Approaches to a total synthesis of pilocarpine

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APPROACHES TO A TOTAL SYNTHESIS OF PILOCARPINE

Submitted by Karen Jayne Percival for the
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DEDICATION

In memory of my Grandmothers.

IF-

If you can keep your head when all about you
Are losing theirs and blaming it on you,
If you can trust yourself when all men doubt you,
But make allowance for their doubting too;
If you can wait and not be tired of waiting,
Or being lied about, don't deal in lies,
Or being hated, don't give way to hating,
And yet don't look too good, nor talk too wise:

Rudyard Kipling.

ACKNOWLEDGEMENTS.

"...but strong in will, to strive, to seek, to find and not to yield..."

Tennyson

I would like to thank Dr Malcolm Sainsbury for his help and guidance throughout the course of this work. My thanks to Dr John Davies for making my stay in Edinburgh enjoyable. Gratitude to Dr Tim Gallagher for his help and friendship; to Dr Paul Graupner, Colin Williams, Melv Giles, Ian Davies, Phil Searle and David Fox for their ideas and good humour, and to MacFarlan Smith for providing the funding. I would also like to thank Sue Boucher and John Bradley for finding things when they appeared to be in the wrong place, Dave Wood and Richard Hartill for running my n.m.r. spectra, Alan Carver for his invaluable help with elemental analysis and Chris Cryer for the mass spectroscopy service he provided.

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My warmest wishes go to my mother and father who have continually supported me throughout my academic career and have always been there to listen and give advice. Finally I would like to express my warmest thanks to Chris whose support, encouragement and love has taken me to new found heights, and simply for being there.

CONTENTS

SUMMARY.

The major aim of this thesis was to explore alternative synthetic routes to the Jaborandi alkaloid pilocarpine, which could subsequently be applied to an asymmetric synthesis of (+)-pilocarpine. Recent interest in this relatively "old" drug stems from a depletion of its natural source making necessary a synthesis, preferably in chiral form.

The initial approach involved attempted coupling of 1-methylimidazol-5-yl-lithium with 3-toluenesulphonyloxymethyl-4-butanolide. This did not succeed because the lithioimidazole species could not be formed.

The second approach was based on the alkylation of 1-methyl-5-ethynylimidazole with ethyl 2-bromobutyrate. The initial target, 1-methyl-5-ethynylimidazole, was prepared by a nine-step synthesis but proved to have very toxic side-effects. The desired alkylation step did not succeed because of side-reactions due to branching of the alkyl halide used.

The toxicity of the imidazolylalkyne prevented further work with it, so an alternative route involving the Michael addition of 1-methyl-5-(1,3-dithianyl)imidazole to 2(5H)furanone was attempted. Literature precedents for such reaction appeared good; however no 1,4-addition product could be recovered.

The fourth route employed the Wittig reaction as its key step, involving ethyl 3-methylenephosphoranylbutanoate. However, both model chemistry and the envisaged strategic reaction failed to give the desired results.

The penultimate approach centred on ring-opening of 1-methyl-5-oxiranylimidazole, a previously unknown compound, with the anion of ethyl butanoate, which was to be followed by several manipulations. These, it was envisaged, would afford access to a selenide which would cyclise (in the presence of azobisisobutyronitrile and tributyl tin hydride) to give pilocarpine. Again problems of severe toxicity were encountered in preparation of the epoxide, rendering further work on these imidazole systems inadvisable.

The final route involved, once again, the use of an alkyne key intermediate to facilitate a radical cyclisation which would form the lactone unit of pilocarpine. Here a convergent synthesis, using butyn-1,4-diol as starting material, was used to build up the lactone and imidazole fragments at opposite ends of the alkyne functional group. The key step involved nucleophilic attack by nitromethane anion on the imine unit of the monoprotected 2-butyn-4-(tetrahydropyranyl)-1-al. It is thought that this step failed as a result of the poor electrophilicity of the aldehyde.

CHAPTER 1

1. GENERAL INTRODUCTION.

"Come forth into the light of things,
Let nature be your teacher."
W. Wordsworth.

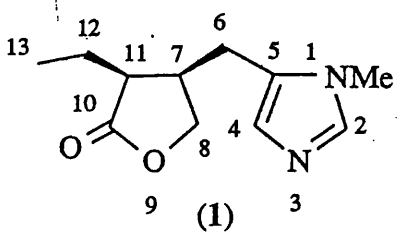
1·1. Occurrence and Isolation.

Pilocarpine (**1**) occurs in plants of the Jaborandi family and most abundantly in the *Pilocarpus* genus, which originates from Brazil. The chemistry and pharmacology of pilocarpine were first investigated in the nineteenth century. In 1875 Gerrard[1] and Hardy,[2] working independently, obtained the alkaloid from *P.jaborandi* extracts, after fractional crystallisation of its mineral acid salts. Samples were supplied to other laboratories for biological assessment.

Although other natural products are also present in the extracts, only pilocarpine is medicinally important. It is used for the treatment of glaucoma, nephritis and Alzheimer's disease.

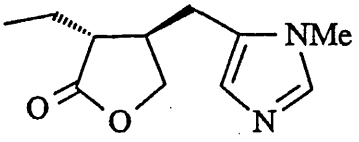
The absolute stereochemistry of the pilocarpine molecule is shown in Figure 1, together with the numbering system used to describe it. Only the *cis*-arrangement of the lactone side-chains is of interest; isopilocarpine (**2**), the *trans*-isomer, is essentially inactive biologically. Very early on, Jowett[3] showed that pilocarpine decomposes readily, in aqueous solution, to the more thermodynamically favourable *trans*-isomer;[4] isopilocarpine's lack of activity is therefore unfortunate.

Currently, all pilocarpine in clinical use is obtained from plant sources, especially



(1)

(+) pilocarpine



(2)

(+) isopilocarpine

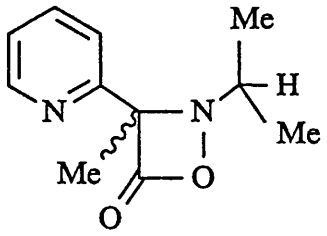
Figure 1.

from *P.mircophyllus*.[5] However, there are at least nine syntheses to the alkaloid - none of which are asymmetric, due to facile epimerisation of the lactone.[6] So, at the *present time*, the natural source is still economically viable.

1·2 Structure Elucidation.

Considering its long history, it is not surprising that the structure of pilocarpine was largely determined by classical methods; *i.e.* degradation and part synthesis. The stereochemistry of the molecule was a source of difficulty to early chemists, who were unable to explain the difference between pilocarpine and isopilocarpine. Furthermore, they noted features in common between both molecules. For example, one of the two nitrogen atoms present was tertiary, in both isomers, and salts of molecular formula $C_{11}H_{16}O_2N_2.RX$ were formed by alkylation of either isomer with alkyl halides (RX).[7]

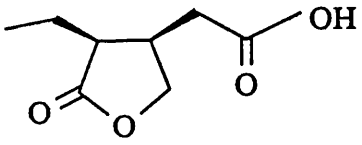
Treatment with alkali gave salts which, when carefully acidified, reformed the alkaloids.[3] Less attention to the conditions of these experiments often led to the isomerisation of pilocarpine. From the behaviour in alkali-acid a lactone function was indicated, but the imidazole nucleus was not recognised. Therefore, representations such as the pyridine derivative (3) were considered,[8] even though this structure has only one stereocentre and could not encompass both pilocarpine



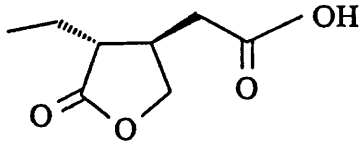
(3)

and isopilocarpine.

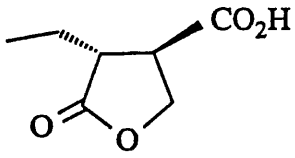
An advance was reported by Jowett[9] who degraded pilocarpine, *via* oxidation with potassium permanganate, into homopilopic acid (4) and homoisopilopic acid (5). Similar treatment of isopilocarpine gave homoisopilopic acid (5) and isopilopic acid (6). An independent study by Pinner and Kohlhammer[10] verified



(4)



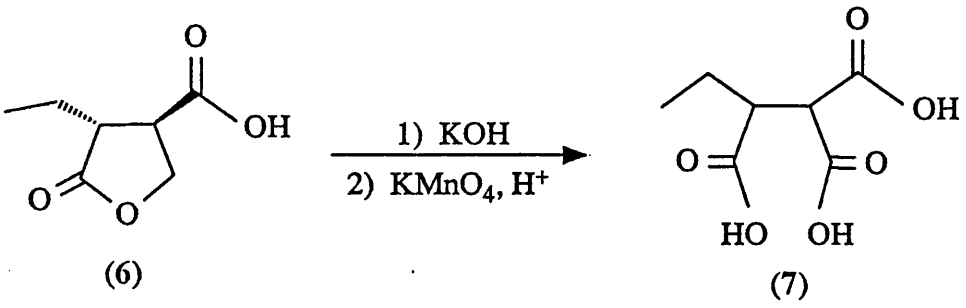
(5)



(6)

this work. Jowett[9] later proved that homoisopilopic acid was formed from both pilocarpine and isopilocarpine. The structures of the products obtained from these degradation studies were worked out by interconversion with known compounds,[11] although the relative and absolute stereochemistries were unknown at that time. However, the lactonic nature of such oxidation products lent support to the existence of a cyclic ester function in the natural alkaloids. Its presence

was inferred by alkaline degradation of compound (6) to the triacid (7).

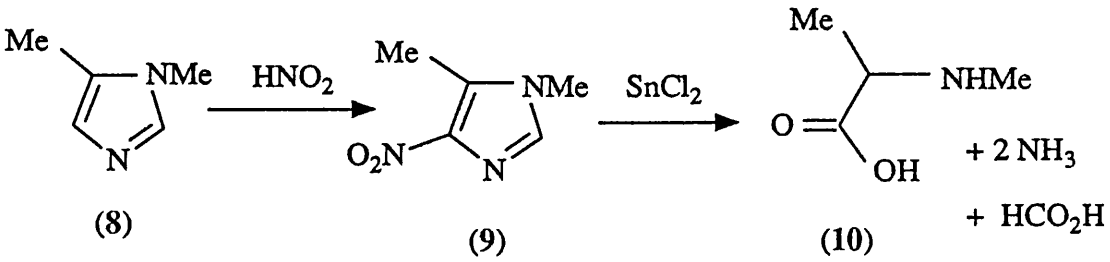


(6) (7)

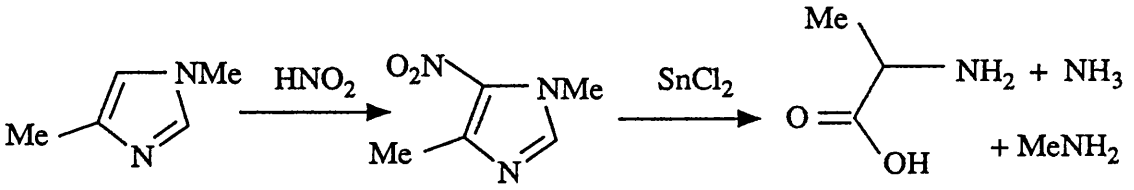
Heating isopilocarpine with soda lime produces ammonia and methylamine, together with three other bases. One of these is 1-methylimidazole, and the others are apparently 1,4(5)-dimethylimidazole and "pentyl-1-methylimidazole.[9] From this experiment, Jowett provided evidence for the nature of a second heterocyclic ring and its substitution pattern.

The structure of pilocarpine still could not be elucidated completely. It was not possible to deduce whether the dimethylimidazole group, present in the original molecule, was 1,4- or 1,5-disubstituted. This problem was eventually solved by Pyman.[12] He carried out further degradation studies on 1,4- (or 1,5-) dimethylimidazole, which Jowett had obtained from isopilocarpine. Nitration of this imidazole, and subsequent reduction with stannous chloride, gave (±)-*N*-methylalanine (**10**). This result allowed the characterisation of Jowett's base as 1,5-dimethylimidazole (**8**), since similar reaction of 1,4-dimethylimidazole (**11**) would produce unmethylated (±)-alanine (**13**) - a fact verified by experiment.

Even so, well respected chemists, such as Pinner,[13] argued that pilocarpine and isopilocarpine were the structural isomers (**14**) and (**15**) - an idea which ignored the facile nature of their interconversion.[6] Again it was Jowett[14] who came to the

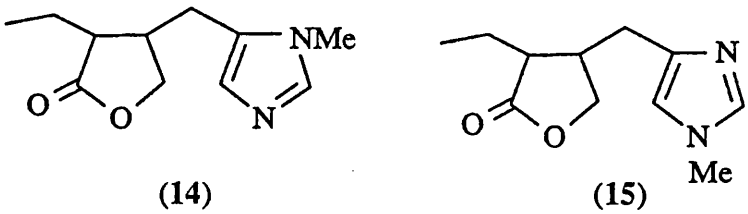


(8) (9) (10)



(11) (12) (13)

correct conclusion - that the difference between these two isomers was one of

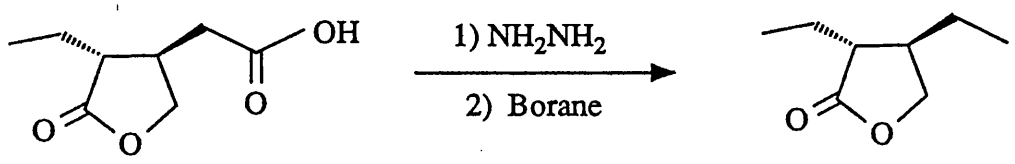


(14) (15)

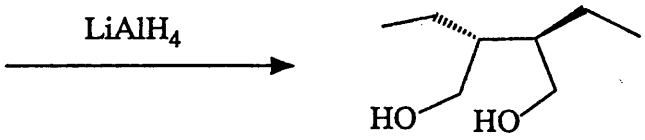
lactone sidechain stereochemistry.[15] Later, Prebrathenski[16] suggested that the less stable alkaloid pilocarpine has the *cis*- arrangement; whereas the *trans*-isomer is isopilocarpine.

1·3 Stereochemistry.

However, the question of the absolute stereochemistry of pilocarpine remained open until 1963. In that year Nagarajan *et al.*[17] showed that homoisopilopic acid (5), on reduction with hydrazine and borane, followed by treatment with lithium aluminium hydride, gave (+)-2,3-diethyl-1,4-butane-1,4-diol (17). They were able to determine the absolute configuration of both (+)-*trans*-2,3-diethyl-4-butanolide (16) and the diol (17).

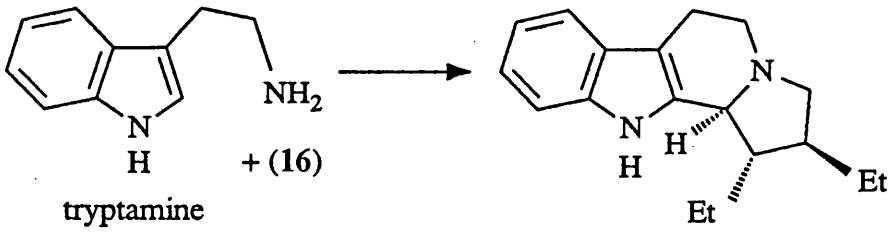


(5) (16)



(17)

Starting from the (-)-butanolide (**16**) and tryptamine, they prepared (-)-16α-strychindol (**18**) - a degradation product of strychnine - the structure of which was secure from earlier X-ray diffraction studies.[18] From this information,

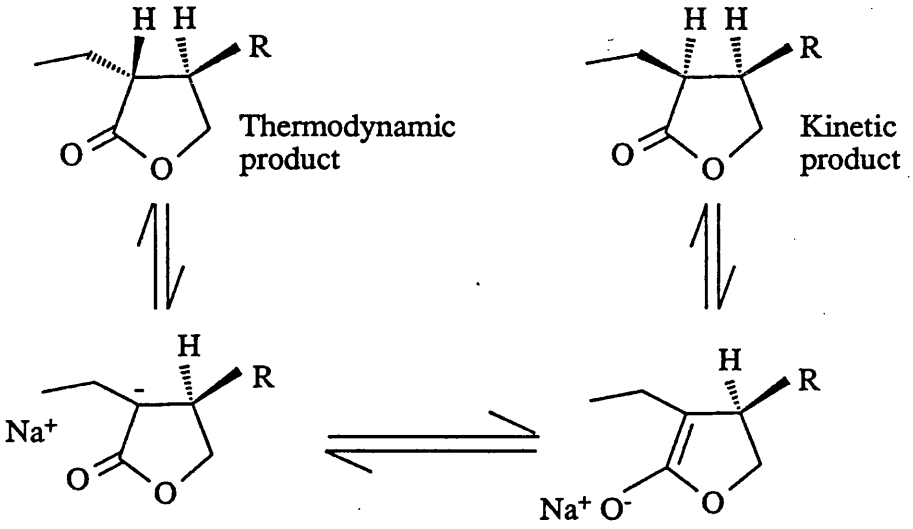


tryptamine (-)-16α-strychindol (**18**)

they could assign the absolute stereochemistry of butanolide (**16**). Later X-ray diffraction analyses of pilocarpine trichlorogermanate (II) hemihydrate confirmed the *cis*- orientation of pilocarpine directly.[19] This X-ray data also verified that the *cis*- arrangement is the less stable one for pilocarpine. Since that time more structural evidence, including that drawn from synthesis, has been accumulated; and it complements the earlier work.[20-24]

1·4 Isomerisation of Pilocarpine to Isopilocarpine.

It has been shown that heating an aqueous solution of pilocarpine causes a structural change.[25-27] In 1968 Döpke and d'Heureuse[28] indicated that isomerisation of pilocarpine is not necessarily caused by opening of the lactone ring, but could result from epimerisation *via* the enolate (Scheme 1).



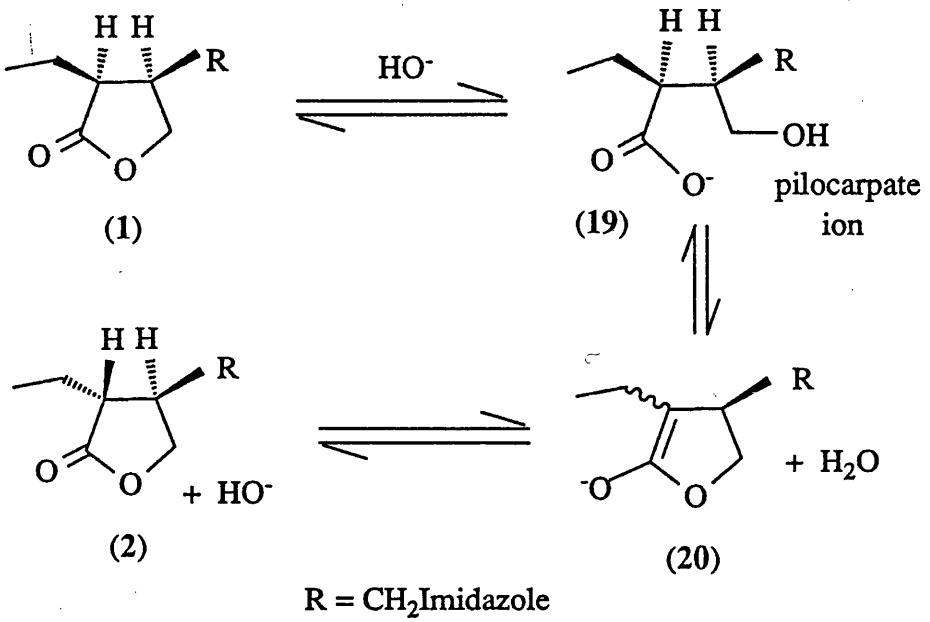
R = CH_2Imidazole

Scheme 1.

Later Nunes and Brochmann-Hanssen[29] proposed two pathways for the degradation of pilocarpine. These involved either hydrolysis[30] of pilocarpine to pilocarpic acid, or epimerisation; both result in loss of pharmacological activity (Scheme 2).

Further work with i.r.,[31] h.p.l.c.[32] and n.m.r.[33] techniques confirmed that epimerisation is more significant than hydrolysis.

As pilocarpine has been used extensively in ophthalmology, methods have been developed to determine the rate of epimerisation to isopilocarpine in aqueous solution. These include thin layer chromatography,[34] electrophoresis,[35] potentiometry with ion-selective membrane electrodes[36] and gas-liquid



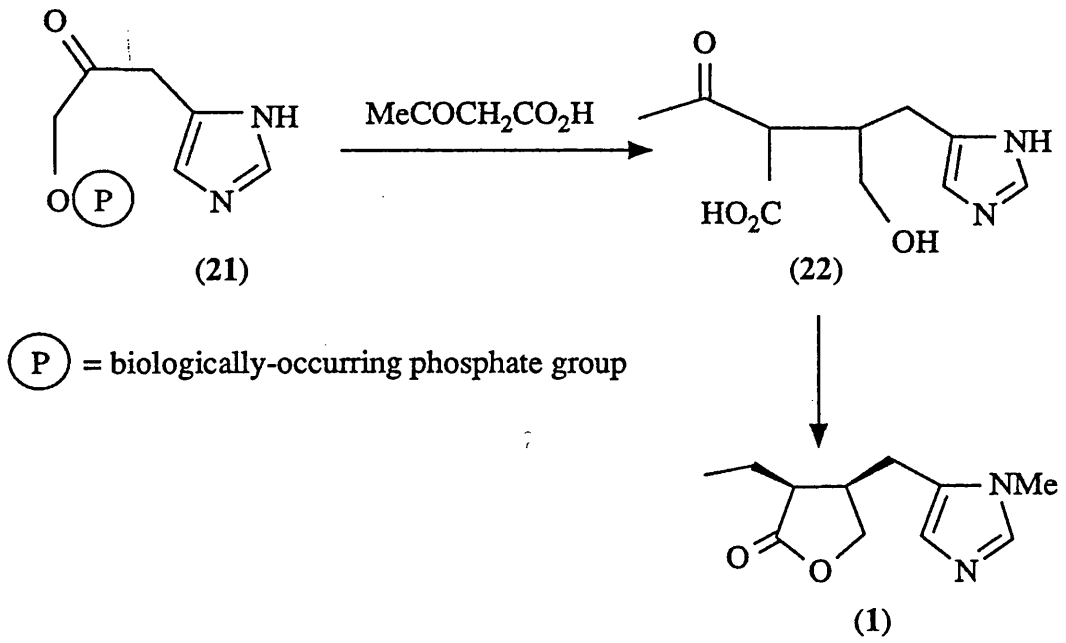
R = CH_2Imidazole

Scheme 2.

chromatography.[37] Of these, high performance liquid chromatography[38] is the most advantageous - due to its high sensitivity (down to 0.1 μg), and applicability to direct analysis of aqueous pilocarpine solutions used in ophthalmology.[39]

1·5 Biosynthesis.

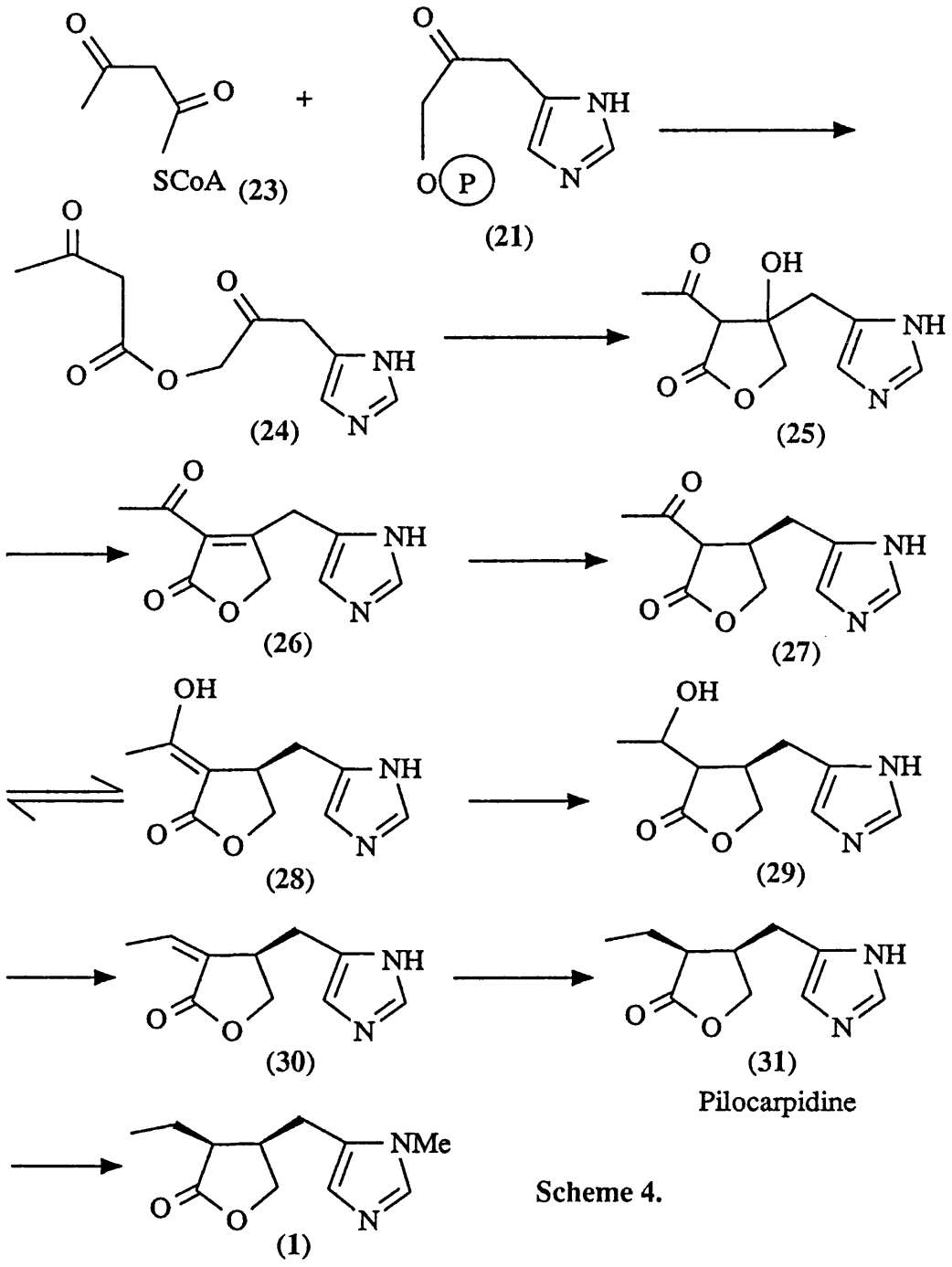
Relatively few alkaloids are known which incorporate the imidazole ring; and, of these, it appears that only pilocarpine is of medical significance. As the structures of pilocarpine and histidine bear considerable resemblances to one another, it was thought that a histamine derivative could be a biosynthetic precursor of the imidazole unit in pilocarpine. For example, in 1955, Robinson[40] published a proposal for the origin of pilocarpine. He suggested that reaction between *O*-phosphoryl-5-(3-hydroxy-2-oxopropyl)imidazole (21) and two molecules of either acetate, or a four-carbon unit such as butyrate or acetoacetate, was involved (Scheme 3). The product (22) could then undergo lactonisation and reduction to produce the alkaloid.



Scheme 3. Robinson's biosynthetic pathway.

Robinson's idea was later elaborated by Boit[41] and Leete.[42] It was considered that a carbon-carbon[43,44] bond-forming reaction is preceded by *O*-acylation. Thus, it is suggested that the co-enzyme A thioacetoacetic acid (or its equivalent) reacts with phosphate (**21**) to afford the ester (**24**). Subsequent cyclodehydration occurs, *via* an intramolecular aldol reaction (Scheme 4). These ideas have parallels in the biosyntheses of digitoxigenin and histidine.

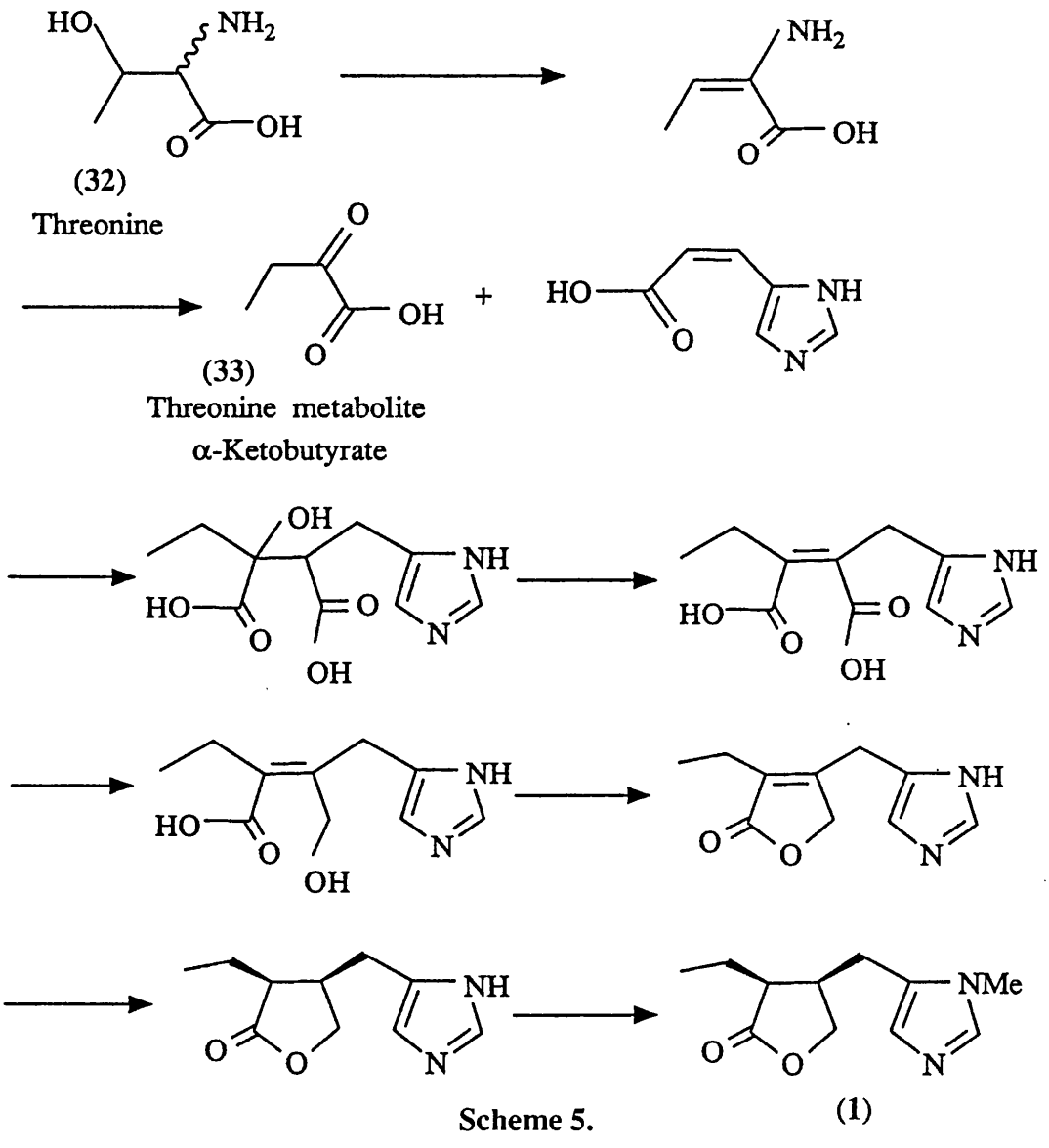
In 1975, Nunes[5,45] proposed a second biosynthetic pathway to pilocarpine. It involves the amino acid threonine, and is based upon an aldol condensation, followed by esterification (Scheme 5). Experimental work has been performed, involving feeding ^{14}C radio-labelled compounds to plants. These studies suggest that pilocarpine is synthesised in the roots of *Pilocarpus* species, and that *N*-methylation - thought to be the final step - occurs in the leaves. However, it has not yet been possible to verify the hypotheses of Nunes and others.



Scheme 4.

1·6 Pharmacological Activity.

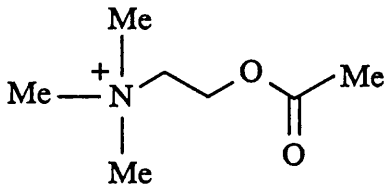
Pilocarpine is an old drug[46] which has been widely studied for its action in the central nervous system (C.N.S.) and elsewhere. It is widely used to counteract the mydriatic effect of atropine,[47] and for the treatment of glaucoma.[48-50] Other uses include stimulation of hair growth[51] and as a diaphoretic to treat nephritis.[52]


HO
NH2
OH
O
NH2
OH
O
(32)
Threonine
O
OH
O
+
HO
NH
O
N
(33)
Threonine metabolite
α-Ketobutyrate
OH
HO
O
O
NH
N
OH
HO
O
O
NH
N
OH
HO
O
NH
N
OH
O
O
NH
N
O
O
NH
N
NMe
(1)

Scheme 5.

Since pilocarpine has such a profound effect upon the parasympathetic nervous system, it has been considered as a chemotherapeutic agent against Alzheimer's disease.[53]

There is interest in determining the relationship between pilocarpine and established neurotransmitting agents, such as acetylcholine (34). The latter compound is released from the presynaptic cleft and received at a receptor site on the other side of the synapse. At this postsynaptic site, it serves to acetylate a hydroxyl group of a serine residue. *O*-Acetylation is rapidly followed by hydrolysis, so that the hydroxyl group is re-established ready to receive the next "message". In the course of this process, acetylcholine is itself cleaved to form choline and acetic acid. Although acetylcholine is not a chiral molecule, the receptor site is, and acetylcholine is required to adopt a specific conformation within the receptor pocket.[54,55]



(34)

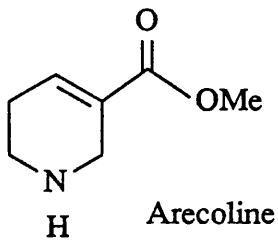
Changes to the structure of acetylcholine will alter the accessibility of this conformation,[56-58] and it has been noted that some of its derivatives have different biological properties. Dale[59] has shown that molecules such as nicotine and muscarinic acid act as agonists and antagonists of acetylcholine. Such a response implies that different types of receptor sites occur within the nervous system. These are now called nicotinic and muscarinic receptors; the former are located at neuromuscular junctions in autonomic ganglia, and the latter occur in

the parasympathetic target organs.[60]

Muscarinic receptors have been subdivided into further categories, M_1, M_2 and M_3. It is noted that modifications to acetylcholine[61] may activate its response within one or another of these sites. In general, muscarinic compounds tend to slow the heart beat, cause reduction in blood pressure,[62] and show depressor activity; while nicotinic compounds have the reverse effect.

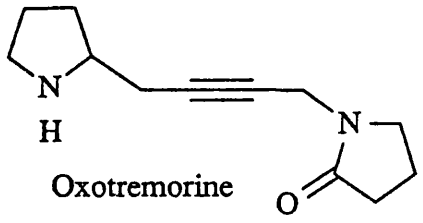
In the case of Alzheimer's disease,[63a] *post mortem* investigations have shown a loss of acetylcholine within the neurons of the brain (down to 30% of normal levels). This is thought to be one of the factors responsible for the condition. It has been found that Alzheimer sufferers exhibit an approximate 20% decrease in the number of M_2 receptors.[63b] M_2 receptors are believed to modulate the release of acetylcholine. However, the M_1 receptors are more highly concentrated in the brain than are M_2, and are believed to be important in the thinking process. Thus the development of a selective M_1 agonist is of appreciable importance. The structures of some cholinergic[64] agonists are shown in Figure 2.

Physostigmine (39) has shown the most encouraging results against Alzheimer's Disease, improving the memory of sufferers. The major disadvantage is its short half life, a common feature of most chemotherapeutic methods used against this disease. All the compounds shown in Figure 3 contain nitrogen atoms which can be protonated, or are already quaternary, like acetylcholine itself. Another common feature is an electrophilic group, most often a carbonyl function (ester or amide) at a specific distance from the potential quaternary centre. The complexity of this problem is exaggerated by the fact that specific structural requirements are not fully understood for the more important two subdivisions of the muscarinic receptor (M_1 and M_2), which are now recognised.



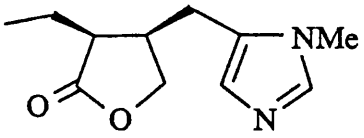
Arecoline

(35)



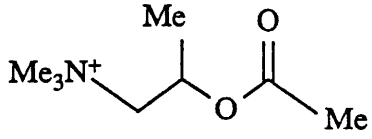
Oxotremorine

(36)



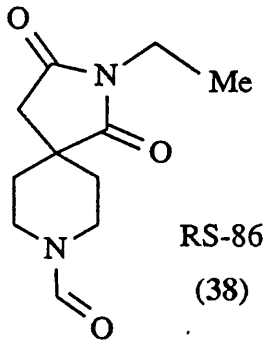
Pilocarpine

(1)



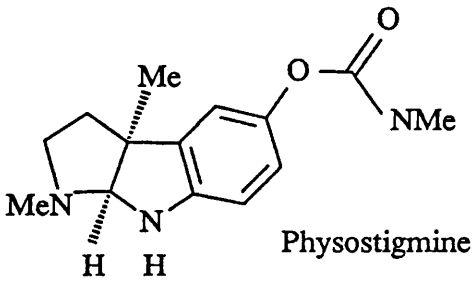
Bethanechol

(37)



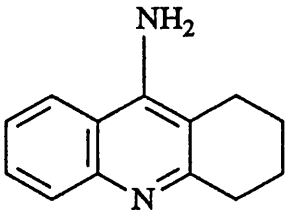
RS-86

(38)



Physostigmine

(39)



THA

(40)

Figure 2.

Most known cholinergic agonists have short half lives *in vivo*, lack specificity,[65] and are poor at permeating the blood brain barrier. They also have adverse side-effects, for example they reduce heart rate and blood pressure. With an aging

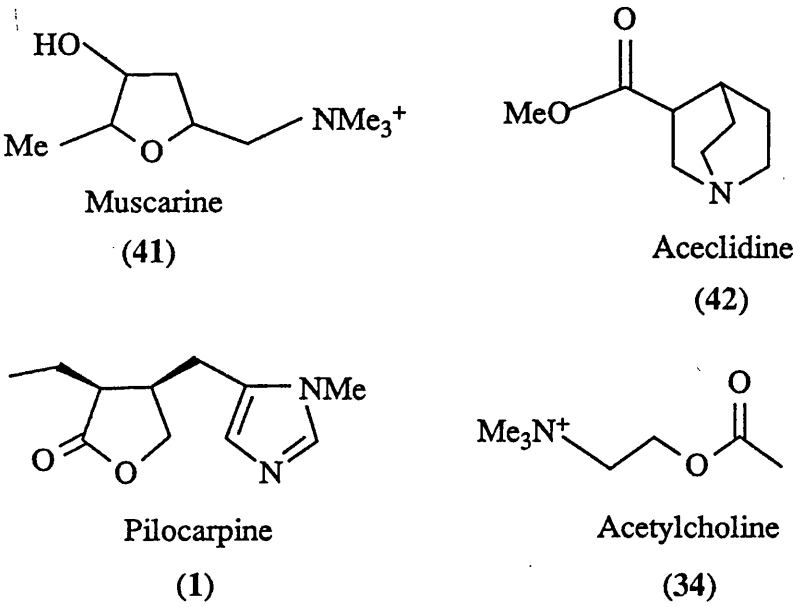


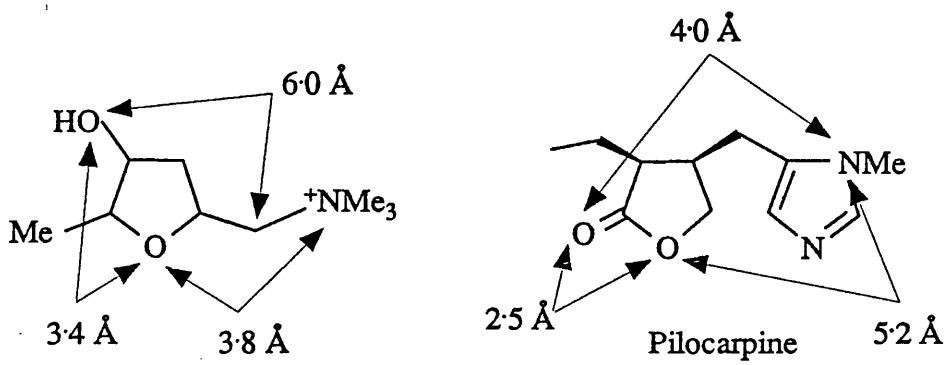
Figure 3.

population, senile dementia is a pressing problem world-wide; most pharmaceutical companies have significant programmes of research in this area.

The structural relationship between muscarine and pilocarpine is not as clear cut as might have been expected. Distances between "significant" atoms in the two molecules do not correlate very well. Nevertheless, the molecules seem to engender similar responses *in vivo*,[51,66-68] due to hydrolysis and formation of a quaternary nitrogen. (Figure 4).

1·7 Syntheses.

The first synthesis of pilocarpine was reported by Preobrashenski *et al.*[69-78] These authors concentrated on building up the imidazole nucleus late in their procedure. Ethylα-formyl-α'-ethylsuccinate (43) was reduced to the corresponding alcohol (44), which was hydrolysed and lactonised to give a mixture of (±)-pilopic and (±)-isopilopic acid. These were separated and resolved (Scheme 6).



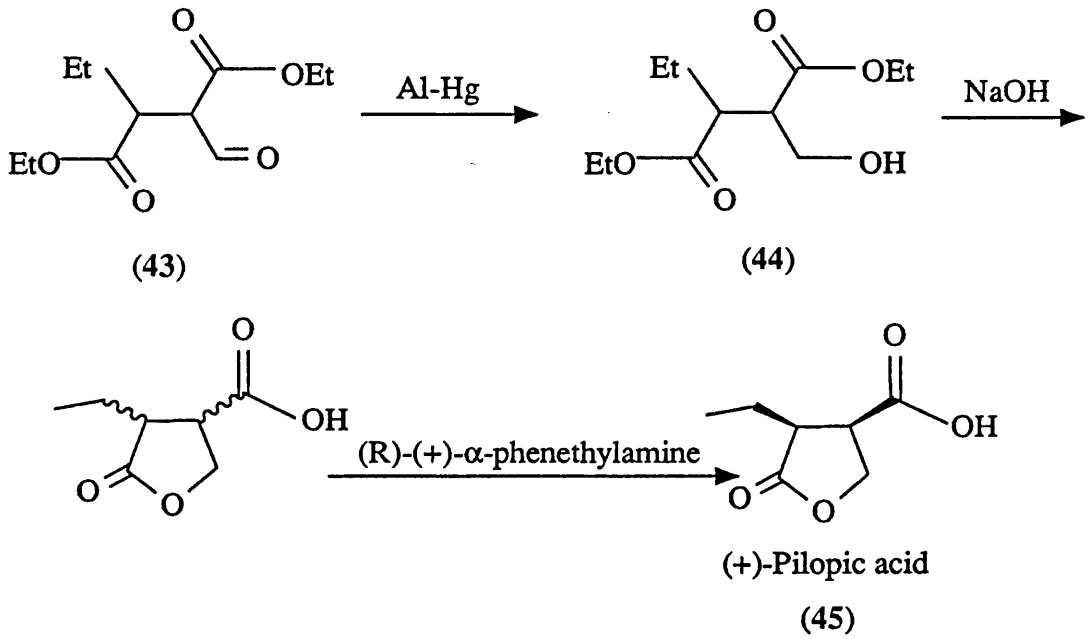
Muscarine

(41)

Pilocarpine

(1)

Figure 4.



(43)

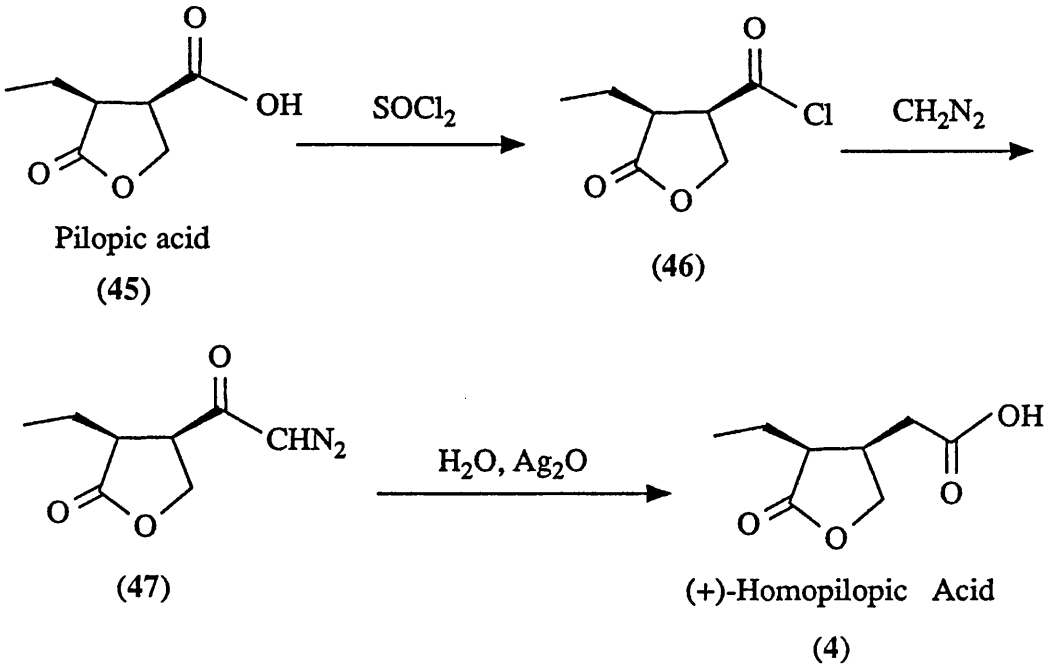
(44)

(+)-Pilopic acid

(45)

Scheme 6.

