THE STILLE REACTION IN NATURAL PRODUCT SYNTHESIS: THE TOTAL SYNTHESIS OF 14,15-ANHYDRO-VIRGINIAMYCIN M_2

by

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A Thesis Submitted to the University of Nottingham

for the Degree of Doctor of Philosophy

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Contents

Declaration

I declare that the substance of this thesis has not been submitted, nor is concurrently being submitted in candidature for any other degree. I also declare that the work embodied in this thesis is the result of my own investigations and that where the work of other investigators has been used, this has been fully acknowledged in the text.

_____S. Jordan

_____G. Pattenden

Dedication

This thesis is dedicated to the memory of my father and grandparents, and to my mother without whose love and support my studies would not have been possible.

Acknowledgements

I would like to thank my supervisor Professor Gerry Pattenden for his enthusiasm, guidance, and help throughout the course of my Ph.D. My sincere thanks also go to Drs. John Montgomery and David Entwistle for their collaboration on the project, and to the technical staff at the University of Nottingham for all their support. I gratefully acknowledge the EPSRC and Parke-Davis (through the CASE scheme) for their financial support. I would also like to thank Drs. Jenny Raphy and David Horwell of Parke-Davis for their interest and encouragement. Finally I would like to thank all my friends and colleagues, both past and present, who have enriched my life during my time at Nottingham.

Abstract

The thesis describes synthetic studies directed towards the total synthesis of 14,15-anhydrovirginiamycin M_2, a streptogramin antibiotic of the virginiamycin family. This novel natural product shows pronounced antibacterial activity against a wide range of potentially lethal bacteria. The Introduction summarises the main therapeutic uses, isolation, structural determination, biosynthesis, and mode of action of the virginiamycins. Also included is a review of synthetic approaches which have been described to access these and similar streptogramin antibiotics by other research groups. A review of the intramolecular Stille coupling reaction within organic synthesis incorporating the most prominent examples of its use over the past ten years in the synthesis of natural products is also presented.

The Discussion part of the thesis contains details of our synthetic studies on suitable model systems, including: a study of conjugated triene formation *via* Stille chemistry; peptidic bond formation; and special reference to the problems involved in the synthesis of the 2,4-disubstituted oxazole contained within the virginiamycins. The studies culminate with a description of the first total synthesis of 14,15-anhydrovirginiamycin M_2, which proved identical to the natural product obtained from a *Streptomyces* fermentation process.

A full description of the experimental work carried out, and spectroscopic data for all compounds synthesised, is contained in an Experimental section.

Abbreviations

Ac	acetyl
AIBN	2,2'-azo*bis*(2-methylpropionitrile)
Boc	*tert*-butyloxycarbonyl
BOP-Cl	*bis*(2-oxo-3-oxazolidinyl)phosphonic chloride
^{t}Bu	*tert*-butyl
DBU	1,8-diazabicyclo[2.2.2]octane
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	di*iso*butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethyl sulphide
DMSO	dimethyl sulphoxide
EDC	1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
h	hour
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HOBt	1-hydroxybenzotriazole
i.r.	infra-red
LDA	lithium di*iso*propylamide
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MEM	2-methoxyethoxymethyl
Mes	mesityl
min	minute

MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
n.m.r.	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Phth	phthalamido
^{i}Pr	*iso*-propyl
py	pyridine
Red-Al	sodium *bis*(2-methoxyethoxy)aluminium hydride
TBAF	tetrabutylammonium fluoride
TBDMS / TBS	*tert*-butyldimethylsilyl
TBDPS / TPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetyl
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Troc	2,2,2-trichloroethoxycarbonyl
TsOH / *p*TSA	*para*-toluenesulphonic acid
u.v.	ultra-violet

1. INTRODUCTION

1.1 Virginiamycin: A General Introduction.

The virginiamycins, and other related compounds of the streptogramin family such as madumycin **(2)** and griseoviridin **(3)** **(Figure 1)**, which are produced as secondary metabolites by a wide range of *Streptomyces* and *Actinoplanes*, have been known since the later half of the 1950's. Their mode of action and their pharmacology have been studied extensively since their isolation, but up until the last fifteen years there had been relatively few synthetic studies undertaken on these molecules. Their unique biological properties as effective antibiotics has led to their continued use in General Practice for over thirty years, especially in the treatment of *Staphylococcal* infections, and in the agricultural industry as a growth promoter. Despite its effectiveness, virginiamycin* and other related compounds, although finding some alternative therapeutic uses have not become more widespread due to their poor water solubility and difficulties associated with their assay in the blood. However the increase in the incidence of resistant strains of *Staphylococcal* infections in hospitals during the late 1970's, and in particular those strains showing multiple resistance to the more commonly used antibiotics, has prompted interest in these compounds once more. It is surprising that even today virginiamycin is still one of the most effective antibiotics available for the treatment of *Staphylococcal* infections, and at present is one of the few antibiotics effective in the treatment of the new deadly multiple resistant strain of *Tuberculosis.*

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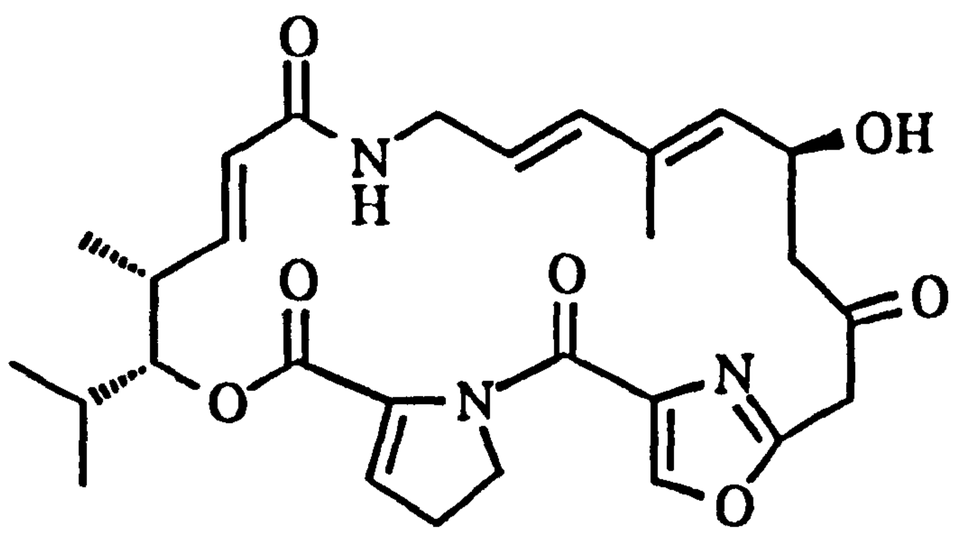
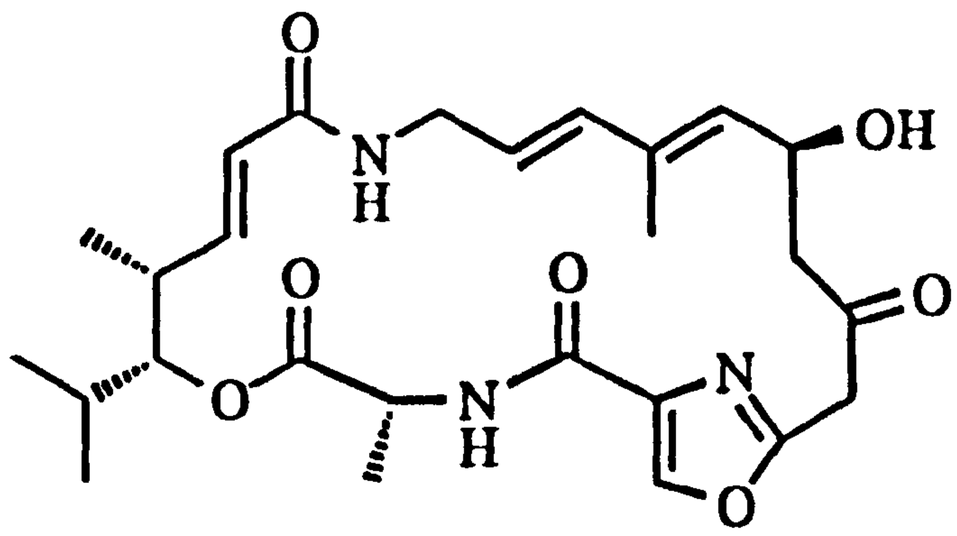
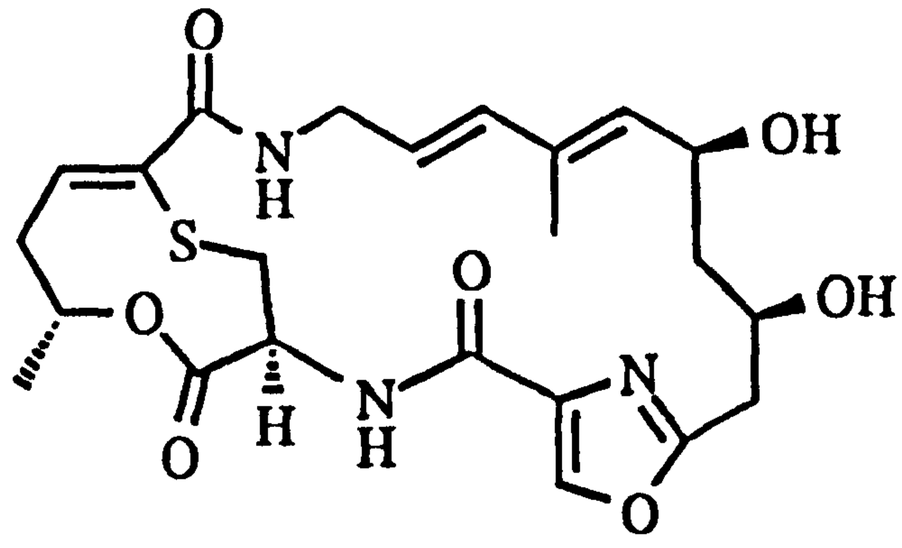
*Where virginiamycin is used without a suffix this refers to the mixture of virginiamycin M and S as isolated from the fermentation broth.



Virginiamycin M_1 (1)



Madumycin I (2)



Griseoviridin (3)

Figure 1

Virginiamycin was first isolated from cultures of the soil organism *Streptomyces Pristinaespiralis* by Preud'homme *et al* in 1955.[1] Annual demands for virginiamycin haven risen dramatically over the past twenty years and production is currently in the hundreds of tons per annum. To accommodate such huge demands virginiamycin is produced by fermentation of specially selected high yielding strains of *Streptomyces Pristinaespiralis.*

As a treatment for *staphylococcal* infection virginiamycin has several distinct advantages over the other MLS (Macrolides-Lincosamides-Streptogramins) antibiotics currently used. Virginiamycin shows a low number of incidents of resistant strains of *Staphylococcus* (only 2-3%, including those isolated in hospital environments),[2] good general tolerance, a low incidence of allergic reactions associated with their use, and good activity against strains of *Staphylococcus* that show resistance to the more commonly used antibiotics (30% of isolated hospital strains of the bacteria show

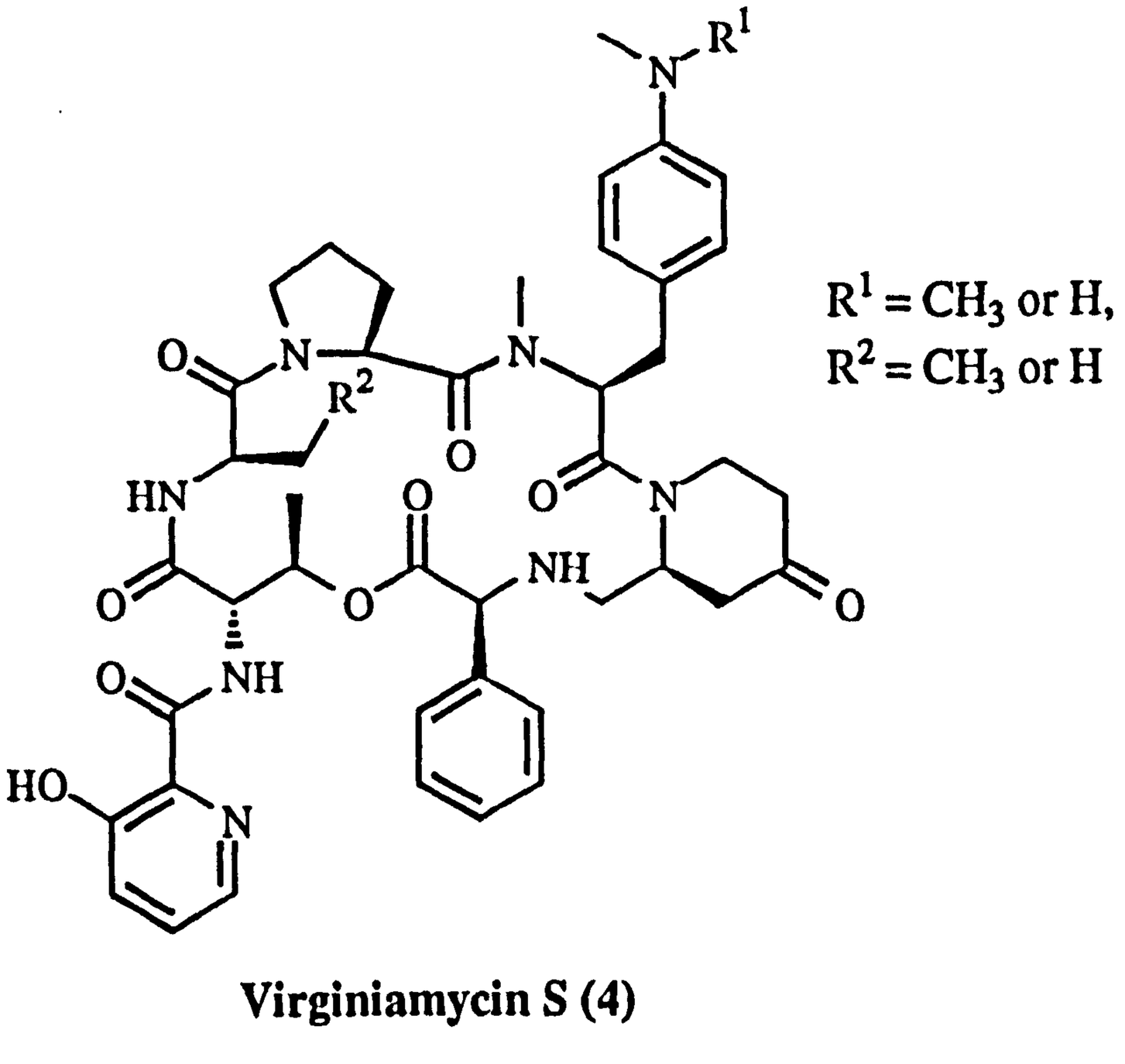
resistance to erythromycin and/or methicillin, and penicillin is inactive against 90% of the *Staphylococcus* strains isolated).[3]

Since 1980 the use of virginiamycin has been extended to the treatment of not only *Staphylococcal* infection but also the more persistent sexually transmitted diseases such as *Mycoplasma, Nasseria* and *Chimydia*,[4] and also to the treatment of lung infections such as *Pneumococcus, Legionnella* and *Haemophilus*.[5] More recently studies have found these compounds to be potent gastrin and cholecystokinin antagonists. Cholecystokinin antagonists are useful as analgesics and in the treatment and prevention of gastrointestinal disorders, and disorders of the central nervous and appetite regulatory systems. Gastrin antagonist block the receptors for gastrin therefore acting as agents in the treatments of ulcers, tumours and other gastrointestinal disorders.[6]

Apart from its therapeutic applications the other main use of virginiamycin is as a growth promoter, thus making virginiamycin an important food additive in the animal farming industry.[7] Studies of young pigs fed on an artificial milk diet containing virginiamycin, with the emphasis of results purely on the nutritional effects and not any underlying clinically associated effects, have shown an increase of 10% in the growth rate and 7% in feed conversion.[8] These results were attributed to the following identified effects: a change in the distribution of intestinal flora giving rise to a new equilibrium of Gram positive flora; a decrease in the microbial production of lactic acid, volatile fatty acids, ammonia and amines thereby reducing the toxic effects of these breakdown compounds; a saving and optimal availability of glucose and amino acids resulting in less wastage; a reduction in the pass through rate of the intestine resulting in the increased absorption of protein, fat and carbohydrates; and a direct influence on the permeability of the intestinal mucosa. The experiments also showed no sign of destruction of the intestinal flora but only changes in the ratio of the different bacterial species present. These results have also been found in the case of poultry, and studies with other animals have shown virginiamycin to be beneficial in most cases. The overall effect of these conditions reduces the metabolism of the bacteria, thus increasing

the amount of nutrients available for the animal. This property has allowed the use of low protein diets, a method for cutting costs in the farming of animal that is becoming ever more prevalent.

The isolated virginiamycin obtained from the fermentation broth comprises two groups of synergistic components: 30-40% virginiamycin S (4)- a group B streptogramin **Figure 2**; and 60-70% virginiamycin M (1)- a group A streptogramin.[9] Antibiotics of the streptogramin family are an association of two groups of compounds: group A streptogramins are polyunsaturated macrolactones; and the group B streptogramins are peptidic macrolactones (depsipeptides). Both groups contain members differing slightly in substituents, functional moieties and amino acid residues.



Virginiamycin S (4)

Figure 2

1.2 The Mode of Action and Biological Activity of Virginiamycin.

Virginiamycin inhibits the multiplication of some procaryotic cells, but has no effect on the growth of most eucaryotic cells. It is active against a wide range of Gram positive bacteria (especially *Staphylococcus*) and has also been shown to affect some Gram negative bacteria such as *Haemophilus*. The two components of virginiamycin, virginiamycin M and virginiamycin S, are synergistic, *i.e.* the activity of the mixture is ten-fold that of the sum of the activities of the individual components. Virginiamycin S is active at about 2 mgL^{-1} on approximately 70% of the isolated strains of *Staphylococcus*, and virginiamycin M is active at about 1 mgL^{-1} on approximately 80% of the isolated strains of *Staphylococcus*. Each component on its own is bacteriostatic, *i.e.* they prevent the multiplication of the bacterial cells. However, the mixture of both of the components has an activity of about 0.1 mgL^{-1} on approximately 97-98% of the isolated strains of *Staphylococcus*, including the multiple resistant strains of *Staphylococcus aureus*. This synergistic behaviour not only increases the spectrum of activity and potency of virginiamycin, but renders the mixture bactericidal, *i.e.* the mixture reduces the number of bacterial cells present.[10]

The mode of action of virginiamycin and related compounds has been extensively studied.[9, 11] The bacteriostatic activity of the single components can be explained as a consequence of cessation of protein synthesis within the bacterial cell, an effect produced almost immediately after incubation with the compound. Each component binds to the 50S ribosomal subunit arresting protein synthesis by preventing the elongation mechanism during the reading of the messenger RNA by the ribosome. Thus production of both RNA and DNA in the bacterium is prevented. This effect however is reversible unless both components are present. Virginiamycin S binds reversibly to the ribosome in a stoichiometric ratio, whereas virginiamycin M binds irreversibly when present stoichiometrically. However explanation of the bactericidal property of the mixture is still unclear at present. It has also been shown that virginiamycin S facilitates the transport of potassium ions across the cell

membrane, the presence of which has been shown to be essential for the irreversible binding of virginiamycin M to the ribosome.[12]

1.3 The Structure of Virginiamycin M.

Natural virginiamycin M is a mixture of two main components: virginiamycin M_1 **(1)** has a dehydroproline ring and constitutes 90-97% of the mixture; and virginiamycin M_2 **(5)** containing a fully saturated (*D*)-proline ring and is present in 3-10% depending on the conditions of fermentation. In addition to these two main forms of virginiamycin M, several other analogues have also been isolated from various strains of *Streptomyces*, with all three compounds **(6)**-**(8)** having also been isolated in the fully saturated proline ring forms.[13] **Figure 3.**

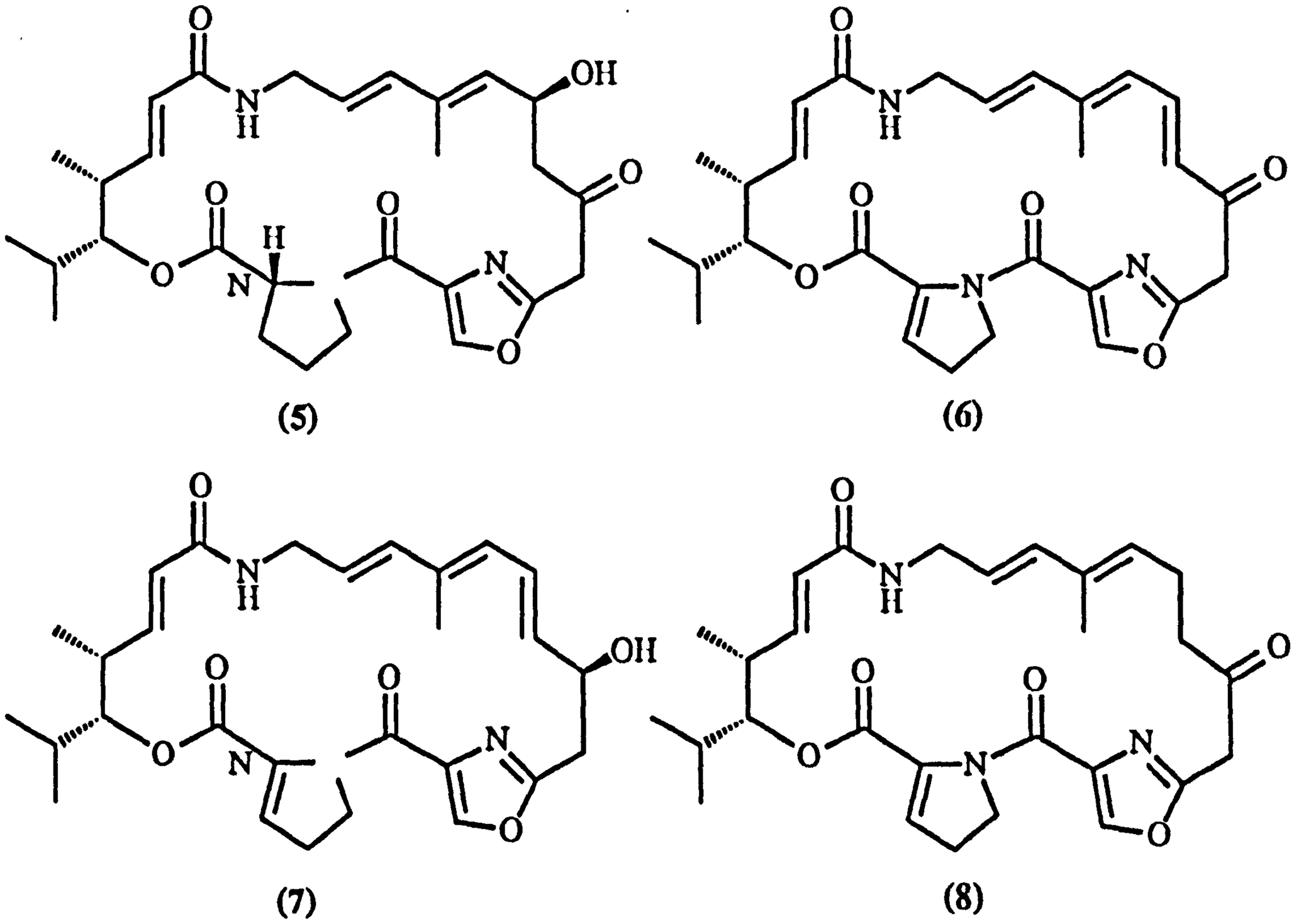


Figure 3

The occurrence of both analogues **(6)** and **(7)** can be rationalised by the dehydration of the secondary alcohol of virginiamycin M_1 with analogue **(8)** presumably resulting from a reductive elimination of the secondary alcohol. As before the occurrence of these analogues, and the relative percentages in which they are produced, is dependent on the conditions of fermentation and the strain of *Streptomyces* used.

With a variety of organisms producing various analogues of virginiamycin M a number of different names arose for these compounds. We have used the name virginiamycin M, but alternatively this compound can also be referred to as pristinamycin II, streptogramin A, mikamycin A, ostreogrycin A, synergistin A and vernamycin A. To avoid confusion Chemical Abstracts have adopted a numbering system that is now recognised by all research groups working on these compounds, and it is this method of numbering that shall be used throughout this thesis. **Figure 4.**

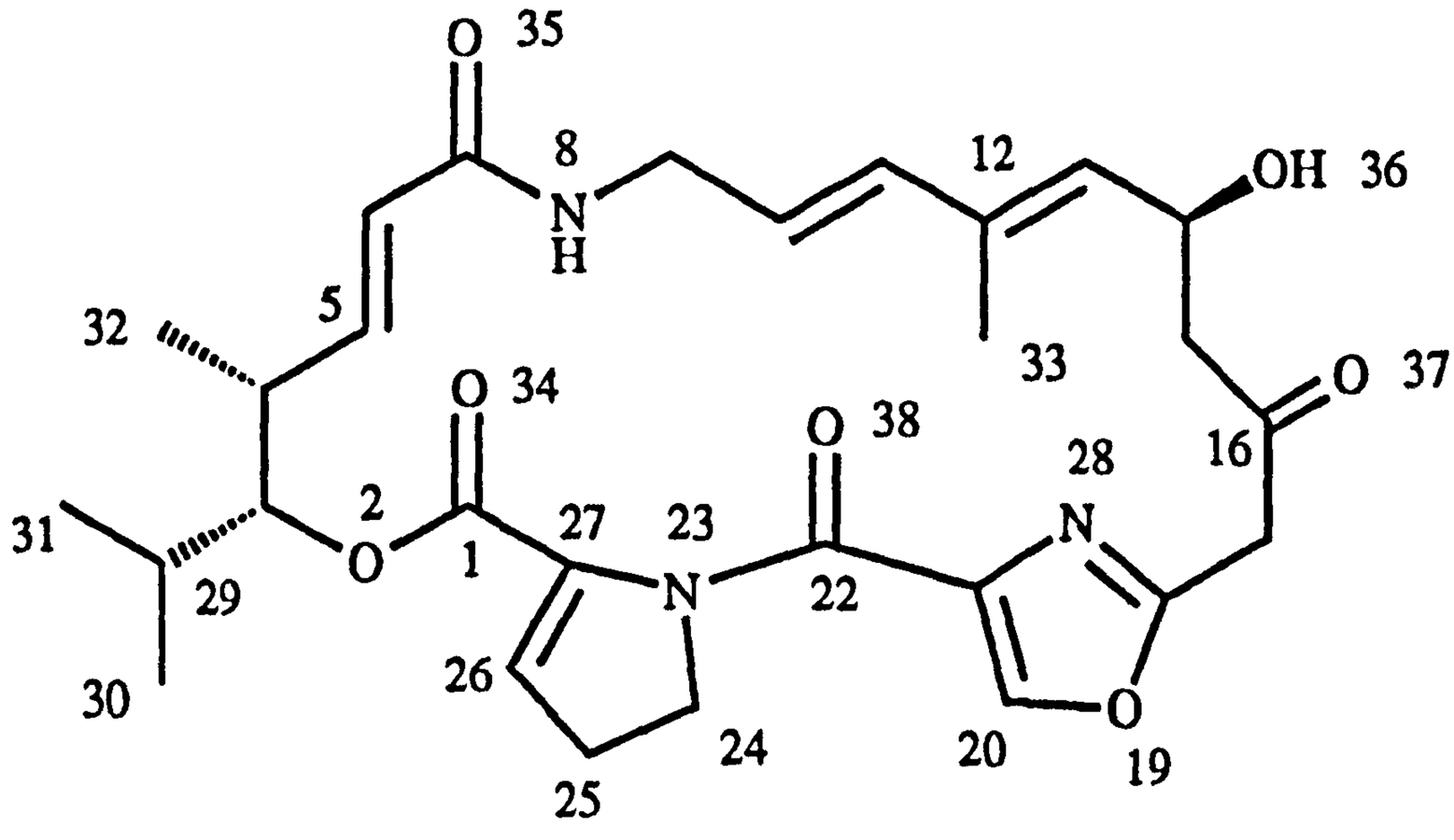


Figure 4

The structure of virginiamycin M_1 was partially elucidated by Preud'homme *et al* in the laboratories of Rhone-Poulenc in the mid 1960's by the use of classical degradation and chemical analysis.[1b, 1c] Final structural elucidation was not achieved until a few years later by Delpierre *et al* using spectroscopic methods in conjunction with classical chemical analysis.[14] The configuration of the molecule was determined in 1974 by Durant *et al* using X-ray crystallography.[15]

Conformational studies of the crystal structure using computer graphic examination has shown the molecule to be fairly compact, with the macrocycle folded in two and held by weak hydrogen bonding between the hydrogen at N-8 and O-38 (a distance of 2.6Å). The three oxygen atoms O-34, O-35 and O-36 are all arranged towards one side of the molecule producing a predominately hydrophilic side to the molecule. The methyl groups, double bonds and the oxazole nucleus are all arranged towards the opposite side of the molecule forming the lipophilic portion of the molecule. Further nmr studies, both ^{1}H and ^{13}C, including quantitative NOE measurements, indicate the conformation in solution to be very close to that of the crystal structure.[16]

1.4 The Biosynthesis of the Virginiamycin M System.

The biosynthesis of virginiamycin M_1 **(1)** has been studied by Kingston *et al*[17] using feeding experiments with ^{13}C labelled precursors incorporated into the PDT 30 strain of *Streptomyces virginiea.* The studies identified six substrates directly used in the biosynthetic pathway, *i.e.* acetate, valine, methyl methionine, serine, proline, and glycine. The majority of the virginiamycin M skeleton was found to derive from acetate units from the polyketide chain indicated by the incorporation of both 1-^{13}C acetate and 2-^{13}C acetate at C-5, -7, -12, -14, -16, -18, and C-4, -6, -11, -13, -15, -17 respectively. In addition to this the experiments indicated that C-33, the vinylic methyl group, was also derived from an acetate unit *via* a hitherto unrecognised pathway. The authors reasoned that the method by which the C-33 methyl was incorporated was *via* the β-hydroxy acid **(10)**, formed by an aldol condensation of an acetate unit, presumably as malonyl coenzyme A, to a preformed polyketide chain **(9)**. The β-hydroxy acid **(10)** then undergoes decarboxylation and dehydration, with reduction of the carbonyl group to give the allylic alcohol system **(11)** of virginiamycin M_1. **Figure 5.**

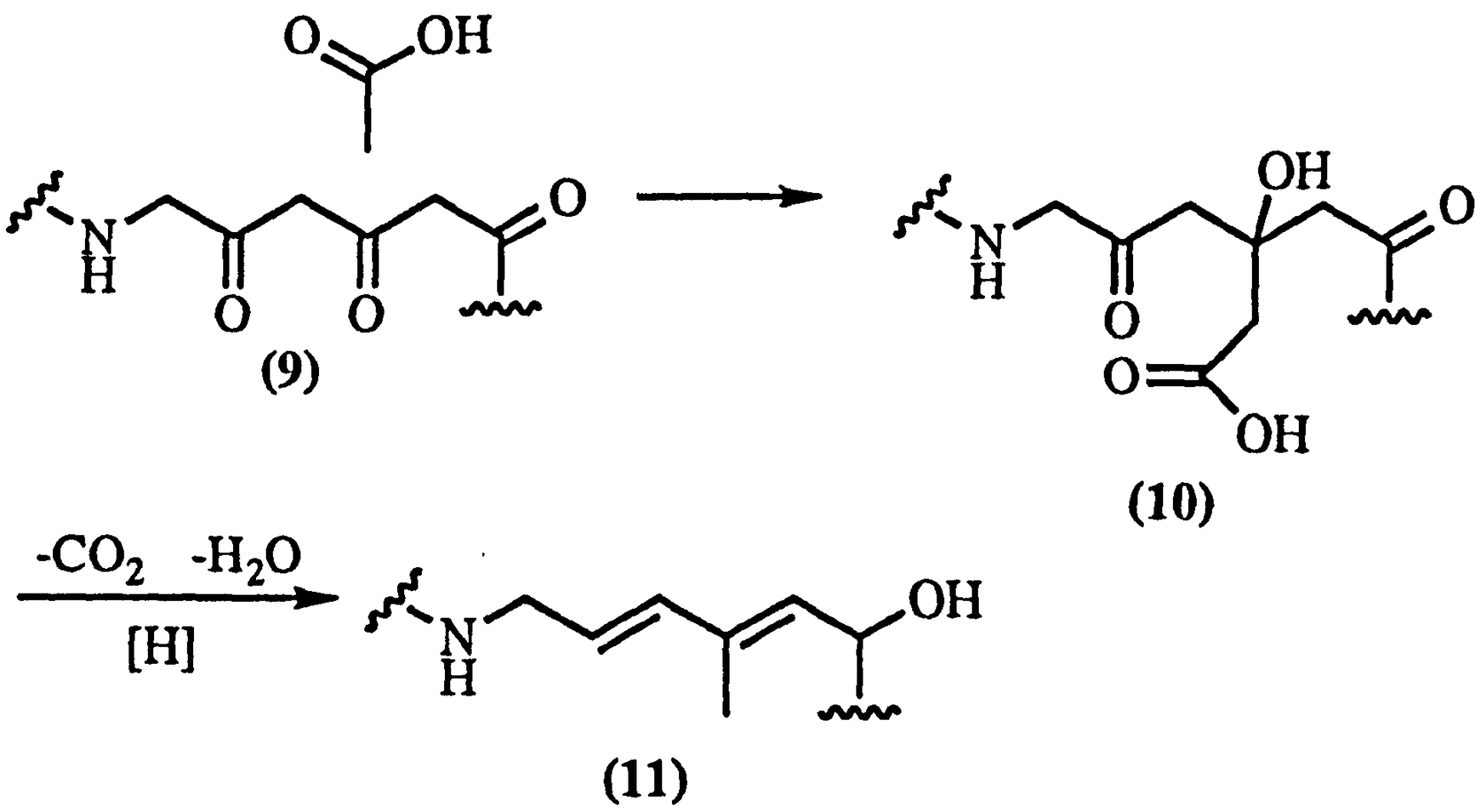
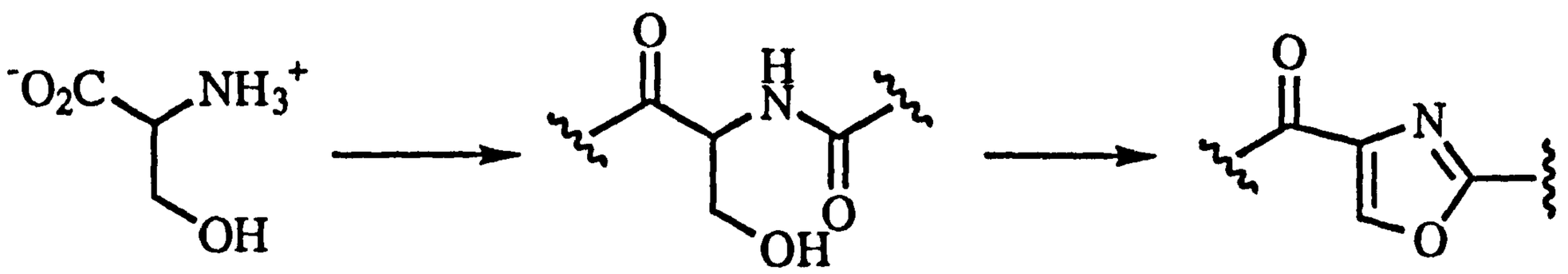


Figure 5

Incorporation of labelled valine at C-3, -29, -30, and -31 clearly indicated that the isopropyl group in virginiamycin M originated from valine. C-32, the adjacent methyl group, derives from methyl methionine *via* the normal recognised pathway for methyl incorporation involving methyl methionine.

The subunit of the virginiamycin M system of most interest is the 2,4-disubstituted oxazole ring. In the case of berninamycin[18], an antibiotic containing a 2,4-disubstituted oxazole with a methyl in the 5-position, the oxazole was found to originate from threonine. It was therefore reasoned that the oxazole in virginiamycin could conceivably originate from serine. Incorporation studies using labelled serine gave ^{13}C enrichment at C-20 in virginiamycin M indicating serine as the source for the oxazole. The pathway proposed for the conversion of serine into the oxazole is thought to proceed *via* the corresponding β-hydroxy amide **(12)**. **Figure 6.**



(12)

Figure 6

The remaining two nitrogen atoms within the system were found to originate from proline itself, and glycine to give the N-8, C-9 and C-10. Combining this information, and the information gained from other studies, the authors proposed precursors for the biosynthesis of the virginiamycin M skeleton as illustrated in **Figure 7**.

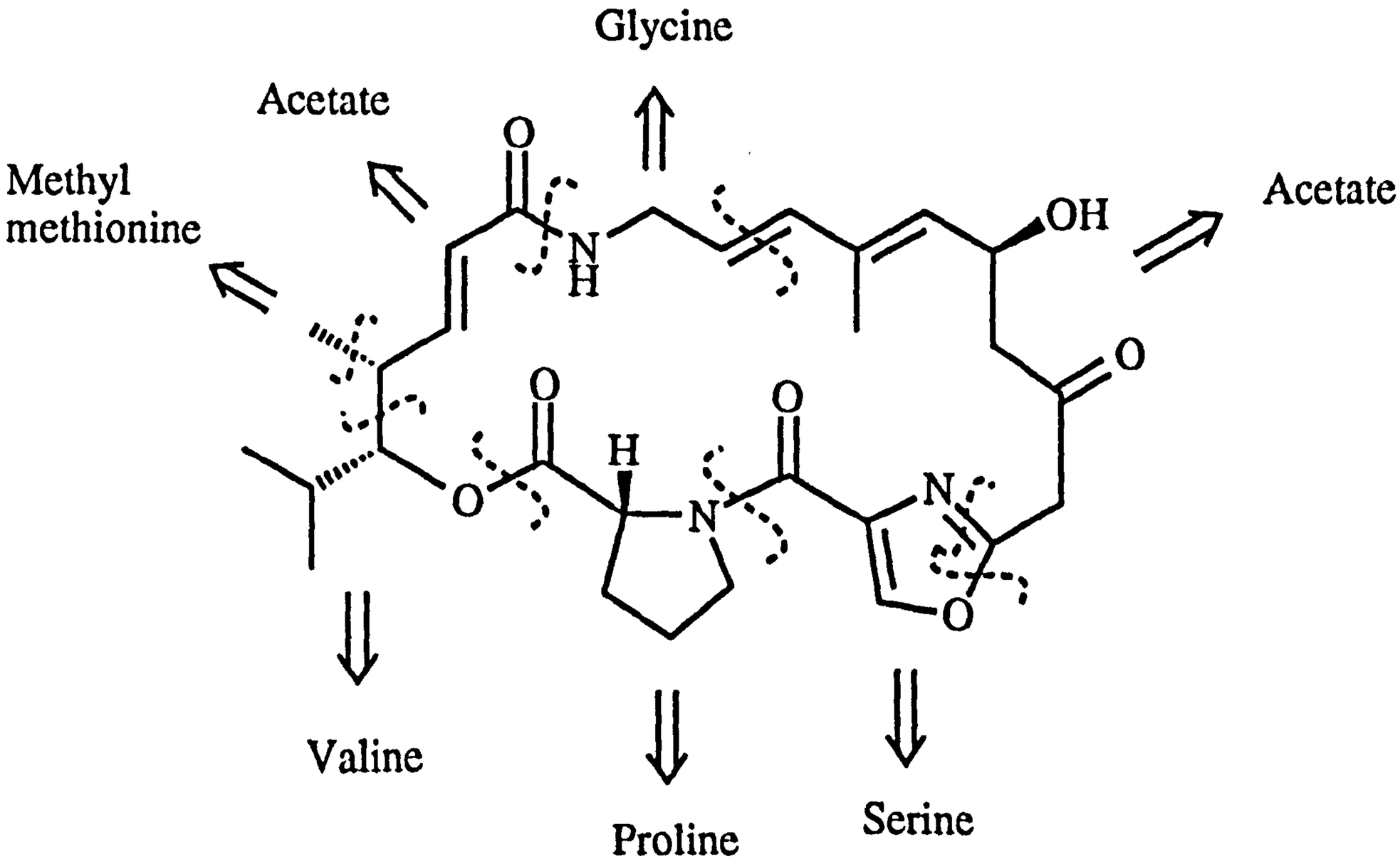


Figure 7

1.5 Synthetic Approaches to the Virginiamycins and Related Group A Streptogramin Antibiotics.

The importance of the virginiamycins as potent antibiotics, coupled with their interesting structural features, have led to these compounds receiving increased attention from synthetic chemists over the past twenty years. One of the pioneers in the search for a synthetic route to virginiamycin M, madumycin, and griseoviridin (**Figure 1**), compounds of great similarity, has been A.I.Meyers from Colorado. His work over the past fifteen years culminated in one of the first syntheses of these group A streptogramin antibiotics, that of madumycin II **(13)**.[19] This work was published simultaneously with the completion of our own studies. The approach used by Meyers *et al* relied on a macrolactamisation between C-7 and N-8, using BOP-Cl to effect the cyclisation to form the 23-membered ring system. Their route proceeds along a convergent synthesis of two fragments resulting from the initial disconnection between C-7 and N-8, as mentioned for the cyclisation, and between C-22 and N-23, as the amide bond formation step to afford the cyclisation precursor. **Figure 8.**

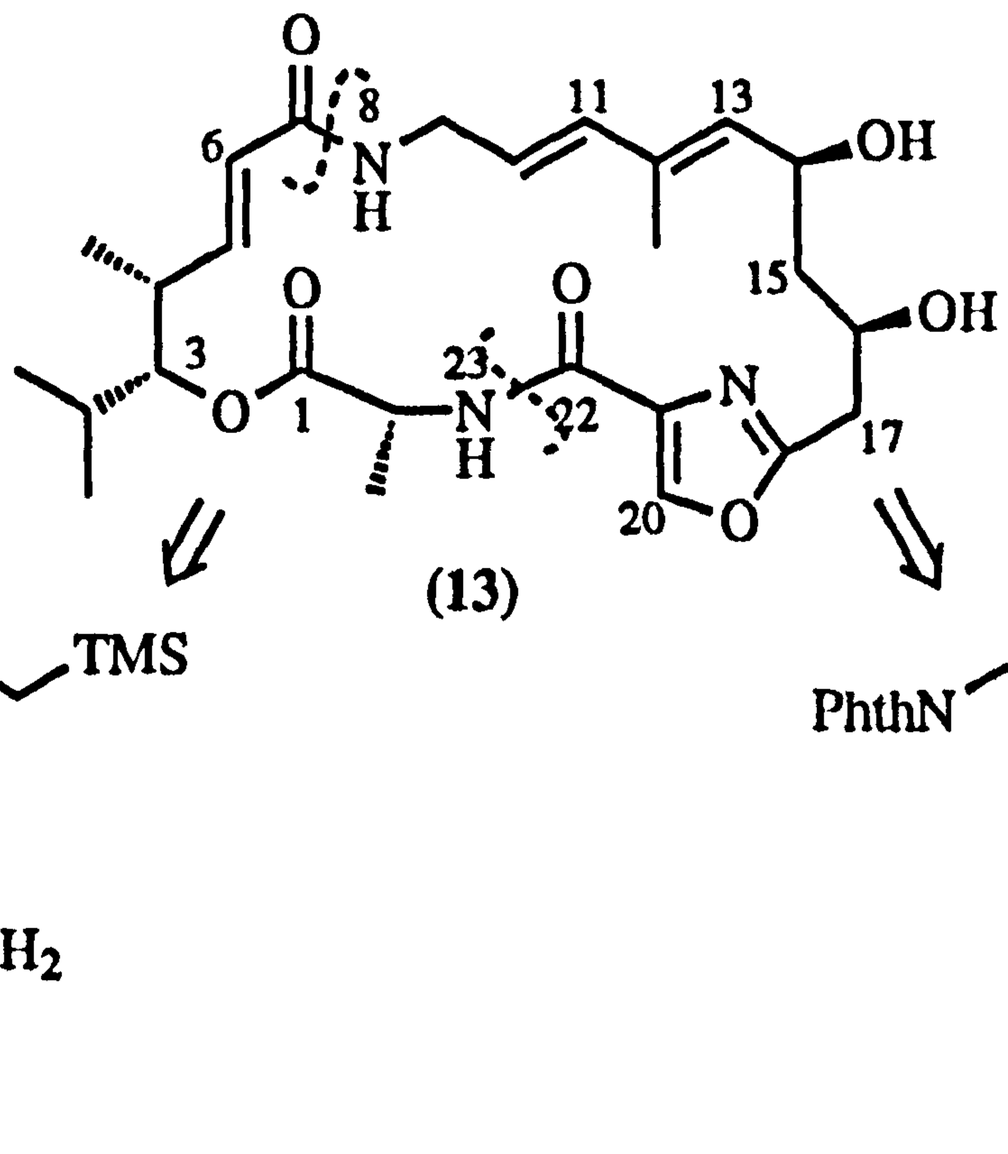
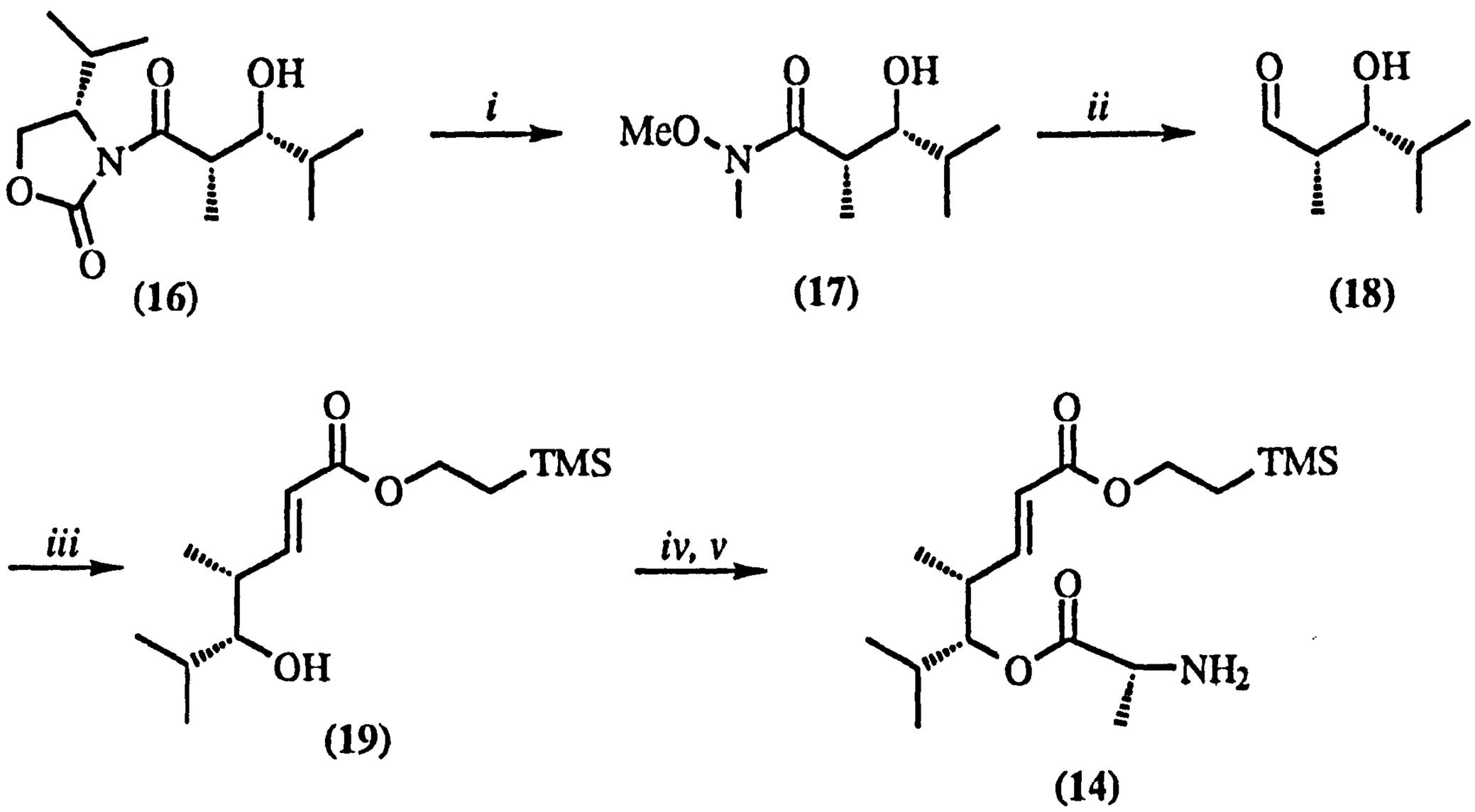


Figure 8

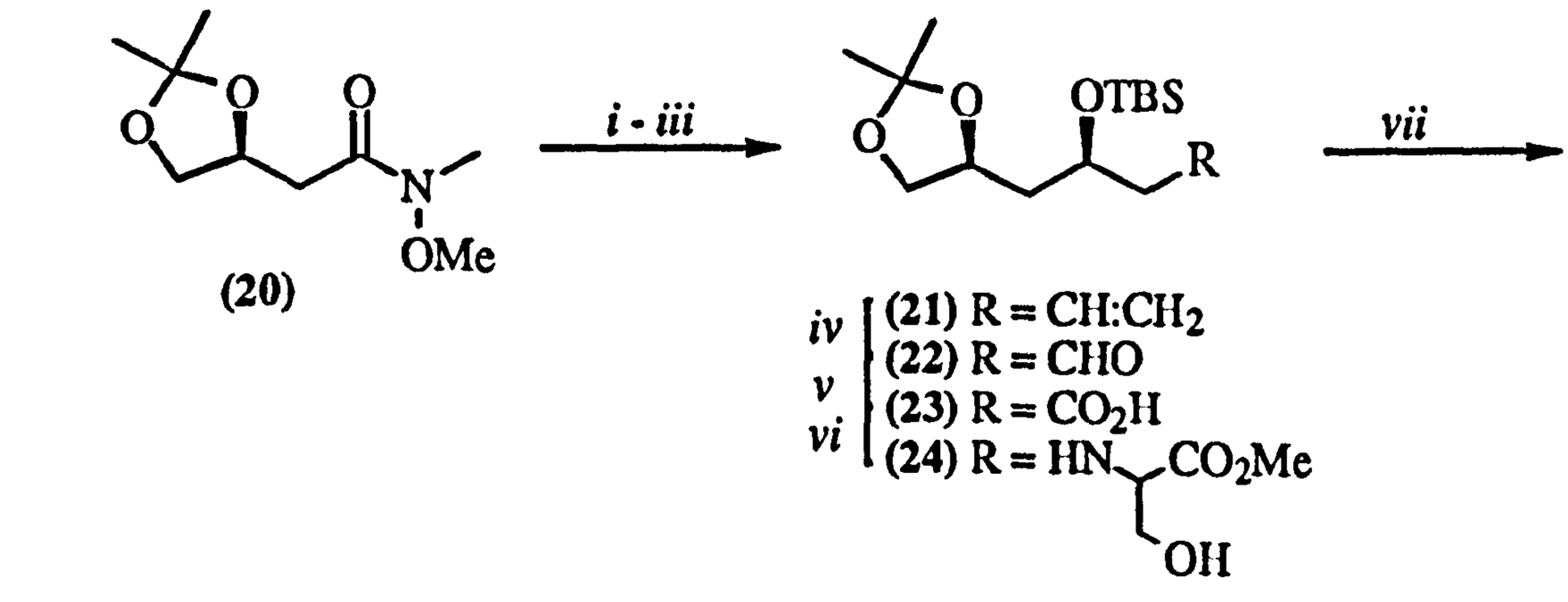
Meyers' synthesis of the left-hand fragment **(14)** utilised the chiral oxazolidinone developed by Evans to form the *syn* adduct **(16)**.[20] The adduct **(16)** was transformed into the Weinreb amide **(17)** before being reduced to the unstable aldol **(18)** with DIBAL-H. The aldol **(18)** was converted to the α,β-unsaturated silyl ester **(19)** in 72% yield using a Horner-Emmons-Wadsworth modified olefination before coupling the free hydroxyl group of **(19)** to *N*-Boc-*D*-alanine in a quantitative yield. Final removal of the Boc protecting group yielded the free amine **(14)**. **Scheme 1.**

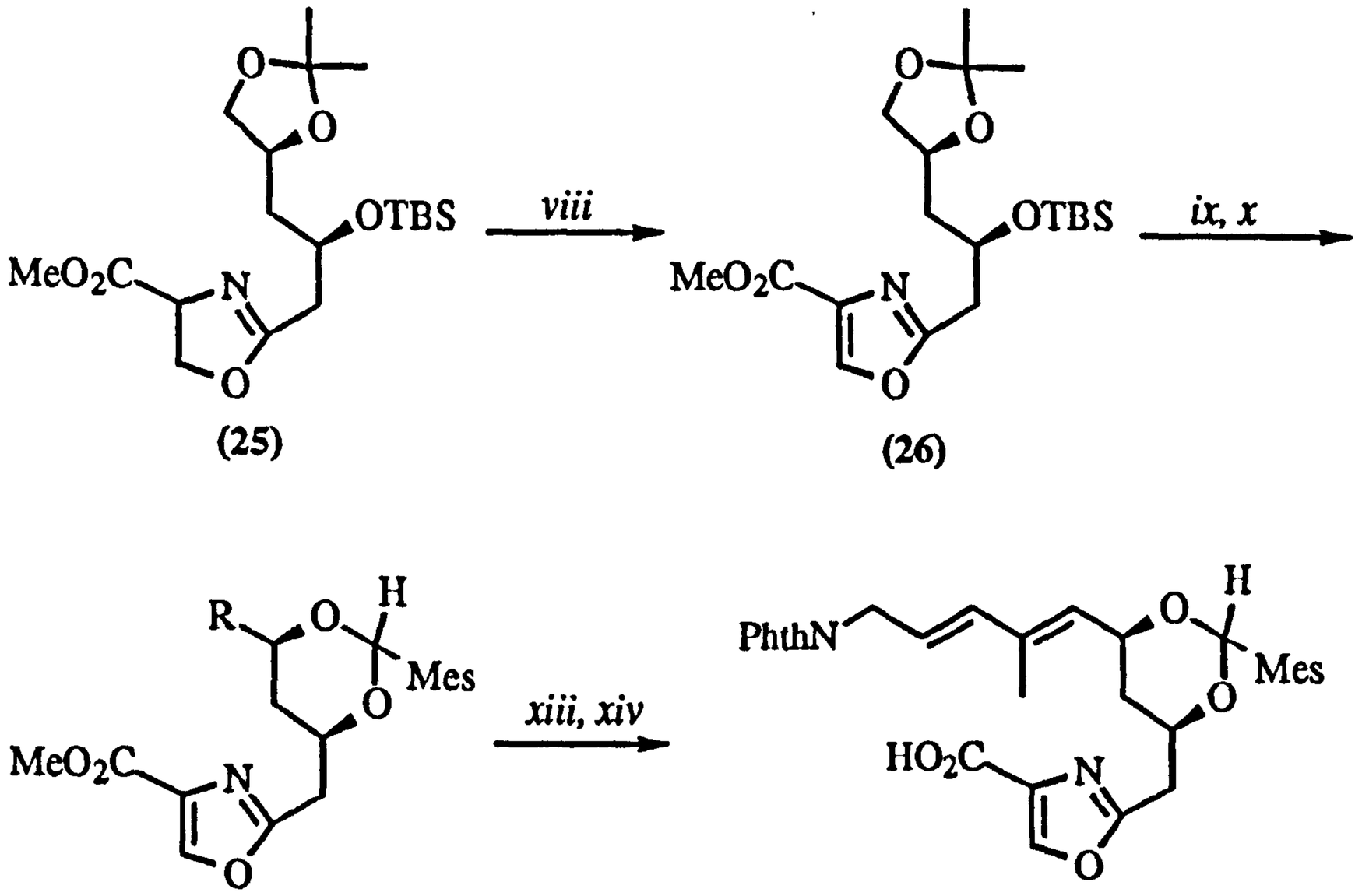


Reagents: *i*, Me_3Al, MeONH(Me).HCl; *ii*, DIBAL-H; *iii*, $(EtO)_2P(O)CHCO_2CH_2CH_2SiMe_3$, LiCl, Hünig's base; *iv*, DCC, *N*-Boc-*D*-alanine; *v*, $TsOH.H_2O$.

Scheme 1

Fragment **(15)** was synthesised from the Weinreb amide **(20)** by treatment with allylmagnesium bromide to give the allyl ketone. **Scheme 2.** Stereoselective reduction of the allyl ketone to the *syn* 1,3-alcohol with $LiAlH_4$ and lithium iodide followed by TBS protection yielded the allyl alcohol **(21)** in 98% yield. Ozonolysis of the double bond in **(21)** gave the aldehyde **(22)**. The aldehyde **(22)** was then oxidised to the carboxylic acid **(23)** which was then coupled to (*S*)-serine methyl ester, *via* the mixed anhydride, to give the hydroxyamide **(24)** in 93% yield. Treatment of the hydroxyamide **(24)** with Burgess reagent afforded the oxazoline **(25)**, in 69% yield, which was then oxidised to the oxazole **(26)** in 81% yield using a Cu(I)-Cu(II) peroxide reagent. The TBS protection of **(26)** was removed with TBAF to give the free alcohol which underwent smooth conversion to the stereochemically pure 1,3-mesityldioxane **(27)** in 74% yield on treatment with 1,3,5-mesitylformaldehyde and catalytic camphorsulphonic acid. Oxidation of the primary alcohol **(27)** to the aldehyde **(28)** using SO_2.py, DMSO and triethylamine, followed by Wittig olefination with α-formylethylidenetriphenylphosphorane gave the *E*-α,β-unsaturated aldehyde **(29)** in 62% yield. Chain extension of the aldehyde was achieved by treatment with vinyl triphenylphosphonium bromide in the presence of potassium phthalimide to give the *E,E*-diene-amide **(30)**. Hydrolysis of the methyl ester with lithium iodide in pyridine finally gave the carboxylic acid **(15)** in 58% yield.





(30)

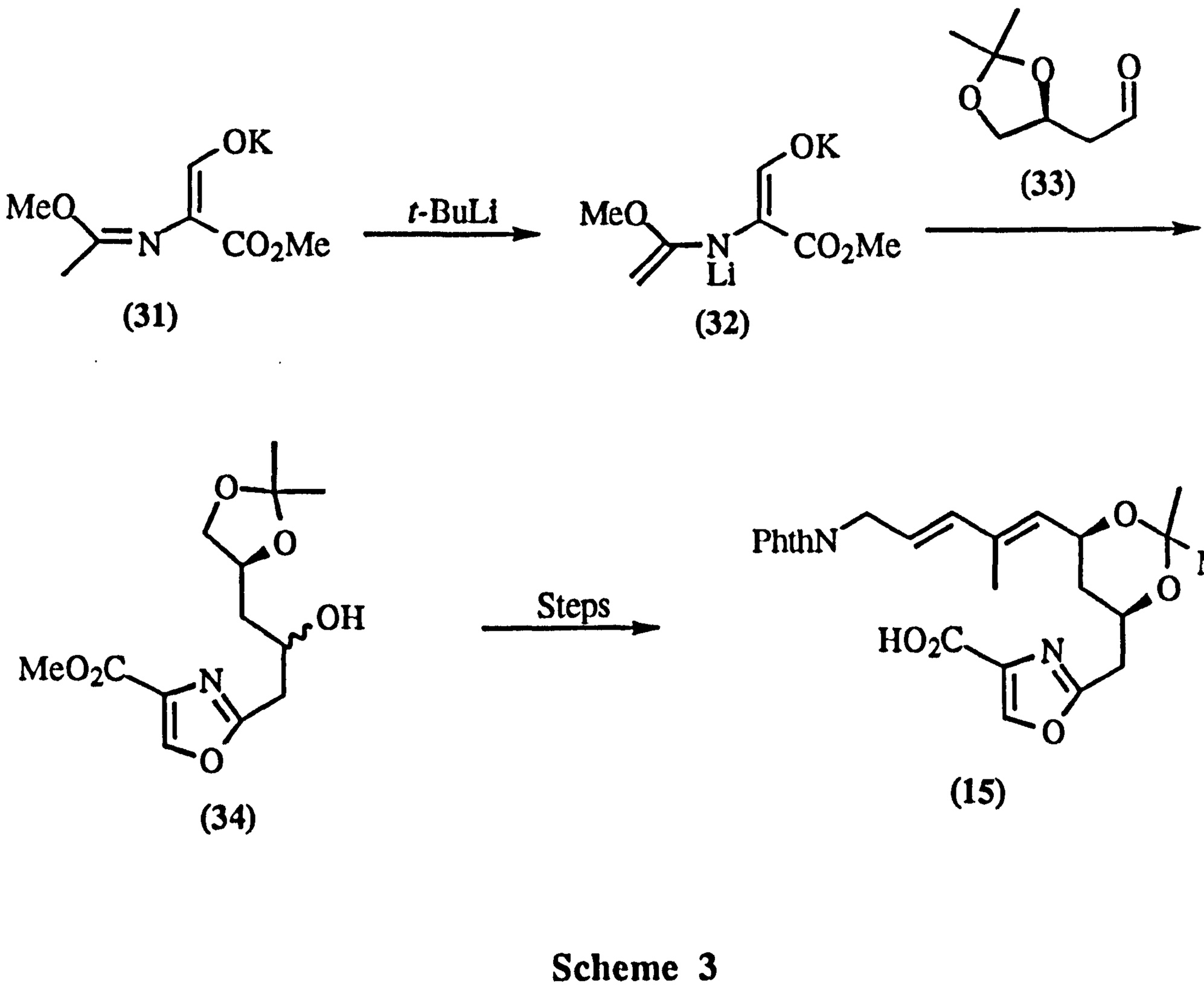
xi (27) R = CH_2OH
xii (28) R = CHO
(29) R = $CHC(CH_3)CHO$

Reagents: i, Allylmagnesium bromide, THF; *ii*, $LiAlH_4$. LiI, Et_2O; *iii*, TBS-Cl, imidazole, DMF; *iv*, O_3, DMS;, *v*, $NaClO_2$, NaH_2PO_4, H_2O_2, CH_3CN-H_2O; *vi*, isobutylchloroformate, *N*-methylmorpholine, serine methyl ester.HCl; *vii*, Burgess reagent; *viii*, *t*-butylperbenzoate, CuBr, $Cu(OAc)_2$, benzene; *ix*, TBAF, THF; *x*, camphorsulphonic acid, 1,3,5-mesityl-formaldehyde CH_2Cl_2; *xi*, SO_2.py, DMSO, Et_3N; *xii*, $Ph_3P{=}C(CH_3)CHO$, benzene; *xiii*, $CH{=}CHPPh_3Br$, potassium phthalimide, THF; *xiv*, LiI, py.

Scheme 2

During the course of their synthetic studies Meyers *et al* published an alternative route to fragment **(15)**.[21] This method utilised Cornforth's method of oxazole synthesis, but with an additional twist. In Cornforth's synthesis of 2-methyl-4-carboxyoxazole

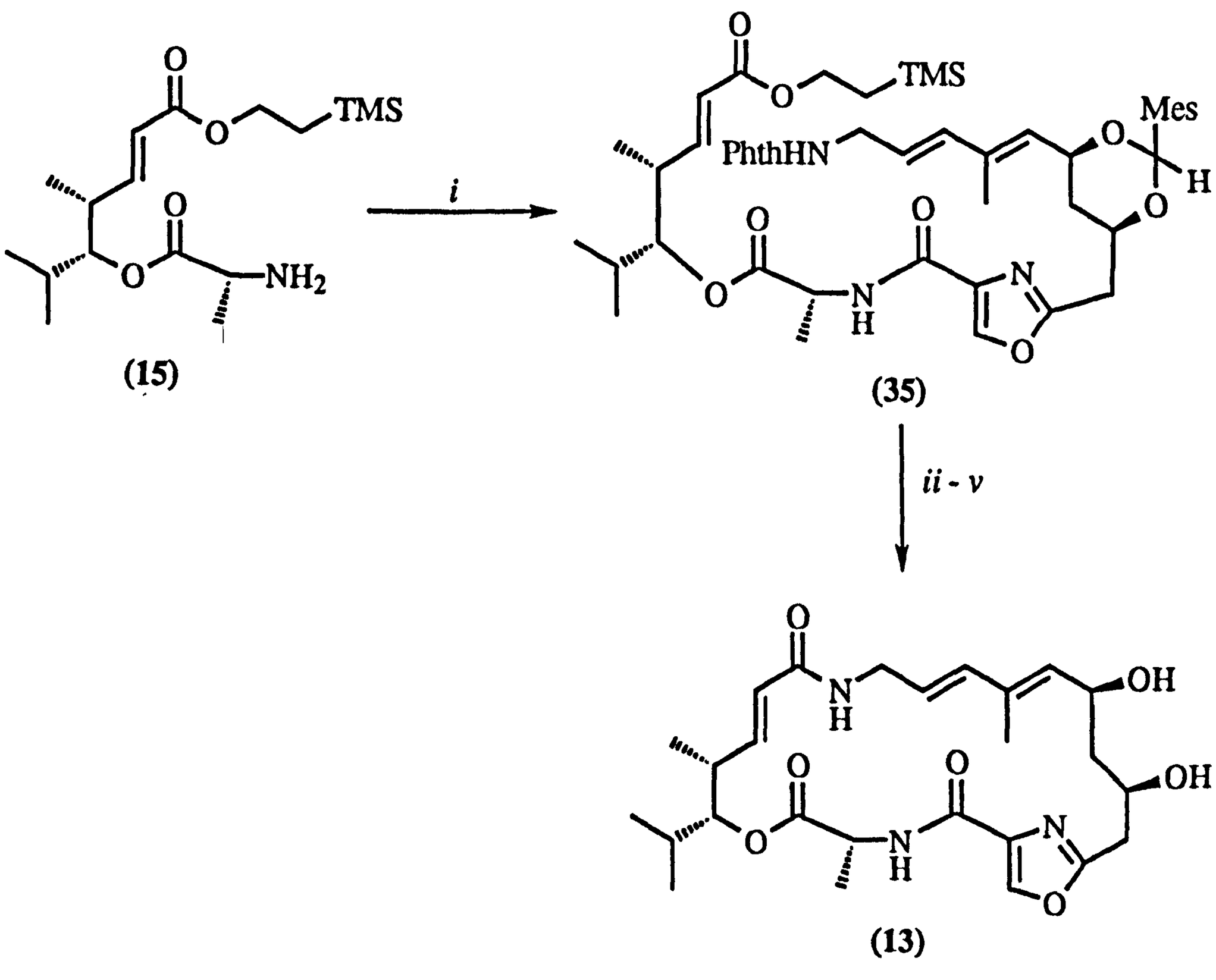
ethyl ester the unstable potassium enolate **(31)** is cyclised to the oxazole directly, using hot glacial acetic acid. Meyers however, deprotonated the potassium enolate **(31)** with *t*-butyllithium, and then added the aldehyde **(33)** to the resulting anion before cyclising with boron trifluoride etherate to give the diastereomeric mixture of the oxazole **(34)**. This method enabled Meyers to elaborate the 2-methyl group into a suitable side-chain before forming the oxazole ring. This method also had the advantage of forming the oxazole ring directly, without the need for the oxidation of the oxazoline to the oxazole, a reaction which at that time was usually achieved using nickel peroxide in very poor yields. The oxazole **(34)** was then carried through to fragment **(15)** in accordance with the method described previously. **Scheme 3.**



Scheme 3

Fragments **(14)** and **(15)** were coupled together using DCC to give the amide **(35)** in 63% yield. **Scheme 4.** After removal of the phthalimide protecting group with methylamine in ethanol-benzene, and removal of the silyl protecting group with TBAF, the amino acid was cyclised with BOP-Cl and Hünig's base to give the

protected madumycin in 32% yield. Finally hydrolysis of the dioxane ring with trifluoroacetic acid gave madumycin II (13).



Reagents; *i*, DCC, DMAP, CH_2Cl_2; *ii*, CH_3NH_2, EtOH-benzene; *iii*, TBAF, THF; *iv*, BOP-Cl, Hünig's base, CH_2Cl_2; *v*, trifluoroacetic acid

Scheme 4

Published simultaneously with Meyers' synthesis was an independent total synthesis of (-) virginiamycin M_2 by Schlessinger *et al.*[22] Schlessinger's approach to the virginiamycin system relied on a macrolactamisation between C-22 and N-23 using the Mukaiyama amide coupling conditions.[23] Disconnection of virginiamycin M_2 (5) in accordance with this methodology, and further disconnection between C-7 and N-8, provided the two main fragments (36) and (39). **Figure 9.** Further disconnection of fragment (36) gave the 2-bromomethyloxazole (38) and the polyunsaturated aminal

chain **(37)**. Disconnection of fragment **(39)** at the ester linkage gave the protected proline **(41)** and the α,β-unsaturated hydroxy acid **(40)**.

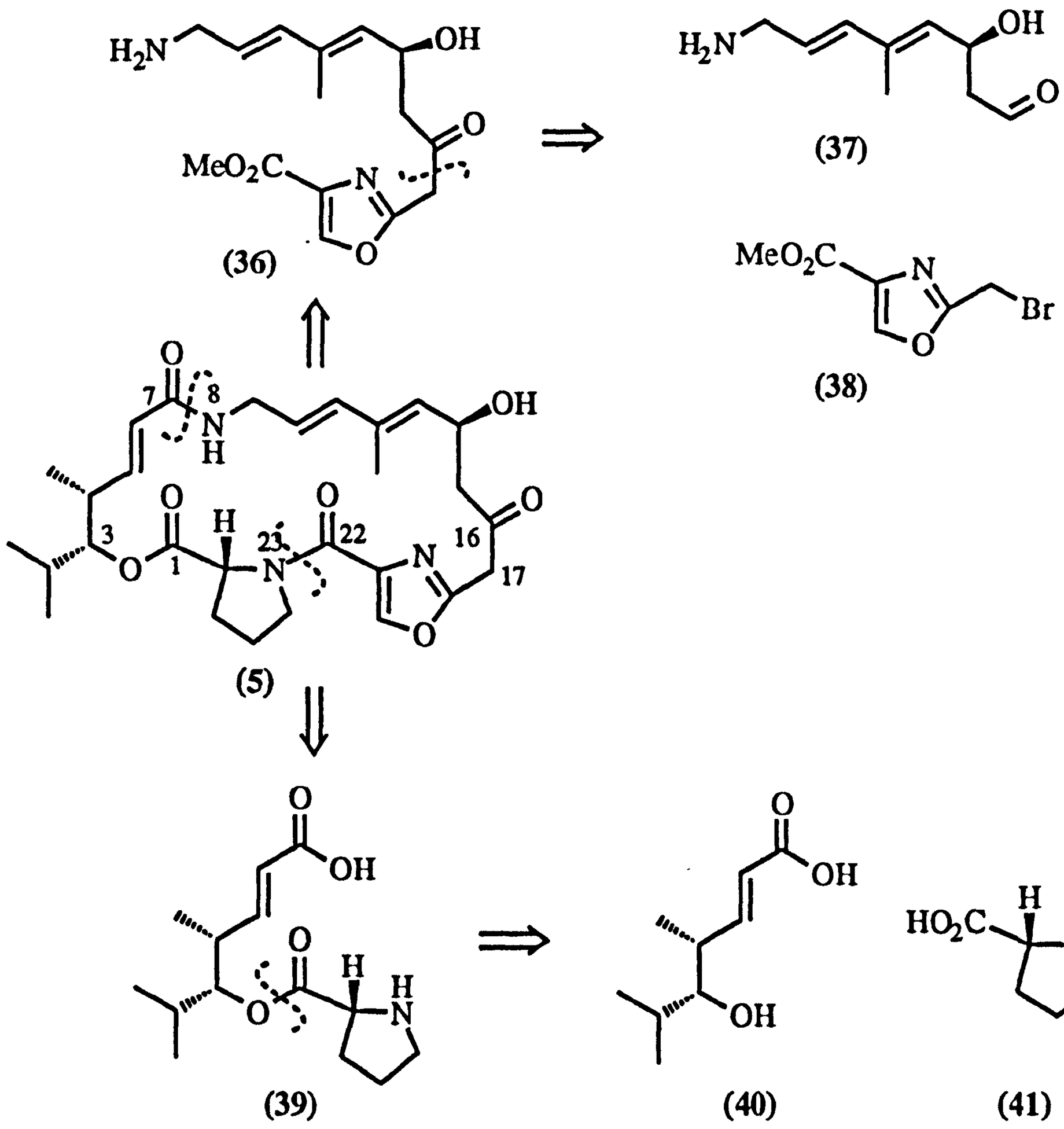
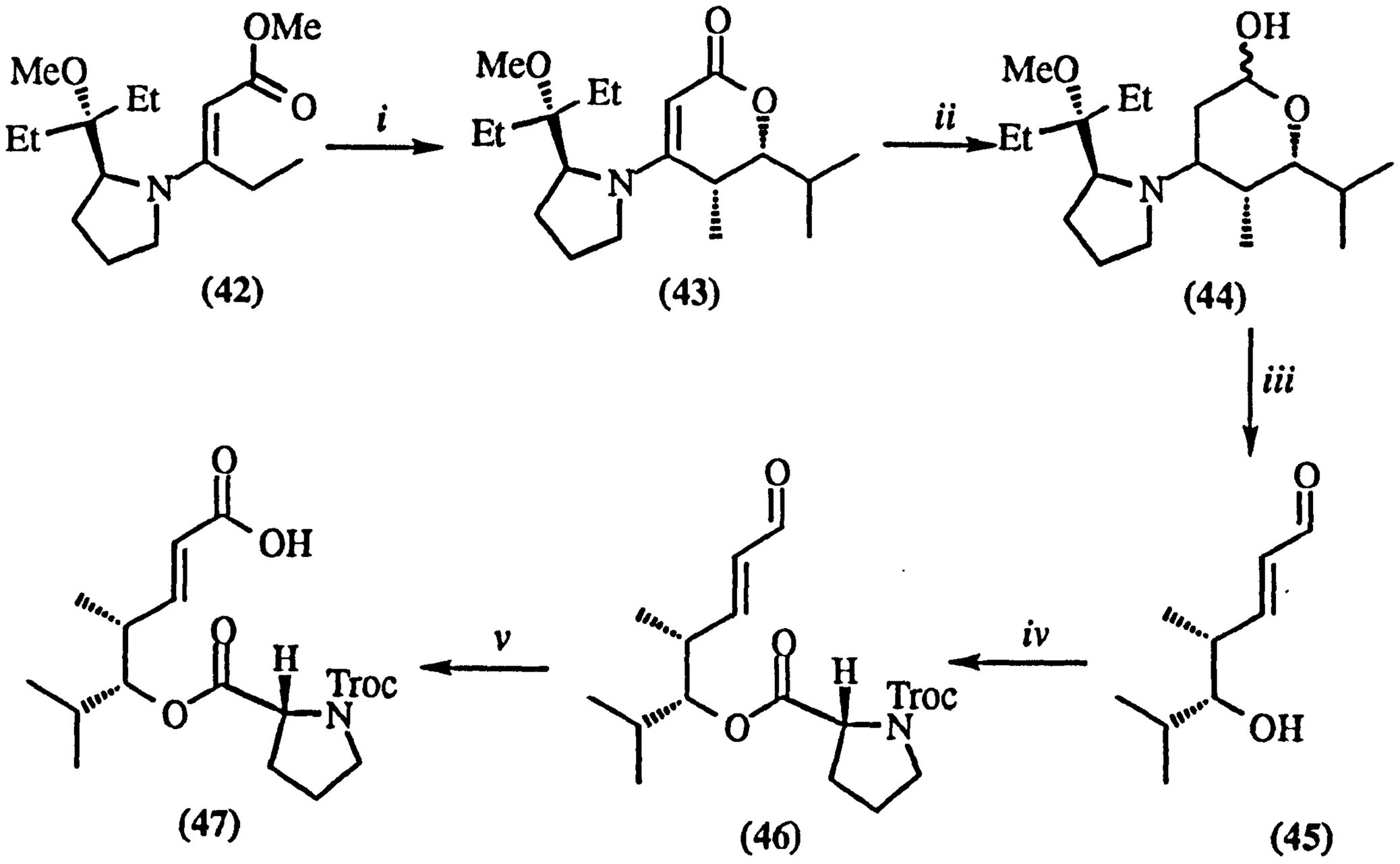


Figure 9

Schlessinger's synthesis of fragment **(39)** used a stereoselective lactonisation reaction.[24] Thus, the lithium enolate of the vinylogous urethane **(42)** was reacted with isobutyraldehyde to give the lactone **(43)** in 87% yield (96% de). **Scheme 5.** Dissolving metal reduction of the lactone **(43)** gave the amino lactol **(44)** which was then oxidatively eliminated with *m*-CPBA and pyridine to give the moderately unstable aldol **(45)**. The aldol **(45)** was immediately esterified with *N*-Troc-*D*-proline using DCC and DMAP to give the ester **(46)** in 92% yield. Oxidation of the aldehyde **(46)**

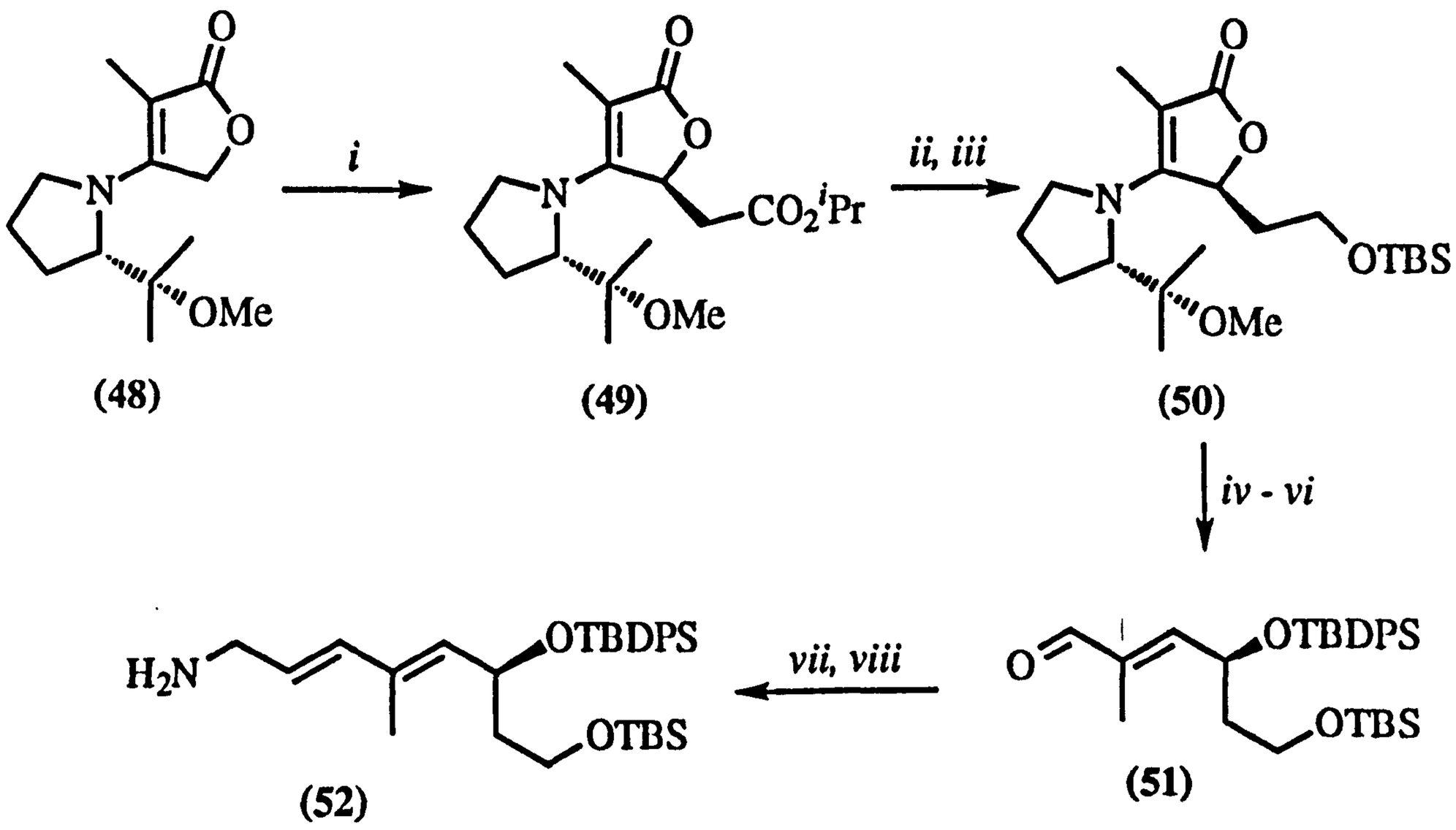
under Lindgrin's conditions with sodium chlorite and sulphamic acid gave the acid **(47)** in 88% yield.



