

ORGANOIRON COMPLEXES AS
REAGENTS FOR SYNTHESIS

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FOR MY PARENTS
AND
MARTYN

ABSTRACT

The prerequisites for sonochemical reactivity are discussed. This is coupled with a critical overview of available literature to establish the potential of ultrasound for widespread application to synthesis.

Ultrasound was exploited in the synthesis of a variety of π -allyl tricarbonyliron(lactone) complexes and the development of a novel route to η^4 -(diene)tricarbonyliron complexes. Yields of complex are substantially higher than those attainable via conventional methodology. A brief investigation into the preparation of disodium tetracarbonylferrate has led to the development of an extremely mild and convenient route to sodium phenylselenide by direct reaction of sodium with diphenyldiselenide. This reagent was employed to introduce phenylseleno- substituents in high yield by displacement of sulphonates, halides, and epoxides.

Routes to optically active π -allyltricarbonyliron(lactone) complexes were developed in approaches to the stereospecific synthesis of a number of naturally occurring δ -lactones; notably, Massoia lactone, Malyngolide, and the sex pheromone of the Oriental hornet. Reaction of a π -allyltricarbonyliron(lactone) complex with trimethyloxonium tetrafluoroborate yields a novel carbene complex.

π -Allyltricarbonyliron(lactone) complexes were converted to their ferrilactam derivatives by Lewis acid mediated insertion of a variety of primary amines. Oxidation of these complexes provides a route to novel monocyclic β -lactams. Manipulation of the β -lactam products produced a route to azetidin-2,3-diones. This culminated in a five step formal synthesis of nocardicin acid in a remarkable 79% overall yield. Finally, extension of this methodology to the preparation of a model carbapenem by simultaneous formation of both the carbocyclic and β -lactam rings was examined. A number of approaches to the required substrate are described.

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REFERENCES

PUBLICATIONS

SYMBOLS AND ABBREVIATIONS

	ultrasound
	reaction stirred
ANA	aminonocardicin acid
BOC	<u>t</u> -butoxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DET	diethyltartrate
DIBAL-H	diisobutylaluminium hydride
DMF	dimethylformamide
DMS	dimethylsulphide
DMSO	dimethylsulphoxide
HMPA	hexamethylphosphoramide
LDA	lithium diisopropylamide
NBS	N-bromosuccinimide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
py	pyridine
RT	room temperature
TBDMS	<u>t</u> -butyldimethylsilyl
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine

CHAPTER 1

ULTRASOUND IN SYNTHESIS

Introduction

Electromagnetic radiation whose wavelength is marginally shorter than the upper limit of perception for the human eye is termed "ultraviolet". By analogy, the term "ultrasound" is used to describe sound waves whose frequencies lie within the range 20 to 10 000 kHz. The effect of ultrasound on chemical¹ and biological² systems has been known for nearly 60 years and yet its use as a tool for the synthetic chemist scarcely predates 1980. However, the widespread availability of cheap and reliable ultrasound generators, in the shape of laboratory cleaning baths, has promoted a resurgence of interest in its effects. In this period of time numerous examples of the profound influence of ultrasound on organic and organometallic reactions have appeared. The purpose of this review is to provide a critical introduction for those intrigued by the synthetic potential of ultrasound. This is reflected in the examples discussed. In addition, a brief overview of the physics of acoustic cavitation is included in order to explain the origin of sonochemical reactivity and the means by which ultrasound can be exploited to its full potential.

1.2 The origin of sonochemical reactivity

The precise details of the way in which ultrasound acts to produce chemical reaction are not known. However, ultrasonic cavitation is well established as the originator of this phenomenon. This review does not attempt to cover all the literature that has been generated on this subject, but rather to present a qualitative overview in an attempt to clarify this subject which tends to be regarded as something of a black art! For a more detailed report, interested readers are referred to Suslick's recently published review which deals comprehensively with this aspect of sonochemistry.³

The chemical effects of ultrasound do not arise from any direct input of sonic energy to species on a molecular level. A quick examination of the physical data for water can be used to illustrate this. The velocity of sound in water is 1500ms^{-1} and the frequency range that is designated "ultrasound" is between 20 and 10,000 KHz. Hence, the wavelength of the vibrations generated is in the region 7.5 to 0.015cm. That is, the direct energy input is not high enough to produce chemical reaction. Rather, direct comparison with the electromagnetic spectrum shows that it corresponds to the energy associated with long wave radio broadcasts (Figure 1).

The marked effects of ultrasound actually arise from the way in which sound is propagated through media. Longitudinal vibration of molecules in a liquid generates a series of compressions and rarefactions, that is areas of high and low local pressure. If the solvent molecules are torn apart with sufficient force during a rarefaction, cavities are formed at the points where the pressure in the liquid drops well below its vapour pressure. This creates a series of gas and vapour filled bubbles for which a variety of fates

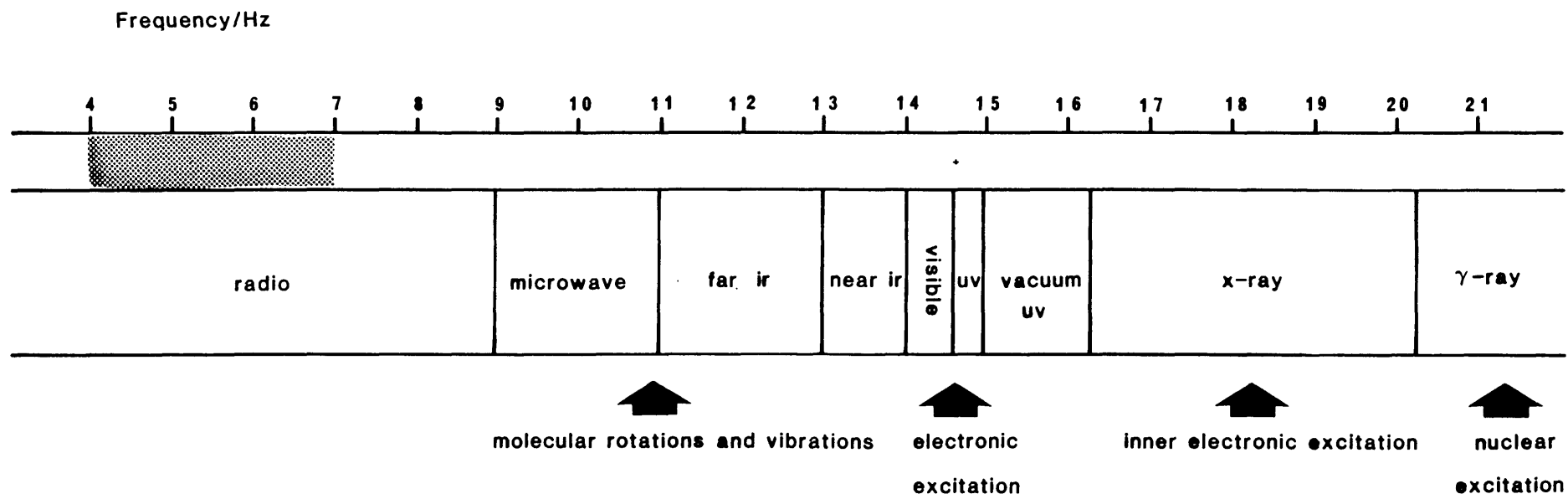


Figure 1

The electromagnetic spectrum, showing the region of equivalent energy to that associated with low frequency ultrasound. (shaded region)

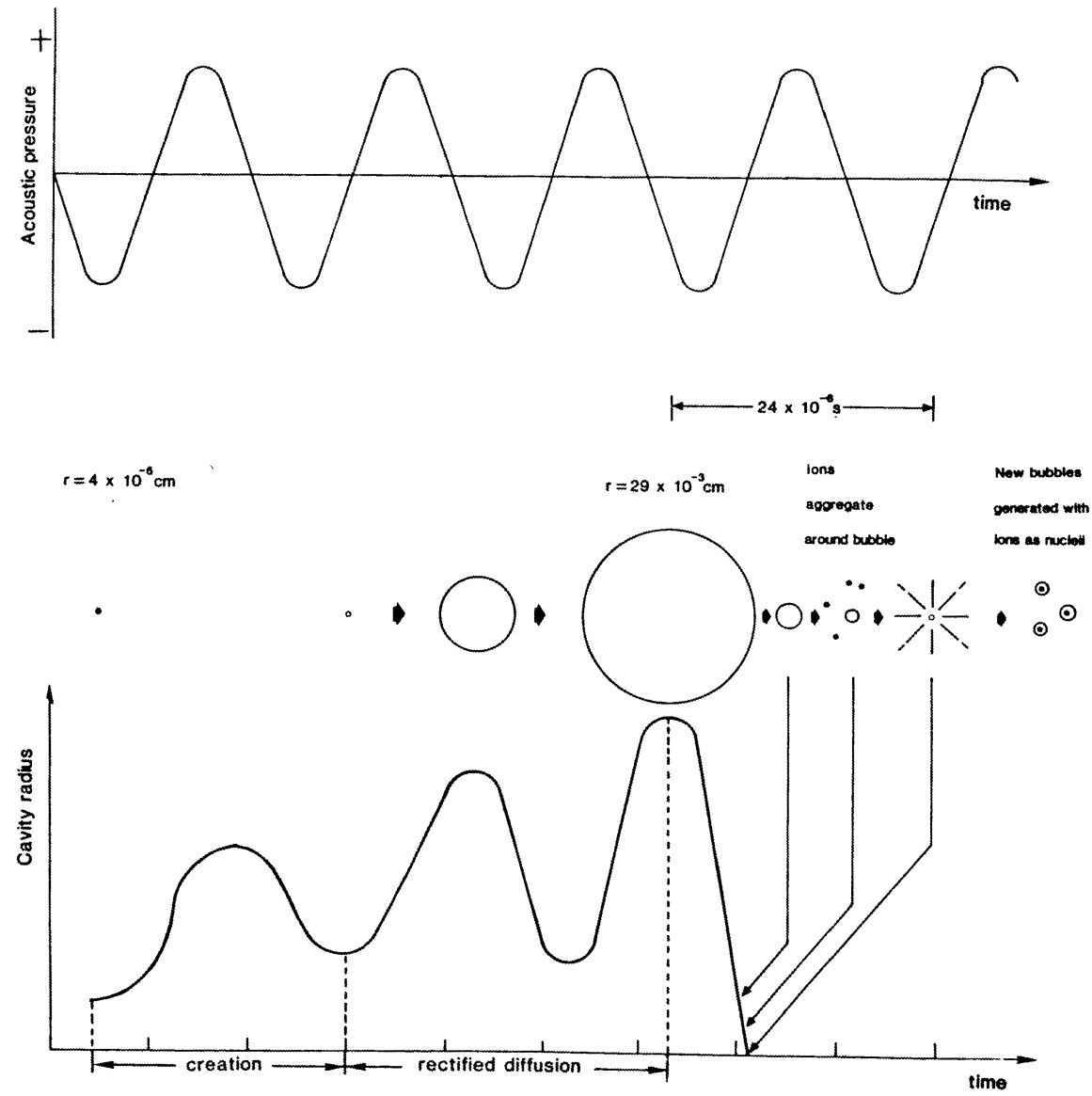


Figure 2
Schematic representation of the lifetime of a transient cavitation bubble.

can be envisaged. Very small bubbles will simply redissolve as fast as they are formed. Large bubbles have long lifetimes with respect to the length of the acoustic cycle. They simply oscillate radially with the sound wave and are not responsible for the chemical effects of ultrasound. This behaviour is termed "stable cavitation".

The process by which chemical reaction occurs is defined by the behaviour of the small bubbles. Their lifetime is only a few acoustic cycles long, during which they expand to 2-3 times their initial size - fed by vapour pumped into the bubble as its surface expands and contracts with the changing pressure in the liquid. The bubbles then gravitate towards the pressure antinodes and collapse violently during the next compression half cycle (Figure 2). The local pressures and temperatures generated by this collapse are enormous. This process is termed "transitional cavitation" and chemical effects observed arise directly from this phenomenon.

At this point it should be stressed that no reaction occurs in the absence of cavitation and a number of published examples contain parallel experiments which show that vigorous stirring or mechanical agitation fails to produce such marked increases in the rate of reaction^{10,124,125}. That is, this is not primarily a mixing effect.

Recent work by Lauterborn et al⁴ on high speed holography has produced pictures of the collapse of bubbles and the shock waves generated (see plates) by sonolysis of water.

The values quoted for the pressure (10^5 kPa) and temperatures (1000 to 3000 K) at the point of collapse have been arrived at by calculation in a number of detailed studies of bubble dynamics^{3,4} and studies of sonoluminescence^{5,6} - another phenomenon associated with cavitation which will not be discussed here. The most recent studies, carried

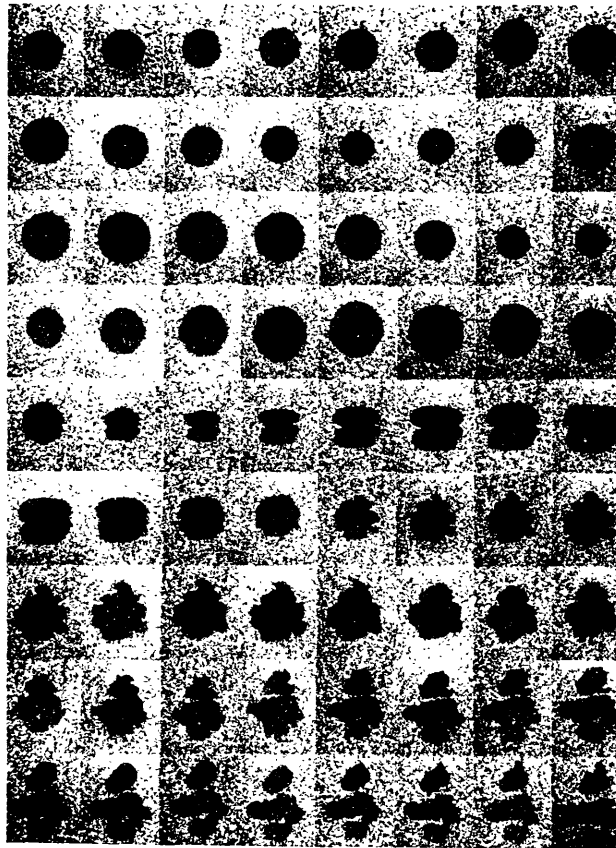


Fig. 3 Spherical oscillations and decay of a single spherical bubble set into motion by a sound field of increasing amplitude at about 7 kHz. The holographic framing rate is 66.7 kHz; the frame size is 2.4 mm x 2.0 mm.



Fig. 4 Collapse of a bubble field with shock wave emission. The bubble field has been produced inside a cylindrical transducer at 18.7 kHz. The holographic framing rate is 14 kHz.

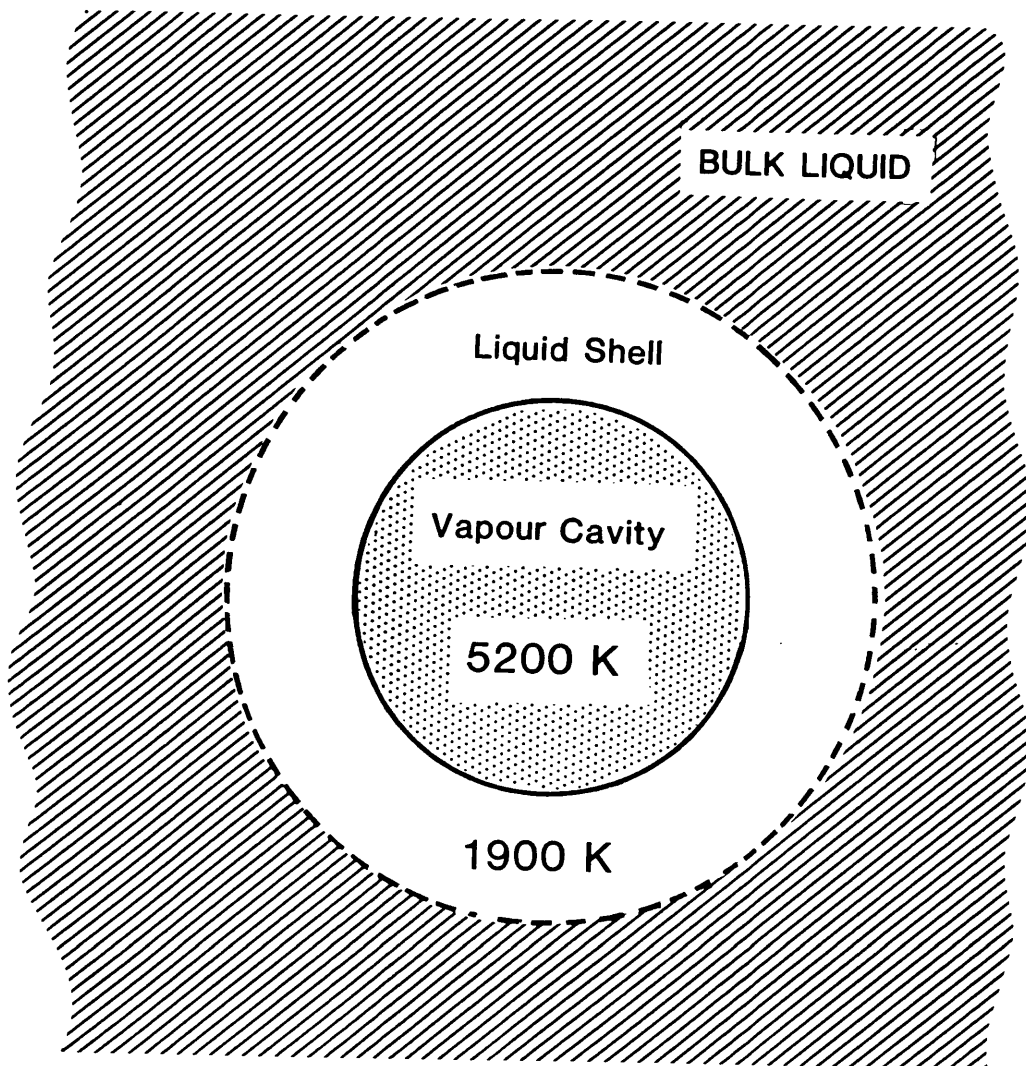


Figure 7

Schematic diagram showing the calculated values for the effective temperatures immediately prior to collapse of a cavitation bubble in heptane/decane, under argon⁷.

out in heptane/decane mixtures, gave a figure for the effective temperature in the bubble of 5200K⁷. But the data, obtained using techniques developed in shock tube experiments, also suggested that the reaction did not occur entirely in the vapour phase. The authors proposed that the thin liquid "shell" surrounding the cavity was the second site of reaction and calculated that the effective temperature in this region was about 1900K. Hence, the mechanism by which reaction occurs is primarily thermal. However, despite the magnitude of the figures quoted, the macroscopic temperature change during the course of a reaction run in a cleaning bath is typically only 10-15°C - most of which occurs within the first few minutes of sonication. In a series of experiments on the saponification of a number of aryl esters, Moon et al¹⁰ showed that mimicking the macroscopic heating effects of ultrasound by immersing the reaction vessel in an oil bath at 100°C for 10min only gave 13% of the product obtained by sonolysis over the same period of time. In fact, 10min sonolysis produced yields equivalent to 90min at reflux. This has clear implications for reactions involving sensitive reagents or products and ultrasound is clearly useful in cases where equivalent thermal conditions produce low yields.

Today, this theory of "hot-spot" pyrolysis on collapse of the cavitation bubbles, which was first proposed in 1950⁸, has become generally accepted. However, a number of other theories have also been proposed to account for sonochemical behaviour. Historically, the first of these⁹ suggested that the cavitation bubbles were created as lenticular rather than spherical cavities in the first instance; "enormous electric stresses" within the bubble were invoked, leading to the generation of moving charges in the surface layer of the bubble. In the case where charge separation is complete, ie the positive charges are distributed diametrically opposite the negative

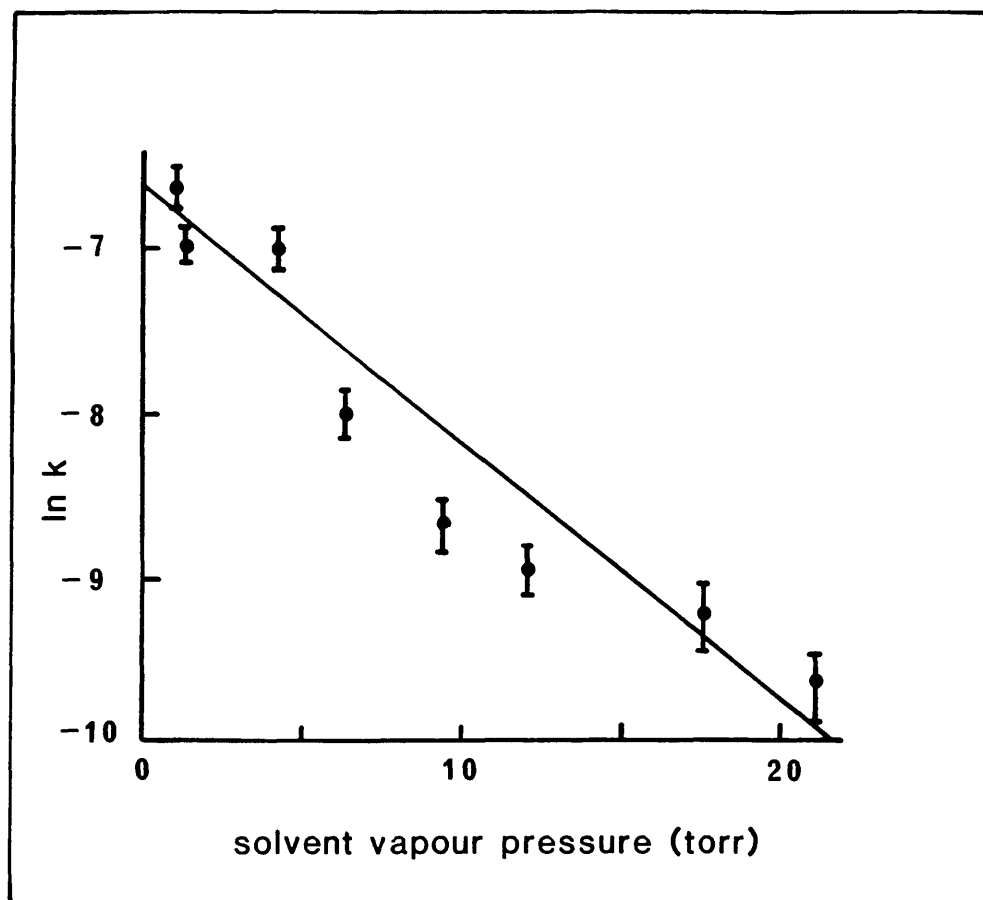


Figure 8

Variation of the rate of decomposition of Fe(CO)_5 with the solvent vapour pressure at 25°C , under argon for the following solvents (in order of increasing solvent vapour pressure): decalin, decane, nonane, 0.22 mole fraction octane in nonane, 0.52 mole fraction octane in nonane, octane, 0.11 mole fraction heptane in octane, and 0.22 mole fraction heptane in octane. Vapour pressures were calculated assuming ideal solution behaviour and the acoustic intensity was 80 Wcm^{-2} .

charges, the electric field strength across the bubble was calculated to be 600 Vcm^{-1} . That is, reactions were thought to be primarily electrochemical in nature.

This theory dominated sonochemistry until the 1970's gaining credence from observations that sonolysis of water produced similar species to those of electrical discharge or radiolysis. It was also responsible for the premise that organic liquids could not support high intensity cavitation as a result of their low dielectric constants. In fact, the first detailed study on cavitation intensity in a range of organic liquids was not published until 1980¹³ (Table 1) and almost all the literature concerning reactions in non-aqueous solvents postdates this. Although these studies, made using a white noise ultrasound generator, ie a cleaning bath, show no clear correlation between any chemical or physical property, Suslick et al¹¹ later demonstrated the link between the intensity of cavitation in a liquid and its vapour pressure. Sonolysis of $\text{Fe}(\text{CO})_5$ results in thermal dissociation of the metal carbonyl. The products of this reaction are $\text{Fe}_3(\text{CO})_{12}$ and finely divided iron. Careful investigation has shown that the rate of this reaction is inversely proportional to the vapour pressure of the surrounding solvent (Figure 8). These findings are justifiable in terms of the "hot spot" mechanism; that is, the adiabatic heating effects of rapid compression are reduced as the vapour recondenses. In addition, conduction of heat to the surroundings reduces the local heating effect still further. The overall effect is that increasing the vapour pressure reduces the intensity of cavitational collapse, the maximum temperature attainable, and consequently the rate of the ongoing reaction.

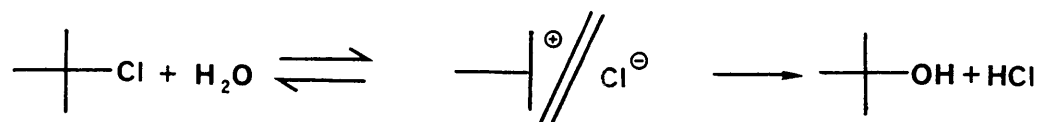
Table 1

Comparison of ultrasonic cavitation intensity in various liquids¹³

Liquid	b.p. [°C]	maximum cavi- tation intensity for a $\lambda/2$ liquid column (46kHz) [%]	Temperature at which cavitation reaches maximum intensity [°C]
1. Water	100	100	35
2. Styrene	146	74	37
3. Toluene	111	71	29
4. Tetralin	207	70	55
5. Cyclohexanone	155	70	36
6. Morpholine	128	65	50
7. Xylene	137	64	26
8. Ethylene glycol	197	61	93
9. Cyclopentanol	141	59	49
10. Trichloroethylene	87	58	20
11. Glycerine	290	57	85
12. n-amyl acetate	149	57	18
13. Tetachloroethylene	121	56	42
14. n-Butyl acetate	126	56	21
15. Pyrrole	130	55	40
16. Methanol	65	52	19
17. Chloroform	61	50	-3
18. n-Amyl alcohol	137	47	23
19. Ethanol	78	46	21
20. Ethyl acetate	77	45	9
21. Acetone	56	44	-36
22. n-Butanol	118	43	32
23. Benzene	80	43	19
24. n-Propanol	97	42	27
25. 1,1,1-Trichloro- ethane	74	41	18
26. Dichloromethane	40	38	-40
27. Methyl acetate	57	38	-32
28. Naphtha	242	38	35
29. Isopropanol	82	38	16
30. Formic acid (85%)	101	37	30
31. Tri-n-butylamine	214	37	31
32. Tetrachloromethane	77	35	8
33. Cyclohexanol	160	23	37
34. Propanoic acid	141	22	32
35. Triethylamine	89	21	1
36. Freon 113	48	15	-20
37. Freon 114B2	47	6	8
38. Acetic acid	118	6	48

Hence, ultrasonic reactions have the curious property that reaction rates decrease as the ambient temperature increases. The electrical discharge theory, which still had its supporters in the mid-1970's, has finally been rejected as being inconsistent with experimentally determined results^{12,13}. Another theory, proposed to account for the degradation of large polymers in ultrasonic fields, suggests that direct mechanical cleavage of bonds may be occurring as a result of the intense shock waves generated by transient cavitation, or indeed, the direct effect of the accelerations produced by the sound field that have been estimated to be as high as 10^5 g at 500kHz¹⁷. However, interaction of the polymer with reactive species produced as a result of solvent breakdown could also account for this.

The final proposal was put forward as a result of studies carried out using binary water/ethanol mixtures.¹⁵ In considering the solvolysis of t-butyl chloride, they surmised that the rate of reaction must be dependent of the degree of solvation in the transition state prior to ionisation.



Hence, the authors suggest that ultrasonic irradiation alters the structure of the liquid facilitating chemical reaction. However, results presented at the recent conference on sonochemistry¹⁹ suggest that the system is too complicated to make generalisations of such a nature at this point in time.

The credibility of the "hot spot" theory is reinforced by its ability

to account for the effects of extrinsic variables on the sonochemical process. An understanding of these effects is necessary in order to successfully apply ultrasound to chemical reactions. For instance, the frequency of ultrasound applied is surprisingly irrelevant. Cleaning baths produce a range of frequencies which often vary during the course of the reaction and yet this has no discernable effect on the sonchemistry observed. Experiments have shown that aqueous sonochemistry is unchanged over the frequency range in which cavitation occurs ie 10Hz to 10MHz²⁰. Since there is no direct coupling of the sound field with species on a molecular level, changing the frequency of the sound input simply alters the resonant size of the cavitation bubble. The effect of this over the range of interest is negligible. It should, however, be noted that although there is both an upper and a lower limit to the frequencies at which cavitation will occur, the band of frequencies used for sonochemistry lies well within these limits. Changing the power input to the transducer alters the volume of liquid which can be forced to cavitate and dramatically affects the observed sonochemical rate. Hence, a number of reactions which give low or erratic yields in cleaning baths, produce high yields when a probe transducer is used, as a result of the ability to control the acoustic intensity input. Increasing the acoustic intensity also extends the range of bubble sizes that will undergo transient cavitation. However, experimental observations show that there is an upper limit beyond which no additional rate increase is seen. Explanations put forward suggest that penetration of sound into the body of the liquid is hindered if cavitation is so intense that the radiating surface becomes shrouded in a layer of bubbles, or that bubble growth becomes so rapid that the boundary for transient cavitation is exceeded before implosive

collapse can occur.

The effects of bulk temperature have already been discussed; however, the results of increasing static pressure are unclear. It could be reasoned that if the total pressure on the system were greater, one would expect the intensity of cavitational collapse to increase. However, the situation is further complicated by consideration of the events which lead to nucleation of the bubbles.

At the present, the generally accepted mechanism for nucleation of bubbles²⁴⁻²⁶ (Figure 9) suggests that gas trapped in small angle crevices of particulate contaminants expands and contracts with the acoustic cycle. As the bubble volume grows two possibilities arise; on the one hand, small gas bubbles may be released into the surrounding liquid; and on the other, implosive collapse of the bubble will release a stream of microcavities at which nucleation can occur.

This theory was proposed in the light of observations that ultrafiltration of the solvent increases the cavitation threshold as do both pressurization and evacuation of the system. Hence, nucleation is suppressed by the flooding of the crevices.

Experimental results obtained on increasing the hydrostatic pressure are not in full agreement²²⁻²⁴. However, this is probably a reflection of the difficulties encountered in maintaining constant temperature in a pressure vessel under ultrasonic irradiation.

Experiments have also shown that sonolysis reactions occur faster in the presence of monoatomic gases than those carried out in the presence of diatomic gases. In fact, the maximum temperature reached

during cavitation is strongly dependent on the polytropic ratio of the ambient gas ($\gamma = C_p/C_v$), its thermal conductivity and its solubility. The former is a measure of the heat released on adiabatic compression of the gas and the latter has a bearing on the number of cavitation nuclei available. Furthermore, it should be noted that H_2 , N_2 , O_2 and CO_2 are not inert during cavitation and will undergo a variety of redox and radical reactions.

The chemical reactivity of the solvent must also be taken into account. No solvent is inert under cavitation conditions and use of halogenated solvents should be avoided. Aromatic hydrocarbons darken as polymerisation occurs on long exposure to ultrasound³⁴ and even linear alkanes undergo cracking under high intensity ultrasound²⁷. As previously discussed, the intensity of cavitational collapse is dependent on the vapour pressure of the solvent and use of involatile solvents is recommended³, although there are a large number of examples where ethereal solvents have been used to good effect. Other liquid properties such as viscosity and surface tension may have some bearing on the threshold at which cavitation will occur, but these are of minor concern.

Aqueous sonochemistry is dominated by reactions of OH and H radicals as a consequence of the high vapour pressure of water relative to any organic or inorganic reagents present and despite the enormous amount of attention it has received²⁸ the number of synthetically useful reactions generated is extremely small.

With careful consideration of these factors, it is clearly possible to 'fine tune' systems to maximise the efficiency of the cavitation process and an understanding of the effects of these parameters on sonochemical processes is clearly of help when attempting to optimise the rates and yields of these reactions.

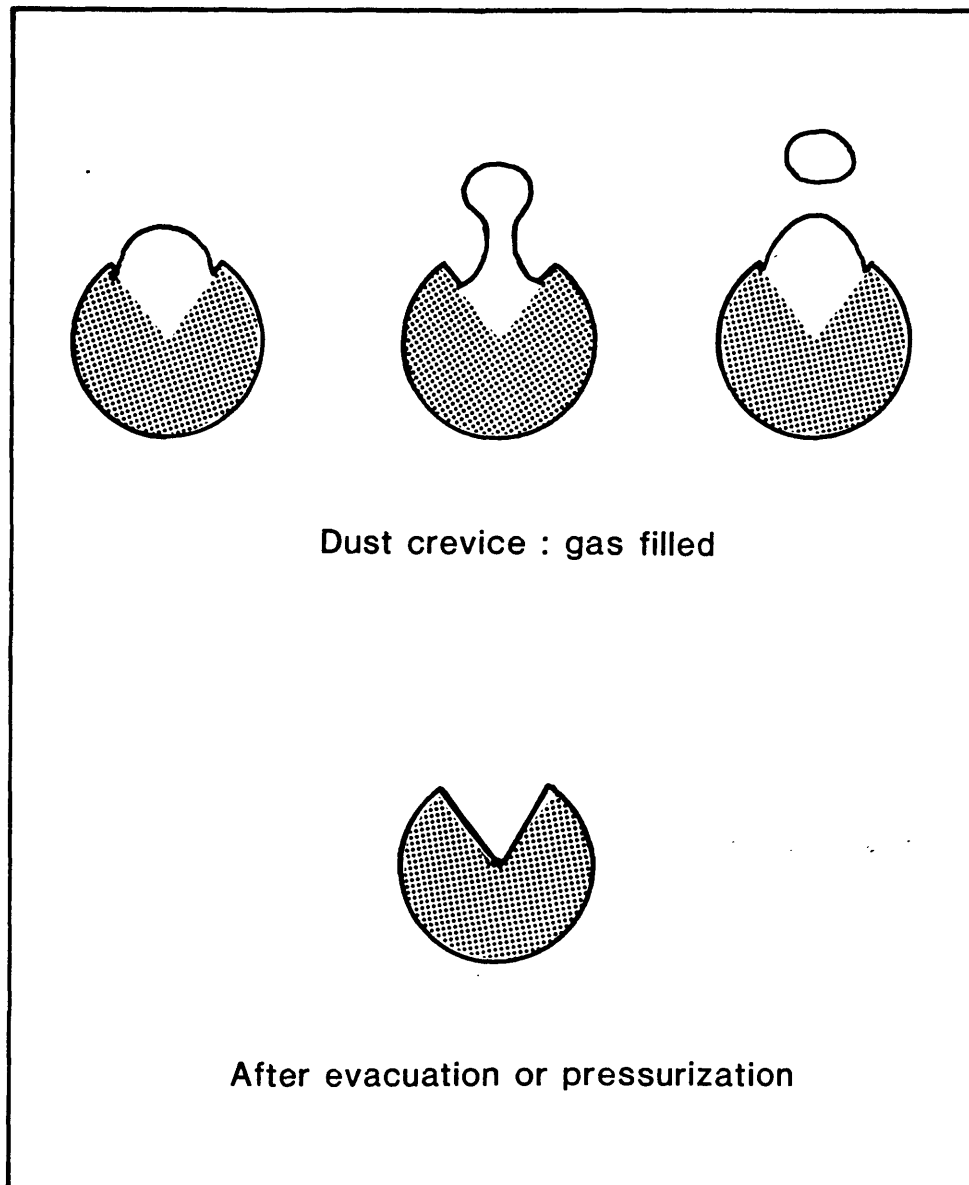


Figure 9

Schematic diagram showing the generally accepted mechanism for nucleation of cavitation bubbles²¹⁻²³.

1.3 The effects of ultrasound on two-phase systems

As previously explained, the effects of ultrasound on homogeneous systems are dominated by the enormous changes in pressure and temperature created at "hot spots" on implosion of the cavitation bubbles. However, in two-phase systems a number of other factors must be taken into consideration. The relative contributions of these phenomena have not been conclusively established in any one case; however, it appears that effects seen in liquid/liquid systems are principally due to emulsification which occurs when the shearing stresses on the liquid are greater than the interfacial surface tension. In a number of cases this enormous increase in surface area of contact completely obviates the need for use of phase transfer catalysts^{10,111} greatly simplifying the work-up procedure for such reactions.

There are also examples where the main effects of sonication arise from improved mass transport within the system. An example of this is the rate increases reported in electrolysis reactions²⁹. The reason for this lies in the increase in momentum brought about as the solvent absorbs energy from the propagating sound wave. This phenomenon is independent of cavitation and is known as "acoustic streaming".

At liquid/solid interfaces the effects of cavitation are seen in the well known cleaning effects of ultrasound. Metal surfaces are eroded and soft metals like potassium can be reduced to colloidal suspensions by low intensity ultrasound³⁰. These effects, coupled with those already detailed, are responsible for the enormous increases in rates of reaction that have been reported in heterogeneous systems. Such reactions form the bulk of those described in this review. Most of these can be carried out using a simple cleaning bath as the source of

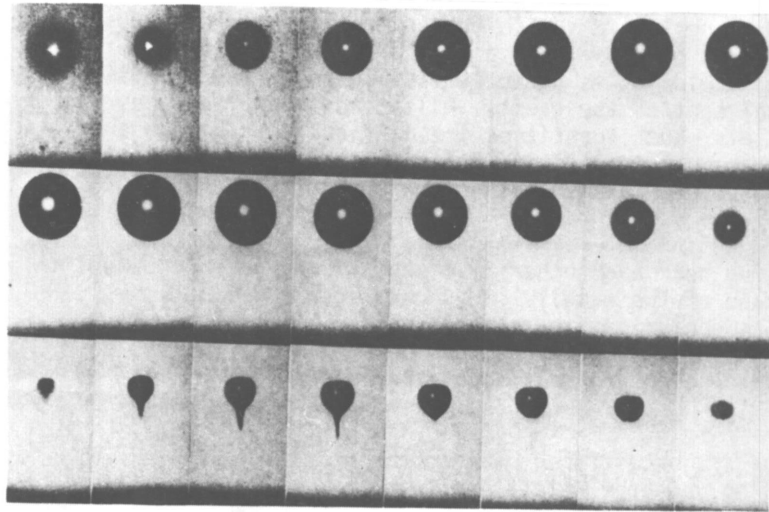


Fig. 5 Jet formation upon collapse of a spherical cavity in the neighbourhood of a plane solid boundary in water. Maximum bubble radius: 1.1 mm, distance of bubble centre from the wall: 4.5 mm, framing rate: 75 000 frames/s. (The first frame (upper left) is doubly exposed with another cavity.)

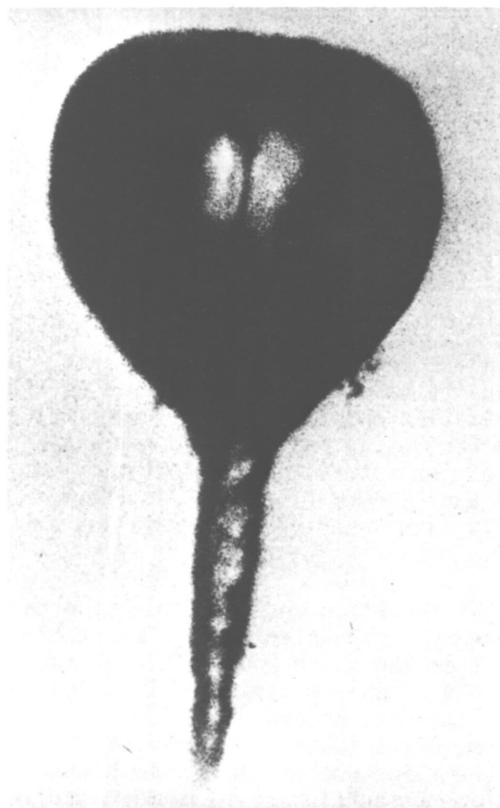


Fig. 6 Cavity in water during its first rebound after collapse near a plane solid boundary below with a typical, well developed jet.

ultrasound. In comparison, homogeneous reactions generally require a more intense and specific input of energy such as that provided by a probe generator. Reactions occurring between species in solution and solid reagents are influenced by a greater number of factors than those which occur within the same phase. The overall rate of reaction is hence a combination of the rates at which species diffuse to and away from the surface as well as a reflection of the number of reaction sites available.

Ultrasound seems to act on all these fronts. For instance, acoustic streaming improves mass transport between the bulk of the liquid and the surface. Similarly, the cleaning effects of ultrasound mean that species can be removed from the surface with equal ease increasing the effective number of sites available for reaction. Cavitation causes erosion of the surface and the intense pressures and temperatures generated on implosion of the bubbles may cause defects and deformations within the solid. Furthermore, calculations suggest that the shock waves generated are of sufficient magnitude to cause plastic deformations in malleable metals (approx. 10^4 atmospheres)³¹. The cumulative result is to increase the actual number of reaction sites on the surface. This is clearly shown in electron micrographs of surfaces activated in this way¹⁹.

High speed microphotographs of bubbles collapsing at a solid boundary show that implosion of the cavity is no longer spherical, but occurs by elongation of the bubble producing a whirling jet. Tip velocities have been estimated to be in excess of 100 ms^{-2} and erosion of the surface occurs at the point of contact³²(see plate 2).

Hence, sonication produces highly active, unpassivated surfaces and although the relative contributions of the effects outlined have not

been fully established; the beneficial effects of ultrasound in such systems is clearly reflected in the large number of literature examples where it has been used to good effect.

1.4 Generation of Ultrasound

It is probably true to say that most workers have access to the small ultrasound baths commonly used for cleaning apparatus or emulsification of samples. Their widespread availability is responsible for the burgeoning number of reports concerned with the effects of ultrasound on heterogeneous systems. In most cases, the reagents are simply mixed together and the reaction flask suspended in the cleaning bath in the position where maximum agitation of the flask contents is observed. The simplicity of this procedure has resulted in a number of fortuitous discoveries by experimenters previously unconnected with this field. However, it should be noted that there are several potential drawbacks to the use of cleaning baths which limit their general applicability; and this restriction has led to the development of ultrasound "probes" by modification of the ultrasonic cell disruptors originally developed for use by biochemists.

In all cases, the ultrasound is generated by the expansion and contraction of a piezoelectric device in the presence of a fluctuating electric field, such as that produced by a high frequency AC voltage. Most cleaning baths have one or two such devices situated at the base of a metal bath. The ultrasound is conducted to the site of action by propagation through a volume of water. The disadvantages of this configuration lie in the lack of control that can be exercised over a number of important parameters. For instance, the acoustic intensity and frequency of ultrasound generated by cleaning baths can vary considerably from manufacturer to manufacturer and, more importantly, over the lifetime of a particular bath. In addition, the positioning of the flask and heights of liquid in both the bath and the reaction vessel become critical to the reproducibility of the reaction (Figure 10) by virtue of the observation that cavitation will not occur at the

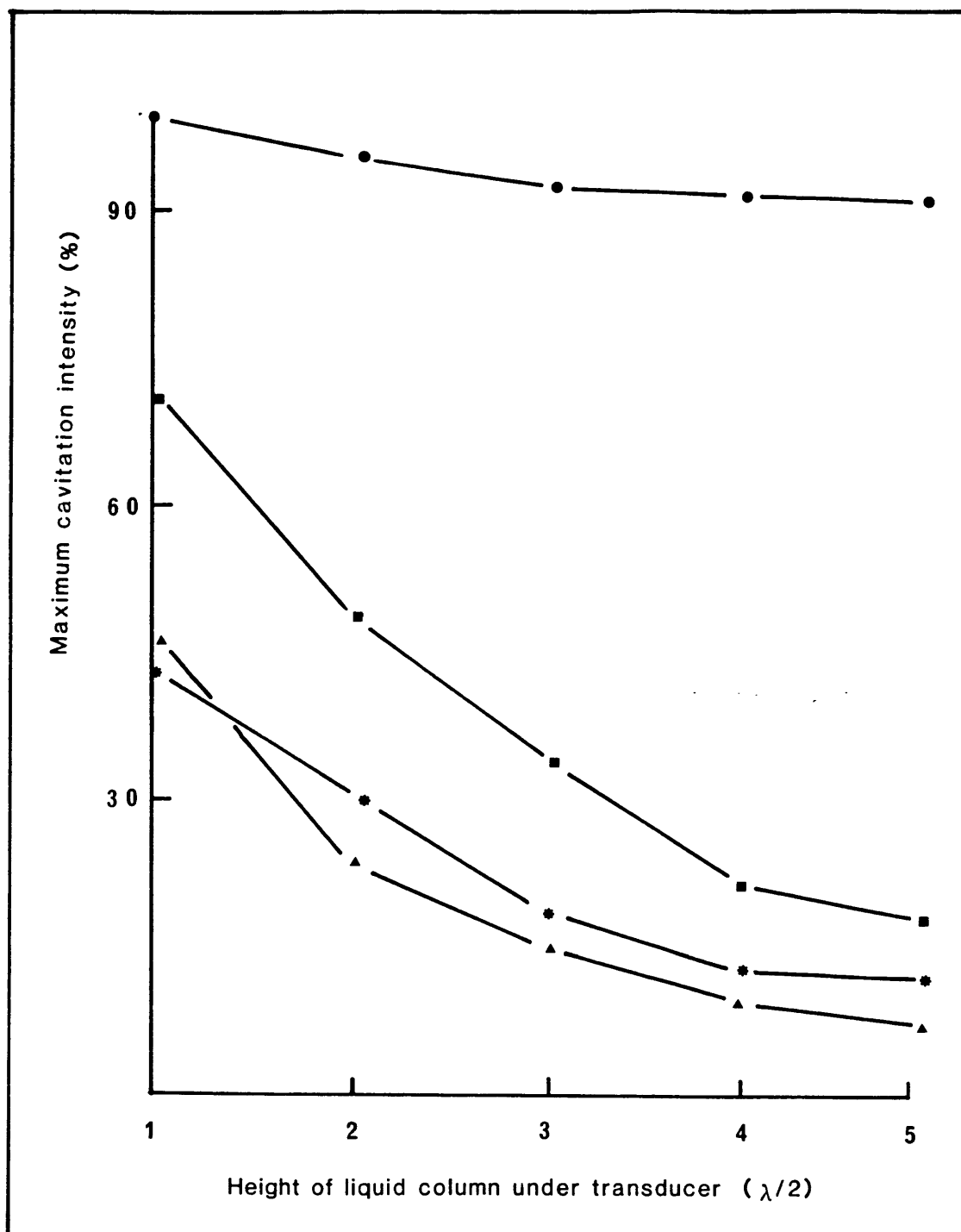


Figure 10
 Maximum cavitation intensities (at 46 kHz) of four liquids as a function of the height of the liquid column under the transducer:
 ● - water; ■ - toluene; * - benzene; ▲ - ethanol³³.

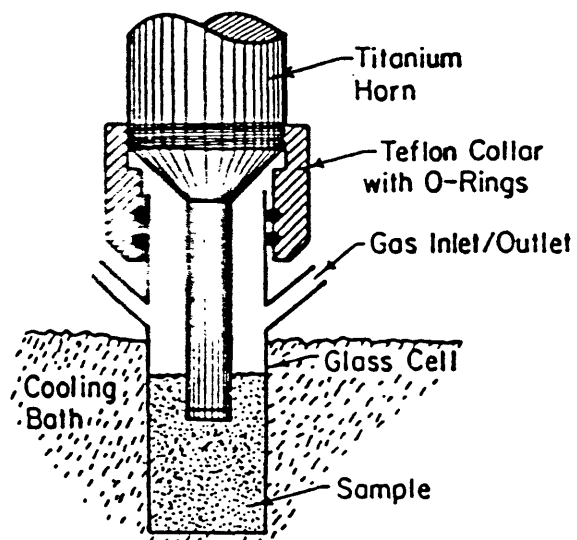


Figure 11
Cup-Horn Sonicator. Modification of a design from Heat Systems-Ultrasonics.

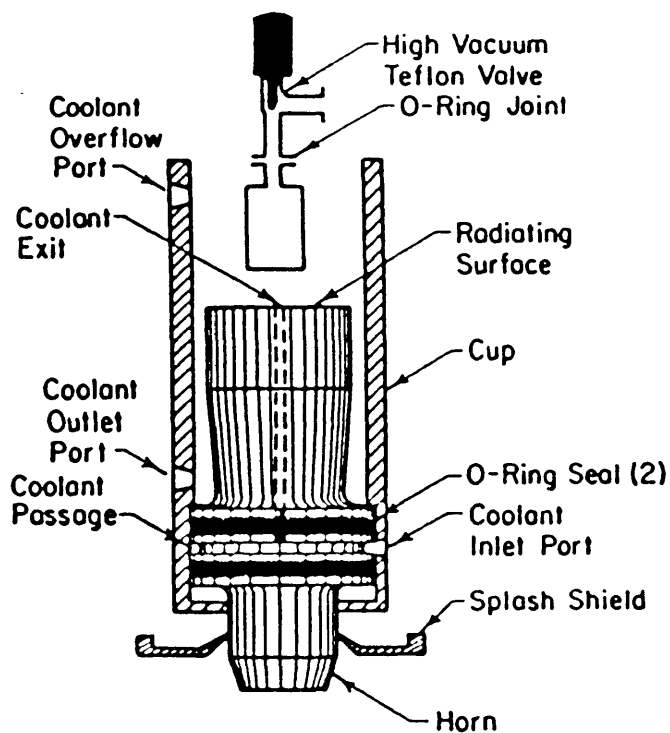


Figure 12
Direct immersion ultrasonic horn equipped for work under inert atmospheres as designed by K.S. Suslick³.

nodes of standing waves set up in the bath³³. Temperature control in such systems is virtually impossible and the ambient temperature is generally about 35°C. This is an important consideration in the view of the inverse relationship between the vapour pressure of a liquid and the maximum intensity of cavitation attainable. Finally, attenuation of the ultrasound as it passes through the water in the cell means that the acoustic intensity is only marginally higher than the lower limit necessary for cavitation and relies on the presence of solid "impurities" within the liquid to lower its tensile strength before cavitation can occur.

This limitation has led to the development of a number of systems that can be used to induce cavitation in homogeneous reaction mixtures. Suslick has given full consideration to the merits of these designs and has clearly favours use of the direct immersion probe on the grounds that it allows access to a wide range of acoustic intensities with a high degree of reproducibility. Furthermore, temperature control is readily achieved by immersion of the reaction vessel in a cooling bath and the availability of commercial flow cells will allow processing of multi-litre quantities of reagents. Fears that erosion of metal from the surface of the probe would lead to contamination of reaction mixtures have been dispelled in a careful study published some years ago³⁴ and corrosion of the horn by reaction media seems unlikely in view of the low reactivity and high tensile strength of titanium.

