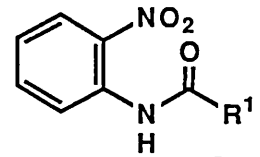
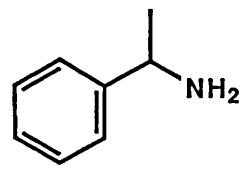
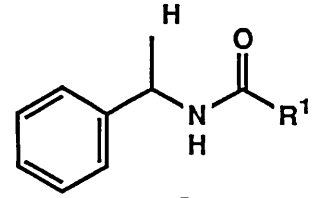
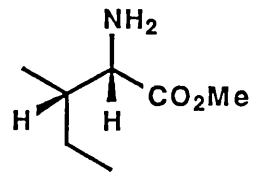
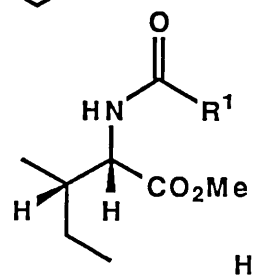
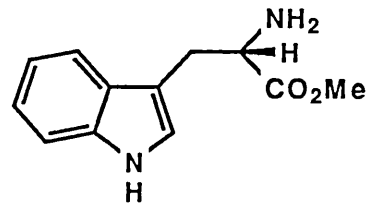
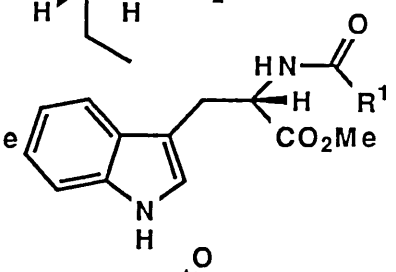
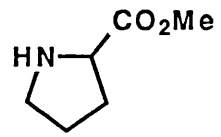
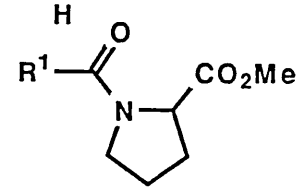
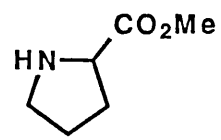
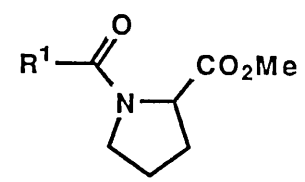
Entry	Thioester R^1COS^tBu	Amine	Product	Yield/%
1	(8)			65
2	(8)			80
3	(153)			54
4	(8)			68
5	(8)			70
6	(2)			60
7	(49)			70

TABLE IV : continued

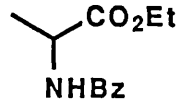
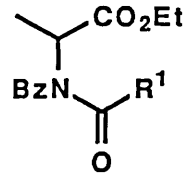
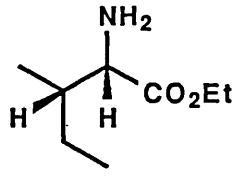
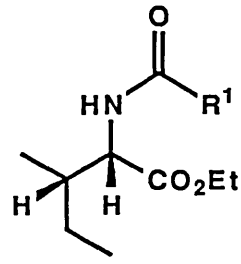
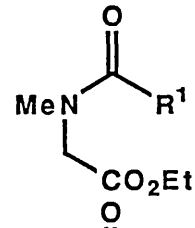
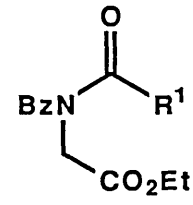
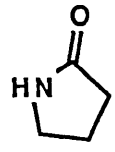
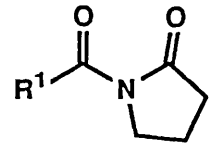
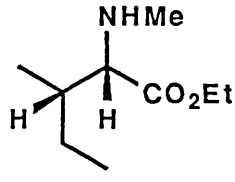
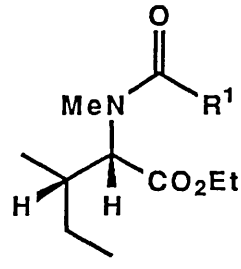
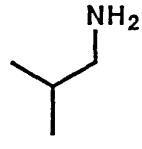
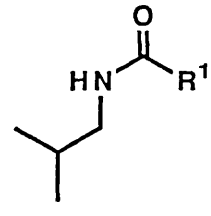
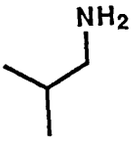
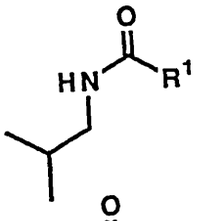
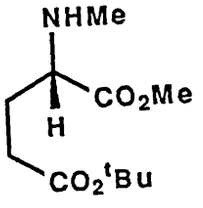
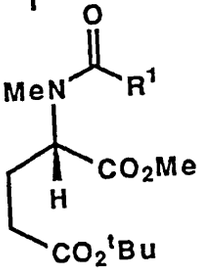
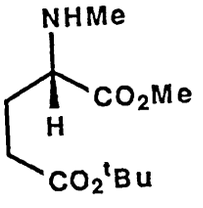
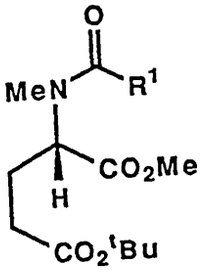
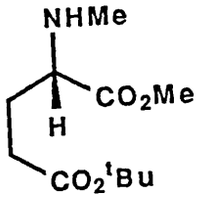
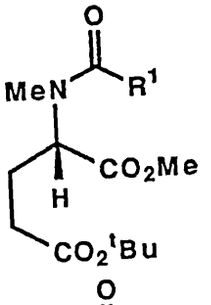
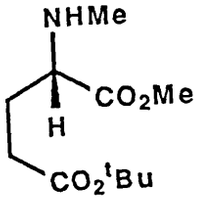
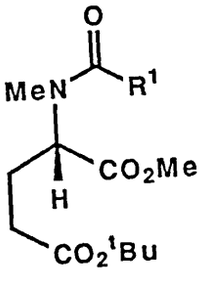
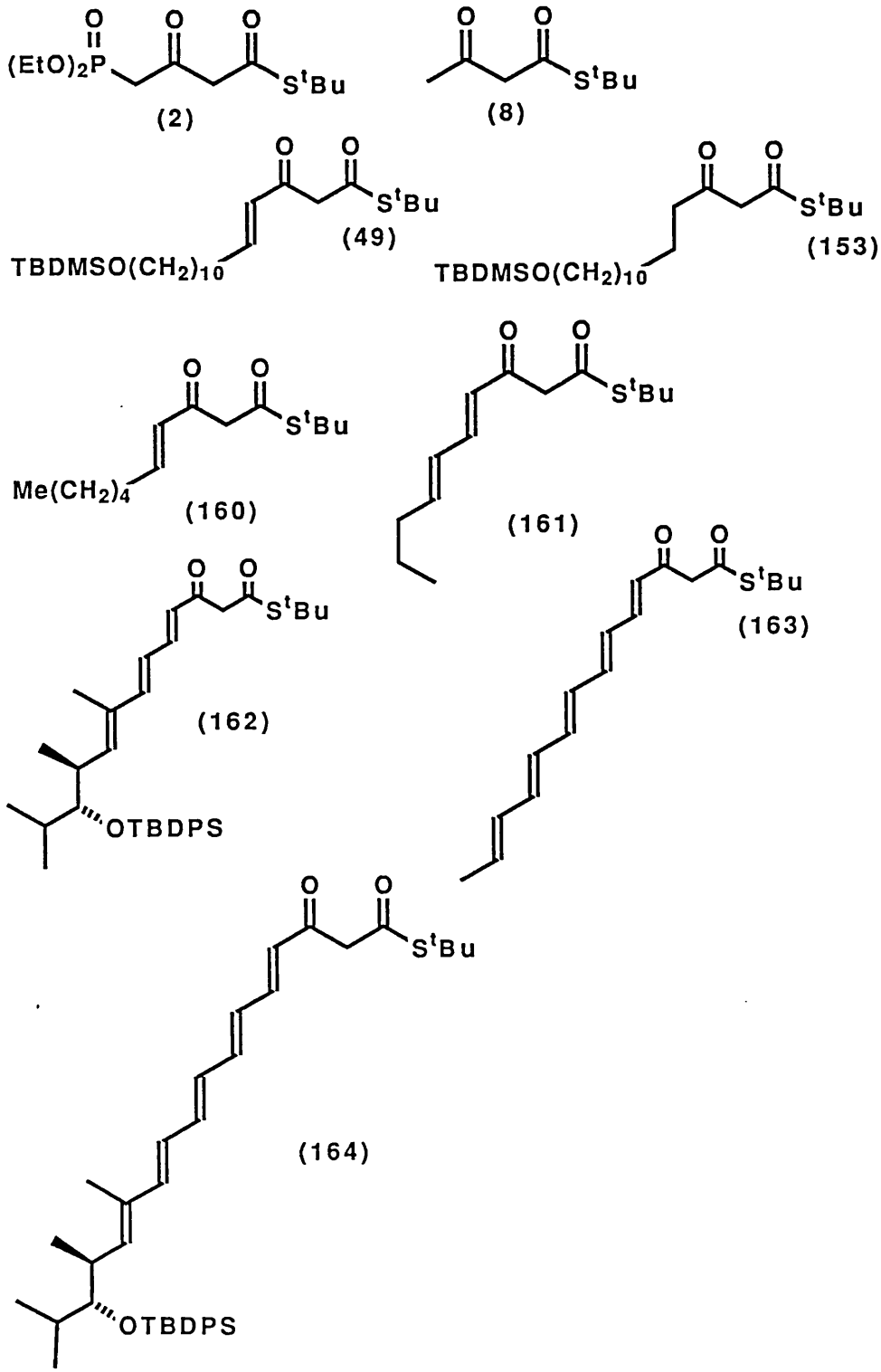
Entry	Thioester R^1COS^tBu	Amine	Product	Yield/%
8	(8)			75
9	(8)			60
10	(8)	$MeNHCH_2CO_2Et$		65
11	(8)	$BzNHCH_2CO_2Et$		65
12	(8)			74
13	(8)			68
14	(161)			77

TABLE IV : continued

Entry	Thioester R^1COS^tBu	Amine	Product	Yield/%
15	(160)			78
16	(162)			67
17	(8)			60
18	(163)			70
19	(164)			44

Thioesters in TABLE IV



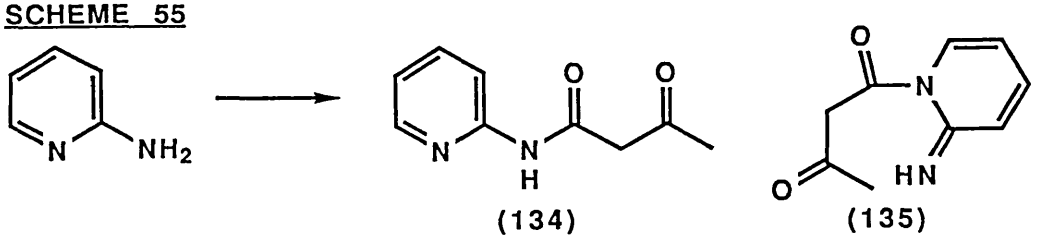
As can be seen from the table the reaction was found to be general and compatible with a wide variety of functional groups.

In entries 3 and 7 the ^{t}butyldimethylsilyl ether group was found to withstand the reaction.

In entries 7, 14, 15, 16, 18, and 19 conjugated double bonds are also found to be stable during the reaction. In entry 6 the phosphonate group and in entries 16, 17, 18, and 19 the acid labile ^{t}butyl ester are stable under the reaction conditions.

o-Nitroaniline (entry 2), an exceptionally electron deficient amine, was found to give a good yield of the β-ketoamide product[106]. 2-Aminopyridine (entry 1) also reacts and could, in principle, give either (134) or (135) (Scheme 55).

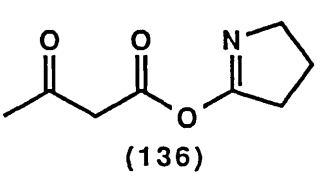
SCHEME 55



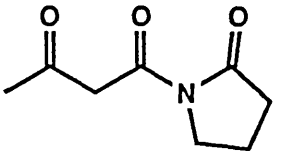
(134) (135)

The product from the thioester reaction had the same physical and spectroscopic properties as (134) a known compound[107/108]. This compound had been previously assigned as the structure (134) on the basis of its u.v. spectrum and the X-ray crystallographic structure of its Cu(I) complex.

The trans-amination reaction was found to be general for both primary and secondary amines bearing either a methyl or a benzyl substituent. In the case of entry 12 where pyrrolidin-2-one was used, the product was tentatively assigned as the imide (137).



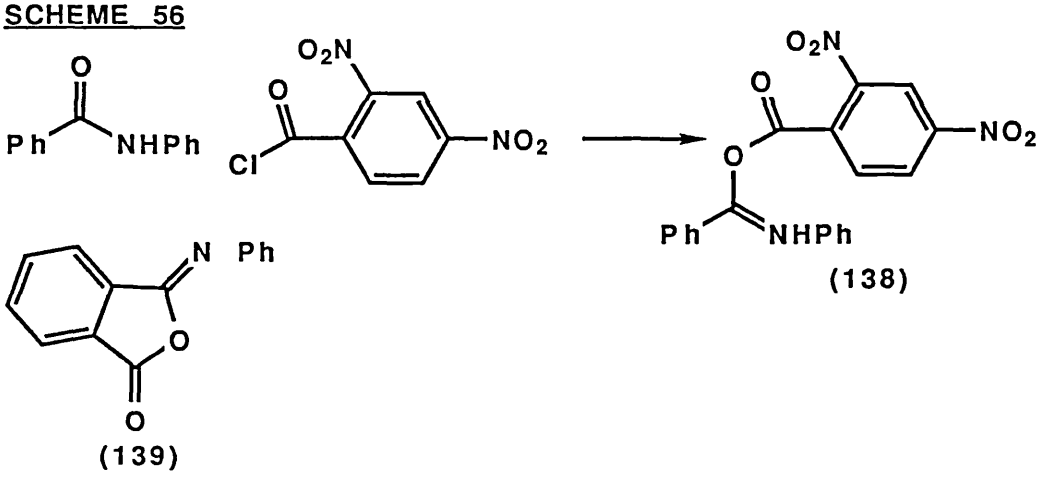
(136)



(137)

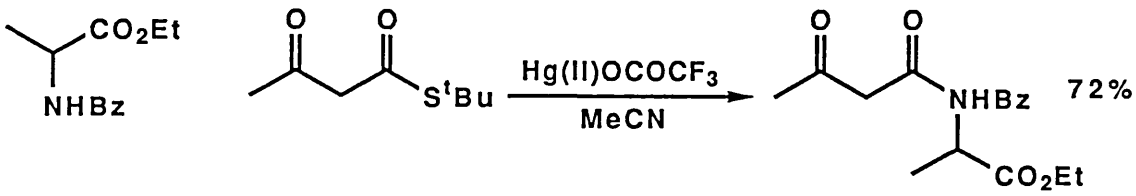
Even after close inspection of the spectroscopic data available it still proved impossible to unambiguously assign the product of the reaction as either (136) or (137). It is known[109/110] that although the kinetic products of the reaction of amides with acylating agents are imidates such as (136), these readily rearrange to give the imide in the case of secondary and tertiary amides. Only in exceptional circumstances such as (138) and (139) are the imidates actually isolated (Scheme 56).

SCHEME 56



All the trans-amination reactions in the table were carried out using silver(I) trifluoroacetate in THF. It was also found that the reaction proceeded satisfactorily if mercury(II) trifluoroacetate in acetonitrile was used as the following example illustrates (Scheme 57, compare entry 8, Table IV).

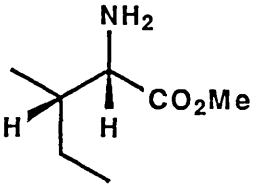
SCHEME 57



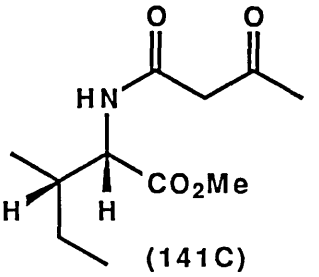
Generally however mercury(II) trifluoroacetate was not used owing to the problems involved in disposing of the waste residues. Copper(I) trifluoroacetate was not investigated because of the problems involved in making and storing this salt which is extremely air and moisture sensitive.

All the reactions carried out in Table IV were found to proceed to completion very rapidly - typically less than 15 minutes at room temperature; the only exception was o-nitroaniline reaction which took 45 minutes to go to completion.

Since most of the amines used contained potentially racemiseable centres it was decided to investigate the fate of these centres during the reaction. The amine chosen for this study was (140), the isoleucine methyl ester from entry 4 in Table IV.



(140)



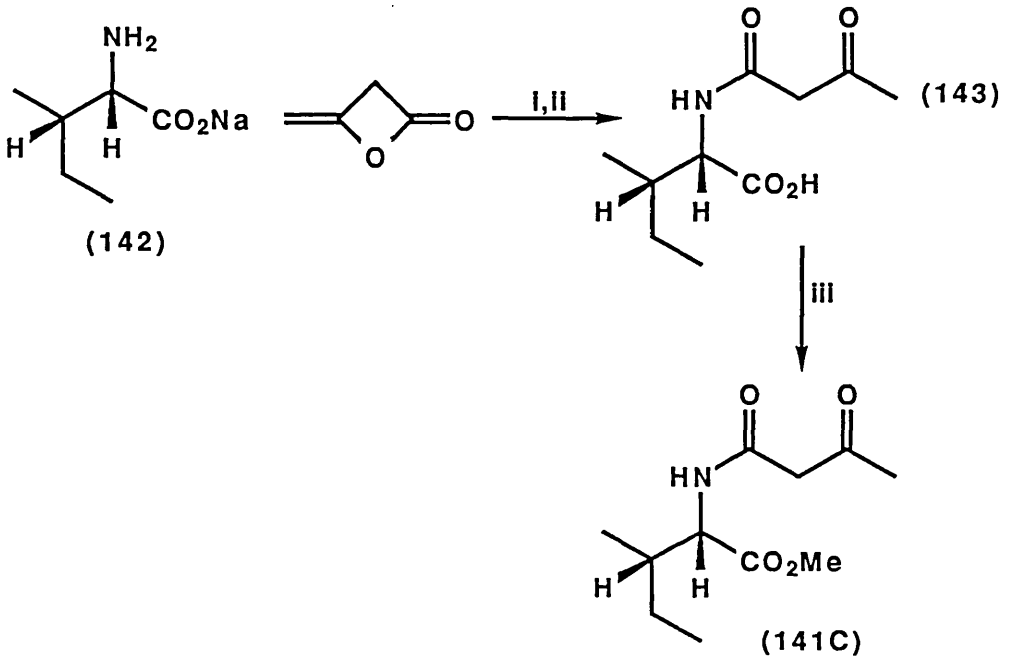
(141C)

Since both (140) and the β-ketoamide ester[23] (141C) are known compounds it was hoped initially to determine whether the centre α to the ester had racemised by a straightforward comparison of optical rotations.

The β-ketoamide ester (141C) prepared by the thioester route was found to have $[\alpha]_{546}^{25}$ = -22^0 (c 2.0, MeOH) compared with the quoted literature rotation by Harris[23] of $[\alpha]_{546}$ = +7^0 (c 2.0, MeOH).

The β-ketoamide ester (141C) was prepared as described by Harris using a Schotten-Baumann reaction followed by esterification. This involved treating the sodium salt of L-isoleucine (142) in aqueous solution with diketene, followed by acidification to give (143). Esterification was effected with diazomethane (Scheme 58).

SCHEME 58



(142)

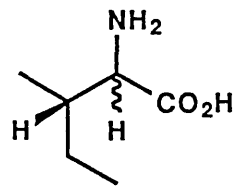
(141C)

Reagents : I, H_2O ; II, H^+ ; III, CH_2N_2

The acid (143) showed a rotation of $[\alpha]_{546}^{25}$ = +6.5^0 (c 2.0 MeOH) compared with the value of $[\alpha]_{546}$ = -122^0 (c 2.0, MeOH) quoted in the Harris paper. After diazomethane esterification, the compound (141C) showed a rotation $[\alpha]_{546}^{25}$ = -21^0 (c 2.0, MeOH) in close agreement with the value of $[\alpha]_{546}^{25}$ = -22^0 (c 2.0, MeOH) shown by that prepared by the thioester route.

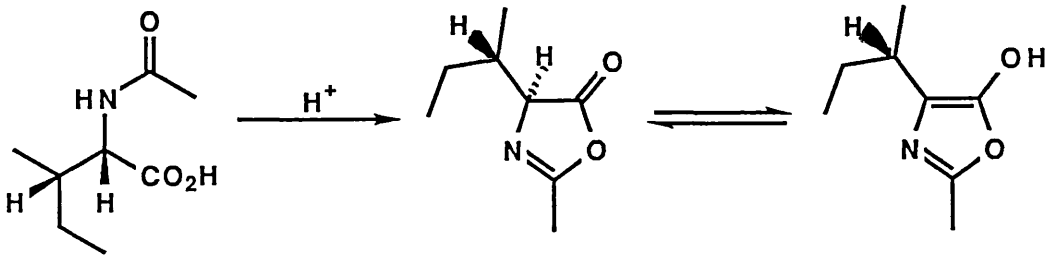
While the muddle over the misquoted optical rotations was being sorted out, it was decided to try and determine whether partial epimerisation had occurred by spectroscopic methods, specifically ^{13}C n.m.r. spectroscopy.

For comparison purposes isoleucine (144) was needed which was a 1:1 mixture of epimers at the α-position. The partial epimerisation was achieved <u>via</u> the N-acetyl derivative (145) through azlactone formation (146 ⇌ 147, Scheme 59)[111].



(144)

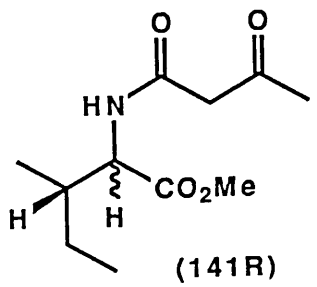
SCHEME 59



(145) (146) (147)

The use of commercially available DL-isoleucine was briefly investigated but this was found to consist of a 2:1 mixture of diastereoisomers by ^{1}H n.m.r. spectroscopy.

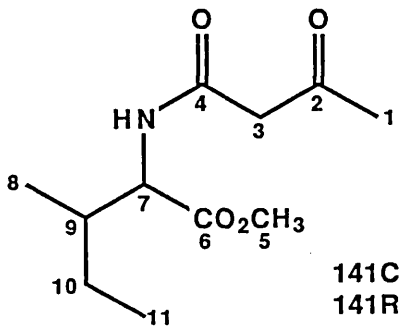
In the ^{13}C n.m.r. spectrum the 2RS, 3S β-ketoamide ester (141R) was found to exhibit doubling up on eight of its signals as Table V shows. Both compounds (141R) and (141C) existed exclusively as the keto tautomers and as single rotamers.



(141R)

TABLE V

Structure for Table V



141C - single epimer at position 7
141R - mixture of epimers at position 7

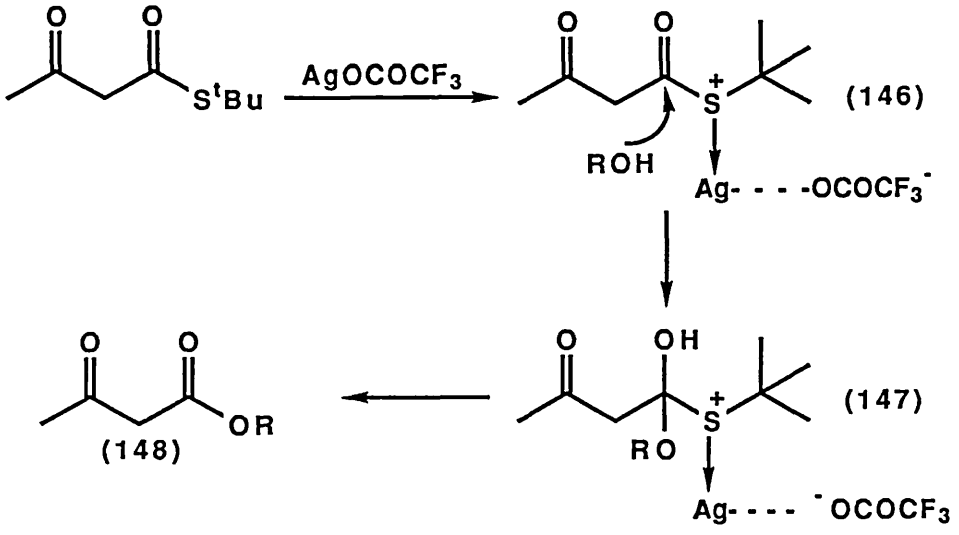
141C/ppm δ	141R/ppm δ	Assignment
11.5	11.3; 11.5	11
15.4	14.4; 15.3	8
25.1	24.9; 26.0	10
30.8	30.5	1
37.6	37.2; 37.4	9
49.5	49.6	3
52.0	51.8; 51.9	5
56.6	55.3; 56.4	7
165.4; 172.0	165.6; 165.7; 171.9; 172.2	4; 6
203.9	203.8	2

The β-ketoamide ester (141C) obtained by the thioester route was found to show only one set of signals. There was no evidence of the other diastereoisomer that would be formed on partial epimerisation.

The signal observed for the proton α to the ester in the ^{1}H n.m.r. spectrum also proved to be quite diagnostic. In compound (141R) overlapping double doublets were observed at 4.48 and 4.59ppm. In the compound obtained from the thioester route only one double doublet was observed centred at 4.48ppm. From these results it can be concluded that there was no detectable epimerisation of the position α to the ester during the β-ketothioester to β-ketoamide conversion.

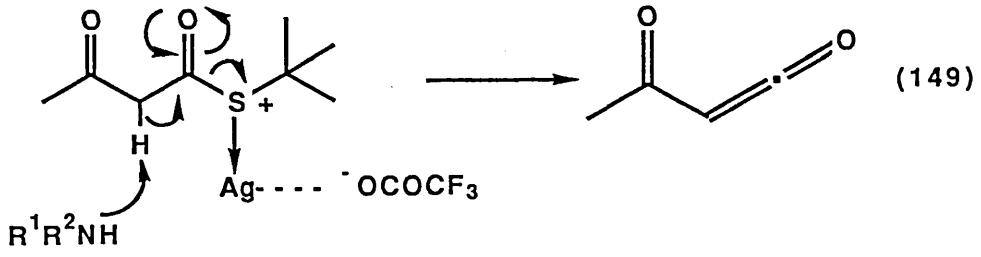
The mechanism of the β-ketothioester to β-ketoamide reaction was not investigated. A mechanism for the reaction of thioesters with alcohols has been proposed by Masamune[112]. Coordination of silver(I) with sulphur atom of the thioester (146) activates the thioester to attack by the alcohol (ROH). Breakdown of the resulting intermediate (147) gives the ester (148, Scheme 60).

SCHEME 60



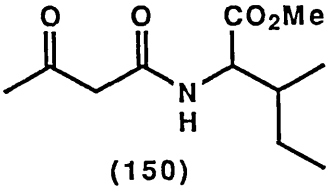
Whether the mechanism for the reactions of amines with thioesters in the presence of thiophilic metals occurs by the above pathway or by an acetylketene (149) intermediate is not known (Scheme 61).

SCHEME 61



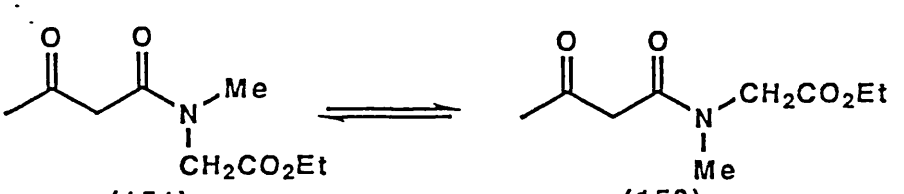
The wide variation in the yields quoted in Table (IV) was due to the scale on which the reaction was carried out. With the larger scale reactions (typically involving over 500mg of silver(I) trifluoroacetate) the removal of the silver residues became a problem. In these reactions several filtration steps were necessary with a consequent decrease in the yield.

β-Ketoamides obtained from primary amines existed as a single rotamer as would be expected[113/114]. This is the trans-rotamer and is shown for (150).



(150)

β-Ketoamides derived from secondary amines existed as a mixture of two rotamers e.g. (151) and (152).



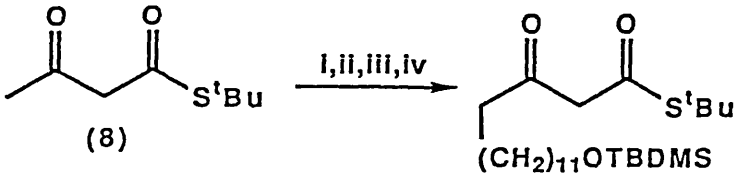
(151) (152)

In the case of the above β-ketoamide ester the conformational equilibrium was investigated by variable temperature ^{1}H n.m.r. spectroscopy. The coalescence temperature at which free rotation about the carbon-nitrogen bond of the amide occurred was found to be approximately $120^{0}C$.

Synthesis of β-Ketothioesters and Amines in Table IV

The β-ketothioester (153)[49] from entry 3 was prepared as shown in Scheme 62.

SCHEME 62



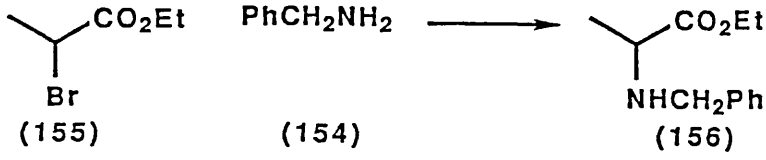
(153)

Reagents : I, NaH,DME ; ii, ^{n}BuLi ; iii, I(CH$_2$)$_{11}$OTBDMS (43) ; iv, H$^+$

The dianion of ^{t}butyl 3-oxobutanthioate (8) was reacted with the protected iodoalcohol (43).

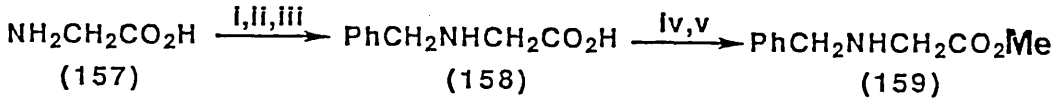
The aminoester (156) in entry 8 was prepared by reaction of benzylamine (154) with racemic ethyl 2-bromopropionate (155, Scheme 63)[115].

SCHEME 63



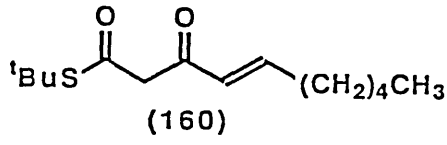
The methyl N-benzylglycinate (159)[116] was prepared by the following reductive alkylation/esterification sequence from glycine (157, Scheme 64).

SCHEME 64

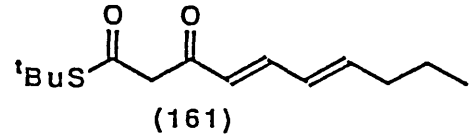


Reagents : i, PhCHO, NaOH ; ii, $NaBH_4$; iii, H^+ ; iv, MeOH, HCl ; v, $NaHCO_3$

The preparation of the unsaturated β-ketothioesters (160) and (161) used in entries 14 and 15 was described in Part A of the thesis.

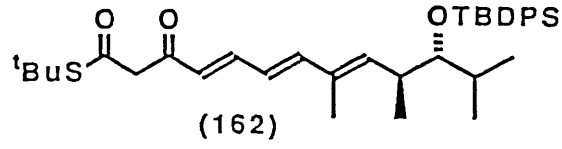


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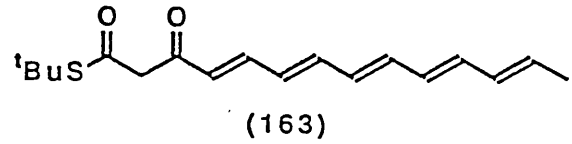


(161)

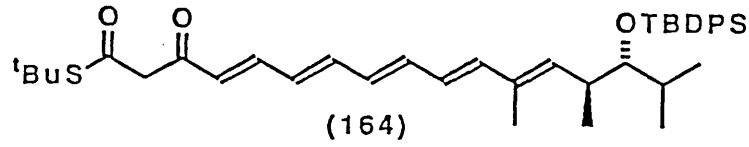
The preparation of the β-ketothioester polyenes (162), (163), and (164) used in entries 16, 18, and 19, the N-methyl glutamate derivate (165) used in entries 16 to 19, and the N-methylisoleucine ester (166) used in entry 13 will be described later in this section.



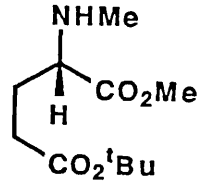
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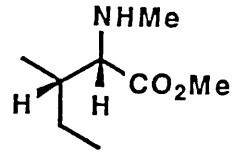
(163)



(164)

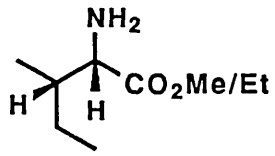


(165S)

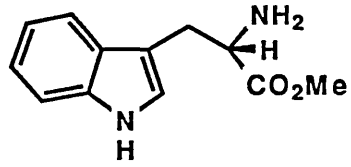


(166)

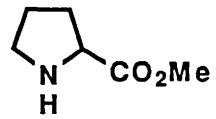
The aminoesters (167) entries 4 and 9, (168) entry 5, and (169) entries 6 and 7 were prepared using HCl and methanol or ethanol.



(167)



(168)



(169)

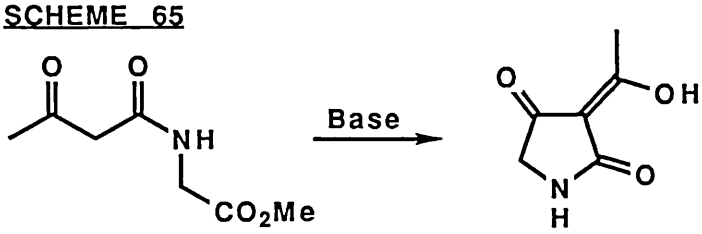
The free amines were liberated from the hydrochloride salts by base treatment (aqueous sodium bicarbonate).

3-Acyltetramic Acids

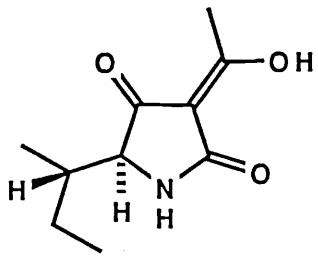
Dieckmann Studies

The most widely employed method for the construction of the 3-acyltetramic acid unit is the base mediated Dieckmann reaction on the appropriately substituted β-ketoamide ester. This is shown for the simplest case of the glycine methyl ester derivative (Scheme 65).

SCHEME 65



The bases generally used are the alkoxide bases; methoxide, ethoxide, and ^{t}butoxide. It is known from work on tenuazonic acid (170) that the usual cyclisation conditions used described by Lacey[22] cause extensive racemisation at the 5 position.

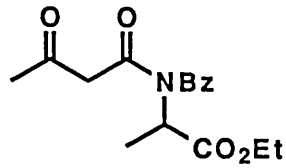
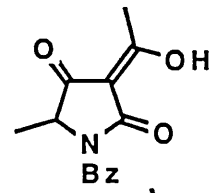
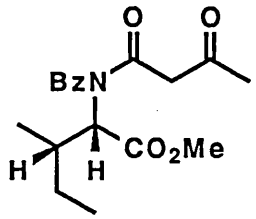
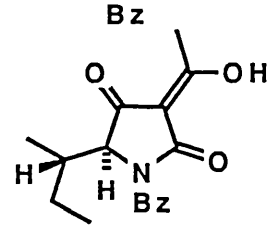
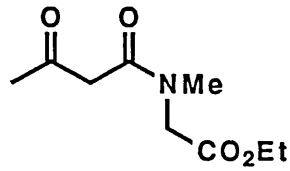
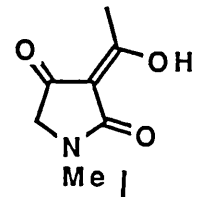
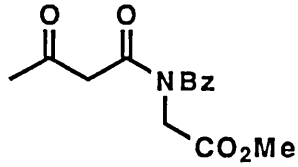
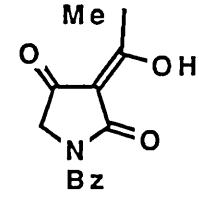
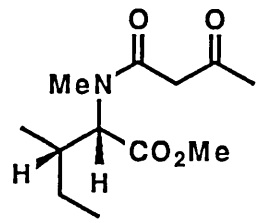
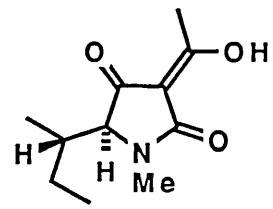
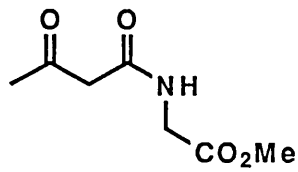
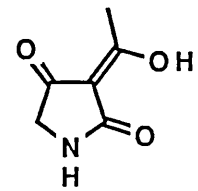
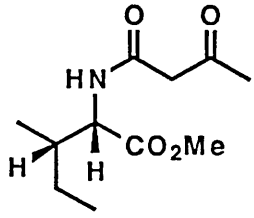
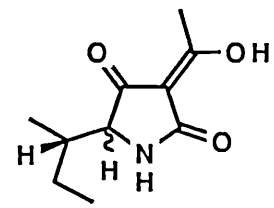


Tenuazonic acid (170)

The preparation of tenuazonic acid described by Harris[23] using a Dieckmann reaction carried out under the Lacey conditions (prolonged reflux with sodium methoxide in methanol/benzene mixture) gave a compound which required four recrystallisations of the copper(II) salt to raise the optical rotation from -76.5^0 to -122^0 (reported rotation -124^0 [3]).

The use of fluoride as a base in organic synthesis is well documented[117]. As described at the beginning of Part B it had been found that the use of TBAF for the Dieckmann reaction to form 3-acyltetronic acids results in no apparent racemisation at the 5-position[75]. It was therefore decided to investigate the use of TBAF for the Dieckmann reaction leading to 3-acyltetramic acids. The results are shown in Table VI.

TABLE VI

Entry	Starting Material	Product	Yield/%
1			92%
2			85%
3			70%
4			78%
5			85%
6			35%
7			55%

It was found that on treatment with 2-2.5 equivalents of TBAF in THF, the β-ketoamide esters of entries 1 to 5 were rapidly converted (5 to 10 minutes) into the 3-acyltetramic acids in excellent yields. However when the cyclisation of secondary amides (entries 6 and 7) was attempted the reaction was found to be exceptionally slow, requiring prolonged heating and many equivalents of TBAF. The reaction in entry 6 required 10 equivalents of TBAF and needed to be boiled for 24 hours. The reaction was found to be extremely slow at room temperature regardless of how much TBAF (up to 30 equivalents) was present.

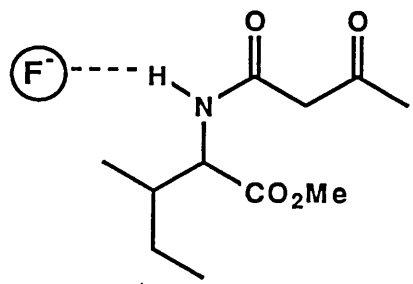
In entry 7 the optical rotation of the product derived from the chiral β-ketoamide ester was found to be considerably lower than that of the product obtained from the reaction carried out under the Lacey conditions as Table VII shows.

TABLE VII

Tenuazonic Acid	Lacey	TBAF
$[\alpha]_{546}$ -124^{0} [72]	$[\alpha]^{25}_{546}$ -96.7^{0}	$[\alpha]^{25}_{546}$ $+5.1^{0}$

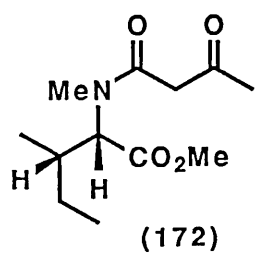
In fact the product of the TBAF mediated cyclisation had a rotation nearer to that of isotenuazonic acid[2]($[\alpha]_{546}$ $+23^{0}$) an equal mixture of 5S and 5R tetramic acids. This was confirmed by the ^{1}H n.m.r. spectrum which showed an almost equal mixture of the two diastereoisomers.

A possible explanation of this problem with TBAF and secondary amides is that hydrogen bonding occurs between the fluoride anion and the proton on the amide (171)[118/119].

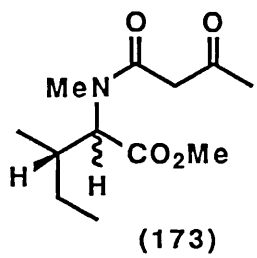


(171)

This hydrogen bonding would lead to an increase in electron density on the amide carbonyl group resulting in a decrease in acidity of the protons on the active methylene group. In the light of the problems experienced with these types of β-ketoamide esters, a different model system was necessary in order to investigate the fate of the stereochemistry at the 5 position in the Dieckmann reaction and the compound used for these epimerisation studies was (172).



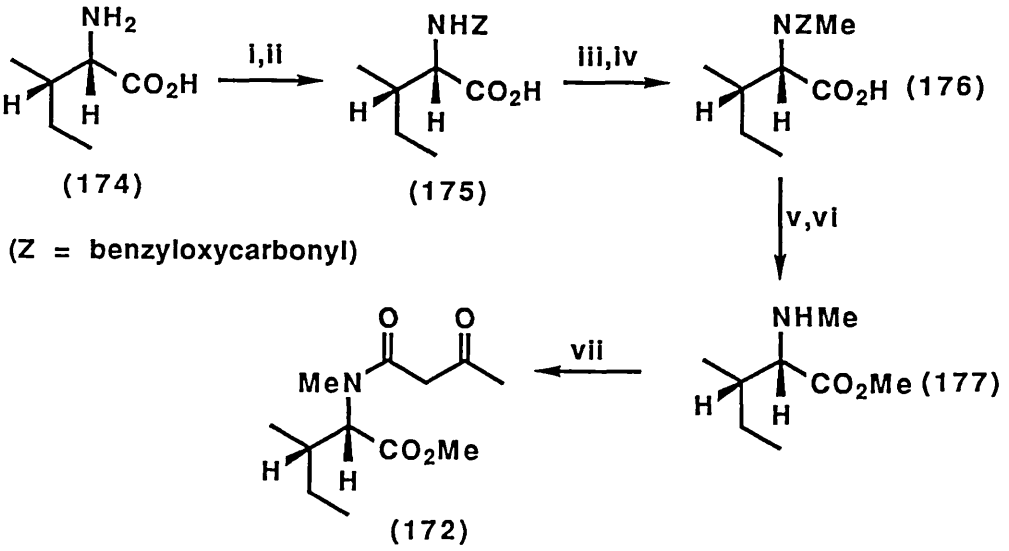
(172)



(173)

Compound (172) was prepared both optically pure from L-isoleucine and as a 1:1 mixture of epimers at the α position to the ester (173) from L-isoleucine which had been partially epimerised at this position by the method previously described[120]. (172) and (173) were prepared as shown in Scheme 66.

