PREPARATION AND PYROLYSIS OF AMINO ACID DERIVED AND CYCLIC PHOSPHORUS YLIDES

by

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B.Sc. (Hons), M.Sc.

Thesis presented for the degree of

DOCTOR OF PHILOSOPHY

University of St. Andrews **August 1999**

DEDICATION

To my Parents

DECLARATION

I, *Tracy Massil*, hereby certify that this thesis is a record of my work, has been composed by myself and that it has not been accepted in partial or complete fulfilment of any other degree or professional qualification.

Signed: Date: 15/8/99

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No. 12 on 1st October 1995 and as a candidate for the degree of Doctor of Philosophy on the 1st of October 1996.

Signed: Date: 15/8/99

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate to the degree of Doctor of Philosophy.

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I would like to thank the past and present members of the lab for their help, support and friendship. To my best friends: Pnina, Eileen, Véronique, Julie, Gillian and Satoko, thank you for your constant support and for the great times we had, have and will have together. I wish them all the very best in the future.

I would also like to record my thanks to the technical staff, especially Melanja Smith, Caroline Horsburgh, Marjory Parker, Sylvia Smith and Colin Miller.

I would like to thank John for his friendship, help and encouragement and finally my parents for everything.

LECTURE COURSES ATTENDED

The following is a statement of the courses attended during the period of research.

Organic Research Seminars	3 years attendance
Introduction to Instrumental Methods	Dr. R. K. Mackie
Transition Metals in Organic Synthesis	Dr. C. Glidewell
Natural Product Synthesis	Prof. R. A. Field
Advanced NMR	Dr. R. K. Mackie
Organic Problem Solving 1	Prof. R. A. Field and Dr. N. P. Botting
EC Funded Short Course on Chemical Information Retrieval, Toulouse, France	Prof. J. Brandt
Interesting Modern Organic Molecular Structures, their Synthesis, Reactions and Uses	Dr. F. G. Riddell
Organic Problem Solving 2	Prof. R. A. Field and Dr. N. P. Botting

ABSTRACT

The bulk of the thesis describes work directed towards exploiting and extending the scope of a new method for the synthesis of chiral acetylenic amino acid derivatives via aminoacyl stabilised phosphorus ylides.

Twelve examples of β-aminoacyl ylides derived from amino acids with hydrocarbon and functionalised side chains have been prepared and fully characterised. Upon flash vacuum pyrolysis (FVP) the hydrocarbon side chain derivatives readily undergo loss of Ph_3PO forming the protected chiral acetylenic amino acid derivatives but the functionalised side chain derivatives do not behave in the same manner and the observed products are discussed.

Further transformations were applied to the chiral acetylenic amino acid derivatives with the aim of preparing chiral 1,4-diamines, potential intermediates in the synthesis of NOS inhibitors of interest to the collaborating company. A number of useful transformations were achieved but the original combination of protecting groups used for the pyrolysis step: the acid as the ethyl ester and the amine as the benzyl carbamate proved not to be suitable for the further transformations.

Other protecting groups for the amine and acid function were therefore examined and six derivatives were prepared and fully characterised. Allyl derivatives - with protection of the acid as the allyl ester and/or the amine as the allyl carbamate proved to be stable to the pyrolysis conditions and this offers a promising avenue for future work on the further transformation into 1,4-diamine derivatives.

An alternative route to the chiral diamines was investigated starting from cyano ylides. A series of four α-cyano β-oxo ylides derived from amino acids were prepared and characterised but upon pyrolysis these compounds did not give the desired loss of Ph_3PO to form the chiral acetylenic amino acid derivatives but the rather interesting products obtained are discussed.

Six α-aminoacyl-β,γ-unsaturated ylides have been prepared and characterised. Upon FVP instead of the expected loss of Ph_3PO these compounds cyclised with loss of methanol or ethanol to form novel seven-membered cyclic ylides with an azepine-2,6-dione structure and

three compounds of this type, which are effectively vinylogous tetramic acids, have been prepared. Attempts to prepare the eight-membered ring in a similar manner were unsuccessful.

Removal of the *N*-protecting group in the amino acid derived ylides followed by thermolysis also resulted in loss of ethanol to give the novel five-membered cyclic ylides with a tetramic acid structure. Deprotection of the β-alanine derivative resulted in the formation of the six-membered analogue.

The final part of the work focused on pyrolysis of cyclic ylides. The five-membered cyclic ylides containing nitrogen gave complicated results upon pyrolysis but some evidence was obtained for formation of an oligomer of 4-methylene-γ-butenolactam in one case. Related oxygen and sulfur containing cyclic ylides broke down both upon neat pyrolysis and in boiling diphenyl ether with loss of CO_2 or COS respectively to give the same known five-membered ring trioxodiylide. A mechanism for this novel reaction involving the intermediacy of triphenylphosphoranylidenecyclopropanedione was proposed and evidence in support of it was obtained using ^{13}C labelling.

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(i) R = CO_2Et **572**

(ii) R = H **573**

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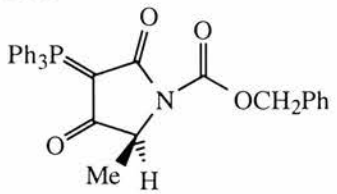

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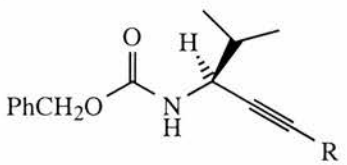

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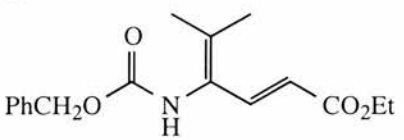
(ii) R = H **576**

(iii) **577**



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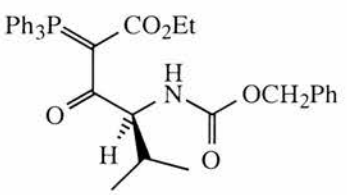

(i) 650 °C

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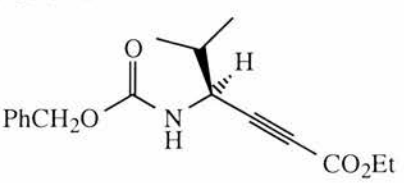

a. MeOH

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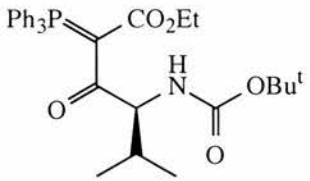

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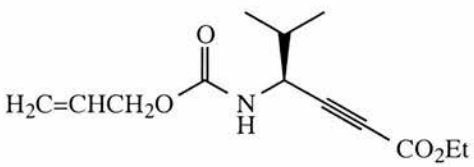

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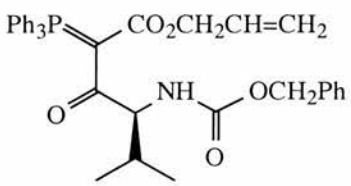

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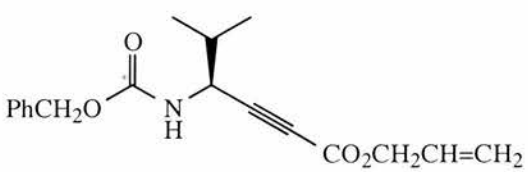

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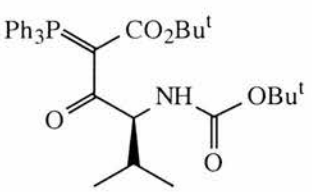

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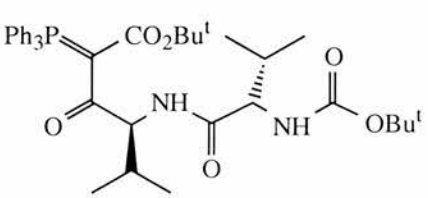

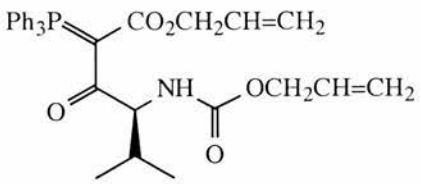

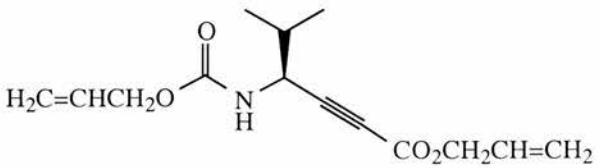

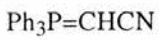

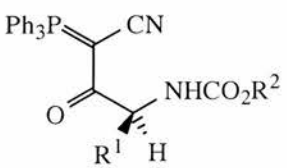

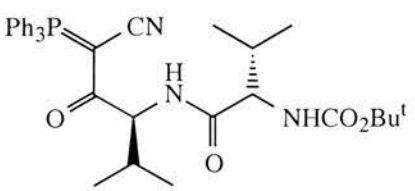

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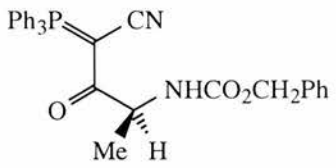
a. Pyrolysis of **659** 110



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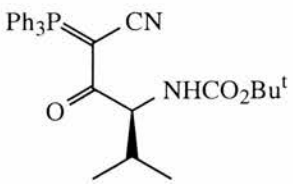

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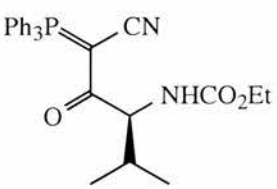

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(ii) 500 °C

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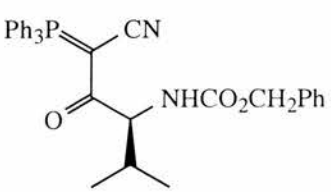

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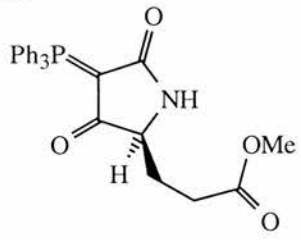

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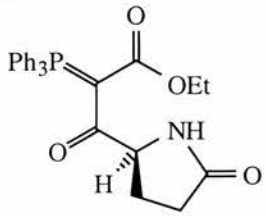

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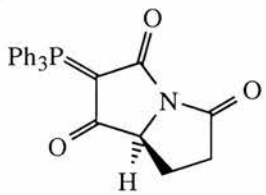

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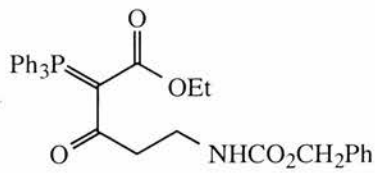

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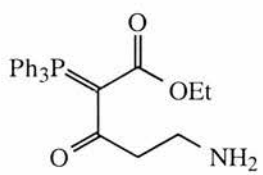

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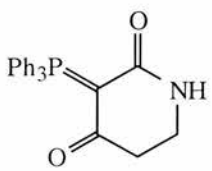

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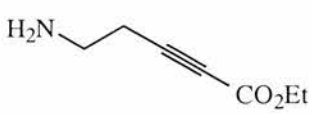
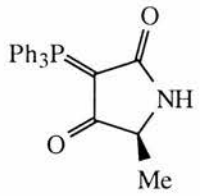
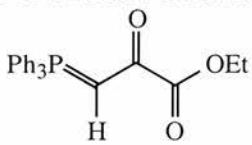
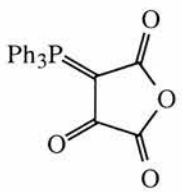
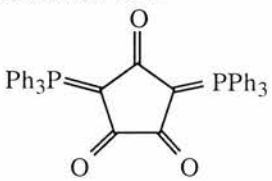


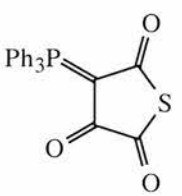


K Pyrolysis of Cyclic Ylides









INTRODUCTION

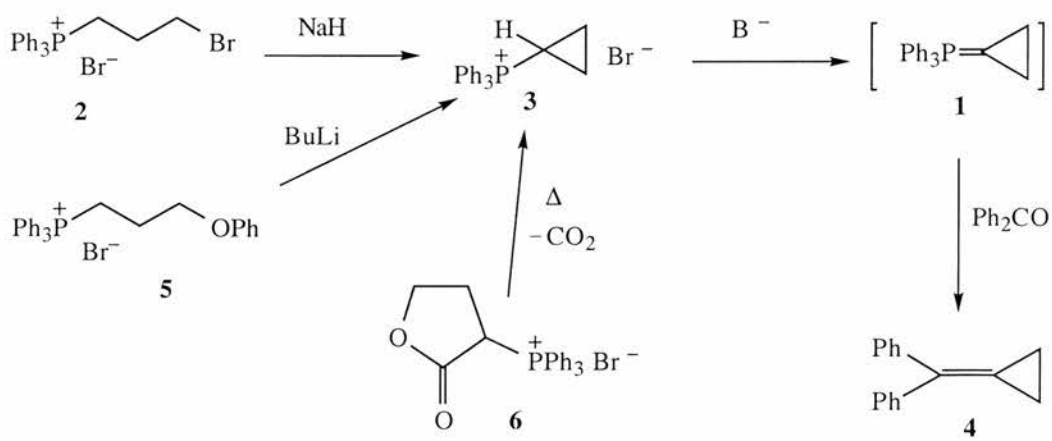
A Synthesis, Structure and Reactivity of (exo) Cyclic Phosphorus Ylides

1 Introduction

Cyclic phosphorus ylides have been studied over the last 50 years. The definition of cyclic phosphorus ylides includes compounds in which a carbanion which is part of a ring system is attached directly to a positively charged phosphorus (V) atom. This review does not include "endocyclic" examples with the phosphorus atom incorporated into the ring system. The main importance of these ylides is their use in the Wittig reaction where the rings are incorporated into the final products.

2 Three-Membered Rings

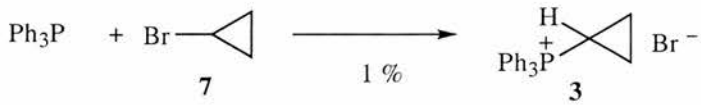
The first report of a three-membered ring ylide was made by Sisido and co-workers.[1] They showed the formation of cyclopropylidenetriphenylphosphorane **1** as an intermediate and its use in the synthesis of alkylidenecyclopropanes. The treatment of 3-bromopropyltriphenyl phosphonium bromide **2** with a sodium hydride resulted in an intramolecular ring closure to give the cyclopropyltriphenylphosphonium bromide **3** and addition of another equivalent of base and benzophenone led to diphenylmethylenecyclopropane **4** in 80% yield.



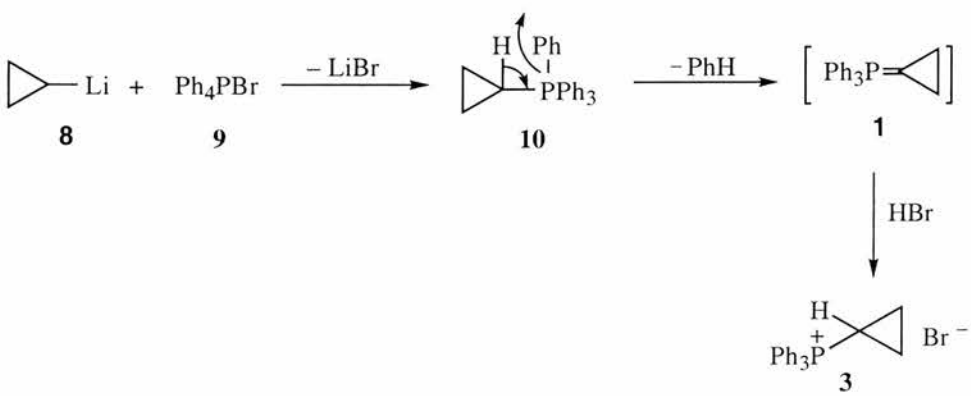
The main precursor to the ylide, cyclopropyltriphenylphosphonium bromide **3**, has been prepared in various ways[2-4] and the starting materials **5** and **6** lack the cyclopropane unit.

Here also, after the preparation of the cyclic salt **3** addition of a base (phenyllithium) generates the ylide intermediate **1**.

Attempts to generate the salt **3** from cyclopropane derivatives **7** and triphenylphosphine have generally been unrewarding.[5,6] The first successful conversion of cyclopropyl halides into the corresponding cyclopropylidenetriphenylphosphorane **1** involved a new method reported in 1967.[7]



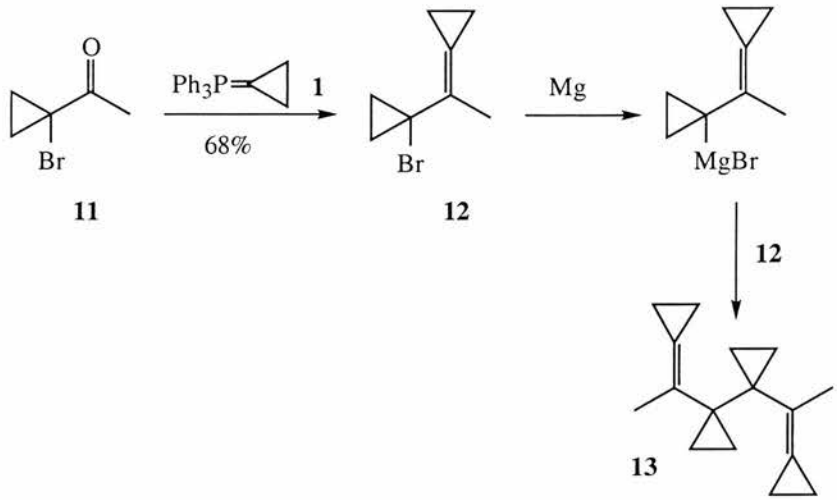
Reaction of cyclopropyllithium **8** and tetraphenylphosphonium bromide **9** results in the formation of a quinquevalent phosphorus intermediate **10**, which loses benzene to afford the ylide **1**, isolated as the hydrogen bromide salt **3**.



The ylide **1** was first isolated and characterised in 1976.[8] The NMR data reported, included a ^{13}P signal at δ_P +16.7 and a ^{13}C signal for the ylide carbon at δ_C 4.3 with a large P-C coupling of 132.8 Hz implying that the carbon must be approximately sp^2 hybridized. Rather surprisingly the CH_2 signal at δ_C 7.7 showed no coupling to phosphorus. Later a crystalline sample was isolated in a pure state from 3-bromopropyltriphenylphosphonium bromide **2** and potassium hydride in tetrahydrofuran at –20 °C.[9] The NMR data differed strongly from those reported earlier because the earlier samples contained traces of salts. A ^{31}P signal at δ_P +15.6 and a ^{13}C signal for the ylide carbon at δ_C 0.13 with a small P-C coupling of 3.9 Hz were indicative of a pyramidal carbanion geometry in solution. The X-ray diffraction analysis confirmed this geometry and showed the molecule to be tetrahedral round the

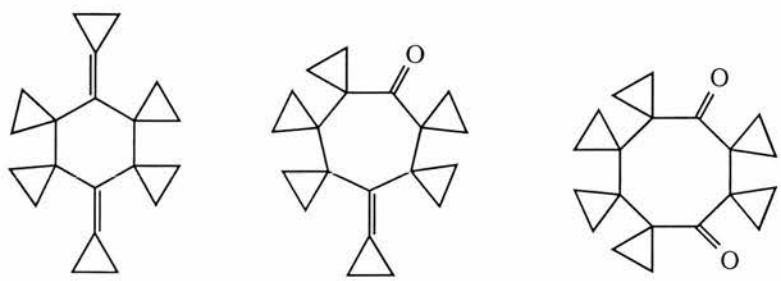
phosphorus and planar at the ylide but yet the C-P bond length of 1.696 Å showed significant double bond character.

Fitjer[10] showed the use of cyclopropylidenetriphenylphosphorane **1** for the synthesis and coupling of vinylcyclopropanes and vinylidenedicyclopropanes, brominated at the allylic position such as **11** and **12**. Upon treatment with magnesium in ether, **12** yields the dimer **13**.



11 **12**

This method can be extended to form the polycyclopropylidenes **14-16** containing a six-, seven- or eight-membered central ring.[11]

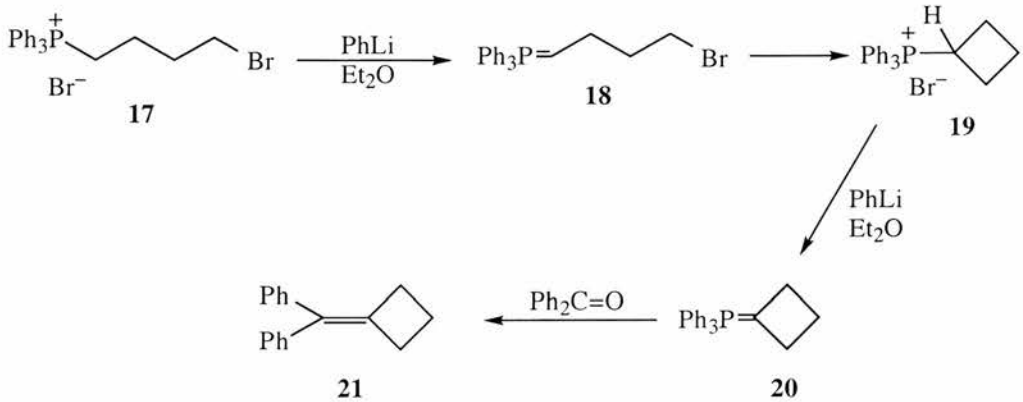


14 **15** **16**

3. Four-Membered Rings

3 a Cyclobutylidene Ylides

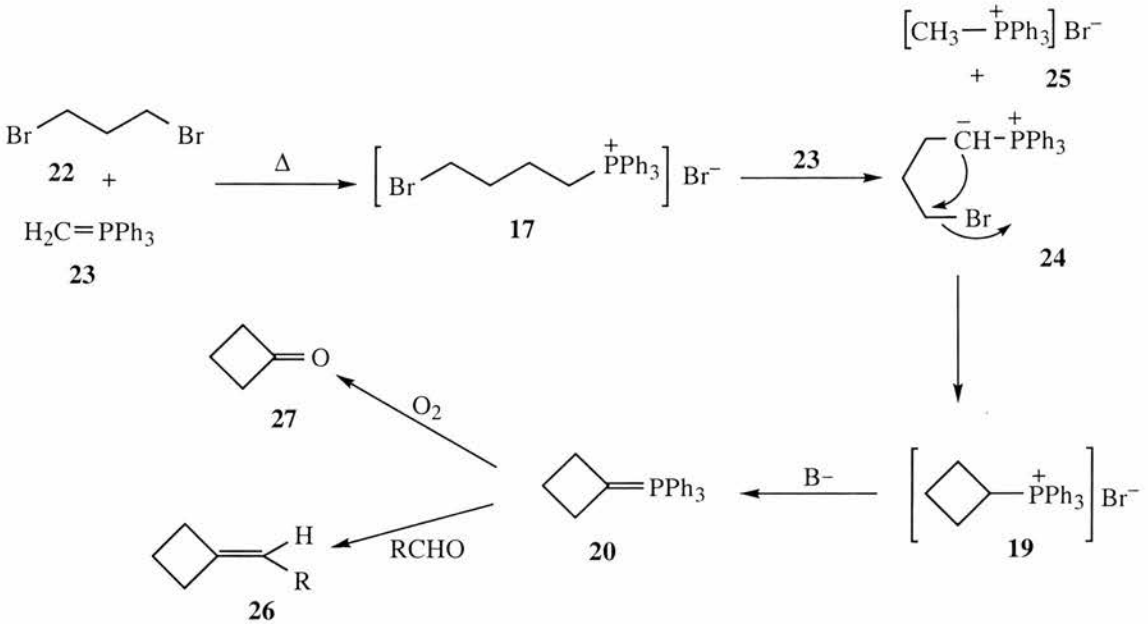
Cyclobutylidenetriphenylphosphorane **20** and its salt are valuable intermediates for the synthesis of cyclobutane derivatives. Preliminary investigations were done by Monden[12] who examined the use of 4-bromobutyltriphenylphosphonium bromide **17** in the Wittig reaction. When the phosphonium salt **17** reacted with phenyllithium a red solution was obtained giving a precipitate from which a new phosphonium salt **19** could be isolated. Later, other workers reported they could not confirm Monden's suggestion because of their failure to isolate cyclobutanone following autoxidation of the ylide **20**.[13,14]



17 **18** **19** **21** **20**

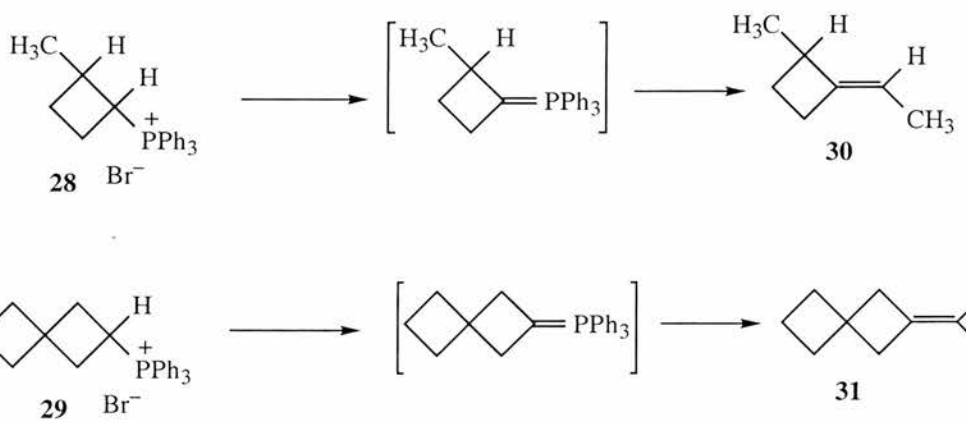
The first definite evidence for these intermediates was reported in 1965.[15] Reaction of 4-bromobutyltriphenylphosphonium bromide **17** with excess phenyllithium in ether gave a red solution of ylide **18**. Addition of dry hydrogen bromide gave the cyclic phosphonium salt **19** as colourless crystals. When the salt **19** was treated with phenyllithium, a clear red solution formed. Addition of benzophenone gave diphenylmethylenecyclobutane **21** in 57% yield.

Bestmann and Kranz[16] showed that the dihalogen compound **22** reacts with methylenetriphenylphosphorane **23** in boiling benzene to give phosphonium salt **17**, which reacts with a second molecule of the phosphorane **23** yielding the ylide **24** and methyltriphenylphosphonium bromide **25**. The alkylidenephosphorane **24** gives the cyclic phosphonium salt **19** by intramolecular C-alkylation.[12,13,17,18] The salt is converted to the ylide **20** by a base and can be used in various reactions.[17,19] The Wittig reaction of the ylide

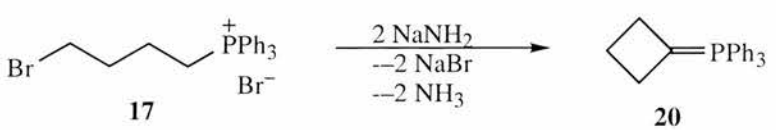


20 with aldehydes gives the alkylidenecyclobutanes **26** and on autoxidation[20] it gives cyclobutanone **27**.

Other substituted cyclobutane derivatives were made[21] starting from the methyl substituted cyclic phosphonium salt **28** and the spiro cyclic phosphonium salt **29** via their ylides to give the Wittig products **30** and **31**.

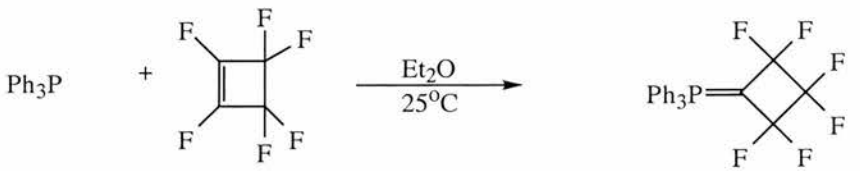


The cyclobutylidene ylide **20** was first isolated in 1976.[8] The NMR data reported, included a ^{31}P signal at δ_P +16.5 and a ^{13}C signal for the ylide carbon at δ_C 14.6 with a large P-C coupling of 77.3 Hz. Crystalline samples of the ylide **20** were obtained from the reaction of (4-bromobutyl) triphenylphosphonium bromide **17** with sodium amide in liquid ammonia.[22]



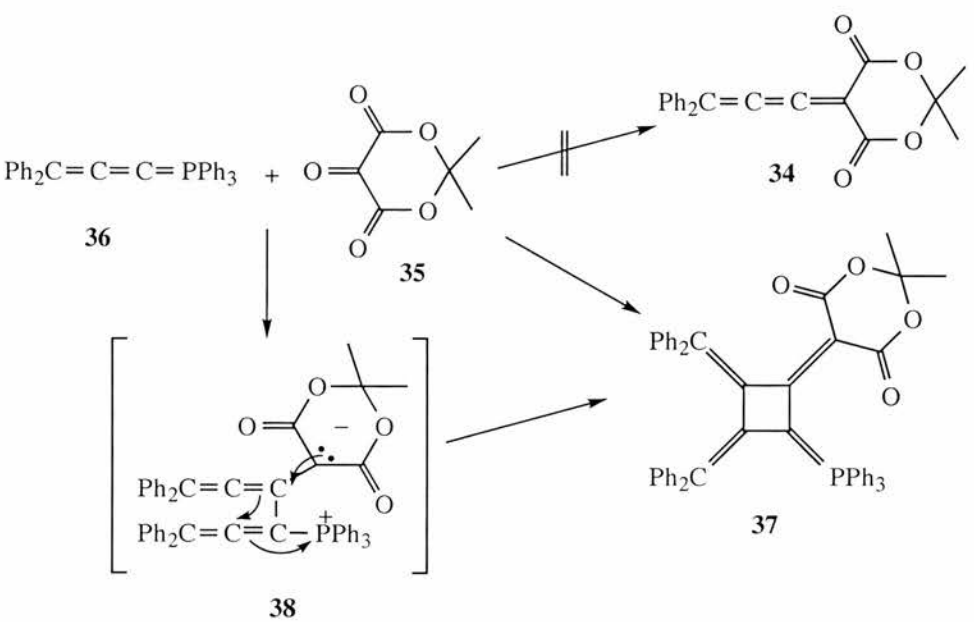
The NMR data was consistent with the above and like the 3-membered unsubstituted ring the X-ray diffraction analysis showed the molecule to be tetrahedral round the phosphorus and planar at the ylide carbon. Also the P-C bond length of 1.668 Å implies some double bond character.

2,2,3,3,4,4-Hexafluoro(triphenylphosphoranylidene)cyclobutane **33** was obtained by reaction of triphenylphosphine and perfluorocyclobutene **32** and its crystal structure was determined.[23] The phosphorus atom has four neighbours at tetrahedral angles and the phosphorus-ylide carbon bond length is 1.713 Å. The phosphorus atom is coplanar with the cyclobutane ring and the carbon-fluorine bond lengths were slightly longer than those in perfluorocyclobutane.



32 **33**

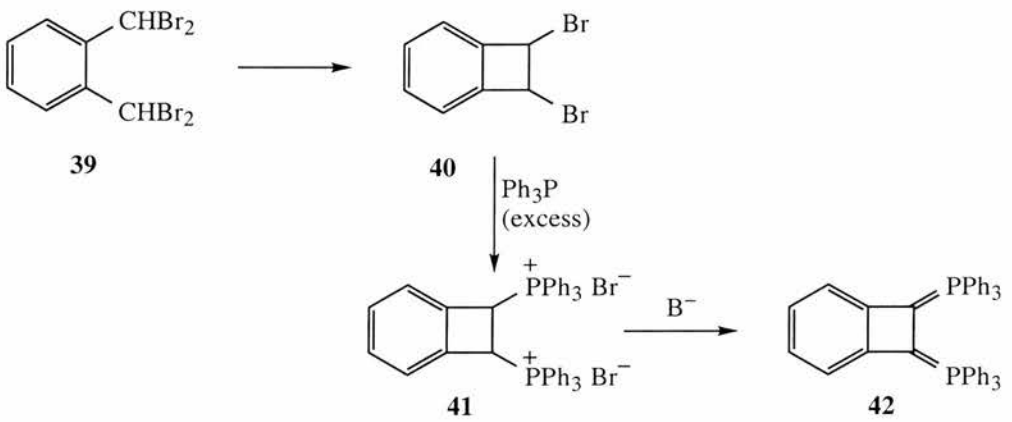
An attempt to obtain diphenylpropadienylidene Meldrum's acid **34** by a Wittig reaction between oxo Meldrum's acid **35** and the phosphorane **36** gave, in low yield, a cycloadduct of **34** and **36,** the ylide **37**.[24] Its structure was confirmed by X-ray crystallography. Consideration of the probable reactivities of the two components led to the proposed stepwise pathway involving **38** as shown below.



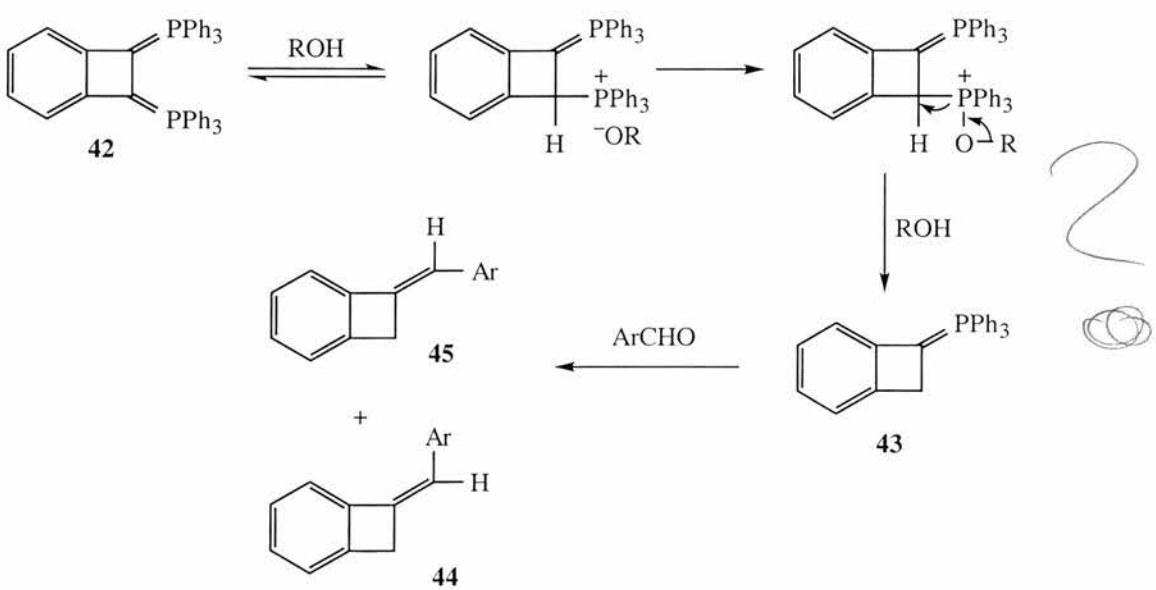
36 **35** **34** **37** **38**

3 b Bis Ylides

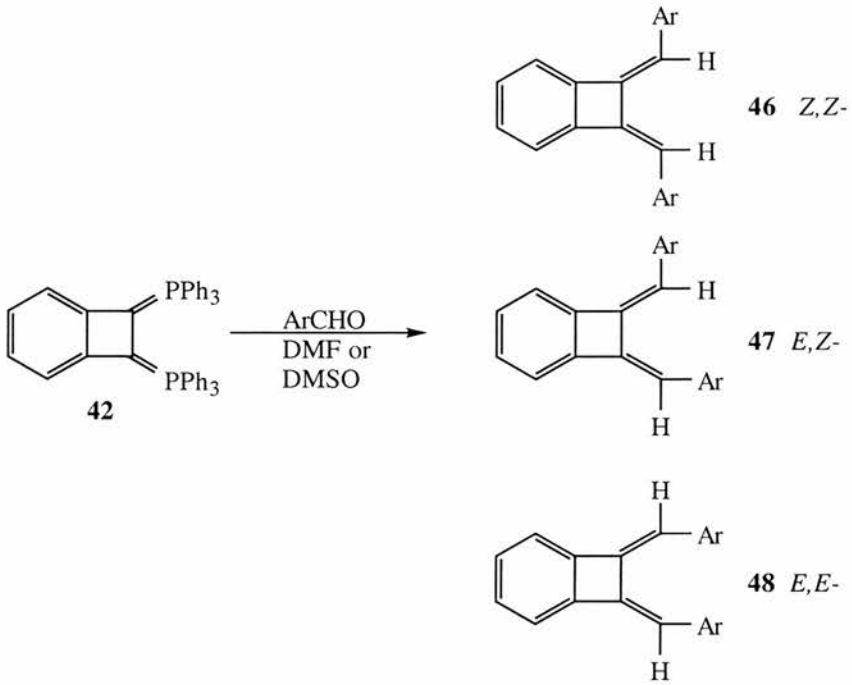
The first example of the preparation of a 1,2-bis-ylide was reported by Blomquist and co-workers.[25,26] Here, α,α,α',α'-tetrabromo-*o*-xylene **39** was converted to trans-1,2-dibromobenzocyclobutene **40**. Reaction of the dibromide **40** with excess triphenylphosphine at 150 °C, under nitrogen, gave the 1,2-bis(triphenylphosphonio)benzocyclobutene dibromide **41** in quantitative yield. Addition of a base to a solution of the salt afforded 1,2-bis(triphenylphosphoranylidene)benzocyclobutene **42** which is stable at low temperatures (< –30 °C) in an inert atmosphere.



Reaction of the ylide **42** with aldehydes gave different results depending on the nature of the solvent. In ethanol, the bis-ylide **42** undergoes ethanolysis to the mono-ylide **43** which on reaction with aldehydes leads to the *E*- and *Z*-1-benzylidenebenzocyclobutenes **44**-**45** corresponding to the particular benzaldehyde derivative used.

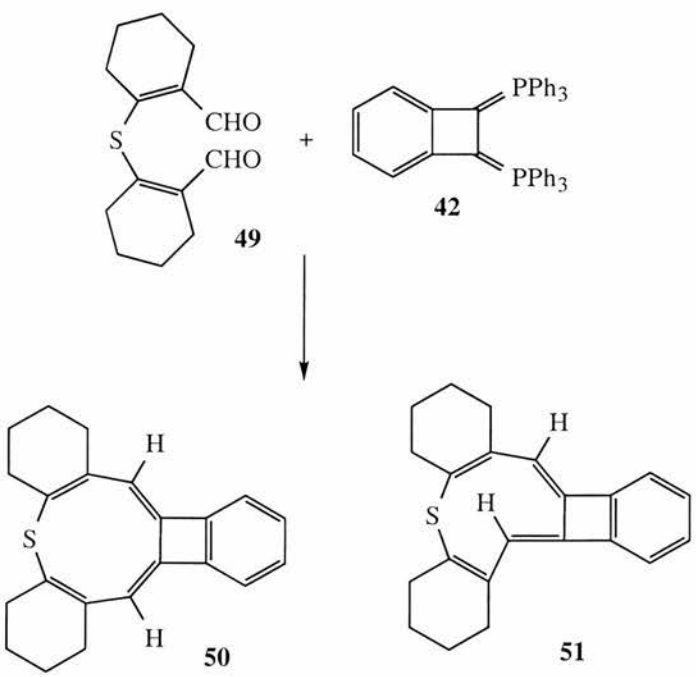


However in DMF or DMSO, the major products were the *E,E*- and/or *E,Z*- and/or *Z,Z*-1,2-bisbenzylidenebenzocyclobutenes **46**-**48**.



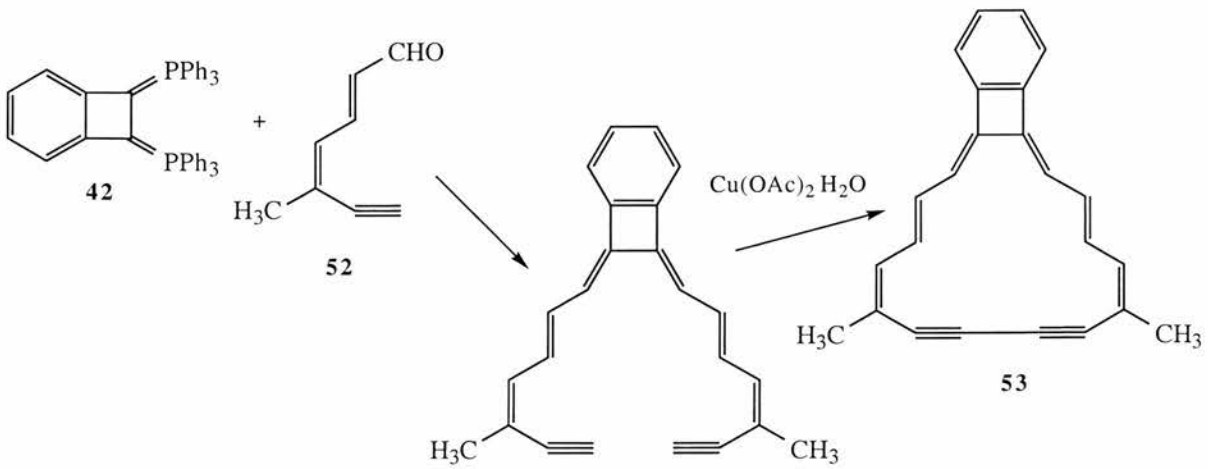
42 **46** *Z,Z*- **47** *E,Z*- **48** *E,E*-

The bis-ylide **42** has been used in the synthesis of large ring compounds. Analogues of biphenylene containing a thionin ring were prepared by a Wittig reaction between the bis-ylide **42** and 2,2'-thiobis(cyclohex-1-enecarbaldehyde) **49**. Both all-*Z*- and mono-*E*- 1,2,3,4,6,7,8,9-octahydrodibenzo[b,h]benzo[3,4]cyclobuta[1,2-e]thionin **50** and **51** were obtained.[27]



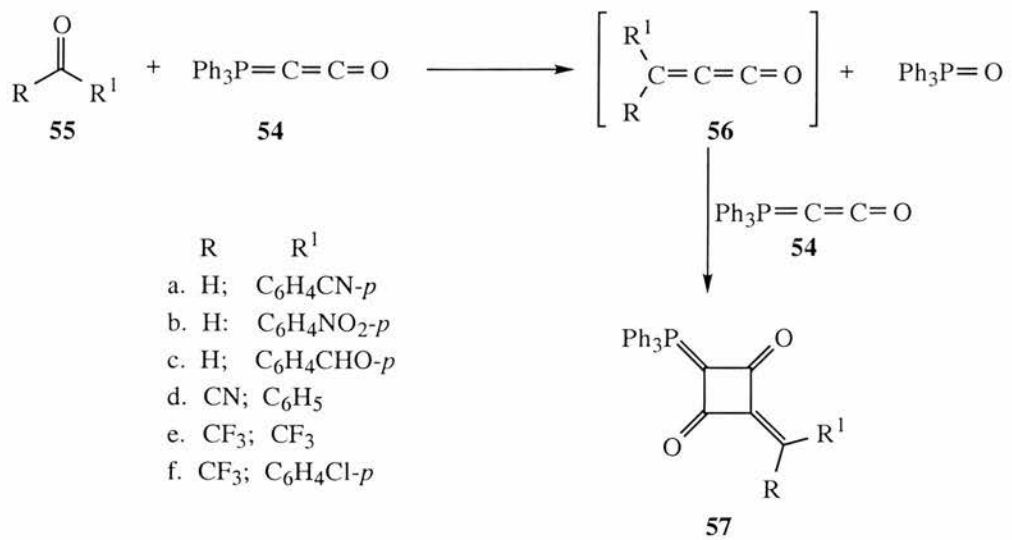
49 **42** **50** **51**

Another large ring analogue of biphenylene was the [16]annulenobiphenylene derivative **53**,[28] derived from the bis-ylide **42** and (E,Z)-5-methylhept-2,4-dien-6-ynal **52.**



3 c Oxo-stabilised cyclobutylidene ylides

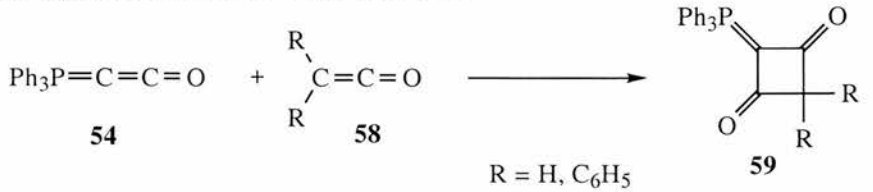
Birum and Matthews[29] reported the synthesis of stable ylide substituted 1,3-cyclobutanediones **57** from the reactive phosphacumulene, triphenylphosphoranylideneketene **54** and aldehydes or activated ketones **55**. The initial step was a Wittig reaction leading to the



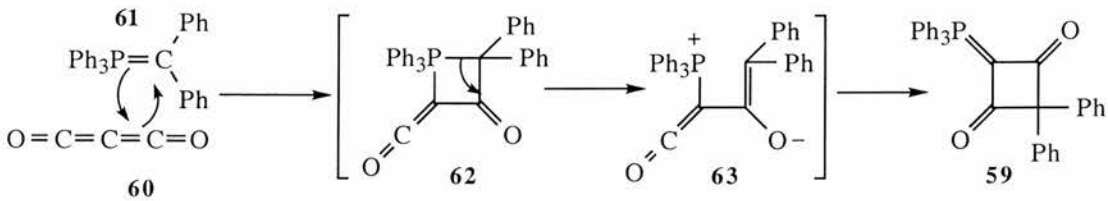
R R^1
a. H; C_6H_4CN-*p*
b. H: $C_6H_4NO_2$-*p*
c. H; C_6H_4CHO-*p*
d. CN; C_6H_5
e. CF_3; CF_3
f. CF_3; C_6H_4Cl-*p*

alkylideneketenes **56**. These reactive intermediates add rapidly to **54** to give the 1,3-cyclobutanediones **57** with ^{31}P NMR shifts at δ_P –2 to 0. The reaction proceeded at room temperature and no reaction occurred with less activated ketones such as acetone and fluorenone. Evidence that the products have carbocyclic rather than lactone structures was

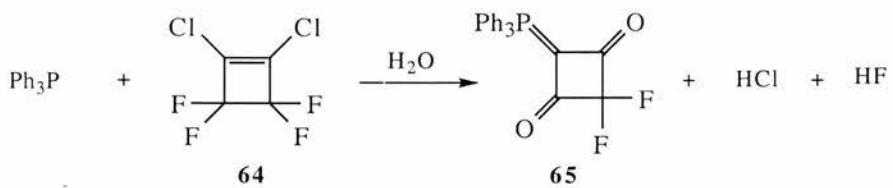
provided by IR, UV, NMR, MS and the marked similarity of **57** to the products **59** (δ_P +3 and +4) obtained by cycloaddition of **54** to ketenes **58**.[29]



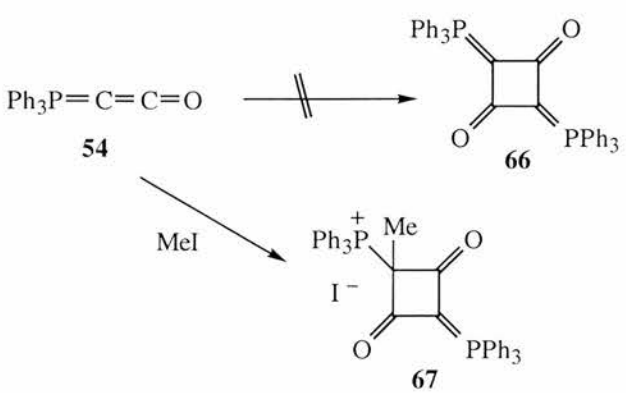
At the same time similar products of this type were reported by two different groups.[30,31] Addition of carbon suboxide **60** to diphenylmethylenetriphenylphosphorane **61** formed the intermediate **62** and, upon rearrangement of **62** via **63**, the cyclobutanedione stabilised ylide **59** was formed.



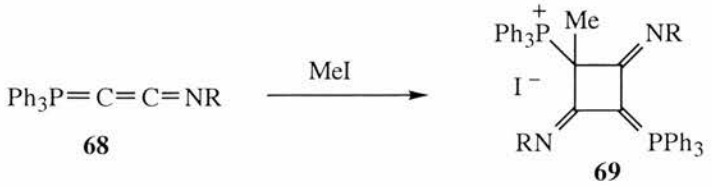
A displacement reaction of triphenylphosphine with dichloroperfluorocyclobutene **64** gave the 1:1 adduct,[31] 4,4-difluoro-2-(triphenylphosphoranylidene)cyclobutane-1,3-dione **65** with a ^{31}P NMR shift at δ_P –3.



Attempts to synthesise the dimer **66** directly from **54** by UV irradiation, heating, or treatment with acids and bases were unsuccessful. A methyl iodide adduct of the dimer **67**



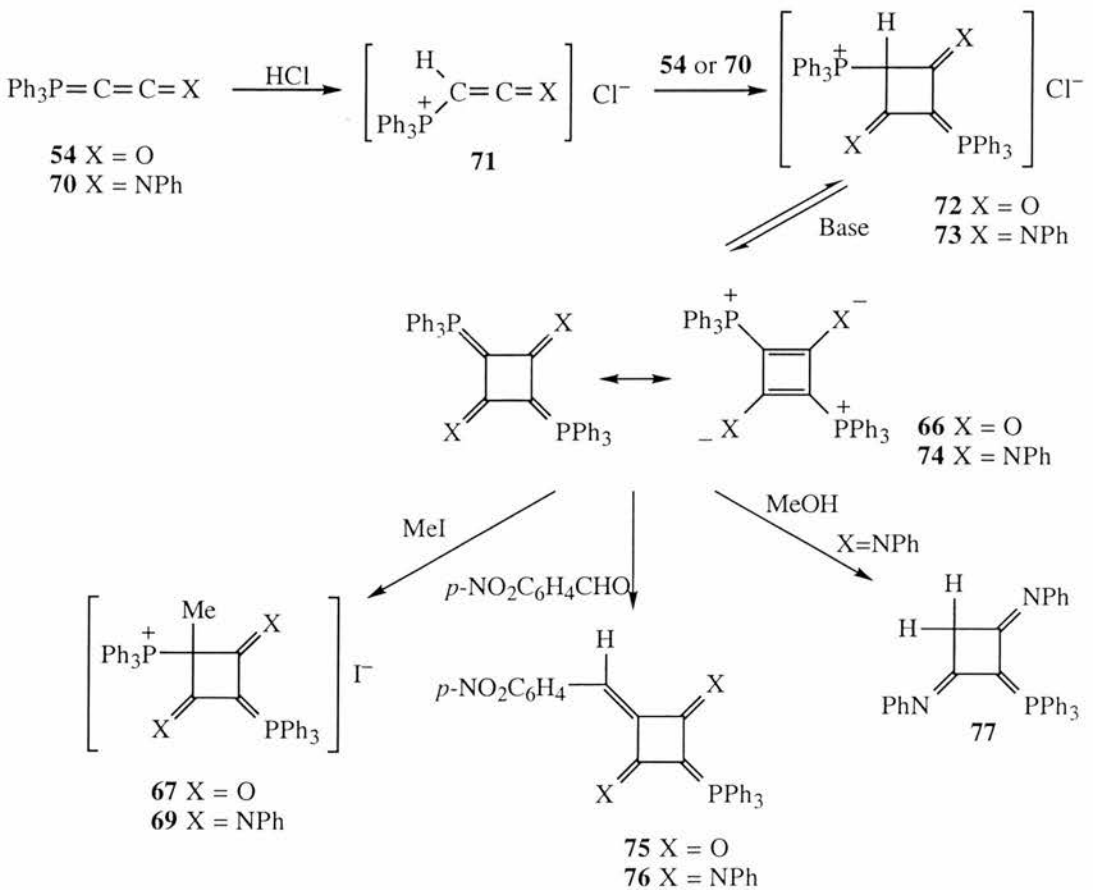
was unexpectedly formed when **54** was treated with methyl iodide (δ_P= 0).[29] Analogous salts **69** were prepared from methyl iodide and triphenylphosphoranylidene-ketenimines **68** (δ_P +4).



68 **69**

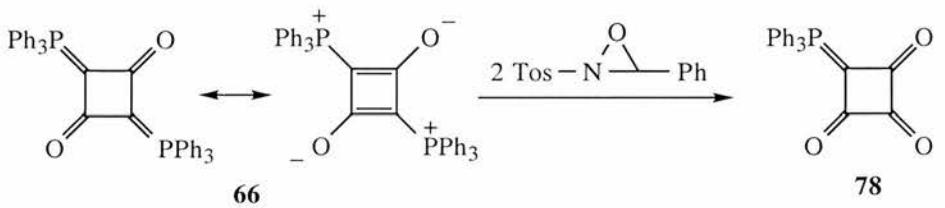
R= C_6H_5; $C_6H_4CH_3$-*p*; $C_6H_4NO_2$-*p*

Dimers of the reactive phosphacumulenes, ketenylidenetriphenylphosphorane **54** and the *N*-phenylketeneiminylidenetriphenylphosphorane **70** were first synthesised by Bestmann and co-workers.[32] Slow addition of half an equvalent of HCl to a solution of the ylides **54** or **70** leads to the phosphonium salts **71**. The salts undergo spontaneous cycloaddition with **54** or **70** to give the 1,3-cyclobutanedione derivatives **72** and **73**, (δ_P +1.36 and +4.08 respectively).



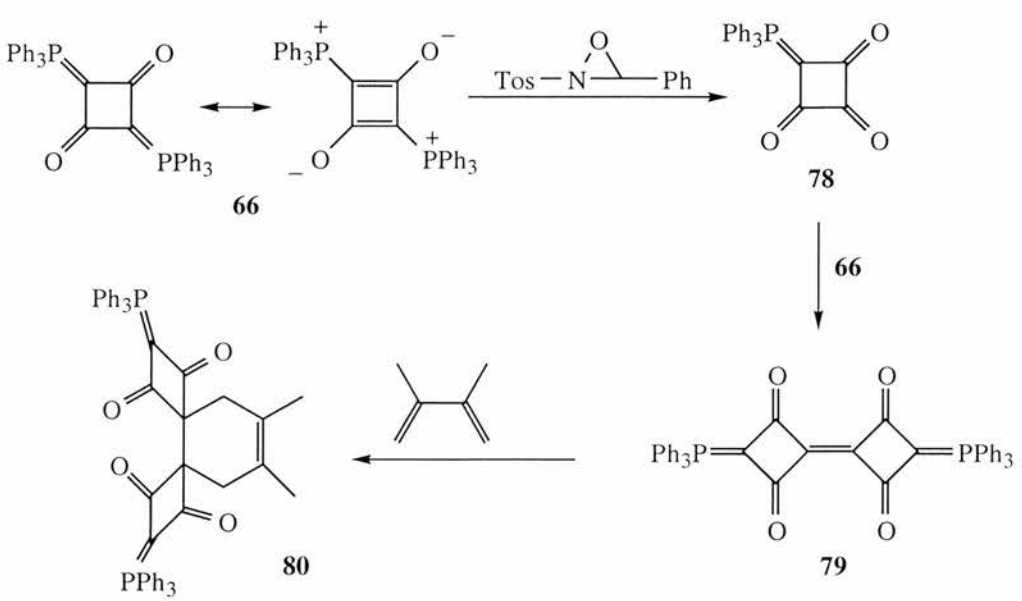
Reaction of the phosphonium salts **72** and **73** with a base (sodium bis(trimethylsilyl)amide), leads to the bis ylides **66** and **74** as yellow crystalline powders. Reaction of **66** and **74** with methyl iodide gives the known phosphonium salts **67** and **69**.[29] On reaction of **66** and **74** with *p*-nitrobenzaldehyde, the phosphoranes **75** and **76** are formed. Hydrolysis of **74** in aqueous methanol affords the monoylide **77**.

Structures and reactions of the oxidation products of the dimeric ketenylidene (triphenyl)phosphorane **66** were investigated.[33] Oxidation of **66** with two equivalents of *N*-*p*-toluenesulfonyl(phenyl)oxaziridine provided the trione **78** in 75% yield. The X-ray structure analysis was the first obtained for a neutral cyclobutanetrione. All C atoms of the four membered ring of **78** lie in one plane. In the ^{13}C NMR spectrum the signal of C3 (δ_C 214.6) appears as expected at higher frequency then the signals of the CO groups adjacent to the ylide (δ_C 194.6). The ^{31}P NMR signal appears at δ_P +8.34, substantially above the values for other acyl ylides with a four-membered ring structure.



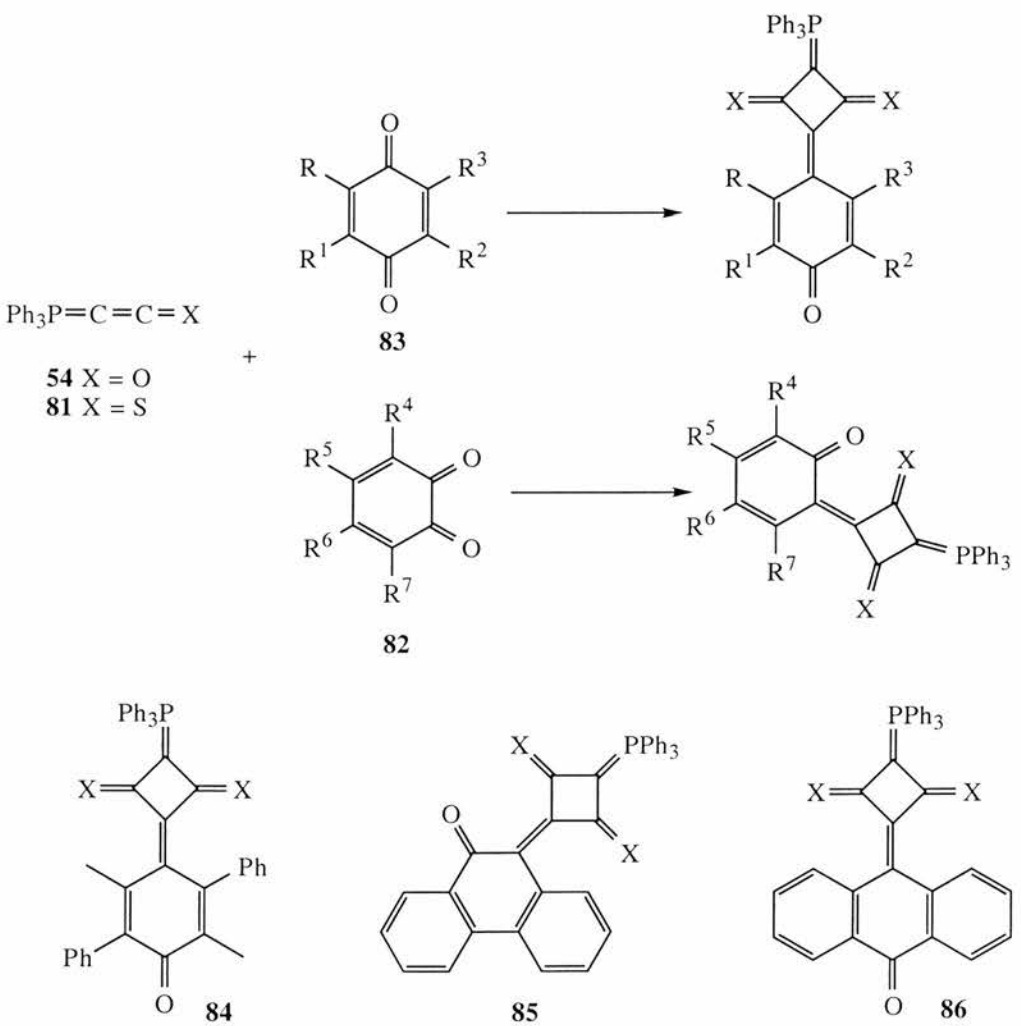
66 **78**

The central CO of **78** is very reactive and on oxidation of **66** with one equivalent of *N*-*p*-toluenesulfonyl(phenyl)oxaziridine, as soon as **78** forms it reacts with unoxidised **66** to give



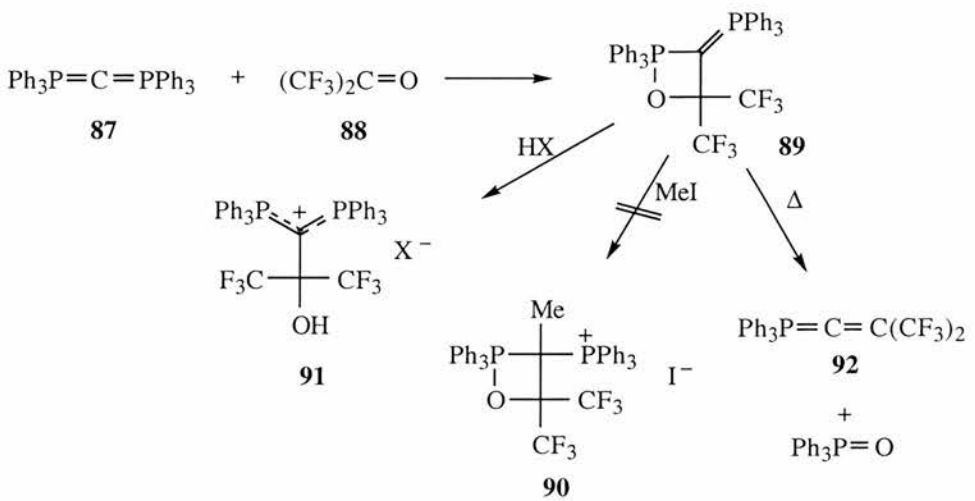
the bicyclic bis-ylide **79**. The bis-ylide **79** can also be obtained by reaction of the trione **78** with the dimer **66**. The ^{31}P NMR signal for the bicyclic product appears at δ_P +1.2 and the central double bond may react as a dienophile in Diels-Alder reactions. When **79** is heated with 2,3-dimethylbutadiene, the bis-spirocyclic compound **80** forms in 58% yield and here the ^{31}P shift appears at δ_P –5.0.

The behaviour of reactive phosphacumulenes towards *o*- and *p*-quinones **82** and **83** has been investigated.[34] The reaction of two equivalents of the **54** and its sulfur analogue **81** with various benzoquinones produced an interesting approach for the preparation of cyclobutane derivatives. This is exemplified by the products **84**-**86** formed in this way as shown below.



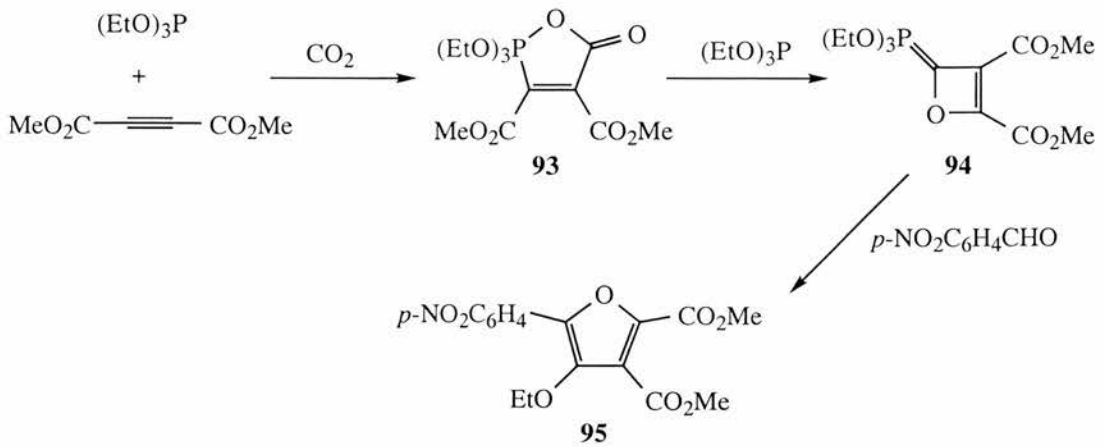
3 d Four-membered cyclic ylides containing ring heteroatoms

The first stable cyclic Wittig intermediate reported was obtained by the reaction of hexaphenylcarbodiphosphorane **87** with hexafluoroacetone **88**.[35] The oxaphosphetane structure **89** was assigned to this 1:1 adduct on the basis of its NMR spectrum. The ^{31}P NMR showed two doublets at δ_P –7.3 and +54.0 and these shifts are consistent with the values found for exocyclic phosphorus ylides and with cyclic structures with phosphorus covalently bonded to five substituents.

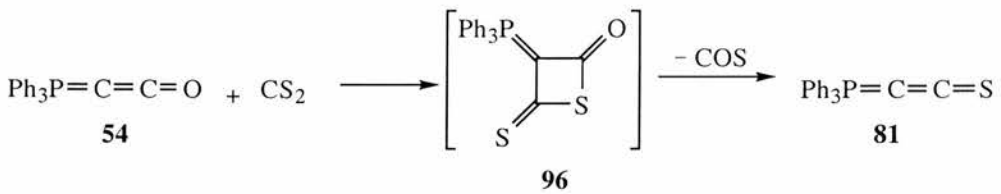


The X-ray crystallographic studies[36] showed that the planar four-membered ring system has a long P–O bond and equal bonds from the phosphorus atoms to the carbon atom. The adduct **89** failed to be alkylated by methyl iodide to give the salt **90** and on acid treatment the ring opened to give the phosphonium salt **91** with equivalent phosphorus atoms (δ_P +22). Warming of **89** in inert solvents yielded equimolar amounts of triphenylphosphine oxide and 2,2-bis(trifluoromethyl)vinylidenetriphenylphosphorane **92**.

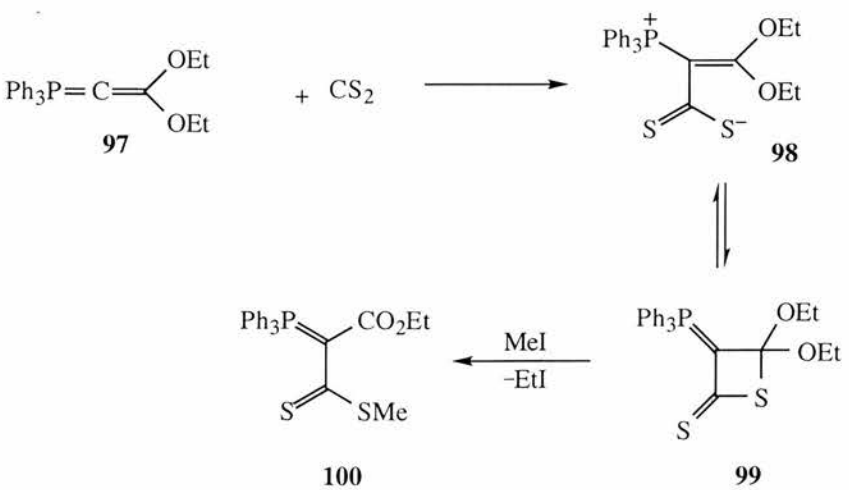
Griffiths and co-worker[37] reported the formation of the ylide **94** by passing carbon dioxide through a solution of DMAD during the addition of two equivalents of triethyl phosphite. The first stage is the formation of **93** which reacts rapidly with a second molecule of triethyl phosphite to form the ylide **94**. The ^{31}P NMR showed a signal at δ_P +40.4 and the ^{13}C NMR showed a characteristically large phosphorus coupling of 250 Hz. The ylide **94** reacts with 4-nitrobenzaldehyde to give a yellow crystalline compound of the furan structure **95** in which the heterocyclic oxygen and one of the β-carbon atoms in the furan ring are derived from the carbon dioxide.



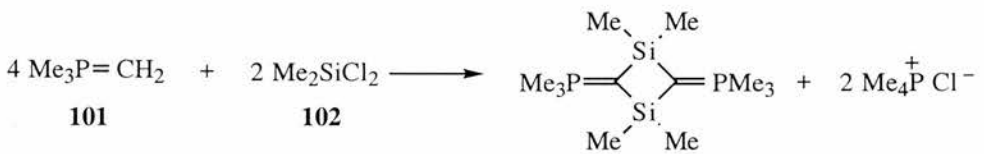
Another type of cyclic four-membered ylide containing a heteroatom is the unstable thiolactone **96** resulting from treatment of triphenylphosphoranylideneketene **54** with carbon disulfide.[29] The product isolated was triphenylphosphoranylidenethioketene **81** which was presumably formed by loss of COS from the intermediate **96**.



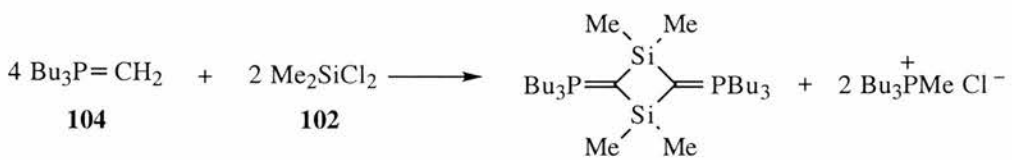
Bestmann and Saalfrank[38] reported the formation of the thiethane **99** from (2,2-diethoxyvinyl- idene)triphenylphosphorane **97** and carbon disulfide. The first step is formation of the betaine **98** which is in equilibrium with the thiethane **99**. The thiethane **99** reacts with methyl iodide to give the ester-stabilised ylide **100** by loss of ethyl iodide.



Not many cyclic four membered phosphoranes containing two heteroatoms are known, Schmidbaur and coworker[39] devised a simple method for the synthesis of silyl-substituted alkylidene phosphoranes. Reaction between methylenetrimethylphosphorane **101** and dimethyldichlorosilane **102** gave the cyclic product **103** in 55% yield. A similar product **105** was obtained by starting with the homologue methylenetri-n-butylphosphorane **104** in 73% yield. The products were characterised by means of chemical analysis and NMR.



103

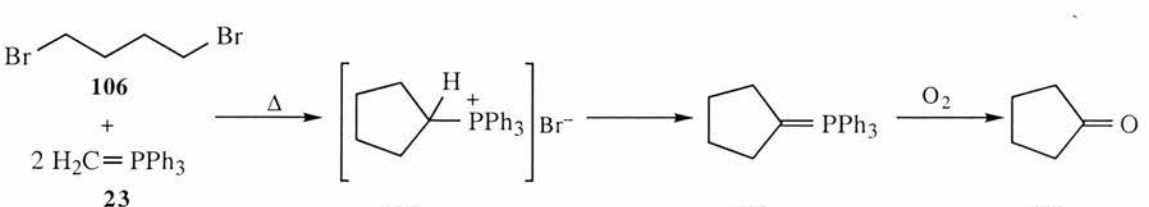


105

4 Five-Membered Rings

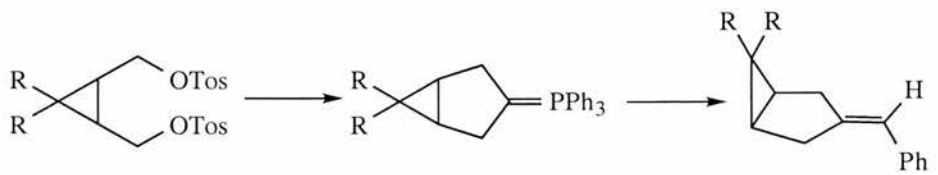
4 a Simple Cyclopentylides

Not many syntheses for the simple five-membered ring ylide, cyclopentylidenetriphenyl phosphorane **108** are known. In 1967 Bestmann and Kranz[16] reported a new ring closure reaction to give ylides with four, five, six and seven membered rings which was mentioned before (see section 3 a). Reaction of 1,4-dibromobutane **106** and 2 equivalents of methylenetriphenylphosphorane **23** in boiling benzene gave the ylide **108** in 12% yield. On autoxidation,[20] the cyclic ketone **109** was obtained. The phosphorus NMR shifts[40] were



107 **108** **109**

δ_P +4.8 for the ylide **108** and δ_P +30.7 for the phosphonium salt **107**. Using a similar scheme various bicyclic compounds were made.[21] 3-Benzylidenebicyclo[3.1.0]hexane **114** and 6,6-diphenyl-3-benzylidenebicyclo[3.1.0]hexane **115** were prepared starting from the bis(tosylate) **110** and the diphenyl bis(tosylate) **111** via the ylides **112** and **113** respectively.

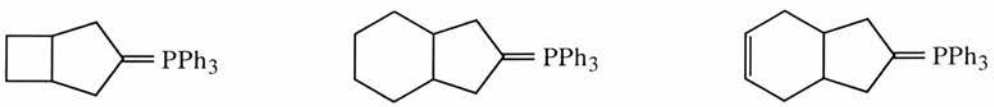


110 R = H
111 R = Ph

112
113

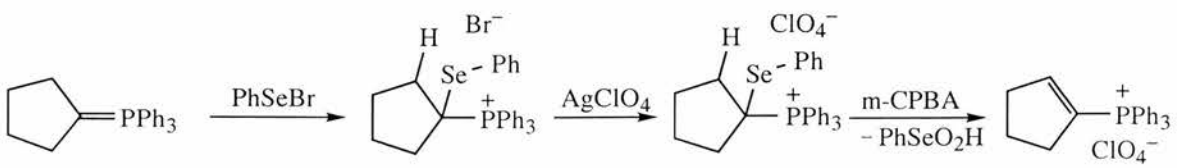
114
115

Other bicyclic ylides similarly prepared and used included the bicyclo[3.2.0]heptane system **116**, the bicyclo[4.3.0]nonane system **117** and the bicyclo[4.3.0]non-3-ene compound **118**.



116 **117** **118**

Minami and co-workers[41] reported the synthesis of 1-cycloalkenylphosphonium salts by selenenylation of phosphorus ylides and subsequent seleninic acid elimination. The cyclic ylide **108** reacts with phenylselenenyl bromide to give the salt **119** and oxidative elimination of the phenylselenenyl residue in **120** as phenylseleninic acid leads to 1-cycloalkenylphosphonium salt **121** in high yield.

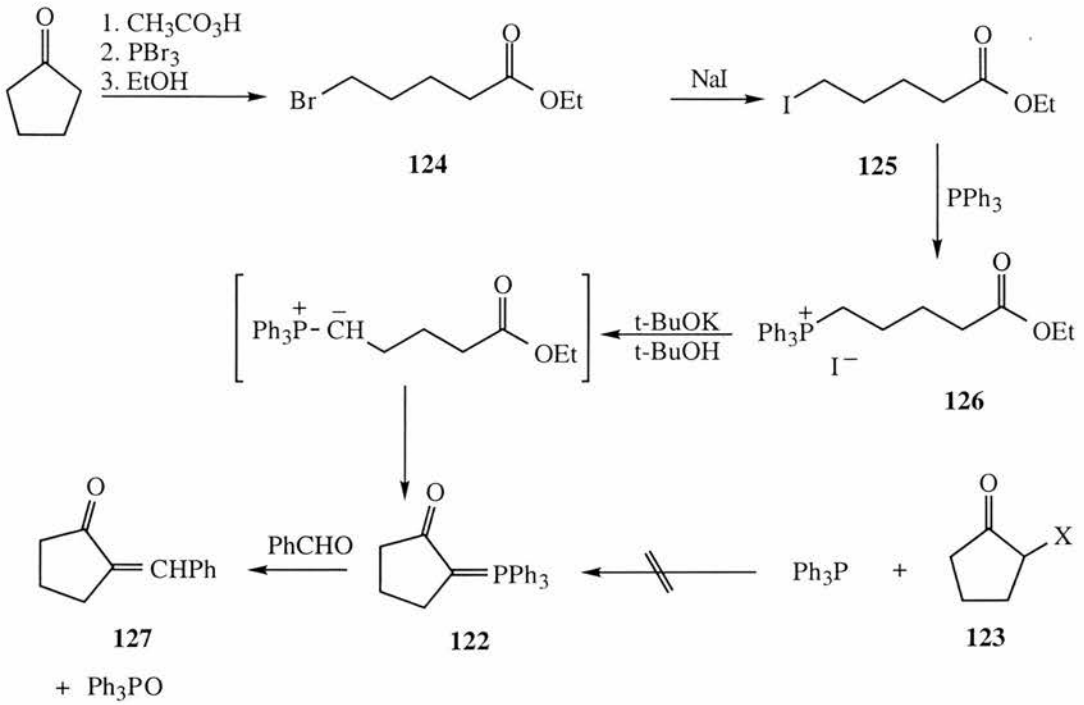


108 **119** **120** **121**

4 b Oxo-Stabilised cyclopentylides

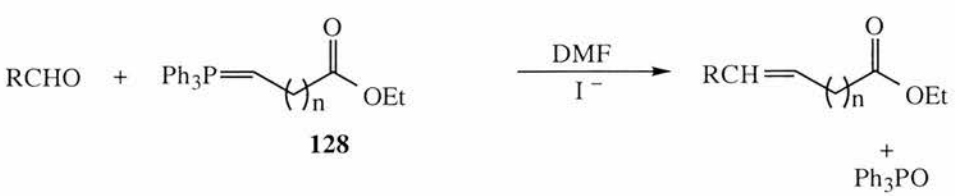
While studying useful routes to cyclic ketones House and Babad[42] found a noteworthy preparative route for the α-oxocyclopentylidenetriphenylphosphorane **122**. These oxo ylides are not accessible via the reaction of the α-halocycloalkanones **123** with triphenylphosphine.[43]

Cyclopentanone reacts with peracetic acid followed by phosphorus tribromide and then ethanol to produce the bromo ester **124**. The bromo ester **124** is converted to the iodo ester **125**



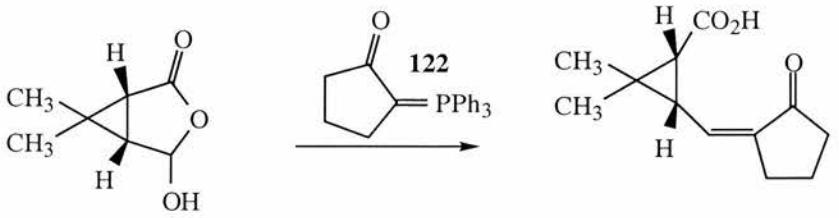
which is then heated with triphenylphosphine to give the phosphonium salt **126** in high yield. Addition of potassium *t*-butoxide to a solution of the salt **126** in *t*-butanol under reflux gave the ylide **122** in 84% yield. The *E*-2-benzylidenecycloalkanone **127** is formed from reaction of **122** and benzaldehyde.

Later that year a Russian group reported similar results while investigating a new stereospecific route for the synthesis of unsaturated fatty acids, based on the condensation of ω-alkoxycarbonyl ylides **128** with aldehydes.[44] A considerable number of natural acids of the



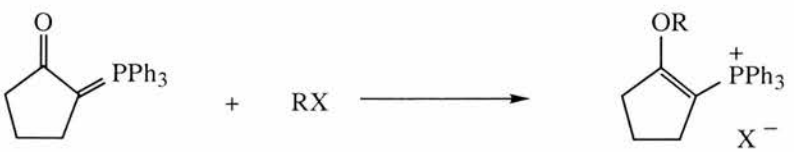
oleic (n=7) and vaccenic (n=9) series were synthesised but when they attempted to synthesise acids of the arachidonic type (n=3) it appeared that the ylide underwent intramolecular acylation as mentioned above to give the cyclic ylide **122**.

When 2-oxocyclopentylidenetriphenylphosphorane **122** was treated with *(1R,3S)-(E)*-2,2-dimethyl-3-formylcyclopropanecarboxylic acid hemiacetal **129**, *(1R,3S)-(E)*-2,2-dimethyl-3-(2'-oxocyclopentylidenemethyl)cyclopropanecarboxylic acid **130** was formed which is useful in the preparation of an insecticide.[45]



129 **131**

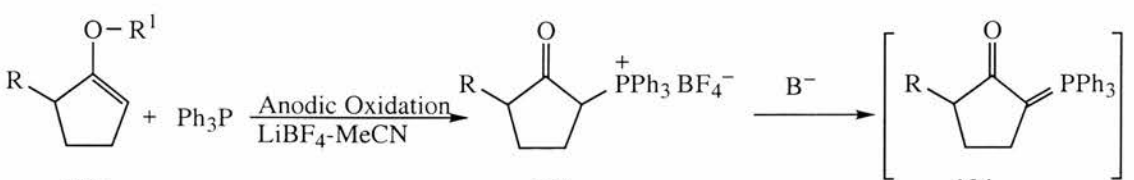
Alkylation of the ylide **122** with alkyl halides gave various phosphonium salts **131** which have been claimed to have analgesic properties.[46]



122 **131**

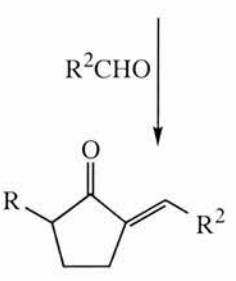
R	X
$PhCH_2$	Br
Me_2CH	I
Me	p-tosylate
$Me_2C{=}CHCH_2$	Br
$PhCH_2$	Br
MeO_2CCH_2	Br

In 1990 a new one step synthesis of 2-oxocycloalkyltriphenylphosphonium salts was reported[47] based on the anodic oxidation of a silyl enol ether, enol phosphate or enol ester **132** in the presence of triphenylphosphine.The silyl enol ether and two enol esters were converted



132 **133** **134**

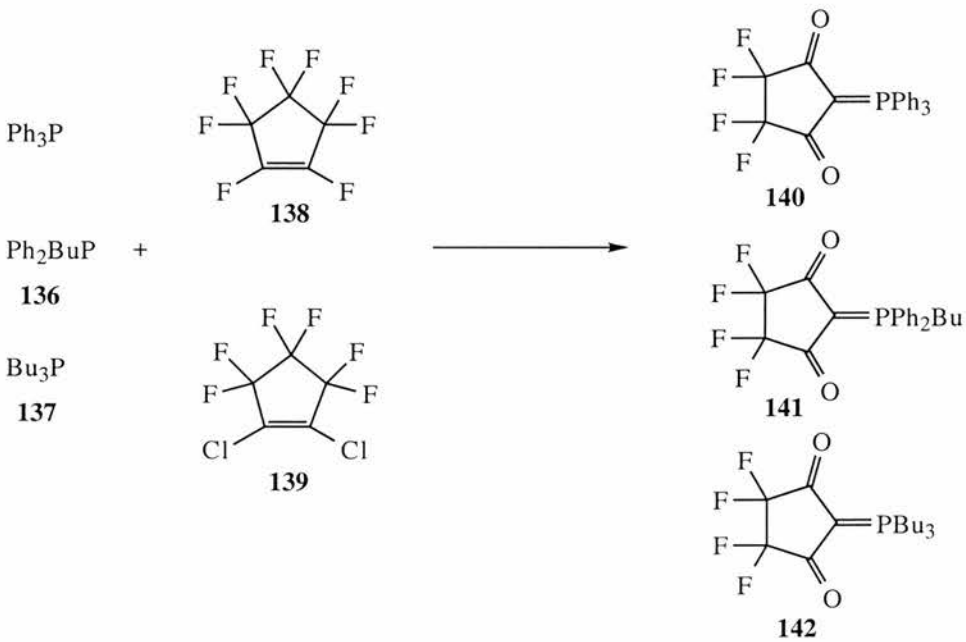
R= H, Me
R^1= $SiMe_3$, $P(O)(OEt)_2$, COMe



135

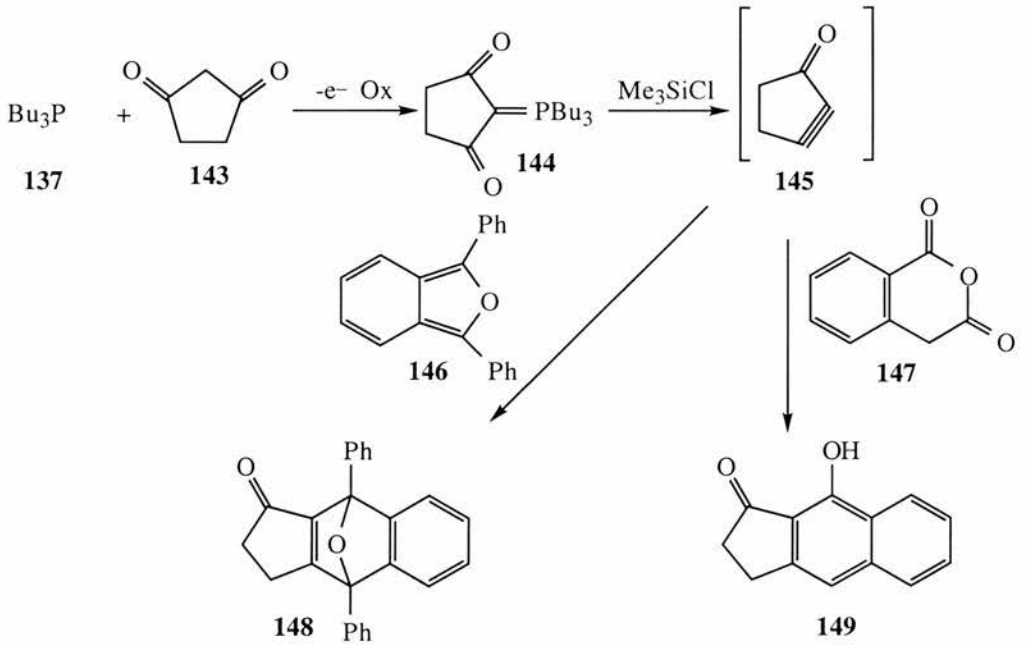
to 2-oxocyclopentyltriphenylphos-phonium tetrafluoroborates **133**. The Wittig reaction of the ylides **134** derived from these salts with aldehydes to give **135** was examined to demonstrate the value of the salts **133** as building blocks in synthetic organic chemistry.

Cyclopentanedione derivatives were prepared as in a similar manner to the cyclobutanediones.[31] Displacement reactions of triphenylphosphine, butyldiphenylphosphine **136** and tributylphosphine **137** with perfluorocyclopentene **138** and 1,2-dichlorohexafluoro-cyclopentene **139** gave the corresponding ylides **140-142** in good yields. The ^{31}P NMR shifts were δ_P +11.2, +13.8 and +22.7 respectively.

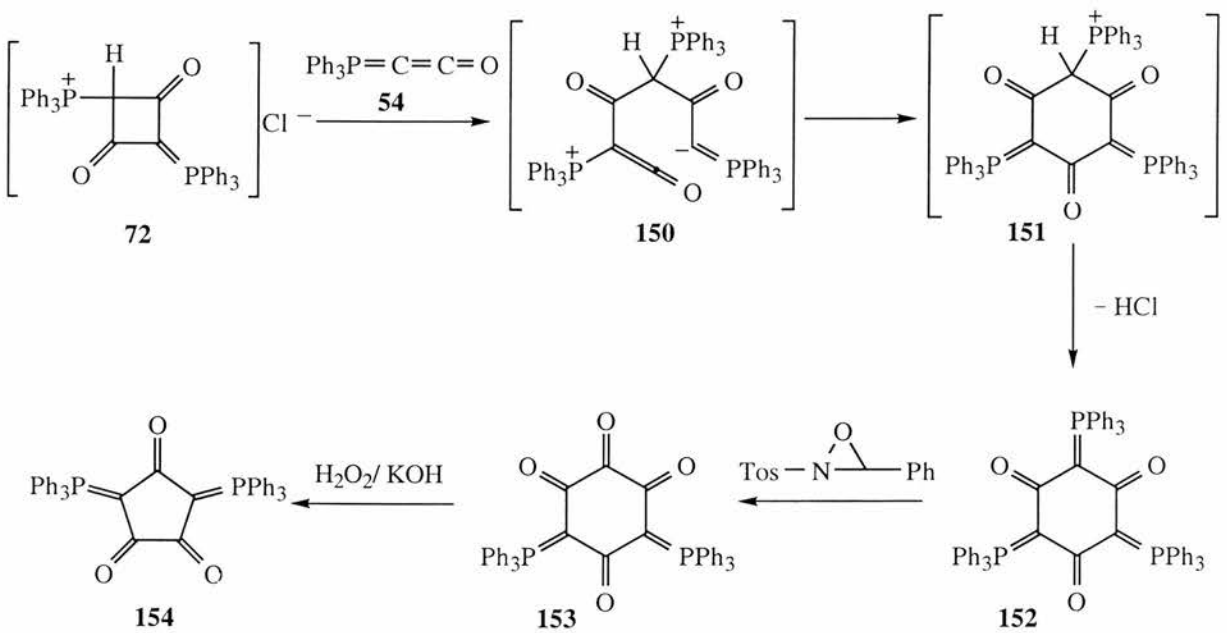


α,α'-Dioxocyclopentylidenetributylphosphorane **144** can also be prepared[48] by electrochemical oxidation of 1,3-cyclopentenedione **143** in the presence of tributylphosphine **137** . The ylide **144** was obtained and isolated in 59% yield. Reaction with Me_3SiCl in the presence of the anhydride **146** or 1,3-diphenylisobenzofuran **147** goes via the cyclopent-2-ynone **145** which is trapped in a Diels-Alder reaction to give the corresponding adducts **148** and **149**.

The only cyclopentanetrione-ylide reported was by Bestmann and co-workers in 1993.[49] This was an extension to the studies done on the dimer of ketenylidene(triphenyl)phos phorane **54** mentioned in section 3 c. The salt of the dimer **72** adds to another equivalent of

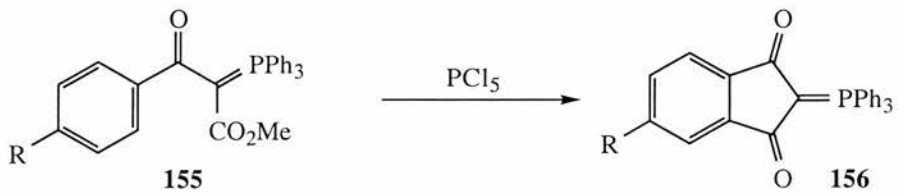


54 to initially give **150**, which is converted to **151** by 1,6-cyclisation. Excess **54** deprotonates **151** to form **152**. Oxidation of **152** with *N*-*p*-tolylsulfonyl(phenyl)oxaziridine gives the tetraoxo bisylide **153** in 92% yield. When **153** is oxidised with H_2O_2 and KOH, the cyclopentanetrione diylide **154** is formed in 92% yield. The X-ray structure of **154** was reported and it had a ^{31}P NMR shift of δ_P +8.8.