Reagents: i, LDA, isobutyraldehyde, THF; *ii,* Li, NH_3, *t*-BuOH; *iii*, *m*-CPBA, THF, py; *iv*, *N*-Troc-*D*-proline, DCC, DMAP; *v*, $NaClO_2$, NH_2SO_3H, THF-H_2O.

Scheme 5

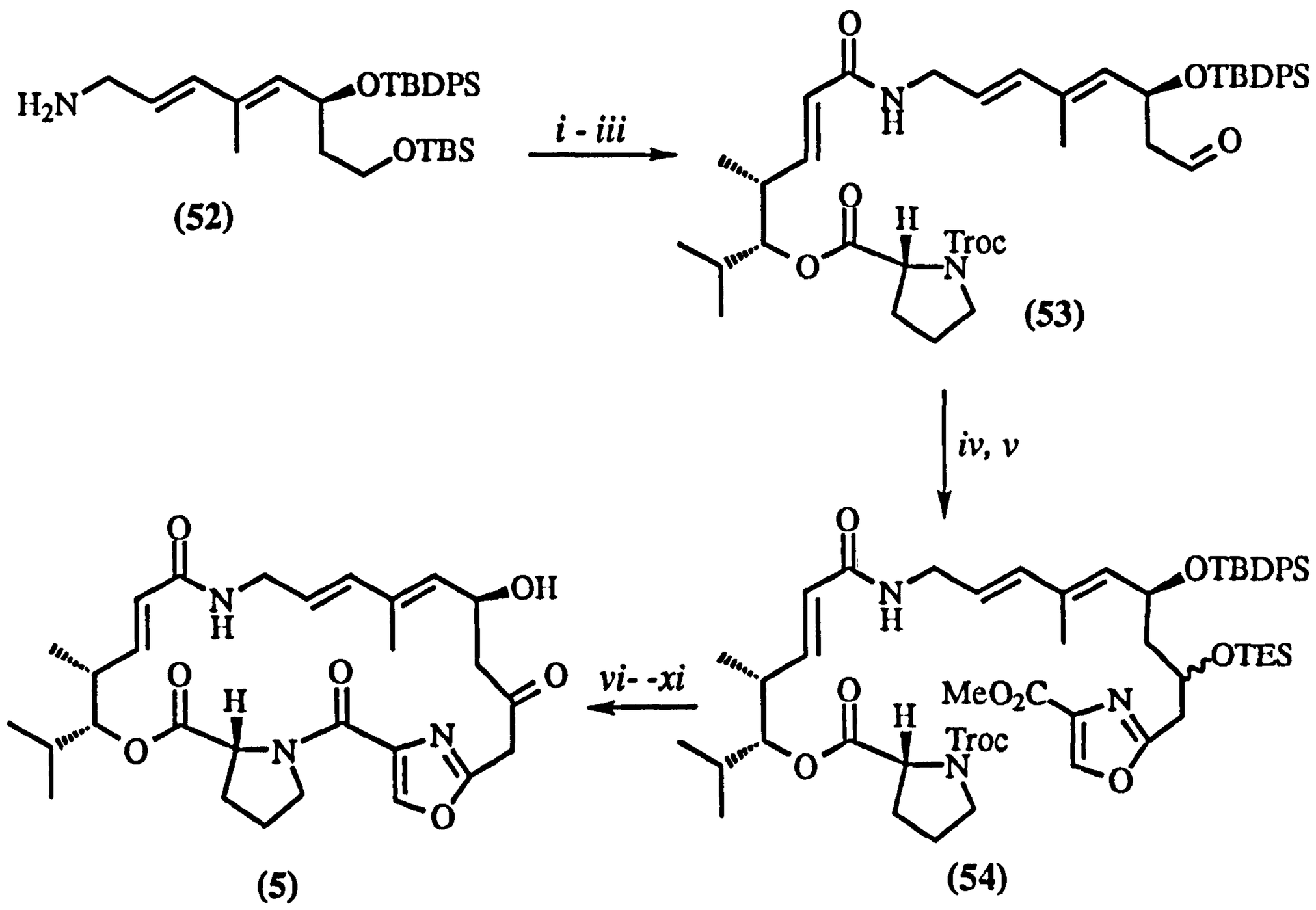
The polyunsaturated aminal **(37)** was also synthesised from a vinylogous urethane. Thus, alkylation of the lithium enolate of urethane **(48)** with isopropyl bromoacetate gave the ester **(49)** in 93% yield. **Scheme 6.** The ester **(49)** was selectively hydrolysed to the primary alcohol and then protected as the TBS ether **(50)**. Reduction of the lactone **(50)** under the Birch conditions afforded the amino lactol, which was oxidatively eliminated to give the aldol and then protected as the TBDPS ether **(51)**. Olefination of the aldehyde **(51)** with cyanomethyl diisopropylphosphonate under the Horner-Emmons conditions, and reduction of the nitrile group with aluminium hydride, gave the allylic amine **(52)**.



Reagents: *i*, *t*-BuLi, isopropyl bromoacetate, THF; *ii*, $LiBH_4$, MeOH. THF; *iii*, TBDMS-Cl, imidazole, CH_2Cl_2; *iv*, Li, NH_3, *t*-BuOH, THF; *v*, *m*-CPBA, py; *vi*, TBDPS-Cl, imidazole, CH_2Cl_2; *vii*, cyanomethyl diisopropylphosphonate, *t*-BuOK, THF; *viii*, AlH_3, THF.

Scheme 6

Acid (**47**) and amine (**52**) were coupled using the Mukaiyama coupling conditions to afford the amide in 89% yield. Deprotection of the primary alcohol and subsequent oxidation with Dess-Martin's periodinane gave the aldehyde (**53**). **Scheme 7.** Treatment of the aldehyde (**53**) and the 2-bromomethyloxazole (**38**) under the Reformatsky conditions, using zinc dust and diethylaluminium chloride, gave a diastereomeric mixture of secondary alcohols which were protected as the TES ether (**54**) in 55% yield (2 steps). Removal of the Troc amine protecting group with zinc, followed by selective hydrolysis of the methyl ester with lithium hydroxide, gave the cyclisation precursor. Cyclisation of the precursor under the Mukaiyama conditions gave the protected macrocycle in 48% yield (3 steps). Final removal of the TES protection and oxidation of the resultant alcohol to the ketone, followed by removal of the TBDPS alcohol protecting group, gave (-) virginiamycin M_2 (**5**).



Reagents: i, **(47)**, 2-chloro-1-methylpyridinium iodide, *n*-Bu_3N, CH_2Cl_2; *ii*, HF.py, THF; *iii*, Dess-Martin periodinane, CH_2Cl_2; *iv*, **(38)**, Zn dust, Et_2AlCl; *v*, TESOTf, 2,6-lutidine, CH_2Cl_2; *vi*, Zn dust, NH_4OAc, THF; *vii*, LiOH, THF-H_2O; *viii*, 2-chloro-1-methylpyridinium iodide, *n*-Bu_3N, CH_2Cl_2; *ix*, AcOH, THF, H_2O; *x*, Dess-Martin periodinane, CH_2Cl_2; *xi*, HF.py, CH_2Cl_2.

Scheme 7

Another eminent chemist who has dedicated much time into studying methods of synthesising the virginiamycin M system is Helquist. Although having not published a total synthesis of these systems to date, Helquist *et al.* have published numerous papers describing their work involved in the syntheses of group A streptogramin antibiotics.[25] Their approach to madumycin once again relies on a macrolactamisation between C-7 and N-8 as the final cyclisation step. **Figure 10.** Further disconnection between C-22 and N-23 yielded the two main fragments **(55)** and **(58)**. Fragment **(55)** was further disconnected to the hydroxy ester **(56)** and protected alanine **(57)**. Fragment **(58)** was disconnected to the aminal **(59)** and the 2-

bromomethyloxazole **(60)**.

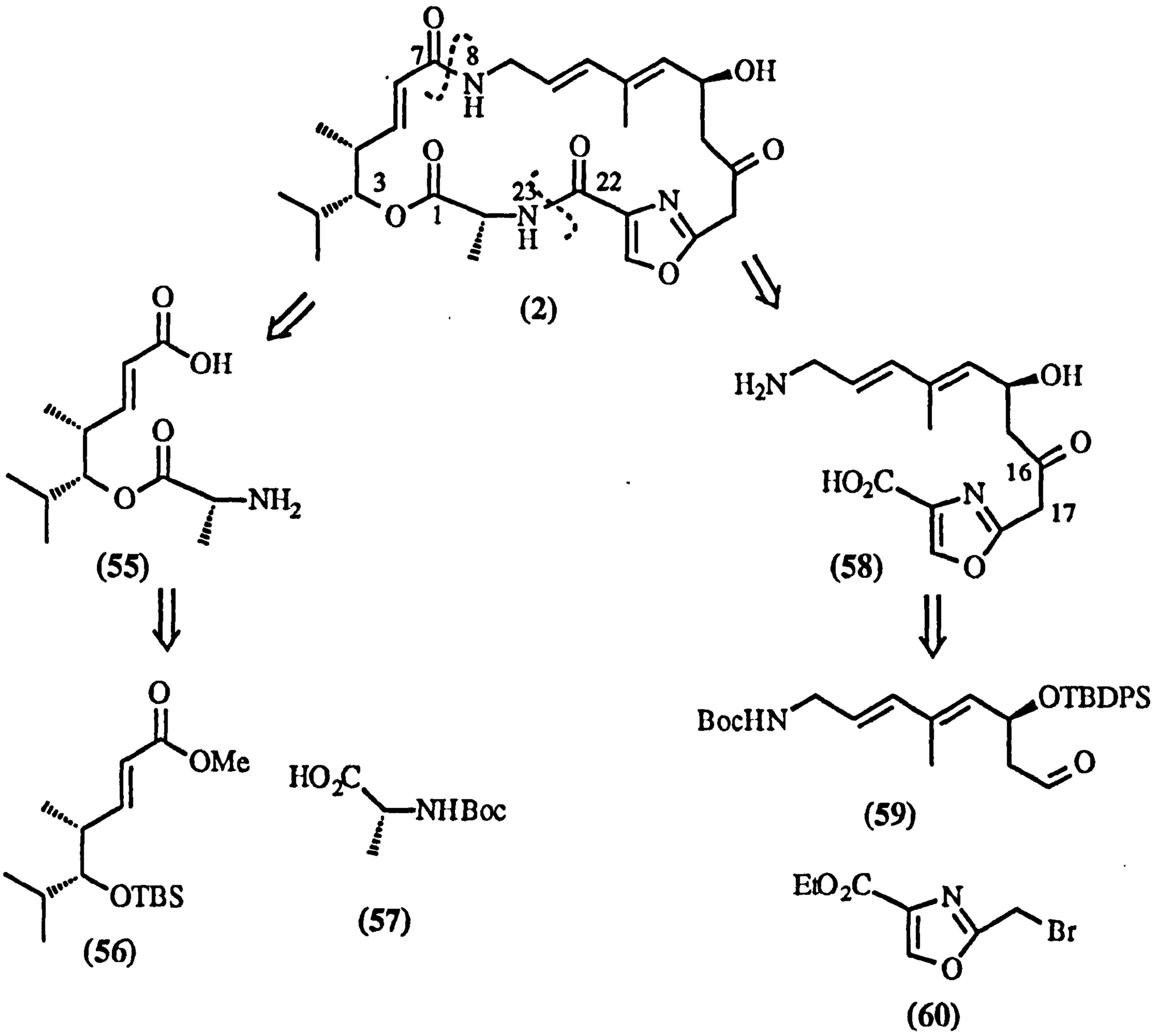
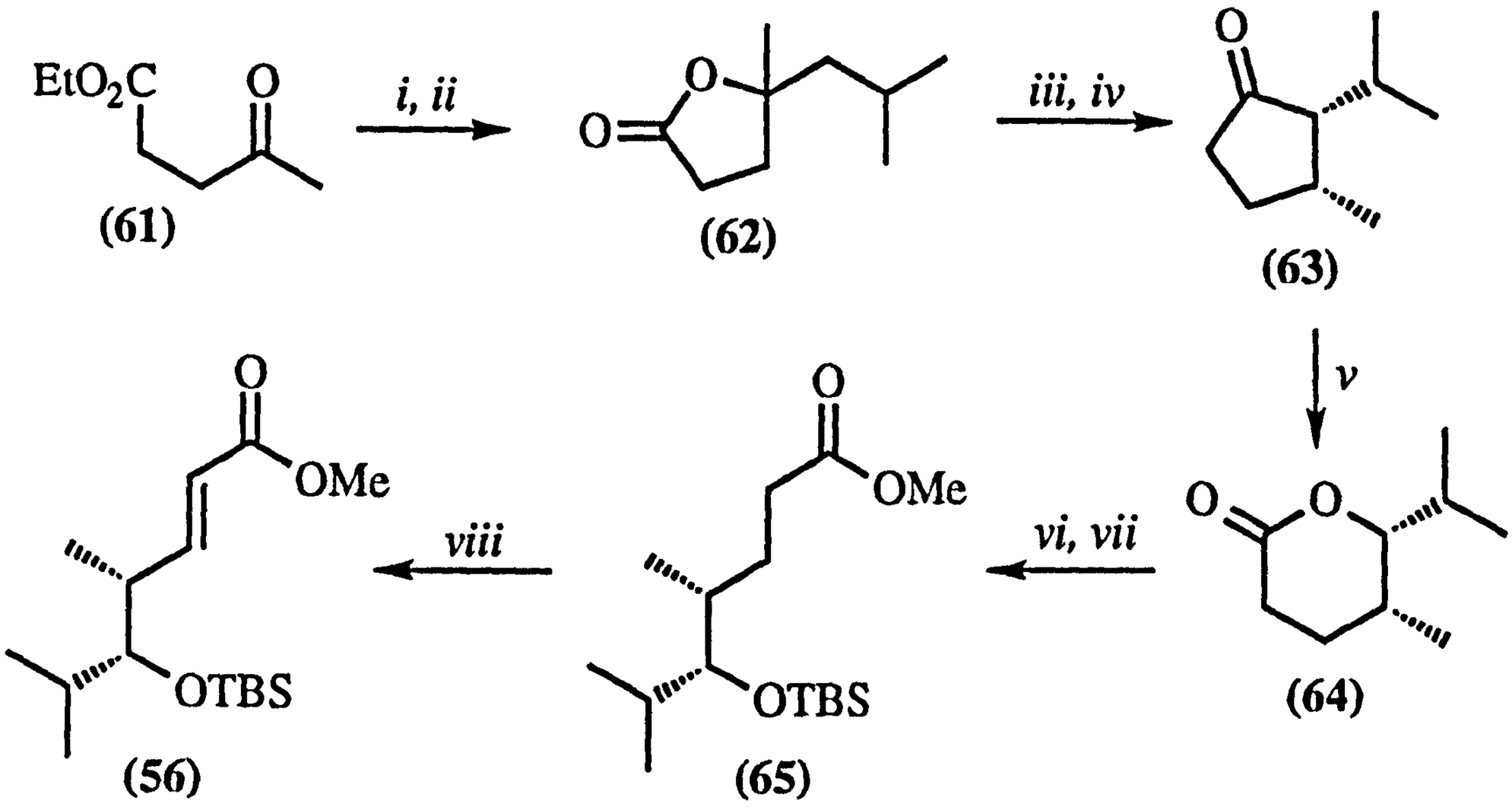


Figure 10

Helquist *et al* reported the synthesis of fragment **(56)** by two routes.[26] The first of their routes began with the conversion of ethyl levulinate **(61)** into the butyrolactone **(62)** by firstly alkylating with isobutylmagnesium bromide and then cyclising under strong acidic conditions to the lactone **(62)** in 56% yield (2 steps). **Scheme 8.** The lactone **(62)** was then converted to the cyclopentenone by treatment with orthophosphoric acid and phosphorous pentoxide in 96% yield. The cyclopentenone was then stereoselectively hydrogenated under Paquette's conditions to give the cyclopentanone **(63)** in 83% yield in a 44:1 ratio of the *syn:anti* isomers. Baeyer-Villiger oxidation of **(63)** with *m*-CPBA gave the valerolactone **(64)**. The lactone

(64) was then ring opened with lithium hydroxide and the resulting alcohol protected as the TBS ether (65). Treatment of (65) with LDA and phenylselenyl bromide, followed by oxidative work-up with hydrogen peroxide, gave the α,β-unsaturated ester (56). The second route described by Helquist *et al* used the more conventional chiral oxazolidinethione to introduce the two adjacent chiral alkyl groups *via* a chiral aldol reaction.

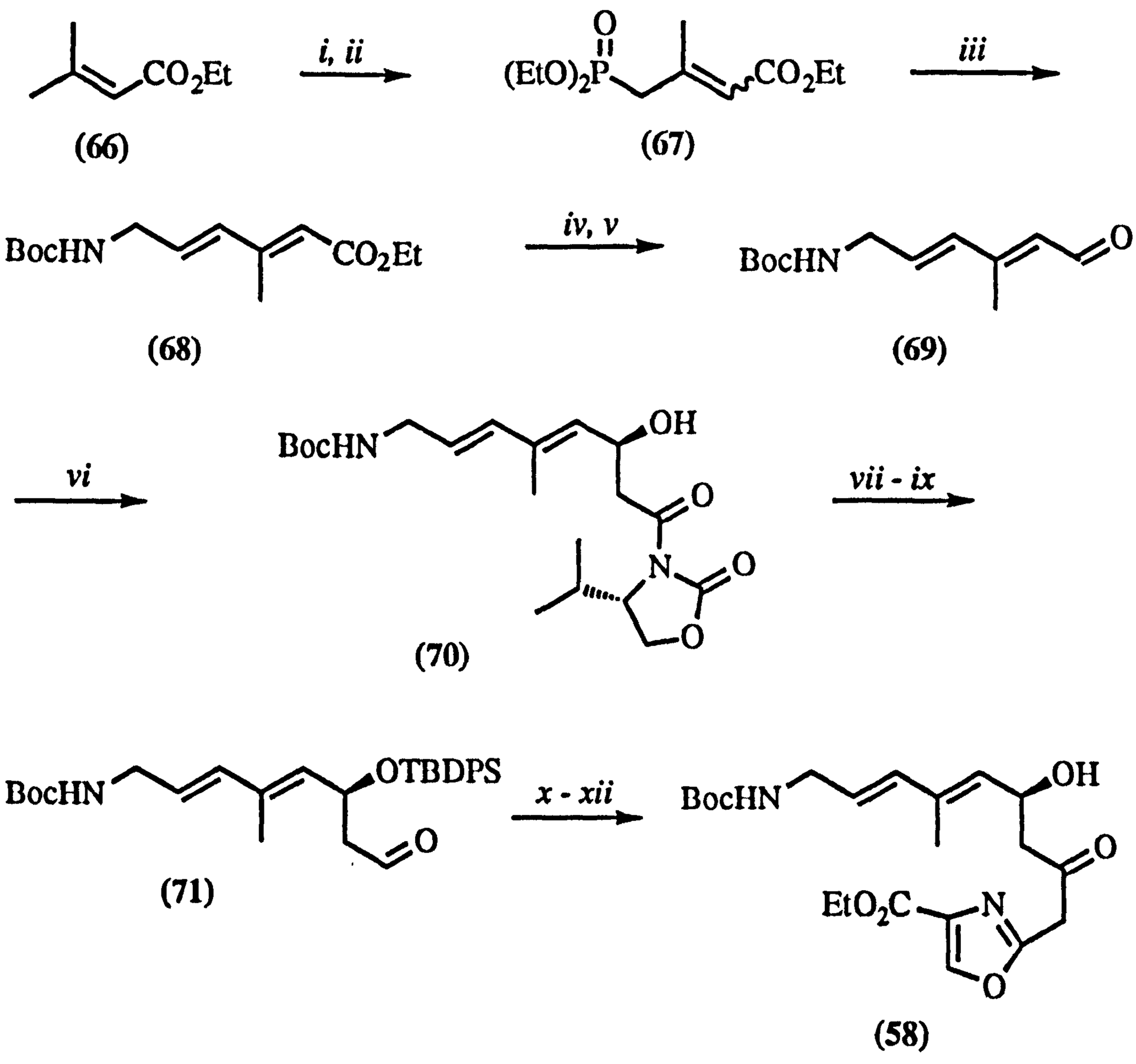


Reagents: i, ^{i}BuMgBr, Et_2O; *ii*, H_2SO_4, H_2O; *iii*, P_2O_5, H_3PO_4; *iv*, H_2 (1 atm), Rh-C, Na_2CO_3, hexane; *v*, *m-CPBA*, $NaHCO_3$; *vi*, LiOH, H_2O; TBDMSOTf, K_2CO, MeOH; *vii*, CH_2N_2, Et_2O; *viii*, LDA, PhSeBr, H_2O_2.

Scheme 8

Helquist *et al* synthesised fragment (58) from ethyl 3-methyl-2-butenoate (66).[27] Scheme 9. Thus, treatment of the ester (66) with NBS in carbon tetrachloride followed by the addition of triethylphosphonate gave a 1:1 *E:Z* mixture of the phosphonate (67) in 70% yield. Horner-Wadsworth-Emmons condensation with *N*-Boc glycinal gave the diene (68) in 68% yield. The ester (68) was reduced to the alcohol with DIBAL-H and then oxidised under the Swern conditions to the aldehyde (69) in 90% yield (2 steps). Stereoselective aldol condensation with the lithium

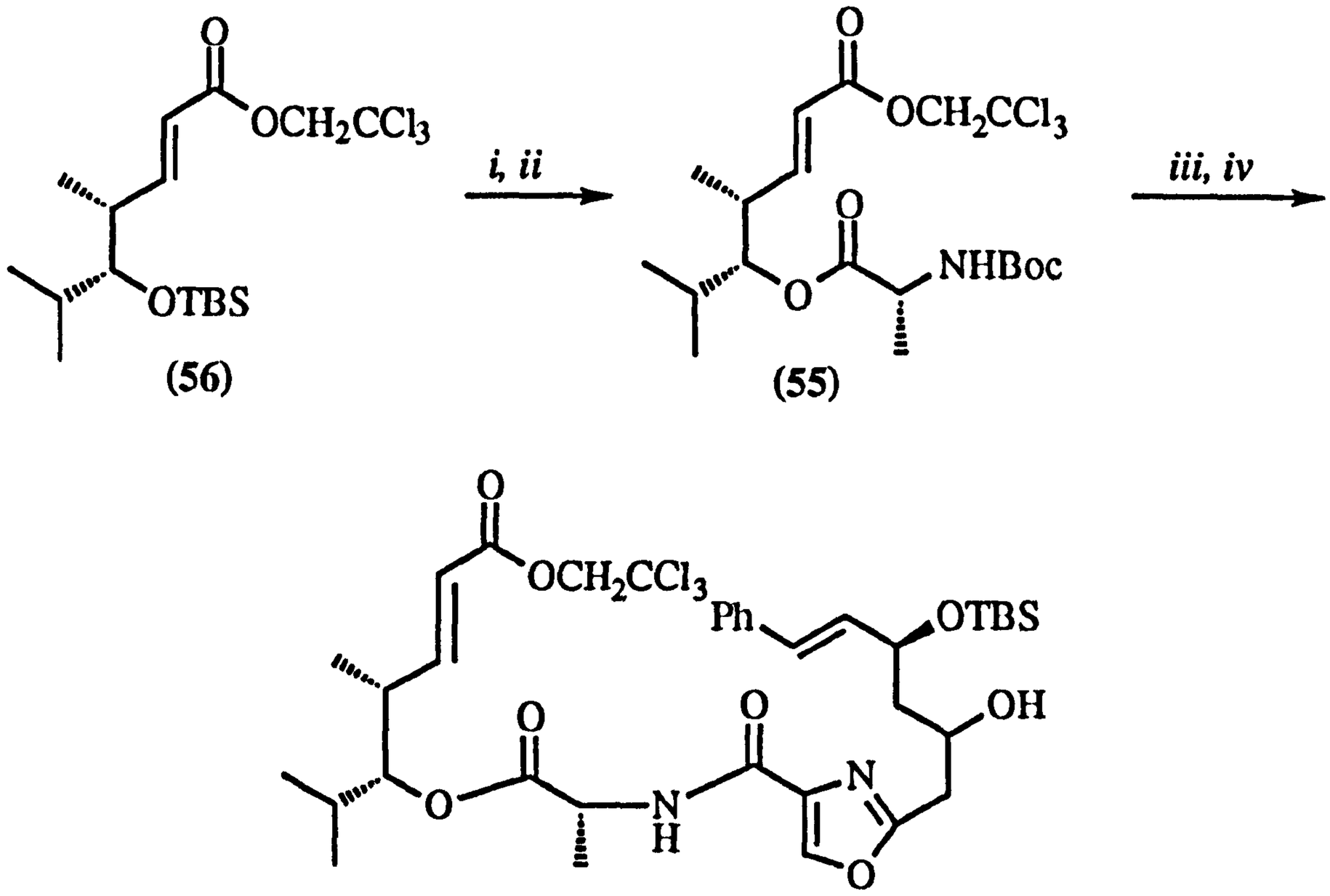
enolate of (*S*)-*N*-acetyl-4-isopropyl-2-oxazolidinone gave a 3:1 mixture of diastereoisomers of the alcohol **(70)**. After removing the unwanted minor isomer the alcohol **(70)** was converted into the Weinreb amide. The free alcohol was protected as the TBDPS ether and the Weinreb amide was then reduced to the corresponding aldehyde **(71)** with DIBAL-H in 60% yield (3 steps). Reaction of the aldehyde **(71)** with the 2-bromo-methyloxazole **(60)** under the Reformatsky conditions gave the secondary alcohol, which was then oxidised under the Swern conditions to give the ketone in 50% yield (2 steps). Finally treatment with TBAF in THF yielded fragment **(58)**.



Reagents: *i*, NBS, CCl_4; *ii*, $P(OEt)_3$; *iii*, *n*-BuLi, *N*-Boc-glycinal, Et_2O; *iv*, DIBAL-H, CH_2Cl_2; *v*, Swern; *vi*, Evans chiral aldol; *vii*, MeNH(OMe).HCl, Me_3Al, THF; *viii*, TBDPS-Cl, imidazole, DMF; *ix*, DIBAL-H; *x*, **(60)**, Zn dust, THF; *xi*, Swern; *xii*, TBAF, THF.

Scheme 9

At the time of publication the remaining coupling reactions in the total synthesis of madumycin had not been completed. However Helquist *et al* had reported the coupling of the free hydroxyl of fragment **(56)** to *N*-Boc-alanine, and the subsequent coupling of the free amine of this fragment **(55)** to an analogue of fragment **(58)** using EDC, HOBt, and triethylamine, to give the amide **(72)**. **Scheme 10.**



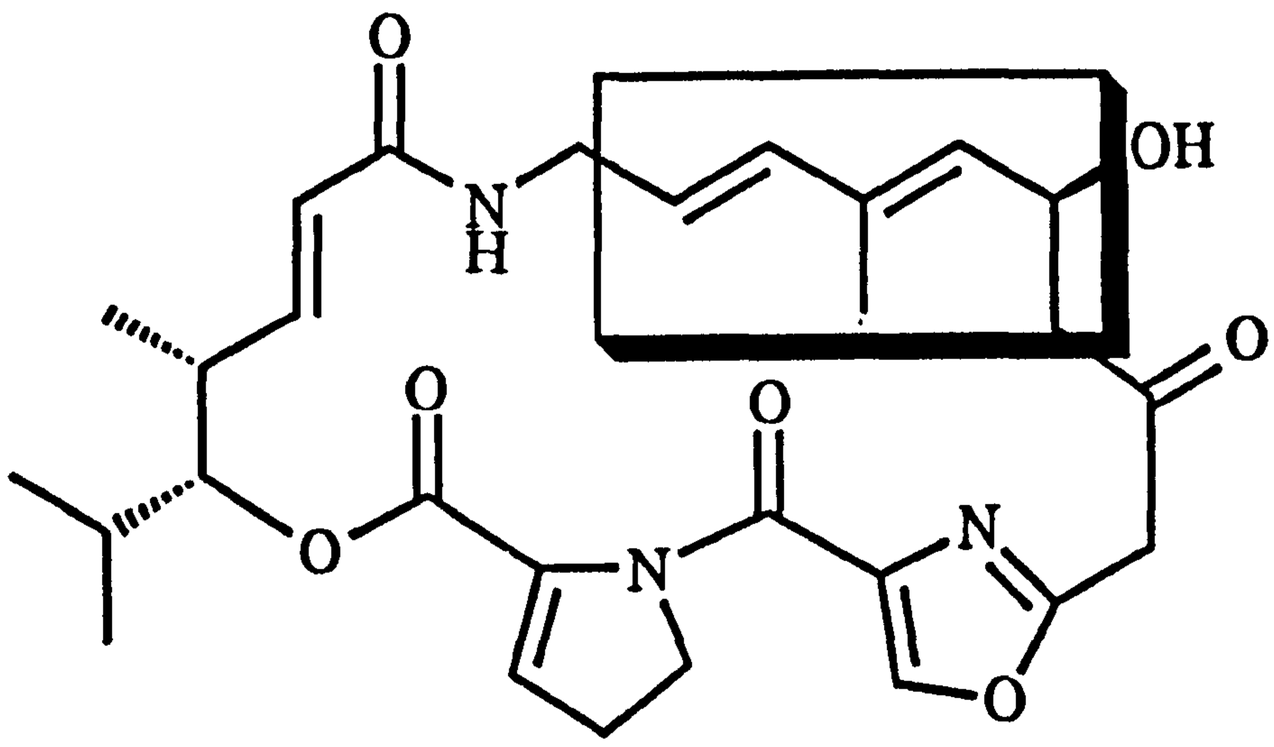
Reagents: *i*, HF, H_2O, CH_3CN; *ii*, *N*-Boc-alanine, DCC, DMAP; *iii*, TMSI; *iv*, EDC, HOBt, Et_3N.

Scheme 10

There have been several other research groups around the world working to solve the synthesis of this group of macrocyclic Group A Streptogramin antibiotics, including both Fujita[28] and Ganem,[29] who provide practical solutions to the synthesis of the 2,4-disubstituted oxazole fragment. However it has been Meyers, Schlessinger and Helquist who have provided the most notable contributions to the synthesis of this group of compounds over the past fifteen years.

1.6 Our Approach to the Synthesis of Virginiamycin M_1: The Stille Reaction and its use in the Synthesis of Ring Systems.

The structure of virginiamycin M_1 (1) presents us with an interesting synthetic challenge. As has already been discussed in some detail within the review of previous approaches to these systems, the main bond linkages of the molecule at which we could disconnect would result in either a macrolactonisation or a macrolactamisation to afford the macrocyclic ring. A portion of the ring however which has received little attention up until now is the *E,E*-1,3-diene system, a subunit present in a number of macrolides which have become of considerable interest in our research group over the past few years. **Figure 11**

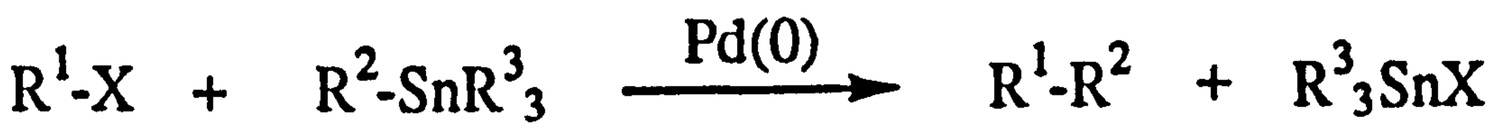


(1)

Figure 11

This interesting approach to the synthesis of virginiamycin M_1 relies on the formation of a single bond between two sp^2 centres , which would need to be accomplished under relatively mild conditions in the presence of a wide range of functional groups. Up until recent years there were very few examples of this type of reaction known, with the exception of the Ulmann diaryl synthesis[30] and the tandem Michael addition-elimination reaction. However with the introduction of transition metal mediated carbon-carbon bond forming reactions, and in particular those of the Group 10

elements such as nickel and palladium, a wide range of carbon-carbon coupling methods have become available. Some of the more notable of these include the Heck reaction[31], the Suzuki reaction[32] and the Stille reaction[33]. These reactions in particular have provided valuable answers to the problems inherent in the coupling of alkenes, allenes, allyl, benzyl, aryl and heteroaryl groups within organic synthesis. Typical organometallic species which have been used in such coupling reactions include the organoborane,[34] the organomagnesium,[35] the organozirconium[36] and the organozinc reagents,[37] but among the most versatile and widely used organometallic species must be the organostannane reagents, especially when used in conjunction with palladium in the Stille reaction. **Figure 12.**



where R^1, R^2 = allyl, vinyl, aryl etc
R^3 = alkyl or phenyl
X = halogen or triflate

Figure 12

The popularity of organostannanes is in the main due to their ease of preparation and purification, and their stability towards many reagents including water and oxygen. Coupled with their high reactivity towards palladium transmetallation and their poor ability to transfer a second group, such as alkyl groups, lends the organostannanes admirably to the Stille reaction.

The proposed catalytic cycle involved in the Stille reaction presumes the active species to be the 14 electron Pd(0) species L_2Pd^0.[33c] **Figure 13.** This undergoes oxidative addition with the electrophilic species R^1-X to generate the 16 electron square planar complex $L_2Pd^0R^1X$, which then undergoes transmetallation with the organostannane $R^2SnR^3_3$ to give the complex $R^1LPd^0LR^2$. This complex undergoes

facile "*syn-anti*" isomerisation to give the *syn* complex $L_2Pd^0R^1R^2$. Reductive elimination of R^1-R^2 finally leaves the active species L_2Pd^0 to continue in the cycle.

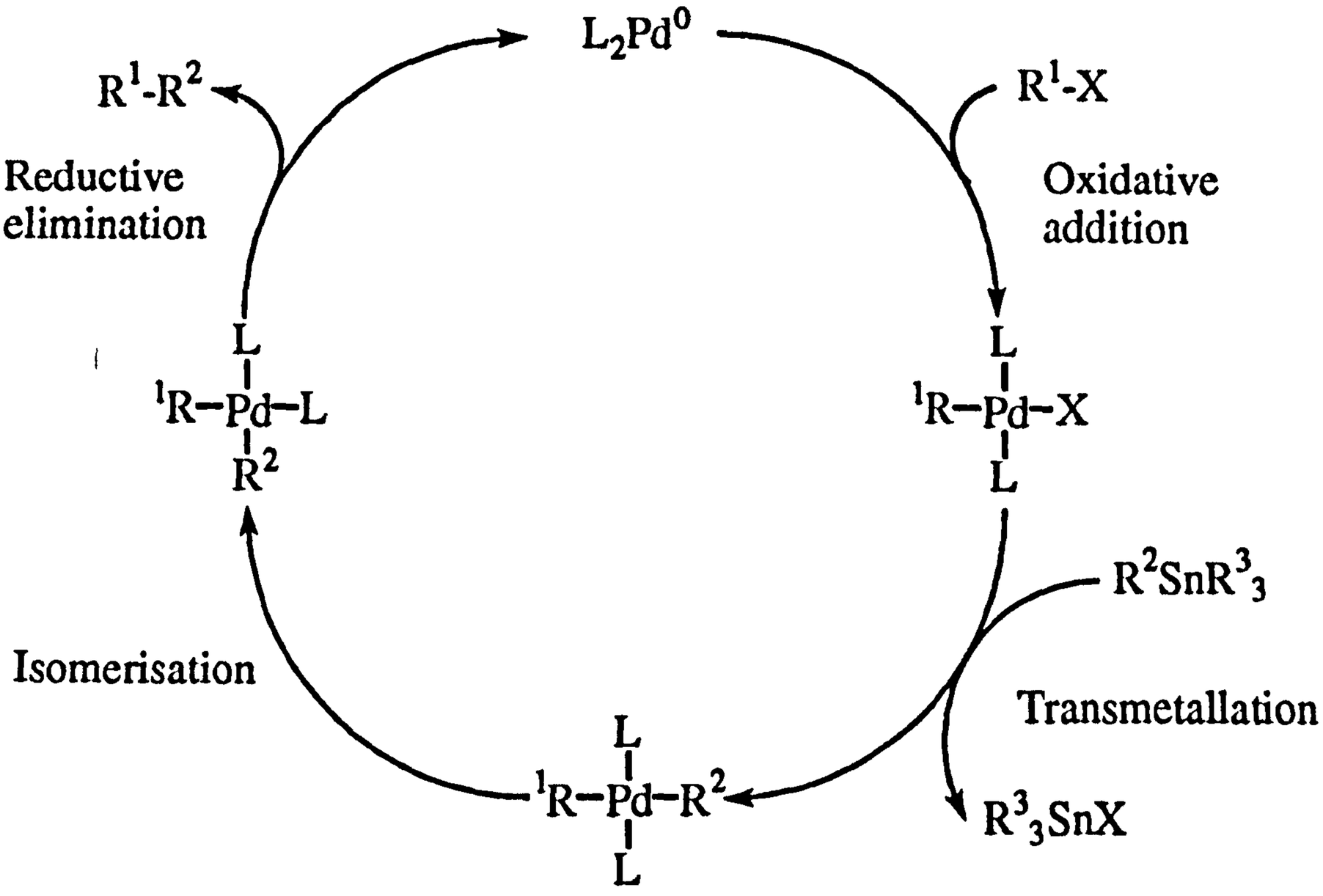


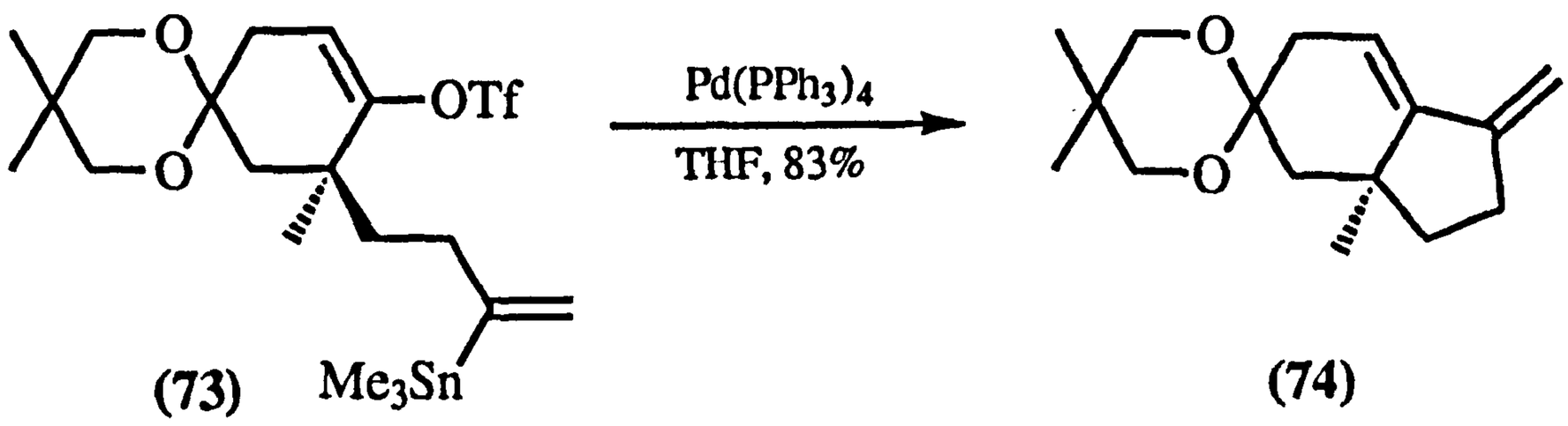
Figure 13

The transmetallation step from tin to palladium has long been established as the rate determining step, and as a result numerous studies have been undertaken to find suitable conditions to increase the rate at which this process will occur. The overall results of these studies identified that addition of lithium chloride or copper salts increase the reaction rate and the yields.[38] The same can be said of using ligands with poor donor ability such as triphenylarsine or tri(2-furyl)phoshine leading to vast increases in rate over the ligand originally used, triphenylphosphine.[39]

The Stille reaction has proved to be a powerful tool in the formation of single bonds between two sp^2 centres and as such has received much attention as an intermolecular coupling reaction. However it is the intramolecular coupling reactions which have shown the Stille reaction to be unparalleled in the area of medium- and macrocyclic ring formation.

The first example of an intramolecular Stille coupling reaction was described by

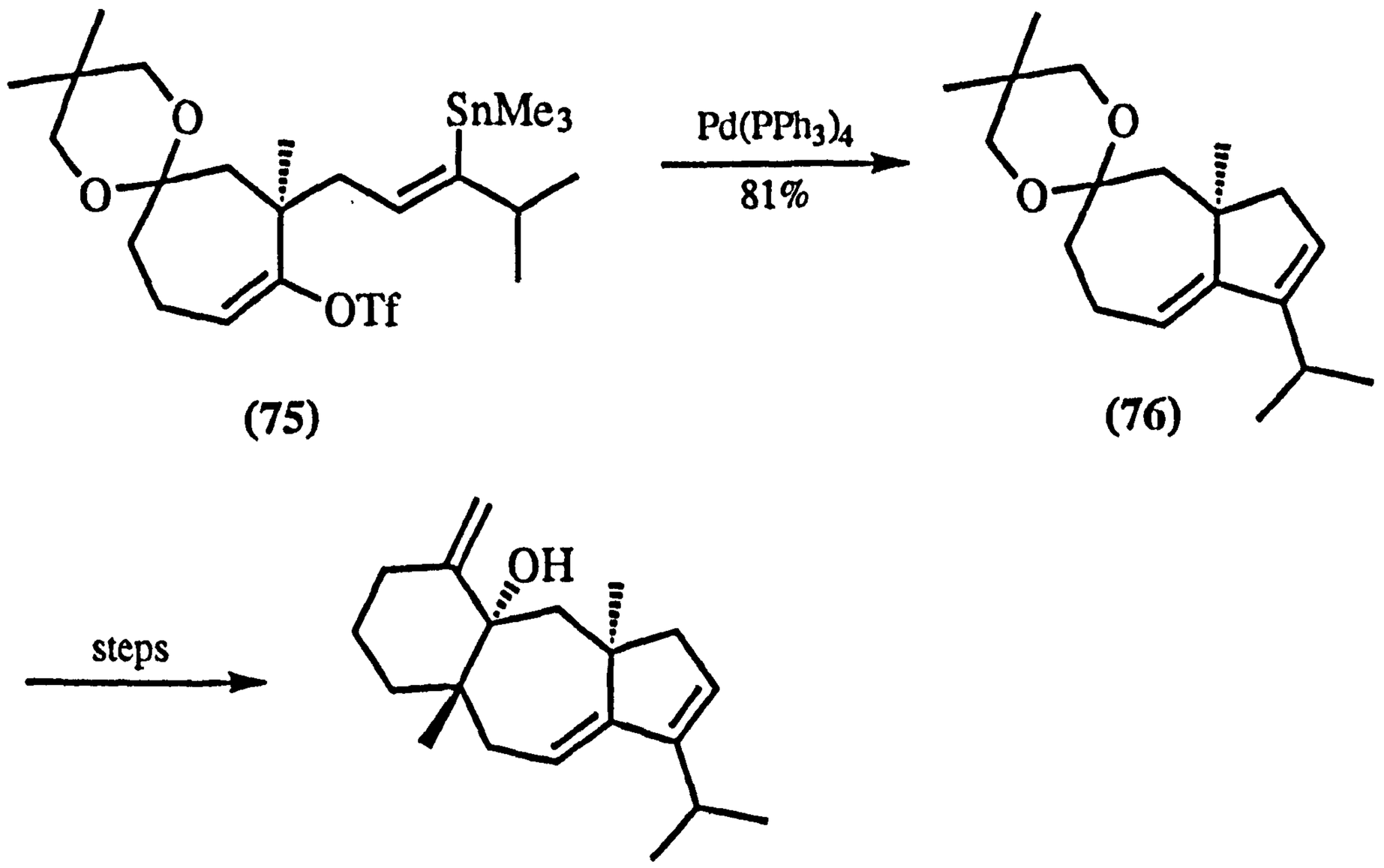
Piers *et al* in 1985.[40] Piers *et al* successfully cyclised the substituted cyclohexene **(73)**, containing a vinyl stannane and a vinyl triflate, to the diene containing 6,5-ring system **(74)**. **Scheme 11.**



(73) **(74)**

Scheme 11

This strategy was successfully used by Piers *et al* in their total synthesis of the diterpenoid marine natural product (+/-)-(14*S*)-dolasta-1-(15)-7,9-trien-14-ol **(77)**,[41] where the key annulation step involved the intramolecular Stille cyclisation of the vinyl triflate **(75)** to the bicycle **(76)**, which was then elaborated to give the natural product **(77)**. **Scheme 12.**

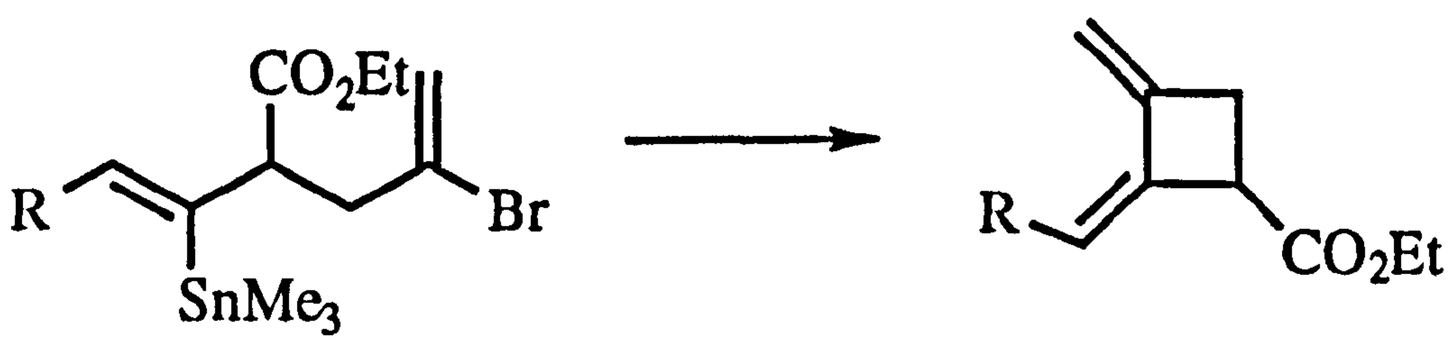


(75) **(76)**

(77)

Scheme 12

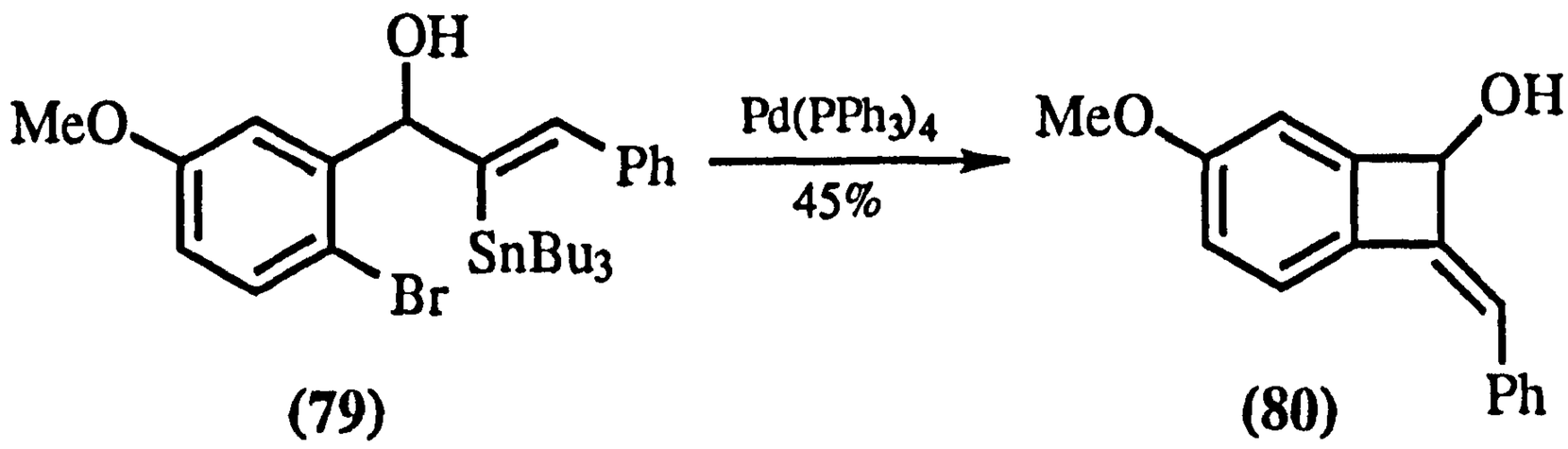
More recently Piers *et al* have also used the Stille coupling reaction in the stereospecific synthesis of small ring cyclobutane carboxylates (78).[42] **Scheme 13.**



(78)

Scheme 13

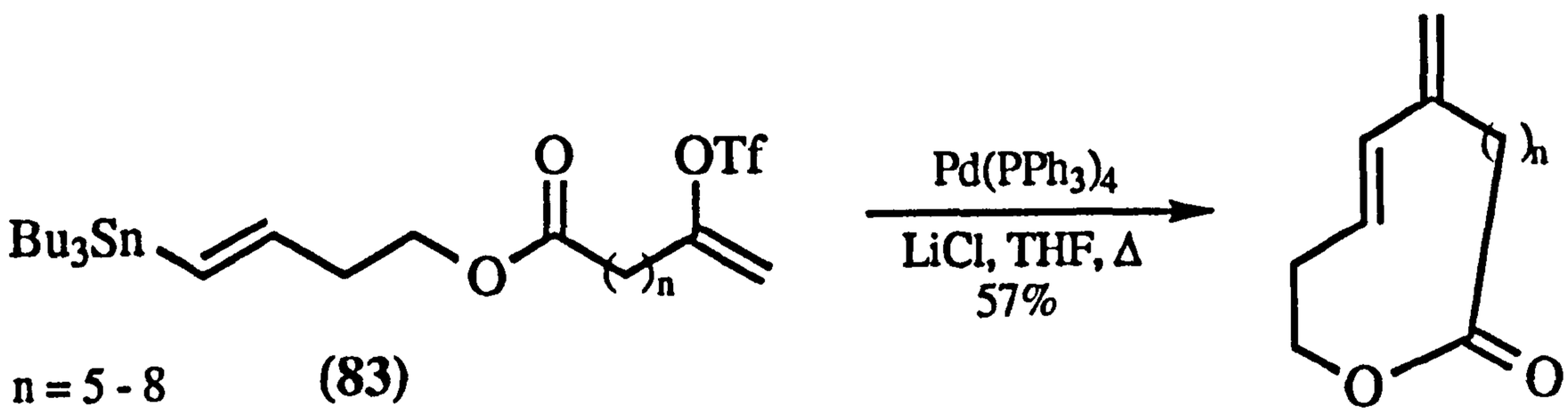
Bradely and Durst have used an identical strategy to form the 2-benzylidene benzocyclobutenol **(80)** *via* the cyclisation of the aromatic bromide **(79).**[43] **Scheme 14.**



(79) **(80)**

Scheme 14

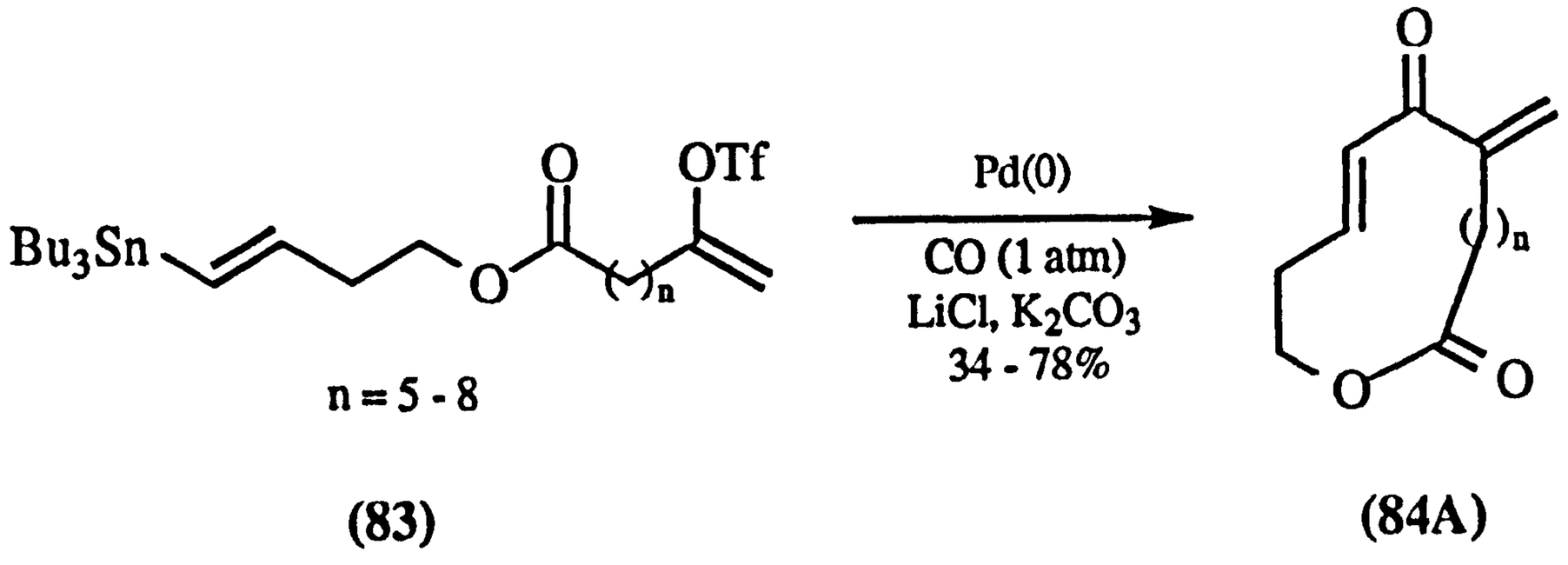
The first use of a sp^2-sp^2 coupling reaction in the formation of macrolide rings was pioneered by Stille in 1987.[44] Stille *et al* cyclised **(81)**, containing the vinyl tin and vinyl triflate groups at the ends of the ester chain, under palladium (0) catalysis, to give the macrolactone **(82). Scheme 15.**



Scheme 15

The yield of the macrolactone **(82)** was found to be insensitive to the ring size with the formation of all ring sizes from 12-membered through to 21-membered proceeding in around 60% yield, and as predicted, no sign of double bond isomerisation. As also expected the rate of cyclisation was shown to be slowest in the case of the 12-membered ring.

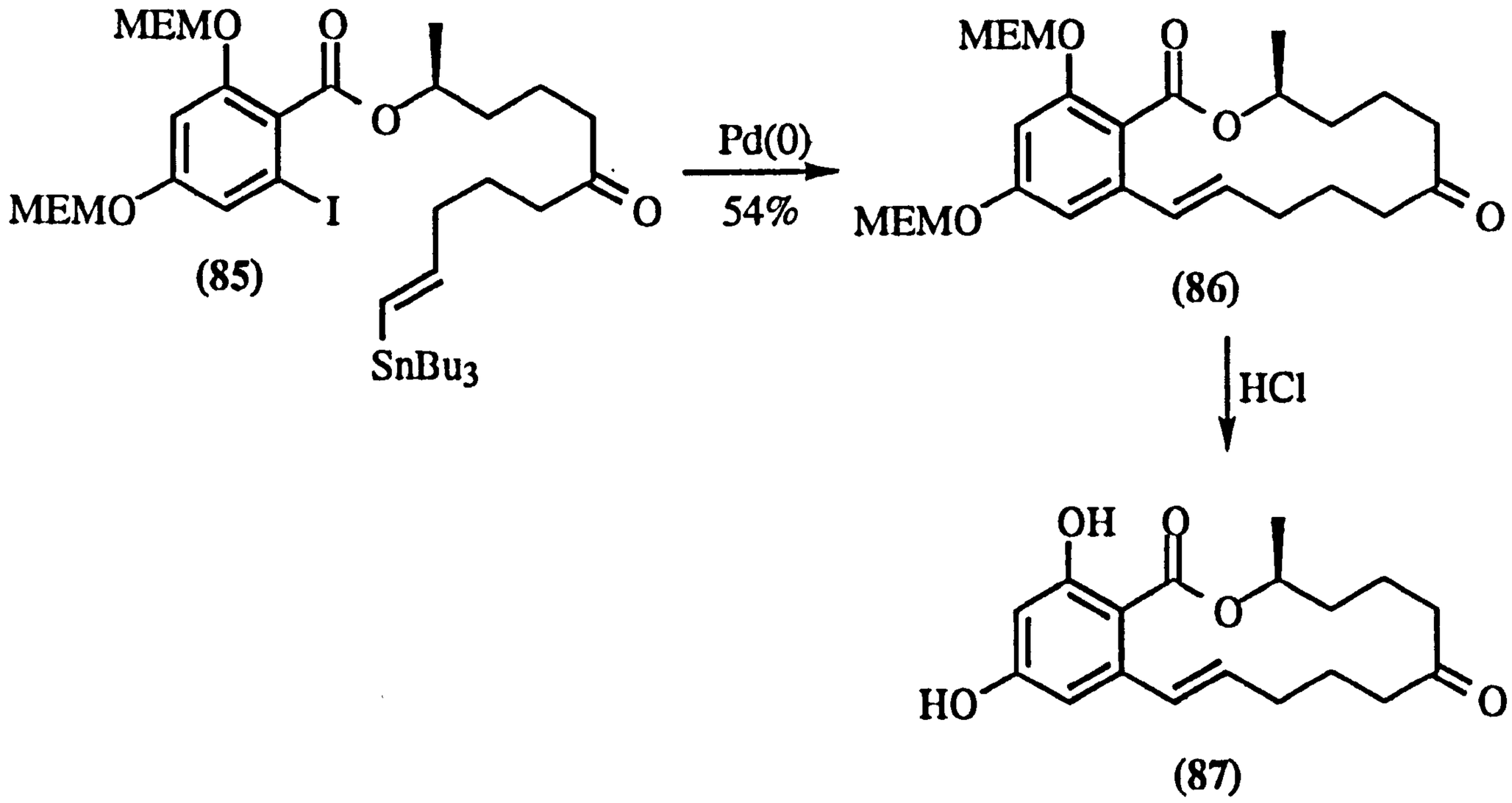
This work was further developed by Stille for the synthesis of large ring keto-lactones **(84A)** by palladium catalysed carbonylative couplings of the esters **(83)**.[45] **Scheme 16.**



Scheme 16

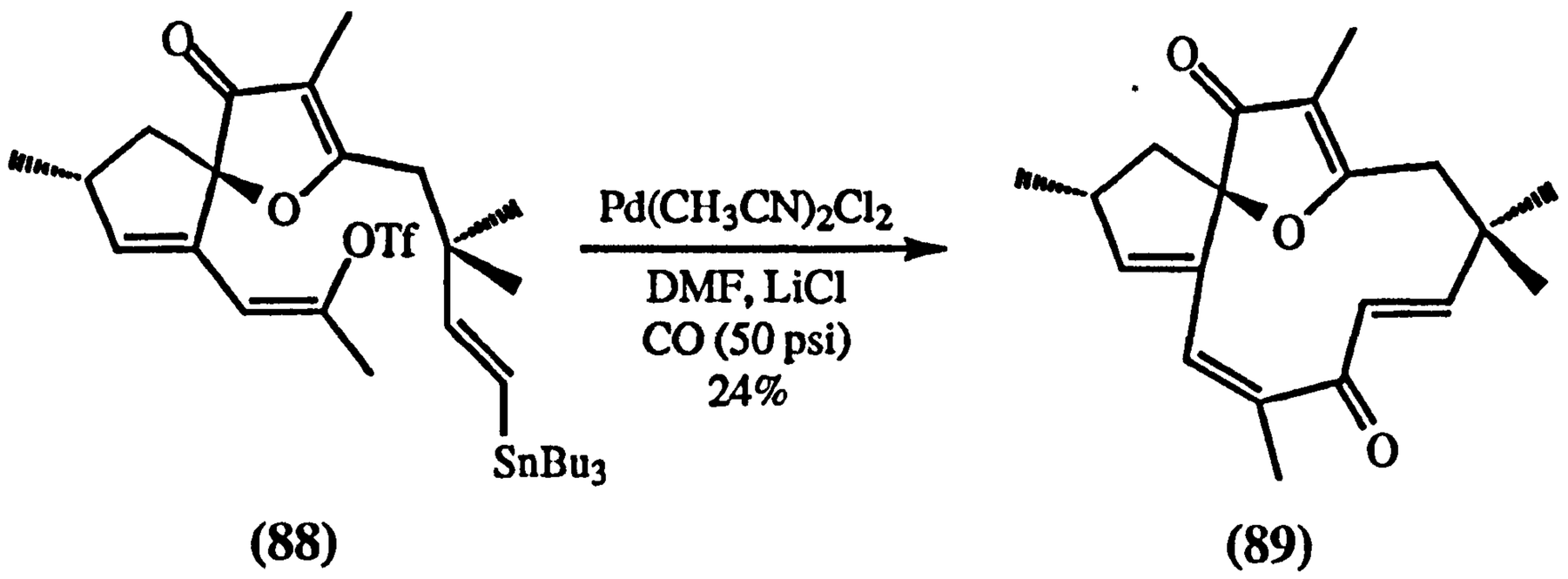
With this novel method identified as an effective route into a wide variety of macrolide products, many research groups around the world subsequently applied the Stille cyclisation reactions to the synthesis of natural products.

One of the first groups to utilise this method was that of Stille himself in the simple, yet elegant, synthesis of the macrolide (*S*)-zearalenone **(87)**.[46] **Scheme 17.** After obtaining low yields during this cyclisation Stille found that the best macrocyclisation yields were achieved by using a polymer supported palladium catalyst. It was noted by the authors that if the iodide and stannane groups in **(85)** were interchanged, the only product isolated was the dehalogenated starting material. The explanation for this outcome was due to the electron withdrawing effect of the *ortho* ester deactivating the tin group towards transmetallation, an observation in accordance with the fact that the rate-determining step is the transmetallation from tin to palladium.



