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SYNTHESIS OF MACROLIDE ANTIBIOTICS

a thesis presented by

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ABSTRACT

This thesis is in two parts. The first part contains a short review on recent methods for the preparation of 3-acyl tetronic acids. The development of a new strategy for the synthesis of 3-acyl tetronic acids is then described. Thus, the dianion of ^tbutyl 3-oxobutane-thioate was efficiently generated, and was shown to react exclusively at the 4-position with alkyl halides, to give the alkylated products in moderate to good yields. The resultant 3-oxothioesters were smoothly transesterified under transition metal salt catalysis to oxoesters in good yield. Transesterification with 2-hydroxy esters led to the required precursors for Dieckmann cyclisation to 3-acyl tetronic acids. The use of tetra ⁿbutyl ammonium fluoride as a mild and efficient base for this transformation is described. In this way, carolic acid, a natural mold metabolite was synthesized in 3 steps in good overall yield. Further studies on both the 3-oxothioesters and 3-acyl tetronic acids are described. The attempted preparation of a model system for the macrocyclic ring system of tetronolide, a natural antibiotic with potent anti-tumour activity is outlined.

The second section deals with the preparation of synthons for the introduction of the C-8 to C-14 side-chain portion in a total synthesis of milbemycin β_1 , a macrocyclic anthelmintic natural product. Thus the geometrically controlled synthesis of a suitable vinyl silane moiety is described, and attempts at its conversion to a corresponding vinyl iodide outlined. Alternative strategies for the introduction of the C-8 to C-14 side-chain are proposed, and preliminary investigations upon these strategies are detailed.

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FOR MY PARENTS

ABBREVIATIONS

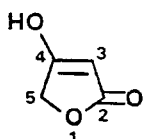
CSA	-	Camphor sulphonic acid
DIBAL	-	Diisobutylaluminium hydride
DMAP	-	N,N-Dimethyl-4-aminopyridine
DME	-	Dimethoxyethane
DMF	-	Dimethylformamide
eq.	-	Equivalents
LDA	-	Lithium diisopropylamide
Na/Hg	-	Sodium/Mercury amalgam
NPSS	-	N-Phenylsulphenosuccinimide
PCC	-	Pyridinium chlorochromate
PDC	-	Pyridinium dichromate
RT	-	Room temperature
TBDMS	-	^t Butyldimethylsilyl
THF	-	Tetrahydrofuran
THP	-	Tetrahydropyran
TLC	-	Thin-layer chromatography
TMS	-	Trimethylsilyl

NEW METHODOLOGY FOR TETRONIC ACID SYNTHESIS

REVIEW

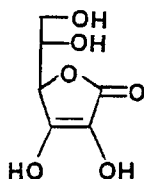
1. INTRODUCTION

"Tetronic acid" is the trivial name given to the 4-hydroxyfuran-2(5H)-one nucleus (1). This nucleus occurs in a large number of



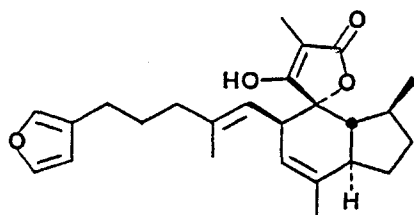
(1)

natural products of widely varying type, many possessing interesting biological properties¹. Perhaps the best known and most important member of the class, at least to humans, is ascorbic acid, Vitamin C, (2) first isolated in 1927.²

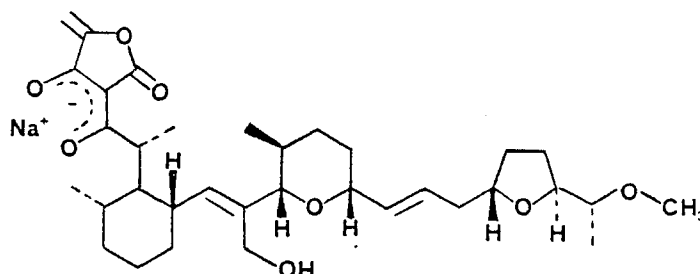


(2)

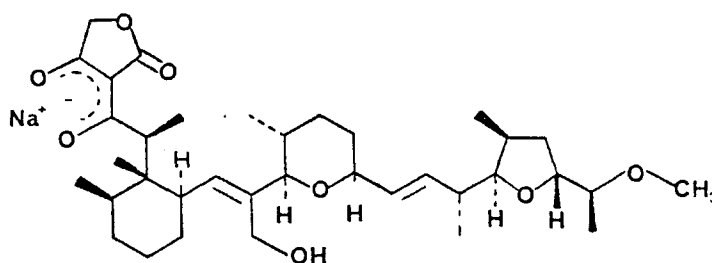
In more recent years several larger natural products containing diverse functionality in addition to the tetronic acid moiety have been isolated, exemplified by ircinianin (3)³, tetronomycin (4)⁴, and M-139603 (5)⁵. These last two compounds show a notable similarity, but somewhat remarkably are reported to possess opposite absolute configurations. Much interest has also focused on the properties of chlorothricolide (6)⁶, tetronolide (7)⁷, and kijanolide (8)⁸, in which the tetronic acid ring is itself embedded into a larger, macrocyclic structure. Chlorothricolide is the aglycon of the antibiotic chlorothricin, which displays activity against Gram-positive bacteria, and



(3)



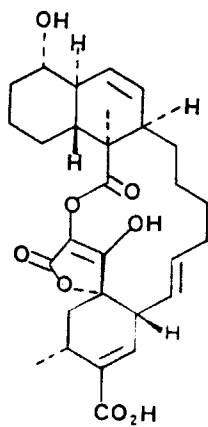
(4)



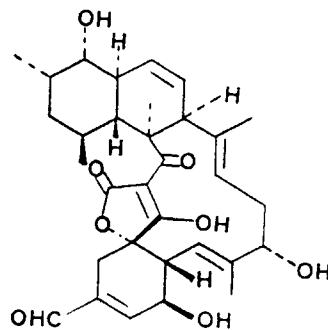
(5)

retains some of the activity of chlorothricin itself.⁹ Tetronolide and kijanolide, the aglycones of the tetrocarcins¹⁰ and kijanimicin⁸ respectively also display activity against Gram-positive bacteria, whilst the tetrocarcins possess potent antitumour activity.¹¹

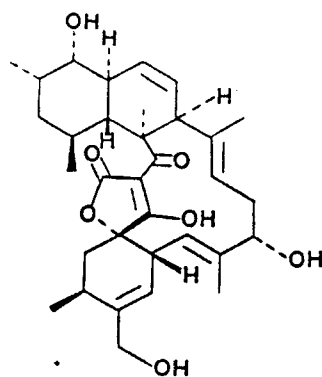
Since Demarcay first prepared 3-methyl tetronic acid in 1879¹², organic chemists have shown constant interest in the synthesis of tetronic acids, and this interest has increased dramatically in recent years with the isolation of compounds such as (6), (7), and (8) possessing potent biological activity. Tetronic acid synthesis has been the subject of several previous reviews.¹³ In the light of this, and of the enormous literature on the subject this review is necessarily



(6)



(7)



(8)

selective, and will concentrate on recent methods for the preparation of 3-acyl tetronic acids.

2. SYNTHESIS OF 3-ACYL TETRONIC ACID DERIVATIVES

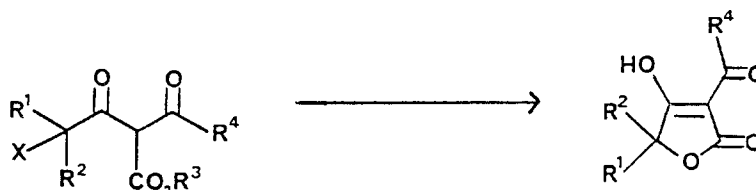
Although a seemingly bewildering number of methods for the synthesis of the title compounds exist examination of the literature reveals that all fall into one of 3 main categories:

- 1) Dieckmann cyclisation of the acylaceto-derivatives of 2-hydroxy esters (Scheme 1)¹⁴;
- 2) cyclisation of 4-substituted-3,3'-dioxoesters^{15,16} (Scheme 2);
- 3) acylation of derivatives bearing the pre-formed tetronic acid nucleus¹⁷⁻²¹ (Scheme 3).

Scheme 1



Scheme 2



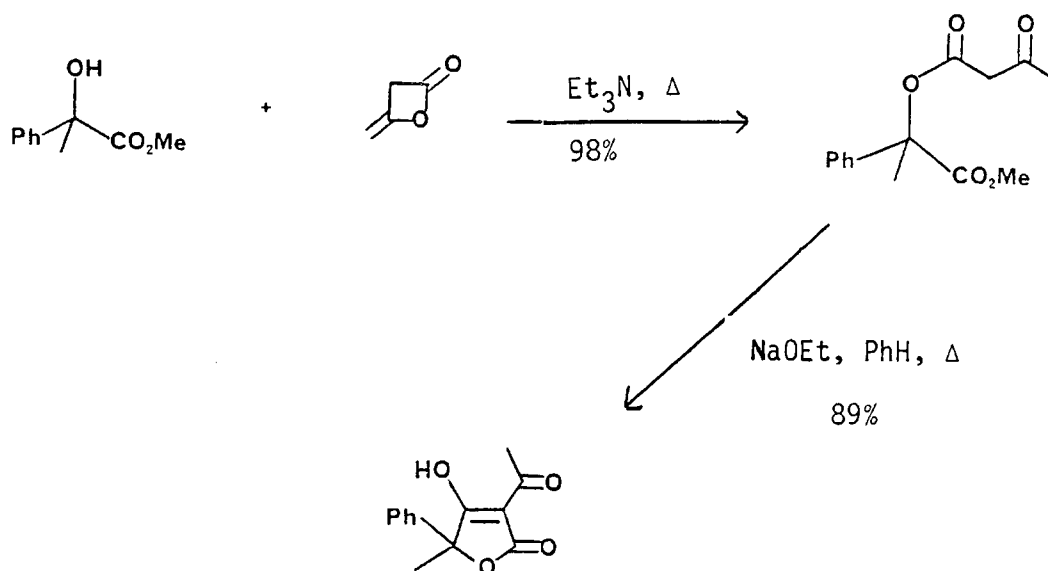
Scheme 3



2.1 Dieckmann cyclisation of acylaceto-derivatives of 2-hydroxy esters

This method is due to Lacey¹⁴, who in the course of pioneering work on the chemistry of β -lactones found that treatment of a 2-hydroxy ester with diketene, followed by cyclisation under standard Dieckmann conditions afforded good yields of 3-acetyl tetronic acids, as exemplified by the case of methyl benzilate (Scheme 4).

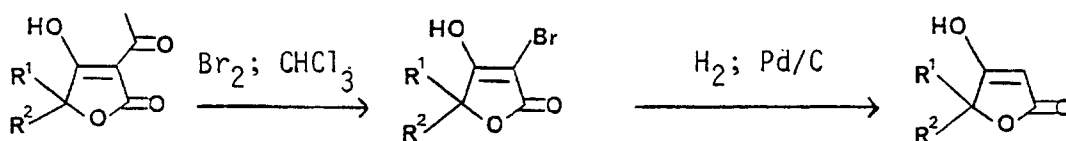
Scheme 4



Yields of tetronic acids from monosubstituted hydroxy-esters were found to be lower than in the disubstituted case, due to competing alcoholysis of the acetoacetate moiety.

The method is limited to the simple acetyl side-chain since substituted diketenes are not available but is otherwise general for a range of 2-hydroxy esters. Extrusion of the acetyl side-chain is readily achieved by treatment with bromine followed by catalytic hydrogenation to give the 3-unsubstituted tetronic acid, Scheme 5.

Scheme 5



The problem of epimerisation of the C-5 centre in the cyclisation of acetoacetates from monosubstituted hydroxy-esters was not addressed by Lacey, but has been investigated elsewhere.²² Results indicate that little epimerisation occurs, although the evidence is less than rigorous and additional data would be welcome.

Although no natural product possesses the simple 3-acetyl side-chain this method has found much use for the simple preparation of the 3-bromo and 3-unsubstituted derivatives *via* the route outlined in Scheme 5.^{20a,b}

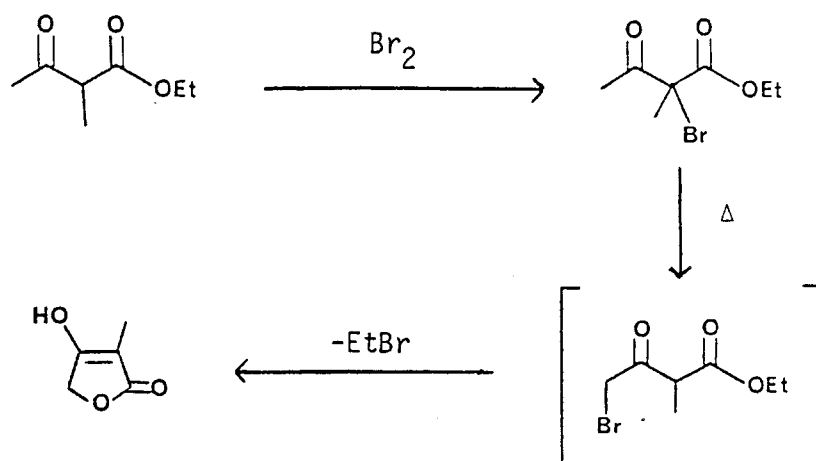
2.2 Cyclisation of 4-substituted-3,3'-dioxoesters

2.2.a *Via* 4-halo-3,3'-dioxoesters

This approach is essentially a variation upon the very first tetronic acid synthesis by Demarcay in which ethyl 2-methyl acetoacetate was brominated at the 2-position and thermally cyclised to the tetronic acid *via* rearrangement to the 4-bromo derivative¹², Scheme 6.

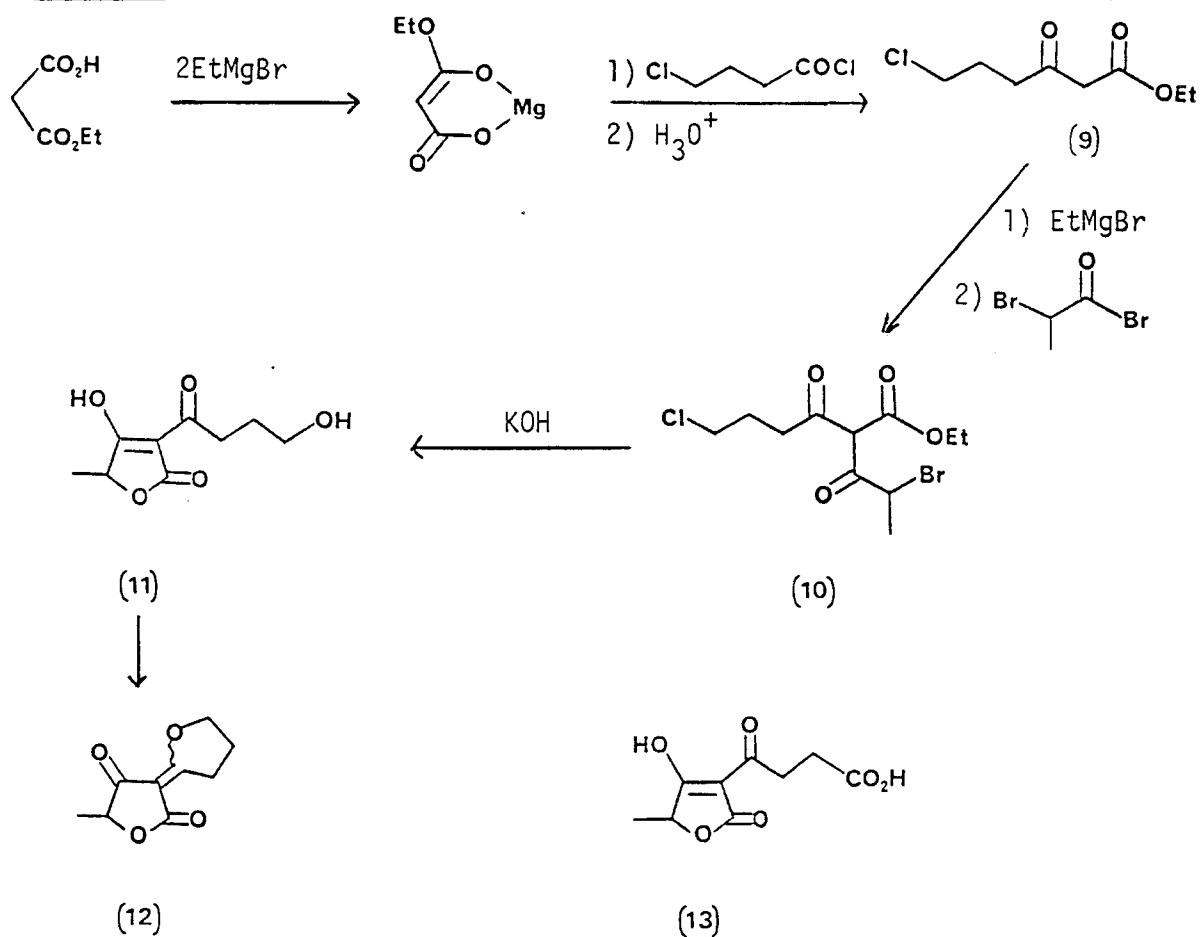
To synthesise 3-acyl tetronic acids the 2-methyl group is replaced by an acyl function, the 4-bromo substituent is often introduced directly rather than by rearrangement of the 2-substituted isomer, and the cyclisation is carried out under basic conditions.

Scheme 6



Hence, treatment of monoethyl malonate with two equivalents of EtMgBr in CH_2Cl_2 followed by quenching with 4-chlorobutyryl chloride and acid hydrolysis afforded (9) in 88% yield¹⁵, Scheme 7.

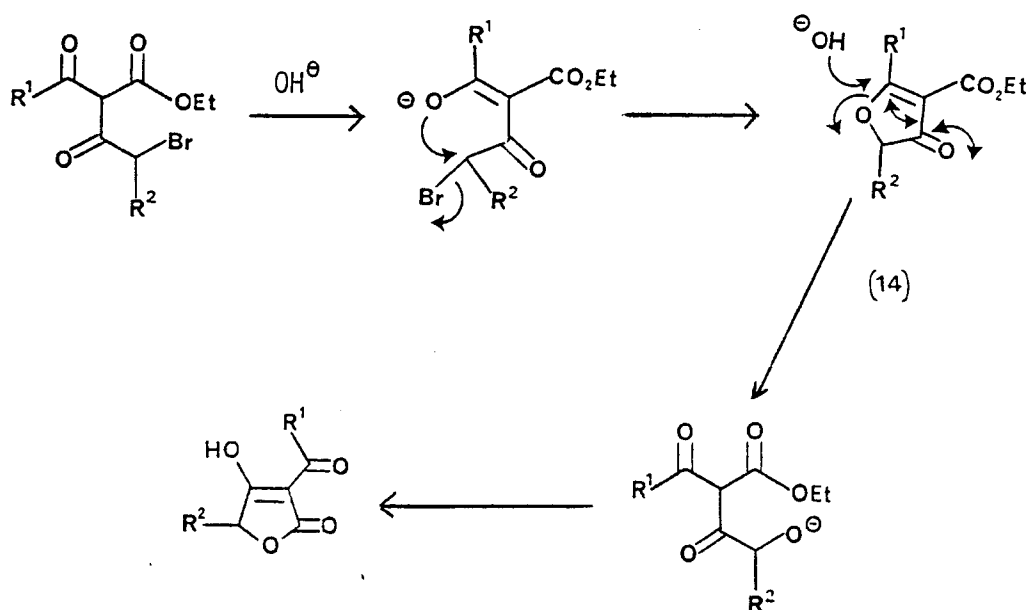
Scheme 7



Condensation with 2-bromopropionyl bromide using EtMgBr as base then gave (10). Reaction of (10) with 2.5M KOH simultaneously induced cyclisation to the tetronic acid and hydrolysis of the chloride substituent affording (11), and hence (12), the mold metabolite carolic acid, though in poor yield. Another mold metabolite carolinic acid (13) has been prepared in similar fashion.

The mechanism of the cyclisation reaction is given in Scheme 8.

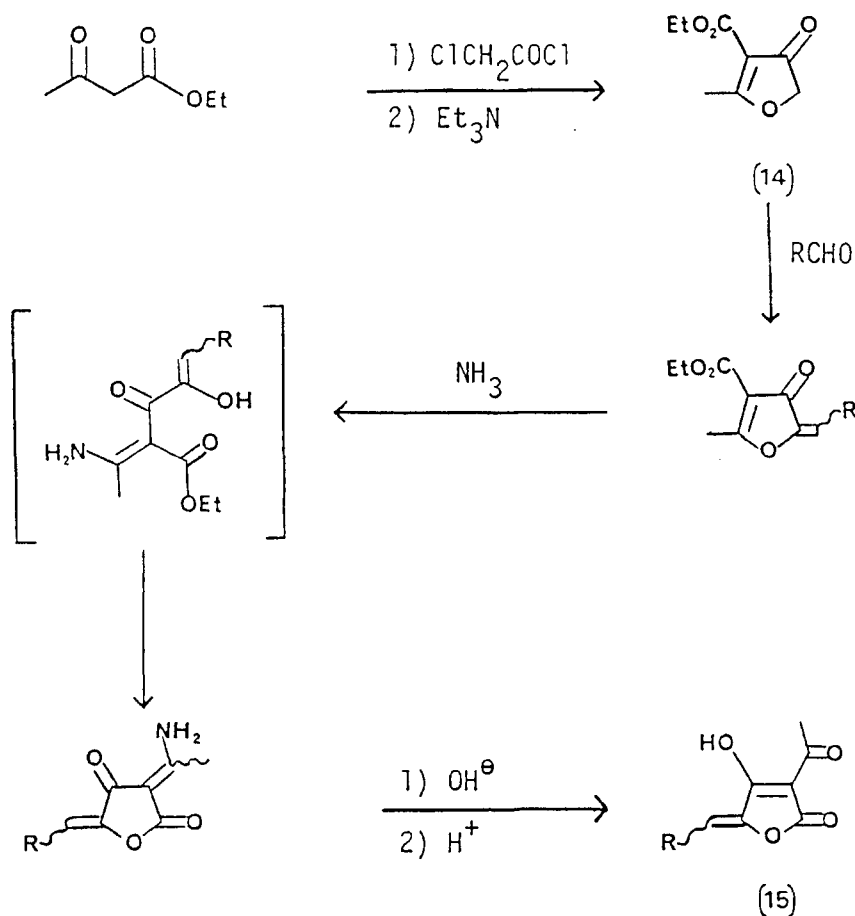
Scheme 8



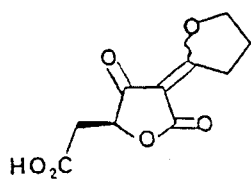
The furan-3(2H)-one intermediate (14) has been prepared and isolated for the case when $R^1 = H, R^2 = CH_3$ by acylation of ethyl acetoacetate with chloroacetyl chloride followed by treatment with Et_3N , Scheme 9.²³ Subsequent condensation with aldehydes, followed by aminolysis and hydrolysis afforded the 5-ylidene tetronic acids (15) in variable yield (30-70%).

When a simple malonate derivative is used (Scheme 8, $R^1 = OR$), the resultant 3-alkoxycarbonyl tetronic acid is readily decarboxylated, a common route to 3-unsubstituted tetronic acid derivatives.²¹

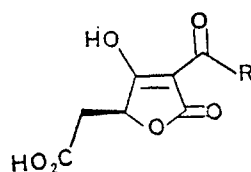
Scheme 9



This method fails in the case of 5,5-disubstituted tetronic acids, and when the 4'-halo substituent is readily eliminated due to the presence of an ester functionality (Scheme 8, $\text{R}^2 = \text{CH}_2\text{CO}_2\text{R}$). This latter drawback prevents the utilisation of this method in the preparation of the mold metabolites carlic acid (16), carlosic acid (17) and viridicatic acid (18).



(16)

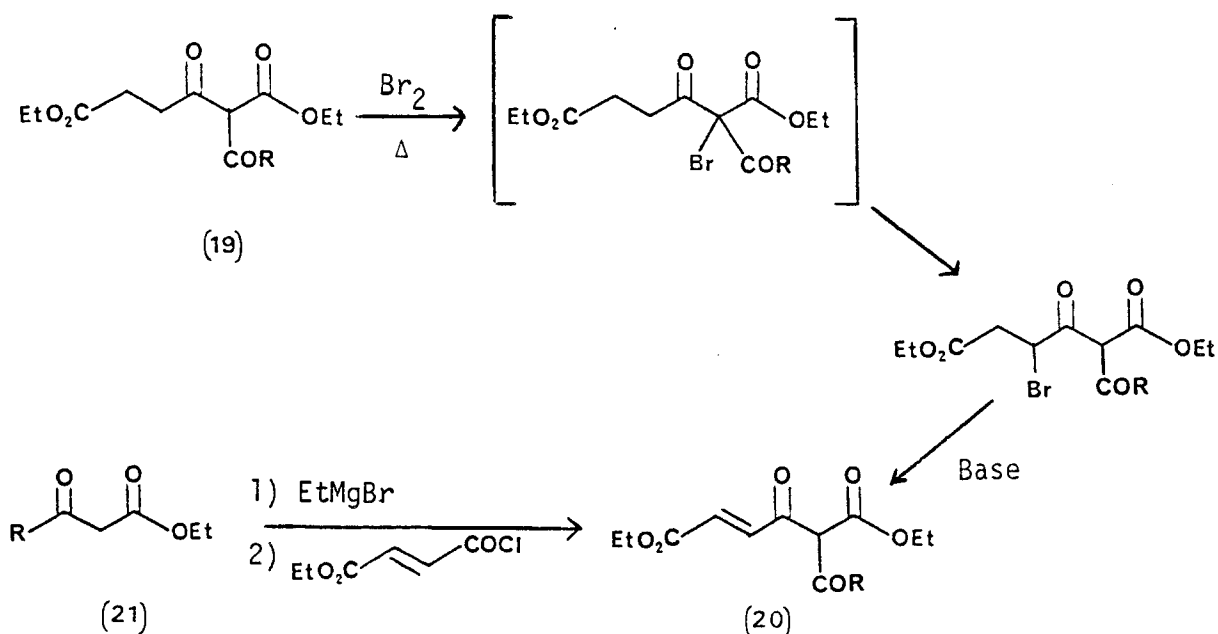
(17) $\text{R} = n\text{-Pr}$ (18) $\text{R} = n\text{-C}_5\text{H}_{11}$

In this case however, cyclisation of 6-alkoxycarbonyl-4-ylidene-3,3'-dioxoesters has proved to be of great utility.

2.2.b Via 6-alkoxycarbonyl-4-ylidene-3,3'-dioxoesters¹⁶

The starting materials for such cyclisations can be prepared either by a bromination-dehydrobromination sequence (eg (19)→(20)) or *in situ* by a more direct acylation route (eg (21)→(20)), Scheme 10, the latter being the method of choice.

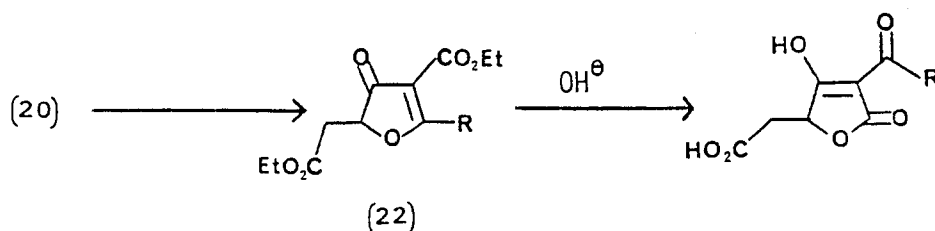
Scheme 10



In the direct acylation case cyclisation to the now familiar furan-3(2H)-one intermediate (22) is spontaneous, whereas when (20) is isolated a further acid-catalysed cyclisation step is required. Base hydrolysis then affords the 3-acyl tetronic acid as before, though yields are usually poor, Scheme 11.

This sequence has been used to synthesise in very poor yields the aforementioned mold metabolites carlosic acid (17) (Scheme 11, $\text{R} = n\text{-Pr}$) and viridicatic acid (18) (Scheme 11, $\text{R} = n\text{-C}_5\text{H}_{11}$) in their racemic modifications.¹⁶ Attempted preparation of carlic acid (16) by this route failed affording only unidentified products.

Scheme 11



This method is of course limited to the preparation of 3-acyl tetronic acids with an electron-withdrawing β -substituent at the 5-position, in order that the Michael-type cyclisation might take place. In addition the nature of the initial cyclisation to the furanone (22) precludes the preparation of tetronic acids chiral at the 5-position, a comment also applicable to the halide cyclisation route outlined in Section 2.2.a.

2.3 3-Acylation of tetronic acid derivatives

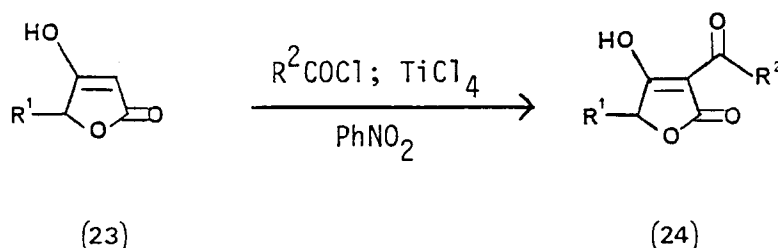
These methods require pre-formation of the tetronic acid nucleus which is then acylated in a Friedel Crafts manner^{20,21}, or metallated at C-3 with an organometallic reagent, with subsequent acylation of the resultant carbanion^{17,19}. The former method allows direct preparation of the free 3-acyl tetronic acid, whereas the latter provides the methyl tetronate (4-methoxy derivative) which must be hydrolysed to the free acid. The requisite precursors for these reactions are often prepared by one of the methods outlined in Sections 2.1 and 2.2.

2.3.a Direct acylation of 3-unsubstituted tetronic acids

The earliest example of this reaction was due to Haynes²⁵, who showed that 5-phenyl tetronic acid could be 3-acylated by treatment with acetyl chloride - SnCl_4 . It has been shown however that this procedure is not applicable in general.

Subsequently, optimum conditions for the acylation have been found to be treatment of the tetronic acid (23) with the requisite acyl chloride and TiCl_4 in nitrobenzene²⁰, Scheme 12.

Scheme 12



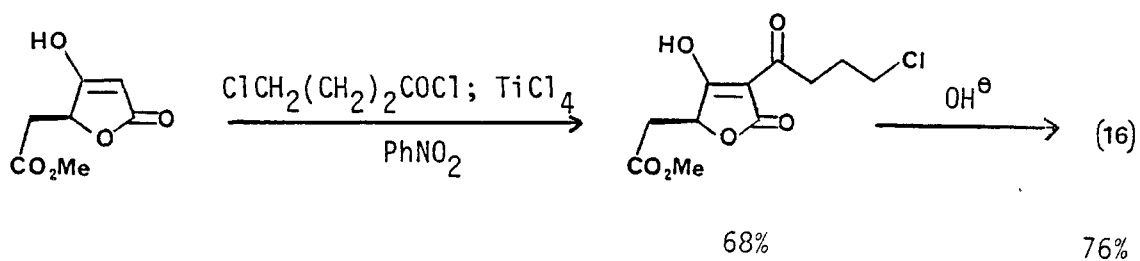
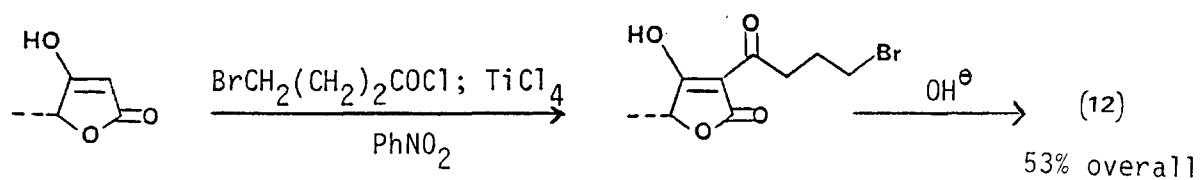
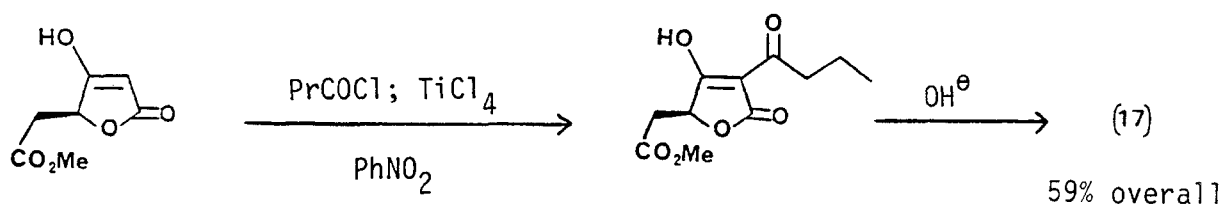
Yields for the process are fair and the preparation of optically active tetronic acids is possible provided that the appropriate chiral starting material is available. Thus, total syntheses of (S)-carlosic acid (17) and the unnatural (S)-carolic acid have been achieved, as have formal syntheses of (R)-carolic acid (12) and (R)-carlic acid (16), in addition to preparation of the racemic modifications²⁰, Scheme 13.

It has also been demonstrated that *O*-acylation of the thallium enolate of a 3-unsubstituted tetronic acid, followed by Fries rearrangement gives rise to 3-acyl tetronic acids²⁰, Scheme 14. The overall yields however are markedly inferior to those obtained by direct acylation.

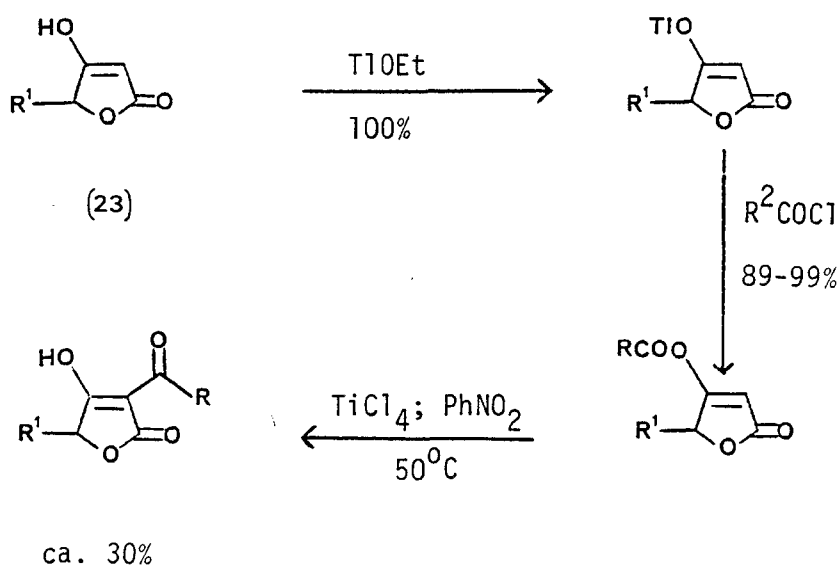
2.3.b Acylation via 3-metallated methyl tetronates

Independently it has been shown by Pattenden¹⁷ and Schmidt¹⁸ that 5,5-disubstituted-3-unsubstituted methyl tetronates of type (25) may be deprotonated at the C-3 position by LDA in THF to give the 3-lithio species (26), Scheme 15.

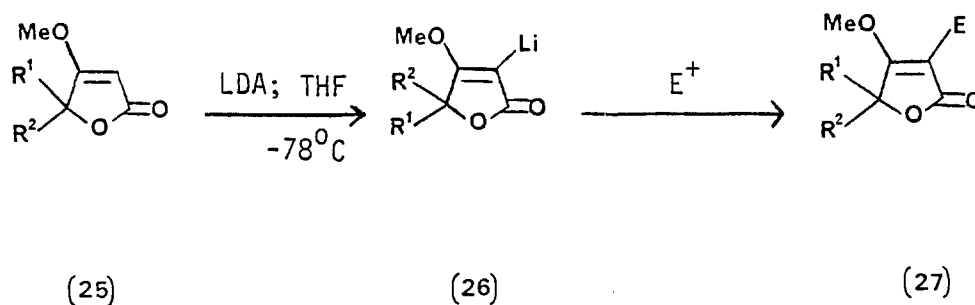
Scheme 13



Scheme 14

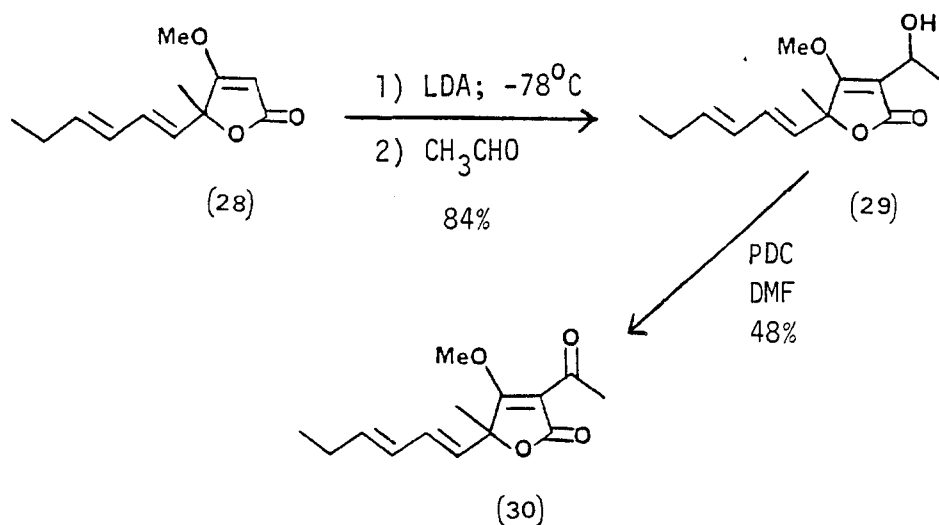


Scheme 15



Reaction of (26) with suitable electrophiles then gave the 3-substituted tetronate in varying yields. It was found that direct reaction with acylating agents afforded only poor to moderate yields of the 3-acyl derivatives. A 2-stage procedure involving reaction with an aldehyde followed by oxidation gave greatly improved yields, Scheme 16.

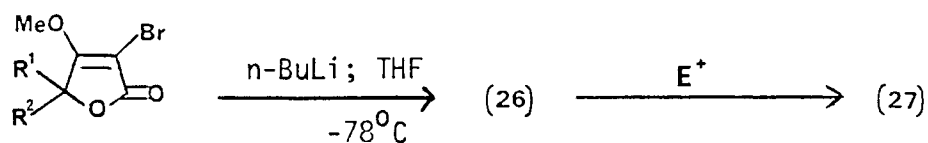
Scheme 16



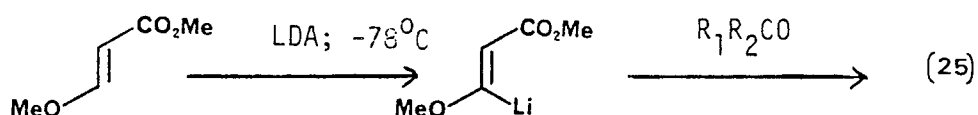
Closely related work by Yoshii¹⁹ generates the lithio intermediates (26) *via* metallation of the 3-bromo derivative with *n*-BuLi Scheme 17.

Both Pattenden and Schmidt utilised the regioselective kinetic deprotonation of (*E*)-3-methoxyacrylates to prepare the starting materials (25), Scheme 18.

Scheme 17

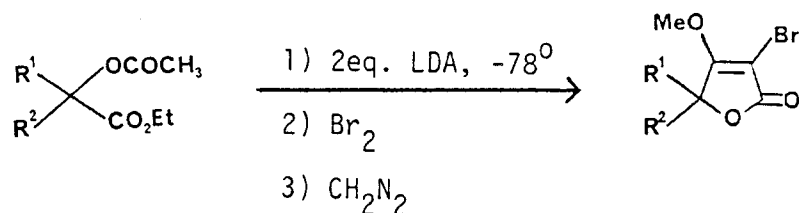


Scheme 18



The 3-bromo tetronic acids required by Yoshii were prepared either *via* the Dieckmann cyclisation/bromination procedure of Lacey discussed earlier, or *via* the Claisen reaction shown in Scheme 19.

Scheme 19

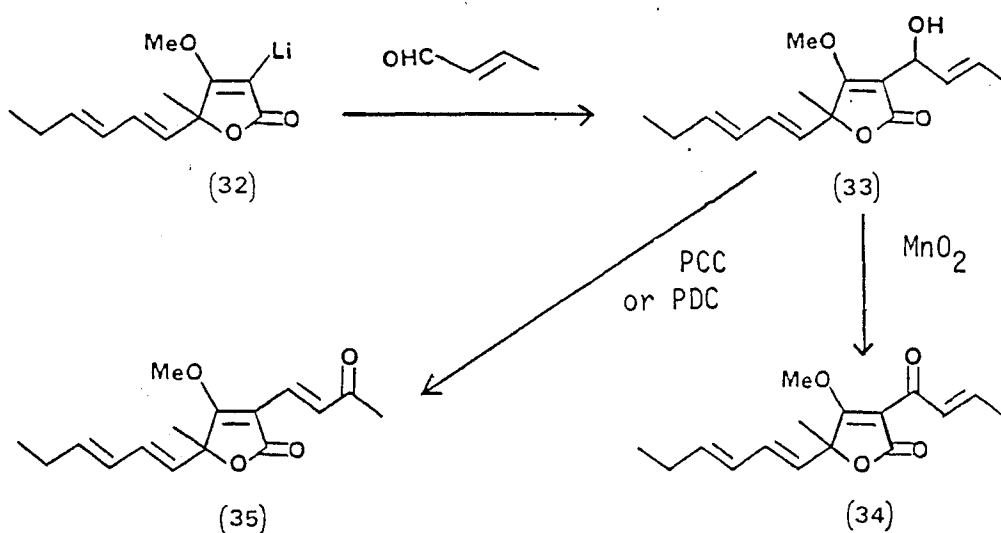


The Claisen route to 3-unsubstituted tetronic acids was initially developed by Haynes²⁶, and Scheme 19 represents a variation on the substantially improved procedure due to Ireland.²⁷

Reactions of the lithio derivative of (28) have been used by all three groups^{17 - 19} to demonstrate that the general structure (31)

previously assigned²⁸ to the aspertetronin (gregatin) group of natural products was erroneous. Hence treatment of (32) with (E)-but-2-enal followed by oxidation with MnO_2 afforded (34), Scheme 20. Substitution of PCC or PDC for the MnO_2 led to oxidation with 1,3-rearrangement, a well known phenomenon, leading to (35).

Scheme 20



Comparison of the spectral data of (34) with that of natural aspertetronin A revealed major differences leading to the conclusion that the aspertetronins possess the isomeric furan-3-one general structure (36).



The method of Schmidt and Pattenden is applicable only to 5,5-disubstituted tetronates, since in monosubstituted cases selective deprotonation at the 3-position is not possible. The method of Yoshii may be applicable to the 5-monosubstituted case provided that metal-bromine exchange occurs preferentially, and that no subsequent equilibration with the 5-lithio isomer occurs.

As in the direct acylation case this method would be applicable to the preparation of chiral 5,5-disubstituted tetronic acids provided that the chiral precursor is available.

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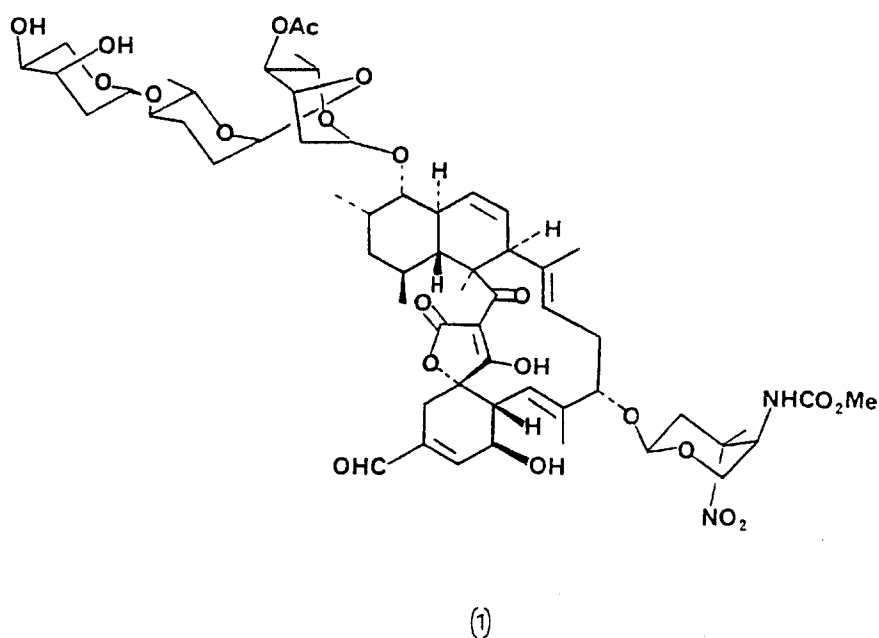
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(c) J.L. Bloomer and F.E. Kappler, *Tetrahedron Lett.*, 1973, 163.
21. F.H. Andresen, A. Svendsen, and P.M. Boll, *Acta Chem. Scand. B*, 1974, 28, 130.

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24. S. Gelin and P. Pollet, *Bull. Soc. Chim. Fr.*, 1975, 307.
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26. L.J. Haynes and A.H. Stanners, *J. Chem. Soc.*, 1956, 4103.
27. R.E. Ireland and W.J. Thompson, *J. Org. Chem.*, 1979, 44, 3041.
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RESULTS AND DISCUSSION

INTRODUCTION

Our interest in the synthesis of 3-acyl tetronic acids stemmed from the disclosure of the diverse biological properties associated with the tetrocarcins, novel antibiotics displaying potent antitumour activity.¹ This group of 7 compounds is exemplified by tetrocarcin B (1).

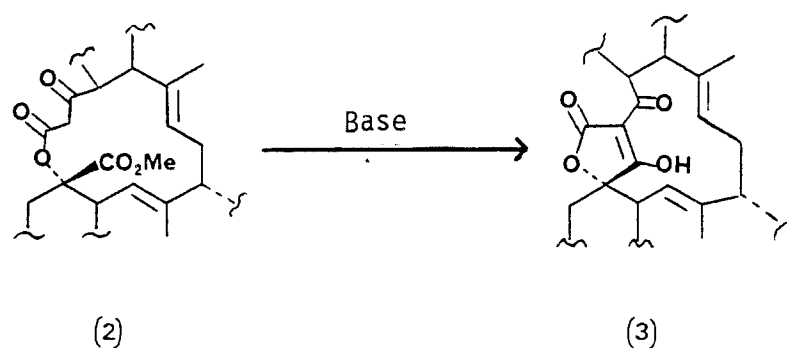


Tetronolide², the architecturally novel aglycone common to all the tetrocarcins, bears a close structural similarity to kijanolide, the aglycone of kijanimicin³ (see Review). Both kijanimicin and the tetrocarcins possess an unusual nitro sugar at C-9, trivially known as α -tetronitroside⁴ (kijanoside).

The challenge of constructing the acyl tetronic moiety within its complex stereochemical framework, together with its biological

activity make tetronolide an attractive synthetic target. It is clear even from casual inspection of the tetronolide molecule that the methodology required to construct the spiro-tetronic acid must accommodate the diverse and potentially labile functionality present elsewhere in the structure. This, together with the requirement that the method should allow synthesis of enantiomerically pure tetronolide, disqualifies most of the known methods for the preparation of 3-acyl tetronic acids. The method which satisfied both of these requirements was the Dieckmann cyclisation method of Lacey⁵ (see Review). We were intrigued as to the possibility of a *trans-annular* Dieckmann cyclisation of a β -keto macrocyclic lactone as the final carbon-carbon bond forming step of the synthesis (Scheme 1).