4 c Aromatic fused cyclopentenylides

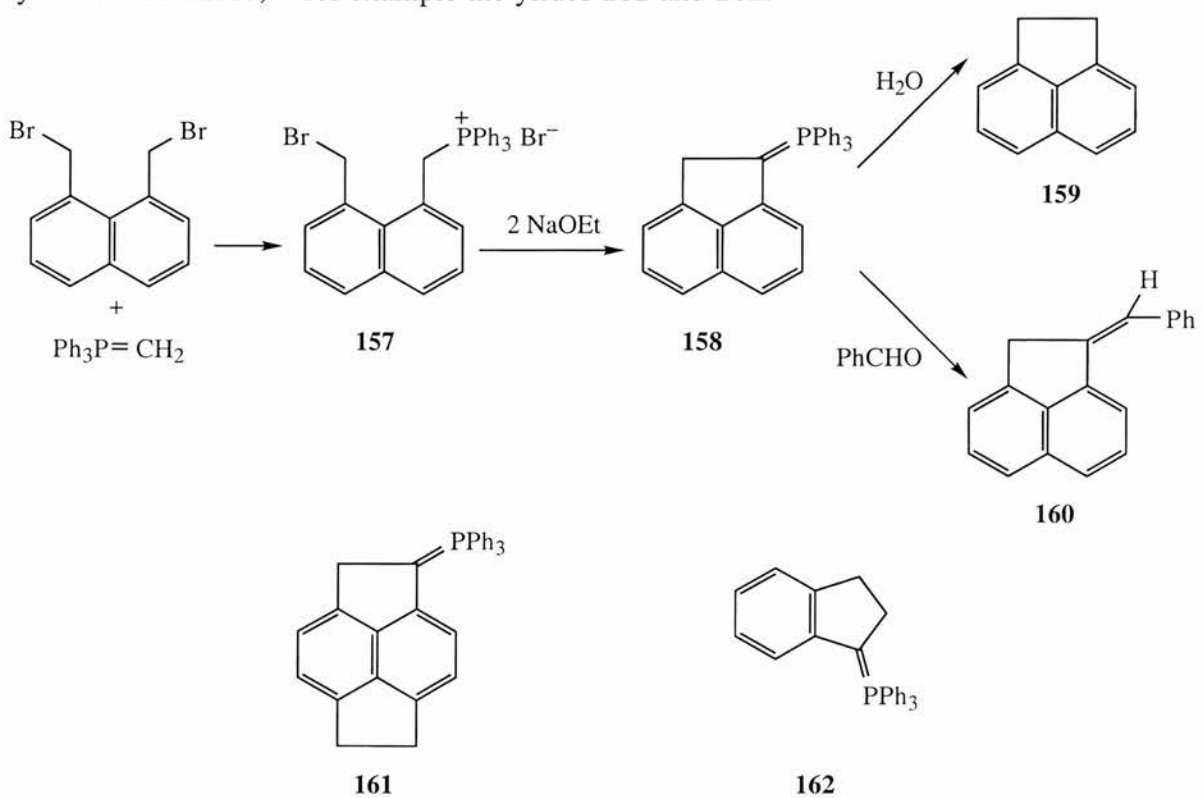
The first compound of this type to be reported was by Märkl in 1962.[50] The ylide **156** which was very stable was obtained in 20–40% yield by reacting the phosphorane **155** with phosphorus pentachloride. When there was no substitution on the aromatic ring dark red crystals were isolated with a high m.p of 294–296 °C. Where a methyl group was present on the aromatic ring the mp was lower at 269–270 °C.



155 **156**

R = H, Me

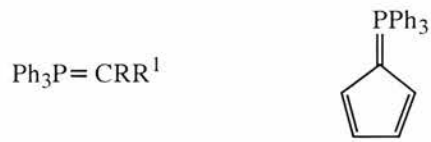
Using the approach of Bestmann and Haberlein,[13] the phosphonium salt **157** reacts with two equivalents of sodium ethoxide to give ylide **158**. Hydrolysis of the ylide resulted in the loss of triphenylphosphine oxide to give acenaphthene **159** and a Wittig reaction using benzaldehyde gave benzylideneacenaphthene **160**. Using analogous methods other ring systems were made,[51] for example the ylides **161** and **162**.



157 **158** **159** **160** **161** **162**

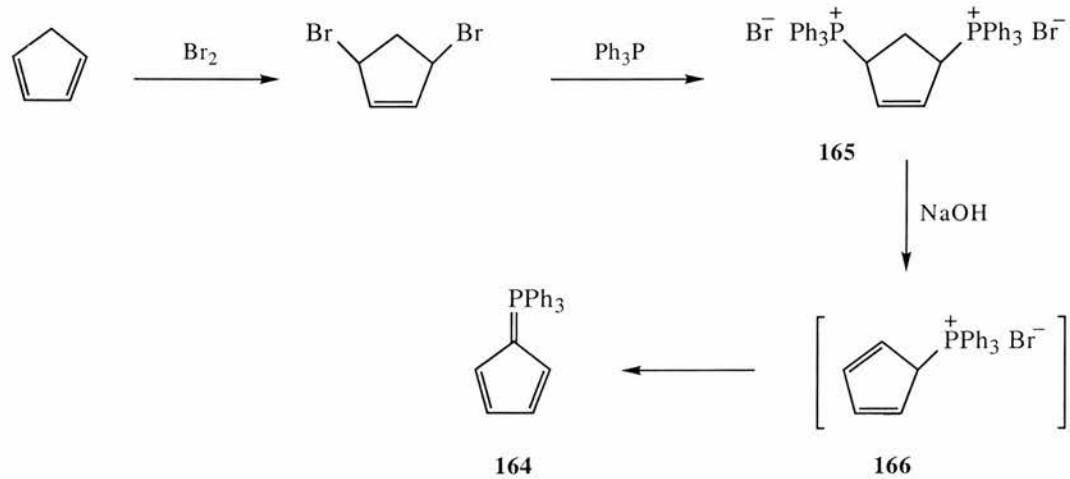
4 d Cyclopentadienylides

Cyclopentadienylides have been known since 1957.[52] The search for correlations between structure, physical and chemical properties of the phosphinemethylenes **163** led to the preparation of triphenylphosphonium cyclopentadienylide **164**.



163 **164**

Bromination of cyclopentadiene and reaction with triphenylphosphine gave the bisphosphonium salt **165**. On addition of sodium hydroxide the bisphosphonium salt eliminates one molecule of Ph_3P to give the mono phosphonium salt **166** which goes on to form triphenylphosphonium cyclopentadienylide **164** in 41% yield as pale yellow crystals.

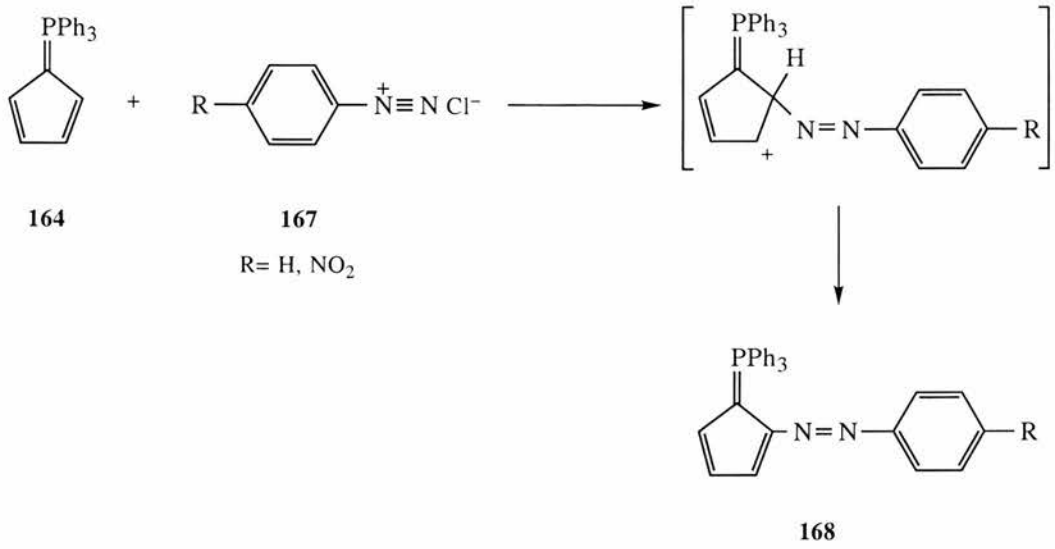


165

164 **166**

The ylide **164** melts at 229–231 °C, is stable in boiling alkali and does not react with ketones. The UV and IR absorption spectra were recorded and both showed a high degree of conjugation in the system. The NMR data for **164** was reported,[8] showing a ^{13}C signal for the ylide carbon at δ_C 78.3 with a large P-C coupling of 113 Hz.

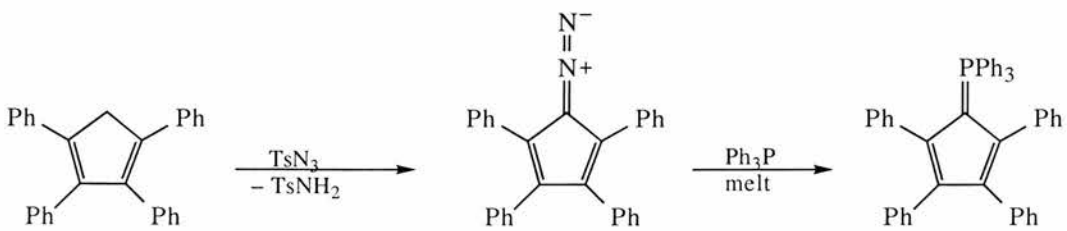
The ylide **164** couples readily with diazonium salts **167** producing a new class of brightly coloured azo dyes **168**.[53]



164 **167** **168**

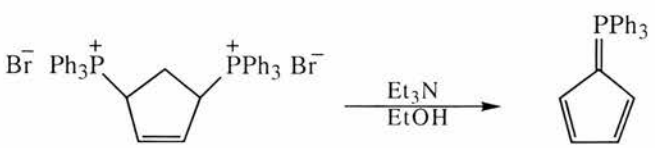
R= H, NO_2

Ten years later, derivatives of **164** were synthesised from diazocyclopentadienes.[54] 1,2,3,4-Tetraphenylcyclopentadiene **166** reacts with *p*-tosyl azide to give the 1-diazo-2,3,4,5-tetraphenylcyclopentadiene **170** in 90% yield. On melting with triphenylphosphine this forms the ylide **171**.



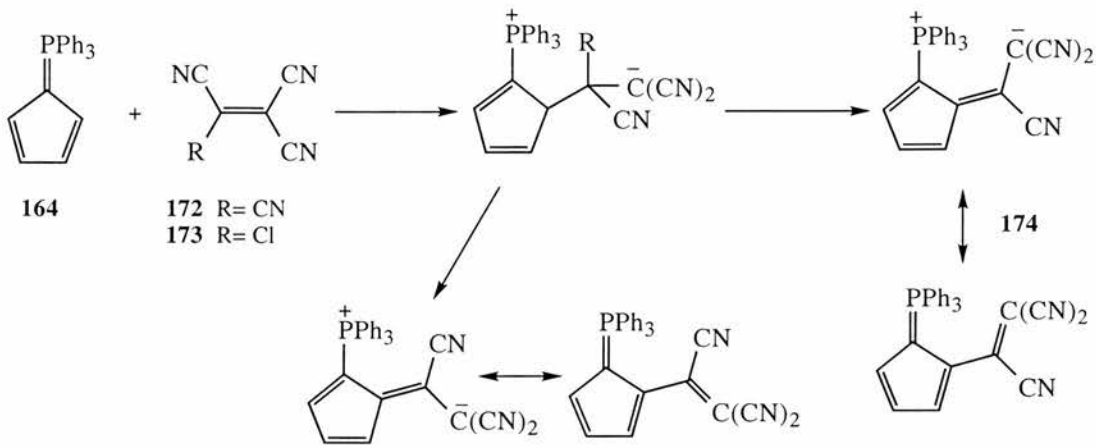
169 **170** **171**

In 1970 the ylide **164** was prepared by a modification of the original method of Ramirez.[55] A solution of the bis-phosphonium salt **165** prepared in chloroform was evaporated to leave a pale yellow residue, which was dissolved in ethanol and treated with two equivalents of triethylamine. The product **164** was obtained in 65% yield. The ^1H NMR spectrum showed two multiplets at δ_H 7.7 and 6.4 representing the phenyls and cyclopentadiene respectively while the ^{31}P NMR spectrum gave a signal at δ_P +12.1.



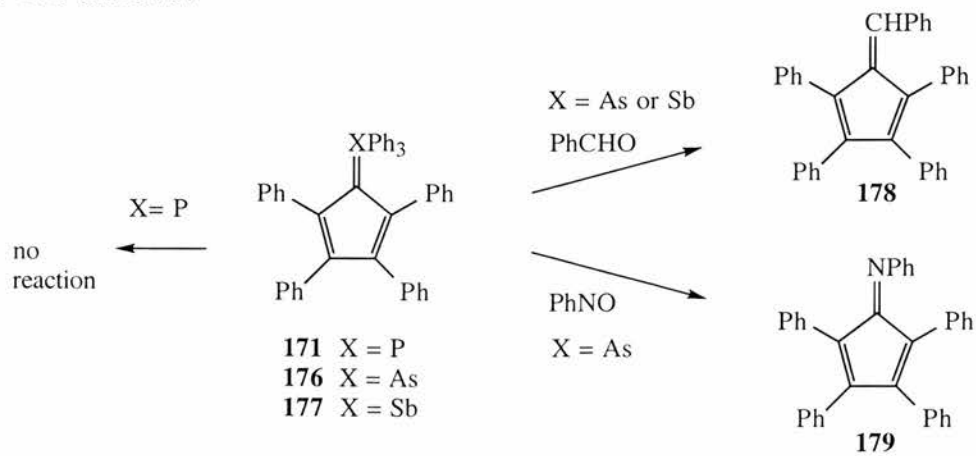
165 **164**

Hall and coworkers[56] reported the reaction of **164** with cyanoalkenes. Equimolar quantities of the phosphorane **164** and tetracyanoethylene **172** were mixed in dichloromethane in the presence of an excess of triethylamine to give a quantitative yield of 2-(1,2,2-tricyanovinyl)cyclopentadienylidenetriphenylphosphorane **174**. The same product was



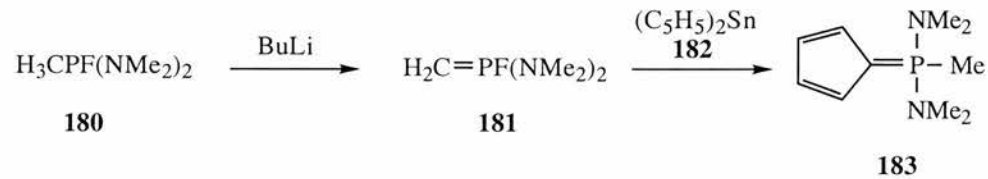
obtained when an equimolar mixture of the ylide **164** and tricyanovinyl chloride **173** reacted without the addition of a base. However, an equimolar mixture of the ylide **164** and tetracyanoethylene **172** in the absence of base gave the product **175** which was the geometrical isomer of **174**. The kinetics and mechanism of these reactions were studied.[56]

The properties of a number of heteronium tetraphenylcyclopentadienides with a variety of heteroatoms were investigated.[57] The cyclopentadienylidenetriphenylphosphorane **171** showed no reactivity towards aldehydes and nitrosobenzene in contrast to some of its analogues, for example the arsonium and stibonium ylides **176** and **177** which gave the products **178** and **179**.



Yoshida and co-workers[58] investigated the reaction of **164** with a number of dienophiles and electrophiles. From its reaction behaviour it was found to have aromatic character in the cyclopentadienyl ring and not the chemical properties expected for ordinary ylides.

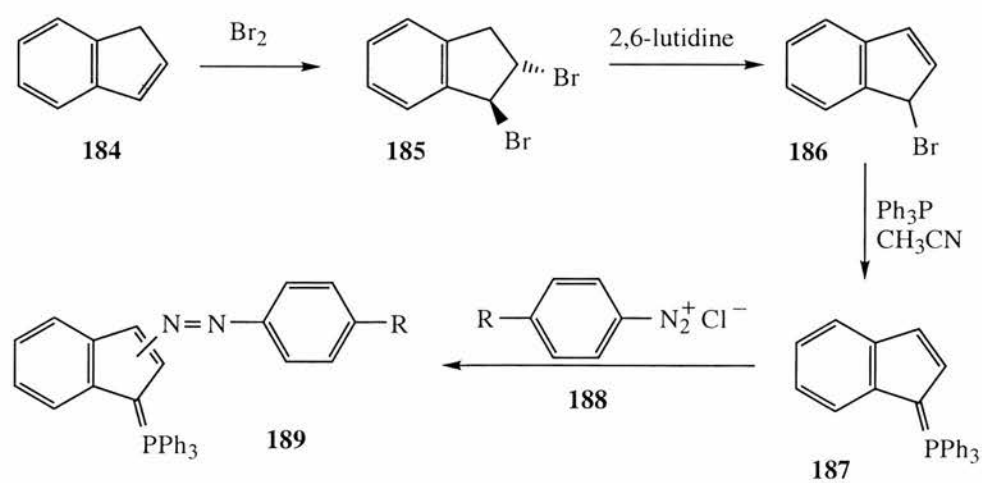
In an interesting reaction Fluck and co-workers obtained methylbis(dimethylamino) phosphonium cyclopentadienylide **183** from dicyclopentadienyl stannane **182** and fluorobis (dimethylamino)phosphonium methylide **181**.[59] The latter compound was obtained from **180** with one equivalent of butyllithium. The NMR data reported, included a ^{31}P signal at δ_P +54.7 and a ^{13}C signal for the ylide carbon at δ_C 83.4 with a large P-C coupling of 141 Hz.



180 **181** **183**

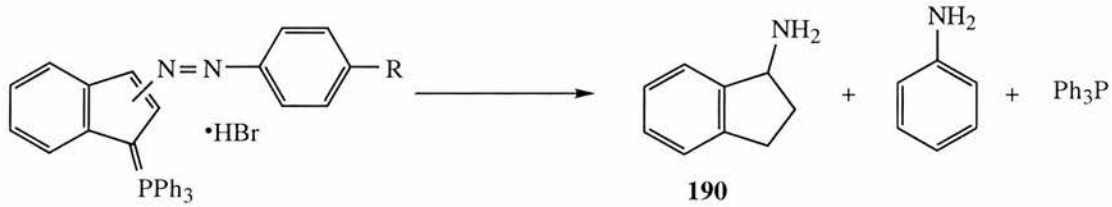
4 e Benzo-fused cyclopentadenylides

The 1-indenylide **187** has been prepared[60] but little of its chemistry has been reported. Bromine was added to indene **184** giving the *trans*-1,2-dibromoindane **185**. Elimination of hydrogen bromide occured when 2,6-lutidine was added to **185** to form 1-bromoindene **186**. The 1-bromoindene **186** was dissolved in acetonitrile and triphenylphosphine was added yielding the product 1-indenylidenetriphenylphosphorane **187**.



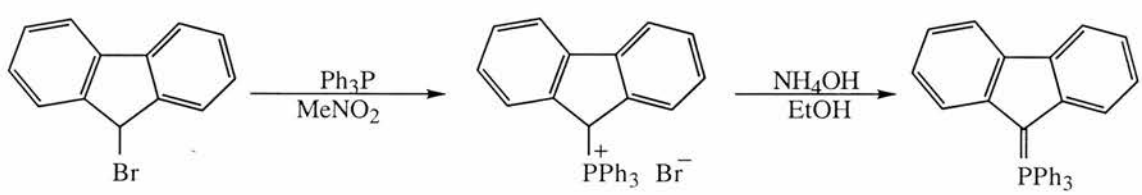
184 **185** **186** **188** **187** **189**

This ylide is stable and couples with diazonium salts to give arylazo-substituted ylides **189** but initial attempts to determine the substitution position were unsuccessful. In later work Ford[61] was successful in establishing the coupling position in **187**. Hydrogenation of the hydrobromide salt of phenylazoindenylidenetriphenylphosphorane **189** in methanol containing platinum oxide gave aniline, triphenylphosphine and a small amount of 1-indanamine **190** which was isolated and identified by comparison with an authentic sample. The degradation of **189** to **190** shows that the reactive position in **187** is at C-3.



190

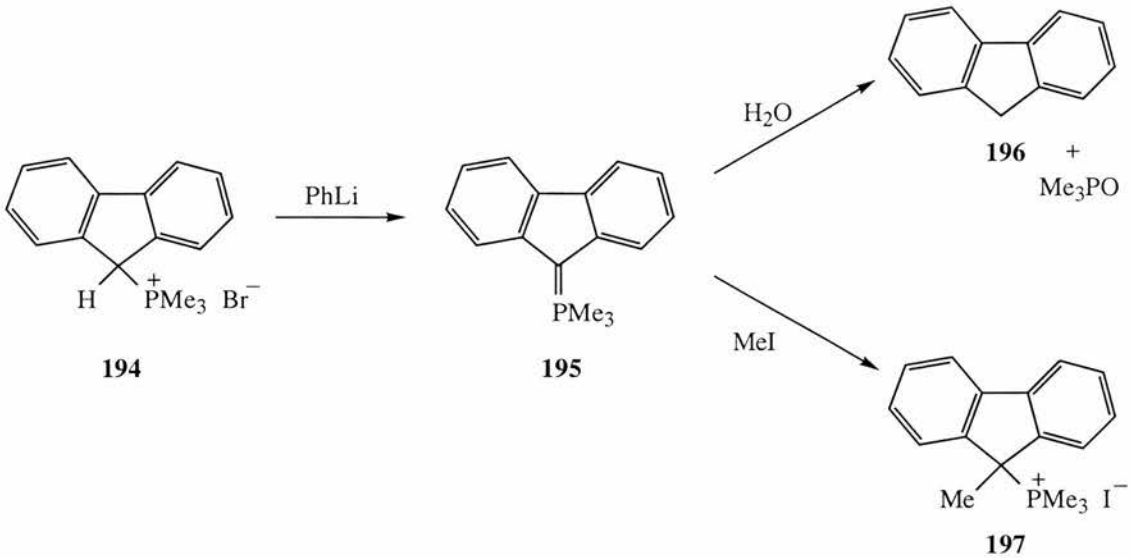
Pinck and Hilbert[62] were the first to prepare and characterise triphenylphosphonium fluorenylide **193**, following an early unsuccessful attempt by Staudinger and Meyer[63] in 1919. Triphenylphosphine was added to a solution of 9-bromofluorene **191** in nitromethane and 9-fluorenyltriphenylphosphonium bromide **192** precipitated out. Addition of ammonium hydroxide to a solution of the salt **192** in boiling ethanol gave triphenylphosphonium fluorenylide **193** as yellow crystals with a mp of 233 °C.



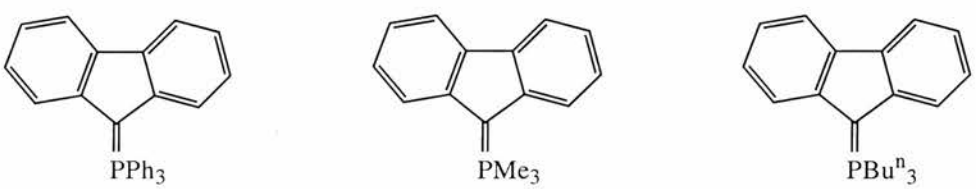
191 **192** **193**

The trimethylphosphonium fluorenylide **195** was similarly prepared[64] by deprotonating the 9-position of the salt **194** using phenyllithum. Hydrolysis of **195** gave fluorene **196** and trimethylphosphine oxide while the addition of methyl iodide gave the corresponding phosphonium salt **197**. The benzyldiethylphosphonium fluorenylide was also made using the same method.[64]

Johnson and co-worker[65] compared the chemistry of the triphenyl-, trimethyl- and tributyl-phosphonium fluorenylides **193**, **195** and **198**. They found that the two alkyl ylides



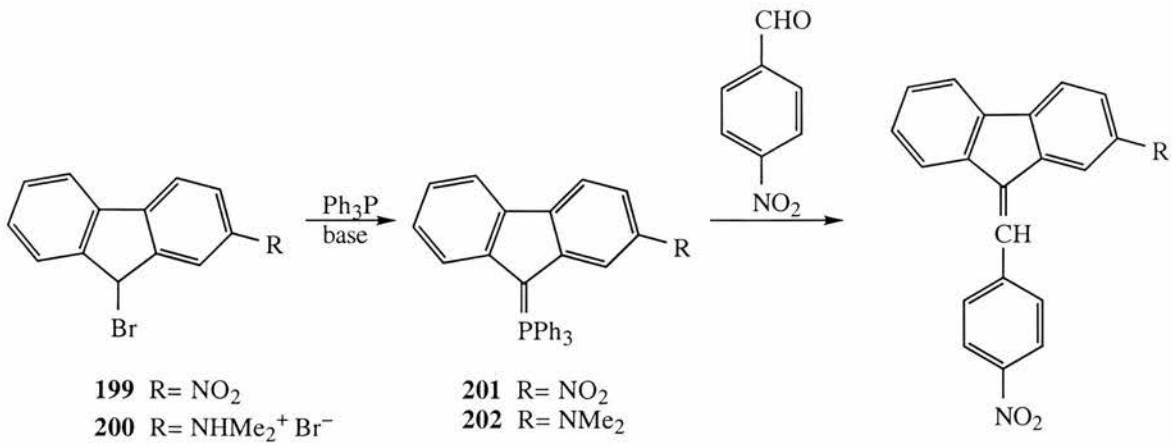
do not differ in their mode of reaction with carbonyl compounds but differ in their stability and reactivity. The trialkyl ylides **195** and **198** are more reactive than the triphenyl ylide **193**. In order to compare the reactivity of **193** with that of the cyclopentadienylide **164** which fails to react with aldehydes or ketones, the condensation of **193** with several carbonyl compounds was studied.[66] It was observed that the ketones failed to react whereas the aldehydes did give the Wittig products in high yields.



193 **195** **198**

Some new ylides of this type were prepared and used in a Wittig reaction to synthesise analogues of 9-*o*-chlorocinnamylidenefluorene for antitumour screening.[67] Triphenylphos phonium 2-nitrofluorenylide **202** and triphenylphosphonium 2-*N,N*-dimethylamino fluorenylide **201** were made starting from 9-bromo-2-nitro fluorene **199** and 9-bromo-2-*N,N*-dimethylaminofluorene hydrobromide **200**[68] to form in quantitative yield the products **201** as a deep purple solid and **202** as a bright yellow solid.

On condensation of these ylides with *p*-nitrobenzaldehyde, the deep purple *E-Z* mixture of 9-*p*-nitrobenzylidene-2-nitrofluorene **203** and the yellow 9-*p*-nitrobenzylidene-2-*N,N*-di methylaminofluorene **204** were obtained in 100 and 87% yields respectively.

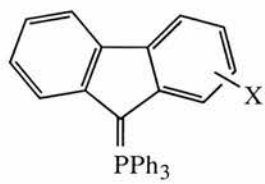


199 R= NO_2
200 R= $NHMe_2^+ Br^-$

201 R= NO_2
202 R= NMe_2

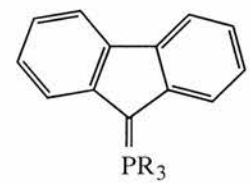
203 R= NO_2
204 R= NMe_2

Other fluorenylides prepared include examples **205** substituted on the fluorene part and examples **206** substituted on the phenyl groups.[69] The basicity of the ylides was decreased by the presence of electron withdrawing substituents on either the fluorene or phosphonium portion of the molecules.



205

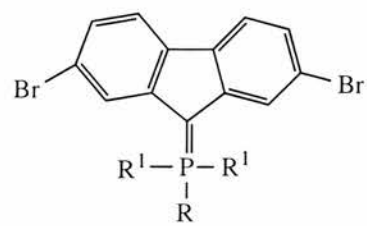
X = 2-MeO, 2-NO_2, 2-Br, 3-Br, 2-NHAc, 2-CN, 2-Me



206

R = *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-MeC_6H_4, *m*-MeC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *o*-FC_6H_4, *m*-FC_6H_4, *p*-FC_6H_4

Goetz and Klabuhn examined the dipole moments, ^1H NMR, IR and UV spectra of some 2,7-dibromo-9-fluorenylidene-aryldipropyl-, -aryldiphenyl- and -triaryl-phosphoranes, **207**, **208** and **209**.[70] They found that the substituents X have an influence over the whole molecule but as expected the effects are small.

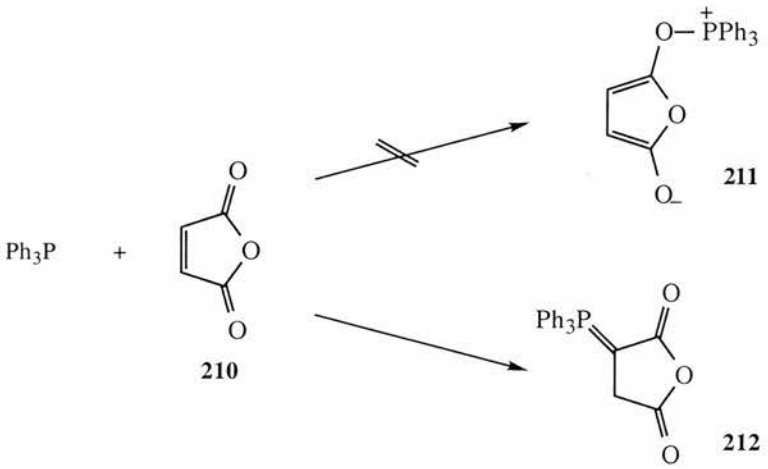


207 R^1=Pr; R= *p*-XC_6H_4(a-g)
208 R^1= C_6H_5; R= *p*-XC_6H_4(a-e)
209 R^1= R= *p*-XC_6H_4(b-d)

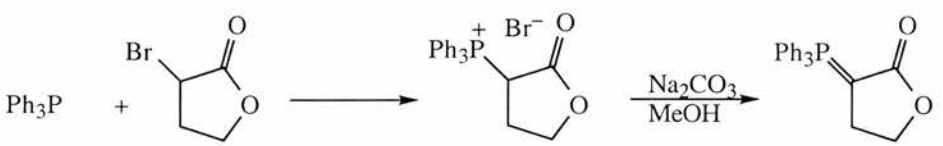
	X
a	H
b	OMe
c	NMe_2
d	Cl
e	Br
f	CN
g	COMe

4 f Five-membered cyclic ylides containing one oxygen

The first five-membered cyclic ylide containing an oxygen was discovered in 1940 by Schönberg and Ismail although they did not recognise it as such.[71] They claimed that a zwitterionic phosphonium salt **211** was formed by reaction of triphenylphosphine with maleic anhydride **210** but Aksnes[72] showed in 1961 that it was a phosphonium ylide **212**.



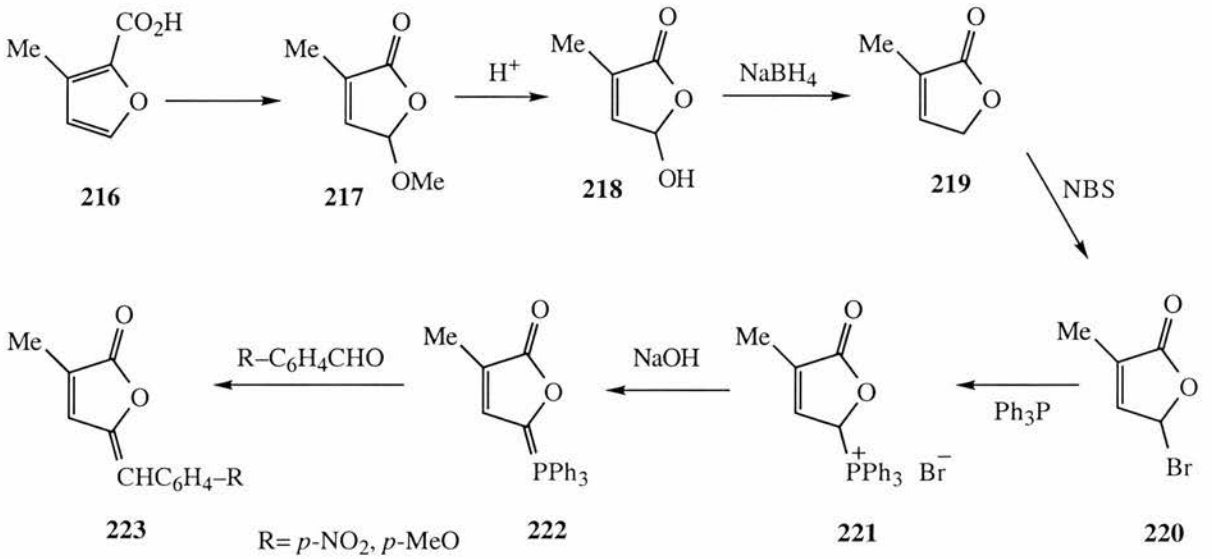
The mono oxo cyclic ylide **215** was prepared[73] by reaction of triphenylphosphine and α-bromo-γ-butyrolactone **213** to give the phosphonium salt **214**. When a solution of sodium carbonate was added to **214** in aqueous methanol it gave the ylide **215** in 80% yield. The ylide **215** was characterised by mp 232–235 °C and microanalysis. The rate constant for the formation of the ylide was determined.



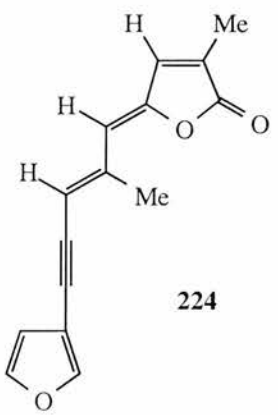
213 **214** **215**

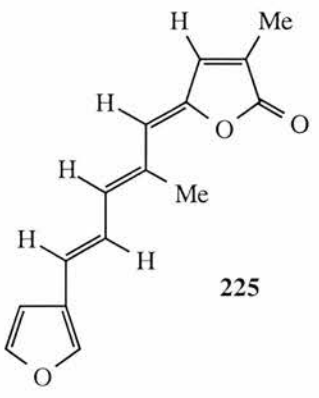
In connection with a projected total synthesis of the biosynthetically unusual diterpene isoeremolactone a mild method for the preparation of 4-benzylidene-2-methylbut-2-enolides **223** was required.[74] Using a Wittig approach, it appeared that an ylide of type **222** would be suitable. Dye-sensitised photo-oxygenation of 3-methyl-2-furoic acid **216** in methanol gave the methoxylactone **217**, which was hydrolysed to the hydroxylactone **218**.The hydroxylactone was reduced with sodium borohydride to the lactone **219**. This was converted

using *N*-bromosuccinimide into the unstable bromolactone **220** which was then reacted with triphenylphosphine to give the phosphonium salt **221**. The salt **221** was treated with a dilute solution of sodium hydroxide forming the ylide **222** as a bright yellow precipitate with a mp of 186–189 °C. The reaction of the ylide **222** with aromatic aldehydes, *p*-nitrobenzaldehyde and *p*-methoxybenzaldehyde, gave 24% and 30% respectively of a single product **223** of unknown stereochemistry.

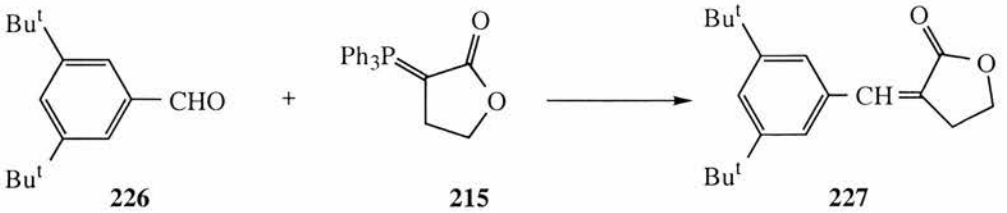


The lactone ylide **222** has also been used for the synthesis of the phenyl analogues of the natural products freelingyne **224** and dihydrofreelingyne **225**.[75] In both cases the sterochemistry of the products was defined.



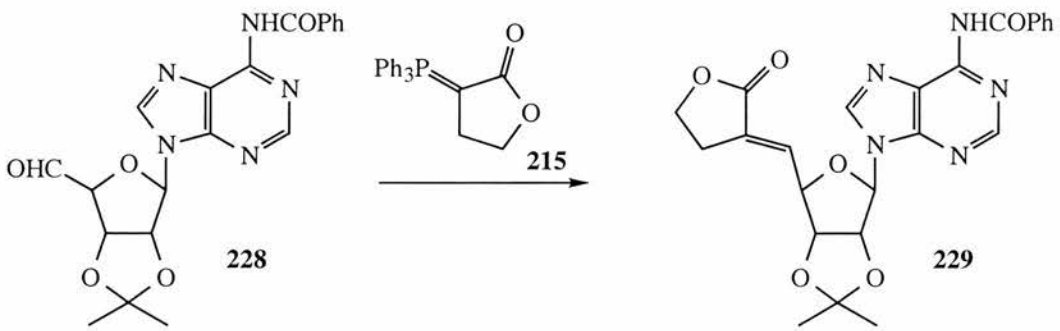


The pharmaceutically active 3,5-di-*t*-butylstyrene derivatives **227**[76] were prepared from 3,5-di-*t*-butylbenzaldehyde **226** and the ylide **215**.



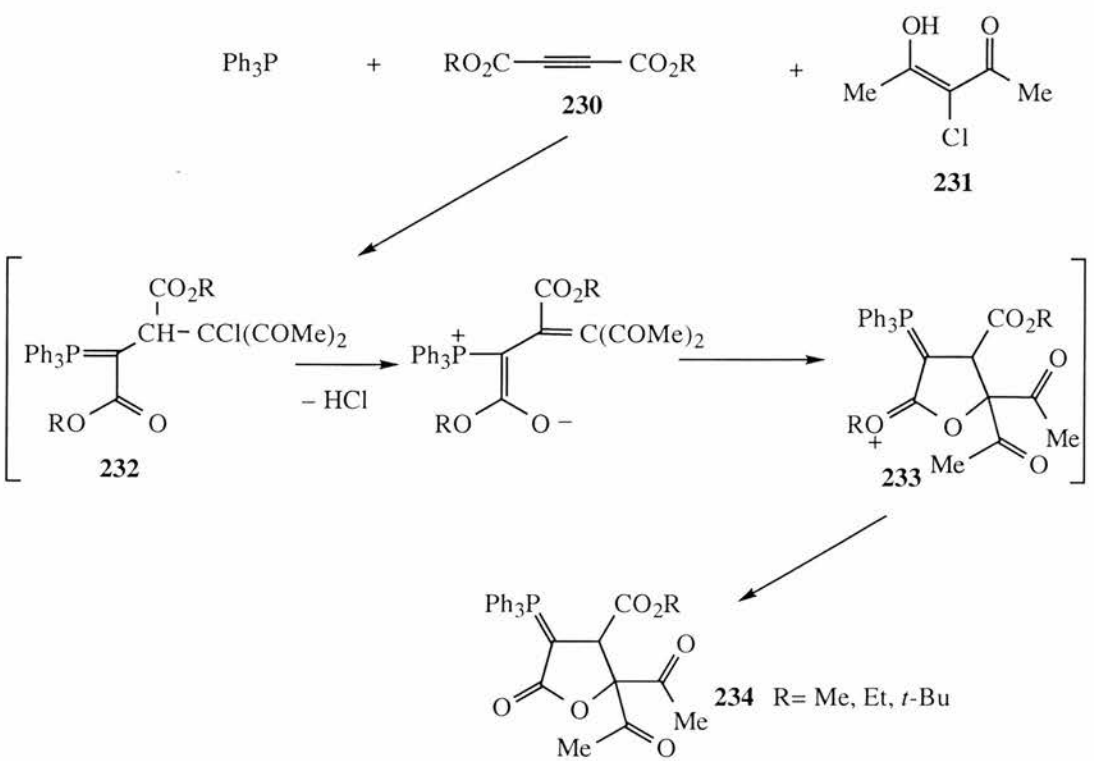
226 **215** **227**

Precursors of the nucleoside antibiotic sinefungin were prepared by chain extension of the blocked adenosine 5'-aldehyde **228**.[77] Condensation of the ylide **215** with anhydrous **228** gave a nucleoside lactone **229**, which was assigned the *E* configuration, in 68% yield.



228 **215** **229**

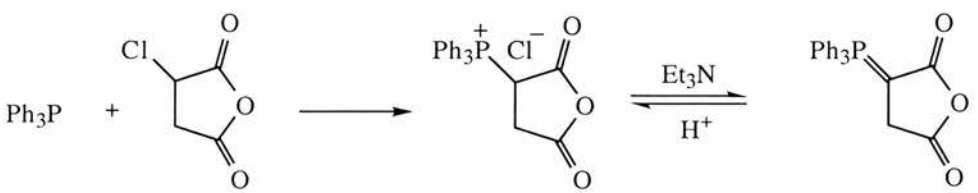
A one pot synthesis of highly functionalised 3-(triphenylphosphoranylidene) butyrolactones **234** was reported in 1997.[78] Reaction between triphenylphosphine, dialkylacetylenedicarboxylates **230** and 3-chloropentane-2,4-dione **231** gave the 3-



230 **231** **232** **233** **234** R= Me, Et, *t*-Bu

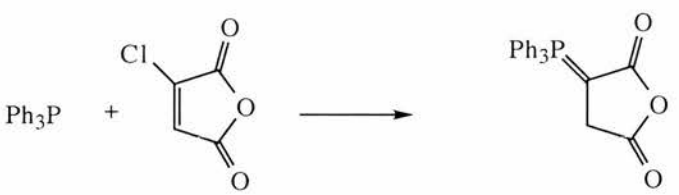
(triphenylphosphoranylidene)butyrolactones **234** in 46-85% yield. All the compounds were stable crystalline solids and were fully characterised. The ylide **234** results from the initial addition of the phosphine to the acetylenic ester followed by attack by the enolate anion to form the intermediate **232**, which is then converted into the butyrolactone **233** by elimination of HCl and ring closure.

The cyclic ylide **212** mentioned earlier can also be prepared[79] by direct reaction between triphenylphosphine, chlorosuccinic anhydride **235** and triethylamine. With aldehydes, it gave zero or low yields of the expected alkenes. Water or alcohols caused the anhydride ring to open to form triphenylphosphine oxide and the corresponding succinic acid derivatives.



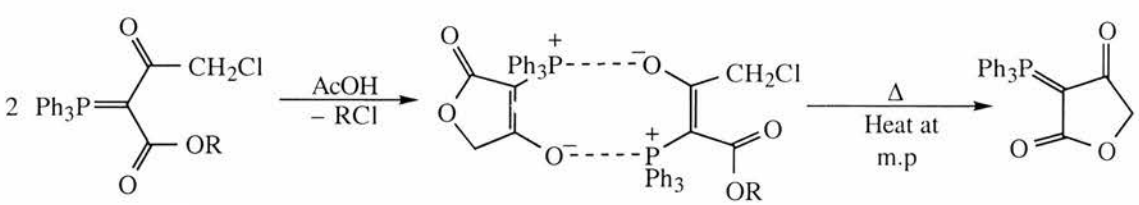
235 **212**

It was also found that chloromaleic anhydride **236** reacts with triphenylphosphine to give **212**, and its ^{31}P NMR spectrum showed a peak at δ_P +13.[80]



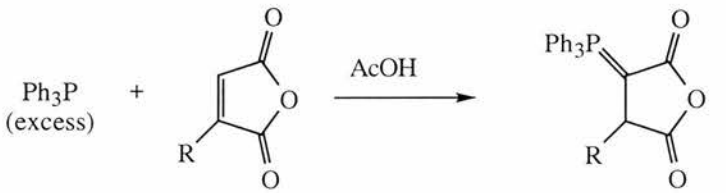
236 **212**

[(Alkoxycarbonyl)(chloroacetyl)methylene]phosphoranes **237** dealkylate in the presence of acids and give the isomer of **212**, the cyclic ylide **239**.[81] The reaction first gives a stable crystalline complex **238** which on heating forms the ylide **239**.



237 **238** **239**

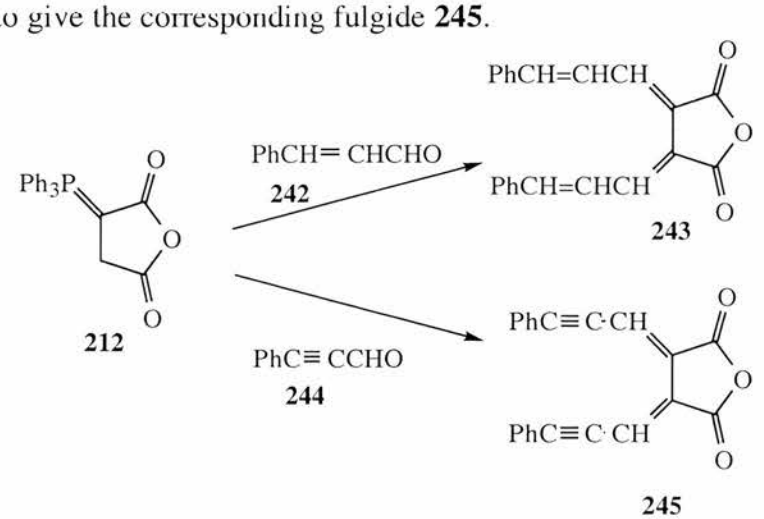
Hedaya and Theodoropulos[82] prepared the triphenylphosphoranylidenesuccinic anhydride **212** by combining an excess of triphenylphosphine and maleic anhydride **210** in glacial acetic acid. Previous workers used other solvents like benzene or acetone but acetic acid led to more easily isolated cleaner products. The ylide **212** was precipitated by addition of an excess of ether to give the product in 46% yield. The citraconic anhydride-triphenylphosphine adduct **241** was also prepared for the first time following the method above to give a stable crystalline solid in 59% yield with a mp of 179-181°C starting from citraconic anhydride **240**.



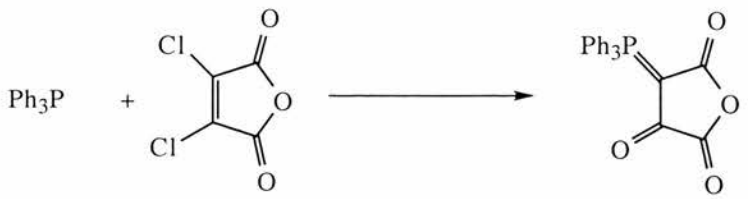
210 R= H
240 R= Me

212 R= H
241 R= Me

The reaction of the ylide **212** with most aldehydes generally gave intractable mixtures and attempts to react the methyl substituted ylide **241** with benzaldehyde were unsuccessful. It was found that the ylide **212** reacts cleanly with cinnamaldehyde **242** to give a red crystalline product which on the basis of the elemental analysis and IR spectrum has the fulgide structure **243**. This was confirmed by synthesis of **243** by the Stobbe condensation of cinnamaldehyde with sodium succinate[83] in very low yields. In the same way phenylpropargyl aldehyde **244** reacts with **212** to give the corresponding fulgide **245**.



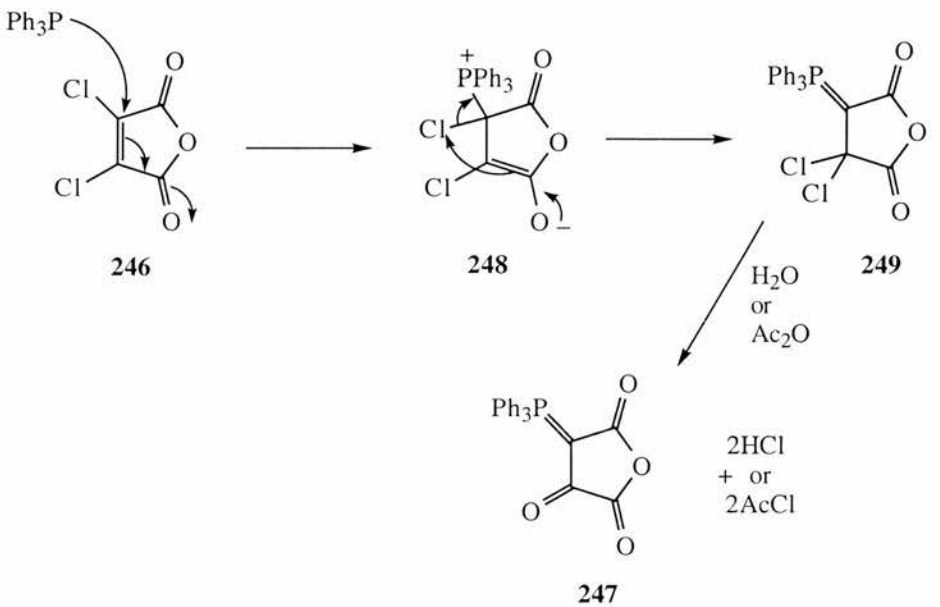
The trioxo ylide **247** may be prepared from dichloromaleic anhydride **246** and triphenylphosphine.[84] The product was obtained in 54% yield when the reaction was carried out in wet THF and 34% in acetic anhydride.



246 **247**

This ylide has a mp of 229–231°C and the NMR data reported included a ^{31}P NMR signal at δ_P +11.4 and a ^{13}C NMR signal for the ylide carbon at δ_C 66.1 with a large P-C coupling of 120 Hz. The structure of ylide **247** was also determined by X-ray crystallography.[85]

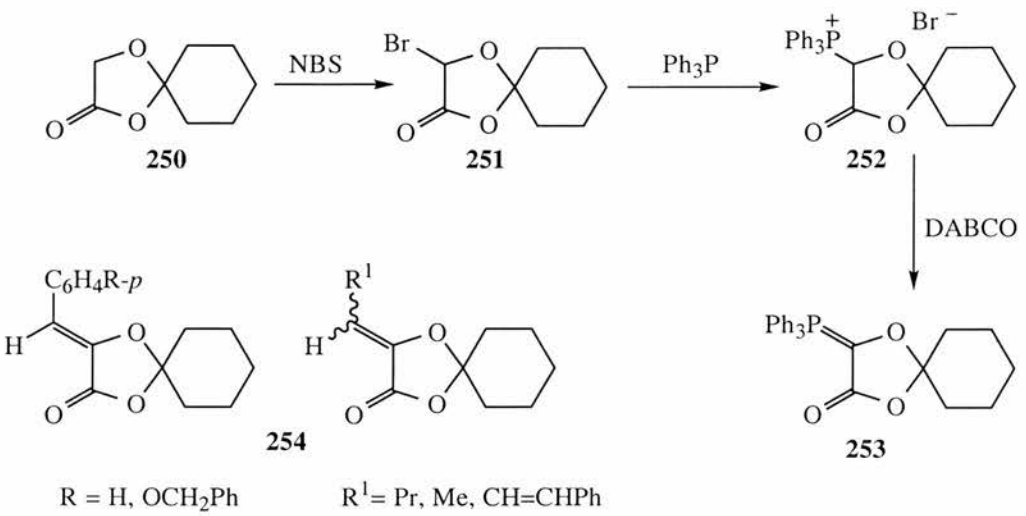
The mechanism involves the initial step of a Michael-type addition to produce the zwitterionic intermediate **248** which then undergoes a chloronium rearrangement to form the ylide **249**. Finally hydrolysis leads to the cyclic ylide **247**.



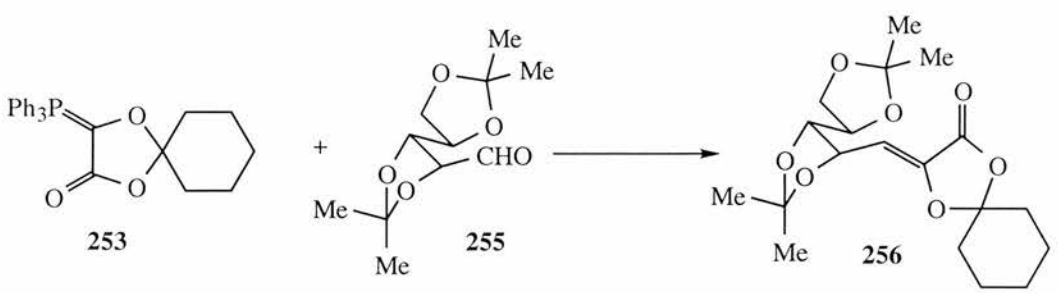
246 **248** **249** **247**

4 g Five-membered cyclic ylides containing two oxygens

2,2-Pentamethylene-1,3-dioxolan-4-one **250** has been elaborated to provide 5-alkylidene derivatives using a Wittig approach involving the ylide **253**.[86] Bromination of **250** using *N*-bromosuccinimide in carbon tetrachloride gave a high yield of the bromide **251**. The bromide **251** was treated immediately with triphenylphosphine in toluene to give the phosphonium salt **252**. The ylide **253** was found to be very unstable and was generated from the salt **252** under an inert atmosphere using 1,4-diazabicyclo[2.2.2]octane (DABCO) in toluene immediately before treatment with a series of aldehydes which gave the 5-alkylidene-2,2-pentamethylene-1,3-dioxolan-4-ones **254**.

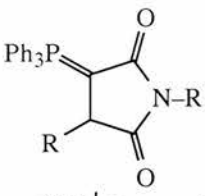


This strategy was also used to provide a versatile and general approach to the synthesis of sugar acids of biosynthetic importance starting from readily available protected aldehydo sugars.[87] For example, the ylide **253** reacts with aldehyde **255** derived from D-arabinose affording the 5-alkylidene-1,3-dioxolan-4-one **256** as a mixture of *E* and *Z* isomers.

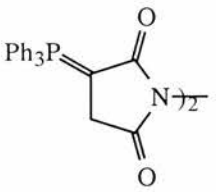


4 h Five-membered cyclic ylides containing nitrogen

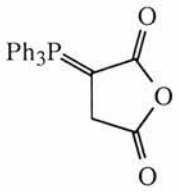
Hedaya and Theodoropulos[82] found that triphenylphosphine reacts with maleimides to give the ylides **257** with structures analogous to the maleic anhydride adduct **212**. The reactions were carried out in acetic acid and the yields were moderate to good.



257	R	R^1
a	H	H
b	H	Ph
c	H	NC_4H_8O
d	Me	Ph

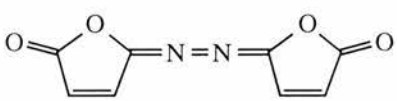


258

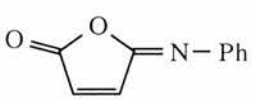


212

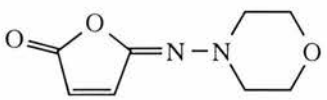
Interestingly, when the isomaleimides **259** and **260** were combined with triphenylphosphine, the same adducts **258** and **257b** were isolated in high yields. It is not known whether prior rearrangement of the isoimide occurs, induced by triphenylphosphine or if an initially formed triphenylphosphine-isoimide adduct rearranges to the imide isomer under the reaction conditions. Also, the triphenylphosphine adduct **257c** was obtained from the readily prepared isoimide **261**.



259

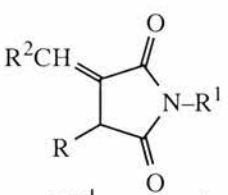


260

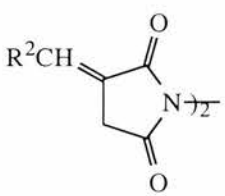


261

In contrast to the triphenylphosphoranylidenesuccinic anhydride **212**, the reaction of a wide variety of aldehydes with the triphenylphosphoranylidenesuccinimide derivatives **257** and **258** gave the crystalline Wittig products **262** and **263** in high yields.

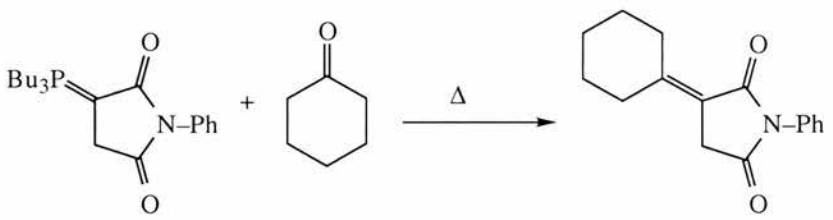


262	R	R^1
a	H	H
b	H	Ph
c	H	NC_4H_8O
d	Me	Ph



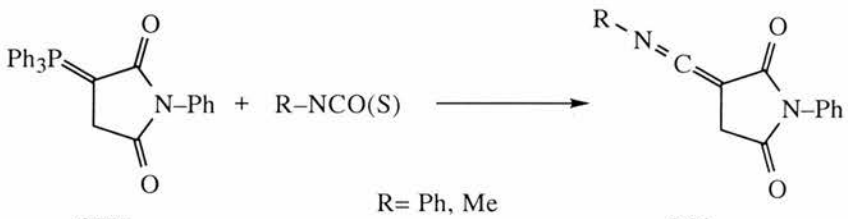
263

None of the triphenylphosphonium ylides **257** reacted with ketones but the tri-n-butylphosphonium analogue **264** did react with cyclohexanone giving the cyclohexylidene derivative **265** in 12% yield.



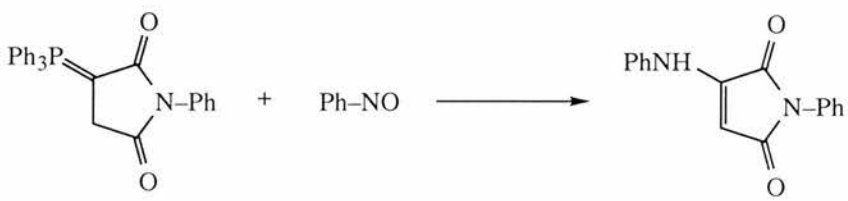
264 **265**

When the ylide **257b** was treated with either phenyl or methyl isocyanate or phenyl isothiocyanate, the corresponding ketenimines **266** were obtained as crystalline solids in high yields.



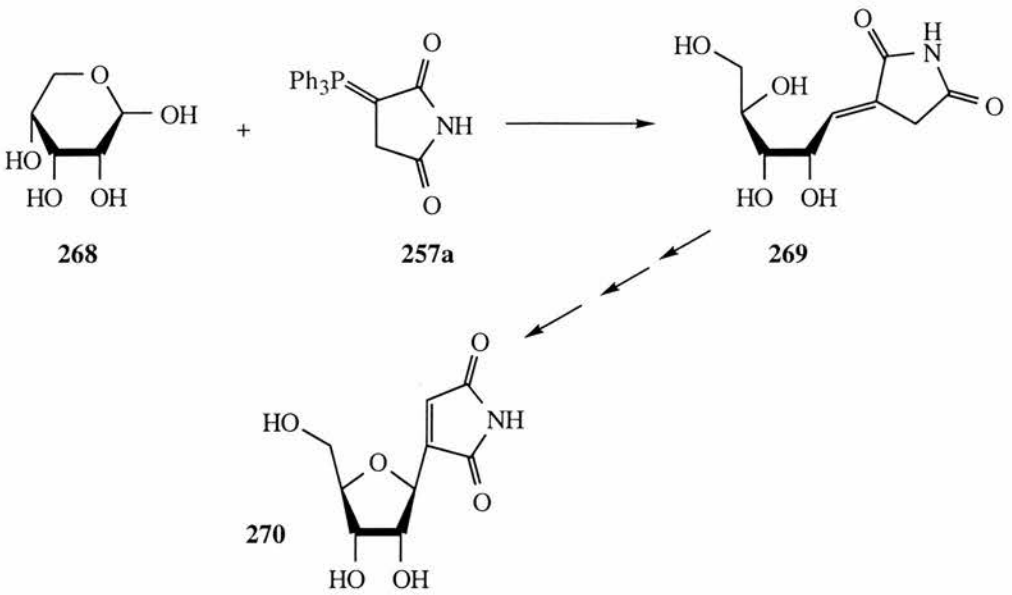
257b **266**

It was also found that **257b** reacts with nitrosobenzene to give the maleimide **267**.

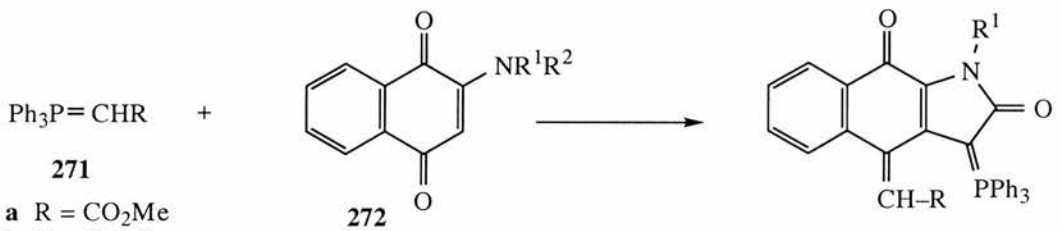


257b **267**

Barrett and co-workers[88] showed the use of triphenylphosphoranylidenesuccinimide derivatives **257** in the synthesis of the natural product showdomycin **270**. Reaction of D-ribose **268** with **257a** in THF under reflux produced **269** in 75% yield. Subsequent cyclization of **269** using phenylselenenyl chloride followed by hydrogen peroxide gave showdomycin **270** in 13% yield.



In 1997 it was reported[89] that the reaction of the ester-stabilised ylides **271** with substituted 2-amino-1,4-naphthoquinones **272** gave the new ylides **273**.

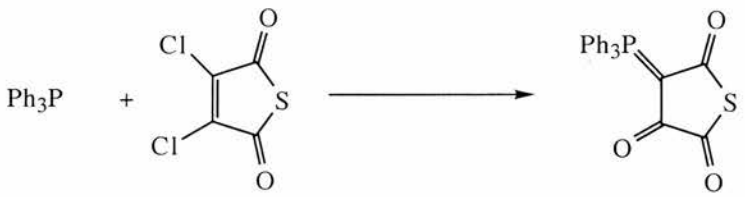


	R^1	R^2
a	H	Me
b	H	Et
c	H	Ph

	R	R^1
a	CO_2Me	Me
b	CO_2Et	Me
c	CO_2Me	Et
d	CO_2Et	Et
e	CO_2Me	Ph
f	CO_2Et	Ph

4 i Five-membered cyclic ylides containing sulfur

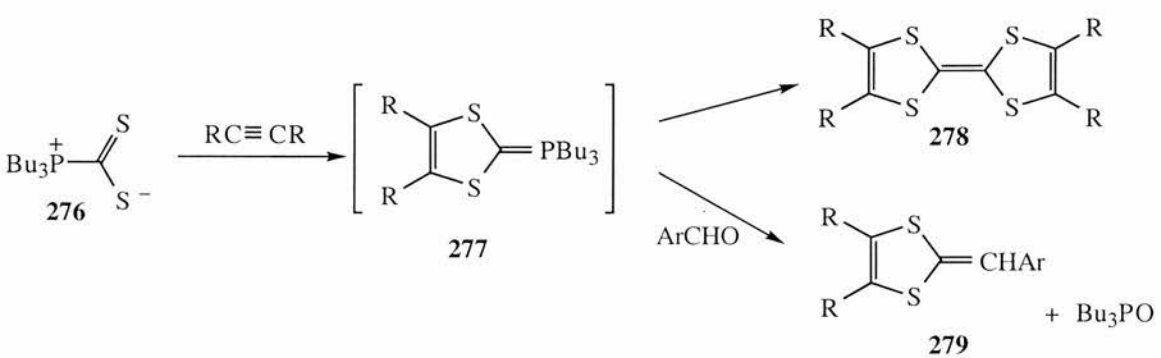
There is only one five-membered cyclic ylide containing a single sulfur atom known in the literature. Skramstad and co-workers[85] described the synthesis of the cyclic ylide **275** using the same method as for the oxygen derivative (see section 4 f). Triphenylphosphine was added to a solution of dichlorothiomaleic anhydride **274** and the product **275** was obtained in 71% yield. The melting point was 190–193 °C and the ^{13}C NMR spectrum showed a signal for the ylide carbon at δ_C 79.2 with a large P–C coupling of 110 Hz.



274 **275**

Many five-membered cyclic ylides containing two sulfur atoms have been reported but none have been isolated. In all cases they are formed as intermediates and are used immediately in the Wittig or other reactions.

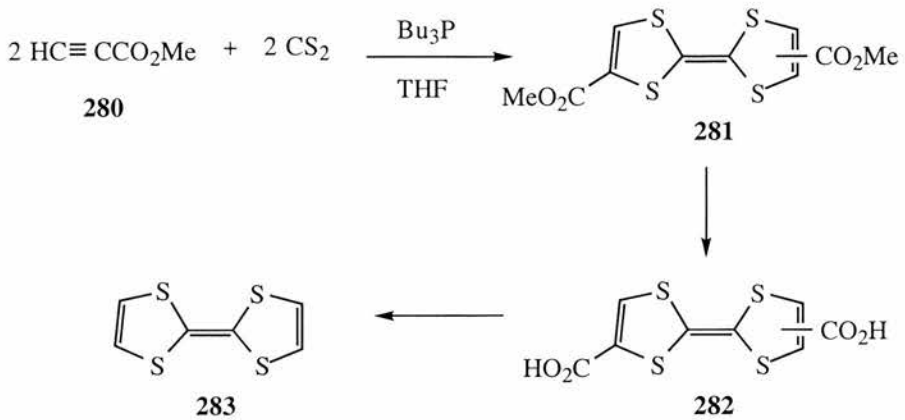
Hartzler reported a general reaction of the adduct of carbon disulfide and tributylphosphine **276** with alkynes and aromatic aldehydes.[90] The adduct **276** reacted with alkynes having at least one electron withdrawing substituent to give the tetrathiafulvalenes **278** in poor yields. When aromatic aldehydes were added, excellent yields of 2-benzylidene-1,3-dithioles **279** were obtained. The reaction involves generation of the ylide **277** which reacts with the aromatic aldehyde in a Wittig reaction to give the product **279**.



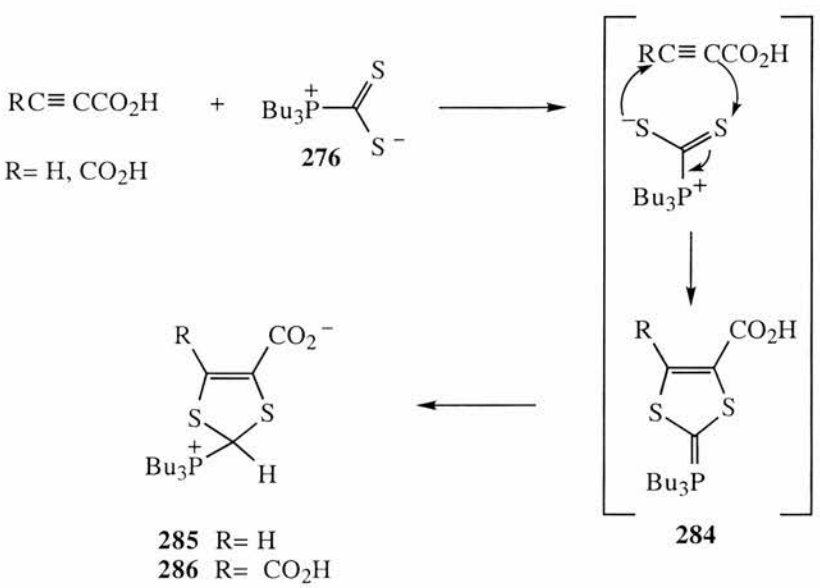
276 **277** **278** **279**

Using this method an improved synthesis of TTF was reported[91] starting from methyl propiolate **280**. The reaction between **280**, tributylphosphine and carbon disulfide gave

4,4'(5')-bis(methoxycarbonyl)-2,2'-bi-1,3-dithiole **281** in low yield. Alkaline hydrolysis of the diester **281** and decarboxylation of the resulting diacid **282** afforded TTF **283** in 13% overall yield.

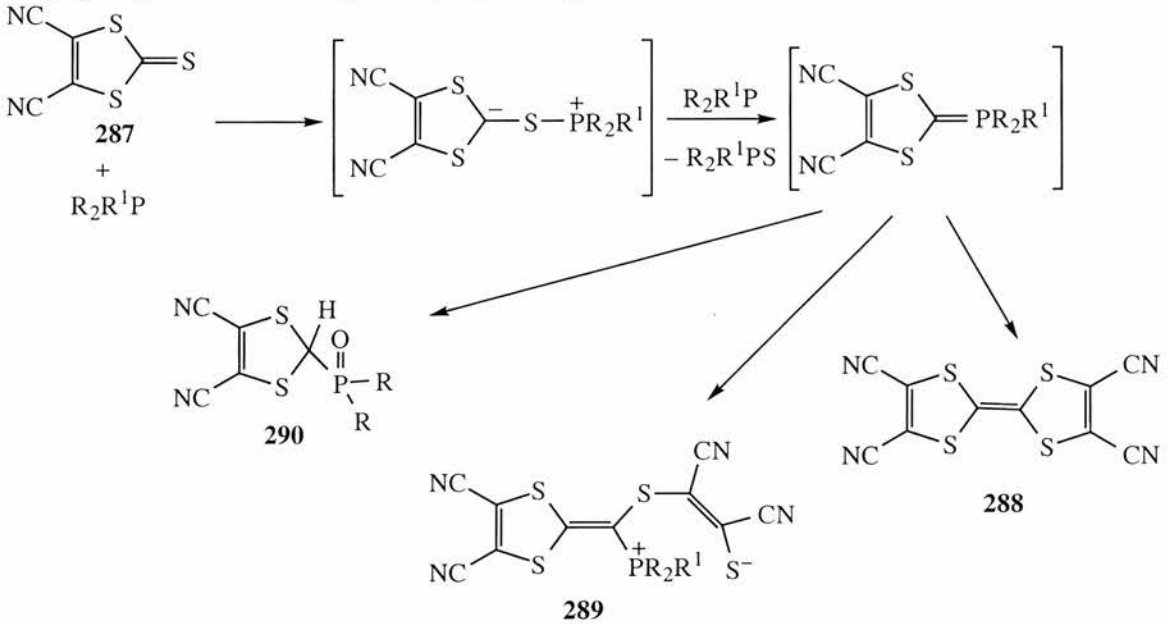


Later, 2-trialkylphosphonio-1,3-dithiole-4-carboxylates were synthesised.[92] Propiolic acid and acetylenedicarboxylic acid were reacted with the adduct **276** to give the adducts **285** and **286** in 53% and 87% respectively. The formation proceeds via a one-step addition forming the ylides **284** which undergo an intramolecular proton transfer to give the stable products **285** and **286**.

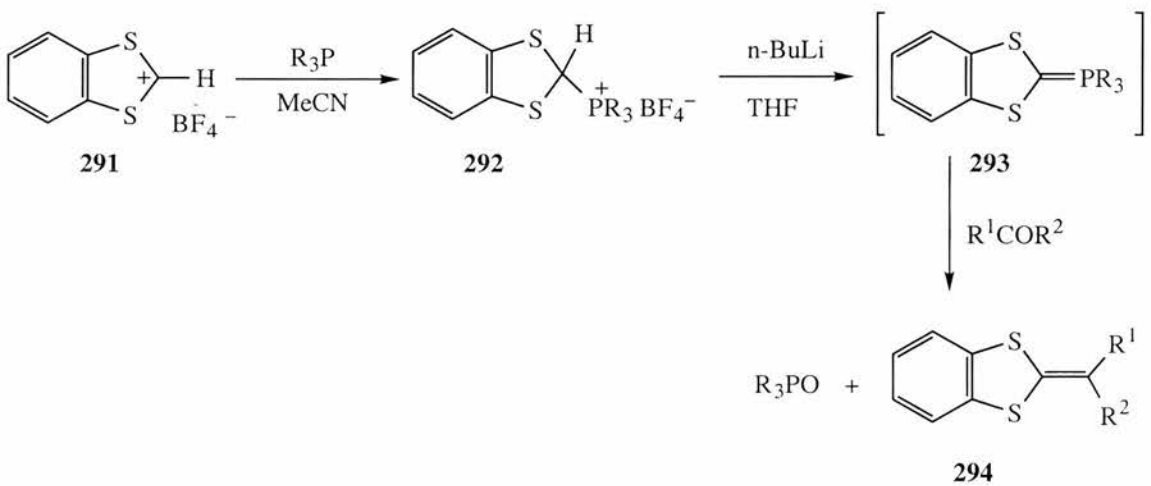


Miles and co-workers[93] have also reported the intermediacy of the same type of phosphorane during desulfurization of 4,5-dicyano-1,3-dithiole-2-thione **287** with tertiary

phosphines and phosphites. Either tetracyanotetrathiafulvalene **288**, a betaine **289**, or a dialkyl phosphonate **290** may form, depending on the choice of reactant and conditions.

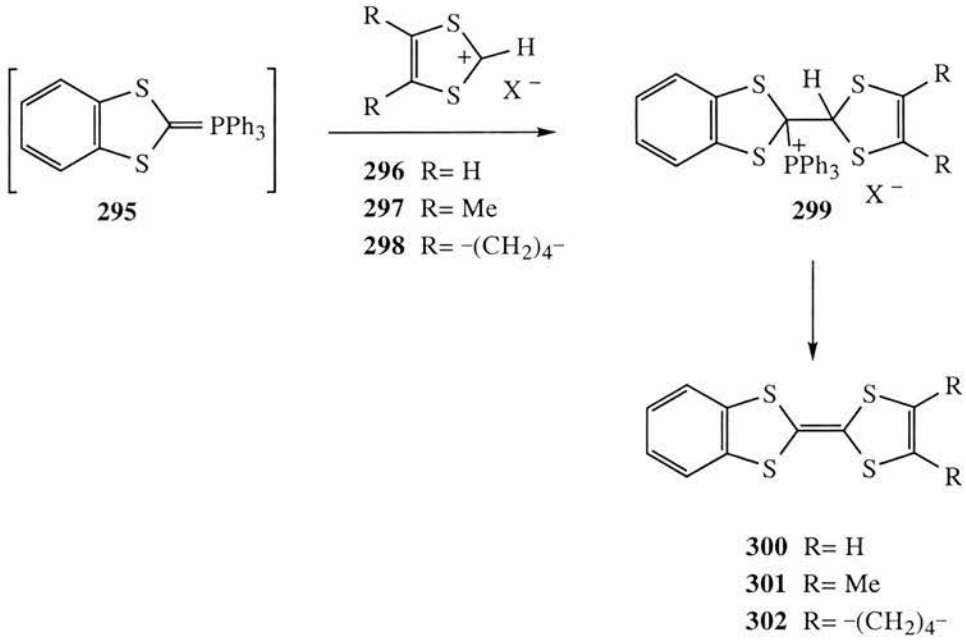


Akiba and co-workers[94] reported the synthesis of phosphonium salts from 1,3-benzodithiolium tetrafluoroborate **291** and their general use in the Wittig reaction to afford 1,4-benzodithiafulvenes **294**. The salt **291** reacts with phosphines in acetonitrile to give the corresponding phosphonium salts **292** in high yield. These were deprotonated with n-butyllithium in THF at –78 °C and the resulting ylides **293** reacted with carbonyl compounds to give 1,4-benzodithiafulvenes **294**.



The method above has been extended to synthesise a number of unsymmetrical tertrathiafulvalenes.[95] The coupling of the ylide **295** with 1,3-dithiolium salts **296**, **297** and

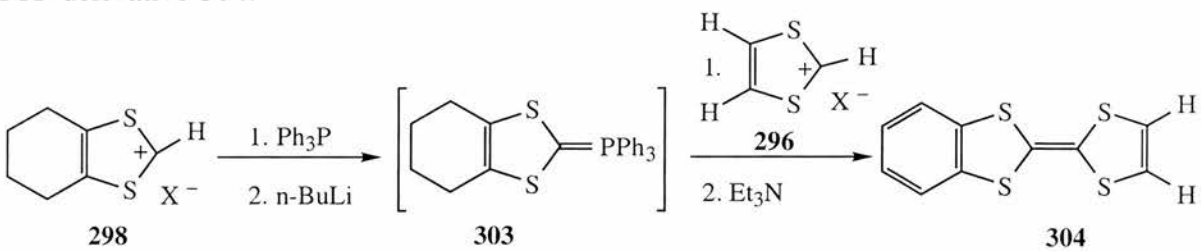
298 formed the intermediates **299**. Addition of triethylamine caused the elimination of triphenylphosphine and the monobenzotetrathiafulvalenes **300**, **301** and **303** were formed.



295 299

300 R= H
301 R= Me
302 R= $-(CH_2)_4-$

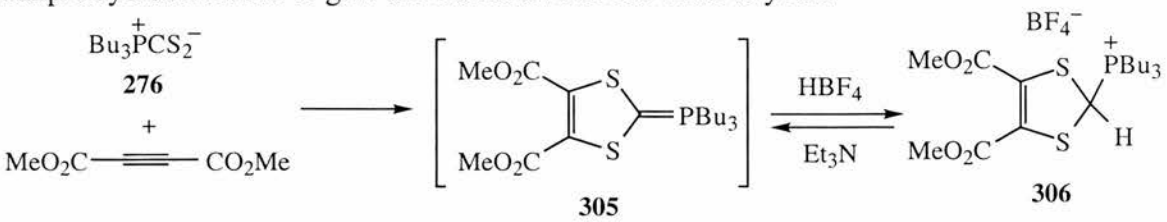
This procedure is not limited to the synthesis of monobenzotetrathiafulvalene derivatives. The addition of triphenylphosphine to tetramethylene-1,3-dithiolium fluorophosphate **298** followed by treatment with butyllithium has been found form the intermediate ylide **303**. This reacts with 1,3-dithiolium fluoroborate **296** to give the mixed TTF derivative **304**.

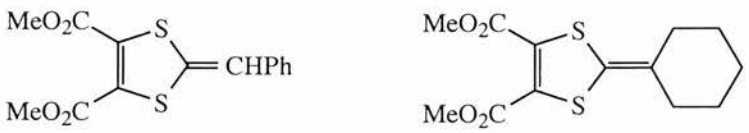


298 **303** **304**

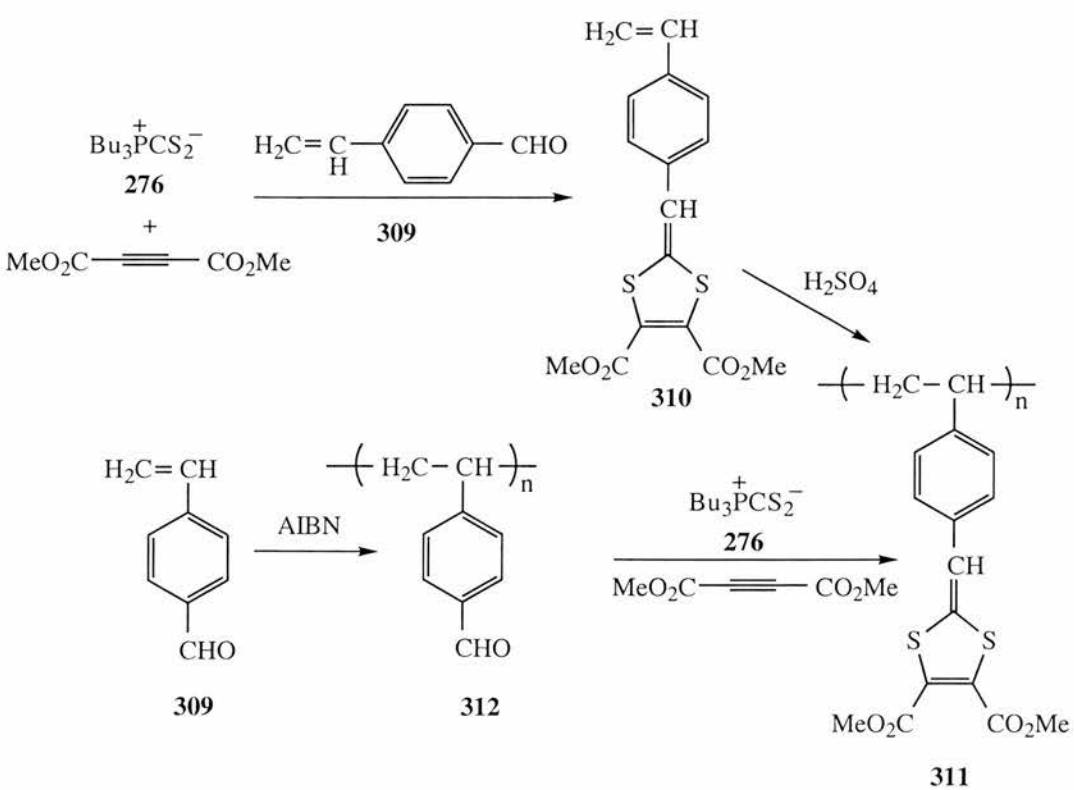
A modification of the Hartzler reaction has been reported[96] which provides a simple and convenient synthesis of (4,5-dimethoxycarbonyl-1,3-dithiol-2-yl)tributylphosphoniumtetra fluoroborate **306**. The phosphonium salt **306** was prepared by the reaction of dimethyl acetylenedicarboxylate and fluoroboric acid with the adduct **276** and serves as a stable precursor of the corresponding unstable ylide **305**. Under aprotic conditions, the salt **306** can be used for the *in situ* generation of the ylide **305**. The reaction of the salt **306** with butyllithium at –78 °C gave the ylide **305** which is stable at this temperature. The solution was

found to react with benzaldehyde to give **307** in 89% yield and with a number of ketones, for example cyclohexanone to give the dithiafulvene **308** in 60% yield.

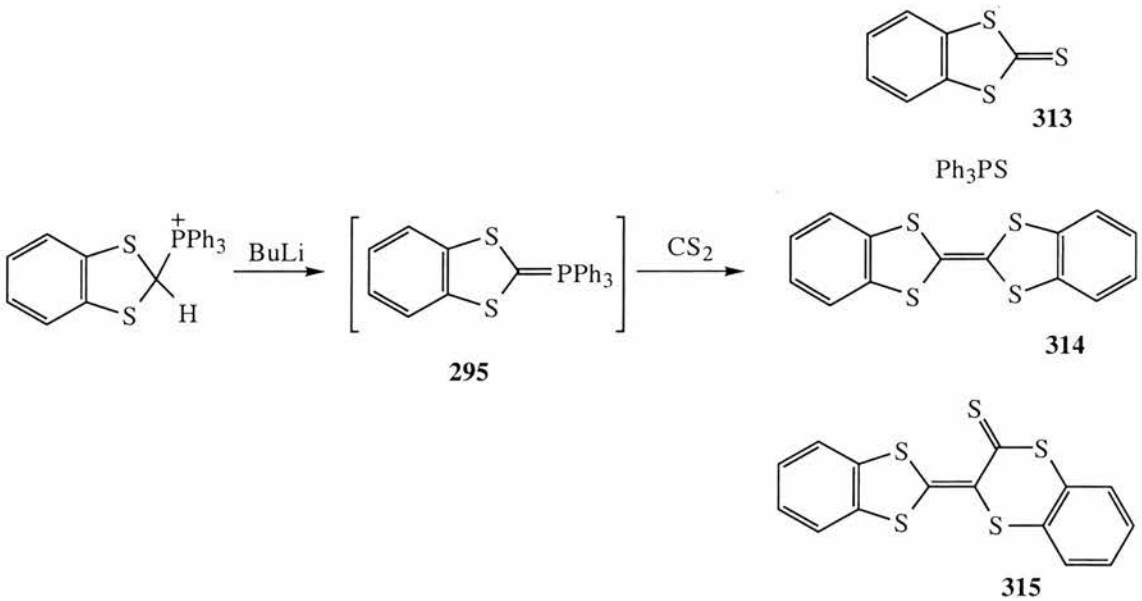




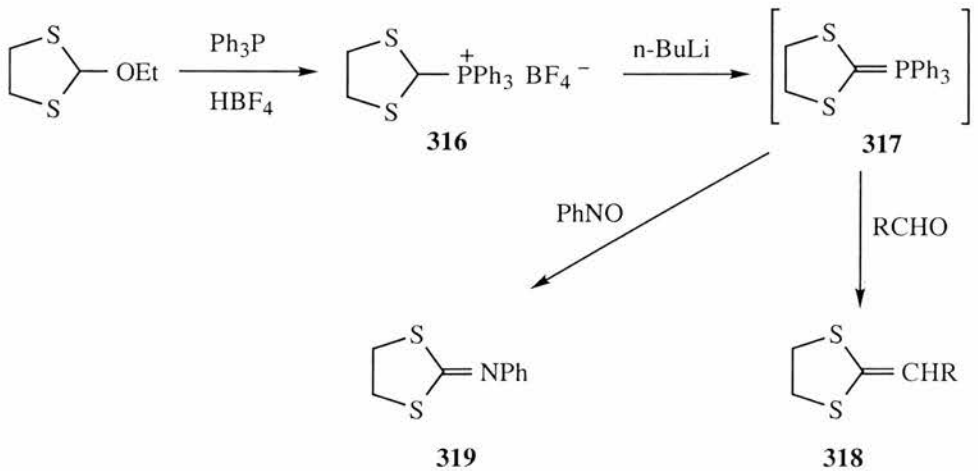
The monomer 2-(*p*-vinylbenzylidene)-1,3-dithiole **310** was prepared by Mulvaney and Chang[97] *via* the ylide **305.** On polymerisation using sulfuric acid the polymer **311** was obtained in 85% yield. The polymer **311** could also be prepared by an alternative route starting from *p*-vinylbenzaldehyde **309** which was polymerised using radical initiation. The polymer **312** was then treated with DMAD and **276** to give the same product **311**.



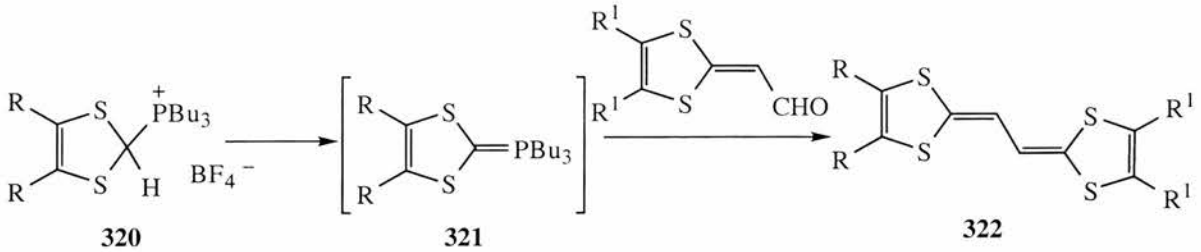
When 1,3-benzodithiol-2-ylidenetriphenylphosphorane **295** was reacted with carbon disulfide, 1,3-benzodithiole-2-thione **313**, dibenzotetrathiafulvalene **314** and an unidentified crystalline red compound were obtained in addition to triphenylphosphine sulfide. A possible solution for the structure for the unidentified crystalline red compound has been proposed by Nakayama *et al* as **315**.[98]



A novel route to ketene S,S-acetals of the general structure **318** was found.[99] The procedure involves the initial formation of the ylide **317** by the action of base on 1,3-dithiolan-2-yltriphenylphosphonium fluoroborate **316** then subsequent Wittig reaction with aliphatic and aromatic aldehydes to form the product **318**. The ylide **317** can also react with nitroso compounds and upon addition of nitrosobenzene for example, 2-phenylimino-1,3-dithiolane **319** was formed in 94% yield.



Extended analogues of TTF were made by Sugimoto and co-workers[100] with the general structure **322**. Here again the ylides used, **321**, were generated from the corresponding phosphonium salt **320** *in situ*.

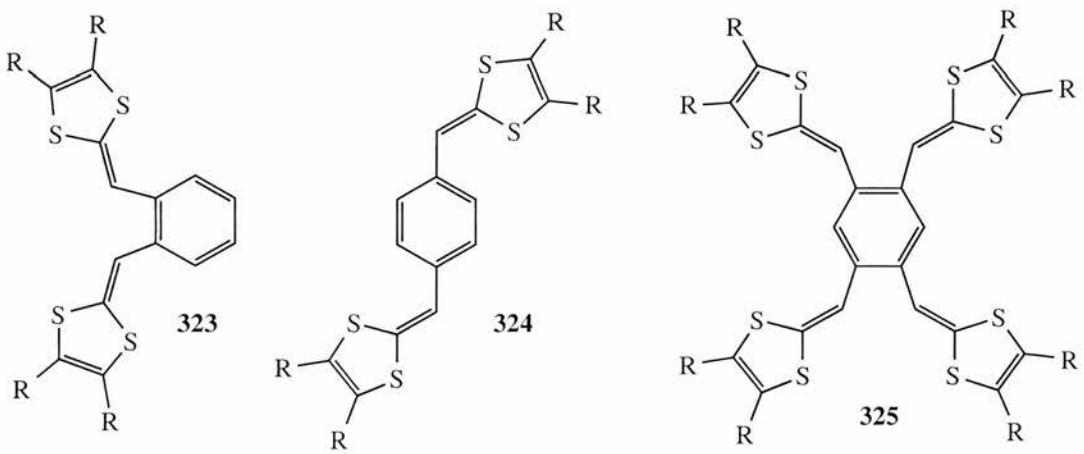


320 **321** **322**

R = Me, MeO_2C, Ph

R^1 = CO_2Me, Me, Ph

Other extended analogues of TTF which have been similarly prepared using ylides **321** are the 1,2-bis-, 1,4-bis-, and 1,2,4,5-tetrakis(1,4-dithiafulven-6-yl)benzenes **323**, **324** and **325**.[101]

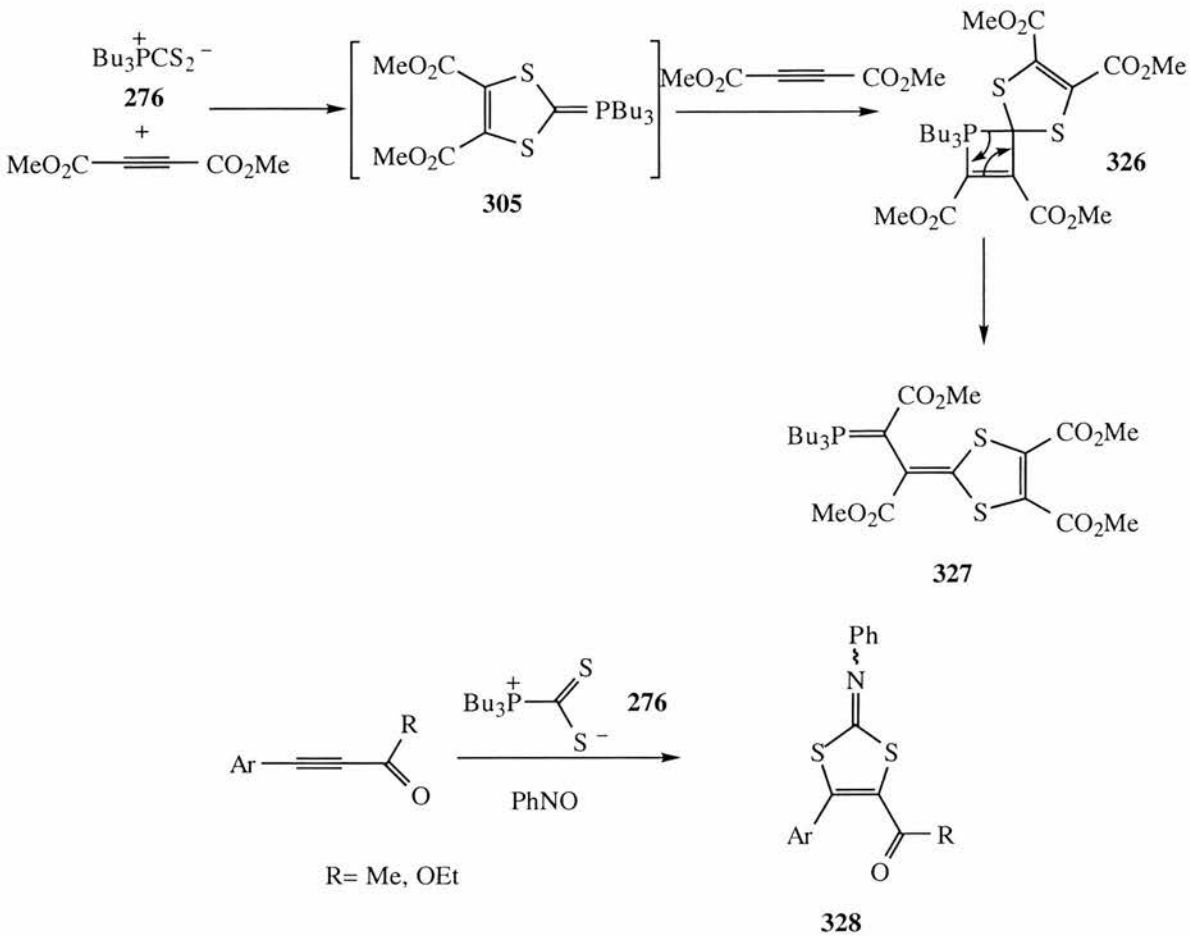


323 **324** **325**

Previous work in this laboratory led to discovery of the formation of a novel 1:2 adduct between Bu_3PCS_2 and electron deficient alkynes.[102] The initial reaction of the adduct **276** and DMAD gave the ylide **305** which then undergoes a [2+2] cycloaddition with a second DMAD molecule to give phosphacyclobutene **326** followed by electrocyclic ring-opening to give **327**.