Scheme 17

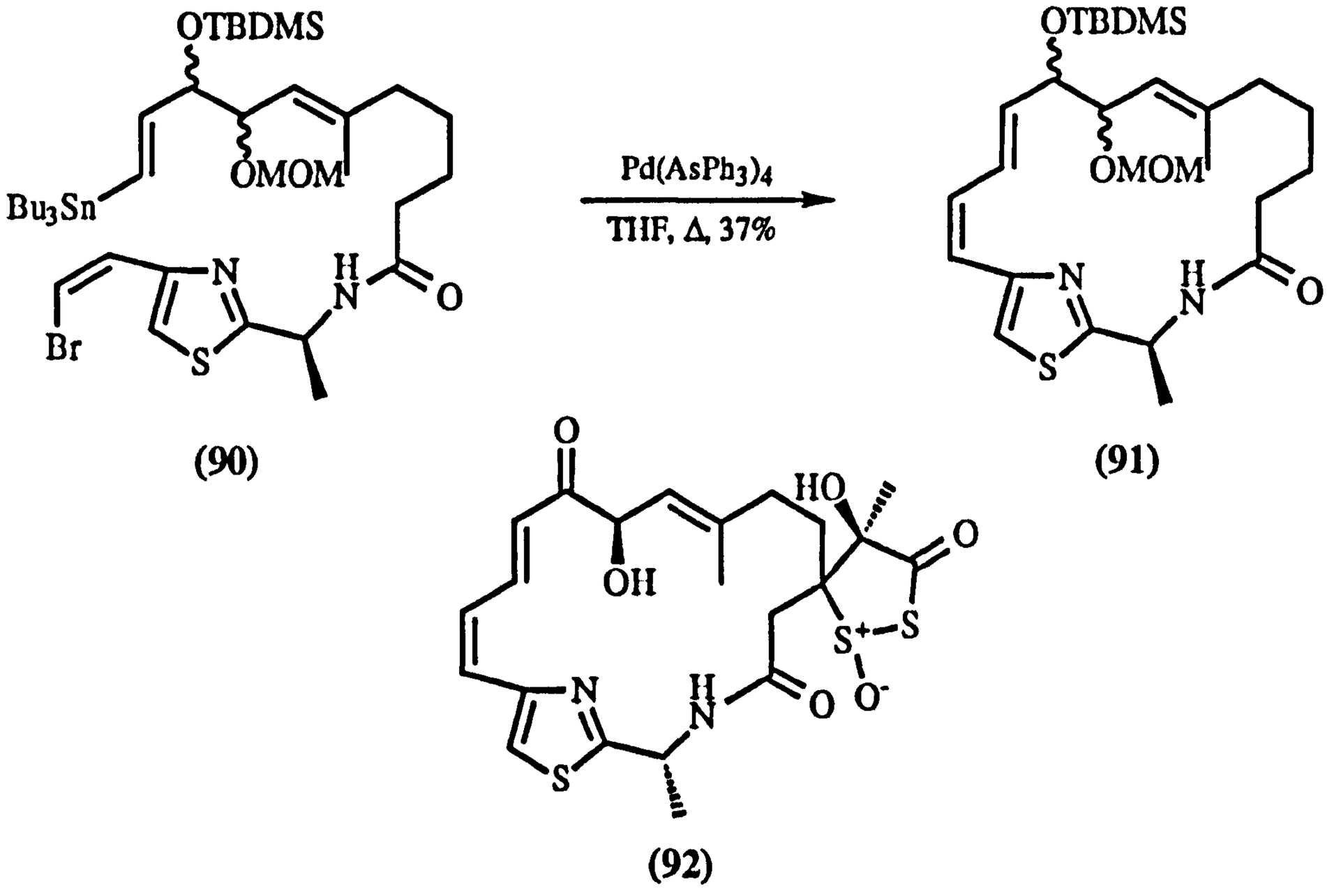
The strategy was further used by Stille *et al* in the total synthesis of (+/-)-jatrophone **(89)**.[47] The key macrocycle forming step was achieved by the carbonylative coupling of the vinyl triflate and vinyl stannane contained within the compound **(88). Scheme 18.**



(88) (89)

Scheme 18

Pattenden and Thom furthered the use of this method of cyclisation with their approach to the polyene macrolactam ring in the antibiotic leinamycin (**92**).[48] Thus, treatment of the *E*-vinyl stannane and *Z*-vinyl bromide containing precursor (**90**) using *tetrakis*(triphenylarsine) palladium (0) (the catalyst developed by Farina[39]), in refluxing THF, produced the macrolactam (**91**) in 37% yield with complete retention of geometries of the double bond unit participating in the coupling reaction. **Scheme 19.**

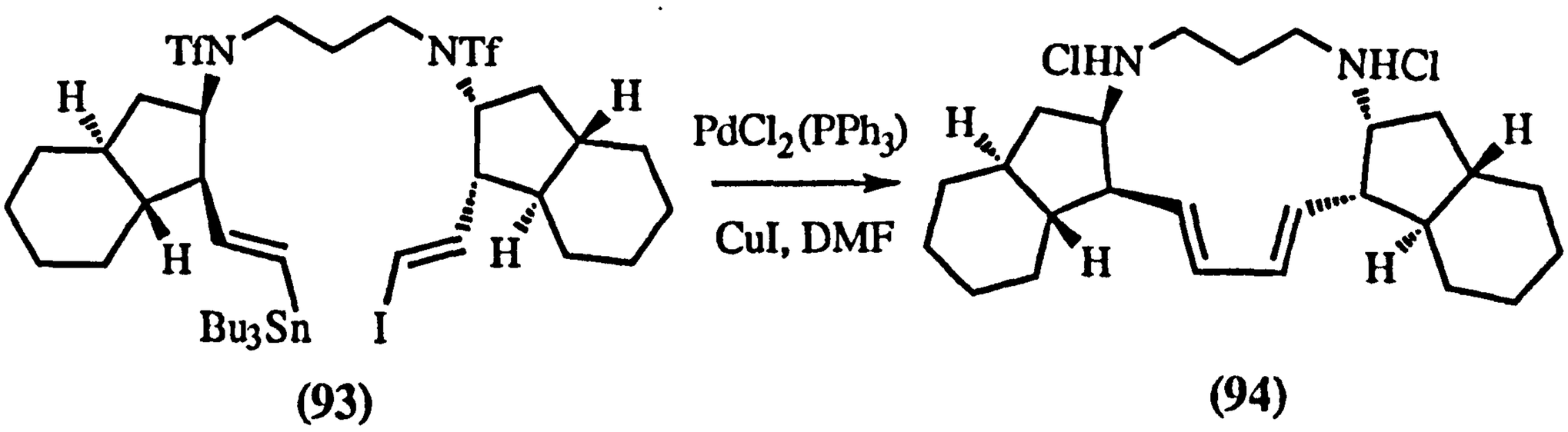


(90) (91)

(92)

Scheme 19

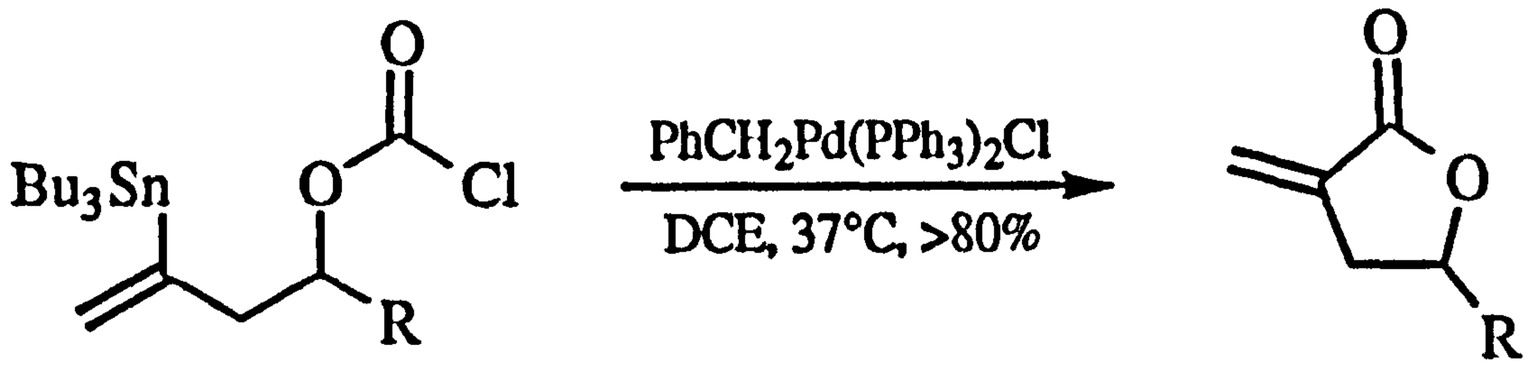
Another advocate of the Stille reaction, Barrett *et al*, completed the total synthesis of the C_2 symmetric pentacyclic diamine papuamine I (**94**), isolated from the marine sponge *Halicona*.[49] The macrocyclisation of the *E*-vinyl stannane precursor (**93**) under palladium (0) catalysis, followed by deprotection and formation of the hydrochloride salt, gave papuamine I (**94**). **Scheme 20.**



(**93**) (**94**)

Scheme 20

Baldwin *et al* have used the intramolecular Stille coupling reaction in the formation of α,β-unsaturated lactones (**96**). This cyclisation used the reactive chloroformates (**95**) to oxidatively add to the palladium, instead of the more commonly used halides.[50] **Scheme 21.**

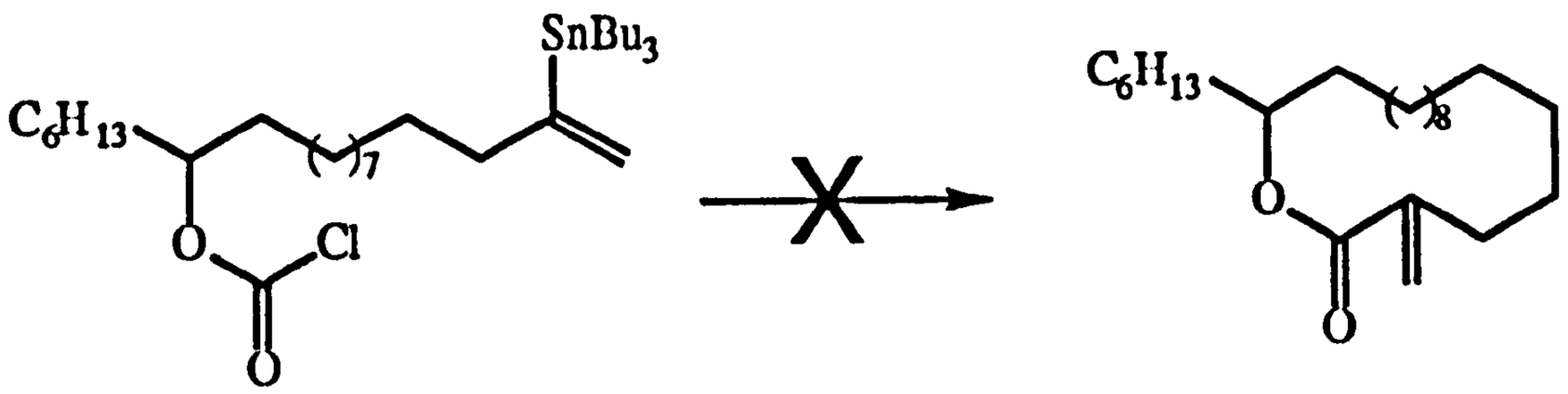


R = C_9H_{19}, C_7H_{15}

(**95**) (**96**)

Scheme 21

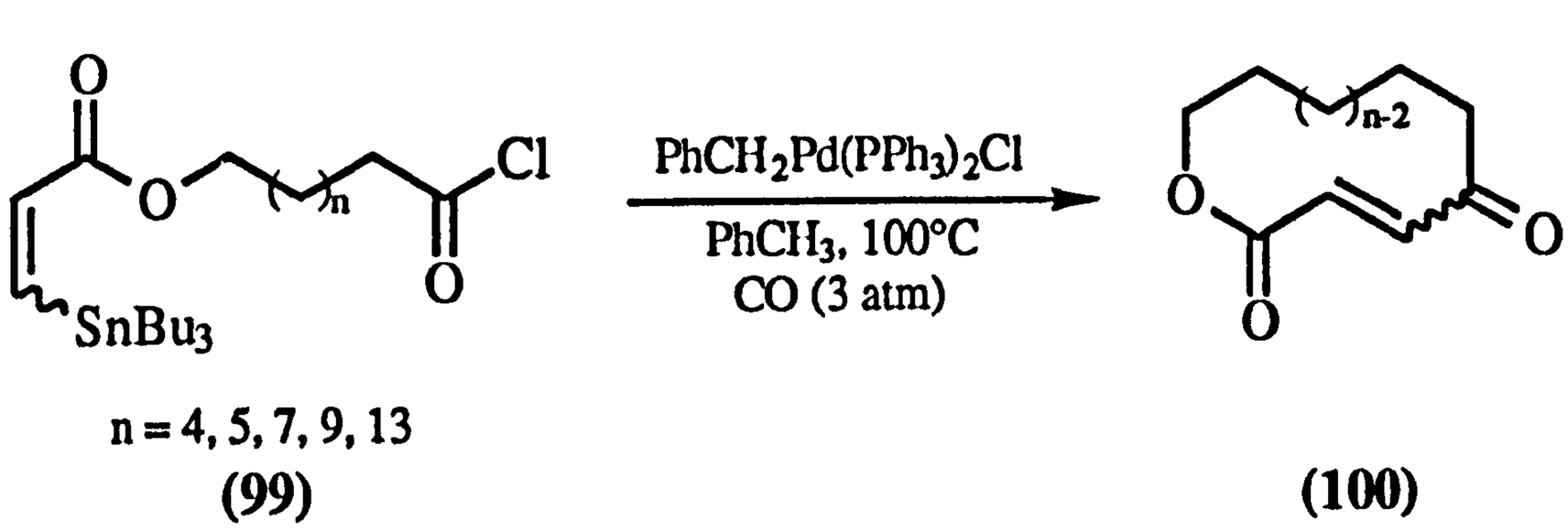
Surprisingly Baldwin found that when the chloroformates of the type (**97**) were treated under the same cyclisation conditions, a precursor to the larger ring α,β-unsaturated lactones, the cyclised material (**98**) was never isolated. **Scheme 22.**



(97) **(98)**

Scheme 22

However Baldwin *et al* did accomplish the intramolecular palladium cross coupling reaction to give the γ-oxo-α,β-unsaturated macrolactones **(100)** directly by subjecting the precursor **(99)** to the carbonylative coupling conditions to give varying yields (15-70%) of the macrocycle **(100)**. Unfortunately the smaller chain length precursor (n = 3) yielded only the dimer.[51] **Scheme 23.**

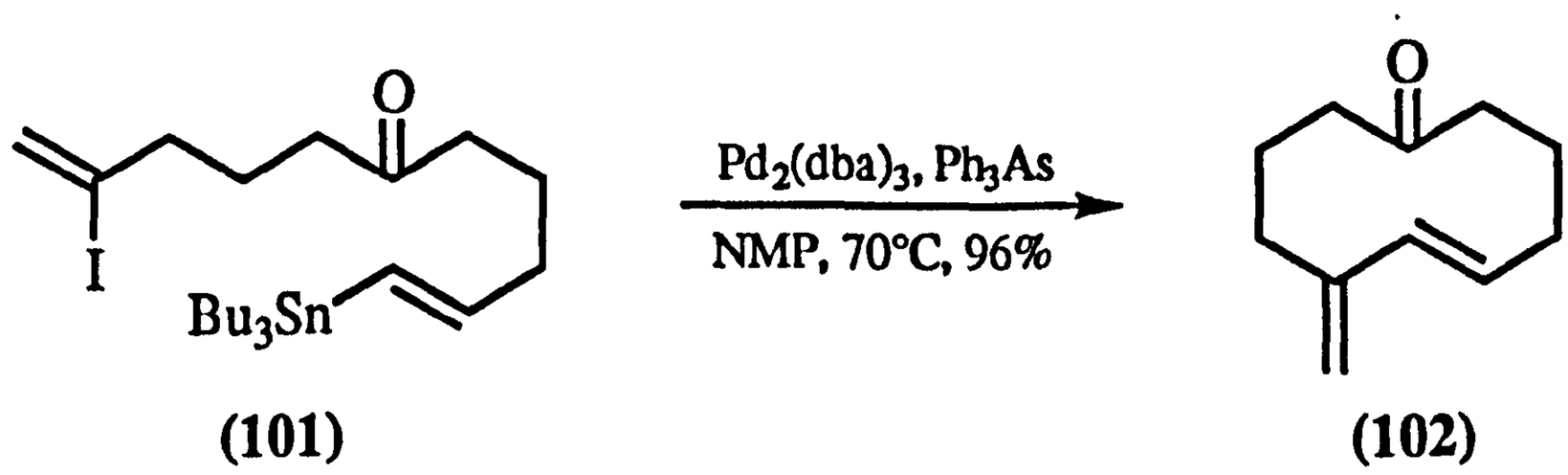


n = 4, 5, 7, 9, 13

(99) **(100)**

Scheme 23

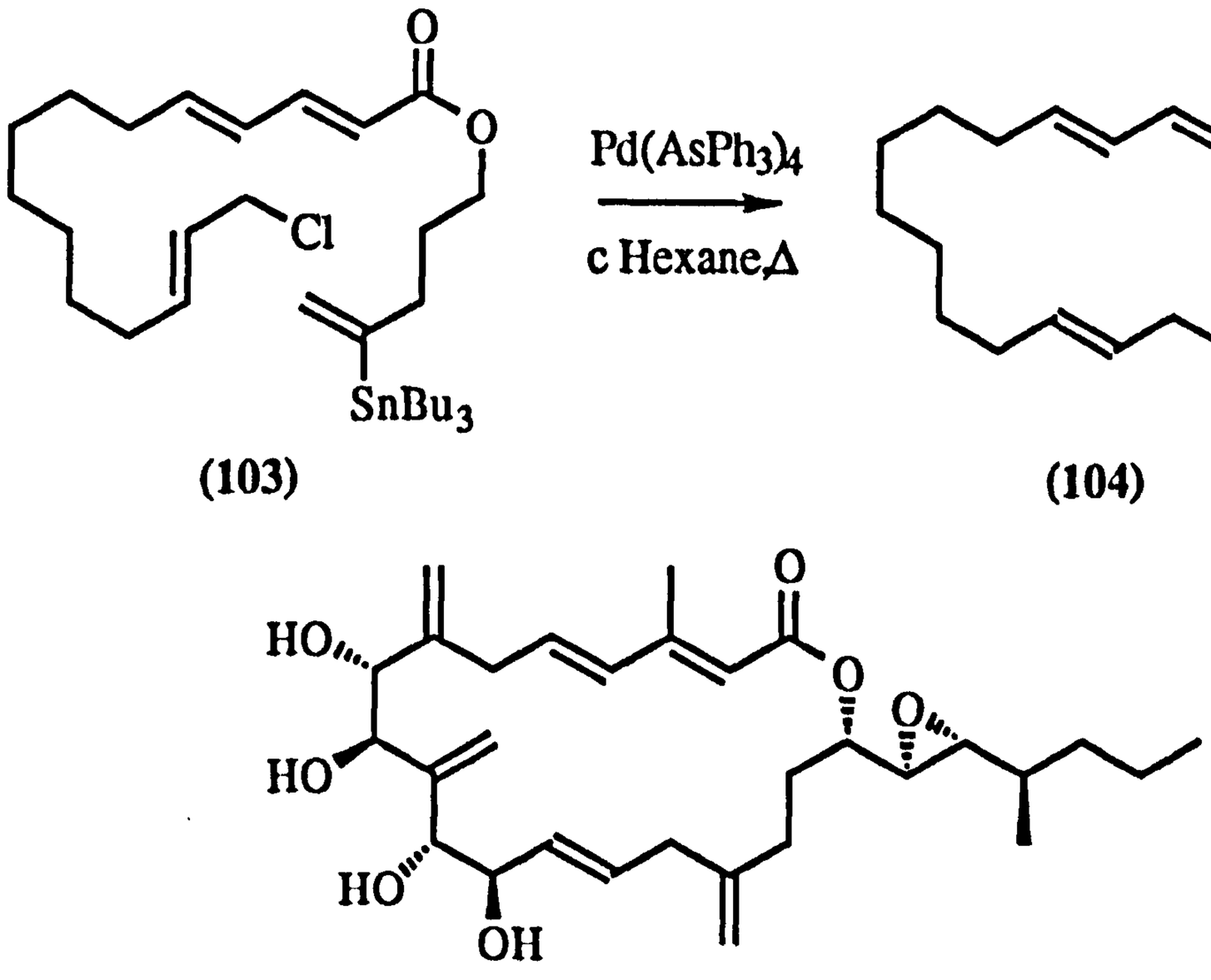
Shortly after Baldwin's publications Hodgson *et al* published an efficient medium ring cyclisation approach to the germacranes.[52] Thus, the *E*-vinyl stannane **(101)** was cyclised to the dienone **(102)** using what has now become the catalyst of choice, Farina's $Pd(AsPh_3)_4$, in an outstanding 96% yield. **Scheme 24.**



(101) (102)

Scheme 24

Although conventional thought would suggest that both stannanes and halides containing sp^3-bonded hydrogen atoms would favour β-elimination in place of cyclisation, this observation does not include the allyl species. This reasoning was explored by Pattenden and Boden in their palladium mediated intramolecular sp^2-sp^3 coupling approach to the amphidinolides, and in particular amphidinolide A (**105**).[53] Hence, the vinyl stannane-allylic chloride precursor **(103)** underwent smooth and efficient coupling with $Pd(AsPh_3)_4$ to give the macrocyclic *E*-1,4-diene **(104)** in 38% yield with only very small amounts of the geometric isomers being isolated. **Scheme 25.**

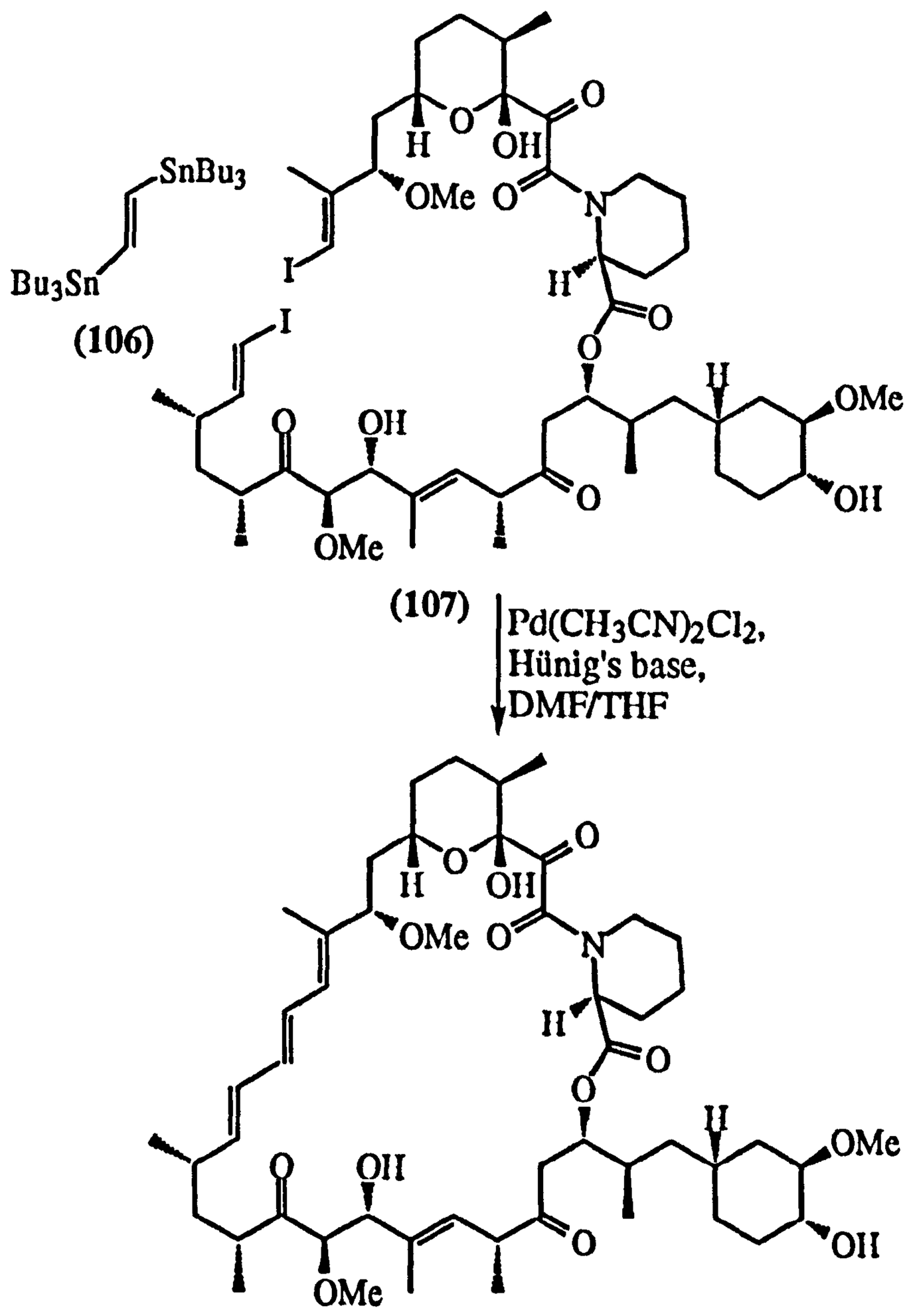


(103) (104)

(105)

Scheme 25

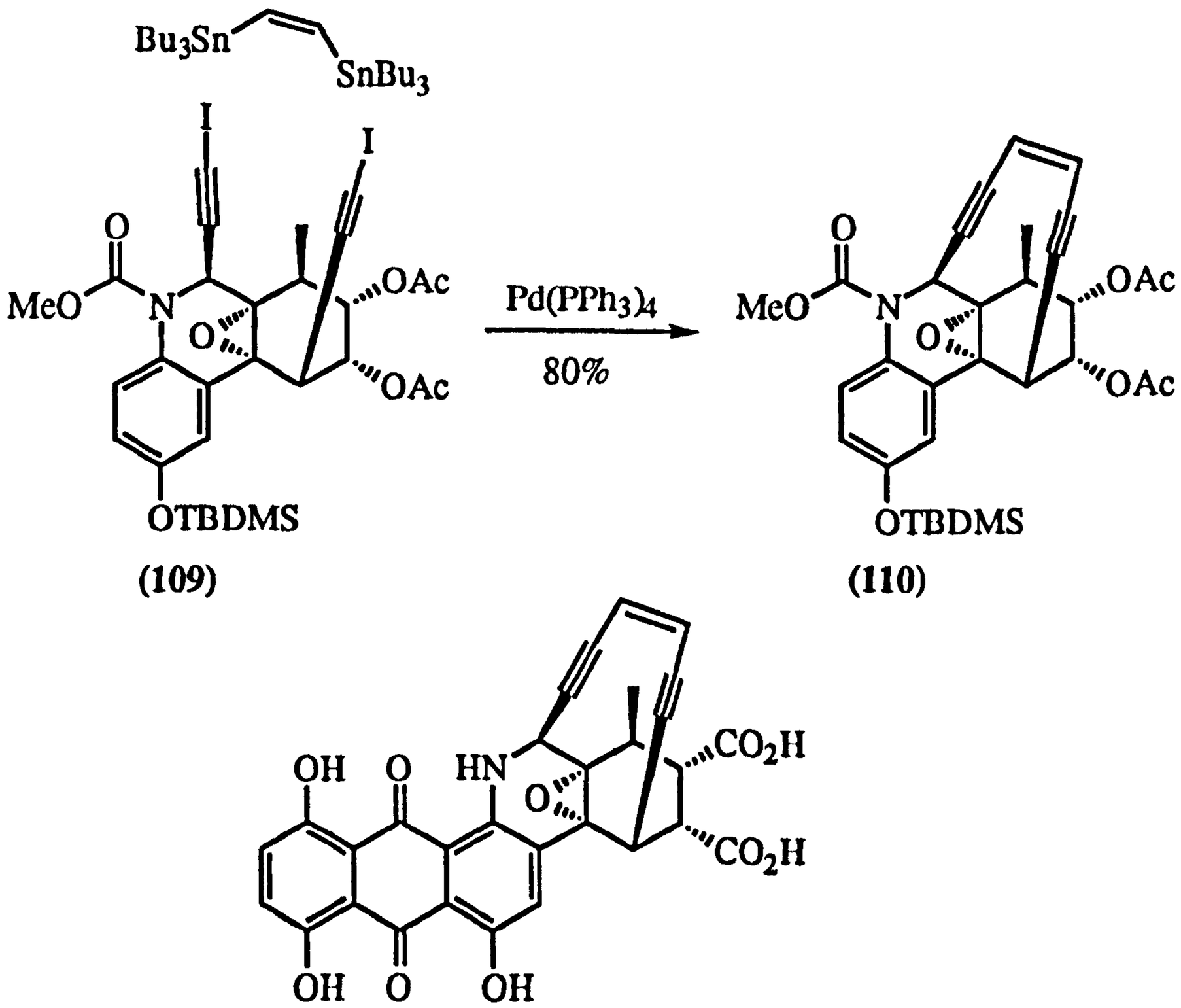
One of the most inspiring examples of the Stille cyclisation in natural product synthesis must be the total synthesis of rapamycin **(108)** by Nicolaou *et al* published in 1993.[54] Their strategy uses a 'stitching' protocol to incorporate ethene-distannane into the molecule *via* a 'one-pot' intermolecular and intramolecular Stille coupling reaction. Thus, treatment of both the distannane **(106)** and the diiodide **(107)** with Pd^2 and Hünig's base in a mixture of DMF and THF gave rapamycin **(108)** in 28% yield along with 30% recovered starting material and 30% of the uncyclised vinyl iodide-vinyl stannane product. This later compound was cyclised in the standard fashion to yield rapamycin **(108)** in 60%. **Scheme 26.**



Scheme 26

A slightly more standard intramolecular sp^2-sp^2 coupling reaction was used by A. B. Smith *et al* in their synthesis of rapamycin.[55] Their strategy proceeded *via* the vinyl bromide-vinyl stannane precursor traditionally used in Stille coupling reactions.

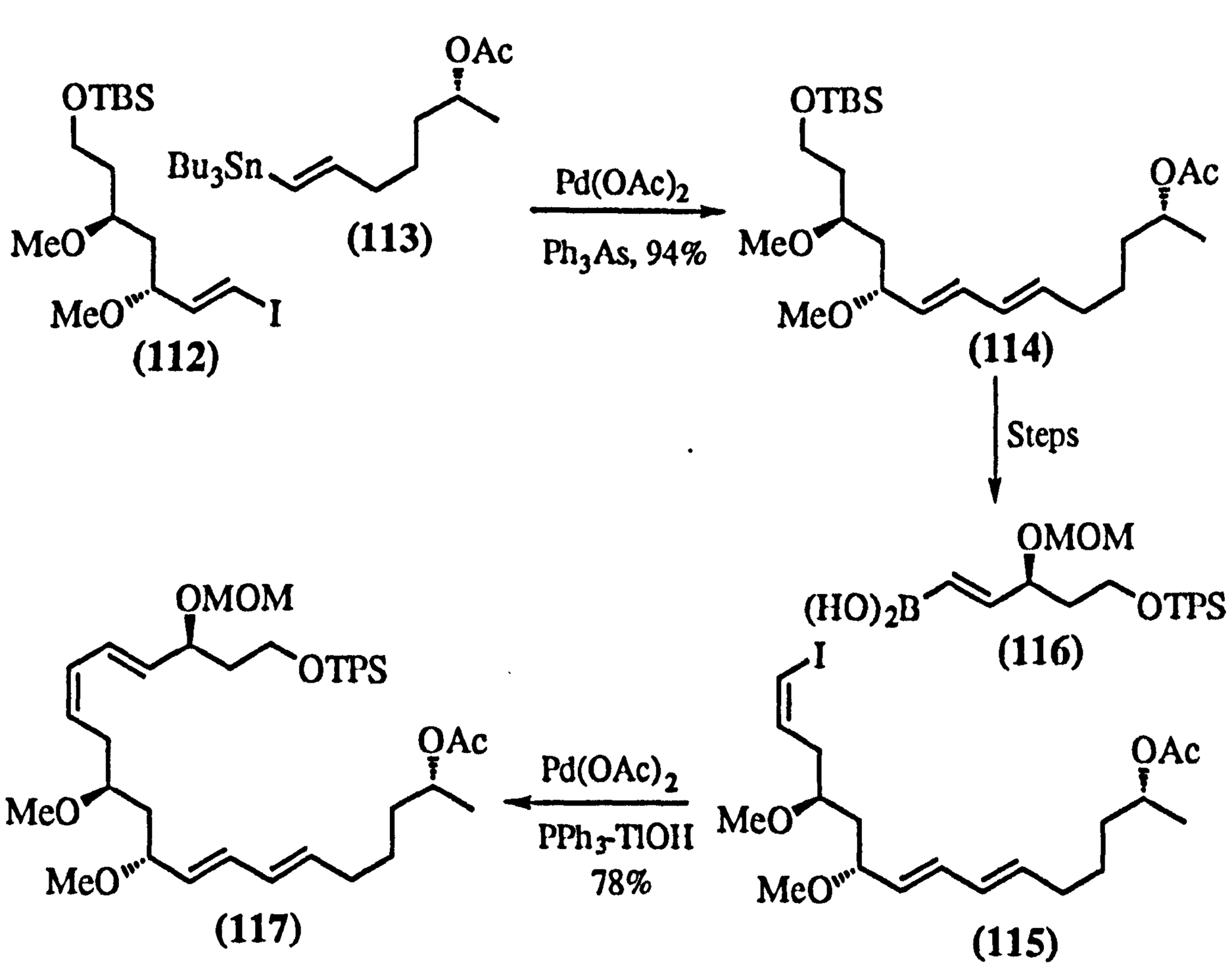
Another interesting and elegant example of the use of the 'stitching' approach to cyclisation is that of Danishefsky *et al* in their synthesis of the enediyne unit present in dynaemicin A **(111)**.[56] Thus, the *bis*(iodideacetylene) **(109)** was coupled with the Z-ethenedistannane to yield the conjugated enediyne **(110)** in a remarkable 80% yield. **Scheme 27.** The authors noted that the epoxide in the molecule was necessary for cyclisation to occur, with its replacement by a double bond resulting in the reaction stopping after the intermolecular reaction had occurred.



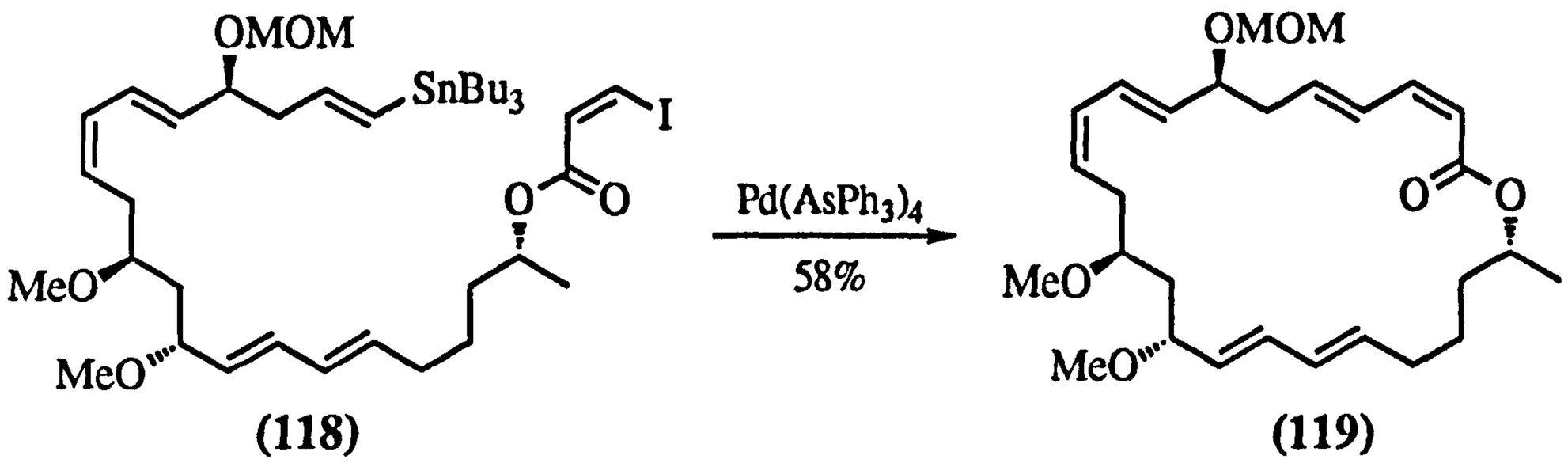
Scheme 27

Another example of this powerful cyclisation method, is the synthesis of

macrolactin A **(119)** by Boyce and Pattenden.[57] The synthesis of the three geometrically constrained diene units present in macrolactin A was achieved by the use of two Stille coupling reactions and one Suzuki coupling reaction. **Schemes 28 and 29.** The formation of the first of these units used an intermolecular Stille coupling reaction. Thus, the vinyl stannane **(113)** was coupled, under Stille conditions using Pd(II)OAc_2 and triphenylarsine, to the vinyl iodide **(112)**, to give the *E,E*-diene **(114)** in an excellent 94% yield. Further elaboration of the diene **(114)** through to the *Z*-vinyl iodide **(115)**, and subsequent Suzuki coupling of this iodide **(115)** to the boronic acid **(116)**, using palladium (0) and thallium (I),[58] gave the second of the diene units, the *E.Z*-diene **(117). Scheme 28.** Finally, after further elaboration of the diene **(117)** to the vinyl stannane-vinyl iodide **(118)**, the synthesis of the final diene unit, and hence the cyclisation of the precursor, was achieved by treatment with the Farina catalyst, $Pd(AsPh_3)_4$, to give the protected form of macrolactin A **(119)** in 58% yield. **Scheme 29**



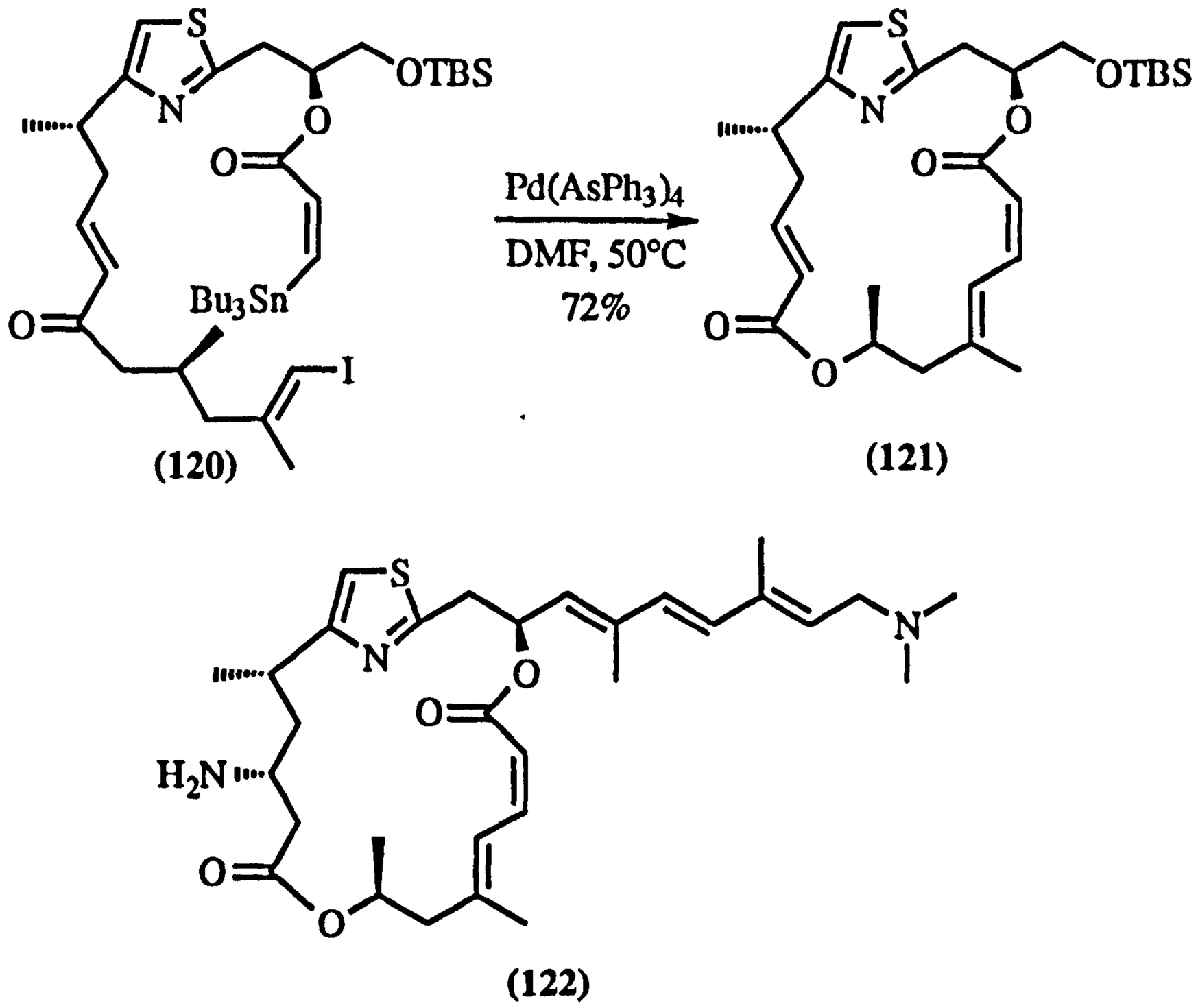
Scheme 28



(118) (119)

Scheme 29

In addition to the previously mentioned examples, Critcher and Pattenden have more recently published the Stille mediated synthesis of the *bis*-lactone core of the antifungal agent pateamine **(122)**.[59] The key step in this synthesis once again was an intramolecular Stille coupling reaction between the *Z*-vinyl stannane and *E*-vinyliodide precursor **(120)**, to give the *bis*-lactone **(121)** in 72% in the presence of Farina's catalyst. **Scheme 30.**



(120) (121)

(122)

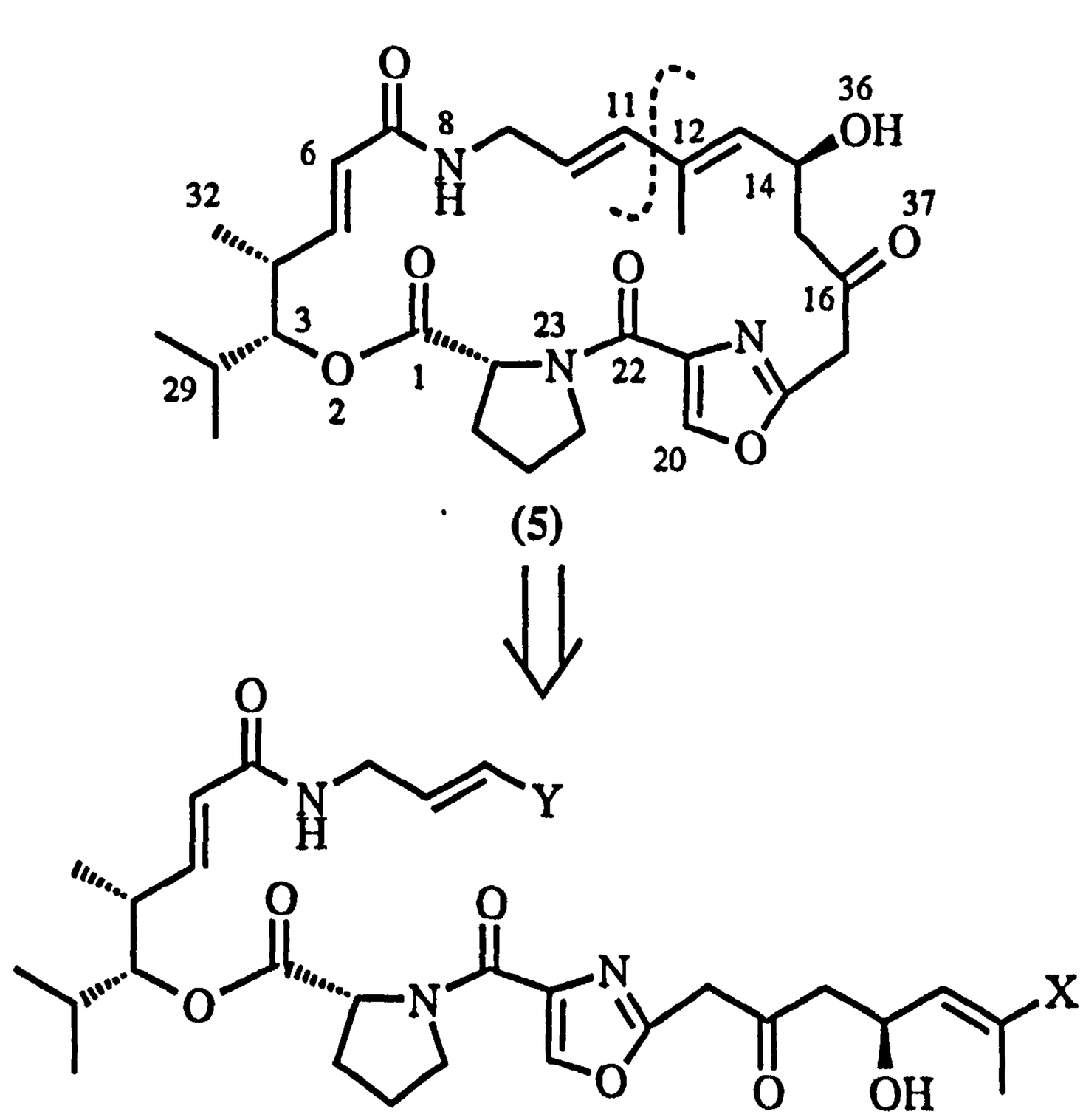
Scheme 30

This brief review of the Stille reaction as a strategy for the synthesis of polyene fragments, especially within ring systems, provides overwhelming evidence for the importance of this reaction within the area of total synthesis. The stereo- and chemo-selectivity of the reaction, coupled to the ease of synthesis of its precursors, make this reaction one of the most important synthetic methods developed within the past 15 years. The improvements in reaction rate and yield resulting from the immense amount of synthetic and mechanistic studies carried out into the catalysts used and their ligands, and the addition of salts to the reaction, only add further support to the importance of the Stille reaction in contemporary synthesis.

2. RESULTS and DISCUSSION

2.1 Initial Disconnections

As discussed earlier in the Introduction, the main approaches to the virginiamycin system have been concentrated on producing the macrocyclic ring *via* a macrolactonisation or a macrolactamisation. Our attention was drawn to the polyene portion of virginiamycin M_2 with the intention of using an intramolecular Stille cyclisation for its construction as our cyclisation step. Work within the Pattenden research group, including the synthesis of the macrolide portion of the natural product leinamycin by Pattenden and Thom[48] using an intramolecular sp^2-sp^2 Stille reaction, gave good precedent for this strategy. Thus, if we disconnect between C-11 and C-12 in **(5)** we obtain the cyclisation precursor **(123)**, where X and Y are the halide and trialkylstannane associated with the Stille coupling. **Figure 14**



(123)

Figure 14

Disconnection of the precursor **(123)** at the ester and amide linkages, between C-1 and O-2, and between C-22 and N-23, then gave us three main fragments: (*i*) fragment **(124)**, the unsaturated hydroxyamide containing the two adjacent chiral alkyl groups; (*ii*) fragment **(125)**, the 2,4-disubstituted oxazole fragment; (*iii*) fragment **(126)**, the commercially available amino acid (*R*)-proline. **Figure 15.**

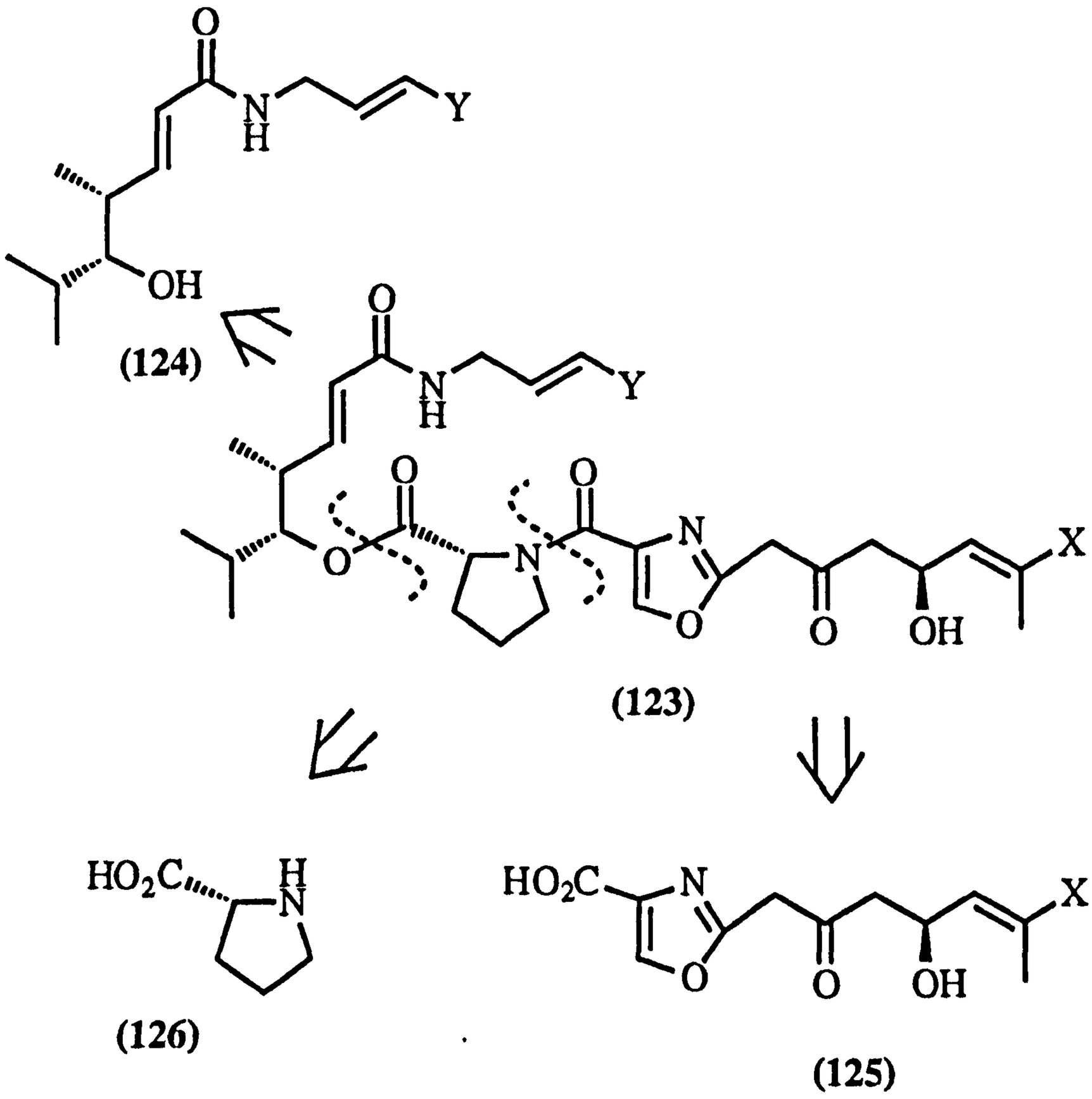


Figure 15

Fragment **(124)** has received much attention over the past ten years, with particular interest being given to the corresponding ethyl ester **(127)**. **Figure 16.**

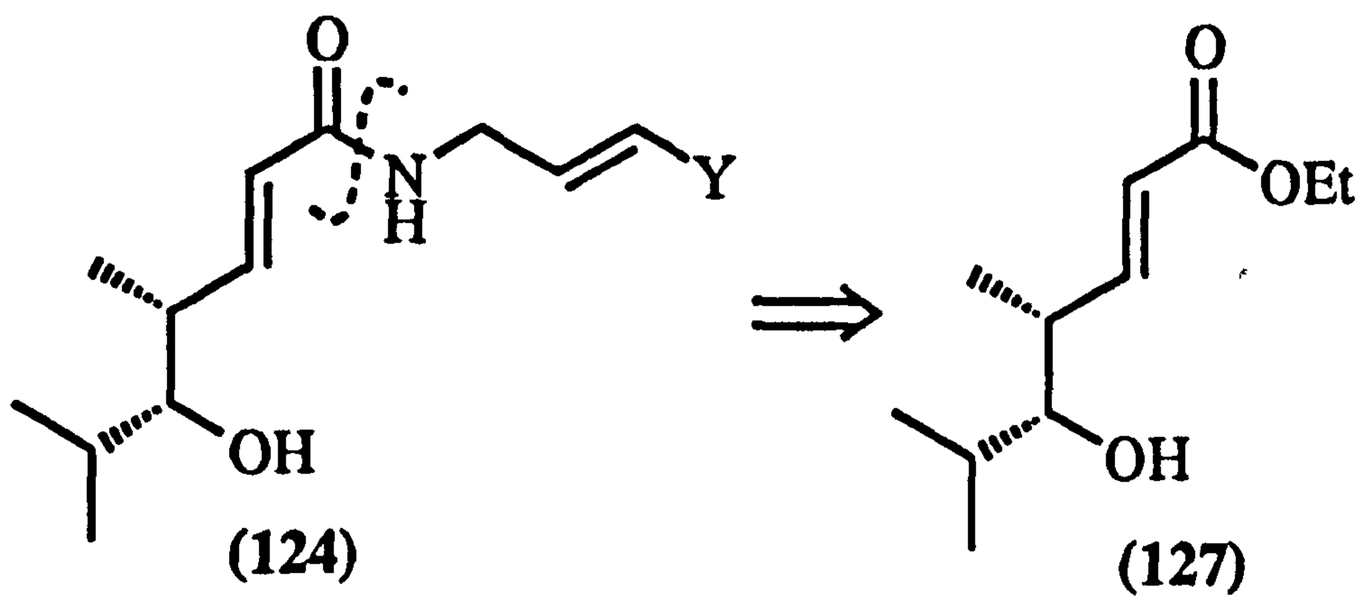
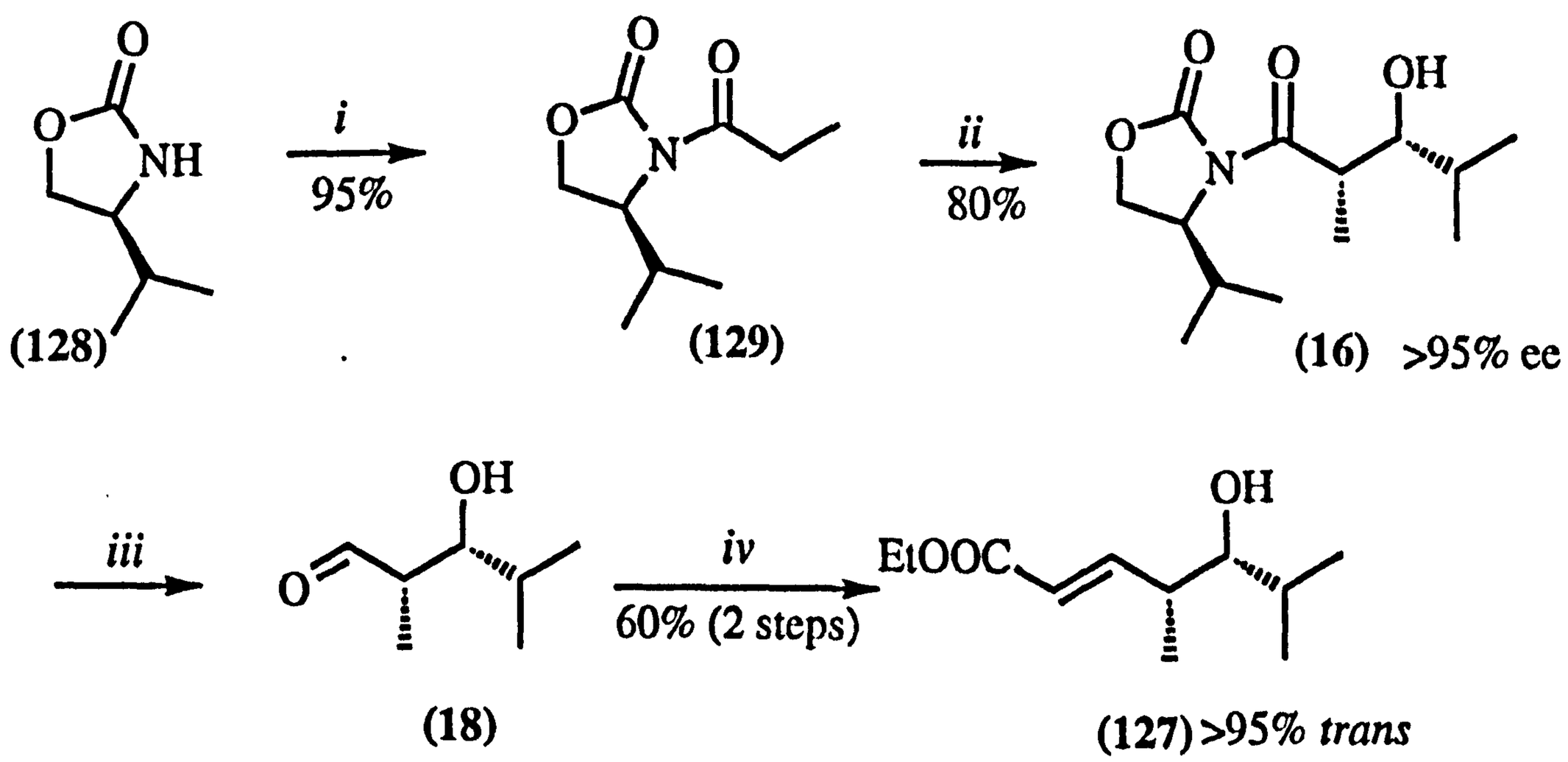


Figure 16

This particular ethyl ester **(127)** has been synthesised by a number of different research groups, using a variety of strategies. Helquist[26] and Ganem[29] used different achiral starting materials and methods to produce a common intermediate, whereas Uguen,[60] Schlessinger,[24] and Meyers[20] have all used chiral auxiliaries to introduce the two adjacent chiral centres in **(127)**. For our synthesis we decided to exploit the method published by Meyers *et al* utilising the Evans' chiral oxazolidinone **(128)**.

Scheme 31.



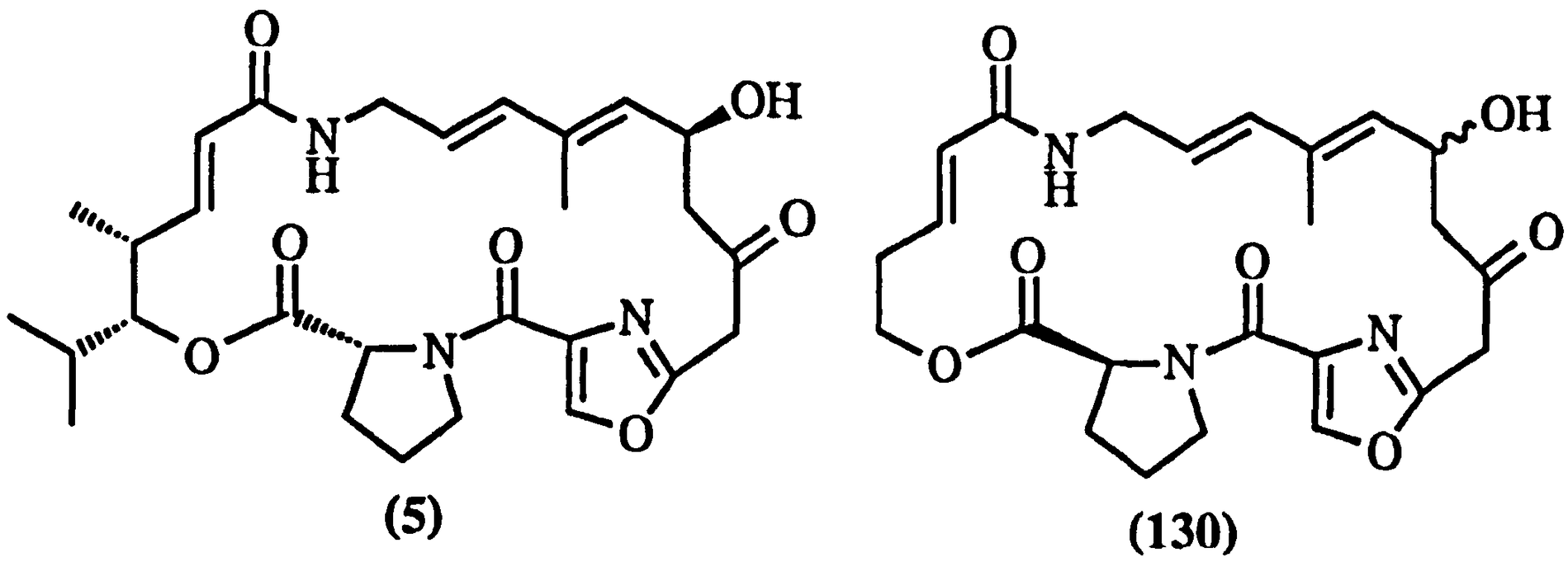
Reagents: *i*, *n*-BuLi, propionyl chloride, THF; *ii*, Bu_2BOTf, Hünigs base, isobutyraldehyde, H_2O_2, CH_2Cl_2; *iii*, Red-Al, THF; *iv*, KO^{t}Bu, $(EtO)_2POCH_2CO_2Et$, THF.

Scheme 31

Thus, (4*S*)-(-)-isopropyloxazolidin-2-one **(128)** was first treated with *n*-butyllithium and propionyl chloride, in THF at -78°C, to give the amide **(129)** in 95% yield. The amide **(129)** was next treated with di-*n*-butylboron triflate and Hünigs base to form the corresponding *Z*-enolate, which was then reacted at -78°C, in CH_2Cl_2, with isobutyraldehyde to give the hydroxyamide **(16)** in 80% yield, with a >95% *ee* (measured by nmr) after recrystallisation. (It was interesting to note that the specific rotation obtained for our product did not match that of the published value. Over repeated measurements we obtained readings between +27.0° to +28.0° (*c* 3.9 in $CHCl_3$) whereas Meyers quotes values of -8.2° (*c* 4.7 in $CHCl_3$); however all values obtained for subsequent compounds were identical to those obtained by Meyers. We can only assume that the value quoted may be that of one of the other isomers produced by the authors). The hydroxyamide **(16)** was then cleaved reductively to the aldol **(18)** using Red-Al at -50°C. Wadsworth-Emmons olefination of the aldol **(18)** using triethyl phosphonoacetate, in THF at -78°C, yielded the *E*-α,β-unsaturated ethyl ester **(127)** in 60% (2 steps) which proved identical to that synthesised by Meyers.[20]

2.2 Work on a Model System for Virginiamycin M_2.

Initial studies, aimed at determining if our strategy utilising the Stille reaction could be applied to the synthesis of the virginiamycin system, were carried out on a model system containing the basic 23-membered macrocyclic ring. For the synthesis of such a model it was decided to remove the two adjacent chiral alkyl groups at C-3 and C-4 and to also have a diastereomeric mixture about the hydroxy group at C-14. It was also decided to replace the unnatural (*R*)-proline with the more readily available (*S*)-proline. These modifications had the advantage of removing the need for expensive chiral auxiliaries and amino acids in our initial studies. We therefore proposed to synthesise the macrocycle **(130)** as a suitable model system for our initial studies in the synthesis of the virginiamycin system. **Figure 17.**

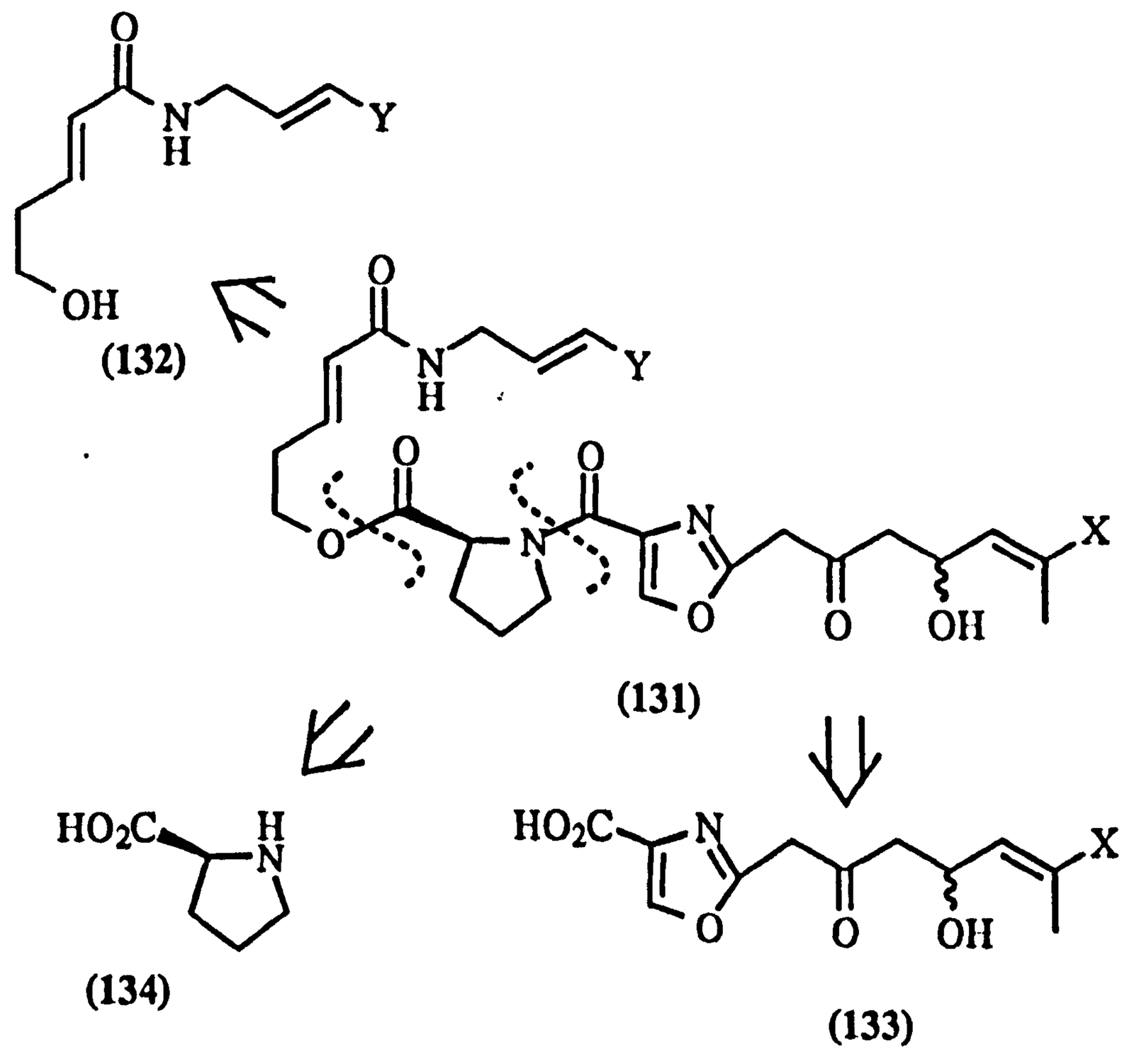


(5)

(130)

Figure 17

Disconnecting **(130)** between C-11 and C-12 for our cyclisation step using a Stille coupling, and then again between C-1 and O-2 and between C-22 and N-23, we once again obtain three main fragments. **Figure 18.** Fragment **(134)** is the commercially available natural amino acid (*S*)-proline, fragment **(133)** is the racemic form of fragment **(125)** **(Figure 15)**, and fragment **(132)** is the α,β–unsaturated amide equivalent to the chiral fragment **(124)** **(Figure 15)**.



(132)

(131)

(134)

(133)

Figure 18

With our model system and its three component fragments identified we then proceeded with our synthesis of the cyclisation precursor **(131)**.

2.2.1 Synthesis of the Left-hand Fragment (132) of the Model System (130).

At this point it was necessary to determine which fragment would contain the vinyl halide and which the vinyl stannane, *i.e.* designate groups X and Y in **(132)** and **(133)**. There exists in the literature numerous methods for the synthesis of vinyl halides and vinyl stannanes. In the case of vinyl halides their syntheses can be achieved by Wittig type reactions such as the chromium mediated Takai reaction,[61] elimination of HX from the 1,2-dihalide formed from the alkene,[62] and substitution of vinyl species such as aluminates,[63] silicates[64] and zirconates.[65] In the case of vinyl stannanes there exist fewer options. The most common methods for introducing vinyl stannanes are either by transmetallation of vinyl organometallic species, or by radical additions to triple bonds.[66] However none of these methods are of use if stereo- and regio-control are poor. After consideration it was decided to attempt to form the vinyl stannane on fragment **(132)** and to this end we chose Boc protected propargylamine **(135)** to ascertain the required conditions. A number of different conditions were tried to effect a radical hydrostannation of the protected propargylamine **(135)** with tri-*n*-butyltin hydride, including thermal and photolytic methods, but all attempts resulted in inseparable mixtures of α- and β-products.[66] **Figure 19.**

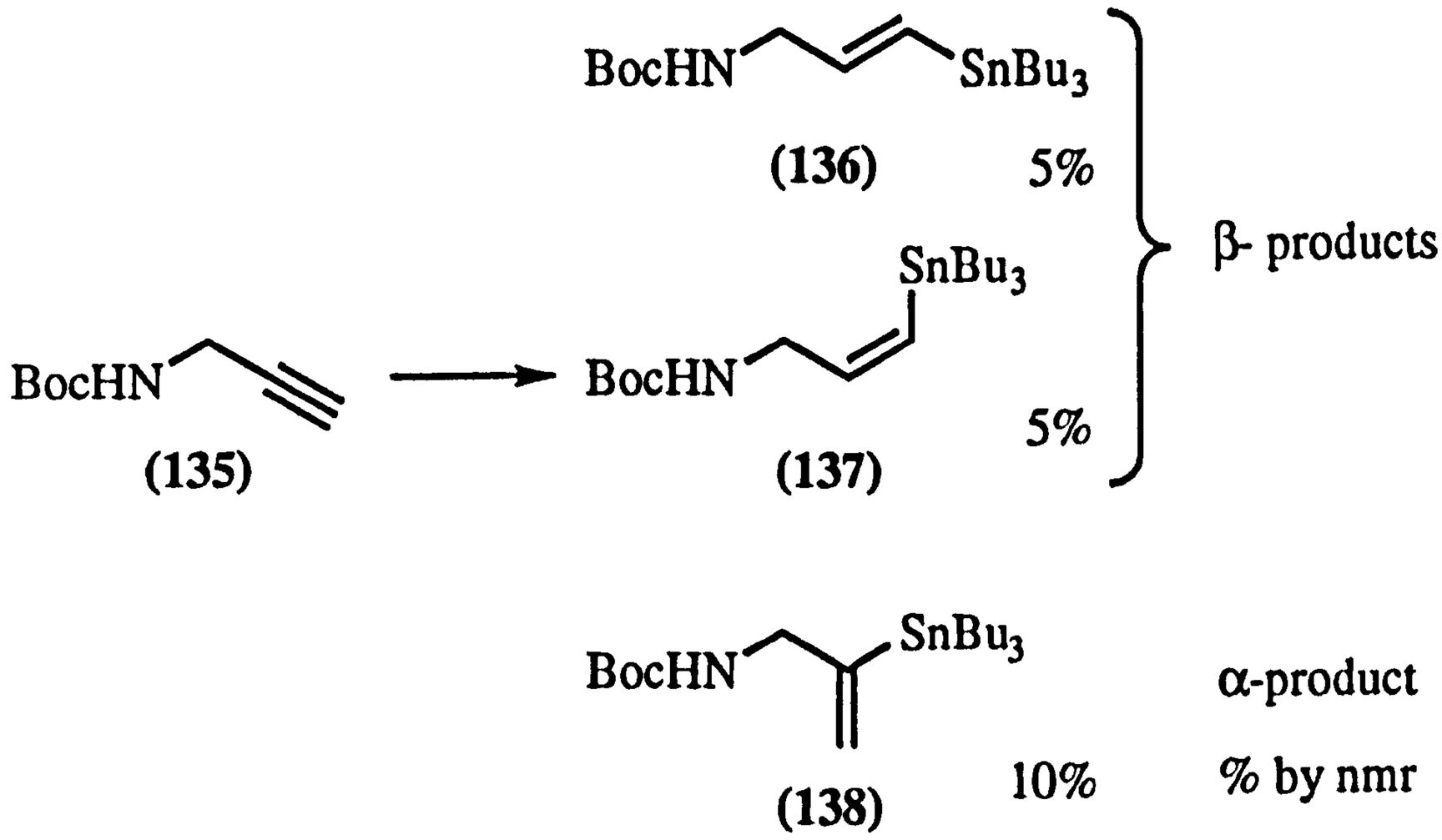


Figure 19

Reginato *et al*[67] reported that protected propargylamines could be hydrostannated to give the *E*-β-product **(136)** exclusively and in good yields by using the high order cuprate $Bu_3Sn(Bu)Cu(CN)Li_2$ **(139)** developed by Lipshutz.[68] **Figure 20.**

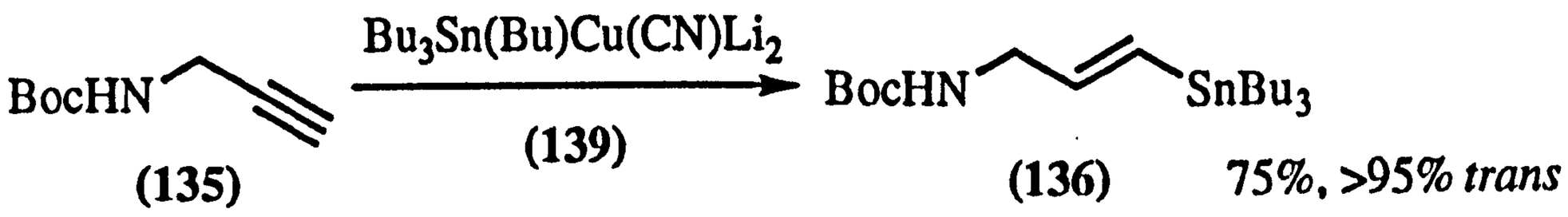
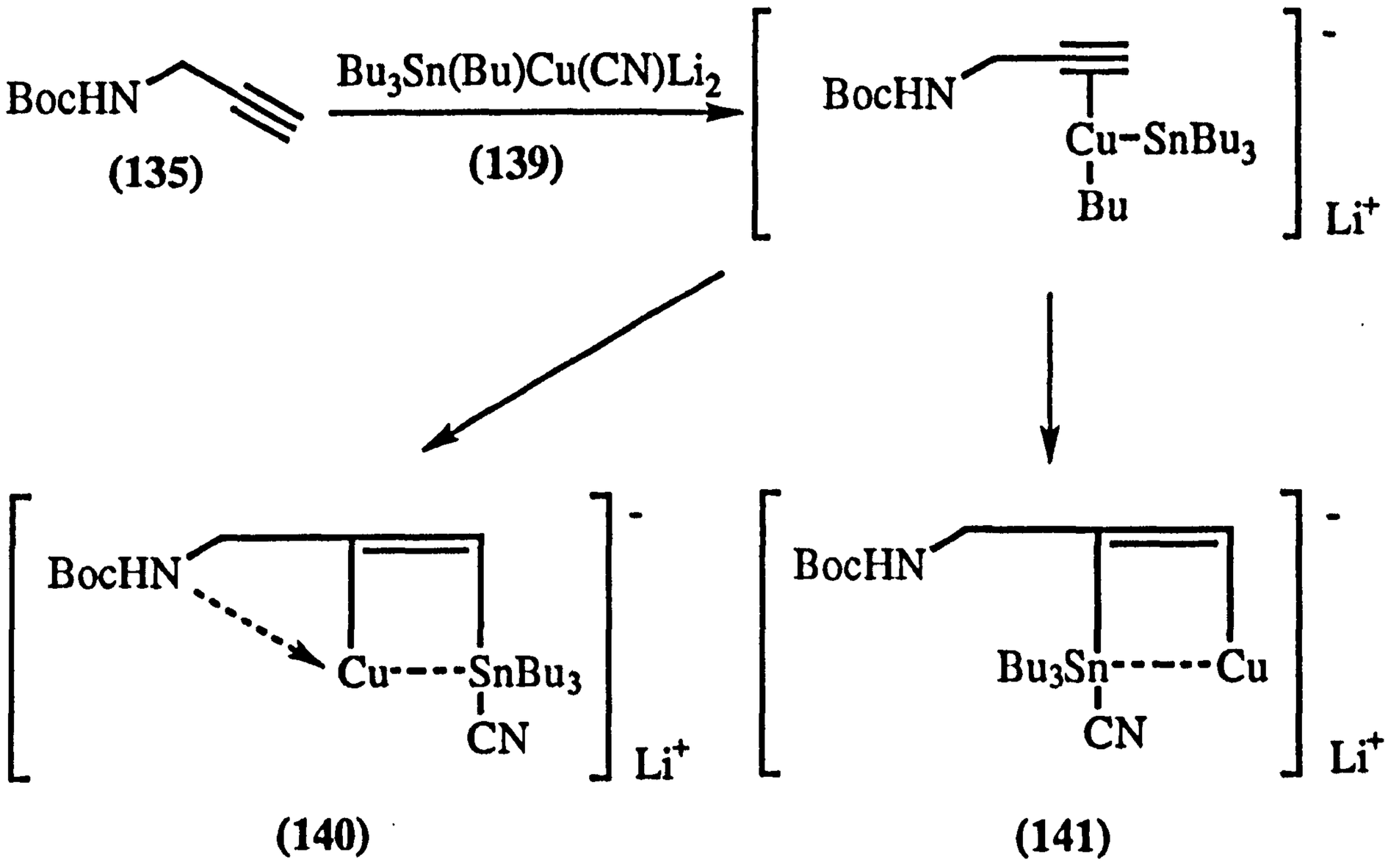


Figure 20

It was proposed that the excellent regiocontrol arose from the stabilisation of complex **(140)**, **Figure 21**, by the additional co-ordination of the copper atom to the

nitrogen of the carbamate, since without this additional co-ordination the reverse transition state **(141)** is observed. Having found a high yielding and highly selective method for the production of the vinyl stannane portion **(143)** of our left-hand fragment **(132)**, we proceeded with the synthesis.

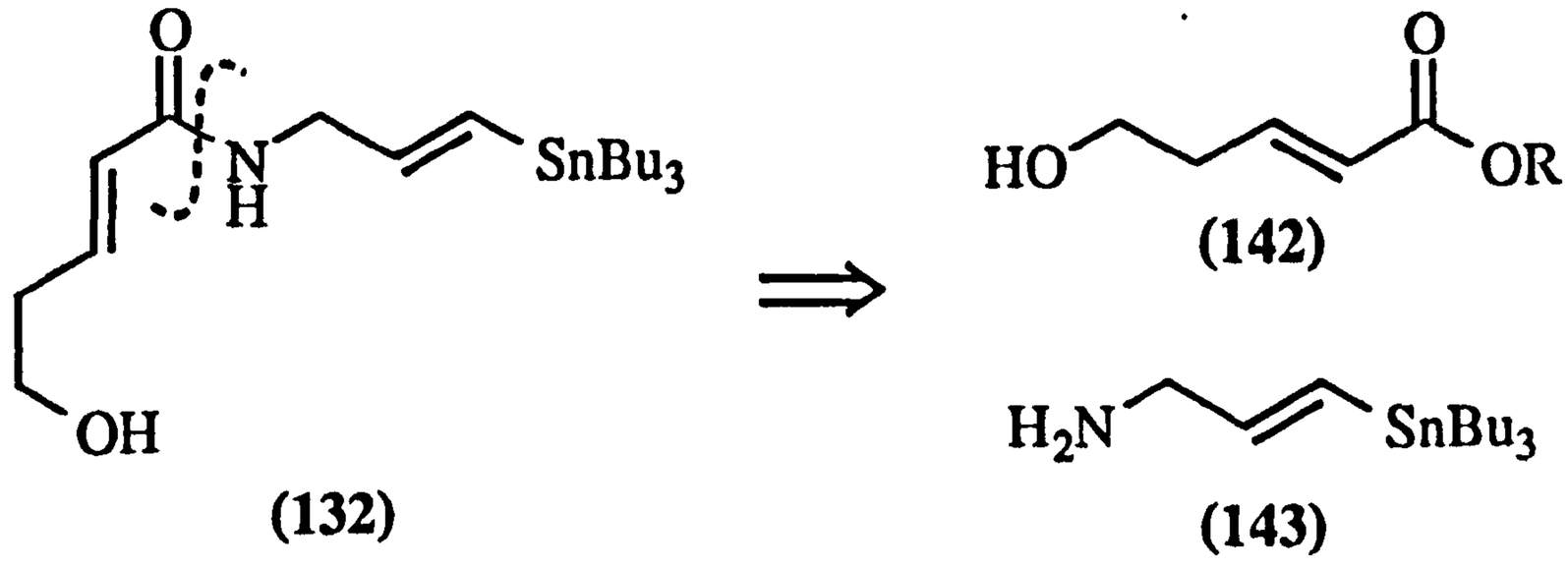


(140) **(141)**

Favoured stabilised complex

Figure 21

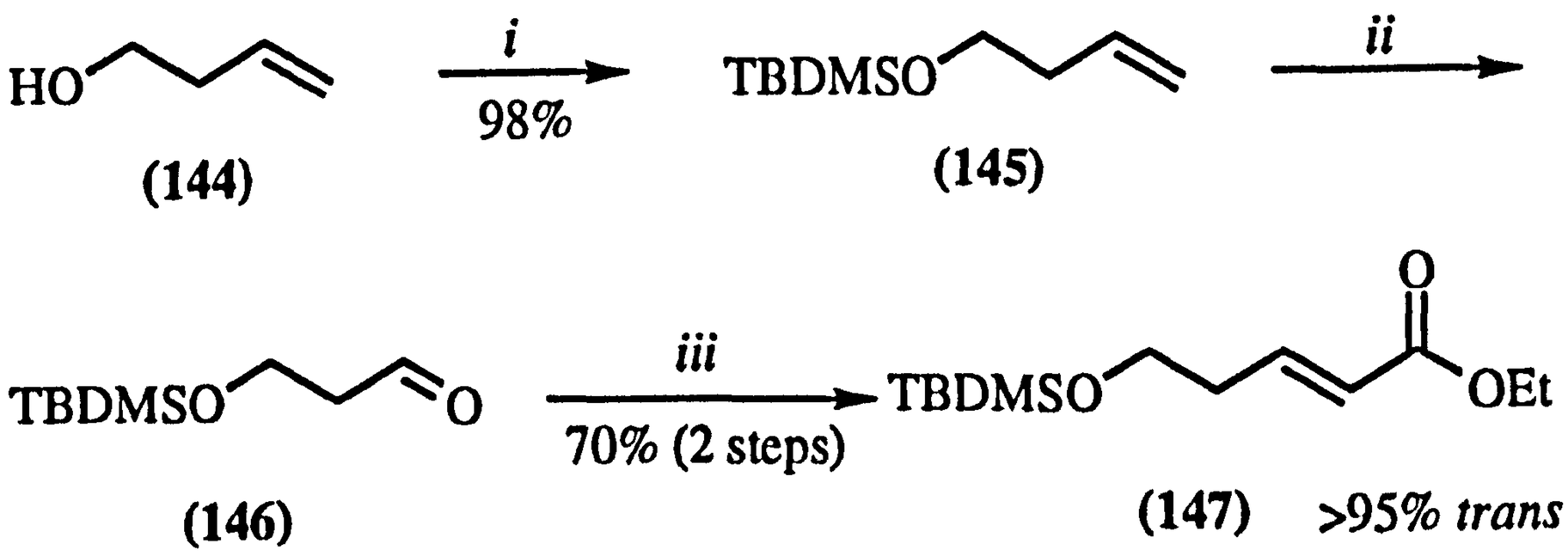
Disconnecting fragment **(132)** at the amide linkage we realise the two fragments, **(142)**, an α,β-unsaturated ester, and **(143)**, the free amine corresponding to the protected vinyl stannane **(136)**. **Figure 22.** Fragment **(142)** was synthesised in its protected form in three steps starting from commercially available 3-butenol **(144)** utilising Wadsworth-Emmons chemistry.[69] **Scheme 32.**



(132) (142) (143)

Figure 22

Thus, 3-butenol **(144)** was first protected using TBDMS-Cl and imidazole in dry DMF to give the silyl ether **(145)** in an excellent 98% yield.[70] **Scheme 32.** The terminal double bond in **(145)** was next cleaved to the aldehyde **(146)** using ozone, at -78°C, in dry CH_2Cl_2 with triphenylphosphine work-up. The aldehyde **(146)** was carried through without further purification into a Wadsworth-Emmons olefination reaction, using potassium *t*-butoxide and triethyl phosphonoacetate in dry THF, at -78°C, to give the ester **(147)** in 70% yield (2 steps).



(144) **(145)** **(146)** **(147)** *>95% trans*

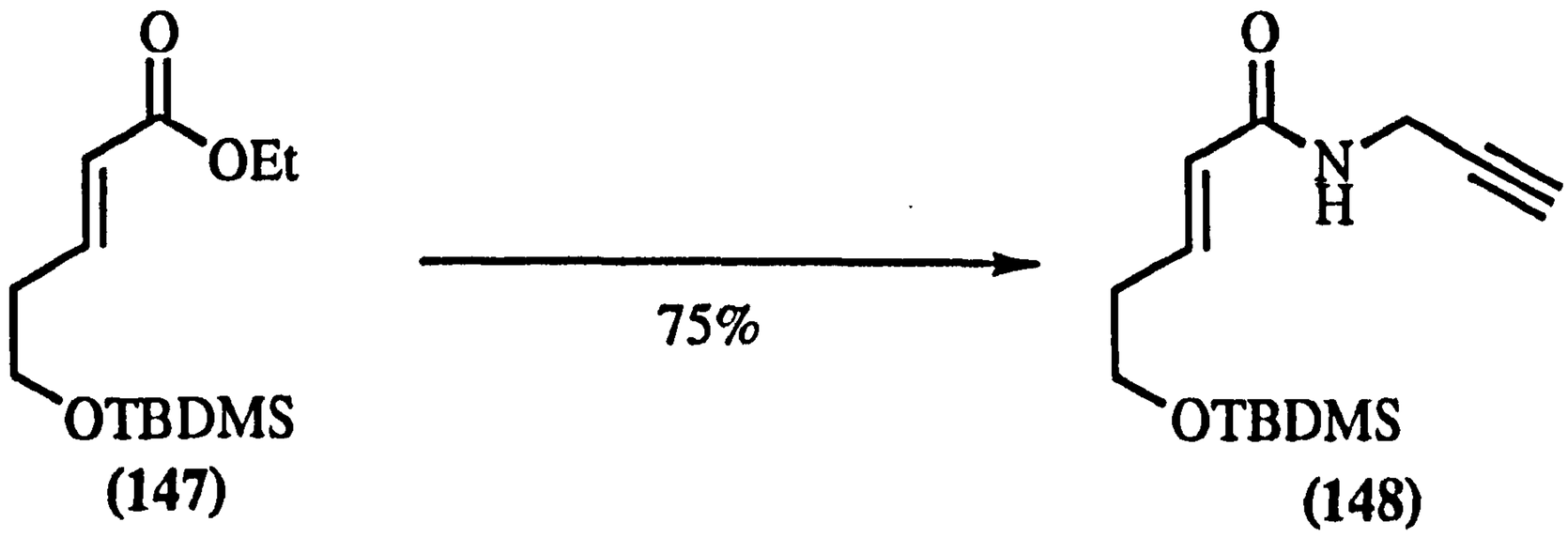
Reagents: *i*, TBDMS-Cl, imidazole, DMF; *ii*, O_3, PPh_3, CH_2Cl_2;

iii, KO^{t}Bu, triethyl phosphonoacetate, THF.