An Arndt-Eistert homologation of (+)-pilopic acid (45) thus obtained gave (+)-homopilopic acid (4), (Scheme 7). The homologation procedure was repeated, affording the diazoketone (49), (Scheme 8). Treatment of this compound with potassium thiocyanate produced the imidazole (50), which was desulphurised by reaction with ferric chloride. Finally imidazole (31) was

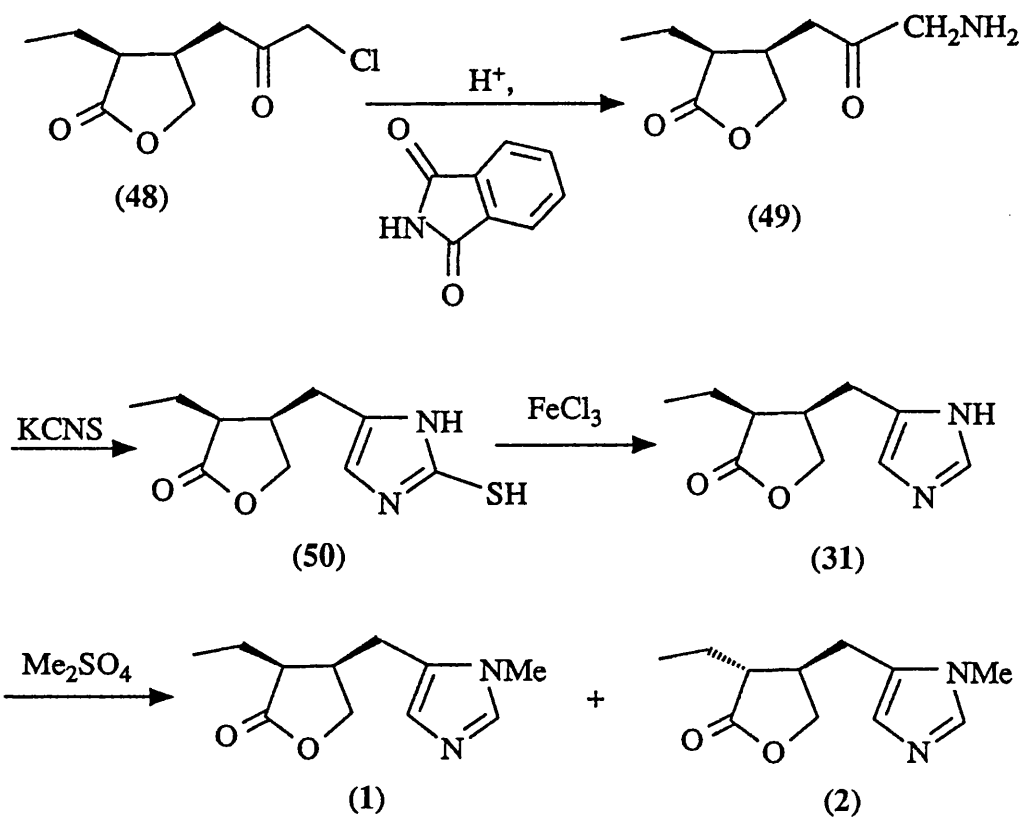


Scheme 7.

methylated by reaction with dimethylsulphate. Sadly, this last reaction displays no selectivity and two mono-*N*-methyl compounds were formed. Additionally, partial isomerisation to isopilocarpine was noted.

Deys[79] approach also adopted homopilopic acid as the first key intermediate. Several steps from ethyl 4-ethoxy-2-butenoic acid afforded the racemic acid, which was converted into the ketone (**52**), Scheme 9. An aldol condensation between this substrate and benzaldehyde, followed by ozonolysis afforded the ketoaldehyde (**53**). Treatment of this with ammonia and formaldehyde gave racemic imidazole (**31**). Again, the question of regioselective *N*-methylation was not addressed. Instead, pilocarpine, isolated from the products of a non-specific methylation, was resolved *via* its tartrate salt (Scheme 9).

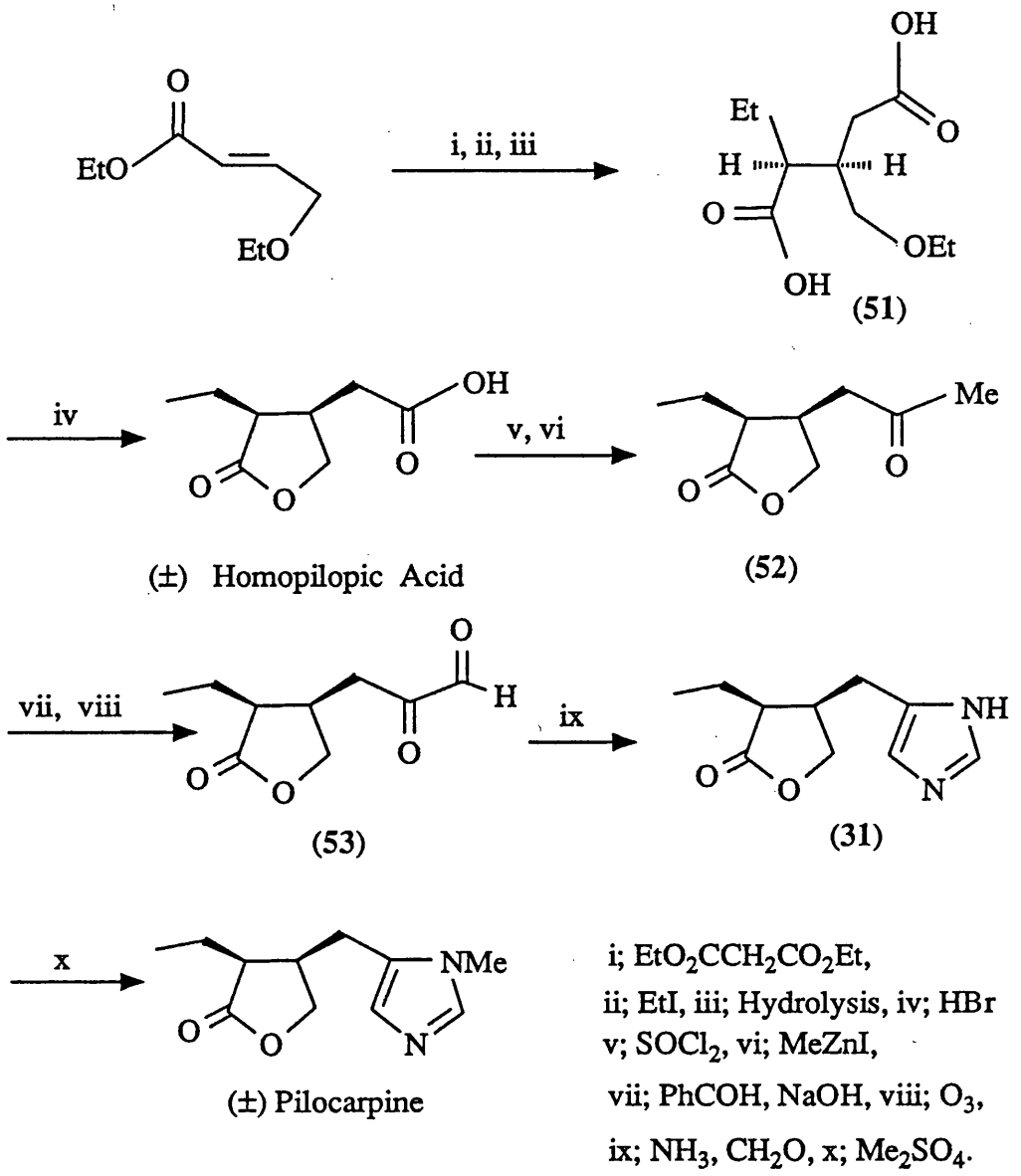
Two other syntheses, by Chumachenko[80,81] and by Degraw,[82] are essentially variants on the earlier approaches already outlined. Starting from furfural, a Michael addition was used to access the lactone.



Scheme 8.

In 1972, Link and Benauer[83] envisioned another route, this time from 5-formyl-1-methylimidazole (55), which was obtained from the corresponding methyl ester(54).[84] By starting from a *N*-methylated imidazole precursor these authors solved, for the first time, the lack of regioselective control inherent in previous syntheses (Scheme 10). A Stobbe reaction upon the aldehyde gave the potassium salt of the mono-esterified diacid (56). Following reduction and cyclisation, this compound afforded pilosine (58). Reaction of its enolate anion with ethyl acetate produced ketone (59), which was reduced to the racemic alcohol epimers (60). Dehydration and catalytic reduction afforded (±)-pilocarpine.

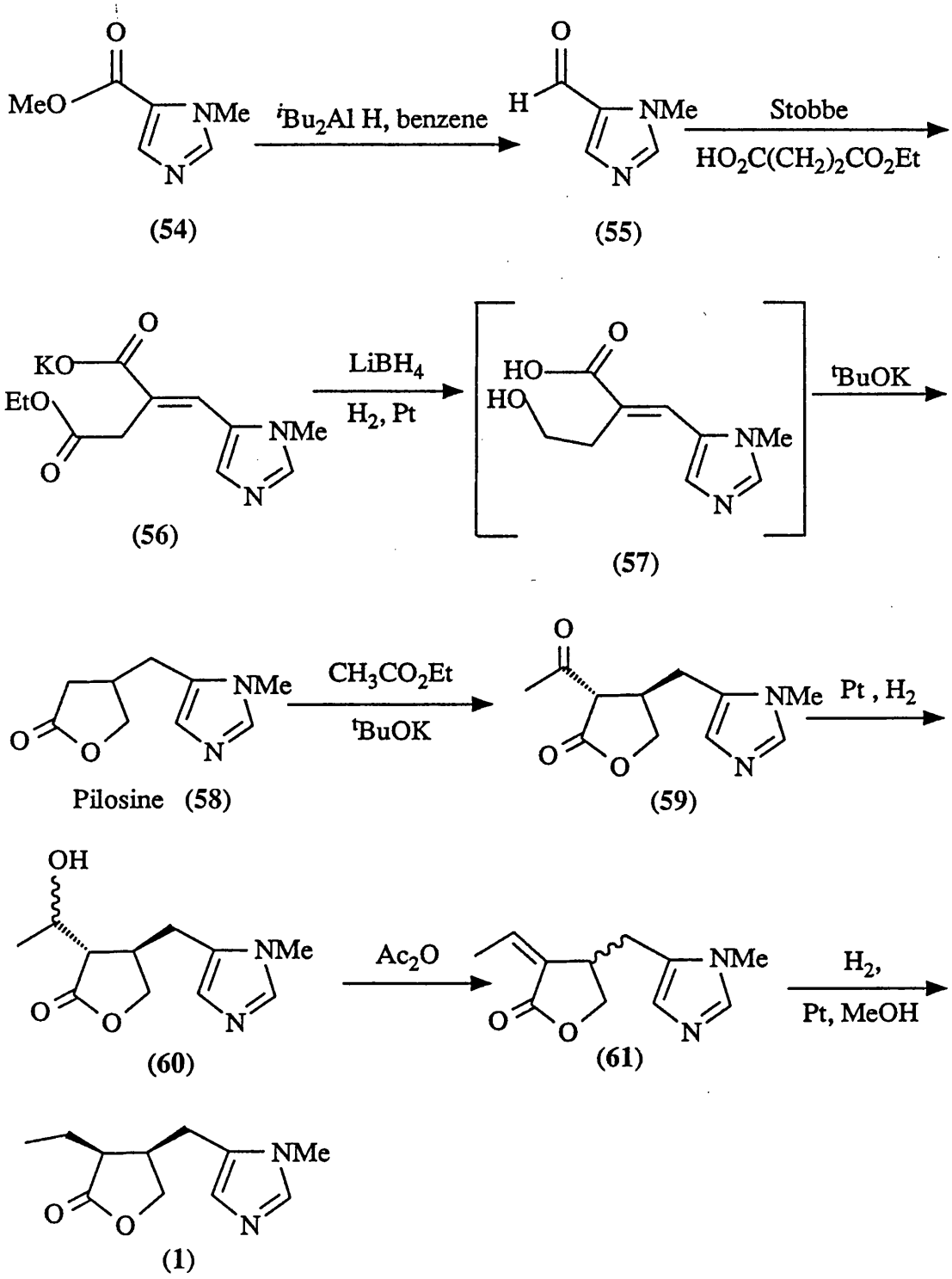
None of the preceding syntheses are very efficient, in terms of their yields. A



Scheme 9.

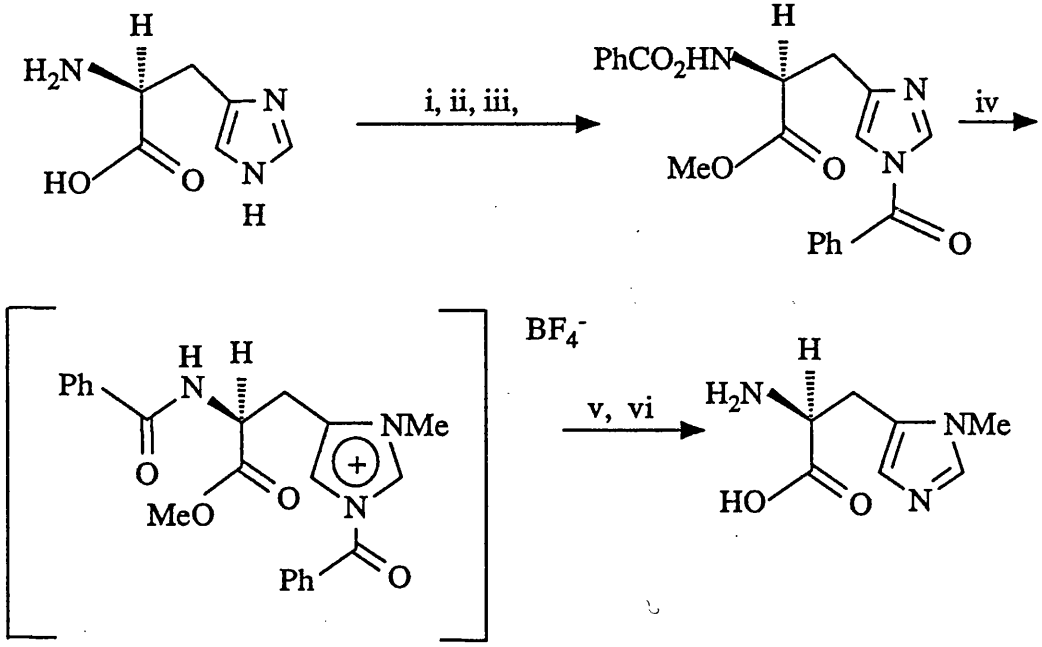
typical overall yield is 0.1% of pilocarpine. Thus, Noordam[85,86] was led to utilise commercially available L-histidine as his starting material. That choice was made favourable because of Bergermann's definition of selective 1-*N*-methylation conditions for the imidazole nucleus[87,88] (Schemes 11 and 12).

In Noordam's synthesis, L-histidine was first converted into (S)-2-hydroxy-3-(imidazol-5-yl)propionic acid (63) using silver nitrite and orthophosphoric acid. After esterification, the resulting product (64) was reacted



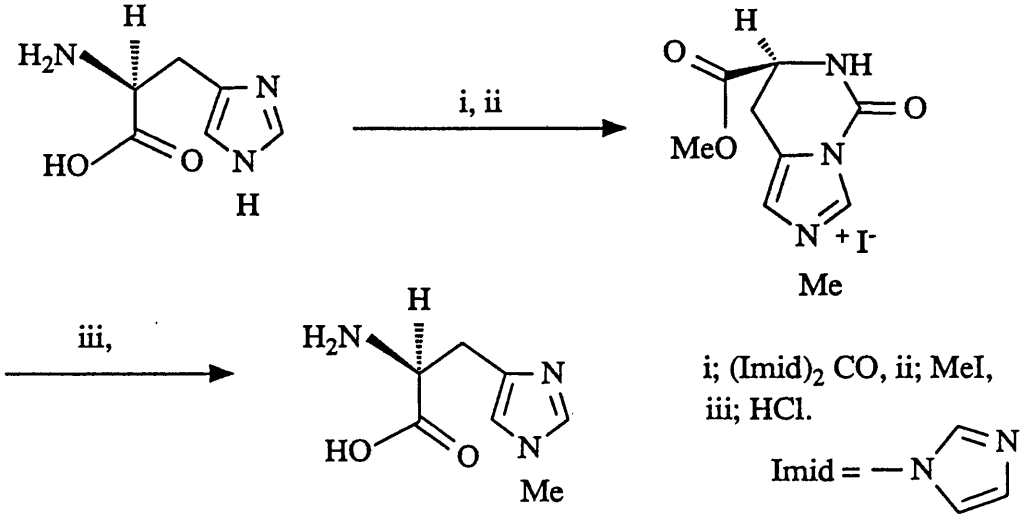
Scheme 10.

with 4-nitrobenzenesulphonyl chloride; effecting sulphonation of the alcohol function and the 3-*N*-position of the imidazole ring. Presumably the latter position is selected by the reagent for steric reasons. Inversion at the chiral centre



i; C_6H_5COCl, ii; MeOH, H^+,
iii; C_6H_5COCl, iv; $Me_3O^+BF_4^-$, v; H_2O, vi; HCl.

Scheme 11.

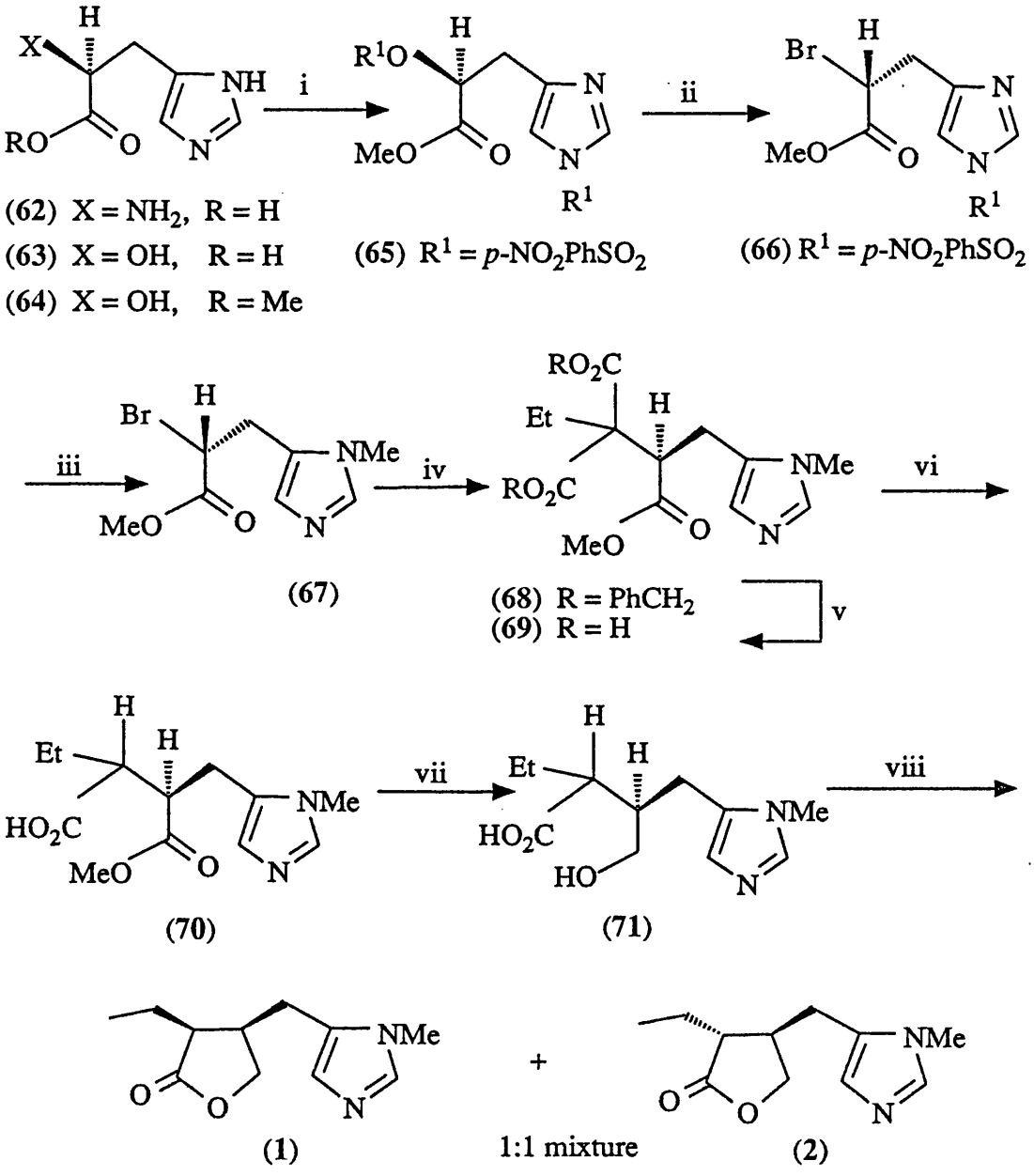


i; $(Imid)_2$ CO, ii; MeI,
iii; HCl.

Scheme 12.

bearing the sulphonate group was achieved using lithium bromide. Methylation of the sulphonamide (66) with Meerwein's salt afforded the *N*-methylimidazole

(67). Next, this was alkylated, by treatment with the anion of dibenzyl ethylmalonate, to yield triester (68). Hydrogenolysis afforded the diacid (69), which was decarboxylated to produce the epimeric monoacids (70). Reduction with lithium borohydride and acidification of the products gave pilocarpine (1), and isopilocarpine (2) in a 1:1 ratio (Scheme 13).



i; p-NO_2PhSO_2Cl, ii; LiBr, iii; Me_3OBF_4, iv; $(RCO_2)_2CHEt$, v; H_2, Pt, vi; 140°C, vii; $LiBH_4$, viii; 2M HCl

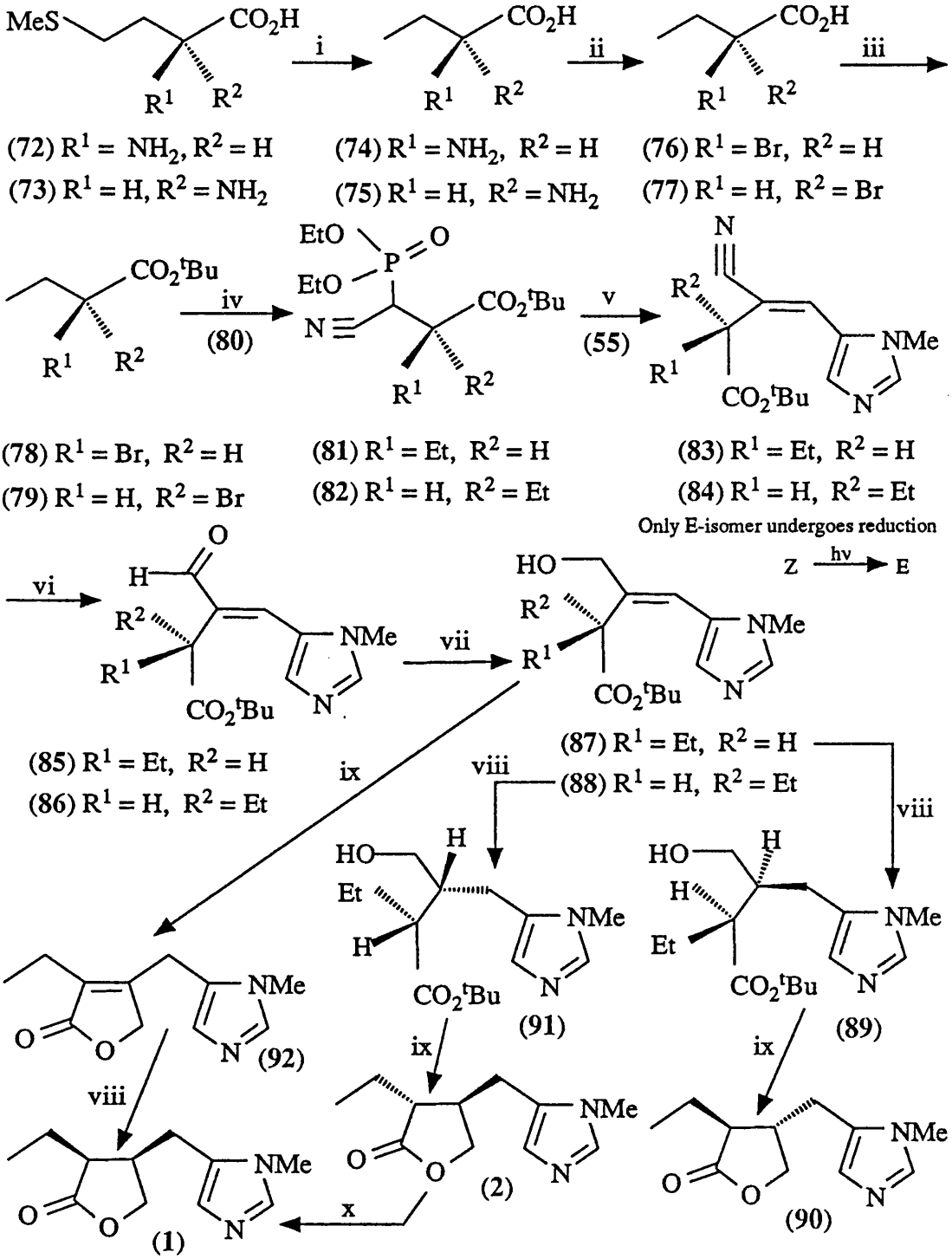
Scheme 13.

It is difficult to see why the monoacids (**70**), or suitable derivatives, were not separated; since in principle this should have avoided the lack of selectivity.

In 1986 Rapoport and Compagnone[89] described a synthesis which incorporates the use of D-methionine (**73**) as the chiral starting material. The use of this compound has the advantage that the C-3 and C-4 stereocentres of pilocarpine are accessed early (Scheme 14).

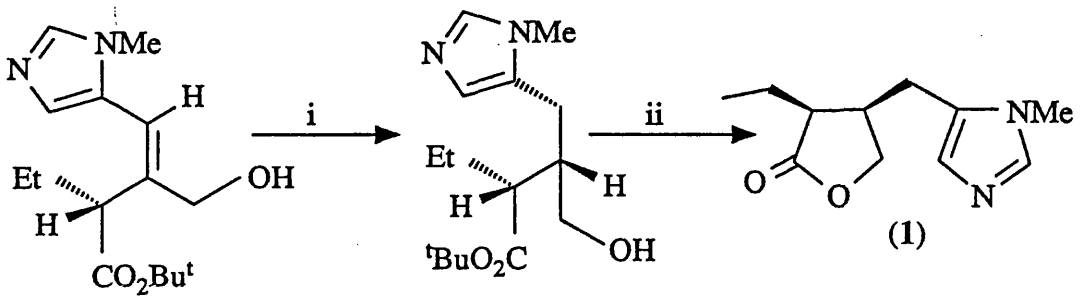
Desulphurisation of D-methionine by treatment with Raney nickel gave the amino acid (**75**), which was reacted with nitrous acid and potassium bromide to afford 2-bromobutanoic acid (**77**). Esterification produced *tert*-butanoate (**79**), which reacted with reagent (**80**) to give the phosphonate (**96**). A Horner-Emmons type reaction between this compound and 5-formyl-1-methylimidazole then gave unsaturated cyanoester (**82**). The cyanide function of this compound was then converted in two steps into the alcohol (**88**).

Rapoport and Compagnone anticipated that alcohol (**88**) would predominantly adopt the conformation shown in Scheme 15, thus catalytic *cis*-hydrogenation would afford the saturated hydroxyester (**93**). When treated with trifluoroacetic acid, this compound should give pilocarpine (**1**). However, the actual products were the hydroxyester (**91**) and isopilocarpine (**2**) (Scheme 14). Reaction of silylated alcohol (**88**) also led to hydrogenation in the same sense as for the free alcohol; indicating that hydrogen bonding was not involved in stabilising the relevant conformation. Rapoport and Compagnone concluded that the observed sterospecificity resulted from spatial demands arising from the steric bulk of the *tert*-butyl ester grouping. The result was that epimerisation was required to complete the synthesis of pilocarpine (**1**).



i; Raney Ni, ii; $NaNO_2$, KBr, H^+, iii; isobutylene, H_2SO_4, iv $NCCH_2PO(OEt)_2$ = (80), v; KH, 1-methyl-5-formyli midazole = (55), vi; Raney Ni, $NaH_2PO(OEt)_2$, vii; $CeCl_3$, $NaBH_4$, viii; Pd, C, H_2, ix; TFA, x; epimerisation.

Scheme 14.



(88)
Conformation expected by Rapoport and Compagnone

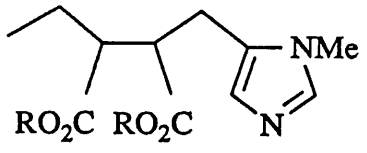
(93)
Anticipated product

i; Pd, C, H_2, ii; CF_3CO_2H

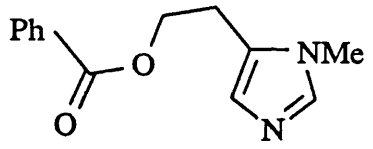
Scheme 15.

1·8 Analogues of Pilocarpine.

With such an important biological profile, it is obvious that a search for analogues of pilocarpine would be actively pursued.[90] As early as 1912, Jowett[91] synthesised the imidazoles (94) and (95) and found that they were inactive. In fact, later work on ring-opened analogues showed that all had little or no



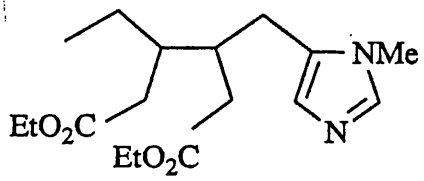
(94)



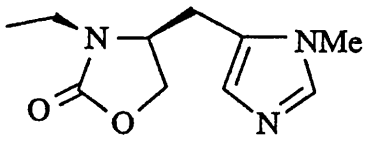
(95)

muscarinic activity.[92] Of all the analogues made to date, those containing the lactone show the greatest effect.

Mutschle and Woo[93] have produced a ring opened derivative (96), which shows only marginal activity when compared with recent cyclic analogues such as the oxazolidinone (97) produced by Rapoport.[94] This has comparable activity to pilocarpine itself.

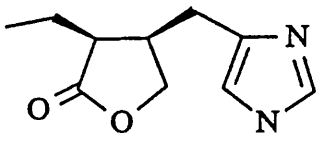


(96)

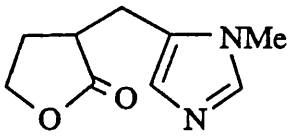


(97)

The analogue of pilocarpine (**98**) having an *N*-methyl group at the 3-position[95] is inactive. Loss of activity also occurs if the methylimidazolyl[96] side chain is relocated to C-3 of the lactone ring, as in compound (**99**). Similarly, omission of the lactone ring, or its presence in ring-opened form,[97] causes inactivity. Conversely, removal of the imidazole group does not have such a profound effect.

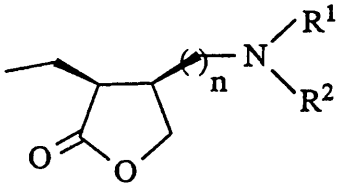


(98)

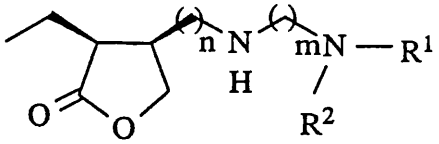


(99)

Hanssen[98] found that only tertiary amines (**100**) and (**102**) possess some activity, but they were much weaker parasympathomimetics than pilocarpine.



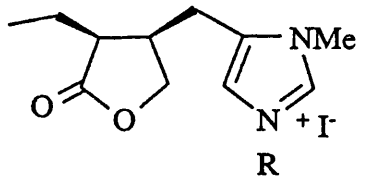
(**100**) R^1 = Me, R^2 = Me
(**101**) R^1 = R^2 = Et
} n = 1, 2



(**102**) R^1 = R^2 = Me
n = 1, m = 2

Quaternisation of the imidazole unit,[99,100] by alkylation with lower alkyl halides,

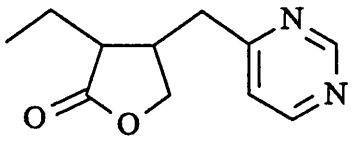
depresses muscarinic activity. This has been attributed to an increase in steric bulk, because activity is seen to fall in the series of salts from (**103**) to (**105**). Such a conclusion must remain tentative, since the ionic species are clearly much more lipophobic and may not cross cell membranes.



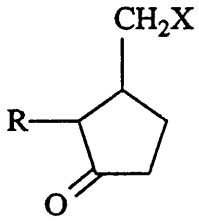
(**103**) R = Me
(**104**) R = $^{n}C_4H_9$
(**105**) R = $^{i}C_5H_{11}$
(**106**) R = *p*-BrPhCH$_2$
(**107**) R = 3,4-Cl$_2$PhCh$_2$
(**108**) R = *p*-BrPhCOCH$_2$

On the other hand, *N*-benzylation[101] promotes a change from muscarinic to anticholinergenic activity. The effect is augmented, as in the series of compounds (**106**) to (**108**), by *para*-substitution of the aryl ring with substituents such as bromine, chlorine or methyl.

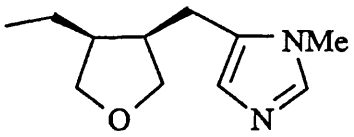
Numerous other analogues have been synthesised, all of which show little or no muscarinic activity.[102-106] Modifications have also been made to the size of the aromatic ring and the lactone.[107] The former has been replaced by a pyrimidine, or pyridine, system; *e.g.* (**109**). Interestingly, of these compounds, only 4-pyrimidyl derivative (**109**) shows any activity. The lactone has also been substituted by the cyclopentanone unit, as in the series (**110**) to (**113**).
The presence of a carbonyl group in the oxygenated ring also seems to be necessary for muscarinic action, since the tetrahydrofuran[108] (**114**) has a hypertensive effect. When it was administered intravenously to mammals, rapid cardiac arrest occurred due to a fall in blood pressure.
Interestingly, the lactams[108] (**115**) (R = H, Me) also cause hypertension - which cannot be modified by the administration of atropine. It therefore appears that the



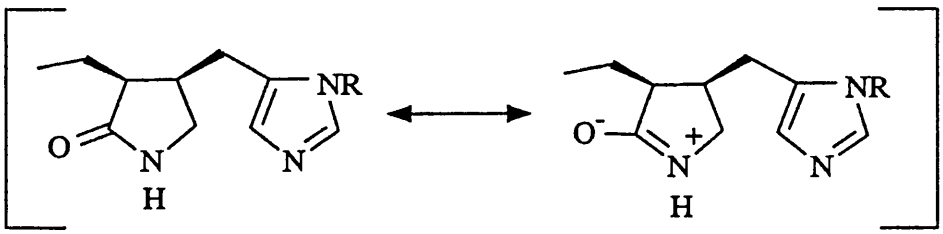
(109)



(110) R = H, X = 2-pyridyl
(111) R = Et, X = 2-pyridyl
(112) R= H, X = 4-pyridyl
(113) R = Et, X = 4-pyridyl



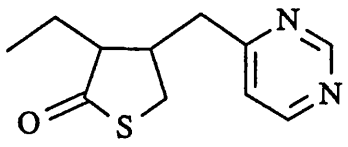
(114)



(115)

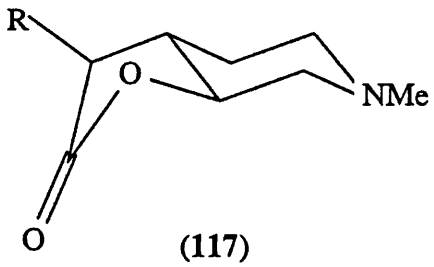
extent of electron depletion at the carbonyl carbon atom is an important factor. Similarly, the thio analogues,[109] *e.g.* thiolactone (**116**), of the pyrimidyl compounds are inactive. Inactivity was thought to arise from sulphur being less electronegative than oxygen, and thus reducing binding to the receptor. The increased C-S-C bond angle, which might lead to a distortion in the lactone ring size, may also reduce binding through steric hindrance.

Attempts have been made to prepare conformationally restricted analogues[110] such as (**117**). These would provide more information about the structural



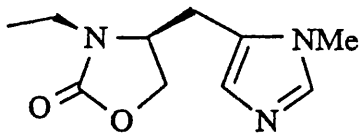
(116)

requirements for pilocarpine's muscarinic activity. To date, all such efforts have failed.



(117)

One may conclude that the topology of the pilocarpine molecule seems to fit very precisely into the muscarinic receptor. Thus, only very closely related compounds, such as the oxazolidinone[94,111] derivative (97), show comparable activity. The most recent analogue to be reported in the literature[111] is a cyclic urea (118), but its activity has not yet been determined.



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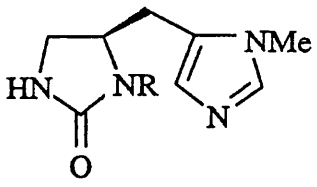


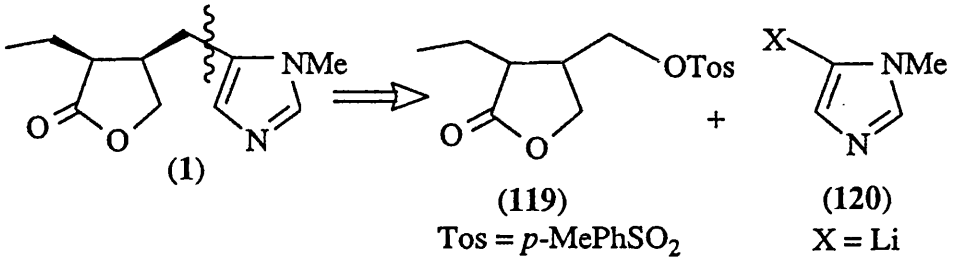
(118) R = Et or ^{t}Bu

1·9 Aims of the Research.

The physiological activity of pilocarpine[5] has long been known, and has resulted in a gradual depletion of the natural supply. Recently, resources have been almost exhausted and so a new asymmetric preparation is required. No existing approach

to this alkaloid is completely asymmetric; so our intention was to develop a short, enantioselective, synthesis of pilocarpine.

In approaching this goal, we considered the disconnection shown in Scheme 16 - which outlines our first retrosynthetic approach to pilocarpine. The attraction of



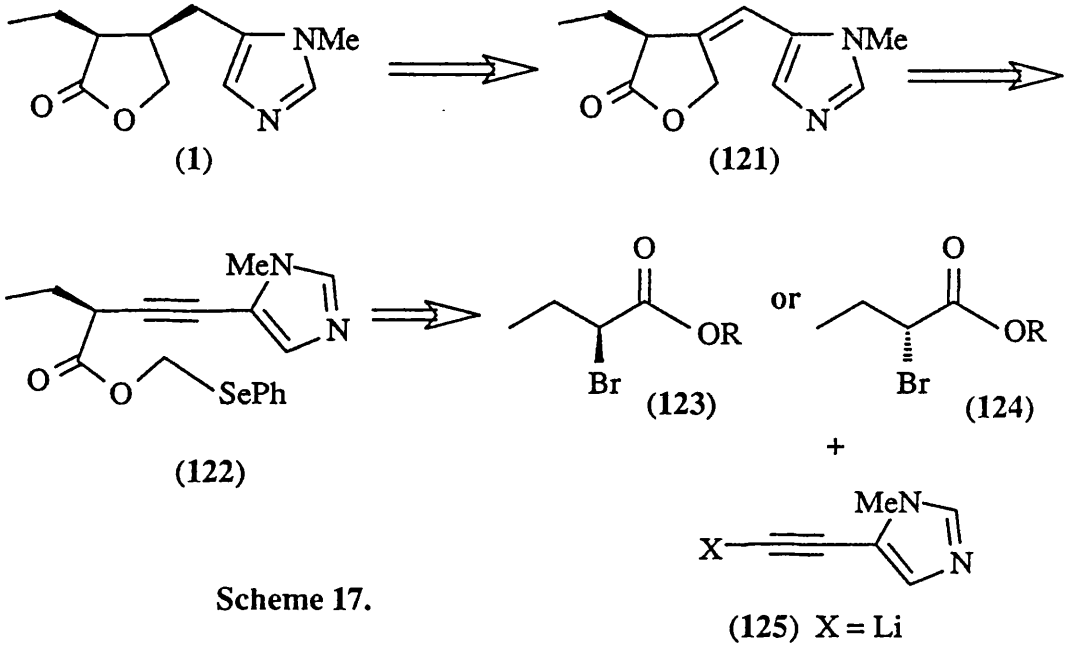
Scheme 16.

this route is its potentially facile access to the target molecule. Both key intermediates, the lactone (**119**) and imidazoles (**120**), X = H and X = Hal, are known,[112,113] so we would rapidly be able to address the key-step of coupling 5-lithiated *N*-methylimidazole with 3-(toluenesulphonyloxymethyl)butanolide; as detailed in Chapter 2.

However, for the synthesis to be asymmetric, chirality would need to be preserved at the centre α- to the carbonyl group of lactone (**119**). Unfortunately, the conditions reported[113,114a] for lithiation of imidazole (**120**) are extremely basic, and metallation is required to enable the key reaction of this synthetic approach. We therefore realised the necessity of investigating milder conditions, and recognised that we might still be unable to prevent a degree of racemisation. Nevertheless, we felt that the simplicity of this approach, if successful, would justify the work involved.

Our reservations about the methodology depicted in Scheme 16 prompted a consideration of alternative disconnections. We required an approach which

would minimise the risk of racemisation, addressing this issue early on. Therefore the exclusive use of mild conditions would be required towards the end of the synthesis. Furthermore, we required a much greater degree of stereochemical control during those later stages. Our second strategy, outlined in Scheme 17 and elaborated in Chapter 3, takes account of these considerations.



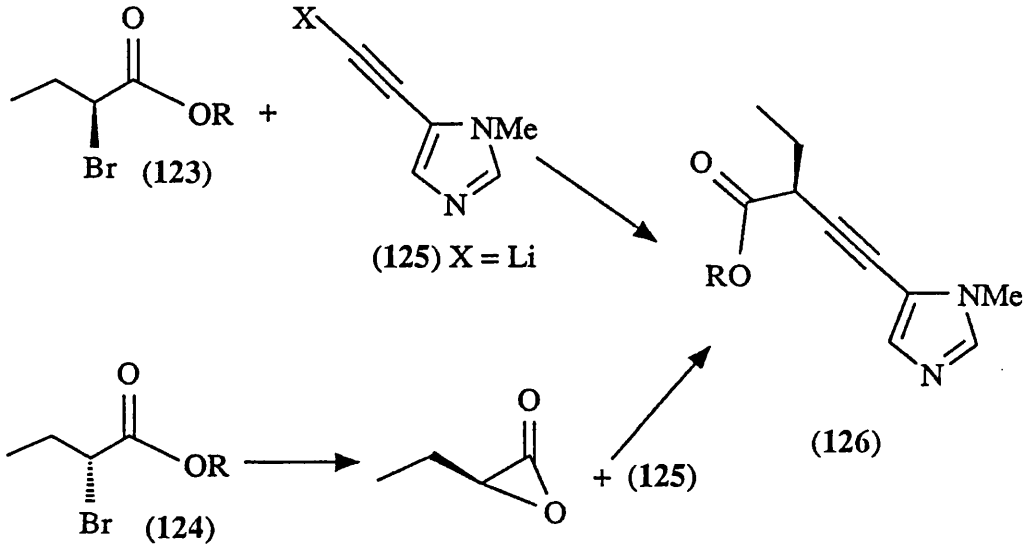
Scheme 17.

The key step is a selenide-mediated lactonisation onto an alkyne, which proceeds *via* a radical mechanism. The ring-closure is of the 5-exo dig type and is favoured by Baldwin's rules;[115] similar reactions have been achieved by Bachi and Bosch.[116a]

Successful cyclisation would result in an exocyclic double bond (the only structural feature differing from pilocarpine) α- to the chiral centre of lactone (**121**). It seemed probable that subsequent hydrogenation would afford a high degree of enantioselectivity. We expected approach of the catalyst to be governed by the stereochemistry of the ethyl group adjacent to the alkene. If so, this reduction would induce the desired stereochemistry at the second asymmetric

centre in pilocarpine, and complete our chiral synthesis.

The only relatively harsh conditions, involving a chiral substrate, are involved in the coupling of bromoester (123) or (124) with the lithiated alkyne (125). Not only did we anticipate the conditions of this reaction to be controllable, but the reaction occurs early in the sequence. It is known[117] that there are two possible mechanisms for such a reaction, depending upon the conditions employed, as shown in Scheme 18. At high concentrations of nucleophile, the reaction would



Scheme 18.

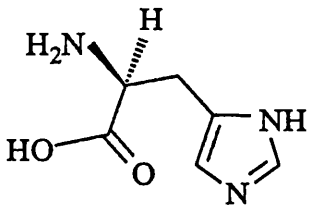
proceed by direct SN2 attack at the bromide centre. However, with a lower presence of lithiated alkene (which should also minimise the chance of racemisation), anchimeric assistance by the ester function occurs. The effect of these successive nucleophilic inversions is that the reaction proceeds with overall retention of stereochemistry. Therefore, the choice of conditions involved will determine the use of (S)-bromoester (123) - which can be made from (S)-methionine - or (R) bromoester (124), which is available from (R)-methionine.[89]

CHAPTER 2

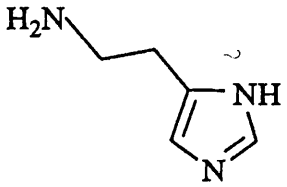
2. EARLY LACTONE CONSTRUCTION AND ATTEMPTED COUPLING REACTIONS *VIA* 5-IMIDAZOLE FUNCTIONALISATION.

2·1 Introduction.

The imidazole unit is widespread in biological molecules; being found principally in amino-acids such as histidine (62) and its decarboxylation product, histamine (127). However, imidazole alkaloids are rare; the only clinically important example being pilocarpine.



(62)

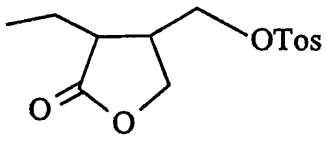


(127)

Histidine residues frequently occur in enzymes, where they appear to function as catalysts for proton-transfer processes. Imidazoles are particularly important in this context, because they can serve as both acids and bases.[118] Free imidazole is a moderately strong base, pK_a 7·0, and a weak acid, pK_a 14·5.