From an industrial point of view, large scale processors, capable of dealing with up to 200 lmin⁻¹ have been available for a number of years and are already in use for degassing liquids, dispersion of solids, formation of emulsions and large scale cell-disruption. Suslick has published a rough comparison between typical sonochemical and photochemical efficiencies which demonstrates that homogeneous

sonochemistry is typically more efficient than photochemistry and that heterogeneous sonochemistry is several orders of magnitude better³.

Table 2

Comparisons between sonochemical and photochemical apparatus

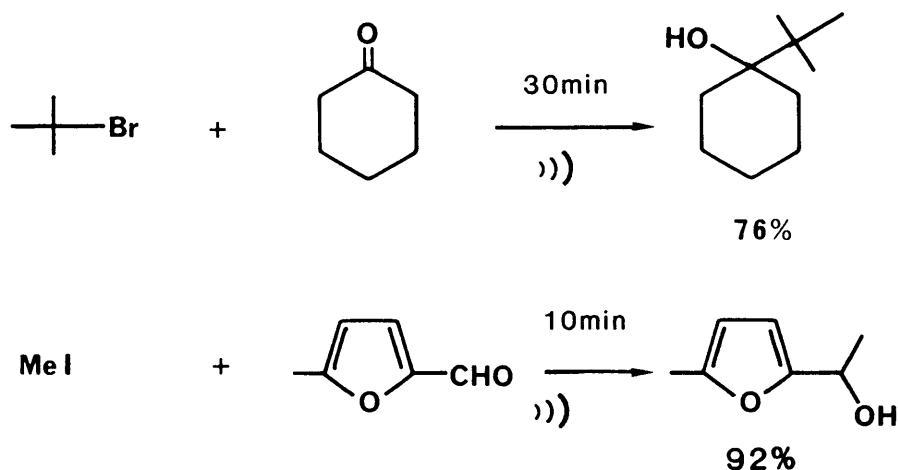
	Photochemistry	Homogeneous sonochemistry	Heterogeneous sonochemistry
Source	250W Quartz-halogen lamp	200W cell disruptor (at 60% power)	150W cleaning bath
Approximate cost	\$1800	\$1900	\$700
Typical rates	7 mol/min	10 mol/min	500 mol/min
Electrical Efficiency	2 mmol/kWH	5 mmol/kWH	200 mmol/kWH

This is of great importance when considering the potential for application of sonochemistry to industrial processes given the current degree of interest in this rapidly expanding field of chemistry.

1.5 Application of ultrasound to the preparation of organolithiums

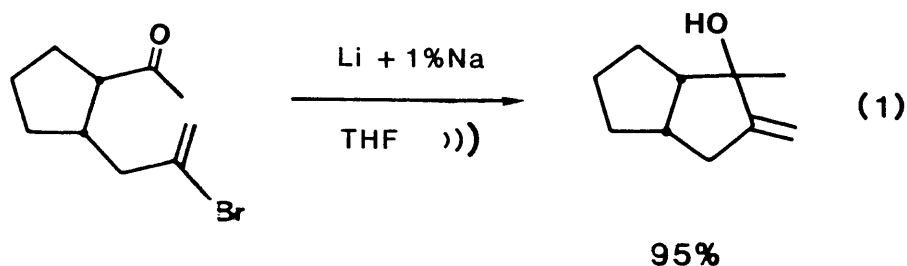
Initial reports by Luche and Damiano³⁵ on the in situ generation of alkyllithium species on sonication of a mixture of alkyl or aryl halides and lithium in THF at room temperature prompted the current interest in this area. The reaction was shown to be generally applicable and excellent yields of n-propyl, n-butyl and phenyllithiums could be obtained (61-95%) even in wet technical grade THF! Reaction with isopropyl and t-butyl halides was sluggish, but this reaction should hold potential for large scale industrial applications ruling out the need for use of initiators and, since reaction is immediate, removing the initiation period which represents a serious problem when working on a large scale.

Reaction of the ultrasonically generated alkyllithiums with carbonyl compounds produced an extremely facile route to secondary and tertiary alcohols in a lithium-mediated Barbier reaction.



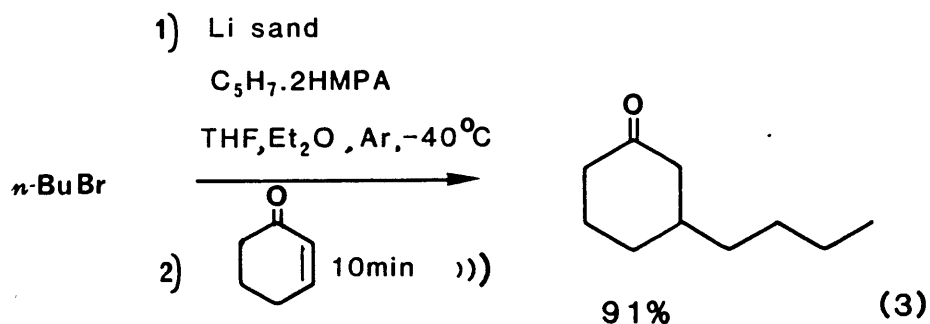
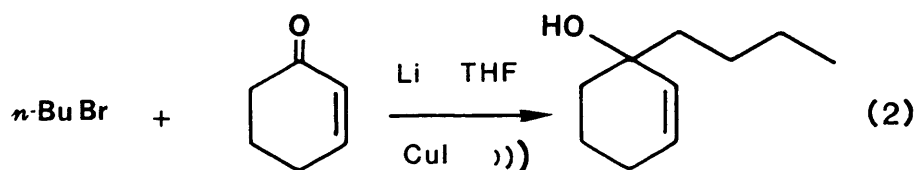
Yields were high and reaction times very short, even for secondary and tertiary halides. Furthermore, the commonly observed side reactions, such as reduction and enolization, were minimal. The reaction also proceeded cleanly with allylic, vinylic and even benzylic halides, where Wurtz coupling normally predominates. Trost and Coppola³⁶ have put this methodology to good use in an intramolecular synthesis of

exo-methylene cyclopentanes (1).

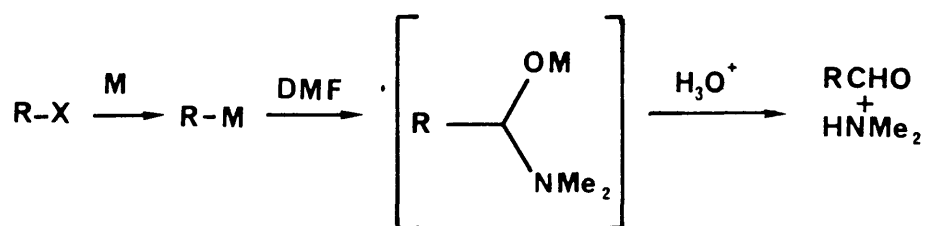


In the examples given, the cyclisation proceeded with retention of configuration at the centres indicated. This includes the synthesis of the highly strained trans-fused system, although competing dehydrobromination reduced the yield to 44%.

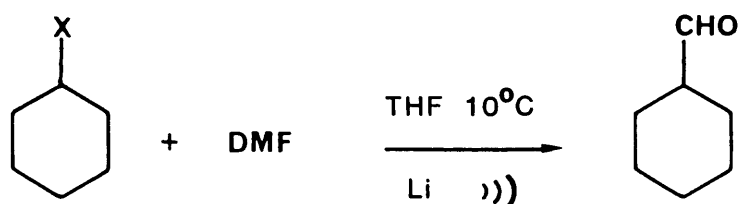
In an extension of their original work, Luche and co-workers³⁷ attempted to generate organocopper species in a one-pot reaction. However, 1,2-addition of the intermediate organolithium proved faster than reaction with the copper iodide. Nevertheless, modifying the reagents used and increasing the power of the ultrasound generator



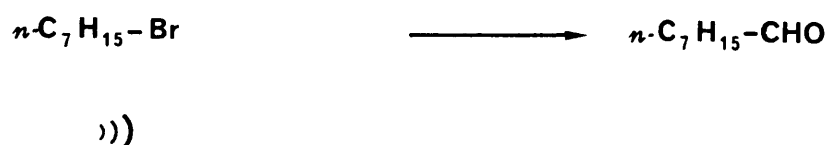
allowed formation of the desired organocopper species at -40°C within 10-30 mins. Addition of the enone and sonication for a further 10 min gave the 1,4-alkylated product (3). The reaction is high yielding and extremely fast although it suffers from the need to use $\text{C}_5\text{H}_7\text{Cu}-2\text{HMPA}$ ³⁸ as the source of copper. Turning their attention to the Bouveault reaction Luche *et al* found that aldehydes could be generated from alkyl halides in a one-pot reaction.



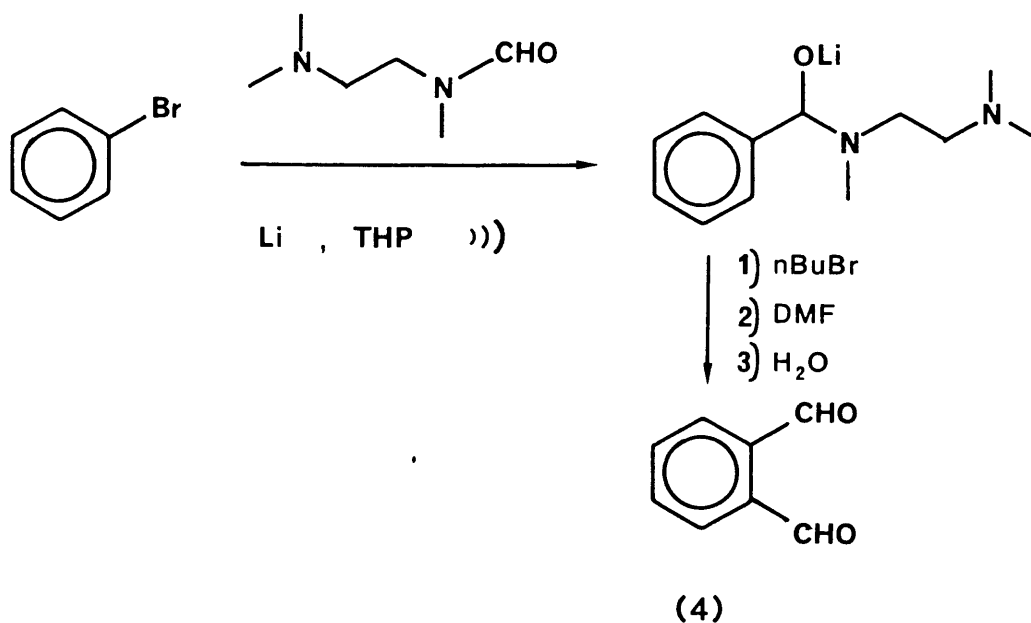
The classic reaction suffers from numerous side reactions and formation of the aldehyde does not always predominate. However, sonolysis of the reaction mixture gives good yields of uncontaminated aldehyde within 5-10 min using a wide range of 1^o, 2^o and 3^o aliphatic and aromatic chlorides and bromides. In contrast, the thermal reaction at -15°C takes considerably longer and yields of aldehyde are lower, particularly in the case of aliphatic substrates³⁹.



$\text{X} = \text{Cl}$ 70 % in 10min
 $\text{X} = \text{Br}$ 76% in 5min



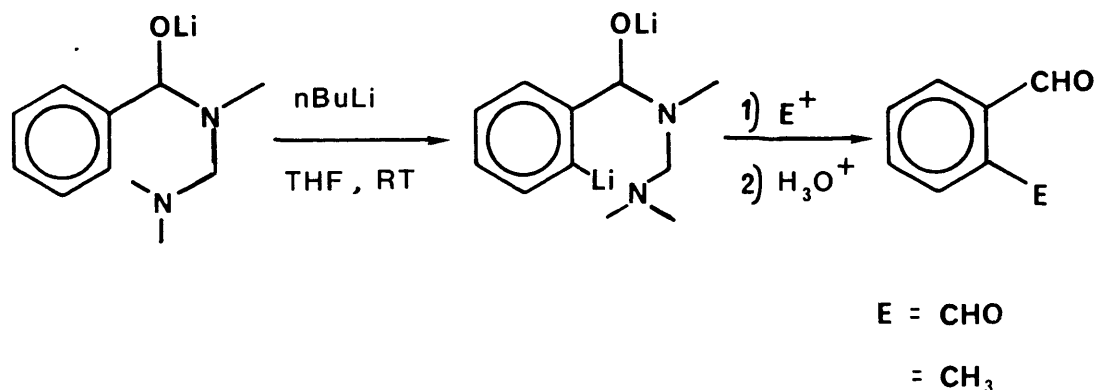
In their most recent work Luche *et al* have extended the scope of these reactions by using formamides to direct ortho lithiation of substituted benzenes, thus generating the ortho-dialdehyde (4) from monohalogenated benzene via a double Bouveault reaction^{40,41}



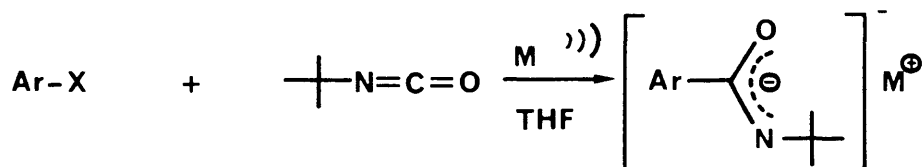
Comparative experiments with DMF and N-formyl-N'-methylpiperazine showed that the stability of the α -aminoalkoxide was independent of

the nature of the formamide ⁴⁰ despite reports to the contrary⁴².

However, the presence of a second heteroatom directs subsequent ortho-lithiation of the aryl ring.

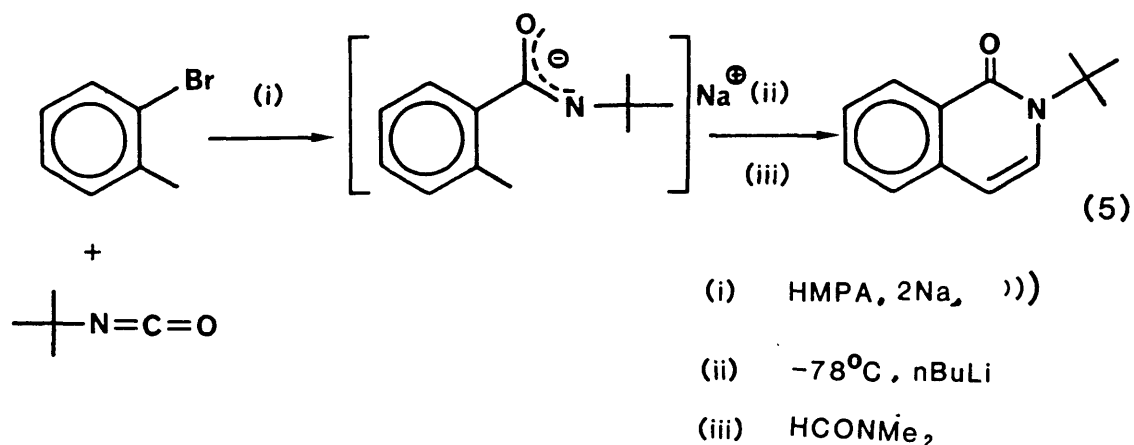


Lithiation proceeds best in tetrahydropyran solution and quenching with DMF or methyl iodide gave 62% yields of the dialdehyde⁴¹ or *o*-methylbenzaldehyde. In fact, addition of butyl bromide to the reaction mixture in place of the butyllithium gave identical results as the alkylbromide reacted with the excess lithium present to generate the alkylolithium in situ.

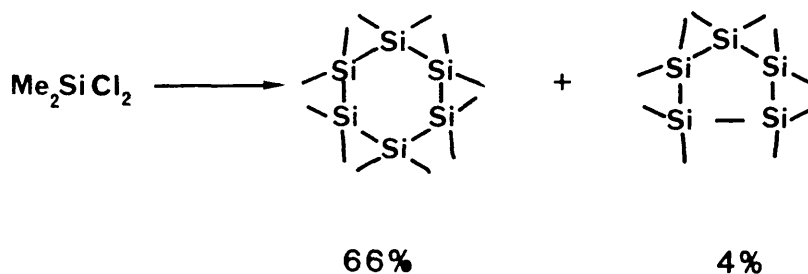


The α -aminoalkoxides are also available from reaction of aryl halides with alkylisocyanates in the presence of a metal⁴³. However, undirected ortho-lithiation of the ring proved much more difficult. Yields of α -aminoalkoxide were highest when magnesium was used but ortho-lithiation of the aryl ring required two equivalents of butyllithium, as one was consumed in transmetallation. Forming the sodium alkoxide overcame this problem but necessitated the use of a full equivalent of HMPA. If *o*-bromotoluene is treated in this way lithiation occurs at the benzylic position and in some cases the final product can be persuaded to cyclise spontaneously to give the benzo-fused heterocycle (5). This methodology has yet to be applied to

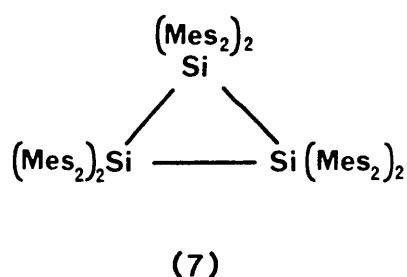
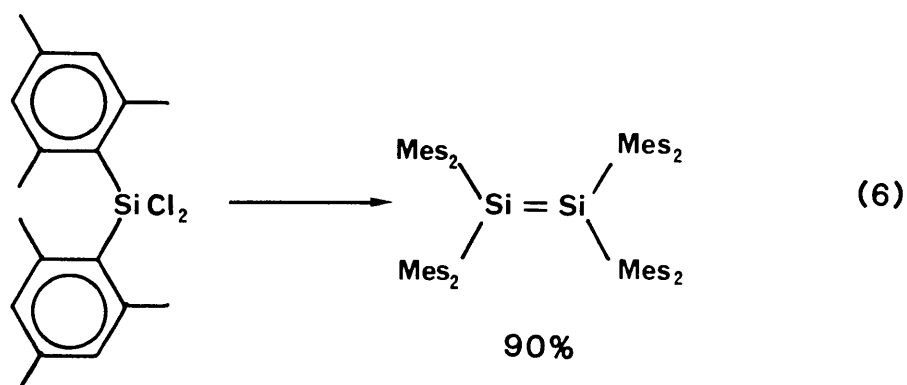
synthesis of any natural products; however, it appears to have given a new lease of life to a very old reaction!



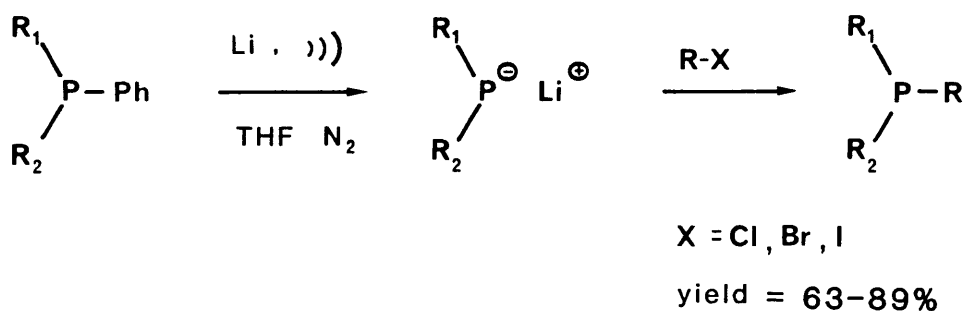
Other workers have reported that prolonged sonolysis of organolithiums derived from organic halides⁴⁴, chlorosilanes and chlorostannanes⁴⁵ results in Wurtz-type coupling. Yields are moderate and the reactions are of little synthetic interest. However, coupling of dichlorosilanes and stannanes produces a novel route to cyclic polysilanes. The product obtained is determined by the steric bulk of the alkyl groups and only low levels of contamination by other silanes is observed.⁴⁵ Silylene intermediates did not appear to be involved; however, Boudjouk *et al*⁴⁶ later reported formation of the tetramesityl silylene (6) which had previously been made by photolysis of (Mes)₂Si(TMS)₂⁴⁷.



Sonolysis of the dichloride with lithium in THF was reported to give a 90% yield of the novel silylene. Unfortunately, these results proved irreproducible and Masamune later pointed out that the product generally obtained is the tricyclic system (7)⁴⁸.



Lastly, some Chinese workers have developed a simple synthesis of tertiary phosphines based on the reductive cleavage of phosphorous-carbon bonds in phenylphosphines^{49,50}.

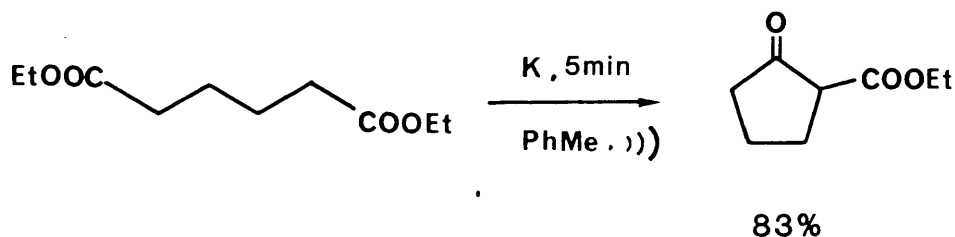


Reaction was complete within 5 min. In comparison, the stirred reaction takes ten times as long⁴⁹. Alkylation of diphenylphosphines

could also be readily achieved to give high yields of uncontaminated product. Previous routes to these important chelating agents had suffered from the extreme sensitivity of the secondary phosphines to air and the difficulty of its exclusion over the long periods of time necessary to obtain satisfactory yields of product.

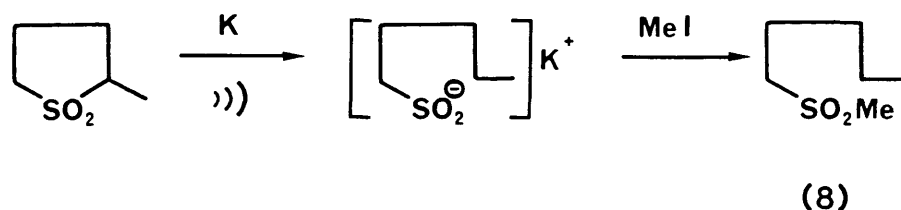
1.6 Reactions with other alkali metals

Reactions involving other alkali metals are not as numerous. Colloidal alkali metals have been known for many years but they remain unexploited in synthesis due to the difficulties associated with their preparation. Luche and co-workers observed that small lumps of potassium could be dispersed in a few minutes by sonication in toluene or xylene at 10°C in a cleaning bath³⁰. The colloid generated was used in a number of reactions; for instance, a Dieckman cyclisation could be effected within 5 min.

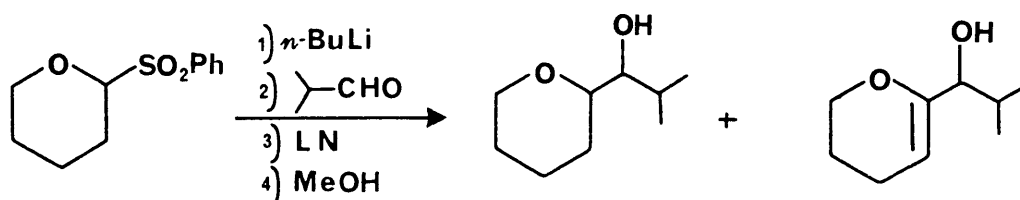


Interestingly, they noted that dispersion could not be effected in THF. Similarly, sodium could only be dispersed in xylene and lithium could not be persuaded to disperse in either of the three solvents tried. We too have observed this whilst attempting to form sodium phenylselenide by reaction of sodium with diphenyl-diselenide⁵¹. Using solid sodium, the reaction time was halved when using xylene in place of THF.

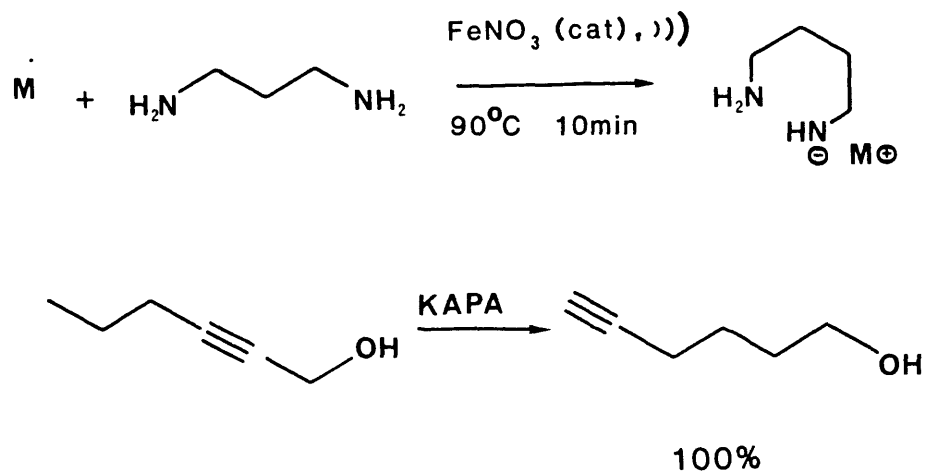
Colloidal potassium was also used to desulphonylate cyclic sulphones⁵². This reaction is only synthetically useful under these conditions and is extremely slow in the absence of ultrasound. Furthermore, the reaction is highly regioselective and reductive cleavage occurs preferentially at the more substituted centre giving the product shown (8).



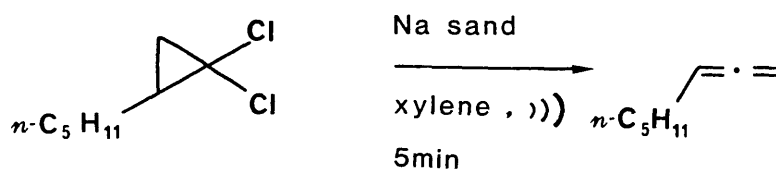
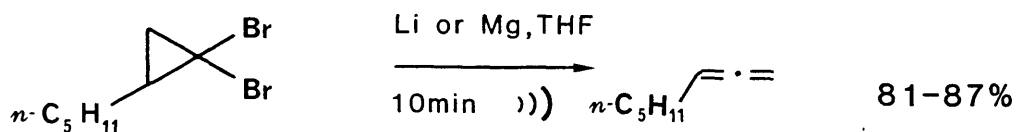
A number of aromatic anions have been generated by sonolysis of mixtures of naphthalene,^{53,54} anthracene, biphenyl⁵⁴ and 5,6-benzoquinoline⁵⁵ with sodium and lithium. Lithium naphthalide (LN), formed as a solution in ethereal solvent, can be transferred easily via syringe and has been used as an effective reducing agent in a number of cases.



In the preparation of KAPA and NAPA, reagents used for the isomerisation of internal acetylenes, sonication of propanediamine with potassium or sodium metal in the presence of a catalytic amount of ferric nitrate generates the reagent in high yield within 10 min.⁵⁶ Previous preparations advocated use of the hazardous and expensive potassium hydride or amide, which must be freshly generated each time. This development is clearly the method of choice.



Ultrasonically dispersed lithium, magnesium and sodium have all been used in the synthesis of allenes⁵⁷ from dihalocyclopropanes.



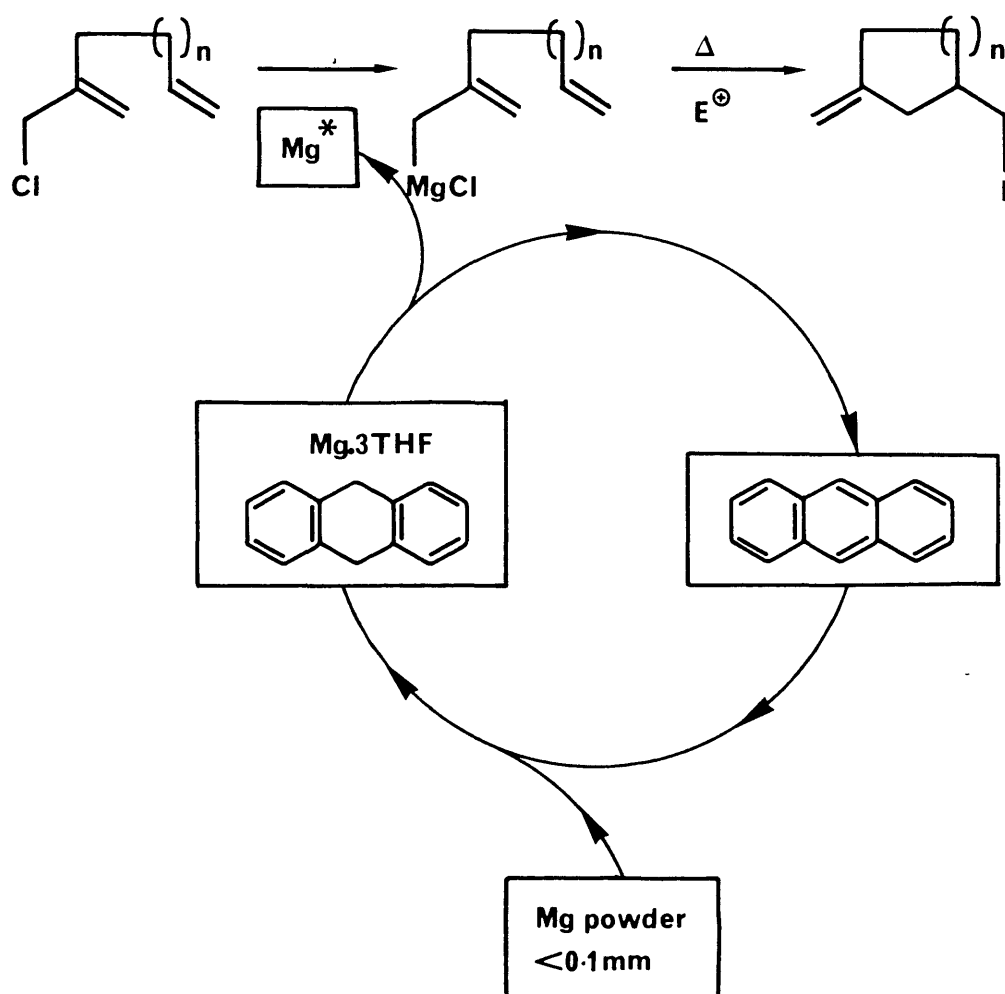
Yields of allene were high despite the fact that these reactions were all carried out in air using commercial THF simply dried over potassium hydroxide.

All these reactions are extremely fast and ultrasound can clearly be exploited to produce highly active dispersions of alkali metals in the

simplest possible way. The full range of synthetic applications for such dispersions is unrealised. Hopefully, these examples will prompt further exploration of their potential.

1.7 Preparation of activated magnesium

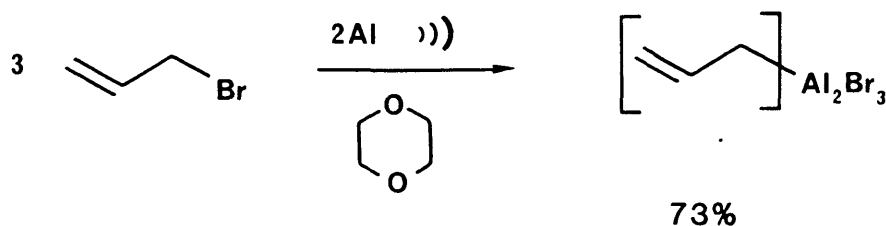
Bonnemann *et al*⁵⁸ have described a method for the preparation of highly activated magnesium which was used in the reductive synthesis of a variety of transition metal complexes known to be active catalysts for organic reactions. Addition of a small amount of anthracene to a suspension of magnesium powder (particle size <0.1mm) in THF gives a sparingly soluble adduct, thought to be (anthracene).Mg.3THF. Sonolysis of the pre-formed complex in the presence of the desired reagents at 65°C releases highly activated magnesium. The anthracene then reacts with more of the magnesium powder, completing the catalytic cycle. That is, its role is effectively one of a phase transfer catalyst.



Oppolzer and Schneider⁵⁹ later used this procedure to prepare allylmagnesium halides when standard procedures proved unreliable. Of the various methods available for the production of highly activated magnesium this was clearly the method of choice, requiring none of the tedious stoichiometrically precise experimentation employed in the preparation of "Rieke-magnesium" or complicated apparatus for vapourisation of metallic magnesium. Yields of the cyclised products were high and the undesired reaction of the Grignard reagent with the starting material was suppressed.

1.8 Preparation of organoaluminium compounds

The first paper describing the application of ultrasound to the preparation of main group organometallic compounds using ultrasound detailed a preparation of trialkylaluminium compounds by direct reaction of Grignard reagents formed in situ, with aluminium powder⁶⁰. Activation of the aluminium, which generally involves use of Al-Mg alloys, proved unnecessary. Recent work has shown that organoaluminium species of the type $R_3Al_2X_3$ are available via reaction of alkyl halides with aluminium powder⁶¹, although yields of subsequent reactions are poor.



However, other workers later exploited this methodology to produce a high yielding synthesis of triethylborane by reaction of the triethylaluminium with trialkylborates⁶².

1.9 Preparation of organozincs

Alkylzincs were amongst the first organometallic compounds to be used in organic synthesis. However, they were rapidly superseded by the Grignard reagents which were easier to handle and more reactive. Nevertheless, they are still commonly employed in both the Reformatskii and Simmons-Smith cyclopropanation reactions and recent work on allylzinc bromides has shown suggests that they are potentially useful precursors of olefinic compounds. Significant improvements in the generation of organozincs for these purposes have been made by employing ultrasound and a number of highly reactive species have been shown to be readily available. Luche and co-workers have published a series of papers on the conjugate addition of dialkyl and diarylzinc compounds, prepared using ultrasound, to α -enones. These latest results increase the scope for use of organozincs by demonstrating the analogies between their behaviour and the commonly used organocopper reagents.

(a) The Reformatskii reaction

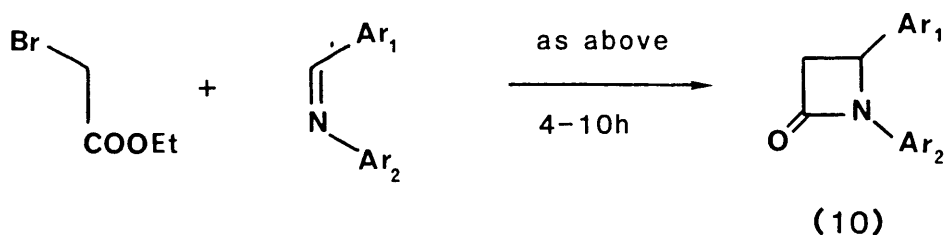
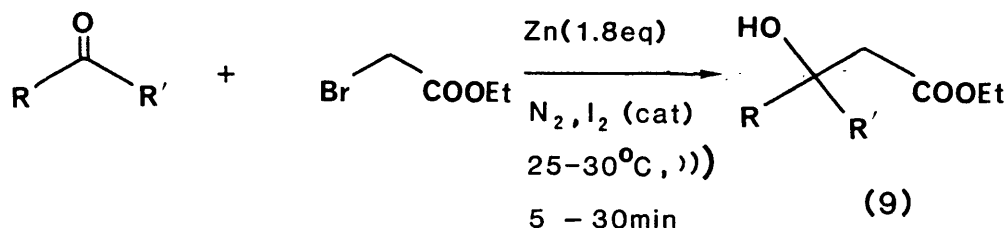
Reaction of a carbonyl compound, commonly an aldehyde or a ketone, with an α -halogenoester in the presence of zinc gives β -hydroxyesters which can be further transformed to give α,β or β,γ -unsaturated esters or, with further elaboration, the dihomologue of the original carbonyl compound. This reaction has found wide application in organic synthesis⁶³.

Modification of the original procedure has resulted in significant improvements in the yields available from this reaction. These include use of freshly prepared zinc powder⁶⁴, a heated column of zinc

dust⁶⁵ and a trimethylborate/tetrahydrofuran solvent system⁶⁶.

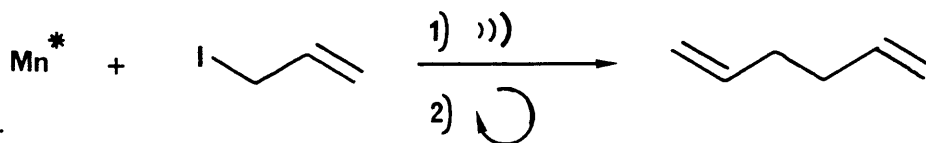
In 1982 Han and Boudjouk⁶⁷ demonstrated that sonication of a mixture of commercial zinc powder, aldehydes or ketones and α -bromoethylacetate gave extremely high yields of hydroxyesters (9) within 5-30 minutes in a one-pot process. Furthermore none of the side products, which result from dehydration of the product or dimerisation of the bromoester, were isolated.

This methodology was also used to provide a synthesis of monocyclic β -lactams (10) in 70-90% yield⁶⁸ from a variety of imines. However, replacing the ethyl bromoacetate by the corresponding propionate of 2-phenylpropionate failed to produce any β -lactam.



Han and Boudjouk discovered that both I_2 and KI could be used to initiate the reaction⁶⁷. Both authors^{68,67} expressed surprise that dioxane proved the optimum solvent in view of its tendency to promote enolisation. However, following an extensive investigation of the reaction conditions, Han and Boudjouk concluded that the reactivity of the system was dominated by the interaction between the zinc surface and the iodine. This is in agreement with observations that metal powders can be activated by halide salts⁶⁹ and evidence produced

by electron microscopy of manganese surfaces activated by iodine in the presence and absence of ultrasound⁷⁰.

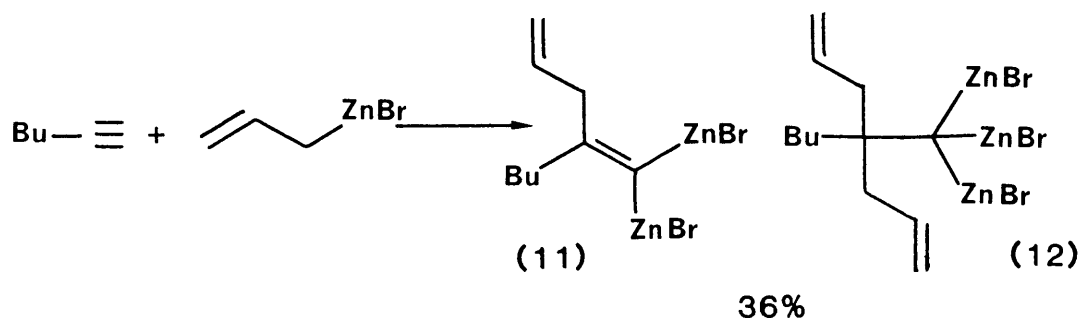


These show that the number of initiation sites generated on the surface of the metal by a short period of sonication far exceed those created by stirring the reagents together for several hours.

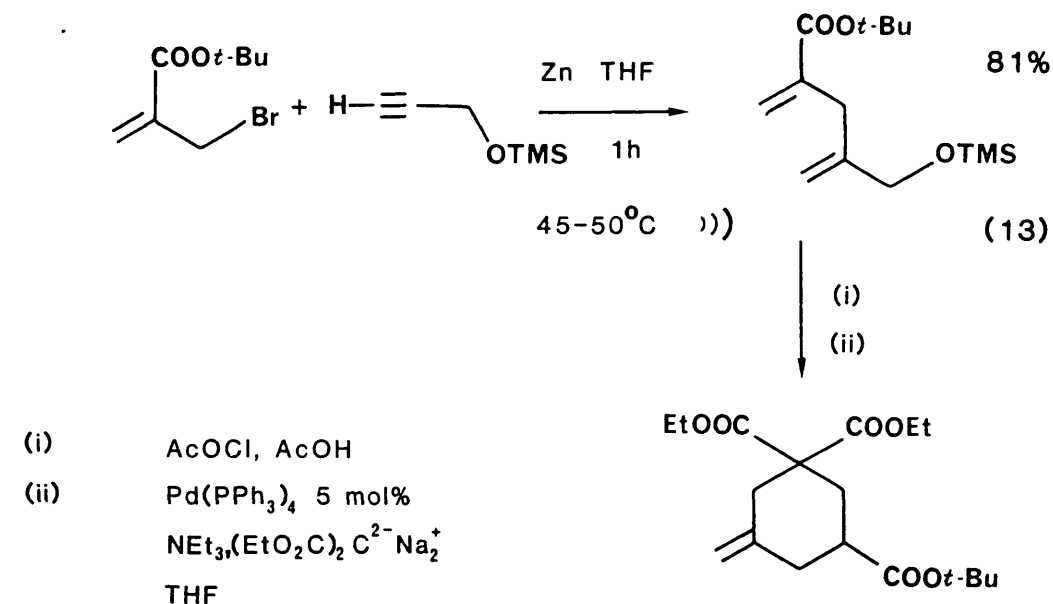
Furthermore, this investigation into the coupling of allylic iodides in the presence of activated manganese conclusively demonstrated that this was the major role of the ultrasound since, once the initiation process was complete, the rate of the ongoing reaction was unchanged by the presence or absence of ultrasound.

(b) Generation of allylzinc reagents

Allylic, benzylic and propargylic bromides will also react with zinc to give the corresponding organozinc bromides. Reaction with both C-C and C-N multiple bonds has already been shown to provide a potentially useful route to some olefinic compounds⁷¹. However, the reaction with terminal acetylenes produces mixtures of mono- and bis-addition products (11) and (12) in low yield⁷².



The synthetic utility of this reaction was greatly increased when Knochel and Normant⁷³ showed that sonicating the reaction mixture allowed mono-addition to predominate giving good yields of highly functionalised dienes (13). Further elaboration gave a variety of six and seven membered carbo- and heterocycles.



(c) Zinc mediated cyclopropanation

Reaction of alkenes with diiodomethane in the presence of a zinc/copper couple produces cyclopropanes by methylene transfer from organozinc species. This is the established method of synthesising cyclopropanes; however, the procedure requires activation of the zinc by use of Zn/Cu , Zn/Ag couples, I_2 or lithium metal. The first of these is most commonly used, but the sensitivity of the system to air makes the results unreproducible and erratic. Furthermore, the reaction which follows has an induction period of indeterminate length and can be extremely violent. Both these factors contribute to making large scale reactions fickle and dangerous.

In 1982 Repic and Vogt⁷⁴ discovered that chemical activation was unnecessary in the presence of ultrasound and yields of cyclopropanated olefins were considerably higher than could be obtained using conventional methods. The reaction was carried out under nitrogen in

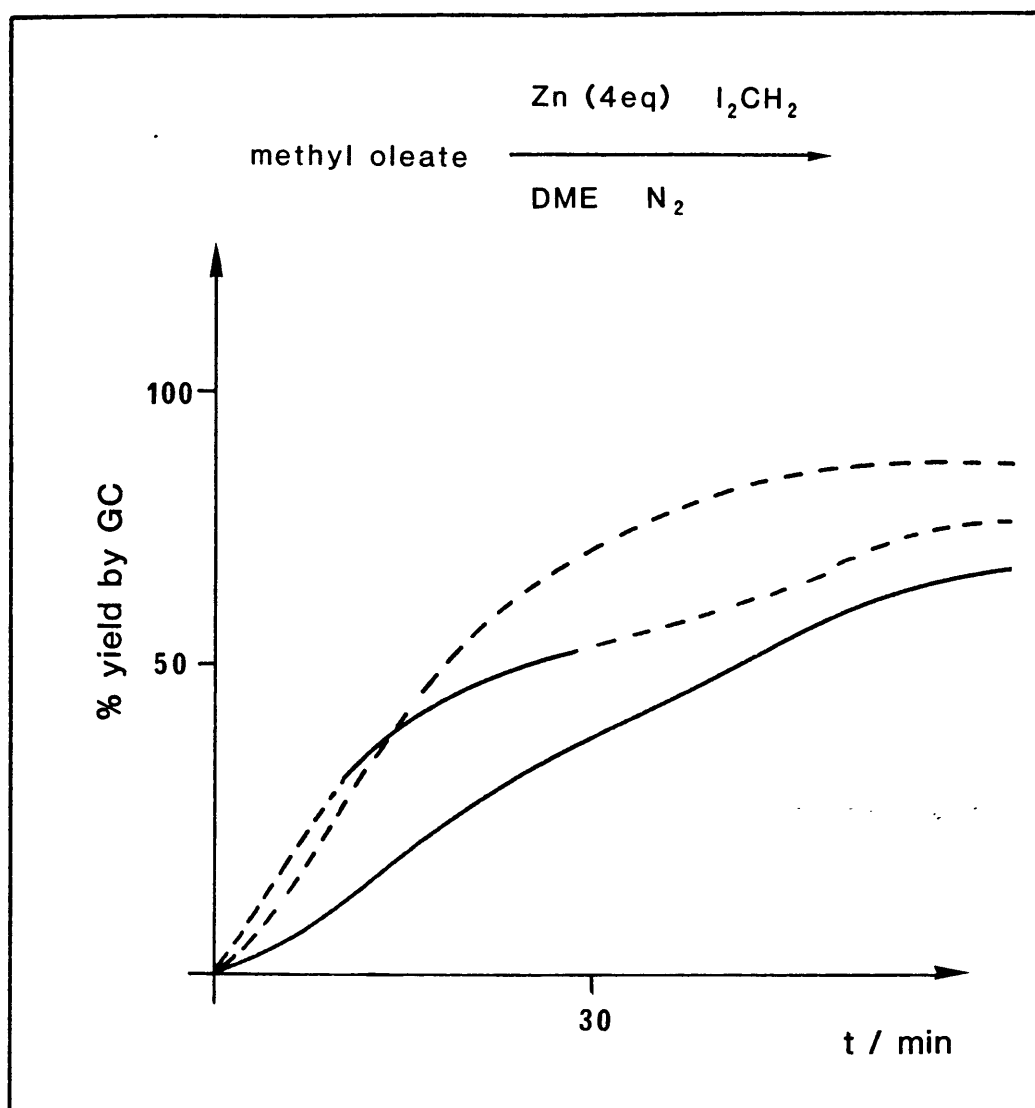


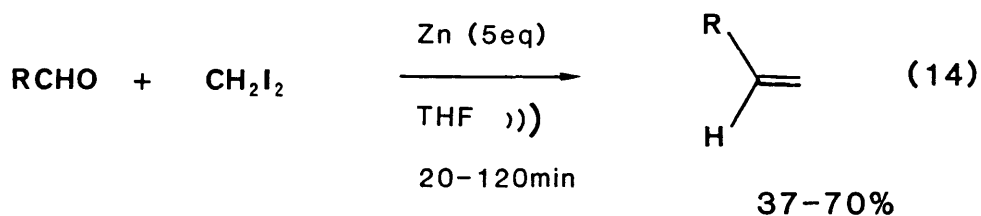
Figure 13

Percentage yield of cyclopropanated material as a function of time for the reaction of methyl oleate with zinc/diiodomethane in dimethoxyethane showing the differences in rate of reaction between the sonicated (- - - -) and stirred (———) reactions ⁷⁴.

refluxing dimethoxyethane, taking care to ensure that all traces of iodine were removed from the diiodomethane prior to its use. Under these conditions reaction was instantaneous and was found to proceed smoothly and rapidly with extremely crude forms of zinc, e.g rods, foils and mossy zinc. Examination of the reaction with methyl oleate in the presence and absence of ultrasound clearly demonstrates the rate increase obtained by sonication of the reaction mixture, this is shown in figure 13. Furthermore switching off the ultrasound source reduces the rate of reaction to that of the stirred reaction.

For reasons previously explained, it seems unlikely that the high temperatures reported are necessary for generation of the organozinc.

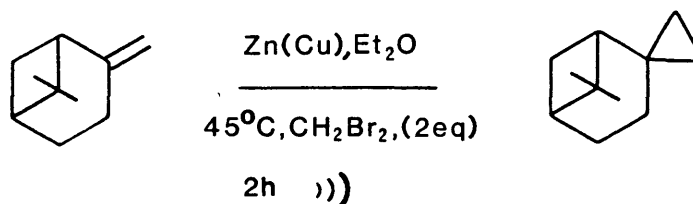
This view is supported by evidence that aldehydes can be methylenated using the same organozinc prepared in THF solution at room temperature⁷⁵. Unoptimised yields of olefin (14) were between 30 and 70% within 20-120 min. Yields obtained using ketonic substrates were



much lower - although comparable to those obtained using an activated Zn/Cu couple. This is of no great consequence as complimentary methodology for the methylenation of ketones already exists.

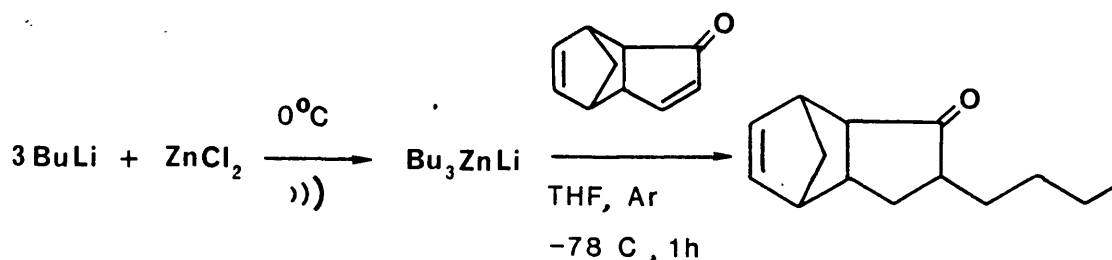
Recently published work⁷⁶ showed that the less reactive dibromomethane could be used for cyclopropanation although the prior activation of the zinc was necessary. The reaction has a long induction period and yields are somewhat lower than those reported using diiodomethane. This effect is particularly noticable in the case of acyclic alkenes, although yields could probably be improved if the reaction was carried out at lower temperature. Nevertheless, the authors argue that the

current disparity between the prices of the two dihalomethanes argues cogently in favour of its use - particularly in the preparation of cyclopropanes from readily available starting materials.