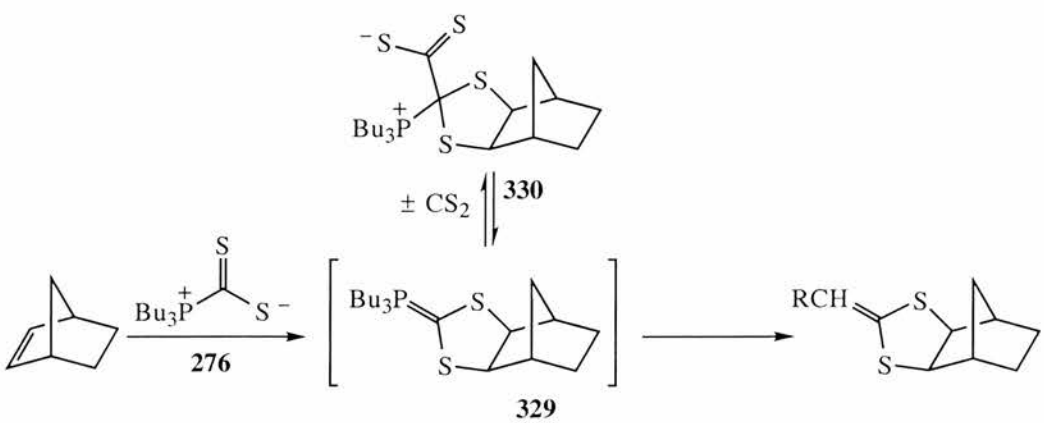
Cycloaddition of activated alkynes with the adduct **276** followed by a Wittig reaction of the resulting phosphorane with carbonyl compounds or nitrosobenzene affords novel 2-

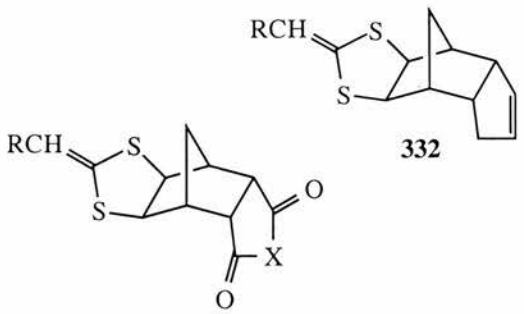
alkylidene- or 2-(phenylimino)-1,3-dithioles **328** in moderate to very good yields.[103] The



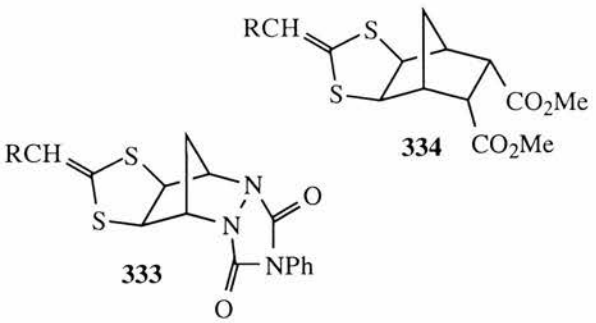
authors applied this method to pterin-substituted species which are potential intermediates in the synthesis of the molybdenum cofactor, essential for the activity of several redox enzymes.

Reaction of the adduct **276** with norbornene[104] gave the novel zwitterionic structure **330**. In solution this dissociates to the ylide **329** which undergoes a Wittig reaction with aldehydes. Using this method the strained double bonds in a variety of bicyclo[2.2.1]alkenes were converted into 2-benzylidene-1,3-dithioles and some examples **331**-**334** are shown.



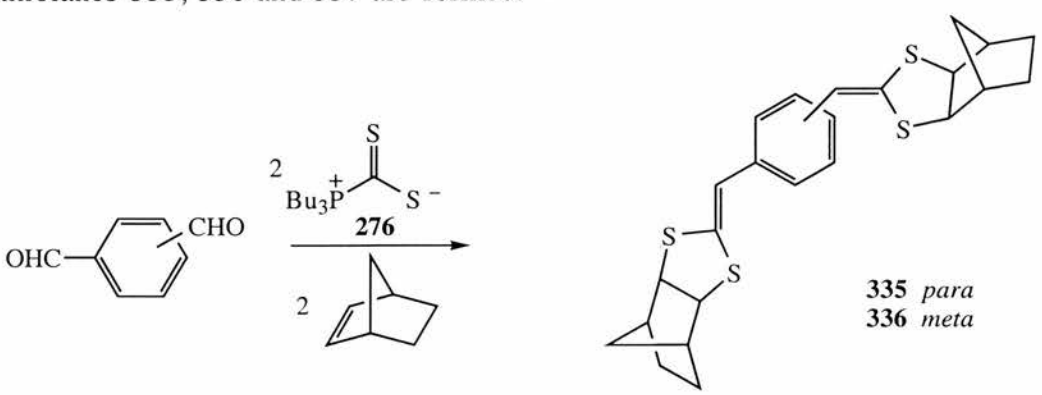


331 X= O, NPh, NMe

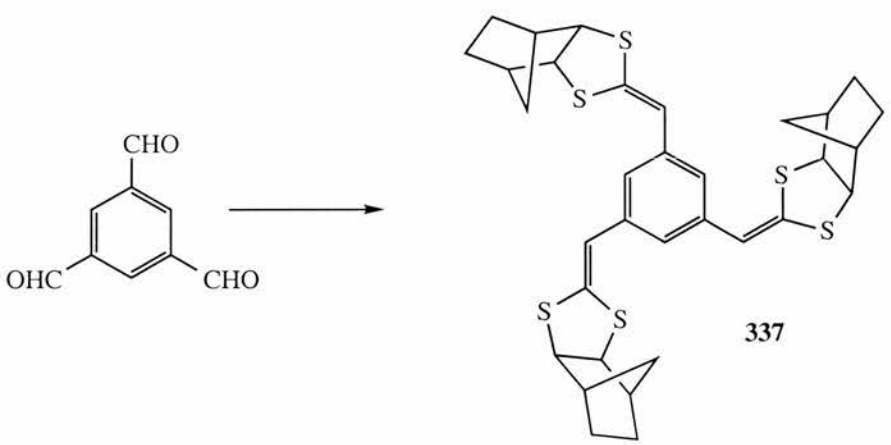


332 **333** **334**

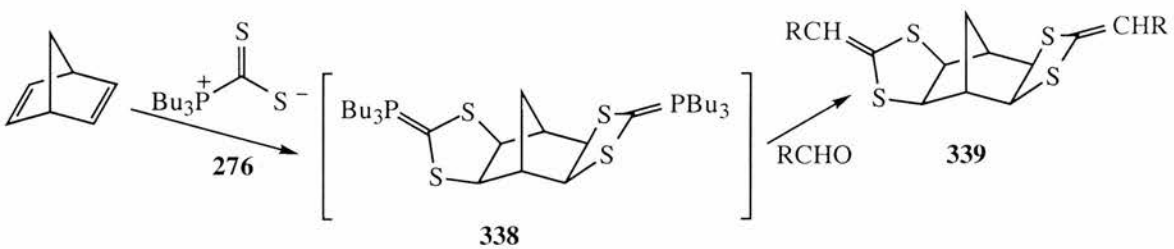
When the norbornene-derived ylide **329** reacts with aromatic di- and trialdehydes the bis- and tris-dithiolanes **335**, **336** and **337** are formed.[105]



335 *para*
336 *meta*



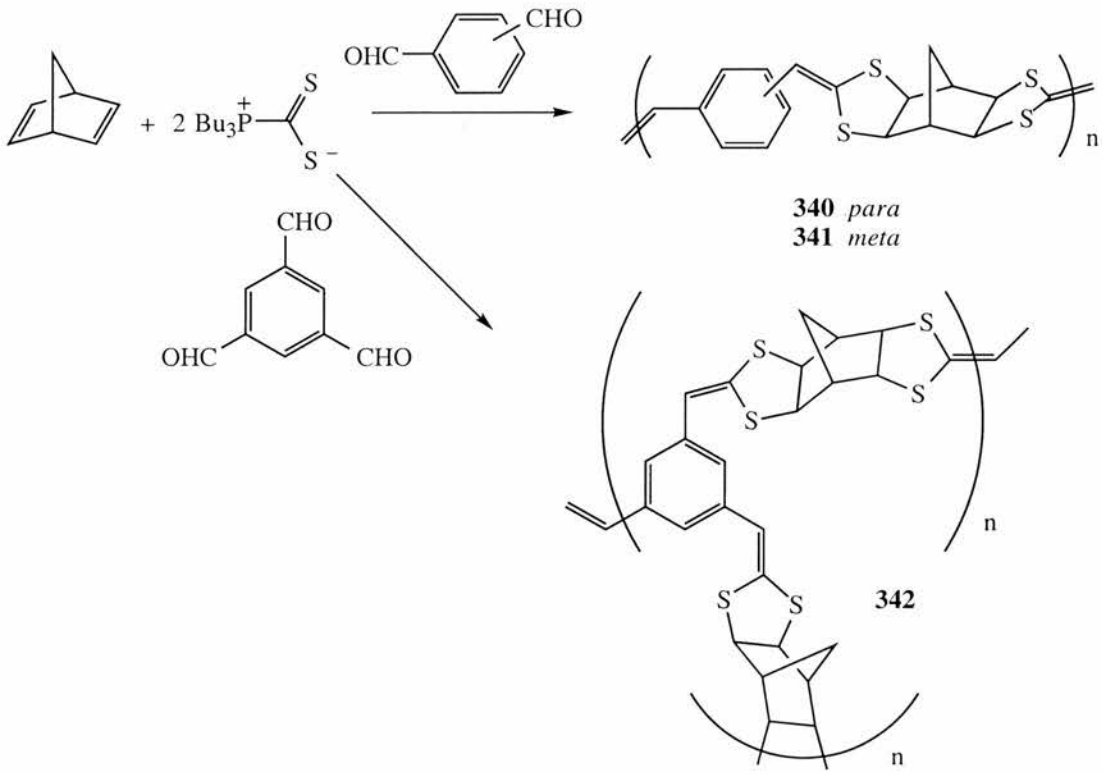
337



276 **338** **339**

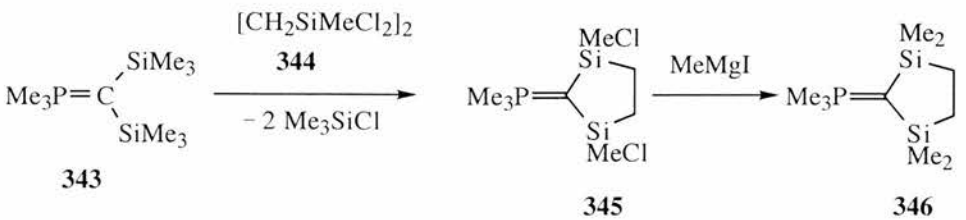
The reaction is also applicable to norbornadiene[104] forming the bis ylide **338** which gives the bisdithiolanes **339**.

As norbornadiene reacts on both double bonds, on the addition of aromatic di- and trialdehydes the novel dithiolane containing polymers **340**, **341** and **342** are obtained.[105]

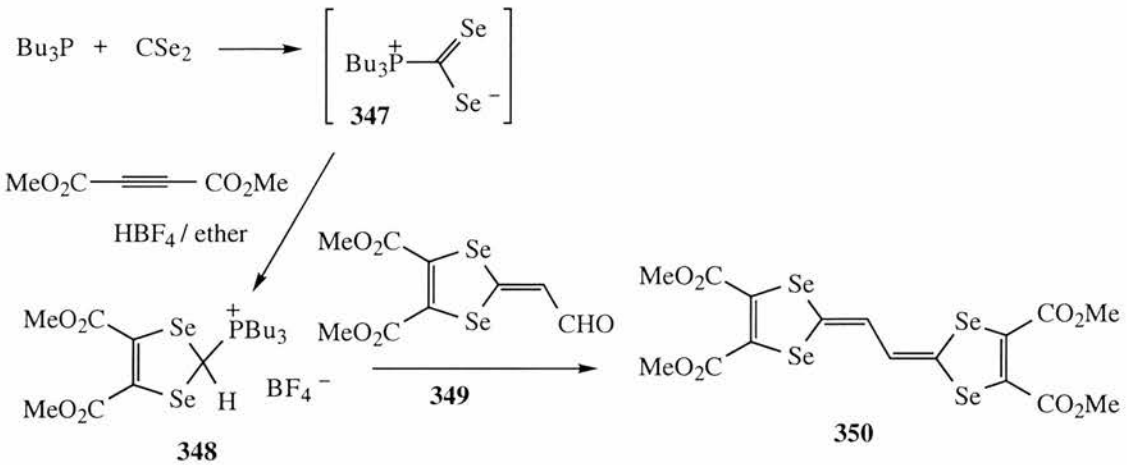


4 j Five-membered cyclic ylides containing other heteroatoms

Not many cyclic ylides containing other heteroatoms are known, Schmidbaur and coworker[38] devised a simple method for the synthesis of silyl-substituted alkylidene phosphoranes. Reaction between the bis(trimethylsilyl)ylide **343** and 1,2-bis(dichloromethylsilyl)ethane **344** gave 1,3-dichloro-1,3-dimethyl-2-trimethylphos phoranylidene-1,3-disilacyclopentane **345** which with a Grignard reagent gave 1,1,3,3-tetramethyl-2-trimethylphosphoranylidene-1,3-disilacyclopentane **346** in 61% yield.



In connection with the studies of the extended TTF analogue **322**,[100] the selenium analogue was also made using (4,5-dicarbomethoxy-1,3-diselenol-2-yl)tri-*n*-butyl phosphonium tetrafluoroborate **348** in place of the sulfur analogue **320**. The salt **348** was prepared in good yield by the reaction of the tributylphosphine-carbon diselenide adduct **347** with DMAD and by treatment with fluoroboric acid etherate.

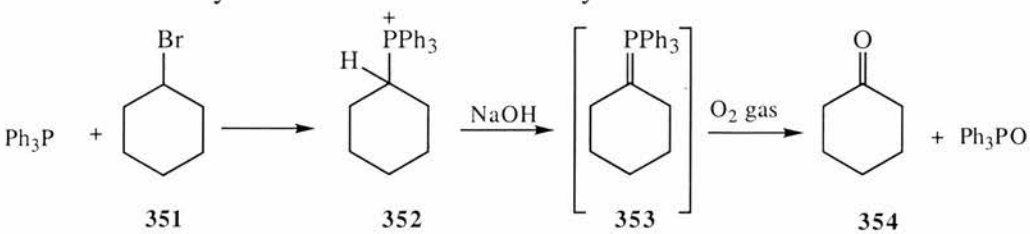


The ylide generated *in situ* from **348** and triethylamine reacted with glyoxal to give the aldehyde **349** in 84% yield. The Wittig reaction of **348** with **349** then gave the tetraester **350** in 94% yield.

5 Six-membered rings

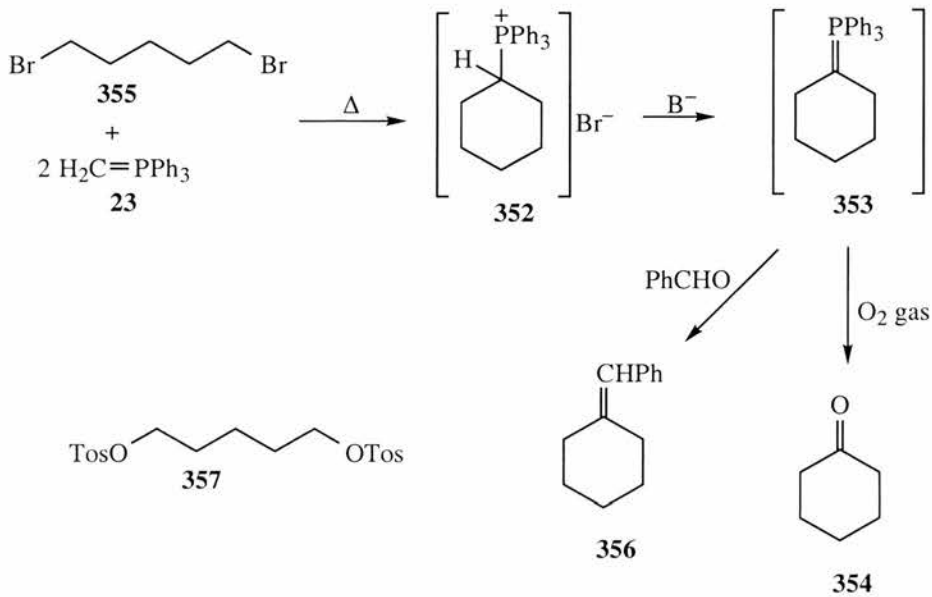
5 a Simple cyclohexylides

The synthesis and use of cyclohexylidenetriphenylphosphorane **353** was reported by Bestmann and Kratzer.[20] The ylide **353** was prepared *via* the standard method from the phosphonium salt **352** starting from triphenylphosphine and bromocyclohexane **351**. Addition of a sodium hydroxide solution forms the ylide **353** which is used *in situ* for further

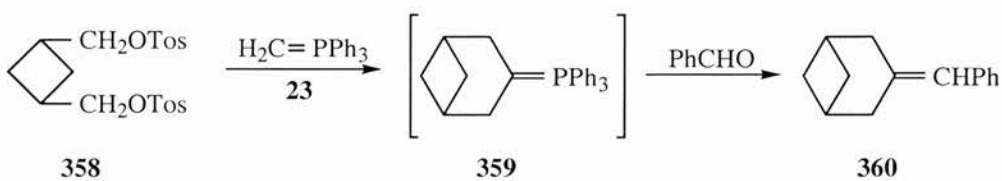


reaction. Autoxidation of this ylide **353** with oxygen gas gave triphenylphosphine oxide and cyclohexanone **354** in 65% yield.

Bestmann and Kranz[16] reported a new ring closure reaction to give ylides with four, five, six and seven membered rings (see section 3 a for mechanism). Reaction of 1,5-dibromopentane **355** with two equivalents of methylenetriphenylphosphorane **23** gave the ylide **353** Here again the ylide was used *in situ* with benzaldehyde[21] to give the Wittig product **356** in 67% and on autoxidation[20] the cyclic ketone **354** was formed. Alternatively, the Wittig product **356** was obtained in higher yield when the pentane-1,5-diol ditosylate **357** was used as the starting material.

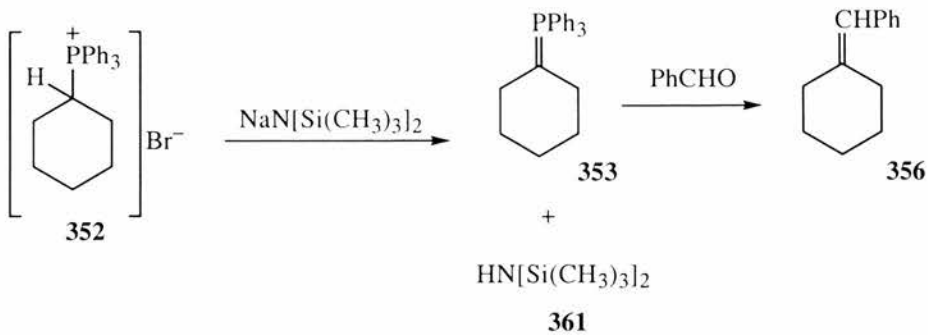


When *cis*-1,3-bis(tosyloxymethyl)cyclobutane **358** was reacted with methylenetriphenylphosphorane **23** and benzaldehyde, the 3-benzylidenebicyclo[3.1.1]heptane **360** was obtained *via* the corresponding ylide **359**.[21]

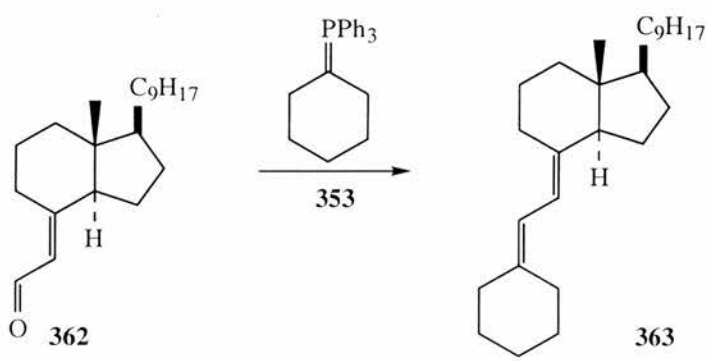


Sodium bis(trimethylsilyl)amide is a useful base for the generation of the phosphorane **353**.[106] This base reacts with the phosphonium salt **352** forming **361** and the ylide **353** which in the presence of benzaldehyde gives the Wittig product **356**. The phosphorus NMR shifts[39] for the ylide **353** and the phosphonium salt **352** were δ_P +6.4 and δ_P +26.6

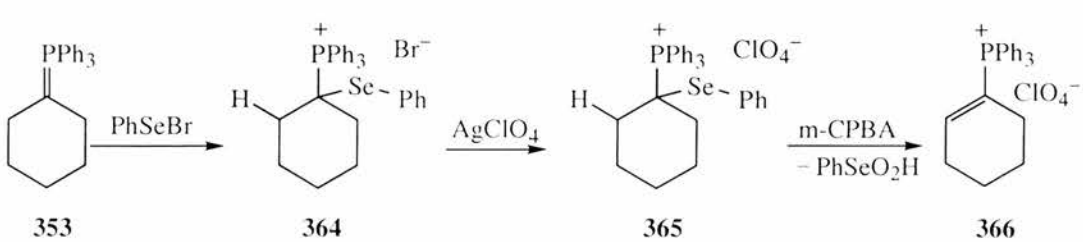
respectively. The ultraviolet-visible spectrum for **353** consisted of two main absorptions λ_{max} 265 and 391 nm.[107]



In 1978 Lythgoe and co-workers[108] showed the use of cyclohexylidenetriphenyl phosphorane **353** in the total synthesis of Vitamin D. The ylide **353** was used in a normal Wittig reaction with the aldehyde **362** to give the conjugated diene **363**, an important building block, in its *E*-configuration.

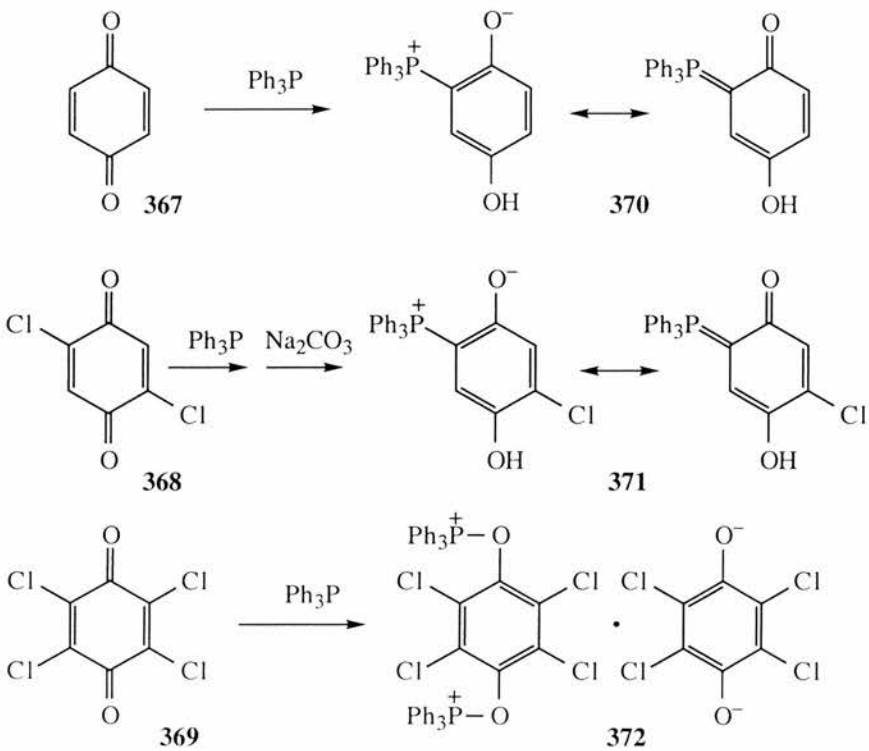


Minami and co-workers[40] reported the synthesis of 1-cycloalkenylphosphonium salts by selenenylation of phosphorus ylides and subsequent seleninic acid elimination. The cyclic ylide **353** reacts with phenylselenenyl bromide to give the salt **364** and oxidative elimination of the phenylselenenyl residue in **365** as phenylseleninic acid leads to 1-cyclohexenylphosphonium salt **366** in high yield.



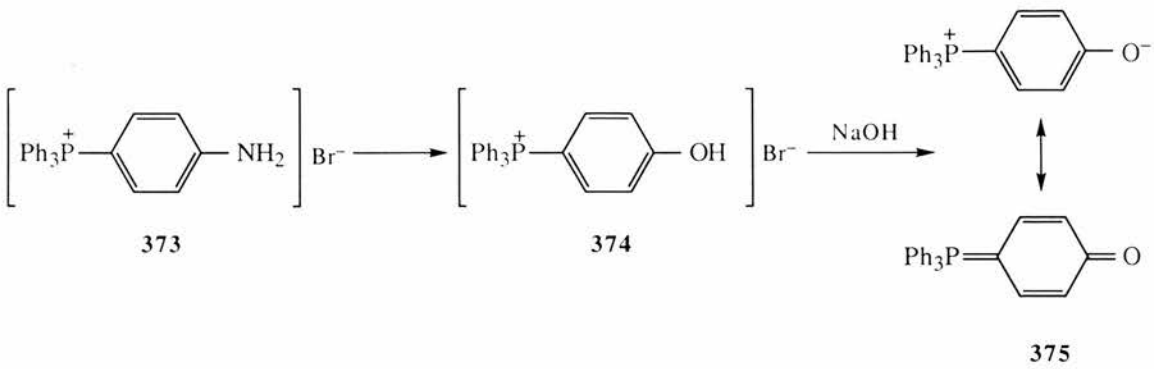
5 b Oxo-stabilised cyclohexylides and cyclohexadienylides

Investigations on the reaction between triphenylphosphine and quinones have been carried out since the late 1930's.[109] Ramirez and Dershowitz[110] were the first to have proof for the oxo-stabilised cyclohexylides proposed. The reactivity of triphenylphosphine with various quinones, *p*-benzoquinone **367**, 2,5-dichloro-*p*-benzoquinone **368** and chloranil **369** were studied and the results are shown below:



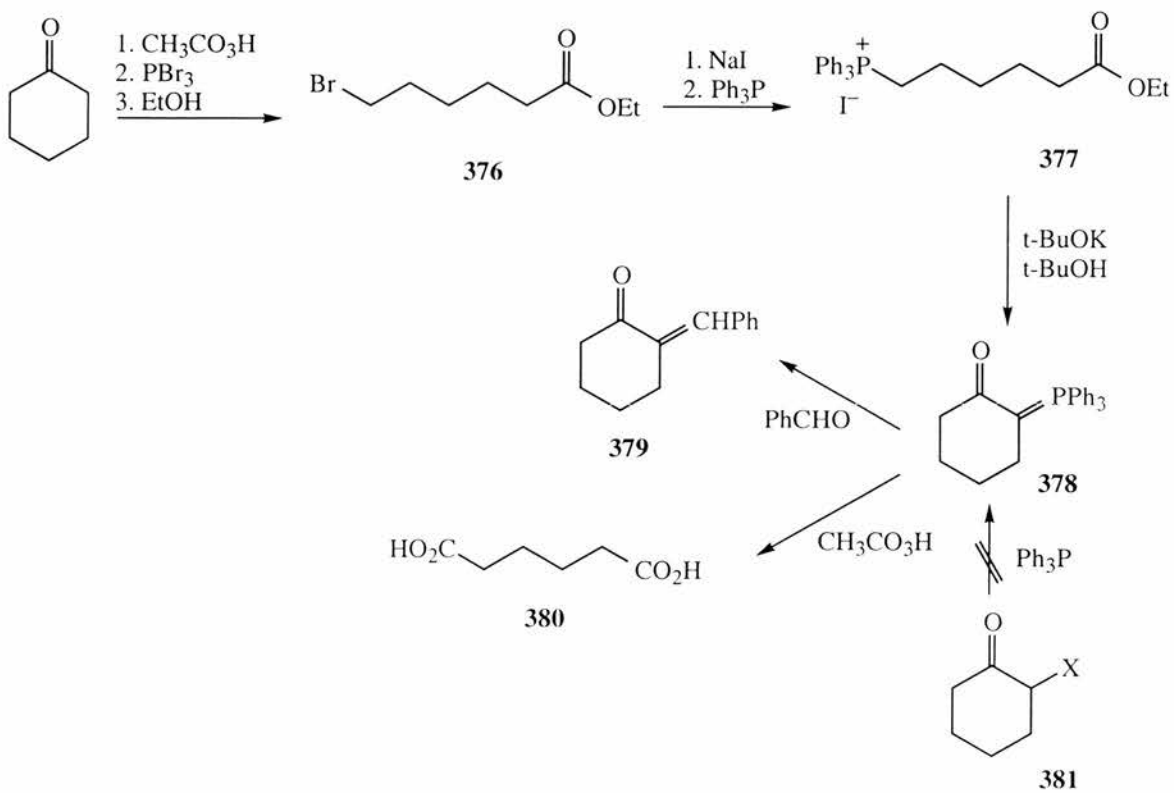
The *p*-benzoquinone **367** and 2,5-dichloro-*p*-benzoquinone **368** gave a 1:1 adduct with triphenylphosphine in which an aryl-phosphorus bond was formed to give the ylides **370** and **371**. The chloranil **369** behaved in a different manner forming the adduct **372** in which the electron-acceptor and the electron-donor are present in a 1:1 mole ratio and here oxygen-phosphorus bonds are formed as indicated by the ultraviolet-visible and infrared spectra.[72, 110]

Horner and co-workers[111] isolated the first *p*-benzoquinone ylide **375**. Triphenyl-*p*-hydroxyphenylphosphonium bromide **374**, which was made from triphenyl-*p*-aminophenyl phosphonium bromide **373**, was treated with a sodium hydroxide solution forming a stable crystalline product **375** whose stability is due to its aromatic zwitterionic structure.



373 **374** **375**

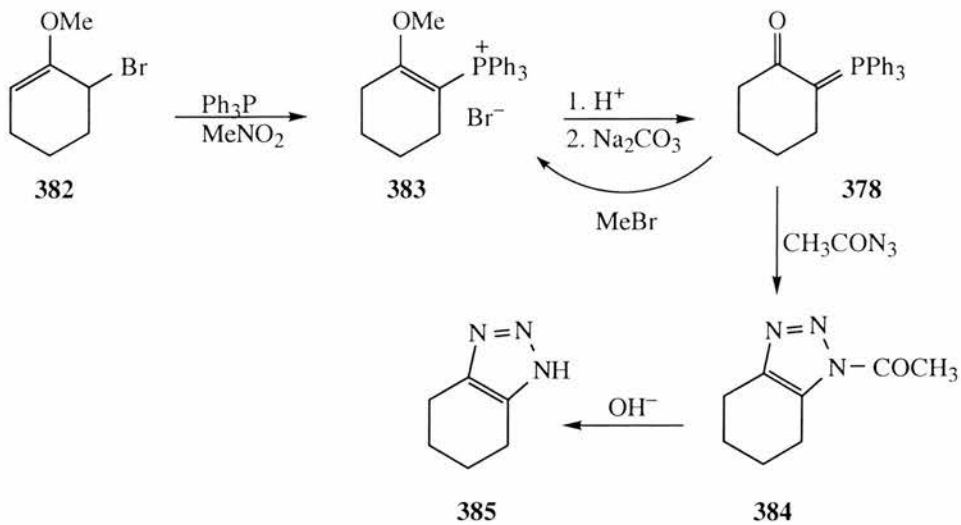
As mentioned in section 4 b, House and Babad[41] found a noteworthy preparative route for the α-oxocycloalkylidenetriphenylphosphoranes in which the six membered was included. Here again these oxo ylides are not accessible *via* the reaction of the α-halocycloalkanones **381** with triphenylphosphine.[42] Cyclohexanone reacts with peracetic acid followed by phosphorus tribromide and ethanol to produce the bromo ester **376**. The bromo ester **376** is converted



376 **377** **379** **378** **380** **381**

to the iodo ester phosphonium salt **377** and addition of potassium *t*-butoxide forms the ylide **378** in 79% yield. The *E*-2-benzylidene cyclohexanone **379** is formed from reaction of **378** and benzaldehyde. The ylide **378** was found to undergo a rapid reaction with three molar equivalents of peracetic acid to form adipic acid **380**.

An alternative route to the cyclic keto ylide **378** was found by Öhler and Zbiral.[112] Bromo enol ether **382** was treated with triphenylphosphine in nitromethane and the cyclohexenylphosphonium salt **383** was formed. The salt **383** was hydrolysed with hydrochloric acid and deprotonated with sodium carbonate to afford the ylide, (2-oxocyclohexylidene)triphenylphosphorane **378**. When the ylide **378** reacted with methyl



382 **383** **378** **385** **384**

bromide the *O*-methyl derivative **383** was reformed, with acetyl azide the acyltriazole **384** was obtained and on treatment of this with potassium hydroxide, the unsubstituted triazole **385** was formed.

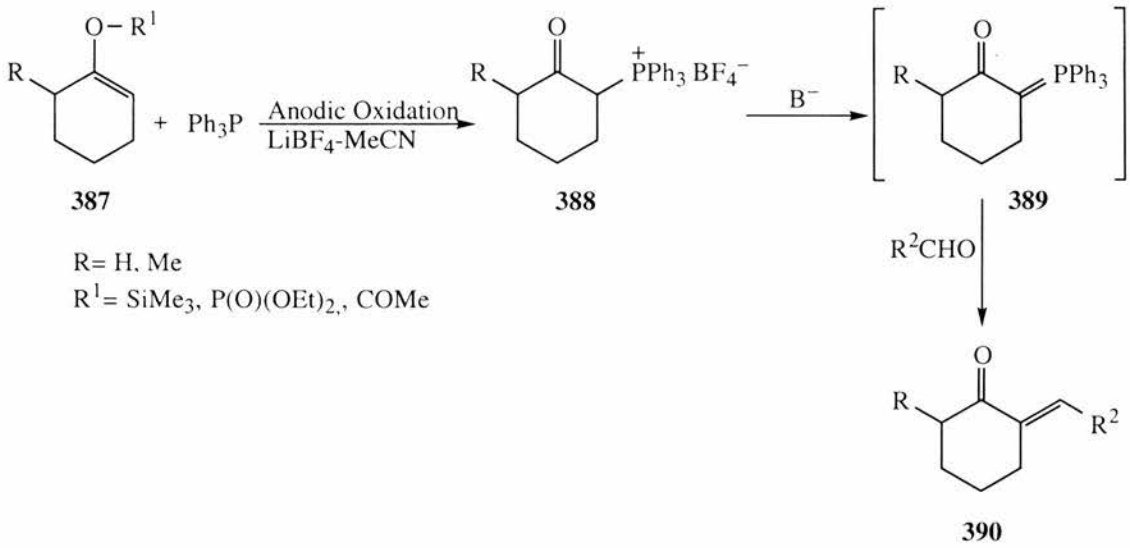
In a similar manner to that seen with five membered rings, alkylation of the six membered ring ylide **378** with alkyl halides gave various phosphonium salts **386** which have been claimed to have analgesic properties.[45]

378 **386**

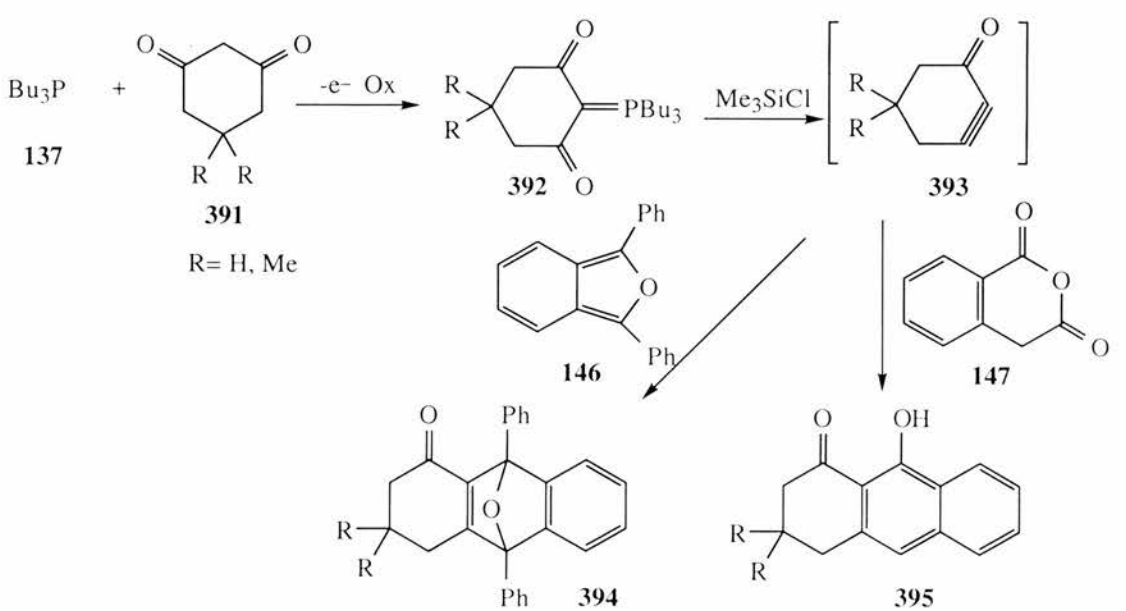
R	X
$PhCH_2$	Br
Me_2CH	I
Me	p-tosylate
$Me_2C{=}CHCH_2$	Br
$PhCH_2$	Br
MeO_2CCH_2	Br

A new one step synthesis of 2-oxocyclohexyltriphenylphosphonium salt **388** was reported based on the anodic oxidation of a silyl enol ether, enol phosphate or enol ester **387** in

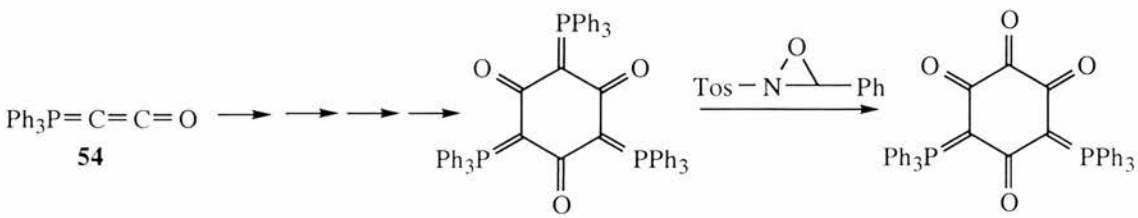
the presence of triphenylphosphine.[46] The Wittig reaction of the corresponding ylides **389** with aldehydes formed the alkenes **390** which were used to demonstrate the value of the salts **388** as building blocks in synthetic organic chemistry.



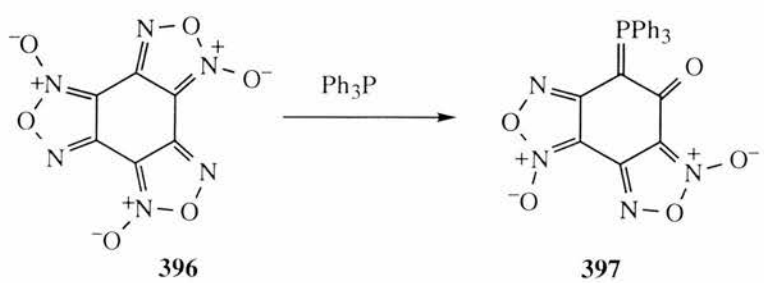
α,α'-Dioxocyclohexylidenetributylphosphoranes **392** were also prepared[47] by electrochemical oxidation of 1,3-cyclohexanediones **391** in the presence of tributylphosphine **137**. The ylides **392** were obtained and isolated in 58-70% yield. Reaction with Me_3SiCl in the presence of the anhydride **147** or 1,3-diphenylisobenzofuran **146** gave the corresponding adducts **395** and **394**, thus suggesting the intermediacy of the cyclohexynone **393** although no mechanism for its formation was proposed.



Studies on the dimer of ketenylidene(triphenyl)phosphorane **54** led to the preparation of the tris-ylide cyclohexanetrione **152** and the bis-ylide cyclohexanetetraone **153**.[49] The X-ray structures of **152** and **153** were reported and the ^{31}P NMR shifts were δ_P +13.7 and +13.8 respectively. The thermolyses of these ylides are currently being studied as extrusion of three or two equivalents of triphenylphosphine oxide could lead to interesting products. Further details of this work are described in the Discussion section.

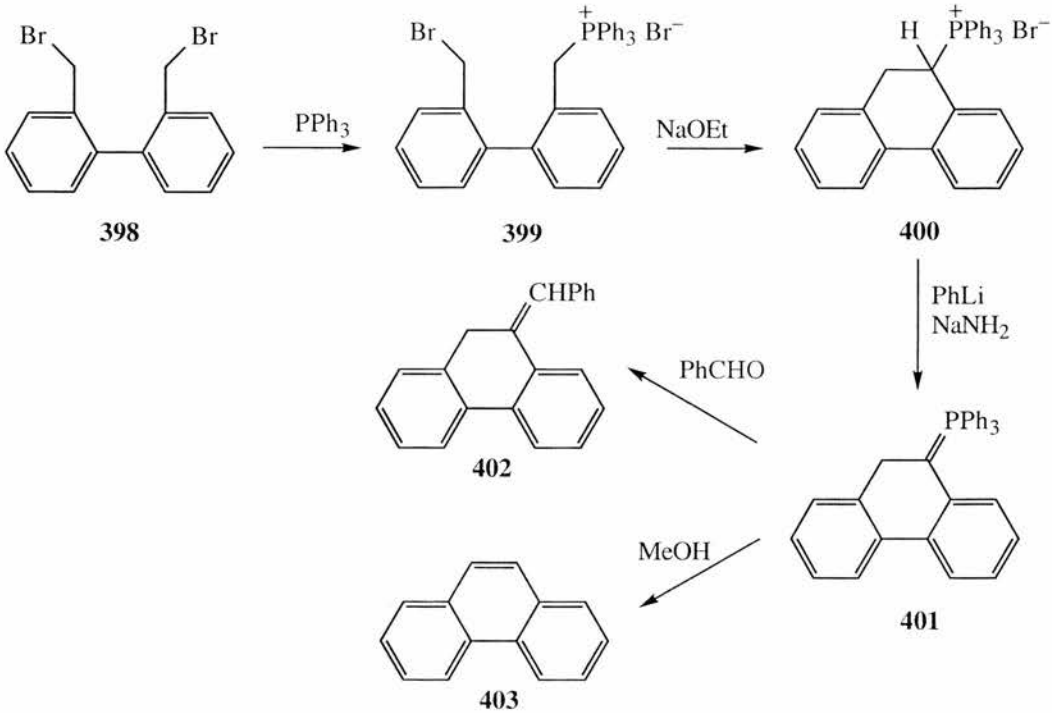


The reaction of benzotrifuroxan **396** with triphenylphosphine gave a large number of coloured products. One of the products isolated in low yield was dark green and its structure was determined by X-ray crystallography to be the ylide **397**.[113]



5 c Aromatic fused cyclohexenylides

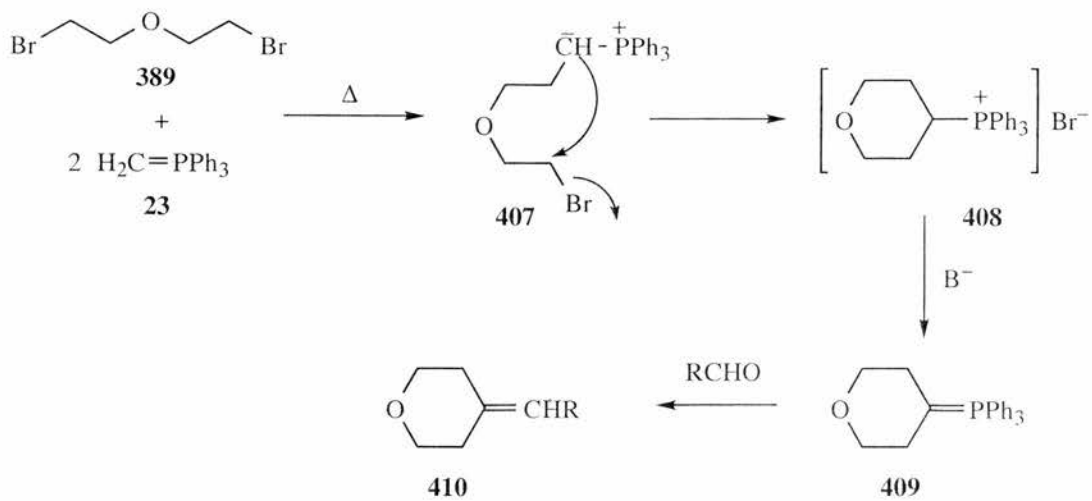
Bestmann and Häberlein[13,18] reported the first aromatic fused cyclohexenylide starting from **398**. The phosphonium salt **399** was made and on addition of sodium ethoxide a ring closure occured and the phosphonium salt **400** was formed. This salt **400** reacts with phenyllithum or sodium amide to give the ylide **401** which can then react in various ways, for example in a Wittig reaction to give **402** or in methanol to give the anthracene **403**.



In the same manner the cyclic ylide **405** was also made starting from the salt **404**.[51]

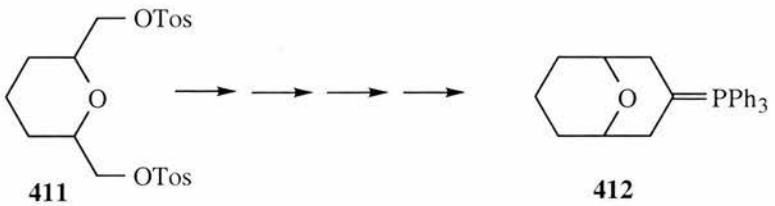
5 d Six-membered cyclic ylides containing oxygen

Bestmann and Kranz[16] prepared the first six-membered cyclic ylide containing an oxygen using their ring-closure method. Bis(2-bromoethyl)ether **406** reacts with two



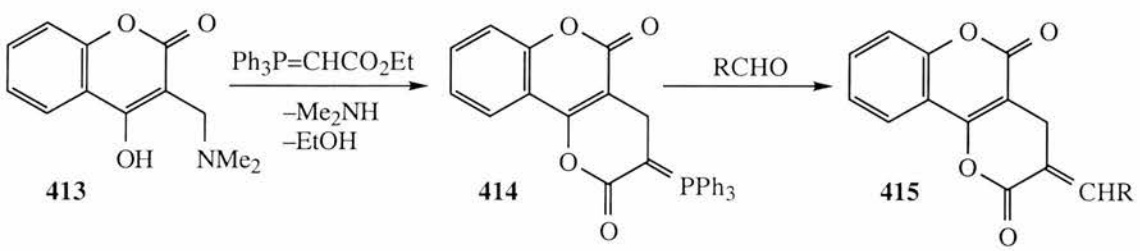
equivalents of methylenetriphenylphosphorane **23** to form the ylide **407** which undergoes a ring closure to give the cyclic phosphonium salt **408**. The cyclic salt **408** is converted to the cyclic ylide **409** with a base[107] and can be used in the Wittig reaction to form **410**.

Using the method above and starting from the bis tosylate **411**, the cyclic ylide **412** could also be made.[21]



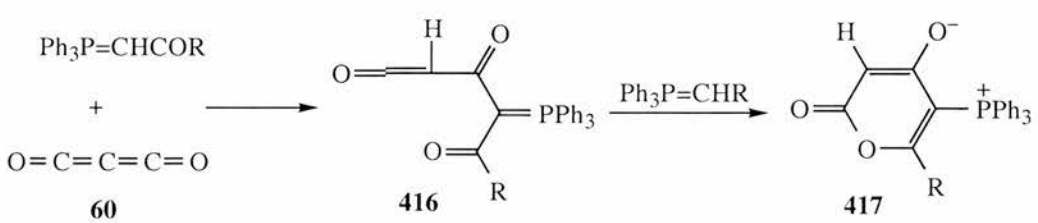
411 **412**

Investigations on the alkylation of phosphoranes with Mannich bases and the synthetic utility of the products of this reaction led to the preparation of the cyclic ylide **414**.[114] Ethoxycarbonylmethylenetriphenylphosphorane reacts readily with the Mannich base **413** to give the ylide **414**. The Wittig reaction with **414** led to β-arylacrylic esters **415** which are not easily available by other methods.



413 **414** **415**

Carbon suboxide **60** reacts with stabilised ylides $Ph_3P{=}CHCOR$ (R= Me, Ph) and the pyrone derivatives **417** are obtained in high yield.[18] The reactions proceed in a stoichiometric ratio 1:1, resulting in the formation of the heterocyclic systems after a nucleophilic intramolecular attack of the ylidic carbonyl group on the ketene moiety in **416**. The ^{31}P NMR



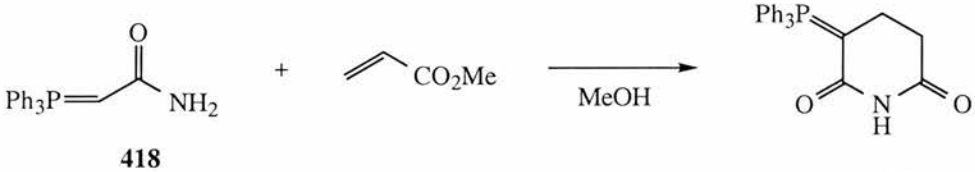
60 **416** **417**

R = Me, Ph

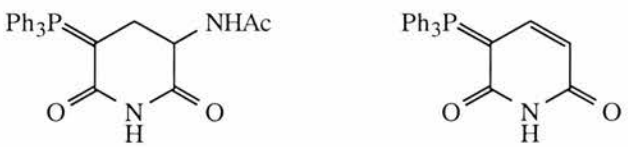
shifts for **417** were δ_P +16.2 (R=Me) and +17.3 (R=Ph) and the X-ray structure of **417** when R= Me was reported.

5 e Six-membered cyclic ylides containing nitrogen

Triphenylphosphoranylideneacetamide **418** reacts with methyl acrylate to give the cyclized product, 2-triphenylphosphoranylideneglutarimides **419**. The reaction can be extended with activated α,β-unsaturated esters to form the substituted and unsaturated glutarimide derivatives **420** and **421**.[115]

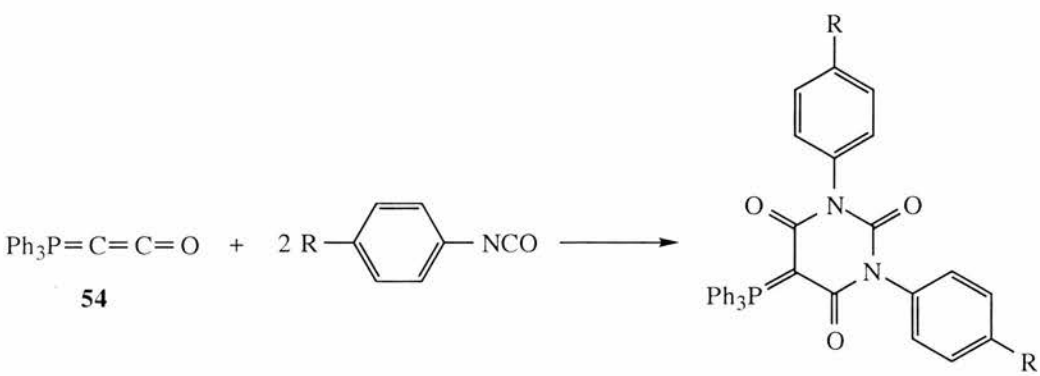


418 **419**



420 **421**

The first six-membered cyclic ylide containing two nitrogens was reported by Birum and Matthews in 1968.[29] Triphenylphosphoranylideneketene **54** reacts readily with aromatic isocyanates to give stable 2:1 adducts having six-membered ring structures **422**.

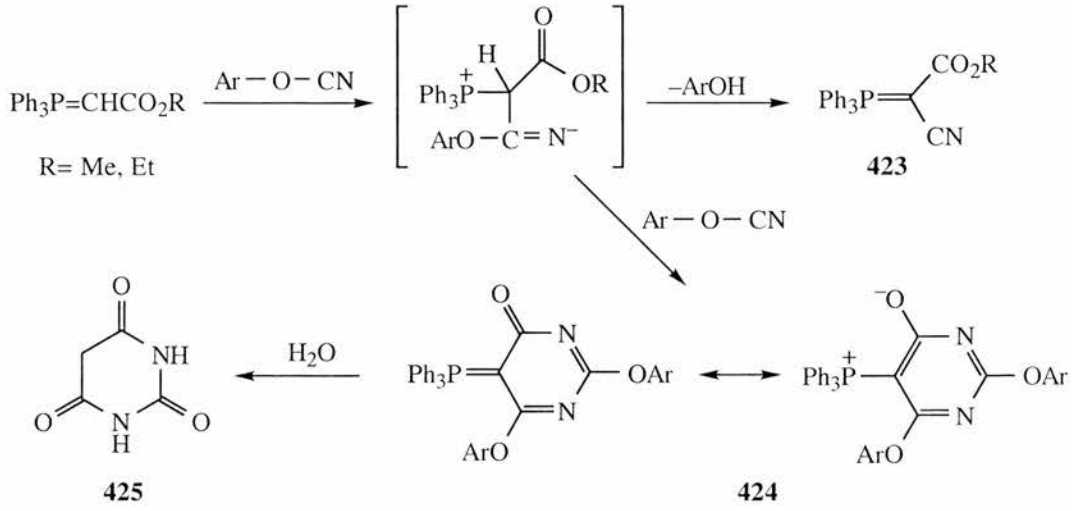


54

R = H, Me, F, CN and NO_2 **422**

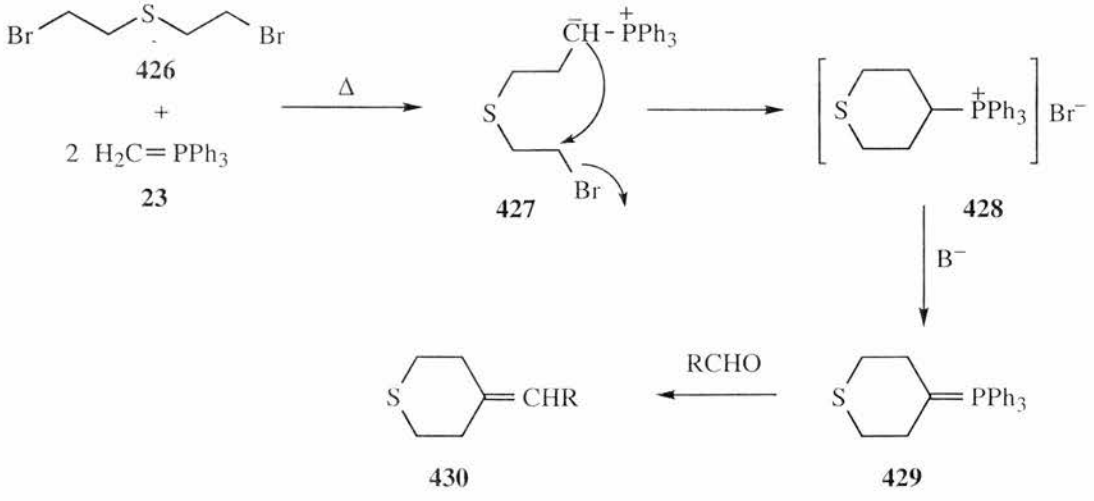
Alkoxycarbonylmethylenetriphenylphosphoranes react with aryl cyanates to give mainly the ylides **423**. In addition to the main product **423** a minor process occurs forming the six-

membered cyclic ylide **424** in 10-15% yield.[116] The ylide **424** was identified by microanalysis, infrared spectrum and the fact that on hydrolysis of this product barbituric acid **425** is obtained.



5 f Six-membered cyclic ylides containing sulfur

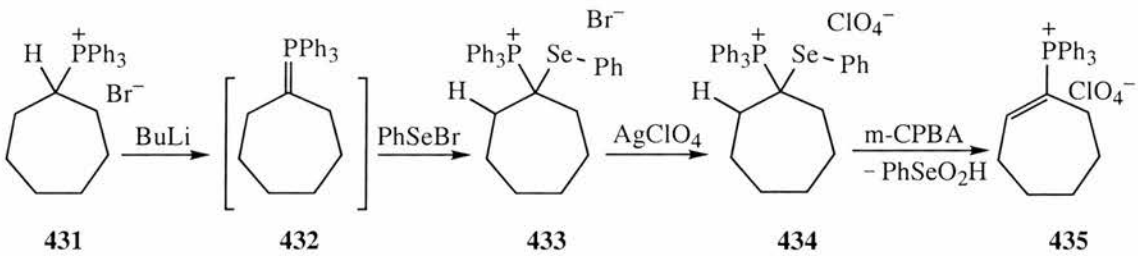
The only six-membered cyclic ylide containing a sulfur was prepared by a ring-closure method in 1969.[16,21] The reaction between bis-(2-bromoethyl)sulfide **426** and two equivalents of methylenetriphenylphosphorane **23** formed the ylide **427** which undergoes a ring closure to give the cyclic phosphonium salt **428**. The cyclic phosphonium salt **428** is converted with base to the cyclic ylide **429** which can be used in the Wittig reaction to form **430**.



6 Seven-Membered Rings

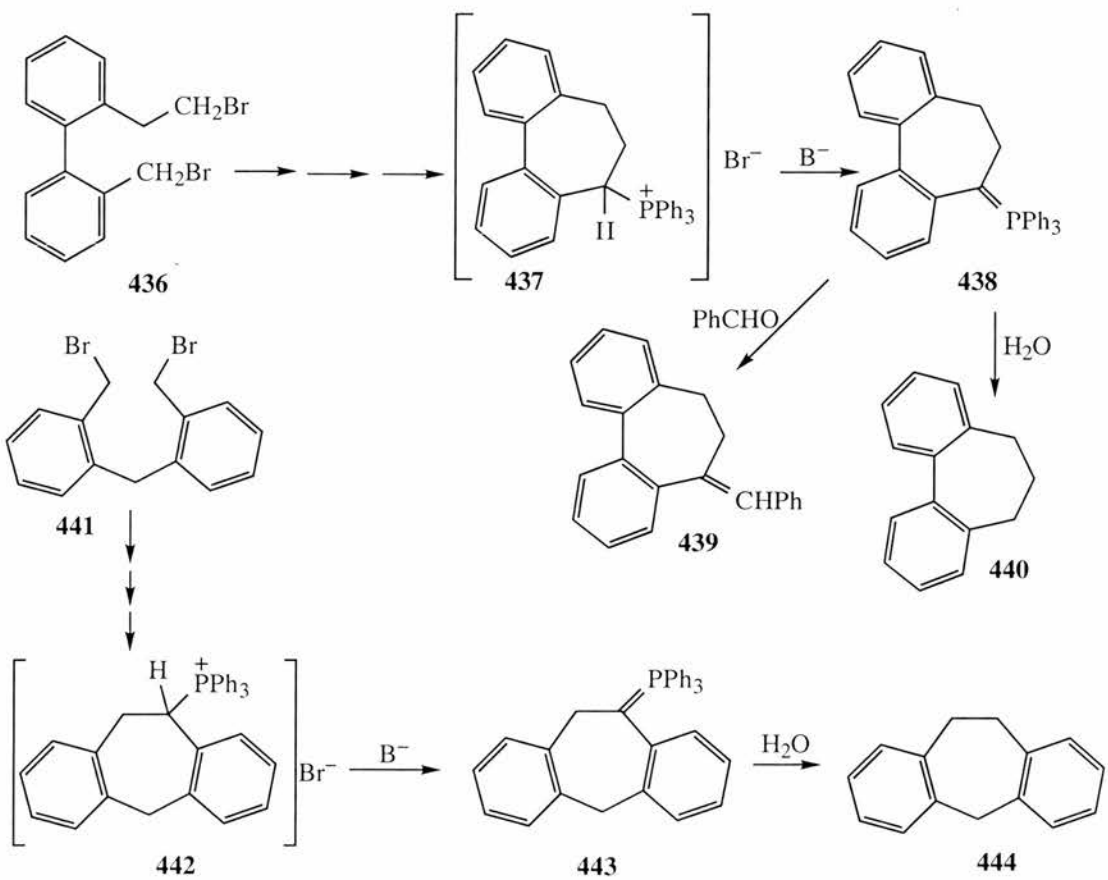
6 a Simple seven-membered rings

The only simple seven-membered cyclic ylide was reported in 1979[40] and was not isolated. The cyclic ylide **432** was prepared from the corresponding cyclic phosphonium salt **431** using butyllithum and in *situ* phenylselenenyl bromide was added to give the salt **433**. Oxidative elimination of the phenylselenenyl residue in **434** as phenylseleninic acid led to the 1-cycloheptenylphosphonium salt **435** in high yield.



431 **432** **433** **434** **435**

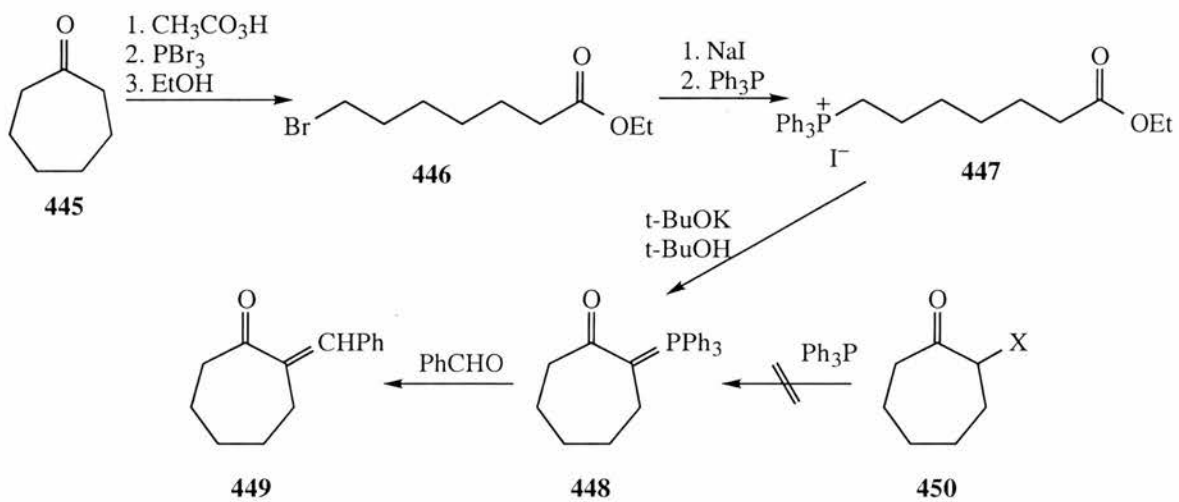
Bestmann and co-workers[51] synthesised aromatic fused cyclic ylides and two with seven membered rings were reported. The cyclic ylides were made by the same method, starting from the dibromide derivatives **436** and **441**. These were converted to the cyclic



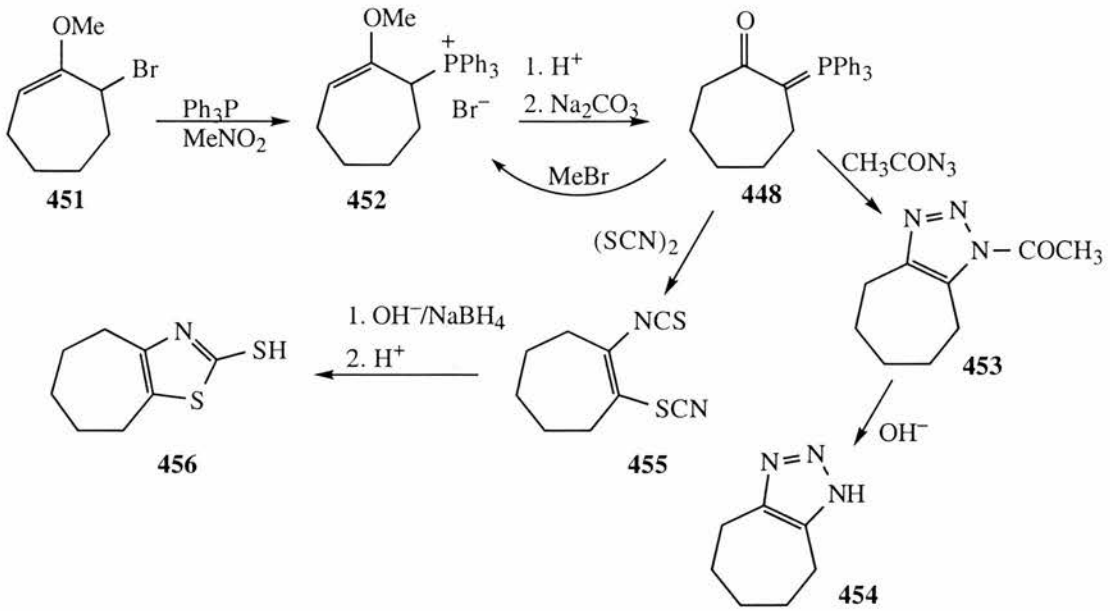
436 **437** **438** **439** **440** **441** **442** **443** **444**

phosphonium salts **437** and **442** and on addition of a base the cyclic ylides **438** and **443** were formed. Hydrolysis of these ylides gave the products **440** and **444** while a Wittig reaction with **438** gave the product **439**.

In 1963 House and Badad[41] prepared the first oxo-stabilised cycloheptylide **448**. These oxo ylides are not accessible via the reaction of the α-halocycloalkanones **450** with triphenylphosphine.[42] Cycloheptanone **445** reacts with peracetic acid followed by phosphorus tribromide and ethanol to form the bromo ester **446**. The bromo ester **446** is converted to the the phosphonium salt **447** *via* the iodo ester and addition of potassium *t*-butoxide gives the ylide **448** in 52% yield. The ylide **448** reacts with benzaldehyde to give the Wittig product **449**.



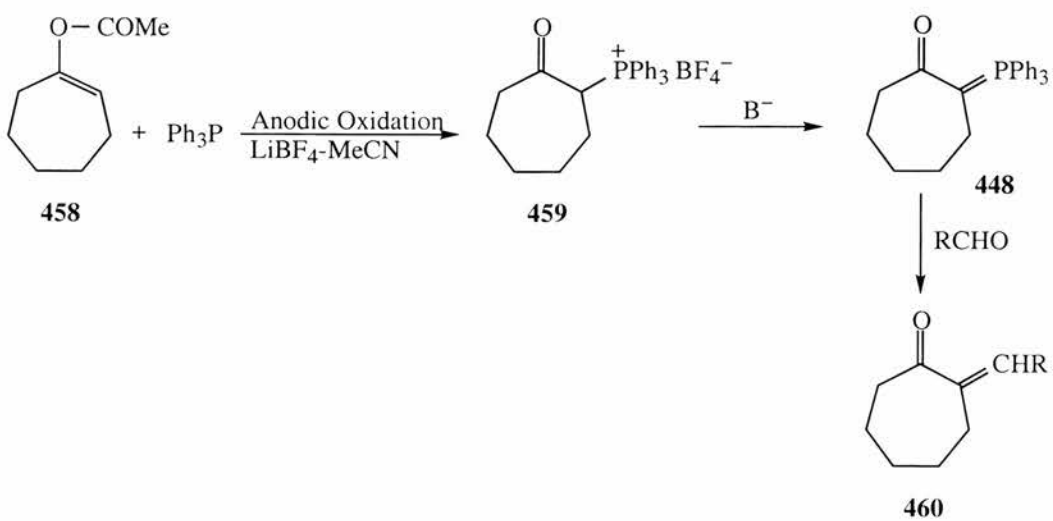
Öhler and Zbiral[113] reported an alternative route to the cyclic keto ylide **448**. The bromo enol ether **451** was treated with triphenylphosphine in nitromethane and the cycloheptenylphosphonium salt **452** was formed. The salt **452** reacted with hydrochloric acid and sodium carbonate to afford the ylide, (2-oxocycloheptylidene)triphenylphosphorane **448**. When the ylide **448** reacted with methyl bromide the *O*-methyl derivative **452** was reformed. With acetyl azide the acyltriazole **453** was obtained and treatment of this with potassium hydroxide formed the unsubstituted triazole **454**. Reaction of the ylide **448** with $(SCN)_2$ yields the cycloheptene derivative **455** which can be cyclised to the thiazole **456**.



Alkylation of the seven membered ring ylide **448** with alkyl halides gave various phosphonium salts **457** which have been claimed to have analgesic properties.[45]

R	X
$PhCH_2$	Br
Me_2CH	I
Me	p-tosylate
$Me_2C{=}CHCH_2$	Br
$PhCH_2$	Br
MeO_2CCH_2	Br

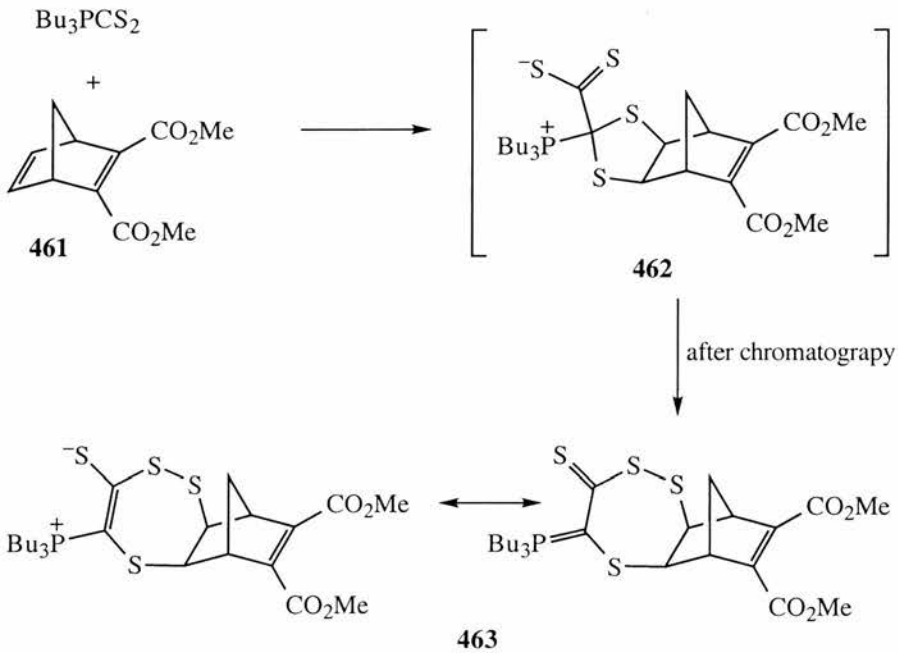
A one step synthesis of 2-oxocycloheptyltriphenylphosphonium salt **459** has been reported.[46] Here, anodic oxidation of the enol ester **458** in the presence of triphenylphosphine



formed the 2-oxocycloheptyltriphenylphosphonium tetrafluoroborate **459**. The salt **459** was converted to the ylide **448** and used in the Wittig reaction with aldehydes to give **460**.

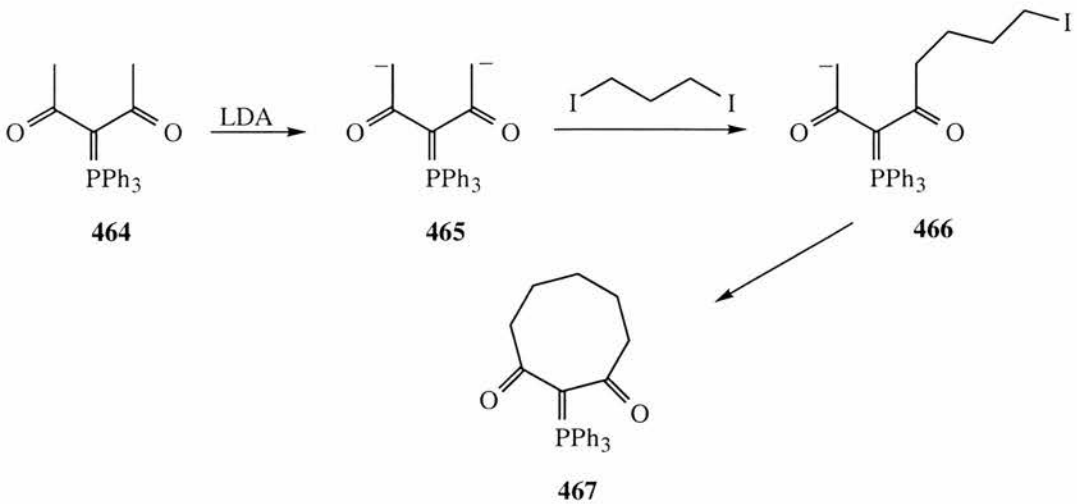
6 b Seven-Membered Rings containing heteroatoms

The only seven-membered ring involving heteroatoms contains three sulfur atoms and was synthesised very recently in this laboratory.[117] An attempt to isolate the zwitterionic structure **462** gave instead a rearrangement product with the novel 1,2,5-trithiepane stabilised ylide structure **463**.



7 Eight-Membered Rings

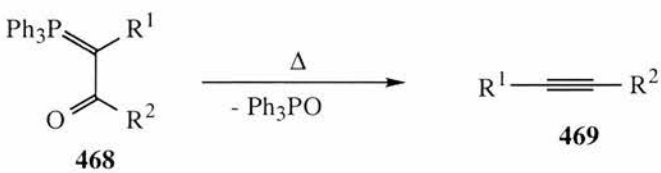
Cooke and Goswami[118] reported the formation of the dianion **465** from diacetylmethylenetriphenylphosphorane **464** and the potential utility of the dianion **465** in the construction of ring systems that would otherwise be different to obtain. Treatment of the diacyl ylide **464** with excess lithium diisopropylamide resulted in the formation of the black dianion **465**. Alkylation of the dianion **465** with 1,3-diiodopropane led to ring formation due to an intramolecular alkylation within the intermediate ylide anion **466** and the eight membered cyclic ylide **467** was isolated in 25% yield.



464 **465** **466** **467**

B Pyrolysis of β-Oxo ylides as a route to Alkynes

Thermal extrusion of triphenylphosphine oxide from β-oxo phosphorus ylides **468** to give the alkynes **469** was first reported by Trippett and Walker in 1959.[119] Here,

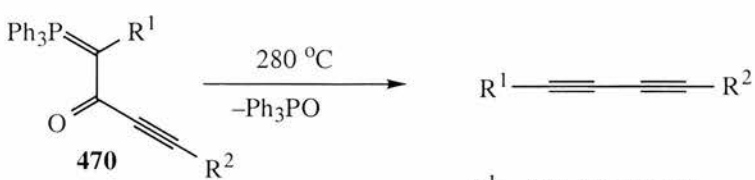


468 **469**

$R^1 = R^2 = Ph$

α-benzoylbenzylidenetriphenylphosphorane was heated at 300 °C for 30 mins and the products diphenylacetylene and triphenylphosphine oxide were obtained in quantitative yield. However, no alkynes were formed when the substituent on the ylidic carbon was H. This method was later extended to ylides in which R^1 = CN and CO_2Et[120] and was used by Märkl to provide a useful synthesis of acetylenic esters ($R^1 = CO_2Me$).[121]

Pyrolysis as a technique is also successful in the preparation of dialkynes.[120] The first investigation was limited to alkynoyl ylides **470** with R^1 as a stabilising group.



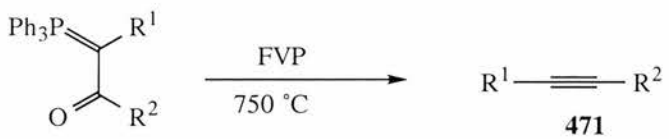
470

R^1 = CN, CO_2Et, Ph;
R^2 = Ph, Bu^n

More recently, this reaction has been used to gain access to a wide variety of alkynes and for its success it is important that R^1 is either an electron withdrawing group or is capable of stabilising the phosphonium ylide. Thus, conventional pyrolysis has been used to obtain a wide range of compounds, for example acetylenic diacids,[122] diarylalkynes,[123] acetylenic ketones,[124] acetylenic thioesters,[125] thioalkynes,[126] arylselenoalkynes,[127] α-haloalkynes[128] etc. The major limitation of the method was that it was only successful for electron-withdrawing groups R^1. In other cases side reactions, including partial extrusion of Ph_3P and isomerisation of the desired alkyne to allenes, occurred making this method useless for the formation of simple aliphatic and terminal alkynes.

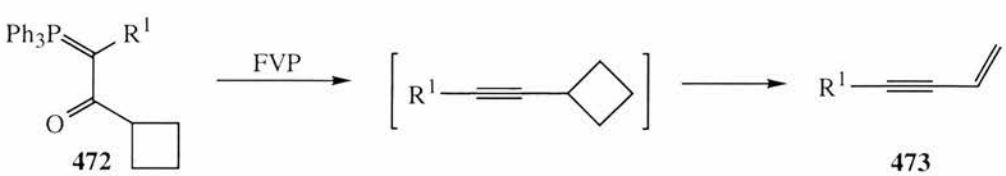
The application of flash vacuum pyrolysis (FVP) has overcome these limitations. Flash vacuum pyrolysis, in contrast to standard pyrolysis, involves a flow system and a combination of high temperatures and low pressure providing a relatively short contact time for the substrate. This technique has given excellent results in a wide variety of thermal extrusion reactions.[129]

The extrusion of Ph_3P from β-oxoalkylidenetriphenylphosphoranes using FVP was first reported from this laboratory in 1985.[130] Pyrolysis of acylated ylides **468** with R^1 = H or alkyl resulted in a clean conversion to the desired alkynes **471**. The experiments were performed at 750 °C and at a pressure of 10^{-2} Torr.



468 **471**

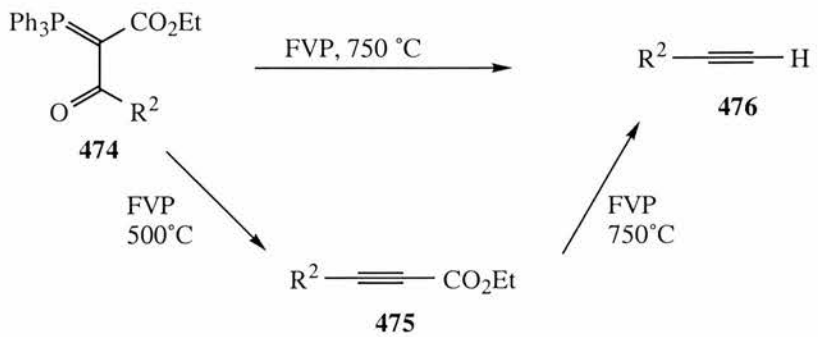
R^1 = H, Me, Pr^n
R^2 = Me, Et, Pr^n, Pr^i, Ph, Bu^n, Bu^t, c-Bu, $Pent^n$, c-Hex, CH=CHMe



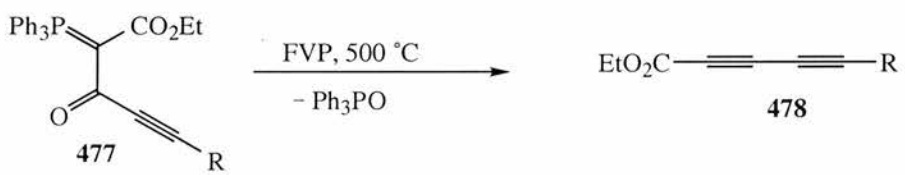
472 **473**

A further fragmentation process was observed in one case **472**, where R^2 = cyclobutyl. It was speculated that the ring strain was relieved by extrusion of ethene, resulting in the formation of a vinyl alkyne **473** in good yield.

Temperature dependent secondary fragmentation processes were also observed.[131] FVP of ylides **474** at 500 °C gave the expected acetylenic esters **475** in good yields. When the same ylides were subjected to FVP at 750 °C, Ph_3PO was again eliminated but this was accompanied by complete loss of CO_2Et group to give the terminal alkynes **476**.

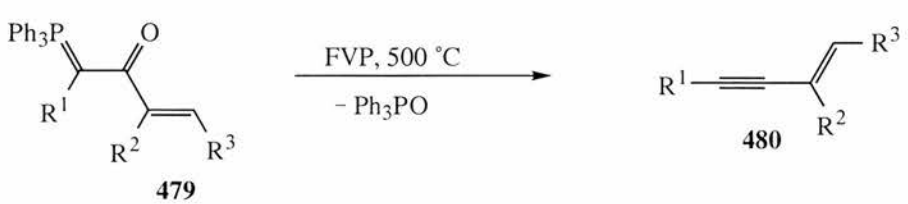


A further report from this laboratory described the extension of this reaction to give diacetylenic esters and terminal 1,3-diynes.[132] The FVP of a series of alkynoyl ylides **477** at 500 °C provided diacetylenic esters **478** in good yields. As expected, FVP of these ylides at 750 °C led to the formation of terminal 1,3-diynes.

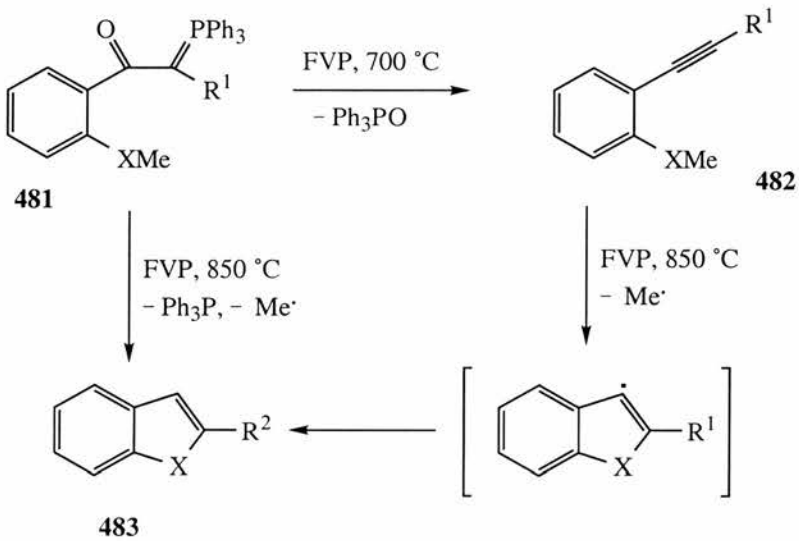


R = Ph, Bu^n, Pr, Ar, furyl, thienyl

The conversion of β-oxo-γ,δ-unsaturated ylides into enynes by use of conventional pyrolysis was reported in early literature.[119,120] Ylides carrying alkyl substituents at the ylidic carbon did not give the enynes, but again this problem has been overcome by the use of FVP.[133] A range of substituted cinnamoyl ylides **479** (R^1 = H, alkyl, aryl) underwent FVP at 500 °C to give the *E* isomer **480** as the major product, whereas FVP at 700 °C gave a mixture of *E* and *Z* isomers.



The oxo ylides **481** possessing *o*-methoxybenzoyl or *o*-(methylsulphanyl)benzoyl groups show interesting thermal behaviour.[134] In these ylides the alkyne obtained by FVP could react further in a secondary fragmentation process to form more complex and synthetically useful molecules. FVP of the ylides **481** at 700 °C affords the expected alkynes **482**. However at 850 °C the extrusion of phosphine oxide is accompanied by the loss of a methyl radical. A radical mechanism is involved to explain the cyclisation to the 2-substituted benzofurans and benzothiophenes **483** and this method was more recently extended to tandem cyclisations.[135]

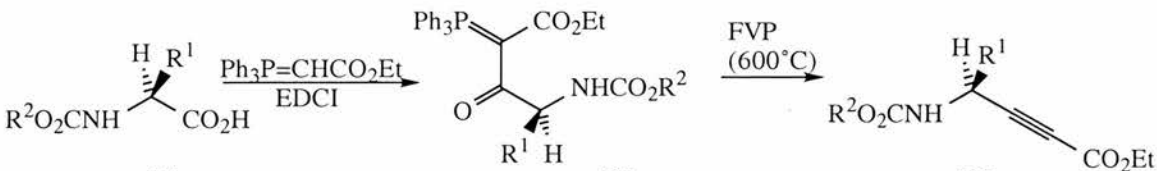


481 **482** **483**

X = O, S; R^1 = alkyl, Ph; R^2 = alkyl

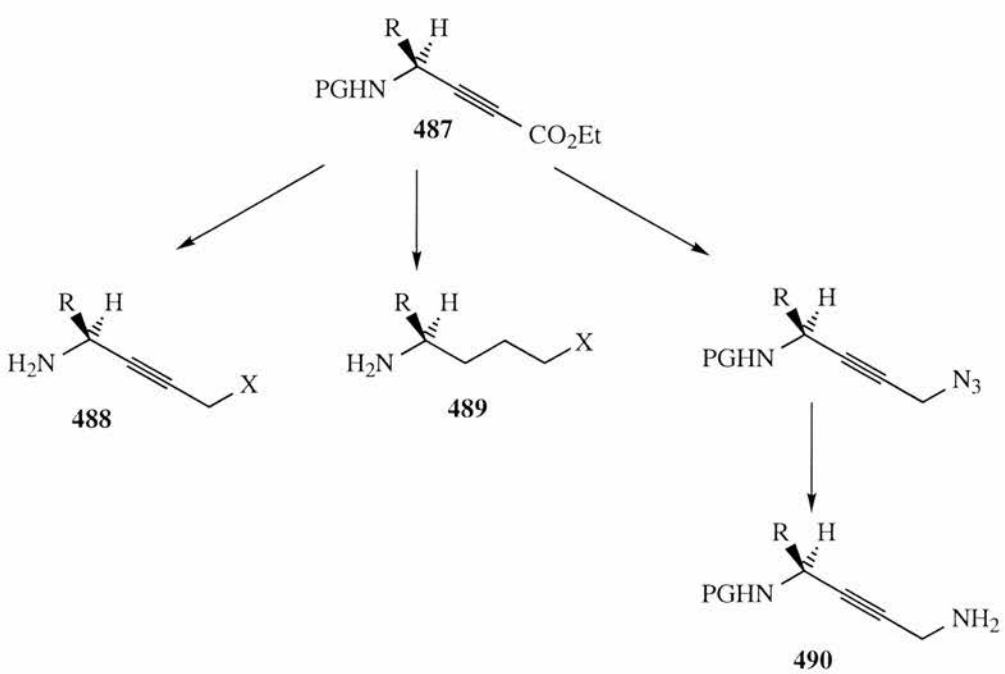
C Programme of Research

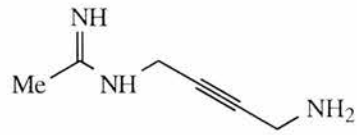
In previous work in this laboratory, *N*-protected amino acids **484** and alkoxycarbonyl stabilised ylides were coupled forming amino acid derived α-aminoacyl ylides **485**. Pyrolytic extrusion of Ph_3PO from these products produced the novel chiral acetylenic amino acid analogues **486**.[136]



484 **485** **486**

The products of such pyrolyses have great interest and potential as chiral intermediates for the synthesis of amino acid analogues with the potential to act selectively on receptors or enzyme targets in their own right or as components of modified peptides and as chiral intermediates for synthesis. In the previous work attention was focused on amino acids with hydrocarbon side-chains and so one objective of the present work was to extend the method to functionalised side chain amino acids. This chemistry also gave the potential for the synthesis of chiral amines **488-490**, potential intermediates in the synthesis of NOS inhibitors, an area where our industrial collaborators have observed activity with a similar acetylenic analogue **491**.[137]

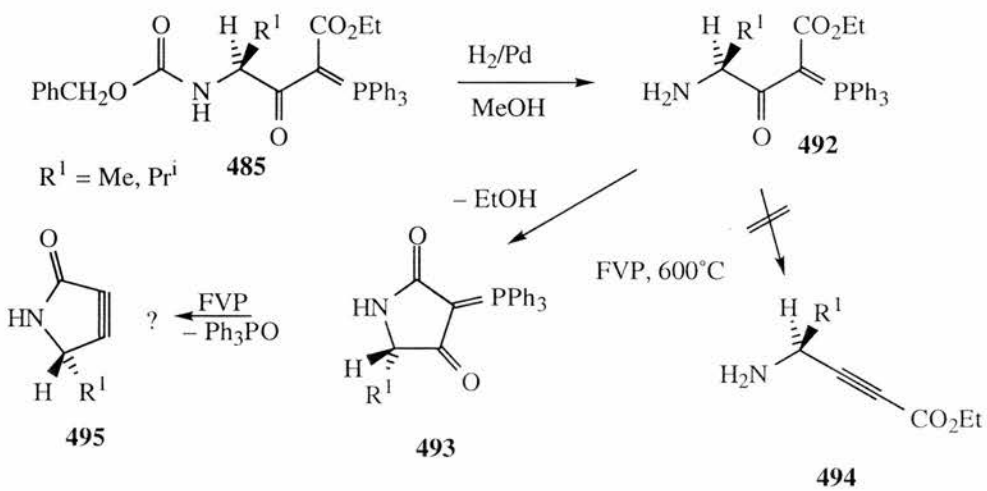




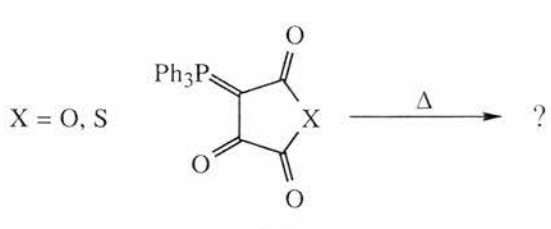
491

To this end various different protecting groups for the amino and carboxyl functions of **487** were to be examined which would survive the pyrolysis conditions but then allow convenient access to the target compounds **488-490**.

Also in the previous work it was thought that the *N*-protection was only required for formation of the ylides **485** and so they could be deprotected prior to pyrolysis to provide direct access to the unprotected acetylenic products **494**. Surprisingly, however deprotection to give **492** followed by FVP gave the novel cyclic ylides **493** by loss of ethanol.[138]



These cyclic ylides possess the tetramic acid ring system which is a component of many natural products which exhibit biological activity.[139] It was of interest to examine the process futher to see whether heterocyclic ylides of different ring sizes could be obtained. In addition it also seemed possible that Ph_3PO could be eliminated from structures such as **493** to give cycloalkynes **495**. Since there were several potential complications in this process it also seemed worthwhile to examine the behaviour of the simpler O- and S- heterocyclic ylides **496**.