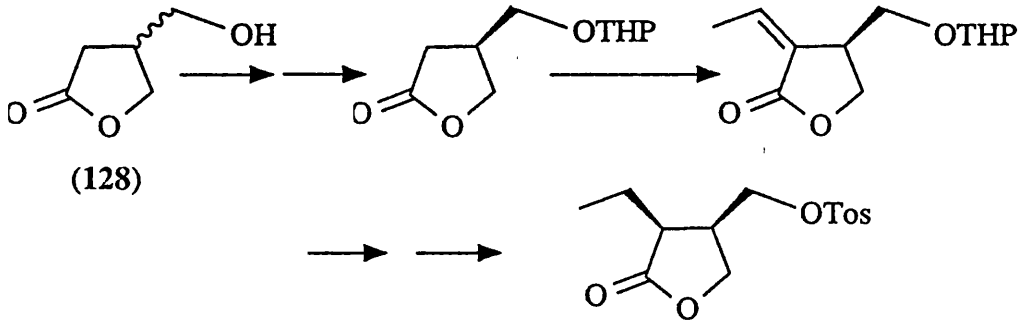
It has been shown[119] that the most acidic proton of the imidazole molecule is at C-2. Despite the higher acidity of H-2, in our work it was important to achieve selective 5-functionalisation of the imidazole - otherwise difficulty in separating the resultant isomers was likely. Therefore, the necessity of protecting the 2-position was anticipated.

Considering access to the butanolide (119), shown as a retrosynthesis in Scheme 16 of Chapter 1, we considered the adoption of a procedure due to Mori and



(119)

Kazusuke[112] and modified by Tocanne and Asselineau.[120] In this work it had been shown that 3-hydroxymethylbutanolide (128) could easily be prepared from diethyl succinate; see Schemes 19 and 20. The tosylate (133) appeared to be a good substrate to test the coupling reaction outlined in Scheme 16, and a simple modification would afford the lactone (119); *i.e.* resolution, vinylation and catalytic reduction. There was also the second option of delaying vinylation, α- to the carbonyl function, until after the coupling reaction had occurred. This could be advantageous, since no easily racemisable chiral centre would be present during the reaction with lithiated species (120).



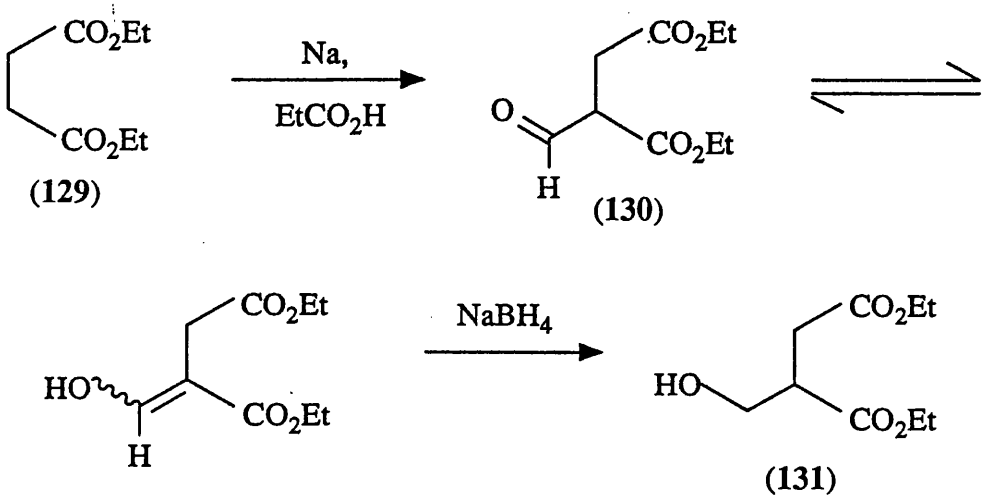
(128)

THP = 2-tetrahydropyranyl

(119)

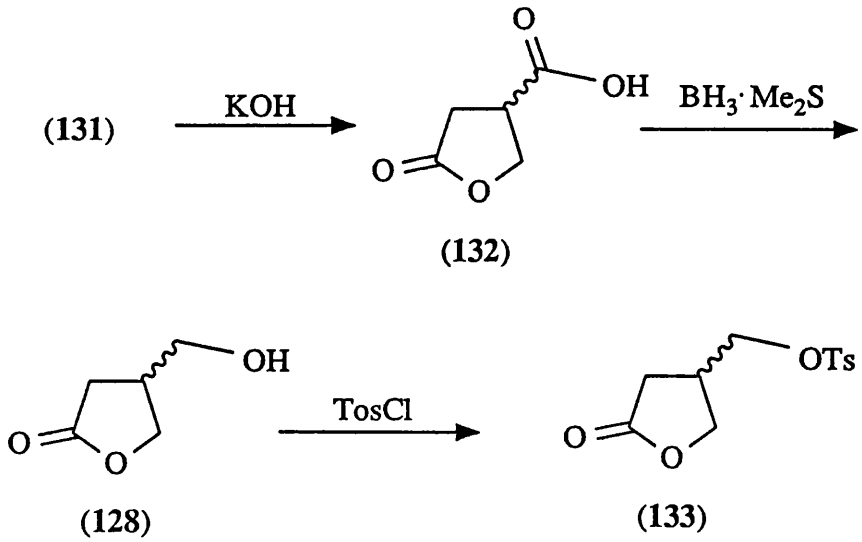
In Mori's synthesis it was noted that a racemic mixture results at the paraconic acid (132) stage of the preparation of the butanolide. Resolution can be achieved with (R)-(+)-α-phenethylamine, affording a salt which, on filtration, gives optically pure (R)-paraconic acid.

Knowing acid (132) could be resolved relatively easily, we chose to test our methodology on the racemate in the first instance. Should our racemic synthesis



Scheme 19.

be successful, the use of chiral materials would test the implementation as a stereospecific route to pilocarpine. Reduction of paraconic acid would give us the corresponding alcohol (**128**), and reaction with toluenesulphonyl chloride should yield the sulphonate (**133**) (Scheme 20). Access to the imidazole (**120**) was not expected to be a problem; see Scheme 16 in Chapter 1.

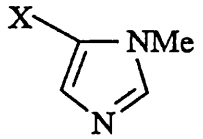


Tos = *p*-$MePhSO_2$

Scheme 20.

2·2 Formation of

4-Toluenesulphonyloxymethyl-1,2,3,4-tetrahydrofuran-2-one (133).



(120)
X = Li

We used Tocanne and Ansselineau's synthesis[120] of the butanolide (**128**), and formylated diethyl succinate (**129**) using ethyl formate and two equivalents of sodium metal. This reaction resulted in the formation of aldehyde (**130**), which is a colourless oil, after purification by distillation (see Scheme 20).

^{1}H n.m.r. spectroscopy showed this product is a tautomeric mixture in which the enol form predominates over the keto in a ratio of 2:3. The hydroxyl proton of the enol resonates as a doublet at δ 11·30, and this proton is exchanged by treatment with D_2O. A second doublet, at δ 7·00, is the signal of the α-allylic proton which becomes a singlet after the D_2O addition. The relative complexity of the n.m.r. spectrum is due to the presence of a chiral centre α- to the formyl group, thus the methylene protons are nonequivalent and exhibit geminal coupling (J = 12 Hz) and vicinal coupling (J = 6 Hz).

Reduction of aldehyde[121] (**130**) with sodium borohydride in 98% ethanol was slower than expected, and this probably reflects the fact that the equilibrium favours the enol form of the compound. Indeed, in the alkaline media, the enolate anion could be present. Given sufficient reaction time, however, the yield of the alcohol (**131**) obtained was a respectable 80-90%. We formed the acid (**132**) by refluxing the alcohol (**131**) in 2M aqueous potassium hydroxide, which effected both hydrolysis and lactonisation. Crystallisation from chloroform gave (±)-paraconic acid (**132**). It was noted that reactions on quantities of the diester

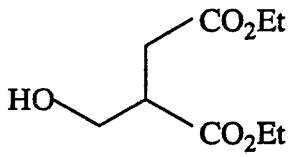
(131) greater than 5 g were not practical. The initial product was a sticky gum, which could not be readily purified. Below this amount, however, the reaction proceeded in 60-70% yield to afford a colourless crystalline product. Physical data were as anticipated; for example, the resonances of the protons of the methylene groups of acid (132), again showed geminal coupling - as befits their nonequivalence.

Treatment of paraconic acid (132) with borane dimethylsulphide[122] gave exclusively 3-hydroxymethylbutanolide (128) - although the yields were not particularly good (32-38%). This was disappointing and, although our efforts were not exhaustive, we did not improve upon the conditions and results quoted in the literature.

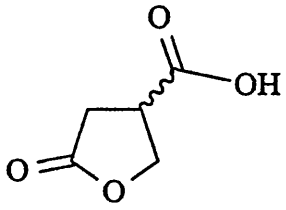
In an attempt to overcome the low yield of this reaction, we sought to prepare the lactone (128) by a shorter route which a Japanese group[123] have recently reported. Three equivalents of sodium borohydride were used to reduce the aldehyde (130). It was stated by these authors that this excess of reagent also results in the reduction of one of the ester groups. They suggest that there is a neighbouring group effect from the hydroxymethyl group, which arises from initial reduction of the aldehyde. A borohydride species, bonded to the oxygen atom of the incipient hydroxyl function, then delivers hydride regiospecifically to one of the ester groups. Sodium borohydride is normally insufficiently potent, under the reaction conditions used, to reduce an ester group.

Attempts to repeat this work by the author were only marginally successful, and gave inconsistent results. However, it became clear from the data we obtained that at least three products were produced - as a direct result of incomplete reduction. Because of the basic nature of the reaction mixture, we suspected that

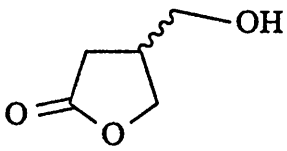
one of the products was paraconic acid. This was confirmed by mass spectrometry and by ^1H n.m.r. spectroscopy, and in addition, the other two products were identified as the hydroxydiester (131) and the diol ester (134).



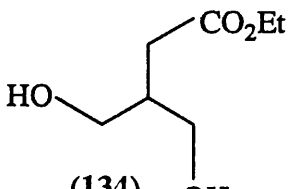
(131)



(132)



(128)

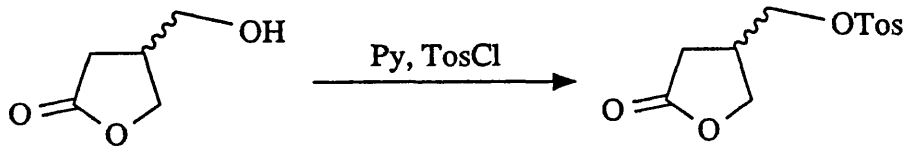


(134)

We discovered that attempts to purify the lactone (128) by chromatography over silica led to large losses of material. We suspected that the relatively high retention time of this compound extended its residence time on the silica long enough to catalyse an appreciable degree of lactone ring-opening. This suggestion is supported by the fact that the chromatographic purification of the silyl ether[124] of the alcohol (128) was much more efficient. The ether is much less polar and was rapidly eluted from the stationary phase, which improved yields by 20%.

Having obtained workable quantities of the lactone (128), we were able to attempt tosylation of its hydroxyl function. Thus a reaction of the alcohol (128) with toluenesulphonyl chloride, in pyridine solvent,[125] afforded the tosylate (133), but only in 10% yield. Since tosylation activates hydroxyl groups by providing a good "leaving" unit, this result is perhaps not surprising. Indeed, there are many literature examples of loss of product[125] during *O*-tosylation of alcohols. We noted that all the starting material was consumed during our

reaction but were unable to determine the identity of the by products.



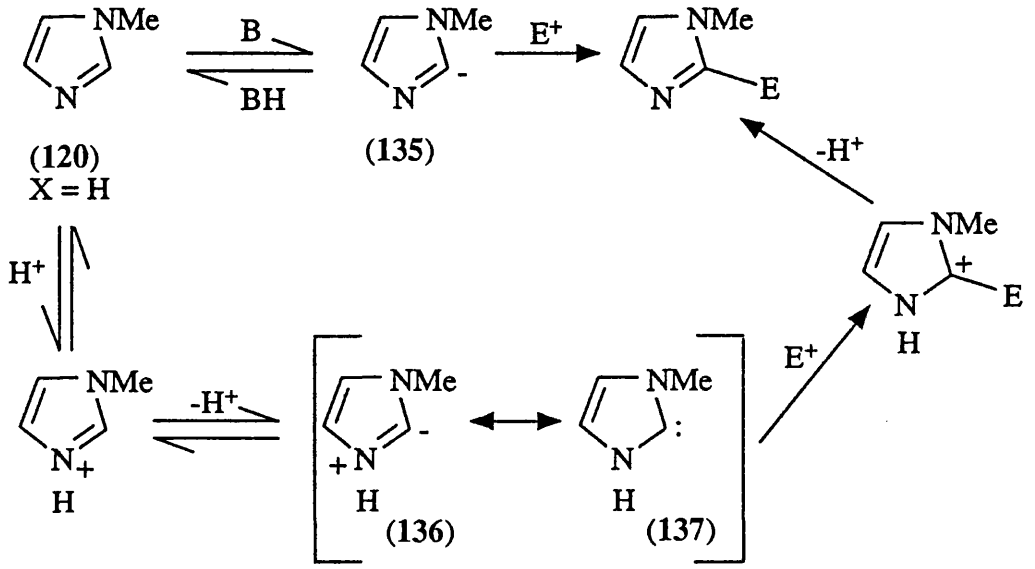
(128) Py = pyridine Tos = *p*-MePhSO$_2$ (133)

We now felt it prudent to investigate the regiospecificity of 5-lithiation of 1-methyl-5-imidazole (**120**), X = H or X = Hal. We were also concerned to explore the nucleophilicity of the lithiated species, by the use of model chemistry. Further effort in optimising the synthesis of the tosylate (**133**) would seem to be wasted were the coupling of imidazole (**120**), X = Li, found to be inefficient.

2·3 Functionalisation of the 5-position of 1-methylimidazole.

We were aware of the reports of several groups;[126,127] that direct 5-lithiation of 1-methylimidazole, to give exclusively one isomer, is almost impossible. There are two problems; the pronounced acidity of the imidazole proton at C-2, which prompts preferential reaction at this site. Also, where this is not an issue, a 4(5) mixture often results, which is difficult to separate.

It is well known[128] that proton abstraction from C-2 of the imidazole ring is a facile process and occurs 10^4-10^5 times faster than the exchange of either H-4 or H-5,[129,130] Scheme 21. Reactivity at C-2 towards electrophiles has also been suggested to involve the initial formation of a ylide species, arising from deprotonation of the protonated imidazole. Possible resonance stabilisation of this ylide by a carbene form has been proposed by Cohen and co-workers,[130] although the nature of the carbene has not been demonstrated. The stability of the anion, it is argued, is due to the inductive influences of the two adjacent nitrogens, which



Scheme 21.

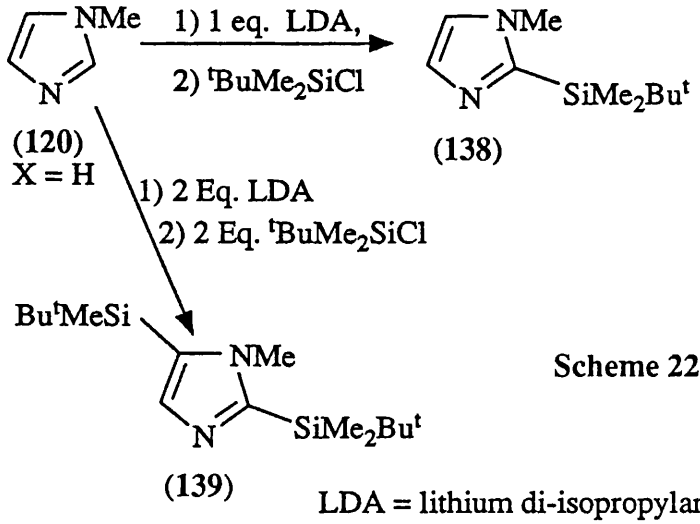
also weaken the C(2) bond in the first instance.

There are two approaches which overcome the undesired reactivity of C-2. Firstly, it should be possible to protect this site prior to attempting deprotonation at C-5. Secondly, an imidazole synthesis may be performed which incorporates functionality at the desired site *before* completion of the imidazole skeleton. For example, preparation of a 5-halogenated 1-methylimidazole, followed by metal-halogen exchange, might be appropriate for our requirements.

It has been reported elsewhere[131] that H-5 is the next most acidic proton.[132] Therefore, after blocking the 2-position[8] of a *N*-substituted imidazole, the addition of a second equivalent of base generally produces an anion at C-5.[119] It was hoped that 1-methylimidazole would behave in this way, and thus permit direct functionalisation of the 5-position. Other workers have blocked the 2- and 4-imidazole positions,[133] using a wide variety of functional groups including thiophenyl, and trimethylsilyl.[134] Iddon,[113] has reviewed this subject.

Germane to our strategy was the ease of deprotection at C-2. Unfortunately, inappropriately forcing conditions are often required to achieve deprotection of many potentially useful groups;[131] but Iddon has recently shown that 1-methyl-2-(trimethylsilyl)imidazole can be prepared,[114] albeit in low yield , and that the silyl group can subsequently be displaced easily. We selected the ^{t}butyldimethylsilyl group, because its derivatives are generally more stable than the trimethyl silyl analogues, and attempted to form the *C*-silylimidazole (139)(Scheme 22).

Lithium di-isopropylamide (LDA) was formed at 0 °C, and cooled to -78 °C, after 90 minutes. A THF solution of 1-methylimidazole was added slowly, and stirred for a further 90 minutes, before *tert*-butyldimethylsilyl chloride in THF was added. It was observed that two compounds formed in a 4:1 ratio. The major



Scheme 22.

LDA = lithium di-isopropylamide

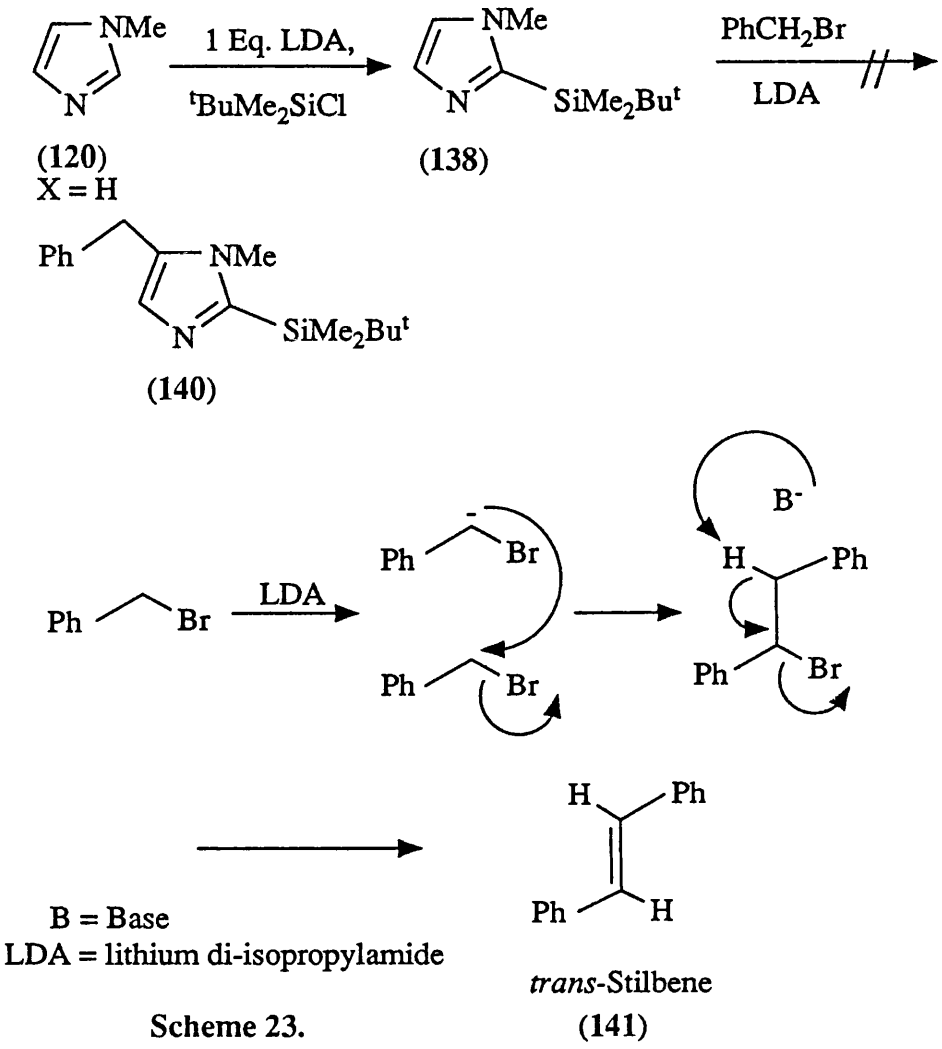
component was the 2-silylated methylimidazole (138), and the minor was the 2,5-disilylmethylimidazole (139). This result confirms that H-5 is the second most acidic proton in the molecule, as expected.

Repetition of the experiment, using two equivalents of lithium di-isopropylamide and 2.5 equivalents of *tert*-butyldimethylsilyl chloride, produced significantly more of the disilyl species (**139**). This particular disilyl species has not been reported elsewhere, and was found to be very unstable and hygroscopic. Overall, this was a good result since it showed that it should be possible to selectively protect C-2 and then to form the anion at C-5.

Thus the mono silyl imidazole (**138**) was prepared *in situ*, as previously, and a second equivalent of lithium di-isopropylamide was added. As a model reaction, an equivalent of benzyl bromide was then added in an attempt to produce the 5-benzyl derivative (**141**). However a clean reaction was not observed and t.l.c. analysis (1:4 ethyl acetate-light petroleum (b.p. 60——80 °C) showed that a total of six compounds were formed. The major component of the mixture had the same R_f as benzyl bromide. This was isolated, and characterised as *trans*-stilbene (**141**), resulting from self-condensation and dehydrohalogenation of the bromide (Scheme 23). The remaining components could not easily be identified, as only trace amounts were obtained. However, it was possible to detect the presence of a small quantity of 1-methyl-2-^{t}butyldimethylsilylimidazole (M^++1 = 197) but none of the desired product (**140**) was observed.

Thus it seems that the imidazole C-5 anion acts as a base towards benzyl bromide, rather than as a nucleophile. In this case the benzylic anion would form which then reacted with more benzyl bromide ultimately yielding stilbene. This caused us to consider that if the tosylate (**133**) was used as the electrophile, these conditions would ionise the rather more acidic protons α- to the lactone carbonyl group, and thus negate our plans.

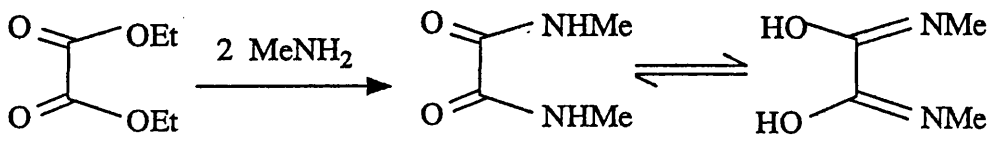
We next sought to investigate the possibilities of metal-halogen exchange at



Scheme 23.

C-5.[114a] The required 1-methyl-5-chloroimidazole is fairly accessible, and both the lithiated imidazole and the formation of the corresponding Grignard reagent seemed practicable.

A general procedure has been reported[135-139] for the synthesis of 1-methyl-5-haloimidazoles, using diethyl oxalate (142) as starting material.[135] *N,N*-dimethyloxamide is generated on addition of methylamine to diethyl oxalate (142), giving excellent (99%) yields of *N,N*-dimethyloxamide (143).[140] This compound was then heated with phosphorus pentachloride to give 1-methyl-5-chloroimidazole (120), X = Cl.

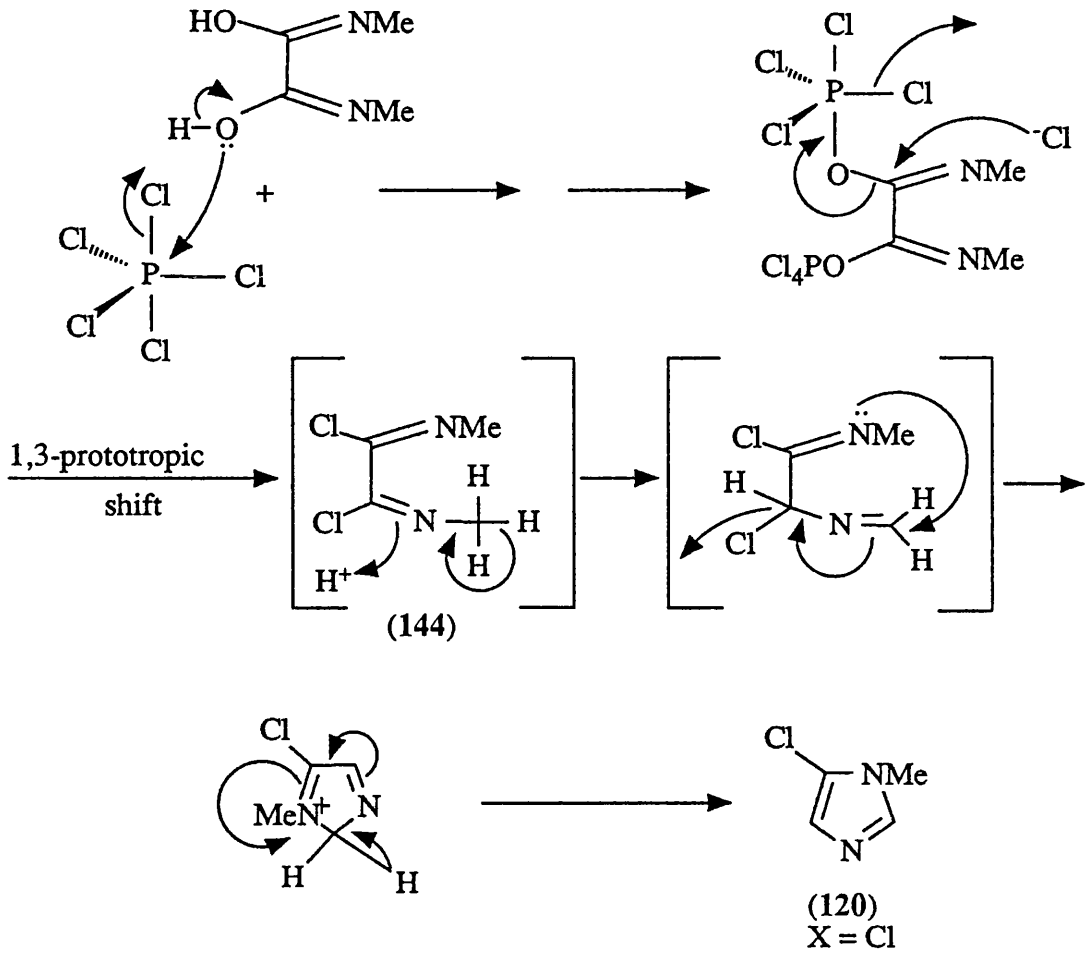


(142) (143)

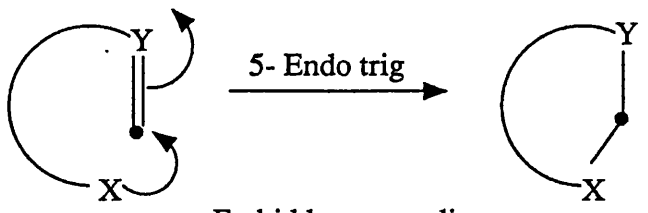
Godefroi and his co-workers[135] suggested a mechanism for this reaction involving a di-imine (**144**) as an intermediate. This, they believe, undergoes a 1,3-hydride shift, followed by cyclisation to imidazole (**120**), X = Cl, through what is a 5-endo trig reaction; not favoured, according to Baldwin's rules.[115] The concept of a hydride shift is implausible, under the acidic conditions, and is more likely to be a prototropic isomerisation. Nevertheless, the observed product does indicate that a disfavoured cyclisation does occur (Scheme 24). Baldwin's rules are predominantly based on considerations of topology and the accessibility of suitable transition states at "low" temperatures. However, Godefroi's reaction conditions require heat and so less favourable geometric arrangements are possible. In addition, entropic factors also favour the ring-closure, elimination of hydrogen chloride serves to increase the disorder of the system.

The same procedure was also applied to the synthesis of the 5-bromo derivative. The major difficulty with such preparations is the solubility of the product in water. An aqueous base work-up is necessary, and this has a significant impact on the yields which are only 45-50%. According to Kochergin,[141] better yields of the corresponding chloro derivative may be obtained by the use of phosphorus oxychloride in place of phosphorus pentachloride. However, we were unable to duplicate this result.

We therefore chose to modify the conditions by combining the methods of



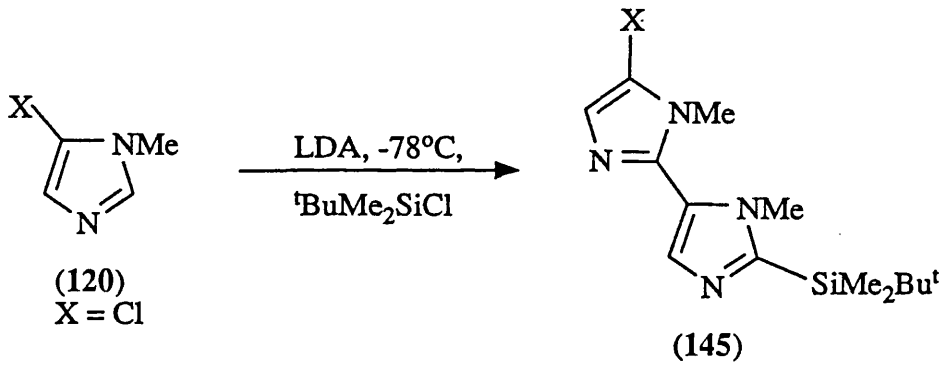
Scheme 24.



Forbidden, according
to Baldwins' Rules.

Godt[136] and Kochergin[141] to our best advantage by heating phosphorus pentachloride with *N,N*-dimethyloxamide (**144**). Extraction still tended to be a problem as a result of the water solubility of the halo compounds. Evidence of formation of the 5-chloro compound (**120**), X = Cl, came directly from the ^{1}H n.m.r. chemical shifts.

Having prepared the 5-chloro compound, (120), X = Cl, we were able to determine the ease with which metal-halogen exchange could be achieved. Initially, we used one equivalent of lithium di-isopropylamide as base, in an attempt to form 2-lithiated 1-methyl-5-chloroimidazole (120), X = Li. After 2 hours at -78 °C, the reaction was quenched, with ^{t}butyldimethylsilyl chloride, and allowed to warm to room temperature. However, many components were seen to have formed; only one of which - the silylated dimer (145) - could be isolated and characterised (Scheme 25).



(120)
X = Cl

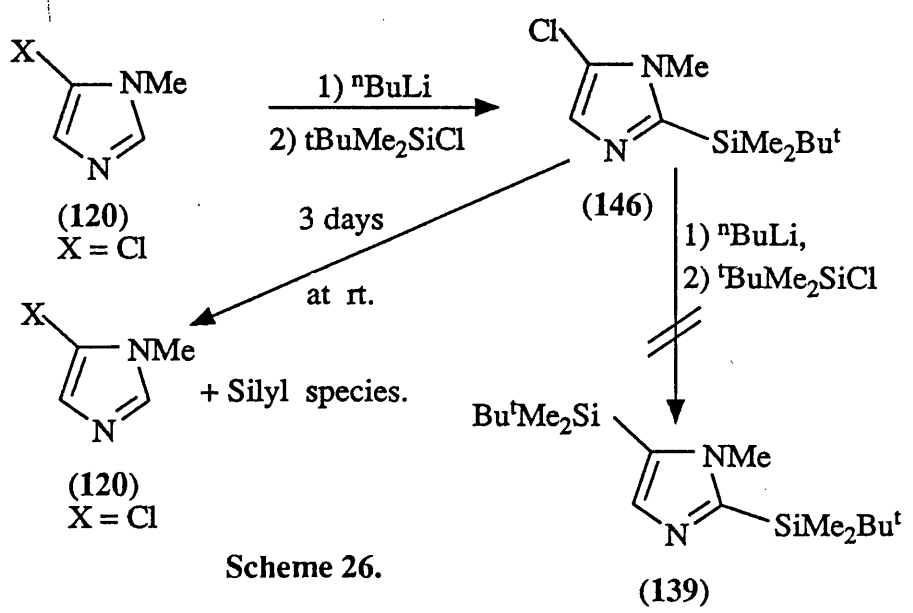
(145)

LDA = lithium di-isopropylamide

Scheme 25.

This result is in contrast to the relatively facile formation of 2-*tert*-butyldimethylsilyl-1-methylimidazole. Clearly the required anion is formed under these conditions, but it may then react with both the silylating agent and the chloroimidazole. Interestingly, when the base was changed to ^{n}butyl lithium the desired product 2-^{t}butyldimethylsilyl-5-chloro-1-methylimidazole (146) was formed and in high yield. There was no evidence for metal halogen exchange since none of the disilylated compound (139) was obtained. The reasons for this are obscure.[113] (Scheme 26).

Chromatography over silica gel afforded the silyl compound (146), together with a quantity of starting material - which had been absent in the crude reaction

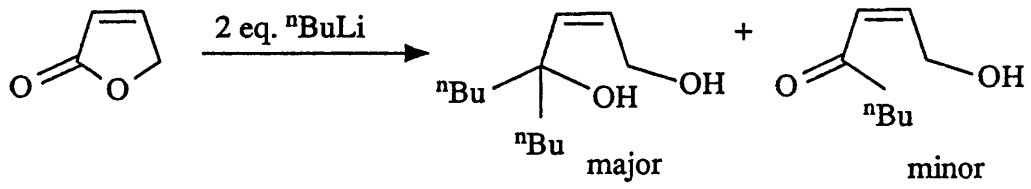


Scheme 26.

mixture.[142] It is thought that partial hydrolysis may have occurred on the silica, resulting in loss of the silyl group. This is supported by the fact that imidazole (146), when stored in contact with air at room temperature, undergoes de-silylation to afford the starting material within three days.

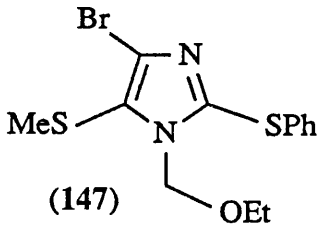
Addition of a second equivalent of ⁿbutyl lithium at -78 °C, and subsequent quenching with D_2O, did not result in incorporation of deuterium at the 5-position. We were surprised to see such complete failure of the reaction; but it is in accordance with literature reports. Five equivalents of ⁿbutyl lithium are reportedly required to facilitate metal-halogen exchange for 5-bromo-1-methylimidazole.[143] Employment of such conditions would undoubtedly lead to ring-opening of the lactone in the coupling step. Benetti *et al*[144] have shown that treatment of lactones with an excess of lithium aryl species leads to high yields of open-chain products, and we confirmed that an analogous reaction occurs with 2(5H)-furanone and ⁿbutyl lithium, as shown in Scheme 27.

Iddon[131,145] has reported that metal-halogen exchange can be achieved easily if



Scheme 27.

all the remaining positions on the imidazole ring have been functionalised, as in the case of 4-bromo-1-ethoxymethyl-5-methylthio-2-phenylthioimidazole (**147**). He also reports[145] that treatment of 4(5)bromoimidazole with ⁿbutyl lithium at

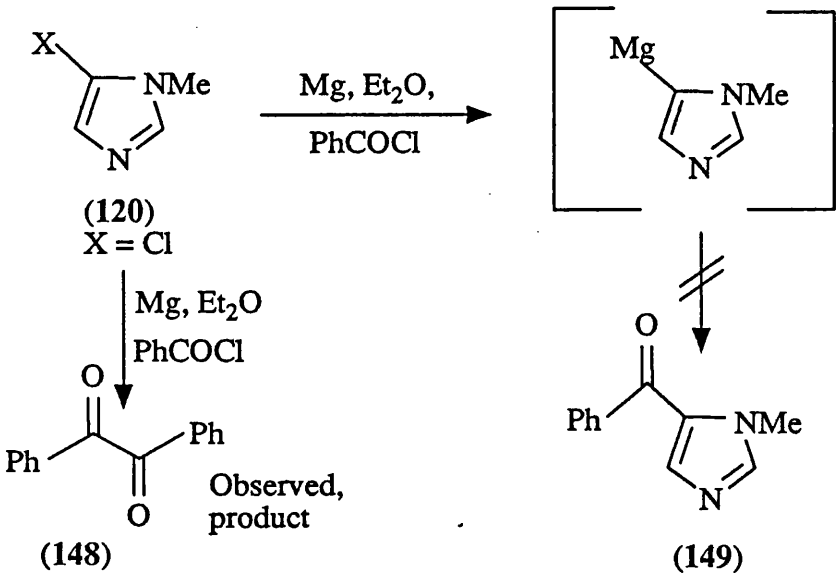


(**147**)

-70 °C and quenching with dimethylsulphate gives methylation at the 1 and 4 positions.

We felt our failure to induce metal-halogen exchange using the silylchloroimidazole (**146**) could be attributed to the strength of the C-Cl bond. The process appears to be more facile with the bromide or iodide. However, attempts to prepare the bromo compound (120) X = Br (by an analogous route) led to a small quantity of product and higher oligomers. These could not be fully characterised, but were tentatively thought to have the formula $(C_4N_2H_4)_n \cdot HBr$, resulting from the stepwise displacement of bromide by the imidazolyl unit. Iddon supports[145] this result and states that "attempts to exchange the bromine atoms for lithium in 1-methyl-5-bromoimidazole failed".

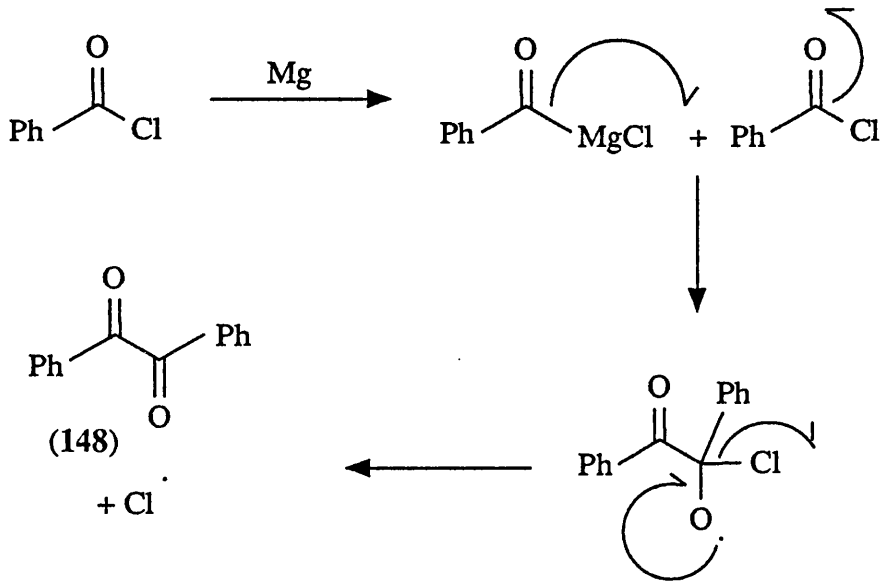
After the failure of the metal-halogen exchange reaction, we sought to investigate the reactions of the corresponding Grignard reagent, if it could be formed. In most aromatic systems Grignard compounds are readily produced from the aryl halide, and we had no reason to suspect that imidazole (**120**), X = Cl, would behave differently. We reacted imidazole (**120**), X = Cl, with magnesium metal and planned to quench it with benzoyl chloride. Indeed the Grignard reagent appeared to form easily enough, but when the ether solution was treated with benzoyl chloride only dibenzoyl was recovered. No starting material was observed, suggesting that perhaps the imidazole ring had been reduced[133] and removed on aqueous extraction (Scheme 28).



Scheme 28.

It is thought that dibenzoyl formation occurs *via* a radical mechanism, in a similar fashion to the initial stages of the pinacol reaction,[146] as proposed in Scheme 29. There is a literature precedent,[147] for an analogous reaction with lithium in place of magnesium.

The failure of the desired coupling reaction, in our model chemistry, did not



Scheme 29.

inspire us to expend further effort on this route. Instead, we turned our attention to the second retrosynthetic strategy, which is detailed in Chapter 3.

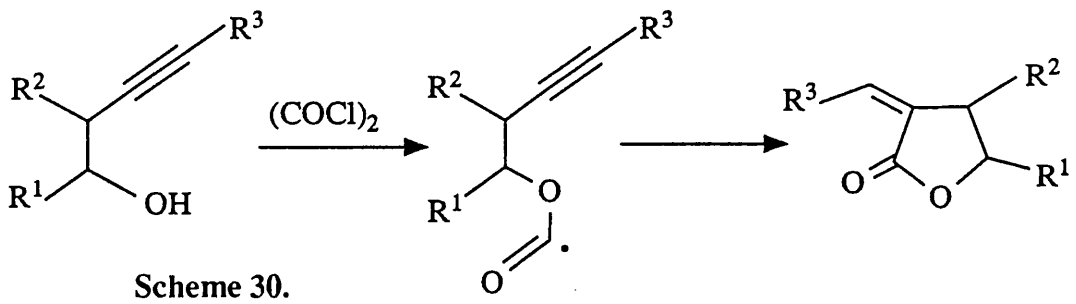
CHAPTER 3

3. CONSTRUCTION OF THE LACTONE AT A LATER STAGE.

3·1. Introduction.

As with our previous attempts, we again sought to construct the lactone ring late *en route* to pilocarpine. Many routes exist for lactonisation *via* free radical mechanisms; including intramolecular addition of alkoxythiocarbonyl free radicals to acetylenes,[148] palladium dihalide mediated closures onto acetylenes,[149] and intramolecular cyclisation of allylic propiolates mediated by stannyl radicals.[150] For a full review on lactonisation reactions involving radicals, see the paper by Surzur and Bertrand.[151]

In our study, we wished to take advantage of the selenide-mediated ring-closure onto an acetylene which is shown in the retrosynthesis outlined in Scheme 17 of section 1·9. Inspiration for this comes from an earlier report by Bachi and Bosch.[116] These authors had shown that when tributyl tin is reacted with selenocarbonate compounds a carbonyl radical is generated. This species subsequently undergoes a 5-exo dig ring-closure onto an adjacent alkyne unit, resulting in lactonisation with concomitant generation of an exocyclic double bond (Scheme 30).

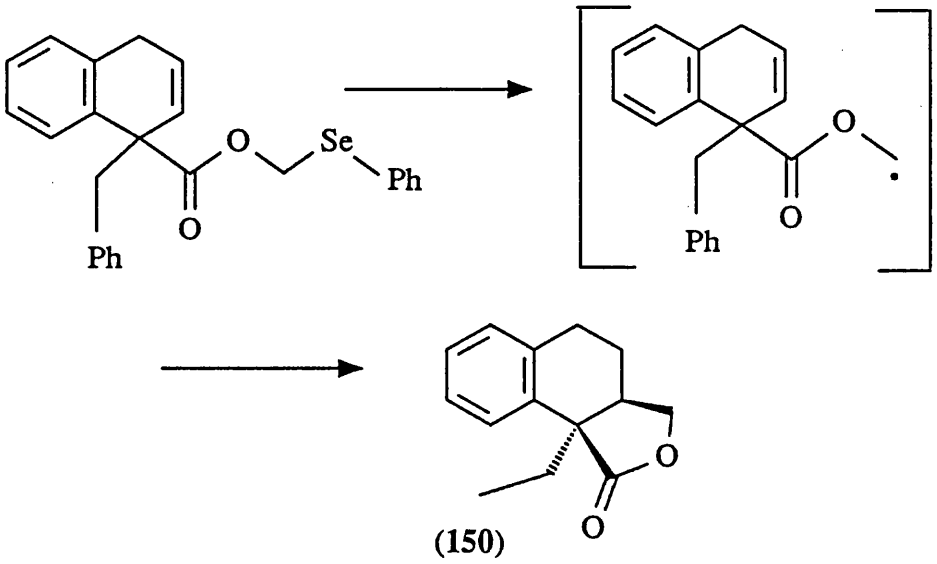


Scheme 30.

Beckwith and co-workers[153] have made use of an alkoxycarbonyl radical,

generated in a similar fashion, which undergoes an intramolecular ring-closure onto a nearby alkene bond, rather than an alkyne. The result is a comparable lactonisation process, though it occurs *via* the formation of a different carbon-carbon bond. We believe this reaction, by Beckwith and co-workers, to be the only example of the use of alkoxycarbonyl radicals to generate lactones such as (**150**). Such a reaction has not been performed using acetylenes, but there seems little reason to doubt that this should be equally successful.

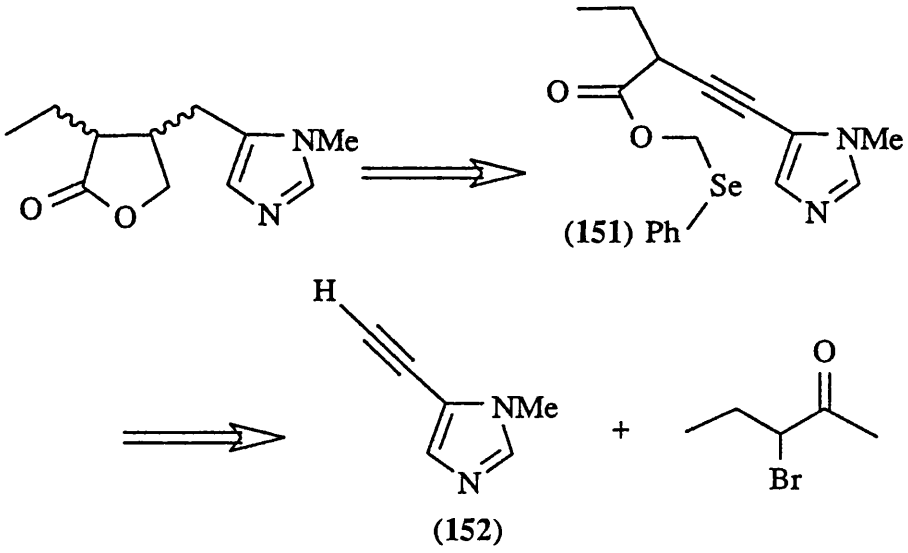
Therefore, the imidazolylalkyne (**151**) became our first key intermediate, see scheme 31. This compound should be available from the alkylation of



(**150**)

ethyl-2-bromobutanoate by the alkyne (**152**), as shown in Scheme 18 of Section 1·9. The (*R*)- and (*S*)-bromobutyric acids (**123**) and (**124**), indicated there, have already been prepared in optically pure form, from natural amino acids, by Rapoport and Compagnone.[89]

An unsuccessful synthesis of the alkyne (**152**) was first reported in 1972 by Shvartsberg *et. al.*,[154] in which they describe the product as a mixture of the desired compound and its 4-substituted isomer. Other products included the



(151)

(152)

Scheme 31.

disubstituted compounds (154) and (155), as well as triacetylenylimidazole (153). The problem with this reaction was that the initial halogenated imidazole was actually a mixture of various mono- and dihaloimidazoles; hence the variety of products shown in Figure 5.