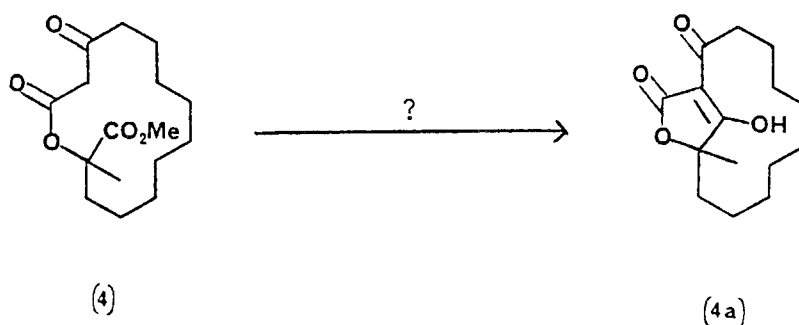
Scheme 1



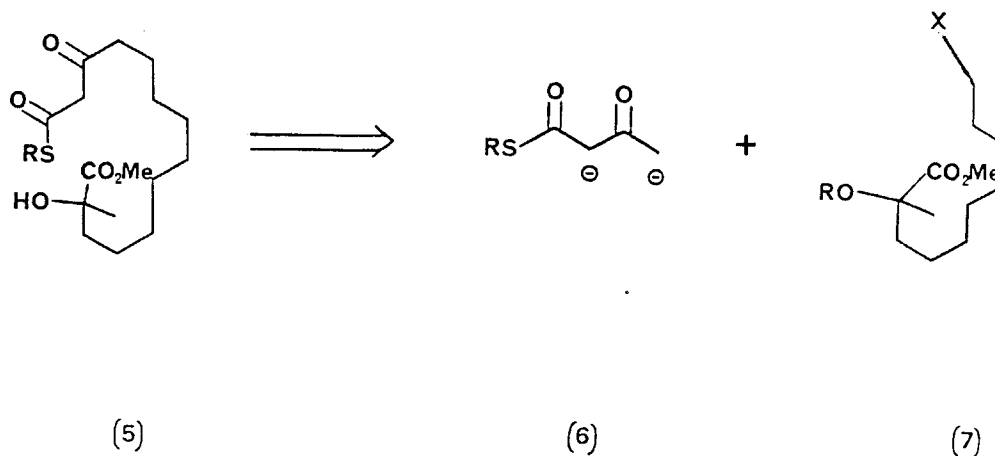
This strategy has several potential advantages: the stereochemistry at C-13 in the precursor (2) defines the stereochemistry at C-13 of the product; the need to carry the tetronic acid nucleus through a lengthy synthetic sequence is avoided, thereby precluding the need to develop protection methodology; and perhaps most important of all it offers a solution to the problem of forming the macrocyclic ring. Efficient methodology for the construction of macrocyclic

lactones is readily available.⁶ Application of this, together with the proposed Dieckmann cyclisation reduces the synthetic problem posed by the tetronolide structure, to one of stereocontrolled construction of a suitable acyclic precursor.⁷

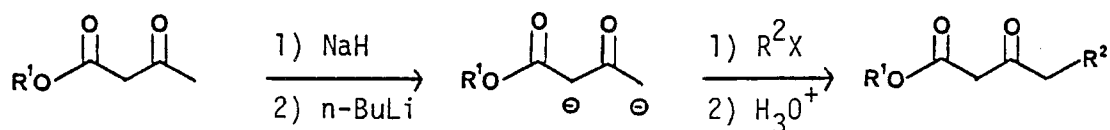
In order to test the feasibility of this Dieckmann cyclisation route it was decided to construct a model system. The simplest possible model was chosen, ie (4)→(4a). The chief problem in preparing (4) is



clearly formation of the 14-membered ring. Of the many methods available for macrolide formation it was decided that the versatile and well-documented method of Masamune, utilising the metal-promoted lactonisation of thioesters, was most suitable.⁸ Thus the required precursor to (4) is the β -ketothioester (5). An attractive and direct way to prepare (5) would be alkylation of the β -ketothioester dianion (6) with the halide (7), Scheme 2. This reaction is analogous to the alkylation of β -ketoesters developed by Weiler.⁹ Such a synthesis of 4-substituted β -ketothioesters would represent a considerable advance on the multi-step procedures previously required.¹⁰ The following sections describe the development of this dianion reaction, its application to the synthesis of (4) and details of the wider synthetic utility of β -ketothioesters.

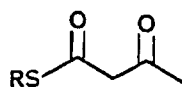
Scheme 2The Preparation and Alkylation of β -ketothioesters

The alkylation of the dianions of β -ketoesters has been shown by Weiler to be a useful synthetic reaction⁹, (Scheme 3).

Scheme 3

The dianion is generated by sequential treatment of the ketoester with sodium hydride and n-BuLi. Quenching with an alkyl halide then leads to the 4-substituted ketoester in good yield.

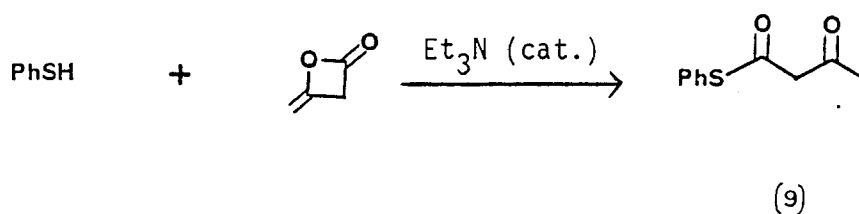
In order to extend this methodology to β -ketothioesters we first required a simple preparation of the unsubstituted β -ketothioester starting material (8).



(8)

The most readily available example of (8) is where $R = \text{Ph}$.¹¹ Hence, treatment of thiophenol with diketene at room temperature afforded the required thioester (9) in essentially quantitative yield (Scheme 4).

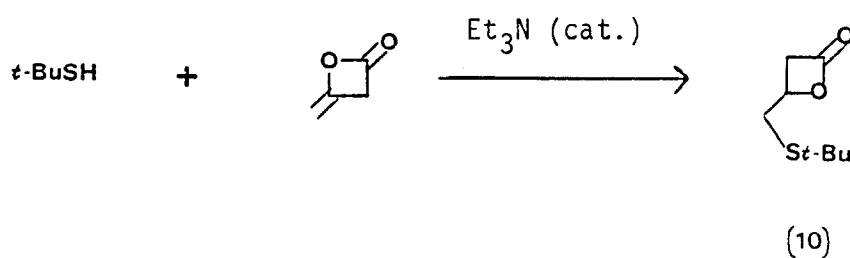
Scheme 4



(9)

In the case of alkyl thiols such as *t*-butyl thiol however, the situation is more complex. Simple treatment of *t*-butyl thiol with diketene in analogous fashion to Scheme 4 leads not to the expected thioester but to the β -lactone derivative (10) by addition of the thiol across the diketene double bond¹² (Scheme 5).

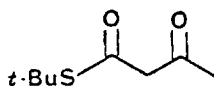
Scheme 5



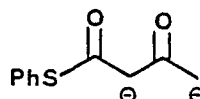
(10)

This result may be rationalised by consideration of Pearson's principle of hard and soft acids and bases.¹³ The less polarisable ("hard") thiophenol sulphur reacts preferentially at the "hard" carbonyl centre of diketene, whereas the more polarisable ("soft") alkyl thiol sulphur reacts with the "soft" diketene double bond.

It has been shown that reaction of *t*-butyl thiol and diketene at reflux leads to a 31% yield of the required thioester (11) after tedious fractional distillation.¹⁴ We sought to avoid this unattractive prospect by making the sulphur atom of *t*-butyl thiol "harder" thus favouring attack at the carbonyl centre of diketene. This was readily achieved by prior conversion of *t*-butyl thiol to the sodium salt with sodium hydride. Quenching of this salt with diketene then led to virtually pure β -ketothioester (11) in 63% yield.



(11)

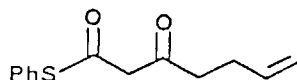


(12)

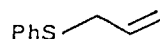
With efficient preparations of (9) and (11) to hand we initially explored the generation of the dianion from (9), since this was more readily available.¹¹

Subjection of (9) to the standard conditions quoted by Weiler for the generation of β -oxoester dianions; i.e. sequential treatment in THF with NaH at 0°C and *n*-BuLi at -20°C,⁹ led to a deep red solution of the dianion (12). Quenching with allyl bromide instantaneously discharged

the colour of the solution, and standard work-up afforded two new compounds by TLC analysis. The two products were separated by chromatography and were shown to be the required substituted thioester (13), formed in 32% yield, and the thioether (14), formed in 28% yield.



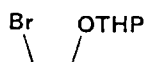
(13)



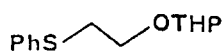
(14)

The formation of (14) must be due to elimination of thiophenolate anion at some stage from the mono- or dianion of (9), followed by trapping with allyl bromide.¹⁵ In order to try and overcome this problem we attempted formation of (12) at lower temperature, reasoning that this should confer greater stability to (12). When (9) was added to two equivalents of LDA at -20° , conditions shown by Weiler⁹ to efficiently generate β -ketoester dianions, the familiar red colour of (12) was observed instantly. Quenching with allyl bromide then led to formation of (13) in 60% yield, but still with appreciable (15-20%) quantities of (14). When this reaction was repeated at -40°C , formation of (12) (as determined by colour change) was significantly slower, and led to a low yield of (13). Eventually it was found that a change of solvent from THF to DME provided the optimum conditions for the reaction. Generation of (12), with two equivalents of LDA at -20°C in DME, followed by quenching with allyl bromide led to isolation of (13) in 68% yield, with only trace amounts of (14). The use of DME was prompted by the observation of Liu *et al.* that β -ketothioesters may be efficiently alkylated at the 2-position in this solvent, although no comparison with equivalent reactions in THF were reported.¹⁶

With this promising result in hand, extension of the alkylation reaction to a range of less reactive alkyl halides was sought. Reaction with the bromide (15), a potential synthon for the synthesis of carolic acid (*vide infra*) led only to recovery of starting material or, if extended reaction times were used, to formation of the unwanted thioether (16) as the only identifiable product.

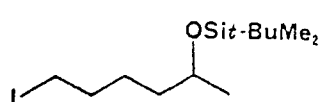


(15)

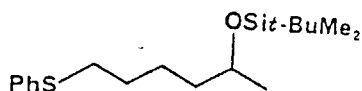


(16)

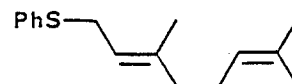
Similar results were experienced in the case of the iodide (17) and also geranyl chloride, the sole new products being the thioethers (18) and (19).



(17)



(18)

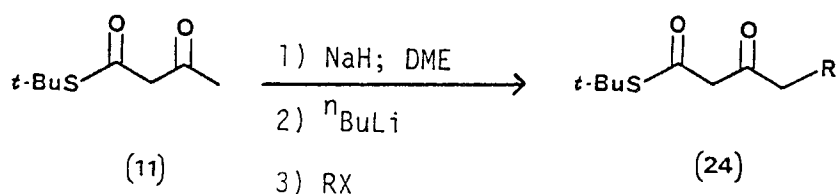


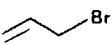
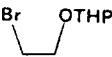
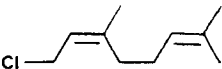
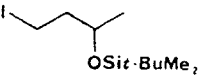
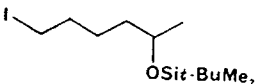
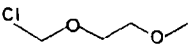
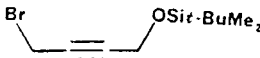
(19)

In all cases extended reaction times (2-3 hours) were used. It thus appears that while (12) is sufficiently stable to react virtually instantaneously with allyl bromide, the elimination process (Scheme 6) occurs more quickly than alkylation with less reactive alkyl halides. The ketene also produced in the elimination presumably decomposes either in the reaction mixture or on work-up, and this is consistent with the large quantities of polymeric material observed in these reactions.

Reversion to the use of NaH/n-BuLi as the bases however provided the key to the reaction. Generation of (20) in DME by sequential treatment with NaH at 0°C and n-BuLi at -30°C followed by quenching with a wide range of alkyl halides afforded the corresponding 4-substituted β -ketothioesters in good yield, with no trace of thioether by-products. Table 1 gives details of a representative sample of results.

Table 1



<u>Entry</u>	<u>RX</u>	<u>Yield %</u>	<u>Product</u>
1	MeI	78 ^a	(25)
2		70	(26)
3		65	(27)
4		60	(28)
5		53	(29)
6		59	(30)
7		36 ^b	(31)
8		43 ^b	(32)

^aReaction performed by C M J Fox

^bNon-optimised

It has also been shown in our laboratory that (20) reacts cleanly and in high yield with aldehydes and some ketones. The alkylated product (25) has also been alkylated further and it was shown that, as expected, the yield of adduct decreases as steric congestion at the reacting centre increases.¹⁷

All the thioesters existed as *keto-enol* mixtures of varying composition. The nature of the 4-substituent had no obvious bearing on this composition.

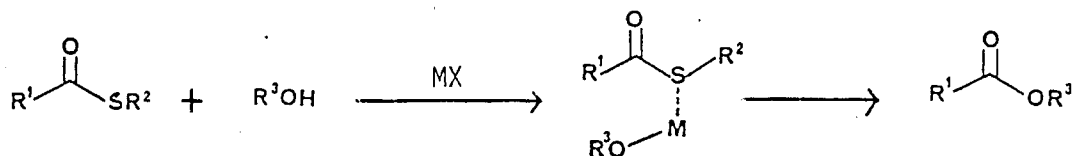
This reaction now clearly constitutes a powerful and direct method of constructing 4-substituted β -ketothioesters in good yield. We next sought to study the transesterification reactions of the β -ketothioesters so produced.

Transesterification/lactonisation reactions of β -ketothioesters

Masamune has demonstrated in a series of elegant syntheses of macrolide antibiotic natural products that the use of *t*-butyl and phenyl thioesters in macrolactonisation reactions constitutes a powerful tool for the synthetic chemist.⁸ The thioesters are stable to a wide variety of common synthetic reagents, and when treated with an appropriate thiophilic metal salt undergo smooth lactonisation with an ω -hydroxy function in good yield. In a transesterification study designed to widen the scope of the reaction, Masamune has also shown that in some cases the structures R^1 and R^2 require modification of the three variables represented by M, X, and R^3 in Scheme 7.¹⁸

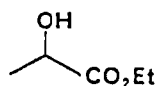
Though the complete mechanism of the reaction is unknown, it is believed to proceed through the intermediate shown in the scheme.

Scheme 7

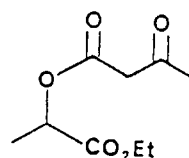


The most evident trend from the results presented is that the more acidic the reacting thiol is, the less thiophilic metal 'M' is suitable for effecting the reaction. Also the effect of the counter-ion X is very marked. For our substituted β -ketothioesters the preferred metal salt is $AgCF_3CO_2$ in the phenylthio case, and in the *t*-butylthio case $Cu^I CF_3CO_2$ is the salt of choice.

We initially studied the transesterification of the phenylthioesters (9) and (13) since the recommended metal salt, $AgCF_3CO_2$ is a stable, commercially available compound. Treatment of a mixture of (9) and ethyl lactate (33) in ether with one equivalent of $AgCF_3CO_2$ led quickly and cleanly to the β -ketoester (34) in near-quantitative yield.

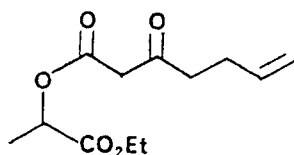


(33)



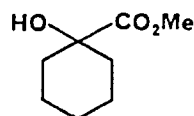
(34)

(34) prepared by this route was identical to material prepared from ethyl lactate and diketene by traditional means.⁵ Substitution of (13) for (9) led to the formation of (35) in a pleasing 94% yield. (35) is clearly a useful precursor to substituted 3-acyl tetronic acids by the Dieckmann cyclisation method of Lacey⁵ (*vide supra*).

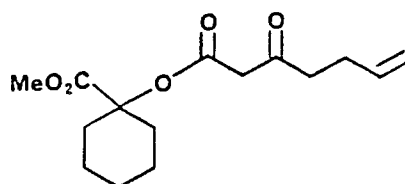


(35)

Similarly, reaction of the α -hydroxy ester (36) with (13) led to the transesterified product (37) in 83% yield.



(36)

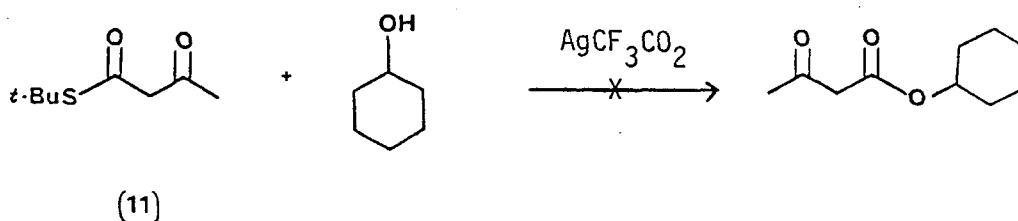


(37)

Attention was next turned to the problem of transesterifying the *t*-butyl thioester produced by the alkylation reaction. Since CuCF_3CO_2 , the recommended thiophilic salt, is air- and moisture-sensitive and, moreover, is not commercially available, an alternative salt more amenable to routine use was sought. Since in some cases Masamune reports that Cu^{II} salts promote the same transesterifications as the corresponding Cu^{I} salts, initial attempts were made with $\text{Cu}(\text{CF}_3\text{CO}_2)_2$ and $\text{Cu}(\text{CF}_3\text{SO}_3)_2$.¹⁸ Treatment of a CH_2Cl_2 solution of ethyl lactate and (11) with $\text{Cu}(\text{CF}_3\text{CO}_2)$ led to products of decomposition only with no trace of the desired (26). A similar reaction in CH_3CN using $\text{Cu}(\text{CF}_3\text{SO}_3)_2$ led to no reaction initially, with decomposition occurring upon addition of more salt. The use of $\text{Tl}(\text{CF}_3\text{CO}_2)_3$ in THF led very rapidly and apparently cleanly to (34), but in a disappointing 36% yield. Finally, reaction with AgCF_3CO_2 in ether containing Na_2HPO_4 buffer led to isolation of an 80% yield of (34). It was found that two full equivalents

of the silver salt were required to force the reaction to completion, and also that the rate was enhanced by using an excess of ethyl lactate. This result is an apparent contradiction of that obtained by Masamune, who observed only recovery of starting materials when (11) was reacted with cyclohexanol using AgCF_3CO_2 ¹⁸ (Scheme 8).

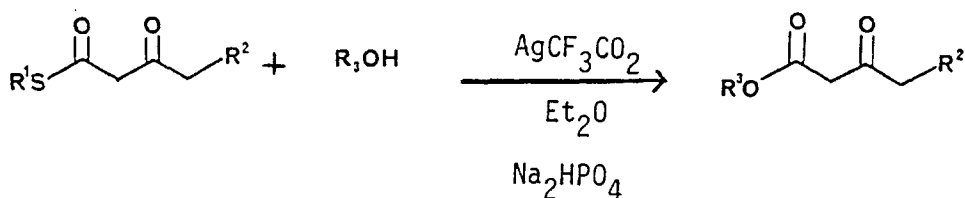
Scheme 8



Thus, preparation of (35) and (37) was also possible from (26) (Table 1, entry 2) and the corresponding hydroxy-esters, albeit less efficiently than from (13) (69 and 76% yields respectively).

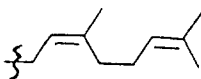
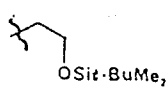
Results of the transesterification reactions using AgCF_3CO_2 are summarised in Table 2.

Table 2



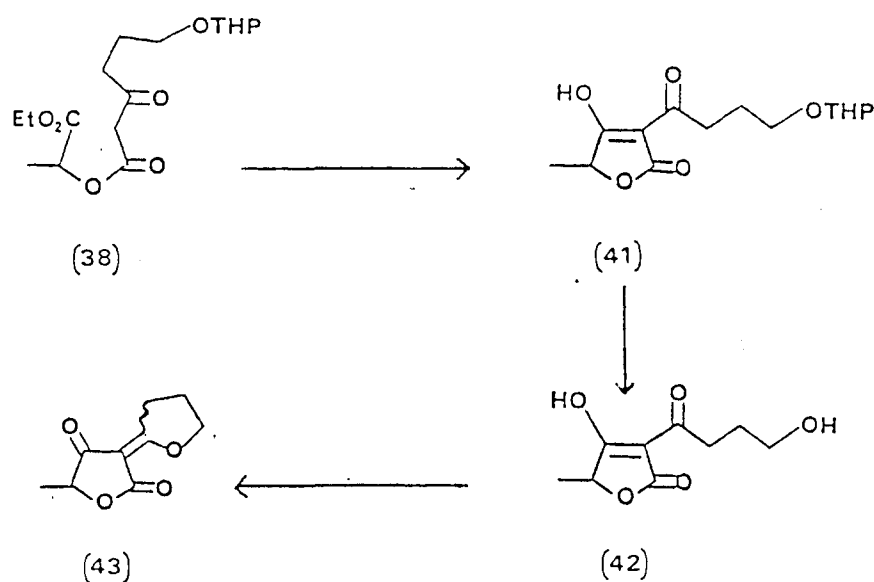
<u>Entry</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>Yield %</u>	<u>Product</u>
1	Ph		(33)	94	(35)
2	Ph		(36)	83	(37)
3	^t Bu		(33)	69	(35)
4	^t Bu		(36)	76	(37)
5	^t Bu		(33)	74	(38)

Table 2 (contd)

Entry	R ¹	R ²	R ³	Yield %	Product
6	<i>t</i> Bu		(36)	73	(39)
7	<i>t</i> Bu		(33)	72	(40)

Entries 5 and 7 of Table 2 constitute preparation of direct precursors to carolic acid (43), a mold metabolite isolated from *Penicillium Charlesii* G. Smith.¹⁹ For example, it can readily be seen that Dieckmann cyclisation of (38) to (41), followed by deprotection would give (42), which is known to dehydrate spontaneously to carolic acid on extraction from aqueous solution²⁰ (Scheme 9).

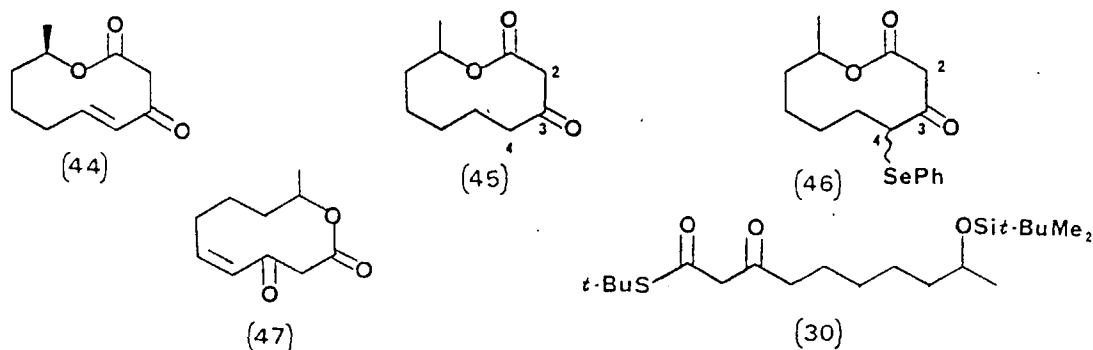
Scheme 9



Using this methodology based on β -ketothioesters we now possessed a two-step route to 3-acyl tetronic acid precursors, as required. We also sought to utilise the ability of thioesters to allow efficient macrolactonisation together with our dianion alkylation reaction to effect a short racemic synthesis of the β -ketolactonic natural product, Diplodialide A (44).²¹

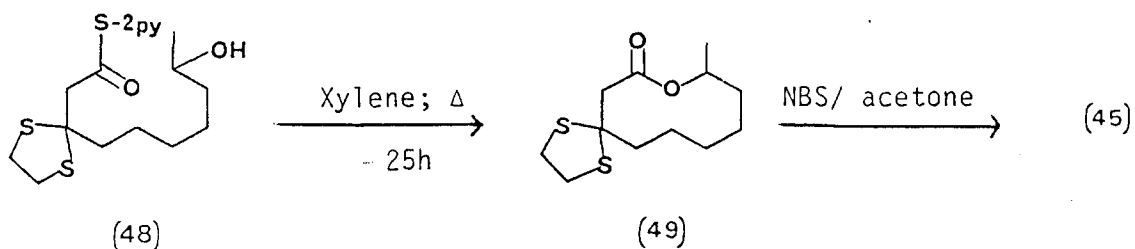
Diplodialide A has been the subject of four successful total syntheses.²²⁻²⁵ Two of these have utilised dihydrodiplodialide A, (45) as a key intermediate.^{22,23} Selenation of (45) at C-4 to give (46) followed by *syn* elimination of the selenoxide furnished the racemic natural product in both cases, although the reported ratios of natural *trans*-diplodialide A to the corresponding *cis* isomer (47) differ.

Our route to (45) and hence to (44) was envisioned to proceed *via* (30), the alkylation product of (11) and a protected 6-iodohexan-2-ol (Table 1, entry 6).



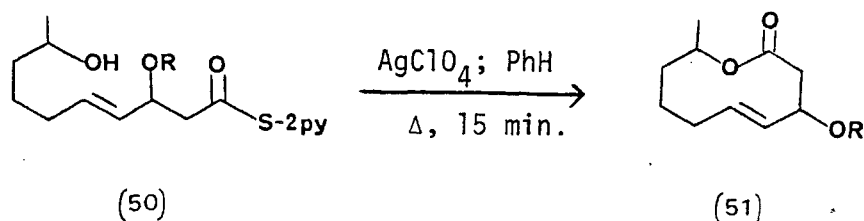
Deprotection and lactonisation was expected to furnish (45) and hence complete a very short formal synthesis of diplodialide A. For the crucial formation of the 10-membered lactone two^{22,24} of the reported syntheses proceed *via* the pyridine-2-thiol "double activation" method of Corey and Nicolaou.²⁶ Wada and Ishida²² cyclised the β -dithiolan precursor (48) under thermal conditions to give (49) in 38% yield which then afforded (45) on deprotection.

Scheme 10

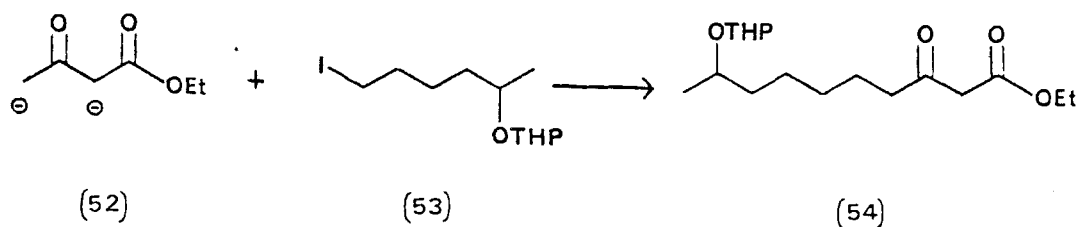


Gerlach *et al.*²⁴ made use of the observation that AgClO_4 promotes the lactonisation reactions of pyridine-2-thiol esters to cyclise (50) to (51) under mild conditions in 67% yield (Scheme 11).

Scheme 11

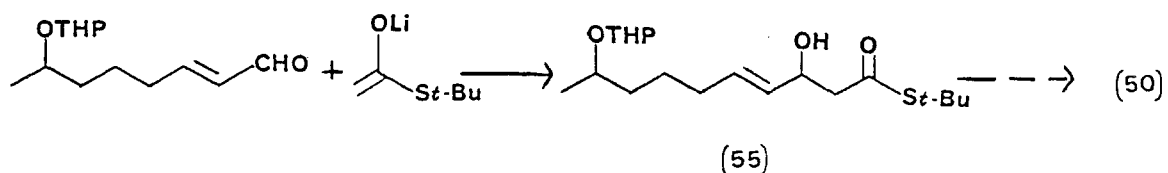


Deprotection and oxidation then furnished the natural product. Further parallels between our proposed route and those of Wada and Gerlach can be seen. Wada prepared (48) *via* alkylation of the dianion (52) with the halide (53) to give (54), in essence the *oxo* derivative of our intermediate (30). Protection of the ketone and conversion to the pyridine-2-thiol ester then afforded (48).



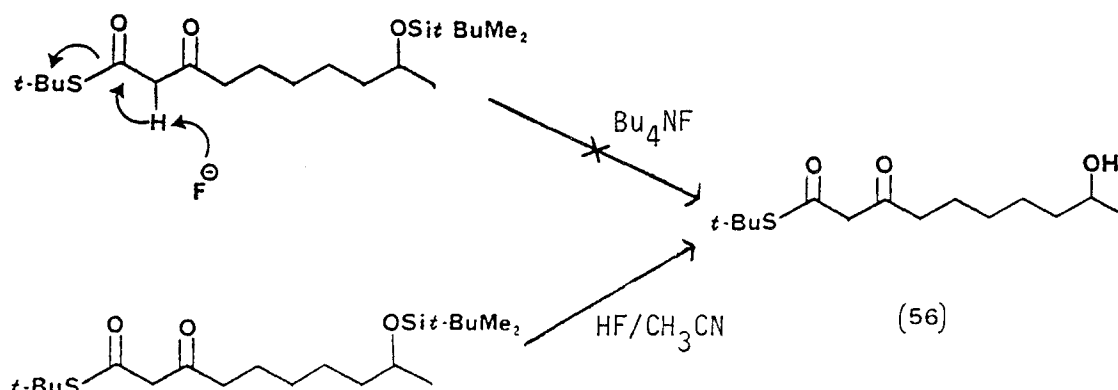
Gerlach actually utilised a *t*-butylthioester (55), prepared by the route shown in Scheme 12. (55) was then hydrolysed and re-esterified to the pyridine-2-thiol ester (50). No mention was made of attempts to directly prepare (50) *via* the enolate of pyridine-2-thiol acetate.

Scheme 12

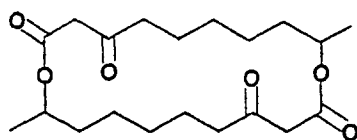


From the above it is readily apparent that the single-step preparation of (30) affords a considerable simplification of the synthetic plan. The necessary deprotection of (30) proved straightforward. Although the use of $n\text{-Bu}_4\text{NF}^{\pm}$ afforded only products of decomposition, presumably *via* elimination of thiolate by the basic reagent, treatment of (30) with $\text{HF}/\text{CH}_3\text{CN}$ ²⁷ rapidly afforded a quantitative yield of (56) (Scheme 13).

Scheme 13



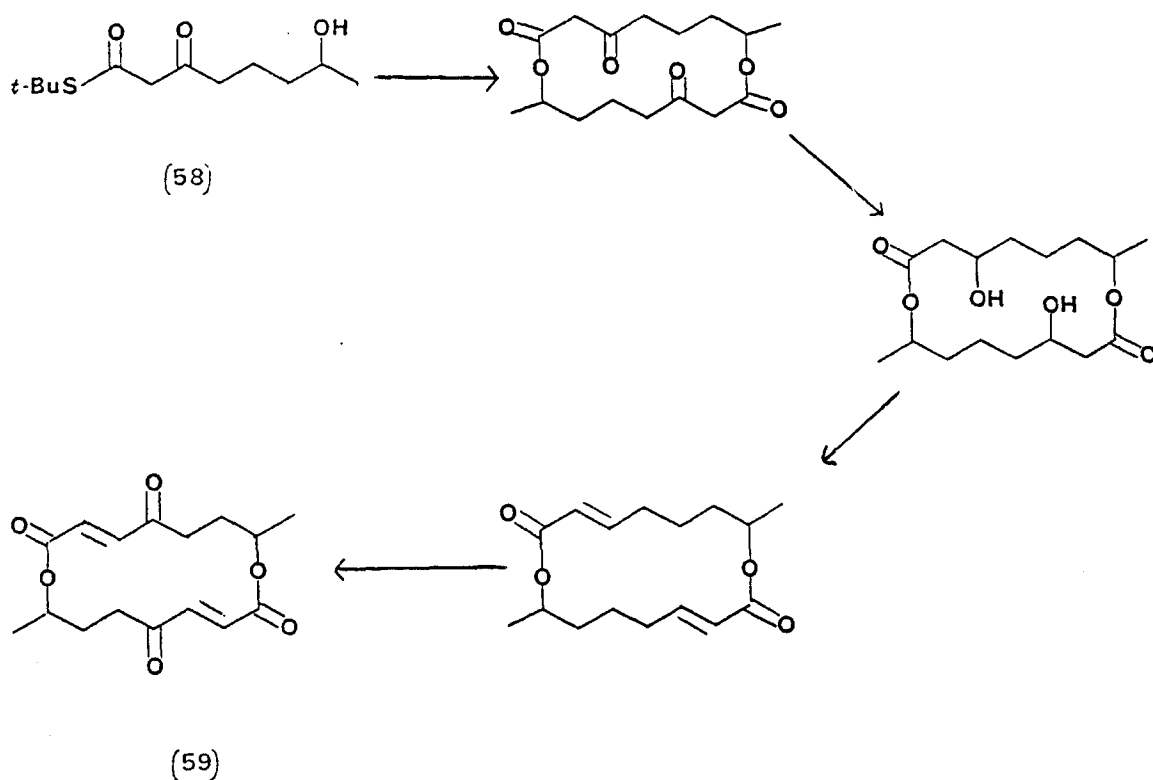
Treatment of (56) with AgCF_3CO_2 in buffered ether or THF led to rapid consumption of starting material, but no new compound was observed by TLC analysis. However, when the reaction was repeated in dry buffered CH_2Cl_2 using freshly prepared CuCF_3CO_2 , clean formation of a single new compound took place. This compound exhibited essentially the same ^1H nmr spectrum as that reported for (45), but after chromatography the compound crystallised, whereas (45) is reported to be an oil. Furthermore, examination of the high field ^1H nmr spectrum revealed the presence of diastereomers, which is, of course, impossible for (45). The suspicion that this new compound was in fact the dimer (57) was confirmed by mass spectroscopic evidence.



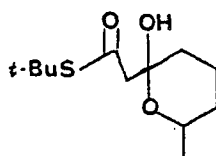
(57)

The yield of (57) realised varied between 25 and 40%. It has subsequently been shown that by increasing the reaction concentration, (45) may be isolated from the reaction mixture, but that (57) is always a significant product.¹⁷ This result, though disappointing in terms of a synthesis of diplodialide A, was nonetheless intriguing, since compound (57) bears structural similarities to pyrenophorin (59).²⁸ If the dimerisation reaction of (56) could be applied to the homologue (58), a reduction, elimination and oxidation sequence would lead to the natural product (Scheme 14).

Scheme 14

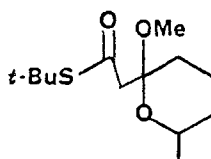


Consequently (29) (Table 1, entry 5) was subjected to the deprotection conditions previously used for (30). Unfortunately only products of decomposition were obtained with no trace of (58). This is readily rationalised by consideration of the 1,5-relationship of the ketone and hydroxy groups in (58). This relationship would favour (58) existing as cyclic hemiketal (60) and this is presumably unstable to the reaction conditions.



(60)

Support for this hypothesis came when it was shown that if the hydrolysis was carried out in acidic aqueous methanol, the anomeric methoxy compound (60a) could be isolated.

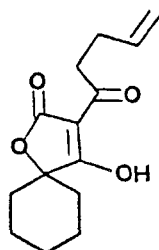


(60a)

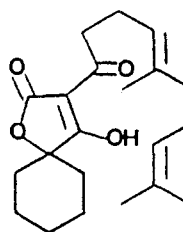
In view of this disappointing result attempts at pyrenophorin synthesis *via* this route were abandoned. Further work is continuing in our laboratory to extend the utility of the β -ketothioester transesterification/lactonisation reaction.

Studies on the Dieckmann cyclisation route to 3-acyl tetronic acids

With a short and efficient synthesis of substituted β -ketoester of α -hydroxy esters available we next sought to effect their cyclisation to afford the desired 3-acyl tetronic acids. Lacey⁵ has reported that in the case of β -ketoesters derived from disubstituted α -hydroxy esters the cyclisation is efficiently carried out by treatment with alkali metal alkoxides. Thus, treatment of (37) with sodium methoxide in refluxing benzene/methanol afforded the allylated acyl tetronic acid (61) in 95% yield. The ¹H nmr spectrum of (62) exhibited at δ 11.34 the characteristic low field signal due to the -OH resonance. Similarly, treatment of (39) under identical conditions led to the formation of (62) in 65% yield.



(61)

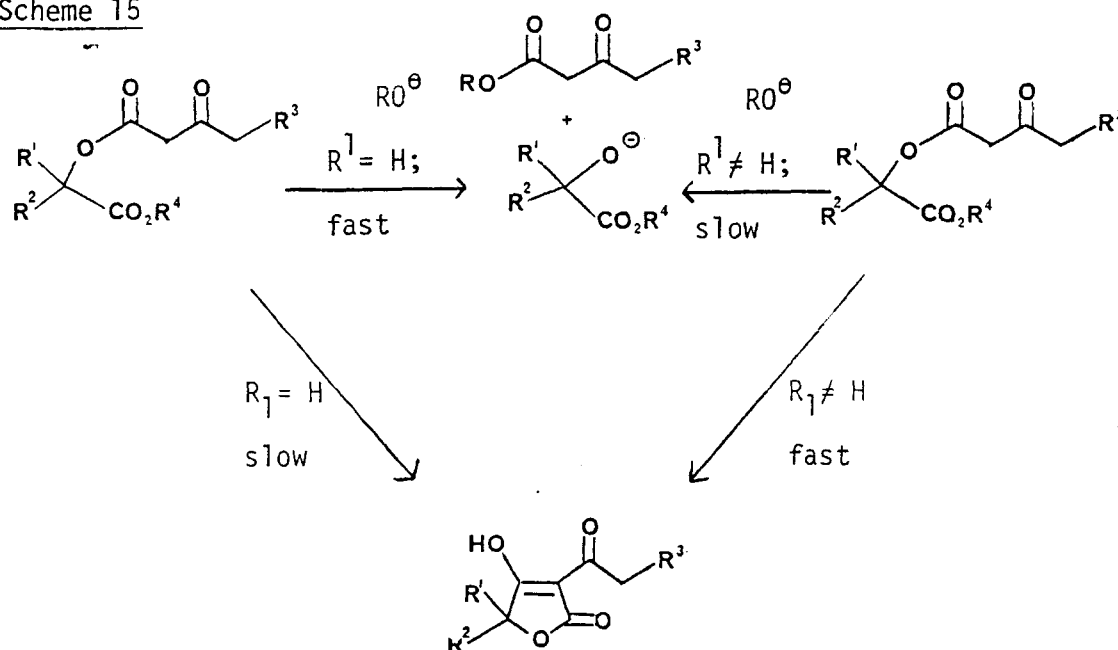


(62)

It is interesting to note that (62), which was surprisingly unstable to storage at room temperature, can be considered a *seco* compound for the tetronolide macrolide structure.

In the case of β -ketoesters derived from monosubstituted α -hydroxy esters Lacey noted that yields of tetronic acids were considerably lower than in the disubstituted case. This was attributed to competing alcoholysis of the β -ketoester moiety. This alcoholysis occurs at a rate greater than that of cyclisation even when hindered tertiary alkoxides are used, leading to greatly reduced yields. In the disubstituted case alcoholysis is much slower at the hindered ester centre and cyclisation is thus the preferred pathway (Scheme 15).

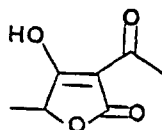
Scheme 15



When the acetoacetate of ethyl lactate (34) was treated with potassium *t*-butoxide as described by Lacey, cyclisation occurred to give a poor yield of the corresponding tetronic acid (63). Furthermore on a small scale the crude product was very difficult to purify, a common problem with 3-acyl tetronic acids. The acidity of these compounds leads to only very poor recovery of material from conventional silica-gel chromatography, even when very polar eluants are used (eg methanol). The usual method of purification is by recrystallisation, but on a small scale (*ca.* 100 mg) this is often impractical due to the high solubility of the products in a wide range of solvents. In the case of the tetronic acids produced from precursors such as (35) the products were often low-melting solids and crystallisation was sometimes difficult to induce at all. All this, together with the low thermal stability of some of the products made purification of small quantities of compound very difficult indeed.

In order to circumvent the low yields of tetronic acids obtained from mono-substituted α -hydroxy esters we examined the use of alternative bases for the cyclisation, chosen to hopefully avoid the alcoholysis side-reaction.

When (34) was treated with NaH in THF, a green solution of the mono-anion was produced, but no cyclisation to (63) was observed, either at room temperature or at reflux.



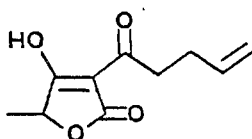
(63)

Use of NaH in dry DMF led only to decomposition of the starting material, as did KO^tBu in DMF. Treatment with K_2CO_3 in DMF, a procedure known²⁹ to allow alkylation at the 2-position of β -ketoesters gave only recovered starting material even after one week. When (34) was reacted with two equivalents of $n\text{-Bu}_4\text{NF}$ however, starting material was rapidly (2h) consumed to give a single polar product (TLC). Work-up with hydrochloric acid followed by extraction with ether afforded crystalline (63). Recrystallisation from ether gave analytically pure (63) in 85% yield. Factors worthy of note in this fluoride-induced cyclisation are the mild conditions and remarkably rapid reaction time. It was also found that with less than two full equivalents of Bu_4NF the cyclisation did not go to completion, even after prolonged reaction. In addition, the ease of reaction varied somewhat depending upon the batch of $n\text{-Bu}_4\text{NF}$ used, although in all cases ostensibly identical 1M solutions in THF supplied by the same manufacturer³⁰ were employed.

When the cyclisation of (34) prepared from optically pure ethyl-(S)-lactate was performed the resultant product had mp $70\text{--}72^\circ\text{C}$, with

$[\alpha]_D$ ($C = 0.74$, H_2O) $- 70.1^\circ C$. This compares favourably with the product prepared previously of mp $63-66^\circ C$, $[\alpha]_D$ ($C = 0.205$, H_2O) $- 58.3^\circ C$, claimed to be of high optical purity.³¹

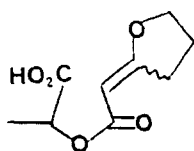
To investigate this fluoride-induced cyclisation further the allylated compound (35) was treated under the same conditions as (34). Cyclisation occurred to give (64) as a low-melting solid in 70% yield.



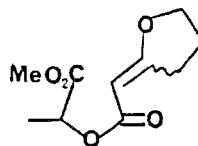
(64)

(64) was thermally unstable which made recrystallisation impossible, though the crude product was of $>95\%$ purity by nmr.

With this efficient cyclisation in hand we sought to synthesise the natural product carolic acid by cyclisation of the precursor (38) (*vide supra*, Scheme 9). As expected, treatment of (38) with $tBuOK/tBuOH$ in refluxing benzene did not efficiently lead to cyclisation. Interestingly, when (38) was treated with five equivalents of $KOtBu$ in $tBuOH$ at room temperature, rapid (5 min) formation of a single polar product was observed. After treatment with acidic methanol to effect THP-deprotection, the low-field ^1H -nmr spectrum appeared to be consistent with the formation of (42), the hydrate of carolic acid. However, high-field decoupling experiments on this compound, together with decoupling data on the product obtained by treatment with diazomethane revealed that the compound was not (42), but in fact the tetrahydrofuran (65). The diazomethane product was thus (66).



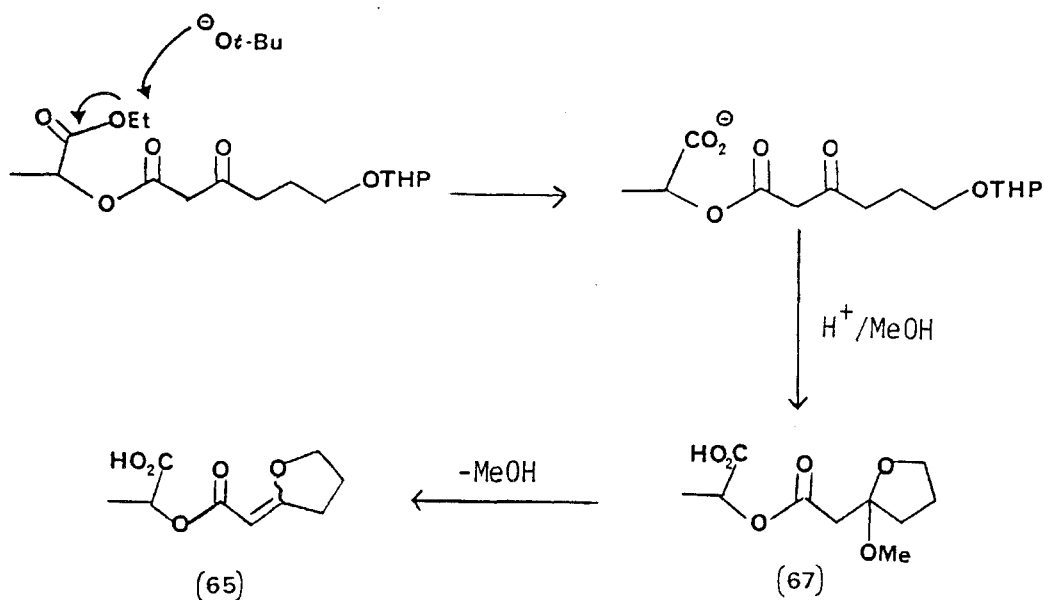
(65)



(66)

Although the high-field spectra showed that (65) was a single isomer about the olefinic bond, the geometry of the bond was not determined. (65) must be formed by a remarkably facile alkyl-oxygen ester cleavage reaction caused by the excess KO^tBu (Scheme 16).

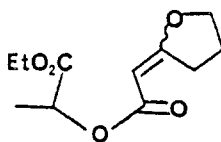
Scheme 16



The deprotection presumably then led to the cyclic ketal (67) which loses methanol to form (65).

When (38) was treated with two equivalents of $n\text{-Bu}_4\text{NF}$ overnight, cyclisation occurred as expected. Acidic work-up did not afford (41) but led to isolation of carolic acid directly in 70% yield. When (38), derived from ethyl-(S)-lactate was used, the synthetic carolic acid was identical in all respects to the natural product except in direction of optical rotation, since natural carolic acid has the (R) configuration.³²

We also hoped that treatment of (40) using three equivalents of $n\text{-Bu}_4\text{NF}$ would induce cyclisation with concomitant deprotection leading to carolic acid. This however relied upon the rate of cyclisation being much greater than that of the deprotection reaction. In fact it was found that the relative rates of cyclisation and deprotection depended upon the batch of $n\text{-Bu}_4\text{NF}$ used. When the reaction worked well, a 70% yield of carolic acid, identical with that obtained from (38) was obtained. However on several occasions the only product isolated was (68), the ethyl isomer of (65), arising from deprotection of (40). As expected, (68) did not cyclise to give the tetronic acid.



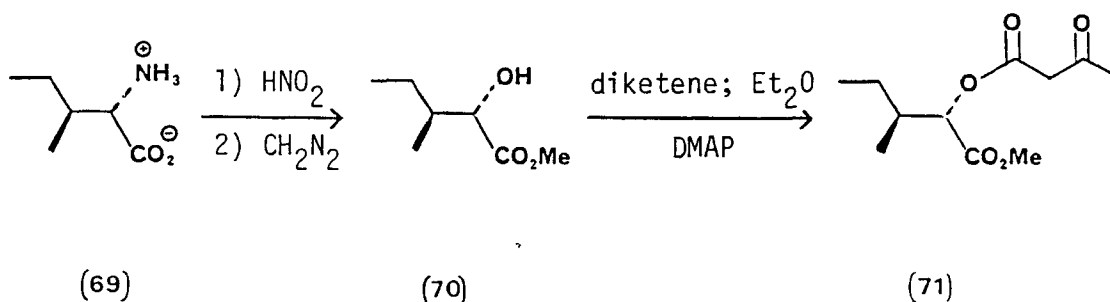
(68)

Thus the method of choice for synthesis of carolic acid was *via* (38). This constituted a 3-step synthesis of (S)-carolic acid in 34% overall yield, a considerable improvement on other syntheses.^{33,34}

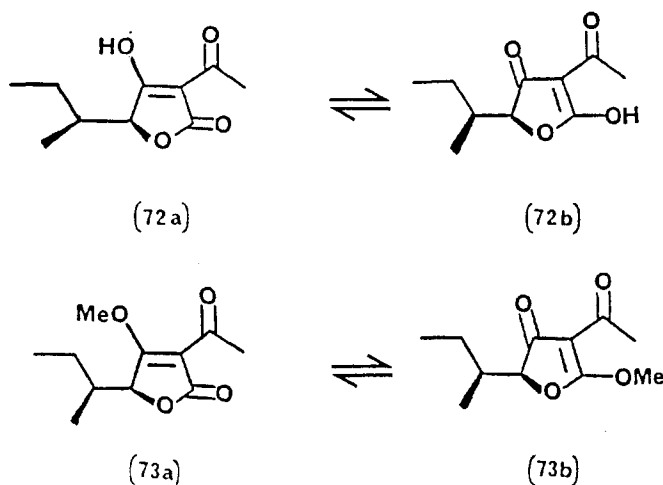
In an attempt to measure directly the amount of epimerisation occurring at the C-5 position of monosubstituted tetronic acids during $n\text{-Bu}_4\text{NF}$ -promoted cyclisation, a suitable substrate containing an additional chiral centre to that at C-5 was required. This would allow direct observation of diastereomers in the ^1H nmr spectrum, and measurement of the diastereomer ratio would give the extent of epimerisation.