Scheme 32

With the ester **(147)** in hand our attention was now drawn to the deprotection of the amine **(136)**. The Boc group is usually cleaved under acidic conditions and can be removed using a variety of inorganic, organic, and Lewis acids.[71] However the

carbon-tin bond is known to readily undergo cleavage under these conditions and we found the Boc protection could not be removed without concomitant protiodestannylation. We therefore decided it would be advantageous to couple propargylamine to the ester **(147)** before attempting hydrostannylation, since a greater range of transformations could be performed on the acetylene than could be on the less robust vinyl stannane. General methods of converting the ester **(147)** into the *N*-propargylamide **(148)** such as direct activation of the ester with cyanide or by hydrolysis of the ester and mixed anhydride formation, only led to decomposition or recovery of the ester **(147)**. However this problem was overcome by using Weinreb's method of amide formation employing trimethylaluminium to activate the amine.[72] The increased nucleophilicity of the nitrogen in the resultant highly reactive amino-aluminium species allows smooth addition into the ester carbonyl under relatively mild conditions giving the corresponding amide cleanly and in good yields. **Scheme 33.**

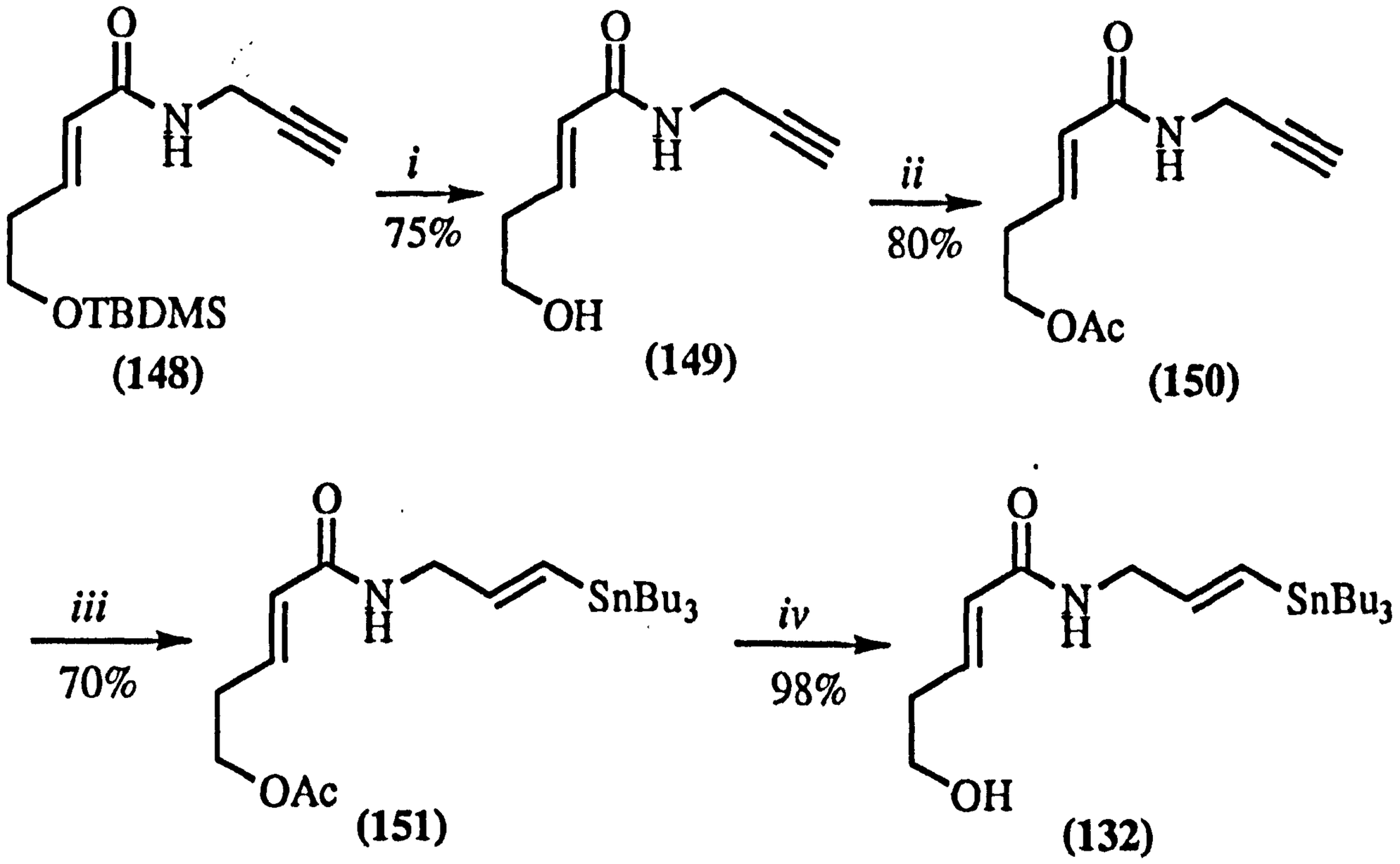


Reagents: Propargylamine, Me_3Al, CH_2Cl_2.

Scheme 33

Thus, propargylamine was treated with trimethylaluminium, at 0°C in dry CH_2Cl_2 under scrupulously dry conditions, to form the active amino-aluminium species. Addition of the ester **(147)** to the mixture at reflux gave the amide **(148)** cleanly, in 75% yield. With the amide **(148)** in hand we began to look at the hydrostannylation of the terminal triple bond. It was at this point that we realised the

problems we would later encounter when removing the silyl protecting group. Removal of a TBDMS group is normally achieved by treatment with either acid or a fluoride ion source, both of which would cause decomposition of the vinyl stannane.[73] It became apparent that the hydroxyl protecting group would have to be changed before we could proceed with the hydrostannation, and to this end we decided to replace the TBDMS group with an acetyl group, as this could be removed by treatment with a mild base such as potassium carbonate. Thus the TBDMS group of **(148)** was removed with *p*TSA in methanol and CH_2Cl_2 to give the alcohol **(149)** in 75% yield. The alcohol **(149)** was acetylated with acetyl chloride and pyridine in CH_2Cl_2 to give the acetoxyamide **(150)** in 80% yield. The amide **(150)** was then hydrostannylated using the high order cuprate **(139)**, in dry THF, to give the stannane **(151)** in 70% yield. The acetyl protection was removed by stirring with potassium carbonate in wet MeOH to give the alcohol **(132)** in 98% yield. **Scheme 34.**

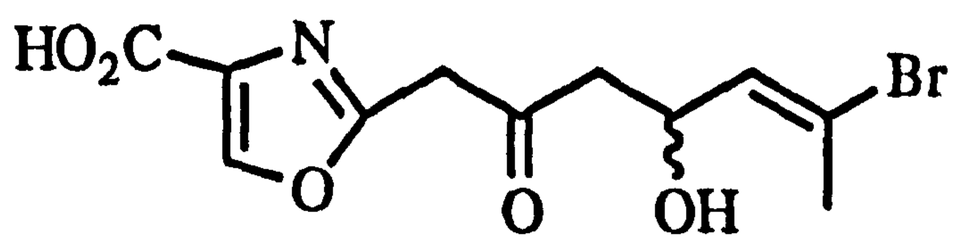


Reagents: *i*, *p*TSA, MeOH, CH_2Cl_2; *ii*, AcCl, py, CH_2Cl_2; *iii*, CuCN, *n*-BuLi, Bu_3SnH, THF; *iv*, K_2CO_3, wet MeOH.

Scheme 34

2.2.2 Synthesis of the Right-hand Fragment (133) of the Model System (130).

With the left-hand fragment **(132)** in hand our attention was drawn to what could be regarded as the more synthetically challenging fragment, **(133)**. **Figure 23.**



(133)

Figure 23

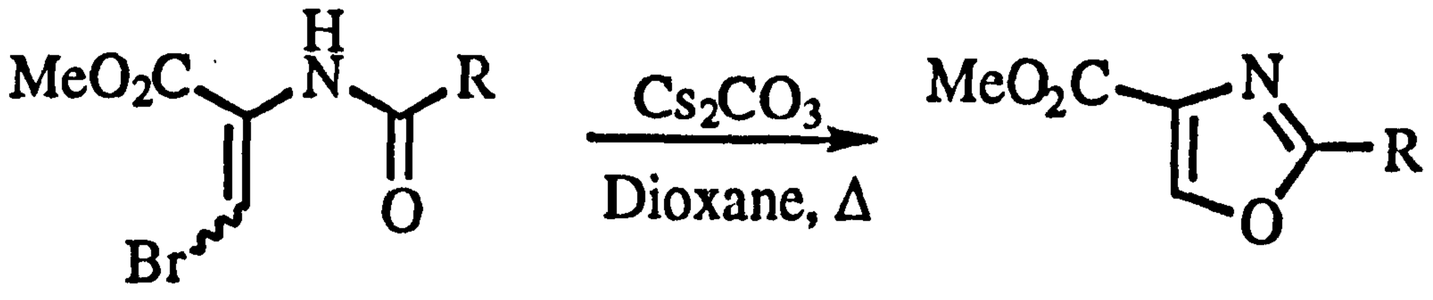
As already shown in the Introduction, the halide of choice would ideally have been the iodide, as this has been shown to react at a faster rate in Stille couplings.[74] However, vinyl iodides are inherently less stable than vinyl bromides and vinyl chlorides. From the synthetic point of view ideally we would choose to synthesise the vinyl chloride, as this would allow us to perform a greater variety of transformations in its presence due to its relative stability. But the vinyl chlorides are known to react sluggishly in Stille couplings, even in the relatively easier intermolecular and medium ring intramolecular cases. Therefore as a compromise between the two extremes it was decided to synthesise the vinyl bromide, which had been shown to be fairly reactive in the Stille reaction, and to be relatively stable under general synthetic conditions.

Looking at fragment **(133)** a number of important questions arose which had to be considered before embarking on a synthesis. Firstly there is the synthesis of the 2,4-disubstituted-1,3-oxazole. This is an interesting synthetic challenge due to the substitution pattern of the oxazole, leaving only a few synthetic alternatives open for

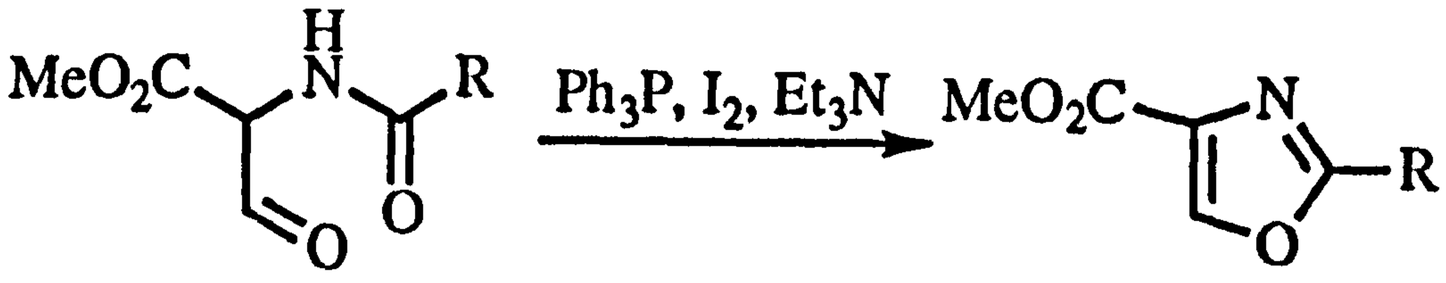
utilisation. In natural products containing oxazole rings the 2,4-disubstituted oxazoles are among the most prevalent. This is thought to be due to the precursor for the biosynthesis to the 2,4-disubstituted oxazole rings having been identified as the naturally occurring amino acid serine.[75] **Figure 5.** This makes routes starting from serine residues an obvious area for consideration. Another question that arises is whether to have the whole or part of the side chain (in the 2-substituent) in place before forming the oxazole ring or whether to form the ring first and construct the side chain afterwards. Finally there is the question of synthesising the side chain and its trisubstituted double bond.

Over the past 20 years there have been many reported solutions to the problem of synthesising 2,4-disubstituted oxazoles. These syntheses can be divided into two main approaches. Firstly there are the methods which cyclise a serine-based precursor to the corresponding oxazoline and then use one of a number of oxidants to oxidise to the oxazole. An example of this method is Pattenden's synthesis of the trisoxazole fragment of the ulapualides.[76] Secondly there are the methods which involve cyclisation to give the oxazole ring directly without involving the oxazoline intermediates. Notably in this later group is the work of Das, who used caesium carbonate to effect the cyclisation of an amido vinyl bromide in his synthesis of thrombaxane A_2 receptor antagonists.[77] The work of Wipf, who uses a mixture of triphenylphosphine, iodine, and triethylamine to effect the cyclisation of an amido aldehyde.[78] The work of Helquist, who forms 2-bromomethyloxazol-4-ethylcarboxylate using the Cornforth method,[79] using the bromide as a handle to elaborate the side chain in the 2-position using Reformatsky chemistry.[25] And finally the work of Meyers, who once again uses Cornforth's method of oxazole synthesis but with the addition of the side chain at the enolate stage before effecting the cyclisation to the oxazole.[21] **Figure 24.**

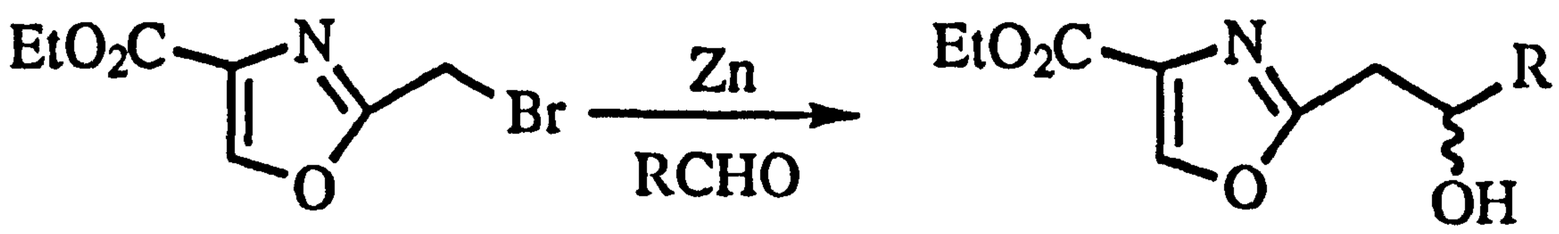
Das



Wipf



Helquist



Meyers

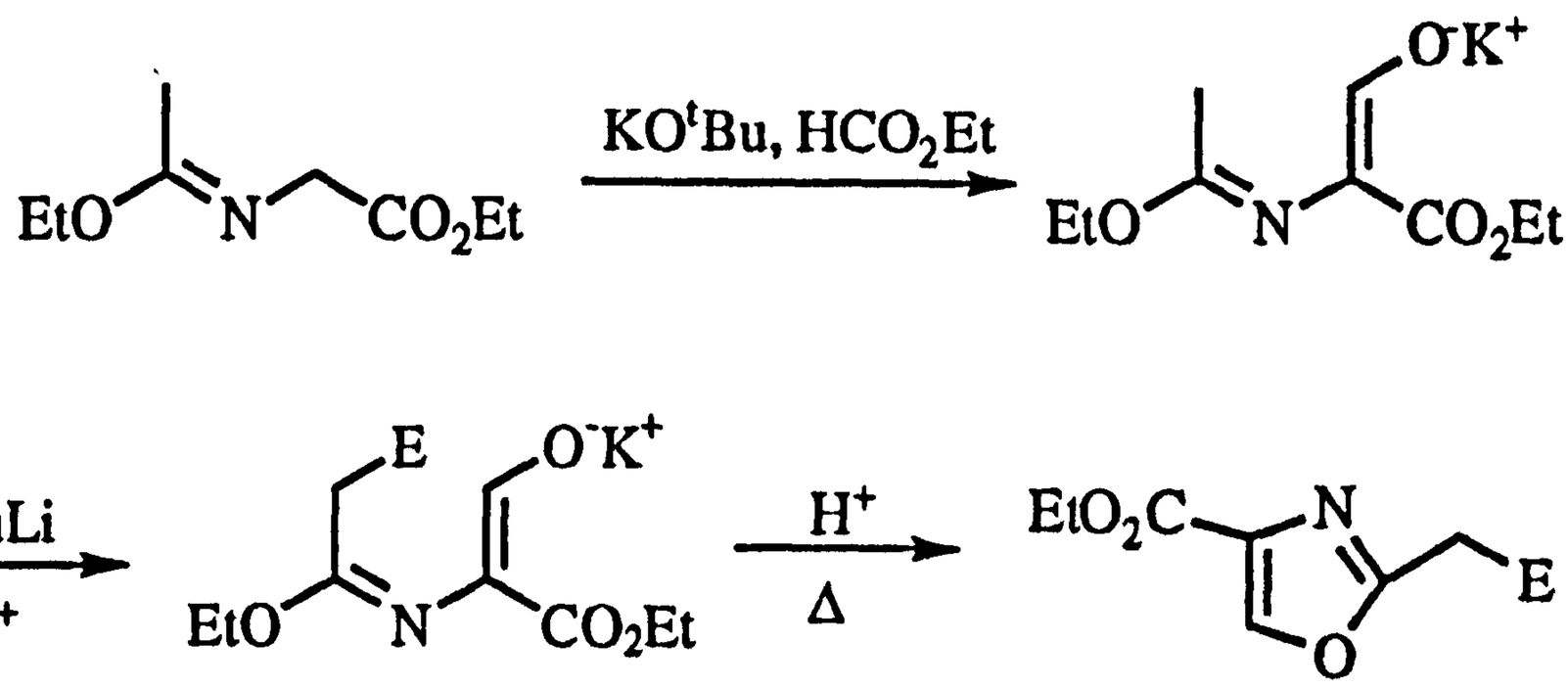


Figure 24

The method published by Das *et al* can be used in the presence of a wide variety of functionality, and so it was decided to attempt to use this methodology in our synthesis. Disconnection of fragment **(133)** between C-14 and C-15 led us back to fragment **(152)** which under the Das protocol would result from the amido vinyl bromide **(154)**. **Figure 25.** The remaining fragment **(153)** could come from the oxidation of the alcohol **(155)** which was synthesised by Corey *et al* in their synthesis of maytansine.[80] In our hands the synthesis of the vinyl bromide **(154)** proceeded smoothly until the final bromination step. **Scheme 35.**

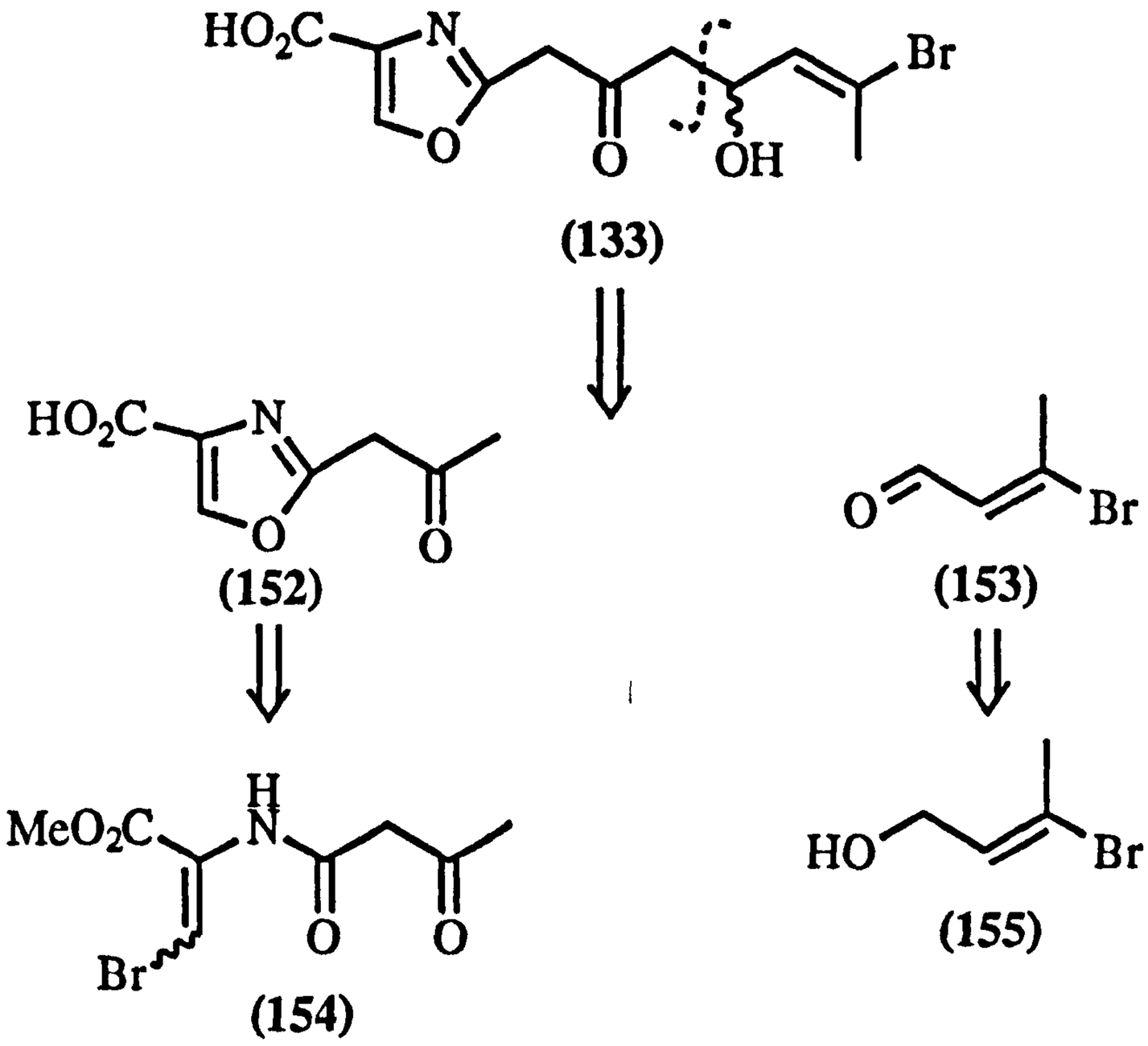
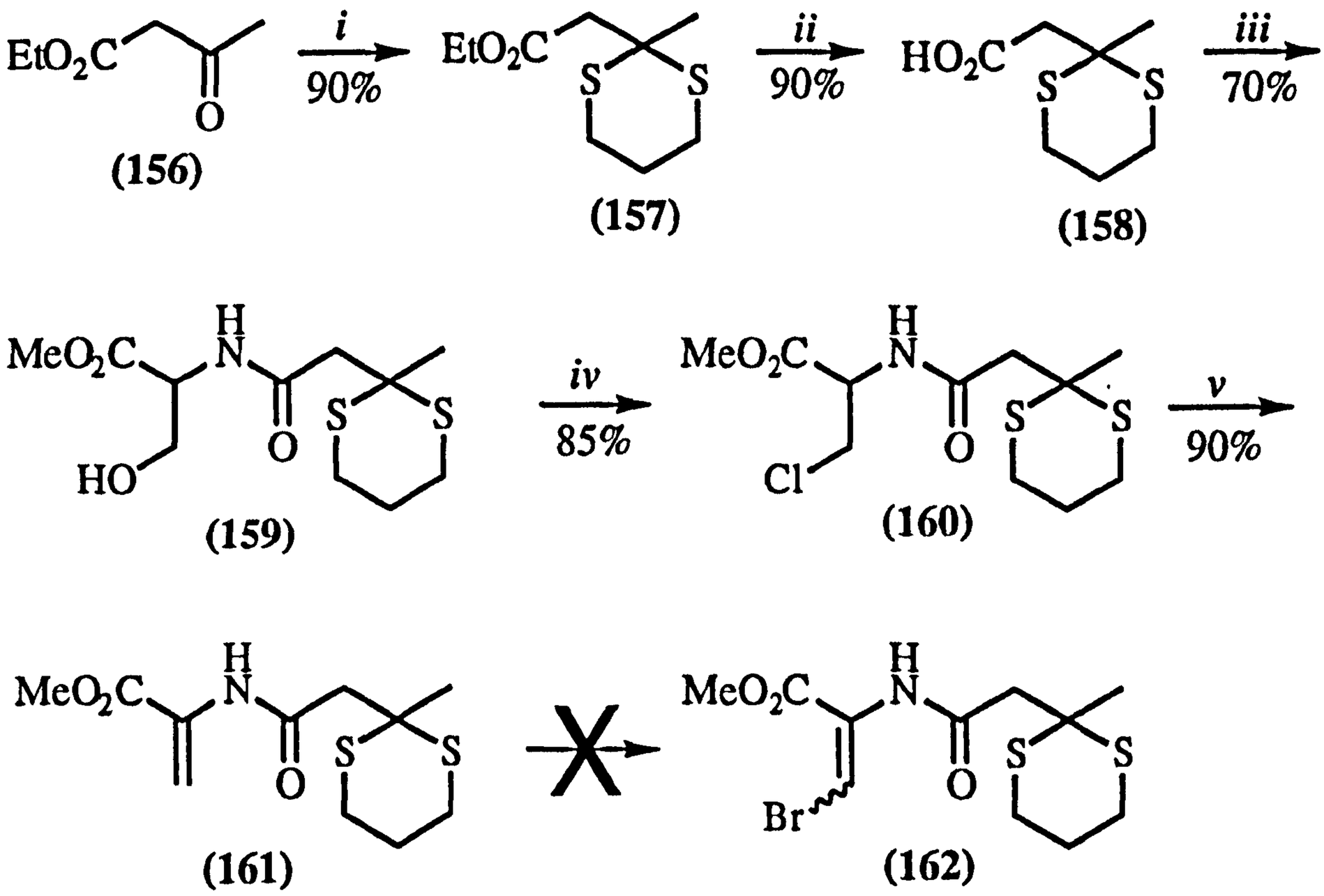


Figure 25

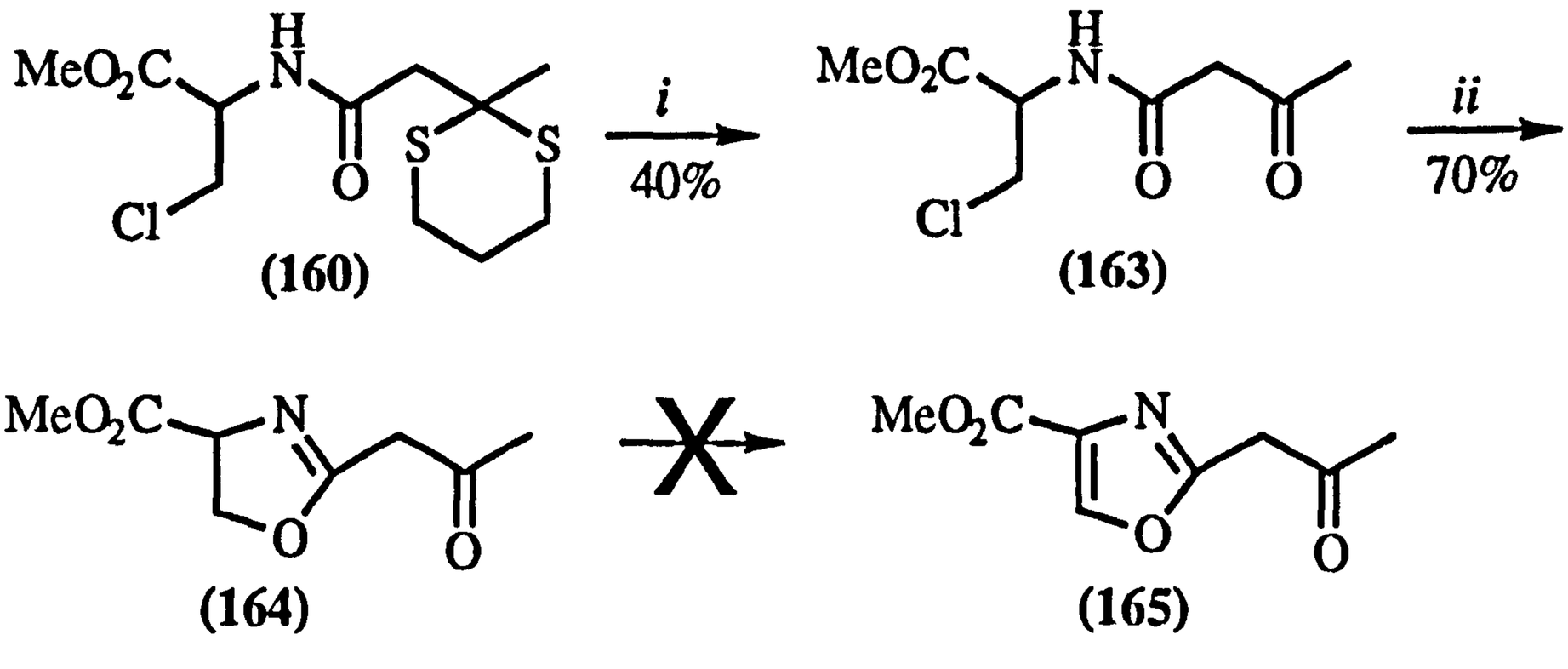
Thus, ethyl acetoacetate **(156)** was protected as its dithiolane acetal **(157)** using 1,3-propanedithiol and chlorotrimethylsilane in 90% yield.[81] The ester was then hydrolysed with lithium hydroxide to give the acid **(158)** in 90% yield. Coupling of the acid **(158)** with the serine methyl ester using DCC and DMAP next gave the hydroxyamide **(159)** in a 70% yield. The alcohol **(159)** was transformed into the chloroamide **(160)**, in 85% yield, using *N*-chlorosuccinimide and triphenylphosphine.[82] The alkene **(161)** was obtained by elimination of the chloroamide **(160)** using DBU in 90% yield. Although many reaction conditions were tried, including NBS, py.HBr/Br_2 and Br_2/Et_3N, bromination of the alkene **(161)** was never achieved; under all the conditions complete decomposition of the starting alkene resulted without any of the desired vinyl bromide **(162)** being isolated.



Reagents: *i*, 1,3-propanedithiol, TMS-Cl, CH_2Cl_2; *ii*, LiOH, THF, MeOH, H_2O; *iii*, Serine methyl ester, DCC,.DMAP, CH_2Cl_2; *iv*, NCS, PPh_3, CH_2Cl_2; *v*, DBU, CH_2Cl_2.

Scheme 35

Since we had the chloroamide **(160)** in hand, it was decided to remove the dithiane protection and effect a cyclisation to the oxazoline **(164)** using silver triflate,[83] and then to oxidise the resulting oxazoline **(164)** to the corresponding oxazole **(165)** using nickel peroxide.[84] **Scheme 36.** Thus, the chloroamide **(160)** was treated with mercuric perchlorate in THF to first give the keto-amide **(163)** in 40% yield.[85] The amide was then cyclised to the oxazoline **(164)** using silver triflate, in benzene, in 70% yield. Attempts to oxidise the oxazoline to the oxazole **(165)** using nickel peroxide only led to complete loss of starting material. This may have been due to the carbonyl group of the side chain leading to additional coordination to the already oxazoline bound nickel peroxide. The coordination of nickel peroxide to oxazolines and the resulting oxazole products has long been a problem in these oxidations, often leading to poor and variable yields.



Reagents: *i*, $Hg(ClO_4)_2$, THF; *ii*, AgOTf, Benzene.

Scheme 36

The lack of oxidants for the oxidation of oxazolines to oxazoles at the time forced us to consider alternative routes to our system. To this end we turned our attention to the work of Helquist.[25] If we look at fragment **(133)** with the aim of utilising Helquist's methodology we require a disconnection of fragment **(133)** between C-16 and C-17.

Figure 25.

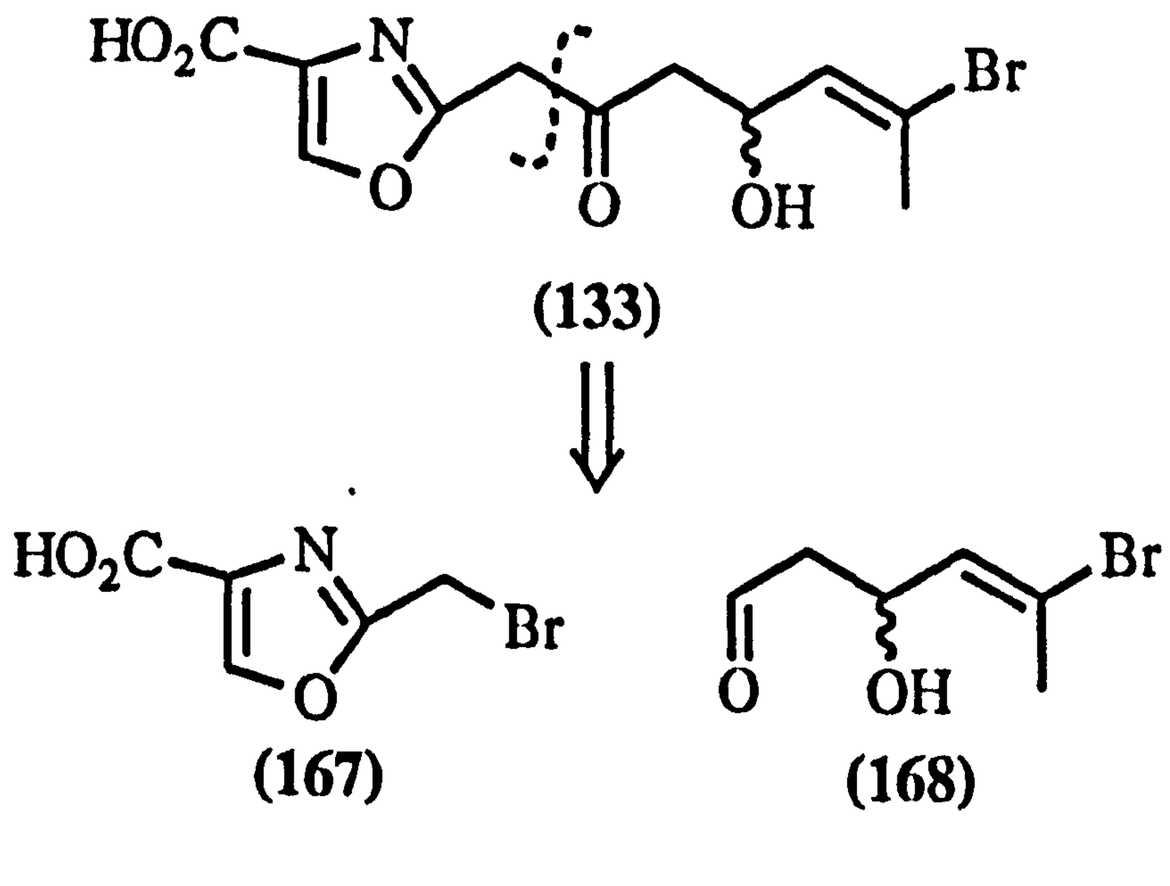
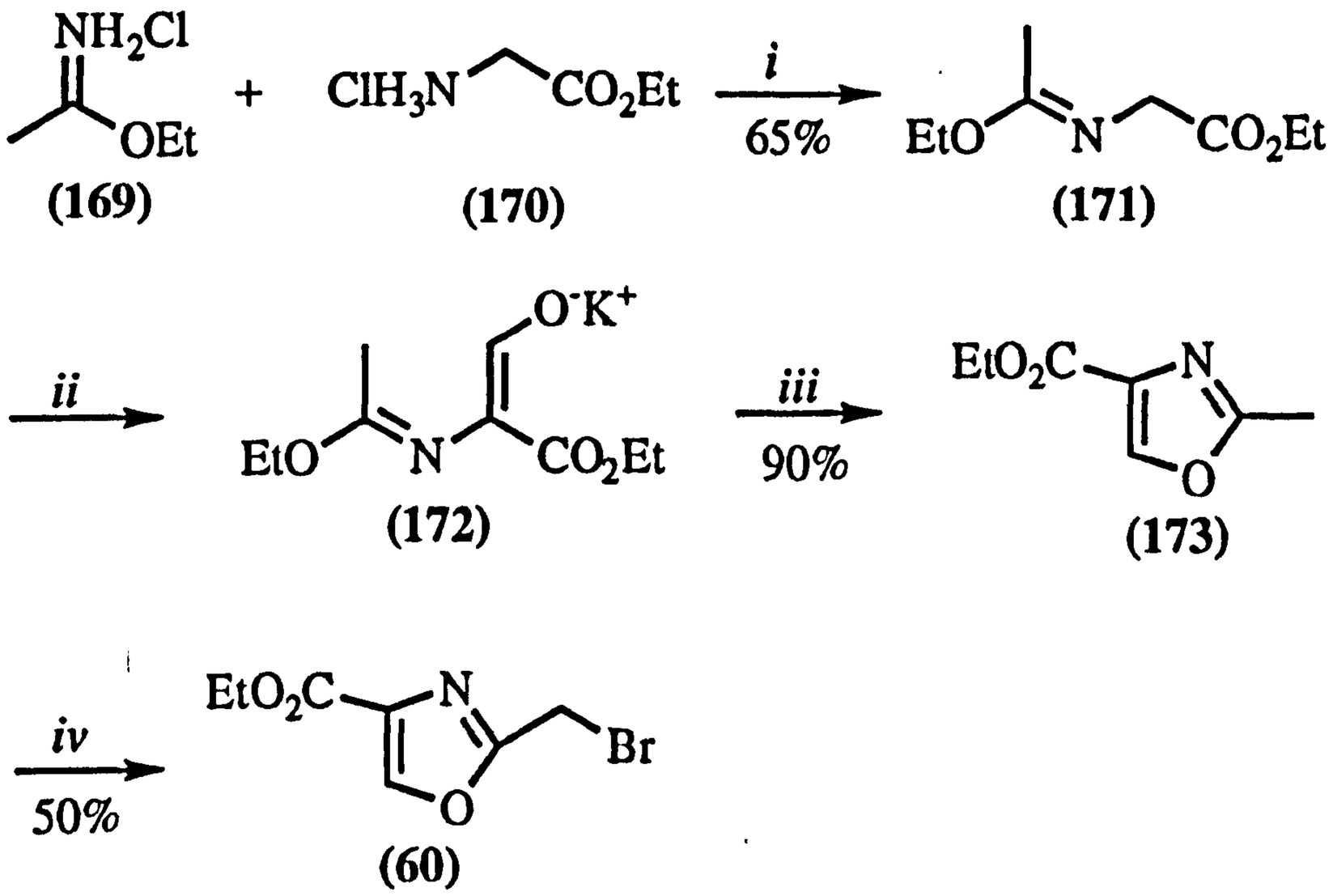


Figure 25

Fragment **(167)**, the 2-bromomethyloxazole, was synthesised from the 2-methyloxazole **(173)** obtained using the methodology developed by Cornforth.[79] **Scheme 37.**



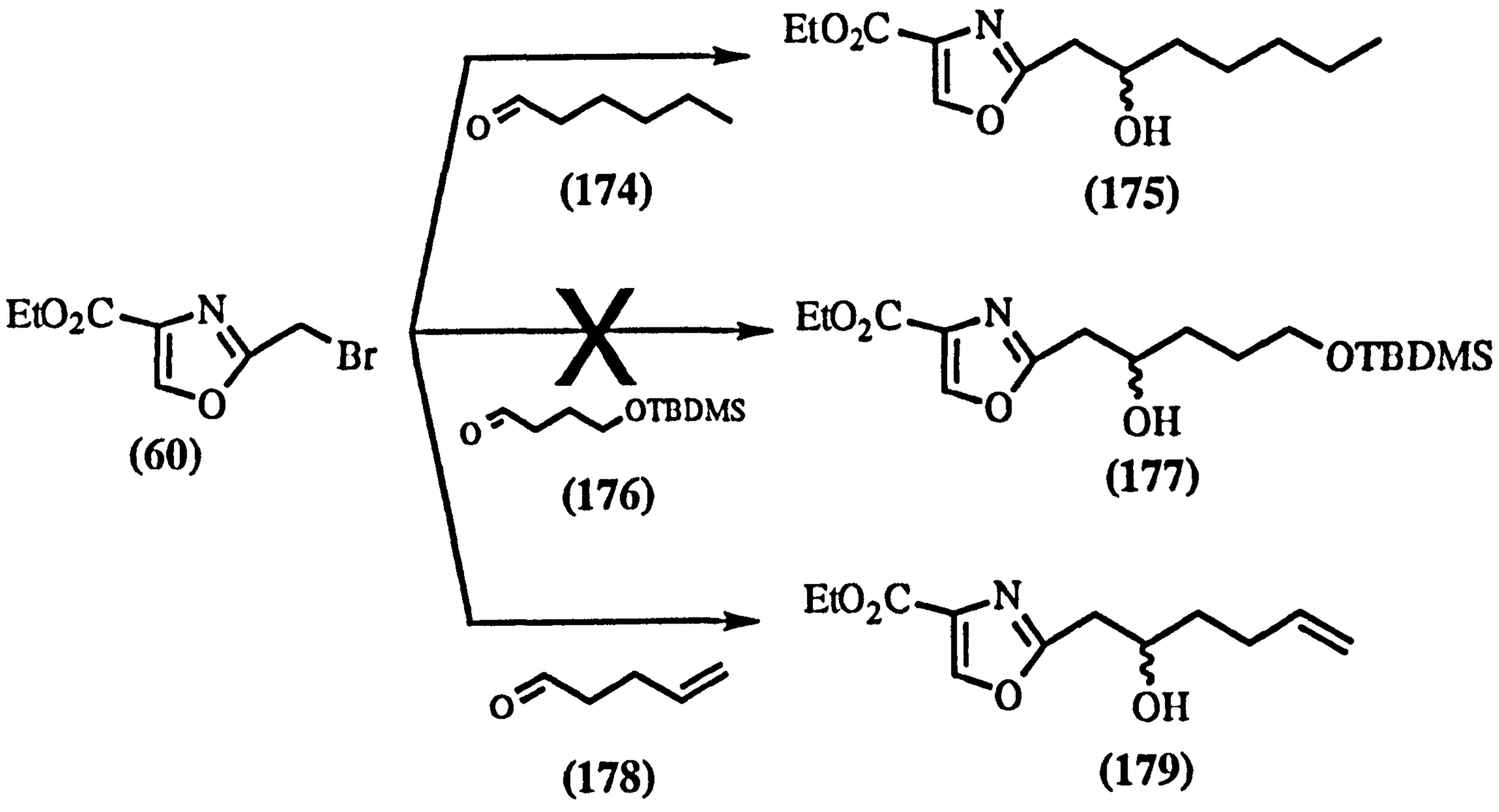
Reagents: *i*, K_2CO_3, Et_2O, H_2O; *ii*, KO^{t}Bu, ethyl formate, THF; *iii*, Hot glacial acetic acid; *iv*, NBS. AIBN, CCl_4.

Scheme 37

Thus, glycine ethyl ester hydrochloride **(170)** was condensed with ethyl acetimidate hydrochloride **(169)** to give the imino ether **(171)** in 65% yield. The imino ether **(171)** was then treated with potassium *t*-butoxide and ethyl formate to give the potassium enolate **(172)**, which was cyclised to the oxazole **(173)** with hot glacial acetic acid in 90% yield without isolation (2 steps). Bromination of the oxazole **(173)** with *N*-bromosuccinimide and AIBN in carbon tetrachloride provided the bromo oxazole **(60)** in 50% yield.[86]

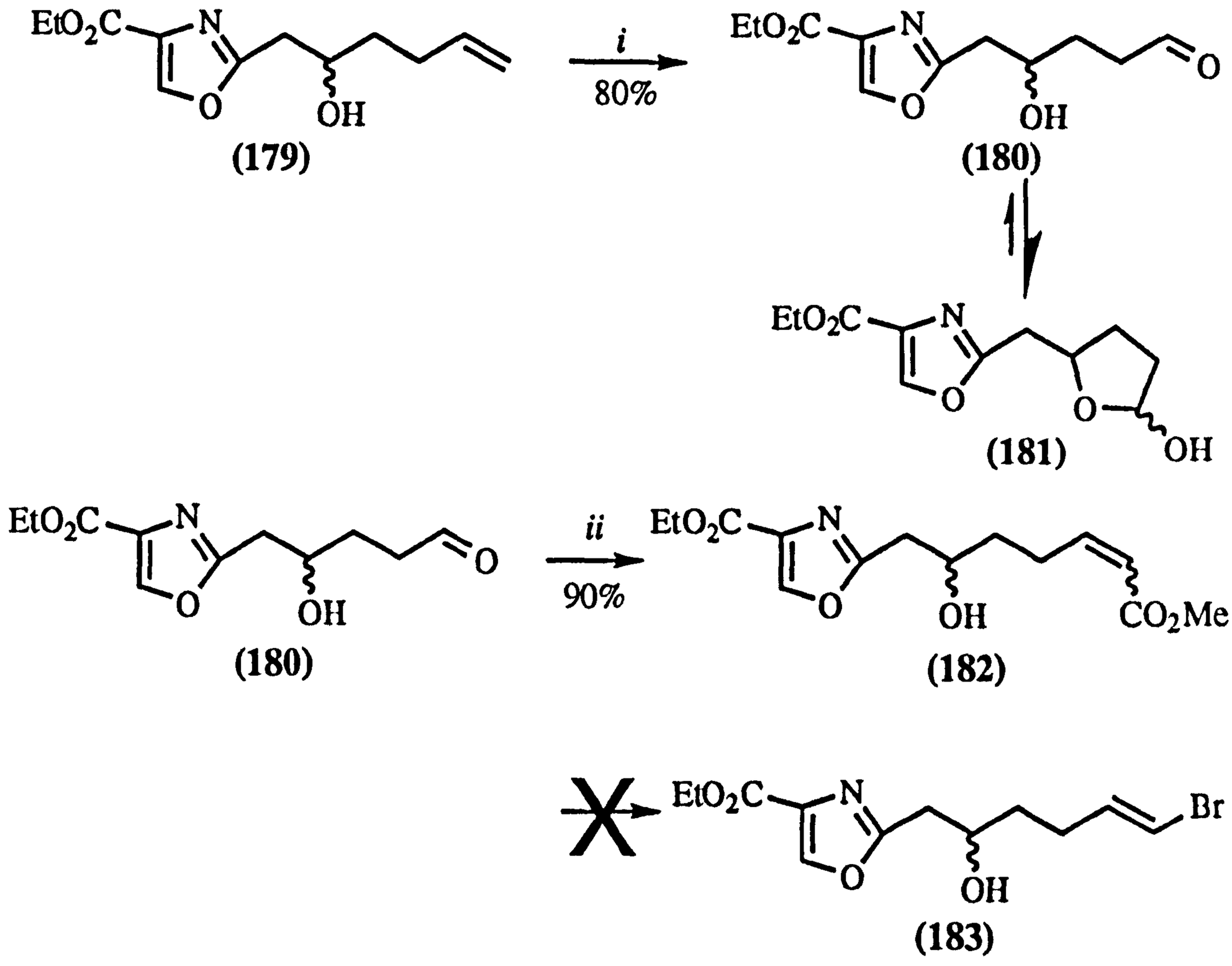
In our initial studies we repeated the work of Helquist starting with the straight-chain aldehyde hexanal **(174)** using a variety of differently activated zinc powders to ascertain which would give us the best results with our bromo oxazole **(60)**. We found that the reaction only gave the desired product **(175)** when sulphuric acid activated zinc powder was used, albeit in an optimised 35% yield. Having gained some insight into the reaction using hexanal, we then moved to a more synthetically useful aldehyde **(176)**, containing a silyl ether to give us a handle into our desired target

compound. This aldehyde had been reported by Helquist to participate in the Reformatsky reaction. However in our hands this aldehyde **(176)** would not react to give the oxazole **(177)** under all conditions tried, and so we moved our attention to the alternative aldehyde, **(178). Scheme 38.**



Scheme 38

In the case of 4-pentenal **(178)**, we once again obtained an optimised 35% yield of the desired oxazole **(179)** when using sulphuric acid activated zinc powder. The terminal double bond in **(179)** was cleaved to the aldehyde **(180)** using osmium tetroxide and sodium periodate.[87] **Scheme 39.** The aldehyde **(180)** was shown by nmr analysis to exist as a 9:1 mixture of the aldehyde and its lactol tautomer **(181).** It was hoped to transform the aldehyde **(180)** to the corresponding *E*-vinyl bromide **(183)** using the Takai proceedure.[61] This method, analogous to a Wittig olefination, uses an intermediate formed from chromium(II)bromide and bromoform, instead of a phosphonium ylide. Although the aldehyde **(180)** reacted with methyl (triphenylphosphoranylidene) acetate in a Wittig reaction to give the α,β-unsaturated ester **(182)** in 90% yield, under the Takai conditions the desired vinyl bromide **(183)** was never obtained.

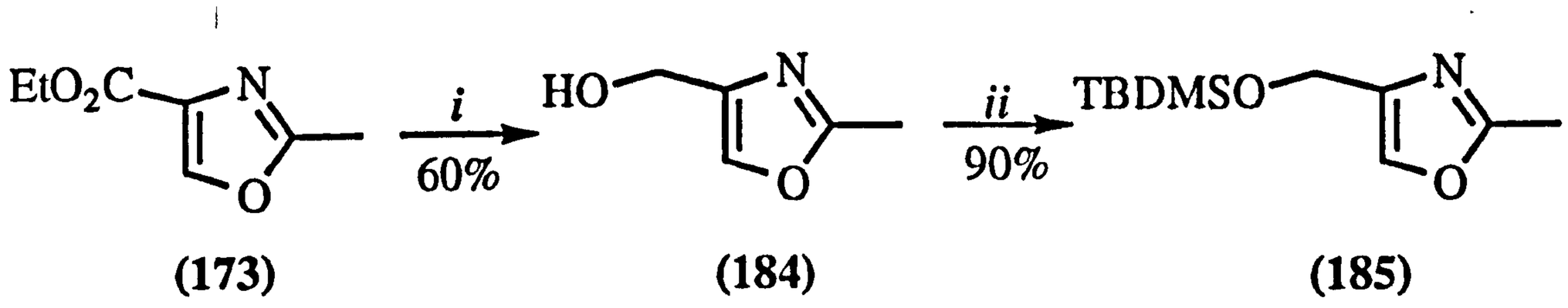


Reagents: *i*, OsO_4, $NaIO_4$, H_2O, MeOH; *ii*, $Ph_3P{=}CHCO_2Me$, CH_2Cl_2.

Scheme 39

Having already synthesised the 2-methyloxazole **(173)** for use in above synthetic route, it was decided to look at the direct deprotonation of the 2-methyl group, and to attempt the addition of a suitable electrophile. It has been well documented that deprotonation of oxazole **(173)** occurs at the 5-position of the ring rather than at the methyl group.[89] This can be attributed to the carboxylate group in the 4-position stabilising the 5-lithium intermediate *via* intramolecular chelation. To overcome this problem three main approaches have been employed by the various research groups working in this area. Firstly we could increase the acidity of the methyl protons of the 2-methyl group. This approach has been used by Fujita *et al*, who used a phenylsulphone group on the methyl to induce deprotonation of the methylene protons exclusively, which the authors removed later in the synthesis with aluminium

amalgam.[28] The second approach is to block the 5-position on the ring with a suitable protecting group which can be removed easily at a later stage. To this end Ganem *et al* used a trimethylsilyl group to block the 5-position, and later removed this with caesium fluoride.[29] The other alternative is to reduce the carboxylate group to the corresponding alcohol, and to protect this with a bulky protecting group such as the TBDMS group. **Scheme 40.**



(173) **(184)** **(185)**

Reagents: *i*, DIBAL-H, CH_2Cl_2; *ii*, TBDMS-Cl, imidazole, DMF.

Scheme 40

Having attempted the first two approaches without great success it was decided to reduce the carboxylate group to the corresponding alcohol **(184)**. Thus, the oxazole **(173)** was first reduced to the corresponding alcohol **(184)** using DIBAL-H, in CH_2Cl_2 at 0°C, in 60% yield. The alcohol **(184)** was then protected with *t*-butyldimethysilyl chloride and imidazole to give the silyl ether **(185)** in 90% yield. Deprotonation of oxazole **(185)** with *n*-butyllithium at -78°C in dry THF and stirring for 15 min at -78°C before addition of deuterium oxide, and then allowing the solution to warm to room temperature, gave 90% deuterium incorporation in the 2-methyl group, and 10% deuterium incorporation in the 5-position of the ring (by ^1H nmr analysis). The degree of incorporation of deuterium in the 5-position increased with the time at which the anion was left at -78°C before adding the deuterium oxide, suggesting deprotonation must first occur at the kinetically favoured 2-methyl position, and then with time forms the more thermodynamically stable anion at the 5-position. The thermodynamic anion is further stabilised by the so called β-effect, a direct result of

chelation of the lithium atom by the oxygen atom of the ether. **Figure 26.**

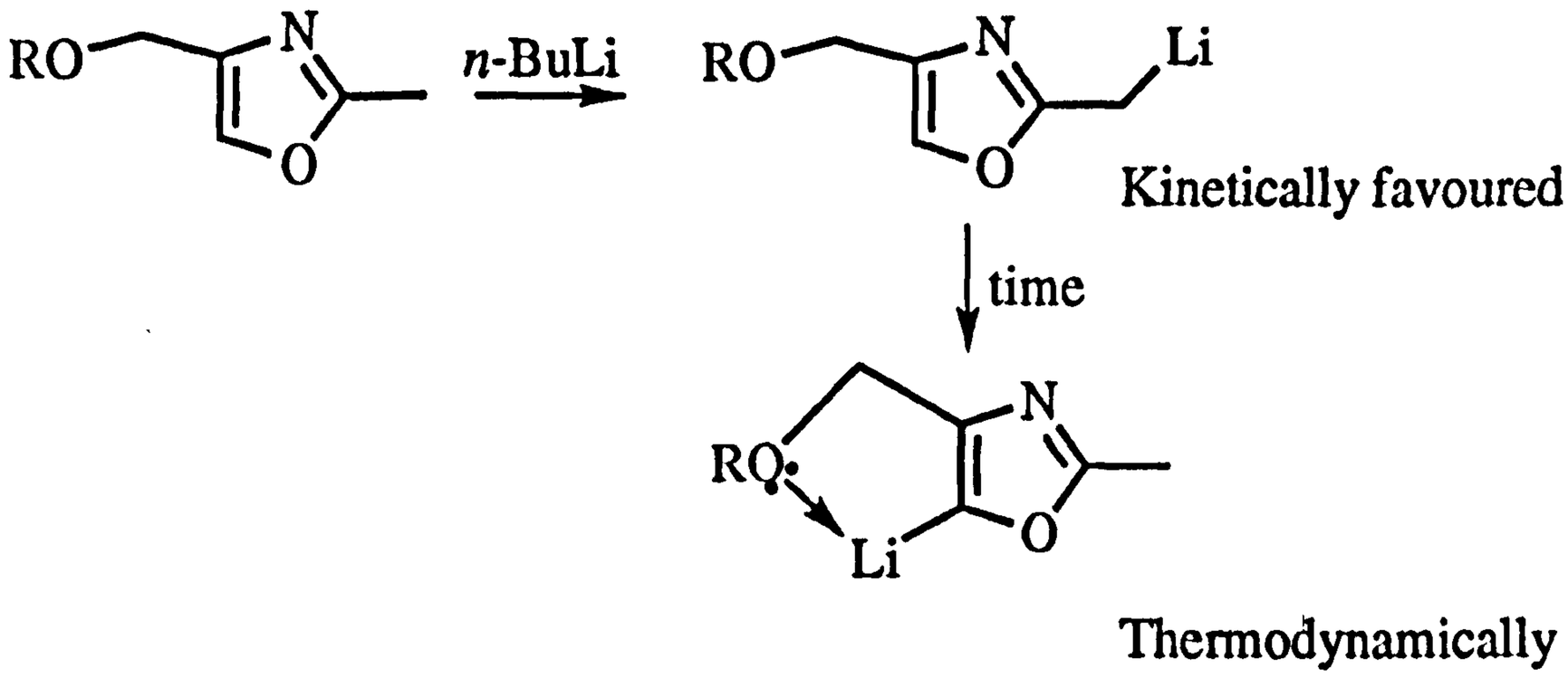


Figure 26

Having shown deprotonation of the 2-methyl group of the oxazole (**185**) could be achieved, we embarked on the synthesis of a suitable fragment to act as an electrophile to yield the desired chain in the 2-position. Looking back at fragment (**133**) we ideally required a fragment which would give us the ketone directly without the need for further manipulation. **Figure 27.**

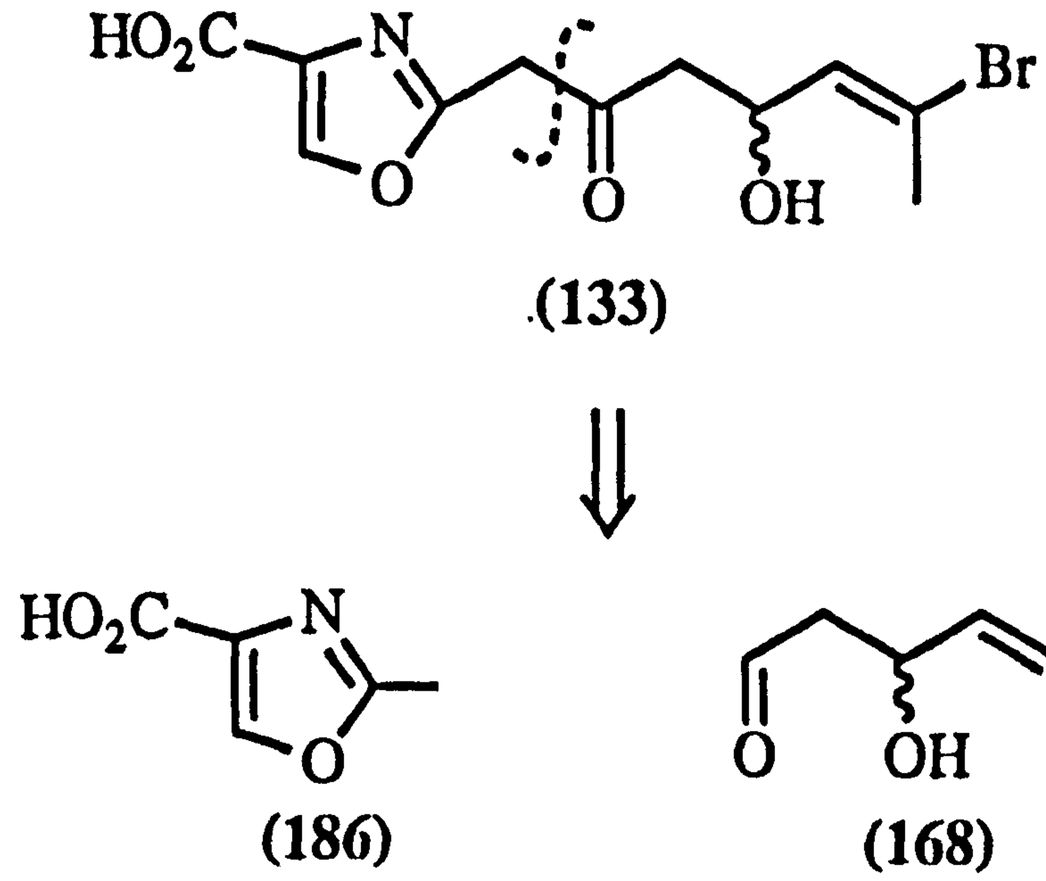
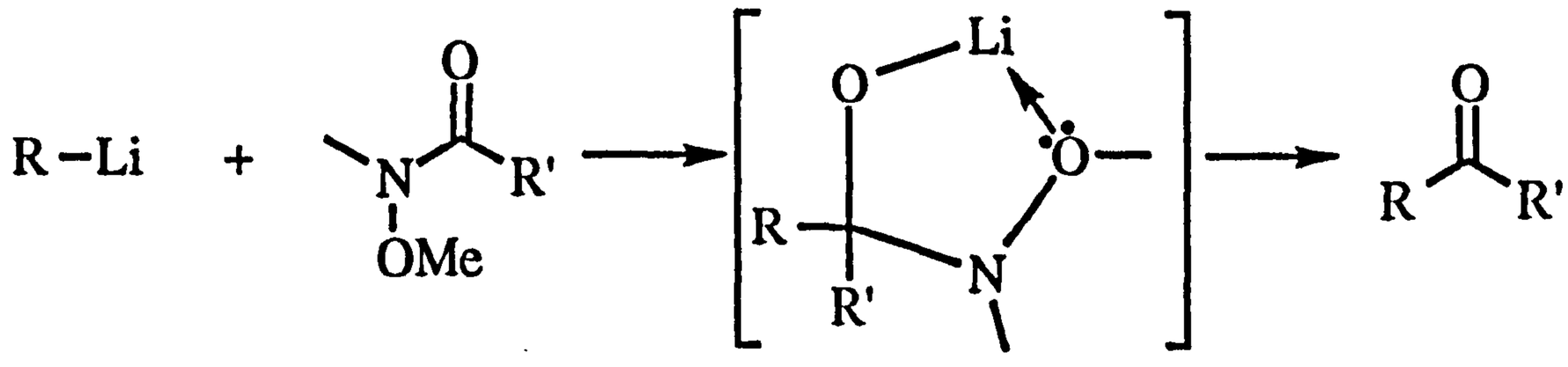


Figure 27

One of the most useful synthons in the direct production of ketones is the Weinreb amide.[89] Weinreb found that by treating an *N*-methoxy-*N*-methylamide with

nucleophilic species, and in particular lithium species and Grignard reagents, the corresponding ketone was obtained directly. The *N*-methoxy-*N*-methylamide possesses this useful synthetic ability due to the chelation of the oxygen atom of the N-methoxy group to the lithium atom of the adduct forming a stable 5-membered intermediate **(187)**. This intermediate then breaks down on addition of a proton source, such as ammonium chloride or water, to give the desired ketone and *N,O*-dimethylhydroxylamine. **Figure 28.**

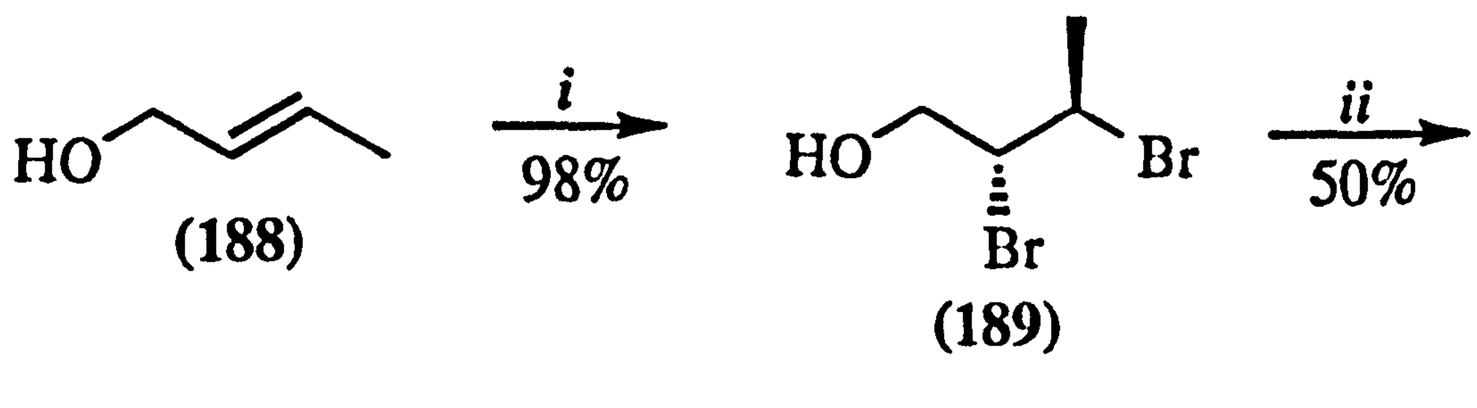


(187)

Figure 28

The formation of the stable intermediate only occurs when the metal ions used are lithium or magnesium, as their small atomic radii, 1.52 Å and 1.6 Å respectively, enables them to form the stable 5-membered ring. Larger alkali metals ions such as sodium and potassium, with atomic radii of 1.85 Å and 2.31 Å respectively, are too large to form the stable 5-membered ring.

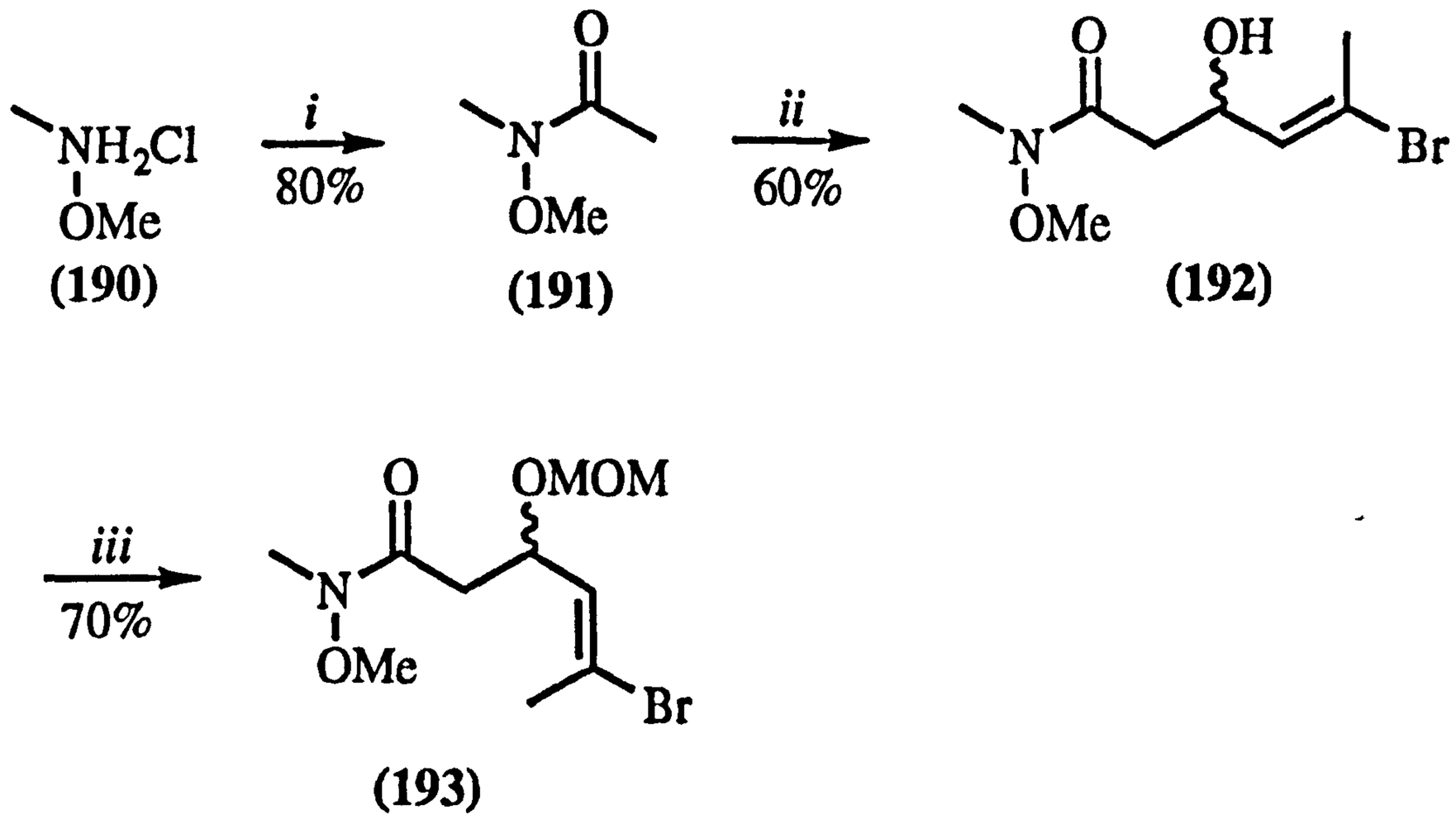
The synthesis of the vinyl bromide aldehyde **(153)** followed Corey's method as mentioned earlier.[80] **Scheme 41.** Thus, *E*-crotyl alcohol **(188)** was first treated with bromine in carbon tetrachloride at -20°C to give the *erythro* dibromide **(189)** in 98% yield. The dibromide **(189)** was then treated at -78°C with 2 equivalents of LDA to give the alcohol **(155)** in 50% yield. The alcohol **(155)** was finally oxidised to the aldehyde **(153)** using activated manganese dioxide in CH_2Cl_2 in 70% yield.



Reagents: *i*, Br_2, CCl_4; *ii*, LDA, THF; *iii*, MnO_2, CH_2Cl_2.

Scheme 41

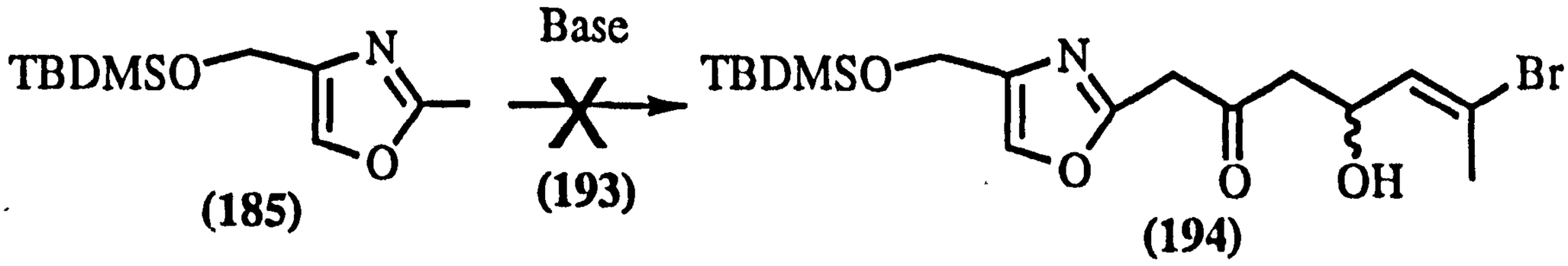
Our next task was to couple the aldehyde **(153)** to the *N*-methoxy-*N*-methylacetamide **(191)**, and to then protect the resultant secondary hydroxyl group. **Scheme 42.**



Reagents: *i*, AcCl, py, CH_2Cl_2; *ii*, KHMDS, **(153)**, THF; *iii*, MOM-Cl, Hünig's base, CH_2Cl_2.

Scheme 42

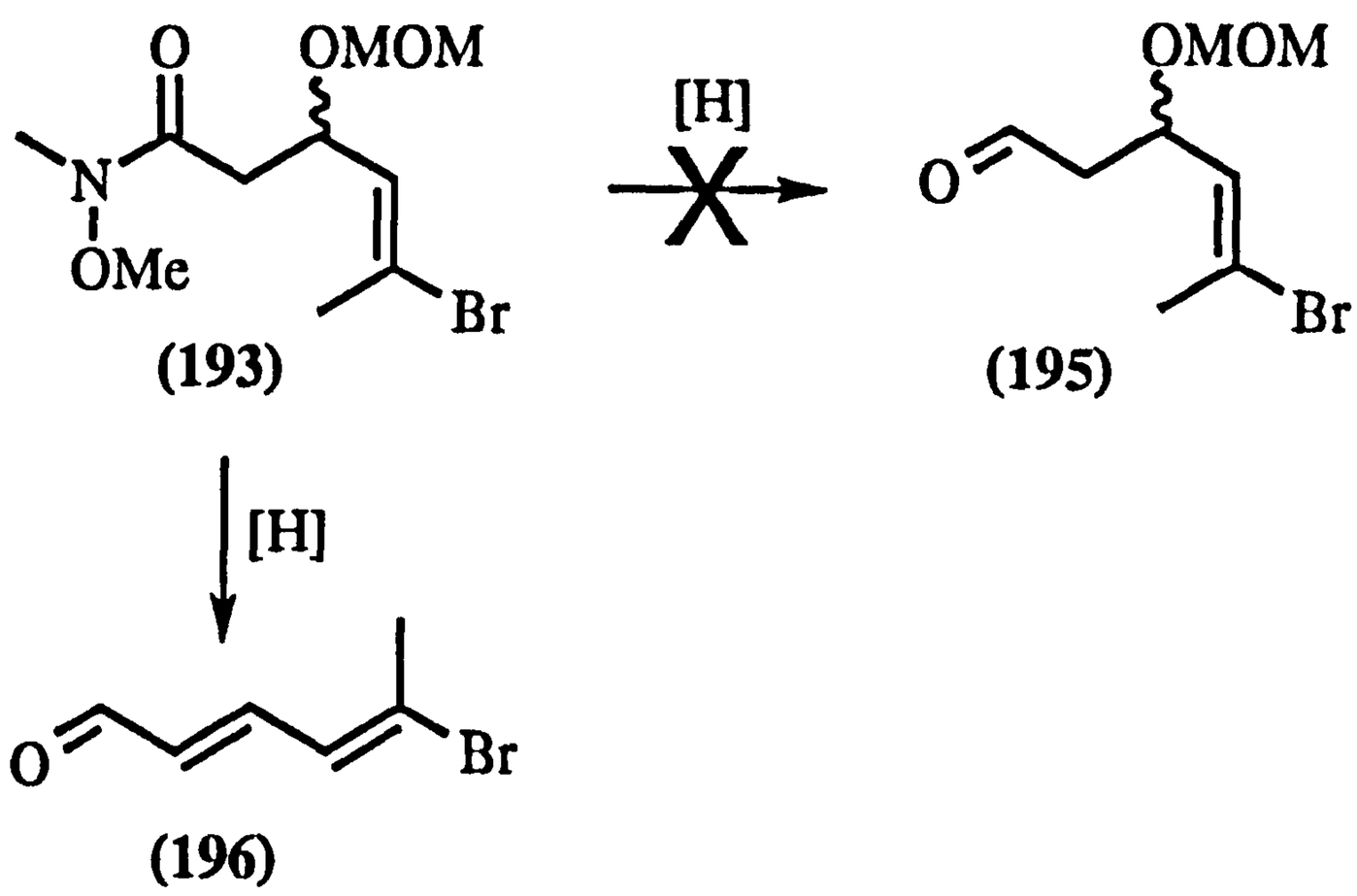
Thus, *N,O*-dimethylhydroxylamine hydrochloride was first acetylated using acetyl chloride and pyridine in CH_2Cl_2, at 0°C, to give *N*-methoxy-*N*-methylacetamide **(191)** in 80% yield. The next step was to deprotonate the acetamide **(191)**. Due to the inherent stability of the intermediates formed by Weinreb amides and lithium ions we found that attempts to deprotonate with lithium bases such as *n*-BuLi and LDA gave no products on addition of electrophiles. To overcome this problem we found it necessary to use a base containing a larger metal ion, *i.e.* potassium, to achieve deprotonation and smooth coupling. Thus, the amide **(191)** was treated with potassium hexamethyldisilazide at -78°C in THF, and addition of the aldehyde **(153)** gave the hydroxyamide **(192)** in 60% yield. The secondary hydroxyl group in **(192)** was protected as the methoxymethyl ether **(193)**, using MOM-Cl and Hünigs base at reflux in dry CH_2Cl_2, in 70% yield. Attempts to add the anion of the oxazole **(185)** into the Weinreb amide **(193)** to give the corresponding ketone **(194)**, only gave starting materials. **Scheme 43**. Numerous bases were used to form the oxazole anion including *n*-BuLi, *t*-BuLi, LDA, LiHMDS, KHMDS, and NaHMDS, at a variety of temperatures, and in a variety of solvents, all of which failed to yield the desired product. The lack of reactivity of the anion of oxazole **(185)** towards Weinreb amides was found to be a problem even with simple Weinreb amides such as the acetamide **(191)**.