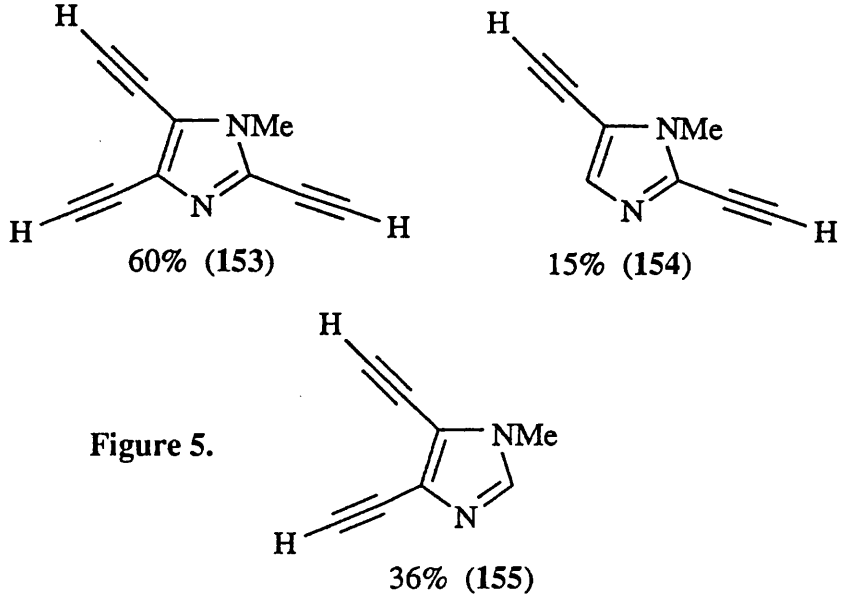
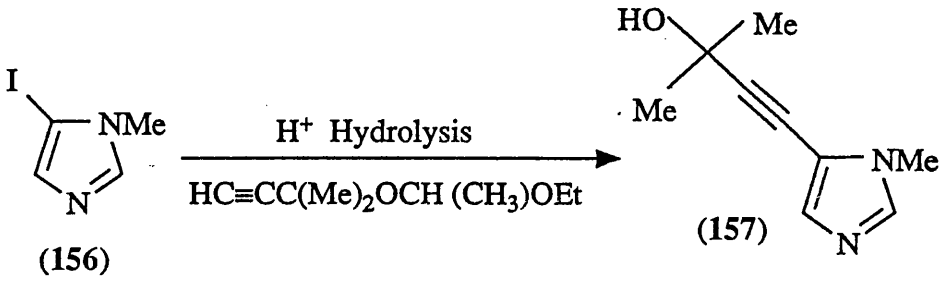
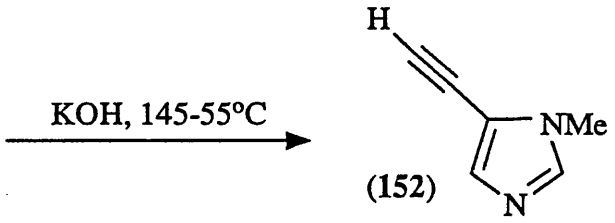


Figure 5.

No further report of 5-ethynylimidazoles appears until several years later,[155]

when the 5-isomer was prepared using the following route. This process, did not



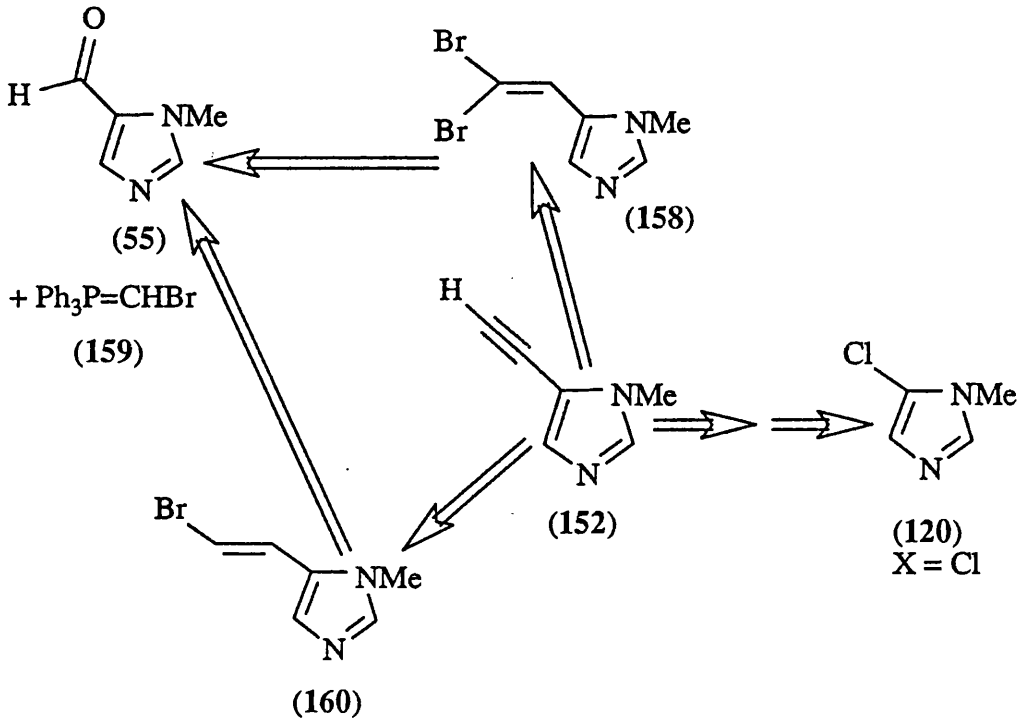


lead to a homogeneous product however, probably because the starting iodo compound (**156**) was contaminated with other isomers.

Given the lack of a suitable preparation for the alkyne (**152**), we set out to develop our own synthesis - which would be specific for the single isomer we required. It seemed likely that access to the acetylene (**152**) could be gained from the known[152,156,157] aldehyde (**55**): by either a Corey-Fuchs methinylation,[158] or *via* a Wittig reaction with the bromomethylenetriphenylphosphorane (**159**). In the later case, a bromoalkene (**160**) would be formed which could then be dehyrobrominated.[159]

3.2 Synthesis of 1-methyl-5-formylimidazole (55).

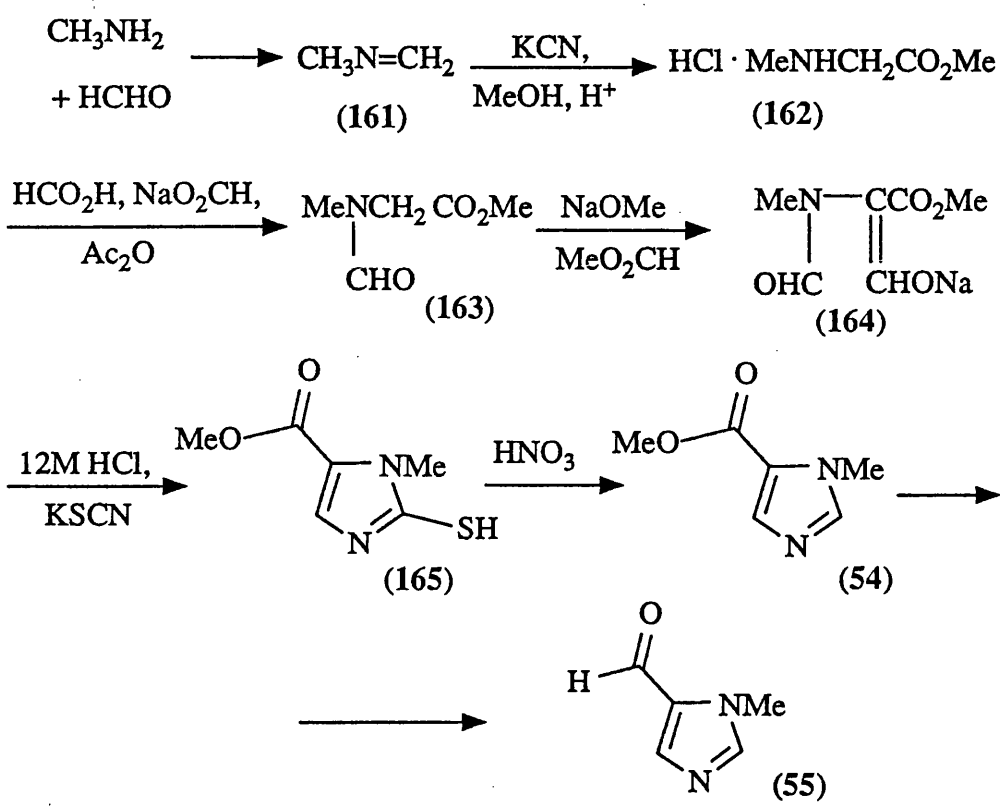
1-Methyl-5-formylimidazole (**55**) was first prepared by Hubbal and Pyman,[157] but in poor yield. Jones and Mclaughlin used a modified method, making first the ester[152] (**54**) which they subsequently converted into the aldehyde (**55**).[156] Their overall synthesis uses methylamine hydrochloride as starting material and



proceeds *via N*-substituted glycine derivatives to give 1,5-disubstituted imidazoles, as shown in Scheme 32. Our initial approach[142] to the aldehyde (55) was a repetition of Jones and Mclaughlin's preparation.

Formation of the *N*-formyl glycine ester (**163**) was achieved cleanly, but the yield was disappointingly low - mostly as a result of problems we encountered in purification of the hydrochloride (**162**). This difficulty was caused by removal of the ammonium chloride formed during solvolysis of the nitrile function in the formation of the ester (**162**). We found no suitable method for separating this salt, other than distillation of the formamide (**163**). This was only partially successful, presumably due to sublimation of the ammonium chloride.

Enolisation of ester (**163**) proceeded smoothly, and was followed by a reaction with methyl formate to give the homologated enolate (**164**). However, nucleophilic attack upon the corresponding aldehyde by potassium thiocyanate, which we had expected to be followed by cyclisation to give



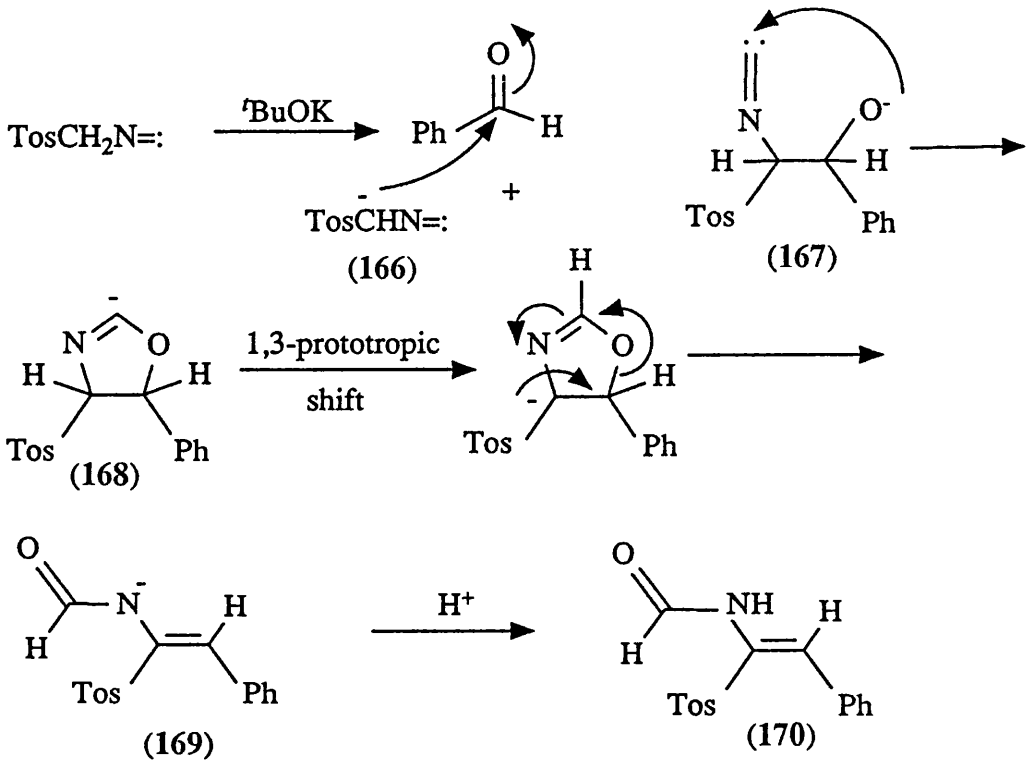
Scheme 32.

2-mercaptoimidazole (**165**), was unsuccessful. The reason for this is not clear, but all our subsequent attempts to obtain this product also failed.

We were also unhappy with this route for several other reasons; it consists of a large number of steps, many of which are low yielding, and it involves a large-scale reaction with potassium cyanide. We therefore sought an alternative approach, and noted the applicability of an imidazole synthesis developed by van Leusen *et. al.*[160,161] which involves the use of toluenesulphonylmethyl isocyanide (TosMIC). These authors had demonstrated that 5-monosubstituted imidazoles are accessible using this reagent, and thus we hoped to extend that method to the synthesis of 1-methyl-5-ethynylimidazole (**151**).

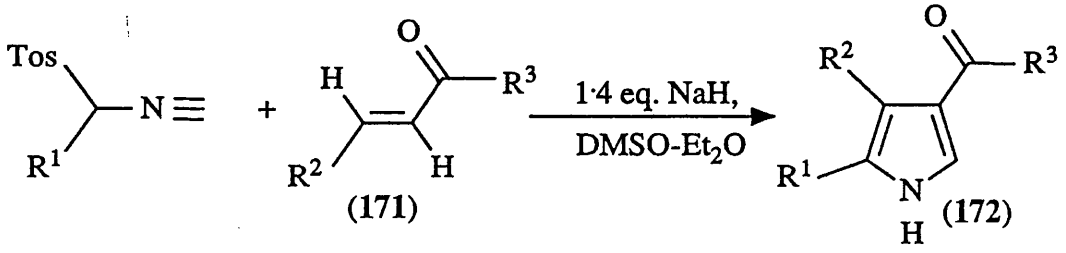
Initially, we believed it prudent to repeat a known synthesis using TosMIC in order to verify that we could reproduce the necessary conditions - which are

critical for success. We chose, as an example, a reaction between TosMIC and benzaldehyde which finally produces 5-phenylimidazole (**174**). The mechanism of the first stage of this process is shown in Scheme 33.

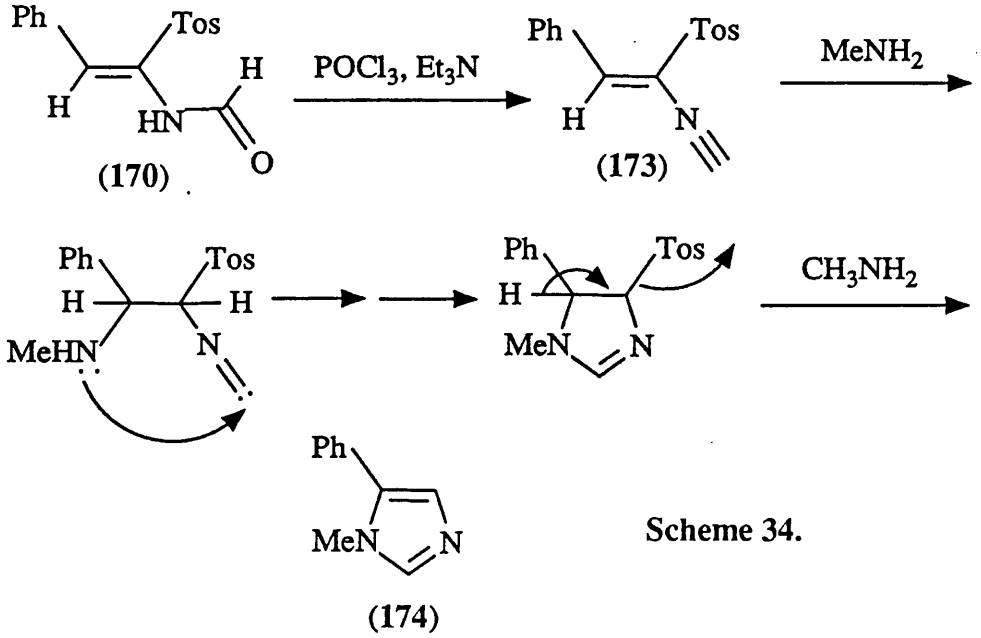


Scheme 33.

The formation of imidazoles occurs by a three-step process: the first of these proceeds *via* the 4-toluenesulphonyl-2-oxazoline species (**168**), which ring-opens to afford the corresponding *N*-(1-toluenesulphonyl-1-alkenyl)formamide (**170**). The reason for the criticality of the reaction conditions is the possibility of β-elimination of *p*-toluenesulphinic acid, which leads to the formation of oxazoles. Such a reaction can dominate at higher temperatures and provides an entry into the oxazole ring system. A further example of the adaptability of the TosMIC reagents, is their use in the synthesis of pyrroles where they react with a Michael acceptor such as the enone (**171**).



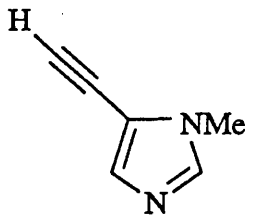
The next step in the formation of the imidazole (**174**) from the *N*-(1-toluenesulphonyl-1-alkenyl)formamide (**170**), is dehydration with phosphorus oxychloride which produces the α-β-unsaturated sulphonylisocyanide (**173**). The last reaction stage in the formation of 1-methyl-5-phenylimidazole (**174**) commences with a Michael-type addition of methylamine to the isocyanide (**173**), followed by ring-closure. Subsequent β-elimination of *p*-toluenesulphinic acid, requiring a second equivalent of base, affords a 51% yield of the imidazole (**174**).



Scheme 34.

In our hands this synthesis worked well, and so we felt confident about applying the methodology to our synthesis of alkyne (**152**); thus we reacted TosMIC with propynal. Unfortunately this initial step failed, giving a black tar which we were

unable to characterise.

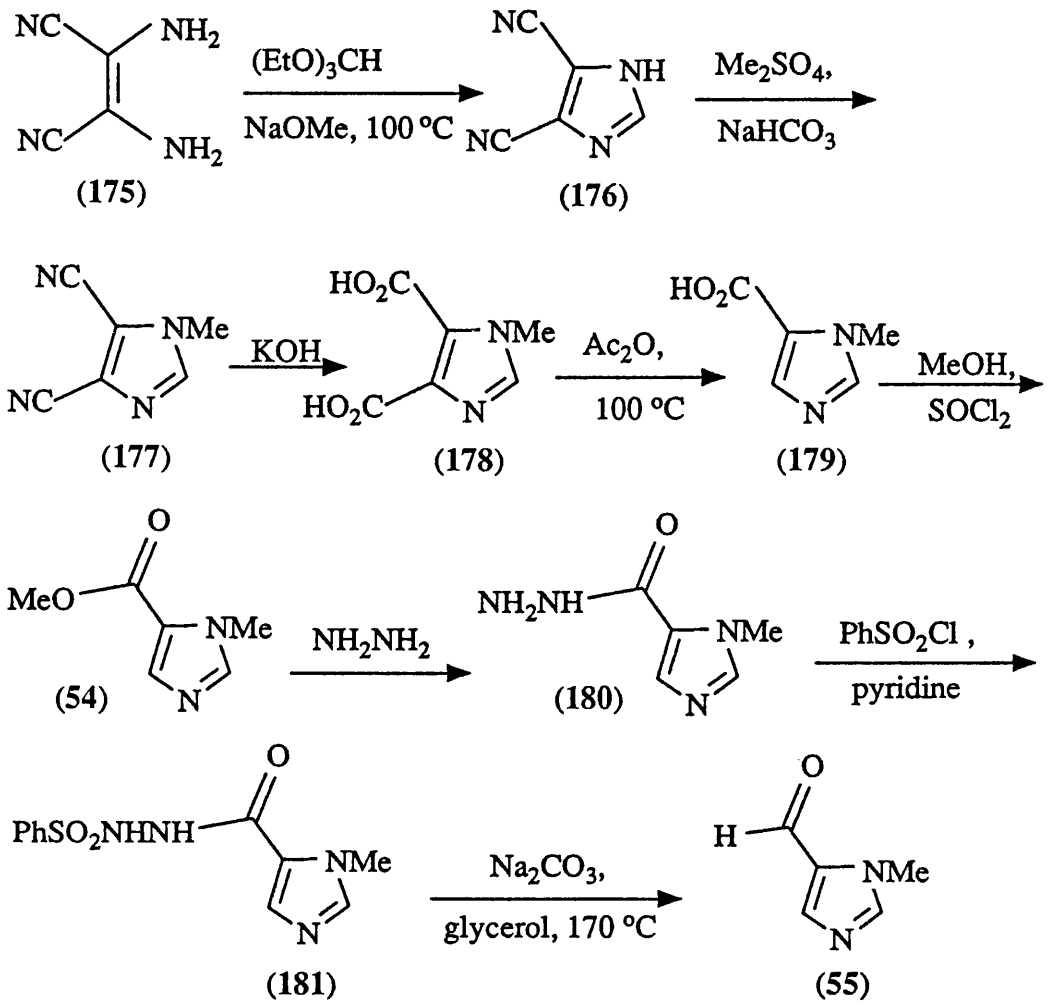


(152)

Our final, successful, approach to the acetylene (152) again involved the aldehyde (55). We discovered a route to the aldehyde (55), starting from 1,2-diaminomaleonitrile, which was based on a literature synthesis, by Rapoport and co-workers,[162] of methyl ester (54). Having succeeded in preparing that compound, we reduced it to the aldehyde (55) using the method of Jones and Mclaughlin.[156] All the yields were good, except for the last one (Scheme 35).

Formation of 4,5-dicyanoimidazole, from the dinitrile (175) and triethylorthoformate, involved distillation of ethanol from the reaction mixture. This has the effect of displacing the equilibrium position in favour of an intermediate product which still contains an ethoxy substituent. This compound must be treated with sodium methoxide in order to obtain the dicyanoimidazole (176) in 90% overall yield. Selective *N*-methylation of asymmetric imidazoles is generally a complicated process;[87] however compound (176) is symmetrical and so methylation affords the mono-methylimidazole (177) as the sole product, in 60-65% yield.

Hydrolysis of the dinitrile (177), by refluxing in potassium hydroxide, gave a 99% yield of a yellow solid, which is the dicarboxylic acid (178). Selective mono-decarboxylation occurs when this is heated in acetic anhydride solvent, and

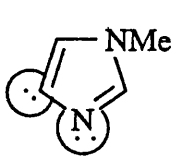


Scheme 35.

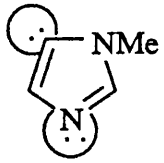
the product is almost exclusively 1-methyl-5-imidazole carboxylic acid (179)(95%) with only a 5% yield of 1-methylimidazole-4-carboxylic acid. It is reported by Takahashi and Mitsuhashi[163] that when the reaction is attempted using *N,N*-dimethylacetamide as solvent, decarboxylation occurs predominantly at C-5 giving a 75% yield of the 4-carboxylic acid.

Cohen and co-workers[130] have carried out extensive ^{1}H n.m.r. studies of the deprotonation-reprotonation of 1-methylimidazole. They discovered an almost exclusive preference for anion formation at C-5, at temperatures above 100 °C, and suggested this effect was due to electrostatic repulsion between the anion

formed at C-4 and the sp^2 lone pair on the adjacent nitrogen atom, so disfavouring this anion, as shown in intermediate (182). In the case of anion formation at C-5, these two electron orbitals are non-adjacent and so that anion (183) is not as disfavoured.

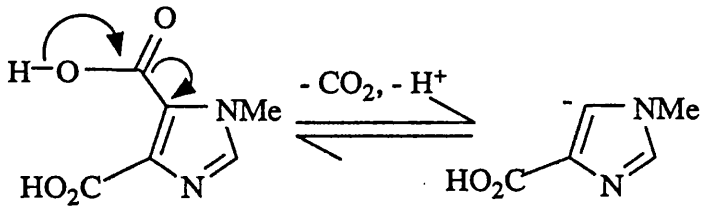


(182)

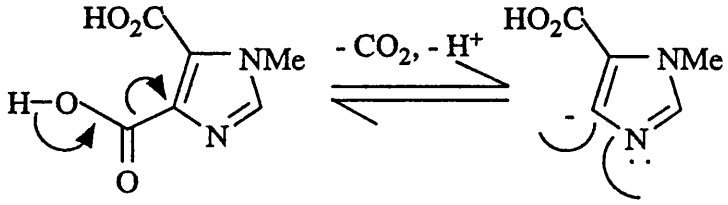


(183)

Takahashi and Mitsuhashi believe similar considerations apply to the decarboxylation reaction of the acid (178), in non-electrophilic solvents such as *N,N*-dimethylacetamide, leading to the 4-carboxyimidazole (187) as the major product. However, in acetic anhydride the possibility of acetylation of the

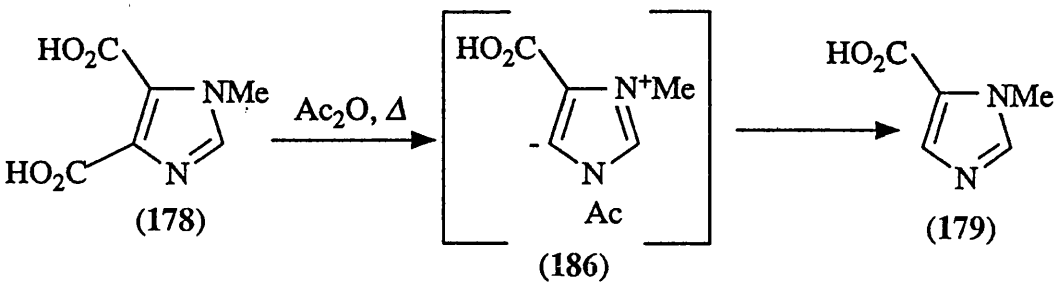


(178) (184)

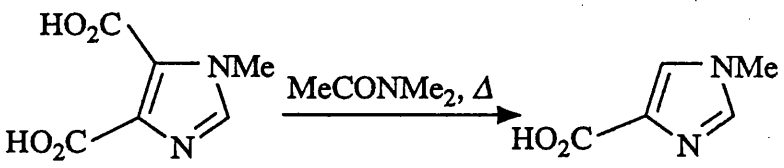


(178) (185)

sp^2-hybridised nitrogen atom has the effect of removing that atom's lone pair, and the electrostatic repulsion with an adjacent carbanion is eliminated.

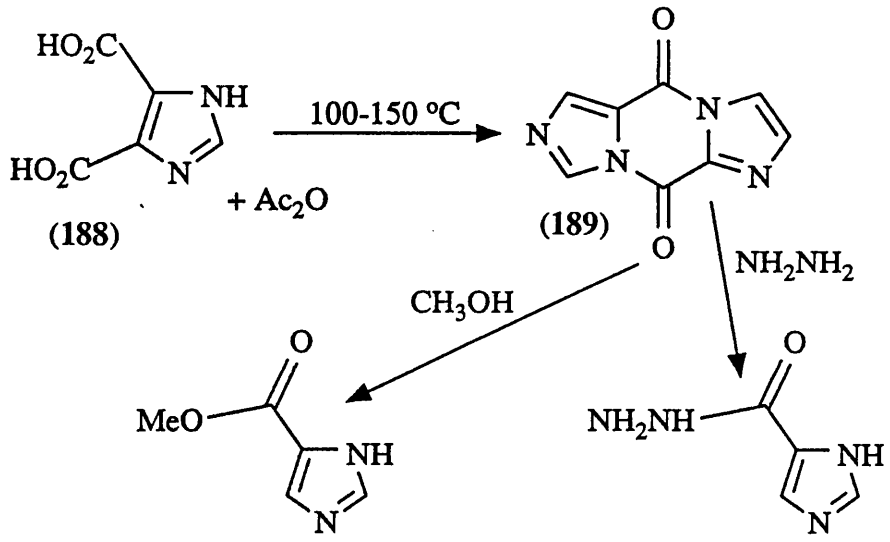


(178) (186) (179)



(178) (187)

Interestingly the temperature of the reaction also appears to be important; we observed that heating the reaction to 140 °C, rather than at 100 °C, for four hours, led to the formation of a black tar which could not be characterised. Other workers[164] have shown that prolonged heating of diacid (188), in boiling acetic anhydride, leads to the formation of diimidazo[3,4-*a*;3',4'-*d*]piperazin-2,5-dione (189) which gain access to 4-substituted imidazoles.



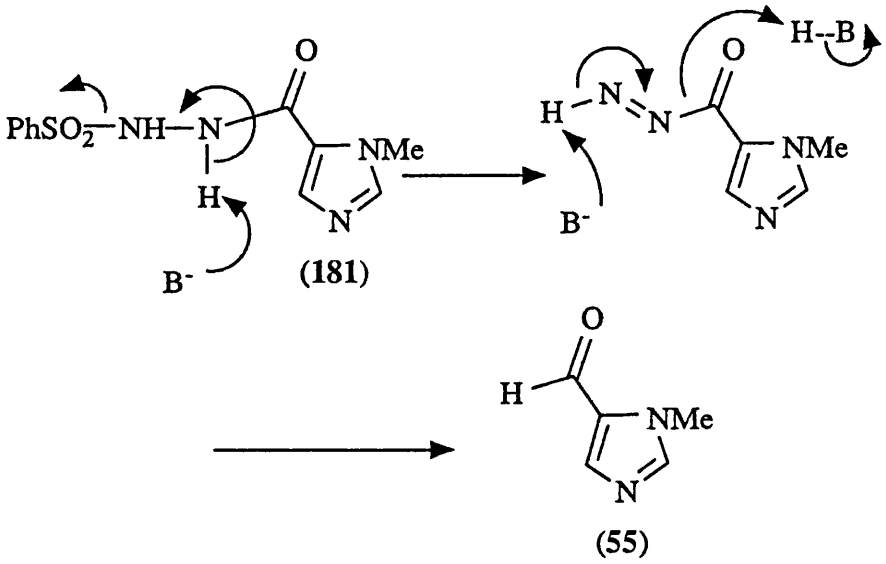
(188) (189)

Throughout this series, the chemical shift values of the H-2 and H-4 proton

resonances tend to be very close. Spin-spin coupling can be observed; between H-2 and H-4, or H-2 and H-5, respectively. These interactions have distinctive coupling constants.[165] In aprotic solvents, such as DMSO-D_6, $J_{2,4}$ is typically smaller than $J_{2,5}$. The former has values ranging from 0·9 to 1·0 Hz, and the latter is in the range from 1·1 to 1·5 Hz. The value we observed for both the acid (**179**) and the subsequent ester (**54**) was J = 0·94 Hz, indicating coupling between H-2 and H-4. In $CDCl_3$ solvent, all coupling was lost and a broad peak for each of the aromatic protons was seen.

An interesting point, which was observed during the course of this work, is the resonance of H-2 for the diacid (**178**) in DMSO-D_6 appears at δ 9·1 - not at the expected value of 7·6, though other data confirmed the structure assigned. In the spectrum of the mono decarboxylated product, the signal in question was again observed at δ 7·6. The reason for this is not clear, but we suggest that the electron-withdrawing effect of the second acid function may be sufficient to increase the lability of H-2 enough for it to undergo exchange with the carboxylic acid protons.

The acid (**179**) was subsequently treated with thionyl chloride, in dry methanol, and distillation of the resultant brown oil produced the methyl ester (**54**), as a colourless crystalline solid, in 56% yield. Nucleophilic displacement of the methoxy group, by treatment with hydrazine hydrate at 40-60 °C, gave the hydrazide (**180**) in 90% yield. This compound was stirred with benzenesulphonyl chloride, using pyridine as base, affording benzenesulphonylhydrazide (**181**). Treatment of compound (**181**) with sodium carbonate, in glycerol at 170 °C, resulted in the evolution of nitrogen gas from the reaction mixture and production of the aldehyde (**55**) in 40% yield. The mechanism for this last reaction is shown in Scheme 36.

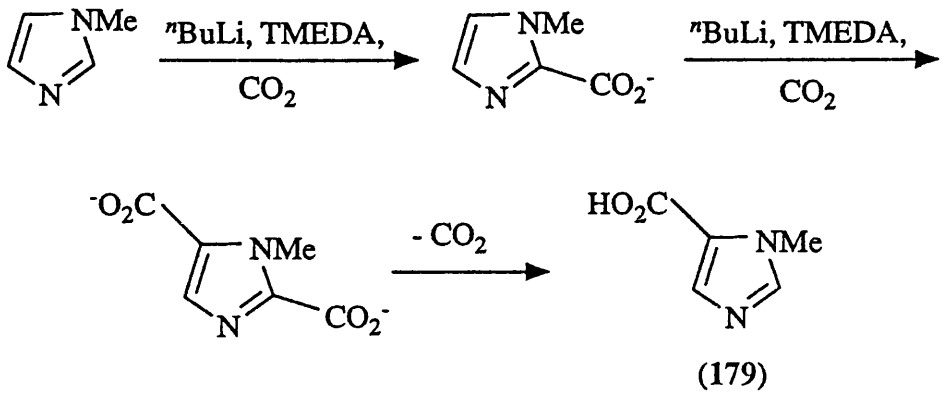


Scheme 36.

It is thought that sodium carbonate abstracts a proton from glycerol, and the resulting alkoxide is the actual base which deprotonates the nitrogen atom α- to the carbonyl group. Elimination of the benzenesulphinyl group, followed by liberation of nitrogen, results in the production of 1-methyl-5-formylimidazole (55).

At this point, we noticed a recent publication by Katritzky and co-workers[166] in which they claim a one-pot synthesis of monoacid (**179**) directly from 1-methylimidazole. These authors state that 1-methylimidazole can be converted to acid (**179**) by treatment with two equivalents of a ^{n}butyl lithium-tetramethylethylenediamine complex and dry carbon dioxide. The intermediate 2,5-dicarboxylic acid is said to undergo C-2 decarboxylation[166] to give monoacid (**179**), as shown.

The attraction of such a facile synthesis is obvious; but we were unable to repeat the preparation, obtaining instead a complex mixture which could not be fully characterised. None of the monocarboxylic acid (**179**) was isolated. Furthermore,



(179)

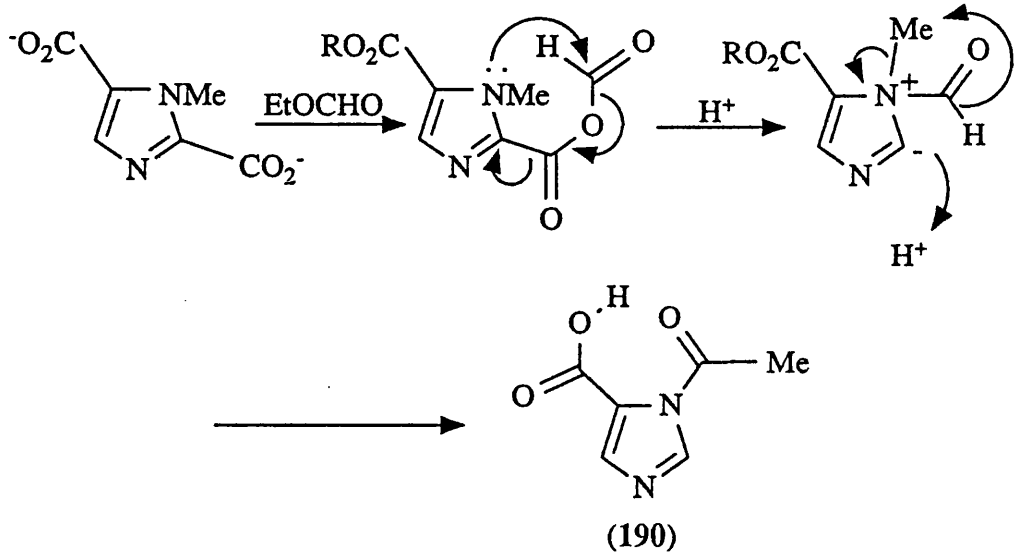
TMEDA= tetramethylethylenediamine

there are anomalies in the data quoted by Katritzky and co-workers.[166] It seems strange that an aqueous work-up should be used, as our experience with this compound has shown it to be extremely water-soluble.

We were puzzled by the claims of these authors to have observed a mass peak of 154 in the 70 eV mass spectrum of the monoacid (179). The highest peak to be found in our mass spectrum of the same compound, formula $C_5H_6N_2O_2$, was the calculated value of 126. Katrizky and co-workers also indicate the presence of a resonance at δ 8·80, assigned to the acidic proton, in their ^1H n.m.r. spectrum of the acid (179) - for which no solvent was quoted. We do not see such a signal in our ^1H n.m.r. spectrum. Although our data otherwise agrees with that of Katritzky's group, their ^{13}C n.m.r. chemical shift figures differed from ours by between 0·5 and 5 p.p.m.

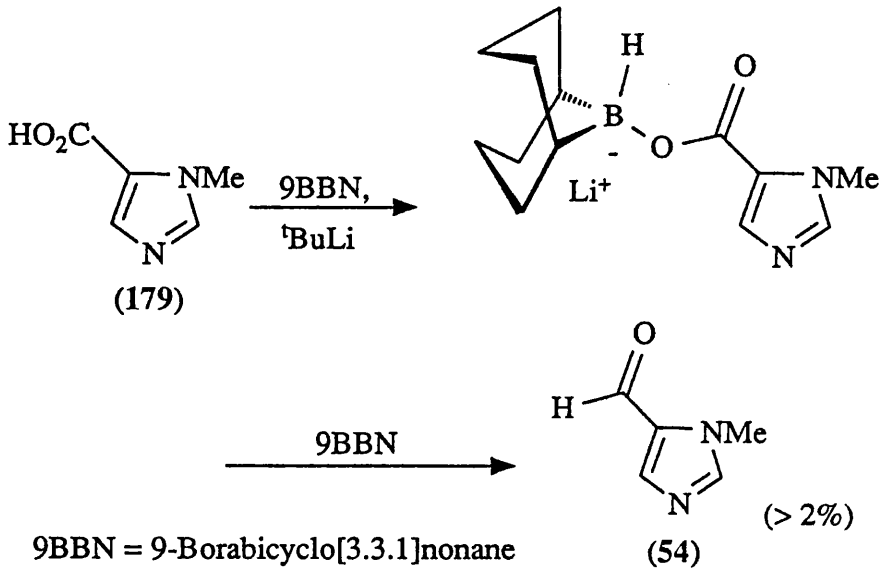
We believe the data quoted by Katritzky is more consistent with the acetamide (190). This compound has formula $C_6H_6N_2O_3$ and molecular weight 154, and we feel it possible that intramolecular hydrogen bonding accounts for the presence of the acidic proton resonance, as well as the apparently reduced water solubility of their product. Since ethyl formate is added to the reaction mixture, presumably to

assist the decarboxylation at C-2, we feel the acetamide (190) may have arisen as shown below.



(190)

We made another attempt to optimise our synthesis of the aldehyde (55) from the acid (179). This compound was reacted with 9-borabicyclo[3.3.1]nonane[167] and ^{t}butyl lithium. Addition of a second equivalent of the borabicyclononane at -20



(179)

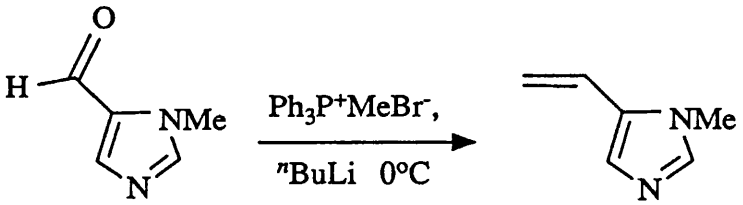
9BBN = 9-Borabicyclo[3.3.1]nonane (54)

°C produced a black material, which on purification gave a brown oil. This proved to be a complex mixture, but a small trace (less than 2%) of the aldehyde (55) was present along with unreacted acid (179). It was concluded that ^{t}butyl

lithium had removed the C-2 proton and the borane complex had only partially formed. Disappointed with this result, we returned to our original synthesis of the aldehyde with no further attempts at optimisation.

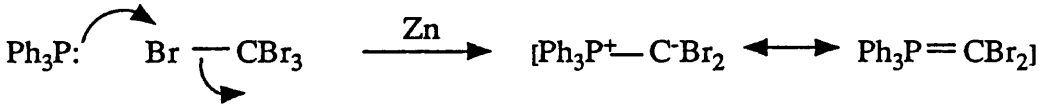
3·3. Investigation of Wittig and Corey-Fuchs reactions aimed at the synthesis of 5-ethynyl-1-methylimidizole (152).

Rapoport had reported[89] that Wittig reactions between certain reagents and the aldehyde (55) could present problems. Therefore we started by performing a simple Wittig reaction between the aldehyde (55) and methyltriphenylphosphonium bromide, using the general procedure of Still.[168] This reaction proceeded smoothly to give alkenylimidazole[169] (**191**)(90%). The ^{1}H n.m.r spectrum contained signals for the resonances of the alkeneic protons at δ 6·50, δ 5·58, and δ 5·22.



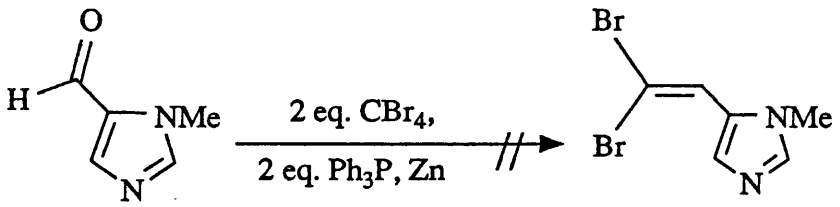
(55) (191)

Satisfied that a Wittig reaction would occur with aldehyde (55), we chose to use the Corey-Fuchs[158,170] reaction in our first attempt to synthesise the acetylene (152). Simply stirring carbon tetrabromide, triphenylphosphine and a catalytic amount of zinc, at room temperature over the course of 48 hours, produced a plum-coloured solution containing dibromotriphenylphosphonium ylide.



However, on addition of aldehyde (55) the colour immediately changed,

producing a brown solution. Unfortunately, analysis by t.l.c. showed that only starting material was present. Repetitions of the reaction, but with stirring for different time intervals, between 24 and 168 hours at room temperature, had no effect and starting material was recovered each time. It seems likely that the ylide simply behaves as a base,[171] and removes a proton from C-2 of the imidazole, resulting in recovery of starting material on work-up.



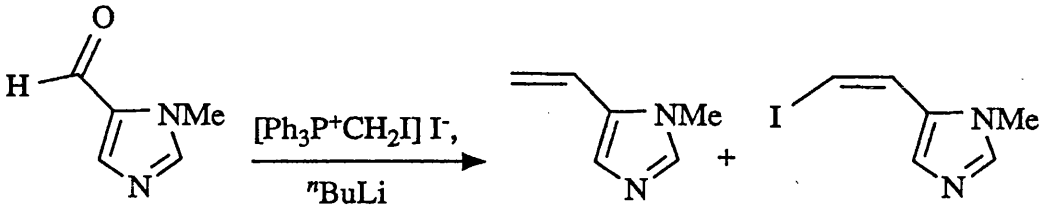
(55) (158)

An alternative explanation is that the oxaphosphetane is formed, but fragments giving a retro-Wittig reaction to starting material. This phenomenon has been observed on a number of occasions[172,173] and appears to be dependent on the structure of the oxaphosphetane intermediate, and on the reaction conditions. Since the dihaloalkene (158) could not be prepared by this route, we turned our attention to formation of the monohaloalkene (192) - from which dehydrohalogenation should give the desired acetylene (152).

Several examples of 1-haloalkene syntheses exist in the literature, most of which rely on halomethylenetriphenylphosphoranes[174] and strong base. However, one route[175] starts with the corresponding alkyne which is treated with CHX_2BH to generate a vinylborane. On treatment with acid this species generates the 1-haloalkene.

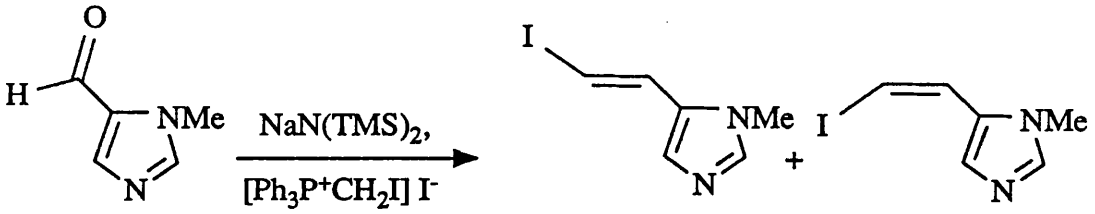
The most general of these routes appears to be the method of Stork,[174a] which we successfully applied to the synthesis of the iodoalkene (192) in 98% yield.

Previously we had tried the method of Seyferth,[174e] but the use of ^{n}butyl lithium had led to metal-halogen exchange with (iodomethylene)triphenylphosphonium iodide resulting in 50% recovery of the dehalogenated alkene.



(191) 50% 30% (192)

The required phosphonium salt was prepared by heating triphenylphosphine with methylene iodide at 45 °C for 4 hours. The best yields of the iodoalkene isomers (192) and (193) resulted from using sodium hexamethyldisilazane as base. It has been shown that the stereoselectivity of the iodo-olefin formed in reactions such as this depends on the temperature. At -78 °C, with an unstabilised ylide, a high proportion of the Z-alkene isomer is recovered. In our case a 40:60 mixture of E:Z isomers was obtained, the ^{1}H n.m.r. spectrum of which showed the olefinic proton resonances of the two isomers with spin-spin coupling constants of 9 and 15 Hz respectively.