Hence, optically pure *iso*-leucine (69) was diazotized by the procedure of Mori³⁵ to give diastereomerically pure (70) in 74% yield after diazomethane work-up (Scheme 17).

Scheme 17



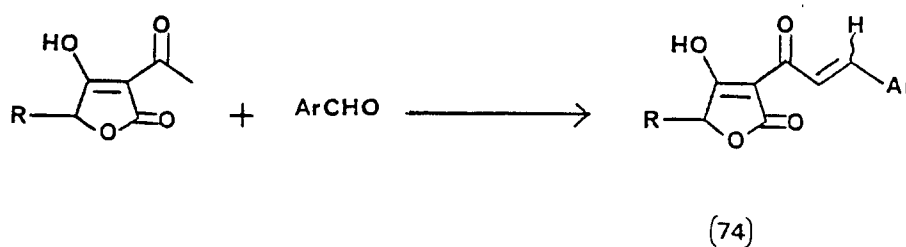
Formation of the β -ketoester (71) was straightforwardly achieved by treatment of (70) with diketene in ether using DMAP as catalyst.³⁶ Cyclisation of (71) to the tetronic acid occurred readily on treatment with *n*-Bu₄NF, affording (72) as a thick oil in 65% yield. (72) defied all attempts at crystallisation. The ¹H nmr spectrum of (72) was broadened by the presence of the tautomeric equilibrium between (72a) and (72b), a well-known phenomenon in 5-monosubstituted tetronic acids³⁷, preventing direct measurement of any diastereomer ratio. Treatment of (72) with diazomethane afforded the methyl "esters" (73). The ratio of (73a) and (73b) was 1:1 and *ca.* 3:1 on the two occasions the reaction was performed. Examination of the ¹H nmr spectrum of these mixtures showed that epimerisation had occurred to an extent of <15%, assuming that the diastereomers reacted in identical manner with diazomethane. The assignment of the ¹H nmr spectrum of the diastereomers was confirmed by repeating the preparation of (73) using partially racemized (70).



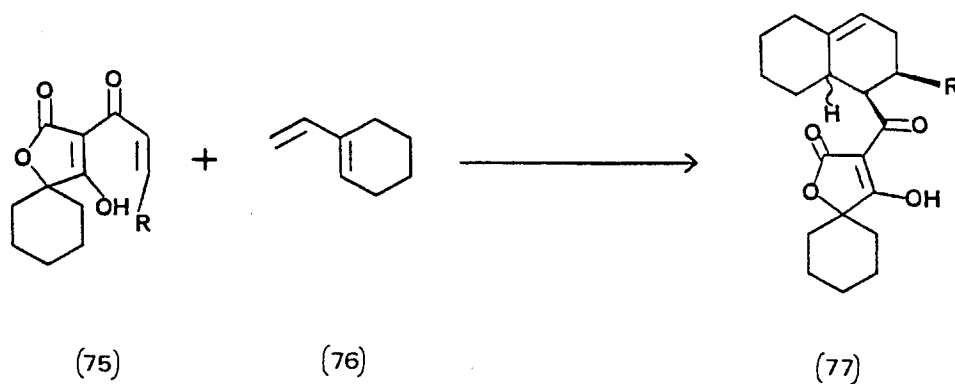
Further studies on 3-acyl tetronic acids

Turner³⁸ has reported that reaction of aromatic aldehydes with 3-acetyl tetronic acids in methanolic HCl leads to the condensation product (74) (Scheme 18).

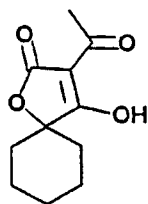
Scheme 18



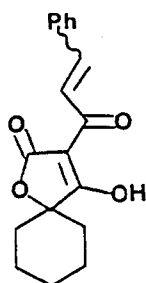
The electron-deficient nature of the olefin in (74) would be expected to make it a reactive dienophile in a Diels-Alder reaction. Reaction of an olefin such as (75) with a diene of type (76) would appear to be an attractive route to developing models of the decalin ring system of tetronolide eg (77).⁷



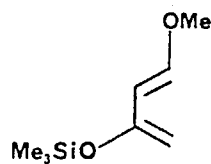
Hence reaction of (78), readily prepared by the method of Lacey⁵, with benzaldehyde in methanolic HCl led to a 90% yield of the adduct (79). Unfortunately replacement of benzaldehyde with straight-chain aldehydes such as geranial or heptanal led only to decomposition of the aldehyde, perhaps not surprisingly.



(78)



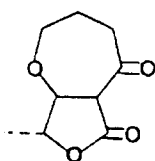
(79)



(80)

Reaction of (79) with the Danishefsky diene³⁹ (80) led to rapid decomposition of the diene, presumably due to the acidity of (79). No further attempts at Diels-Alder reactions of (79) were made.

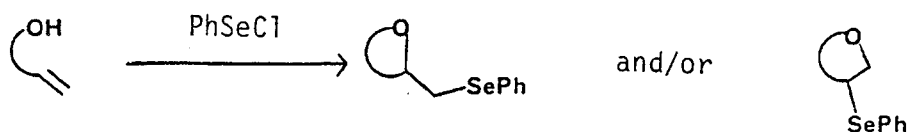
Before the definitive structural revision work of Boll *et al.*⁴⁰, carolic acid (43) was assumed to have the novel ether structure (81).



(81)

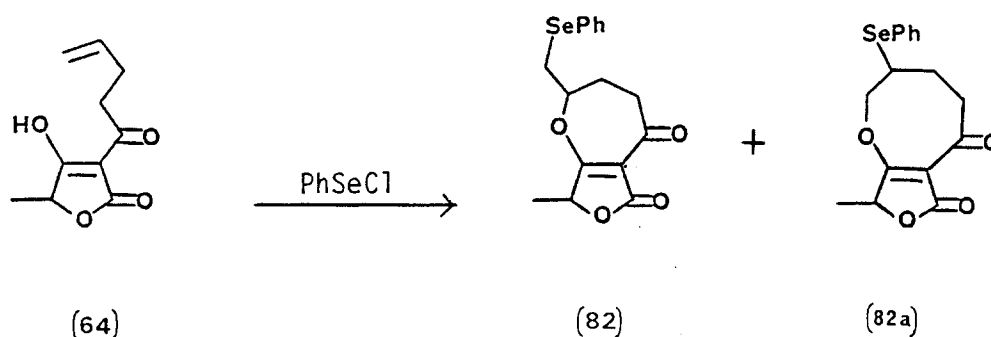
In an attempt to construct the ring system of (81), the selenation reaction of compound (64) was investigated. Nicolaou⁴¹ has demonstrated that selenium cyclisations to form ethers is a facile process, even for ring sizes which are not usually easy to prepare (Scheme 19).

Scheme 19



Thus it was hoped that treatment of (64) with PhSeCl would lead to the seleno-ether (82). Consideration of Baldwin's Rules⁴² suggested that concomitant formation of (82a) was also possible (Scheme 20).

Scheme 20

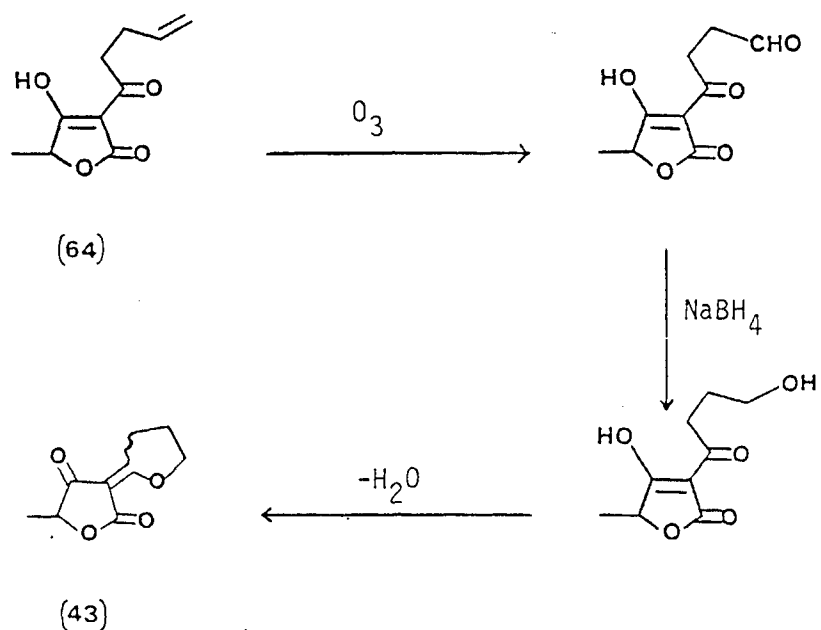


When PhSeCl was added to a solution of (64) in CDCl₃ in an nmr tube, rapid consumption of starting material was observed, with loss of the olefinic resonances. However, the spectrum of the reaction mixture displayed many non-assignable resonances indicating that even if (82) or (82a) was formed, neither were major products. TLC analysis of the reaction mixture also indicated the presence of multiple products. Accordingly the seleno-etherification reaction was not pursued further.

As an alternative route to carolic acid (43) it was hoped that ozonolysis of (64) with sodium borohydride work-up would furnish the natural product (Scheme 21).

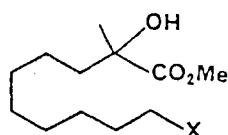
When ozone was bubbled through a methanol solution of (64) an instantaneous blue colouration was observed and TLC indicated absence of (64). Addition of sodium borohydride followed by acid work-up afforded no identifiable product. The instantaneous blue colouration perhaps indicates that the tetronic acid nucleus of (64) is unstable to ozone, since ozonolysis of the olefin would be expected to be relatively slow. Lack of material precluded further investigation of the reactions of (64).

Scheme 21



Attempted synthesis of a model for the tetronolide ring structure

For the preparation of the model compound (4) (*vide supra*) via the β -ketothioester methodology the required alkyl halide is (83), where X is Br or I.

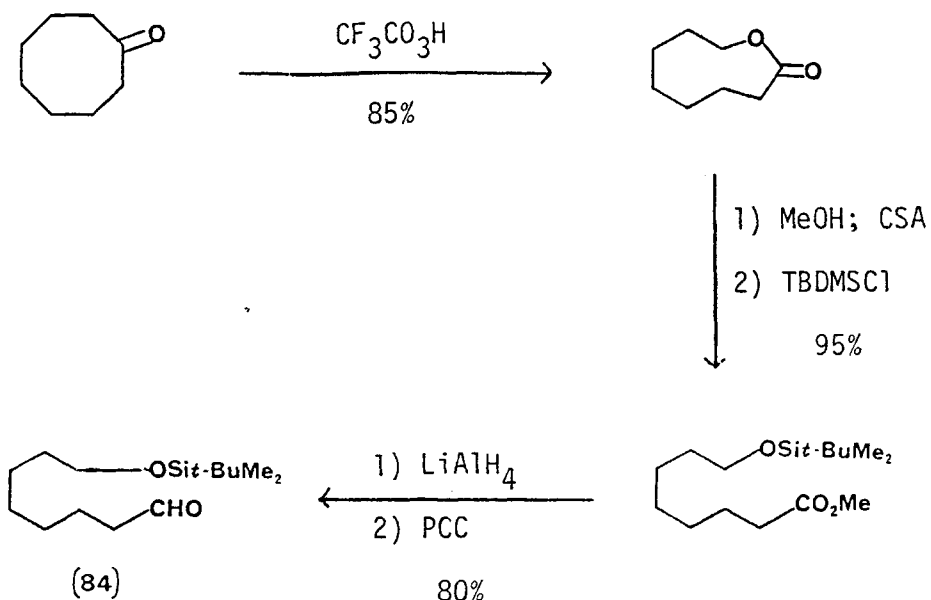


(83)

Ten-carbon synthons functionalised at suitable positions for the synthesis of (83) are not readily commercially available. The required C_{10} chain was however prepared in straightforward fashion by homologation of an eight-carbon precursor.

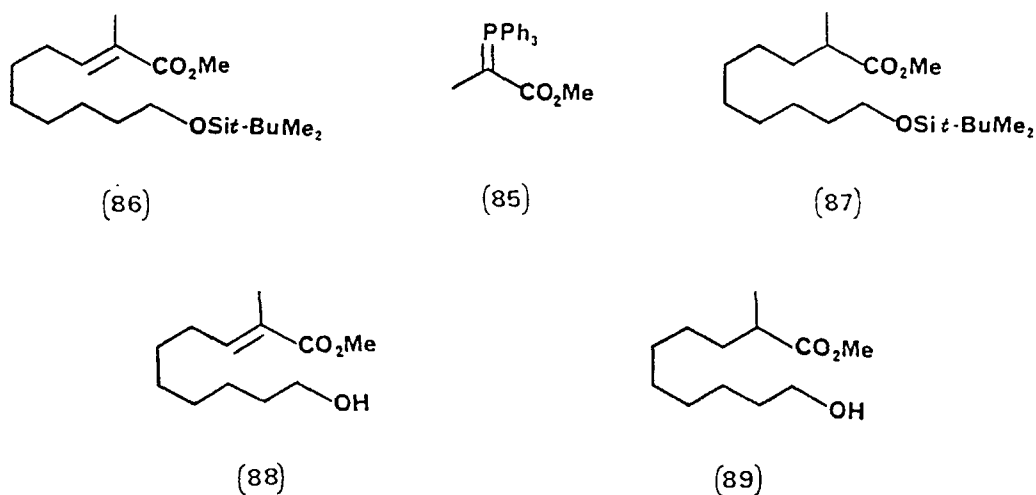
Hence, the protected form of 8-hydroxy octanal⁴³ (84) was routinely prepared according to Scheme 22.

Scheme 22

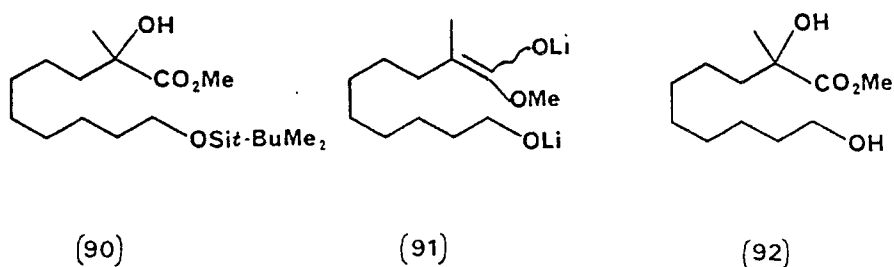


Though the route is lengthy for such a simple synthon, all the steps were easy to perform and applicable to multi-gram scale. Thus by this route (84) was available in 5g quantities in 65% overall yield from cyclooctanone.

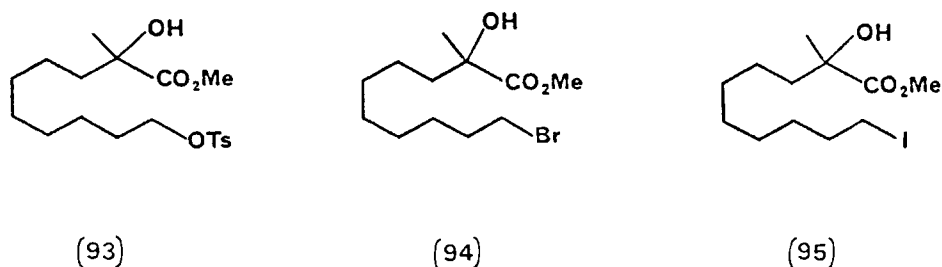
Reaction of (84) with the stabilized phosphorane (85)⁴⁴ proceeded smoothly in 76% yield to afford (86). Hydrogenation of (86) under standard conditions then gave (87) in near-quantitative yield. Alternatively deprotection of (86) to (88) with $n\text{-Bu}_4\text{NF}$ followed by hydrogenation produced (89) in 93% yield.



The hydroxylation reactions of (87) and (89) were then studied. It has been shown⁴⁵ that quenching of enolates formed at tertiary centres by molecular oxygen leads to good yields of the tertiary alcohol after reduction of the intermediate hydroperoxide. Thus, when the enolate of (87), generated by treatment with LDA at -78° to -40°C , was quenched at -40°C with dry oxygen, a 68% yield of (90) was realised. More routinely (89) was treated with two equivalents of LDA at -78°C to afford the dianion (91) before quenching with O_2 to give (92) in 83% yield. Formation of (91) was readily monitored by observing the formation of a milky suspension of the poorly soluble dianion.

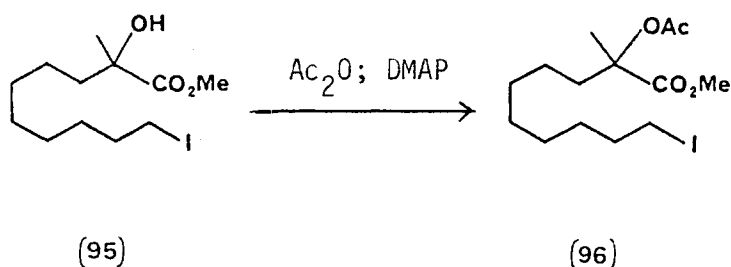


In both hydroxylation reactions the initially formed hydroperoxide was reduced with PPh_3 , since work-up with NaHSO_3 as recommended in the literature⁴⁵ afforded incomplete reduction. Selective tosylation of the primary hydroxyl function of (92) proceeded smoothly to give (93) in 84% yield. Halide displacement of (93) was accomplished with LiBr in THF, or more usually NaI in acetone, to form (94) and (95) in 98% and 96% yields respectively.

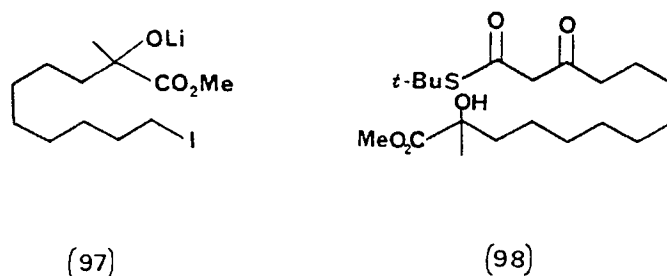


The hydroxyl function of (95) could not be protected as either the TBDMS or THP ether under standard conditions, due to its hindered nature.

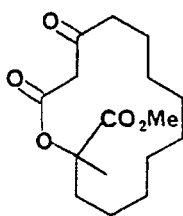
Acetylation under forcing conditions however gave the acetate (96) in 62% yield.



Surprisingly, treatment of (96) with the β -ketothioester dianion (20) afforded only recovered (95), presumably due to preferential attack of the dianion at the acetate centre. Treatment of the dianion with the lithioalkoxide (97), generated by treatment of (95) with LDA at -78°C , proceeded smoothly however to give (98) in 56% yield.

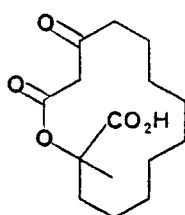


Exposure of (98) to a buffered, ethereal solution of AgCF_3CO_2 led only to products of decomposition, as expected from the result obtained with the dipiodalide precursor (56). As in that case, the use of *freshly prepared* CuCF_3CO_2 in CH_2Cl_2 proved crucial to the success of the reaction. Treatment of (98) with excess CuCF_3CO_2 in CH_2Cl_2 promoted smooth lactonisation affording (4) as sole product in 38-40% yield. When older samples of CuCF_3CO_2 were used the yield of (4) dropped dramatically to *ca.* 20%. That (4) possessed the monomeric structure shown, and not that of the corresponding dimer was clear from mass spectroscopic evidence.



(4)

Treatment of (4) with an excess of $n\text{-Bu}_4\text{NF}$ in THF led only to recovery of starting material, even on prolonged exposure. Reaction with one equivalent of KO^tBu in refluxing benzene containing catalytic $^t\text{BuOH}$ gave the same disappointing result. Use of excess KO^tBu led to formation of a single polar product by TLC. This proved, however, not to be the desired tetronic acid (4a), but the acid (99), produced by cleavage of the methyl ester, a process previously observed in the conversion of (38) to (65). Diazomethane treatment of (99) gave a sample of (4) identical to that prepared previously, confirming the structural assignment of (99).



(99)

The mono-anion of (4) was readily generated by treatment with NaH in toluene containing catalytic methanol. Heating of this solution to reflux, even for extended periods did not effect Dieckmann cyclisation of (4). Replacement of the toluene with xylene led to the same negative result. Lack of time and material precluded further experimentation on

(4) though related studies are continuing in our laboratory.

It thus appears that even under forcing conditions (4) does not cyclise to the tetronic acid (4a) to any appreciable extent. This may be due to (4) existing in some conformation in which the reacting centres are insufficiently close in space for the reaction to occur. Alternatively adoption of the transition state conformation necessary for cyclisation may induce sufficient strain in the macrocyclic ring structure such that cyclisation becomes energetically unfavourable. Neither of these two possibilities is readily apparent from consideration of simple molecular models of structures (4) and (4a).

Minimum-energy calculations are currently being performed in order to try to predict the preferred conformations of (4) and hopefully to rationalise its failure to cyclise in the desired manner. Results from these calculations have not yet been received⁴⁶.

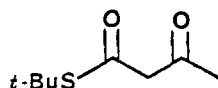
Of course it is quite likely that in the real tetronolide system, precursor (2) will adopt a conformation very different from that of (4), but in the light of the cyclisation studies on (4) it would be an act of remarkable confidence to prepare (2), *via* a long synthetic sequence, without further precedent for the *trans-annular* Dieckmann cyclisation.

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotation measurements were conducted using a Perkin-Elmer 141 polarimeter at ambient temperature. Infra-red spectra were recorded on Perkin-Elmer 298 and 983G grating infra-red spectrophotometers using a thin film or solution in chloroform. ^1H n.m.r. spectra were obtained for solutions in CDCl_3 using tetramethylsilane or residual CHCl_3 as internal standard, and were recorded at 60 MHz on a Varian EM-360A, at 90 MHz on a Jeol FX 90Q or at 250 MHz on a Bruker WM-250 machine. Mass spectra were determined with a VG micromass 7070 B instrument. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory.

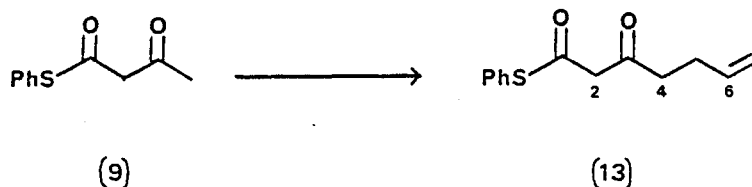
Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel F_{254} plates. Preparative chromatography was carried out on columns of Merck Kieselgel 60 (230-400 mesh).

Petrol refers to the fraction with b.p. $40-60^\circ$. All solvents were purified by standard techniques. Solutions were dried over anhydrous sodium sulphate and evaporated with a rotary evaporator, followed by static evaporation with an oil pump.

1) Preparation of *tert*-Butyl 3-oxobutanethioate (11)

(11)

To a suspension of sodium hydride (1.76g of a 50% dispersion in oil, 36.7 mmol), previously washed with dry petrol (2 x 25 ml), in THF (50 ml), cooled to 0°C, was added slowly a solution of *tert*-butyl thiol (3.0g, 33.3 mmol) in THF (5 ml). Upon completion of addition a white precipitate was observed. After stirring for 10 min a solution of diketene (2.8g, 33.3 mmol) in THF (5 ml) was added slowly. The solution was stirred for 15 min and quenched with saturated NH₄Cl solution (20 ml). The mixture was extracted into ether (250 ml) and the ethereal extracts were dried (Na₂SO₄), evaporated, and chromatographed (5% ether-petrol) to yield *tert*-butyl-3-oxobutanethioate (3.62g, 63%) as a pink oil with properties identical to those previously reported.

2) Preparation of Phenyl 3-oxo-hept-6-enethioate (13)

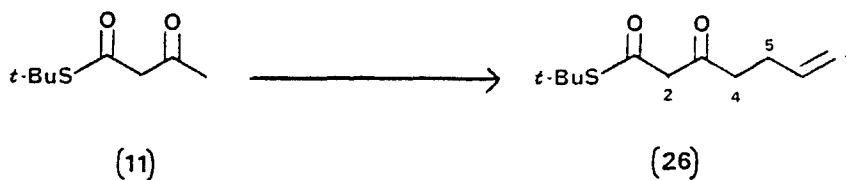
(9)

(13)

To neat diisopropylamine (250 mg, 2.47 mmol) stirred at -6°C was added dropwise *n*-butyl lithium (1.40 ml of a 1.58M solution in hexanes, 2.21 mmol). After 5 minutes, DME (1 ml) was added and the solution

cooled to -20°C . To this solution was added dropwise over 5 min (9) (194 mg, 1 mmol) as a solution in DME (1 ml). The resultant deep-red solution was allowed to warm to 0°C over 20 min and allyl bromide (121 mg, 1 mmol) was added in one portion, whereupon the colour of the solution was instantly discharged. The reaction mixture was stirred at 0°C for 20 min, and saturated aqueous ammonium chloride (1 ml) was added. The reaction mixture was extracted into ether (25 ml) and the ethereal solution washed with dilute hydrochloric acid (5 ml) and brine (5 ml), dried, and concentrated under reduced pressure. The crude product was chromatographed (5% ether/petrol) to afford pure (13) as a pink oil (159 mg, 68%) as a 2.6 : 1 *keto-enol* mixture; δ (250 MHz): *Keto*; 2.24 - 2.40 (2H, m, C-5 H_2), 2.64 - 2.73 (2H, t, J 7 Hz, C-4 H_2), 3.76 (2H, s, C-2 H_2), 4.96 - 5.12 (2H, m, C-7 H_2), 5.70 - 4.90 (1H, m, C-6 H), and 7.43 (5H, br s, aromatics); *Enol*; 2.24 - 2.40 (4H, m, C-4 H_2 + C-5 H_2), 4.96 - 5.12 (2H, m, C-7 H_2), 5.50 (1H, s, C-2 H), 5.70 - 5.90 (1H, m, C-6 H), and 7.43 (5H, br s, aromatics); ν_{max} (film): 3077, 2919, 1723, 1695, 1617, 1099, and 748 cm^{-1} ; m/z 234 (M^+), 208 ($\text{M}^+ - \text{C}_2\text{H}_2$), 125 ($\text{M}^+ - \text{PhS}$), and 110 (PhSH). (Found: C, 66.58; H, 6.04; S, 13.82. $\text{C}_{13}\text{H}_{14}\text{O}_2\text{S}$ requires C, 66.64; H, 6.02; S, 13.68%).

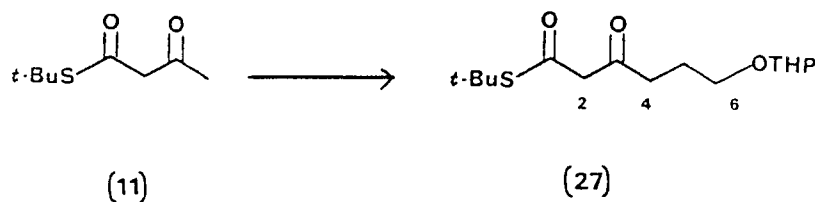
3) Preparation of *tert*-butyl 3-oxohept-6-enethioate (26)



To a suspension of sodium hydride (53 mg of a 50% suspension in oil, 1.1 mmol), pre-washed with dry petrol (2 x 5 ml) in DME (2 ml) at

0°C was added dropwise a solution of the β -ketothioester (11) (174 mg, 1 mmol) in DME (2 ml). The resultant clear solution was stirred for 5 min and cooled to -35°C. *n*-Butyl lithium (0.70 ml of a 1.58M solution in hexanes, 1.1 mmol) was added dropwise over 5 min, maintaining the temperature between -30°C and -35°C. The deep red dianion solution was allowed to warm to -20°C and allyl bromide (0.13 ml, 181 mg, 1.1 mmol) was added neat in one portion. After 20 min, sat. NH_4Cl solution (5 ml) was added and the mixture extracted with ether (2 x 25 ml). The combined ethereal extracts were dried (Na_2SO_4) and evaporated to give a red oil. Chromatography (25% Et_2O /petrol) afforded the pure (26) as a pink oil (150 mg, 70%) in a 2:1 *keto-enol* equilibrium; δ (250 MHz): 1.47 (9H, s, *keto* ^tBu), 1.51 (9H, s, *enol* ^tBu), 2.24 (2H, t, J 8 Hz, *enol* C-4 H_2), 2.33 (2H, m, C-5 H_2), 2.64 (2H, t, J 8 Hz, *keto* C-4 H_2), 3.57 (2H, s, *keto* C-2 H_2), 4.95 - 5.10 (2H, m, C-7 H_2), 5.32 (1H, s, *enol* C-2 H), 5.79 (1H, m, C-6 H), and 12.83 (1H, s, *enol* OH); ν_{max} : 2950, 1720, 1660, and 1610 cm^{-1} ; m/z 214 (M^+), 157 ($\text{M}^+ - ^t\text{Bu}$), 124 ($\text{M}^+ - ^t\text{BuSH}$), and 83; (Found: C, 61.74; H, 8.58; S, 14.70. $\text{C}_{11}\text{H}_{18}\text{O}_2\text{S}$ requires: C, 61.64; H, 8.46; S, 14.96%).

4) Preparation of *tert*-Butyl 3-oxo-6-(tetrahydropyran-2-yloxy)hexane-thioate (27)



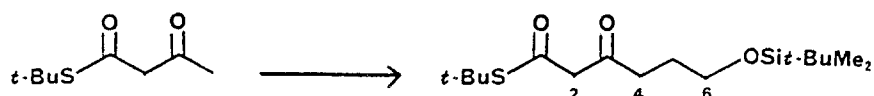
To a solution of the dianion (prepared from 734 mg, 4.22 mmol of the thioester (11)) generated as described previously, in DME (5 ml) at

-20°C, was added a solution of 1-bromo-2-(tetrahydropyran-2-yloxy)ethane (1.32g, 6.33 mmol) in DME (2 ml). The solution was warmed to RT over 2h and quenched with saturated NH₄Cl solution (3 ml). The product was extracted into ether (2 x 100 ml), and the combined ethereal extracts were dried, evaporated and chromatographed (25% ether-petrol) to afford pure (27) (828 mg, 65%); δ (250 MHz): *keto*; 1.48 (9H, s, ^tBuS), 1.45 - 1.95 (8H, m), 2.66 (2H, dt, J 3, 6.5 Hz, C-4 H₂), 3.35 - 3.55 (2H, m, C-11 H₂), 3.60 (2H, s, C-2 H₂), 3.68 - 3.90 (2H, m, C-6 H₂), and 5.56 (1H, m, C-7 H); *enol*; 1.51 (9H, s, ^tBuS), 1.45 - 1.91 (8H, m), 2.25 (2H, t, J 6.5 Hz, C-4 H₂), 3.35 - 3.55 (2H, m, C-11 H₂), 3.68 - 3.90 (2H, m, C-6 H₂), 5.36 (1H, s, C-2 H), and 5.56 (1H, m, C-7 H); ν_{max} (neat): 2910, 1715, 1670 and 1610 cm⁻¹; m/z 245 (M⁺-^tBu), 217 (M⁺-THP), 213 (M⁺-^tBuS), and 200 (M⁺-THP-OH).

5) Preparation of *tert*-Butyl 6-(^tbutyldimethylsilyloxy)-3-oxohexanethioate (27a)

-20°C, was added a solution of 1-bromo-2-(tetrahydropyran-2-yloxy)ethane (1.32g, 6.33 mmol) in DME (2 ml). The solution was warmed to RT over 2h and quenched with saturated NH₄Cl solution (3 ml). The product was extracted into ether (2 x 100 ml), and the combined ethereal extracts were dried, evaporated and chromatographed (25% ether-petrol) to afford pure (27) (828 mg, 65%); δ (250 MHz): *keto*; 1.48 (9H, s, ^tBuS), 1.45 - 1.95 (8H, m), 2.66 (2H, dt, J 3, 6.5 Hz, C-4 H₂), 3.35 - 3.55 (2H, m, C-11 H₂), 3.60 (2H, s, C-2 H₂), 3.68 - 3.90 (2H, m, C-6 H₂), and 5.56 (1H, m, C-7 H); *enol*; 1.51 (9H, s, ^tBuS), 1.45 - 1.91 (8H, m), 2.25 (2H, t, J 6.5 Hz, C-4 H₂), 3.35 - 3.55 (2H, m, C-11 H₂), 3.68 - 3.90 (2H, m, C-6 H₂), 5.36 (1H, s, C-2 H), and 5.56 (1H, m, C-7 H); ν_{max} (neat): 2910, 1715, 1670 and 1610 cm⁻¹; m/z 245 (M⁺-^tBu), 217 (M⁺-THP), 213 (M⁺-^tBuS), and 200 (M⁺-THP-OH).

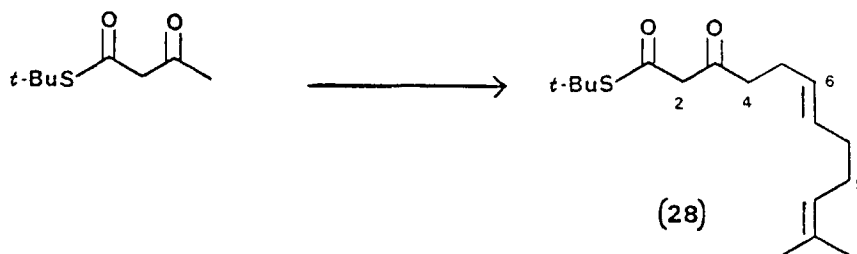
5) Preparation of *tert*-Butyl 6-(^tbutyldimethylsilyloxy)-3-oxohexanethioate (27a)



To a suspension of sodium hydride (61 mg of a 50% suspension in mineral oil, 1.27 mmol, previously washed with dry petrol) in dry DME (0.5 ml) at 0°C was added a solution of the thioester (11) (179 mg, 1.03 mmol) in DME (0.5 ml). After stirring for 10 min the clear solution was cooled to -30°C and *n*-BuLi (0.83 ml of a 1.33M solution in hexane, 1.10 mmol) was added dropwise. The mixture was warmed slowly to -8°C and a solution of the iodide (366 mg, 1.28 mmol) in DME (0.5 ml)

was added. After stirring at room temperature for 1.5h, the reaction was quenched by addition of saturated NH_4Cl solution (1 ml). The product was extracted into ether (2 x 20 ml) and the combined ethereal extracts were washed with dilute HCl (5 ml) and dried (Na_2SO_4). Evaporation under reduced pressure and chromatography (5% ether/petrol) afforded the pure oxothioester (27a) (215 mg, 63%) in a 2:1 *keto-enol* ratio; δ (250 MHz): *keto*: 0.20 (6H, s, SiMe_2), 0.87 (9H, s, $^t\text{BuSi}$), 1.46 (9H, s, ^tBuS), 1.80 (2H, m, C-5 H_2), 2.62 (2H, t, J 7 Hz, C-4 H_2), 3.67 (2H, s, C-2 H_2), and 3.50 (2H, m, C-6 H_2); *enol*: 0.21 (6H, s, SiMe_2), 0.88 (9H, s, $^t\text{BuSi}$), 1.50 (9H, s, ^tBuS), 1.80 (2H, m, C-5 H_2), 2.21 (2H, t, J 7 Hz, C-4 H_2), 3.60 (2H, m, C-6 H_2), 5.34 (1H, s, C-2 H), and 9.88 (1H, br s, OH); ν_{max} (neat): 2950, 2910, 1720, 1675, and 1610 cm^{-1} ; m/z 332 (M^+), 275 ($\text{M}^+ - ^t\text{Bu}$), and 242 ($\text{M}^+ - ^t\text{BuSH}$); (Found: $\text{M}^+ - ^t\text{Bu}$, 275.1137, calc., 275.1137); (Found: C, 57.91; H, 9.98; S, 9.75. $\text{C}_{16}\text{H}_{32}\text{SSiO}_3$ requires: C, 57.78; H, 9.70; S, 9.64%).

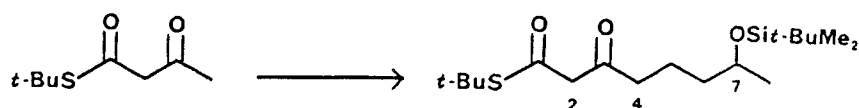
6) Preparation of (E)-*tert*-Butyl 7,11-dimethyl-3-oxododeca-6,10-diene-thioate (28)



To a suspension of sodium hydride (192 mg of a 60% suspension in oil, 4.80 mmol) previously washed with dry petrol (2 x 10 ml) in DME (10 ml) cooled to 0°C , was added dropwise a solution of (11) (714 mg, 4.10 mmol) in DME (1 ml). After stirring for 10 min the clear, colourless solution was cooled to -30°C and $^n\text{BuLi}$ (3.01 ml of a 1.50 M

solution in hexanes, 4.52 mmol) was added slowly, maintaining the cooling bath temperature between -35° and -30°C . The deep red reaction mixture was allowed to warm to -20°C over 5 min and geranyl chloride (872 mg, 5.07 mmol) was added as a solution in DME (1 ml). The solution was warmed slowly to 0°C , stirred for 2h and quenched with saturated NH_4Cl solution (10 ml). The mixture was extracted into ether (150 ml), dried (Na_2SO_4) and chromatographed (5% ether-petrol) to afford the *geranyl-3-oxothioester* (28) (760 mg, 60%) as a 3.5 : 1 *keto-enol* mixture; δ (250 MHz): *keto*: 1.47 (9H, s, ^tBu), 1.60 (6H, br s, C-12 H_3 + C-14 H_3), 1.68 (3H, br s, C-13 H_3), 1.97 (4H, m, C-8 H_2 + C-9 H_2), 2.28 (2H, m, C-5 H_2), 2.57 (2H, t, J 8 Hz, C-4 H_2), 3.56 (2H, s, C-2 H_2) and 5.07 (2H, m, C-6 H + C-10 H); *enol*: 1.51 (9H, s, ^tBu), 1.60 (6H, br s, C-12 H_3 + C-14 H_3), 1.68 (3H, br s, C-13 H_3), 1.97 (4H, m, C-8 H_2 + C-9 H_2), 2.04 (2H, m, C-4 H_2), 2.28 (2H, m, C-5 H_2), 5.07 (2H, m, C-6 H + C-10 H) and 5.33 (1H, s, C-2 H); ν_{max} (neat): 2966, 2923, 1722, 1675, and 1616 cm^{-1} ; m/z 310 (M^+), 253 ($\text{M}^+ - ^t\text{Bu}$) and 221 ($\text{M}^+ - ^t\text{BuS}$); (Found: C, 69.92; H, 9.94; S, 10.03. $\text{C}_{18}\text{H}_{30}\text{O}_2\text{S}$ requires C, 69.63; H, 9.74; S, 10.33%).

7) Preparation of *tert*-Butyl 7-(^{t} butyldimethylsilyloxy)-3-oxooctane-thioate (29)

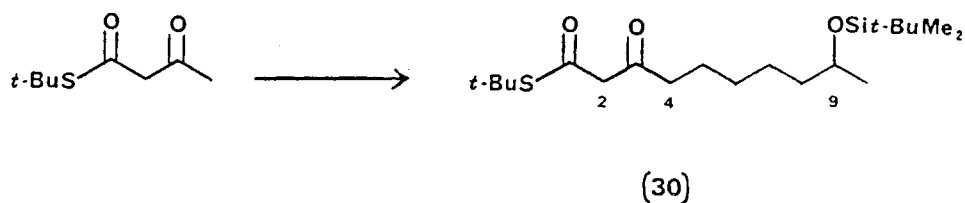


(29)

To a solution of the dianion (prepared from 185 mg, 1.06 mmol of the thioester (11)), generated as described previously, in DME (1 ml)

at -15°C was added a solution of 3-(*t*-butyldimethylsilyloxy-1-iodobutane (363 mg, 1.16 mmol) in DME (0.5 ml). The reaction mixture was allowed to warm to room temperature, stirred for 3h and quenched by addition of saturated aq. NH_4Cl solution (1 ml). The product was extracted with ether (50 ml), and the ether layer washed with dilute HCl (10 ml), dried (Na_2SO_4) and evaporated to give a pink oil. Chromatography (5% ether/petrol) afforded the pure thioester () (204 mg, 53%) as a pink oil in a 1:1 *keto-enol* ratio; δ (250 MHz): *keto*: 0.03 (6H, s, Me_2Si), 0.87 (9H, s, $^t\text{BuSi}$), 1.12 (3H, d, J 5 Hz, C-8 H_3), 1.47 (9H, s, ^tBuS), 1.30 - 1.70 (4H, m, $(\text{CH}_2)_2$), 2.54 (2H, t, J 7 Hz, C-4 H_2), 3.55 (2H, s, C- H_2), and 3.79 (1H, m, C-7 H); *enol*: 0.03 (6H, s, Me_2Si), 0.87 (9H, s, $^t\text{BuSi}$), 1.13 (3H, d, J 5 Hz, C-8 H_3), 1.50 (9H, s, ^tBuS), 1.30 - 1.70 (4H, m, $(\text{CH}_2)_2$), 2.13 (2H, t, J 7 Hz, C-4 H_2), 3.79 (1H, m, C-7 H), 5.32 (1H, s, C-2 H), and 9.89 (1H, s, OH); ν_{max} (neat): 2980, 1725, 1680, and 1680 cm^{-1} ; m/z 303 ($\text{M}^+ - ^t\text{Bu}$), 247, 229 and 213; (Found: $\text{M}^+ - ^t\text{Bu}$, 303.1453, calc., 303.1450); (Found: C, 59.72; H, 10.28; S, 8.78. $\text{C}_{18}\text{H}_{36}\text{O}_3\text{SiS}$ requires C, 59.95; H, 10.06; S, 8.89%).

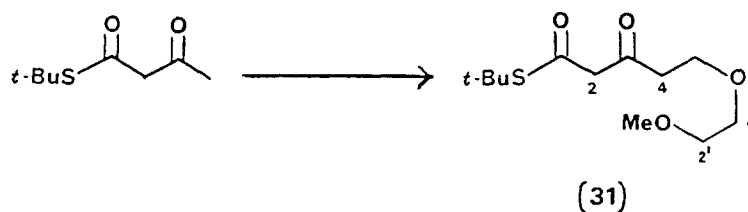
8) Preparation of *tert*-Butyl 3-oxo-9-(*t*-butyldimethylsilyloxy)decane-thioate (30)



To a suspension of sodium hydride (61 mg of a 50% suspension in oil, 1.27 mmol) previously washed with dry petrol (2 x 5 ml) in DME (2 ml), cooled to 0°C , was added dropwise a solution of the thioester

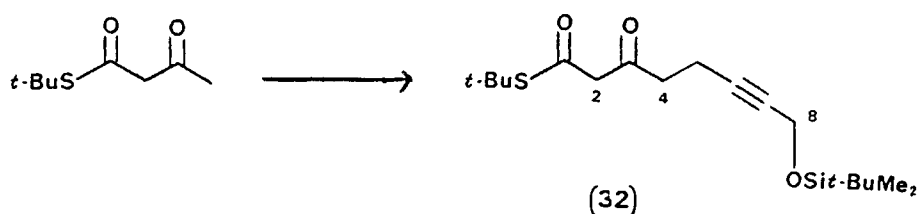
(11) (181 mg, 1.04 mmol) in DME (1 ml). After stirring for 5 minutes the clear solution was cooled to -30°C and BuLi (0.67 ml of a 1.56M solution in hexanes, 1.04 mmol) added slowly over 10 min, maintaining the temperature between -25° and -35°C . The deep red dianion solution was then allowed to warm quickly to room temperature, and a solution of 5-(*t*-butyldimethylsilyloxy-1-iodohexane (390 mg, 1.14 mmol) in DME (1 ml) was added in one portion. After stirring for 45 min at room temperature, sat. NH_4Cl solution (5 ml) was added and the mixture extracted with ether (2 x 50 ml). The combined ethereal extracts were washed with 5% HCl (2 x 10 ml), dried, evaporated and chromatographed (5% ether-petrol) to yield the substituted thioester (30) (238 mg, 59%) as a pale pink oil, in a 2:1 *keto-enol* ratio; δ (250 MHz): *keto*: 0.05 (6H, s, SiMe_2), 0.88 (9H, s, Si^tBu), 1.10 (3H, d, J 6.5 Hz, C-10 H_3), 1.47 (9H, s, S^tBu), 1.17 - 1.67 (8H, m, $(\text{CH}_2)_4$), 2.53 (2H, t, J 7 Hz, C-4 H_2), 3.56 (2H, s, C-2 H_2), and 3.75 (1H, m, C-9 H); *enol*: 0.05 (6H, s, SiMe_2), 0.88 (9H, s, Si^tBu), 1.10 (3H, d, J 6.5 Hz, C-10 H_3), 1.50 (9H, s, S^tBu), 1.17 - 1.67 (8H, m, $(\text{CH}_2)_4$), 2.13 (2H, t, J 7 Hz, C-4 H_2), 3.75 (1H, m, C-9 H), and 5.32 (1H, s, C-2 H); ν_{max} (neat): 2980, 1725, 1677, and 1615 cm^{-1} ; m/z 331 ($\text{M}^+ - ^t\text{Bu}$), 299 ($\text{M}^+ - ^t\text{BuS}$), 257 ($\text{M}^+ - \text{OTBDMS}$), and 229 ($\text{M}^+ - \text{C}_2\text{H}_3\text{OTBDMS}$); (Found: C, 62.05; H, 10.54; S, 8.08. $\text{C}_{20}\text{H}_{40}\text{O}_3\text{SSi}$ requires: C, 61.80; H, 10.37; S, 8.25%).

9) Preparation of *tert*-Butyl 5-(2'-[methoxy]ethoxy)-3-oxopentanethioate (31)



To a solution of the dianion (5.54 mmol, from 964 mg of oxothioester) in DME (11 ml), prepared as before, cooled to -13°C was added neat MEM-chloride (0.95 ml, 8.0 mmol). The mixture was warmed to 0°C and quenched with saturated NH_4Cl solution (2 ml). The product was extracted into ether (2 x 50 ml) and the combined ethereal extracts dried, evaporated and chromatographed (25% ether/petrol) to afford the substituted oxothioester (31) (520 mg, 36%) as a clear oil in a 5:1 *keto-enol* equilibrium; δ (250 MHz): *keto*: 1.42 (9H, s, $t\text{Bu}$), 2.78 (2H, t, J 7 Hz, C-4 H_2), 3.32 (3H, s, OMe), 3.57 (2H, s, C-2 H_2), 3.43 - 3.60 (4H, m, C-1' H_2 + C-2' H_2), and 3.69 (2H, t, J 7 Hz, C-5 H_2); *enol*: 1.46 (9H, s, $t\text{Bu}$), 2.39 (2H, t, J 7 Hz, C-4 H_2), 3.33 (3H, s, OMe), 3.43 - 3.60 (4H, m, C-1' H_2 + C-2' H_2), 3.64 (2H, t, J 7 Hz, C-5 H_2), and 5.35 (1H, s, C-2 H); ν_{max} (neat): 3429, 2879, 1721, 1673, and 1619 cm^{-1} ; m/z 262 (M^+), 230 ($\text{M}^+ - \text{CH}_3\text{OH}$), 205 ($\text{M}^+ - t\text{Bu}$), and 173 ($\text{M}^+ - t\text{BuS}$); (Found: C, 55.08; H, 8.71. $\text{C}_{12}\text{H}_{22}\text{S}\text{O}_4$ requires C, 54.94; H, 8.45%).