(d) Formation of $\text{R}_3\text{ZnLi} \cdot 2\text{LiCl}$

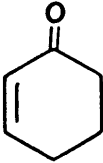
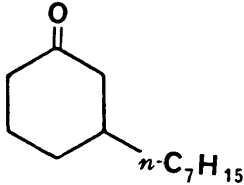
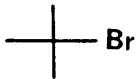
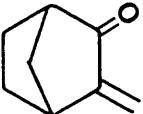
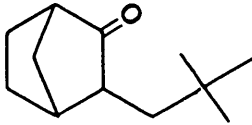
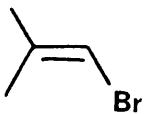
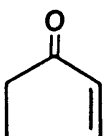
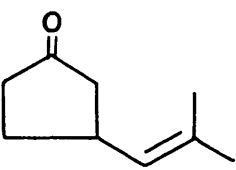
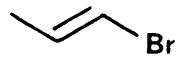
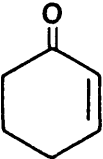
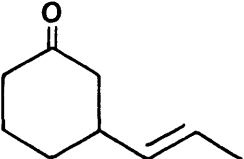
In 1977 Isobe et al reported that $\text{R}_3\text{ZnLi} \cdot 2\text{LiCl}$ species would add conjugatively to α -enones in a 1,4 fashion. Transfer of the alkyl groups proceeded in high yield, although neither phenyl nor acetylenic substrates could be persuaded to react at all⁷⁷.



In 1983 Luche's group discovered that sonolysis of a mixture of aryl bromide, lithium wire and zinc bromide in an ethereal solvent at 0°C resulted in the formation of organozinc species without the need for use of air sensitive alkyllithiums.

These would add conjugatively to α -enones in the presence of Ni(acac)_2 . Side reactions, eg Wurtz coupling, were minimal and the reaction gave good yields of the 1,4-addition products - even in the case of β, β -disubstituted enones⁷⁸. This was essentially a one-pot reaction and complimented the results of Isobe's original report⁷⁷. However, the addition of alkyl and vinyl bromides was reported to be

"unoptimised", that is to say that results obtained using a Sonoclean (40kHz, 96Wl⁻¹) bath were both erratic and unreproducible.

Halide	Enone	Adduct	% Yield
$n\text{-C}_7\text{H}_{15}\text{Br}$			88
			78
			21
			83

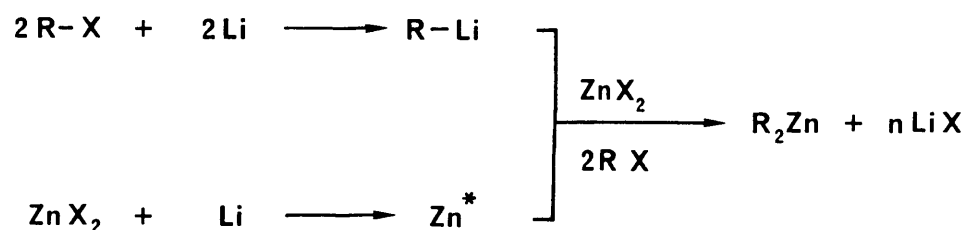
This problem was overcome by use of a cell-disruptor type ultrasound generator. This modification permitted much greater control of the sonication conditions and allowed addition of 1°, 2°, 3° alkyl and allylic groups in essentially quantitative yield within 10–20min⁷⁹.

This development allows analogies to be drawn between the synthetic utility of the organozinc reagents and the organocuprates commonly used for such transformations. The thermal stability of the organozincs compares well against the sensitivity of the

organocuprates, although the stoichiometry of the reaction still requires the use of two equivalents of alkyl bromide. Recent attempts to overcome this problem by use of $RZnX$ species failed to result in any significant transfer of the alkyl group to the α -enone.⁸⁰



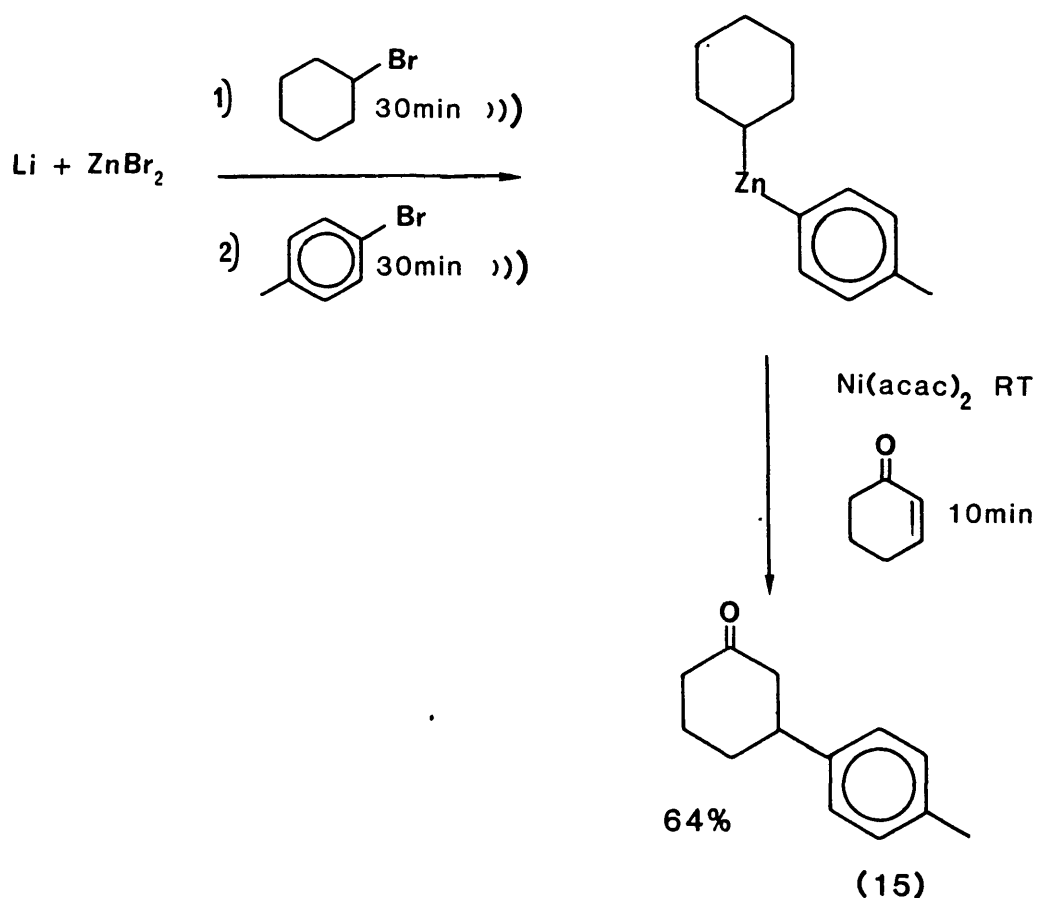
In their original communication⁷⁸ Luche et al had assumed that the active species was a diarylzinc on the basis of the stoichiometry of the reagents used. They suggested that such species could be generated via one of two possible pathways. The primary process could either be envisaged in terms of formation of an aryllithium followed by transmetallation with zinc bromide to give the organozinc; or generation of activated zinc resulting from reduction of the zinc halide by the lithium. Reaction with the aryl halide in situ would then lead to formation of the arylzinc.



The second pathway is analogous to the reaction of an activated metal, similar to those generated using Riecke's methodology, with alkyl halides. However, Luche reports that pre-activation of the zinc gave poor yields of organozinc under sonochemical conditions. It should also be noted that a large excess of lithium was used in all cases. The primary difference between these pathways is surely that the former requires double the stoichiometric amount of lithium compared to the latter. Luche has not published any experimental data concerning this discrepancy although he appears to favour the

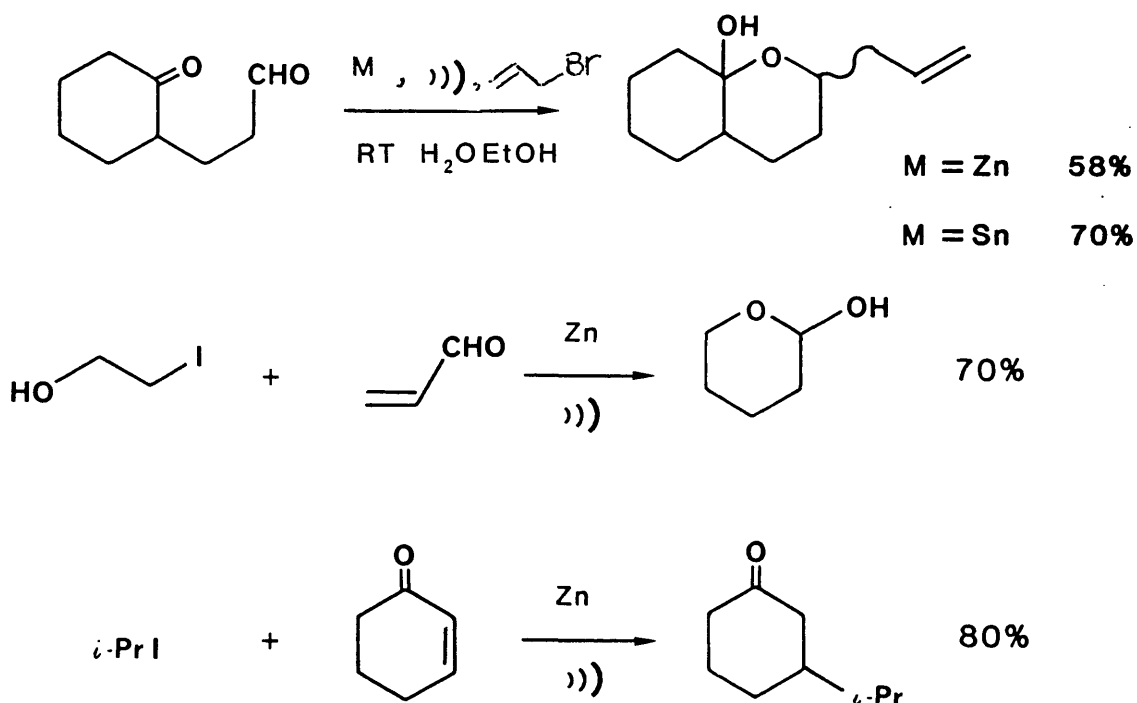
transmetallation argument.

In the same paper⁸⁰ Luche et al have also shown that this methodology can be applied to the formation of mixed organozincs in the manner shown below. The only product isolated (15) arises from transfer of the aryl group to the enone. This compliments the behaviour of mixed organocuprates which will transfer unsaturated alkyl groups in preference to saturated ligands. In their most recent publications Petrier and Luche⁸¹ have published some interesting work concerning the reaction of allylzinc and tin species with aldehydes in aqueous media. Yields for both the stirred and sonicated reactions were of the same order of magnitude, although the zinc reagents appeared to be less sensitive to steric crowding than the corresponding tin analogues. Competitive reaction between aldehydes and ketones favoured addition to aldehydes and even unactivated alkyl halides could be persuaded to add conjugatively to α -enones if the zinc was activated by a copper couple⁸².



Reactions have been reported in aqueous solutions of ethanol, acetone, THF and pyridine, and even in pure water itself. The mechanism for this is not understood although a plausible suggestion would be that the reaction proceeds via a radical pathway, which would be promoted by the presence of water, rather than any discrete organometallic species.

As yet, this methodology remains unexploited. In addition, the comparative hardness and rapid, facile preparation of these reagents should make this methodology of great interest to synthetic organic chemists and Luche and co-workers have clearly demonstrated the scope of organozincs as alternatives to organocuprates.

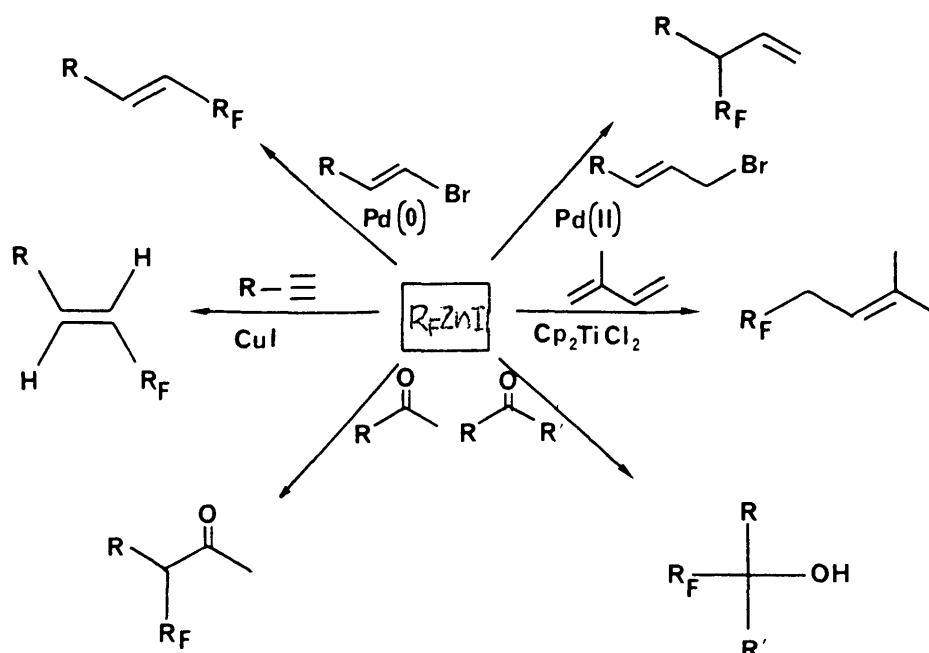


(e) Zinc mediated perfluoroalkylation

Perfluoroalkylmetals are not commonly used in synthesis - presumably because of their low stability. The driving force behind this is the elimination of the metal halide leaving the perfluoroolefin.

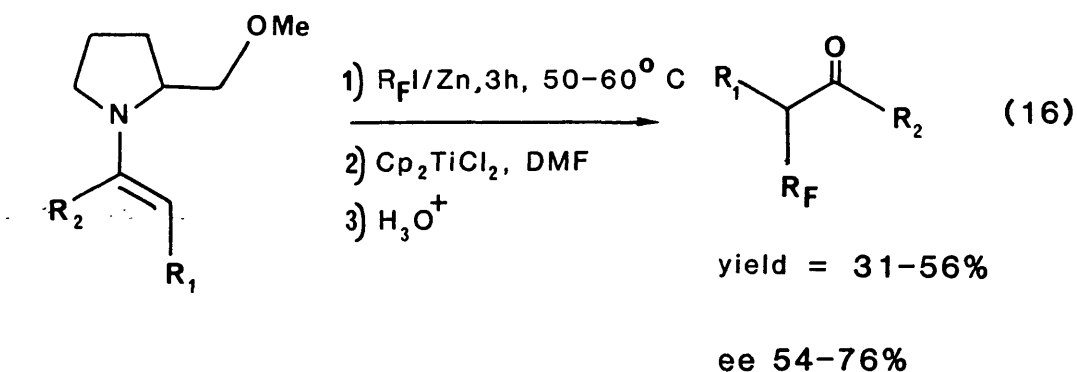
Kitazume and Ishikawa have published a number of communications on the regiospecific zinc mediated perfluoroalkylation of a variety of substrates⁸³⁻⁸⁶. A compilation of these results appeared in 1985⁸⁷ (Figure 14). Secondary alcohols are available in moderate yield by reaction of perfluoroalkyl halides (R_FX) with aldehydes as the result of a modified Barbier-type reaction^{83,87}.

However, reaction with ketones gave low yields of the expected tertiary alcohol, although these could be doubled by reaction in the presence of a bis[π -cyclopentadienyl]titanium(II) catalyst, which was prepared in situ by reduction of the dichloride with zinc in the presence of ultrasound. In contrast, it should be noted that, yields in the analogous lithium mediated reaction were consistently higher without the need for use of any additional catalysis³⁵.

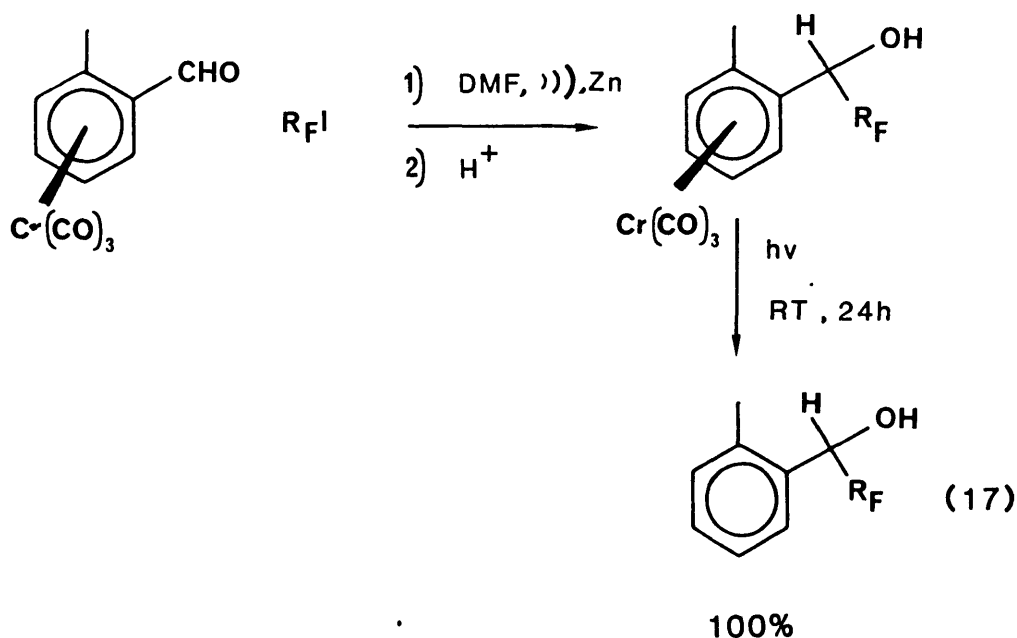


Both vinylic, allylic and aryl perfluoroalkylzinc compounds^{84,87} could also be generated in the presence of palladium catalysts. The regiospecificity of the reaction was reported to be better than 95% although yields of the alkylated product were only moderately good. The addition of perfluoroalkylzincs to alkynes and dienes was regio- but not stereospecific^{86,87} and, as in all cases, yields of alkylated products were consistently higher using alkyl iodides than with the equivalent alkyl bromides.

A brief investigation using chiral auxiliaries, in this case Ender's RAMP and SAMP, provided a route to α -disubstituted ketones (16) with a moderate degree of chiral induction⁸⁷.



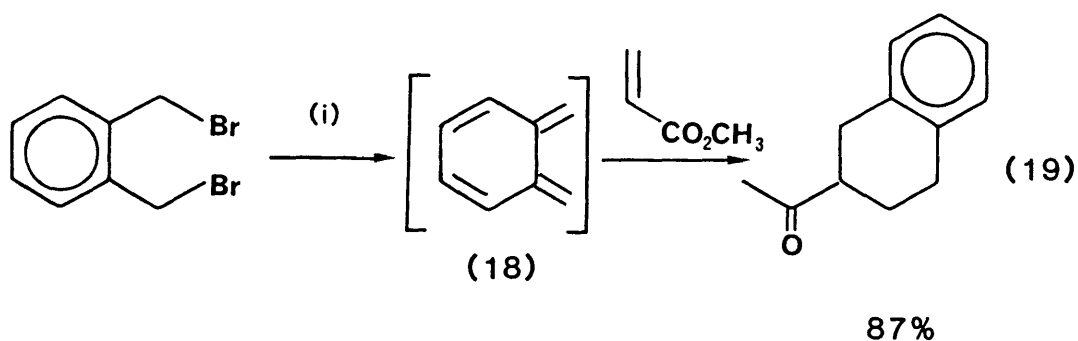
The only other example of a stereospecific perfluoroalkylation reaction also used Kitazume's methodology⁸⁸. Using a chromium tricarbonyl moiety as the chiral auxiliary gave high yields of



benzylic alcohol (17) via a modified Barbier reaction. However, the degree of asymmetric induction using unbranched perfluoroalkyl halides was low, although a marginal increase was seen when using branched halides. The chromium tricarbonyl moiety is readily removed by photolysis and yields of alcohol are virtually quantitative.

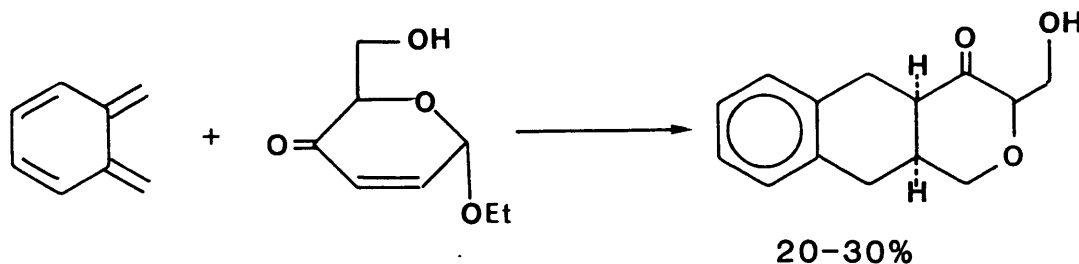
(f) Preparation of reactive intermediates

Ultrasound has been exploited in the zinc mediated generation of a number of reactive intermediates. Most of these are only normally attainable in very low yield as a result of the forcing conditions necessary for their generation. For instance, Han and Boudjouk showed that orthoxylylene (18) was readily available from o-dibromoxylene. Trapping the intermediate tetraene with methyl acrylate gave an 87% yield of the product (19) arising from Diels-Alder reaction with the exocyclic diene⁸⁹.



(i) Zn, dioxane))

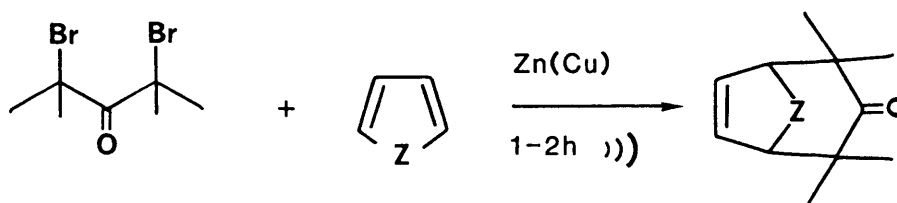
This methodology has been exploited in the synthesis of a number of tri- and tetracyclic systems related to the fungal metabolite altersolanol A and the anthracyclinone β -rhodomycinone. As expected, cycloaddition occurred from the β -face of the dieneophile providing a stereospecific, if low yielding, route to these systems⁹⁰.



The potential for introduction of chiral centres using a Diels-Alder approach makes this a particularly attractive route to benzo-fused cyclohexanes. However, the chemistry of orthoxylylenes is relatively unexplored as previous routes to this elusive intermediate involved use of reagents such as disodium tetracarbonylferrate. This reagent is extremely intolerant of other functional groups, mainly as a result of its high basicity and yields obtained are only a fraction of those available using the zinc/ultrasound route.

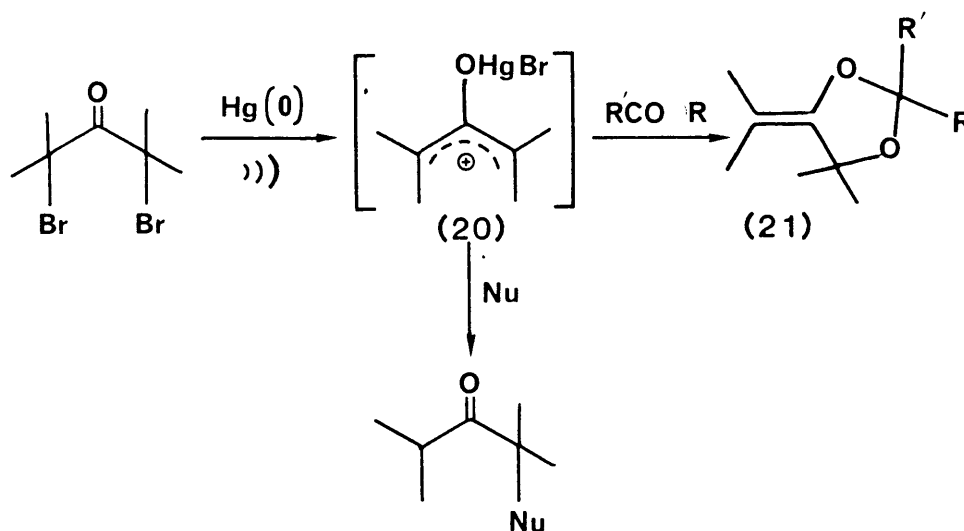
Preparation of bicyclic systems via the reductive coupling of 1,3-dienes with α,α' -dibromoketones to give bicyclic systems has been known for some time. Hoffmann discovered that moderate yields of coupled product were available using a zinc/copper couple. The reaction took between 12-80h⁹¹; however, yields could be significantly improved by use of a trimethylsilylchloride mediator⁹². Complementary work by Noyori⁹³ had already shown that use of diironnonacarbonyl led to significant increases in yield despite the obvious disadvantages of its expense and toxicity. Hoffmann has recently examined the effects of ultrasound on his original reaction⁹⁴. He reports that the reaction proceeded smoothly even in the absence of the silyl chloride, although reaction times could be

reduced to less than 30min in its presence. In fact, the highest yields were obtained using sterically hindered tetrasubstituted ketones and the method appears to be indispensable in such cases. In addition, ultrasound was reported to promote the diironnonacarbonyl mediated reaction, although reaction times were somewhat longer.



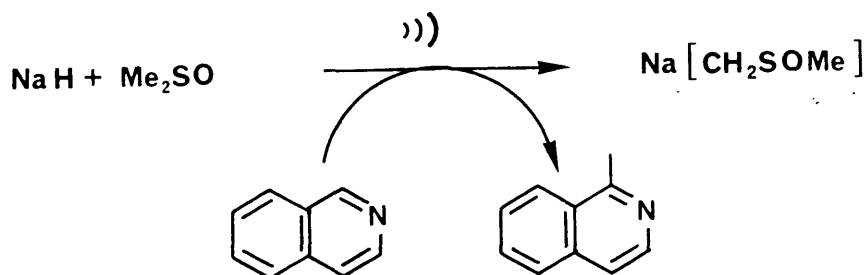
71-91%

Extensive investigations into the alkylation of α,α' -dibromoketones using mercury dispersions have been carried out by Fry and co-workers⁹⁵⁻¹⁰². Comparison with the equivalent electrochemical route⁹⁵ showed that reduction with ultrasonically dispersed mercury gave a higher degree of regioselectivity. Alkylation proceeded smoothly with a variety of nucleophiles and condensation with ketones produced a one-pot synthesis of 4-isopropylidene-1,3-dioxalans (21). Reaction is thought to proceed through the 2-hydroxyallyl cation (20) and mono-substitution of the parent ketone predominates - even in the case of sterically undemanding substrates. Fry believes that this is purely a mixing effect and reports that the reaction proceeds equally well using a high speed laboratory homogeniser.



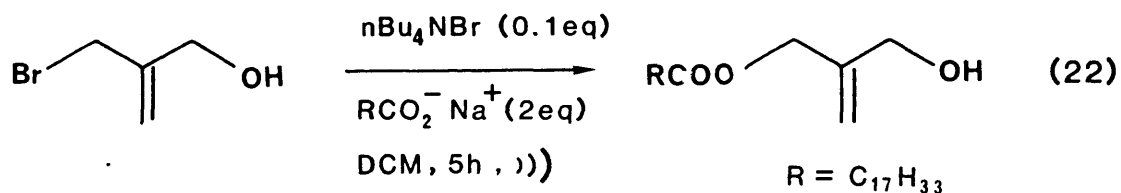
1.10 Ultrasonic acceleration of organic reactions

Although most of the examples in this review deal with the interaction of metals with organic substrates, the effects observed are not limited to organometallic systems and a number of useful procedures for transformations involving non-metals have been published. For instance, amines can be N-alkylated by alkyl halides in the presence of potassium hydroxide and a phase transfer catalyst.¹⁰³ Similarly, direct displacement of halides by the thiocyanate anion proceeds smoothly to give high yields of the corresponding alkylthiocyanate¹⁰⁴. Alkylation of isoquinoline using ultrasonically generated dimethyl sodium¹⁰⁵ was also recently reported by workers using methodology developed in 1966¹⁰⁶.

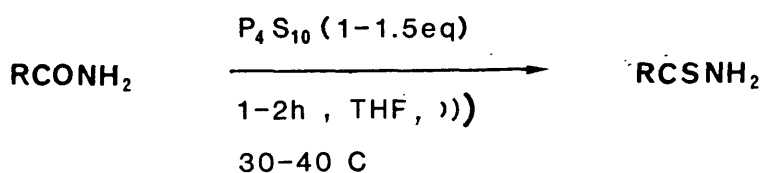


Long chain α -bromo- ω -carboxylic acids were converted to their 128-iodo-derivatives in quantitative yield simply by sonolysis of the acid with 128-iodine in ethyl acetate solution for 20min¹⁰⁷. As yet there are no examples of this simple procedure being used in place of the commonly used Finkelstein method¹⁰⁸ for preparation of alkyl iodides from the equivalent bromide.

Homologation of an allyl bromide was achieved by sonolysis of a long chain fatty acid in the presence of the sodium salt. The reaction was catalysed by tetrabutylammonium bromide and the product (22) used in a synthesis of a type I cyanolipid¹⁰⁹.

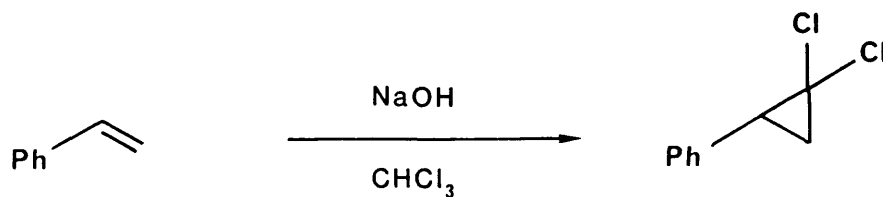


Preparation of thioamides from amides was also shown to proceed faster and more efficiently under ultrasonic conditions. Yields of between 77 and 97% were obtained within 1-2h¹¹⁰. In contrast, the standard reaction involves use of a large excess of reagent as a result of the insolubility of P_4S_{10} , and results obtained using Lawesson's reagent tend to be unpredictable.



Sonolysis of powdered sodium hydroxide and chloroform with concomitant stirring leads to generation of dichlorocarbene. This could be trapped by a variety of olefins providing a high yielding synthesis of dichlorocyclopropanes¹¹¹. Competition experiments showed that the carbene produced was selective for highly substituted double bonds and that its behaviour was analogous to that produced in potassium *t*-butoxide/chloroform systems. Interestingly, sonication or stirring alone do not produce such a marked effect. This is probably due to the increase in mass transport effected by the stirring. The reaction is carried out in a low intensity cleaning bath and the authors had already remarked that large scale reactions (ie >5mmol of alkene) gave poor yields of cyclopropane on this account. However, its major advantage is that the reaction proceeds without the need for

the phase transfer catalysts that are normally required and this modification considerably simplifies the work-up procedure.



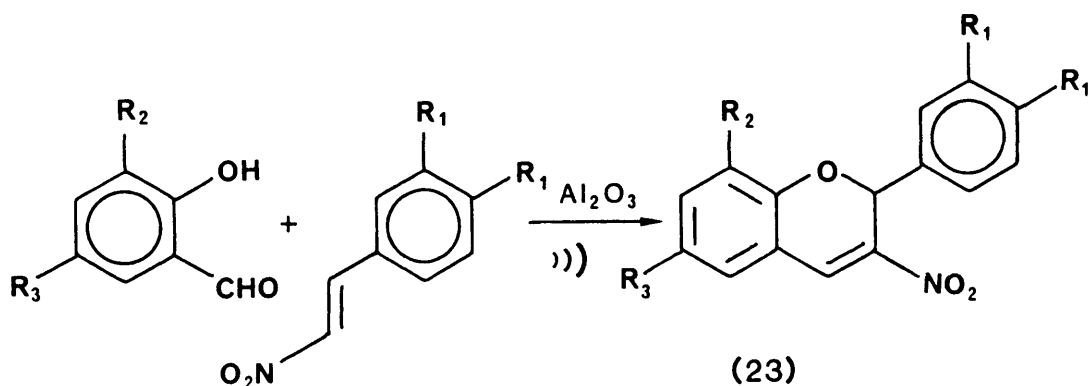
conditions used

% yield

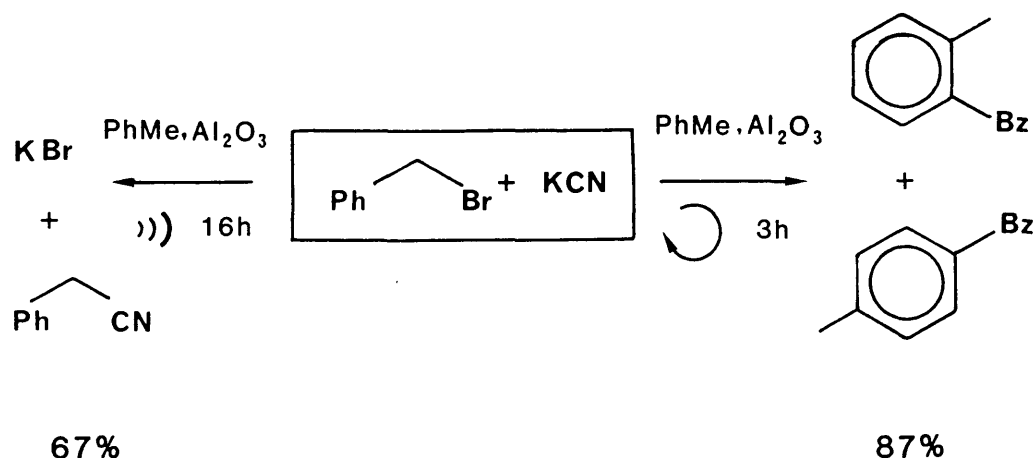
	)))	1.5h	95
	—	16h	31
—	)))	20h	38

A number of liquid/liquid biphasic systems have also been shown to benefit from ultrasonic emulsification. These include the formation of organic azides from activated primary chlorides and bromides¹¹², saponification of aryl esters¹¹³ and nitriles¹¹⁴ to give the corresponding carboxylic acid.

Application of ultrasound to a number of alumina catalysed aldol reactions has also been found to be beneficial. Initial reports stated that self-condensation of ketones was enhanced by a factor of two over the acid catalysed dimerisation¹¹⁵.



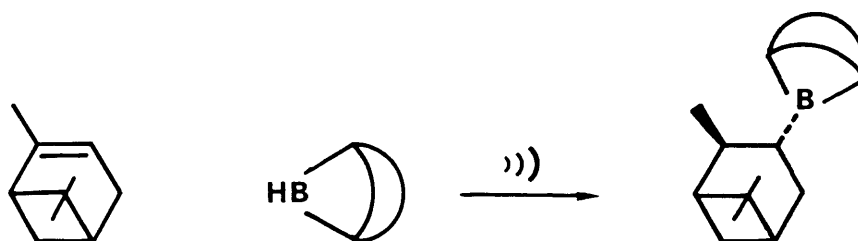
This was later exploited in a synthesis of 3-nitro-2H-chromenes (23)¹¹⁶ with a variety of electron withdrawing substituents in moderate to good yield. In 1983 Ando *et al*¹¹⁷ had reported the synthesis of aryl nitriles from the corresponding chlorides by direct displacement with potassium cyanide.



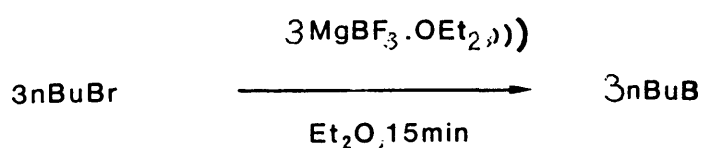
Extending this to the synthesis of aryl nitriles they found that yields obtained were low (27%) but could be significantly augmented by the presence of a basic alumina catalyst and a trace of water^{118, 119}. However, the stirred reaction gives a mixture of *o*-

and *p*-benzyltoluene resulting from Friedel-Crafts attack on the solvent. This variation in reaction pathway appears to be due to the formation of active ion aggregates on sonolysis of the alumina which block those surface sites normally associated with its Lewis acid nature, coupled with the enhanced nucleophilicity of the cyanide anion. Further examination of this effect¹²⁰ showed that ultrasound was essential for nucleophilic substitution to take place. Both the Friedel-Crafts reaction and the cyanide substitution were retarded when sonication was ceased after pre-treatment of the KCN/alumina mixture was complete, but before addition of the bromide.

Brown and Racherla have also exploited ultrasound to speed up hydroboration of substrates which react extremely slowly with a wide variety of hydroborating agents¹²¹. Of particular note is the reaction of (-)- α -pinene with 9-BBN to give alpine-borane (24) - a useful reagent for the asymmetric reduction of α,β -acetylenic ketones and other prochiral carbonyl compounds. The authors report that the reaction takes 12h in THF at 65°C, although this can be reduced to 1h by using the neat reagents which give a quantitative yield of alpine-borane. Once again, this is in complete accordance with the predictions of the "hot spot" theory.

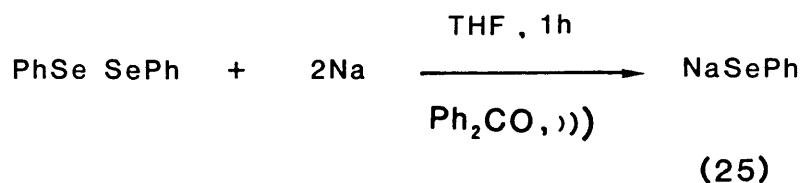


In situ generation of Grignard reagents also allows access to a variety of trialkylorganoboranes which are unavailable by hydroboration. For example, triisopropyl, benzyl, phenyl and allylboranes can be prepared in 10-30 min by sonolysis of a mixture of boron trifluoride diethyletherate, magnesium turnings and a crystal of iodine in ether. Dropwise addition of the alkyl halide gives the desired product within minutes without the need for pre-formation of the Grignard reagent.¹²²

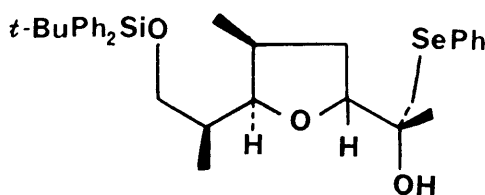


Finally, ultrasound has been used in the preparation of a variety of organoselenium and organotellurium compounds by reaction of alkyl halides, tosylates, mesylates and epoxides with the phenylselenium anion⁵¹ and direct reaction with the Se_2^{2-} , Se^{2-} , Te_2^{2-} and Te^{2-} anions produced by electrochemical reduction of the insoluble elements²⁹.

In the first case⁵¹, we have prepared sodium phenylselenide (25) in 1h by sonolysis of diphenyldiselenide with sodium in the presence of benzophenone, which acts as an electron transfer agent.



This obviates the need to use complicated reagents and the odiferous, unpleasant reagent is prepared in a sealed flask ready for use. Yields of phenylselenol obtained using this reagent were virtually quantitative – even in cases where competing reactions might have been expected to prove problematic. For example, a fragment of the ionophore antibiotic M139603 (26) was prepared using this methodology¹²³.

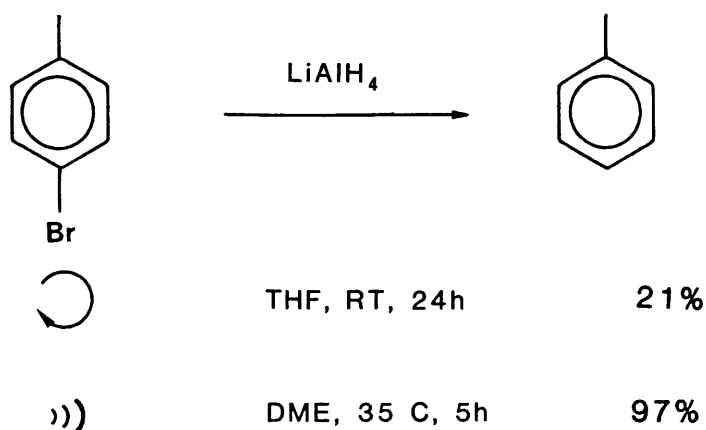


(26)

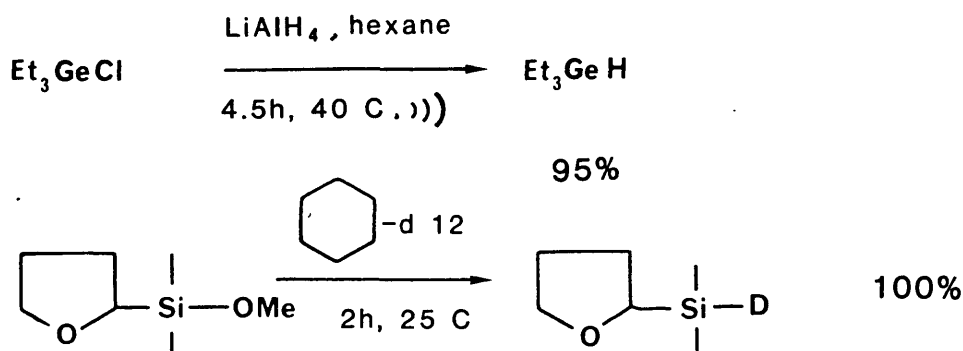
In the second²⁹, sequential synthesis of the E_2^{2-} and E^{2-} anions by electrochemical reduction of the elements provides a route to both dialkyldi- and monoselenides and tellurides.

1.10 Ultrasonic acceleration of redox reactions

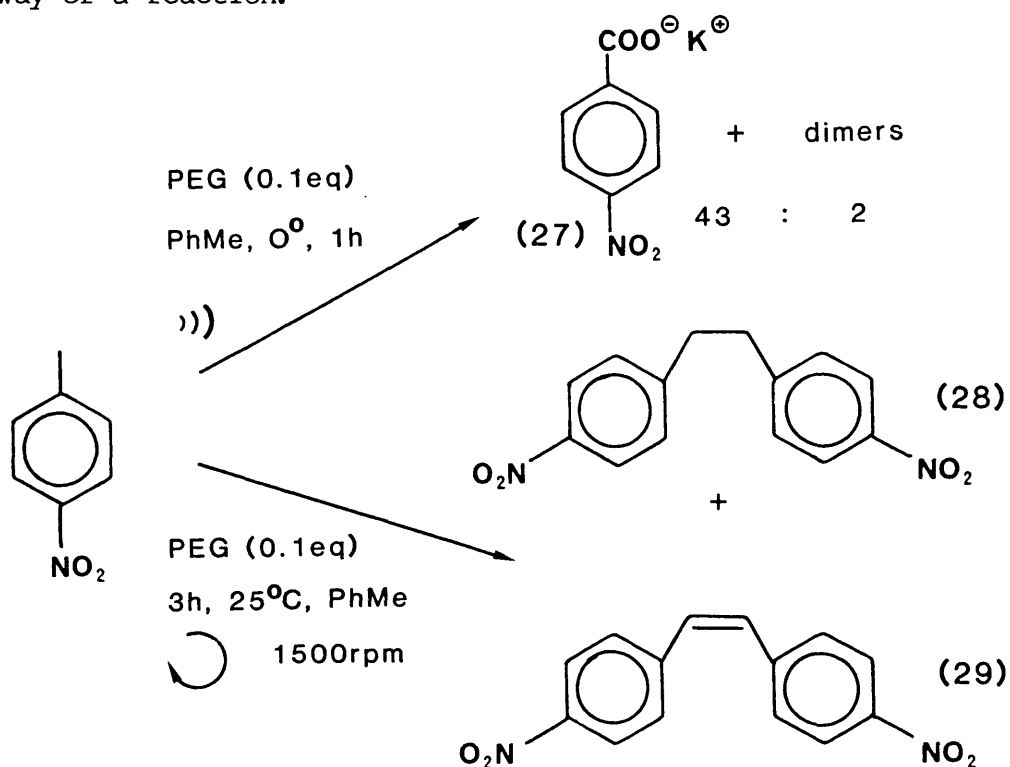
The well-documented effects of ultrasound on heterogeneous systems have been exploited to produce beneficial increases in the rates of a number of reactions that would more commonly be executed under homogeneous conditions. For instance, the reduction of aryl halides with lithium aluminium hydride occurs extremely slowly in THF solution; however, Han and Boudjouk have reported that the reaction can be carried out in a fraction of the time if dimethoxyethane (DME) is used in its place¹²⁴. Sonolysis of the heterogeneous reaction mixture gives high yields (70–99%) of the reduced product. The effect was particularly marked in the case of deactivated aryl halides; for example, *p*-bromotoluene gave a 97% yield of toluene in 5h. In contrast, the yield of the stirred reaction was a modest 21% after 24h at room temperature in THF.



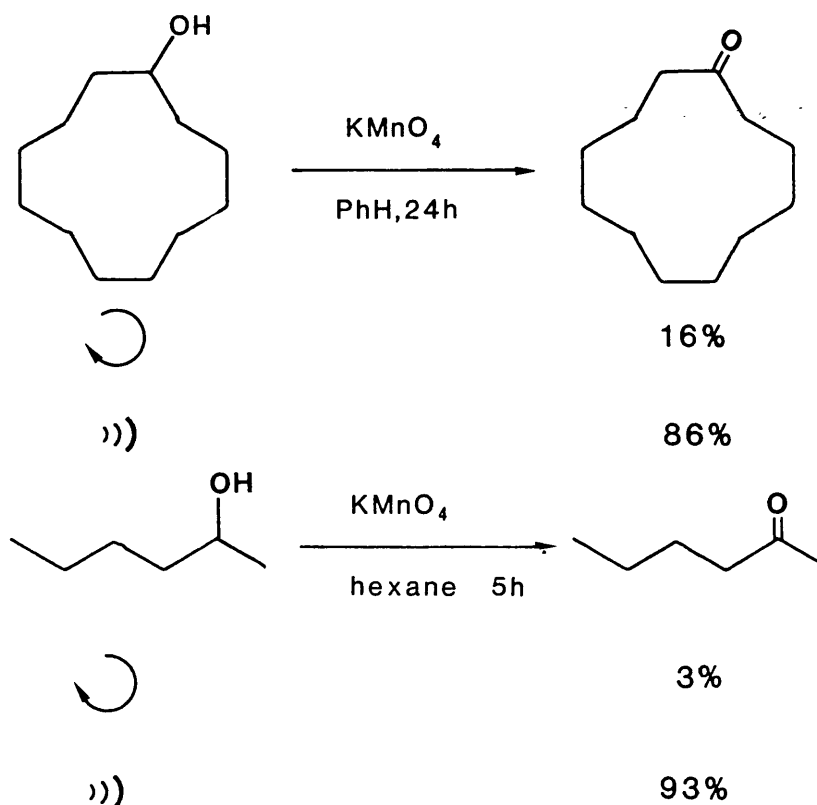
This discovery was exploited by Lukevics *et al*¹²⁵, providing a route to the hydrides of a number of group IV element derivatives from the corresponding halo, alkoxy and amino compounds. The reaction is completely dependent on sonication and does not occur in its absence.



Sonolysis of a variety of alkyl substituted nitrobenzenes under an oxygen atmosphere in the presence of solid potassium hydroxide and a polyethylene glycol phase transfer catalyst gave moderate yields of the corresponding carboxylic acid salt (27). Interestingly, the stirred reaction gave no acid and the products observed, (28) and (29), arose from dimerisation of the starting material¹²⁶. This is one of the few cases where the application of ultrasound actually changes the pathway of a reaction.



Studies on the homogeneous system had previously shown that the acid was the predominant product if the concentration of the reagents was low, or the partial pressure of oxygen was high ¹²⁷. These conditions are satisfied if one assumes that the involatility of potassium hydroxide leads to an extremely low concentration of base in the vapour phase, that is, at the site at which reaction occurs. Oxidation of secondary alcohols to ketones can also be effected in good yield using solid potassium permanganate¹²⁸ in hydrocarbon solvents. However, reaction with aryl compounds was slow and primary alcohols gave mixtures of the aldehyde and the corresponding carboxylic acid.



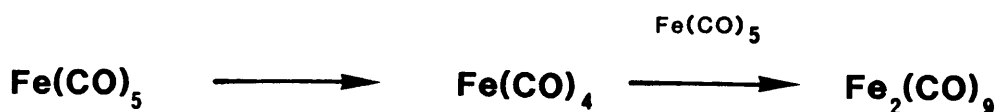
1.12 The effects of ultrasound on transition metal catalysed reactions

There is extensive literature, published some years ago, concerning the action of ultrasound on transition metal catalysts¹²⁹. Most of which lies beyond the scope of this review. The primary effects appear to be due to a rise in the efficiency of mass transport¹³⁰, although factors already outlined for other heterogeneous systems must also be taken into consideration. Recent investigations have shown that platinum catalysed hydrosilation reactions are promoted by ultrasound and high yields of the desired product are obtained within extremely short periods of time¹³¹. Furthermore, Han and Boudjouk have demonstrated that formic acid can be used as a source of hydrogen in palladium catalysed reductions¹³². Ultrasound can also be used to promote the cleavage of benzyl ether protecting groups¹³³. In general, the rate increases are less than ten-fold. Ultrasound has also been shown to play a role in a number of industrially important processes. These include the liquefaction of coal by hydrogenation with Cu/Zn¹³⁴, ammonia synthesis¹³⁵ and a number of polymerisation reactions¹³⁶.

1.13 Transition metal carbonyls and ultrasound

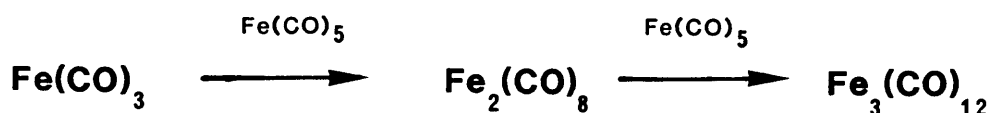
Vinyl epoxides will react with the coordinatively unsaturated tetracarbonyliron moiety to give π -allyltricarbonyliron species¹³⁷. Work in our laboratories had shown that these were useful precursors for a wide range of naturally occurring β and δ -lactones and lactams¹³⁸.

The tetracarbonyliron species had originally been generated by photolysis of iron pentacarbonyl¹³⁷. However, the hazardous nature of this reagent prompted us to examine other methods for its generation. Experiments showed that ferrilactones were readily available as a result of treatment of vinyl epoxides with diiron nonacarbonyl in THF solution. Diiron nonacarbonyl itself is partially soluble in THF and IR studies clearly show the presence of $\text{Fe}(\text{CO})_5$ in solution accompanied by "at least one other carbonyl species"¹³⁹. Cotton has suggested that coordination of a THF molecule to the vacant site of the iron may be occurring¹⁴⁰ indicating that the active species is in fact $\text{Fe}(\text{CO})_4\cdot\text{THF}$. Aumann has also invoked the intermediacy of a tetracarbonyliron species to explain the results of the photolytic reaction¹³⁷. This is supported by the availability of diiron nonacarbonyl on photolysis of iron pentacarbonyl which probably occurs by reaction of a tetracarbonyliron species with excess starting material.