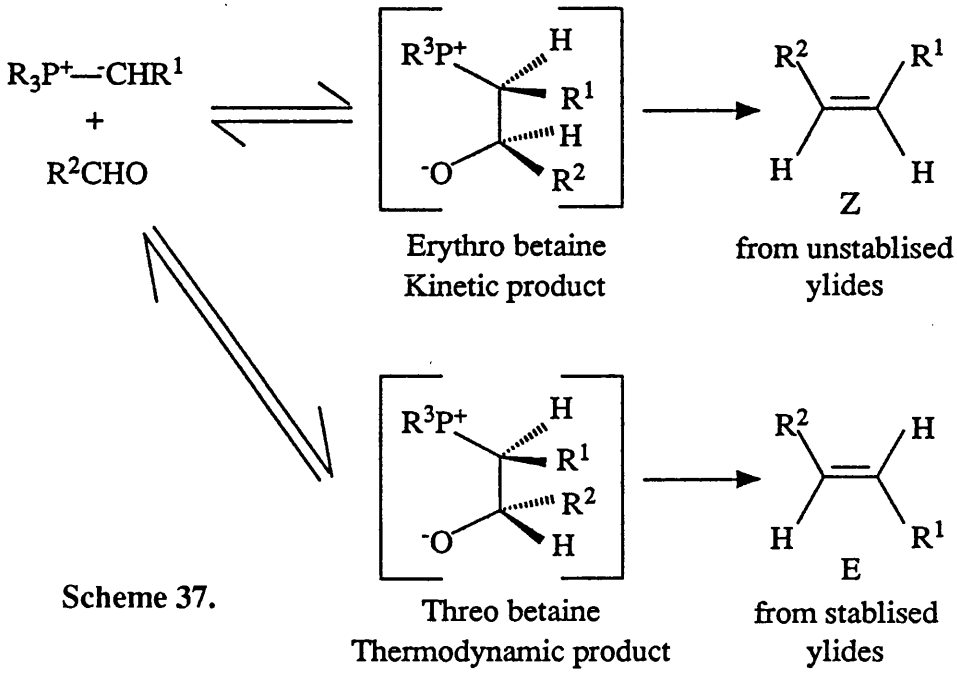
(55) (193) (192)

E Z

40: 60 mixture

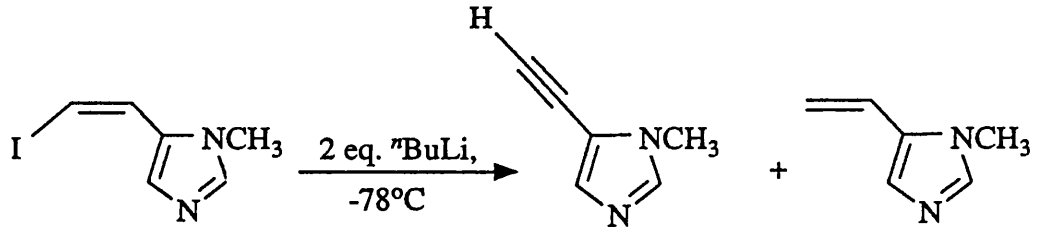
The Z isomer predominates as the ylide used in this reaction is unstabilised.[176] In this case the kinetically preferred erythro betaine collapses irreversibly to give the Z-alkene. When a stabilised ylide is the reagent the erythro betaine is in equilibrium with the more stable threo form, which leads in turn to the thermodynamically preferred alkene (see Scheme 37).

Formation of alkyne (152) followed from simply treating the iodoalkene (192)



Scheme 37.

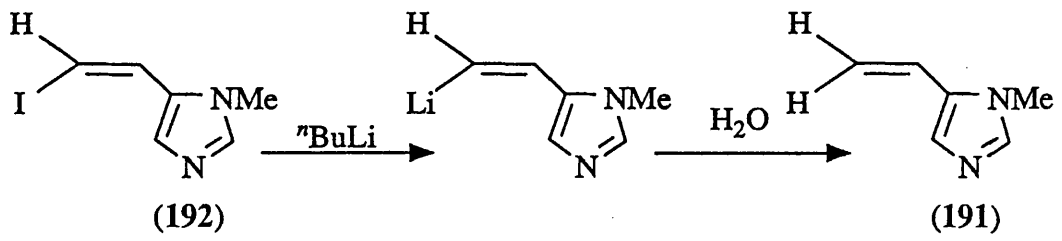
with two equivalents of ^{n}butyl lithium, leading to dehydrohalogenation. T.l.c. analysis indicated that two products were produced; the less polar component was very volatile, and proved to be the desired alkyne (**152**), whilst the more polar compound was the vinylimidazole (**191**). Unfortunately the latter



(**192**) (**152**) (**191**)

compound predominated in a 3:2 molar ratio. A large excess of base did nothing to improve this ratio in favour of the alkyne. It was thought that metal-halogen exchange also occurred during the reaction affording the vinyl anion which on work-up simply gave the alkene (**191**).

During the purification of the alkyne (**152**), the compound was found to have a profound effect upon the author. Symptoms included; dryness of the throat, hot



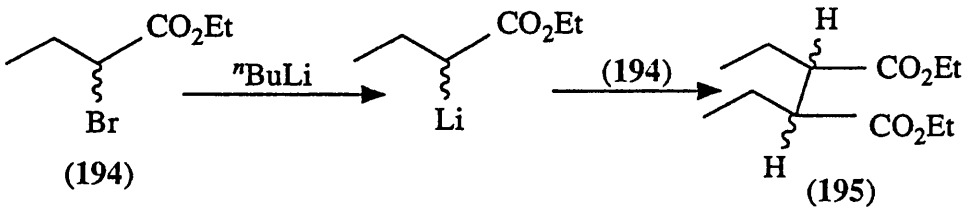
(192) (191)

flushes, faintness, numbness, spasms and stiffness in the muscles of the stomach and legs, difficulty in breathing, and a sensation of extreme intoxication. Some of these effects manifested themselves only gradually, taking up to several hours to appear. It is possible that alkyne (152) may behave as a muscarinic agonist, since decreased blood pressure was diagnosed. The structural requirements for a muscarinic agonist[64] are all fulfilled by the alkyne; namely, it possesses a tertiary nitrogen centre, and an electron-rich side chain.

Only miligramme quantities of the alkyne were enough to cause this effect, even as small as the loading on a t.l.c. plate. Possibly the volatility of this compound contributes to this problem. The C-silyl derivative had an even greater effect on both the author and a colleague. Sensitisation of the author to the compound was demonstrated by the fact that each exposure led to a more drastic response. It is noted that the author's supervisor and a second colleague did not exhibit the symptoms after handling the alkyne (152).

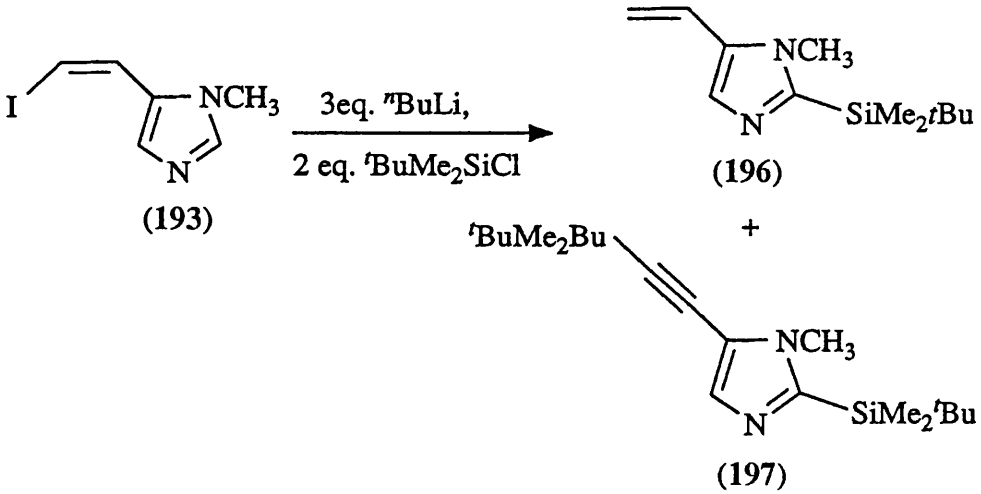
Because of these difficulties, the alkyne (152) was never completely purified, but sufficient data were obtained (see Experimental) to confirm its structure. Because of the sensitivity of the author to alkynylimidazoles, all further work in this area was performed by other workers. An attempt was made by the author's supervisor to convert the iodoalkene into its lithio-derivative, and to react this with ethyl 2-bromobutyrate. Only one product was observed by t.l.c. analysis

which later proved to be the diethyl succinate derivative (195) produced from a two step dimerisation of the bromoester.



No imidazole containing product was isolated, although it must be acknowledged that the material balance of the reaction was poor.

An undergraduate project student[177] showed that treatment of the iodoalkene (193) with three equivalents of ^{n}butyl lithium, and two equivalents of ^{t}butyldimethylsilyl chloride, led to the production of two major products. These were identified as the C2-silylated alkene (196) and the disilylated alkyne (197). 1-Methyl-2-silyl-5-ethenylimidazole (196) was fully characterised, but

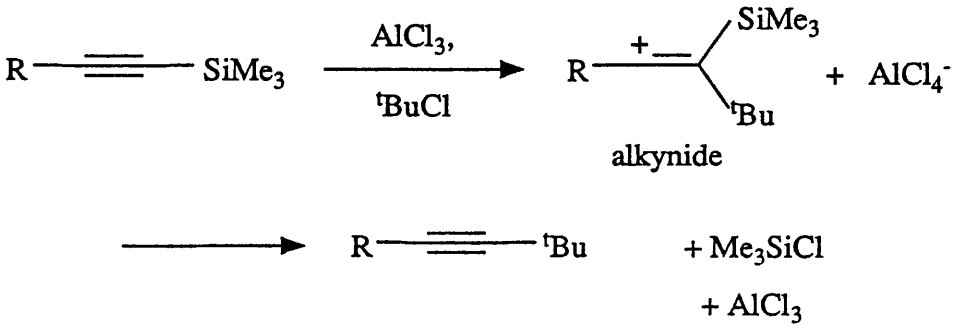


unfortunately the disilyl compound was not easy to handle. It was volatile and potentially toxic; as a result it was treated with great caution and only a mass spectrum was recorded. This showed a molecular ion peak at *m/z* 338.

Having shown, albeit tentatively, that alkylation of alkyne (152) with

'butyldimethylsilyl chloride was possible, we applied the same conditions to a subsequent reaction. This time the alkylation was attempted using a 5% solution of ethyl 2-bromobutyrate, since we hoped that using a dilute solution of the bromoester would prevent dimerisation. However, no alkylated product was isolated and only the vinylimidazole (**196**) was obtained. A possible explanation for this result stems from the observation that only primary alkyl halides[178,179] unbranched at the β-position give good yields on alkylation with acetylenes.

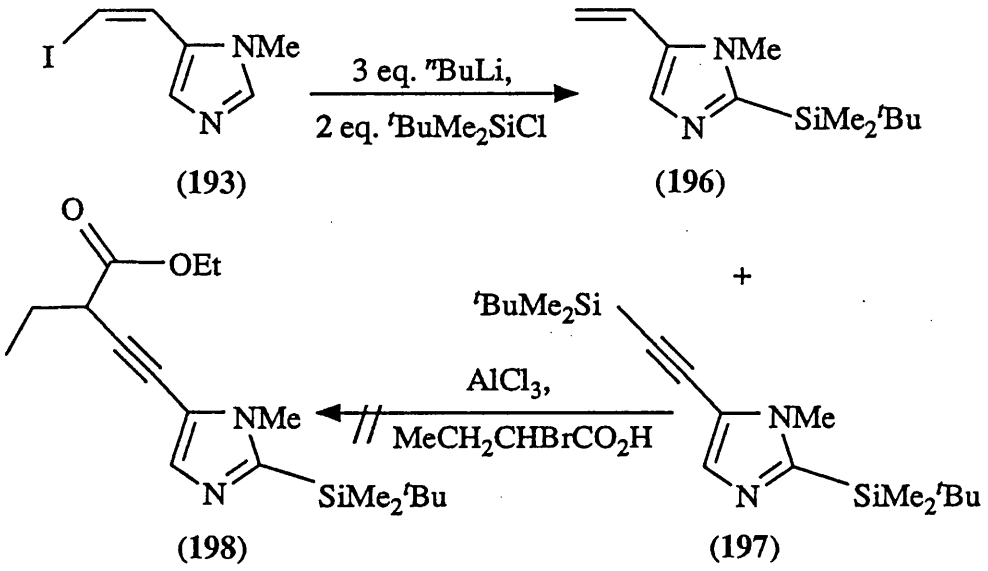
It has been reported[180] that silyl acetylenes react with tertiary halides, in the presence of a Lewis acid catalyst, giving tertiary alkyl-substituted alkynes. This reaction results from the facile fission of the C-Si bond in the presence of halide ions. Since we believed we had prepared the disilylacetylenylimidazole (**197**), we hoped we could apply such a reaction to our synthesis of pilocarpine. The mechanism of this reaction is thought[180] to involve a carbonium ion, generated from alkyl halides by a Lewis acid. It is suggested that this species reacts with a silylacetylene to give a vinyl cation, which undergoes elimination of the silyl group and forms an alkylated alkyne (Scheme 38).



Scheme 38.

This reaction has so far not been successful when applied to primary and secondary alkyl halides. However we thought it was sufficiently promising to be

worthy of investigation. We repeated the reaction of the iodoalkenylimidazole (193) with ^{n}butyl lithium and ^{t}butyldimethylsilyl chloride to generate disilylalkynylimidazole (197), then added aluminium trichloride, followed by the racemic bromoester (194). However, the desired reaction failed and the ^{1}H n.m.r. spectrum indicated 2-^{t}butyldimethylsilyl-5-ethenyl-1-methylimidazole (196) to be the major product. None of the bromoester starting material was isolated, nor had it been converted into its dimer (ethyl crotonate).

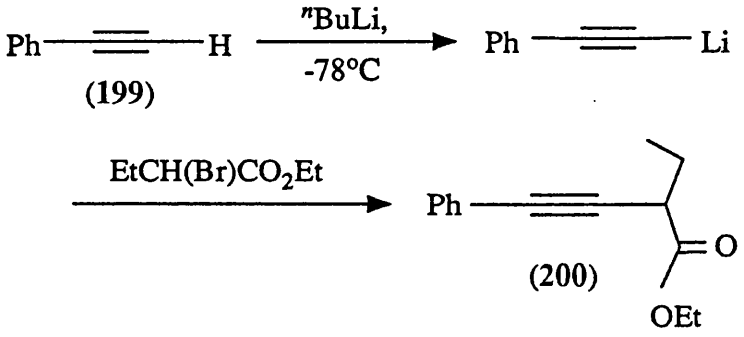


After the failure of our earlier work, we wished to investigate if such difficulties characterise the alkylation reactions of simpler aromatic acetylenes. Thus we reacted phenylacetylene dissolved in THF with ^{n}butyl lithium at -78 °C, to form an anion. When the reaction mixture was allowed to warm above -78 °C, a white precipitate separated. Earlier reports[181] have shown that lithioacetylene compounds are very sensitive to temperature. A temperature rise of just 10 °C produces a precipitate which will not redissolve whether, or not, the temperature is depressed again.

In our experiment a constant temperature of -78 °C was maintained, but the

addition of ethyl 2-bromobutyrate produced a black solution. Analysis of this by t.l.c. indicated the formation of a single product, but also showed that a considerable amount of starting material remained. An attempt to purify the product by chromatography over silica gel resulted in uncharacterisable materials - indicating decomposition on the silica.

Repeating the experiment, this time using a Kugelrohr apparatus to distill out the product, led to the recovery of bromoester starting material - but no phenylacetylene and none of the desired product. We cannot explain the disappearance of the starting alkyne, and base-mediated dehalogenation of the



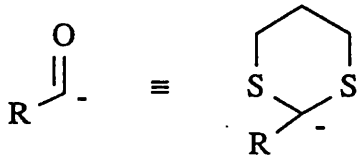
bromoester does not appear to occur.

A final attempt at generation of the acetylene anion was made, using an equimolar quantity of a mixture of ⁿbutyl lithium[182] and potassium ᵗbutoxide (2:1) in tetrahydrofuran-hexane at -78 °C. This time, only unreacted bromoester and phenylacetylene were recovered. We now sought to use a more reactive nucleophile in order to achieve coupling of the lactone and imidazole halves of pilocarpine.

3·4. Attempted access to the pilocarpine skeleton *via* Michael addition of 5-dithianylimidizole to 2(5H)furanone.

3·4·1. Introduction.

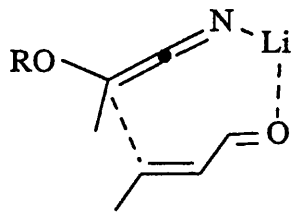
Thioacetals are versatile reagents, allowing reactions[183] such as nucleophilic attack of the *S,S*-acetal unit on an electrophilic species; a reaction which would not be possible using carbonyl compounds directly (an Umpolung process).

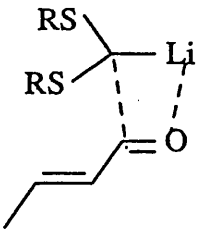


The high stability of the 1,3-dithiane function, towards elevated temperatures, acids, bases, and during the course of chromatography, makes the use of 2-lithio-1,3-dithianes especially appropriate early in a multistep synthesis. A comprehensive review of thioacetal chemistry has been published by Gobel and Seebach.[184]

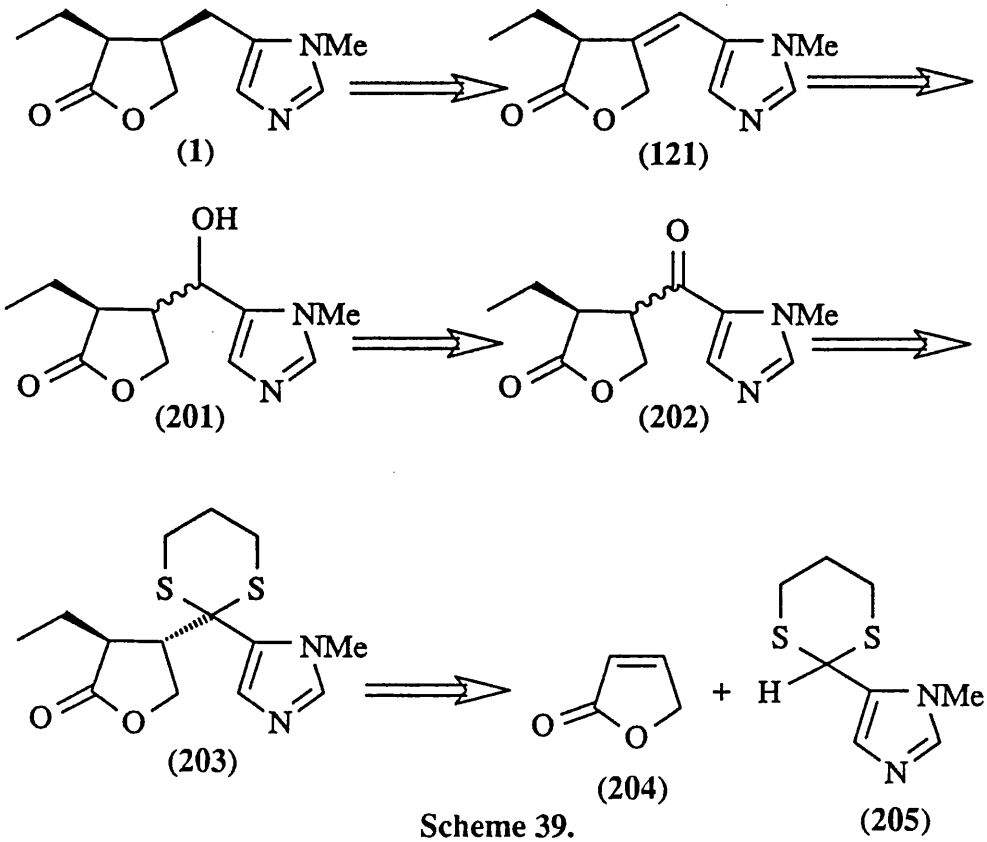
Given the facile lithiation of 1,3-dithianes, many nucleophilic reactions are possible, but our attention was drawn to the conjugate addition of dithianes to α,β-unsaturated aldehydes, ketones, and cyclic esters. It has been shown that metallated thioacetals demonstrate a high preference for non-conjugate 1,2-addition to α,β-unsaturated carbonyl compounds,[185] and Stork argued that, in the case of a lithiated thioacetal, coordination of the metal with the oxygen atom of the Michael acceptor may be important.

However, it has recently come to light that smooth 1,4-addition of a lithiodithiane to an enone can sometimes occur; this appears to be related to the intrinsic stability of the dithiane anion.[186-188] We were particularly intrigued by recent work concerning the production of lignanic lactones using this approach.[189,190] We considered that the pilocarpine skeleton could be constructed by just such a





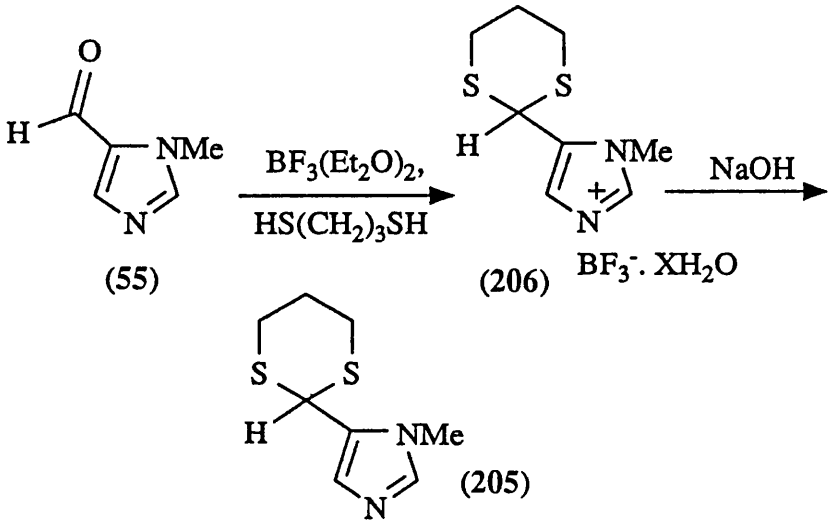
Michael addition. Our retrosynthetic plan is shown in Scheme 39, the key step involving 1,4-addition of 5-(1,3-dithian-2-yl)-1-methylimidazole to 2(5H)-furanone, followed by quenching of the resultant anion with ethyl iodide. We hoped that the steric bulk of the thioacetal would lead predominantly to the *trans*- product (**203**).



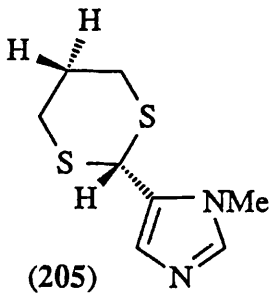
Scheme 39.

3·4·2. Preparation and some nucleophilic reactions of 5-(1,3-dithian-2-yl)-1-methylimidazole.

Formation of the dithiane (205) proceeded smoothly, using the procedure of Marshall and Belletire.[191] To ensure complete reaction, 2·5 equivalents of borane trifluoride etherate was required. Removal of the solvent left a colourless solid which proved to be the boron salt (206) of the required compound. Subsequent treatment with 2M sodium hydroxide, at room temperature, liberated free imidazole (205) in good yield.



Formation of the borane salt caused a large difference in the chemical shift of the imidazole proton resonances in the ^{1}H n.m.r. spectrum; that due to 2-H appeared at δ 9·07, as opposed to δ 7·38 in the parent molecule. The ^{1}H n.m.r. signals corresponding to the methylene protons at C-5' exhibit geminal coupling, as well as a difference in chemical shift, with one multiplet at δ 1·85 and another at δ 2·07. This is because they are now diastereotopic, such that one of the protons maintains a *cis*- relationship to the imidazolyl unit, whilst the other is *trans*- to it. We envisaged a problem in generating the lithiodithiane due to the higher acidity of the 2-H proton, $pK_a = 6$, compared with a $pK_a = 29$ to 30 for the dithiane. We

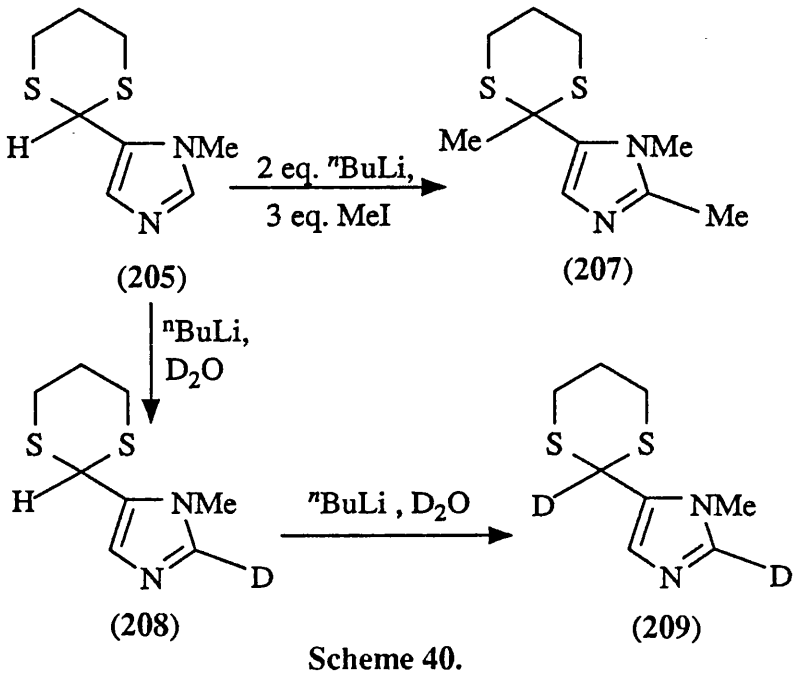


(205)

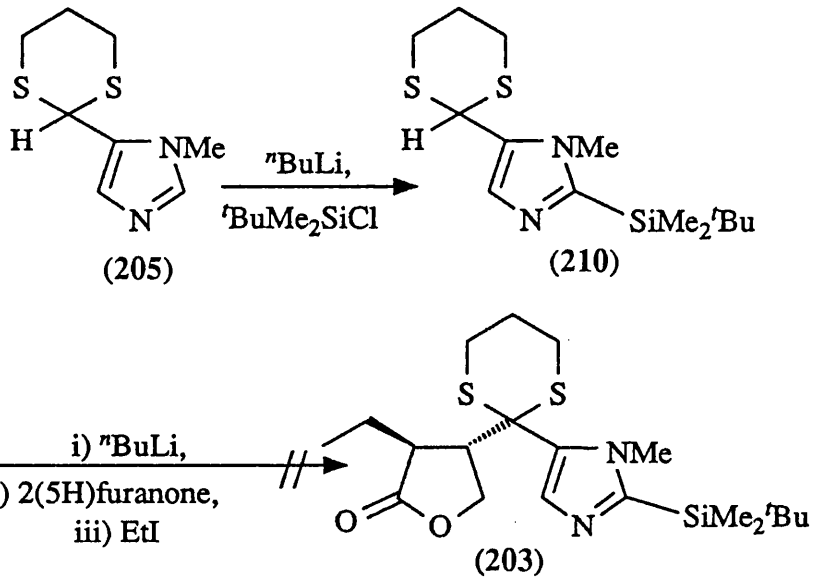
therefore carried out a deuteration and methylation study, in order to verify our assumption. We treated the molecule with one equivalent of ^{n}butyl lithium, and quenched the mixture with D_2O. Indeed, we found the intensity of the signal of the 2-H proton, at δ 7·3, was substantially reduced - as opposed to the signal corresponding to the 2-proton of the dithiane unit which remained unchanged. Encouraged, we proceeded to treat the thioacetal with two equivalents of ^{n}butyl lithium, followed by three equivalents of methyl iodide. The resultant compound (207) exhibited a ^{1}H n.m.r. spectrum containing three methyl group signals. We were confident, from the physical data, that initial methylation of C-2 had been followed by lithiation and methylation of the thioacetal unit, as we had hoped (Scheme 40).

We now required, once again, to achieve selective protection of the imidazole C-2 position - in order to allow an unhindered reaction between the lithiated thioacetal group and 2(5H)furanone. Having achieved good results using ^{t}butyldimethylsilyl as a protecting group, this was again selected. Silylation of imidazole (**205**) was achieved readily, giving a 90% yield of 1-methyl-2-^{t}butyldimethylsilyl-5-(1,3-dithian-2-yl)imidazole (**210**) (Scheme 41).

Treatment of silyldithianylimidazole (**210**) with an equivalent of ^{n}butyl lithium led to the formation of a deep orange solution, as we had observed in our earlier



Scheme 40.

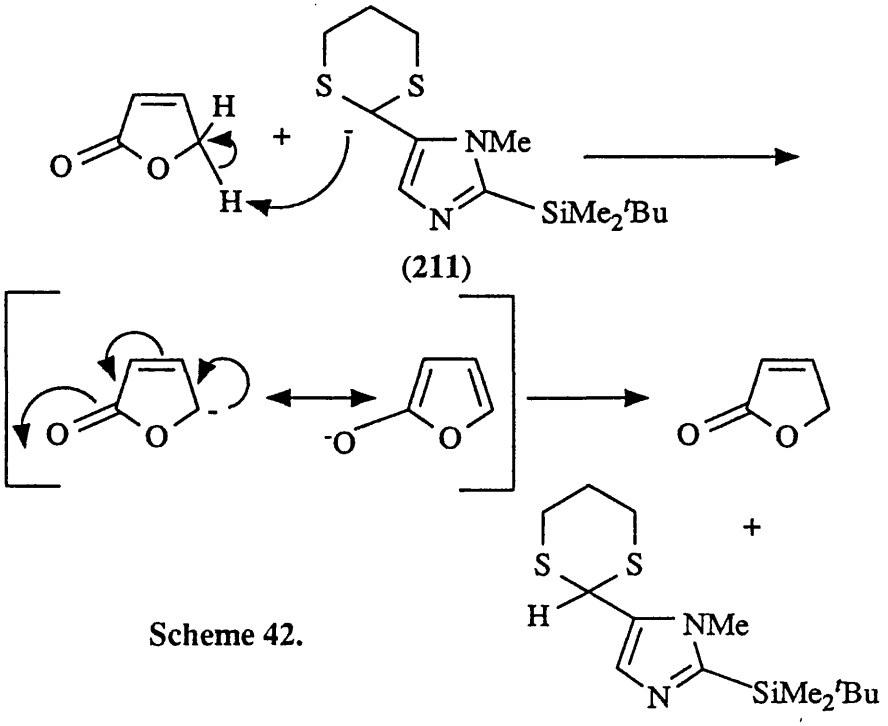


Scheme 41.

formation of other lithiated dithianes. Freshly distilled 2(5H)furanone was added to the reaction mixture, after which the intense colour gradually faded. Analysis of the mixture indicated a number of products had formed, but starting materials predominated. The reaction mixture was allowed to warm to room temperature, ethyl iodide was added, and the mixture was extracted; however only starting

material was recovered. Too little of the minor components were present to allow their identification. We subsequently repeated the reaction several times, varying the conditions: temperatures in the range -20 °C to -80 °C were employed, and copper (I) iodide was introduced in an attempt to produce the corresponding cuprate. All of these modifications had no significant effect on the outcome, and at no time could any trace of the 1,2- addition adduct be detected. A modified work-up was employed, using 2M hydrochloric acid, but this merely resulted in desilylation of the starting imidazole.

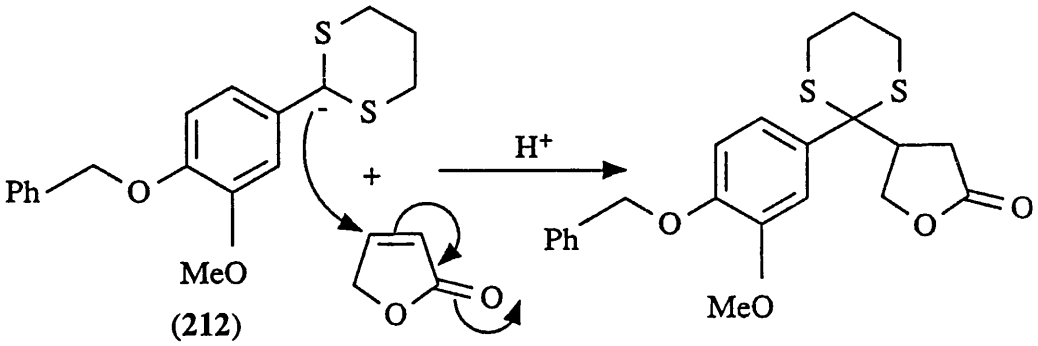
Lithiation at C-2 of the dithiane unit was not in doubt from the earlier deuteration and methylation studies. We therefore believed that the lithiodithiane behaves as a base, rather than as a nucleophile, leading to deprotonation of 2(5H)furanone, and subsequent recovery of starting material on work-up (Scheme 42).



Scheme 42.

In preceding cases where aryldithianyl anions undergo Michael addition to 2-(5H)furanone an activated aromatic system has been present in the nucleophile.

For example,[189b] a *para*-benzyloxy electron-releasing substituent acted to increase the electron density at the anionic centre and improve the nucleophilic reactivity of the dithiane anion (**212**). In our system no such activating group was



(**212**)

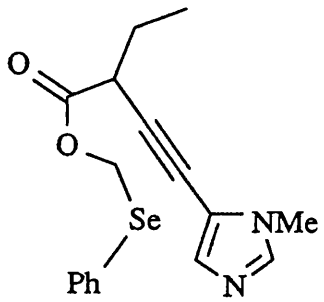
conjugated to the aromatic ring, and the reactivity of the anion (**211**) may even be reduced by delocalisation of the charge into the ring.

CHAPTER 4

4. LATE LACTONISATION INVOLVING ATTEMPTED ALKENE FORMATION, AND ITS SUBSEQUENT ELABORATION, FROM 1-METHYL-5-FORMYLIMIDAZOLE *VIA* A WITTIG REACTION.

4·1 Introduction.

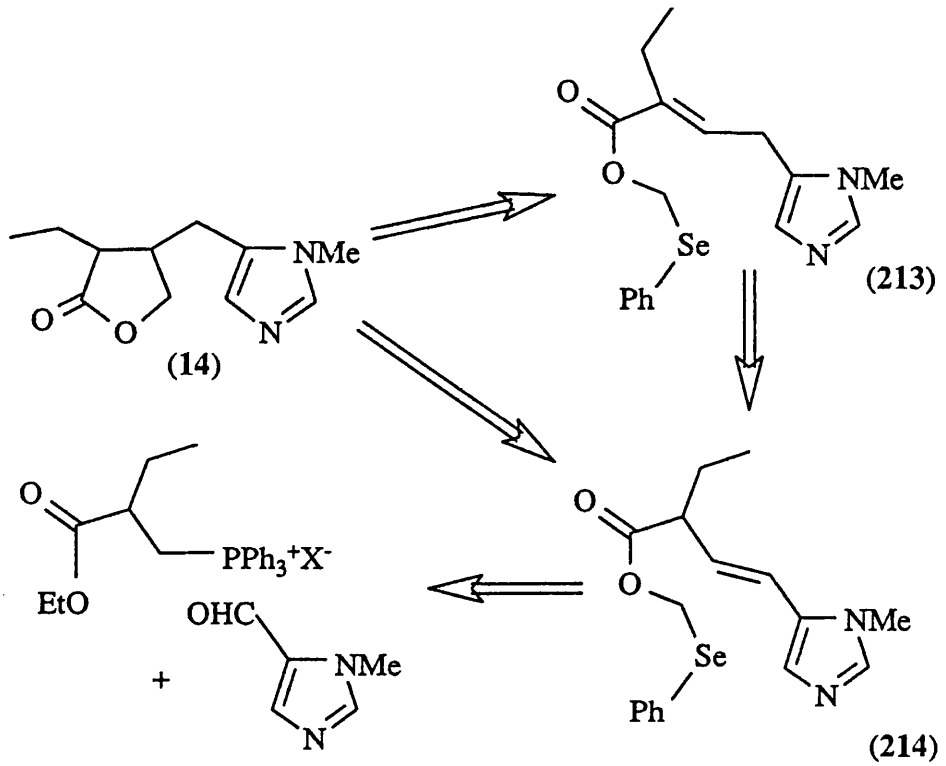
We now sought to apply the lessons we had learned from our previous experiments. We still favoured the strategy based upon a radical induced lactonisation, which was proposed in section **3·1**, but which had foundered due to the failure of the synthesis of the alkyne (**151**). However, analogous



(151)

cyclisations of radical species onto alkenes, affording lactones, are also well known.[192,193] We wished to investigate this strategy using selenide (**214**), which would be available by the methods of Beckwith[194] and Pigou,[153] in the lactonisation step as shown in Scheme 43.

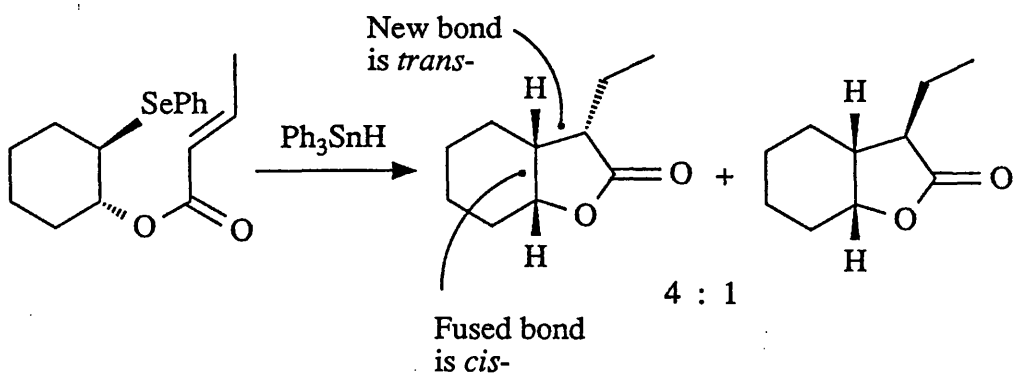
We believed that the alkene (**214**) would be accessible through established methodology such as the Wittig reaction, but we were aware of the possibility of double bond migration into conjugation with the ester group. However, such an isomerisation would lead to the alkene (**213**), which may also be a suitable candidate for radical-induced lactonisation.



Scheme 43.

The lactone (14), obtained from cyclisation of either alkene (213) or (214), would lack the exocyclic double bond arising from reaction of the corresponding alkyne. There would also be no preference in the absolute stereochemistry of the lactone substituents, since precursors (213) and (214) are achiral. Furthermore, the relative stereochemistry of these groups would be determined by the outcome of the cyclisation; we could not induce a *cis*- relationship by alkene reduction, as proposed in Chapter 1.

Unfortunately, literature examples[192,193] indicate that the *trans*-cyclisation product predominates in such processes - especially for acyclic precursors.[193] There are known examples of such cyclisations giving *cis*- ring-fused products, but not in the sense we require. In such cases, the bond which is *cis*- is that which is common to both rings; however the example[192] in Scheme 44 illustrates that the stereochemistry about the *new* bond is almost invariably *trans*-, presumably

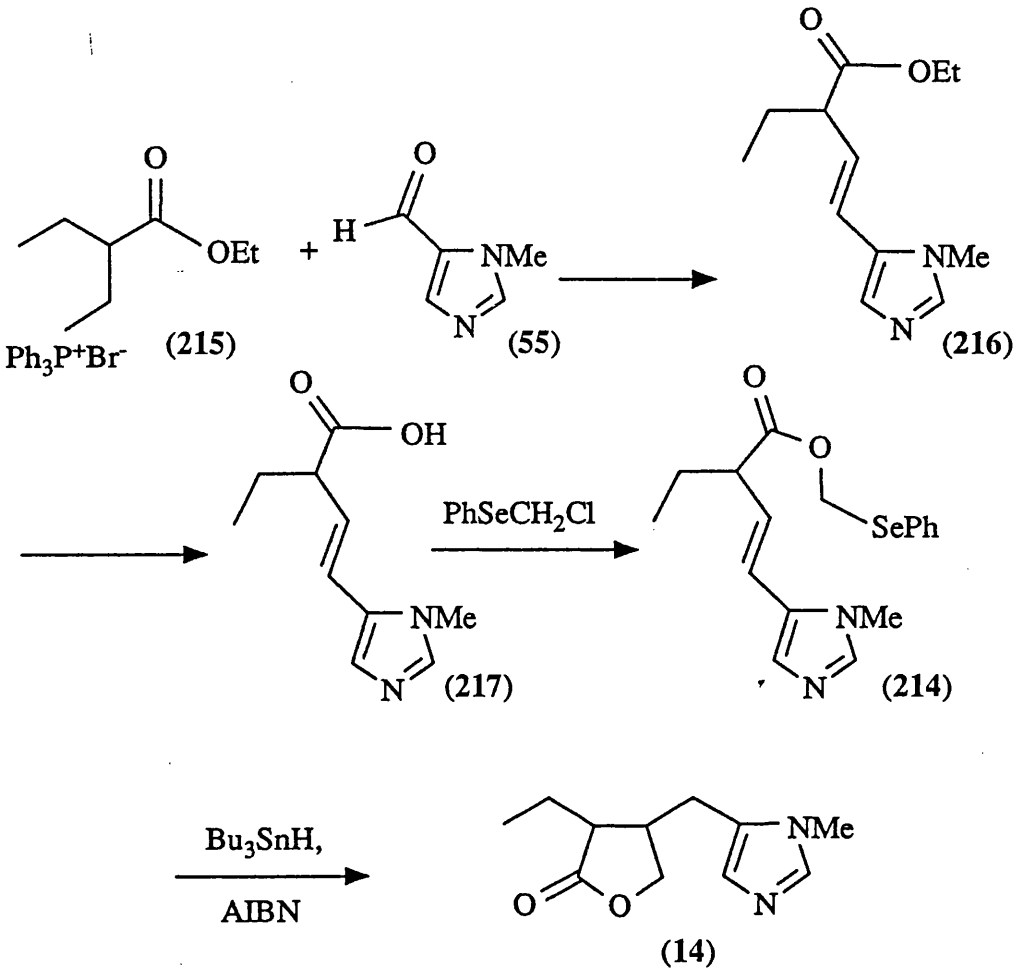


Scheme 44.

due to steric factors. In the cyclisation we propose, of selenide (213) or (214), steric repulsion between the ethyl and imidazolylmethyl groups would probably lead to the *trans*-product. Such a synthesis would produce, predominantly, racemic isopilocarpine; requiring resolution and epimerisation. However, this was also the case in Rapoport's synthesis, and we judged that a short and efficient procedure would justify such a necessity.

4·2 Application of the Wittig Chemistry to the formation of 5-(3-carboxyethylpent-1-enyl)-1-methylimidazole (216).

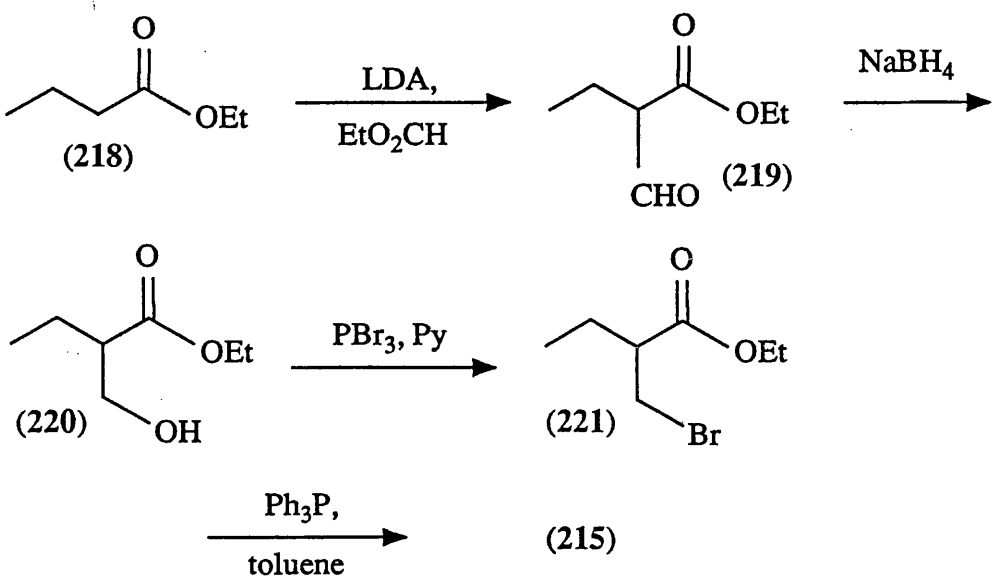
The synthesis of alkene (214) was undertaken using the reactions outlined in Scheme 45. The starting material was ethyl butanoate which was *C*-formylated by the procedure of Klioze and Darmary,[195] using lithium di-isopropylamide and ethyl formate, to yield the aldehydic ester (219). Reduction with sodium borohydride afforded the alcohol (220), however bromination of this compound with triphenylphosphine and carbon tetrabromide[196-199] failed. Recourse to phosphorus tribromide[200] in pyridine was successful, and the bromoester (221) was eventually obtained in a modest yield of 58%.



AIBN = azobisisobutyronitrile

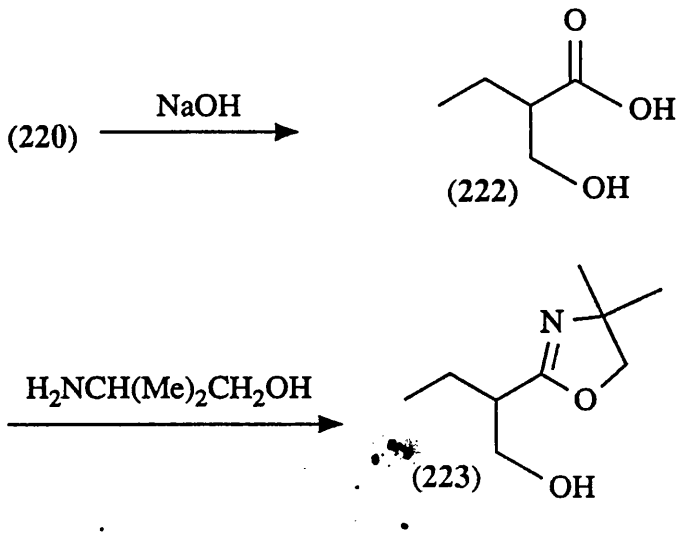
Scheme 45.

Our first choice of starting material, ethyl butanoate, was occasioned by its cheapness and availability; but dictated ester hydrolysis in order to form the selenide (**214**). We recognised that deprotection of the ester (**216**) would probably isomerise the double bond into conjugation with the carboxyl group. This would afford us with target molecule (**213**), but would defeat our access to isomer (**214**). Consequently, we attempted to mask the carboxylate function as the 1,3-oxazolinyl derivative (**223**). The merits of this protecting group are its relative inertness to reducing conditions,[201] and facile removal under acidic conditions[202] that are far milder than those required for ethyl ester hydrolysis; which reduces the chance of double bond isomerisation.