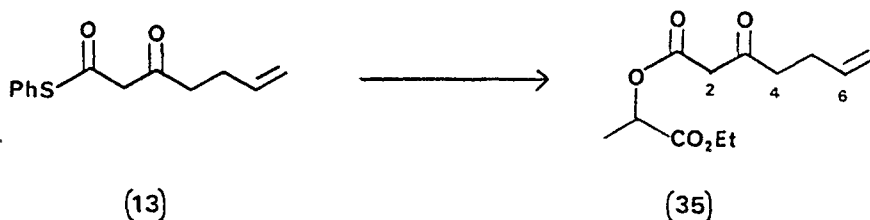
10) Preparation of *tert*-Butyl 8-(t butyldimethylsilyloxy)-3-oxo-oct-6-ynethioate (32)



To a solution of the dianion (1.96 mmol, from 341 mg of oxothioester) in DME (10 ml) generated as before, cooled to -15°C , was added a solution of the acetylenic bromide (752 mg, 2.86 mmol). The mixture was warmed slowly to 0°C , quenched by addition of saturated NH_4Cl

solution and extracted with ether (2 x 50 ml). The combined ethereal extracts were dried, evaporated and chromatographed (5% ether-petrol) to afford the pure substituted oxothioester (32) (296 mg, 43%) as a pale pink oil in a 3:1 *keto-enol* equilibrium; δ (250 MHz): *keto*: 0.09 (6H, s, SiMe₂), 0.89 (9H, s, Si^tBu), 1.47 (9H, s, S^tBu), 2.46 (2H, dt, J 7, 1 Hz, C-5 H₂), 2.76 (2H, t, J 7 Hz, C-4 H₂), 3.57 (2H, s, C-2 H₂), and 4.26 (2H, t, J 1 Hz, C-8 H₂); *Enol*: 0.09 (6H, s, SiMe₂), 0.89 (9H, s, Si^tBu), 1.50 (9H, s, S^tBu), 2.30 (2H, t, J 7 Hz, C-4 H₂), 2.46 (2H, dt, J 7, 1 Hz, C-5 H₂), 4.27 (2H, t, J 1 Hz, C-8 H₂), 5.36 (1H, s, C-2 H), and 12.82 (1H, br s, OH); $\nu_{\max}$ (neat): 3427, 2959, 2930, 2236, 1724, 1675, and 1620 cm⁻¹; m/z 299 (M⁺-^tBu), 267 (M⁺-^tBuS), 243, and 209.

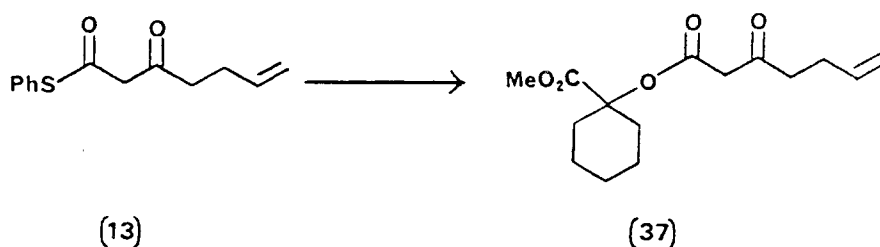
11) Preparation of (1'-Ethoxycarbonyl)ethyl 3-oxohept-6-enoate (35)



To a rapidly stirred solution of (13) (660 mg, 2.82 mmol) and ethyl lactate (370 mg, 3.13 mmol, 1.1 eq) in dry ether (25 ml) was added a solution of silver trifluoroacetate (750 mg, 3.39 mmol 1.2 eq) in ether (10 ml) in one portion. After 5 min a yellow precipitate was observed. The reaction mixture was stirred at room temperature for 30 min when TLC analysis showed reaction to be complete. The reaction mixture was filtered through a pad of celite and evaporated under reduced pressure. Chromatography of the resultant oil (25% ether/petrol) afforded (35) as a clear oil (641 mg, 94%); δ (60 MHz): 1.30 (3H, t, J 7 Hz, ester CH₃), 1.50 (3H, d, J 8 Hz, C-2' H₃), 2.10 - 2.90 (4H, m, C-4 H₂ + C-5 H₂),

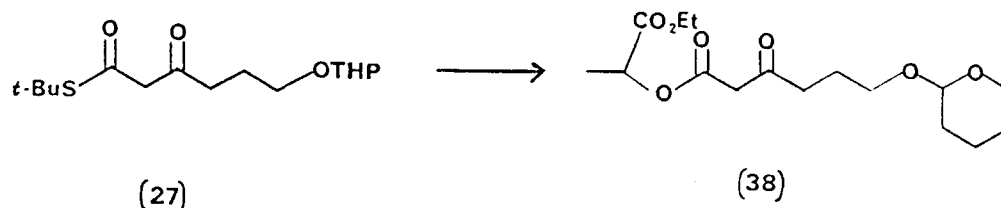
3.50 (2H, s, C-2 H₂), 4.20 (2H, q, J 7 Hz, ester CH₂), 4.75 - 5.35 (3H, m, C-7 H₂ + C-2' H), and 5.50 - 6.18 (1H, m, C-6 H); $\nu_{\max}$ (film): 2986, 1752, 1719, and 1639 cm⁻¹; m/z 242 (M⁺), 197 (M⁺-OEt), and 169 (M⁺-CO₂Et). (Found: C, 59.70; H, 7.70. C₁₂H₁₈O₅ requires C, 59.49; H, 7.49%).

12) Preparation of (1'-Methoxycarbonyl)cyclohexyl 3-oxohept-6-enoate
(37)



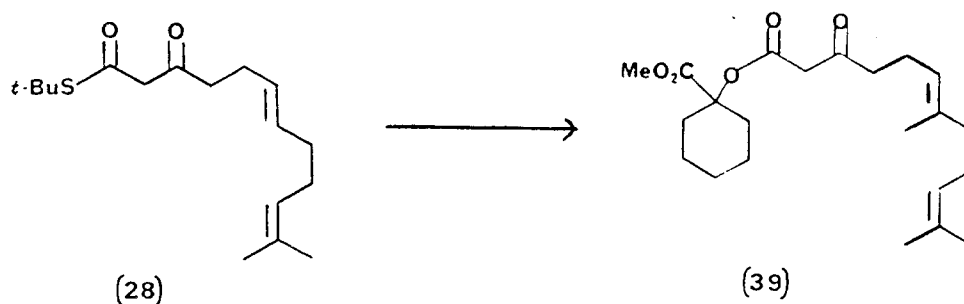
To a solution of the thioester (13) (155 mg, 0.66 mmol) and hydroxy-ester (36) (115 mg, 0.73 mmol, 1.1 eq) in dry ether (10 ml) was added a solution of AgCF₃CO₂ (176 mg, 0.8 mmol, 1.2 eq) in ether (5 ml). A yellow solid was instantaneously precipitated. After stirring at RT for 10 min, the mixture was filtered through silica, evaporated under reduced pressure and chromatographed to yield (37) as a clear oil (150 mg, 83%); δ (250 MHz): 1.19 - 1.88 (8H, m, (CH₂)₄), 1.14 (2H, m, CH₂ ring), 2.36 (2H, m, C-4 H₂), 2.68 (2H, t, J 7.8 Hz, C-3 H₂), 3.47 (2H, s, C-2 H₂), 3.72 (3H, s, OMe), 5.02 (2H, m, C-7 H₂), and 5.80 (1H, m, C-6 H); $\nu_{\max}$ (film): 2920, 2850, 1735, 1715, 1630, and 1130 cm⁻¹; m/z 282 (M⁺), 250 (M⁺-CH₃OH), 223 (M-CO₂Me), and 141. (Found: C, 64.06; H, 7.97. C₁₅H₂₂O₅ requires: C, 63.81; H, 7.85%).

13) Preparation of (1'-Ethoxycarbonyl)ethyl 3-oxo-6-(tetrahydropyran-2-yloxy)hexanoate (38)



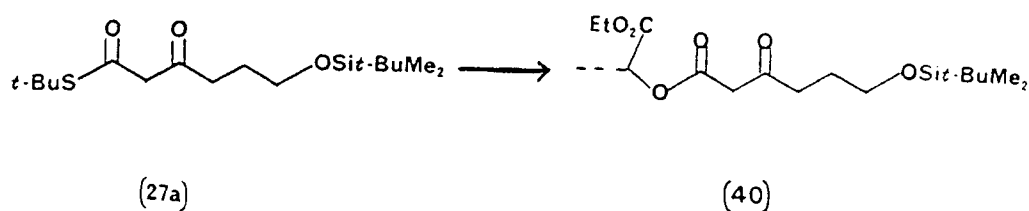
To a mixture of (27) (298 mg, 0.99 mmol) and ethyl lactate (233 mg, 1.97 mmol) in ether was added AgCF_3CO_2 (450 mg, 2.04 mmol). The black solution was stirred at RT for 2h and poured into water. The resulting mixture was filtered and the organic layer dried, evaporated, and chromatographed (50% ether-petrol) to yield pure (38) on a clear oil (241 mg, 74%); δ (250 MHz): (major diastereomer): 1.29 (3H, t, J 7 Hz, ester CH_3), 1.51 (3H, d, J 7 Hz, C-2' H_3), 1.45 - 2.00 (6H, m), 1.91 (2H, m, C-5 H_2), 2.50 (2H, m, C-4 H_2), 3.35 - 3.55 (2H, m, C-6 H + C-11 H), 3.56 (2H, s, C-2 H_2), 3.70 - 3.90 (2H, m, C-6 H + C-11 H), 4.23 (2H, q, J 7 Hz, ester CH_2), 4.55 (1H, m, C-7 H), and 5.13 (1H, q, J 7 Hz, C-1' H); ν_{max} (neat): 2920, 1740, 1715, and 1630 cm^{-1} ; m/z 330 (M^+), 245 ($\text{M}^+ - \text{THP}$), 229 ($\text{M}^+ - \text{OTHP}$), and 201 ($\text{M}^+ - \text{THP} - \omega_2$).

14) Preparation of (E)-(1'-Methoxycarbonyl)cyclohexyl-7,11-dimethyl-3-oxododeca-6,10-dienoate (39)



To a mixture of the substituted β -ketothioester (28) (146 mg, 0.47 mmol) and the hydroxy ester (36) (86 mg, 0.54 mmol, 1.16 eq) in dry ether (10 ml) at room temperature was added a solution of AgCF_3CO_2 (129 mg, 0.58 mmol, 1.24 eq) in ether (5 ml). The reaction mixture immediately turned orange, and after 15 min a yellow precipitate was observed. After stirring for 1h, the reaction mixture was diluted with ether (50 ml), washed with water (10 ml), dried (Na_2SO_4), evaporated and chromatographed (25% ether-petrol) to give the transesterified product (39) as a clear oil (130 mg, 73%): δ (250 MHz): 1.58 (3H, br s, C_{12}H_3), 1.60 (3H, br s, C_{14}H_3), 1.68 (3H, br s, C_{13}H_3), 1.20 - 2.35 (16H, m, $(\text{CH}_2)_5 + \text{C-5 H}_2 + \text{C-8 H}_2 + \text{C-9 H}_2$), 2.62 (2H, t, J 8 Hz, C-4 H_2), 3.48 (2H, s, C-2 H_2), 3.71 (3H, s, OMe) and 5.10 (2H, m, C-6 H + C-10 H); ν_{max} (neat): 2910, 1740, 1710, and 1650 cm^{-1} ; m/z 378 (M^+), 360 ($\text{M}^+ - \text{H}_2\text{O}$), 346 ($\text{M}^+ - \text{CH}_3\text{OH}$), and 220; (Found: C, 69.51; H, 9.26. $\text{C}_{22}\text{H}_{34}\text{O}_5$ requires C, 69.81; H, 9.05%).

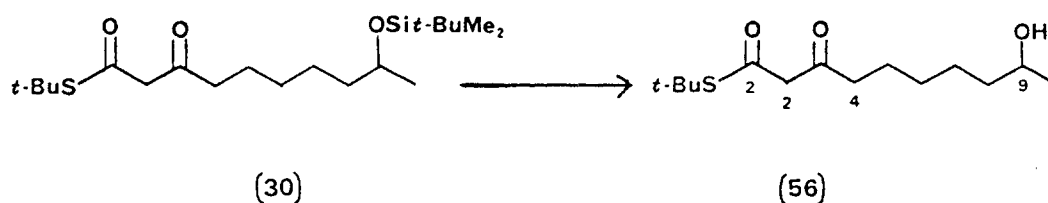
15) Preparation of (1'-Ethoxycarbonyl)ethyl 6-(^tbutyldimethylsilyloxy)-3-oxohexanoate (40)



To a mixture of (27a) (77 mg, 0.23 mmol) and ethyl lactate (74 mg, 0.63 mmol, 2.7 eq) in ether (4 ml) containing Na_2HPO_4 buffer (150 mg) was added a solution of AgCF_3CO_2 (0.46 mmol, 2 eq). The resulting black solution was stirred for 1h at room temperature, when TLC analysis showed reaction to be complete. The reaction mixture was poured into

dilute HCl (3 ml) and extracted with more ether (25 ml). The ethereal solution was dried (Na_2SO_4), filtered through a short pad of silica, and evaporated under reduced pressure. Chromatography (25% ether/petrol) afforded pure exoester (40) (60 mg, 72%) as a colourless oil in a 7:1 *keto-enol* ratio; δ (250 MHz); *keto*: 0.03 (6H, s, SiMe_2), 0.87 (9H, s, $^t\text{BuSi}$), 1.27 (3H, t, J 8 Hz, ester CH_3), 1.50 (3H, d, J 8 Hz, C-2' H_3), 1.82 (2H, m, C-5 H_2), 2.66 (2H, t, J 8 Hz, C-4 H_2), 3.53 (2H, s, C-2 H_2), 3.62 (2H, t, J 6 Hz, C-6 H_2), 4.20 (2H, q, J 8 Hz, ester CH_2) and 5.12 (1H, q, J 8 Hz, C-1' H); *Enol*: as above except: 2.30 (2H, t, J 8 Hz, C-4 H_2) and 10.95 (1H, br s, *enol* OH); ν_{max} (neat): 3426, 2931, 1750, and 1719 cm^{-1} ; m/z 314 (M-EtOH), 303 (M- ^tBu), and 243; (Found: $\text{M}^+ - ^t\text{Bu}$, 303.12673, calc., 303.1264); (Found: C, 56.80; H, 9.21. $\text{C}_{17}\text{H}_{32}\text{O}_6\text{Si}$ requires: C, 56.64; H, 8.95%).

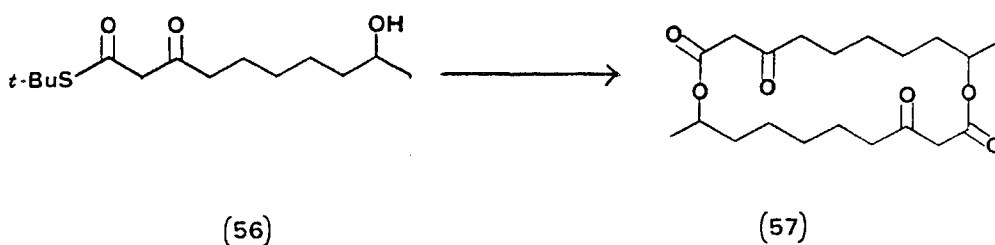
16) Preparation of *tert*-Butyl 9-hydroxy-3-oxobutanethioate (56)



To the neat β -oxothioester (30) (215 mg, 0.55 mmol) was added a solution of HF in CH_3CN (2 ml of a 1M solution, 2 mmol, 3.6 eq) at room temperature. After stirring for 10 min, the reaction mixture was diluted with water (10 ml) and extracted with chloroform (50 ml). The chloroform layer was dried (Na_2SO_4), evaporated and chromatographed (50% ether-petrol) to yield the *hydroxy*- β -oxothioester (56) (151 mg, 100%) as an oil in a 1.25:1 *keto-enol* ratio; δ (250 MHz): *keto*: 1.17 (3H, d, J 5 Hz, C-10 H_3), 1.47 (9H, s, ^tBu), 1.22 - 1.66 (8H, m, $(\text{CH}_2)_4$),

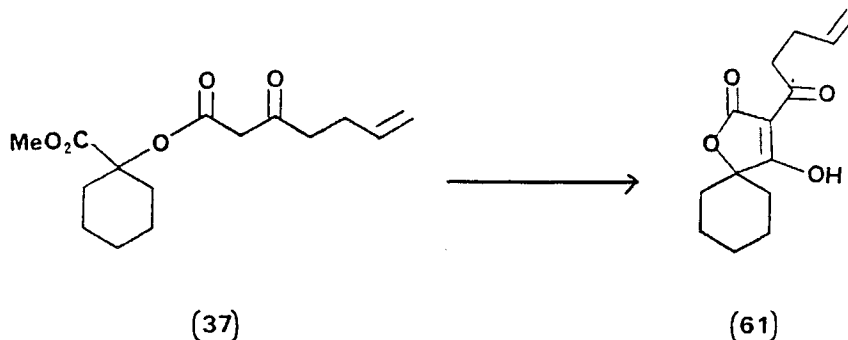
2.54 (2H, t, J 7 Hz, C-4 H₂), 3.57 (2H, s, C-2 H₂) and 3.78 (1H, m, C-9 H); *enol*: 1.18 (3H, d, J 5 Hz, C-10 H₃), 1.51 (9H, s, ^tBu), 1.22 - 1.66 (8H, m, (CH₂)₄), 2.13 (2H, t, J 7 Hz, C-4 H₂), 3.78 (1H, m, C-9 H) and 5.33 (1H, s, C-2 H); $\nu_{\max}$ (neat): 3381, 2931, 1721, 1675, and 1616 cm⁻¹; m/z 259 (M⁺-Me), 242, 215 (M⁺-^tBu), and 185 (M⁺-^tBuS); (Found: C, 61.27; H, 9.78; S, 11.92. C₁₄H₂₆O₃S requires: C, 61.28; H, 9.55; S, 11.68%).

17) Preparation of 3-Oxodecan-9-diolide (57)



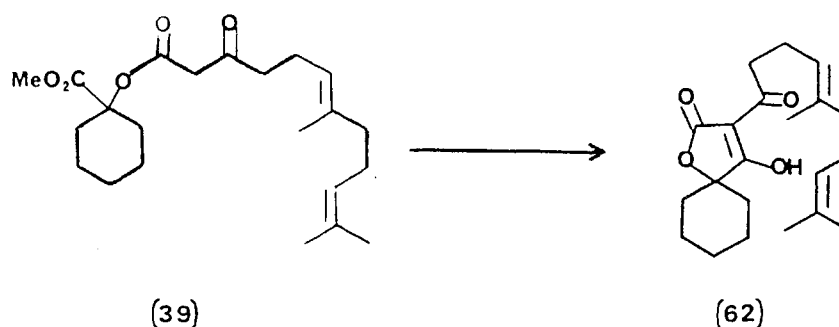
To a solution of (56) (84 mg, 0.31 mmol) in dry CH₂Cl₂ (2 ml) containing Na₂HPO₄ (500 mg) was added CuCF₃CO₂ (200 mg, 1.13 mmol). The reaction mixture was stirred for 30 min and poured into saturated NH₄Cl solution (2 ml). The product was extracted into CH₂Cl₂ (25 ml), and the organic layer dried and evaporated. Chromatography (25% ether-petrol) afforded pure (57) as white crystals (22 mg, 40%), m.p. 76 - 78°C; δ (250 MHz): major diastereomer: 1.22 (6H, d, J 7 Hz, 2 x C-10 H₃), 1.15 - 1.40 (16H, m), 2.42 - 2.66 (4H, m, 2 x C-4 H₂), 3.30 - 3.50 (4H, m, 2 x C-2 H₂), and 4.90 - 5.05 (2H, m, 2 x C-9 H₂); $\nu_{\max}$ (CHCl₃): 2937, 1738, 1709, and 1259 cm⁻¹; m/z 368 (M⁺) and 353 (M⁺-CH₃); (Found: M⁺, 368.2190. C₂₀H₃₂O₆ requires M⁺, 368.2199).

18) Preparation of 5,5-Cyclohexyl-4-hydroxy-2-(1-oxopent-4'-enyl)-furan-2-one (61)



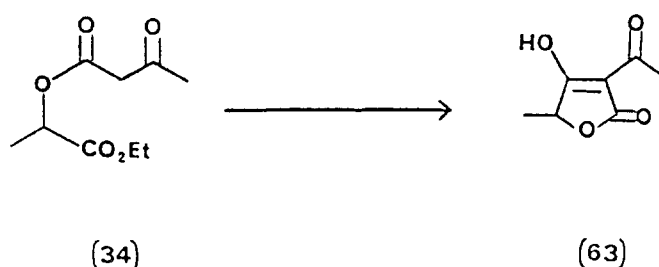
To a solution of NaOMe (20 mg, 0.37 mmol, 1.2 eq) in methanol (3 ml) at RT was added a solution of (37) (90 mg, 0.32 mmol) in benzene (6 ml). The mixture was heated under reflux for 4h and allowed to stand overnight. The solution was diluted with water (1 ml) followed by conc. (36%) HCl (10 drops), and extracted with ether (25 ml). The aqueous layer was further extracted with chloroform (20 ml). The combined organic extracts were dried and evaporated under reduced pressure to afford (61) as an oil which crystallized on cooling (82 mg, 95%), m.p. 42-44°C; (250 MHz): 1.75 (10H, m, (CH₂)₅), 2.46 (2H, q, J 8 Hz, C-2' H₂), 3.02 (2H, m, C-3' H₂), 4.97 - 5.16 (2H, m, C-5' H₂), 5.82 (1H, m, C-4' H), and 11.34 (1H, br s, OH); $\nu_{\max}$ (CHCl₃): 3536, 3078, 1751, 1683, 1645 and 1602 cm⁻¹; m/z 250 (M⁺), 232 (M⁺-H₂O), and 177. (Found: M⁺, 250.1208. C₁₄H₁₈O₄ requires M⁺, 250.1205).

19) Preparation of 5,5-Cyclohexyl-3-([E]-5',9'-dimethyl-1'-oxodeca-4',10'-dienyl)-4-hydroxyfuran-2-one (62)



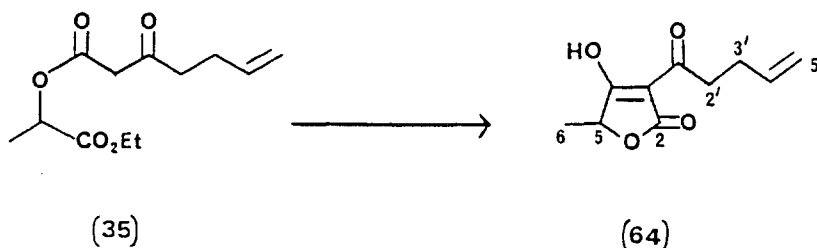
To a solution of NaOMe (15 mg, 0.29 mmol) in methanol (1 ml) at RT was added a solution of (39) (98 mg, 0.26 mmol) in benzene (6 ml). The mixture was heated under reflux for 4h and allowed to stand overnight. The solution was diluted with water (1 ml) and conc. HCl (10 drops), and the product extracted into ether (50 ml). The ether layer was dried and evaporated to yield (62) as a thick syrup (58 mg, 65%); δ (250 MHz): 1.55 - 2.12 (10H, m), 1.60 (3H, br s), 1.62 (3H br s), 1.66 (3H, br s), 2.40 (2H, m, C-3' H₂), 2.95 (2H, m, C-2' H₂), 5.01 - 5.20 (2H, m, C-4' H + C-8' H), and 11.12 (1H, br s, OH); $\nu_{\max}$ (CHCl₃): 3422, 2937, 1740, 1716, and 1623 cm⁻¹; m/z 346 (M⁺), 328 (M⁺-H₂O), 251, and 220. (Found: M⁺, 346.2142. C₂₁H₃₀O₄ requires M⁺, 346.2144).

20) Preparation of 3-Acetyl-4-hydroxy-5-methylfuran-2(5H)-one (63)



To the neat ester (34) (1.20g, 6 mmol), rapidly stirred under argon was added $n\text{-Bu}_4\text{NF}$ (12 ml of a 1M solution in THF, 12 mmol, 2 eq), and the solution stirred overnight. Volatiles were removed *in vacuo* and 10% HCl (15 ml) was added. The resulting clear solution was extracted with ether (5 x 50 ml) and the combined organic extracts dried and evaporated to yield crude (63) as a white solid. Recrystallisation from ether afforded the pure tetronic acid (63) as white crystals (789 mg, 85%); m.p. $70\text{--}72^\circ$; $[\alpha]_{\text{D}}^{25}$ ($C = 0.74$, H_2O) -70.1° ; δ (250 MHz); 1.53 (3H, d, J 8 Hz, C-6 H_3), 2.56 (3H, s, C-8 H_3), 4.80 (1H, q, J 8 Hz, C-5 H), and 11.41 (1H, br s, OH); ν_{max} (CHCl_3): 3682, 3619, 3078, 1761, 1689, and 1619 cm^{-1} ; m/z 156 (M^+), 138 ($\text{M}^+ - \text{H}_2\text{O}$), and 84. (Found: C, 53.60; H, 5.00. $\text{C}_7\text{H}_8\text{O}_4$ requires: C, 53.85; H, 5.16%).

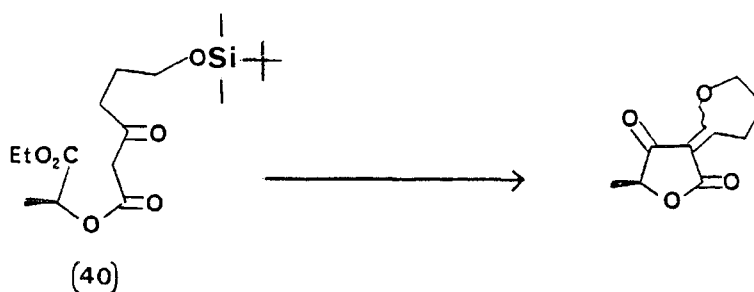
21) Preparation of 4-Hydroxy-5-methyl-2-(1-oxopent-4'-enyl)furan-2(5H)-one (64)



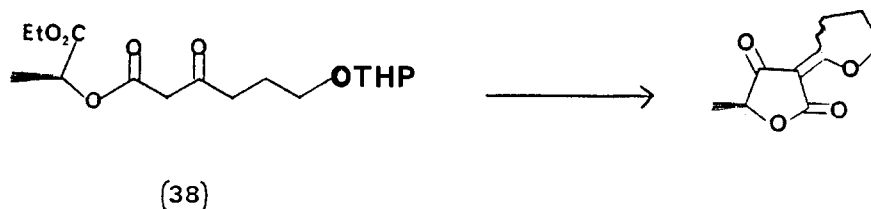
To the neat ester (35) (294 mg, 1.21 mmol), stirred under argon, was added $n\text{-Bu}_4\text{NF}$ (2.43 ml of a 1M solution in THF, 2.43 mmol, 2 eq). The mixture was stirred at room temperature for 3h and then evaporated to give a brown syrup. This was diluted with water (5 ml) and conc. HCl (5 drops) was added. The acidified solution was extracted with ether (2 x 25 ml) and the ethereal extracts combined, dried, and evaporated to give the tetronic acid (64) as a white solid (167 mg, 70%), m.p. $40\text{--}42^\circ$; δ (250 MHz): 1.47 (3H, d, J 8 Hz, C-6 H_3), 2.40 (2H,

m, C-2' H₂), 3.05 (2H, m, C-3' H₂), 4.50 - 5.29 (3H, m, C-5' H₂ + C-5 H), 5.75 (1H, m, C-4' H) and 12.70 (1H, br s, OH); $\nu_{\max}$ (CHCl₃): 3411, 3080, 2984, 1763, 1689, 1656, and 1603 cm⁻¹; m/z 196 (M⁺), 178 (M⁺-H₂O), and 141; (Found: M⁺, 196.0743. C₁₀H₁₂O₄ requires M⁺, 196.0736.

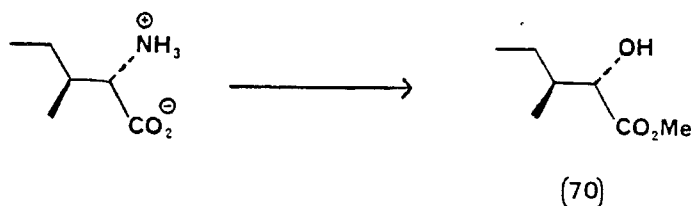
22) Preparation of (S)-Carolic acid



To the neat β -ketoester (40) (62 mg, 0.17 mmol) was added $n\text{-Bu}_4\text{NF}$ (0.6 ml of a 1M solution in THF, 0.6 mmol, 3.5 eq) and the mixture stirred overnight. Volatiles were removed *in vacuo*, and the residue dissolved in 10% HCl (5 ml). The acid solution was stirred for 10 minutes and extracted with ether (10 x 20 ml). The combined ethereal extracts were dried, and evaporated to give a viscous orange oil. This oil was treated with activated charcoal in boiling methanol to afford a buff semi-solid. Recrystallisation from ethyl acetate-petrol afforded (S)-carolic acid (14 mg, 70%) identical in all respects to the natural product except in direction of optical rotation.

23) Preparation of (S)-Carolic acid

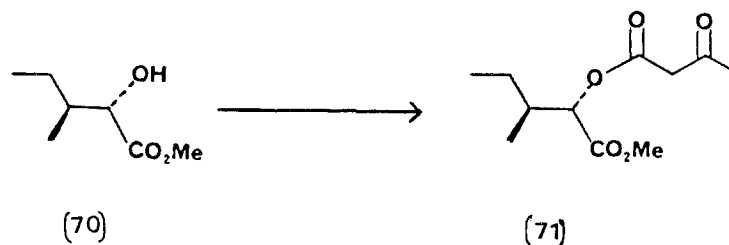
To neat (38) (148 mg, 0.45 mmol) was added $n\text{-Bu}_4\text{NF}$ (1 ml of a 1M solution in THF, 1 mmol).. The mixture was stirred overnight and poured into 10% HCl (2 ml). Extraction with ether (4 x 20 ml), drying of the combined organic extracts, and evaporation gave a buff solid. Recrystallisation from ethyl acetate/petrol afforded (S)-carolic acid, identical with the previously prepared sample.

24) Preparation of Methyl 2-(S)-hydroxy-3-(S)-methyl pentanoate (70)

To a solution of iso-leucine (0.75g, 5.72 mmol) in 1N H_2SO_4 (35 ml) containing 10 drops 96% H_2SO_4 to aid dissolution, cooled to 0°C , was added a solution of NaNO_2 (0.63g, 9.13 mmol) in water (2 ml) dropwise over 30 min. The solution was stirred overnight and then extracted with ether (2 x 100 ml). The ethereal solution was dried and evaporated to afford crude the hydroxy-acid as a white solid. This white solid was dissolved in ether (5 ml) and excess diazomethane bubbled through the solution until a yellow colour persisted. Evaporation under reduced pressure and chromatography (25% ether-petrol) afforded

the diastereomerically pure hydroxy-ester (616 mg, 74%); δ (250 MHz): 0.90 (3H, t, J 7.5 Hz, C-5 H₃), 0.98 (3H, d, J 7 Hz, C-6 H₃), 1.30 (2H, m, C-4 H₂), 1.81 (1H, m, C-3 H), 2.71 (1H, br s, OH), 3.79 (3H, s, OMe), and 4.09 (1H, d, J 4.5 Hz, C-2 H); $\nu_{\max}$ (neat): 3489, 2965, 2879, 1737, and 1646 cm⁻¹; m/z 147 (M⁺+H), 128 (M⁺-H₂O), 114 (M⁺-MeOH), and 87 (M⁺-CO₂Me).

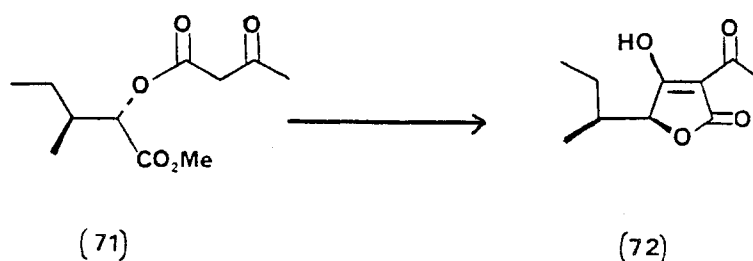
25) Preparation of Methyl 3-(S)-Methyl-2-(S)-(3'-oxobutanoyloxy)-pentanoate (71)



To a solution of the hydroxy ester (70) (200 mg, 1.37 mmol) in ether (10 ml), cooled to 0°C was added Et₃N (3 ml) and DMAP (3 crystals), followed by diketene (230 mg, 2.74 mmol). The mixture was stirred at 0°C for 2h, diluted with ether (50 ml) and washed with 10% HCl (5 ml) and brine (5 ml). The ethereal solution was evaporated and chromatographed (50% ether-petrol) to afford the ketoester (161 mg, 51%) as a 1.5 : 1 *keto-enol* mixture; δ (250 MHz): *keto*: 0.92 (3H, t, J 8 Hz, C-5 H₃), 0.97 (3H, d, J 7.5 Hz, C-6 H₃), 1.30 (1H, m, C-4 H), 1.48 (1H, m, C-4 H), 2.00 (1H, m, C-3 H), 2.32 (3H, s, C-4' H₃), 3.55 (2H, s, C-2' H₂), 3.75 (3H, s, OMe), and 4.97 (1H, d, J 5.5 Hz, C-2 H); *enol*: 0.92 (3H, t, J 8 Hz, C-5 H₃), 0.97 (3H, d, J 7.5 Hz, C-6 H₃), 1.30 (1H, m, C-4 H), 1.48 (1H, m, C-4 H), 1.97 (3H, s, C-4' H₃), 2.00 (1H, m, C-3 H), 3.75 (3H, s, OMe), 4.95 (1H, d, J 5.5 Hz, C-2 H), 5.12 (1H, s, C-2' H), and 11.09 (1H, s, OH); $\nu_{\max}$ (neat): 3427, 2968, 1750, 1720,

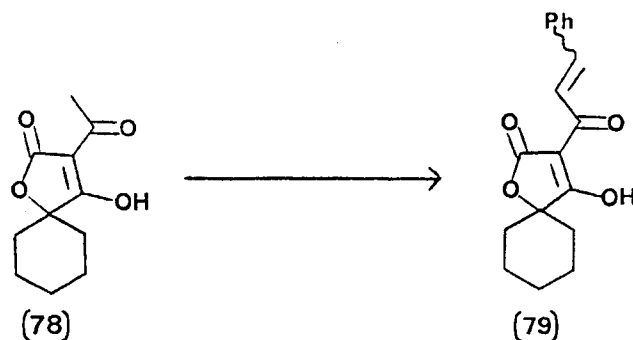
1629, and 1599 cm^{-1} ; m/z 230 (M^+), 199 ($\text{M}^+ - \text{OMe}$), 188 ($\text{M}^+ - \text{CH}_2\text{CO}$), and 177 ($\text{M}^+ - \text{CO}_2\text{Me}$).

26) Preparation of 3-Acetyl-4-hydroxy-5-(S)-(6-(S)-methyl)propylfuran-2-one (72)



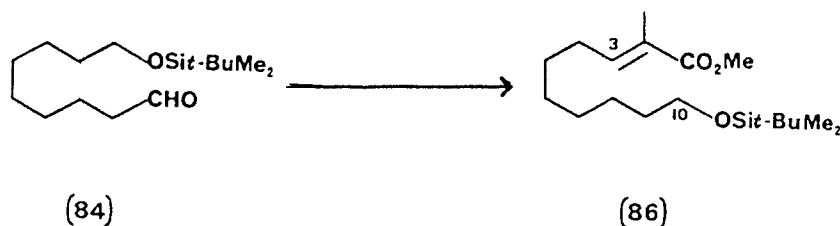
To the neat ketoester (71) (157 mg, 0.68 mmol) was added $n\text{-Bu}_4\text{NF}$ (1.40 ml of a 1.0M solution in THF, 1.40 mmol) and the solution stirred overnight. The mixture was poured into 10% aq. HCl and extracted with ether (3 x 20 ml). The combined organic extracts were dried and evaporated to yield (72) as an oil (88 mg, 65%); δ (250 MHz): 0.92 (3H, m, C-8 H_3), 1.06 (3H, d, J 7 Hz, C-9 H_3), 1.22 - 1.55 (2H, m, C-7 H_2), 2.04 (1H, m, C-6 H), 2.54 (3H, s, C-2' H_3), 4.55 ($\frac{1}{4}\text{H}$, d, J 3 Hz, $\frac{1}{4}$ C-5 H), 4.67 ($\frac{3}{4}\text{H}$, d, J 4 Hz, $\frac{3}{4}$ C-5 H), and 12.00 (1H, br s, OH); ν_{max} (neat): 3540, 2968, 1764, 1694, 1658, and 606 cm^{-1} ; m/z 198 (M^+), 169 ($\text{M}^+ - \text{C}_2\text{H}_5$), 155 ($\text{M}^+ - \text{CH}_3\text{CO}$), and 142 ($\text{M}^+ - \text{C}_4\text{H}_8$).

27) Preparation of 5,5-Cyclohexyl-4-hydroxy-3-(1'-oxo-3'-phenylprop-2-enyl)furan-2-one (79)



Gaseous hydrogen chloride was bubbled through a stirred solution of (78) (500 mg, 2.35 mmol) and benzaldehyde (500 mg, 4.72 mmol, 2 eq) in methanol (100 ml) until TLC analysis showed complete consumption of starting material (approximately 2h). The orange solution was evaporated under reduced pressure to yield (79) as orange crystals. Recrystallisation from methanol afforded pure (79) as yellow crystals (638 mg, 90%); m.p. 237-239°C; δ (250 MHz): 1.75 (10H, br s), 7.45 (2H, br s, aromatics), 7.69 (3H, br s, aromatics), 7.89 (2H, m, olefinics), and 11.20 (1H, br s, OH); $\nu_{\max}$ (CHCl₃): 3590, 2943, 1752, 1683, 1641, and 1599 cm⁻¹; m/z 298 (M⁺), 280 (M⁺-H₂O), 243, 200, and 171.

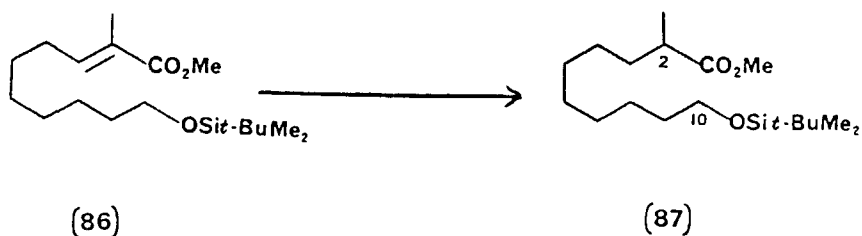
28) Preparation of (E)-Methyl 10-(^tbutyldimethylsilyloxy)-2-methyldec-2-enoate (86)



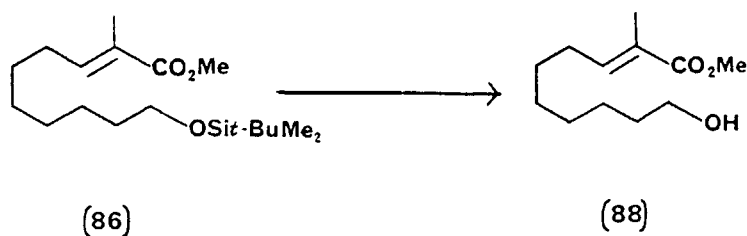
To a solution of the aldehyde (84) (1.80g, 6.98 mmol) in dichloromethane (20 ml) was added in one portion the phosphorane (85) (2.44g, 7.00 mmol, 1.005 eq). An exothermic reaction ensued and the resultant

solution was stirred at room temperature for 30 min. The solution was concentrated to approximately 10 ml and triturated with petrol (75 ml). The resultant precipitate of triphenylphosphine oxide was removed by filtration and the filtrate concentrated under reduced pressure to an oil. Chromatography (5% ether/petrol) afforded the protected *hydroxy-ester* as a clear oil (1.75g, 76%); δ (250 MHz): 0.04 (6H, s, SiMe₂), 0.89 (9H, s, Si^tBu), 1.23 - 1.70 (10H, m), 1.82 (3H, d, J 1.5 Hz, C-11 H₃), 2.16 (2H, m, C-4 H₂), 3.59 (2H, t, J 6.5 Hz, C-10 H₂), 3.73 (3H, s, OMe), 6.76 (1H, qt, J 1.5, 7.6 Hz, C-3 H); $\nu_{\max}$ (film): 2930, 1716, 1648, 1257, 1100, and 836 cm⁻¹; m/z 271 (M⁺-Bu^t), 239, and 202; (Found: C, 66.01; H, 10.99. C₁₈H₃₆O₃Si requires C, 65.80; H, 8.50%).

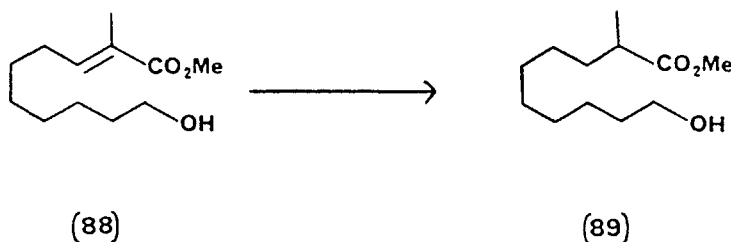
29) Preparation of Methyl 10-(^tbutyldimethylsilyloxy)-2-methyldecanoate
(87)



To a suspension of Pd on carbon (20 mg) in ethyl acetate (5 ml) under hydrogen was added a solution of (86) (1.28g, 3.90 mmol) in ethyl acetate (15 ml). The mixture was stirred overnight under an atmosphere of hydrogen, filtered through silica and evaporated to give the *saturated ester* (87) as an oil (1.26g, 98%); δ (250 MHz): 0.02 (6H, s, SiMe₂), 0.87 (9H, s, Si^tBu), 1.12 (3H, d, J 6.5 Hz, C-11 H₃), 1.18 - 1.80 (14H, m), 2.41 (1H, m, C-2 H), 3.27 (2H, t, J 6.5 Hz, C-10 H₂), and 3.64 (3H, s, OMe); $\nu_{\max}$ (neat): 2920, 1740, and 1460 cm⁻¹; m/z 299 (M⁺-OMe), 273 (M⁺-^tBu), and 241 (M⁺-MeOH-^tBu).

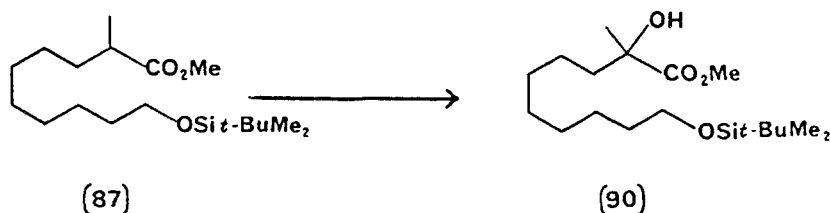
30) Preparation of Methyl 10-hydroxy-2-methyldec-2-enoate (88)

To a solution of ester (86) (234 mg, 0.71 mmol) in THF (2 ml) was added a solution of $n\text{-Bu}_4\text{NF}$ (0.78 ml of 1M solution in THF, 0.78 mmol, 1.1 eq). The mixture was stirred for 1h at room temperature and poured into 10% aq. HCl (5 ml). The aqueous solution was extracted with ether (50 ml), and the ethereal layer washed with saturated aq. NaHCO_3 solution (10 ml) and brine (10 ml), dried (Na_2SO_4) and evaporated to give a clear oil. Chromatography (50% ether/petrol) afforded the pure hydroxy ester (88) as a clear oil (148 mg, 97%); δ (250 MHz): 1.30 – 1.70 (10H, m, $(\text{CH}_2)_5$), 1.83 (3H, d, J 1 Hz, C-11 H_3), 2.10 (1H, br s, OH), 2.19 (2H, m, C-4 H_2), 3.63 (2H, t, J 6.5 Hz, C-10 H_2), 3.73 (3H, s, OMe), 6.75 (1H, qt, J 1, 7.5 Hz, C-3 H); ν_{max} (neat): 3370, 2931, 2857, 1713 and 1647 cm^{-1} ; m/z 214 (M^+), 182 ($\text{M}^+ - \text{CH}_3\text{OH}$), and 95; (Found: C, 67.24; 10.55. $\text{C}_{12}\text{H}_{22}\text{O}_3$ requires C, 67.26; H, 10.35%).

31) Preparation of Methyl 10-hydroxy-2-methyldecanoate (89)

To a suspension of Pd on carbon (15 mg) in ethyl acetate (3 ml) under hydrogen was added a solution of the unsaturated hydroxy-ester (88) (149 mg, 0.7 mmol) in ethyl acetate (7 ml). The mixture was stirred for 2 days at room temperature, filtered through silica and evaporated to afford the saturated *hydroxy-ester* (89) as a clear oil (145 mg, 96%); δ (250 MHz): 1.15 (3H, d, J 7.0 Hz, C-11 H), 1.20 - 1.90 (14H, m, (CH₂)₇), 2.41 (1H, m, C-2 H), 2.85 (1H, br s, OH), 3.61 (2H, t, J 6.6 Hz, C-10 H₂), and 3.65 (3H, s, OMe); $\nu_{\max}$ (film): 3400, 2930, 2850, 1730, 1460, and 1195 cm⁻¹; m/z 216 (M⁺), 198 (M⁺-H₂O), and 185 (M⁺-OMe); (Found: C, 66.76; H, 11.30. C₁₂H₂₄O₃ requires C, 66.63; H, 11.18%).

32) Preparation of Methyl 10-(^tbutyldimethylsilyloxy)-2-methyldecanoate (90)

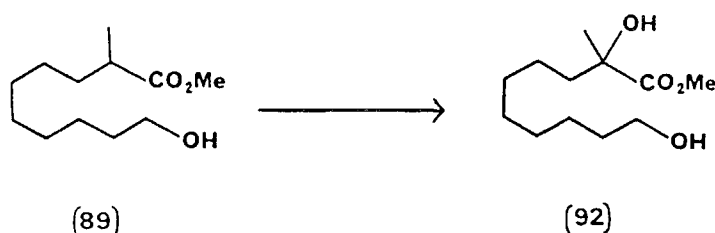


To neat diisopropylamine (202 mg, 2.0 mmol) stirred at 0°C under argon was added n-BuLi (1.33 ml of a 1.51M solution in hexanes, 2.0 mmol) dropwise over 5 min. After stirring for 5 min at 0°C, the viscous reaction mixture was diluted with THF (20 ml) and cooled to -78°C. A solution of the ester (87) (600 mg, 1.82 mmol) in THF (10 ml) was added dropwise over 10 min and then the solution was allowed to warm slowly to -40°C. Dry oxygen was bubbled through the mixture for 5 min before addition of saturated aq. NH₄Cl (5 ml) to quench the reaction. The product was extracted into ether (2 x 50 ml), the combined organic

extracts dried (Na_2SO_4), and evaporated under reduced pressure.

Chromatography (25% ether/petrol) afforded the hydroxy-ester (428 mg, 68%) as a clear oil; δ (250 MHz): 0.05 (6H, s, SiMe_2), 0.85 (9H, s, Si^tBu), 1.30 (3H, s, C-11 H_3), 0.90 - 1.90 (14H, m, $(\text{CH}_2)_7$), 3.52 (2H, t, J 7 Hz, C-10 H_2), and 3.70 (3H, s, OMe); ν_{max} (neat): 3520, 2920, 2840, 1725, and 1595 cm^{-1} ; m/z 331 ($\text{M}^+ - \text{CH}_3$), 303 ($\text{M}^+ + 1 - \text{CO}_2$), and 290 ($\text{M}^+ + 1 - ^t\text{Bu}$).

