

**THE ENANTIOSELECTIVE SYNTHESIS OF 3-  
POLYENOYL TETRAMIC ACIDS**

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Finally, thanks to all my friends in and around Lab. 29.

*Kraft durch Freude*

## ABSTRACT OF THESIS

The total synthesis of the 3-polyenoyltetramic acid antibiotic altamycin A has been attempted *via* a novel method of preparing enantiomerically pure tetramic acids.

Thus two target fragments were identified: (a) the tetramic acid and (b) the polyenal fragment. The chirality present in the latter was introduced (enantioselectively) through the catalytic Sharpless epoxidation of an isomerically pure allylic alcohol. This epoxide was then elaborated, using Wittig technology, into the aforementioned polyenal unit.

The chiral tetramic acid was readily available through reaction of an ester enolate with an oxazolidine-2,5-dione of desired stereochemistry.

The coupling of these fragments was studied - several methods being tried then evaluated according to their expediency.

This approach to altamycin A is sufficiently flexible to allow the preparation of other members of this interesting class of naturally occurring compounds.

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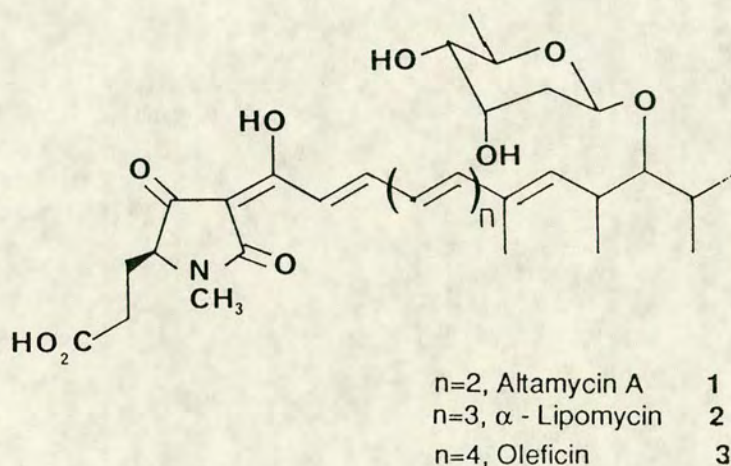
## ABBREVIATIONS

<b>Ac</b>	acetyl
<b>AIBN</b>	azo- <i>bis</i> -(isobutyronitrile)
<b>(aq)</b>	aqueous
<b>Bu</b>	butyl
<b>Bzl</b>	benzyl
<b>CHA</b>	cyclohexylamine
<b>DCHA</b>	dicyclohexylamine
<b>DCM</b>	dichloromethane
<b>DET</b>	diethyl tartrate
<b>DIBAL</b>	diisobutylaluminium hydride
<b>DMAP</b>	4-dimethylamino pyridine
<b>DMB</b>	2,4-dimethoxybenzyl
<b>DMF</b>	dimethylformamide
<b>DMS</b>	dimethylsulphide
<b>DMSO</b>	dimethylsulphoxide
<b>E<sup>+</sup></b>	an electrophile
<b>Et</b>	ethyl
<b>(g)</b>	gaseous
<b>HMDS</b>	1,1,1-3,3,3-hexamethyldisilazane
<b><i>i</i></b>	isomeric ( <i>iso</i> )
<b>(l)</b>	liquid
<b>Me</b>	methyl
<b>MOC</b>	methoxycarbonyl
<b><i>n</i></b>	normal
<b>NBS</b>	<i>N</i> -bromosuccinimide
<b>NMNO</b>	<i>N</i> -methylmorpholine <i>N</i> -oxide
<b>P</b>	protecting group
<b><i>p</i></b>	para
<b>PCC</b>	pyridinium chlorochromate
<b>Ph</b>	phenyl
<b>Pr</b>	propyl
<b>R</b>	alkyl group
<b><i>s</i></b>	secondary ( <i>sec</i> )
<b><i>t</i></b>	tertiary ( <i>tert</i> )

<b>TBDMS</b>	<i>tert</i> -butyldimethylsilyl
<b>TFA</b>	trifluoroacetic acid
<b>TMEDA</b>	<i>N,N,N',N'</i> -tetramethylethylenediamine
<b>TMS</b>	trimethylsilyl
<b>Tos</b>	<i>p</i> -toluenesulphonyl
<b>TPAP</b>	tetra- <i>n</i> -propylammonium per-ruthenate

## 1. INTRODUCTION

Altamycin A [1]<sup>1</sup>,  $\alpha$ -lipomycin [2]<sup>2</sup> and oleficin [3]<sup>3</sup> are members of a growing class of naturally occurring antibiotics, mycotoxins and pigments collectively termed the 3-acyltetramic acids.



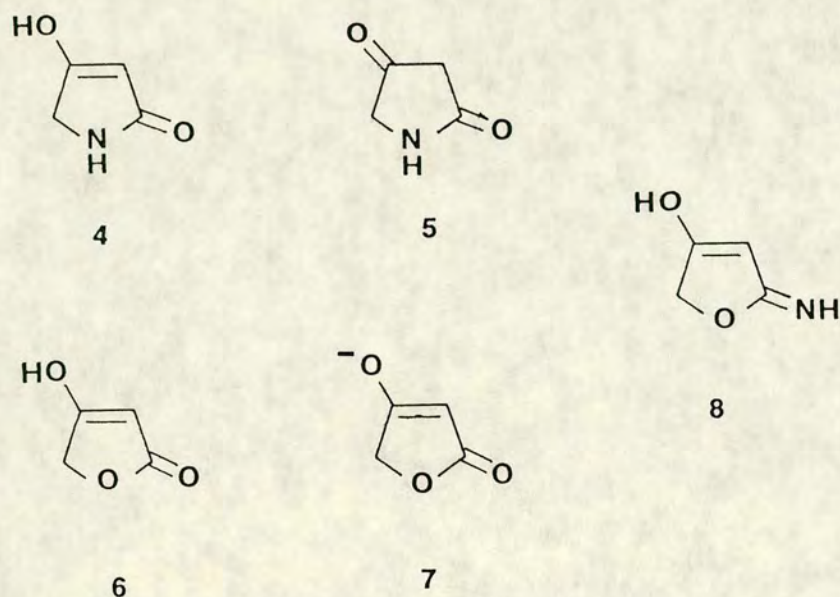
The total synthesis of these molecules presents a great challenge to the organic chemist as there are three chiral centres and an all-*trans* polyene chain to be constructed in the correct manner. Thus a synthesis must be flexible in two ways; (a) to enable polyenes of varying length to be made and (b) to allow synthesis of all four diastereoisomers. The fulfilment of these requirements will allow the determination of the absolute stereochemistry of the natural products and provide material for the detailed study of the biological action of these systems.

A discussion of the structure of the tetramic acid heterocycle and the naturally occurring tetramic acids is presented to show the importance of this class of compounds in nature. A brief review of previous synthetic strategies directed towards the construction of tetramic acids is included to give an indication of their strengths and weaknesses and foster an appreciation of the difficulties encountered in this area.



## 1.1 THE STRUCTURE OF TETRAMIC ACIDS

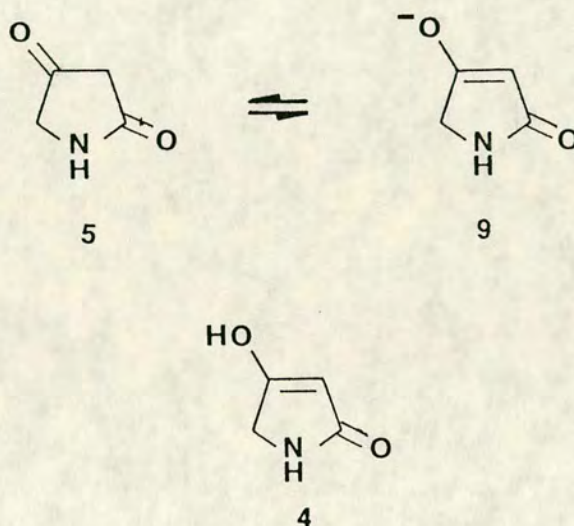
Tetramic acids have been represented as derivatives of the enolic 4-hydroxy-3-pyrroline-2-one tautomer [4] of the corresponding pyrrolidine-2,4-dione keto form [5]. This was done by analogy with tetronic acid [6], on the assumption that such derivatives would show similar physical and chemical properties. Tetronic acid was first synthesised in 1896<sup>4</sup> and is strongly acidic ( $pK_a=3.76^5$ ) in aqueous solution. The solid-state infrared spectrum is consistent with the enolic structure [6]<sup>6</sup> showing absorptions at  $1690(C=O)$  and  $1635(C=C)$   $cm^{-1}$  whilst the ultraviolet spectrum in aqueous ethanol showed absorptions at  $\lambda_{max}$  223 nm and 248 nm due to the enol [6] and the enolate [7], the proportion of each being pH dependent<sup>7</sup> (Scheme 1).



SCHEME 1

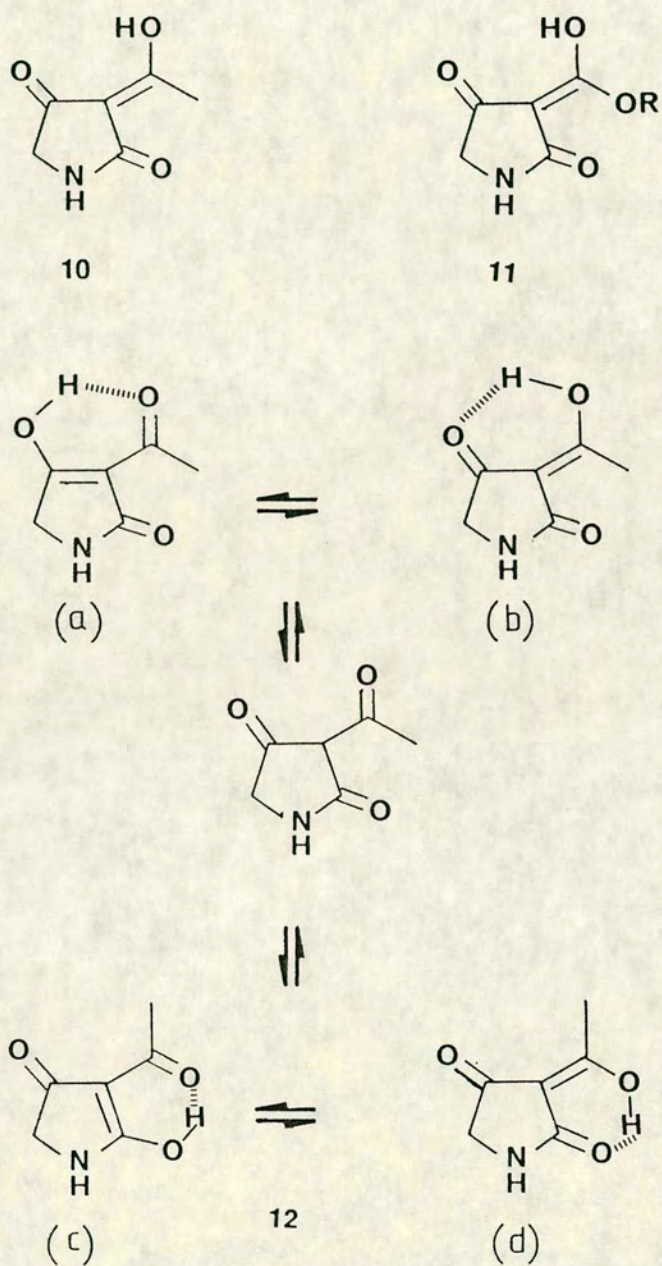
Tetramic acid [5] was surprisingly not synthesised until 1972<sup>8</sup> (earlier attempts resulted in the formation of the isomeric 2-iminotetronic acid [8]<sup>9,10</sup>), and is a much weaker acid than tetronic acid with  $pK_a=6.4$  in aqueous solution<sup>8</sup>. Consequently tetramic acid [5] is not highly enolised and exists mainly in the 2,4-diketo form (Scheme 1). The solid state i.r. spectrum shows absorptions at 3230 (NH stretch), 1696 (lactam C=O), 1670 (NH bend) and  $1782\text{ cm}^{-1}$  which was assigned to the C-4

ketone carbonyl group. This band was also observed in the solution i.r. spectrum so it was concluded that the lactam group participates in hydrogen bonding in the solid state. Ultraviolet spectroscopy showed a single absorption at  $\lambda_{\text{max}}$  260 nm due to the enolate species [9] with the intensity being strongly pH dependent. This meant that the ionised form [9] exists predominately in equilibrium with the 2,4-diketo form [5] in aqueous solution, with the enolic tautomer [4] being absent (Scheme 2).



SCHEME 2

Tetramic acids bearing acyl or alkoxy carbonyl substituents at the 3-position are found to have much increased acidity. The former [10] have pKa values in the range 3.0 - 3.5<sup>11,12</sup> whilst the latter [11] are in the range 2.3 - 2.5<sup>5</sup>. Proton n.m.r. spectra indicate the complete enolisation of these systems although the presence of several tautomeric forms complicates the spectra. The tautomerism of 3-acyltetramic acids was explained by a mechanism which involves two sets of rapidly interchanging internal tautomers [12a  $\rightleftharpoons$  12b] and [12c  $\rightleftharpoons$  12d], where each set arises from proton transfer along the intramolecular hydrogen bond, together with two pairs of slowly interconverting external tautomers [12a, b]  $\rightleftharpoons$  [12c, d], arising from the rotation of the acyl side chain (Scheme 3)<sup>13</sup>.



$$a:b:c:d = 5:15:0:80$$

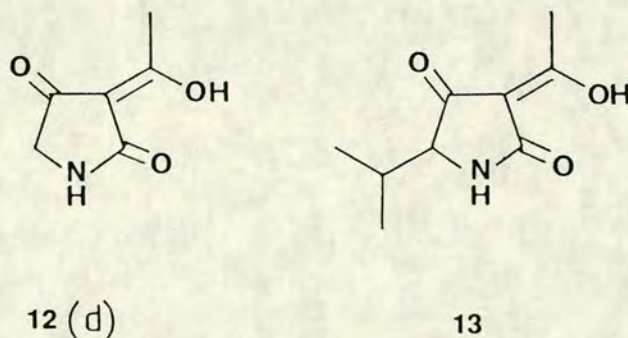
**SCHEME 3**

The internal tautomerisation of these derivatives occurs too rapidly to be detected on the time scale of an n.m.r. experiment; the external tautomerism, however, is of a rate which can be measured by n.m.r. methods and this has provided an interesting insight into this dynamic equilibrium. The ratios

of the external tautomers have been determined by Steyn and Wessels<sup>14,15(a)</sup> in a comprehensive analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r. characteristics of 3-acyltetramic acids of type [12c, d] with the observed chemical shifts and coupling constants representing the weighted averages of the corresponding values of the internal tautomers [12a  $\rightleftharpoons$  b] and [12c  $\rightleftharpoons$  d].

Steyn and Wessels<sup>14,15(a)</sup> found  $^{13}\text{C}$  n.m.r. spectroscopy more useful for the study of the tautomerisation in tetramic acids as the chemical shift of the  $^{13}\text{C}$  nucleus depends on the hybridisation of the carbon atom and is hardly affected by the anisotropy of neighbouring functional groups. The carbon resonances were assigned using off-resonance proton decoupled and single frequency nuclear Overhauser effect (n.O.e.)  $^{13}\text{C}$  n.m.r. spectra and they were then able to deduce the main tautomers with the help of some earlier work by Strothers and Lauterbur<sup>16</sup> which showed that enolic carbon atoms resonate at lower frequency than the corresponding keto carbons, and that hydrogen bonded carbonyl carbon atoms resonate at higher frequency than a corresponding free carbonyl. The enolic forms [12b] and [12d] (Scheme 3) were deduced to be the main tautomers from the predominance of the lower frequency C-6 enolic carbon atom resonance. The predominance of the higher frequency C-2 hydrogen bonded carbonyl signal led to the conclusion that the *exo*-enol [12d] is the main tautomeric form.

The approximate ratios of each of the tautomers was also calculated in the same study. This gave the ratio of individual tautomers [12a]:[12b]:[12c]:[12d] for simple 3-acyltetramic acids as 5:15:0:80<sup>15(a)</sup> and although this contradicted the results of Yamaguchi<sup>15(b)</sup>, based on  $^1\text{H}$  n.m.r. work, the conclusions of Steyn and Wessels<sup>15(a)</sup> are unequivocally substantiated by the X-ray crystallographic structure determination of tetramic acid [13], found to exist in the *exo*-*endo* enolic form (Scheme 4).



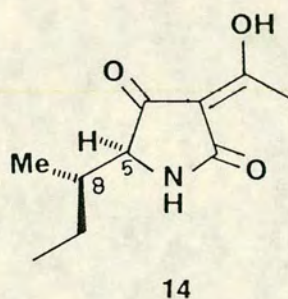
**SCHEME 4**

## 1.2 THE NATURALLY OCCURRING TETRAMIC ACIDS

The literature covering the isolation, characterisation, structural assignment and chemical synthesis of naturally occurring tetramic acids has been reviewed, at some length, recently<sup>17,18,19</sup>. In view of this it is intended that the following review be a concise summary of the previous articles that has been updated so as to include the most recent literature.

### 1.2.1 THE 3-ACYLTETRAMIC ACIDS

Pyrrolidine-2,4-diones bearing a 3-acyl substituent are the most commonly found tetramic acids in nature. Tenuazonic acid [14] is the simplest 3-acyltetramic acid and was isolated in 1957 by Stickings group<sup>20</sup> from the culture filtrate of *Alternaria tenuis* auct. Degradation by acidic hydrolysis gave *L*-isoleucine, establishing the absolute stereochemistry at C-5 and C-8, and its structure was subsequently shown to be 3-<sup>ethyl</sup>acetyl-5-*sec*-butyltetramic acid [14]<sup>21</sup> (Scheme 5).

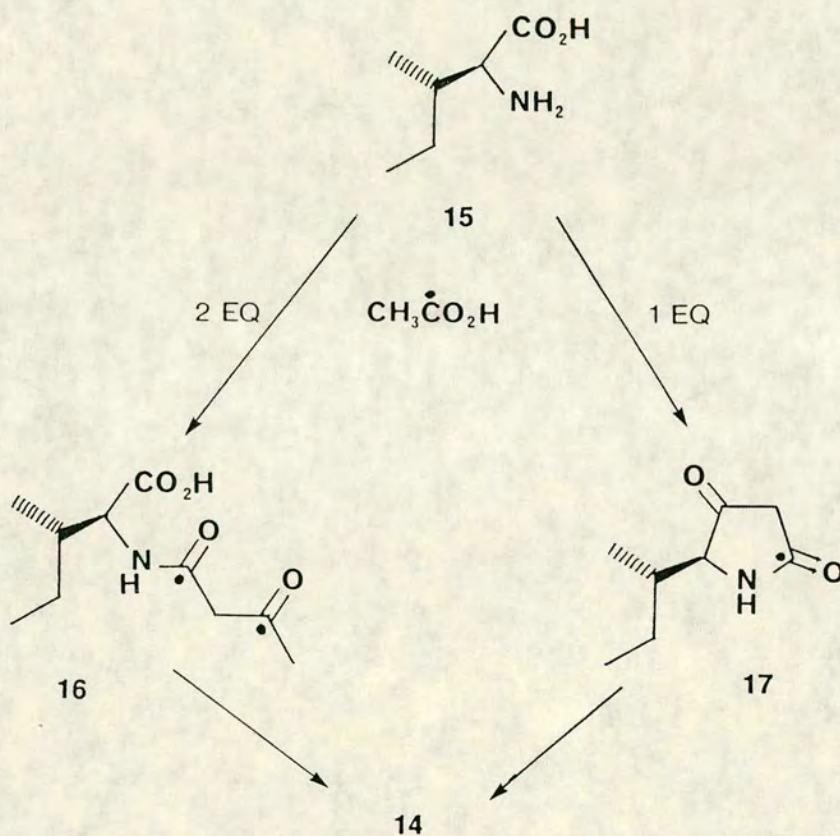


SCHEME 5

Tenuazonic acid exhibits a low level of antibacterial activity<sup>22</sup>, and inhibits a number of viruses at high dose levels including Measles (Enders), Vaccinia and Herpes Simplex (HF)<sup>23</sup>. Tenuazonic acid also shows the ability to inhibit human adenocarcinoma growing in the embryonated egg<sup>24</sup>

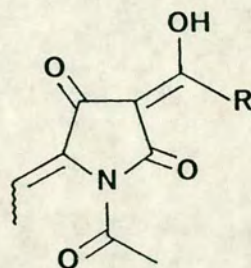
with the mode of action proposed to involve the inhibition of incorporation of amino acids into proteins<sup>2</sup>. Much attention has been given to tenuazonic acid because of the broad spectrum of biological activity it displays but it has been of limited value due to its extreme toxicity<sup>25,27</sup>.

Studies into the biosynthesis of tenuazonic acid [14] led to the isolation of radioactive *N*-acetoacetyl-*L*-isoleucine [16] from feeding experiments using [1-<sup>14</sup>C] labelled acetate and it was concluded<sup>28,29,30</sup> that the biosynthetic pathway involved cyclisation of an *N*-acetoacetyl-*L*-isoleucine [16] species rather than cyclisation of *N*-acetyl-*L*-isoleucine to deacetyltenuazonic acid [17] followed by acylation at C-3 (Scheme 6).



**SCHEME 6**

Kohl and his colleagues<sup>31</sup> isolated the antibiotic magnesidin from *Pseudomonas magnesorubia* sp. nov. as a 1:1 mixture of the covalent magnesium chelates of 1-acetyl-5-ethylidene-3-hexanoyltetramic acid [18] and its 3-octanoyl derivative [19] (Scheme 7).



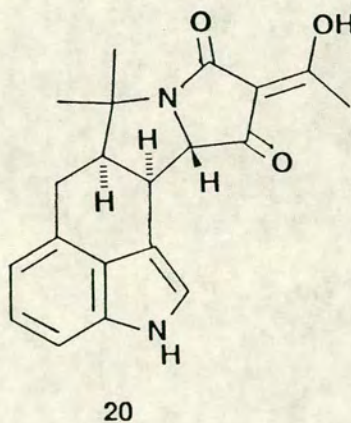
18, R =  $-(\text{CH}_2)_4\text{CH}_3$

19, R =  $-(\text{CH}_2)_6\text{CH}_3$

### SCHEME 7

The structures of [18] and [19] were determined by chemical degradation<sup>31</sup> and magnesidin was shown to inhibit various Gram-positive bacteria in very low concentrations without the toxicity found in tenuazonic acid<sup>32</sup>. In fact, since tenuazonic acid has also been isolated as a mixture of magnesium and calcium complexes<sup>33,34</sup> and previous isolation techniques<sup>20</sup> involved an acidification step, it has been suggested that the natural form of this and related compounds may well be as covalent metal chelates.

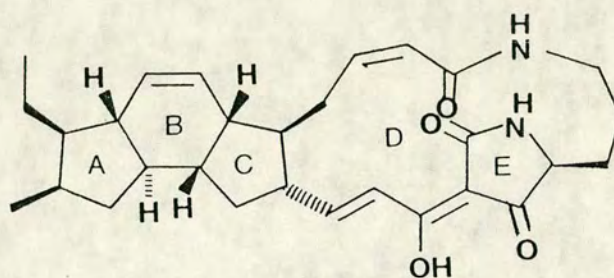
The structurally interesting mycotoxin,  $\alpha$ -cyclopiazonic acid [20], is produced by the fungus *Penicillium cyclopium* Westling; Holzappel<sup>35</sup> used chemical and spectroscopic evidence to assign the structure and relative stereochemistry. Biosynthetic studies<sup>36,37,38</sup> identified the incorporation of *L*-tryptophan indicating the absolute stereochemistry of  $\alpha$ -cyclopiazonic acid [20] is as shown (Scheme 8).



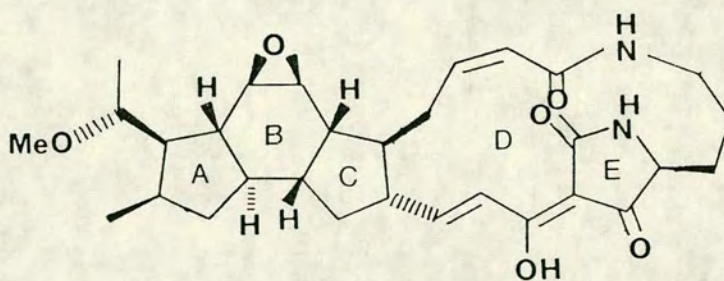
20

### SCHEME 8

Ikarugamycin [21] was isolated from the culture broth of *Streptomyces phaeochromogens* var. *ikarugamycin* Sakai<sup>39</sup> and shows strong specific antiprotozoal activity, *in vitro* antiamoebic activity as well as activity against some Gram-positive bacteria. It contains some very unusual structural features; an enoyltetramic acid which is part of a macrocyclic lactam and the *trans-anti-cis*-decahydro-*as*-indacene ring-system. The structure and absolute stereochemistry of ikarugamycin [21] were determined by an elegant structure proof carried out by Ito and Hirata<sup>40</sup>. The related antibiotic capsimycin<sup>41</sup> [22] is the only other known example of a tetramic acid with this interesting tricyclic system. The structure was determined by comparison of spectral data with that of ikarugamycin and from X-ray work<sup>41</sup> (Scheme 9).



21

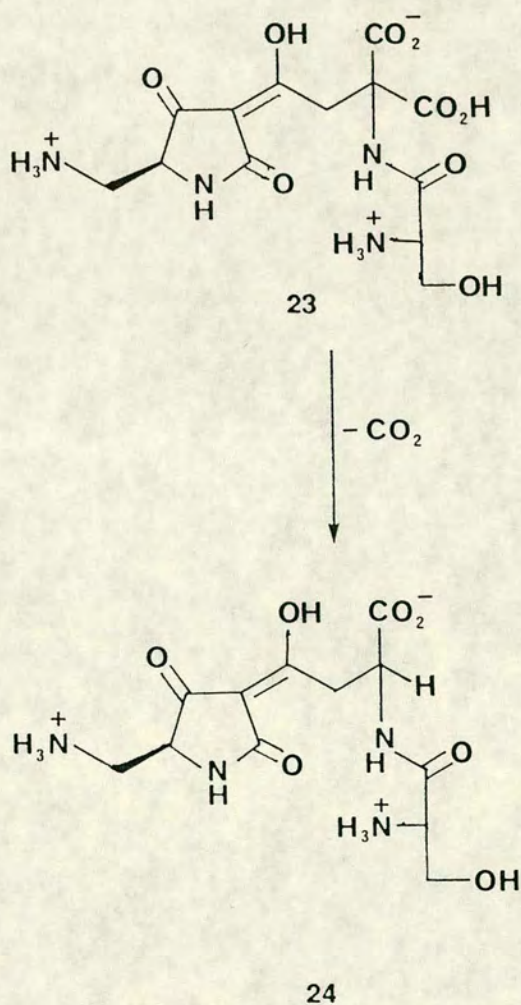


22

SCHEME 9



The structure of malonomycin [23], an antiprotozoal compound isolated from *Streptomyces rimosus* var. *paromomycinus*<sup>42</sup>, was elucidated by Batelaan and co-workers<sup>43,44</sup> in 1972. The unique aminomalonic acid moiety that forms part of the 3-acyl sidechain of the tetramic acid was found to be essential for the biological activity of the compound. Decarboxylation by brief reflux in water gave the inactive derivative [24]<sup>43</sup> (Scheme 10). Biosynthetic studies on malonomycin have indicated that the aminomethyl group at C-5 originates from *L*-2,3-diaminopropionic acid<sup>45</sup>.

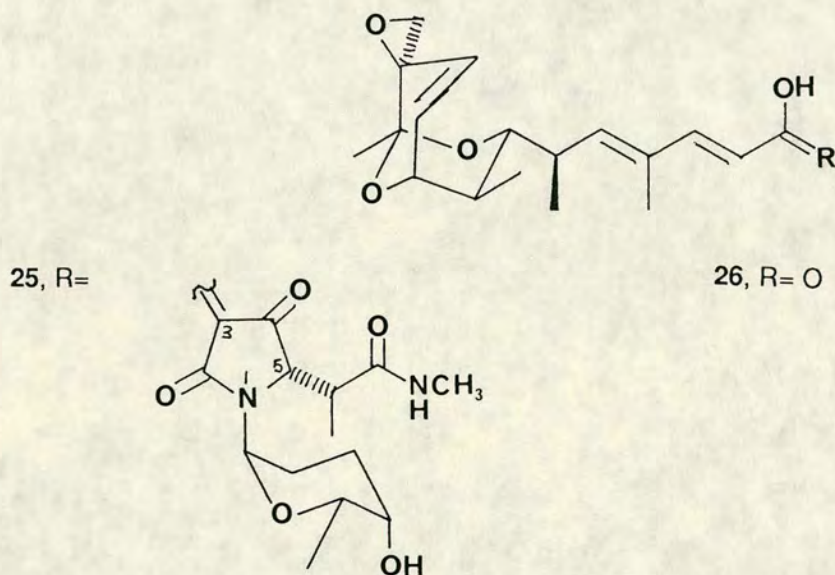


SCHEME 10

### 1.2.2 THE 3-POLYENOYLTETRAMIC ACIDS

The title compounds form a sub-group of 3-acyltetramic acids which exhibit a range of biological activity including antiviral, antibiotic and antitumoural activity. Structural features common to members of this sub-group are a tetramic acid nucleus with a polyenoyl substituent at C-3; there is, however, much diversity in the functionalisation of the polyene chain and the substitution at N-1 and C-5 of the heterocyclic ring.

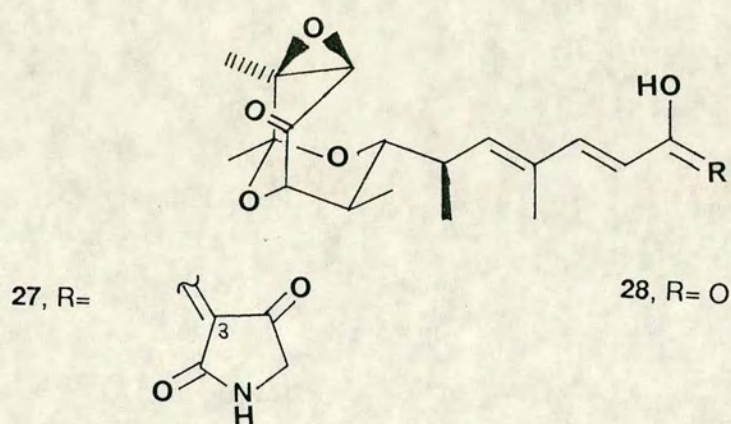
The first of the dienoyl tetramic acids to be isolated was streptolydigin [25]<sup>46</sup> which has a fairly complex set of substituents; a methyl propionamide at C-5, a 2,3,6-trideoxyaldohexose at N-1 and 2,9-dioxabicyclo[3,3,1] nonane subunit. The structure was assigned by study of the chromophore<sup>47</sup> along with synthetic work on streptolic acid<sup>48</sup> [26], which is the periodate oxidation product of streptolydigin [25]. The stereochemistry was not determined. Synthesis established the hexose component as 2,3,6-trideoxy-*L*-threo-aldohexose<sup>49</sup> (Scheme 11).



SCHEME 11

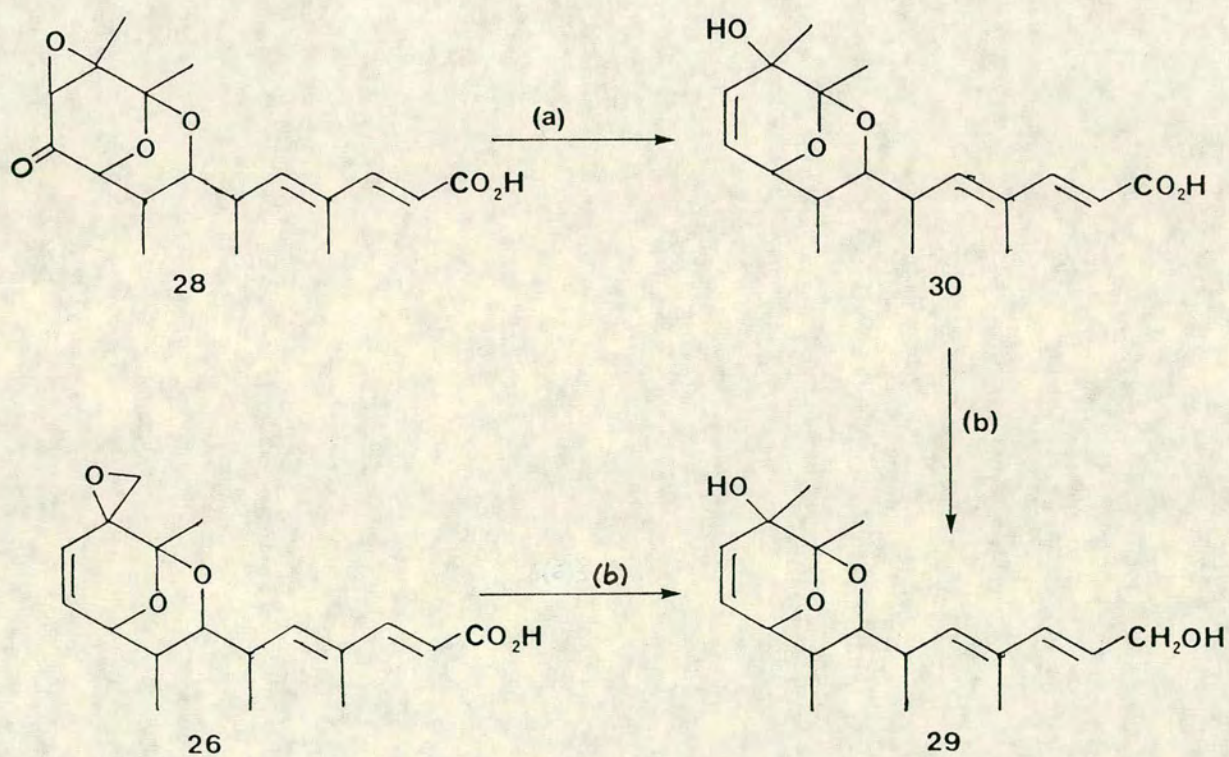
Mayer isolated<sup>50</sup> tirandamycin [27] from *Streptomyces tirandis* var. *tirandis* in 1971 and the compound was found to have similar biological properties to streptolydigin [25]. In common with

streptolydigin, tirandamycin A has attracted considerable interest due to its potent inhibition of bacterial DNA-directed RNA polymerase<sup>51</sup> and selective inhibition of terminal deoxynucleotidyl transferase from leukemic cells<sup>52</sup>. The structure was assigned by comparison of the spectral properties of streptolydigin and tirandamycin A [27]<sup>53</sup>. X-ray crystal structure studies on the *p*-bromophenacyl ester of tirandamycic acid [28], which was obtained by periodate oxidation of [27]<sup>54</sup>, allowed the absolute stereochemistry of tirandamycin A to be determined (Scheme 12).



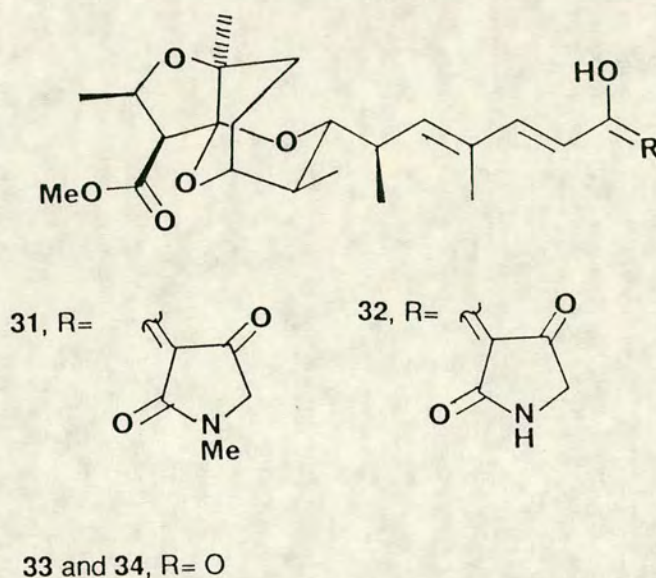
SCHEME 12

Tirandamycic acid [28] and streptolic acid [26] were both converted to streptolol [29] (Scheme 13) thus proving that the overall stereochemistry of streptolic and tirandamycic acids was identical; this enabled the structure [25] to be assigned unambiguously to streptolydigin<sup>54</sup>.



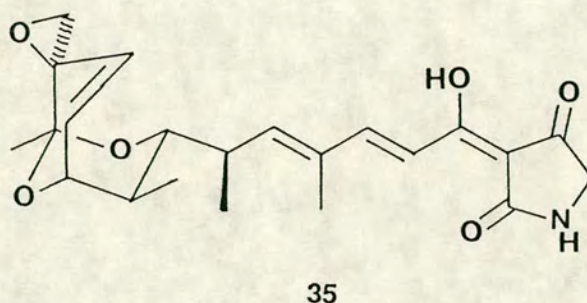
**SCHEME 13**, reagents: (a) hydrazine, AcOH; (b) lithal, ether.

Two closely related 3-dienoyltetramic acids Bu2313A [31] and Bu2313B [32] have been isolated<sup>55</sup> from an unidentified oligosporic strain of an actinomycete. Both are broad spectrum antibiotics, effective against Gram-positive and Gram-negative anaerobic bacteria as well as some aerobic bacteria such as *Streptococci*<sup>55</sup>. Their structures were also determined<sup>55</sup> by X-ray crystal structure work on the respective *p*-bromophenacyl esters of the two periodate oxidation products [33] and [34] (Scheme 14).



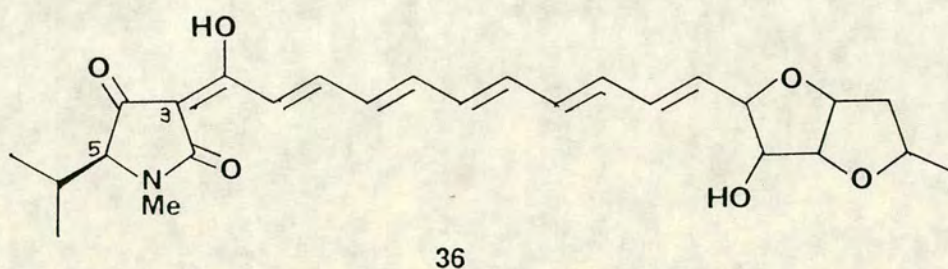
**SCHEME 14**

A structurally unique hybrid of the streptolydigin-tirandamycin families of antibiotics, tirandalydigin [35], has recently been isolated<sup>56</sup> from the fermentation beers of *Streptomyces* sp. AB-1006A-9. This anti-anaerobic antibiotic<sup>57</sup> has been assigned structure [35] on the basis of u.v., n.m.r. and mass spectrometric data, although there is no firm evidence to prove the absolute stereochemistry. The configuration shown for structure [35] (Scheme 15) is assumed because of similarities with streptolydigin and the postulated view that a common biosynthetic pathway to these compounds exists<sup>56</sup>.



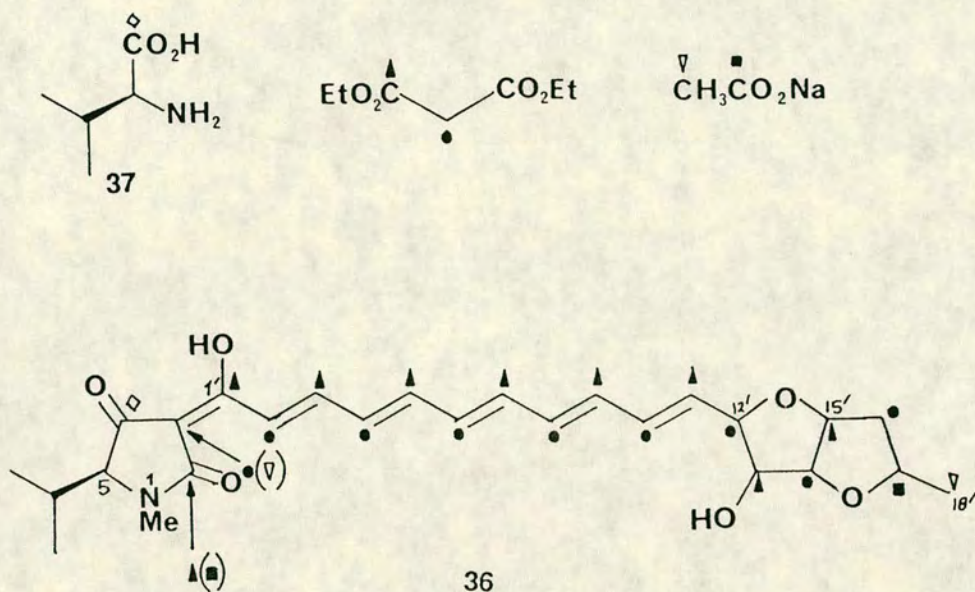
SCHEME 15

Naturally occurring tetramic acids with a polyene chromophore include the orange-red pigment of *Penicillium islandicum* Sopp., erythrokyrine [36]<sup>58</sup>. Erythrokyrine was shown to contain the 3-pentaenoyl substituent by spectral evidence and the absolute configuration at C-5 was determined as (S) by degradation to *L*(+)-*N*-methylvaline, however the question of the stereochemistry in the bicyclic ring system was not addressed<sup>58</sup> (Scheme 16).



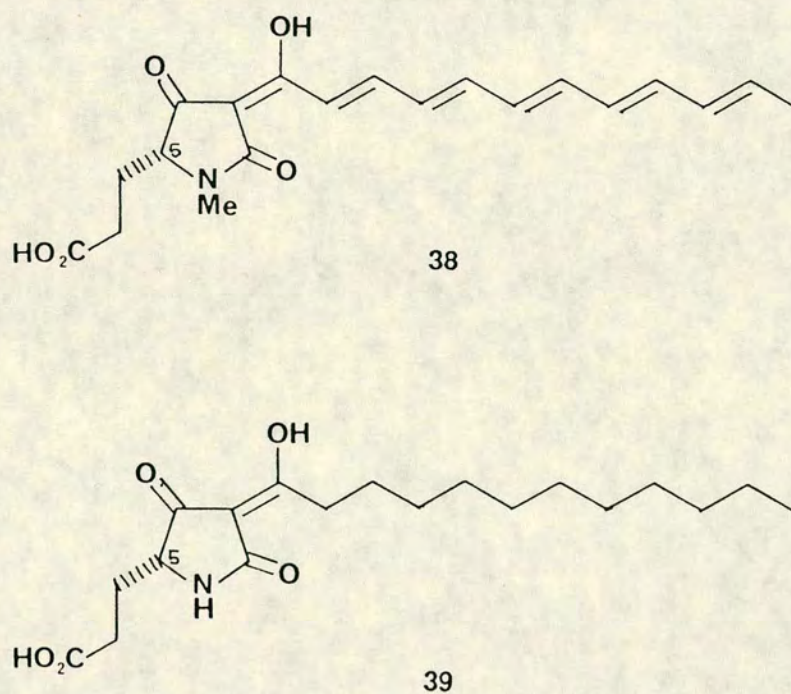
SCHEME 16

Feeding studies<sup>59</sup>, using [1-<sup>14</sup>C] or [2-<sup>14</sup>C] labelled sodium acetate and [1-<sup>14</sup>C] or [2-<sup>14</sup>C] diethyl malonate, showed that C-1' to C-16' were derived from malonate whilst C-17' and C-18' were acetate derived. The amino acid constituent in the tetramic acid was shown to be from *L*-valine [37] by uptake of <sup>14</sup>C-carboxyl labelled material into erythrokyrine. The biosynthetic origin of the *N*-methyl group as well as C-2 and C-3 of the tetramic acid could not be determined due to inconclusive results (Scheme 17).