LDA = lithium di-isopropylamine
py = pyridine

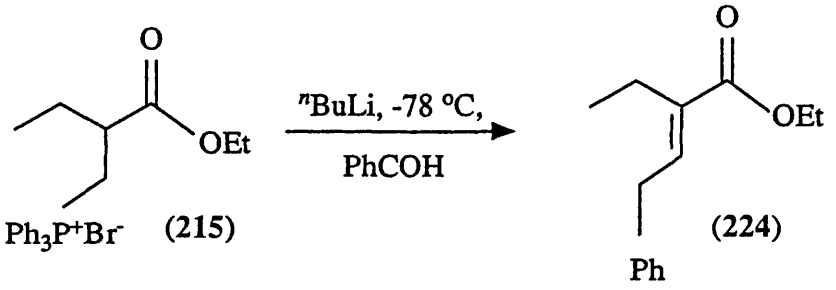
Scheme 46.



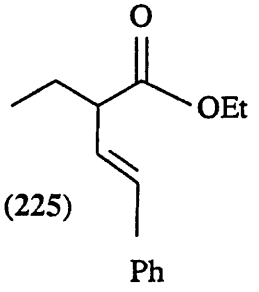
Hydrolysis of the hydroxyester (220) with 2M sodium hydroxide solution afforded the hydroxy acid (222), but, disappointingly, its reaction with 2-amino-2-methylpropanol[203] failed. A red-orange gum was obtained, which was insoluble in most solvents. We could have protected the primary alcohol prior to

reaction with the aminopropanol, but we decided that investigation of the key Wittig olefination reaction had a higher priority.

Phosphonium salt (215) was prepared by reaction between bromoester (221) and triphenylphosphine. Rather than use the imidazolylaldehyde (55), we utilised benzaldehyde as a model substrate and reacted it with the ylide of the phosphonium salt (215) (formed *in situ* by the addition of ^{n}butyl lithium). This reaction gave a very low yield (2 %) of an unsaturated ester, for which the ^{1}H

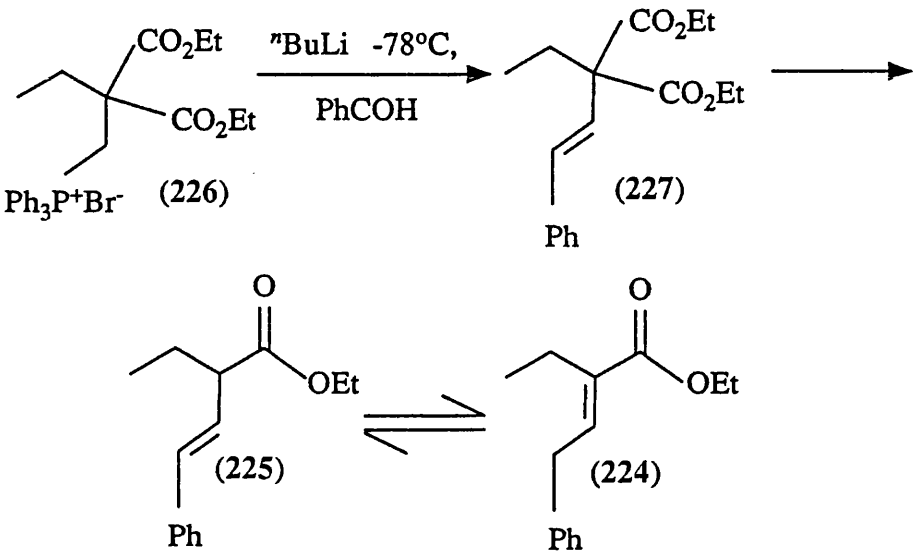


n.m.r. spectrum exhibited signals due to five aromatic proton resonances and those of an ethoxycarbonyl group. However, only one alkenic signal was present, as a triplet (J = 8 Hz) at δ 5·60, indicating that spin-spin coupling occurs between this resonance and that of an adjacent methylene group. This evidence that, as we had predicted, isomerisation of the double bond had occurred under the basic reaction conditions; leading to the α,β- unsaturated ester (224), rather than its isomer (225). Although we could have used this compound *en route* to a model

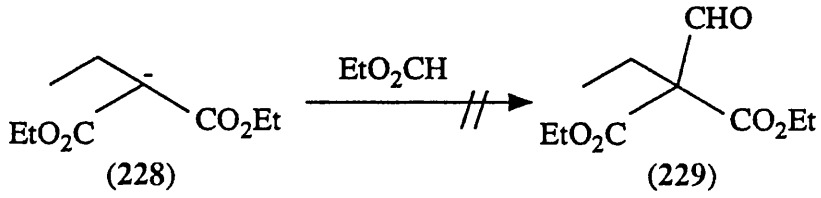


synthesis of the target molecule (213), the yield in the Wittig reaction was most discouraging.

An alternative, olefination of the phosphonium salt (226) was performed, in an attempt to achieve a workable yield. The expected product (227) could then be hydrolysed and decarboxylated.



Surprisingly, all attempts to *C*-formylate diethyl ethyl malonate failed, perhaps because the electrophile ethyl formate is insufficiently reactive to combine with the enolate anion (228). However, vigorous effervescence was observed on addition of ethyl formate, which was consumed during the reaction, and the formylating agent triethylorthoformate also failed to react with the enolate anion. Therefore, it seems more likely that the desired reaction occurs; but elimination of the stabilised anion (228) follows, liberating carbon monoxide and regenerating the starting diester. We noted that the literature[203a] indicates very forcing conditions are often required to alkylate diethyl malonate.



As with all model reactions which fail, we were overcome by temptation to

repeat the procedure with the actual substrates we had planned - in order to verify the applicability of the model results. Thus, a Wittig reaction was undertaken between 5-formyl-1-methylimidazole and the phosphorane formed from salt (215); however this failed completely, and only the starting aldehyde was recovered. It is possible that the electron-releasing effect of the imidazole ring lowers the electrophilicity of the aldehyde. It is also known[204,205] that the negative charge of phosphoranes can be delocalised into the d-orbitals of the phosphorus atom, reducing the reactivity of the ylide.

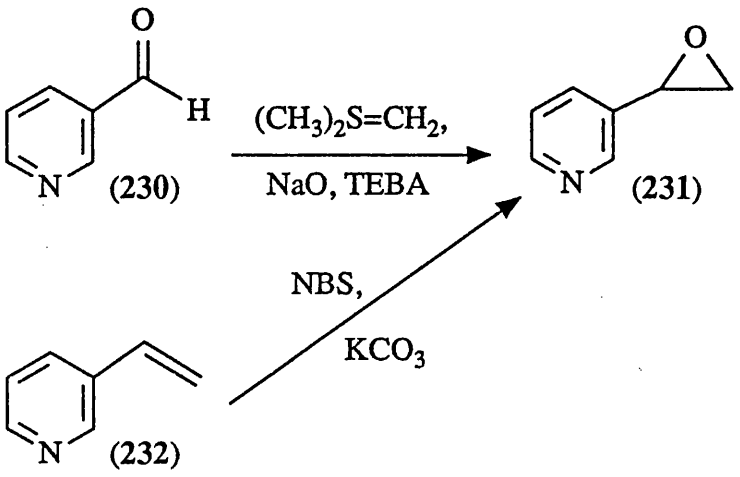
These disappointing results brought this line of enquiry to a close. Our experience did not convince us that clear-cut and facile Wittig-type reactivity was feasible for the aldehyde (55), or that this approach was worthy of more effort, and so we chose to look at other methodologies.

4·3 Formation of 1-Methyl-5-oxiranylimidazole.

4·3·1 Introduction to some epoxide chemistry.

Epoxides represent very useful synthetic tools in natural product synthesis.[206] This is particularly true of the diastereomerically pure products obtained from application of Sharpless epoxidation[207] conditions to allylic alcohols. Extensive reviews[208] of this reaction have been published.

As well as direct epoxidation of alkenes,[209] epoxides are commonly formed from aldehydes using dimethyloxosulphonium methylide - otherwise known as Corey's ylide.[210] The known compound 3-oxiranylpyridine (231) is reported[211] to be very unstable, readily undergoing ring-opening at the less sterically hindered end to form the corresponding diol. Syntheses of 3-oxiranylpyridine (231) use either the appropriate aldehyde (230) or the olefin (232) (Scheme 47).

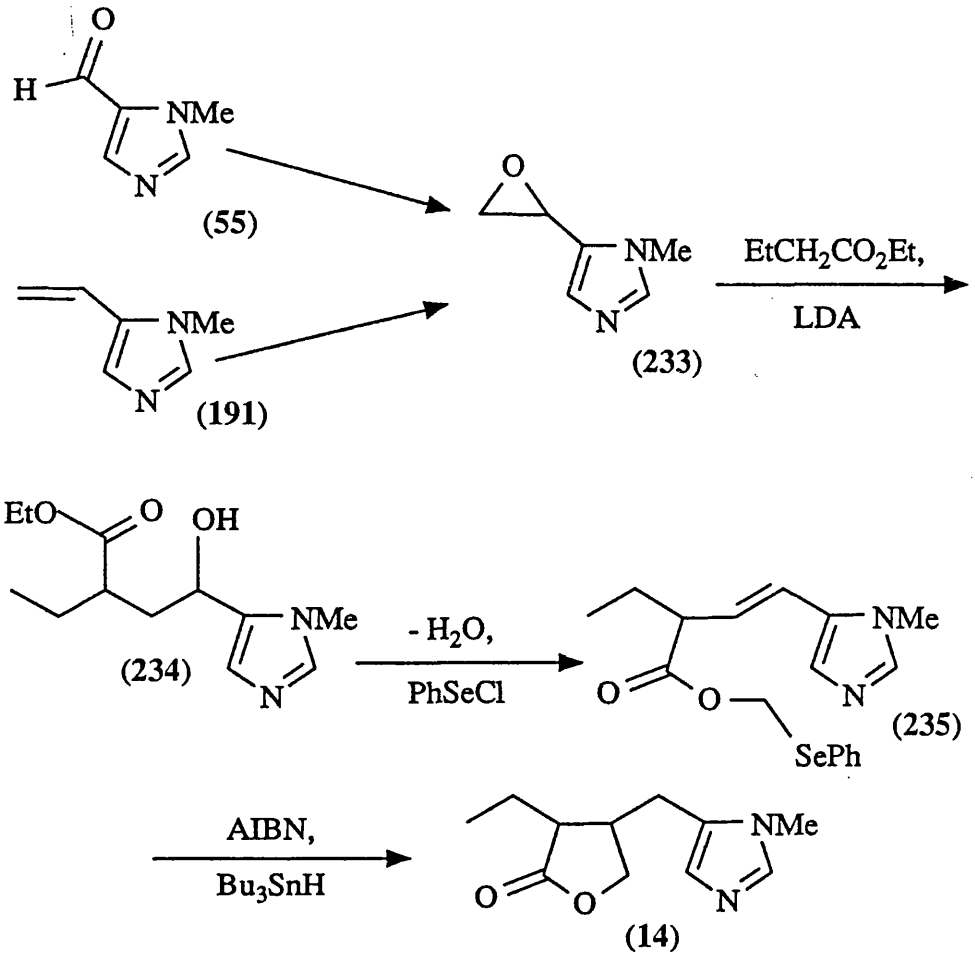


NBS = *N*-bromosuccinamide
TEBA = benzyltriethylammonium chloride

Scheme 47.

The analogous 5-oxiranyl-1-methylimidazole (233) is a novel compound. Nevertheless, we expected it to behave in a similar fashion to compound (231), thereby presenting a key intermediate in a possible synthesis of pilocarpine. We aimed to generate this species and ring-open it *in situ*, with the enolate anion of ethyl propionate, to give the alcohol (234). Dehydration to form an alkene, for subsequent ring-closure *via* a selenide, would give a mixture of (±)-pilocarpine and its isomer, see Scheme 48.

The route as it stands is not asymmetric, and any attempt at a chiral preparation of the epoxide (233) would be rendered valueless by the subsequent dehydration step. Nonetheless alkene (235) does look an attractive intermediate, due to its potential for synthetic flexibility. Standard methodology might allow its manipulation to form cyclisation candidates such as alkyne (236) (or its equivalent allene (237)), and the diene (238). Successful radical lactonisation would afford a dehydropilocarpine, whose hydrogenation would again introduce the possibility of stereoselectivity.

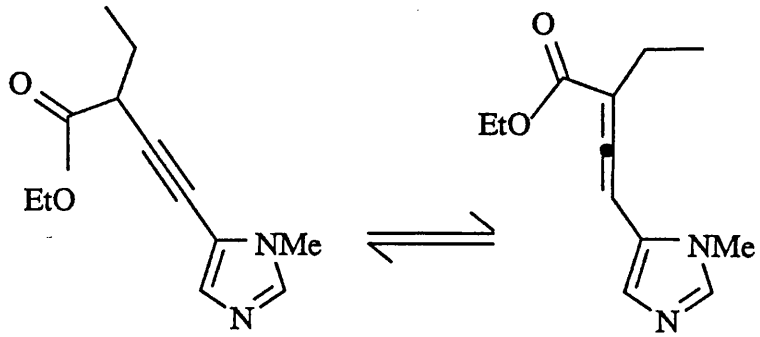


AIBN = azobisbutyronitrile
LDA = lithium di-isopropylamide

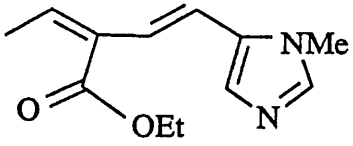
Scheme 48.

4·3·2. Epoxidation and subsequent ring-opening of 1-methyl-5-formylimidazole (55) and 5-ethenyl-1-methylimidazole (191).

Having available a ready supply of both aldehyde (**55**) and alkene (**191**), we were able to perform a variety of manipulations. *Meta*-chloroperbenzoic acid[212] has often been used successfully to generate epoxides from alkenes. As the conditions employed are relatively mild, this reagent was our first choice. However, on treatment of alkene (**191**) with *meta*-chloroperbenzoic acid, a white precipitate immediately began to form. After stirring the reaction mixture for 24 hours, no starting material was observed by t.l.c. analysis; but on work-up of the mixture, only starting material was recovered! Apparently,

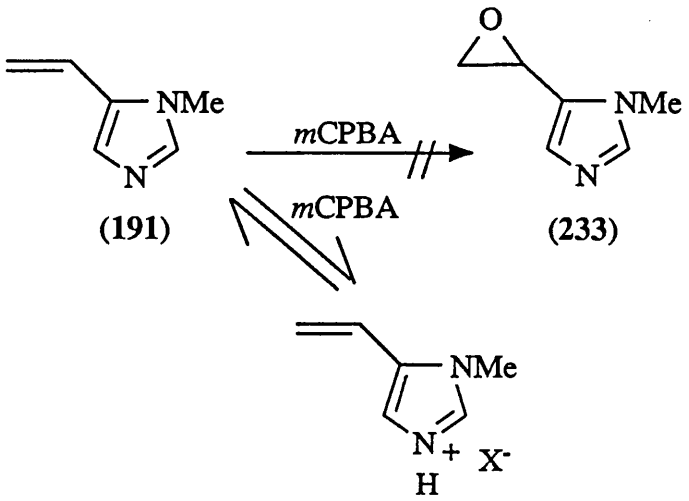


(236) (237)



(238)

meta-chloroperbenzoic acid is sufficiently acidic to protonate the tertiary nitrogen lone pair of imidazole (**191**). This would lead to precipitation of the imidazole salt out of solution, hence preventing further reaction (Scheme 49).



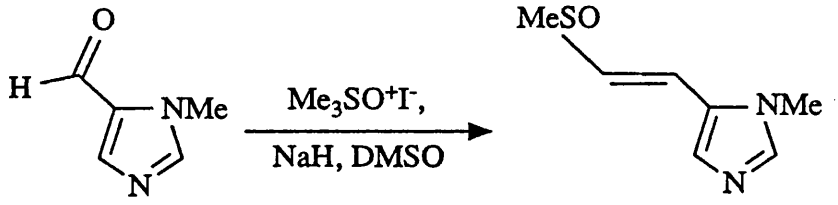
*m*CPBA = *meta*-chloroperbenzoic acid

Scheme 49.

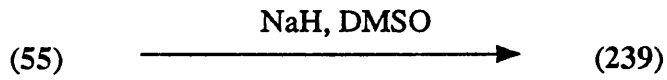
We next turned our attention to the aldehyde (**55**) and the use of Corey's ylide.

The dimethyloxosulphonium methylide is very nucleophilic and serves to transfer methylene groups to electophilic substituents such as aldehydes and ketones. This reaction is generally carried out by treating the aldehyde with sodium hydride and the sulphoxonium salt in dimethylsulphoxide solvent. In practice we observed that such a reaction of the aldehyde (55) led to rapid liberation of hydrogen, and after 2 to 3 hours all starting material had disappeared.

Only one product was isolated, and surprisingly this proved to be the sulphoxyalkene (239). When the experiment was repeated using only dimethylsulphoxide and sodium hydride as reagents, the same product was formed. Clearly deprotonation of dimethylsulphoxide is competitive with



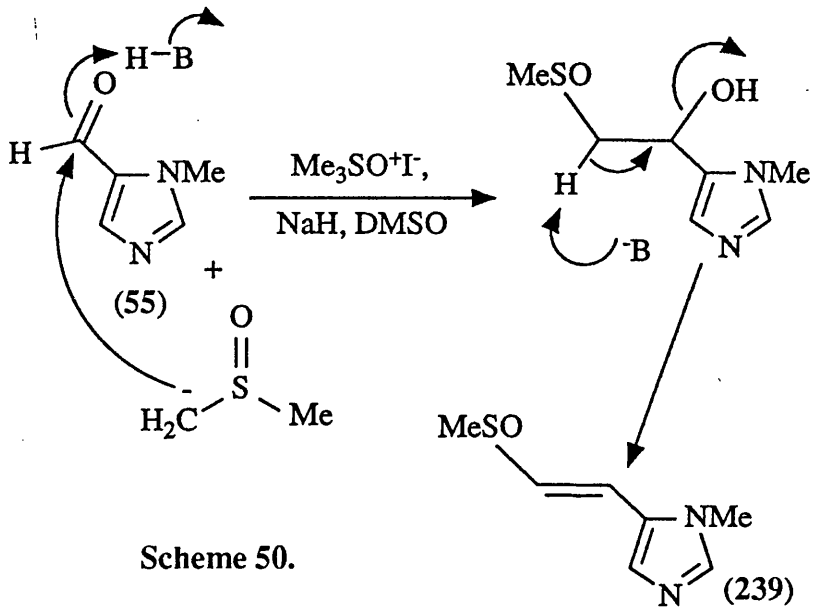
(55) (239)



(55) (239)

deprotonation of the sulphonoxonium salt, and the resultant anion of dimethylsulphoxide attacks the carbonyl preferentially. Once this happens, the sulphone group facilitates deprotonation at the α-proton, and hence dehydration to give the alkene (239), as shown in Scheme 50. Interestingly, there appears to be no report of this type of side reaction occurring during reactions with Corey's ylide.

The yields for these reactions were poor (20%), but this can be attributed to loss of the water-soluble product during the work-up procedure. Prolonged reaction times did not alter the result, and heating the reaction mixture to 60-70 °C for 24

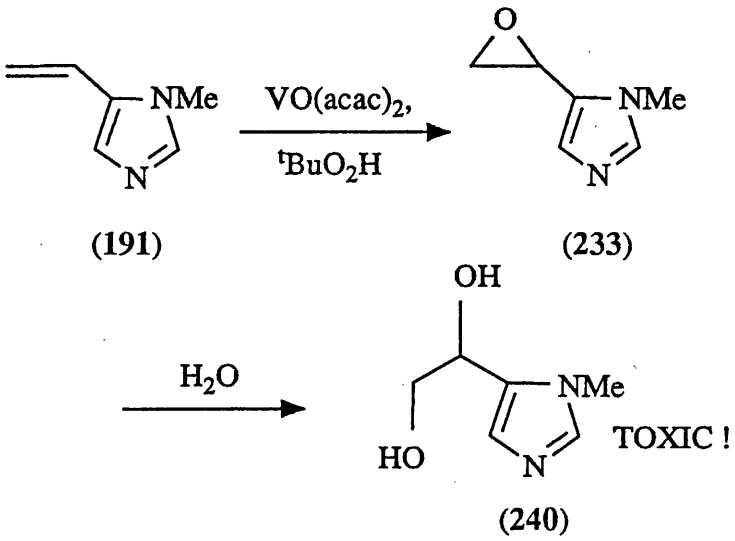


Scheme 50.

hours simply decomposed the starting material. It seems likely that both the ylide and the anion are formed under the reaction conditions, but that the ylide benefits from resonance stabilisation. Therefore, the unstabilised anion is more reactive towards the aldehyde, dictating the product and excluding the desired reaction between ylide and aldehyde.

Although an interesting outcome, this result did not help us in our synthetic aims, and so we returned to alkene (**191**) and its epoxidation. Sharpless[213] epoxidising conditions were chosen, using vanadyl acetylacetonate as catalyst. The reaction proceeded as stated for literature examples, culminating in the production of a single compound as shown by t.l.c. analysis. An aqueous wash and subsequent extraction with ethyl acetate afforded a brown oil, containing only a trace of the alkene (**191**). However, the aqueous phase was intensely u.v. active, and we assumed it to contain the diol (**240**) or a related derivative.

This compound could not be characterised, as it affected the author severely. Exposure, even to a t.l.c. plate dosed with the extract, was sufficient to cause



(191) (233)

(240)

acac = acetylacetonate

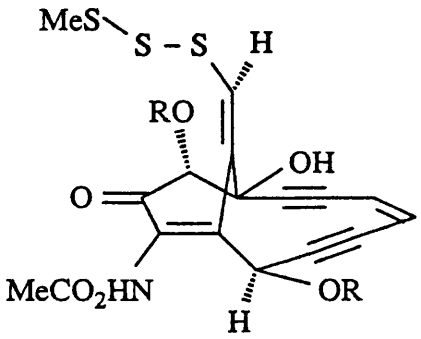
breathlessness and giddiness. These symptoms, experienced by the author and one of her colleagues, were similar to those detailed in Chapter 3. An attempt was made to freeze dry and extract the aqueous phase but, again, alarming chronic symptoms were developed by those exposed to the material. On this occasion, another worker was severely affected six or seven hours after leaving the same laboratory, and subsequently required medical treatment. As a safety precaution all further work in this area of imidazole chemistry was immediately suspended, due to a concern that continued handling of these materials could have proved life-threatening. However, we wished to continue the theme of acetylene-selenide ring closure, and our final route is described in chapter 5.

CHAPTER 5

5. CONSTRUCTION OF THE IMIDAZOLE RING AT A LATE STAGE.

5·1. Introduction.

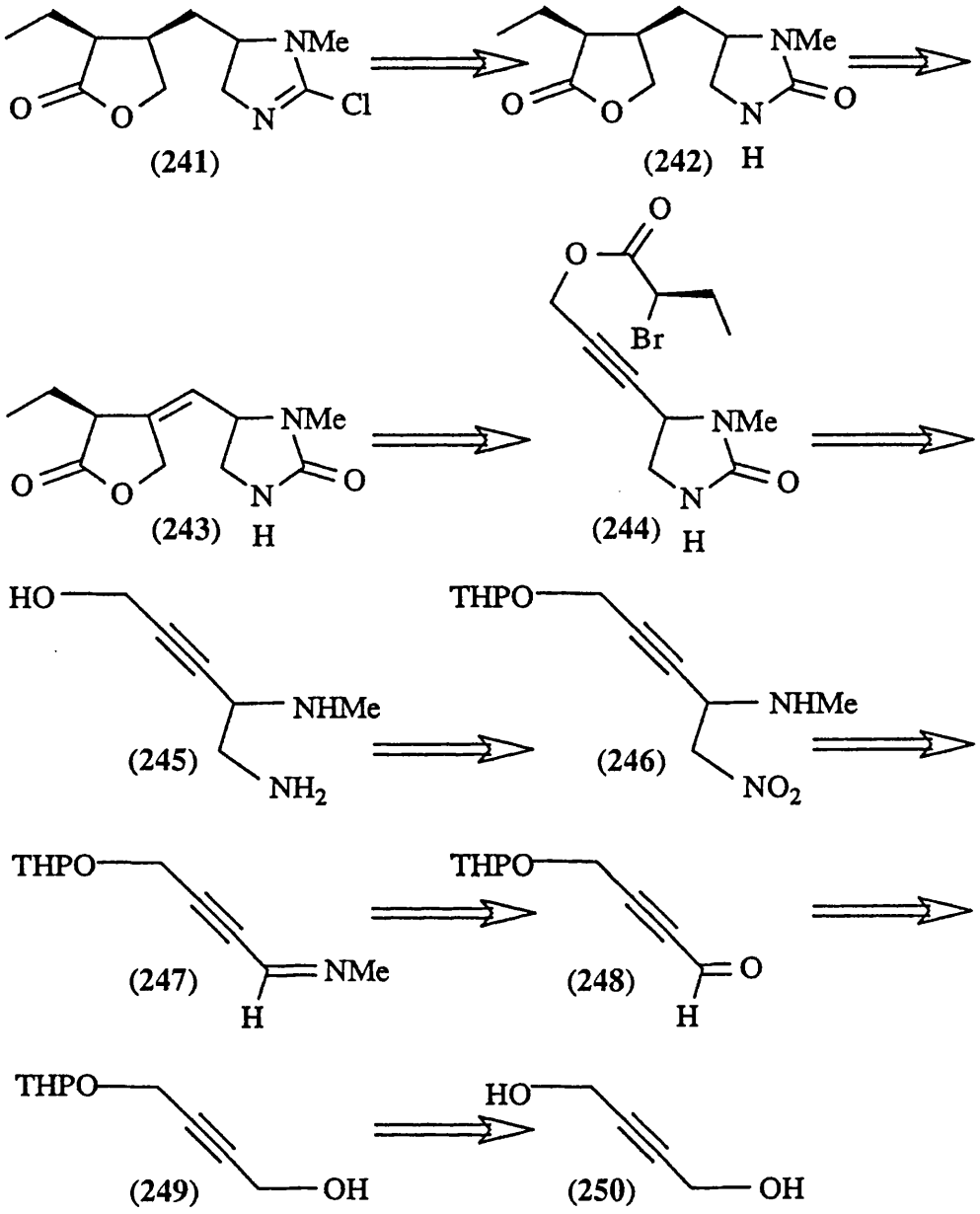
Having been frustrated by the unwanted toxic side-effects of the imidazolylalkyne (Chapter 3) and diol (Chapter 4) intermediates in our earlier approaches, we wished to develop a new strategy to avoid that problem. Propargyl alcohols[214] have proved to be very useful organic synthetic reagents, particularly for use as precursors to natural products such as Esperamycin[215] A_1. We believed that the use of such a species would allow us to construct the imidazole, at a late stage in the synthesis, from a cyclic urea.



Esperamycin A_1

2-Butyne-1,4-diol was chosen as starting material, because we hoped the use of such a bifunctional molecule would allow construction of both the lactone and imidazole portions without the hazards of a convergent synthesis. An outline of this idea is shown in Scheme 51. The key step is represented by the nucleophilic attack of nitromethane upon the imine (247). Only one literature precedent[216] exists for this type of reaction.

We did not anticipate that the lactonisation step would present any significant



THP = 2-tetrahydropyranyl

Scheme 51.

problems, because comparable reactions between propargyl bromoesters and tributyltin hydride are known.[217] This reaction occurs *via* a 5-exo-dig cyclisation, and proceeds much more rapidly with a C-C triple bond than with an alkene bond; presumably the higher rate results from the alkyne bond being a faster radical acceptor.[217] That property is no doubt associated with the linear orientation (greater steric accessibility), and higher energy (2 π-orbitals and

greater electron density), of the C-C triple bond.

Once access to the cyclic urea (**242**) had been gained, treatment with a halophosphorus species[218] should give the α-haloimine (**241**). This compound should readily isomerise and eliminate hydrogen chloride.

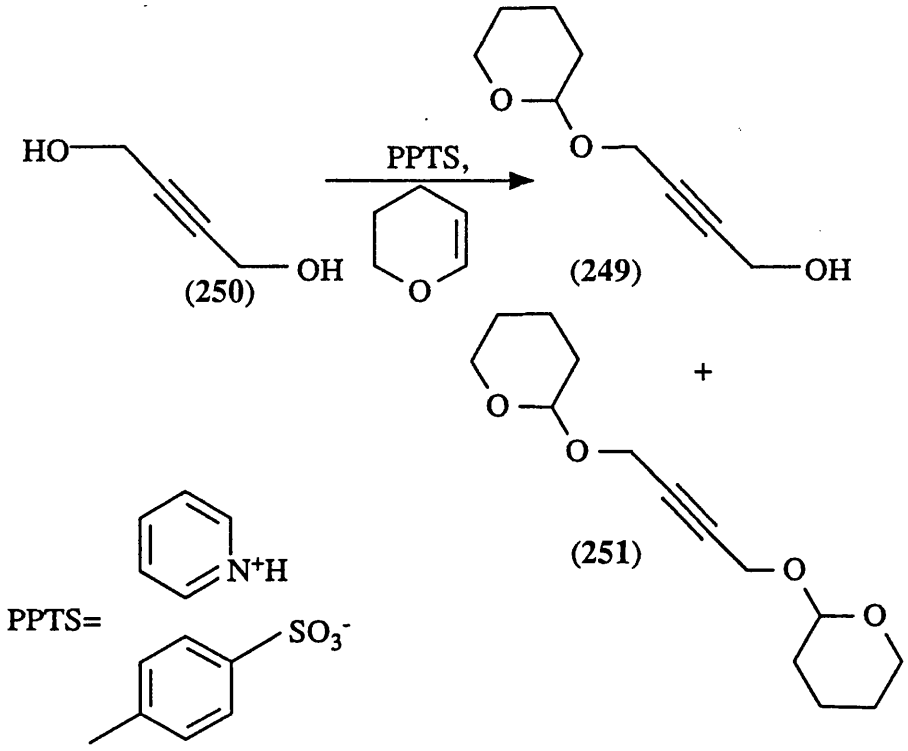
5·2 Attempted functionalisation of a disubstituted alkyne.

Our initial synthetic target was the monoprotected diol (**249**). We envisaged at least two methods of synthesising this compound; protection of propargyl alcohol, followed by lithiation and reaction with formaldehyde, or direct monoprotection of 2-butyne-1,4-diol. The latter route, *via* the diol (**250**), was adopted because the starting material can be obtained in large quantities and cheaply. We chose to monoprotect the diol using dihydropyran and an acidic catalyst.

The literature procedure[219] uses concentrated hydrochloric acid, but we concluded that these reaction conditions were too harsh. We chose to use a milder acid catalyst, namely pyridinium *p*-toluenesulphonate;[220] however, we found that in practice more forcing conditions were required for the reaction to proceed, needing the mixture to be heated to 60-70 °C (oil bath temperature). Another problem was the low solubility of 2-butyne-1,4-diol in dichloromethane at room temperature; fortunately this is overcome by warming the mixture to 60 °C.

As expected, this reaction afforded a mixture of the mono- and diprotected tetrahydropyranyl alkynediols (**249**) and (**251**). However, column chromatography over silica gel cleanly separated the two compounds; using a concentration gradient from 1:199 to 1:1 ethyl acetate-light petroleum (b.p.

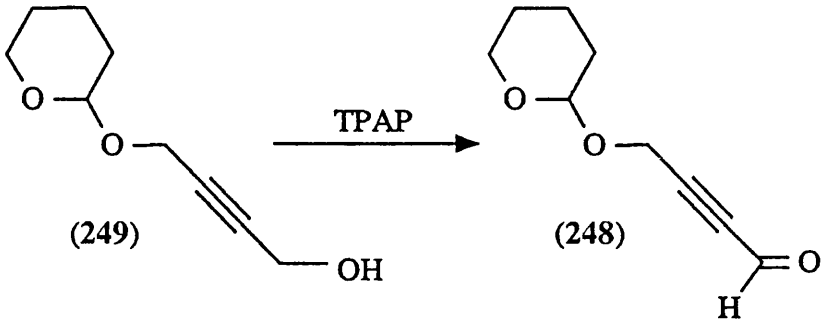
60——80 °C). It is probable that an alternative preparation of the monoprotected diol (249), from propargyl alcohol and formaldehyde, would be more efficient. However, we had sufficient material with which to work, and decided to postpone optimisation of the synthesis until we had investigated its key reactions.



Oxidation of alcohol (249), to the propargyl aldehyde (248), was readily achieved using tetra-^{n}propylammonium perruthenate[221] (TPAP). This reagent was selected because it is effective under mild non-acidic reaction conditions, which do not displace the tetrahydropyranyl protecting group. In the case of the alcohol (249), the reaction went to completion after two hours at room temperature.

As propargyl aldehydes are known to be highly air sensitive,[215] the tetra-^{n}propylammonium was removed by filtering the reaction mixture through a short pad of silica gel under a nitrogen atmosphere. We made no attempt to isolate the aldehyde (248), but immediately performed the reaction to form the imine. In order to confirm the necessity for such precautions, we demonstrated

that removal of solvent, and exposure of aldehyde (248) to air, results in its immediate oxidation to the corresponding carboxylic acid.



TPAP = tetra-^{n}propylammonium perruthenate

The imine (247) was prepared *in situ* by passing methylamine gas into dry methanol and adding the resultant solution to that of the aldehyde. Stirring the mixture at room temperature for two hours gave the desired product. Subsequent addition of nitromethane anion (generated with sodium methoxide) at 0 °C, followed by warming to room temperature, gave a single product. Isolation and characterisation of this material showed it to be the amide (252); see Scheme 53.

It is thought that the formation of the imine is successful, but that nitromethane is too poor a nucleophile - under these conditions - to attack that reactive species. The literature[222] indicates that proton abstraction from nitroalkanes is not particularly easy. Scheme 52 shows the rate of ionisation of nitroalkanes at 25 °C.

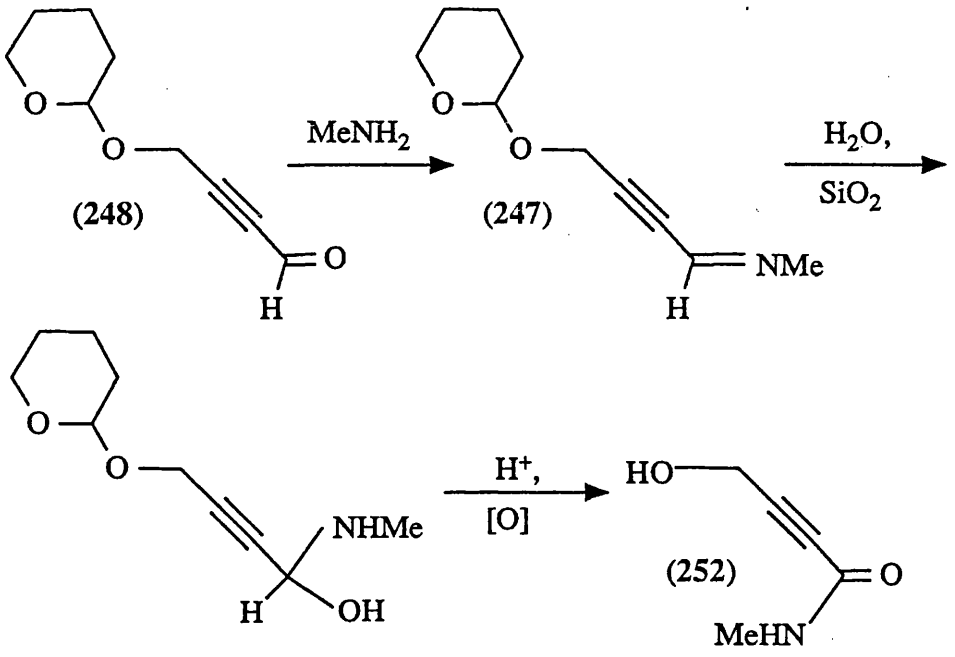
$$B^- A^+ + H_2CHNO_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} [H_2C{=}NO_2]^- A^+ + BH$$

$K_a(k_2/k_{-2})$	pK_a	k_{-2} mol min^{-1}	k_2 mol min^{-1}
6.1×10^{-11}	10·21	$4{\cdot}1 \times 10^{4}$	$2{\cdot}5 \times 10^{-6}$

Scheme 52. Rate of ionisation of nitromethane[223] at 25 °C

It can be seen that the equilibrium at room temperature lies heavily to the left;

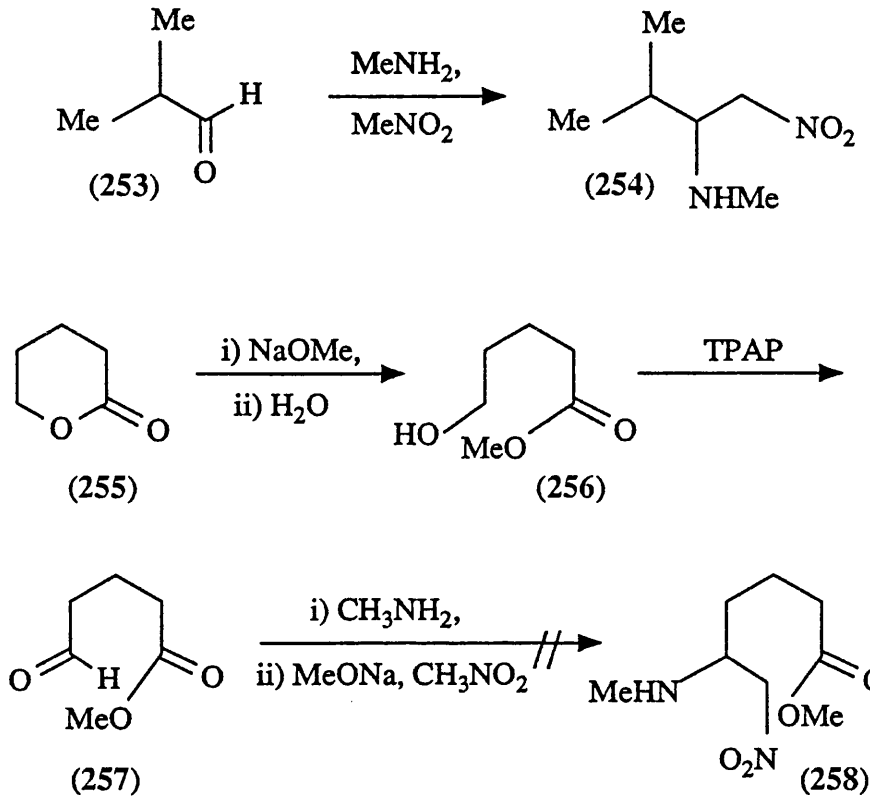
even when the mixture was refluxed there was no effect on the outcome of the reaction. Formation of amide (252) could result from reaction between the imine and water on silica gel, producing a hydroxylamine which oxidises to the amide.



Scheme 53. Possible mechanism for the formation of amide (252).

It also appears that the desired reaction of the aldehyde (248) is hindered by the presence of the carbon-carbon triple bond. Its electron-releasing effect is likely to have a detrimental effect on the electrophilicity of the imine (247), thus reducing the probability of nucleophilic attack.

In order to ascertain the practicality of optimising the reaction between the imine (247) and nitromethane, we pursued some model chemistry. Firstly we investigated a reaction using isobutyraldehyde (253), and with this system we showed that the desired product (254) could be produced in good yield (90%). As this reaction proceeded smoothly, we sought to extend our model chemistry, using a substrate obtained from δ-valerolactone (255). All steps proceeded smoothly, until addition of nitromethane to the imine, formed *in situ* from aldehyde (257), which produced an intractable mixture.



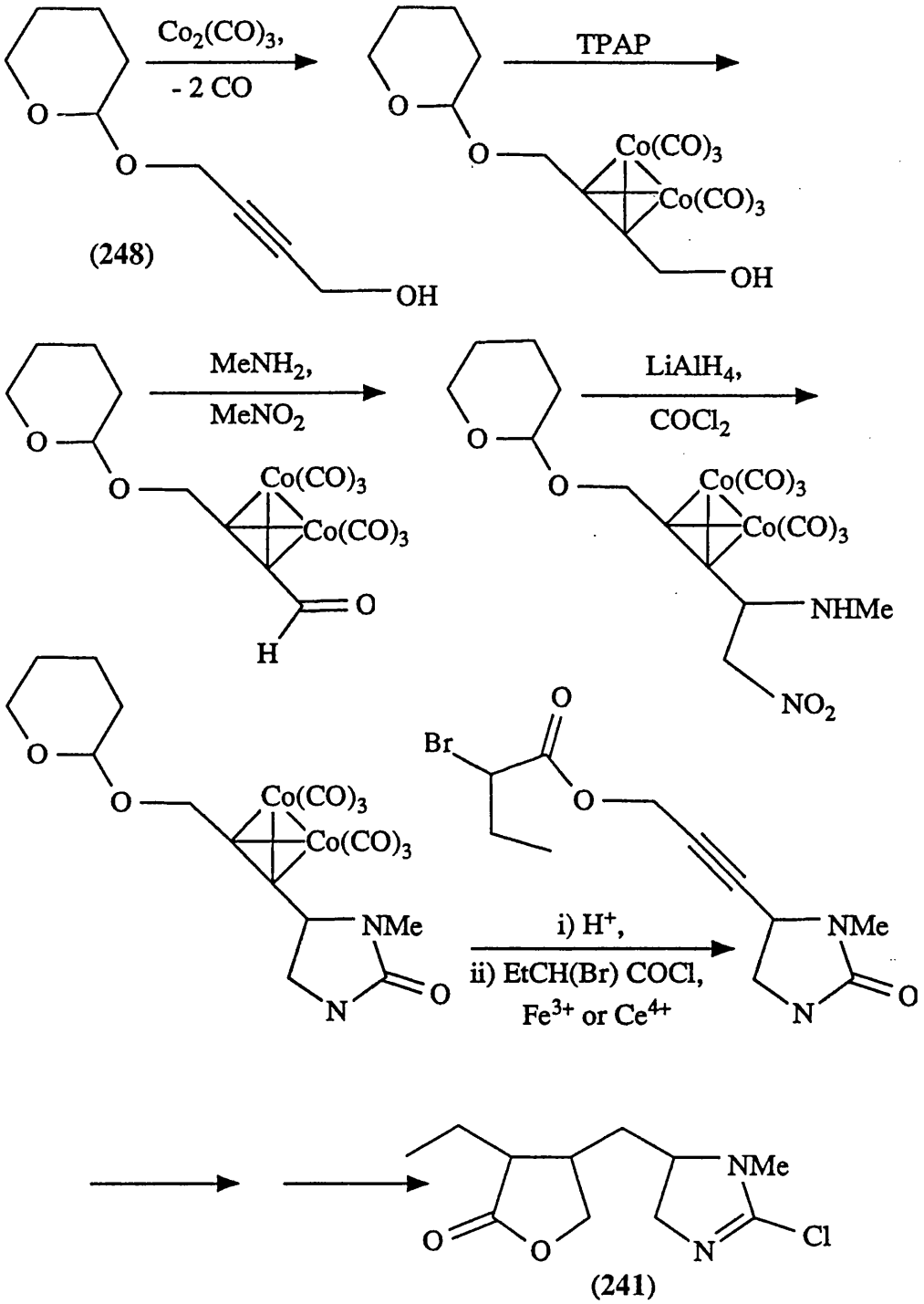
TPAP = tetra-^{n}propylammonium perruthenate

We felt this indicated that the nitromethane reaction could only be made to work with substrates which contained a limited range of non-reactive functionalities. Therefore, it seemed necessary suitably to protect the alkyne were we to continue with this strategy for pilocarpine synthesis. We devised the modifications outlined in the next section, but did not have available the time to implement them.

5·3 Future Work.

Nicholas[224] has shown that it is possible to stabilise propargyl species by the use of dicobalt octacarbonyl. Such a reaction is easily achieved at room temperature,[225] and the cobalt complex is readily displaced by either iron (III)

nitrate or cerium (IV) ammonium nitrate. This protection not only prevents self condensation of the alkyne, but greatly increases both the stability and ease of formation of subsequent products (Scheme 54).



TPAP = tetra-^{n}propylammonium perruthenate

Scheme 54.

We expect many of these compounds would be crystalline solids, and that their reactivity will be lessened by the reduced availability of the four π-electrons. A diminution of side-reactions should follow, making much easier the isolation of intermediates. We believe the application of this organometallic chemistry may overcome the problems we have so far encountered, and that use of these robust cobalt complexes may enable completion of our synthetic route outlined in this chapter.

CHAPTER 6

EXPERIMENTAL

6. EXPERIMENTAL

Melting points were recorded on an Electrothermal Mk. II, or a Gallenkamp melting point apparatus, and are uncorrected.

Elemental analyses were performed on a Carlo Erba 1106 Elemental Analyser.

Infrared spectra were determined as either a thin liquid film, a Nujol mull, or a chloroform solution, as stated. A Perkin-Elmer 1310 Infrared Spectrophotometer was used.

All n.m.r. spectra were recorded in solution using tetramethylsilane (δ 0·00, s) as the internal standard. Assignment of signals was made by comparison with the most appropriate correlation table.[226]

^{1}H n.m.r. spectra were recorded on either a Varian EM 360 (60 MHz) or a Jeol GMNGXFT-270 spectrometer (270 MHz). Multiplicities of the signals quoted with the spectroscopic data are; multiplet (m), quartet (q), triplet (t), doublet (d), and singlet (s). All values of chemical shifts and coupling constants for 60 MHz are approximate.

^{13}C n.m.r. were recorded on a Jeol GMNGXFT-270 spectrometer (67.8 MHz). All signals were proton decoupled during acquisition. The degree of substitution for each atom was determined by DEPT experiments and, although not quoted, was at all times consistent with the assignments given. Assignments of signals was made with an appropriate correlation table.[226]

Mass spectrometry was carried out on a VG 7070 E instrument, using a VG 200

data system. The spectra were determined under electron impact (70 or low eV), chemical ionisation (using isobutane), or Fast Atom Bombardment (FAB), as stated. Where appropriate, High Resolution (HR) accurate mass data are quoted.

Thin-layer chromatography was performed using Merck Kieselgel 60 F_{254} silica on aluminium foil plates. Plates were developed in unlined tanks, with the eluant stated.

Column chromatography was performed using the medium pressure[227] or dry[228] "flash" techniques, with Merck Kieselgel 60_H No. 7736 silica gel, unless stated otherwise.

Measurement of pH was carried out using the appropriate range Whatman indicator paper.