(185) (193) (194)

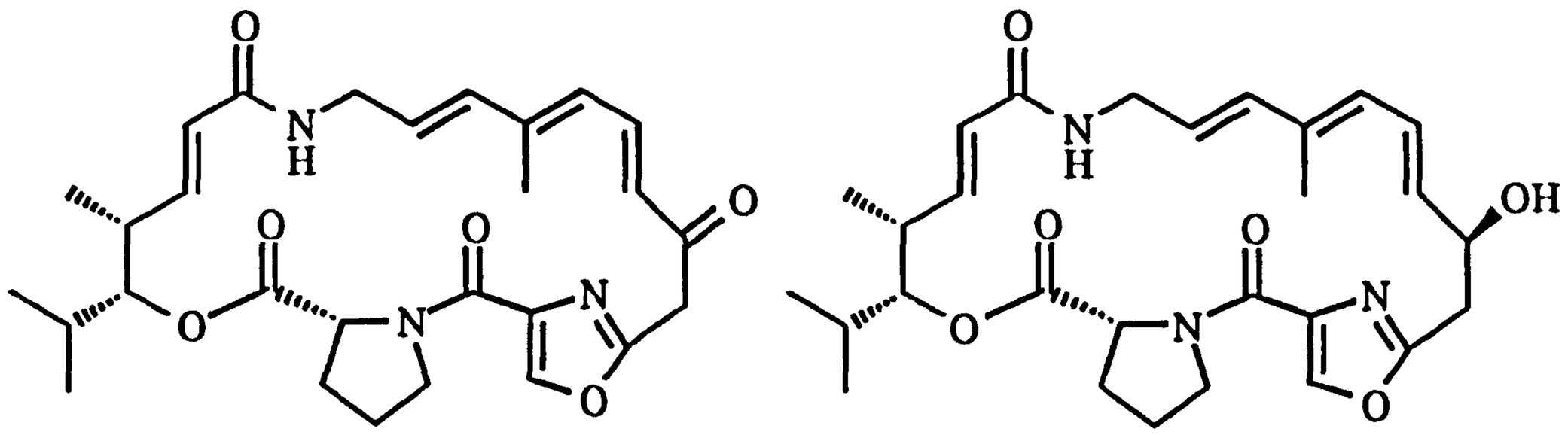
Scheme 43

However earlier studies had shown that the anion of the oxazole **(185)** would react with aldehydes such as acetaldehyde and isobutyraldehyde to give the corresponding secondary alcohols. It was therefore decided to utilise the other useful property of the Weinreb amides, *i.e.* their ease of reduction to the corresponding aldehyde.[90] Treatment of Weinreb amides with excess DIBAL-H or $LiAlH_4$ had been reported, in most cases, to give the corresponding aldehydes directly in good yields. However in the case of amide **(193)**, only the fully conjugated aldehyde **(196)** was isolated, a result of the simultaneous elimination of the protected hydroxyl group, without isolation of any of the desired aldehyde **(195)**. **Scheme 44.**



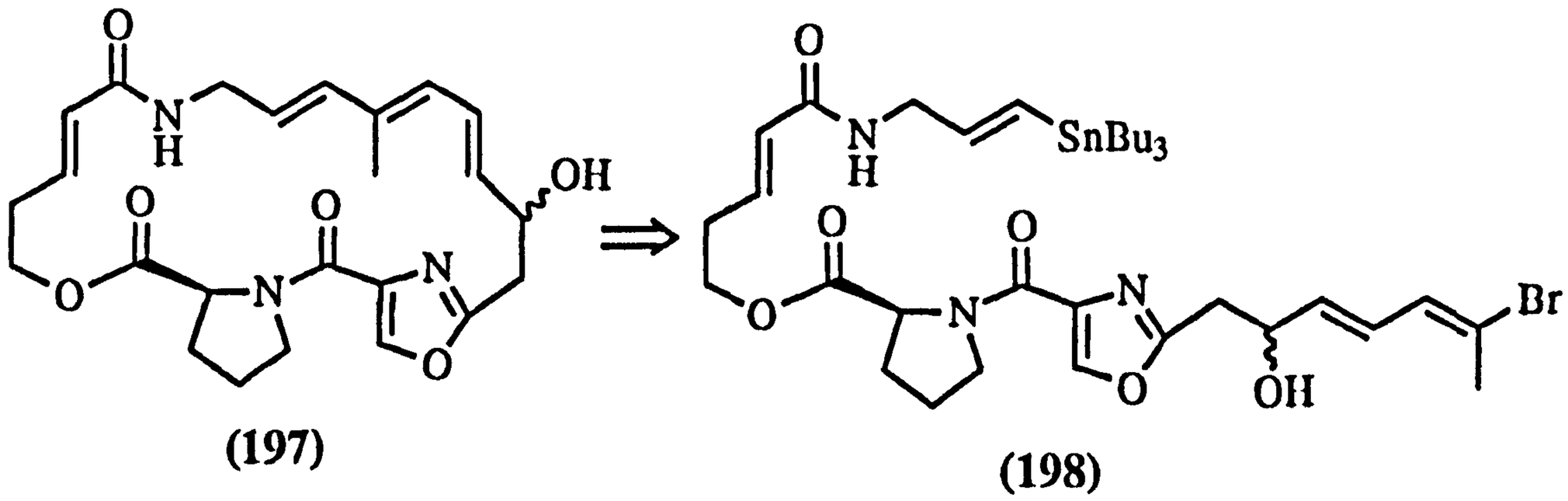
Scheme 44

Rather than seeking an alternative route to obtain the intended aldehyde **(195)** we noted that certain members of the virginiamycin family, *e.g.* **(6)** and **(7)**, contained conjugated triene systems corresponding to the aldehyde **(196)**, instead of the aldehyde **(195)** in the case of **(5)**. **Figure 29.** Combining the trienol system of **(7)** with our proposed model system **(130)** revealed a revised target macrocycle **(197)** to act as our model system. **Figure 30.**



(6A) (7A)

Figure 29



(197) (198)

Figure 30

Disconnection of the cyclisation precursor **(198)** led us to the left-hand fragment **(132)** and *L*-proline **(134)** as before, together with the new right-hand fragment **(199)**. **Figure 31.**

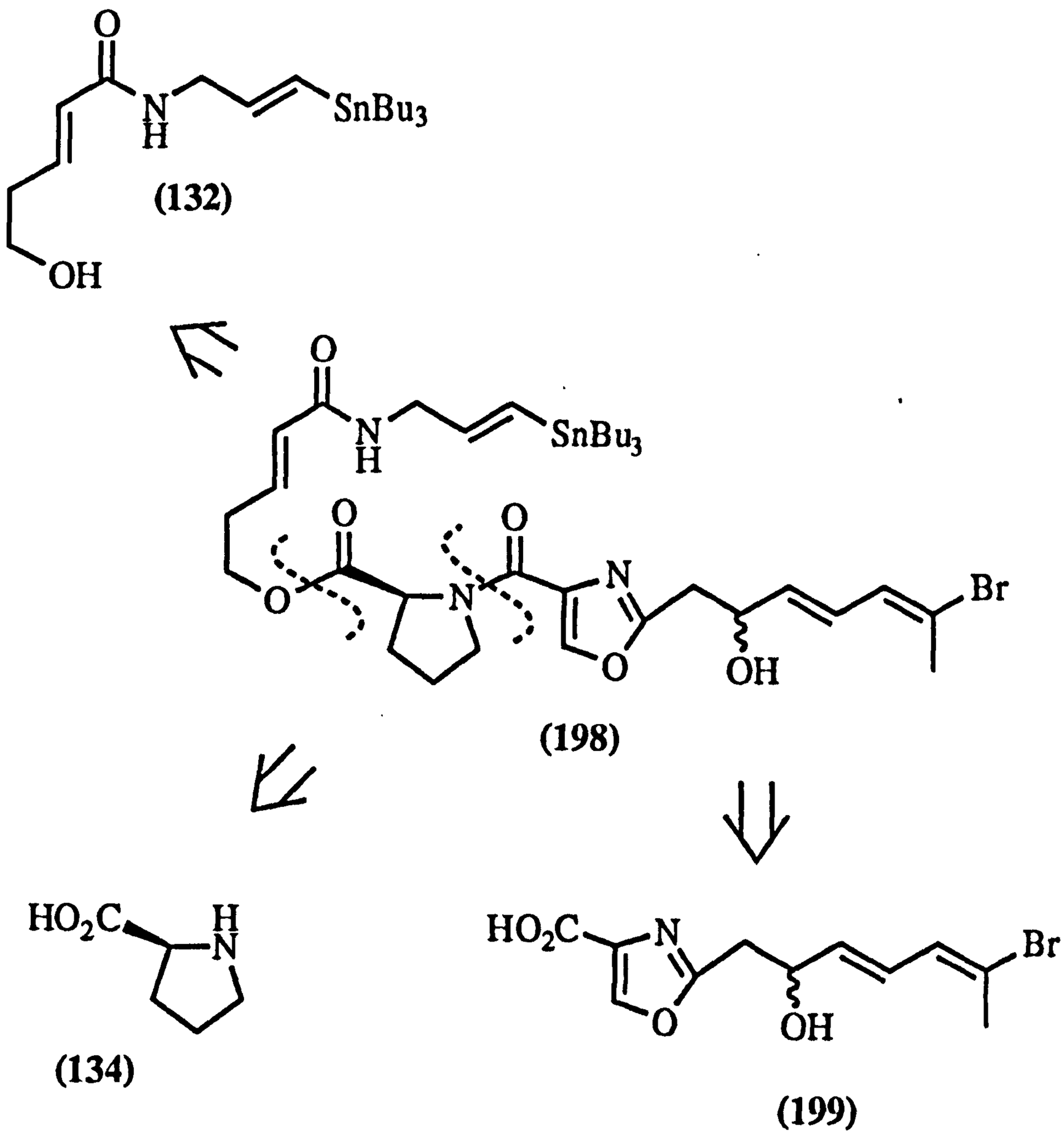


Figure B31

Disconnection of fragment **(199)** between C-16 and C-17, as with fragment **(133)**, led us to the 2-methyloxazole **(186)** and the conjugated aldehyde **(196)**, previously obtained in the reduction of the Weinreb amide **(193)**. **Figure 32.**

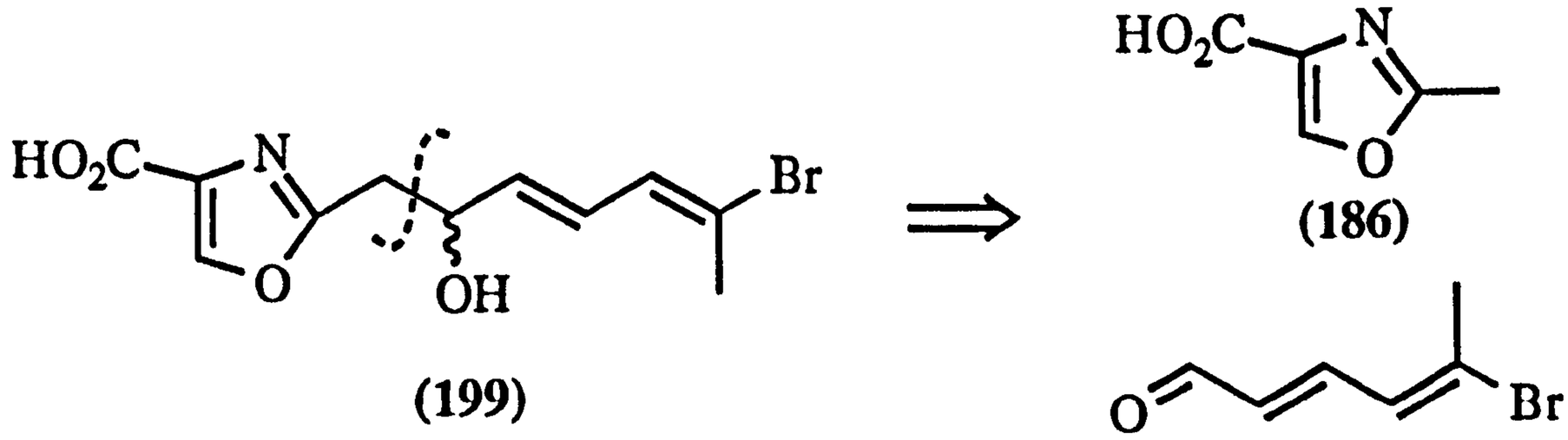
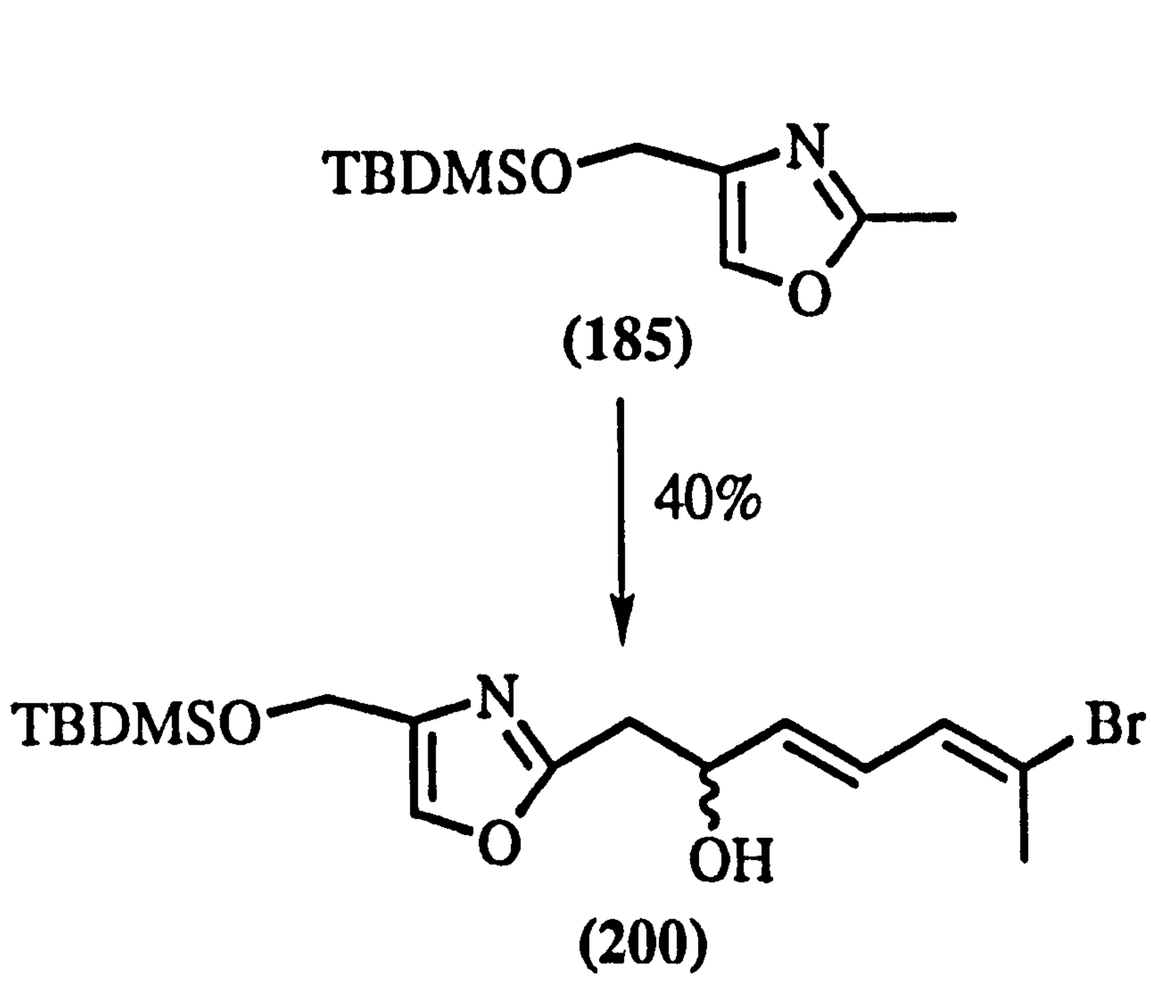


Figure 32

Following the success obtained in the depronation studies of the oxazole **(185)** it was decided to employ this methodology in the synthesis of fragment **(199)**. Thus, the oxazole **(185)** was deprotonated using *n*-BuLi, in THF, at -78°C. After addition of the aldehyde **(196)** the hydroxyoxazole **(200)** was obtained in 40% yield. **Scheme 45.**



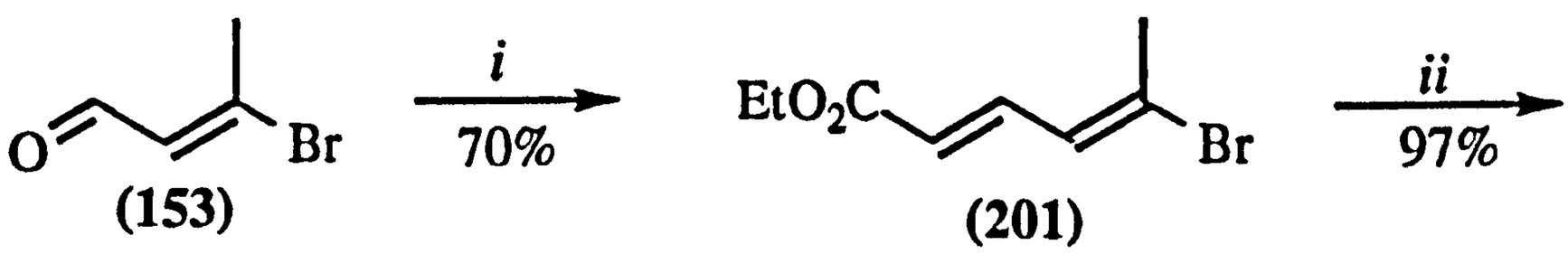
Reagents: *n*-BuLi, **(196)**, THF.

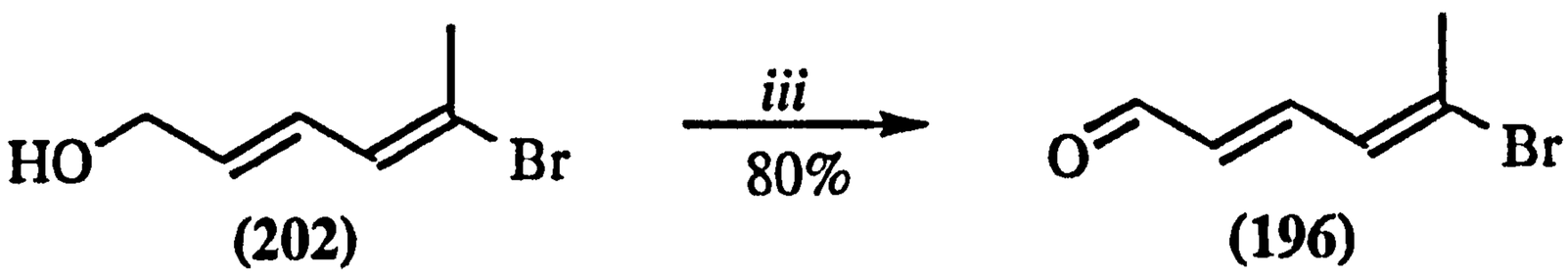
Scheme 45

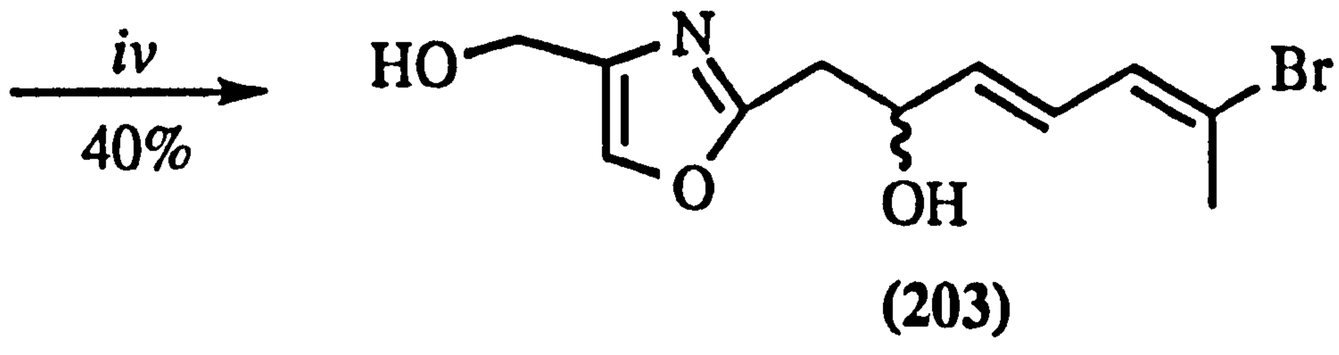
At this point it was interesting to note that the unprotected oxazole **(184)** also gave the same regiocontrol and yield as the protected oxazole **(185)** and so subsequent reactions

were carried out using the unprotected oxazole, thus removing the need for the protection and deprotection steps.

The route by which the aldehyde **(196)** was obtained was altered to a more conventional route, replacing the *N*-methoxy-*N*-methylamide group with an ester. **Scheme 46.** Thus, the aldehyde **(153)** was transformed into the *E,E*-diene ester **(201)** using triethyl phosphonoacetate under the Wadsworth-Emmons olefination conditions in 70% yield. Reduction of the ester **(201)** to the alcohol **(202)** was next achieved using DIBAL-H in CH_2Cl_2 at -78°C in 97% yield. The alcohol **(202)** was then oxidised to the aldehyde **(196)** in 80% yield using activated manganese dioxide in CH_2Cl_2. The aldehyde **(196)** was finally coupled to the unprotected oxazole **(184)** using *n*-BuLi in THF at -78°C, leading to the diol **(203)** in 40% yield.





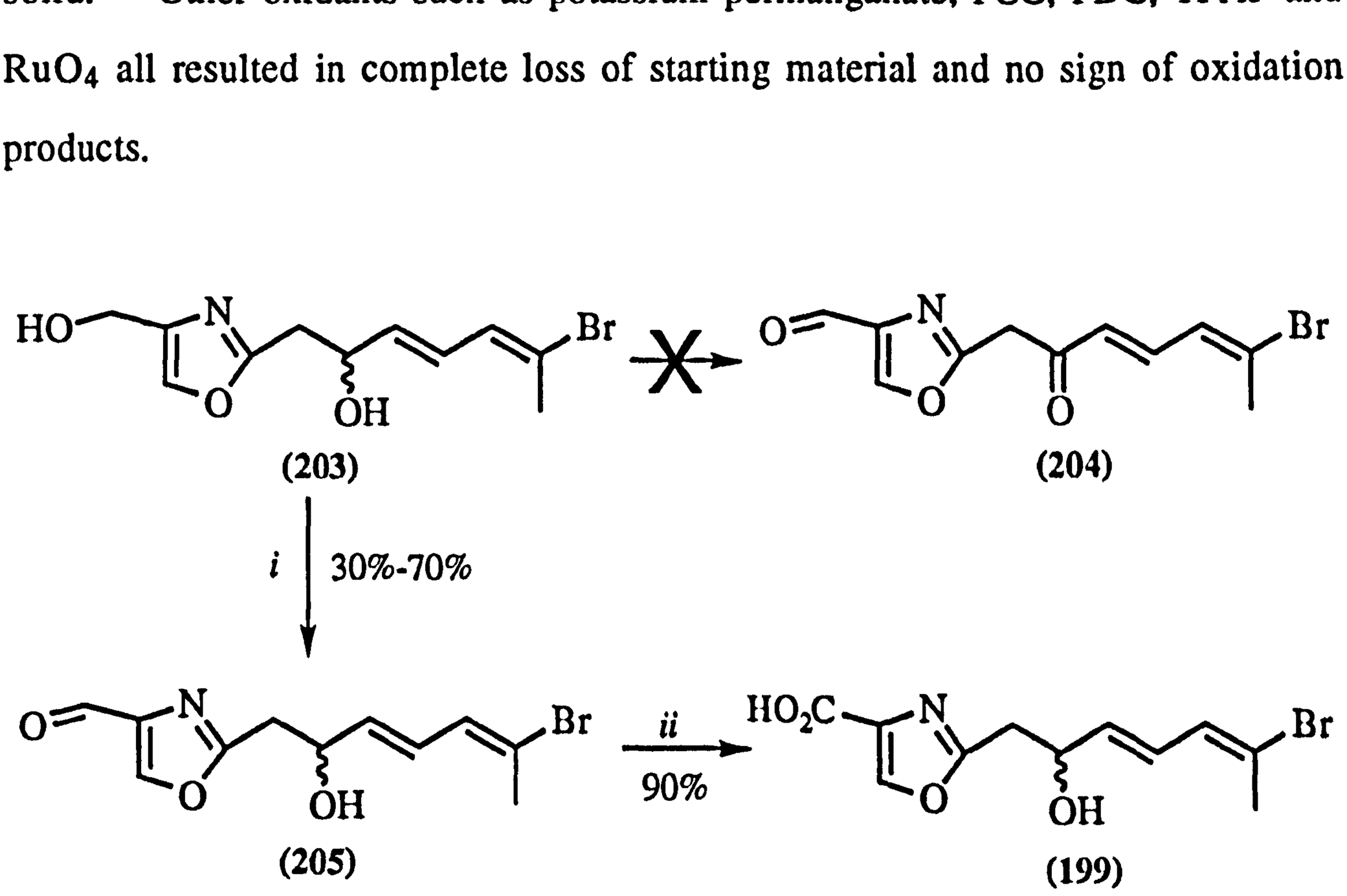


Reagents: *i*, KO^{t}Bu, triethyl phosphonoacetate, THF; *ii*, DIBAL-H, CH_2Cl_2; *iii*, MnO_2, CH_2Cl_2; *iv*, *n*-BuLi, **(184)**, THF.

Scheme 46

Oxidation of the primary allylic alcohol in **(203)** to the hydroxy aldehyde **(205)** was achieved using activated manganese dioxide in 30-70% yields. Attempts to simultaneously oxidise both the primary and secondary allylic alcohols with activated

manganese dioxide, barium manganate and Dess-Martin periodinane, to give the right-hand fragment **(204)**, only gave the hydroxy aldehyde **(205)**. **Scheme 47**. We reasoned that the secondary hydroxyl group would require longer reaction times or more forcing conditions to give the corresponding keto aldehyde **(204)**. Subjecting the diol **(203)** to excess reagents for long periods predominately gave the products of the retro-aldol reaction, as well as oxidation of the primary hydroxyl group. It should also be noted that the outcome of the manganese dioxide and barium manganate oxidations were highly dependent on the qualities of the oxidants used, with some batches giving sluggish oxidation and other more active batches giving only the retro-aldol products. To overcome this problem we found it necessary to use 10 equivalents of activated manganese dioxide (as supplied by Aldrich) which was filtered off when the reaction was seen to be about 50% complete by tlc. The aldehyde **(205)** was then oxidised to the corresponding carboxylic acid **(199)** using buffered sodium chlorite solution and 2-methyl-2-butene in *t*-butanol and water in 90% yield as a hygroscopic solid.[91] Other oxidants such as potassium permanganate, PCC, PDC, TPAP and RuO_4 all resulted in complete loss of starting material and no sign of oxidation products.

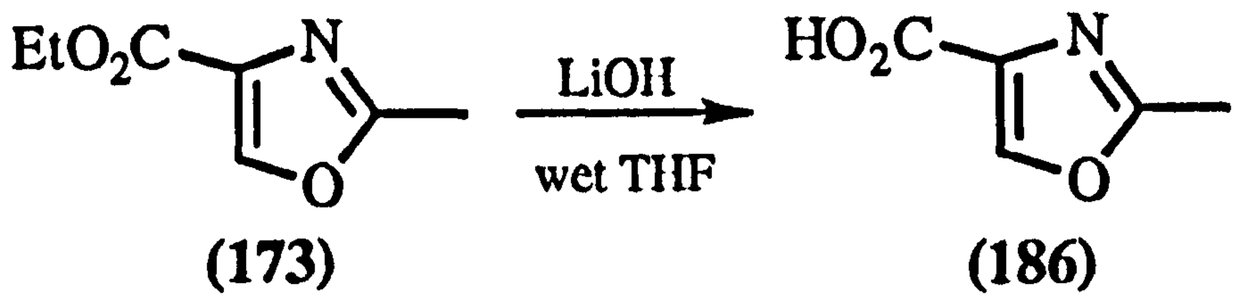


Reagents: *i*, MnO_2, CH_2Cl_2; *ii*, $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, H_2O, ^tBuOH.

Scheme 47

2.2.3 Peptidic Coupling Reactions of Fragments (132) and (199) to Proline.

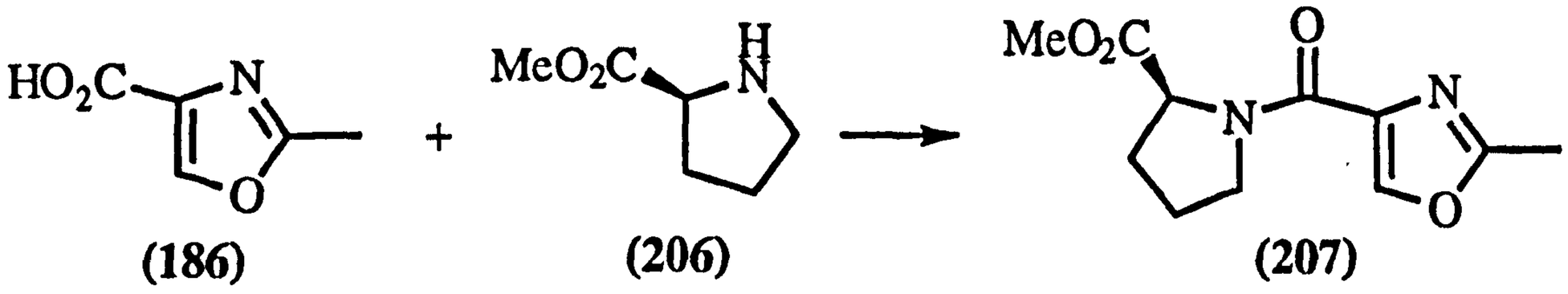
With the fragments **(132)** and **(199)** in hand it became necessary to ascertain the conditions required for the coupling of these two fragments to proline to afford the cyclisation precursor **(198)**. To model the amide bond formation between the oxazole acid **(199)** and proline, our first studies were carried out using the 2-methyloxazole acid **(186)** instead of the synthetically valuable oxazole acid **(199)**. The acid **(186)** was obtained by hydrolysis of the oxazole ethyl ester **(173)** using lithium hydroxide in wet THF in 60% yield. **Scheme 48.**



(173) **(186)**

Scheme 48

In the virginiamycin M family the members containing a fully saturated proline rings all contain the unnatural *D*- (or *R*-) proline, which is rather more expensive than the more readily available *L*- (or *S*-) proline. It was therefore decided to use the less expensive *L*-proline for all of our model studies as this was deemed to have little or no effect on the information we would obtain concerning reaction conditions. In our initial studies we coupled the oxazole acid **(186)** to *L*-proline methyl ester **(206)** using DCC and DMAP in dry CH_2Cl_2 to give the amide **(207)** in 70% yield. **Scheme 49.**



Reagents: DCC, DMAP, CH_2Cl_2.

Scheme 49

The nmr spectra of the amide **(207)** indicated that the amide existed as a 1:1 mixture of rotamers.[92] This phenomenon although causing no problems synthetically, did lead to complicated nmr spectra, especially when the molecules became more complicated as in the case of our later molecules. **Figure 33.**

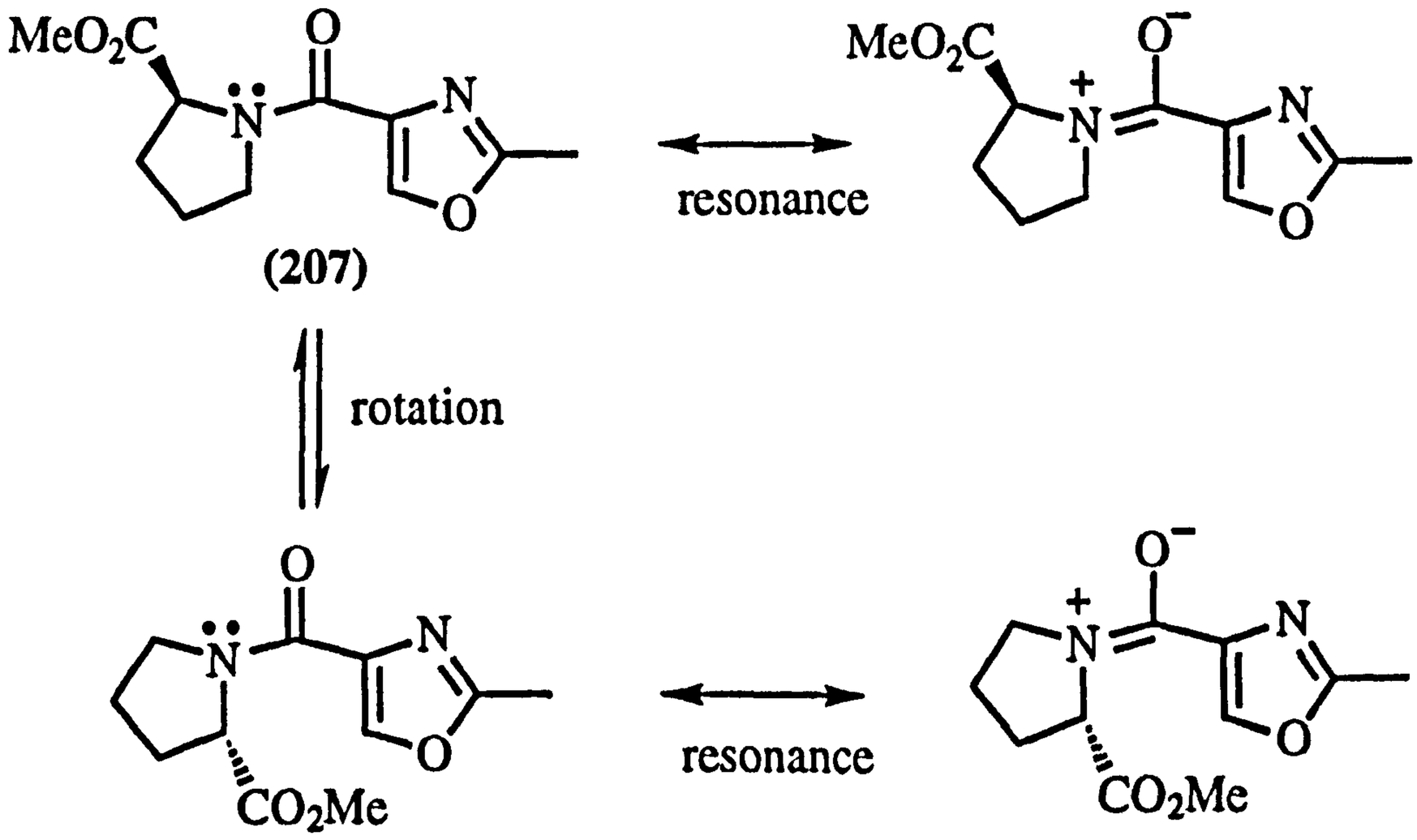
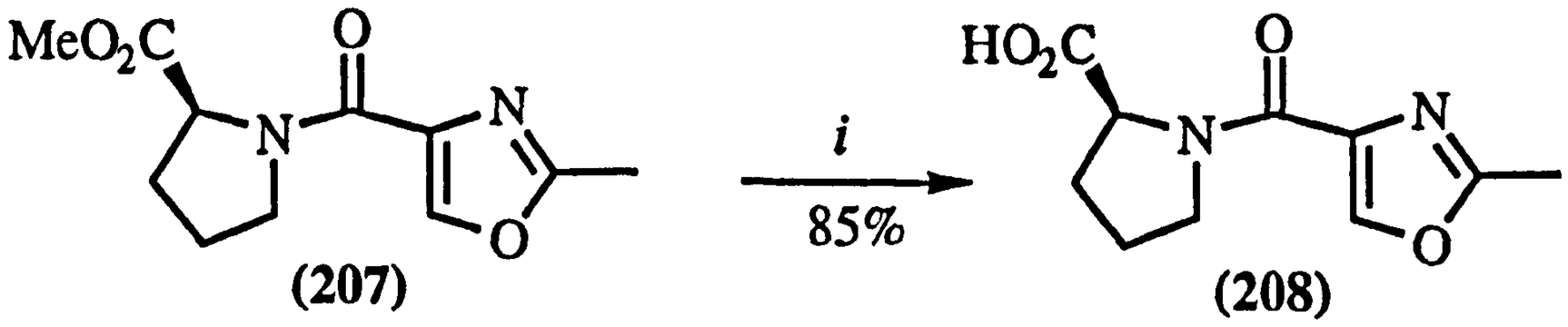
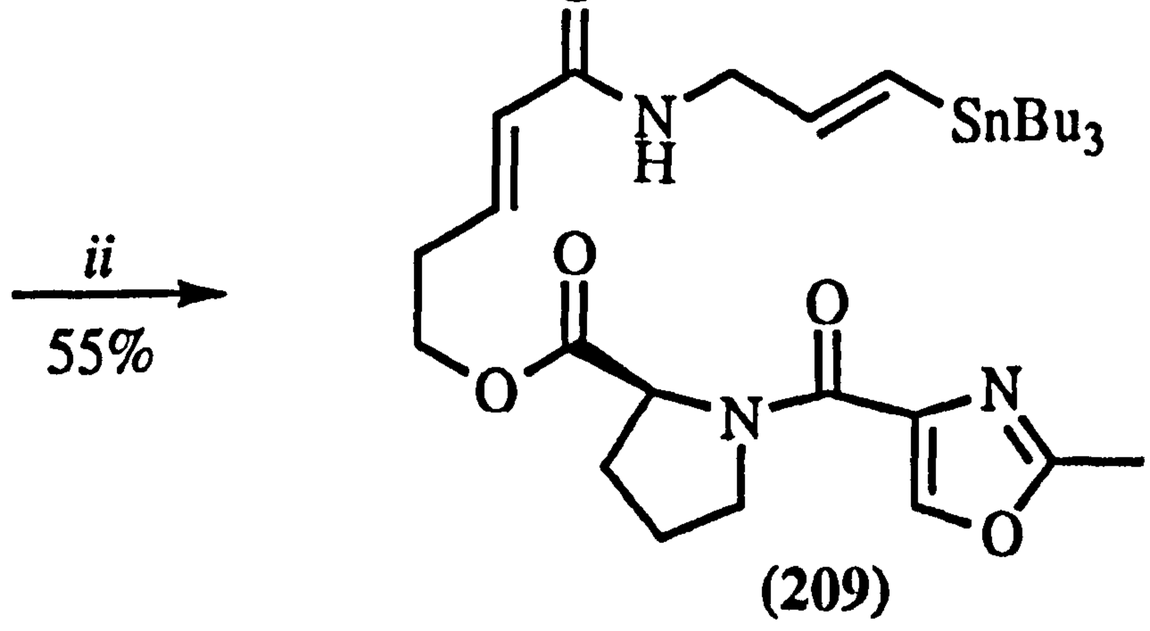


Figure 33

The ester group of the amide **(207)** was next hydrolysed to the acid **(208)** using lithium hydroxide in wet THF in 85% yield. The acid **(208)** was then coupled to fragment **(132)** using EDC, DMAP and DMAP.HCl in dry CH_2Cl_2 to give the ester **(209)** in 55% yield.[93] **Scheme 50.**

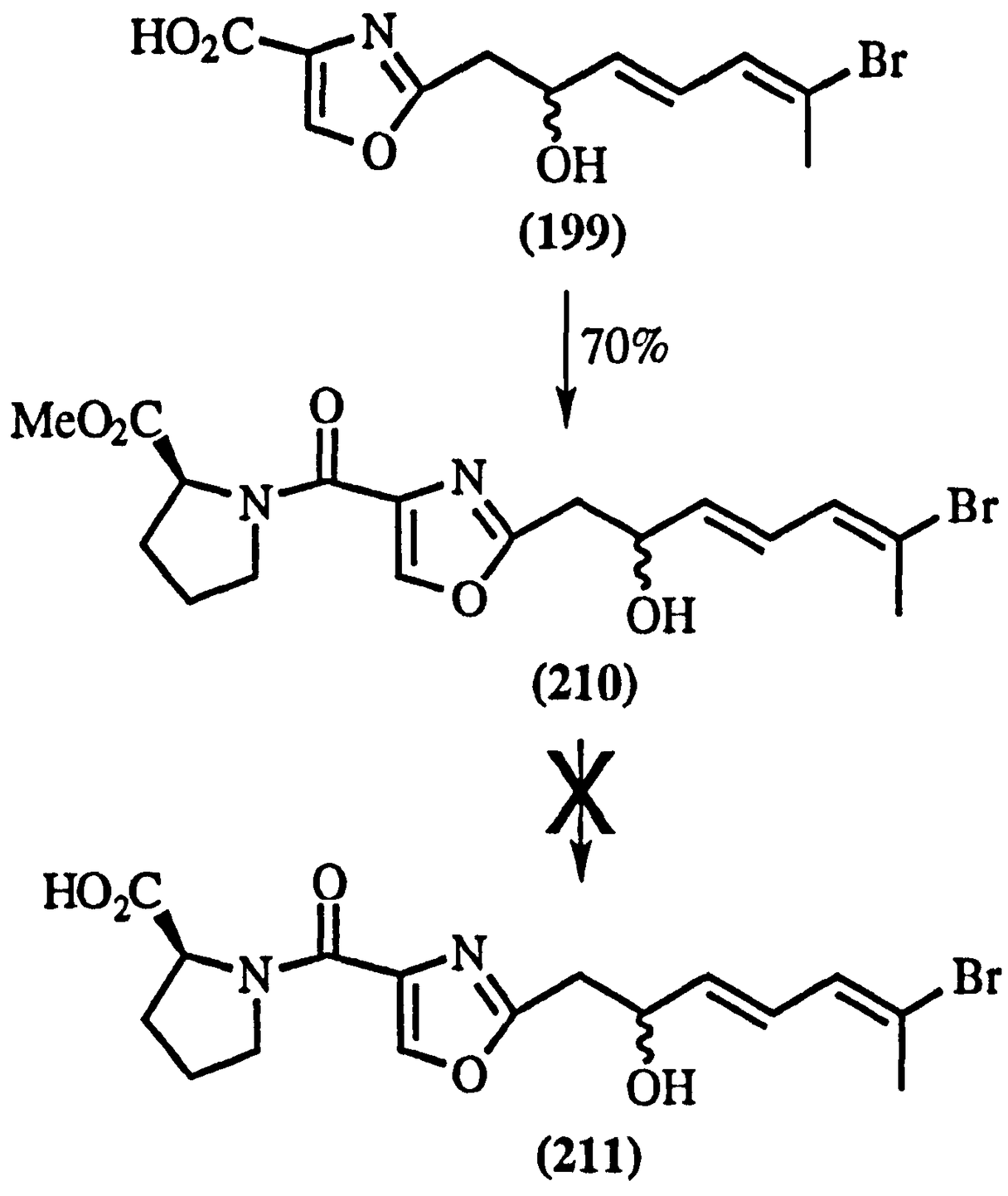




Reagents: *i*, LiOH, wet THF; *ii*, **(132)**, EDC, DMAP, DMAP.HCl, CH_2Cl_2.

Scheme 50

Having ascertained coupling conditions which would be tolerated by the fragile vinyl stannane moiety present in fragment **(132)**, we attempted to use the same route with the right-hand fragment **(199)**. The reaction of the acid **(199)** with *L*-proline methyl ester **(206)** using DCC and DMAP proved very slow and low yielding, and so it was decided to changed the reagents to EDC, HOBt and Et_3N as these conditions had been shown to give better results in some cases. Thus, the acid **(199)** was coupled to *L*-proline methyl ester **(206)** using EDC, HOBt and triethylamine in dry CH_2Cl_2, to give the amide **(210)** in 70% yield. **Scheme 51.**

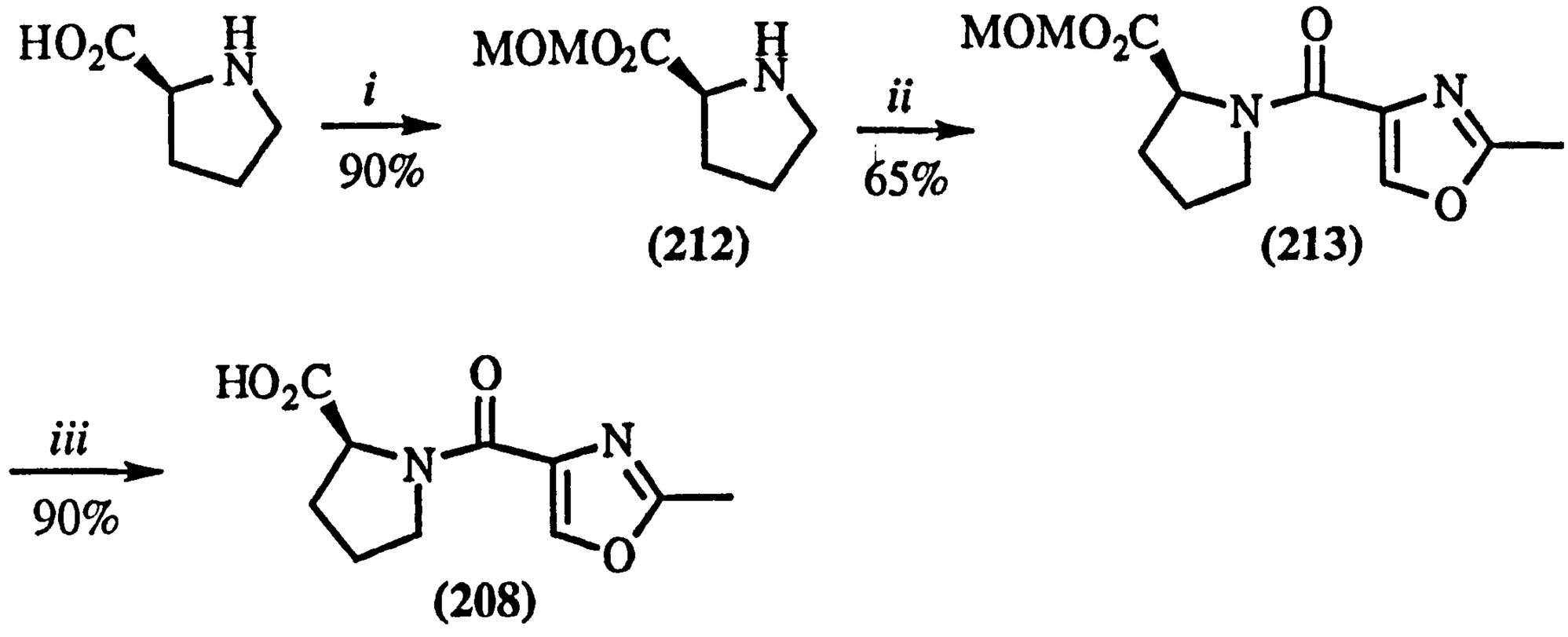


Reagents: **(206)**, EDC, HOBt, Et_3N, CH_2Cl_2.

Scheme 51

Attempts to hydrolyse the methyl ester group of amide **(210)** using basic conditions led to complete decomposition of the molecule with none of the desired acid **(211)** being isolated. It was thought that under the basic conditions of the hydrolysis the side chain in the 2-position of **(210)** may have undergone a retro-aldol elimination. It was hoped that by changing the base-labile methyl ester to the acid-labile methoxymethyl ester, that the acid **(211)** would be obtained without decomposition. Thus, *L*-proline **(206)** was esterified with chloromethylmethyl ether and triethylamine in dry CH_2Cl_2 to give *L*-proline methoxymethyl ester **(212)** in 90% yield. The general lability of the methoxymethyl ester in **(212)** led to some decomposition on exposure to flash chromatography and therefore the proline **(212)** was used without further purification.

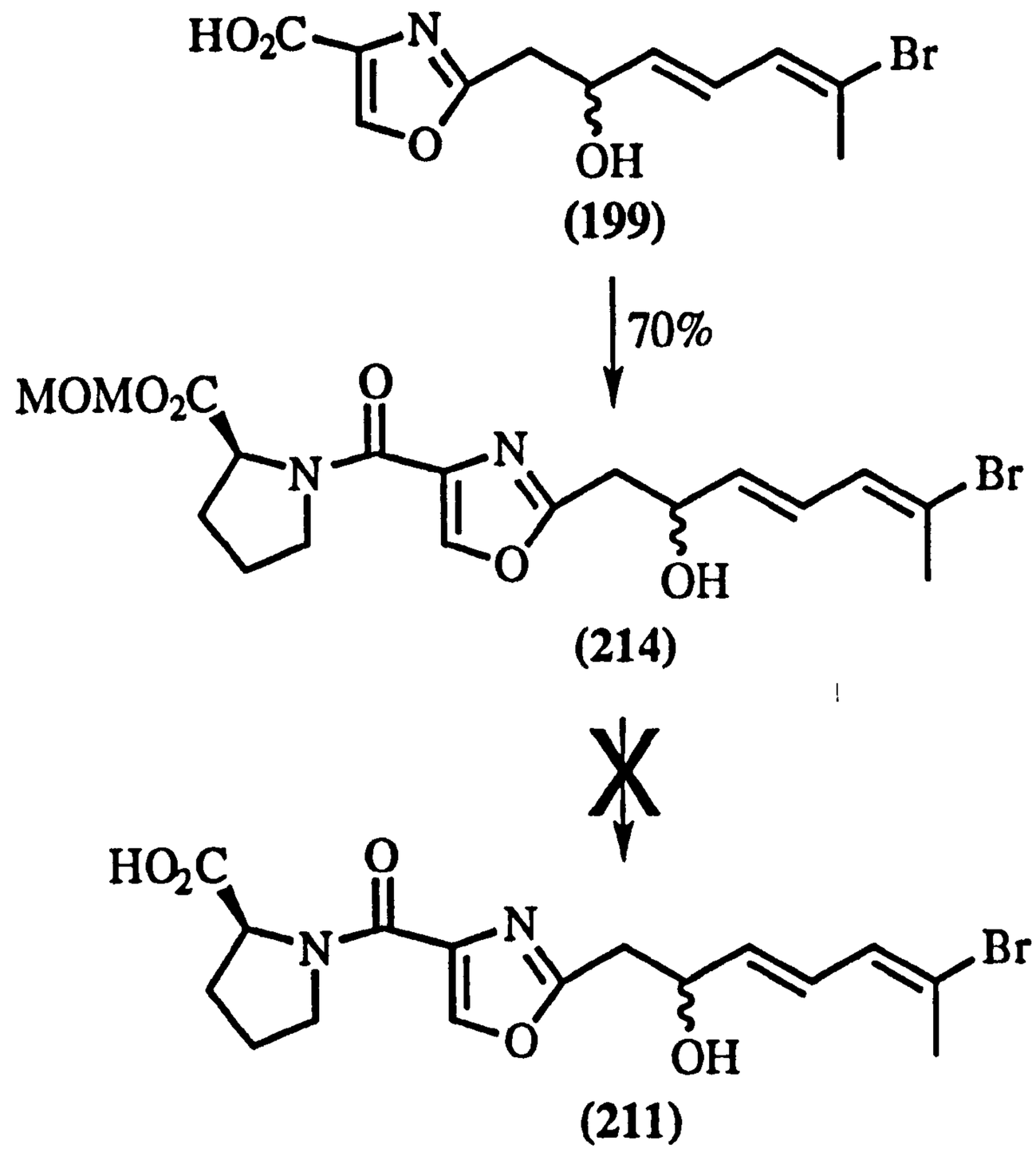
To determine if the MOM ester group would withstand our coupling conditions, and to ascertain the degree of lability of the MOM ester to mild acidic conditions, the proline **(212)** was coupled to the 2-methyloxazole acid **(186)** using EDC, HOBt and Et_3N in CH_2Cl_2, to give the amide **(213)** in 60% yield. **Scheme 52.**



Reagents: *i*, MOM-Cl, Et_3N, CH_2Cl_2; *ii*, **(186)**, EDC, HOBt, Et_3N, CH_2Cl_2; *iii*, 2*M* HCl, THF.

Scheme 52

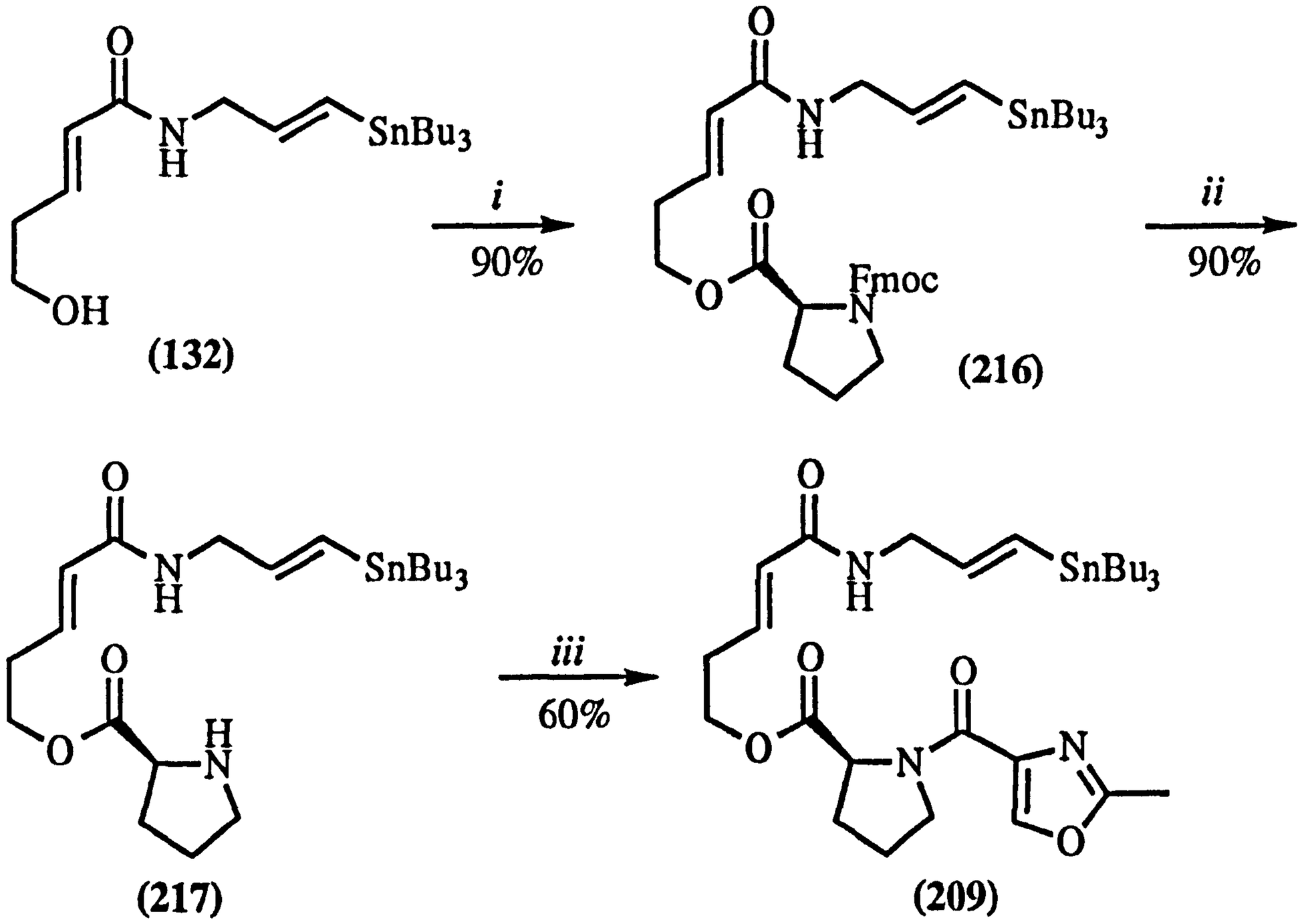
Treatment of the amide **(213)** with 2*M* HCl gave the acid **(208)**, identical to that produced by base hydrolysis of the methyl ester **(207)**, in 90% yield. The *L*-proline methoxymethyl ester **(212)** was then coupled to the oxazole acid **(199)**, using EDC, HOBt and triethylamine in dry CH_2Cl_2, to give the amide **(214)** in 70% yield. However on treatment of the amide **(214)** with 2*M* HCl none of the desired acid **(211)** or starting material were isolated. **Scheme 53.**



Scheme 53

Concurrently with this work we had been looking at the coupling of proline to the left-hand fragment **(132)** prior to coupling to the right-hand oxazole acid **(199)**. For this strategy we required a base-labile group for protection of the nitrogen of the proline during the esterification with the left-hand fragment **(132)**. This would allow its subsequent removal in the presence of the acid sensitive vinyl stannane mqiety, allowing us to continue with the subsequent coupling of the resulting fragment to the oxazole acid **(199)**. To this end the 9-fluorenylmethyloxycarbonyl (Fmoc) group was chosen as this had been shown to be readily attached and removed under mild conditions (properties which have resulted in the Fmoc group becoming widely used as a protecting group in peptide synthesis). Thus, commercial *N*-Fmoc-*L*-proline **(215)** was coupled to the alcohol **(132)** using DCC and DMAP in dry CH_2Cl_2 to give the

amide **(216)** in 90% yield. The Fmoc protection in **(216)** was then removed by stirring at room temperature with 5 equivalents of piperidine in acetonitrile to yield the free amine **(217)** in 90% yield. Fragment **(217)** was then coupled to the oxazole acid **(186)** using EDC, HOBt and triethylamine in dry CH_2Cl_2, to give the amide **(209)**, identical to that formed from fragments **(132)** and **(208)**, in 60% yield. **Scheme 54.**



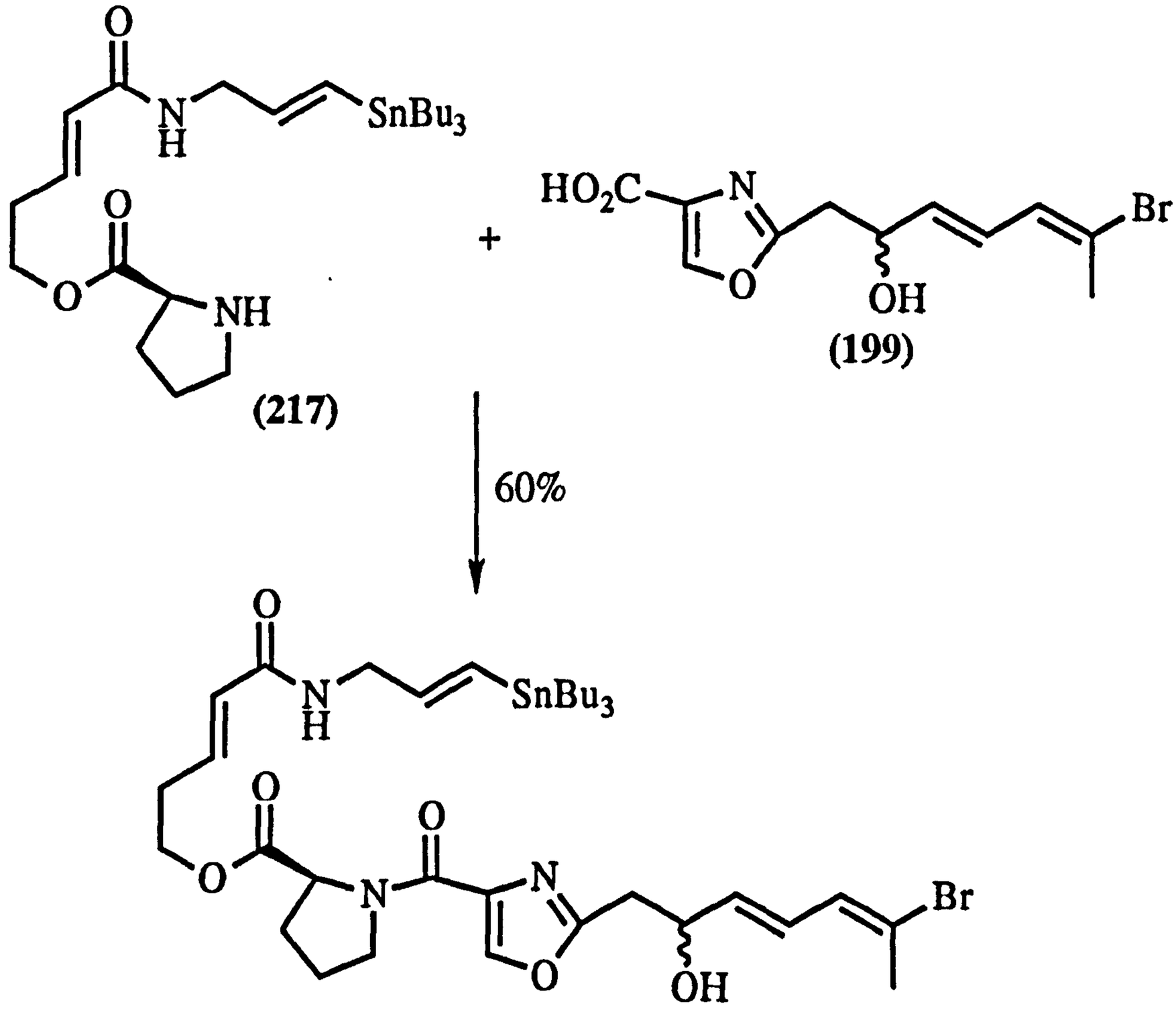
Reagents: *i*, **(215)**, DCC, DMAP, CH_2Cl_2; *ii*, Piperidine, CH_3CN;

iii, **(186)**, EDC, HOBt, Et_3N, CH_2Cl_2.

Scheme 54

It was found that the coupling reactions using EDC and HOBt resulted in protiodestannylation of the vinyl stannane. This was thought to be due to the release of HCl from the EDC during the reaction. Therefore, when using EDC as its normally supplied salt form, an equimolar amount of triethylamine was used to neutralise any acid produced.

Having ascertained suitable conditions for the coupling of fragments **(217)** and **(199)** to proline, we proceeded with the formation of the cyclisation precursor. **Scheme 55.**



Reagents:- EDC, HOBt, Et_3N, CH_2Cl_2.

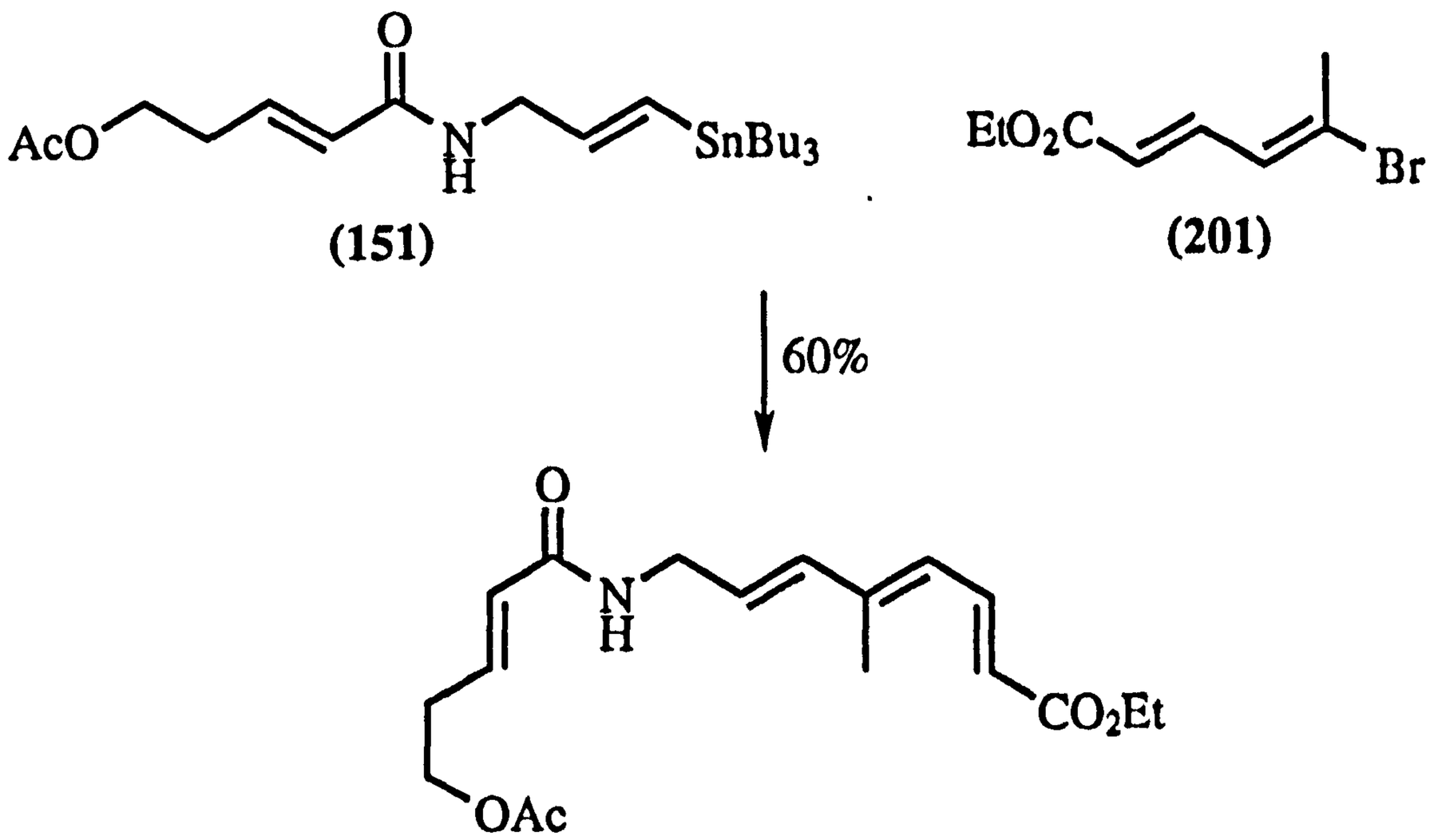
Scheme 55

Thus the oxazole acid **(199)** was coupled to the amine **(217)** using EDC, HOBt, and triethylamine in dry CH_2Cl_2, to give the cyclisation precursor **(198)** in a 60% yield as a mixture of rotamers and diastereoisomers.

2.3 Stille Coupling Reactions

Before attempting an intramolecular Stille cyclisation of the precursor **(198)** of the model system **(197)**, we wanted to gain some insight into the coupling reaction between a *E*-vinyl stannane and a trisubstituted *E*-vinyl bromide to obtain a triene system. It was hoped that by coupling various bromides and stannanes fragments prepared throughout our synthetic work, we would obtain valuable information about the properties of the resultant triene systems. As already mentioned there have been a number of different palladium catalysts used in Stille coupling reactions. One catalyst which has shown excellent activity and functional group tolerance is tetrakis(triphenylarsine) palladium(0), as developed by Farina[39], and which was decided to be a good starting point in our own studies. Thus, the vinyl stannane **(151)** was coupled with the vinyl bromide **(201)** in THF, at reflux, with 1% $Pd(0)(Ph_3As)_4$, to give the triene **(218)** in 60% yield. The triene **(218)** was obtained exclusively as the all *E*-isomer with no sign of double bond isomerisation (by nmr analysis).

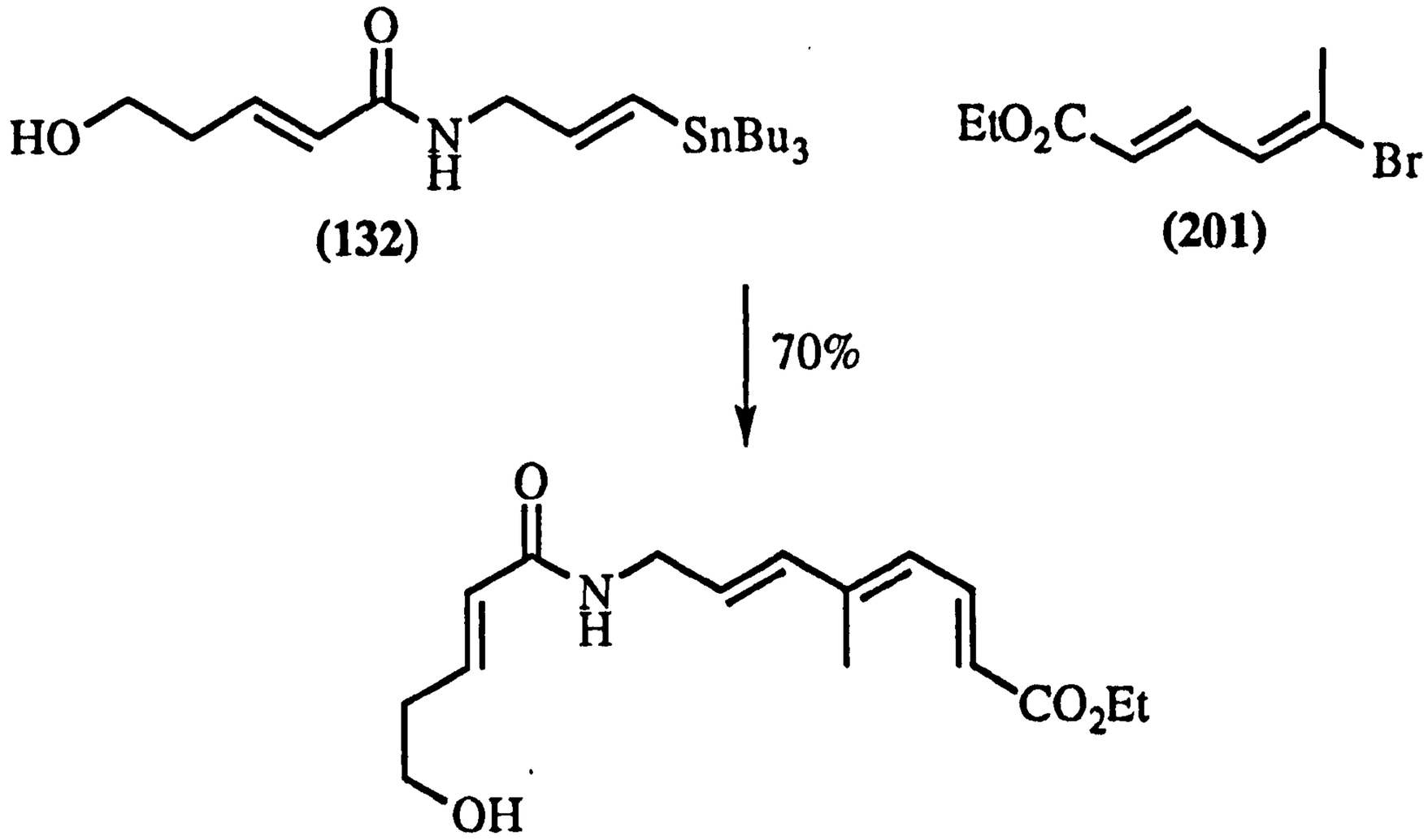
Scheme 56.



Reagents: $Pd(0)(Ph_3As)_4$, THF.

Scheme 56

The reaction was repeated with the deprotected vinyl stannane **(132)** to ascertain if the reaction would tolerate the presence of a free hydroxyl group. The reaction proceeded as before to give the triene **(219)** in 70% yield, and once again showed no sign of double bond isomerisation. **Scheme 57.** Both of the trienes **(218)** and **(219)** however were found to be unstable at room temperature for more than a few hours, especially in the presence of light, making purification and characterisation difficult.

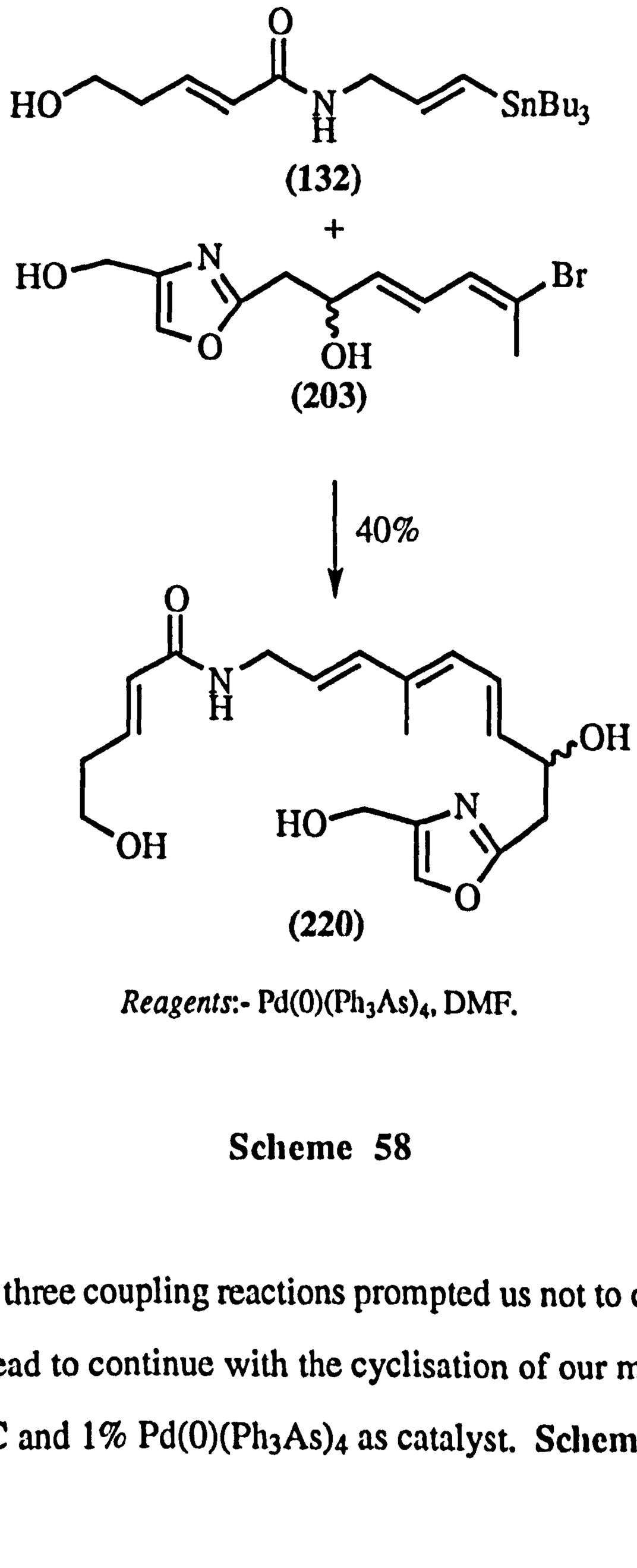


Reagents: $Pd(0)(Ph_3As)_4$, THF.

Scheme 57

With these coupling reactions in hand, our attention moved to a closer representative of the triene system present in our model cyclisation. It was necessary to couple fragment **(132)** with fragment **(203)** to give the trienol present in **(197)**, this would not only give us a greater understanding of the cyclisation, but also give us an indication of what the nmr spectra may look like for this trienol system. We also wanted to take the opportunity to move away from THF, as this had been shown to be a poor solvent in studies of intramolecular Stille cyclisation, an observation made during other studies of the Stille cyclisation method within the laboratories at Nottingham. We therefore decided to run the reaction between the bromide **(203)** and the stannane **(132)** in

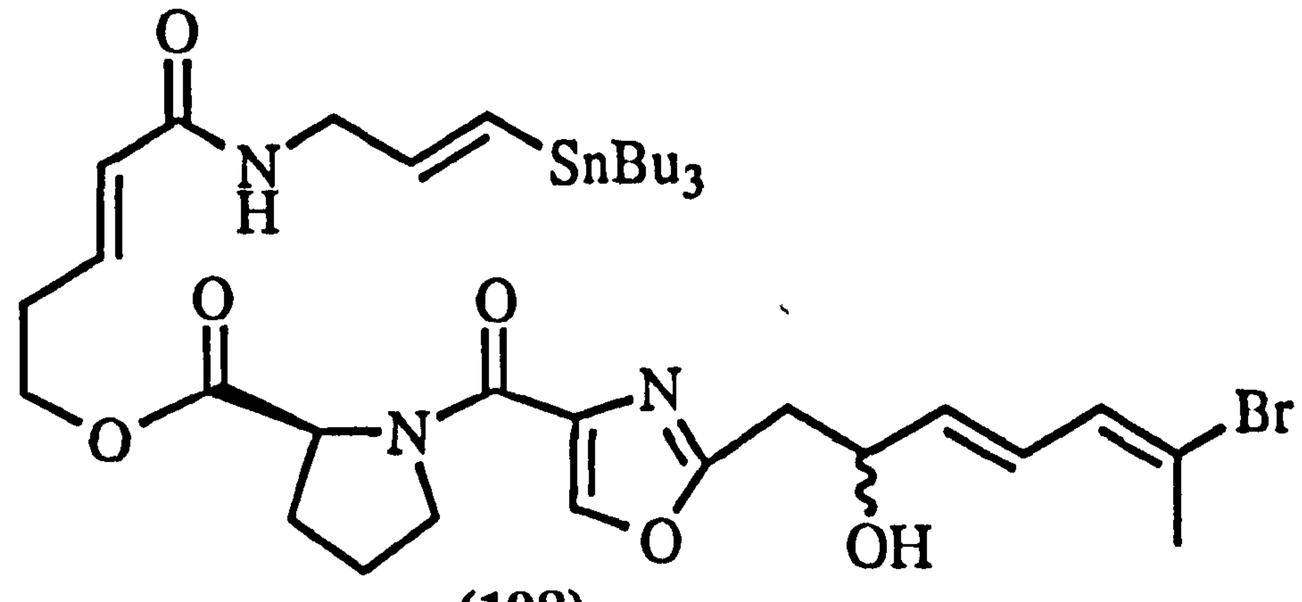
DMF, a polar solvent which has been shown to promote reactions where non-polar THF had failed. Thus, the vinyl bromide **(203)** and the vinyl stannane **(132)** were coupled in DMF at 100°C, using 1% $Pd(0)(Ph_3As)_4$ as catalyst, to give the trienol **(220)** in 40% yield. **Scheme 58.** The lower yield in this case was attributed to the difficulty in purifying the triol **(220)** and its general instability as with the previous two triene systems **(218)** and **(219)**.