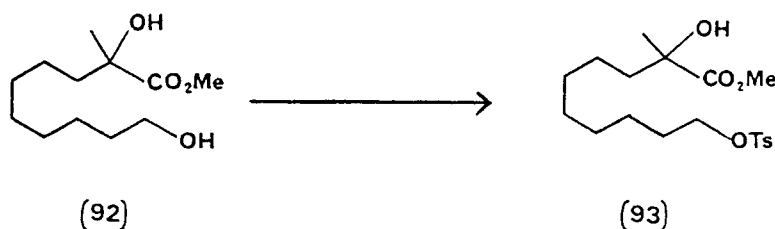
33) Preparation of Methyl 2,10-dihydroxy-2-methyldecanoate (92)



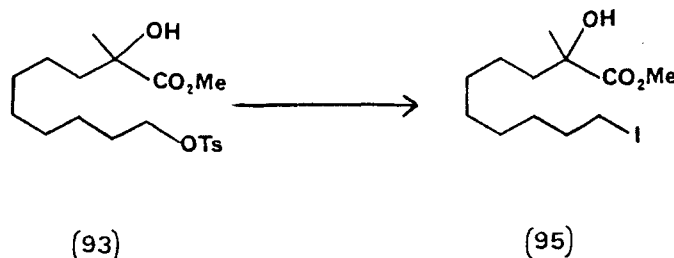
To a solution of diisopropylamine (810 mg, 8 mmol) in THF (10 ml) at 0°C was added dropwise n -butyl lithium (4.1 ml of a 1.61M solution in hexanes, 6.6 mmol). The solution was stirred for 5 min, diluted with 60 ml THF and cooled to -78°C . A solution of (89) (648 mg, 3 mmol) in THF (5 ml) was added dropwise over 10 min. After stirring for 30 min the clear solution became cloudy. This mixture was allowed to warm slowly to -40°C and dry oxygen was bubbled into the solution until TLC analysis indicated complete consumption of starting material. Saturated aqueous sodium sulphite solution (10 ml) was added and the mixture extracted with ether (2 x 75 ml). The ethereal extracts were combined, dried and filtered. To the resultant solution, triphenylphosphine was added in small (20 mg) portions until TLC analysis indicated consumption of hydroperoxide. The solution was evaporated under reduced pressure and the resultant oil chromatographed (ether) to

afford (92) as a clear, viscous oil (576 mg, 83%); δ (250 MHz): 1.45 (3H, s, C-11 H₃), 1.00 - 1.90 (14H, m, (CH₂)₇), 2.30 (1H, br s, OH), 3.25 - 3.80 (3H, m, C-10 H₂ + OH), and 3.75 (3H, s, OMe); $\nu_{\max}$ (film): 3400, 2900, 2830, 1720, 1450, and 1170 cm⁻¹; m/z 216 (M⁺-H₂O), 200 (M⁺-MeOH), and 173 (M⁺-CO₂Me). (Found: C, 62.08; H, 10.20. C₁₂H₂₄O₄ requires C, 62.04; H, 10.41%).

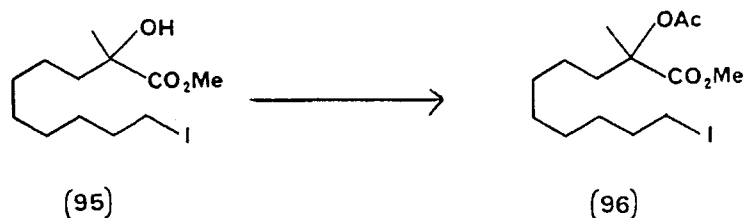
34) Preparation of Methyl 2-hydroxy-2-methyl-10-(tosyloxy)decanoate
(93)



To a solution of the diol ester (92) (226 mg, 0.98 mmol) in dry pyridine (2.5 ml) and chloroform (2 ml), cooled to 0°C, was added tosyl chloride (380 mg, 2 mmol, 2 eq) in small portions over 10 min. The homogeneous solution was stored overnight at 0°C, diluted with ether (50 ml) and washed with dilute HCl (2 x 10 ml), water (5 ml), and saturated CuSO₄ solution (2 x 10 ml). Evaporation of solvents under reduced pressure followed by chromatography (50% ether/petrol) gave the tosylate (93) (315 mg, 84%); δ (250 MHz): 1.40 (3H, s, C-11 H₃), 0.80 - 2.80 (14H, m), 2.40 (3H, s, tosyl CH₃), 3.20 (1H, br s, OH), 3.70 (3H, s, OMe), 3.90 (2H, t, J 7 Hz, C-10 H₂), 7.35 (2H, d, J 9 Hz, aromatic CH₂), and 7.79 (2H, d, J 9 Hz, aromatic CH₂); $\nu_{\max}$ (neat): 3500, 2910, 2820 and 1720 cm⁻¹; m/z 386 (M⁺), 368 (M⁺-H₂O), 336 (M⁺-H₂O-MeOH), and 327 (M⁺-CO₂Me). (Found: C, 59.22; H, 8.02. C₁₉H₃₀O₆S requires C, 59.04; H, 7.82%).

35) Preparation of Methyl 2-hydroxy-10-iodo-2-methyldecanoate (95)

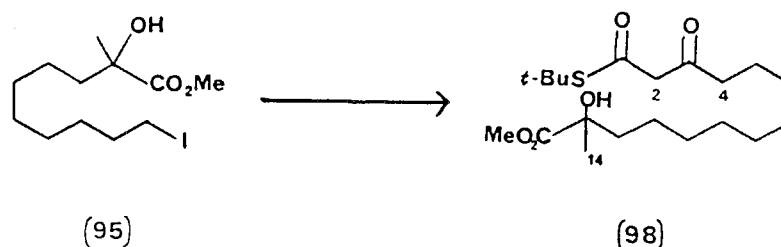
To a solution of sodium iodide (1g, 67 mmol) in acetone (5 ml), cooled to 0°C, was added the tosylate (93) (196 mg, 0.51 mmol) as a solution in acetone (1 ml). The mixture was stirred overnight at room temperature, diluted with ether (40 ml) and filtered through a silica pad. Removal of solvents under reduced pressure followed by chromatography (25% ether/petrol) afforded the pure iodide (95) as a pale yellow oil (167 mg, 96%); δ (250 MHz): 1.40 (3H, s, C-11 H₃), 1.00 - 1.88 (14H, m, (CH₂)₇), 3.13 (1H, br s, OH), 3.17 (2H, t, J 7.5 Hz, C-10 H₂), and 3.78 (3H, s, OMe); ν_{max} (film): 3500, 2920, 2850, 1725, 1600, and 1460 cm⁻¹; m/z 342 (M⁺), 310 (M⁺-CH₃OH), 283 (M⁺-CO₂CH₃), and 215 (M⁺-I). (Found: C, 42.42; H, 7.09. C₁₂H₂₃O₃I requires C, 42.12; H, 6.77).

36) Preparation of Methyl 1-acetoxy-10-iodo-1-methyldecanoate (96)

To a solution of the iodohydroxyester (95) (139 mg, 0.41 mmol) in dry pyridine (0.5 ml) cooled to 0°C under argon, was added a solution of acetic anhydride (1 ml) in pyridine (1 ml), followed by 2 crystals

of DMAP. The mixture was stirred for 1h at room temperature, and poured into ether (50 ml). The ethereal solution was washed sequentially with sat. NaHCO_3 (2 x 5 ml), 5% HCl (3 x 5 ml) and brine (5 ml) and dried Na_2SO_4 . Evaporation and chromatography (25% ether/petrol) afforded the iodoacetoxyster (96) as a clear oil (96 mg, 62%); δ (250 MHz): 1.20 - 1.40 (14H, m, $(\text{CH}_2)_7$), 1.40 (3H, s, C-11 H_3), 2.18 (3H, s, OAc), 3.14 (2H, t, J 7 Hz, C-10 H_2), and 3.67 (3H, s, OMe); ν_{max} (neat): 2920, 2870, 1740, and 1450 cm^{-1} .

37) Preparation of *tert*-Butyl 13-(methoxycarbonyl)-13-hydroxy-3-oxo-tetradecanethioate (98)

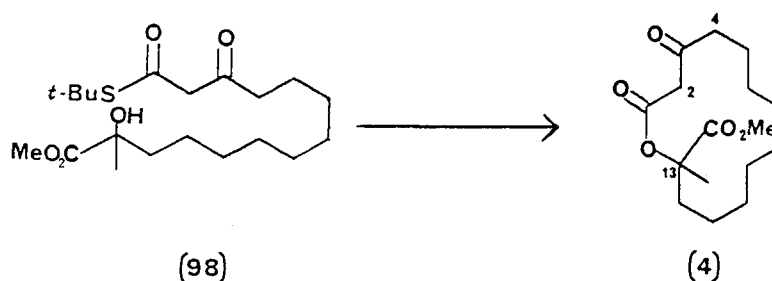


To di-isopropylamine (37 mg, 0.37 mmol) stirred at 0°C under argon was added $n\text{-BuLi}$ (0.20 ml, 0.30 mmol) dropwise. On completion of addition the mixture was diluted with DME (0.5 ml) and cooled to -20°C when the iodide (95) (96 mg, 0.28 mmol) was added slowly as a solution in DME (1.5 ml).

To a suspension of sodium hydride (16 mg of a 50% dispersion in oil, 0.33 mmol) previously washed with dry petrol (2 x 1 ml), in DME (0.5 ml), cooled to 0°C was added the thioester (11) (54 mg, 0.31 mmol) as a solution in DME (0.5 ml). After stirring for 5 min the solution was cooled to -25°C and $n\text{-BuLi}$ (0.22 ml of a 1.52M solution in hexanes, 0.33 mmol) was added. The deep orange dianion solution was warmed to

-20°C and the lithioiodide (prepared as described above) added. The reaction mixture was warmed to RT and stirred for 90 min. The reaction was quenched with saturated NH₄Cl solution (2 ml), and extracted with ether (2 x 25 ml). The combined ethereal extracts were washed with brine (5 ml), dried (Na₂SO₄), evaporated and chromatographed (25% ether/petrol) to yield (98) (61 mg, 56%) as a pale yellow oil in a 3:1 *keto-enol* ratio; δ (250 MHz): *keto*: 1.40 (3H, s, C-14 H₃), 1.48 (9H, s, ^tBu), 1.21 - 1.76 (16H, m, (CH₂)₈), 2.52 (2H, t, J 7 Hz, C-4 H₂), 3.12 (1H, br s, OH), 3.55 (2H, s, C-2 H₂) and 3.78 (3H, s, OMe); *enol*: 1.40 (3H, s, C-14 H₃), 1.51 (9H, s, ^tBu), 1.21 - 1.76 (16H, m, (CH₂)₈), 2.12 (2H, t, J 7 Hz, C-4 H₂), 3.12 (1H, br s, OH), 3.78 (3H, s, OMe) and 5.32 (1H, s, C-2 H); $\nu_{\max}$ (neat): 3529, 2928, 2856, 1728, 1674, and 1614 cm⁻¹; m/z 282 (M⁺-OMe-^tBu-H₂O), 240 (M⁺-^tBuS-CO₂Me), and 198 (M⁺-^tBuS-CO₂Me-C₂H₃OH).

38) Preparation of 13-(Methoxycarbonyl)-3-oxotetradecan-13-olide (4)



To a stirred solution of CuCF₃CO₂ (200 mg, 1.13 mmol) in dry CH₂Cl₂ (2 ml) at room temperature was added a solution of (98) (68 mg, 0.17 mmol) in CH₂Cl₂ (3 ml). The mixture was stirred for 30 min and poured into saturated NH₄Cl solution (3 ml). Extraction with CH₂Cl₂ (20 ml), drying of the organic layer and evaporation afforded a brown oil. Chromatography (25% ether/petrol) gave pure (4) as a clear oil

(21 mg, 40%); δ (250 MHz): 1.20 - 2.05 (16H, m), 1.60 (3H, s, C-14 H₃), 2.49 (1H, ddd, J 17, 7.5, 7 Hz, C-4 H), 2.79 (1H, ddd, J 17, 8.5, 7.5 Hz, C-4 H), 3.46 (2H, m, C-2 H₂), and 3.73 (3H, s, OMe); ν_{max} (neat): 2929, 2857, 1740, and 1717 cm⁻¹; m/z 298 (M⁺), 283 (M⁺-Me), 267 (M⁺-OMe), 239 (M⁺-CO₂Me), and 197 (M⁺-CO₂Me-C₂H₂O); (Found: M⁺, 298.1790. C₁₆H₂₆O₅ requires M⁺, 298.1750).

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46. We thank Dr. M. Tute (Pfizer UK Ltd) for kindly offering to undertake these calculations.

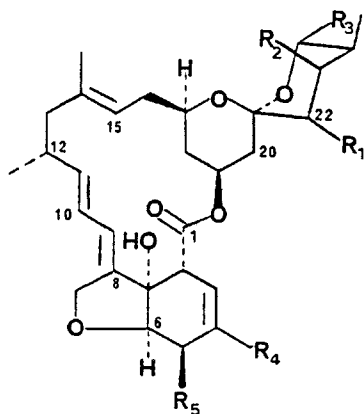
STUDIES ON THE SYNTHESIS OF MILBEMYCIN β_1

INTRODUCTION

Since their isolation, in 1975 and 1979 respectively, the milbemycin and avermectin classes of compounds have been the subject of intense chemical and biological interest.

The milbemycins ¹, fermentation products of *Streptomyces hygroscopicus* subsp. *aureolacrimosus*, have been shown to display broad spectrum anthelmintic, insecticidal and acaricidal activity. The class subdivides into two series, the pentacyclic α series (Figure 1), of which fifteen examples are at present known, and the tetracyclic β series (Figure 2) of which there are five examples. The major structural features common to both series are: a macrocyclic 16-membered lactone ring, a 5,5-dioxaspiroundecane (spiro-ketal) moiety, and a cyclohexenyl ring. In addition, the α series possess a tetrahydrofuranyl ring *cis* fused to the cyclohexenyl moiety.

The avermectins ² (Figure 3), of which eight examples are currently known, were isolated from the mycelia of *Streptomyces avermitilis*. They are pentacyclic glycoside derivatives bearing a disaccharide function at C₁₃, plus a more highly functionalised second ring in the spiro-ketal portion, but otherwise displaying essentially identical structural features to the milbemycin α series. They possess potent activity against helminths and arthropods, in doses as low as 10 $\mu\text{g kg}^{-1}$, although they lack the antibacterial properties commonly associated with macrolide antibiotics. They are not ionophores, nor do they interfere with protein synthesis, but appear to act by perturbation of the neurotransmission systems of invertebrates. The disaccharide function is crucial to the biological activity of the avermectins, with removal of one sugar reducing the activity by 50%, with a drop to a mere 3% of full activity being observed on removal of both sugars. ³

Figure 1: Structures of the Milbemycin α series

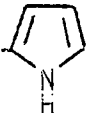
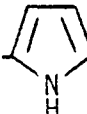
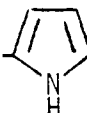
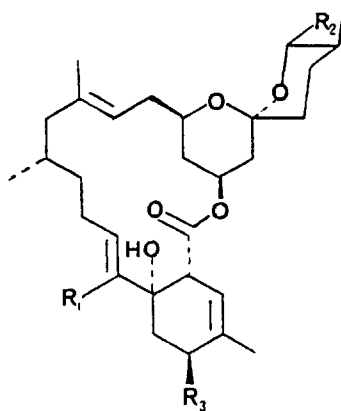
Milbemycin	R ₁	R ₂	R ₃	R ₄	R ₅
α_1	H	H	CH ₃	CH ₃	OH
α_2	H	H	CH ₃	CH ₃	OCH ₃
α_3	H	H	C ₂ H ₅	CH ₃	OH
α_4	H	H	C ₂ H ₅	CH ₃	OCH ₃
α_5	OH	OCOCH(CH ₃)C ₄ H ₉	CH ₃	CH ₃	OH
α_6	OH	OCOCH(CH ₃)C ₄ H ₉	CH ₃	CH ₃	OCH ₃
α_7	OH	OCOCH(CH ₃)C ₄ H ₉	C ₂ H ₅	CH ₃	OH
α_8	OH	OCOCH(CH ₃)C ₄ H ₉	C ₂ H ₅	CH ₃	OCH ₃
α_9	H	H	CH ₃	CH ₂ OCO- 	OH
α_{10}	H	H	C ₂ H ₅	CH ₂ OCO- 	OH
D	H	H	CH(CH ₃) ₂	CH ₃	OH
F	H	H	CH(CH ₃) ₂	CH ₂ OCO- 	OH
G	H	H	CH(CH ₃) ₂	CH ₃	OCH ₃
J	H	H	CH ₃	CH ₃	=O
K	H	H	C ₂ H ₅	CH ₃	=O

Figure 2: Structures of the Milbemycin β series

	R_1	R_2	R_3
β_1	CH_2OH	CH_3	OCH_3
β_2	CH_2OH	C_2H_5	OCH_3
E	CH_2OH	$\text{CH}(\text{CH}_3)_2$	OCH_3
H	CH_3	$\text{CH}(\text{CH}_3)$	$=\text{O}$

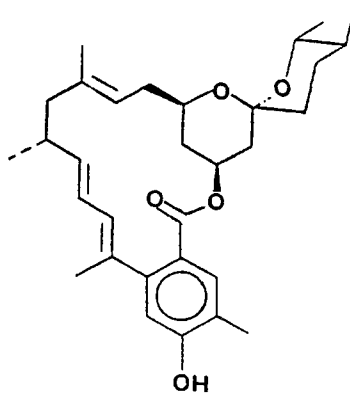
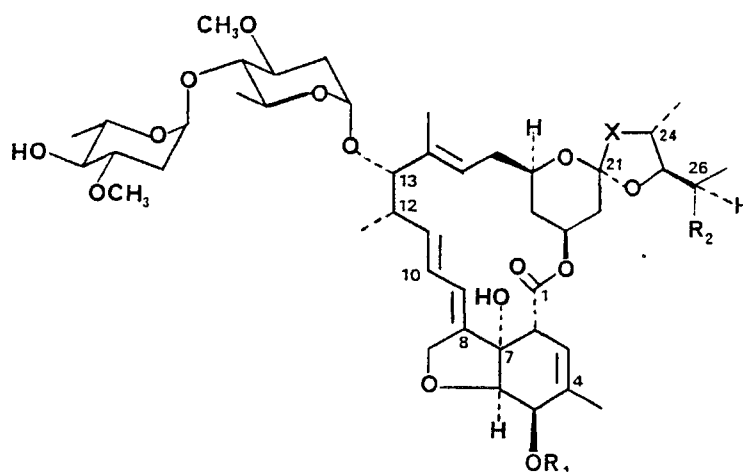
Milbemycin β_3 

Figure 3: Structures of the Avermectins



Avermectin	R ₁	R ₂	X
A _{1a}	CH ₃	C ₂ H ₅	$\begin{array}{c} \text{OH} \\ \\ -\text{CH}_2-\text{CH}- \\ 22 \quad 23 \end{array}$
A _{1b}	CH ₃	CH ₃	$\begin{array}{c} \text{OH} \\ \\ -\text{CH}_2-\text{CH}- \end{array}$
A _{2a}	CH ₃	C ₂ H ₅	-CH=CH
A _{2b}	CH ₃	CH ₃	-CH=CH
B _{1a}	H	C ₂ H ₅	$\begin{array}{c} \text{OH} \\ \\ -\text{CH}_2-\text{CH}- \end{array}$
B _{1b}	H	CH ₃	$\begin{array}{c} \text{OH} \\ \\ -\text{CH}_2-\text{CH}- \end{array}$
B _{2a}	H	C ₂ H ₅	-CH=CH-
B _{2b}	H	CH ₃	-CH=CH-

In view of their potent biological activity and the dense and varied array of chemical functionality they contain, the great interest shown in the milbemycins and avermectins by synthetic chemists is hardly surprising.

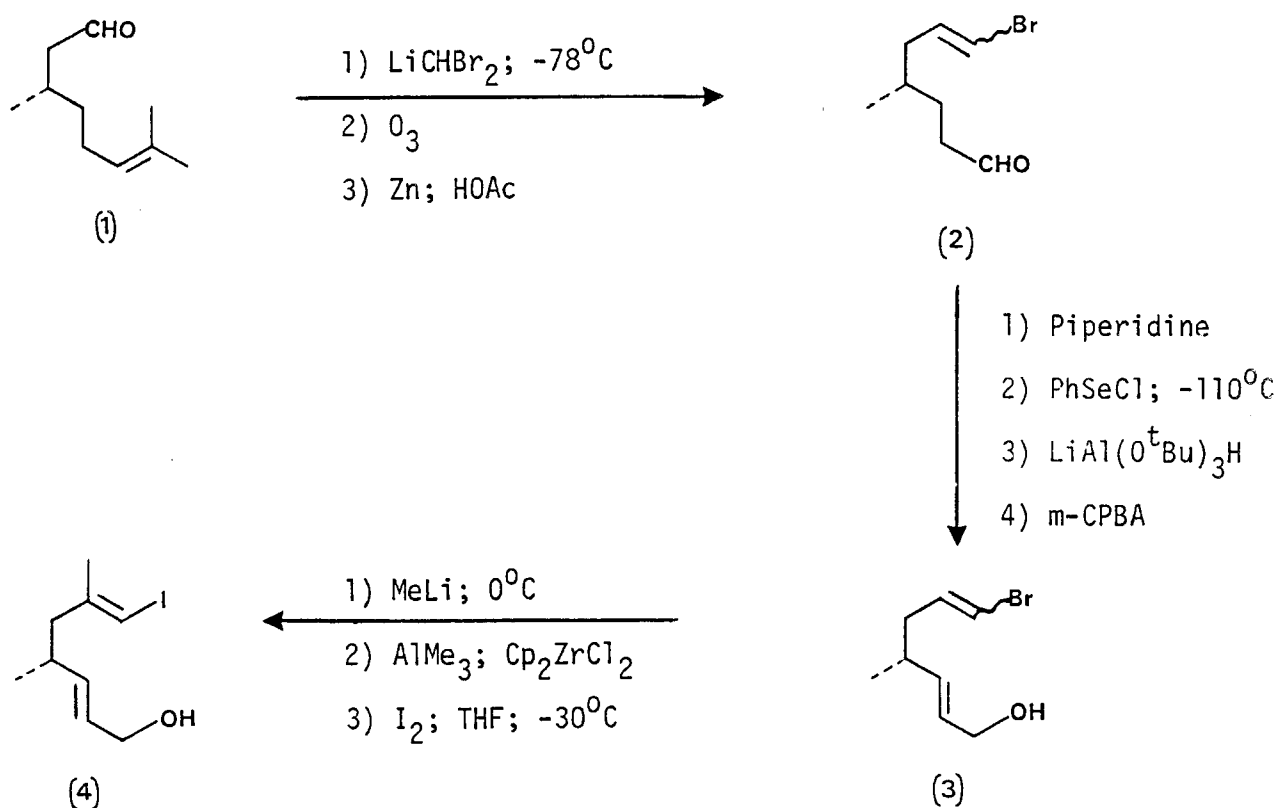
To date, only two total syntheses have been achieved, both of the simplest member of the milbemycin class, milbemycin β_3 .^{4, 5} Paradoxically, β_3 displays no biological activity and is no longer produced by *Streptomyces hygroscopicus*, reportedly due to mutation of the strain. It appears quite possible in the light of this that it is not a true natural product, but an artefact of the isolation procedure. Subsequently, four more syntheses of the spiro-ketal moiety common to milbemycins β_1 and β_3 have appeared^{6 - 9}, and one of the avermectin B_{1a} spiro-ketal.¹⁰ In addition, a synthesis of the L-oleandrosyl sugar portion of the avermectins has been described.¹¹

The work to be described in the results and discussion part of this section deals with attempts to prepare suitable synthons for introduction of the side-chain ($C_{8a}-C_{14a}$) into milbemycin β_1 . Although milbemycin β_3 does not possess the potentially labile allylic diol system present at C_{7-8a} of β_1 , it is instructive to consider the methodology utilised in the aforementioned total syntheses of this molecule, particularly since the strategy involved in the formation of the trisubstituted (E)- $C_{14}-C_{15}$ olefinic linkage should be directly applicable to milbemycin β_1 .

The strategy described by Williams⁴ leading to the chiral side-chain begins with (-)-(3S)-citronellal (1) (Scheme 1). Addition of lithiodibromomethane was followed by ozonolysis, with subsequent zinc/acetic acid treatment affording simultaneous ozonide reduction and bromoalkene formation to give (2) in 60% yield. Enamine formation followed by treatment with PhSeCl afforded the selenylaldehyde, which

was reduced to the selenyl alcohol. Oxidative elimination afforded the (E)-allylic alcohol (3) in 76% overall yield from (2). Introduction of the (E)-olefinic linkage in this way circumvents any possibility of epimerisation of the chiral methyl substituent. Elimination of HBr from (3) (formed in a 55:45 E:Z ratio about the bromoalkene) to give the terminal alkyne and subsequent elaboration *via* methodology

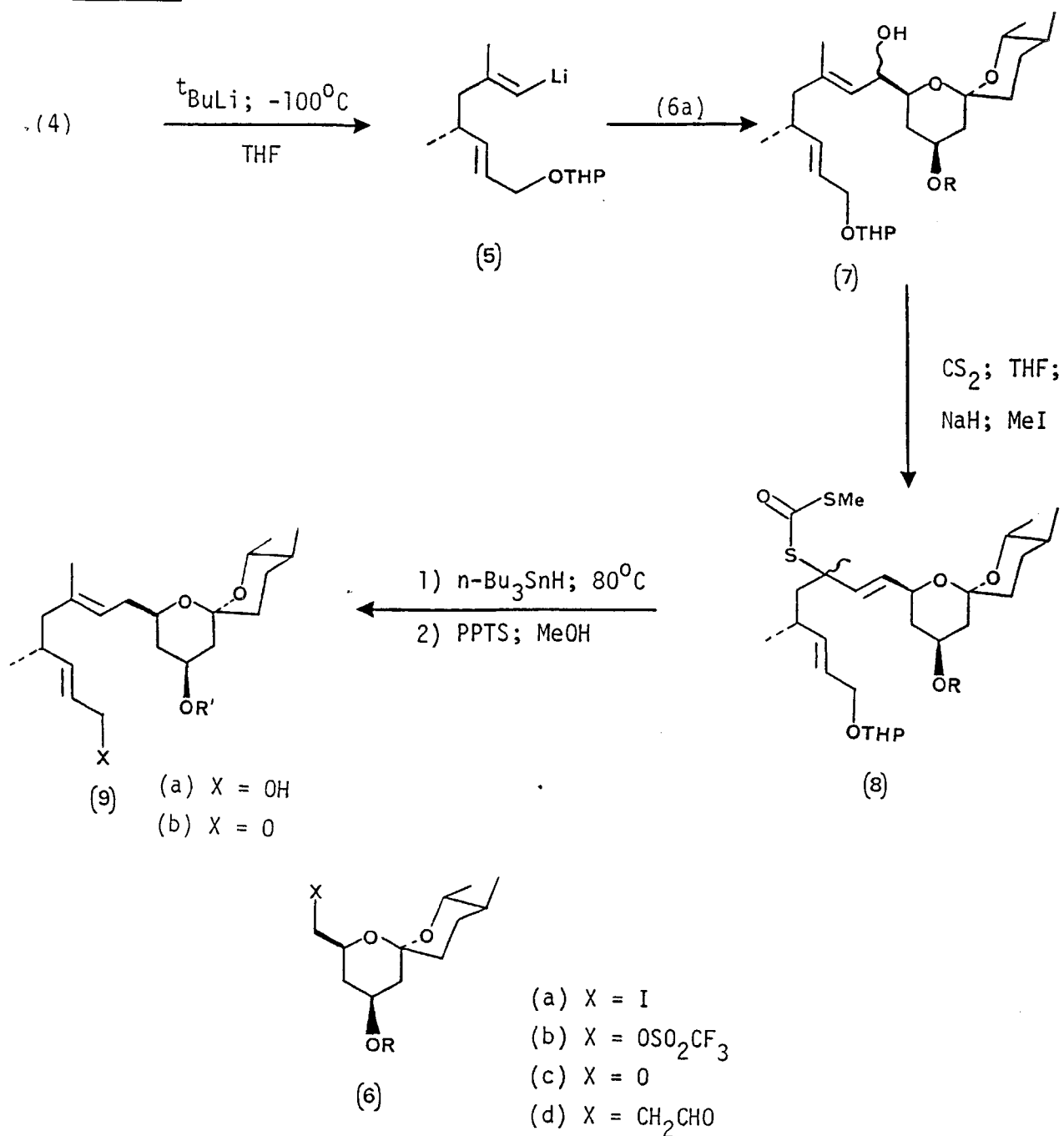
Scheme 1



developed by Negishi¹² stereospecifically produced the (E)-vinyl iodide (4) in a yield of 71%. The THP ether of (4) was metallated using the Seebach procedure²¹ to give the lithio anion (5), which unfortunately failed to undergo any alkylation reaction with the spiro-ketal synthon (6a), as did the corresponding mixed cuprate reagents derived from (5). This lack of reaction is attributable to the retarding effect of the β -oxygen in the spiro-ketal ring, a well-known phenomenon. Subsequent work in other fields suggests that utilisation of the more reactive triflate (6b) might have avoided this problem.¹³

Reaction of (5) with the aldehyde (6c) however, rapidly afforded (7) in 73% yield (Scheme 2). Formation of the xanthate (8) proceeded

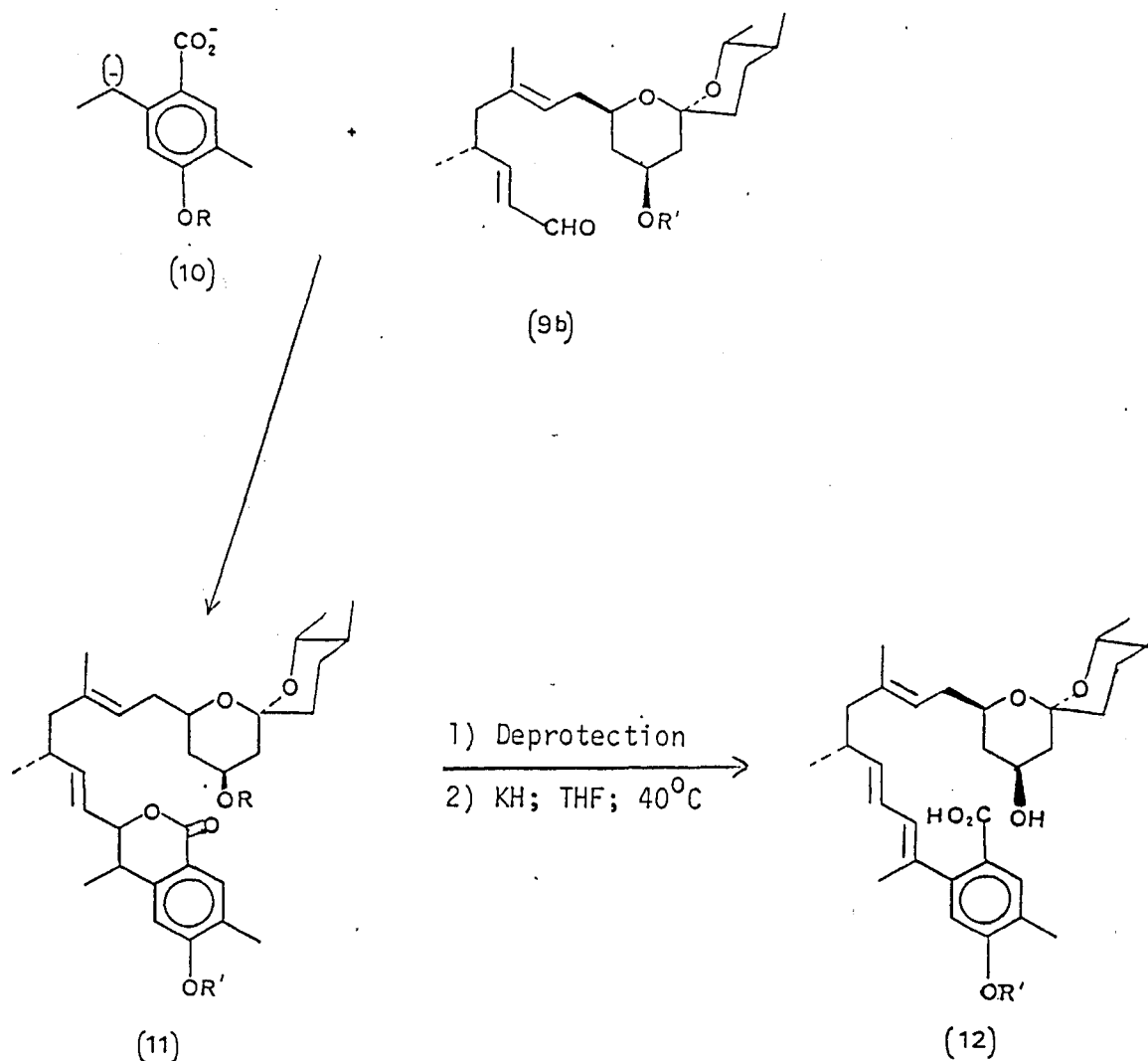
Scheme 2



with [3,3] sigmatropic rearrangement in 90% yield. Reduction proceeded with another rearrangement giving (9a) in 76% yield after alcohol deprotection.

Swern oxidation ¹⁴ gave the aldehyde (9b) which was coupled with the aromatic dianion (10) to afford lactone (11) in 74% yield (Scheme 3). Subsequent elimination with KH gave the desired (E,E) diene (12) in 85%

Scheme 3

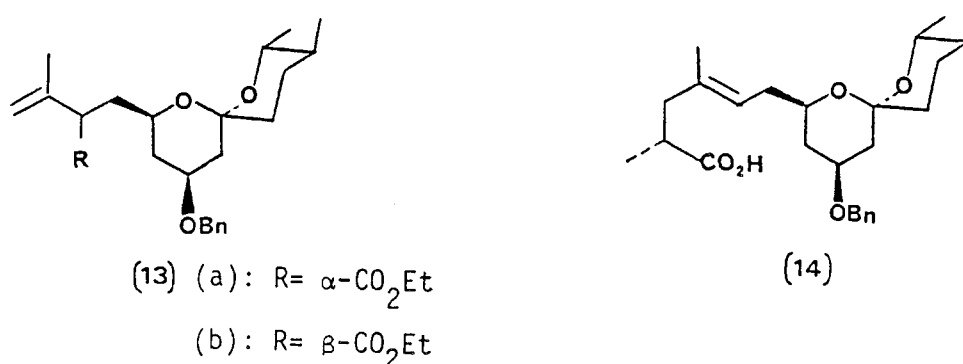


yield after alcohol deprotection. Macrolactonization and deprotection then afforded the natural product in 85% yield.

The second approach, this time to racemic milbemycin β_3 is due to Smith. ⁵ Addition of isopropenyl Grignard to the homologous aldehyde (6d) and subsequent propanoylation afforded a separable 2:1 mixture of the propionates (13a) and (13b) in 71% yield. The separate isomers

were then independently subjected to the highly stereoselective ester-enolate Claisen rearrangement developed by Ireland¹⁵, making use of Ireland's observation that selective (E) and (Z) enolate generation is possible by correct choice of reaction solvents (Scheme 4). Both isomers gave predominantly the acid (14) with the correct double-bond geometry and relative stereochemistry at the methyl group. The yield from the α -isomer was 78% and from the β -isomer, 57%, with stereoselectivities of 3:1 and 6:1 respectively.

Scheme 4



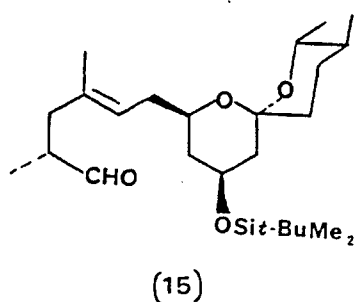
Conditions : (13a) $\longrightarrow$ (14):

- 1) LDA; DME; -78°C
- 2) HMPA; -78°C
- 3) TMSCl; -78°C
- 4) ^tBuOH; -78°C $\longrightarrow$ 25°C

(13b) $\longrightarrow$ (14):

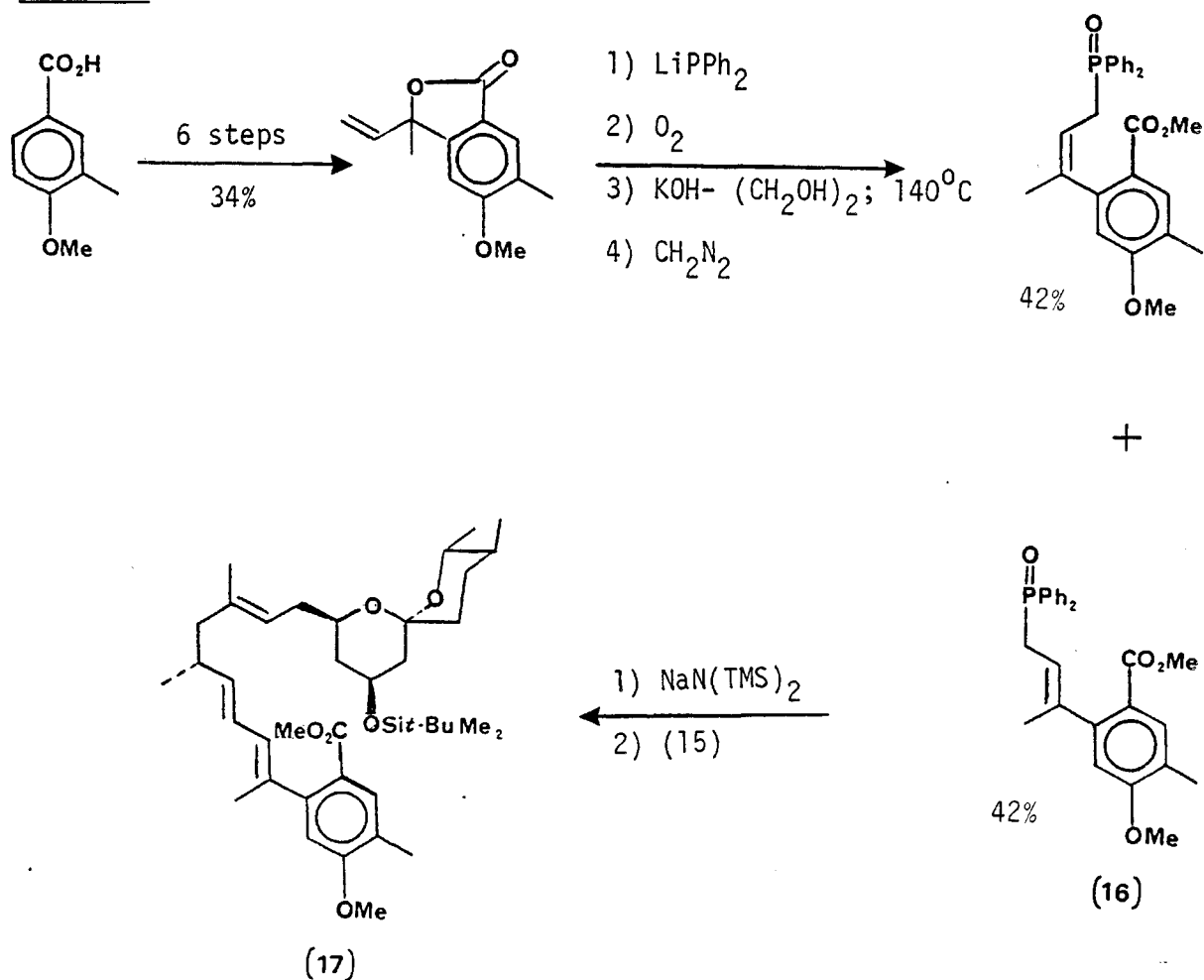
- 1) KN(TMS)₂; -78°C
- 2) TMSCl; -78°C $\longrightarrow$ 25°C

(14) was then straightforwardly transformed to the aldehyde (15) by standard procedures in 59% overall yield.



The required (E)-C₁₀-C₁₁ double bond was then generated *via* coupling with the sodium anion of the phosphine oxide (16), prepared from 3-methyl-*p*-anisic acid (Scheme 5).

Scheme 5



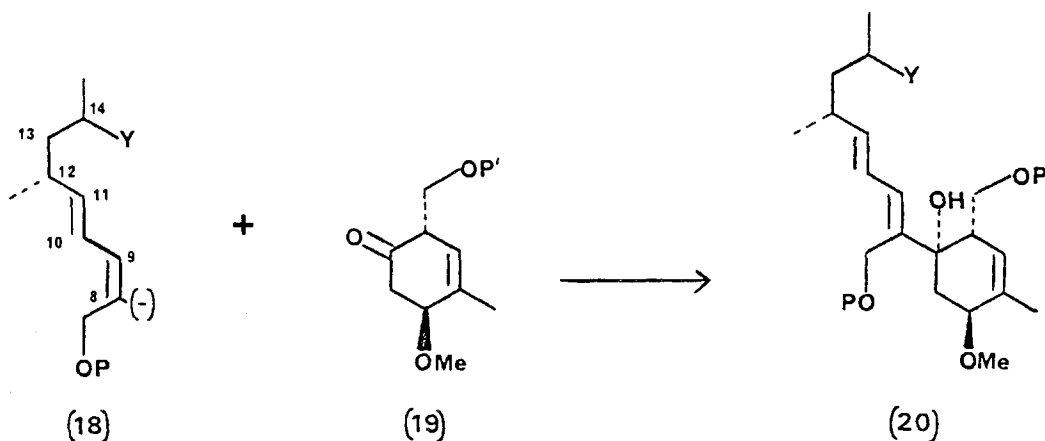
Deprotection of (17) followed by macrolactonization then afforded racemic milbemycin β_3 .

Our own synthetic interest in this area lay initially in a projected chiral synthesis of milbemycin β_1 , utilising a sufficiently flexible route such that subsequent modification would permit preparation of the avermectins, our ultimate aim. Clearly the coupling methods described by Williams and Smith for the formation of the C₁₄-C₁₅ olefinic linkage of milbemycin β_3 are both modifiable to a synthesis of β_1 . The more complex C₇-C₈ substitution pattern of the latter plainly requires the

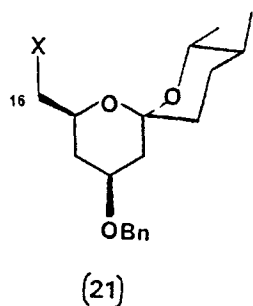
development of new coupling strategies. The account below details approaches directed towards the development of such a strategy, together with the preparation of suitable synthons for a potentially more direct construction of the C₁₄-C₁₅ linkage.

RESULTS AND DISCUSSION

Our main synthetic effort was aimed at developing a method to allow the stereocontrolled formation of the C₇-C₈ linkage with concomitant introduction of at least the whole C_{8a}-C_{14a} side-chain carbon framework. Our strategy relied upon the premise that addition of a geometrically defined vinyl carbanion such as (18) to a suitably protected cyclohexenone derivative such as (19) should proceed in a manner dictated by steric approach control to afford (20) stereoselectively.



Ideally (18) would bear the previously introduced spiro-ketal substituent, leaving only oxidation at C₁, deprotection and macro-lactonization to complete the synthesis. Hence the problem reduces to preparation of a suitable precursor to (18), which in turn raises the difficulty of constructing the C₁₄-C₁₅ double bond in a geometrically-controlled process. Our approach to this latter task was governed by the knowledge that the synthesis of the spiro-ketal synthon (21a) was already at an advanced stage in our laboratory, a synthesis subsequently brought to a successful conclusion.⁶

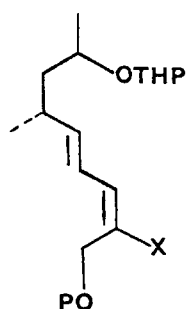
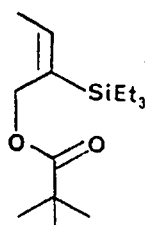


- (a) X = OH
- (b) X = I
- (c) X = CH₂P(=O)(Ph)₂
- (d) X = CH₂SO₂Ph
- (e) X =
- (f) X = CHO
- (g) X = SO₂CF₃

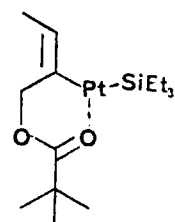
Manipulation of the substituent at C₁₆ *via* the iodide (21b) or triflate (21g) would allow the preparation of suitable "nucleophile" synthons for the study of methods of directly forming the C₁₄-C₁₅ bond. It should be noted in advance that direct construction in a geometrically predetermined manner of triply substituted olefins is still frequently problematic in organic chemistry, and although we were confident that coupling could be achieved, there was little precedent to enable confident prediction of its geometrical outcome. We chiefly envisaged utilising the phosphine oxide (21c) or the sulphone (21d), employing methodology developed by Warren¹⁶ and Julia¹⁷ respectively. As an alternative to employing (21c) or (21d) as a nucleophile in the coupling reaction, the possibility of preparing the aldehyde (21f) *via* the dithiane (21e) was considered, allowing the use of the spiro-ketal as an electrophilic partner in the union, perhaps with a sulphone carbanion at C₁₄ of the side chain.

Since we ultimately aimed to prepare (18) already bearing the spiro-ketal substituent, we initially decided to pursue the preparation of (18) with a protected alcohol function at C₁₄. Thus, preparation of the ketone or sulphone required for the C₁₄-C₁₅ olefin formation was facilitated, and by careful choice of the THP protecting group we hoped to mimic the reactivity of the spiro-ketal to subsequent reaction conditions until such a time as when realistic quantities of the required spiro-ketal became available.

It thus remained to devise a method for the geometrically controlled production of the vinyl carbanion. One of the better methods for generating vinyl anions is the Shapiro reaction utilising tosylhydrazones.¹⁸ However, this has only seldom been used to generate anions where a possibility of geometrical isomerism has existed¹⁹, and with so little precedent the method was rejected. The choice thus fell between transmetallation of a vinyl stannane²⁰ using alkyl lithium reagents, or metallation of a vinyl halide to give the Grignard or lithio reagent.²¹ Both of these methods were known to give the vinyl anions with retention of olefin geometry, thus requiring the preparation of precursors of the appropriate geometry. At the commencement of this work this was not feasible for the stannane precursor, but work reported by Stork²² and Chan²³ led us to believe that production of the iodide (22b) was possible. Stork had observed that hydrosilylation of the pivalate derived from but-2-yn-1-ol with H_2PtCl_6 as catalyst afforded the vinyl silane (23) selectively, presumably *via* an intermediate of type (24).

(22) (a): $\text{X} = \text{SiEt}_3$ (b): $\text{X} = \text{I}$ 

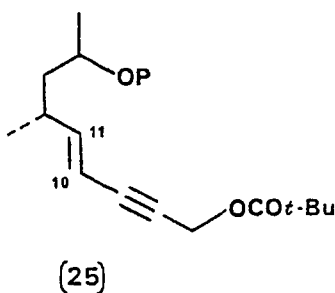
(23)



(24)

Chan reported that treatment of vinyl silanes with iodine in CH_2Cl_2 at room temperature afforded the vinyl iodide with retention of olefin geometry in good yield. Hence it was reasoned that hydrosilylation of

the enynol derivative (25) using Stork's conditions, followed by treatment with iodine would give (22b). It was also argued that the di-substituted C₁₀-C₁₁ olefin should be unaffected by the iodine treatment,



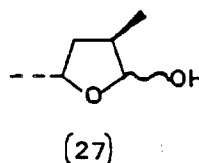
since the propensity of vicinal diiodides to revert to iodine and an olefin is well known.²⁴

Initially it was envisioned that (25) should be produced *via* Wittig coupling of the phosphorane (26) and the lactol (27).



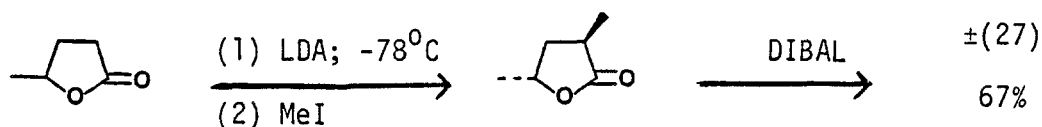
(26) (a): P=TBDMs

(b): P=THP



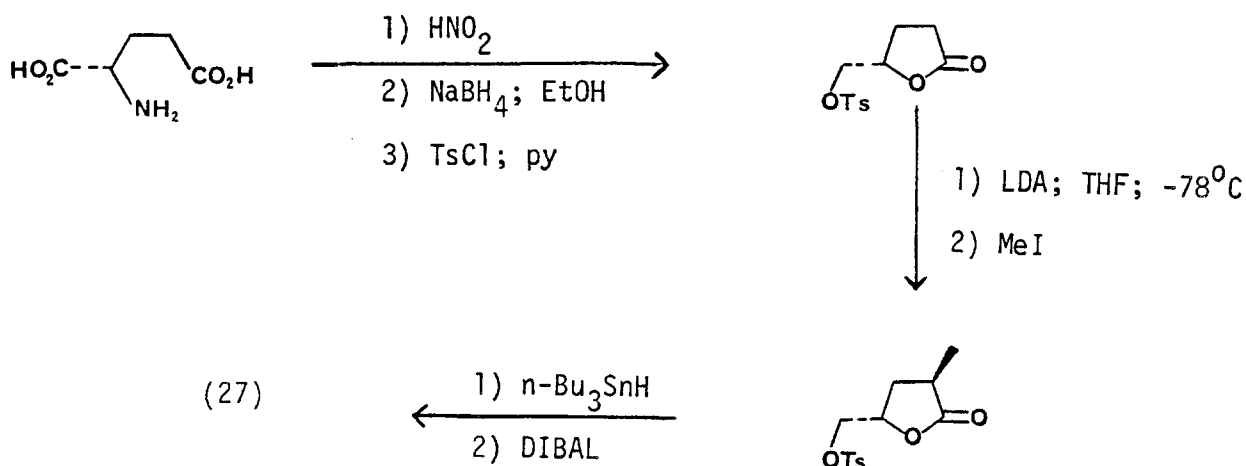
Racemic lactol (27) was readily prepared from γ -valerolactone in two steps by generation of the lithium enolate, quenching with methyl iodide, and DIBAL reduction of the resultant dimethyl lactone (Scheme 6).