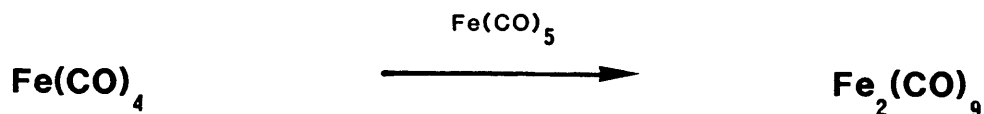


We have also discovered that sonolysis of slurries of diiron nonacarbonyl and vinyl epoxide in benzene solution also gives good yields of the required product. However, Suslick reports that the

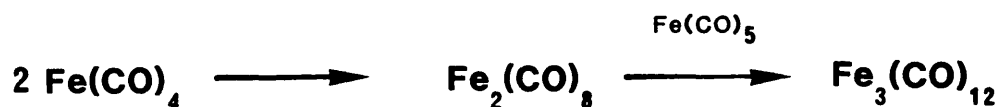
only products generated by sonolysis of $\text{Fe}_2(\text{CO})_9$ are $\text{Fe}(\text{CO})_5$ and finely divided iron¹⁴¹. Sonolysis of $\text{Fe}(\text{CO})_5$ itself leads to formation of the dark green $\text{Fe}_3(\text{CO})_{12}$. In considering the mechanism of this reaction Suslick concluded that the initial step was formation of a tricarbonyliron intermediate. Subsequent reaction with $\text{Fe}(\text{CO})_5$ could then be invoked to explain the presence of $\text{Fe}_3(\text{CO})_{12}$.



The intermediacy of $\text{Fe}(\text{CO})_4$ was ruled out on the grounds that it would be trapped by excess $\text{Fe}(\text{CO})_5$ as soon as it was formed producing $\text{Fe}_2(\text{CO})_9$.

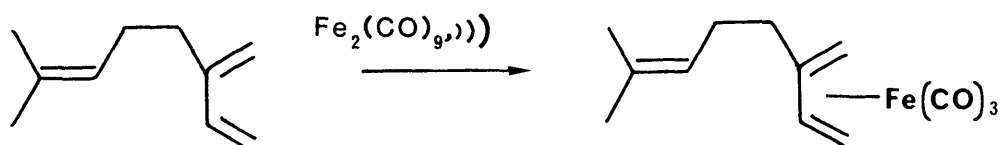


Diiron nonacarbonyl was not observed as a product of this reaction and despite his observation that sonochemical cleavage of this species occurred as fast as that of $\text{Fe}_3(\text{CO})_{12}$ production, Suslick emphatically concluded that $\text{Fe}(\text{CO})_4$ was not an intermediate on the pathway to $\text{Fe}_3(\text{CO})_{12}$. However, he later conceded that the presence of $\text{Fe}(\text{CO})_4$ species could not be ruled out³



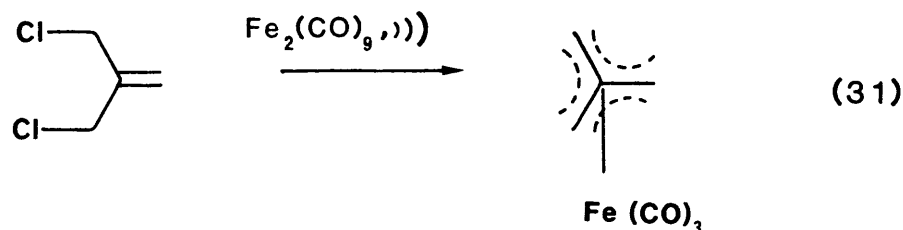
We have not been able to reproduce this reaction using Fe(CO)_5 in our laboratories; however, this is probably due to the low intensities of ultrasound obtainable using a cleaning bath. Whilst this is clearly sufficient to produce cavitation in heterogeneous slurries of $\text{Fe}_2(\text{CO})_9$ it is inadequate for the corresponding homogeneous reaction for reasons already discussed. Suslick has shown that Fe(CO)_5 will undergo substitution by phosphines under more intense irradiation, although the sequential loss of carbonyl ligands is not a feature of either the thermal or photolytic reactions.

Further studies have shown that Fe(CO)_3 species are readily trapped by 1,3-conjugated dienes and the η^4 -(diene) Fe(CO)_3 complexes are isolated in virtually quantitative yield¹⁴². This reaction is of great synthetic use in the light of the interesting chemistry of these complexes and the number of methods in existence for the recovery of the diene which suggest that the tricarbonyliron moiety may be a useful protecting group for conjugated dienes. Despite this, yields of the equivalent thermal reaction between the diene and Fe(CO)_5 are extremely modest.



Similarly, we have also demonstrated that trimethylenemethane tricarbonyliron (30) is readily available by sonolysis of equimolar

amounts of $\text{Fe}_2(\text{CO})_9$ and 3-chloro-2-chloro-methylprop-1-ene in 30/40° petroleum ether. This gives a remarkable 90% yield of the desired product¹⁴². In contrast, the highest recorded yield was a meagre 30% described by Emerson et al¹⁴³



Suslick has made an extensive study of the sonochemistry of $\text{Fe}(\text{CO})_5$ which he has used as a probe to explore the chemical effects of high intensity ultrasound. The result of this work are summarised elsewhere in this review. Suslick and Johnson¹⁴³ have also shown that sonication greatly facilitates the preparation of early transition metal carbonyl anions. Hence, sonication of vanadium trichloride and sodium sand in THF solution gave a 35% yield of $\text{NaV}(\text{CO})_6$ under 4.4 atmospheres of carbon monoxide at 10°C. The equivalent thermal reaction requires the reaction to be carried out at 160°C under 200 atmospheres of carbon monoxide. That is, the temperatures and pressures produced by cavitation are comparable to the bomb conditions normally required for the preparation of these compounds¹⁴⁴. Suslick's review³ presents further work in support of this original observation; however, no details of this work have appeared to date.

A variety of coordinatively unsaturated metal carbonyl species are known to be potent homogeneous catalysts. Sonication of 1-pentene in the presence of $\text{Fe}(\text{CO})_5$ produces the thermodynamic mixture of cis and trans pent-2-ene¹⁴⁵. Under these conditions the reaction is 10^5 times faster than the equivalent thermal reaction¹⁴¹. The increase is less

marked in the case of sterically hindered alkenes, eg 2-ethylpent-1-ene, and does not occur in the absence of β -hydrogens. This is consistent with the reaction occurring via a hydrido- π -allyl intermediate and FT IR spectroscopy implies the presence of $\text{Fe}(\text{CO})_4(\text{pentene})$ under these conditions¹⁴⁵.

The examples given demonstrate the ease with which coordinatively unsaturated transition metal carbonyl species can be generated. The specificity of the reactions carried out at, or slightly below, ambient temperature contrasts with the low yields of products obtained via equivalent thermal reactions and clearly shows potential for the preparation of a wide variety of organometallic complexes. Suggestions that high pressure carbonylations can be carried out without call for complicated and expensive apparatus clearly merit further investigation. Hopefully, Suslick et al will shed some light on this matter when full details of their recent work appear.

1.14 Conclusion

In conclusion, the beneficial effects of ultrasound on reactions in non-aqueous solvents have only been appreciated within the past few years and a great deal more exploration is required before its potential for application to synthesis is fully realised. The sheer variety of reactions detailed in this review demonstrate the relevance of this work to synthetic chemists. Furthermore, the current level of interest in this topic is increasing at such a rate that the widespread acceptance of ultrasound as a synthetic tool may only be a matter of time.

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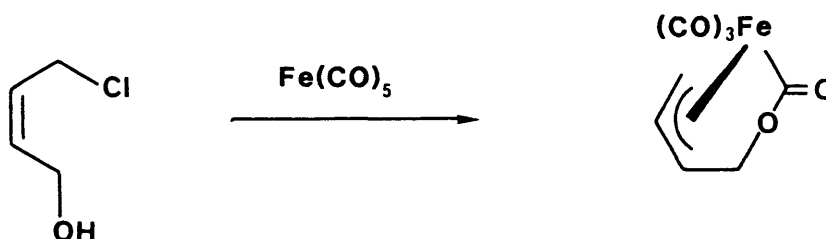
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CHAPTER 2

Introduction

In 1964, Heck and Boss ¹ discovered that treatment of certain chloroallylic alcohols with $\text{Fe}(\text{CO})_5$ produced novel π -allylferrilactone species.



Subsequent work showed that ferrilactones could be derived from a variety of substrates²⁻⁶; however, their synthetic potential remained unexplored and unrealised.

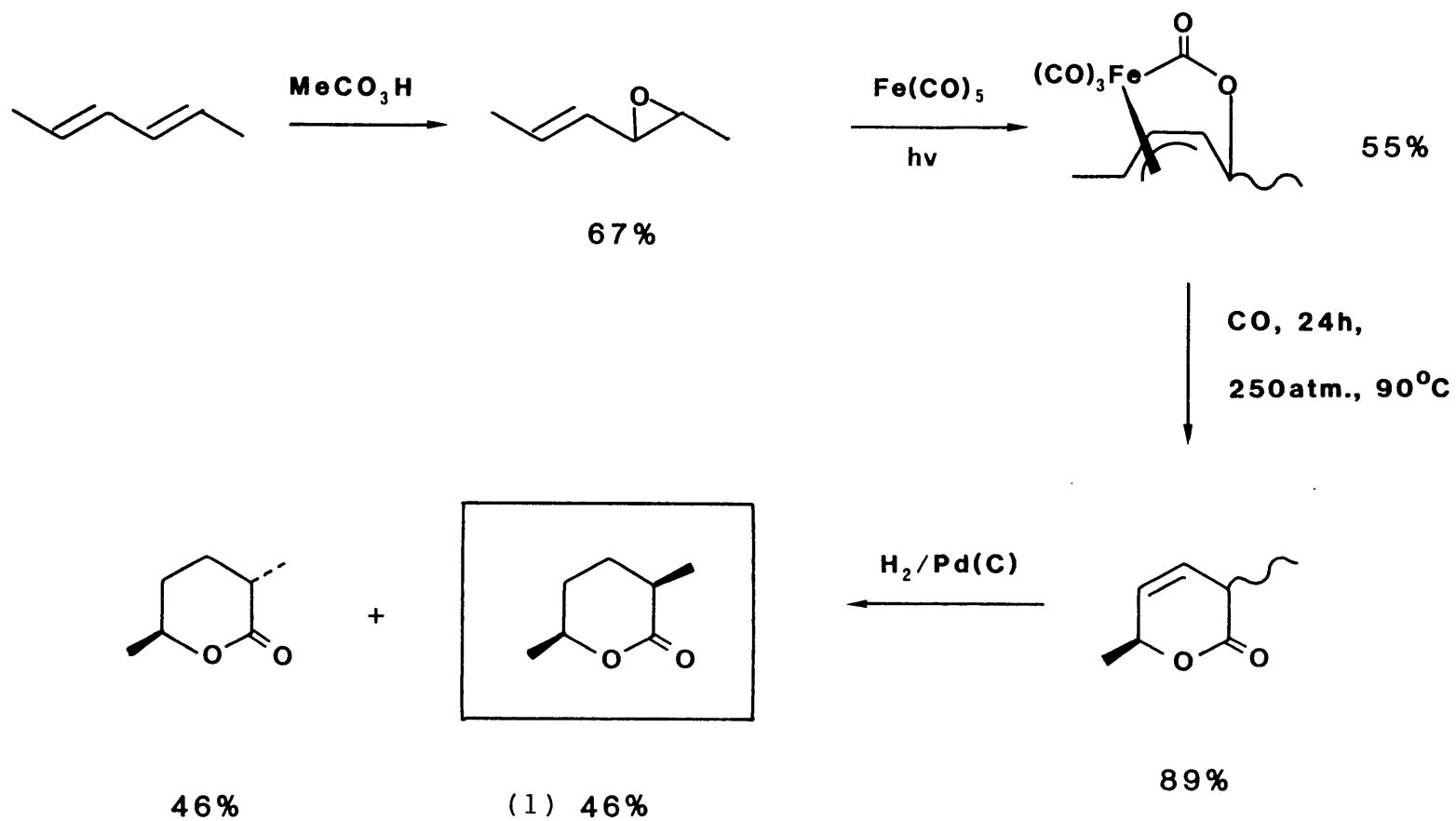
The most general procedure described for the synthesis of ferrilactones involves the insertion of a carbonyl group from a coordinatively unsaturated tetracarbonyliron moiety into the C-O bond of a vinyl epoxide. The reactive intermediate was originally generated by thermolysis of iron pentacarbonyl²; however, subsequent work showed that more consistent results were obtained under photolytic conditions⁴⁻⁶.

Work in our laboratories later established that these complexes were versatile intermediates for the synthesis of a variety of lactones⁷⁻¹⁰. Cerium (IV) oxidation of ferrilactones produces good yields of the β -lactone arising from coupling of the lactone carbonyl to C-2 of the π -allyl unit. That is, the overall transformation is equivalent to formal addition of carbon monoxide across the oxirane ring. In certain examples, oxidative coupling

between C-4 at the π -allyl terminus and the lactone carbonyl predominated leading to isolation of the six-membered δ -lactone. At about the same time, Aumann and co-workers⁶ reported that exhaustive carbonylation of these complexes (200–300 atm.) produced the δ -lactone to the exclusion of any other product⁶. Hence, we have access to two complimentary processes for the preparation of either β - or δ -lactones from any one ferrilactone.

Both processes are extremely facile and produce high yields of the desired product. Furthermore, the ferrilactones themselves are obtained as air stable, crystalline yellow solids and can be stored under refrigeration for periods of up to a year without appreciable decomposition. The complexes are isolated using standard organic techniques and can be easily purified by silica gel chromatography. The accessibility of this methodology and the specificity with which the desired products could be obtained prompted us to investigate whether it could be applied to more complex systems. For example, δ -lactones occur widely through nature in a variety of interesting guises. A number of these possess interesting biological properties and new routes to such compounds are constantly sought. On a simplistic level, the sex pheromone of the Brazillian Carpenter bee (1) is readily available by monoepoxidation of E,E-hexa-2,4-diene followed by reaction with iron carbonyl. Carbonylation of the resultant ferrilactone and catalytic hydrogenation of the unsaturated δ -lactone obtained gives the required δ -lactone¹¹ (Scheme 1).

This synthesis highlights several of the problems inherent in the original methodology. Firstly, since the photolysis reaction must be carried out under conditions of high dilution, using the extremely toxic and volatile pentacarbonyliron, the process can only be carried



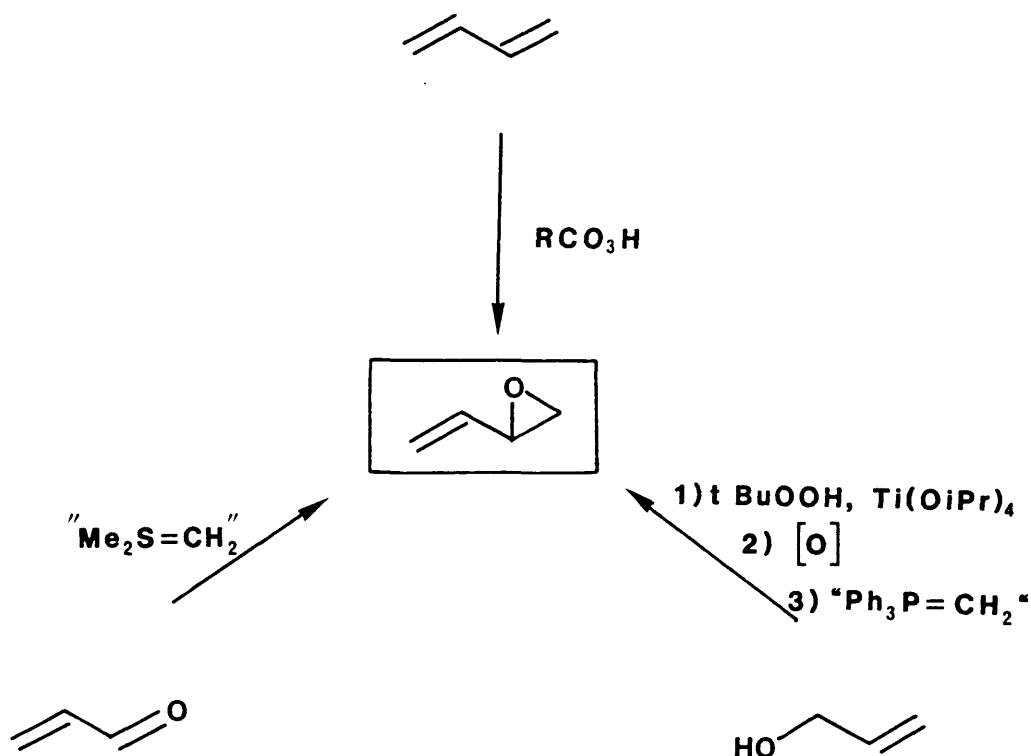
Scheme 1
 Racemic synthesis of the sex pheromone of the Carpenter bee¹¹.

out on a small scale, that is <10mmol, and multigram quantities are only available by parallel processing of separate batches of vinyl epoxide. Secondly, carbonylation of the diastereoisomeric mixture of ferrilactones produces a 1:1 mixture of the required β,γ -unsaturated δ -lactone and its C-2 epimer, drastically reducing the overall yield of the naturally occurring product. This question of diastereoselectivity is particularly important with regard to the biological properties of organic molecules since the effects of the "wrong" diastereoisomer cannot be extrapolated from those of the natural product.

In this particular case, separation of the diastereoisomeric ferrilactones is easily achieved by column chromatography. Nevertheless, this process is extremely wasteful and stereospecific routes to ferrilactones were sought.

(b) Approaches to the synthesis of vinyl epoxides

Vinyl epoxides are versatile synthetic intermediates and can be prepared by a number of existing routes. Those most commonly employed include regioselective epoxidation of conjugated dienes by peracids¹⁸ or reaction of α,β -unsaturated carbonyl compounds with dimethylsulphonium methylid¹⁹. On the other hand, there are a number of strategies available for the preparation of epoxyalcohols via transition metal catalysed reaction with allylic alcohols. Subsequent oxidation of the alcohol functionality followed by methyleneation of the carbonyl group provides a third route to vinyl epoxides. More importantly, modification of this last route should allow access to optically active vinyl epoxides and hence ferrilactones when taken in conjunction with methodology developed by Sharpless and co-workers over the past few years.²⁰

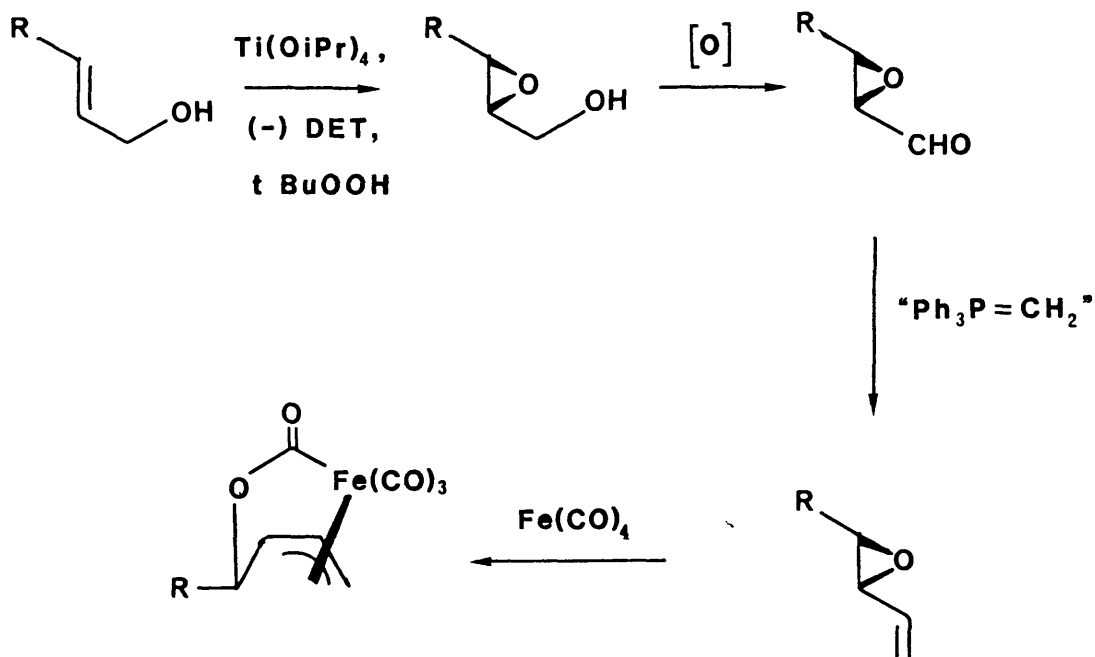


They have shown that titanium mediated epoxidation of allylic alcohols with t-butylhydroperoxide allows introduction of two new chiral centres of pre-determined stereochemistry with >95% selectivity in most cases.

The products of this reaction have been used as precursors for the total synthesis of a range of interesting and important natural products²¹, for example erythromycins and leukotrienes, and this powerful technique has found a wide range of elegant applications since it was first reported in 1980.

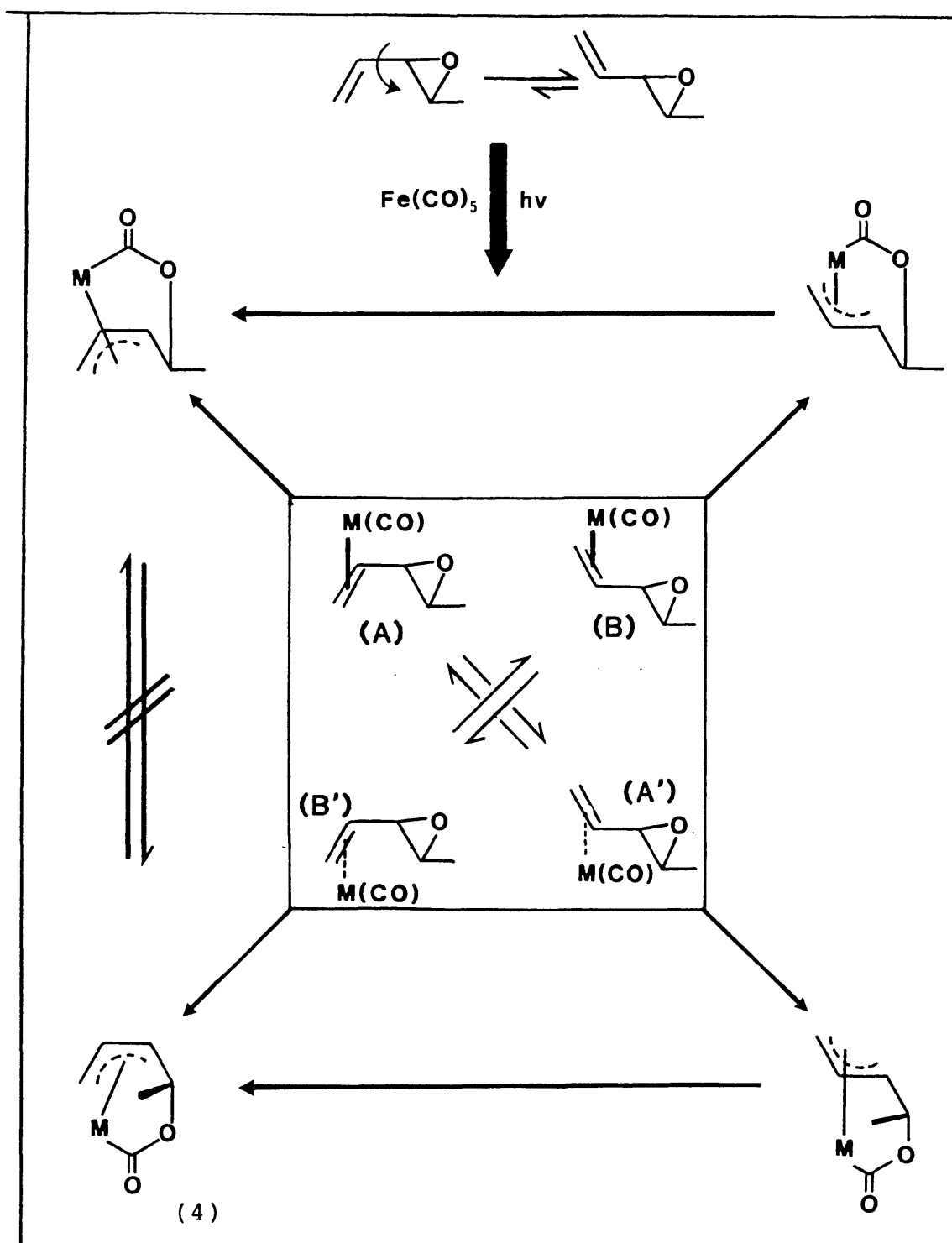
Hence, we can envisage that epoxidation of an allylic alcohol under the conditions specified, followed by oxidation of the hydroxyl group and methylenation with the requisite Wittig reagent should produce a vinyl epoxide of known absolute stereochemistry, which could presumably be transformed into the desired ferrilactone by treatment

with a suitable source of tetracarbonyliron.

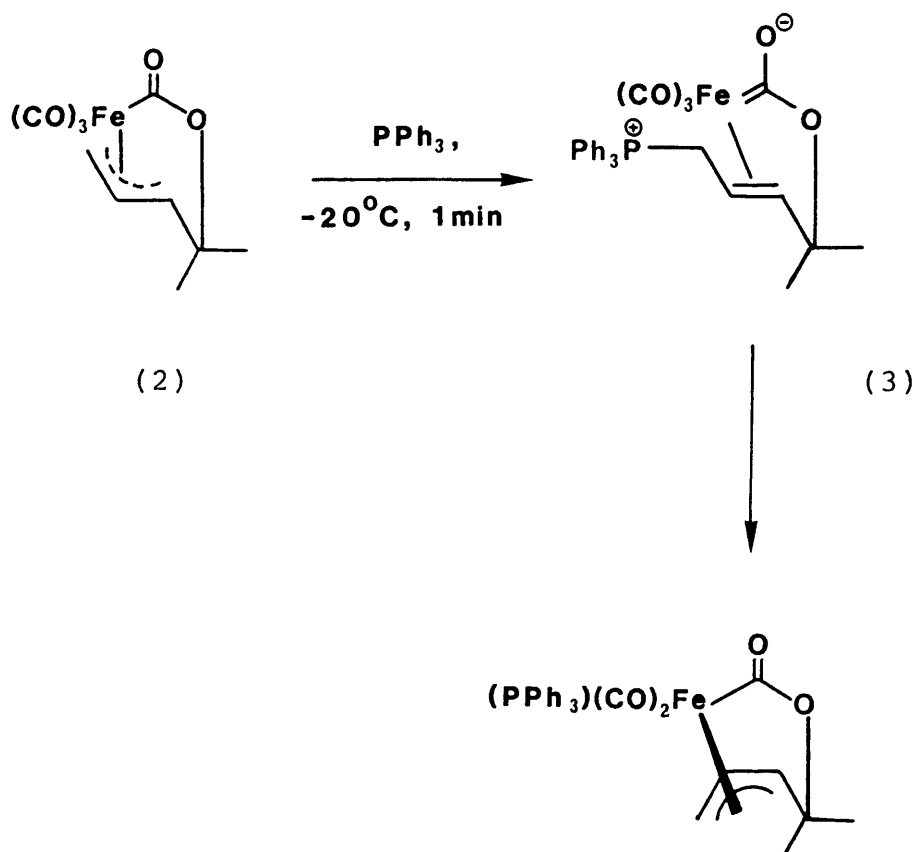


(c) The reaction of vinyl epoxides with iron carbonyl

Aumann has proposed a mechanism for the formation of ferrilactones⁶ (Scheme 2). He assumed that the reactive intermediate was a tetracarbonyliron species generated by photolytic degradation of Fe(CO)_5 . On this basis he proposed that the first step was coordination of the tetracarbonyliron to the double bond, followed by insertion of a carbonyl ligand into the C-O bond of the oxirane ring. The products of such a reaction would be expected to include complexes where the π -allyl ligand existed in both cis and trans configurations. However, trans-ferrilactones have only been isolated in cases where the termini of the π -allyl ligand are highly substituted⁶, implying that cis/trans isomerisation normally occurs rapidly on the reaction timescale in the unhindered system.

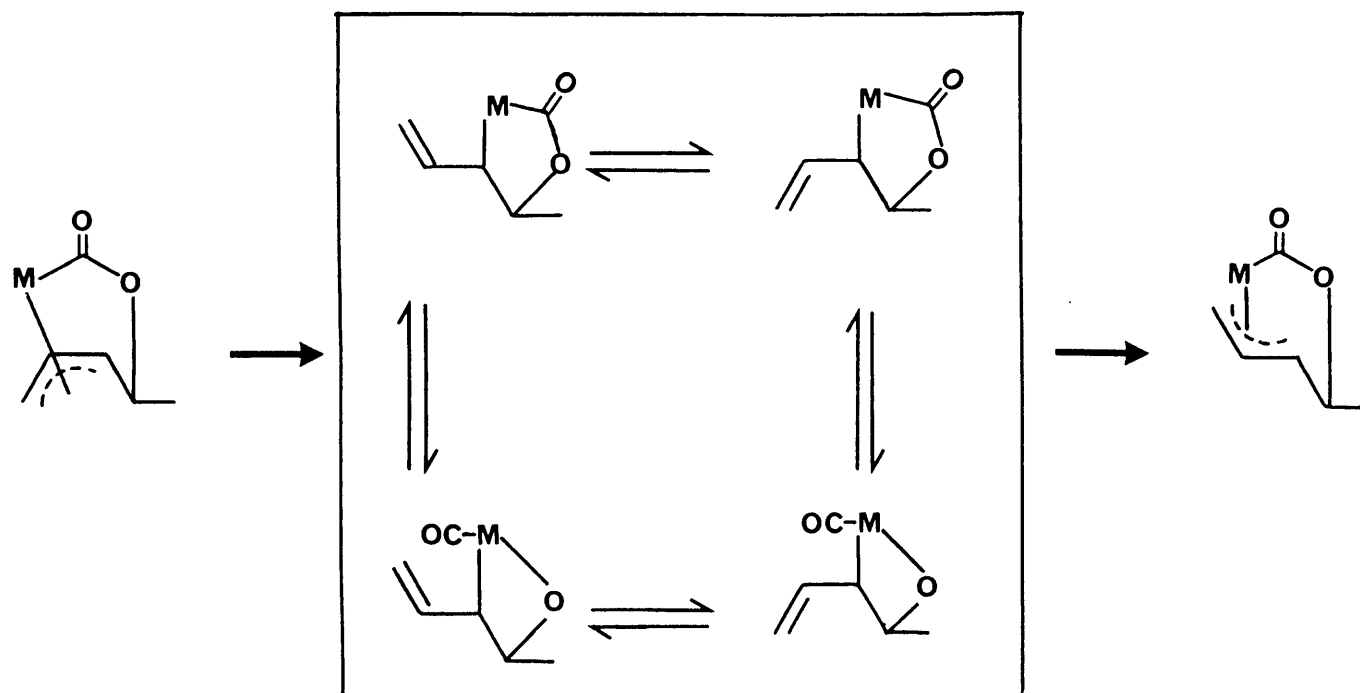


Scheme 2
Proposed mechanism for the formation of ferrilactone complexes⁶.



Such an interconversion could occur via four or five-ring intermediates, as illustrated in Scheme 3. Evidence for this proposal is provided by the reaction of the trans-ferrilactone (2) with triphenylphosphine. Primary attack of the phosphine occurs at the terminus of the π -allyl ligand producing the stable zwitterionic complex (3). Ligand exchange with carbon monoxide gives the cis-ferrilactone.

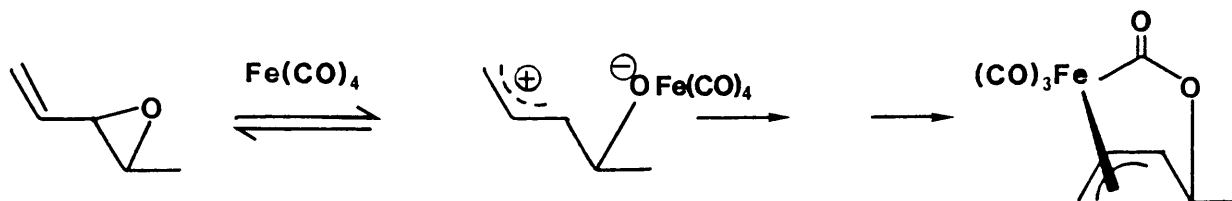
However, close examination of the proposed mechanism suggests that Aumann's proposals do not account for the isolation of the endo ferrilactone complex (4). That is, rotation about the C-3/C-4 axis in the case of the intermediates (A') and (B'), would be expected to produce the exo rather than the stated endo complex, whose presence can only be accounted for if one assumes that inversion of the configuration at C-2 and C-3 is occurring.



Scheme 3

Proposed mechanism for the interconversion between cis and trans ferrilactone complexes⁶.

Prior coordination of the tetracarbonyliron to the oxygen of the epoxide cannot be ruled out, although this path would appear to be energetically less favourable from the point of view that the allyl cation intermediate (5) cannot be stabilised by the metal.



(5)

In conclusion, Aumann's proposals do not fully account for the products isolated and the complex nature of this reaction suggests that further investigation is required to clarify the situation.

(d) Preparation of π -allyltricarbonyliron(lactone) complexes

In relative terms, iron carbonyls are the least toxic and expensive of the transition metal carbonyls. Of these, iron pentacarbonyl $\text{Fe}(\text{CO})_5$, diiron nonacarbonyl $\text{Fe}_2(\text{CO})_9$ and triiron dodecacarbonyl $\text{Fe}_3(\text{CO})_{12}$ are most extensively used in organic synthesis. In each of these stable complexes the iron atoms possess full valence shells and are said to be coordinatively saturated. As such they will only undergo slow ligand exchange - with the exception of diiron nonacarbonyl, which has a very high reactivity towards ligands. However, transitory reactive species possessing coordinative unsaturation may be generated by photolytic or thermal degradation of the appropriate complex. For reasons previously discussed, the photolytic route is inconvenient and unsuited to large scale reactions. The corresponding thermal reactions with $\text{Fe}(\text{CO})_5$ ² and $\text{Fe}_2(\text{CO})_9$ ⁵ have also been reported to produce ferrilactones; however, use of such harsh conditions limits the general applicability of this methodology - making it unsuitable for use with complex substrates which possess sensitive organic functionalities. Furthermore, work in our laboratories has shown that ferrilactones are thermally unstable and will readily rearrange via decarbonylation and carboxylation pathways^{8,9} when heated. Hence, more amenable routes were sought for the generation of ferrilactones.

The first of these arose from observations that diiron nonacarbonyl dissociated in THF solution to give a red solution containing iron pentacarbonyl "and at least one other carbonyl containing species"¹². THF is commonly used as a reaction medium for reactions with $\text{Fe}_2(\text{CO})_9$ on the basis that the transition metal carbonyl is partially soluble in this solvent. In practise, treatment of vinyl epoxides with $\text{Fe}_2(\text{CO})_9$ in THF results in dissolution of the solid carbonyl over

30min-1h at room temperature. Once sequestration of the vinyl epoxide is complete, a dark green colouration indicates the endpoint of the reaction. This arises conveniently from the trimerisation of excess $\text{Fe}(\text{CO})_4$ to give green $\text{Fe}_3(\text{CO})_{12}$. Concentration of the reaction mixture and silica gel chromatography of the residue produces high yields of the corresponding ferrilactone complexes (see Table 1).

Cotton has suggested that dissociation of $\text{Fe}_2(\text{CO})_9$ under carbon monoxide results in formation of $\text{Fe}(\text{CO})_5$ and $\text{Fe}(\text{CO})_4\cdot\text{THF}$ ¹³.

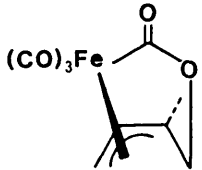
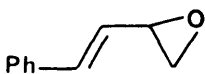
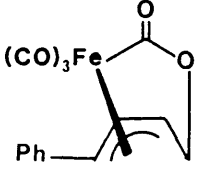
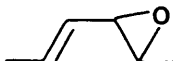
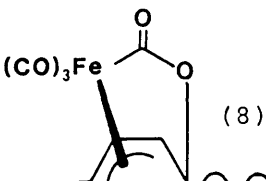
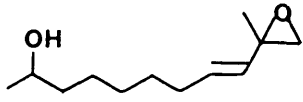
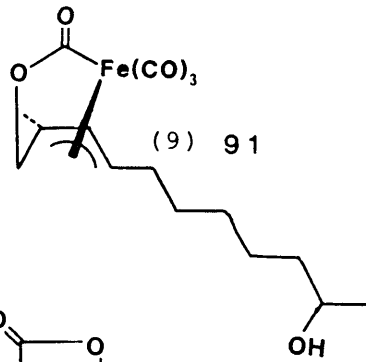
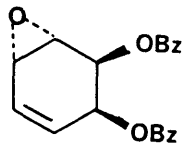
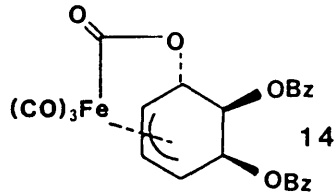


Displacement of the labile THF ligand from this latter species would provide a ready source of $\text{Fe}(\text{CO})_4$. Formation of the ferrilactone can then be invoked by reference to Aumann's proposed mechanism⁶.

However, as Cotton points out, the situation is more complex when carbon monoxide pressure is not maintained and, to our surprise, the reaction was found to be faster and cleaner in its absence¹¹. The reason for this is unclear but may be due to the exchange of labile carbon monoxide ligands between the complex and its surroundings promoting formation of transitory coordinatively unsaturated species.

A complimentary route was suggested by reports that sonolysis of $\text{Fe}(\text{CO})_5$ in hydrocarbon solvents led to formation of $\text{Fe}_3(\text{CO})_{12}$ and finely divided iron¹⁴. However, the authors suggested that initial dissociation of two CO ligands results in formation of a tricarbonyliron intermediate. Subsequent reaction with two equivalents of iron carbonyl was then invoked to account for the

Table 1

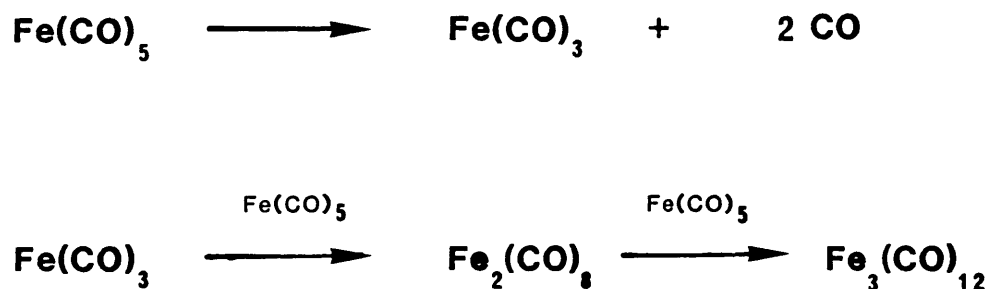
<u>vinyl epoxide</u>	<u>Ferrilactone</u>	% Yield	
		$\text{Fe}_2(\text{CO})_9 / \text{THF}$	$\text{Fe}_2(\text{CO})_9 / \text{))}$
	 (6)	75 ^a	90 ^b
	 (7)	100 ^a	68 ^a
	 (8)	64 ^b	55 ^b
	 (9)	91	91
 (10)	 (11)		100 [*]

* used 4 equivalents $\text{Fe}_2(\text{CO})_9$

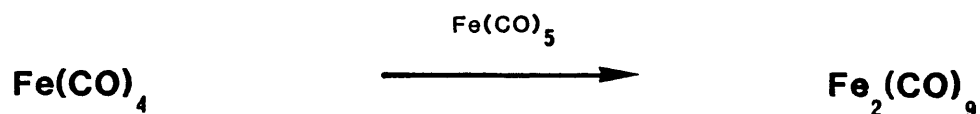
^a Results in agreement with those obtained by D.M. Hollinshead⁶⁵

^b Results in agreement with those obtained by A.M. Horton¹¹

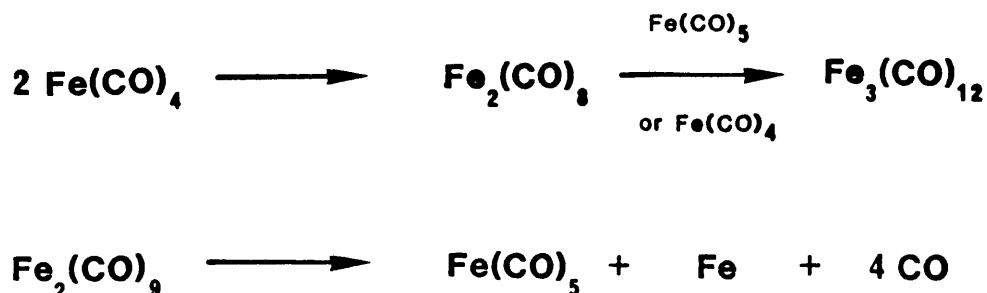
formation of the triiron complex. The reaction of $\text{Fe}_2(\text{CO})_8$ with $\text{Fe}(\text{CO})_5$ is thought to proceed via initial dissociation of the octacarbonyl to give $\text{Fe}_2(\text{CO})_7$. Evidence for the formation of such a species was provided by analogy with the chemistry of $\text{Fe}(\text{C}_4\text{H}_4)(\text{CO})_3$. Photolysis of this complex produces $\text{Fe}_2(\text{C}_4\text{H}_4)_2(\text{CO})_3$ which has been trapped and characterised in frozen matrices ¹⁵.



The intermediacy of a tetracarbonyliron species was ruled out on the grounds that it would be trapped by excess $\text{Fe}(\text{CO})_5$ as soon as it was formed.



Diiron nonacarbonyl is not observed as a product of this reaction and although it should be noted that sonochemical cleavage of this species occurs faster than the rate of formation of $\text{Fe}_3(\text{CO})_{12}$ from $\text{Fe}(\text{CO})_5$, Suslick emphatically concluded that $\text{Fe}(\text{CO})_4$ was not an intermediate on the pathway to $\text{Fe}_3(\text{CO})_{12}$.



However, results obtained on sonication of $\text{Fe}(\text{CO})_5$ in the presence of a variety of phosphines and phosphites forced him to concede that the presence of $\text{Fe}(\text{CO})_4$ species could not be entirely ruled out¹⁶.

Disappointingly, initial attempts to react vinyl epoxides with $\text{Fe}(\text{CO})_5$ by immersion of the reaction vessel in an ultrasound cleaning bath (Semat 80W, 55kHz) failed to produce any of the desired ferrilactone. However, sonolysis of a heterogeneous slurry of $\text{Fe}_2(\text{CO})_9$ in the presence of the requisite vinyl epoxide gave the ferrilactone complex, accompanied by $\text{Fe}_3(\text{CO})_{12}$, in high yield. This is a reflection of the low intensities of ultrasound that are produced by cleaning baths; which whilst clearly sufficient to produce cavitation in heterogeneous slurries of $\text{Fe}_2(\text{CO})_9$, are inadequate for the corresponding homogeneous reaction, for reasons already discussed (see Chapter 1).

Hence, collation of the available evidence suggests that the sonolysis reaction is more likely to occur via a tetracarbonyliron species than the suggested tricarbonyliron moiety. Nevertheless, it should be recognised that this has not been conclusively established; however, later work has clearly demonstrated the intermediacy of tetracarbonyliron species (see section 2.4) formed by sonolytic degradation of $\text{Fe}_2(\text{CO})_9$.

Yields of complex obtained under these conditions are comparable to those obtained with $\text{Fe}_2(\text{CO})_9$ in THF and both methods can be used routinely in the preparation of simple ferrilactones (Table 1).

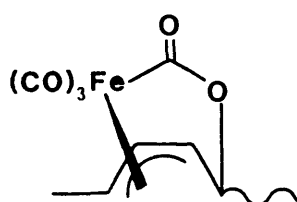
Interestingly, reaction of vinyl epoxide (10) with $\text{Fe}_2(\text{CO})_9$ under standard sonolysis conditions led to isolation of a 33% yield of the ferrilactone complex (11) accompanied by 66% of the unreacted starting material. Conversely, reaction in the presence of four equivalents of iron carbonyl produces quantitative conversion to the ferrilactone

(11) within 1h. This suggests that reaction with this vinyl epoxide is occurring considerably slower than those with simpler substrates. However, coordination of the reactive species to the oxygens of the cis-dibenzoyl system may also account for this observation, by way of a reduction in the effective concentration of tetracarbonyliron available.

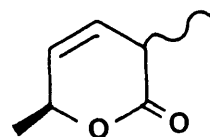
Use of the solid diiron nonacarbonyl appreciably reduces the hazards associated with handling these compounds in the light of its greatly reduced volatility. Furthermore, both methods have been applied to preparation of larger quantities of ferrilactone (ca.10-15g) without any noticeable decrease in yield. Both processes occur conveniently at ambient temperature and produce high yields of the desired complex. Hence, ferrilactones are readily available by two discrete pathways and synthesis of more complex substrates could be contemplated.

(e) Preparation of δ -lactones from ferrilactone complexes

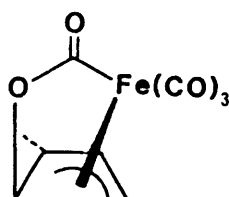
In 1979 Aumann reported that carbonylation of ferrilactones under 200 atmospheres of carbon monoxide at 75°C gave mixtures of α,β -, β,γ -, and γ,δ -unsaturated lactones⁶. Work in our laboratories showed that raising the reaction temperature to 130°C, in conjunction with lowering the gas pressure to 60 atmospheres allowed the α,β -unsaturated lactones to predominate²² albeit in somewhat reduced yield. Further manipulation of the reaction conditions showed that high yields of the β,γ -unsaturated lactones could be obtained as the exclusive products of the reaction at 60°C under 300 atmospheres of carbon monoxide¹¹. Indeed carbonylation of the ferrilactone complexes (8) and (9) under these conditions gave the expected β,γ -unsaturated δ -lactones, (12) and (13) - uncontaminated by any of the possible side products.



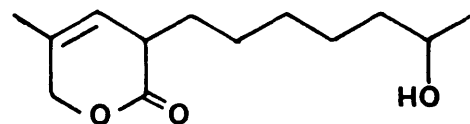
(8)



(12)



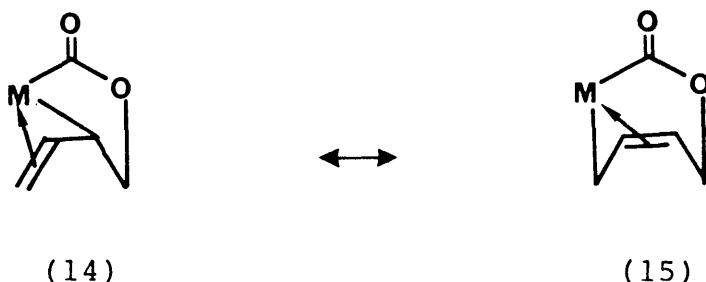
(9)



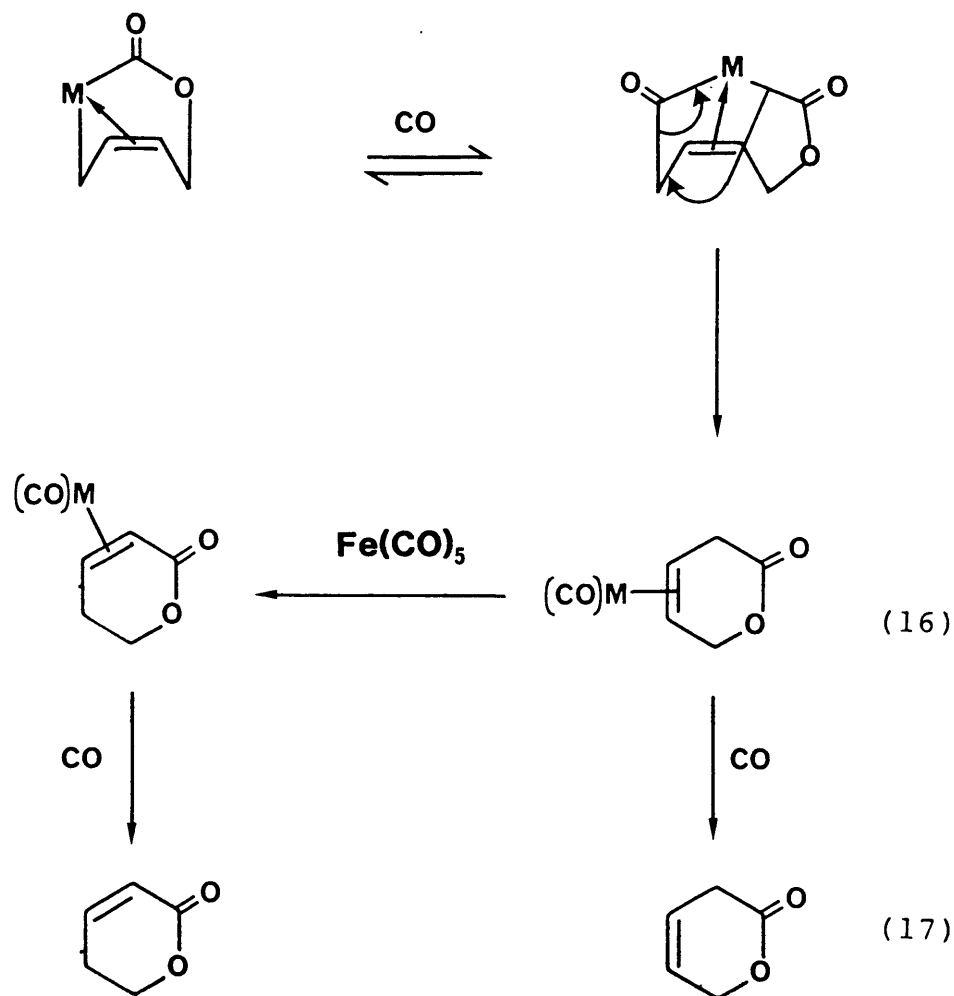
(13)

We can speculate that this degree of selectivity is a reflection of the lower temperatures used, in view of the propensity of $\text{Fe}(\text{CO})_5$ to promote isomerisation of double bonds at high temperatures. This has been remarked upon many times and can be incorporated into a proposed mechanism to account for the distribution of products obtained under the various reaction conditions described.