SCHEME 66



Reagents : i, $PhCH_2OCOCl$, NaOH ; ii, H^+ ; iii, NaH, MeI ; iv, H^+ ; v, DCC, MeOH, DMAP ; vi, / Pd/C ; vii, t-Butyl 3-oxobutanthioate, Silver(I) Trifluoroacetate.
CYCLOHEXENE

Treatment of Z-L-isoleucine (175) (Z=benzyloxycarbonyl) with 3 equivalents of sodium hydride followed by methyl iodide gave the N-Z N-methyl derivative (176)[121]. Esterification of (176) under neutral conditions using dicyclohexylcarbodiimide, 4,4-dimethylaminopyridine, and methanol[122/123] followed by removal of the Z group by hydrogenation gave (177). Treatment of (177) with t-butyl 3-oxobutanthioate gave the desired β-ketoamide ester (172).

Comparison of the ^{13}C n.m.r. decoupled spectra of compounds (172 and 173) showed that no epimerisation of the α position had occurred in the synthesis from L-isoleucine.

Treatment of both the optically pure and racemic compounds with 2.5 equivalents of TBAF (1 mol dm^{-3}) led rapidly (5 minutes) to the 3-acyl-tetramic acid (after acidification) in 85% yield (entry 5, Table VI). Comparison of the decoupled ^{13}C n.m.r. spectra clearly showed that there had been no epimerisation at the 5 position of the 3-acetyltetramic acid during the reaction. It was decided to compare other base systems for the Dieckmann reaction. This was done by comparison of optical rotations as the optical rotation of the chiral 3-acetyltetramic acid was now known. The results of these studies are shown in Table VIII.

TABLE VIII

Entry	Reagents and conditions	$[\alpha]_D^{25}$	Yield
1	TBAF/THF/5 min/RT	-36^0	85%
2	NaOMe/MeOH/BENZENE/3 hrs reflux, stand overnight	$+15^0$	74%
3	NaOMe/MeOH/5 min/RT	-36^0	78%
4	NaOMe/MeOH/24 h/RT	-31^0	75%
5	$KO^tBu/^tBuOH$/2 h/reflux	-25^0	88%
6	$KO^tBu/^tBuOH$/5 min/RT	-36^0	90%

Entry 1 in the table shows the TBAF reaction and the rotation of the 3-acetyltetramic acid which was shown to be optically pure by ^{13}C n.m.r. spectroscopy.

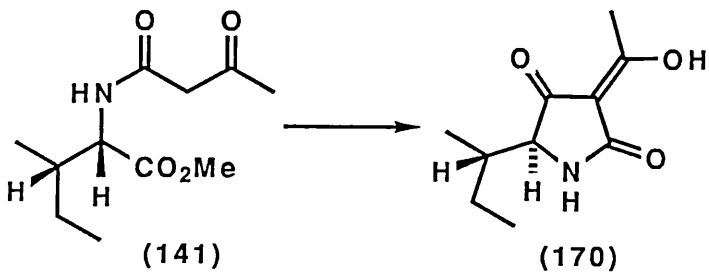
Entry 2 is the Dieckmann reaction carried out under typical Lacey conditions[22]. The ^{13}C n.m.r. decoupled spectrum showed that a 1:1 mixture of diastereoisomers had been formed. However on closer inspection the NaOMe/MeOH mediated cyclisation was found to proceed extremely quickly at room temperature to give optically pure product (entry 3).

When this reaction was left on longer than necessary (24 hours at room temperature, entry 4) some epimerisation was observed.

A similar situation was found to occur when the $KO^tBu/^tBuOH$ base system used by Bloomer and Kappler in their tetronic acid work[124] was employed. Treatment of the β-ketoamide ester under the typical cyclisation conditions described in the paper for tetronic acids caused some epimerisation of the 5 position (entry 5). Close monitoring of this reaction by TLC showed the cyclisation also went to completion very quickly giving optically pure product (entry 6).

It was decided to reinvestigate the cyclisation of the β-ketoamide ester (141) leading to tenuazonic acid (170, Scheme 67) to see if the literature conditions were actually necessary (3 hours reflux with sodium methoxide in methanol/benzene, left to stand at room temperature overnight)[22].

SCHEME 67



(141) (170)

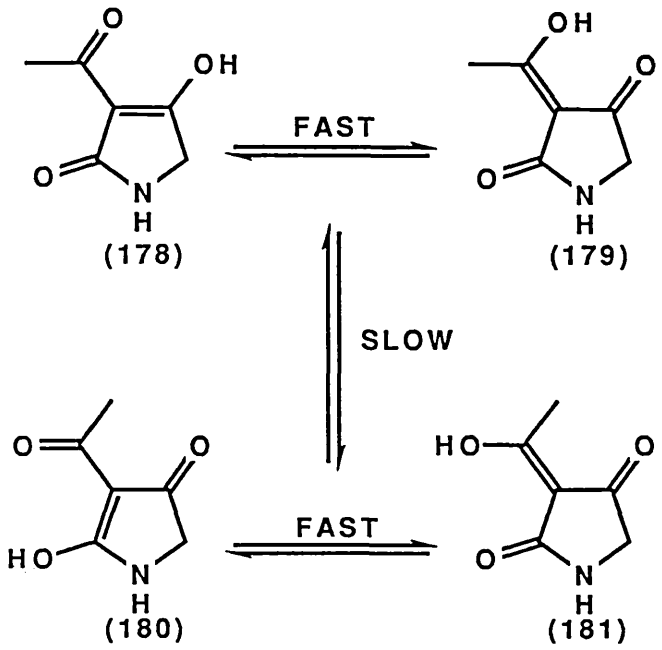
Treatment of (141) over a prolonged period (2 days) at room temperature with 2 equivalents of sodium methoxide in methanol did not result in complete reaction. Thus the conditions described do seem to be necessary in order to effect this particular cyclisation. Again this could be a consequence of the hydrogen bonding between the methoxide anion with the amide proton or perhaps even competing removal of this proton. The considerably longer reaction time with TBAF (48 hours at reflux, 5 equivalents of TBAF) could be due to the stronger hydrogen bond formed between the fluoride anion and the amide proton.

In summary these cyclisation studies have shown that high yield cyclisations with no epimerisation can be achieved with tertiary β-ketoamide esters using TBAF/THF, NaOMe/MeOH, or $KO^tBu/^tBuOH$ base systems provided prolonged treatment with the base is avoided.

Tautomerism Studies

The ^1H n.m.r. spectra of the 3-acyltetramic acids in Table VI in deuteriochloroform all showed the presence of two compounds in ratios ranging between 5:1 and 8:1. ^{13}C N.m.r. studies by Steyn and Wessels[125] have shown that these two sets of signals arise from the four different enolic forms (178 to 181, Scheme 68).

SCHEME 68

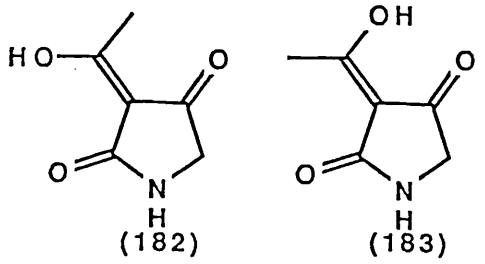


Interconversion between the internal tautomers (178 ⇌ 179 and 180 ⇌ 181) would be expected to be rapid since only proton transfer is required. By contrast, interconversion between the external tautomers (178, 179 ⇌ 180, 181) should be much slower since bond rotation as well as proton transfer is required. If the equilibria 178 ⇌ 179 and 180 ⇌ 181 were fast on an nmr time scale and the equilibrium 178, 179 ⇌ 180, 181 slow, this would lead to two sets of signals.

Steyn proposes that the two observed sets of signals are due to the interconversion of the external tautomers 178, 179 ⇌ 180, 181, the conversion between the internal tautomers occuring too quickly to be observed. Thus each of the observed set of signals represents an averaged chemical shift for each of the two pairs of internal tautomers (178 and 179, 180 and 181). By comparing ^{13}C n.m.r. shifts of carbons in the 3-acyltetramic acids with carbons in model compounds he was able to assign the two preferred tetramic acid tautomers as (179) and (181), the major tautomer being (181).

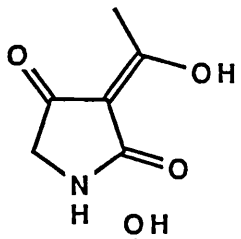
We also decided to investigate this tautomeric equilibrium by theoretical MNDO calculations. The results are shown in Table IX. The heat of formation of eight of the possible tautomers was calculated.

The MNDO calculated energies for these tautomers were found to agree qualitatively with the observations of Steyn and Wessels. Thus the two tautomers (182) and (183) were found to be the most preferred in terms of energy.

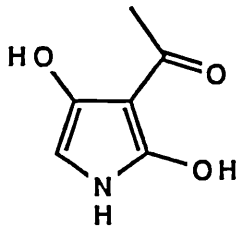


(182) (183)

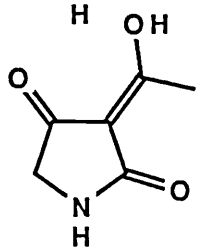
TABLE IX (showing calculated heat of formation / kcal mol^{-1})



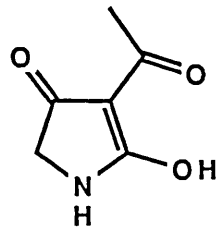
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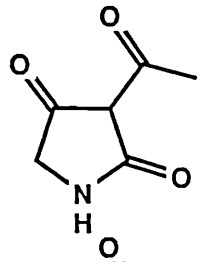
-106.32



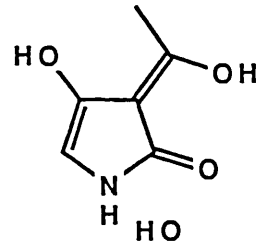
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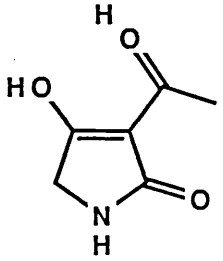
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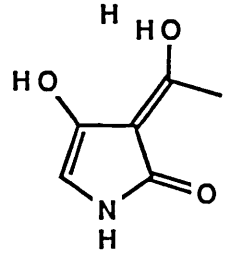
-108.81



-103.41



-107.49



-101.53

However the calculated value of the equilibrium constant K from the heat of formation ΔH_f was found not to agree with the observed value.

K was calculated as follows:

$\Delta G = \Delta H - T\Delta S$ G = Gibb's free energy

S = entropy T = temperature

For tautomers (182) and (183) ΔS was assumed to be the same.

$\therefore \Delta G = \Delta H$

also $\Delta G = -RT \ln K$ R = Gas constant

$\therefore \Delta H = -RT \ln k$

$\therefore \ln K = \frac{\Delta H}{-RT}$

$\Delta H = -2.4 \text{kcal mol}^{-1} = 2400 \text{ cal mol}^{-1}$

$R = 1.98 \text{ cal mol}^{-1}K^{-1}$

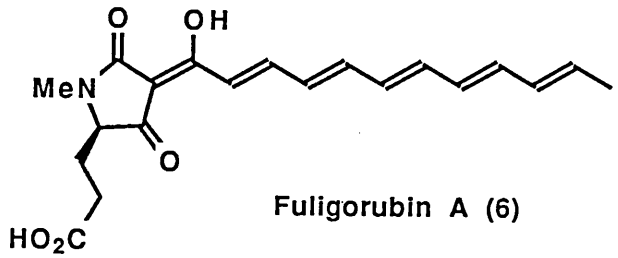
$T = 298K$

$\ln K = \frac{-2400}{-1.98 \times 298} = 4.07$

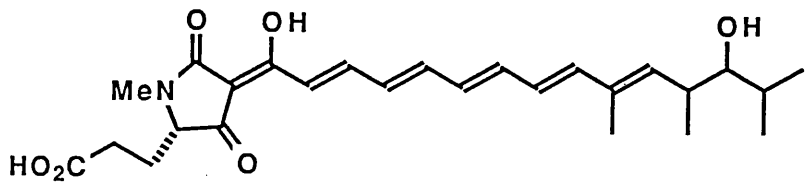
$K = 58.$

The observed value for the equilibrium ratio is 6:1 in deuteriochloroform. This wide quantitative difference is not surprising since the MNDO calculations fail to take into account any solvent effects or intermolecular interactions which would be expected to be highly influential in these tautomeric equilibria.

Using the β-ketoamide methodology developed and the clearer understanding of the experimental requirements of the Dieckmann reaction it was decided to embark on the synthesis of the 3-acyltetramic acid natural products fuligorubin A (6)[8] and β-lipomycin (7)[10].



Fuligorubin A (6)

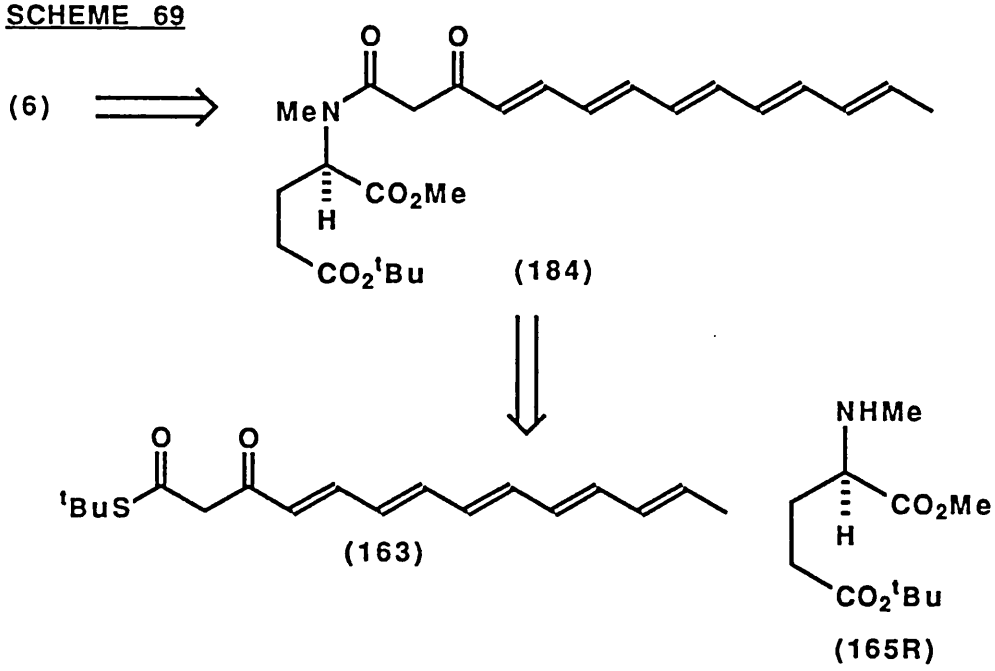


β-Lipomycin (7)

Fuligorubin A

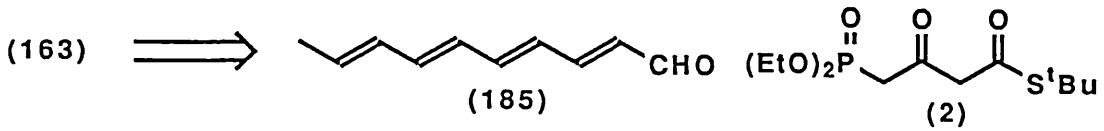
Fuligorubin A (6) was recently isolated[8] from the plasmodia of the flowers of tan, Fuligo septica (L.) Wiggers. After damp weather the flowers form yellow slime masses - the plasmodia. Light plays an important role in the complex life cycle of slime moulds and it was originally assumed that the yellow colour was due to the presence of flavins, flavones, polyenes, pteridines or phenolic compounds. It has now been shown that this yellow colour was due to the presence of fuligorubin A. The stereochemistry at the 5 position of the tetramic acid ring was shown to be (R) by circular dichroism. A possible retrosynthetic analysis of (6) is shown below (Schemes 69 and 70) which employs the methodology developed.

SCHEME 69



The final steps of the proposed synthesis involve the Dieckmann reaction followed by hydrolysis of the ^{t}butyl ester, the immediate precursor being the β-ketoamide diester (184) which should be available by trans-amination from the β-ketothioester polyene (163) and the glutamic acid derivative (165R). (163) should be available by reaction of the thioester phosphonate (2), described in Part A, with the polyene aldehyde (185, Scheme 70).

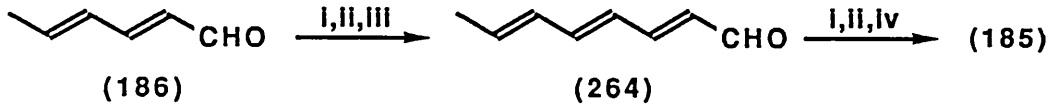
SCHEME 70



Synthesis

The polyene aldehyde (185)[126] was prepared in an overall yield of 24% from commercially available trans,trans-hexa-2,4-dienal (186, Scheme 71).

SCHEME 71

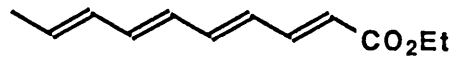


(186) (264)

Reagents : I, $(EtO)_2P(O)CH_2CO_2Et$, NaH ; II, DIBAL ; III, MnO_2 ; IV, $BaMnO_4$

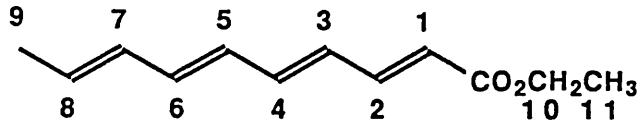
The only problem with this preparation occurred with the second allylic oxidation stage to give (185). TLC monitoring of the reaction using manganese dioxide for the oxidation indicated a rapid quantitative transformation to the aldehyde. Unfortunately only a 27% isolated yield of the aldehyde could be realised. It was necessary to use 30 equivalents of MnO_2 to effect the oxidation and the low yield was attributed to the difficulty in recovering the product from the solid matrix left after the reaction. The reaction using $BaMnO_4$[127] required only 8 equivalents of oxidant and gave a 76% yield of the aldehyde.

The coupling constants in the 500 MHz ^{1}H n.m.r. spectrum showed that the polyene ester (187) contained only trans double bonds. The coupling constants between each pair of vinylic protons on the double bonds were between 14.8 and 15.3 Hz. It proved possible to assign every proton in this spectrum and the shifts and coupling constants are shown in Table X. The spectrum showed the ester to be greater than 95% of the desired all trans compound; there were only minor traces of the other geometrical isomers.



(187)

TABLE X

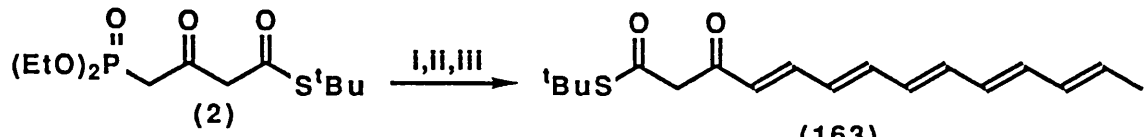


(187)

Shift/ppm δ	Multiplicity	J/Hz	Assignment (No. of H)
1.29	t	7.2	11(3H)
1.81	d	6.8	9(3H)
4.20	q	7.2	10(2H)
5.84	d	15.3	1(1H)
5.85	dq	6.8; 15.0	8(1H)
6.14	dd	10.8; 15.0	7(1H)
6.18	dd	11.0; 14.9	5(1H)
6.28	dd	11.5; 14.8	3(1H)
6.37	dd	10.8; 14.9	6(1H)
6.56	dd	11.0; 14.8	4(1H)
7.31	dd	11.5; 15.3	2(1H)

Reaction of the thioester phosphonate (2) with the polyene aldehyde (185, Scheme 72) gave a 61% yield of the β-ketothioester polyene (163).

SCHEME 72



(2) (163)

Reagents : I, NaH, THF ; II, (185) ; III, H^+

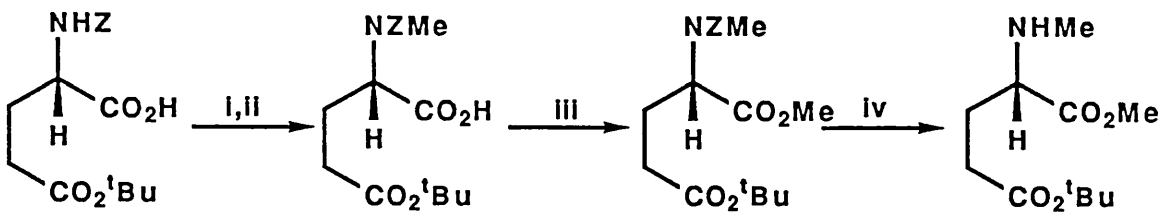
Careful interpretation of the ^1H n.m.r. spectrum showed the geometry of the newly generated double bond to be (E) (J 14.8 Hz). This compound was found to exist exclusively as the enol tautomer in deuteriochloroform solution.

The stereochemistry of fuligorubin A at the 5 position had, as already mentioned, been determined as (R) from circular dichroism experiments. This would require the use of the unnatural (R) glutamic acid derivative. The enantiomer (165S) derived from the natural (S) amino acid had already been synthesised in gram quantities for the β-lipomycin work (vide infra). For the fuligorubin A work it was

decided initially to use the natural glutamic acid derivative (165S) in order to test the suitability of the methodology for the total synthesis.

The glutamic acid derivative (165S) required for the next step was prepared from the commercially available derivative (188) as shown in Scheme 73.

SCHEME 73



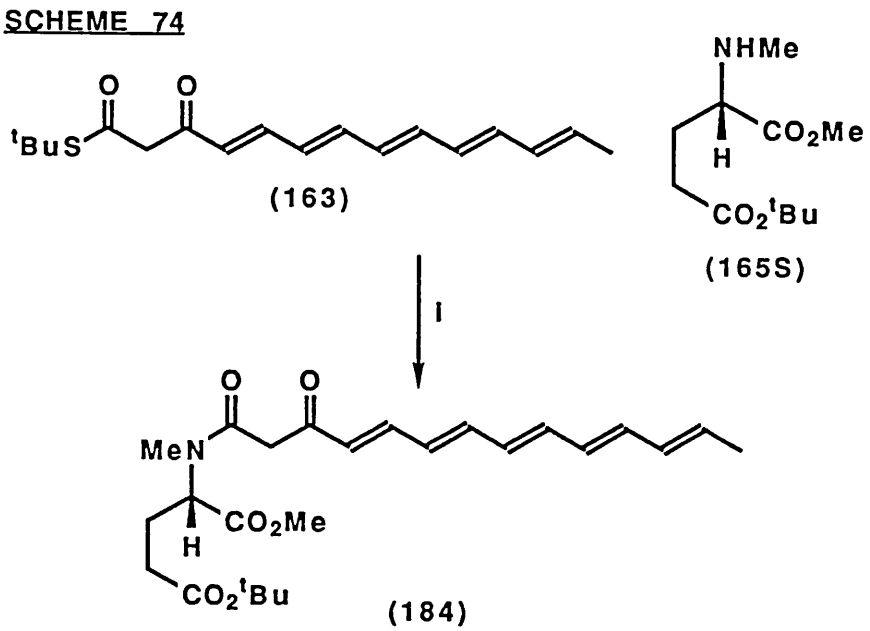
(188) (189) (190) (165S)

Reagents : I, NaH, MeI ; II, H^+ ; III, DCC, DMAP, MeOH ; Iv, H_2 Pd/C

Treatment of (188) with 3 equivalents of sodium hydride followed by 5 equivalents of methyl iodide gave, after careful acidification, the N-methylated derivative (189) in 63% yield[121]. Mild esterification using dicyclohexylcarbodiimide, 4-N,N-dimethylaminopyridine and methanol gave (190) in 85% yield[122/123]. The benzyloxycarbonyl group was removed by catalytic hydrogenation in the usual way to give (165S) in 94% yield.

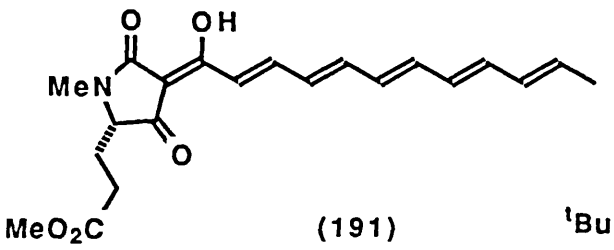
Treatment of a mixture of the β-ketothioester polyene (163) and the glutamic acid derivative (165S) in THF with silver(I) trifluoroacetate led to the rapid consumption of the starting materials with the formation of a single product by TLC. This was the β-ketoamide (184) formed in an isolated yield of 70% (Scheme 74).

SCHEME 74

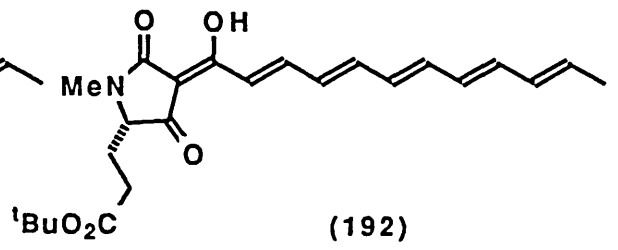


Reagents : I, $Ag(I)OCOCF_3$, THF

The Dieckmann reaction was tried initially using the sodium methoxide/methanol base system. On a small scale (5mg) this reaction appeared to work quite well by TLC. However, not surprisingly, some transesterification of the ^{t}butyl ester took place to give a mixture of (191) and (192).



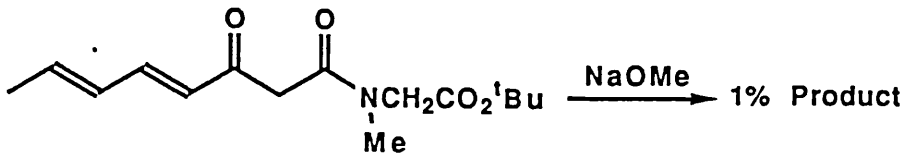
(191)



(192)

Therefore the ^{t}butyl ester was hydrolysed first using neat formic acid[128] and then treated with sodium methoxide/methanol. On a small scale (2mgs) the cyclisation appeared to work well by TLC and ^{1}H n.m.r. However, on scaling up (100mgs) a very low yield of product was obtained and unfortunately extensive polymerisation was observed. Later it was found that Rinehart had also reported problems using this base system in the Dieckmann reaction on similar systems (Scheme 75)[25].

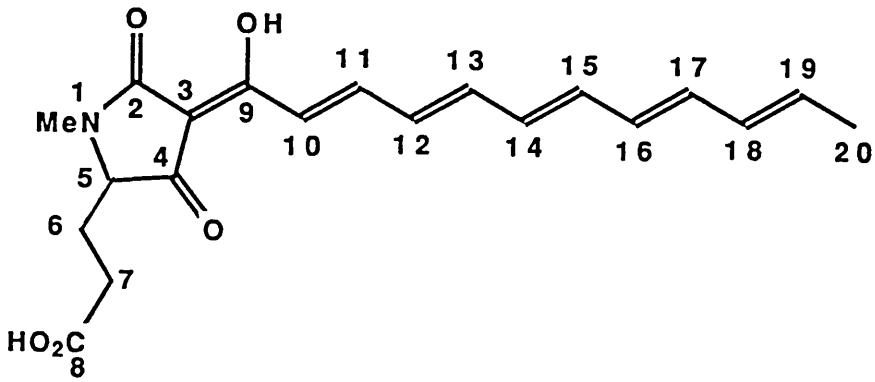
SCHEME 75



The large scale reaction gave a crude yield of only 5mg of material. Problems were also encountered when attempts were made to purify this material. The purification procedure involved column chromatography on silica gel pretreated with aqueous oxalic acid using oxalic acid saturated chloroform as the eluent. This technique had been used by Zeeck in the isolation and purification of β-lipomycin. The product was contaminated with oxalic acid which proved very difficult to remove. Satisfactory data could not be obtained on the compound but the best data obtained is listed below and is compared with that of the natural product[8] (Table XI).

TABLE XI

Numbering System



Fuligorubin A - Published Spectral Data (d_6 Acetone)

Shift/ppm δ	Multiplicity	J/Hz	No. of H	Assign.
1.80	d	7	3	20-Me
2.20	m	-	2	6-CH_2
2.31	m	-	2	7-CH_2
3.0	s	-	3	N-Me
3.9	m	-	1	5H
5.88	dq	16; 7	1	19H
6.20	dd	16; 11	1	18H
6.31	dd	16; 11	1	16H
6.42	dd	16; 11	1	17H
6.48	dd	16; 11	1	14H
6.60	m	-	2	12H;15H
6.90	dd	16; 11	1	13H
7.13	d	16	1	10H
7.51	dd	16; 11	1	11H

Table XI (continued)

Synthetic Material (Deuteriochloroform)

Shift/ppm δ	Multiplicity	J/Hz	No. of H	Assign.
1.83	d	7	3	20-Me
2.06	m	-	2	6-CH_2
2.37	m	-	2	7-CH_2
3.0	s	-	3	N-Me
3.76	m	-	1	5H
5.86	dd	16; 7	1	19H
6.20 (6:1→ 6.3)	m	-	2	
6.35 (6.3→ 6.4)	m	-	2	12-18H
6.50 (6.4→ 6.6)	m	-	2	
6.75 (6.6→ 6.9)	m	-	1	
7.16	d	16	1	10H
7.53	dd	16; 11	1	11H

Due to the lack of material (<0.25mg) it was decided to run the ^1H n.m.r. spectrum in deuteriochloroform solution even though the data on the isolated natural product was obtained in d_6 acetone. Therefore the shifts of corresponding signals do not exactly match. Also, in deuteriochloroform, the compound was found to exist as a 5:1 tautomeric mixture which considerably complicated the spectrum of the polyene protons. Only one tautomer was reported in d_6 acetone. In Table XI only the data on the major tautomer in deuteriochloroform is reported.

Ultraviolet Spectrum/nm (EtOH)		EtOH and one drop of NaOH	
Reported (log ε)	Found	Reported	Found
243 (4.16)	256(m)	243	254
271 (sh, 4.11)	280 (sh, s)	377	384
425 (4.43)	446 (l)		

The extinction coefficient ε could not be reliably calculated for the synthesised material because of the oxalic acid present. The synthetic material showed similar u.v. behaviour when one drop of sodium hydroxide was added. Again the wavelengths of the peaks do not correspond exactly, presumably because of the oxalic acid present.

Mass Spectrum

This was found to contain all the major peaks present in the published data.

M^+ 357, 339, 212, 194, 172, and 145.

Infra-red Spectrum

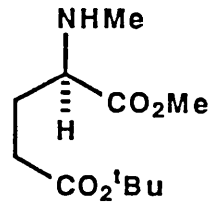
No meaningful i.r. spectrum could be obtained because of the oxalic acid present.

CONCLUSION

That the enantiomer of fuligorubin A was synthesised is beyond doubt as can be seen from the data listed. A better yield in the Dieckmann reaction would have been obtained by using the $KO^tBu/^tBuOH$ base system. However the superiority of this system for cyclisations with these polyene substrates was not realised until it was too late.

An alternative method of purification of these types of compounds obviously needs to be found. The natural product was purified by gel filtration, but in our case, lack of material, time, and expertise in this technique ruled it out as a means of purification. Another possible purification technique could be reverse phase HPLC. This has recently been found to work very well for other 3-acyltetramic acids.

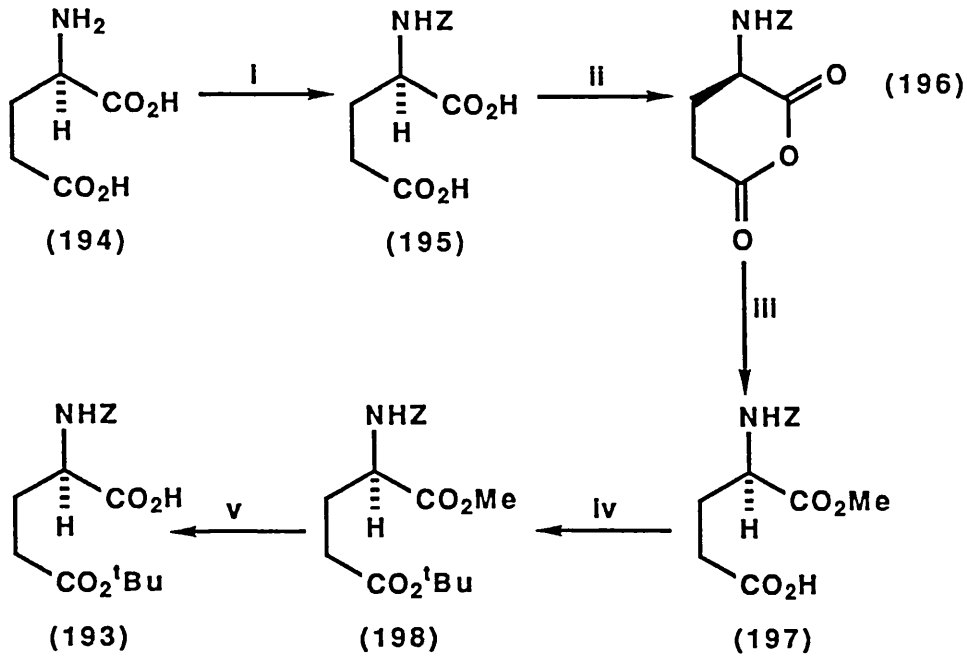
For a successful synthesis of the natural enantiomer of fuligorubin A the other enantiomer (165R) of the glutamic acid derivative (165S) would be required.



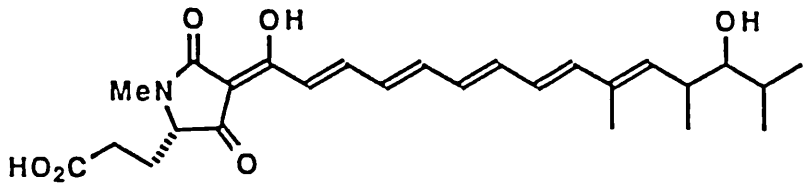
(165R)

(193) is commercially available but quite expensive. It could be prepared by the following route starting from (R) glutamic acid (194), (Scheme 76).

SCHEME 76



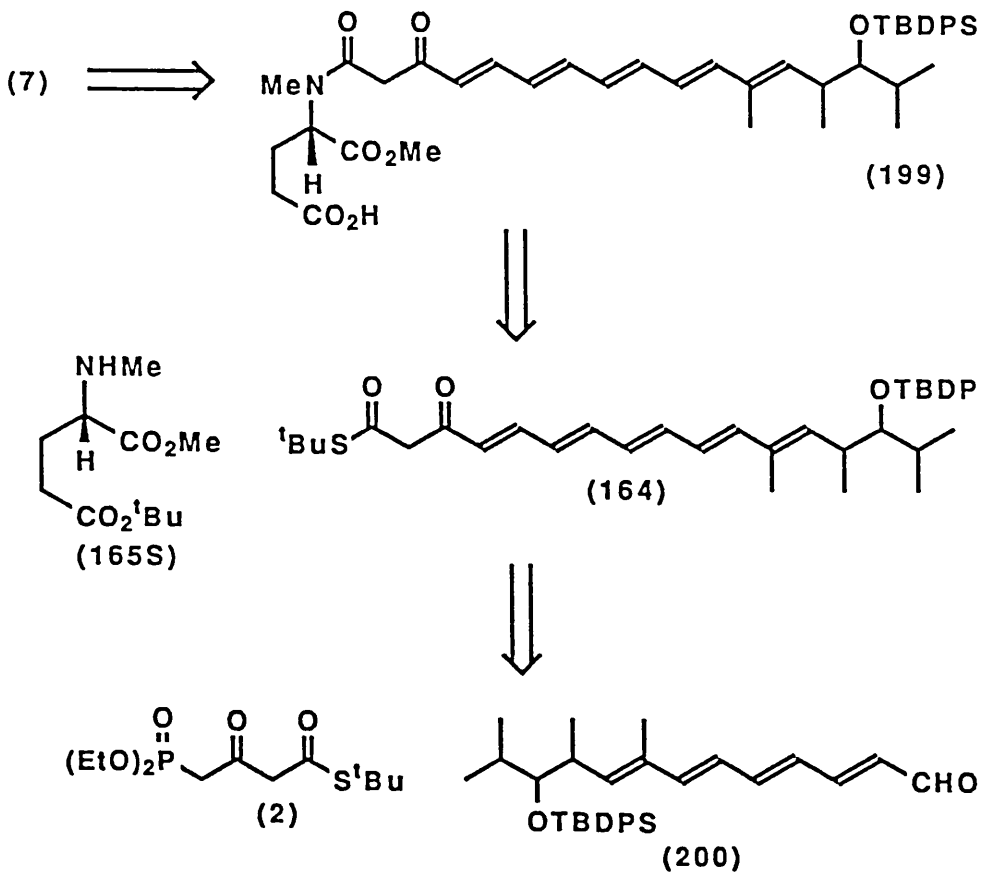
Reagents : I, Z-Cl, NaOH ; II, DCC ; III, NaOMe ; Iv, ^{t}BuOAc, $HClO_4$; v, NaOH, H_2O



β-Lipomycin (7)

β-Lipomycin (7) was isolated in 1973 by A. Zeeck from *Streptomyces aureofaciens*[10]. It was found to possess activity against Gram-positive bacteria. Unfortunately Zeeck was unable to determine either the relative or absolute configuration of the two chiral centres on the polyene side chain. The absolute configuration of the 5-position was shown to be (S) by degradation of the natural product to (S)-N-methyl-glutamic acid. For this reason it was decided to embark on a racemic synthesis of β-lipomycin polyene, while using the glutamic acid derivative (165S) derived from the natural (S) amino acid. The retro-synthetic scheme is shown (Scheme 77).

SCHEME 77

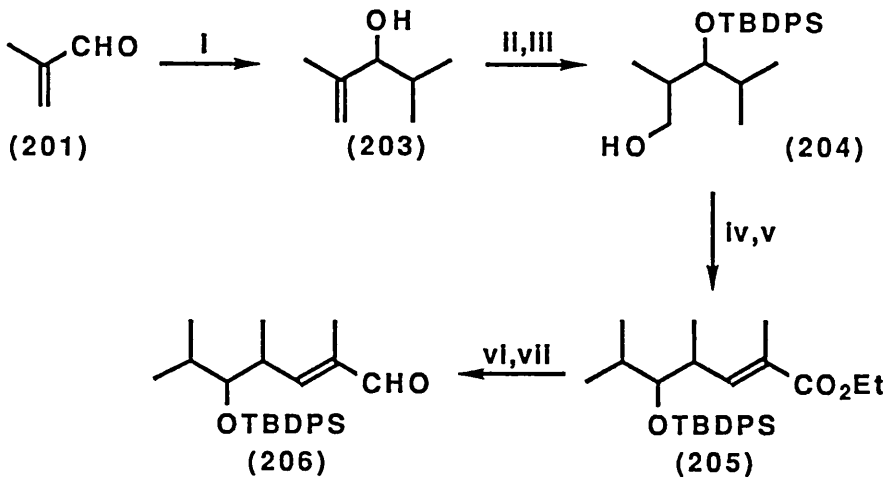


Dieckmann reaction of the β-ketoamide polyene (199) followed by removal of the ^{t}butyldiphenylsilyl protecting group would give β-lipomycin (7). The amide would be available after ^{t}butyl ester hydrolysis from reaction of the β-ketothioester polyene (164) and the glutamic acid derivative (165S). The β-ketothioester polyene (164) could be prepared by reaction of the polyene aldehyde (200) with the thioester phosphonate (2).

Synthesis

Intermediate (206) for the racemic polyene aldehyde (200) was synthesised by the following route (Scheme 78).

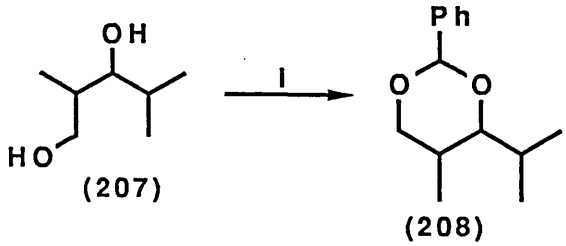
SCHEME 78



Reagents : I, ^{i}PrMgCl (202) then H^{+} ; II, TBDPSCl, Imidazole, DMF ; III, BH_3.DMS, THF then H_2O_2, NaOH/H_2O ; iv, PCC ; v, $Ph_3P{=}C(Me)CO_2Et$; vi, DIBAL ; vii, MnO_2

Reaction of isopropylmagnesium chloride (202) with methacrolein (201) gave exclusively the product of 1,2 addition (203) in 65% yield[129]. Protection of the allylic alcohol as the ^{t}butyldiphenylsilyl ether[130] followed by hydroboration and oxidative work up gave the alcohol (204) in 68% overall yield. Some stereoselectivity was observed in this reaction - a 2:1 ratio of diastereoisomers was obtained. A sample of the mixture was separated by column chromatography and the major diastereoisomer was deprotected (207, 3% HCl/MeOH) and converted into the benzylidene acetal (208) in a yield of 87% (Scheme 79).

SCHEME 79



(207) (208)

Reagents : I, PhCHO, PTSA

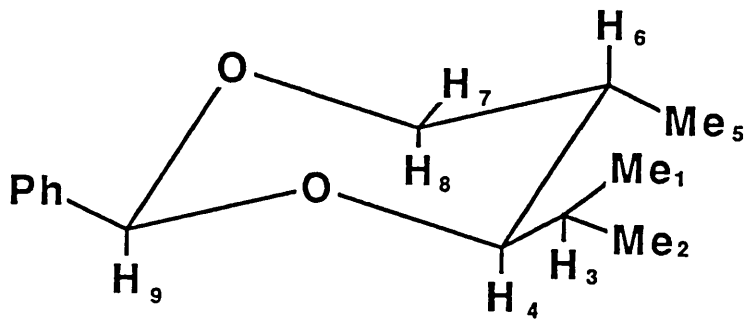
The ^{1}H n.m.r. data on the cyclic acetal (208) is shown in Table XII.

From the Table it can be seen that proton 4 is coupled to proton 6 with a coupling constant of 10.0Hz. Thus protons 4 and 6 are diaxial. Protons 6 and 8 are coupled with a coupling constant of 11.1Hz and are thus diaxial. Protons 6 and 7 are coupled with a coupling constant of 4.7Hz and are thus axial and equatorial respectively. Therefore the relative stereochemistry of protons 6 and 8 can be assigned as diaxial as shown in (209). The relative stereochemistry of the acetal is as shown in (209) and the major diastereoisomer produced during the hydroboration process is 2S*,3R* (210), after deprotection.

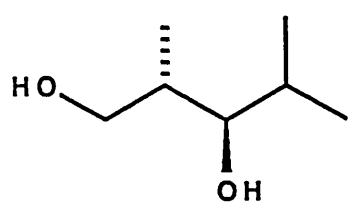
(Asterisks are used to indicate relative stereochemistry).

TABLE XII

Shift/ppm δ	Multiplicity	J/Hz	No. of H	Assignment
0.77	d	6.7	3	5-Me
0.98	d	6.9	3	1 & 2 Me's
1.07	d	6.9	3	1 & 2 Me's
1.98	m	-	2	3 & 6H
3.31	dd	2.1/10.0	1	4H
3.50	t	11.1	1	8H
4.10	dd	4.7/11.1	1	7H
5.47	s	-	1	9H
7.28→7.53	m	-	5	Aromatics

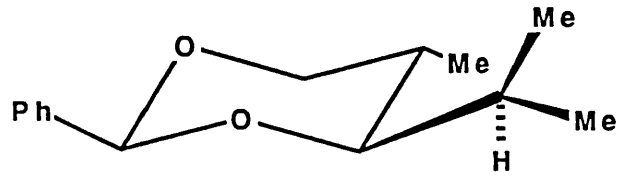


(209)



(210)

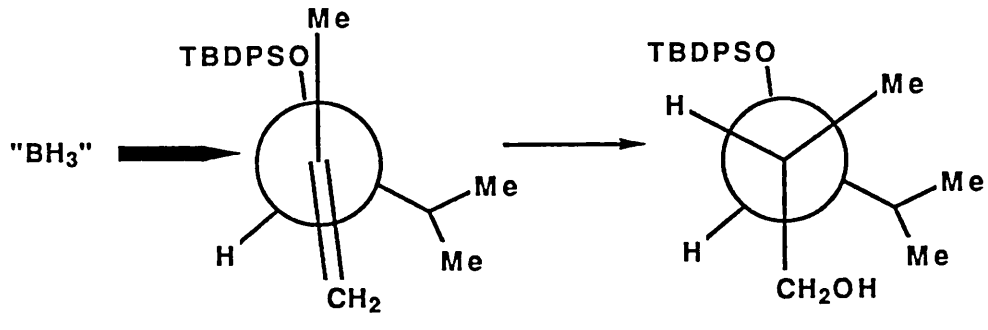
The low value for the coupling constant of proton 4 with proton 3 on the isopropyl group is probably due to the conformational preference shown by the isopropyl group as depicted in (211).