Scheme 6



The initial methylation proceeded to give a 7:1 ratio of the *trans* to *cis* lactone. A route to enantiomerically pure (27) with the correct absolute configuration for milbemycin synthesis had previously been developed in our laboratory *via* known intermediates readily available from L-glutamic acid²⁵, Scheme 7.

Scheme 7



A single recrystallization after the methylation step allowed removal of trace amounts of unwanted *cis* methylated product.

Preparation of the three monohalo derivatives of butyn-1,4-diol was readily achieved *via* literature procedures²⁶, and protection as the TBDMS or THP ethers also proceeded routinely to produce the protected halo alkynols (28 a - f).



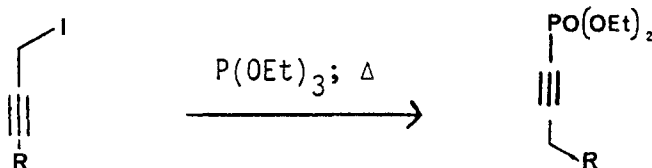
- | | |
|---------------------|--|
| (a) P = THP, X = Cl | (d) P = TBDMS, X = Cl |
| (b) P = THP, X = Br | (e) P = TBDMS, X = Br |
| (c) P = THP, X = I | (f) P = TBDMS, X = I |
| | (g) P = TBDMS, X = SO ₂ Ph. |

Reaction of any of these compounds with PPh₃ did not produce however the anticipated phosphonium salt, giving dark oils, or air-unstable solids displaying aromatic protons only in the n.m.r. spectrum. These

possibly arose from direct attack of PPh_3 at the halide atom, a known process for activated halides.

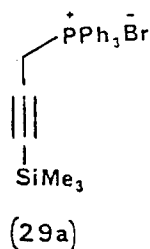
Treatment of the iodide (28f) with sodium benzenesulphinate afforded a white crystalline solid, which appeared by n.m.r. to be a mixture of isomers. The isomers were separable by rapid column chromatography, but the isomer corresponding to (20g) by n.m.r. rapidly reisolomerised (by TLC), suggesting that (28g) was possibly thermodynamically unstable. Treatment of (28f) with $\text{P}(\text{OEt})_3$ under standard Arbuzov conditions returned only starting material, although it should be noted that propargylic phosphonates have been shown under the conditions of their formation to isomerise completely to the terminal phosphonate²⁷ (Scheme 8).

Scheme 8



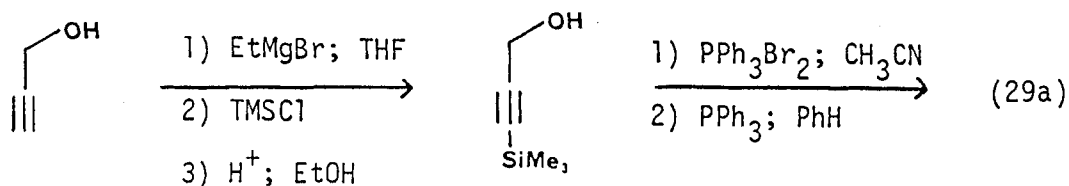
Addition of (28f) to a deep-red THF solution of lithium diphenylphosphide produced an instantaneous discharge of the red colouration, but attempted work-up of the reaction mixture with H_2O_2 to give the phosphine oxide caused a violent explosion. In the light of these results, a more indirect approach to (22b) was pursued.

Phosphorane (29b) has been utilised by both Corey²⁸ and Jones²⁹ in the preparation of enyne systems and has been observed to display moderate *trans* enyne selectivity.



The requisite phosphonium salt (29a) was readily prepared *via* a modification of the route of Jones²⁹ (Scheme 9).

Scheme 9

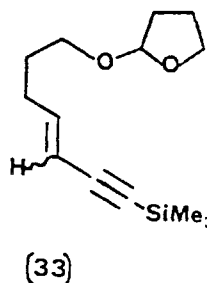
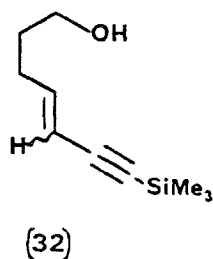
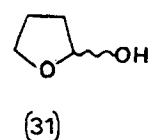
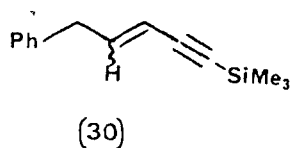


It was found that doubling of the quantity of solvent used in the initial silylation step, and employment of the modified work-up/monodeprotection procedure described by Whittle³⁰ allowed isolation of pure TMS-propargyl alcohol in near quantitative yield, double that reported by Jones. Also, a change of solvent from DMF to CH₃CN in the bromination step avoided the need for the tedious chromatography and fractional distillation reported in the literature, although the yield of the bromide was identical.

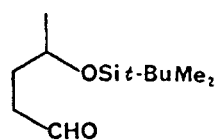
In view of the somewhat conflicting reports in the literature of the E:Z enyne selectivity of (29b)^{28, 29}, a brief study of its reactions with different aldehydes and lactols was undertaken.

Treatment of (29a) with *n*-BuLi in THF at -78° to -40°C, followed by quenching with one equivalent of phenylacetaldehyde at -40° to 0°C produced enyne (30) in 41% yield with a 3:1 E/Z ratio; this ratio is in good agreement with those obtained by Corey and Jones. Reaction

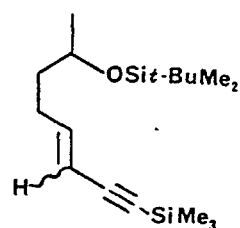
of (29b) in similar manner with 0.5 equivalents of the lactol (31) afforded (32) as a 4.5:1 E/Z mixture in 46%, together with *ca.* 10% of the by-product (33), presumably derived from reaction of (32) with a further molecule of (31).



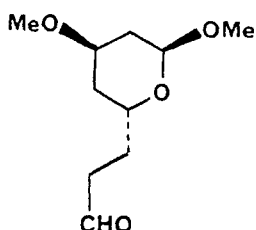
Reaction of (29b) with 0.7 equivalents of the aldehyde (34), as a means of comparing the reaction of a lactol and a similar open-chain protected hydroxy-aldehyde afforded a 45% yield of (35) in a 2.6:1 E/Z ratio when the reaction was conducted under identical conditions to those with (31). The same reaction at -78°C afforded a low yield of (35) as a *ca.* 1:1 E/Z mixture, in accordance with the findings of Jones²⁹ that the E/Z ratio of (29) decreased at low temperature. This contrasts sharply with the findings of Grieco³¹ that reaction of (29b), generated under identical conditions, at -78°C with the aldehyde (36) gives only the (E)-enyne (37). (35) was readily *O*-desilylated by treatment with $\text{HF}/\text{CH}_3\text{CN}$ ³² to give (38) in 84% yield. No *C*-desilylation was observed. Oxidation of (36) to the ketone (39) using PCC proceeded smoothly in 89% yield. (39) proved to be a useful compound for studying coupling reactions with model spiro-ketal systems.



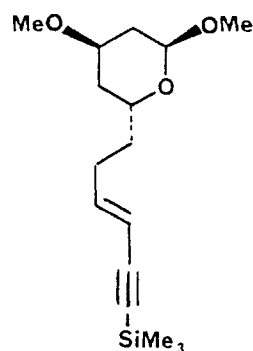
(34)



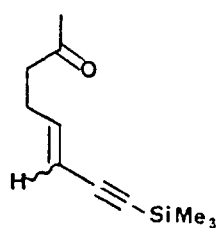
(35)



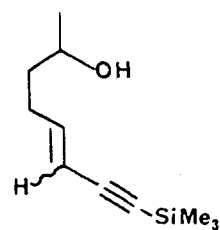
(36)



(37)



(39)

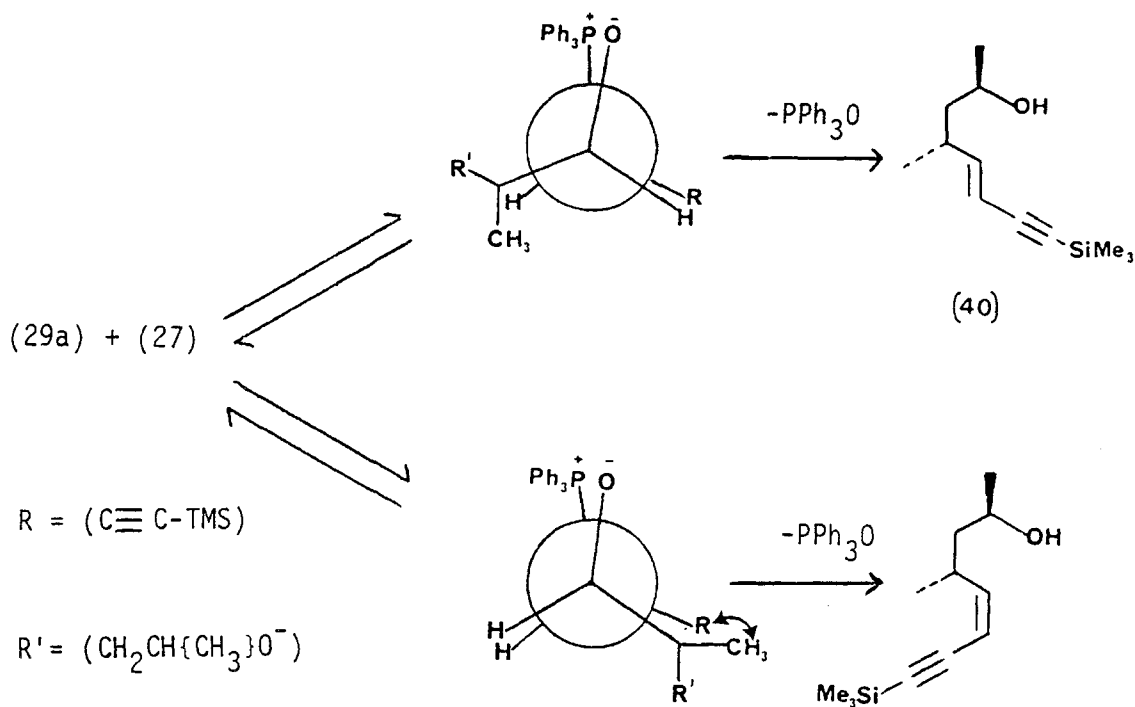


(38)

Reactions of (29b) with racemic lactol (27) were then studied. Optimum conditions were found to utilise a 4-fold excess of (29b) at -30° to 0°C , affording (40) in 58% yield with a highly satisfactory E/Z ratio of greater than 30:1. The remarkably increased E/Z ratio in this reaction, over that of the reaction to give (32) is possibly accounted for by the effect of the methyl substituent α to the reacting centre. In the transition state leading to decomposition of the *erythro* betaine, considerable steric buttressing between this methyl group and the linear acetylene moiety is present. In the

threo betaine, such buttressing is absent. Thus elimination of the *threo* betaine would be a thermodynamically favoured event over the *erythro* case, even though it is thought that initial formation of the *erythro* betaine is kinetically favoured³³ (Scheme 10).

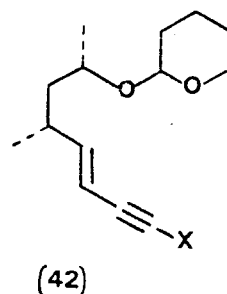
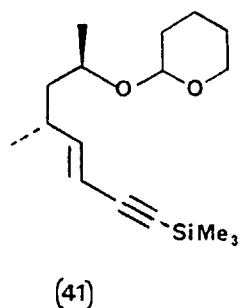
Scheme 10



The linearity of the acetylene side-chain prevents its adoption of a conformation in which the steric buttressing may be avoided.

Interestingly, substitution of DME for THF in the reactions of phosphorane (29b) led to multiple products and a poor yield of the required enyne.

Since we ultimately planned to couple the spiro-ketal moiety to the side-chain at this point, the alcohol function of (40) was protected as its THP ether (41), in quantitative yield, in order to mimic the spiro-ketal reactivity as previously discussed.



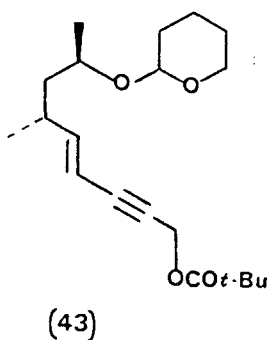
(a): X = H

(b): X = CO₂Me

(c): X = CH₂OH

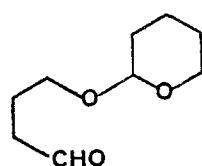
The MeLi-induced simultaneous deprotection-lithio anion formation from silyl alkynes described by Holmes³⁴ returned only unreacted starting material from subjection of (41) to the given conditions. Treatment with *n*-Bu₄NF in THF however rapidly afforded the deprotected enyne (42a) in 87% yield. Introduction of the propargylic alcohol function was achieved in a simple two-step process. Treatment of (42a) with *n*-BuLi at -78°C, followed by quenching with excess MeOCOCl, gave (42b) in quantitative yield. Reduction of the ester function with three equivalents of DIBAL then gave (42c) in 91% yield. (42c) could also, in principle, be prepared from (42a) by quenching of the lithio-anion with formaldehyde, but such reactions are often capricious and the route described is both simple to perform and high yielding.

Treatment of (42c) with pivalic anhydride in pyridine then gave (43), the required substrate for the hydrosilylation reaction, in 90% yield.

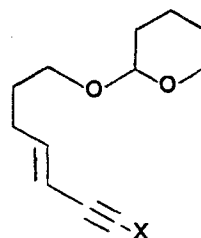


Exposure of (43) to the hydrosilylation conditions described by Stork²² (10% aq. H_2PtCl_6 , Et_3SiH , 120°C) led rapidly to formation of a new single spot on TLC analysis. However, examination of the high field n.m.r. spectrum of this material showed clearly that the hydrosilylation had afforded a mixture of diene isomers, together with over-reduced material. Prolonged reaction times led to some THP-deprotection, but only after hydrosilylation had occurred. It was noted that the reaction time for hydrosilylation of (43) (ca. 20 minutes) was much shorter than that reported by Stork (ca. 3 hrs), although the reason for this is not clear. Attempts to modify the hydrosilylation procedure were hampered by lack of material, and thus it was decided to study the reaction on a model system which would be available in larger quantities.

Thus, reaction of (29b) with the readily prepared aldehyde (44) at 0°C gave (45a) in a gratifying yield of 77%, although only as a 1:1 E/Z mixture.



(44)



(45)

(a): X = TMS

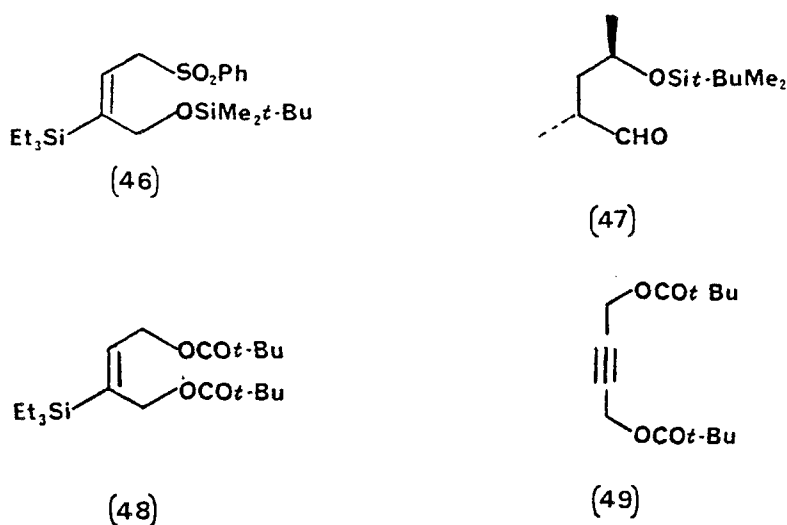
(b): X = H

(c): X = CO_2Me (d): X = CH_2OH (e): X = $\text{CH}_2\text{OCO}^t\text{Bu}$

(45a) was then converted to (45e) *via* an identical series of reactions to that utilised to prepare (43), in 53% overall yield. With material in hand, the hydrosilylation reactions of (45e) were studied. Repetition of the Stork procedure led to the same disappointing result as with (43). Use of isopropanol as solvent, as described by Russian workers³⁵,

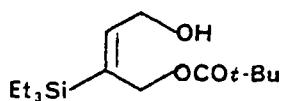
unsurprisingly led to deprotection of the THP ether, followed by silylation of the resultant alcohol. Although many different hydrosilylation conditions were tried, including modifying the alcohol protecting group, in all cases hydrosilylation either did not proceed at all, or gave isomeric mixtures. In the light of these disappointing reactions, it was decided to pursue an alternative approach to (22a).

This approach relied on constructing the disubstituted olefinic linkage of (22a) from the sulphone (46), bearing the preformed vinyl silane of correct geometry, and the aldehyde (47).

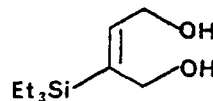


Early attempts at regioselective hydrosilylation of suitable non-symmetrical acetylene precursors to (46) had been unsuccessful. Hence, preparation of (46) was envisaged from selective deprotection of (48), the steric bulk of the Et_3Si - group enabling chemical differentiation of the pivalate groups. (48) was readily prepared by hydrosilylation of (49) in quantitative yield to give a single isomer. Assignment of (E)-geometry to (48) was based on literature precedent³⁶, since hydrosilylation has been shown to proceed in a *cis* manner. Treatment of (48) with 2 equivalents of MeLi in ether at 0°C afforded the mono-

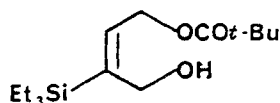
deprotected (50) in 49% yield, together with 16% of the diol (51), the steric bulk of the Et_3Si -group thus seeming to favour attack at the remote ester function. However, repetition of the reaction at -78°C rapidly gave a mixture containing only 27% of (50), together with 43% of its isomer (52), and 6% of the diol (51).



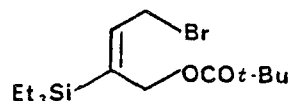
(50)



(51)



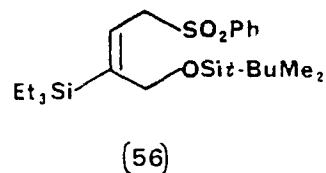
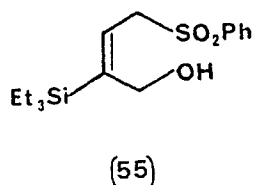
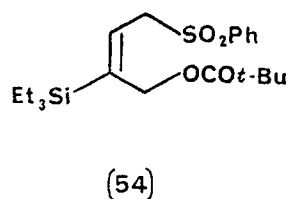
(52)



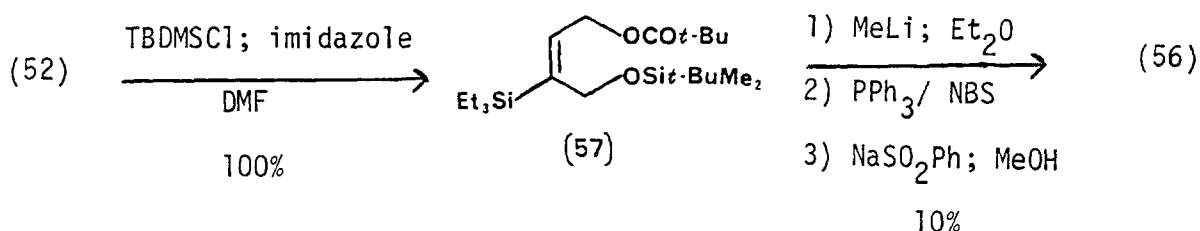
(53)

Reaction at -78°C in THF gave (50), (51) and (52) in yields of 16%, 20% and 42% respectively. These results preclude a simple rationalisation based on steric approach control, since the reaction at lower temperature would be expected to favour this effect. At the present time this puzzling result defies rationalisation.

Bromination of (50) was achieved by treatment with NBS/ PPh_3 to afford (53) in 73% yield. Displacement of bromide with NaSO_2Ph in methanol smoothly gave the sulphone in 90% yield after chromatography. Removal of the unwanted pivaloyl group of (54) was accomplished by treatment with excess LiAlH_4 at -78° in ether, affording the labile alcohol (55). This was immediately converted to the TBDMS ether under standard conditions to give (56) as a waxy solid in 80% yield from (54).



It was found to be crucial to strictly maintain the reaction temperature of the reduction step at -78° in order to avoid formation of multiple by-products, presumably *via* sulphone reduction, with a consequent sharp decrease in yield. (56) was also readily prepared from (52) *via* the sequence outlined below

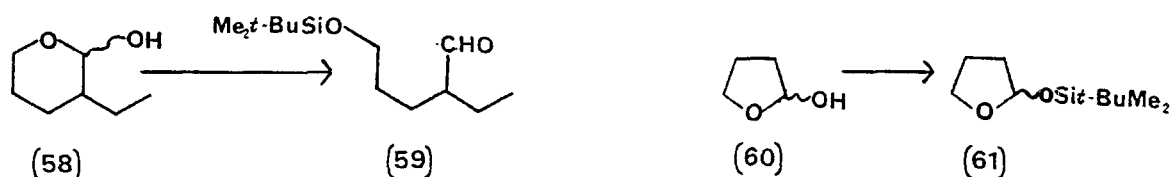


Unfortunately the yield for the bromination step was very low, presumably due to the instability of the TBDMS protecting group to the reaction conditions.

With the sulphone (56) in hand we turned our attention to preparation of the aldehyde (47) required for construction of the required diene system. Since both the chiral and racemic modifications of the lactol (27) were readily available, and noting that this in itself was a masked hydroxy-aldehyde, we sought an efficient process for conversion of (27) to (47).

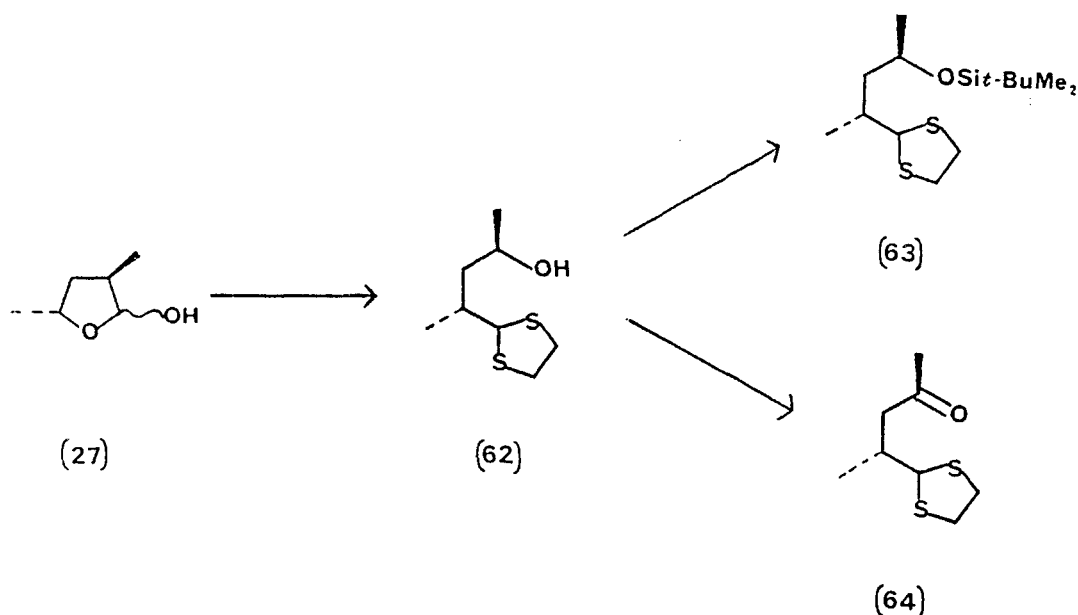
In contrast to the behaviour of δ -lactols, which on silylation readily give the protected hydroxy-aldehyde as the chief product

(eg (58) $\rightarrow$ (59))³⁷, γ -lactols are known to be much less prone to ring-opening, and silylation usually affords the ring-closed product, eg (60) $\rightarrow$ (61).



An expeditious method to circumvent this propensity of γ -lactols to remain in the cyclic form has recently been described by Paquette.³⁸ Hence, 1,3-dithiolane formation using ethanedithiol and, crucially, TiCl_4 as catalyst, in THF at -78°C affords the hydroxy-dithiolane in high yield. Thus exposure of racemic (27) to these reaction conditions led cleanly to the hydroxy-dithiolane (62) in quantitative yield, Scheme 11. Protection of (62) under standard conditions³⁹ smoothly gave the silyloxydithiolane (63) in 97% yield. Alternatively, oxidation of (62) with PCC afforded the dithiolane ketone (64) in 74% yield.

Scheme 11

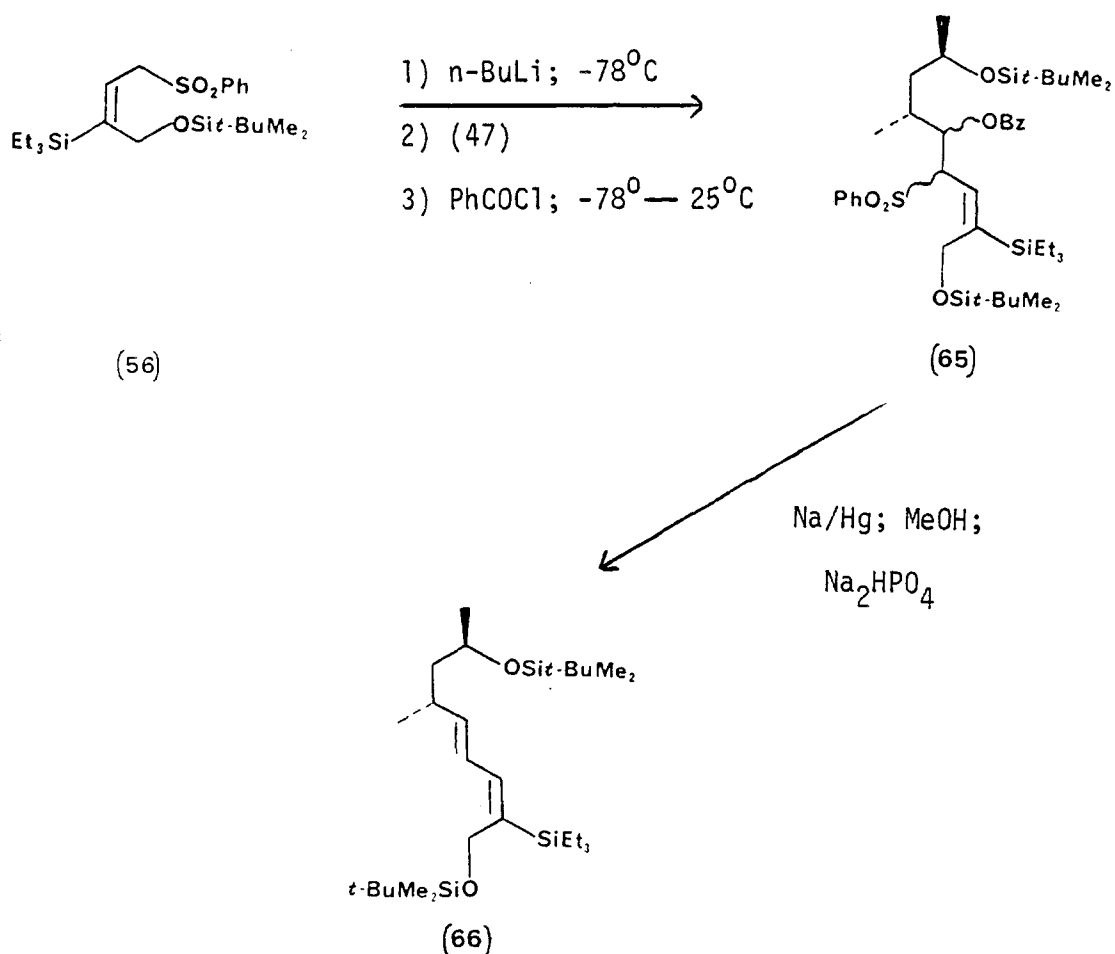


(64) was intended to be a crucial synthon in our overall strategy since we ultimately envisioned coupling the spiro-ketal moiety to the side-chain at this juncture.

Deprotection of 1,3-dithiolanes often requires vigorous conditions and/or prolonged reaction times. However, previous work in our laboratory has shown the $\text{Tl}(\text{CF}_3\text{CO}_2)_3$ method of Ho and Wong⁴⁰ to be both reliable and generally applicable. Hence, exposure of (63) to two equivalents of $\text{Tl}(\text{CF}_3\text{CO}_2)_3$ in THF at room temperature led rapidly and cleanly to the required aldehyde (47), but in a disappointing 40% yield.

Diene formation *via* the Lythgoe⁴¹ modification of the Julia¹⁷ method proved straightforward. Deprotonation of (56) was achieved with *n*-BuLi at -78°C , and addition of (47) followed by quenching with benzoyl chloride led smoothly to the benzoyloxysulphone (65) as a mixture of isomers, Scheme 12.

Scheme 12



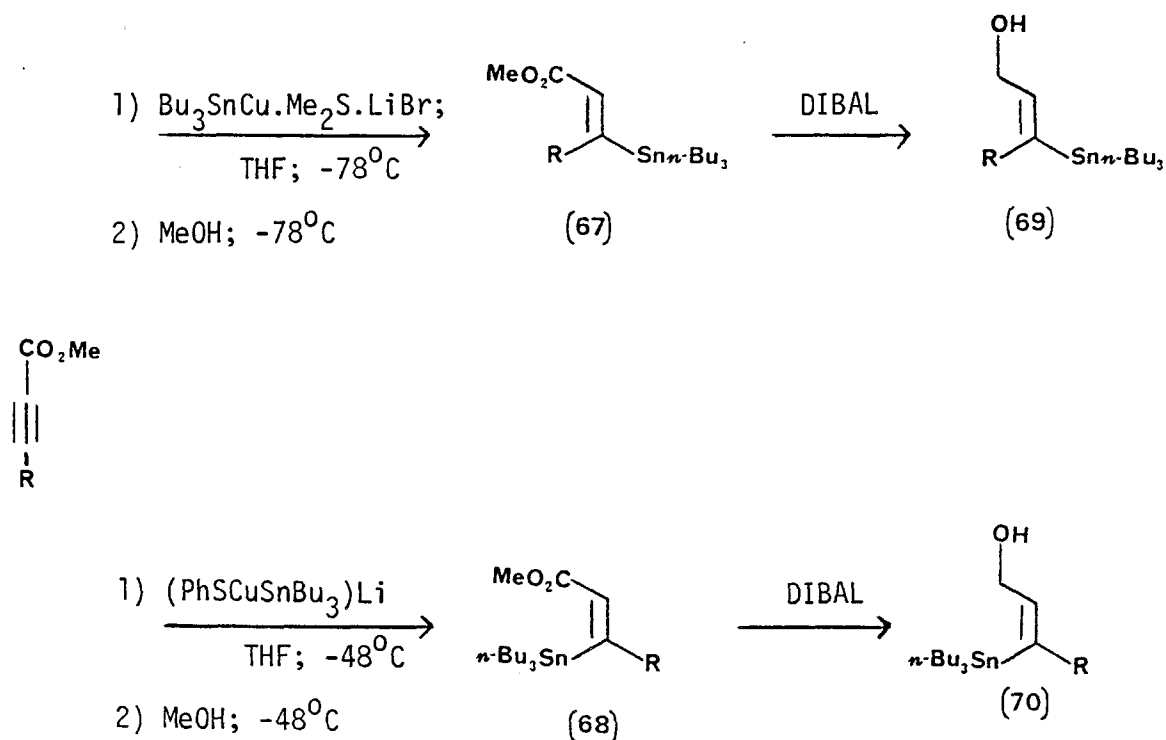
Reduction of (65) using Na/Hg amalgam in buffered methanol/THF then gave the (E,E)-diene (66) in 46% yield from (56). Comparison of the high field n.m.r. spectrum of (66) with that of the mixture obtained by hydrosilylation of (43) confirmed the presence of the required (E,E)-diene in the mixture.

Treatment of (66) with iodine using the conditions reported by Chan²³ did not, however, give the required vinyl iodide. Starting material was rapidly consumed upon exposure to the iodine but formation of a new product was not observed by TLC, and the n.m.r. spectrum of the crude product indicated only total decomposition. In view of this very disappointing result, the iodination procedure was tested on some of the vinyl silane precursors to (66). Thus, exposure of (49), (50), (53), (54) and (56) to iodine under the literature conditions²³ led only to recovery of starting material or minor products of decomposition. Heating the reaction mixture to reflux only hastened the decomposition process. The conclusion to be drawn from these results appears to be that the iodination of vinyl silanes is not a procedure widely applicable to substrates containing varied functionality. It also might appear that our belief that iodine addition across the disubstituted olefin of the diene moiety might be reversible was unfounded, since decomposition of (66) was much more rapid than that of any of the other vinyl silanes tested, indicating that the vicinal diiodide may decompose *via* an alternative pathway.

In the light of these results it was decided to abandon the vinyl silane route to the side-chain vinyl iodide.

Recent work by Piers⁴² offers a solution to the preparation of our required vinyl anion. It was shown that the geometry of addition of stannyl cuprates to a propiolic ester may be controlled by varying the nature of the cuprate, Scheme 13.

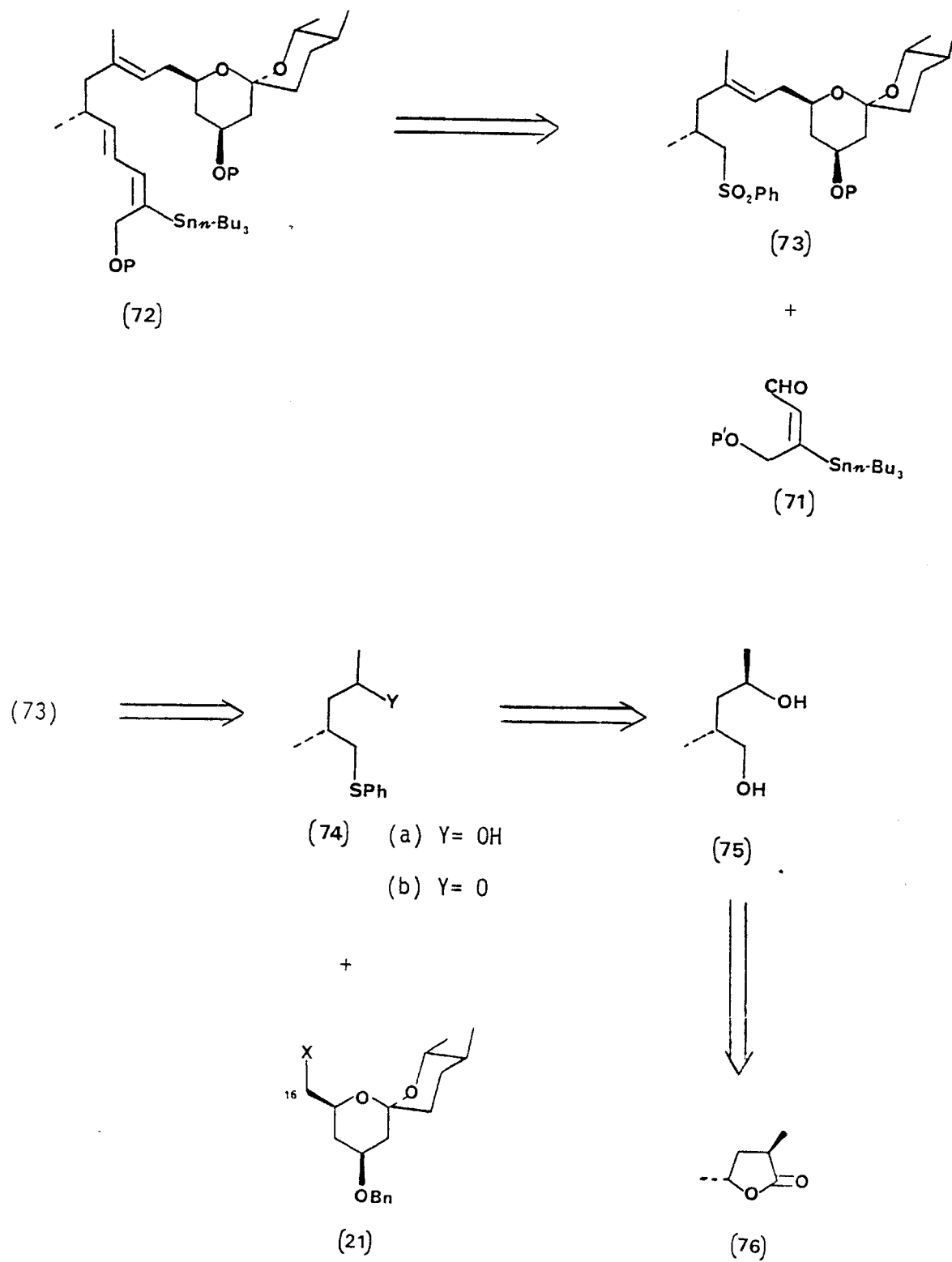
Scheme 13



The ester function of (67) and (68) may be reduced by excess DIBAL to the allylic alcohol in high yield. The vinyl stannane is also stable to reduction with LiAlH_4 .

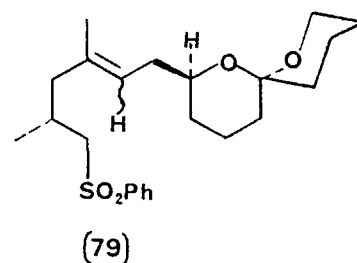
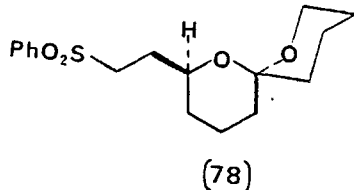
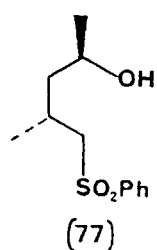
The applicability of this work to the milbemycin β_1 side-chain is readily seen by substituting $\text{R} = \text{CH}_2\text{OP}$ into Scheme 13, where P is a suitable protecting group. Semi-reduction of (67) to the unsaturated aldehyde (71), and olefin formation would yield a dienyl stannane of the required geometry such that transmetallation should readily afford the long-sought vinyl carbanion (18). In order to selectively form the (E,E)-diene the Julia-Lythgoe sulphone methodology⁴¹ once again should be the method of choice, since sulphones are readily prepared under mild conditions, and olefin formation is highly selective for the (E)-isomer. The latest retro-synthetic scheme is outlined in Scheme 14.

Scheme 14



Once again, the chirality at C₁₂ is derived from the dimethyl lactone (76).

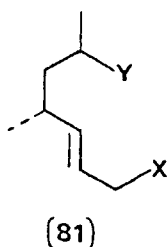
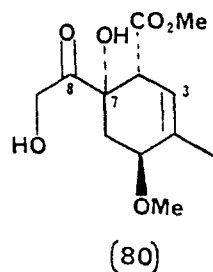
Reduction of racemic (76) with LiAlH₄ in THF cleanly afforded a 75% yield of the polar diol (75). On treatment with Bu₃P/(PhS)₂⁴³ in THF, selective monosulphenylation occurred to give (74a) in 66% yield. No trace of sulphenylation at the secondary centre was observed, even after prolonged reaction. Oxidation of (74a) to the ketone (74b) proceeded smoothly in 59% yield using PCC as oxidant. Alternatively (74a) was treated with mCPBA to afford the sulphone (77) in near-quantitative yield.



Coupling of the ketone (74b) with the model sulphone (78) in standard fashion was carried out by my colleague Dr. A.C. Jackson, but unfortunately formation of olefin (79) was non-selective affording a *ca.* 1.5:1 ratio of isomers in 30% overall yield. Attempts to prepare aldehyde (71) are as yet at an early stage in our laboratory, but have so far been very promising.

Alternative coupling strategies for the C₇-C₈ moiety

In addition to synthetic efforts towards (19) suitable for the strategy detailed above, a simultaneous study was underway in our laboratory towards the synthesis of the fragment (80) *via* a Diels-Alder strategy.

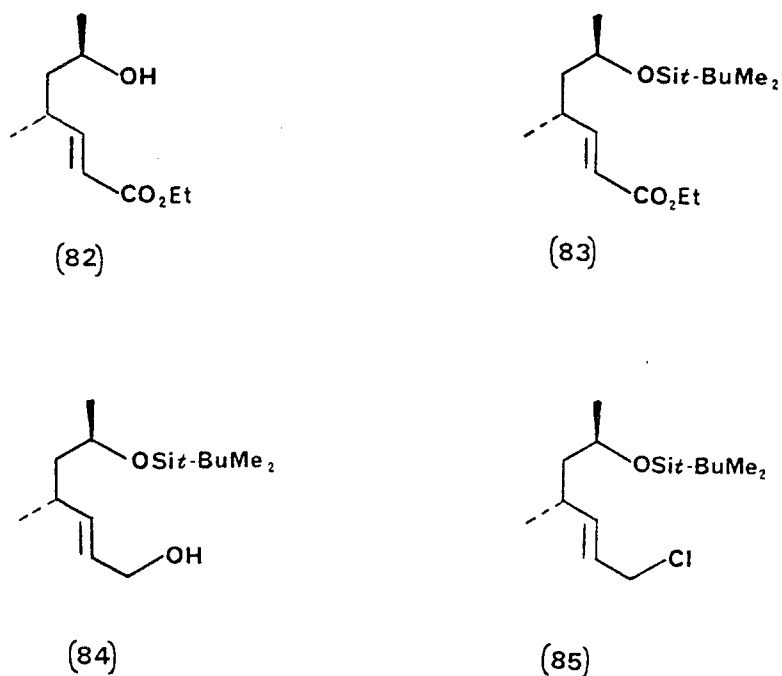


- (a) Y = OTBDMS, X = $\text{P}^+\text{Ph}_3\text{X}^-$
 (b) Y = OTBDMS, X = POPh_2
 (c) Y = OTBDMS, X = $\text{PO}(\text{OEt})_2$
 (d) Y = OTBDMS, X = SO_2Ph

Clearly the inclusion of this in a route to milbemycin β_1 requires the development of alternative coupling strategies since (80) already bears the C₇-C₈ linkage with correct relative stereochemistry. The work outlined below describes some very preliminary approaches to such strategies. Obviously, the strategy for construction of the C₁₄-C₁₅ linkage is essentially unaffected by the use of (80) rather than (19) in the reaction sequence, but now formation of the C₈-C₉ olefinic bond becomes of crucial importance. Hence, compounds of type (81) were required to test the feasibility of this approach, where X is some appropriate anion stabilising group, and Y is subject to the same considerations as in the earlier work. Suitable choices for X and Y were deemed to be (81)a-d and we sought a route to all those *via* a common precursor.

Treatment of racemic lactol (27) with carboethoxymethylene triphenylphosphorane afforded the (E)- α,β -unsaturated ester (82) in 85% yield, Scheme 15.

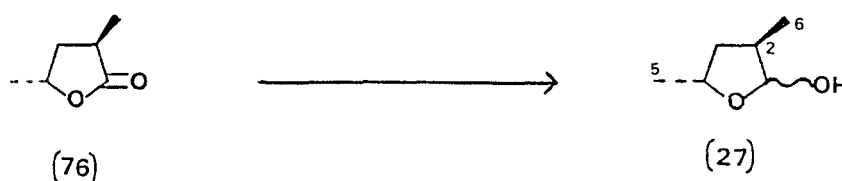
Scheme 15



Protection, as the TBDMS ether, proceeded routinely in 90% yield to give (83). Reduction of the ester substituent with excess DIBAL afforded the monoprotected diol (84) in 55% yield. Exposure of (84) to the direct tosylation-chlorination procedure recently described by Nicolaou⁴⁴ smoothly yielded the allylic chloride (85) in 74% yield. It is readily apparent that (85) is potentially a common precursor to (81)a→d. Alternatively, (81d) could be prepared *via* sulphenylation of the allylic alcohol (84) using standard procedures⁴⁵, followed by oxidation to the sulphone. Unfortunately treatment of (85) with PPh₃ in benzene gave none of the desired phosphonium salt, with only decomposition products being observed. Lack of material and time prevented further work on this route.

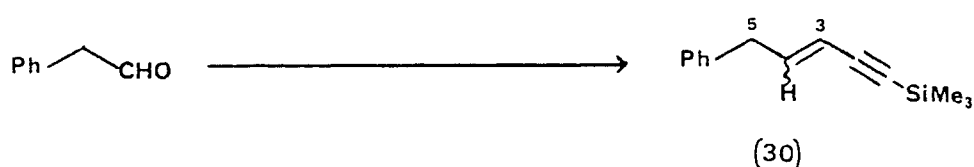
EXPERIMENTAL1) Preparation of ($\pm$)-2-(R)-Methylpentan-4-(R)-olide (76)

To a solution of di-isopropylamine (7.08g, 70 mmol) in dry THF (35 ml), cooled to 0°C was added n-BuLi (47 ml of a 1.5M solution in hexanes, 70 mmol). After stirring for 10 min, THF (35 ml) was added and the solution cooled to -78°C. γ -Valerolactone (7g, 70 mmol) was added dropwise and the resultant solution stirred for 1h at -78°C when MeI (6.27 ml, 14.2g, 100 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 1h and quenched with saturated NH_4Cl solution. Extraction with ether (3 x 100 ml), drying of the combined organic extracts, evaporation and kugelröhr distillation afforded the pure *dimethyl lactone* (76) (5.91g, 74%), b.p. 120° at 10 mmHg (oven temperature); δ (250 MHz): 1.27 (3H, d, J 7.5 Hz, C-6 H_3), 1.39 (3H, d, J 7 Hz, C-5 H_3), 2.09 (2H, m, C-3 H_2), 2.75 (1H, m, C-2 H), and 4.70 (1H, m, C-4 H); ν_{max} (neat): 2978, 1773, 1458, and 1385 cm^{-1} ; m/z 115 ($\text{M}^+ + \text{H}$), 99 ($\text{M}^+ - \text{Me}$), 70 ($\text{M}^+ - \text{CO}_2$), and 55 ($\text{C}_3\text{H}_3\text{O}^+$).

2) Preparation of ($\pm$)-1-Hydroxy-2-(R)-4-(R)-dimethyltetrahydrofuran (27)

To DIBAL (37.3 ml of a 1.53M solution in toluene, 57 mmol), cooled to -78°C was added dropwise a solution of the lactone (76) (5.91g, 51.8 mmol) in toluene (7 ml). The solution was stirred at -78°C for 3 hours and quenched by the addition of glacial acetic acid (9 ml) and water (5 ml). Solid NaHCO_3 (excess) was added and the mixture filtered. The alum cake was washed with ethyl acetate (3 x 100 ml) and the combined filtrates dried and evaporated. Kugelrohr distillation afforded the pure *dimethyl lactol* (5.53g, 92%) b.p. 120° at 12 mmHg (oven temperature) as a 2:1 mixture of diastereomers; δ (250 MHz) major isomer: 1.18 (3H, d, J 7 Hz, C-6 H_3), 1.28 (3H, d, J 6.5 Hz, C-5 H_3), 2.15 (2H, m, C-3 H_2), 2.65 (1H, m, C-2 H), 4.59 (1H, m, C-4 H), 5.21 (1H, d, J 5 Hz, C-1 H), and 5.30 (1H, br s, OH); ν_{max} (neat): 3421, 2972, 1770, and 1457 cm^{-1} .