SCHEME 17

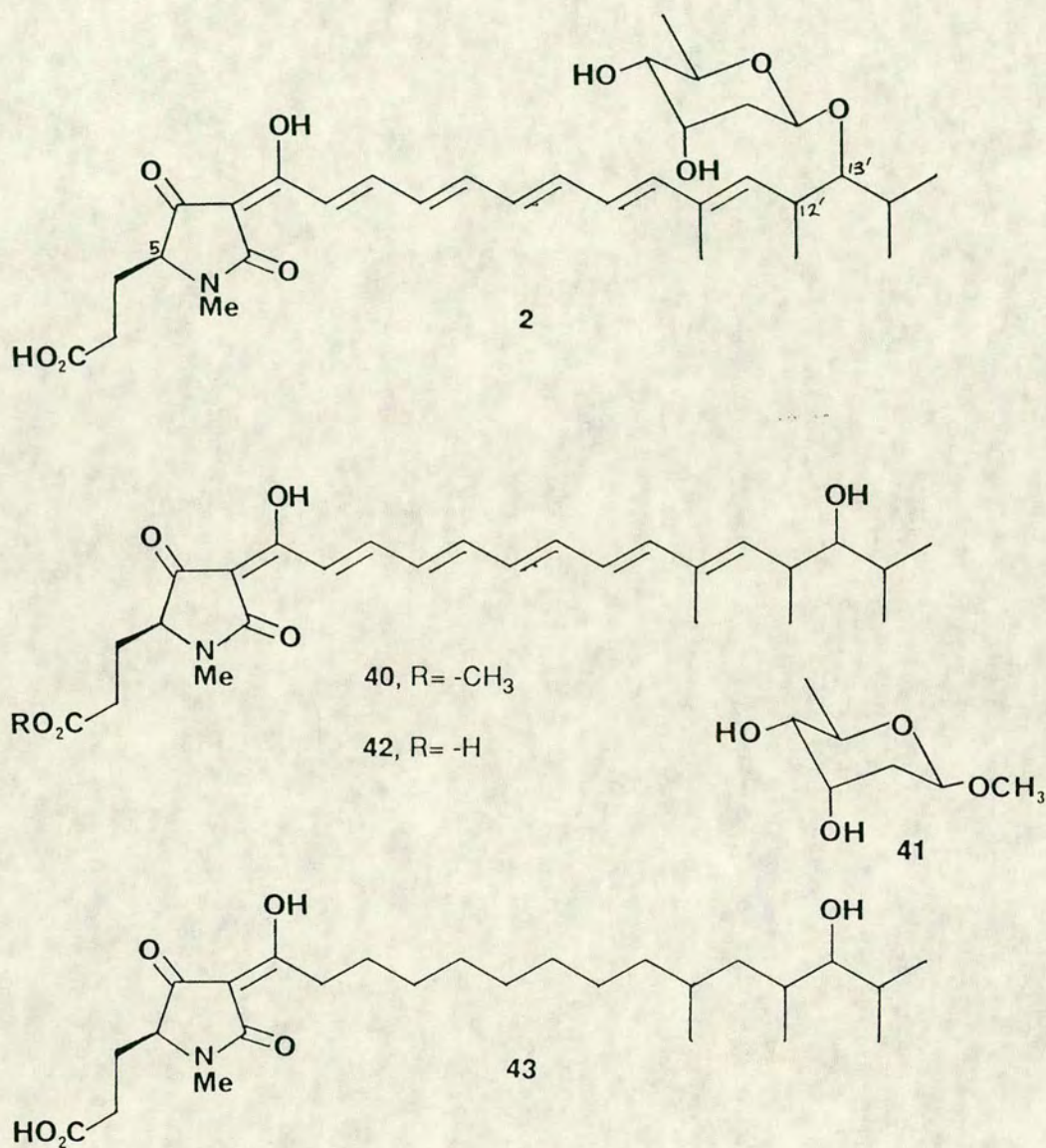
Fuligorubin A [38] was isolated from the slime mould *Fuligo septica* (L.) Wiggers by Steglich<sup>60</sup>, who showed that it was responsible for the yellow appearance of the slime mould because of the polyenoyltetramic acid chromophore. The structure of fuligorubin A [38] was deduced from spectral data whilst studies of the chiroptic properties of decahydrofuligorubin A [39] led to the absolute configuration being determined as (5R) (Scheme 18).



SCHEME 18

A 3-polyenoiltetramic acid with the same chromophore as erythrokyrine [36] was isolated from *Streptomyces aureofaciens* in 1972 by Zeeck<sup>61</sup> and subsequently assigned structure [2]<sup>62</sup>. Methanolysis of  $\alpha$ -lipomycin [2], using a trace of acid, afforded  $\alpha$ -lipomycin methyl ester [40] and methyl- $\beta$ -*D*-digitoxoside [41]. The stereochemical identity of the sugar was confirmed by comparison with an authentic sample. Chromatography of  $\alpha$ -lipomycin on silica gel (impregnated with oxalic acid) gave the aglycone  $\beta$ -lipomycin [42] which was found to absorb five equivalents of hydrogen upon hydrogenation over palladium on carbon yielding decahydro- $\beta$ -lipomycin [43] (Scheme 19).

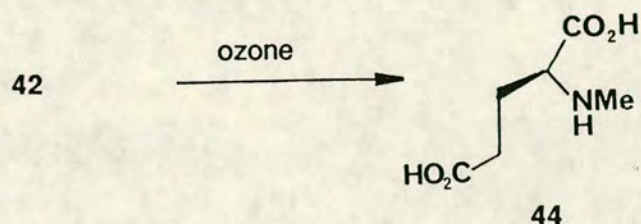




SCHEME 19

The decadehydro derivative [43] was shown to have similar spectroscopic properties to tenuazonic acid [14] whilst  $\alpha$ - and  $\beta$ -lipomycin contained the same chromophore as erythrokyrine [36]. The absolute configuration at C-5 of the tetramic acid was determined to be (S) by degradation (ozonolysis, followed by acidic hydrolysis) of  $\beta$ -lipomycin [42] which gave *L*-*N*-methylglutamic acid [44]. Further chemical studies were carried out to determine the position of the isopropyl group

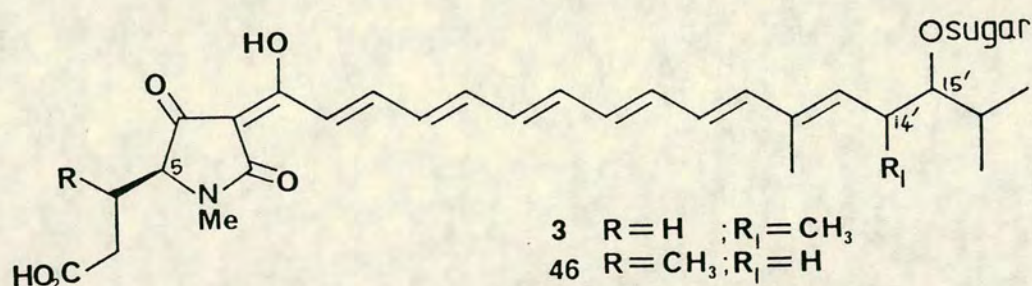
but the stereochemistry (both relative and absolute) of C-12' and C-13' could not be assigned (Scheme 20)<sup>62</sup>.



**SCHEME 20**

$\alpha$ -Lipomycin [2] and  $\beta$ -lipomycin [42] both exhibited selective inhibition of the growth of Gram-positive bacteria but have no effect on the growth of fungi or yeasts<sup>61</sup>.

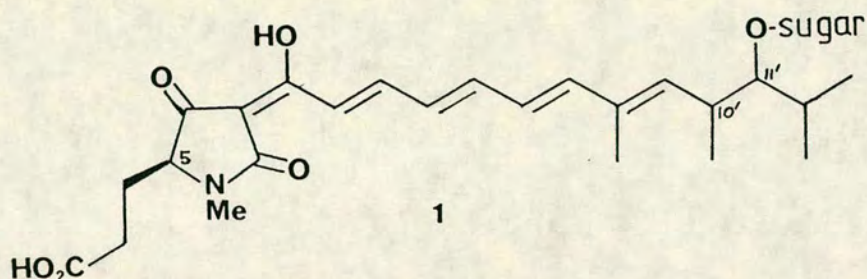
The structurally related  $\beta$ -glycoside oleficin [3] was isolated as a deep red powder from a strain of *Streptomyces parvulus*, and showed biological activity similar to the lipomycins<sup>63</sup>, with only the growth of Gram-positive bacteria being inhibited. Initially the structure was assigned as [46]<sup>64</sup> but this was later revised such that oleficin [3] differs from  $\alpha$ -lipomycin [2] only in the length of the polyene chain<sup>65</sup>. Determination of the relative and absolute stereochemistry at C-14' and C-15' was likewise precluded as oleficin is also a waxy non-crystalline solid making X-ray studies impracticable (Scheme 21).



**SCHEME 21**

A third compound in this family, altamycin A [1], was isolated recently by Shenin<sup>66</sup>. The structure was determined as [1] by the same protocols that had been used for oleficin and the lipomycins, and again the absolute stereochemistry at C-10' and C-11' remained unresolved whilst that at C-5 was

found to be derived from the *L*-amino acid. Altamycin A [1] was found to contain a tetraene system as well as the  $\beta$ -*D*-digitoxose moiety<sup>66</sup>; its biological activity was in accordance with the other members of this series (Scheme 22).

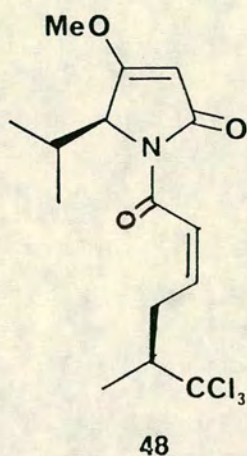


**SCHEME 22**

### 1.2.3 *N*-ACYL-4-METHOXY-3-PYRROLINE-2-ONES

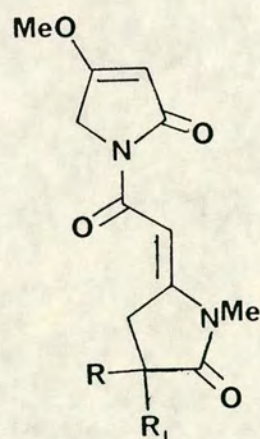
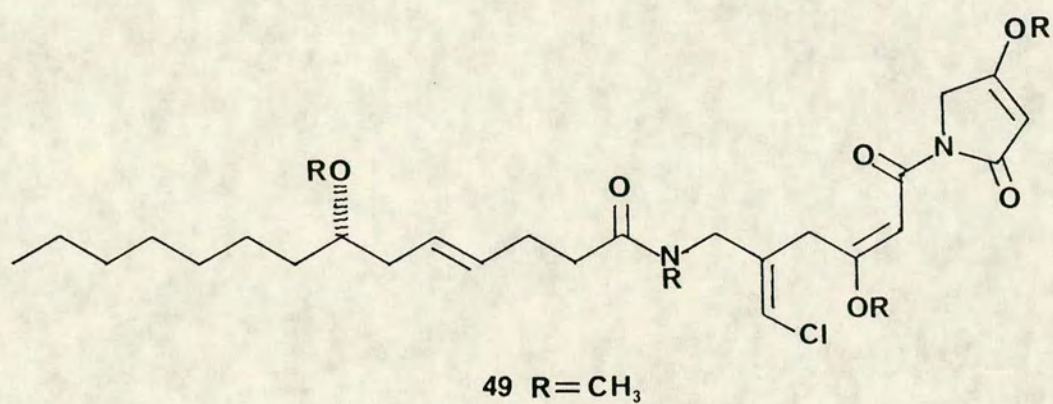
The title compounds form the second group of natural products that contain the tetramic acid moiety; occurring as the 4-*O*-methyl ether, unsubstituted at C-3 and acylated on the ring nitrogen.

The first member of this small class to be isolated was dysidin [48], a chlorine containing secondary metabolite of the Indo-Pacific sponge *Dysidea herbacea*<sup>67</sup>. The structure [48] was assigned after X-ray crystal studies; the C-5 substitution is so far unique amongst naturally occurring *N*-acyl-4-methoxy-3-pyrroline-2-ones (Scheme 23).

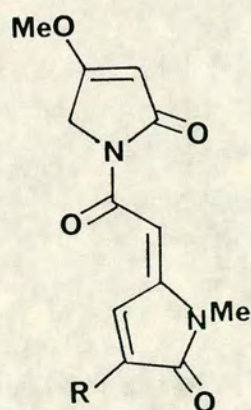


**SCHEME 23**

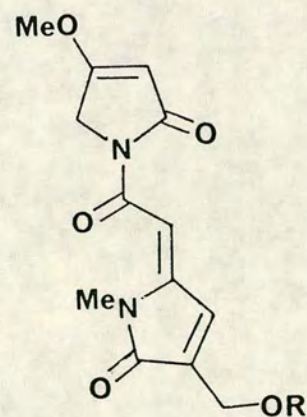
Malingamide A [49], a more complex chlorine containing derivative, was isolated from the marine cyanophyte *Lyngbya majuscula*<sup>68</sup>; its structure was assigned by chemical and spectral means. The same workers subsequently isolated<sup>69</sup> seven related compounds from the same blue-green algae. They all lacked the fatty acid side chain of malingamide A [49] and were termed the pukeleimides (A to G), their structures being resolved by X-ray data (Scheme 24).



C,52; R = -CH<sub>2</sub>OMe, R<sub>1</sub> = -OH  
 D,53; R = -CH<sub>2</sub>OH, R<sub>1</sub> = -OH  
 E,54; R = R<sub>1</sub> = -CH<sub>3</sub>



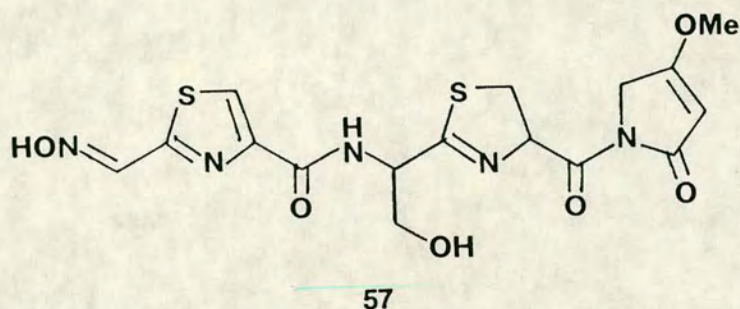
A,50; R = -CH<sub>2</sub>OH  
 G,56; R = -CH<sub>2</sub>Me



B,51; R = -H  
 F,55; R = -CH<sub>3</sub>

**SCHEME 24**

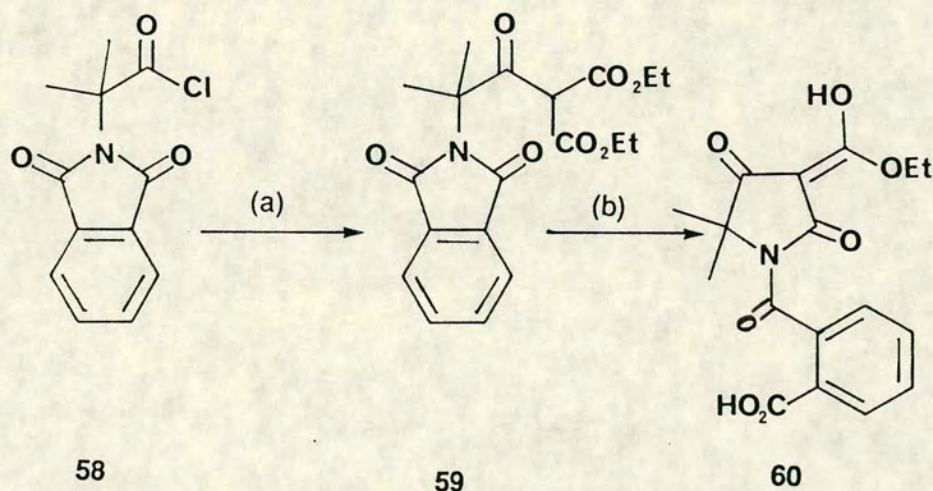
Althiomycin [57]<sup>70,71</sup> was isolated from *Streptomyces althioticus* and has been the subject of attention for several groups<sup>72,73</sup>. Althiomycin [57] exhibits a broad spectrum of antibacterial activity against both Gram-positive and Gram-negative micro-organisms, although its instability limits its practical value (Scheme 25).



SCHEME 25

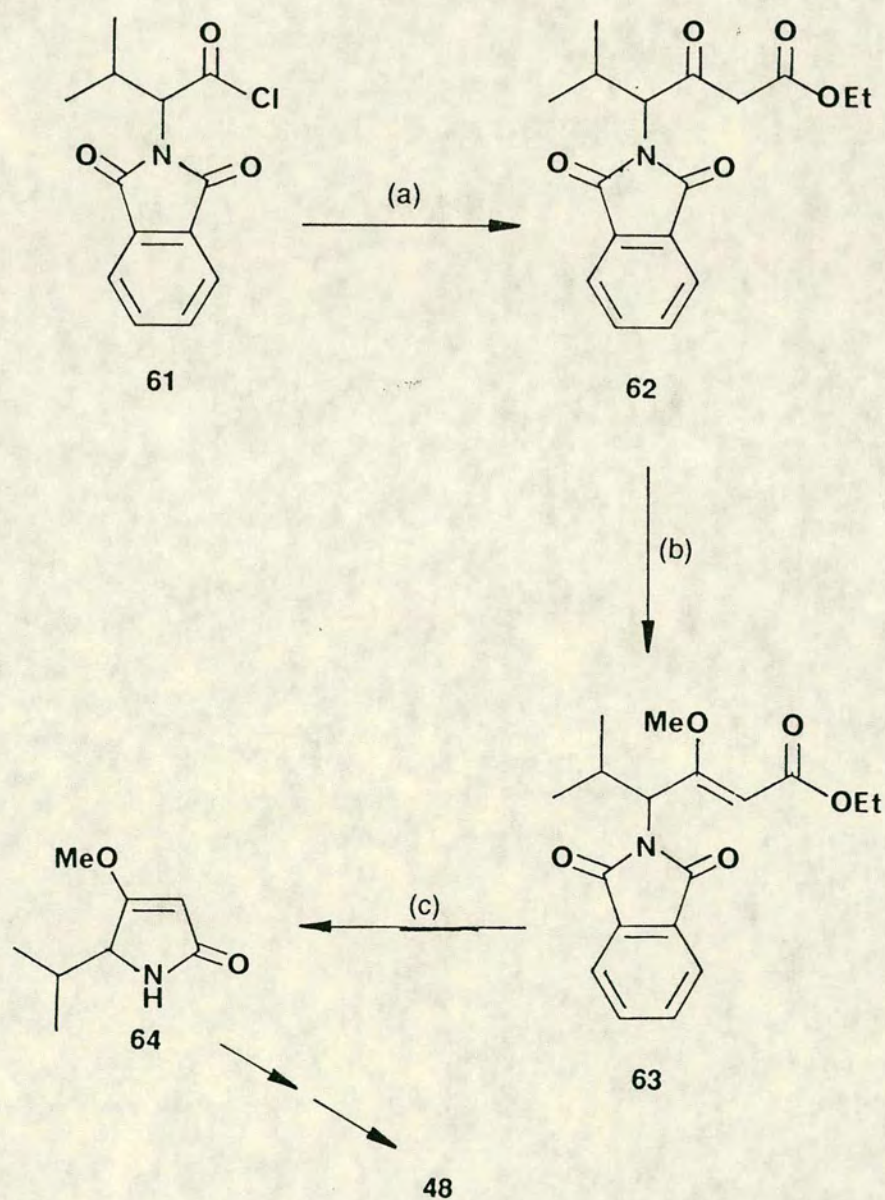
### 1.3 SYNTHETIC ROUTES TO TETRAMIC ACIDS

Gabriel achieved the first synthesis of a tetramic acid derivative in 1914<sup>74</sup>. Reaction of phthalimidoisobutyryl chloride [58] with diethyl sodiomalonate gave [59], which on treatment with concentrated sulphuric acid cyclised to the 3-ethoxycarbonyltetramic acid [60] (Scheme 26).



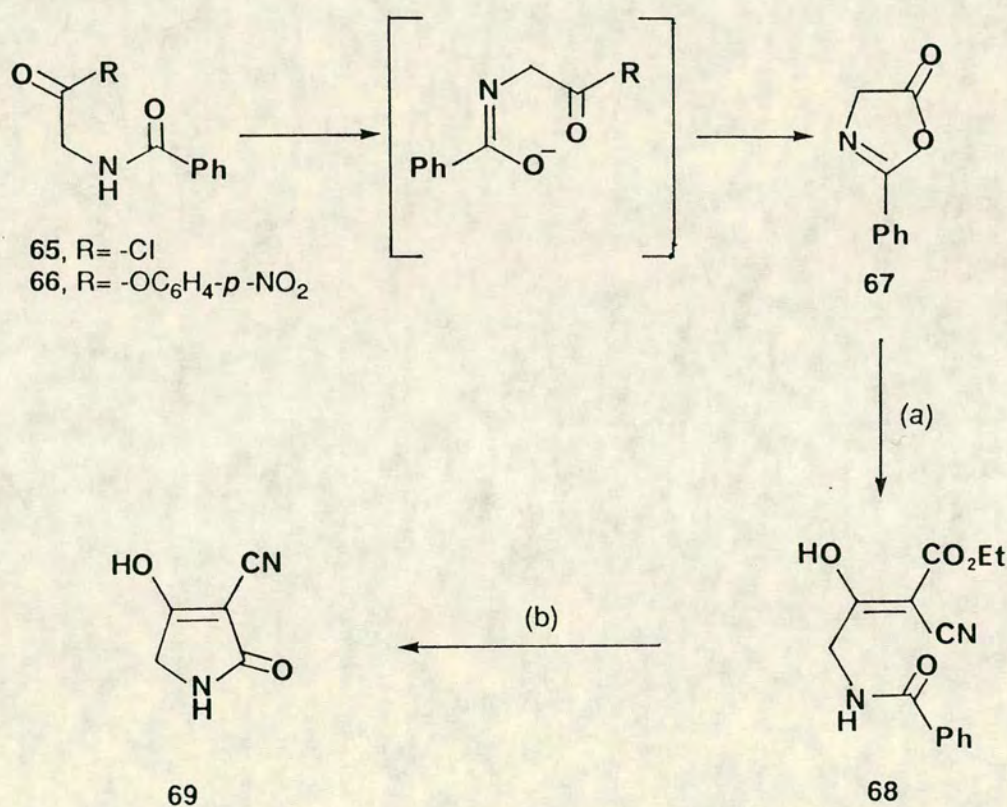
SCHEME 26, reagents: (a) diethyl sodiomalonate; (b) conc.  $H_2SO_4$ .

Similar methodology was applied to the total synthesis of dysidin [48]<sup>75</sup>. The acid chloride of ( $\pm$ )-*N*-phthaloylvaline [61] was homologated to the ketoester [62] by reaction with the dianion of monoethyl malonate. *O*-Methylation was carried out by treating [62] with potassium hydride and methyl fluorosulphonate giving methoxy enol [63] which on treatment with hydrazine gave the 4-*O*-methyltetramic acid [64], which could be elaborated to dysidin [48] (Scheme 27)



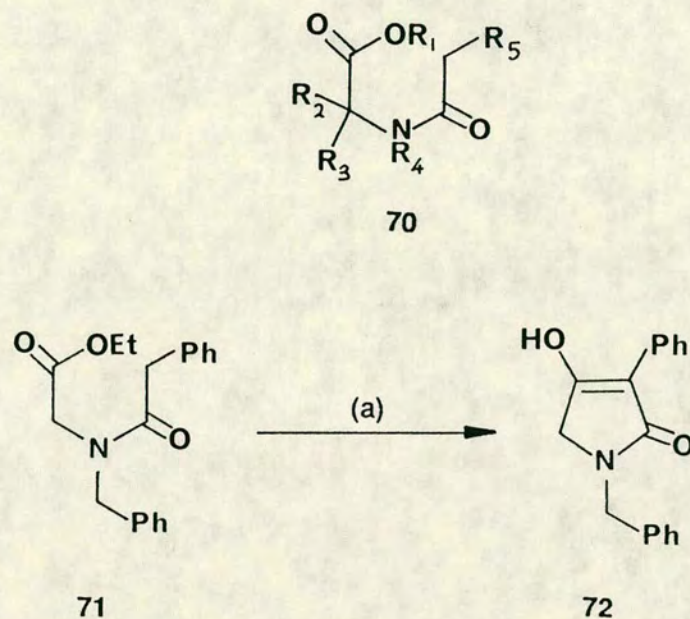
SCHEME 27, reagents: (a) ethyl disodiomalonate; (b) KH, MeOSO<sub>2</sub>F; (c) hydrazine.

The versatility of hippuryl chloride [65] and *p*-nitrophenyl hippurate [66] as intermediates in the synthesis of 3-substituted tetramic acids has been demonstrated<sup>76</sup>. Condensation of [65] or [66] with ethyl sodiocyanoacetate gives the corresponding benzoylaminoacetyl compound [68] in moderate yield; these were formed *via* the 2-phenyloxazolone intermediate [67]. Cyclisation of [68] using excess sodium ethoxide was observed to proceed with concomitant ~~with~~ debenzoylation resulting in the formation of the 3-substituted tetramic acid [69]<sup>76</sup> (Scheme 28).



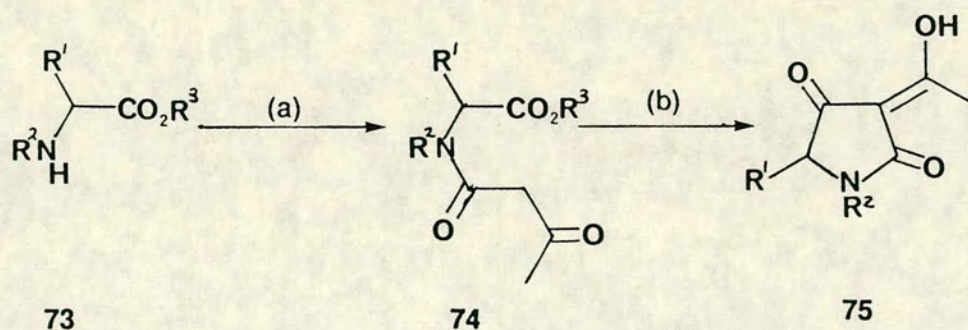
**SCHEME 28**, reagents: (a) ethyl sodiocyanoacetate; (b) NaOEt.

The Dieckmann cyclisation of *N*-acylaminoesters of the type [70] offers a route to the tetramic acid ring system which is potentially very versatile, and indeed this approach has received much attention. The formation of 1-benzyl-3-phenyltetramic acid [72] by treatment of [71] with sodium ethoxide was reported in 1950<sup>77</sup> and a series of 3-alkyltetramic acids has been prepared by this method<sup>78</sup> (Scheme 29)



SCHEME 29, reagents: (a) NaOEt.

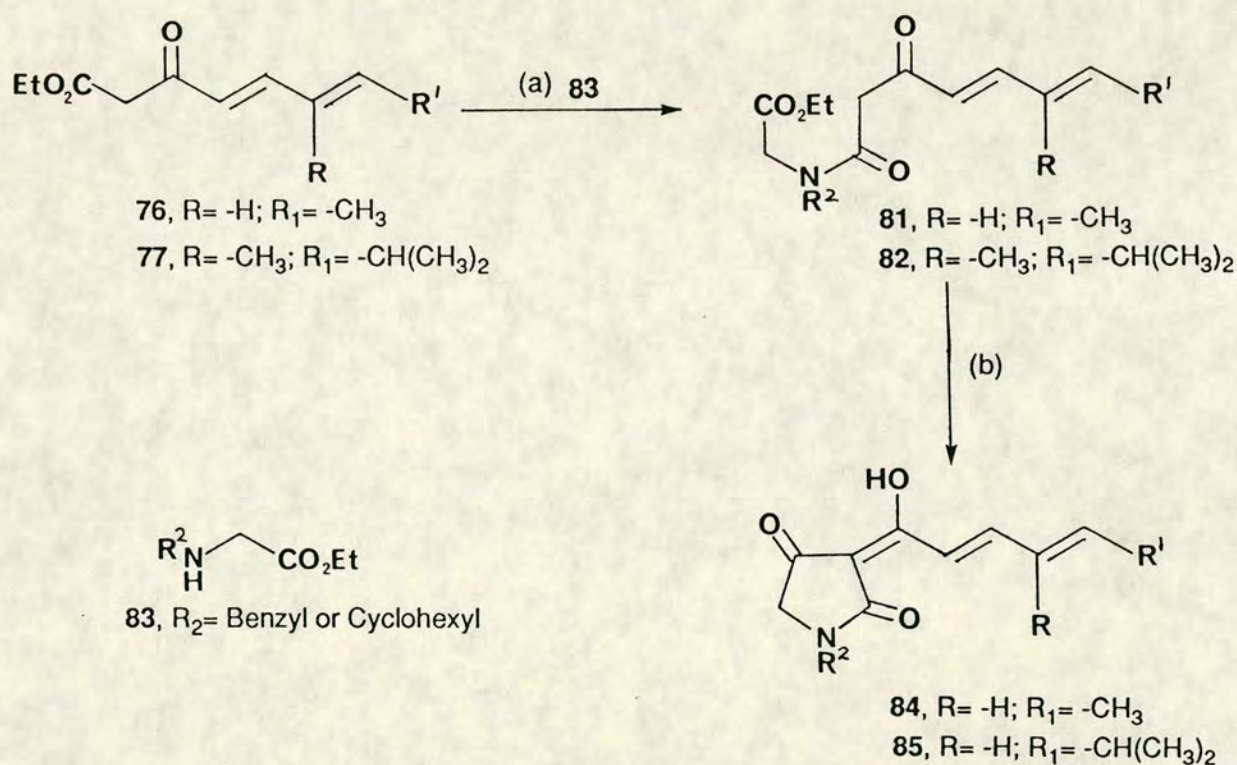
In 1954, Lacey reported a convenient two step synthesis of 3-acyltetramic acids from readily available  $\alpha$ -amino-esters<sup>79</sup>. This strategy has since become widely adopted in the construction of the tetramic acid ring. The original method involved condensation of an  $\alpha$ -amino-ester [73] with diketene to give an acetoacetamide [74], which cyclised to the 3-acyltetramic acid [75] on exposure to sodium ethoxide<sup>79</sup> (Scheme 30).



SCHEME 30, reagents: (a) diketene; (b) NaOEt.

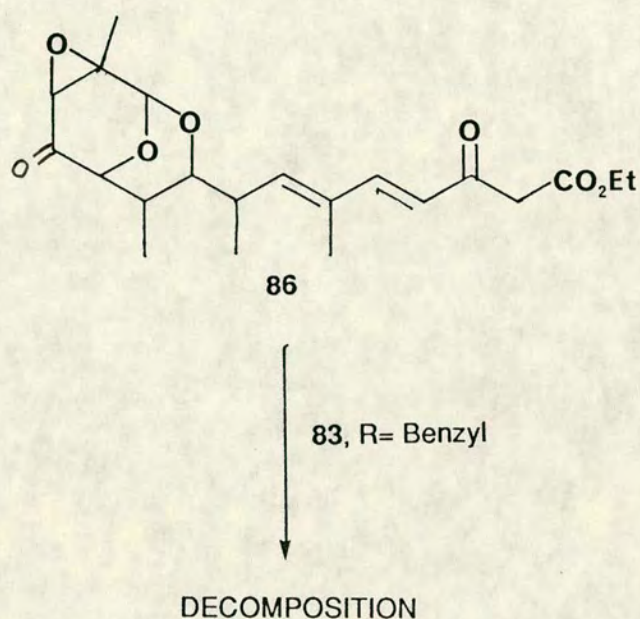


Tenuazonic acid [14] was prepared from ethyl *L*-isoleucinate and diketene by Miller and co-workers<sup>23</sup>. Harris and colleagues<sup>22</sup> similarly prepared a series of 3-acyltetramic acids from other amino acids in order to investigate their biological activity. Rinehart Jr. has investigated the applicability of this methodology to the synthesis of 3-dienoyltetramic acids related to streptolydigin [25] and tirandamycin A [27]<sup>80</sup>. However, in view of the basic reaction conditions, stereocontrol of the chiral centre at C-5 is very difficult. The condensation of dienoylacetyl esters [76] and [77] with a range of ethyl *N*-alkylglycinates [83] to give the corresponding acetoacetamides [81] and [82] was also published by Rinehart Jr. in the same paper<sup>80</sup>. When treated with sodium ethoxide the two acetoacetamides [81] and [82] afforded the dienoyltetramic acids [84] and [85] (Scheme 31).



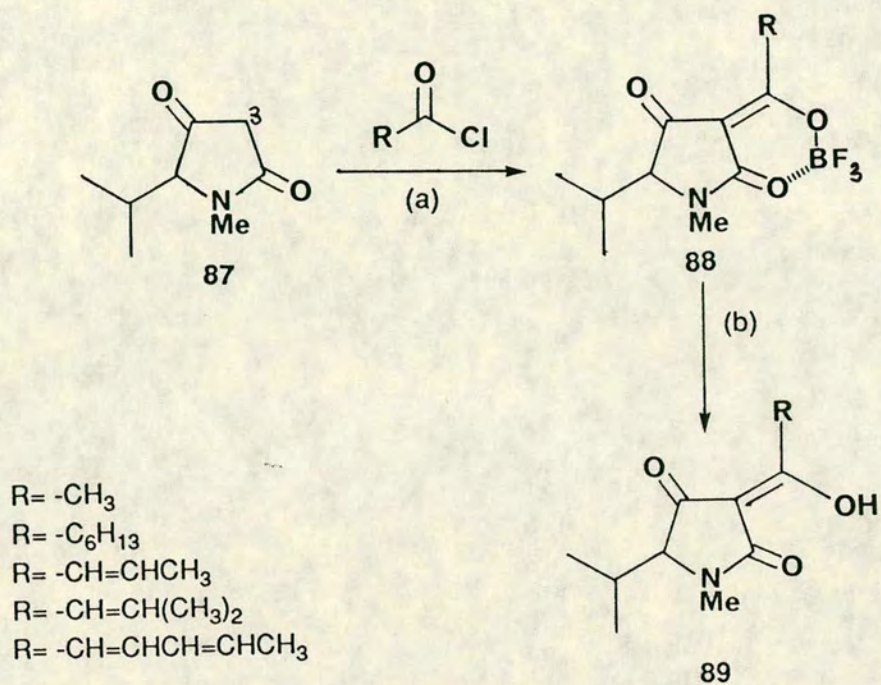
**SCHEME 31,** reagents: (a) toluene 110 °C; (b) NaOEt.

Unfortunately, when an analogous condensation of ethyl tirandamycylacetate [86] (prepared from tirandamycinic acid [28] and ethyl *N*-benzylglycinate [83]) was tried, only decomposition of the  $\beta$ -ketoester [86] was observed<sup>80</sup> (Scheme 32).



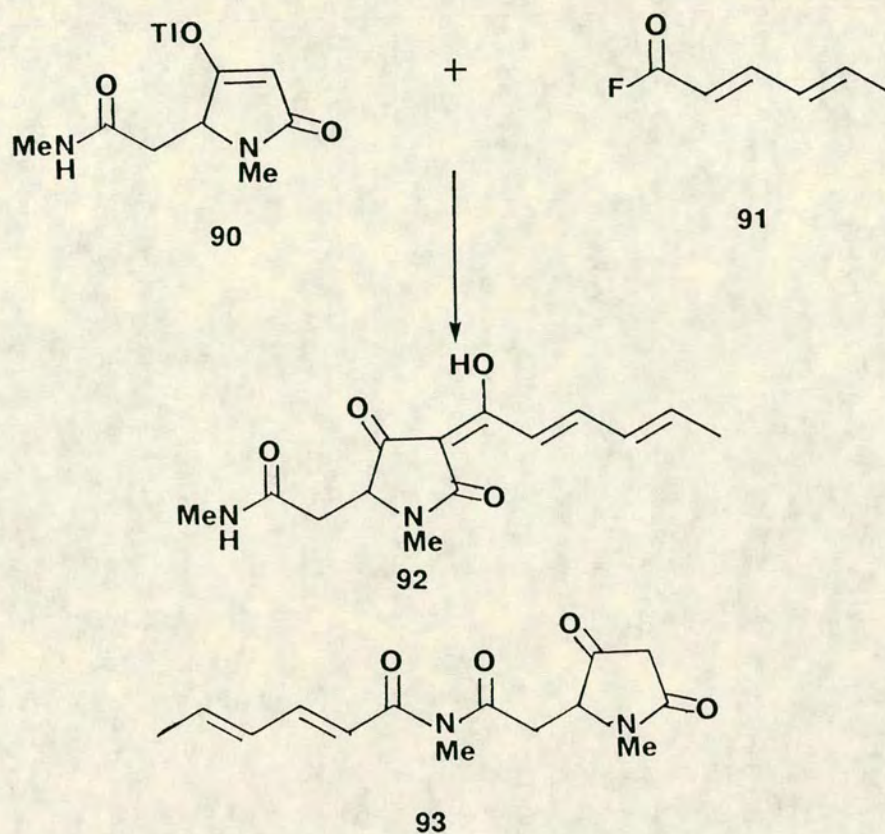
### SCHEME 32

The acylation of 3-unsubstituted pyrrolidine-2,4-diones was regarded as a promising alternative strategy in view of the requirement of an acyl substituent at C-3 (of the tetramic acid ring) in many of the biologically active natural systems. Kohl was the first to use this strategy, in the synthesis of magnesidin [18,19]<sup>31</sup>. The value of this strategy in the synthesis of models of the complex naturally occurring 3-polyenoyltetramic acids was investigated by Jones<sup>81</sup>. Initial results were not encouraging as the product was being lost in the basic work-up required for the Lewis-acid mediated acylation. This problem was overcome by isolating the 3-acyltetramic acid products as their boron trifluoride complexes [88]. These were obtained in 50 - 78% yields *via* acylation of the pyrrolidine-2,4-dione [87]. The 3-acyltetramic acids [89] were obtained by treatment of the complexes [83] with methanol<sup>82</sup> (Scheme 33).



**SCHEME 33**, reagents: (a)  $BF_3OEt_2$ ; (b) MeOH.

*C*-acylation of the thallium(I)enolate<sup>83</sup> of a pyrrolidine-2,4-dione using an acyl fluoride to give the 3-acyltetramic acid was investigated by Rinehart Jr.<sup>80</sup>. Thallium(I)enolate [90] when reacted with sorbyl fluoride [91] gave the *C*-acylation product [92], a model of streptolydigin [25], in only 4% yield. The major product [93] of the reaction arose from *N*-acylation of the C-5 side chain, with products from *O*-acylation also being detected (Scheme 34).

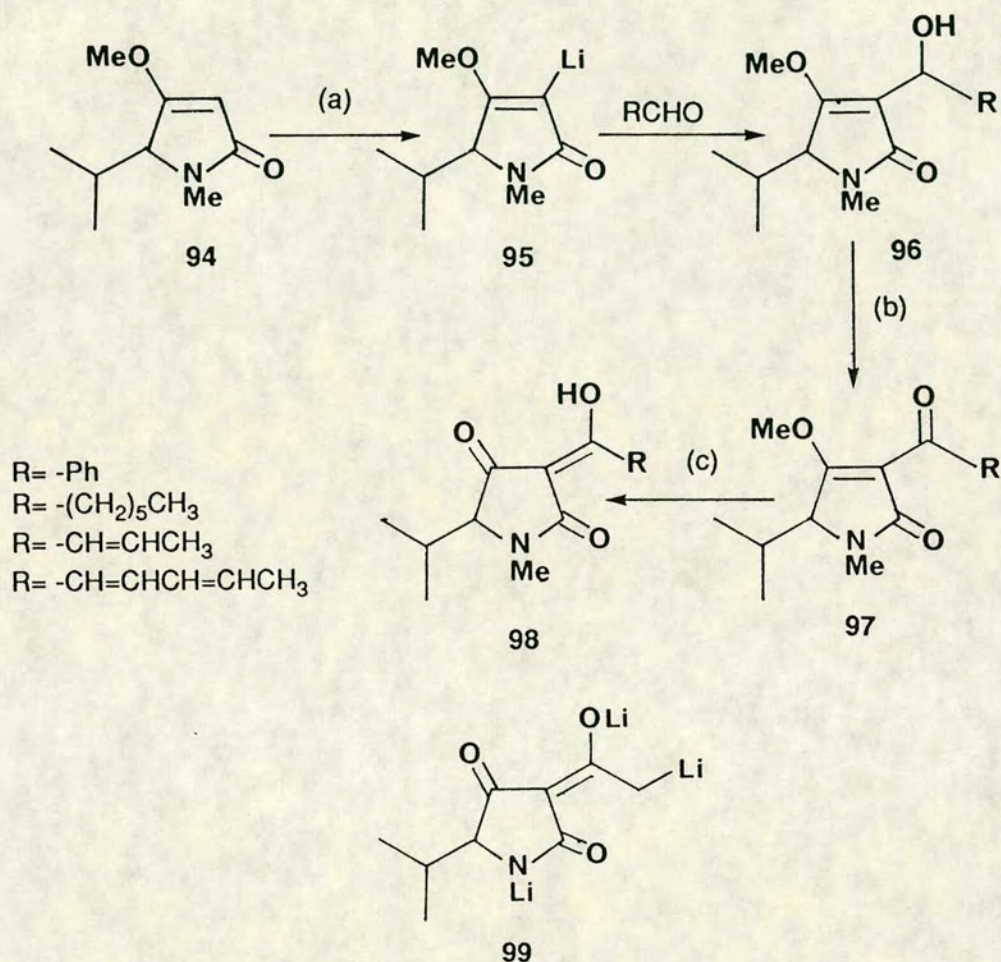


SCHEME 34

Acylation at C-3 of a pyrrolidine-2,4-dione clearly lacked the selectivity required for application to the synthesis of a naturally occurring 3-acyltetramic acid. Furthermore, as this strategy still relied on basic cyclisation of an *N*-acylaminoester for production of the tetramic ring, it would also not be possible to obtain 3-acyltetramic acids with a chiral centre at C-5.