(211)

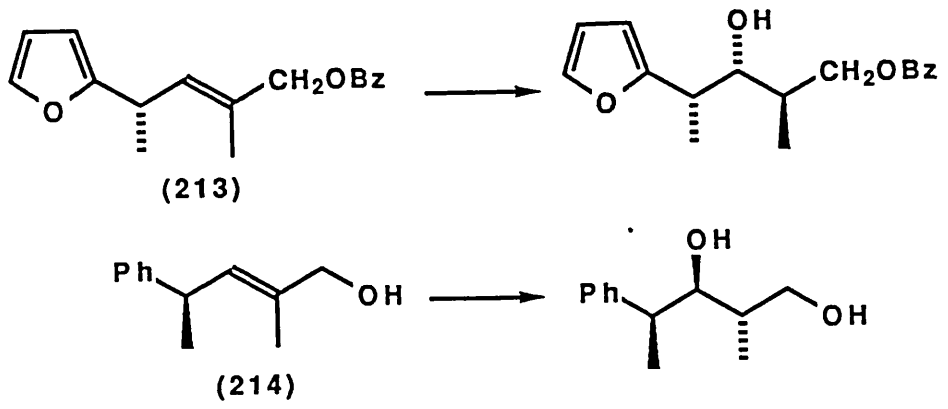
This orientation would minimise any steric interactions with the 5 methyl group and would result in a dihedral angle between the proton 4 and proton 5 of between 75^0 to 85^0.

The origin of the hydroboration stereoselectivity, albeit modest, probably arises from the conformational preference shown by the molecule. These types of system tend to adopt the eclipsed conformation shown (212) and attack by the borane reagent occurs from the less hindered <u>si</u> face of the double bond in a Cram sense as shown[131].



(212)

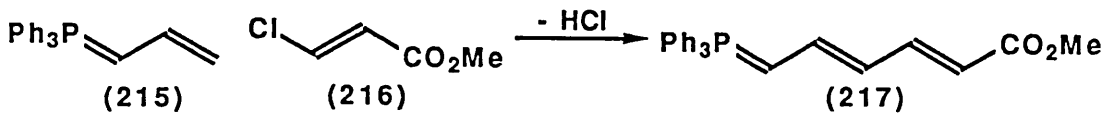
Higher stereoselectivities have been observed with hydroborations in other related systems by Kishi (213)[132] and Matsumoto (214)[133].



PCC oxidation of (204) (Scheme 78) followed by Wittig reaction with 1-carbethoxyethylidenetriphenylphosphorane gave the desired α,β-unsaturated ester (205) in an overall yield of 67%. The allylic alcohol obtained from (205) by DIBAL[134] reduction was examined in a nuclear Overhauser experiment and was found to have the (E) geometry. A small amount (<5%) of what was presumably the (Z) α,β-unsaturated ester was also formed in the Wittig reaction but this could be separated by column chromatography. DIBAL reduction and MnO_2 allylic oxidation of (205) gave the aldehyde (206).

Two routes were examined for the elaboration of (206) into the required polyene aldehyde (200). The first and most direct route involved chemistry developed by Vedejs[135] and recently modified and used by Hanessian[136]. Vedejs has shown that reaction of triphenylallylphosphorane (215) with β-chloroacrylate esters (216) occurs <u>via</u> the γ carbon of the ylide and the β-carbon of the unsaturated ester to give after elimination of chloride and base treatment the phosphorane (217) (Scheme 80).

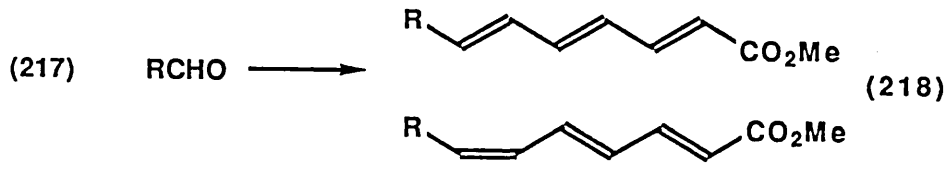
SCHEME 80



(215) (216) (217)

The phosphorane (217) is not isolated but is reacted in situ with aldehydes to give the polyene esters (218) as a mixture of isomers about the 6-7 double bond (Scheme 81).

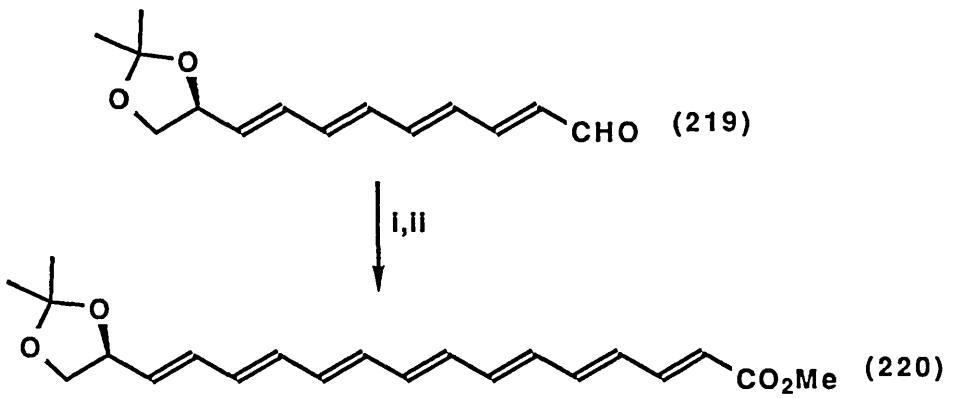
SCHEME 81



(218)

Hanessian used an adaptation of this procedure involving the addition of 2,6-di-^{t}butylphenol (10%) as a radical scavenger and proton source. It reportedly gave consistently cleaner reactions and one example is shown in Scheme 82.

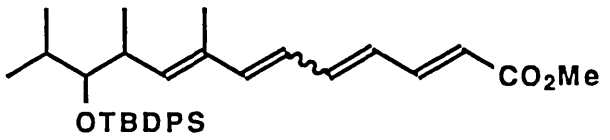
SCHEME 82



Reagents : I, (217) ; II, catalytic I_2, CH_2Cl_2

Reaction of the phosphorane with the polyene aldehyde (219) gave a 1:1.75 mixture of heptaene double bond isomers (cis-trans about 6 double bond). Treatment of this mixture with a catalytic amount of iodine in CH_2Cl_2 gave the all trans compound (220) in 74% overall yield.

In our case treatment of the aldehyde (206) under the Hanessian reaction conditions gave none of the desired polyene (221), only unconverted aldehyde starting material being recovered.



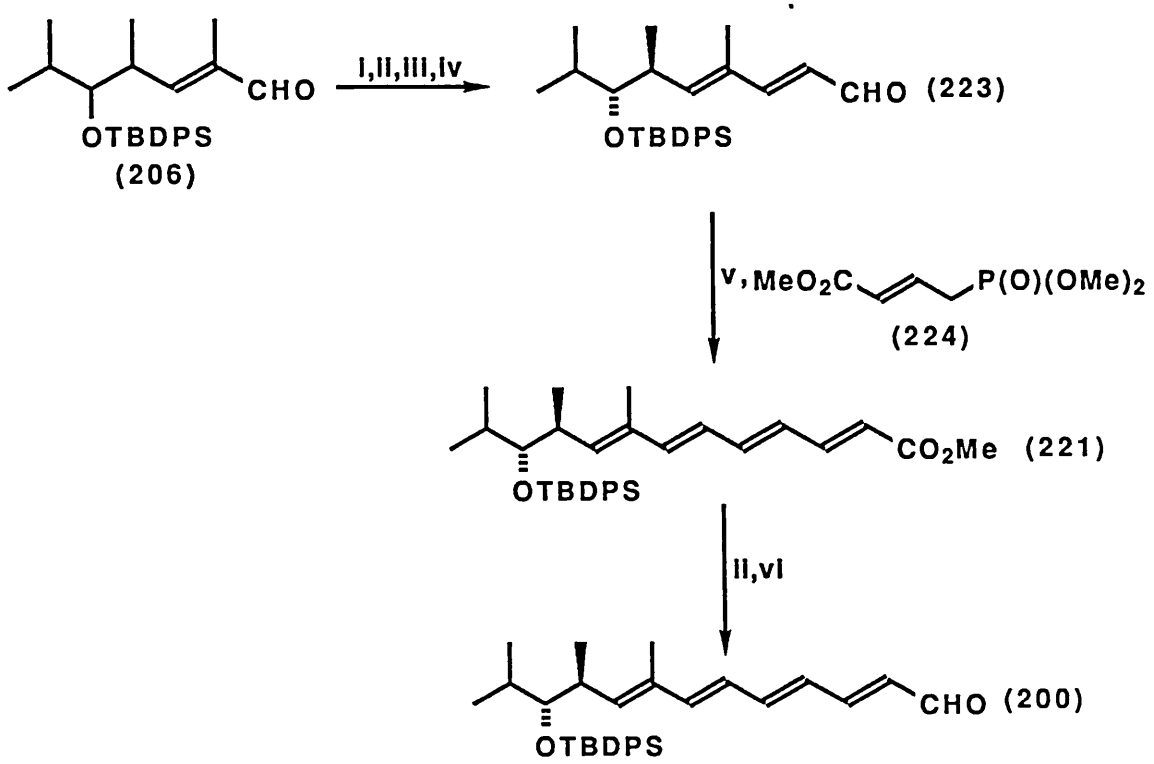
(221)

The use of forcing conditions (2 days at reflux in THF) had no effect but carrying out the reaction under the Vedejs conditions did give an 18% yield of the desired polyene (221) as a 6:5 ratio of geometric isomers about the 6 double bond.

The Vedejs conditions do not involve the use of 2,6-di-^{t}butylphenol and require an excess of the aldehyde.

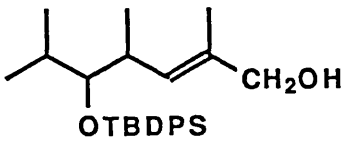
However the double bond isomer mixture could not be isomerised using iodine in CH_2Cl_2, only decomposition occurring. No other isomerisation methods were tried and this approach was abandoned. The second route, although involving more steps was successful (Scheme 83).

SCHEME 83

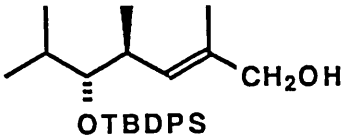


Reagents : I, $Ph_3P{=}CHCO_2Et$ (222) ; II, DIBAL ; III, HPLC separation ; Iv, MnO_2 ; v, NaOMe, DMF ; vI, $BaMnO_4$

Reaction of the aldehyde (206) with the phosphorane (222) followed by DIBAL reduction and MnO_2 allylic oxidation gave the aldehyde (223) in 44% overall yield. Only one double bond isomer could be detected by ^1H n.m.r. spectroscopy. It was found that the two diastereoisomers of the allylic alcohol (271) could be readily separated by HPLC.



(271)

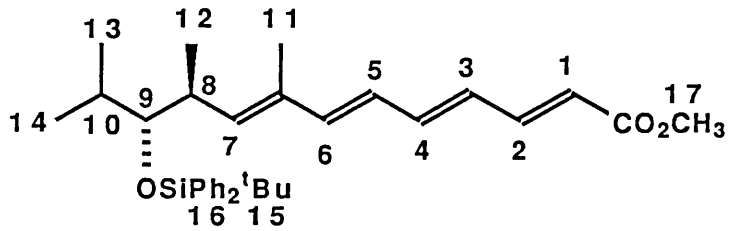


(272)

The major diastereoisomer (272) , previously shown to be of 6R*,7S* relative configuration was taken through the rest of the synthesis.

Treatment of a mixture of the aldehyde (223) and the crotonylphosphonate (224)[137] in DMF with sodium methoxide gave a 46% yield of the polyene ester (221) after chromatography. Careful inspection of the ^{1}H n.m.r. spectrum showed this compound to be one major double bond isomer (>90%) which could be assigned as all trans from the relevant coupling constants (Table XIII).

TABLE XIII

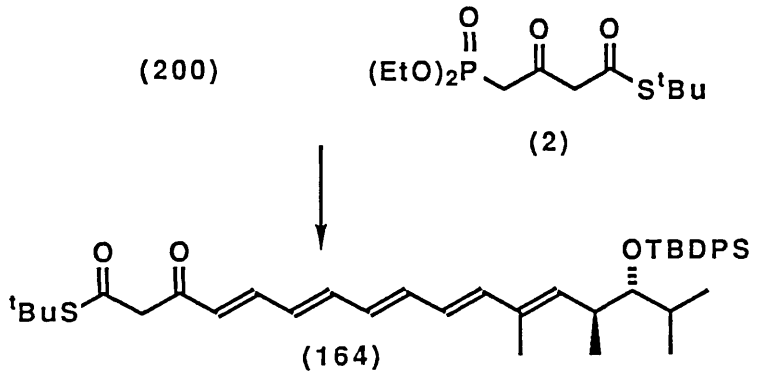


(221)

Shift/ppm δ	Multiplicity	J/Hz	No. of H	Assignment
0.8→0.9	m	-	9	12,13 & 14-Me's
1.1	s	-	9	t-Butyl (15)
1.59	s	-	3	11-Me
1.80	m	-	1	10H
2.65	m	-	1	8H
3.50	m	-	1	9H
3.75	s	-	3	17-Me
6.33	d	15.3	1	1H
7.35	dd	15.3;11.3	1	2H
6.30	dd	14.7;11.3	1	3H
6.60	dd	14.7;10.8	1	4H
6.14	dd	15.2;10.8	1	5H
5.85	d	15.2	1	6H
5.76	d	9.5	1	7H
7.3→7.45;7.7	m	-	10	aromatics

DIBAL reduction followed by oxidation gave the tetraene aldehyde (200) in an overall yield of 72%. Reaction of (200) with the thioester phosphonate (2) gave a 62% yield of the β-ketothioester polyene (164) (Scheme 84).

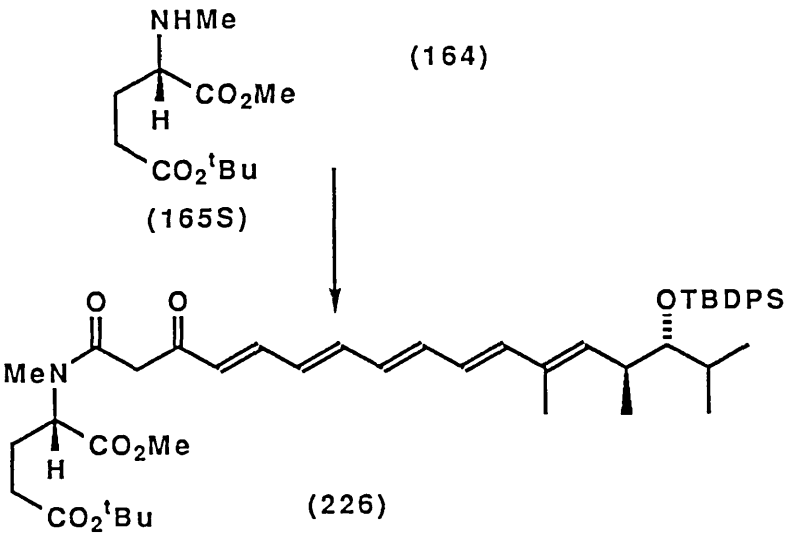
SCHEME 84



This compound existed exclusively as the enol tautomer and the geometry of the new double bond could be assigned as (E) from the coupling constant (J = 15.0Hz) in the ^1H n.m.r. spectrum.

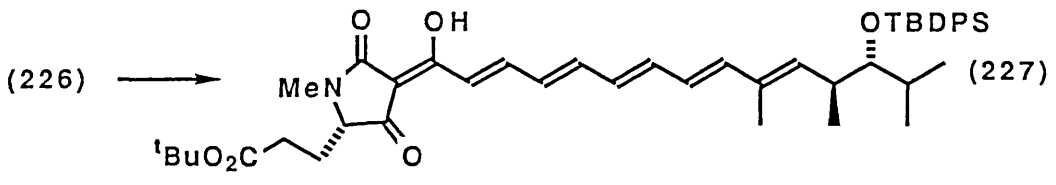
Treatment of a mixture of the β-ketothioester polyene (164) and the glutamic acid derivative (165S) in buffered THF at room temperature with silver(I) trifluoroacetate gave the desired β-ketoamide polyene (226) in 49% yield (Scheme 85).

SCHEME 85



As a result of experience gained in the synthesis of fuligorubin A isomer it was decided to try the Dieckmann reaction with $KO^tBu/^tBuOH$. This was found to rapidly and cleanly cyclise (226) to the 3-acyl-tetramic acid (227)in an isolated yield of 85% (Scheme 86).

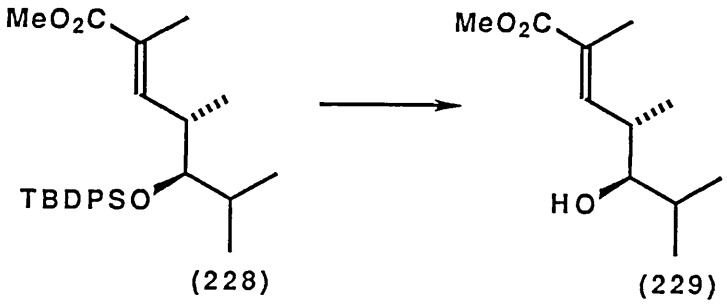
SCHEME 86



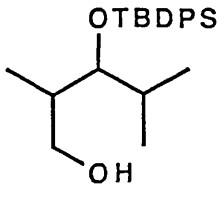
Attempted cyclisation with TBAF at room temperature proved to be extremely slow. This created problems since it was hoped that TBAF could be used to remove the silyl protecting group. Due to the value and the shortage of material at this stage it was decided to look at model systems to investigate alternative methods of removing the silyl protecting group.

With compound (228), TBAF was found to remove the silyl ether only very slowly, taking 14 days at room temperature for the reaction to go to completion giving (229) in only 35% yield (Scheme 87).

SCHEME 87

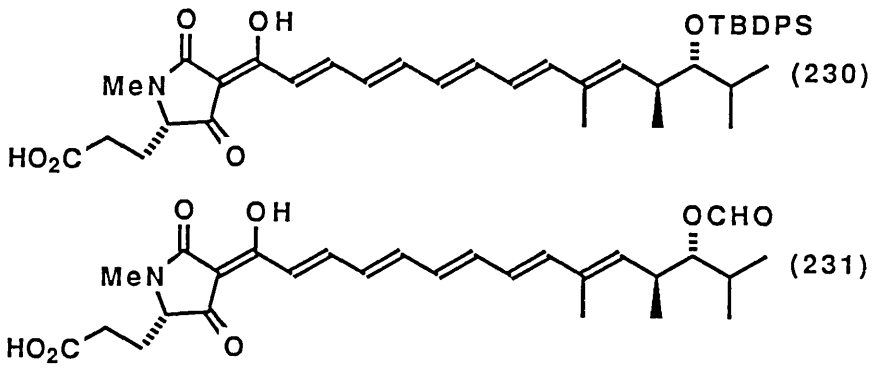


3% HCl/MeOH[138] was also tried and found to be even slower. The reaction did not reach completion even after 3 weeks. With compound (204) used in the benzylidene acetal studies 3% HCl/MeOH removed the silyl protecting group quite cleanly over two days at room temperature to give the diol in 87% yield.



(204)

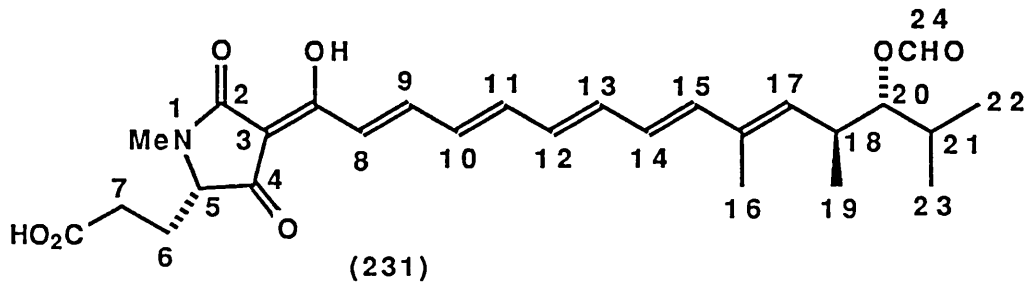
After these unsuccessful attempts to remove the protecting group it was decided to turn attention to the hydrolysis of the ^{t}butyl ester. Trifluoroacetic acid in CH_2Cl_2[139] was tried initially but this led rapidly to decomposition of the compound. Neat formic acid[128] rapidly removed the ester (15 minutes at room temperature) but gave a mixture of two compounds and examination of the mass spectrum and ^{1}H n.m.r. spectrum of this mixture indicated that it consisted of the desired acid (230) and the formate ester (231).



It was found that prolonged treatment (48 hours) of (227) resulted in complete removal of the ^{t}butyldiphenylsilyl group to give the formate ester. TLC analysis of the reaction mixture showed that no decomposition had occurred.

Compound (231) was purified on silica gel treated with oxalic acid as before. The same problems encountered with fuligorubin A involving the removal of the oxalic acid were experienced with (231). The spectral data for the formate ester (231) is shown below in Table XIV.

TABLE XIV



(231)

^{1}H n.m.r. DATA

Shift/ppm δ	Multiplicity	No. of protons	Assignment
0.8→1.0	m	9	19,22 & 23-Me's
1.82	s	3	16-Me
2.05	m	1	18H
2.2→2.5	m	4	6 & 7-Me's
3.0	s	3	N-Me
3.8	m	1	5H
4.8	m	1	20H
6.2→7.5	m	-	8→15 & 17H
8.05 & 8.14	s	1	24H
Proton 21 under broadened H_2O peak			

TABLE XIV (continued)

MAIN MASS SPECTRUM PEAKS

485 (M^+), 457 ($M^+ - CO$), 439 ($M^+ - H_2O$), 385, 212, 185, and 125

Conversion of (231) to β-lipomycin was attempted using K_2CO_3/ MeOH[140]. TLC analysis of the reaction mixture after 14 hours indicated the reaction had gone to completion and apparently quite cleanly. The product was again purified by chromatography on silica gel impregnated with oxalic acid, but due to the small scale of the reaction (<0.2mg) sufficient material could not be isolated for full characterisation. A problem here seemed to be the affinity of the final compound for the drying agents used during the oxalic acid removal procedure.

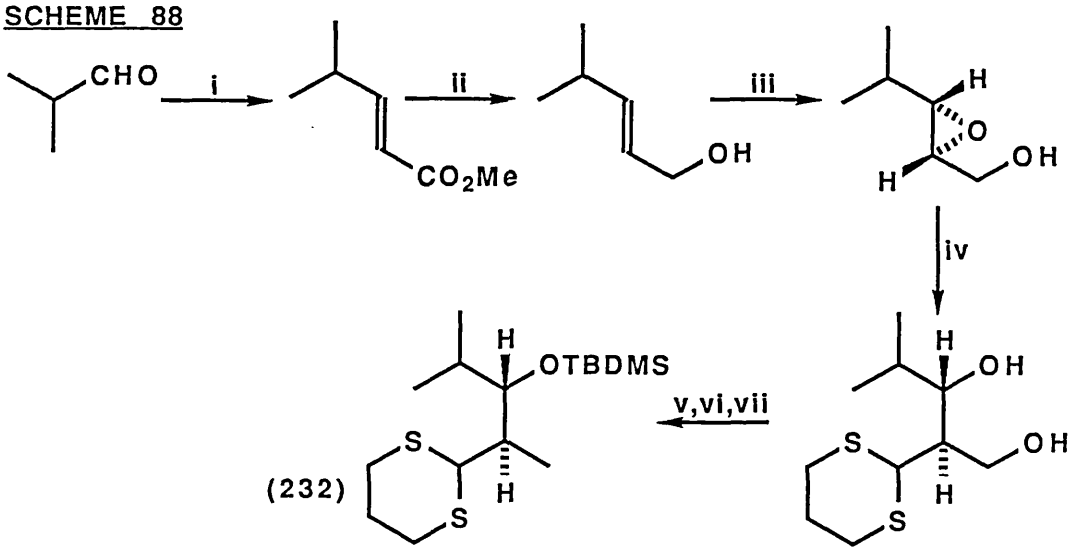
The most effective method tried to remove the oxalic acid was to wash the solid obtained from the reaction copiously (25 to 30 times) with water. The compound is then dissolved in CH_2Cl_2 and dried over magnesium sulphate or sodium sulphate. Even after washing the solid 30 times with water, oxalic acid still remained. It was during the drying process over magnesium sulphate that the product was lost owing to adhesion onto the drying agent. The same result occurred with sodium sulphate and it could not be washed off either solid.

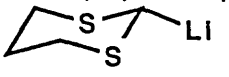
Conclusion

Assuming that the absolute stereochemistry is still unknown, the synthesis of the natural enantiomer of the β-Lipomycin would require all four stereoisomers of the two chiral centres on the polyene, and both glutamic acid enantiomers.

A recently publication by Lipshutz[141] on his studies towards roflamycoin describes the preparation of the fragment (232) by the following reaction sequence (Scheme 88).

SCHEME 88



Reagents : i, $(MeO)_2P(O)CH_2CO_2Me$, NaH ; ii, $LiAlH_4$; iii, Sharpless Epoxidation (+)Diethyl Tartrate ; iv,  ;

v, TsCl ; vi, $LiAlH_4$; vii, TBDMSOTf

This sequence could be extended to prepare all four stereoisomers of (232) which might be required for a synthesis of optically pure β-lipomycin.

Summary

It has been demonstrated that the silver(I) mediated conversion of β-ketothioesters into β-ketoamides is a viable process for a wide range of substituted β-ketothioesters and amines. It occurs rapidly, under mild conditions, and usually in good yield.

Studies on the Dieckmann reaction to form 3-acyltetramic acids have shown that several base systems can be used for the cyclisation, which under carefully monitored conditions, result in no epimerisation at the 5 position of the tetramic acid. This methodology has been shown to be applicable to the synthesis of a variety of 3-acyltetramic acids.

The overall synthetic strategies used for β-lipomycin and fuligorubin A are quite viable provided the Dieckmann reactions are carried out using the $KO^tBu/^tBuOH$ base system and an alternative protecting group is chosen for the sidechain OH of the β-lipomycin synthesis (e.g. ^{t}butyldimethylsilyl).

Recent work on the purification of 3-acetyltetramic acids using reverse phase HPLC has given very good results and looks quite promising as a means of purification.

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer 983G as a thin-film, a nujol mull, or in chloroform solution. ^{1}H N.m.r. spectra were recorded at 90MHz on a Jeol FX 90Q, at 250 MHz on a Bruker WM-250, and at 500 MHz on a Bruker AM-500 instrument. Mass spectra were measured on a VG micromass 7070B instrument. Elemental microanalyses were performed by the staff of the Imperial College Chemistry Department microanalytical laboratory.

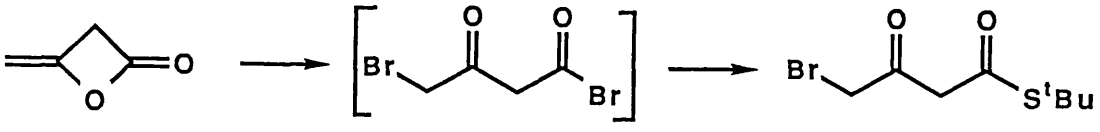
Analytical thin-layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and preparative chromatography was conducted under low pressure using MN Kieselgel 60 (230-400 mesh); silica-gel refers to this grade of Kieselgel.

Petrol refers to redistilled, light petroleum ether with b.p. 40-60^{0}C and ether refers to diethyl ether and was undistilled for all column chromatography. Ether, tetrahydrofuran and 1,2-dimethoxyethane for reaction purposes were distilled from sodium-benzophenone ketyl under an argon atmosphere immediately prior to use. Anhydrous dimethylformamide was purchased from Aldrich Chemical Co. Ltd. and was used without further purification. Benzene and toluene were dried over sodium wire and toluene was distilled under an argon atmosphere before

use. Acetonitrile was dried by distillation from finely-powdered calcium hydride, and dichloromethane by distillation from phosphorus pentoxide immediately prior to use. Triethylamine was distilled from and stored over potassium hydroxide pellets, under argon. All other solvents and reagents were purified by standard methods. Brine refers to a saturated solution of sodium chloride in water.

1. Preparation of ^{t}Butyl 4-Bromo-3-oxobutanthioate (14)

(a) From Diketene

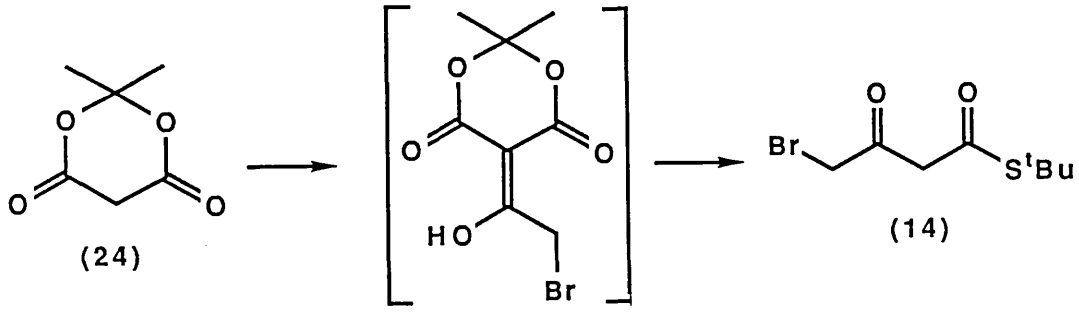


(16) (17) (14)

Bromine (0.88ml, 17mmol) was added dropwise to a stirred solution of diketene (16) (1.35ml, 18mmol) in CCl_4 (50ml) at -10^{0}C under argon. The pale orange colour of the mixture was allowed to decolourise after each addition. The resulting pale yellow clear solution was stirred at -10^{0}C for a further 15 min after the bromine addition had been completed. This solution was transferred by cannula into a stirred solution of ^{t}butylthiol (9.7ml, 86mmol) in CH_2Cl_2 (100ml) at -10^{0}C under argon. The resulting solution was stirred for a further 30 min, allowed to warm to room temperature, and poured into water (200ml). The organic phase was washed with water (2 x 100ml), saturated $NaHCO_3$ (1 x 100ml), and brine (1 x 100ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (40% CH_2Cl_2-petrol) gave ^{t}butyl 4-bromo-3-oxobutanthioate (14) (3.14g, 73%) as a pale yellow, malodorous oil: δ_H (60MHz, $CDCl_3$) (35% enol form) 1.45 and 1.50 (9H, 2s, S^{t}Bu),

3.75 and 3.85 (2H, 2s, H-4 enol and keto respectively), 4.10 (1.6H, s, H-2 keto), and 5.55 (0.2H, s, H-2 enol); ν_{max} (film) 2 963, 1 723, 1 670, 1 622, 1 364, and 1 072cm^{-1}; m/z 254 and 252 (M+), 198, 173, 165, 163, and 57. (Found: C,38.2; H,5.31. $C_8H_{13}O_2BrS$ requires C,38.0; H,5.18%).

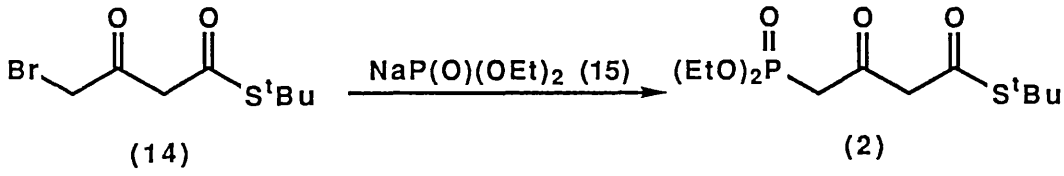
(b) From Meldrum's Acid



Bromoacetyl bromide (0.72ml, 8.3mmol) was added dropwise to a stirred solution of Meldrum's acid (24) (1.085g, 7.5mmol) and pyridine (1.22ml, 15.1mmol) in CH_2Cl_2 (15ml) at 0^{0}C under argon. The resulting orange suspension was stirred for 1h after addition and allowed to warm to room temperature. The suspension was diluted with CH_2Cl_2 (50ml) and poured into 2N aq. HBr (100ml) containing crushed ice. The organic layer was separated and washed with 2N aq. HBr (2 x 50ml), H_2O (1 x 50ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 233). The resulting orange solid was dissolved in benzene (15ml), ^{t}butyl thiol (1.6ml, 14.2mmol) added and the resulting solution stirred

and heated under reflux under argon for 1h. The solvent was removed under reduced pressure. Chromatography (40% CH_2Cl_2-petrol) gave ^{t}butyl 4-bromo-3-oxobutanthioate (14) (1.45g, 76%).

2. Preparation of ^{t}Butyl 4-Diethylphosphono-3-oxobutanthioate (2)



(14) (2)

Diethyl phosphite (6.61ml, 51.3mmol) was added dropwise to a stirred suspension of sodium (2.36g, 103mmol) in THF (100ml) at room temperature under argon. After the addition was complete, the suspension was heated under reflux for 90 min and then cooled to -10^{0}C.

The bromothioester (14) (11.8g, 46.6mmol) was added dropwise to a stirred suspension of sodium hydride (2.05g, 60% oil dispersion, 51.3mmol) in THF (120ml) at -10^{0}C under argon. After the addition the solution was stirred for a further 30 min at -10^{0}C.

The sodium diethylphosphite (15) was added dropwise by cannula to the monoanion of the bromothioester (14). After the addition the resulting mixture was stirred for a further 60 min at -10^{0}C and then allowed to warm to room temperature overnight and poured into saturated

aqueous NH_4Cl solution (200ml) and diethyl ether (400ml). The organic phase was separated, the aqueous phase re-extracted with ether (2 x 100ml). The combined organic phases were washed with water (2 x 100ml), brine (1 x 100ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. The product ^{t}butyl 4-diethylphosphono-3-oxobutanthioate (2) was an orange malodorous oil (12.3g, 85%) and required no further purification; δ_H (250 MHz, $CDCl_3$) (28% enol form) 1.33 (6H, t, J 6.8 Hz, 2 x CH_3 CH_2O), 1.44 and 1.50 (9H, 2s, S^{t}Bu keto and enol respectively), 2.69 and 3.23 (2H, 2d, J 24.0 Hz, H-4 enol and keto respectively), 3.78 (1.4H, s, H-2 keto), 4.14 (4H, multiplet, 2 x CH_3CH_2O), and 5.45 (0.3H, d, J 2.7 Hz, H-2 enol) ν_{max} (film) 2 964, 2 926, 1 723, 1 674, 1 617, 1 456, and 1 262cm^{-1}; m/z 310 (M^+), 253, 221, 194, 179, and 57. (Found: C,46.1; H,7.57. $C_{12}H_{23}O_5PS$ requires C,46.4; H,7.47%).

3. Preparation of 1-^{t}Butyldimethylsilyloxy-11-iodoundecane (43)

$$\underset{(41)}{Br(CH_2)_{11}OH} \longrightarrow \underset{(42)}{Br/Cl(CH_2)_{11}OTBDMS} \longrightarrow \underset{(43)}{I(CH_2)_{11}OTBDMS}$$

Imidazole (6.8g, 100mmol) and ^{t}butyldimethylsilyl chloride (7.2g, 48mmol) were added to a stirred solution of 11-bromoundecan-1-ol (41) (10g, 40mmol) in DMF (40ml) at 0^{0}C under argon. The reaction was allowed to warm to room temperature after the addition and was stirred for a further 18h. The resulting solution was poured into water (200ml), extracted with ether (2 x 150ml), and the combined organic extracts were washed with water (2 x 100ml), brine (1 x 100ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude ^{t}butyldimethylsilyloxyhaloalkane (42).

The crude bromide/chloride mixture was dissolved in acetone (100ml) saturated with sodium iodide and the solution was heated under reflux for 24h. The bulk of the solvent was removed under reduced pressure, the residue suspended in ether (200ml), washed with water (2 x 100ml), 5% aqueous solution of $Na_2S_2O_3$ (2 x 100ml), and brine (1 x 100ml). The

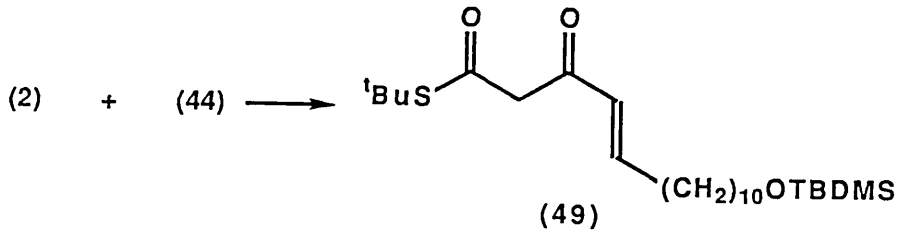
organic phase was separated, dried ($MgSO_4$) and the solvent was removed under reduced pressure. Chromatography (20% CH_2Cl_2-petrol) gave 1-^{t}butyldimethylsilyloxy-11-iodoundecane (43) as a pale yellow oil (14.3g, 87%); δ_H (90MHz, $CDCl_3$) 0.04 (6H, s, OSiMe_2 ^{t}Bu), 0.90 (9H, s, OSiMe_2 ^{t}Bu) 1.29 (16H, br s, I CH_2 (CH_2)$_8$ CH_2CH_2OP), 1.80 (2H, m, H-2), 3.18 (2H, t, J 6.4 Hz, H-11), and 3.60 (2H, t, J 6.4 Hz, H-1); ν_{max} (film) 2 927, 1 461, 1 254, 1 100, 836, and 775cm^{-1}; m/z 355 (M$^+$ -^{t}Bu), 227, and 75. (Found M$^+$ -^{t}Bu, 355.0946. $C_{13}H_{28}OSiI$ (M$^+$ -^{t}Bu) requires 355.0954. Found: C,49.7; H,9.20. $C_{17}H_{37}OSiI$ requires C,49.5; H,9.04%).

4. Preparation 11-^{t}Butyldimethylsilyloxyundecanal (44)

$$\underset{(43)}{I(CH_2)_{11}OTBDMS} \longrightarrow \underset{(44)}{CHO(CH_2)_{10}OTBDMS}$$

Compound (43) (1.05g, 2.55mmol) was added to a stirred suspension of $NaHCO_3$ (4g, 47.6mmol) in DMSO (15ml) at 150^{0}C. After 4 min the reaction was rapidly cooled and poured into ice-water (50ml) and ether (50ml). The layers were separated and the aqueous layer extracted with ether (3x50ml). The combined organic phases were washed with water (3x100ml), brine (1x100ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (40% CH_2Cl_2-petrol) gave 11-^{t}butyldimethylsilyloxyundecanal (44) as a colourless oil (0.56g, 73%); δ_H (250MHz, $CDCl_3$) 0.02 (6H, s, Si$\underline{Me}_2$), 0.88 (9H, s, Si$^{t}\underline{Bu}$), 1.27 (12H, br s, $CHOCH_2CH_2(\underline{CH_2})_6$ CH_2CH_2OP), 1.48 and 1.61 (4H, 2t, $\underline{J}$ 7.0 Hz, $CHOCH_2\underline{CH_2}(CH_2)_6\underline{CH_2}CH_2OP$), 2.40 (2H, dt, $\underline{J}$ 1.5, 6.6Hz, $CHO\underline{CH_2}$), 3.58 (2H, t, $\underline{J}$ 5.7 Hz, $\underline{CH_2}OP$), and 9.73 (1H, t, $\underline{J}$ 1.5 Hz, $\underline{CH}O$); ν_{max} (film) 2 928, 2 855, 1 724, 1 254, and 1 099; $\underline{m/z}$ 243 ($M^+ - {}^{t}Bu$), 131, 109, 95, and 75. (Found $M^+ - {}^{t}Bu$ 243.1783. $C_{13}H_{27}O_2Si$ ($M^+ - {}^{t}Bu$) requires 243.1780.

5. Preparation of ^{t}Butyl (4E)-15-^{t}Butyldimethylsilyloxy-3-oxo-4-pentadecenthioate (49)

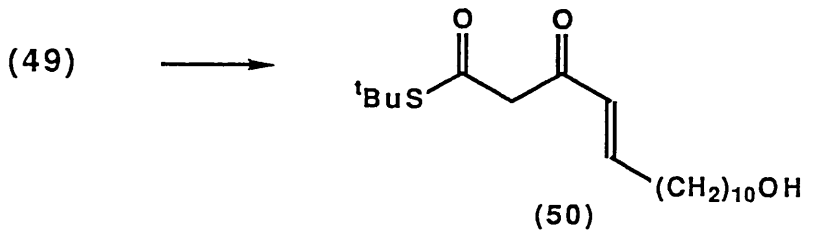


(49)

Thioesterphosphonate (2) (0.49g, 1.58mmol) was added to a stirred suspension of sodium hydride (0.126g, 60% oil dispersion, 3.15mmol) in THF (40ml) at 0^{0}C under argon. The suspension was stirred at 0^{0}C for 1h, the aldehyde (44) (0.316g, 1.05mmol) was added, and the mixture allowed to warm to room temperature and stirred for a further 6h. The resulting clear solution was poured into sat. aq. NH_4Cl solution (50ml) and ether (50ml), the layers were separated, and the aqueous phase washed with ether (2 x 50ml). The combined organic phases were washed with water (2 x 50ml), brine (1 x 50ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (25% CH_2Cl_2-petrol) gave ^{t}butyl (4E)-15-^{t}butyldimethylsilyloxy-3-oxo-4-pentadecenthioate (49) as a pale yellow oil (0.40g, 84%); δ_H (250MHz, $CDCl_3$) (50% enol form) 0.02

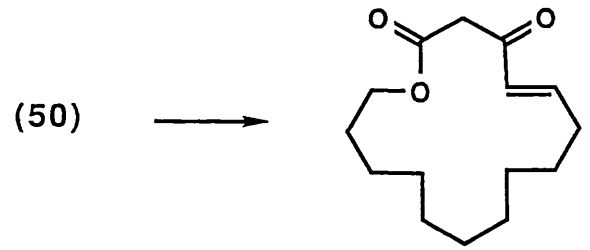
(6H, s, $SiMe_2$), 0.84 (9H, s, Si^tBu), 1.23 (16H, br s, $CHCH_2(CH_2)_8CH_2OP$), 1.42 and 1.46 (9H, 2s, S^tBu enol and keto), 2.17 (2H, m, $=CHCH_2$), 3.54 (2H, t, J 6.5 Hz, CH_2OP), 3.67 (1.0 H, s, H-2 keto), 5.27 (0.5H, s, H-2 enol), 5.63 and 6.10 (1.0H, 2dt, J 15.5, 1.5 Hz, H-4 keto and enol), 6.65 and 6.86 (1H, s, dt, J 15.5, 7Hz, H-5 keto and enol), and 12.57 (0.5H, s, OH enol); ν_{max}(film) 2 927, 2 854, 1 653, 1 585, 1 254, 1 078, and 836cm^{-1}; m/z 399 ($M^+ - {}^tBu$), 385, 367, 343, and 57. (Found: C65.9; H,10.8. $C_{25}H_{48}O_3SiS$ requires C,65.7; H,10.6%).