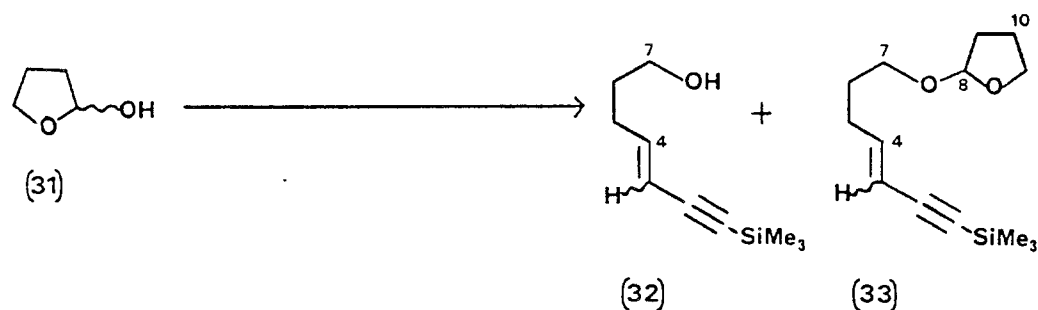
3) Preparation of (EZ)-5-Phenyl-1-(trimethylsilyl)-pent-3-en-1-yne
(30)



To a suspension of the phosphonium salt (29a) (336 mg, 0.74 mmol) in dry THF (2 ml), cooled to 0°C was added dropwise $n\text{-BuLi}$ (0.50 ml of a 1.57M solution, 0.79 mmol) over 2 min to give a deep burgundy solution. This solution was stirred for 10 min at 0°C and phenylacetaldehyde (90 mg, 0.74 mmol) was added dropwise, causing instantaneous discharge of the red colouration. The mixture was stirred for 15 min at 0°C , quenched with saturated NH_4Cl solution, and the product extracted into 50:50 ether-petrol (50 ml). The organic solution was

washed with dilute HCl (aq.) (10 ml), dried, and filtered through a plug of celite. Evaporation under reduced pressure and chromatography (5% ether-petrol) afforded the pure enyne (30) (65 mg, 41%) as a 3:1 *trans-cis* mixture; δ (250 MHz): *Trans*: 0.20 (9H, s, TMS), 3.45 (2H, dd, J 1.5, 6.5 Hz, C-5 H₂), 5.56 (1H, dt, J 16, 1.5 Hz, C-3 H), 6.39 (1H, dt, J 16, 6.5 Hz, C-4 H) and 7.15 - 7.40 (5H, m, aromatics); *Cis*: 0.25 (9H, s, TMS), 3.71 (2H, br d, J 7.5 Hz, C-5 H₂), 5.63 (1H, dt, J 11, 1.5 Hz, C-3 H), 6.13 (1H, dt, J 11, 7.5 Hz, C-4 H), and 7.15 - 7.40 (5H, m, aromatics); $\nu_{\max}$ (neat): 3067, 2960, 2129, and 1603 cm⁻¹; m/z 214 (M⁺), 186 (M⁺H-PhCH₂), 141 (M⁺-TMS), 91 (PhCH₂⁺), and 73 (TMS).

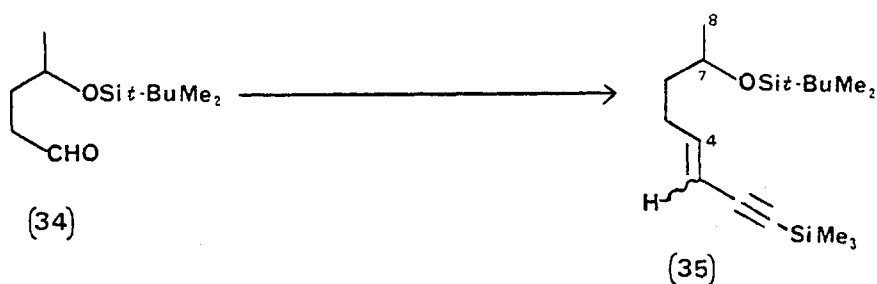
4) Preparation of (EZ)-7-Hydroxy-1-(trimethylsilyl)-hept-3-en-1-yne
(32)



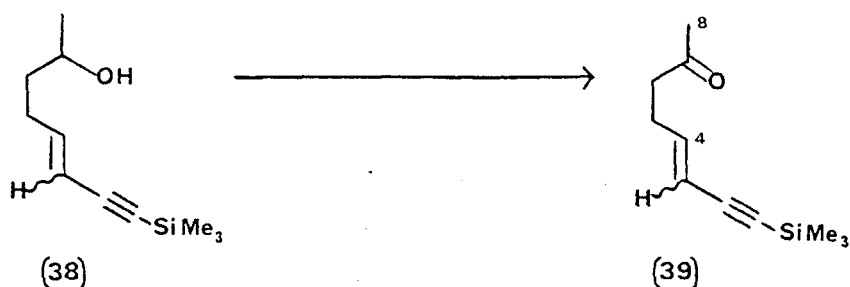
To a suspension of the phosphonium salt (29a) (606 mg, 134 mmol) in THF (5 ml) cooled to -78°C was added *n*-BuLi (0.90 ml of a 1.5M solution in hexane, 1.35 mmol) dropwise. The resultant deep red solution was stirred at -40°C for 30 min when the lactol (31) (59 mg, 0.67 mmol) was added as a solution in THF (0.5 ml). The -78°C bath was replaced by an ice bath and the solution stirred for 2h. Hexane (30 ml) was added and the solution filtered through a short column of acidic alumina. Evaporation followed by chromatography of the residue (25% ether-petrol) gave first the tetrahydrofuran derivative (33) as a 4.5:1 *trans-cis* mixture; δ (250 MHz): *Trans*: 0.18 (9H, s, TMS),

1.66 - 2.20 (8H, m, C-6 H₂ + C-9 H₂ + C-10 H₂ + C-5 H₂), 3.37 (1H, m, C-11 H), 3.65 (1H, m, C-11 H), 3.87 (2H, m, C-7 H₂), 5.09 (1H, m, C-8 H), 5.51 (1H, dt, J 16, 1 Hz, C-3 H), and 6.21 (1H, dt, J 16, 7 Hz, C-4 H); $\nu_{\max}$ (neat): 2957, 2176, 1627, and 1250 cm⁻¹; m/z 252 (M⁺), 237 (M⁺-Me), 234 (M⁺-H₂O), 182 (M⁺-THF), 179 (M⁺-TMS), and 164 (M⁺-THF-H₂O), followed by (32) (59 mg, 46%) as a 4.5:1 *trans-cis* mixture; δ (250 MHz): *Trans*: 0.18 (9H, s, TMS), 1.66 (2H, m, C-6 H₂), 2.19 (2H, m, C-5 H₂), 3.63 (2H, t, J 7 Hz, C-7 H₂), 5.53 (1H, dt, J 16, 1 Hz, C-3 H), and 6.21 (1H, dt, J 16, 7 Hz, C-4 H); $\nu_{\max}$ (neat): 3395, 3022, 2246, and 1630 cm⁻¹; m/z 182 (M⁺), 167 (M⁺-Me), 109 (M⁺-TMS), and 73 (TMS).

5) Preparation of (EZ)-7-(*t*-Butyldimethylsilyloxy)-1-(trimethylsilyl)-oct-3-en-1-yne (35)

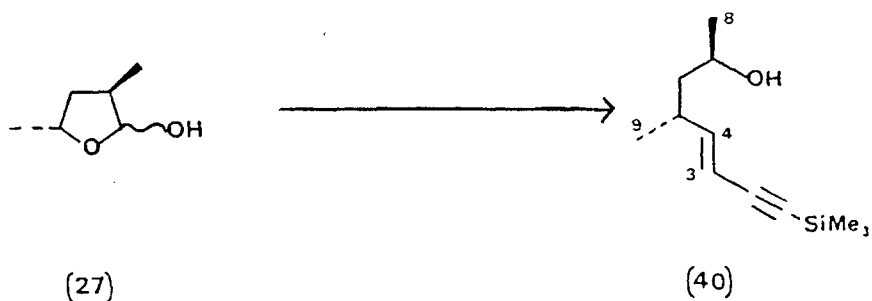


To a solution of the phosphorane (29b) (generated as in experiment (4) from the phosphonium salt [578 mg, 1.27 mmol]) cooled to -78°C was added the neat aldehyde (193 mg, 0.89 mmol) in one portion. The -78°C bath was replaced by an ice bath and the solution stirred at 0°C for 1h, when it was poured into hexane (30 ml). The resultant mixture was filtered through a plug of acidic alumina, evaporated, and chromatographed (5% ether-petrol) to yield the enyne (35) (125 mg, 45%) as an oil in a 2.6:1 *trans-cis* ratio; δ (250 MHz): *Trans*: 0.04 (6H, s, Me₂Si), 0.18 (9H, s, TMS), 0.88 (9H, s, ^{*t*}BuSi), 1.13 (3H, d, J 8 Hz, C-8 H₃), 1.38 - 1.62 (2H, m, C-6 H₂), 2.03 - 2.50 (2H, m, C-5 H₂), 3.80 (1H, m,

7) Preparation of (E)-7-Oxo-1-(trimethylsilyl)oct-3-en-1-yne (39)

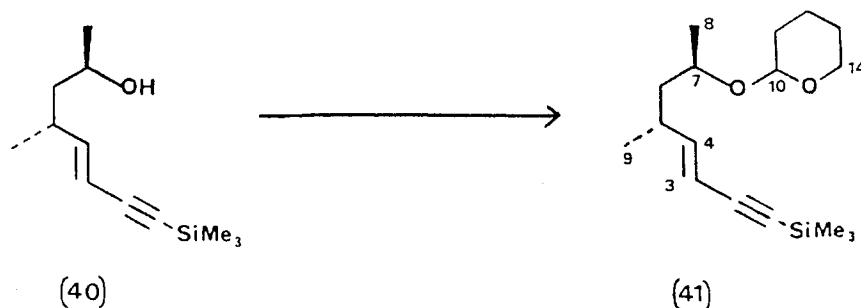
To a slurry of PCC (238 mg, 1.11 mmol) in dry CH_2Cl_2 (5 ml) was added a solution of the alcohol (38) (145 mg, 0.74 mmol) in CH_2Cl_2 (1 ml). The mixture was stirred for 3h and then diluted with ether (50 ml). The ethereal solution was filtered through a pad of florisil and evaporated under reduced pressure. Chromatography (25% ether-petrol) afforded the pure ketone (39) (128 mg, 89%) as an oil;

δ (250 MHz): *Trans*: 0.15 (9H, s, TMS), 2.12 (3H, s, C-8 H_3), 2.34 (2H, m, C-5 H_2), 2.51 (2H, m, C-6 H_2), 5.50 (1H, dt, J 16, 1.5 Hz, C-3 H), and 6.15 (1H, dt, J 16, 6.5 Hz, C-4 H); ν_{max} (neat): 3000, 2270, 2170, and 1720 cm^{-1} ; m/z 194 (M^+), 179 ($\text{M}^+ - \text{CH}_3$), 163, 151 ($\text{M}^+ - \text{CH}_3\text{CO}$), and 73 (TMS).

8) Preparation of ($\pm$)-(E)-7-(R)-Hydroxy-5-(S)-methyl-1-(trimethylsilyl)oct-3-en-1-yne (40)

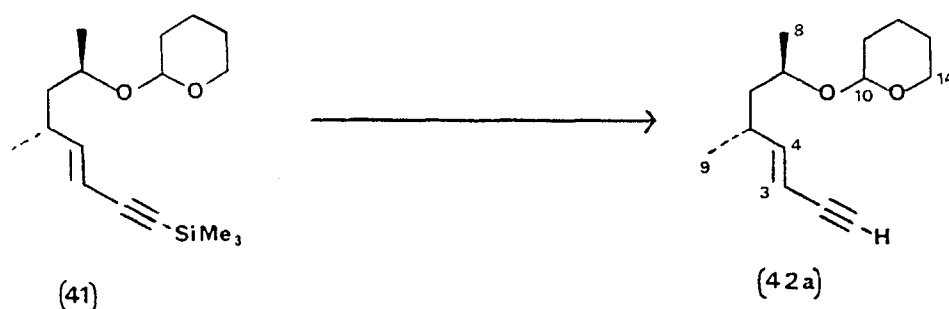
To a suspension of the phosphonium salt (29a) (3.34g, 7.36 mmol) in THF (18 ml), cooled to -78°C was added $n\text{-BuLi}$ (5.0 ml of a 1.62M solution in hexane, 8.1 mmol). The solution was warmed to -35°C over 30 min and the freshly distilled lactol (27) (242 mg, 2.09 mmol) was added as a solution in THF (1 ml). The mixture was warmed slowly to room temperature, stirred for a further 30 min and quenched with saturated NH_4Cl solution (5 ml). The product was extracted into 50% ether-petrol (100 ml), and the organic layer washed with dilute HCl (10 ml), dried and evaporated. Chromatography (25% ether-petrol) afforded the pure enyne (40) (254 mg, 58%) in a $>30:1$ *trans-cis* ratio; δ (250 MHz): 0.15 (9H, s, TMS), 1.00 (3H, d, J 8 Hz, C-9 H_3), 1.15 (3H, d, J 8 Hz, C-8 H_3), 1.25 - 1.60 (3H, m, C-6 H_2 + OH), 2.45 (1H, m, C-5 H), 3.78 (1H, m, C-7 H), 5.52 (1H, dd, J 15.5, 1 Hz, C-3 H), and 6.04 (1H, dd, J 15.5, 8 Hz, C-4 H); ν_{max} (neat): 3450, 2940, 2184, and 1630 cm^{-1} ; m/z 210 (M^+), 195 ($\text{M}^+ - \text{CH}_3$), 192 ($\text{M}^+ - \text{H}_2\text{O}$), 177 ($\text{M}^+ - \text{CH}_3\text{OH}_2$), 151, and 73 (TMS). Treatment of a portion of (40) with *m*-dinitrobenzoyl chloride in pyridine afforded the crystalline dinitrobenzoate, m.p. $98\text{--}100^{\circ}$ (Found: C, 56.29; H, 6.05; N, 6.84. $\text{C}_{19}\text{H}_{24}\text{SiN}_2\text{O}_6$ requires C, 56.42; H, 5.98; N, 6.92%).

9) Preparation of ($\pm$)-(E)-5-(S)-Methyl-7-(R)-(tetrahydropyran-2-yloxy)-1-(trimethylsilyl)oct-3-en-1-yne (41)



To a solution of the enyne alcohol (40) (40 mg, 0.19 mmol) in dry CH_2Cl_2 (1 ml) at room temperature was added dihydropyran (30 mg, 0.36 mmol) and CSA (3 crystals). The solution was stirred for 1 h and volatiles were removed *in vacuo*. Chromatography of the residue (25% ether-petrol) afforded the protected *hydroxy enyne* (41) (49 mg, 88%) as a clear oil; δ (250 MHz): 0.16 (9H, s, TMS), 1.00 ($1\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-9 H₃), 1.01 ($1\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-9 H₃), 1.09 ($1\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-8 H₃), 1.12 ($1\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-8 H₃), 1.15 - 1.90 (8H, m, $(\text{CH}_2)_3$ + C-6 H₂), 2.25 - 2.60 (1H, m, C-5 H), 3.42 - 3.98 (3H, m, C-14 H₂ + C-7 H), 4.58 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-10 H), 4.65 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-10 H), 5.45 ($\frac{1}{2}$ H, dd, J 15, 1 Hz, $\frac{1}{2}$ C-3 H), 5.53 ($\frac{1}{2}$ H, dd, J 15, 1 Hz, $\frac{1}{2}$ C-3 H), and 6.02 - 6.21 (1H, m, C-4 H); ν_{max} (neat): 2955, 2160, and 1455 cm^{-1} ; m/z 294 (M^+), 210 (M^+ -THP), 192 (M^+ -THP- H_2O), and 177 (M^+ -THP- CH_3OH_2).

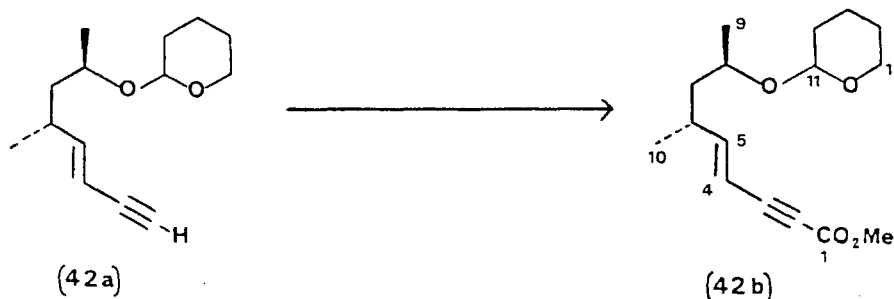
10) Preparation of ($\pm$)-(E)-5-(S)-Methyl-7-(R)-(tetrahydropyran-2-yloxy) oct-3-en-1-yne (42a)



To a solution of the protected silyl enyne (41) (48 mg, 0.16 mmol) in THF (2 ml) was added $n\text{Bu}_4\text{NF}$ (0.20 ml of a 1M solution in THF, 0.20 mmol) and the solution stirred at room temperature overnight. The mixture was diluted with ether (20 ml), washed with dilute HCl (5 ml), dried, and evaporated. Chromatography (25% ether-petrol) afforded the pure enyne (42a) (36 mg, 99%) as an oil; δ (250 MHz): 0.98 ($1\frac{1}{2}$ H, d,

J 8 Hz, $\frac{1}{2}$ C-9 H₃), 1.00 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-9 H₃), 1.07 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-8 H₃), 1.20 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-8 H₃), 1.19 - 1.90 (8H, m, (CH₂)₃ + C-6 H₂), 2.23 - 2.60 (1H, m, C-5 H), 2.76 ($\frac{1}{2}$ H, d, J 3 Hz, $\frac{1}{2}$ C-1 H), 2.77 ($\frac{1}{2}$ H, d, J 3 Hz, $\frac{1}{2}$ C-1 H), 3.40 - 3.52 (1H, m, C-7 H), 3.57 - 3.96 (2H, m, C-14 H₂), 4.56 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-10 H), 4.62 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-10 H), 5.38 ($\frac{1}{2}$ H, ddd, J 16, 3, 2 Hz, $\frac{1}{2}$ C-3 H), 5.46 ($\frac{1}{2}$ H, ddd, J 16, 3, 2 Hz, $\frac{1}{2}$ C-3 H), 6.07 ($\frac{1}{2}$ H, dd, J 16, 9 Hz, $\frac{1}{2}$ C-4 H), and 6.13 ($\frac{1}{2}$ H, dd, J 16, 9 Hz, $\frac{1}{2}$ C-4 H); $\nu_{\max}$ (neat): 3300, 2950, 2860, 2240, 2095, and 1640 cm⁻¹.

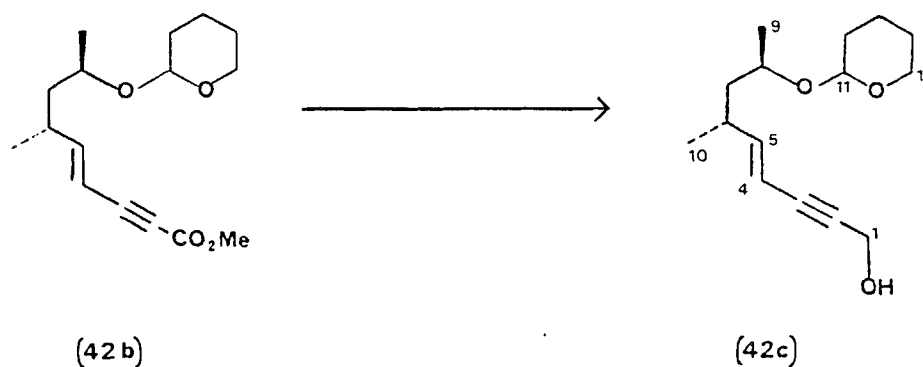
11) Preparation of ($\pm$)-(E)-Methyl-6-(S)-methyl-8-(R)-(tetrahydropyran-2-yloxy)non-4-en-2-ynoate (42b)



To a solution of the enyne (42a) (35 mg, 0.16 mmol) in THF (1 ml) cooled to -78°C was added n-BuLi (0.15 ml of a 1.26M solution in hexane, 0.19 mmol) dropwise. The dark solution was stirred for 5 min and methyl chloroformate (0.1 ml, excess) was added neat in one portion. After stirring for 10 min the reaction was quenched with saturated NH₄Cl solution (1 ml), extracted with ether (2 x 20 ml) and the combined ethereal extracts dried and evaporated. Chromatography afforded the pure *enyne ester* (42b) (44 mg, 100%) as an oil; δ (250 MHz): 0.98 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-10 H₃), 0.99 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-10 H₃), 1.06 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-9 H₃), 1.20 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-9 H₃), 0.95 - 1.90 (8H, m, (CH₂)₃ + C-7 H₂), 2.52 (1H, m, C-6 H),

3.85 (3H, s, OMe), 3.39 - 3.95 (3H, m, C-15 H₂ + C-8 H), 4.51 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-11 H), 4.56 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-11 H), 5.47 ($\frac{1}{2}$ H, dd, J 16, 1.5 Hz, $\frac{1}{2}$ C-4 H), 5.58 ($\frac{1}{2}$ H, dd, J 16, 1.5 Hz, $\frac{1}{2}$ C-4 H), 6.36 ($\frac{1}{2}$ H, dd, J 16, 8 Hz, $\frac{1}{2}$ C-5 H), and 6.39 ($\frac{1}{2}$ H, dd, J 16, 8 Hz, $\frac{1}{2}$ C-5 H); $\nu_{\max}$ (neat): 2980, 2970, 2215, 1720, and 1630 cm⁻¹; m/z 262 (M⁺-H₂O), 249 (M⁺-OMe), 236 (M⁺-CO₂), 221 (M⁺-CO₂Me), and 196 (M⁺-THP). (Found: C, 68.47; H, 8.81. C₁₆H₂₄O₄ requires C, 68.55; H, 8.63%).

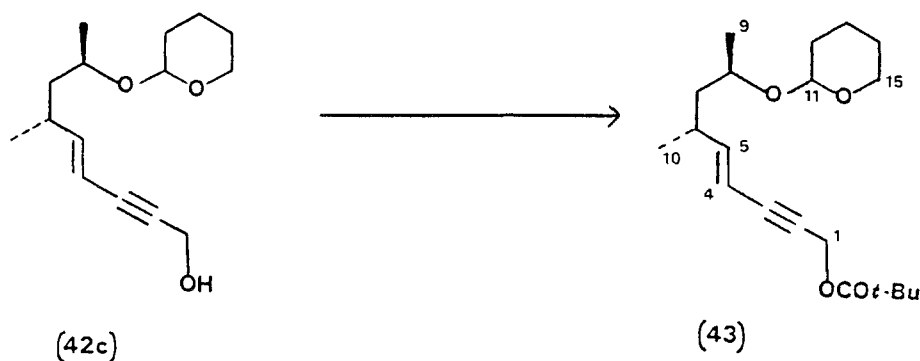
12) Preparation of ($\pm$)-(E)-6-(S)-Methyl-8-(R)-(tetrahydropyran-2-yloxy)non-4-en-2-ynol (42c)



To the neat enyne ester (42b) (44 mg, 0.16 mmol), cooled to -78^oC under argon was added DIBAL (0.25 ml of a 1.53M solution in toluene, 0.38 mmol) dropwise. The mixture was allowed to warm slowly to -20^oC when TLC analysis showed reaction to be complete. The solution was re-cooled to -78^oC and quenched with glacial acetic acid (1 ml). The mixture was poured into ethyl acetate (10 ml) and solid NaHCO₃ added until the organic solution was clear. The mixture was filtered, and the residual solid alum washed with further portions of ethyl acetate (2 x 10 ml). The combined organic extracts were evaporated and chromatographed (25% ether-petrol) to give the pure *enyne alcohol* (42c) (36 mg, 91%); δ (250 MHz): 1.01 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-10 H₃), 1.03 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-10 H₃), 1.10 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-9 H₃), 1.23 (1 $\frac{1}{2}$ H, d,

J 8 Hz, $\frac{1}{2}$ C-9 H₃), 0.80 - 1.95 (8H, m, (CH₂)₃ + C-7 H₂), 2.07 (1H, br s, OH), 2.45 (1H, m, C-6 H), 3.40 - 3.55 (1H, m, C-15 H), 3.58 - 4.00 (2H, m, C-8 H + C-15 H), 4.36 (2H, br s, C-1 H₂), 4.58 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-11 H), 4.66 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-11 H), 5.49 (1H, m, C-4 H), 6.02 ($\frac{1}{2}$ H, dd, J 16, 8 Hz, $\frac{1}{2}$ C-5 H), and 6.05 ($\frac{1}{2}$ H, dd, J 16, 8 Hz, $\frac{1}{2}$ C-5 H); $\nu_{\max}$ (neat): 3419; 2929, 2868, 2213, 1628 and 1540 cm⁻¹; m/z 168 (M⁺-THP), 150 (M⁺-THP-H₂O), and 135 (M⁺-THP-CH₃-H₂O).

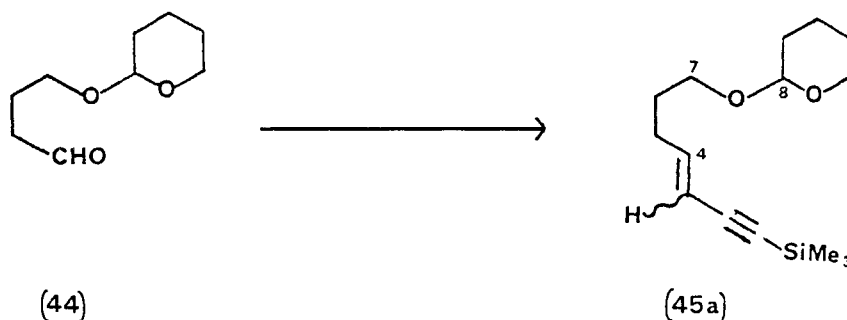
13) Preparation of (±)-(E)-6-(S)-Methyl-8-(R)-(tetrahydropyran-2-yloxy)-1-(trimethylacetoxynon-4-en-2-yne (43)



To a solution of the alcohol (42c) (434 mg, 1.72 mmol) in pyridine (1 ml) was added pivalic anhydride (2 ml, excess) and DMAP (4 crystals). The mixture was stirred overnight, quenched with water (3 ml) and extracted with ether (2 x 50 ml). The combined organic extracts were washed with 10% KOH solution (2 x 10 ml), dried, evaporated and chromatographed (5% ether-petrol) to yield the *enyne pivalate* (43) (496 mg, 85%); δ (250 MHz): 0.98 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-10 H₃), 1.00 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-10 H₃), 1.09 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-9 H₃), 1.23 (1 $\frac{1}{2}$ H, d, J 8 Hz, $\frac{1}{2}$ C-9 H₃), 1.23 (9H, s, ^tBu), 0.80 - 1.90 (8H, m, (CH₂)₃ + C-7 H₂), 2.45 (1H, m, C-6 H), 3.46 (1H, m, C-15 H), 3.77 (2H, m, C-8 H + C-15 H), 4.58 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-11 H), 4.64 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-11 H),

4.75 (2H, d, J 3 Hz, C-1 H₂), 5.43 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-4 H), 5.50 ($\frac{1}{2}$ H, m, $\frac{1}{2}$ C-4 H), 6.04 ($\frac{1}{2}$ H, dd, J 16, 8 Hz, $\frac{1}{2}$ C-5 H), and 6.07 ($\frac{1}{2}$ H, dd, J 16, 8 Hz, $\frac{1}{2}$ C-5 H); $\nu_{\max}$ (neat): 2985, 2880, 1740, and 1480 cm⁻¹; m/z 336 (M⁺), 279 (M⁺-^tBu), 252 (M⁺-THP), and 150. Treatment of (43) with methanol/CSA afforded the free *C*-8 hydroxy enyne (43a) for analysis: (Found: C, 71.13; H, 9.34. C₁₅H₂₄O₃ requires C, 71.39; H, 9.59%).

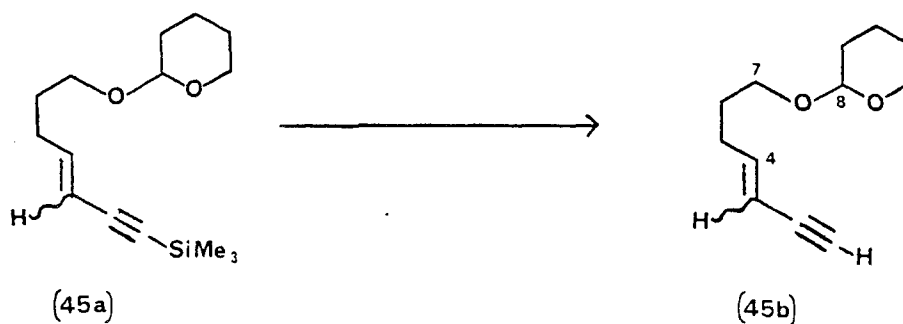
14) Preparation of (EZ)-7-(Tetrahydropyran-2-yloxy)-1-(trimethylsilyl)-hept-3-en-1-yne (45a)



To a suspension of the phosphonium salt (29a) (2.44g, 5.4 mmol) in dry THF (25 ml) cooled to -78⁰C was added *n*-BuLi (4.30 ml of a 1.39M solution in hexane, 5.98 mmol) dropwise over 5 minutes. The resultant red solution was stirred at -40⁰C for 20 min, and at 0⁰C for 30 min followed by addition of the aldehyde (44) (598 mg, 3.44 mmol) as a solution in THF (5 ml). After stirring for 30 min at 0⁰C the reaction was quenched by addition of saturated ammonium chloride solution (10 ml). The product was extracted into ether and the ethereal layer washed with 5% HCl (10 ml), dried, and evaporated under reduced pressure. Chromatography (5% ether-petrol) afforded the pure enyne (45a) (701 mg, 77%) as a clear oil in a 1:1 *cis-trans* ratio; δ (250 MHz): *Trans*: 0.16 (9H, s, TMS), 1.40 - 1.90 (8H, m, (CH₂)₃ + C-6 H₂), 2.12 - 2.25

(2H, m, C-5 H₂), 3.31 - 3.54 (2H, m, C-7 H + C-12 H), 3.68 - 3.91 (2H, m, C-7 H + C-12 H), 4.56 (1H, m, C-8 H), 5.51 (1H, dt, J 17, 1 Hz, C-3 H), and 6.10 (1H, dt, J 17, 8 Hz, C-4 H); *Cis*: 0.18 (9H, s, TMS), 1.40 - 1.90 (8H, m, (CH₂)₃ + C-6 H₂), 2.29 - 2.50 (2H, m, C-5 H₂), 3.31 - 3.54 (2H, m, C-7 H + C-12 H), 3.68 - 3.91 (2H, m, C-7 H + C-12 H), 4.56 (1H, m, C-8 H), 5.48 (1H, dt, J 11, 1 Hz, C-3 H), and 5.95 (1H, dt, J 11, 8 Hz, C-4 H); $\nu_{\max}$ (neat): 2947, 2140, 1441, and 1250 cm⁻¹; m/z 266 (M⁺), 251 (M⁺-Me), 193 (M⁺-TMS), and 182 (M⁺-THP). (Found: C, 67.67; H, 9.92. C₁₅H₂₆SiO₂ requires C, 67.62; H, 9.84%).

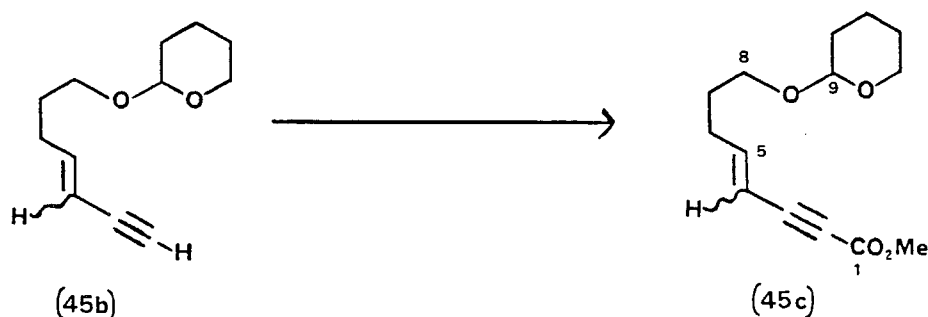
15) Preparation of (EZ)-7-(Tetrahydropyran-2-yloxy)hept-3-en-1-yne
(45b)



Treatment of silyl-enyne (45a) (670 mg, 2.52 mmol) with ⁿBu₄NF in analogous manner to experiment (10) afforded the deprotected enyne (48) (454 mg, 93%) as a clear oil; δ (250 MHz): *Trans*: 1.37 - 1.92 (8H, m, C-6 H₂ + (CH₂)₃), 2.21 (2H, ddt, J 7, 2, 7 Hz, C-5 H₂), 2.78 (1H, d, J 2 Hz, C-1 H), 3.30 - 3.56 (2H, m, C-7 H + C-12 H), 3.66 - 3.93 (2H, m, C-7 H + C-12 H), 4.56 (1H, m, C-8 H), 5.48 (1H, ddt, J 16.5, 2, 2 Hz, C-3 H), and 6.26 (1H, dt, J 16.5, 7 Hz, C-4 H). *Cis*: 1.37 - 1.92 (8H, m, C-6 H₂ + (CH₂)₃), 2.25 - 2.50 (2H, m, C-5 H₂), 3.06 (1H, dd, J 2, 0.5 Hz, C-1 H), 3.30 - 3.56 (2H, m, C-7 H + C-12 H), 3.66 - 3.93 (2H, m, C-7 H + C-12 H), 4.56 (1H, m, C-8 H), 5.49 (1H, ddt, J 11, 2, 2 Hz,

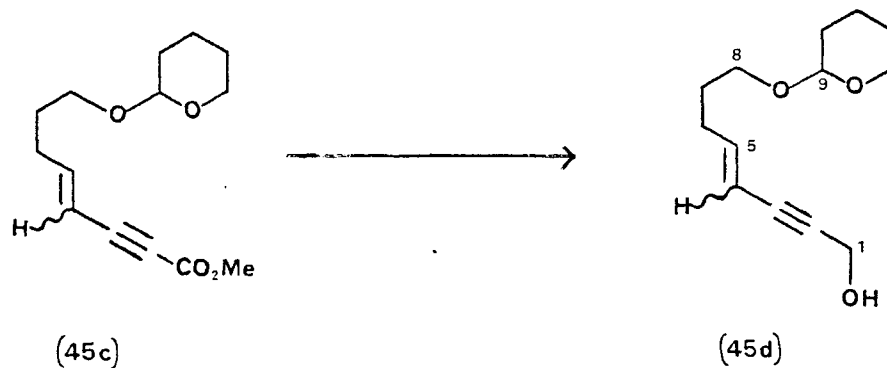
C-3 H), and 6.01 (1H, ddt, J 11, 0.5, 7 Hz, C-4 H); $\nu_{\max}$ (neat): 3296, 2943, 2103, and 1629 cm^{-1} ; m/z 193 (M^+-1), 126 ($M^+-C_5H_8$), 91 ($M^+-THP-H_2O$), and 85 (THP).

16) Preparation of (EZ)-Methyl-8-(tetrahydropyran-2-yloxy)oct-4-en-2-ynoate (45c)



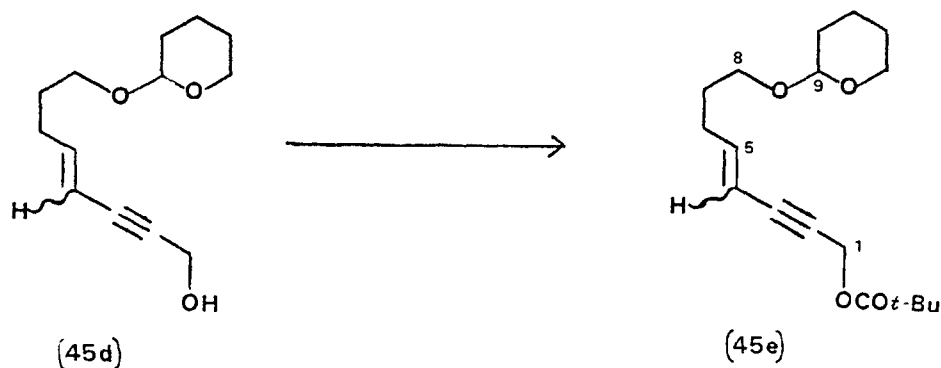
Treatment of the enyne (45b) (454 mg, 2.34 mmol) with $n\text{BuLi}$ (1.9 ml of a 1.44M solution, 2.74 mmol) followed by methyl chloroformate (1 ml, excess) in analogous fashion to experiment (11) afforded the *enyne ester* (45c) (477 mg, 81%); δ (250 MHz): *Trans*: 1.30 - 1.89 (8H, m, C-7 H₂ + (CH₂)₃), 2.12 - 2.30 (2H, m, C-6 H₂), 3.24 - 3.48 (2H, m, C-8 H + C-13 H), 3.70 (3H, s, OMe), 3.60 - 3.88 (2H, m, C-8 H + C-13 H), 4.49 (1H, m, C-9 H), 5.52 (1H, dt, J 16, 1.5 Hz, C-4 H), and 6.46 (1H, dt, J 16, 7 Hz, C-5 H); *Cis*: 1.30 - 1.89 (8H, m, C-7 H₂ + (CH₂)₃), 2.35 - 2.48 (2H, m, C-6 H₂), 3.24 - 3.48 (2H, m, C-8 H + C-13 H), 3.71 (3H, s, OMe), 3.60 - 3.88 (2H, m, C-8 H + C-13 H), 4.49 (1H, m, C-9 H), 5.54 (1H, dt, J 10.5, 1.5 Hz, C-4 H), and 6.22 (1H, dt, J 10.5, 7.5 Hz, C-5 H); $\nu_{\max}$ (neat): 2947, 2216, 1713, 1625, and 1435 cm^{-1} ; m/z 252 (M^+), 221 ($M^+-\text{OMe}$), 193 ($M^+-\text{CO}_2\text{Me}$), and 169 ($M^++1-\text{THP}$).

17) Preparation of (EZ)-8-(Tetrahydropyran-2-yloxy)oct-4-en-2-ynol
(45d)



Reduction of the enyne ester (45c) (470 mg, 1.86 mmol) with DIBAL (4.9 ml of a 1.53M solution in toluene, 7.50 mmol) in analogous fashion to experiment (12) afforded the *enyne alcohol* (45d) (343 mg, 83%); δ (60 MHz): 1.2 - 2.6 (10H, m, $(\text{CH}_2)_5$), 3.7 (4H, m, C-8 H_2 + C-13 H_2), 4.4 (2H, br s, C-1 H_2), 4.7 (1H, br s, C-9 H), and 5.4 - 6.6 (2H, m, C-5 H + C-4 H); ν_{max} : 3422, 2942, 2215, 1628, and 1441 cm^{-1} ; m/z 193 ($\text{M}^+ - \text{OMe}$), 122 ($\text{M}^+ - \text{THP} - \text{H}_2\text{O}$), and 108 ($\text{M}^+ - \text{CH}_2\text{OTHP}$).

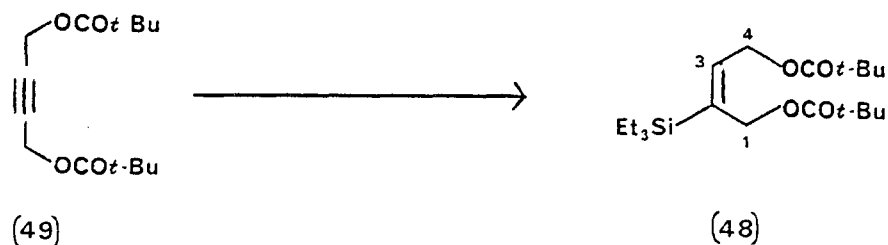
18) Preparation of (EZ)-8-(Tetrahydropyran-2-yloxy)-1-(trimethylacetoxyl)-oct-4-en-2-yne (45e)



Treatment of the enyne alcohol (45d) (340 mg, 1.51 mmol) with excess pivaloyl chloride in pyridine in analogous fashion to experiment (13) afforded the pivalate (45e) (399 mg, 85%) as an oil; δ (250 MHz):

Trans: 1.21 (9H, s, t Bu), 1.40 - 1.90 (8H, m, C-7 H₂ + (CH₂)₃), 2.20 (2H, q, J 7.5 Hz, C-6 H₂), 3.30 - 3.55 (2H, m, C-8 H + C-13 H), 3.66 - 3.91 (2H, m, C-8 H + C-13 H), 4.56 (1H, m, C-9 H), 4.74 (2H, d, J 1.5 Hz, C-1 H₂), 5.50 (1H, dt, J 16, 1.5 Hz, C-4 H), and 6.19 (1H, dt, J 16, 7.5 Hz, C-5 H); *Cis*: 1.22 (9H, s, t Bu), 1.40 - 1.90 (8H, m, C-7 H₂ + (CH₂)₃), 2.38 (2H, q, J 7.5 Hz, C-6 H₂), 3.30 - 3.55 (2H, m, C-8 H + C-13 H), 3.66 - 3.91 (2H, m, C-8 H + C-13 H), 4.56 (1H, m, C-9 H), 4.79 (2H, d, J 1.5 Hz, C-1 H₂), 5.47 (1H, dt, J 11, 1.5 Hz, C-4 H), and 5.96 (1H, dt, J 11, 7.5 Hz, C-5 H); $\nu_{\max}$ (neat): 2943, 2224, 1737, and 1478 cm⁻¹; m/z 251 ($M^+ - t$ Bu), 224 ($M^+ - \text{THP}$), and 206 ($M^+ - \text{HCO}_2\text{Bu}$).

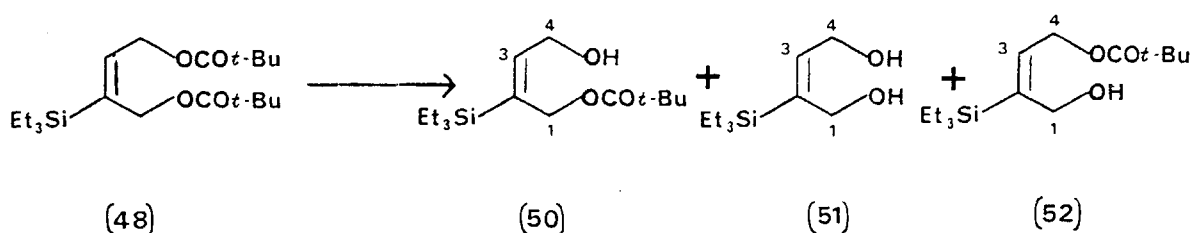
19) Preparation of (E)-1,4-di-(Trimethylacetox)-2-(triethylsilyl)-but-2-ene (48)



To a mixture of the dipivalate (49) (12.7g, 50 mmol) and Et₃SiH (5.8g, 50 mmol) was added a solution of H₂PtCl₆ (10 mg) in i PrOH (1 ml). The mixture was warmed at 50°C for 6h and allowed to stand overnight. The product was diluted with ether (200 ml), filtered through a pad of silica and evaporated to give the *vinyl silane* (48) (18.5g, 100%) of sufficient purity for subsequent reactions. A portion was chromatographed (5% ether-petrol) to afford an analytically pure sample; δ (60 MHz): 0.40 - 1.10 (15H, m, SiEt₃), 1.30 (18H, s, t Bu₂), 4.60 (2H,

s, C-1 H₂), 4.65 (2H, d, J 6 Hz, C-4 H₂), and 5.90 (1H, t, J 6 Hz, C-3 H); $\nu_{\max}$ (neat): 2959, 2877, 1730, 1480, and 1143 cm⁻¹; m/z 341 (M⁺-Et), 313 (M⁺-^tBu), 285 (M⁺-^tBuCO), and 255 (M⁺-SiEt₃). (Found: C, 64.87; H, 10.42. C₂₀H₃₈SiO₄ requires C, 64.82; H, 10.34%).

20) Preparation of (E)-3-(Triethylsilyl)-4-(trimethylacetoxyl)but-2-en-ol (50)

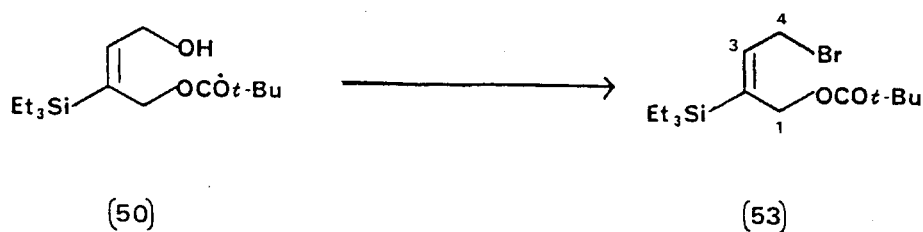


(a) To a solution of the diester (48) (3.7g, 10 mmol) in dry ether (50 ml), cooled to 0°C under argon, was added MeLi (16 ml of a 1.25M solution in ether, 20 mmol) dropwise over 10 min. After stirring for 10 min saturated aq. NH₄Cl solution (10 ml) was added to quench the reaction. The ether layer was separated and the aqueous layer further extracted with ether (100 ml). The combined organic extracts were dried (Na₂SO₄), evaporated and chromatographed (25% ether-petrol → ether) to yield first the *mono-ester* (50) (1.4g, 49%); δ (250 MHz): 0.63 (6H, q, J 8 Hz, Si(CH₂)₃), 0.91 (9H, t, J 8 Hz, Si-(CH₃)₃), 1.19 (9H, s, ^tBu), 2.27 (1H, t, J 6 Hz, OH), 4.31 (2H, t, J 6 Hz, C-4 H₂), 4.65 (2H, s, C-1 H₂), and 6.10 (1H, t, J 6 Hz, C-3 H); $\nu_{\max}$ (neat): 3400, 2961, 1718, 1462, and 1155 cm⁻¹; m/z 187 (M⁺-CO₂^tBu), 155, and 127. (Found: C, 63.12; H, 10.64. C₁₅H₃₀SiO₃ requires C, 62.89; H, 10.56%); followed by the diol (51) (318 mg, 16%); δ (60 MHz): 0.50 - 1.20 (15H, m, SiEt₃), 3.55 (2H, br s, (OH)₂), 4.20 (2H, s, C-1 H₂), 4.25 (2H, d, J 6 Hz, C-4 H₂), and 6.05 (1H, t, J 6 Hz, C-3 H);

$\nu_{\max}$ (neat): 3332, 2954, and 1047 cm^{-1} .

(b) To a solution of the diester (3.7g, 10 mmol) in dry ether (50 ml), cooled to -78°C was added MeLi (16 ml of a 1.25M solution, in ether, 20 mmol) dropwise. After stirring for 10 min, the reaction was quenched by addition of saturated aq. NH_4Cl solution (10 ml). Work-up as before, followed by chromatography (25% ether-petrol $\rightarrow$ ether) afforded first the *mono-ester* (52) (1.23g, 43%); δ (60 MHz): 0.50 - 1.10 (15H, m, SiEt_3), 1.20 (9H, s, ^tBu), 4.10 (2H, br s, C-1 H_2), 4.75 (3H, br d, J 7 Hz, C-4 H_2 + OH), and 5.80 (1H, t, J 7 Hz, C-3 H); $\nu_{\max}$ (neat): 3488, 2957, 1729, and 1157 cm^{-1} ; followed by the *mono-ester* (50) (0.76g, 27%), identical to the previous sample; followed by diol (51) (0.13g, 6%), identical to the previous sample.

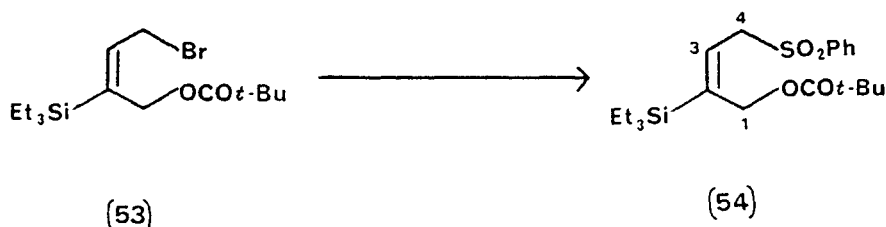
21) Preparation of (E)-4-Bromo-2-(triethylsilyl)-1-(trimethylsilyl)-but-2-ene (53)



To a solution of hydroxy-ester (50) (0.30g, 1.05 mmol) and triphenylphosphine (330 mg, 1.26 mmol) in dry CH_2Cl_2 (10 ml) was added slowly in portions NBS (224 mg, 1.26 mmol). After completion of addition, the reaction was warmed to 50°C for 10 min, and stirred for a further 15 min at room temperature. Water (5 ml) was added and the resultant purple mixture was poured into 5% ether-petrol (40 ml). The organic layer was separated, washed with water (10 ml), saturated aq.