An alternative method of acylation at C-3 (of a pyrrolidine-2,4-dione) has been described by Jones<sup>84</sup> and its applicability to the synthesis of complex 3-acyltetramic acids has been further investigated<sup>85,86,87</sup>. Directed metallation at C-3 of the 4-methoxypyrrol-2(5H)-one [94] gave the vinyl lithium derivative [95] which when reacted with a range of aldehydes gave the hydroxy adducts [96] in good yields<sup>84</sup>. Oxidation of the adducts [96] with manganese dioxide gave the corresponding keto derivatives [97] which on treatment with sodium hydroxide liberated the free 3-acyltetramic acids [98]. Extension of this methodology represented a method for the construction of

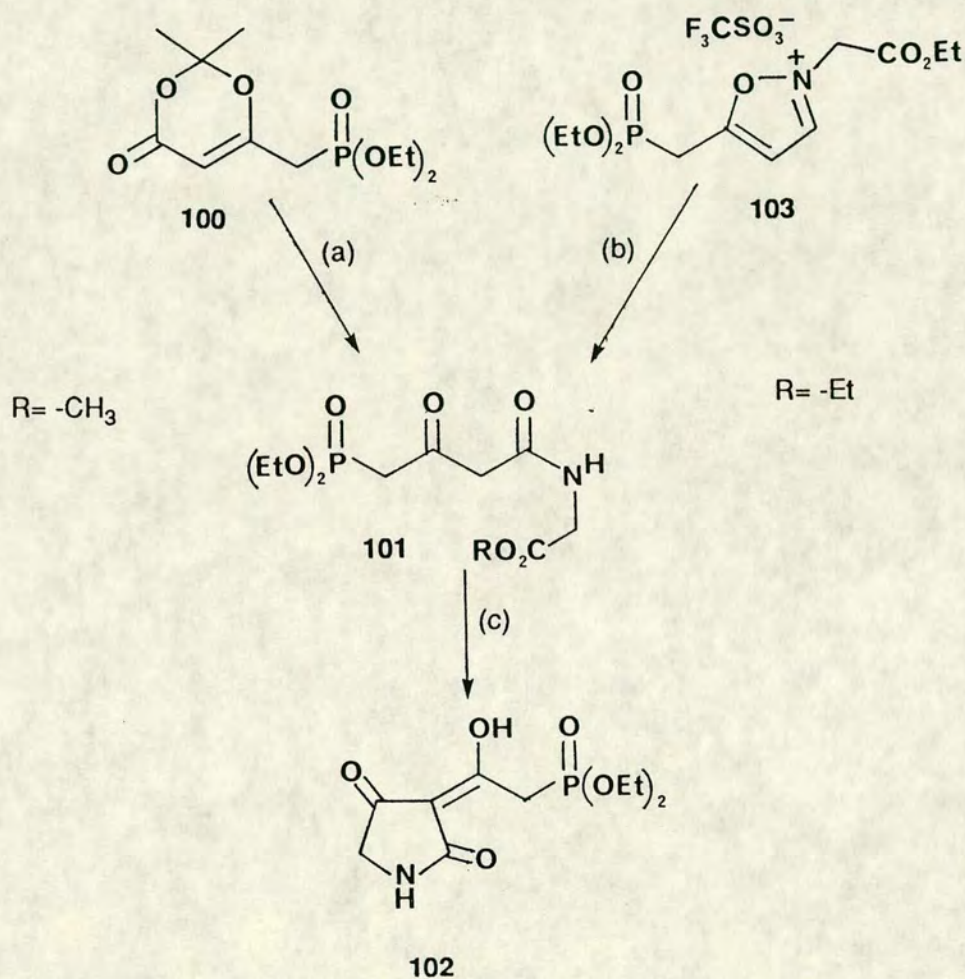
3-dienoyltetramic acids by nucleophilic reaction of organometallics of the type [99] carrying no activation at C-7 or protection at N-1<sup>86</sup> (Scheme 35).



**SCHEME 35**, reagents: (a) *n*-BuLi; (b) MnO<sub>2</sub>; (c) NaOH.

Boeckmann<sup>88</sup> reported the synthesis of a tetramic acid nucleus with the 3-acyl group suitably functionalised for further elaboration by means of a phosphonate-activated tetramic acid [102]. This was prepared by a modification of Lacey's method<sup>79</sup> for synthesising tetramic acids. Phosphonate [100] was reacted with methyl glycinate under mild acid catalysis to give the phosphonoacetylacetamide [101] which cyclised, on treatment with sodium methoxide, to give the 7-diethylphosphono-activated tetramic acid [102] (Scheme 36).

Some evidence was presented<sup>88</sup> that the stereochemical integrity of a chiral centre at C-5 could be preserved. Although, in view of the basic reaction conditions used to perform the cyclisation, this could not be considered to be a synthetically reliable route to optically active 3-acyltetramic acids.

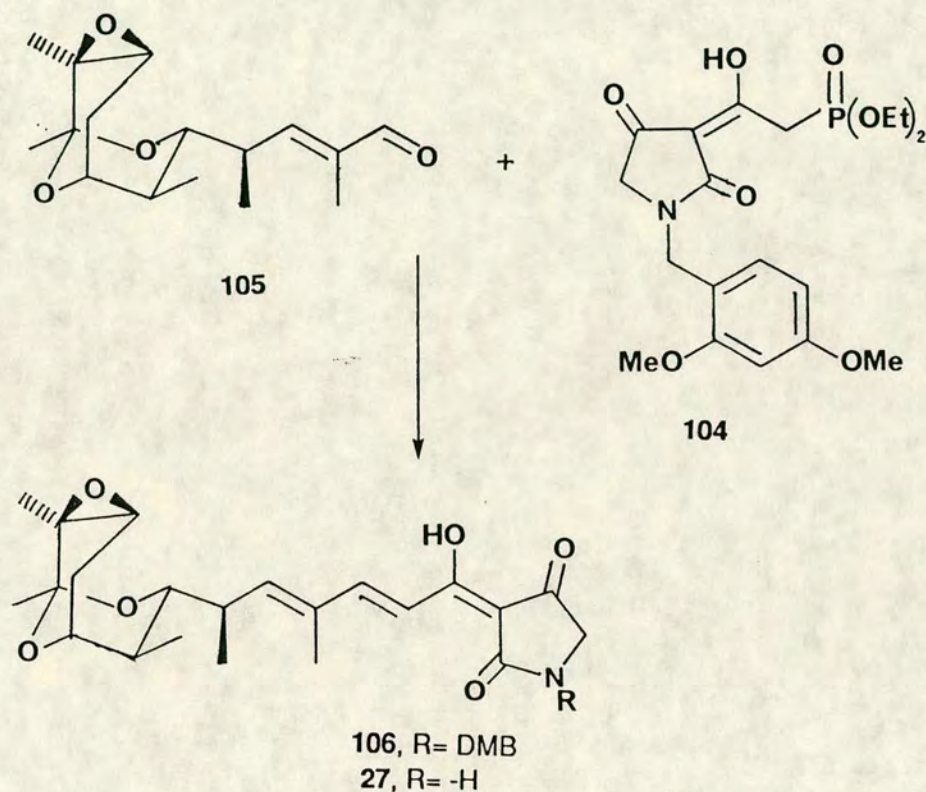


**SCHEME 36**, reagents: (a) NH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Me; (b) NaHCO<sub>3</sub>; (c) NaOMe.

Tetramic acid [102] has been prepared by an alternative route<sup>90,91</sup>. The isoxazolium salt [103] was treated with sodium bicarbonate to induce fragmentation into the previously obtained acetoacetamide [101]. Again, this afforded the activated tetramic acid on treatment with base (Scheme 36) and likewise the same drawbacks are also applicable to this strategy.

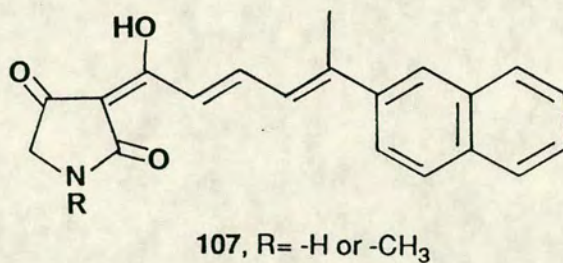
A modification of this technique was applied recently to the total synthesis of (-)-tirandamycin A [27]<sup>92</sup>. Reaction of the dianion of [104] (under milder conditions than previously possible) with

freshly prepared aldehyde [105] gave the Emmons adduct [106], which on treatment with trifluoroacetic acid gave (-)-tirandamycin A [27] (Scheme 37).



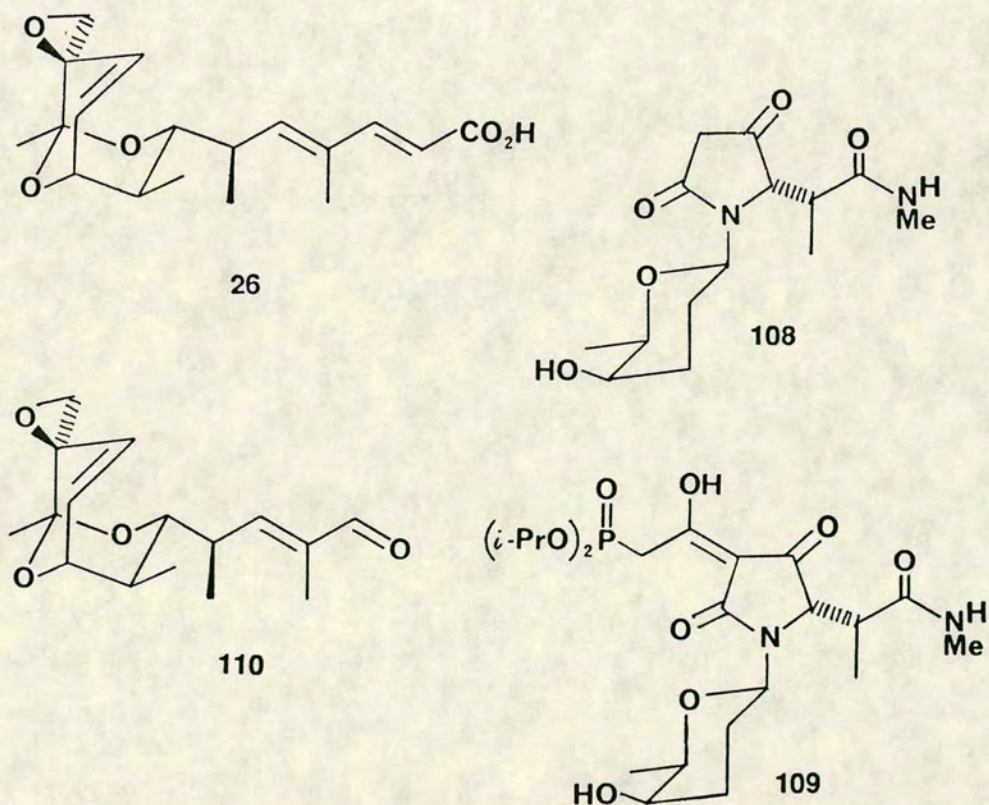
### SCHEME 37

The total synthesis of tirandamycin A in its racemic form has been achieved by Boeckmann<sup>93</sup>, Bartlett<sup>94(a)</sup> and Ireland<sup>94(b)</sup> and, although this no longer represents the state of the art, the methodology employed is of some interest. Rosen and his colleagues at Abbott Laboratories<sup>95</sup> used Schlessinger's<sup>92</sup> phosphonate-activated tetramic acid strategy to prepare a long series of 3-dienoyltetramic acids which were then evaluated according to their biological activity. The most potent agents in this series [107] had an unsubstituted naphthalene group attached to the terminus with a methyl group adjacent to the diene terminus (Scheme 38)<sup>95</sup>. The activities of these agents were quite sensitive to structural modification; those without a diene unit were devoid of biological activity.



SCHEME 38

Now that the total synthesis of (-)-tirandamycin A [27]<sup>92</sup> has been accomplished the synthetic horizon becomes the complex naturally occurring polyenoyltetramic acids which contain a chiral centre at C-5 of the tetramic acid nucleus. The research groups of Ireland<sup>96</sup> and Schlessinger<sup>97</sup> are independently pursuing the total synthesis of streptolydigin [25]. Ireland's group<sup>96</sup> are investigating a strategy based on the acylation of a tetramic acid [108] with streptolic acid [26] whilst the latter group<sup>97</sup> are studying the use of his phosphonate-activated methodology, utilising the intermediates [109] and [110]<sup>98</sup> (Scheme 39).

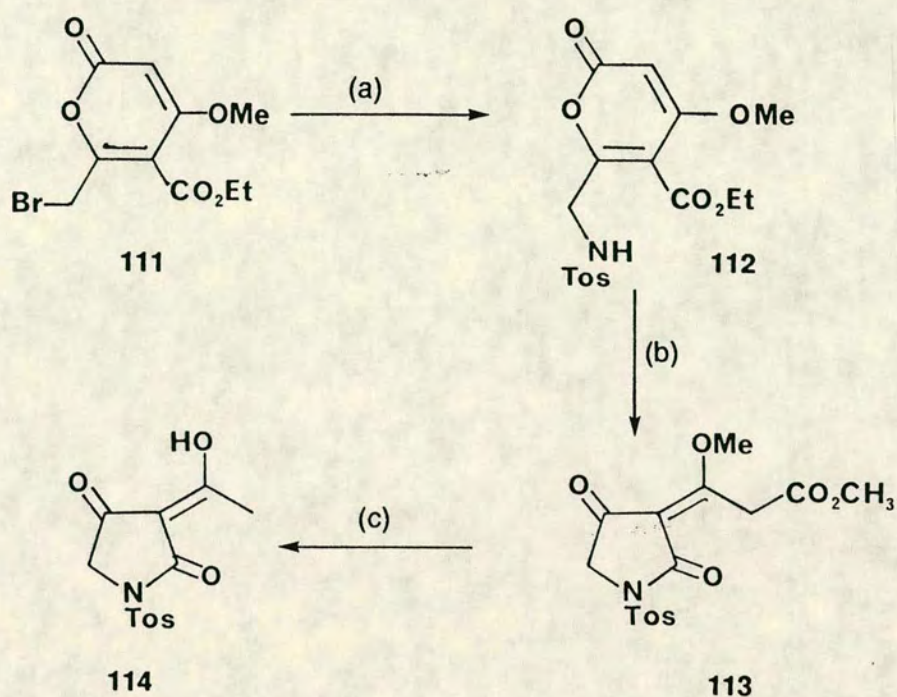


SCHEME 39



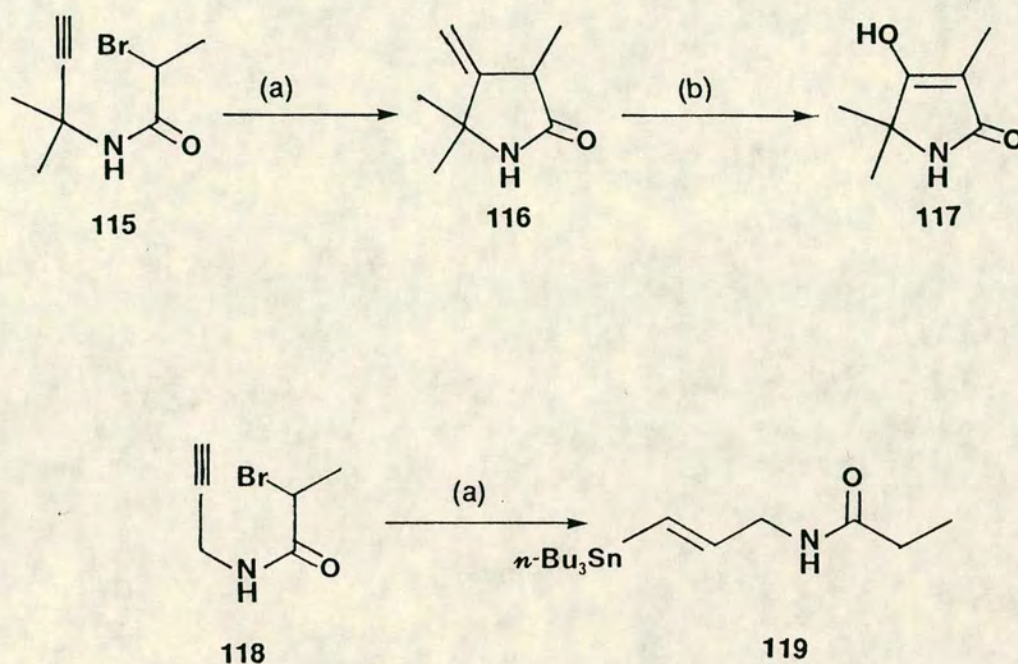
Enantioselective total syntheses of fuligorubin A [38]<sup>99</sup> and (+)-ikarugamycin [21]<sup>100,101</sup> have been published recently. The chiral tetramic acid ring, in each case, is formed by Dieckmann cyclisation<sup>77</sup> of chiral *N*-acetoacetyl- $\alpha$ -amino-esters using one<sup>101</sup> or two<sup>99,100</sup> equivalents of potassium *tert*-butoxide as the base. The reaction, when carried out at 0 °C over a short period of time, is said to take place without any detectable racemisation occurring. Some doubt is cast over these results as one paper<sup>101</sup> offers no evidence in support of this. Two of the articles<sup>99,100</sup> do quote optical rotations that are in excellent agreement with those of the authentic materials. However, a subsequent study - by Poncet<sup>102</sup> - of racemisation during the Dieckmann cyclisation, showed (by <sup>1</sup>H n.m.r. and chemical correlation techniques) that non-negligible C-5 epimerisation (10 - 30%) occurs even under carefully controlled reaction conditions. This suggests that the method cannot be regarded as a reliable means for synthesising chiral tetramic acids.

Last year Jones described<sup>103</sup> a novel route to 3-acyltetramic acids which involves the ring-opening of a pyrone system. Treatment of bromomethyl pyrone [111] with sodium *p*-toluenesulphonamide afforded sulphonamide [112] which, when reacted with sodium methoxide, led to the formation of the nitrogen heterocycle [113]. The 3-acyltetramic acid [114] was easily obtained by alkaline hydrolysis of [113] (Scheme 40). Elaboration of the pyrone [111] at C-3 or C-7 would allow more complex tetramic acids (with substituents at C-5 or C-7) to be made using this strategy.



**SCHEME 40**, reagents: (a) NaNHTos; (b) NaOMe; (c) NaOH(aq).

The latest method to appear in the literature<sup>104</sup> for synthesising tetramic acids employs a 5-*exo*-dig radical cyclisation to form the heterocyclic ring. Exposure of a solution of the bromoamide [115] to tri-*n*-butyltin hydride in the presence of azo-*bis*-(isobutyronitrile) produced the crystalline lactam [116]. This was treated with ozone, using a triphenylphosphine work-up, to obtain the corresponding tetramic acid [117] (Scheme 41). Attempted cyclisation of a bromoamide [118] lacking substitution at the propargylic methylene yielded (under analogous conditions) only the vinylstannane [119], revealing the approach to be somewhat limited in scope.



**SCHEME 41**, reagents: (a)  $n$ -Bu<sub>3</sub>SnH, AIBN; (b) ozone, MeOH, PPh<sub>3</sub>.

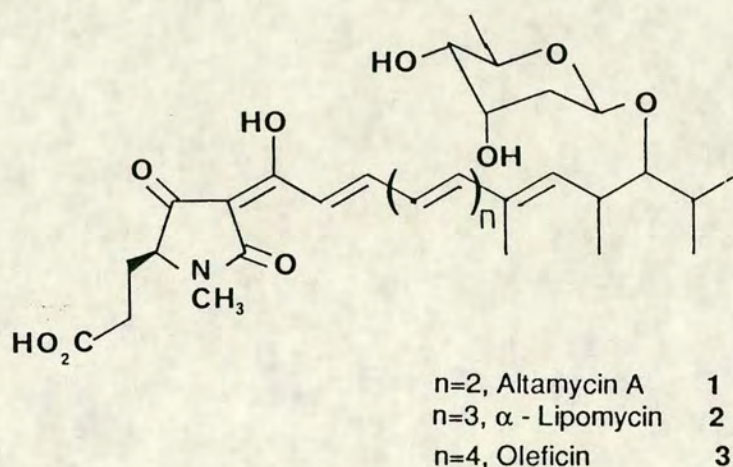
Although promising methodology is available in the literature the problem of controlling the stereochemical integrity of the C-5 asymmetric centre of a tetramic acid has yet to be overcome satisfactorily. Consequently, the total synthesis of the complex chiral 3-polyenoyltetramic acids is still far from being a trivial exercise.

#### 1.4 SYNTHESIS OF POLYENES

As one would expect from the vast array of naturally occurring biologically active compounds that contain a polyene unit, there has been an enormous amount of work carried out concerning the chemical synthesis of such systems. The literature in this field has been reviewed recently<sup>19,105</sup> in depth and, as the methodology involved can be regarded mainly as a standard part of the organic chemist's range of techniques, a review of this area of organic chemistry will not be included herein.

## 2. DISCUSSION

The general aim of this research project is to achieve the total synthesis of the naturally occurring 3-polyenoyltetramic acid antibiotic altamycin A [1] and its stereoisomers as single enantiomers. The primary aim was, in view of the unfeasibility of X-ray crystallography, to firmly establish the absolute stereochemistry of the natural product. Secondly, it was intended that the synthetic route be of sufficient latitude to encompass the total syntheses of other related tetramic acids, namely  $\alpha$ -lipomycin [2] and oleficin [3] (Scheme 42).

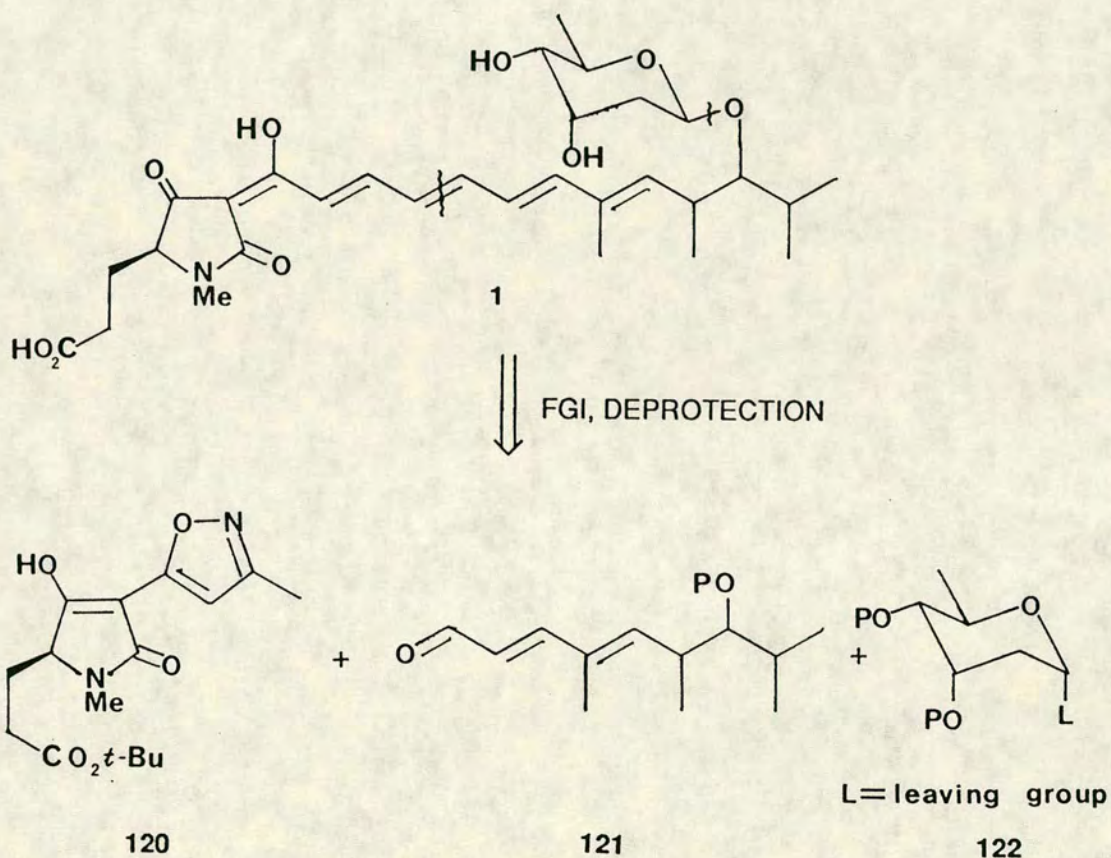


**SCHEME 42**

Once the aforementioned objectives have been reached, studies on structure-activity relationships will be facilitated, subsequently allowing a complete rationalisation of the structure and biological function of these intriguing compounds to be presented.

The major synthetic hurdles are; the formation of a tetramic acid in an enantiomerically pure form, the construction of an all-*trans* polyene unit possessing two asymmetric centres with a 1,2 relationship and the coupling of these to form the desired carbon skeleton. The sugar fragment, *D*-digitoxose, is commercially available and has been synthesised<sup>106</sup> previously so, consequently, the only problem is the selective formation of the glycosyl linkage in the  $\beta$ -anomeric form.

Careful consideration of the implications of the stereochemical features of altamycin A [1] resulted in a convergent approach to its total synthesis being envisaged from the retrosynthetic analysis shown (Scheme 43). This provided two target fragments for the synthesis of the aglycone of altamycin A [1]. The approaches to each of these intermediates and the investigation into the coupling of them will now be discussed.

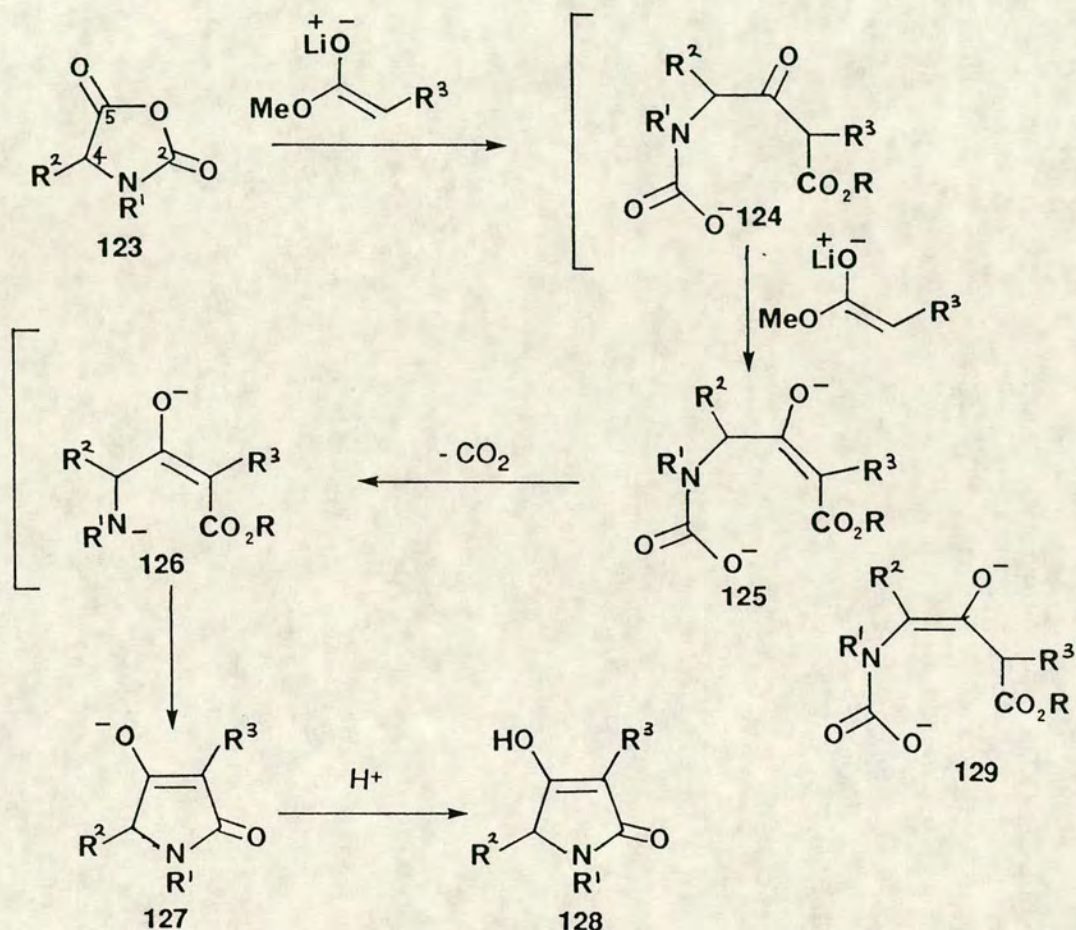


SCHEME 43

## 2.1 THE TETRAMIC ACID FRAGMENT

Earlier work by Mitchell<sup>17</sup> and Jenkins<sup>18</sup> led to the development of a novel route to chiral tetramic acids which represents a significant breakthrough in the synthesis of complex naturally occurring tetramic acids. The tetramic acid is formed by the reaction of an oxazolidine-2,5-dione (an  $\alpha$ -

amino-acid-*N*-carboxyanhydride) with the enolate anion of an ester *via* the mechanism outlined in Scheme 44.

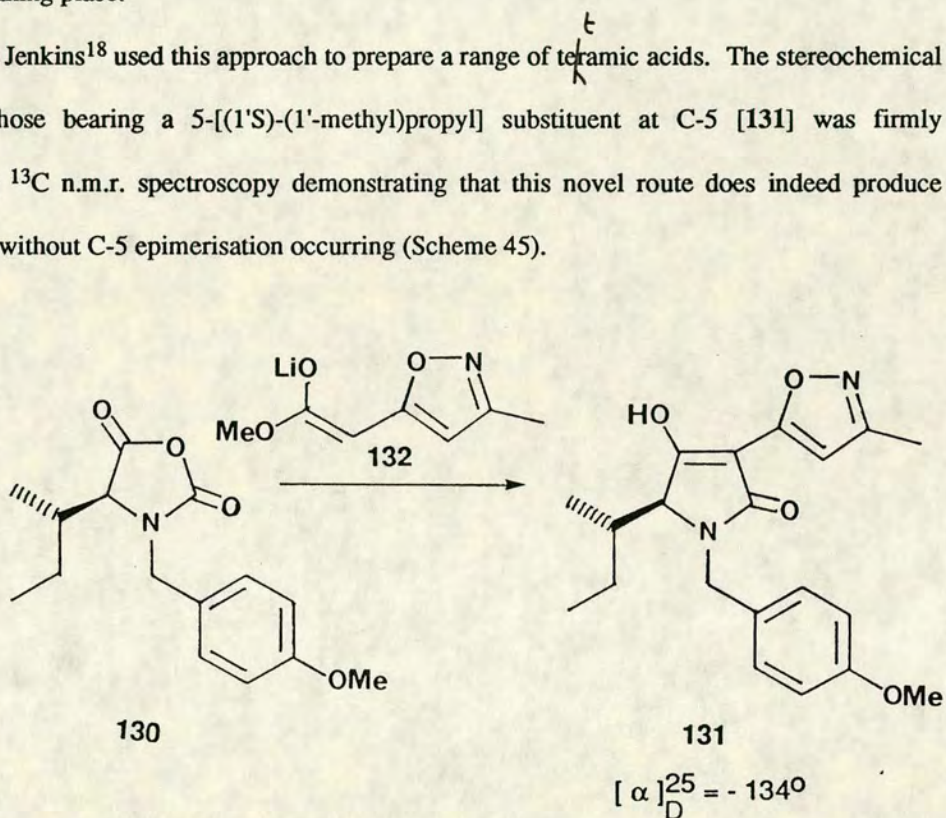


SCHEME 44

The mechanistic scheme makes it clear that two equivalents of the enolate are required. The first performs a nucleophilic attack at C-5 of the oxazolidinone-2,5-dione [**123**] to give the  $\beta$ -ketoester adduct [**124**]. The second equivalent of enolate selectively deprotonates [**124**] at the 2-position resulting in the formation of dianion [**125**]. This enolate is stabilised by conjugation with the two functional groups CO<sub>2</sub>R and R<sup>3</sup>. In contrast to the problematic Dieckmann cyclisation of intermediates of the type [**74**] (Scheme 30), this conjugation with two functional groups results in sufficient stabilisation of [**125**] that deprotonation at the 4-position does not occur. This is explained

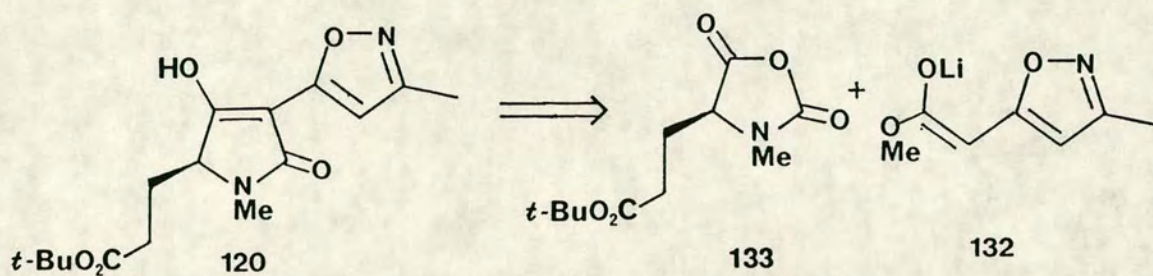
by the fact that deprotonation at the 4-position results in an enolate [129] which is not conjugated to any functional groups and therefore is significantly less stable than [125]. Loss of carbon dioxide to [126] and cyclisation to [127] then led to isolation of the tetramic acid [128] on acidification during work-up. As no deprotonation occurs at the 4-position, if an oxazolidine-2,5-dione which is chiral at C-4 is used, then the chirality will be transferred through to the tetramic acid without any racemisation taking place.

Mitchell<sup>17</sup> and Jenkins<sup>18</sup> used this approach to prepare a range of tetramic acids. The stereochemical integrity of those bearing a 5-[(1'S)-(1'-methyl)propyl] substituent at C-5 [131] was firmly established by <sup>13</sup>C n.m.r. spectroscopy demonstrating that this novel route does indeed produce tetramic acids without C-5 epimerisation occurring (Scheme 45).



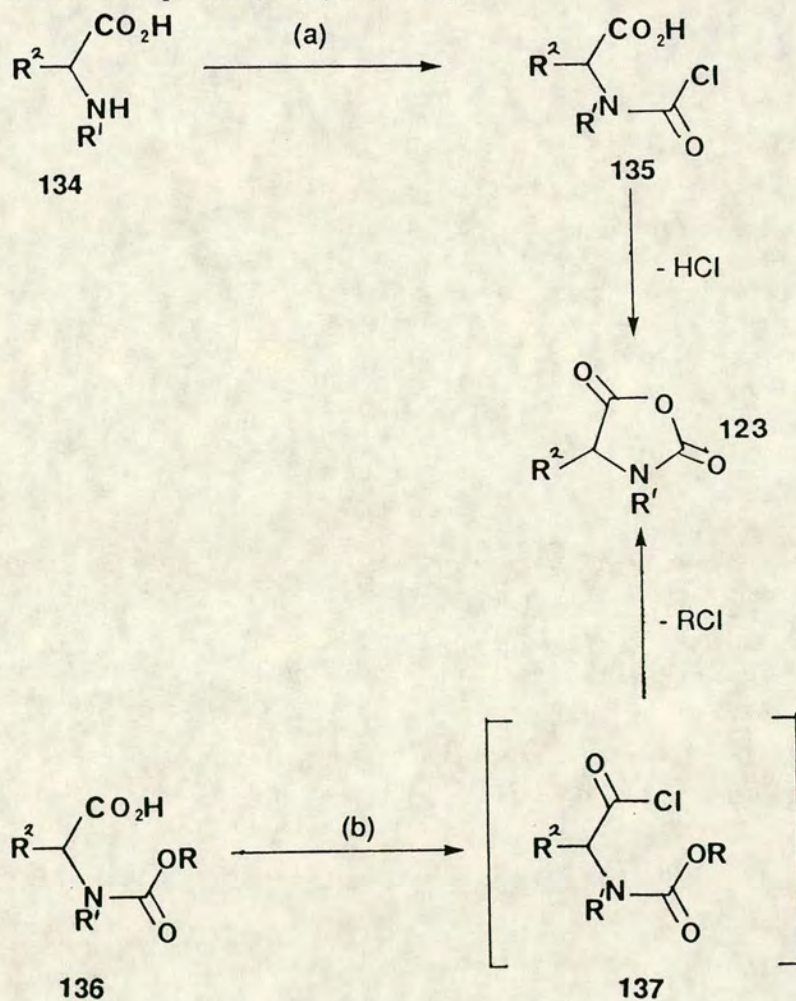
**SCHEME 45**

Application of this methodology to a retrosynthetic analysis of the tetramic acid fragment [120], required for the synthesis of altamycin A, makes it clear that the desired intermediate [120] will be formed by the reaction of oxazolidine-2,5-dione ( $\alpha$ -amino-acid-*N*-carboxyanhydride, NCA) [133] with the lithium enolate of methyl 3-methyl-5-isoxazoleacetate [132] (Scheme 46).



SCHEME 46

The chemistry, including methods of preparation, of  $\alpha$ -amino-acid-*N*-carboxyanhydrides has been reviewed by Hirschmann<sup>107</sup> showing that there are two main routes to this heterocyclic system. The Fuchs-Farthing method<sup>108,109</sup> involves the reaction of an  $\alpha$ -amino-acid [134] with phosgene at 30 - 60 °C in an inert solvent to produce the intermediate [135] which readily loses hydrochloric acid giving the NCA [123]. Leuchs<sup>110</sup> described the alternative method involving the chlorination of an *N*-alkoxycarbonylamino-acid [136] which occurs with concomitant elimination of the alkyl halide during cyclisation to the desired product [123] (Scheme 47).

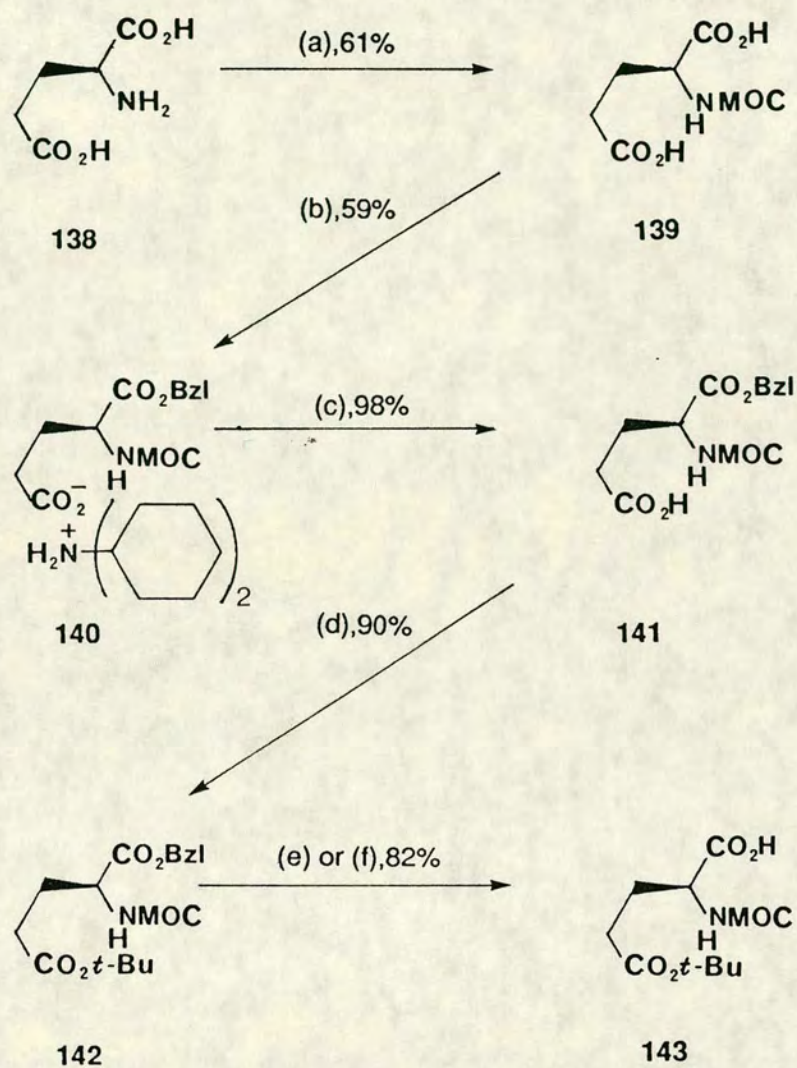


SCHEME 47, reagents: (a) phosgene; (b) thionyl chloride.



The Leuchs method was considered to be the more expedient of the two routes, especially if the *N*-methoxycarbonyl group is used, as the methyl chloride by-product of the cyclisation is very easily removed as well as being non-acidic. Jenkins<sup>18</sup> had found that *N*-benzyloxycarbonyl urethanes gave very impure NCA derivatives, due to the presence of benzyl chloride, compared with the methoxy analogues.