496

EXPERIMENTAL

A Symbols and Abbreviations

Boc	*t*-butoxycarbonyl
bp	boiling point
br, s, d, t, q, m	broad, singlet, doublet, triplet, quartet, multiplet
c	concentration in g per 100 cm^3 of solvent
Cbz	benzyloxycarbonyl
CI	chemical ionisation
δ	chemical shift in parts per million
DMAP	4-dimethylaminopyridine
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EI	electron impact
eq.	equivalent
ether	diethyl ether
FAB	fast atom bombardment
FVP	flash vacuum pyrolysis
h, min	hours, minutes
J	spin-spin coupling constant in Hertz
M	mole dm^{-3}
M^+	mass of molecular ion
mp	melting point
m/z	mass to charge ratio
mmol	millimoles
MS	mass spectrometry
υ_{max}	infra-red absorption wavenumber
NOS	Nitric oxide synthase
NMR	nuclear magnetic resonance
ppm	parts per million
THF	tetrahydrofuran
TLC	thin layer chromatography

B Instrumentation and General Techniques

NMR Spectroscopy

^{1}H NMR

Routine spectra were obtained at 200 MHz on a Varian Gemini 200. High resolution spectra were obtained at 300 MHz on a Bruker AM-300 spectrometer and at 300 MHz on a Varian Gemini 2000 operated by the author.

^{13}C NMR

Spectra were obtained at 75 MHz on a Bruker AM-300 or a 300 MHz Varian Gemini 2000 spectrometer and at 50 MHz on a Varian Gemini 200 operated by the author.

All ^{13}C and ^{1}H spectra were obtained from solutions in deuteriochloroform except where indicated otherwise and chemical shifts are expressed in parts per million to high frequency of internal tetramethylsilane.

^{31}P NMR

Spectra were obtained at 121 MHz on a Varian Gemini 2000 spectrometer operated by the author. Spectra are referenced to 85% phosphoric acid as the external standard.

Infrared Spectroscopy

Spectra were obtained on a Perkin-Elmer 1420 ratio recording spectrophotometer or on a Perkin-Elmer 1710 fourier transform spectrophotometer, as Nujol mulls for solids and as films for liquids, using matched sodium chloride plates. Spectra were calibrated with the polystyrene peak at 1603 cm^{-1}.

Mass Spectrometry

Mass spectra and accurate mass measurements were obtained on an A.E.I./Kratos M.S.–50 spectrometer operated by Mr C. Millar. Unless otherwise indicated, the spectra were obtained

using EI (70 eV). CI spectra were obtained on a VG Autospec using isobutane as the ionising gas. FAB spectra were obtained using 3-nitrobenzyl alcohol as the matrix.

Elemental Analysis

Microanalyses for carbon, hydrogen and nitrogen were carried out on a Carlo-Erba 1106 elemental analyser operated by Mrs S. Williamson.

Melting points

Melting points, both routine and for new compounds were determined on a Reichert hot-stage microscope. All melting points are uncorrected.

Thin layer Chromatography

This was carried out using 0.2 mm layers of silica (Merck, Kieselgel $60F_{254}$) on aluminium sheets. The components were observed under ultraviolet light.

Preparative Thin Layer Chromatography

This was carried out using 1.0 mm layers of silica (Merck, Kieselgel 60G, particle size 5-40 μm), containing 0.5% Woelm fluorescent green indicator, on glass plates. After locating the components with ultraviolet light, the bands were scraped off and the products removed from the support by soaking in dichloromethane for 30 min.

Column Chromatography

This was carried out using BDH "flash chromatography grade" silica gel (120 mesh).

Drying and Evaporation of Organic Solutions

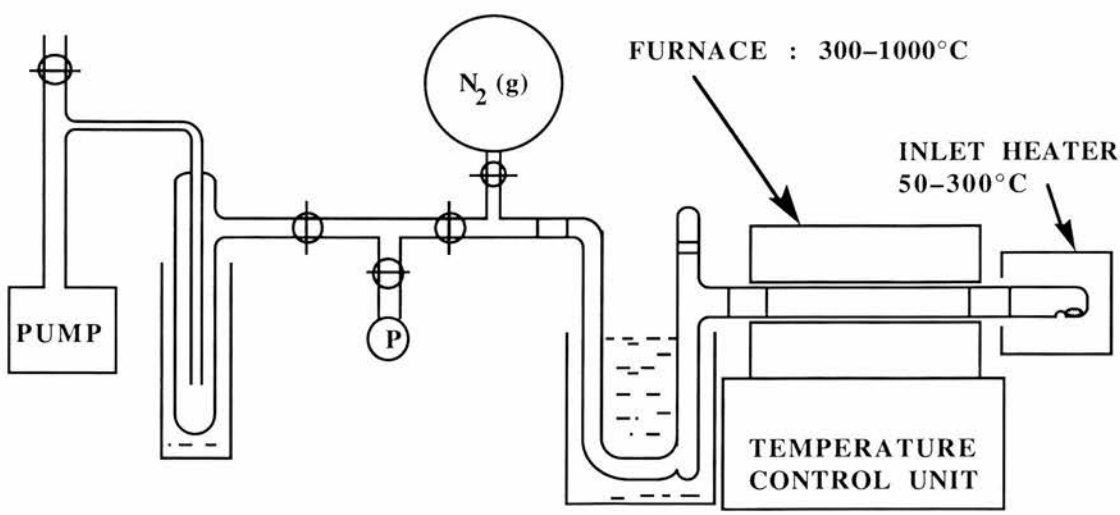
Organic solutions were dried by standing over anhydrous magnesium sulphate and were evaporated under reduced pressure on a Büchi rotary evaporator.

Drying and Purification of Solvents

Commercially available solvents were used without further purification unless otherwise indicated. Methanol was the commercially available A.R. grade solvent. Dry dichloromethane was distilled from phosphorus pentoxide and stored over molecular sieves. Dry ether and dry toluene were prepared by the addition of sodium wire. Extra dry ether was prepared by preliminary drying with sodium wire and then distilling from sodium benzophenone ketyl.

Flash Vacuum Pyrolysis

The apparatus used was based on the design of W. D. Crow, Australian National University. A similar set up is illustrated in a recent monograph by Brown.[140] The essential features of the apparatus are shown below. The sample was volatilised from a horizontal inlet tube, heated via an external heat source, through a 30 x 2.5 cm silica tube. This was heated at temperatures in the range of 400–600°C by a Carbolite Eurotherm Tube Furnace MTF-12/38A, the temperature being measured by a Pt/Pt-13% Rh thermocouple situated at the centre of the furnace. The non-volatile products were collected at the furnace exit and the volatile products collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} to 10^{-3} Torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured on a Pirani gauge situated between the trap and the pump. Under these conditions the contact time in the hot zone was estimated to be in the range 1–10 ms.



After the pyrolysis the system was isolated from the pump. The products were then either dissolved out of the trap in deuteriochloroform, and analysed directly by NMR or dissolved out in CH_2Cl_2 and purified by column chromatography.

Optical Rotation

Optical rotation measurements were preformed with an Optical Activity AA–1000 polarimeter operating at 589 nm using a 5 cm^3 solution cell with a 10 cm path length or a 1 cm^3 solution cell with a 20 cm path length. Values for $[\alpha]_D$ are expressed in units of 10^{-1} deg cm^2 g^{-1}.

C Preparation of Phosphonium Salts and Ylides

1. (Methoxycarbonylmethyl)triphenylphosphonium bromide **497**

To a solution of triphenylphosphine (40.0 g, 153 mmol) in dry toluene (250 cm^3) was added methyl bromoacetate (14.5 cm^3, 23.4 g, 153 mmol). The mixture was then heated under reflux for 2 h and left to stir overnight. The off-white precipitate which formed was filtered off, washed with toluene and dried to furnish the product (49.3 g, 78%) as a white powder, mp 160–162 °C (lit.,[141] 162 °C); δ_P +23.4.

2. (Methoxycarbonylmethylene)triphenylphosphorane **501**

(Methoxycarbonylmethyl)triphenylphosphonium bromide (44.7 g, 107 mmol) was dissolved in water (500 cm^3), and the solution filtered through celite and extracted with ether to remove any residual triphenylphosphone present. The solution was stirred vigorously as sodium hydroxide (4.3 g, 107 mmol) in water (10 cm^3) was added rapidly. The mixture was extracted with ethyl acetate (2 x 250 cm^3) and the combined organic phase washed with water (250 cm^3), dried and evaporated to furnish the crude product. Recrystallisation using ethyl acetate gave the product (31.3 g, 87%) as colourless crystals, mp 160–161°C (lit.,[142] 163 °C); δ_P +17.9 (lit.[143] δ_P +17.0).

3. (Ethoxycarbonylmethyl)triphenylphosphonium bromide **498**

This was prepared as in 1. using triphenylphosphine (262 g, 1.0 mol) and ethyl bromoacetate (111 cm^3, 167 g, 1.0 mol) to furnish the product (374 g, 87%) as colourless crystals, mp 150–152 °C (lit.,[141] 158 °C); δ_P +23.0.

4. (Ethoxycarbonylmethylene)triphenylphosphorane **502**

This was prepared as in 2. using (ethoxycarbonylmethyl)triphenylphosphonium bromide (100.0 g, 230 mmol) to furnish the product (61 g, 75%) as colourless crystals, mp 120–122 °C (lit.,[142] 118 °C); δ_P +18.1 (lit.,[143] δ_P +17.0).

5. (t-Butoxycarbonylmethyl)triphenylphosphonium chloride **499**

This was prepared as in 1. using triphenylphosphine (34.8 g, 0.13 mol), t-butyl chloroacetate (20 g, 0.13 mol) and reflux for 18 h to furnish the product (45.1 g, 84%) as a white solid, mp 188–189 °C (lit.,[144] 185 °C); δ_P +21.4.

6. (t-Butoxycarbonylmethylene)triphenylphosphorane **503**

This was prepared as in 2. using (t-butoxycarbonylmethyl)triphenylphosphonium bromide (10.0 g, 23 mmol) to furnish the product (4.77 g, 55%) as colourless crystals, mp 155–156 °C (lit.,[145] 154–155 °C); δ_P +17.6.

7. (Allyloxycarbonylmethyl)triphenylphosphonium chloride **500**

This was prepared as in 1 using triphenylphosphine (56.4 g, 215 mmol) and allyl chloroacetate (25 cm^3, 28.4 g, 215 mmol) at room temperature to furnish the product (21.0 g, 25%) as a beige solid, mp 134–136 °C (lit.,[146] 135–137 °C); (Found: M^+–HCl, 360.1265. $C_{23}H_{21}O_2P$ requires *M*$^+$–*HCl*, 360.1279.); ν_{max} /cm^{-1} 3190, 1767, 1689, 1550, 1367, 1265, 1088, 745 and 698; δ_H 7.98–7.66 (15 H, m, 3 x Ph), 5.74–5.55 (3 H, m, PCH_2 + =CH), 5.20–5.09 (2 H, m, CH=CH_2) and 4.46 (2 H, d, *J* 8, CO_2CH_2); δ_C 163.6 (d, *J* 4, CO), 134.5 (=CH), 133.1 (d, *J* 10, 6 x C-2 of P-Ph), 129.7 (C-4 of P-Ph), 129.5 (d, *J* 11, 6 x C-3 of P-Ph), 119.0 (CH=CH_2), 117.1 (d, *J* 89, C-1 of P-Ph), 66.4 (d, *J* 12, CO_2CH_2) and 31.9 (d, *J* 56, PCH_2); δ_P +21.1; *m/z* (EI) 359 (M^+–HCl, 16%), 303 (30), 277 (100), 262 (27), 201 (23), 183 (35), 165 (8) and 152 (13).

8. (Allyloxycarbonylmethylene)triphenylphosphorane **504**

This was prepared as in 2. using (allyloxycarbonylmethyl)triphenylphosphonium chloride (1.0 g, 2.52 mmol) to furnish the product (0.91 g, 98%) as an oil; δ_H 7.78–7.40 (15 H, m, 3 x Ph), 5.82 (1 H, br s, C*H*=CH_2), 5.06 (2 H, m, CH=CH_2) and 4.47 (2 H, d, CO_2CH_2); δ_C 170.1 (d, *J* 12, CO_2), 134.2 (=CH), 132.3 (d, *J* 10, 6 x C-2 of P-Ph), 131.4 (d, *J* 3, C-4 of P-Ph), 128.2 (d, *J* 12, 6 x C-3 of P-Ph), 127.0 (d, *J* 80, C-1 of P-Ph), 115.2

(CH=CH_2), 62.3 (CO_2CH_2) and 29.6 (d, J 126, PCH_2); δ_P +17.9; m/z (EI) 361 (M^+, 38%), 319 (20), 303 (63), 279 (100), 263 (59), 203 (12), 185 (8), 101 (6) and 57 (9).

D Preparation of N-Benzoxycarbonyl and N-Ethoxycarbonyl Protected Amino Acids

Note: In the NMR data of these compounds * is used to denote the signals due to the minor carbamate rotamer.

1. *N*-Benzoxycarbonylglycine **505**

To a stirred solution of glycine (10.0 g, 133 mmol) in 2 M NaOH (68 cm^3, 133 mmol) at 0 °C were added simultaneously benzyl chloroformate (20.9 cm^3, 25.0 g, 147 mmol) and 2M NaOH (68 cm^3, 133 mmol) dropwise. The mixture was stirred at 0 °C for 3 h then washed with ether (150 cm^3). The aqueous phase was acidified with 2M HCl and extracted with ethyl acetate (3 x 150 cm^3). The combined organic phase was dried and the solvent evaporated to furnish the product (9.04 g, 33%) as colourless needles, mp 121–122 °C (lit.,[147] 120 °C); δ_H 7.37 (5 H, s, Ph), 6.75 (1 H, br s), 6.60 (1 H, br s), 5.15 (2 H, s, OCH_2) and 4.02 (2 H, d, J 6, CH_2).

2. (*S*)-*N*-Benzoxycarbonylalanine **506**

Reaction as in 1. using (*S*)-alanine (10.0 g, 112 mmol) and benzyl chloroformate (17.5 cm^3, 20.9 g, 123 mmol) gave the title compound (13.4 g, 54%) as a colourless solid, mp 83–85 °C (lit.,[148] 83–84 °C); δ_H 9.64 (1 H, br s, OH), 7.38 (5 H, s, Ph), 6.83* and 5.40 (1 H, 2 x d, J 8, NH), 5.09 (2 H, s, OCH_2), 4.42 (1 H, m, CH) and 1.46 (3 H, d, J 6, CH_3).

3. (*S*)-*N*-Benzoxycarbonylvaline **507**

Reaction as in 1. using (*S*)-valine (10.0 g, 85 mmol) and benzyl chloroformate (14.1 cm^3, 16.8 g, 94 mmol) gave the title compound (10.0 g, 47%) as a colourless crystals, mp 58-60 °C (lit.,[149] 66-67 °C); δ_H 10.34 (1H, br s, COOH), 7.35 (5 H, s, Ph), 6.41* and 5.34 (1

H, 2 x d, *J* 8, NH), 5.16 (2 H, s, CH_2O), 4.37 and 4.20* (1 H, 2 x m, CHNH), 2.22 (1 H, m, C*H*Me), 1.03 (3 H, d, *J* 7, Me) and 0.95 (3 H, d, *J* 7, Me).

4. (*S,S*)-*N*-Benzoxycarbonylisoleucine **508**

Reaction as in 1. using (*S,S*)-isoleucine (10.0 g, 76 mmol) and benzyl chloroformate (12 cm^3, 14.3 g, 84 mmol) gave the title compound (11.5 g, 62%) as a colourless oil; δ_H 9.03 and 8.63* (1 H, br s, OH), 7.36 (5 H, s, Ph), 6.36* and 5.40 (1 H, br m, NH), 5.13 (2 H, s, CH_2O), 4.38 and 4.22* (1 H, m, C*H*NH), 1.93 (1 H, m, C*H*Me), 1.59–1.09 (2 H, m, CH_2CH_3) and 0.92 (6 H, m, CH*Me* and CH_2Me).

5. (*S*)-*N*-Benzoxycarbonylmethionine **509**

Reaction as in 1. using (*S*)-methionine (5.0 g, 33.5 mmol) and benzyl chloroformate (4.8 cm^3, 5.7 g, 33.5 mmol) gave the title compound (5.2 g , 54%) as a white solid, mp 109–110 °C (lit.,[147] 110–112 °C); δ_H 10.72 (1 H, br s, OH), 7.30 (5 H, s, Ph), 6.78* and 5.59 (1 H, 2 x d, *J* 8, NH), 5.12 (2 H, s, CH_2O), 4.54 and 4.42* (1 H, m, C*H*NH), 2.54 (2 H, m, $CHCH_2$) and 2.29–1.92 (5 H, m, SMe and SCH_2).

6. (*S*)-5-Methyl *N*-benzoxycarbonylglutamate **510**

a 5-Methyl (*S*)-glutamate hydrochloride

(*S*)-Glutamic acid (5.0 g, 34.0 mmol) was suspended in dry methanol (100 cm^3) under a nitrogen atmosphere while trimethylsilyl chloride (9.5 cm^3, 8.1 g, 75 mmol) was added dropwise. After 15 min the solution was evaporated to give the title compound (5.36 g, 80%) as a colourless solid, mp 156–157 °C (lit.,[150] 157–158 °C); δ_H (D_2O) 4.01 (1 H, t, *J* 7, CHN), 3.62 (3 H, s, OMe), 2.54 (2 H, t, *J* 8, CH_2CO) and 2.14 (2 H, m, CH_2).

b. To a stirred solution of 5-methyl (*S*)-glutamate hydrochloride (6.7 g, 34 mmol) in water (35 cm^3) at 0 °C, sodium carbonate (4.0 g, 41 mmol) was added portionwise. When the evolution of carbon dioxide had ceased, benzyl chloroformate (6.00 cm^3, 7.1 g, 41 mmol) and a solution of sodium carbonate (2.2 g, 20 mmol) in water (17 cm^3) were added dropwise

simultaneously to the vigorously stirred mixture. The reaction mixture was allowed to warm to room temperature and left to stir for 3 hr. The mixture was extracted with ether (3 x 50 cm^3) which was discarded. The aqueous layer was acidified to pH 1 and extracted with ethyl acetate (4 x 50 cm^3). The combined extracts were dried and evaporated to yield an oil which solidified after 2 days to give the product (4.5 g, 45%) as colourless crystals, mp 68–70 °C (lit.,[151] 72–73 °C); δ_H 10.69 (1 H, br s, OH), 7.34 (5 H, s, Ph), 6.65* and 5.60 (1 H, br d, NH), 5.09 (2 H, s, OCH_2), 4.42 (1 H, m, C*H*NH), 3.63 (3 H, s, OMe), 2.45 (2 H, m, CH_2) and 2.22 (2 H, m, CH_2).

7. (*S*)-4-Methyl N-benzoxycarbonylaspartate **511**

a. 4-Methyl (*S*)-aspartate hydrochloride

This was prepared as in 6a. using (*S*)-aspartic acid (5.0 g, 37.6 mmol) and trimethylsilyl chloride (10.5 cm^3, 9.0 g, 82.7 mmol) to give 4-methyl (*S*)-aspartate hydrochloride (6.8 g, 95%) as colourless crystals, mp 189–190 °C (lit.,[152] 192–193 °C); δ_H (D_2O) 4.31 (1 H, t, *J* 7, CHN), 3.63 (3 H, s, OMe) and 3.04 (2 H, d, *J* 7, CH_2CO).

b. Reaction as in 6b. using 4-methyl (*S*)-aspartate hydrochloride (8.6 g, 47 mmol) and benzyl chloroformate (8.8 cm^3, 10.5 g, 55 mmol) gave the title compound (3.8 g, 29%) as colourless crystals, mp 97–98 °C (lit.,[153] 98 °C); δ_H 10.42 (1 H, br s, OH), 7.38 (5 H, s, Ph), 5.89 (1 H, br d, NH), 5.04 (2 H, s, OCH_2), 4.65 (1 H, m, C*H*NH), 3.72 (3 H, s, OMe) and 3.05 and 2.88 (2 H, AB pattern of d, *J* 16, 6, CH_2).

8. (*2S*)-(Benzoxycarbonylamino)-4-methylsulfinylbutanoic acid **512**

To a solution of N-benzoxycarbonyl-(*S*)-methionine **509** (1.0 g, 3.5 mmol) in methanol (10 cm^3) at 0 °C was added dropwise a solution of sodium periodate (0.82 g, 3.85 mmol) in water (12 cm^3). The cooling bath was removed and the mixture was stirred for 18 hr. The methanol was evaporated and the aqueous solution was extracted with dichloromethane (2 x 50 cm^3). The organic layer was washed with water (50 cm^3) and brine (50 cm^3), dried and evaporated to yield the title compound (0.75 g, 71%) as a colourless oil, a

1:1 mixture of diastereomers at SO; δ_H 7.32 (5 H, s, Ph), 6.07 (1 H, br m, NH), 5.09 (2 H, s, OCH_2), 4.45 (1 H, m, NHC*H*), 2.84 (2 H, m, CH_2), 2.62/2.58 (3 H, 2 x s, Me) and 2.27 (2 H, m, CH_2); δ_C 172.8 (CO_2H), 155.9 (NHCO), 136.0 (C-1 of Ph), 128.4 (2 C, Ph), 128.0 (3 C, Ph), 66.9 (OCH_2Ph), 52.7/52.4 (CHN), 48.9 (CH_2SO) 37.2/37.0 (SOMe) and 25.8/25.4 (CH_2); *m/z* (CI) 300 (M + H^+, 7%), 282 (8), 236 (9), 206 (5), 192 (25), 176 (7), 155 (9) and 147 (100).

9. (*S,S*)-N-Ethoxycarbonylisoleucine **513**

Reaction as in 1. using (*S,S*)-isoleucine (5.0 g, 38 mmol) and ethyl chloroformate (3.4 cm^3, 4.1 g, 38 mmol) gave the title compound (6.4 g, 83%) as a colourless oil; δ_H 11.17 (1 H, br s, OH), 6.45* and 5.27 (1 H, 2 x d, *J* 8, NH), 4.31 and 4.08* (1 H, m, C*H*NH), 4.09 (2 H, q, *J* 7, OCH_2), 1.91 (1 H, m, C*H*Me), 1.42 (1 H, m, CH_2Me), 1.20 (3 H, t, J 7, OCH_2Me) 1.18 (1 H, m, CH_2Me) and 0.99–0.83 (6 H, m, CH_2Me and CH*Me*).

10. (*S*)-*N*-Ethoxycarbonylmethionine **514**

Reaction as in 1. using (*S*)-methionine (5.0 g, 33.5 mmol) and ethyl chloroformate (3.2 cm^3, 3.8 g, 33.5 mmol) gave the title compound (5.8 g, 84%) as a colourless oil; δ_H 11.12 (1 H, br s, OH), 6.69* and 5.62 (1 H, 2 x d, *J* 8, NH), 4.49 and 4.10* (1 H, br m, C*H*NH), 4.19 (2 H, m, OCH_2), 2.58 (2 H, m, CH_2), 2.09 (3 H, s, SMe), 2.28–1.92 (2 H, m, CH_2) and 1.25 (3 H, t, *J* 7, Me).

11. (*S*)-*N*-Allyloxycarbonylvaline **515**

Reaction as in 1. using (*S*)-valine (5.0 g, 43 mmol) and allyl chloroformate (5 cm^3, 5.74 g, 43 mmol) gave the title compound (6.82 g, 79%) as a colourless oil; (Found: M+H^+, 201.1006. $C_9H_{15}NO_4$ requires *M*+H, 201.1001.); δ_H 8.18 (1 H, br s, COOH), 6.20* and 5.36 (1 H, br d, NH), 5.92 (1 H, m, H_2C=*CH*), 5.60 (2 H, m, H_2C=CH), 4.58 (2 H, d, *J* 6, OCH_2), 4.33 (1 H, dd, *J* 10, 5, *CH*NH), 2.24 (1 H, m, *CH*Me_2), 0.98 (3 H, d, *J* 7, Me) and 0.93 (3 H, d, *J* 7, Me); δ_C 175.9 (CO_2H), 156.3 ($NHCO_2$), 132.4 (H_2C=*C*H), 117.7

(H_2C=CH), 65.9 (OCH_2), 58.7 (NHCH), 30.9 ($CHMe_2$), 18.8 (Me) and 17.2 (Me); *m/z* (CI) 202 ($M+H^+$, 100%), 184 (23), 156 (91), 144 (15), 116 (39) and 112 (11).

12. *N*-Benzoxycarbonyl-α-aminoisobutyric acid **516**

Reaction as in 1 using α-aminoisobutyric acid (5.0 g, 48 mmol) and benzyl chloroformate (7.0 cm^3, 8.3 g, 48 mmol) for 48 hr gave the title compound (2.5g, 22%) as colourless crystals, mp 64–65 °C (lit.,[154] 66–67 °C); δ_H 9.72 (1 H, br s, OH), 7.37 (5 H, s, Ph), 5.49 (1 H, br s, NH), 5.11 (2 H, s, OCH_2) and 1.58 (6 H, s, 2 x Me).

13. *N*-Benzoxycarbonyl-β-alanine **517**

Reaction as in 1. using β-alanine (10.0 g, 112 mmol) and benzyl chloroformate (17.5 cm^3, 20.9 g, 123 mmol) gave the title compound (13.5 g, 54%) as a colourless solid, mp 109–111 °C (lit.,[147] 111–113 °C); δ_H 7.35 (5 H, s, Ph), 6.50 (1 H, br s), 5.13 (2 H, s, OCH_2), 3.42 (2 H, q, *J* 7, CH_2) and 2.48 (2H, t, *J* 7, CH_2).

E Preparation and Pyrolysis of Amino Acid Derived Ylides

1. Preparation of α-ethoxycarbonyl-β-aminoacyl ylides

a. *Ethyl 4-benzoxycarbonylamino-3-oxo 2-triphenylphosphoranylidenebutanoate* **550**

To a stirred solution of (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol) and *N*-benzoxycarbonylglycine (1.09 g, 5.2 mmol) in dry dichloromethane (15 cm^3) at 0 °C was added EDCI (1.0 g, 5.2 mmol) and DMAP (cat.). The mixture was stirred at this temperature for 30 min then allowed to warm up to room temperature. When all the starting material was consumed (monitored by TLC) the mixture was poured into brine, extracted with CH_2Cl_2 (3 x 25 cm^3) and the combined organic extracts dried. The solvent was removed under reduced pressure to give the crude product. Chromatography (ethyl acetate-hexane, 1:1) followed by recrystallisation from ethyl acetate–ether yielded the title compound (0.50 g, 18%) as colourless crystals, mp 132–134 °C (Found: C, 70.9; H, 5.5; N, 2.6. $C_{32}H_{30}NO_5P$ requires C, 71.2; H, 5.6; N, 2.6%); ν_{max} /cm^{-1} 3255, 1735, 1711, 1654, 1376, 1299, 1259,

1106, 743 and 691; δ_H 7.76–7.19 (20 H, m, Ph), 5.86 (1 H, br s, NH), 5.08 (2 H, d, OCH_2Ph), 4.59 and 4.02* (2 H, d, CH_2NH), 3.77 (2 H, m, OCH_2) and 0.73 and 0.67* (3 H, m, Me); δ_C 190.4 (d, *J* 4, P=C–*C*O), 167.3 (d, *J* 15, CO_2Et), 156.1 (NHCO), 137.0 (C-1 of Ph), 133.1 (d, *J* 10, 6 x C-2 of P-Ph), 131.9 (d, *J* 2, 3 x C-4 of P-Ph), 128.6 (d, *J* 12, 6 x C-3 of P-Ph), 128.3 (C-3 of Ph), 128.1 (C-4 of Ph), 127.7 (C-2 of Ph), 125.8 (d, *J* 94, 3 x C-1 of P-Ph), 67.4 (d, *J* 105, P=C), 66.2 (OCH_2Ph), 58.7 (OCH_2), 49.3 (d, *J* 9, CH_2NH) and 13.8 (Me); δ_P +17.8; *m/z* (EI) 540 (M^+, 23%), 492 (5), 375 (100), 303 (39), 262 (14) and 183 (14).

b. Ethyl (*4S*)-4-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenepentanoate **551**

Reaction as in a. using (*S*)-*N*-benzoxycarbonylalanine (1.16 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) yielded the product (0.45 g, 16%) as colourless crystals, mp 150–152 °C (lit.,[138] 140–142 °C); δ_P +17.5 (lit.,[138] δ_P +17.5).

c. *Ethyl 5-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenepentanoate* **562**

Reaction as in a. using *N*-benzoxycarbonyl-β-alanine (1.8 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.8 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) yielded the product (1.7 g, 59%) as colourless crystals, mp 98–100 °C (Found: C, 71.4; H, 5.8; N, 2.6. $C_{33}H_{32}NO_5P$ requires C, 71.6; H, 5.8; N, 2.5%); ν_{max} /cm^{-1} 3272, 1715, 1662, 1552, 1438, 1330, 1264, 1088, 742 and 695; δ_H 7.73–7.24 (20 H, m, Ph), 5.43 (1 H, br s, NH), 5.09 (2 H, s, OCH_2Ph), 3.75 (2 H, q, *J* 7, OCH_2Me), 3.47 (2 H, q, *J* 7, CH_2CO), 3.16 (2 H, t, CH_2NH) and 0.68 (3 H, t, *J* 7, Me); δ_C 195.7 (P=C–*C*O), 167.7 (d, *J* 15, CO_2Et), 156.1 (NHCO), 136.9 (C-1 of Ph), 132.8 (d, *J* 10, 6 x C-2 of P-Ph), 131.5 (d, *J* 3, 3 x C-4 of P-Ph), 128.4 (d, *J* 13, 6 x C-3 of P-Ph), 128.2 (3C of Ph), 127.7 (2C of Ph), 126.2 (d, *J* 93, 3 x C-1 of P-Ph), 71.3 (d, *J* 117, P=C), 65.9 (OCH_2Ph), 58.3 (OCH_2), 39.8 (d, *J* 6,CH_2CH_2N), 37.3 (CH_2CH_2N) and 13.5 (Me); δ_P +17.9; *m/z* (EI) 553

(M^+, 23%), 375 (47), 348 (72), 303 (34), 277 (41), 262 (82), 201 (15), 183 (29) and 86 (100).

d. *Ethyl (4S)-4-benzoxycarbonylamino 5 methyl-3-oxo-2-triphenylphosphoranylidene--hexanoate* **552**

Reaction as in a. using (*S*)-*N*-benzoxycarbonylvaline (1.3 g, 0.01 mol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 0.01 mol), EDCI (1.0 g, 0.01 mol) and DMAP (cat.) yielded the product (1.00 g, 34%) as colourless crystals, mp 145–146 °C; (Found: C, 72.3; H, 6.3; N, 2.4. $C_{35}H_{36}NO_5P$ requires C, 72.3; H, 6.2; N, 2.4%); ν_{max} /cm^{-1} 3390, 1710, 1640, 1550, 1275, 1220, 1090, 1065, 1000, 740, 710 and 680; δ_H 7.79–7.25 (15 H, m, Ph), 5.63 (1 H, d, *J* 9, NH), 5.49 (1 H, m, *CH*NH), 5,07 (2 H, s, OCH_2Ph), 3.76 (2 H, m, OCH_2Me), 2.40 (1 H, br m, CH), 1.05 (3 H, d, CH*Me*), 0.72 (3 H, t, CH_2*Me*) and 0.63 (3 H, d, CH*Me*); δ_C 194.1 (P=C–*C*O), 166.8 (d, *J* 14, CO_2Et), 156.6 (NHCO), 137.0 (C-1 of Ph), 133.1 (d, *J* 10, 6 x C-2 of P-Ph), 131.8 (d, *J* 2, 3 x C-4 of P-Ph), 128.5 (d, *J* 13, 6 x C-3 of P-Ph), 128.3 (2C of Ph), 127.7 (3C of Ph), 126.0 (d, *J* 93, 3 x C-1 of P-Ph), 70.0 (d, *J* 110, P=C), 66.1 (OCH_2Ph), 60.4 (d, *J* 9, CHNH), 58.7 (OCH_2), 32.3 (*CH*Me_2), 20.7 (CH*Me*), 15.9 (CH*Me*) and 13.8 (OCH_2*Me*); δ_P +18.3; *m/z* (FAB) 582 ($M + H^+$, 16%), 492 (5), 375 (100), 303 (39), 262 (14) and 183 (14).

e. *Ethyl (4S,5S)-4-benzoxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylid--eneheptanoate* **553**

Reaction as in a. using (*S,S*)-*N*-benzoxycarbonylisoleucine (1.4 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) yielded the product (0.26 g, 8%) as an oil and as a mixture of carbamate rotamers; (Found: M+H^+, 596.2578. $C_{36}H_{38}NO_5P$ requires *M*+H, 596.2566); $[\alpha]_D^{20}$ +2.4 (*c* 0.5 in CH_2Cl_2); ν_{max} /cm^{-1} 3410, 1719, 1644, 1560, 1485, 1438, 1351, 1279, 1106, 1081, 748 and 692; δ_H 7.76–7.56 (6 H, m, Ph), 7.55–7.37 (9 H, m, Ph), 7.29 (5 H, m, Ph), 5.65 (2 H, m, NH and CH), 5.07 (2 H, s, OCH_2Ph), 3.76 (2 H, m, OCH_2Me), 2.10 (1 H, m, CH), 1.05 (3 H, m, OCH_2Me), 0.87 (2 H, m, $CHCH_2$) and 0.72 (3 H, m, CH_2*Me*) and 0.58

(3 H, d, *J* 8, CH*Me*); δ_C 194.4 (P=C–*C*O), 166.9 (d, *J* 14, *C*O_2Et), 156.6 (NHCO), 137.1 (C-1 of Ph), 133.2 (d, *J* 10, 6 x C-2 of P-Ph), 131.8 (3 x C-4 of P-Ph), 128.5 (d, *J* 12, 6 x C-3 of P-Ph), 128.3 (2 C, Ph), 127.72 (2 C, Ph), 127.67 (1 C, Ph), 126.1 and 126.0* (d, *J* 93, 3 x C-1 of P-Ph), 70.2 and 69.9* (d, *J* 110, P=C), 66.2 (O*C*H_2Ph), 60.7 and 59.4* (d, *J* 8, CHNH), 58.8 (OCH_2), 39.5 and 38.9* (*CH*CH_2), 27.8* and 22.8 (CH*C*H_2Me), 16.8 (CH*Me*), 13.9 (OCH_2*Me*), 12.9* and 12.1 (CH_2*Me*); δ_P +18.33* and +18.28; *m/z* (CI) 596 (M + H^+, 100%), 551 (6), 279 (73), 263 (21), 226 (5), 203 (7), 187 (11) and 107 (10).

f. *Ethyl (4S)-4-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidene-7-thia -octanoate* **554**

Reaction as in a. using *N*-benzoxycarbonyl-(*S*)-methionine (1.47 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) yielded the product (1.07 g, 34%) as colourless crystals, mp 111–112 °C (Found: C, 68.2; H, 6.2; N, 2.1. $C_{35}H_{36}NO_5PS$ requires C, 68.5; H, 5.9; N, 2.3%); $[\alpha]_D^{20}$ +7.9 (*c* 0.5 in CH_2Cl_2); ν_{max} /cm^{-1} 3298, 1710, 1664, 1560, 1440, 1272, 1248, 1104, 1077, 1045, 756 and 688; δ_H 7.75–7.62 (6 H, m, Ph), 7.61–7.43 (9 H, m, Ph), 7.36–7.23 (5 H, m, Ph), 5.88 (1 H, br d, NH), 5.58 (1 H, m, CH), 5.08 (2 H, s, OCH_2Ph), 3.73 (2 H, m, O*C*H_2Me), 2.63 and 1.88 (2 H, AB pattern of m, CH_2), 2.46 (2 H, m, CH_2), 2.10 (3 H, s, SMe) and 0.72 (3 H, t, *J* 7, OCH_2*Me*); δ_C 193.0 (P=C–*C*O), 166.5 (d, *J* 14, *C*O_2Et), 155.8 (NHCO), 136.7 (C-1 of Ph), 132.9 (d, *J* 10, 6 x C-2 of P-Ph), 131.8 (d, *J* 2, 3 x C-4 of P-Ph), 128.4 (d, *J* 12, 6 x C-3 of P-Ph), 128.1 (2 C, Ph), 127.5 (3 C, Ph), 125.6 (d, *J* 93, 3 x C-1 of P-Ph), 69.3 (d, *J* 109, P=C), 66.0 (O*C*H_2Ph), 58.6 (OCH_2), 56.0 (d, *J* 8, CHNH), 34.7 (CH*C*H_2), 30.2 (CH_2S), 15.4 (SMe) and 13.6 (Me); δ_P +18.1; *m/z* (CI) 614 (M + H^+, 78%), 568 (15), 506 (39), 434 (22), 354 (8), 319 (6), 279 (22), 263 (100), 243 (11), 201 (10) and 187 (59).

g. *1-Ethyl 7-methyl (4S)-4-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidene--heptanedioate* **555**

Reaction as in a. using 5-methyl (*S*)-*N*-benzoxycarbonylglutamate (1.54 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) followed by recrystallisation from ethyl acetate/ether yielded the product (0.65 g, 22%) as colourless crystals, mp 123–125 °C (Found: C, 69.0; H; 5.8, N; 2.1. $C_{36}H_{36}NO_7P$ requires C, 69.1; H, 5.8; N, 2.2%); $[\alpha]_D^{20}$ +0.91 (*c* 1.38 in CH_2Cl_2); ν_{max} /cm^{-1} 3273, 1735, 1681, 1654, 1594, 1294, 1265, 1103, 1084, 734 and 690; δ_H 7.74–7.60 (6 H, m, Ph), 7.52–7.38 (9 H, m, Ph), 7.25 (5 H, s, Ph), 5.83 (1 H, br d, NH), 5.54 (1 H, br m, C*H*NH), 5.06 (2 H, s, OCH_2Ph), 3.69 (2 H, m, OCH_2Me), 3.56 (3 H, s, OMe), 2.50 (2 H, m, CH_2), 1.96 (2 H, m, CH_2) and 0.72 (3 H, t, *J* 7, Me); δ_C 193.0 (P=C–*C*O), 174.0 (CO_2Me), 166.5 (d, *J* 14, *C*O_2Et), 155.9 (NHCO), 136.7 (C-1 of Ph), 132.9 (d, *J* 10, 6 x C-2 of P-Ph), 131.8 (C-4 of P-Ph), 128.4 (d, *J* 13, 6 x C-3, P-Ph), 128.1 (2 C, Ph), 127.5 (3 C, Ph), 125.6 (d, *J* 93, 3 x C-1 of P-Ph), 69.3 (d, *J* 110, P=C), 66.0 (OCH_2Ph), 58.6 (OCH_2), 55.7 (d, *J* 8, CHNH), 51.2 (OMe), 30.5 (CH_2), 29.8 (CH_2) and 13.6 (Me); δ_P +18.1; *m/z* (CI) 626 (M + H^+, 76%), 594 (7), 518 (35), 414 (9), 348 (7), 279 (100), 263 (91), 243 (7), 203 (8), 187 (42) and 147 (51).

h. *1-Ethyl 6-methyl (4S)-4-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidene--hexanedioate* **556**

Reaction as in a. using 4-methyl (S)-*N*-benzoxycarbonyl-(*S*)-aspartate (1.46 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) followed by recrystallisation from ethyl acetate/ether yielded the product (0.32 g, 10%) as colourless crystals, mp 135–137 °C (Found: C, 68.9; H; 5.7, N; 2.5. $C_{35}H_{34}NO_7P$ requires C, 68.7; H, 5.6; N, 2.3%); $[\alpha]_D^{20}$ +7.5 (*c* 0.4 in CH_2Cl_2); νmax /cm^{-1} 3404, 1719, 1664, 1560, 1485, 1352, 1278, 1169, 1105, 1085, 1028, 749 and 693; δ_H 7.76–7.59 (6 H, m, Ph), 7.55–7.38 (9 H, m, Ph), 7.22 (5 H, s, Ph), 5.90 (1 H, br m, NH), 5.75 (1 H, br m, C*H*NH), 5.06 (2 H, s, OCH_2Ph), 3.72 (2 H, m, OCH_2Me), 3.55 (3 H, s, OMe), 3.10 (1 H, half AB pattern of d, *J* 14, 5), 2.82 (1 H, half AB pattern of d, *J* 14, 7) and

0.72 (3 H, t, *J* 7, Me); δ_C 192.0 (P=C–*C*O), 171.5 (*C*O_2Me), 166.8 (d, *J* 14, *C*O_2Et), 155.7 (NHCO), 137.0 (C-1 of Ph), 133.2 (d, *J* 10, 6 x C-2 of P-Ph), 131.9 (C-4 of P-Ph), 128.6 (d, *J* 13, 6 x C-3 of P-Ph), 128.3 (2 C, Ph), 127.7 (3 C, Ph), 125.8 (d, *J* 94, 3 x C-1 of P-Ph), 69.4 (d, *J* 110, P=C), 66.2 (OCH_2Ph), 58.8 (OCH_2), 53.7 (d, *J* 9, CHNH), 51.5 (OMe), 38.6 (CH_2) and 13.7 (Me); δ_P +18.2; *m/z* (CI) 612 (M + H^+, 100%), 504 (6), 432 (16), 375 (5), 352 (8), 334 (7), 279 (50), 263 (66), 203 (6), 187 (28) 172 (5) and 147 (9).

i. *Ethyl (4S)-4-benzoxycarbonylamino-3,7-dioxo-2-triphenylphosphoranylidene-7-thia--octanoate* **557**

Reaction as in a. using (2*S*)-2-(benzoxycarbonylamino)-4-methylsulfinylbutanoic acid (0.35 g, 1.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (0.22 g, 1.2 mmol) and DMAP (cat.) yielded the product (0.15 g, 20%) as an oil; (Found: M+H+O$^+$, 646.2014. $C_{35}H_{36}NO_6PS$ requires *M*+H+O, 646.2028); $[\alpha]_D^{20}$ +1.87 (*c* 0.2 in CH_2Cl_2) ν_{max} /cm^{-1} 3377, 2955, 1719, 1656, 1561, 1439, 1370, 1301, 1106 and 693; δ_H 7.8–7.5 (15 H, m), 7.35–7.25 (5 H, m), 5.94 (1 H, br d, *J* 8, NH), 5.59 (1 H, m, CH), 5.05 (2 H, s, OCH_2), 3.71 (2 H, q, *J* 7, O*C*H_2Me), 3.22 (1 H, half AB pattern of m), 2.93 (3 H, s, SMe), 2.68 (2 H, m, CH_2), 2.11 (1 H, half AB pattern of m) and 0.69 (3 H, t, *J* 7, Me); δ_C 191.7 (P=C–*C*O), 166.6 (d, *J* 13, *C*O_2Et), 156.2 (NHCO), 136.7 (C-1 of Ph), 133.2 (d, *J* 10, 6 x C-2 of P-Ph), 132.2 (d, *J* 2, 3 x C-4 of P-Ph), 128.8 (d, *J* 12, 6 x C-3 of P-Ph), 128.4 (2 C of Ph), 127.9 and 127.8 (3 C of Ph of 2 diastereomers), 125.5 (d, *J* 94, 3 x C-1, P-Ph), 69.6 (d, *J* 109, P=C), 66.5 (O*C*H_2Me), 58.9 (OCH_2), 54.9 (d, *J* 8, CHNH), 51.5 (CH_2SO), 40.5 (SOMe), 27.8 (CH*C*H_2) and 13.6 (OCH_2*Me*); δ_P +18.2; *m/z* (CI) 646 (M + H^++ O, 10%), 463 (14), 368 (10), 279 (100), 263 (40), 187 (6), 147 (18), 107 (32) and 81 (20).

j. *Ethyl (4S, 5S)-4-ethoxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylidene--heptanoate* **558**

Reaction as in a. using (*S, S*)-*N*-ethoxycarbonylisoleucine (1.06 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol)

and DMAP (cat.) followed by recrystallisation from ethyl acetate/ether yielded the product as colourless crystals (0.58 g, 21%), mp 148–149 °C (Found: C, 69.7; H, 6.7; N, 2.7. $C_{31}H_{36}NO_5P$ requires C, 69.8; H, 6.8 N; 2.6%); $[\alpha]_D^{20}$ +6.1 (*c* 1.9 in CH_2Cl_2); ν_{max} /cm^{-1} 3386, 1705, 1666, 1588, 1494, 1438, 1222, 1072, 744 and 688; δ_H 7.72–7.64 (6 H, m, Ph), 7.57–7.48 (3 H, m, Ph), 7.47–7.41 (6 H, m, Ph), 5.55 (1 H, m, NH), 5.47 (1 H, m, CHN), 4.05 (2 H, q, *J* 7, OCH_2), 3.79 (2 H, m, OCH_2), 1.64 (1 H, m, CH), 1.17 (3 H, t, *J* 7, OCH_2Me), 1.10–0.95 (3 H, m, CH_2Me), 0.86 (2 H, m, $CHCH_2$), 0.74 (3 H, t, *J* 7, OCH_2Me) and 0.58 (3 H, d, *J* 7, CHMe); δ_C 193.9 (P=C–*C*O), 163.3 and 166.2* (d, *J* 14, CO_2Et), 156.4 (NHCO), 132.6 (d, *J* 10, 6 x C-2 of P-Ph), 131.2 (3 x C-4 of P-Ph), 127.9 (d, *J* 12, 6 x C-3 of P-Ph), 125.65 and 125.6* (d, *J* 110, 3 x C-1 of P-Ph), 60.0 and 58.6* (d, *J* 8, CHNH), 59.7 (OCH_2), 58.1 (OCH_2), 38.9 and 38.3* (*C*HMe), 27.3 and 22.2* ($CHCH_2$), 16.2 (CH*Me*), 14.1 (OCH_2Me), 13.3 (OCH_2Me) and 12.3 and 11.6* ($CHCH_2Me$); δ_P +18.3, 18.2*; *m/z* (CI) 534 (M + H^+, 100 %), 488 (11), 263 (11) and 183 (12).

k. *Ethyl (4S)-4-ethoxycarbonylamino-3-oxo-2-triphenylphosphoranylidene-7-thiaoctan -oate* **559**

Reaction as in a. using (*S*)-*N*-ethoxycarbonylmethionine (1.08 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) followed by recrystallisation from ethyl acetate/ether yielded the product (0.5 g, 17%) as colourless crystals, mp 118–120 °C (Found: M+H^+, 552.1967. $C_{30}H_{34}NO_5PS$ requires *M*+H, 552.1974); $[\alpha]_D^{20}$ +48.8 (*c* 2.0 in CH_2Cl_2); ν_{max} /cm^{-1} 3390, 1700, 1658, 1588, 1566, 1372, 1294, 1277, 1088, 761 and 677; δ_H 7.71–7.60 (6 H, m, Ph), 7.59–7.51 (3 H, m, Ph), 7.50–7.39 (6 H, m, Ph), 5.65 (1 H, br d, NH), 5.5 (1 H, m, CH), 4.14 (2 H, q, *J* 7, OCH_2), 3.75 (2 H, q, *J* 7, OCH_2), 2.63 and 1.81 (2 H, AB pattern of m, CH_2), 2.46 (2 H, m, CH_2), 2.08 (3 H, s, SMe), 1.18 (3 H, t, *J* 7, Me) and 0.73 (3 H, t, *J* 7, Me); δ_C 193.1 (P=C–*C*O), 163.3 (d, *J* 14, CO_2Et), 156.0 (NHCO), 132.7 (d, *J* 10, 6 x C-2 of P-Ph), 131.5 (d, *J* 2, 3 x C-4 of P-Ph), 128.2 (d, *J* 13, 6 x C-3 of P-Ph), 125.5 (d, *J* 93, 3 x C-1, P-Ph), 68.9 (d, *J* 110, P=C), 59.9 (OCH_2), 58.3 (OCH_2), 55.8 (d, *J* 8, CHNH), 34.6 ($CHCH_2$), 30.1 (CH_2S), 15.2 (SMe), 14.2 (Me) and 13.6 (Me); δ_P +18.1; *m/z* (CI) 552 (M +

H^+, 100%), 506 (27), 467 (23), 369 (13), 291 (12), 263 (22), 247 (17), 201 (22), 187 (32), 159 (29) and 147 (72).

l. *Ethyl (4S)-4-t-butoxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylidene hexanoate* **560**

Reaction as in a. using (*S*)-*N*-t-butoxycarbonylvaline (1.13 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) yielded the product (1.10 g, 39 %) as a colourless oil; (Found: M+H^+, 548.2553. $C_{32}H_{38}NO_5P$ requires *M*+H, 548.2566); $[\alpha]_D^{20}$ +30.6 (*c* 1.14 in CH_2Cl_2); ν_{max} /cm^{-1} 3415, 1715, 1664, 1556, 1461, 1375, 1282, 1170, 1079, 710 and 691; δ_H 7.74–7.63 (6 H, m, Ph), 7.58–7.50 (3 H, m, Ph), 7.49–7.41 (6 H, m, Ph), 5.42–5.28 (2 H, m, NH and*CH*NH), 3.80 (2 H, m, O*CH*$_2$Me), 2.42 (1 H, br m, CH), 1.41 (9 H, s, CMe_3), 1.09 (3 H, d, *J* 7, CH*Me*), 0.78 (3 H, t, *J* 7, CH_2*Me*) and 0.63 (3 H, d, *J* 7, CH*Me*); δ_C 194.1 (P=C–*C*O), 166.1 (d, *J* 14, *C*O_2Et), 155.6 (NHCO), 132.5 (d, *J* 10, 6 x C-2 of P-Ph), 131.2 (3 x C-4 of P-Ph), 127.9 (d, *J* 12, 6 x C-3 of P-Ph), 125.6 (d, *J* 94, 3 x C-1 of P-Ph), 69.3 (d, *J* 109, P=C), 59.6 (*C*Me_3), 59.3 (d, *J* 8, CHNH), 57.9 (O*C*H_2Me), 31.7 (*C*HMe_2), 27.8 (C*Me*$_3$), 20.2 (CH*Me*), 15.3 (CH*Me*) and 13.2 (CH_2*Me*); δ_P +17.9; *m/z* (CI) 548 (M + H^+, 60%), 472 (7), 340 (6), 299 (5), 263 (11), 241 (60), 190 (20), 173 (12), and 146 (6).

m. *Allyl (4S)-4-ethoxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylidinehex anoate* **561**

Reaction as in a. using (*S*)-*N*-allyloxycarbonylvaline (1.04 g, 5.2 mmol), (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) yielded the product (1.09 g, 39 %) as a colourless crystals, mp 147–148 °C; (Found: C, 69.9; H, 6.5; N, 2.6. $C_{31}H_{34}NO_5P$ requires C, 70.0; H, 6.5; N, 2.6%); $[\alpha]_D^{25}$ +1.38 (*c* 1.38 in CH_2Cl_2); ν_{max} /cm^{-1} 3398, 2925, 1708, 1658, 1595, 1489, 1373, 1287, 1227, 1187, 1080, 756 and 696; δ_H 7.71–7.35 (15 H, m, Ph), 5.86 (1 H, m, C*H*=CH_2), 5.60* and 5.54 (1 H, br s, NH), 5.45 and 5.42* (1 H, 2 x d, J 3, CHN), 5.25–5.05 (2 H, m, CH=CH_2), 4.47 (2 H, d, *J* 5, OCH_2CH=), 3.89–3.57 (2 H, m, OCH_2Me), 2.37 (1 H, m,

*CH*Me$_2$), 1.02 (3 H, d, *J* 7, CH*Me*), 0.70 (3 H, t, *J* 7, CH$_2$*Me*) and 0.60 (3 H, d, *J* 7, CH*Me*); δ_C 193.9 (P=C–*C*O), 166.6 (d, *J* 12, *C*O$_2$allyl), 156.2 (NHCO), 133.0 (*C*H=CH$_2$), 132.8 (d, *J* 10, 6 x C-2 of P-Ph), 131.5 (d, *J* 3, 3 x C-4 of P-Ph), 128.2 (d, *J* 13, 6 x C-3 of P-Ph), 125.7 (d, *J* 93, 3 x C-1 of P-Ph), 116.4 (CH=*C*H$_2$), 69.5 (d, *J* 110, P=C), 64.6 (O*C*H$_2$CH=), 59.9 (d, *J* 9, CHNH), 58.2 (O*C*H$_2$Me), 31.8 (*C*HMe$_2$), 22.6 (CH*Me*), 15.4 (CH*Me*) and 13.3 (CH$_2$*Me*); δ_P +18.2; *m/z* (CI) 532 (M + H$^+$, 40%), 486 (7), 456 (12), 375 (14), 279 (52), 226 (17), 187 (23), 146 (100), and 128 (26).

2. Pyrolysis of α-ethoxycarbonyl-β-aminoacyl ylides

a. *(4S)-1-ethyl 7-methyl 4-(benzyloxycarbonylamino)hept-2-yne-1,7-dioate* **565**

FVP of the ylide **555** (80 mg, 0.13 mmol, 600 °C, 3 x 10^{-3} Torr) gave a dark solid at the furnace exit which was shown by ^{1}H and ^{31}P NMR to be a mixture of Ph$_3$PO and the desired product. Chromatography on silica (ether–petroleum 40-60 1:1) gave the title product as a colourless oil (10 mg, 22%); (Found: M+H$^+$, 348.1438. C$_{18}$H$_{22}$NO$_6$ requires *M*+H, 348.1447); $[\alpha]_D^{20}$ –18.4 (*c* 0.54 in CH$_2$Cl$_2$); ν_{max} /cm^{-1} 3324, 2962, 2242, 1713, 1524, 1451, 1376, 1261, 1103, 1024, 800 and 699; δ_H 7.60 (5 H, s, Ph), 5.50 (1 H, br d, NH), 4.65 (1 H, m, NHC*H*), 4.16 (2 H, q, *J* 7, OC*H*$_2$Me), 3.62 (3 H, s, OMe), 2.44 (2 H, m, CH$_2$), 2.02 (2 H, m, CH$_2$) and 1.22 (3 H, t, *J* 7, OCH$_2$*Me*); δ_C 172.9 (CO$_2$Me), 155.2 (CO$_2$), 153.0 (NHCO), 135.9 (C-1 of Ph), 128.5 (Ph), 128.3 (Ph), 128.2 (Ph), 84.9 (C≡C), 75.7 (C≡C), 67.3 (O*C*H$_2$Ph), 62.2 (O*C*H$_2$Me), 51.9 (OMe), 42.7 (NHCH), 30.1 (CH$_2$), 29.7 (CH$_2$) and 14.0 (OCH$_2$*Me*); *m/z* (CI) 348 (M + H$^+$, 7%), 304 (67), 276 (24), 258 (8), 240 (9), 232 (68), 200 (9), 149 (16), and 91 (100).

b. Attempted FVP of ylide **555** (large scale)

FVP of the ylide **555** (0.3 g, 0.48 mmol, 600 °C, 4.8 x 10^{-3} Torr) gave a yellow oil in the cold trap which was shown by ^{1}H and ^{31}P NMR to be a mixture of Ph$_3$PO, benzyl alcohol and ethanol.

Benzyl alcohol δ_H 7.35 (5 H, s, Ph) and 4.68 (1 H, s, CH$_2$).

Ethanol δ_H 3.72 (2 H, q, OCH$_2$) and 1.23 (3 H, t, Me).

c. Attempted FVP of ylide **550**

(i) FVP of the ylide **550** (0.34 g, 0.63 mmol, 600 °C, 8.0 x 10^{-3} Torr) gave a brown oil in the cold trap which was shown by ^{1}H and ^{31}P NMR to be a mixture of benzyl alcohol, ethanol and Ph_3PO. The furnace exit contained Ph_3PO only and the inlet tube contained unreacted starting material.

(ii). FVP of the ylide **550** (0.34 g, 0.63 mmol, 500 °C, 8.0 x 10^{-3} Torr) gave a yellow oil in the cold trap which was shown by ^{1}H NMR to be a mixture of benzyl alcohol and ethanol. The furnace exit contained a mixture of mainly Ph_3PO and some unidentified product as shown by ^{1}H and ^{31}P NMR.

d. FVP of the ylide **554**

(i). FVP of the ylide **554** (0.23 g, 550 °C, 5 x 10^{-3} Torr) gave a black oil at the furnace exit which was shown by ^{1}H and ^{31}P NMR to be a mixture of Ph_3PO, Ph_3P and Ph_3PS δ_P –5.2, +29.9 and +43.6. The inlet tube contained a black solid (0.11 g) which seemed like two cyclic products **570** and **571** by ^{1}H and ^{13}C NMR.

570; δ_H 7.7–7.4 (15 H, m), 3.95 (1 H, m, C*H*NH), 2.60 (2 H, m) and 2.1–1.9 (5 H, m); δ_C 196.3 (d, *J* 7, CO), 176.5 (d, *J* 16, NHCO), 134.1 (d, *J* 11, 6 x C-2 of P-Ph), 133.0 (3 x C-4 of P-Ph), 128.9 (d, *J* 13, 6 x C-3 of P-Ph), 123.0 (d, *J* 93, 3 x C-1 of P-Ph), 61.7 (d, *J* 13, CHNH), 32.0, 30.6 (CH_2S), 29.0 (d, *J* 98, P=C) and 15.3 (SMe); δ_P +10.7

571; δ_H 7.7–7.4 (15 H, m), 5.6 (1 H, m, =CH), 5.3 (2 H, m, $=CH_2$) and 4.3 (1 H, m, C*H*NH); δ_P +11.1.

The pyrolysis at 600 °C and 500 °C gave mainly Ph_3P, Ph_3PO, Ph_3PS and unidentified products.

e. (i) Preparation of (4S)-ethyl 4-(benzoxycarbonylamino)pent-2-ynoate **572**

FVP of the ylide **551** (1.00 g, 1.8 mmol, 600 °C, 5 x 10^{-3} Torr) gave a yellow liquid in the cold trap which was shown by ^{1}H NMR to contain mainly benzyl alcohol and ethanol. A beige solid was found at the furnace exit and was shown by ^{1}H and ^{31}P NMR to be a

mixture of Ph_3PO and two products. Chromatography on silica (ether–hexane ,1:2) gave and the title compound (90 mg, 18 %) as a pale yellow oil; δ_H 7.40 (5 H, s, Ph), 5.14 (2 H, s, OC*H*$_2$Ph), 5.06 (1 H, br d, NH), 4.72 (1 H, m, NHC*H*), 4.24 (2 H, q, *J* 7, OC*H*$_2$Me), 1.48 (3 H, d, *J* 7, CH*Me*) and 1.32 (3 H, t, *J* 7, OCH$_2$*Me*); δ_C 155.6 (CO_2), 152.8 (NHCO), 136.0 (C-1 of Ph), 128.5 (2 C), 128.4 (C-4 of Ph), 128.3 (2 C), 87.0 (C≡C), 74.2 (C≡C), 67.0 (O*C*H$_2$Ph), 62.0 (O*C*H$_2$Me), 38.7 (NHCH), 21.4 (CH*Me*) and 16.3 (OCH$_2$*Me*) (^{1}H and ^{13}C NMR as lit.,[138]).

(ii) Procedure as above to get the terminal alkyne (3S)-3-(benzoxycarbonylamino)but-1-yne **573** as a yellow oil (56 mg, 15%); (Found: M$^+$, 203.0954. $C_{12}H_{13}NO_2$ requires *M*$^+$, 203.0946.); $[\alpha]_D^{22}$ –3.43 (*c* 0.84 in CH_2Cl_2); ν_{max} /cm^{-1} 3405, 2926, 2253, 1708, 1525, 1224, 1049, 752 and 698; δ_H 7.40 (5 H, s, Ph), 5.14 (2 H, s, OC*H*$_2$Ph), 5.06 (1 H, br d, NH), 4.72 (1 H, m, NHC*H*), 2.62 (1 H, d, *J* 2, ≡CH) and 1.48 (3 H, d, *J* 7, CH*Me*); δ_C 155.2 (CO_2), 136.2 (Ph C-1), 128.5 (2 C), 128.2 (Ph C-4), 128.1 (2 C), 84.1 (*C*≡CH), 70.6 (C≡*C*H), 67.0 (O*C*H$_2$Ph), 38.9 (NH*C*H) and 22.5 (Me); *m/z* (EI) 203 (M$^+$, 8%), 149 (9), 112 (5), 108 (80), 91 (100), 79 (16) and 65 (14).

f. Pyrolysis of ylide **551** at increased pressure

FVP of the ylide **551** (1.20 g, 600 °C, 2 x 10^{-1} Torr) gave a black solid in the inlet tube which proved to be (5S)-1-benzoxycarbonylamino-5-methyl-3-triphenylphos phoranylidenepyrrolidine-2,4-dione **574** as a black oil (0.62 g, 77%); (Found: M$^+$, 507.1589. $C_{31}H_{26}NO_4P$ requires *M*$^+$, 507.1599.); $[\alpha]_D^{22}$ +0.5 (*c* 0.02 in CH_2Cl_2); ν_{max} /cm^{-1} 3413, 2927, 1733, 1601, 1461, 1377, 1289, 1124, 1073, 722 and 690; δ_H 7.73–7.20 (20 H, s, 4 x Ph), 5.30 and 5.24 (2 H, AB pattern, *J* 10, OC*H*$_2$Ph), 4.26 (1 H, m, NHC*H*) and 1.38 (3 H, d, *J* 7, Me); δ_C 194.4 (d, *J* 6, 4-CO), 170.5 (d, *J* 17, 2-CO), 151.1 (NCO_2), 136.2 (C-1 of Ph), 134.2 (d, *J* 11, C-2 of P-Ph), 133.2 (d, *J* 2, C-4 of P-Ph), 129.0 (d, *J* 13, C-3 of P-Ph), 128.5 (2 C), 128.2 (2 C), 128.0 (C-4 of Ph), 122.1 (d, *J* 93, 3 x C-1 of P-Ph), 77.1 (d, *J* 122, P=C), 67.2 (O*C*H$_2$Ph), 61.0 (d, *J* 11, NCH) and 17.9 (Me); δ_P +11.1; *m/z* (EI) 507 (M$^+$, 7%), 373 (38), 301 (63), 277 (72), 262 (100), 201 (18), 183 (55), 165 (18), 149 (43), 108 (14) and 91 (47).

g. (i) *Preparation of (4S)-ethyl 4-(benzoxycarbonylamino)-5-methylhex-2-ynoate* **575**

FVP of the ylide **552** (0.3 g, 0.5 mmol, 600 °C, 2 x 10^{-2} Torr) gave a brown solid at the furnace exit which was shown by ^{1}H and ^{31}P NMR to be a mixture of Ph_3PO and other products. Chromatography on silica (ether–hexane, 1:2) gave in addition to Ph_3PO three other products :

the pure title compound (91 mg, 58 %) as colourless crystals, mp 60–62 °C;δ_H 7.38 (5 H, s, Ph), 5.10 (3 H, br s, OCH_2Ph and NH), 4.53 (1 H, m, NHC*H*), 4.21 (2 H, q, *J* 7, OCH_2Me), 1.98 (1 H, m, C*H*Me_2), 1.27 (3 H, t, *J* 7, OCH_2*Me*) and 1.02 (6 H, m, CH*Me*$_2$); δ_C 155.6 (CO_2), 153.8 (NHCO), 136.1 (Ph, C-1), 128.6 (2 C), 128.3 (Ph, C-4), 128.2 (2 C), 85.1 (C≡), 75.8 (C≡), 67.1 (OCH_2Ph), 62.0 (OCH_2Me), 49.0 (NHCH), 32.8 (*C*HMe_2), 18.4 (CH*Me*), 17.7 (CH*Me*) and 13.8 (OCH_2*Me*) (^{1}H and ^{13}C NMR as lit.,[138]).

(ii) *(3S)-3-Benzoxycarbonylamino-4-methylpent-1-yne* **576**

Procedure as above to form the title product after chromatography as a colourless oil (13 mg, 10%) (Found: M^+, 231.1253. $C_{14}H_{17}NO_2$ requires *M*$^+$, 231.1259.); $[\alpha]_D^{22}$ –2.7 (*c* 0.25 in CH_2Cl_2); ν_{max} /cm^{-1} 3307, 2963, 2243, 1708, 1526, 1467, 1238, 1028, 754 and 697; δ_H 7.37 (5 H, s, Ph), 5.11 (2 H, s, OCH_2), 4.92 (1 H, br s, NH), 4.37 (1 H, m, NHC*H*), 2.28 (1 H, d, *J* 2, ≡CH), 1.92 (1 H, m, C*H*Me_2) and 0.98 (6 H, d, *J* 8, CH*Me*$_2$); δ_C 155.5 (NHCO), 136.2 (Ph C-1), 128.5 (2 C), 128.2 (2 C), 125.5 (Ph C-4), 81.6 (*C*≡CH), 72.1 (C≡*C*H), 67.0 (OCH_2Ph), 49.1 (NHCH), 32.8 (*C*HMe_2), 18.6 (CH*Me*) and 17.5 (CH*Me*); *m/z* (EI) 231 (M^+, 3%), 188 (8), 144 (11), 108 (13), 91 (100), and 65 (6).

(iii) *(E)-ethyl 4-benzoxycarbonylamino-5-methylhexa-2,4-dienoate* **577**

Procedure as above to form the title product after chromatography as a yellow oil (18 mg, 11%); (Found: M^+–$PhCH_2$, 212.0931. $C_{17}H_{21}NO_4$ requires *M–PhCH*$_2$, 212.0923.); ν_{max} /cm^{-1} 3322, 2981, 1728, 1625, 1371, 1279, 1176, 1029, 747 and 699; δ_H 7.80 (1 H, d, *J* 15, HC=), 7.38 (5 H, s, Ph), 5.88 (1 H, d, *J* 15, HC=), 5.68 (1 H, br s, NH), 5.16 (2 H, s, CH_2Ph), 4.20 (2 H, q, *J* 7, OCH_2Me), 2.03 (3 H, s, Me), 1.86 (3 H, s, Me) and 1.32 (3 H, t, *J* 7, OCH_2*Me*); δ_C 167.3 (CO_2), 154.3 (NHCO), 144.3 (NH*C*=), 138.8 (=CH), 136.2 (Ph C-

1), 128.6 (2 C), 128.2 (2 C), 127.6 (Ph C-4), 125.9 (=*C*Me$_2$), 116.7 (=CH), 67.2 (O*C*H$_2$Ph), 60.4 (O*C*H$_2$Me), 21.5 (CH*Me*), 20.3 (CH*Me*) and 14.3 (Me)

h. FVP of the ylide **552**

(i). FVP of the ylide **552** (58 mg, 650 °C, 1 x 10^{-2} Torr) gave a beige solid at the furnace exit which was shown by ^{1}H and ^{31}P NMR to be a mixture of Ph_3PO, benzyl alcohol and the acetylenic ester **575**. In the cold trap a mixture of benzyl alcohol, the acetylenic ester **575** and the terminal alkyne **576** were found.

(ii). FVP of the ylide **552** (85 mg, 700 °C, 1.2 x 10^{-2} Torr) gave a beige solid at the furnace exit which was shown by ^{1}H and ^{31}P NMR to be mainly Ph_3PO. In the cold trap a mixture of benzyl alcohol, the terminal alkyne **576** and an allene product were found.

(iii). FVP of the ylide **552** (110 mg, 750 °C, 1.2 x 10^{-2} Torr) gave a brown solid at the furnace exit which was shown by ^{1}H and ^{31}P NMR to be mainly Ph_3PO. In the cold trap mainly benzyl alcohol was found. Most of the material was in the inlet tube which was mainly unreacted starting material and a small amount of both the cyclic product analogous to **574**; δ_P +10.7 and the terminal alkyne **576**; (Found: M+H$^+$, 232.1349. $C_{14}H_{18}NO_2$ requires *M*+H, 232.1338.); *m/z* (CI) 232 (M+H$^+$, 25%), 221 (7), 213 (45) and 91 (100).

F Further Transformations - Towards Chiral 1,4-Diamines

1. Hydrogenation of ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate **575**

a. To a solution of ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate **14** (0.35 g, 1.2 mmol) in methanol (15 cm^3) was added 10% Pd/C catalyst (0.16 g) and the mixture was stirred under a hydrogen atmosphere for several hours. The mixture was filtered through Celite and the filtrate concentrated to give the crude product (0.2 g), (*5S*)-5-isopropylpyrrolidin-2-one **597** as a yellow oil; δ_H 7.48 (1 H, br s, NH), 3.33 (1 H, q, *J* 8, NHC*H*), 2.28 (3 H, m, CH$_2$ + C*H*Me$_2$), 1.62 (2 H, m, CH$_2$), 0.87 (3 H, d, J 7, Me) and 0.78 (3 H, d, J 7, Me); δ_C 179.1

(NHCO), 60.6 (CHN), 33.2 (*C*HMe$_2$) 30.4 (CH_2CO), 24.3 ($CHCH_2$) 18.8 (CH*Me*) and 17.8 (CH*Me*).

b. To a solution of ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate **575** (0.12 g, 0.66 mmol) in AR methanol (10 cm^3) was added 10% Pd/C catalyst (0.1 g) and the mixture was stirred under a hydrogen atmosphere for several hours. The mixture was filtered through Celite and the filtrate concentrated to give the crude product (0.1 g) as a 2:1 mixture of the cyclic product **597**; spectra as above, and ethyl (*4S*)-4-amino-5-methylhexanoate **594**; δ_H 7.28 (2 H, br s, NH_2), 4.20 (2 H, q, *J* 7, OCH_2), 3.12 (1 H, m, C*H*NH_2), 2.51 (1 H, m, *CH*Me$_2$), 2.11 (2 H, m, CH_2), 1.70 (2 H, m, CH_2), 1.22 (3 H, t, *J* 7, OCH_2*Me*), 1.04 (3 H, d, *J* 7, CH*Me*) and 0.84 (3 H, d, *J* 7, CH*Me*); δ_C 172.6 (CO), 60.6 ($CHNH_2$), 56.9 (OCH_2), 33.4 (*C*HMe$_2$) 30.4 (CH_2CO_2), 24.3 ($CH_2CH_2CO_2$), 17.9 (CH*Me*), 17.8 (CH*Me*) and 14.1 (OCH_2*Me*).

2. Attempted ring opening of **597** to the ester **594**

The cyclic product **597** (0.2 g, 1.6 mmol) was heated under reflux with excess $SOCl_2$ (2 cm^3) in ethanol (15 cm^3) for one hour. The solution was concentrated and a pale brown solid was obtained (0.18 g) which appeared to be the hydrochloride of (*4S*)-4-amino-5-methylhexanoic acid **599**; δ_H 11.58 (3 H, br s, NH_3^+), 10.12 (1 H, br s, OH), 4.12 (1 H, m), 2.89 (2 H, t, *J* 7), 2.31 (1 H, m, C*H*Me$_2$), 1.93 (2 H, m), 1.03 (3 H, d, *J* 7, CH*Me*) and 0.98 (3 H, d, *J* 7, CH*Me*); δ_C 180.9 (CO), 64.4 (CHN), 31.8 (*C*HMe$_2$), 30.1 (CH_2), 22.5 (CH_2), 18.3 (Me) and 17.2 (Me).

3. Attempted reduction of a mixture of **597** and **594**

A mixture of the cyclic product **597** and the ester **594** (0.1 g) was dissolved in dry THF (10 cm^3) and excess lithium aluminium hydride (0.02 g) was added. The mixture was heated under reflux for 2 hours and left to cool to room temperature. Finely ground sodium sulphate decahydrate was added to destroy the excess lithium aluminium hydride. The salts were

filtered off and washed with ether. Concentration of the filtrate gave the cyclic product **597** as a colourless oil. See data above.

4. Attempted deprotection of **575** using barium hydroxide

To a solution of ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate **575** (0.4 g, 1.3 mmol) in glyme (20 cm^3) barium hydroxide octahydrate in H_2O (15 cm^3) was added. The mixture was heated under reflux for 48 hours and the mixture left to cool to room temperature. CO_2 was bubbled through the solution to precipitate the barium salts. The mixture was filtered and the filtrate concentrated to give a colourless oil. NMR showed this to be a complex mixture.

5. Reduction of **575** using lithium aluminium hydride

A solution of ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate **575** (0.4 g, 1.3 mmol) in dry THF (10 cm^3) was added dropwise to a suspension of lithium aluminium hydride (0.10 g, 2.6 mmol) in dry THF (30 cm^3). The mixture was heated under reflux for 2 hours and the reaction monitored by TLC. The solution was left to cool and finely ground sodium sulphate hexahydrate was added to destroy excess lithium aluminium hydride. The salts were filtered off and the filtrate concentrated to give a yellow oil (0.35 g). This was purified using a kugelrohr (110 °C, water pump) to give a colourless oil (0.13 g) which contained a mixture of benzyl alcohol;

δ_H 7.38 (5 H, s, Ph), 4.61 (2 H, s, CH_2) and 3.19 (1 H, br s, OH); δ_C 141.2 (C-1 of Ph), 128.2 (2 C, Ph), 127.1 (C-4 of Ph), 126.7 (2 C, Ph) and 64.4 (CH_2).

and (*4S*)-5-methyl-4-methylaminohex-2-en-1-ol **606** as a colourless oil (Found: M+H^+, 144.1380. $C_8H_{17}NO$ requires *M+H*, 144.1388); $[\alpha]_D^{20}$ –7.10 (*c* 0.48 in CH_2Cl_2); ν_{max} /cm^{-1} 3317, 2961, 1701, 1536, 1467, 1388, 1246, 1091, 1017, 739 and 698; δ_H 5.66 (1 H, dt, *J* 15, 6, =C*H*CH_2), 5.38 (1 H, dd, *J* 15, 10, NHCHC*H*=), 4.04 (2 H, d, *J* 6, CH_2OH), 2.60 (1 H, m, C*H*NH), 2.23 (3 H, s, NMe), 1.69 (1 H, m, C*H*Me_2), 0.88 (3 H, *J* 7, Me) and 0.84 (3 H, d, *J* 7, Me); δ_C 133.0 (NHCH*C*H=), 130.1 (=*C*HCH_2), 68.3 (*C*HNH), 62.4 (*C*H_2OH), 33.8 (*C*HMe_2), 31.7 (NMe), 19.4 (CH*Me*) and 17.9 (CH*Me*); *m/z* (CI) 144 (M+H^+, 22%), 126 (55) and 100 (100).

A second product left in the distillation flask proved to be (*4S*)-4-benzoxycarbonylamino-5-methylhex-2-en-1-ol **603** as a yellow oil (very small amount) (Found: M+H$^+$, 264.1604. $C_{15}H_{21}NO_3$ requires *M*+H, 264.1600); $[\alpha]_D^{22}$ –1.23 (*c* 0.15 in CH_2Cl_2); ν_{max} /cm^{-1} 3323, 2960, 2887, 1656, 1467, 1395, 1369, 1093, 1014 and 978; δ_H 7.33 (5 H, s, Ph), 5.76 (1 H, m, =C*H*CH$_2$), 5.41 (1 H, m, NHCHC*H*=), 5.09 (2 H, s, OCH$_2$), 4.80 (1 H, br s, NH), 4.16 (2 H, s, C*H*$_2$OH), 4.07 (1 H, m, C*H*NH), 1.80 (1 H, m, C*H*Me$_2$) and 0.90 (6 H, d, *J* 7, CH*Me*$_2$); δ_C 156.0 (CONH), 136.4 (C-1 of Ph), 131.0 (NHCH*C*H=), 130.6 (2 C of Ph), 129.9 (=*C*HCH$_2$), 128.4 (2 C of Ph), 128.0 (C-4 of Ph), 66.7 (OCH$_2$), 62.7 (*C*H$_2$OH), 57.8 (*C*HNH), 32.3 (*C*HMe$_2$), 18.7 (CH*Me*) and 18.1 (CH*Me*); *m/z* (EI) 221 (M$^+$–C$_3$H$_6$, 5%), 220, (40), 176 (16), 114 (30) and 91 (100); *m/z* (CI) 264 (M+H$^+$, 11%), 246 (100), 220 (20), 156 (38), 140 (27) and 91 (34).

6. Reduction of **575** using sodium borohydride/ iodine

Sodium borohydride (0.03 g, 0.76 mmol) was added to ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate **575** (0.1 g, 0.33 mmol) in dry THF (3 cm^3). A solution of iodine (0.084 g, 0.33 mmol) in dry THF (30 cm^3) was added under nitrogen at 0 °C. The mixture was heated under reflux for 3 hours, cooled and acidified to pH 1 with 2M HCl. The solution was extracted with ethyl acetate which was dried and evaporated to give a brown oil (0.02 g). This was shown spectroscopically to be a mixture of starting material **575** and 4-iodobutanol **612**; δ_H 3.80 (2 H, m, CH$_2$O), 3.24 (2 H, t, *J* 7, CH$_2$I), 1.90 (2 H, m, CH$_2$) and 1.65 (2 H, m, CH$_2$); δ_C 62.2 (OCH$_2$), 33.0 (CH$_2$), 32.6 (CH$_2$) and 0.66 (CH$_2$I).

7. Attempted reduction of **575** using Borane in THF

A 1M solution of borane in THF (0.2 cm^3, 1.6 mmol) was added dropwise to ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate **575** (0.05 g, 0.16 mmol) in dry THF (1 cm^3) and the mixture was left to stir at room temperature for 24 hours. Water (1 cm^3) was added and the mixture was extracted with dichloromethane which was dried and evaporated to give a colourless oil (0.04 g) which was a mixture of starting material **575** and 4-iodobutanol **612**.

8. Attempted protection with *p*-toluenesulfonyl chloride

To a solution of the deprotected ester **594** (0.03 g, 0.17 mmol) in pyridine (1 cm^3) was added dropwise a suspension of *p*-toluenesulfonyl chloride (0.06 g, 0.32 mmol) in pyridine (1 cm^3) at 0 °C and the mixture was left to stir for 12 hours. The solution was poured into 10% H_2SO_4 and extracted with dichloromethane. Drying and evaporation gave a yellow oil (0.02 g) which was mainly the cyclic product **597**.

9. Introduction of an *N*-*t*-butoxycarbonyl group

To a solution of ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate **575** (0.30 g, 1.0 mmol) in ethyl acetate (10 cm^3), triethylamine (0.14 cm^3, 1.0 mmol), di-*tert*-butyl dicarbonate (0.43 g, 2.0 mmol) and DMAP (0.12 g, 1.0 mmol) were added. The mixture was left to stir under a hydrogen atmosphere for 48 hours. The mixture was filtered through celite and washed with 1M HCl, dried and evaporated to give a yellow oil (0.22 g) which proved to be a 1:2 mixture of an unidentified product and ethyl (*4S*)-4-(t-butoxycarbonylamino)-5-methylhexanoate **614**; (Found: M+H$^+$, 274.2009. $C_{14}H_{27}NO_4$ requires *M*+H, 274.2018.); $[\alpha]_D^{22}$ –2.07 (*c* 0.12 in CH_2Cl_2); ν_{max} /cm^{-1} 3372, 2965, 2887, 1735, 1526, 1450, 1368, 1251, 1176, 1043, 867 and 738; δ_H 4.46 (1 H, br d, NH), 4.12 (2 H, q, *J* 7, OCH_2), 3.43 (1 H, m, C*H*NH), 2.58 (1 H, m, C*H*Me_2), 1.50–1.90 (4 H, m, 2 x CH_2), 1.45 (9 H, s, C*Me*$_3$), 1.27 (3 H, t, *J* 7, Me), 0.94 (3 H, d, *J* 7, CH*Me*) and 0.90 (3 H, d, *J* 7, CH*Me*); δ_C 158.7 (CO_2), 155.8 (NHCO), 78.7 (*C*Me_3), 60.2 (OCH_2), 55.2 (NHCH), 32.4 (*C*HMe_2), 31.2 (*C*H_2CO_2), 28.1 (C*Me*$_3$), 27.8 (CH*C*H_2), 18.8 (CH*Me*), 17.6 (CH*Me*) and 14.0 (Me); *m/z* (CI) 274 (M+H$^+$, 48%), 262 (6), 246 (21), 230 (19), 218 (100), 200 (19), 157 (6) and 130 (19).

10. Attempted introduction of an *N*-*t*-butoxycarbonyl group

Ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate **575** (0.22 g, 0.72 mmol) was heated in 2M NaOH (1.5 cm^3) for 4 hours. Di-*tert*-butyl dicarbonate (0.19 g, 0.87 mmol) in dioxane (1 cm^3) was added and the mixture left to stir at room temperature for 12 hours. The mixture was acidified to pH 1, washed with ether and concentrated to give a yellow oil.

NMR of the products was inconclusive.

11. Protection of cyclic product **597** to give **618**

To a solution of (*5S*)-5-isopropylpyrrolidin-2-one **597** (0.06 g, 0.47 mmol) in dichloromethane (5 cm^3), triethylamine (0.07 cm^3, 0.47 mmol), di-*tert*-butyl dicarbonate (0.21 g, 0.94 mmol) and DMAP (0.06 g, 0.47 mmol) were added and the mixture was left to stir for 48 hours. The mixture was washed with 1M HCl and evaporated to give (*5S*)-1-*t*-butoxycarbonylamino-5-isopropylpyrrolidin-2-one **618** as a yellow oil (0.05 g); δ_H 4.03 (1 H, m, NCH), 2.37 (1 H, m, C*H*Me_2), 2.33–2.01 (2 H, m, CH_2), 1.98–1.61 (2 H, m, CH_2), 1.45 (9 H, s, C*Me*$_3$), 0.87 (3 H, d, *J* 7, CH*Me*) and 0.78 (3 H, d, *J* 7, CH*Me*).

12. Base hydrolysis of **618** to give the *N*-Boc-γ-amino acid **619**

The product **618** (0.05 g, 0.22 mmol) was dissolved in AR acetone (3 cm^3) and 1 M NaOH (0.7 cm^3) was added and the mixture was left to stir at room temperature for 30 mins. The mixture was concentrated then diluted with water (2 cm^3) and acidified with 6 M HCl to pH 1–2. The solution was extracted with dichloromethane which was dried and evaporated to give (*4S*)-4-(t-butoxycarbonylamino)-5-methylhexanoic acid **619** as to a yellow oil (0.04 g); (Found: M+H^+, 246.1705. $C_{12}H_{24}NO_4$ requires *M*+H, 246.1670.); δ_H 4.43 (1 H, br d, NH), 3.44 (1 H, m, C*H*NH), 2.37 (3 H, m, CH_2+C*H*Me_2), 1.71 (2 H, m, CH_2), 1.44 (9 H, s, C*Me*$_3$), 0.92 (3 H, d, *J* 7, CH*Me*) and 0.88 (3 H, d, *J* 7, CH*Me*); δ_C 178.2 (CO_2H), 156.2 (NHCO), 79.2 (*C*Me_3), 55.3 (NHCH), 32.5 (*C*HMe_2), 31.4 (*C*H_2CO_2), 28.3 (C*Me*$_3$), 27.7 (CH*C*H_2), 18.9 (CH*Me*) and 17.7 (CH*Me*); *m/z* (CI) 246 (M+H^+, 10%), 202 (10), 190 (100), 172 (12), 146 (23), 128 (25),and 102 (6).

13. Attempted reduction of the acid **619** using borane

A 1M solution of borane in THF (0.2 cm^3, 1.6 mmol) was added dropwise to the acid **41** (0.04 g, 0.16 mmol) in dry THF (2 cm^3) and the mixture was left to stir at room temperature for 24 hours. Water (1 cm^3) was added and the mixture was extracted with

dichloromethane. This was dried and evaporated to give a colourless oil (0.03 g) which proved to be a mixture of starting material **619** and 4-iodobutanol **612**.

G Use of Different Nitrogen Protecting Groups

1. Pyrolysis of the ylide **560**

a. FVP of the ylide **560** (0.343 g, 0.63 mmol, 600 °C, 7 x 10^{-3} Torr) gave a yellow oil in the cold trap, a brown solid at the furnace exit and black tar left in the inlet tube. The ^{1}H, ^{13}C and ^{31}P NMR showed:

cold trap: ethanol and isobutylene δ_C 24.1 (2 x Me), 110.5 and 141.6.

furnace exit: Ph_3PO, Ph_3P (small amount) and cyclic product; δ_P +10.7

inlet tube: (*5S*)-Isopropyl-3-triphenylphosphoranylidenepyrrolidine **626**; δ_H 7.80–7.42 (15 H, m, 3 x Ph), 5.11 (1 H, br s, NH), 3.78 (1 H, m, NHC*H*), 2.23 (1 H, m, C*H*Me_2), 1.02 (3 H, d, *J* 7, Me) and 0.85 (3 H, d, *J* 7, Me); δ_C 196.5 (d, *J* 7, P=C*C*O), 176.9 (d, *J* 17, NC=O), 134.1 (d, *J* 11, 6 x C-2 of P-Ph), 132.8 (d, *J* 3, 3 x C-4 of P-Ph), 128.7 (d, *J* 13, 6 x C-3 of P-Ph), 123.0 (d, *J* 93, 3 x C-1 of P-Ph), 67.3 (d, *J* 12, NCH), 64.5 (d, *J* 122, P=C), 29.7 (*C*HMe_2), 19.9 (CH*Me*) and 15.4 (CH*Me*) ; δ_P +10.7 (lit.,[138] δ_P +10.8, δ_H and δ_C identical to data above).

b. FVP of the ylide **560** (0.200 g, 0.36 mmol, 500 °C, 1 x 10^{-2} Torr) gave a brown solid at the furnace exit. The ^{1}H and ^{31}P NMR showed mainly Ph_3PO and the cyclic product formed above.

2. *(4S)-Ethyl 4-allyloxycarbonylamino-5-methylhex-2-ynoate* **628**

FVP of the ylide **561** (0.100 g, 0.19 mmol, 600 °C, 7 x 10^{-3} Torr) gave a beige solid at the furnace exit. The NMR spectra showed a mixture of Ph_3PO and the expected product. Purification by column chromatography (ether–hexane, 1:2) gave the title compound (17 mg, 35%) as a colourless oil; (Found: M+H^+, 254.1402. $C_{13}H_{19}NO_4$ requires *M*+H, 254.1392); $[\alpha]_D^{20}$ –4.22 (*c* 0.37 in CH_2Cl_2); ν_{max} /cm^{-1} 3322, 2967, 2877, 2238, 1713, 1526, 1467,

1246, 1030, 753 and 699; δ_H 5.92 (1 H, m, H_2C=C*H*CH_2), 5.25 (2 H, m, CH_2=CH), 5.05 (1 H, br d, NH), 4.58 (2 H, d, *J* 5, CH_2=CHCH_2), 4.52 (1 H, m, NHC*H*), 4.23 (2 H, q, *J* 7, CH_2Me), 1.98 (1 H, m, C*H*Me_2), 1.31 (3 H, t, *J* 7, CH_2*Me*) and 1.03 (6 H, d, *J* 7, 2xMe); δ_C 155.3 (NCO_2), 153.2 (CO_2Et), 132.4 (*C*H=CH_2), 118.0 (CH=*C*H_2), 85.2 (C≡C), 75.8 (C≡C), 65.9 (O*C*H_2CH=CH_2), 62.1 (O*C*H_2Me), 49.0 (NH*C*H), 32.9 (*C*HMe_2), 18.6 (CH*Me*), 17.9 (CH*Me*) and 13.9 (CH_2*Me*); *m/z* (EI) 254 (MH^+, 6%), 210 (100), 166 (38), 153 (7), 138 (11), 122 (8), 109 (11) and 91 (48).

3. *(4S)-Allyl 4-benzoxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylidenehexanate* **630**

To a stirred solution of the allyl ylide **504** (0.9 g, 2.8 mmol) and *N*-benzoxycarbonylvaline (0.70 g, 2.8 mmol) in dry dichloromethane (15 cm^3) at 0 °C was added EDCI (0.54 g, 2.8 mmol) and DMAP (cat.). The mixture was stirred at this temperature for 30 min and then allowed to warm up to RT. When all the starting material was consumed (monitored by TLC) the mixture was poured into brine, extracted with CH_2Cl_2 and the combined organic extracts dried and evaporated to give the crude product as a brown oil. Chromatography (ethyl acetate–hexane, 1:1) followed by recrystallisation from ethyl acetate–hexane yielded the title compound (0.74 g, 45%) as colourless crystals, mp 125–126 °C (Found: C, 72.5; H, 6.2; N, 2.4. $C_{36}H_{36}NO_5P$ requires C, 72.8; H, 6.1; N, 2.4 %); $[\alpha]_D^{20}$ +4.6 (*c* 0.64 in CH_2Cl_2); ν_{max} /cm^{-1} 3401, 2924, 1719, 1675, 1579, 1499, 1465, 1380, 1321, 1284. 1230, 1102, 755 and 692; δ_H 7.75–7.60 (6 H, m, Ph), 7.58–7.38 (9 H, m, Ph), 7.33 (5 H, s, Ph), 5.64 (1 H, br d, NH), 5.47 (2 H, m, OCH_2CH), 5.40 (1 H, m, C*H*=CH_2), 5.08 (2 H, s, OCH_2Ph), 4.96 (2 H, m, CH=CH_2), 4.31 (1 H, m, CHN), 2.40 (1 H, m, C*H*Me_2), 1.05 (3 H, d, *J* 7, Me) and 0.63 (3 H, d, *J* 7, Me); δ_C 193.9 (P=C–*C*O), 166.1 (d, *J* 14, *C*O_2), 156.0 (NHCO), 136.8 (Ph C-1), 132.8 (d, *J* 10, 6 x C-2 of P-Ph), 132.6 (C=C), 131.6 (d, *J* 2, 3 x C-4 of P-Ph), 128.3 (d, *J* 12, 6 x C-3 of P-Ph), 128.0 (2 C), 127.4 (3 C), 125.5 (d, *J* 94, 3 x C-1, P-Ph), 117.1 (C=C), 69.7 (d, *J* 110, P=C), 65.9 (OCH_2CH), 63.7 (OCH_2Ph), 60.2 (d, *J* 8, CHNH), 32.1 (*C*HMe_2), 20.5 (Me) and 15.7 (Me); δ_P +18.4; *m/z*

(CI) 595 ($M+H^+$, 64%), 537 (13), 519 (9), 487 (4), 387 (54), 342 (33), 316 (21), 298 (36), 272 (83), 206 (25) and 91 (100).