X-ray crystallographic studies on ferrilactone complexes clearly demonstrate that the π -allyl ligand is not planar, as would be anticipated, but distorted^{6,23}. This implies that the terminal carbon atoms exhibits a high degree of sp^3 character. Consideration of the two possible canonical structures, (14) and (15), which contribute to the

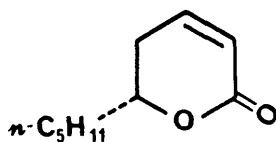


overall resonance hybrid suggest the presence of a higher proportion of the resonant structure (15). Insertion of carbon monoxide between the iron atom and the terminus of the π -allyl system, followed by rearrangement as shown would give the η^2 -(olefin) $\text{Fe}(\text{CO})_4$ complex (16). Ligand exchange between carbon monoxide and the organic ligand can then be invoked to account for isolation of the β,γ -unsaturated lactone (17). However, the concomitant formation of $\text{Fe}(\text{CO})_5$ may well promote isomerisation of the double bond at higher temperatures - leading to the isolation of mixtures of δ -lactones.

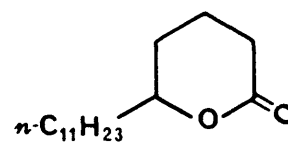


Having established that this methodology can be exploited to provide a high yielding synthesis of δ -lactones, we are now in a position to explore synthesis of more complex substrates. With this aim in mind we decided to examine novel routes to a number of δ -lactones whose interesting biological properties have made them the object of much synthetic attention. A number of approaches to the synthesis of these molecules have been published; however, most use routine organic methodology and very few address the problem of synthesis in an optically pure form. For this reason, we decided to explore the possibilities for application of our novel organoiron methodology to the synthesis of these compounds in an effort to develop a concise and stereospecific route to δ -lactone natural products from achiral starting materials.

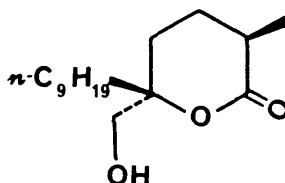
2.2 Synthesis of δ -lactone natural products via π -allyl
tricarbonyliron(lactone) complexes



(18) Massoia lactone



(19) Sex pheromone of
the oriental hornet



(20) Malyngolide

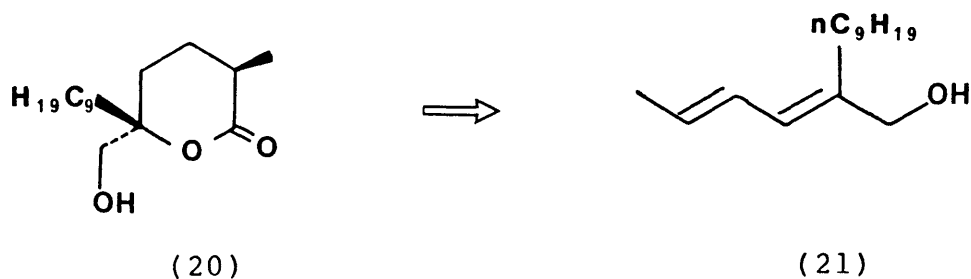
Our chosen targets were the three δ -lactones shown. These molecules exhibit a range of interesting biological properties. For example, the C_{11} -substituted δ -lactone (19) is the sex pheromone of the Oriental Hornet (*Vespa Orientalis*)²⁴. Insect pheromones, many of which possess δ -lactone functionality, are currently being exploited in a novel method of pest control. Their attraction lies in the specificity of the interaction between the pheromone and members of a particular species, which allows agricultural pests to be segregated from harmless organisms by use of pheromone-doped traps. This represents a more acceptable method of pest control by considerably reducing the need for blanket use of pesticides whose ecological properties are not fully understood.

On the other hand, Massoia lactone (18), despite its structural similarities to the pheromone (19), is a powerful skin irritant and has been shown to produce systolic standstill in frogs²⁵. It was first

isolated from Massoia bark oil, from which it derives its name, and has long been used in native medicine in Papua New Guinea. Interestingly, it has also been isolated from the mandibular glands of two species of formicine ant^{26,27} and occurs in low concentration in margarine.

The third, and most structurally complex δ -lactone shown is a natural product isolated from the blue green algae Lyngbya majuscula^{28,29} and was shown to exhibit antibiotic activity against mycobacterium smegmatis and micrococcus pyogenes²⁸.

The synthesis of Massoia lactone and the sex pheromone of *Vespa Orientalis* can clearly be approached in a similar manner as the two molecules differ only in the length of the unbranched alkyl side chain and the presence, or absence, of unsaturation in the six-membered ring. On the other hand, examination of the structure of Malyngolide (20) suggests that the C-5 hydroxymethyl group could be exploited to direct Sharpless epoxidation of a dieneol (21), allowing control of the stereochemistry at the quarternary centre.



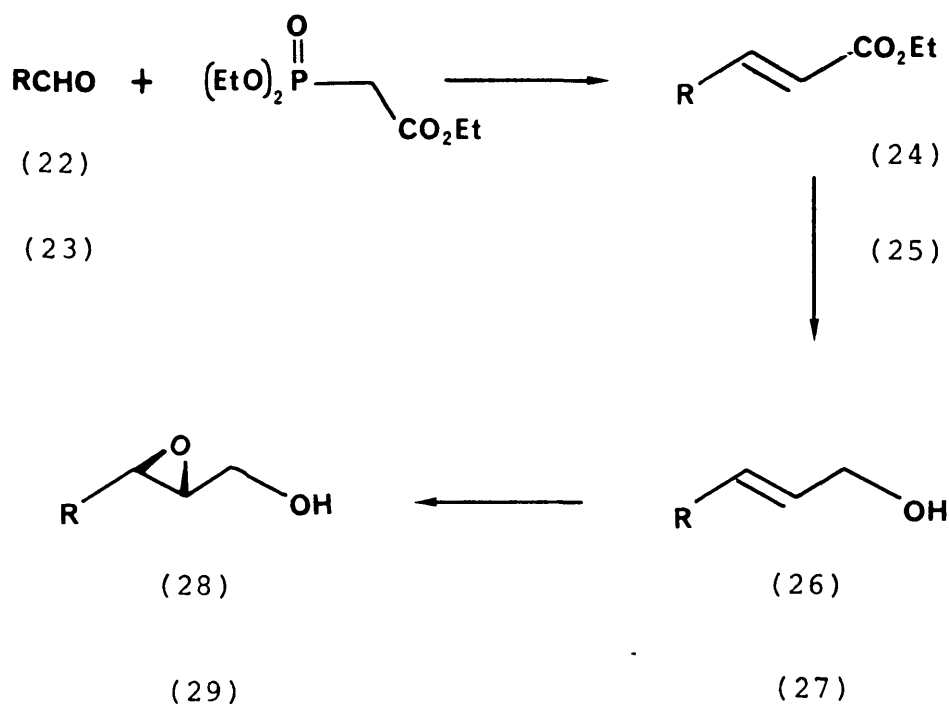
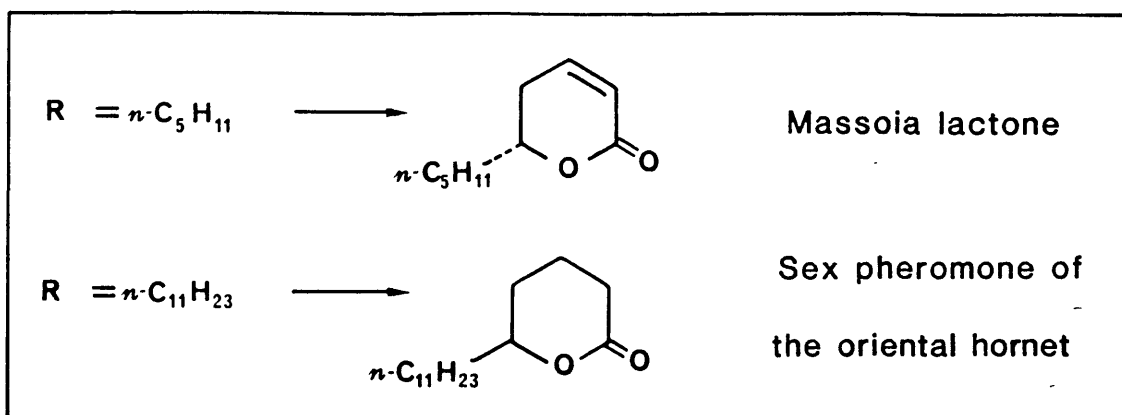
Initial studies had shown that the epimeric δ -lactones could be derived from racemic mixtures of ferrilactone precursors^{10,22}. However, it remained to be seen whether synthesis of the diastereoisomerically pure vinyl epoxide would provide access to the required natural products.

(a) Approaches to the synthesis of Massoia lactone and the sex pheromone of the Oriental Hornet

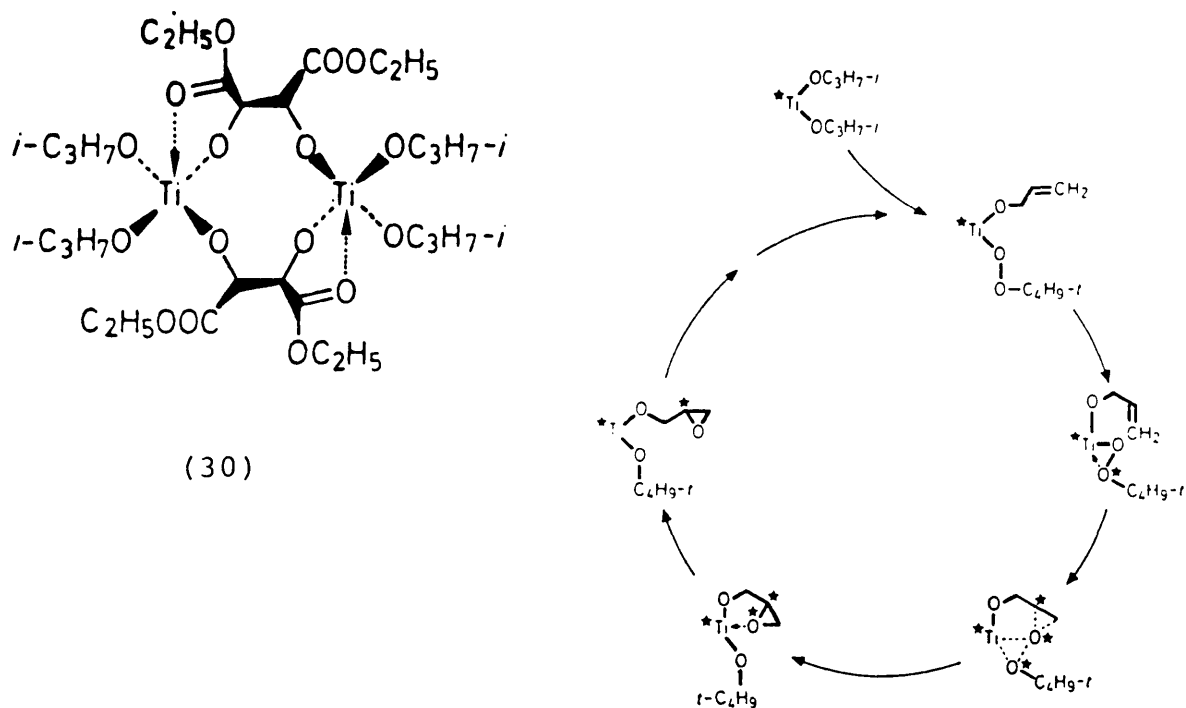
For reasons previously explained, our strategy was based on the preparation of chiral epoxyalcohols using Sharpless' methodology. The desired allylic alcohols were readily available by homologation of the appropriate aldehydes. Wadsworth-Emmons condensation of the long chain aldehydes (22) and (23) with diethylphosphonoacetate gave virtually quantitative yields of the required diene esters (24) and (25). Finally, low temperature reduction of the ester functionality with DIBAL-H gave the allylic alcohols shown, (26) and (27), in good yield.

The epoxidation procedure described by Sharpless involves formation of what is currently thought to be a binuclear cluster complex (30) between titanium tetrakisopropoxide, diethyl tartrate and the allylic alcohol. Displacement of the isopropoxide ligands and addition of *t*-butyl hydroperoxide effects the epoxidation in a stereospecific manner that is determined by the stereochemistry of the tartrate ligand²⁰ (Scheme 4). Hence, on an empirical basis, use of (-)-diethyltartrate (DET) gives the (2R),(3R) epoxyalcohol and use of (+)-DET gives the (2S),(3S) epoxide (Scheme 5). The selectivity of this process for simple straight chain alcohols is generally better than 99%, and hence we are now in a position to predetermine the stereochemistry of the epoxyalcohols at two centres.

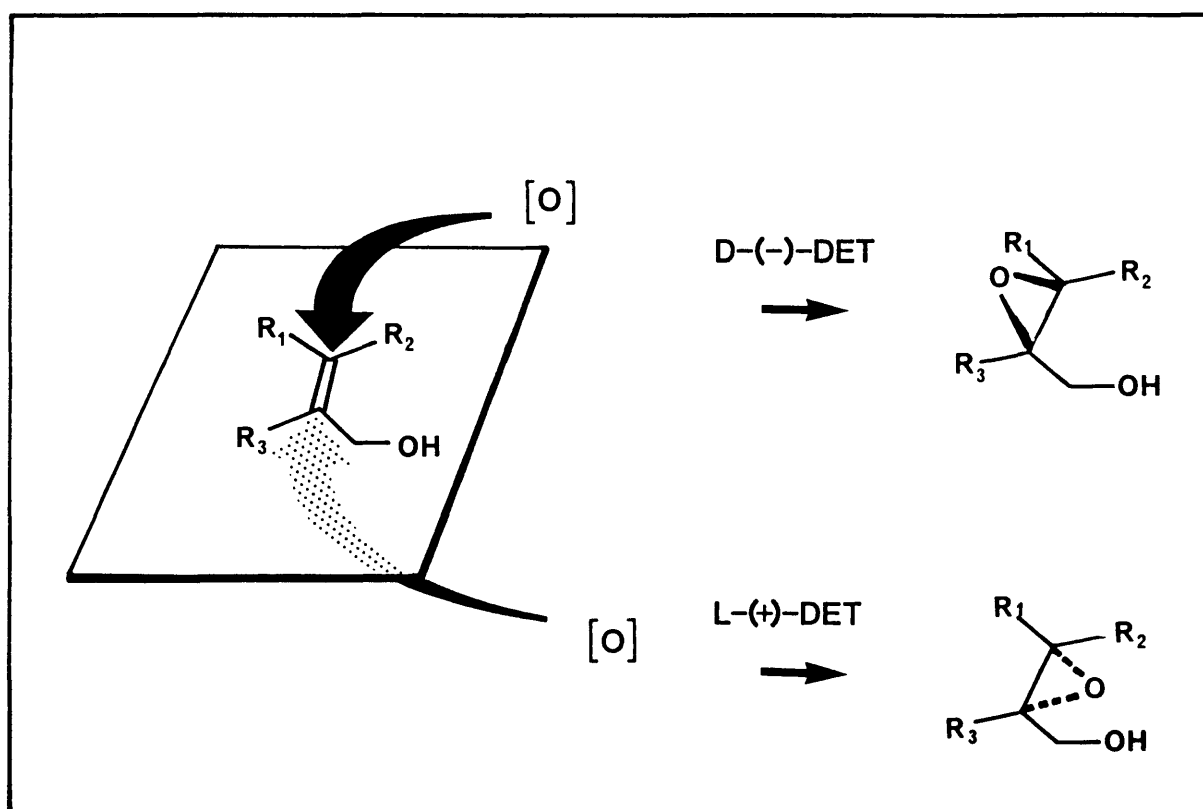
The processes involved in formation of (a) the ferrilactone complex and (b) the δ -lactone, are primarily those of carbon monoxide insertion and decarbonylation. Literature precedents suggest that these processes should occur with retention of configuration. For example, a number of elegant ¹Hnmr experiments have demonstrated that insertion of carbon monoxide into complex (31) occurs with complete retention



Product	$R = n\text{C}_5\text{H}_{11}$		$R = n\text{C}_{11}\text{H}_{23}$	
	(a)	(24) 99%	(25)	98%
	(b)	(26) 75%	(27)	80%
	(c)	(28) 73%	(29)	85%

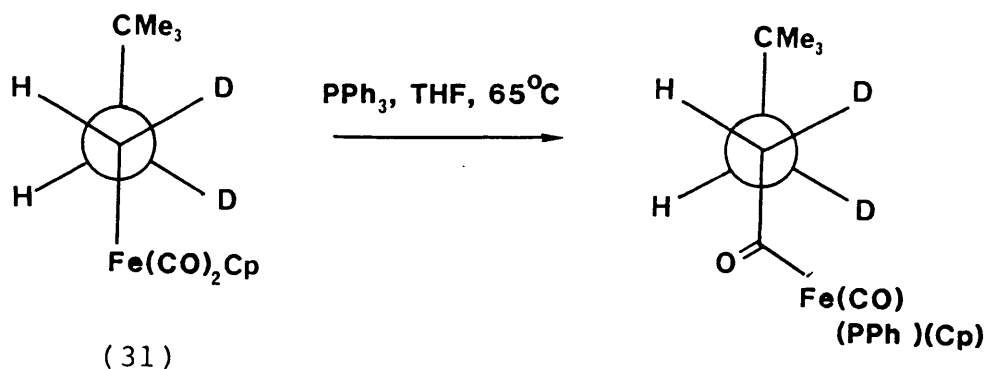
**Scheme 4**

Proposed mechanism for the mechanism of the Sharpless epoxidation²⁰.

**Scheme 5**

Qualitative representation of the products obtained from titanium mediated epoxidation of allylic alcohols in the presence of (+) and (-)-diethyl tartrate (DET).

of configuration at the α -carbon³⁰.



Similarly, decarbonylation of a number of optically active aldehydes has been achieved using Wilkinson's catalyst without loss of optical activity³¹. If this is indeed the case then ferrilactone and δ -lactone formation will also occur with retention of configuration and the required (5R)-substituted δ -lactones should be directly available from the (2R),(3R)-epoxyalcohols. Hence, (2R),(3R)-epoxyoctanol (28) and (2R),(3R)-epoxytetradecanol (29) were prepared using Sharpless' published procedure³². Epoxidation of the C-5 substituted allylic alcohol (26) proceeded smoothly at -80°C ; however, the equivalent C-11 substrate was found to be insoluble in DCM below -12°C . As a result, the reaction was carried out at 0°C and an 85% yield of the epoxyalcohol (29) was obtained after 2h without any noticeable loss of optical activity.

Oxidation of the alcohol functionalities and olefination of the resultant aldehydes proved to be more difficult than had been originally anticipated. The base sensitivity of the chiral epoxyalcohols and the desired epoxyaldehydes prompted us to examine whether chromium oxidising agents, most of which are either neutral or slightly acidic, could be used to effect the oxidation of the primary alcohol. The results of this investigation are summarised below (Table 2). In most cases, oxidation of the epoxyalcohol, as evidenced

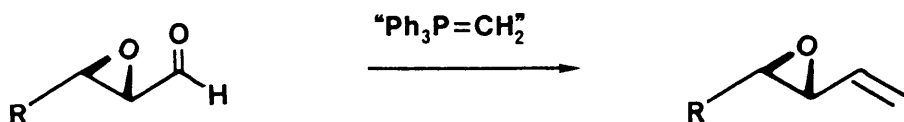
by the disappearance of the starting material, was complete within a short period of time. However, isolated yields of epoxyaldehyde were generally lower than would be anticipated. Sequestration of oxygenated substrates by chromium species is a well known phenomenon; however, attempted Swern oxidation³³ and oxidation with triphenylbismuthcarbonate failed to give any of the desired product. Nevertheless, (2R),(3R)-epoxyoctanal (32) can be obtained in 75% yield using Collin's reagent ($\text{CrO}_3 \cdot 2\text{py}$) and oxidation of (2R),(3R)-epoxytetradecanol (29) with pyridinium dichromate in the presence of powdered 3A molecular sieves produces a quantitative yield of the corresponding epoxyaldehyde (33).

Table 2

Oxidising agent	% Yield	
		
	R = $n\text{-C}_5\text{H}_{11}$	R = $n\text{-C}_{11}\text{H}_{23}$
1. CrO_3 , pyridine, DCM, celite, RT, 1h	75	14
2. PCC, powdered 3A sieves (2g/mmol), DCM, RT	27	30
3. PDC, celite, DCM, RT	18	22
4. PDC, powdered 3A sieves (2g/mmol), DCM, RT, 1h	-	23
5. as above, 24h	-	100

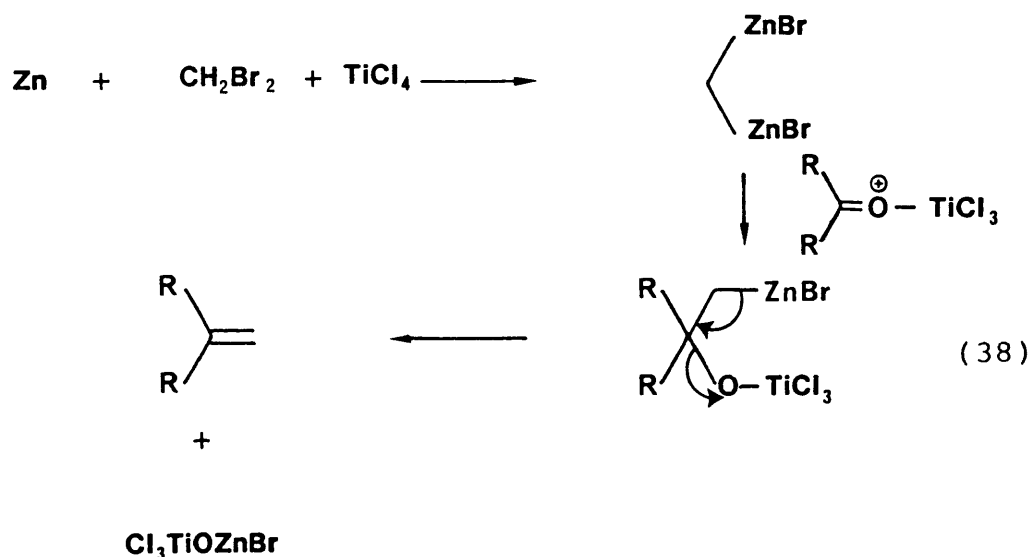
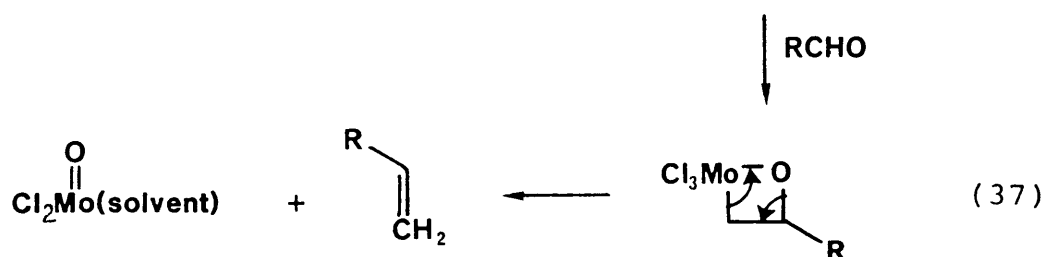
Methylenation of the epoxyaldehyde was carried out by Wittig reaction with methylenetriphenylphosphorane. The corresponding phosphonium iodide was deprotonated by treatment with one equivalent of n-butyl-

lithium at -78°C . The reaction mixture was then warmed to 0°C and stirred for an hour to ensure complete formation of the Wittig reagent, before addition of the base sensitive epoxyaldehyde.



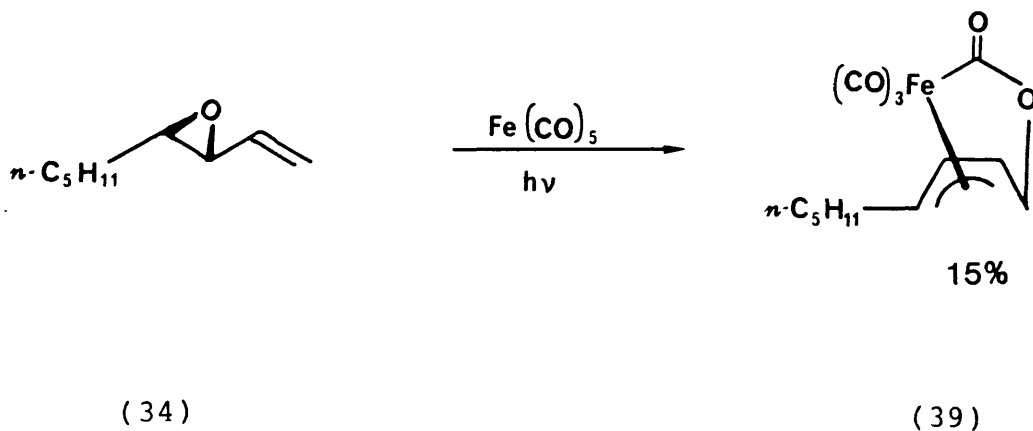
(34) $\text{R} = n\text{-C}_5\text{H}_{11}$ 65%

Purification of the sensitive vinyl epoxide was carried out by flash column chromatography on silica that had been doped with 1% triethylamine. This process gave respectable yields of vinyl epoxide and proved to be the most satisfactory method of those tried; given that the sensitivity of the vinyl epoxide to both acid and base precludes use of the Peterson olefination³⁴. In addition, reaction with the novel organometallic methylene transfer agents, for example $[\text{Cl}_3\text{Mo}(\text{CH}_2)_2]_2$ ³⁵ (36), and the reagent derived from zinc, dibromomethane and titanium tetrachloride³⁶ was investigated. Methylene transfer from the metallacycle (37) and what is thought to be the gem-dimetallic species (38) has been shown to produce high yields of olefin in cases where standard Wittig methodology has failed. Unfortunately, reaction with our epoxyaldehydes failed to produce any identifiable vinyl epoxide¹¹. Nevertheless, the low yield obtained using the Wittig reagent is offset by the ease with which large quantities of epoxyalcohol are available using the route outlined.



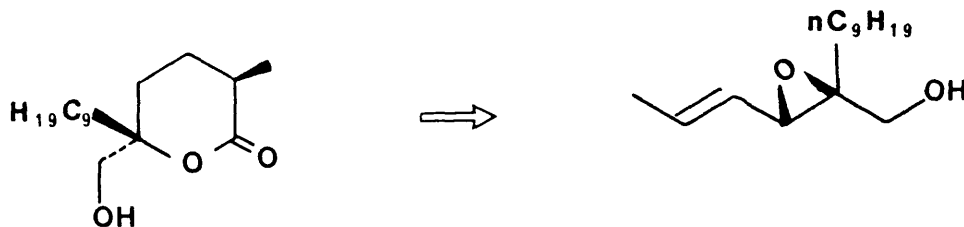
The next step was to form the ferrilactone by reaction of the optically active vinyl epoxides with iron carbonyl. We have developed three methods for formation of these complexes; however, reaction with $\text{Fe}_2(\text{CO})_9$ in THF solution failed to give the anticipated ferrilactone complex. In fact, the standard procedure gave a high yield of a yellow microcrystalline solid as the major product. Infrared spectroscopy demonstrated the absence of the characteristic stretch due to the bridging carbonyl of the ferrilactones and the mass spectrum of the complex shows the sequential loss of at least four carbon monoxide ligands, suggesting that the complex might be a diiron species, although this could not be confirmed.

Finally, we resorted to the photochemical reaction with $\text{Fe}(\text{CO})_5$ and obtained a low yield of the optically active ferrilactone complex (39). High pressure carbonylation of the complex and isomerisation of the

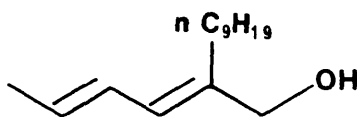


double bond are required to complete the synthesis of Massoia lactone. Carbonylation at high temperature has been found to lead directly to the desired α,β -unsaturated δ -lactone²². However, repetition of the procedure described produced a large number of products, none of which was identifiable as Massoia lactone. As previously discussed, results obtained subsequently¹¹ have shown that higher yields of lactone can be obtained using higher pressures of gas at lower temperatures. Isomerisation of the double bond in the presence of platinum will hopefully provide a route to Massoia lactone in its optically pure form.

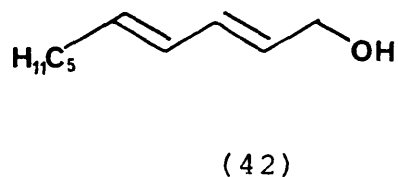
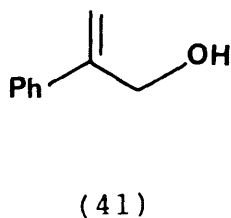
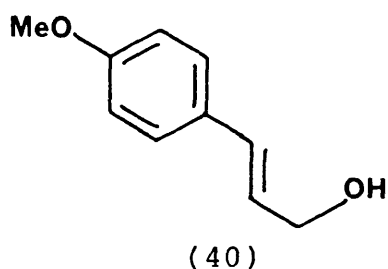
2.2 Approaches to the synthesis of the δ -lactone antibiotic Malyngolide



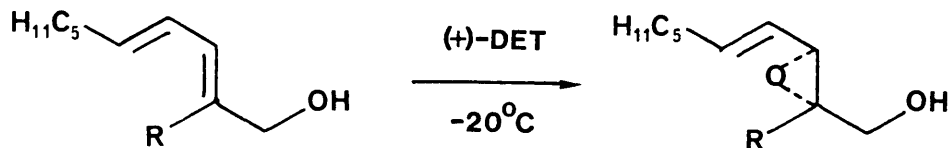
As previously explained, we decided to approach synthesis of this δ -lactone by exploiting the C_5 -hydroxymethyl group to direct the stereochemistry at the quaternary centre via Sharpless epoxidation of the dieneol (47).



Sharpless has reported that epoxidation of the conjugated dienes (40), (41), and (42) gave minimal yields of epoxide under the standard conditions, that is using a stoichiometric amount of titanium/tartrate catalyst. This was attributed to the instability of the product to



the reaction conditions²⁰. However, alkyl substituents at C-2 should stabilise the highly reactive epoxides to decomposition. This effect is graphically illustrated by the example below where the methyl substituted epoxide (44) can be prepared in 80% yield. In contrast, treatment of the straight chain dieneol under identical conditions fails to produce any of the desired epoxide (43).

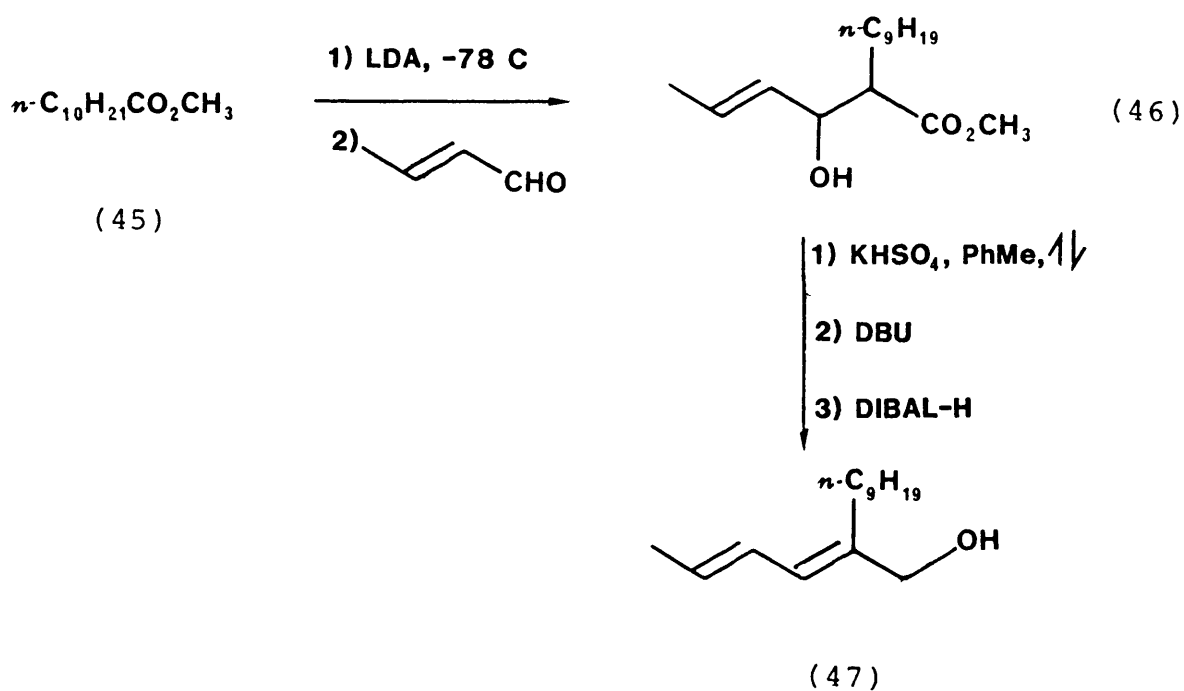


(43) $R=H$ 0%

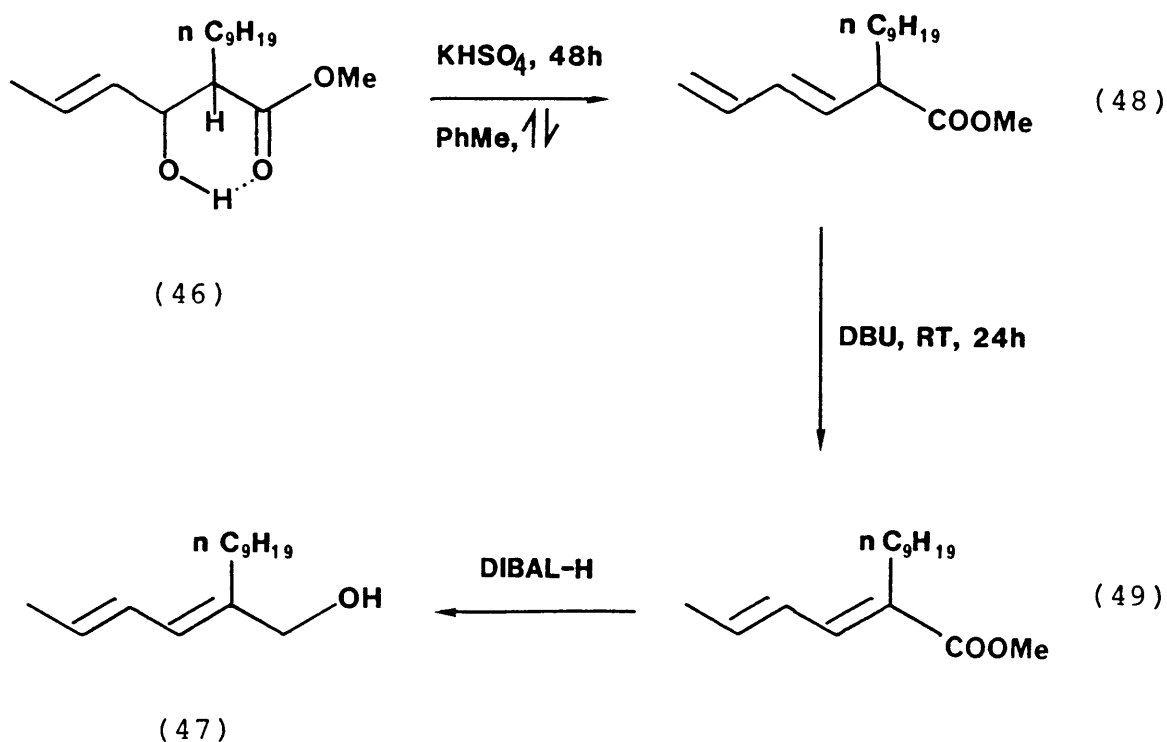
(44) $=Me$ 80%

A survey of the literature demonstrated that this was the only reference to use of Sharpless' methodology for the stereospecific preparation of vinyl epoxides. Hence, we decided to investigate the general applicability of such a route to the preparation of the ferrilactone necessary for the synthesis of Malyngolide.

The E,E-dieneol (47) was prepared from undecanoic acid as illustrated. The methyl ester (45) was formed in virtually quantitative yield by acid catalysed esterification in the presence of methanol. Aldol condensation with crotonaldehyde gave 5-carbomethoxytetradec-2-en-3-ol (46). Elimination of water was then expected to give the required

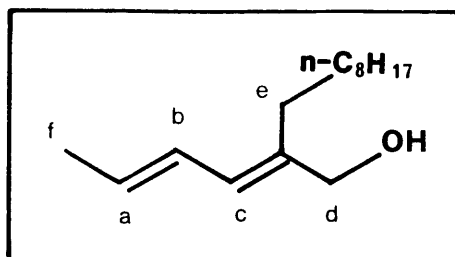


conjugated diene ester (49). However, the alcohol (46) proved to be extremely resistant to dehydration - probably because access to the proton α to the ester is sterically hindered by the long aliphatic chain, and treatment with potassium bisulphate in refluxing toluene gave the unexpected unconjugated diene ester (48) after 48h, as evidenced by the position of the carbonyl stretch in the infrared spectrum at 1720 cm^{-1} . Hence, the crude mixture was treated with DBU at room temperature. The reaction was monitored by tlc until conversion to the conjugated diene ester (49) was complete (24h).



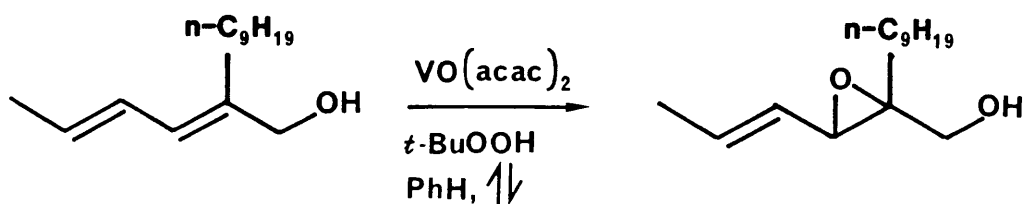
Attempts to shorten this procedure by using DBU alone gave mixtures of unconjugated and conjugated diene esters accompanied by unreacted starting material, and reaction at elevated temperature resulted in appreciable amounts of polymerisation. The crude reaction mixture was then reduced with DIBAL-H at -78°C to give the required dieneol in 91% overall yield from the alcohol (46). In contrast, reduction with lithium aluminium hydride at 0°C produced mixtures of the required dieneol, the fully saturated alcohol and the two alkenols.

The configuration of the dieneol was conclusively established by n.o.e. difference ^1H nmr.

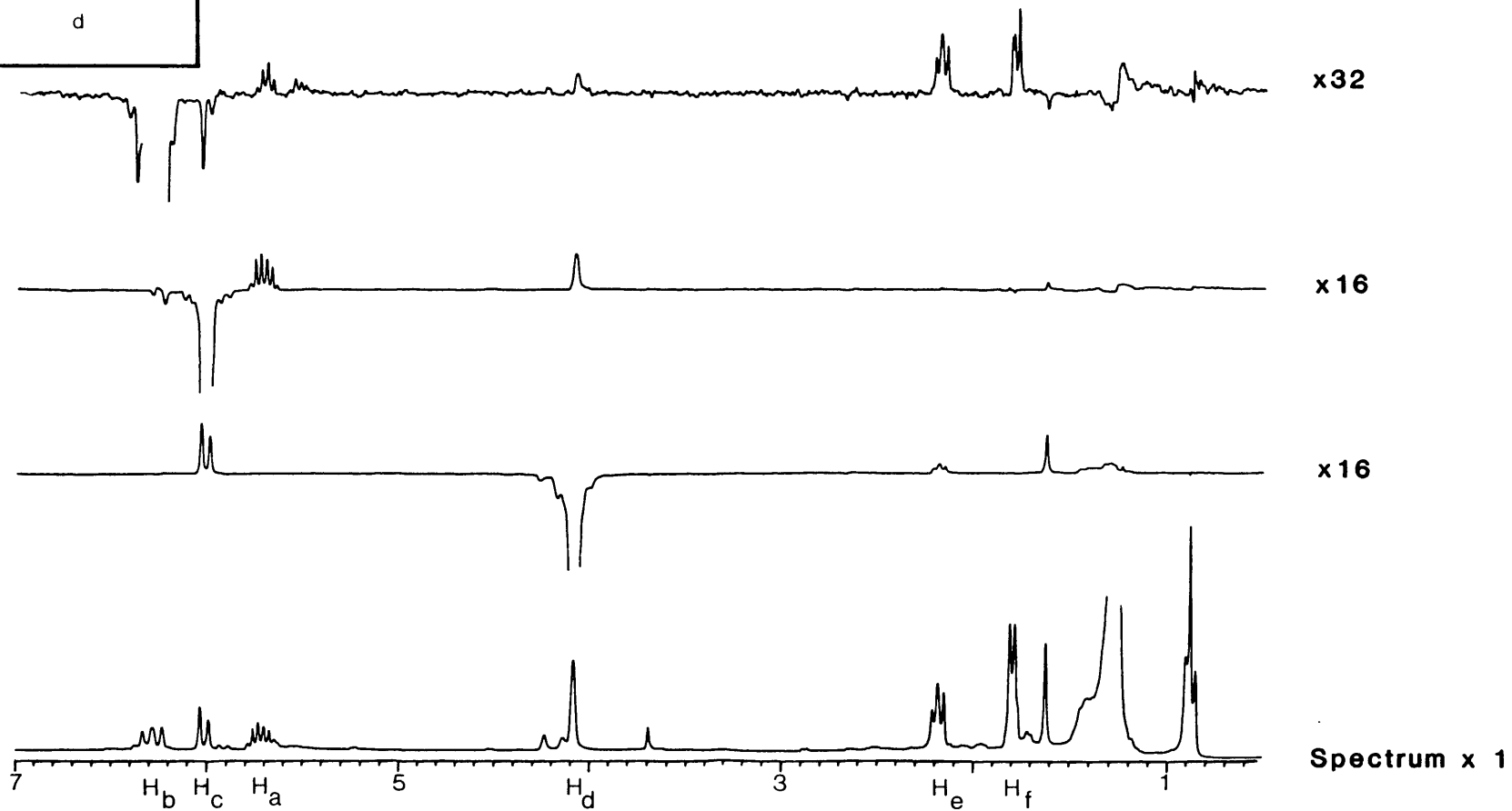
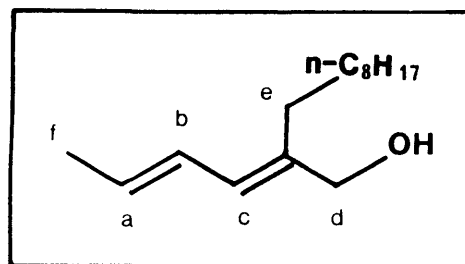


		% enhancement in proton resonance					
		H_a	H_b	H_c	H_d	H_e	H_f
proton decoupled	H_d	—	—	8.3	—	4.1	—
	H_c	9.4	—	—	2.4	—	—
	H_b	—	—	—	—	3.0	2.1

Sharpless epoxidation of the dieneol (47) was carried out using a stoichiometric quantity of titanium/tartrate complex at -20°C . The reaction was monitored by gc which implied formation of a product which was identical to that obtained by epoxidation with *t*-butylhydroperoxide and vanadyl bisacetoacetate $[\text{VO}(\text{acac})_2]$.



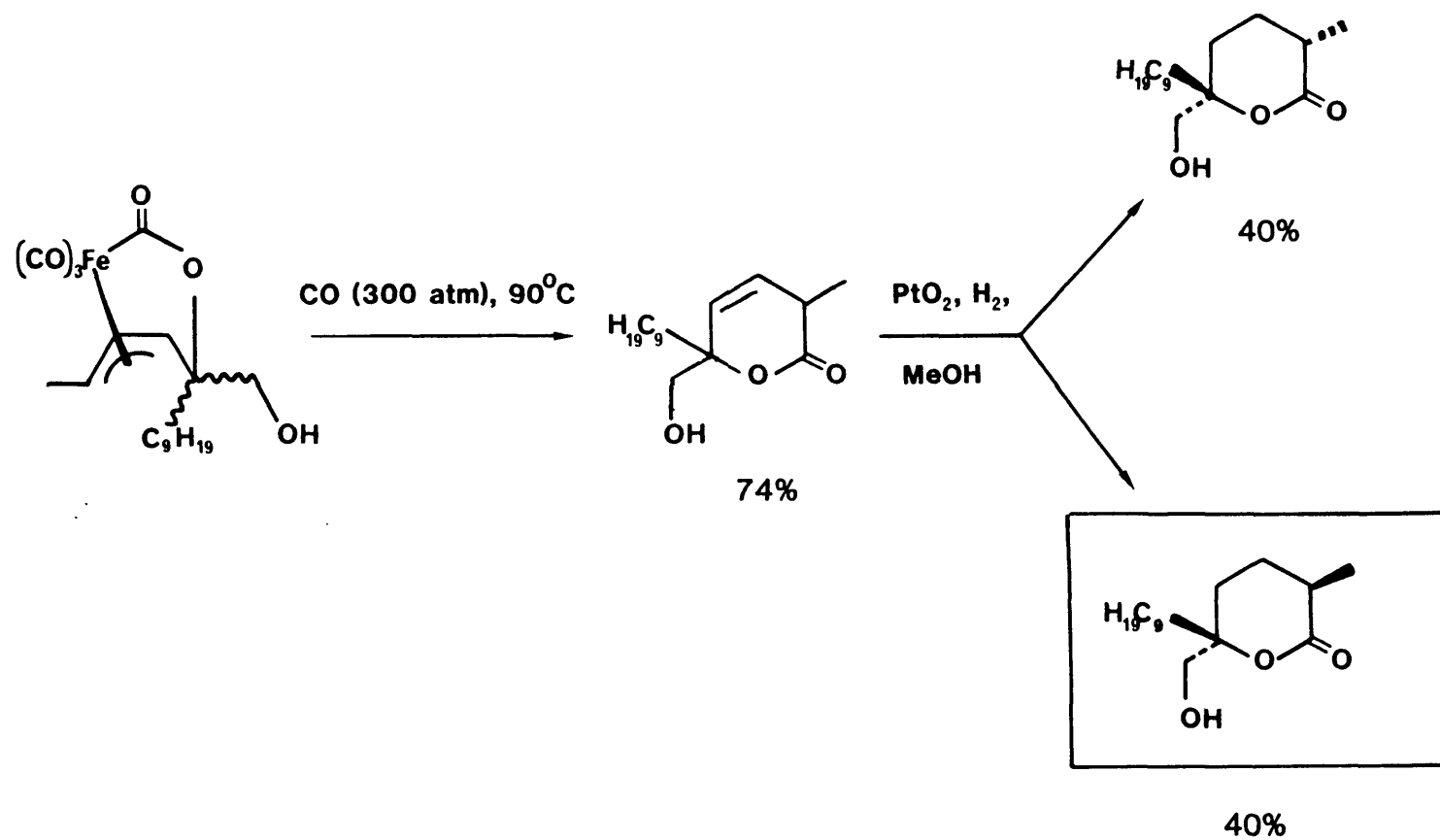
However, isolation of the optically active vinyl epoxide could not be achieved using any of the work-up procedures described by Sharpless and co-workers ^{32,37}. This is most probably due to ring-opening of the epoxide since the Lewis-acidic titanium/tartrate epoxidation catalyst is also known to catalyse this reaction in the presence of an attacking nucleophile, such as isopropanol, the allylic alcohol,



n.O.e. spectrum (250 MHz) of E,E-5-hydroxymethyltetradeca-2,4-diene.

epoxyalcohol or t-butyl hydroperoxide, all of which are present in the reaction mixture.

As yet this remains the major barrier to the preparation of Malyngolide in its optically active form, since previous investigations have shown that the racemic material is readily available from the vinyl epoxide (50) by way of the proposed route ¹¹ (Scheme 6)

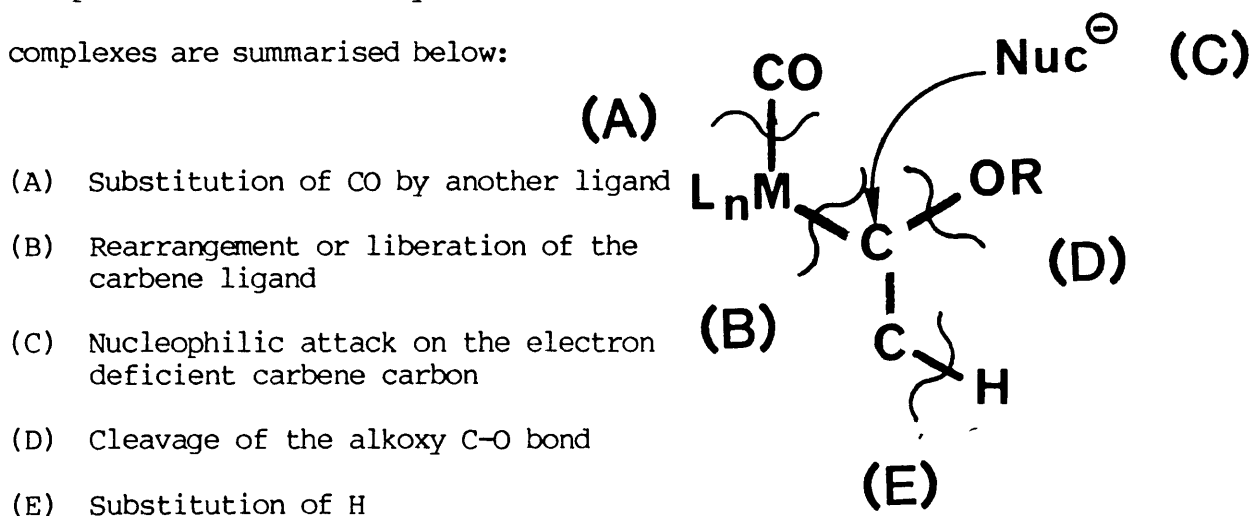


Scheme 6
Racemic synthesis of Malyngolide¹¹.

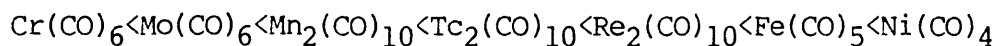
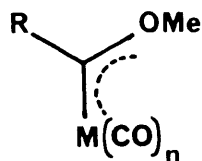
2.3 Preparation of a novel transition metal carbene complex

Metal carbene complexes have been implicated as intermediates in a number of reactions. In addition, there are a number of methods in existence for the preparation of carbene complexes that are stabilised by the presence of electron releasing groups capable of stabilising the electron deficient carbene-like carbon atom, and complexes containing oxygen or nitrogen heteroatom substituents are amongst those most commonly isolated. Recent years have witnessed an exponential increase in the number of publications concerned with the preparation of these complexes. These include a variety of examples in which these complexes have been employed in a number of elegant syntheses³⁸.