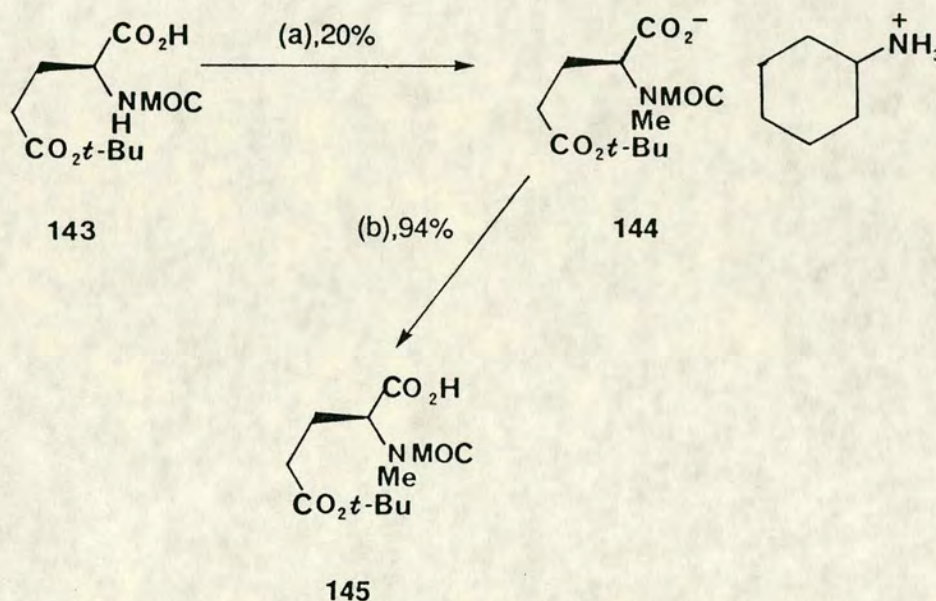
*L*-Glutamic acid [138] was acylated using methyl chloroformate (MOC-Cl), in aqueous solution at pH 10.0, giving the urethane [139] as a white solid after trituration in petrol. The  $\alpha$ -carboxylic acid group was then selectively esterified on treatment with one equivalent each of benzyl bromide and triethylamine in dry dimethylformamide. The benzyl ester [141] was purified by *in situ* formation of the  $\gamma$ -dicyclohexylamine (DCHA) salt [140] followed by liberation of the free-acid with aqueous citric acid. Protection of the  $\gamma$ -carboxylic acid function as the *tert*-butyl ester was achieved by reaction of [141] with isobutene (using acid catalysis) in a sealed tube at room temperature over ten days. The di-ester [142] was obtained, as a pale yellow syrup which could not be crystallised, in 90% yield. The benzyl ester group could be cleaved in two ways to give the *tert*-butyl mono-ester [143]. The first, and generally used procedure, was by alkaline hydrolysis with sodium hydroxide which afforded [143] as a white solid in 87% yield. The second procedure used was hydrogenolysis of the benzyl group in 10% aqueous methanol over a 10% palladium on charcoal catalyst. This gave [143] as before, albeit in slightly poorer yield (75%, Scheme 48).



**SCHEME 48**, reagents: (a) MOC-Cl, NaOH(aq); (b) (i) Bzl-Br, Et<sub>3</sub>N, (ii) DCHA; (c) citric acid, H<sub>2</sub>O; (d) isobutylene, conc. H<sub>2</sub>SO<sub>4</sub>; (e) 1.0 equivalent NaOH; (f) hydrogen, Pd-C.

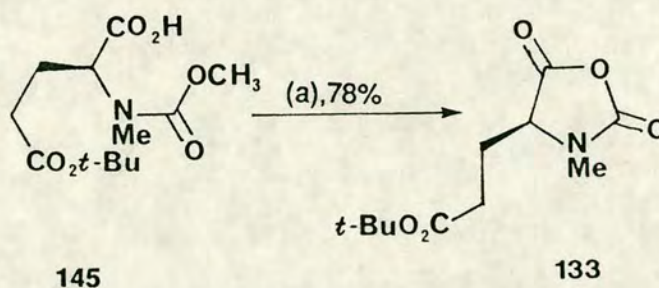
Benoiton's procedure<sup>111</sup> for the racemisation free *N*-methylation of *N*-alkoxycarbonyl amino-acids caused two problems when urethane [143] was treated with sodium hydride in the presence of methyl iodide. The product [145] was very impure and it was isolated in poor yield (35%). Recrystallisation of the crude [145] proved difficult so a more effective means of purification was sought. Instead of isolating the alkylated material, the crude product was stirred in 50% ether-petrol with one equivalent (based on the starting material [143]) of cyclohexylamine which afforded the salt [144] as a white solid that was easily purified by recrystallisation from ethyl acetate-petrol.

Proton n.m.r. showed splitting of the methoxy and *N*-methyl signals due to the presence of *cis* and *trans* isomers of the urethane function. These result from hindered rotation about the amide C-N bond caused by its partial double bond character. Treatment of the salt [144] with aqueous citric acid gave the free-acid [145] as a white solid in a yield of 94% (Scheme 49). The *N*-methyl amino-acid [145] had an optical rotation of  $-24.2^\circ$  and n.m.r. spectroscopy again indicated that the compound existed as a mixture of *cis* and *trans* isomers.



**SCHEME 49**, reagents: (a) (i) MeI, NaH, (ii) CHA; (b) citric acid,  $\text{H}_2\text{O}$ .

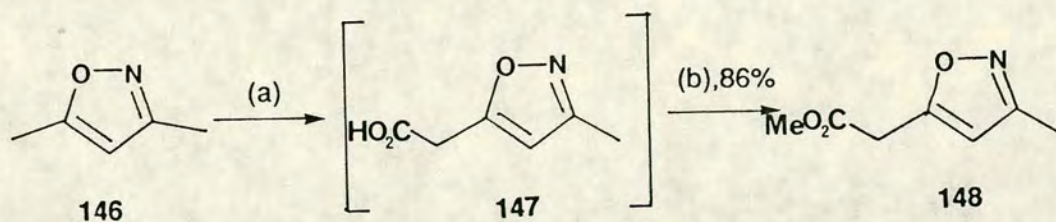
The *N*-methylurethane [145] was treated with freshly distilled thionyl chloride at  $0^\circ\text{C}$  for five minutes, the excess thionyl chloride was then removed *in vacuo*. The residue was warmed to  $55^\circ\text{C}$  (to bring about the cyclisation) whilst the pressure was maintained at *circa* 5 torr to ensure the complete removal of the by-products. Once cool, the flask was brought to atmospheric pressure and the residue triturated with petrol to give (S)-4-[2'-(*tert*-butyloxycarbonyl)ethyl]-3-methyloxazolidine-2,5-dione [133] as white crystals m.p.  $81 - 82^\circ\text{C}$  (Scheme 50).



**SCHEME 50**, reagents: (a) thionyl chloride.

The i.r. spectrum of NCA [133] showed three carbonyl stretching bands at 1850, 1785 and 1725  $\text{cm}^{-1}$  indicating that a cyclic anhydride group was present. As anhydrides of this type are sensitive to moisture as well as heat care was taken to ensure the compound never became exposed to such harmful conditions.

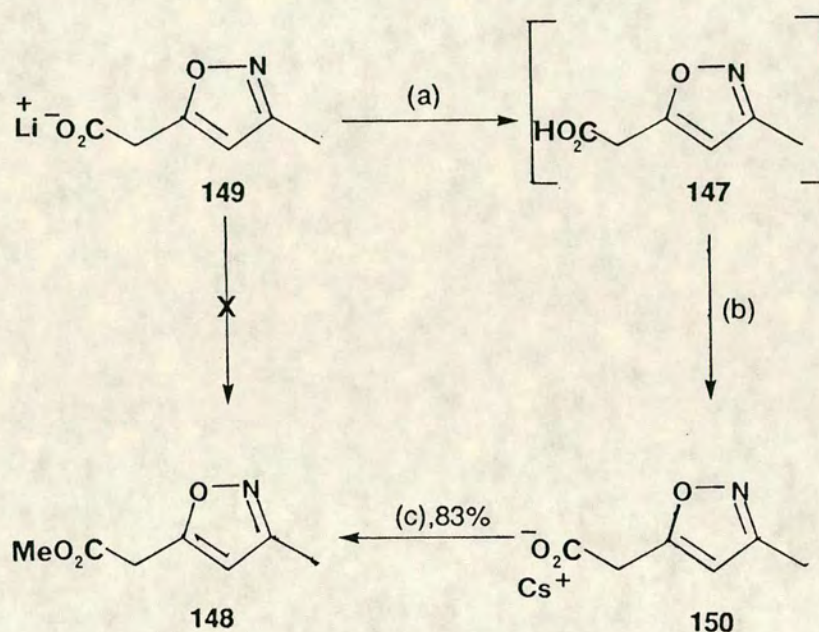
As mentioned earlier, the 3-isoxazolytetramic acids have been found<sup>18</sup> to be excellent precursors for 3-acyltetramic acids because they are readily converted, in a one-pot hydrogenation and hydrolysis sequence, to the 3-acetoacyltetramic acids. The required ester, needed for reaction with the NCA [133], was prepared from the readily available 3,5-dimethylisoxazole [146] using Micetich's method<sup>112</sup>. Deprotonation of the 5-methyl group with *n*-butyllithium followed by reaction of the anion with dry carbon dioxide gave, on acidic work-up, the carboxylic acid [147]. Esterification of this acid using ethereal diazomethane produced the desired acetate ester [148] in good yield (Scheme 51).



**SCHEME 51**, reagents: (a) (i) *n*-BuLi, CO<sub>2</sub>, (ii) H<sub>3</sub>O<sup>+</sup>; (b) diazomethane.

The use of diazomethane in the esterification step was found to be inconvenient as only small quantities could be prepared at any one time so, as a fairly substantial quantity of the ester [133] was required, an alternative methylation strategy was necessary. Initial attempts at methylation of the lithium salt [147] with methyl iodide in dry dimethylformamide and anhydrous HCl-methanol were

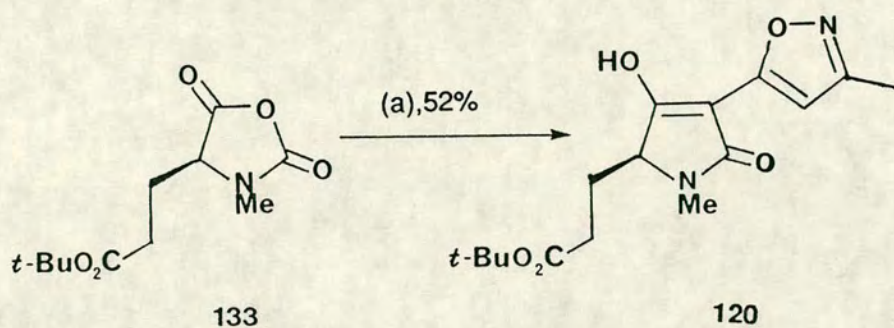
unsuccessful. This was attributed to the fact that the small lithium cation was too tightly bound to the carboxylate anion. The problem was circumvented by utilisation of Wang's<sup>113</sup> esterification procedure, where the caesium salt of a carboxylic acid is reacted with an alkyl halide to form the ester. The caesium salt [150] was prepared by titrating an aqueous solution of the acid [147] to pH 7.0 with 20% aqueous caesium carbonate then lyophilising the neutral solution. The methyl ester [148] was obtained by stirring the salt [150] with methyl iodide in dimethylformamide (Scheme 52).



SCHEME 52, reagents: (a) H<sub>3</sub>O<sup>+</sup>; (b) 20% CsCO<sub>3</sub>(aq); (c) MeI.

Reaction of the oxazolidine-2,5-dione [133] with two equivalents of the lithium enolate of methyl 3-methylisoxazole-5-acetate [132] for four hours gave (5*S*)-5-[2'-(*tert*-butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-methylisoxazolyl)]tetramic acid [120] on acidification (pH 1.0) of an aqueous solution of the reaction products (Scheme 53). The tetramic acid [120], obtained as a white

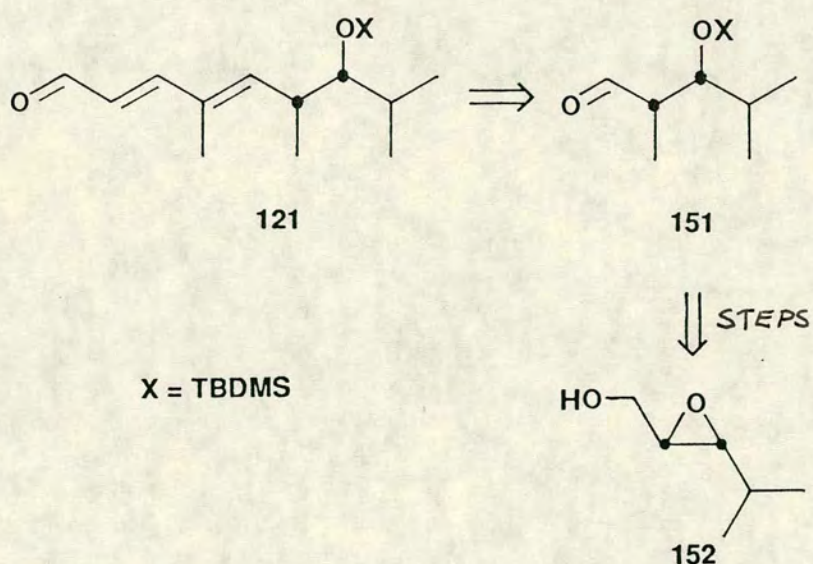
crystalline solid, had an optical rotation of  $-69.4^\circ$  and m.p.  $153 - 154^\circ\text{C}$ .



**SCHEME 53**, reagents: (a) (i) 2.0 equivalents [132], TMEDA, (ii)  $\text{H}_3\text{O}^+$ .

## 2.2 PREPARATION OF THE NONADIENAL UNIT

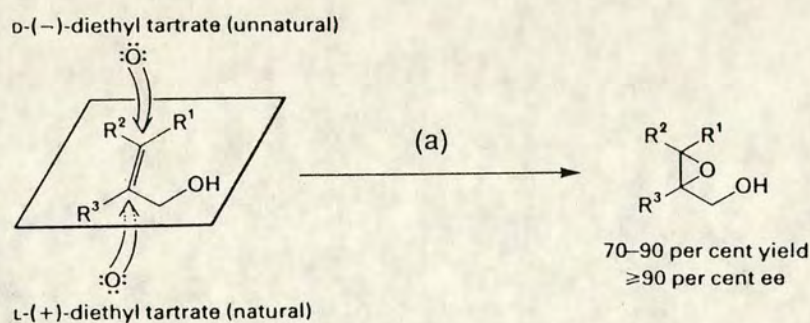
Retrosynthetic analysis of altamycin A [1] showed the nine carbon  $\alpha,\beta$ -unsaturated aldehyde derivative [121] to be the best intermediate building-block for the right hand side of the molecule. Analysis of the polyenal [121] makes it clear that an aldehyde [151] forms a key synthon for [121]. The Sharpless<sup>114</sup> epoxidation could then be used to prepare an enantiomerically pure epoxide of the type [152], the cuprate ring-opening of which would lead to the requisite aldehyde [151] (Scheme 54).



**SCHEME 54**

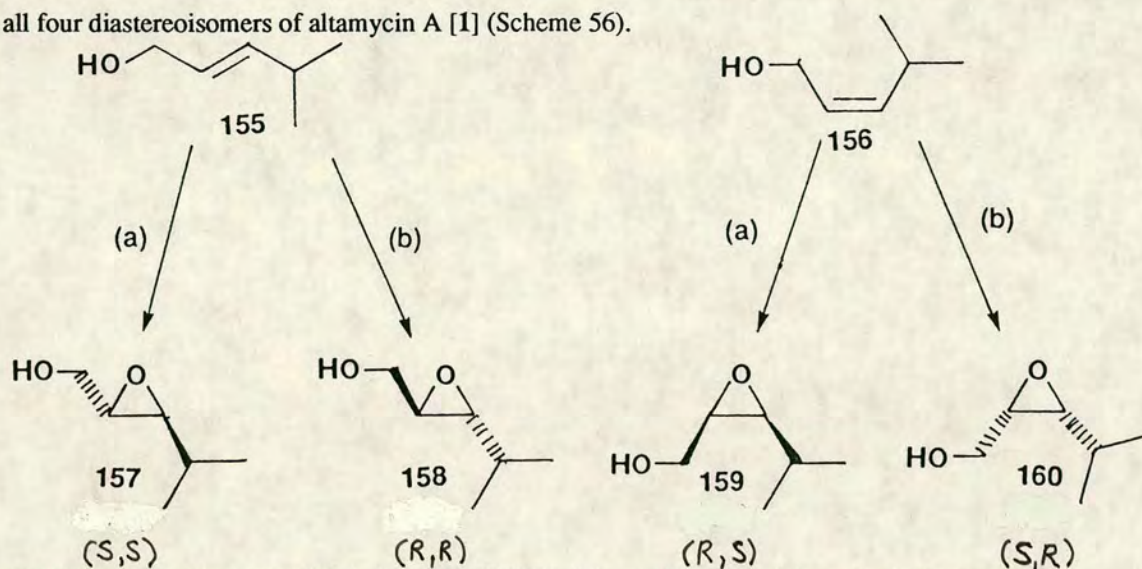
Lewis<sup>19</sup> and Jenkins<sup>18</sup> had pioneered the synthesis of nonadienal [121] and their synthetic route was used, with only minor modifications, in this work.

Titanium tartrate mediated asymmetric epoxidation of allylic alcohols, first reported by Sharpless<sup>114</sup> in 1980, has been widely recognised as being a tremendously useful way of introducing (with high enantioselectivity) chirality into achiral substrates. The mechanism of this reaction<sup>115,116</sup> has been given some considerable attention and the structural as well as stereoelectronic characteristics<sup>117</sup> have also been studied. The interest in asymmetric epoxidation in this research, however, was from a purely synthetic perspective and this has been covered by the publication of review articles<sup>118,119</sup>. The absolute-stereochemistry of the epoxy alcohol obtained from a given tartrate ester is illustrated in Scheme 55 and has been shown to be reliable for a wide range of substituted allylic alcohols<sup>114,115</sup>.



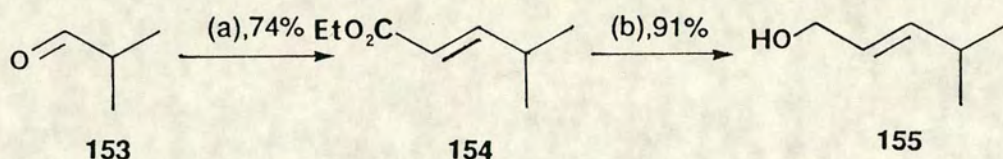
**SCHEME 55**, reagents: (a) tartrate,  $\text{Ti}(\text{O}i\text{-Pr})_4$ , *t*-BuOOH.

The above scheme allows one to predict which product will be obtained from either the *cis*- or *trans*- allylic alcohols. Thus we can prepare all four possible diastereoisomeric epoxides and hence all four diastereoisomers of altamycin A [1] (Scheme 56).



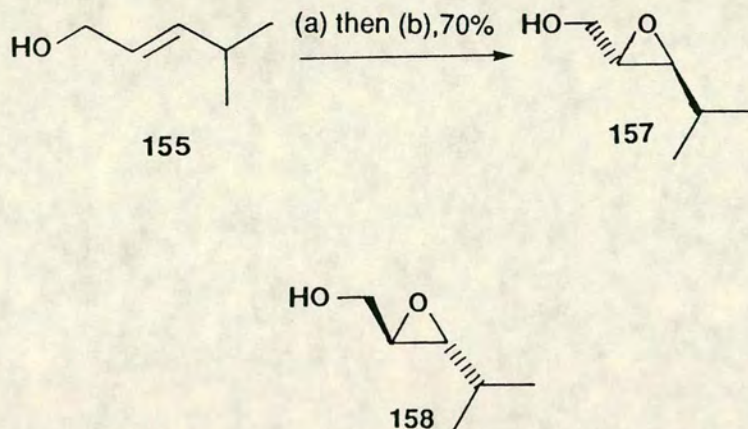
**SCHEME 56**, reagents: (a) *L*-(+)-DET,  $\text{Ti}(\text{O}i\text{-Pr})_4$ , *t*-BuOOH; (b) as for (a) except *D*-(-)-DET.

The allylic alcohol [155] required for the Sharpless epoxidation was prepared by Wittig condensation of the stabilised ylide carboethoxymethylidinetriphenylphosphorane and isobutyraldehyde [153] to give the  $\alpha,\beta$ -unsaturated ester [154]. The *trans* relationship of the two vinylic protons was confirmed by the 15.7 Hz coupling constant observed for the signals at  $\delta$  5.74 and 6.92 p.p.m. in the proton n.m.r. spectrum. Reduction of this ester with three molar equivalents of diisobutylaluminium hydride (DIBAL) gave the isomerically pure *trans*-allylic alcohol [155] as a clear, colourless liquid in 91% yield (Scheme 57).



**SCHEME 57**, reagents: (a)  $\text{EtO}_2\text{CCH}=\text{PPh}_3$ ; (b) DIBAL,  $-78^\circ\text{C}$ .

Asymmetric epoxidation of [155] was achieved in 70% yield via the catalytic procedure described by Sharpless<sup>120</sup> (Scheme 58) using his modified<sup>115(a)</sup> dimethylsulphide work-up. The catalytic method uses only 10 mol % titanium tetraisopropoxide and 13% mol % *L*-(+)-diethyl tartrate so purification of the epoxy alcohol [157] is much easier than in the stoichiometric procedure.

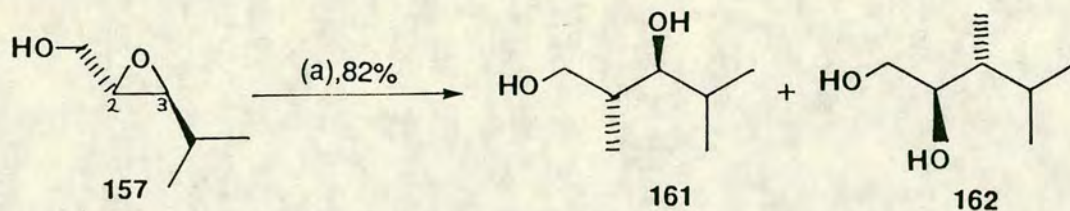


**SCHEME 58**, reagents: (a) *L*-(+)-DET,  $\text{Ti}(\text{O}i\text{-Pr})_4$ , *t*-BuOOH, 4A sieves; (b) DMS, NaF.



The optical rotation of [157] was  $-34.8^\circ$  ( $c = 1.02$  in chloroform) which concurred with the results of Lewis<sup>19</sup>, who carried out a detailed study of the optical purity of the product from the catalytic reaction. Lewis found<sup>19</sup> that none of the other enantiomer [158] (Scheme 58) could be detected on exposure of a solution of [157] to a europium(III) chiral shift reagent; *id est* no signals due to [158] were observed in the proton n.m.r. spectrum. Sharpless had noted<sup>120</sup> that the enantioselectivity was more variable in the catalytic reaction as even small amounts of moisture could interfere with the catalyst, so recommended the use of finely powdered 4A molecular sieves to ensure completely anhydrous conditions. Indeed, by following his recommendations and thoroughly drying all glassware prior to use, the catalytic method was found to yield products whose optical purity was equal to that of epoxy alcohols prepared by the stoichiometric method.

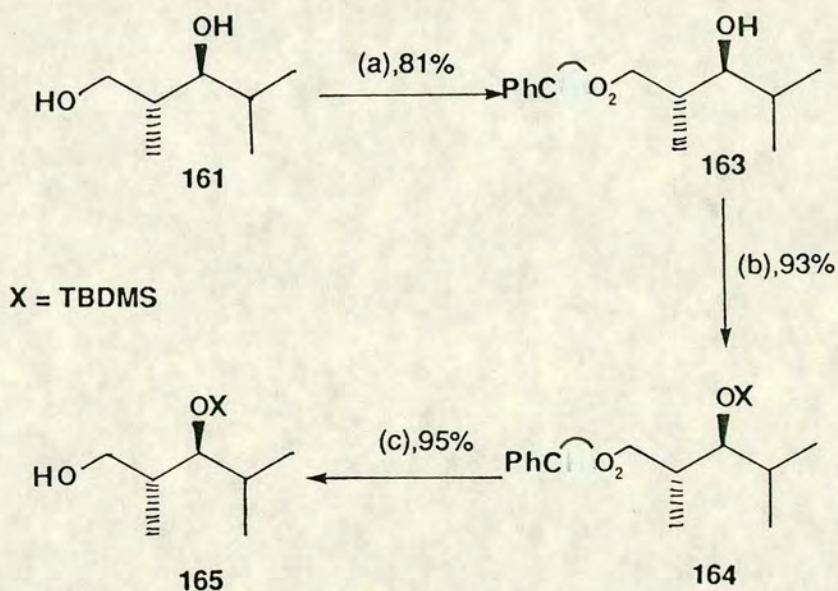
Kishi<sup>121</sup> had demonstrated the high regio- and stereoselectivity of chiral epoxide ring-opening reactions using organocuprates. Lewis<sup>19</sup> and Jenkins<sup>18</sup> found that the highest regioselectivity was obtained when the hydroxyl function of the epoxy alcohol was left unprotected. A reaction temperature of  $-40^\circ\text{C}$  gave a regioselectivity of 8:1 in favour of the desired regioisomer, which was obtained in good yield. They could achieve higher yields by varying reaction temperature but this resulted in poorer regioselectivity. Thus, epoxy alcohol [157] was treated with 7.5 equivalents of lithium dimethylcuprate at  $-40^\circ\text{C}$  in anhydrous ether for eighteen hours which gave, after purification by flash column chromatography (to remove small amounts of the regioisomer [162] caused by attack at C-3 of the epoxy alcohol [157]), the desired 1,3-diol [161] as a cream low-melting waxy solid (yield 82%, Scheme 59).



**SCHEME 59**, reagents: (a)  $\text{Me}_2\text{CuLi}$ ,  $-40^\circ\text{C}$ .

The enantiomer of [161] had been prepared by Baker and co-workers<sup>122</sup>, as an intermediate in the synthesis of avermectins, who reported its optical rotation to be  $+16.5^\circ$  ( $c = 1.1$  in dichloromethane). It was found that the 1,3-diol [161] gave an optical rotation of  $-20.8^\circ$  ( $c = 1.4$  in chloroform) indicating that the required 2R,3S stereochemistry was present.

Protection of the secondary hydroxyl function, thus allowing the C-3 hydroxyl group to be oxidised selectively, could not be performed directly on diol [161] so a circuitous route was employed. The primary hydroxyl group of [161] was esterified with benzoyl chloride in dry pyridine producing benzoate [163]. Silylation of the hindered secondary hydroxyl group needed fairly strong reaction conditions (*tert*-butyldimethylsilyl chloride, imidazole and 4-dimethylaminopyridine at 50 °C) and a reaction time of five days before the orthogonally protected diol [164] could be obtained in a satisfactory yield (93%). Methanolysis of the benzoate ester with Claisen's alkali afforded the monoprotected diol [165] in 95% yield (Scheme 60).

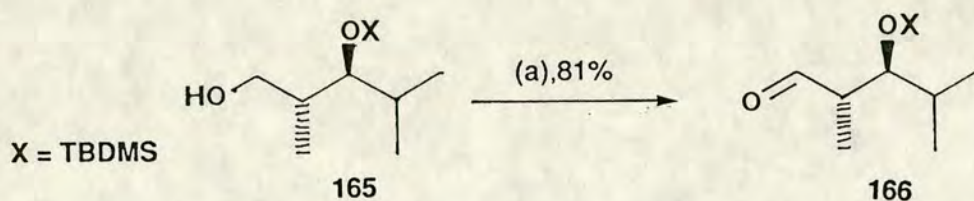


**SCHEME 60**, reagents: (a) PhCO-Cl, pyridine; (b) TBDMS-Cl, imidazole, DMAP, 50 °C; (c) KOH, MeOH.

Oxidation of the primary alcohol [165] had been effected<sup>19</sup> by a modified Moffat oxidation which gave crude material of sufficient purity to allow its use without chromatography. Ley and Griffith



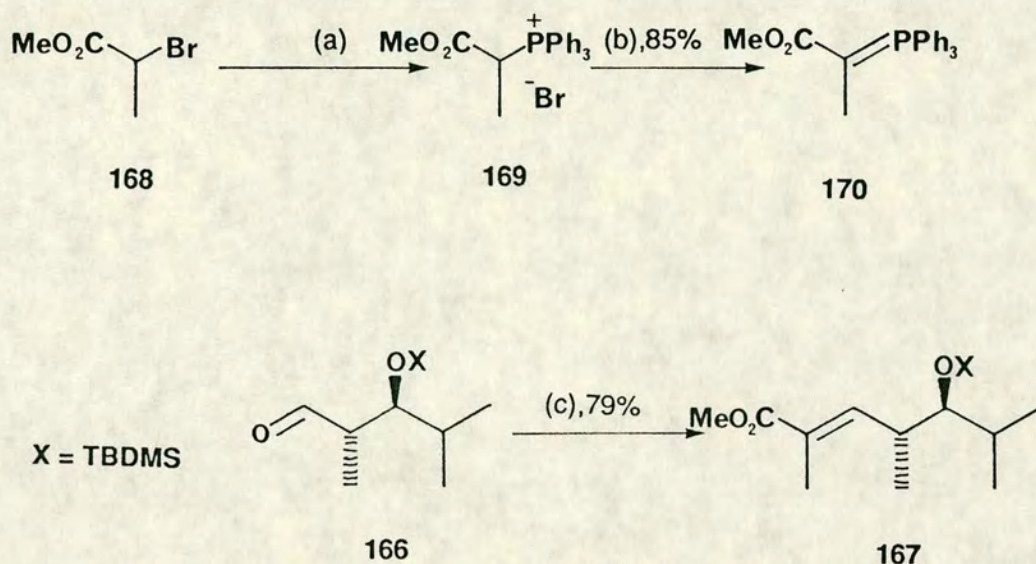
developed<sup>123</sup> the novel catalytic oxidant, tetra-*n*-propylammonium per-ruthenate (TPAP) which is used with *N*-methylmorpholine *N*-oxide as a co-oxidant. This reagent is a very mild system and gives excellent yields of the aldehydic compounds. It should also be noted that any chirality in the substrate is completely unaffected by this oxidation. For these reasons, the decision was taken to use the catalytic ruthenium-based method in the preparation of the required aldehyde [166]. In a typical reaction, the alcohol [165] was dissolved in dry dichloromethane then *N*-methylmorpholine *N*-oxide (1.5 equivalents) and powdered 4A molecular sieves were added. Finally, TPAP (0.005 equivalent) was added and the resultant green mixture stirred at room temperature for sixteen hours overnight. The reaction mixture was diluted with dichloromethane then washed with aqueous sodium sulphite, brine and aqueous copper(II)sulphate. Concentration of the dried organic liquors gave the crude product which was purified by dry flash chromatography to give the desired aldehyde [166] in a yield of 81% (Scheme 61).



**SCHEME 61**, reagents: (a)  $n\text{-Pr}_4\text{N}^+\text{RuO}_4^-$ , NMNO, 4A sieves.

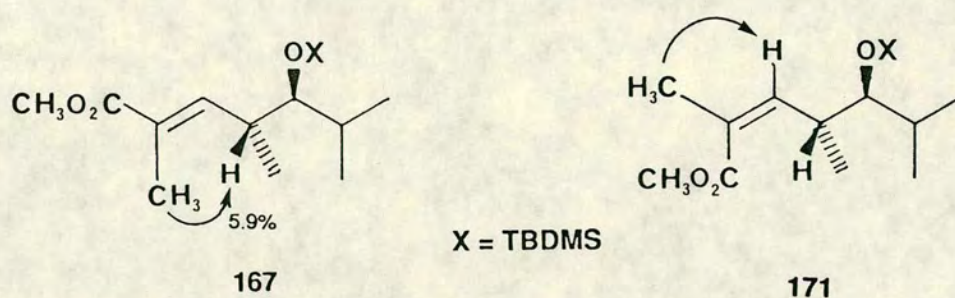
Now that the chiral aldehyde [166], which would form one end of the polyene chain, had been prepared the next task was to build the all *trans* diene unit on to the optically active pentanal intermediate. Antecedent work by Lewis<sup>19</sup> had demonstrated that the most expedient route to the polyenal fragment was construction of the olefinic bonds one at a time. Although more laborious than using reagents that already contained unsaturated units, it was found to be far more reliable when the question of isomeric purity of the double bonds arose. To this end, aldehyde [166] was condensed with the stabilised phosphorane [170]<sup>124</sup> which gave enone ester [167].

In order to achieve satisfactory yields of the product a reaction time of five days in refluxing benzene was necessary. Carbomethoxyethylidinetriphenylphosphorane [170] was prepared by reacting ( $\pm$ )-methyl 2-bromopropionate [168] with triphenylphosphine then treating the precipitated phosphonium salt [169] with aqueous sodium hydroxide (1.0 equivalent) (Scheme 62).



**SCHEME 62**, reagents: (a)  $\text{PPh}_3$ ; (b)  $\text{NaOH}(\text{aq})$ ; (c) [170], benzene,  $80^\circ\text{C}$ .

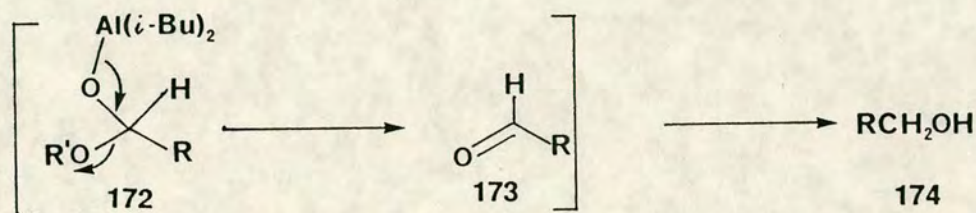
The nuclear Overhauser effect (n.O.e.) provided an excellent means<sup>19</sup> of confirming the double bond geometry: irradiation of the 2- $\text{CH}_3$  at  $\delta$  1.84 gave rise to a notable 5.9% enhancement of the 4-H resonance at  $\delta$  2.56 - 2.72 (Scheme 63). Consequently the 2- $\text{CH}_3$  and 4-H moieties must be close in space, and the only way this can happen is if the olefin is of *trans* geometry. In the *cis* compound [171] one would expect to see no enhancement of the 4-H resonance but an effect on the 3-H signal (Scheme 63).



**SCHEME 63**

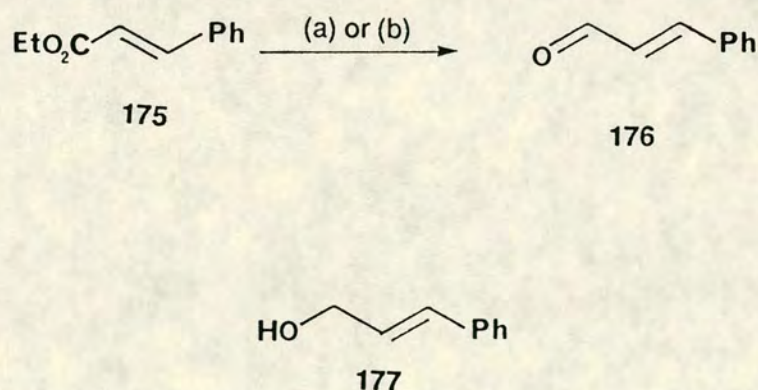
Previously, the ester function in [167] had been reduced and the alcohol subsequently oxidised to afford the aldehyde. Obviously if the ester could be reduced to the aldehyde in a single step this would result in a much shorter synthesis. Unfortunately, the chemical literature is devoid of reliable

methods to carry out this transformation so an effort was made to solve this problem. Mechanistically, the reduction of esters with DIBAL seemed to offer the best prospect for finding a viable solution to this problem as the corresponding aldehydes are intermediates formed on the way to the alcohols. It was hoped that silylation of the acetal intermediate [172], achieved by doing the reaction in the presence of a silylating agent, would prevent formation of the aldehyde [173] during the reduction and hence stop production of the alcohol [174] (Scheme 64).



SCHEME 64

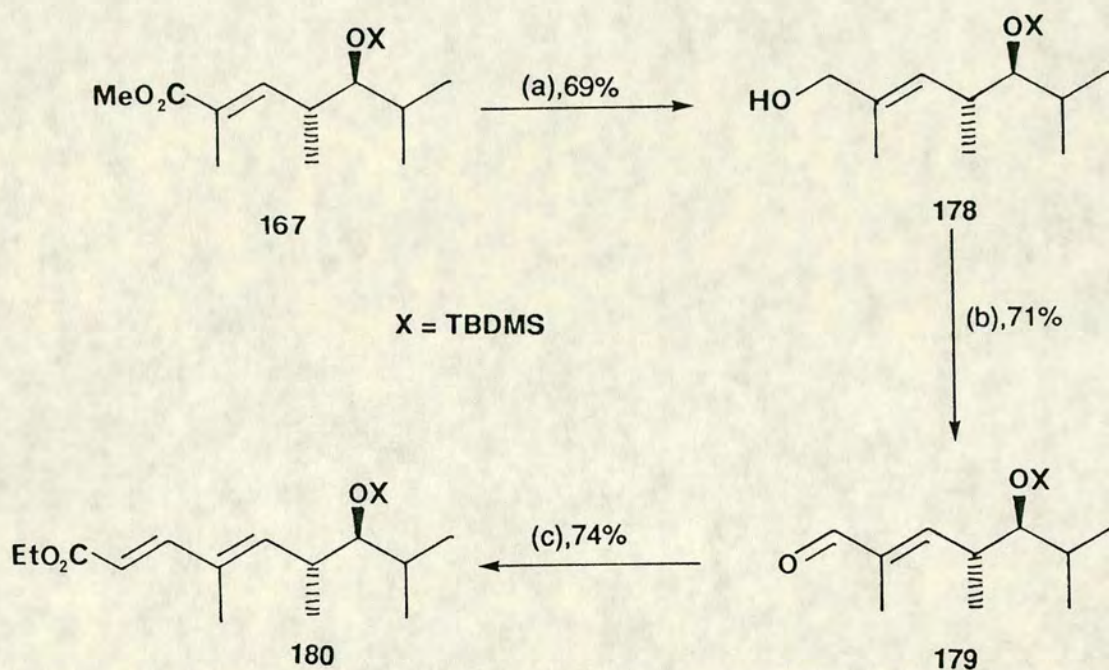
The hypothesis was tested by carrying out the reduction of ethyl cinnamate [175], using DIBAL (1.0 equivalent) and trimethylsilyl chloride or 1,1,1-3,3,3-hexamethyldisilazane (1.0 equivalent) at  $-40^\circ\text{C}$  and  $-95^\circ\text{C}$ . In all cases the product mixture (obtained in excellent yield) consisted of [175] and cinnamyl alcohol [177] in a ratio of 2:1 as observed by proton n.m.r. spectroscopy. Only a trace of cinnamaldehyde [176] was observed as a third spot on t.l.c. (Scheme 65).



SCHEME 65, reagents: (a) DIBAL, TMS-Cl,  $-40$  or  $-95^\circ\text{C}$ ; (b) DIBAL, HMDS,  $-40$  or  $-95^\circ\text{C}$ .

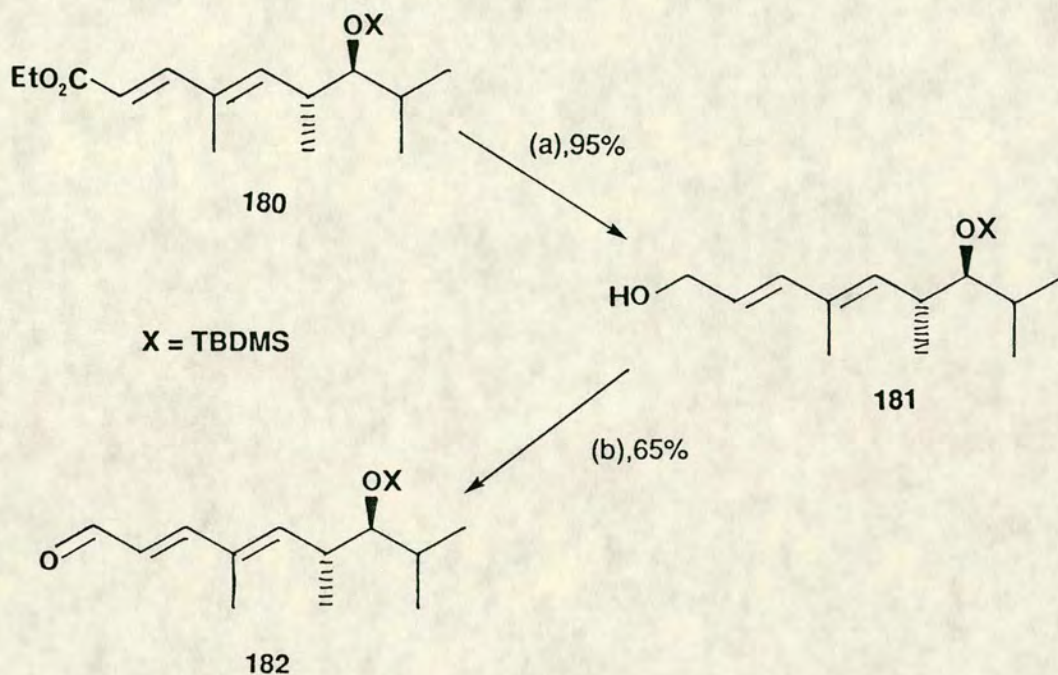
Thus, ester [167] was reduced to the allylic alcohol [178] using DIBAL at  $-78^\circ\text{C}$  in 69% yield. Oxidation of [178] was accomplished by treatment with TPAP and *N*-methylmorpholine *N*-oxide.

The pure unsaturated aldehyde [179] had an optical rotation of  $+4.7^\circ$  and showed a  $\lambda_{\text{max}}$  at 233 nm in the u.v. spectrum. The olefinic chain of [179] was then extended by a Wittig reaction using ethoxycarbonylmethylenetriphenylphosphorane in benzene at reflux for five days. The pure (E,E)-diene [180] was obtained (95% yield) after chromatography on silica gel. Proton n.m.r. spectroscopy showed a coupling constant of 15.5 Hz between the 2-H and 3-H resonances at  $\delta$  7.34 and  $\delta$  5.72 confirming that the double bond adjacent to the ester group was of *trans* geometry (Scheme 66).



**SCHEME 66**, reagents: (a) DIBAL,  $-78^\circ\text{C}$ ; (b) TPAP, NMNO, 4A sieves; (c)  $\text{EtO}_2\text{CCH}=\text{PPh}_3$ ,  $80^\circ\text{C}$ .

Synthesis of the polyenal fragment was completed by transformation of the ethyl ester [180] into the corresponding alcohol [181] using DIBAL as the reducing agent. This alcohol was then oxidised, with the catalytic TPAP/NMNO system, to afford the aldehyde [182] which had been identified as the synthon for the polyene unit of our target system. [182] had an optical rotation of  $+4.6^\circ$  and a  $\lambda_{\text{max}}$  of 279 nm with the proton n.m.r. spectrum again showing that the all-*trans* geometry was present exclusively (Scheme 67).