6. Preparation of ^{t}Butyl (4E)-15-Hydroxy-3-oxo-4-pentadecenthioate (50)



Thioester (49) (0.445g, 0.974mmol) was dissolved in acetonitrile (10ml) and the stirred solution at RT was treated with 40% aq. HF (0.5ml). The solution was stirred for 15 min, poured into water (50ml) and extracted with CH_2Cl_2 (3 x 50ml). The combined organic phases were washed with water (2 x 50ml), brine (1 x 50ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (50% ether-petrol) gave ^{t}butyl (4E)-15-hydroxy-3-oxo-4-pentadecenthioate (50) (0.327g, 98%) as a pale yellow oil; δ_H (250MHz, $CDCl_3$) (30% enol form) 1.30 (15H, br s, $CH_2CHCH_2(CH_2)_7$) and 15-OH, 1.45 and 1.51 (9H, 2s, S^{t}Bu enol and keto), 1.50 (2H, m, CH_2CH_2OH), 2.20 (2H, m, CH_2=CHCH_2), 3.63 (2H, t, J 6.5 Hz, CH_2OH), 3.70 (1.4H, s, H-2 keto), 5.30 (0.3H, s, H-2 enol), 5.36 (0.7H, d, J 16.0 Hz, H-4 keto), 6.14 (0.3H, d, J 16.0 Hz, H-4 enol), 6.69 (0.7H, dt, J 16.0, 7.0 Hz, H-5 enol), 6.91 (0.3H, dt, J 16.0, 7.0 Hz H-5 enol), and 12.61 (0.3H, br s, OH enol); ν_{max} (film) 3 347, 2 925, 2 853, 1 652, 1 584, and 1077cm^{-1}; m/z 342 (M^+), 286, 253, and 57. (Found: C,66.4, H,10.1. $C_{19}H_{34}O_3S$ requires C,66.6; H,10.0%).

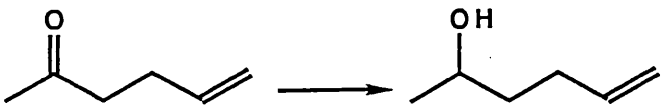
7. Preparation of (4E)-3-Oxo-4-pentadecenolide (51)



(51)

Thioester (50) (0.118g, 0.345mmol) in dry degassed CH_2Cl_2 (150ml) was added to copper(I) trifluoroacetate (1.22g, 6.91mmol) and Na_2HPO_4 (1.91g, 13.5mmol) in dry, degassed CH_2Cl_2 (100ml) and the reaction mixture was stirred for 10 min at room temperature. The solution was poured into CH_2Cl_2 (200ml) and sat. aq. NH_4Cl solution (200ml) containing 0.88 NH_3 (1ml) and stirred vigorously for 20 min. The mixture was filtered through a plug of glass wool to remove the precipitated salts, the layers separated, and the aqueous phase re-extracted with CH_2Cl_2 (2 x 100ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (CH_2Cl_2) gave (4E)-3-oxo-4-pentadecenolide (51) (30.5mg, 35%) as a white solid. Recrystallisation (petrol) gave the product as colourless prisms, m.p. 54^{0}C; δ_H (250MHz, $CDCl_3$) 1.26 and 1.57 (16H, 2 br m, $CH{=}CH_2CH_2(\underline{CH_2})_8$) 2.26 (2H, m, $CH{=}CH{-}\underline{CH_2}$) 3.50 (2H, s, H-2), 4.14 (2H, t, J 6.5 Hz, $\underline{CH_2}O$) 6.21 (1H, dt, J 15.0, 1.5 Hz, H-4), and 6.90 (1H, dt, J 15.0, 7.6 Hz); ν_{max} (film) 2 930, 2 856, 1 736, 1 691, 1 674, 1 623, 1 458, and 1 256cm^{-1}; 252 (M^+), 234, 224, 150, 95 and 81. (Found: C,71.7; H,9.71. $C_{15}H_{24}O_3$ requires C,71.4; H,9.59%).

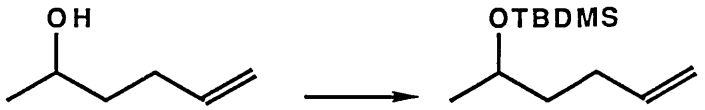
8. Preparation of (±)-5-Hexen-2-ol (45)



(234) (45)

Sodium borohydride (3.16g, 83.5mmol) was carefully added to a stirred solution of 5-hexen-2-one (234) (4.10g, 41.8mmol) in ethanol (50ml) at 0^0C. The resulting solution was allowed to warm to room temperature and stirred for 12h. The solution was carefully poured into a cooled, stirred, sat. aq. NH_4Cl solution (150ml), and when effervescence had ceased, the mixture was extracted with ether (3 x 100ml), the combined extracts washed with brine (1 x 200ml), dried ($MgSO_4$), and the solvent carefully removed under reduced pressure. The product (45) was obtained as a colourless, volatile oil (3.85g, 92%) and required no further purification; δ_H (60MHz, $CDCl_3$) 1.2 (3H, d, J 8 Hz, $\underline{CH_3}$ CH), 1.6 (2H, m, (OH)CH$\underline{CH_2}CH_2$), 2.0 (2H, m, $\underline{CH_2}CH{=}CH_2$), 2.6 (1H, br s, $\underline{OH}$), 3.7 (1H, m, $\underline{CH}$(OH)), and 4.9, 5.9 (3H, 2br m, $\underline{CH{=}CH_2}$); ν_{max} (film) 3 394, 2 972, 2 929, 1 634, and 1 375cm^{-1}.

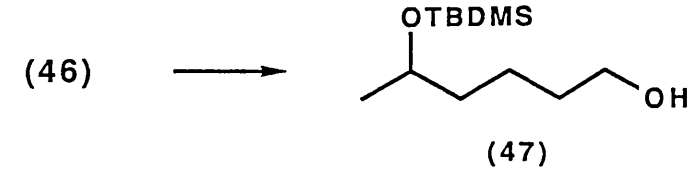
9. Preparation of (±)-2-^{t}Butyldimethylsilyloxy-5-hexene (46)



(45) (46)

(±)-5-Hexen-2-ol (45) (3.70g, 36.9mmol) and imidazole (5.03g, 73.9mmol) were dissolved in DMF (35ml) and cooled to 0^{0}C under argon. To the stirred solution was added ^{t}butyldimethylsilyl chloride (6.96g, 46.2mmol). The solution was allowed to warm to room temperature and stirred for 16h. The solution was poured into water (200ml), extracted with ether (2 x 150ml), the combined organic extracts washed with water (2 x 150ml), brine (1 x 100ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (1% ether-petrol) gave (±)-2-^{t}butyldimethylsilyloxy-5-hexene (46) as a colourless oil (6.88g, 87%); δ_H (60MHz, $CDCl_3$) 0.1 (6H, s, $\underline{Me_2}Si$), 0.9 (9H, s, $^{t}\underline{Bu}Si$), 1.1 (3H, d, $\underline{J}$ 8 Hz, $\underline{CH_3}CH$), 1.5 (2H, m, $CH\underline{CH_2}$), 2.0 (2H, m, $\underline{CH_2}CH=CH_2$), 3.8 (1H, m, $\underline{CH}OP$), and 4.9, 5.7 (3H, 2 br m, $\underline{CH=CH_2}$); ν_{max} (film) 2 956, 2 930, 1 636, 1 460, and 1 255cm^{-1}.

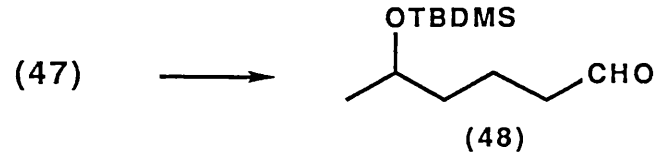
10. Preparation of (±)-5-^{t}Butyldimethylsilyloxyhexan-1-ol (47)



(47)

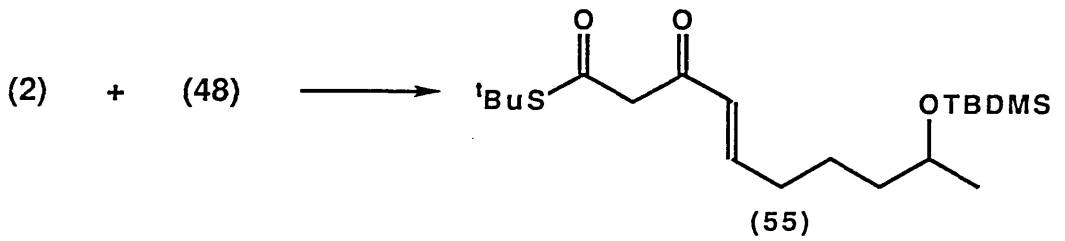
Borane-dimethyl sulphide complex (1.86ml, 10M solution in THF, 18.6mmol) was added dropwise to a stirred solution of the alkene (46) (3.99g, 18.6mmol) in THF (50ml) at 0^0C under argon. The solution was allowed to warm to room temperature, stirred for 1h, and recooled to 0^0C. Water (2ml) was carefully added followed by 3N aq. NaOH (19ml) and 30% aq. H_2O_2 (6.5ml). The mixture was poured into water (150ml) and extracted with CH_2Cl_2 (3 x 100ml). The combined CH_2Cl_2 layers were washed with water (2 x 100ml), brine (1 x 100ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (30% ether-petrol) gave (±)-5-^{t}butyldimethylsilyloxyhexan-1-ol (47) as a colourless oil (3.98g, 92%); δ_H (60MHz, $CDCl_3$) 0.1 (6H, s, Me_2Si), 0.7 (9H, s, $^{t}BuSi$), 0.9 (3H, d, J 8 Hz, CH_3CH), 1.2 (6H, br s, H2-H4), 2.3 (1H, br s, OH), and 3.4 (3H, br m, 2 x H-1, 1 x H-5); ν_{max} (film) 3 345, 2 930, 2 858, 1 459, 1 373, 1 254, and 1 064cm^{-1}; m/z 231 (M+-H), 217, 175, 159, 119, 83, and 75. (Found: C,61.9; H,12.2. $C_{12}H_{28}O_2Si$ requires C,62.0; H,12.1%).

11. Preparation of (±)-5-^{t}Butyldimethylsilyloxyhexanal (48)



PCC (5.33g, 24.7mmol) was added to a stirred solution of alcohol (47) (2.30g, 9.90mmol) in CH_2Cl_2 (800ml) at room temperature under argon. The solution was stirred for 14h, filtered through a short pad of silica, and the solvent removed under reduced pressure. Chromatography (10% ether-petrol) gave (±)-5-^{t}butyldimethylsilyloxyhexanal (48) as a colourless oil (1.64g, 72%); δ_H (60MHz, $CDCl_3$) 0.1 (6H, s, $\underline{Me_2}Si$), 0.9 (9H, s, $^{t}\underline{Bu}Si$), 1.1 (3H, d, $\underline{J}$ 8 Hz, $\underline{CH_3}$), 1.4 (4H, br m, $(\underline{CH_2})_2$ CH_2CHO), 2.4 (2H, m, $\underline{CH_2}CHO$), 3.8 (1H, br m, $\underline{CH}(OP)$), and 9.8 (1H, m, $\underline{CHO}$); ν_{max} (film) 2 954, 2 929, 2 711, 1 724, 1 255, 1 140, 835, and 809cm^{-1}.

12. Preparation of ^{t}Butyl (±)-(4E)-9-^{t}Butyldimethylsilyloxy-3-oxo-4-decenthioate (55)

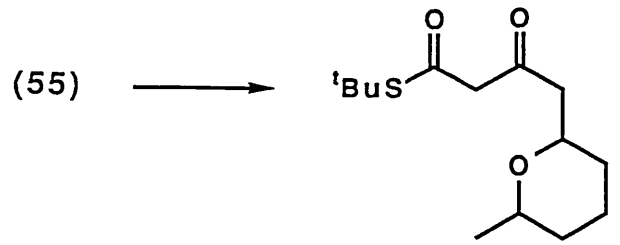


(55)

Thioester phosphonate (2) (0.118g, 0.380mmol) was added dropwise to a stirred suspension of sodium hydride (37mg, 60% oil dispersion, 0.925mmol) in THF (12ml) at 0^{0}C under argon. The suspension was stirred for 1h and then the aldehyde (48) (70mg, 0.303mmol) was added. The reaction was allowed to warm to room temperature, stirred for 16h, poured into sat. aq. NH_4Cl (40ml) and ether (40ml), the layers separated and the aqueous layer re-extracted with ether (2 x 40ml). The combined organic phases were washed with water (2 x 40ml), brine (1 x 40ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (2% ether-petrol) gave ^{t}butyl (±)-(4E)-9-^{t}butyldimethylsilyloxy-3-oxo-4-decenthioate (55) (98.7mg, 84%) as a pale yellow oil; δ_H (250MHz, $CDCl_3$) (70% enol form) 0.05 (6H, s, Me_2Si), 0.89 (9H, s, ^{t}BuSi), 1.02 (3H, d, J 8.0 Hz, H-10 methyl), 1.36 (2.7H, s, ^{t}BuS keto), 1.42 (6.3H, s, ^{t}BuS enol), 1.38 (4H, br m, 2 x H-7,8), 2.20 (2H, br m, 2 x H-6), 3.71 (0.6H, s, 2 x H-2 keto), 3.80 (1H, br m, H-9),

5.30 (0.7H, s, H-2 enol), 5.68 (0.7H, dt, J 15.0, 1.6 Hz, H-4 enol), 6.16 (0.3H, dt, J 15.0, 1.6 Hz, H-4 keto), 6.69 (0.7H, dt, J 15.0, 6.9 Hz, H-5 enol), 6.90 (0.3H, dt, J 15.0, 6.9 Hz, H-5 keto) and 12.61 (0.7H, br s, OH enol); ν_{max} (film) 2 957, 2 928, 1 653, 1 585, 1 077, and 835cm^{-1}; m/z 386 (M^+), 329 ($M^+ - {}^tBu$), 273, 165, 111, and 57. (Found: C,62.3; H,10.2. $C_{20}H_{38}O_3SiS$ requires C,62.1, H,9.91%).

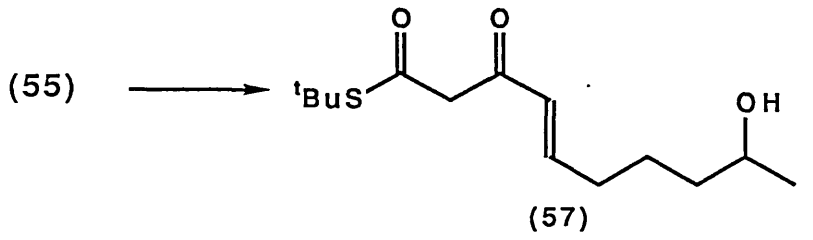
13. Preparation of ^{t}Butyl (±)-3-Oxo-4[2(6-methyltetrahydropyranyl]-butanthioate (56)



(56)

40% HF (1 drop) was added to a stirred solution of the silyl ether (55) (29.5mg, 76.3μmol) in acetonitrile (1ml) at room temperature. The mixture was stirred for 20h, poured into water (5ml), extracted with CH_2Cl_2 (3 x 5ml), the combined CH_2Cl_2 phases washed with water (2 x 10ml), brine (1 x 5ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Chromatography (5% ether-petrol) gave ^{t}butyl (±)-3-oxo-4[2(6-methyltetrahydropyranyl]-butanthioate (56) as a colourless oil (14.5mg, 70%); δ_H (250MHz, $CDCl_3$) (75% keto form) 1.13 (2.25H, d, J 6.0 Hz, CH_3 keto), 1.15 (0.75H, d, J 6.0 Hz, CH_3 enol), 1.48 (6.75H, s, ^{t}BuS keto), 1.52 (2.25H, s ^{t}BuS enol), 1.55, 1.80 (6H, 2 br m, $(CH_2)_3$ tetrahydropyran), 2.16 (0.25H, dd, J 15.0, 7.5 Hz, 1 x H-4 enol), 2.41 (0.25H, dd, J 15.0, 6.9 Hz, 1 x H-4 enol), 2.54 (0.75H, dd, J 15.0, 5.0 Hz, 1 x H-4 keto), 2.73 (0.75H, dd, J 15.0, 7.5 Hz, 1 x H-4 keto), 3.43 (1H, m, CH_3 CH), 3.65 (1.5H, s, H-2 keto), 3.65 (0.25H, m, CH_2CH(O) enol), 3.78 (0.75H, m, CH_2CH(O) keto), 5.40 (0.25H, s, H-2 enol), and 12.86 (0.25H, s, OH enol); ν_{max} (film) 2 965, 2 930, 2 859, 1 721, 1 675, 1 617, 1 364, 1 183, 1 160, 1 083, and 1 061cm^{-1}; m/z 272 (M^+), 215 ($M^+ - {}^{t}Bu$), 183, 165, 99, and 57. (Found: C,61.7; H,8.72. $C_{14}H_{24}O_3S$ requires C,61.7, H,8.88%).

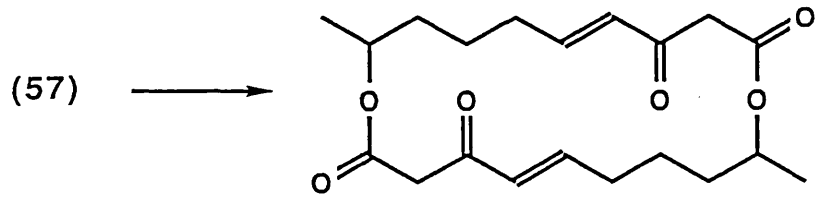
14. Preparation of ^{t}Butyl (±)-(4E)-9-Hydroxy-3-oxo-4-decenthioate (57)



(57)

TBAF (3ml, 1M in THF, 3mmol) was added to a stirred solution of the silyl ether (55) (0.1909g, 0.494mmol) in THF (5ml) at room temperature. The solution was stirred for 4h, poured into pH7 buffer solution (20ml) and ether (20ml), the layers separated, and the aqueous layer re-extracted with ether (2 x 20ml). The combined ether layers were washed with brine (1 x 50ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (30% ether-petrol) gave ^{t}butyl (±)-(4E)-9-hydroxy-3-oxo-4-decenthioate (57) as a colourless oil (0.114g, 85%); δ_H (250MHz, $CDCl_3$) (50% enol form) 1.19, 1.21 (3H, 2d, J 8.0 Hz, 3 x H-10), 1.45, 1.50 (9H, 2s, ^{t}BuS), 1.40 (5H, br s, 2 x H-7, 2 x H-8, OH), 2.22 (2H, m, H-6), 3.69 (1H, s, H-2 keto), 3.79 (1H, m, H-9), 5.29 (0.5H, s, H-2 enol), 5.67 (0.5H, br d, J 15.7 Hz, H-4), 6.15 (0.5H, dt, J 15.7, 1.7 Hz, H-4), 6.66 (0.5H, dt, J 15.7, 6.6 Hz, H-5), 6.90 (0.5H, dt, J 15.7, 6.6 Hz, H-5), and 12.60 (0.5H, br s, OH enol); ν_{max} (film) 3 383, 2 961, 2 926, 2 863, 1 652, 1 584, and 1 078cm^{-1}; m/z 272 (M^+), 215 ($M^+ - {}^{t}Bu$), 183, 165, 99, and 57. (Found: C,61.5, H,9.16. $C_{14}H_{24}O_3S$ requires C,61.7, H,8.88%).

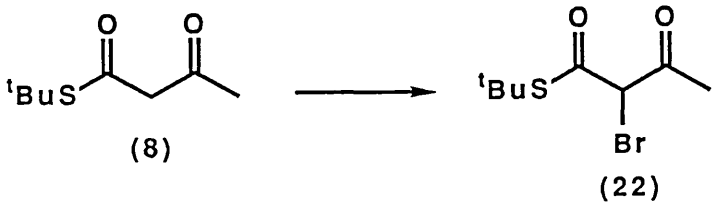
15. Preparation of (±)-(4E)-3-Oxo-4-decendiolide (59)



(57) (59)

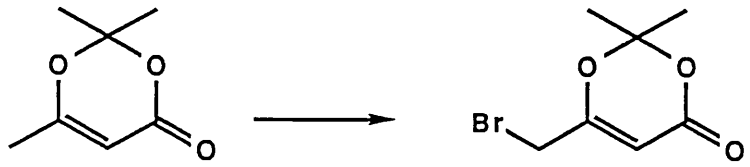
Thioester alcohol (57) (0.856g, 3.14mmol) in CH_2Cl_2 (100ml) was slowly added over 60 min to a stirred solution of copper(I) trifluoroacetate (5.54g, 31.4mmol) and Na_2HPO_4 (8.92g, 62.8mmol) in CH_2Cl_2 (200ml) at room temperature under argon. The solution was stirred for 2h after completion of addition and then poured into sat. aq. NH_4Cl (500ml) containing 0.88 NH_3 (5ml) and stirred vigorously for 20 min. The mixture was filtered through a plug of glass wool to remove the precipitated salts, the layers separated and the aqueous phase re-extracted with CH_2Cl_2 (2 x 200ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (40% ether-petrol) gave (±)-(4E)-3-oxo-4-decendiolide (59) as a colourless, viscous oil (0.40g, 35%); δ_H (250MHz, $CDCl_3$) 1.23 (6H, m, 2 x Me), 1.55 (8H, br s, 2 x $(CH_2)_2CH(O)$), 2.20 (4H, m, 2 x CH=CH-CH_2) 3.58 (4H, br s, 2 x $COCH_2$), 4.96 (2H, br m, 2 x CH_3 CH(O)), 6.14 (2H, br d, J 16.8 Hz, 2 x COCH=CH), and 6.86 (2H, m, 2 x CH=CHCH$_2$); ν_{max} ($CDCl_3$ solution) 2 980, 2 938, 2 865, 1 726, 1 670, 1 625, 1 257, and 1 229cm^{-1}; m/z 364 (M^+), 292, 182, 164, 139, 123, and 81. (Found: C,65.7; H,7.77. $C_{20}H_{28}O_6$ requires C,65.9; H,7.75%). (Found: 182 ($M^+/2$) 182.0943. $C_{10}H_{14}O_3$ ($M^+/2$) requires 182.0943).

16. Preparation of ^{t}Butyl (±)-2-Bromo-3-oxobutanthioate (22)



^{t}Butyl 3-oxobutanthioate (8) (1.143g, 6.56mmol) in CH_2Cl_2 (10ml) was added to a stirred solution of bromine (1.048g, 6.56mmol) in CH_2Cl_2 (150ml) at -78^{0}C under argon. The resulting solution was allowed to warm to room temperature, washed with sat. aq. sodium thiosulphate (2 x 100ml), water (1 x 100ml), brine (1 x 100ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (CH_2Cl_2) gave ^{t}butyl (±)-2-bromo-3-oxobutanthioate (22) as a pale yellow fuming oil (1.41g, 85%); δ_H (60MHz, $CDCl_3$) 1.5 (9H, s, ^{t}Bu), 2.4 (3H, s, 3 x H-4), and 4.7 (1H, s, H-2).

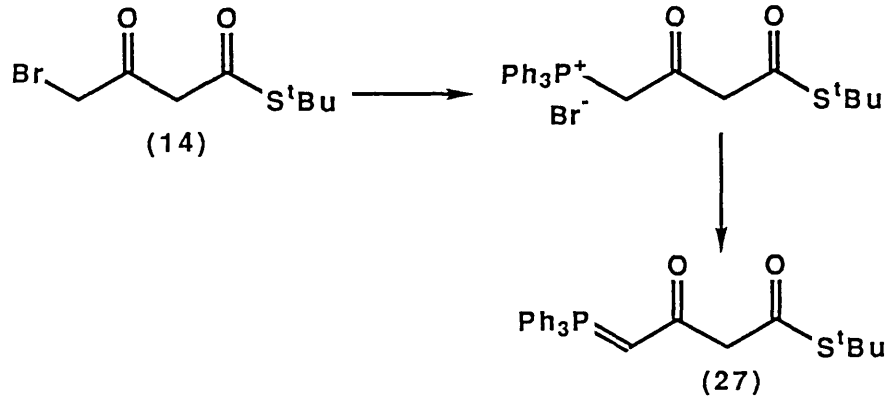
17. Preparation of 6-Bromomethyl-2,2-dimethyl-1,3-dioxo-5-en-3-one (25)



(24) (25)

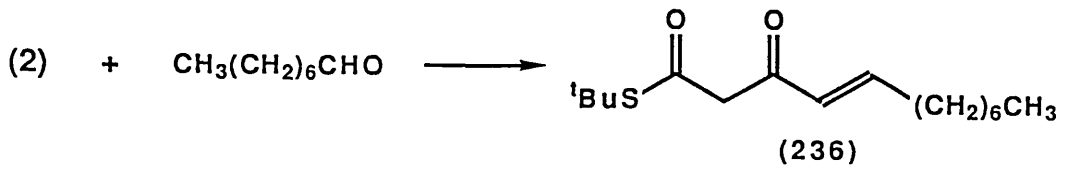
N-Bromosuccinimide (2.38g, 13.4mmol) was added to a stirred solution of the acetone-diketene adduct (24) (1.82g, 12.8mmol) and benzoyl peroxide (31mg, 0.128mmol) in CCl_4 (150ml) at room temperature. The reaction was irradiated with a 750W tungsten lamp for 1h and the solvent was removed under reduced pressure. Chromatography (25% CH_2Cl_2-petrol) gave 6-bromomethyl-2,2-dimethyl-1,3-dioxo-5-en-3-one (25) as a pale yellow oil (0.99g, 35%); δ_H (60MHz, $CDCl_3$) 0.8 (6H, s, 2 x CH_3) 3.9 (2H, s, CH_2), and 5.6 (1H, s, H-5). (Found: C,38.1; H,4.30. $C_7H_9BrO_3$ requires C,38.0; H,4.10%).

18. Preparation of ^{t}Butyl 3-Oxo-4-triphenylphosphoranylbutanthioate (27)



Triphenylphosphine (0.656g, 2.50mmol) was added to a stirred solution of the bromothioester (14) (0.528g, 2.09mmol) in benzene (10ml) at room temperature. The solution was stirred for 2h and then the precipitated solid was filtered and washed with benzene (2 x 5ml). This gave the pure phosphonium salt (235) (0.97g, 90%) (Found: C,60.6; H,5.24. $C_{26}H_{28}BrO_2PS$ requires C,60.6; H,5.48%). The phosphonium salt (235) (0.85g, 1.65mmol) was suspended in water (15ml) and saturated Na_2CO_3 (5ml) added. The suspension was vigorously stirred at room temperature for 8h, then extracted with CH_2Cl_2 (3 x 20ml), the CH_2Cl_2 extracts combined, washed with brine (1 x 50ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (ether) gave ^{t}butyl 3-oxo-4-triphenylphosphoranylbutanthioate (27) (0.47g, 66%) as a white solid; δ_H (250MHz, $CDCl_3$) 1.48 (9H, s, ^{t}BuS), 3.47 (2H, d, J 1.7 Hz, H-2), and 7.60 (16H, br m, aromatics and H-4); δ_P ($CDCl_3$) 15.5ppm; ν_{max} ($CDCl_3$) 3 035, 2 959, 2 922, 1 675, 1 542, 1 481, 1 381, and 1 185cm^{-1}; m/z 435 (M$^+$). (Found: C,71.6; H,6.14. $C_{26}H_{27}O_2PS$ requires C,71.9; H,6.26%).

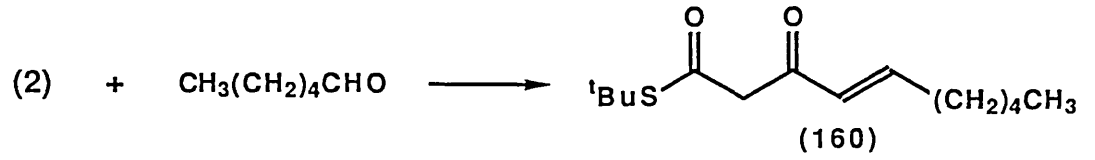
19. Preparation of ^{t}Butyl (4E)-3-Oxo-4-dodecenthioate (236)



(236)

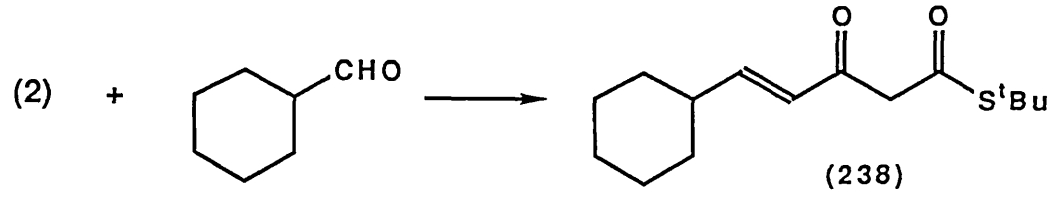
Thioester phosphonate (2) (3.04g, 9.80mmol) was added to a stirred suspension of NaH (0.862g, 60% oil dispersion, 21.6mmol) in THF (50ml) at 0^{0}C under argon. The suspension was stirred for 1h at 0^{0}C and then octanal (1.05g, 8.19mmol) was added. The reaction was allowed to warm to room temperature and stirred for 16h. The clear solution was poured into sat. aq. NH_4Cl (100ml) and ether (100ml), the layers separated and the aqueous phase re-extracted with ether (2 x 100ml). The combined organic phases were washed with water (2 x 100ml), brine (1 x 100ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (20% CH_2Cl_2-petrol) gave ^{t}butyl (4E)-3-oxo-4-dodecenthioate (236) as a pale yellow oil (1.35g, 58%); δ_H (250MHz, $CDCl_3$) (70% enol form) 0.88 (3H, t, J 8.8 Hz, 3 x H-12), 1.28 (10H, br s, 2 x H-7, 8, 9, 10, and 11), 1.47 (2.7H, s, ^{t}BuS keto), 1.51 (6.3H, s, ^{t}BuS enol), 2.21 (2H, m, 2 x H-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 Hz, H-4 enol), 6.16 (0.3H, dt, J 15.9, 1.5 Hz, H-4 keto), 6.70 (0.7H, dt, J 15.9, 6.8 Hz, H-5 enol), 6.91 (0.3H, dt, J 15.9, 6.8 Hz, H-5 keto), and 10.14 (0.7H, br s, OH enol); ν_{max} (film) 3 386, 2 925, 2 855, 1 653, 1 584, and 1 077cm^{-1}; m/z 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%).

20. Preparation of ^{t}Butyl (4E)-3-Oxo-4-decenthioate (160)



Thioester phosphonate (2) (2.75g, 8.86mmol) was added to a stirred suspension of NaH (0.78g, 60% oil dispersion, 19.5mmol) in THF (230ml) at 0^{0}C under argon. The resulting suspension was stirred for 1h and then hexanal (0.68g, 6.79mmol) was added. The reaction was allowed to warm to room temperature and stirred for 16h. The resulting clear solution was poured into sat. aq. NH_4Cl (250ml) and ether (200ml), the layers separated and the aqueous phase re-extracted with ether (2 x 200ml). The combined organic phases were washed with water (2 x 200ml), brine (1 x 100ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (0.5% ether-petrol) gave ^{t}butyl (4E)-3-oxo-4-decenthioate (160) as a pale yellow oil (1.19g, 68%); δ_H (90MHz, d^6 DMSO) (20% enol form), 0.88 (3H, t, J 8.0 Hz, 3 x H-10), 1.24 (6H, br s, 2 x H-7, 8, and 9), 1.25, 1.40 (9H, 2s, ^{t}BuS, keto and enol), 2.20 (2H, m, 2 x H-6), 3.75 (1.6H, s, 2 x H-2 keto), 5.63 (0.2H, s, H-2 enol), 6.08 (0.8H, dm, J 16.0 Hz, H-4 keto), 6.85 (1.2H, m, H-4 enol and H-5 keto, enol), and 12.40 (0.2H, br s, OH enol); ν_{max} (film) 3 384, 2 926, 2 852, 1 653, 1 585, and 1 077cm^{-1}; m/z 256 (M^+), 200, 167 and 57. (Found: C,65.5; H,9.31. $C_{14}H_{24}O_2S$ requires C,65.6; H,9.44%).

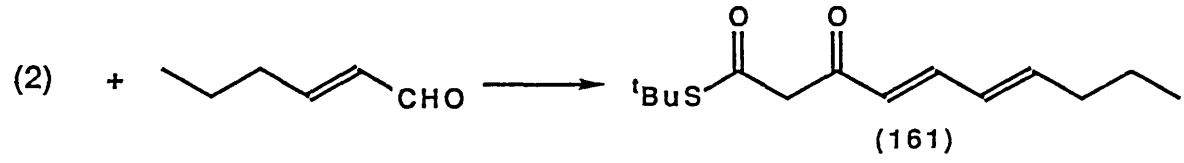
21. Preparation of ^{t}Butyl (4E)-5-Cyclohexyl-3-oxo-4-pententhioate (238)



(238)

Thioester phosphonate (2) (0.1304g, 0.420mmol) was added to a stirred suspension of NaH (37mg, 60% oil dispersion, 0.925mmol) in THF (5ml) at 0^{0}C under argon. The resulting suspension was stirred for 1h and then cyclohexanecarboxaldehyde (48mg, 0.43mmol) was added. The reaction was allowed to warm to room temperature and stirred for 16h. The resulting clear solution was poured into sat. aq. NH_4Cl (10ml) and ether (10ml), the layers separated and the aqueous phase re-extracted with ether (2 x 10ml). The combined organic phases were washed with water (2 x 20ml), brine (1 x 20ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (30% CH_2Cl_2-petrol) gave ^{t}butyl (4E)-5-cyclohexyl-3-oxo-4-pententhioate (238) as a pale yellow oil (93.2mg, 81%); δ_H (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 Hz, H-4), 6.09 (0.5H, dm, J 17.9 Hz, H-4), 6.64 (0.5H, dd, J 17.9, 2.5 Hz, H-5), 6.83 (0.5H, dd, J 17.9, 2.5 Hz, H-5), and 12.62 (0.5H, br s, OH enol); ν_{max} (film) 2 925, 2 852, 1 650, 1 583, and 1 076cm^{-1}; m/z 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%).

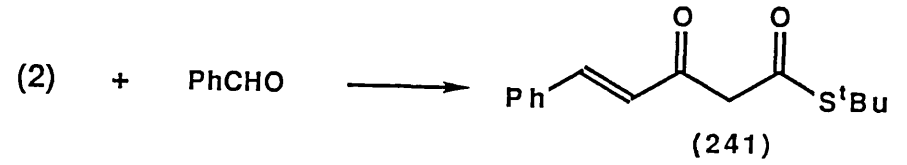
22. Preparation of ^{t}Butyl (4E,6E)-3-Oxo-4,6-decadienthioate (161)



(161)

Thioester phosphonate (2) (1.008g, 3.25mmol) was added to a stirred suspension of NaH (0.312g, 60% oil dispersion, 7.8mmol) in THF (20ml) at 0^{0}C under argon. The suspension was stirred for 1h and then trans-2-hexenal (0.225g, 2.30mmol) was added. The reaction was allowed to warm to room temperature and stirred for 16h. The resulting clear suspension was poured into sat. aq. NH_4Cl (50ml) and ether (50ml), the layers separated and the aqueous layer re-extracted with ether (2 x 50ml). The combined organic phases were washed with water (2 x 50ml), brine (1 x 50ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (1% ether-petrol) gave ^{t}butyl (4E,6E)-3-oxo-4,6-decadienthioate (161) as a pale yellow oil (0.296g, 50%); δ_H (250MHz, $CDCl_3$) (30% keto form) 0.91 (2.1H, t, J 7.0 Hz, 3 x H-10 enol), 0.92 (0.9H, t, J 7.0 Hz, 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 Hz, 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 Hz, H-5 enol), 7.20 (0.3H, dd, J 15.8, 10.5 Hz, H-5 keto), and 12.58 (0.7H, br s, OH enol); ν_{max} (film) 3 209, 2 960, 2 925, 1 627, 1 566, and 1 076cm^{-1}; m/z 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%).

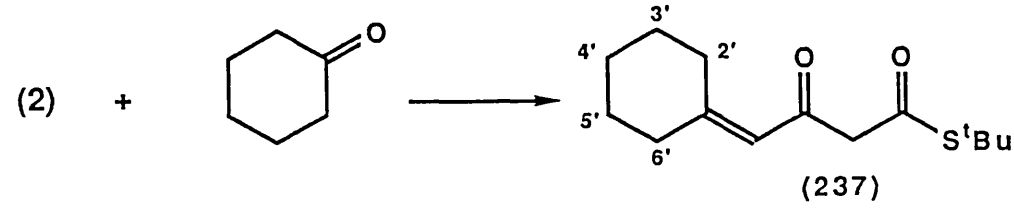
23. Preparation of ^{t}Butyl (4E)-3-Oxo-5-phenyl-4-pententhioate (241)



(241)

Thioester phosphonate (2) (0.296g, 0.954mmol) was added to a stirred suspension of NaH (77mg, 60% oil dispersion, 1.93mmol) in THF (40ml) at 0^{0}C under argon. The suspension was stirred for 1h and then benzaldehyde (84.4mg, 0.795mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16h. The clear solution was poured into sat. aq. NH_4Cl (50ml) and ether, the layers separated and the aqueous layer re-extracted with ether (2 x 50ml). The combined organic extracts were washed with water (2 x 100ml), brine (1 x 100ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Chromatography (5% ether-petrol) gave ^{t}butyl (4E)-3-oxo-5-phenyl-4-pententhioate (241) as a pale yellow solid (mp 60-62^{0}C, 0.115g, 55%); δ_H (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 Hz, H-4 enol), 6.82 (0.3H, d, J 17.1 Hz, H-4 keto), 6.50 (6H, br m, H-5 and aromatics), and 12.70 (0.7H, br d, J 1.9 Hz, OH enol); ν_{max} (film) 3 300, 3 058, 3 025, 2 996, 1 636, 1 585, 1 569, and 1 077cm^{-1}; m/z 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%).

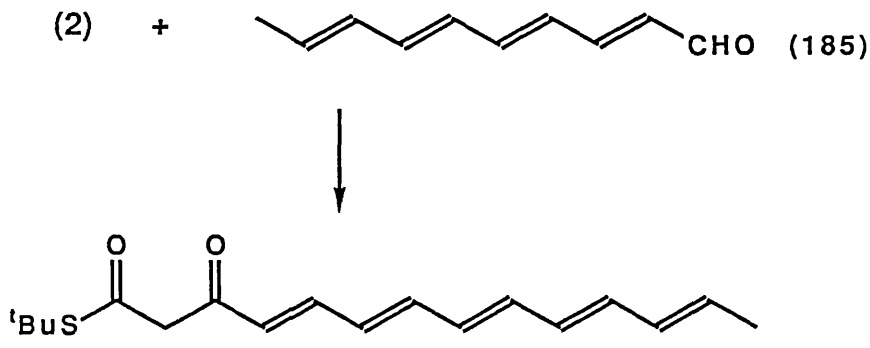
24. Preparation of ^{t}Butyl 4-Cyclohexylidenyl-3-oxo-butanthioate (237)



(237)

Thioester phosphonate (2) (0.9635g, 3.11mmol) was added to a stirred suspension of NaH (0.250g, 60% oil dispersion, 6.25mmol) in THF (10ml) at 0^{0}C under argon. The resulting suspension was stirred for 1h and then cyclohexanone (0.203g, 2.07mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16h. The resulting clear solution was poured into sat. aq. NH_4Cl (15ml) and ether (15ml), the layers separated, the aqueous layer re-extracted with ether (2 x 20ml), the combined organic layers washed with water (2 x 20ml), brine (1 x 20ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (1% ether-petrol) gave ^{t}butyl 4-cyclohexylidenyl-3-oxobutanthioate (237) as a pale yellow solid (mp 33-35^{0}C, 0.353g, 67%); δ_H (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 Hz; 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); ν_{max} (film) 2 929, 2 856, 1 671, 1 645, 1 613, 1 574, and 1 081cm^{-1}; m/z 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%).

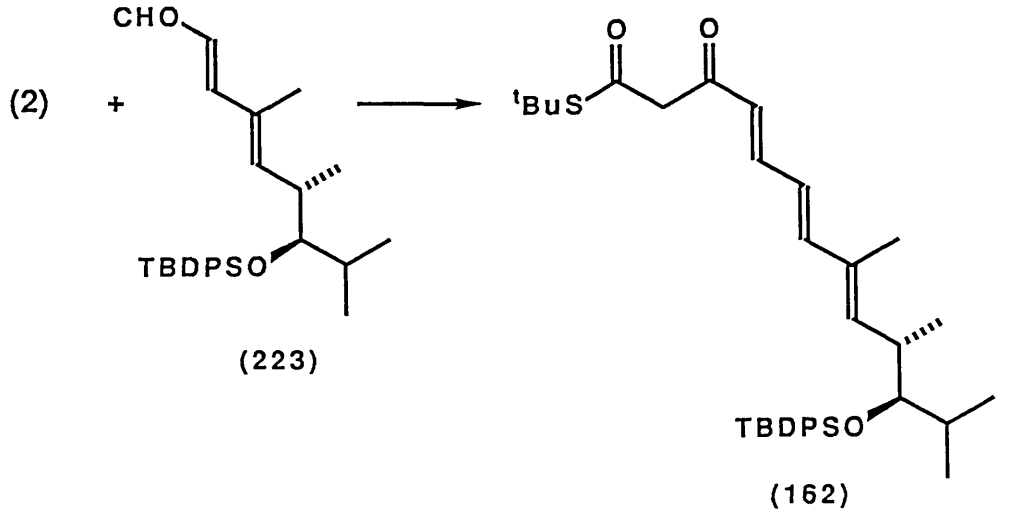
25. Preparation of ^{t}Butyl (4E,6E,8E,10E,12E)-3-Oxo-4,6,8,10,12-tetradecapentaenthioate (163)



(163)

Thioester phosphonate (2) (0.7328g, 2.36mmol) was added to a stirred suspension of NaH (190mg, 60% oil dispersion, 4.75mmol) in THF (75ml) at 0^{0}C under argon. The suspension was stirred for 1h and the aldehyde (185) (0.1777g, 1.20mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16h. The resulting clear solution was poured into sat. aq. NH_4Cl (100ml) and ether (75ml), the layers separated, and the aqueous phase re-extracted with ether (2 x 100ml). The combined organic phases were washed with water (2 x 100ml), brine (1 x 100ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (1% ether-petrol) gave ^{t}butyl (4E,6E, 8E,10E,12E)-3-oxo-4,6,8,10,12-tetradecapentaenthioate (163) as an orange waxy solid (0.222g, 61%); δ_H (90MHz, $CDCl_3$) (80% enol form) 1.50, 1.51 (9H, 2s, ^{t}BuS keto and enol), 1.80 (3H, d, J 5.9 Hz, 3 x H-14), 3.70 (0.4H, s, H-2 keto), 5.37 (0.8H, s, H-2 enol), 6.05 (9H, br m, H-4, H-6 to H-13), 7.15 (1H, dd, J 14.8, 10.8 Hz, H-5 keto and enol), and 12.55 (0.8H, br s, OH enol); m/z 304 (M^+), 262 and 57. (Found: M^+ 304.1496. $C_{18}H_{24}O_2$ (M^+) requires 304.1497).