4. *(4S)-Allyl 4-benzoxycarbonylamino-5-methylhex-2-ynoate* **631**

FVP of the ylide **630** (0.150 g, 0.25 mmol, 600 °C, 9 x 10^{-3} Torr) gave a brown solid at the furnace exit and a yellow oil in the cold trap. The NMR showed a benzyl alcohol in the cold trap and mixture of Ph_3PO and the expected product at the furnace exit. Purification by column chromatography (ether–hexane, 1:2) gave the title compound (30 mg, 38%) as a colourless oil, (Found: $M+H^+$, 316.1559. $C_{18}H_{21}NO_4$ requires *M*+H, 316.1549); $[\alpha]_D^{20}$ –17.12 (*c* 0.27 in CH_2Cl_2); ν_{max} /cm^{-1} 3440, 2966, 2929, 2238, 1718, 1510, 1457, 1266, 1028, 739 and 702; δ_H 7.35 (5 H, s, Ph), 5.92 (1 H, m, CH_2=C*H*), 5.30 (2 H, m, C*H*$_2$=CH), 5.11 (2 H, s, OCH_2Ph), 5.06 (1 H, br d, NH), 4.65 (2 H, d, *J* 5, CH_2=CHC*H*$_2$), 4.50 (1 H, m, NHC*H*), 1.97 (1 H, m, C*H*Me_2) and 1.02 (6 H, d, *J* 7, 2 x Me); δ_C 155.4 (NCO_2), 152.8 (*C*O_2CH_2), 136.0 (Ph C-1), 131.0 (*C*H=CH_2), 128.5 (2 C), 128.2 (2 C), 128.1 (Ph C-4), 119.4 (CH=*C*H_2), 85.7 (C≡C), 75.7 (C≡C), 67.2 (OCH_2Ph), 66.5 (O*C*H_2CH=CH_2), 49.1 (NH*C*H), 32.9 (*C*HMe_2), 18.6 (CH*Me*) and 17.9 (CH*Me*); *m/z* (CI) 316 (MH^+, 18%), 272 (23), 254 (25), 232 (79), 219 (5), 208 (55), 183 (46), 152 (30), 131 (15), 108 (19) and 91 (100).

5. *(4S)-t-Butyl 4-t-butoxycarbonylamino-5-methyl-3-oxo 2-triphenylphosphoranylidene-hexanoate* **632**

Reaction as 3. using *N*-t-butyloxycarbonyl-(*S*)-valine (1.12 g, 5.2 mmol), (t-butoxycarbonylmethylene)triphenylphosphorane **503** (1,96 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) yielded the title product (0.52 g, 17 %) as a colourless oil; (Found: $M+H^+$, 576.2879. $C_{34}H_{42}NO_5P$ requires *M*+H, 576.2865); $[\alpha]_D^{20}$ –6.7 (*c* 0.59 in CH_2Cl_2); ν_{max} /cm^{-1} 3414, 1713, 1668, 1556, 1462, 1364, 1298, 1165, 1106, 1079, 710 and 692; δ_H 7.75–7.65 (6 H, m, Ph), 7.54–7.39 (9 H, m, Ph), 5.41 (2 H, br s, NH and C*H*NH), 2.33 (1 H, m, C*H*Me_2), 1.41 (9 H, s, OC*Me*$_3$), 1.12 (9 H, s, OC*Me*$_3$), 1.02 (3 H, d, J 7, CH*Me*) and 0.59 (3 H, d, *J* 7, CH*Me*); δ_C 196.7 (d, *J* 3, P=C–*C*O), 165.9 (d, *J* 13, *C*O_2Bu^t), 155.7

(NHCO), 132.6 (d, *J* 10, 6 x C-2 of P-Ph), 131.3 (3 x C-4 of P-Ph), 128.1 (d, *J* 12, 6 x C-3 of P-Ph), 126.1 (d, *J* 93, 3 x C-1 of P-Ph), 78.5 (O*C*Me$_3$), 77.6 (O*C*Me$_3$), 69.8 (d, *J* 109, P=C), 59.0 (d, *J* 9, *CH*NH), 32.1 (*CH*Me$_2$), 28.1 (C*Me$_3$*), 27.8 (C*Me$_3$*), 20.2 (CH*Me*) and 15.7 (CH*Me*); δ_P +18.3; *m/z* (CI) 576 (MH^+, 100%), 500 (9), 403 (11), 343 (25), 289 (30), 279 (55), 243 (85), 232 (25), 189 (27), 173 (33) and 146 (27).

6. *(4S)-t-Butyl 4-(2S-t-butoxycarbonylamino-3-methylbutyrylamino)-5-methyl-3-oxo-2-triphenylphosphoranylidenehexanoate* **633**

Chromatography of the product from the above reaction 5. also yielded the title product (0.41 g, 12 %) as a colourless oil in a 3:1 ratio of carbamate rotamers,

major carbamate rotamer:

δ_H 7.78–7.59 (6 H, m, Ph), 7.58–7.36 (9 H, m, Ph), 6.60 (1 H, br m, NH), 5.66 (1 H, dd, C*H*NH), 5.24 (1 H, br d, NH), 3.88 (C*H*NH), 2.29 (1 H, m, C*H*Me$_2$), 1.95 (1 H, m, C*H*Me$_2$), 1.42 (9 H, s, OC*Me$_3$*), 1.14 (9 H, s, OC*Me$_3$*), 0.97 (3 H, m, CH*Me*), 0.83 (6 H, m, 2 x CH*Me*) and 0.71 (3 H, d, *J* 7, CH*Me*); δ_C 192.4 (d, *J* 3, P=C–*C*O), 170.6 (NH*C*O), 166.0 (d, *J* 14, *C*O$_2$Bu^t), 155.4 (NH*C*O$_2$Bu^t), 132.6 (d, *J* 10, 6 x C-2 of P-Ph), 131.5 (d, *J* 3, 3 x C-4 of P-Ph), 128.3 (d, *J* 12, 6 x C-3 of P-Ph), 126.0 (d, *J* 93, 3 x C-1 of P-Ph), 78.8 (O*C*Me$_3$), 78.6 (O*C*Me$_3$), 71.2 (d, *J* 108, P=C), 59.5 (*C*HNH), 57.7 (d, *J* 6, *C*HNH), 31.9 (*C*HMe$_2$), 31.5 (*C*HMe$_2$), 28.0 (C*Me$_3$*), 27.9 (C*Me$_3$*), 20.1 (CH*Me*), 18.9 (CH*Me*), 17.6 (CH*Me*) and 16.4 (CH*Me*); δ_P +17.7.

minor carbamate rotamer:

δ_H 7.78–7.59 (6 H, m), 7.58–7.36 (9 H, m), 6.60 (1 H, br m, NH), 5.75 (1 H, dd, C*H*NH), 5.24 (1 H, br d, NH), 4.02 (C*H*NH), 2.29 (1 H, m, C*H*Me$_2$), 1.95 (1 H, m, C*H*Me$_2$), 1.42 (9 H, s, OC*Me$_3$*), 1.14 (9 H, s, OC*Me$_3$*), 0.97 (6 H, m, 2 x CH*Me*), 0.83 (3 H, m, CH*Me*) and 0.63 (3 H, d, *J* 7, CH*Me*); δ_C 192.6 (d, *J* 4, P=C–*C*O), 170.5 (NH*C*O), 165.9 (d, *J* 13, *C*O$_2$Bu^t), 155.3 (NH*C*O$_2$Bu^t), 132.7 (d, *J* 10, 6 x C-2 of P-Ph), 131.5 (d, *J* 3, 3 x C-4 of P-Ph), 128.3 (d, *J* 12, 6 x C-3 of P-Ph), 125.9 (d, *J* 93, 3 x C-1 of P-Ph), 78.8 (O*C*Me$_3$), 78.6 (O*C*Me$_3$), 71.2 (d, *J* 108, P=C), 59.2 (*C*HNH), 57.7 (d, *J* 6, *C*HNH), 32.5 (*C*HMe$_2$), 31.8

(*C*HMe$_2$), 28.0 (C*Me$_3$*), 27.9 (C*Me$_3$*), 20.4 (CH*Me*), 19.2 (CH*Me*), 16.8 (CH*Me*) and 16.1 (CH*Me*); δ_P +17.9.

both rotamers

(Found: M+H$^+$, 675.3549. $C_{39}H_{51}N_2O_6P$ requires *M+H*, 675.3563); $[\alpha]_D^{23}$ –4.3 (*c* 0.17 in CH_2Cl_2); ν_{max} /cm^{-1} 3374, 1715, 1669, 1485, 1466, 1440, 1366, 1170, 1107, 710 and 682; *m/z* (CI) 675 (M+H$^+$, 14%), 566 (6), 505 (12), 431 (5), 403 (5), 391 (7), 317 (10), 279 (100), 263 (9), 189 (22) and 175 (6).

7. *(4S)-Allyl 4-allyloxycarbonylamino-5-methyl-3-oxo 2 triphenylphosphoranylidenehexanoate* **636**

Reaction as 3. using *N*-allyloxycarbonyl-(*S*)-valine (1.20 g, 6.0 mmol), (allyloxycarbonylmethylene)triphenylphosphorane **504** (1.88 g, 6.0 mmol), EDCI (1.14 g, 56.0 mmol) and DMAP (cat.) followed by column chromatography (ethyl acetate-petroleum ether (40–60), 1:1) gave the title compound (1.40 g, 43 %) as colourless crystals, mp 102–104 °C (Found: C, 70.95; H, 6.2; N, 2.5. $C_{32}H_{34}NO_5P$ requires C, 70.7; H, 6.3; N, 2.6 %) (Found: M+H$^+$, 544.2242. $C_{32}H_{34}NO_5P$ requires *M+H*, 544.2253); $[\alpha]_D^{20}$ +1.4 (*c* 0.84 in CH_2Cl_2); ν_{max} /cm^{-1} 3401, 2927, 1709, 1665, 1592, 1462, 1378, 1285, 1107, 1070, 722 and 697; δ_H 7.76–7.61 (6 H, m, Ph), 7.59–7.39 (9 H, m, Ph), 5.89 (1 H, m, HC=), 5.57 (1 H, br d, NH), 5.52–5.36 (2 H, m, HC= and OCH$_2$), 5.22 (2 H, m, CH=C*H$_2$*), 4.93 (2 H, m, CH=C*H$_2$*), 4.54 (2 H, d, *J* 4, OCH$_2$), 4.30 (1 H, m, C*H*NH), 4.14 (1 H, m, OCH$_2$), 2.40 (1 H, m, C*H*Me$_2$), 1.07 (3 H, d, *J* 7, Me) and 0.64 (3 H, d, *J* 7, Me); δ_C 194.0 (P=C–*C*O), 166.1 (d, *J* 14, *C*O$_2$), 156.2 (NHCO), 133.0 (C=C), 132.8 (d, *J* 10, 6 x C-2 of P-Ph), 132.5 (C=C), 131.6 (3 x C-4 of P-Ph), 128.2 (d, *J* 12, 6 x C-3 of P-Ph), 125.5 (d, *J* 94, 3 x C-1, P-Ph), 117.0 (C=C), 116.3 (C=C), 69.5 (d, *J* 110, P=C), 64.6 (OCH$_2$), 63.4 (OCH$_2$), 59.9 (d, *J* 9, CHNH), 32.8 (*C*HMe$_2$), 20.2 (Me) and 15.4 (Me); δ_P +18.4; *m/z* (CI) 544 (M+H$^+$, 60%), 468 (13), 387 (14), 279 (100), 263 (16), 226 (12) and 187 (29).

8. *(4S)-allyl 4-allyloxycarbonylamino-5-methylhex-2-ynoate* **637**

FVP of the ylide **636** (50 mg, 0.19 mmol, 600 °C, 9 x 10^{-3} Torr) gave a brown solid at the furnace exit and a yellow oil in the cold trap. The NMR showed benzyl alcohol in the cold trap and a mixture of Ph_3PO and the expected product at the furnace exit. Purification by column chromatography (ether–hexane, 1:2) gave the title product (17 mg, 35%) as a colourless oil, (Found: M+H$^+$, 266.1385. $C_{14}H_{19}NO_4$ requires *M+H*, 266.1392); $[\alpha]_D^{20}$ –88.45 (*c* 0.40 in CH_2Cl_2); ν_{max} /cm^{-1} 3317, 2967, 2877, 2238, 1718, 1526, 1467, 1229, 1037, 777 and 752; δ_H 5.92 (2 H, m, 2 x CH_2=C*H*), 5.41–5.20 (4 H, m, 2 x CH_2=CH), 5.05 (1 H, br d, NH), 4.66 (2 H, d, *J* 5, OCH_2), 4.59 (2 H, d, *J* 5, OCH_2), 4.52 (1 H, m, NHC*H*), 1.99 (1 H, m, C*H*Me_2) and 1.03 (6 H, d, *J* 7, 2xMe); δ_C 155.3 (*C*O_2CH_2), 152.8 (NCO), 132.4 (*C*H=CH_2), 131.0 (*C*H=CH_2), 119.4 (CH=*C*H_2), 11.0 (CH=*C*H_2), 85.7 (C≡C), 75.6 (C≡C), 66.5 (OCH_2), 66.0 (OCH_2), 49.0 (NHCH), 33.0 (*C*HMe_2), 18.6 (CH*Me*) and 17.9 (CH*Me*); *m/z* (CI) 266 (M+H$^+$, 100%), 242 (25), 222 (23), 208 (54), 182 (9) and 164 (15).

H Preparation and Pyrolysis of α-Cyano-β-Aminoacyl Ylides

1. Preparation of starting materials

a. *(Cyanomethyl)triphenylphosphonium chloride* **647**

To a solution of triphenylphosphine (26.2 g, 0.1 mol) in ethyl acetate (20 cm^3) was added chloroacetonitrile (6.3 cm^3, 7.6 g, 0.1 mol). The mixture was then heated under reflux for 90 min and left to cool to RT. The white precipitate which formed was filtered off and washed with ether to furnish the product (22 g, 65%) as a white solid. mp 268–270 °C (lit.,[155] 265–267 °C); δ_H 8.02–7.88 (9 H, m, Ph), 7.88–7.77 (6 H, m) and 6.13 (2 H, d, *J* 16, CH_2); δ_P +21.5.

b. *(Cyanomethylene)triphenylphosphorane* **644**

(i) method 1[155]

(Cyanomethyl)triphenylphosphonium chloride (4.0 g, 12 mmol) was dissolved in water (150 cm^3) and the solution extracted with ether to remove any residual triphenylphosphine

present. The solution was stirred vigorously as sodium hydroxide (0.48 g, 12 mmol) in water (3 cm^3) was added rapidly. A solid precipitated out and was filtered off immediately. Recrystallisation using ethyl acetate gave the product (1.5 g, 42%) as beige crystals, mp 195–197 °C (lit.,[155] 190–192°C) (Found: C, 79.6; H, 5.4; N, 4.5. $C_{20}H_{16}NP$ requires C, 79.7; H, 5.5; N, 4.6%); δ_H 7.8–7.4 (15 H, m, Ph) and 1.65 (1 H, br s, CH), ; δ_C 132.8 (d, *J* 11, 6 x C-2 of P-Ph), 132.8 (3 x C-4 of P-Ph), 129.2 (d, *J* 13, 6 x C-3 of P-Ph), 127.5 (d, *J* 92, 3 x C-1 of P-Ph) and –2.1 (d, *J* 137, P=C); δ_P +23.4.

(ii) method 2[156]

(Cyanomethyl)triphenylphosphonium chloride (5.0 g, 14 mmol) was suspended in dry dichloromethane (75 cm^3). Triethylamine (3.7 g, 5.1 cm^3, 36 mmol) was added over a period of 15 mins. The solution was stirred for a further 25 mins, washed with cold water (50 cm^3) dried and evaporated to furnish the product as a beige solid (3.31 g, 79%) with physical and spectroscopic properties identical to above.

2. Preparation of amino acyl cyano ylides

a. *(4S)-4-Benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenevaleronitrile* **659**

To a stirred solution of (cyanomethylene)triphenylphosphorane **644** (0.78 g, 2.6 mmol) and *N*-benzoxycarbonyl-(*S*)-alanine (0.58 g, 2.6 mmol) in dry dichloromethane (20 cm^3) at 0 °C was added EDCI (0.5 g, 2.6 mmol) and DMAP (cat.). The mixture was stirred at this temperature for 30 min and then allowed to warm up to RT. When all the starting material was consumed (monitored by TLC) the mixture was poured into brine, extracted with CH_2Cl_2 and the combined organic extracts dried and evaporated to give the crude product as a brown oil. Chromatography (ethyl acetate–hexane, 1:1) followed by recrystallisation from ethyl acetate–hexane yielded the title product (0.34 g, 22%) as colourless crystals, mp 79–80 °C (Found: C, 73.2; H, 5.5; N, 5.3. $C_{31}H_{27}N_2O_3P$ requires C, 73.5; H, 5.4 N; 5.3%); $[\alpha]_D^{20}$ +12.7 (*c* 1.2 in CH_2Cl_2); ν_{max} /cm^{-1} 3393, 2176, 2863, 1719, 1585, 1438, 1350, 1109, 719 and 692; δ_H 7.70–7.50 (15 H, m, Ph), 7.30 (5 H, s, Ph), 5.78 (1 H, br d, *J* 8, NH), 5.09 (2 H, s, OCH_2), 4.95 (1 H, quintet, *J* 8, C*H*NH) and 1.53 (3 H, d, *J* 8, Me); δ_C 194.5 (d, *J* 3,

P=C–*C*O), 155.3 (NHCO), 136.7 (4ry), 133.4 (d, *J* 10, 6 x C-2 of P-Ph), 133 3 (3 x C-4 of P-Ph), 129.1 (d, *J* 13, 6 x C-3 of P-Ph), 128.2 (2 C), 127.7 (3 C), 122.5 (d, *J* 94, 3 x C-1 of P-Ph), 120.7 (d, *J* 15, CN), 66.1 (OCH_2), 52.4 (d, *J* 9, CHN), 46.6 (d, *J* 127, P=C) and 19.5 (Me); δ_P +20.9; *m/z* (CI) 507 ($M+H^+$, 100%), 399 (8), 263 (13), 247 (8), 187 (41) and 147 (28).

b. *(4S)-4-Benzyloxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylidenehexano -nitrile* **660**

Reaction as in a. using *N*-benzoxycarbonyl-(*S*)-valine (2.0 g, 8.0 mmol), (cyanomethylene)triphenylphosphorane **644** (2.4 g, 8.0 mmol), EDCI (1.5 g, 8.0 mmol) and DMAP (cat.) yielded the product (1.74 g, 40%) as a white solid, mp 78–80 °C (Found: C, 73.9; H, 5.8; N, 5.2. $C_{33}H_{31}N_2O_3P$ requires C, 74.1; H, 5.9 N; 5.2%); $[\alpha]_D^{20}$ +13.3 (*c* 1.5 in CH_2Cl_2); ν_{max} /cm^{-1} 3277, 2176, 1718, 1583, 1438, 1377, 1027, 693 and 567; δ_H 7.73–7.57 (9 H, m, Ph), 7.56–7.43 (6 H, m, Ph), 7.32 (5H, s, Ph), 5.49 (1 H, br d, *J* 8, NH), 5.12 (2 H, s, OCH_2Ph), 4.88 (1 H, m, C*H*NH), 2.40 (1 H, m, *CH*Me_2), 1.08 (3 H, d, *J* 7, CH*Me*) and 0.81 (3 H, d, *J* 7, CH*Me*); δ_C 194.1 (P=C–*C*O), 156.3 (NHCO), 136.8 (4ry), 133.6 (d, *J* 10, 6 x C-2 of P-Ph), 133 2 (3 x C-4 of P-Ph), 129.2 (d, *J* 13, 6 x C-3 of P-Ph), 128.4 (2 C), 127.8 (3 C), 122.7 (d, *J* 94, 3 x C-1 of P-Ph), 121.0 (d, *J* 15, CN), 66.4 (OCH_2), 61.0 (d, *J* 9, CHN), 48.4 (d, *J* 126, P=C), 31.9 (*C*HMe_2), 20.0 (Me) and 19.5 (Me); δ_P +20.9; *m/z* (CI) 535 ($M+H^+$, 90%), 459 (7), 391 (9), 333 (43), 279 (76), 252 (34), 206 (13), 187 (14), 147 (23) and 58 (100).

c. *4-(S)-Ethoxycarbonylamino-5-methyl-3-oxo-2 triphenylphosphoranylidenehexanonitrile* **661**

Reaction as in 2a. using *N*-ethoxycarbonyl-(*S*)-valine (0.88 g, 4.7 mmol), (cyanomethylene)triphenylphosphorane **644** (1.40 g, 4.7 mmol), EDCI (0.89 g, 4.7 mmol) and DMAP (cat.) yielded the product (1.04 g, 45%) as a white solid mp 148–150 °C (Found: C, 71.0; H, 6.2; N, 5.9. $C_{28}H_{29}N_2O_3P$ requires C, 71.2; H, 6.2 N; 5.9%) (Found: $M+H^+$, 473.1985. $C_{128}H_{29}N_2O_3P$ requires *M+H*, 473.1994); $[\alpha]_D^{20}$ +34.2 (*c* 2.2 in CH_2Cl_2); ν_{max}

/cm^{-1} 3302, 2923, 2854, 2172, 1711, 1591, 1457, 718 and 692; δ_H 7.68–7.56 (9 H, m, Ph), 7.55–7.47 (6 H, m, Ph), 5.44 (1 H, br d, *J* 8, NH), 4.89 (1 H, m, C*H*NH), 4.08 (2 H, q, *J* 7, OC*H*$_2$Me), 2.40 (1 H, m, C*H*Me$_2$), 1.23 (3 H, t, *J* 7, OCH$_2$*Me*), 1.06 (3 H, d, *J* 7, CH*Me*) and 0.83 (3 H, d, *J* 7, CH*Me*); δ_C 193.7 (P=C–*C*O), 156.1 (NHCO), 133.0 (d, *J* 10, 6 x C-2 of P-Ph), 132.9 (3 x C-4 of P-Ph), 128.7 (d, *J* 13, 6 x C-3 of P-Ph), 122.1 (d, *J* 94, 3 x C-1 of P-Ph), 120.6 (d, *J* 16, CN), 60.3 (d, *J* 9, *C*HNH), 60.0 (OCH$_2$), 47.7 (d, *J* 126, P=C), 31.4 (*C*HMe$_2$), 19.5 (CH*Me*), 16.2 (CH*Me*) and 14.1 (CH$_2$*Me*); δ_P +20.8; *m/z* (CI) 473 (M+H$^+$, 100%), 397 (22), 263 (6), 213 (29) and 187 (17).

d. *(4S)-4-t-Butoxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylidenehexanonitrile* **662**

Reaction as in 2a. using *N*-t-butoxycarbonyl-(*S*)-valine (1.12 g, 5.2 mmol), (cyanomethylene)triphenylphosphorane **65** (1.55 g, 5.2 mmol), EDCI (1.0 g, 5.2 mmol) and DMAP (cat.) yielded the product (1.09 g, 41%) as a white solid, mp 92–94 °C (Found: M+H$^+$, 500.2218 $C_{30}H_{33}N_2O_3P$ requires *M+H*, 500.2228); $[\alpha]_D^{20}$ +30.0 (*c* 1.6 in CH_2Cl_2); ν_{max} /cm^{-1} 2925, 2863, 2188, 1459, 1377, 1170 and 1120; δ_H 7.63–7.50 (9 H, m, Ph), 7.49–7.38 (6 H, m, Ph), 5.10 (1 H, br d, *J* 8, NH), 4.70 (1 H, m, C*H*NH), 2.27 (1 H, m, C*H*Me$_2$), 1.38 (9 H, s, CMe$_3$), 0.98 (3 H, d, *J* 7, CH*Me*) and 0.73 (3 H, d, *J* 7, CH*Me*); δ_C 194.5 (d, *J* 3, P=C–*C*O), 155.7 (NHCO), 132.2 (d, *J* 11, 6 x C-2 of P-Ph), 132.9 (d, *J* 3, 3 x C-4 of P-Ph), 128.8 (d, *J* 13, 6 x C-3 of P-Ph), 122.5 (d, *J* 94, 3 x C-1 of P-Ph), 120.8 (d, *J* 16, CN), 78.5 (O*C*Me$_3$), 60.3 (d, *J* 8, *C*HNH), 47.9 (d, *J* 126, P=C), 31.2 (*C*HMe$_2$), 28.0 (C*Me*$_3$), 19.8 (CH*Me*) and 16.6 (CH*Me*); δ_P +20.8; *m/z* 501 (M$^+$, 3%), 328 (100), 300 (10), 277 (10), 262 (18), 201 (6) and 183 (17).

e. *(4S)-4-(2S-t-Butoxycarbonylamino-3-methylbutyrylamino)-5-methyl-3-oxo-2-triphenylphosphoranylidenehexanonitrile* **663**

A second product was obtained from chromatography of the product from the above reaction as a colourless oil (0.47 g, 15%); ν_{max} /cm^{-1} 3405, 3320, 2181, 1715, 1677, 1596, 1572, 1500, 1466, 1439, 1367, 1160, 1109, 754, 719, 692 and 540; δ_H 7.76–7.52 (9 H, m,

Ph), 7.51–7.40 (6 H, m, Ph), 6.34 (1 H, br d, *J* 8, NH), 5.15 (1 H, br d, *J* 8, NH), 5.07 (1 H, m, C*H*NH), 3.86 (1 H, m, C*H*NH), 2.33 (1 H, m, C*H*Me_2), 1.98 (1 H, m, C*H*Me_2), 1.35 (9 H, s, CMe_3), 0.97 (3 H, d, *J* 7, CH*Me*) and 0.82 (9 H, m, 3 x CH*Me*); δ_C 193.5 (d, *J* 3, P=C–*C*O), 170.8 (NHCO), 155.5 (CO_2Bu^t), 133.3 (d, *J* 10, 6 x C-2 of P-Ph), 133.1 (3 x C-4 of P-Ph), 129.0 (d, *J* 13, 6 x C-3 of P-Ph), 122.4 (d, *J* 94, 3 x C-1 of P-Ph), 120.6 (d, *J* 16, CN), 79.2 (O*C*Me_3), 59.7 (*C*HNH), 58.9 (d, *J* 9, *C*HNH), 48.6 (d, *J* 127, P=C), 31.8 (*C*HMe_2), 31.4 (*C*HMe_2), 28.0 (C*Me*$_3$), 19.8 (CH*Me*), 18.9 (CH*Me*), 17.7 (CH*Me*) and 16.9 (CH*Me*); δ_P +20.9; *m/z* (CI) 600 ($M+H^+$, 100%), 526 (10), 501 (42), 446 (5), 328 (9) and 279 (21).

3. Pyrolysis of amino acyl cyano ylides

a. Pyrolysis of ylide **659**

(i) FVP of the ylide (101 mg, 0.20 mmol) at 600 °C gave a brown solid at the furnace exit which proved by ^1H and ^{31}P NMR to be Ph_3PO and Ph_3P in a ratio of 4:1, in the cold trap a yellow oil which was shown by ^1H NMR to contain mainly benzyl alcohol; δ_H 7.37 (5H, s, Ph), 4.6 (2H, s, CH_2) and 2.05 (1H, br s, OH).

and in the inlet tube a black solid (30 mg) which was shown by ^1H, ^{13}C and ^{31}P NMR to contain mainly a heterocyclic product; δ_H 7.82–7.40 (5 H, m, Ph), 4.38 (1 H, q) and 1.62 (3 H, d, Me); δ_C 193.2 (d, *J* 6), 170.8 (d, *J* 16), 155.8, 148.1, 134.2 (d, *J* 11), 133.7 (d, *J* 2), 129.2 (d, *J* 13), 120.8 (d, *J* 94), 66.7 (d, *J* 119), 60.4 (d, *J* 10) and 16.2; δ_P +10.4.

After storage for a period of months, mass spectroscopic analysis showed the aminoacyl amide **666** resulting from hydrolysis of a cyclic amidine (Found: $M+H^+$, 391.1575 $C_{23}H_{24}N_2O_2P$ requires *M+H*, 391.1590); *m/z* (CI) 391 ($M+H^+$, 4%), 279 (100), 257 (6), 223 (7) 135 (8), 121 (7) and 107 (10).

(ii) FVP of the ylide (120 mg, 0.24 mmol) at 550 °C gave a brown solid at the furnace exit which proved by ^1H and ^{31}P NMR to be Ph_3PO, Ph_3P and a small amount of heterocyclic product in a ratio of 81:8:11, in the cold trap a yellow oil which was shown by ^1H NMR to contain mainly benzyl alcohol, data as in (i), and in the inlet tube a black solid which was shown by ^1H and ^{31}P NMR to contain mainly a heterocyclic product, data as in i.

In this case mass spectroscopic analysis showed the presence of two components corresponding to formulae of $C_{25}H_{20}N_3O_3P$ (HRMS: found M^+-H, 440.1190. $C_{25}H_{20}N_3O_3P$ requires *M–H*, 440.1164) and $C_{32}H_{26}N_3O_3P$ (HRMS: found M^+-H, 530.1493. $C_{32}H_{26}N_3O_3P$ requires *M–H*, 530.1634). The possible structures corresponding to these formulae are described in the Discussion.

(iii) FVP of the ylide (120 mg, 0.24 mmol) at 500 °C gave a brown solid at the furnace exit which proved by ^1H and ^{31}P NMR to be Ph_3PO, Ph_3P, in the cold trap a yellow oil which was shown by ^1H NMR to contain mainly benzyl alcohol, data as in (i), and in the inlet tube a black solid which was shown by ^1H, ^{13}C and ^{31}P NMR to contain mainly a heterocyclic product, data as in (i).

b. Pyrolysis of ylide **662**

(i) FVP of the ylide (275 mg, 0.54 mmol) at 600 °C gave a brown solid at the furnace exit which proved by ^1H and ^{31}P NMR to be Ph_3PO and Ph_3P in a ratio of 9:1, in the cold trap a yellow oil which was shown by ^1H NMR to contain a mixture of ethanol and t-butanol; δ_H 2.23 and in the inlet tube a black solid which was shown by ^{31}P NMR to contain many products.

(ii) FVP of the ylide (250 mg, 0.49 mmol) at 500 °C gave a brown solid at the furnace exit which proved by ^1H and ^{31}P NMR to be a 62:4:34 ratio of Ph_3PO, Ph_3P and a heterocyclic product, δ_P +9.6, in the cold trap a yellow oil which was shown by ^1H and ^{31}P NMR to be Ph_3P, Ph_3PO and mainly t-butanol, and in the inlet tube a black solid which was shown by ^{31}P NMR to contain many products.

c. Pyrolysis of ylide **661**

(i) FVP of the ylide (304 mg, 0.62 mmol) at 600 °C gave a brown solid at the furnace exit which proved by ^1H and ^{31}P NMR to be Ph_3PO and an unidentified product and in the cold trap a yellow oil which was shown by ^1H and ^{31}P NMR to be Ph_3PO and another product.

(ii) FVP of the ylide (290 mg, 0.60 mmol) at 500 °C gave a brown solid at the furnace exit which proved by ^1H and ^{31}P NMR to be Ph_3PO in the cold trap a yellow oil which was shown

by ^{1}H and ^{31}P NMR to be Ph_3PO and in the inlet tube a black solid which was shown by ^{1}H, ^{13}C and ^{31}P NMR to be an unexpected product lacking the OEt group. The structural possibilities for this are described in the Discussion; (HRMS: found M^+, 468.1724. $C_{27}H_{25}N_4O_2P$ requires *M*, 468.1715);δ_H 7.80–7.30 (15 H, m), 4.28 (1 H, d, *J* 2), 2.78 (1 H, m), 1.10 (3 H, d, *J* 7, CH*Me*) and 0.96 (3 H, d, *J* 7, CH*Me*); δ_C 192.2 (d, *J* 6), 171.6 (d, *J* 16), 155.6, 148.1, 134.2 (d, *J* 11), 133.7 (d, *J* 3), 129.2 (d, *J* 13), 121.1 (d, *J* 94), 68.7 (d, *J* 118), 68.3 (d, *J* 10), 29.2, 17.8 and 16.6; δ_P + 10.4; *m/z* 468 (M^+, 45%), 427 (48), 384 (20), 328 (80) and 277 (100).

4. Hydrogenation of ylide **660**

To a solution of ethyl 4-(*S*)-ethoxycarbonylamino-5-methyl-3-oxo-2-triphenylphos phoranylidenehexanonitrile **660** (0.28 g, 0.52 mmol) in ethyl acetate (25 cm^3) was added 10% Pd/C catalyst (0.1 g) and the mixture stirred under a hydrogen atmosphere for 48 hours. The mixture was filtered through celite and the filtrate concentrated to give the crude product as a colourless oil (0.25 g). ^{31}P showed three products, starting material, deprotected product and some kind of cyclic product; δ_P + 20.9, +20.5 and +9.6. Attempt to isolate the products were unsuccessful.

I Preparation and Pyrolysis of Vinylogous Aminoacyl Ylides

1. Preparation of the starting ylides

a. *Methyl 4-triphenylphosphoniobut-2-enoate bromide* **680**

To a solution of triphenylphosphine (14.5 g, 55 mmol) in toluene (150 cm^3) was added methyl 4-bromocrotonate (10 g, 55 mmol) and the mixture stirred at room temperature for 60 h. The precipitate was filtered off and washed with ether (25 cm^3) to yield the desired salt (10.9 g, 69%) as a colourless solid, mp 178–180 °C (lit.,[157] 179–180 °C); δ_H 7.98–7.60 (15 H, m, Ph), 6.75 (1 H, m, =CH), 6.44 (1 H, m, =CH), 5.20 (2 H, dd, *J* 16, 8, PCH_2) and 3.65 (3 H, s, OMe); δ_C 164.7 (CO), 134.8 (3 x C-4 of P-Ph), 133.3 (d, *J* 10, 6 x C-3 of P-Ph), 132.4 (d, *J* 9, =C), 128.0 (d, *J* 41, =C), 116.7 (d, *J* 87, 3 x C-1 of P-Ph), 51.2 (OMe) and 26.9 (d, *J* 51, PCH_2); δ_P +22.0.

b. *Ethyl 4-triphenylphosphoniobut-2-enoate bromide* **681**

Reaction as in a. with triphenylphosphine (14.7 g, 52 mmol) in toluene (150 cm^3) and ethyl 4-bromocrotonate (10 g, 52 mmol) gave the desired salt as a colourless solid (17.2 g, 73%), mp 183–185 °C (lit.,[158] 189–191 °C); δ_H 7.95–7.50 (15 H, m, Ph), 6.65 (1 H, m, =CH), 6.40 (1 H, m, =CH), 5.16 (2 H, dd, *J* 16, 8, PCH_2), 4.05 (2 H, q, *J* 7, OCH_2) and 1.15 (3 H, t, *J* 7, Me); δ_C 164.9 (CO), 135.4 (3 x C-4 of P-Ph), 133.9 (d, *J* 10, 6 x C-2 of P-Ph), 132.6 (d, *J* 7, =C), 130.5 (d, *J* 13, 6 x C-3 of P-Ph), 128.6 (d, *J* 59, =C), 117.3 (d, J 86, 3 x C-1 of P-Ph), 60.6 (OCH_2), 27.3 (d, *J* 49, PCH_2) and 13.9 (Me); δ_P +22.2.

c. *Methyl 4-triphenylphosphoranylidenebut-2-enoate* **682**

Methyl 4-triphenylphosphoniobut-2-enoate bromide (3.08 g, 7.2 mmol) was dissolved in water (150 cm^3) and the solution extracted with ether (25 cm^3), then filtered through celite. The solution was stirred while sodium hydroxide (0.3 g, 7.2 mmol) in water (1 cm^3) was added dropwise. The mixture was extracted with ethyl acetate which was dried and evaporated to furnish the title compound (1.20 g, 46%) as an orange solid, mp 178–180 °C (lit.,[157] 175–179 °C); δ_H 7.7–7.4 (15 H, m, Ph), 6.40 (1 H, m, =CH), 5.61–5.40 (1 H, m, =CH), 5.15 (1 H, d, *J* 12, P=CH) and 3.60 (3 H, s, OMe); δ_C 170.5 (CO), 151.8 (=C), 133.0 (d, *J* 10, 6 x C-2 of P-Ph), 132.5 (3 x C-4 of P-Ph), 129.0 (d, *J* 12, 6 x C-3 of P-Ph), 126.6 (d, *J* 89, C-1 of P-Ph), 90.0 (d, *J* 22, P=C–C=*C*), 49.5 (OMe) and 47.4 (d, *J* 123, P=C); δ_P +19.3.

d. *Ethyl 4- triphenylphosphoranylidenebut-2-enoate* **683**

Reaction as in c. with ethyl 4-triphenylphosphoniobut-2-enoate bromide (6.82 g, 15 mmol) and sodium hydroxide (0.6 g, 15 mmol) gave after recrystallisation from ethyl acetate the title compound (5.5 g, 98%) as orange crystals, mp 171–172 °C; (lit.,[158] 165–167 °C); δ_H 7.73–7.40 (15 H, m, Ph), 6.40 (1 H, m, =CH), 5.60–5.40 (1 H, m, =C), 5.16 (1 H, d, *J* 12, P=CH), 4.10 (2 H, q, *J* 7, CH_2) and 1.20 (3 H, t, *J* 7, Me); δ_C 170.4 (CO), 151.8 (C=C), 133.1 (d, *J* 10, 6 x C-2 of P-Ph), 129.1 (d, *J* 4, 3 x C-4 of P-Ph), 128.5 (d, *J* 12, 6 x C-3 of P-Ph), 127.4 (d, *J* 89, 3 x C-1 of P-Ph), 90.7 (d, *J* 23, P=C–C=*C*), 57.7 (OCH_2), 47.1 (d, *J* 120, P=C) and 14.7 (Me); δ_P +17.9.

2. Preparation of the aminoacyl β,γ-unsaturated ylides

a. *Methyl (6S)-6-benzyloxycarbonylamino-5-oxo-4-triphenylphosphoranylidenehept-2-enoate* **686**

To a solution of methyl 4-triphenylphosphoranylidenebut-2-enote (2.04 g, 5.6 mmol) and *N*-benzoxycarbonyl-(*S*)-alanine (1.25 g, 5.6 mmol) in dry CH_2Cl_2 (40 cm^3) at 0 °C was added EDCI (1.0 g, 5.6 mmol) and DMAP (cat). The mixture was stirred at this temperature for 30 mins and then allowed to warm up and stir overnight. Once all starting materials were consumed (indicated by TLC) the mixture was poured into brine (30 cm^3), extracted with CH_2Cl_2 (2 x 30 cm^3) and the combined organic phase dried and evaporated to furnish the crude product. Chromatography on silica (ethyl acetate-hexane, 2:1) gave the title compound (1.06 g, 33%) as an orange solid, m.p 86–87 °C (Found: C, 72.7; H, 5.75; N, 2.1. $C_{34}H_{33}NO_5P$ requires C, 72.2; H, 5.7; N, 2.5%) (HRMS: found: M+H$^+$, 566.2090. $C_{34}H_{32}NO_5P$ requires *M+H*, 566.2096); $[\alpha]_D^{20}$ –36.02 (*c* 0.44 in CH_2Cl_2); ν_{max}/cm^{-1} 3394, 1719, 1664, 1584, 1464, 1378, 1267, 1163, 1111, 1024, 855, 721 and 692; δ_H 7.76–7.54 (15 H, m, Ph), 7.45 (1 H, m, HC=), 7.30 (5 H, m, Ph), 6.94 (1 H, m, HC=), 6.25 (1 H, br d, *J* 7, NH), 5.43 (1 H, m, C*H*NH), 5.07 (2 H, s, OCH_2), 3.63 (3 H, s, OMe) and 1.36 (3 H, d, *J* 7, Me); δ_C 193.9 (P=C–*C*O), 169.3 (*C*O_2Me), 155.5 (NHCO), 155.5 (d, *J* 7, =C), 136.7 (C-1 of Ph), 137.2 (C-4 of Ph), 133.6 (d, *J* 2, 3 x C-4 of P-Ph), 133.5 (d, *J* 10, 3 x C-2 of P-Ph), 129.6 (d, *J* 12, 6 x C-3 of P-Ph), 128.3 (Ph), 127.7 (Ph), 123.1 (d, *J* 90, 3 x C-1 of P-Ph), 100.3 (d, *J* 16, P=C–C=*C*), 75.6 (d, *J* 101, P=C), 65.9 (OCH_2), 53.0 (CHN), 50.2 (OMe) and 20.9 (Me); δ_P +21.3; *m/z* (CI) 566 (M+H$^+$, 4%), 401 (11), 387 (100), 277 (29), 262 (53), 183 (42), 108 (21) and 91 (85).

b. *Methyl (6S)-6-benzyloxycarbonylamino-7-methyl-5-oxo-4-triphenylphosphoranylideneoct-2-enoate* **687**

Reaction as in a. with methyl 4-triphenylphosphoranylidenebut-2-enoate (1.02 g, 2.8 mmol), *N*-benzoxycarbonyl-(S)-valine (0.79 g, 2.8 mmol) and EDCI (0.5 g, 2.6 mmol) gave the crude product. Chromatography on silica (ethyl acetate-hexane, 2:1) gave the title compound (0.6 g, 36%) as an orange oil, (HRMS: found M$^+$–MeOH, 561.2057.

$C_{36}H_{36}NO_5P$ requires *M–MeOH*, 561.2069); $[\alpha]_D^{20}$ +6.02 (*c* 0.05 in CH_2Cl_2); ν_{max}/cm^{-1} 3397, 1716, 1586, 1498, 1437, 1390, 1269, 1165, 1105, 1026, 861, 722 and 694; δ_H 7.90–7.25 (15 H, m, Ph), 7.25–7.10 (5 H, m, Ph), 7.00–6.80 (2 H, m, =CH), 6.10 (1 H, d, *J* 7, NH), 5.60–5.40 (1 H, m, C*H*NH), 5.20–5.00 (2 H, d, OCH_2), 3.62 (3 H, s, OMe), 2.29–2.10 (1 H, m, C*H*Me_2), 1.04 (3 H, d, *J* 7, Me) and 0.80 (3 H, d, *J* 7, Me); δ_C 193.4 (P=C–*C*O), 169.3 (*C*O_2Me), 156.6 (NHCO), 155.5 (=C), 137.0 (C-1 of Ph), 133.4 (3 x C-4 of P-Ph), 133.3 (d, *J* 10, 6 x C-2 of P-Ph), 129.4 (d, *J* 12, 6 x C-3 of P-Ph), 128.3 (Ph), 127.9 (Ph), 123.0 (d, *J* 89, 3 x C-1 of P-Ph), 101.2 (d, *J* 16, P=C–C=*C*), 74.6 (d, *J* 101, P=C), 65.8 (OCH_2), 60.9 (CHN), 49.9 (OMe) 32.0 (*C*HMe_2), 20.4 (Me) and 16.0 (Me); δ_P +21.2; *m/z* 593 (M^+, 2%), 561 (12), 519 (16), 387 (90), 277 (70), 262 (84), 183 (67) and 91 (100).

c. *Ethyl 6-benzyloxycarbonylamino-5-oxo-4-triphenylphosphoranylidenehex-2-enoate* **688**

Reaction as in a. with ethyl 4-triphenylphosphoranylidenebut-2-enoate (1.42 g, 3.8 mmol), *N*-benzoxycarbonylglycine (0.79 g, 3.8 mmol) and EDCI (0.73 g, 3.8 mmol) gave the crude product. Chromatography on silica (ethyl acetate) gave the title compound (0.98 g, 46%) as a brown oil; ν_{max}/cm^{-1} 3397, 3059, 2978, 1718, 1665, 1595, 1510, 1439, 1396, 1270, 1168, 1111, 1029, 861, 723 and 694; δ_H 7.77–7.48 (15 H, m, Ph), 7.34 (5 H, m, Ph), 7.26 (1 H, m, =CH), 6.94 (1 H, m, =CH), 6.22 (1 H, br d, *J* 7, NH), 5.12 (2 H, s, OCH_2), 4.51 (2 H, d, J 7, C*H*$_2$NH), 4.12 (2 H, q, *J* 7, OC*H*$_2$Me) and 1.20 (3 H, t, *J* 7, CH_2*Me*); δ_C 188.6 (P=C–*C*O), 168.4 (*C*O_2Et), 155.8 (NHCO), 154.4 (d, *J* 10, =C), 136.7 (C-1 of Ph), 133.3 (d, *J* 3, 3 x C-4 of P–Ph), 133.0 (d, *J* 10, 6 x C-2 of P-Ph), 129.1 (d, *J* 12, 6 x C-3 of P-Ph), 127.9 (Ph), 127.8 (Ph), 127.2 (Ph), 122.5 (d, *J* 90, 3 x C-1 of P-Ph), 100.5 (d, *J* 16, P=C–C=*C*), 74.4 (d, *J* 101, P=C), 65.5 (O*C*H$_2$Ph), 58.0 (O*C*H$_2$Me), 49.6 (*C*HNH) and 14.1 (CH_2*Me*); δ_P +21.3; *m/z* no M^+ observed using EI, CI or FAB.

d. *Ethyl (6S)-6-benzyloxycarbonylamino-5-oxo-4-triphenylphosphoranylidenehept-2-enoate* **689**

Reaction as in a. with ethyl 4-triphenylphosphoranylidenebut-2-enoate (0.88 g, 2.3 mmol), *N*-benzoxycarbonyl-(*S*)-alanine (0.51 g, 3.2 mmol) and EDCI (0.5 g, 2.6 mmol) gave the crude product. Chromatography on silica (ethyl acetate) gave the title compound (0.67 g, 32%) as a yellow oil, (HRMS: found M^+, 579.2159. $C_{35}H_{34}NO_5P$ requires *M*, 579.2175); $[\alpha]_D^{20}$ –29.59 (*c* 0.49 in CH_2Cl_2); ν_{max}/cm^{-1} 3409, 1718, 1664, 1586, 1508, 1438, 1393, 1341, 1267, 1169, 1110, 1026, 857, 722 and 693; δ_H 7.82–7.51 (15 H, m, Ph), 7.31 (5 H, s, Ph), 7.24 (1 H, m, HC=), 7.00 (1 H, m, HC=), 6.28 (1 H, br d, *J* 7, NH), 5.50 (1 H, m, C*H*NH), 5.06 (2 H, s, OCH_2Ph), 4.09 (2 H, q, *J* 7, OCH_2Me), 1.37 (3 H, d, *J* 7, CH*Me*) and 1.19 (3 H, t, *J* 7, CH_2Me); δ_C 193.6 (P=C–*C*O), 168.4 (CO_2Et), 155.3 (d, *J* 10, =C), 155.1 (NHCO), 136.9 (C-1 of Ph), 133.4 (d, *J* 2, 3 x C-4 of P–Ph), 133.2 (d, *J* 10, 6 x C-2 of P-Ph), 129.3 (d, *J* 12, 6 x C-3 of P-Ph), 128.0 (Ph), 127.3 (Ph), 122.7 (d, *J* 90, 3 x C-1 of P-Ph), 100.0 (d, *J* 16, P=C–C=*C*), 75.0 (d, *J* 99, P=C), 65.5 (OCH_2Ph), 58.3 (OCH_2Me), 52.7 (CHN), 20.7 (CH*Me*) and 14.2 (Me); δ_P +21.5; *m/z* 579 (M^+, 2%), 502 (5), 444 (12), 277 (12), 241 (100) and 91 (72).

e. *Ethyl (6S)-6-benzyloxycarbonylamino-7-methyl-5-oxo-4-triphenylphosphoranylideneoct-2-enoate* **690**

Reaction as in a. with ethyl 4-triphenylphosphoranylidenebut-2-enoate (2.17 g, 5.2 mmol), *N*-benzoxycarbonyl-(*S*)-valine (1.48 g, 5.2 mmol) and EDCI (1.0 g, 5.2 mmol) gave the crude product. Chromatography on silica (ethyl acetate) gave the title compound (1.40 g, 40%) as a yellow oil (HRMS: not obtainable); $[\alpha]_D^{24}$ –22.73 (*c* 0.55 in CH_2Cl_2); ν_{max}/cm^{-1} 3422, 1719, 1664, 1586, 1498, 1439, 1390, 1370, 1331, 1266, 1164, 1104, 736 and 694; δ_H 7.80–7.51 (15 H, m, Ph), 7.35 (5 H, s, Ph), 7.27 (1 H, m, =CH), 6.90 (1 H, m, =CH), 6.04 (1 H, m, C*H*NH), 5.51 (1 H, br d, *J* 7, NH), 5.10 (2 H, s, OCH_2Ph), 4.15 (2 H, m, OCH_2Me), 2.19 (1 H, m, C*H*Me_2), 1.22 (3 H, t, *J* 7, CH_2Me) 1.02 (3 H, d, *J* 7, CHMe_2) and 0.74 (3 H, d, *J* 7, CHMe_2); δ_C 193.3 (P=C–*C*O), 168.8 (CO_2Et), 156.5 (NHCO), 155.4 (d, *J* 10, =C), 137.0 (C-1 of Ph), 133.4 (3 x C-4 of P-Ph), 133.2 (d, *J* 10, 6 x C-2 of P-Ph),

129.3 (d, *J* 12, 6 x C-3 of P-Ph), 128.0 (Ph), 127.5 (Ph), 127.4 (Ph), 123.0 (d, *J* 90, 3 x C-1 of P-Ph), 101.0 (d, *J* 16, P=C–C=*C*), 74.2 (d, *J* 100, P=C), 65.7 (OCH_2Ph), 60.7 (CHN), 58.3 (OCH_2Me), 31.8 ($CHMe_2$), 20.2 (Me), 15.9 (Me) and 14.2 (CH_2Me); δ_P +21.5; *m/z* (FAB) 609 ($M+2H^+$, 25%), 401 (30), 302 (32), 154 (100) and 136 (70).

f. *Methyl 7-benzyloxycarbonylamino-5-oxo-4-triphenylphosphoranylidenehept-2-enoate* **691**

Reaction as in a. with methyl 4-triphenylphosphoranylidenebut-2-enoate (1.62 g, 4.5 mmol), *N*-benzoxycarbonyl-β-alanine (1.00 g, 4.5 mmol) and EDCI (0.87 g, 4.5 mmol) gave the crude product. Chromatography on silica (ethyl acetate) gave the title compound (1.01 g, 40%) as a brown oil; ν_{max}/cm^{-1} 3423, 3059, 2947, 1714, 1661, 1587, 1505, 1437, 1391, 1266, 1165, 1119, 1069, 857, 722 and 694; δ_H 7.79–7.41 (15 H, m, Ph), 7.35 (5 H, m, Ph), 7.30 (1 H, m, =CH), 6.86 (1 H, m, =CH), 5.81 (1 H, br t, *J* 7, NH), 5.07 (2 H, s, OCH_2), 3.64 (3 H, s, OMe), 3.54 (2 H, q, *J* 7, CH_2NH) and 1.36 (2 H, t, *J* 7, CH_2CO); δ_C 194.6 (P=C–*C*O), 169.4 (CO_2Me), 155.9 (NHCO), 153.9 (d, *J* 10, =C), 136.5 (C-1 of Ph), 132.9 (C-4 of P-Ph), 132.7 (d, *J* 10, 6 x C-2 of P-Ph), 128.8 (d, *J* 12, 6 x C-3 of P-Ph), 127.7 (Ph), 127.6 (Ph), 122.5 (d, *J* 89, 3 x C-1 of P-Ph), 102.4 (d, *J* 14, P=C–C=*C*), 73.3 (d, *J* 100, P=C), 65.2 (OCH_2), 49.2 (OMe) 40.3 (CH_2NH) and 37.0 (CH_2CO); δ_P +21.3; *m/z* no M^+ observed using EI, CI or FAB.

3. Pyrolysis of the aminoacyl β,γ-unsaturated ylides

a. Pyrolysis of ylide **686**

FVP of the ylide **686** (50 mg, 0.09 mmol) at 600 °C and 7.9 x 10^{-3} Torr resulted with Ph_3P and Ph_3PO in the cold trap. However in the inlet tube was the product of interest, obtained as a black oil (6 mg, 13%). This turned out to be (*7S*)-1-benzyloxycarbonylamino-7-methyl-5-triphenylphosphoranylidene-1,5,6,7-tetrahydro[2*H*]azepine-2,6-dione **693**, (HRMS: found M^+, 533.1747. $C_{33}H_{28}NO_4P$ requires *M* 533.1756); ν_{max}/cm^{-1} 3111, 1770, 1712, 1639, 1556, 1459, 1390, 1317, 1127, 859, 742 and 708; δ_H 7.90–7.60 (20 H, m, Ph), 7.40–6.90 (2 H, 2 x m, HC=CH), 5.30 (2 H, s, OCH_2), 4.10 (1 H, q, *J* 7, C*H*Me) and 1.48 (3 H, d, *J* 7, Me); δ_C 193.3 (P=C–*C*O), 170.4 (C=C–*C*O), 151.9 (NCO), 147.8 (P=C–*C*), 136.3

(C-1 of Ph), 134.1 (d, *J* 2, C-4 of P-Ph), 133.5 (d, *J* 10, 6 x C-2 of P-Ph), 129.8 (d, *J* 12, 6 x C-3 of P-Ph), 128.4 (Ph), 127.7 (Ph), 121.8(d, *J* 91, 3 x C-1 of P-Ph), 99.6 (d, *J* 18, P=C–C=*C*), 80.4 (d, *J* 102, P=C), 67.0 (OCH_2), 58.8 (CHN) and 17.5 (Me); δ_P +21.0; *m/z* 533 (M^+, 7%), 489 (2), 399 (36), 328 (12), 300 (16), 277 (34), 262 (95), 183 (62) and 91 (100).

b. Pyrolysis of ylide **690**

FVP of the ylide **690** (50 mg, 0.08 mmol) at 600 °C and 7.9 x 10^{-3} Torr produced Ph_3P and Ph_3PO in the cold trap. However as above in the inlet tube was the product of interest, obtained as a black oil (12 mg, 26%). This turned out to be (7S)-1-benzyloxycarbonylamino-7-isopropyl-5-triphenylphosphoranylidene-1,5,6,7-tetrahydro[2*H*]azepine-2,6-dione **695** (HRMS: found M+2H$^+$, 563.2261. $C_{35}H_{32}NO_4P$ requires *M+2H*, 563.2225); ν_{max}/cm^{-1} 3059, 2964, 1720, 1660, 1582, 1497, 1266, 1166, 1021, 860, 782 and 699; δ_H 7.90–7.50 (20 H, m, Ph), 7.50–6.90 (2 H, 2 x m, =CH), 5.30 (2 H, s, OCH_2), 4.08 (1 H, s, CHN), 2.44 (1 H, m, C*H*Me_2), 1.16 (3 H, d, *J* 7, Me) and 0.88 (3 H, d, *J* 7, Me); δ_C 192.4 (P=C–*C*O), 171.0 (C=C–*C*O), 152.1 (NCO), 147.8 (br, P=C–*C*=), 136.3 (C-1 of Ph), 133.9 (d, *J* 2, C-4 of P-Ph), 133.4 (d, *J* 10, 6 x C-2 of P-Ph), 129.7 (d, *J* 12, 6 x C-3 of P-Ph), 128.4 (Ph), 127.6 (Ph), 127.5 (Ph), 121.9 (d, *J* 91, 3 x C-1 of P-Ph), 101.4 (d, *J* 18, P=C–C=*C*), 79.2 (d, *J* 101, P=C), 66.9 (OCH_2), 66.5 (CHN), 30.0 (*C*HMe_2), 18.3 (Me) and 15.9 (Me); δ_P +21.0; *m/z* (FAB) 563 (M+2H$^+$, 80%), 519 (20), 454 (25), 428 (32), 384 (30), 277 (100) and 262 (65).

c Pyrolysis of ylide **688**

FVP of the ylide **688** (100 mg, 0.18 mmol) at 600 °C and 8 x 10^{-3} Torr produced Ph_3P and Ph_3PO in the cold trap. However as above in the inlet tube was the product of interest, obtained as a black oil (18 mg, 20%). This turned out to be 7-(S)-1-benzyloxycarbonylamino-5-triphenylphosphoranylidene-1,5,6,7-tetrahydro[2*H*]azepine-2,6-dione **694**; ν_{max}/cm^{-1} 3423, 2963, 1719, 1680, 1438, 1262, 1180, 1120, 802, 722 and 695; δ_H 7.80–7.22 (20 H, m, Ph), 7.40–6.86 (2 H, 2 x m, HC=CH), 5.28 (2 H, s, OCH_2) and 3.98 (2 H, s, CH_2); δ_C 190.0 (P=C–*C*O), 170.7 (C=C–*C*O), 151.8 (NCO), 147.9 (C=C), 136.3 (C-1 of

Ph), 134.1 (d, *J* 2, C-4 of P–Ph), 133.5 (d, *J* 10, 3 x C-2 of P-Ph), 129.8 (d, *J* 12, 3 x C-3 of P-Ph), 128.4 (Ph), 127.8 (Ph), 121.9 (d, *J* 91, 3 x C-1 of P-Ph), 101.4 (d, *J* 18, P=C–C=*C*), 79.9 (d, *J* 102, P=C), 67.1 (OCH_2) and 52.7 (CHN); δ_P +21.0; *m/z* no M^+ observed using EI, CI or FAB.

J Preparation and Cyclisation of *N*-Deprotected Aminoacyl Ylides

1. Pyrolysis of ylide **551**

a. *(5S)-5-Methyl-3-triphenylphosphoranylidenepyrrolidine-2,4-dione* **701**

To a solution of ethyl (4*S*)-4-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenepentanoate **551** (0.4 g, 0.72 mmol) in methanol (15 cm^3) was added 10% Pd/C catalyst (0.1 g) and the mixture stirred under a hydrogen atmosphere for several hours. The mixture was filtered through celite and the filtrate concentrated to give the crude product. Recrystallisation from ethyl acetate yielded the title compound (0.15 g, 56%) as colourless crystals, mp 197–199 °C (Found: C, 73.5; H, 5.3; N, 3.6. $C_{23}H_{20}NO_2P$ requires C, 73.8; H, 5.4; N, 3.7%) (HRMS: found M^+, 373.1232 $C_{23}H_{20}NO_2P$ requires *M* 373.1232); $[\alpha]_D^{25}$ –9.9 (*c* 0.9 in CH_2Cl_2); ν_{max} /cm^{-1} 3321, 1671, 1608, 1317, 1109, 756, 719 and 690; δ_H 7.82–7.58 (9 H, m, Ph), 7.58–7.44 (6 H, m, Ph), 5.25 (1 H, br s, NH), 3.88 (1 H, q, *J* 8, CH) and 1.37 (3 H, d, *J* 8, Me); δ_C 197.3 (d, *J* 7, P=C–*C*O), 176.1 (d, *J* 16, NCO), 133.9 (d, *J* 11, 6 x C-2 of P-Ph), 132.7 (d, *J* 2, 3 x C-4 of P-Ph), 128.6 (d, *J* 13, 6 x C-3 of P-Ph), 122.9 (d, *J* 93, 3 x C-1 of P-Ph), 63.1 (d, *J* 123, P=C), 57.9 (d, *J* 13, NCH) and 18.4 (Me); δ_P +10.7; *m/z* (EI) 373 (M^+, 76%), 301 (66), 262 (100), 196 (7), 183 (33), 165 (12) and 108 (10).

b. (4S)-Ethyl 4-amino-3-oxo-2-triphenylphosphoranylidenepentanoate **700**

In a second run, a solution of ethyl 4-(*S*)-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenepentanoate **551** (1.5 g, 2.70 mmol) in methanol (35 cm^3) was added 10% Pd/C catalyst (0.3 g) and the mixture stirred under a hydrogen atmosphere for several hours. The mixture was filtered through celite and the filtrate concentrated to give the crude product which was a 2:1 mixture of the cyclic product **701** and the deprotected amino acid ylide **700**.

The crude product was dissolved in ethyl acetate and filtered hot. Concentration of the filtrate gave mainly the cyclic product **701** (0.60 g, 58%) as colourless crystals, data as above.

The white solid filtered off was the title compound **700** (0.29 g, 28%); mp 200–202 °C (lit.,[138] 203–204 °C); δ_H 7.79–7.67 (9 H, m, Ph), 7.66–7.42 (6 H, m, Ph), 5.04 (1 H, q, *J* 8, CH), 3.74 (2 H, m, C*H*$_2$Me), 1.57 (3 H, d, *J* 8, Me) and 0.68 (3 H, t, *J* 7, CH$_2$*Me*); δ_C 192.0 (d, *J* 4, P=C–*C*O), 166.0 (d, *J* 13, CO_2), 132.4 (d, *J* 11, 6 x C-2 of P-Ph), 131.4 (d, *J* 3, 3 x C-4 of P-Ph), 128.2 (d, *J* 13, 6 x C-3 of P-Ph), 125.6 (d, *J* 93, 3 x C-1 of P-Ph), 68.7 (d, *J* 109, P=C), 58.1 (OCH_2), 57.6 (d, *J* 13, NCH) 17.7 (CH*Me*) and 13.0 (OCH_2*Me*); δ_P +18.1.

2. Pyrolysis of ylide **700**

FVP of the mixture of ylides (from 2.) (0.33 g, 600 °C, 1.0 x 10^{-2} Torr) gave ethanol in the cold trap and a pale yellow solid at the furnace exit. Recrystallisation of the product from ethyl acetate gave the cyclic ylide **701** as colourless crystals (0.10 g, 56%); data as in 1.

3. *Ethyl 4-amino-3-oxo-2-triphenylphosphoranylidenebutanoate* **702**

Reaction as in 1. using ethyl 4-benzoxycarbonylamino-3-oxo-2-triphenylphos phoranylidenebutanoate **550** (0.25 g, 0.46 mmol) gave the title product (0.07 g, 37%) as an orange oil; (Found: M+H$^+$, 406.1592 $C_{24}H_{24}NO_3P$ requires *M+H*, 406.1598); ν_{max} /cm^{-1} 3337, 1687, 1605, 1417, 1309, 1110, 789, 721 and 693; δ_H 7.76–7.55 (9 H, m, Ph), 7.54–7.34 (6 H, m, Ph), 4.01 (2 H, br s, CH_2), 3.73 (2 H, q, *J* 8, C*H*$_2$Me), 2.14 (2 H, br s, NH_2) and 0.66 (3 H, t, *J* 7, CH$_2$*Me*); δ_C 195.9 (P=C–*C*O), 167.4 (d, *J* 15, CO_2), 132.7 (d, *J* 10, 6 x C-2 of P-Ph), 131.4 (d, *J* 2, 3 x C-4 of P-Ph), 128.2 (d, *J* 13, 6 x C-3 of P-Ph), 125.9 (d, *J* 93, 3 x C-1 of P-Ph), 68.2 (d, *J* 110, P=C), 58.1 (OCH_2), 49.6 (d, *J* 7, NCH) and 13.4 (Me); δ_P +17.2; *m/z* (EI) 406 (M$^+$, 4%), 375 (100), 359 (29), 301 (31), 277 (40), 262 (55) and 183 (25).

4. *3-Triphenylphosphoranylidenepyrrolidine-2,4-dione* **703**

FVP of the ylide ethyl 4-amino-3-oxo-2-triphenylphosphoranylidenebutanoate **702** (0.07 g, 600 °C, 2.0 x 10^{-2} Torr) gave ethanol in the cold trap and a pale yellow solid at the furnace exit. The ^{31}P NMR spectrum showed Ph_3PO, Ph_3P and the title product **8** (0.03 g, 56%) as a white solid, mp 210–212 °C; (Found: M+H$^+$, 360.1174. $C_{22}H_{18}NO_2P$ requires *M+H*, 360.1153); ν_{max} /cm^{-1} 3278, 1688, 1638, 1407, 1322, 1101, 856, 769 and 691; δ_H 7.71–7.56 (9 H, m, Ph), 7.55–7.37 (6 H, m, Ph) and 3.85 (2 H, s, CH_2); δ_C 194.6 (d, *J* 8, P=C–*C*O), 177.4 (d, *J* 17, CO_2), 134.0 (d, *J* 11, 6 x C-2 of P-Ph), 133.0 (d, *J* 2, 3 x C-4 of P-Ph), 128.8 (d, *J* 13, 6 x C-3 of P-Ph), 122.4 (d, *J* 94, 3 x C-1 of P-Ph), 65.2 (d, *J* 123, P=C) and 52.3 (d, *J* 13, CH_2); δ_P +10.8; *m/z* (CI) 360 (M+H$^+$, 6%), 319 (7), 279 (100), 217 (4) and 201 (5).

5. Deprotection of 1-ethyl 7-methyl (4S)-4-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidene heptanedioate **555**

To a solution of 1-ethyl 7-methyl 4-(S)-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylideneheptane-1,7-dioate **555** (0.8 g, 1.3 mmol) in methanol (25 cm^3) was added 10% Pd/C catalyst (0.1 g) and the mixture stirred under a hydrogen atmosphere for several hours. The mixture was filtered through celite and the filtrate concentrated to give the crude product. This was purified by column using 2% methanol in dichloromethane to give a mixture of unreacted starting material, Ph_3PO and two cyclic products **705** and **706**.

a. *(5S)-5-(2-Methoxycarbonylethyl)-3-triphenylphosphoranylidenepyrrolidine-2,4-dione* **705** was obtained as a colourless oil (0.12 g, 20%); (HRMS: found M$^+$, 445.1455. $C_{26}H_{24}NO_4P$ requires *M* 445.1443); $[\alpha]_D^{25}$ –8.3 (*c* 0.54 in CH_2Cl_2); ν_{max} /cm^{-1} 3423, 1741, 1668, 1610, 1439, 1377, 1170, 1109, 723 and 693; δ_H 7.87–7.59 (9 H, m, Ph), 7.58–7.40 (6 H, m, Ph), 5.18 (1 H, br s, NH), 3.92 (1 H, t, *J* 7, CH) 3.67 (3 H, s, OMe) and 2.60–1.80 (4 H, m, CH_2CH_2); δ_C 196.0 (d, *J* 8, P=C–*C*O), 176.5 (d, *J* 17, NCO), 173.8 (CO_2), 134.0 (d, *J* 11, 6 x C-2 of P-Ph), 133.0 (d, *J* 2, 3 x C-4 of P-Ph), 128.8 (d, *J* 13, 6 x C-3 of P-Ph), 122.8 (d, *J* 93, 3 x C-1 of P-Ph), 64.2 (d, *J* 123, P=C), 61.3 (d, *J* 13, NCH), 51.5

(OMe), 29.5 (CH_2) and 27.4 (CH_2); δ_P + 10.8; *m/z* (EI) 445 (M^+, 16%), 396 (100), 359 (15), 301 (16), 389 (38), 277 (97), 262 (27), 201 (19) and 183 (24).

b. *Ethyl 3-oxo-3-(S-pyrrolidin-2-one-5-yl)-2-triphenylphosphoranylidenepropionate* **706** was obtained as a colourless oil (0.07 g, 12%); $[\alpha]_D^{25}$ –2.33 (*c* 0.17 in CH_2Cl_2); ν_{max} /cm^{-1} 3428, 1655, 1634, 1439, 1377, 1190, 1109, 723 and 693; δ_H 7.77–7.33 (15 H, m, Ph), 6.38 (1 H, br s, NH), 5.01 (1 H, t, *J* 7, C*H*NH), 3.68 (2 H, q, *J* 7, OCH_2), 1.82–2.60 (4 H, m, CH_2CH_2) and 0.62 (3 H, t, *J* 7, OCH_2*Me*); δ_C 193.5 (d, *J* 3, P=C–*C*O), 178.4 (NCO), 167.4 (d, *J* 13, CO_2), 134.2 (d, *J* 11, 6 x C-2 of P-Ph), 132.1 (3 x C-4 of P-Ph), 129.0 (d, *J* 13, 6 x C-3 of P-Ph), 126.0 (d, *J* 94, 3 x C-1 of P-Ph), 69.1 (d, *J* 110, P=C), 59.8 (d, *J* 8, NCH), 58.7 (O*C*H_2Me), 30.1 (CH_2), 24.1 (CH_2) and 13.6 (Me); δ_P + 17.8.

c. *2,4,8-Trioxo-3-triphenylphosphoranylidene-1-azabicyclo[3.3.0]octane* **707** was formed from **706** on standing for 3 months the NMR spectra showed new peaks corresponding to the bicyclic product; δ_C 195.9 (d, *J* 6, P=C–*C*O), 176.5, 173.0, 134.4 (d, *J* 11, 6 x C-2 of P-Ph), 132.8 (3 x C-4 of P-Ph), 128.6 (d, *J* 13, 6 x C-3 of P-Ph), 120.1 (d, *J* 91, 3 x C-1 of P-Ph), 67.1 (d, *J* 111, P=C), 64.6 (d, *J* 9, NCH), 30.0 (CH_2) and 26.8 (CH_2); δ_P + 10.0

6. Hydrogenation of Ethyl 5-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranyli--denepentanoate **562**

Reaction as in 6. using **562** (0.35 g, 0.46 mmol) gave a yellow oil (0.16 g, 83%) which was a 1:1 ratio of ethyl 5-amino-3-oxo-2-triphenylphosphoranylidenepentonate **708** and an additional product which we could not identify; δ_H 7.77–7.30 (m, Ph), 3.70 (m), 3.42 (m), 3.13–2.72 (m), 1.68 (br s) and 0.64 (q, *J* 7, Me); δ_C 196.1 (d, *J* 3, P=C–*C*O), 196.0 (d, *J* 3, P=C–*C*O), 167.3 (d, *J* 15, CO_2), 167.0 (d, *J* 16, CO_2), 132.5 (d, *J* 9, 6 x C-2 of P-Ph), 132.5 (d, *J* 10, 6 x C-2 of P-Ph), 131.1 (d, *J* 2, 3 x C-4 of P-Ph), 130.9 (d, *J* 2, 3 x C-4 of P-Ph), 128.0 (d, *J* 12, 6 x C-3 of P-Ph), 127.9 (d, *J* 12, 6 x C-3 of P-Ph), 126.5 (d, *J* 93, 3 x C-1 of P-Ph), 126.2 (d, *J* 93, 3 x C-1 of P-Ph), 74.0 (CH_2), 70.8 (d, *J* 110, P=C), 70.6 (d, *J*

111, P=C), 57.8 (CH_2Me), 49.2 (CH_2), 43.2 (CH_2), 38.1 (CH_2), 38.0 (d, *J* 6, $COCH_2$), 13.4 (Me) and 13.3 (Me); δ_P + 17.9 and + 17.7.

7. *3-Triphenylphosphoranylidenepiperidine-2,4-dione* **709**

FVP of the ylide **708** (from 7.) (0.16 g, 600 °C, 1.0 x 10^{-2} Torr) gave ethanol and a yellow solid at the furnace exit. The ^{31}P NMR spectrum showed Ph_3PO, the title product **709** and the deprotected acetylenic product **710**.

a. Cyclic product **709** (0.06 g, 42%); δ_H 7.73–7.28 (15 H, m, Ph), 4.0 (2 H, m, CH_2) and 3.39 (2 H, m, CH_2); δ_C 192.0 (d, *J* 4, P=C–*C*O), 171.2 (d, *J* 11, NCO), 133.4 (d, *J* 10, 6 x C-2 of P-Ph), 132.9 (3 x C-4 of P-Ph), 131.6 (d, *J* 12, 6 x C-3 of P-Ph), 124.9 (d, *J* 93, 3 x C-1 of P-Ph), 70.2 (d, *J* 116, P=C), 38.0 (CH_2N) and 37.1 (d, *J* 9, $COCH_2$); δ_P +14.5; *m/z* (CI) 375 ($M+H^+$, 0.1%), 353 (0.3), 339 (0.4) and 319 (10) [Ph_3PO *m/z* 278 = 100%].

b. *Ethyl 5-aminopent-2-ynoate* **710** (0.01 g, 19%); δ_H 4.10 (OCH_2), 3.14 (CH_2), 2.40 (CH_2) and 1.24 (Me); δ_C 170.5 (CO_2), 86.2 (C≡), 73.8 (C≡), 61.7 (OCH_2), 22.8 (CH_2), 19.4 (CH_2) and 17.1 (Me).

8. FVP of (*5S*)-5-methyl-3-triphenylphosphoranylidenepyrrolidine-2,4-dione **701**

FVP of the ylide **701** (0.06 g, 800 °C, 1.0 x 10^{-2} Torr) gave a brown solid at the furnace exit. The NMR spectra showed Ph_3PO and unreacted starting material **701** and an additional very minor product **712**; δ_C 156.9 (4ry), 131.7 (4ry), 119.5 (CH), 115.5 (CH) and 29.7 (CH_2).

K Pyrolysis of Cyclic Ylides

1. Attempted preparation of 4-triphenylphosphoranylidenetetrahydrofuran-2,3,5-trione **726**

Triphenylphosphine (1.75 g, 6.70 mmol) in THF (13 cm^3) was added dropwise to a solution of dichloromaleic anhydride (1.11 g, 6.70 mmol) in THF (7 cm^3) at 0 °C. A few drops of water was added and the mixture was left to stir and heat to room temperature over 1

hour. The white precipitate was filtered off and attempted recrystallisation from ethanol failed. The solvent was evaporated to give ethyl 2-oxo-3-triphenylphosphoranylidenepropionate **728** (0.97 g, 39%) as a white solid; δ_H 7.74–7.37 (15 H, m, Ph), 4.71 (1 H, d, *J* 25, CH), 4.24 (2 H, q, *J* 8, CH_2) and 1.32 (3 H, t, *J* 8, Me); δ_C 173.9 (d, *J* 5, CO), 165.6 (d, *J* 21, CO_2Et), 133.0 (d, *J* 10, 6 x C-3 of P-Ph), 132.4 (d, *J* 3, 3 x C-4 of P-Ph), 128.9 (d, *J* 12, 6 x C-2 of P-Ph), 125.1 (d, *J* 92, 3 x C-1 of P-Ph), 61.1 (OCH_2), 56.6 (d, *J* 108, P=C) and 14.0 (Me); δ_P +17.0. (lit.,[159] ^1H, ^{13}C and ^{31}P data identical to above).

2. Preparation of 4-triphenylphosphoranylidenetetrahydrofuran-2,3,5-trione **726**

Reaction as in 1. but with no attempt to recrystallise gave the title product (1.22 g, 50%) as colourless crystals, mp 233–234 °C (lit.,[84] 229–231 °C); δ_H 7.82–7.55 (15 H, m, Ph); δ_C 174.4 (d, *J* 8, 3-CO), 166.3 (d, *J* 16, 2-CO), 161.6 (d, *J* 22, 5-CO), 134.1 (d, *J* 3, 3 x C-4 of P-Ph), 133.8 (d, *J* 11, 6 x C-2 of P-Ph), 129.4 (d, *J* 13, 6 x C-3 of P-Ph), 119.8 (3 x C-1 of P-Ph) and 67.5 (d, *J* 118, P=C); δ_P +11.6 (lit.,[84] δ_P +11.4).

3. Pyrolysis of 4-triphenylphosphoranylidenetetrahydrofuran-2,3,5-trione **726**

a. FVP of the ylide **726** (36.5 mg, 0.1 mmol, 400 °C, 1.2 x 10^{-2}) gave a brown solid at the furnace exit which proved by ^1H and ^{31}P NMR to contain mainly Ph_3PO, some starting material and other minor unidentified components and in the cold trap a white solid. Methanol was added to the cold trap at –78 °C under a nitrogen atmosphere to trap any reactive products and then removed and evaporated but the ^1H and ^{31}P NMR spectra showed only methanol and no phosphorus containing products.

b. FVP of the ylide **726** (320 mg, 0.85 mmol, 200 °C, 1.1 x 10^{-2}) gave a white solid at the furnace exit which proved by ^1H and ^{31}P NMR to be Ph_3P and Ph_3PO in a ratio of 3:5. In the inlet tube there was a pink solid left which proved by ^1H and ^{31}P NMR to be the 3,5-bis(triphenylphosphoranylidene)cyclopentane-1,2,4-trione **732** (22 mg, 9%); δ_H 7.75–7.40 (15 H, m, Ph); δ_C 196.4 (t, *J* 10, CO), 187.6 (dd, *J* 20, 6, COCO), 134.1 (d, *J* 11, 6 x C-2 of

P-Ph), 132.3 (d, *J* 2, 3 x C-4 of P-Ph), 128.5 (d, *J* 13, 6 x C-3 of P-Ph), 124.6 (d, *J* 92, 3 x C-1 of P-Ph) and 67.6 (dd, *J* 112, 4, P=C); δ_P +9.0 (lit.,[49] δ_P +8.8)

4. Pyrolysis of 4-triphenylphosphoranylidenetetrahydrothiophene-2,3,5-trione **727**

FVP of the ylide **727** kindly supplied by Professor J. Skramstad, University of Oslo[85] (29 mg, 0.07 mmol, 600 °C, 2 x 10^{-2}) gave a white solid at the furnace exit which was shown to consist of 4 products by ^1H and ^{31}P NMR which were Ph_3PO; δ_P +29.2, Ph_3PS; δ_P +43.6 another product; δ_P +22.1 and a large amount of ketenylidenetriphenylphosphorane **731**; δ_P +5.7. In the cold trap a white solid was present and when methanol was added to the cold trap at –78 °C under a nitrogen atmosphere then removed and evaporated the ^1H NMR showed no products. In the inlet tube there was a small amount of black solid which proved to be unreacted starting material.

5. Solution pyrolysis of 4-triphenylphosphoranylidenetetrahydrofuran-2,3,5-trione **727**

a. A solution of the ylide **726** (100 mg, 0.27 mmol) in 1,2-dichlorobenzene (4 cm^3) was heated under reflux for 24 hours. The ^1H and ^{31}P NMR spectra showed unreacted starting material.

b. A solution of the ylide **726** (44 mg, 0.12 mmol) in diphenyl ether (2 cm^3) was heated under reflux for 30 mins and a black solution was formed. The ^1H and ^{31}P NMR spectra showed 3,5-bis(triphenylphosphoranylidene)cyclopentane-1,2,4-trione **732** and small amounts of Ph_3PO and Ph_3P. The solvent was evaporated using a kugelrohr and a mixture of the bis ylide and Ph_3PO was left.

6. Solution pyrolysis of 4-triphenylphosphoranylidenetetrahydrothiophene-2,3,5-trione

A solution of the ylide **727** (20 mg, 0.05 mmol) in diphenyl ether (1 cm^3) was heated under reflux for 4 hours and a black solution was formed. The ^1H and ^{31}P NMR spectra showed 3,5-bis(triphenylphosphoranylidene)cyclopentane-1,2,4-trione **732** and small amounts

of Ph_3PO and Ph_3P. The solvent was evaporated using a kugelrohr and a mixture of the bis ylide **732** and Ph_3PO were left.

7. Neat pyrolysis of 4-triphenylphosphoranylidenetetrahydrofuran-2,3,5-trione **726**

The ylide **726** (20 mg, 0.05 mmol) was heated in the kugelrohr to 250 °C and left at that temperature for 1.5 hours. The resulting black solid was found to be mainly 3,5-bis(triphenylphosphoranylidene)cyclopentane-1,2,4-trione **732** by TLC and NMR.

8. Neat pyrolysis of 4-triphenylphosphoranylidenetetrahydrothiophene-2,3,5-trione **727**

The ylide **727** (10 mg, 0.03 mmol) was heated in the kugelrohr to 250 °C and left at that temperature for 3 hours. The resulting black solid turned black was found to be mainly starting material by NMR.

9. Preparation of ketenylidenetriphenylphosphorane **731**

To a solution of (methoxycarbonylmethylene)triphenylphosphorane **501** (10.0 g, 0.03 mol) in dry toluene (80 cm^3), sodium amide (4.66 g, 0.11 mol) was added and the mixture was heated under reflux for 48 hours under a nitrogen atmosphere. The mixture was cooled and the solid (NaOMe) was filtered off under a nitrogen atmosphere. The filtrate was left to stand and white crystals precipitated out which were filtered off to give the title compound (1.5 g, 17%), mp 173–174 °C (lit.,[160] 172–173.5); δ_C 145.3 (d, *J* 45, C=O), 132.0 (3 x C-4 of P-Ph), 131.9 (d, *J* 11, 6 x C-2 of P-Ph), 129.1 (d, *J* 105, 3 x C-1 of P-Ph), 128.6 (d, *J* 13, 6 x C-3 of P-Ph) and –10.7 (d, *J* 188, P=C) [(lit.,[161] 145.5 (d, *J* 45, C=O) and –10.5 (d, *J* 187.7, P=C)]; δ_P +5.0 (lit.,[162] δ_P +5.4).

10. Solution pyrolysis of ketenylidenetriphenylphosphorane **731** and 4-triphenylphosphor--anylidenetetrahydrofuran-2,3,5-trione **726**

A mixture of the ketenylidenetriphenylphosphorane **731** (32 mg, 0.11 mmol) and 4-triphenylphosphoranylidenetetrahydrofuran-2,3,5-trione **726** (40 mg, 0.11 mmol) was heated in diphenyl ether (1 cm^3) under reflux for 2 hours. The solution went black and the ^{31}P NMR

spectrum showed the presence of 3,5-bis(triphenylphosphoranylidene)cyclopentane-1,2,4-trione **732** (20%) in addition to Ph_3PO and Ph_3P.

11. Solution pyrolysis ketenylidenetriphenylphosphorane **731**

The ketenylidenetriphenylphosphorane (46 mg, 0.15 mmol) was heated in diphenyl ether (1.5 cm^3) under reflux for 30 mins. The solution went black and the ^{31}P NMR spectrum showed, in addition to Ph_3PO and Ph_3P, a new peak for 2,4,6-tris(triphenylphosphoranylidene) cyclohexane-1,3,5-trione **733** (46%) at δ_P +13.9 (lit.,[49] δ_P +13.7).

12. Neat pyrolysis of ketenylidenetriphenylphosphorane **731**

The ylide **731** (250 mg, 0.83 mmol) was heated in the kugelrohr to 200 °C and left at that temperature for 3 hours. A colourless oil was distilled off which was shown by ^{31}P NMR to be Ph_3PO and a black tar was left which was mainly the 2,4,6-tris(triphenylphosphoranylidene)cyclohexane-1,3,5-trione **732** (60%); δ_C 184.3 (3 x CO), 133.6 (*J* 10 , 6 x C-2 of P-Ph), 130.4 (3 x C-4 of P-Ph), 128.3 (*J* 91, 3 x C-1 of P-Ph), 127.6 (*J* 12, 6 x C-3 of P-Ph) and 74.3 (dt, *J* 116, 10, P=C); δ_P +13.4 (lit.,[49] δ_P +13.7).

13. Preparation of tri(*p*-tolyl)phosphine **745**

Sodium metal (24 g, 1.04 mole) was added over a period of 3 hours to a mixture of *p*-bromotoluene (56.4 g, 0.33 mole) and phosphorus trichloride (15.5 g, 0.11 mole) in dry ether (200 cm^3) under a nitrogen atmosphere. The mixture was left to reflux for 48 hours and the solution became dark green. The solid was filtered off and washed with ether and the filtrate was concentrated to give a white solid. The product was recrystallised from ethanol to give the title compound (5.0 g, 7%) as colourless crystals, mp 145–147 °C; δ_H 7.36–7.09 (12 H, m, Ph) and 2.31 (9 H, s, Me), δ_C 138.5 (3 x C-4 of P-Ph), 134.3 (d, *J* 10, 3 x C-1 of P-Ph), 133.7 (d, *J* 19, 6 x C-2 of P-Ph), 129.3 (d, *J* 6, 6 x C-3 of P-Ph) and 21.2 (Me) (lit.,[162] ^1H and ^{13}C data identical to the above); δ_P –7.6.

14. Attempted preparation of 4-tri(*p*-tolyl)phosphoranylidenetetrahydrofuran-2,3,5-trione **743**

Dichloromaleic anhydride (1.0 g, 6.0 mmol)was dissolved in THF (7 cm^3) at 0 °C while tri(*p*-tolyl)phosphine (1.83 g, 6.0 mmol) and 4 drops of water in THF (13 cm^3) was added dropwise over 1 hour. The ice was removed and the mixture left to stir for 2 hours. The solvent was evaporated and a brown oil (1.5 g) was left which did not contain the desired compound by ^{31}P NMR.

15. Attempted preparation of (methoxycarbonylmethyl)tri-*p*-tolylohosphonium bromide **748**

To a solution of tri-p-tolylphosphine (0.25 g, 0.82 mmol) in dry toluene (4 cm^3) was added dropwise a solution of methyl bromoacetate (0.125 g, 0.82 mmol) in dry toluene (1 cm^3). The mixture was left to stir under reflux for 2 hours and then left to stir at room temperature overnight. The solvent was evaporated to give a black oil which was mainly the methyl tri-p-tolylphosphonium bromide **750** (0.32 g, 98%); δ_H 7.73–7.42 (12 H, m, Ph), 3.07 (3 H, d, *J* 15, P-Me) and 2.45 (9 H, s, Me); δ_C 145.5 (d, *J* 2, 3 x C-4 of P-Ph), 132.3 (d, *J* 11, 6 x C-2 of P-Ph), 130.4 (d, *J* 13, 6 x C-3 of P-Ph), 115.2 (d, *J* 91, 3 x C-1 of P-Ph), 21.1 (Me) and 10.2 (d, *J* 58, P-Me); δ_P +20.5.

16. Preparation of (methoxycarbonylmethyl)tri-*p*-tolylphosphonium bromide **748**

To a solution of tri(*p*-tolyl)phosphine (0.1 g, 0.33 mmol) in dry toluene (2 cm^3) was added dropwise a solution of methyl bromoacetate (0.05 g, 0.33 mmol) in dry toluene (1 cm^3). The mixture was left to stir at room temperature overnight. The white solid formed was filtered off, washed with ether and dried to furnish the product (0.13 g, 87%) as a white powder, mp 187–189 °C; δ_H 7.80–7.66 (6 H, m, Ph), 7.50–7.39 (6 H, m, Ph), 5.37 (2 H, d, *J* 12, CH_2), 3.59 (3 H, s, OMe) and 2.48 (9 H, s, Me); δ_C 165.2 (CO_2), 146.3 (d, *J* 3, 3 x C-4 of P-Ph), 133.7 (d, *J* 11, 6 x C-2 of P-Ph), 130.9 (d, *J* 14, 6 x C-3 of P-Ph), 114.6 (d, *J* 92, 3 x C-1 of P-Ph), 33.0 (d, *J* 58, CH_2) and 21.8 (Me); δ_P +20.2.

17. Preparation of (methoxycarbonylmethylene)tri-*p*-tolylphosphorane **749**

(Methoxycarbonylmethyl)tri-*p*-tolylphosphonium bromide **748** (2.5 g, 5.5 mmol) was dissolved in water (20 cm^3) and the solution filtered through celite and extracted with ether. The aqueous phase was stirred while sodium hydroxide (0.22 g, 5.5 mmol) was added rapidly. The mixture was extracted with ethyl acetate which was dried and evaporated to furnish the title compound (1.6 g, 77%) as a yellow solid, mp 85–87 °C; (Found: $M+H^+$, 377.1665. $C_{24}H_{26}O_2P$ requires *M+H*, 377.1670); ν_{max} /cm^{-1} 2924, 2855, 1728, 1460, 1377, 1271, 1118 and 808; δ_H 7.65–7.48 (6 H, m, Ph), 7.36–7.20 (6 H, m, Ph), 3.52 (3 H, s, OMe) and 2.38 (9 H, s, Me); δ_C 170.8 (d, *J* 11, CO_2), 142.5 (3 x C-4 of P-Ph), 132.8 (d, *J* 10, 6 x C-2 of P-Ph), 129.4 (d, *J* 13, 6 x C-3 of P-Ph), 123.5 (d, *J* 96, 3 x C-1 of P-Ph), 49.8 (OMe), 30.4 (d, *J* 119, P=C) and 21.4 (Me); δ_P +18.3; *m/z* (CI) 377 ($M+H^+$, 34%), 361 (6), 345 (24), 321 (100), 305 (11) and 57 (10).

18. Preparation of the keteneylidenetri-*p*-tolylphosphorane **746**

To a solution of (methoxycarbonylmethylene)tri-*p*-tolylphosphorane **749** (0.95 g, 2.5 mmole) in dry toluene (10 cm^3) sodium amide (0.34 g, 8.7 mmole) was added and the mixture was heated under reflux for 24 hours under a nitrogen atmosphere. The mixture was cooled and the solid filtered off under a nitrogen atmosphere, the filtrate was concentrated and NMR showed a mixture of the right product (0.4 g), δ_C 142.6 (d, *J* 39); δ_P +5.3 and Tol_3PO δ_P +29.4.

19. Attempted solution pyrolysis of the keteneylidenetri-*p*-tolylphosphorane **749** and 4-tri--phenylphosphoranylidenetetrahydrofuran-2,3,5-trione **726**

A mixture of keteneylidenetri-*p*-tolylphosphorane **746** and tri-*p*-tolylphosphine oxide (115 mg) with 4-triphenylphosphoranylidenetetrahydrofuran-2,3,5-trione **726** (126 mg, 0.33 mmol) was heated in diphenyl ether (4 cm^3) under reflux for 1.5 hours. The solution went black and the ^{31}P NMR spectrum showed mainly Tol_3PO and other unidentified products.

20. Solution pyrolysis of keteneylidenetri-*p*-tolylphosphorane **749**

The keteneylidenetri-*p*-tolylphosphorane **749** (120 mg, 0.35 mmol was heated in diphenyl ether (1.5 cm^3) under reflux for 1.5 hours. The solution went black and the ^{31}P NMR spectrum showed only Tol_3PO present.

21. Neat pyrolysis of keteneylidenetri-*p*-tolylphosphorane **749**

The keteneylidenetri-*p*-tolylphosphorane(25 mg, 0.07 mmol) was heated in the kugelrohr to 170 °C and left at that temperature for 1 hour. The compound had turned black and the ^{31}P NMR spectrum showed mainly Tol_3PO and other small impurities.

22. Preparation of methyl bromoacetate **759**

Thionyl chloride (3.42 g, 2.3 cm^3, 28 mmol) was added dropwise to a solution of bromoacetic acid (2.0 g, 14 mmol) in methanol (25 cm^3). The mixture was left to stir at room temperature for 2 hours. The mixture was evaporated and the residue was distilled at atmospheric pressure to give the product (1.74 g, 81%) as a colourless liquid, bp 135–140 °C (lit.,[163] 144 °C); δ_H 2.95 (2 H, s, CH_2) and 2.92 (3 H, s, OMe); δ_C 167.6 (CO_2), 53.1 (OMe) and 25.4 (CH_2).

23. Preparation of ^{13}C-labelled methyl bromoacetate **758**

Reaction as in 22. using 20% ^{13}C CO labelled bromoacetic acid **760** (5 g, 36 mmol) and thionyl chloride (9.3 g, 5.7 cm^3, 78 mmol) in methanol (50 cm^3) gave the title product (5.0 g, 90%); δ_C 167.7 (C^*O_2, 20 x enhanced compared to product from 22.), 53.2 (OMe) and 25.5 (CH_2).