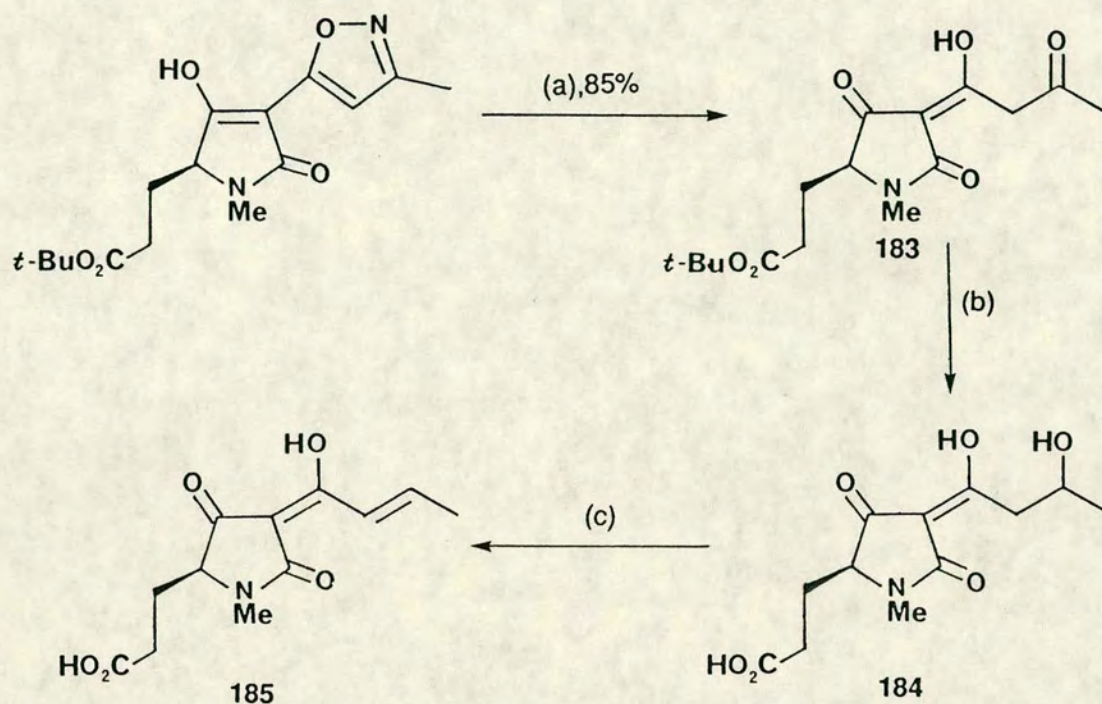


**SCHEME 67**, reagents: (a) DIBAL,  $-78\text{ }^{\circ}\text{C}$ ; (b) TPAP, NMNO, 4A sieves.

### 2.3 STUDIES TOWARDS COUPLING THE KEY INTERMEDIATES

Coupling the tetramic acid and dienal fragments represents the point of convergence in this synthetic route. Consequently, this step forms the crux of the *modus operandi* so any chemical reaction employed to achieve the union of the intermediates must be both selective and high-yielding.

Jenkins prepared<sup>18</sup> the 3-butenoyltetramic acid [185] with a view to utilising the masked enone moiety as a means of producing the reactivity required for coupling to an electrophile. The latent 1,3-dicarbonyl functionality of the isoxazolyltetramic acid [120] was unmasked *via* a one-pot hydrogenation/hydrolysis procedure. This gave the acetoacetyl derivative [183] in a yield of 85%. Proton n.m.r. spectroscopy indicated that the 1,3-diketone compound was present as the 2"-CH<sub>2</sub> showed a resonance at  $\delta$  3.98. Jenkins elaborated<sup>18</sup> [183] into the 3-butenoyltetramic acid [185] by reduction of the 3'-carbonyl group with sodium borohydride followed by acid-catalysed dehydration of the resulting alcohol [184] (Scheme 68).

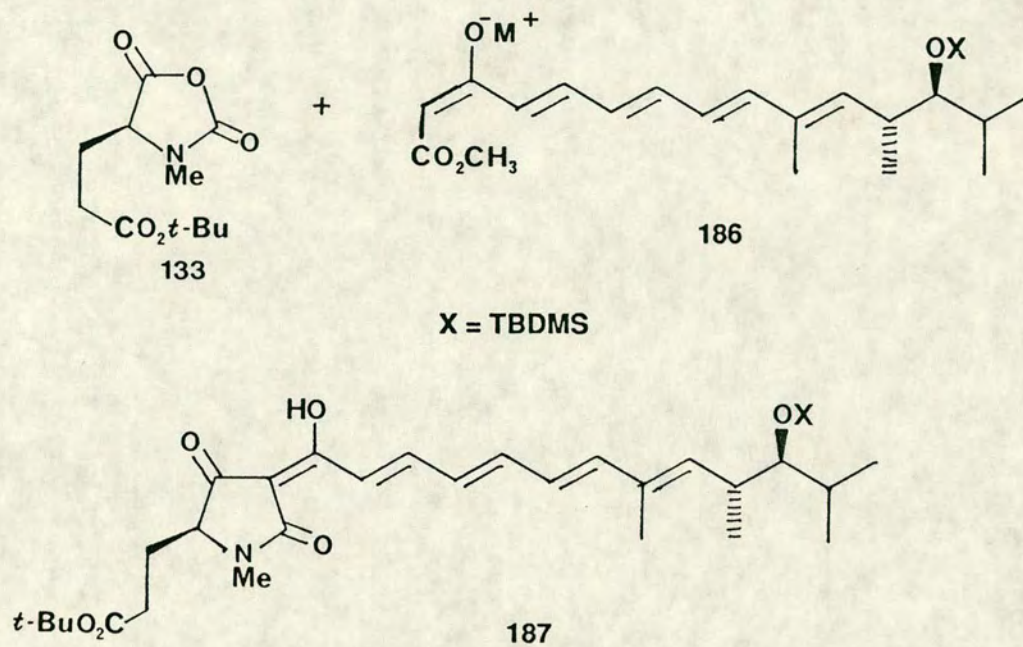


SCHEME 68, reagents: (a) (i) hydrogen, Pd-C, (ii) H<sub>3</sub>O<sup>+</sup>; (b) NaBH<sub>4</sub>; (c) TosOH.

Rather than continue with the development of the Jenkins' approach<sup>18</sup> it was attractive to pursue a less cumbersome route. This, it was hoped, would lead to a much more efficient (with respect to both time and materials) synthetic route to the target structure.

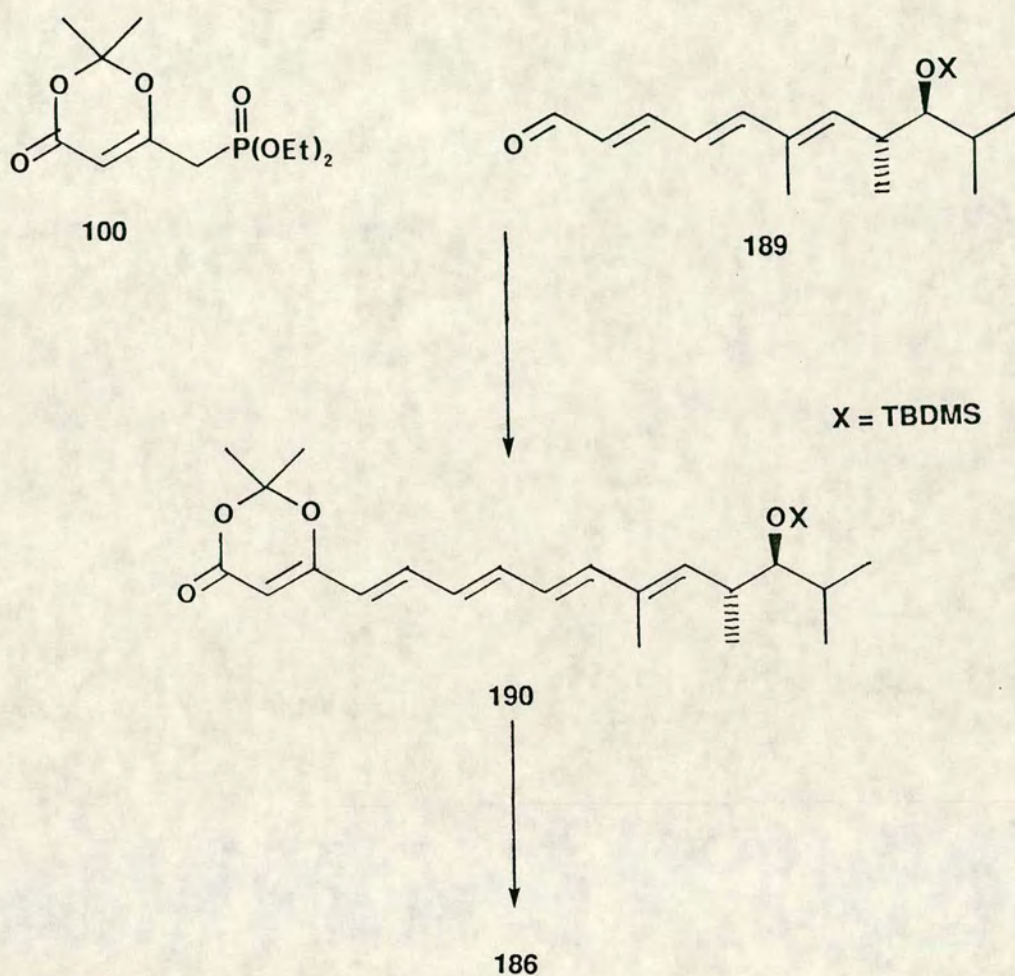
The most obvious way of reducing the length of the synthesis is by combining the coupling and tetramic acid ring-forming steps. This could be achieved if the enolate used to attack the *N*-carboxyanhydride [133] was part of the polyene unit [186] (Scheme 69).





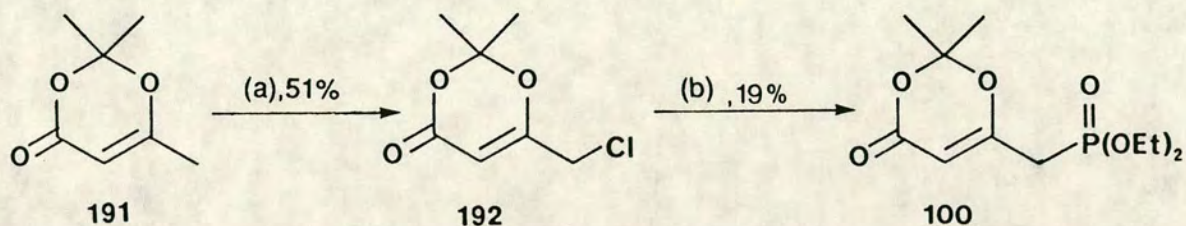
SCHEME 69

Reaction of polyunsaturated aldehyde [189] with the phosphonate [100]<sup>88,89</sup> would give the substituted 1,3-diox-5-enone [190] which on treatment with methanol then base would produce the desired enolate species [186] (Scheme 70).

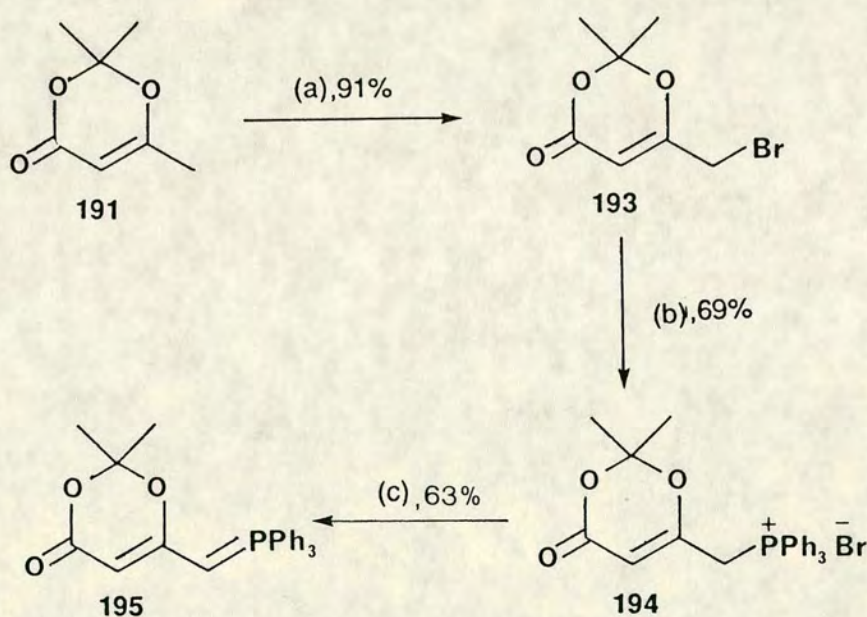


SCHEME 70

Boeckmann's procedure<sup>89</sup> was followed in an attempt to prepare the phosphonate [100]. Accordingly, 2,2,6-trimethyl-1,3-diox-5-en-4-one [191] was chlorinated at the 6-methyl position by treatment of the corresponding lithium enolate with hexachloroethane. The chloride [192] was then stirred with the potassium salt of diethyl phosphite. Unfortunately, the 6-diethylphosphonomethyl compound was obtained in very poor yield (19%) and always contained a trace of impurity as evidenced by the presence of a second spot on t.l.c. (Scheme 71).

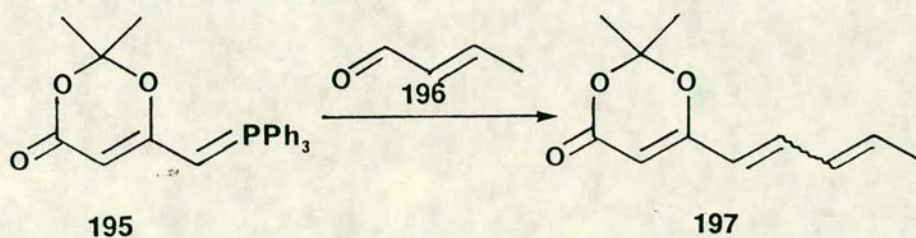
SCHEME 71, reagents: (a) (i) *n*-BuLi, C<sub>2</sub>Cl<sub>6</sub>, (ii) KO<sup>t</sup>-Bu, H(O)P(OEt)<sub>2</sub>.

Due to the significant problems of poor yield and arduous purification the related phosphorane [195]<sup>88</sup> was seen as a superior reagent because of the ease of preparation. Dioxenone [191] was brominated at the allylic methyl position using *N*-bromosuccinimide in carbon tetrachloride at reflux. The crude bromide [193] (a lachrymatory oil) was added to a solution of triphenylphosphine in toluene and the phosphonium salt [194] precipitated out. The white salt [194] was then shaken with aqueous potassium carbonate to generate the phosphorane [195]. Ylide [195], isolated as green-yellow crystals, appeared to be stable for long periods if stored at -20 °C in a freezer (Scheme 72). Other methods which were tried in an effort to obtain [195] (*id est* DABCO and aqueous sodium hydroxide) led to decomposition of the phosphonium salt [194].



SCHEME 72, reagents: (a) NBS, CCl<sub>4</sub>, reflux; (b) PPh<sub>3</sub>; (c) potassium carbonate (aq).

Phosphorane [195] was then reacted with crotonaldehyde [196] (chosen as a model for the unsaturated aldehyde [189] that would be reacted with [195] to produce the required intermediate [190]) under a variety of conditions to try to find the best procedure for the Wittig coupling (Scheme 73).

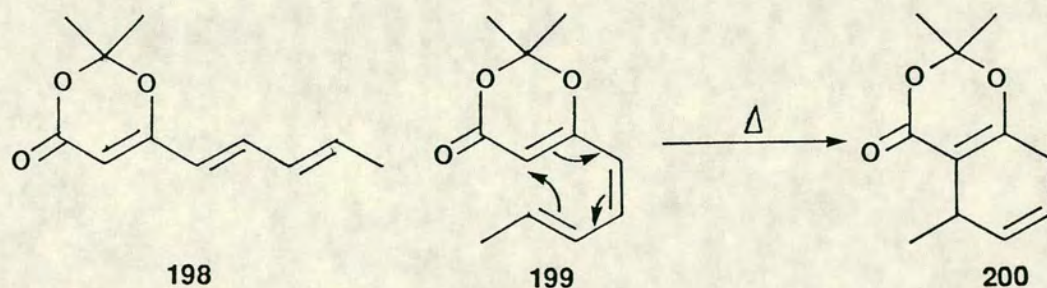


SCHEME 73

Initially, the reaction was carried out at room temperature which led to the isolation of a 1:1 mixture of *cis* and *trans* isomers [197] in varying yields; the results are summarised in the following table:

Solvent	% Yield [197]	t/days
Toluene	no reaction	3
CH <sub>3</sub> CN	5	3
CH <sub>2</sub> Cl <sub>2</sub>	8	6
Benzene	19	3
DMSO	12	6

To try and improve the yields of desired product the reaction was carried out at 40 °C over three days. These experiments gave the *trans* diene [198], with  $\lambda$  max 303 nm, and a bicyclic product [200] which had  $\lambda$  max 223 nm in the u.v. spectrum. This product arises from thermally induced electrocycloislation of the three pi-bonds in the *cis* product [199]. Only *cis* orientation of the diene allows the molecule to obtain the necessary planar arrangement that facilitates such a cyclisation (Scheme 74).

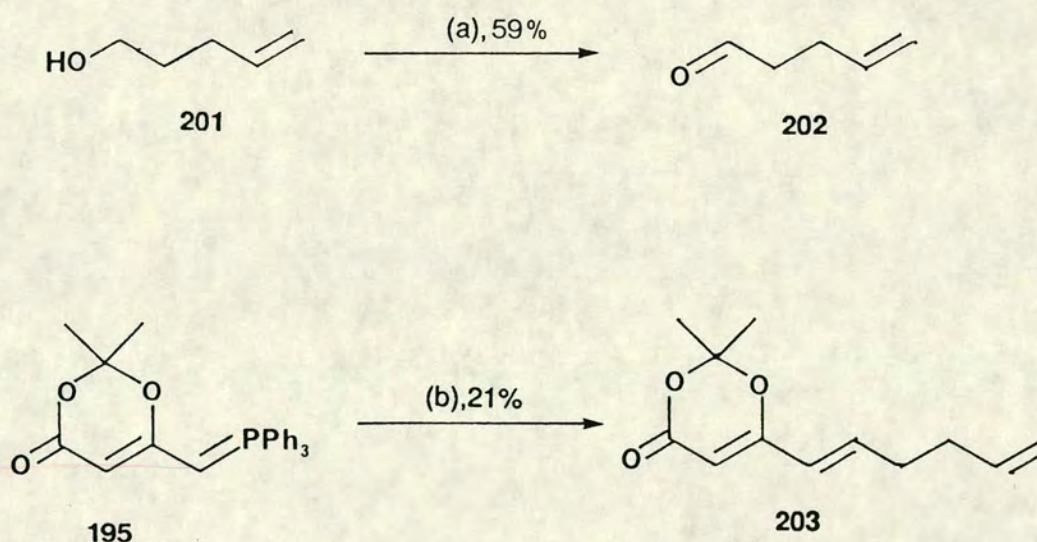


SCHEME 74

The yields of desired product in the elevated temperature runs, although better, were still unacceptable, as can be seen from the table (*vide infra*). In both cases, the rest of the material recovered from the crude reaction product was a yellow solid (eluted from the silica column with acetone). This solid, which could not be identified, had a very broad u.v. absorption of 200 - 350 nm and probably resulted from decomposition of the phosphorane species [195]:-

Solvent	T/°C	% yield [198]	% yield [200]
CH <sub>3</sub> CN	40	11	9
CH <sub>2</sub> Cl <sub>2</sub>	40	8	8
Benzene	40	12	9
DMSO	40	12	10

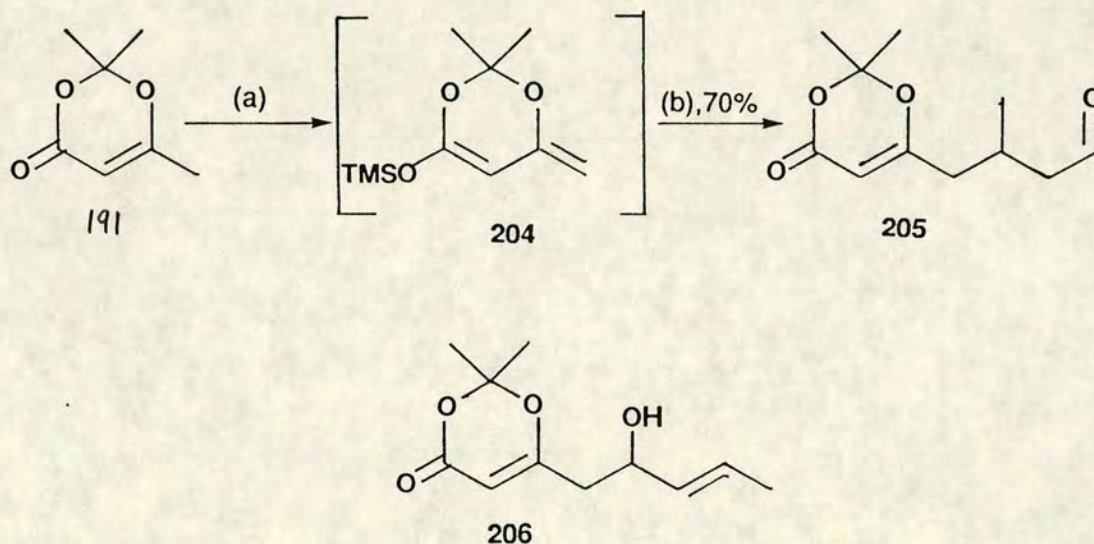
It was reasoned that phosphorane [195] would react more readily with an  $\alpha,\beta$ -saturated aldehyde. With this in mind, pent-4-enal [202] was prepared by oxidation of pent-4-en-1-ol [201] using pyridinium chlorochromate. Wittig reaction of [195] and [202] in dry benzene at 40 °C followed the same pattern as before with the adduct [203] being isolated in only 21% yield (Scheme 75). Only the *trans* isomer was isolated after irradiation of the crude mixture with a tungsten lamp (500W).



SCHEME 75, reagents: (a) PCC; (b) [202].

The inefficacious addition of the dioxenone unit *via* phosphorus methodology meant that an alternative procedure was sought after. Treatment of the trimethyldioxenone [191] with *n*-butyllithium followed by trimethylsilyl chloride generated trimethylsilyloxy diene [204] *in situ*. This was then used to perform a Lewis-acid catalysed aldol reaction on crotonaldehyde [196] at -78 °C.

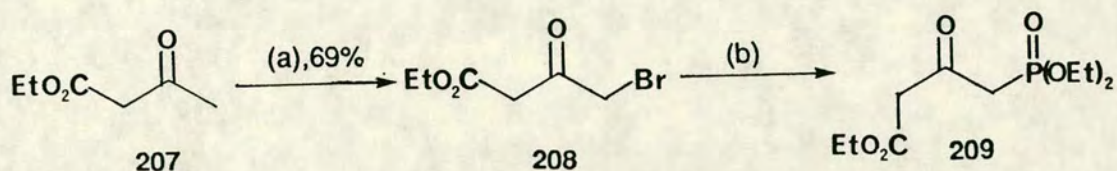
Catalytic quantities of tin(IV)chloride and zinc(II)iodide were used in separate experiments. In both cases, only the Michael-addition product [205] was isolated with none of the expected 1,2-addition compound [206] being observed (Scheme 76). This result was somewhat surprising as it is well known<sup>125</sup> that  $\alpha,\beta$ -unsaturated aldehydes normally undergo 1,2 addition. Obviously the method was of little use for the purpose of this work and hence was not investigated any further.



**SCHEME 76**, reagents: (a) *n*-BuLi, TMS-Cl, -78 °C; (b) [196], SnCl<sub>4</sub> or ZnI<sub>2</sub>, -78 °C.

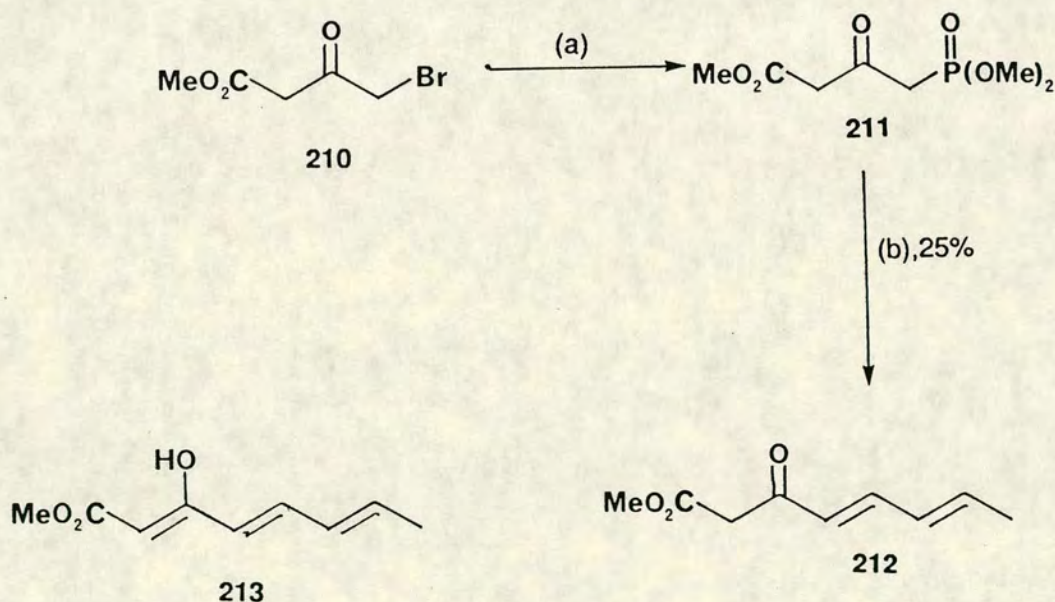
The acetoacetate system represents another way of introducing functionality from which an enolate species could be generated. Bodalski had reported<sup>126</sup> the preparation of ethyl 4-(diethylphosphono)-3-oxobutyrates [209] and described its use in introducing the  $\beta$ -ketoester unit. Thus, ethyl 4-bromo-3-oxobutyrates [208] was converted to its sodium salt then treated with sodium diethylphosphite. The crude material showed a signal at  $\delta$  18.98 in the phosphorus n.m.r. spectrum which is consistent with a phosphonate species<sup>126</sup> but, on distillation, the material decomposed. Compound [208] was prepared exactly according to Duthailer's<sup>127</sup> method; ethyl acetoacetate was brominated at the 2-

position with liquid bromine then oxygen was passed through the reaction mixture to effect rearrangement to the 4-bromo derivative [208] (Scheme 77).



**SCHEME 77**, reagents: (a) (i)  $\text{Br}_2(\text{l})$ ,  $-10\text{ }^\circ\text{C}$ , (ii)  $\text{O}_2(\text{g})$ ; (b) (i)  $\text{NaH}$ ,  $0\text{ }^\circ\text{C}$ , (ii)  $\text{NaP}(\text{O})(\text{OEt})_2$ .

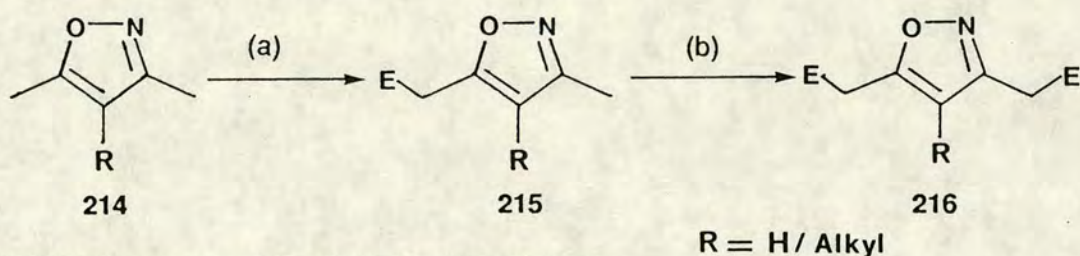
The related dimethylphosphonate [211] was prepared, in the same manner, from methyl 4-bromo-3-oxobutanoate [210]<sup>127</sup>. Again, attempts to purify the crude phosphonate led to decomposition - despite literature reports to the contrary<sup>126</sup>. Crotonaldehyde [196] was reacted with the dianion of crude [211] to give the dienone [212] in 25% yield after chromatography (Scheme 78). Proton n.m.r. spectroscopy of [212] showed that there was *circa* 22% of the enolic form [213] present. The u.v. spectrum showed a bathochromic shift when a drop of sodium hydroxide was added to the cell:  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ ) 276nm,  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN} + \text{NaOH}$ ) 340nm.



**SCHEME 78**, reagents: (a) (i)  $\text{NaH}$ , (ii)  $\text{NaP}(\text{O})(\text{OMe})_2$ ,  $0\text{ }^\circ\text{C}$ ; (b) (i)  $\text{NaH}$ ,  $0\text{ }^\circ\text{C}$ , (ii) [196].

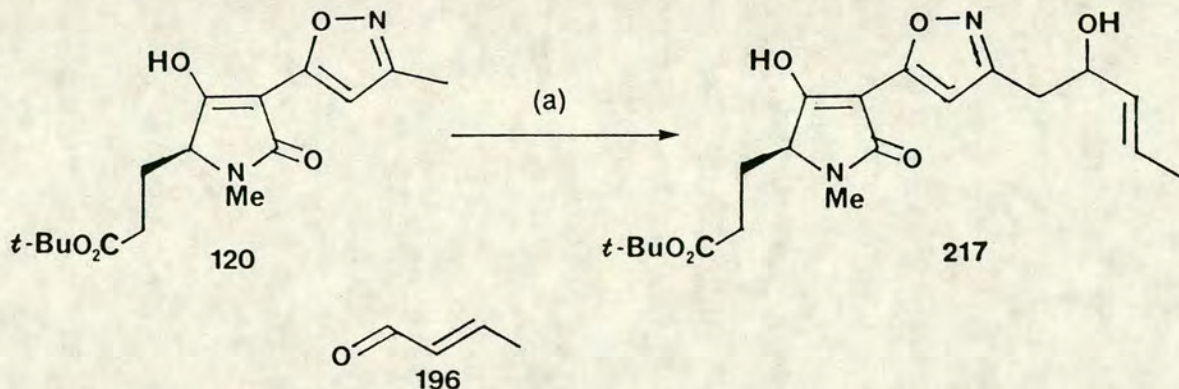
The lack of success with both of the phosphorus reagents led to the combined tetramic acid-formation and coupling protocol being abandoned. Instead attention was turned to exploitation of the reactivity of isoxazoles.

The acidity of  $\alpha$ -hydrogens of 3-, and especially, 5-alkyl side chains on isoxazole rings is enhanced by the ring nitrogen<sup>128</sup>. Aldol-type condensations involving such groups have been known for many years and can be performed without additional activation if strong bases (*exempli gratia* alkyl-lithium compounds and lithium dialkylamides) are employed<sup>129</sup>. In 3,5-dimethylisoxazoles [214] the 5-position is the more reactive. So treatment of [214] with *n*-butyllithium then an electrophile gives the 5-substituted derivative [215]<sup>129</sup>. Lithiation of the 3-methyl group will now take place in an analogous fashion using *sec*-butyllithium<sup>130,131</sup> (Scheme 79).



SCHEME 79, reagents: (a) *n*-BuLi, E<sup>+</sup>; (b) *s*-BuLi, E<sup>+</sup>.

In the isoxazolyltetramic acid [120] only the 3-position of the isoxazole has a substituent bearing  $\alpha$ -hydrogens. Lithiation of this group should occur readily on treatment with an appropriate base. To this end, [120] was treated with *n*-butyllithium at -78 °C in dry tetrahydrofuran. Crotonaldehyde [196] was then added to the yellow solution and the mixture was stirred for four hours. Analysis of the crude product indicated that the desired aldol product [217] had been formed, with the u.v. spectrum showing  $\lambda$  max 268 nm and 315 nm. High resolution (FAB) mass spectrometry detected the ion; C<sub>20</sub>H<sub>29</sub>N<sub>2</sub>O<sub>6</sub>: MH<sup>+</sup>, 393.20253 which corresponds to the structure [217] (Scheme 80).

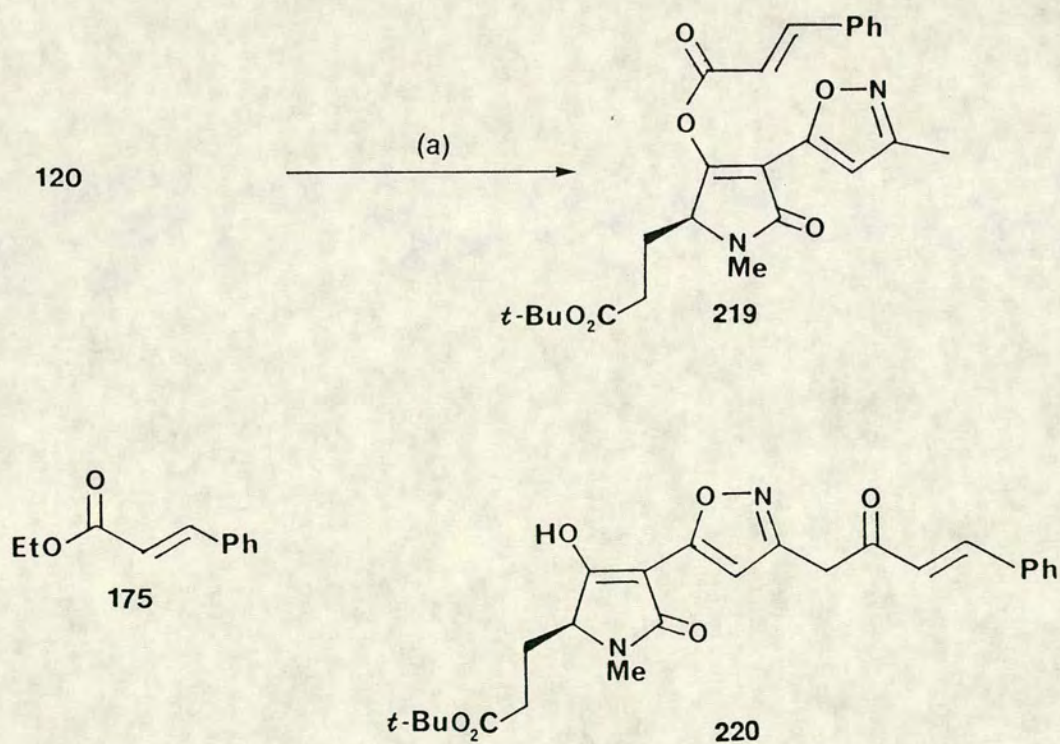


SCHEME 80, reagents: (a) (i) *n*-BuLi (2.0 equiv.), [196], (ii) H<sub>3</sub>O<sup>+</sup>.



The coupling was tried utilising lithium diisopropylamide and likewise *sec*-butyllithium as the deprotonating agents. The experimental results were similar to the previous attempt where the complex reaction products contained, *inter alia*, starting material and [217].

Ethyl cinnamate [175] was reacted with the lithio derivative of [120] (generated using *sec*-butyllithium) to determine if the more electrophilic ester carbonyl group would react in a superior fashion to that of an aldehyde. The product obtained was the di-ester [219], resulting from attack by the oxygen of the enolate ion, and not the desired enone [220] (Scheme 81).

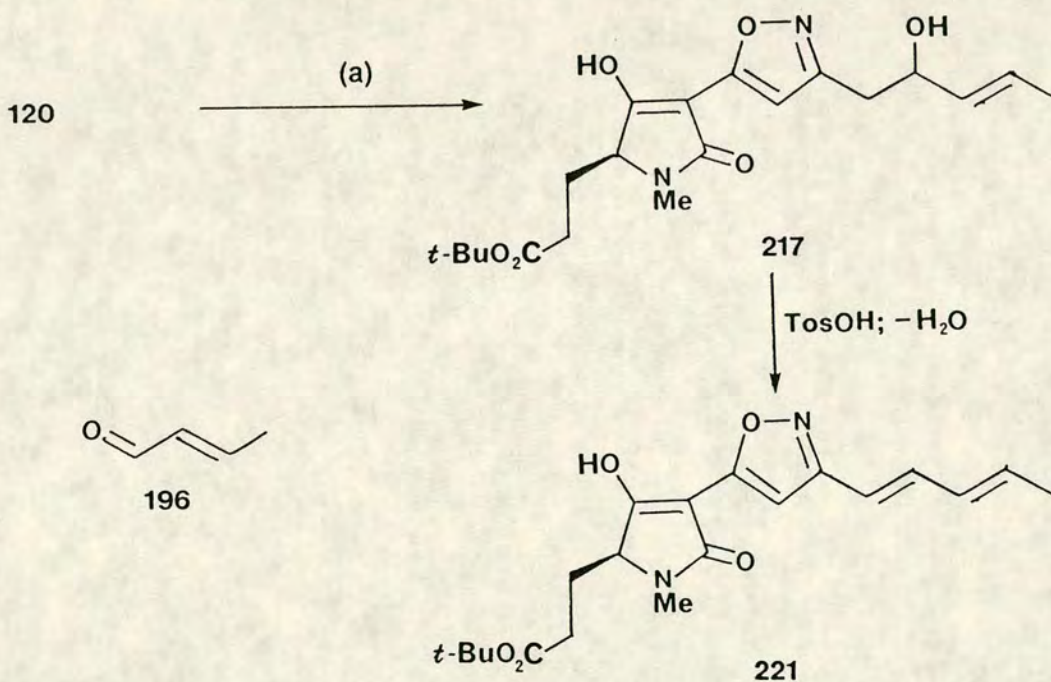


**SCHEME 81**, reagents: (a) *s*-BuLi (2.0 equiv.), [175], -78 °C.

This seemed to indicate that reaction occurred preferentially at the oxygen anion (formed by deprotonation of the enol with one equivalent of the base) which, in the case of an aldehyde as the

electrophile, would result in the formation of a hemi-acetal. Such a species would, of course, be hydrolysed back to the enol during acidic work-up. Blocking this nucleophilic site with a silicon-based group should lead to selective reaction at the carbanion.

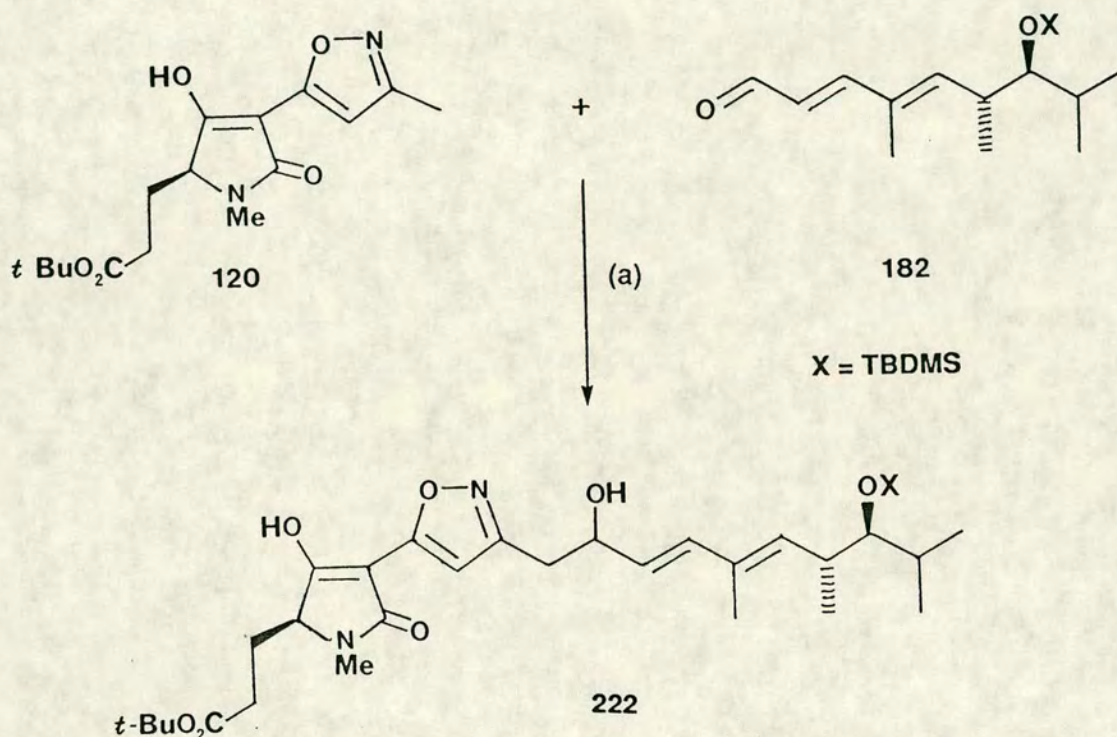
To achieve this, one equivalent of *sec*-butyllithium was added to the tetramic acid [120] followed by an equivalent of *tert*-butyldimethylsilyl chloride. A second equivalent of *sec*-butyllithium was introduced then succeeded by one equivalent of the aldehyde [196]. After three hours at  $-78\text{ }^{\circ}\text{C}$  the reaction was worked up. The product [217] was obtained as a green solid foam. Spectral data concurred with the predicted structure; the u.v. spectrum showed  $\lambda\text{ max}$  239 and 272 nm which upon addition of base shifted to  $\lambda\text{ max}$  271 and 306 nm confirming the presence of the tetramic acid unit. When [217] was heated to reflux in dichloromethane with a crystal of *p*-toluenesulphonic acid, the u.v. spectrum showed  $\lambda\text{ max}$  of 269, 304 and 358 nm. This indicated that water had been eliminated from [217] to afford the diene [221] (Scheme 82).



**SCHEME 82**, reagents: (a) (i) *s*-BuLi (1.0 equiv.), TBDMS-Cl,  $-78\text{ }^{\circ}\text{C}$ , (ii) *s*-BuLi (1.0 equiv.), [196],  $-78\text{ }^{\circ}\text{C}$ , (iii)  $\text{H}_3\text{O}^+$ .

Now that a coupling method finally showed promise the reaction was carried out using the nonadienal fragment [182] as the electrophile (Scheme 83). Disappointingly, analysis of the crude complex reaction products by t.l.c., proton n.m.r. spectroscopy and u.v. spectroscopy showed that

mainly starting materials were present. The high resolution (FAB) mass spectrum showed an ion 633.39353 (calc. for  $C_{34}H_{57}N_2O_7Si$ :  $MH^+$ , 633.39348) which does correspond to the coupled species.