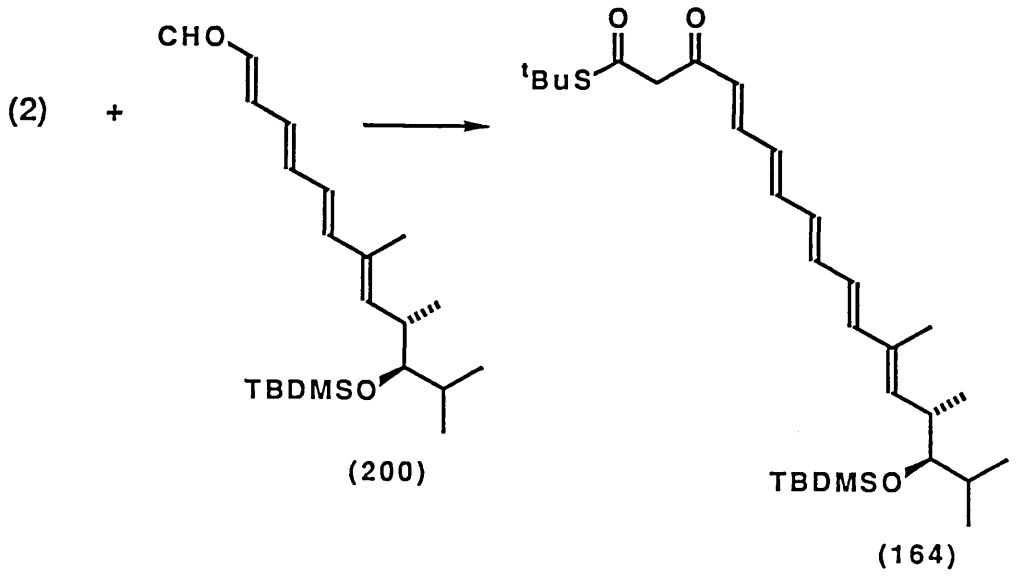
26. Preparation of ^{t}Butyl (10S*,11R*)(4E,6E,8E)-11-^{t}Butyldiphenylsilyloxy-8,10,12-trimethyl-3-oxo-4,6,8-tridecatrienthioate (162)



Thioester phosphonate (2) (0.194g, 0.625mmol) was added to a stirred suspension of NaH (52.4mg, 60% oil dispersion, 1.31mmol) in THF (30ml) at 0^{0}C under argon. The suspension was stirred for 1h and then the aldehyde (223) (0.2468g, 0.568mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16h. The resulting clear solution was poured into sat. aq. NH_4Cl (50ml) and ether (30ml), the layers separated, and the aqueous layer re-extracted with ether (2 x 50ml). The combined organic layers were washed with water (2 x 30ml), brine (1 x 30ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (1% ether-petrol) gave ^{t}butyl (10S*,11R*)(4E,6E,8E)-11-^{t}butyldiphenylsilyloxy-8,10,12-trimethyl-3-oxo-4,6,8-tridecatrienthioate (162) as a foam (0.258g, 77%); δ_H

(90MHz, $CDCl_3$) (80% enol form) 0.9 (6H, m, $(CH_3)_2CH$), 1.1 (9H, s, ^tBuSi), 1.6 (16H, m, ^tBuS, 8 and 10 methyls, 1 x H-12), 2.7 (1H, m, H-10), 3.5 (1H, m, H-11), 3.70 (0.4H, s, H-2 keto), 5.4 (0.8H, s, H-2 enol), 6.1 (4H, br m, H-4, 6, 7, and 9), 7.2 (1H, dd, J 16.1, 9.6 Hz, H-5), 7.4, 7.7 (10H, 2m, Ph_2Si), and 12.6 (0.8H, br s, OH enol); ν_{max} (film) 3 400, 2 961, 2 858, 1 685, 1 633, 1 605, 1 559, 1 110 and 1 077cm^{-1}; m/z 590 (M^+), 533, 518, 417, 405, 311, 135, and 57. (Found: M^+, 590.3245. $C_{36}H_{50}O_3SSi$ (M^+) requires 590.3250).

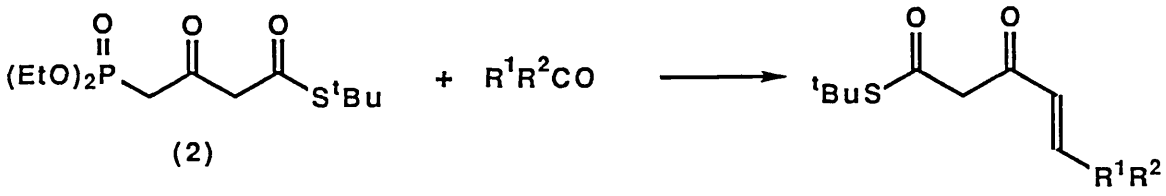
27. Preparation of ^{t}Butyl (14S*,15R*)(4E,6E,8E,10E,12E)-15-^{t}Butyldiphenylsilyloxy-12,14,16-trimethyl-3-oxo-4,6,8,10,12-heptadecapentaenthioate (164)



Thioester phosphonate (2) (44.6mg, 0.144mmol) was added to a stirred supension of NaH (11.5mg, 0.288mmol) in THF (10ml) at 0^{0}C under argon. The resulting suspension was stirred for 1h and then the aldehyde (200) (70.1mg, 0.144mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16h. The resulting clear solution was poured into sat. aq. NH_4Cl (15ml) and ether (10ml), the layers separated, and the aqueous layer re-extracted with ether (2 x 15ml). The organic layers were combined, washed with water (2 x 20ml), brine (1 x 20ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (1% ether-petrol) gave ^{t}butyl (14S*,15R*)(4E, 6E,8E,10E,12E)-15-^{t}butyldiphenylsilyloxy-12,14,16-trimethyl-3-oxo-4,6,8, 10,12-heptadecapentaenthioate (164) as an orange-red foam (57.2mg, 62%);

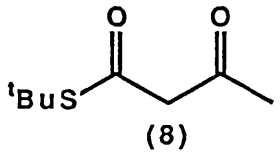
δ_H (500MHz, $CDCl_3$) (80% enol form) 0.81 (6H, m, $(CH_3)_2CH$), 0.86 (3H, d, J 6.7 Hz, 14-CH_3), 1.06 (9H, s, ^tBuSi), 1.53 (1.8H, s ^tBuS keto), 1.56 (7.2H, s, ^tBuS enol), 1.58 (2.4H, s, 12-CH_3 enol) 1.59 (0.6H, s, 12-CH_3 keto), 1.78 (1H, m, H-16), 2.64 (1H, m, H-14), 3.50 (1H, m, H-15), 3.72 (0.2H, s, H-2 keto), 5.37 (0.8H, s, H-2 enol), 5.70 (1H, d, J 10.1 Hz, H-13), 5.74 (0.2H, d, J 14.8 Hz, H-4 keto), 5.76 (0.8H, d, J 14.8 Hz, H-4 keto), 6.10 to 6.60 (6H, br m, H-6 to H-11), 7.16 (1H, dd, J 15.0, 11.4 Hz, H-5), and 7.39, 7.69 (10H, 2m, Ph_2Si); ν_{max} (film) 3 300 2 963, 1 665, 1 640, 1 615, 1 566, 1 108, and 1 075cm^{-1}; m/z 533, 507, 467, 395, 379, 339, 311, 90, and 57.

28. General procedure for the preparation of ^{t}Butyl 3-Oxo-4(E)-alkenthioates



The thioester phosphonate (2) (1.1 to 1.2 equiv. with respect to aldehyde/ketone) is added to a stirred suspension of NaH (60% oil dispersion, 2.2 to 2.4 equiv. w.r. to phosphonate) in THF (a final reactant concentration of 1% should be aimed for) at 0^{0}C under argon. The suspension is stirred for 1h and the aldehyde/ketone is added. The reaction is allowed to warm to room temperature and stirred until reaction is complete. The resulting clear solution is poured into sat. aq. NH_4Cl (same volume) and ether, the layers separated, and the aqueous re-extracted with ether (x 2). The combined organic phases are washed with water (x 2), brine (x 1), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography gives the product.

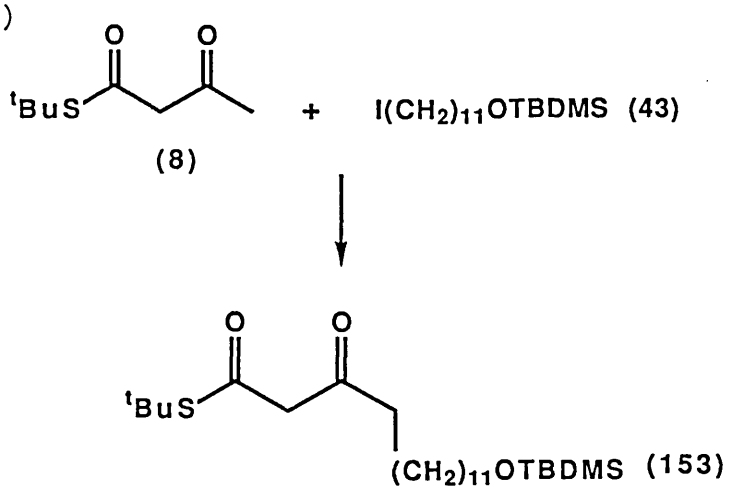
29. Preparation of ^{t}Butyl 3-Oxobutanthioate (8)



(8)

^{t}Butylthiol (3.8ml, 33mmol) in THF (5ml) was added dropwise to a suspension of sodium hydride (1.47g, 60% oil dispersion, 36.6mmol) in THF (50ml) at 0^{0}C under argon to give a white precipitate. After stirring for 5 min, a solution of diketene (2.6ml, 33mmol) in THF (5ml) was added dropwise. The solution was stirred for 10 min to give a yellow-green solution which was poured into sat. aq. NH_4Cl (50ml) and extracted with ether (200ml). The organic phase was washed with water (2 x 50ml), dried (Na_2SO_4), and the solvent removed under reduced pressure. Chromatography (5% ether-petrol) gave ^{t}butyl 3-oxobutanthioate (8) (2.7g, 48%)[74/75] as a pale red oil; δ_H (60MHz, $CDCl_3$) (23% enol form) 1.5 (9H, s, S^{t}Bu), 1.9 and 2.2 (3H, 2s, H-4 enol and keto), 3.5 (1.6H, s, H-2 keto), and 5.3 (0.2H, s, H-2 enol); ν_{max} (film) 2 965, 1 721, 1 676, 1 621, 1 364, and 1 082cm^{-1}.

30. Preparation of ^{t}Butyl 15-(^{t}Butyldimethylsilyloxy)-3-oxopentadecanthioate (153)



^{t}Butyl 3-oxobutanthioate (8) (5g, 29.0mmol) in DME (20ml) was added dropwise to a stirred suspension of sodium hydride (1.2g, 60% oil dispersion, 29.0mmol) in DME (40ml) at -20^{0}C under argon. After stirring for 5 min, the colourless solution was cooled to -40^{0}C and ^{n}butyl lithium (18.5ml, 1.55M solution, 29.0mmol) was added to generate the dianion. The resulting yellow solution was allowed to warm to -20^{0}C, stirred for 5 min, and recooled to -40^{0}C. The iodide (43) (6g, 14.5mmol) in DME (10ml) was added dropwise and the reaction mixture allowed to warm to 0^{0}C over 1h. The solution was poured into sat. aq. NH_4Cl (100ml) and extracted with ether (3 x 150ml). The combined organic phases were washed with water (1 x 200ml) and brine (1 x 100ml) and the aqueous washes re-extracted with ether (1 x 200ml). The combined organics were dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (5% ether-petrol) gave ^{t}butyl 15-(^{t}butyldimethylsilyloxy)-3-oxopentadecanthioate (153) (4.5g, 67%) as a

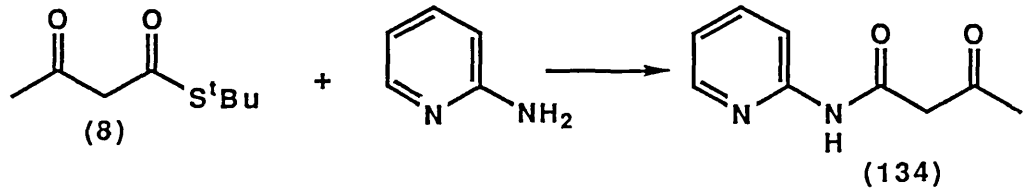
pale red oil; δ_H (250MHz, $CDCl_3$) (55% enol form) 0.03 (6H, s, $OSiMe_2$), 0.87 (9H, s, $OSiMe_2$ ^tBu), 1.25-1.60 (29H, m, including δ 1.46 and 1.50, 2s, S^tBu keto and enol, $COCH_2(CH_2)_{10}$ CH_2OSi), 2.12 and 2.53 (2H, 2t, J 7.5 Hz, H-4 enol and keto), 3.56 (0.9H, s, H-2 keto), 3.61 (2H, t, J 6.7 Hz, H-15), 5.35 (0.55H, s, H-2 enol), and 9.88 (0.55H, s, OH enol); ν_{max}(film) 2 927, 1 723, 1 675, 1 613, 1 460, 1 254, 1 099, 836, and 775 cm^{-1}; m/z 401 (m-^tBu), 345, 312, 285, 261, 90, 75, and 57. (Found: C,65.3; H,11.1; S, 7.25. $C_{25}H_{50}O_3SSi$ requires C,65.5; H,11.0; S,6.99%).

31. General procedure for the preparation of β-ketoamides from β-ketothioesters

Silver(I) trifluoroacetate (1.1 equiv) is added to a stirred solution of the amine (1 equiv) and the thioester (1.1 equiv) in THF (10% dilution of reactants) at room temperature under argon. If the thioester is the more valuable reagent the amine can be used in excess (1.1 equiv). The reactions are followed by TLC until complete.

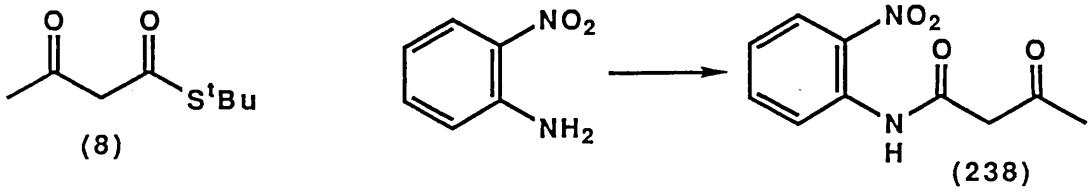
The reactions are best left stirring even after TLC indicates completion until the silver salt precipitates. This greatly facilitates the work up procedure. The reactions are worked up by removing the solvent under reduced pressure, resuspending the solid in ether, filtering, and the filtrate kept. This precipitation/filtration procedure is repeated until most of the silver residues are removed (once or twice more). The solvent is removed under reduced pressure and the residue purified by column chromatography. It is important to remove as much of the silver residues as possible before attempting chromatography since the silver salts are eluted slowly from the column.

32. Preparation of N-(2-Pyridyl)-3-oxobutanamide (134)



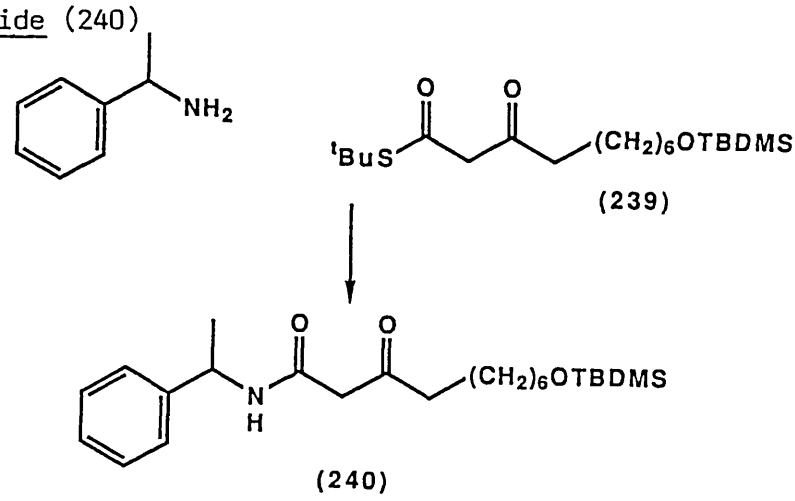
Silver(I) trifluoroacetate (0.434g, 1.97mmol) was added to a stirred solution of 2-aminopyridine (0.168g, 1.78mmol) and ^{t}butyl 3-oxobutanthioate (8) (0.327g, 1.88mmol) in THF (5ml) at room temperature under argon. The reaction was stirred for 5 min and worked up by the usual procedure. Chromatography (40% to 80% ether-petrol) gave N-(2-pyridyl)-3-oxobutanamide (134)[107/108] as a pale orange amorphous solid (0.205g, 65%, mp 109-110^{0}C lit.[107] 113-114^{0}C); δ_H (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}); ν_{max} (KBr disc) 3 242, 3 058, 1 718, 1 666, 1 576, 1 542, and 1 434cm^{-1}; m/z 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%).

33. Preparation of N- (2-Nitrophenyl)-3-oxobutanamide (238)



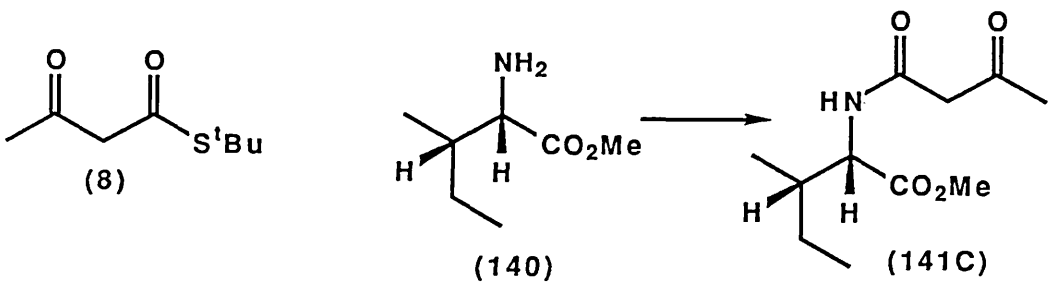
Silver(I) trifluoroacetate (0.512g, 2.32mmol) was added to a stirred solution of o-nitroaniline (0.291g, 2.11mmol) and ^{t}butyl 3-oxobutanthioate (8) (0.386g, 2.21mmol) in THF (6ml) at room temperature under argon. The solution was stirred for 3h. The reaction was complete after 45 min but the silver salts did not start to precipitate until after 2h. The resulting suspension was filtered, the solvent removed under reduced pressure, the residue resuspended in ether (20ml), and the solvent removed again under reduced pressure. It was necessary to repeat this procedure to remove most of the silver salts. Chromatography (20-40% ether-petrol) gave N-(2-nitrophenyl)-3-oxobutanamide (238)[106] as a pale yellow solid (0.376g, 80%); m.p. 64^{0}C (lit.[106] mp 66-67^{0}C); δ_H (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); ν_{max}($CHCl_3$) 3 515, 3 398, 1 624, 1 572, 1 511, and 1 346cm^{-1}; m/z 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%).

34. Preparation of (±)-10-^{t}Butyldimethylsilyloxy-N-(α-methylbenzyl)-3-oxodecanamide (240)



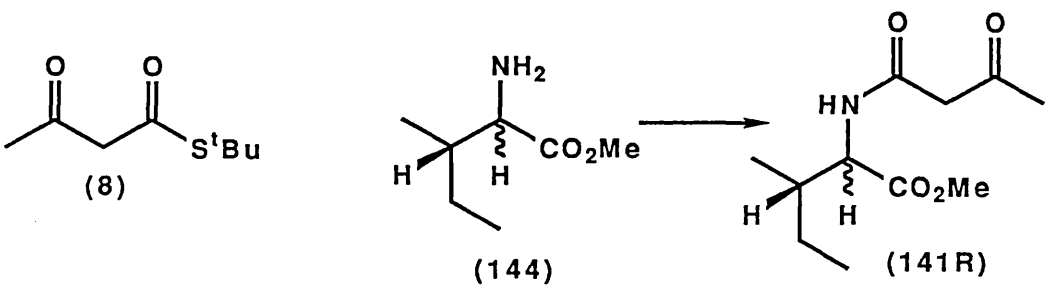
Silver(I) trifluoroacetate (0.40g, 1.82mmol) was added to a stirred solution of thioester (239) (0.71g, 1.82mmol) and (±)-α-methyl benzylamine (0.20g, 1.65mmol) in THF (20ml) at room temperature under argon. The solution was stirred for 3h (15min for reaction to complete and 2¾ h for the silver salts to precipitate). Work up by the usual procedure and chromatography (20% ether-petrol) gave (±)-10-(^{t}butyldimethylsilyloxy)-N-(α-methylbenzyl)-3-oxodecanamide (240) as a colourless oil (0.375g, 54%); δ_H (60MHz, $CDCl_3$) 0.1 (6H, s, $\underline{Me_2}Si$), 0.9 (9H, s, $^{t}\underline{Bu}Si$), 1.3 to 1.6 (13H, m, including δ 1.4 d, J 7 Hz, $\underline{CH_3}CH$, $COCH_2(\underline{CH_2})_5$), 2.5 (2H, t, J 6.5 Hz, $CO\underline{CH_2}(CH_2)_5$), 3.3 (2H, s, H-2), 3.60 (2H, t, J 7.0 Hz, H-10), 5.1 (1H, m, $CH_3\underline{CH}N$), 7.3 (5H, s, aromatics), and 8.0 (1H, br s, N$\underline{H}$); ν_{max} (film) 3 296, 2 930, 2 857, 1 717, 1 621, 1 543, and 1 255cm^{-1}; m/z 419 (M^+) and 362. (Found: C,68.6; H,9.72;; N,3.30. $C_{24}H_{41}NO_3Si$ requires C,68.7; H,9.85; N,3.34%).

35. Preparation of (2S,3S)-N-Acetoacetylisoleucine methyl ester (141C)



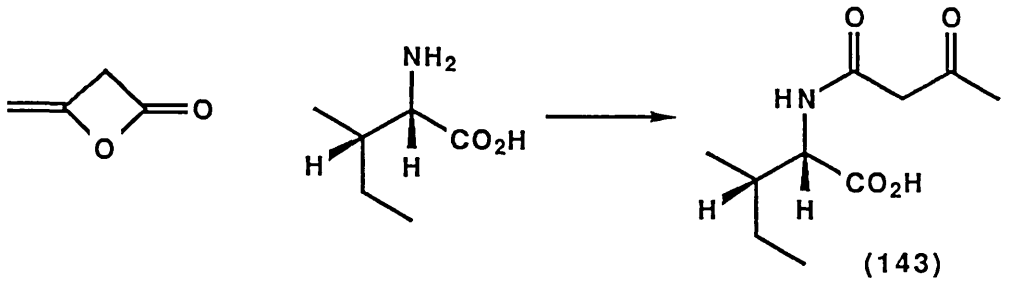
Silver(I) trifluoroacetate (0.478g, 2.16mmol) was added to a stirred solution of methyl (2S,3S)-isoleucinate (140)[142] (0.227g, 1.73mmol) and ^{t}butyl 3-oxobutanthioate (8) (0.332g, 1.90mmol) in THF (15ml) at room temperature under argon. The reaction was stirred for 3h and worked up by the usual procedure. Chromatography (ether) gave (2S,3S)-N-aceto- acetylisoleucine methyl ester (141C)[23] as a colourless oil (0.253g, 60%); $[\alpha]_{546}^{25}$ -22^0 (c 2.0 MeOH) δ_H (90MHz, $CDCl_3$) 0.90 (6H, m, $\underline{CH_3}CH_2CH\underline{CH_3}$), 1.30 (2H, m, $CH_3\underline{CH_2}CHCH_3$), 1.90 (1H, m, $CH_3CH_2\underline{CH}CH_3$), 2.26 (3H, s, $\underline{CH_3}CO$), 3.43 (2H, s, $CO\underline{CH_2}CON$), 3.72 (3H, s, $\underline{CH_3}O$), 4.56 (1H, dd, $\underline{J}$ 8.2, 4.6 Hz, $\underline{CH}CO_2Me$), and 7.35 (1H, br d, $\underline{NH}$); δ_C (22.5MHz, $CDCl_3$, decoupled) 11.45 ($\underline{CH_3}CH_2CHCH_3$), 15.42 ($CH_3CH_2CH\underline{CH_3}$), 25.06 ($CH_3\underline{CH_2}CHCH_3$), 30.80 ($\underline{CH_3}CO$), 37.57 ($CH_3CH_2\underline{CH}CH_3$), 49.54 ($CO\underline{CH_2}CON$), 51.98 ($\underline{CH_3}O_2C$), 56.55 ($NH\underline{CH}CO_2Me$), 165.37, 171.96 ($CH_2\underline{C}ONH$, $\underline{C}O_2Me$), and 203.94 ($CH_3\underline{C}OCH_2$); ν_{max} (film) 3 315, 2 966, 2 879, 1 735, 1 712, 1 648, 1 512, and 1 301cm^{-1}.

36. Preparation of (2RS,3S)-N-Acetoacetylisoleucine methyl ester (141R)



Silver(I) trifluoroacetate (0.431g, 1.95mmol) was added to a solution of methyl (2RS,3S) isoleucinate (144) (0.257g, 1.77mmol) and ^{t}butyl 3-oxobutanthioate (8) (0.324g, 1.86mmol) in THF (5ml) at room temperature under argon. The reaction was stirred for 3h and worked up by the usual procedure. Chromatography (ether) gave (2RS,3S)-N-acetoacetylisoleucine methyl ester (141R) as a colourless oil (0.252g, 62%); $[\alpha]_{546}^{25}$ -0.42^0 (c 2.0, MeOH); δ_H(90MHz, $CDCl_3$) 0.82 (6H, m, $\underline{CH_3}CH_2CH\underline{CH_3}$), 1.20 (2H, m, $CH_3\underline{CH_2}CHCH_3$), 1.79 (1H, m, $CH_3CH_2\underline{CH}CH_3$), 2.17 (3H, s, $\underline{CH_3}CO$), 3.38 (2H, s, $COCH_2CONH$), 3.62 (3H, s, $\underline{CH_3}O_2C$), 4.52 (1H, m, $NHCHCO_2Me$) and 7.40 (1H, br d, NH); δ_C (22.5MHz, $CDCl_3$, decoupled) (1:1 diastereoisomer mixture) 11.27, 11.45 ($\underline{CH_3}CH_2CHCH_3$), 14.44, 15.30 ($CH_3CH_2CH\underline{CH_3}$), 24.94, 26.04 ($CH_3\underline{CH_2}CHCH_3$), 30.49 ($\underline{CH_3}CO$), 37.21, 37.39 ($CH_3CH_2\underline{CH}CH_3$), 49.60 ($CO\underline{CH_2}CON$), 51.79, 51.92 ($\underline{CH_3}O_2C$), 55.33, 56.43 ($NH\underline{CH}CO_2Me$), 165.56, 165.74, 171.90, 172.21 ($CH_2\underline{C}ONH$, $\underline{C}O_2Me$), and 203.82 ($CH_3\underline{C}OCH_2$).

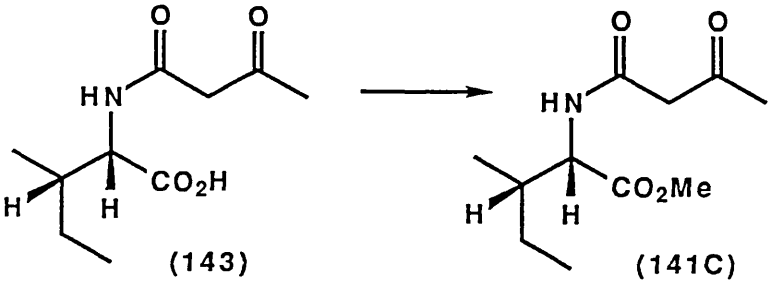
37. Preparation of (2S,3S)-N-Acetoacetylisoleucine (143)



(143)

L-Isoleucine (5.00g, 38.1mmol) was dissolved in a stirred solution of sodium hydroxide (1.52g, 38.1mmol) in water (19ml) at room temperature. The clear solution was cooled to 0^0C and diketene (3.2ml, 40.1mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 3h, acidified to pH 1 with 2N aq. HCl and extracted with ether (3 x 50ml). The combined ether layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Recrystallisation from ether gave (2S,3S)-N-acetoacetylisoleucine (143) (6.32g, 77%) as a white crystalline solid (m.p. 119^0C, lit. 120-121^0C)[22]; $[\alpha]_{546}^{25}$ 6.5^0 (c 2.0, MeOH), lit. $[\alpha]_{546}^{25}$ -122^0 (c 2.0, MeOH)[22]; δ_H (90MHz, $CDCl_3$) 0.90 (6H, m, $CH_3CH_2CHCH_3$), 1.30 (2H, m, CH_3 CH_2CHCH_3), 1.90 (1H, m, $CH_3CH_2CHCH_3$), 2.26 (3H, s, CH_3COCH_2), 3.50 (2H, s, CH_2CONH), 4.54 (1H, dd, J 4.5, 8.2 Hz, $NHCHCO_2H$), 7.67 (1H, d, J 8.2 Hz, NH), and 8.90 (1H, br s, CO_2H); δ_C (22.5MHz, $CDCl_3$, decoupled), 11.58 ($CH_3CH_2CHCH_3$), 15.60 ($CH_3CH_2CHCH_3$), 25.00 ($CH_3CH_2CHCH_3$), 30.92 (CH_3COCH_2), 37.33 ($CH_3CH_2CHCH_3$), 48.99 ($COCH_2CONH$), 56.74 ($NHCHCO_2H$), 166.35, 175.08 (CH_2CONH, CO_2H), and 204.49 (CH_3COCH_2); m/z 215 (M^+), 170, 159, and 141. (Found: C,55.6; H,8.07; N,6.45. $C_{10}H_{17}NO_4$ requires C,55.8; H,7.96; N,6.51%).

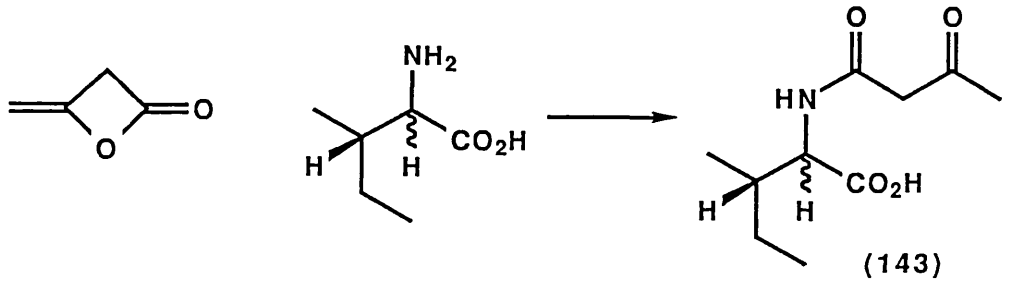
38. Preparation of (2S,3S)-N-Acetoacetylisoleucine methyl ester (141C)



(143) (141C)

Diazomethane was passed through a stirred solution of the acid (143) (1.50g, 6.97mmol) in ether (500ml) at room temperature until the yellow colour of the diazomethane persisted in the ether solution. The diazomethane was generated by treating a solution of Diazald® (N-methyl-N-nitroso-p-toluenesulphonamide, 8.0g, 37.3mmol) in ethanol (40ml) and ether (18ml) with potassium hydroxide solution (11ml, 180mg per ml). Argon was passed through this solution and through the ether solution of the acid. When the reaction had finished acetic acid was carefully added to destroy the excess diazomethane. The solution was passed through a pad of florisil and the solvent was removed under reduced pressure giving (2S,3S)-N-acetoacetylisoleucine methyl ester (141C)[22] as a colourless oil (1.52g, 95%); $[\alpha]_{546}^{25}$ -21^0 (c 2.0, MeOH) lit.[22] $[\alpha]_{546}$ 7^0 (c 2.0, MeOH); δ_H, δ_C, and ν_{max} same as compound (141C) prepared in experiment 35; m/z 229 (M^+), 170, and 86. (Found: C,57.3; H,8.55; N,6.18. $C_{11}H_{19}NO_4$ requires C,57.6; H,8.35; N,6.11%).

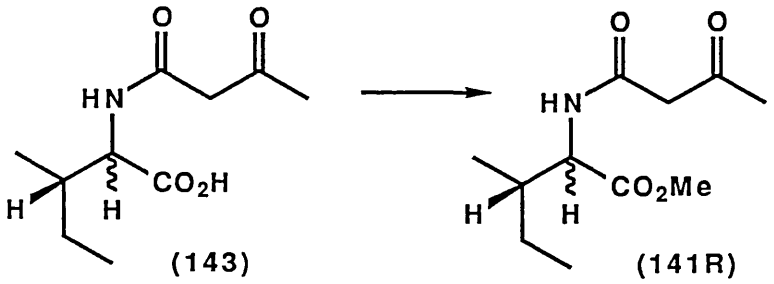
39. Preparation of (2RS,3S)-N-Acetoacetylisoleucine (143)



(143)

(2RS,3S)-N-Acetoacetyl-isoleucine was prepared from (2RS,3S)-isoleucine (1.0g, 8.39mmol) and diketene (1.31ml, 1.68mmol) as before (experiment 37). Recrystallisation from ether gave (2RS,3S)-N-acetoacetylisoleucine (143) (1.48g, 82%); $[\alpha]_{546}^{25}$ -2.8^0 (c 2.0, MeOH); δ_H (90MHz, $CDCl_3$) (1:1 diastereoisomeric mixture) 0.90 (6H, m, $C\underline{H}_3CH_2CHC\underline{H}_3$), 1.30 (2H, m, $CH_3C\underline{H}_2CHCH_3$), 1.92 (1H, m, $CH_3CH_2C\underline{H}CH_3$), 2.20, 2.22 (3H, 2s, $C\underline{H}_3COCH_2$), 3.48, 3.50 (2H, 2s, $COC\underline{H}_2CONH$), 4.10 (1H, m, $NC\underline{H}CO_2H$), 7.70 (1H, br d, $N\underline{H}$), and 8.30 (1H, br s, $CO_2\underline{H}$); δ_c (22.5MHz, $CDCl_3$, decoupled) 11.58, 11.70 ($\underline{C}H_3CH_2CHCH_3$), 14.57, 15.54 ($CH_3CH_2CH\underline{C}H_3$), 25.00, 26.34 ($CH_3\underline{C}H_2CHCH_3$), 30.86 ($\underline{C}H_3CO$), 37.15, 37.33 ($CH_3CH_2\underline{C}HCH_3$), 48.99 ($CO\underline{C}H_2CONH$), 55.52, 56.80 ($N\underline{C}HCO_2H$), 166.59, 166.72, 174.89, 175.32 ($\underline{C}ONH$, $\underline{C}O_2H$), and 204.55 ($CH_3\underline{C}O$).

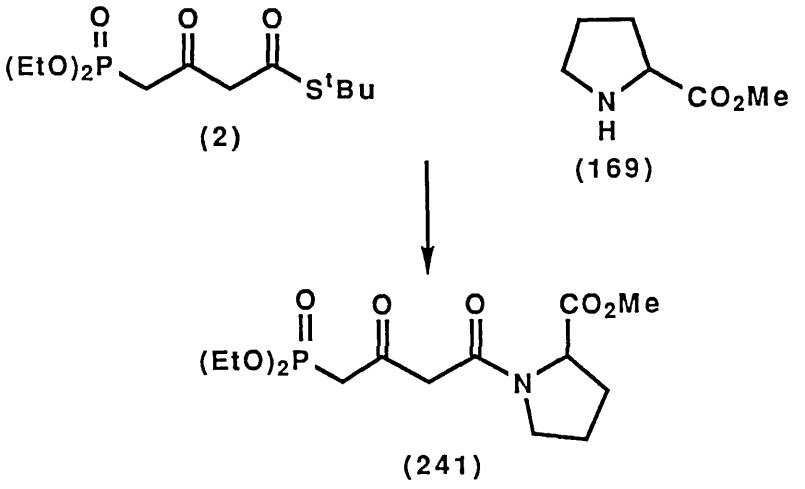
40. Preparation of (2RS,3S)-N-Acetoacetylisoleucine methyl ester (141R)



(143) (141R)

Compound (141R) was prepared using the same method as that used in experiment (38). Treatment of the acid (143) (80mgs, 0.371mmol) in ether (50ml) with diazomethane after workup gave (2RS,3S)-N-acetoacetyl-isoleucine methyl ester (141R) as a colourless oil (78.3mg, 92%); $[\alpha]_{546}^{25}$ -0.50^0 (c 2.0, MeOH); all spectral data identical to compound (141R), experiment (36).

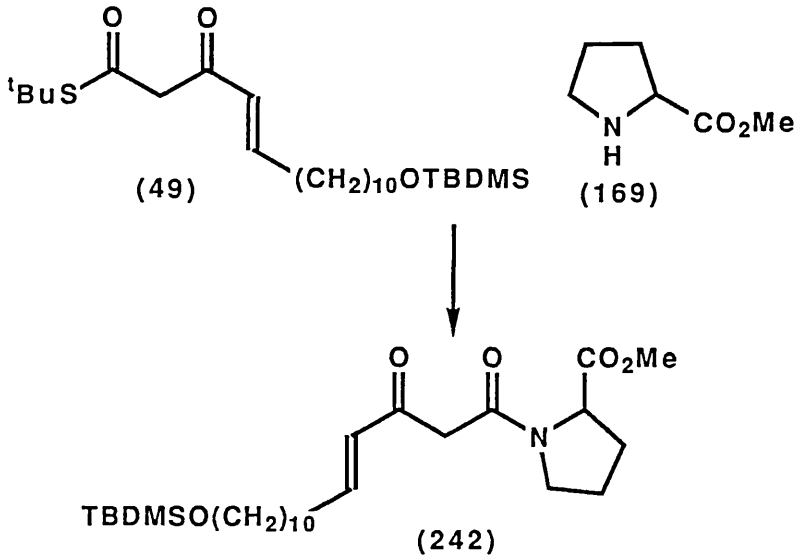
41. Preparation of (±)-N-(4-Diethylphosphono-3-oxobutanoyl)-proline methyl ester (241)



Silver(I) trifluoroacetate (0.288g, 13.0mmol) was added to a stirred solution of phosphonate thioester (2) (0.386g, 12.5mmol) and methyl (±)-prolinate (169)[143] (0.153g, 11.9mmol) in THF (8ml) at room temperature under argon. The mixture was stirred for 16h and worked up by the usual procedure. Chromatography (10% isopropyl alcohol-CH_2Cl_2) gave (±)-N-(4-diethylphosphono-3-oxobutanoyl)-proline methyl ester (241) as a colourless oil (0.248g, 60%); δ_H (250MHz, $CDCl_3$) (35% enol form, 4:1 rotamer mixture) 1.24 (6H, t, J 7.0 Hz, $(CH_3CH_2O)_2P$), 1.90, 2.24 (4H, 2m, 2 x H-3, 2 x H-4 proline), 2.67 (0.14H, d, J 21.3 Hz, PCH_2CO enol rotamer), 2.70 (0.56H, d, J 21.3 Hz, PCH_2CO enol rotamer), 3.23 (1.3H,

d, J 21.3 Hz, 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 Hz, $(CH_3CH_2O_2)P$), 4.40 (1H, m, $NCHCO_2Me$), 4.90 (0.07H, d, J 3 Hz, H-2 enol rotamer), 5.60 (0.28H, d, J 3.0 Hz, H-2 enol rotamer), 14.40 (0.28H, br s, OH enol rotamer), and 14.70 (0.07H, br s, OH enol rotamer); ν_{max} (film) 3 466, 2 982, 1 743, 1 639, 1 599, 1 252, and 1 025cm^{-1}; m/z 349 (M^+), 221, 179, and 151. (Found: 349.1299 (M^+). $C_{14}H_{24}N O_7P$ requires 349.1290).

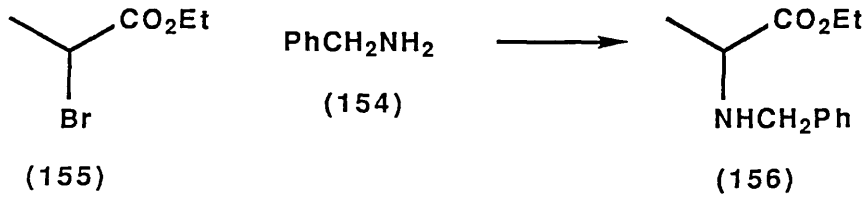
42. Preparation of (±)-N-[(4E)-15-^{t}Butyldimethylsilyloxy-3-oxo-4-pentadecenoyl]proline methyl ester (242)



Silver(I) trifluoroacetate (162mg, 0.733mmol) was added to a stirred solution of thioester (49) (0.318g, 0.696mmol) and methyl (±)-prolinate (169)[143] (86mg, 0.666mmol) in THF (5ml) at room temperature under argon. The reaction was stirred for 16h and worked up as usual. Chromatography (30% ether-petrol) gave (±)-N-[(4E)-15-^{t}butyldimethylsilyloxy-3-oxo-4-pentadecenoyl]proline methyl ester (242) as a colourless oil (0.214g, 65%); δ_H (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 Hz, 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_2Me keto), 4.50 (0.7H, m, NCHCO_2Me 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 Hz, H-4 enol rotamer), 5.77 (0.56H, d, J 15.2 Hz, H-4 enol rotamer), 6.15 (0.06H, d, J 17.0 Hz, H-4 keto rotamer), 6.19 (0.24H, d, J 17.0 Hz, H-4 keto rotamer), 6.50 (0.7H, dt, J 15.2, 6.8 Hz, H-5 enol), 6.96 (0.3H, dt, J 17.0, 6.8 Hz, H-5 keto), 13.92 (0.56H, br s, OH enol rotamer), and 14.21 (0.14H, br s, OH enol rotamer); ν_{max} (film) 2 928, 2 855, 1 747, 1 657, and 1 596cm^{-1}; m/z 495 (M^+), 480, and 438. (Found: 438.2683 ($M^+ - {}^tBu$). $C_{23}H_{40}NO_5Si$ requires 438.2676).

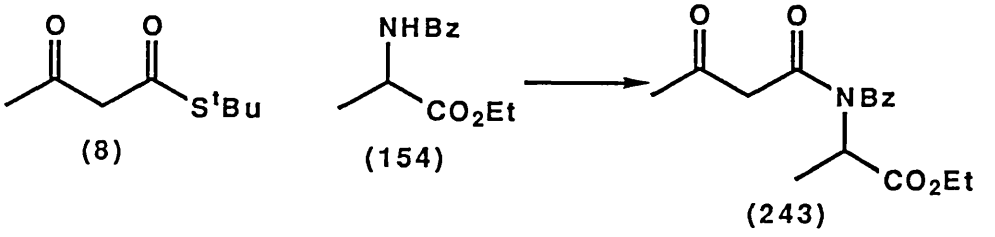
43. Preparation of (±)-N-Benzylalanine ethyl ester (156)



(155) (156)

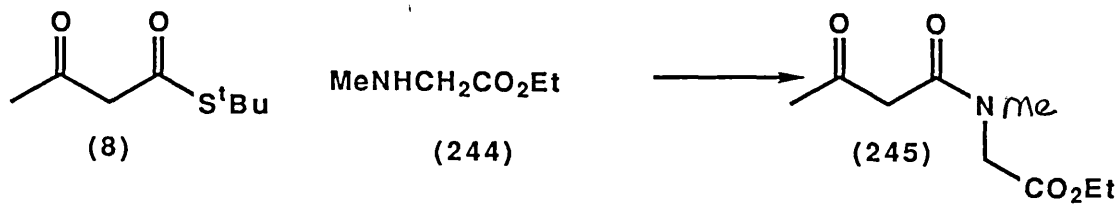
A mixture of ethyl (±)-α-bromoacetate (155) (4.18g, 23.1mmol) and benzylamine (154) (4.95g, 46.2mmol) in toluene (50ml) was heated under reflux for 24h. The reaction was cooled to room temperature and the solvent removed under reduced pressure. Chromatography (5% ether-petrol) gave (±)-N-benzylalanine ethyl ester (156)[115] as a colourless oil (3.65g, 76%); δ_H (60MHz, $CDCl_3$) 1.25 (3H, t, J 7.0 Hz, $\underline{CH_3}CH_2O$), 1.30 (3H, d, J 7.0 Hz, 3 x H-3), 1.85 (1H, br s, NH), 3.30 (1H, q, J 7.0 Hz, H-2), 3.70 (2H, d, J 2.0 Hz, NCH_2Ph), 4.15 (2H, q, J 7.0 Hz, $CH_3\underline{CH_2}O$), and 7.20 (5H, s, aromatics); ν_{max} (film) 3 330, 2 980, 2 935, 1 730, 1 451, 1 188, and 1 153cm^{-1}.