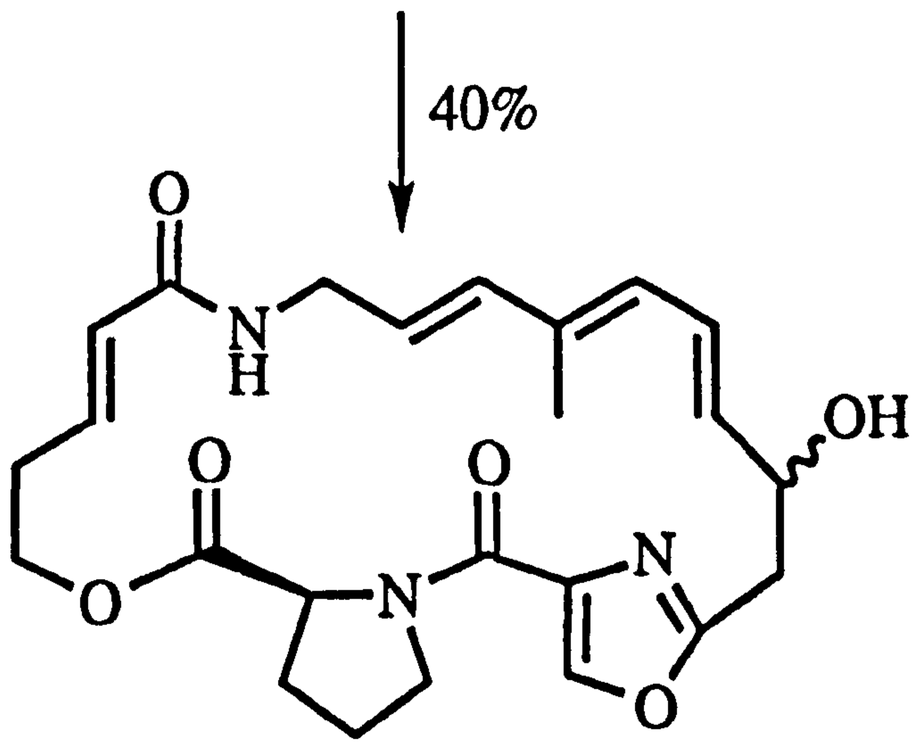
Reagents:- $Pd(0)(Ph_3As)_4$, DMF.

Scheme 58

The success of these three coupling reactions prompted us not to change the conditions any further, but instead to continue with the cyclisation of our model precursor **(198)** using DMF at 100°C and 1% $Pd(0)(Ph_3As)_4$ as catalyst. **Scheme 59.**



(198)



(197)

Reagents: Pd(0)(Ph_3As)$_4$, DMF.

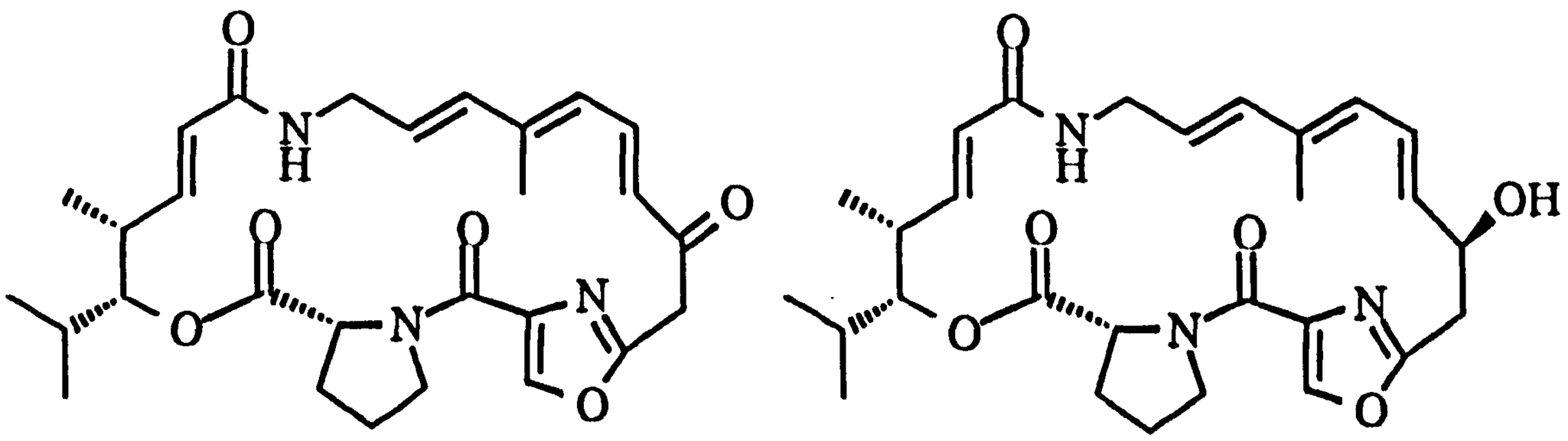
Scheme 59

Thus, the model precursor **(198)** was added to a solution of 1% Pd(0)(Ph_3As)$_4$ in dry DMF and the mixture was heated at 100°C for 18 h. After careful purification the trienol macrocycle **(197)** was obtained in 40% yield. Although the macrocycle proved to be very unstable at room temperature, it could however be stored at -20°C in acid free $CDCl_3$ for several days. It was interesting to note that the rate and success of the Stille coupling reaction was dependent not only on the concentration of the precursor (intramolecular couplings being favoured by low concentrations), but more so by the concentration of the catalyst present. It was found that at concentrations of less than 0.1 *mM* of catalyst gradual decomposition of the precursor occurred at a faster rate than the cyclisation to the macrocycle.

The successful macrocyclisation to the model system **(197)** had provided valuable evidence that the Stille methodology could be used to overcome the cyclisation difficulties experienced in the formation of the virginiamycin M series of compounds. It now remained to go back and modify our synthesis to introduce the features required for a total synthesis of members of the family of the virginiamycin M antibiotics.

2.4 Synthesis of 14,15-Anhydro-16,37-dihydrovirginiamycin M_2

On examination of the virginiamycins **(6A)** and **(7A)**, it is possible to identify the portion of the left-hand-side common to all the virginiamycin M compounds, *i.e.* ester **(127)**, which we had previously synthesised using Meyers methodology.[20] We also possessed the right-hand oxazole acid **(199)**, albeit in a racemic form, required for the synthesis of the virginiamycin **(7A)**. **Figure 34.** Disconnecting **(7A)** according to our Stille protocol, followed by further disconnections as before, led us once again to the three main fragments: (*i*) fragment **(222)**, the left-hand fragment contains the two adjacent chiral alkyl groups (to be incorporated using Meyers method); (*ii*) *D*-proline; (*iii*) the oxazole acid **(199)**. **Figure 35.**



(6A) **(7A)**

Figure 34

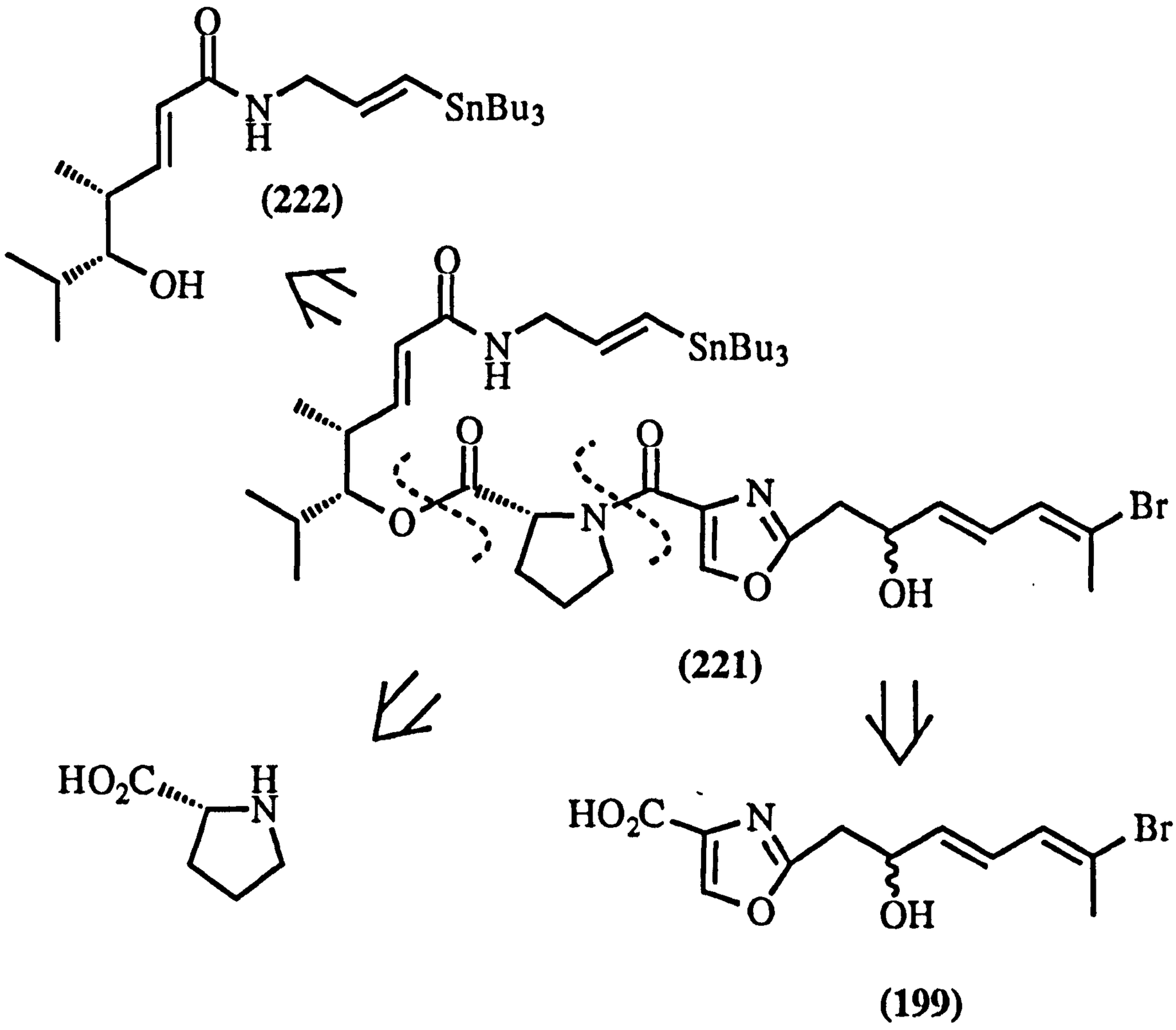
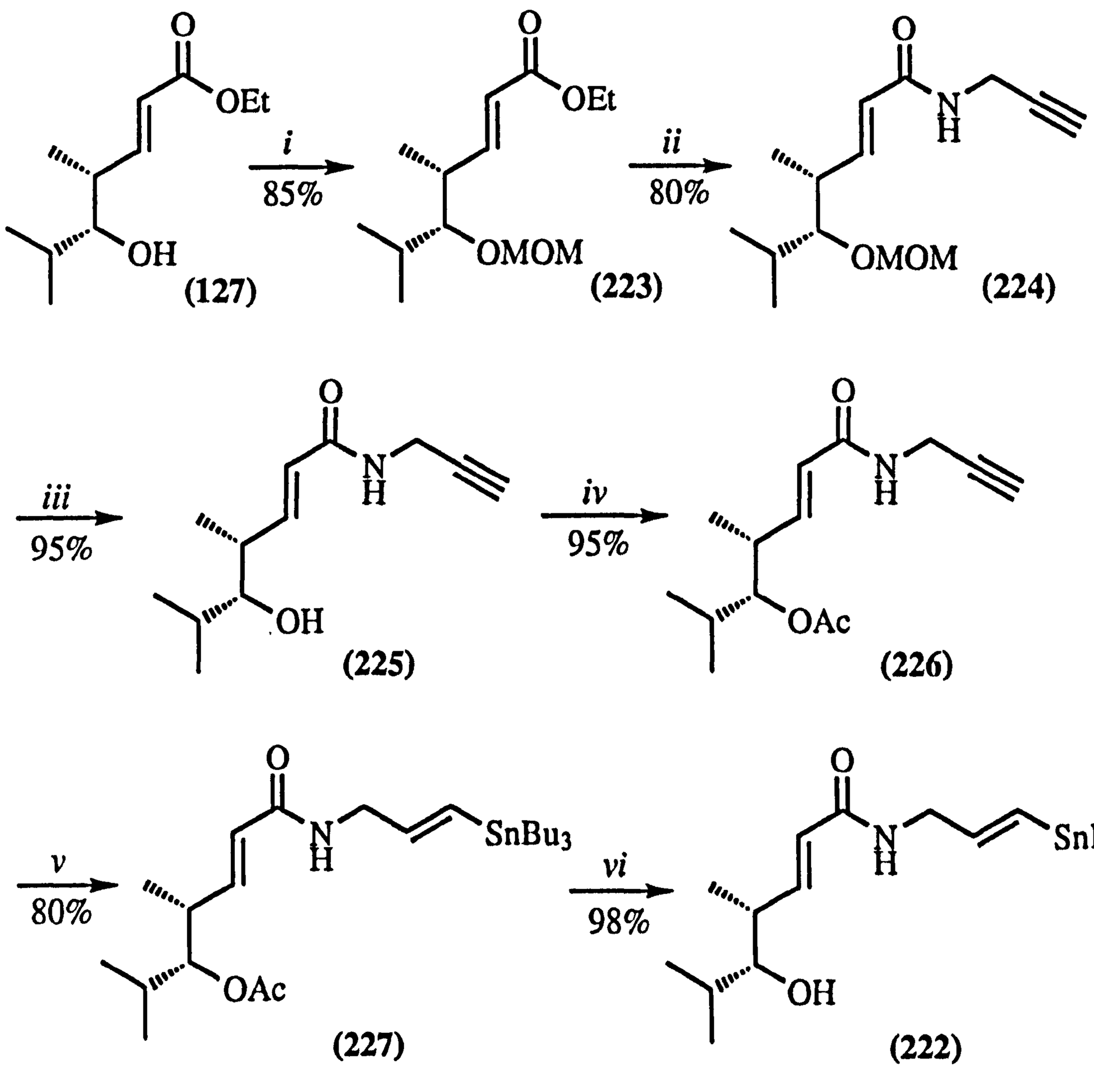


Figure 35

It was hoped that the same methodology could be employed in the conversion of the chiral ester **(127)** into fragment **(222)** as had been used in the synthesis of fragment **(132)** during the model studies. The chiral ester **(127)** was synthesised as described earlier in this discussion (**Scheme 31**). The protecting group chosen for the hydroxyl group in the ester **(127)** needed to withstand the conditions employed in the synthesis of the amide **(224)**, namely the conditions used in Weinreb's method of amide formation, *i.e.* treatment with the trimethylaluminium species. It also needed to be removed easily in the presence of the acid-sensitive vinyl stannane moiety, *i.e.* it needed to be base-labile. Once again no one suitable protecting group could be found, and so we were forced to resort to a change of protecting group halfway through our synthesis. Thus, the hydroxyl group in the ester **(127)** was first protected as its methoxymethyl ether **(223)** using chloromethylmethyl ether and Hünig's base, in dry CH_2Cl_2 under reflux, in 85% yield. **Scheme 60.** The protected ester **(223)** was

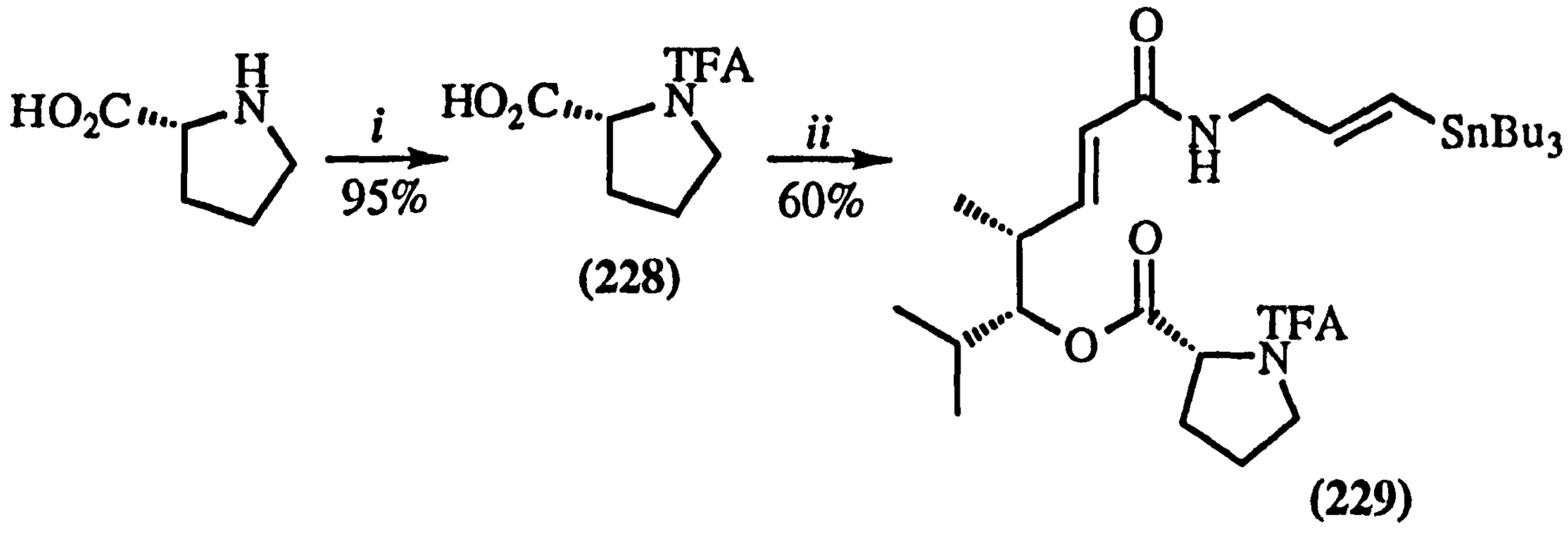
converted into the propargylic amide **(224)** using Weinreb's method in dry CH_2Cl_2, in 80% yield.[72] The MOM ether in **(224)** was then cleaved to the alcohol **(225)** using bromotrimethylsilane, in dry CH_2Cl_2 at -78°C, in 95% yield. The alcohol **(225)** was then reprotected as the acetate using acetyl chloride and pyridine in dry CH_2Cl_2 to give the ester **(226)** in 95% yield. Hydrostannylation of the ester **(226)**, using the high order cuprate developed by Lipshutz,[68] gave the vinyl stannane **(227)** in 80% yield. The acetate protection in **(227)** was then removed using excess potassium hydroxide in wet methanol to give fragment **(222)** in 98% yield.



Reagents: *i*, MOM-Cl, Hünig's base, CH_2Cl_2; *ii*, Propargylamine, Me_3Al, CH_2Cl_2; *iii*, TMS-Br, CH_2Cl_2; *iv*, AcCl, py, CH_2Cl_2; *v*, CuCN, *n*-BuLi, Bu_3SnH, THF; *vi*, KOH, MeOH.

Scheme 60

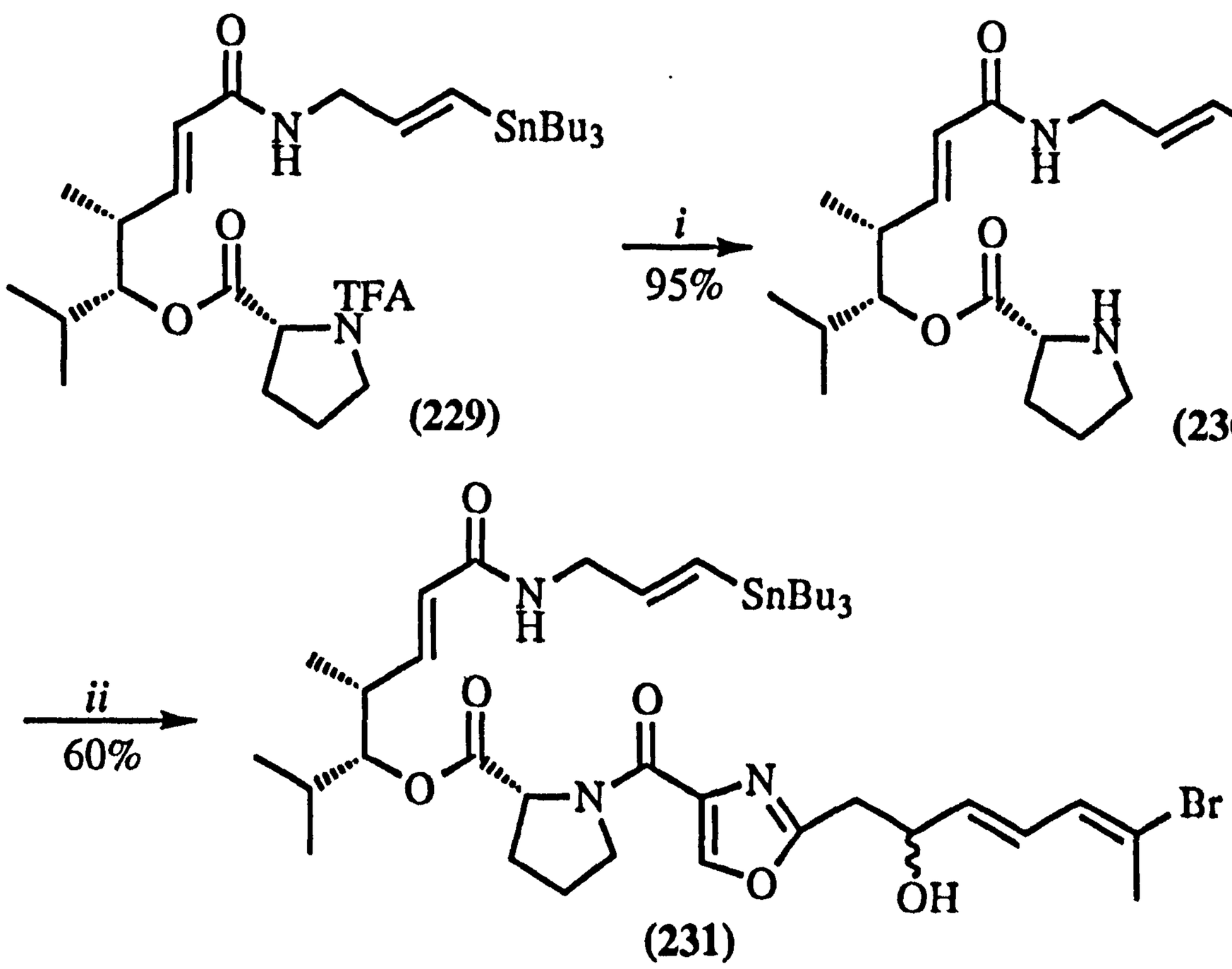
The next step in the synthesis was to couple the *N*-protected *D*-proline to fragment **(222)**. We decided to retain the Fmoc protection used in the synthesis of our model system, as this had been shown to work well, and was also commercially available. Meyers *et al* had reported coupling a Boc-protected alanine residue to the free alcohol of a system containing the (4*R*)-methyl-(5*R*)-hydroxy-6-methyl-2-pentenamide fragment (present in our system) using DCC and DMAP in dry CH_2Cl_2.[20] However using these conditions with *N*-Fmoc-*D*-proline and the alcohol **(222)** only gave 5% yield of the desired ester, with mostly recovered starting material. It was noted that the acetylation of the alcohol **(225)** had taken considerably longer than the corresponding example without the two chiral alkyl groups. It was also noted that the cleavage of the acetyl group in **(227)** required several equivalents of potassium hydroxide at room temperature over several hours, whereas a normal non-hindered acetate hydrolysis usually occurs using potassium carbonate at 0°C. These observations, and the fact that on attempting to couple *N*-Fmoc-*D*-proline and the alcohol **(222)** only gave very low yields of product, led to the conclusion that the alcohol must be too hindered to allow the bulky *N*-Fmoc-*D*-proline to approach easily enough for the reaction between the acid and the alcohol to proceed at a reasonable rate. It was hoped that by using a less bulky protecting group for the proline nitrogen that a better yield may be obtained for the coupling. It was therefore decided to use a trifluoroacetyl group instead of the Fmoc group. Trifluoroacetamides had been shown to be easily cleaved by weak bases such as sodium carbonate, but this would cause problems if readily hydrolysed esters were also present in the molecule. In our case however the ester in **(227)** had already shown itself to be too hindered for easy hydrolysis, especially by weak bases such as sodium carbonate, and so would cause no problems when removing the TFA group. Thus, *D*-proline was protected as its trifluoroethylacetamide **(228)** using ethyl trifluoroacetate and triethylamine in dry methanol, in 95% yield.[94] The *N*-TFA-*D*-proline **(228)** was then coupled to fragment **(222)** using DCC and DMAP in the minimum of dry CH_2Cl_2, to give the ester **(229)** in 60% yield. **Scheme 61.**



Reagents: *i*, Ethyl trifluoroacetate, Et_3N, MeOH; *ii*, **(222)**, DCC, DMAP, CH_2Cl_2.

Scheme 61

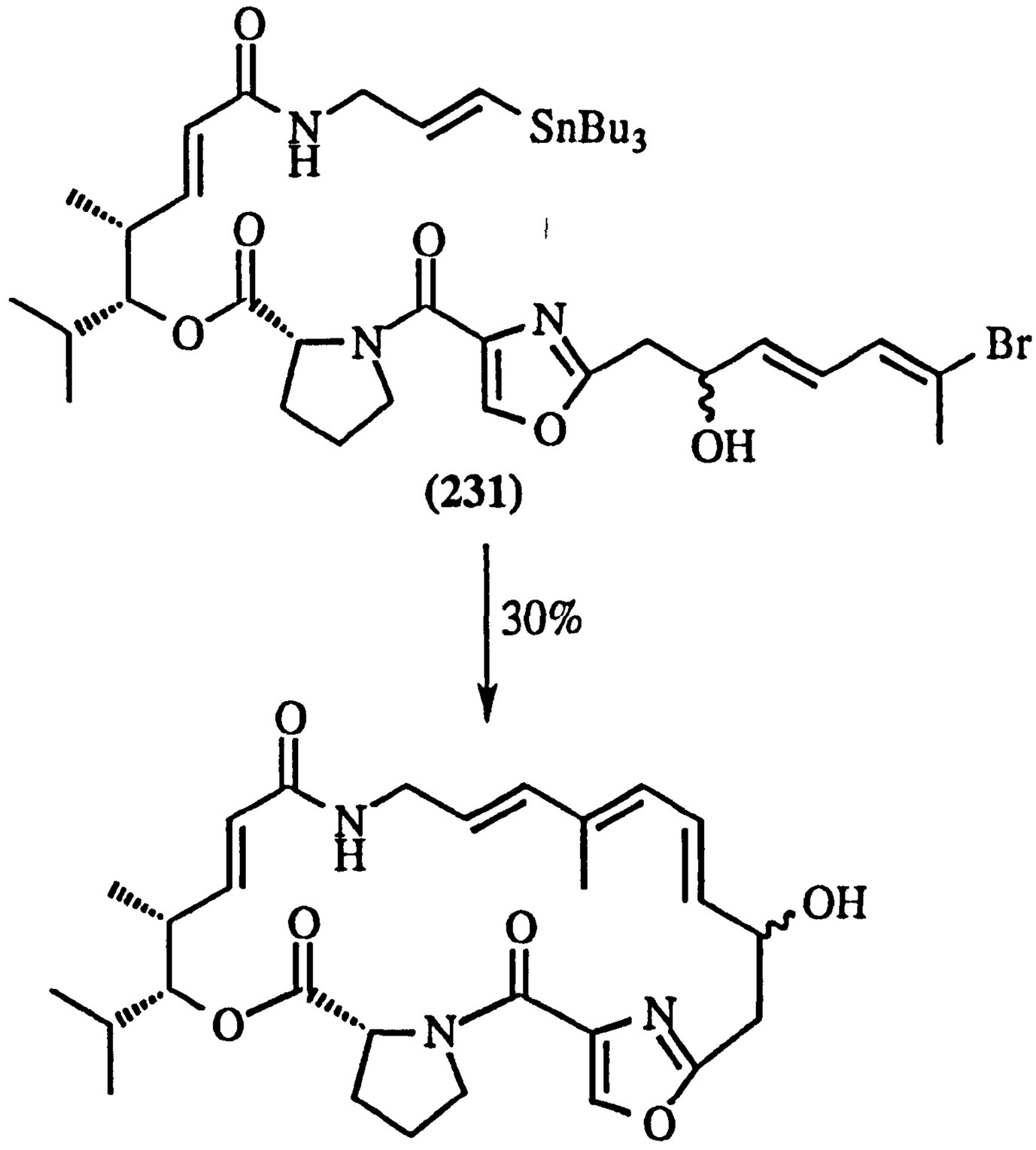
The TFA protection in **(229)** was removed with sodium carbonate in wet methanol to give the amine **(230)** in 95% yield. The amine **(230)** was then coupled to the oxazole acid **(199)** using EDC, HOBt and triethylamine, to give the cyclisation precursor **(231)** in 60% yield. **Scheme 62.**



Reagents: *i*, Na_2CO_3, wet MeOH; *ii*, **(199)**, EDC. HOBt, Et_3N, CH_2Cl_2.

Scheme 62

Cyclisation of **(231)** using 1% $Pd(0)(Ph_3As)_4$ in dry DMF at 100°C for 18 h finally gave 14,15-anhydro-16,37-dihydrovirginiamycin M_2 in a 30% yield as a mixture of secondary hydroxyl epimers. **Scheme 63.**



(231)

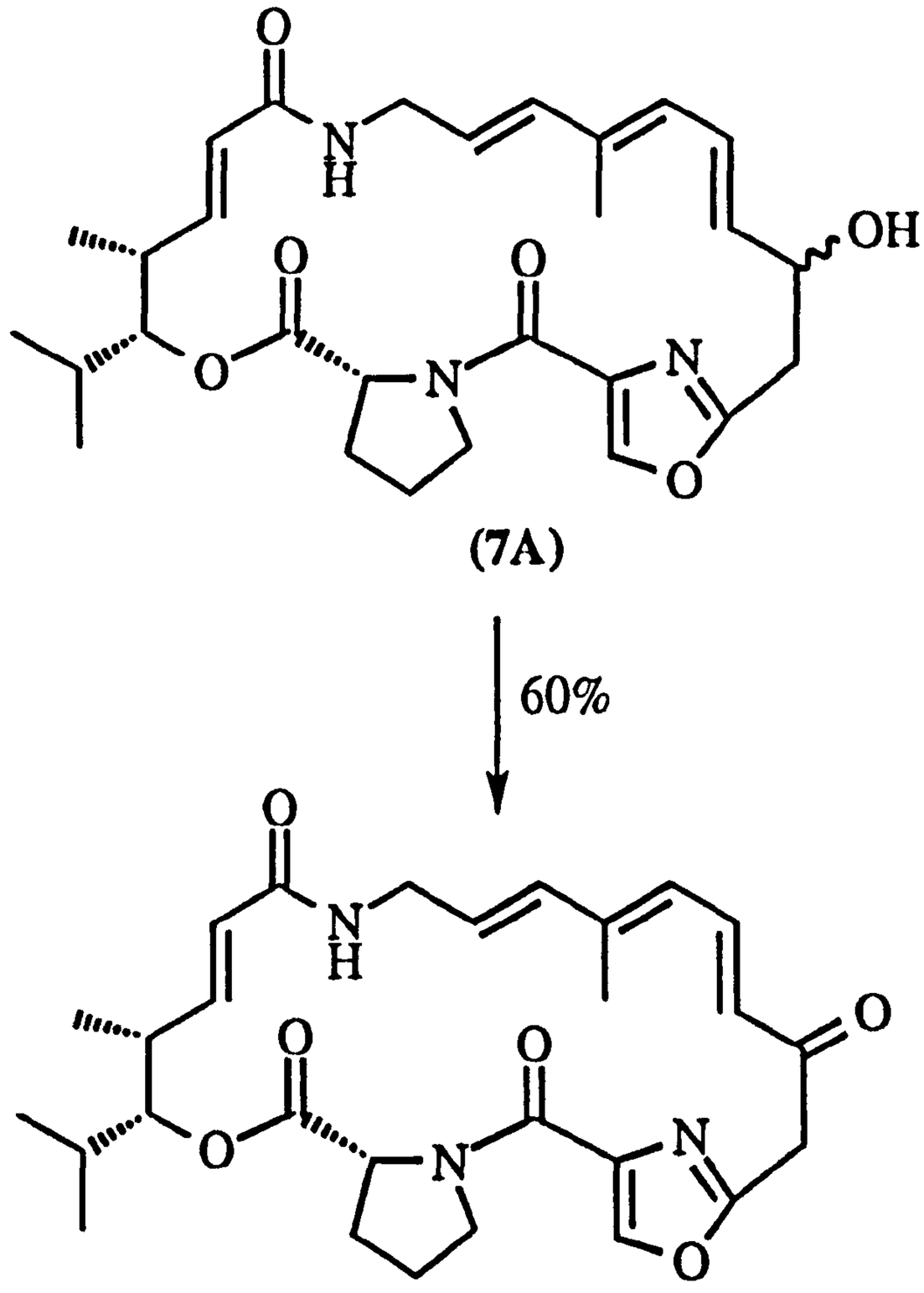
(7A)

Reagents: $Pd(0)(Ph_3As)_4$, DMF.

Scheme 63

The macrocycle **(7A)** proved to be unstable at room temperature for any length of time, which we felt was a major factor in the low to moderate yields obtained in the cyclisation. It was hoped that the racemic alcohol could be oxidised to the ketone to give 14,15-anhydrovirginiamycin M_2 **(6A)**, which had been reported to be relatively more stable at room temperature.[95] Attempts to oxidise this alcohol before cyclisation had only led to decomposition of the precursor **(231)** with no indication of oxidation of the secondary alcohol. Attempts to oxidise the alcohol after cyclisation was hindered

by the instability of the macrocycle and the sheer lack of material on which to work. Oxidants tried included activated manganese dioxide, activated manganese dioxide on carbon, barium manganate, DDQ,[96] and bis(tributyltin)oxide/iodine,[97] all of which gave none of the desired ketone **(6A)**. **Scheme 64.**



Reagents:- Dess Martin periodinane, CH_2Cl_2.

Scheme B59

However oxidation was finally achieved using Dess-Martin's periodinane in dry CH_2Cl_2, to give 14,15-anhydrovirginiamycin M_2 **(6)** in 60% yield.[98] Verification that virginiamycin **(6)** had been synthesised was obtained by comparison of the ^1H and ^{13}C nmr spectra of a sample of natural 14,15-anhydrovirginiamycin M_2 with our synthetic sample.[99] Further confirmation that the intramolecular Stille cyclisation had taken place was gained by reduction of the natural 14,15-anhydrovirginiamycin M_2 to a

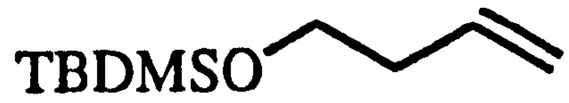
product identical to the synthetic 14,15-anhydro-16,37-dihydrovirginiamycin M_2 (7) in all respects except diastereoisomeric ratio.

The total synthesis of two members of the virginiamycin family, albeit if in a mixture of diastereoisomers in the case of (7), along with the model studies have shown the importance of the Stille reaction in the synthesis of polyunsaturated macrolide ring systems. The reaction's tolerance to a wide range of functional groups and the retention of alkene geometry in the product adds further credence to the versatility of the Stille reaction within natural product synthesis.

3. EXPERIMENTAL

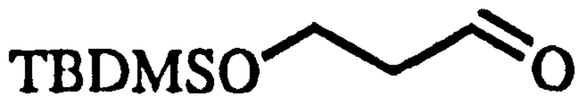
General Details - Melting point determinations were made on a Reichert Kofler micro hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1720 or 1600 Series FT-IR and were calibrated using a standard polystyrene film; the spectra were recorded as thin films. UV spectra were recorded as solutions in spectroscopic grade ethanol using a Philips PU 8720 or a Perkin-Elmer Lambda 16 spectrophotometer. Specific rotations were measured at 25°C in chloroform on a Jasco DIP-370 polarimeter. Unless stated otherwise, solutions in deuteriochloroform were used for the determination of NMR spectra. Shifts are expressed in ppm downfield from Me_4Si as internal standard. The ^1H and ^{13}C nmr spectra were recorded on a 250 MHz Bruker WM250, 270 MHz Jeol EX-270, 400 MHz Bruker AM400, or a 500 MHz Bruker DRX500 instrument. Signals were singlets unless specified otherwise: *i.e.* d = doublet, t = triplet, q = quartet, quint. = quintet, sext = sextet, sept = septet, oct = octet, m = multiplet, br = broad and combinations thereof. Assignments in the ^1H spectra were consistent with signal intensities, and in the ^{13}C spectra with the results of the DEPT pulse sequence. Assignments were supported by 2D H-H and H-C COSY experiments where necessary. Mass spectra were recorded on an VG Autospec or a MM-701CF instrument, using electron impact ionisation at 70 eV unless stated otherwise. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser. Flash chromatography was performed using Merck silica gel 60, and all solvents were redistilled before use. Light petroleum refers to the fraction b.p. 40-60 °C. All reactions were monitored by TLC using Merck silica gel 60 F254 precoated aluminium plates. Organic extracts were dried over anhydrous magnesium sulfate prior to removal using a Büchi rotary evaporator.

***4-(tert-Butyldimethylsilyloxy)butene* (145).[100]**



3-Butenol (17.20 cm^3, 0.2 mol) was added dropwise, over 30 min, to a stirred solution of t-butyldimethylchlorosilane (33.16 g, 0.22 mol) and imidazole (14.98 g, 0.22 mol) in dry DMF (100 cm^3) at 0°C, and the mixture was then stirred overnight while allowing it to warm to room temperature. Water (500 cm^3) was added and the mixture was then extracted with ether (3 x 200 cm^3). The extracts were combined and washed with water (200 cm^3) and the dried solution ($MgSO_4$) was concentrated *in vacuo* to leave the crude *silyl ether* (37 g, 98%) as a colourless oil; $\nu_{max}(cm^{-1})$: 1674 (C=C) and 835 (Si-O); δ_H (250 MHz $CDCl_3$): 5.82 (m, 1 H, $CH_2C\underline{H}:CH_2$), 5.08 (m, 2 H, $CH:C\underline{H_2}$), 3.67 (t, *J* 6.8 Hz, $OC\underline{H_2}CH_2$), 2.28 (q, *J* 6.8 Hz, $OCH_2C\underline{H_2}$), 0.90 ($OSiC(C\underline{H_3})_3$) and 0.06 ($OSi(C\underline{H_3})_2$); δ_C (68.7 MHz $CDCl_3$): 135.4 (d), 116.3 (t), 62.8 (t), 37.5 (t), 25.7 (q), 18.4 (s) and -5.3 (q); *m/z* (EI): 171 (10%, M^+-CH_3), 115 (20, $TBDMS^+$), 89 (60), 75 (95), 73 (100) and 57 (20, ^tBu).

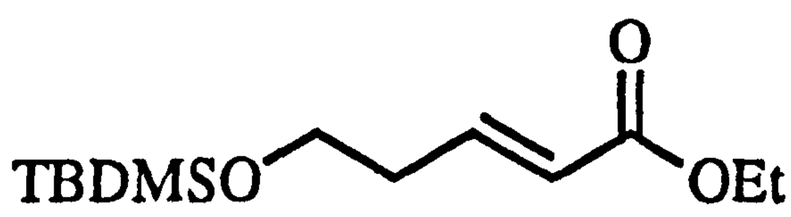
***3-(tert-Butyldimethylsilyloxy)propanal* (146).[101]**



Ozone was bubbled through a solution of the silyl ether **(145)** (50 g, 0.2688 mol) in dry CH_2Cl_2 (500 cm^3) at -78°C under an atmosphere of nitrogen. Once the mixture had turned blue, oxygen was bubbled through the mixture until the blue colouration had disappeared indicating the removal of the excess ozone. Triphenylphosphine (70.49 g, 0.2688 mol) was added in one portion and the mixture was stirred for 1 h while allowing it to warm to room temperature. The solvent was removed *in vacuo* and the residue was stirred with pentane (500 cm^3) for 30 min. The solid precipitate was

filtered off and washed with pentane, and the filtrate was then concentrated *in vacuo*. The residue was stirred with pentane (500 cm^3) once more and the precipitate filtered off. The filtrate was concentrated *in vacuo* to give the crude *aldehyde* (68 g) as a colourless oil. The aldehyde was carried through crude without further purification; $\nu_{max}(cm^{-1})$: 1723 (aldehyde C=O) and 835 (Si-O); δ_H (400 MHz $CDCl_3$): 9.81 (t, *J* 2.5 Hz, C<u>H</u>O), 4.00 (t, *J* 7.0 Hz, SiOC<u>H</u>$_2$), 2.62 (dt, *J* 2.5 and 7.0 Hz, C<u>H</u>$_2$CHO), 0.92 (SiC(C<u>H</u>$_3$)$_3$) and 0.11 (Si(C<u>H</u>$_3$)$_2$); δ_C (100 MHz $CDCl_3$): 202.3 (d), 57.8 (t), 46.9 (t), 26.2 (q), 18.6 (s) and -5.1 (q).

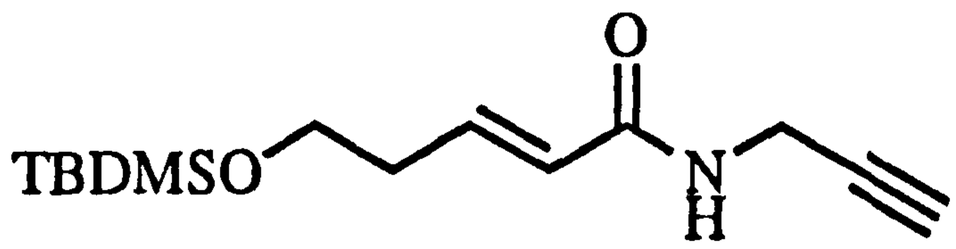
***(E)-Ethyl 5-(tert-butyldimethylsilyloxy)-2-pentenoate* (147).**



Triethyl phosphonoacetate (19.84 cm^3, 100 mmol) was added dropwise, over 30 mim, to a stirred suspension of potassium *t*-butoxide (11.22 g, 100 mmol) in dry THF (200 cm^3) at 0°C under an atmosphere of nitrogen and the mixture stirred at 0°C for 30 min. The mixture was then cooled to -78°C and the aldehyde **(146)** (18.8 g, 100 mmol) was added dropwise, over 20 min. The mixture was stirred overnight while allowing it to warm to room temperature. Water (25 cm^3) was added and the mixture was extracted with ethyl acetate (3 x 50 cm^3), and the extracts were then combined and washed with brine. The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was purified using flash chromatography (10% Et_2O in petroleum ether) to give the *ester* (20.7 g, 80%) as a colourless oil; (Found: C, 60.6; H, 10.4%; M^+, 258.1678. $C_{13}H_{26}O_3Si$ requires C, 60.4; H, 10.1%; M^+, 258.1651); $\nu_{max}(cm^{-1})$: 1724 (C=O), 1656 (C=C), 981 (*trans*-C=C-H), 837 and 777 (Si-O); λ_{max} (EtOH)/nm (ε) 210 (16 409); δ_H (400 MHz $CDCl_3$): 6.95 (dt, *J* 15.7 and 7.1 Hz, COCH:C<u>H</u>), 5.87 (dt, *J* 15.7 and 1.6 Hz, COC<u>H</u>:), 4.2 (q, *J* 7.1 Hz, $CH_3C\underline{H}_2O$), 3.73 (t, *J* 7.1 Hz,

SiOC$\underline{H}_2$), 2.43 (app dq, *J* 1.6 and 7.1 Hz, $CH_2C\underline{H}_2CH$:), 1.29 (t, *J* 7.1 Hz, $C\underline{H}_3CH_2O$), 0.89 ($SiC(C\underline{H}_3)_3$) and 0.06 ($Si(C\underline{H}_3)_2$); δ_C (67.8 MHz $CDCl_3$): 166.7 (s), 146.1 (d), 123.2 (d), 61.8 (t), 60.4 (t), 36.0 (t), 26.1 (q), 18.6 (s), 14.5 (q) and -5.1 (q); *m/z* (EI): 213 (7%, M^+-OEt), 201 (36, M^+-^{t}Bu), 145 (8), 133 (39), 103 (100) 89 (76) and 73 (57).

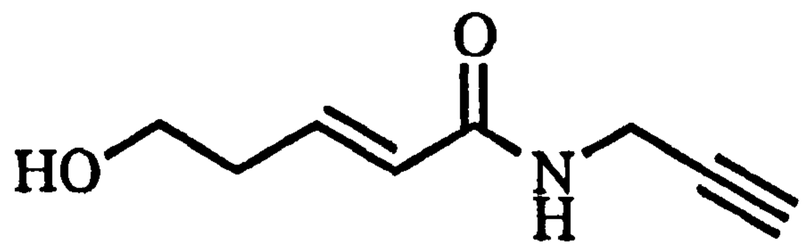
(E)-N-Propargyl-5-(tert-butyldimethylsilyloxy)-2-pentenamide **(148).**



Trimethylaluminium 2*M* in CH_2Cl_2 (33.42 cm^3, 67.83 mmol) was added dropwise, over 20 min, to a stirred solution of propargylamine (4.65 cm^3, 67.83 mmol) in dry CH_2Cl_2 (200 cm^3) at 0°C under an atmosphere of nitrogen in a scrupulously dried flask, and the mixture was then stirred for 30 min while allowing it to warm to room temperature. The mixture was heated to reflux and the ester **(147)** (10 g, 38.76 mmol) was added in one portion. The mixture was heated under reflux for 2 h, then cooled to 0°C, and quenched cautiuosly with 1*M* HCl until no further reaction occurred. The mixture was diluted with water (50 cm^3) and then extracted with CH_2Cl_2 (3 x 100 cm^3). The extracts were combined and washed with brine. The dried solution ($MgSO_4$) was evaporated *in vacuo* and the residue was purified using flash chromatography (CH_2Cl_2) to give the *amide* (9.1 g, 88%) as a colourless oil; ν_{max}(cm^{-1}): 3310 (N-H), 1672 (amide C=O), 1632 (C=C), 1538 (amide dimer), 978 (trans C=C-H), 837 and 779 (Si-O); λ_{max} (EtOH)/nm (ε) 217 (38 016); δ_H (400 MHz $CDCl_3$): 6.85 (dt, *J* 15.3 and 7.1 Hz, COCH:C$\underline{H}$), 5.85 (dt, *J* 15.3 and 1.6 Hz, COC$\underline{H}$), 5.63 (CON$\underline{H}$), 4.12 (dd, *J* 2.5 and 5.3 Hz, $CC\underline{H}_2NH$), 3.71 (t, *J* 6.9 Hz, :$CHCH_2C\underline{H}_2O$), 2.41 (app dq, *J* 1.6 and 6.9 Hz, :$CHC\underline{H}_2$), 2.24 (t, *J* 2.5 Hz, $\underline{H}CCCH_2$), 0.89 ($SiC(C\underline{H}_3)_3$) and 0.05 ($Si(C\underline{H}_3)_2$); δ_C (67.8 MHz $CDCl_3$): 165.6 (s),

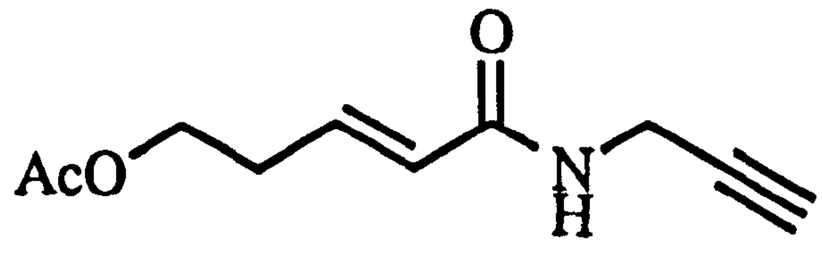
141.7 (d), 124.7 (d), 79.6 (d), 71.3 (s), 61.6 (t), 35.5 (t), 29.0 (t), 25.8 (q), 18.1 (s) and -5.4 (q); *m/z* (FAB): 268 (38%, MH^+), 252 (10, M^+-Me), 210 (38, M^+-^{t}Bu), 155 (38), 136 (6, M^+-OTBDMS), 115 (6, TBDMS$^+$) and 73 (100).

(E)-N-Propargyl-5-hydroxypent-2-enamide **(149).**



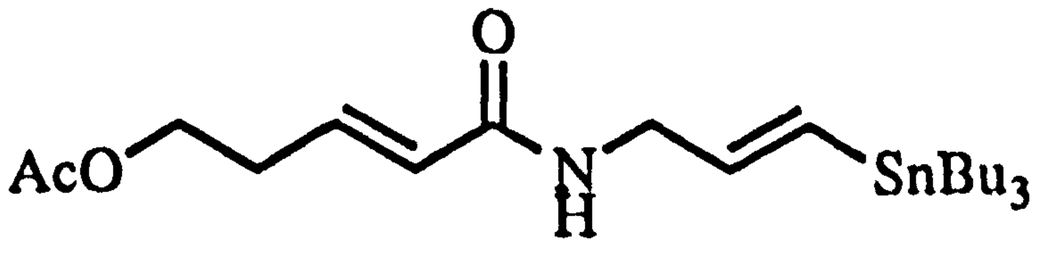
p-Toluenesulphonic acid (1.4 g, 7.31 mmol) was added, in one portion, to a stirred solution of the amide **(148)** (9.76 g, 36.53 mmol) in a mixture of CH_2Cl_2 (92 cm^3) and MeOH (8 cm^3) and the mixture was then stirred overnight at room temperature. The mixture was washed with brine (5 cm^3) and the dried solution ($MgSO_4$) was then concentrated *in vacuo*. The residue was purified using flash chromatography (5% MeOH in CH_2Cl_2) to give the *hydroxyamide* (4.2 g, 75%) as a white solid m.p. 84-85°C (CH_2Cl_2); (Found: C, 62.4; H, 7.4; N, 9.4%; M^+, 153.0788. $C_8H_{11}NO_2$ requires C, 62.7; H, 7.2; N, 9.2%; M^+, 153.0790); ν_{max}(cm^{-1}): 3287 (O-H), 1667 (amide C=O), 1632 (C=C), 1538 (amide dimer) and 983 (*trans* C=C-H); λ_{max} (EtOH)/nm (ε): 216 (18 850); δ_H (400 MHz $CDCl_3$): 6.87 (dt, *J* 15.3 and 7.1 Hz, COCH:C<u>H</u>), 5.90 (dt, *J* 15.3 and 1.4 Hz, COC<u>H</u>:), 5.81 (N<u>H</u>), 4.13 (dd, *J* 2.5 and 5.3 Hz, NHC<u>H</u>$_2$CCH), 3.77 (t, *J* 6.9 Hz, C<u>H</u>$_2$OH), 2.46 (app dq, *J* 1.4 and 6.9 Hz, :CHC<u>H</u>$_2$), 2.26 (t, *J* 2.5 Hz, CH$_2$CC<u>H</u>) and 1.76 (O<u>H</u>); δ_C (67.8 MHz $CDCl_3$): 168.1 (s), 143.0 (d), 125.8 (d), 80.5 (d), 72.2 (s), 61.5 (t), 36.2 (t) and 29.5 (t); *m/z* (EI): 153 (15%, M^+), 135 (13, M^+-H_2O), 122 (70), 108 (95), 99 (96), 96 (30, M^+-propargylamine), 81 (45), 69 (95), 55 (90, propargylamine), 43 (50) and 41 (100).

(E)-N-Propargyl-5-acetoxypent-2-enamide **(150).**



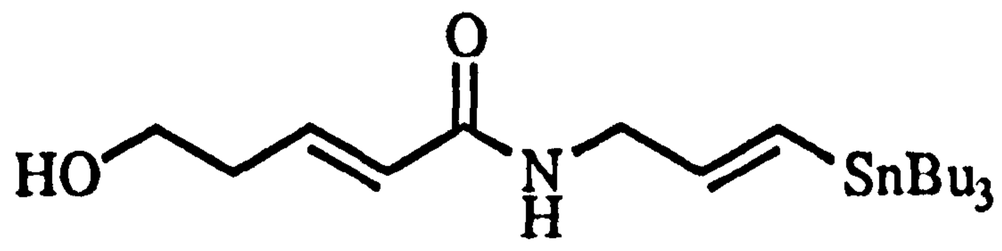
Acetic anhydride (6.8 cm^3, 71.81 mmol) was added dropwise, over 10 min, to a stirred solution of the amide **(149)** (5 g, 32.64 mmol) and pyridine (5.8 cm^3, 71.81 mmol) in dry CH_2Cl_2 (300 cm^3) at 0°C. DMAP (20 mg) was added and the mixture was stirred overnight while allowing it to warm to room temperature. The mixture was washed with 1*M* HCl (50 cm^3), then washed with saturated Na_2CO_3 (50 cm^3), and finally washed with brine (50ml). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was purified using flash chromatography (3% MeOH in CH_2Cl_2) to give the *amide* (5.1 g, 80%) as a colourless oil; (Found: C, 54.4; H, 8.7; N, 2.7%, $C_{10}H_{13}NO_3$ requires C, 54.3; H, 8.3; N, 2.9%); $\nu_{max}(cm^{-1})$: 3287 (N-H), 1732 (ester C=O), 1674 (amide C=O), 1633 (C=C), 1538 (amide dimer) and 974 (*trans* C=C-H); δ_H (400 MHz $CDCl_3$): 6.85 (dt, *J* 15.4 and 6.9 Hz, COCH:C<u>H</u>), 5.86 (dt, *J* 15.4 and 1.5 Hz, COC<u>H</u>:), 5.70 (N<u>H</u>), 4.18 (t, *J* 6.9 Hz, AcOC<u>H</u>$_2$), 4.14 (dd, *J* 2.6 and 5.3 Hz, NHC<u>H</u>$_2$CCH), 2.53 (app dq, *J* 1.5 and 6.9 Hz, :CHC<u>H</u>$_2$CH$_2$), 2.25 (t, *J* 2.6 Hz, CH_2CC<u>H</u>) and 2.06 (OC<u>H</u>$_3$); δ_C (67.8 MHz $CDCl_3$): 170.8 (s), 165.3 (s), 139.9 (d), 125.1 (d), 79.4 (d), 71.1 (s), 62.4 (t), 30.9 (t), 28.8 (t) and 20.8 (q).

(E,E)-N-(3-tri-n-Butylstannyl)prop-2-enyl-5-acetoxypent-2-enamide **(151).**



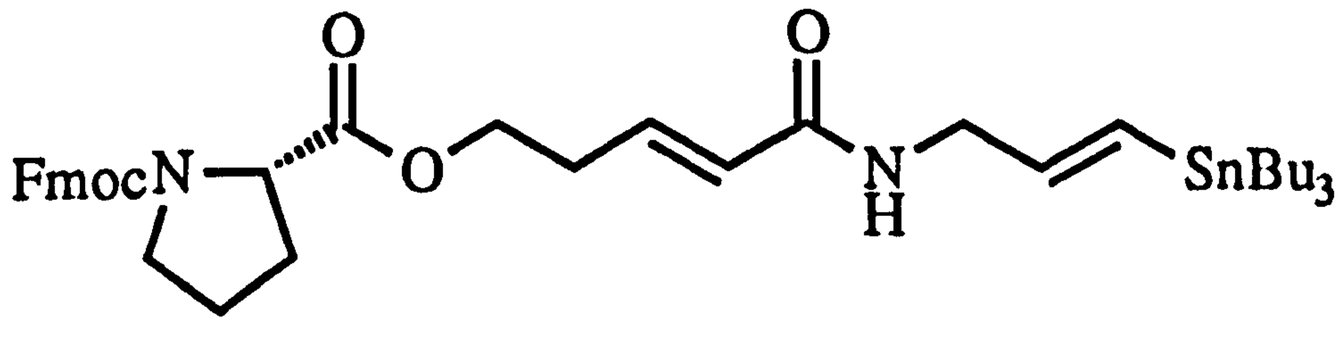
Copper (I) cyanide (1.65 g, 18.44 mmol) was suspended in dry THF (150 cm^3) under an atmosphere of nitrogen in a scrupulously dried flask. The mixture was cooled to -78°C and *n*-butyllithium 1.6*M* in hexanes (24.2 cm^3, 38.75 mmol) was added dropwise, over 15 min, and the mixture was then stirred at -78°C for 15 min. Tri-*n*-butyltin hydride (10.41 cm^3, 38.75 mmol) was added dropwise, over 10 min, and the mixture was then stirred for a further 15 min at -78°C. A solution of the amide (150) (3.6 g, 18.44 mmol) in dry THF (5 cm^3) was added dropwise, over 5 min, and the mixture was then stirred for 30 min at -78°C before being quenched with 10% NH_3/NH_4Cl solution (5 cm^3). The mixture was allowed to warm to room temperature and the solids were filtered off. The filtrate was extracted with ethyl acetate (3 x 50 cm^3) and the extracts were combined. The dried solution ($MgSO_4$) was concentrated *in vacuo* and the was residue purified using flash chromatography (10% ethyl acetate in petroleum ether) to give the *vinyl stannane* (5.6 g, 70%) as a colourless oil; (Found MH^+(FAB) 488.2182, $C_{22}H_{41}NO_3Sn$ requires MH^+ 488.2186); $\nu_{max}(cm^{-1})$: 3277 (N-H), 1742 (ester C=O), 1671 (amide C=O), 1630 (C=C), 1547 (amide dimer) and 983 (*trans* C=C-H); λ_{max} (EtOH)/nm (ε): 208 (64 092), 213 (69 538) and 216 (71 609); δ_H (400 MHz $CDCl_3$): 6.83 (dt, *J* 15.3 and 6.7 Hz, COCH:C<u>H</u>), 6.13 (dt, *J* 19 and 1.2 Hz, SnC<u>H</u>:), 5.96 (dt, *J* 19 and 5.3 Hz, SnCH:C<u>H</u>). 5.89 (dt, *J* 15.3 and 1.5 Hz, COC<u>H</u>:), 5.57 (N<u>H</u>), 4.17 (t, *J* 6.7 Hz, AcOC<u>H_2</u>), 4.01 (app dt, *J* 1.1 and 5.3 Hz, NHC<u>H_2</u>CH:), 2.52 (app dq, *J* 1.5 and 6.7 Hz, :CHC<u>H_2</u>CH_2), 2.05 (OC<u>H_3</u>), 1.48 (pent, *J* 7.1 Hz, $SnCH_2C\underline{H_2}CH_2$), 1.31 (hext, *J* 7.1, $SnCH_2CH_2C\underline{H_2}CH_3$) and 0.88 (t, *J* 7.1 Hz, $SnC\underline{H_2}CH_2CH_2CH_3$); δ_C (67.8 MHz $CDCl_3$): 170.8 (s), 165.0 (s), 143.2 (d), 139.2 (d), 129.8 (d), 125.7 (d), 62.5 (t), 44.7 (t), 31.0 (t), 29.0 (t), 27.4 (t), 20.6 (q), 13.5 (q) and 9.2 (t); *m/z* (FAB): 488 (20%, MH^+), 430 (100, M^+-Bu), 291 (20, Bu_3SnH), 177 (100), 99 (60, M^+-$HNCH_2CH$:$CHSnBu_3$) and 55 (16, propargylamine).

***(E,E)-N-(3-tri-n-Butylstannylprop-2-enyl)-5-hydroxypent-2-enamide* (132).**



Potassium carbonate (1.07 g, 7.1 mmol) was added, in one portion, to a stirred solution of the acetoxyamide **(151)** (3.43 g, 7.06 mmol) in wet methanol (30 cm^3) at 0°C and the mixture was then stirred for 1 h at room temperature. Brine (30 cm^3) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 cm^3). The extracts were combined and the dried solution ($MgSO_4$) was concentrated in vacuo to leave the *hydroxyamide* (3.2 g, 98%) as a colourless oil; (Found:MH^+, 446.2140. $C_{20}H_{40}NO_2Sn$ requires MH^+, 446.2090); $\nu_{max}(cm^{-1})$: 3290 (N-H, O-H), 1670 (amide C=O), 1633 (C=C) and 1540 (amide dimer); λ_{max} (EtOH)/nm (ε): 202 (85 688) and 214 (112 119); δ_H (270 MHz $CDCl_3$): 6.85 (dt, *J* 15.5 and 6.9 Hz, COCH:C<u>H</u>), 6.11 (dt, *J* 18.8 and 1.3 Hz, SnC<u>H</u>:CH), 5.96 (dt, *J* 18.8 and 9.9 Hz, SnCH:C<u>H</u>), 5.92 (dt, *J* 15.5 and 1.3 Hz, COC<u>H</u>:CH), 5.52 (N<u>H</u>CO), 4.00 (dt, *J* 1.3 and 6.9 Hz, C<u>H</u>$_2$OH), 3.77 (app q, *J* 6.0 Hz, NHC<u>H</u>$_2$CH:), 2.47 (app dq, *J* 1.3 and 6.9 Hz, COCH:CHC<u>H</u>$_2$), 1.50 (pent, *J* 6.9 Hz, SnCH$_2$C<u>H</u>$_2$), 1.30 (hext, *J* 6.9 Hz, SnCH$_2$CH$_2$C<u>H</u>$_2$) and 0.89 (t, *J* 6.9 Hz, SnC<u>H</u>$_2$CH$_2$CH$_2$C<u>H</u>$_3$); δ_C (67.8 MHz $CDCl_3$): 165.7 (s), 143.2 (d), 141.1 (d), 130.1 (d), 125.6 (d), 60.7 (t), 44.8 (t), 35.2 (t), 28.9 (t), 27.2 (t), 13.6 (q) and 9.3 (t); *m/z* (FAB): 446 (15%, MH^+), 388 (30, M^+-Bu), 291 (10, Bu_3SnH), 274 (15), 235 (25) and 177 (100).

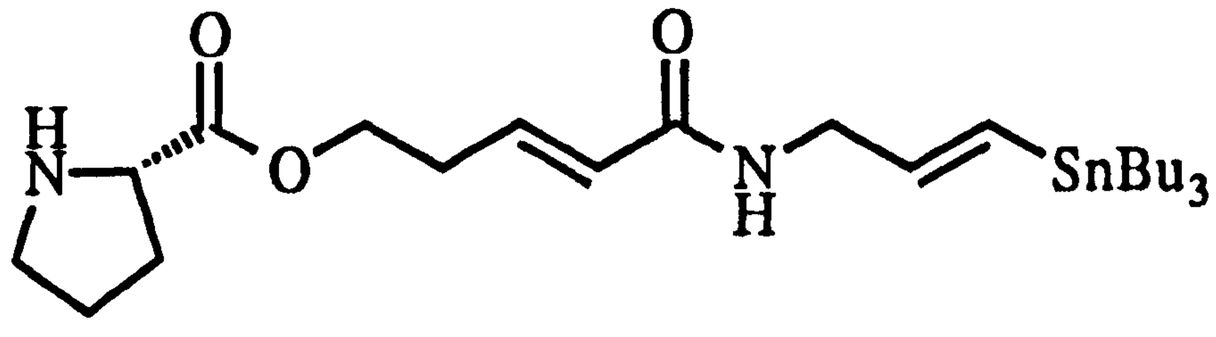
***(-)-(E,E)-N-(3-tri-n-Butylstannylprop-2-enyl)-5-(N-(9-fluorenyl-methoxy carbonyl)-(S)-prolinoyloxypent-2-enamide* (216).**



DCC (1.43 g, 6.93 mmol) was added, in one portion, to a suspension of N-Fmoc-*L*-proline (4.67 g, 13.85 mmol) (from Novo Biochem) in dry CH_2Cl_2 (50 cm^3) at 0°C under an atmosphere of nitrogen. The mixture was stirred at this temperature for 30 min and the hydroxyamide **(132)** (2.05 g, 4.62 mmol) and DMAP (0.69 g, 4.7 mmol) were then added in one portion. The mixture was stirred for 3 h and the solid precipitate was then filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified using flash chromatography (5% MeOH in CH_2Cl_2) to give the *proline ester* (3.7 g, 90%) as a colourless sticky solid as a mixture of rotamers; (Found: C, 62.6; H, 7.4; N, 3.5%. $C_{40}H_{56}N_2O_5Sn$ requires C, 62.9; H, 7.4; N, 3.7%); $[\alpha]_D$ -6.10 (*c* 1.405 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3306 (N-H), 1741 (ester C=O), 1701 (amide C=O), 1631 (C=C), 1536 (amide dimer), 987 (*trans*-C=C-H), 739 and 702 (aromatic C-H); δ_H (400 MHz $CDCl_3$): 7.75 (t, *J* 7.2 Hz, 2 H, aromatic C<u>H</u>), 7.61 (t, *J* 7.2 Hz, 2 H, aromatic C<u>H</u>), 7.40 (t, *J* 7.2 Hz, 2 H, aromatic C<u>H</u>), 7.31 (t, *J* 7.2 Hz, 2 H, aromatic C<u>H</u>), 6.82 (m, 1 H, COCH:C<u>H</u>), 6.12 (dt, *J* 18.5 and 1.2 Hz, SnC<u>H</u>:), 5.95 (dt, *J* 18.5 and 5.4 Hz, SnCH:C<u>H</u>), 5.87 (dt, *J* 15.3 and 1.2 Hz, COC<u>H</u>), 5.69 (m, 1 H, N<u>H</u>), 4.40 (m, 2 H, OCH_2CH), 4.30 (m, 1 H, O_2CCHN), 4.20 (m, 3 H, OCH_2CH and OCH_2CH_2), 3.99 (t, *J* 5.4 Hz, $NHCH_2CH$:), 3.50-3.65 (m, 2 H, $CONCH_2$), 2.52 (app q, *J* 6.6 Hz, OCH_2CH_2), 1.80-2.20 (m, 4 H, $COCHCH_2$ and $CONCH_2CH_2$), 1.46 (pent *J* 6.6 Hz, $SnCH_2CH_2$), 1.29 (hext, *J* 6.6 Hz, $SnCH_2CH_2CH_2$) and 0.89 (t, *J* 6.6 Hz, $SnCH_2CH_2CH_2CH_3$); δ_C (67.8 MHz $CDCl_3$): 172.8 (s), 172.6 (s), 165.8 (s), 165.4 (s), 155.1 (s), 154.8 (s), 144.3 (d), 144.2 (d), 141.5 (s), 139.1 (d), 138.7 (d), 130.0 (d), 129.7 (d), 128.0 (d), 127.4 (d), 126.6 (d),

126.5 (d), 125.4 (d), 125.3 (d), 120.3 (d), 67.8 (t), 67.7 (t), 63.3 (t), 60.6 (t), 59.5 (t), 59.2 (t), 47.5 (d), 47.4 (d), 47.2 (t), 46.8 (t), 45.1 (t), 45.0 (t), 31.3 (t), 31.0 (t), 29.3 (t), 27.5 (t), 24.7 (t), 23.6 (t), 14.0 (q) and 9.7 (t); *m/z* (FAB): 714 (100%), 656 (10), 544 (15), 426 (10), 368 (10), 291 (10, Bu_3SnH), 254 (10), 235 (35), 179 (75), 133 (15), 91 (10) and 73 (20).

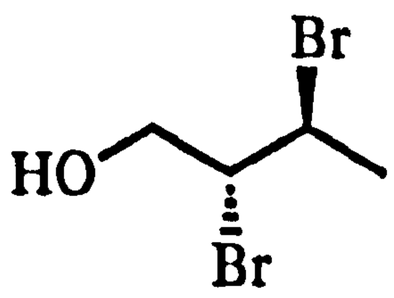
(-)-(E,E)-N-(3-Tri-n-butylstannylprop-2-enyl-)5-(S)-prolinoyloxypent-2-enamide **(217).**



The Fmoc-proline ester **(216)** (1 g, 1.13 mmol) was added, in one portion, to a solution of piperidine (0.4 cm^3, 4.5 mmol) in acetonitrile (4 cm^3) and the solution was then stirred at room temperature for 30 min. The mixture was concentrated *in vacuo* and the residue was then purified using flash chromatography (5% MeOH in ethyl acetate) to give the *proline ester* (560 mg, 90%) as a colourless oil; (Found: C, 55.3; H, 8.85; N, 4.85%. $C_8H_{11}NO_2$ requires C, 55.5; H, 8.6; N, 5.2%); $[\alpha]_D$ -9.20 (*c* 1.96 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3286 (N-H), 1731 (ester C=O), 1673 (amide C=O), 1633 (C=C), 1555 (amide dimer) and 983 (*trans* C=C-H); λ_{max} (EtOH)/nm (ε): 207 (63 841) and 216 (70 148); δ_H (400 MHz $CDCl_3$): 6.82 (dt, *J* 15.4 and 6.6 Hz, COCH:C<u>H</u>), 6.10 (dt, *J* 19 and 1.3 Hz, SnC<u>H</u>:CH), 5.96 (dt, *J* 19 and 5.4 Hz, SnCH:C<u>H</u>), 5.87 (dt, *J* 15.4 and 1.3 Hz, COC<u>H</u>:CH), 5.71 (N<u>H</u>CO), 4.22 (t, *J* 6.6 Hz, $CO_2C\underline{H}_2$), 3.98 (app t, *J* 5.4 Hz, NHC<u>H</u>$_2$CH:), 3.73 (dd, *J* 5.5 and 8.2 Hz, HNC<u>H</u>CO_2), 3.05 (dt, *J* 6.4 and 10.0 Hz, HNC<u>H</u>HCH_2), 2.88 (dt, *J* 6.4 and 10.0 Hz, HNCH<u>H</u>CH_2), 2.53 (app q, *J* 6.6 Hz,OCH$_2$C<u>H</u>$_2$CH:), 2.18 (CH_2N<u>H</u>CH), 2.10 (app dq, *J* 8.2 and 12.6 Hz, HNCHC<u>H</u>H), 1.80 (app dq, *J* 8.2 and 12.6 Hz, HNCHC<u>H</u>H), 1.74 (m, 2H,

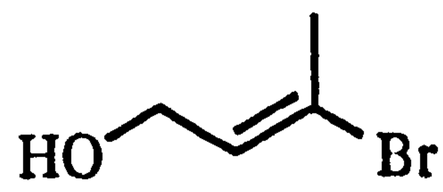
$HNCH_2C\underline{H}_2$), 1.47 (pent, *J* 6.6 Hz, $SnCH_2C\underline{H}_2$), 1.29 (hext, *J* 6.6 Hz, $SnCH_2CH_2C\underline{H}_2$) and 0.88 (t, *J* 6.6 Hz, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); δ_C (67.8 MHz $CDCl_3$): 174.9 (s), 164.7 (s), 143.3 (d), 138.6 (d), 129.5 (d), 125.8 (d), 62.7 (t), 59.3 (d), 46.7 (t), 44.6 (t), 30.9 (t), 30.0 (t), 28.7 (t), 26.9 (t), 25.2 (t), 13.4 (q), and 9.1 (t); *m/z* (FAB): 525 (20%), 469 (10), 432 (20), 376 (95), 347 (10), 283 (15), 266 (25), 229 (45), 172 (100), 134 (15), 118 (25), 97 (55) and 69 (45).

erythro-2,3-Dibromobutanol **(189).**[80]



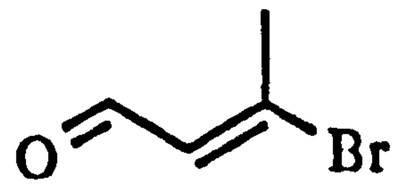
A solution of bromine (60 cm^3, 1.16 mol) in carbon tetrachloride (50 cm^3) was added dropwise, over 2 h, to a stirred solution of *E*crotyl alcohol (80 g, 1.11 mol) in carbon tetrachloride (500 cm^3) at -20°C under an atmosphere of nitrogen The mixture was stirred for an additional 2 h at -20°C and then allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue was distilled to give the *dibromide* (206 g, 80%) as a low melting colourless solid, m.p.35-36°C, b.p. 119°C @ 18 mmHg (Lit.[80] m.p. 36°C, b.p. 117°C @ 17 mmHg); ν_{max} (cm^3): 3361 (O-H), 1450 (C-H) and 1065 (C-O); δ_H (270 MHz $CDCl_3$): 4.32 (m, $C\underline{H}BrCH_3$), 4.22 (m, $C\underline{H}BrCH_2OH$), 4.05 (t, *J* 2 Hz, $CHBrC\underline{H}_2$) and 1.90 (d, *J* 6.6 Hz, $CHBrC\underline{H}_3$); δc (67.8 MHz $CDCl_3$): 65.8 (t), 61.9 (d), 47.6 (d) and 25.2 (q).

(E)-3-Bromo-2-butenol **(155)[80].**



n-Butyllithuim 1.6*M* in hexanes (103 cm^3, 165.6 mmol) was added slowly to a stirred solution of diisopropylamine (22.4 cm^3, 158.7 mmol) in dry THF (225 cm^3) at -20°C under an atmosphere of nitrogen The mixture was stirred for 15 min at -20°C and then cooled to -78°C. A solution of the dibromide **(189)** (16 g, 69 mmol), in dry THF (25 cm^3), was added dropwise over 2 h while maintaining the temperature at -78°C. The mixture was stirred at -78°C for a further 1 h and then allowed to warm to -50°C before it was quenched with water (50 cm^3). The mixture was allowed to warm room temperature, and then 1*M* HCl (200 cm^3) was added. The mixture was extracted with ethyl acetate (3 x 200 cm^3), and the extracts were then combined and washed with 1*M* HCl (200 cm^3) and brine. The dried solvent ($MgSO_4$) was concentrated *in vacuo* and the residue was purified using flash chromatography (5% Et_2O in CH_2Cl_2) to give the *alcohol* (4.3 g, 43%) as a pale yellow oil; $\nu_{max}(cm^{-1})$: 3329 (O-H) and 1651 (C=C); δ_H (270 MHz $CDCl_3$): 6.11 (dt, *J* 1.3 and 6.9 Hz, $HOCH_2CH$:), 4.13 (t, *J* 6.9 Hz, CH_2OH), 2.31 (CH_3) and 1.38 (t, *J* 6.9, CH_2OH); δ_C (67.8 MHz $CDCl_3$): 130.7 (d), 123.7 (s), 59.1 (t) and 23.4 (q).

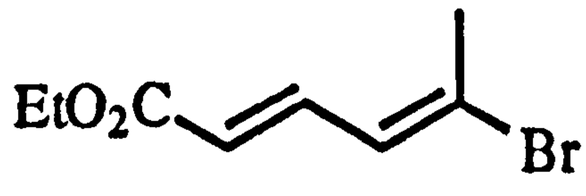
(E)-3-Bromo-2-butenal **(153).**



Activated manganese dioxide (28.8 g, 0.3312 mol) was added carefully, in one portion, to a stirred solution of alcohol **(155)** (5 g, 33.12 mmol) in dry CH_2Cl_2 (150

cm^3) and the mixture was then stirred at room temperature overnight. The mixture was filtered through celite and the solvent was then removed carefully *in vacuo*. The residue was purified using flash chromatography (CH_2Cl_2) to give the *aldehyde* (3.4 g, 70%) as a pale yellow oil (identical to that in ref. 102); ν_{max} (cm^{-1}): 1700 (aldehyde C=O) and 1623 (C=C); λ_{max} (EtOH)/nm (ε) 284 (18 558); δ_H (270 MHz $CDCl_3$): 9.80 (d, *J* 7.5 Hz, CHO), 6.52 (d, *J* 7.5 Hz, CHO:CH) and 2.80 (:CHBrCH$_3$); δ_C (67.8 MHz $CDCl_3$) 186.9 (d), 148.9 (s), 133.3 (d) and 25.0 (q).