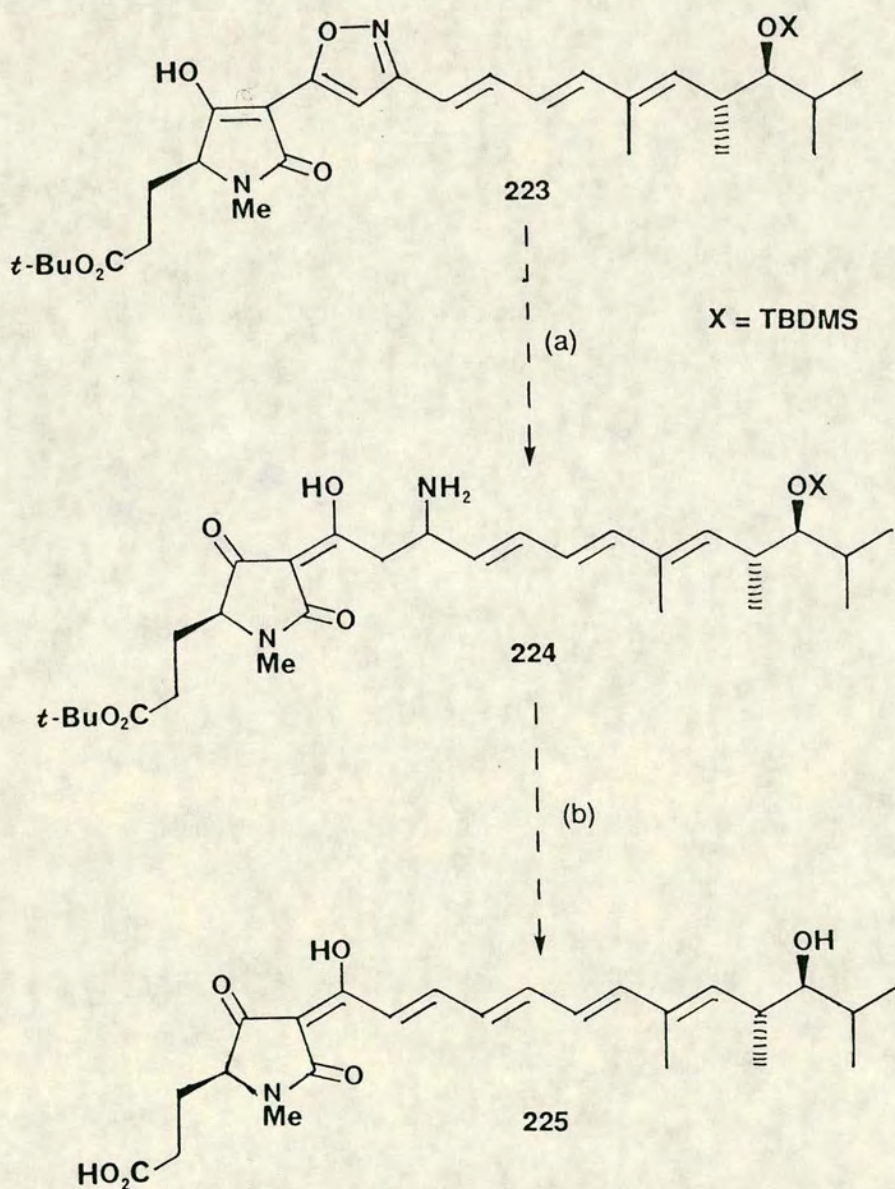
**SCHEME 83**, reagents: (a) (i) *s*-BuLi (1.0 equiv.), TBDMS-Cl, -78 °C, (ii) *s*-BuLi (1.0 equiv.), [182], -78 °C, (iii)  $H_3O^+$ .

These results illustrate that the aforementioned methodology represents a viable means of achieving the coupling of [120] and [182]. Obviously, there is room for improvement in the procedure and this might be accomplished through further scrutiny.

## 2.4 SUMMARY AND FUTURE WORK

The synthesis of the two key intermediates, namely (5*S*)-5-[2'-(*tert*-butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-methylisoxazolyl)]tetramic acid [120] and (2*E*,4*E*;6*R*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-4,6,8-trimethylnona-2,4-dienal [182], has been executed in an enantioselective manner.

The coupling of these key fragments has been the subject of thorough investigation. Consequently, a protocol for the accomplishment of this objective has been elucidated, though further work is required to realise its full potential. Reductive cleavage of the isoxazole ring<sup>134</sup> (of the dehydration product [223]) with samarium diiodide then reduction of the resultant enamine with sodium cyanoborohydride would give the  $\beta$ -amino-ketone [224]. Quaternisation of the amino group would facilitate a base-catalysed elimination of the quaternary ammonium salt giving, after deprotection, the aglycone of altamycin A [225] (Scheme 84).



SCHEME 84, reagents: (a)  $\text{SmI}_2$ , MeOH; (b) (i) MeI, base, (ii) TFA.

Future research could investigate other coupling strategies based around the tetramic acid unit, *exempli gratia* alternative methodologies for activation of this moiety. The final synthetic hurdle to be overcome will be to form the  $\beta$ -*O*-glycosidic linkage with *D*-digitoxose. Hopefully, this should be straightforward as there has been very considerable research carried out in this field<sup>132</sup>.

Finally, this research has potentially unearthed the key which can (*in futurus*) unlock the door to a complete understanding of the biological, chemical and pharmacological behaviour of these, and related, natural products.

### 3. EXPERIMENTAL

All solvents were distilled before use. Unless otherwise stated, petrol refers to the fraction of petroleum ether boiling in the range 40 - 60 °C. Benzene, toluene and diethyl ether were dried by storage over sodium wire. Dichloromethane, dimethylformamide and acetonitrile were dried by distillation from calcium hydride. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl immediately before use. Chloroform and carbon tetrachloride were dried by distillation from phosphorus pentoxide and methanol was dried by distillation from magnesium-iodine. Dimethylsulphoxide was dried by distillation from lithium aluminium hydride at reduced pressure and was stored under nitrogen over 4A molecular sieves. Diisopropylamine, pyridine, tetramethylethylenediamine (TMEDA) and triethylamine were all distilled from potassium hydroxide pellets and stored over 4A molecular sieves. Dry carbon dioxide gas for carboxylation reactions was obtained by sublimation of commercially available dry-ice followed by passage through concentrated sulphuric acid then through a column of silica gel desiccant. All other purchased chemicals were used as received. Every reaction involving the use of strong bases and air or moisture sensitive reagents was performed in oven dried glassware (at 140 °C) under an argon atmosphere. The argon for such experiments was purified by passage through columns of silica gel (60H, impregnated with chromium trioxide) and silica gel desiccant.

Ethereal solutions of diazomethane were prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulphonamide using an 'Aldrich' "mini-diazald" apparatus.

Flash column chromatography refers to the technique described by Still<sup>133</sup>. Dry flash chromatography was carried out on 'Merck' Kieselgel 60H. The technique involved a cylindrical glass sinter (porosity 3) being filled with silica which was compacted by applying suction and pressing it down with a flat spatula. The column was solvated with the least polar component of the intended eluent and sucked dry. The mixture to be separated was dissolved in the minimum volume of the least polar solvent then loaded, as evenly as possible, to the top of the column. Elution with equal volumes of solvent mixtures of increasing polarity, ensuring that the column was sucked to dryness between fractions, then effected the desired purification. Thin layer chromatography (t.l.c.)

was carried out on aluminium sheets precoated with silica gel 60G F-254 (Merck 5735) in the following solvent systems: (A) ether, (B) 50% ether-petrol, (C) 30% ether-petrol, (D) 20% ether-petrol, (E) 10% ether-petrol, (F) 5% ether-petrol, (G) petrol, (H) 20% ethyl acetate-hexane and (I) ethyl acetate. Visualisation of the compounds was achieved by a suitable combination of the following methods: iodine vapour, u.v. absorption at 254 or 366 nm, neutral potassium permanganate solution/bromophenol blue solution and 6M sulphuric acid solution.

Infrared spectra were recorded on a Perkin Elmer 781 spectrophotometer in the solvent indicated. Ultraviolet spectra were recorded on a Varian Cary 210 spectrophotometer. Mass spectra and high resolution mass spectra were recorded on a Kratos MS50TC spectrometer with xenon as the bombardment source.  $^1\text{H}$  n.m.r. spectra were recorded on either Jeol PMX60 (60MHz), Bruker WP80 (80MHz), WP200 (200MHz) or WH360 (360MHz) machines in fully deuterated solvents, with tetramethylsilane (TMS) as the external standard ( $\delta_{\text{H}}/\text{ppm}$  0.00).  $^{13}\text{C}$  n.m.r. spectra were recorded on either Bruker WP200 (50MHz) or WH360 (90MHz) machines with TMS as the external standard ( $\delta_{\text{C}}/\text{ppm}$  0.00).  $^{31}\text{P}$  n.m.r. were recorded on a Jeol FX90Q (36MHz) machine with 85% aqueous phosphoric acid as the external standard ( $\delta_{\text{P}}/\text{ppm}$  0.00). Optical rotation  $[\alpha]$  values were determined on an Optical Activity AA1000 automatic polarimeter using a 10.0 cm (1.0 dm) cell at 589 nm (sodium D line). Elemental analyses were carried out on a Carlo-Erba elemental analyser model 1106. Melting point determinations were carried out on a Kofler hot-stage microscope and are uncorrected.

#### *N*-Methoxycarbonyl-*L*-Glutamic acid [139] (MOC-Glu)

*L*-Glutamic acid (147.1 g, 1 mol) was dissolved in a mixture of sodium bicarbonate (1M(aq); 1 dm<sup>3</sup>) and sodium hydroxide (4M (aq); 800 ml) and the stirred solution was cooled in an ice/salt bath. Methyl chloroformate (142.0 g, 1.5 mol) was then added dropwise over 30 minutes before the reaction mixture was allowed to warm to room temperature and stirred overnight. The aqueous liquors were washed with ether (2 x 600 ml), cooled in an ice-bath then acidified to pH 1.0 with conc. HCl. The aqueous solution was saturated with sodium chloride prior to extraction of the product into ethyl acetate (3 x 800 ml). The organic extracts were combined and dried (MgSO<sub>4</sub>) before removal of the solvent *in vacuo* to give a viscous golden syrup.

Crystallisation was observed on storage in a freezer under petrol at  $-20\text{ }^{\circ}\text{C}$  producing the *title compound* as a white solid (125.15 g, 0.61 mol, 61%), m.p.  $62\text{-}64\text{ }^{\circ}\text{C}$ ;  $[\alpha]^{20} = -9.1^{\circ}$  ( $c=1.12$ , MeOH); (Found:  $\text{MH}^+$ , 206.06644 Calc. for  $\text{C}_7\text{H}_{12}\text{NO}_6$ :  $\text{MH}^+$ , 206.06645);  $\nu$  max ( $\text{CH}_2\text{Cl}_2$ )  $3600\text{-}2600$  ( $\text{CO}_2\text{H}$ ), 1745 ( $\text{C}=\text{O}$ ), 1510 (amide II of urethane), 1380, 1250 and  $1050\text{ cm}^{-1}$ ;  $\delta_{\text{H}}/\text{ppm}$  (200MHz,  $\text{DMSO-d}_6$ ) 1.64 - 2.34 (4H,m,Glu  $\beta$ - and  $\gamma$ -  $\text{CH}_2$ 's), 3.50 (3H,s,- $\text{OCH}_3$ ), 3.92 (1H,M,Glu  $\alpha$ - CH), 7.38 (1H,br d,  $J=10\text{Hz}$ , -NH), 11.34 (2H,br s,- $\text{CO}_2\text{H}$ );  $m/z(\text{FAB})$  206, 188, 160 and 142.

$\alpha$ -Benzyl-*N*-methoxycarbonyl-*L*-glutamate.dicyclohexylamine salt [140] (MOC-Glu(OH,DCHA)-OBzl)

Triethylamine (143.6 ml, 1.03 mol) and benzyl bromide (125.9 ml, 1.06 mol) were added sequentially to a solution of MOC-Glu (210.97 g, 1.03 mol) in dry dimethylformamide (500 ml) at  $0\text{ }^{\circ}\text{C}$ . The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into iced water ( $1.5\text{ dm}^3$ ) and the resultant oil extracted into ethyl acetate (4 x 500 ml). The combined organic extracts were washed with water (2 x 500 ml), dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo* to a volume of *circa* 800 ml. Ether ( $1.5\text{ dm}^3$ ) was added and the solution cooled to  $0\text{ }^{\circ}\text{C}$  before dicyclohexylamine (125.6 ml, 1.03 mol) was added dropwise over 45 minutes. Ether was added as necessary to keep the stirred mixture mobile as the salt precipitated out. The reaction mixture was left standing in a refrigerator overnight. The solids were collected by filtration, washed thoroughly with ether, dried and recrystallised from ether/ethanol to give the *title compound* as white crystals (289.8 g, 0.61 mol, 59%), m.p.  $154\text{-}155\text{ }^{\circ}\text{C}$ ;  $[\alpha]^{20} = -16.8^{\circ}$  ( $c=1.02$ ,  $\text{CHCl}_3$ ); (Found:  $\text{MH}^+$ , 477.2964. Calc. for  $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_6$ :  $\text{MH}^+$ , 477.2964); (Found: C, 65.3%; H, 8.2%; N, 6.1%.  $\text{C}_{26}\text{H}_{40}\text{N}_2\text{O}_6$  requires C, 65.5%; H, 8.5%; N, 5.9%);  $\nu$  max ( $\text{CH}_2\text{Cl}_2$ ) 2940(CH), 1730( $\text{C}=\text{O}$ ), 1630 and  $1510\text{ cm}^{-1}$  (amide II of urethane);  $\delta_{\text{H}}/\text{ppm}$  (200MHz,  $\text{CDCl}_3$ ) 1.05-2.05 (22H,m,cyclohexyl H's), 2.20(2H,m,Glu  $\beta$ - $\text{CH}_2$ ), 2.80(2H,m,Glu  $\gamma$ - $\text{CH}_2$ ), 3.60(3H,s,- $\text{OCH}_3$ ), 4.20 (1H,m,Glu  $\alpha$ -CH), 5.10 (2H,s,benzyl  $\text{CH}_2$ ), 7.27 (5H,s,aromatic CH), 7.40 (1H, br s,Glu NH), 9.20 (2H,br s,- $\text{NH}_2^+$ );  $\delta_{\text{C}}/\text{ppm}$  (50MHz,  $\text{CDCl}_3$ ) 24.40, 24.69, 28.58 (cyclohexyl  $\text{CH}_2$ 's), 51.42 (- $\text{OCH}_3$ ), 52.01 (cyclohexyl CH's), 54.65 (Glu  $\alpha$ -CH), 66.15 (benzyl  $\text{CH}_2$ ), 127.51, 127.70, 128.02 (aromatic CH's), 135.38 (aromatic quat.C), 156.60, 172.11, 177.96 (carbonyl C's);  $m/z(\text{FAB})$  477, 461, 445, 387, 296, 272, 212 and 182.



$\alpha$ -Benzyl-*N*-methoxycarbonyl-*L*-glutamate [141] (MOC-Glu-OBzl)

A solution of citric acid (111.37 g, 530 mmol) in water (500 ml) was added slowly to a rapidly stirred suspension of MOC-Glu(OH.DCHA)-OBzl (249.13 g, 523 mmol) in ethyl acetate (1.75 dm<sup>3</sup>). The two-phase mixture was stirred vigorously for 3 hours. The layers were separated and the aqueous layer extracted with ethyl acetate (400 ml). The extract was combined with the organic layer then washed with water (800 ml) and brine (800 ml) before being dried (MgSO<sub>4</sub>). Removal of the solvent *in vacuo* gave a thick golden syrup which on trituration with petrol gave a white solid which was recrystallised from ethyl acetate/petrol to give the *title compound* as white crystals (152.05 g, 515 mmol, 98%), m.p.75-76 °C;  $[\alpha]^{20} = -25.6^{\circ}$  (c=0.71, MeOH); (Found: MH<sup>+</sup>, 296.11339. Calc. for C<sub>14</sub>H<sub>18</sub>NO<sub>6</sub>: MH<sup>+</sup>, 296.11340); (Found: C, 57.3%; H, 6.1%; N, 4.9%; C<sub>14</sub>H<sub>17</sub>NO<sub>6</sub> requires C, 57.0%; H, 5.8%; N, 4.7%);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 3440 br (acid OH), 2960 (CH), 1720 br (C=O), 1510 (amide II of urethane) and 1070 cm<sup>-1</sup>;  $\delta_{\text{H}}$ /ppm (200MHz, CDCl<sub>3</sub>) 1.93 - 2.21 (2H, m, Glu  $\beta$ -CH<sub>2</sub>), 2.36 - 2.45 (2H, m, Glu  $\gamma$ -CH<sub>2</sub>), 3.64 (3H, s, -OCH<sub>3</sub>), 4.43 (1H, m, Glu  $\alpha$ -CH), 5.15 (2H, s, benzyl CH<sub>2</sub>), 5.64 (1H, bd, J=8.2 Hz, Glu NH), 7.33 (5H, s, aromatic CH's), 10.30 (1H, bs, CO<sub>2</sub>H);  $\delta_{\text{C}}$ /ppm (50MHz, CDCl<sub>3</sub>) 27.09, 29.66 (Glu CH<sub>2</sub>'s), 52.32 (CH<sub>3</sub>), 53.13 (Glu  $\alpha$ -CH), 67.20 (benzyl CH<sub>2</sub>), 127.22, 127.41, 128.11, 128.35, 128.45 (aromatic CH's), 134.93 (aromatic quat.C), 156.64, 171.71 and 177.55 (carbonyl C's); m/z (FAB) 296, 278, 250, 188 and 160.

$\alpha$ -Benzyl- $\gamma$ -*tert*-butyl-*N*-methoxycarbonyl-*L*-glutamate [142] (MOC-Glu-(*O**t*-Bu)-OBzl)

Isobutene (*circa* 100 ml) was condensed into a conical flask cooled by a dry ice/acetone bath. The isobutylene was then poured quickly into a re-sealable bottle containing a solution of MOC-Glu-OBzl (28.64 g, 97 mmol) in dry dichloromethane (250 ml) which had been cooled to -78 °C (dry ice/acetone). Concentrated sulphuric acid (2 ml) was added along with cuprous chloride (500 mg) and the bottle was sealed and allowed to warm to room temperature before standing, with occasional swirling, for 10 days. The reaction vessel was cooled to -78 °C then opened. Aqueous sodium carbonate (1M; 80ml) was added and the vessel allowed to attain room temperature then left overnight so that the excess isobutene would evaporate. The organic layer was separated and dried

(MgSO<sub>4</sub>) then the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (250 ml), washed with water (100 ml), and dried (MgSO<sub>4</sub>). Removal of the solvent *in vacuo* gave the *title compound* as a pale yellow oil which could not be crystallised (30.59 g, 87.1 mmol, 90%),  $[\alpha]^{20} = -26.7^\circ$  (c=0.24, MeOH); (Found: MH<sup>+</sup>, 352.17600); (Found: C, 61.9%; H, 7.6%; N, 3.8%. C<sub>18</sub>H<sub>25</sub>NO<sub>6</sub> requires C, 61.5%; H, 7.2%; N, 4.0%);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 3430 (NH), 2980 (CH), 1730 br (C=O) and 1510 (amide II of urethane) cm<sup>-1</sup>,  $\delta_{\text{H}}$ /ppm (200MHz, CDCl<sub>3</sub>) 1.37 (9H,s,*t*-butyl), 1.90-2.07 (2H,m,Glu β-CH<sub>2</sub>), 2.15-2.25 (2H,m,Glu γ-CH<sub>2</sub>), 3.59 (3H,s,-OCH<sub>3</sub>), 4.36 (1H,m,Glu α-CH), 5.11 (2H,s,benzyl CH<sub>2</sub>), 5.70 (1H,br d, J=8.3 Hz, -NH), 7.29 (5H,s,aromatic CH's);  $\delta_{\text{C}}$ /ppm (50MHz, CDCl<sub>3</sub>) 27.19, 31.08 (Glu β- and γ-CH<sub>2</sub>'s), 27.72 (*t*-butyl CH<sub>3</sub>'s), 52.00 (-OCH<sub>3</sub>), 53.26 (Glu α-CH), 66.87 (benzyl CH<sub>2</sub>), 80.39 (*t*-butyl quat.C), 127.95, 128.13, 128.30 (aromatic CH's), 135.04 (aromatic quat.C), 156.36, 171.67, 171.78 (C=O's), m/z (FAB) 352, 296, 278, 261, 206, 188 and 160.

*γ-tert*-Butyl-*N*-methoxycarbonyl-L-glutamate [143]

(MOC-Glu-(*Ot*-Bu)-OH)

METHOD A

Aqueous sodium hydroxide (1M; 370 ml, 370 mmol) was added dropwise to a stirred solution of MOC-Glu-(*Ot*-Bu)-OBzl (126.81 g, 361 mmol) in acetone (600 ml) during 20 minutes. The reaction mixture was stirred for a further 30 minutes before the acetone was removed *in vacuo*. The residual aqueous liquors were washed with ether (2 x 200 ml), cooled to 0 °C in an ice bath, then acidified to pH 4.0 with 1M HCl(aq). The aqueous solution was extracted with ethyl acetate (3 x 600 ml) and the combined extracts were washed with water (2 x 250 ml) and brine (300 ml) before being dried (MgSO<sub>4</sub>). Removal of the solvent *in vacuo* gave a golden syrup which crystallised on trituration with petrol to give the *title compound* as a white solid which was recrystallised from ethyl acetate/petrol (79.35 g, 304 mmol, 82%), m.p. 58 °C;  $[\alpha]^{20} = -6.87^\circ$  (c=1.21, MeOH); (Found: MH<sup>+</sup>, 262.12904. Calc. for C<sub>11</sub>H<sub>20</sub>NO<sub>6</sub>: MH<sup>+</sup>, 262.12905); Found: C, 50.3%; H, 7.4%; N, 5.6%. C<sub>11</sub>H<sub>19</sub>NO<sub>6</sub> requires C, 50.6%; H, 7.4%; N, 5.4%);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 3430 (NH), 1725 br (C=O), 1510 (amide II of urethane) and 1060 cm<sup>-1</sup>;  $\delta_{\text{H}}$ /ppm (200MHz, CDCl<sub>3</sub>) 1.41 (9H,s,*t*-butyl), 1.92 - 2.24 (2H,m,Glu β-CH<sub>2</sub>), 2.27 - 2.39 (2H,m,Glu γ-CH<sub>2</sub>), 3.65 (3H,s,-OCH<sub>3</sub>), 4.29 (1H,m,Glu α-

CH), 5.62 (1H, br d, J=8 Hz, Glu NH), 8.94 (1H, br s, CO<sub>2</sub>H);  $\delta_C$ /ppm (50MHz, CDCl<sub>3</sub>) 27.06, 30.98 (Glu  $\beta$ - and  $\gamma$ -CH<sub>2</sub>'s), 27.72 (*t*-butyl CH<sub>3</sub>'s), 52.29 (OCH<sub>3</sub>), 52.86 (Glu  $\alpha$ -CH), 80.92 (*t*-butyl quat.C), 157.35, 172.41, 175.27 (C=O's); m/z (FAB) 262, 246, 188 and 160.

#### METHOD B

A solution of MOC-Glu-(*Ot*-Bu)-OBzl (2.153 g, 6.1 mmol) in 10% water-methanol (35 ml) was cooled to -78 °C (dry ice/acetone) and 10% palladium on charcoal (215.3 mg) was added slowly with gentle swirling of the flask. The reaction mixture was stirred vigorously under a hydrogen atmosphere at room temperature and atmospheric pressure for 12 hours. The black suspension was filtered through a 1cm pad of Celite and this was washed with methanol (20 ml). The filtrate and washings were combined then poured into aqueous sodium bicarbonate (1M; 80ml). The aqueous solution was extracted with ether (2 x 50ml), cooled in ice and acidified to pH 4.0 with 2M HCl(aq) before being extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with water (60 ml), brine (60 ml) and dried (MgSO<sub>4</sub>). Removal of the solvent *in vacuo* gave a golden syrup which crystallised on trituration with petrol to give a white solid which was recrystallised from ethyl acetate/petrol to afford the *title compound* as white crystals (1.190 g, 4.6 mmol, 75%), m.p. 57-58 °C;  $[\alpha]^{20}_D = -7.1^\circ$  (c=0.62, MeOH); (Found: MH<sup>+</sup>, 262.12905. Calc. for C<sub>11</sub>H<sub>20</sub>NO<sub>6</sub>: MH<sup>+</sup>, 262.12905); (Found: C, 50.5%; H, 7.2%; N, 5.2%. C<sub>11</sub>H<sub>19</sub>NO<sub>6</sub> requires C, 50.6%; H, 7.4%; N, 5.4%);  $\nu_{max}$  (CH<sub>2</sub>Cl<sub>2</sub>) 3430 (NH), 1725 br (C=O), 1510 (amide II of urethane) and 1060 cm<sup>-1</sup>;  $\delta_H$ /ppm (200MHz, CDCl<sub>3</sub>) 1.39 (9H, s, *t*-butyl), 1.81-2.23 (2H, m, Glu  $\beta$ -CH<sub>2</sub>), 2.26 - 2.44 (2H, m, Glu  $\gamma$ -CH<sub>2</sub>), 3.64 (3H, s, OCH<sub>3</sub>), 4.32 (1H, m, Glu  $\alpha$ -CH), 5.6 (1H, br d, J=7.1 Hz, NH), 9.3 (1H, br s, CO<sub>2</sub>H); m/z (FAB) 262, 246, 188 and 160.

#### $\gamma$ -*tert*-Butyl-*N*-methyl-*N*-methoxycarbonyl-*L*-glutamate.

#### cyclohexylamine salt [144] (MOC(Me)-Glu-(*Ot*-Bu)-OH.CHA)

Methyl iodide (distilled, 88.30 g, 0.62 mol) was added to a solution of MOC-Glu-(*Ot*-Bu)-OH (20.29 g, 77.7 mmol) in anhydrous tetrahydrofuran (200 ml) and this mixture was cooled in an ice bath and stirred rapidly. Sodium hydride (50% w/w in oil; 11.18 g, 233 mmol) was added in small portions (so as to avoid very rapid evolution of hydrogen) and the reaction was stirred at room

temperature under nitrogen for 6 days. Ethyl acetate (200 ml) and water (40 ml, carefully) were added to the stirred reaction mixture then the organic solvents were removed *in vacuo*. The aqueous residues were partitioned between water (300 ml) and ether (200 ml). The layers were separated, the ethereal layer being extracted with 5% w/v aqueous sodium bicarbonate (200 ml). The aqueous portions were combined, cooled in ice and acidified carefully to pH 3.0 with 2M HCl(aq). The acidic liquors were immediately extracted with ethyl acetate (4 x 250 ml) and the combined extracts were washed with water (200 ml), 5% w/v aqueous sodium thiosulphate (2 x 300 ml), water (200 ml) and brine (200 ml). The organics were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a golden syrup (7.776 g).

The viscous syrup was dissolved in dry ether (35 ml) and the solution cooled in ice before cyclohexylamine (2.796 g, 28.2 mmol) was added dropwise. Petrol (45 ml) was added to the stirred reaction mixture, which was allowed to attain room temperature and stirred overnight for 16 hours. The white precipitate which had formed was collected by filtration then washed several times with dry ether. The resultant white solid was recrystallised from ethyl acetate/petrol to give the *title compound* as white crystals (5.912 g, 15.8 mmol, 20%), m.p. 109-111 °C;  $[\alpha]^{20} = -16.8^\circ$  (c=0.72, CHCl<sub>3</sub>); (Found: MOC(Me)-Glu-(Ot-Bu)-O<sup>-</sup>, 274.12876. Calc. for C<sub>12</sub>H<sub>20</sub>NO<sub>6</sub>, MOC(Me)-Glu-(Ot-Bu)-O<sup>-</sup>, 274.12877); (Found: C,57.4%; H,9.2%; N,7.4%. C<sub>18</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub> requires C,57.7%; H,9.1%; N,7.5%);  $\nu_{\max}$  (CH<sub>2</sub>Cl<sub>2</sub>) 2950 (CH), 1730 br (C=O) and 900 cm<sup>-1</sup>;  $\delta_{\text{H}}$ /ppm (200MHz, CDCl<sub>3</sub>) 1.07 - 1.31 (6H,m,cyclohexyl  $\beta$ - and  $\gamma$ -CH<sub>2</sub>'s), 1.36 (9H,s,t-butyl), 1.54 - 1.91 (6H,m,cyclohexyl  $\alpha$ -CH<sub>2</sub>'s and Glu  $\beta$ -CH<sub>2</sub>), 2.10 - 2.19 (2H,m,Glu  $\gamma$ -CH<sub>2</sub>), [2.73, 2.74] (3H, split due to rotational isomerism, NCH<sub>3</sub>), 2.80 - 2.87 (1H,m,cyclohexyl CH), [3.58, 3.60] (3H, split due to rotational isomerism, OCH<sub>3</sub>), 4.30 - 4.33 (1H,m,Glu  $\alpha$ -CH), 7.75 (3H,br s,NH<sub>3</sub><sup>+</sup>);  $\delta_{\text{C}}$ /ppm (50MHz, CDCl<sub>3</sub>) [24.29, 24.66], [30.36, 30.86] (split due to rotational isomerism Glu  $\beta$ - and  $\gamma$ -CH<sub>2</sub>'s) 25.24, 25.66, 28.61 (cyclohexyl CH<sub>2</sub>'s), 27.86 (t-butyl CH<sub>3</sub>'s), 31.42 (Glu  $\alpha$ -CH), 49.92 (cyclohexyl CH), 52.28 (OCH<sub>3</sub>), [60.20, 60.59] (split due to rotational isomerism NCH<sub>3</sub>), 79.84 (t-butyl quat.C), [157.39, 157.50] (split due to rotational isomerism MOC C=O), 172.28, 176.40 (C=O's); m/z (FAB) 274, 256, 218, 200 and 107.

$\gamma$ -tert-Butyl-N-methyl-N-methoxycarbonyl-L-glutamate [145](MOC(Me)-Glu-(Ot-Bu)-OH)

A solution of citric acid (2.749 g, 13 mmol) in water (30 ml) was added dropwise to a rapidly stirred slurry of MOC(Me)-Glu-(Ot-Bu)-OH.CHA (4.417 g, 11.8 mmol) in ethyl acetate (80 ml) and the biphasic mixture was stirred for 3 hours at room temperature. The layers were separated, the aqueous liquors being extracted with ethyl acetate (50ml). The organics were combined then washed with water (2 x 100 ml), brine (100 ml) and dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo* and the resultant golden syrup was triturated with petrol to induce solidification. The solid was recrystallised from ether/petrol to give the *title compound* as white crystals (3.067 g, 11.1 mmol, 94%), m.p. 69-71 °C;  $[\alpha]^{20} = -24.2^{\circ}$  (c=0.98, CHCl<sub>3</sub>); (Found: MH<sup>+</sup>, 276.14471. Calc. for C<sub>12</sub>H<sub>22</sub>NO<sub>6</sub>: MH<sup>+</sup>, 276.14470); (Found: C, 52.2%; H, 7.7%; N, 5.1%. C<sub>12</sub>H<sub>21</sub>NO<sub>6</sub> requires C, 52.4%; H, 7.7%; N, 5.1%);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 3500 - 2800 br (CO<sub>2</sub>H), 2980 (CH), 1730 br (C=O), 1510 (amide II of urethane), 1065 and 850 cm<sup>-1</sup>;  $\delta_{\text{H}}$ /ppm (200MHz, CDCl<sub>3</sub>) 1.38 (9H,s,t-butyl), 1.90 - 2.07 (2H,m,Glu  $\beta$ -CH<sub>2</sub>), 2.17 - 2.24 (2H,m,Glu  $\gamma$ -CH<sub>2</sub>), [2.76, 2.79] (3H, split due to rotational isomerism, NCH<sub>3</sub>), [3.59, 3.62] (3H, split due to rotational isomerism, OCH<sub>3</sub>), 4.53 - 4.72 (1H,m,Glu  $\alpha$ -CH), 10.22 (1H, br s, CO<sub>2</sub>H);  $\delta_{\text{C}}$ /ppm (50MHz, CDCl<sub>3</sub>) [23.52, 23.75], (31.33, 31.74) (split due to rotational isomerism, Glu  $\beta$ - and  $\gamma$ -CH<sub>2</sub>'s), 27.74 (t-butyl CH<sub>3</sub>'s), [30.67, 30.95] (split due to rotational isomerism, Glu  $\alpha$ -CH), 52.95 (OCH<sub>3</sub>), [57.59, 57.89] (split due to rotational isomerism, NCH<sub>3</sub>), 80.63 (t-butyl quat.C), [156.79, 156.93], [171.74, 171.90], 175.02, 175.51] [split due to rotational isomerism, C=O's]; m/z (FAB) 276, 262, 220, 206 and 174.

(S)-4-[2'(tert-Butyloxycarbonyl)ethyl]-3-methyloxazolidine-2,5-dione [133]

MOC(Me)-Glu-(Ot-Bu)-OH (1.034 g, 3.76 mmol) was dissolved in freshly distilled thionyl chloride (6 ml) and the solution was stirred at 0 °C for 15 minutes before a pressure of *circa* 5 mm Hg was applied to the reaction vessel. The evacuated flask was warmed to 55 °C for 25 minutes then cooled to room temperature once all the volatile material had been removed. The flask was returned to atmospheric pressure and the residue dissolved in carbon tetrachloride (15 ml) then the solvent was removed *in vacuo*. The brown residue crystallised spontaneously and recrystallisation from dry ether/petrol gave the *title compound* as white crystals (713 mg, 2.93 mmol, 78%), m.p. 81-82 °C;

$[\alpha]^{20} = -51.6^{\circ}$  ( $c=1.16$ ,  $\text{CHCl}_3$ ); (Found: C,54.0%; H,6.9%; N,5.7%.  $\text{C}_{11}\text{H}_{17}\text{NO}_5$  requires C,54.3%; H,7.0%; N,5.8%);  $\nu$  max ( $\text{CH}_2\text{Cl}_2$ ) 2980 (CH), 1850, 1785, 1725 (cyclic anhydride and ester C=O's), 1155 and 975  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ /ppm (200MHz,  $\text{COCl}_2$ ) 1.44 (9H,s,*t*-butyl), 2.02 - 2.29 (2H,m,1'-CH<sub>2</sub>), 2.32 - 2.43 (2H,m,2'-CH<sub>2</sub>), 2.99 (3H,s,NCH<sub>3</sub>), 4.20 - 4.25 (1H,m,4-H);  $\delta_{\text{C}}$ /ppm (50MHz,  $\text{CDCl}_3$ ), 23.69, 29.09 (CH<sub>2</sub>'s), 28.41 (4-C), 59.96 (NCH<sub>3</sub>), 81.21 (*t*-butyl quat.C), 151.66, 168.29, 170.82 (C=O's); m/z (FAB) 236, 218, 174 and 162.

#### Methyl 3-methylisoxazole-5-acetate [148]

##### METHOD A

The required compound, prepared by the method of Micetich<sup>112</sup>, was obtained as a clear colourless liquid (11.34 g, 73 mmol, 86%), b.p. 70 °C/0.5 mm Hg (lit.<sup>112</sup>, 67 °C/0.2 mm Hg); (Found:  $\text{MH}^+$ , 156.16263. Calc. for  $\text{C}_7\text{H}_{10}\text{NO}_3$ :  $\text{MH}^+$ , 156.16264); (Found: C,53.9%; H,5.6%; N,8.9%.  $\text{C}_7\text{H}_9\text{NO}_3$  requires C,54.2%; H,5.8%; N,9.0%);  $\nu$  max ( $\text{CH}_2\text{Cl}_2$ ) 2960 (CH), 1740 (C=O), 1610 (aromatic), 1440 and 1020  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ /ppm (80MHz,  $\text{CDCl}_3$ ) 2.19 (3H,s,3-CH<sub>3</sub>), 3.65 (3H,s,OCH<sub>3</sub>), 3.70 (2H,s,CH<sub>2</sub>), 6.02 (1H,s,4-H); m/z (FAB) 156, 115, 97, 83 and 69.

##### METHOD B

A solution of 3,5-dimethylisoxazole (29.133 g, 300 mmol) in dry tetrahydrofuran (300 ml) was cooled to -78 °C (dry-ice/acetone) under an argon atmosphere. *n*-Butyllithium (1.6M in hexanes; 187.5 ml, 300 mmol) was added slowly through a double-ended needle and the resultant yellow solution stirred for 30 minutes before dry carbon dioxide gas was passed through the reaction mixture at a steady rate for 2 hours whilst the flask returned to room temperature. The solvent was removed *in vacuo* and the residual yellow solid was dissolved in water (500 ml). The aqueous solution was extracted with ether (2 x 250 ml), cooled in ice, and acidified carefully to pH 1.5 with 2M HCl (aq) before being extracted with ethyl acetate (4 x 200 ml). The extracts were dried ( $\text{MgSO}_4$ ) then the solvent was removed *in vacuo* to give a brown solid which was dissolved in 50% methanol/water (60 ml). This solution was titrated to pH 7 with 20% w/w aqueous caesium carbonate. The solvents were then removed *in vacuo* leaving a thick brown sludge from which a precipitate formed upon the addition of dimethylformamide. A solid was obtained on removal of

the solvent *in high vacuo* and the caesium salt was partially dissolved in dry dimethylformamide (100 ml) then methyl iodide (37.3 ml, 85.16 g, 0.6 mol) was added to the stirred slurry. Complete dissolution of the solids occurred after 5 minutes and, after 10 minutes, a white precipitate (CsI) had formed. The reaction was stirred for 2 hours then the solvent was removed *in vacuo* at 50 °C to leave a brown residue which was partitioned between water (600ml) and ethyl acetate (300 ml). The aqueous layer was extracted with ethyl acetate (2x250ml) and the combined organic portions were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a brown liquid which was distilled to yield the *required compound* as a clear colourless liquid (38.63 g, 249 mmol, 83%), b.p.69-71% °C/0.5 mm Hg (lit.<sup>112</sup>, 67 °C/0.2 mm Hg); (Found: MH<sup>+</sup>, 156.16263. Calc for C<sub>7</sub>H<sub>10</sub>NO<sub>3</sub>: MH<sup>+</sup>, 156.16264); (Found: C,54.1%; H,5.5%; N,8.8%. C<sub>7</sub>H<sub>9</sub>NO<sub>3</sub> requires C,54.2%; H,5.8%; N,9.0%);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 2960 (CH), 1740 (C=O), 1610 (aromatic), 1440 and 1020 cm<sup>-1</sup>;  $\delta$ <sub>H</sub>/ppm (200MHz, CDCl<sub>3</sub>) 2.14 (3H,s,3-CH<sub>3</sub>), 3.61 (3H,s,OCH<sub>3</sub>), 3.66 (2H,s,CH<sub>2</sub>), 5.99 (1H,s,4-H);  $\delta$ <sub>C</sub>/ppm (50MHz, CDCl<sub>3</sub>) 10.91 (3-CH<sub>3</sub>), 32.03 (CH<sub>2</sub>), 52.07 (OCH<sub>3</sub>), 103.70 (4-C), 159.60, 164.43 (3-C and 5-C), 167.76 (C=O); m/z (FAB) 156, 115, 97, 83 and 69.

(5S)-5-[2'-(*tert*-Butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-methylisoxazole)]tetramic acid [120]

Lithium diisopropylamide (1.5M in cyclohexane; 5.35 ml, 8 mmol) was stirred in dry tetrahydrofuran (35 ml) under argon and this solution was cooled to -78<sup>o</sup> (dry ice/acetone). A solution of methyl 3-methylisoxazole-5-acetate (1.24 g, 8 mmol) in dry tetrahydrofuran (15 ml) was added dropwise followed by *N,N,N',N'*-tetramethylethylenediamine (1.21 ml, 929 mg, 8 mmol) the resultant yellow reaction mixture being stirred for 30 minutes. (4S)-4-[2'-(*tert*-Butyloxycarbonyl)ethyl]-3-methyloxazolidine-2,5-dione (1.06 g, 4 mmol) was dissolved in dry tetrahydrofuran (10 ml) and this solution was added dropwise to the reaction mixture which subsequently was stirred for a further 4 hours at -78 °C and then allowed to warm to room temperature during a further 2 hour period. Removal of the solvents *in vacuo* gave a pale yellow gum which was partitioned between ether (50 ml) and water (50 ml). The layers were separated, the aqueous being extracted with ether (50ml) before it was cooled in ice and carefully acidified to pH 1.0 with 2M HCl(aq). A precipitate formed on standing and this was filtered off, washed quickly with ether (15 ml) and dried *in vacuo* overnight to afford the *title compound* as white crystals (670

mg, 2.08 mmol, 52%), m.p. 153-154 °C;  $[\alpha]^{20} = -69.4^{\circ}$  ( $c=0.17$ , MeOH); (Found:  $MH^+$ , 323.16066. Calc. for  $C_{16}H_{23}N_2O_5$ :  $MH^+$ , 323.16068); (Found: C,59.2%; H,7.1%; N,8.5%.  $C_{16}H_{22}N_2O_5$  requires C,59.6%; H,6.9%; N,8.7%);  $\lambda$  max (CH<sub>3</sub>CN) 243 nm ( $\epsilon$  11600), 272 nm ( $\epsilon$  14300),  $\lambda$  max (CH<sub>3</sub>CN + 1 drop 1M NaOH(aq)) 218 nm ( $\epsilon$  7400), 272 nm ( $\epsilon$  17650), 303 nm ( $\epsilon$  19950);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 2980 (CH), 1715, 1690 (ester and amide C=O's), 1610 (aromatic) and 1150  $cm^{-1}$ ;  $\delta_H/ppm$  (200MHz, CDCl<sub>3</sub>) 1.40 (9H,s,t-butyl), 2.12 - 2.28 (4H,m,CH<sub>2</sub>'s), 2.34 (3H,s,3"-CH<sub>3</sub>), 2.95 (3H,s,NCH<sub>3</sub>), 4.05 - 4.08 (1H,m,5-H), 6.66 (1H,s,isoxazole 4"-H);  $\delta_C/ppm$  (50MHz, CDCl<sub>3</sub>) 11.05 (3"-CH<sub>3</sub>), 23.38, 28.49 (CH<sub>2</sub>'s), 26.65 (5-C), 27.92 (t-butyl CH<sub>3</sub>'s), 60.34 (NCH<sub>3</sub>), 80.74 (t-butyl quat.C), 97.00 (3-C), 100.61 (4"-C), 159.83, 162.45 (3"- and 5"-C's), 168.06, 169.78, 171.92 (4-C and C=O's); m/z (FAB) 645, 323, 267 and 98.

#### Ethyl (E)-4-methylpent-2-enoate [154]

Freshly distilled isobutyraldehyde (72.11 g, 1 mol) was added to a solution of carboethoxymethylidinetriphenylphosphorane (279.31 g, 0.8 mol) in dry dichloromethane (500 ml). The reaction mixture was stirred for 18 hours overnight then concentrated *in vacuo* to a volume of *circa* 200 ml. The liquors were diluted with petrol (600 ml) and the precipitated triphenylphosphine oxide filtered off and this process was repeated until removal of the solvent *in vacuo* gave a yellow liquid. Distillation of this crude product through a 15 cm Vigreux column gave the *title compound* as a clear, colourless liquid (84.18g, 0.59 mol, 74%), b.p. 55 °C/15mmHg; t.l.c.(A)  $R_f = 0.6$ ; (Found:  $M^+$ , 142.09937. Calc. for  $C_8H_{14}O_2$ :  $M^+$ , 142.09958);  $\lambda$  max (CH<sub>3</sub>CN) 207 nm ( $\epsilon$  14700);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 2980 (CH), 1730 (C=O), 1660 (C=C), 1045 and 870  $cm^{-1}$ ;  $\delta_H/ppm$  (200MHz,CDCl<sub>3</sub>) 1.06(6H,d,J=6.7Hz, 4-CH<sub>3</sub>'s), 1.24 (3H,t,J=7.2 Hz, ester CH<sub>3</sub>), 2.40 (1H,m,4-H), 4.09 (2H,q, J=7.2 Hz, ester CH<sub>2</sub>), 5.74 (1H,dd, J=1.2,15.7 Hz, 2-H), 6.92 (1H,dd, J=6.7,15.7 Hz, 3-H);  $\delta_C/ppm$  (50MHz, CDCl<sub>3</sub>) 14.11 (ester CH<sub>3</sub>), 21.01 (4-CH<sub>3</sub>'s), 59.95 (ester CH<sub>2</sub>), 118.39, 155.16 (C-2, C-3), 166.81 (C=O); m/z (EI) 142, 114, 99, 97, 81 and 69.