44. Preparation of (±)-N-Acetoacetyl-N-benzylalanine ethyl ester (243)



Silver(I) trifluoroacetate (0.527g, 2.39mmol) was added to a stirred solution of ^{t}butyl 3-oxobutanthioate (8) (0.416g, 2.39mmol) and (±)-N-benzylalanine ethyl ester (154) (0.45g, 2.17mmol) in THF (25ml) at room temperature under argon. The reaction was stirred for 16h and worked up by the usual procedure. Chromatography (40% ether-petrol) gave (±)-N-acetoacetyl-N-benzylalanine ethyl ester (243) as a colourless oil (0.474g, 75%); δ_H(60MHz, $CDCl_3$) (75% enol form) 1.20 (3H, t, J 7.5 Hz, CH_3CH_2O), 1.40 (3H, d, J 6.0 Hz, 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); ν_{max} (film) 3 200, 2 985, 1 738, 1 633, 1 589, 1 479, and 1 026cm^{-1}.

45. Preparation of N-Acetoacetyl-N-methylglycine ethyl ester (245)



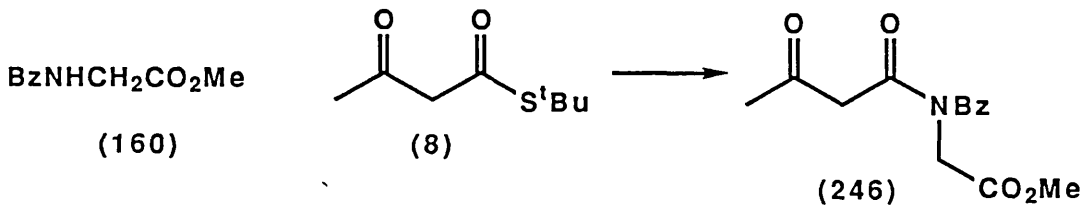
Silver(I) trifluoroacetate (1.40g, 6.34mmol) was added to a stirred solution of ^{t}butyl 3-oxobutanthioate (8) (1.10g, 6.31mmol) and ethyl sarcosinate (244)[144] (0.67g, 5.72mmol) in THF (12ml) at room temperature under argon. The reaction was stirred for 16h and worked up by the usual procedure. Chromatography (ether) gave N-acetoacetyl-N-methylglycine ethyl ester (245)[24] as a colourless oil (0.748g, 65%); δ_H (90MHz, $CDCl_3$) (87% keto form, 3:1 rotamer mixture) 1.30 (3H, 2q, J 7.1 Hz, $CH_3CH_2O_2C$), 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 Hz, CH_3CH_2O), 5.20 (0.13H, br s, 1 x H-2 enol), and 13.9 (0.13H, br s, OH enol); m/z 201 (M^+), 183, 155, and 128.

46. Preparation of N-Benzylglycine methyl ester (166)

$NH_2CH_2CO_2H$ (157) + PhCHO ⟶ $BzNHCH_2CO_2H$ (158) ⟶ $BzNHCH_2CO_2Me$ (166)

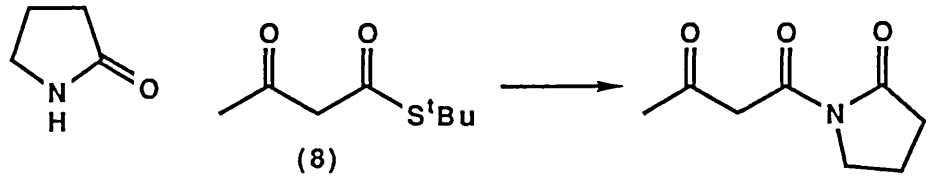
Benzaldehyde (10.15ml, 0.10mol) was added to a vigorously stirred solution of glycine (157) (5.0g, 0.067mol) and sodium hydroxide (2.66g, 0.067mol) in water (35ml). The solution was stirred for 30 min and then sodium borohydride (2.52g, 0.067mol) was carefully added portionwise. After the addition the solution was stirred for 24h, cooled to 0^0C, and acidified with 1N aq. HCl to pH1. The water was removed under reduced pressure. The residue was dissolved in methanol (300ml) and concentrated aq. HCl (5ml). The solution was heated under reflux for 8h, the solvent removed under reduced pressure and the residue partitioned between ether (400ml) and sat. aq. $NaHCO_3$ (300ml). The layers were separated and the aqueous phase re-extracted with ether (2 x 300ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (30% ether-petrol) gave N-benzylglycine methyl ester (166)[116] as a colourless oil (8.05g, 67%); δ_H (60MHz, $CDCl_3$) 2.20 (1H, s, NH), 3.30 (2H, s, $PhCH_2N$), 3.65 (3H, s, CO_2Me), 3.75 (2H, s, CH_2CO_2Me), and 7.20 (5H, s, aromatics); ν_{max} (film) 3 330, 3 062, 2 957, 1 741, 1 494, 1 451, 1 435, and 1 198cm^{-1}.

47. Preparation of N-Acetoacetyl-N-benzylglycine methyl ester (246)



Silver(I) trifluoroacetate (1.03g, 4.67mmol) was added to a stirred solution of N-benzylglycine methyl ester (166) (0.76g, 4.24mmol) and ^{t}butyl 3-oxobutanthioate (8) (0.81g, 4.67mmol) in THF (40ml) at room temperature under argon. The reaction was stirred for 16h and worked up by the usual procedure. Chromatography (75% ether-petrol) gave N-acetoacetyl-N-benzylglycine methyl ester (246) as a colourless oil (0.76g, 65%), δ_H (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), ν_{max} (film) 3 400, 2 936, 1 747, 1 647, 1 492, and 1 203cm^{-1}; m/z 263 (M^+), 178, 120, and 91. (Found: C,63.8; H,6.55; N,5.29. $C_{14}H_{17}NO_4$ requires C,63.9; H,6.51; N,5.32%).

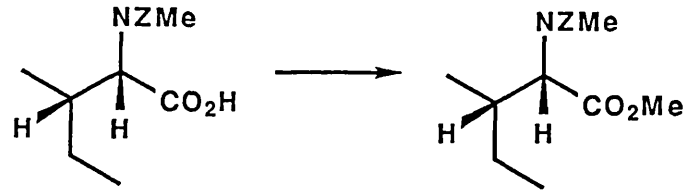
48. Preparation of N-Acetoacetylpyrrolidin-2-one (137)



(8) (137)

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 (8) (1.15g, 6.60mmol) in THF (20ml) at room temperature under argon. The reaction was stirred for 3h and worked up by the usual procedure. Chromatography (75% ether-petrol) gave N-acetoacetylpyrrolidin-2-one (137) as a colourless oil (0.823g, 74%); δ_H (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 Hz 2 x H-3 pyrrolidinone), 3.75 (2H, t, J 7.0 Hz, 2 x H-5 pyrrolidinone), and 3.89 (2H, s, 2 x H-2); δ_C (22.5Hz, $CDCl_3$, decoupled) 16.70 (C-4 pyrrolidinone), 29.88 (C-3 pyrrolidinone), 32.94 (C-4), 44.90 (C-5 pyrrolidinone), 52.04 (C-2), 166.72 (C-2 pyrrolidinone), 175.44 (C-1), and 201.08 (C-3); ν_{max} (film) 2 937, 1 735, 1 689, 1 628, 1 364, 1 326, and 1 190cm^{-1}. (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%).

49. Preparation of (2S,3S)-N-Benzyloxycarbonyl-N-methylisoleucine methyl ester (247)

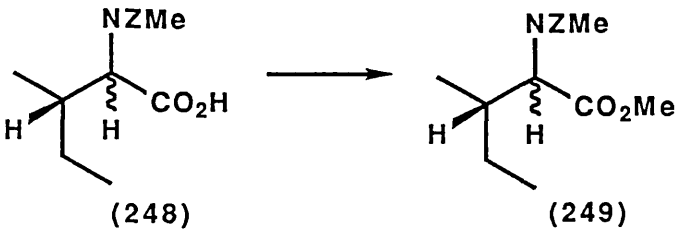


(176) (247)

Z = $PhCH_2OCO$

Dicyclohexylcarbodiimide (0.40g, 1.94mmol) was added to a stirred solution of acid (176)[145] (0.484g, 1.73mmol), methanol (80µl, 1.98mmol), and DMAP (22mg, 0.18mmol) in CH_2Cl_2 (10ml) at room temperature under argon. The reaction was allowed to stir for 3h, the precipitated solid filtered off under suction, and the filtrate washed with water (3 x 60ml), 5% aq. HOAc (3 x 60ml), and water (1 x 60ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (10 to 15% ether-petrol) gave (2S,3S)-N-benzyloxycarbonyl-N-methylisoleucine methyl ester (247) as a colourless oil (0.376g, 74%); $[\alpha]_D^{25}$ 84^0 (c 1.45, $CHCl_3$); δ_H (90MHz, $CDCl_3$ (>90% single rotamer) 0.90 (6H, m, $\underline{CH_3}CH_2CH\underline{CH_3}$), 1.82 (2H, m, $CH_3\underline{CH_2}CHCH_3$), 1.95 (1H, m, $CH_3CH_2\underline{CH}CH_3$), 2.91 (3H, s, N-Me), 3.70 (3H, s, $CO_2\underline{Me}$), 4.50 (1H, m, H-2), 5.15 (2H, s, $\underline{CH_2}$ benzyl), and 7.35 (5H, s, aromatics); ν_{max} (film) 2 963, 1 741, 1 701, 1 586, 1 309, and 1 148cm^{-1}; m/z 293 (M^+), 234, 190, and 91. (Found: C,65.4; H,7.86; N,4.72. $C_{16}H_{23}NO_4$ requires C,65.5%; H,7.90; N,4.78%).

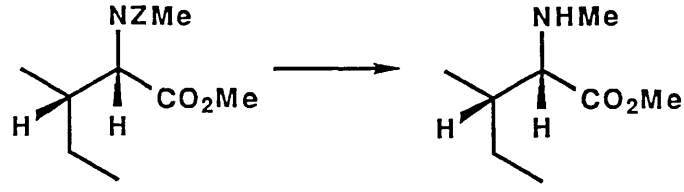
50. Preparation of (2RS,3S)-N-Benzyloxycarbonyl-N-methylisoleucine methyl ester (249)



(248) (249)

Dicyclohexyldiimide (5.20g, 25.2mmol) was added to a stirred solution of the acid (248) (6.40g, 22.9mmol), methanol (1.02ml, 25.2mmol), and DMAP (0.28g, 2.29mmol) in CH_2Cl_2 (50ml) at room temperature under argon. The reaction was stirred for 2h and worked up as before. Chromatography (15% ether-petrol) gave (2RS,3S)-N-benzyloxycarbonyl- N-methylisoleucine methyl ester (249) as a colourless oil (4.58g, 68%); $[\alpha]_D^{25}$ 0.1^0 (c 1.5, $CHCl_3$); δ_H (90MHz, $CDCl_3$) (1:1 diastereomer mixture) 0.88 (6H, m, $C\underline{H}_3CH_2CHC\underline{H}_3$), 1.30 (2H, m, $CH_3C\underline{H}_2CHCH_3$), 1.90 (1H, m, $CH_3CH_2C\underline{H}CH_3$), 2.88 (3H, s, N-Me), 3.64, 3.68 (3H, 2s, $CO_2C\underline{H}_3$), 4.40 (1H, m, H-2), 5.08, 5.14 (2H, 2s, $C\underline{H}_2$ Ph), and 7.30 (5H, s, aromatics).

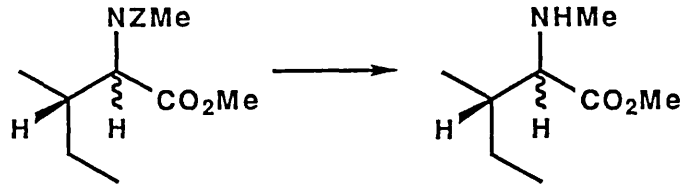
51. Preparation of (2S,3S)-N-Methylisoleucine methyl ester (177)



(247) (177)

A suspension of the ester (247) (158mg, 0.539mmol), cyclohexene (0.55ml, 5.43mmol), and 10% palladium on carbon (25mg) was heated under reflux for 3h, the solution filtered, and the volatile material removed under reduced pressure. Chromatography (40% ether-petrol) gave (2S,3S)-N- methylisoleucine methyl ester (177)[146] as a colourless oil (74.9mg, 87%, b.p. 125°C/20mmHg); $[\alpha]_D^{25}$ 7.3° (c 2.9, $CHCl_3$); δ_H (90MHz, $CDCl_3$) 0.88 (6H, m, $C\underline{H}_3CH_2CHC\underline{H}_3$), 1.00 to 1.80 (4H, m, $CH_3C\underline{H}_2C\underline{H}CH_3$, including N$\underline{H}$), 2.30 (3H, s, N-$\underline{Me}$), 2.95 (1H, d, $\underline{J}$ 5.7 Hz, $\underline{H}$-2), and 3.68 (3H, s, $CO_2\underline{Me}$); ν_{max} (film) 3 340, 2 963, 1 734, and 1 119cm^{-1}; $\underline{m/z}$ 159 (M^+) and 100 (M^+-CO_2Me). (Found: C,60.4; H,10.8; N,8.74. $C_8H_{17}NO_2$ requires C,60.3; H,10.8; N,8.80%).

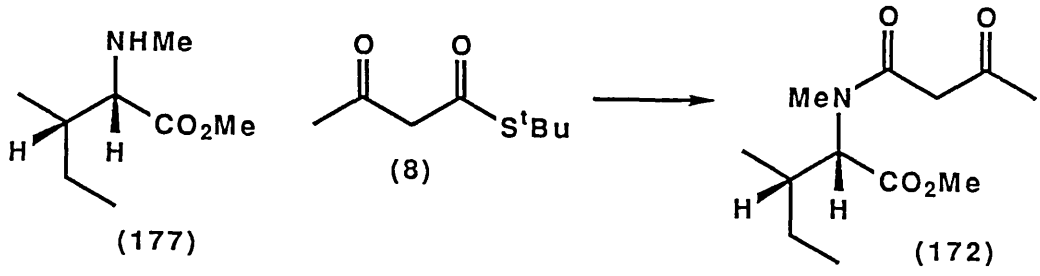
52. Preparation of (2RS,3S)-N-Methylisoleucine methyl ester (250)



(249) (250)

A suspension of 10% palladium on carbon (50mg) and ester (249) (0.37g, 1.32mmol) in methanol (10ml) was hydrogenated at room temperature and atmospheric pressure for 3h. The solution was filtered and the volatile material removed under reduced pressure. Chromatography (40% ether-petrol) gave (2RS,3S)-N-methylisoleucine methyl ester (250) as a colourless oil (187mg, 89%); $[\alpha]_D^{25}$ 0.0^0 (c 2.9, $CHCl_3$); δ_H(90MHz, $CDCl_3$) (1:1 diastereomer mixture) 0.82 (6H, m, $\underline{CH_3}CH_2CH\underline{CH_3}$), 0.95 to 1.75 (4H, m, $CH_3\underline{CH_2}\underline{CH}CH_3$, including 1.45, s, $\underline{NH}$), 2.30 (3H, s, N-$\underline{Me}$), 2.89, 2.94 (1H, m, $\underline{H\text{-}2}$), and 3.65 (3H, s, $CO_2\underline{Me}$).

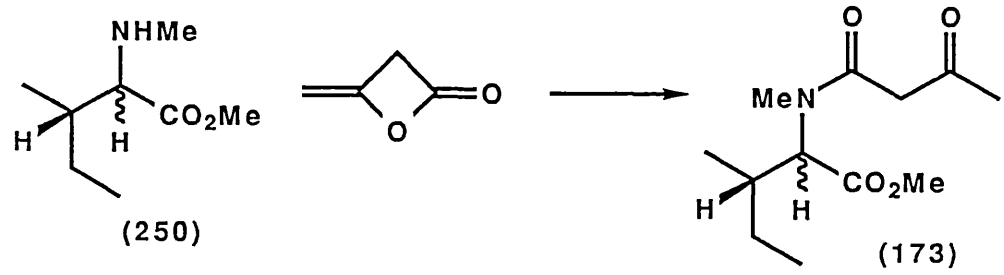
53. Preparation of (2S,3S)-N-Acetoacetyl-N-methylisoleucine methyl ester (172)



Silver(I) trifluoroacetate (61.6mg, 0.279mmol) was added to a stirred solution of aminoester (177) (40.4mg, 0.254mmol) and ^{t}butyl 3-oxobutanthioate (8) (50.0mg, 0.287mmol) in THF (5ml) at room temperature under argon. The reaction was stirred for 20h and worked up as usual. Chromatography (15% ether-petrol) gave (2S,3S)-N-acetoacetyl-N-methylisoleucine methyl ester (172)[23] as a colourless oil, (42.1mg, 68%); $[\alpha]_D^{25}$ -131^0 (c 2.4, $CHCl_3$); b.p. 178→180^{0}C/0.04mmHg; δ_H (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 Hz, H-2 keto major rotamer), 3.61 (0.28H, d, J 3 Hz,

H-2 keto minor rotamer), 3.71 (2.1H, s, CO_2Me keto), 3.74 (0.9H, s, CO_2 Me enol), 5.00, 5.02 (1H, 2d, J 10 Hz, 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); ν_{max} (film) 3 400, 1 737, 1 647, and 1 201cm^{-1}; m/z 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%).

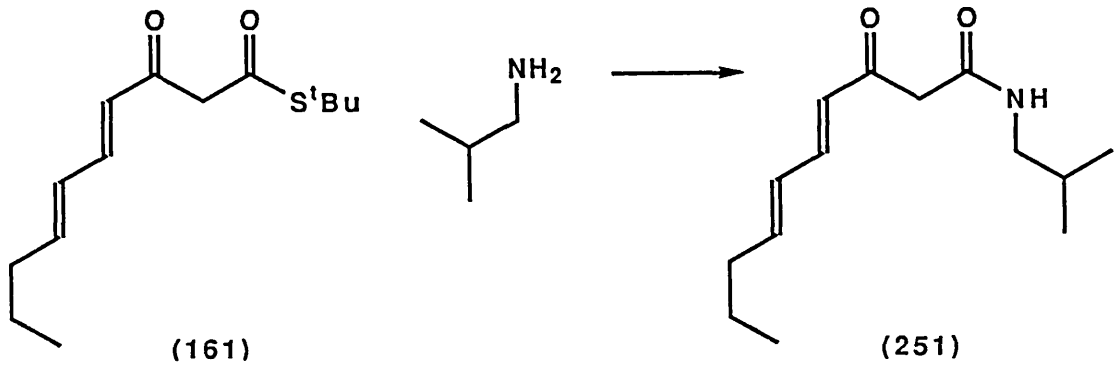
54. Preparation of (2RS,3S)-N-Acetoacetyl-N-methylisoleucine methyl ester (173)



(250) (173)

Diketene (0.52ml, 6.64mmol) was added to a stirred solution of aminoester (250) (0.694g, 4.36mmol) in CH_2Cl_2 (10ml) at 0^0C under argon. The solution was allowed to warm to room temperature, stirred for 16h, and the volatile material was removed under reduced pressure. Chromatography (40% ether-petrol) gave (2RS,3S)-N-acetoacetyl-N-methylisoleucine methyl ester (173) as a colourless oil (0.831g, 78%); $[\alpha]_D^{25}$ 0.0^0 (c 3.5, $CHCl_3$); δ_H (500MHz, $CDCl_3$) (30% enol form, 1:1 diastereomer mixture, 4:1 rotamer mixture) 0.90 (6H, m, $C\underline{H}_3CH_2CHC\underline{H}_3$), 1.10 (1H, m, 1x $CH_3C\underline{H}_2CHCH_3$), 1.42 (1H, m, 1 x $CH_3C\underline{H}_2CHCH_3$), 2.0 (1.9H, m, $CH_3CH_2C\underline{H}CH_3$, including 0.9H, s, 3 x H-4 enol), 2.25 (2.1H, s, 3 x H-4 keto), 2.95 (3H, m, N-Me), 3.59 (1.12H, d, J 3 Hz, H-2 keto major rotamer), 3.61 (0.28H, d, J 3 Hz, H-2 keto minor rotamer), 3.71 (2.1H, s, CO_2Me keto), 3.74 (0.9H, 2s, CO_2Me enol rotamers or diastereoisomers), 5.05 (1H, m, $C\underline{H}CO_2Me$), 5.14 (0.24H, s, H-2 enol major rotamer), 5.22 (0.06H, s, H-2 enol minor rotamer), and 14.60 (0.3H, 3s, enol OH); ν_{max} (film) 3 400, 1 737, 1 647, and 1 201cm^{-1}; m/z 243 (M^+), 225, 212, 184, and 100. (Found: C,59.4; H,8.85; N,5.70. $C_{12}H_{21}NO_4$ requires C,59.2; H,8.70; N,5.76%).

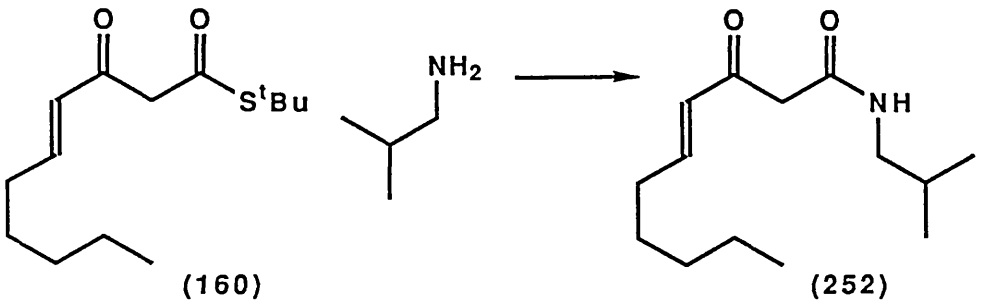
55. Preparation of (4E,6E)-N-Isobutyl-3-oxo-4,6-decadienamide (251)



(161) (251)

Silver (I) trifluoroacetate (0.351g, 1.59mmol) was added to a stirred solution of thioester (161) (0.3678g, 1.45mmol) and 2-methylpropylamine (0.201ml, 1.73mmol) in THF (6ml) at room temperature under argon. The reaction was stirred for 30 min and worked up as usual. Chromatography (35% ether-petrol) gave (4E,6E)-N-isobutyl-3-oxo-4,6-decadienamide (251) as a colourless oil (0.264g, 77%); δ_H (500MHz, $CDCl_3$) 0.92 (6H, d, J 6.7 Hz, CH_3CHCH_3), 0.94 (3H, t, J 6.0 Hz, 3 x H-10), 1.48 (2H, h, J 6.0 Hz, 2 x H-9), 1.79 (1H, s, J 6.7 Hz, CH_3CHCH_3), 2.18 (2H, q, J 6.0 Hz, 2 x H-8), 3.10 (2H, dd, J 6.7, 6.0 Hz, NCH_2CH), 3.53 (2H, s, 2 x H-2), 6.11 (1H, d, J 17 Hz, 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); ν_{max} (film) 3 310, 2 959, 1 637, 1 587, 1 412, and 1 117cm^{-1}; m/z 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%).

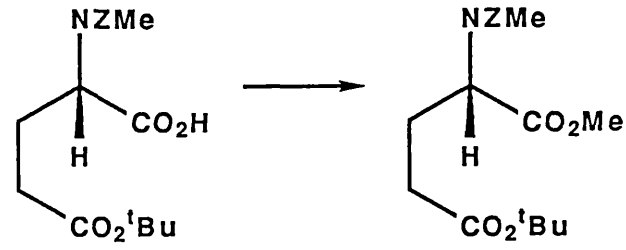
56. Preparation of (4E)-N-Isobutyl-3-oxo-4-decenamide (252)



(160) (252)

Silver(I) trifluoroacetate (0.62g, 2.81mmol) was added to a stirred solution of thioester (160) (0.65g, 2.54mmol) and 2-methylpropylamine (0.36ml, 3.10mmol) in THF (30ml) at room temperature under argon. The reaction was stirred for 3h and worked up as usual. Chromatography (35% ether-petrol) gave (4E)-N-isobutyl-3-oxo-4-decenamide (252) as a colourless oil (0.474g, 78%); δ_H (90MHz, $CDCl_3$) 1.44 (9H, m, 3 x H-10, CH_3CHCH_3), 1.85 (6H, m, 2 x H-7, H-8, and H-9), 2.30 (1H, m, CH_3CHCH_3), 2.72 (2H, m, 2 x H-6), 3.61 (2H, t, J 6.4 Hz, NCH_2CH), 4.05 (2H, s, 2 x H-2), 6.62 (1H, dt, J 17.4, 1.3 Hz, H-4), 7.51 (1H, dt, J 17.4, 6.7 Hz, H-5), and 7.65 (1H, br, s, NH); ν_{max} (film) 3 310, 2 929, 1 654, 1 551, and 1 118cm^{-1}; m/z 239 (M^+), 196, 184, 167, and 142. (Found: C,70.1; H,10.6; N,5.91. $C_{14}H_{25}NO_2$ requires C,70.3; H,10.5; N,5.85%).

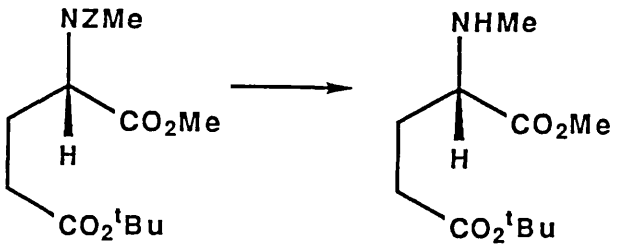
57. Preparation of (2S)-N-Benzyloxycarbonyl-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (190)



(189) (190)

DCC (0.37g, 1.79mmol) was added to a stirred solution of (189)[121] (0.571g, 1.63mmol), DMAP (20mg, 0.164mmol), and methanol (72μl, 1.78mmol) in CH_2Cl_2 (10ml) at room temperature under argon. The reaction was stirred for 10 min, filtered, and the filtrate washed with water (3 x 10ml), 5% HOAc (3 x 60ml), and water (1 x 10ml). The CH_2Cl_2 solution was dried ($MgSO_4$) and the volatile material was removed under reduced pressure. Chromatography (20% ether-petrol) gave (2S)-N-benzyloxycarbonyl-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (190) as a colourless, viscous oil (0.502 g, 85%); $[\alpha]_D^{25}$ 26.6^0 (c 1.9, $CHCl_3$); δ_H(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); ν_{max} (film) 2977, 1741, 1717, 1704, 1451, and 1154cm^{-1}; m/z 365 (M$^+$), 323, 309, 250, 206, and 91. (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%).

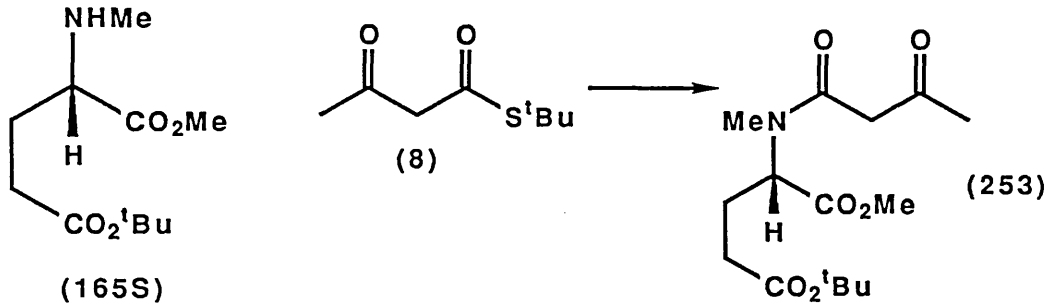
58. Preparation of (2S)-N-Methylglut amic acid α-methyl ester γ-^{t}butyl ester (165S)



(190) (165S)

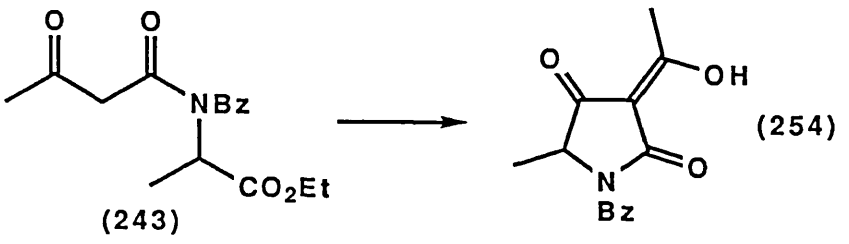
A stirred suspension of 10% palladium on carbon (30mg) and diester (190) (0.200g, 5.47mmol) in ethyl acetate (10ml) was hydrogenated at room temperature and pressure for 16h, filtered and the volatile material was removed under reduced pressure. Chromatography (40% ether-petrol) gave (2S)-N-methylglutamic acid α-methyl γ-^{t}butyl diester (165S) as a colourless oil (119mg, 94%); $[\alpha]_D^{25}$ -0.9^0 (c 5.2, $CHCl_3$); δ_H (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); ν_{max} (film) 3 340, 2 977, 1 732, and 1 154cm^{-1}; m/z 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%).

59. Preparation of (2S)-N-Acetoacetyl-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (253)



Silver(I) trifluoroacetate (0.110g, 0.498mmol) was added to a stirred solution of glutamate (165S) (0.105g, 0.452mmol) and ^{t}butyl 3-oxobutanthioate (8) (86.6mg, 0.497mmol) in THF (5ml) at room temperature under argon. The reaction was stirred for 2h and worked up as usual. Chromatography (60% ether-petrol) gave (2S)-N-acetoacetyl-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (253) as a colourless oil (91.4mg, 64%); $[\alpha]_D^{25}$ -29.2^0 (c 2.6, $CHCl_3$); δ_H(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$_2$Me); ν_{max} (film) 3 430, 2 978, 1 724, 1 647, and 1 154cm^{-1} m/z 315 (M$^+$), 259, 205, 158, and 116. (Found: 315.1688(M$^+$). $C_{15}H_{25}NO_6$ (M$^+$) requires 315.1682).

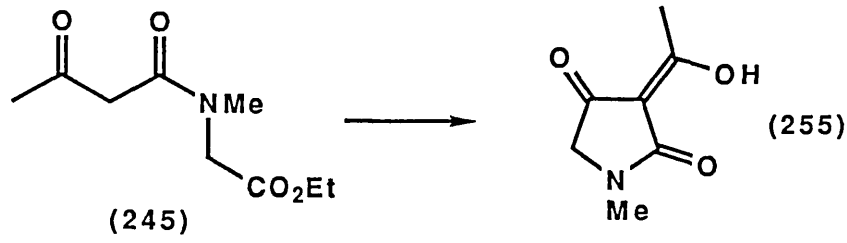
60. Preparation of (±)1-Benzyl-3-[(Z)-1-hydroxyethylidene]-5-methyl-2,4-pyrrolidinedione (254)



TBAF (0.73ml, 1 M solution in THF, 0.73mmol) was added to a stirred solution of (243) (0.170g, 0.584mmol) in THF (3ml) at room temperature under argon. The reaction was stirred for 5 min, the volatiles removed under reduced pressure, water (5ml) added, and the solution acidified to pH1 with 5% H_2SO_4. The aqueous suspension was extracted with ether (3 x 15ml), the ether layers combined, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was distilled (kugelrohr) to give (±)1-benzyl-3-[(Z)-1-hydroxyethylidene]-5-methyl-2,4-pyrrolidinedione (254)[24] as a pale yellow viscous oil (0.124g, 92%); δ_H (250MHz, $CDCl_3$) (85:15 tautomer ratio) 1.28 (2.55H, d, J 6.1 Hz, CH_3CH major tautomer), 1.38 (0.45H, d, J 6.1 Hz, 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 Hz, H-5 major tautomer), 3.75 (0.15H, q, J 6.1 Hz,

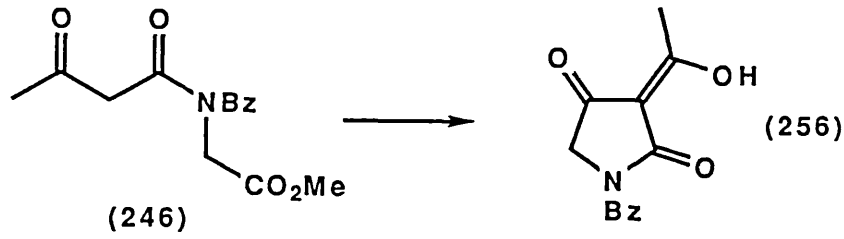
H-5 minor tautomer), 4.05 (0.15H, d, J 14.5 Hz, 1 x CH_2Ph minor tautomer), 4.10 (0.85H, d, J 14.5 Hz, 1 x CH_2Ph major tautomer), 5.10 (0.85H, d, J 14.5 Hz, 1 x CH_2Ph major tautomer), 5.16 (0.15H, d J 14.5 Hz, 1 x CH_2Ph minor tautomer), and 7.27 (5H, m, aromatics) (OH not detected); δ_H (90MHz, d^6 acetone) (single tautomer) 1.23 (3H, d, J 6.5 Hz, CH_3CH), 2.39 (3H, s, CH_3 3-acetyl), 3.70 (1H, q, J 6.5 Hz, H-5), 4.32 (1H, d, J 14.6 Hz, 1 x CH_2Ph), 4.99 (1H, d, J 14.6 Hz, 1 x CH_2Ph), and 7.32 (5H, s, aromatics) (OH not detected); δ_C (22.5MHz, 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 ($CH_3C(OH)=$), and 194.95 (C-4); ν_{max} (film) 3 400, 1 709, 1 629, 1 237, and 929cm^{-1}; m/z 245 (M^+), 106, and 91. (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%). (Found: 245.1057 (M^+). $C_{14}H_{15}NO_3$ (M^+) requires 245.1052).

61. Preparation of 3-[(Z)-1-Hydroxyethylidene]-1-methyl-2,4-pyrrolidinedione (255)



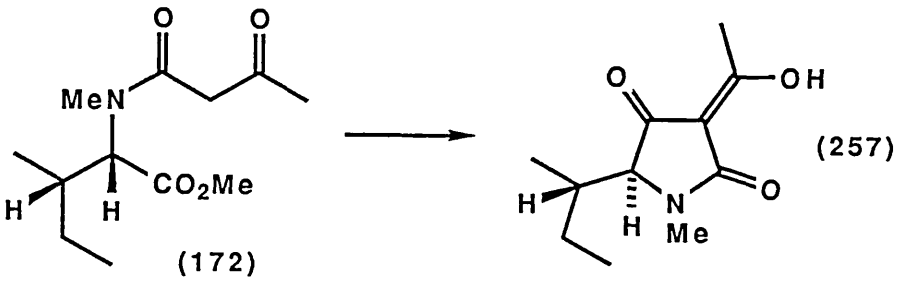
TBAF (1.6ml, 1M solution in THF, 1.6mmol) was added to a stirred solution of amide (245) (0.210g, 1.05mmol) in THF (5ml) at room temperature under argon. The reaction was stirred for 30 min, the solvent removed under reduced pressure, water added (10ml), acidified to pH 1 with 5% H_2SO_4 and extracted with ether (3 x 20ml). The combined ether layers were dried ($MgSO_4$), the solvent removed under reduced pressure, and the residue sublimed (0.01mmHg) giving 3-[(Z)-1-hydroxyethylidene]-1-methyl-2,4-pyrrolidinedione (255)[24] as a white amorphous solid (0.113, 70%); m.p. 50-51°C; δ_H (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); δ_H (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); ν_{max} ($CHCl_3$) 3 400, 2 962, 1 709, 1 637, and 1 251cm^{-1}; λ_{max} (EtOH) 233 (sh), 245, and 281nm (ε_{max} 7 500, 9 000, and 12 500 dm^3 mol^{-1} cm^{-1}); m/z 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%).

62. Preparation of 1-Benzyl-3-[(Z)-1-hydroxyethylidene]-2,4- pyrrolidinedione (256)



TBAF (1.90ml, 1 M solution in THF, 1.90mmol) was added to a stirred solution of amide (246) (0.2486g, 0.944mmol) in THF (5ml) at room temperature under argon. The reaction was stirred for 30 min and worked up as exp. 61. Recrystallisation gave 1-benzyl-3-[(Z)-1-hydroxyethylidene]-2,4-pyrrolidinedione (256)[24] (0.171g, 78%) as needles, m.p. 78°C (from petrol) (lit.[24] 74-76°C); δ_H (90MHz, $CDCl_3$) (4:1 ratio of tautomers) 2.48 (2.4H, s, $\underline{CH}_3$ 3-acetyl major tautomer), 2.59 (0.6H, s, $\underline{CH}_3$ 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, $NC\underline{H}_2Ph$), 7.32 (5H, m, aromatics), and 10.5 (1H, br s, OH); δ_C (22.5MHz, $CDCl_3$) (two tautomers) 19.39, 19.75 ($\underline{C}H_3$ 3-acetyl), 45.33 ($Ph\underline{C}H_2N$), 51.92, 54.97 (C-5), 102.21 (C-3), 128.08, 128.88, 135.22, 136.14 (aryl carbons), 166.59, 172.94 (C-2), 183.68, 187.40 ($CH_3\underline{C}(OH)=$), and 191.31, 197.54 (C-4); ν_{max} ($CHCl_3$) 2 919, 2 800 (v.br.), 1 712, 1 617, 1 496, and 1 232cm^{-1}; m/z 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%).

63. Preparation of (5S)-3-[(Z)-1-Hydroxyethylidene]-1-methyl-5-[(S)-1-methylpropyl]-2,4-pyrrolidinedione (257)



TBAF (5.7ml, 1 M solution in THF, 5.7mmol) was added to a stirred solution of amidoester (172) (0.690g, 2.84mmol) in THF (7ml) at room temperature under argon. The reaction was stirred for 45 min and worked up as exp. 61. The residue was distilled to give (5S)-3-[(Z)-1-hydroxyethylidene]-1-methyl-5-[(S)-1-methylpropyl]-2,4-pyrrolidinedione (257)[23] as a pale yellow viscous oil (b.p. 150°C, 0.01mmHg, 0.508g, 85%); $[\alpha]_D^{25}$ -36° (c 3.7, $CHCl_3$); δ_H (90MHz, $CDCl_3$) (4:1 tautomer ratio) 0.83 (3H, t, J 7.2 Hz, $\underline{CH_3}CH_2CHCH_3$), 0.97 (3H, d, J 6.4 Hz, $CH_3CH_2CH\underline{CH_3}$), 1.52 (2H, m, $CH_3\underline{CH_2}CHCH_3$), 1.90 (1H, m, $CH_3CH_2\underline{CH}CH_3$), 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 Hz, H-5 major tautomer), 3.75 (0.2H, d, J 3.1 Hz, H-5 minor tautomer) (OH not detected); δ_C (125.8MHz, d^6 acetone) (9:1 tautomer ratio, decoupled spectrum) 11.95 ($\underline{C}H_3CH_2CHCH_3$), 13.38 ($CH_3CH_2CH\underline{C}H_3$), 18.80 ($\underline{C}H_3$ 3-acetyl) 24.40, 24.64 ($CH_3\underline{C}H_2CHCH_3$), 26.37, 26.85 (N-$\underline{C}H_3$), 34.49, 34.78 ($CH_3CH_2\underline{C}HCH_3$), 69.37 (C-5), 102.27 (C-3), 172.45 (C-2), 181.70 ($CH_3\underline{C}(OH)=$), and 194.05 (C-4); ν_{max} (film) 3 000 (v.br.), 2 964, 1 708, 1 637, 1 457, and 1 168cm^{-1}; m/z 211 (M^+) and 155. (Found: 211.1209 (M^+). $C_{11}H_{19}NO_3$ (M^+) requires 211.1208).

Dieckmann Racemisation Studies

(a) NaOMe, MeOH, PhH (Lacey conditions)[22] Cyclisation

Sodium methoxide in methanol (1.05ml, 3.70M, 3.89mmol) was added to a stirred solution of the amide (172) (0.79g, 3.25mmol) in benzene (1.6ml) at room temperature under argon. The mixture was then heated under reflux for 3h and allowed to stand for 16h. Water was added (10ml), the solution carefully acidified with 4N H_2SO_4, and extracted with ether (3 x 20ml). The combined ether layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Distillation of the residue gave (257) (1:1 diastereomer ratio) as a pale yellow viscous oil (b.p. 150°C/0.01mmHg, 0.506g, 74%); $[\alpha]_D^{25}$ + 15° (c 3.9, $CHCl_3$).

(b) NaOMe, MeOH, 5 min, RT

Sodium methoxide in methanol (0.85ml, 3.70M, 3.15mmol) was added to a stirred solution of amide (172) (0.69g, 2.84mmol) in methanol (5ml) at room temperature under argon. The solution was stirred for 5 min, water added (15ml), the aqueous solution acidified with 4N H_2SO_4, and extracted with ether (3 x 20ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Distillation of the residue gave (257) as a pale yellow viscous oil (b.p. 150^0C, 0.01mmHg, 0.469g, 78%); $[\alpha]_D^{25}$ -36^0 (c 3.6, $CHCl_3$).

(c) NaOMe, MeOH, 24h, RT

The reaction was carried out as in 63b except the reaction was stirred for 24h after the sodium methoxide addition. The product (257) was obtained as a mixture of diastereomers in 75% yield after distillation; $[\alpha]_D^{25}$ -31^0 (c 3.6, $CHCl_3$).

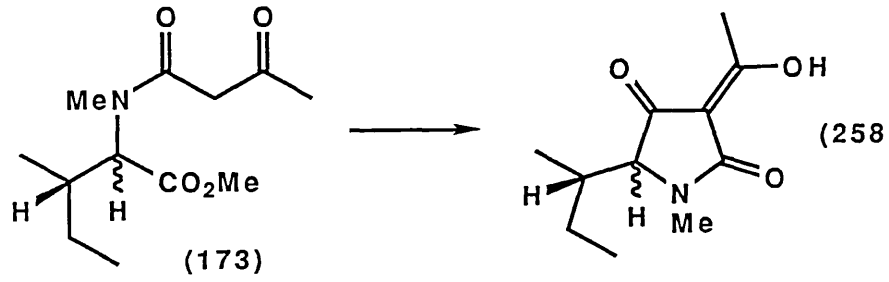
(d) KO^tBu, ^tBuOH, 3h reflux (Kappler conditions)[124]

A mixture of KO^tBu (0.222g, 1.98mmol) and amide (172) (0.48, 1.97mmol) in ^tBuOH (8ml) under argon was heated under reflux for 3h, cooled, acidified with 6N HCl, water added (10ml), and the solution extracted with ether (3 x 15ml). The combined ether layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Distillation gave the product (257) as a mixture of diastereomers (b.p. 150^0C/0.01mmHg, 0.368g, 88%) $[\alpha]_D^{25}$ -25^0 (c 3.9, $CHCl_3$).