The patterns of reactivity exhibited by heteroatom substituted carbene complexes are summarised below:

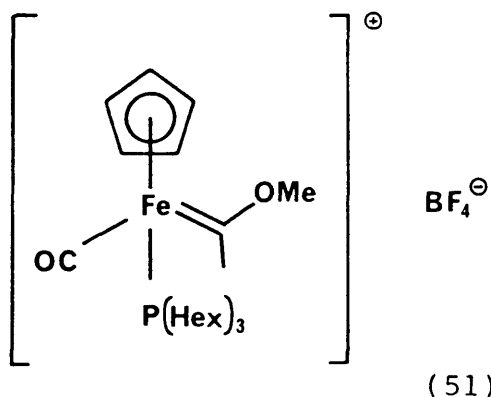


In addition, close examination of the data available for a series of methoxycarbene complexes derived from a variety of metal carbonyls has shown that the iron complexes are amongst the most labile of those prepared⁴⁰, suggesting that they may display some interesting individualistic properties.



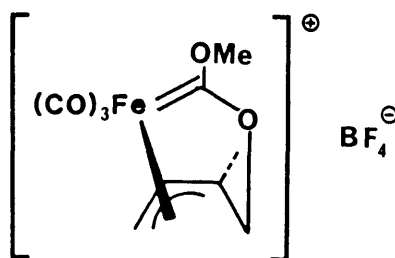
—————→
increasing lability

In 1971 Green and co-workers described the preparation of the carbene complex (51) by treatment of the corresponding acetyl complex with Meerwein's salt ($\text{Me}_3\text{O}^+\text{BF}_4^-$)³⁹.



Hence we turned our attention to the following questions; firstly, could we derive stable carbene complexes from ferrilactones using Green's methodology, and secondly, would the complex formed exhibit any interesting patterns of reactivity? This last point is of interest with respect to the potential for chiral induction in the presence of optically active carbene complexes which would presumably be readily available from the corresponding ferrilactone complex.

In answer to the first question, treatment of the ferrilactone complex (6) with Meerwein's reagent (4.5 equivalents) at room temperature gave the carbene complex (52) in 97% yield.

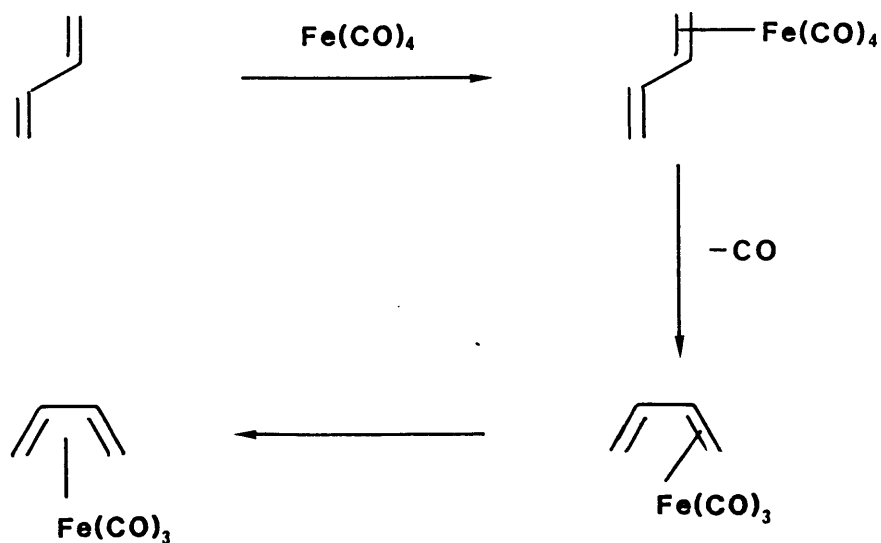


However, reaction in the presence of a wide variety of reagents, at room temperature under argon, failed to produce any identifiable products. The reagents used included the following: organometallic reagents (phenylmagnesium bromide and methyllithium); oxidising agents (hydrogen peroxide and ceric ammonium nitrate); reducing agents (sodium borohydride and DIBAL-H); nitrogen-containing compounds (N-phenylmethylenedianiline, allylamine, O-benzylhydroxylamine, N-hydroxysuccinimide, and indole); aldehydes and ketones; unsaturated compounds (1,4-bis(trimethylsilyl)buta-1,3-diyne, 2-methyl-1-epoxydec-3-ene, cyclohexene, methyl acrylate/h ν , and 3-hydroxybut-1-yne); alkyl bromides; methyl chloroformate; sodium acetate; acetic anhydride, and sodium hydride.

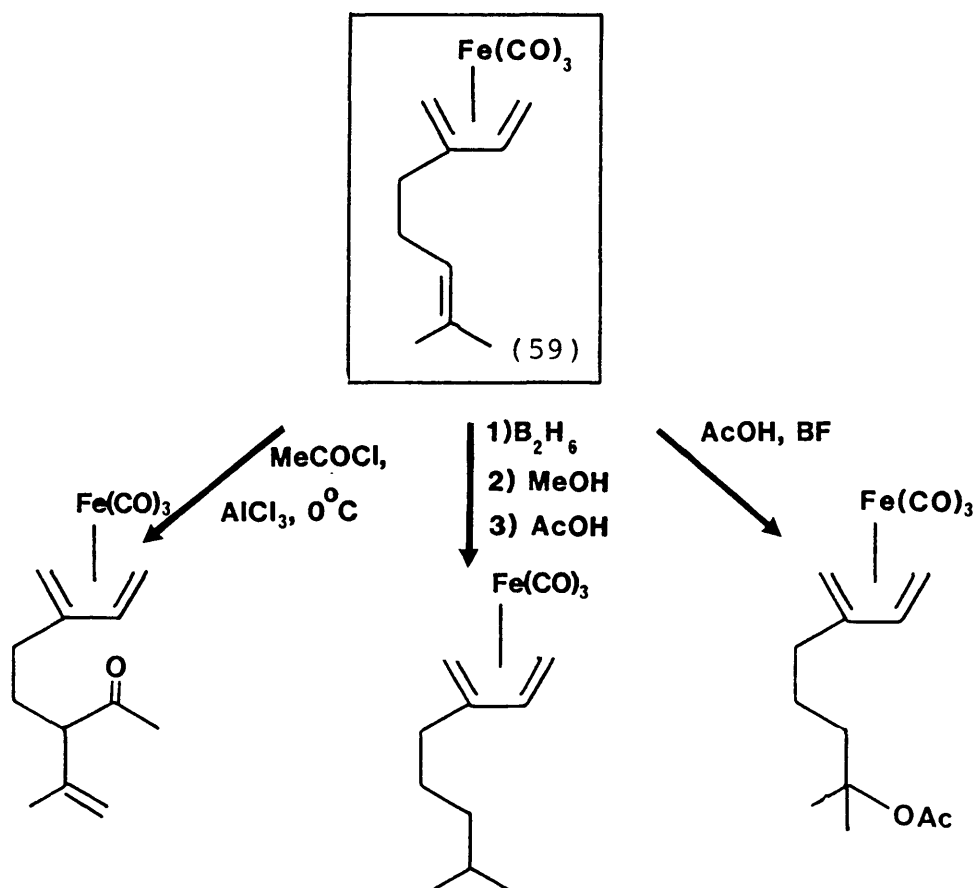
The reasons for this are unclear, although we can speculate that the patterns of reactivity ascribed to the "Fischer-type" complexes are precluded by the absence of an α -carbon atom. On the other hand, it may be that extensive delocalisation around the carbene carbon restricts reaction under the conditions examined. Corroborative evidence from complexes where the carbene carbon is coordinated to two heteroatoms is unavailable, although diamino complexes are known to be exceptionally unreactive due to effective electron transfer from the nitrogens to the carbene carbon atom ³⁸.

2.4 Application of ultrasound to the preparation of η^4 -(diene)-tricarbonyliron complexes

Suslick has proposed that sonolysis of $\text{Fe}(\text{CO})_5$ in hydrocarbon solvents leads to formation of $\text{Fe}_3(\text{CO})_{12}$ via coordinatively unsaturated $\text{Fe}(\text{CO})_4$ or $\text{Fe}(\text{CO})_3$ intermediates¹⁶ Taken in conjunction with the observation that sonolytic degradation of $\text{Fe}_2(\text{CO})_9$ produces elemental iron and $\text{Fe}(\text{CO})_5$, the probability that similar reactive species are generated appears to be quite high. We have already demonstrated that $\text{Fe}(\text{CO})_4$ species can be trapped by vinyl epoxides and this reaction has been exploited in the synthesis of a number of ferrilactones. We were intrigued by the possibility that the mild conditions used to good effect in the synthesis of ferrilactone complexes could be exploited in a route to η^4 -(diene)tricarbonyliron complexes. Tricarbonyliron diene complexes had already been shown to be stable under ultrasonic irradiation¹⁷; however, it remained to be seen whether conjugated dienes could be used to trap $\text{Fe}(\text{CO})_4$ species formed on sonolysis of $\text{Fe}_2(\text{CO})_9$ in the light of the proposed mechanism⁴¹.



Recent investigations into the properties of such complexes have begun to demonstrate their potential for use as synthetic intermediates⁴². Furthermore, interest in the properties of the coordinated ligand coupled with the number of methods available for removal of the tricarbonyliron moiety, has led to exploitation of these species as protecting and stabilising groups for conjugated dienes^{40,43,44}. For example, extensive investigation has shown that the isolated double bond in the (β -myrcene)-tricarbonyliron complex (59) can be modified in a number of ways without affecting the diene- $\text{Fe}(\text{CO})_3$ unit⁴⁵.

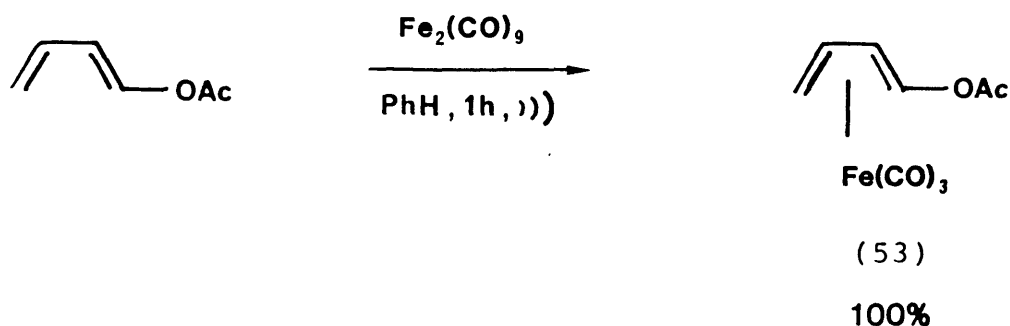


However, thorough examination of the literature showed that, despite the number of published examples detailing the reaction of dienes with iron carbonyl species, yields of complex obtained under the influence of both heat and ultraviolet radiation are seldom better than low to moderate⁴⁶. This obviously constitutes a major barrier to the general acceptance of these species as synthetic intermediates which has yet

to be overcome.

Problems arising from the sensitivity of both products and starting materials to aerial oxidation dictate that reactions must be carried out under inert atmospheres. The most commonly employed procedure involves heating a mixture of the diene and $\text{Fe}(\text{CO})_5$ in a high boiling, inert solvent, such as di-*n*-butylether, for long periods of time. However, the sensitivity of the complex to peroxides present in these solvents make it imperative to filter the solvent through basic alumina immediately prior to use. A number of other modifications have also been suggested, and yet, yields of the desired complex remain disappointingly low, considerably reducing the synthetic potential of these complexes.

Against this background, we decided to see whether sonolysis of $\text{Fe}_2(\text{CO})_9$ in the presence of conjugated dienes would provide a route to these complexes. In the initial attempt 1-acetoxybuta-1,3-diene and $\text{Fe}_2(\text{CO})_9$ were sonolysed together in benzene solution and, to our great delight, a quantitative yield of the η^4 -(diene)tricarbonyliron complex (53) was isolated. Interestingly, this compares to the 15% yield obtained when the reaction was carried out using $\text{Fe}_2(\text{CO})_9$ in THF solution. This is in sharp contrast to its efficacy as a source of tetracarbonyliron in the preparation of ferrilactones from vinyl epoxides.



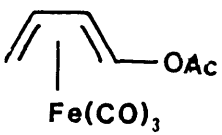
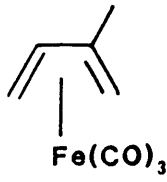
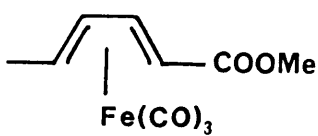
Extension of the methodology showed that the method was generally applicable to a variety of conjugated dienes and tolerant of both electron donating (53) and electron withdrawing groups (56). At this point it should be stressed that the reaction is carried out at ambient temperature, without exclusion of air and without prior purification or drying of the solvent. Despite this, the unoptimised yields of complex obtained are consistently higher than previous literature preparations. Reaction was assumed to be complete once the solid carbonyl had disappeared and concentration of the reaction mixture, followed by silica gel chromatography of the residue, separated the required complex from any inorganic species. The results of these experiments are summarised in Table 3. In general, yields of these reactions were essentially quantitative and were only limited by the volatility of the product, as evidenced by the reduced yields of lower molecular weight complexes.

The complexes, with few exceptions, were isolated as yellow oils which, although sensitive to aerobic oxidation, could be stored at -20°C without appreciable decomposition. Infrared spectroscopy clearly shows the characteristic absorptions associated with the $\text{Fe}(\text{CO})_3$ moiety at ca. 2080 and 1970 cm^{-1} ; of which the latter was generally resolved into two bands. Results obtained with a variety of complexes show that the presence of electron-withdrawing substituents on the diene moiety shifts these bands to higher frequencies. The effect is reversed in the case of electron donors, as illustrated below. This is a consequence of the effect of the substituent on the diene-metal and hence metal-CO $d\pi-p\pi$ interactions, and probably attributable to shifts in the energy levels of the diene HOMO and LUMO. Coordination to the iron also shifts the diene C=C stretching band to much lower frequency, for example the C=C stretch in β -myrcene moves from 1639 cm^{-1} in the uncomplexed system to 1476 cm^{-1} in the analogous

Table 3

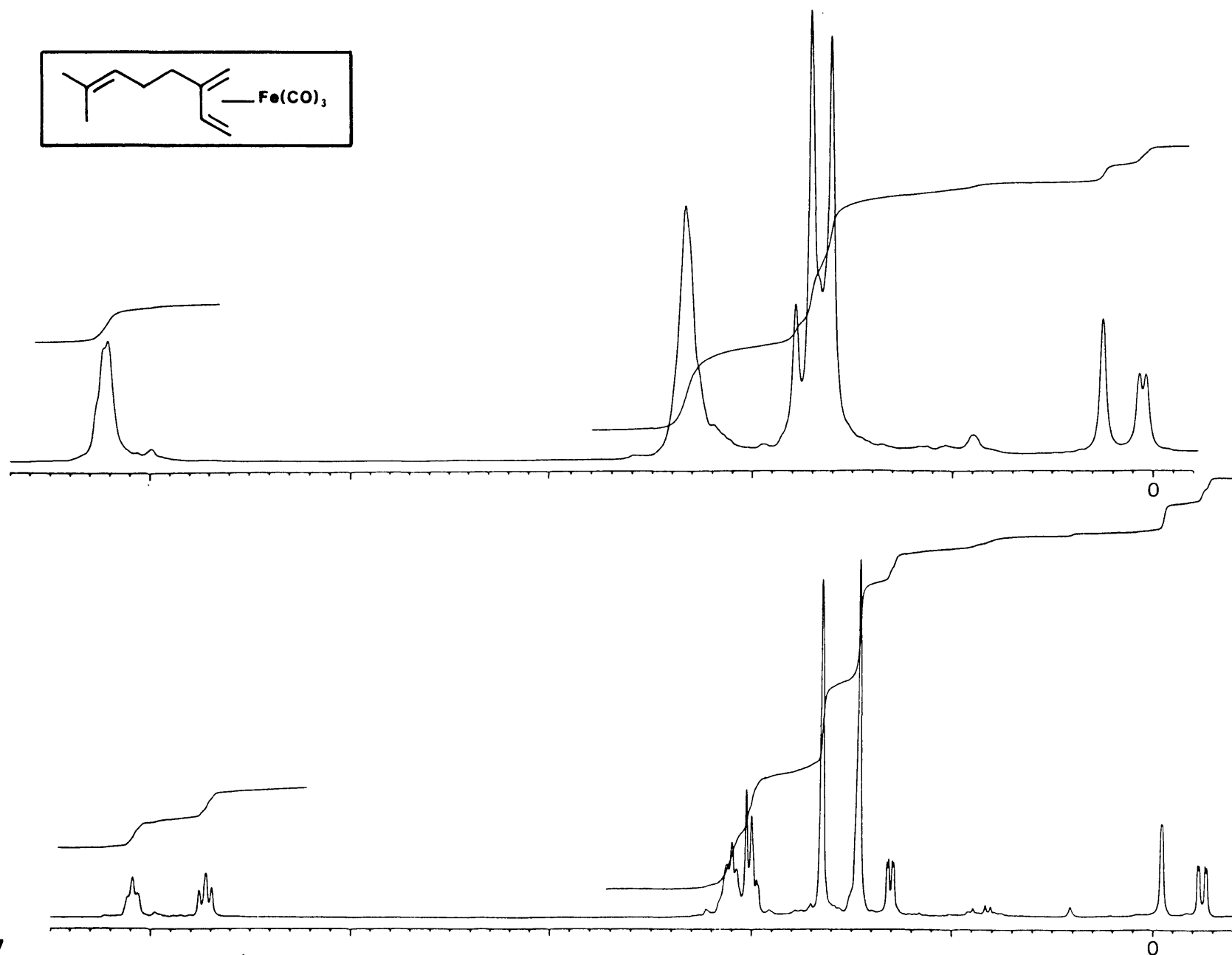
Diene	Complex	% Yield
	 (53)	100
	 (54)	70
	 (55)	50
	 (56)	100
	 (57)	51
	 (58)	75
	 (59)	95

tricarbonyliron complex.

	$\nu_{\text{C-O}} / \text{cm}^{-1}$		
	2082	1955	1945
	2085	2000	1968
	2092	2050	2000

Reaction with more complex polyenes showed a number of interesting features. For example, reaction with β -myrcene gives a 95% yield of the product shown (59). That is, reaction occurs specifically with the conjugated diene and the product isolated is uncontaminated by species arising from complexation of the isolated double bond.

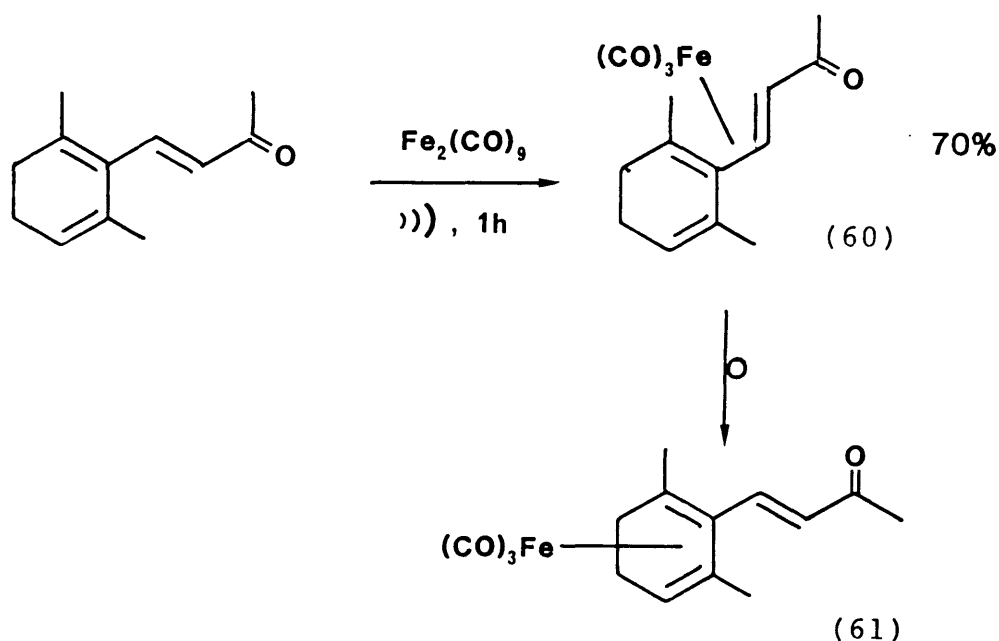
High field ^1H nmr studies of these complexes in CDCl_3 correlated with published data; however, samples were subject to rapid decomposition, despite careful preparation, and little information could be gleaned from the spectra obtained. We had previously encountered the same problem when attempting to obtain spectra of certain ferrilactones under similar conditions. This appears to be a reflection of the acidity of the solvent and d^6 -benzene had proved to be a more suitable solvent in such cases. Comparison of the 250MHz ^1H nmr spectra of $(\beta\text{-myrcene})\text{-Fe(CO)}_3$ in the two solvents shows a degree of fine structure in the spectrum in C_6D_6 solution that is noticeably absent in the equivalent spectrum in CDCl_3 solution (Scheme7). The shielding effect of the tricarbonyliron moiety results



Scheme 7
250 MHz ^1H nmr spectra of $\eta^4-(\beta\text{-myrcene})\text{-tricarbonyliron}$ in (a) deuteriochloroform, and (b) C_6D_6 .

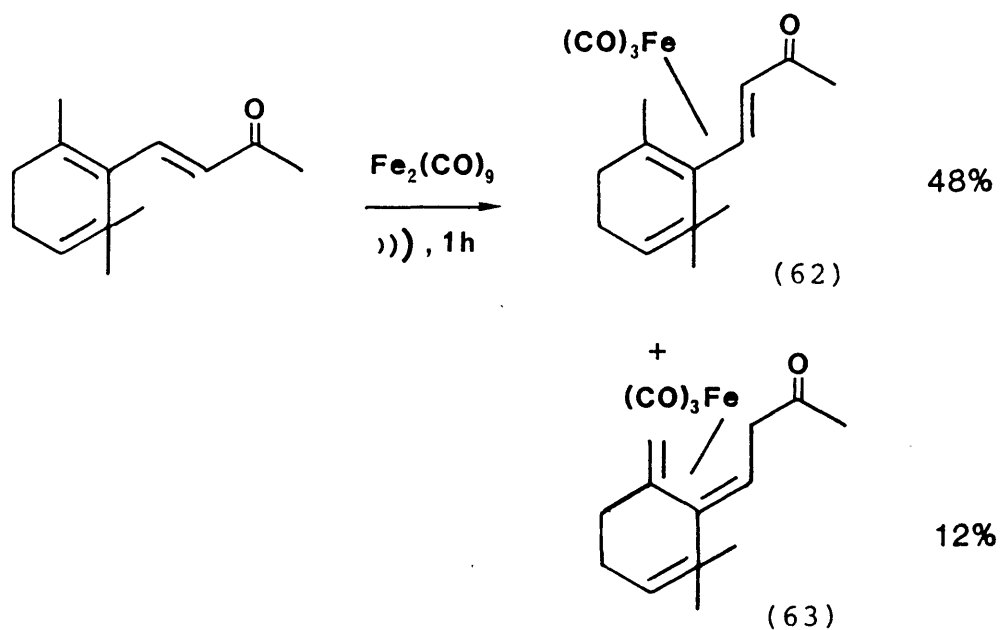
in enormous upfield shifts of the resonances associated with what could be described as the "endo" methylene protons which occur at -0.05 and -0.25ppm , in contrast to the "exo" methylene protons which resonate ca. 1.5ppm further downfield.

The reaction with pseudionone is of particular interest in that it was possible to isolate a 75% yield of the kinetic product (60) after 1h of sonolysis. Further exposure to ultrasound led to isomerisation and a 1:2 ratio of the exocyclic and endocyclic diene complexes was obtained. The latter is presumably the thermodynamic product of the reaction as storing the 3,5-diene complex (60) at -20°C results in almost complete conversion to the 5,9-diene complex (61). Hence, variation of the reaction time allows selective access to good yields of both isomers. This is not possible by conventional methods and reflects the mild conditions used.



In the analogous reaction of β -ionone with $\text{Fe}_2(\text{CO})_9$, 1h of sonolysis gave a 4:1 mixture of endo and exo complexes, (62) and (63). In contrast, Cais and Maoz have reported that the thermal reaction of the diene with $\text{Fe}(\text{CO})_5$ leads to isolation of a 3:1 ratio of products in

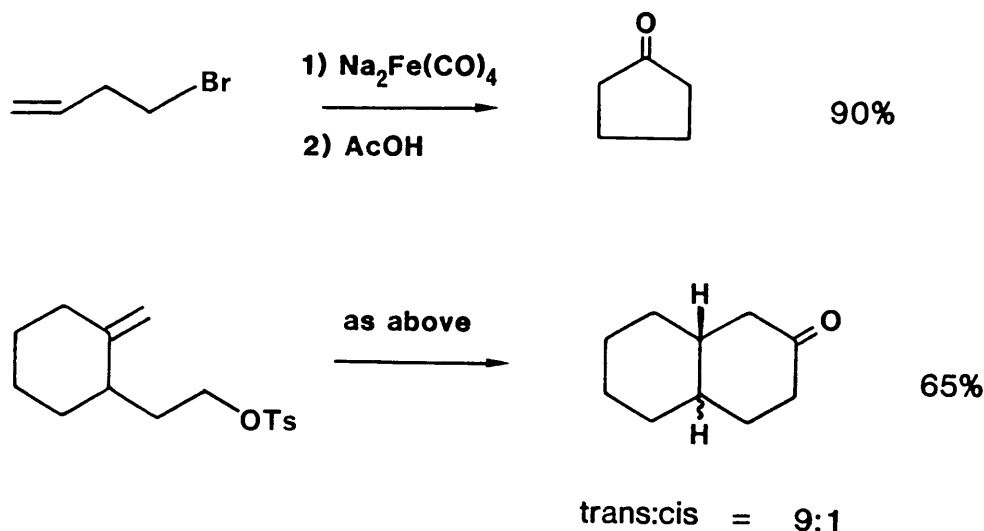
favour of the exo isomer⁴⁷. However, it should be noted that the combined yield of this reaction was only 21%, that is a factor of three less than that obtained using our methodology.



In conclusion, we have demonstrated the ease with which high yields of these complexes can be obtained in the presence of a variety of functional groups and hope that this will promote increased use of such species as synthetic intermediates.

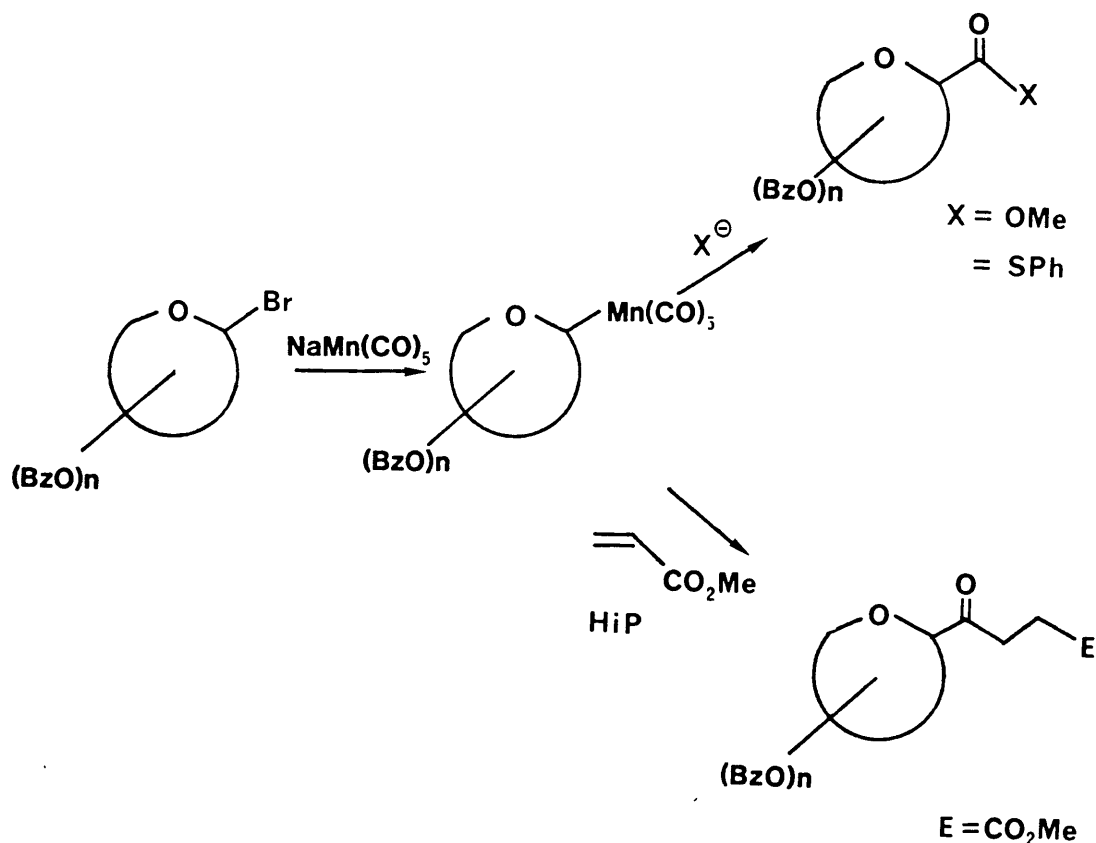
2.5 The effects of ultrasound on the formation of disodium tetracarbonylferrate

The encouraging results obtained from application of ultrasound to the preparation of ferrilactone complexes prompted us to examine whether ultrasound could be usefully exploited in the preparation of other iron carbonyl species. For example, disodium tetracarbonylferrate has been used as a source of CHO^- and RCO^- , that is, as an acyl anion equivalent.



The yields of this reaction are generally good⁴⁸ suggesting definite possibilities for application to synthesis.

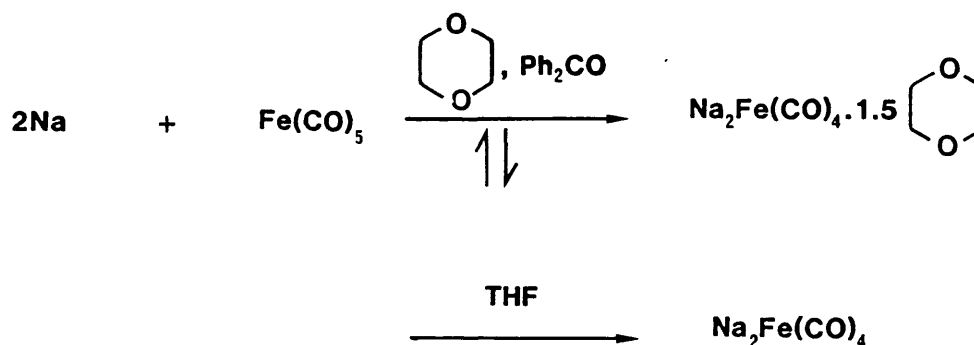
In addition, we were intrigued by recent reports that sugar derivatives could be acylated at anomeric centres via the appropriate manganese pentacarbonyl sigma complex. The reaction proceeds with a high degree of stereospecificity. Nevertheless, the general applicability of this methodology is limited by a number of factors: firstly, that the price of dimanganese decacarbonyl is currently a factor of twenty higher than that of iron pentacarbonyl; and secondly, the pressures necessary to effect reaction are considerably higher than would be inferred from DeShong's original communication^{49(a)}. In



fact, these are of the order of 8000 atmospheres or 6 kbar. Apparatus for the generation of such enormous pressures is not generally available and it later transpired^{49(b)} that the reactions had been executed in a modified, heavy duty, hydraulic car jack!

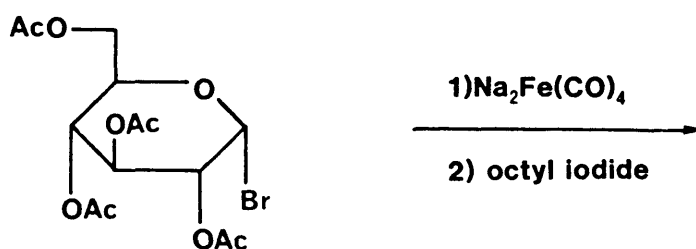
It was for these reasons that we decided to investigate the analogous reaction could be using disodiumtetracarbonylferrate to provide a more accessible method of acylation at anomeric centres. Reaction of simple straight chain alkyl bromides, iodides and tosylates were

precedented in the literature⁴⁸; however, the reagent, which is usually generated by reduction of iron pentacarbonyl with sodium benzophenoneketyl, is extremely oxygen sensitive and spontaneously inflammable in air. The literature preparations^{48,50} stress that the



Fe(CO)_5 must be added dropwise to a refluxing solution of sodium benzophenoneketyl in dioxane over a period of up to 16h. Hence, any shortening of this reaction time would reduce the hazards associated with preparation of this useful but fickle reagent.

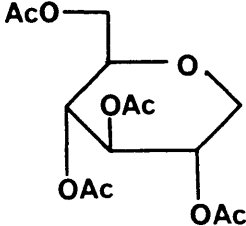
This led us to examine whether the reaction could be carried out at room temperature under the influence of ultrasound. Details of these investigations are given in Table 4. The products of these reactions were used to examine the reaction between the carbohydrate derivative containing an anomeric bromide (64)⁵¹ and octyl iodide. Unfortunately, the products most generally isolated were the reduced sugar bromide (65) or unchanged starting material.



(64)

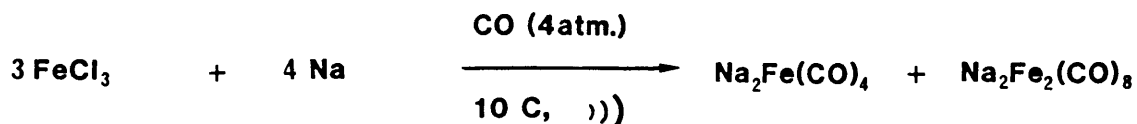
Table 4

Attempted preparation of disodium tetracarbonylferrate by reaction of $\text{Fe}(\text{CO})_5$ with sodium in the presence of ultrasound.

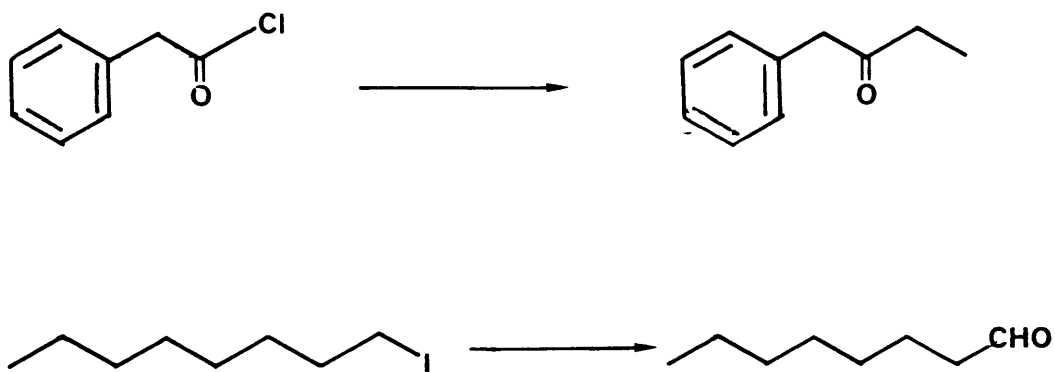
Conditions used	Results of the reaction with bromide () and octyl iodide
1. Solid Na, THF, Ph_2CO , $\text{Fe}(\text{CO})_5$, 12h	no reaction
2. (i) Solid Na, THF, , 8h (ii) $\text{Fe}(\text{CO})_5$, Ph_2CO , 4h	no reaction
3. (i) Solid Na, toluene, , 8h (ii) $\text{Fe}(\text{CO})_5$, Ph_2CO , 4h	no reaction
4. (i) Solid Na, xylene, , 8h (ii) $\text{Fe}(\text{CO})_5$, Ph_2CO , 4h	starting material +
 (65)	
5. (i) 50% commercial dispersion of Na in paraffin ^a , xylene (ii) $\text{Fe}(\text{CO})_5$, Ph_2CO , 1h	as above
6. Commercial $\text{Na}_2\text{Fe}(\text{CO})_4 \cdot 1.5$ dioxane	no reaction

a supplied by Aldrich Chemical Co. Ltd.

This appears to be a reflection of the incomplete formation of disodium tetracarbonyl ferrate which appears to be reacting further with excess iron carbonyl to give $\text{Na}_2\text{Fe}_2(\text{CO})_8$. The mixture of $\text{Na}_2\text{Fe}(\text{CO})_4$ and $\text{Na}_2\text{Fe}_2(\text{CO})_8$ is well known as a powerful reducing agent and would account for the predominance of the reduced product. In fact, Suslick has also reported a route for preparation of $\text{Na}_2\text{Fe}(\text{CO})_4$ / $\text{Na}_2\text{Fe}_2(\text{CO})_8$ by sonolysis of iron (III) chloride and sodium under four atmospheres of carbon monoxide⁵².



Despite this, reactions with simple alkyl halides gave the expected product on a number of occasions. For example reaction with phenylacetyl chloride, followed by aqueous ethanol gave the predicted ketone, phenylbutan-2-one. In addition, reaction with octyl iodide gave an intermediate showing a strong carbonyl absorption at 1881 cm^{-1} . Treatment with acetic acid then gave octanal ($\nu_{\text{C=O}} 1714 \text{ cm}^{-1}$). Nevertheless, these results were not generally reproducible. This illustrates the point made in the review that reactions carried out in ultrasound cleaning baths have a tendency to give erratic results, due to their inconsistent generation of levels of ultrasound necessary for transient cavitation.



Interestingly, we observed marked differences in the ability of ultrasound to disperse solid sodium in the solvents tested. In fact the sodium showed a marked tendency to aggregate in THF, although an adequate dispersion could be formed in xylene. This has also been

commented on by Luche and co-workers⁵³ who observed the same pattern on attempting to form colloidal dispersions of a variety of alkali metals in a range of solvents using an ultrasound probe.

Our results clearly show that the reaction is dependent on the degree to which dispersion of the metal is effected and the incomplete reaction may be a feature of the low intensities of ultrasound produced by laboratory cleaning baths. Hence, there is a possibility that complete formation of $\text{Na}_2\text{Fe}(\text{CO})_4$ could be achieved under these conditions using a high intensity probe as the ultrasound source .

2.6 Ultrasonic formation of sodium phenylselenide

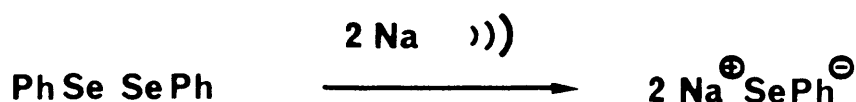
The impact that organoselenium chemistry has had on modern organic synthesis is undisputed. Many methods have been developed for the introduction of the seleno-substituent; however, use of phenylselenide anions is especially common. Nevertheless, despite extensive investigations, problems arise from the odiferous nature of certain reagents, the use of toxic or incompatible solvents, and the lack of reactivity of some of the salts.

Work within our group had shown that ultrasound could be used to increase the rate of the reaction between diphenyldiselenide and solid sodium to a degree that the reaction, which is virtually negligible at room temperature, was complete after four days⁵⁴. The sodium phenylselenide is obtained as a homogeneous colloidal suspension which can be conveniently transferred by syringe or cannula to the reaction vessel. The suspension was found to be stable in the absence of oxygen and could be stored in a sealed flask for up to one week without any noticeable decrease in reactivity. Hence, the only major disadvantage of this procedure appears to be the length of time required to bring the reaction to completion. In common with the reaction of sodium with $\text{Fe}(\text{CO})_5$, this can be attributed to the limited surface area of sodium available and hence we decided to investigate this reaction further, in line with our previous observations.

In common with Luche *et al*⁵³ we have noted a tendency for sodium to aggregate in THF and found that the reaction time could be halved by using xylene in its place. However, from a practical point of view, the high boiling point of xylene makes it difficult to remove from the reaction mixture, and isolation of volatile or thermally unstable selenides would become virtually impossible. In fact, a control

experiment showed that dispersion of solid sodium in xylene took 8h in our low intensity ultrasound cleaning bath. Hence, we turned our attention to the commercially available sodium dispersions which have the advantage of being easier to handle in small quantities than the equivalent rod sodium. This produced a gratifying five-fold decrease in the reaction time. However, the greatest enhancement in rate of reaction was observed when a catalytic amount of benzophenone

Table 5



Conditions	reaction time/h
1. Solid sodium cut into small lumps/THF	96
2. as above/xylene	31
3. Commercial sodium dispersion ^a /THF	21
4. as above/benzophenone	1

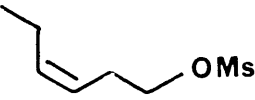
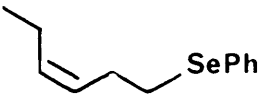
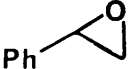
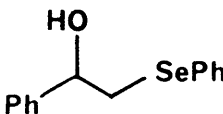
^a = 50% dispersion in paraffin from Aldrich

was added to the reaction mixture as an electron carrier. This modification had the added advantage that the reaction became self-indicating as a result of the presence of the characteristically dark blue sodium benzophenoneketyl. From a practical point of view, dropwise addition of a solution of diphenyldiselenide, in a minimal volume of THF, to the dark blue reaction mixture appears to result in virtually instantaneous formation of the cream coloured sodium phenylselenide. The reaction was complete when the last mauve tinges

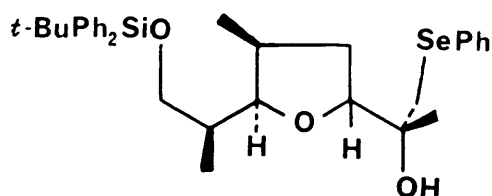
of sodium benzophenoneketyl had disappeared. This generally took slightly less than an hour and represents a 96-fold increase in the rate of the reaction! We believe that this extremely mild and convenient method supercedes other routes and is highly recommended for the simple preparation of sodium phenylselenide.

A brief study of its reactivity showed that nucleophilic reaction with halides, sulphonates and epoxides proceeded in high yield.

Table 6

	Substrate	Product	% Yield
1		 (66)	92
2		 (67)	100
3		 (68)	97
4		 (69)	78

This reagent was also recently used to successfully introduce a phenylseleno substituent into a fragment (71) of the ionophore antibiotic M139603 by mesylate displacement⁵⁵. In contrast, other literature methods to introduce the phenylseleno group or to directly reduce the mesylate group rather than proceed through the selenide had failed.



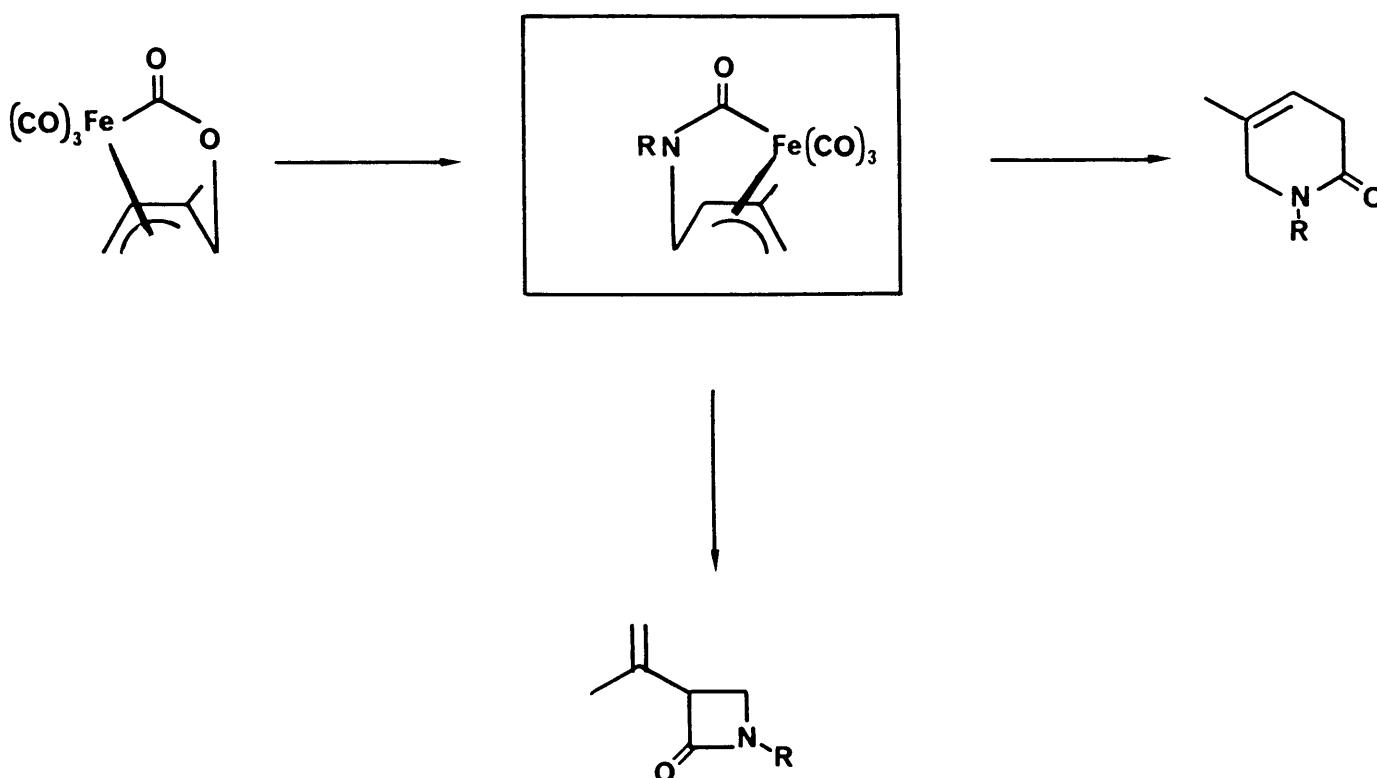
(71)

In principle, the ultrasonic technique described should be applicable, not only to the preparation of a wide range of diselenides, but also to sulphides and tellurides, and indeed, sodium methane thiolate has been prepared from dimethyldisulphide using this methodology⁵⁶.

2.7 Synthesis of β -lactams from π -allyltricarbonyliron(lactone) complexes

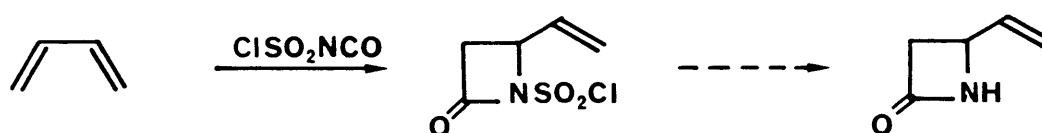
(a) Introduction

Work carried out in our laboratories has shown that ferrilactones are not only useful precursors for the synthesis of δ -lactones, but can also provide a novel route to monocyclic β -lactams. Initial work had shown that treatment of ferrilactone complexes with benzylamine in the presence of zinc chloride gave the corresponding π -allyltricarbonyliron(lactam) complexes via an S_N2' -like mechanism. As previously explained, cerium (IV) oxidation of ferrilactones had been shown to give good yields of the four-membered δ -lactone. Similarly, low temperature oxidation of ferrilactams gave N-benzyl β -lactams in good yield. Application of this methodology to a number of systems demonstrated that the major product obtained was almost invariably the β -lactam and significant amounts of δ -lactam were only evident in one case^{57,58}.



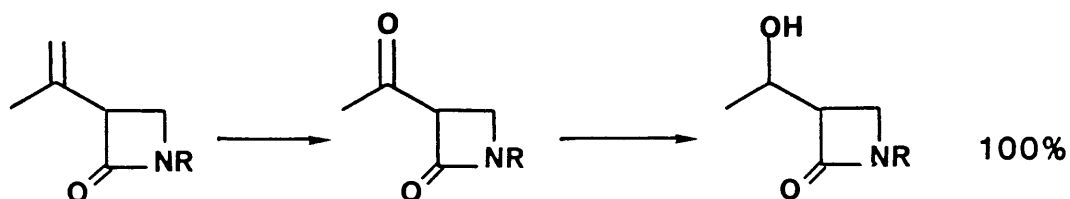
A great deal of attention has been focused on approaches to the synthesis of monocyclic β -lactams since the discovery of a number of non-classical β -lactam antibiotics which were found to inhibit β -lactamase activity, in addition to their potent antibiotic activity. Extensive investigation over the last 10 years has led to the discovery of a series of such compounds exemplified by thienamycin⁵⁹, the olivanic acids⁶⁰, nocardicins⁶¹, and the monobactams⁶². As a direct consequence, new methods for the construction of monocyclic β -lactams that can accommodate the appropriate functionality are constantly sought. Our methodology is particularly useful in that the β -lactams produced possess unsaturated side chains at C-3; that is, the overall process is analogous to regioselective $2\pi + 2\pi$ addition of an isocyanate equivalent to a diene using existing methodology.

The utility of such an approach is mirrored in the popularity of the reaction between dienes and chlorosulphonylisocyanate (CSI) which is routinely used in the preparation of β -lactams⁶³. The products of this reaction arise from bonding between the carbonyl group and the least substituted position of the double bond. Hence, the two methods are complimentary in that the organoiron approach can be used to prepare compounds which may be considered to be the regioisomers of those obtained using existing methodology.

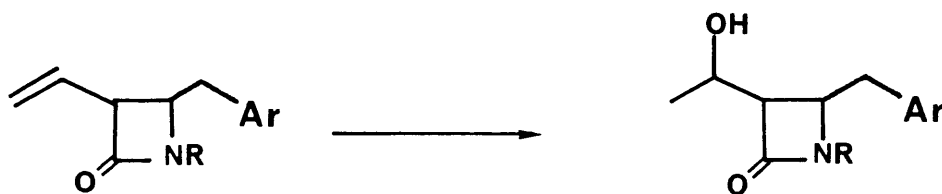


Further examination of the products of the organoiron reaction suggest that the route might be generally applicable to the synthesis of a wide range of β -lactam antibiotics. For example, thienamycin and the olivanic acids possess hydroxyethyl substituents at C-3. Introduction

of such a functionality can be readily envisaged by elaboration of the corresponding isopropyl substituent.