#### (E)-4-Methylpent-2-en-1-ol [155]

Diisobutylaluminium hydride (1M in dichloromethane; 500 ml, 0.5 mol) was added slowly (*via cannula*) to a solution of ethyl-(E)-4-methylpent-2-enoate (28.44 g, 0.2 mol) in dry



dichloromethane (100 ml) under an atmosphere of argon and maintained at a temperature of  $-78\text{ }^{\circ}\text{C}$  (dry ice/acetone). The reaction was stirred at this temperature for 3 hours then 2M HCl(aq) (200 ml) was added very slowly over a period of 1 hour and the mixture was allowed to attain room temperature overnight. The layers were separated, the organic layer being washed with brine (300 ml) then dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to leave an oil. The oil was distilled to give the *required compound* as a clear, colourless liquid (18.23 g, 182 mmol, 91%); b.p.  $67\text{ }^{\circ}\text{C}/18\text{ mm Hg}$  (lit.<sup>135</sup>,  $65\text{ }^{\circ}\text{C}/20\text{ mm Hg}$ ); (Found:  $\text{M}^+$ , 100.08885. Calc. for  $\text{C}_6\text{H}_{12}\text{O}$ :  $\text{M}^+$ , 100.08881);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ ) 3350 br (OH), 2980 (CH), 1660 (C=C), 1460 and  $970\text{ cm}^{-1}$ ;  $\delta_{\text{H}}/\text{ppm}$  (200MHz,  $\text{CDCl}_3$ ) 0.93 (6H,d,J=7 Hz, 4- $\text{CH}_3$ 's), 2.25 (1H,m,4-H), 2.45 (1H,br s,exc.  $\text{D}_2\text{O}$ , OH), 3.99 (2H,m,1- $\text{CH}_2$ ), 5.53 (2H,m,2-H and 3-H);  $\delta_{\text{C}}/\text{ppm}$  (50MHz,  $\text{CDCl}_3$ ) 21.95 (4- $\text{CH}_3$ 's), 30.40 (4-C), 63.29 (1-C), 125.71, 139.71 (2-C and 3-C); m/z (EI) 100, 93, 69, 57 and 32.

(2S, 3S) 2,3-Epoxy-4-methylpentan-1-ol [157]

An oven dried flask was filled with argon and charged with anhydrous dichloromethane (500 ml), powdered 4A molecular sieves (2.60 g) then cooled to  $-23\text{ }^{\circ}\text{C}$  (dry ice/ $\text{CCl}_4$ ). Titanium tetraisopropoxide (3.87 ml, 13 mmol) and *L*-(+)-diethyltartrate (3.48 g, 16.9 mmol) in anhydrous dichloromethane (20 ml) were added *via* syringe and the mixture stirred for 10 minutes before the addition of (E)-4-methylpent-2-en-1-ol (13.00 g, 130 mmol) in anhydrous dichloromethane (15 ml). The mixture was stirred for 30 minutes to allow the catalyst to form and then age, before a solution of *tert*-butylhydroperoxide (2.74M in isooctane, anhydrous, freshly prepared according to the method of Sharpless<sup>120</sup>; 71.2 ml, 195 mmol) was added *via* double-ended needle at such a rate that no temperature increase in the reaction flask occurred. The reaction was stirred at  $-23\text{ }^{\circ}\text{C}$  for 2 hours then stored in a freezer at  $-20\text{ }^{\circ}\text{C}$  for 24 hours. The flask was cooled to  $-23\text{ }^{\circ}\text{C}$  (dry ice/ $\text{CCl}_4$ ) then dimethylsulphide (38 ml, 0.52 mol) was added *via* syringe and the mixture stirred for 1 hour. The cold (*circa*  $0^{\circ}$ ) reaction mixture was then poured into a saturated aqueous solution of sodium fluoride (108 g in  $1.2\text{ dm}^3\text{ H}_2\text{O}$ ) and the two-phase system was stirred for 24 hours at room temperature. Sodium chloride (75 g) was added to saturate the aqueous layer and the two-phase mixture was filtered through a 1 cm **Celite** pad. The layers were separated, the aqueous being extracted with dichloromethane (3 x 400 ml) and the combined organic liquors were dried

(Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent *in vacuo* gave 18.661 g of crude product containing dimethylsulphoxide and *L*-(+)-diethyl tartrate. Kugelrohr distillation (b.p. 95 °C/18 mm Hg) gave a mixture of the epoxide and dimethylsulphoxide which was purified by flash column chromatography (SiO<sub>2</sub>/ether) to give the *title compound* as a clear colourless liquid (10.52 g, 90.5 mmol, 70%); b.p. 95 °C/18 mm Hg; t.l.c.(A) R<sub>f</sub> = 0.30; [α]<sup>20</sup> = -34.8° (c=1.02, CHCl<sub>3</sub>); (Found: MH<sup>+</sup>, 117.09154. Calc. for C<sub>6</sub>H<sub>13</sub>O<sub>2</sub>: MH<sup>+</sup>, 117.09155); (Found): C,61.8%; H,10.2%. C<sub>6</sub>H<sub>12</sub>O<sub>2</sub> requires C,62.0%; H,10.4%); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3420br (OH), 2980 (CH), 1460 (OH bend), 1065 and 895 cm<sup>-1</sup>; δ<sub>H</sub>/ppm (200MHz, CDCl<sub>3</sub>) 0.92 (3H,d,J=7.0 Hz,CH<sub>3</sub>), 0.97 (3H,d,J=7.0 Hz,CH<sub>3</sub>), 1.50 (1H,m,4-H), 2.69 (1H,d of d,J=2.5,7.0 Hz,3-H), 2.80 (1H,br s,OH), 2.93 (1H,m,2-H), 3.46 - 3.89 (2H,ABX,J=5.0,15.0 Hz,CH<sub>2</sub>); δ<sub>C</sub>/ppm (50MHz,CDCl<sub>3</sub>) 18.12, 18.77 (4-CH<sub>3</sub>'s), 29.85 (4-C), 57.58 (3-C), 61.09 (2-C), 61.83 (CH<sub>2</sub>); m/z (FAB) 117, 99, 79 and 58.

#### (2R,3S)-2,4-Dimethylpentan-1,3-diol [161]

Copper(I)Iodide (which had been extracted with tetrahydrofuran in a Soxhlet apparatus then dried thoroughly *in vacuo* at 100 °C; 74.10 g, 390 mmol) was suspended in anhydrous ether (400 ml) under argon and the magnetically stirred slurry was cooled to -45 °C (dry ice/MeCN). Methylolithium (1.4M in ether; 537 ml, 780 mmol) was added slowly (double-ended needle) to the suspension. A yellow colour was observed immediately, then the mixture was stirred for 30 minutes at -45 °C before the addition of (2S,3S)-2,3-epoxy-4-methylpentan-1-ol (6.00 g, 51.6 mmol) in anhydrous ether (60 ml) over 15 minutes. The reaction mixture was stirred at -45 °C and quenched by the careful addition of a mixture of saturated aqueous ammonium chloride (270 ml) and concentrated aqueous ammonia solution (30 ml) over a period of 1 hour then allowed to warm to room temperature over a further 1 hour. The layers were separated, the aqueous being extracted with ether (3 x 500 ml), and the combined organic liquors were washed with brine (750 ml) then dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo* to afford 5.992 g of a yellow oil which was purified by flash column chromatography (SiO<sub>2</sub>/ether) to give the *title compound* as a cream coloured waxy solid (5.592 g, 42.3 mmol, 82%), m.p. 50-52 °C; t.l.c. (A) R<sub>f</sub> = 0.2; [α]<sup>20</sup> = -20.8° (c=1.40, CHCl<sub>3</sub>); (Found: MH<sup>+</sup>, 133.12285. Calc. for C<sub>7</sub>H<sub>17</sub>O<sub>2</sub>: MH<sup>+</sup>, 133.12285); (Found: C,63.5%; H,12.2% . C<sub>7</sub>H<sub>16</sub>O<sub>2</sub> requires C,63.6%;H,12.2%); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3420 br (OH), 2960

(CH) and  $1070\text{ cm}^{-1}$ ;  $\delta_{\text{H}}/\text{ppm}$  (200MHz,  $\text{CDCl}_3$ ) 0.83 (3H,d,J=7.0 Hz,4- $\text{CH}_3$ ), 0.89 (3H,d,J=7.0 Hz,4- $\text{CH}_3$ ), 0.93 (3H,d,J=7.0 Hz, 3- $\text{CH}_3$ ), 1.79 (2H,m,2-H,4-H), 3.28 (1H,d of d,J=4.0,7.0 Hz,3-H), 3.56 - 3.71 (2H,AB q, $\text{CH}_2$ ). 3.80 (2H, br s, OH's);  $\delta_{\text{C}}/\text{ppm}$  (50MHz, $\text{CDCl}_3$ ) 13.69, 14.84 (4- $\text{CH}_3$ 's), 19.69 (2- $\text{CH}_3$ ), 30.10 (4-C), 36.88 (2-C), 67.75 ( $\text{CH}_2$ ), 81.61 (3-C); m/z (FAB) 133, 117, 103, 97 and 75.

(2R,3S)-3-Hydroxy-2,4-dimethylpentyl benzoate [163]

Distilled benzoyl chloride (2.33 g,16.6 mmol) in dry pyridine (30 ml) was added to a solution of (2R,3S)-2,4-dimethylpentan-1,3-diol (2.00 g, 15.1 mmol) in dry pyridine (40 ml) which had been cooled in ice. The mixture was stirred at room temperature for 18 hours overnight under a nitrogen atmosphere then the cloudy suspension was poured into cold 10% HCl(aq) (1 dm<sup>3</sup>) and shaken with ether (600 ml). The layers were separated and the aqueous extracted with ether (3 x 100 ml) and the combined organics were washed with brine (150 ml) then dried ( $\text{MgSO}_4$ ). The solvent was removed *in vacuo* to afford 3.795 g of a yellow oil which was purified by dry flash chromatography ( $\text{SiO}_2$ /petrol - 50% ether/petrol gradient) to give the *title compound* as a clear colourless liquid (2.916 g,12.3 mmol,81%), b.p.  $120\text{ }^\circ\text{C}/1.0\text{ mm Hg}$ ; t.l.c. (C)  $R_f = 0.4$ ;  $[\alpha]^{20} = +8.3^\circ$  (c=1.52, $\text{CHCl}_3$ ); (Found:  $\text{MH}^+$ , 237.14905. Calc. for  $\text{C}_{14}\text{H}_{21}\text{O}_3$ :  $\text{MH}^+=237.14906$ ); Found: C,70.9%; H,8.3%.  $\text{C}_{14}\text{H}_{20}\text{O}_3$  requires C,71.2%; H,8.5%;  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ ) 3480 br (OH), 3070 (aromatic CH), 2960 (CH), 1710 (C=O), 1605 (aromatic C=C) and  $710\text{ cm}^{-1}$ ;  $\delta_{\text{H}}/\text{ppm}$  (200MHz,  $\text{CDCl}_3$ ) 0.87 - 1.04 (9H, 3 x d, J=6.7 Hz, 3- $\text{CH}_3$  and 4- $\text{CH}_3$ 's), 1.79 - 1.88 (1H,m,4-H), 2.00 - 2.12 (1H,m,2-H), 2.36 (1H,br s,OH), 3.22 - 3.28 (1H,d of d,J=4.2, 7.8 Hz, 3-H), 4.44 (2H,d,J=5.2 Hz,  $\text{CH}_2$ ), 7.34 - 7.56 (3H,m, $\text{H}_b$  and  $\text{H}_c$  of aromatic), 7.99 - 8.06 (2H,m, $\text{H}_a$  of aromatic);  $\delta_{\text{C}}/\text{ppm}$  (50MHz,  $\text{CDCl}_3$ ) 14.32, 15.12 (4- $\text{CH}_3$ 's), 19.96 (2- $\text{CH}_3$ ), 29.71 (4-C), 36.13 (2-C), 67.17 ( $\text{CH}_2$ ), 77.50 (3-C), 128.19, 129.35, 132.75 (aromatic CH's), 130.07 (aromatic quat.C), 166.78 (C=O); m/z (FAB) 237, 219, 202, 181 and 165.

(2R,3S)-3-(tert-Butyldimethylsilyloxy)-2,4-dimethylpentyl benzoate [164]

Imidazole (recrystallised; 3.349 g, 49.2 mmol), *tert*-butyldimethylsilyl chloride (3.708 g, 24.6 mmol) and 4-dimethylamino pyridine (150 mg, 1.2 mmol) were dissolved in dry

dimethylformamide (10 ml) then a solution of (2R,3S)-3-hydroxy-2,4-dimethylpentyl benzoate (2.916 g, 12.3 mmol) in dry dimethylformamide (10 ml) was added to the mixture. The reaction mixture was stirred at 45 °C under nitrogen for 5 days, cooled to room temperature, diluted with water (60 ml) and extracted with petrol (5 x 50 ml). The combined organic extracts were washed in brine (50 ml) and dried (MgSO<sub>4</sub>) then concentrated *in vacuo* to give 5.760 g of a yellow liquid which was purified by dry flash chromatography (SiO<sub>2</sub>/10% ether-petrol) to give the *title compound* as a clear colourless liquid (4.032 g, 11.5 mmol, 93%), b.p. 143 °C/15 mm Hg; t.l.c. (E) R<sub>f</sub> = 0.35; [α]<sup>20</sup> = +15.4° (c=1.16, CHCl<sub>3</sub>); (Found: MH<sup>+</sup>, 351.58614. Calc. for C<sub>20</sub>H<sub>35</sub>O<sub>3</sub>Si: MH<sup>+</sup>, 351.58615); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3040 (aromatic CH), 2980 (CH), 1725 (C=O), 1605 (aromatic C=C), 1390 and 710 cm<sup>-1</sup>; δ<sub>H</sub>/ppm (200MHz, CDCl<sub>3</sub>) [0.03, 0.05] (6H, split due to diastereotopicity, Si CH<sub>3</sub>'s), 0.85 - 0.89 (6H, 2 x d, J=7.0 Hz, 4-CH<sub>3</sub>'s), 0.91 (9H, s, *t*-butyl), 0.96 (3H, d, J=7.0 Hz, 2-CH<sub>3</sub>), 1.75 - 1.90 (1H, m, 4-H), 1.94 - 2.17 (1H, m, 2-H), 3.40 - 3.46 (1H, d of d, J=4.2, 5.0 Hz, 3-H), 3.96 - 4.48 (2H, ABX, CH<sub>2</sub>), 7.24 - 7.51 (3H, m, H<sub>b</sub> and H<sub>c</sub> of aromatic), 7.97 - 8.09 (2H, m, H<sub>a</sub> of aromatic); δ<sub>C</sub> (50MHz, CDCl<sub>3</sub>) -4.10 (Si-CH<sub>3</sub>'s), 18.52 (*t*-butyl CH<sub>3</sub>'s), 29.86 (4-C), 36.36 (2-C), 66.87 (CH<sub>2</sub>), 78.02 (3-C), 127.91, 128.75, 132.43 (aromatic CH's), 131.18 (aromatic quat.C), 167.62 (C=O); m/z (FAB) 351, 293, 187, 185, 179, 105 and 97.

(2R,3S)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol [165]

A solution of (2R,3S)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentyl benzoate (4.032 g, 11.5 mmol) and potassium hydroxide (1.24 g, 22.1 mmol) in dry methanol (50 ml) was stirred under nitrogen at 40 °C for 16 hours overnight. The solvent was removed *in vacuo* and the residue partitioned between ether (100 ml) and saturated aqueous ammonium chloride (100 ml). The layers were separated, the aqueous being extracted with ether (2 x 60 ml) and the combined organic liquors were washed with brine (100 ml) and dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo* to give 3.097 g of a yellow oil which was purified by flash-column chromatography (SiO<sub>2</sub>/10% ether-petrol) to afford the *title compound* as a clear colourless oil (2.687 g, 10.9 mmol, 95%), b.p. 110 °C/18 mm Hg; [α]<sup>20</sup> = +6.6° (c=0.95, CHCl<sub>3</sub>); (Found: MH<sup>+</sup>, 247.20934. Calc. for C<sub>13</sub>H<sub>31</sub>O<sub>2</sub>Si: MH<sup>+</sup>, 247.20932); (Found: C, 63.2%; H, 12.1%. C<sub>13</sub>H<sub>30</sub>O<sub>2</sub>Si requires C, 63.3%; H, 12.3%); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3350 br (OH), 2960 (CH), 1460, 1250 and 770 cm<sup>-1</sup>; δ<sub>H</sub>/ppm (200MHz, CDCl<sub>3</sub>) [0.07 -

0.10] (6H, split due to diastereotopicity), 0.89 (3H,d,J=7.0 Hz, 4-CH<sub>3</sub>), 0.91 (9H,s,*t*-butyl), 0.94 (3H,d,J=7.0 Hz, 4-CH<sub>3</sub>), 0.98 (3H,d,J=7.0 Hz, 2-CH<sub>3</sub>), 1.80-1.85 (2H, overlapping multiplet, 2-H and 4-H), 2.61 (1H,br s,OH), 3.41 (1H,t,J=5.0 Hz,3-H), 3.57-3.63 (2H, ABX, CH<sub>2</sub>);  $\delta_C$ /ppm (50MHz, CDCl<sub>3</sub>) -4.07 (Si-CH<sub>3</sub>'s), 16.20, 18.21 (4-CH<sub>3</sub>'s), 18.97 (2-CH<sub>3</sub>), 26.04 (*t*-butyl CH<sub>3</sub>'s), 33.01 (4-C), 37.50 (2-C), 65.90 (CH<sub>2</sub>), 77.54 (*t*-butyl quat.C), 82.00 (3-C), m/z (FAB) 247, 229, 217, 203, 187, 133, 115 and 97.

(2R,3S)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpentanal [166]

(2R,3S)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol (1.179 g, 4.9 mmol) and *N*-methylmorpholine *N*-oxide (844 mg, 7.2 mmol) were dissolved in dry dichloromethane (20 ml) containing powdered 4A molecular sieves (500 mg). Tetra-*n*-propylammonium per-ruthenate (8.4 mg, 24.0  $\mu$ mol) was added and the mixture stirred under nitrogen for 16 hours overnight after which the reaction was diluted to a volume of 50 ml with dichloromethane. The solution was washed with aqueous sodium sulphite (50 ml), brine (50 ml) and aqueous copper sulphate (50 ml) then dried (MgSO<sub>4</sub>). Removal of the solvent *in vacuo* gave 1.286 g of a yellow oil which was purified by dry-flash chromatography (SiO<sub>2</sub>/10% ether-petrol) to give the *title compound* as a clear colourless oil (954 mg, 3.9 mmol, 81%) t.l.c. (E) R<sub>f</sub> = 0.86;  $[\alpha]^{20} = +32.4^{\circ}$  (c=0.99, CHCl<sub>3</sub>); (Found: MH<sup>+</sup>, 244.45289. Calc. for C<sub>13</sub>H<sub>28</sub>O<sub>2</sub>Si: MH<sup>+</sup>, 244.45291);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 2960, 2710 (CH), 1710 (C=O), 1460, 1360, 1220 and 840 cm<sup>-1</sup>;  $\delta_H$ /ppm (200MHz, CDCl<sub>3</sub>) [0.03, 0.05] (6H, split due to diastereotopicity, Si-CH<sub>3</sub>'s), 0.81 - 1.03 (15H,m,Si *t*-butyl CH<sub>3</sub>'s, 4-CH<sub>3</sub>'s), 1.09 (3H,d,J=7.0 Hz, 2-CH<sub>3</sub>), 1.85 (1H,m,4-H), 2.49 (1H,m,2-H), 3.62 (1H, overlapping d of d, 3-H), 9.72 (1H,d,J=3.0 Hz, CHO);  $\delta_C$ /ppm (50MHz, CDCl<sub>3</sub>) [-4.47, -4.30] (split due to diastereotopicity, Si-CH<sub>3</sub>'s), 14.57, 18.62 (4-CH<sub>3</sub>'s), 19.23 (2-CH<sub>3</sub>), 25.47 (*t*-butyl CH<sub>3</sub>'s), 32.61 (4-C), 49.70 (2-C), 77.56 (*t*-butyl quat.C), 79.97 (3-C), 204.61 (C=O); m/z (FAB) 244, 202, 187, 143, 129, 117 and 75.

Carbomethoxyethylidinetriphenylphosphorane [170]

Methyl-2-bromopropionate (100.10 g, 0.6 mol) was added to a solution of triphenylphosphine (78.60 g, 0.3 mol) in dry toluene (200 ml) and the stirred mixture was warmed to 50 °C and stirred for 18 hours. The mixture was allowed to cool to room temperature during 1 hour and the white solid was

collected by filtration and washed with ether (3 x 100 ml) then dried in a vacuum oven at 40 °C. The phosphonium salt was then dissolved in dichloromethane (500 ml) and the solution cooled in ice before aqueous sodium hydroxide (1M) was added dropwise until the phenolphthalein indicator remained pink. The layers were separated immediately, the aqueous layer being extracted with dichloromethane (2 x 150 ml), and the combined organic liquors were dried (MgSO<sub>4</sub>). Removal of the solvent *in vacuo* gave a yellow solid which was recrystallised from 50% ethyl acetate-petrol to yield the *required compound* as fine yellow crystals (89.38 g, 256 mmol, 85%), m.p. 149-151 °C (lit.<sup>124</sup>, m.p. 152-153 °C); (Found: MH<sup>+</sup>, 349.13575. Calc. for C<sub>22</sub>H<sub>22</sub>O<sub>2</sub>P: MH<sup>+</sup>, 349.13578); (Found: C,75.7%; H,5.9%. C<sub>22</sub>H<sub>21</sub>O<sub>2</sub>P requires C, 75.8%; H,6.1%; ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3040 (aromatic CH), 2980 (CH), 1700 (C=O), 1315, 1100 and 1000 cm<sup>-1</sup>; δ<sub>H</sub>/ppm (200MHz, CDCl<sub>3</sub>) 1.50-1.68 (3H,d,J=14.0 Hz, P-C-CH<sub>3</sub>), 3.30 (3H,s, OCH<sub>3</sub>), 7.37-7.73 (15H,m,aromatic CH's); m/z (FAB) 349, 333, 317, 289, 252, 183 and 165.

Methyl (2E:4R,5S)-5-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylhept-2-enoate [167]

Carbomethoxyethylidinetriphenylphosphorane (2.037 g,5.85 mmol) was added to a solution of (2R,3S)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylpentanal (954 mg, 3.9 mmol) in dry benzene (25ml) and the resulting yellow solution was refluxed under nitrogen for 5 days. The reaction volume was reduced *in vacuo* to *circa* 10 ml then diluted with petrol (30 ml). The white precipitate was filtered off, washed with petrol (50 ml), and the combined filtrate and washings were evaporated *in vacuo* to leave a yellow oil. This was purified by dry-flash chromatography (SiO<sub>2</sub>/10% ether-petrol) to give the *title compound* as a clear colourless oil (968 mg, 3.08 mmol, 79%), t.l.c. (D) R<sub>f</sub> = 0.40; [α]<sup>20</sup> = +7.6° (c=1.02, CHCl<sub>3</sub>); (Found: MH<sup>+</sup>, 315.23506. Calc. for C<sub>17</sub>H<sub>35</sub>O<sub>3</sub>Si: MH<sup>+</sup>, 315.23507); λ max (CH<sub>3</sub>CN) 225 nm (ε 6400); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 2960 (CH), 1710 (C=O), 1460, 1240 and 840 cm<sup>-1</sup>; δ<sub>H</sub>/ppm (200MHz, CDCl<sub>3</sub>) [0.01,0.03] (6H, split due to diastereotopicity, Si-CH<sub>3</sub>'s), 0.80 - 0.87 (6H, overlapping pair of doublets, 6-CH<sub>3</sub>'s), 0.91 (9H,s,*t*-butyl), 0.95 (3H,d,J=7.0 Hz, 4-CH<sub>3</sub>), 1.65 - 1.80 (1H,m,6-H), 1.84 (3H,s,2-CH<sub>3</sub>), 2.59 - 2.72 (1H,m,4-H), 3.33 - 3.36 (1H, overlapping d of d, 5-H), 3.69 (3H,s, OCH<sub>3</sub>), 6.81 (1H,d,J=10.0 Hz, 3-H); δ<sub>C</sub>/ppm (50MHz, CDCl<sub>3</sub>) -4.01 (Si-CH<sub>3</sub>'s), 12.30, 17.81, 18.24, 19.35 (6-CH<sub>3</sub>'s, 4-CH<sub>3</sub> and 3-CH<sub>3</sub>), 25.98 (Si *t*-butyl CH<sub>3</sub>'s), 32.48 (6-C), 36.64 (4-C), 51.41 (OCH<sub>3</sub>), 77.12 (*t*-butyl quat.C),

80.42 (5-C), 125.71 (2-C), 145.57 (3-C), 168.77 (C=O); m/z (FAB) 315, 300, 280, 263, 243, 183, 147 and 133.

(2E:4R,5S)-5-(tert-Butyldimethylsilyloxy)-2,4,6-trimethylhept-2-en-1-ol [178]

Diisobutylaluminium hydride (1M in dichloromethane; 13.25 ml, 13.25 mmol) was added to a solution of methyl (2E:4R,5S)-5-(tert-butyldimethylsilyloxy)-2,4,6-trimethylhept-2-enoate (1.681 g, 5.3 mmol) in dry dichloromethane (30 ml) which had been cooled to -78 °C (dry ice/acetone) under an argon atmosphere. The reaction mixture was stirred for 3 hours at -78°C before the reaction was quenched by the careful addition of water (5 ml) then allowed to warm to room temperature during 30 minutes. The mixture was transferred to a separating funnel containing saturated sodium potassium tartrate (250 ml) and dichloromethane (200 ml), shaken, then the layers were separated and the aqueous extracted with dichloromethane (4 x 300 ml). The combined organic liquors were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give 1.336 g of a yellow oil. This was purified by dry-flash chromatography (SiO<sub>2</sub>/petrol - 30% ether-petrol gradient) to give the *title compound* as a clear colourless liquid (1.048 g, 3.66 mmol, 69%), t.l.c.(B) R<sub>f</sub> = 0.38; [α]<sup>20</sup> = +4.7° (c=0.81, CHCl<sub>3</sub>); (Found: MH<sup>+</sup>, 287.22450. Calc. for C<sub>16</sub>H<sub>35</sub>O<sub>2</sub>Si: MH<sup>+</sup>, 287.22452); (Found: C,66.8%; H,12.2%. C<sub>16</sub>H<sub>34</sub>O<sub>2</sub>Si requires C,67.1%; H,12.0%); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3600 (OH), 2980 (CH), 1665 (C=C), 1460, 1050 and 840 cm<sup>-1</sup>; δ<sub>H</sub>/ppm (200MHz, CDCl<sub>3</sub>) [-0.02, 0.00] (6H, split due to diastereotopicity, Si CH<sub>3</sub>'s), 0.75 - 0.84 (6H, overlapping pair of doublets, 6-CH<sub>3</sub>'s), 0.91 (9H,s,*t*-butyl), 0.93 (3H, overlapping doublet, 4-CH<sub>3</sub>), 1.62 (3H,s,2-CH<sub>3</sub>), 1.66 - 1.78 (1H,m,6-H), 2.42 - 2.65 (1H,m,4-H), 3.28 (1H, overlapping d of d, J = 6.1, 6.1 Hz, 5-H), 3.50 (1H, br s, OH), 5.47 (1H, d, J=10.0 Hz, 3-H); δ<sub>C</sub>/ppm (50MHz, CDCl<sub>3</sub>) -4.01 (SiCH<sub>3</sub>'s), 13.61, 18.12, 18.51, 19.74 (6-CH<sub>3</sub>'s, 4-CH<sub>3</sub> and 2-CH<sub>3</sub>), 25.96 (*t*-butyl CH<sub>3</sub>'s), 32.17 (6-C), 35.79 (4-C), 68.85 (CH<sub>2</sub>), 77.01 (*t*-butyl quat.C.), 80.83 (5-C), 129.48, 132.98 (2-C, 3-C); m/z (FAB) 287, 269, 251, 225, 207, 187, 165 and 137.

(2E:4R,5S)-5-(tert-Butyldimethylsilyloxy)-2,4,6-trimethylhept-2-enal [179]

(2E:4R,5S)-5-(tert-Butyldimethylsilyloxy)-2,4,6-trimethylhept-2-en-1-ol (888 mg, 3.1 mmol) was dissolved in dry dichloromethane (20 ml) containing powdered 4A molecular sieves (500 mg). *N*-

Methylmorpholine *N*-oxide (545 mg, 4.65 mmol) and tetra-*n*-propylammonium per-ruthenate (5.4 mg, 15.5  $\mu$ mol) were then added to the solution and the resulting dark green reaction mixture was stirred at room temperature under a nitrogen atmosphere for 5 hours. The mixture was diluted with dichloromethane (50 ml) then washed with aqueous sodium sulphite (50 ml), brine (50 ml) and aqueous copper sulphate (50 ml) before being dried ( $\text{MgSO}_4$ ). Removal of the solvent *in vacuo* gave 799 mg of a green oil which was purified by dry-flash chromatography ( $\text{SiO}_2$ ) petrol - 20% ether-petrol, gradient) to give the *title compound* as a clear colourless oil (620 mg, 2.2 mmol, 71%), t.l.c. (E)  $R_f = 0.30$ ; (Found:  $\text{MH}^+$ , 285.20857. Calc. for  $\text{C}_{16}\text{H}_{33}\text{O}_2\text{Si}$ :  $\text{MH}^+$ , 285.20858);  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ ) 233 nm ( $\epsilon$  10000);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ ) 2960, 2700 (CH), 1680 (C=O), 1460, 1050 and 840  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}/\text{ppm}$  (200MHz,  $\text{CDCl}_3$ ) [-0.03, 0.04] (6H, split due to diastereotopicity, Si  $\text{CH}_3$ 's), 0.72 - 0.91 (15H, overlapping m, 6- $\text{CH}_3$ 's and *t*-butyl), 0.94 - 1.05 (3H,d,J=7.5 Hz, 4- $\text{CH}_3$ ), 1.10 - 1.32 (1H,m,6-H), 1.72 (3H,d, J=1.0 Hz, 2- $\text{CH}_3$ ), 2.66 - 2.98 (1H,m,4-H), 3.32 - 3.48 (1H,d of d, J=6.0, 6.0 Hz, 5-H), 6.53 - 6.71 (1H,d of d, J=1.0, 10.0 Hz, 3-H), 9.35 (1H,s,CHO); m/z (FAB) 285, 269, 242, 214, 187, 137 and 115.

Ethyl (2E,4E;6R,7S)-7-(*tert*-butyldimethylsilyloxy)-4,6,8-trimethylnona-2,4-dienoate [180]

(2E;4R,5S)-5-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylhept-2-enal (620 mg, 2.2 mmol) was dissolved in dry benzene (25 ml) then carboethoxymethylidinetriphenylphosphorane (1.150 g, 3.3 mmol) was added and the colourless solution heated under gentle reflux in a nitrogen atmosphere for 5 days. The solvent was removed *in vacuo* and the residual sludge purified by dry-flash chromatography ( $\text{SiO}_2$ /petrol - 15% ether-petrol, gradient) to give a clear colourless oil (733 mg, 2.1 mmol, 95%). The mixture of 2E and 2Z isomers was dissolved in dry dichloromethane (20 ml) and iodine (5 mg) was added to the stirred solution. The purple solution was irradiated with a 500W tungsten lamp for 4 hours then washed with saturated aqueous sodium thiosulphate (2 x 20 ml), water (20 ml) and brine (20 ml) before being dried ( $\text{MgSO}_4$ ). The solvent was removed *in vacuo* to give the isomerically pure diene (739 mg) which was purified in the same manner as before so that the *title compound* was obtained as a clear colourless oil (730 mg, 2.06 mmol, 94%), t.l.c. (F)  $R_f = 0.31$ ;  $[\alpha]^{20} = + 1.8^\circ$  ( $c=1.21$ ,  $\text{CHCl}_3$ ); (Found:  $\text{MH}^+$ , 355.26685. Calc. for  $\text{C}_{20}\text{H}_{39}\text{O}_3\text{Si}$ :  $\text{MH}^+$ , 355.26683);  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ ) 268 nm ( $\epsilon$  26200);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ ) 3030



(alkene CH), 2980 (CH), 1720 (C=O), 1640 (C=C), 1460, 1150 and 840 $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ /ppm (200MHz,  $\text{CDCl}_3$ ) [0.02, 0.04] (6H, split due to diastereotopicity, Si  $\text{CH}_3$ 's), 0.80 - 0.91 (15H, overlapping m, 8- $\text{CH}_3$ 's and *t*-butyl), 0.96 - 0.99 (3H,d,J=5.0 Hz, 6- $\text{CH}_3$ ), 1.29 (3H,t, J=7.1 Hz, ester  $\text{CH}_3$ ), 1.65 - 1.71 (1H,m,8-H), 1.76 (3H,s,4- $\text{CH}_3$ ), 2.62 - 2.75 (1H,m,6-H), 3.34 (1H,d of d,J=5.0, 5.0 Hz, 7-H), 4.15 - 4.26 (2H,q,J=7.1 Hz, ester  $\text{CH}_2$ ), 5.72 (1H,d,J=15.5 Hz, 3-H), 6.00 (1H,d,J=10.0 Hz, 5-H), 7.34 (1H,d,J=15.5 Hz, 2-H);  $\delta_{\text{C}}$ /ppm (50MHz,  $\text{CDCl}_3$ ) -3.93 (Si  $\text{CH}_3$ 's), 12.89 (4- $\text{CH}_3$ ), 13.52, 13.92, 18.31, 19.22 (6- $\text{CH}_3$ , 8- $\text{CH}_3$ 's and ester  $\text{CH}_3$ ), 25.88 (*t*-butyl  $\text{CH}_3$ 's), 32.86 (8-C), 36.53 (6-C), 60.15 (ester  $\text{CH}_2$ ), 78.01 (*t*-butyl quat.C), 81.21 (7-C), 115.95, 145.87 (3-C, 5-C), 130.78 (4-C), 151.06 (2-C), 194.92 (C=O); m/z (FAB) 355, 340, 326, 310, 298, 253, 215, 187, and 115.

(2E,4E;6R,7S)-7-(*tert*-Butyldimethylsilyloxy)-4,6,8-trimethylnona-2,4-dien-1-ol [181]

A solution of ethyl (2E,4E;6R,7S)-7-(*tert*-butyldimethylsilyloxy)-4,6,8-trimethylnona-2,4-dienoate (700 mg, 2.0 mmol) in dry dichloromethane (40 ml) was cooled to -78  $^{\circ}\text{C}$  (dry ice/acetone) under argon. Diisobutylaluminium hydride (1.0M in dichloromethane; 5.0 ml, 5.0 mmol) was added and the mixture stirred at -78  $^{\circ}\text{C}$  for 3 hours then quenched by the careful addition of water (15 ml) before being warmed to room temperature over 30 minutes. The two-phase mixture was transferred to a separatory funnel containing dichloromethane (200 ml) and saturated aqueous sodium potassium tartrate (200ml), shaken and separated. The aqueous layer was extracted with dichloromethane (4 x 100ml) and the combined organic liquors were dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to leave a pale yellow liquid. This was purified by dry-flash chromatography ( $\text{SiO}_2$ /30% ether-petrol) to give the *title compound* as a clear colourless oil (602 mg, 1.9 mmol, 95%), t.l.c. (B)  $R_f$  = 0.35;  $[\alpha]^{20} = +1.17^{\circ}$  (c=0.99,  $\text{CHCl}_3$ ); (Found:  $\text{MH}^+$ , 313.25628. Calc. for  $\text{C}_{18}\text{H}_{37}\text{O}_2\text{Si}$ :  $\text{MH}^+$ , 313.25627);  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ ) 236 nm ( $\epsilon$  21000);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ ) 3320 br (OH), 2960, 2860 (CH), 1645 (C=C), 1255 and 770  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ /ppm (200MHz,  $\text{CDCl}_3$ ) [0.02, 0.03] (6H, split due to diastereotopicity, Si $\text{CH}_3$ 's), 0.81 - 0.90 (15H, overlapping m, 8- $\text{CH}_3$ 's and *t*-butyl  $\text{CH}_3$ 's); 0.93 - 0.97 (3H,d,J=7.0 Hz, 6- $\text{CH}_3$ ), 1.65 - 1.77 (1H,m,8-H), 1.74 (3H,s,4- $\text{CH}_3$ ), 2.61 - 2.74 (1H,m,6-H), 3.30 - 3.35 (1H,d of d, J=5.1, 5.1 Hz, 7-H), 4.17 - 4.21 (2H,d of d, J=1.1, 6.1 Hz,  $\text{CH}_2$ ), 5.55 - 5.60 (1H,d,J=10.0 Hz,5-H), 5.66 - 5.77 (1H,d of t, J=6.1, 15.0 Hz, 2-H), 6.22 - 6.29 (1H,d,J=15.0 Hz, 3-H);  $\delta_{\text{C}}$ /ppm (50MHz,  $\text{CDCl}_3$ ) -3.91 (Si $\text{CH}_3$ 's), 12.44 (4- $\text{CH}_3$ ), 18.71, 19.48,

20.63 (8-CH<sub>3</sub>'s and 6-CH<sub>3</sub>), 26.12 (*t*-butyl CH<sub>3</sub>'s), 32.47 (8-C), 35.98 (6-C), 68.74 (CH<sub>2</sub>), 80.77 (7-C), 124.71 (5-C), 132.96 (4-C), 136.62 (2-C), 137.35 (3-C); m/z (FAB) 313, 311, 269, 235, 215, 201 and 115.

(2E,4E;6R,7S)-7-(*tert*-Butyldimethylsilyloxy-4,6,8-trimethylnona-2,4-dienal [182]

(2E,4E;6R,7S)-7-(*tert*-Butyldimethylsilyloxy-4,6,8-trimethylnona-2,4-dien-1-ol (582 mg, 1.86 mmol) was dissolved in dry dichloromethane (20 ml) containing powdered 4A molecular sieves (400mg). *N*-Methylmorpholine *N*-oxide (328 mg, 2.8 mmol) and tetra-*n*-propylammonium perchlorate (3.4 mg, 9.3 μmol) were added and the green mixture was stirred under nitrogen for 24 hours at room temperature. The mixture was diluted with dichloromethane (30 ml) then washed with aqueous sodium sulphite (50 ml), water (50 ml) and aqueous copper sulphate (50 ml) before the organic liquors were dried (MgSO<sub>4</sub>). The solvent was removed *in vacuo* and the brown residue purified by dry-flash chromatography (SiO<sub>2</sub>/petrol) to give the *title compound* as a clear colourless oil (374.4 mg, 1.21 mmol, 65%), t.l.c. (E) R<sub>f</sub> = 0.30; [α]<sup>20</sup> = +4.6° (c=0.85, CHCl<sub>3</sub>); (Found: MH<sup>+</sup>, 3.11.24064. Calc. for C<sub>18</sub>H<sub>35</sub>O<sub>2</sub>Si: MH<sup>+</sup>, 311.24062); λ max (CH<sub>3</sub>CN) 279 nm (ε 24500); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 2960, 2850 (CH), 1670 (C=O), 1615 (C=C), 1120 and 835 cm<sup>-1</sup>; δ<sub>H</sub>/ppm (200MHz, CDCl<sub>3</sub>) [0.03, 0.05] (6H, split due to diastereotopicity, SiCH<sub>3</sub>'s), 0.81 - 0.90 (15H, overlapping M, 8-CH<sub>3</sub>'s and *t*-butyl CH<sub>3</sub>'s), 0.99 (3H,d,J=7.0Hz, 6-CH<sub>3</sub>), 1.68 - 1.74 (1H,m,8-H), 1.80 (3H,s,4-CH<sub>3</sub>), 2.72 - 2.79 (1H,m,6-H), 3.36 - 3.41 (1H, overlapping d of d, J=5.1, 5.1 Hz, 7-H), 6.02 - 6.12 (1H, d of d, J=7.8, 15.6 Hz, 2-H), 6.13 (1H,d, J=10.3Hz, 5-H), 7.10 (1H,d,J=15.6 Hz, 3-H), 9.55 (1H,d,J=7.8 Hz, CHO); m/z (FAB) 311, 309, 295, 253, 239, 215, 201 and 115.

Attempted preparation of cinnamaldehyde [176]

METHOD A

A solution of ethyl cinnamate (8.811 g, 50 mmol) in dry dichloromethane (50 ml) was stirred under argon and cooled either to -95 °C (liq. nitrogen-acetone) or -40 °C (dry ice-CH<sub>3</sub>CN) then diisobutylaluminium hydride (1.0M in dichloromethane; 50 ml, 50 mmol) was added (double-ended needle) followed immediately by trimethylsilyl chloride (6.35 ml, 5.43 g, 50 mmol). The reaction mixture became yellow and was stirred at the chosen temperature for 3 hours before being quenched

by the careful addition of aqueous hydrochloric acid (2M; 25ml) over 30 minutes then allowed to warm to room temperature. The layers were separated, the aqueous layer was extracted with dichloromethane (50 ml), and the combined organic liquors dried ( $\text{MgSO}_4$ ). Removal of the solvent *in vacuo* gave 8.921 g of a pale yellow liquid. Examination of the crude product showed that it was mainly unreacted ester containing cinnamyl alcohol [177] in a 2:1 ratio as estimated by  $^1\text{H}$  n.m.r. A trace of the aldehyde was observed on t.l.c. (C)  $R_f = 0.15$  ( $\text{CH}_2\text{OH}$ ), 0.75 (ester) and 0.90 (CHO);  $\nu$  max (neat) 3500 br (OH), 3035 (aromatic CH), 2980, 2840 (CH), 1715 (C=O), 1640 (C=C), 1580 (aromatic C=C), 1450 and 770  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ /ppm (80MHz,  $\text{CDCl}_3$ ) 1.33 (3H,t,J=7.1 Hz, ester  $\text{CH}_3$ ), 1.65 (0.5H, br s, OH), 4.13-4.39 (3H, overlapping m and q, J=7.1 Hz, ester  $\text{CH}_2$  and  $\text{CH}_2\text{OH}$ ), 6.29 - 6.51 (2H, overlapping m and d, J=16.0 Hz, ester  $\alpha$ -CH and CH's of alcohol), 7.19 - 7.55 (7.5 H,m,aromatic CH's), 7.62 (1H,d,J=16.0 Hz,  $\beta$ -CH of ester); m/z (FAB) 177 ( $\text{MH}^+$ , ester), 133 ( $\text{MH}^+$ , CHO), 117 ( $\text{MH}^+ - \text{H}_2\text{O}$ , alcohol), 103 and 74.