(e) KO^tBu, ^tBuOH, 5 min, RT

KO^tBu (0.295g, 2.63mmol) was added to a stirred solution of amide (172) (0.64g, 2.63mmol) in ^tBuOH (10ml) under argon at room temperature. The reaction was stirred for 5 min and worked up as in (d). Distillation gave the product (257) as a single enantiomer (b.p. 150^0C/ 0.01mmHg, 0.501g, 90%); $[\alpha]_D^{25}$ -36^0 (c 3.8, $CHCl_3$).

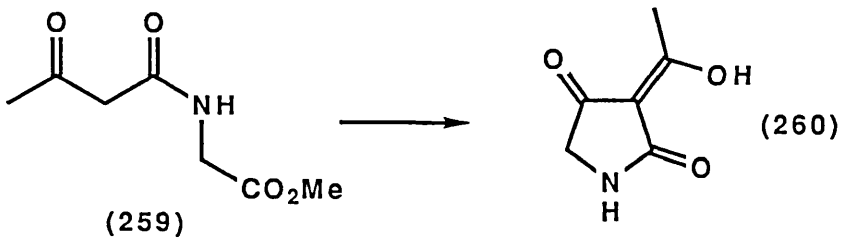
64. Preparation of (5RS)-3-[(Z)-1-Hydroxyethylidene]-1-methyl-5-[(S)-1-methylpropyl]-2,4-pyrrolidinedione (258)



TBAF (2.2ml, 1 M solution in THF, 2.20mmol) was added to a stirred solution of the amide (173) (0.350g, 1.44mmol) in THF (8ml) under argon at room temperature. The mixture was stirred for 15 min and worked up as in experiment 61. Distillation of the residue gave (5RS)-3-[(Z)-1-hydroxyethylidene]-1-methyl-5-[(S)-1-methylpropyl]-2,4-pyrrolidinedione (258) (b.p. 150°C, 0.01mmHg, 0.230g, 76%); $[\alpha]_D^{25}$ 15° (c 3.7, $CHCl_3$); δ_H (90MHz, $CDCl_3$) (1:1 diastereomer mixture, 4:1 tautomer ratio) 0.85 (6H, m, $C\underline{H}_3CH_2CHC\underline{H}_3$) 1.48 (2H, m, $CH_3C\underline{H}_2CHCH_3$), 1.89 (1H, m, $CH_3CH_2C\underline{H}CH_3$), 2.34 (2.4H, s, N-Me major tautomer), 2.42 (0.6H, s, N-Me minor tautomer), 2.86 (0.6H, s, $C\underline{H}_3$ 3-acetyl minor tautomer), 2.92

(2.4H, s, $\underline{CH}_3$ 3-acetyl major tautomer), 3.55 (0.8H, d, J 2.6 Hz, H-5 major tautomer), 3.72 (0.2H, d, J 3.1 Hz, H-5 minor tautomer) (OH not detected); δ_C (125.8MHz, d^6 acetone) (19:1 tautomer ratio, decoupled spectrum) 11.97 ($\underline{CH}_3CH_2CHCH_3$) 13.40, 13.85 ($CH_3CH_2CH\underline{C}H_3$ diastereomers), 18.95 ($\underline{CH}_3$ 3-acetyl), 24.34, 24.41, 24.50, 24.64 ($CH_3\underline{C}H_2CHCH_3$), 26.40, 26.87, 27.15 ($N\text{-}CH_3$), 34.50, 34.78, 35.33 ($CH_3CH_2\underline{C}HCH_3$), 69.26 (C-5), 102.39 (C-3), 172.26 (C-2), 181.87 ($CH_3\underline{C}(OH)=$), and 194.21 (C-4); ν_{max} (film) 3 060 (v.br.), 2 964, 1 708, 1 637, 1 457, and 1 168cm^{-1}.

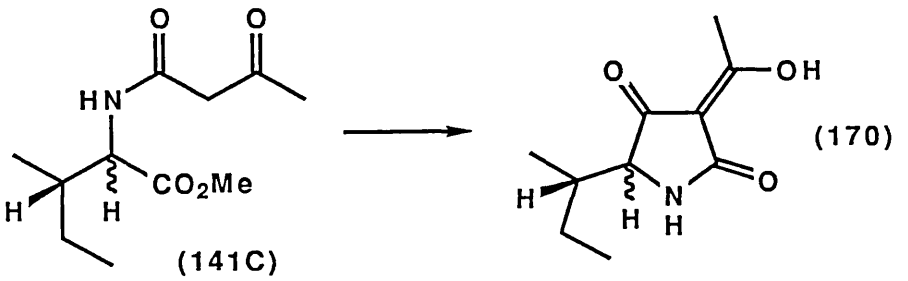
65. Preparation of 3-[(Z)-1-Hydroxyethylidene]-2,4-pyrrolidinedione (260)



A solution of amidoester (259) (0.52g, 3.00mmol) in TBAF/THF solution (30ml, 1 M solution, 30.0mmol) was heated under reflux for 24h, cooled and the solvent was removed under reduced pressure. Water (15ml) was added to the residue and was acidified to pH 1 with 4N aq. H_2SO_4. The aqueous suspension was extracted with petrol (5 x 50ml). The combined petrol layers were dried ($MgSO_4$) and the solvent removed under reduced pressure.

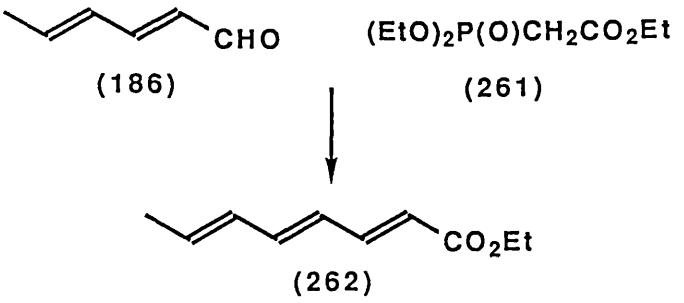
Recrystallisation of the residue from ethyl acetate gave 3-[(Z)-1-hydroxyethylidene]-2,4-pyrrolidinedione (260)[22] as colourless micro-needles (m.p. 154-155^{0}C, 0.148g, 35%) (lit.[22] 155^{0}C); δ_H (90MHz, $CDCl_3$) (3:1 tautomer ratio) 2.46 (2.25H, s, Me 3-acetyl major tautomer), 2.51 (0.75H, s, 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); δ_H (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).

66. Preparation of (5RS)-3-[(Z)-1-Hydroxyethylidene]-5-[(S)-1-methylpropyl]-2,4-pyrrolidinedione (170)



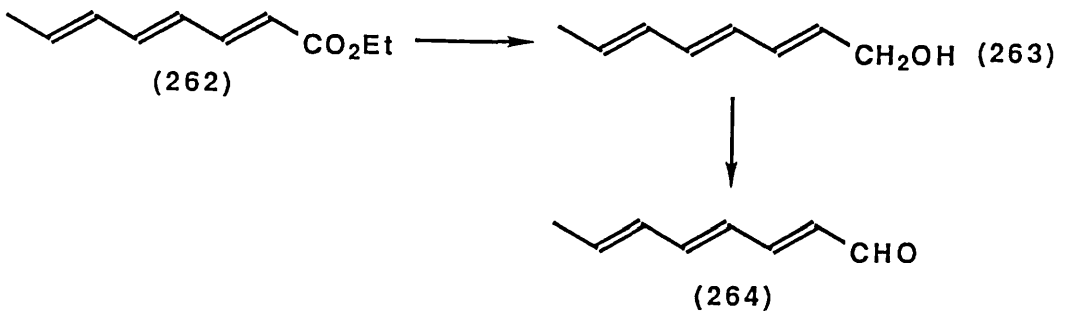
A solution of amidoester (141C) (1.15g, 5.02mmol) in TBAF/THF solution (50ml, 1 M solution, 50.0mmol) was heated under reflux for 24h, cooled, and the solvent removed under reduced pressure. Water (100ml) was added and the solution acidified to pH 1 with 4N aq. H_2SO_4. The aqueous suspension was extracted with petrol (3 x 250ml), the combined extracts dried ($MgSO_4$), and the solvent removed under reduced pressure. Distillation of the residue gave (5RS)-3-[(Z)-1- hydroxyethylidene]-5-[(S)-1-methylpropyl]-2,4-pyrrolidinedione (170)[23] (b.p. 200°C, 0.03mmHg) as a pale yellow viscous oil (0.543g, 55%); $[\alpha]_{246}^{25}$ 5.1° (c 3.2, $CHCl_3$); δ_H (90MHz, $CDCl_3$) (7:3 tautomer ratio, approximately 1:1 diastereomer ratio) 0.90 (6H, m, $C\underline{H}_3CH_2CHC\underline{H}_3$), 1.30 (2H, m, $CH_3C\underline{H}_2CHCH_3$), 1.96 (1H, m, $CH_3CH_2C\underline{H}CH_3$), 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, N-H) (OH not detected); ν_{max} (film) 3 300, 2 965, 1 707, 1 653, and 1 220cm^{-1}; λ_{max} (EtOH) 243 and 277nm (ε_{max} 8 100 and 14 300dm^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%).

67. Preparation of Ethyl (2E,4E,6E)-2,4,6-Octatrienoate (262)



Triethyl phosphonoacetate (261) (25.65g, 0.114mol) was added dropwise to a stirred suspension of sodium hydride (4.58g, 60% oil dispersion, 0.115mol) in THF (200ml) cooled to 0^0C under argon. The mixture was allowed to stir until clear (1h) and then the aldehyde (186) (10g, 0.104mol) was added. The reaction was allowed to warm to room temperature and was stirred for 16h. The reaction mixture was poured into sat. aq. NH_4Cl (500ml) and extracted with ether (3 x 500ml). The combined ether extracts were washed with water (2 x 100ml), brine (1 x 100ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (2% ether-petrol) gave ethyl (2E, 4E,6E)-2,4,6-octatrienoate (262)[147] as a colourless, waxy solid (11.28g, 65%, m.p. 30^0C); δ_H(90MHz, $CDCl_3$) 1.28 (3H, t, J 7.1 Hz, Me of ethyl ester) 1.82 (3H, d, J 5.7 Hz, 3 x H-8), 4.20 (2H, q, J 7.1 Hz, CH_2 of ethyl ester), 5.70 to 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 Hz, H-3); ν_{max} (film) 2 984, 1 696, 1 622, 1 596, 1 128, and 1 009cm^{-1}; m/z 166 (M^+), 137, 121, and 93.

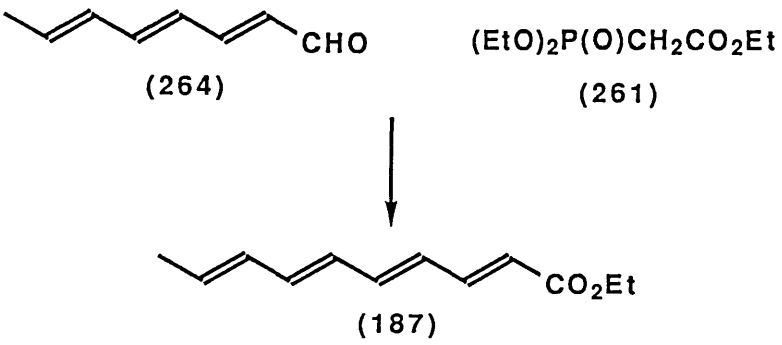
68. Preparation of (2E,4E,6E)-2,4,6-Octatrienal (264)



DIBAL (27.5ml, 1.5M solution in toluene, 41.3mmol) was added dropwise to a stirred solution of triene ester (262) (2.28g, 13.7mmol) in toluene (100ml) at -78^0C under argon. The solution was stirred at -78^0C for 15min, water (15ml) was carefully added and the mixture allowed to warm to room temperature. The two-phase mixture was poured into a stirred suspension of $NaHCO_3$ (50g) and $MgSO_4$ (50g) in ethyl acetate (500ml). The suspension was filtered under suction and the solvent removed from the filtrate under reduced pressure. The crude allylic alcohol (263)[148] was not purified but oxidised directly with MnO_2 (29.8g, 0.343mol) in CH_2Cl_2 (500ml). The suspension was stirred for 1h, and filtered under suction. The filter cake was thoroughly washed with ethyl acetate (15 x 50ml) and the solvent was removed under reduced pressure. The aldehyde (264)[149] was obtained as a colourless oil (1.27g, 76% overall yield from (262)); δ_H(90MHz, $CDCl_3$)

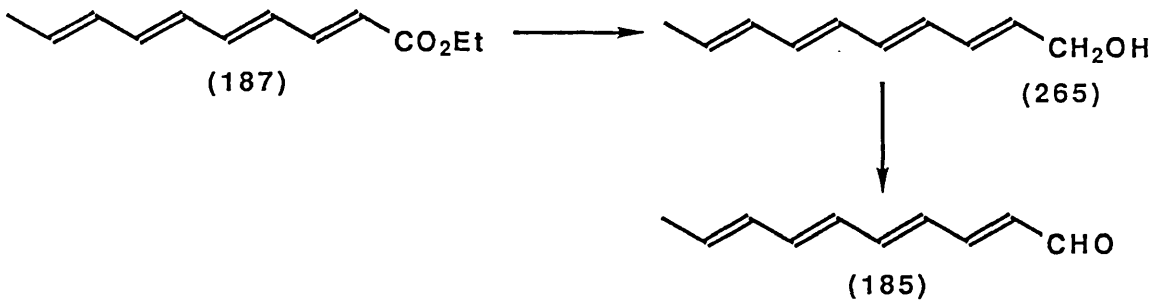
2.11 (3H, d, J 5.3 Hz, 3 x H-8), 6.10 to 7.20 (5H, m, H-2, H-4, H-5, H-6, and H-7), 7.40 (1H, dd, J 15.1, 10.5 Hz, H-3), and 9.80 (1H, d, J 7.9 Hz, H-1); ν_{max} (film) 3 021, 2 816, 2 746, 1 676, 1 610, 1 162, 1 117, 1 014, and 993cm^{-1}.

69. Preparation of Ethyl (2E,4E,6E,8E)-2,4,6,8-Decatetraenoate (187)



Triethyl phosphonoacetate (261) (0.97g, 4.33mmol) was added dropwise to a stirred suspension of sodium hydride (0.173g, 60% oil dispersion, 4.33mmol) in THF (15ml) at 0^0C under argon. The reaction mixture was stirred until clear (1h) and then the aldehyde (264) (0.480g, 3.93mmol) was added. The resulting clear solution was allowed to warm to room temperature, stirred for 16h, poured into sat. aq. NH_4Cl (50ml) and the resulting two phase mixture extracted with ether (3 x 100ml). The combined ether extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (2% ether-petrol) gave ethyl (2E,4E,6E,8E)-2,4,6,8-decatetraenoate (187)[147] as a yellow, waxy solid (0.598g, 79%); δ_H (500MHz, $CDCl_3$) 1.29 (3H, t, J 7.2 Hz, Me of ethyl ester), 1.81 (3H, d, J 6.8 Hz, 3 x H-10), 4.20 (2H, q, J 7.2 Hz, CH_2 of ethyl ester), 5.84 (1H, d, J 15.3 Hz, H-2), 5.85 (1H, dq, J 15.0, 6.8 Hz, H-9), 6.14 (1H, dd, J 15.0, 10.8 Hz, H-8), 6.18 (1H, dd, J 14.9, 11.0 Hz, H-6), 6.28 (1H, dd, J 14.8, 11.5 Hz, H-4), 6.37 (1H, dd, J 14.9, 10.8 Hz, H-7), 6.56 (1H, dd, J 14.8, 11.0 Hz, H-5), and 7.31 (1H, dd, J 15.3, 11.5 Hz, H-3); m/z 192 (M^+), 163, 147, 119, and 91.

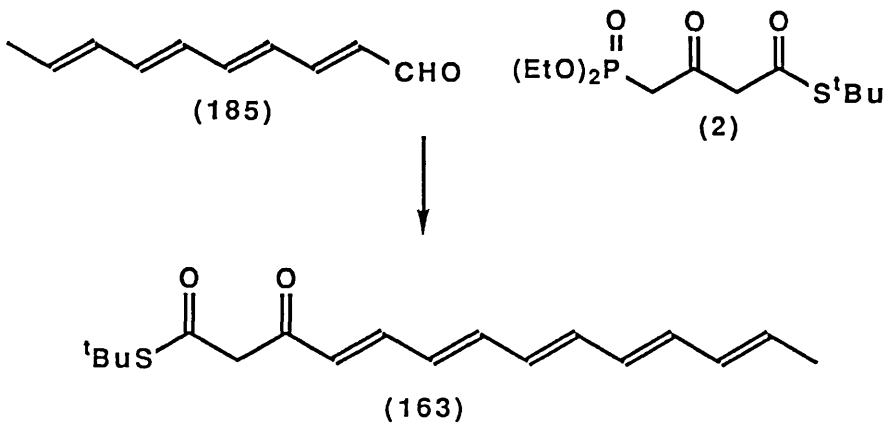
70. Preparation of (2E,4E,6E,8E)-2,4,6,8-Decatetraenal (185)



DIBAL (4.72ml, 1.5 M solution in toluene, 7.08mmol) was added dropwise to a stirred solution of the tetraene ester (187) (0.453g, 2.36mmol) in toluene (40ml) at -78^{0}C under argon. The solution was stirred at -78^{0}C for 75min, water (3ml) added and the reaction was allowed to warm slowly to room temperature. The heterogeneous solution was poured into ethyl acetate (200ml) with $NaHCO_3$ (20g) and $MgSO_4$ (20g) suspended in it. The suspension was filtered and the solvent removed under reduced pressure giving (2E,4E,6E,8E)-2,4,6,8-decatetraen-1-ol (265)[148]; m/z 150 (M^+). The allylic alcohol was not purified but oxidised directly with barium manganate (4.83g, 18.9mmol) in CH_2Cl_2 (50ml). The suspension was stirred for 3h at room temperature, filtered, the filtered solid was washed thoroughly with ethyl acetate

(15 x 10ml) and the solvent removed under reduced pressure. Chromtography (2% ether-petrol) gave (2E,4E,6E,8E)-2,4,6-8-decatetraenal (185)[126] as a pale yellow, waxy solid (0.217g, 62% overall yield from ester); δ_H (90MHz, $CDCl_3$) 2.09 (3H, d, J 5.9 Hz, 3 x H-10), 6.0 to 7.25 (7H, m, H-2, H-4 to H-9 inclusive), 7.40 (1H, dd, J 15.1, 10.5 Hz, H-3), and 9.81 (1H, d, J 7.9 Hz, H-1); ν_{max} (film) 1 668, 1 588, and 1 017cm^{-1}.

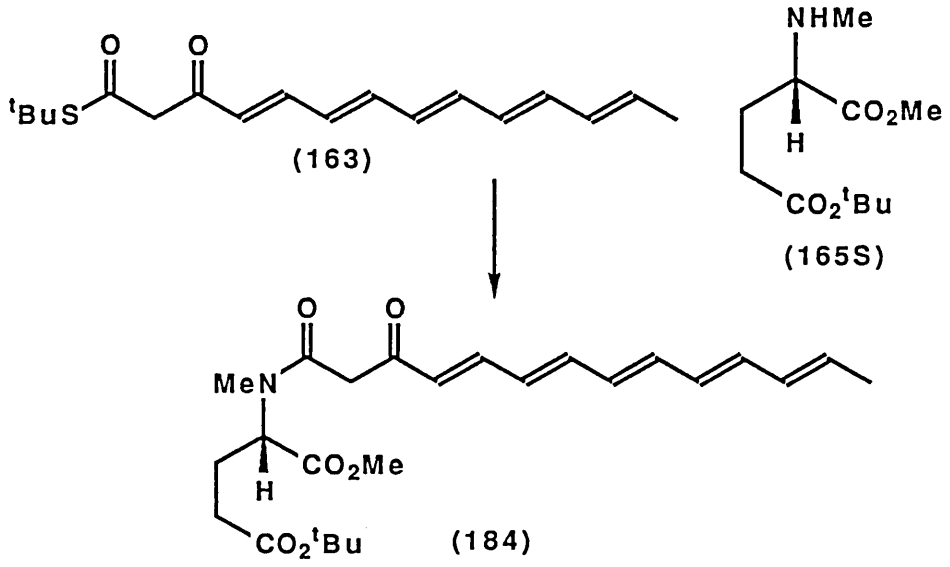
71. Preparation of ^{t}Butyl (4E,6E,8E,10E,12E)-3-Oxo-4,6,8,10,12-tetradecapentaenthioate (163)



Thioester phosphonate (2) (0.733g, 2.36mmol) was added to a stirred suspension of sodium hydride (0.190g, 60% oil dispersion, 4.75mmol) in THF (75ml) at 0^{0}C under argon. The suspension was stirred for 30min and then the aldehyde (185) (0.178g, 1.20mmol) in THF (5ml) was added. The reaction was allowed to warm to room temperature and stirred for 16h and poured into sat. aq. NH_4Cl (250ml) and ether (150ml). The layers were separated and the aqueous layer re-extracted with ether (3 x 200ml). The combined ether extracts were dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (1% to 2% ether-petrol) gave

^{t}butyl (4E,6E,8E,10E,12E)-3-oxo-4,6,8,10,12-tetradecapentaenthioate (163) as an orange, waxy solid (0.222g, 61%); δ_H (90MHz, $CDCl_3$) (85% enol form) 1.50 (1.35H, s, ^{t}Bu keto), 1.55 (7.65H, s, ^{t}Bu enol), 1.80 (3H, d, J 5.9 Hz, 3 x H-14), 3.70 (0.3H, s, 2 x H-2 keto), 5.40 (0.85H, s, H-2 enol), 5.60 to 6.50 (9H, m, H-4, H-6, to H-13 inclusively), 7.17 (1H, dd, J 14.8, 10.8 Hz, H-5), and 12.56 (0.85H, d, J 1.3 Hz, enol OH); m/z 304 (M^+), 248, 111, 90, and 57. (Found: 304.1496 (M^+). $C_{18}H_{24}O_2S$ requires 304.1497).

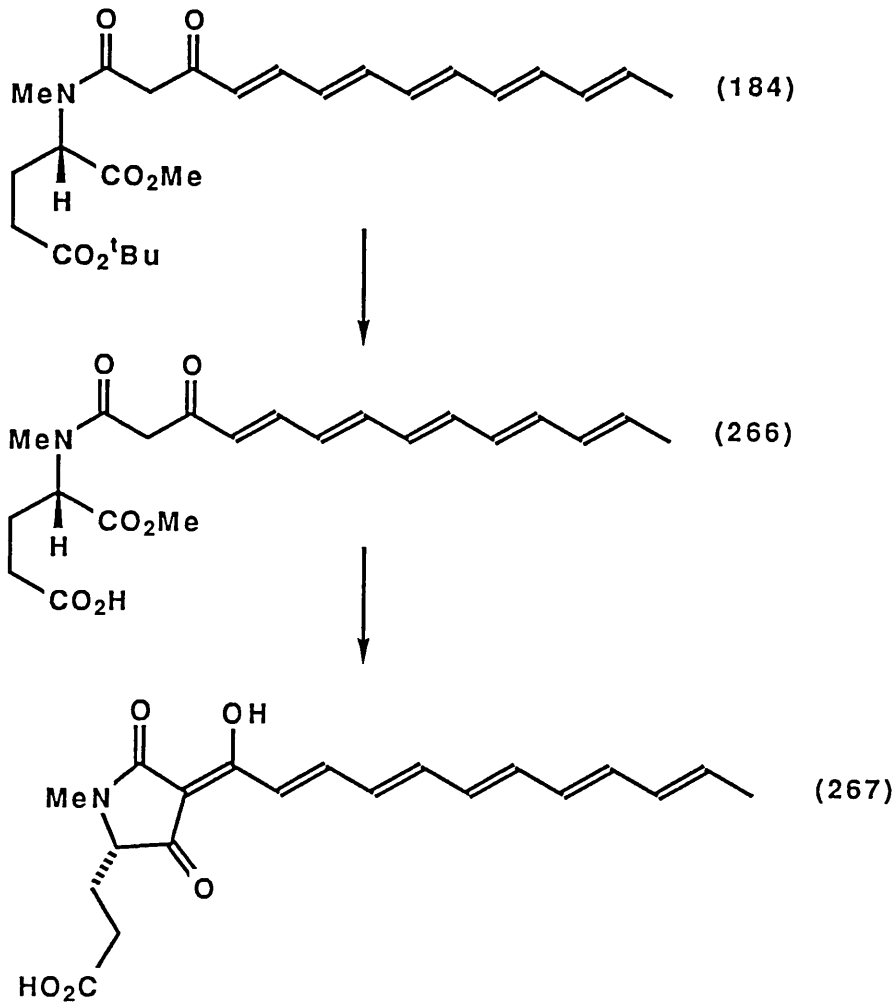
72. Preparation of (2S)-N-Methyl-N-[(4E,6E,8E,10E,12E)3-oxo-4,6,8,10,12-tetradecapentaenoyl]glutamic acid α-methyl ester γ-^{t}butyl ester (184)



Silver(I) trifluoroacetate (147mg, 0.666mmol) was added to a stirred suspension of thioester (163) (0.125g, 0.412mmol), aminoester (165S) (279mg, 1.21mmol), and Na_2HPO_4 (292mg, 2.06mmol) in THF (10ml) at room temperature under argon. The reaction was stirred for 20min and the solvent removed under reduced pressure. The residue was suspended in CH_2Cl_2 (20ml) and silica gel (3.5g) added. The solvent was

removed under reduced pressure, and all residual solvent removed on a high vacuum pump. Chromatography (40% ether-petrol) gave (2S)-N-methyl-N-[(4E,6E,8E,10E,12E)-3-oxo-4,6,8,10,12-tetradecapentaenoyl]glutamic acid α-methyl ester γ-^{t}butyl ester (184) as an orange solid (m.p. 168^{0}C (dec.), 0.128g, 70%); $[\alpha]_{D}^{25}$ -66.4^{0} (c 1.6, $CHCl_3$); δ_H (500MHz, $CDCl_3$) (3:1 rotamer mixture, all enol tantomer) 1.43 (9H, s, ^{t}Bu ester), 1.80 (3H, d, J 6.0 Hz, 3 x H-14), 1.98, 2.28 (4H, 2m, $CH_2CH_2CO_2$ ^{t}Bu), 2.86 (0.75H, s, N-Me minor rotamer), 2.93 (2.25H, s, N-Me major rotamer), 3.72 (2.25H, s, CO_2Me major rotamer), 3.75 (0.75H, s, CO_2Me minor rotamer), 5.21 (2H, m, including 5.22 1H, s, $CHCO_2Me$ H-2), 5.79 (1H, dq, J 14.5, 6.0 Hz, H-13), 5.92 (1H, d, J 16.5 Hz, H-4), 6.1 to 6.4 (6H, m), 6.51 (1H, dd, H-6 to H-12 inclusively), 7.11 (1H, dd, J 15.0, 11.5 Hz, H-5) (OH not detected); m/z 445 (M^+), 389, 215, 158, and 116. (Found: 445.2462 (M^+). $C_{25}H_{35}NO_6$ (M^+) requires 445.2464).

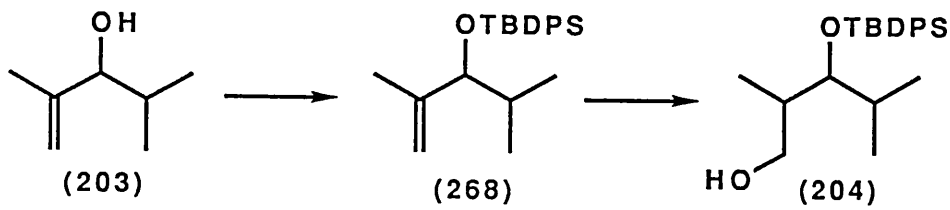
73. Preparation of 3S{3(Z)-[(2E,4E,6E,8E,10E)-1-Hydroxy-2,4,6,8,10-dodecylidenyl]-2,4-pyrrolidinedione}propanoic acid (267)



Formic acid (1ml, 98%) was added to the diester (184) (0.114g, 0.257mmol) and the resulting solution was stirred at room temperature for 10 min and the solvent removed under reduced pressure. The acid was not purified but taken directly onto the cyclisation stage. The

resulting orange solid was dissolved in methanol (1ml) under argon and the stirred solution treated with sodium methoxide in methanol (78μl, 3.70 M, 0.289mmol). The reaction was stirred for 5 min, the solvent removed under reduced pressure, water (5ml) added and the solution acidified with 4N aq. H_2SO_4 to pH1. The resulting suspension was extracted with ethyl acetate (3 x 15ml), the combined organic extracts dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatrography (10% acetone-chloroform) on silica pre-treated with oxalic acid (vide infra) gave unnatural Fuligorubin A (267) heavily contaminated with oxalic acid. Some of the oxalic acid was removed by repeatedly (x 20) washing the red amorphous solid with water (5ml), centrifuging, and removing the aqueous layer; m.p. 154°C (lit.[8] 150°C); δ_H (500MHz, $CDCl_3$) (5:1 tautomer ratio) 1.83 (3H, d, J 7.0 Hz, 3 x H-11), 2.06 (2H, m, $CHCH_2CH_2$), 2.37 (2H, m, $CHCH_2CH_2$), 2.95 (0.5H, s, N-Me, minor tautomer), 3.0 (2.50H, s, N-Me, major tautomer), 3.76 (1H, m, $NCHCH_2$), 5.86 (1H, dq, J 16.0, 7.0 Hz, H-11), 6.1 to 6.9 (7H, m, H-4 to H-10 inclusively), 7.16 (1H, d, J 16.0 Hz, H-2), and 7.53 (1H, dd, J 16.0, 7.0 Hz, H-3); (OH and CO_2H not detected); ν_{max} and $[\alpha]_D$too heavily contaminated with oxalic acid; m/z 357 (M^+), 339, 212, 194, 172, and 145; UV (EtOH): λ_{max} 256, 280 sh, and 446 nm; after the addition of one drop of NaOH λ_{max} = 254 and 384 nm.

74. Preparation of 3-^{t}Butyldiphenylsilyloxy-2,4-dimethylpentan-1-ol (204)



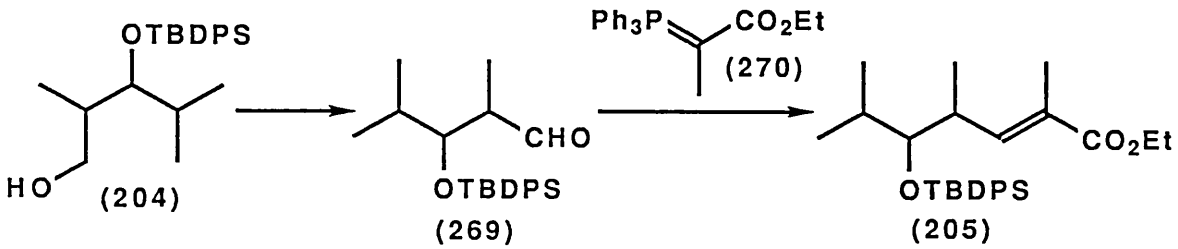
(203) (268) (204)

TBDPSCl (12.03g, 43.8mmol) in DMF (10ml) was added to a stirred solution of allylic alcohol (203)[129] (4.00g, 35.0mmol), imidazole (4.77g, 70.1mmol), and DMAP (100mg) in DMF (15ml) at 0^{0}C under argon. The mixture was allowed to warm to room temperature and was heated at 60^{0}C for 2 days. The reaction was cooled, poured into water (500ml) and was extracted with ether (3 x 300ml). The combined ether extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure.

The residue was dissolved in CH_2Cl_2 (100ml) and filtered through a pad of silica under suction. The solvent was removed under reduced pressure

giving 3-^{t}butyldiphenylsilyloxy-2,4-dimethylpent-1-ene (268) (12.20g) as a viscous oil; δ_H (90MHz, $CDCl_3$) 0.70, 0.85 (6H, 2d, J 6.4 Hz, 3 x H-5, 4-methyl, diastereotopic methyl groups), 1.10 (9H, s, ^{t}Bu), 1.73 (4H, m, including 1.69, 3H, s, allylic methyl, H-4), 3.77 (1H, d, J 7.2 Hz, H-3), 4.68 (2H, br d, 2 x H-1), and 7.4, 7.7 (10H, 2 m, 2 x Ph); ν_{max} (film) 3 071, 2 959, 2 850, 1 590, 1 470, 1 427, 1 111, and 1 062cm^{-1}. Borane-dimethyl sulphide complex (10.4ml, 10 M solution in THF, 0.104mol) was added to a stirred solution of the protected olefin (268) (12.20g, 34.6mmol) in THF (100ml) at 0^{0}C under argon. The reaction was allowed to warm to room temperature and stirred for 16h, recooled to 0^{0}C, water (10ml) carefully added, followed by 3N aq. NaOH (100ml), and 30% aq. H_2O_2 (35ml). The layers were separated, the aqueous re-extracted with ether (3 x 200ml), the combined organic layers were washed with water (1 x 100ml), brine (1 x 100ml), dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (15% ether-petrol) gave 2,4-dimethyl-3-^{t}butyldiphenylsilyloxypentan-1-ol (204) as a colourless, viscous oil (8.88g, 68%, b.p. 200^{0}C/0.02mmHg); δ_H (90MHz, $CDCl_3$) 0.86 (9H, m, 3 x H-5, 2 and 4 methyls), 1.10 (9H, s, ^{t}Bu), 1.85 (2H, br m, H-2, H-4), 3.5 (3H, m, 2 x H-1, H-3), and 7.40, 7.70 (10H, 2 m, 2 x Ph) (OH not detected); ν_{max} (film) 3 370, 3 071, 2 960, 2 857, 1 471, 1 427, and 1 111cm^{-1}; m/z 327 (M$^+$-isopropyl), 313 (M$^+$-^{t}butyl) and 199. (Found: C,74.4; H,9.22. $C_{23}H_{34}O_2Si$ requires C,74.5; H,9.24%).

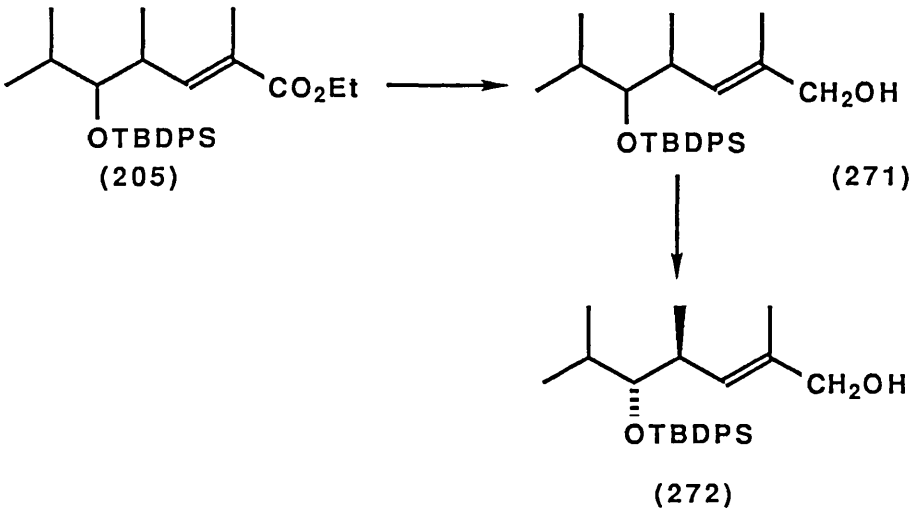
75. Preparation of Ethyl (2E)-2,4,6-Trimethyl-5-^{t}butyldiphenylsilyloxy-2-heptenoate (205)



PCC (17.0g, 79.0mmol) was added to a vigorously stirred solution of the alcohol (204) (7.49g, 20.2mmol) in CH_2Cl_2 (1200ml) at room temperature under argon. The reaction was stirred for 16h, filtered through a pad of silica under suction, the pad was washed with CH_2Cl_2 (3 x 100ml), the combined CH_2Cl_2 solutions were evaporated under reduced pressure to give 3-^{t}butyldiphenylsilyloxy -2,4-dimethylpentanal (269) (6.18g, 83%) as a colourless oil; ν_{max} (film) 2 961, 2 858, 1 725, 1 470,

1 427, and 1 111cm^{-1}. The aldehyde (269) (61.8g, 16.8mmol) and the phosphorane (270) (12.2g, 33.5mmol) were dissolved in $CHCl_3$ (250ml) and the stirred mixture was heated under reflux for 48h, cooled, and the solvent removed under reduced pressure. The residual solvent was thoroughly removed on a high vacuum pump. The crude material was dissolved in CH_2Cl_2 (100ml) and preabsorbed onto silica (40g). Chromatography (1% ether-petrol) gave ethyl (2E)-5-^{t}butyldiphenylsilyloxy-2,4,6-trimethyl-2-heptenoate (205) as a viscous, colourless oil (b.p. 225^{0}C/0.01mmHg, 6.13g, 81%); δ_H(90MHz, $CDCl_3$) (2:1 diastereoisomer mixture) 0.80 (9H, m, 3 x H-7, 4, 6 methyls), 1.05 (9H, s, ^{t}Bu), 1.25 (1H, t, J 7.2 Hz, CH_3CH_2O, minor diastereoisomer), 1.30 (2H, t, J 7.2 Hz, CH_3CH_2O, major diastereoisomer), 1.70 (1H, m, H-6), 1.75 (3H, 2s, 2-methyl), 2.62 (1H, m, H-4), 3.45 (1H, m, H-5), 4.25 (2H, q, J 7.2 Hz, $CH_3CH_2O_2C$), 6.58 (0.33H, dq, J 10.3 Hz, H-3, minor diastereoisomer), 7.04 (0.67H, dq, J 10.3 Hz, H-3, major diastereoisomer), and 7.4, 7.7 (10H, 2 m, 2 x Ph); ν_{max} (film) 2961, 1709, 1589, 1462, 1236, and 1110cm^{-1}; m/z 395 (M^+ - ^{t}butyl), 311, 239, and 199. (Found: C,74.4; H,9.36. $C_{28}H_{40}O_3Si$ requires C,74.3; H,8.91%). (Found: 395.2042 (M^+ - ^{t}butyl). $C_{24}H_{31}O_3Si$ (M^+ - ^{t}butyl) requires 395.2042).

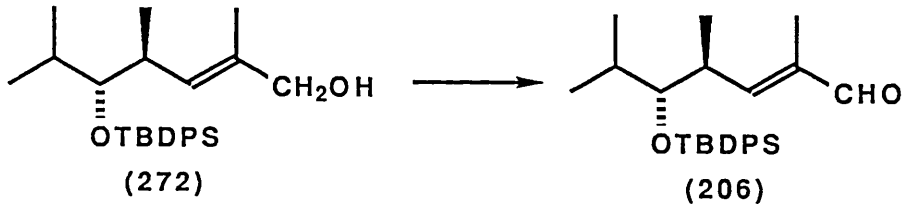
76. Preparation of (2E)(4S*,5R*)-5-^{t}Butyldiphenylisilyloxy-2,4,6-trimethyl-2-hepten-1-ol (272)



DIBAL (18.8ml, 1.5 M solution in toluene, 28.2mmol) was added dropwise to a stirred solution of ester (205) (5.00g, 11.1mmol) in toluene (100ml) at -78^{0}C under argon. The reaction was stirred for 30min, water (9.5ml) was added and the reaction was allowed to warm to room temperature. The heterogeneous reaction was poured into a stirred suspension of $NaHCO_3$ (50g) and $MgSO_4$ (50g) in ethyl acetate (250ml), the resulting mixture filtered under suction and the solvent removed under reduced pressure. Chromatography (15% ether-petrol) gave

(2E)-5-^{t}butyldiphenylsilyloxy-2,4,6-trimethyl-2-hepten-1-ol (271) as a viscous, colourless oil (b.p. 225^{0}C/0.10mmHg 4.16g, 92%). The 2:1 mixture of diastereoisomers were separated by HPLC (DYNAMAX 60A, 40ml/min, 1% IPA-petrol, 254nm, retention times: major diastereomer 30min (2E)(4S*,5R*)-5-^{t}butyldiphenylsilyloxy-2,4,6-trimethyl-2-hepten-1-ol (272); minor diastereoisomer 35min; δ_H (500MHz, $CDCl_3$) 0.81 (3H, d, J 7.0 Hz, 4-methyl), 0.88, 0.92 (6H, 2d, J 6.9 Hz, 3 x H-7, 6-methyl), 1.03 (9H, s, ^{t}Bu), 1.43 (3H, d, J 1.1 Hz, 2-methyl), 1.57 (1H, br s, OH), 1.82 (1H, d quintets, J 6.9, 3.5 Hz, H-6), 2.54 (1H, m, H-4), 3.50 (1H, dd, J 3.5, 5.2 Hz, H-5), 3.74 (2H, d, J 3.3 Hz, 2 x H-1), 5.27 (1H, dd, J 9.2, 1.1 Hz, H-3), and 7.3, 7.6 (10H, 2m, 2 x Ph); ν_{max} (film) 3340, 2960, 1460, 1427, 1110, and 703cm^{-1}; m/z 367 (M^+ - isopropyl), 327 (M^+ - ^{t}butyl) and 199. (Found: C,76.2; H,9.64. $C_{26}H_{38}O_2Si$ requires C,76.0; H,9.33%).

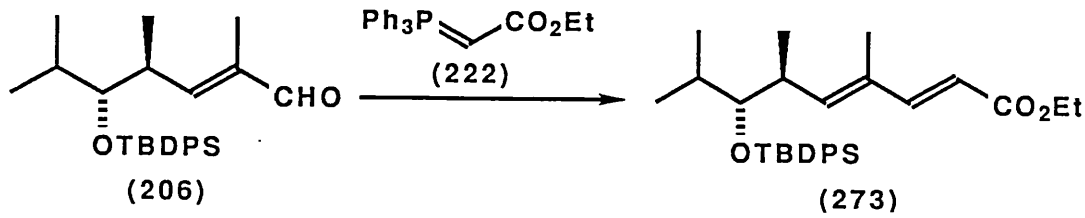
77. Preparation of (2E)(4S*,5R*)-5-^{t}Butyldiphenylsilyloxy-2,4,6-trimethyl-2-heptenal (206)



(272) (206)

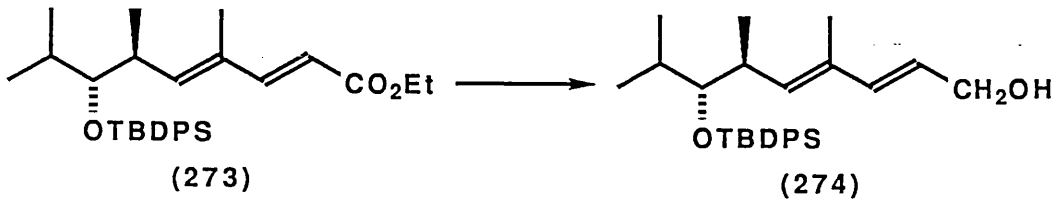
MnO_2 (2.00g, 23.0mmol) was added to a stirred solution of the allylic alcohol (272) (0.185g, 0.451mmol) in CH_2Cl_2 (15ml) at room temperature. The reaction was stirred for 5h, filtered under suction, and the filtered solid was thoroughly washed with ethyl acetate (10 x 10ml). The solvent was removed from the combined filtrates under reduced pressure. Chromatography (2% ether-petrol) gave (2E)(4S*,5R*)-5-^{t}butyldiphenylsilyloxy-2,4,6-trimethyl-2-heptenal (206) as a colourless oil (0.140g, 76%); δ_H (90MHz, $CDCl_3$) 0.90 (9H, m, 3 x H-7, 4 and 6-methyls), 1.10 (9H, s, ^{t}butyl), 1.64 (3H, d, J 1.0 Hz, 2-methyl), 1.82 (1H, m, H-6), 2.85 (1H, m, H-4), 3.60 (1H, m, H-5), 6.21 (1H, dd, J 6.4, 1.0 Hz, H-3), 7.4, 7.7 (10H, 2m, 2 x Ph), 9.32 (1H, s, H-1); ν_{max} (film) 2 933, 2 707, 1 686, 1 639, 1 589, 1 111, 1 083, and 703cm^{-1}.