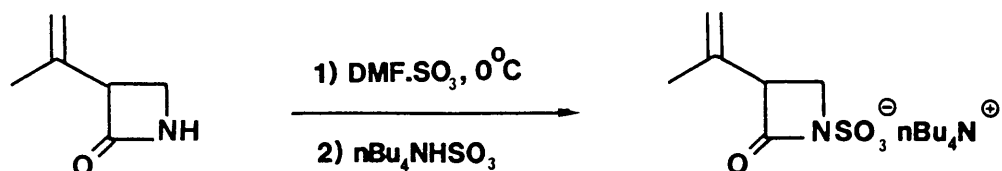
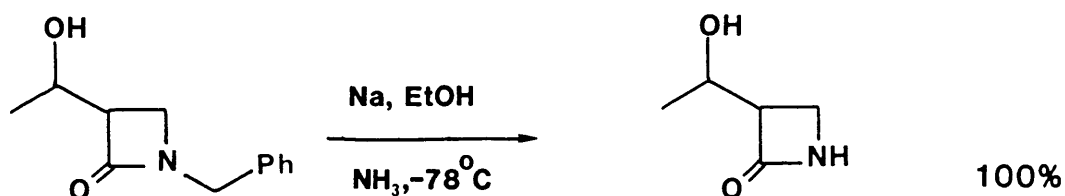


On the other hand, a recent Japanese patent has described the synthesis of C-3 hydroxyethyl substituted azetidinones from the equivalent vinyl compounds by reaction with mercury (II) acetate, followed by demercuration with a reducing agent. However, no details of the origin of the substrate were given⁶⁴.



Similarly, strategies for degradation of the alkenyl side chain and introduction of a 3-amino function would allow access to another large group of naturally occurring β -lactam antibiotics.

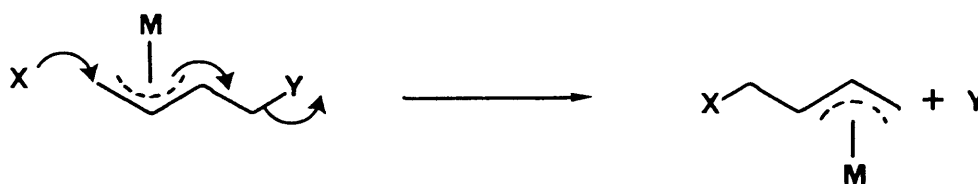
We have also shown that variation of the N-substituent can be readily achieved by reaction of the requisite ferrilactone complex with a range of primary amines. This allows for introduction of structurally complex amino functionalities, such as those found in the nocardicins. On the other hand, work in our laboratories has shown that N-benzyl and α -substituted benzyl groups can be removed in virtually quantitative yield by treatment with sodium in liquid ammonia⁶⁵. The free NH β -lactams could be efficiently transformed into novel monobactams by treatment with the dimethylformamide-sulphur trioxide complex (DMF. SO_3)⁶⁶ developed by workers at Squibb.



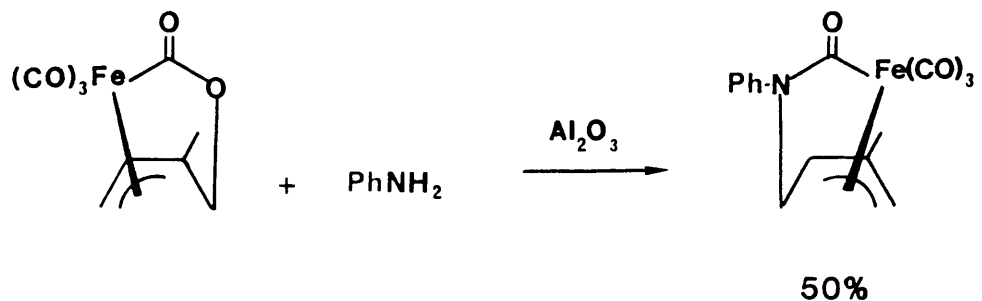
Hence, the β -lactam products derived from ferrilactam complexes would appear to be versatile intermediates for the synthesis of a wide range of β -lactam antibiotics. In particular, those whose biological properties are currently under active investigation by the pharmaceutical industry.

(b) Formation of π -allyltricarbonyliron(lactam) complexes

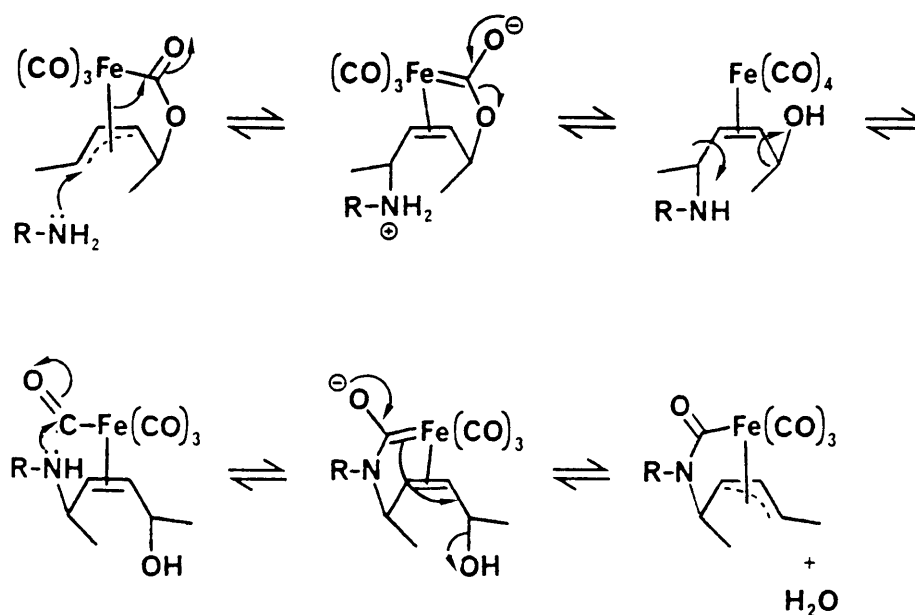
Ferrilactones react with primary amines to give the ferrilactam complexes arising from an S_N2' -like mechanism. The reaction is reported to occur spontaneously in the case of nucleophilic amines, such as methylamine⁶; however, reactions are generally carried out in the presence of Lewis acids such as basic or neutral alumina³



or zinc chloride^{57,59}. The products appear to result from S_N2' attack by the amine on the complexed π -allyl system with concomitant migration of the π -allyl bond. This result was later confirmed by labelling studies in the example shown below:⁶⁷

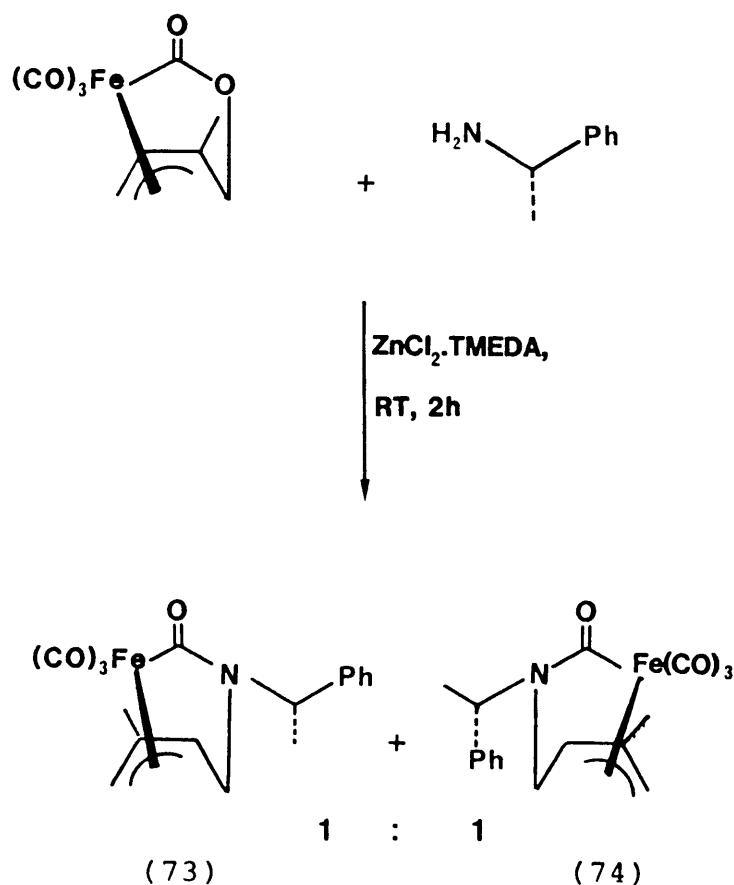


Examination of the Lewis acid mediated reaction between substituted ferrilactones and amines led Aumann and co-workers⁶ to propose a mechanism for the observed inversion at C-1 and C-4 and the migration of the π -allyl unit.

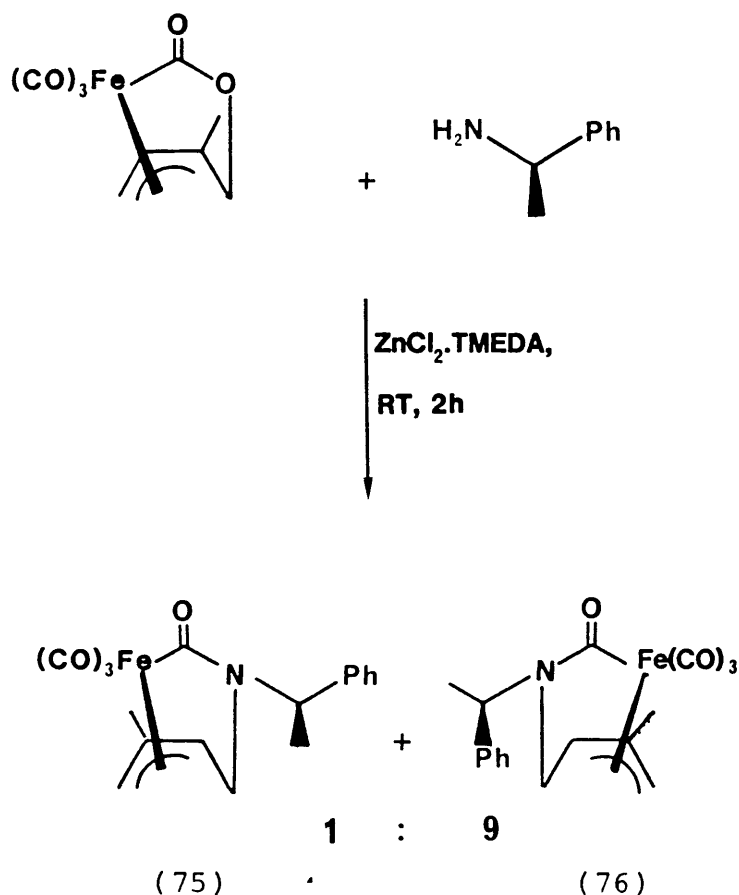


Hence, "exo" attack by the incoming nucleophile at C-4 of the π -allyl terminus, followed by rotation about the C-3/C-4 bond allows the amine to attack one of the carbonyl ligands. At the same time, rotation about the C-1/C-2 bond positions the hydroxyl group anti to the oxygen anion and expulsion of water gives the ferrilactam complex.

A thorough investigation of this reaction showed that zinc chloride was the Lewis acid of choice; however, optimum conditions required use of 10-12 equivalents of amine and 4 equivalents of ferrilactone⁶⁸. Furthermore, the reaction often proved capricious - most probably as a result of the sequestration of water by hygroscopic zinc chloride. Later results showed that only 2-4 equivalents of amine were required if the zinc chloride/tetramethylethylenediamine complex ($\text{ZnCl}_2 \cdot \text{TMEDA}$)⁶⁹ was used in place of ZnCl_2 . Its enhanced activity is probably a feature of the presence of the chelating ligand which blocks two of the zinc's available coordination sites, thus reducing the propensity of the zinc to sequester excess amine. This mild Lewis acid proved an admirable reagent for use with α -substituted alkylamines and the insertion of (S)-(-)- α -methylbenzylamine into the ferrilactone complex (6) proceeded smoothly to give a quantitative yield of the diastereoisomeric ferrilactam complexes (73) and (74) as a 1:1 mixture⁶⁵.

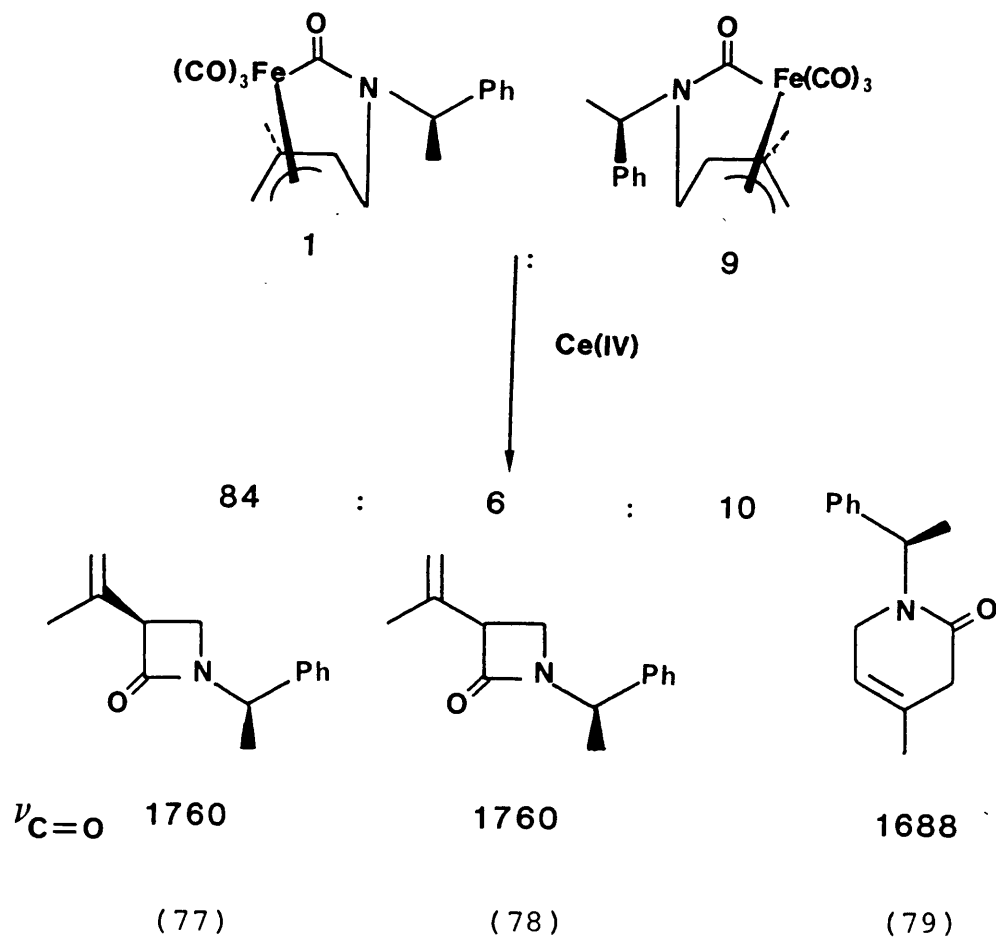


Interestingly, the analogous reaction with the (R)-diastereoisomer appeared to proceed at a slower rate and so the reaction mixture was cooled to 0°C, to prevent thermal decomposition of any ferrilactam formed, and worked up after a further 12h. To our surprise the ratio of the diastereoisomeric ferrilactam complexes (75) and (76) obtained was no longer 1:1 but 1:9. That is, lowering the reaction temperature leads to kinetic resolution of the ferrilactam complexes. The reasons

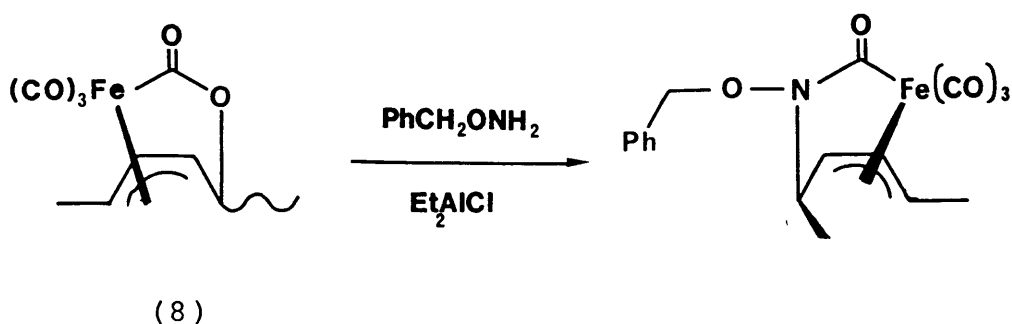
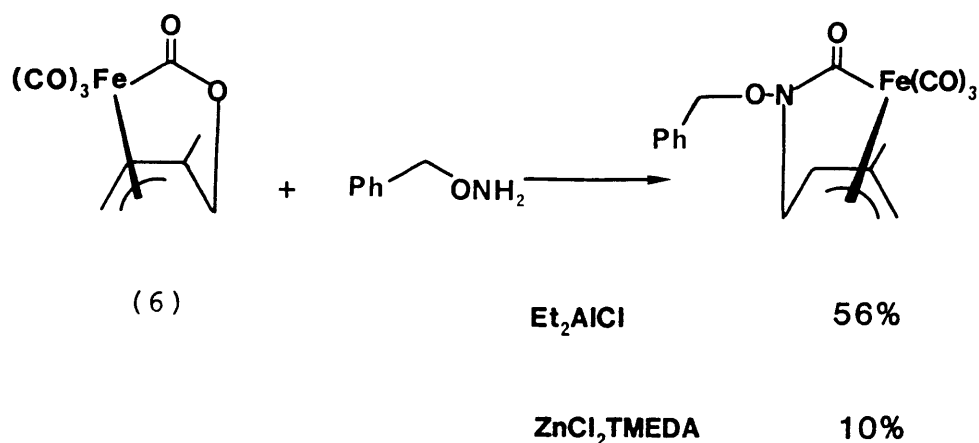


for the differing stabilities of the two ferrilactam complexes are not immediately obvious; however, the result is of interest from the point of view that oxidation of the mixture of ferrilactams gives a 14:1 ratio of the corresponding β -lactams, (78) and (77), accompanied by a small proportion of the δ -lactam (79) - as evidenced by the position of the carbonyl stretch in its infrared spectrum. The diastereoisomeric β -lactams are readily separable by silica gel chromatography and hence a slight modification of the conditions used

for preparation of the ferrilactam complex leads to isolation of an 84% yield of the 3(R)-isopropyl β -lactam (77) with an enantiomeric excess of 86%.



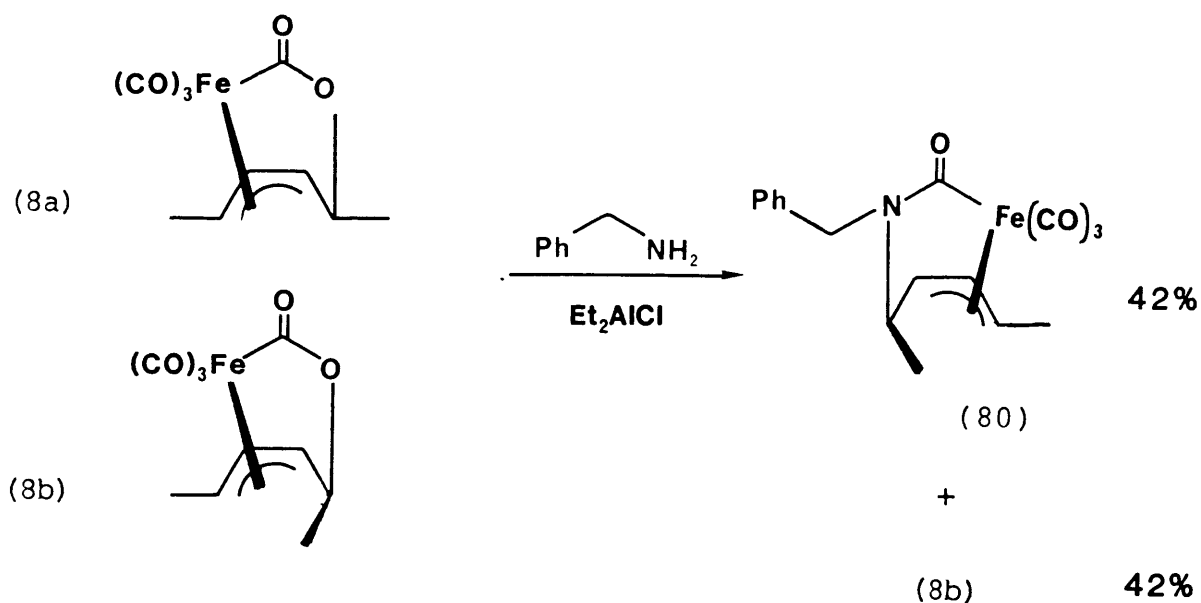
Experiments with more complex primary amines, such as tosamide, O-tetrahydropyranyloxyamine, t-butyldimethylsilamide failed to produce any of the desired ferrilactam in the presence of zinc chloride⁶⁵. This was attributed to the decreased nucleophilicity of the amine functionality, relative to the simple alkylamines, and/or the increased steric demand of those amines which would be expected to be strongly nucleophilic. The only exception to this was O-benzylhydroxylamine, which gave a low yield of ferrilactam on reaction with ferrilactones (6) and (8).



On the other hand, reaction in the presence of a stronger Lewis acid, diethylaluminium chloride, gave a 56% yield of ferrilactam complex.

In fact, it appears to be a general rule that insertion of α -substituted primary amines occurs more efficiently in the presence of zinc chloride.TMEDA whereas α -methylene alkylamines give higher yields of ferrilactam in the presence of diethylaluminium chloride.

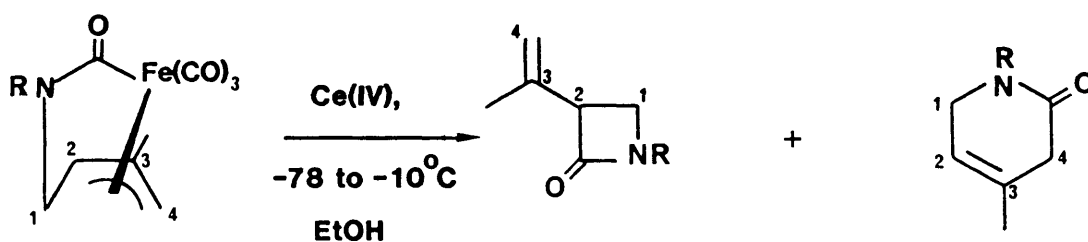
An interesting result was obtained when attempting to insert benzylamine into the 1:1 diastereoisomeric mixture of ferrilactones (8a) and (8b) obtained from reaction of 2,3-epoxyhex-4-ene with diiron nonacarbonyl. The reaction was carried out under the usual conditions; however, the ferrilactam product isolated was found to be the endo/exo complex (80) and the equivalent ferrilactone (8b) was recovered virtually quantitatively. Further investigation showed that



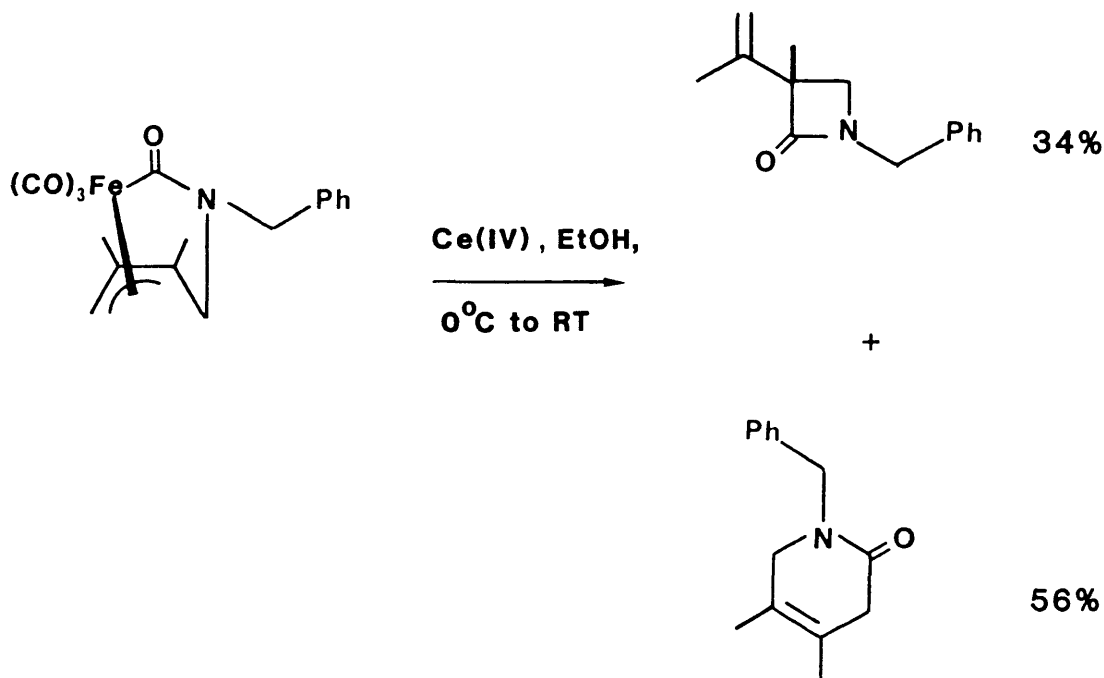
whilst a series of amines would insert into the exo/exo ferrilactone complex (8a), reaction with the exo/endo complex (8b) always resulted in isolation of the unchanged starting material. This can be rationalised if one considers that the product formed would be that where the two methyl groups were in closest proximity and steric repulsion between the alkyl groups would be expected to disfavour formation of such a complex.

(c) Formation of β -lactams by oxidation of π -allyltricarbonyliron(lactam) complexes

Low temperature cerium (IV) oxidation of π -allyltricarbonyliron (lactam) complexes generates the β -lactams as the product of coupling between the lactam carbonyl and the C-2 terminus of the π -allyl system. The β -lactam products are generally accompanied by small proportions of the δ -lactam, which is generated by coupling with the opposite end of the π -allyl system.



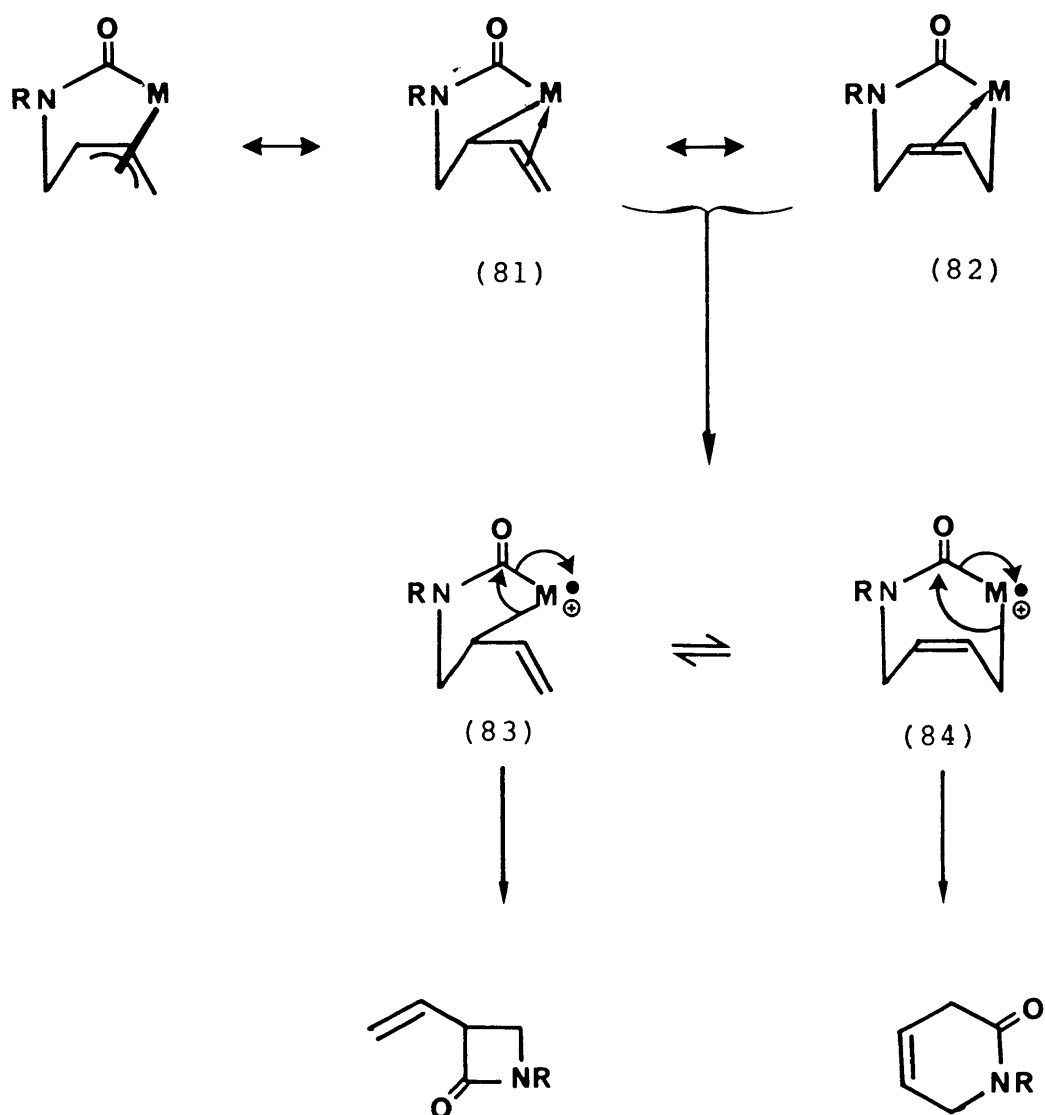
However, formation of the six-membered δ -lactam can be made to predominate at elevated temperatures¹.



We have proposed the following mechanism to account for the formation of both products, drawing evidence for the suggested rationale from

crystallographic studies on tricarbonyliron(lactam) complexes⁷⁰.

In common with the ferrilactone complexes^{6,71} the π -allyl system is not planar, as would be expected, but highly distorted, suggesting that the carbon atoms at the termini of the π -allyl system display a high degree of sp^3 character. This implies that the structure of the complex can be represented equally well by the canonical structures (81) and (82). One electron oxidation of the complex would produce an equilibrating mixture of intermediate radical cations. Concerted

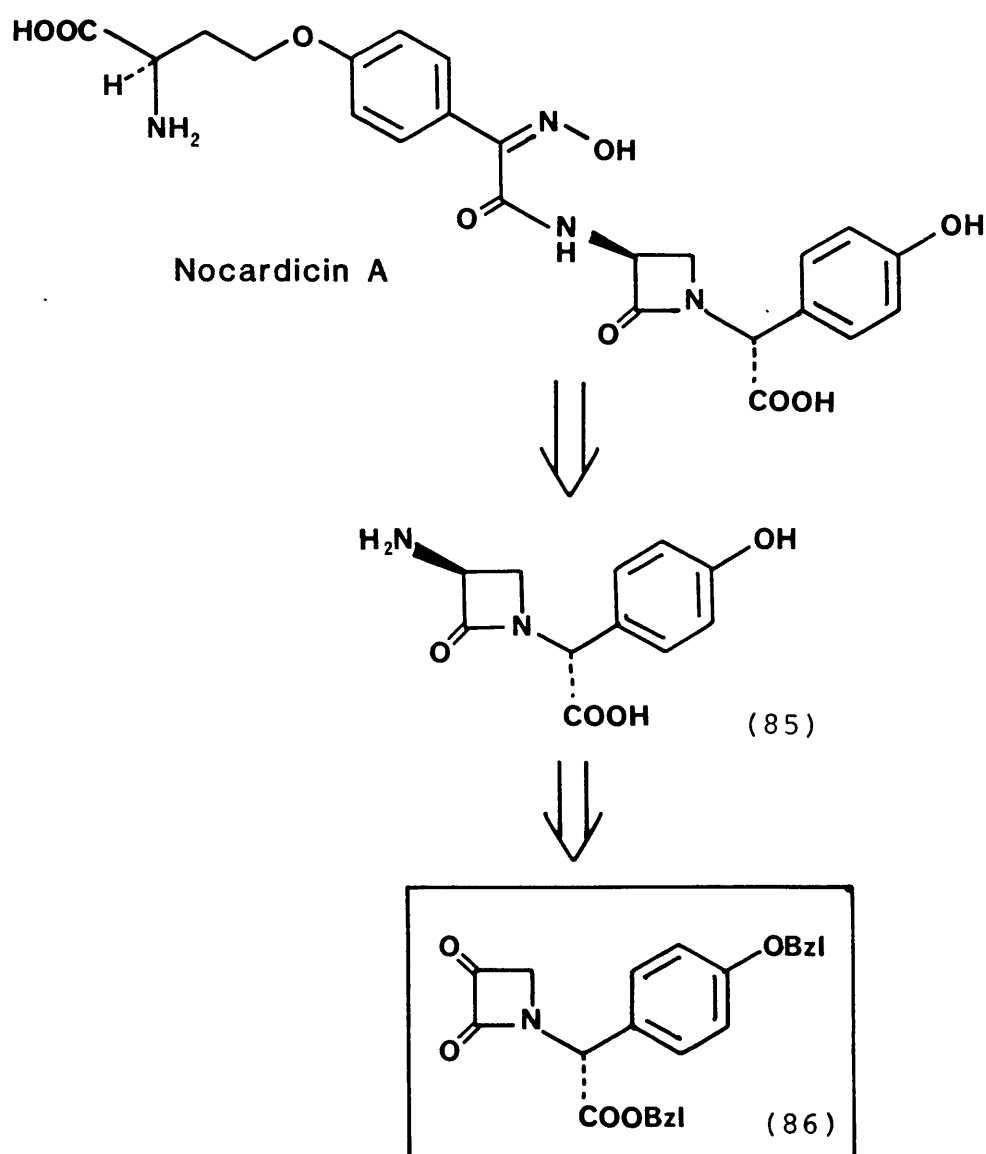


fragmentation and extrusion of the iron from the 5-ring radical cation (83) would then give the β -lactam, and similarly, decomposition of the 7-ring intermediate (84) would account for formation of the δ -lactam. The predominance of the β -lactam products is presumably a reflection of the inherent stability of a 5-membered ring over its 7-membered counterpart.

An alternative suggestion is that oxidative degradation of the complexes occurs via allylic cation intermediates. However, the absence of solvent trapped products suggests that this is unlikely.

2.8 The formal synthesis of (-)-3-aminonocardicinic acid

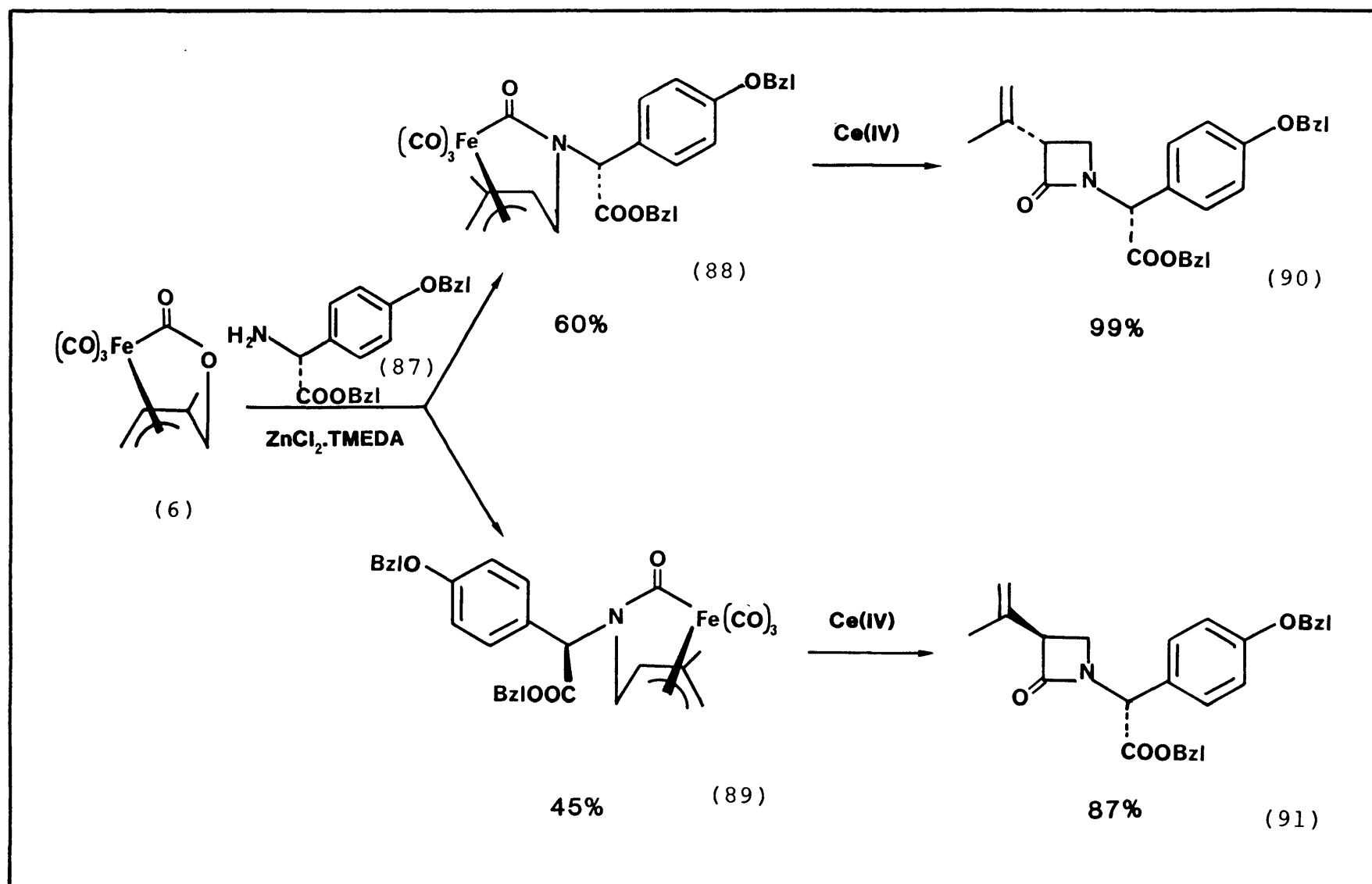
The nocardicin antibiotics, typified by nocardicin A, were first isolated from a strain of actinomycetes in 1976⁷². Interest in the synthesis of these novel monocyclic β -lactams has been prompted by the wide spectrum of activity these compounds exhibit against a range of Gram-negative bacteria. In particular, attention has been focused on the preparation of the (-)-3-aminonocardicinic acid nucleus (85) - a key feature of all biologically active nocardicins, which has been successfully exploited as a general precursor in the synthesis of a number of nocardicins⁷³⁻⁷⁶.

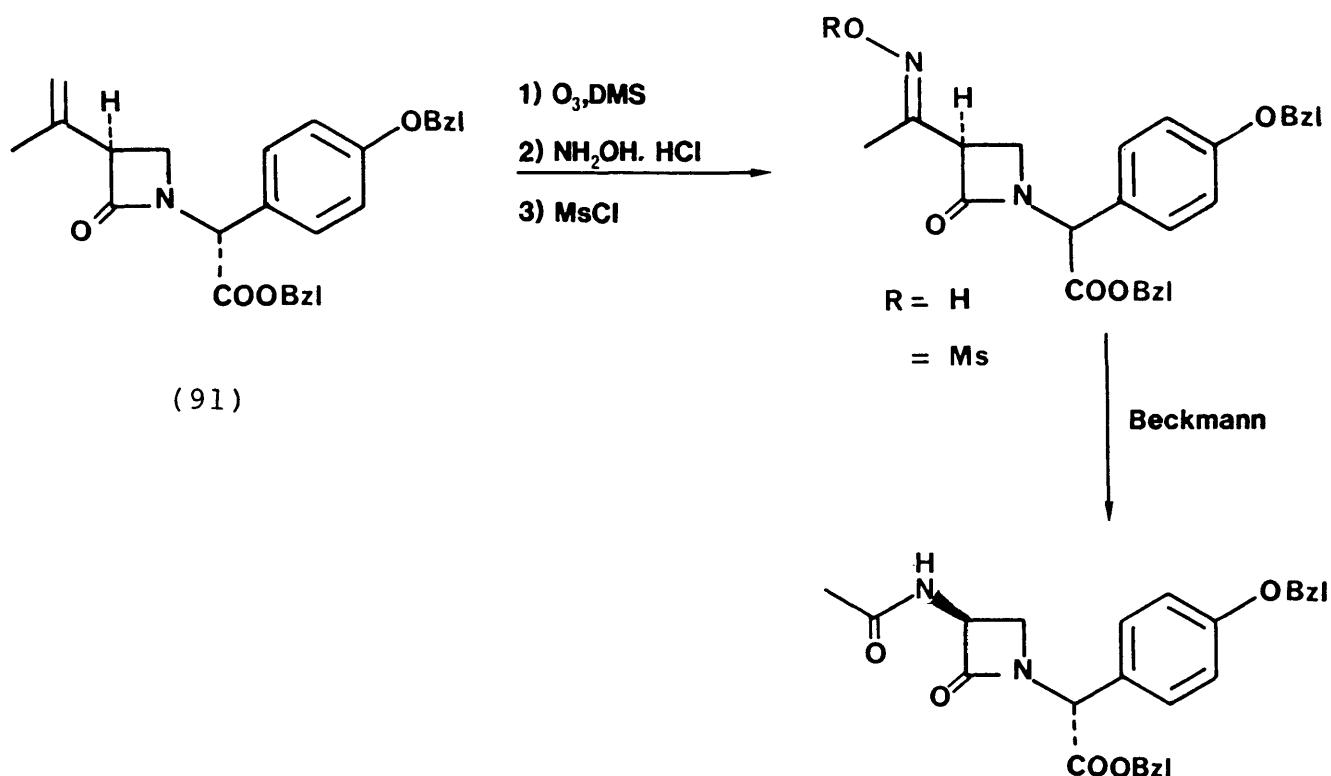


Close inspection of (-)-3-aminonocardicinic acid itself suggest that this key intermediate could be conveniently synthesised using our novel organoiron methodology. This approach appears to be particularly attractive in view of the facility with which nitrogen substituents can be introduced via the π -allyltricarbonyliron lactam complexes. In conjunction with a suitable strategy for the degradation of the alkenyl side chain at C₃, this should constitute a concise synthesis of (-)-3-ANA in its optically pure form.

Earlier observations had shown that the isopropenyl substituted β -lactams (90) and (91) were available in high yield from isoprene monoepoxide by way of a three step process⁶⁵. The tricarbonyliron lactone precursor (6) was prepared in the usual manner by treatment of isoprene monoepoxide with diiron nonacarbonyl in THF. The requisite, suitably protected N-substituent could then be introduced in its entirety by reaction of the ferrilactone with the dibenzylated derivative of D-(-)-*p*-hydroxyphenylglycine (87) in the presence of ZnCl₂.TMEDA. The diastereomeric ferrilactam complexes, (88) and (89), were isolated in 95% combined yield and oxidation of the individual isomers, which were readily separable by column chromatography, gave excellent yields of the required β -lactams (90) and (91). Two possible routes to (-)-3-ANA could then be envisaged. The first, and most direct approach would be to introduce the amino group at C-3 by means of a Beckmann-type rearrangement. Such a process would exploit the existing chirality of the 3 β -substituted azetidinone.

However, since the rearrangement would be expected to proceed with retention of configuration, the availability of (-)-3-ANA becomes limited by the supply of (3S)- β -lactam (91). This approach was later

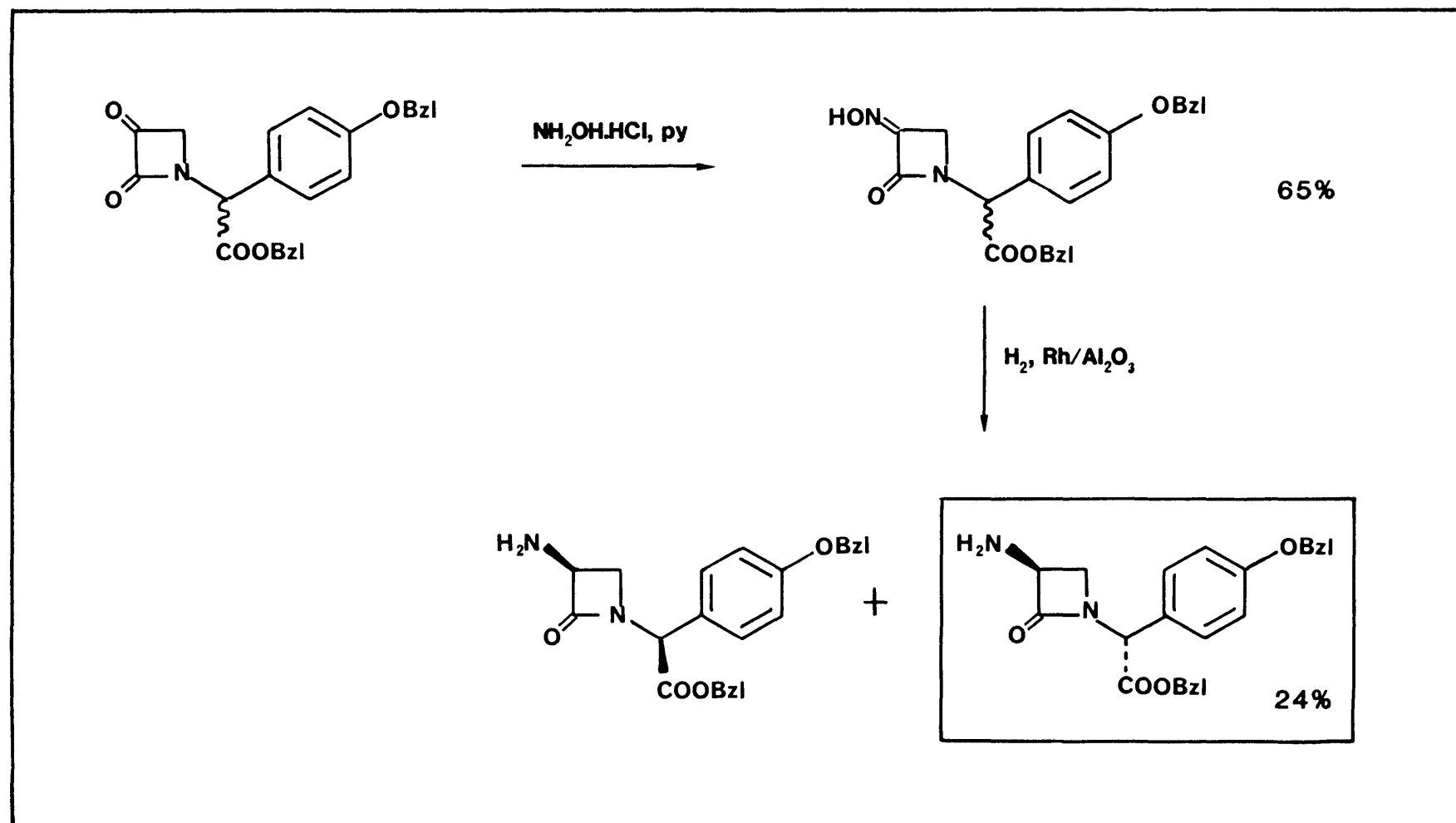




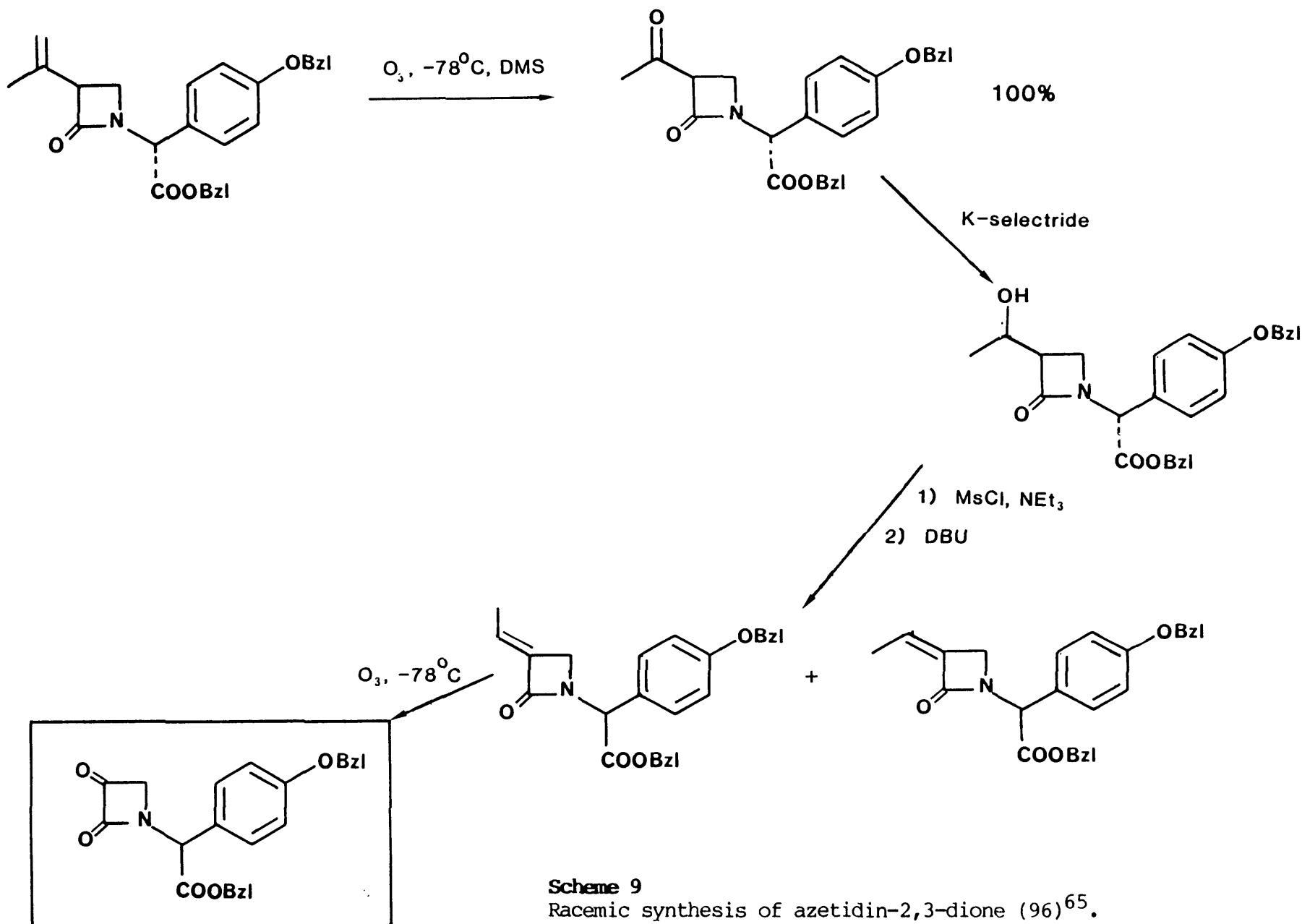
abandoned when model studies showed that none of the oximes prepared could be induced to rearrange in the desired manner⁶⁵. This was attributed to the reluctance of the β -lactam nucleus to stabilise a partial positive charge at C-3 in the transition state for migration.