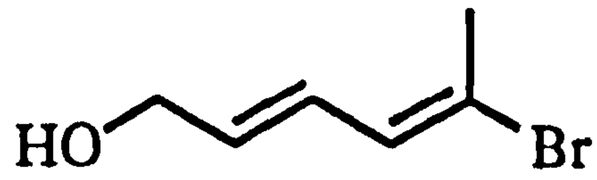
***(E,E)-Ethyl 5-bromohexa-2,4-dienoate* (201).**



Triethyl phosphonoacetate (6.26 cm^3, 31.54 mmol) was added dropwise, over 10 min, to a stirred suspension of potassium *t*-butoxide (3.54 g, 31.54 mmol) in dry THF (100 cm^3) at 0°C under an atmosphere of nitrogen. The mixture was stirred at 0°C for 30 min, then cooled to -78°C when the aldehyde **(153)** (4.7 g, 31.54 mmol) was added dropwise over 10 min. The mixture was stirred at -78°C for 2 h, then water (25 cm^3) was added slowly and the mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 x 50 cm^3) and the extracts were then combined and washed with brine. The dried ($MgSO_4$) extracts were concentrated *in vacuo* and the residue was purified using flash chromatography (10% ethyl acetate in petroleum ether) to give the *ester* (4.6 g, 68%) as a pale yellow oil (Found: C, 43.6; H, 5.2; Br, 36.2%; M^+, 217.9913. $C_8H_{11}BrO_2$ requires C, 43.8; H, 5.1; Br, 36.5%; M^+, 217.9943); ν_{max}(cm^{-1}): 1714 (C=O), 1626 (C=C) and 975 (*trans*-C=C-H); λ_{max} (EtOH)/nm (ε): 272 (35 100); δ_H (400 MHz $CDCl_3$): 7.34 (dd, *J* 11.6 and 15.2 Hz, COCH:CH:CH), 6.60 (d, *J* 11.6 Hz, :CHCBr(CH_3)), 5.82 (d, *J* 15.2 Hz, COCH:CH), 4.22 (q, *J* 7.1 Hz, OCH_2CH$_3$), 2.48 (:CHBr(CH_3)) and 1.30 (t, *J* 7.1

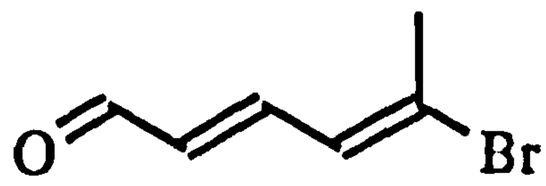
Hz, $C\underline{H}_3CH_2O$); δ_C (67.8 MHz $CDCl_3$): 167.8 (s), 137.9 (d), 132.3 (s), 130.3 (d), 121.5 (d), 60.5 (t), 24.4 (q) and 14.2 (q); *m/z* (EI) 219 (20%, M^+), 173 (29, M^+-OEt), 139 (15, M^+-Br) and 111 (100, M^+-OEt, -Br).

(E,E)-5-Bromo-2,4-hexadienol **(202).**



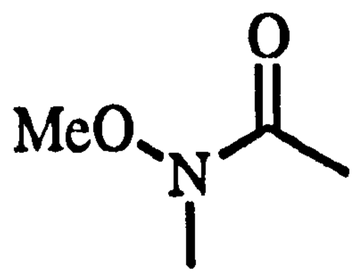
Diisobutylaluminium hydride 1*M* in CH_2Cl_2 (196 cm^3, 195.5 mmol) was added dropwise, over 1 h. to a stirred solution of the ester **(201)** (21 g, 96.77 mmol) in dry CH_2Cl_2 (400 cm^3) at -78°C under an atmosphere of nitrogen, and the mixture was then stirred at -78°C for 1 h. The mixture was allowed to warm to room temperature, and then methanol (20 cm^3) and $MgSO_4$ were added and the mixture was stirred vigorously until the aluminium salts had precipitated out. The solid precipitates were filtered off (celite) and washed repeatedly with CH_2Cl_2. The filtrate and washings were combined and concentrated *in vacuo* to leave the *alcohol* (17g, 98%) as a colourless oil; (Found: M^+ 175.9834. C_6H_9BrO requires M^+ 175.9837); $\nu_{max}(cm^{-1})$: 3382 (O-H), 1652 (C=C) and 965 (*trans* -C=C-H); λ_{max} (EtOH)/nm (ε): 239 (5621); δ_H (250 MHz $CDCl_3$): 6.49 (dd, *J* 1.2 and 14.9 Hz, $C\underline{H}$:C(CH_3)Br), 6.31 (tt, *J* 1.2 and 14.9 Hz, $HOCH_2CH$:$C\underline{H}$), 5.83 (dt, *J* 14.9 and 5.3 Hz, $HOCH_2C\underline{H}$:), 4.19 (d, *J* 5.3 Hz, $HOC\underline{H}_2CH$:), 2.36 (d, *J* 1.2 Hz, $C\underline{H}_3$) and 1.57 ($O\underline{H}$); δ_C (100 MHz $CDCl_3$):132.7 (d), 131.2 (d), 125.2 (d), 122.9 (s), 62.5 (t) and 23.6 (q); *m/z* (EI): 176 (30%, M^+), 97 (100, M^+-Br) and 43 (95), which was used without further purification.

(E,E)-5-Bromo-2,4-hexadienal **(195).**



Activated manganese dioxide (12.3 g, 141.2 mmol) was carefully added, in one portion, to a stirred solution of the alcohol **(202)** (2.5 g, 14.12 mmol) in dry CH_2Cl_2 (100 cm^3) and the mixture was stirred at room temperature overnight. The mixture was filtered through celite and the solvent was then removed *in vacuo*. The residue was purified using flash chromatography (CH_2Cl_2) to give the *aldehyde* (1.9 g, 80%) as a pale yellow oil; $\nu_{max}(cm^{-1})$: 1684 (aldehyde C=O), 1617 (C=C) and (*trans*-C=C-H); λ_{max} (EtOH)/nm (ε) 284 (18 558); δ_H (270 MHz $CDCl_3$): 9.6 (d, *J* 8.1 Hz, C$\underline{H}$O), 7.20 (dd, *J* 11.6 and 15.0 Hz, C$\underline{H}$:CHCHO), 6.76 (d, *J* 11.6 Hz, C$\underline{H}$:CBr(CH_3)), 6.15 (dd, *J* 15.0 and 8.1 Hz, C:C$\underline{H}$CHO) and 2.54 (C$\underline{H}_3$); δ_C (67.8 MHz $CDCl_3$): 193.2 (d), 144.7 (d), 134.5 (s), 131.3 (d), 130.5 (d) and 24.4 (q).

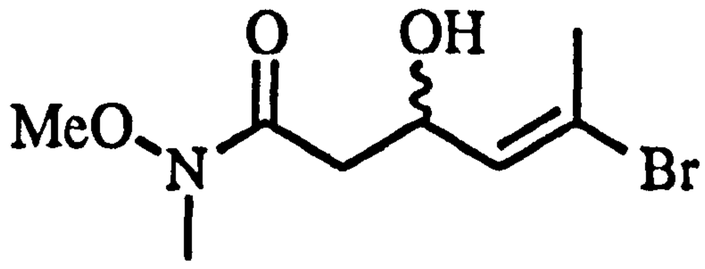
N-Methoxy-N-methylacetamide **(191).**[103]



Acetyl chloride (4 cm^3, 56.34 mmol) was added dropwise, over 10 min, to a stirred solution of N,O-dimethylhydroxylamine hydrochloride **(190)** (5 g, 51.25 mmol) and triethylamine (15 cm^3, 107.6 mmol) in dry CH_2Cl_2 (100 cm^3) at 0°C under an atmosphere of nitrogen. The mixture was stirred overnight and was then washed with 2*M* HCl (50 cm^3), and washed with brine (50 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* to give the *amide* (4.20 g, 80%) as a colourless oil; $\nu_{max}(cm^{-1})$: 1664 (amide C=O); δ_H (400 MHz $CDCl_3$): 3.69 (OC$\underline{H}_3$), 3.18 (NC$\underline{H}_3$) and 2.13

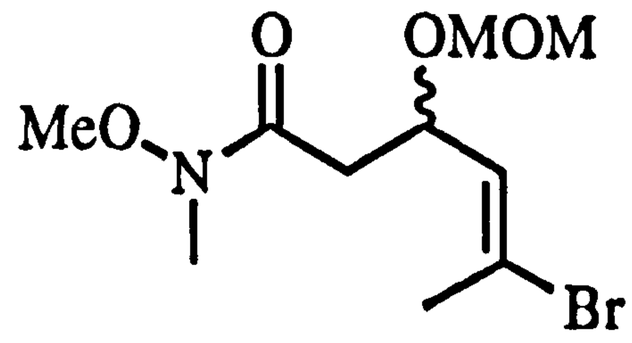
($COCH_3$); δ_C (67.8 MHz $CDCl_3$): 171.6 (s), 60.7 (q), 31.6 (q) and 19.5 (q).

***(+/-)-(E)-N-Methoxy-N-methyl-5-bromo-3-hydroxy-4-hexenamide* (192).**



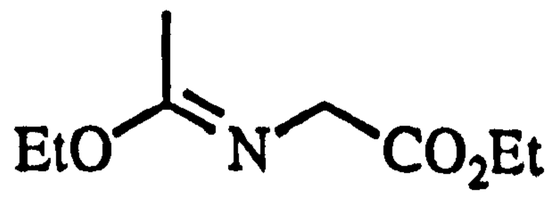
A solution of potassium hexamethyldisilazane 0.5*M* in THF (21 cm^3, 10.50 mmol) was added dropwise, over 30 min, to a stirred solution of the amide (**191**) (1.03g, 10 mmol) in dry THF (100 cm^3) at -78°C under an atmosphere of nitrogen. The mixture was stirred at -78°C for 10 min and then a solution of the aldehyde (**153**) (1.56 g, 10.50 mmol), in dry THF (3 cm^3), was added dropwise over 5 min. The mixture was stirred at -78°C for 1 h and quenched with saturated NH_4Cl solution (5 cm^3). Water (50 cm^3) was added and the mixture was then extracted with ethyl acetate (3 x 50 cm^3). The extracts were combined and washed with brine, and the dried solution ($MgSO_4$) was concentrated *in vacuo*. The residue was purified using flash chromatography (2% MeOH in CH_2Cl_2) to give the *hydroxyamide* (1.4 g, 60%) as an orange oil as a racemic mixture: (Found: C, 40.9; H, 6.0; N, 5.9%. $C_8H_{14}BrNO_3$ requires C, 40.7; H, 6.0; N, 5.9%); $\nu_{max}(cm^{-1})$: 3416 (O-H), 1721 (amide C=O), 1653 (C=C) and 989 (*trans*-C=C-H); δ_H (250 MHz $CDCl_3$): 5.95 (dd, *J* 1.1 and 8.5 Hz, CHOHC<u>H</u>:), 4.72 (dt, *J* 8.5 and 6.0 Hz, $CH_2C\underline{H}OH$), 3.88 (O<u>H</u>), 3.68 ($OC\underline{H}_3$), 3.19 ($NC\underline{H}_3$), 2.64 (d, *J* 6.0 Hz, $COC\underline{H}_2CH$), 2.31 (d, *J* 1.1 Hz, :C($C\underline{H}_3$)Br); δ_C (67.8 MHz $CDCl_3$): 172.8 (s), 133.2 (d), 124.0 (s), 66.0 (d), 61.5 (q), 38.1 (t), 32.1 (q) and 24.2 (q); *m/z* (EI): 254 (100%, M^+), 172 (60, M^+-Br), 154 (40, M^+-Br, -H_2O), 149 (30, aldehyde from retro-aldol), 111 (20), 69 (20), 61 (N,O-dimethyl hydroxylamine), 43 (70).

(+/-)-(E)-N-Methoxy-N-methyl-5-bromo-3-(methoxy)methoxy-4-hexenamide **(193).**



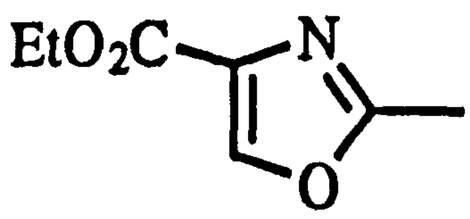
Chloromethyl methyl ether (1.57 ml, 20.7 mmol) was added in four portions, at 30 min intervals, to a solution of the hydroxy-amide **(192)** (580 mg, 2.30 mmol) and diisopropylethylamine (0.8 ml, 4.6 mmol) in dry CH_2Cl_2 (25 ml) which was heated to reflux, under an atmosphere of nitrogen. The mixture was heated for a further 30 min and then allowed to cool to room temperature. The mixture was washed with water (20 ml) and the dried solution ($MgSO_4$) was concentrated *in vacuo*. The residue was purified using flash chromatography (CH_2Cl_2) to give the *amide* (470mg, 70%) as a colourless oil; υ_{max}(cm^{-1}): 1651 (C=O) and 918 (*trans*-C=C-H); δ_H (400 MHz $CDCl_3$): 5.79 (dd, *J* 1.6 and 9.7 Hz, CHORC<u>H</u>:), 4.81 (dt, *J* 5.2 and 9.7 Hz, $CH_2C\underline{H}OR$), 4.52-4.67 (dd, *J* 6.8 and 6.8 Hz, $OC\underline{H}_2OCH_3$), 3.71 ($NOC\underline{H}_3$), 3.36 (OCH_3), 3.19 (NCH_3), 2.89 (dd, *J* 8 and 14.8 Hz, COC<u>H</u>HCHOR), 2.52 (dd, *J* 5.2 and 14.8 Hz, COCH<u>H</u>CHOR), 2.35 (:CBr(CH_3)); δ_C (100 MHz $CDCl_3$): 170.9 (s), 131.3 (d), 125.2 (s), 93.7 (t), 68.8 (d), 61.4 (q), 55.5 (q), 37.6 (t), 32.1 (q), 24.1 (q); m/z EI): 250 (2%), 216 (15, M^+-Br), 154 (7, M^+-Br, -OMOM), 61 (8, $MOMO^+$), 45 (100, MOM^+).

Ethyl 2-((ethoxyethylidene)amino)acetate **(171).**[79]



Ethyl acetimidate hydrochloride **(169)** (50 g, 0.4046 mol) and cold ether (200 cm^3) were placed in a seperating funnel and a slurry of potassium carbonate (66.2 g, 0.48 mol), in cold water (100 cm^3), was added. The mixture was shaken vigorously for 5 min and the organic layer was then removed. The aqueous layer was extracted with ether (200 cm^3) and the organic layers were combined and placed in a clean seperating funnel. A solution of glycine ethyl ester hydrochloride **(170)** (56.4 g, 0.4046 mol), in cold water (100 cm^3), was added to the organic extracts and the mixture was shaken vigorously for 15 min. The organic layer was removed and dried ($MgSO_4$), and the solvent was carefully removed *in vacuo* to give the imino ether (44 g, 63%) as a colourless oil: $\nu_{max}(cm^{-1})$: 1748 (ester C=O) and 1682 (C=N); δ_H (250 MHz $CDCl_3$): 4.16 (q, *J* 7 Hz, $CO_2CH_2CH_3$), 4.08 (q, *J* 7 Hz, $CH_3CH_2OC{:}N$), 4.02 ($:NCH_2CO$), 1.89 (CH_3), 1.22 (t, *J* 7 Hz, $CO_2CH_2CH_3$) and 1.12 (t, *J* 7 Hz, $CH_3CH_2OC{:}N$); δ_C (100 MHz $CDCl_3$): 171.0 (s), 164.7 (s), 80.8 (t), 80.6 (t), 14.1 (q) and 14.0 (q).

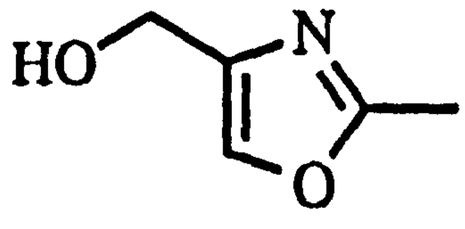
2-Methyloxazole-4-ethylcarboxylate **(173).**[79]



The imino ether **(171)** (100 g, 0.578 mol) was added dropwise, over 30 min, to a suspension of potassium *t*-butoxide (71.3 g, 0.6358 mol) in dry THF (150 cm^3) at -20°C under an atmosphere of nitrogen, and ethyl formate (51.4 cm^3, 0.6358 mol) was added dropwise over 30 min. The mixture was stirred at -20°C for 2 h, then dry ether (300 cm^3) was added, and the mixture was stirred at -20°C for a further 2 h. The mixture was allowed to warm to room temperature and the solvent was then removed *in vacuo*. Hot glacial acetic acid (150 cm^3) was added to the residue, and the mixture was then heated under reflux until all the solids had dissolved. The mixture was cooled in an ice-bath and then basified cautiously with sodium carbonate. The mixture was

diluted with water (150 cm^3) and then extracted with ethyl acetate (3 x 200 cm^3). The organic extracts were combined and washed with brine. The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was purified using flash chromatography (20% ethyl acetate in petroleum ether) to give the oxazole (66 g, 88%) as a colourless oil; $\nu_{max}(cm^{-1})$: 1735 (C=O) and 1592 (cyclic C=N-); δ_H (250 MHz $CDCl_3$): 8.11 (oxazole :C<u>H</u>), 4.35 (q, *J* 7.1 Hz, $CH_3C\underline{H}_2O$), 2.50 ($C\underline{H}_3$) and 1.36 (t, *J* 7.1 Hz, $C\underline{H}_3CH_2O$); δ_C (67.8 MHz $CDCl_3$): 161.5 (s), 160.3 (s), 143.0 (d), 132.6 (s), 60.0 (t), 13.23 (q) and 12.8 (q).

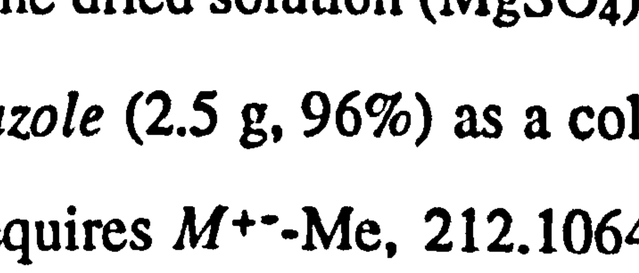
4-Hydroxymethyl-2-methyloxazole **(184).**[29]



A solution of diisobutylaluminium hydride 1.5*M* in hexanes (86 cm^3, 0.1289 mol) was added dropwise, over 1 h, to a stirred solution of the oxazole **(173)** (10 g, 64.45 mmol) in dry CH_2Cl_2 (200 cm^3) at -78°C under an atmosphere of nitrogen and the mixture was then stirred at -78°C for 3 h. The mixture was allowed to warm to room temperature and then methanol (20 cm^3) and $MgSO_4$ were added and the mixture stirred vigorously until the aluminium salts had precipitated out. The solids were filtered off and washed repeatedly with CH_2Cl_2. The filtrate and washings were combined and concentrated *in vacuo* and the residue was purified using flash chromatography (CH_2Cl_2) to give the *alcohol* (4.8g, 60%) as an off white solid, m.p. 52-53°C (ether); (Found: C, 52.8; H, 6.5; N, 12.3%; M^+, 113.0477. $C_5H_7NO_2$ requires C, 53.1; H, 6.2; N, 12.4%; M^+, 113.0477); $\nu_{max}(cm^{-1})$: 3351 (O-H), 1650 (C=C) and 1580 (cyclic C=N); δ_H (250 MHz $CDCl_3$): 7.49 (oxazole :C<u>H</u>), 4.56 (d, *J* 3.8 Hz, $C\underline{H}_2OH$), 2.64 (t, *J* 3.8 Hz, O<u>H</u>) and 2.46 (CH_3); δ_C (67.8 MHz $CDCl_3$): 162.0 (s), 140.2 (s), 134.8 (d), 55.5 (t) and 13.5 (q); *m/z* (EI): 113 (100%, M^+), 112 (99, M^+-H), 96 (16,

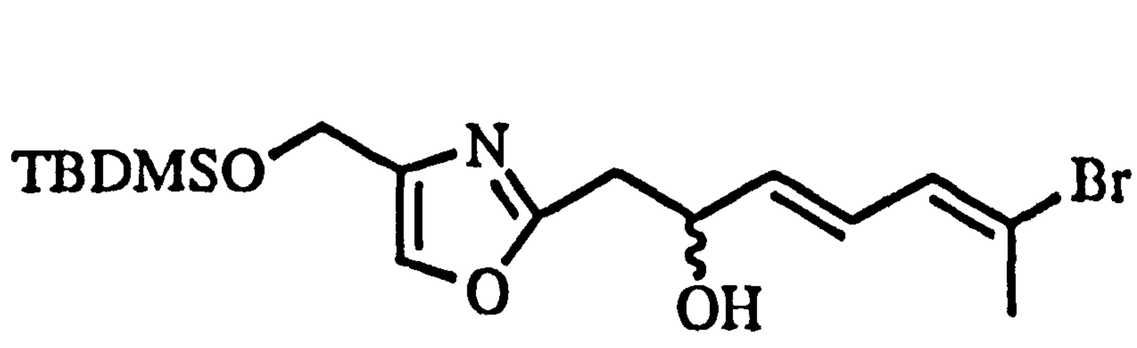
M^+-OH), 84 (71), 82 (7, M^+-CH_2OH), 71 (82), 43 (79) and 42 (98).

4-(tert-Butyldimethylsiloxymethyl)-2-methyloxazole **(185).**



A solution of the oxazole **(184)** (1.2 g, 10.61 mmol), in dry DMF (5 cm^3), was added dropwise, over 10 min, to a stirred solution of imidazole (0.8 g, 11.67 mmol) and chloro-tert-butyldimethylsilane (1.76 g, 11.67 mmol) in dry DMF (15 cm^3), at 0°C, under an atmosphere of nitrogen. The mixture was stirred overnight and then poured into iced water (100 cm^3). The mixture was extracted with ether (3 x 50 cm^3) and the extracts were combined and the dried solution ($MgSO_4$) was concentrated *in vacuo* to give the crude protected *oxazole* (2.5 g, 96%) as a colourless oil; (Found $M^{+\cdot}$-Me, 212.1076. $C_{11}H_{21}NO_2Si$ requires $M^{+\cdot}$-Me, 212.1064); $\nu_{max}(cm^{-1})$: 1582 (cyclic C=N) and 838 and 779 (Si-O); δ_H (270 MHz $CDCl_3$): 7.42 (oxazole :C<u>H</u>), 4.62 (HOC<u>H_2</u>), 2.42 (C<u>H_3</u>), 0.92 (OSi(C(C<u>H_3</u>)$_3$) and 0.11 (OSi(C<u>H_3</u>)$_2$); δ_C (67.8 MHz $CDCl_3$): 161.4 (s), 141.4 (s), 134.6 (d), 58.5 (t), 25.8 (q), 18.3 (s) and -5.5 (q); *m/z* (EI): 212 (15%, $M^{+\cdot}$-Me), 170 (100, $M^{+\cdot}$-^{t}Bu), 96 (70, $M^{+\cdot}$-TBDMSO) and 75 (90).

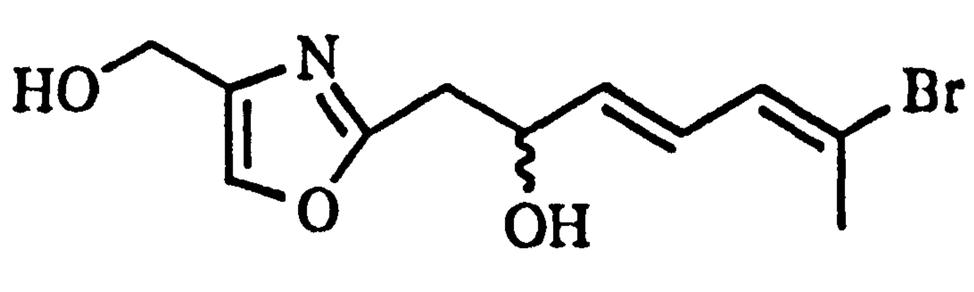
(+/-)-2-((E,E)-6-Bromo-2-hydroxyhepta-3,5-dienyl)-4-(tert-butyldimethyl-siloxymethyl)oxazole **(200).**



A solution of *n*-butyllithium 1.6*M* in hexanes (3.2 cm^3, 5.143 mmol) was added dropwise, over 5 min, to a stirred solution of the protected oxazole **(185)** (1.25 g,

5.143 mmol) in dry THF (50 cm^3), at -78°C, under an atmosphere of nitrogen. The mixture was stirred at -78°C for 15 min and then the aldehyde **(193)** (1 g, 5.714 mmol) was added dropwise, over 1 min, and the mixture was stirred at -78°C for a furhter 30 min. The mixture was allowed to warm to room temperature over 30 min and was then quenched with saturated NH_4Cl solution (10 cm^3). The mixture was extracted with ethyl acetate (3 x 25 cm^3) and the extracts were combined. The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was purified using flash chromatography (2% MeOH in CH_2Cl_2) to give the *oxazole* (884 mg, 38%) as a brown oil; (Found: M^+, 401.1022. $C_{17}H_{28}BrNO_3Si$ requires M^+, 401.1022); $\nu_{max}(cm^{-1})$: 3356 (O-H), 1646 (C=C), 1568 (cyclic C=N), 969 (*trans*-C=C-H) and 839 and 779 (Si-O); δ_H (270 MHz $CDCl_3$): 7.47 (oxazole :C<u>H</u>), 6.42 (dd, *J* 1.1 and 11.2 Hz, :CHC<u>H</u>:CBr), 6.36 (dd, *J* 11.2 and 14.2 Hz, CHOHCH:C<u>H</u>), 5.73 (dd, *J* 6.1 and 14.2 Hz, CHOHC<u>H</u>:), 4.68 (m, C<u>H</u>OH), 4.66 (SiOC<u>H_2</u>), 2.95 (m, C<u>H_2</u>CHOH), 2.36 (:C(C<u>H_3</u>)), 0.92 (OSi(C(C<u>H_3</u>)$_3$)) and 0.11 (OSi(C<u>H_3</u>)$_2$); δ_C (67.8 MHz $CDCl_3$): 162.8 (s), 140.8 (s), 134.8 (d), 134.3 (d), 131.1 (d), 125.2 (d), 123.5 (s), 69.0 (d), 58.2 (t), 35.5 (t), 25.7 (q), 23.6 (q), 18.2 (s) and -5.4 (q); *m/z* (CI): 401 (5%, M^+), 344 (40, M^+-^{t}Bu), 252 (15, M^+-TBDMSO), 227 (oxazole portion from retro-aldol), 170 (50), 95 (85) and 75 (100).

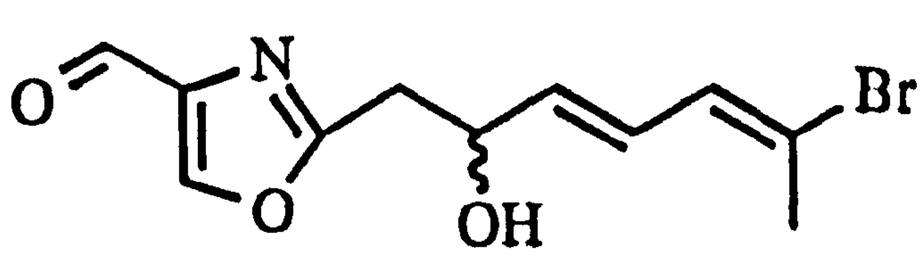
(+/-)-2-((E,E)-6-Bromo-2-hydroxyhepta-3,5-dienyl)-4-hydroxymethyloxazole **(203).**



A solution of *n*-butyllithium 2.5*M* in hexanes (23.1 cm^3, 60 mmol) was added dropwise, over 15 min, to a stirred solution of the hydroxy oxazole **(184)** (3.23 g, 28.6 mmol) in dry THF (50 cm^3) at -78°C under an atmosphere of nitrogen. The

mixture was stirred at -78°C for 15 min and then the aldehyde **(195)** (5 g, 28.6 mmol) was added dropwise, over 10 min, and the mixture was stirred at -78°C for a furhter 30 min. The mixture was allowed to warm to room temperature over 30 min and then quenched with saturated NH_4Cl solution (10 cm^3). The mixture was extracted with ethyl acetate (3 x 50 cm^3) and the extracts were combined. The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was purified using flash chromatography (3% MeOH in CH_2Cl_2) to give the *diol* (3 g, 45%) as an orange oil; (Found: C, 45.5; H, 4.9; N, 4.7%; M^+-H_2O, 269.0052. $C_8H_{11}NO_2$ requires C, 45.85; H, 4.9; N, 4.9%;M^+-H_2O, 269.0051); ν_{max}(cm^{-1}): 3384 (O-H), 3156 (O-H), 1647 (C=C), 1565 (cyclic C=N-), 1318 (O-H) and 968 (*trans* C=C-H); λ_{max} (EtOH)/nm (ε): 233 (8044) and 256 (6794); δ_H (400 MHz $CDCl_3$): 7.53 (oxazole :C<u>H</u>), 6.45 (dd, *J* 1.2 and 11.1 Hz, :CHC<u>H</u>:CBr), 6.38 (dd, *J* 11.1 and 14.8 Hz, CHOHCH:C<u>H</u>), 5.74 (dd, *J* 5.8 and 14.8 Hz, CHOHC<u>H</u>:), 4.66 (app q, *J* 5.8 Hz, $CH_2C\underline{H}OH$), 4.56 ($HOC\underline{H}_2$), 3.63 (OH), 2.96 (m, 2H, $C\underline{H}_2CHOH$), 2.71 (OH) and 2.35 ($C\underline{H}_3$); δ_C (67.8 MHz $CDCl_3$): 162.4 (s), 139.7 (d), 135.2 (d), 134.4 (d), 130.9 (d), 125.0 (d), 123.6 (s), 68.9 (d), 55.5 (t), 35.8 (t) and 23.5 (q); *m/z* (CI): 287 (11%, M^+), 270 (37, M^+-H_2O), 208 (18, M^+-Br), 190 (8, M^+-Br, -H_2O), 175 (26, aldehyde from retro aldol), 113 (96, oxazole from retro aldol), 95 (100, aldehyde-HBr) and 67 (20).

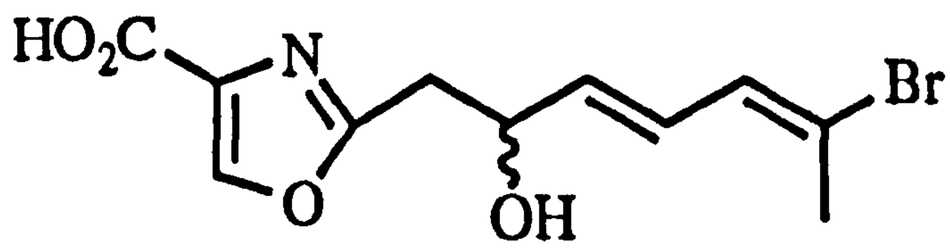
***(+/-)-2-((E,E)-6-Bromo-2-hydroxyhepta-3,5-dienyl)-4-formyloxazole* (205).**



Activated manganese dioxide (24.6 g, 260 mmol) was added carefully, in one portion, to a stirred solution of the diol **(203)** (2 g, 12.98 mmol) in dry CH_2Cl_2 (150 ml) and the mixture was stirred at room temperature overnight. The mixture was filtered

through celite and the filtrate concentrated *in vacuo*. The residue was purified using flash chromatography (CH_2Cl_2) to give the *aldehyde* (1.3 g, 70%) as an orange solid, m.p.30-32°C; (Found: M^+-H_2O, 266.9670. $C_{10}H_{11}BrNO_2$ requires M^+-H_2O, 266.9695); ν_{max}(cm^{-1}): 3382 (O-H), 1694 (aldehyde C=O), 1651 (C=C), 1587 (cyclic C=N-) and 968 (*trans* C=C-H); δ_H (400 MHz $CDCl_3$): 9.89 (aldehyde C<u>H</u>), 8.22 (oxazole :C<u>H</u>), 6.44 (dd, *J* 1.2 and 11.1 Hz, :CHC<u>H</u>:CBr), 6.37 (dd, *J* 11.1 and 14.3 Hz, CHOHCH:C<u>H</u>), 5.74 (dd, *J* 5.8 and 14.3 Hz, CHOHC<u>H</u>:), 4.73 (app q, *J* 5.8 Hz, $CH_2C\underline{H}OH$), 3.32 (CHO<u>H</u>), 3.05 (m, 2H, $C\underline{H}_2CHOH$) and 2.33 ($C\underline{H}_3$); δ_C (100 MHz $CDCl_3$): 183.4 (d), 163.5 (s), 145.2 (d), 140.4 (s), 135.8 (d), 130.8 (d), 125.5 (d), 124.0 (s), 69.0 (d), 35.6 (t) and 23.6 (q); *m/z* (EI): 204 (100%, M^+-HBr), 175 (25, aldehyde from retro-aldol), 163 (20), 145 (10), 135 (10), 110 (45, oxazole from retro-aldol), 82 (25), 65 (60), 54 (40) and 43 (35).

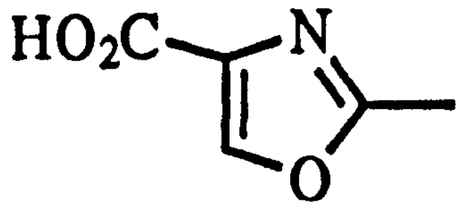
(+/-)-2-((E,E)-6-Bromo-2-hydroxyhepta-3,5-dienyl)-4-oxazolic acid (199).



A solution of 80% sodium chlorite (138 mg, 1.526 mmol) and potassium hydrogen orthophosphate (243 mg, 1.785 mmol), in water (1 cm^3), was added dropwise, over 2 min, to a stirred solution of the aldehyde **(205)** (292 mg, 1.021 mmol) and 2-methyl-2-butene (0.541 cm^3, 5.105 mmol) in *t*-butanol (10 cm^3) at 0°C and the mixture was then stirred overnight while allowing to warm to room temperature. The *t*-butanol was removed *in vacuo* and the residue was partitioned between ethyl acetate (10 cm^3) and 5 *M* HCl (5 cm^3). The mixture was seperated and the aqueous layer was then extracted with ethyl acetate (2 x 10 cm^3). The extracts were combined and the dried solution ($MgSO_4$) was concentrated *in vacou* to give the *acid* (270 mg, 80%) as a yellow

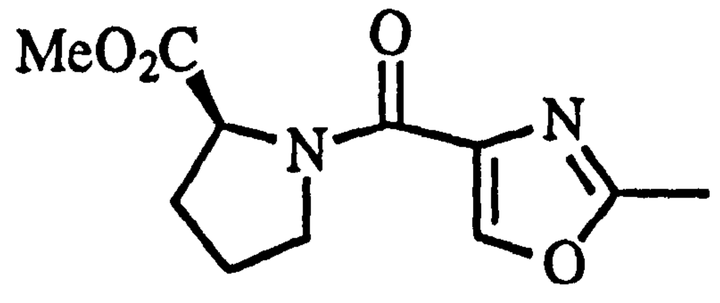
hydroscopic solid; (Found: M^+ 300.9949. $C_{11}H_{12}BrNO_4$ requires M^+ 300.9950); ν_{max}(cm^{-1}): 3424 (O-H), 1718 (acid C=O), 1653 (C=C) and 1570 (cyclic C=N-); λ_{max} (EtOH)/nm (ε): 236 (8010) and 318 (1649); δ_H (400 MHz CD_3OD): 8.40 (oxazole :CH), 6.42 (m, 2 H, CHOHCH:CHCH:), 5.78 (dd, *J* 6.1 and 14.4 Hz, CHOHCH:), 4.61 (q, *J* 6.1 Hz, CH_2CHOH), 3.01 (d, *J* 6.1 Hz, CH_2CHOH), 2.55 (d, *J* 1 Hz, OH) and 2.33 (d, *J* 1 Hz, CH_3); δ_C (100 MHz CD_3OD): 164.6 (s), 163.8 (s), 145.8 (d), 136.2 (d), 134.4 (s), 132.4 (d), 126.4 (d), 124.4 (s), 70.5 (d), 37.0 (t) and 23.9 (q); *m/z* (EI): 301 (5%, M^+), 282 (10, M^+-H_2O), 204 (20), 177 (35), 164 (95), 127 (100), 189 (75), 96 (50), 91 (35) and 80 (40).

***2-Methyloxazole-4-carboxylic acid* (186).[79]**



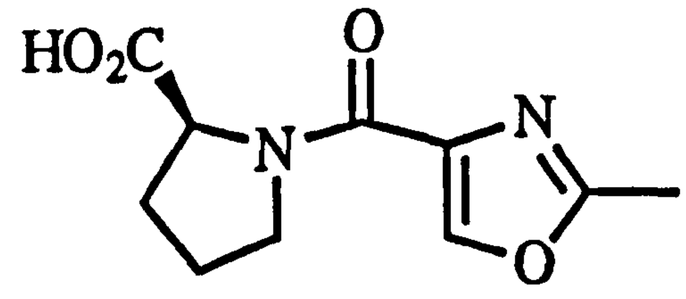
Lithium hydroxide (450 mg, 16.22 mmol) was added, in one portion, to a stirred solution of ester **(173)** (1 g, 6.448 mmol) in wet THF (10 cm^3) and the mixture was then stirred overnight at room temperature. 2*M* HCl (5 cm^3) was added and the mixture was then extracted with ethyl acetate (3 x 20 cm^3). The organic extracts were combined and washed with brine (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the crude solid was recrystallised from ether to give the *acid* (490 mg, 60%) as a colourless solid, m.p. 182°C (ether) (Lit.[79] m.p. 184°C); (Found: C, 47.4; H, 4.1; N, 11.3%; M^+, 127.0278. $C_8H_{11}NO_2$ requires C, 47.3; H, 3.9; N, 11.0%; M^+, 127.0269); ν_{max}(cm^{-1}): 3436 (O-H), 1718 (acid C=O) and 1587 (cyclic C=N-); δ_H (270 MHz $CDCl_3$): 8.38 (oxazole :CH) and 2.49 (CH_3); δ_C (67.8 MHz $CDCl_3$): 164.7 (s), 164.1 (s), 146.1 (d), 134.7 (s) and 13.8 (q); *m/z* (EI): 127 (90%, M^+), 110 (30, M^+-OH) and 82 (15, M^+-CO_2H).

***(-)-N-(2-Methyloxazol-4-ylcarbonyl)-(S)-proline methyl ester* (207).**



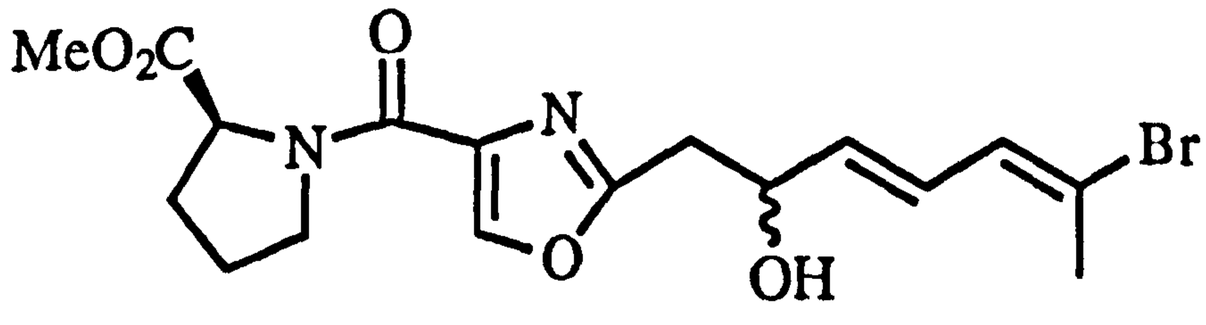
DCC (190 mg, 0.9057 mmol) was added, in one portion, to a stirred solution of the acid (**186**) (230 mg, 1.811 mmol) in dry CH_2Cl_2 (10 cm^3) at 0°C. The mixture was stirred at 0°C for 30 min and the *L*-proline methyl ester (**206**) (100 mg, 0.6038 mmol of *L*-proline methyl ester hydrochloride was stirred for 15 min with triethylamine (0.131 cm^3, 0.9057 mmol)) in dry CH_2Cl_2 (5 cm^3) at 0°C under an atmosphere of nitrogen) was then added dropwise over 5 min. DMAP (10 mg) was added and the mixture was then stirred overnight while allowing it to warm to room temperature. The solid precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was then purified using flash chromatography (3% methanol in CH_2Cl_2) to give the *amide* (98 mg, 68%) as a colourless oil: (Found: M^+, 238.0955. $C_8H_{11}NO_2$ requires M^+, 238.0954); $[\alpha]_D$ -67.40 (*c* 1.115 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 1746 (ester C=O), 1622 (amide C=O) and 1588 (amide dimer); δ_H (250 MHz $CDCl_3$): 8.13 (0.5 H, oxazole :C**H**), 8.11 (0.5 H, oxazole :C**H**), 5.28 (dd, *J* 1.3 and 5.5 Hz, 0.5 H, COC**H**NCO), 4.61 (dd, *J* 2.5 and 5.5 Hz, 0.5 H, COC**H**NCO), 4.09 (t, *J* 6.0 Hz, CONC**H**H), 3.65-3.85 (m, 4 H, CONCH**H** and OC**H**$_3$), 2.49 (1.5 H, C**H**$_3$), 2.39 (1.5 H, C**H**$_3$) and 1.80-2.35 (m, 4 H, COCHC**H**$_2$C**H**$_2$); δ_C (67.8 MHz $CDCl_3$): 172.9 (s), 172.1 (s), 160.3 (s), 160.0 (s), 142.8 (d), 136.6 (s), 136.4 (s), 59.9 (d), 59.3 (d), 51.7 (q), 48.2 (t), 46.9 (t), 31.1 (t), 28.1 (t), 24.8 (t), 21.4 (t) and 13.4 (q); *m/z* (EI): 238 (15%, M^+), 206 (10, M^+-MeOH), 179 (75, M^+-MeOOC), 128 (20, proline methyl ester), 110 (100, M^+-proline methyl ester) and 82 (10, 2-methyloxazole).

N-(2-Methyloxazol-4-ylcarbonyl)-(S)-proline **(208).**



Lithium hydroxide (1.6 g, 64.49 mmol) was added, in one portion, to a stirred solution of the oxazole **(207)** (2 g, 12.90 mmol) in wet THF (50 cm^3) and the mixture was then stirred at room temperature overnight. 2*M* HCl (10 cm^3) was added and the mixture was then extracted with ethyl acetate (3 x 50 cm^3). The organic extracts were combined and the dried solution ($MgSO_4$) was concentrated *in vacuo*. The residue was recrystalized from methanol to give the *acid* (1.5 g, 85%) as a colourless solid, m.p. 217-219°C; (Found: M^+, 224.0795. $C_{10}H_{12}N_2O_4$ requires M^+, 224.0797); $[\alpha]_D$ -95.60 (*c* 0.09 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3480 (O-H), 1730 (acid C=O) and 1590 (amide C=O); δ_H (250 MHz $CDCl_3$): 11.40 ($CO_2\underline{H}$), 8.12 (0.5 H, oxazole :C$\underline{H}$), 8.11 (0.5 H, oxazole :C$\underline{H}$), 5.27 (d, *J* 5.5 Hz, 0.5 H, NC$\underline{H}CH_2$), 4.64 (d, *J* 5.5 Hz, 0.5 H, NC$\underline{H}CH_2$), 4.04 (app q, *J* 7.6 Hz, $CH_2C\underline{H}HNCO$), 3.71 (m, $CH_2C\underline{H}HNCO$), 2.44 (1.5 H, C$\underline{H}_3$), 2.36 (1.5 H, C$\underline{H}_3$) and 1.88-2.24 (m, 4 H, $CHC\underline{H}_2C\underline{H}_2CH_2N$); δ_C (67.8 MHz $CDCl_3$): 175.9 (s), 174.6 (s), 160.9 (s), 160.7 (s), 143.8 (d), 143.6 (d), 136 3 (s), 136.1 (s), 60.4 (d), 60.2 (d), 49.0 (t), 47.4 (t), 31.2 (t), 28.0 (t), 25.1 (t), 21.7 (t) and 13.6 (q); *m/z* (EI): 224 (8%, M^+), 179 (40, M^+-CO_2H), 110 (100, M^+-proline), 82 (10, 2-methyloxazole) and 70 (45).

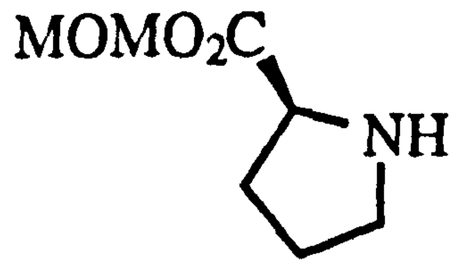
***(E,E)-N-(2-(6-Bromo-2-hydroxyhepta-3,5-dienyl)oxazol-4-ylcarbonyl)-(S)-proline methyl ester* (210).**



EDC (67 mg, 0.3507 mmol) was added, in one portion, to a stirred solution of the acid **(199)** (100 mg, 0.2505 mmol) in dry CH_2Cl_2 (7 cm^3) at 0°C under an atmosphere of nitrogen. The mixture was stirred for 30 min and then HOBt (42 mg, 0.3131 mmol) and triethylamine (0.039 cm^3, 0.2610 mmol) were added, in one portion, followed by dropwise addition of the *L*-proline methyl ester **(206)** (46 mg, 0.2610 mmol of proline methyl ester hydrochloride was stirred with triethylamine (0.039 cm^3, 0.2610 mmol) in dry CH_2Cl_2 (3 cm^3) at 0°C under an atmosphere of nitrogen). The mixture was stirred overnight at room temperature and then washed with water (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (3% methanol in CH_2Cl_2) to give a mixture of diastereoisomers of the *amide* (85 mg, 64%) as a pale orange oil; (Found: M^+, 412.0578. $C_{17}H_{21}BrN_2O_5$ requires M^+ 412.0584); $[\alpha]_D$ -19.30 (*c* 0.82 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3360 (O-H), 1745 (ester C=O), 1617 (amide C=O) and 913 (*trans*-C=C-H); δ_H (400 MHz $CDCl_3$): 8.18 (m, oxazole :C<u>H</u>), 6.42 (m, 2 H, CHOHC<u>H</u>:C<u>H</u>C<u>H</u>:), 5.74 (m, CHOHC<u>H</u>:), 5.26 (dd, *J* 2.6 and 8.7 Hz,0.5 H, COC<u>H</u>N), 5.13 (dd, *J* 2.6 and 8.7 Hz, 0.5 H, COC<u>H</u>N), 4.55-4.70 (m, $CH_2C\underline{H}OHCH$:), 4.08 (app q, *J* 6.7 Hz, CHNC<u>H</u>H), 3.82 (app dq, *J* 2.6 and 6.7 Hz, CHNCH<u>H</u>), 3.75 (1.5 H, OCH_3), 3.73 (1.5 H, OCH_3), 3.50 (O<u>H</u>), 2.85-3.10 (m, 2 H, $C\underline{H}_2CHOH$), 2.36 (d, *J* 1 Hz, $C(C\underline{H}_3)Br$) and 1.85-2.35 (m, 4 H, $COCHC\underline{H}_2C\underline{H}_2$); δ_C (67.8 MHz $CDCl_3$): 173.7 (s), 172.5 (s), 161.5 (s), 161.4 (s), 143.7 (d), 143. 5 (d), 136.5 (s), 136.4 (s), 133.9 (d), 125.5 (d), 125.3 (d), 123,8 (s), 69.1 (d), 68.5 (d), 60.5 (d), 59.8 (d), 52.4 (t), 52.2 (t), 35.7 (t), 35.5 (t), 31.6 (t), 28.5 (t), 25.2 (t), 21.7 (t) and 23.7 (q); *m/z* (EI):

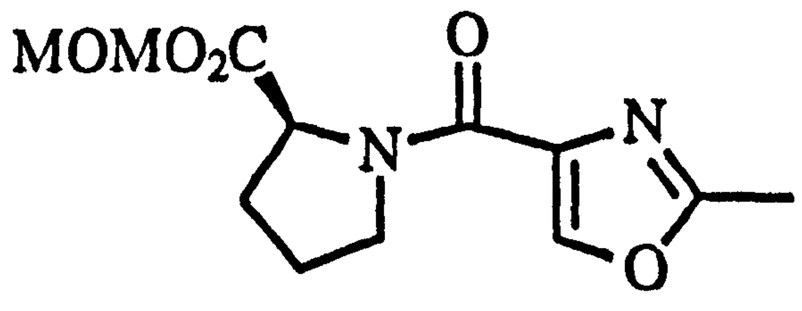
412 (25%, M^+), 331 (20, M^+-HBr), 238 (10, **(207)** from retro-aldol), 207 (20, **(207)**-OMe), 136 (75), 128 (40, proline-H), 83 (45, 2-methyloxazole) and 69 (80, oxazole).

***(S)-Proline methoxymethy ester* (212).**



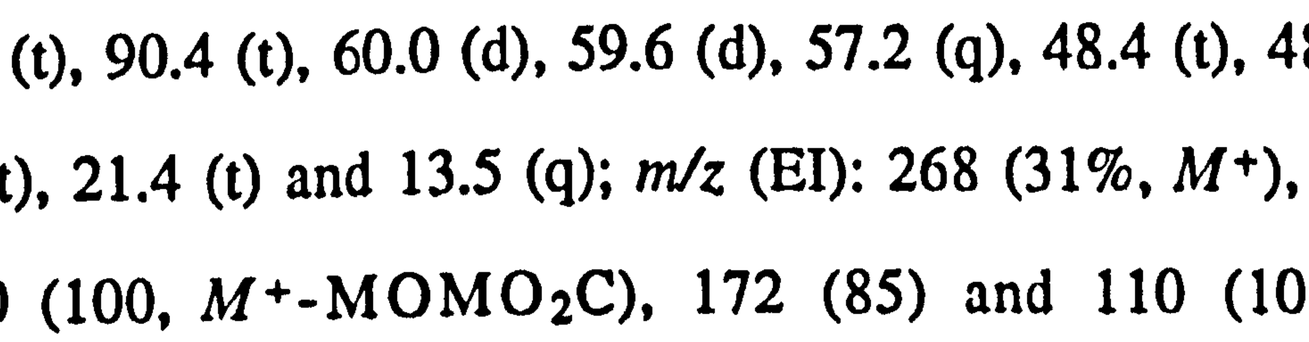
Chloromethyl methyl ether (0.82 cm^3, 10.40 mmol) was added dropwise, over 5 min, to a stirred solution of *L*-proline (1 g, 8.686 mmol) and triethylamine (1.33 cm^3, 9.923 mmol) in dry CH_2Cl_2 (25 cm^3) at room temperature under an atmosphere of nitrogen. The mixture was stirred overnight and was then washed with saturated $NaHCO_3$ solution (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* to leave the crude *ester* (0.98 g, 90%) as a pale yellow oil: $\nu_{max}(cm^{-1})$: 3408 (N-H) and 1743 (ester C=O); δ_H (400 MHz $CDCl_3$): 5.34 ($OC\underline{H}_2O$), 3.40-3.55 (m, 4 H, $OC\underline{H}_3$ and $COC\underline{H}NH$), 3.12 (m, 1 H, $NHCH\underline{H}$), 2.68 (m, 1 H, $NHC\underline{H}H$), 1.75-2.20 (m, 4 H, $CHC\underline{H}_2C\underline{H}_2$) and 1.40 (t, *J* 9.8 Hz, $N\underline{H}$); δ_C (67.8 MHz $CDCl_3$): 173.4 (s), 89.8 (t), 63.6 (d), 57.0 (q), 51.3 (t), 28.9 (t) and 23.0 (t).

***(-)-N-(2-Methyloxazol-4-ylcarbonyl)-(S)-proline methoxymethyl ester* (213).**



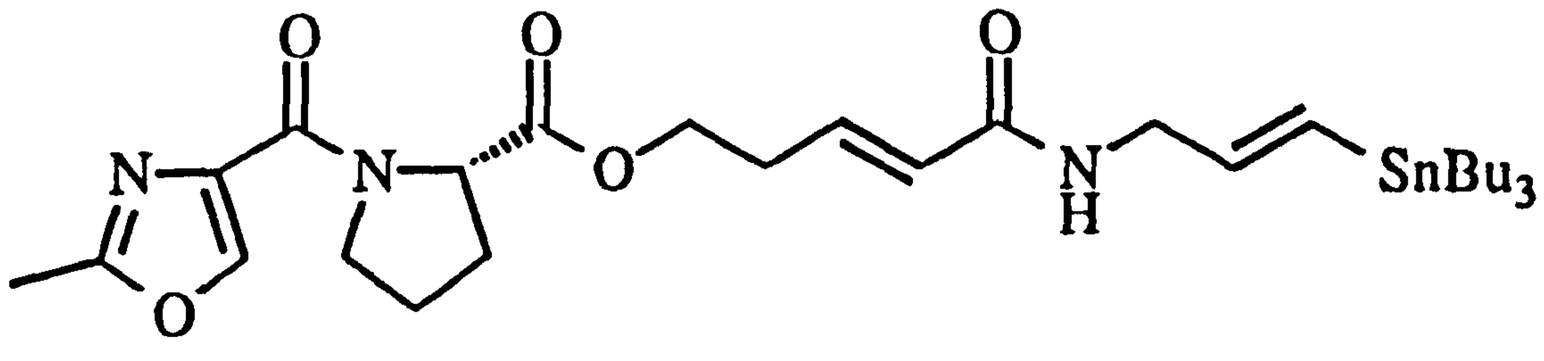
EDC (210 mg, 1.1015 mmol) was added, in one portion, to a stirred solution of the acid **(186)** (100 mg, 0.7868 mmol) in dry CH_2Cl_2 (10 cm^3), at 0°C, under an atmosphere of nitrogen. The mixture was stirred for 30 min and then HOBt (133 mg, 0.9835 mmol) and triethylamine (0.121 cm^3, 0.8655 mmol) were added, in one portion, followed by the addition of the *L*-proline methyoxymethyl ester **(212)** (125 mg, 0.7868 mmol). The mixture was stirred overnight and then washed with water (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (3% MeOH in CH_2Cl_2) to give the *amide* (85 mg, 64%) as a colourless oil; (Found:M^+, 268.1084. $C_{12}H_{16}N_2O_5$ requires M^+ 268.1069); $[\alpha]_D$ -42.60 (*c* 0.865 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 1747 (ester C=O), 1632 (amide C=O) and 1588 (amide dimer); δ_H (400 MHz $CDCl_3$): 8.13 (0.5 H, oxazole :C<u>H</u>), 8.11 (0.5 H, oxazole :C<u>H</u>), 5.34 (m, 1 H, OC<u>H</u>HO), 5.26 (m, 1.5 H, OCH<u>H</u>O and COC<u>H</u>NH), 4.65 (dd, *J* 4.1 and 8.4 Hz, 0.5 H, COC<u>H</u>NH), 4.12 (m, 1 H, NHC<u>H</u>HCH$_2$), 3.70-3.90 (m, 1H, NHCH<u>H</u>CH$_2$), 3.46 (1.5 H, OC<u>H</u>$_3$), 3.44 (1.5 H, OC<u>H</u>$_3$), 2.45 (1.5 H, C<u>H</u>$_3$), 2.43 (1.5 H, C<u>H</u>$_3$) and 1.80-2.40 (m, 4 H, NHCHC<u>H</u>$_2$C<u>H</u>$_2$) δ_C (67.8 MHz $CDCl_3$): 172.2 (s), 171.4 (s), 160.5 (s), 160.2 (s), 143.1 (d), 142.9 (d), 136.7 (s), 136.5 (s), 90.6 (t), 90.4 (t), 60.0 (d), 59.6 (d), 57.2 (q), 48.4 (t), 48.0 (t), 31.2 (t), 28.3 (t), 25.0 (t), 21.4 (t) and 13.5 (q); *m/z* (EI): 268 (31%, M^+), 207 (100, M^+-$C_2H_4O_2$), 180 (100, M^+-$MOMO_2C$), 172 (85) and 110 (100, 2-methyl-4-formyloxazole).

(E,E)-N-(2-(6-Bromo-2-hydroxyhepta-3,5-dienyl)oxazol-4-ylcarbonyl)-(S)-proline methoxymethyl ester **(214).**



EDC (67 mg, 0.3507 mmol) was added in, one portion, to a stirred solution of the acid **(199)** (100 mg, 0.2505 mmol) in dry CH_2Cl_2 (10 cm^3), at 0°C, under an atmosphere of nitrogen. The mixture was stirred for 30 min and then HOBt (42 mg, 0.3131 mmol) and triethylamine (0.039 cm^3, 0.2610 mmol) were added, in one portion, followed by the addition of the *L*-proline methoxymethyl ester **(212)** (44 mg, 0.2610 mmol). The mixture was stirred overnight at room temperature and then washed with water (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was purified using flash chromatography (3% MeOH in CH_2Cl_2) to give a mixture of diastereoisomers of the *amide* (94 mg, 72%) as a pale orange oil; (Found: M^+, 442.0716. $C_{18}H_{23}BrN_2O_6$ requires M^+ 442.0740); $[\alpha]_D$ -20.40 (*c* 0.225 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3408 (O-H), 1747 (ester C=O), 1614 (amide C=O), 1586 (amide dimer) and 952 (*trans*-C=C-H); δ_H (400 MHz $CDCl_3$): 8.19 (m, 1 H, oxazole :C<u>H</u>), 6.44 (m, 2 H, COHCH:C<u>H</u>C<u>H</u>:), 5.74 (m, 1 H, COHC<u>H</u>:), 5.18-5.42 (m, 2 H, $CH_3OC\underline{H}_2O$), 4.63 (m, 1 H, $CH_2C\underline{H}OHCH$:), 4.10 (m, 0.5 H, $NC\underline{H}HCH_2$), 3.70-3.90 (m, 0.5 H, $NCH\underline{H}CH_2$), 3.40 (1.5 H, $OC\underline{H}_3$), 3.34 (1.5 H, $OC\underline{H}_3$), 2.85-3.10 (m, 2 H, $C\underline{H}_2CHOH$), 2.37 (d, *J* 0.9 Hz, CH:C(C<u>H</u>$_3$)Br) and 1.85-2.30 (m, 4 H, $CHC\underline{H}_2C\underline{H}_2CH_2N$); δ_C (67.8 MHz $CDCl_3$): 172.5 (s), 171.5 (s), 161.7 (s), 161.4 (s), 143.7 (d), 143.4 (d), 136.7 (s), 136.5 (s), 134.0 (d), 133.9 (d), 131.0 (d), 125.5 (d), 125.3 (d), 123.5 (s), 123.4 (s), 91.0 (t), 90.8 (t), 68.6 (d), 68.5 (d), 60.6 (d), 59.9 (d), 57.6 (q), 48.7 (t), 47.5 (t), 35.9 (t), 35.5 (t), 31.6 (t), 28.5 (t), 25.2 (t), 23.7 (q) and 21.8 (t); *m/z* (EI): 442 (5%, M^+), 353 (20, M^+-CO_2MOM), 268 (20), 70 (20) and 45 (100).

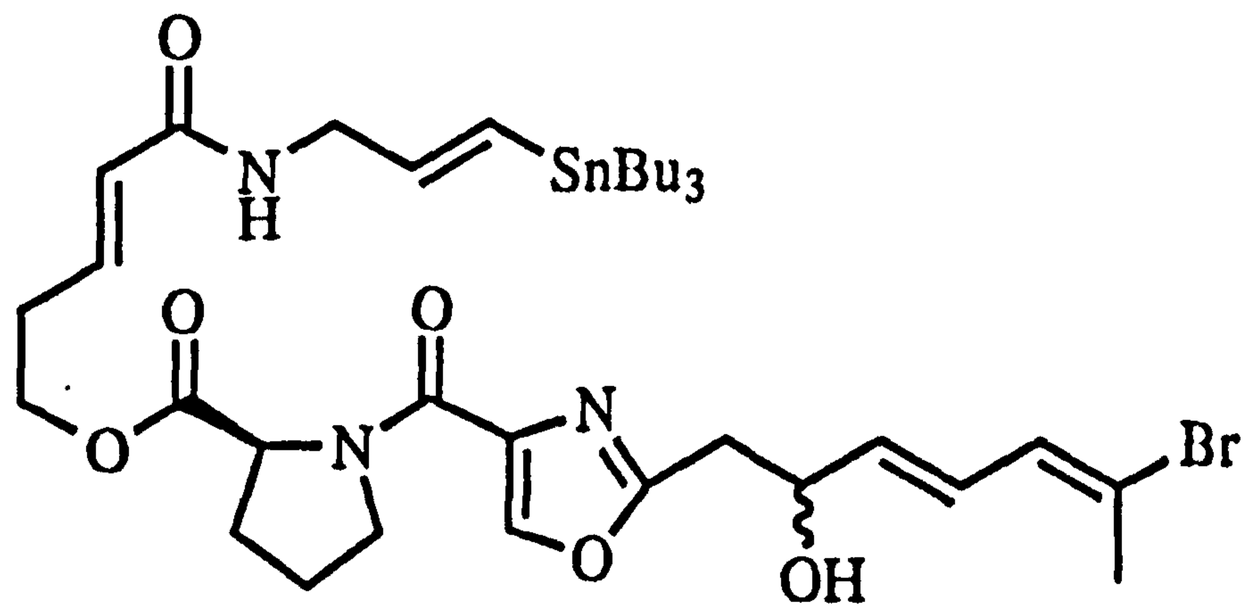
(-)-(E,E)-N-(3-Tri-n-butylstannylprop-2-enyl)-5-(N'-(2-methyloxazol-4-ylcarbonyl)-(S)-prolinoyloxy)pent-2-enamide **(209).**



Method A:- EDC (60 mg, 0.3151 mmol) was added, in one portion, to a stirred solution of the acid **(208)** (50 mg, 0.2251 mmol) in dry CH_2Cl_2 (5 cm^3) at 0°C under an atmosphere of nitrogen. The mixture was stirred for 30 min and DMAP (34 mg, 0.2814 mmol) and DMAP.HCl (45 mg, 0.2814 mmol) were then added, in one portion, followed by addition of the alcohol **(132)** (100 mg, 0.2251 mmol). The mixture was stirred overnight and then washed with water (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (2% MeOH in CH_2Cl_2) to give the *amide* (69 mg, 53%) as a colourless oil; *Method B*:- EDC (50 mg, 0.2586 mmol) was added, in one portion, to a stirred solution of the acid **(186)** (26 mg, 0.2032 mmol) in dry CH_2Cl_2 (5 cm^3) at 0°C under an atmosphere of nitrogen. The mixture was stirred for 30 min and then HOBt (31 mg, 0.2309 mmol) and triethylamine (0.036 cm^3, 0.2586 mmol) were added, in one portion, followed by addition of the *a*mine **(217)** (100 mg, 0.1847 mmol). The mixture was stirred overnight and was then washed with water (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was purified using flash chromatography (2% MeOH in CH_2Cl_2) to give the *amide* (72 mg, 60%) as a colourless oil. Both methods gave identical products by nmr and ir; (Found: C, 55.1; H, 7.9; N, 6.4%; M^+ 651.2773. $C_8H_{11}NO_2$ requires C, 55.4; H, 7.6; N, 6.5%; M^+651.2794); $[\alpha]_D$ -6.05 (*c* 2.75 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3300 (N-H), 1746 (ester C=O), 1673 (amide C=O), 1633 (C=C), 1538 (amide dimer), 1180 (C-O) and 982 (*trans*-C=C-H); λ_{max} (EtOH)/nm (ε): 216 (64 050) and 315 (1710); δ_H (400 MHz $CDCl_3$): 8.09 (0.5 H, oxazole :CH), 8.04 (0.5 H, oxazole :CH), 6.72-6.82 (m, 1 H,

COCH:CH), 6.57 (bt, 0.5 H, NH), 5.70-6.15 (m, 3 H, COCH: and SnCH:CH), 5.32 (m, 0.5 H, NH), 4.58 (dd, *J* 4.5 and 9.0 Hz, 0.5 H, COCHNCO), 4.42 (m, 0.5 H, COCHNCO), 4.17 (t, *J* 6.4 Hz, CH_2OCO), 4.09 (app t, *J* 6.4 Hz, :$CHCH_2CH_2$), 3.98 (app t, *J* 5.6 Hz, :$CHCH_2N$), 3.62-3.82 (m, 2 H, $CHNCH_2$), 2.52 (m, 1 H, COCHCHH), 2.46 (1.5 H, CH_3), 2.38 (1.5 H, CH_3), 1.80-2.35 (m, 3 H, CHCHHCH), 1.46 (m, 6 H, $SnCH_2CH_2$), 1.28 (m, 6 H, $SnCH_2CH_2CH_2$) and 0.89 (m, 15 H, $SnCH_2CH_2CH_2CH_3$); δ_C (100 MHz $CDCl_3$): 172.5 (s), 172.1 (s), 165.9 (s), 160.8 (s), 160.5 (s), 143.9 (d), 143.4 (d), 143.3 (d), 136.9 (s), 136.7 (s), 130.0 (d), 129.6 (d), 126.4 (d), 126.2 (d), 63.0 (t), 62.8 (t), 60.5 (d), 59.9 (d), 48.8 (t), 47.4 (t), 44.8 (t), 31.0 (t), 30.8 (t), 30.4 (t), 28.5 (t), 29.0 (t), 27.2 (t), 25.3 (t), 21.7 (t), 13.8 (q), 13.6 (q) and 9.3 (t); *m/z* (FAB): 651 (5%, M^+), 594 (15, M^+-Bu), 538 (5, M^+-4-formyloxazole), 388 (15, M^+-N-oxazoloylproline), 291 (10, Bu_3SnH) and 55 (propargylamine).

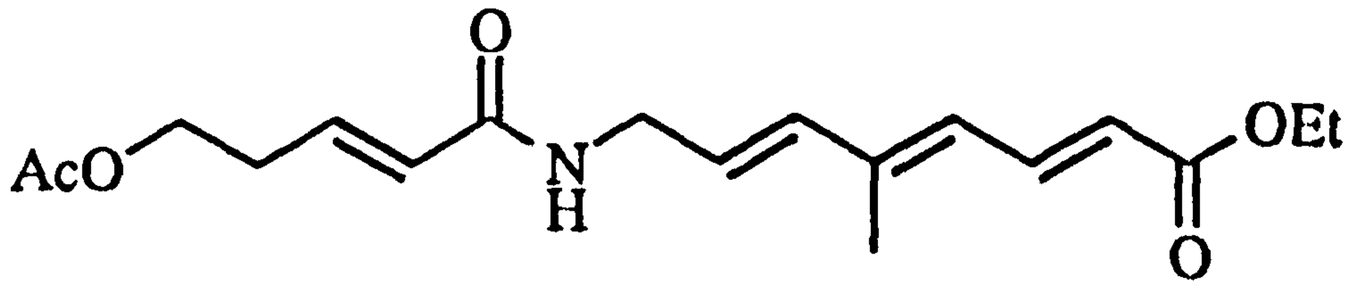
(E,E,E,E)-N-(3-Tri-n-butylstannylprop-2-enyl)-5-(N'-(2-(6-bromo-2-hydroxypent-3,5-dienyl)oxazol-4-ylcarbonyl)-(S)-prolinoyloxy)pent-2-enamide **(198).**



EDC (89 mg, 0.4634 mmol) was added, in one portion, to a stirred solution of the acid **(199)** (100 mg, 0.3310 mmol) in dry CH_2Cl_2 (5 cm^3), at 0°C, under an atmosphere of nitrogen. The mixture was stirred for 30 min and then HOBt (56 mg, 0.4138 mmol) and triethylamine (0.051 cm^3, 0.3641 mmol) were added, in one portion, followed by

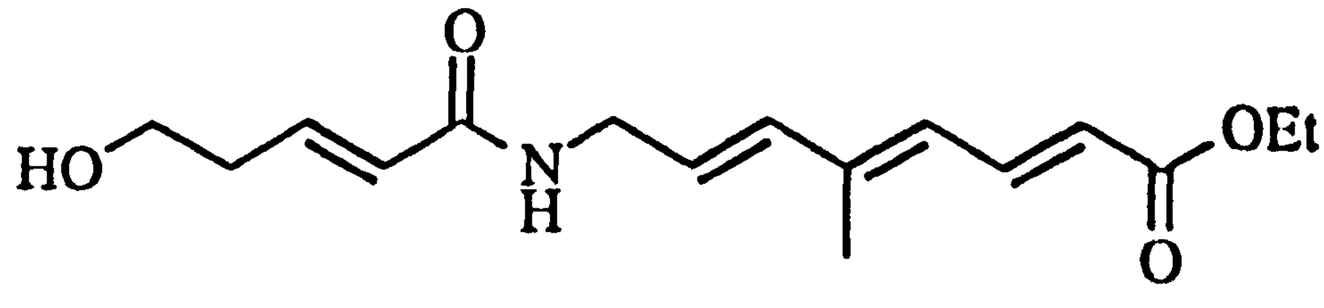
the addition of the amine **(217)** (197 mg, 0.3641 mmol). The mixture was stirred overnight while allowing it to warm to room temperature and then washed with water (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (2% MeOH in CH_2Cl_2) to give a mixture of diastereoisomers of the *amide* (165 mg, 61%) as an orange oil; $\nu_{max}(cm^{-1})$: 3420 (O-H)„ 1744 (ester C=O), 1653 (amide C=O), 1636 (C=C) and 973 (*trans*-C=C-H); λ_{max} (EtOH)/nm (ε): 217 (60 150), 237 (8150) and 315 1650 (1650); δ_H (500 MHz $CDCl_3$): 8.12 (m, 1 H, oxazole :C<u>H</u>), 6.74 (m, 1 H, COCH:C<u>H</u>), 6.46 (m, 1 H, C<u>H</u>:C(CH_3)Br), 6.39 (m, 1 H, CHOHCH:C<u>H</u>), 6.1 (app ddd, *J* 1.5, 7.0 and 19.0 Hz, SnC<u>H</u>:), 5.97 (dt, *J* 19.0 and 3.8 Hz, SnCH:C<u>H</u>), 5.86 (app dd, *J* 1.9 and 15.3 Hz, COC<u>H</u>:CH), 5.72 (m, 1 H, CHOHC<u>H</u>:), 5.29 (dd, *J* 2.5 and 9.0 Hz, 0.5 H, COCHN), 5.19 (dd, *J* 2.5 and 9.0 Hz, 0.5 H, COC<u>H</u>N), 4.60-4.75 (m, 1 H, $CH_2C\underline{H}OH$), 3.90-4.40 (m, 7 H, $NC\underline{H}_2CH$:, :$CHC\underline{H}_2C\underline{H}_2O$ and COCHC<u>H</u>H), 3.70-3.85 (m, 1 H, COCHCH<u>H</u>), 3.02 (m, 2 H, $C\underline{H}_2CHOH$), 2.50 (m, 1 H, CONC<u>H</u>H), 2.39 (d, *J* 1.2 Hz, $C\underline{H}_3$), 2.23 (m, 1 H, CONCH<u>H</u>), 1.85-2.05 (m, 2 H, $CONCH_2C\underline{H}_2$), 1.78 (O<u>H</u>), 1.51 (pent, *J* 7.1 Hz, $SnCH_2C\underline{H}_2$), 1.30 (hext *J* 7.1 Hz, $SnCH_2CH_2C\underline{H}_2$) and 0.89 (t, *J* 7.1 Hz, $SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); δ_C (125 MHz $CDCl_3$): 172.8 (s), 171.8 (s), 165.6 (s), 165.2 (s), 161.5 (s), 161.3 (s), 160.3 (s), 143.6 (d), 143.1 (d), 139.3 (d), 138.4 (d), 136.6 (s), 136.4 (s), 134.3 (d), 134.2 (d), 131.1 (d), 131.0 (d), 130.1 (d), 129.6 (d), 125.9 (d), 125.2 (d), 125.1 (d), 125.0 (d), 123.6 (d), 123.4 (d), 69.0 (d), 68.7 (d), 63.4 (t), 62.7 (t), 60.6 (d), 59.9 (t), 48.6 (t), 44.8 (t), 44.7 (t), 35.9 (t), 35.8 (t), 31.5 (t), 30.7 (t), 30.4 (t), 28.9 (t), 27.1 (t), 25.2 (t), 23.6 (q), 21.6 (t), 13.5 (q) and 9.3 (t).

(E,E,E,E)-N-(7-Ethoxycarbonyl-4-methylhepta-2,4,6-trienyl)-5-acetoxypent-2-enamide **(218).**



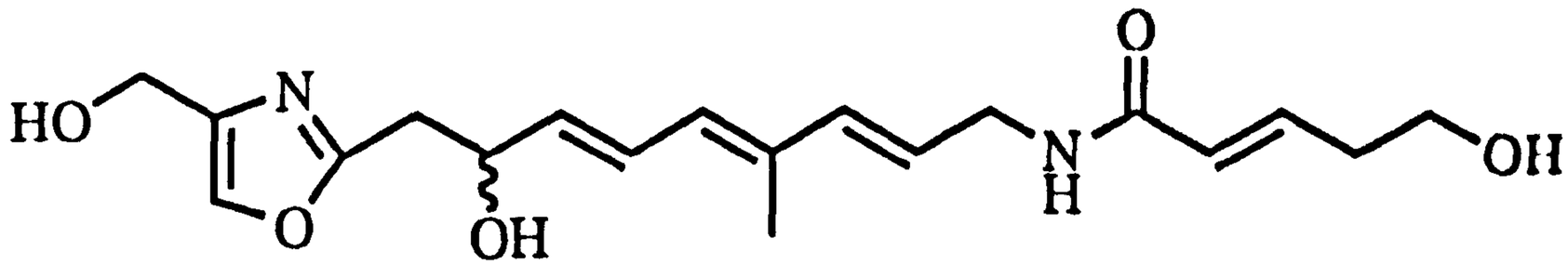
A solution of triphenylarsine (5.04 mg, 16.44 μmol) in dry THF (1 cm^3) was added dropwise, over 5 min, to a stirred solution of tris(benzylideneacetone)dipalladium(0) (1.9 mg, 2.06 μmol) in dry THF (12 cm^3) at room temperature, under an atmosphere of nitrogen, in a scrupulously dried flask. The mixture was stirred for 30 min and a solution of the amide **(151)** (100 mg, 0.2056 mmol), in dry THF (1 cm^3), and then a solution of the ester **(201)** (45 mg, 0.2056 mmol), in dry THF (1 cm^3), were added dropwise. The mixture was heated under reflux for 2 h and was then allowed to cooled to room temperature. The solvent was removed *in vacuo* and the residue was then purified using flash chromatography (10% ethylacetate in petroleum ether) to give the *amide* (39 mg, 62%) as a pale yellow oil; $\nu_{max}(cm^{-1})$: 3270 (N-H), 1742 and 1712 (ester C=O), 1670 (amide C=O), 1630 (C=C), 1550 (amide dimer) and 980 (*trans*-C=C-H); λ_{max} (EtOH)/nm (ε): 208 (71 231) and 304 (60 688); δ_H (400 MHz $CDCl_3$): 7.63 (dd, *J* 11.8 and 15.3 Hz, COCH:C<u>H</u>CH), 6.83 (dt, *J* 15.3 and 6.9 Hz, COCHC<u>H</u>), 6.26 (d, *J* 15.6 Hz, $NHCH_2CH$:C<u>H</u>), 6.14 (d, *J* 11.8 Hz, $C(CH_3)$:C<u>H</u>CH:), 5.90 (m, 3 H, NHCOC<u>H</u>:, COC<u>H</u>:CH and $NH_2CHC\underline{H}$:), 5.80 (N<u>H</u>), 4.24 (m, 4 H, $OC\underline{H}_2CH_3$ and $AcOC\underline{H}_2CH_2$), 4.05 (app t, *J* 5.6 Hz, $NHC\underline{H}_2CH$:), 2.52 (app dq, *J* 1.4 and 6.9 Hz, $AcOCH_2C\underline{H}_2$), 2.04 ($COC\underline{H}_3$), 1.96 (:CHC($C\underline{H}_3$):CH) and 1.29 (t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$); δ_C (67.8 MHz $CDCl_3$): 170.9 (s), 167.2 (s), 165.2 (s), 142.6 (s), 140.1 (d), 140.0 (d), 135.7 (d), 128.5 (d), 123.4 (d), 122.5 (d), 116.5 (d), 62.5 (t), 60.3 (t), 41.4 (t), 31.2 (t), 20.8 (q), 14.2 (q) and 13.2 (q).