78. Preparation of Ethyl (2E,4E)(6S*,7R*)-7-^{t}Butyldiphenylsilyloxy-4,6,8-trimethyl-2,4-nonadienoate (273)



A solution of the aldehyde (206) (0.60g, 1.47mmol) and the phosphorane (222) (2.55g, 7.34mmol) in $CHCl_3$ (100ml) was heated under reflux for 72h, cooled, silica (8.0g) was added and the volatile material was thoroughly removed under reduced pressure. Chromatography (2% ether- petrol) gave ethyl (2E,4E)(6S*,7R*)-7-^{t}butyldiphenylsilyloxy-4,6,8-tri-methyl-2,4-nonadienoate (273) as a colourless oil (0.448g, 64%); δ_H (500MHz, $CDCl_3$) 0.83, 0.85 (6H, 2d, J 6.9 Hz, 3 x H-9, 8-Me), 0.91 (3H, d, J 7.0 Hz, 6-Me), 1.10 (9H, s, ^{t}Bu), 1.35 (3H, t, J 7.2 Hz, $OCH_2\underline{CH_3}$), 1.64 (3H, s, 4-Me), 1.81 (1H, m, H-8), 2.69 (1H, m, H-6), 3.53 (1H, t, J 3.6 Hz, H-7), 4.26 (2H, q, J 7.2 Hz, $O\underline{CH_2}CH_3$), 5.75 (1H, d, J 15.7 Hz, H-2), 6.07 (1H, d, J 9.5 Hz, H-5), 7.28 (1H, d, J 15.7 Hz, H-3), and 7.4, 7.7 (10H, 2m, 2 x Ph); ν_{max} (film) 2 961, 1 710, 1 623, 1 172, and 1 111cm^{-1}; m/z 478 (M^+), 435 (M^+ - isopropyl), 421 (M^+ - ^{t}butyl), 311, and 199. (Found: 478.2893 (M^+). $C_{30}H_{42}O_3Si$ (M^+) requires 478.2903).

79. Preparation of (2E,4E)(6S*,7R*)-7-^{t}Butyldiphenylsilyloxy-4,6,8-trimethyl-2,4-nonadien-1-ol (274)

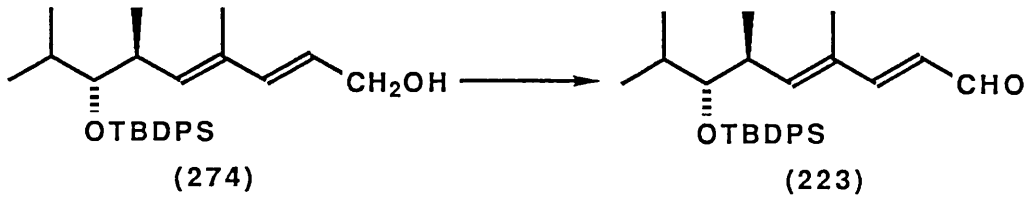


(273) (274)

DIBAL (2.27ml, 1.5 M solution in toluene, 3.41mmol) was added dropwise to a stirred solution of unsaturated ester (273) (0.651g, 1.36mmol) in toluene (10ml) at -78^{0} under argon. The reaction was stirred for 15min, water (1.1ml) added, and the reaction allowed to warm to room temperature. The resulting white suspension was poured into a vigorously stirred suspension of $NaHCO_3$ (50g) and $MgSO_4$ (50g) in ethyl acetate (100ml), the suspension was filtered under suction and the solvent removed under reduced pressure. Chromatography (15% ether-petrol) gave (2E,4E)(6S*,7R*)-7-^{t}butyldiphenylsilyloxy-4,6,8-trimethyl-2,4-nonadien-1-ol (274) as a colourless viscous oil (0.506g, 85%); δ_H (500MHz, $CDCl_3$) 0.80, 0.82, 0.87 (9H, 3d, J 6.9, 7.0, 7.0 Hz respectively, 6-Me, 8-Me, 3 x H-9), 1.07 (9H, s, ^{t}Bu), 1.28 (1H, br s,

OH), 1.57 (3H, d, J 1.2 Hz, 4-Me), 1.77 (1H, m, H-8), 2.62 (1H, m, H-6), 3.48 (1H, t, J 3.8 Hz, H-7), 4.18 (2H, d, J 6.0 Hz, 2 x H-1), 5.64 (2H, m, H-2, H-5), 6.18 (1H, dd, J 15.6, 0.6 Hz, H-3), and 7.4, 7.7 (10H, 2m, 2 x Ph); ν_{max} (film) 3 330, 2 959, 2 858, 1 461, 1 110, and 703cm^{-1}; m/z 435 (M^+ - H), 393 (M^+ - isopropyl), 379 (M^+ - ^{t}butyl), 311, 199, and 135. (Found: 393.2252 ($M^+ - {}^i$Pr). $C_{28}H_{40}O_2Si$ ($M^+ - {}^i$Pr) requires 393.2250).

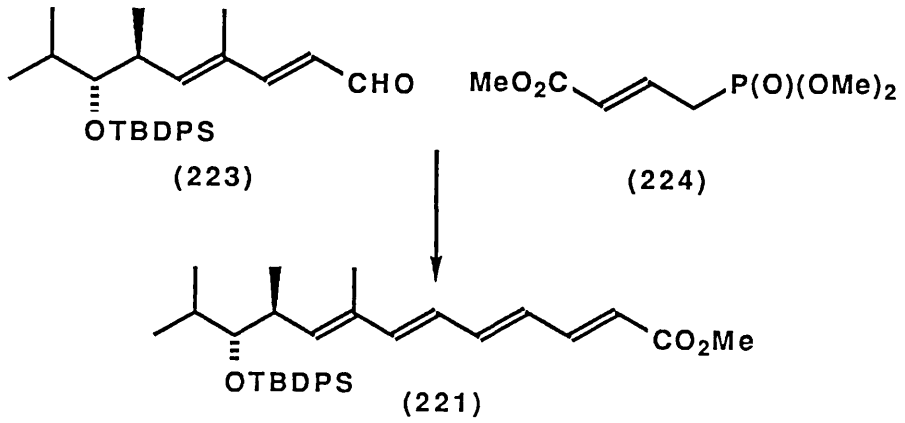
80. Preparation of (2E,4E)(6S*,7R*)-7-^{t}Butyldiphenylsilyloxy-4,6,8-trimethyl-2,4-nonadienal (223)



(274) (223)

MnO_2 (1.53g, 17.6mmol) was added to a stirred solution of alcohol (274) (0.260g, 0.594mmol) in CH_2Cl_2 (50ml) at room temperature. The suspension was stirred for 30 min, filtered under suction, the filtered solid thoroughly washed with ethyl acetate (10 x 10ml), the filtrates combined and the solvent removed under reduced pressure giving (2E,4E)(6S*,7R*)-7-^{t}butyldiphenylsilyloxy-4,6,8-trimethyl-2,4- nonadienal (223) as a colourless oil (0.210g, 81%), δ_H (90MHz, $CDCl_3$) 0.90 (9H, m, 6-Me, 8-Me, 3 x H-9), 1.10 (9H, s, ^{t}Bu), 1.70 (3H, s, 4-Me), 1.80 (1H, m, H-8), 2.70 (1H, m, H-6), 3.6 (1H, m, H-7), 6.1 (2H, m, H-2, H-5), 7.0 (1H, d, J 16.1 Hz, H-3), 7.4, 7.7 (10H, 2m, 2 x Ph), and 9.55 (1H, d, J 6.6 Hz, H-1); ν_{max} (film) 2 961, 1 678, 1 619, and 1 111cm^{-1}.

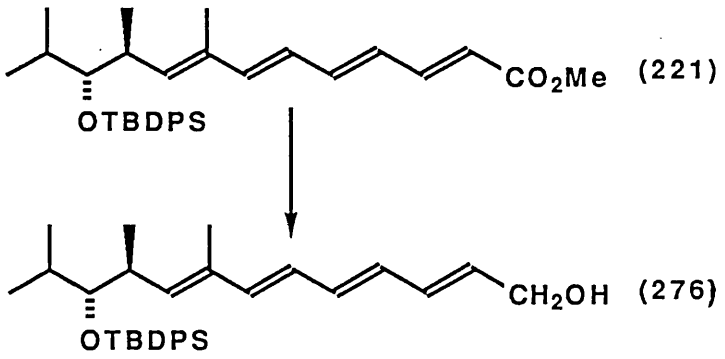
81. Preparation of Methyl (2E,4E,6E,8E)(10S*,11R*)-11-^{t}Butyldiphenylsilyloxy-8,10,12-trimethyl-2,4,6,8-tridecatetraenoate (221)



Sodium methoxide solution (0.328ml, 3M in methanol, 0.972mmol) was added to a stirred solution of the crotonyl phosphonate (224) (0.170g, 0.817mmol) in DMF (10ml) at 0^{0}C under argon. The resulting black suspension was stirred at 0^{0}C for 1h and then the aldehyde (223) (0.356g, 0.819mmol) was added. The reaction was allowed to warm to room temperature and stirred for 18h, poured into sat. aq. NH_4Cl (20ml) and ether (40ml), the layers were separated and the aqueous phase extracted

with ether (3 x 50ml). The combined ether extracts were washed with water (1 x 50ml), brine (1 x 50ml), dried ($MgSO_4$), and the volatile material removed under reduced pressure. Chromatography (2% ether-petrol) gave methyl (2E,4E,6E,8E)- (10S*,11R*)-11-^{t}butyldiphenylsilyl-oxy-8,10,12-trimethyl-2,4,6,8-trideca- tetraenoate (221) as a yellow, viscous oil (0.196g, 46%); δ_H (500MHz, $CDCl_3$) 0.8 to 0.9 (9H, m, 10-Me, 12-Me, 3 x H-13), 1.10 (9H, s, ^{t}BuSi), 1.59 (3H, s, 8-Me), 1.80 (1H, m, H-12), 2.65 (1H, m, H-10), 3.50 (1H, m, H-11), 3.75 (3H, s, MeO_2C), 5.76 (1H, d, J 9.5 Hz, H-9), 5.85 (1H, d, J 15.2 Hz, H-7), 6.14 (1H, dd J 15.2, 10.8 Hz, H-6), 6.30 (1H, dd, J 14.7, 11.3 Hz, H-4), 6.33 (1H, d, J 15.3 Hz, H-2), 6.60 (1H, dd, J 14.7, 10.8 Hz, H-5), 7.35 (1H, dd, H 15.3, 11.3 Hz, H-3), and 7.40, 7.70 (10H, 2m, 2 x Ph); ν_{max} (film) 2 959, 2 858, 1 714, 1 619, 1 596, 1 134, and 1 111cm^{-1}; m/z 516 (M^+), 473 (M^+ - isopropyl), 459 (M^+ -^{t}butyl), 365, 351, 311, 279, 199, and 135. (Found: 459.2350 (M^+ - ^{t}Bu). $C_{29}H_{35}O_3Si$ (M^+ - ^{t}Bu) requires 459.2356).

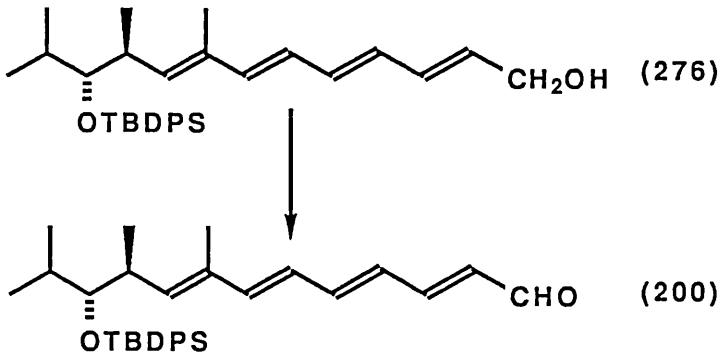
82. Preparation of (2E,4E,6E,8E)(10S*,11R*)-11-^{t}Butyldiphenylsilyloxy-8,10,12-trimethyl-2,4,6,8-tridecatetraen-1-ol (276)



DIBAL (0.64ml, 1.5M solution in toluene, 0.96mmol) was added dropwise to a stirred solution of polyene ester (221) (0.165g, 0.32mmol) in toluene (10ml) at -78^{0}C under argon. The reaction was stirred at -78^{0}C for 10 min, water (0.4ml) added, and allowed to warm to room temperature. The resulting emulsion was poured into a stirred suspension of ethyl acetate (200ml), $NaHCO_3$ (20g), and $MgSO_4$ (20g). The suspension was filtered under suction and the solvent was removed under

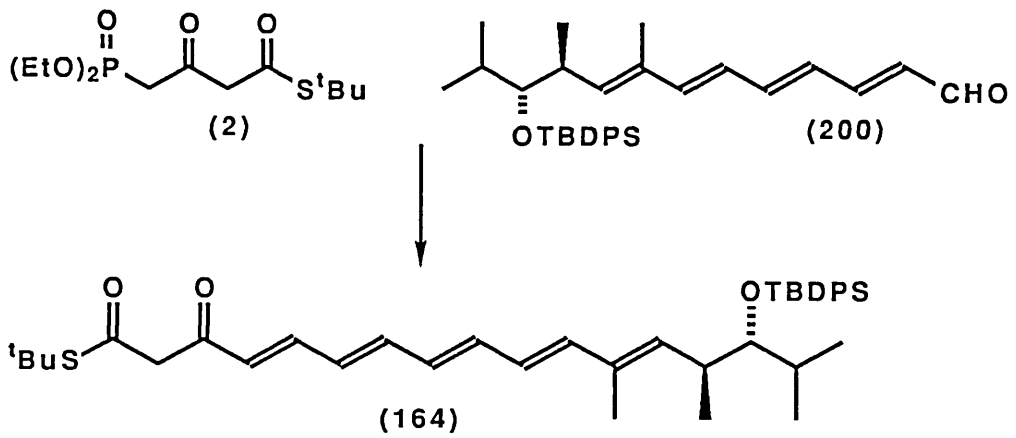
reduced pressure. Chromatography (20% ether-petrol) gave (2E,4E,6E,8E)-(10S*, 11R*)-11-^{t}butyldiphenylsilyloxy-8,10,12-trimethyl-2,4,6,8-tridecatetraen-1-ol (276) (0.144g, 92%) as a colourless, unstable oil; δ_H (90MHz, $CDCl_3$) 0.85 (9H, m, 10-Me, 12-Me, 3 x H-13), 1.10 (9H, s, ^{t}BuSi), 1.60 (3H, s, 8-Me), 1.80 (1H, m, H-12), 2.65 (1H, m, H-10), 3.50 (1H, m, H-11), 4.20 (2H, m, 2 x H-1), 5.5 to 6.4 (7H, m, H-2 to H-7, H-9), 7.35, 7.70 (10H, 2m, 2 x Ph); ν_{max} (film) 3 380, 2 960, 1 588, 1 462, 1 427, and 1 111cm^{-1}.

83. Preparation of (2E,4E,6E,8E)(10S*,11R*)-11-^{t}Butyldiphenylsilyloxy-8,10,12-trimethyl-2,4,6,8-tridecatetraenal (200)



Barium manganate (0.581g, 2.27mmol) was added to a stirred solution of the alcohol (276) (0.134g, 0.274mmol) in CH_2Cl_2 (20ml) at room temperature under argon. The reaction was stirred for 16h, filtered, and the volatile material removed under reduced pressure. Chromatography (25% ether-petrol) gave (2E,4E,6E,8E)(10S*,11R*)-11-^{t}butyldiphenylsilyloxy- 8,10,12-trimethyl-2,4,6,8-tridecatetraenal (200) as a yellow, viscous oil (0.104g, 78%); δ_H (90MHz, $CDCl_3$) 0.88 (9H, m, 10-Me, 12-Me, 3 x H-13), 1.10 (9H, s, ^{t}Bu), 1.64 (3H, s, 8-Me), 1.82 (1H, m, H-12), 2.55 (1H, m, H-10), 3.55 (1H, m, H-11), 5.75 to 7.85 (17H, m, including 7.4, 7.7, 10H, 2m, 2 x Ph, H-2 to H-7, H-9), and 9.59 (1H, d, J 7.9 Hz, H-1); ν_{max} (film) 2 961, 1 675, 1 588, and 1 111cm^{-1}.

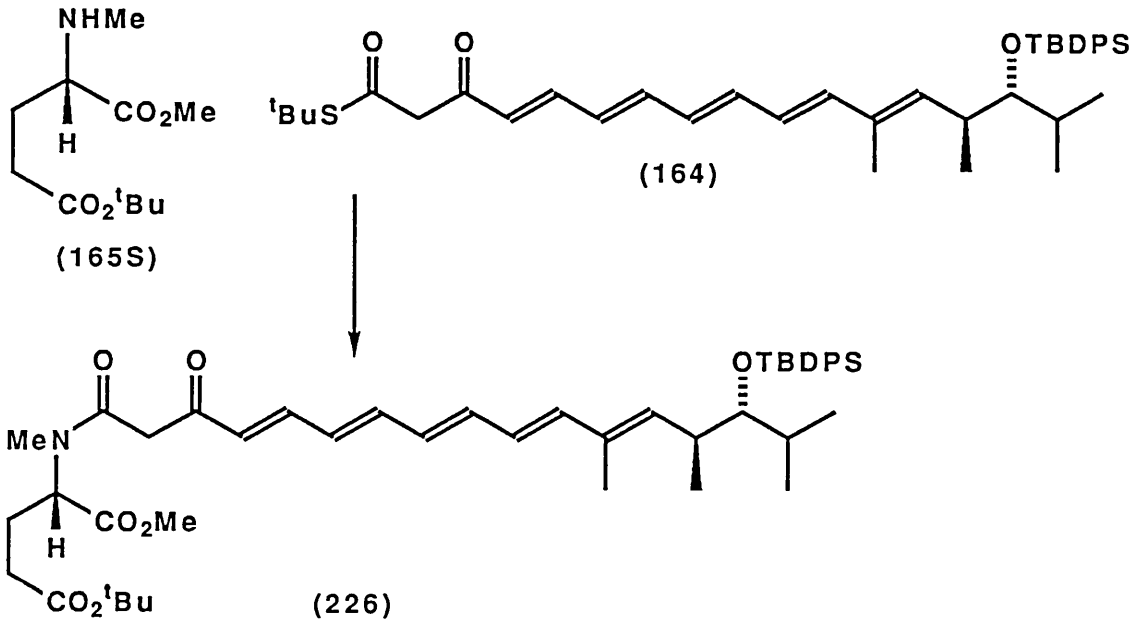
84. Preparation of ^{t}Butyl (4E,6E,8E,10E,12E)(14S*,15R*)-15-^{t}Butyldiphenylsilyloxy-12,14,16-trimethyl-3-oxo-4,6,8,10,12-heptadecapentaenthioate (164)



Thioester phosphonate (2) (89.2mg, 0.287mmol) was added to a stirred supension of sodium hydride (25.2mg, 60% oil dispersion, 0.632mmol) in THF (10ml) at 0^{0}C under argon. The reaction was stirred for 1h and then the aldehyde (200) (67.6mg, 0.139mmol) was added. The reaction was allowed to warm to room temperature, stirred for 16h,

poured into sat. aq. NH_4Cl (20ml) and ether (20ml), the layers separated, and the aqueous layer extracted with ether (3 x 30ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (1% ether-petrol) gave ^{t}butyl (4E,6E,8E,10E,12E)(14S*,15R*)-15-^{t}butyldiphenylsilyloxy- 12,14,16-trimethyl-3-oxo- 4,6,8,10,12-heptadecapentaenthioate (164) as an orange foam (55.5mg, 62%); δ_H (500MHz, $CDCl_3$) (80% enol form) 0.81 (6H, m), 0.88 (3H, d, J 6.7 Hz, 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 Hz, H-5), and 7.39, 7.69 (10H, 2m, 2 x Ph) (OH enol not detected); ν_{max}(film) 3 330, 2 963, 1 665, 1 640, 1 615, 1 566, 1 426, 1 108, and 1 075cm^{-1}; m/z 526, 495, 469, 339, 311, and 216.

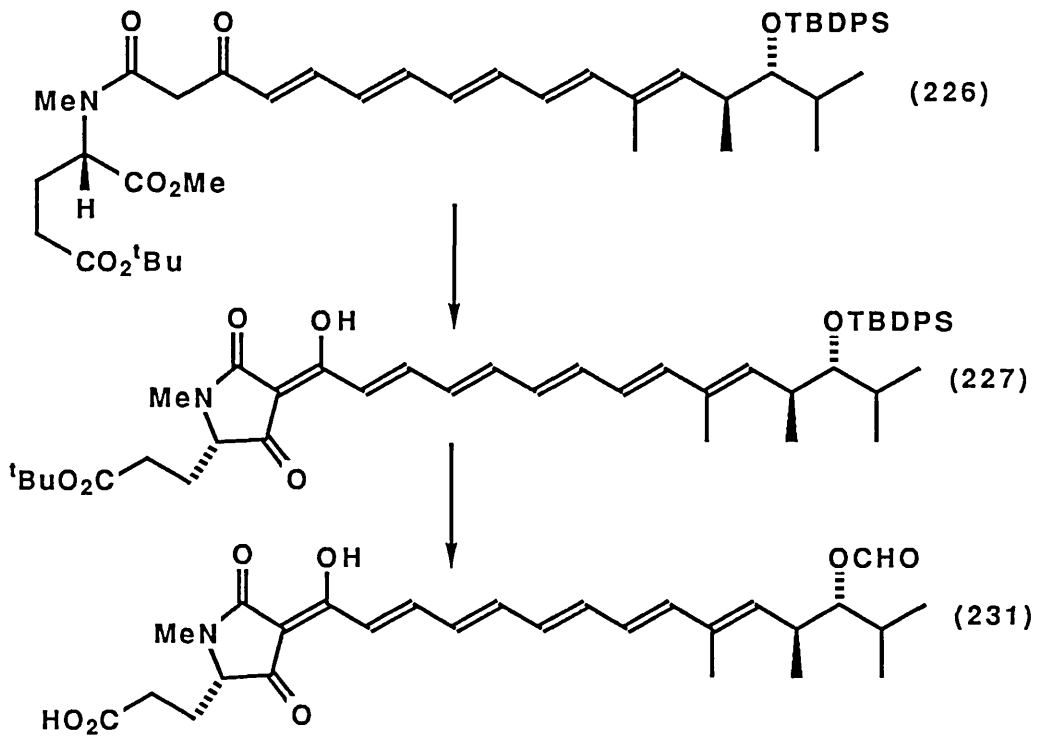
85. Preparation of (2S)-N-[(4E,6E,8E,10E,12E)(14S*,15R*)-15-^{t}Butyldiphenylsilyloxy-12,14,16-trimethyl-3-oxo-4,6,8,10,12-heptadecapentaenoyl]-N-methylglutamic acid α-methyl ester γ^{t}-butyl ester (226)



Silver(I) trifluoroacetate (26.9mg, 0.122mmol) was added to a stirred solution of thioester (164) (52.3mg, 81.3μmol) and aminodiester (165S) (56.4mg, 0.244mmol) in THF (5ml) at room temperature under argon. The reaction was stirred for 15 min and the volatile material thoroughly removed under reduced pressure and in vacuo. The residue was

preabsorbed onto the silica (3g) and chromatography (20% to 40% ether-petrol) gave (2S)-N-[(4E,6E,8E,10E,12E)(14S*,15R*)-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 (226) (31.3mg, 49%), δ_H (500MHz, $CDCl_3$) (70% enol form, mixture of rotamers and diastereoisomers) 0.82 (6H, m), 0.87 (3H, d, J 6.7 Hz, 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 Hz, H-5), and 7.40, 7.70 (10H, 2m, 2 x Ph) (OH enol not detected); ν_{max} (film) 3 400, 2 960, 1 735, 1 628, 1 586, 1 481, 1 152, and 1 110cm^{-1}; m/z 726 (M^+ - ^{t}butyl), 495, 311, 199, and 135. (Found: 726.3840 (M^+ - ^{t}Bu) $C_{43}H_{56}NO_7Si$ (M^+ - ^{t}Bu) requires 726.3826).

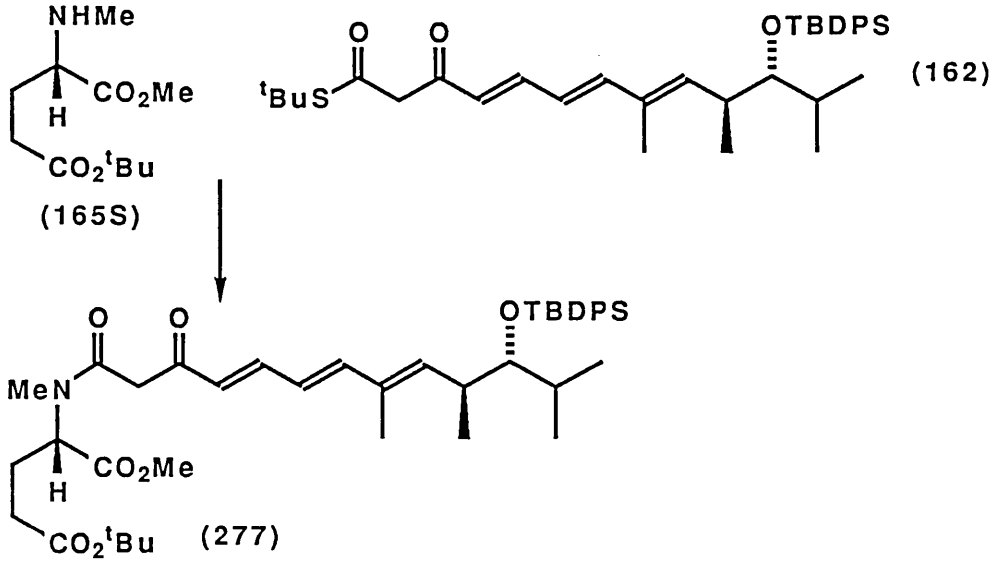
86. Preparation of 3S{3Z[(2E,4E,6E,8E,10E)(12S*,13R*)-13-*O*-Formyl-1,13-dihydroxy-10,12,14-trimethyl-2,4,6,8,10-pentadecapentaenylidenyl]-2,4-pyrrolidinedione}propanoic acid (231)



KO^tBu (10mg, 89.1μmol) was added to a stirred solution of (226) (27.7mg, 35.3μmol) in ^tBuOH (2ml) at room temperature under argon. The solution was stirred for 2 min and the volatiles removed under reduced pressure. Water (10ml) was added to the residue, the solution was

acidified to pH2 with 0.5M aq. oxalic acid, and the aqueous suspension extracted with ethyl acetate (3 x 15ml). The combined organic layers were dried ($MgSO_4$) giving the crude tetramic acid (227) (22.6mg, 85%) as a dark red powder. This was taken straight through to the next step. Formic acid (2ml, 98%) was added to (227) and the resulting solution stirred at room temperature for 48h. The solvent was removed under reduced pressure and the residue chromatographed (8% acetone-$CHCl_3$, oxalic acid treated silica) giving 3S{3Z[(2E,4E,6E,8E,10E)(12S*,13R*)-13-O-formyl-1,13-dihydroxy-10,12,14-trimethyl-2,4,6,8,10-pentadecapentaenylidene]-2,4-pyrrolidinedione}propanoic acid (231) heavily contaminated with oxalic acid; δ_H (500MHz, $CDCl_3$) (mixture of tautomers) 0.8 to 1.0 (9H, m, 12-Me, 14-Me, 3 x H-15), 1.82 (3H, s, 10-Me), 2.05 (1H, m, H-12), 2.10, 2.38 (4H, 2m, $CH_2CH_2CO_2H$), 3.0 (3H, 2s, N-Me), 3.80 (1H, m, H-5), 4.8 (1H, m, H-13), 5.8 to 7.6 (9H, m, H-2 to H-9 inclusively, H-11), 8.04, 8.15 (1H, 2s, HCO_2) (OH, CO_2H not detected, H-14 presumed under water peak at 1.6); m/z 485 (M^+), 457 (-CO), 439 ($-HCO_2H$), 385, 212, 185, 125, and 98; no i.r. data because of oxalic acid contamination.

87. Preparation of (2S)-N-[(4E,6E,8E)(10S*,11R*)-11-^{t}Butyldiphenylsiloxy-8,10,12-trimethyl-3-oxo-4,6,8-tridecatrienoyl]-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (277)

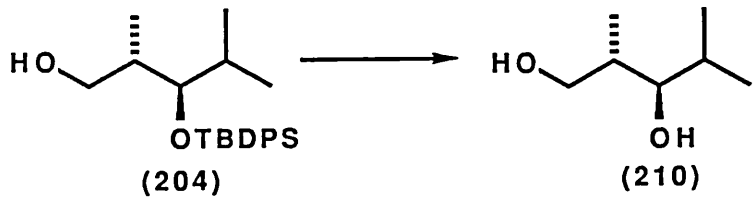


Silver(1) trifluoroacetate (24.1mg, 0.109mmol) was added to a stirred solution of thioester (162) (64.6mg, 0.109mmol) and aminodiester (165S) (23.0mg, 99.4mmol) in THF (4ml) at room temperature under argon.

The solution was stirred for 1h, the volatile material thoroughly removed under reduced pressure and in vacuo, and the residue preabsorbed onto silica (0.5g). Chromatography (40% ether-petrol) gave (2S)-N-[(4E,6E,8E)(10S*,11R*)-11-^{t}butyldiphenylsilyloxy-8,10,12-trimethyl-3-oxo-4,6,8-tridecatrienoyl]-N-methylglutamic acid α-methyl ester γ-^{t}butyl ester (277) as a pale yellow viscous oil (48.5mg, 67%);

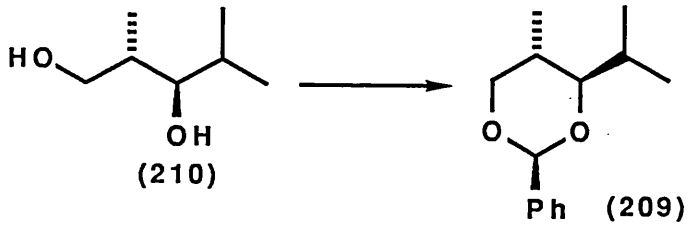
$[\alpha]_D^{25}$ 33^0 (c 3.0, $CHCl_3$); δ_H (90MHz, $CDCl_3$) (100% enol form, mixture of rotamers and diastereoisomers) 0.85 (9H, m, 10-Me, 12-Me, 3 x H-13), 1.05 (9H, s, ^tBuSi), 1.42 (9H, s, $^tBuO_2C$), 1.60 (4H, m, including 3H, s, 8-Me, H-12), 1.90, 2.25 (4H, 2m, $CH_2CH_2CO_2$ ^tBu), 2.65 (1H, m, H-10), 2.95 (3H, in N-Me), 3.49 (1H, m, H-11), 3.72 (3H, s, MeO_2C), 5.20 (2H, m, including 1H, s, H-2 enol, $CHCO_2Me$), 5.7-7.2 (5H, m, H-4 to H-7 inclusively, H-9), and 7.35, 7.70 (10H, 2m, 2 x Ph) (OH enol not detected); ν_{max} (film) 2 959, 1 736, 1 609, 1 569, 1 481, 1 153, 1 111, and 704cm^{-1}; m/z 732 (M^+), 674 (M^+ - ^tBu), 659, 618, 421, and 311. (Found: 731.4200 (M^+). $C_{43}H_{61}NO_7Si$ requires 731.4217).

88. Preparation of (2S*,3R*)-2,4-Dimethylpentan-1,3-diol (210)



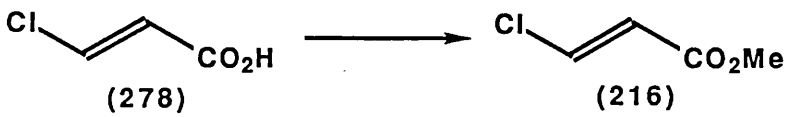
TBAF (1.70ml, 1 M solution in THF, 1.70mmol) was added to a stirred solution of the protected alcohol (204) (0.125g, 0.337mmol) in THF (5ml) at room temperature under argon. The solution was stirred for 5 days and the volatile material removed under reduced pressure. Chromatography (50% ether-petrol) gave (2S*,3R*)-2,4-dimethylpentan-1,3-diol (210)[150-154] as a colourless, viscous oil (19.6mg, 44%); δ_H (90MHz, $CDCl_3$) 0.90 (9H, m, 2-Me, 4-Me, 3 x H-5), 1.80 (2H, m, H-2, H-4), 2.70, 3.05 (2H, 2 br s, 2 x OH), 330 (1H, dd, J 3.9, 7.7 Hz, H-3), and 3.65 (2H, m, 2 x H-1); ν_{max} (film) 3 350, 2 962, 1 465, 1 069, and 990cm^{-1}.

89. Preparation of (2S*,4R*,5S*)-4-Isopropyl-5-methyl-2-phenyl-1,3-dioxane (209)



A solution of the diol (210) (22.2mg, 0.168mmol), benzaldehyde (20µl, 0.197mmol) and p-toluenesulphonic acid (5mg) in benzene (10ml) was heated under reflux for 2h, cooled, and the volatile material removed under reduced pressure. Ether (5ml) and sat. aq. $NaHSO_3$ (5ml) were added to the residue and the mixture stirred vigorously for 20h. The layers were separated, and the aqueous phase extracted with ether (3 x 10ml), the combined ether layers were washed with brine (2 x 10ml), dried ($MgSO_4$), and the volatiles removed under reduced pressure. Chromatography (1% ether-petrol) gave (2S*,4R*,5S*)-4-isopropyl-5-methyl-2-phenyl-1,3-dioxane (209) as a colourless oil (32.2mg, 87%); δ_H (500MHz, $CHCl_3$) 0.77 (3H, d, J 6.7 Hz, 2-Me), 0.98, 1.07 (6H, 2d, J 6.9H Hz, 3 x H-5, 4-Me), 1.98 (2H, m, H-4, H-2), 3.31 (1H, t, J 11.1 Hz, 1 x H-1 axial), 4.10 (1H, dd, J 11.1, 4.7 Hz, 1 x H-1 equatorial), 5.47 (1H, s, benzylidene acetal), and 7.28 - 7.53 (5H, m, Ph); ν_{max} (film) 2 962, 1 457, 1 395, 1 031, and 698cm^{-1}; m/z 220 (M^+), 177, and 107. (Found: 220. 1467 (M^+). $C_{14}H_{20}O_2$ (M^+) requires 220.1463).

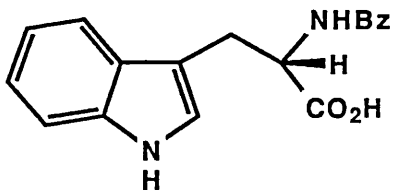
90. Preparation of Methyl (2E)-3-Chloro-2-propenoate (216)



(278) (216)

Concentrated sulphuric acid (10 drops) was added to a solution of 3-chloro-(E)-acrylic acid (278) (1.0g, 9.37mmol) in methanol (12ml), and the mixture heated under reflux for 16h, cooled, and the methanol carefully distilled off. The residue was treated with sat. aq. $NaHCO_3$ and the emulsion was extracted with the ether (3 x 25ml). The combined ether extracts were dried ($MgSO_4$) and the solvent distilled off at atmospheric pressure. Distillation of the residue gave methyl (2E)-3-chloro-2-propenoate (216)[155] as a colourless, mobile oil (bp. 118°C, 0.868g, 77%); δ_H (90MHz, $CDCl_3$) 3.74 (3H, s, CO_2 Me), 6.22 (1H, d, J 13.4 Hz, H-2), and 7.36 (1H, d, J 13.4 Hz, H-3); ν_{max} (film) 2 954, 1 718, 1 609, 1 437, 1 274, 1 167, 1 037, and 837cm^{-1}.

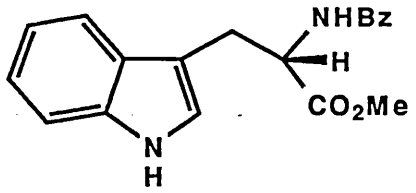
91. Preparation of (2S)-N^{α}-Benzyltryptophan (279)



(279)

L-Trytophan (4.00g, 19.6mmol) was dissolved in aq. sodium hydroxide (20ml, 2N solution, 40mmol) at room temperature to give a clear homogeneous solution. Benzaldehyde (2.6g, 24.5mmol) was slowly added and the solution stirred until clear (30 min). After stirring for a further hour the solution was washed with ether (2 x 5ml) to remove excess benzaldehyde and cooled to 0^0C. Sodium borohydride (0.75g, 19.6mmol) was added portion-wise maintaining the temperature below 15^0C, effervescence was apparent. After stirring for 16h, the solution was washed with ether (2 x 20ml). Dilute aq. hydrochloric acid was added until pH8 was obtained. The precipitate was filtered under suction, washed with saturated aq. $NaHCO_3$ and dried under vacuum yielding (2S)-N^{α}-benzyltryptophan (279)[156] (3.75g, 67%) as an amorphous solid (m.p. 205 to 210^0C); δ_H (90MHz, D_2O/NaOD) 2.60 to 2.90 (2H, m, $\underline{CH_2}CH$), 3.0 to 3.5 (3H, m, $\underline{CH_2}Ph$, $CH_2\underline{CH}$), 6.60 to 7.10 (10H, m, aromatics); ν_{max} (nujol mull) 3 405, 3 215, 2 915, 1 645, 1 600, and 1 465cm^{-1}.

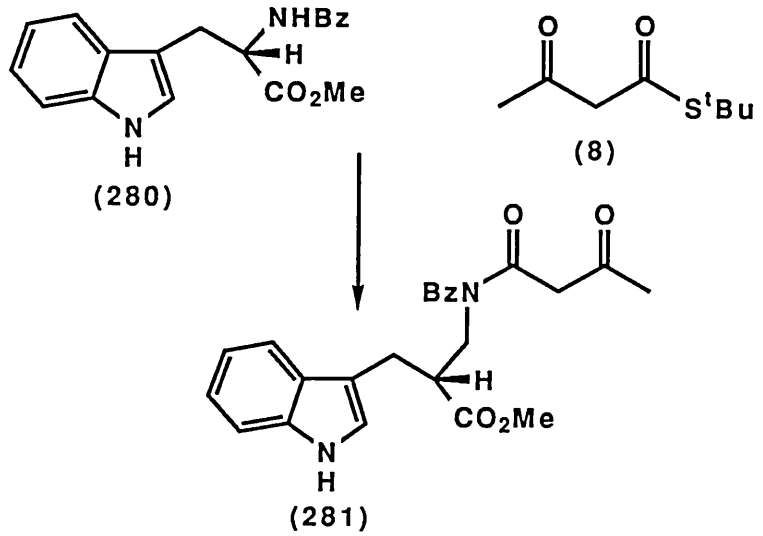
92. Preparation of (2S)-N^{α}-Benzyltryptophan methyl ester (280)



(280)

A solution of N-benzyltryptophan (279) (3.5g, 11.9mmol) in methanol (70ml) and concentrated hydrochloric acid (3.3ml, 36.3mmol) was heated under reflux for 20h, the volatile material removed under reduced pressure, and the residue treated with sat. aq. $NaHCO_3$ (50ml). The emulsion was extracted with ether (5 x 100ml), the combined ether extracts dried ($MgSO_4$), and the solvent removed under reduced pressure. Chromatography (ether-petrol) gave (2S)-N^{α}-benzyltryptophan methyl ester (280) as an amorphous colourless solid (m.p. 108 - 110°C, 1.39g, 38%); $[\alpha]_D^{25}$ -16° (c 2.0, $CHCl_3$); δ_H(250MHz, $CDCl_3$) 1.77 (1H, br, s, NHBz), 3.17 (2H, m, CH_2-CH), 3.63 (3H, s, CH_3 O_2C), 3.67 (1H, t, J 6.5 Hz, $CHCO_2Me$), 3.65 to 3.85 (2H, 2d, CH_2 Ph), 7.01 to 7.60 (10H, m, aromatics), and 8.15 (1H, br s, NH indole); ν_{max}(nujol mull) 3 395, 3 190, 2 915, 2 830, 1 745, 1 465, and 1 380; m/z 308 (M^+), 249, 178, 130, and 91. (Found: C,74.1; H,6.56; N,9.02. $C_{19}H_{20}N_2O_2$ requires C,74.0; H,6.54; N,9.09%).

93. Preparation of (2S)-N^{α}-Acetoacetyl-N^{α}-benzylytryptophan methyl-ester (281)



Silver(I) trifluoroacetate (64mg, 0.29mmol) was added to a stirred solution of aminoester (280) (74mg, 0.24mmol) and ^{t}butyl 3-oxobutanthioate (8) (45mg, 0.27mmol) in THF (4ml) at room temperature under argon. The reaction mixture was stirred for 30 minutes and worked up by the usual procedure. Chromatography (ether-petrol) gave (2S)-N^{α}-acetoacetyl-N^{α}-benzyltryptophan methyl ester (281) as needles (m.p. 94-100^{0}C, 70mg, 74%); δ_H(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_2-CH), 3.61 and 3.67 (1.5H, 2s, $COCH_2CO$, two rotamers), 3.84-4.44 (2H, two sets of 2d, NCH_2 Ph), 4.49-4.80 (1H, m, CH_2 CH), 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); ν_{max} (nujol mull) 3 380, 2 995, 2 940, 1 725, 1 630, 1 440, and 1 350cm^{-1}; m/z 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%).

94. Preparation of Copper(I) Trifluoroacetate

Copper(I) oxide (15g, 0.1mol) was added to trifluoroacetic acid (22ml, 0.27mol) under argon with rapid stirring. Trifluoroacetic anhydride (31ml, 0.22mol) was added dropwise to bring the solution to boiling and the reaction mixture was boiled for a further 1h to give a white solid. The solution was cooled and the mother liquors removed by catheter. The crude product was washed with dry degassed 30-40^0 petrol (2 x 70ml) and dissolved in dry degassed CH_2Cl_2 (70ml). The blue-green solution was filtered under argon through a filter stick into dry degassed petrol (100ml) to give a white solid. The mixture was cooled to -78^{0}C, the mother liquors removed and the solid washed with petrol (2 x 50ml). The product was purified a second time as above and dried under a stream of dry argon to give a white solid (10g).

95. Preparation of Silver Trifluoroacetate[157]

A solution of sodium hydroxide (4.7g, 0.12mmol) in water (20ml) was added to a solution of silver nitrate (20g, 0.12mol) in water (20ml) and the resulting precipitate of silver oxide was filtered and washed free of base. Trifluoroacetic acid (18ml, 0.24mol) in water (30ml) was added to the freshly precipitated silver oxide (0.12mol) to give a colourless solution which was evaporated to dryness. The crude product was dissolved in ether (150ml), filtered through decolourising charcoal and evaporated under reduced pressure to give the product as a white crystalline solid (19.3g, 74%).

96. Preparation of Oxalic Acid Silica

Silica (1kg) was added slowly to a stirred oxalic acid solution (2 litres, 0.5M). The suspension was stirred for 15min, poured into a flat glass dish and dried at 170^{0}C (48h). The resulting cake was ground to a fine powder.

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