Preparation of Diethylformylsuccinate[120] (**130**).——To stirred sodium-dried ether (160 cm^3), under nitrogen, was added diethyl succinate (26·5 g, 150 mmol) and ethyl formate (15·9 g, 200 mmol). The mixture was cooled to 0 °C, sodium metal (4·0 g, 0·36 mol) was added under nitrogen and the mixture was stirred for 16-24 hours. The yellow-brown solution was quenched with water, acidified with 2M sulphuric acid (50 cm^3), extracted with ether (5 x 100 cm^3), dried over sodium sulphate, and solvent was evaporated to give an orange oil, which was distilled to yield a colourless oil (25·4 g, 84%), b.p. 94-96 °C/0·03 mm (lit.[120] 125-140 °C/12-15 mm)(Found: C, 53·6; H, 7·43. Calc. for $C_{10}H_{14}O_5$: C, 53·5; H, 6·9%); $\upsilon_{max.}$ ($CHCl_3$) 3350br (OH), 2995 (CH), 1750 (C=O), 1650 (C-O) and 1610br cm^{-1} (C=C); δ_H (270 MHz; $CDCl_3$) 1·25 (6H, t, *J* 7 Hz, CH_2CH_3), 2·60, 2·90,* and 3·80* (2H, s, CH_2C=CHOH; t,* *J* 6 Hz, CH_2CHCHO), 3·70, and 11·50*,* (1H, t, *J* 2 Hz, CHCHO; d,* *J* 7 Hz, OH), 4·15 (4H, q, *J* 7 Hz, CH_2CH_3), 7·00,* and 9·90* (1H, d, *J* 7 Hz, CH_2C=CHOH; s,* CHO); δ_C (68 MHz; $CDCl_3$), 13·8 (CH_2CH_3), 28·7 (CH_2CH_3), 29·5 (CH_2C=CHOH), 32·5 (CH_2CHCHO), 102·9 (C=COH), 155·5 (C=CHOH), 162·3 (CO_2Et), 195·4 (CHO); *m/z* (70 eV EI) 129 (M^+-73, 80%).

*Signals due to aldo and enol forms.

*Signal at 11·50 was removed, and signal at 7·00 collapsed to a singlet, on addition of D_2O.

2-Hydroxymethyldiethylsuccinate[120] (**131**)——To a stirred solution of succinate (**130**) (5 g, 25 mmol) in methanol (50 cm^3) was added, with cooling, sodium borohydride (1 g, 26 mmol). The mixture was stirred at 0 °C for 2 hours, quenched with ice, extracted with dichloromethane (4 x 50 cm^3), dried over sodium sulphate, and solvent was evaporated to give a yellow oil (4·38 g, 87%). Further purification was not necessary, (Found: C, 53·0; H, 7·9; Calc. for

$C_9H_{16}O_5$: C, 52·9; H, 7·8%); $\upsilon_{max.}$ ($CHCl_3$) 3400br (OH), 3000 (CH), 1740 (C=O), 1380 (CO_2), and 1035 cm^{-1} (C-O); δ_H (270 MHz; $CDCl_3$) 1·25 (6H, t, *J* 7 Hz, CH_2CH_3), 2·63 (2H, d, *J* 4 Hz, CH_2OH), 2·77 (1H, m, *J* 4 and 6 Hz, R_2CHCH_2OH), 3·01 (1H, t, OH), 3·75, and 3·81 (2H, t, *J* 6 Hz, CH_2CO_2Et), and 4·17 (4H, q, *J* 7 Hz, CH_2CH_3); δ_C (68 MHz; $CDCl_3$), 13·5 (CH_2CH_3), 32·3 (CH_2CO_2Et), 43·5 ($CHCH_2OH$), 60·0 (CH_2CH_3), 61·9 (CH_2OH), and 172·0 (CO_2Et); *m/z* (^{i}BuH CI) 159 (M^+-45, 100%).

Paraconic acid[112] (**132**).——To a stirred and heated solution of alcohol (**131**) (3·05 g, 15 mmol) in 95% ethanol (20 cm^3), was added, over a period of 1 hour, an aqueous solution of potassium hydroxide (2·3 g) in water (100 cm^3). The mixture was refluxed for 2 hours, cooled, 5M hydrochloric acid (50 cm^3) was added, and the liquid was removed by evaporation. The resultant residue was washed with tetrahydrofuran, dried over sodium sulphate and solvent was evaporated. The product was a hygroscopic white solid, which was recrystallised from chloroform, yielding paraconic acid (**132**), which was stored *in vacuo*, (1·73 g, 89%), m.p. 60-64 °C (lit.[112] 60-63 °C)(Found: C, 45·6; H, 4·8. Calc. for $C_5H_6O_3$: C, 46·0; H, 4·6%); $\upsilon_{max.}$ ($CHCl_3$) 3400br (OH), 3000 (CH), 1770 (lactone C=O), and 1720 cm^{-1} (acid C=O); δ_H (270 MHz; $CDCl_3$), 2·85 (2H, d, *J* 8 Hz, CH_2CO), 3·60 (1H, m, $CHCO_2H$), 4·55 (2H, d, *J* 8 Hz, CH_2O), and 12·50 (1H, br s, OH); *m/z* (^{i}BuH CI) 131 (M^++1, 100%).

4-Hydroxymethyl-1,2,3,4-tetrahydrofuran-2-one (**128**).——

Method 1.[112] To a stirred and cooled solution of acid (**132**)(2·6 g, 20 mmol) dissolved in dry tetrahydrofuran (17·8 cm^3), under nitrogen, was added a 2M solution, in tetrahydrofuran, of borane dimethylsulphide (12·4 cm^3, 24.8 mmol).

The mixture was kept at 0-5 °C for 5 hours, then methanol was added to destroy any remaining borane dimethylsulphide. The resulting mixture was stirred overnight and concentrated, prior to the addition of more methanol (3 x 20 cm^3). Each addition of methanol was followed by concentration, in order to ensure that all the borane dimethylsulphide had been removed. After the final evaporation of solvent, a brown-green oil was obtained (2·6 g). Chromatography of this crude oil over silica gel, using ethyl acetate as eluant, led to low yields of purified butanolide (**128**)(0.43 g, 32%), (Found: C, 51·4; H, 6·88. Calc. for $C_5H_8O_3$: C, 51·7; H, 6·89%); $\upsilon_{max.}$ ($CHCl_3$) 3480br (OH), 3040 (CH), 1720 (lactone C=O), and 1390 cm^{-1} (C-O); δ_H (270 MHz; $CDCl_3$) 2·38 (1H, dd, *J* 5 and 18 Hz, 3-H), 2·64 (1H, dd, *J* 9 and 18 Hz, 3-H), 2·80 (1H, m, 4-H), 3·66 (2H, dd, *J* 3 and 6 Hz, CH_2OH), 4·22 (1H, dd, *J* 5 and 9 Hz, 5-H), 4·46 (1H, dd, *J* 7 and 9 Hz, 5-H), and 5·1 (1H, s, OH); δ_C (68 MHz; $CDCl_3$), 31.0 (C-3), 37.0 (C-4), 62·9 (CH_2OH), 71·1 (C-5) and 178·3 (C=O); *m/z* (^{t}BuH CI) 117 (M^++1, 100%).

Method 2.[123] To a stirred solution of diethyl formylsuccinate (5 g, 20 mmol) in ethanol (40 cm^3) was added slowly, with cooling, sodium borohydride (2·27 g, 60 mmol). The reaction mixture was stirred for 2 hours at room temperature, diluted with 5M hydrochloric acid, filtered, and evaporated to dryness. The resulting residue was extracted with ethyl acetate, dried over sodium sulphate, and solvent was evaporated to give a yellow oil (0·97 g). The oil was dissolved in methanol (20 cm^3) and water (10 cm^3), and potassium carbonate (3 g, 20 mmol) was added. The solution was refluxed for 2 hours, 4M hydrochloric acid 50 cm^3) was added, and the mixture was concentrated. The residue was extracted with ethyl acetate, dried over sodium sulphate, and solvent was evaporated to give a crude product (0.96 g), containing a mixture of components which could not be separated.

4-Toluenesulphonyloxymethyl-1,2,3,4-tetrahydrofuran-2-one (133).—— To a solution of alcohol (128)(0·86 g, 74 mmol) in pyridine (15 cm^3) was added *p*-toluenesulphonyl chloride (2·82 g, 148 mmol) and *N,N*-dimethylaminopyridine (0.075 g, 0·6 mmol). The mixture was stirred at 0 °C for 48 hours under nitrogen, diluted with cold 1M hydrochloric acid (4 x 50 cm^3) and extracted with ethyl acetate (50 cm^3). The organic layer was washed with brine, dried over sodium sulphate, and solvent was evaporated. Chromatography over silica gel, with ethyl acetate-light petroleum (b.p. 60——80 °C)(1:4) yielded a red-brown oil in very poor yield (0.2 g, 10%). Insufficient sample was available for an elemental analysis; $\upsilon_{max.}$ ($CHCl_3$) 3001 (CH), and 1768 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 2·47 (3H, s, CH_3), 2·75 (1H, m, C*H*CH_2O), 2·66 (2H, dd, *J* 9, and 18 Hz, CH_2CO), 4·04 (4H, m, CH_2SO_3, OC*H*$_2$CH), 7·35 (2H, d, *J* 8 Hz, 3'-H, and 5'-H) and 7·80 (2H, d, 2'-H, and 6'-H); δ_C (68 MHz; $CDCl_3$) 21·6 (CH_3), 30·5 (CH*C*H_2CO), 34·7 (*C*HCH_2O), 69·2 (CH_2SO_3), 69·3 (CH*C*H_2O), 77·4 (C-4'), 130·1 (Ar), and 145·4 (C=O); *m/z* (^{i}BuH CI) 271 (M^++1, 100%).

2,5-Di(^{t}butyldimethylsilyl)-1-methylimidazole (139).——To a solution of di-isopropylamine (3·36 cm^3, 24 mmol) in dry tetrahydrofuran (20 cm^3) was added a 1·6M hexane solution of ^{n}butyl lithium (15 cm^3, 24 mmol) at 0 °C and the resulting solution was stirred for 1 hour at 0 °C. A solution of 1-methylimidazole (2 g, 24 mmol) in dry tetrahydrofuran (2 cm^3) was added at -78 °C resulting in a yellow solution. The solution was stirred for 3 hours at -78 °C and quenched with a solution of ^{t}butydimethylsilyl chloride (3·6 g, 24 mmol) in dry tetrahydrofuran (8 cm^3), producing a white precipitate. The reaction was warmed to room temperature poured into ice-saturated ammonium chloride solution, extracted with ether, dried over sodium sulphate and evaporated to give a yellow oil (see below) and a white solid,

2,5-di(ᵗbutyldimethylsilyl)-1-methylimidazole (0·425 g, 10%), m.p. 106-108 °C. (Found: C, 60·0; H, 11·1; N, 9·2. $C_{16}H_{34}N_2Si_2$ requires C, 62·0; H, 11·0; N, 9·0%); $\upsilon_{max.}$ ($CHCl_3$) 2900 (CH), 2470 (C=N), 1450 (C-N) and 800 cm^{-1} (C-Si); δ_H (270 MHz; $CDCl_3$), 0·29 (6H, s, $(CH_3)_2$Si-C-5), 0·39 (6H, s, $(CH_3)_2$Si-C-2), 0·89 (9H, s, $(CH_3)_3$CSi-C-5), 0·92 (9H, s, $(CH_3)_3$CSi-C-2), 3·76 (3H, s, CH_3N) and 7·27 (1H, s, 4-H); δ_C (68 MHz; $CDCl_3$), -4·67 ($(CH_3)_3CSi$), -4·47 ($(CH_3)_3CSi$), 26·5 ($(CH_3)_3$CSi), 26·2 (NCH_3), 36·0 (C-5), 130·1 (C-4) and 141·2 (C-2); *m/z* (70 eV EI and ⁱBuH CI) 311 (M^++1, 20%).

The reaction was repeated as above, except that the time for carbanion formation was halved to 90 minutes, resulting in the formation of a yellow oil, *2-ᵗbutyldimethylsilyl-1-methylimidazole* (138)(0.425 g, 90%) (Found: C, 60·7; H, 11·1; N, 11·2. $C_{10}H_{20}N_2Si$ requires C, 61·2; H, 10·2; N, 14·28%); $\upsilon_{max.}$ ($CHCl_3$) 1460 (C=N) and 800 cm^{-1} ((C-Si); δ_H (270 MHz; $CDCl_3$), 1·03 (9H, s, $(CH_3)_3$CSi), 3·83 (3H, s, CH_3N), 7·03 (1H, d, *J* 2 Hz, 4-H) and 7·26 (1H, d, *J* 2 Hz, 5-H); δ_C (68 MHz; $CDCl_3$) -4·99 ($(CH_3)_2$Si), -3·6 ($(CH_3)_3CSi$), 17·5 ($(CH_3)_3$CSi), 34·6 (NCH_3), 123·0 (C-4 and C-5); *m/z* (ⁱBuH CI) 197 (M^++1, 100%).

Attempted Preparation of 5-Benzyl-2-ᵗbutyldimethylsilyl-1-methylimidazole (140).——To a solution of di-isopropylamine (3·36 cm^3, 24 mmol) in dry tetrahydrofuran (25 cm^3) cooled to 0 °C was added a 1·6M hexane solution of ⁿbutyl lithium (15 cm^3, 24 mmol). The solution was stirred for 1 hour, cooled to -78 °C and a solution of 1-methylimidazole (2 cm^3, 24 mmol) in tetrahydrofuran (5 cm^3) was added slowly, giving a yellow solution. The reaction was stirred at -78 °C for 1·5 hours, a solution of ᵗbutyldimethylsilyl chloride (3·6 g, 24 mmol) in tetrahydrofuran (20 cm^3) was added, and the mixture allowed to warm to room

temperature. After 3 hours the mixture was again cooled to -78 °C and a second equivalent of lithium di-isopropylamide was added, the mixture was stirred for 1·5 hours, and benzyl bromide (3·9 g, 24 mmol) in dry tetrahydrofuran (10 cm^3) was added. The reaction was again warmed to room temperature, poured onto ice-saturated ammonium chloride, extracted with ether, dried over sodium sulphate, and evaporated *in vacuo* to give a yellow-white solid (0.415 g). Recrystallisation from ethanol gave a white crystalline solid, *trans*-stilbene, m.p. 120 °C (lit.[229] 122 °C)(Found: C, 93·5; H, 6·66. Calc. for $C_{14}H_{12}$: C, 93·3; H, 6·66%); $\upsilon_{max.}$ ($CHCl_3$) 3000 (Ar-H), 1580 (C=C) and 650 cm^{-1} (Ar-H); δ_H (270 MHz; $CDCl_3$), 7·19 (2H, s, CH=CH) and 7·56 (10H, m, Ar); *m/z* (70 eV EI) 180 (M^+, 100%).

N,N-*Dimethyloxamide*[135] (**143**).——To a stirred and cooled solution of 33% (w/v) methylamine (in methylated spirits 93 cm^3, 1·0 mol), in ethanol (100 cm^3), was added slowly, over 15 minutes, diethyl oxalate (50 cm^3, 0·3 mol). On addition of the oxalate, an immediate precipitate of *N,N*-dimethyloxamide was formed. The mixture was stirred for 2-3 hours to give needles of a white solid, which was recrystallised from ethanol, yielding *N,N*-dimethyloxamide (33.32 g, 98%), m.p. 215-217 °C (lit.[135] 216-217 °C)(Found: C, 40·4; H, 7·0; N, 24·1. Calc. for $C_4H_8N_2O$: C, 41·4; H, 6·9; N, 24·1%); $\upsilon_{max.}$ ($CHCl_3$) 3385 (NH), 2940 (CH), and 1650 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$), 2·91 (6H, d, *J* 4 Hz, CH_3) and 7·49 (1H, br s, NH); δ_C (68 MHz; $CDCl_3$) 25·9 (CH_3) and 160·3 (C=O); *m/z* (70 eV EI) 116 (M^+, 100%).

5-Chloro-1-methylimidazole[136] (**120**, X = Cl).——Oxamide (**143**)(10·0 g, 86 mmol) was added to phosphorus pentachloride (35 g, 170 mmol) under nitrogen

and heated cautiously to initiate the reaction (oil bath temperature 100-110 °C). Once the solids had partially melted the reaction was heated to 120 °C, producing a homogeneous solution, and kept at this temperature for 2-3 hours. Phosphorus oxychloride was removed from the resulting dark red-brown solution by distillation. Water was added cautiously, to destroy any remaining phosphorus pentachloride, and the mixture was heated with charcoal to remove any remaining dimethyloxamide. This mixture was filtered, the colourless filtrate was neutralised with 6M sodium hydroxide solution, and immediately extracted with chloroform (10 x 100 cm^3). The organic phase was dried over sodium sulphate, and solvent was evaporated to produce a red-brown solid (5 g). Distillation gave a colourless oil which rapidly developed a yellow colouration (1·48 g, 15%), b.p. 38-40 °C/0·1 mm, (lit.[140] 53-54 °C/0·8 mm)(Found: C, 42·0; H, 5·2; N, 23·1. Calc. for $C_4H_5N_2Cl$: C, 41·4; H, 4·31; N, 24·1%); $\upsilon_{max.}$ ($CHCl_3$) 3100 (Ar-H), 2900 (CH), 1720 (C=N) and 1650 (C=C); δ_H (270 MHz; $CDCl_3$) 3·59 (3H, s, CH_3), 6·93 (1H, s, 4-H), and 7·44 (1H, s, 2-H); δ_C (68 MHz; $CDCl_3$) 31·4 (NCH_3), 118·1 (*C*Cl), 125·6 (N*C*=CCl) and 136·9 (NC=N); *m/z* (70 eV EI) 116 (M^+, 80%) 118 (M^++2, 30%).

Attempted preparation of 2-^{t}Butydimethylsilyl-5-chloro-1-methylimidazole (**146**).——To a solution of freshly distilled di-isopropylamine (0·12cm^3, 0·86 mmol) in dry tetrahydrofuran (5 cm^3), cooled to -78 °C, was added a 1·6M hexane solution of ^{n}butyl lithium (0·5 cm^3, 0·86 mmol). On addition of ^{n}butyl lithium a white precipitate formed, indicating the formation of lithium di-isopropylamide. The solution was stirred at 0 °C for 1 hour in order to ensure complete formation of the lithiated species. The solution was again cooled to -78 °C and a solution of (**120, X = Cl**) (0·1 g, 0·86 mmol) in dry tetrahydrofuran (1 cm^3) was added, producing a yellow solution which was stirred for 2 hours at -78

°C, then quenched with a solution of ^{t}butyldimethylsilyl chloride (0·14 g, 0·86 mmol) in dry tetrahydrofuran (2 cm^3). The reaction was then allowed to warm to room temperature, poured onto saturated ammonium chloride, extracted with ether, dried over sodium sulphate, and evaporated to give a yellow-brown oil. Chromatography on silica gel using ethyl acetate-petroleum (b.p. 60——80 °C)(1:1) as eluant produced poor separation of the many components observed. Only one product could be characterised tentatively as the dimer (**145**). δ_H (270 MHz; $CDCl_3$), 0·87 (6H, s, $(CH_3)_2Si$), 1·25 (9H, s, $(CH_3)_3Si$), 3·95 (6H, s, CH_3N) and 7·08 (2H, s, 4-H); *m/z* (^{i}BuH CI) 310 (M^+, 50%) 312 (M^++2, 20%).

2-^{t}Butyldimethylsilyl-5-chloro-1-methylimidazole (**146**).——To a stirred solution of chloroimidazole (**120, X = Cl**)(0·11 g, 1 mmol) in sodium-dried tetrahydrofuran (5 cm^3) was added a 1·6M hexane solution of ^{n}butyl lithium (0·52 cm^3, 1·3 mmol) at -78 °C. The solution was stirred for 45 minutes then a solution of ^{t}butyldimethylsilyl chloride (0·15 g, 1 mmol) in dry tetrahydrofuran (5 cm^3) was added and the reaction mixture allowed to warm to room temperature. The solution was quenched with water (10 cm^3) and extracted with ether (3 x 30 cm^3). The organic layer was dried over magnesium sulphate, filtered and evaporated *in vacuo*. Chromatography over silica gel using ethyl acetate-petroleum ether (b.p. 60——80 °C) (1:49) yielded a colourless oil (0.05 g, 22%), $C_{10}H_{19}N_2SiCl$ requires *M*, 230·8120 but fragments too rapidly therefore M^+-57 peak (low eV EI) was used; M^+-57 = 173·6968 ($C_6H_{10}N_2SiCl$ requires *M*, 173·6969); δ_H (270 MHz; $CDCl_3$), 0·25-0·9 (15H, ^{t}BuMe$_2$Si), 3·59 (3H, s, NCH_3) and 7·05 (1H, s, 4-H); δ_C (68 MHz; $CDCl_3$) -3·6 ($Si(CH_3)_2$), 17·7 (C-2), 25·6 ($(CH_3)_3C$), 31·6 (NCH_3), 125·6 (C-4) and 137 (C-5); *m/z* (^{i}BuH CI) 230 (M^+, 20%), 232 (M^++2, 20%).

Reaction of 2(5H)-Furanone with ⁿButyl lithium.——To a solution of 2(5H)-furanone (2 g, 24 mmol) in dry tetrahydrofuran (30 cm^3), cooled to -78 °C, was added a 1·6M hexane solution of ⁿbutyl lithium (30 cm^3, 48 mmol). The mixture was stirred at -78 °C for 90 minutes and then allowed to warm slowly to room temperature, at which point the mixture was quenched with ice-saturated ammonium chloride solution. The reaction mixture was extracted with ethyl acetate (2 x 15 cm^3) and dried over sodium sulphate. Evaporation gave an orange-yellow oil, and chromatography over silica gel with ethyl acetate-petroleum ether (b.p. 60——80 °C) (1:4) as eluant yielded 4-ⁿbutyloct-2-en-1,4-diol (2·3 g, 50%), (Found: C, 73·0; H, 12·3. Calc. for $C_{12}H_{24}O_2$: C, 71·9; H, 12·1%); $\upsilon_{max.}$ ($CHCl_3$) 3300br (OH), 2900 (CH), and 1700 cm^{-1} (C=C); δ_H (270 MHz; $CDCl_3$) 0·89 (12H, m, CH_2), 1·54 (6H, m, CH_3), 3·84 (2H, br s, OH), 4·25 (2H, d, *J* 8 Hz, CH_2CH=CH), 5·38 (1H, d, *J* 8 Hz, CH_2CH=C*H*), and 5·65 (1H, m, *J* 6 and 8 Hz, CH_2CH=CH); δ_C (68 MHz; $CDCl_3$) 14·2 (CH_3CH_2), 23·3 (CH_2CH_3), 26·0 (CH_2CH_2), 42·0 (CH_2CR_2OH), 58·9 (CH_2OH), 128·4 (CH_2CH=CH) and 138·0 (CH_2CH=CH); *m/z* (ⁱBuH CI) 201 (M^++1, 20%), 143 (M^+-ⁿBuH, 100%).

Attempted preparation 5-Benzoyl-1-methylimidazole (**149**).——To a solution of oven-dried magnesium metal (0·1 g, 4·3 mmol) in dry tetrahydrofuran (20 cm^3) was added 5-chloro-1-methylimidazole (0·5 g, 4·3 mmol) and a crystal of iodine. The reaction was refluxed for 5-6 hours until a precipitate formed and the solution turned orange. Benzoyl chloride (0·6 g, 4·3 mmol) in dry tetrahydrofuran (5 cm^3) was added and the reaction was refluxed for a further 2 hours, quenched in ice-saturated ammonium chloride solution, extracted into ether (3 x 15 cm^3), dried over magnesium sulphate and evaporated *in vacuo* to

give a viscous orange oil. After chromatography over silica gel using ethyl acetate-light petroleum (b.p. 60——80 °C)(1:5) as eluant, the oil gave dibenzoyl, $\upsilon_{max.}$($CHCl_3$) 3000 (Ar-H) and 1650 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 7·35 (10H, m, Ar); *m/z* (^{i}BuH CI) 211 (M^+, 20%).

N-*Formyl*-N-*methylglycine methyl ester*[152, 156] (163).——A mixture of methylamine hydrochloride (135 g, 2 mol), a 37% aqueous solution of formalin (270 cm^3) and water (100 cm^3) was cooled in an ice bath, and with continuous stirring, a cold concentrated aqueous solution of potassium cyanide (130 g, 2 mol) was added over about 2 hours. The temperature was kept below 10 °C and a little solid carbon dioxide was added from time to time to maintain a carbon dioxide atmosphere. The reaction mixture was stirred for 1 hour and then extracted into a total of 1 litre of dichloromethane. After drying over calcium chloride and filtration, the solvent was evaporated *in vacuo*. The yellow oil obtained was dissolved in dry methanol (2·5 litres) which had been saturated with hydrogen chloride. The resulting solution was allowed to stand overnight, under nitrogen, and then refluxed for 4 hours. The reaction mixture was reduced in volume and the precipitated ammonium chloride was removed. The crude *N*-methylglycine methyl ester hydrochloride was dissolved by warming in 98% formic acid (250 cm^3). To this solution was added a hot solution of sodium formate (150 g) in 98% formic acid (200 cm^3). After the mixture had stood for 1 hour it was filtered through "celite" to remove the precipitated sodium chloride. To the remaining solution was added acetic anhydride (450 cm^3), in portions, producing a vigorous reaction. When this had subsided, the mixture was heated at 70-80 °C for 1·5 hours and then evaporated to remove the formic and acetic acids. The residual liquid was taken into 1 litre of acetone and sodium chloride was precipitated. The solution was then filtered, the solvent evaporated, and the

residual material, a dark brown viscous oil which contained some inorganic material, was distilled under reduced pressure to yield 43·4 g (18·5%) of *N*-formyl-*N*-methylglycine methyl ester as a colourless oil, b.p. 86-88 °C/0·2 mm. $\upsilon_{max.}$ ($CHCl_3$) 1730 (C=O ester), 1690 (C=O aldehyde) and 1070 cm^{-1} (C-O); δ_H (270 MHz; $CDCl_3$) 2·4 (3H, s, NCH_3), 3·1 (2H, s, NCH_2CO), 3·8 (3H, s, CO_2CH_3) and 8·1 (1H, s, CHO); *m/z* (70 eV EI) 132 (M^++1, 100%).

Condensation of N-*Formyl*-N-*methylglycine methyl ester with Methyl Formate to give enone* (**164**).——To a stirred solution of ester (**163**)(43·4 g, 0·37 mol) in dry methyl formate (70 cm^3, 1·11 mol) at 0-5 °C was added, in five portions over 1 hour, freshly prepared sodium methoxide (9·2 g, 0·4 mol) in dry benzene (75 cm^3). The sodium methoxide was prepared by dissolving sodium in dry methanol (16·2 cm^3, 0·4 mol) and a temperature below 15 °C was maintained for 1 hour. The mixture (a pale cream suspension) was allowed to stand in the refrigerator for 18 hours. The enolate was not isolated, but a small sample was taken and added to ether yielding an off white solid, from which it was assumed that reaction had taken place.[156]

Methyl 2-mercapto-1-methyl-5-imidazolecarboxylate (**165**).——The suspension of the sodium enolate prepared as above was shaken with water (100 cm^3) whereupon the suspended solid dissolved and the aqueous layer was separated. This was then cooled in an ice bath and stirred with 36% hydrochloric acid (75 cm^3, 0·85 mol). The mixture was warmed to 60-70 °C for 2 hours, allowed to stand overnight and then cooled in an ice bath. A small quantity of the solid precipitated was collected. ^1H n.m.r. showed no signals in the aromatic region, and an absence of the S-H signal at δ 1-2. Attempts to retrieve any solid material

by reducing the volume of the aqueous phase were unsuccessful, so water was removed *in vacuo* and the remaining solid was triturated with $CHCl_3$, ethyl acetate, and ethyl acetate-methanol. The residual solid, which was water soluble, was assumed to be mostly inorganic, and a dark brown oil was obtained after evaporation of the organic solutions, $\upsilon_{max.}(CHCl_3)$ 2040 (NCS), 1730br vw, 1620br vw cm^{-1}; δ_H (270 MHz; $CDCl_3$) 3·0-5·0 (m), 8·1 (s) and 7·5 (s).

N-(α-Toluenesulphonylstyryl)formamide[160, 161] (**170**).——A solution of toluenesulphonylmethyl isocyanide (TosMIC)(1 g, 5·37 mmol) in dry 1,2-dimethoxyethane (5 cm^3) was added dropwise with stirring to a suspension of ^{t}BuOK (0·76 g, 5·37 mmol) in 1,2-dimethoxyethane under nitrogen between -30 to -10 °C. To the reaction mix was added a solution of benzaldehyde (0·55 cm^3, 5·37 mmol) in 1,2-dimethoxyethane (3 cm^3) at -40 °C. After stirring for 30 minutes at -30 °C, the mixture was poured into ice-water, acidified with acetic acid, extracted with dichloromethane, washed with water, dried over magnesium sulphate, evaporated and treated with methanol at -20 °C to give a white solid, N-(α-toluenesulphonylstyryl)formamide (0.53 g, 33%), m.p. 150-152 °C (lit.[160] 146-150 °C). (Found: C, 63·5; H, 4·94; N, 4·69. Calc. for $C_{15}H_{16}O_3S_2N$: C, 61·3; H, 4·8; N, 4·5%); $\upsilon_{max.}$ ($CHCl_3$), 3320 (NH), 1690 (C=O), 1645 (C=C) and 1330 cm^{-1} (SO_2); δ_H (270 MHz; $CDCl_3$), 2·40 and 2·43 (3H, s, $ArCH_3$ E, Z isomers), 7·02 and 7·06 (1H, NH, E and Z isomers), 7·55 (10H, m, Ar, CH=C) and 8·06 (1H, s, CHO); δ_C (68 MHz; $CDCl_3$), 21·6 (CH_3), 128·5, 129·3 (C=C), 130·6-134·7 (Ar) and 163·4 (NCOH); *m/z* (^{t}BuH CI) 302 (M^+, 100%).

1-Isocyano-2-phenyl-1-toluenesulphonylethene (**173**).——To a solution of the formamide (**170**) (0·1 g, 0·32 mmol) in dry 1,2-dimethoxyethane (2 cm^3) at -5 °C

was added triethylamine (0.27 cm^3, 1.9 mmol), followed by the slow addition of phosphorus oxychloride (0.08 cm^3, 0.957 mmol) in dry 1,2-dimethoxyethane (0.5 cm^3) over 5-10 minutes. The solution was then stirred for 1 hour at 0 °C to give a yellow-white precipitate, poured into ice-water, extracted with dichloromethane, dried over magnesium sulphate, evaporated and treated with methanol at -20 °C (CCl_4-CO_2) to give a white solid. Recrystallisation from methanol gave 1-isocyano-2-phenyl-1-tolunesulphonylethene 50 mg (50%), m.p. 79-80 °C (lit.[160] 80 °C); $\upsilon_{max.}$ ($CHCl_3$) 2900 (CH_3Ar), 2400 (C=N) and 1650 cm^{-1} (C=C); δ_H (270 MHz; $CDCl_3$) 2·43 (3H, s, CH_3Ar) and 7·55 (10H, m, Ar and CH=C); *m/z* (^{t}BuH CI) 127 (*M*$^+$-156, 50%) 91 (*M*$^+$-192, 20%).

1-Methyl-5-phenylimidazole (**174**).——Methylamine (33% in methylated spirits) (0·09 cm^3, 7·76 mmol), was added to a solution of alkene (**173**) (0·11 g, 3·88 mmol) in methanol (5 cm^3) and stirred for 5 minutes at room temperature. After diluting with water, extracting with dichloromethane, drying (magnesium sulphate), evaporation of solvent and sublimation (80-100 °C/0·2 mm) a white solid was produced (50 mg, 51%), m.p. 92-94 °C (lit.[160] 90-94 °C). $\upsilon_{max.}$ ($CHCl_3$) 3300 (NH) and 3000 cm^{-1} (Ar-H); δ_H (270 MHz; $CDCl_3$) 3·6 (3H, s, NCH_3) and 7·5 (7H, m, Ar, Imid); *m/z* (^{t}BuH CI) 159 (*M*$^+$, 25%).

4,5-Dicyanoimidazole[162] (**176**).——A mixture of diaminomaleonitrile (5 g, 46·2 mmol) and triethylorthoformate (9 g, 61 mmol) in anisole (30 cm^3) was heated on an oil bath at 135 °C for 30 minutes, whilst ethanol (7 g) was distilled out of the reaction mixture. Sodium methoxide (18 mg) was added and heating continued until no more distillate was collected. The solution was filtered hot and the filtrate, on cooling, produced a dark red-brown solid (5·3 g, 98%).

Recrystallisation from water gave a pale brown crystalline solid (4·9 g, 90%), m.p. 174-75 °C (lit.[162] 175 °C) $\upsilon_{max.}$ (nujol) 3400 (NH) and 2220 cm^{-1} (CN); δ_H (270 MHz; DMSO-D_6) 8·27 (1H, s, 2-H); δ_C (68 MHz; DMSO-D_6) 111·3 (CN), 115·3 (*C*-CN) and 141·9 (C-2); *m/z* (low eV EI) 118 (M^+, 100%).

4,5-Dicyano-1-methylimidazole. (**177**).——To a suspension of imidazole (**176**) (5 g, 42 mmol) in water (50 cm^3) was added slowly a solution of sodium hydrogencarbonate (6·72 g, 80 mmol). The reaction mixture was then heated to 65 °C and dimethylsulphate (5·68 g, 45 mmol) was added slowly over 1 hour. The mixture was heated for an additional hour, allowed to cool, and extracted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution (4 x 100 cm^3), dried over sodium sulphate and evaporated to give a straw coloured solid (2·14 g, 39%), m.p. 82-84 °C (lit.[162] 84-86 °C)(Found: C, 54·1; H, 2·96; N, 42·2. Calc. for $C_6H_4N_2$: 54·3; H, 3·03; N, 42·4%); $\upsilon_{max.}$ ($CHCl_3$) 3000 (CH), and 2200 cm^{-1} (CN); δ_H (270 MHz; $CDCl_3$) 3·9 (3H, s, NCH_3) and 7·68 (1H, s, CH); *m/z* (low eV EI) 132 (M^+, 100%).

1-Methyl-4,5-imidazoledicarboxylic acid (**178**).——A solution of dicyanoimidazole (**177**) (26 g, 196 mmol) in 6M NaOH solution was refluxed for 2 hours with vigorous stirring. The solution was carefully acidified while hot with concentrated hydrochloric acid. At pH 1-2 a yellow-white solid was produced. The solution was allowed to cool to room temperature and the solid was filtered and dried to give the desired product (30·5 g, 98%). Recrystallisation did not improve the quality of the product, m.p. 258-260 °C (lit.[162] 259-260 °C)(Found: C, 42·2; H, 3·52; N, 16·6. Calc. for C, 42·3; H, 3·5; N, 16·4%); $\upsilon_{max.}$(Nujol) 3350 (OH), and 1700 cm^{-1}; δ_H (270 MHz; DMSO-D_6) 3·80 (3H, s, NCH_3), 5·6

(2H, br, CO_2H), and 9·10 (1H, s, CH); δ_C (68 MHz; DMSO-D_6) 37·5 (NCH_3), 128.0 (C-4), 130.0 (C-5), 138·9 (C-2) and 160·5 (CO_2H); *m/z* (^{i}BuH CI) 170 (M^+, 100%).

1-Methyl-5-imidazolecarboxylic acid (**179**).——A suspension of 1-methyl-4,5-imidazoledicarboxylic (**178**) acid (7 g, 40 mmol) in acetic anhydride (200 cm^3), dried over 4 Å molecular sieves, was heated at 100 °C (oil bath) for 4 hours with vigorous stirring, producing a blue-black solution. The acetic anhydride was removed *in vacuo* (20 °C/5 mm) to give a grey-black solid, which was triturated with acetone to yield a pale grey solid (4.5 g, 95%). m.p. 253-255 °C (lit.[162] 256-257 °C). $\upsilon_{max.}$ (Nujol) 3400 (OH) and 1760 cm^{-1} (CO_2); δ_H (270 MHz; DMSO-D_6), 3·84 (3H, s, CH_3), 7·61 (1H, d, *J* 0·94 Hz, 2-H), and 7·94 (1H, d, *J* 0·94 Hz, 4-H); δ_C (68 MHz; D_2O) 34·76 (CH_3), 128·56 (C-4), 135·63 (C-2), 141·02 (C-5) and 164·05 (CO_2H); *m/z* (low eV EI) 126 (M^+, 100%).

Methyl 1-methyl-5-imidazolecarboxylate (**54**).——To dry methanol (20 cm^3), cooled to -45 °C, was added thionyl chloride (1·76 g, 20 mmol). After 30 minutes, solid 1-methyl-5-imidazolecarboxylic acid (1 g, 7·93 mmol) was added. The mixture was then allowed to warm to room temperature and subsequently refluxed under nitrogen for 24 hours. On cooling to 40 °C, solid sodium hydrogen carbonate was added to raise the pH to 8, resulting in the production of a brown-orange solution after filtration. The filtrate was evaporated, the residue extracted with chloroform (50 cm^3), and evaporated again to give a brown crystalline solid. Bulb to bulb distillation using Kugelrohr apparatus (60 °C/0·3 mm) gave a colourless crystalline solid (0·5 g, 50%), m.p. 55-56 °C (lit.[162] 56-57

°C)(Found: C, 51·5; H, 5·8; N, 20·1. Calc. for $C_6H_8N_2O$: C, 51·4; H, 5·7; N, 20%); $\upsilon_{max.}$ ($CHCl_3$) 3400 (NH) and 1700 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 3·91 (3H, s, CH_3O), 3·85 (3H, s, NCH_3), 7·6 (1H, d, *J* 0·94 Hz, 4-H), 7·71 (1H, d, *J* 0·94 Hz, 2-H); δ_C (68 MHz; $CDCl_3$) 33·7 (NCH_3), 51·1 (CH_3O), 122·4 (C-4), 137·2 (C-2), 142·0 (C-5) and 160·3 (CH_3C=O); *m/z* (low eV EI) 140 (M^+, 80%) and 109 (M^+-31, 100%).

1-Methyl-5-imidazolecarboxyhydrazide[156] (**180**).——Ester (**54**) (0·525 g, 3·75 mmol) was dissolved in the minimum amount of warm ethanol (2 cm^3). To this was added an equal weight of hydrazine hydrate (10·5 mmol) and the reaction mixture was warmed to 40-60 °C. After 20 minutes at 40 °C a white solid began to precipitate out of solution, and increasing the temperature slightly led to the dissolution of the material. After 1 hour, the solvent was removed *in vacuo* and a white residue was produced. This was washed with dry ether and air-dried to give hydrazide (**180**)(0·465 g, 89%). m.p. 185-186 °C (lit.[156] 188-189 °C). (Found: C, 42·8; H, 5·71; N, 40·0. Calc. for $C_5H_8N_4O$: C, 42·8; H, 5·71; N, 40·0%); $\upsilon_{max.}$ (Nujol), 3400 (NH) and 1660 cm^{-1} (C=O); δ_H (270 MHz; DMSO-D_6) 3·50 (2H, br s, NH_2), 3·82 (3H, s, NCH_3), 7·59 (1H, s, NHC=O), 7·72 (1H, d, *J* 0·94 Hz, 4-H) and 7·73 (1H, d, *J* 0·94 Hz, 2-H); *m/z* (low eV EI) 140 (M^+, 50%).

1-Methyl-5-imidazolecarboxybenzenesulphonylhydrazide (**181**).——Hydrazide (**180**) (0·465 g, 3·32 mmol) was suspended in pyridine (4 cm^3) and to this stirred mixture was added 1·1 equivalents of benzenesulphonyl chloride (0·47 cm^3) slowly. A marked colour change was observed in the mixture, from colourless to yellow-orange. The mixture was stirred for an additional 15 minutes and then diluted with water (40 cm^3), affording a yellow precipitate which was

recrystallised from ethanol to give hydrazide (**181**)(0·8 g, 92%). m.p. 210-212 °C (lit.[156] 212-213 °C). (Found: C, 46·9; H, 4·17; N, 19·5. Calc. for $C_{11}H_{12}N_4O_3$: C, 47·1; H, 4·28; N, 19·99); $\upsilon_{max.}$ (Nujol) 3156 (CH) and 1660 cm^{-1} (C=O); δ_H (270 MHz; DMSO-D_6) 3·56 (3H, s, NCH_3), 7·65 (7H, m, Ar), 9·9 (1H, s, NHCO) and 10·4 (1H, s, $NHSO_2$); *m/z* (^{t}BuH CI) 281 (M^++1, 13%) and 143 (M^+-138, 100%).

5-Formyl-1-methylimidazole[156] (**55**).——Carboxyhydrazide (**181**) (0·1 g, 0·36 mmol) was suspended in glycerol (10 cm^3) and sodium carbonate (0·1 g, 0·9 mmol) was added. The mixture was placed in an oil bath at 150-170 °C. Vigorous foaming was observed and the suspension rapidly became soluble in glycerol to give a deep orange solution. Heating was continued until foaming ceased. The mixture was rapidly cooled in ice, diluted with water, and extracted with chloroform (4 x 100 cm^3). The organic phase was dried over sodium sulphate and evaporated to give a brown crystalline solid. Bulb to bulb distillation using Kugelrohr apparatus (110 °C/12 mm) gave a white crystalline solid (0.014 g, 35%), m.p. 52-54 °C (lit.[156] 53-54 °C)(Found: C, 54·6; H, 5·61; N, 25·1. Calc. for $C_5H_6N_2O$: C, 54·5; H, 5·45; N, 25·4); $\upsilon_{max.}$ (Nujol) 3300 (NH) and 1650 cm^{-1} (C=O); δ_H (270 MHz; DMSO-D_6) 3·90 (3H, s, NCH_3), 7·92 (1H, br s, 4-H), 8·13 (1H, br s, 2-H) and 9·76 (1H, s, CHO); δ_C (68 MHz; DMSO-D_6) 33·9 (NCH_3), 143·2 (C-4), 143·9 (C-2) and 179·3 (C=O); *m/z* (low eV EI) 110 (M^+, 100%).

5-Ethenyl-1-methylimidazole (**191**).——To a suspension of methyltriphenylphosphonium bromide (0·24 g, 0·67 mmol) in dry tetrahydrofuran (3 cm^3) under nitrogen was added a 1·6M hexane solution of ^{n}butyl lithium (0·42 cm^3, 0·67 mmol) at 0 °C.[168] A bright orange colour immediately developed, and after 2 hours aldehyde (**55**) (50 mg, 0·45 mmol) in

dry tetrahydrofuran (3 cm^3) was slowly added at room temperature. The orange colour discharged immediately and a precipitate was observed. The resulting solution was stirred under nitrogen overnight, extracted with ethyl acetate (20 cm^3), and washed with ammonium chloride solution. The organic phase was dried over sodium sulphate and evaporated to give the crude product as a yellow solid (0·14 g). Chromatography on silica gel using ethyl acetate-petroleum (b.p. 60——80 °C)(1:1) as eluant gave a white solid (triphenylphosphine oxide) and a pale yellow oil, ethylenylimidazole (**191**)(48 mg, 80%), M^+ = 108·0685 (Calc. for $C_6H_8N_2$: *M*, 108·0687); $\upsilon_{max.}$ ($CHCl_3$) 3300 (NH) and 1740 (C=C); δ_H (270 MHz; $CDCl_3$) 5·22 (1H, dd, *J* 1 and 11 Hz, C*H*=C), 5·58 (1H, dd, *J* 1 and 17 Hz, C*H*=C), 6·5 (1H, dd, *J* 11 and 17 Hz, CH_2=C*H*), 7·2 (1H, s, 4-H) and 7·5 (1H, s, 2-H); δ_C (68 MHz; $CDCl_3$) 33·8 (NCH_3), 114 (CH_2=C), 122·6 (CH_2=*C*), 133·5 (C-5), 134.2 (C-4) and 138·1 (C-2); *m/z* (low eV EI) 108 (M^+, 100%).

Attempted formation of 5-Dibromoethenyl-1-methylimidazole[158] (**158**).——A solution of carbon tetrabromide (0·59 g, 1·8 mmol), triphenylphosphine (0·47 g, 1·8 mmol) and zinc dust (0·12 g, 1·8 mmol) in dry dichloromethane (8 cm^3) was stirred under nitrogen at room temperature for 48 hours to produce a plum coloured solution. To this solution was added 5-formyl-1-methylimidazole (**55**) (90 mg, 0·89 mmol), an immediate precipitate was seen to form and the solution once again became brown in colour. The reaction was allowed to stir at room temperature for 4 hours, at which point t.l.c. analysis indicated no more aldehyde was present. Pentane was added, causing precipitation of inorganic material, followed by filtration and the filtrate was evaporated, and the residue was re-worked to extract more material. However the purified white solid obtained was shown to be unreacted aldehyde (**55**), $\upsilon_{max.}$ ($CHCl_3$) 1650 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 3·9 (3H, s, NCH_3), 7·9 (1H, br s, 4-H), 8·13 (1H, br s, 2-H) and

9·76 (1H, s, CHO); *m/z* (low eV EI) 110 (100%).

(Iodomethyl)triphenylphosphonium iodide[174e].——A solution of triphenylphosphine (30 g, 115 mmol) and methylene iodide (12·8 cm^3, 150 mmol) in dry benzene (30 cm^3) under nitrogen was protected from light by aluminium foil. The flask was fitted with a reflux condenser and the reaction mixture was stirred at 45 °C in an oil bath for 4 hours. After a few minutes it was noted that some cloudiness had developed, and after 4 hours a solid mass of the phosphonium salt was produced. This was filtered and washed with a small amount of benzene (10 cm^3) to give the desired salt (22 g, 36%), m.p. 225-230 °C (lit.[174e] 230-231 °C)(Found: C, 43·2; H, 3·18; Calc. for $C_{19}H_{17}I_2P$: C, 43·1; H, 3·2%).