24. Preparation of 20% ^{13}C-labelled (methoxycarbonylmethyl)triphenylphosphonium bromide **761**

The labelled methyl bromoacetate **758** prepared in 23. (5.0 g, 33 mmol) was added to a solution of triphenylphosphine (8.56 g, 33 mmol) in dry toluene (30 cm^3). The mixture was stirred for 48 hours and a white solid precipitated out which was filtered off to give the product

(11.03 g, 81%) as colourless crystals, mp 161–162 °C (lit.,[141] 162 °C); δ_C 164.8 (d, *J* 3, C^*O_2), 135.0 (d, *J* 2, 3 x C-4 of P-Ph), 133.7 (d, *J* 11, 6 x C-2 of P-Ph), 130.1 (d, *J* 13, 6 x C-3 of P-Ph), 117.5 (d, *J* 89, 3 x C-1 of P-Ph), 53.2 (OMe) and 32.7 (d, *J* 57, CH_2); δ_P +22.8 (lit.,[141] δ_P +23.4)

25. Preparation of 20% ^{13}C CO-labelled (methoxycarbonylmethylene)triphenylphosphorane **762**

Reaction as in 21. using the labelled (methoxycarbonylmethyl)triphenylphosphine bromide **761** (4.0 g, 9.6 mmol) and sodium hydroxide (0.39 g, 9.6 mmol) furnished the product (2.6 g, 81%) as a white solid, mp 163–164 °C (lit.,[142] 163 °C); δ_C 171.5 (d, *J* 12, C^*O_2), 132.8 (d, *J* 10, 6 x C-2 of P-Ph), 131.8 (3 x C-4 of P-Ph), 128.6 (d, *J* 12, 6 x C-3 of P-Ph), 127.7 (d, *J* 91, 3 x C-1 of P-Ph), 49.6 (OMe) and 29.7 (d, *J* 127, P=C); δ_P +18.2 (lit.[143] δ_P +17.0).

26. Preparation of 20% ^{13}C CO labelled ketenylidenetriphenylphosphorane **756**

Reaction as in 11. using the labelled ylide **762** (1.4 g, 4.2 mmol) and sodium amide (0.4 g, 10 mmol) in dry toluene (7 cm^3) gave a 1:2 mixture of Ph_3PO and the title product (0.63 g, 50%); δ_C 145.6 (d, *J* 43, *C=O), 132.2 (d, *J* 11, 6 x C-2 of P-Ph), 132.1 (3 x C-4 of P-Ph), 129.1 (d, *J* 105, 3 x C-1 of P-Ph), 128.8 (d, *J* 13, 6 x C-3 of P-Ph) and –10.5 (d, *J* 189, P=C); δ_P +5.6. (lit.,[164] ^{13}C and ^{31}P data identical to the above)

27. Solution pyrolysis of 20% ^{13}C CO labelled ketenylidenetriphenylphosphorane **756** and the 4-triphenylphosphoranylidenetetrahydrofuran-2,3,5-trione **726**

Reaction was carried out as in 12. using the labelled ketenylidenetriphenylphosphorane **756** (0.17 g, 0.56 mmol) and the 4-triphenylphosphoranylidenetetrahydrofuran-2,3,5-trione **726** (0.21 g, 0.56 mmol) in diphenyl ether (4 cm^3). The ^{31}P NMR spectrum showed the presence of 3,5-bis(triphenylphosphoranylidene)cyclopentane-1,2,4-trione **757b**; δ_P +9.1 in addition to Ph_3PO, Ph_3P and other unidentified products.

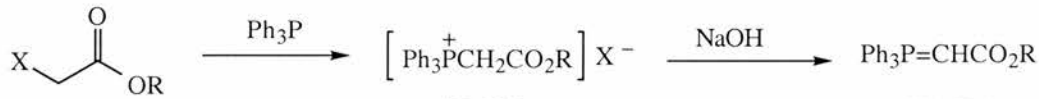
In the carbonyl region of the ^{13}C NMR spectrum the signal at δ_C 196.0 (t, *J* 9, 4-CO) showed *ca.* 20 x enhancement compared to the signal at δ_C 187.2 (dd, *J* 20, 6, 1,2-CO).

DISCUSSION

A Preparation of Starting Materials

1. Preparation of phosphonium salts and ylides

The ester stabilised ylides **501-504** were readily prepared using known methods. The initial step involves the preparation of the precursor phosphonium salts **497-500**. These salts were synthesised in good yield by a modification of the method of Michaelis and Gimborn.[165] The addition of one equivalent of sodium hydroxide to an aqueous solution of the salts gave the corresponding ylides in moderate to good yield after recrystallisation. The ylides and salts prepared are shown below.



497-500 **501-504**

	Salt			Ylide		
R		%	δ_P		%	δ_P
Me	**497**	78	+23.4	**501**	87	+17.9
Et	**498**	87	+23.0	**502**	75	+17.0
Bu^t	**499**	84	+21.4	**503**	55	+17.6
Allyl	**500**	25	+21.1	**504**	98	+17.9

2. Preparation of *N*-alkoxycarbonyl amino acids

Based on previous work[138] the choice of the alkoxycarbonyl family of protecting groups for the amine function was found to be suitable for this study. These protecting groups are commonly used in peptide synthesis due to their stability, ease of removal, and most importantly, immunity to racemisation.

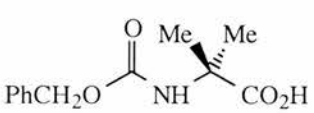
Previous work involved hydrocarbon side chain amino acids and in addition to these systems we focused on amino acids with functionalised side chains. Various amino acids were converted to the alkoxycarbonyl derivatives **505-515** via formation of the salt, followed by reaction with the benzyl, ethyl or allyl chloroformate. The derivatives are shown in Table 1:

505-515

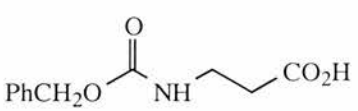
Table 1: Preparation of *N*-alkoxycarbonyl Amino Acids

	R^1	R^2	Yield %	amino acid derived from:
505	H	$PhCH_2$	33	glycine
506	Me	$PhCH_2$	54	alanine
507	Pr^i	$PhCH_2$	47	valine
508	Bu^s	$PhCH_2$	62	isoleucine
509	$(CH_2)_2SMe$	$PhCH_2$	54	methionine
510	$(CH_2)_2CO_2Me$	$PhCH_2$	45	methyl glutamate
511	CH_2CO_2Me	$PhCH_2$	29	methyl aspartate
512	$(CH_2)_2SOMe$	$PhCH_2$	71	methionine
513	Bu^s	Et	83	isoleucine
514	$(CH_2)_2SMe$	Et	84	methionine
515	Pr^i	Allyl	39	valine

Other derivatives made were the *N*-benzoxycarbonyl-α-aminoisobutyric acid **516** which was obtained in 22% yield and the unnatural amino acid *N*-benzoxycarbonyl-β-alanine **517** in 54% yield.

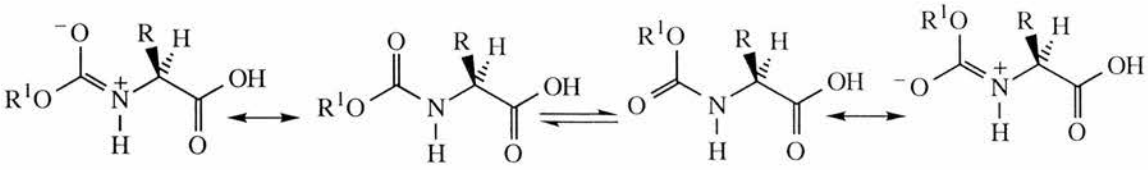


516



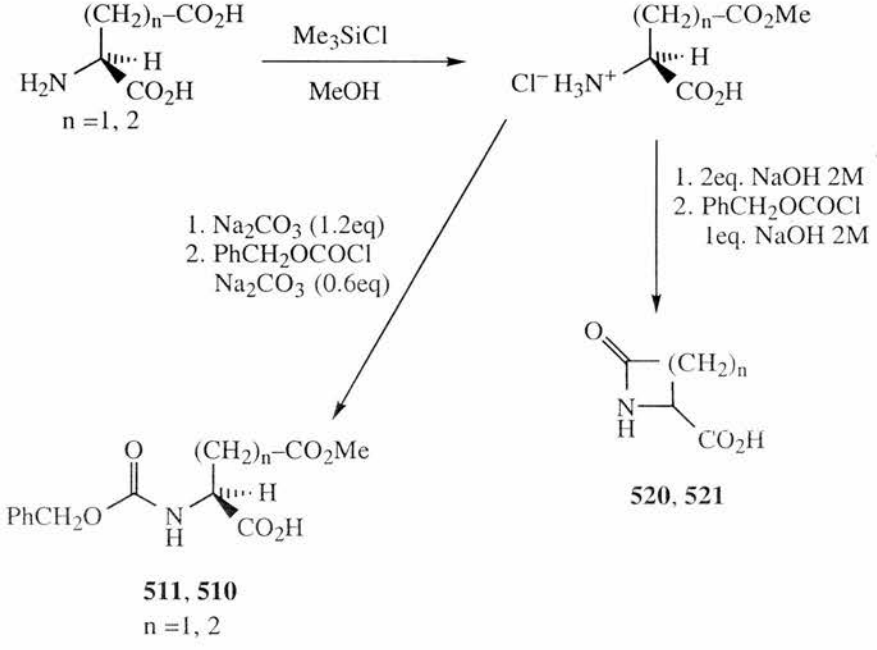
517

The effect of restricted rotation about the N-CO_2R group on the ^1H and ^{13}C NMR spectra may be seen in many examples. The *E/Z* isomerism that they display is shown below by structures **518** and **519**.



518 **519**

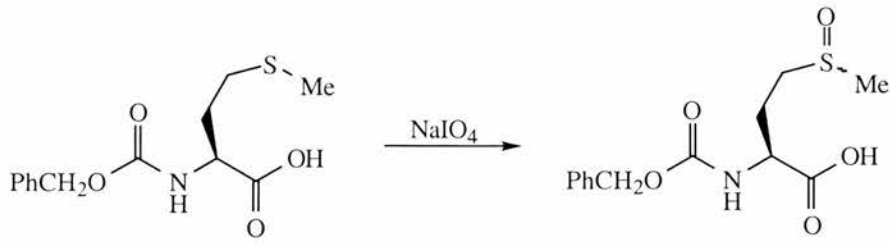
Most of the protected amino acids were prepared *via* the above method using a NaOH solution to form the salt. Attempts to prepare the *N*-benzoxycarbonyl-(*S*)-aspartic acid β-methyl ester **511** and (*S*)-glutamic acid γ-methyl ester **510** using the same conditions failed. The solids obtained were not soluble in chloroform and it seemed that after the addition of 2 equivalents of base to the methyl ester salts an intramolecular reaction occurred forming a β- or γ-lactam derivative **520** or **521**. The desired products were later obtained in moderate yields using milder conditions (Na_2CO_3) following a literature procedure.[153]



520, 521

511, 510
n =1, 2

A sulfoxide side chain derivative **512** derived from the protected methionine **509** was prepared using sodium periodate in aqueous methanol[150] and the product was obtained in good yield. The formation of the sulfoxide introduces a second stereogenic centre at the SO and a 1:1 mixture of diastereomers was observed by NMR.

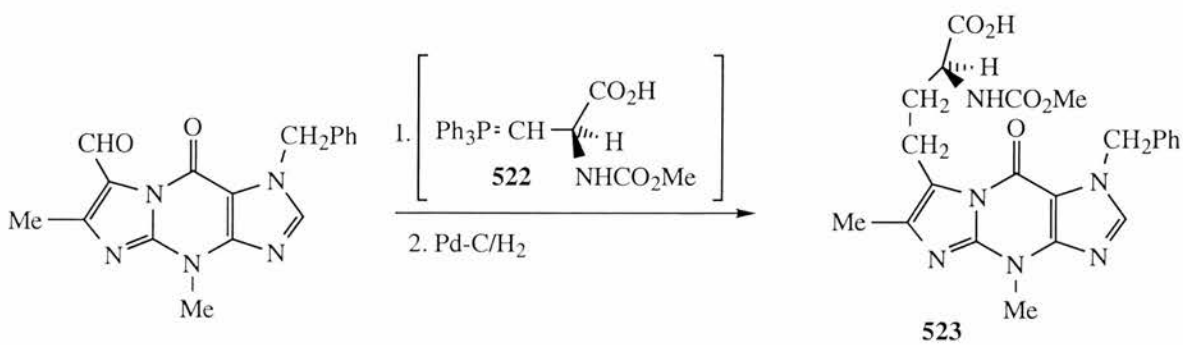


509 512

B Preparation and pyrolysis of α-ethoxycarbonyl β-oxo ylides derived from amino acids

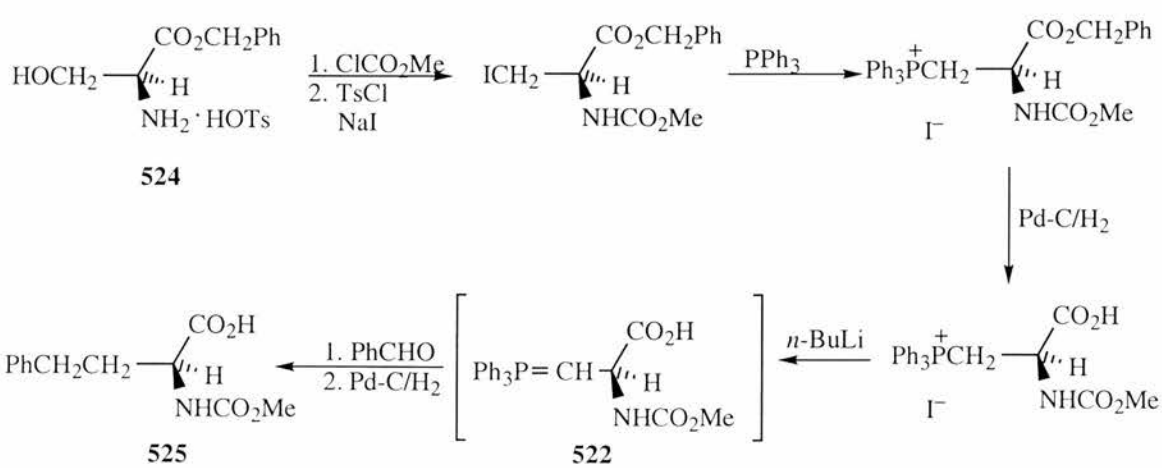
1. Introduction

There are only a few α-ethoxycarbonyl β-oxo ylides derived from amino acids known in the literature. The ylide **522** derived from serine was used in the first synthesis of the optically active form of (*S*)-wybutine **523** in 1985.[166]



523

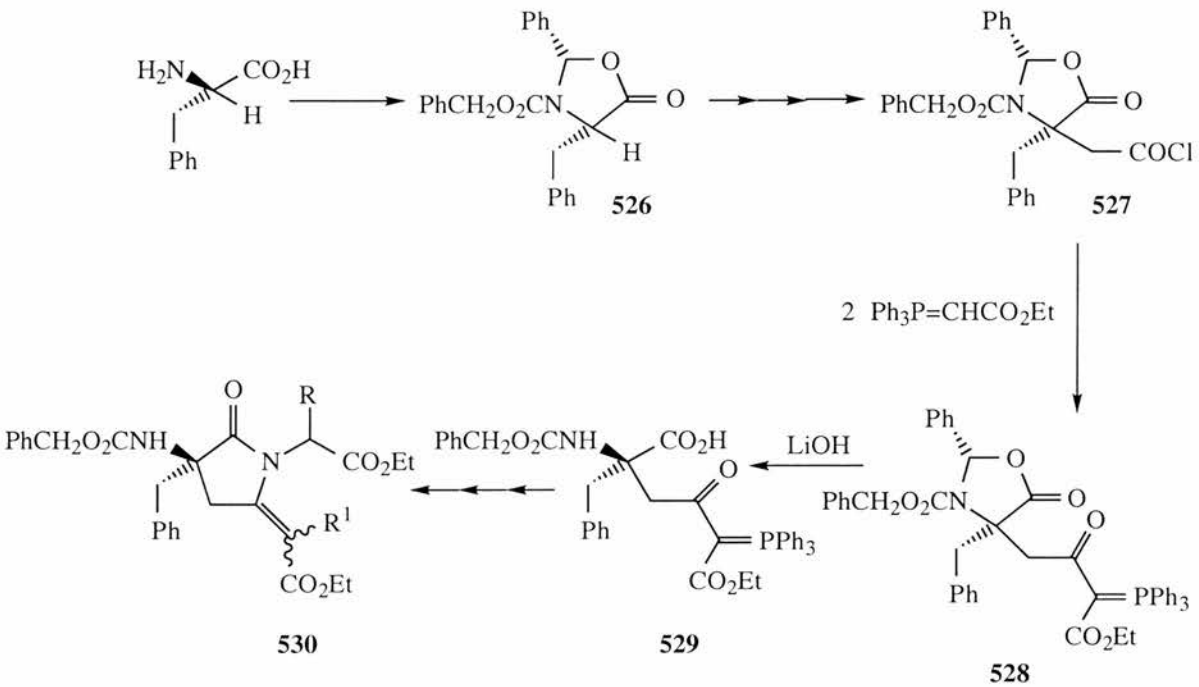
(*S*)-Serine benzyl ester tosylate **524** was treated with methyl chloroformate and the carbamate formed was transformed into the iodide through the tosylate. This reacted with



524 525 522

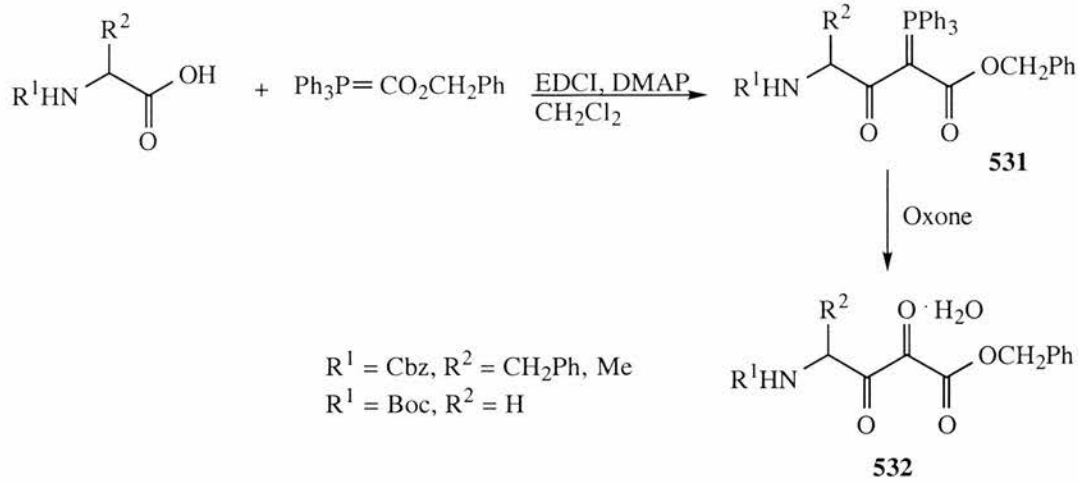
triphenylphosphine and the resulting salt had the benzyl ester removed before reaction with butyllithium to form the ylide **522** which was used *in situ*. The Wittig reaction of ylide **522** with benzaldehyde followed by catalytic hydrogenation gave the modified amino acid **525**. This ylide is efficient as a chiral building block for construction of homologues of alanine.

Abell and co-worker[167] reported the use of the ylide **528** in the synthesis of cyclic enamino ester dipeptide analogues **530** which can be used as inhibitors of serine protease.

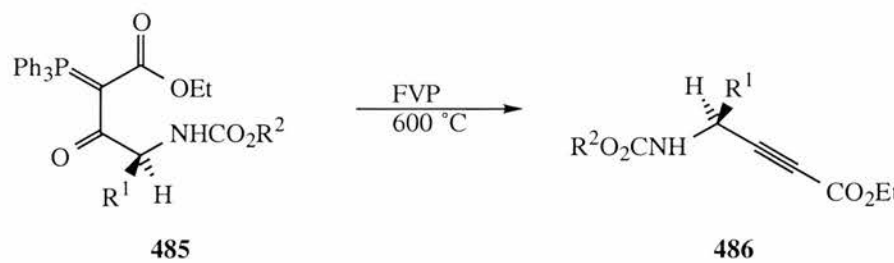


The ylide **528** was prepared from the oxazolidinone **526** derived from phenylalanine. The oxazolidinone **526** is converted to the acid chloride **527** after various transformations. Reaction with (ethoxycarbonylmethylene)triphenylphosphorane gave the ylide **528** and selective hydrolysis of the oxazolidinone ring gave the ylide **529**. Bromo lactonization and introduction of an amino acid into the enol lactones gave the peptide analogues **530**.

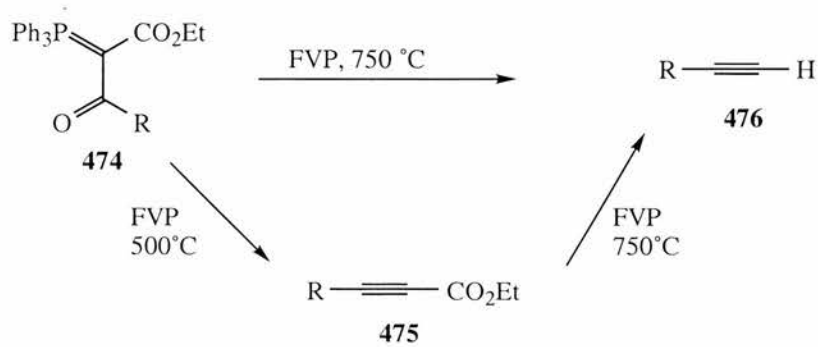
Wasserman and co-workers[168] showed that amino acids are readily converted into peptidyl tricarbonyls in two mild steps via EDCI-promoted coupling to give the ylide **531** and oxidation. From the tricarbonyl derivatives **532** formed, several products were shown to be potent inhibitiors of serine proteases.



As mentioned in the Programme of Research, α-ethoxycarbonyl β-oxo ylides **485** derived from amino acids were previously prepared and their pyrolysis provided a method for formation of novel chiral acetylenic amino acid analogues **486**.[139]

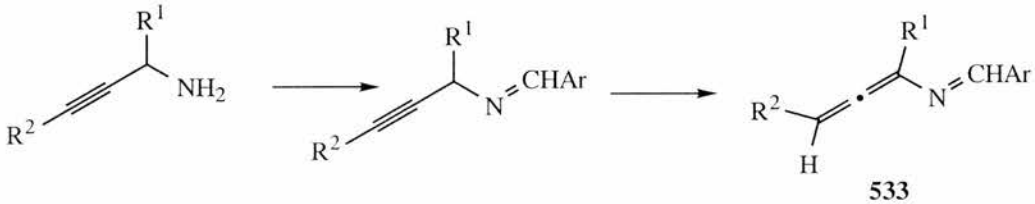


The original reason for using α-ethoxycarbonyl ylides was the previous discovery that FVP of the ylide **474** at 750 °C, led to loss of the CO_2Et group in addition to triphenylphosphine oxide and so provided access to terminal alkynes **476**.[131]



The considerable current interest in unsaturated amino acids is stimulated in part by their potential biological activity as specific irreversible enzyme inhibitors. The compounds containing a carbon-carbon triple bond have been found to act on enzymes that catalyse

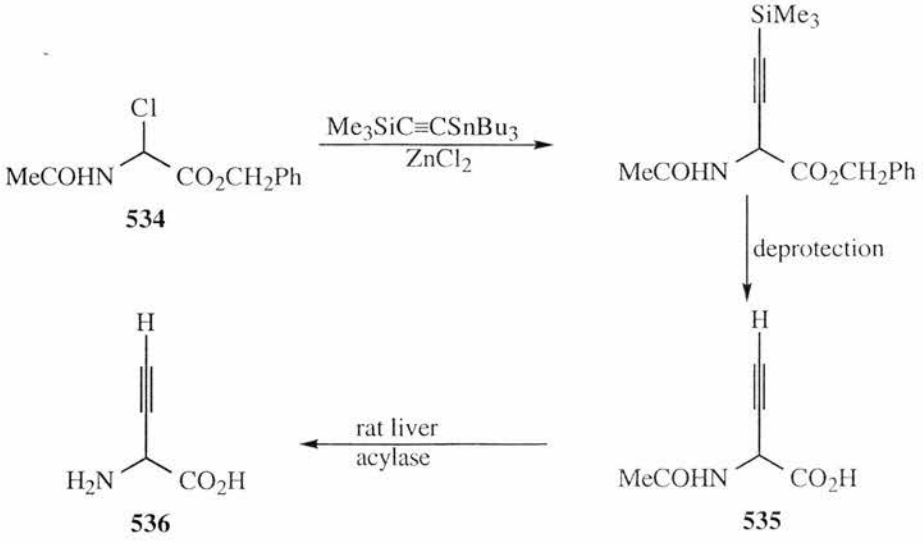
isomerisation, oxidation, elimination and transamination.[170] The potent action of these acetylenic compounds, which are not very chemically reactive, is explained by the fact that they can be converted enzymically to the isomeric allenes **533** which are strong Michael acceptors.



533

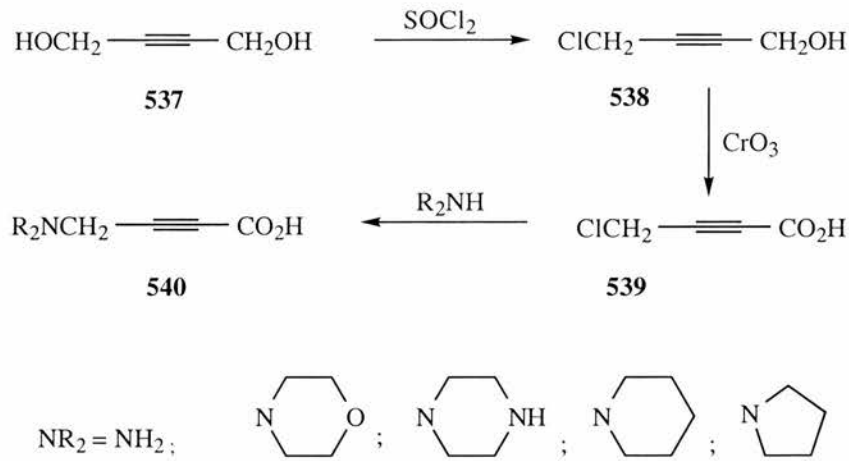
The mechanism of acetylenic inhibitors involves an electrophilic species on the inhibitor being unmasked in the active site and attacked by a nucleophilic side chain of an enzyme amino acid. Considerable effort has been employed on the development of synthetic approaches to this type of compounds. In addition to their biological activity they are also very important as chiral building blocks for synthesis.

The first synthesis of ethynylglycine **536** was reported by Williams and coworkers.[169] The strategy involved the coupling of an alkynyltin reagent with an α-chloroglycinate **534** in the presence of zinc chloride. Deprotection afforded the stable *N*-acetylethynylglycine **535**. The final step was performed enzymically by rat liver acylase to produce the product **536**. The labile amino acid **536** had previously been isolated by Kuroda et al.[171] as a natural product from *Strepotomyces catenulae* in 1980 as its *N*-acetyl derivative and is known to be an antibiotic and an inhibitor of alanine racemase.

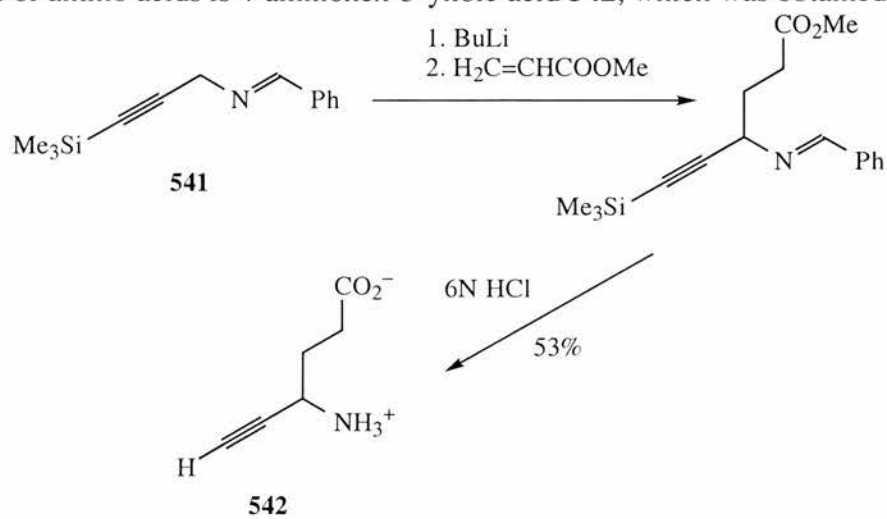


534 **535** **536**

Beart and Johnston[172] were the first group to consider the potential biological activity of acetylenic γ-amino acids. 4-Aminotetrolic acid and its derivatives **540** which are simple, conformationally constrained analogues of the neurotransmitter γ-aminobutyric acid (GABA) were prepared. Conversion of the diol **537** to its chloride **538** and oxidation using CrO_3 furnished the chloro-acid **539**. A direct nucleophilic attack of the appropriate amine on **539** provided the products **540**. They were all shown to be inhibitors of the stimulation of central neurones, but to be less active in comparison to GABA.

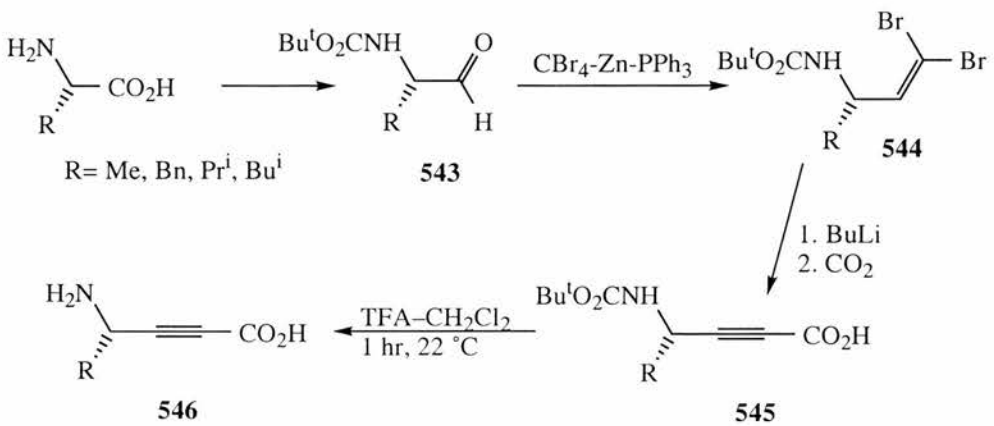


γ-Ethynyl analogues of GABA are of great interest because they have proved to be active inhibitors of GABA α-ketoglutarate transaminase from mammalian brain. Therefore they have considerable potential for application in therapy as psychotropic agents. An example of this class of amino acids is 4-aminohex-5-ynoic acid **542**, which was obtained by alkylation

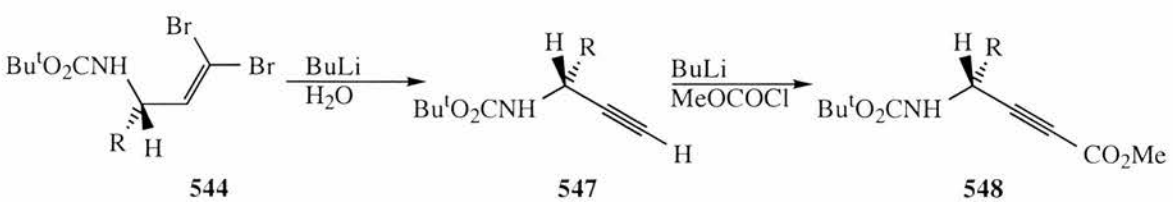


of the protected aldimine **541**.[173,174] By varying the electrophilic reagent, Metcalf and Jung[175] obtained a wide range of amino acids related to **542** in racemic and enantiomerically pure forms.

Recently while our work was in progress, Reetz and co-workers[176] reported the synthesis and properties of enantiomerically pure alkynylogous amino acids **546**. Boc-protected α-amino aldehydes **543** derived from the corresponding (*S*)-α-amino acids are converted *via the* Corey-Fuchs reaction into the *N*-protected alkynylogous amino acids **545**, which on deprotection yield the enantiomerically pure acids **546**.

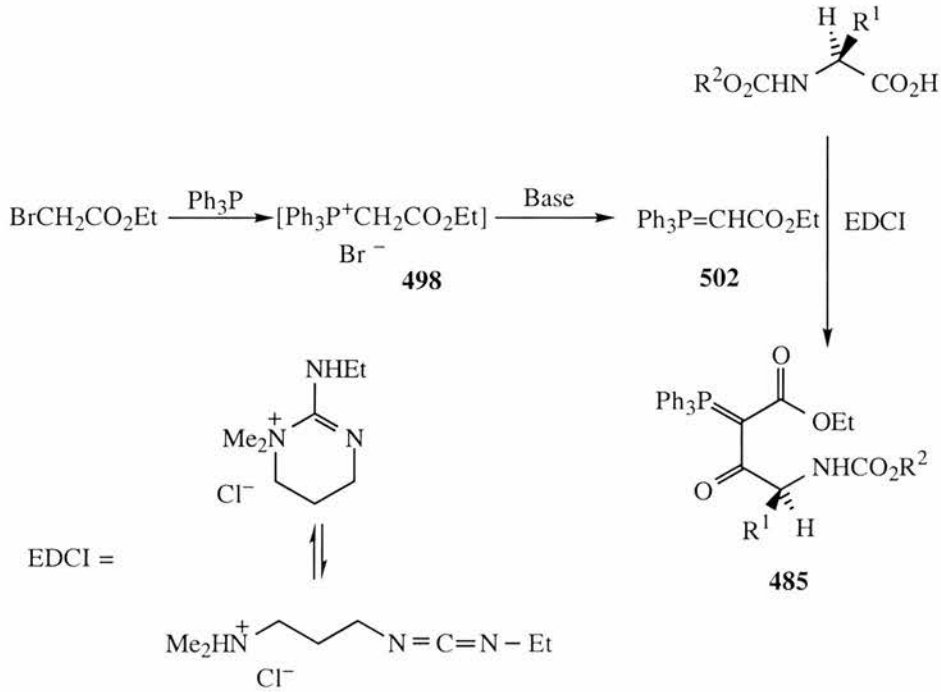


At around the same time a closely similar approach was described by Reginato and co-workers.[177] This proceeds in the same manner up to the stage of **544** but this is now treated with butyllithum followed by aqueous work-up to give the terminal acetylenes **547**. In a more recent extention of the work the subsequent reaction of **547** with butyllithium and methyl chloroformate gave the corresponding esters **548**.[178]



2. Synthesis of α-ethoxycarbonyl β-oxo ylides derived from amino acids

A series of chiral stabilised ylides **485** were prepared by acylation of (ethoxycarbonylmethylene)triphenylphosphorane **502** with *N*-alkoxycarbonylamino acids in the presence of the peptide coupling reagent, EDCI.[168] A catalytic amount of DMAP was found to enhance the reaction.



During the work we noticed a dramatic decrease in yields of **485** when certain reactions were repeated. The ^{31}P NMR spectrum of (ethoxycarbonylmethylene)triphenylphosphorane **502** which was repeated after 5 months showed over 50% decomposition to a mixture containing four different products and the melting point was over 30 °C higher than in the literature. We found it essential to recrystallise the product **502** from ethyl acetate and using the product purified in this way further problems were avoided. Following the manufacturers instructions and keeping the EDCI in the damp atmosphere of the refrigerator was also found to be counterproductive and it is best stored in a desiccator at room temperature. For the reaction it is important to use a dry solvent to avoid hydrolysis of the coupling reagent and we used dichloromethane dried over P_2O_5.

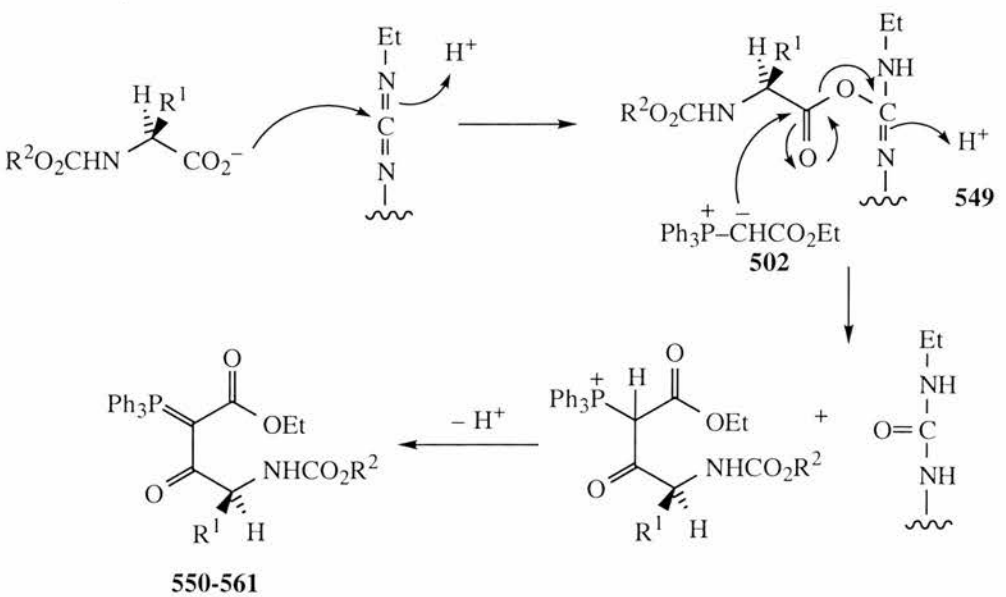
The ylides **550-561** were obtained in moderate to low yields after chromatography and recrystallisation (Table 2).

Table 2: γ-Amino-β-oxo ylides

	R^1	R^2	amino acid derived from	yield (%)	δ_P
550	H	CH_2Ph	glycine	18	17.8
551	Me	CH_2Ph	alanine	16	17.5
552	Pr^i	CH_2Ph	valine	22	18.3
553	(*S*)-Bu^s	CH_2Ph	isoleucine	8	18.3,18.2*
554	$(CH_2)_2SMe$	CH_2Ph	methionine	34	18.1
555	$(CH_2)_2CO_2Me$	CH_2Ph	methyl glutamate	22	18.1
556	CH_2CO_2Me	CH_2Ph	methyl aspartate	10	18.2
557	$(CH_2)_2SOMe$	CH_2Ph	methionine	12	18.2
558	(*S*)-Bu^s	Et	isoleucine	21	18.3,18.2*
559	$(CH_2)_2SMe$	Et	methionine	17	18.1
560	Pr^i	Bu^t	valine	39	17.9
561	Pr^i	Allyl	valine	33	18.3

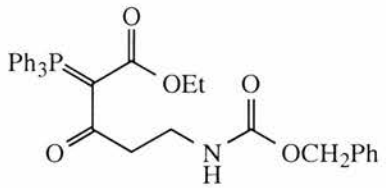
* Two configurations due to restricted rotation about the N-CO_2R^2 group.

The proposed reaction pathway for the coupling procedure assumes that the acid and carbodiimide react initially forming an *O*-acylisourea **549**. Nucleophilic attack by the ylidic carbon affords the β-aminoacyl ylides **550-561**.



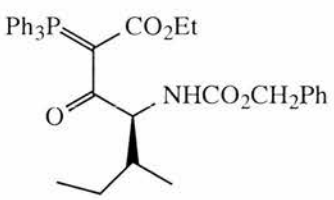
550-561

An additional ylide was prepared starting from the unnatural protected amino acid, *N*-benzoxycarbonyl-β-alanine. The ylide **562** was obtained in 59 % yield and showed a ^{31}P NMR shift of +17.9 which is a close value to the ylides mentioned above.



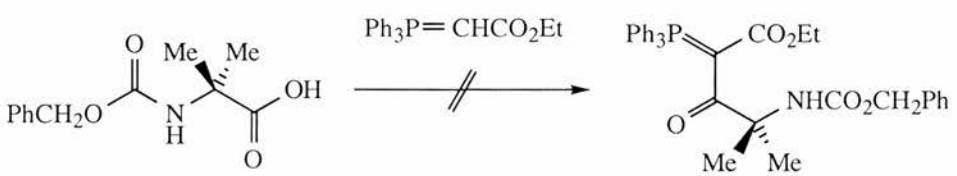
562

Together with the ylides **550-562**, unreacted starting materials and triphenylphosphine oxide were also isolated from the column. As these compounds are still only starting materials for the overall project it was important to try to increase the yield of the coupling step. Increasing the reaction time and/or temperature failed to improve the yields and in the second case caused more products to appear by TLC accompanied by a smaller amount of the desired product. The time factor did not increase the overall yield but a reaction did occur between the N-benzoxycarbonylisoleucine **508** and the ylide **502** after standing for nearly a month (before, between 3-48 hours there was no reaction) and in this way we obtained the desired product **553** after purification in low yield.



553

All attempts to prepare the aminoacyl ylide from *N*-benzoxycarbonyl-α-aminoisobutyric acid **516** failed, and only the two starting materials were observed by TLC.



516

Table 3: ^{13}C NMR Spectra of *N*-alkoxycarbonyl Ylides **550-562**, δ_C (J_{P-C})

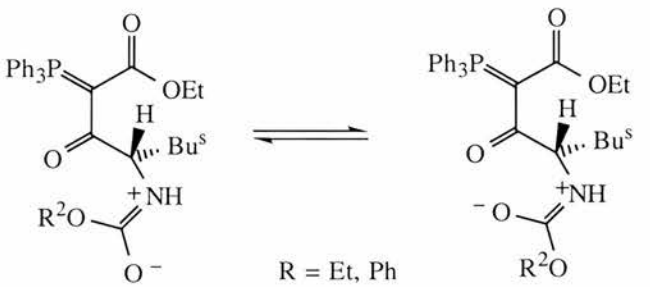
				CO_2Et			NCO_2R		P–Phenyl				
	CHN	P=C	COCN	CO	CH_2	CH_3	NCO_2	R	C–1	C–2	C–3	C–4	R signals
R								CH_2 Ph					
550	49.3 (9)	67.4 (105)	190.4(4)	167.3 (15)	58.7	13.8	156.1	66.2 137.0(4ry), 128.3, 127.7, 127.6	125.8 (94)	133.1 (10)	128.6 (12)	131.9 (2)	
562	37.3	71.3 (117)	195.7	167.7 (15)	58.3	13.5	156.1	65.9 136.9(4ry), 128.2, 127.7, 127.6	126.2 (93)	132.8 (10)	128.4 (13)	131.5 (3)	39.8 (6)
552	60.4 (9)	70.0 (110)	194.1	166.8 (14)	58.7	13.8	156.6	66.1 137.0(4ry), 128.3, 127.7, 127.6	126.0 (93)	133.1 (10)	128.5 (13)	131.8 (2)	32.3, 20.7, 15.9
553	60.7 (8) 59.4 (8)	70.2 (111) 69.9 (110)	194.4	166.9 (14)	58.8	13.9	156.6	66.2 137.1(4ry), 128.3, 127.7, 127.6	126.1 (93) 126.0 (93)	133.2 (10)	128.5 (12)	131.8	39.5, 27.8, 16.8, 12.1 38.9, 22.8, 12.9, 12.1
554	56.0 (8)	69.3 (109)	193.0	166.5 (14)	58.6	13.6	155.8	66.0 136.7(4ry), 128.1, 127.5 (3C)	125.6 (93)	132.9 (10)	128.4 (12)	131.8 (2)	34.7, 30.2, 15.4
555	55.7 (8)	69.3 (110)	193.0	166.5 (14)	58.6	13.6	155.9	66.0 136.7(4ry), 128.1, 127.5 (3C)	125.6 (93)	132.9 (10),	128.4 (13)	131.8	174.0, 51.2, 30.5, 29.8
556	53.7 (9)	69.4 (110)	192.0	166.8 (14)	58.8	13.7	155.7	66.2 137.0(4ry), 128.3, 127.7 (3C)	125.8 (94)	133.2 (10),	128.6 (13)	131.9	171.5, 51.6, 38.7
557	54.9 (8)	69.7 (109)	191.7	166.6 (13)	58.9	13.7	156.2	66.5 136.7(4ry), 128.4, 127.9, 127.8	125.3 (94)	133.2 (10)	128.8 (12)	132.2 (2)	51.5, 40.5, 27.8
R								CH_2 CH_3					
558	60.0 (8) 58.6 (8)	69.5 (110) 69.3 (110)	193.9	166.4 (14) 166.3 (14)	58.1	13.3	156.4	59.7 14.1	125.65(93) 125.60(93)	132.6 (10)	127.9 (12)	131.2	38.9, 27.3, 16.2, 12.3 38.3, 22.2, 11.6
559	55.8 (8)	68.9 (110)	193.1	166.3 (14)	58.3	13.4	156.0	59.9 14.2	125.5 (93)	132.7 (10)	128.2 (13)	131.5 (2)	34.6, 30.1, 15.2
R								C Me_3					
560	59.3 (8)	69.3 (109)	194.1	166.1 (15)	57.9	13.2	155.6	59.6 27.8	125.6 (94)	132.5 (10)	127.9 (12)	131.2	31.4, 20.2, 15.3
R								CH_2 CH= $=CH_2$					
561	60.0 (9)	69.5 (110),	193.9	166.6 (12)	58.2	13.3	156.2	64.6 116.4 133.0	125.7 (93)	132.8 (10)	128.2 (13)	131.5 (3)	31.8, 20.2, 15.4

* The signals for both carbamate rotamers are given where they differ.

This may be due to the steric hindrance on the α-carbon which interferes with the formation of the reactive anhydride in the coupling step.

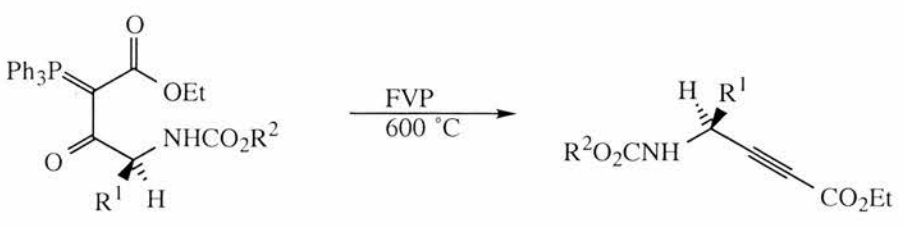
For the ylides **550-562**, the effect of restricted rotation about the N-CO_2R^2 group on the ^{13}C NMR spectra was again observed. The ^{13}C chemical shifts and the magnitude of the observed P-C coupling constants (Table 3) provide excellent conformation of the structures.

The ^{31}P NMR spectra were found to form a consistent pattern with signals at δ_P +17.5 – +18.3. In the isoleucine derivatives **553** and **558** certain ^{13}C resonances are doubled and the ^{31}P NMR spectra show two distinctive peaks in a 1:1 ratio due to the rotamers **563** and **564**.

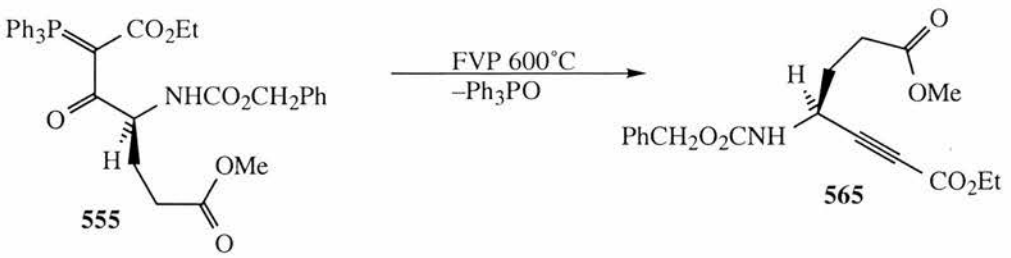


3. Pyrolysis of β-aminoacyl ylides

As mentioned above, FVP of the β-aminoacyl ylides **485** provides access to α,β-acetylenic-γ-amino acid derivatives **486** which are of considerable interest. Following the success of previous work with aliphatic side chain amino acids one of the aims of this work was to extend the method to substituted side chain amino acids. The products obtained could be useful as potential inhibitors which may have importance in the formation of modified peptides and also be useful as building blocks for synthesis. The ethoxy and benzoxycarbonyl groups were used as the *N*-protecting groups for the amine and ester as they had proved to be stable to FVP conditions.

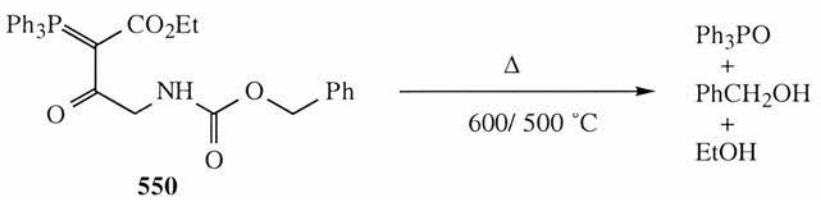


FVP of a small quantity of the glutamic acid derived ylide **555** at 600 °C and 3 x 10^{-3} Torr resulted in the desired loss of Ph_3PO and the formation of the protected acetylenic amino acid diester **565**. The product was obtained after purification by chromatography in low yield.

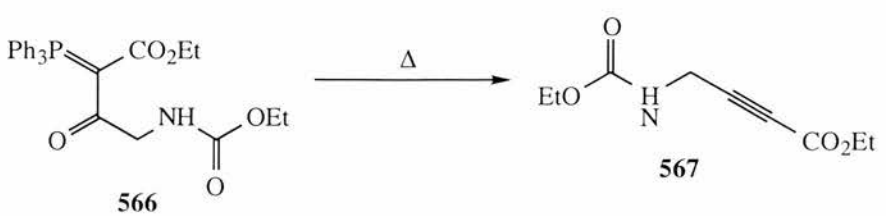


Repeated attempts to scale up this reaction were unsuccessful. Benzyl alcohol and ethanol were found in the cold trap and at the furnace exit we found Ph_3PO and no sign of the desired product. This result was quite surprising because until now compounds containing benzoxycarbonyl as the protecting group were stable to FVP conditions. The cleavage of the protecting groups was an important new observation and other cases will be seen later.

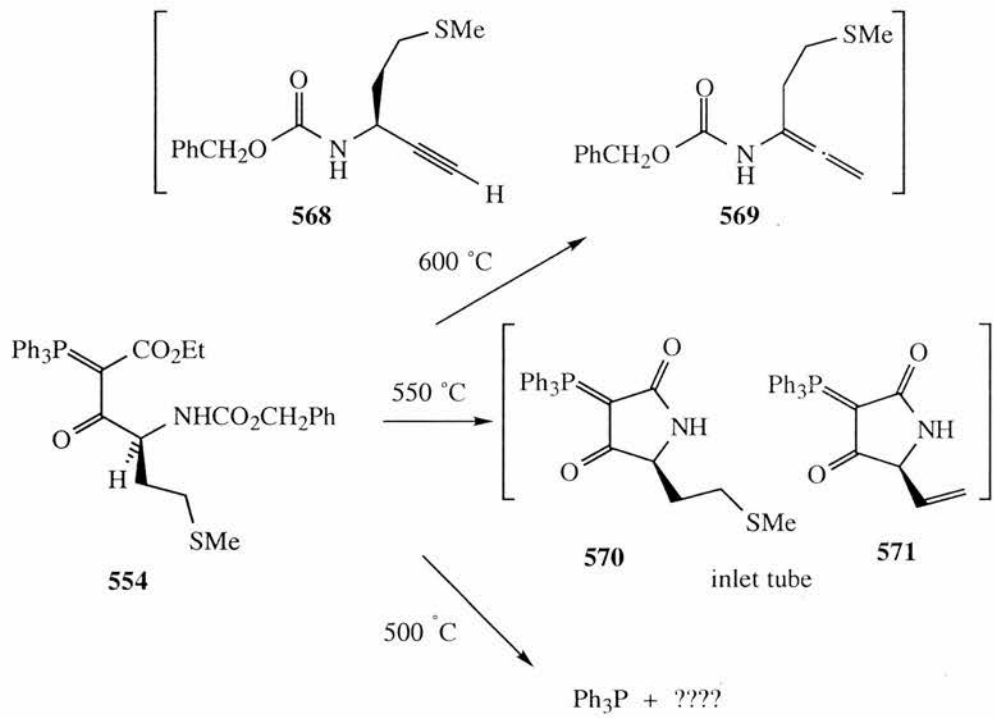
Pyrolysis of the glycine ylide **550** at two different temperatures gave similar results. At 600°C, ^1H and ^{31}P NMR showed benzyl alcohol and ethanol in the cold trap and at the furnace exit Ph_3PO was found. There was still some material in the inlet tube which was mainly unreacted starting material.



Pyrolysis at 500 °C resulted in the same products at the furnace exit and cold trap that were found at 600 °C but no starting material was found in the inlet tube. These results were unusual considering that in previous work the ethoxycarbonyl analogue **566** gave the desired acetylenic product **567**.[138]



Several attempts at FVP of the methionine ylide **554** gave interesting results. At 600 °C, Ph_3PO was obtained and ^1H NMR showed the absence of the ethyl ester group. A mixture of products was obtained for which possible structures include, for example, **568** and **569**.

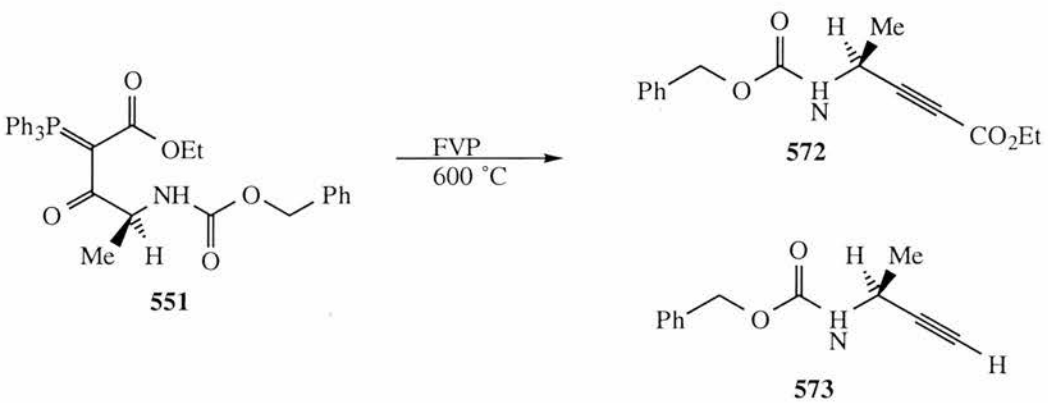


Since the ethyl ester group was lost at 600 °C, an attempt was made to try using lower temperatures. On pyrolysis at 550 °C, Ph_3PO, Ph_3P and even a small amount of Ph_3PS were produced in the trap but most of the material was still in the inlet tube and was identified by NMR. The ^{31}P NMR spectrum showed two peaks at δ_P +10.7 and +11.1 and in the ^1H and ^{13}C NMR spectra the ethyl ester and the benzoxycarbonyl groups could not be seen. This was taken to indicate the possible formation of the two cyclic products, one with a methionine side chain **570** and the other with a vinyl side chain **571**. These products contain the tetramic acid ring system as will be discussed again in section **G**. The inlet was heated at a higher temperature than in the previous case which probably encouraged the cyclisation and elimination of MeSH to occur.

At 500 °C, ^{31}P NMR showed mainly loss of Ph_3P and a smaller amount of the expected Ph_3PO and other products that so far have not been identified.

The substituted side chain derivatives seem to interfere with the pyrolysis reactions and do not behave in the expected manner. Although the products obtained were interesting our priority was to prepare acetylenic derivatives for the collaborating company and we decided to try and establish a general route to these type of compounds working with known aliphatic amino acid ylides.

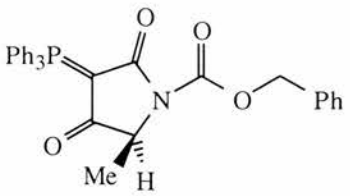
The first amino acid we investigated was the alanine derivative **551**. Pyrolysis of this at 600 °C and 3 x 10^{-3} Torr resulted in the desired loss of Ph_3PO and the formation of the protected acetylenic amino acid ester **572** at the furnace exit. In the cold trap we identified a mixture of benzyl alcohol and ethanol. The product was purified by chromatography and a low yield was obtained. While purifying the product some of the fractions were found to be a



551 **572** **573**

mixture of the acetylenic product and an additional interesting product which showed no evidence of an ethoxy group. The ^1H and ^{13}C NMR spectra showed typical peaks related to a terminal acetylene product **573** including an additional doublet in the ^1H NMR at δ_H 2.62 and a new peak at δ_C 70.6 for ≡CH.

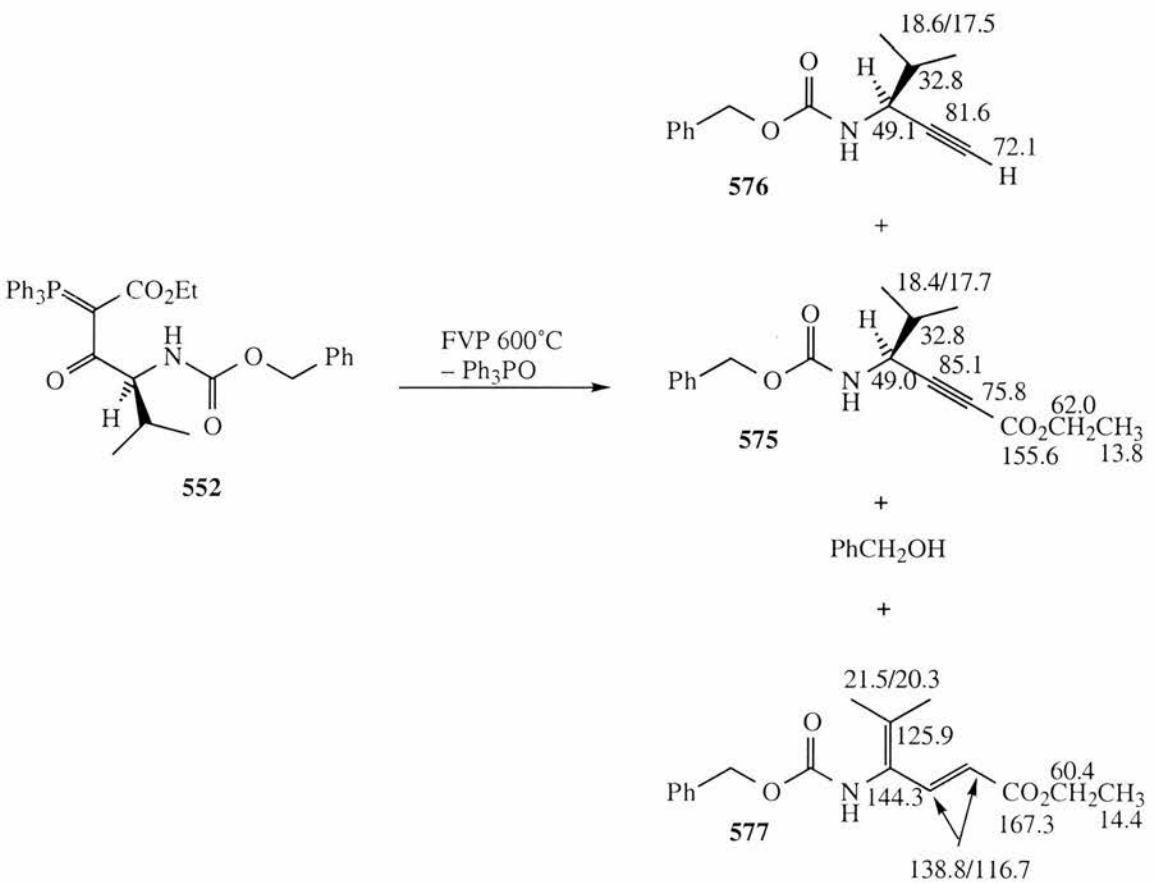
During several pyrolysis attempts the pressure was increased to 10^{-1} Torr during the process which resulted in mainly Ph_3PO, benzyl alcohol and ethanol at the furnace exit and cold trap. Only minor quantities of the desired product were found by quantitative NMR. In the inlet tube we noticed a resonable quantity of a black solid which showed a peak in the ^{31}P NMR spectrum at δ_P +11.06. This product appears to be the cyclic 5-membered ring system **574** since there was no sign of the ethoxy group but the benzoxycarbonyl peak was present in the ^1H NMR spectrum.



574

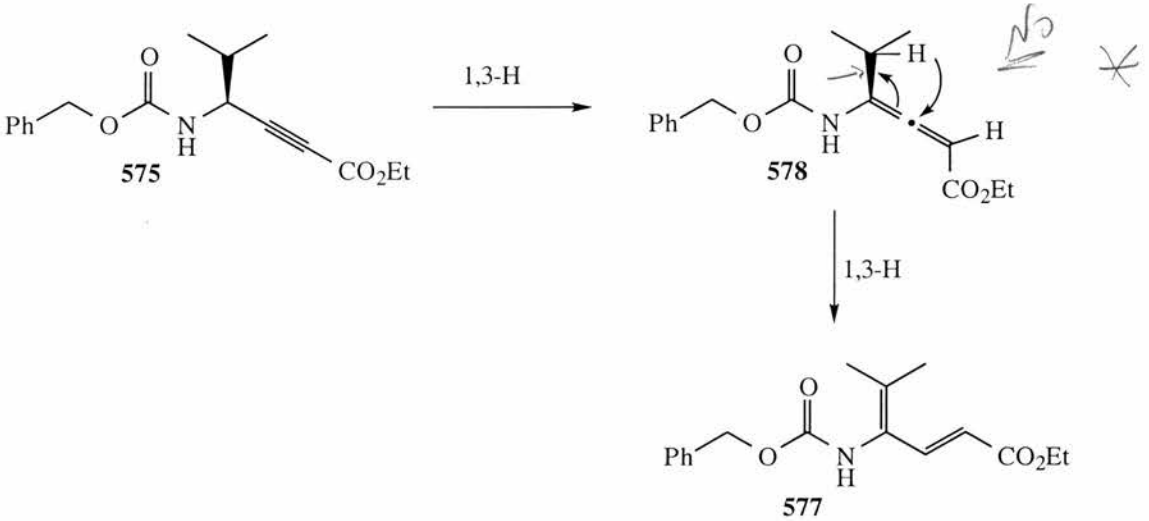
This was the first time that we obtained cyclisation with the amide instead of the free amine as in previous cases. All attempts to scale up this reaction were unsuccessful and we decided to try a different aliphatic amino acid, the valine derivative.

Pyrolysis of ylide **552** at 600 °C gave the protected acetylenic amino acid ester **575** in good yield. Attempts to scale up this reaction gave moderate yields and on purification we succeeded in isolating four different products. As in the previous case the first product showed no evidence for the ethoxy group and the ^{1}H and ^{13}C NMR spectra showed peaks typical of the terminal acetylene product **576**. The second product isolated was the desired acetylenic amino acid **575**. The spectra of the third product showed it to be benzyl alcohol and the final

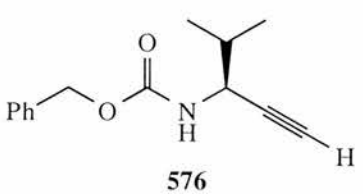


product was the most interesting. The ^{1}H, ^{13}C and DEPT NMR showed no sign of a triple bond or a $CHMe_2$ group present. Instead the spectra were in full agreement with 1,3-diene structure **577**.

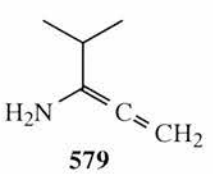
This diene is thought to be formed from **575** by isomerisation to the allene **578** followed by a further hydrogen shift, and its reactivity including Diels Alder reactions may be of great interest. The products are shown above with their relavent ^{13}C NMR shifts.



Further work was done on the pyrolysis of ylide **552** to try and increase the yield of the desired product **575**. Pyrolyses at higher temperatures were done and the observations were interesting. At 650 °C, Ph_3PO, a small amount of benzyl alcohol and the expected acetylenic product **575** were found at the furnace exit and in the cold trap a mixture of benzyl alcohol, **574** and also the terminal acetylene **576** were present. The overall yield of the acetylenic product was lower than that obtained at 600 °C. At 700 °C, Ph_3PO was found to be the major product at the furnace exit and the contents of the cold trap indicated that in addition to benzyl alcohol there were two other products which were the terminal acetylene **576** and the deprotected allene **579**.



576



579

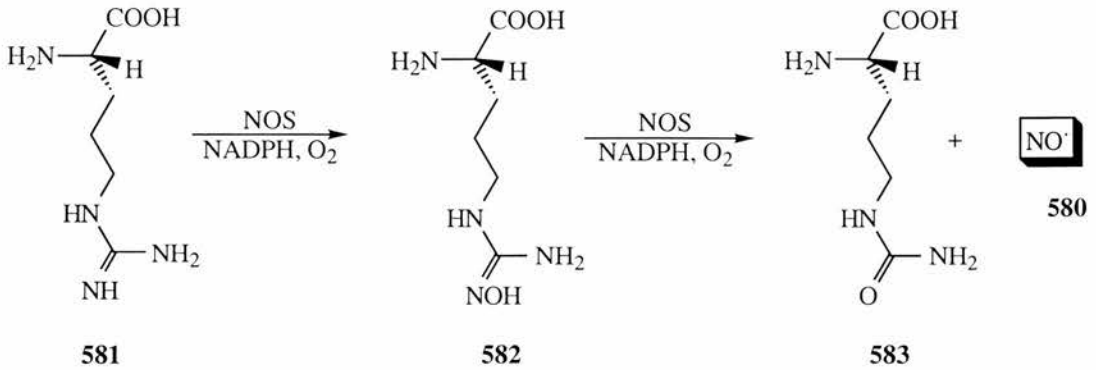
The final pyrolysis on this ylide was done at 750 °C. At the furnace exit the ^{1}H and ^{31}P NMR of the products showed mainly Ph_3PO and benzyl alcohol. Some unidentified products were found in the cold trap. Most of the material seemed to be the inlet tube and was mainly unreacted starting material. In addition to this a small peak was observed by ^{31}P NMR at δ_P +11.4 which represents the cyclic product analogous to **574** and mass spectrometric evidence for a small proportion of terminal alkyne **576** was also obtained.

The pyrolysis at 600 °C seems to give optimum yield for this ylide. This pyrolysis was repeated many times to prepare the acetylenic product for further transformations (see section C) and this could be obtained reproducibly in an acceptable yield of 58%. The pyrolysis of substituted side chain derivatives is still an important area. Other ylides with different protecting groups should be made and their pyrolysis examined.

C Further Transformations - Towards Chiral 1,4-Diamines

1. Introduction

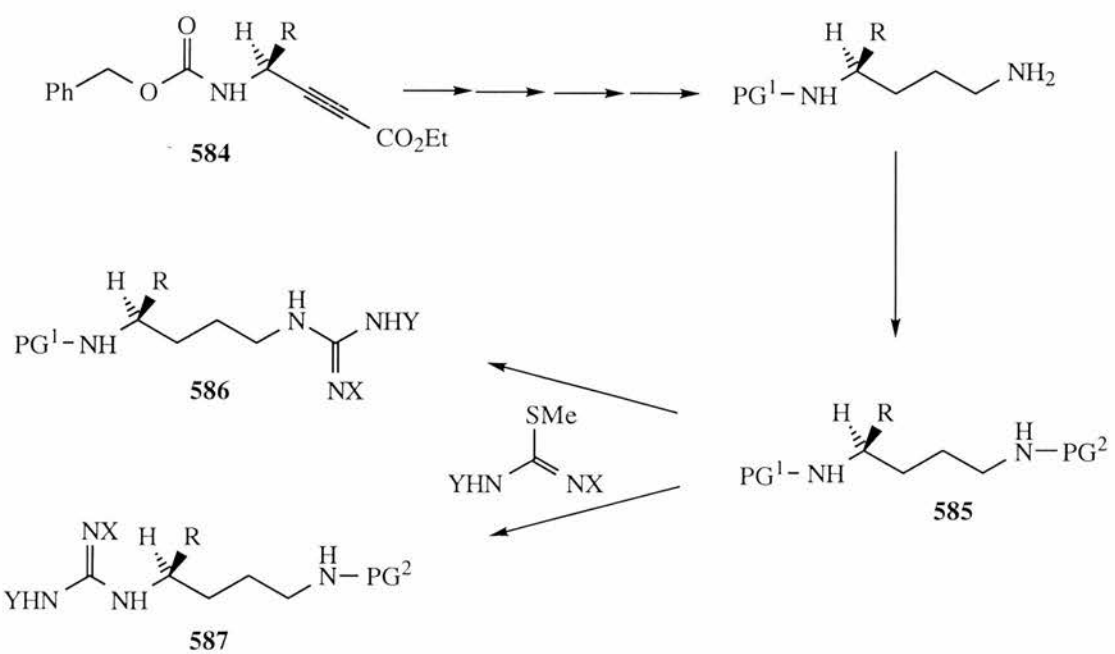
Nitric oxide (NO·) **580**[179,180] has become the subject of growing interest since it has been shown to play a significant role as a cell signalling agent which regulates many different physiological functions. These include control of blood pressure by regulation of smooth muscle relaxation; platelet aggregation, therby acting as an antithrombotic agent; antitumor, antibacterial and antiviral action of macrophages; brain development, learning and memory. Since nitric oxide **580** is a free radical, an excess of nitric oxide can cause deleterious effects, including post ischemic stroke damage, septic shock, schizophrenia, migrane headaches, Alzheimer's disease, tolerance to and dependence on morphine, development of colitis, tissue damage and inflammation, rheumatoid arthritis, destruction of photoreceptors in the retina and long-term depression. NO· **580** is generated by a family of enzymes called NO synthases (NOS) which catalyse both the transformation of (*S*)-arginine **581** into N^{ω}-hydroxy-(*S*)-arginine (NHA) **582** and then the further conversion of NHA to (*S*)-citrulline **583** and NO· **580**.



The oxygen atoms in nitric oxide **580** and the urea carbonyl of (*S*)-citrulline **583** are derived from molecular oxygen, the nitrogen atom of nitric oxide is derived from the guanidine nitrogen of (*S*)-arginine **581**. A variety of reasonable mechanisms for NOS have been suggested, but many are minor modifications of each other.

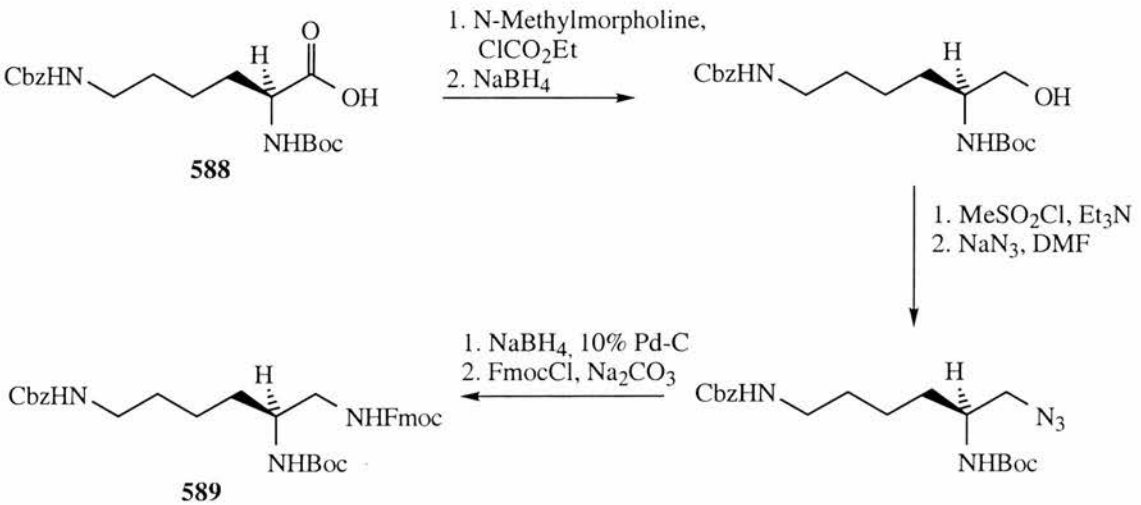
Due to the important physiological role of NO· **580**, one of our main aims was to develop for the collaborating company an easy synthetic route to monosubstituted guanidines **586** and **587** as potential substrates or inhibitors for NO synthases (NOS).

The general strategy was to use the chiral acetylenic amino acid esters **584** obtained as described in section **B** and to perform further transformations to form the diamine compounds **585**. At this stage depending on the selectivity of the protecting group on both amines the

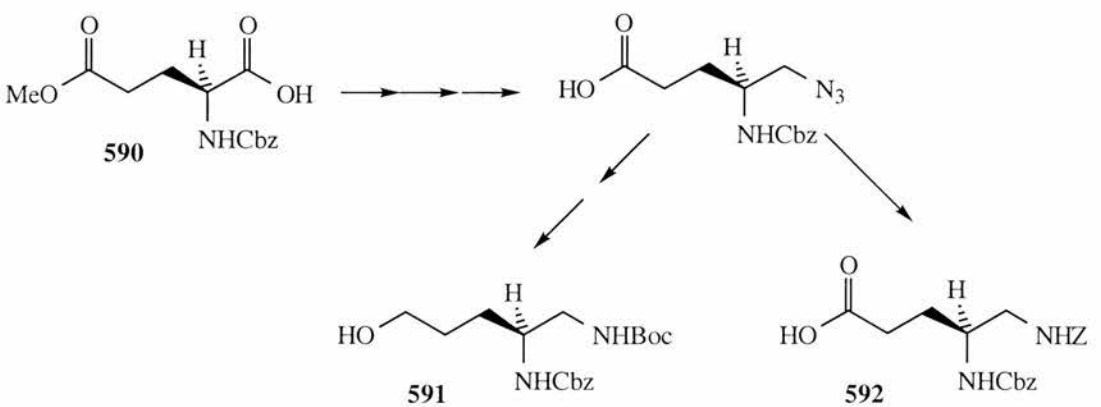


guanidine unit can be added to either amine which would have the advantage of introducing chirality at different places relative to the guanidine unit providing a wide variety of possible NOS substrates or inhibitors.

Kokotos and co-workers[181] reported the synthesis of chiral triamines and diamines from amino acids. Triamines and vicinal diamines are important intermediates in the synthesis of ligands used for radiolabelling and imaging, in chelation chemistry and can exhibit interesting biological properties. Although there are many approaches for the preparation of racemic compounds, only a few for the enantiomerically pure forms exist.

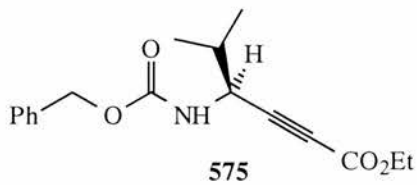


Selectively protected (*2S*)-1,2,6-triaminohexane **589** was prepared from (*S*)-lysine **588** by reduction of the amino acid, replacement of the hydroxy group by an azido group and selective reduction. Following the same method vicinal diamines **591** and **592** with a third functional group were synthesisied from (*S*)-glutamic acid **590**.



As mentioned in part **B** of the disscusion the collaborating company were interested in derivatives derived from amino acids with functionalised side chains. We have shown in the previous section that we met with difficulties during the pyrolysis stage and it was therefore decided to concentrate on amino acids with aliphatic side chains. If we could develop a method to the desired diamines using aliphatic side chain amino acids, the method could be extended to functionalised side chain amino acids which were more of interest.

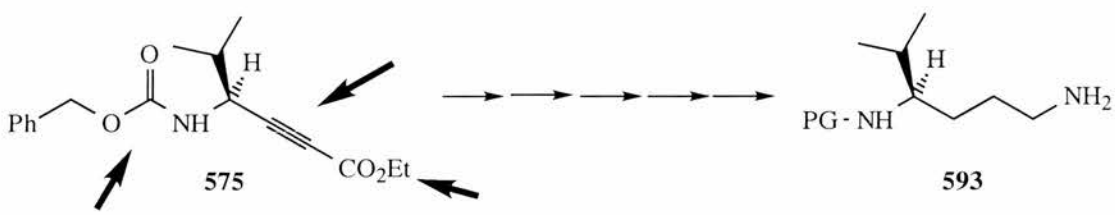
We concentrated on the *N*-benzoxycarbonyl acetylenic valine derivative **575**, ethyl (*4S*)-4-(benzoxycarbonylamino)-5-methylhex-2-ynoate because this gave the highest yield.



575

To form the desired diamine **593** derivative the following is needed (see scheme below):

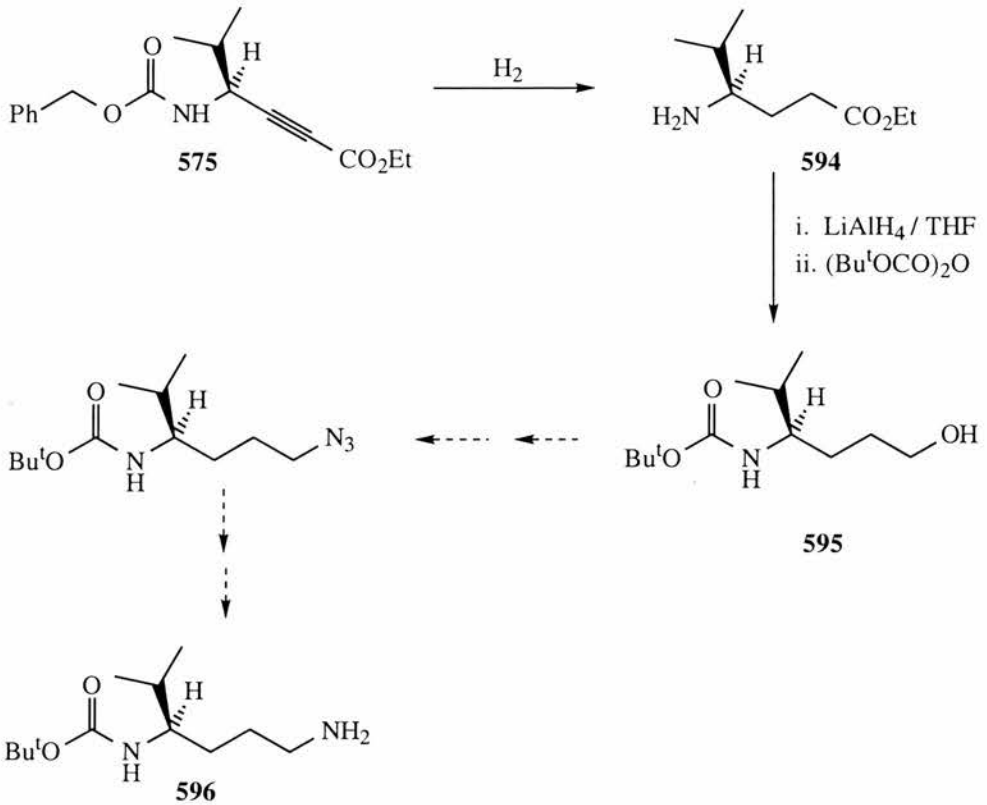
1. transformation of the ester to an amine via an alcohol
2. reduction of the triple bond
3. selective deprotection and protection of the amine



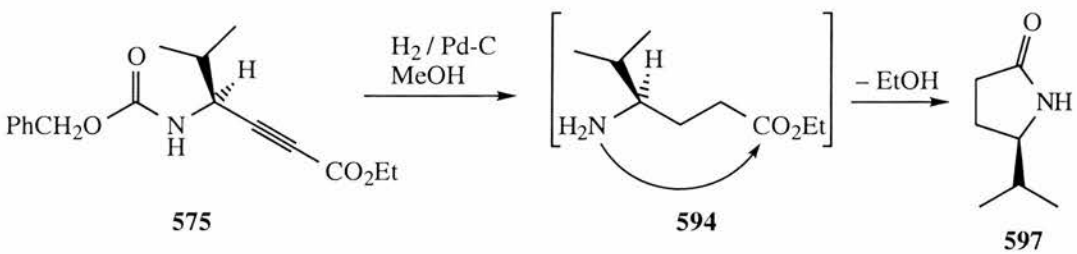
575 **593**

2. Approaches based on initial hydrogenation

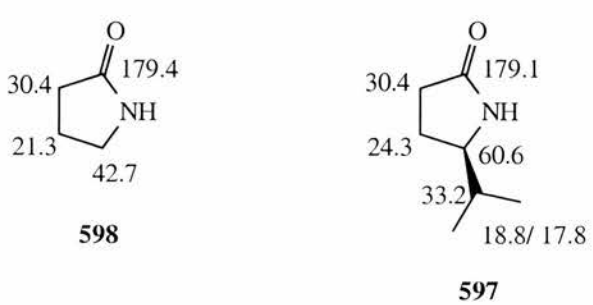
The first approach was based on deprotection of the benzoxycarbonyl group and reduction of the triple bond, followed by reduction of the ester to the alcohol to give **594**. This then can undergo further transformations to the desired diamines **596** as seen in the scheme below:



Attempts to hydrogenate the acetylenic ester **575** in methanol gave a small amount of starting material and another main product that did not contain the ethoxy group by NMR. The ^1H, ^{13}C and DEPT NMR spectra confirmed this product to be the the lactam **597**.

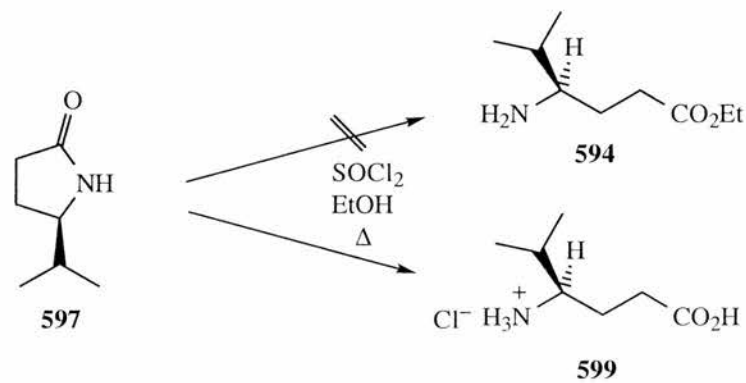


Deprotection to the free amine and reduction of the triple bond led to the desired γ-amino ester **594** but this readily cyclises with loss of ethanol to give the stable lactam **597**. The ^{13}C NMR

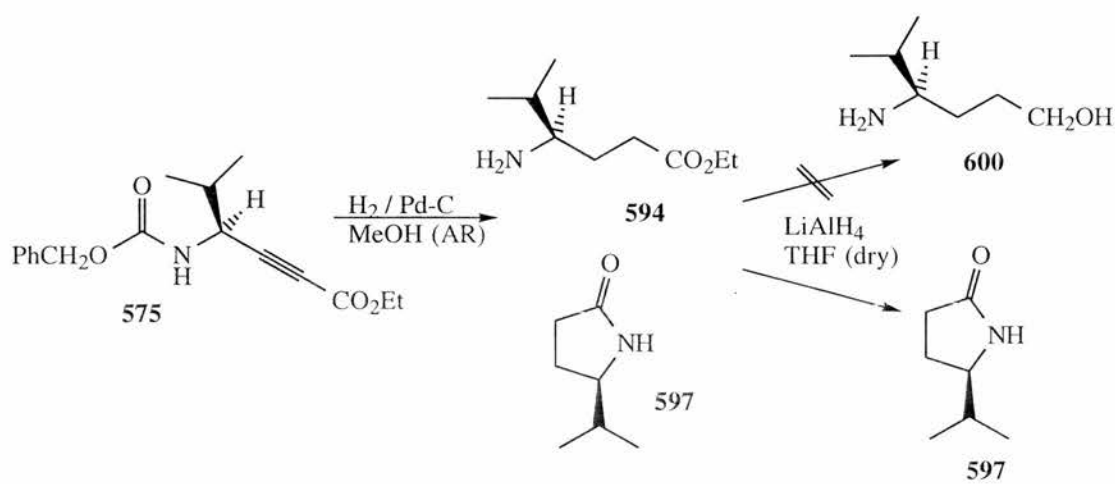


data was compared to 2-pyrrolidone **598** found in the literature,[182] and this confirmed the structure.

The formation of the cyclic product **597** was unexpected and our immediate aim was now to try and form the deprotected ester **594** as planned, by ring opening and esterification.



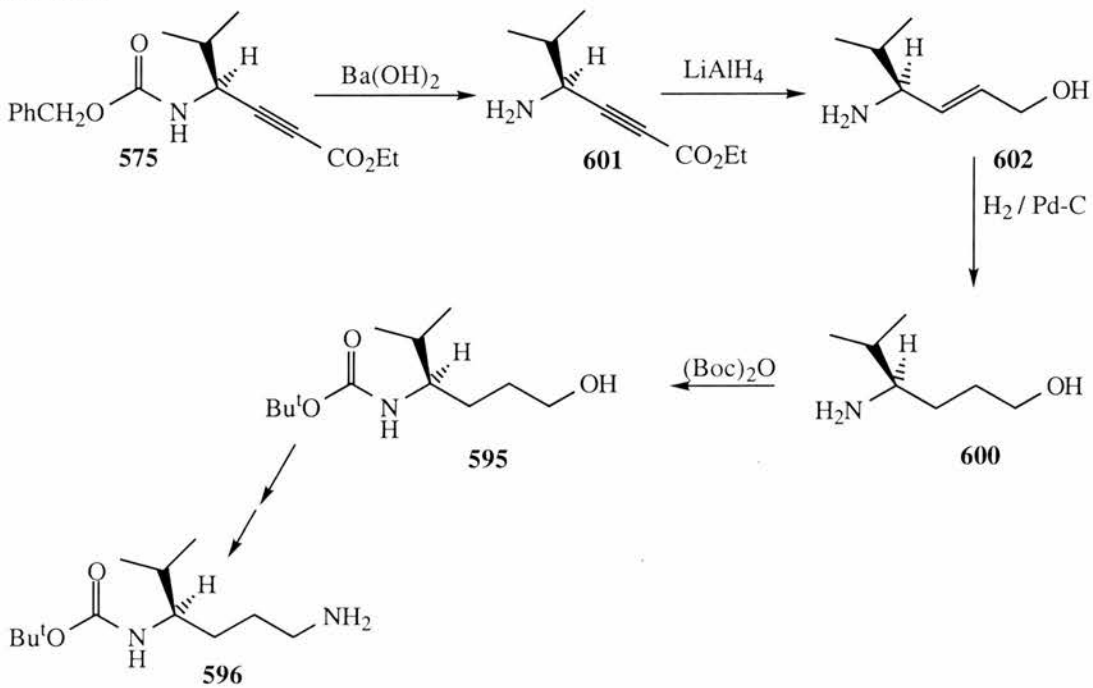
The cyclic product **597** was heated under reflux with $SOCl_2$ in ethanol for 4 hrs and after work up the NMR spectra suggested that the free amino acid hydrochloride **599** had been formed.



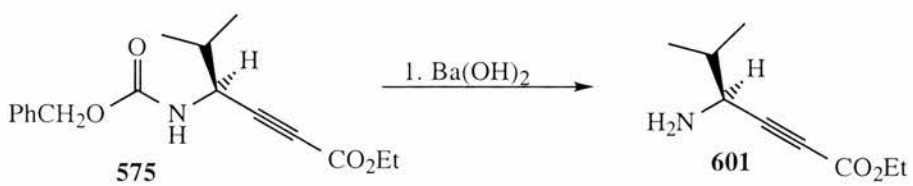
On repeating the hydrogenation reaction in AR methanol we obtained a 1:2 mixture of the deprotected ester **594** and the cyclic product **597** formed as before. Due to the difficulty in isolating these products we applied further transformations to the crude mixture. An attempt to reduce this mixture to the alcohol **600** using lithium aluminium hydride, resulted here only in the conversion of **594** into **597**.

3. Routes avoiding initial hydrogenation

To try and avoid the situation of cyclisation we considered a second approach which differed from the first by altering the order of transformations. At the first stage, selective deprotection of the amine without affecting the triple bond and ester was needed. Further reduction of the ester **601** to the alcohol **602** followed by reduction of the double bond in that order should avoid the cyclisation process and we should be able to form the deprotected alcohol **600**.



Following a literature procedure,[183] selective deprotection of the benzoxycarbonyl group without affecting other functionalities was attempted by boiling **575** with barium hydroxide octahydrate in a mixture of water-glyme for 48 hours. When the mixture was cooled, CO_2 gas was bubbled through the solution to precipitate the barium salts.

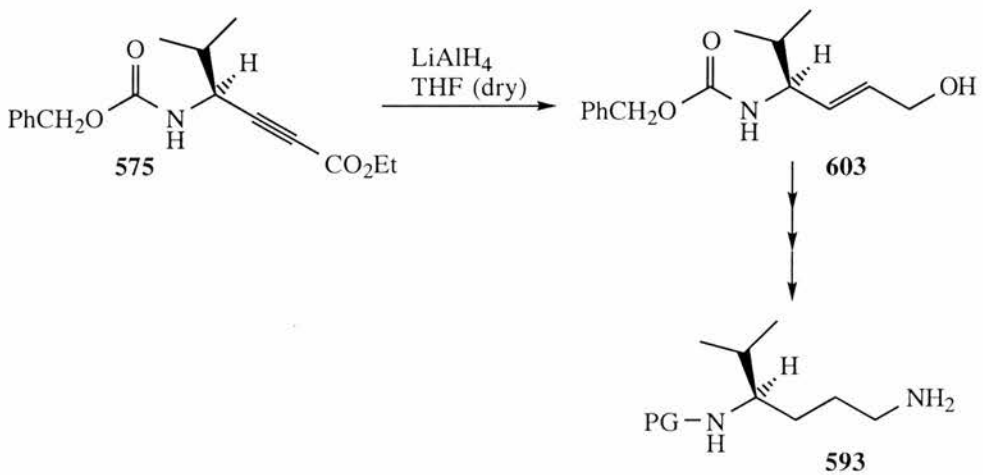


To make sure that no further cyclisation had occured we boiled the concentrated filtrate with $SOCl_2$ in methanol and the crude product obtained looked promising. The ^1H NMR spectrum showed no sign of the benzyl group but many additional peaks in the aliphatic area were

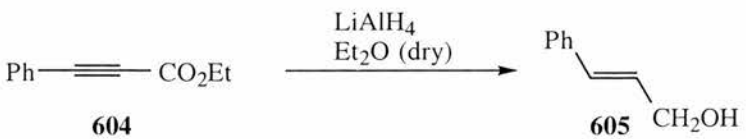
formed. Attempts to purify the product on a preparative TLC failed and this approach was also abandoned.

4. Initial reduction of the ester

The failure of these two approaches served to demonstrate the critical importance of the order of transformations and while the deprotection of the amine before the formation of the alcohol and reduction of the triple bond failed we considered a third approach which again changed the order of the three transformations required. The first step would be reduction of the ester and the triple bond to form **603** before deprotecting the amine to avoid further complications like cyclisation.

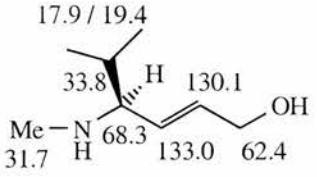


It is already know from the literature that α,β-acetylenic esters **604** are reduced to *E*-allylic alcohols **605** with lithium aluminium hydride.[184]



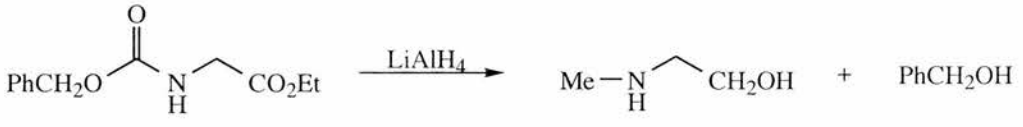
The reaction of acetylenic ester **575** with lithium aluminium hydride gave interesting results. The ^{1}H NMR spectrum of the crude product showed, in addition to the expected signals typical of a double bond, an additional peak at 2.35 ppm which was shown to be a methyl signal by DEPT. Benzyl alcohol could also be identified indicating the loss of the benzoxycarbonyl protecting group. The ^{13}C NMR data confirmed these conclusions and the additional signal that represented a methyl group was at a higher frequency than expected,

therefore attached to a heteroatom. The structure **606** is in full agreement with the spectroscopic data



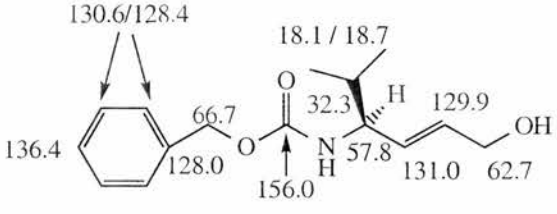
606

This type of behaviour was first reported in the early 1950's,[185] when the benzoxycarbonylglycine ester **607** was treated with lithium aluminium hydride to give *N*-methylethanolamine **608** and benzyl alcohol.