#### METHOD B

Essentially the same procedure as for Method A was used except that 1,1,1-3,3,3-hexamethyldisilazane (8.07 g, 50 mmol) was used instead of trimethylsilyl chloride and, after quenching with aqueous hydrochloric acid, the reaction mixture was shaken with saturated aqueous sodium potassium tartrate (100 ml). Again, a pale yellow liquid was obtained (8.781 g) which proved to be identical to the product described in Method A.

#### 2,2-Dimethyl-1,3-diox-5-en-4-one-6-methylenetriphenylphosphonium bromide [194]

A mixture of freshly distilled 2,2,6-trimethyl-1,3-diox-5-en-4-one (59.00 g, 415 mmol), *N*-bromosuccinimide (76.54 g, 430 mmol) and benzoyl peroxide (121 mg, 0.5 mmol) in dry carbon tetrachloride (500 ml) was heated under reflux then irradiated with a 500W tungsten lamp for 4 hours. The light was removed and the mixture cooled to 0  $^{\circ}\text{C}$  and the floating white solids were removed by filtration of the mixture through a 1 cm pad of silica. The silica pad was washed with carbon tetrachloride (100 ml) and the combined filtrate and washings were concentrated *in vacuo* to give 6-bromomethyl-2,2-dimethyl-1,3-diox-5-en-4-one [193] as a yellow lachrymatory liquid (83.46 g, 378 mmol, 91%).

The crude bromide was dissolved in dry toluene (600 ml) and a solution of triphenylphosphine (104.92 g, 0.4 mol) in dry toluene (400 ml) was added dropwise over 45 minutes. The mixture was stirred for 12 hours and the precipitate was collected by filtration. Recrystallization from solution in dichloromethane with ethyl acetate gave the *title compound* as a white solid (121.38 g, 252 mmol, 65%), m.p. 200 °C (dec); (Found: M<sup>+</sup> of cation, 403.44202. Calc. for C<sub>25</sub>H<sub>24</sub>O<sub>3</sub>P<sup>+</sup>: M<sup>+</sup>, 403.44203); (Found: C, 61.9%; H, 4.8%. C<sub>25</sub>H<sub>24</sub>BrO<sub>3</sub>P requires C, 62.1%; H, 5.0%); λ max (CH<sub>3</sub>CN) 252 nm (ε 10700), 342 nm (ε 3300); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3050 (aromatic CH), 2980 (CH), 1735 (C=O), 1640 (C=C), 1595 (aromatic C=C), 1205 and 1115 cm<sup>-1</sup>; δ<sub>H</sub>/ppm (80MHz, CDCl<sub>3</sub>) 1.35 (6H, s, 2-CH<sub>3</sub>'s), 5.46 (2H, d, J=15.6 Hz, 6-CH<sub>2</sub>), 6.03 (1H, s, 5-H), 7.61 - 8.06 (15H, m, aromatic CH's); m/z (FAB) 403, 345, 319, 303, 275, 262, 183 and 152.

#### 2,2-Dimethyl-1,3-diox-5-en-4-one-6-methylidetriphenylphosphorane [195]

The phosphonium salt (30.00 g, 62 mmol) was added to a solution of potassium carbonate (9.40 g, 68 mmol) in water (160 ml) and the suspension was shaken for 22 hours at room temperature. The white solids were collected by filtration and dried *in vacuo* at 40 °C then recrystallized from solution in chloroform with ether to afford the *title compound* as yellow-green crystals (15.836 g, 39 mmol, 63%), m.p. 138-140 °C; (Found:) MH<sup>+</sup>, 403.14633. Calc. for C<sub>25</sub>H<sub>24</sub>O<sub>3</sub>P: MH<sup>+</sup>, 403.14630); λ max (CH<sub>3</sub>CN) 340 nm (ε 18200); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3040 (aromatic CH), 2960 (CH), 1730 (C=O), 1660 (C=C), 1595 (aromatic C=C), 1100 and 920 cm<sup>-1</sup>, δ<sub>H</sub>/ppm (80MHz, CDCl<sub>3</sub>) 1.15 (6H, br s, 2-CH<sub>3</sub>'s), 4.62 (1H, br s, 5-H), 7.24 - 7.76 (16H, m, 6-CH and aromatic CH's); δ<sub>C</sub>/ppm (50MHz, CDCl<sub>3</sub>) 24.52 (2-CH<sub>3</sub>'s), 103.06 (2-C), 125.82, 127.67 (5-C and 6-C), 128.74, 128.97, 132.02, 132.86 (aromatic CH's and quat. C's), 163.36 (CH=P), 171.29 (C=O); δ<sub>P</sub>/ppm (36MHz, CDCl<sub>3</sub>) 15.21; m/z (FAB) 403, 345, 303, 275, 262, 183 and 108.

#### 6-Chloromethyl-2,2-dimethyl-1,3-diox-5-en-4-one [192]

This was prepared according to the method of Boeckmann Jr. *et alia* <sup>89</sup>. Thus the *required compound* was obtained as a yellow liquid (9.92 g, 56 mmol, 51%), t.l.c. (H) R<sub>f</sub> = 0.17; (Found: MH<sup>+</sup>, 177.03184. Calc. for C<sub>7</sub>H<sub>9</sub><sup>35</sup>ClO<sub>3</sub>: MH<sup>+</sup>, 177.03184); λ max (CH<sub>3</sub>CN) 249 nm (ε 8500); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3020 (alkene CH), 2980 (CH), 1740 (C=O), 1645 (C=C), 1390 and 1020 cm<sup>-1</sup>;

$\delta_{\text{H}}/\text{ppm}$  (200MHz,  $\text{CDCl}_3$ ) 1.66 (6H,s,2- $\text{CH}_3$ 's), 3.99 (2H,d,J=0.7 Hz,  $\text{CH}_2$ ), 5.50 (1H,t,J=0.7 Hz,5-H);  $\delta_{\text{C}}/\text{ppm}$  (50MHz,  $\text{CDCl}_3$ ) 24.63 (2- $\text{CH}_3$ 's), 40.84 ( $\text{CH}_2$ ), 95.42 (5-C), 107.39 (2-C), 160.26 (6-C), 164.41 (C=O); m/z (FAB) 177, 142, 121, 75 and 62.

6-Diethylphosphonomethyl-2,2-dimethyl-1,3-diox-5-en-4-one [100]

This was prepared according to the procedure of Boeckmann Jr. *et alia* <sup>89</sup>. Thus the *required compound* was obtained as a pale yellow oil (2.78 g, 10.0 mmol, 19%), t.l.c. (I)  $R_f = 0.16$ ; (Found:  $\text{MH}^+$ , 279.09974. Calc. for  $\text{C}_{11}\text{H}_{20}\text{O}_6\text{P}$ :  $\text{MH}^+$ , 279.09974);  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ ) 249 nm ( $\epsilon$  6400);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ ) 2960 (CH), 1725 (C=O), 1630 (C=C), 1370, 1270 and 900  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}/\text{ppm}$  (200MHz,  $\text{CDCl}_3$ , *inter alia*) 1.37 (6H,t,J=7.5 Hz, phosphonate  $\text{CH}_3$ 's), 1.61 (6H,s,2- $\text{CH}_3$ 's), 2.70 (2H,d,J=22.0 Hz,  $\text{CH}_2$ ), 3.98 - 4.13 (4H,2 x quartets, overlapping, phosphonate  $\text{CH}_2$ 's), 5.29 (1H,s,5-H);  $\delta_{\text{C}}/\text{ppm}$  (50MHz,  $\text{CDCl}_3$ ) 16.12 (phosphonate  $\text{CH}_3$ 's), 24.65 (2- $\text{CH}_3$ 's), 33.43 (6- $\text{CH}_2$ ), 64.42 (phosphonate  $\text{CH}_2$ 's), 95.93 (5-C), 106.82 (2-C), 160.25 (6-C), 162.87 (C=O);  $\delta_{\text{P}}/\text{ppm}$  (36MHz,  $\text{CDCl}_3$ ) 20.73; m/z (FAB) 279, 261, 221, 193, 179, 169 and 123.

Attempted preparations of 2,2-dimethyl-6-(penta-1',3'-dienyl)-1,3-diox-5-en-4-one [197]

METHOD A

The phosphorane [195] (402 mg, 1 mmol) was added to a solution of (E)-but-2-enal (92.7  $\mu\text{L}$ , 70.0 mg, 1 mmol) in the appropriate solvent (15 ml) and the mixture was stirred at room temperature under nitrogen until no aldehyde was seen on t.l.c. [(B),  $R_f = 0.8$ ; reaction times varied from 1 to 6 days]. The solvent was removed *in vacuo* and the yellow residue purified by flash column chromatography ( $\text{SiO}_2/50\%$  ether-petrol) to give the *title compound* as a pale yellow liquid. The reaction was carried out in the following solvents: toluene (no reaction occurred); acetonitrile (9.7 mg, 0.05 mmol, 5%); dichloromethane (15.5 mg, 0.08 mmol, 8%); benzene (37.0 mg, 0.19 mmol, 19%); dimethylsulphoxide (23.3 mg, 0.12 mmol, 12%); the product was obtained as a 1:1 mixture of 1'E and 1'Z isomers. The remainder of the mass from each reaction was obtained as a yellow solid by flushing the column with acetone. These solids could not be identified and showed a very broad u.v. absorbance; t.l.c. (B)  $R_f = 0.4$  and 0.5; (Found:  $\text{MH}^+$ , 195.24038. Calc. for  $\text{C}_{11}\text{H}_{15}\text{O}_3$ :  $\text{MH}^+$ , 195.24040);  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ ) 225 nm ( $\epsilon$  4400), 303 nm ( $\epsilon$  15600);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ ) 3030 (alkene

CH), 2970 (CH), 1735 (C=O), 1640 (C=C), 1385 and 1020  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ /ppm (80MHz,  $\text{CDCl}_3$ ) 1.67 (6H,s,2- $\text{CH}_3$ 's), 1.82 (3H,d,4'- $\text{CH}_3$ ,  $J=5.0$  Hz), 5.24 (1H,s,5-H), 5.74 - 6.17 (3H,m,alkene CH's), 6.72 - 6.91 (1H,m,alkene CH);  $m/z$  (FAB) 195, 149, 139, 122 and 96.

#### METHOD B

The phosphorane [195] (402 mg, 1 mmol) was added to a solution of (E)-but-2-enal (82.7  $\mu\text{L}$ , 70.0 mg, 1 mmol) in the appropriate solvent (15 ml) and the mixture was heated to 40  $^{\circ}\text{C}$  in a thermostated oil-bath (under an atmosphere of nitrogen) for 3 days. The mixture was cooled to room temperature and the solvent removed *in vacuo* to give a solid yellow residue which was purified by flash column chromatography ( $\text{SiO}_2$ /50% ether-petrol) to give a 1:1 mixture of the 1'E isomer of the *title compound* and another product which appeared to have arisen from cyclisation of the 1'Z isomer. The reaction was carried out in the following solvents: dichloromethane (15.5 mg, 0.08 mmol, 8% of desired product and 15.0 mg, 0.08 mmol, 8% of cyclised product); acetonitrile (21.4 mg, 0.11 mmol, 11% and 17.5 mg, 0.09 mmol, 9%); dimethylsulphoxide (23.3 mg, 0.12 mmol, 12% and 19.4 mg, 0.1 mmol, 10%); benzene (23.3 mg, 0.12 mmol, 12% and 17.5 mg, 0.09 mmol, 9%). Near quantitative mass recovery was achieved on flushing the column with acetone: this gave a yellow solid material similar to that obtained in method A. The desired product which on t.l.c. (B) had  $R_f = 0.5$  gave identical spectral data to that reported previously. The data for the cyclised product [200] were as follows: t.l.c. (B)  $R_f = 0.35$ ; (Found:  $\text{MH}^+$ , 195.24039. Calc. for  $\text{C}_{11}\text{H}_{15}\text{O}_3$ :  $\text{MH}^+$ , 195.24040);  $\lambda_{\text{max}}$  223 nm ( $\epsilon$  9800), 282nm ( $\epsilon$  2100), 310 nm ( $\epsilon$  2500);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ ) 3040 (alkene CH), 2980 (CH), 1740 (C=O), 1640 (C=C), 1390 and 1020 $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ /ppm (60MHz,  $\text{CDCl}_3$ ) 1.0 - 1.3 (9H,m,2- $\text{CH}_3$ 's and 4'- $\text{CH}_3$ ), 2.0 (2H,m,1'- $\text{CH}_2$ ), 2.4 (1H,m,4'-H), 5.7 - 6.6 (2H,m,2'-H and 3'-H);  $m/z$  (FAB) 195, 136, 121, 108 and 68.

#### Pent-4-enal [202]

A solution of pent-4-en-1-ol (10.35 g, 120 mmol) in dry dichloromethane (60 ml) was added rapidly to a vigorously stirred slurry of pyridinium chlorochromate (38.80 g, 180 mmol) in dry dichloromethane (360 ml) and the reaction was stirred for 18 hours. Ether (500 ml) was added and the supernatant liquid decanted off. The black residual tar was triturated with ether (2 x 500 ml)

until it became a granular solid and the combined organic liquors were filtered through a 2 cm silica pad then concentrated *in vacuo* to give a green liquid which was purified by Kugelrohr distillation to afford the *title compound* as a colourless liquid (stencil!) (5.95 g, 70.8 mmol, 59%), b.p. 80 °C/45 mm Hg; t.l.c. (B)  $R_f = 0.9$ ; (Found:  $MH^+$ , 85.12586. Calc. for  $C_5H_9O$ :  $MH^+$ , 85.12688);  $\nu_{max}$  (neat) 3090 (alkene CH), 2960 (CH), 2830, 2730 (CHO), 1730 (C=O), 1650 (C=C) and  $920\text{cm}^{-1}$ ;  $\delta_H/\text{ppm}$  (60MHz,  $CDCl_3$ ) 2.3 - 2.6 (4H,m,2- $CH_2$  and 3- $CH_2$ ), 4.9 - 5.3 (2H,m,5- $CH_2$ ), 5.7 - 6.1 (1H,m,4-H), 9.9 (1H,t,J=2.0 Hz, CHO); m/z (FAB) 85 and 57.

2,2-Dimethyl-6-(hexa-1',5'-dienyl)-1,3-diox-5-en-4-one [203]

2,2-Dimethyl-1,3-diox-5-en-4-one-6-methylidetriphenylphosphorane (804 mg, 2 mmol) was added to a solution of pent-4-enal (168 mg, 2 mmol) in dry benzene (20 ml) and the mixture was heated to 40 °C in a thermostated oil-bath (under an argon atmosphere) for 22 hours. Analysis of the reaction mixture by t.l.c. (B) showed baseline material plus two spots  $R_f = 0.4$  and 0.6. The reaction mixture was irradiated with a 500W tungsten lamp for 4 hours after which only the baseline and  $R_f = 0.4$  spots were seen. The solvent was removed *in vacuo* and the yellow solid residue was purified by flash column chromatography ( $SiO_2/50\%$  ether-petrol) to give the *title compound* as a pale yellow liquid (87.5 mg, 0.42 mmol, 21%). Again, when the column was flushed with acetone, near quantitative mass recovery of a yellow solid with a very broad u.v. absorbance was achieved; t.l.c. (B)  $R_f = 0.4$ ; (Found:  $MH^+$ , 209.26747. Calc. for  $C_{12}H_{17}O_3$ :  $MH^+$ , 209.26749);  $\lambda_{max}$  ( $CH_3CN$ ) 230 nm ( $\epsilon$  4100), 279nm ( $\epsilon$  11400);  $\nu_{max}$  ( $CH_2Cl_2$ ) 3035 (alkene CH), 2980 (CH), 1740 (C=O), 1635 (C=C), 1390 and  $1025\text{cm}^{-1}$ ;  $\delta_H/\text{ppm}$  (200MHz,  $CDCl_3$ ) 1.69 (6H,s,2- $CH_3$ 's), 2.14 - 2.33 (4H,m,3'- and 4'- $CH_2$ 's), 4.95 - 5.07 (2H,m,6'- $CH_2$ ), 5.23 (1H,s,5-H), 5.69 - 5.94 (2H, overlapping m and d, J=15.0 Hz, 5'-H and 1'-H), 6.46 - 6.61 (1H,dt,J=7.5,15.0 Hz, 2'-H);  $\delta_C/\text{ppm}$  (50MHz,  $CDCl_3$ ) 16.05 (2- $CH_3$ 's), 31.84, 32.20 (3'- and 4'- $CH_2$ 's), 93.32 (5-C), 106.14 (2-C), 115.44 (6'- $CH_2$ ), 122.77, 136.92, 141.33 (1-,2'- and 5'-CH's), 161.86 (6-C), 163.13 (C=O); m/z (FAB) 209, 201, 185, 168, 151 and 139.

Attempted preparation of ( $\pm$ )-6-(pent-3-en-2-yl)-2,2-dimethyl-1,3-diox-5-en-4-one [206]

## METHOD A

A solution of diisopropylamine (3.67 g, 36.3 mmol) in anhydrous tetrahydrofuran (25 ml) was cooled to 0 °C (ice bath) under argon and *n*-butyllithium (1.6M in hexanes; 22 ml, 34 mmol) was added and the mixture stirred for 30 minutes. The mixture was cooled to -78 °C (dry ice/acetone) then a solution of 2,2,6-trimethyl-1,3-diox-5-en-4-one (3.55 g, 25 mmol) in anhydrous tetrahydrofuran (10 ml) was added (double-ended needle) and the mixture stirred until a white precipitate had formed. Distilled trimethylsilyl chloride (3.26 g, 30 mmol) in anhydrous tetrahydrofuran (10 ml) was added *via* syringe and the precipitate disappeared as the silyl dienol ether formed. After 15 minutes a solution of (E)-but-2-enal (1.756 g, 25 mmol) in anhydrous tetrahydrofuran (15 ml) was introduced followed immediately by anhydrous tin tetrachloride (0.3 ml, 651 mg, 2.5 mmol) and the reaction was stirred at -78 °C for 3 hours before being quenched by the addition of aqueous HCl (2M;100ml). The reaction was warmed to room temperature during 30 minutes then transferred to a separatory funnel containing ether (100 ml). The layers were separated, the aqueous being extracted with ether (100 ml) and the combined organic extracts were washed with aqueous sodium bicarbonate (80 ml), water (100 ml) and brine (100 ml) then dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The yellow residue (4.709 g) was purified by flash column chromatography (SiO<sub>2</sub>/ether-petrol) to give the starting material (t.l.c. (B) R<sub>f</sub> = 0.2, 860 mg) followed by 6-(4'-oxo-2'-methylbutyl)-2,2-dimethyl-1,3-diox-5-en-4-one [205] as a pale yellow liquid (3.767 g, 17.8 mmol, 71%), t.l.c. (B) R<sub>f</sub> = 0.1; (Found: MH<sup>+</sup>, 213.11268. Calc. for C<sub>11</sub>H<sub>17</sub>O<sub>4</sub>: MH<sup>+</sup>, 213.11267); λ max (CH<sub>3</sub>CN) 247 nm (ε 9000); ν max (CH<sub>2</sub>Cl<sub>2</sub>) 3030 (alkene CH), 2980 (CH), 2830, 2720 (CHO), 1725 br (C=O), 1630 (C=C), 1010 and 900 cm<sup>-1</sup>; δ<sub>H</sub>/ppm (200MHz, CDCl<sub>3</sub>) 1.00 (3H,d,J=6.0 Hz, 2'-CH<sub>3</sub>), 1.65 (6H,s,2-CH<sub>3</sub>'s), 2.12 - 2.46 (5H,m,1'- and 2'-CH<sub>2</sub>'s plus 2'-H), 5.20 (1H,s,5-H), 9.75 (1H,t,J=2.0 Hz,CHO); δ<sub>C</sub>/ppm (50MHz, CDCl<sub>3</sub>) 19.46 (2-CH<sub>3</sub>'s), 24.69, 25.39 (2'-C and 2'-CH<sub>3</sub>), 40.18, 49.76 (1'- and 3'-CH<sub>2</sub>'s), 94.40 (5-C), 106.22 (2-C), 160.69 (6-C), 169.54 (C=O), 200.74 (aldehyde C=O); m/z (FAB) 213, 195, 155, 147, 137 and 113.

## METHOD B



The procedure was the same as for method A except zinc (II) iodide (798mg, 2.5mmol) in anhydrous tetrahydrofuran (5ml) was added instead of tin tetrachloride. Thus, starting material (884mg) and 6-(4'-oxo-2'-methylbutyl)-2,2-dimethyl-1,3-diox-5-en-4-one [205] (3.650 g, 17.2 mmol, 69%) were obtained and gave identical spectral data to that reported above.

#### Methyl 4-bromo-3-oxobutyrate [210]

This was prepared exactly according to the procedure of Duthailer<sup>127</sup>. Thus, the *required compound* was obtained as a clear colourless liquid (67.28 g, 345 mmol, 69%), b.p. 60 °C/0.3 mm Hg (lit.<sup>127</sup> b.p. 57 °C/0.1 mm Hg); (Found: MH<sup>+</sup>, 194.96571. Calc. for C<sub>5</sub>H<sub>7</sub>Br O<sub>3</sub>: MH<sup>+</sup>, 194.96573);  $\nu$  max (neat) 2960 (CH), 1735 (C=O), 1660, 1630 (enol form C=O and C=C), 1440 and 1010 cm<sup>-1</sup>;  $\delta_{\text{H}}$ /ppm (80MHz, CDCl<sub>3</sub>) 3.61 (2H,s,2-CH<sub>2</sub>), 3.71 (3H,s,-OCH<sub>3</sub>), 3.96 (2H,s,4-CH<sub>2</sub>); also present were signals due to the enolic form (*circa* 16%) 3.74 (s,OCH<sub>3</sub>), 3.83 (s,4-CH<sub>2</sub>), 5.23 (s,2-CH), 11.87 (br s,OH);  $\delta_{\text{C}}$ /ppm (90MHz, CDCl<sub>3</sub>) 33.70 (C-2), 45.53 (C-4), 52.31 (CH<sub>3</sub>), 166.76 (C-1), 194.16 (C-3); m/z (FAB) 194, 163 and 115.

#### Ethyl 4-bromo-3-oxobutyrate [208]

This was prepared by using the procedure reported by Duthailer<sup>127</sup>. Thus, the *title compound* was obtained as a clear colourless liquid (72.31 g, 346 mmol, 69%), b.p. 68 °C/1.0 mm Hg; (Found: MH<sup>+</sup>, 210.05378. Calc. for C<sub>6</sub>H<sub>10</sub>Br O<sub>3</sub>: MH<sup>+</sup>, 210.05380);  $\nu$  max (neat) 2980 (CH), 1735 br (C=O), 1655, 1635 (enol form C=O and C=C), 1450 and 1030 cm<sup>-1</sup>;  $\delta_{\text{H}}$ /ppm (80MHz, CDCl<sub>3</sub>) 1.24 (3H,t,J=7.0Hz,CH<sub>3</sub>), 3.65 (2H,s,2-CH<sub>2</sub>), 4.01 (2H,s,2-CH<sub>2</sub>), 4.12 (2H,q,J=7.0 Hz, ester CH<sub>2</sub>); also present were signals due the to enolic form (*circa* 30%) 3.81 (s,4-CH<sub>2</sub>), 5.24 (s,2-CH), 11.85 (br s, OH); m/z (FAB) 210, 181, 165, 131 and 117.

#### Methyl 4-(dimethylphosphono)-3-oxobutyrate [211]

The procedure published by Bodalski *et alia*<sup>126</sup> was employed in an attempt to prepare the *title compound*. Unfortunately, none of the desired phosphonate could be isolated from the crude product as it decomposed on distillation. Analysis of the crude product showed  $\delta_{\text{P}}$ /ppm (36MHz, CDCl<sub>3</sub>) 19.62 consistent with a phosphonate species.

Ethyl 4-(diethylphosphono)-3-oxobutyrate [209]

The procedure of Bodalski *et alia* <sup>126</sup> was followed in an attempt to prepare the *required compound*. The crude product showed  $\delta_P$ /ppm (36MHz, CDCl<sub>3</sub>) 18.98, [lit.<sup>126</sup>  $\delta_P$ /ppm (CHCl<sub>3</sub>) = 18.96; b.p. 120 °C/0.4 mm Hg] consistent with the presence of a phosphonate species, but the material decomposed on distillation leaving an intractable black tar.

Methyl (4E,6E)-3-oxo-octa-4,6-dienoate [212]

A solution of the crude methyl 4-(dimethylphosphono)-3-oxobutyrate (2.02 g, *circa* 9 mmol) in anhydrous tetrahydrofuran (10 ml) was added slowly to a slurry of sodium hydride (50% w/w in oil; 864 mg, 18 mmol) in anhydrous tetrahydrofuran (20 ml) and the mixture was stirred under argon until no more hydrogen gas was evolved (*circa* 30 minutes). (E)-But-4-enal (631 mg, 9 mmol) in anhydrous tetrahydrofuran (5 ml) was added to the brick-red solution and the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured carefully on to brine (100 ml) then aqueous hydrochloric acid (2M; 10ml) was added and the aqueous mixture extracted with ether (4 x 50 ml). The combined extracts were dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo* to leave an orange-yellow sludge (1.43 g) which was purified by flash-column chromatography to give the *title compound* as a yellow semi-solid (381 mg, 2.3 mmol, 25%), t.l.c. (C) R<sub>f</sub> = 0.50; (Found: MH<sup>+</sup>, 169.20215. Calc. for C<sub>9</sub>H<sub>13</sub>O<sub>3</sub>: MH<sup>+</sup>, 169.20216);  $\lambda$  max (CH<sub>3</sub>CN) 276 nm ( $\epsilon$  8900), 340 nm ( $\epsilon$  5400), (CH<sub>3</sub>CN + 1 drop NaOH) 244nm ( $\epsilon$  8400), 340 nm ( $\epsilon$  9250);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 2980 (CH), 1745 (C=O), 1665, 1630 (C=O and C=C of enol), 1420 and 1230 cm<sup>-1</sup>;  $\delta_H$ /ppm (200MHz, CDCl<sub>3</sub>) 0.99 (3H,d,J=7.5 Hz, 7-CH<sub>3</sub>), 3.16 (2H,s,CH<sub>2</sub>), 3.71 (3H,s,OCH<sub>3</sub>), 5.95 - 6.29 (3H,m,5-,6- and 7-H's), 7.00 - 7.25 (1H,m,4-H); also present were signals due to the enolic form [213] (*circa* 22%) 3.77 (s,OCH<sub>3</sub>), 5.02 (s,CH), 12.16 (s,OH); m/z (FAB) 169, 141, 138, 128 and 125.

(5S)-5-[2 (Hydroxycarbonyl)ethyl]-1-methyl-3-(3"-oxobutanoyl)tetramic acid [183]

(5S)-5-[2'-(*tert*-Butyloxycarbonyl)ethyl]-1-methyl-3-[5"-(3"-methylisoxazolyl)]tetramic acid (62.5 mg, 0.19 mmol) was dissolved in aqueous sodium hydroxide (0.4M; 12ml) then 10% palladium on charcoal catalyst (6.2 mg) was added and the mixture stirred under a hydrogen atmosphere at

standard temperature and pressure for 20 hours. The catalyst was removed by filtration through a Celite pad, the alkaline liquors were then cooled (ice-bath) and acidified to pH 1.0 with 2M HCl(aq) before being extracted with ethyl acetate (2 x 50 ml). The combined extracts were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give the *title compound* as a pale yellow oil (43.5 mg, 0.16 mmol, 85%),  $[\alpha]^{20} = -43.7^\circ$  (c=1.01, CHCl<sub>3</sub>);  $\lambda$  max (CH<sub>3</sub>CN) 225 nm ( $\epsilon$  7500), 282 nm ( $\epsilon$  8700), (CH<sub>3</sub>CN + 1 drop 1M NaOH) 246 nm ( $\epsilon$  11200), 284 nm ( $\epsilon$  11800), 356 nm ( $\epsilon$  5200);  $\nu$  max (CH<sub>2</sub>Cl<sub>2</sub>) 3500 br (CO<sub>2</sub>H), 2960 (CH), 1740 sh, 1710 (C=O), 1650, 1630 (C=O and C=C of enol) and 1150cm<sup>-1</sup>;  $\delta_{\text{H}}$ /ppm (200MHz, CDCl<sub>3</sub>) 2.04 - 2.39 (4H,m,1'- and 2'-CH<sub>2</sub>'s), 2.26 (3H,s,COCH<sub>3</sub>), [2.99, 3.01] (3H, split due to tautomerism, NCH<sub>3</sub>), 3.89-3.99 (1H,m,5-H), 3.98 (2H,s,2"-CH<sub>2</sub>), 10.45 (2H,br s, CO<sub>2</sub>H and enol OH); m/z (FAB) 270, 252, 228 and 224.

Silylation of (5S)-5-[2-(hydroxycarbonyl)ethyl]-1-methyl-3-(3"-oxobutanoyl)tetramic acid [183]

Triethylamine (265  $\mu$ L, 1.9mmol) was added to a solution of (5S)-5-[2'-(hydroxycarbonyl)ethyl]-1-methyl-3-(3"-oxobutanoyl)tetramic acid (86 mg, 0.32 mmol) in dry dimethylformamide (2.5 ml) and the mixture stirred under argon before trimethylsilyl chloride (143  $\mu$ L, 1.12 mmol) was introduced *via* syringe. The resulting reaction mixture was then stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue partitioned between ether (10 ml) and water (10 ml). The layers were shaken and separated, and the ethereal layer washed with water (10 ml), then dried (MgSO<sub>4</sub>). Concentration of the liquors *in vacuo* gave 10.9 mg of the crude tris (trimethylsilyl) derivative,  $\lambda$  max (CH<sub>3</sub>CN) 260 nm ( $\epsilon$  3400), 382 nm ( $\epsilon$  1700),  $\lambda$  max (CH<sub>3</sub>CN + 1 drop 1M NaOH) 265 nm ( $\epsilon$  3400), 354 nm ( $\epsilon$  12900).

Attempted preparations of (5S)-5-[2'-(tert-butyloxycarbonyl)ethyl]-1-methyl-3-[5"-(3"-{2"-hydroxypent-3"-enyl}isoxazolyl)]tetramic acid [217]

METHOD A

(5S)-5-[2'-tert-Butyloxycarbonyl)ethyl]-1-methyl-3-[5"-(3"-methylisoxazolyl)]tetramic acid (29.0 mg, 0.09 mmol) was dissolved in anhydrous tetrahydrofuran (2 ml) then cooled to -78 °C (dry ice/acetone) under argon. *n*-Butyllithium (1.3M in hexanes; 0.14 ml, 0.18 mmol) was added slowly (*via* syringe) and a yellow colour was observed immediately. A solution of crotonaldehyde (6.3 mg,

0.09mmol) in anhydrous tetrahydrofuran (1ml) was introduced using a syringe causing the reaction mixture to turn pale yellow. The reaction was stirred at  $-78\text{ }^{\circ}\text{C}$  for 4 hours then allowed to attain room temperature over a period of 30 minutes. The solvents were then removed by concentration *in vacuo* and the residual pale yellow solids were partitioned between ether (15 ml) and water (15 ml), the layers being shaken then separated. The aqueous liquors were cooled in ice and carefully acidified to pH 2.0 with aqueous HCl (0.7M). The cloudy acidic solution was extracted immediately with ethyl acetate (3 x 25 ml) and the extracts were combined before being dried ( $\text{MgSO}_4$ ). Removal of the solvent *in vacuo* gave a pale yellow oil (36.5 mg) which appeared to contain the *title compound*; (Found):  $\text{MH}^+$ , 393.20253. Calc. for  $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_6$ :  $\text{MH}^+$ , 393.20253. Calc. for  $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_6$ :  $\text{MH}^+$ , 393.20255);  $\lambda$  max ( $\text{CH}_3\text{CN}$ ) 268 nm ( $\epsilon$  12900), 315 nm ( $\epsilon$  17800);  $^1\text{H}$  n.m.r. showed signals corresponding to the title compound but was too complex for full assignment; m/z (FAB) 393, 375, 365, 337, 319, 267, 207, 193 and 138.

#### METHOD B

Exactly the same reaction conditions and work-up were used (as those in Method A) except lithium diisopropylamide (2.0 equivalents; 1.5M in cyclohexane; 0.15 ml, 0.224 mmol) was employed as the base. This gave 52.6 mg of a yellow oil which was identical to that obtained previously, *id est* spectral evidence suggested that the desired product was present in the complex crude mixture.

#### METHOD C

The third method attempted differed from the first two in the following ways: the base employed was *sec*-butyllithium (2.0 equivalents; 1.3M in cyclohexane; 0.57 ml, 0.74 mmol) and the reaction was carried out at  $-20\text{ }^{\circ}\text{C}$  (dry ice/carbon tetrachloride) for 4 hours. The same work-up was used giving 140.4 mg of a green-yellow oil; (Found:  $\text{MH}^+$ , 393.20257. Calc. for  $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_6$ :  $\text{MH}^+$ , 393.20255); other spectral data was similar to the earlier attempts.

(5S)-5-[2'-(*tert*-Butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-{2'''-oxo-4'''-phenylbut-3'''-enyl}-isoxazolyl)]tetramic acid [220]

Essentially the same procedure was followed as for method C (preceding experiment) except that ethyl cinnamate (1.0 equivalent; 71.0 mg, 0.4 mmol) was used as the electrophile and the reaction temperature was  $-78\text{ }^{\circ}\text{C}$  (dry ice/acetone) throughout. An identical work-up of the reaction gave 284.0 mg of a yellow-green oil. This crude product was found to be not the title compound but (5S)-5-[2'-(*tert*-butyloxycarbonyl)ethyl]-1-methyl-4-*O*-cinnamoyl-3-[5''-(3''-methylisoxazolyl)]-tetramic acid [219]; (Found:  $\text{MH}^+$ , 453.20256. Calc. for  $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_6$ :  $\text{MH}^+$ , 453.20255);  $\lambda_{\text{max}}$  ( $\text{CH}_3\text{CN}$ ) 273 nm ( $\epsilon$  12200), 298 nm ( $\epsilon$  8800);  $\nu_{\text{max}}$  ( $\text{CH}_2\text{Cl}_2$ ) 3030 (aromatic CH), 2980 (CH), 1710 br (C=O), 1640 (C=C), 1605 (aromatic C=C), 1000,  $650\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ /ppm (200MHz,  $\text{CDCl}_3$ ) 1.41 (9H,s,*t*-butyl), 2.16 - 2.30 (4H,m, $\text{CH}_2$ 's), 2.33 (3H,s,isoxazole  $\text{CH}_3$ ), 2.95 (3H,s, $\text{NCH}_3$ ), 4.05 - 4.12 (1H,m,5-H), 6.40 (1H,d, $J=16.0\text{ Hz}$ ,cinnamoyl CH), 6.65 (1H,s,isoxazole CH), 7.31-7.38 (3H,m,aromatic  $\text{H}_b$  and  $\text{H}_c$ ), 7.41 - 7.52 (2H,m,aromatic  $\text{H}_a$ ), 7.63 (1H,d, $J=15.0\text{ Hz}$ , cinnamoyl CH);  $m/z$  (FAB) 453, 425, 395, 379, 347, 321, 283, 264, 207 and 131.

(5S)-5-[2'-(*tert*-Butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-{2'''-hydroxypent-3'''-enyl}-isoxazolyl)]tetramic acid [217]

#### METHOD D

(5S)-5-[2'-(*tert*-Butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-methylisoxazolyl)]tetramic acid (161 mg, 0.5 mmol) was dissolved in anhydrous tetrahydrofuran (10 ml) and the solution was cooled to  $-78\text{ }^{\circ}\text{C}$  (dry ice/acetone) under argon. *sec*-Butyllithium (1.3M in cyclohexane; 0.38 ml, 0.5 mmol) was added and the yellow mixture stirred for 5 minutes before a solution of *tert*-butyldimethylsilyl chloride (75.4 mg, 0.5 mmol) in anhydrous tetrahydrofuran (1 ml) was introduced into the reaction vessel. After another 5 minute period a second equivalent of *sec*-butyllithium (1.3M in cyclohexane; 0.38ml, 0.5mmol) was added and the orange-yellow mixture stirred at  $-78\text{ }^{\circ}\text{C}$  for 10 minutes. A solution of crotonaldehyde (35.0 mg, 0.5 mmol) in anhydrous tetrahydrofuran (1 ml) was then added and the resulting mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 3 hours then allowed to warm to room temperature during 30 minutes. Removal of the solvents *in vacuo* gave a yellow residue which was partitioned between ether (30 ml) and water (30 ml). The immiscible layers were shaken

then separated. The aqueous layer was extracted with ether (2 x 15 ml) and the combined organic liquors were dried ( $\text{MgSO}_4$ ) before being evaporated under reduced pressure. The resulting green syrup (255.1 mg) was triturated with ether to give an unidentified white solid (100 mg, u.v. inactive). Concentration of the supernatant liquors *in vacuo* afforded a green solid-foam in which the *title compound* was present; (Found:  $\text{MH}^+$ , 393.20253. Calc. for  $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_6$ :  $\text{MH}^+$ , 393.20255);  $\lambda$  max ( $\text{CH}_3\text{CN}$ ) 239 nm ( $\epsilon$  10000), 272 nm ( $\epsilon$  8000),  $\lambda$  max ( $\text{CH}_3\text{CN}$  + 1 drop 1M NaOH) 271 nm ( $\epsilon$  11000), 306nm ( $\epsilon$  15300);  $\delta_{\text{H}}$ /ppm (360MHz,  $\text{CDCl}_3$ , *inter alia*) 1.40 (9H,s,*t*-butyl), 2.03 - 2.25 (4H,m, $\text{CH}_2$ 's), 2.97 (3H,s, $\text{NCH}_3$ ), 3.22 (2H,m,1- $\text{CH}_2$ ), 4.00 - 4.07 (1H,m,5-H), 5.42 - 5.85 (2H,m, $\text{CH}=\text{CH}$ ), 6.63 (1H,s, isoxazole CH); m/z (FAB) 393, 375, 365, 337, 319, 267, 193 and 138.

(5S)-5-[2'-(*tert*-Butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-[penta-1''',3'''-dienyl]-isoxazolyl)]tetramic acid

[221]

A single crystal of *p*-toluenesulphonic acid was added to a solution of (5S)-5-[2'-(*tert*-butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-{2'''-hydroxypent-3''-enyl}isoxazolyl)]tetramic acid (13.8 mg, 35.2  $\mu\text{mol}$ ) in dry dichloromethane (6 ml) and the mixture was refluxed for 4 hours. The solution was diluted to a volume of 20 ml with dichloromethane then washed with aqueous sodium bicarbonate (10 ml), water (10 ml) and brine (10 ml). The organic liquor was then dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give a yellow sludge (12.5 mg) which contained the *title compound*; (Found:  $\text{MH}^+$ , 375.19198. Calc. for  $\text{C}_{20}\text{H}_{27}\text{N}_2\text{O}_5$ :  $\text{MH}^+$ , 375.19198);  $\lambda$  max ( $\text{CH}_3\text{CN}$ ) 269 nm ( $\epsilon$  9500), 304 nm ( $\epsilon$  11000), 358 nm ( $\epsilon$  3600); m/z (FAB) 375, 347, 323, 267, 217 and 149.

Attempted coupling of (5S)-5-[2'-(*tert*-butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-methylisoxazolyl)]tetramic acid [120] and (2E,4E;6R,7S)-7-(*tert*-butyldimethylsilyloxy)-4,6,8-trimethylnona-2,4-dienal [182]

The coupling was carried out under identical conditions to those described earlier (Method D), with (2E,4E;6R,7S)-7-(*tert*-butyldimethylsilyloxy)-4,6,8-trimethylnona-2,4-dienal (155.3 mg, 0.5 mmol) being used as the electrophile. The work-up was slightly different; the reaction solvent was

removed *in vacuo* and the yellow residue partitioned between ether (30 ml) and water (30 ml). The layers were shaken and separated - the aqueous layer was cooled in ice and acidified to pH 1.5 with 0.7M HCl (a deep red colour was seen). The acidic solution was extracted immediately with ether (3 x 60 ml) until the colour was no longer apparent in the aqueous layer and the organic extracts were dried (MgSO<sub>4</sub>). The solvents were removed *in vacuo* giving a brown residue which was purified by dry-flash chromatography (SiO<sub>2</sub>/50% ethylacetate-hexane - ethyl acetate gradient). The material which had R<sub>f</sub> = O (I) (74.7 mg) appeared to contain a tetramic acid - mainly starting material with some (3''E,5''E;5S,7''R,8''S)-5-[2'-(tert-butyloxycarbonyl)ethyl]-1-methyl-3-[5''-(3''-[2''-hydroxy-8''-(tert-butyldimethylsilyloxy)-5'',7'',9''-trimethyldeca-3'',5''-dienyl]isoxazolyl)]-tetramic acid [222] being present; (Found: MH<sup>+</sup>, 633.39353. Calc. for C<sub>34</sub>H<sub>57</sub>N<sub>2</sub>O<sub>7</sub>Si: MH<sup>+</sup>, 633.39348); λ max (CH<sub>3</sub>CN) 272 nm (ε 10900), 305 nm (ε 7400), λ max (CH<sub>3</sub>CN + 1 drop 1M NaOH) 272 nm (ε 12600); <sup>1</sup>H n.m.r. on the crude material indicated that the main constituents of the mixture were the two starting compounds; m/z (FAB) 633, 615, 560, 518, 502, 445, 429, 405, 323, 267, 217 and 187.

#### 4. APPENDIX: COURSES ATTENDED

Organic Research Seminars 1988, 1989 and 1990, (various speakers).

Medicinal Chemistry, (Professor P.G. Sammes, Brunel University).

Medicinal Chemistry, (Dr M. Paton, University of Edinburgh, 4th year lecture course).

Advances in Organic Chemistry 1988, 1989 and 1990, (various lecturers, University of Edinburgh).

Two-dimensional Nuclear Magnetic Resonance Spectroscopy, (Dr I.H. Sadler, University of Edinburgh).

Industrial Processes, (various speakers, I.C.I. Grangemouth and Department of Chemical Engineering, University of Edinburgh).

Scientific German: Introductory Reading and Translation, (Dr G.M. Burnett, German Department, University of Edinburgh).



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