Reaction of 5-Formyl-1-methylimidazole with (Iodomethyl)triphenylphosphonium iodide and ⁿButyl lithium to give Alkene (**191**) *and Iodoalkene* (**192**).——To a suspension of (iodomethyl)triphenylphosphonium iodide (0·24 g, 0·45 mmol) in dry tetrahydrofuran (10 cm^3) was added, at -78 °C, a 1·6M hexane solution of ⁿbutyl lithium (0·3 cm^3, 0·5 mmol). This resulted in the production of an orange solution which was stirred at room temperature for 30 minutes, cooled to -78 °C and the aldehyde (**55**) (50 mg, 0·45 mmol) was added in dry tetrahydrofuran (2 cm^3) under nitrogen. This resulted in the immediate disappearance of the orange colouration and formation of a yellow-white precipitate. On stirring for 1 hour at room temperature, it was noted that the precipitate gradually dispersed to give a pale yellow solution. The reaction was subsequently washed with ammonium chloride solution, extracted with ethyl acetate, dried over sodium sulphate and evaporated to give a yellow oil. Chromatography on silica gel produced two

products, alkene and iodoalkene, (70:30 mixture), $\upsilon_{max.}$ ($CHCl_3$) 3400 (NH) and 1720 cm^{-1} (C=C). Iodoalkene (**192**); δ_H (270 MHz; $CDCl_3$) 3·95 (3H, s, NCH_3), 6·6 (2H, dd, *J* 9 and 15 Hz C*H*I=CH), 7·42 (2H, dd, *J* 9 and 15 Hz, CHI=C*H*), 7·7 (1H, s, 4-H) and 8·1 (1H, s, 2-H); *m/z* (low eV EI) 234 (M^++1, 100%) and 107 (M^+-128, 40%). Alkene (**191**); δ_H (270 MHz; $CDCl_3$) 3·7 (3H, s, NCH_3), 5·25 (1H, d, *J* 12 Hz, C*H*=CH), 5·6 (1H, d, *J* 17 Hz, C*H*=CH), 6·2 (1H, m, CH_2=C*H*) and 7·3 (2H, s, H-4 and H-2); *m/z* (low eV EI) 108 (M^+, 20%).

5-Iodoethenyl-1-methylimidazole (**192**).——To a suspension of (iodomethyl)triphenylphosphonium iodide (0·3 g, 0·56 mmol) in dry tetrahydrofuran (12 cm^3) was added slowly, at room temperature, a 1M tetrahydrofuran solution of sodium hexamethyldisilazane (0·56 cm^3, 0·56 mmol). After stirring for 1 minute the solution was cooled to -78 °C and the aldehyde (**55**) (50 mg, 0·45 mmol), in dry tetrahydrofuran (2 cm^3), was added under nitrogen, leading to a lightening of the brown colouration and formation of a precipitate. The mixture was allowed to warm to room temperature, and stirring continued for 30 minutes. The reaction mixture was subsequently washed with a solution of ammonium chloride and extracted with ethyl acetate, dried over sodium sulphate and evaporated to give a brown oil. Chromatography over silica gel, using ethyl acetate as eluant, isolated two compounds, the first being triphenylphosphine oxide and the other the halogenated alkene (**192**)(88 mg, 98%), M^+ = 233·9649 ($C_6H_7IN_2$ requires *M*, 233·9655); $\upsilon_{max.}$ ($CHCl_3$) 3300 (NH) and 1734 cm^{-1} (C=C); δ_H (270 MHz; $CDCl_3$) 3·61 (3H, s, NCH_3), 3·63 (3H, s, NCH_3), 6·68 (1H, dd, *J* 9 and 15 Hz, CI*H*=CH *cis* and *trans*), 7·42 (1H, dd, *J* 9 and 15 Hz, CHI=C*H*), 7·7 (1H, s, 4-H) and 8·1 (1H, s, 2-H); δ_C (68 MHz; $CDCl_3$) 31·5 (NCH_3), 79·8 (I*C*H=C), 87·8 (ICH=*C*H), 130·7 (C-5), 134.2 (C-4) and 136.5 (C-2); *m/z* (low eV EI) 234 (M^++1, 100%) and 107 (M^+-127, 40%).

5-Ethynyl-1-methylimidazole (**152**).——N.B. HAZARD! This compound is *highly toxic*. To a solution of the iodoalkene (**192**)(0·195 g, 0·82 mmol) in dry tetrahydrofuran (3 cm^3) was added a 1·6M hexane solution of ^{n}butyl lithium (1 cm^3, 1·6 mmol) at -78 °C. The mixture was stirred at -78 °C for 30 minutes, giving a bright yellow solution, which was quenched on addition of water and subsequently extracted with ethyl acetate, dried over sodium sulphate and evaporated to afford a yellow oil. Chromatography over silica gel, using ethanol-dichloromethane (1:25) as eluant, gave two compounds, alkene (**191**) and alkyne (**152**) in a 60:40 ratio, $\upsilon_{max.}$ (film) 3450 (C≡CH), 2990 (CH) and 2100 cm^{-1} (C=C); δ_H (270 MHz; DMSO-D_6) 3·62 (3H, s, NCH_3), 4·66 (1H, s, C≡CH), 7·14 (1H, s, 4-H) and 7·59 (1H, s, 2-H); *m/z* (low eV EI) 106 (M^+, 100%).

Attempted Alkylation of 5-Ethynyl-1-methylimidazole.——To a solution of the alkynylimidazole (**152**)(0·12 g, 0·5 mmol) in dry tetrahydrofuran (5 cm^3) at -78 °C was added ^{t}butyl lithium (0·35 cm^3, 0·5 mmol). The reaction mixture was allowed warm to room temperature and stirred for 30 minutes. ^{n}Butyl lithium (0·35 cm^3, 0·5 mmol) was added, producing a yellow solution, the solution was stirred for a further 30 minutes at room temperature and then quenched with a large excess of ethyl 2-bromobutyrate (5 g, 27·9 mmol). Stirring was continued for another hour, after which all cloudiness disappeared to give a yellow solution. The reaction mixture was washed with brine (5 cm^3), extracted with ethyl acetate, dried over sodium sulphate and evaporated *in vacuo* producing a yellow oil. Chromatography over silica gel, using ethanol-dichloromethane (1:25) as eluant, yielded one major compound, which was identified as a dimer of the bromoester (**195**) (0·1 g, 60%), $\upsilon_{max.}$ ($CHCl_3$) 1700 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 0·96

(6H, t, *J* 7 Hz, CH_3CH_2), 1·2 (6H, t, *J* 7 Hz, CH_3CH_2O), 2·0 (4H, m, *J* 5·9 and 7 Hz, CH_3CH_2CHCO), 4·2 (4H, dq, *J* 7 Hz, $CH_3CH_2CO_2$) and 4·53 (2H, dt, *J* 5·9 and 7 Hz, CHCO); *m/z* (70 eV EI and ^{t}BuH CI) no mass peak observed.

Attempted Protection of Alkyne (**152**) *with* ^{t}*Butyldimethylsilyl chloride*[178].——To a solution of the iodoalkene (**192**) (0·12 g, 0·5 mmol) in dry tetrahydrofuran (4 cm^3) under nitrogen, cooled to -78 °C, was added a 1·6M hexane solution of ^{n}butyl lithium (1 cm^3, 1·53 mmol) and the resulting mixture was left to stir at -78 °C for 2 hours. ^{t}Butyldimethylsilyl chloride (0·12 g, 1 mmol) in dry tetrahydrofuran (3 cm^3) was added and the reaction allowed to warm to room temperature. The crude reaction mixture was poured into water, extracted with ethyl acetate (3x 20 cm^3), dried over sodium sulphate, and evaporated *in vacuo* to give a yellow oil silylalkenylimidazole (**196**)(60 mg, 60%), δ_H (270 MHz; $CDCl_3$) 0·9 (15H, s, $(CH_3)_3Si(CH_3)_2$), 3·5 (3H, s, NCH_3), 5·2 (1H, dd, *J* 1 and 11 Hz, CH_2=CH), 5·6 (1H, dd, *J* 1 and 18 Hz, CH_2=CH), 6·4 (1H, m, CH_2=CH) and 7·3 (1H, s, 4-H); δ_C (68 MHz; $CDCl_3$) 19·7 ($(CH_3)_3C$), 31.4 ($(CH_3)_2Si$), 35·0 (C-Si), 122·2 (SiC=C), 126·0 (SiC=C) and 144·8 (C-4); *m/z* (70 eV EI) 223 (M^++1, 80%).

Attempted alkylation of Phenylacetylene (**199**).——To a stirred solution of phenylacetylene (0·5 g, 4·89 mmol) in dry tetrahydrofuran (7 cm^3) cooled to -78 °C, was added a 1·6M hexane solution of ^{n}butyl lithium (3 cm^3, 4·89 mmol). This produced a cloudy orange solution which was allowed to stir for 1 hour at room temperature. The reaction was then quenched with 1·5 equivalents of ethyl 2-bromobutyrate (2 g, 7·3 mmol). The cloudiness of the solution was immediately seen to disappear and the reaction mixture was stirred for an

additional 30 minutes at room temperature, washed with brine and extracted with ethyl acetate to give a yellow solution. The organic phase was dried over sodium sulphate and evaporated *in vacuo* producing an orange-yellow oil. T.l.c. analysis indicated the presence of one new component, but attempts at column chromatography lead to further decomposition. A further repetition of this reaction, followed by bulb to bulb distillation using Kugelrohr apparatus, succeeded only in the recovery of unreacted bromoester.

5-(1,3-Dithian-2-yl)-1-methylimidazole trifluoroborate (206).——To a solution of the aldehyde (55) (0·2 g, 1·8 mmol) in dry dichloromethane (10 cm^3) under nitrogen was added 1 equivalent of propane-1,3-dithiol[191] (0·19 g, 1·8 mmol). The mixture was cooled to 0 °C and borane trifluoride etherate (0·64 g, 4·54 mmol) was added slowly. An immediate precipitate formed which persisted for 1 hour, and the solution then became clear and was stirred at room temperature for an additional 2 hours. The reaction was washed with brine, extracted with ethyl acetate, dried over sodium sulphate, and evaporated *in vacuo* to give a white solid *5-(1,3-dithian-2-yl)-1-methylimidazole trifluoroborate* (0·3 g, 90%), m.p. 105-107 °C (Found; C, 29·8; H, 4·12; N, 8·5. $C_8H_{15}N_2S_2O_2BF_3$ requires C, 29·9; H, 3·8; N, 8·7%); $\upsilon_{max.}$ (Nujol) 3400 cm^{-1} (C=N); δ_H (270 MHz; DMSO-D_6) 1·85 (1H, m, SCH_2CH_2), 2·07 (1H, m, SCH_2CH_2), 3·00 (4H, m, *J* 3, 6 and 10 Hz, SCH_2), 3·88 (3H, s, NCH_3), 5·71 (1H, s, SCHS), 7·81 (1H, s, 4-H) and 9·07 (1H, s, 2-H); δ_C (68 MHz; DMSO-D_6) 24·4 ($CH_2CH_2CH_2$), 28·9 (CH_2S), 35·8 (SCHS), 38·8 (NCH_3), 118·4 (C-4), 132·3 (C-5) and 136.0 (C-2); *m/z* (^{i}BuH CI) 201 (M^+, 80%).

Conversion of 5-(1,3-Dithian-2-yl)-1-methylimidazole trifluoroborate to 5-(1,3-Dithian-2-yl)-1-methylimidazole (205).——To a suspension of the trifluoroborate (0.07 g, 0·37 mmol) in dry tetrahydrofuran (3 cm^3) was added a 1·6M hexane solution of ^{n}butyl lithium (0·23 cm^3, 0·37 mmol) at -78 °C. An immediate yellow solution developed which was stirred at -78 °C for 2 hours and then quenched with brine and allowed to warm slowly to room temperature, extracted with ethyl acetate, dried over sodium sulphate and evaporated *in vacuo* to give a white solid *5-(1,3-dithian-2-yl)-1-methylimidazole* (25 mg, 60%), m.p. 120-122 °C; M^+ = 200·0440 ($C_8H_{12}N_2S_2$ requires *M*, 200·0428); (Found: C, 47·6; H, 6·0; N, 13·3. $C_8H_{12}N_2S_2$ requires C, 48·0; H, 6·0; N, 14%); $\upsilon_{max.}$ ($CHCl_3$) 3300 (NH) and 1220 cm^{-1} (S-CH_2); δ_H (270 MHz; $CDCl_3$) 1·97 (1H, m, *J* 2, 6 and 10 Hz, SCH_2CH_2), 2·0 (1H, m, SCH_2CH_2), 3·0 (4H, m, $(SCH_2)_2$), 3·73 (3H, s, NCH_3), 5·22 (1H, s, SCHS), 7·13 (1H, s, 4-H) and 7·44 (1H, s, 2-H); δ_C (68 MHz; $CDCl_3$) 25·0 ($SCH_2CH_2CH_2S$), 31·4 (SCH_2), 32·0 (NCH_3), 40·0 (SCH), 128·9 (C-4) and 139 (C-2); *m/z* (70 eV EI) 200 (M^+, 80%).

Deuteration Studies on 5-(1,3-Dithian-2-yl)-1-methylimidazole (205).——To a solution of dithiane (205)(0.055 g, 0·27 mmol) in dry tetrahydrofuran (2 cm^3) under nitrogen, at -78 °C, was added a 1·6M hexane solution of ^{n}butyl lithium (0·16 cm^3, 0·27 mmol). An immediate orange-brown colour developed, and the solution was stirred for 1 hour at -78 °C to ensure complete formation of the anion. The reaction mixture was then warmed to room temperature and quenched with D_2O (0·2 cm^3), with simultaneous discharging of the orange colour. The mixture was stirred at room temperature for 30 minutes to ensure complete quenching, giving a pale yellow solution which was extracted with chloroform, washed with brine, dried over sodium sulphate and evaporated *in vacuo* to yield a white solid *2-deutero-5-(1,3-Dithian-2-yl)-1-methylimidazole* (0.04 g, 72%), m.p.

120-122 °C. $\upsilon_{max.}$ ($CHCl_3$) 3400 (NH) and 1100 cm^{-1} (SCH); δ_H (270 MHz; $CDCl_3$) 1·94 (1H, m, SCH_2CH_2), 2·13 (1H, m, SCH_2CH_2), 2·94 (4H, m, SCH_2), 3·73 (3H, s, NCH_3), 5·24 (1H, s, SCHS), 7·1 (1H, s, 4-H) and 7·3 (<1H, s, 2-H); δ_C (68 MHz; $CDCl_3$) 24·8 ($SCH_2CH_2CH_2S$), 27·7 (SCH_2CH_2), 31·9 (NCH_3), 39·9 (SCH_2S), 128·8 (C-4) and 139·2 (C-2); *m/z* (^{i}BuH CI) 201 (M^++1, 100%).

Methylation of 5-(1,3-Dithian-2-yl)-1-methylimidazole (205).——To a solution of imidazole (205) (0·1 g, 0·6 mmol) in dry tetrahydrofuran (10 cm^3), cooled to -78 °C, was added a 1·6M hexane solution of ^{n}butyl lithium (1 cm^3, 1·15 mmol). This produced a clear yellow solution which was stirred for 2 hours at -78 °C, quenched with methyl iodide (0·1 cm^3, 1·8 mmol) and slowly warmed to room temperature to give a cloudy yellow solution. Extraction with chloroform (3 x 5 cm^3), washing with brine (3 x 5 cm^3) afforded a yellow solution which was dried over magnesium sulphate and evaporated *in vacuo* to yield a yellow oil (0·13 g, 96%). T.l.c. analysis, using ethanol-dichloromethane (1:25) as eluant, showed a single component and further purification was not required, $\upsilon_{max.}$ ($CHCl_3$) 2900 (CH) and 1200 cm^{-1} (SCH); δ_H (270 MHz; $CDCl_3$) 1·94 (1H, m, SCH_2CH_2), 2·0 (3H, s, CH_3CS), 2·57 (1H, m, SCH_2CH_2), 2·91 (4H, m, SCH_2), 3·90 (3H, s, CH_3N), 4·00 (3H, s, CH_3), 7·27 (1H, s, 4-H) and 7·40 (>1H, s, 2-H); *m/z* (70 eV EI) 229 (M^++1, 45%).

2-^{t}Butyldimethylsilyl-5-(1,3-dithian-2-yl)-1-methylimidazole (210).——To a solution of thioacetal (205) (0.055 g, 0·28 mmol) in dry tetrahydrofuran (2 cm^3) under nitrogen at -78 °C was added a 1·6M hexane solution of ^{n}butyl lithium (0·16 cm^3, 0·28 mmol). An immediate orange brown colour developed, as before, and the reaction mixture was stirred for 1 hour at -78 °C to ensure complete

formation of the anion. ^{t}Butyldimethylsilyl chloride (0.045 g, 0·28 mmol) in dry tetrahydrofuran (2 cm^3) was added and the solution was stirred at room temperature for 2 hours. The reaction mixture was subsequently extracted with chloroform, washed with brine, dried over sodium sulphate and evaporated *in vacuo* to give a yellow-white solid *2-^{t}Butyldimethylsilyl-5-(1,3-dithian-2-yl)-1-methylimidazole* (0.08 g, 90%). m.p. 170-172 °C (Found: C, 53·5; H, 8·58; N, 8·5. $C_{14}H_{26}N_2S_2Si$ requires: C, 53·5; H, 8·28; N, 8·9 %); $\upsilon_{max.}$ ($CHCl_3$) 3200 (NH), 1250 ($SiCH_3$) and 650-800 cm^{-1} (SiC); δ_H (270 MHz; $CDCl_3$) 0·3 (6H, s, $Si(CH_3)_2$), 0·85 (9H, s, $SiC(CH_3)_3$), 1·82 (1H, m, SCH_2CH_2), 1·87 (1H, m, SCH_2CH_2), 2·94 (4H, m, $(SCH_2)_2$), 3·7 (3H, s, NCH_3), 5·14 (1H, s, SCHS) and 7·19 (1H, s, 4-H); δ_C (68 MHz; $CDCl_3$) -4·8 $(Si(CH_3))_2$, 24·9 ($SCH_2CH_2CH_2S$), 25·6 (SiC), 26·4 ($SiC(CH_3)_3$), 31·5 SCH_2), 32·7 (NCH_3), 40·5 (SCHS), 129·9 (C-4) and 131 (C-2); *m/z* (^{t}BuH CI) 315 (M^++1, 78%), 257 (M^+-57, 100%).

*Attempted Michael Addition of 2-^{t}Butyldimethylsilyl-5-(1,3-dithian-2-yl)-1-methylimazole (***210***) to 2(5H)-Furanone.*——To a solution of thioacetal (**210**) (0.02 g, 0·065 mmol) in dry tetrahydrofuran (2 cm^3) was added ^{n}butyl lithium (0·04 cm^3, 0·065 mmol) at -78 °C and the mixture was stirred for 2 hours. Freshly distilled 2(5H)-furanone (0·01 cm^3, 0·065 mmol) was added and the mixture stirred for a further 30 minutes at -78 °C, producing a pale yellow solution. This was subsequently quenched with iodoethane (0·195 g, 1·25 mmol) and allowed to warm slowly to room temperature, and extraction with chloroform to give a yellow gum (50 mg). Only starting material could be isolated after chromatography over silica gel using chloroform as eluant.

Attempted 1,4-Addition to 2(5H)-Furanone using imidazole (**210**) *and Copper (I) iodide.*——To a stirred solution of the thioacetal (**210**) (0.086 g, 0·43 mmol) in dry tetrahydrofuran (3 cm^3) cooled to -78 °C was added ^{n}butyl lithium (0·54 cm^3, 0·86 mmol). The resulting orange solution was stirred for 2 hours at -78 °C, dried cuprous iodide (0.081 g, 0·43 mmol) was added, and the was reaction stirred for an additional hour. The solution became dark brown and the cuprous iodide was seen to dissolve. Freshly distilled 2(5H)-furanone was added (0·03 cm^3, 0·4 mmol) and the solution immediately lightened in colour, subsequently becoming cloudy and grey on standing. The resulting mixture was stirred for 2 hours then quenched with water at -78 °C and slowly warmed to room temperature, producing a grey precipitate. The material was extracted with chloroform and washed with ammonium chloride solution, dried over sodium sulphate, and evaporated *in vacuo* to give a yellow oil (20 mg). Chromotogaphy over silica gel, using ethyl acetate-light petroleum (b.p. 60——80 °C)(1:1) as eluant, gave two major products corresponding to starting materials.

Attempted Reaction of 2-^{t}Butyldimethylsilyl-5-(1,3-dithian-2-yl)-1-methylimidazole (**210**) *with Ethyl acrylate.*——To a solution of thioacetal (**205**)(0·1 g, 0·5 mmol) in dry tetrahydrofuran (2 cm^3), cooled to -78 °C, was added a 1·6M hexane solution of ^{n}butyl lithium (0·31 cm^3, 0·5 mmol). The mixture was stirred for 1 hour at -78 °C then quenched with ^{t}butyldimethylsilyl chloride (75 mg, 0·5 mmol) and warmed to room temperature. After quenching was complete (2 hours), the reaction was again cooled to -78 °C and a second equivalent of ^{n}butyl lithium (0·31 cm^3, 0·5 mmol) was added to give a deep orange solution which was stirred for 1 hour. Ethyl acrylate (0.05 g, 0·5 mmol) was added and the mixture was warmed to -50

°C, quenched with water, allowed to warm to room temperature overnight, extracted with ethyl acetate, washed with water, dried over sodium sulphate, and evaporated to give a white solid (16 mg), which contained only starting material.

Ethyl 2-formylbutyrate[195] (**219**).——A solution of di-isopropylamine (5·06 g, 50 mmol) in dry tetrahydrofuran (50 cm^3) was treated with a 1·6M hexane solution of ^{n}butyl lithium at 0 °C (31·2 cm^3, 50 mmol) to give a yellow solution which was stirred for 1 hour at 0 °C and then cooled to -78 °C. A solution of ethyl butyrate (5·81 g, 50 mmol) in dry tetrahydrofuran (15 cm^3) was added, the resulting mixture was stirred for 30 minutes at -78 °C, ethyl formate (11·1 g, 150 mmol) added, and the mixture allowed to warm to room temperature. Acetic acid was added (9 g), excess tetrahydrofuran was removed before the solution was diluted with ether, washed with water (2x 100 cm^3) and saturated sodium hydrogen carbonate solution, dried over sodium sulphate, and evaporated *in vacuo* to give a pale yellow oil which was distilled to afford a colourless oil (2.9 g, 40%) b.p. 70-72 °C/15 mm (lit.[157] 76-81 °C/23 mm).(Found: C, 57·9; H, 8·8; Calc. for $C_7H_{12}O_3$: C, 58·3; H, 8·3%); $\upsilon_{max.}$ ($CHCl_3$) 3500 (OH) and 1700 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 1·03 (3H, t, *J* 7 Hz, CH_3CH_2), 1·35 (3H, t, *J* 7 Hz, CH_3CH_2CO), 2·2 (2H, m, *J* 7 Hz, CH_3CH_2), 3·34 (0·5H, dt, *J* 2, 7 Hz, CH), 4·27 (2H, q, *J* 7 Hz, CH_3CH_2CO), (0·5H, d, *J* 2 Hz, CHO) and 11·41 (0·5H, d, *J* 12 Hz, OH); *m/z* (^{i}BuH CI) 145 (M^++1, 100%).

Ethyl 2-hydroxymethylbutyrate (**220**).——To a solution of ethyl 2-formylbutyrate (**219**)(2 g, 14 mmol) in methanol (20 cm^3), stirred at 0 °C, was added slowly sodium borohydride (0·52 g, 30 mmol). The mixture was stirred for 4 hours at 0 °C, neutralised with 2M hydrochloric acid, excess methanol was removed, the

mixture was washed with saturated ammonium chloride and extracted with ether. The organic phase was dried over sodium sulphate and evaporated *in vacuo* to give a yellow oil *ethyl 2-hydroxymethylbutyrate* (220) (0.19 g, 97%)(Found: C, 56·8; H, 9·87. $C_7H_{14}O_3$ requires: C, 57·5; H, 9·6%); $\upsilon_{max.}$ ($CHCl_3$) 3420 (OH) and 1700 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 0·95 (3H, t, *J* 7 Hz, CH_3CH_2CH), 1·29 (3H, t, *J* 7 Hz, CH_3CH_2O), 1·65 (2H, m, *J* 7 and 12 Hz, CH_3CH_2C), 2·38 (1H, br s, OH), 2·51 (1H, m, CH_2CH), 3·74 (2H, dd, *J* 8 and 12 Hz, CH_2OH) and 4·18 (2H, q, *J* 7 and 12 Hz, CH_3CH_2O); δ_C (68 MHz; $CDCl_3$); 11·5 (CH_3CH_2), 11·7 (CH_3CH_2O), 21·6 (CH_3CH_2CH), 48·9 (CHCO), 60·2 (CH_2CO), 62·7 (CH_2O) and 171·6 (CO); *m/z* (^{t}BuH CI) 147 (M^++1, 95%).

Attempted preparation of Ethyl 2-bromomethylbutyrate[196,197] (221).——To a stirred solution of butyrate (220)(0·25 g, 1·71 mmol) in dry tetrahydrofuran (5 cm^3) was added carbon tetrabromide (1·7 g, 5·1 mmol). After stirring for 5 minutes, triphenylphosphine (0·22 g, 2·5 mmol) was added in dry tetrahydrofuran (10 cm^3). The mixture was stirred at room temperature for 24 hours and, as no significant change had been observed, the reaction was refluxed for 3-4 hours, extracted into ether, washed with ice-saturated ammonium chloride, dried over sodium sulphate and evaporated *in vacuo* to give a brown oil (50%). Chromatography over silica gel with ethyl acetate-light petroleum (b.p. 60——80 °C)(1:1) as eluant produced a mixture of triphenylphosphine oxide and tribromomethane, but no starting material was isolated. The reaction was repeated in the absence of any solvent, carbon tetrabromide (6·81 g, 20 mmol) and triphenylphosphine (2·69 g, 10·3 mmol) were heated together until the mixture melted. The reaction was cooled slightly and 2-hydroxymethylbutanoate (1 g, 6·8 mmol) was added. Much effervescence was observed and after heating for 3 hours a blood-red solution was produced. The reaction was extracted into

ether, washed with ammonium chloride, dried over sodium sulphate and evaporated to give a red oil. Chromatography on silica gel using ethyl acetate-light petroleum (b.p. 60——80 °C)(1:1) as eluant afforded an orange-yellow oil (1·4 g, 50%). None of the starting material and no product were present.

Ethyl 2-bromomethylbutanoate[200] (**221**).——To a solution of ethyl 2-hydroxymethylbutanoate (1 g, 6·8 mmol) in dry pyridine (5 cm^3) was added slowly, and with cooling at 0 °C, phosphorus tribromide (0·6 g, 2·2 mmol). An immediate yellow-white precipitate was formed and the reaction mixture was stirred for 4 hours at 0 °C and then for 2 hours at room temperature. The reaction mixture was extracted with ether, washed with ice-water, dried over sodium sulphate and evaporated to give a pale yellow oil. Chromatography over silica gel using ethyl acetate-light petroleum (b.p. 60——80 °C)(1:9) as eluant yielded a pale yellow oil *ethyl 2-bromomethylbutanoate* (510 mg, 58%)(Found: C, 43·9; H, 7·05. $C_7H_{13}O_2Br$ requires C, 40·2; H, 6·2%); $\upsilon_{max.}$ (film); 1720 (C=O); δ_H (270 MHz; $CDCl_3$) 0·94 (3H, t, *J* 7 Hz, CH_3CH_2CH), 1·28 (3H, t, *J* 7 Hz, CH_3CH_2O), 1·68 (2H, m, CH_3CH_2CH), 2·73 (1H, m, $CHCH_2$), 3·3 (2H, dd, *J* 7 and 14 Hz, $CHCH_2Br$) and 4·19 (2H, q, *J* 7 and 14 Hz, CH_3CH_2O); δ_C (68 MHz; $CDCl_3$) 11·4 (CH_3CH_2), 14·2 (CH_3CH_2C), 24·3 (CH_3CH_2CH), 32·1 (CH_2Br), 49·5 (CHCO), 60·7 (CH_2CO) and 173 (CO_2Et); *m/z* (^{i}BuH CI) 211 (M^++2, 60%) and 209 (M^+ 60%).

Ethyl 2-methylphosphoniumbutanoate bromide (**215**).——To a solution of butanoate (**221**) (0·225 g, 0·95 mmol) in dry toluene was added triphenylphosphine (0·32 g, 1·4 mmol), and the mixture was refluxed for 12

hours then slowly cooled to room temperature, to produce a yellow white gum. The remaining toluene was decanted along with any unreacted triphenylphosphine, and the crude bromide (215)(0·15 g, 30%) was dried and used in the next step without further purification, δ_H (270 MHz; $CDCl_3$) 0·95 (3H, br t, *J* 7 Hz, CH_3CH_2CH), 1·02 (3H, br t, *J* 7 Hz, CH_3CH_2O), 1·90 (2H, m, CH_3CH_2), 2·82 (1H, br m, $CHCH_2$), 3·49 (2H, q, *J* 8 Hz, CH_3CH_2O), 3·64 (2H, br dd, CH_2P) and 7·85 (15H, m, Ph); δ_C (68 MHz; $CDCl_3$) 10·9 (CH_3CH_2C), 13·6 (CH_3CH_2O), 27·5 (CH_3CH_2), 27·6 (CH_2P), 40·8 (CH), 60·9 (CH_2O), 116-135 (Ph) and 173·6 (C=O); *m/z* (FAB +) 391 (M^+, 50%), 279 ($OPPh_3$, 100%).

2-Hydroxymethylbutanoic acid (222).——To a solution of butyrate (220) (0·5 g, 3·4 mmol) in ethanol (10 cm^3) was added a large excess of 2M NaOH (10 cm^3). The mixture was refluxed for 3 hours, concentrated to half its original volume, was cooled, and 2M sulphuric acid was added to raise the pH to 5. The solution was extracted into ether, which was washed with saturated ammonium chloride solution, dried over sodium sulphate and evaporated to give a yellow oil (0·3 g, 72%), which was distilled at reduced pressure to produce a colourless oil, b.p. 102-104 °C/0·3 mm (lit.[197a] 102-104 °C/0·25 mm) (Found: C, 50·4; H, 8·2. Calc. for $C_5H_{10}O_3$: C, 50·8; H, 8·47%); $\upsilon_{max.}$ ($CHCl_3$) 3400 (OH) and 1700 cm^{-1} (C=O); δ_H (270 MHz; DMSO-D_6), 0·93 (3H, t, *J* 7 Hz, CH_3CH_2), 1·53 (2H, q, *J* 7 and 10 Hz, CH_3CH_2), 2·35 (1H, q, *J* 7 and 14 Hz, CH), 3·55 (2H, dq, *J* 5 and 14 Hz, CH_2-O) and 12·00 (1H, br s, OH); δ_C (68 MHz; DMSO-D_6), 11·9 (CH_3CH_2), 21·5 (CH_3CH_2), 50·0 (CH), 62·2 (CH_2OH) and 176·1 (CO_2H); *m/z* (^{t}BuH CI) 119 (M^++1, 20%) and 101 (M^+-18, 100%).

Attempted Protection of 2-Hydroxymethylbutanoic acid[203] *to give oxazoline* (223).——To a stirred solution of 2-hydroxymethylbutanoic acid (0·08 g, 0·67 mmol) in dry toluene (5 cm^3) was added 2-amino-2-methyl-1-propanol (0·18 g, 2 mmol). The reaction mixture was then refluxed for 24 hours, after which toluene was removed giving a yellow viscous gum which was insoluble in all solvents tried and could not be characterised.

Attempted Wittig Reaction between Ethyl 2-methylphosphoniumbutanoate bromide (215), *^{n}butyl lithium and Benzaldehyde to give alkene* (224).——To a suspension of phosphonium bromide (215)(0·15 g, 0·32 mmol) in dry tetrahydrofuran (5 cm^3) cooled to -78 °C was added a 1·6 M hexane solution of ^{n}butyl lithium (0·2 cm^3, 0·32 mmol), and the mixture was stirred for 1 hour at -78 °C producing a clear orange solution. Freshly distilled benzaldehyde (0·04 g, 0·32 mmol) was added and the orange colour immediately disappeared. The reaction was slowly allowed to warm to room temperature, poured into ice-water, extracted with ether, dried over sodium sulphate and evaporated to give a yellow oil. Chromatography, using ethyl acetate-light petroleum (b.p. 60——80 °C)(1:99) as eluant, on silica gel yielded a number of components, including starting material, and the double bond migration product, alkene (224) (20 mg, 30%), $\upsilon_{max.}$ ($CHCl_3$) 1700 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 0·91 (3H, br t, *J* 7 Hz, CH_3CH_2), 1·26 (3H, t, *J* 7 Hz CH_3CH_2O), 1.74 (4H, br q, CH_2), 2.31 (2H, d, *J* 7 Hz, CH_2Ar), 5.65 (1H, t, *J* 8 Hz, C=CH), and 7.35 (5H, m, Ar); *m/z* (^{i}BuH CI) 219 (M^+, 0.8%).

Attempted Olefination of 5-Formyl-1-methylimidazole with Ethyl 2-methylphosphoniumbutanoate bromide (**215**).——To a solution of the phosphorane (0·18 g, 0·37 mmol) in dry tetrahydrofuran (3 cm^3) under nitrogen was added a 1·6M hexane solution of ^{n}butyl lithium (0·25 cm^3, 0.3 mmol) at -78 °C. The solution became yellow immediately, and was stirred at -78 °C for 20 minutes, then 1-methyl-5-carboxyimidazole (0.005 g, 0·37 mmol) in dry tetrahydrofuran (2 cm^3) was added and the reaction allowed to warm to room temperature, washed with brine, extracted into ethyl acetate, dried over sodium sulphate and evaporated to give a yellow viscous oil. Chromatography on silica gel with ethyl acetate-light petroleum (b.p. 60——80 °C)(1:1) produced two compounds which were identified as triphenylphosphine oxide and unreacted aldehyde.

Attempts to prepare 1-Methyl-5-oxiranylimidazole. (**233**).——To a suspension of *meta*-chloroperoxybenzoic acid (*m*-CPBA) (0·32 g, 1·85 mmol) in dry dichloromethane (4 cm^3) under nitrogen was added 5-ethenyl-1-methylimidazole (**191**)(0·1 g, 0·92 mmol) in dry dichloromethane (2 cm^3). The solution was seen to become yellow on the initial addition but after 30 minutes a white precipitate began to form and this was seen to increase with time. The mixture was left to stir at room temperature for 24 hours poured into water and shaken with saturated sodium hydrogen carbonate solution, extracted with $CHCl_3$ (3 x 10 cm^3), dried over magnesium sulphate and evaporated to give a yellow viscous oil (65 mg, 65%). However proton n.m.r. showed that this was unreacted alkene.

Attempted formation of 1-Methyl-5-oxiranylimidazole using Corey's Ylide,[210] *yielding alkene (239).*——To a flask purged with nitrogen was added sodium hydride (0.03 g, 0·12 mmol) and trimethyloxosulphonium iodide (0·26 g, 0·12 mmol). Dimethylsulphoxide (5 cm^3) was added slowly, resulting in the rapid liberation of hydrogen and the production of a cloudy solution, which was stirred for 15 minutes at room temperature and 5-formyl-1-methylimidazole (55) (0·1 g, 0·9 mmol) in dry DMSO (1 cm^3) was added slowly. Stirring was continued for 3 hours at room temperature producing a blood-red solution, which was washed with water and extracted with ethyl acetate to give a glassy yellow oil (0·22 g, 95%), which proved not to be the epoxide but the dimethylsulphoxyalkene (239), M^+ = 170·04691 ($C_7H_{10}N_2OS$ requires *M*, 170·2288); $\upsilon_{max.}$ ($CHCl_3$) 3400 (NH), 1620 cm^{-1} (C=C); δ_H (270 MHz; $CDCl_3$) 2·62 (6H, s, SCH_3), 3·95 (3H, s, NCH_3), 6·78 (1H, d, *J* 15 Hz, C*H*=C), 7·13 (1H, d, *J* 15 Hz, C=C*H*), 7·38 (1H, s, 4-H), and 7·5 (1H, s, 2-H); δ_C (68 MHz; $CDCl_3$) 29·7 (NCH_3), 41·0 ($SOCH_3$), 121 (RSO_2HC=C), 128 (RSO_2HC=*C*), 130·6 (C-4), 132 (C-2) and 140 (C-5); *m/z* (low eV EI) 170 (M^+, 78%).

1-Methyl-5-oxiranylimidazole[213] (233).——N.B. HAZARD! This compound is *highly toxic.* To a solution of alkene (191) (0.065 g, 0·59 mmol) in dry benzene (5 cm^3) and a catalytic amount of vanadyl acetylacetonate (0.002 g, 0·01 mmol) was added, with refluxing a 3M 2,4,4-pentane solution of ^{t}butylhydroperoxide (0·19 cm^3, 0·59 mmol) over 5-10 minutes. On addition of the vanadyl acetylacetonate, the solution became blue-green and on heating this colour faded slightly. Addition of ^{t}butylhydroperoxide resulted in an immediate orange-red colouration, but after heating the reaction mixture for 2 hours the orange colour faded to yellow-brown, and after 4 hours the solution turned green. The organic phase was washed with aqueous bisulphite, dried over sodium sulphate and

evaporated to give a brown oil (11 mg). However this proved to be unreacted starting material and the major product, believed to be the diol (240), was found in the aqueous phase but was so toxic it could not be characterised.

Pyridinium para-*toluenesulphonate*[220].——To dry pyridine (12 cm^3) was added *para*-toluenesulphonic acid monohydrate (95·7 g, 72 mmol) and the resulting mixture was stirred for 20 minutes at room temperature. The excess pyridine was removed *in vacuo* to give a yellow-white solid which was recrystallised from acetone to yield solid pyridinium *para*-toluenesulphonate (6·8 g, 60%). m.p. 116-118 °C (lit.[220] 120 °C)(Found: C, 56·3; H, 5·25; N, 5·52. Calc. for $C_{11}H_{10}NO_2S$: C, 57·3; H, 5·2; N, 5·57%).

2-Butyne-4-(tetrahydropyranyloxy)-1-ol[220] (249).——To a suspension of 2-butyne-1,4-diol (10 g, 116 mmol) in dry dichloromethane (25 cm^3) containing a catalytic amount of pyridinium *para*-toluenesulphonate (2·76 g, 10 mmol) was added dihydropyran (13·9 g, 116 mmol) and the mixture was heated to 50-60 °C for 6 hours, cooled, washed with brine and extracted with ethyl acetate (3 x 30 cm^3), dried over sodium sulphate, and evaporated *in vacuo* to give a viscous yellow oil. Chromatography over silica gel, using ethyl acetate-light petroleum (b.p. 60——80 °C)(1:1) as eluant afforded the diprotected alcohol (13.88 g, 70%) and the monoprotected compound (4.07 g, 30%).

Monoprotected diol (249). $\upsilon_{max.}$ ($CHCl_3$) 3400 (OH), 2900 (CH) and 1302 cm^{-1} (CO); δ_H (270 MHz; $CDCl_3$) 1·64 (6H, m, pyran), 3·26 (1H, s, OH), 3·56 (1H, m, CH_2O), 3·84 (1H, m, CH_2O), 4·29 (4H, s, $(CH_2)_2C\equiv$), and 4·84 (1H, dd, *J* 3 and 4 Hz, CHO_2); *m/z* (^{i}BuH CI) 171 (M^++1, 15%).

Diprotected diol (251). $\upsilon_{max.}$ ($CHCl_3$) 2900 (CH) and 1302 cm^{-1} (CO); δ_H (270 MHz; $CDCl_3$) 1·67 (12 H, m, pyran), 3·50 (2H, m, CH_2O), 3·83 (2H, m, CH_2O), 4·28 (4H, s, $(CH_2)_2C\equiv$), 4·81 (2H, s, CHO_2); *m/z* (^{t}BuH CI) 255 (M^++1, 2%).

2-Butyne-4-(tetrahydropyranyloxy)-1-al[221] (248).——To a solution of the monoprotected alcohol (249) (0·385 g, 2·28 mmol) in dry dichloromethane (5 cm^3) containing 4-methylmorpholine N-oxide (0·4 g, 3·4 mmol) and 3 Å molecular sieves stirred at room temperature, was added tetrapropylammonium perruthenate (TPAP)(5% mole 0.04 g, 0·11 mmol). This produced a dark green-black solution. After stirring for 1·5-2 hours all starting material had disappeared and a single component was observed by t.l.c. (ethyl acetate-light petroleum (b.p. 60——80 °C)(1:4)). The reaction mixture was filtered through a pad of silica gel, under nitrogen, to give the aldehyde (248)(0·2 g, 70%) which was found to be unstable in air and was used directly in the following step, $\upsilon_{max.}$($CHCl_3$) 2900 (CH) and 1700 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 1·69 (6H, m, pyran), 3·56 (1H, m, CH_2O), 3·83 (1H, m, CH_2O), 4·46 (2H, s, $CH_2C\equiv$), 4·81 (1H, br t, CHO_2) and 9·2 (1H, s, CHO); *m/z* (70 eV EI) peak at 101 observed, corresponding to M^++1 of the deprotected acid.

Attempted Formation of 2-Butyne-4-(tetrahydropyranyloxy)-1-imine (247) *and subsequent nucleophilic addition of Nitromethane.*——To a solution of 2-butyne-4-(tetrahydropyranyloxy)-1-al (248)(0·645 g, 3·8 mmol) in ethyl acetate-light petroleum (b.p. 60——80 °C)(1:4) (20 cm^3), containing magnesium sulphate, was added an excess of methylamine in dry methanol (30 cm^3). The reaction was allowed to warm slowly to room temperature for 2 hours and

sodium methoxide (0·2 g, 3·8 mmol) and nitromethane (0·2 g, 3·8 mmol) in dry dichloromethane (5 cm^3) were added at -78 °C. The mixture was again allowed to warm slowly to room temperature, producing an orange-yellow solution. Solvents were removed and the resulting material was filtered through a pad of silica gel and washed with ethyl acetate as eluant (R_f 0·8) to give a red oil, which crystallised under reduced pressure to yield a crystalline solid (0·9 g, 70%), which proved to be the deprotected amide (252), $\upsilon_{max.}$ ($CHCl_3$) 3450 (OH), 3350 (NH) and 1740 cm^{-1} (NHC=O); δ_H (270 MHz; $CDCl_3$) 2·0 (3H, s, CH_3N), 2·76 (1H, s, OH), 2·78 (2H, d, *J* 5 Hz, CH_2OH) and 7·60 (1H, s, NH); δ_C (68 MHz; $CDCl_3$) 25·0 (CH_2OH), 25·6 (CH_3N), 61·9 (C≡*C*C=O), 96 (C≡*C*CH_2) and 173·7 (CH_3NC=O); *m/z* (70 eV EI) 113 (M^+, 2%).

Formation of a Nitroamine (254) *from Isobutyraldehyde* (253).——To a solution of isobutyraldehyde (1 g, 13·8 mmol), in dry dichloromethane (10 cm^3), was added magnesium sulphate and methylamine and the resulting solution was stirred at room temperature for 20 hours. Freshly distilled nitromethane (0·84 g, 13·8 mmol) and sodium methoxide (0·84 g, 13·8 mmol) were added and the mixture was heated for 20 hours at 70-80 °C. Solvent was evaporated to give an orange solution which was filtered through a pad of silica gel and eluted with ethyl acetate-light petroleum (b.p. 60——80 °C)(1:1) to yield a pale yellow oil nitroamine (254)(0·65 g, 30%), $\upsilon_{max.}$ ($CHCl_3$) 3300 (NH) and 1560 cm^{-1} (NO_2); δ_H (270 MHz; $CDCl_3$) 1·0 (6H, dd, *J* 7 Hz, (CH_3)$_2$CH), 1·92 (1H, m, (CH_3)$_2$CHC*H*CH_2) and 4·4 (2H, m, NO_2CH_2CH); *m/z* (70 eV EI) 145 (M^+, 2%).

Methyl 1-hydroxypentanoate (256).——To a solution of δ-valerolactone (0·1 g, 0·99 mmol) in dry methanol (20 cm^3) under nitrogen was added sodium

methoxide (0·16 g, 3 mmol), the mixture was heated to reflux for 5 hours, cooled, and acidified to pH 2 with 2M hydrochloric acid. Excess methanol was removed by evaporation *in vacuo*, the residue was extracted with ethyl acetate (3 x 50 cm^3), dried over magnesium sulphate and evaporated to give a pale yellow oil (0·1 g, 95%) which did not require further purification, $\upsilon_{max.}$ ($CHCl_3$) 3400 (OH), and 1720 cm^{-1} (C=O); δ_H (270 MHz; $CDCl_3$) 1·9 (2H, m, CH_2CH_2CO), 2·3 (2H, m, CH_2CH_2OH), 2·5 (2H, t, *J* 7 Hz, CH_2CO), 2·8 (1H, br, OH) and 3·6 (5H, s and t, *J* 6 Hz, CH_3O and CH_2OH); *m/z* (^{t}BuH CI) 133 (M^++1, 50%).

Methyl 5-formylpentanoate (257).——To a solution of penanoate (256) (0.05 g, 0·56 mmol) in dry dichloromethane (5 cm^3) was added powdered 3Å molecular sieves, *N*-morpholine *N*-oxide (0.06 g, 0·56 mmol) and 5% mole of tetrapropylammonium perruthenate (0·6 g, 0·02 mmol). The mixture gave a bottle-green coloured solution, which was stirred at room temperature for 1 hour, then filtered through a pad of silica gel and eluted with ethyl acetate, to yield the aldehyde as a pale yellow oil (20 mg, 42%), $\upsilon_{max.}$ ($CHCl_3$) 1720 (C=O) and 1650 cm^{-1} C=O); δ_H (270 MHz; $CDCl_3$) 1·98 (2H, m, CH_2CH_2C=O), 2·35 (2H, m, CH_2CH_2OH), 2·56 (2H, t, *J* 7 Hz, CH_2CO), 3·68 (3H, s, CH_3OCO) and 9·77 (1H, s, CHO); *m/z* (70 eV EI) 130 (M^+, 2%).

Attempted Reaction between Nitromethane Anion and the Imine formed from Methyl 5-formylpentanoate.——To a solution of the aldehyde (0·05 g, 0·38 mmol) in dichloromethane (5 cm^3), containing magnesium sulphate, was added an excess of methylamine gas and the solution was stirred overnight to ensure complete formation of the imine. Freshly distilled nitromethane (0·2cm^3, 3·69 mmol) and sodium methoxide (0·2 g, 3·69 mmol) were added, and the reaction

mixture was refluxed for 5 hours, under nitrogen, giving an orange solution. The excess solvent was evaporated and the mixture was acidified and filtered to remove inorganic material. The filtrate was extracted with ethyl acetate (3 x 20 cm^3), dried over magnesium sulphate, and evaporated to give an orange-brown oil which could not be characterised.

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