607 **608**

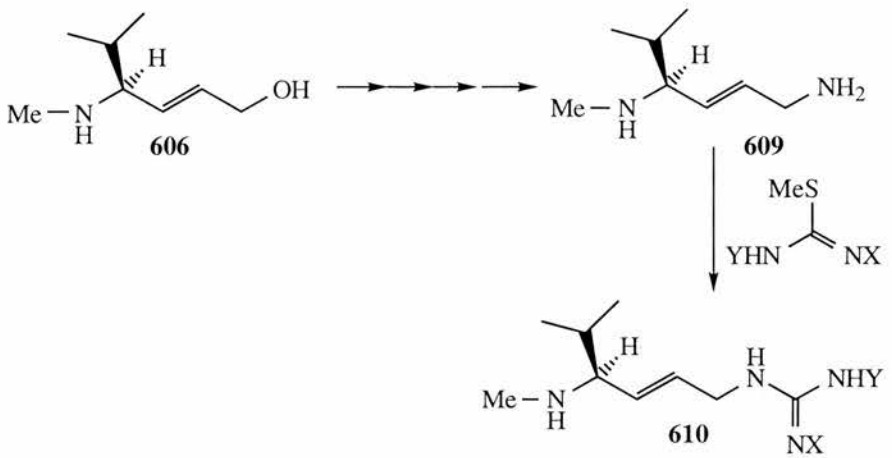
Kugelrohr distillation of the reduction product gave a mixture of benzyl alcohol and **606**. A small amount of yellow oil was left in the distillation flask and this was shown spectroscopically to be similar to the first product but instead of the N–Me group the benzoxycarbonyl group was present. The ^{1}H and ^{13}C NMR data are in full agreement with the stucture **603**.



603

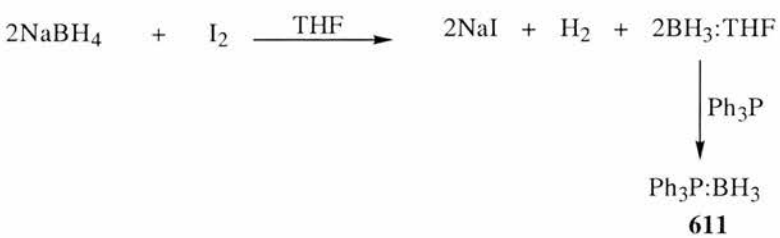
Product **603** was one of the target intermediates but unfortunately it was not obtained in every reaction and when obtained the yields were very low. The product **606** was not the desired product but it still had its applications. In a modification of the original route we could apply further transformations to **606** to form the diamine derivatives **609**. These too serve the same

purpose as our main target molecules and with the guanidine unit a different series of potential inhibitors **610** could be prepared.

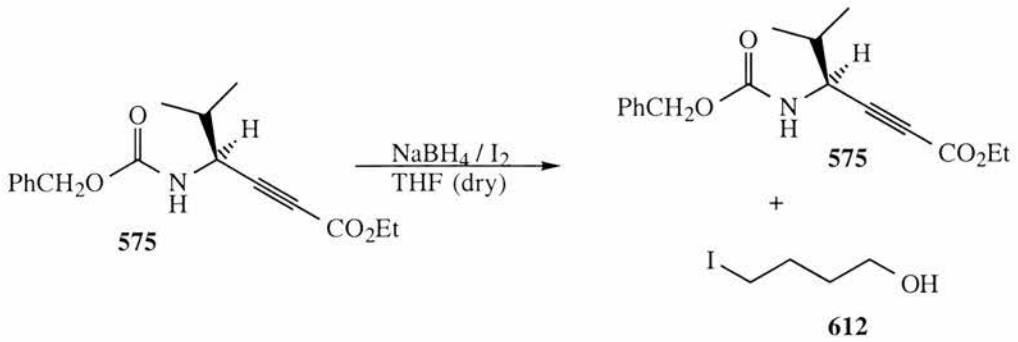


The yields of the *N*-methyl product were low and it was difficult to isolate the product for the further steps.

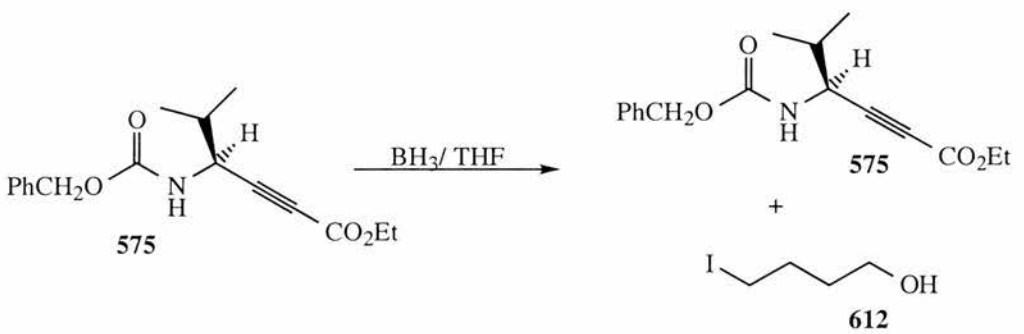
In an attempt to avoid attack at the benzoxycarbonyl group other milder reducing reagents were applied. Periasamy and co-workers[186] reported a convenient procedure for the reduction of carboxylic esters and acids into alcohols using the sodium borohydride/ iodine in THF system. Addition of iodine to sodium borohydride in THF at 0°C followed by the addition of triphenyphosphine gave the phosphine-borane adduct **611** indicating the formation of borane-THF in the reaction of sodium borohydride with iodine.



Two attempts were made with this system. In the first case iodine was added to a mixture of the acetylenic ester **575** and sodium borohydride in dry THF and in the second case the acetylenic ester was added to a mixture of the sodium borohydride and iodine. In both cases the ^{1}H and ^{13}C NMR spectra of the products showed only unreacted starting material and a product derived from THF cleavage, 4-iodobutanol **612** to be present.



Borane in THF was also examined as a reducing agent but here too the products obtained were unreacted starting material and 4-iodobutanol **612**. We repeated this reaction with a larger excess of borane but the results remained the same.



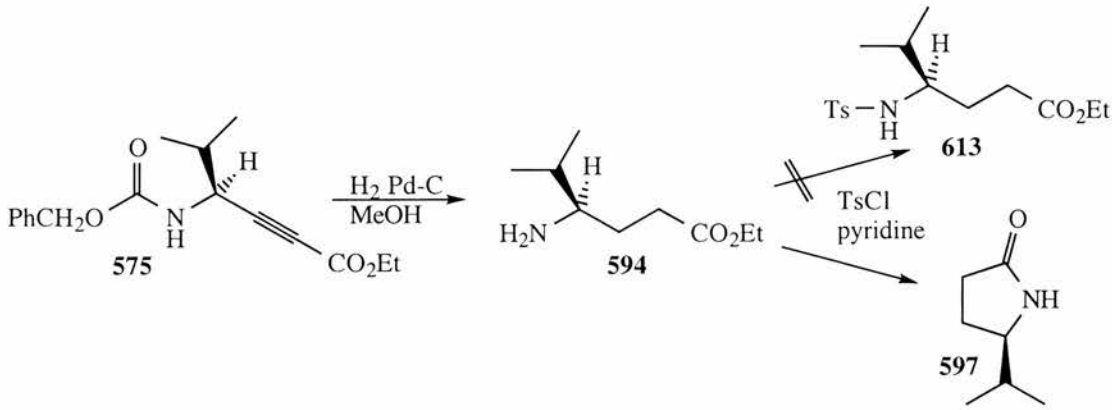
5. Changing the benzoxycarbonyl protecting group before reduction

Up to now the third approach was the closest to success: the ester group and the triple bond should be reduced first while there is a protecting group on the amine but the protecting group should not belong to the carbamate family.

To try and achieve this we needed to change our strategy. Before we deal with the ester group and the triple bond we need to replace the benzoxycarbonyl protecting group with a different protecting group that will be stable to the various reaction conditions.

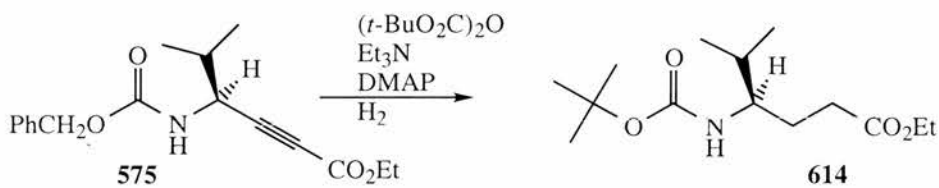
The *p*-toluenesulfonyl group was chosen since it is reported in the literature that this group is stable to severe reduction conditions.[187] Deprotection of the benzoxycarbonyl group under hydrogenation conditions to give the free amine **594** and addition of this product to a suspension of *p*-toluenesulfonyl chloride in pyridine gave after work up a mixture of products. The ^{1}H NMR spectrum showed no sign of the desired product **613** and since the peaks for the

OEt group were very small, it seemed that the cyclic product **597** had again formed under the basic conditions used.

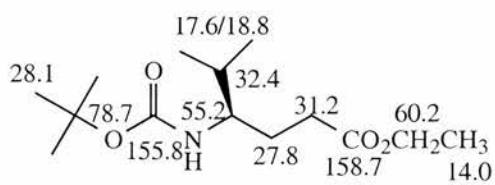


The *tert*-butoxycarbonyl (Boc) group was a further option for a protecting group, it is known to be stable under a variety of conditions and is conveniently removed by acid under mild conditions[188] which should not interfere in our further transformations.

An attempt to replace the Cbz group with the Boc group in one pot was performed. Triethylamine, di-*tert*-butyl dicarbonate and DMAP were added to a solution of the acetylenic ester **614** in ethyl acetate, the mixture was left to stir under a hydrogen atmosphere. This was supposed to result in deprotection of the Cbz group and protection with the new Boc group *in situ*.[189]



The ^{1}H and ^{13}C NMR spectra of the product looked promising as there was no sign of a benzyl group present and there was a new large peak for the Boc group but the product seemed to be

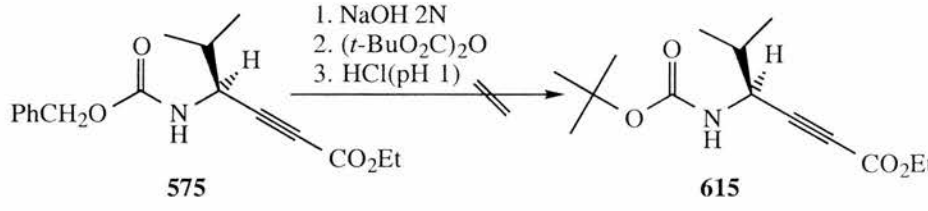


614

present as a 2:1 mixture with an unidentified impurity. The DEPT spectrum helped us to assign the signals for the product **614** as shown, confirming its structure. This product was a good

intermediate for further transformations but its purification and isolation were not easy and while attempts to purify it were proceeding other methods were used.

Our last attempt at replacing the protecting group on the acetylenic product **575** was run again with the Boc group but under different conditions to form **615** following a literature procedure.[190] The acetylenic product **575** was heated with a solution of sodium hydroxide and di-*tert*-butyl dicarbonate. The mixture was acidified to pH 1 and extracting this solution with ether led to a yellow oil.

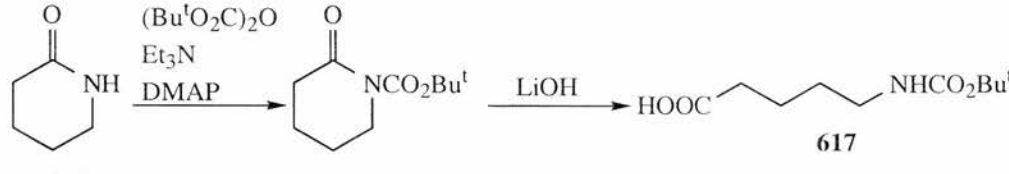


575 **615**

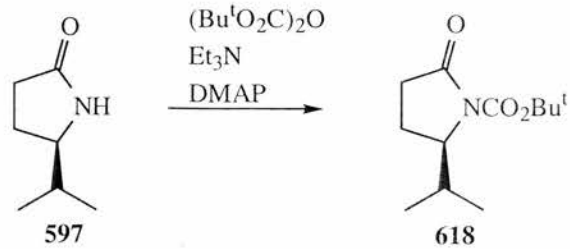
The NMR spectra obtained were very complex and this reaction was abandoned.

6. Further transformations based on the lactam 597

The cyclic product **597** tends to form easily under most conditions but we met with difficulties when trying to open the ring and esterify this product. In the literature we found a mild and efficient procedure for the hydrolysis/ alcoholysis of lactams **616**.[189] Furthermore, the method gives the product **617** with the amino function in a protected form, thus permitting further elaboration of the carboxylic acid residue.

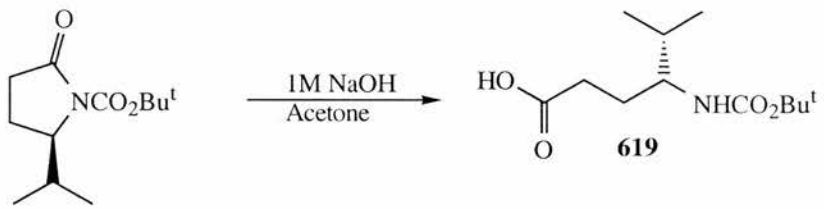


616 **617**



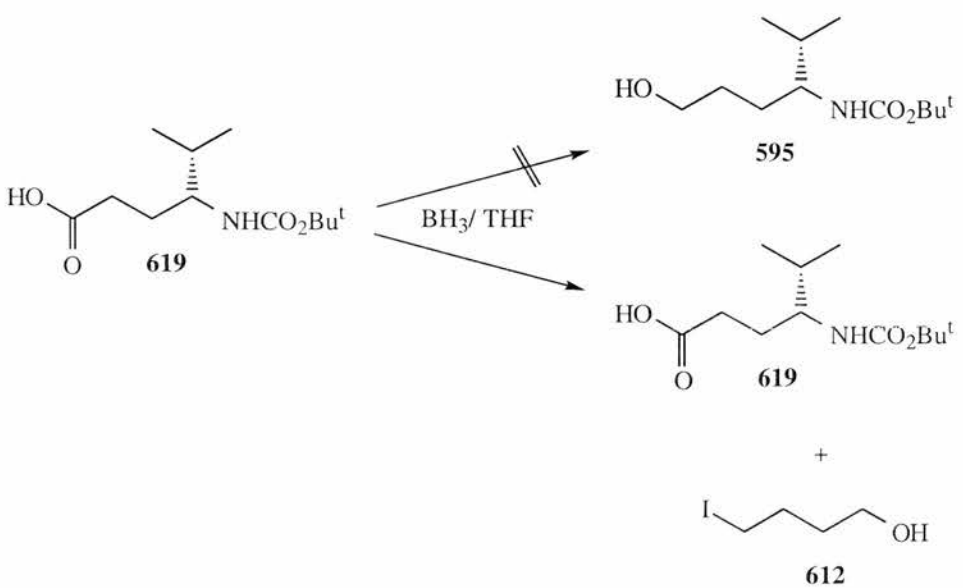
597 **618**

By application of these conditions to our cyclic product **597** it seemed that the desired product **618** was obtained as indicated by NMR. There was a new large peak representing the Boc group. Alkaline hydrolysis of the product **618** with a solution of sodium hydroxide in aqueous acetone[191] should give the *N*-Boc-γ-amino acid **619**.



618 **619**

The hydrolysis was successful and the *N*-Boc-γ-amino acid **619** was obtained in addition to some impurities. As we were using small amounts of materials we did not purify the product and used it crude in the next step. One attempt was made to try and reduce the acid to the alcohol **595**. Borane in THF was used as the reducing reagent and the mixture was left to stir at room temperature for 48 hours.



619 **595** **619** **612**

Unfortunately the reaction did not take the desired course and the NMR spectra showed only unreacted starting material **619** and 4-iodobutanol **612**. Other reducing reagents need to be tried.

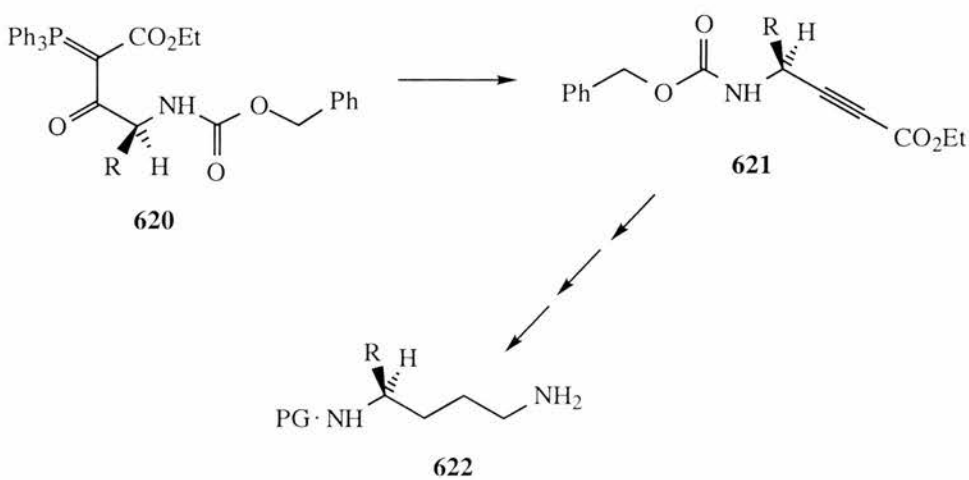
7. Conclusion

Although the results in this area were generally disappointing, we were able to learn something about the inherent problems of these systems which will help for future investigations. It is clearly essential to plan the order of transformations depending on the protecting groups. The benzoxycarbonyl group was used because of its ability to survive the FVP conditions but has proved to be unsuitable for further transformations. Replacement of the protecting group was possible but the yields obtained were low which discouraged us from continuing with the 5–6 remaining steps. Reduction of the acetylenic ester **575** gave interesting results. The *N*-Me products have potential but their preparation needs to be scaled up for the further transformations to be completed.

D Use of Different Nitrogen Protecting Groups

1. Introduction

The preparation and pyrolysis of amino acid ylides **620** with the ethyl ester and the Cbz protecting groups were discussed in section **B**. These were prepared with the aim of providing substituted acetylenic amino acid products **621** which were to be used for further transformations to the diamines **622** of interest to the collaborating company (see section **C**). We focused on these groups because they were stable to the pyrolysis conditions but as we showed in section **C**, the deprotection conditions were not suitable for applying further transformations and other protecting groups needed to be considered.



The aim of this part was to prepare amino acid ylide derivatives with various protecting groups and to study their pyrolysis behaviour. A suitable protecting group must fulfil the following conditions: it must be stable to the FVP conditions, give high yields and its removal must be different to the methods used up to now. Various esters on the ylide and carbamates on the amino acid were examined because it was already known that they fulfil two out of the three conditions and the third condition needed to be investigated.

With this aim in mind and the possibility of varying the two different protecting groups, it was decided to check and compare three different possibilities:

a. The ylide with the EtO_2C group with various protected amino acids.

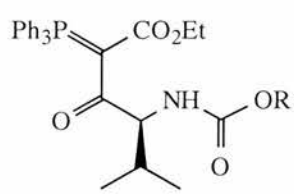
b. The Cbz protected amino acids with various protecting groups on the ylide.

c. Different protecting groups on both ylide and amino acid.

The preparation of all starting ylides and protected amino acids used in this section was discussed in section A. The amino acid valine was used in all cases to reduce the total number of varibles. The pyrolysis of the ylides was performed under the same conditions of 600 °C and 7–8 x 10^{-3} Torr and the results in each category led to the preparation of other derivatives.

2. Ylides with the EtO_2C group and various protected amino acids

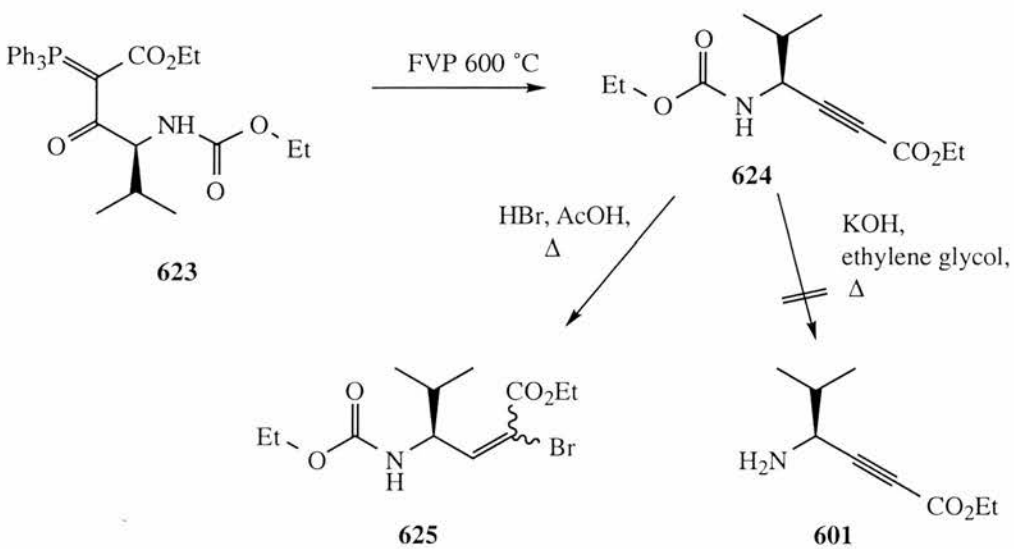
The preparation of ylides of this category was discussed in section B following the standard procedure for the coupling of the ethoxycarbonyl ylide with the protected amino acids. The ethoxy-, t-butoxy- and allyloxy- carbonyl were used as protecting groups for the amino acid and the yields and ^{31}P NMR data for the resulting ylides **623**, **560** and **561** is shown.



	R	%	δ_P
623	Et	45	17.8
560	Bu^t	39	17.9
561	$H_2C{=}CHCH_2$	33	18.3

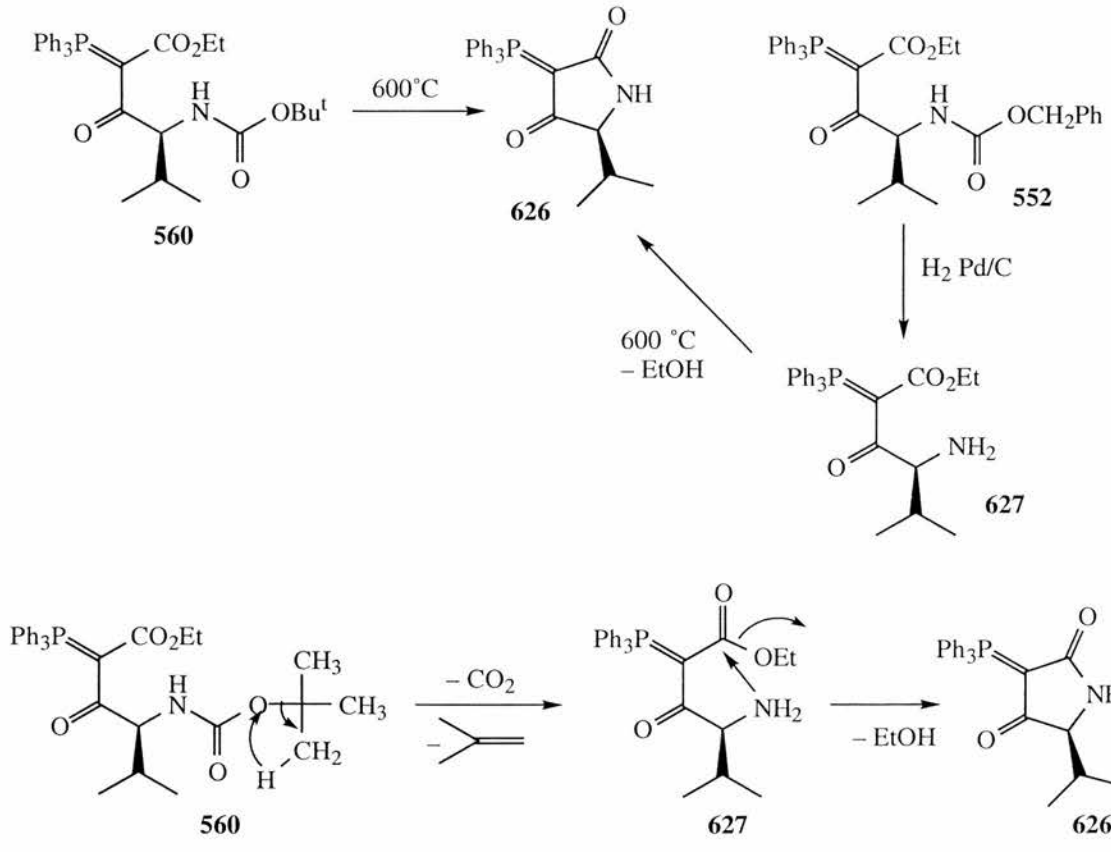
The pyrolysis of the ethoxycarbonyl derivative **623** was found in previous work[138] to give the acetylenic product **624** in 34% yield after purification. The deprotection conditions for the ethoxycarbonyl group involve the use of strong bases or strong acids which are not suitable. A base may react with the ethyl ester group and on addition of an acid, for example HBr, an addition to the triple bond occurs to give an equal mixture of *E* and *Z* isomers **625**.[138]

Pyrolysis of the ethoxycarbonyl ylide with t-butoxycarbonyl group **560** at 600 °C gave interesting and unexpected results. Ph_3PO, ethanol and isobutylene were found in the cold trap and at the furnace exit the ^1H and ^{31}P NMR spectra showed Ph_3PO, a small amount of Ph_3P and 20% of an additional product with a ^{31}P NMR shift at δ_P +10.7. A black solid was left in the inlet tube and it showed the same ^{31}P NMR shift. The ^1H and ^{13}C NMR spectra confirmed the structure to be the cyclic product **626** shown.



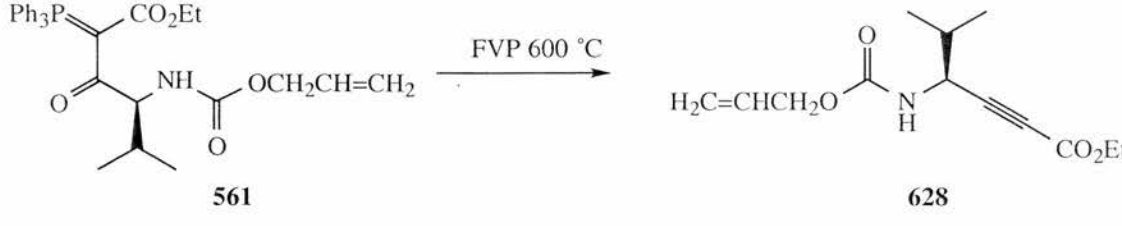
This cyclic product consists of the tetramic acid ring unit and has already been prepared in our laboratory from the ethoxycarbonyl Cbz-valine ylide **552**.[138] The ylide **552** was deprotected under hydrogenation conditions to give the amine **627** and on pyrolysis at 600 °C the same cyclic ylide **626** was formed by loss of ethanol.

The mechanism here is believed to go via a proton shift with the elimination of isobutylene and CO_2 to also give the deprotected amine **627**, which loses ethanol to form the cyclic product **626**.



When the pyrolysis was repeated at a lower temperature of 500 °C, there was no material left in the inlet tube and at the furnace exit Ph_3PO and the same cyclic product **626** was found. Although the Boc derivative **560** gave interesting results it does not fulfil the three conditions we set for our required protecting group and this idea was abandoned.

Final investigations on ethoxycarbonyl ylides were run with the valine protected with the allyloxycarbonyl group. The pyrolysis of the allyl derivative **561** gave successful results. In addition to Ph_3PO the expected product **628** was obtained in 35% yield after purification.



561 628

The success with this group is promising because the deprotection conditions involved for the allyl carbamate group are different to what we have used up to now. This group as a protecting group looks promising and the deprotection conditions and their advantages will be discussed later on.

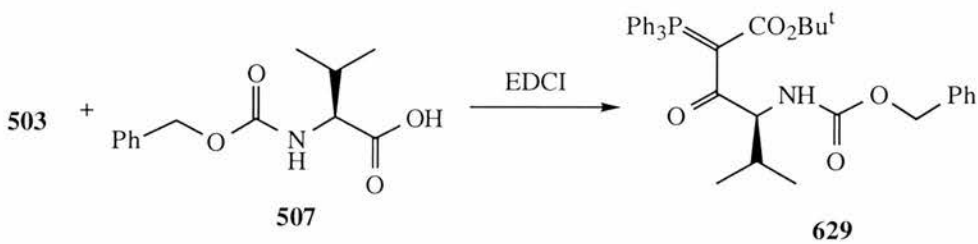
3. Cbz protected amino acids with various protecting groups on the ylide

The ylides of interest in this part were the t-butoxycarbonyl and allyloxycarbonyl ylides **503** and **504** whose preparation was discussed in section **A**.

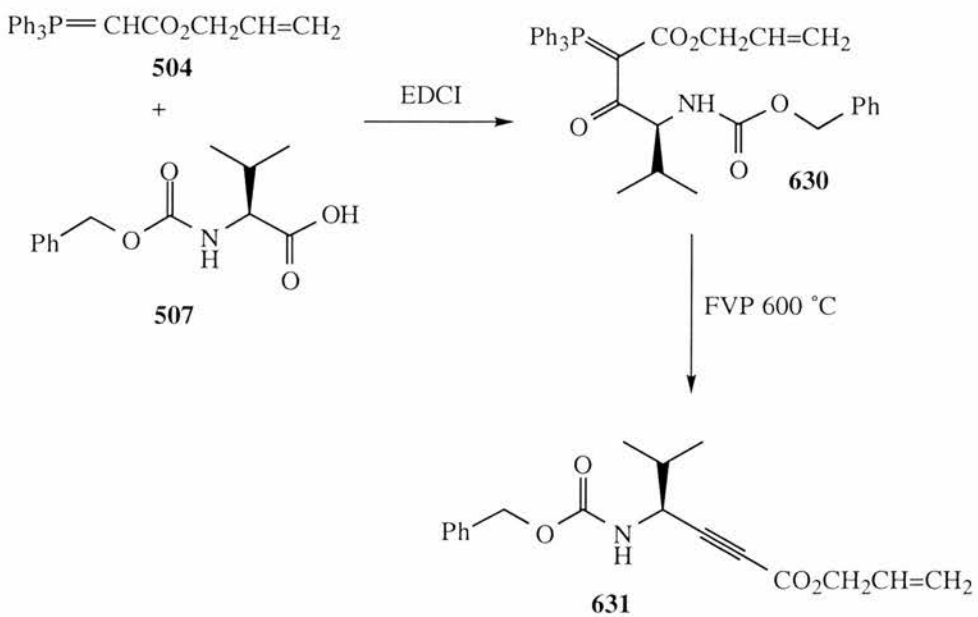
$Ph_3P{=}CHCO_2Bu^t$ **503**

$Ph_3P{=}CHCO_2CH_2CH{=}CH_2$ **504**

Our first intention was to make the t-butoxycarbonyl Cbz-valine ylide derivative **629** but this idea was abandoned after the pyrolysis results from the previous catagory where the Bu^tO group proved to be unstable to the FVP conditions.



As the allyloxy group was stable to pyrolysis in the previous category, we prepared by a similar method the allyloxycarbonyl Cbz-valine ylide **630**. This ylide was obtained in 45% yield. Pyrolysis at 600 °C gave after purification the acetylenic product **631** in 38% yield.

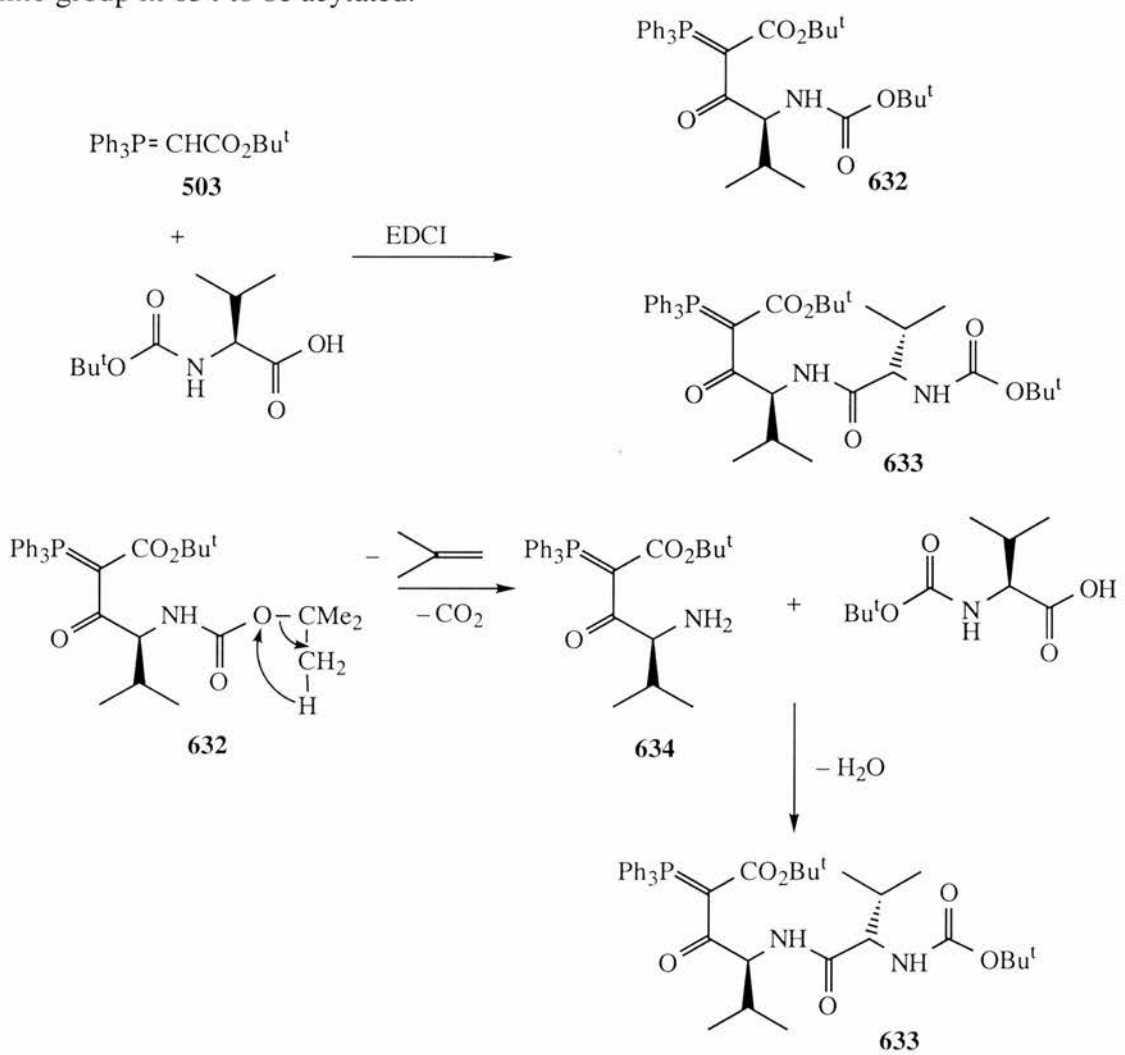


Here again the results are very promising because now we have seen that the allyoxycarbonyl group is stable at both positions and we will confim this in the next category.

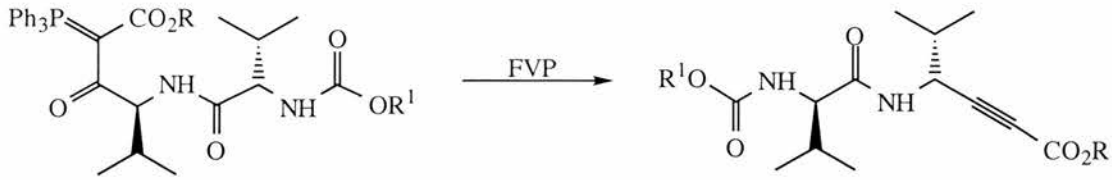
The possibility here of having two different protecting groups with different deprotection conditions is an advantage and this will be disscused later in this section.

4. Different protecting groups on both ylide and amino acid

Two compounds of this type were prepared, we had already prepared the amino acid-ylide with the both Bu^tO groups **632** before investigating the pyrolysis of its analogue and for the reasons mentioned earlier its pyrolysis was not performed. While preparing this derivative **632** *via* the general coupling procedure, we isolated an interesting additional product **633**. The new product that was isolated was very similar to the expected product **632** and proved to be the dipeptide derivative **633**. The dipeptide derivative **633** consisted of a 3:1 mixture of rotamers which are represented by multiple peaks in the ^1H, ^{13}C and ^{31}P NMR spectra. It seems that the Boc group was partly lost during the the coupling step allowing the resulting free amino group in **634** to be acylated.



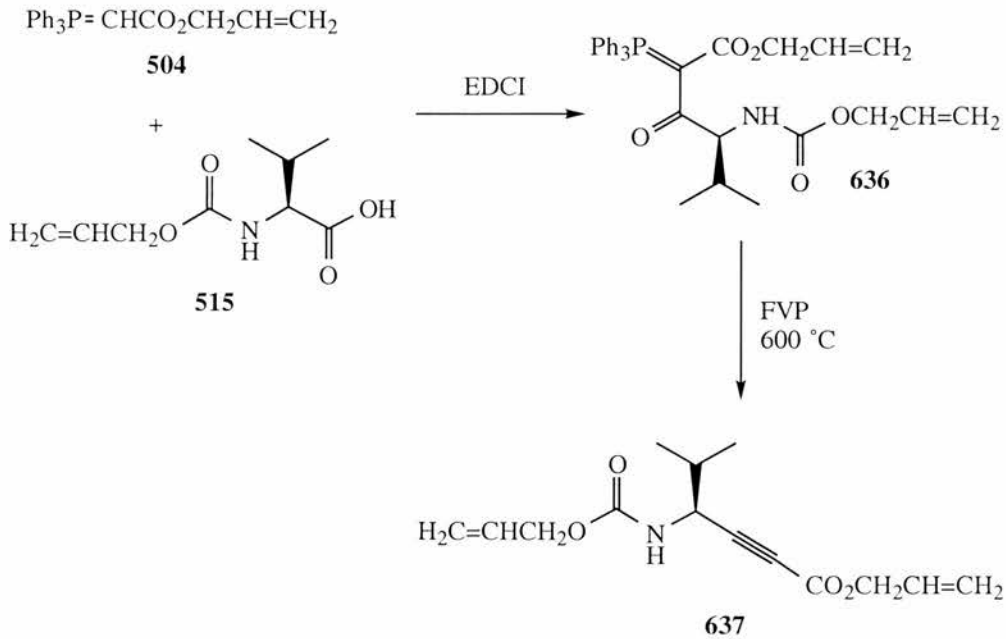
The pyrolysis of the dipeptide ylides **633** could be of interest because elimination of Ph_3PO would result in the formation of an acetylenic unit connected to the dipeptide as in **635** and compounds of this type are useful in peptide synthesis. The dipeptide ylides would not be of the Boc type as they are unstable and other groups would have to be considered here too.



633 **635**

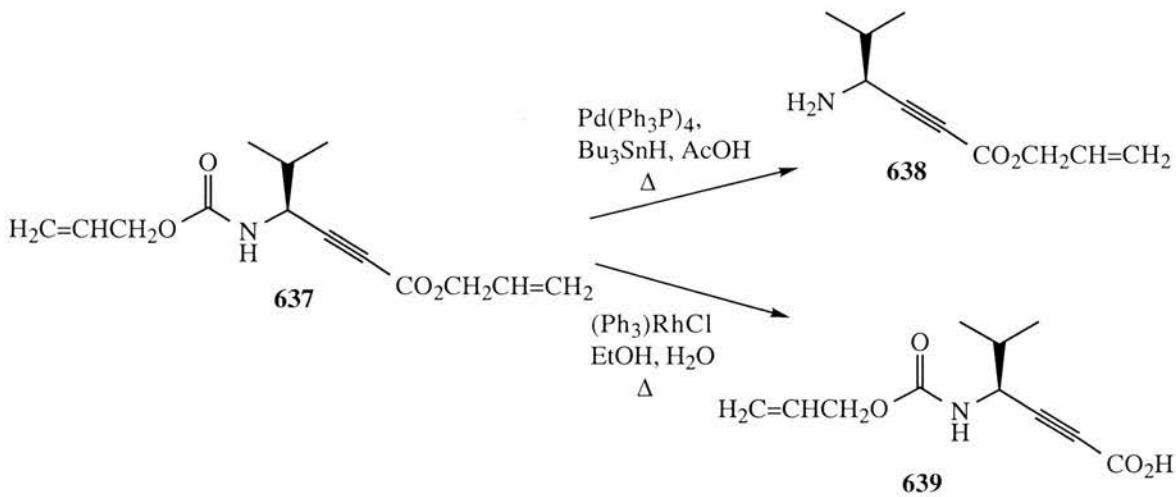
The other amino acid-ylide with the same protecting groups made was with the allyoxycarbonyl group. This group was proved to be stable to the pyrolysis conditions in the two previous categories. The preparation and pyrolysis of the diallyloxycarbonyl amino acid ylide would confirm this.

The diallyloxycarbonyl amino acid ylide was prepared by the general coupling method and the coupled product **636** was obtained in 43% yield after column chromatography. Pyrolysis at 600 °C gave the diallyloxycarbonyl acetylenic product **637** in 43% yield after purification.



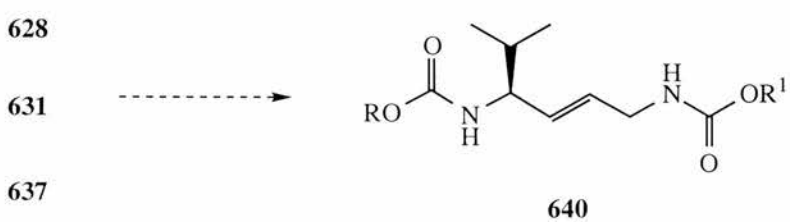
This result confirms the observations in both the previous categories and fulfils our requirements for a protecting group. The allyoxy group is stable to the pyrolysis conditions

when protecting the amide and the ester function. The cleavage conditions of the allyloxycarbonyl group depend on the function it is protecting. When protecting the amino group as the allyl carbamate the cleavage is accomplished using the catalyst $Pd(Ph_3P)_4$ to form the free amine **638** while the allyl ester is cleaved with a different catalyst $(Ph_3P)_3RhCl$ to the acid **639**. It is important to emphasise here that these conditions do not affect each other and specific deprotection can be achieved.



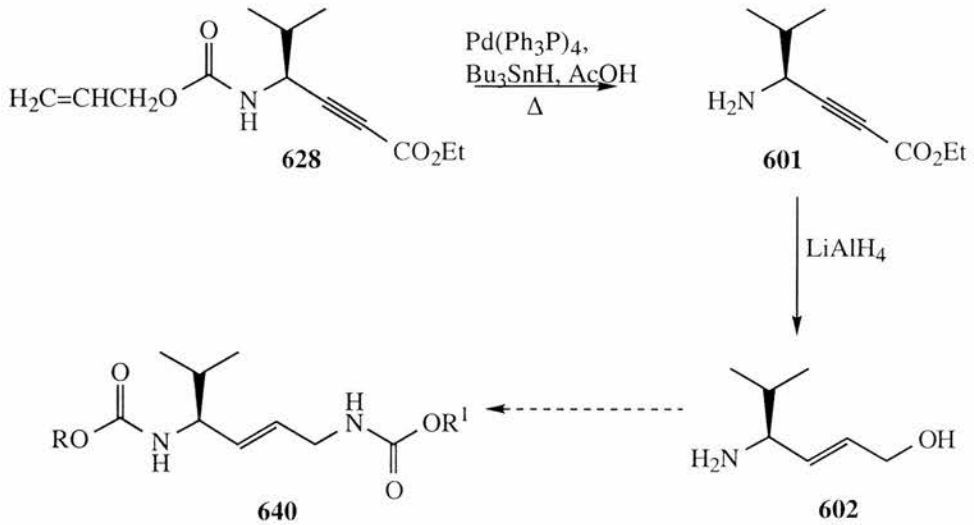
5. Conclusion

Use of the allyloxy group has permitted us to prepare three different acetylenic products **628**, **631** and **637** which were isolated in moderate yields after pyrolysis. These three derivatives have potential for further transformations to the desired diamine **640** discussed in the previous section.

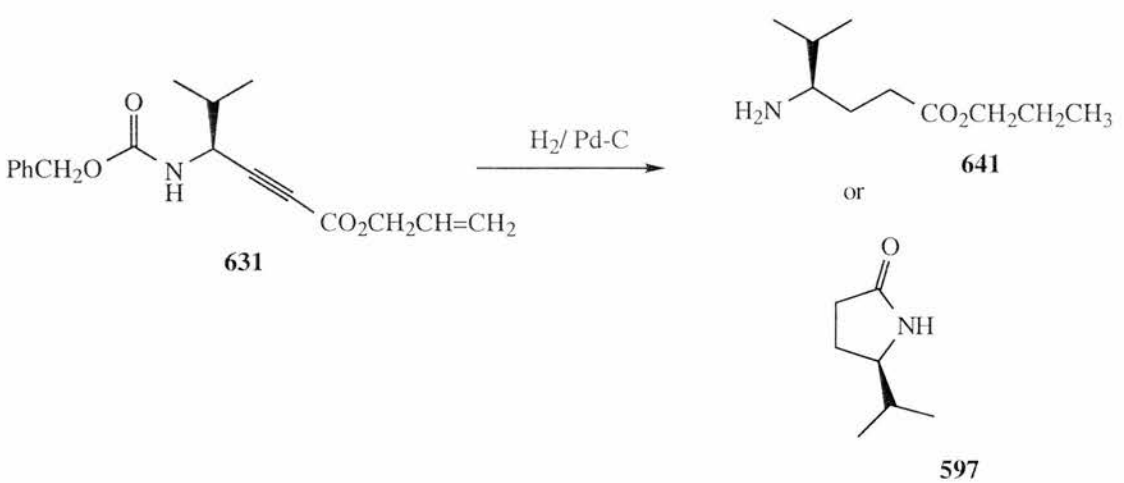


Our first strategy in the previous section involved deprotection of the amine followed by reduction of the ester group while the system is kept unsaturated to avoid cyclisation. Cleavage of the allyl carbamate from derivative **628** using the $Pd(Ph_3P)_4$ catalyst would lead to the free amino ester **601**. The deprotection conditions should not interfere with the ester and triple bond and hence the next step of reduction to the alcohol **602** that we showed in the previous

section with $LiAlH_4$ can be applied. Further transformations to the amine and protecting strategies need to be applied to form the desired diamine **640**.

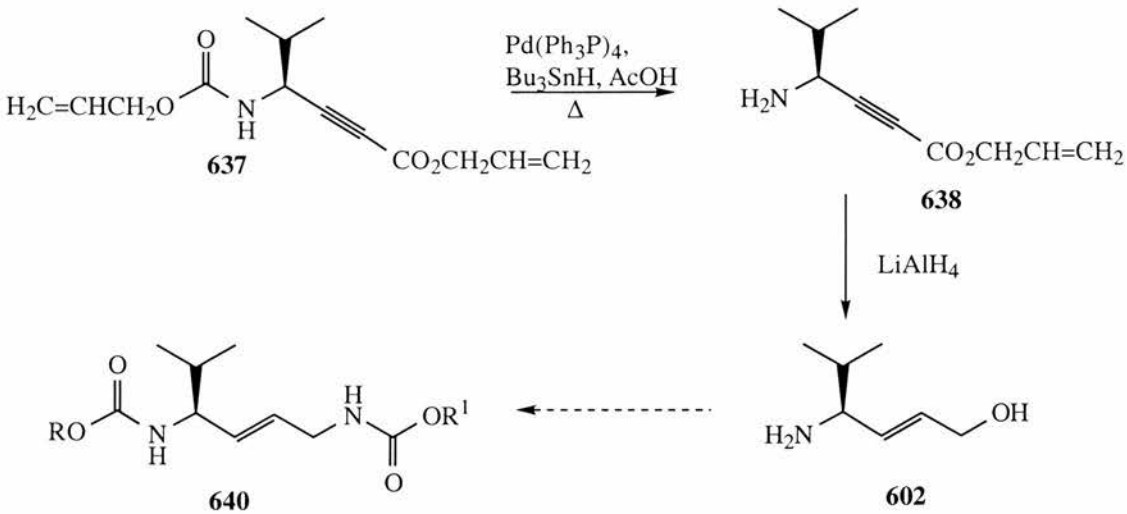


The same approach could apply to the second derivative **631**. Deprotection to the free amine followed by reduction of the ester to the alcohol may lead to the same problem we had when the ethyl ester was present. Deprotection to the free amine **641** by hydrogenation would also reduce the triple bond which would encourage cyclisation to occur to give **597** but this depends on the stability of the allyloxy group as a leaving group. In comparison to the previous example **628**, this derivative **631** is not worth continuing with in light of our previous experience in section **C**.



As discussed previously, the third derivative **637** is also suitable for further transformation to the diamine. The carbamate group is cleaved using $Pd(Ph_3P)_4$ catalyst which

would not effect the triple bond leading to the free amine **638**. The allyl ester is reduced to the alcohol **602** and converted to the amine while the other amine is reprotected to give **640**.

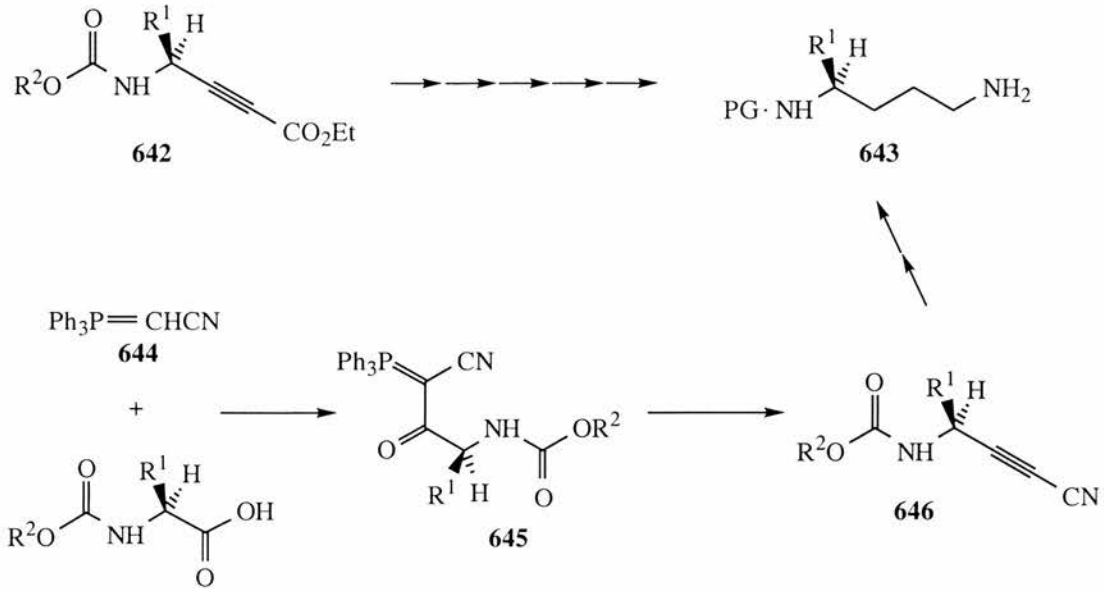


The allyloxy group seems suitable for use for further synthesis. Its cleavage conditions both as a carbamate and ester do not effect each other and this protecting group could be a starting point for future work involving pyrolysis.

E Preparation and Pyrolysis of α-Cyano β-oxo Ylides

1. Introduction

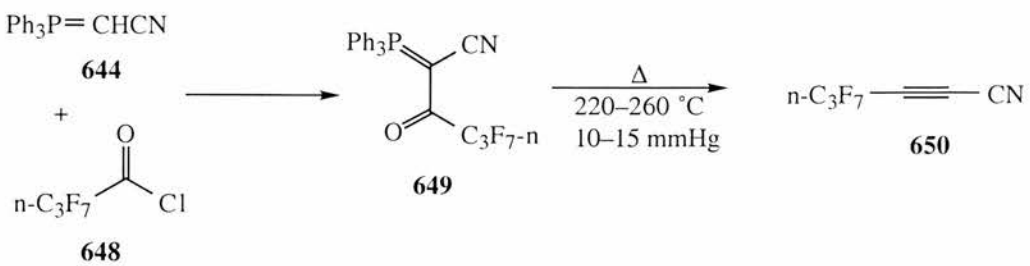
As discussed in section **C**, we have done work of interest to the collaborating company using the acetylenic amino acid esters **642** derived from α-ethoxycarbonyl β-oxo ylides with an aim to synthesise chiral 1,4-diamines **643**. In parallel to this we worked on a similar method starting from a different type of starting ylide, the cyano ylide **644**. Following our previous method the cyano ylide can be coupled to amino acids and on pyrolysis we would expect the cyano acetylenes **646** to be obtained. A simple straightforward reduction would lead to the desired chiral diamine derivatives **643** avoiding several steps in comparison to the acetylenic ester case which is an advantage and this approach is discussed here.



The cyanomethylenetriphenylphosphorane **644** was first prepared by Schiemenz and coworkers in 1961.[155] The synthesis involved the preparation of the precursor phosphonium salt **647** by reaction between triphenylphosphine and chloroacetonitrile followed by removal of an α-proton from this phosphonium salt **647** using NaOH to give the ylide **644**.

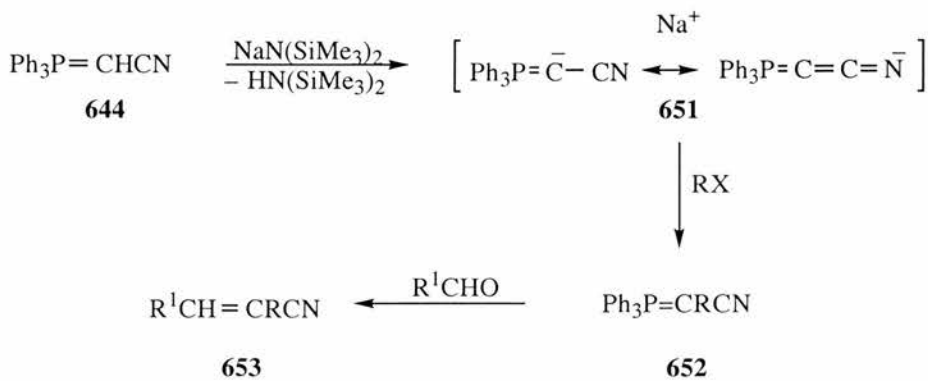
An improved procedure based on a method by Wasserman involved preparation of the precursor phosphonium salt as above and removal of the α-proton from this phosphonium salt using triethylamine to give the ylide in higher yield.[156]

Acyl cyanophosphoranes are known in the literature and some examples of their synthesis and uses are shown here. The cyanomethylene triphenylphosphorane **644** is used in the synthesis of perfluoro-2-alkynenitriles **649**.[192] Two equivalents of the cyanomethylene triphenylphosphorane **644** are added to heptafluoro-n-butyryl chloride **648** and on heating the

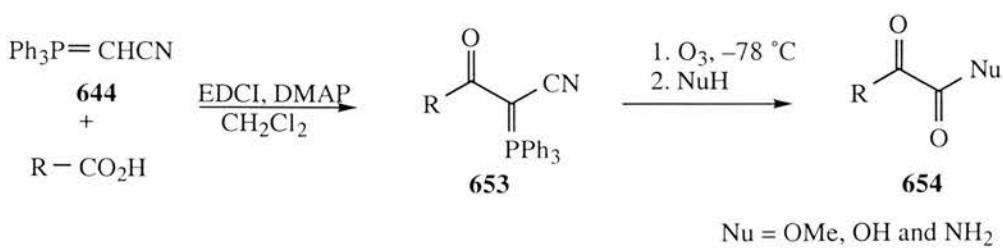


heptafluoro-n-butyrylcyanomethylene triphenylphosphorane **649** is formed. The phosphorane is heated under nitrogen and the solid collected was identified as heptafluorohept-2-ynonitrile **650**.

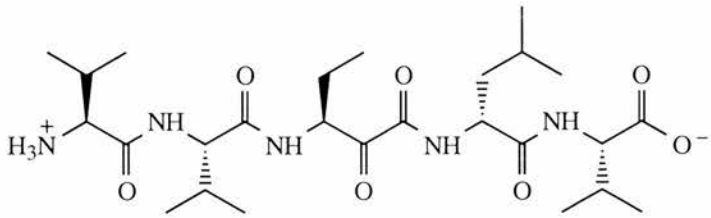
Bestmann and Schmidt have previously reported the synthesis of nitriles *via* the ylide anion, sodium cyanotriphenylphosphoranylidenemethanide.[193] Cyanomethylenetriphenylphos phorane **644** is deprotonated with a benzene solution of sodium bis(trimethylsilyl)amide to give the salt **651** with an ylide anion. This salt reacts with alkyl halides to give cyanomethylene triphenylphosphoranes **652** which are thus easily accessible in a wider variety than found previously. These cyano ylides can react with aldehydes to give α,β-unsaturated nitriles **653**.



Carboxylic acids react with cyanomethylenetriphenylphosphorane **644** in the presence of EDCI to form cyano keto phosphoranes **653** which then can be oxidatively cleaved to form α,β-diketo nitriles.[194] These nitriles can be converted in situ to α-keto acids, esters and amides **654**, for example this procedure has been used in the total synthesis of poststatin **655** which is a potential enzyme inhibitor.[156]



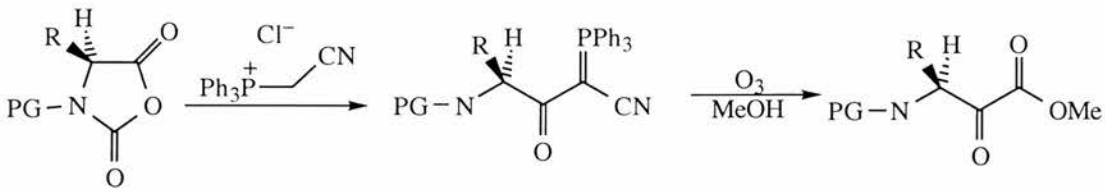
Nu = OMe, OH and NH_2



655

Poststatin: H-Val-Val-Pos-D-Leu-Val-OH;
Pos=Postine

Recently, the synthesis of cyanoketophosphoranes of *N*-protected amino acids **657** which are precursors of β-amino-α-ketoesters **658** were reported starting from *N*-protected α-amino acid *N*-carboxyanhydrides **656** and cyanomethyltriphenylphosphonium chloride.[195]

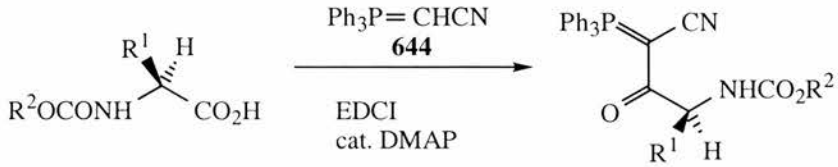


656 **657** **658**

2. Preparation of the α-cyano β-oxo ylides derived from amino acids

The starting ylide, cyanomethylenetriphenylphosphorane **644** was prepared by Schiemenz method (see above) and we initially met with a problem. After the addition of the base, a mixture of triphenylphosphine oxide and a small amount of the product was obtained. Several attempts showed that it was necessary to filter off the precipitate immediately and recrystallise from ethyl acetate to obtain the ylide **644** as beige needles in moderate to low yield. The improved method using triethylamine[156] was applied and this time the solid was contaminated with less than 5% triphenylphosphine oxide and could be condensed successfully with the carboxylic acids. The ^{13}C NMR shift of δ_C –2.1 for the ylide carbon of **644** shows a remarkable degree of shielding.

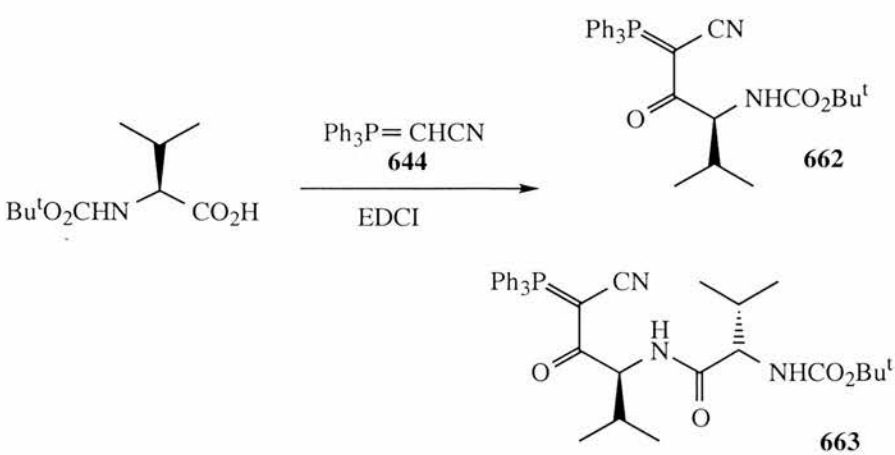
The acyl cyanophosphoranes were formed by the coupling of the protected amino acids with cyanomethylenetriphenylphosphorane **644** using EDCI and DMAP. As this was a new area amino acids with aliphatic side chains were first tried as these were shown to behave in the right manner with the ethoxycarbonyl ylide series. The protecting group was also varied to give the new products **659-662** in moderate yields as shown.



659-662

	R^1	R^2	amino acid derived from	yield%	δ_P
659	Me	CH_2Ph	alanine	22	20.9
660	$CHMe_2$	CH_2Ph	valine	40	20.9
661	$CHMe_2$	Et	valine	45	20.8
662	$CHMe_2$	Bu^t	valine	41	20.8

In part **D** we showed an interesting result obtained from the coupling of *N*-*t*-butoxycarbonyl valine and the *t*-butoxycarbonylmethylenetriphenylphosphorane **503**; in addition to the expected coupling product a dipeptide coupled product was formed. A similar result was



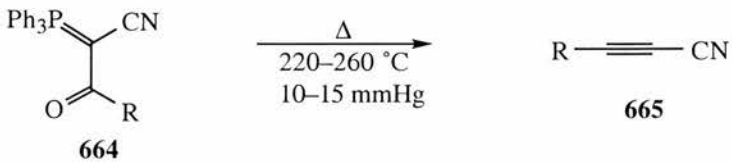
obtained here from *N*-tert-butoxycarbonylvaline and cyanomethylenetriphenylphosphorane **644** and the second product isolated after column chromatography was also identified to be the dipeptide derivative **663**.

Two sets of valine peaks were present in both ^{13}C and ^{1}H NMR spectra and the molecular ion of 600 matches the molecular weight for this product. As in the related case the Boc group has been partly lost during the coupling allowing the resulting free amino group to

be acylated. For all the acyl cyanophosphoranes **659-662** the ^{13}C chemical shift values and the magnitude of the observed P-C coupling constants are in agreement with the expected values. Doubling of signals arising from phosphorus coupling is seen throughout the P-phenyl groups. Likewise, the ^{31}P NMR spectra form a consistent pattern.

3. Pyrolysis of the α-cyano β-oxo ylides derived from amino acids

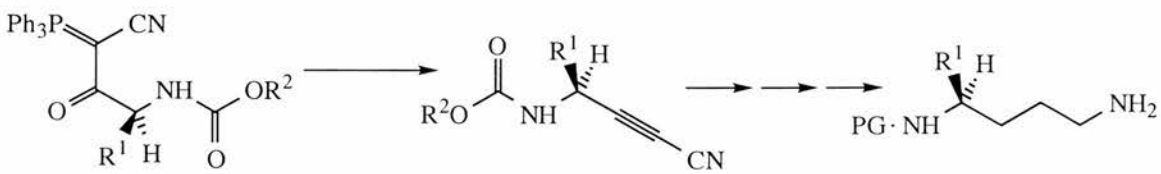
The only example of pyrolysis of an α-cyano β-oxo ylide reported was by Huang and co-workers.[192] The acyl cyano ylides **664** were prepared and heated at 220–260 °C and at a pressure of 10–15 Torr to form the perfluoro-2-alkynenitriles **665**. The acyl group used was only of the perfluoro type and no simple acyl derivatives have been reported.



664 **665**

R = CF_3, C_2F_5, C_3F_7

Following the pyrolysis results of the β-aminoacyl ylides discussed in part **B** and the cyano example given above we investigated here the behaviour of various cyano ylides **645** under pyrolysis conditions expecting to obtain the corresponding cyano acetylenes **646**. The desired products, if prepared would be expected to undergo further transformations to the target diamine **643**.

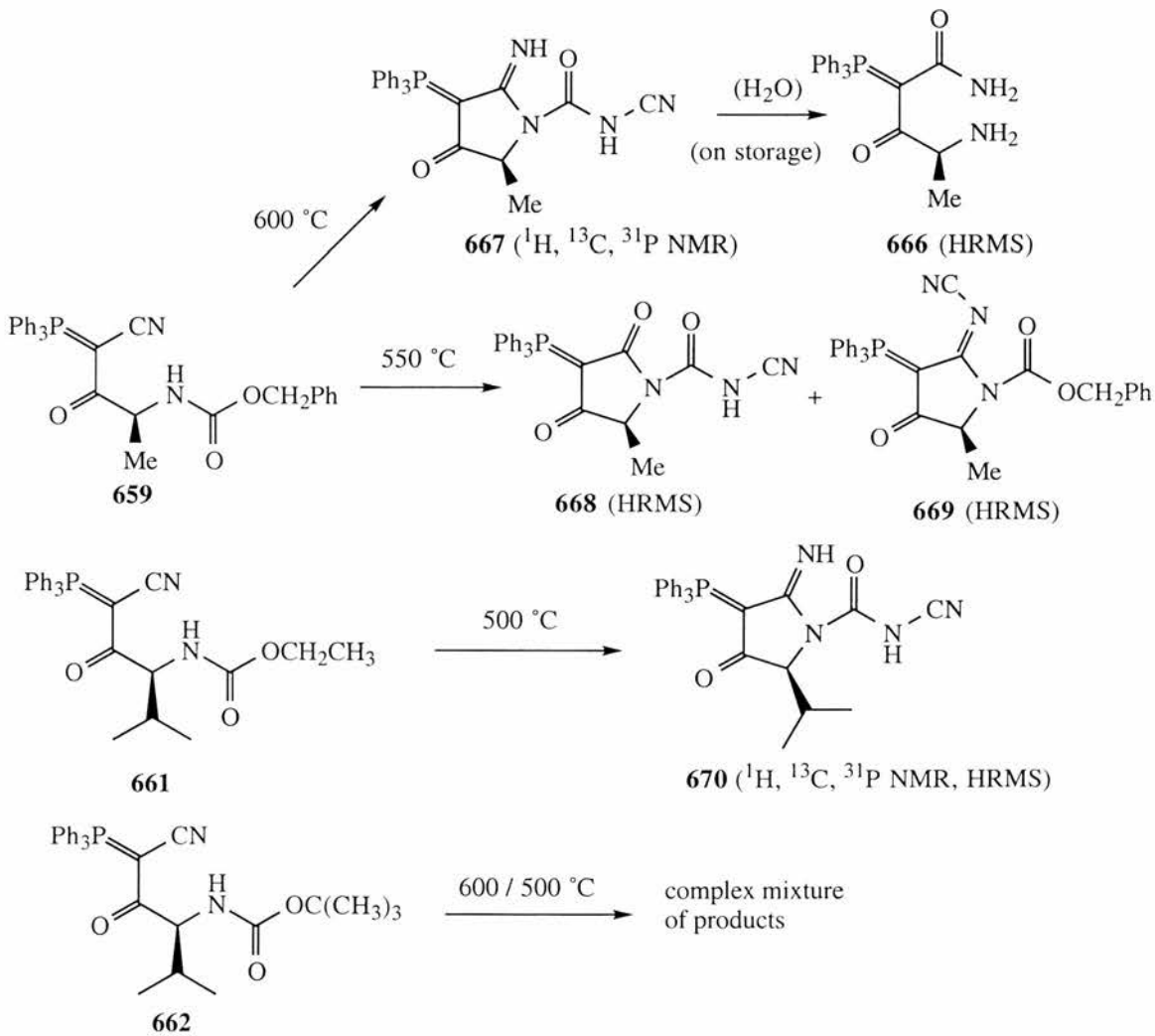


645 **646** **643**

FVP of the derivative **659** at 600, 550 and 500 °C gave mainly Ph_3PO and a small amount of Ph_3P at the furnace exit, benzyl alcohol in the cold trap and interesting products in the inlet tube. The ^1H, ^{13}C and ^{31}P NMR spectra of the black solid in the inlet tube at 600 °C showed no evidence of the benzyl group present and there were a total of 4 ^{13}C NMR signals above 140 ppm: two coupled to P and two not. This information together with the low ^{31}P NMR shift of +10.4 which has previously been typical of five-membered ring cyclic ylides,

leads us to propose the cyclic ylide structure **667** for the product. Additional support for this was obtained by high and low resolution mass spectrometry after storage of the material for a period of months which gave results in agreement with the aminoacyl amide **666** expected from hydrolysis **667**.

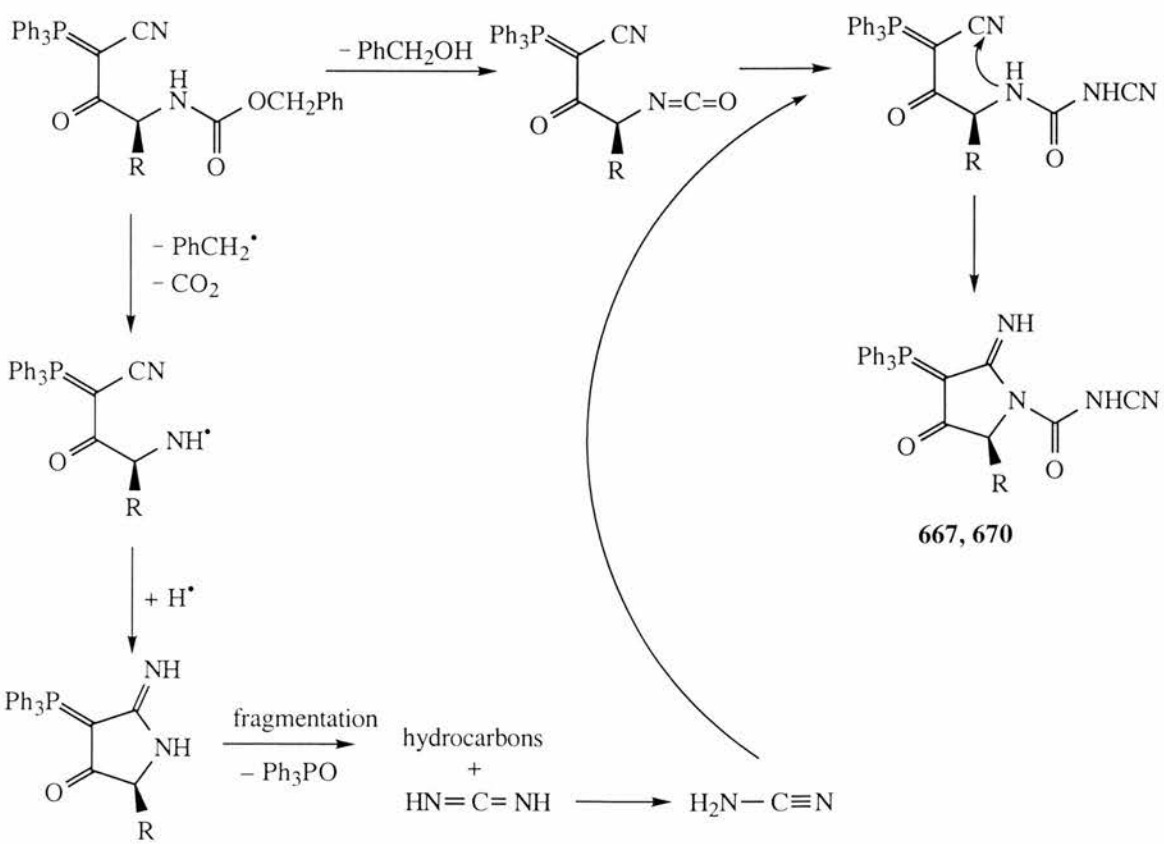
Mass spectrometric analysis of the product left in the inlet tube after pyrolysis at 550 °C gave values consistent with the formulae represented by structures **668** and **669**. The value obtained for the first of these differed from that expected for **668**–H by 6 ppm whereas it was over 80 ppm out from the value expected for **667**. Nonetheless we believe that **667** may be the initial product obtained which undergoes slow hydrolysis to afford **668**. This is supported by the results for the valine-derived cyano ylide **661** where both the NMR data (consistent with **667**) and HRMS results support the formulation of the product obtained at 500 °C as **670**.



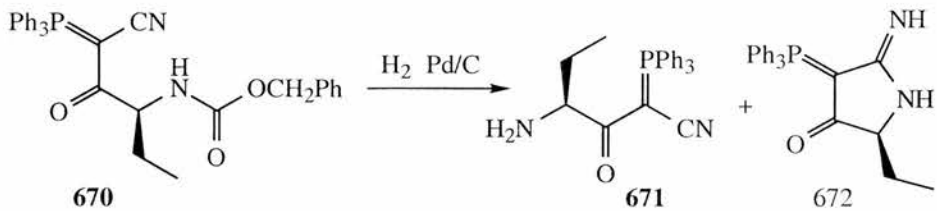
Attempts to obtain any of these compounds in analytically pure form were unsuccessful and it should be stressed that their structures are somewhat tentative at present. In particular a range of other isomeric formulations could be made which would agree with the HRMS results but not so well with the NMR data. In particular the *N*-cyanourea goes some way to explain the presence of two high frequency quaternary ^{13}C NMR signals not coupled to P in the spectra of both **667** and **670** although the chemical shifts involved (δ_H 156 and 148) may be more consistent with an isocyano than a cyano group.

FVP of the Boc-Val derivative **662** at 600 and 500 °C gave similar results: t-butanol in the cold trap and at the furnace exit Ph_3PO, Ph_3P and a product which seems to be heterocyclic by ^{31}P NMR. However in this case the product was a good deal more complex and no useful ^1H or ^{13}C NMR data could be obtained.

A proposed mechanism for the formation of such hetrocyclic ylide products is shown below and the most difficult thing to account for is the apparent production of cyanamide, $H_2N–CN$, in the reaction and its availability to react with the isocyanate function to give the *N*-cyanourea and also with a carbonyl group to give the *N*-cyanoimine present in **669**. Clearly more work is required to fully elucidate the interesting processes which appear to be involved here.

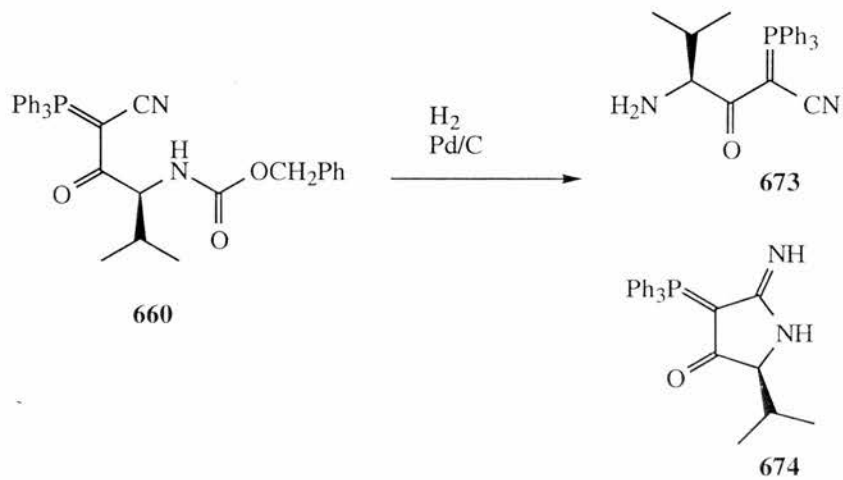


A compound of similar structure was reported recently,[156] to be obtained by removal of the protecting group from cyano ylide **670** by hydrogenolysis over Pd/C. Along with the expected amine **671**, the cyclic amidine **672** was formed in 21% yield by intramolecular aminolysis of the cyano group and this provides a good precedent for the final reaction step shown on the previous page.



670 **671** 672

We tried in the same way to obtain the corresponding amidines by applying hydrogenation to some of our ylides so that we could compare their spectroscopic data to the pyrolysis products obtained. Ylides **659** and **660** were examined and unfortunately in the first case, which was repeated several times, only the starting material was obtained.



660 **673** **674**

In the case of the valine derivative **660** a mixture of three products was obtained. The ^{31}P NMR spectrum showed three peaks and together with the ^{13}C data showed that the mixture consisted of starting material **660**, deprotected product **673** and another product that appeared to be a cyclic product **674**. Attempts to purify the products using preparative TLC were unsuccessful as the only product isolated from the plate was the starting material. The remaining products were not isolated and are believed to have decomposed or stuck to the silica plate.

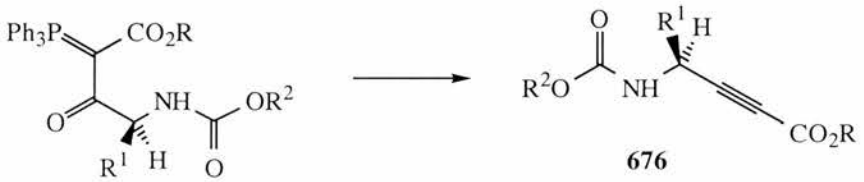
4. Summary

While these results are interesting they do not provide the desired products for our target intermediates. We recommend to concentrate on the ethoxycarbonyl ylide route with various protecting groups (see Part **D**) which we believe will be the best route to provide the diamine for the collaborating company in future.

F Preparation and Pyrolysis of Vinylogous Aminoacyl Ylides

1. Introduction

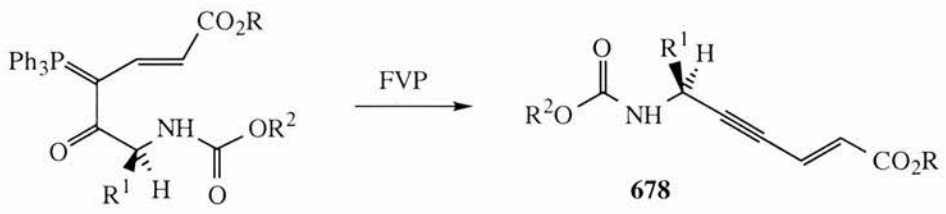
In the discussion parts **B** and **D** we studied the preparation and pyrolysis of aminoacyl ylides **675** and focused on the ester stabilised ylides where R was ethyl, butyl and allyl. We showed that the pyrolysis worked when we used the ethyl and allyl ester and various protected acetylenic amino acid esters **676** were obtained.



R = Et, $CH_2CH{=}CH_2$
R^1 = Me, $CHMe_2$
R^2= CH_2Ph, $CH_2CH{=}CH_2$

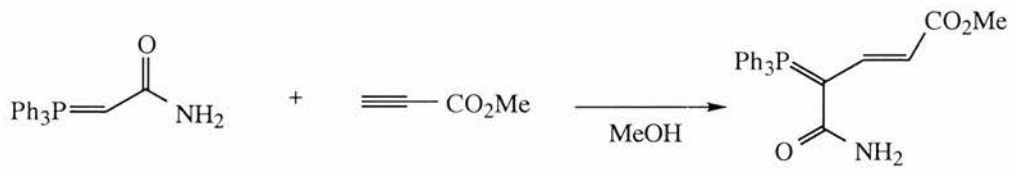
In addition to their potential biological activity, these type of compounds are important as chiral intermediates for synthesis. With this important application in mind we decided to try and extend this method to other homologues which would allow us to insert other functionalities into the chiral products.

We became interested in β,γ-unsaturated ylides **677**. These ylides would enable us to insert an additional double bond into the chiral acetylenic product **678** making these products important chiral intermediates which may have use in various other reactions, for example in the Diels Alder reaction.



677 678

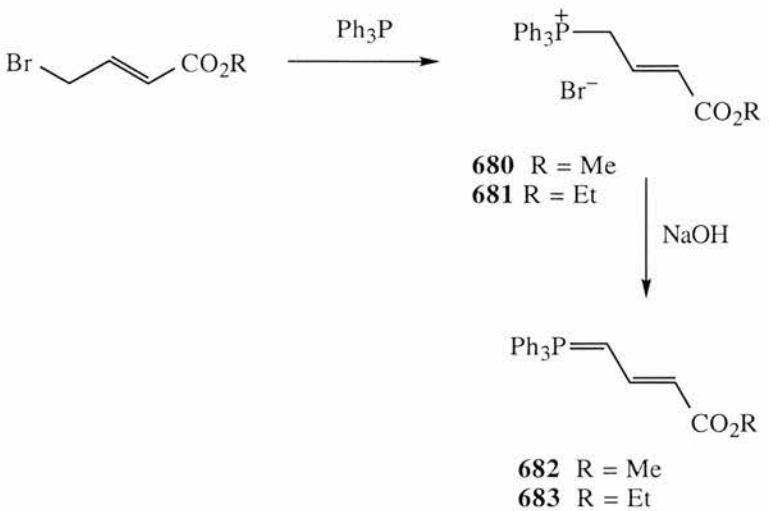
An example of a β,γ-unsaturated ylide was reported by Koomen and Wanner.[115] When triphenylphosphoranylideneacetamide **418** reacts with methyl propiolate the adduct **679** was isolated in 65% yield.



418 679

2. Preparation of aminoacyl ylides from the β,γ-unsaturated ylides

The unsaturated ylides have been reported by Buchta and Andree[157] in 1959 and were obtained using a similar method to that for the preparation of the related ester ylides. The reaction between triphenylphosphine and methyl or ethyl bromocrotonate gave the β,γ-

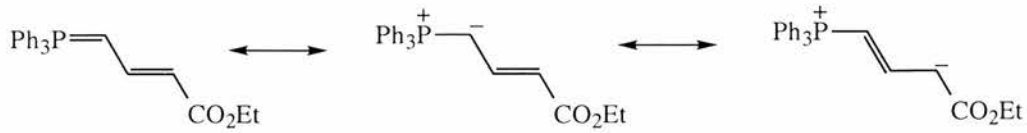


680 R = Me
681 R = Et

682 R = Me
683 R = Et

unsaturated phosphonium salts **680** and **681**. Deprotonation with a sodium hydroxide solution gave the corresponding unsaturated ylides **682** and **683**. The ^1H spectra of both the ylides and their salts show a complex pattern in the double bond region which may be

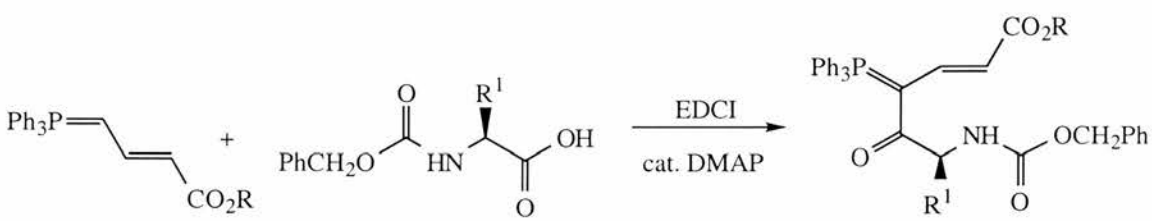
explained by the different resonance forms **684** and **685** which may lead to restricted rotation around various bonds.[158]



683 **684** **685**

We found that these ylides were not very stable and on standing for a short time we could see that they were decomposing to Ph_3PO by ^{31}P NMR. For use in further reactions we prepared the ylide and immediately took it on to the next step which seemed to work more efficiently.

The aminoacyl ylides were prepared from the β,γ-unsaturated ylides and various Cbz protected amino acids in the presence of the coupling reagent EDCI. A series of aminoacyl ylides were made and are shown below.



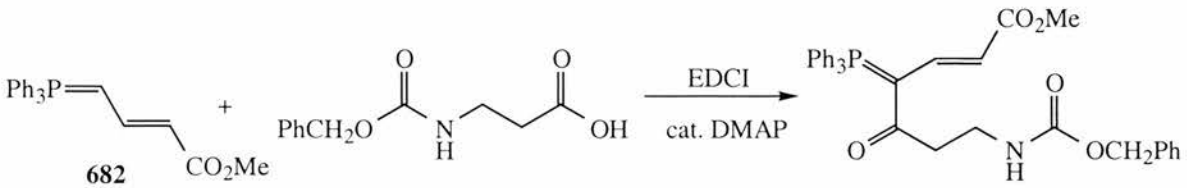
686-690

	R	R^1	amino acid derived from:	Yield %	δ_P
686	Me	Me	alanine	33	21.3
687	Me	Pr^i	valine	36	21.4
688	Et	H	glycine	46	21.6
689	Et	Me	alanine	32	21.5
690	Et	Pr^i	valine	44	21.3

An additional aminoacyl ylide was prepared with the unnatural amino acid β-alanine; the aminoacyl ylide **691** was obtained in 40% yield with δ_P at +21.3.

Table 4: ^{13}C NMR Spectra of *N*-Benzoxycarbonyl ylides **686-691** and Cyclic ylides **693-694**, δ_C (J_{P-C})

				CO_2R			NCO_2CH_2Ph			P–Phenyl				
	CHN	P=C	COCN	CO_2	R	C=C	NCO_2	CH_2	Ph	C–1	C–2	C–3	C–4	R signals
686	53.0	75.6 (101)	193.9	169.3	50.2	100.3 (16), 155.5 (7)	155.5	65.9	137.2, 128.3 (3C), 127.7	123.1 (90)	133.5 (10)	129.6 (12)	133.6 (2)	20.9
687	60.9	74.6 (101)	193.4	169.3	49.9	101.2 (16), 155.5	156.6	65.8	137.0, 128.3 (3C), 127.9	123.0 (89)	133.3 (10)	129.4 (12)	133.4	32.0, 20.4, 16.0
691	37.0	73.3 (100)	194.6	169.4	49.2	102.4 (14), 153.9 (10)	155.9	65.2	136.5, 127.7 (3C), 127.6	122.5 (89)	132.7 (10)	128.8 (12)	132.9	40.3
688	49.6	74.4 (101)	188.6	168.4	58.0, 14.1	100.5 (16), 154.4 (10)	155.8	65.5	136.7, 127.9, 127.8, 127.2	122.5 (90)	133.0 (10)	129.1 (12)	133.3 (3)	
689	52.7	75.0 (99)	193.6	168.4	58.3, 14.2	100.0 (16), 155.3 (10)	155.1	65.5	136.9, 127.3 (3C), 128.0	122.7 (90)	133.2 (10)	129.3 (12)	133.4 (2)	20.7
690	60.7	74.2 (100)	193.3	168.8	58.3, 14.2	101.0 (16), 155.4 (10)	156.5	65.7	137.0,128.0, 127.5, 127.4	123.0 (90)	133.2 (10)	129.3 (12)	133.4	31.8, 20.2, 15.9
694	52.7	79.9 (102)	190.0	170.7		101.4 (18), 147.9	151.8	67.1	136.3, 128.4 (C), 127.8	121.9 (91)	133.5 (10)	129.8 (12)	134.1 (2)	
693	58.8	80.4 (102)	193.3	170.4		99.6 (18), 147.8 (7)	151.9	67.0	136.3, 127.5 (3C), 128.4	121.8 (91)	133.5 (10)	129.8 (12)	134.1 (2)	17.5
695	66.9	79.2 (101)	192.4	171.0		101.4 (18), 147.8 (br)	152.1	66.9	136.3, 128.3, 127.5, 127.6	121.9 (91)	133.4 (10)	129.7 (12)	133.9 (2)	30.0, 18.3, 16.6

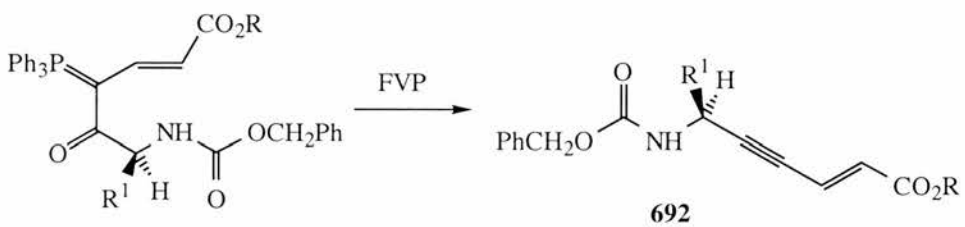


691

The products **686-691** were generally obtained after column chromatography as oils and only **686** was a solid. The structure of these compounds is clear from the highly consistent and informative patterns in the ^{13}C NMR spectra shown in Table 4.

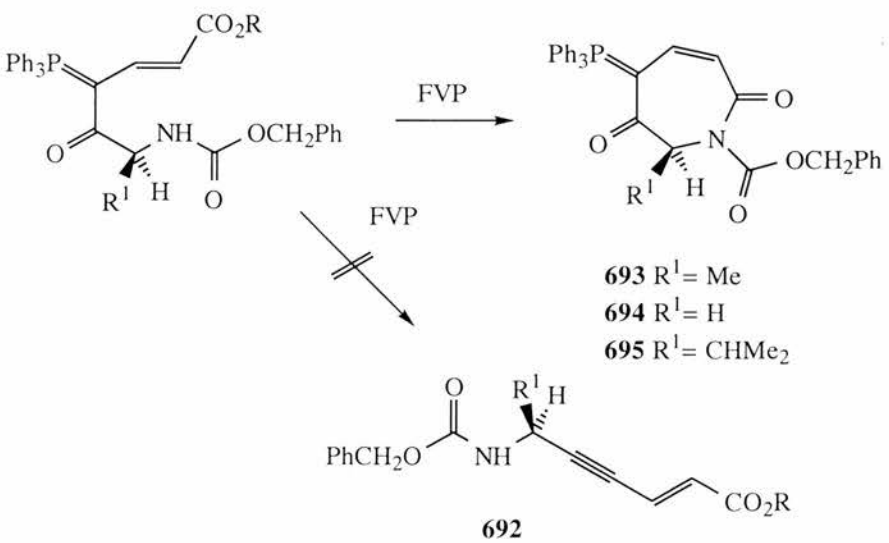
3. Pyrolysis of the aminoacyl β,γ-unsaturated ylides

Pyrolysis of the analogous ester stabilised ylides gave a series of chiral acetylenic amino acid esters and based on these results we expected to obtain the corresponding enyne derivatives **692**.