NaHCO₃ (5 ml), dried (Na₂SO₄) and filtered through a plug of silica. Evaporation under reduced pressure afforded the *bromo-ester* (53) (268 mg, 73%) as a clear oil; δ (250 MHz): 0.67 (6H, q, J 8 Hz, Si(CH₂)₃), 0.93 (9H, t, J 8 Hz, Si(CH₃)₃), 1.21 (9H, s, ^tBu), 4.08 (2H, d, J 8 Hz, C-4 H₂), 4.71 (2H, d, J 1 Hz, C-1 H₂), and 6.18 (1H, dt, J 8, 1 Hz, C-3 H); $\nu_{\max}$ (neat): 2957, 1727, 1476, and 1460 cm⁻¹; m/z 320, 318 (M⁺-Et), 269 (M⁺-Br), and 187. (Found: C, 51.78; H, 8.56. C₁₅H₂₉SiBrO₂ requires C, 51.57; H, 8.37%).

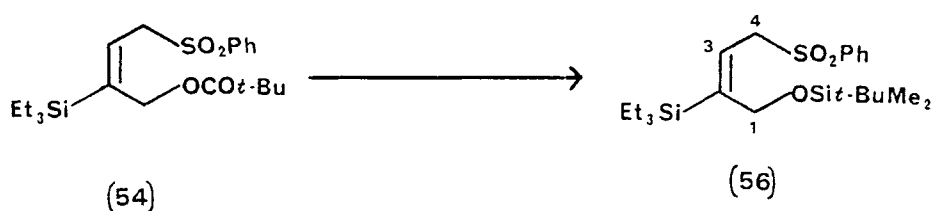
22) Preparation of (E)-4-(Phenylsulphonyl)-2-(triethylsilyl)-1-(trimethylacetoxyl)but-2-ene (54)



To a solution of the bromoester (53) (260 mg, 0.74 mmol) in dry methanol (3 ml) was added sodium benzenesulphonate (160 mg, 0.97 mmol) in one portion. The mixture was stirred at room temperature for 3 days and then concentrated under reduced pressure. The residue was suspended in ether (20 ml) and filtered. The filtrate was evaporated and chromatographed (25% ether-petrol) to yield the *sulphone ester* (54) as an oil (275 mg, 90%); δ (250 MHz): 0.58 (6H, q, J 8 Hz, Si(CH₂)₃), 0.85 (9H, t, J 8 Hz, Si(CH₃)₃), 1.11 (9H, s, ^tBu), 4.08 (2H, d, J 8 Hz, C-4 H₂), 4.29 (2H, s, C-1 H₂), 5.89 (1H, t, J 8 Hz, C-3 H), and 7.60 - 7.90 (5H, m, aromatics); $\nu_{\max}$ (neat): 2958, 1722, 1612, 1316, and 1147 cm⁻¹; m/z 319, 217, 187, and 169 (M⁺-PhSO₂H-CO₂^tBu). (Found:

C, 61.20; H, 8.46; S, 7.74. $C_{21}H_{34}SSiO_4$ requires C, 61.42; H, 8.35; S, 7.81%).

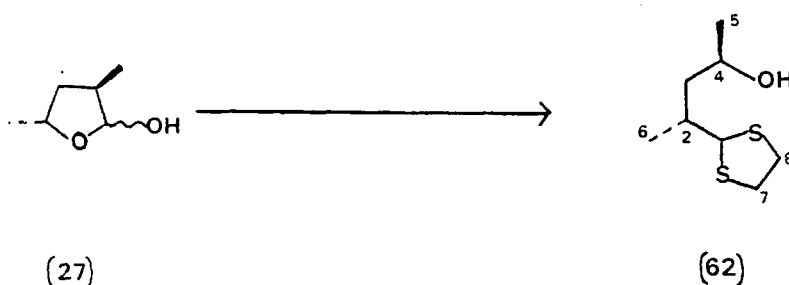
23) Preparation of (E)-1-(t-Butyldimethylsilyloxy)-4-(phenylsulphonyl)-2-(triethylsilyl)but-2-ene (56)



To a solution of sulphone-ester (54) (221 mg, 0.54 mmol) in dry ether (15 ml), cooled to -78°C under argon was added solid LiAlH_4 (40 mg, 1.05 mmol) in one portion. After stirring for 3h at -78°C , water (1 ml) was added cautiously, followed by excess, freshly prepared saturated K_2CO_3 solution. The mixture was filtered, and the solid alum washed with further portions of ether (5 x 20 ml). The combined organic extracts were evaporated under reduced pressure to yield the crude, labile, hydroxy-sulphone (55). This was immediately dissolved in a solution of imidazole (73 mg, 1.08 mmol) in DMF (1 ml), and $^t\text{BuMe}_2\text{SiCl}$ (81 mg, 0.54 mmol) was added. The mixture was stirred at room temperature for 1h, and diluted with ether (30 ml). The ethereal solution was washed with dilute HCl (5 ml), 5% NaHCO_3 solution (5 ml) and brine (5 ml), dried, and evaporated under reduced pressure. Chromatography (10% ether-petrol) afforded the protected *hydroxy sulphone* (56) as a white solid (190 mg, 80%); m.p. $68-71^{\circ}$. δ (250 MHz): -0.02 (6H, s, SiMe_2), 0.57 (6H, q, J 8 Hz, $\text{Si}(\text{CH}_2)_3$), 0.85 (9H, s, Si^tBu), 0.86 (9H, t, J 8 Hz, $\text{Si}-(\text{CH}_3)_3$), 3.89 (2H, d, J 1.5 Hz, C-1 H_2), 4.06 (2H, d, J 8 Hz, C-4 H_2), 5.65 (1H, tt, J 8, 1.5 Hz, C-3 H), and

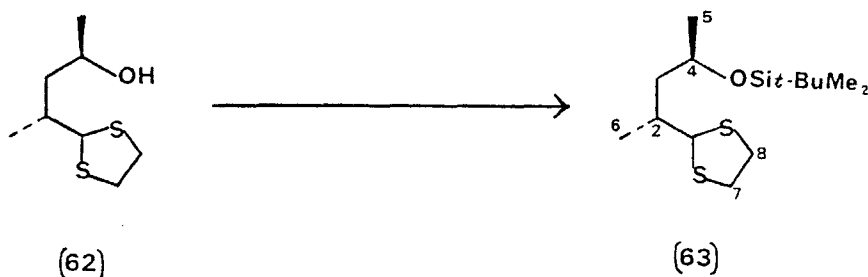
7.50 - 7.90 (5H, m, aromatics); $\nu_{\max}$ (CHCl_3): 2948, 1611, 1586, 1312, and 1145 cm^{-1} .

24) Preparation of ($\pm$)-1,1-(Ethylenedithio)-2-(R)-methylpent-4-(R)-ol
(62)



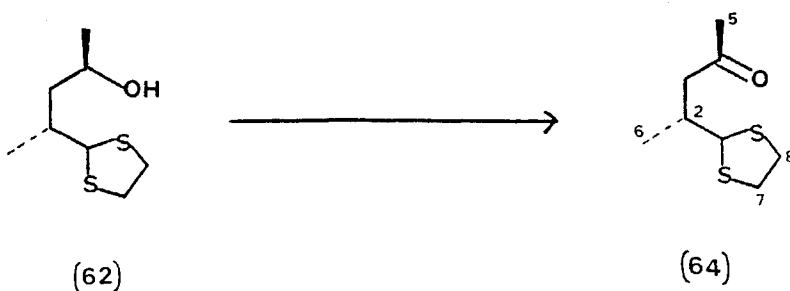
To a solution of the lactol (27) (1.13g, 9.74 mmol) in dry CH_2Cl_2 (30 ml) was added ethanedithiol (3.27 ml, 39.0 mmol), and the mixture cooled to -78°C . TiCl_4 (1.85g, 1.07 ml, 9.75 mmol) was added dropwise to give an orange solution which was allowed to warm slowly to room temperature. The mixture was diluted with CH_2Cl_2 (100 ml), washed with saturated NH_4Cl solution (2 x 20 ml), dried and evaporated. Chromatography (50% ether-petrol) afforded the *hydroxydithiolane* (62) (1.87g, 100%); δ (250 MHz): 1.00 (3H, d, J 7 Hz, C-5 H_3), 1.11 (3H, d, J 6 Hz, C-6 H_3), 1.50 (2H, m, C-3 H_2), 1.86 (1H, m, C-2 H), 2.31 (1H, br s, OH), 3.11 (4H, m, C-7 H_2 + C-8 H_2), 3.83 (1H, m, C-4 H), and 4.54 (1H, d, J 6 Hz, C-1 H); $\nu_{\max}$ (neat): 3378, 2966, 2925, 1755, and 1454 cm^{-1} ; m/z 197 (M^+), 146 ($\text{M}^+ - \text{C}_2\text{H}_4\text{O}$), 136 ($\text{M}^+ - \text{C}_2\text{H}_4\text{S}$), and 105 (dithiolane). (Found: C, 50.05; H, 8.50. $\text{C}_8\text{H}_{16}\text{S}_2\text{O}$ requires C, 49.96, H, 8.38%).

25) Preparation of ($\pm$)-1,1-(Ethylenedithio)-2-(R)-methyl-4-(R)-(t-butyltrimethylsilyloxy)pentane (63)



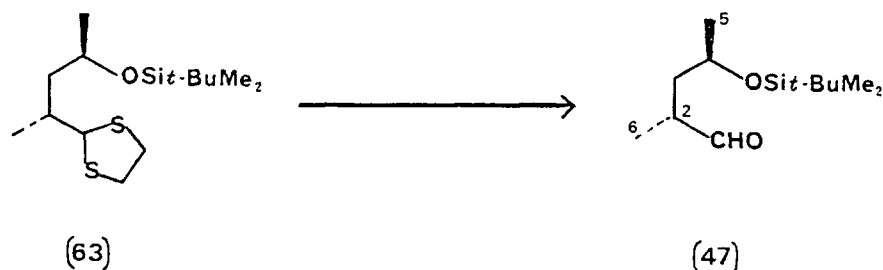
To a solution of the hydroxydithiolane (62) (0.82g, 4.27 mmol) in dry DMF (3 ml) was added imidazole (0.75g, 11.10 mmol) followed by **TBDMSCl** (0.82g, 5.44 mmol). The mixture was stirred at room temperature for 1h, poured into dilute HCl (5 ml) and the product extracted into ether (75 ml). The ethereal solution was dried, evaporated, and chromatographed (5% ether-petrol) to afford the protected *hydroxy dithiolane* (63) (1.27g, 97%); δ (250 MHz): 0.05 (6H, s, SiMe₂), 0.97 (9H, s, ^tBu), 1.05 (3H, d, J 7 Hz, C-5 H₃), 1.13 (3H, d, J 6 Hz, C-6 H₃), 1.38 - 1.65 (2H, m, C-3 H₂), 1.89 (1H, m, C-2 H), 3.18 (4H, m, C-7 H₂ + C-8 H₂), 3.89 (1H, m, C-4 H), and 4.60 (1H, d, J 6 Hz, C-1 H); $\nu_{\max}$ (neat): 2959, 2930, 2858, 1462, and 1375 cm⁻¹; m/z 249 (M⁺-^tBu), 189 (M⁺-^tBu-C₂H₄S), and 159 (C₂H₅O TBDMS). (Found: C, 54.99; H, 10.09; S, 20.47. C₁₄H₃₀S₂SiO requires C, 54.84; H, 9.86; S, 20.92%).

26) Preparation of 1,1-(Ethylenedithio)-2-methylpentan-4-one (64)



To a slurry of PCC (72 mg, 0.33 mmol) in dry CH_2Cl_2 (5 ml) was added the hydroxydithiolane (62) (43 mg, 0.23 mmol) as a solution in CH_2Cl_2 (2 ml). After stirring at room temperature for 2h the mixture was diluted with ether (25 ml) and the ethereal solution filtered through a pad of florisil, evaporated and chromatographed (25% ether-petrol) to afford the *keto dithiolane* (64) (31 mg, 74%) as an oil; δ (250 MHz): 1.03 (3H, d, J 6 Hz, C-6 H_3), 2.12 (3H, s, C-5 H_3), 2.36 (2H, m, C-3 H + C-2 H), 2.75 (1H, dd, J 10, 8 Hz, C-3 H), 3.16 (4H, m, C-7 H_2 + C-8 H_2), and 4.50 (1H, d, J 6 Hz, C-1 H); ν_{max} (neat): 2965, 2927, 1712, 1422, and 1362 cm^{-1} ; m/z 190 (M^+), 132 ($\text{M}^+ - \text{C}_2\text{H}_5\text{O}$), and 105 (dithiolane).

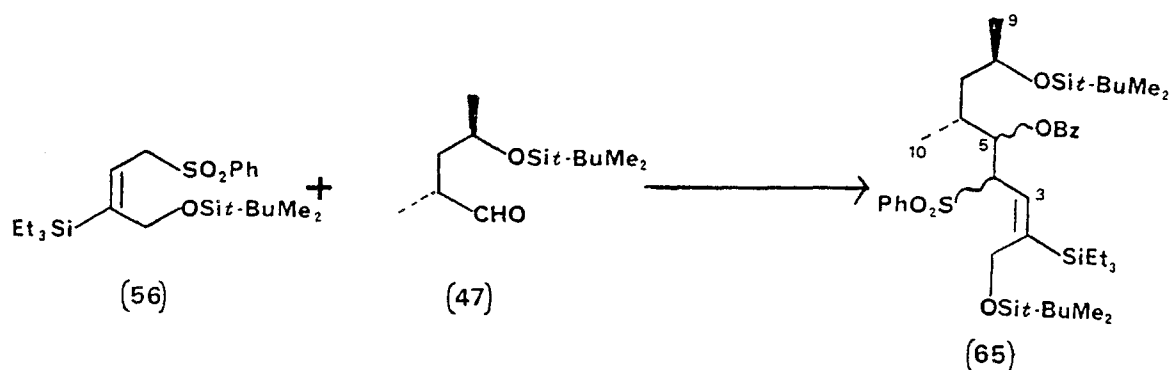
27) Preparation of ($\pm$)-2-(R)-Methyl-4-(R)-(t-butyl dimethylsilyloxy)-pentanal (47)



To a solution of the dithiolane (63) (1.05g, 3.6 mmol) in dry THF (25 ml) containing Na_2HPO_4 buffer (5g, excess) was added $\text{Ti}(\text{CF}_3\text{CO}_2)_3$ (4.00g, 7.4 mmol), to give an initial red-brown solution. After stirring at room temperature for 30 min the now purple mixture was poured into saturated aq. NaHCO_3 solution (5 ml) and the product extracted into ether (100 ml). The ethereal solution was dried, filtered through a short pad of silica and evaporated to give a clear oil. This was chromatographed (5% ether-petrol) to afford the pure aldehyde (47)

(336 mg, 40%); δ (60 MHz): 0.10 (6H, s, SiMe₂), 0.90 (9H, s, Si^tBu), 1.05 (3H, J 7 Hz, C-5 H₃), 1.20 (3H, J 7 Hz, C-6 H₃), 1.60 (2H, m, C-3 H₂), 2.50 (1H, m, C-2 H), 3.75 (1H, m, C-4 H), and 9.65 (1H, d, J 2 Hz, C-1 H); $\nu_{\max}$ (neat): 2958, 2932, 1726, and 1255 cm⁻¹; m/z 173 (M⁺-^tBu).

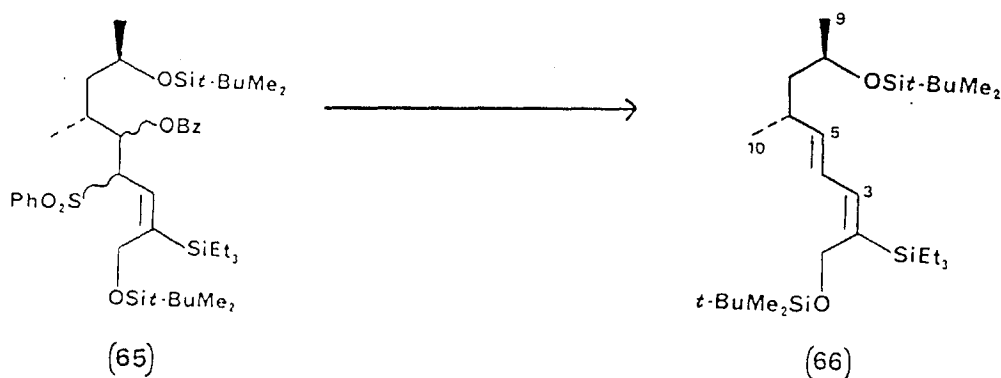
28) Preparation of ($\pm$)-(E)-5-(Benzoyloxy)-1,8-(R)-di-(*t*-butyldimethylsilyloxy)-6-(R)-methyl-4-(phenylsulphonyl)-2-(triethylsilyl)non-2-ene (65)



To a solution of the sulphone (56) (100 mg, 0.227 mmol) in THF (1 ml) cooled to -78⁰C was added *n*-BuLi (0.16 ml of a 1.54M solution, 0.25 mmol) dropwise over 5 min. The resultant pale yellow solution was stirred at -78⁰C for 15 min, after which a solution of the aldehyde (47) (52 mg, 0.226 mmol) in THF (0.5 ml) was added. After 1h at -78⁰C, benzoyl chloride (52 μ l, 0.45 mmol) was added and the solution allowed to warm to 0⁰C over 2h. 1-Amino-3-*N,N*-(dimethylamino)-propane (57 μ l, 0.454 mmol) was added and after stirring for 10 min the mixture was quenched by addition of saturated NH₄Cl solution. Extraction with ether (2 x 20 ml), drying of the combined organic extracts, evaporation and chromatography (25% ether-petrol) afforded the pure *benzoyloxy-sulphone* (65) (132 mg, 75%) as a mixture of

isomers; δ (250 MHz): 0.05 (12H, m, (SiMe₂)₂), 0.60 (6H, m, Si(CH₂)₃), 0.75 - 1.60 (36H, m, (Si^tBu) + Si-(CH₃)₃ + C-9 H₃ + C-7 H₂ + C-6 H + C-10 H₃), 3.75 - 4.51 (3H, m, C-1 H₂ + C-8 H), 4.70 (1H, m, C-4 H), 5.22 - 5.41 (1H, m, C-5H), 5.60 - 6.00 (1H, m, C-3 H), and 7.30 - 8.20 (10H, m, aromatics); $\nu_{\max}$ (neat): 2956, 1723, 1462, 1314, 1266, and 1147 cm⁻¹.

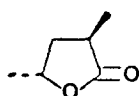
29) Preparation of ($\pm$)-(E,E)-1,8-(R)-Di-(*t*-butyldimethylsilyloxy)-6-(R)-methyl-2-(triethylsilyl)nona-2,4-diene (66)



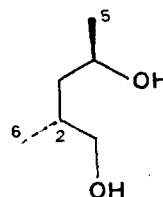
To a solution of the benzoyloxy-sulphone (65) (132 mg, 0.171 mmol) in 3:1 THF/MeOH (3.2 ml) containing Na₂HPO₄ (245 mg, 1.71 mmol) cooled to -20°C was added 6% Na/Hg (450 mg, 1.71 mmol). The mixture was stirred at -20°C for 1h and water (2 ml) was cautiously added. The solution was extracted with ether (3 x 20 ml) and the combined ethereal extracts dried, evaporated and chromatographed (1% ether-petrol) to yield the pure E,E-diene (54 mg, 62%); δ (250 MHz): 0.05 (6H, s, SiMe₂), 0.08 (6H, s, SiMe₂), 0.65 (6H, q, J 8 Hz, Si(CH₂)₃), 0.87 (9H, s, Si^tBu), 0.89 (9H, s, Si^tBu), 0.89 (9H, t, J 8 Hz, Si-(CH₃)₃), 1.01 (3H, d, J 6.5 Hz, C-10 H₃), 1.11 (3H, d, J 6.5 Hz, C-9 H₃), 1.20 - 1.40 (1H, m, C-7 H), 1.41 - 1.57 (1H, m, C-7 H), 2.38 (1H, m, C-6 H), 3.79 (1H, m, C-8 H), 4.41 (2H, m, C-1 H₂), 5.57 (1H, dd, J 16, 8.5 Hz, C-5 H), 6.17 (1H, br d, J 11 Hz, C-3 H), and 6.33 (1H, ddd, J 16, 11, 1 Hz,

C-4 H); $\nu_{\max}$ (neat): 2955, 2931, 1633, and 1577 cm^{-1} ;

30) Preparation of 2-(R)-Methylpentan-1,4-(R)-diol (75)



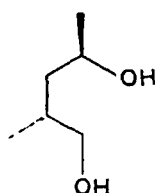
(76)



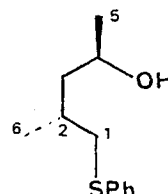
(75)

To a solution of the lactone (76) (210 mg, 1.84 mmol) in THF (10 ml) was added LiAlH_4 (70 mg, 1.84 mmol). The mixture was stirred at room temperature for 1h and quenched by addition of water (1 ml). Solid K_2CO_3 (10g) was added and the mixture filtered. The alum cake was washed with further portions of THF (3 x 20 ml) and the combined THF filtrates evaporated and chromatographed (Et_2O) to yield the pure diol (75) (162 mg, 75%) as a viscous oil; δ (60 MHz): 0.86 (3H, d, J 7 Hz, C-6 H_3), 1.13 (3H, d, J 7 Hz, C-5 H_3), 1.46 (2H, m, C-3 H_2), 1.80 (1H, m, C-2 H), 3.39 (2H, d, J 5 Hz, C-1 H_2), 3.90 (1H, m, C-4 H), and 4.10 (2H, br s, $(\text{OH})_2$); $\nu_{\max}$ (neat): 3349, 2965, and 1459 cm^{-1} .

31) Preparation of ($\pm$)-2-(R)-Methyl-1-(phenylsulphenyl)pentan-4-(R)-ol (74a)



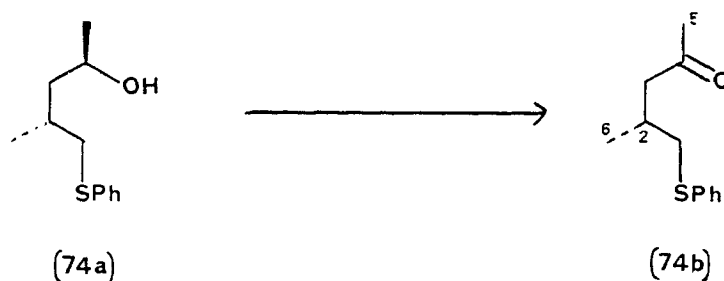
(75)



(74a)

A solution of $n\text{Bu}_3\text{P}$ (416 mg, 2.06 mmol), $(\text{PhS})_2$ (450 mg, 2.06 mmol) and the diol (75) (162 mg, 1.37 mmol) in THF (4 ml) was stirred at room temperature for 2 days under argon, when TLC showed complete consumption of starting material. The mixture was poured into saturated NH_4Cl solution, and the aqueous solution extracted with ether (3 x 30 ml). The combined organic extracts were dried, evaporated, and chromatographed (25 $\rightarrow$ 50% ether-petrol) to yield the pure *hydroxy sulphide* (74a) (188 mg, 66%) as an oil; δ (250 MHz): 1.04 (3H, d, J 7 Hz, C-6 H_3), 1.14 (3H, d, J 6 Hz, C-5 H_3), 1.41 (1H, dd, J 13.5, 7 Hz, C-3 H), 1.54 (1H, ddd, J 13.5, 7.5, 1 Hz, C-3 H), 1.91 (1H, m, C-2 H), 2.01 (1H, br s, OH), 2.78 (1H, dd, J 12.5, 7.5 Hz, C-1 H), 2.97 (1H, dd, J 12.5, 6 Hz, C-1 H), 3.87 (1H, m, C-4 H), and 7.08 - 7.36 (5H, m, aromatics); ν_{max} (neat): 3373, 2963, 2924, 1583, and 1478 cm^{-1} ; m/z 210 (M^+), 192 ($\text{M}^+ - \text{H}_2\text{O}$), and 150 ($\text{M}^+ - \text{C}_3\text{H}_8\text{O}$).

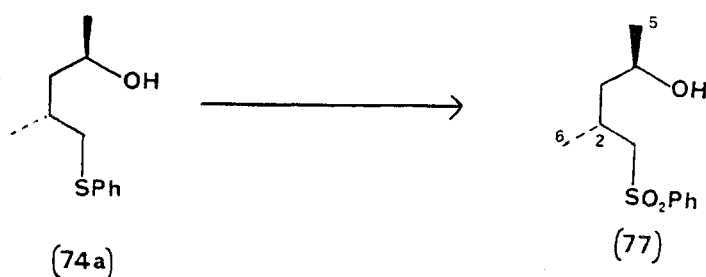
32) Preparation of 2-Methyl-1-(phenylsulphenyl)pentan-4-one (74b)



To a slurry of PCC (158 mg, 0.73 mmol) in dry CH_2Cl_2 (20 ml) was added the neat hydroxy sulphide (74a) (77 mg, 0.37 mmol). The mixture was stirred for 3h, and ether (100 ml) was added. The resultant slurry was filtered through a florisil pad and evaporated to yield the lactone (74b) (45 mg, 59%) as a clear oil; δ (60 MHz): 0.90 (3H, d, J 6 Hz, C-6 H_3), 1.95 (3H, s, C-5 H_3), 2.40 (3H, m, C-2 H + C-3 H_2), 2.75 (2H, d, J 6 Hz, C-1 H_2), and 7.00 - 7.25 (5H, m, aromatics); ν_{max} (neat):

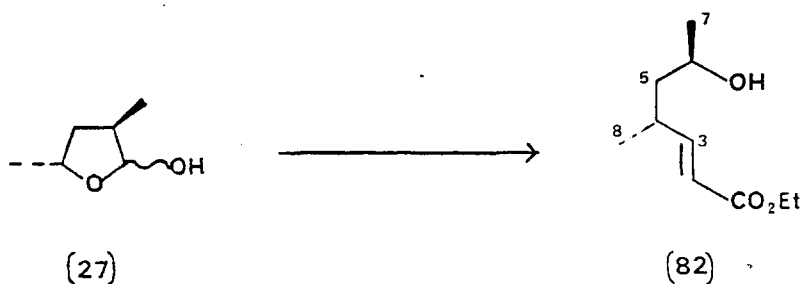
2960, 2927, 1709, and 1366 cm^{-1} ; m/z 208 (M^+), 150 ($\text{M}^+ - \text{C}_3\text{H}_6\text{O}$), 123 (PhSCH_2^+), 110 (PhSH), and 99 ($\text{M}^+ - \text{PhS}$).

33) Preparation of ($\pm$)-2-(R)-Methyl-1-(phenylsulphonyl)pentan-4-(R)-ol
(77)



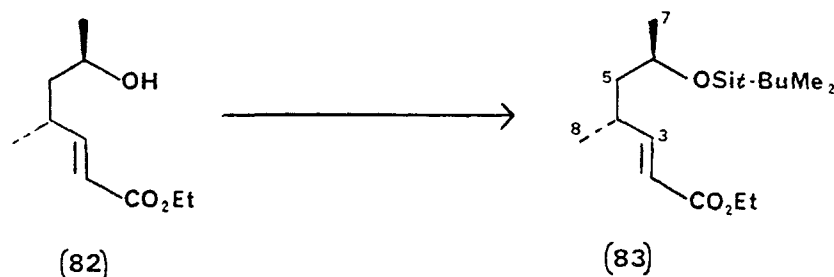
To a solution of the sulphide (74a) (64 mg, 0.30 mmol) in CH_2Cl_2 (10 ml) was added 80% *m*-CPBA (164 mg, 0.76 mmol) and the solution was stirred for 2h at room temperature. The mixture was evaporated and redissolved in ether (50 ml). The ethereal solution was washed with 5% NaOH (3 x 5 ml), dried, evaporated and chromatographed (ether) to yield the *hydroxy sulphone* (69 mg, 94%) as an oil; δ (250 MHz): 1.07 (3H, d, J 7 Hz, C-6 H_3), 1.17 (3H, d, J 6 Hz, C-5 H_3), 1.52 (2H, m, C-3 H_2), 1.59 (1H, br s, OH), 2.35 (1H, m, C-2 H), 2.96 (1H, dd, J 14.5, 6.5 Hz, C-1 H), 3.27 (1H, dd, J 14.5, 5 Hz, C-1 H), 3.90 (1H, m, C-4 H), and 7.52 - 7.96 (5H, m, aromatics); ν_{max} (neat): 3512, 2967, 2928, 1303, and 1146 cm^{-1} ; m/z 242 (M^+), 227 ($\text{M}^+ - \text{CH}_3$), 198 ($\text{M}^+ - \text{C}_2\text{H}_4\text{O}$), 156 ($\text{M}^+ - \text{C}_5\text{H}_{10}\text{O}$), and 143 ($\text{PhSO}_2\text{H}_2^+$).

34) Preparation of ($\pm$)-(E)-Ethyl-6-(R)-hydroxy-4-(R)-methylhept-2-enoate (82)



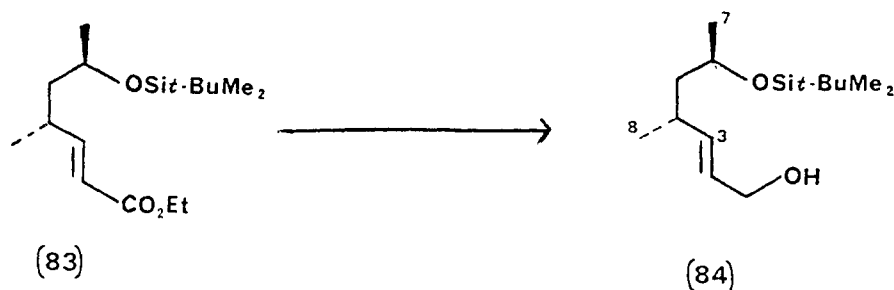
To a solution of the lactol (27) (2.05g, 17.7 mmol) in CH_2Cl_2 (30 ml) was added carboethoxymethylene triphenylphosphorane (7.40g, 21.3 mmol) in one portion. The mixture was stirred at room temperature for 4 days and evaporated. The solid residue was triturated with 50% ether-petrol (100 ml) and the mixture filtered. The filtrate was evaporated and chromatographed (50% ether-petrol) to yield the α,β -unsaturated ester (82) (2.92g, 89%) as an oil; δ (250 MHz): 1.05 (3H, d, J 7 Hz, C-8 H_3), 1.16 (3H, d, J 7 Hz, C-7 H_3), 1.18 (3H, t, J 7 Hz, ester CH_3), 1.35 - 1.65 (2H, m, C-5 H_2), 1.66 (1H, br s, OH), 2.55 (1H, m, C-4 H), 3.78 (1H, m, C-6 H), 4.16 (2H, q, J 7 Hz, ester CH_2), 5.81 (1H, dd, J 16, 1 Hz, C-2 H), and 6.82 (1H, dd, J 16, 9 Hz, C-3 H); ν_{max} (neat): 3464, 2969, 1762, 1708, and 1650 cm^{-1} ; m/z 186 (M^+), 141 ($\text{M}^+ - \text{OEt}$), and 113 ($\text{M}^+ - \text{CO}_2\text{Et}$). (Found: C, 64.37; H, 9.93. $\text{C}_{10}\text{H}_{18}\text{O}_3$ requires C, 64.48; H, 9.74%).

35) Preparation of ($\pm$)-(E)-Ethyl-6-(R)-(t-butyldimethylsilyloxy)-4-(R)-methylhept-2-enoate (83)



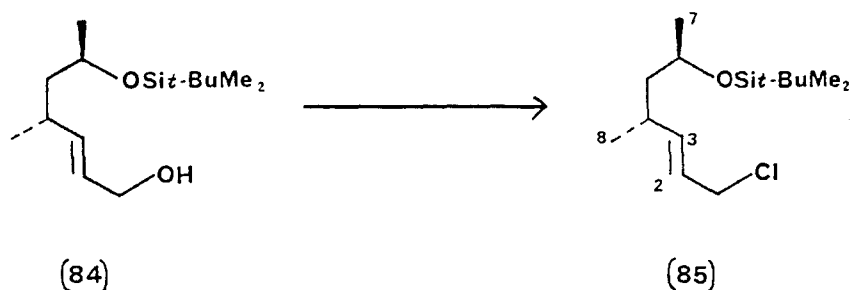
To a solution of the hydroxy ester (82) (113 mg, 0.01 mmol) in DMF (1 ml) was added imidazole (91 mg, 1.34 mmol) followed by TBDMSCl (100 mg, 0.66 mmol). The mixture was stirred at room temperature for 1h and poured into dilute HCl (2 ml). The product was extracted into ether (30 ml), and the ethereal solution dried and evaporated. Chromatography (5% ether-petrol) afforded the pure protected *hydroxy ester* (83) (164 mg, 90%); δ (250 MHz): 0.01 (6H, s, SiMe₂), 0.89 (9H, s, Si^tBu), 1.03 (3H, d, J 7 Hz, C-8 H₃), 1.09 (3H, d, J 7 Hz, C-7 H₃), 1.27 (3H, t, J 7 Hz, ester CH₃), 1.35 - 1.65 (2H, m, C-5 H₂), 2.49 (1H, m, C-4 H), 3.78 (1H, m, C-6 H), 4.16 (2H, q, J 7 Hz, ester CH₂), 5.76 (1H, dd, J 15.5, 1 Hz, C-2 H), and 6.85 (1H, dd, J 15.5, 8 Hz, C-3 H); $\nu_{\max}$ (neat): 2959, 2931, 1721, and 1648 cm⁻¹.

36) Preparation of ($\pm$)-(E)-6-(R)-(t-Butyldimethylsilyloxy)-4-(R)-methylhept-2-en-1-ol (84)



To a solution of DIBAL (1.80 ml of a 1.53M solution in toluene, 2.75 mmol) cooled to -78°C , was added a solution of the ester (83) (318 mg, 1.06 mmol) in toluene (3 ml). The mixture was allowed to warm to room temperature over 1h, re-cooled to -78°C and quenched with glacial acetic acid (2 ml). Excess solid NaHCO_3 was added and the resultant alum washed with ether (3 x 30 ml). Evaporation of the combined ethereal extracts and chromatography (50% ether-petrol) afforded the *allylic alcohol* (84) (210 mg, 77%) as an oil; δ (250 MHz): 0.04 (6H, s, SiMe_2), 0.89 (9H, s, Si^tBu), 0.98 (3H, s, J 7 Hz, C-8 H_3), 1.10 (3H, s, J 6.5 Hz, C-7 H_3), 1.20 - 1.57 (3H, m, C-5 H_2 + OH), 2.31 (1H, m, C-4 H), 3.80 (1H, m, C-6 H), 4.08 (2H, d, J 5 Hz, C-1 H_2), and 5.58 (2H, m, C-2 H + C-3 H); ν_{max} (neat): 3352, 2984, 2962, and 1470 cm^{-1} ; m/z 243 ($\text{M}^+ - 15$), 241 ($\text{M}^+ + 1 - \text{H}_2\text{O}$), and 201 ($\text{M}^+ - t\text{Bu}$).

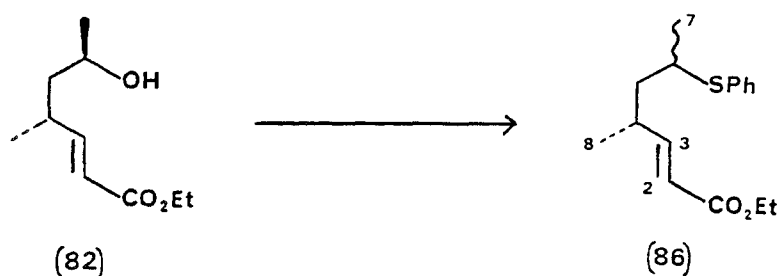
37) Preparation of ($\pm$)-(E)-6-(R)-(t-Butyldimethylsilyloxy)-1-chloro-4-(R)-methylhept-2-ene (85)



To a solution of the alcohol (84) (45 mg, 0.17 mmol) in CH_2Cl_2 (3 ml) was added DMAP (26 mg, 0.21 mmol) and tosyl chloride (40 mg, 0.21 mmol). The mixture was stirred at room temperature for 3h and poured into ether (50 ml). The ethereal solution was washed with 10% NaHCO_3 solution (10 ml) and brine (10 ml), dried, evaporated and chromatographed (5% ether-petrol) to give the *allylic chloride* (36 mg, 74%); δ (250 MHz): 0.06 (6H, s, SiMe_2), 0.89 (9H, s, Si^tBu), 0.99 (3H,

d, J 7 Hz, C-8 H₃), 1.12 (3H, d, J 7 Hz, C-7 H₃), 1.28 - 1.55 (2H, m, C-5 H₂), 2.35 (1H, m, C-4 H), 3.80 (1H, m, C-6 H), 4.03 (2H, d, J 5.5 Hz, C-1 H₂), and 5.60 (2H, m, C-2 H + C-3 H); $\nu_{\max}$ (neat): 2958, 2930, 1663, 1459, 1373, and 1254 cm⁻¹; m/z 276 (M⁺), 261 (M⁺-15), 241 (M⁺-Cl), and 219 (M⁺-^tBu).

38) Preparation of (±)-(E)-Ethyl-4-(R)-methyl-6-(RS)-(phenylsulphenyl)-hept-2-enoate (86)



To a solution of NPSS (407 mg, 2.02 mmol) in dry THF (5 ml) was added ⁿBu₃P (407 mg, 2.01 mmol) to give a deep purple solution. This solution was stirred for 15 min at room temperature and the hydroxy ester (82) (125 mg, 0.67 mmol) was added as a solution in THF (2 ml). Stirring was continued for 3 days and the reaction mixture poured into saturated NaHCO₃ solution (20 ml). Extraction with ether (2 x 50 ml), drying, evaporation and chromatography (5% ether-petrol) afforded the sulphide (86) (110 mg, 59%) as an oil; δ (250 MHz): major isomer: 1.05 (3H, d, J 7 Hz, C-8 H₃), 1.25 (3H, d, J 6.5 Hz, C-7 H₃), 1.28 (3H, q, J 7 Hz, ester CH₃), 1.50 (1H, m, C-5 H), 1.72 (1H, m, C-5 H), 2.61 (1H, m, C-4 H), 3.15 (1H, m, C-6 H), 4.19 (2H, q, J 7 Hz, ester CH₂), 5.79 (1H, dd, J 16, 1 Hz, C-2 H), 6.81 (1H, dd, J 16, 7.5 Hz, C-3 H), and 7.18 - 7.40 (5H, m, aromatics); $\nu_{\max}$ (neat): 3059, 2965, 1716, 1648, 1584, and 1272 cm⁻¹; m/z 278 (M⁺), 233 (M⁺-OEt), 1.80 (M⁺-C₅H₆O₂), and 137.

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PUBLICATIONS

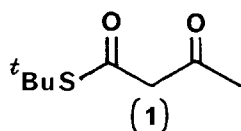
**REGIOSPECIFIC ALKYLATION OF β -KETOTHIOESTERS AND
 USE IN THE SYNTHESIS OF ACYL-TETRONIC ACIDS**

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Summary: Anions of t-butylacetothioacetate (1) react with alkylhalides and carbonyl compounds in a regiospecific manner to afford products which are versatile synthetic intermediates as exemplified by short syntheses of the mold metabolites carolic acid (2) and carlosic acid (3).

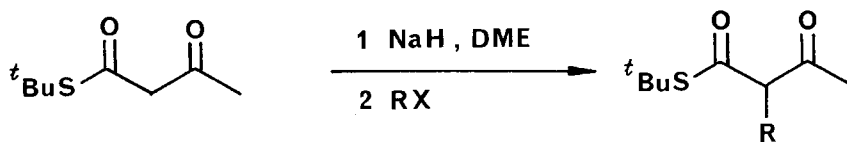
The utility of thioesters in organic synthesis is well known¹. They are of particular value in the formation of large ring lactones². Similarly, β -ketoesters have been shown to be versatile synthetic intermediates³. It is reasonable therefore to expect that β -ketothioesters, and especially t-butylacetothioacetate (1) might well combine the myriad properties of the two systems.



Compound (1) was prepared in 65% yield by treatment of diketene with sodium t-butylthiolate in T.H.F. Use of the thiolate anion in this manner circumvents the addition of thiol to the double bond of diketene noted elsewhere.⁴

Alkylation of (1) at the 2-position was achieved by anion formation with sodium hydride in 1,2-dimethoxyethane (D.M.E.) at 0°C followed by reaction with the alkyl halide at room temperature (Scheme 1).

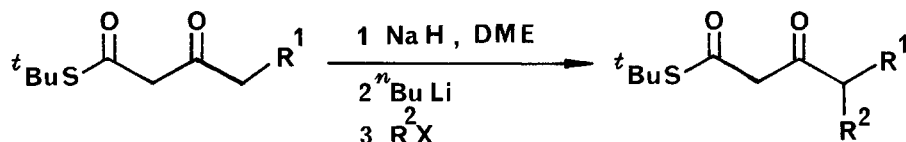
Scheme 1



Entry	R	X	Yield %
1	$\text{CH}_2=\text{CH}.\text{CH}_2$	Br	46
2	CH_3	I	65

Generation of the dianion from (1) involved sequential treatment with sodium hydride (at 0°C) and n-butyl lithium in DME (at -20°C). Reaction of this dianion, and others, with alkyl halides gave the alkylated products in moderate to good yields (Scheme 2).

Scheme 2

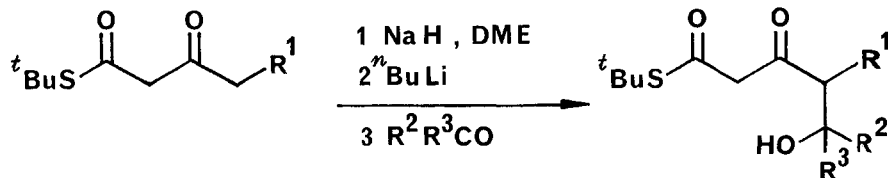


Entry	R ¹	R ²	X	Yield %
1	H	CH ₃	I	78
2	CH ₃	CH ₃	I	69
3	(CH ₃) ₂	CH ₃	I	34
4	H	CH ₂ =CH·CH ₂	Br	70
5	H	CH ₂ CH ₂ OSiMe ₂ ^t Bu	I	63
6	H	(CH ₂) ₂ CHCH ₃ OSiMe ₂ ^t Bu	I	53
7	H	(CH ₂) ₄ CHCH ₃ OSiMe ₂ ^t Bu	I	59
8	H	(CH ₂) ₈ C-CO ₂ Me OLi	I	56

Use of solvents other than D.M.E., e.g. T.H.F., led to very low yields and many unwanted side products. The entries in Scheme 2 demonstrate, as expected, that alkylation yields decrease as the steric congestion at the reacting centre increases.

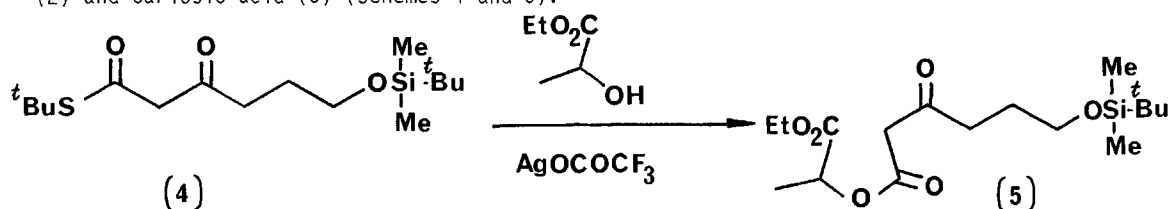
In a brief study, the t-butylacetothioacetate dianions were also shown to react with carbonyl compounds in good yield (Scheme 3). In entry 1 of the Scheme no diastereomeric preference of the product was observed.

Scheme 3

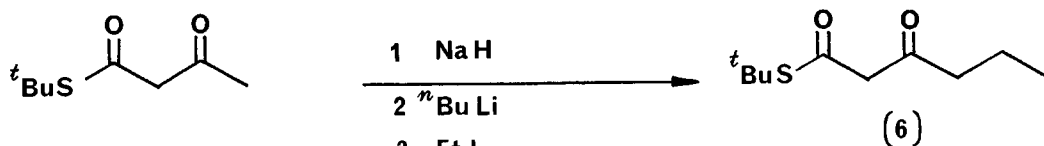
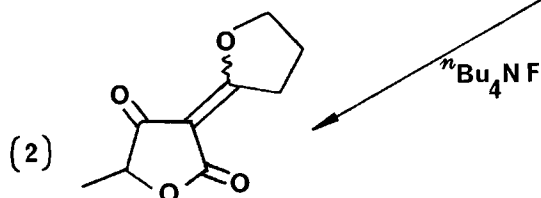


Entry	R ¹	R ²	R ³	Yield %
1	CH ₃	Ph	H	64
2	H	R ² =R ³ =cyclohexyl		80
3	CH ₃	R ² =R ³ =cyclohexyl		73

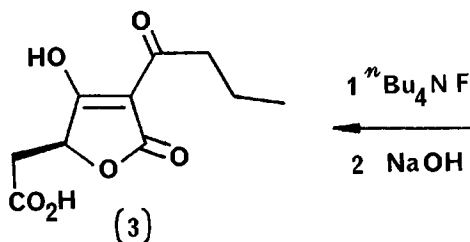
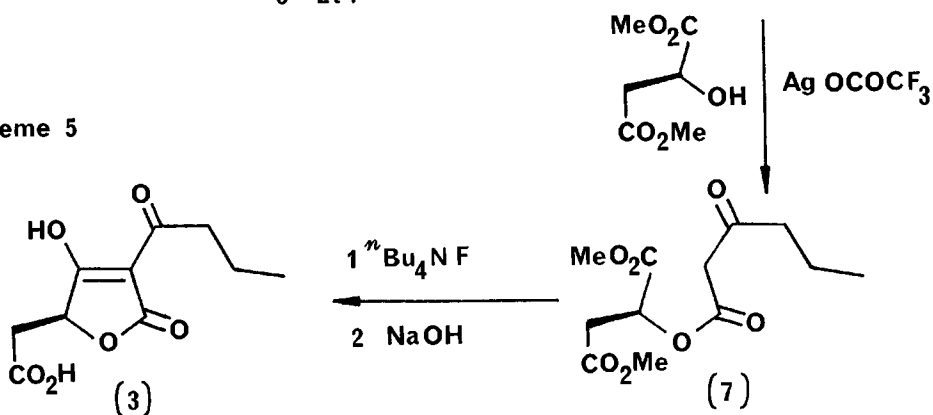
β -Ketothioesters may be transesterified under very mild conditions to oxo-esters by reaction with alcohols under metal catalysis⁵. This reaction was used together with the previously described alkylations to effect very short syntheses of the mold metabolites, carolic acid (2) and carlosic acid (3) (Schemes 4 and 5).



Scheme 4



Scheme 5



Thus, compound (4) (product from entry 5, Scheme 2) was transesterified with ethyl lactate using AgOCOCF_3 (2 eq, Et_2O , Na_2HPO_4 buffer) to afford (5) in 75% yield. Simultaneous Dieckmann cyclisation and deprotection of (5) was carried out by treatment with 3 eq of tetra-*n*-butylammonium fluoride to give carolic acid⁶ (2) in 90% yield. In a similar way, alkylation of the dianion from (1) with ethyl iodide gave (6) in 70% yield. Treatment of (6) with (*S*)-dimethylmalate, in T.H.F., and with 1 eq. of AgOCOCF_3 afforded (7) in 75% yield. Dieckmann cyclisation was achieved using 1 eq tetra-*n*-butylammonium fluoride in T.H.F. followed by hydrolysis to give (*S*)-carlosic acid⁶ (3) in 60% overall yield from (7). It is noteworthy that the use of bases other than $n\text{Bu}_4\text{NF}$ on similar malate derived systems led to dimethyl fumarate as the only identifiable product as a result of a facile β -elimination of

the acetoacetate moiety⁶. Use of the conditions described above completely avoids these problems.

Use of other β -ketothioesters in the above reactions, for example phenylacetothioacetate, was much less satisfactory owing to instability of the resulting anions decomposing by loss of phenylthiolate. The reactions described with t-butylacetothioacetate (1), however, constitute a useful synthetic procedure as, in principle, it behaves as a synthetic equivalent to diketene.

We thank the S.E.R.C. for a research studentship (to PMB), G.D. Searle Ltd, High Wycombe (CASE award to CMJF), the Royal Society of Chemistry for the Hickinbottom Research Fellowship and Dr. H.J. Wadsworth (G.D. Searle) for useful discussions.

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