(E,E,E,E)-N-(7-Ethoxycarbonyl-4-methylhepta-2,4,6-trienyl)-5-hydroxypent-2-enamide **(219).**



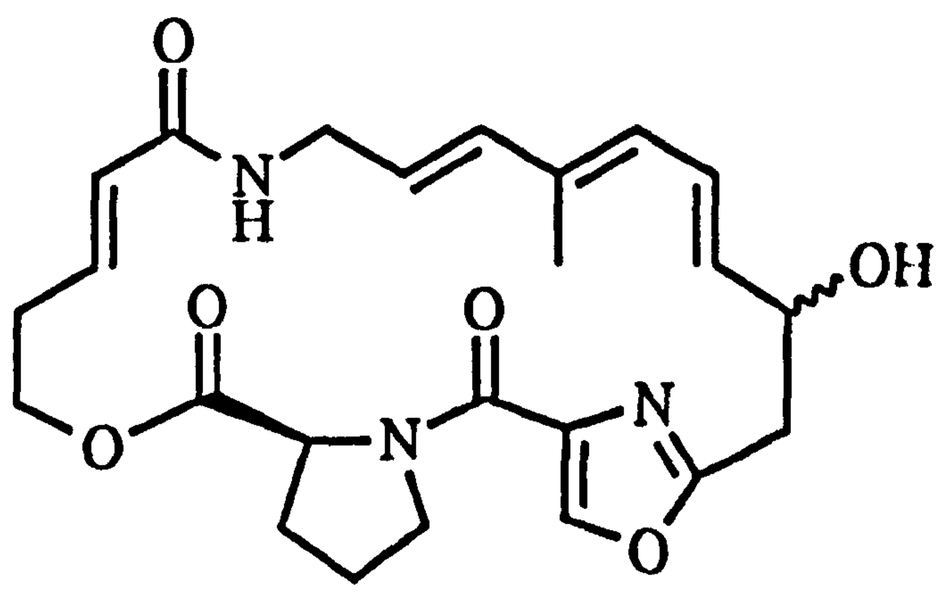
A solution of triphenylarsine (5.6 mg, 18 μmol) in dry THF (1 cm^3) was added dropwise, over 2 min, to a stirred solution of tris(benzylideneacetone)dipalladium(0) (2.1 mg, 2.25 μmol) in dry THF (12 cm^3) at room temperature, under an atmosphere of nitrogen, in a scupulously dried flask. The mixture was stirred for 30 min and a solution of the alcohol **(132)** (100 mg, 0.2251 mmol), in dry THF (1 cm^3), and then a solution of the ester **(201)** (49 mg, 0.2251 mmol), in dry THF (1 cm^3), were added dropwise over 5 min. The mixture was heated under reflux for 2 h and was then allowed to cooled to room temperature. The solvent was removed *in vacuo* and the residue was then purified using flash chromatography (10% ethylacetate in petroleum ether) to give the *hydroxyamide* (45 mg, 67%) as a pale yellow oil; $\nu_{max}(cm^{-1})$: 3290 (O-H and N-H), 1713 (ester C=O), 1660 (amide C=O), 1632 (C=C), 1558 (amide dimer) and 975 (*trans*-C=C-H); λ_{max} (EtOH)/nm (ε): 210 (60 150) and 308 (58 450); δ_H (400 MHz $CDCl_3$): 7.64 (dd, *J* 11.8 and 15.3 Hz, COCH:C**H**CH), 6.84 (dt, *J* 15.3 and 7.1 Hz, COCHC**H**), 6.25 (d, *J* 15.3 Hz, $NHCH_2CH$:C**H**), 6.14 (d, *J* 11.8 Hz, $C(CH_3)$:C**H**CH:), 6.05 (t, *J* 6.1 Hz, N**H**), 5.90 (m, 3 H, NHCOC**H**:, COC**H**:CH and NH_2CHC**H**:), 4.20 (q, *J* 7.1 Hz, $OC\mathbf{H}_2CH_3$), 4.03 (t, *J* 5.6 Hz, $HOC\mathbf{H}_2CH_2$), 3.74 (app t, *J* 6.1 Hz, $NHC\mathbf{H}_2CH$:), 2.43 (app q, *J* 5.6 Hz, $HOCH_2C\mathbf{H}_2$), 1.95 (:CHC($C\mathbf{H}_3$):CH) and 1.30 (t, *J* 7.1 Hz, OCH_2CH_3); δ_C (67.8 MHz $CDCl_3$): 167.3 (s), 165.8 (s), 142.7 (s), 141.4 (d), 140.1 (d), 135.6 (d), 128.5 (d), 125.6 (d), 121.3 (d), 60.9 (t), 60.3 (t), 41.4 (t), 35.3 (t), 14.3 (q) and 13.2 (q).

(E,E,E,E)-N-(8-hydroxy-4-methyl-9-(4-hydroxymethyloxazol-2-ylnona-2,4,6-trienyl))-5-hydroxypent-2-enamide **(220).**



A solution of triphenylarsine (4.25 mg, 13.88 μmol) in dry DMF (1 cm^3) was added dropwise, over 2 min, to a stirred solution of tris(benzylideneacetone)dipalladium(0) (1.59 mg, 1.735 μmol) in dry DMF (7 cm^3) at room temperature, under an atmosphere of nitrogen, in a scrupulously dried flask. The mixture was stirred for 30 min and a solution of the bromide **(203)** (50 mg, 0.1735 mmol), in dry DMF (1 cm^3), and then a solution of the stannane **(132)** (77 mg, 0.1735 mmol), in dry DMF (1 cm^3), were added dropwise over 2 min. The mixture was heated at 100°C for 18 h and was then allowed to cooled to room temperature. The solvent was removed *in vacuo* and the residue was then purified using flash chromatography (5% MeOH in CH_2Cl_2) to give the *triol* (25 mg, 40%) as a pale sticky yellow solid; $\nu_{max}(cm^{-1})$: 3300 (O-H), 1682 (amide C=O), 1635 (C=C), 1575 (amide dimer), 1565 (cyclic C=N) and 953 (*trans* C=C-H); λ_{max} (EtOH)/nm (ε): 214 (60 050) and 310 (57 320); δ_H (500 MHz CD_3OD): 7.69 (oxazole :C<u>H</u>), 6.78 (dt, *J* 15.4 and 6.4 Hz, COCH:C<u>H</u>), 6.62 (ddd, *J* 1.2, 11.2 and 15.1 Hz, $CH_2CHOHC\underline{H}$:), 6.22 (d, *J* 15.6 Hz, $NHCH_2CH:C\underline{H}$), 6.04 (d, *J* 15.1 Hz, :CHC(CH_3):C<u>H</u>), 5.98 (dd, *J* 1.4 and 15.4 Hz, COC<u>H</u>:), 5.75 (dd, *J* 6.4 and 15.1 Hz, CHOHCH:C<u>H</u>), 5.72 (dt, *J* 15.6 and 6.4 Hz, $NHCH_2C\underline{H}$:), 5.71 (m, N<u>H</u>), 4.62 (app q, *J* 6.4 Hz, C<u>H</u>OH), 4.48 ($HOC\underline{H}_2C(N):CH$), 3.92 (t, *J* 6.4 Hz, $HOC\underline{H}_2CH_2$), 3.64 (app t, *J* 6.4 Hz, $NHC\underline{H}_2$), 2.96 (dd, *J* 1.2 and 6.4 Hz, $C\underline{H}_2CHOH$), 2.39 (app dq, *J* 1.4 and 6.4 Hz, $HOCH_2C\underline{H}_2$) and 1.82 ($C\underline{H}_3$); δ_C (100 MHz CD_3OD): 168.2 (s), 164.1 (s), 142.5 (d), 141.8 (s), 139.3 (d), 137.0 (s), 136.2 (d), 132.2 (d), 131.1 (d), 127.1 (d), 126.3 (d), 125.9 (d), 71.2 (d), 61.6 (t), 57.8 (t), 42.3 (t), 37.3 (t), 36.3 (t) and 12.8 (q).

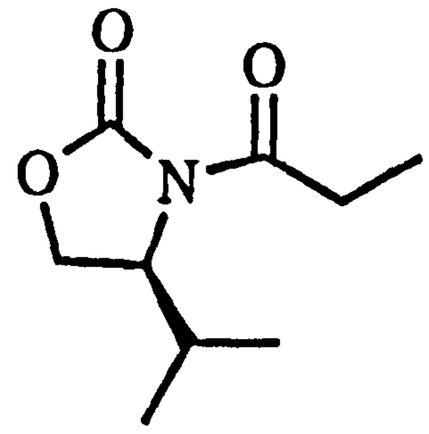
***Virginaimycin model* (197).**



A solution of triphenylarsine (2.12 mg, 7.752 μmol) in dry DMF (1 cm^3) was added dropwise, over 2 min, to a stirred solution of tris(benzylideneacetone)dipalladium(0) (0.79 mg, 0.969 μmol) in dry DMF (8 cm^3) at room temperature, under an atmosphere of nitrogen, in a scrupulously dried flask. The mixture was stirred for 30 min and a solution of the precursor (**198**) (80 mg, 0.0969 mmol), in dry DMF (1 cm^3), was added dropwise over 2 min. The mixture was heated at 100°C for 18 h and then allowed to cooled to room temperature. The solvent was removed *in vacuo* and the residue was then purified using flash chromatography (5% MeOH in CH_2Cl_2) to give a mixture of diastereomers of the *macrolide* (19 mg, 40%) as a pale yellow oil. (The product was found to decompose readily at room temperature or over longer periods at -20°C); $\nu_{max}(cm^{-1})$: 3415 (O-H), 1738 (ester C=O), 1666 (amide C=O), 1632 (C=C), 1552 (amide dimer) and 971 (*trans*-C=C-H); λ_{max} (EtOH)/nm (ε): 278 (54 078) and 288 (58 245); δ_H (500 MHz $CDCl_3$): 8.09 (oxazole :C<u>H</u>), 6.52 (m, 2 H, COCH:C<u>H</u> and CHOHCH:C<u>H</u>), 6.28 (d, *J* 13.5 Hz, $NHCH_2CH$:C<u>H</u>), 6.00 (d, *J* 11.1 Hz, CHOHCH:CHC<u>H</u>:), 5.80 (d, *J* 15.4 Hz, COC<u>H</u>:CH), 5.72 (m, 2 H, CHOHC<u>H</u>: and $NHCH_2C\underline{H}$:), 5.62 (t, *J* 5.6 Hz, N<u>H</u>), 4.62-4.74 (m, 3 H, $CH_2C\underline{H}_2OCOC\underline{H}N$), 4.16 (dt, *J* 3.4 and 4.5 Hz, $CH_2C\underline{H}OH$), 3.85-3.95 (m, 3 H, $NHC\underline{H}_2CH$: and COCHC<u>H</u>H), 3.58 (dt, *J* 2.5 and 8.6 Hz, COCHCH<u>H</u>), 3.16 (dd, *J* 4.5 and 6.6 Hz, $C\underline{H}_2CHOH$), 2.68 (d, *J* 6.8 Hz, CONC<u>H</u>H), 2.45-2.53 (m, 2 H, $OCH_2C\underline{H}_2$), 2.10 (m, 1 H, CONCH<u>H</u>), 1.94 (m, 1H, $CONCH_2C\underline{H}H$), 1.80 ($C\underline{H}_3$) and 1.76 (m, $CONCH_2CH\underline{H}$); δ_C (125 MHz $CDCl_3$): 171.4 (s), 165.5 (s), 160.5 (s), 160.3 (s), 143.1 (d), 139.4 (d), 138.7 (d), 136.6 (s), 135.5 (d), 134.9 (s), 130.3 (d), 126.9 (d),

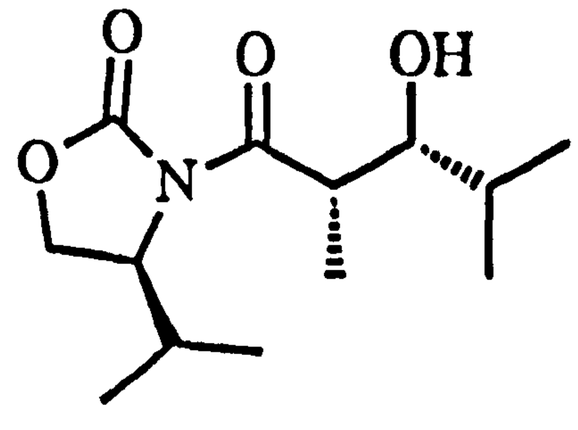
126.6 (d), 124.1 (d), 69.3 (d), 59.6 (d), 49.0 (t), 40.6 (t), 35.7 (t), 33.1 (t), 27.9 (t), 24.6 (t), 17.5 (t) and 13.6 (q).

N-Propionyl-(4S)-isopropyloxazolidin-2-one **(129).**[20]



A solution of *n*-butyllithium 2.5*M* in hexanes (16.1 cm^3, 39.80 mmol) was added dropwise, over 20 min, to a stirred solution of (4*S*)-(-)-isopropyloxazolidin-2-one (5.13 g, 39.72 mmol) in dry THF (150 cm^3), at -78°C, under an atmosphere of nitrogen. The mixture was stirred at this temperature for 15 min and propionyl chloride (3.5 cm^3, 39.80 mmol) was then added dropwise over 10 min. The mixture was stirred at -78°C for 30 min and the reaction then quenched with saturated NH_4Cl solution (100 cm^3). The mixture was extracted with ethyl acetate (3 x 100 cm^3) and the organic extracts were combined and washed with brine. The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (10% ethyl acetate in petroleum ether) to give the oxazolidinone (7.5 g, 95%) as a colourless oil; $\nu_{max}(cm^{-1})$: 1778 (urethane C=O) and 1692 (amide C=O); δ_H (270 MHz $CDCl_3$): 4.42 (dt, *J* 8.8 and 3.1 Hz, $OCH_2CH(^iPr)$), 4.28 (app t, *J* 8.8 Hz, $OCHHCH(^iPr)$), 4.20 (dd, *J* 3.1 and 8.8 Hz, $OCHHCH(^iPr)$), 2.94 (q, *J* 6.9 Hz, $COCH_2CH_3$), 2.38 (dsept, *J* 3.1 and 6.9 Hz, $OCH_2CH(CH(CH_3)_2)N$), 1.17 (t, *J* 6.9 Hz, $COCH_2CH_3$) and 0.89 (dd, *J* 3.1 and 6.9 Hz, $CH(CH(CH_3)_2)$); δ_C (67.8 MHz $CDCl_3$): 174.0 (s), 154.6 (s), 63.3 (t), 58.4 (d), 29.1 (t), 28.3 (d), 17.9 (q), 14.6 (q) and 8.4 (q).

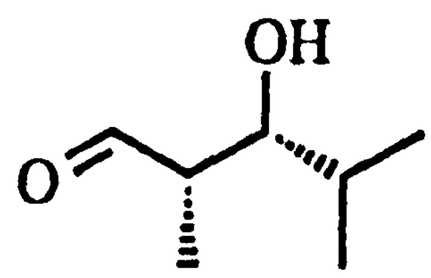
N-((2S)-Methyl-(3R)-hydroxy-4-methylpentanoyl)-(4S)-isopropyl oxazolidin-2-one **(16).**[20]



A solution of di-*n*-butylboron triflate 1*M* in CH_2Cl_2 (17.82 cm^3, 16.30 mmol) was added dropwise, over 10 min, to a stirred solution of the oxazolidinone **(129)** (3 g, 16.20 mmol) in dry CH_2Cl_2 (60 cm^3), at 0°C, under an atmosphere of nitrogen. Diisopropylethylamine (3.4 cm^3, 16.40 mmol) was added dropwise, over 5 min, and the mixture was then stirred at 0°C for 30 min. The mixture was cooled to -78°C and stirred for a further 30 min and then isobutyraldehyde (1.62 cm^3, 16.30 mmol) was added dropwise over 5 min. After stirring at -78°C for 30 min the mixture was allowed to warm to room temperature and stirred for 1.5 h. The mixture was cooled to 0°C and then quenched with a mixture of methanol (80 cm^3) and pH 7 buffered water (40 cm^3) and was then stirred for 1 h at 0°C with 30% hydrogen peroxide (40 cm^3). The mixture was extracted with ether (3 x 100 cm^3) and then washed with brine. The dried solution ($MgSO_4$) was concentrated *in vacuo* and the colourless residue was then purified using flash chromatography (10% ethyl acetate in petroleum ether). The resulting solid was recrystallized (diethyl ether) to give the hydroxyoxazolidinone (3.4 g, 80%) as colourless crystalline solid as one diastereomer, m.p. 86°C (Lit.[20] m.p. 85°C); $[\alpha]_D$ +27.7° (*c* 3.90 in $CHCl_3$) (Lit.[20] -8.22 (*c* 4.70 in $CHCl_3$))$\nu_{max}(cm^{-1})$: 3472 (O-H), 1779 (urethane C=O) and 1692 (amide C=O); δ_H (400 MHz $CDCl_3$): 4.47 (dt, *J* 3.2 and 8.9 Hz, $OCH_2C\underline{H}(^iPr)$), 4.29 (app t, *J* 8.9 Hz, $OC\underline{H}HCH(^iPr)$), 4.22 (dd, *J* 3.2 and 8.9 Hz, $OCH\underline{H}CH(^iPr)$), 3.97 (dq, *J* 2.0 and 6.9 Hz, $COC\underline{H}(CH_3)$), 3.51 (app dt, *J* 2.0 and 6.9 Hz, $C\underline{H}OH(^iPr)$), 3.05 (d, *J* 3.0 Hz, $CHO\underline{H}(^iPr)$), 2.35 (dsept, *J* 3.2 and 6.9 Hz, $OCH_2CH(C\underline{H}(CH_3)_2)N$), 1.70 (dsept, *J* 2.0 and 6.9 Hz, $CHOH(C\underline{H}(CH_3)_2)$), 1.23 (d, *J* 6.9 Hz, $COCH(C\underline{H}_3)$), 1.02 (d, *J* 6.9

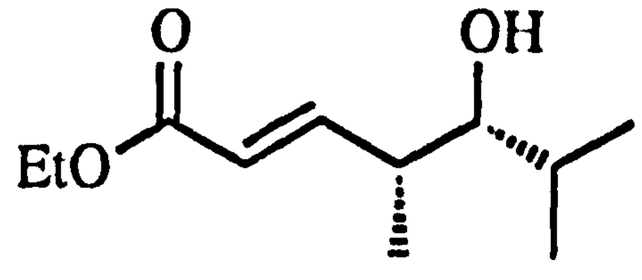
Hz, $OCH_2CH(CH(C\underline{H}_3)CH_3)N$), 0.92 (d, *J* 6.9 Hz, $OCH_2CH(CH(CH_3)C\underline{H}_3)N$) and 0.90 (app dd, *J* 2.0 and 6.9 Hz, $CHOH(CH(C\underline{H}_3)_2)$); δ_C (67.8 MHz $CDCl_3$): 178.3 (s), 153.5 (s), 76.5 (d), 63.4 (t), 58.3 (d), 39.5 (d), 30.7 (d), 28.4 (d), 19.4 (q), 19.0 (q), 18.0 (q), 14.8 (q) and 10.4 (q).

(2S)-Methyl-(3R)-hydroxy-4-methylpentanal **(18).**[20]



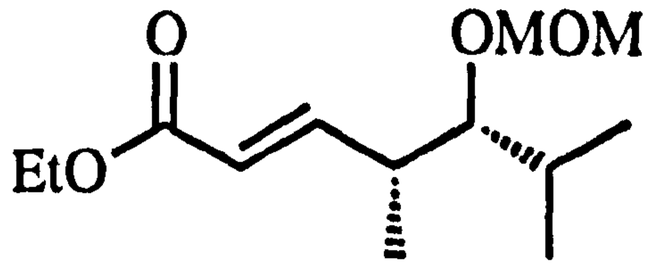
A solution of the hydroxyoxazolidinone (**16**) (3.47 g, 14.40 mmol) in dry THF (2 cm^3) was added dropwise, over 5 min, to a stirred solution of sodium bis(2-methoxyethoxy) aluminium hydride 3.4*M* in toluene (5.1 cm^3, 14.60 mmol) in dry THF (100 cm^3) under an atmosphere of nitrogen. The mixture was cooled to -78°C and then stirred for 30 min. The mixture was allowed to warm to -50°C and stirred for a further 1 h. After quenching the reaction with a mixture of ethyl acetate (20 cm^3) and methanol (5 cm^3), the solution was poured into a mixture of 2*M* HCl (60 cm^3) and ether (120 cm^3) at -20°C and stirred for 15 min. The organic layer was decanted from the resultant gel and the gel was then washed with ether (2 x 50 cm^3) at -20°C. The ether washings were combined and the dried solution (K_2CO_3) concentrated *in vacuo* to leave a colourless oil (3.4 g). The aldehyde was carried through crude without further purification; $\nu_{max}(cm^{-1})$: 3474 (O-H) and 1716 (aldehyde C=O); δ_H (400 MHz $CDCl_3$): 9.65 (d, *J* 6.9 Hz, C$\underline{H}$O), 3.28 (app dt, *J* 2.0 and 6.9 Hz, C$\underline{H}$OH(^{i}Pr)), 2.51 (m, 1 H, OHCC$\underline{H}$(CH_3)), 1.72 (dsept, *J* 2.0 and 6.9 Hz, C$\underline{H}$(CH_3)$_2$), 1.40 (d, *J* 5.5 Hz, O$\underline{H}$), 1.11 (d, *J* 6.9 Hz, CH($C\underline{H}_3$)) and 0.93 (app dd, *J* 4.0 and 6.9 Hz, CH($C\underline{H}_3$)$_2$); δ_C (67.8 MHz $CDCl_3$): 201.8 (d), 79.2 (d), 30.8 (d), 19.6 (q), 14.1 (q) and 13.9 (q).

***(E)-Ethyl-(4R)-methyl-(5R)-hydroxy-6-methyl-2-heptenoate* (127).[20]**



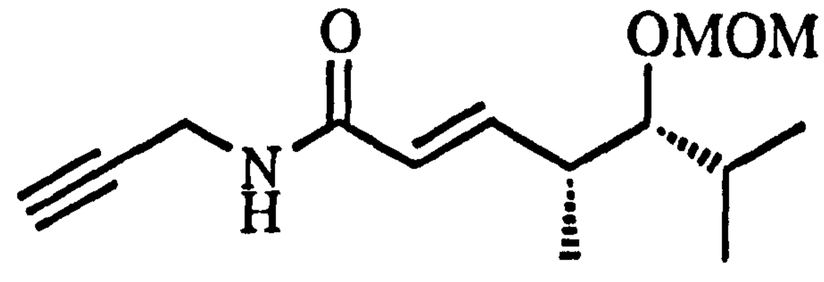
Triethyl phosphonoacetate (2.86 cm^3, 14.50 mmol) was added dropwise, over 10 min, to a stirred suspension of potassium *t*-butoxide (1.54 g, 14.40 mmol) in dry THF (100 cm^3), at 0°C, under an atmosphere of nitrogen. The mixture was stirred at this temperature for 30 min and was then cooled to -78°C. The crude aldehyde (18) (14.40 mmol based on starting hydroxy oxazolidinone) was added dropwise, over 10 min, and the mixture was stirred for 3 h while allowing to warm to room temperature. The reaction was quenched with saturated NH_4Cl solution (5 cm^3), the mixture was then diluted with ethyl acetate (100 cm^3) and washed with water (3 x 50 cm^3). The dried organic layer ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (10% ethyl acetate in petroleum ether) to give the *h*ydroxyester (1.6 g, 60% over 2 steps) as a colourless oil; $[\alpha]_D$ +18.10 (*c* 1.89 in $CHCl_3$) (Lit.[20] +18.97 (*c* 5.83 in $CHCl_3$)); $\nu_{max}(cm^{-1})$: 3476 (O-H), 1714 (ester C=O), 1650 (C=C), 1369 (O-H) and 989 (*trans* C=C-H); δ_H (400 MHz $CDCl_3$): 6.92 (dd, *J* 6.8 and 15.8 Hz, COCH:C<u>H</u>), 5.85 (dd, *J* 1.2 and 15.8 Hz, COC<u>H</u>:CH), 4.20 (q, *J* 7.1 Hz, O<u>C</u>H_2CH_3), 3.28 (app q, *J* 6.8 Hz, C<u>H</u>OH(^{i}Pr)), 2.50 (app dq, *J* 1.2 and 6.8 Hz, :CHC<u>H</u>(CH_3)), 1.72 (app oct, *J* 6.8 Hz, CH(C<u>H</u>(CH_3)$_2$)), 1.41 (d, *J* 5.3 Hz, CHO<u>H</u>(^{i}Pr)), 1.30 (t, *J* 6.8 Hz, OCH$_2$C<u>H</u>$_3$), 1.11 (d, *J* 6.8 Hz, CH(C<u>H</u>$_3$)CHOH) and 0.94 (app dd, *J* 3.9 and 6.8 Hz, CH(C<u>H</u>$_3$)$_2$); δ_C (67.8 MHz $CDCl_3$): 166.6 (s), 151.8 (d), 120.6 (d), 78.8 (d), 60.1 (t), 39.8 (d), 30.8 (d), 19.6 (q), 16.4 (q) and 13.9 (q).

(E)-Ethyl (4R)-methyl-(5R)-(methoxy)methoxy-6-methyl-2-heptenoate (223).



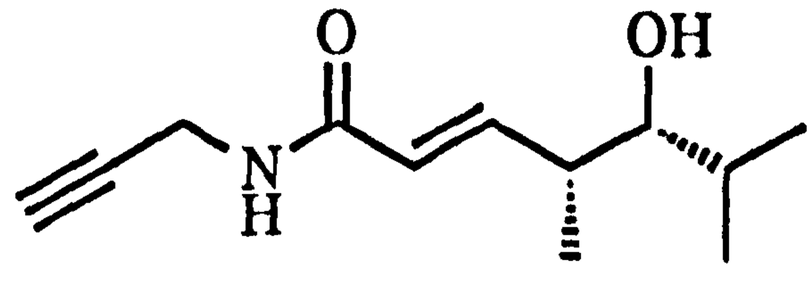
Chloromethyl methyl ether (2 cm^3, 27 mmol) was added in four portions, at 30 min intervals, to a stirred solution of the hydroxyester **(127)** (634 mg, 3.368 mmol) and diisopropylethylamine (1 cm^3, 5.75 mmol) in dry CH_2Cl_2 (20 ml), at reflux, under an atmosphere of nitrogen. The mixture was heated for a further 30 min and was then allowed to cool to room temperature before washing with water (20 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (10% ethyl acetate in petroleum ether) to give the protected *hydroxyester* (596 mg, 85%) as a colourless oil; (Found: C, 63.6; H, 10.3%; M^+-OCH_3, 213.1463. $C_{13}H_{24}O_4$ requires C, 63.9; H, 9.9%; M^+-OCH_3, 213.1480); $[\alpha]_D$ +25.75 (*c* 1.165 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 2850 (OCH_3), 1722 and 1714 (ester C=O) and 1650 (C=C); δ_H (400 MHz $CDCl_3$): 6.97 (dd, *J* 7.9 and 15.7 Hz, COCH:C<u>H</u>), 5.82 (dd, *J* 1.2 and 15.7 Hz, COC<u>H</u>:CH), 4.63 ($OC\underline{H}_2OCH_3$), 4.18 (q, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 3.39 ($OC\underline{H}_3$), 3.20 (t, *J* 5.4 Hz, C<u>H</u>OH(^{i}Pr)), 2.59 (app hext, *J* 6.9 Hz, :CHC<u>H</u>(CH_3)), 1.80 (app oct, *J* 5.4 Hz, CH(C<u>H</u>(CH_3)$_2$)), 1.29 (t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$), 1.10 (d, *J* 6.9 Hz, CH($C\underline{H}_3$)CHOH) and 0.93 (app dd,*J* 6.9 and 9.2 Hz, CH($C\underline{H}_3$)$_2$); δ_C (100 MHz $CDCl_3$): 166.5 (s), 152.0 (d), 120.4 (d), 98.1 (t), 86.9 (d), 60.1 (t), 55.9 (q), 39.4 (d), 30.7 (d), 20.0 (q), 17.4 (q), 14.7 (q) and 14.2 (q); *m/z* (EI): 213 (34%, M^+-OCH_3), 183 (16, M^+-OMOM), 141 (80) and 45 (100,$MOMO^+$).

***(E)-N-Propargyl-(4R)-methyl-(5R)-(methoxy)methoxy-6-methyl-2-heptenamide* (224).**



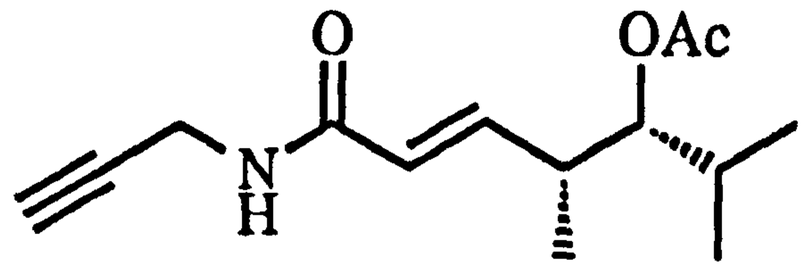
A solution of trimethylaluminium 2*M* in CH_2Cl_2 (78.35 cm^3, 156.7 mmol) was added dropwise, over 30 min, to a stirred solution of propargylamine (10.75 cm^3, 156.7 mmol) in dry CH_2Cl_2 (250 cm^3) at 0°C, under an atmosphere of nitrogen, in a scrupulously dried flask. The mixture was stirred at room temperature for 30 min and the protected hydroxyester **(223)** (9.57 g, 39.17 mmol) was added in one portion. The mixture was heated under reflux for 3 h and then cooled to 0°C before carefully quenching with water (50 cm^3). The mixture was extracted with CH_2Cl_2 (3 x 100 cm^3) and the extracts were combined. The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (3% MeOH in CH_2Cl_2) to give the *amide* (7.5 g, 80%) as a colourless oil; (Found: C, 66.4; H, 9.3; N, 5.4%; M^+-OCH_3, 222.1506. $C_{14}H_{23}NO_3$ requires C, 66.4; H, 9.2; N, 5.5%; M^+-OCH_3, 222.1494); $[\alpha]_D$ +17.25 (*c* 1.125 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3480 (N-H), 1667 (amide C=O), 1633 (C=C) and 1537 (amide dimer); δ_H (400 MHz $CDCl_3$): 6.84 (dd, *J* 8.0 and 15.4 Hz, COCH:CH), 5.85 (NHCO), 5.80 (dd, *J* 1.2 and 15.4 Hz, COCH:CH), 4.64 (OCH_2OCH_3), 4.12 (dd, *J* 1.7 and 2.8 Hz, $HCCCH_2$), 3.39 (OCH_3), 3.17 (app t, *J* 5.4 Hz, CHOR(^{i}Pr)), 2.56 (app hext, *J* 6.7 Hz, :CHCH(CH_3)), 2.24 (t, *J* 2.8 Hz, $HCCCH_2$), 1.79 (app hext, *J* 6.7 Hz, $CH(CH(CH_3)_2)$), 1.09 (d, *J* 6.7 Hz, $CH(CH_3)CHOH$) and 0.91 (app dd, *J* 5.3 and 6.7 Hz, $CH(CH_3)_2$); δ_C (67.8 MHz $CDCl_3$): 165.7 (s), 148.1 (d), 122.1 (d), 98.2 (t), 87.4 (d), 79.5 (d), 71.3 (s), 55.9 (q), 39.2 (d), 30.6 (d), 28.9 (t), 20.0 (q) and 18.8 (q); *m/z* (EI): 222 (95%, M^+-OCH_3), 192 (45, M^+-OMOM), 150 (100), 68 (85) and 45 (100).

(E)-N-Propargyl-(4R)-methyl-(5R)-hydroxy-6-methyl-2-heptenamide (225).



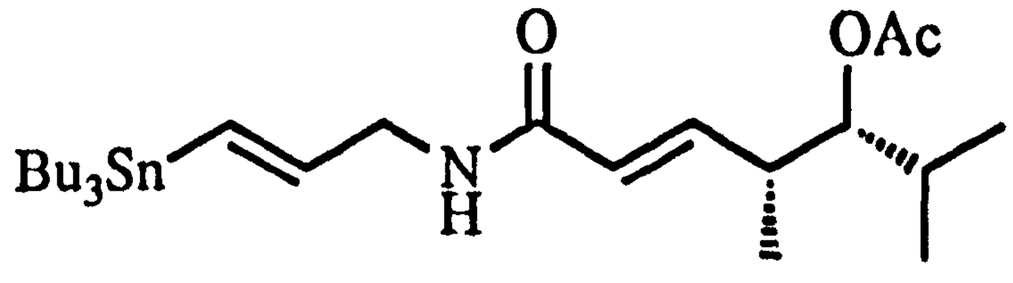
Bromotrimethylsilane (1.18 cm^3, 9.172 mmol) was added dropwise, over 5 min, to a stirred solution of the MOM ether **(224)** (581 mg, 2.293 mmol) in dry CH_2Cl_2 (50 cm^3), at -78°C, under an atmosphere of nitrogen. The mixture was stirred at this temperature for 1h and water (10 cm^3) was added and the mixture then allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (50 cm^3) and the extracts were then combined and washed with brine (2 x 25 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* to leave the *hydroxyamide* (524 mg, 95%) as a colourless oil: (Found: M^+-isobutyraldehyde, 137.0846 . $C_{12}H_{19}NO_2$ requires M^+-isobutyraldehyde, 137.0841); $[\alpha]_D$ +19.70 (*c* 0.355 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3432 (N-H and O-H), 1738 (amide C=O), 1242 (O-H) and 966 (*trans* C=C-H); λ_{max} (EtOH)/nm (ε): 215 (6066); δ_H (500 MHz $CDCl_3$): 6.84 (dd, *J* 7.8 and 15.4 Hz, COCH:C<u>H</u>), 6.05 (N<u>H</u>CO), 5.85 (dd, *J* 1.0 and 15.4 Hz, COC<u>H</u>:CH), 4.11 (dd, *J* 2.5 and 5.0 Hz, HCCC<u>H</u>$_2$), 3.26 (app t, *J* 6.8 Hz, C<u>H</u>OH(^{i}Pr)), 2.49 (app dq, *J* 0.8 and 6.8 Hz, :CHC<u>H</u>(CH_3)), 2.24 (t, *J* 2.5 Hz, <u>H</u>CCCH$_2$), 2.09 (CHO<u>H</u>), 1.71 (app oct, *J* 6.8 Hz, CHOH(C<u>H</u>(CH_3)$_2$), 1.08 (d, *J* 6.8 Hz, :CHCH(C<u>H</u>$_3$)) and 0.92 (app dd, *J* 3.4 and 6.8 Hz, CHOH(CH(C<u>H</u>$_3$)$_2$); δ_C (100 MHz $CDCl_3$): 166.1 (s), 148.5 (d), 122.4 (d), 79.1 (d), 71.4 (s), 39.5 (d), 30.8 (d), 29.9 (t), 19.6 (q), 17.2 (q) and 13.5 (q); *m/z* (EI): 181 (15%), 169 (15), 137 (30, M^+-isobutyraldehyde), 82 (25, M^+-isobutyraldehyde, -propargylamine), 69 (100) and 55 (30, propargylamine).

***(E)-N-Propargyl-(4R)-methyl-(5R)-acetoxy-6-methyl-2-heptenamide* (226).**



Acetyl chloride (0.273 cm^3, 3.723 mmol) was added dropwise, over 1 min, to a stirred solution of the hydroxyamide **(225)** (524 mg, 2.327 mmol.) and pyridine (0.309 cm^3, 3.723 mmol.), in dry CH_2Cl_2 (20 cm^3), at 0°C. DMAP (10 mg) was added and the mixture was then stirred overnight while allowing to warm to room temperature. The mixture was washed with 1*M* HCl (50 cm^3), then washed with saturated Na_2CO_3 (50 cm^3), and finally with brine (50ml). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (3% MeOH in CH_2Cl_2) to give the *amide* (542 mg, 95%) as a colourless oil; (Found: M^+-acetic acid, 192.1395 . $C_{14}H_{21}NO_3$ requires M^+-acetic acid, 192.1388); $[\alpha]_D$ +5.50 (*c* 1.055 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3269 (N-H), 1731 (ester C=O), 1667 (amide C=O), 1632 (C=C), 1537 (amide dimer) and 985 (*trans* C=C-H); λ_{max} (EtOH)/nm (ε): 216 (6300); δ_H (500 MHz $CDCl_3$): 6.74 (dd, *J* 8.1 and 15.4 Hz, COCH:C**H**), 5.82 (dd, *J* 0.9 and 15.4 Hz, COC**H**:CH), 5.64 (N**H**CO), 4.78 (dd, *J* 5.0 and 7.0 Hz, CH(CH_3)C**H**OAc), 4.12 (dd, *J* 2.6 and 5.3 Hz, HCCC$\underline{H}_2$), 2.63 (app sext, *J* 7.0 Hz, :CHC**H**(CH_3)), 2.25 (t, *J* 2.6 Hz, **H**CCC$\underline{H}_2$), 2.08 (COC$\underline{H}_3$), 1.87 (app doct, *J* 1.6 and 5.0 Hz, CHOAc(C**H**(CH_3)$_2$), 1.03 (d, *J* 7.0 Hz, :CHCH($C\underline{H}_3$)) and 0.88 (app dd, *J* 5.0 and 7.0 Hz, CHOH(CH($C\underline{H}_3$)$_2$); δ_C (100 MHz $CDCl_3$): 170.8 (s), 165.4 (s), 145.8 (d), 123.2 (d), 79.5 (d), 71.2 (s), 38.2 (d), 29.6 (d), 28.9 (t), 20.6 (q), 19.5 (q), 16.1 (q) and 15.2 (q); *m/z* (EI): 251 (3%, M^+), 137 (80, M^+-Ac, -isobutyraldehyde), 69 (85), 55 (20, propargylamine) and 43 (100, Ac).

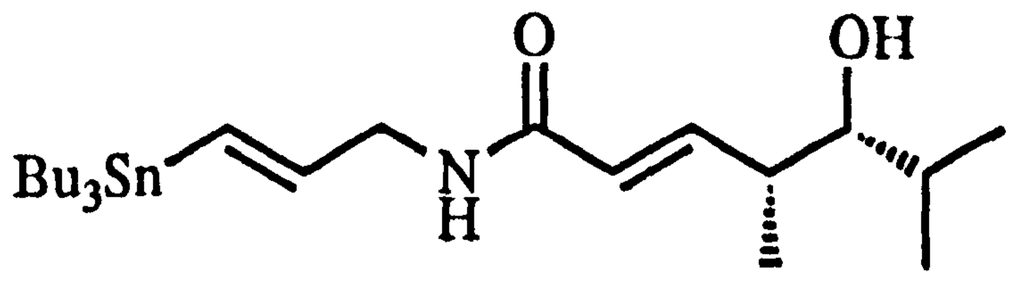
***(E)-N-(3-tri-n-butylstannylprop-2-enyl)-(4R)-methyl-(5R)-acetoxy-6-methyl-2-heptenamide* (227).**



Copper (I) cyanide (190 mg, 2.123 mmol) was suspended in dry THF (40 cm^3), under an atmosphere of nitrogen, in a scrupulously dried flask. The mixture was cooled to -78°C and a solution of *n*-butyllithium 1.6*M* in hexanes (2.53 cm^3, 4.053 mmol) was added dropwise, over 5 min, and the mixture was then stirred at -78°C for 15 min. Tri-*n*-butyltin hydride (1.10 cm^3, 4.053 mmol) was added dropwise, over 5 min, and the mixture was then stirred for a further 15 min at -78°C. A solution of the amide (226) (485 mg, 1.930 mmol) in dry THF (1 cm^3) was added dropwise, over 5 min, and the mixture was stirred for 30 min at -78°C before being quenched with 10% NH_3/NH_4Cl solution (5 cm^3). The mixture was allowed to warm to room temperature and the solids were filtered off. The filtrate was extracted with ethyl acetate (3 x 25 cm^3) and the extracts were then combined and washed with brine. The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (10% ethyl acetate in petroleum ether) to give the *vinyl stannane* (711 mg, 70%) as a colourless oil; (Found: MH^+, 540.2816. $C_{26}H_{49}NO_3Sn$ requires MH^+, 540.2808); $[\alpha]_D$ +0.75 (*c* 0.805 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3275 (N-H), 1744 (ester C=O), 1668 (amide C=O), 1633 (C=C), 1556 (amide dimer) and 986 (*trans* C=C-H); λ_{max} (EtOH)/nm (ε): 214 (12 996); δ_H (500 MHz $CDCl_3$): 6.69 (dd, *J* 8.2 and 15.4 Hz, COCH:C<u>H</u>), 6.10 (dt, *J* 19.0 and 1.3 Hz, SnC<u>H</u>:CH), 5.96 (dt, *J* 19.0 and 5.3 Hz, SnCH:C<u>H</u>), 5.83 (dd, *J* 0.8 and 15.4 Hz, COC<u>H</u>:CH), 5.68 (t, *J* 5.3 Hz, N<u>H</u>CO), 4.75 (dd, *J* 5.0 and 7.4 Hz, $CH(CH_3)C\underline{H}OAc$), 3.97 (app dt, *J* 1.4 and 5.3 Hz, :$CHC\underline{H}_2$), 2.60 (app sext, *J* 7.4 Hz, :$CHC\underline{H}(CH_3)$), 2.05 ($COC\underline{H}_3$), 1.86 (app oct, *J* 5.0 Hz, $CHOAc(C\underline{H}(CH_3)_2)$, 1.52 (pent, *J* 7.4 Hz, $SnCH_2C\underline{H}_2$), 1.28 (sept, *J* 7.4 Hz, $SnCH_2CH_2C\underline{H}_2$), 1.03 (d, *J* 7.4 Hz, :$CHCH(C\underline{H}_3)$) and 0.88 (app t, *J* 7.4 Hz,

CHOH(CH(C<u>H</u>$_3$)$_2$) and SnC<u>H</u>$_2$CH$_2$CH$_2$C<u>H</u>$_3$); δ_C (125 MHz $CDCl_3$): 170.9 (s), 165.4 (s), 145.3 (d), 143.5 (d), 130.3 (d), 123.9 (d), 79.8 (d), 44.9 (t), 38.4 (d), 29.8 (d), 29.1 (t), 27.3 (t), 20.9 (q), 19.7 (q), 16.4 (q), 15.4 (q), 13.7 (q) and 9.5 (t); *m/z* (EI): 543 (3%, M^+), 486 (20, M^+-Bu), 426 (65, M^+-Ac, -isobutyraldehyde), 291 (10, Bu_3SnH), 69 (100), 55 (10, propargylamine) and 43 (40, Ac).

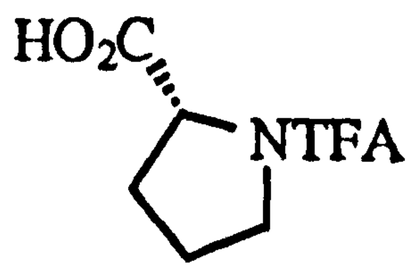
(E)-N-(3-tri-n-butylstannylprop-2-enyl)-(4R)-methyl-(5R)-hydroxy-6-methyl-2-heptenamide **(222).**



Potassium hydroxide (273 mg, 4.867 mmol) was added, in one portion, to a stirred solution of the acetoxyamide **(227)** (563 mg, 0.9733 mmol) in wet methanol (15 cm^3) and the mixture was then stirred at room temperature for 3 h. Brine (5 cm^3) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 cm^3) and the extracts then combined. The dried solution ($MgSO_4$) was concentrated *in vacuo* to leave the *hydroxyamide* (4.9g, 98%) as a colourless oil; (Found: C, 57.6; H, 9.65; N, 3.1%; M^+-Bu, 444.1148. $C_{24}H_{46}NO_3Sn$ requires C, 57.5; H, 9.4; N, 2.8%; M^+-Bu, 444.1166); $[\alpha]_D$ +14.55 (*c* 0.275 in $CHCl_3$); ν_{max}(cm^{-1}): 3288 (N-H), 1667 (amide C=O), 1632 (C=C), 1557 (amide dimer) and 986 (*trans* C=C-H); λ_{max} (EtOH)/nm (ε): 208 (12 404) and 220 (13 798); δ_H (500 MHz $CDCl_3$): 6.83 (dd, *J* 7.9 and 15.4 Hz, COCH:C<u>H</u>), 6.13 (dt, *J* 19.0 and 1.3 Hz, SnC<u>H</u>:CH), 5.98 (dt, *J* 19.0 and 5.3 Hz, SnCH:C<u>H</u>), 5.85 (dd, *J* 1.0 and 15.4 Hz, COC<u>H</u>:CH), 5.54 (N<u>H</u>CO), 4.00 (app t, *J* 5.3 Hz, :CHC<u>H</u>$_2$), 3.28 (app q, *J* 5.3 Hz, CH(CH$_3$)C<u>H</u>OH), 2.51 (app sext, *J* 6.7 Hz, C<u>H</u>(CH$_3$)CHOH), 1.75 (app oct, *J* 6.7 Hz, :CHC<u>H</u>(CH$_3$)), 1.52 (pent, *J* 6.7 Hz, SnCH$_2$C<u>H</u>$_2$), 1.28 (sept, *J* 6.7 Hz, SnCH$_2$CH$_2$C<u>H</u>$_2$), 1.03 (d, *J* 6.7 Hz, :CHCH(C<u>H</u>$_3$)) and 0.88 (app t, *J* 6.7 Hz, CHOH(CH(C<u>H</u>$_3$)$_2$) and

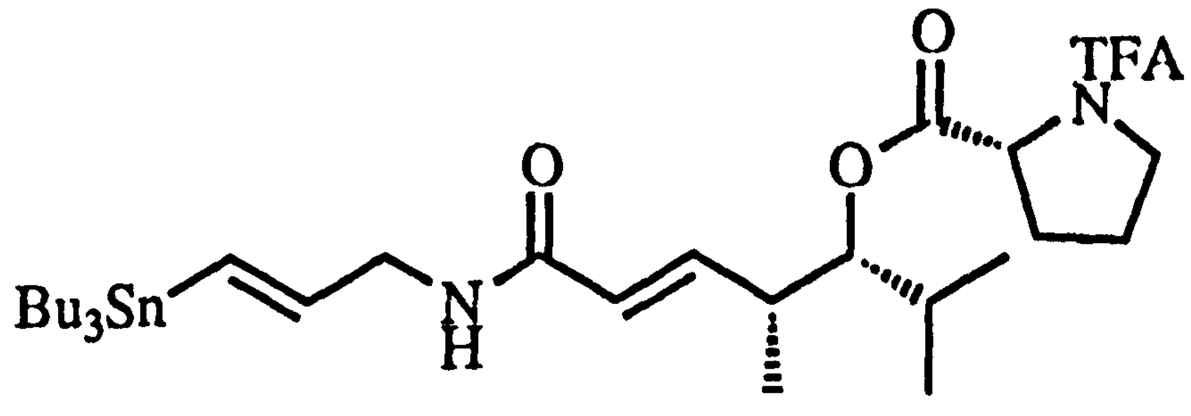
$SnC\underline{H}_2CH_2CH_2C\underline{H}_3$); δ_C (67.8 MHz $CDCl_3$): 165.8 (s), 147.5 (d), 143.3 (d), 129.9 (d), 123.1 (d), 79.0 (d), 39.5 (d), 30.7 (d), 28.9 (t), 27.1 (t), 19.6 (q), 16.9 (q), 13.7 (q), 13.5 (q) and 9.2 (t); *m/z* (EI): 444 (5%, M^+-Bu), 372 (45, M^+-Bu, -isobutyraldehyde), 119 (55) and 69 (100).

N-Trifluoroacetate-(R)-proline **(228).**[104]



Triethylamine (0.581 cm^3, 4.169 mmol) was added dropwise, over 2 min, to a stirred solution of (*R*)-proline (480 mg, 4.169 mmol) in dry MeOH (5 cm^3), at room temperature, under an atmosphere of nitrogen. Ethyl trifluoroacetate (0.595 cm^3, 5 mmol) was added dropwise and the mixture was then stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (10 cm^3). The solution was washed with 2*M* HCl (5 cm^3) and the dried solution ($MgSO_4$) was conentrated *in vacuo* to leave a 4:1 mixture of rotamers of the protected *proline* (752 mg, 86%) as a colourless sticky solid: $\nu_{max}(cm^{-1})$: 3160 (O-H), 1732 (acid C=O), 1683 (amide C=O) and 1232 and 758 (C-F); δ_H (400 MHz $CDCl_3$): 4.71 (d, *J* 8.9 Hz, 0.2 H, $HO_2CC\underline{H}$), 4.57 (dd, *J* 3.9 and 8.9 Hz, 0.8 H, $HO_2CC\underline{H}$), 3.84 (m, 1 H, $CONC\underline{H}H$), 3.76 (m, 1 H, $CONCH\underline{H}$), 2.30 (m, 1 H, $COCHC\underline{H}H$) and 2.05-2.20 (m, 3 H, $COCHCH\underline{H}$ and $COCHCH_2C\underline{H}_2$); δ_C (67.8 MHz $CDCl_3$): 176.2 (s), 156.6 (q, *J* 5.8 Hz, $\underline{C}OCF_3$), 116.2 (q, *J* 24.5 Hz, $CO\underline{C}F_3$), 69.0 (d), 59.2 (d), 48.0 (t), 47.2 (t), 31.5 (t), 28.4 (t), 24.8 (t) and 21.0 (t).

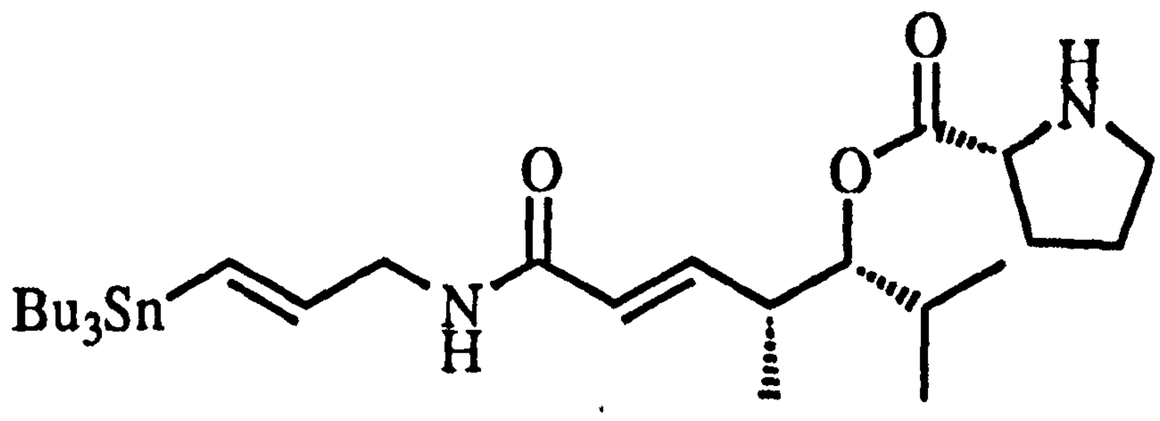
***(E,E)-N-(3-tri-n-butylstannylprop-2-enyl)-(4R)-methyl-(5R)-(N'-trifluoro acetoxy-(R)-prolinoyloxy)-6-methyl-2-heptenamide* (229).**



DCC (124 mg, 0.5995 mmol) was added, in one portion, to a stirred solution of the proline (**228**) (116 mg, 0.5496 mmol), DMAP (122 mg, 0.9992 mmol), and the alcohol (**222**) (250 mg, 0.4996 mmol) in dry CH_2Cl_2 (2 cm^3), at 0°C, under an atmosphere of nitrogen. The mixture was stirred for 48 h and was then washed with water (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (2% MeOH in CH_2Cl_2) to give a 4:1 mixture of rotamers of the *ester* (350 mg, 61%) as a colourless oil; (Found: C, 54.1; H, 7.9; N, 4.4%; *MH*$^+$, 691.3029. $C_{31}H_{53}F_3N_2O_4Sn$ requires C, 53.6; H, 7.7; N, 4.0%; *MH*$^+$, 691.3053); ν_{max}(cm^{-1}): 3210 (N-H), 1747 (ester C=O), 1697 (amide C=O), 1634 (C=C) and 1539 (amide dimer); λ_{max} (EtOH)/nm (ε): 211 (9852); δ_H (500 MHz $CDCl_3$): 6.64 (dd, *J* 6.6 and 15.5 Hz, COCH:C<u>H</u>), 6.12 (d, *J* 19 Hz, SnC<u>H</u>:), 5.98 (dt, *J* 19.0 and 5.2 Hz, SnCH:C<u>H</u>), 5.83 (d, *J* 15.5 Hz, COC<u>H</u>:CH), 5.72 (t, *J* 5.2 Hz, N<u>H</u>), 4.81 (app t, *J* 6.6 Hz, CH(CH_3)C<u>H</u>(^{i}Pr)), 4.60 (dd, *J* 3.6 and 8.7 Hz, COC<u>H</u>NCO), 3.99 (app q, *J* 5.2 Hz, NHC<u>H_2</u>CH:), 3.82 (m, COCHC<u>H</u>H), 3.74 (m, COCHCH<u>H</u>), 2.66 (app hext, *J* 6.6 Hz, :CHC<u>H</u>(CH_3)), 2.25 (m, CHN(CO)C<u>H</u>H), 2.08 (m, 3 H, CHN(CO)CH<u>H</u>C<u>H_2</u>), 1.92 (app oct, *J* 6.6 Hz, CH(C<u>H</u>(CH_3)$_2$)), 1.47 (pent, *J* 7.4, SnC<u>H_2</u>C<u>H_2</u>), 1.30 (hext, *J* 7.4 Hz, SnC<u>H_2</u>C<u>H_2</u>C<u>H_2</u>), 1.04 (d, *J* 6.6 Hz, :CHCH(CH_3)), 0.92 (app dd, *J* 6.6 and 9.2 Hz, CH(CH(CH_3)$_2$)) and 0.89 (t, *J* 7.4 Hz, SnC<u>H_2</u>C<u>H_2</u>C<u>H_2</u>C<u>H_3</u>); δ_C (125 MHz $CDCl_3$): 170.4 (s), 165.4 (s), 155.7 (q, *J* 6.0 Hz, <u>C</u>OCF_3), 144.7 (d), 143.4 (d), 130.3 (d), 124.3 (d), 116.0 (q, *J* 24.7 Hz, CO<u>C</u>F_3), 81.5 (d), 60.4 (d), 47.1 (t), 44.9 (t), 37.9 (d), 29.8 (t), 29.0 (d), 28.7 (t), 27.3 (t), 24.9 (t), 19.5 (q), 17.1 (q), 14.3 (q), 13.7 (q) and 9.4 (t); *m/z* (FAB): 695

(85%, MH^+), 637 (60, M^+-Bu), 426 (75, M^+-Bu, -TFApro), 291 (15, Bu_3SnH) and 177 (100).

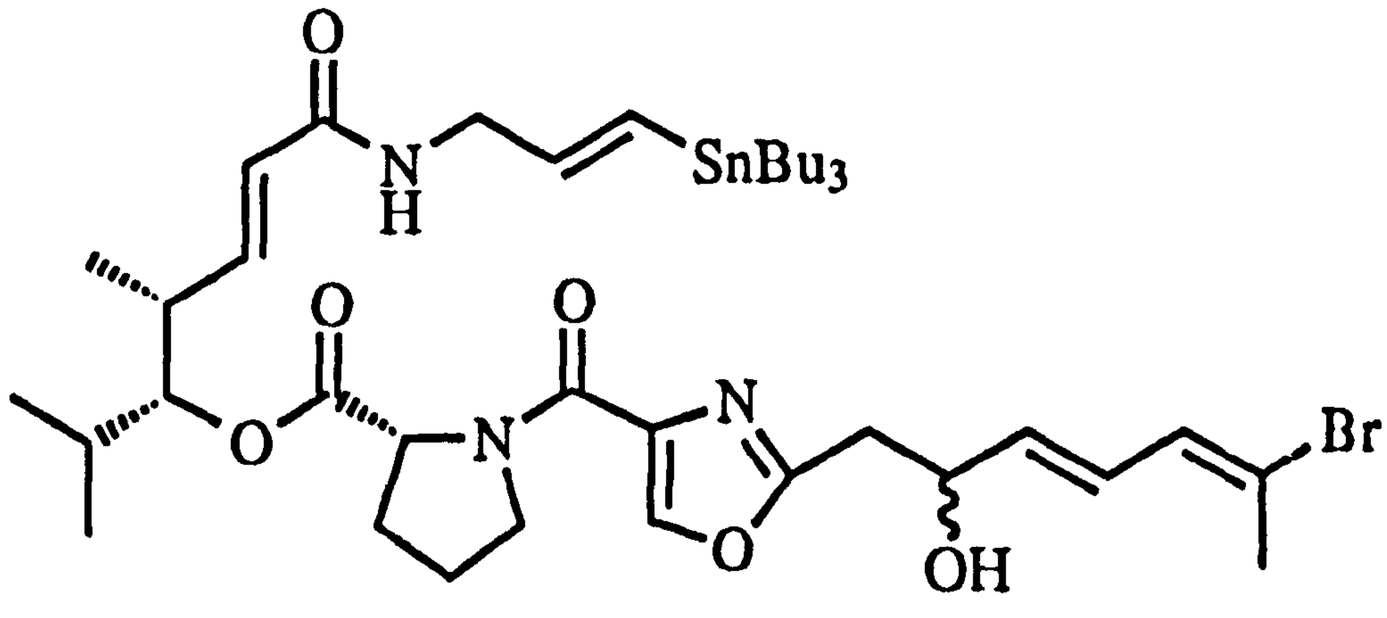
(E,E)-N-(3-tri-n-butylstannylprop-2-enyl)-(4R)-methyl-(5R)-((R)-prolinoyloxy)-6-methyl-2-heptenamide **(230).**



Potassium carbonate (84 mg, 0.6043 mmol) was added, in one portion, to a stirred solution of the ester **(229)** (381 mg, 0.5494 mmol) in wet MeOH (5 cm^3) at room temperature, and the mixture was stirred overnight. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (5 cm^3). The solution was washed with saturated Na_2CO_3 (5 cm^3) and the dried solution ($MgSO_4$) was concentrated *in vacuo*. The residue was purified using flash chromatography (5% MeOH in ethyl acetate) to give the *amine* (301 mg, 95%) as a colourless oil; $[\alpha]_D$ +16.20 (*c* 0.42 in $CHCl_3$); $\nu_{max}(cm^{-1})$: 3300 (N-H), 1738 (ester C=O), 1680 (amide C=O), 1650 (C=C) and 1570 (amide dimer); λ_{max} (EtOH)/nm (ε): 210 (10 306); δ_H (500 MHz $CDCl_3$): 6.71 (dd, *J* 7.8 and 15.4 Hz, COCH:C<u>H</u>), 6.13 (dt, *J* 19.0 and 1.0 Hz, SnC<u>H</u>:), 5.97 (dt, *J* 19.0 and 5.6 Hz, SnCH:C<u>H</u>), 5.84 (dd, *J* 0.8 and 15.4 Hz, COC<u>H</u>:), 5.56 (t, *J* 5.6 Hz, CON<u>H</u>), 4.83 (app t, *J* 6.8 Hz, C<u>H</u>OR(^{i}Pr)), 4.00 (app q, *J* 5.6 Hz, NHC<u>H</u>$_2$CH:), 3.80 (dd, *J* 5.4 and 8.4 Hz, COC<u>H</u>NH), 3.09 (dt, *J* 10.2 and 6.8 Hz, NHC<u>H</u>HCH$_2$), 2.92 (dt, *J* 10.2 and 6.8 Hz, NHCH<u>H</u>CH$_2$), 2.67 (app sext, *J* 6.8 Hz, :CHC<u>H</u>(CH$_3$)), 2.42 (m, 1 H COCHC<u>H</u>H), 2.15 (m, 1 H COCHCH<u>H</u>), 1.89 (app oct, *J* 6.8 Hz, CHOR(C<u>H</u>(CH$_3$)$_2$)), 1.70-1.82 (m, 2 H, COCHCH$_2$C<u>H</u>$_2$), 1.49 (pent, *J* 7.2 Hz, SnCH$_2$C<u>H</u>$_2$), 1.31 (hext, *J* 7.2 Hz, SnCH$_2$CH$_2$C<u>H</u>$_2$), 1.05 (d, *J* 6.7 Hz, :CHCH(C<u>H</u>$_3$)) and 0.89 (app t, *J* 7.2 Hz, SnC<u>H</u>$_2$CH$_2$CH$_2$C<u>H</u>$_3$ and

CHOR(CH($C\underline{H}_3$)$_2$)); δ_C (125 MHz $CDCl_3$): 175.2 (s), 165.3 (s), 145.2 (d), 143.4 (d), 130.4 (d), 123.9 (d), 80.5 (d), 59.9 (d), 46.9 (t), 44.9 (t), 38.2 (d), 30.5 (t), 29.7 (d), 29.0 (t), 27.3 (t), 25.4 (t), 19.6 (q), 16.8 (q), 14.7 (q), 13.7 (q) and 9.4 (t);

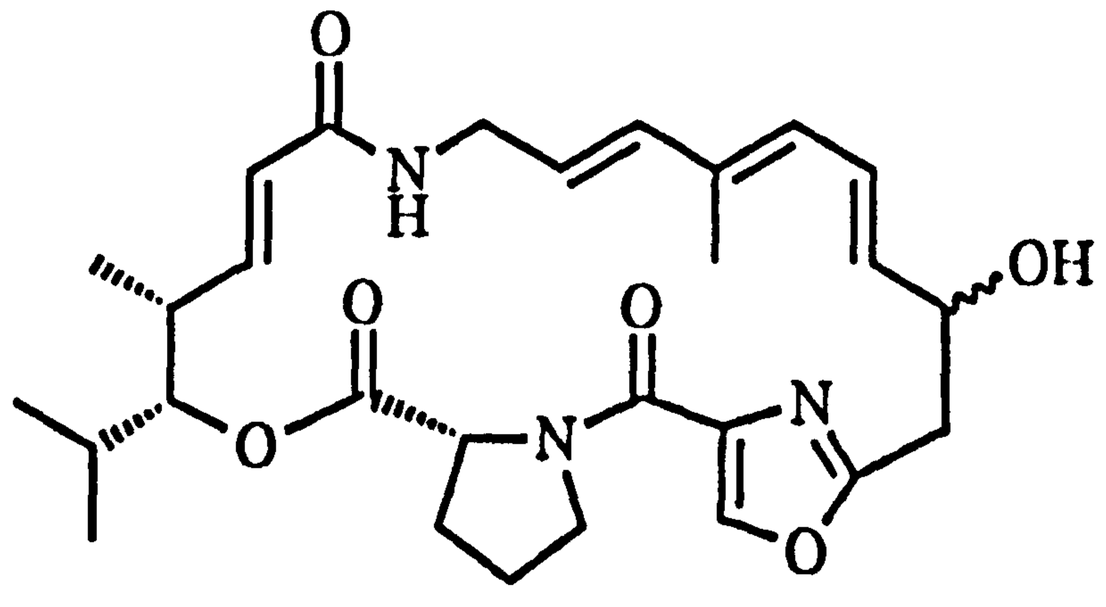
(E,E,E,E)-N-(3-Tri-n-butylstannylprop-2-enyl)-(4R)-methyl-(5R)-N'-((2-(6-bromo-2-hydroxypent-3,5-dienyl)oxazol-4-ylcarbonyl)-(R)-prolinoyl oxy)-6-methylhept-2-enamide **(221).**



EDC (48 mg, 0.2511 mmol) was added, in one portion, to a stirred solution of the acid **(199)** (56 mg; 0.1841 mmol) in dry CH_2Cl_2 (5 cm^3), at 0°C, under an atmosphere of nitrogen. The mixture was stirred for 30 min and then HOBt (29 mg, 0.2093 mmol) and triethylamine (0.035 cm^3, 0.2511 mmol) were added, in one portion, followed by the addition of the amine **(230)** (100 mg, 0.1674 mmol). The mixture was stirred overnight and then washed with water (10 cm^3). The dried solution ($MgSO_4$) was concentrated *in vacuo* and the residue was then purified using flash chromatography (2% MeOH in CH_2Cl_2) to give a mixture of diastereoisomers of the *amide* (165 mg, 61%) as an orange oil as; ν_{max}(cm^{-1}): 3293 (N-H, O-H), 1742 (ester C=O), 1668 (amide C=O), 1631 (C=C), 1548 (amide dimer) and 985 (*trans*-C=C-H); λ_{max} (EtOH)/nm (ε): 222 (12 098) and 232 (9870); δ_H (500 MHz $CDCl_3$): 8.14 (m, 1 H, oxazole :C$\underline{H}$), 6.61 (ddd, *J* 7.6, 15.6 and 15.6 Hz, COCH:C$\underline{H}$), 6.35-6.50 (m, 2 H, CHOHC$\underline{H}$:CHC$\underline{H}$:C), 6.13 (dd, *J* 4.2 and 19.0 Hz, SnC$\underline{H}$:), 5.95-6.05 (m, 1 H, SNCH:C$\underline{H}$), 5.97 (d, *J* 15.6 Hz, COC$\underline{H}$:CH), 5.65-5.75 (m, 2 H, N$\underline{H}$ and

CHOHCH:C<u>H</u>), 4.80 (m, 1 H, C<u>H</u>OR(^{i}Pr)), 4.66 (dd, *J* 3.8 and 8.0 Hz, COC<u>H</u>N), 4.10 (m, 1 H, CONC<u>H</u>H), 3.96 (m, 2 H, CONHC<u>H</u>$_2$), 3.92 (m, 1 H, CONCH<u>H</u>), 3.78 (m, 1 H, CH$_2$C<u>H</u>OH), 2.85-3.05 (m, 2 H, C<u>H</u>$_2$CHOH), 2.64 (hext, *J* 6.6 Hz, :CHC<u>H</u>(CH$_3$)), 2.39 (d, *J* 4.3 Hz, C(C<u>H</u>$_3$)Br), 2.25-2.30 (m, 2 H, COCHC<u>H</u>$_2$), 1.98-2.08 (m, 2 H, COCHCH$_2$C<u>H</u>$_2$), 1.80 (O<u>H</u>), 1.46 (app dpent , *J* 2.2 and 8.0 Hz, SnCH$_2$C<u>H</u>$_2$), 1.28 (app dhext, *J* 2.2 and 8.0 Hz, SnCH$_2$CH$_2$C<u>H</u>$_2$), 1.01 (app dd, *J* 1.0 and 6.6 Hz, :CHCH(C<u>H</u>$_3$)), 0.93 (app dd, *J* 2.2 and 6.6 Hz, CH(CH(C<u>H</u>$_3$)$_2$)) and 0.89 (t, *J* 8.0 Hz, SnC<u>H</u>$_2$CH$_2$CH$_2$C<u>H</u>$_3$); δ_C (100 MHz $CDCl_3$): 172.7 (s), 171.7 (s), 165.1 (s), 161.9 (s), 161.8 (s), 160.1 (s), 143.6 (d), 143.5 (d), 143.4 (d), 143.3 (d), 136.7 (s), 136.6 (s), 134.5 (d), 134.4 (d), 131.3 (d), 131.1 (d), 130.4 (d), 130.2 (d), 125.2 (d), 125.1 (d), 124.1 (d), 124.0 (d), 123.7 (d), 123.6 (d), 81.2 (d), 81.1 (d), 69.2 (d), 69.1 (d), 61.2 (d), 61.0 (d), 47.3 (t), 47.2 (t), 45.0 (t), 44.9 (t), 37.9 (d), 37.8 (d), 31.6 (t), 30.2 (d), 30.1 (d), 29.0 (t), 27.3 (t), 25.3 (t), 23.8 (q), 23.7 (q), 21.6 (t), 19.6 (q), 19.5 (q), 17.9 (q), 17.8 (q), 14.3 (q), 14.2 (q), 13.6 (q) and 9.4 (t);

14,15-Anhydro-16,37-dihydrovirginiamycin M_2 (7).

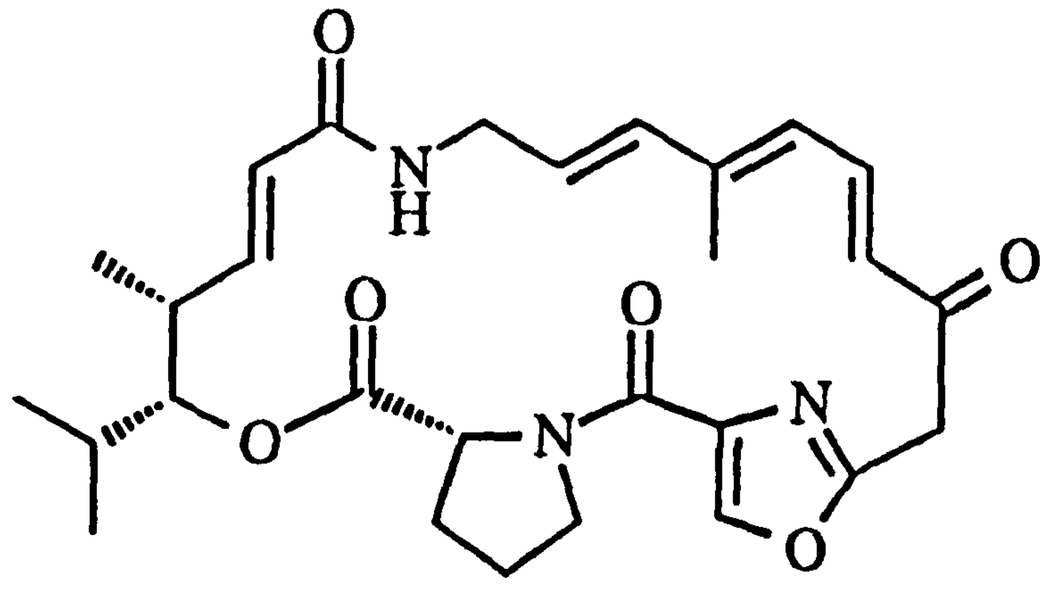


A solution of triphenylarsine (2.25 mg, 7.352 μmol) in dry DMF (1 cm^3) was added dropwise, over 2 min, to a stirred solution of tris(benzylideneacetone)dipalladium(0) (0.84 mg, 0.919 μmol) in dry DMF (8 cm^3) at room temperature, under an atmosphere of nitrogen, in a scrupulously dried flask. The mixture was stirred for 30 min and a solution of the precursor **(221)** (81 mg, 0.0919 mmol), in dry DMF (1 cm^3), was

added dropwise over 2 min. The mixture was heated at 100°C for 18 h and was then allowed to cooled to room temperature. The solvent was removed *in vacuo* and the residue was purified using flash chromatography (5% MeOH in CH_2Cl_2) to give the *tmacrolide* (21 mg, 40%) as a pale yellow oil as a mixture of diastereomers. (The product was found to decompose readily at room temperature or over long periods at -20°C); (Found M^++Na (Electrospray) 534.2492. $C_{28}H_{37}N_3O_6$ requires M^++Na 534.2580); ν_{max}(cm^{-1}): 3385 (NH and OH), 1741 (ester C=O), 1678 (amide C=O), 1618 (C=C) and 969 (*trans*-C=C-H); λ_{max} (EtOH)/nm (ε): 210 (91 000) and 278 (84 850); δ_H (500 MHz $CDCl_3$): 8.12 (oxazole :CH, 0.6 H), 8.10 (oxazole :CH, 0.4 H), 6.51 (dd, *J* 5.3 and 16.1 Hz, 0.6 H, COCH:CH), 6.47 (dd, *J* 5.3 and 16.1 Hz, 0.4 H, COCH:CH), 6.41 (ddd, *J* 1.9, 11.1 and 15.1 Hz, 0.6 H, CHOHCH:), 6.32 (ddd, *J* 1.9, 11.1 and 15.1 Hz, 0.6 H, CHOHCH:), 6.24 (d, *J* 15.1 Hz, CH:CHC(CH_3)), 5.98 (app t, *J* 11.1 Hz, C(CH_3):CHCH:), 5.77 (dd, *J* 1.9 and 16.1 Hz, 0.6 H, COCH:), 5.75 (dd, *J* 1.9 and 16.1 Hz, 0.4 H, COCH:), 5.66-5.75 (m, $NHCH_2CH$:), 5.65 (dd, *J* 7.1 and 15.1 Hz, CHOHCH:CH), 5.61 (m, NH), 4.74 (dd, *J* 1.9 and 10.3 Hz, 0.6 H, CH(^{i}Pr)OR), 4.71 (dd, *J* 1.9 and 10.3 Hz, 0.4 H, CH(^{i}Pr)OR), 4.67 (dd, *J* 1.9 and 8.7 Hz, 0.6 H, COCH:), 4.63 (dd, *J* 1.9 and 8.7 Hz, 0.4 H, COCH:), 4.03 (app pent, *J* 7.1 Hz, CONCHH), 3.91 (m, 2 H, $NHCH_2CH$:), 3.76 (m, CONCHH), 3.67 (ddd, *J* 1.9 and 7.1 and 11.1 Hz, 0.6 H, CH_2CHOH), 3.56 (ddd, *J* 1.9 and 7.1 and 11.1 Hz, 0.4 H, CH_2CHOH), 3.04-3.26 (m, CH_2CHOH), 2.72 (m, :CHCH(CH_3)), 2.06 (m, 2 H, $COCHCH_2$), 1.80-1.98 (m, 3 H, $COCHCH_2CH_2$ and CHOR(CH(CH_3)$_2$)), 1.79 (2 H, C(CH_3):CH), 1.77 (1 H, C(CH_3):CH), 1.08 (d, *J* 5.3 Hz, 2 H, :CHCH(CH_3)), 1.07 (d, *J* 5.3 Hz, 1 H, :CHCH(CH_3)), 0.94 (app t, *J* 7.0 Hz, 4 H, CHOR(CH(CH_3)$_2$)) and 0.91 (app t, *J* 7.0 Hz, 2 H, CHOR(CH(CH_3)$_2$)); δ_C (125 MHz $CDCl_3$): 171.5 (s), 166.6 (s), 160.5 (s), 160.2 (s), 145.4 (d), 145.3 (d), 143.2 (d), 138.8 (d), 138.5 (d), 136.8 (s), 135.5 (s), 135.2 (d), 134.9 (d), 130.3 (d), 129.9 (d), 127.5 (d), 127.0 (d), 124.2 (d), 124.1 (d), 124.0 (d), 81.7 (d), 81.6 (d), 70.6 (d), 70.7 (d), 59.5 (d), 59.4 (d), 48.9 (t), 48.8 (t), 41.4 (t), 41.1 (t), 37.0 (d), 36.9 (d), 36.1 (t), 36.0 (t), 28.9 (t), 24.6 (t), 19.9 (q), 18.7 (q),

13.0 (q), 9.8 (q) and 9.6 (q); *m/z* (Electrospray): 550 (15%, M^++K), 534 (100, M^++Na) and 512 (20, M^++H).

14,15-Anhydrovirginiamycin M_2 (6).[98]



Dess-Martin's periodinane (21 mg, 0.05 mmol) was added carefully, in one portion, to a stirred solution of the macrocycle (7) (21 mg, 0.04 mmol) in dry CH_2Cl_2 (2 cm^3) and the mixture was then stirred at room temperature for 10 min. Dess-Martin's periodinane (63 mg, 0.15 mmol) was agian added, in three portions, at 10 min intervals, and the mixture was stired for a further 10 min. The mixture was washed with sodium thiosulphate solution (5 cm^3) and then extracted with ether. The dried solution (Na_2SO_4) was concentrated *in vacuo* and the residue was then purified using flash chromatography (5% MeOH in CH_2Cl_2) to give 14,15-anhydrovirginiamycin M_2 (12 mg, 59%) as a pale yellow foam; (Found: M^+, 510.2590. $C_{28}H_{30}N_3O_6$ requires M^+, 510.2604); ν_{max} (cm^{-1}): 3448 (N-H), 1738 (ester C=O), 1674 (ketone and amide C=O), 1623 (C=C), 1558 (amide dimer) and 978 (*trans*-C=C-H); δ_H (500 MHz $CDCl_3$): 8.18 (oxazole C-H), 7.57 (dd, *J* 15.0 and 11.7 Hz, $C(CH_3)$:CHCH:CH), 6.65 (dd, *J* 15.7 and 5.7 Hz, $CH(CH_3)$CH:CHCO), 6.33 (d, *J* 15.0 Hz, $C(CH_3)$:CHCH:CHCO), 6.29 (d, *J* 15.6 Hz, $NHCH_2$CH:CH), 6.17 (d, *J* 11.7 Hz, $C(CH_3)$:CHCH:CH), 5.95 (dt, *J* 15.6 and 6.2 Hz, $NHCH_2$CH:CH), 5.79 (dd, *J* 15.7 and 1.6 Hz, $CH(CH_3)$CH:CHCO), 5.68 (t, *J* 6.1 Hz, NH, 4.79 (m, OCH(^{i}Pr)CH), 4.14 (dt, *J* 15.4 and 6.4 Hz, CONHCHHCH:), 3.93 (CH:CHCOCH_2), 3.91-3.76 (m, CONHCHHCH: and CONCH_2), 2.25 (m, CH(^{i}Pr)CH(CH_3)), 2.09 (m,

COCHCHHCH$_2$), 2.02 (CH:CHC(CH$_3$):CH), 1.95 (m, COCH(CH(CH$_3$)$_2$) and COCHCHHCH$_2$), 1.78 (m, COCHCH$_2$CHH), 1.65 (m, COCHCH$_2$CHH), 1.11 (CH(^{i}Pr)CH(CH$_3$)), 0.99 (COCH(CH(CH$_3$)$_2$)) and 0.96 (COCH(CH(CH$_3$)$_2$)); δ_C (125 MHz $CDCl_3$): 192.9 (s), 170.8 (s), 165.5 (s). 160.1 (s), 158.2 (s), 146.8 (d), 144.5 (s), 143.8 (d), 139.1 (d), 138.3 (d), 137.3 (s), 128.9 (d), 128.4 (d), 128.3 (d), 123.4 (d), 81.6 (d), 59.4 (d), 48.9 (t), 42.0 (t), 40.4 (t), 36.9 (d), 29.6 (d), 28.6 (t), 24.5 (t), 19.7 (q), 18.8 (q), 13.9 (q) and 10.4 (q); *m/z* (FAB): 510 (100%, M^+), 357 (5), 311 (16), 242 (4), 205 (7), 178 (21), 154 (40), 137 (46) and 95 (48.

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