686-690 **692**

The pyrolysis of three of the aminoacyl β,γ-unsaturated ylides **686**, **688** and **690** was performed at 600 °C and 7–8 x 10^{-3} Torr and we obtained interesting and unexpected results.



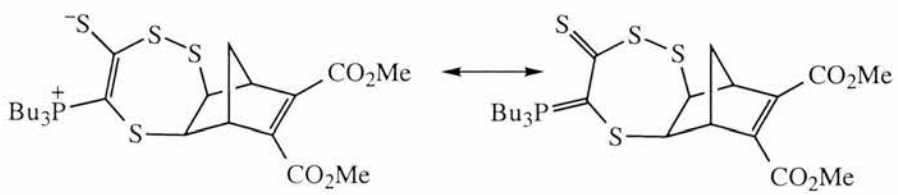
693 R^1= Me
694 R^1= H
695 R^1= $CHMe_2$

692

The unsaturated compounds did not come over into the pyrolysis trap where small amounts of triphenylphosphine and triphenylphosphine oxide were found. The ^{1}H and ^{13}C NMR spectra showed a small amount of product at the furnace exit but most of the material was still left in the inlet tube. On analysis by ^{1}H and ^{13}C NMR there was no sign of the methoxy and ethoxy groups present and it appeared that compounds **686**, **688** and **690** cyclised in the inlet tube with loss of ROH forming the 7-membered rings **693**, **694** and **695**.

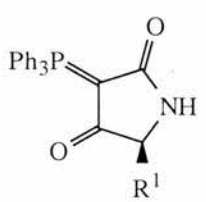
The unexpected formation of the 7-membered ring is significant because cyclic ylides containing seven membered rings are not widely known in the literature (see Introduction section 6 and 7). The ability to synthesise these ylides is a challenge as they are generally difficult to obtain by the normal methods used to make four, five and six membered rings.

The only other seven-membered ring ylide involving heteroatoms known was synthesised very recently in this laboratory and contains three sulfur atoms **463** and more about this compound is given in the Introduction part 7.[117]



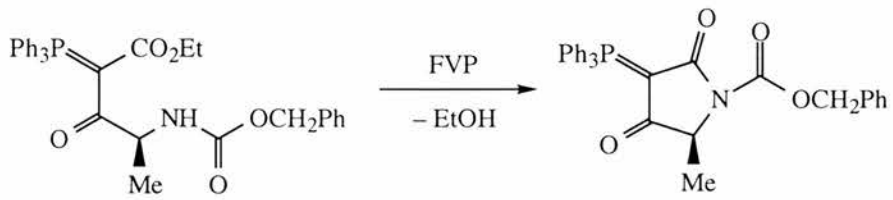
463

Similar cyclisation was encountered in the discussion part **D** with the simpler ester ylide. The five membered ring systems containing the tetramic acid unit were unexpectedly obtained.



R^1 = Me, $CHMe_2$

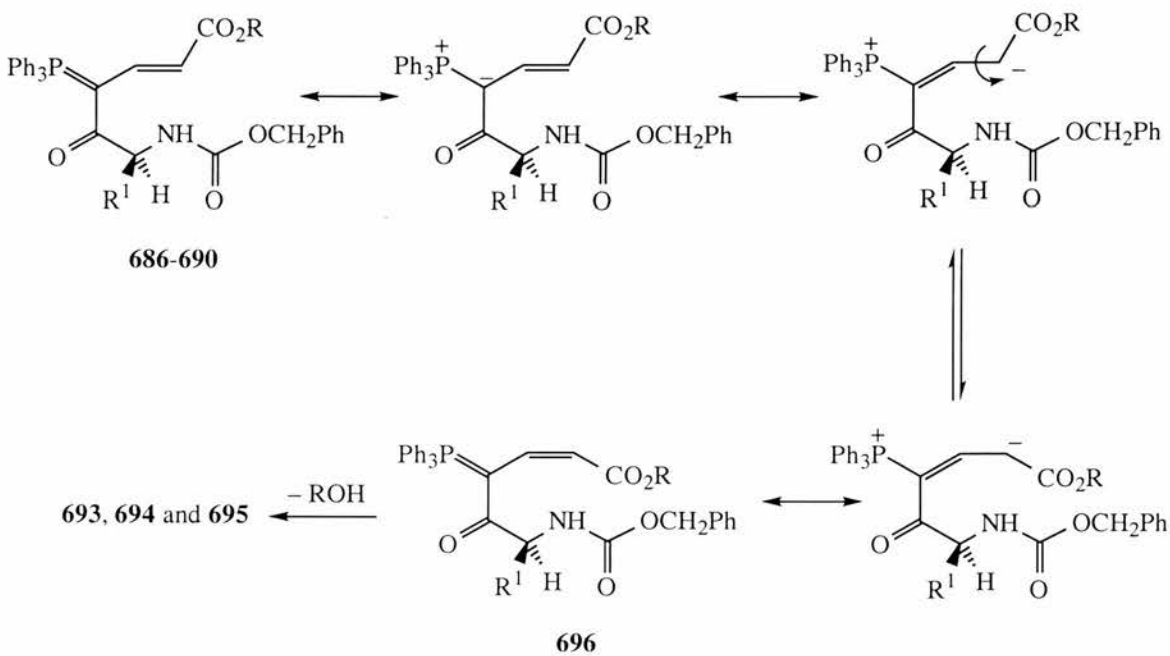
We have also shown one previous case where during the pyrolysis the pressure was increased and led to the formation of the five membered ring **574** but this time the benzoxycarbonyl group was still present on the nitrogen as in the seven membered case mentioned above.



551 **574**

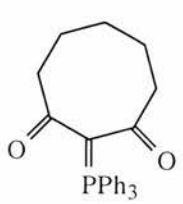
More about cyclisation and formation of five membered rings will be discussed in the next section.

The formation of these novel azepinedione structures is of great interest and it is surprising that the cyclisation takes place here with the electron-withdrawing benzoxycarbonyl group still in place to give the less favourable seven membered ring. For the cyclisation to occur it requires an E to Z isomerisation of the double bond but this is readily achieved by means of the resonance forms shown to give **696** which can then cyclise.



686-690 **696**

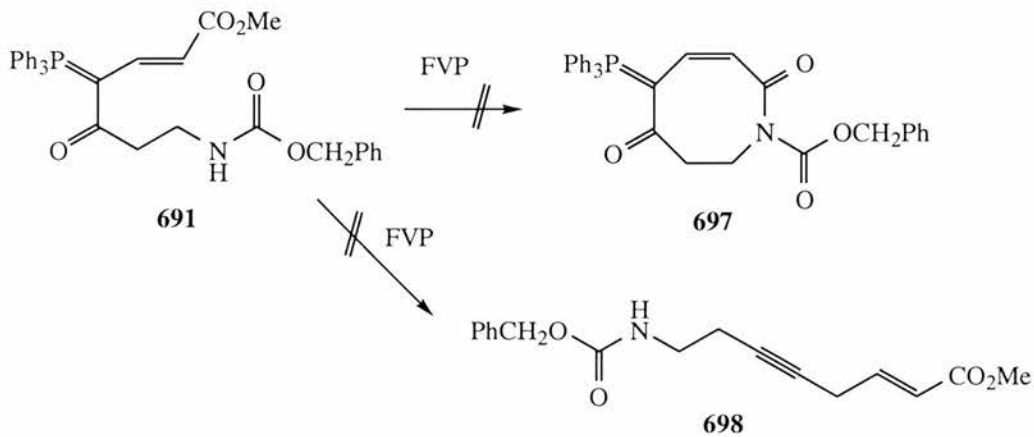
The only eight membered ring ylide described in the literature is the dioxo compound **467**[118] and no eight membered ring ylides containing heteroatoms are known.



467

The ability to synthesise an eight membered ring containing a heteroatom would be a greater challenge and we were hoping to accomplish this.

Using the same method as above we prepared the aminoacyl β,γ-unsaturated ylide **691** derived from β-alanine. We hoped that the new derivative would act in the same way as its analogues and instead of the seven membered ring systems an eight membered ring **697** would be formed.



Pyrolysis of the β-alanine derivative resulted in formation of Ph_3P and Ph_3PO at the furnace exit but unfortunately this time there was no sign of a cyclic product. The expected enyene product **698** was also not present and the crude material obtained contained a small amount of some product which was difficult to identify.

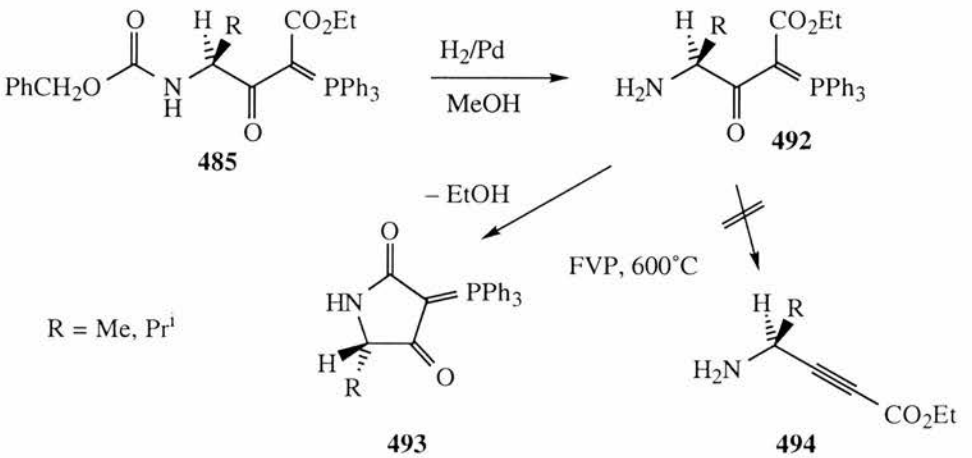
4. Summary

Although the proposed enyne compounds were not formed we have succeeded in preparing the 7-membered ring ylide systems containg a heteroatom, the azepinediones. These are the first 7-membered ring ylides containing a nitrogen atom known and are interesting in containing a vinylogous tetramic acid structure. The reactivity of these novel ylides is of great interest and will be the subject of future study.

G Preparation and Cyclisation of *N*-Deprotected Aminoacyl Ylides

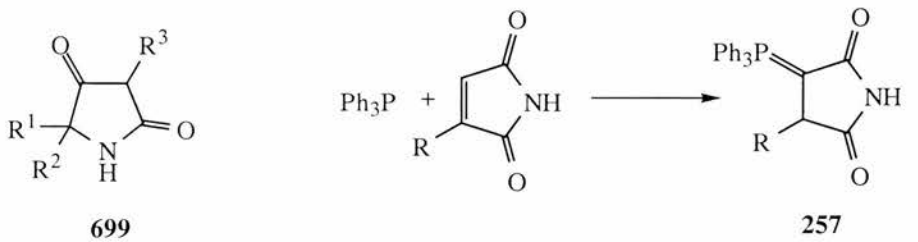
1. Introduction

In the programme of research we mentioned that in previous work it was thought that the *N*-protecting group on the amino acid was only needed for the formation of the amino acid-ylides **485** and not for the later pyrolysis stage. The deprotection prior to the pyrolysis was supposed to provide direct access to the unprotected acetylenic amino acid ester products **494**. Surprisingly, deprotection to the free amino ylides **492** followed by pyrolysis gave the novel cyclic ylides **493** by loss of ethanol instead of the expected products **494**.[138]

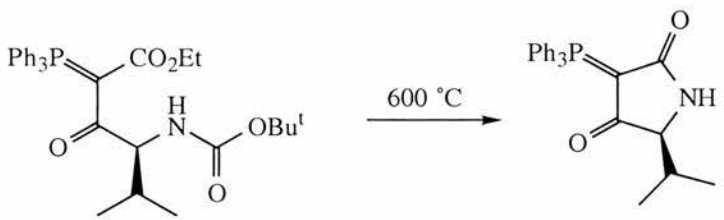


These cyclic ylides possess the tetramic acid ring system **699** which is a component of many natural products which exhibit biological activity.[139] These molecules exhibit mainly antibiotic or antiviral activity and the synthesis of compounds of this type is a challenge.

The isomeric products **257** are already known from 1968 and were formed by the reaction of triphenylphosphine and maleimides.[82]



We have already seen compounds from this family in the discussion part **D** when the pyrolysis was done on the tert-butoxycarbonyl protected amino acid ylide. A product was found in the inlet tube of the system and was identified as the cyclic ylide **626**.

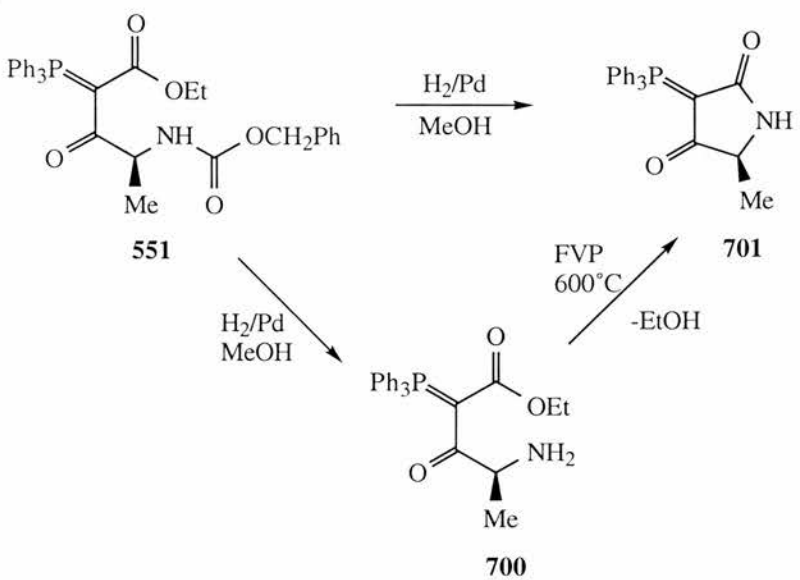


560 **626**

Based on the route mentioned above we were interested in investigating and preparing other related systems and to see if we could extend this method to make the six-membered analogue.

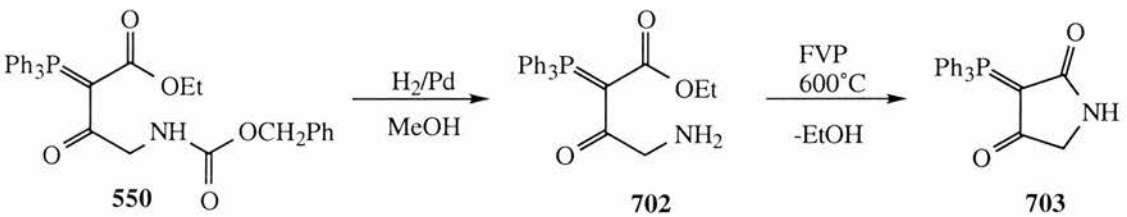
2. *N*-Deprotection and cyclisation

In previous work deprotection of the *N*-protected ylide **551** under catalytic hydrogenation conditions gave the free amino acid ylide **700**. We repeated this reaction and were surprised to find that the cyclic ylide **701** was formed directly after hydrogenation which had shortened the route mentioned above. The only difference was at the work up stage. After hydrogenation the catalyst is filtered off and the filtrate is concentrated. In our case while evaporating the solvent the water bath was heated and the solution was left to evaporate for a period of time.



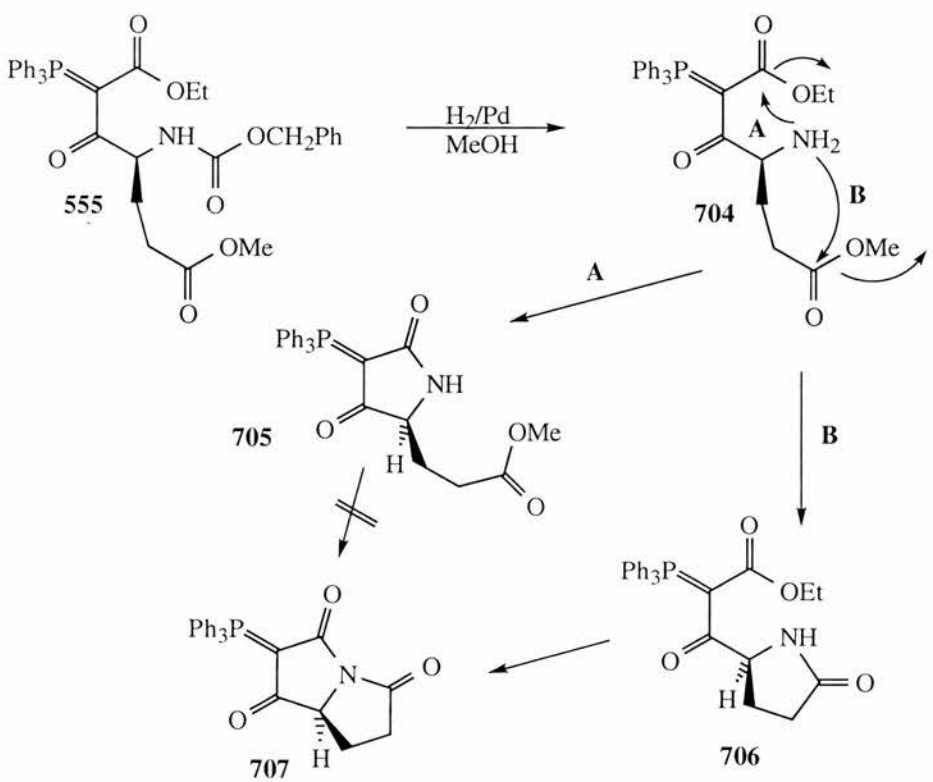
When repeating this work on a larger scale to prepare more of the cyclic ylide for further work we obtained a 2:1 mixture of the cyclic ylide **700** and the deprotected aminoacyl ylide **700**. Following the previous work, pyrolysis at 600 °C resulted in complete conversion of the mixture into **701**.

Deprotection of the glycine derivative **550** following our procedure gave mainly the deprotected derivative **702** and less than 20% of the cyclic ylide **703**. Here also on pyrolysis of this mixture we obtained full conversion to the cyclic ylide **703** but also found in the ^{31}P NMR spectrum small amounts of Ph_3PO and Ph_3P which we found unusual.



550 **702** **703**

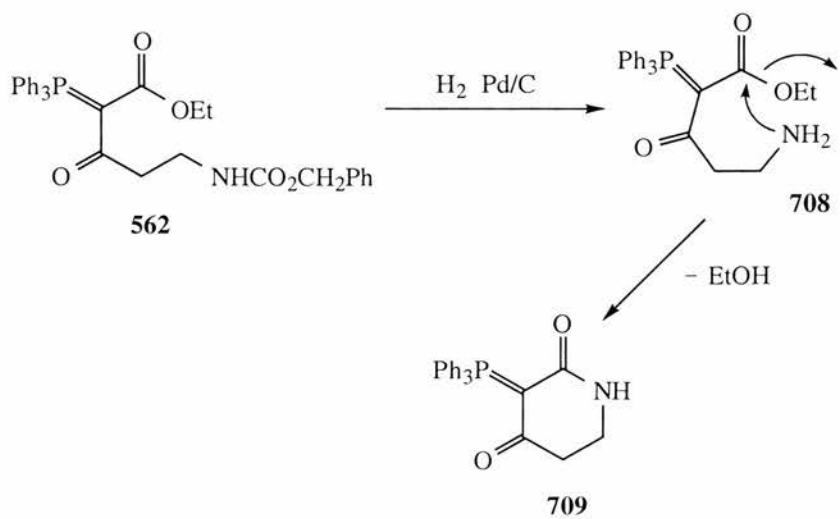
Based on these results we were interested to find out what happens in a compound where there are two possibilities for ring closure to occur. We decided that the methyl glutamate ylide **555** was a good example. This ylide contains two different ester groups and



555 **704** **705** **706** **707**

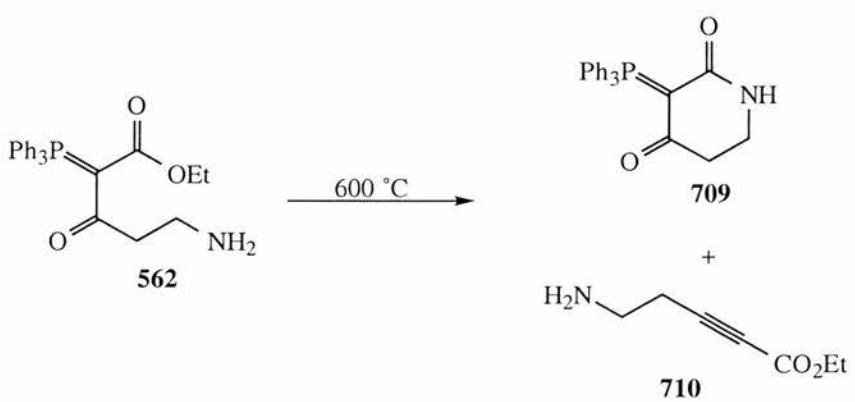
after deprotection forming **704** there would be two possibilities for ring closure following path **A** and or **B**. Both possible rings are five-membered and we could see if the formation of one of them is favoured. After the hydrogenation we obtained a mixture of products, Ph_3PO, unreacted starting material and two products with ^{31}P NMR shifts at δ_P +10.8 and 17.8. The products were characterised by ^{1}H and ^{13}C NMR to be the tetramic acid ylide with an ester side chain **705** as the major product and the ylide with a pyrrolidinone substituent **706** as the minor product. When repeating characterisation of **706** after storage for a few weeks the ^{13}C and ^{31}P NMR spectra showed smaller peaks for the product and the appearance of new peaks which were consistent with the bicyclic product **707**. With this sample we tried to drive the second cyclisation to completion by heating for various times but the ratio of the two products remained the same. We also looked into the possibility of the other cyclic product **705** undergoing a second cyclisation to give the same bicyclic product **707**. Here too we heated the sample but no bicyclic product was found. The tetramic acid product **705** which is the major product is stable while the cyclic compound with a pyrrolidinone substituent **706** is less stable which leads to the more stable bicyclic product **707**.

Because this was a short and direct route to five membered cyclic ylides we were interested in extending this reaction to prepare the six membered analogue. We have shown in the introduction that there are few six-membered cyclic ylides containing nitrogen known in the literature. To proceed with this idea we would need to start from the β-alanine ylide derivative **562** whose preparation was described in part B.



Hydrogenation of the β-alanine derived ylide **562** gave two products, the deprotected derivative **708** and another product in a 1:1 ratio and their ^{31}P and ^{13}C NMR shifts were very similar. For both products there was no sign of the benzoxycarbonyl group present by NMR and the shifts were similar in the carbonyl, aromatic, ylide and methyl region. Four methylene groups of the β-alanine were present in total but only one of them was coupled to the phosphorus which belongs to the deprotected derivative and although there are two methyl groups only one seemed to be part of an ethyl ester group. An additional methylene peak is present but at a much higher shift of δ_C 74.0 than expected which may go with the additional methyl group. We could not identify the second product or distinguish between the shifts for the two products in the ^{31}P, ^{13}C and ^{1}H NMR spectra. All shifts are listed in the experimental section.

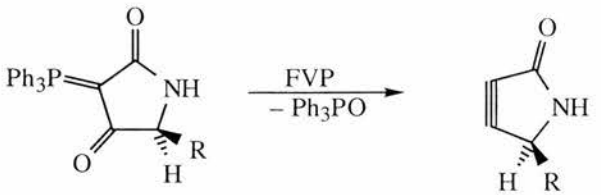
Pyrolysis of the deprotected product **708** at 600 °C gave two products in addition to Ph_3PO. The cyclic six membered ylide **709** with a ^{31}P NMR shift at +14.5 and the deprotected acetylenic product **710** in a 2:1 ratio. This is the first time in the present and previous work where an acetylenic product has been obtained which was the primary aim of deprotecting the ylides. Also, the formation of the six membered cyclic ylide is novel because not many others of this type are known.



3. Pyrolysis of a cyclic ylide

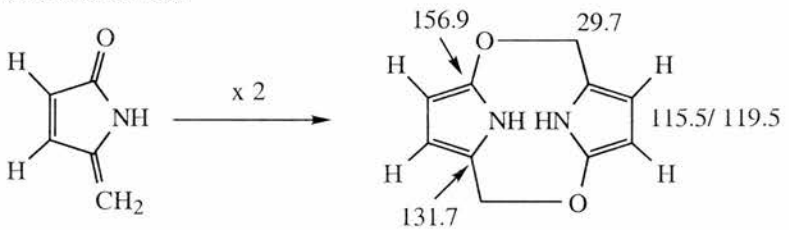
One of the aims of this thesis was to investigate the behaviour of various acyl ylides towards pyrolysis and the cyclic ylides obtained in the previous part were our next option. It seemed possible that Ph_3PO could be eliminated from these cyclic ylides **493** to give

cycloalkynes **495**. Such products might be expected to be highly reactive but might find application for example in the Diels Alder reaction .



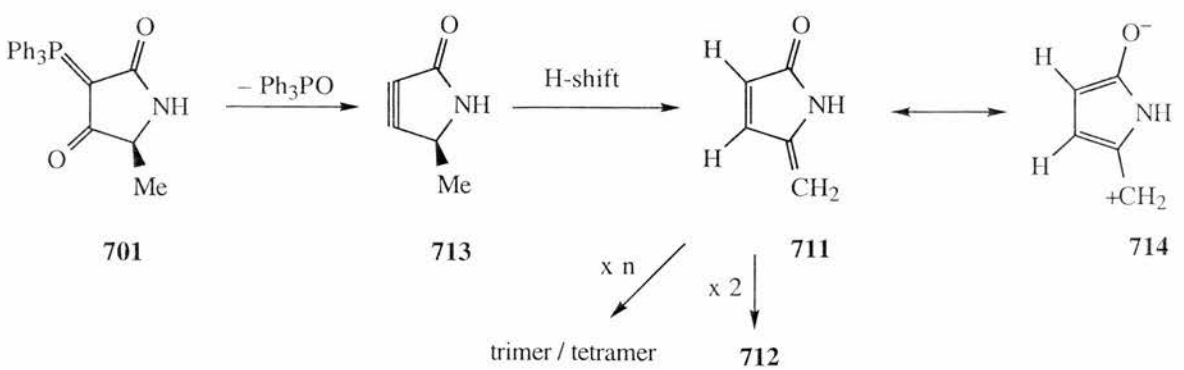
493 **495**

Pyrolysis of the cyclic ylide **701** derived from alanine at 650, 700 and 750 °C gave unreacted starting material at the furnace exit in all cases. At 850 °C we observed mainly Ph_3PO and still some unreacted starting material. The pyrolysis at 800 °C gave interesting results; in addition to unreacted starting material and Ph_3PO we found five additional peaks in the ^{13}C NMR spectrum. The DEPT showed a CH_2 at δ_C 29.7, two CH in the double bond region at δ_C 115.5 and 119.5 and two quaternary carbons at δ_C 131.7 and 156.9. We propose the structure **711** below which can dimerise readily to give **712** which goes some way to explaining the observed shifts.



711 **712**

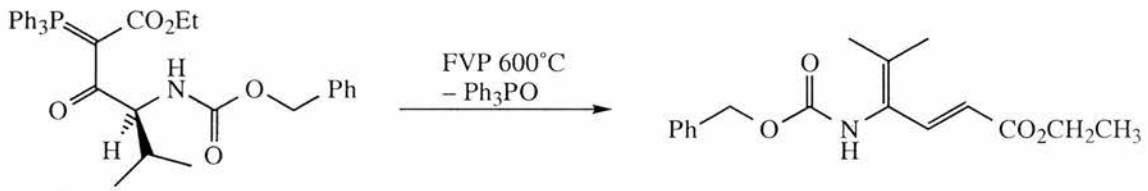
Our proposed mechanism starts with the elimination of Ph_3PO from the cyclic alanine ylide **701** to give the cycloalkyne **713** which undergoes two successive 1,3-hydrogen shifts to form **711**. This might be considered to exist partly in the dipolar form **714** and can add to another equivalent of **711** to form the dimer **712**. Alternatively **711** may form a cyclic trimer or



701 **713** **711** **714** **712**

tetramer which would also fit the observed NMR data but unfortunately due to the relative involatility of the product and its contamination with a much larger amount of Ph_3PO, mass spectroscopy gave no useful information on this.

Ii is worth pointing out that the formation of **711** is exactly analogous to the formation of the diene **577** in the pyrolysis of **552** already described in section **B**.

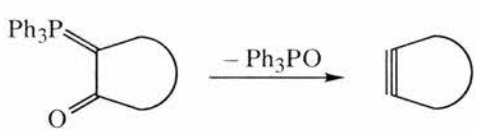


552 **577**

H Pyrolysis of Cyclic Ylides

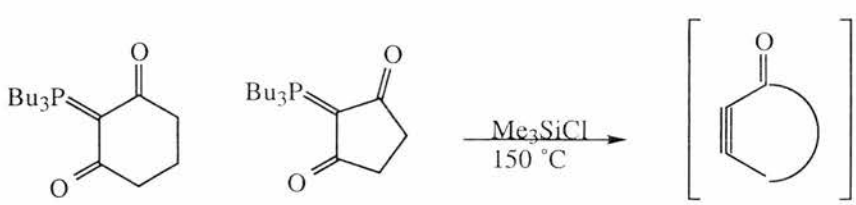
1. Introduction

In the Introduction of this thesis we have seen that there has not been much work done on the pyrolysis of cyclic β-oxo ylides **715**. The elimination of Ph_3PO would be expected to generate cycloalkynes **716** which is an interesting area of study.



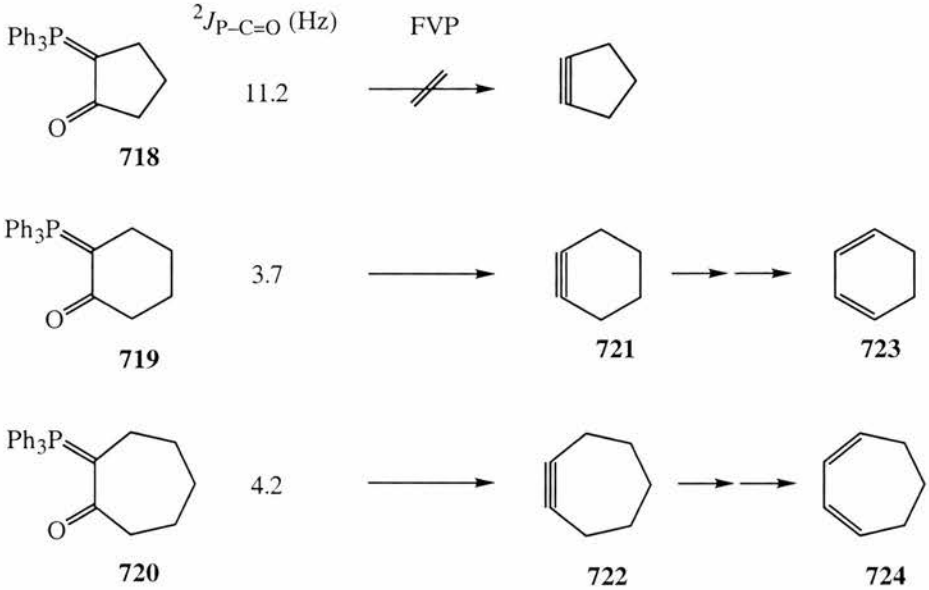
715 **716**

In 1988 Ohmori reported heating five and six membered cyclic tributylphosphonium ylides **144** and **392** with Me_3SiCl at 150 °C in toluene and the cycloalkynones **717** were formed which could be trapped by a Diels Alder reaction but no mechanism of elimination was proposed.[48]

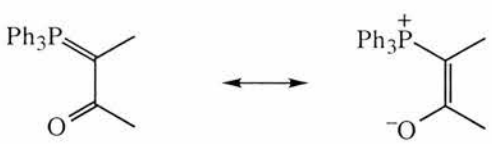


392 **144** **717**

Our group has previously investigated the pyrolysis of five, six and seven membered cyclic β-oxo ylides **718**-**720**.[195] As expected Ph_3PO was eliminated but only from the six and seven membered systems to form the cycloalkynes **721** and **722** which isomerised to the corresponding 1,3-dienes **723** and **724**. However for the five membered cyclic ylide **718** there was no sign of the loss of Ph_3PO even under severe conditions.

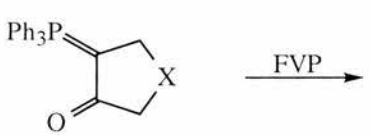


Studies on a wide variety of β-oxo ylides have shown that there is a connection between the value of the coupling constant between P and the carbonyl carbon and their pyrolysis behaviour.[195] Compounds with values smaller than 10 Hz undergo thermal elimination of Ph_3PO while those with larger values do not. This explains the results obtained above and is thought to be due to a high coupling constant indicating a small contribution from the phosphonium enolate tautomer **725** necessary for the elimination to occur.

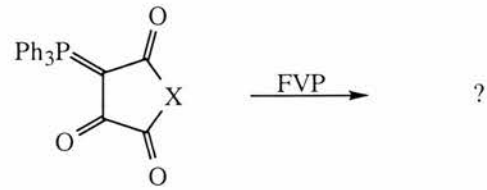


725

With this factor in mind we would expect hererocyclic ylides to undergo thermal elimination of Ph_3PO since the values of $^2J_{P-CO}$ are between 3-8 Hz.



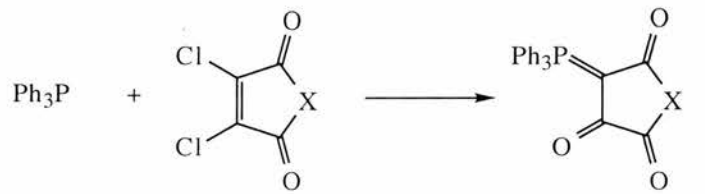
We discussed the pyrolysis of the nitrogen analogue in the previous section which gave interesting but somewhat inconclusive results. In order to try and understand more about this system we decided to study other related heterocyclic ylides, the oxygen and sulfur containing trioxo cyclic ylides **726** and **727** and this section concentrates on these systems.



726 X=O
727 X=S

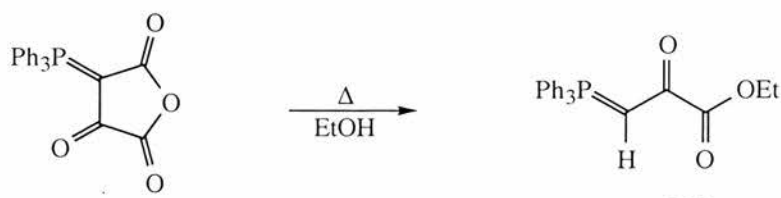
2. Preparation of the starting materials

The sulfur containing trioxo cyclic ylide **727** was sent to us by Professor Skramstad from Norway.[85] Both the oxygen and sulfur derivatives were prepared by the reaction of triphenyl phosphine with dichloromaleic anhydride or dichlorothiomaleic anhydride in the presence of water.[84] The mechanism of formation is shown in the Introduction section 4.f.



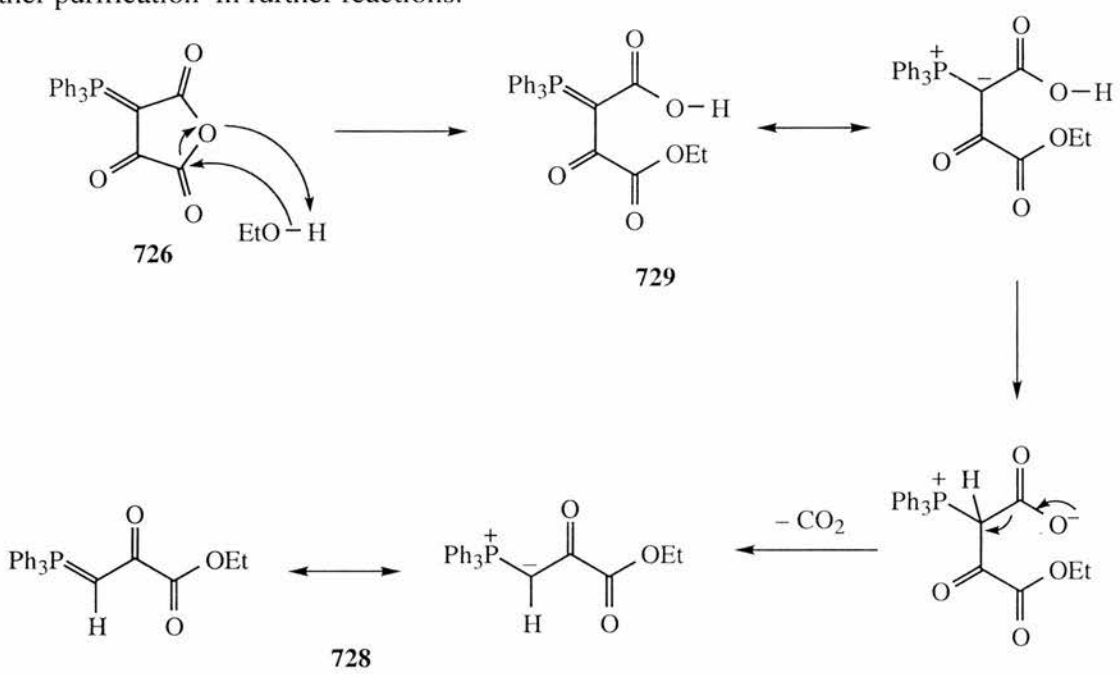
726 X= O
727 X= S

In our first attempt to prepare the oxygen derivative we tried to recrystallise the product from ethanol as described in the literature but no crystals were formed. The solvent was evaporated off and the product left was not the desired product but the dioxo ylide **728**. This product has already been made in our group and its NMR data was identical.[158]



726 **728**

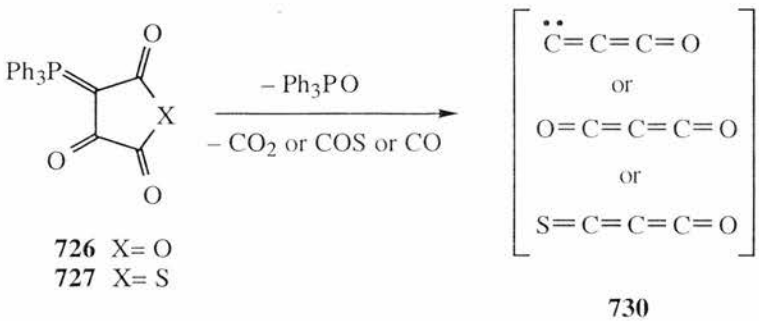
Heating in ethanol causes the ring to open and the half ester **729** is formed. This can undergo a proton shift and after loss of CO_2 the dioxo product **728** is formed. NMR of the crude solid before recrystallisation showed the desired product in 50% yield and this was used without further purification in further reactions.



726 **729** **728**

3. Pyrolysis

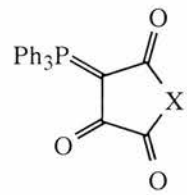
On pyrolysis of these heterocyclic compounds we expected in addition to the loss of Ph_3PO the loss of CO_2 /COS or CO and possibly the formation of one or more of the intermediates **730**. Intermediates of this type are already known in the literature and can be trapped by the addition of methanol.[197] After each pyrolysis we added methanol to the cold trap which was still cooled in liquid nitrogen under a nitrogen atmosphere, excess methanol was evaporated off and the NMR was obtained.



726 X= O
727 X= S

730

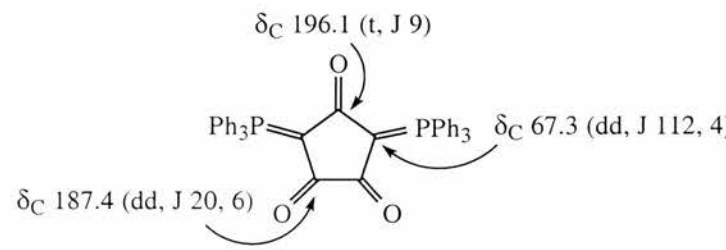
Pyrolysis of these ylides at various temperatures gave mainly Ph_3PO and Ph_3P for the oxygen derivative **726** and for the sulfur derivative **727** we found in addition to Ph_3PO, small amounts of Ph_3PS and some of the triphenylphosphoranylideneketene **731** at the furnace exit, which was very interesting.



726 X = O $Ph_3PO + Ph_3P$

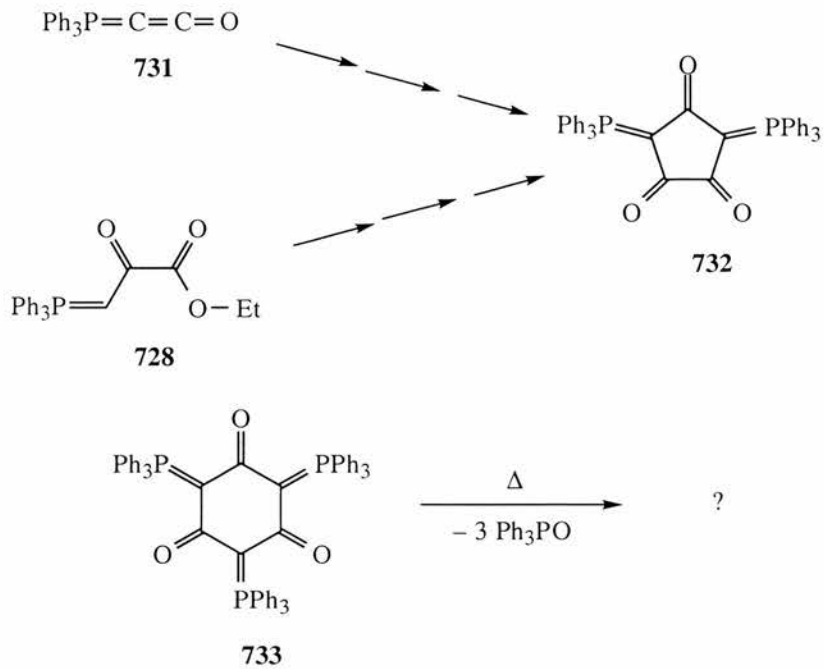
727 X = S $Ph_3PO + Ph_3PS + Ph_3P{=}C{=}C{=}O$ **731**

During the pyrolysis of the oxygen derivative **726** we noticed a pink solid collecting in the inlet tube. Analysis of this solid showed it most unexpectedly to be the five membered trioxo bisylide **732**. Its identity was clear from the highly distinctive ^{13}C NMR shifts shown below. The ylide carbon gives a double doublet, showing coupling to both phosphorus atoms.

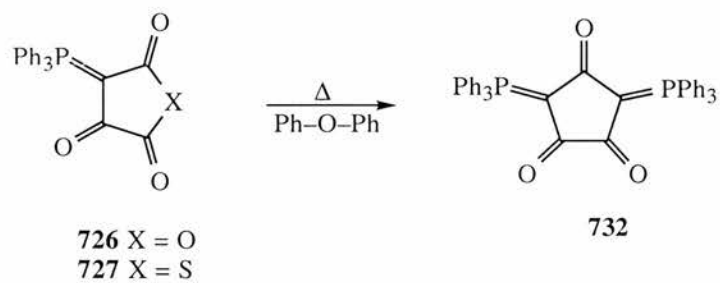


732 δ_P +9.0

The two adjacent carbonyls are also split twice by the two phosphorus atoms to give double doublets. The isolated carbonyl is split to a triplet by the two adjacent phosphorus atoms. This bisylide **732** has already been prepared by two seperate methods by Bestmann and co-workers.[49,198] The first method involved a multistep procedure. While studying the formation of a dimer from triphenylphosphoranylideneketene **731**, they were mainly interested to see whether a cyclic trimer **733** could also be prepared. The trimer system is very interesting because on decomposition three equivalents of Ph_3PO might be released and it could lead to C_6 or a derived oligomer. The second method started from two equivalents of the dioxo ylide **728** in the presence of a strong base and here too the bisylide **732** was formed.



Once it was clear that an intermolecular reaction was involved, we tried solution pyrolysis. The cyclic ylides **726** and **727** were heated in various high boiling point solvents and diphenyl ether with a boiling point of 259 °C proved to give the best results. The bisylide was obtained in both cases in moderate yields. The same product was also obtained when **726** was heated neat at 250 °C and this was identical with an authentic sample provided by Bestmann. The sulfur derivative **727** gave only unreacted starting material when heated at a higher temperature and for a longer period.



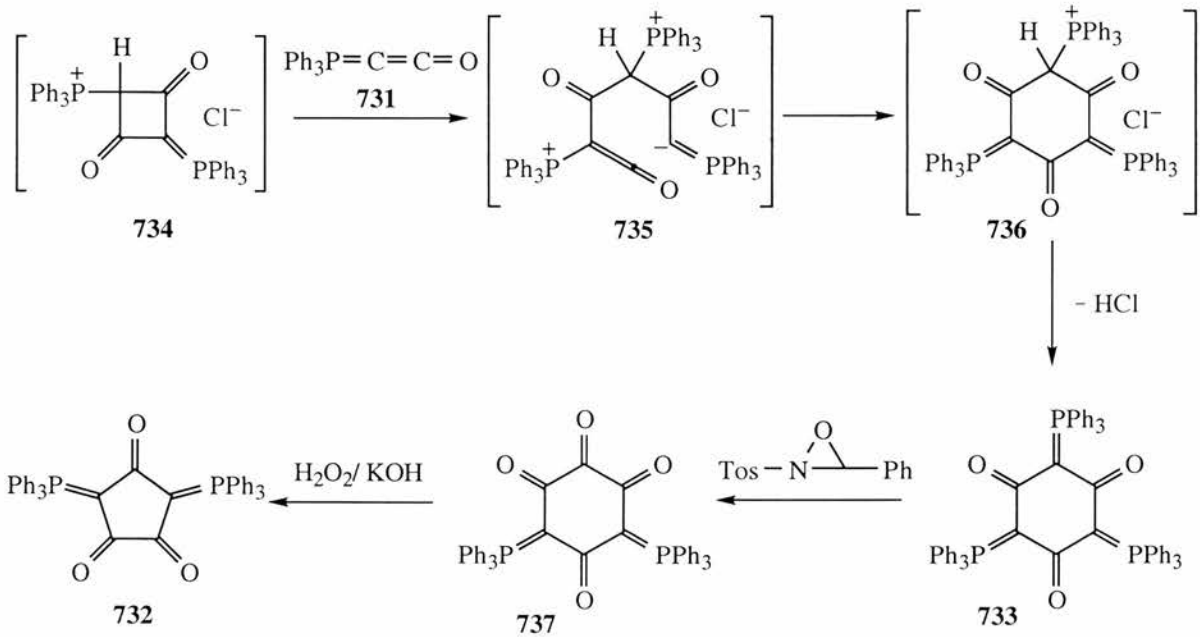
726 X = O
727 X = S

732

4. Mechanisms

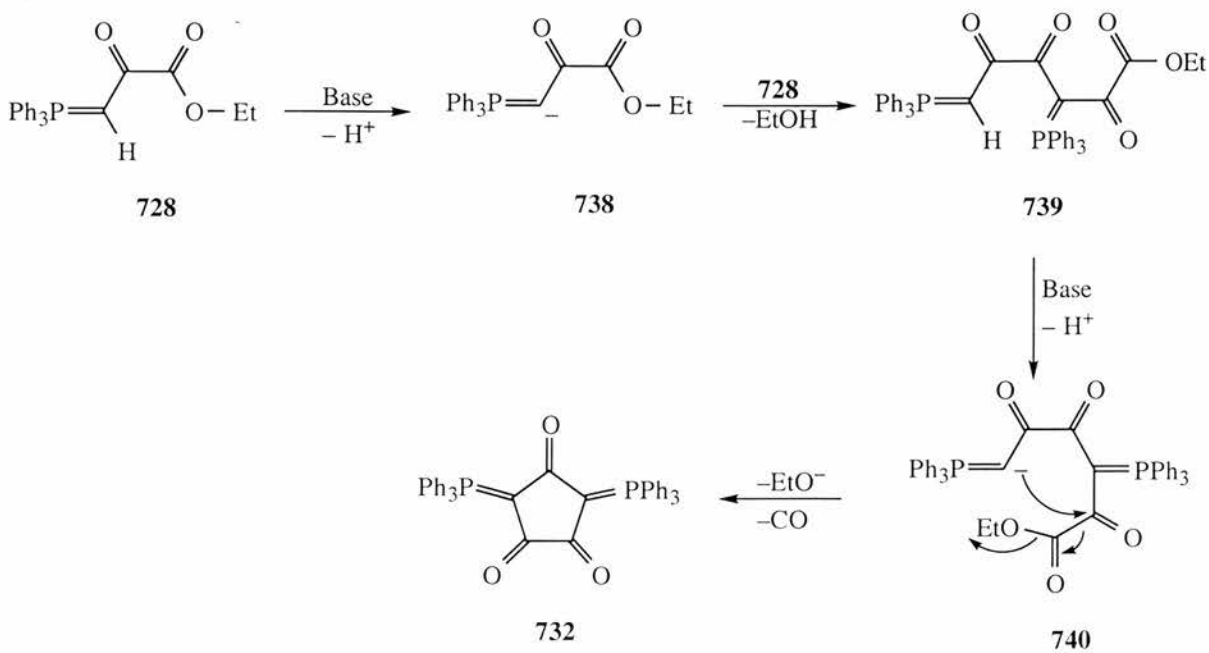
The mechanism for the first method published by Bestmann involves the triphenylphosphoranylideneketene **731**. This ketene is converted to its salt and on cycloaddition to another equivalent of ketene **731**, the salt of the dimer **734** is formed. Addition to another equivalent of ketene gives the intermediate **735** which undergoes a ring

closure to form **736** which then loses HCl to form the stable trimer **733**. Oxidation of the trimer leads to the tetraoxo bisylide system **737** which can undergo ring contraction upon reaction with HOO^- to give the bis ylide **732**.[33, 49]



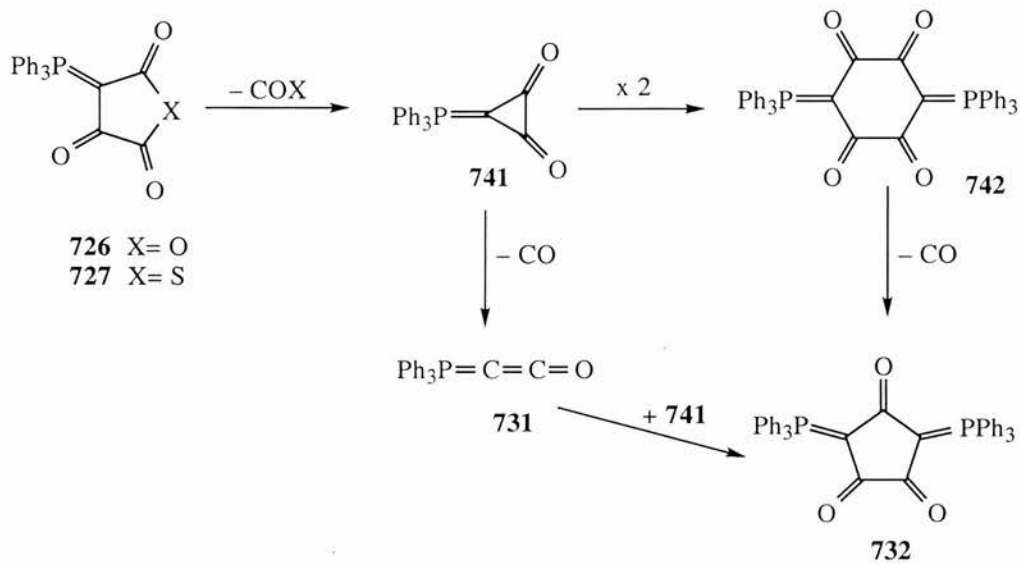
734 735 736 732 737 733

The second method to prepare the bisylide **732** starts from the dioxo ylide **728** and in the presence of a base the proton of the ylide is lost forming **738**. This adds to another equivalent of the dioxo ylide **734** to give **739** by loss of an ethoxy group, again in the presence of a base and with loss of the ylidic proton to get intermediate **740**. This intermediate was then proposed to cyclise with loss of an ethoxy group and CO to form the bisylide **732**.[199]



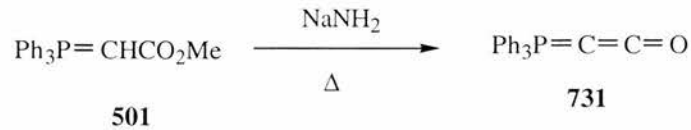
728 738 739 740 732

The mechanism of our process is of great interest and two different possibilities can be identified. First the initial loss of CO_2 or COS from **726** or **727** may form the three membered dioxo ylide intermediate **741**. This can dimerise to give the tetraoxo bisylide **742** which loses CO forming the bisylide **732**. Alternatively, after the initial loss of CO_2 or COS to form the three membered dioxo ylide **741**, this can lose CO to give the known ketene ylide **731**. A reaction between **741** and the ketene **731** would then lead to the bisylide **732**.



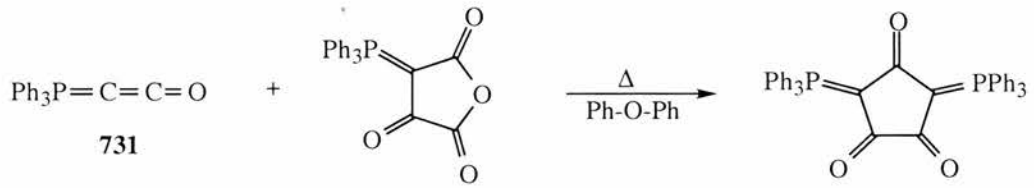
To try and understand more about the mechanism for the formation of the bis ylide **732** and to find out which intermediates are involved, the first question we asked was does the reaction go via the six membered ring or is the ketene involved? To answer this we prepared the ketene **731** and carried out solution pyrolysis of a mixture of the ketene and one of the cyclic trioxo ylides.

The ketene was prepared following a literature procedure starting from the methoxycarbonyl ylide **501** prepared in part A.[199] Boiling the ylide with sodium amide in dry toluene gave the ketene **731** in 30% yield. The ketene shows a ^{31}P NMR shift at δ_P +5.0 and a distinctive ^{13}C NMR shift for the ylide carbon at δ_C –10.4 with a coupling of 187 Hz.

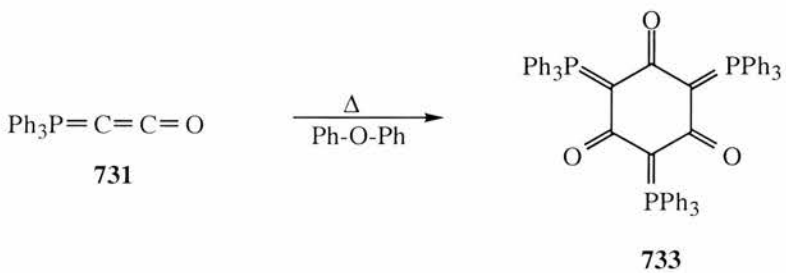


501 **731**

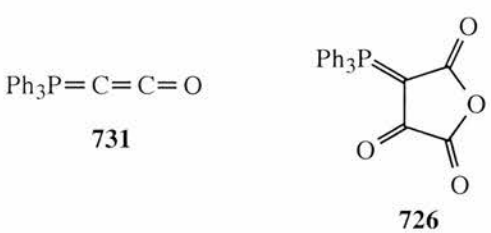
Solution pyrolysis of the ketene **731** with the oxygen trioxo ylide **726** in diphenyl ether gave mainly the bisylide **732** and no new phosphorus-containing product implying that the ketene is used up by reaction with the trioxo ylide.



As a control reaction we heated the ketene itself in diphenyl ether and surprisingly the cyclic trimer **733** was formed. This is the same cyclic trimer prepared as shown before by Bestmann and co-workers but our route is more direct. The cyclic trimer **733** obtained was identical with an authentic sample provided by Bestmann, the ^{31}P NMR shift was at δ_P +13 and in the ^{13}C NMR we could see a broad singlet for the carbonyls. The ylidic carbon gave a double triplet with a large (^1J_P) and a small (^3J_P) coupling constant.

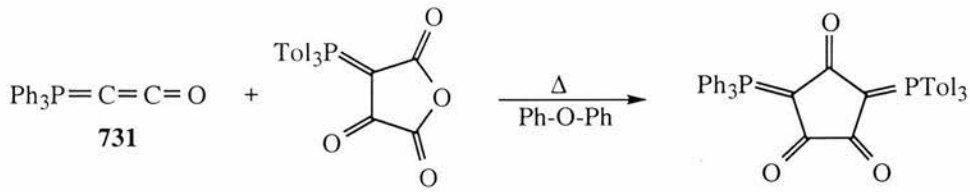


We now have evidence that the bisylide **732** is not formed *via* the six membered ring and the ketene **731** is involved. To prove the involvement of the ketene we must be able to distinguish between the two ylides or the carbonyls in the final product and this can be done by labelling one of the starting materials **731** or **726** which would help us to identify its presence in the product.

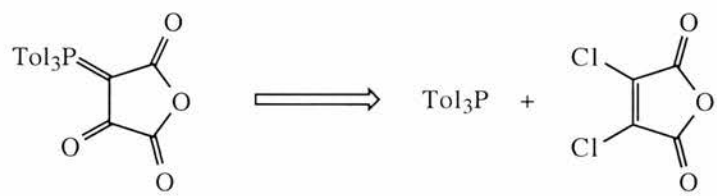


5. Proof of mechanism

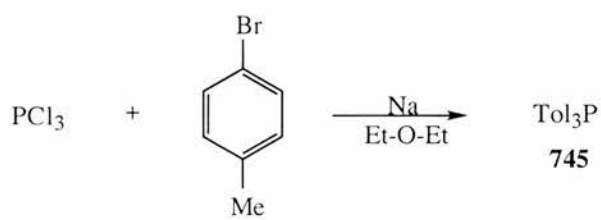
Our first attempt involved the labelling of the cyclic starting material **726**. We thought of making a new cyclic ylide, the tri-*p*-tolylphosphonium ylide **743**. If the solution pyrolysis of this new cyclic ylide and the ketene would give the mixed bis cyclic ylide **744** we will have evidence for the involvement of the ketene **731**.



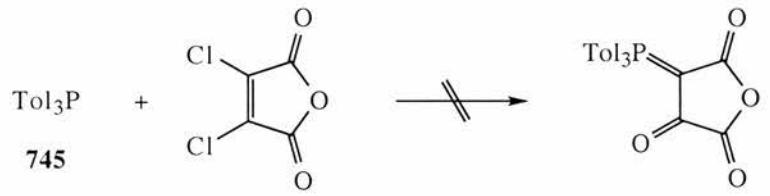
To make the tri-p-tolylphosphonium ylide **743** we needed to prepare the tritolylphosphine and react it with dichloromaleic anhydride in a similar manner to the preparation of **726** and **727**.



The tri-p-tolylphosphine **745** was prepared by a literature procedure from 1901.[200] Sodium metal was added to a mixture of *p*-bromotoluene and phosphorus trichloride in dry ether. The mixture was heated under reflux for 48 hours and after recrystallisation the product was obtained in low yield.



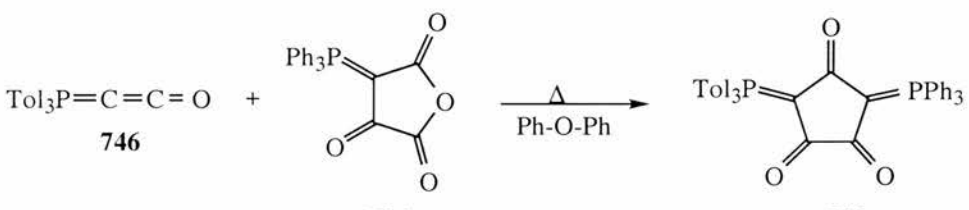
Tri-*p*-tolylphosphine **745** was added to dichloromaleic anhydride in THF and after the workup a brown oil was formed which contained a mixture of products by ^{31}P NMR.



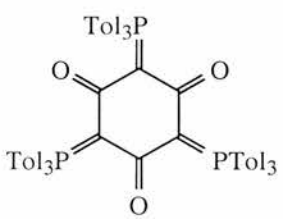
743

As we were having difficulties preparing this ylide we decided to abandon this and moved on to try labelling the other starting material, the ketene **731**.

In the same manner as the first attempt if we can prepare a labelled ketene, a mixed product would support the involvement of the ketene. Here too we used the tri-*p*-tolylphosphine **745** in an attempt to make tri-*p*-tolylphosphoranylideneketene **746**. If this was obtained we could heat this analogue alone to try and form the new six membered trimer with *p*-tolyl groups **747**.

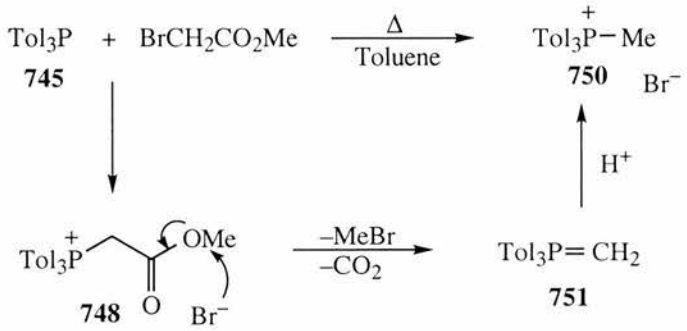


726 744

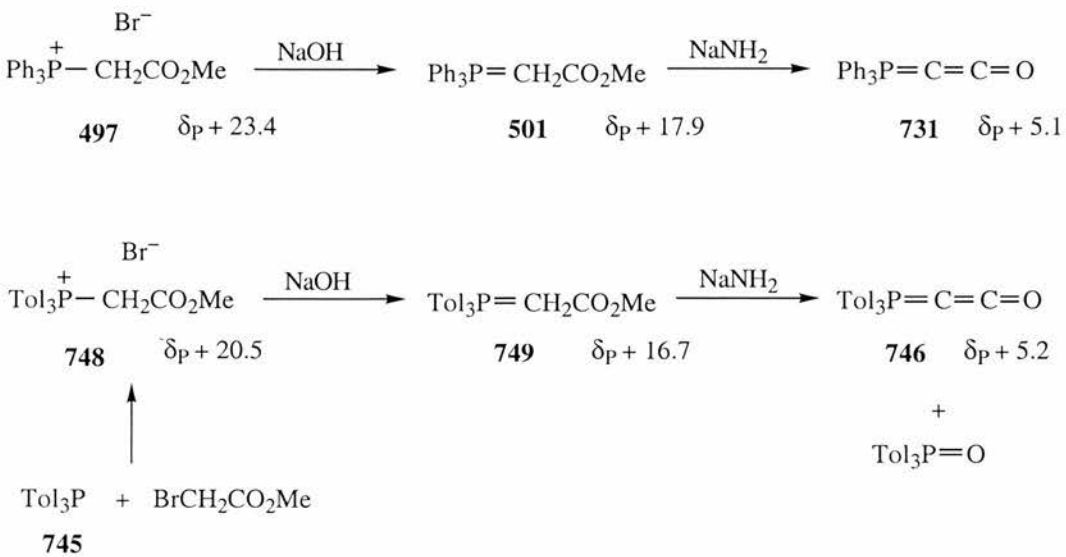


747

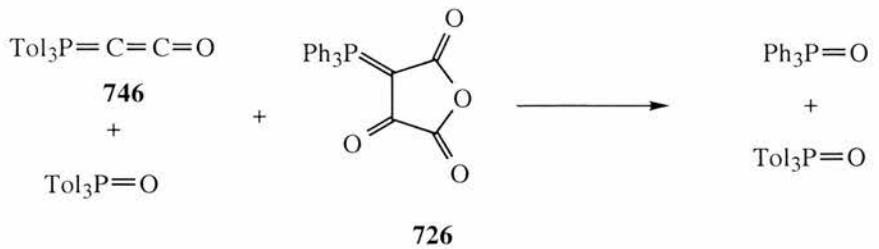
The tri-*p*-tolyl ketene **746** was prepared in a similar manner to its triphenyl analogue starting from the corresponding methoxycarbonyl ylide **749**. In our first attempt to prepare the phosphonium salt **748** the mixture was heated under reflux for 2 hours and a black oil was formed. The ^{1}H and ^{13}C NMR spectra showed the absence of the methoxy group but the presence of a doublet at δ_H 3.07 with a coupling of 15 Hz and at δ_C 10.2 with a coupling of 58 Hz. The ^{31}P NMR spectrum showed a peak at δ_P +20.5 and these data correspond to the phosphonium salt **750**. After the salt **748** is formed, on heating the bromide attacks the methyl group of the ester to form methyl bromide and the ylide **751**. The ylide picks up a proton and the salt **750** is formed.



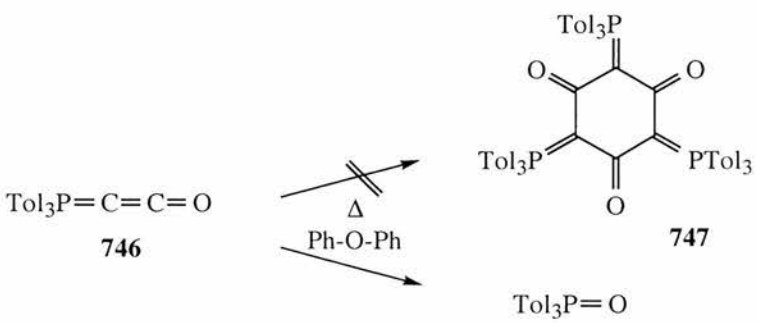
The second attempt was more successful in forming the phosphonium salt **748** when the reaction was done at room temperature. The ylide **749** was prepared as before using one equivalent of base with the salt. The preparation of the ketene **746** was more difficult than for the phenyl analogue. The results were inconsistent and numerous repetitions were needed for it to work. Finally, a dark red solid was obtained but unfortunately this was highly air sensitive and decomposed on standing. It was difficult to isolate and we managed to characterise spectroscopically it as a 1:1 mixture of the ketene and the oxide. It was interesting to see the closely corresponding spectroscopic data for the two analogues.



Although we could not seperate the tri-*p*-tolyl ketene **746** from the oxide we decided to continue with the mixture and this was heated with the trioxo oxygen ylide **726** but unfortunately the results were disappointing and all attempts led to its complete conversion into tri-*p*-tolylphosphine oxide.



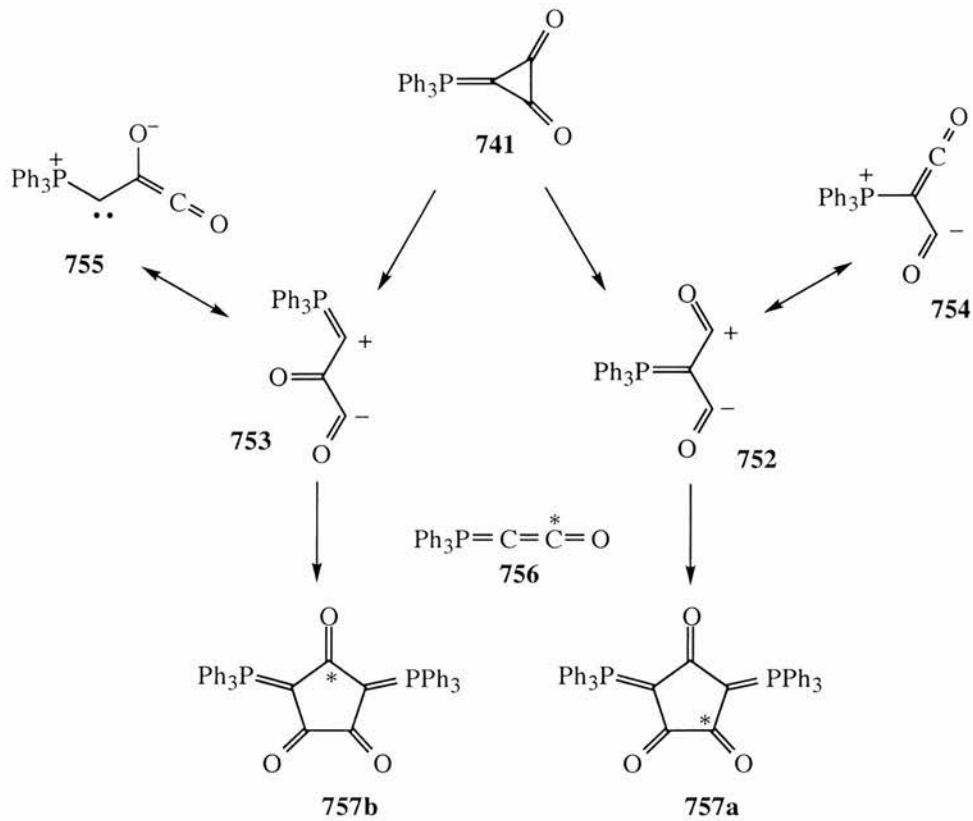
Attempts to prepare the new cyclic trimer **747** also failed. Here too the ketene was air sensitive and the oxide was mainly formed. As these attempts were unsuccessful we decided to abandon this approach.



The third approach involved working with a ^{13}C labelled compound. If we could prepare the carbonyl labelled ketene, in addition to confirming the involvement of both starting materials we could also learn about the intermediates involved.

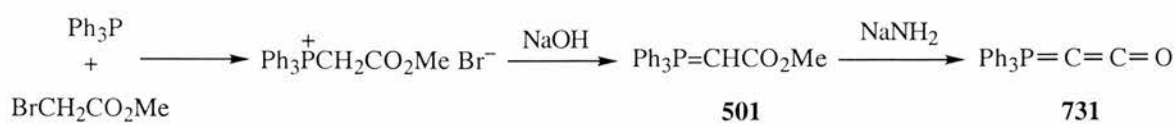
The interaction of the three membered dioxo intermediate **741** with the ketene **731** to give the bis ylide **732** clearly involves ring-opening of the three membered intermediate **741**. Either the ylide-carbonyl bond or the carbonyl-carbonyl bond may break and the intermediate may be diradical or dipolar. We favoured a dipolar intermediate and both the 1,3-dioxo **752** or the 2,3-dioxo **753** intermediates can be stabilised to some extent by delocalisation as shown by forms **754** and **755**. If one of these intermediates are involved it should be easily determined by the ^{13}C labelling. If the mechanism proceeds *via* the ring opening between the two carbonyls to give the 1,3-dioxo intermediate **752**, on heating with the labelled ketene **756** we would expect to see the labelled carbonyl at one of the adjacent carbonyls as in **757a** which would be reflected in the ^{13}C NMR as an enhanced double doublet compared to the other triplet. If the ring opens at the ylide-carbonyl bond forming the 2,3-dioxo intermediate **753**,

on reaction with the labelled ketene we should expect to see the labelled carbonyl at the isolated position as in **757b** and the ^{13}C NMR will show an enhanced triplet in the carbonyl area.

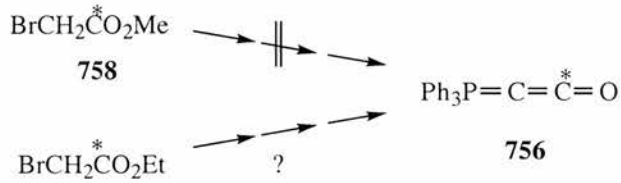


6. Preparation of the labelled ketene

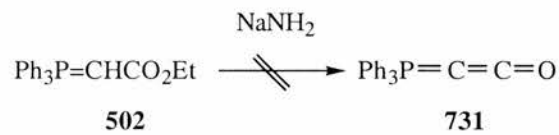
In this chapter section 4. we showed the preparation of the ketene **731**. We started from available starting materials, triphenylphosphine and methyl bromoacetate to get the methoxycarbonyl ylide **501** followed by elimination with sodium amide to give the desired ketene **731**.



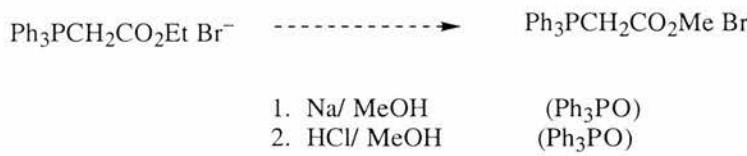
To make the labelled ketene **756** in a similar way we need to start from the carbonyl labelled methyl bromoacetate **758** which is not commercially available. We looked for other related compounds that could be useful and found that the carbonyl labelled ethyl bromoacetate was available.



Before ordering the carbonyl labelled ethyl bromoacetate we wanted to see if the ketene **731** can be prepared from the corresponding ethoxycarbonyl ylide **502** and this was tried out on unlabelled material. All attempts to react the ethoxycarbonyl ylide **502** with sodium amide resulted mainly in the formation of Ph_3PO and some starting material and a few other small peaks were found in the ^{31}P NMR spectrum. This result was surprising because we expected the methoxy- and ethoxycarbonyl ylides to behave in a similar manner. However it appears that precipitation of NaOMe fron the reaction medium occurs more readily than NaOEt and this provides the driving force for the reaction. It is therefore essential to use the methoxycarbonyl ylide **501**.

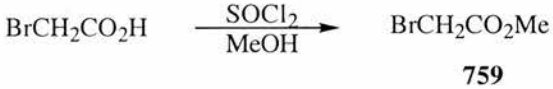


Based on this result our next step was to try and convert the ethyl ester to the methyl ester at one of the stages. The phosphonium salt is the most stable intermediate and we decided to try the conversion at that stage. Basic and acidic transesterifications were attempted by using sodium methoxide and concentrated hydrochloric acid in methanol. In both cases the transesterification failed and Ph_3PO was formed. As this transformation was problematic we decided to look for another route to obtain the carbonyl labelled ketene **756**.



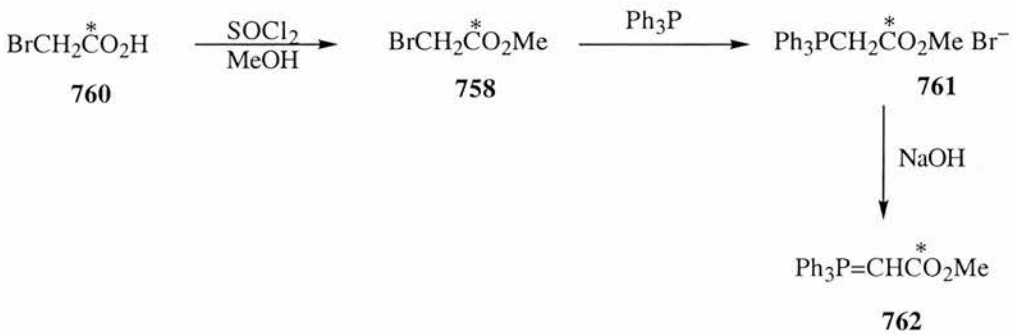
Another labelled starting material available was the carbonyl labelled bromoacetic acid for which conversion to the methyl ester **759** would successfully lead to the labelled ketene **756**. Here again we first tried the conversion on unlabelled material and when bromoacetic

acid was heated with thionyl chloride in methanol the desired product methyl bromoacetate was isolated after distillation.



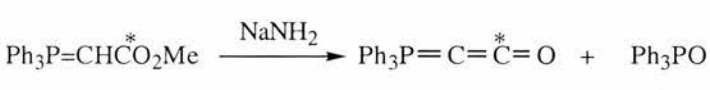
759

The reaction was repeated with a 1:4 mixture of the carbonyl labelled bromoacetic acid **760** and the unlabelled bromoacetic acid forming the 20% ^{13}C-carbonyl labelled methyl bromoacetate **758** in high yield. This was taken on to form the carbonyl labelled phosphonium salt **761** and the carbonyl labelled methoxycarbonyl ylide **762** was formed after the addition of sodium hydroxide. All the labelled compounds prepared showed an enhanced ^{13}C NMR peak for the labelled carbonyl.



760 **758** **761** **762**

Many attempts at heating the labelled methoxycarbonyl ylide **762** with sodium amide were unsuccessful and small amounts of the ketene were obtained with Ph_3PO as the major product. In one of our attempts we obtained a 1:1 mixture of the labeled ketene **756** and Ph_3PO and decided to proceed to the next step using this mixture.



762 **756**

The mixture of the labelled ketene **756** and Ph_3PO as heated with the oxygen trioxo cyclic ylide **726** in diphenyl ether and the ^{31}P NMR spectrum showed a new peak at δ_P +9 which looked promising for the bisylide product. The mixture was concentrated and a ^{13}C NMR spectrum was run. As this was a mixture we had to eliminate the peaks relating to the other products such as Ph_3PO but our main interest was the in the carbonyl region. The ^{13}C

NMR spectrum showed an enhanced triplet in comparison to the double doublets which is shown below (Figure 1).

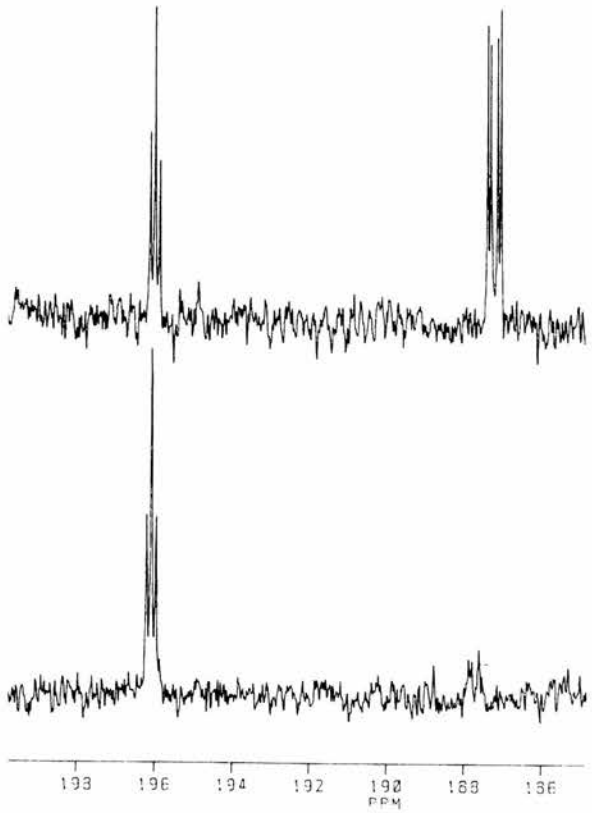


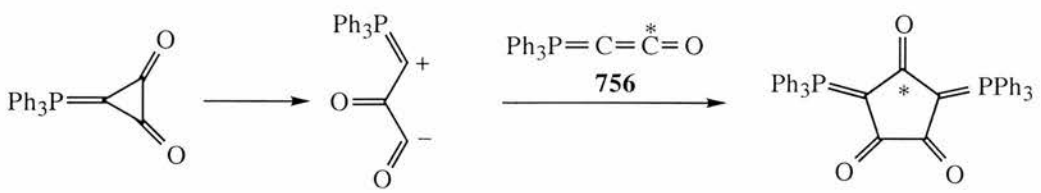
Figure 1

^{13}C NMR spectra (carbonyl region)

a. Unlabelled cyclic ylide **732**

b. Labelled ylide **757b** obtained from reaction of **726** and **756**

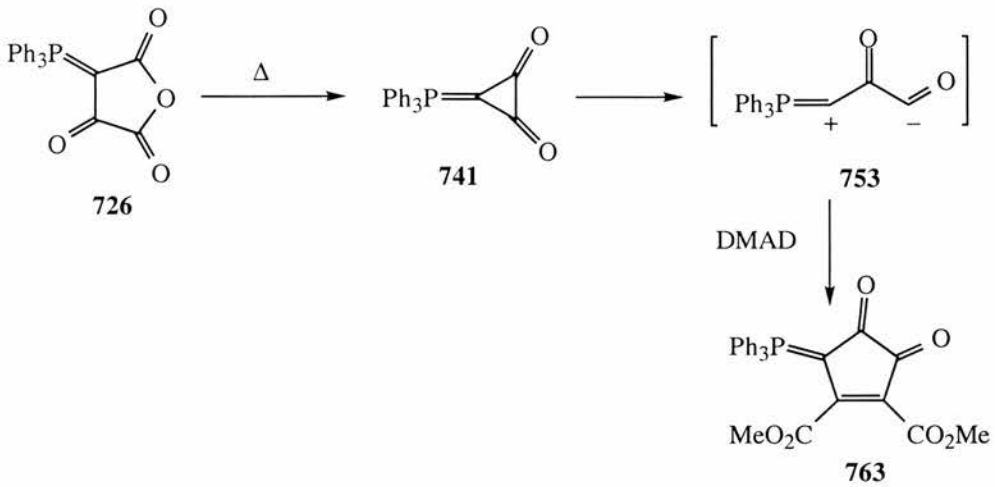
The enhancement of the triplet due to the isolated carbonyl clearly shows that we have obtained the bisylide product **757b**. This means that to form the product the three membered dioxo ylide **741** opens at the ylide-carbonyl bond forming the 2,3-dioxo intermediate **753**. This intermediate **753** reacts with the labelled ketene **756** and the bisylide product formed is of type **757b**.



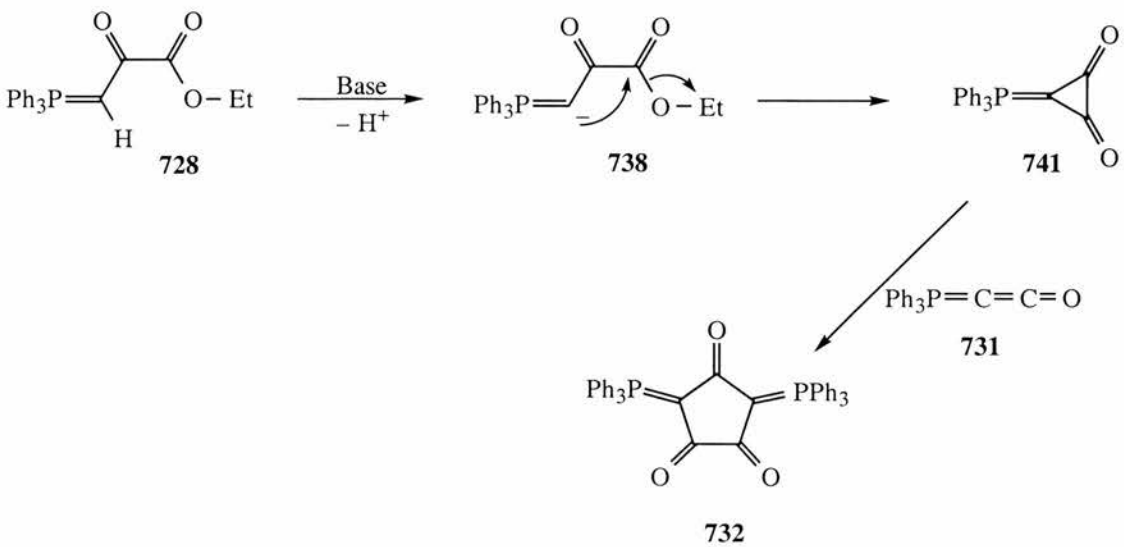
741 **753** **757b**

From the experiments with the labelled ketene we have proved not only the involvement of the ketene in the formation of the bisylide product but also confirmed the type of intermediates involved. The mechanism goes via the three membered dioxo ylide **742** and the ring opens at the carbonyl ylide bond followed by addition to the ketene to give the bisylide.

Another important experiment to confirm this would be to try and trap the 2,3-dioxo



intermediate and this could be done using DMAD which would be added while heating the trioxo oxygen ylide. The intermediate formed could react with the alkyne to form **763** which could be isolated and identified.



Based on our proved mechanism we propose that the mechanism for the second method for the formation of the bisylide reported by Bestmann and coworkers[198] may also go *via* the same intermediates. The dioxo ylide loses a proton in the presence of a base and a ring closure with loss of the ethoxy group occurs to form the 1,2-dioxo intermediate **741**. This may then be converted into **732** as we have already shown and this avoids the need for the rather unlikely loss of the ethoxycarbonyl group as EtO^- and CO involved in the other mechanism.

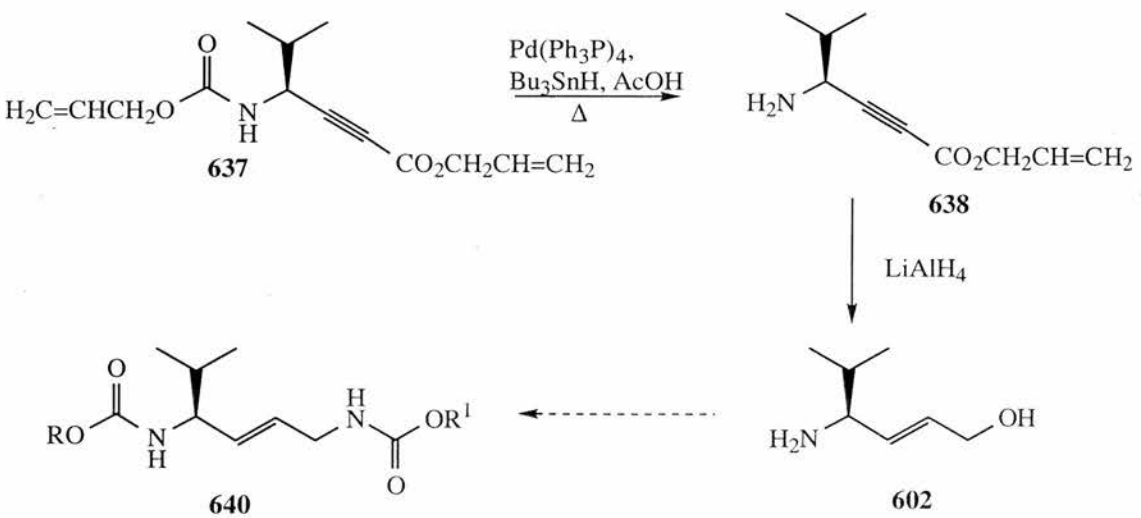
I Conclusions and Prospects for Future Work

In Section B the pyrolysis of aminoacyl stabilised phosphorus ylides, which was previously successful in producing chiral acetylenic amino acid derivatives for examples derived from amino acids with hydrocarbon side chains, was examined for examples with functionalised side chains. It was discovered that this resulted in the processes occurring becoming considerably more complex and of limited synthetic value, although further study will be required to understand exactly what happens in some cases.

In Sections C and D the chiral acetylenic amino acid derivatives illustrated by the example **575** were subjected to further transformations with the aim of preparing chiral 1,4-diamines **593**, potential intermediates in the synthesis of NOS inhibitors of interest to the

575 **593**

collaborating company. Although the results in this area were generally disappointing, we were able to learn something about the inherent problems of these systems which will help for future investigations. It is clearly essential to plan the order of functional group transformations carefully and make a careful choice of the protecting groups. The

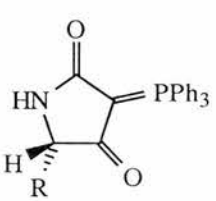


637 **638** **640** **602**

benzoxycarbonyl group was originally used because of its ability to survive the FVP conditions but has proved to be unsuitable for further transformations. After examining various combinations of groups the allyl derivatives - either protection of the acid as the allyl ester and/or the amine as the allyl carbamate proved to be stable to the pyrolysis conditions and this offers a promising avenue for future work on the further transformation into 1,4-diamine derivatives as shown in the example of **637** giving **640** shown on the previous page. The *N*-methylamino allylic alcohols such as **606** formed by reduction of the acetylenic ester **575** also have potential but their preparation needs to be scaled up for the further transformations to be completed.

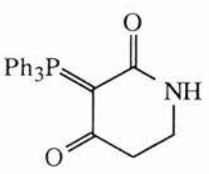
An alternative route to the chiral diamines using α-cyano-β-oxo ylides did not proceed in the expected sense. The cyano group turned out to be reactive towards cyclisation and a variety of heterocyclic products with the oxo ylide function still in place were formed. The chemically novel structure of these is of considerable interest and worthy of further study.

As described in Sections F and G, a series of five, six and seven-membered cyclic ylides such as **493**, **709** and **693–695** were prepared unexpectedly. The five and six-membered cyclic ylides containing the tetramic acid structure were formed by removal of the *N*-protecting group in the amino acid derived ylides followed by thermolysis The novel seven-membered cyclic ylides with an azepine-2,6-dione structure, which are effectively vinylogous tetramic acids were prepared from the α-aminoacyl-β,γ-unsaturated ylides with loss of methanol or ethanol. Attempts to prepare an eight-membered ring in a similar manner were unsuccessful. The reactivity of these novel ylides is of great interest and will be the subject of future study.

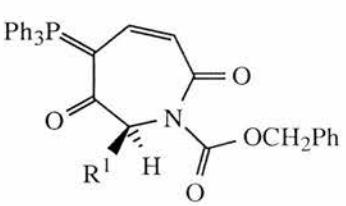


493

R = Me, Pr^i

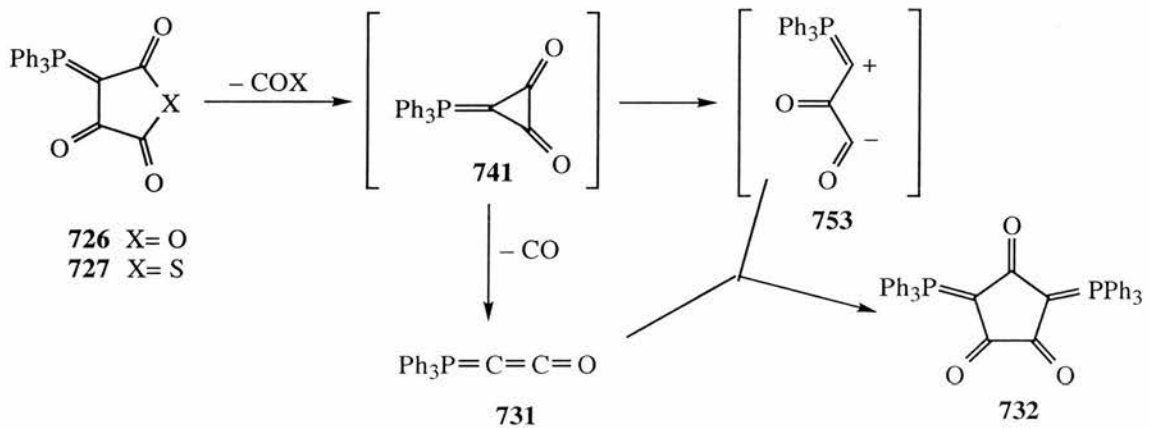


709



693 R^1= Me
694 R^1= H
695 R^1= $CHMe_2$

The final part of the work, described in Section H, focused on pyrolysis of cyclic ylides. The five-membered cyclic ylides **493** containing nitrogen gave complicated results upon pyrolysis but some evidence was obtained for formation of an oligomer of 4-methylene-γ-butenolactam in one case. Most unexpectedly, the related oxygen and sulfur containing cyclic ylides **726** and **727** broke down, both upon neat pyrolysis and in boiling diphenyl ether, with loss of CO_2 or COS respectively to give the same known five-membered ring trioxo diylide **732**. A mechanism for this novel reaction involving the intermediacy of triphenylphosphoranylidenecyclopropanedione and triphenylphosphoranylideneketene was proposed and evidence in support of it was obtained using ^{13}C labelling.



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