The alternative approach was to prepare the azetidin-2,3-dione (86), which could then be converted to (-)-3ANA by means of a reductive amination sequence. Ban *et al* had already demonstrated the feasibility of such an approach in their synthesis of the racemic material⁷⁴ (Scheme 8).

Degradation of the isopropenyl side chain was carried out in the following manner (Scheme 9): low temperature ozonolysis of the isopropyl β -lactams gave the corresponding 3-acetyl derivatives (92) and (93) in quantitative yield. Reduction with K-selectride or zinc borohydride gave the hydroxyethyl substituted compounds and subsequent mesylation and regiospecific elimination with DBU gave a mixture of E



Scheme 8
Racemic synthesis of 3-aminonocardicinic acid **74**.

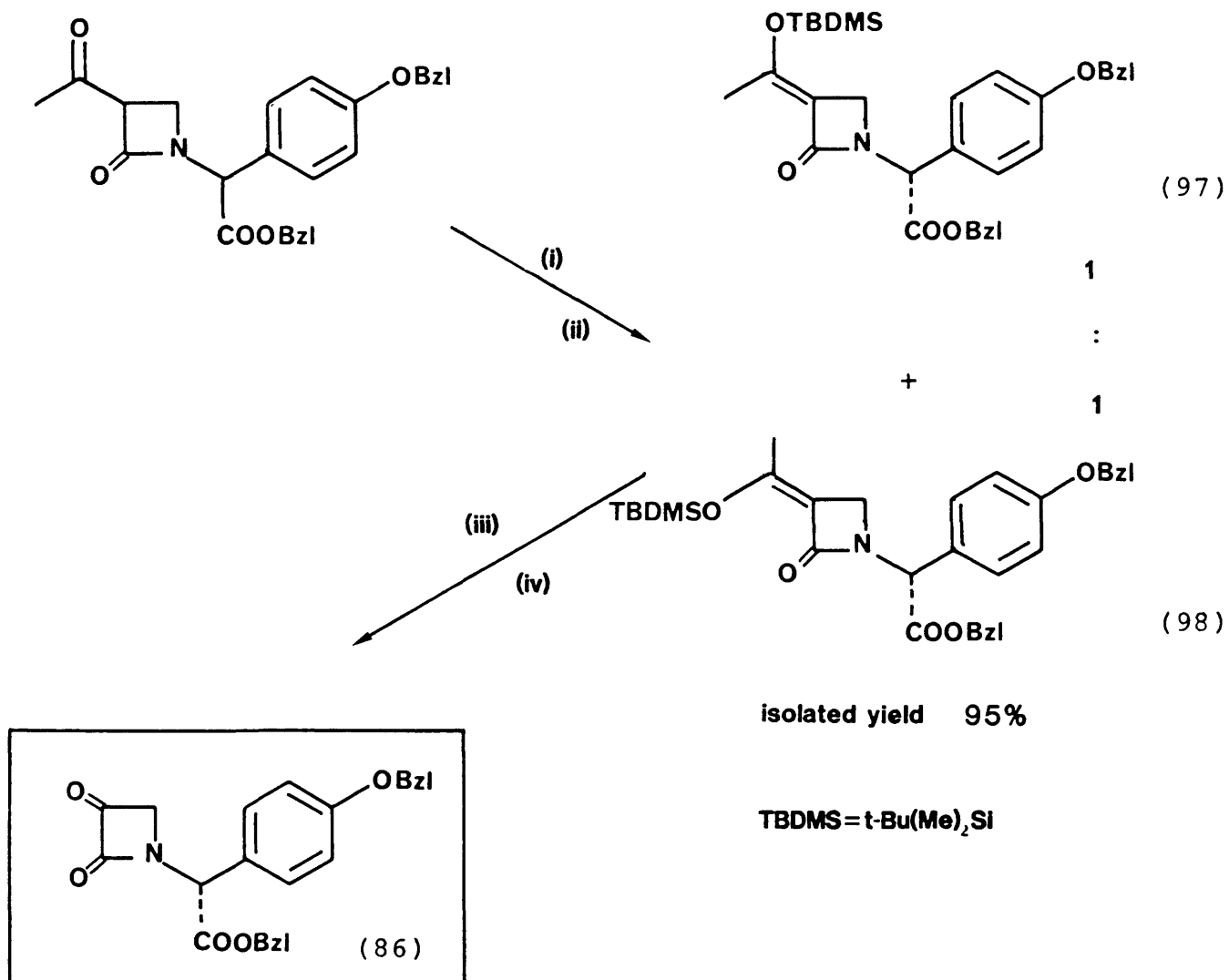


and Z-enelactams, (94) and (95). However, polarimetry measurements at this point showed that racemisation had occurred at the benzylic centre and ozonolysis of the mixture gave the racemic azetidin-2,3-dione⁶⁵. The base lability of the proton at this activated benzylic position has been commented on a number of times; but extensive investigations failed to unearth alternative conditions for effecting the elimination of the mesylates without epimerisation of the chiral centre.

The third strategy was suggested as a result of the following observations. Formation of the 3-acetyl derivatives occurs stereoselectively in the first instance; however, storing the individual diastereoisomers at 0°C overnight resulted in epimerisation at C-3. Investigations showed that the labile C-3 proton could be removed by treatment with triethylamine at 0°C. Furthermore, these conditions were mild enough to prevent epimerisation at the sensitive benzylic centre. Silylation of the resultant enolate anion with t-butyldimethylsilyltriflate led to regiospecific formation of the diastereoisomeric silyl enol ethers, (97) and (98), in virtually quantitative yield.

Isolation of these compounds is unnecessary since low temperature (-78°C) ozonolysis of the crude reaction mixture, followed by reductive work-up, gave the optically pure (-)-azetidin-2,3-dione (86) in 84% yield. Taken in conjunction with previous results, we have now shown that optically pure (-)-3-ANA is available in five steps from isoprene monoepoxide. The whole sequence proceeds in a remarkably high 79% overall yield.

Since the azetidin-2,3-dione (86) has been converted to 3-ANA and hence the nocardicins themselves, this new route should be considered as potential enantioselective synthesis of these systems.



overall yield 88%

$[\alpha]_D^{29} -33.2^\circ$ (c, 0.46 in CHCl₃)

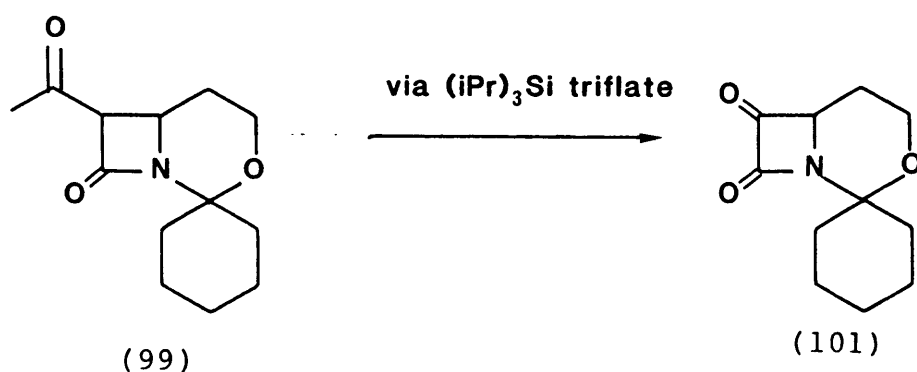
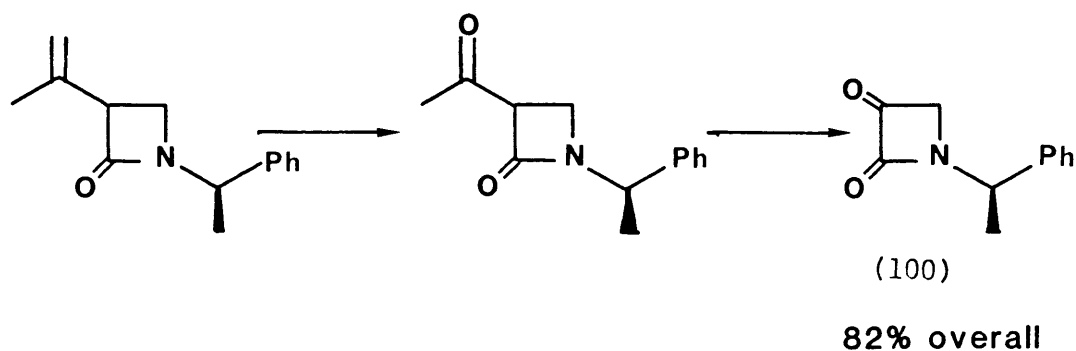
(i) NEt₃, 0°C

(ii) t-Bu(Me)₂Si triflate

(iii) O₃, DCM, MeOH, -78°C

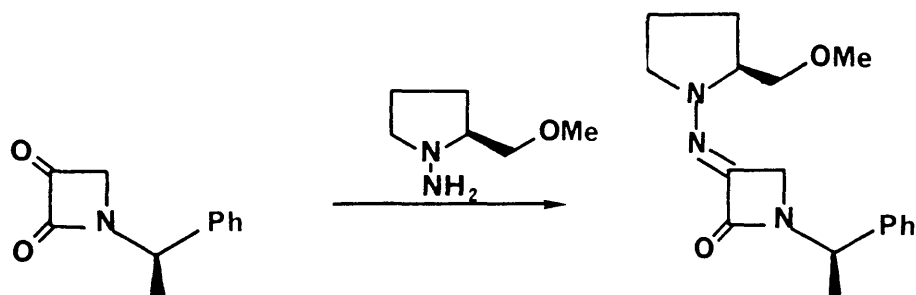
(iv) Zn, AcOH

We then turned our attention to the problems associated with reductive amination of the azetidin-2,3-dione. As previously described, Ban *et al*⁷⁴ had achieved this by formation of the oxime followed by hydrogenation in the presence of a rhodium catalyst⁷⁴. However, the overall yield of this two step process was only a little over 15% and so we decided to carry out a brief investigation into other methods of achieving this transformation. Hence, in order to achieve sufficient quantities of material with which to carry out our investigation the 3-isopropyl substituted β -lactams, (77) and (78), and the acetyl derivative (99)⁷⁷ were transformed into the equivalent azetidin-2,3-diones using the procedure described.

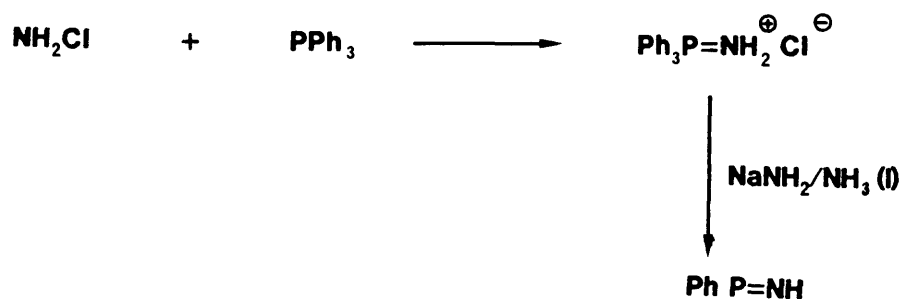


Both reactions proceeded smoothly and the method appears to be generally applicable to the synthesis of azetidin-2,3-diones. However, the tricyclic β -lactam (101) was not inordinately stable and so attention was focused on the simple alkylamino azetidin-2,3-dione (100). Our initial plan was to condense the 3-keto lactam with a chiral hydrozone on the basis that it might induce an element of

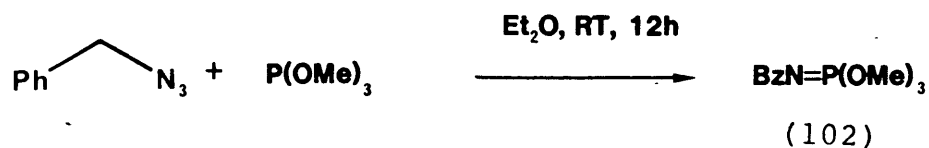
diastereoselectivity into the reduction of the intermediate imine. However, all attempts at condensation of the azetidin-2,3-dione with (S)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP), the chiral hydrazone developed by Enders and co-workers⁷⁸, failed to produce any of the desired imine. Hence, we abandoned this approach and turned



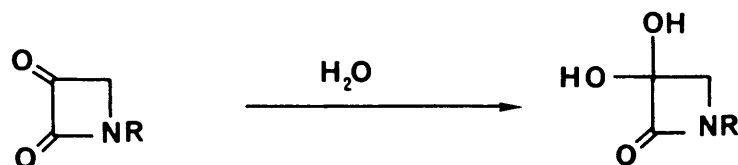
our attention to the iminophosphorane reagents developed by Apfel and co-workers some years ago⁷⁹ which demonstrates a literature precedent for the formation of amines via the reaction of $\text{Ph}_3\text{P}=\text{NH}$ with carbonyl compounds. Reduction of the intermediate imine is then achieved by hydrogenolysis in the presence of Raney nickel. the hydrochloride salt of the iminophosphorane is formed by reaction of monochloroamine with triphenylphosphine. The free reagent is then liberated by treatment with sodamide in liquid ammonia⁸⁰.



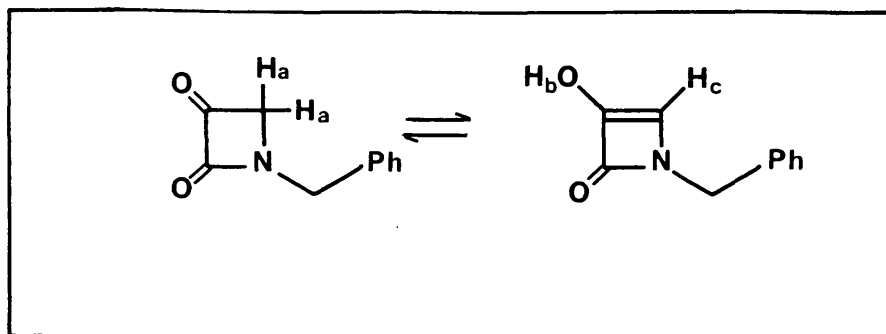
However, reaction of this iminophosphorane and the related benzyl derivative (102) with the azetidin-2,3-dione (100) failed to give any



of the desired product. This unfortunate lack of reactivity can be rationalised in two ways. Firstly, models of the azetidin-2,3-dione nucleus indicate that the system is extraordinarily strained and we have noticed, in common with workers at Beecham Pharmaceuticals⁸¹, that hydration of the azetidin-2,3-dione occurs extremely rapidly. The driving force for this reaction is presumably the release of ring



strain on regeneration of the sp^3 centre at C-3. Secondly, the 250MHz $^1\text{Hnmr}$ spectrum of the azetidin-2,3-diones in deuteriochloroform indicate the presence of a substantial proportion of the enol tautomer (103). This was also noted by Ban *et al*⁶⁴ who reported that the spectrum of the *N*-benzylazetidin-2,3-dione in carbon tetrachloride was substantially different from that obtained in $\text{CD}_3\text{OD}-\text{CD}_3\text{COD}_3-\text{CDCl}_3$ mixtures. On close examination, they concluded that the compound existed as a 1:1 mixture of keto and enol tautomers in carbon tetrachloride solution.



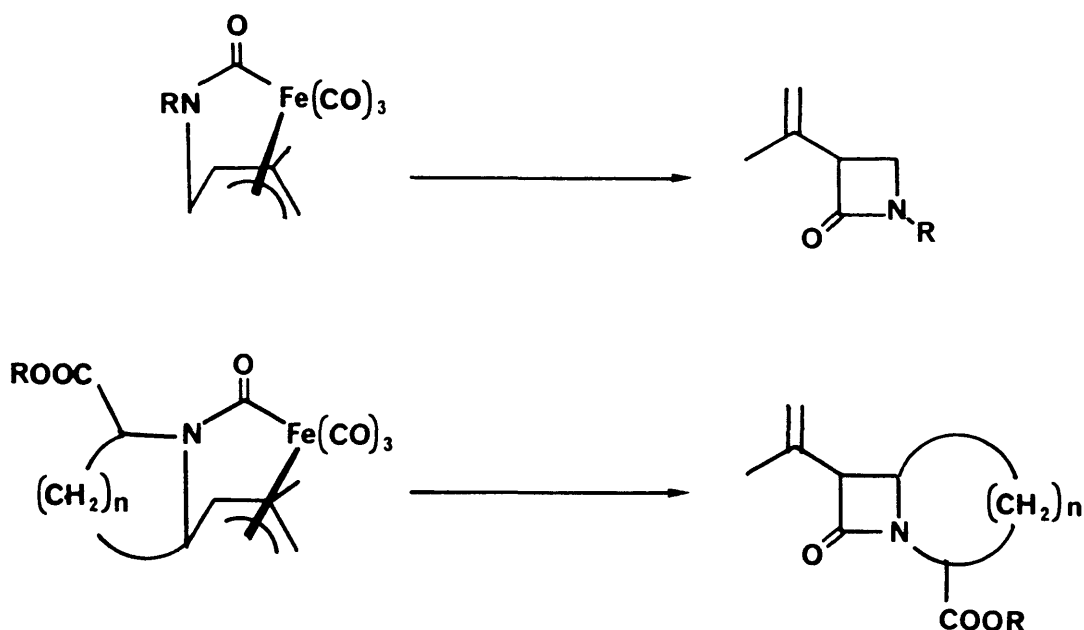
<u>CD₃OD-CD₃OCD₃-CDCl₃</u>	<u>CCl₄</u>
3.30 (s, 2H, <u>H_a</u>)	3.24 (s, 1H, <u>H_a</u>)
4.45 (s, 2H, <u>CH₂</u> Ph)	3.71 (s, 1H, <u>CH₂</u> Ph)
	4.40 (s, 1H, <u>CH₂</u> Ph)
	4.72 (s, 1H, <u>H_c</u>)
	6.25 (brs, 1H, <u>H_b</u>)

However, this effect is not seen in the case of the azetidin-2,3-dione (86) which appears to exist entirely in the keto form. Nevertheless, our attempts at formation of (-)-3-ANA met with little success.

2.9 Attempted formation of a carbapenem via tricarbonyliron(lactam) complexes

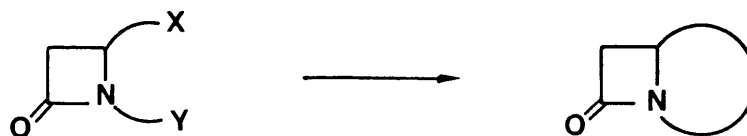
Until recently, most of the pharmaceutically important β -lactam antibiotics were characterised by the presence of a common nucleus; that is, a β -lactam ring fused to a five or six-membered sulphur-containing ring. This system is common to all the penicillin and cephalosporin antibiotics and numerous routes have been developed for the formation of such compounds. Recent developments have shown that the oxygen and carbon analogues of these compounds are also potent antibiotics and strategies for their synthesis are currently attracting a great deal of interest.

We have demonstrated that monocyclic β -lactams are readily available by cerium (IV) oxidation of ferrilactam complexes. Hence, we were intrigued to know whether bicyclic β -lactams could be obtained from the analogous complexes in which the amine functionality was attached to the terminus of the π -allyl system.

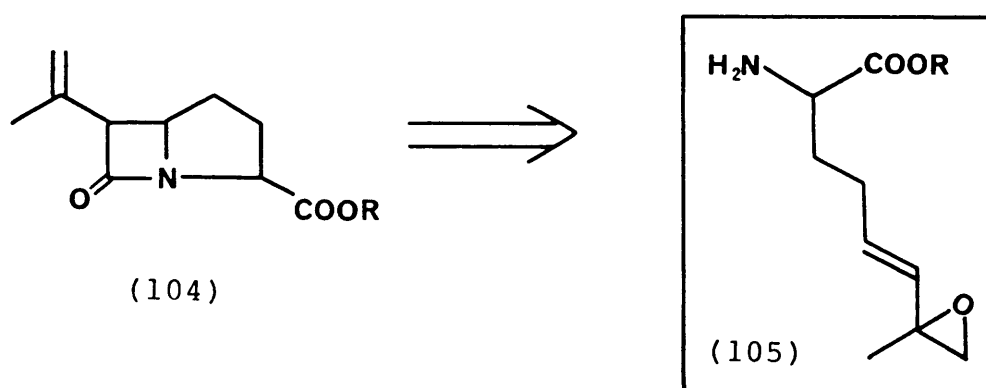


Examination of the available literature shows that such a strategy is unprecedented and most published syntheses rely on formation of a

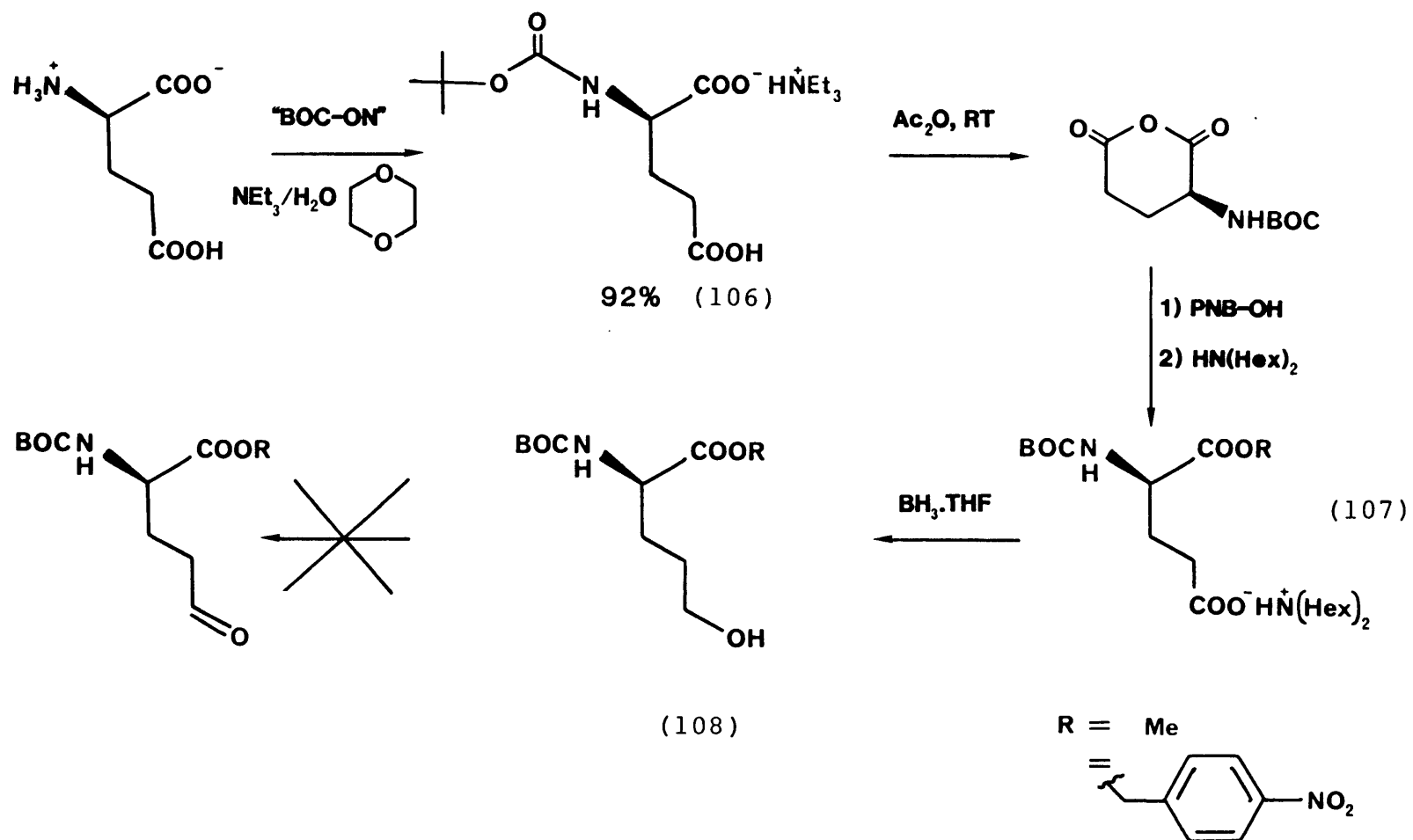
suitably substituted monocyclic β -lactam. Subsequent ring closure then gives the bicyclic system.



In order to test our hypothesis, we chose to attempt the synthesis of the carbapenem (104) shown below. The reasons for this choice are two-fold.



Firstly, the model compound is closely related to the powerful antibiotic thienamycin. Secondly, the presence of the C-6 ester group suggest that the compound could be derived from the vinyl epoxide (105), which should, in its turn, be available from glutamic acid. This would also allow predetermination of the stereochemistry at C-6, since both (D) and (L)-Glutamic acid are commercially available. Initial investigations quickly demonstrated that suitable protecting groups for the α -amino acid would have to be found owing to the complete insolubility of glutamic acid in any organic solvent! Hence, the *t*-butyloxycarbamate (BOC) derivative (106) was prepared by treatment of the triethylamine salt of glutamic acid with "BOC-ON", 2-*t*-butyloxycarbonyloxyimino-2-phenylacetonitrile⁸³ (Scheme 10). Freeze drying the aqueous extract gave the *N*-protected amino acid in 92% yield as its mono-triethylamine salt, as indicated



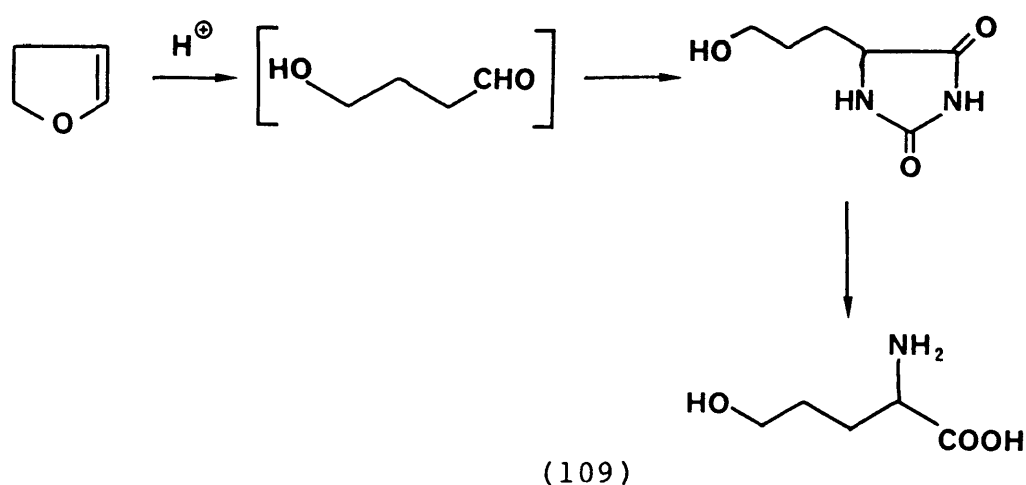
Scheme 10
Preparation of diprotected amino acid alcohol from L-glutamic acid.

by the FAB spectrum of the compound in glycerol and the characteristic infrared stretches indicating the presence of an α -carboxylate anion (1591 and 1394 cm^{-1}) and that at 1700 cm^{-1} due to the carbonyl stretch of the free carboxylic acid.

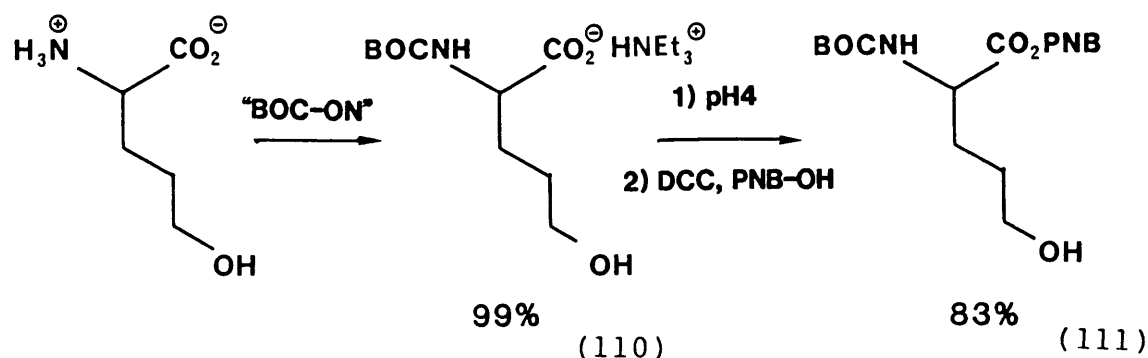
Treatment of the amino acid with acetic anhydride followed by *p*-nitrobenzyl alcohol gave the diprotected amino acid (107), which was isolated as its dicyclohexylamine salt⁸⁴. The reaction proceeds via the 6-membered anhydride and gives the α -aminoacid ester as the sole product of the reaction as a result of attack at the most electron deficient centre.

Protonation of the carboxylate anion gave the free carboxylic acid, which was reduced by treatment with borane.THF⁸⁵ to give the diprotected amino acid alcohol (108).

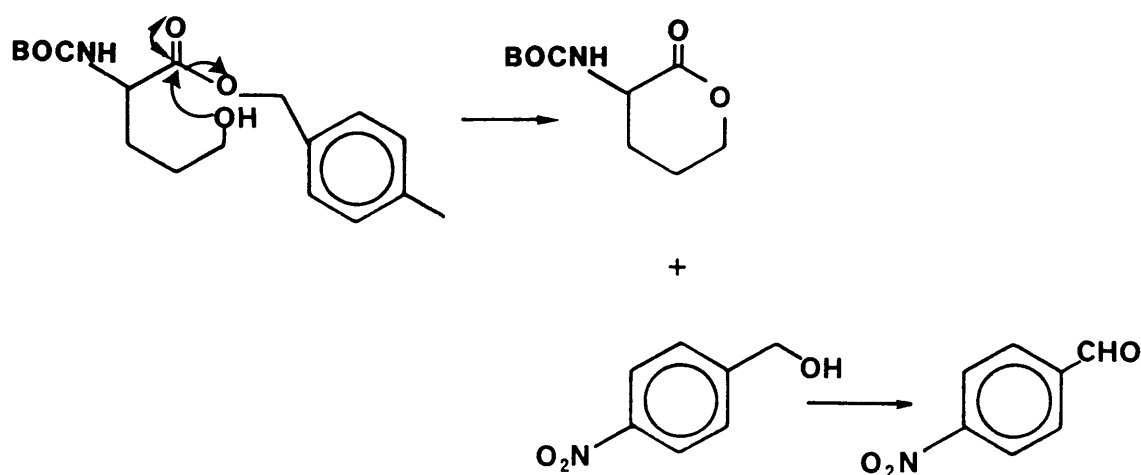
In addition, large quantities of the racemic material were available by diprotection of the amino acid alcohol (109) which had been prepared via a Strecker-type synthesis⁷⁷.



The amino function was then protected as its BOC-derivative (110) and the carboxylic acid esterified by condensation with *p*-nitrobenzyl alcohol in the presence of dicyclohexylcarbodiimide (DCC), (111)⁸⁶.



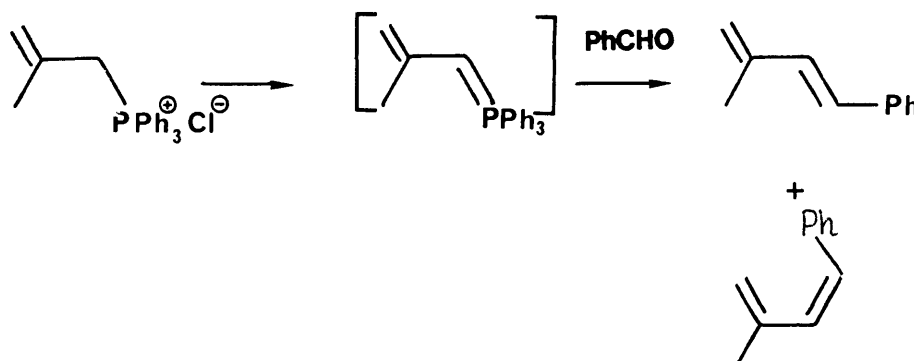
However, oxidation of the primary hydroxyl group proved to be far from trivial and use of $\text{CrO}_3 \cdot 2\text{py}$, pyridinium dichromate, pyridinium chlorochromate and oxalyl chloride/DMSO³³ produced large amounts of *p*-nitrobenzaldehyde accompanied by starting material or the corresponding δ -lactone, depending on the work-up conditions



employed. Given the strength of the driving force for formation of the six-ring lactone, a number of oxidation systems involving prior derivatisation of the free hydroxyl were examined. For example, formation of the tosylate followed by oxidation with trimethylamine N-oxide is reported to give good yields of aldehyde⁸⁷. However, in our hands displacement of the tosylate predominated and none of the desired aldehyde could be isolated. Similarly, formation of the boron ester⁸⁵ followed by oxidation with PCC⁸⁸ failed to give any of the aldehyde and resulted in extensive decomposition of the reaction mixture.

In anticipation of a solution to this problem we turned our attention to the problems associated with the synthesis of conjugated dienes via Wittig methodology. A survey of the literature indicates that yields for these reactions are extremely modest - commonly between 10 and 30%. A brief investigation showed that deprotonation of the phosphonium chloride occurred extremely slowly using *n*-butyllithium and quenching with benzaldehyde gave a meagre 8% of the diene. The yield obtained using lithium diisopropylamide was considerably higher (79%); however, close observation suggested that the insolubility of the phosphonium salt in THF was a major barrier to the formation of the Wittig reagent. Ultrasound is well known for its ability to

Table 7

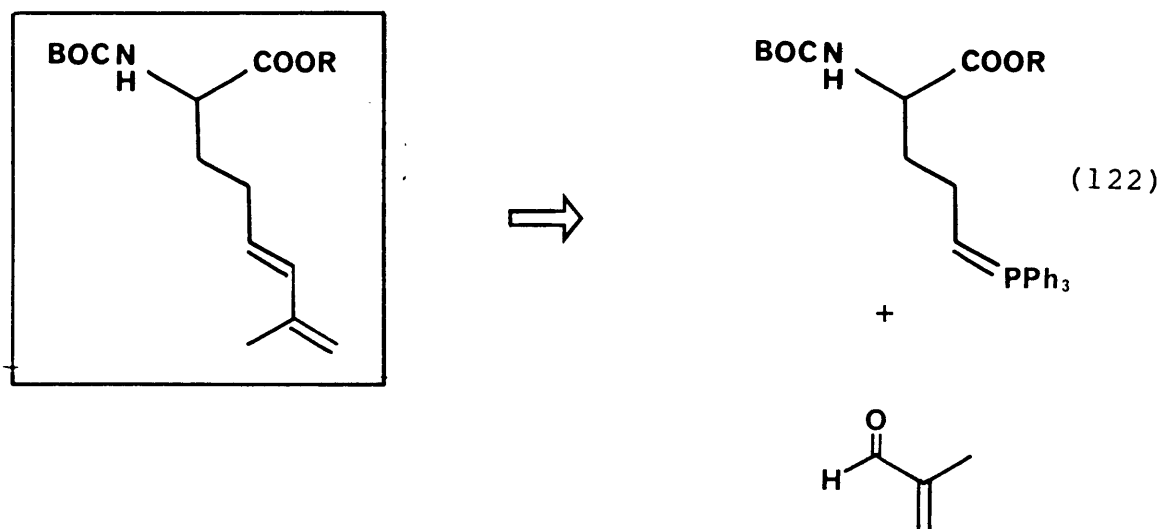


Deprotonation conditions	Yield of diene	Ratio of cis : trans diene
1. <i>n</i> -BuLi/RT/20h	8%	1 : 1
2. LDA/RT/2h	79%	1 : 2.3
3. <i>n</i> -BuLi/))) /1h	91%	2 : 3

promote dispersion of solids in heterogeneous systems and so we decided to examine whether sonication of the reaction mixture would promote deprotonation of the phosphonium salt in this case. We

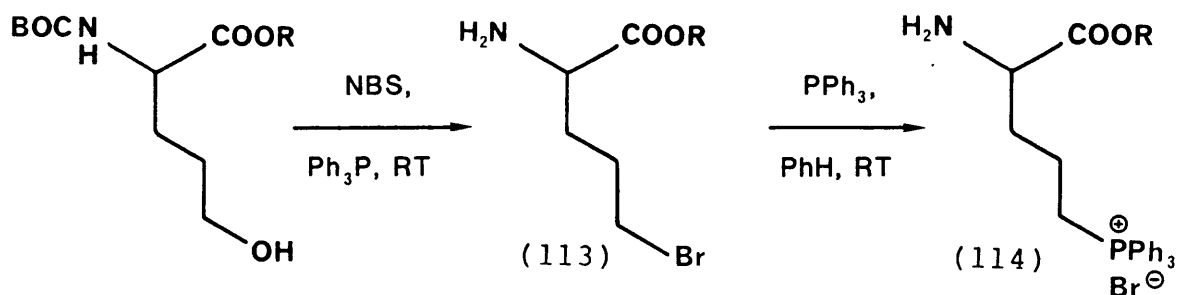
repeated the experiment (entry 1) in the presence of ultrasonic radiation and found that formation of the deep red Wittig reagent was complete after 1h. To our delight, quenching the reaction mixture with benzaldehyde gave a remarkable 91% yield of the cis and trans dienes in a ratio of 2:3. This represents a substantial improvement on any of the available literature methods, relieves us of the need to preform LDA in situ, and produces a degree of selectivity in favour of the E,E-diene. Hence, this appears to be the method of choice for isoprenylation of aldehydes via Wittig methodology although its general applicability to the synthesis of conjugated dienes remains untested.

In view of the problems encountered in preparation of the required amino acid aldehyde, we decided to reverse our original strategy, that is to couple the Wittig reagent derived from the amino acid alcohol

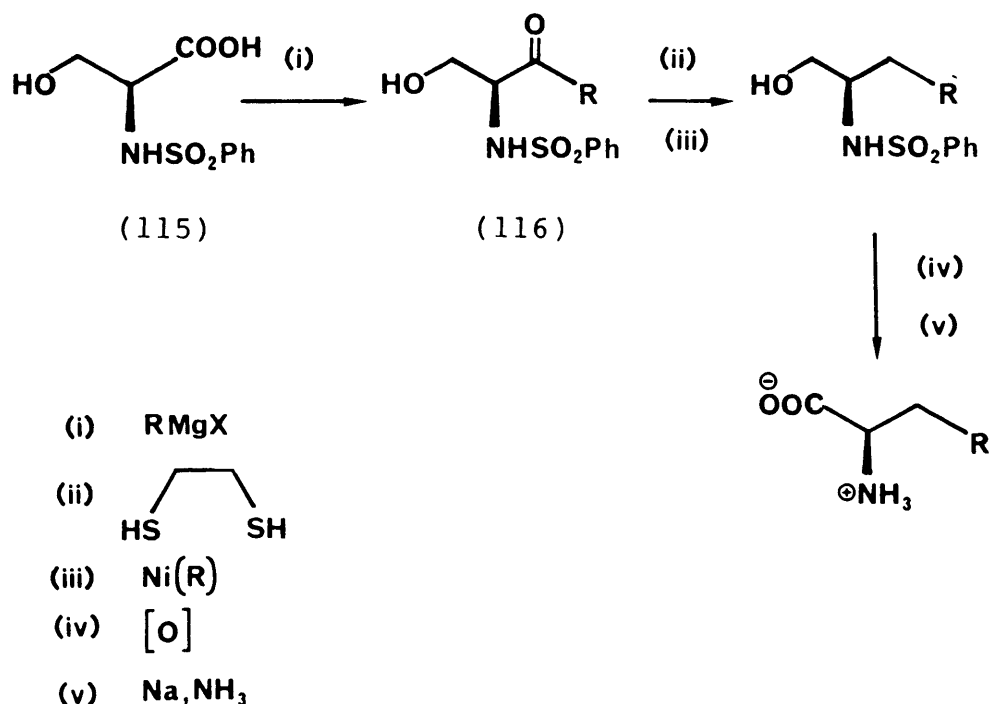


(111) with methacrolein. Bromination of the amino acid alcohol was effected with N-bromosuccinimide (NBS) in the presence of triphenylphosphine⁸⁹. However, reaction under these conditions also removed the BOC-protecting group and gave the free amine (113), probably due to contamination of the NBS by residual hydrogen bromide.

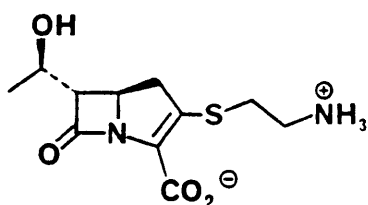
Nevertheless, treatment with triphenylphosphine in benzene gave the phosphonium bromide as a white crystalline solid. Unfortunately, this line of enquiry was terminated by the discovery that treatment of the phosphonium bromide with two equivalents of *n*-butyllithium at -78°C led to the formation of a pungent red colour that was not dispelled by addition of the aldehyde and appeared to be indefinitely stable at room temperature! This is presumably due to formation of a stable radical by reaction with the *p*-nitrobenzyl ester which dominates the reactivity of this system.



Once again, this demonstrates the unsuitability of the *p*-nitrobenzyl protecting group, and although the route described can be readily adapted to accommodate alternative ester groups we decided to investigate a number of alternative routes to the desired amino acid.



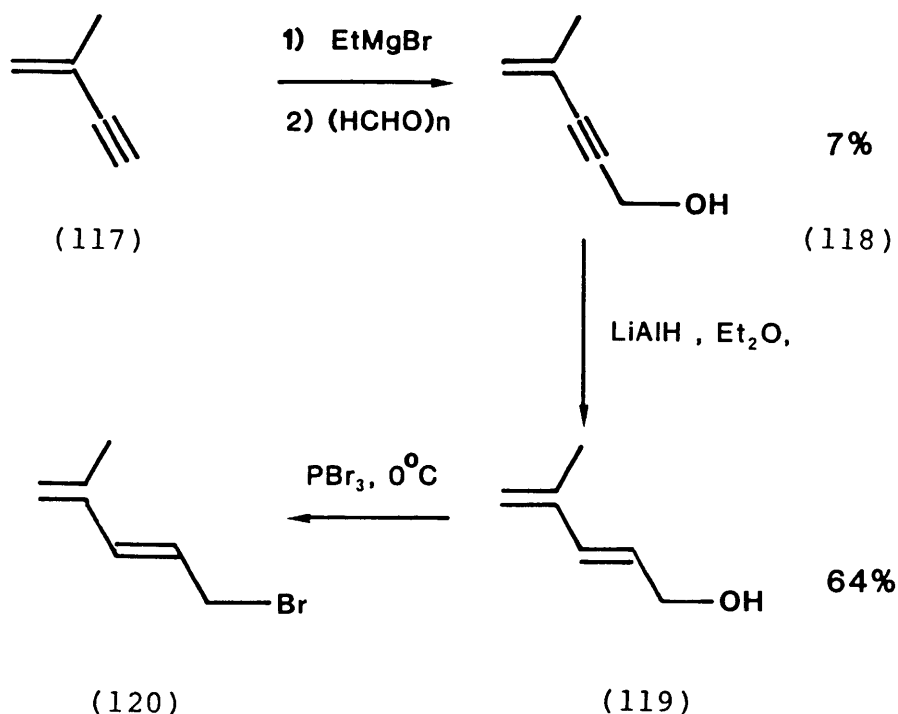
In particular, we were attracted by a recent publication describing the stereospecific preparation of L-amino acids from D-serine⁹⁰. The route, as summarised above, would appear to incorporate a number of features which could be exploited to our advantage - not least that naturally occurring D-serine is considerably cheaper than the commercially available L- α -amino acids. This is of importance in view of the fact that the stereochemistry at C-6 of the naturally occurring penicillins and cephalosporin antibiotics is the same as that found in the L-series of α -amino acids. Secondly, preparation of thienamycin analogues would be facilitated by the presence of the C-3 carbonyl group present in the initial adduct (116). This would allow



introduction of suitable side chains at the position which corresponds to C-5 in the carbapenem system. Thirdly, we foresaw that a number of the problems encountered whilst working with α -amino acids could be avoided if oxidation of the serine hydroxyl was left to a later stage of the synthesis. In conclusion, this would appear to be an ideal route for stereospecific synthesis of the required substrate. This was reinforced by preliminary investigations that demonstrated that the N-phenylsulphonyl protecting group could be removed in the presence of a ferrilactone complex. The original procedure had used sodium in liquid ammonia to effect this transformation. However, N-phenylsulphonyl groups can also be removed in the presence of sodium naphthalide (SN)⁹¹. This latter reagent is readily available by sonolysis of a mixture of sodium and naphthalene in THF⁹². Treatment of a cooled (-78°C) solution of N-phenylsulphonyl serine and ferrilactone (8) with the dark green solution of sodium naphthalide

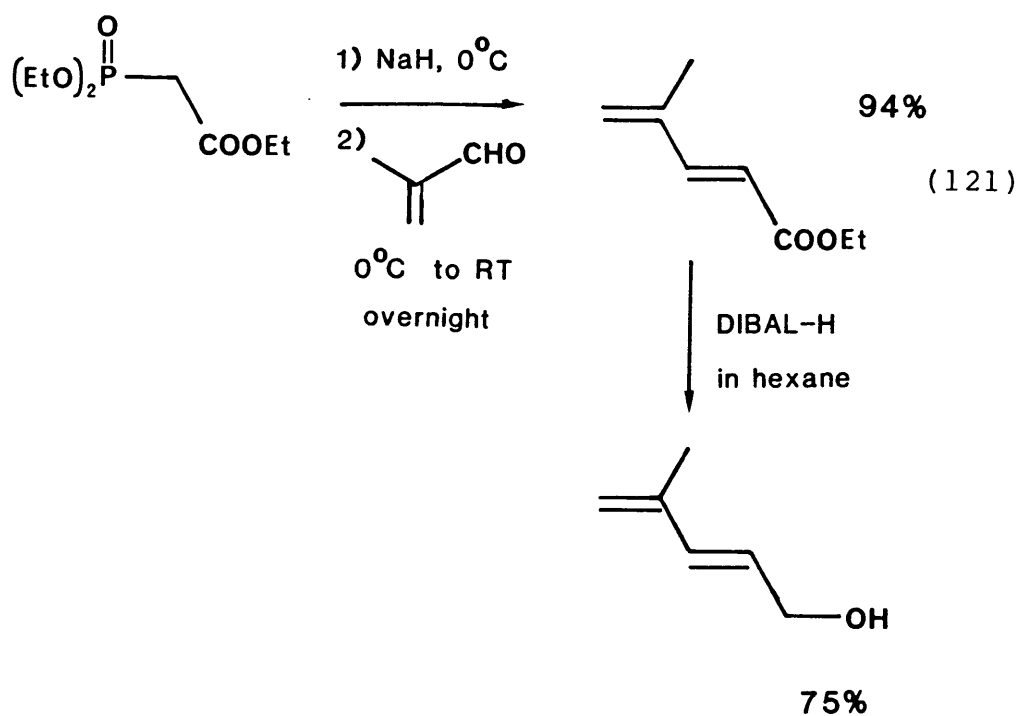
led to quantitative desulphonylation of the amino acid and isolation of 80% of the unchanged ferrilactone complex.

This encouraging result directed us towards preparation of a suitable Grignard reagent with which to effect the initial coupling reaction. Preparation of 1-bromo-4-methylpenta-2,4-diene (120) has been described by Ollis *et al*⁹³ who derived the dieneol precursor from 2-methylbut-3-en-1-yne (117) in the manner shown below. However, the

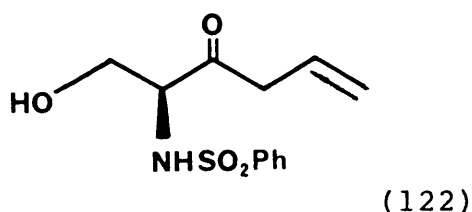


published procedure gave a disappointing yield of dieneol (119) in our hands and Wadsworth-Emmons condensation of methacrolein with diethylphosphonoacetate, followed by DIBAL-H reduction of the intermediate diene ester (121) provided a more reliable route to the required dieneol.

The dieneol obtained in this manner was then treated with phosphorus tribromide using the literature procedure⁹³. The authors have remarked upon the instability of the bromide and its tendency to



rearrange on standing or attempted purification. With this in mind, the crude bromide was used directly to prepare the Grignard reagent. Disappointingly, the reaction with N-phenylsulphonyl serine under the conditions described by Rapoport *et al*⁹⁰ failed to produce any of the desired adduct. In contrast, reaction with the Grignard reagent derived from 1-bromoprop-3-ene proceeded smoothly to give the adduct (122) under identical conditions.



This unfortunate result is most probably due to the problems associated with bromination of the dieneol. However, reaction could not be effected using the product derived from bromination with NBS/triphenylphosphine, suggesting that it may also be connected with inherent instability of allylmagnesium halides. Oppolzer and Schneider⁹⁴ have reported that these problems may be overcome by

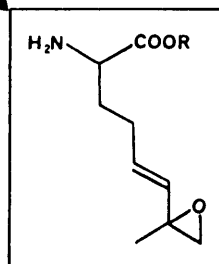
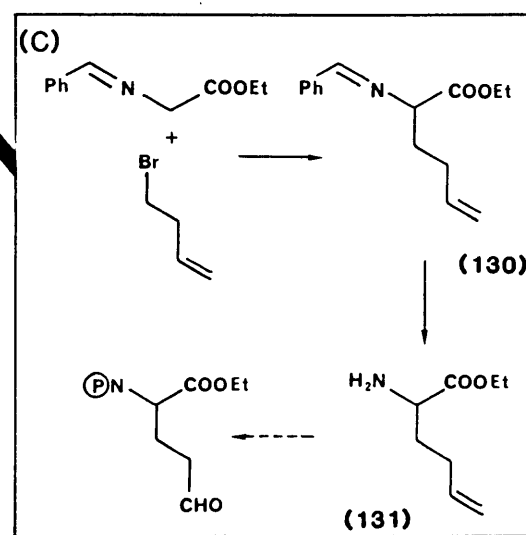
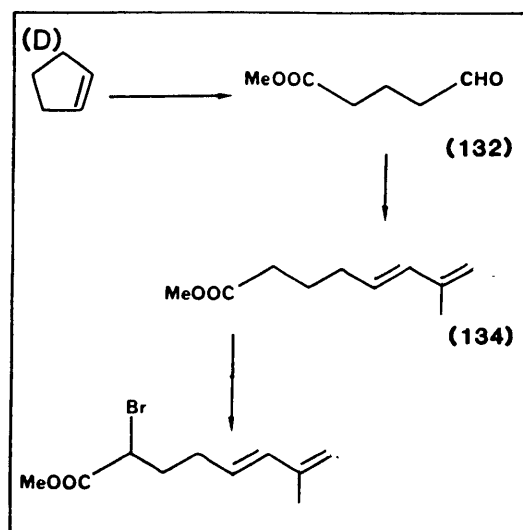
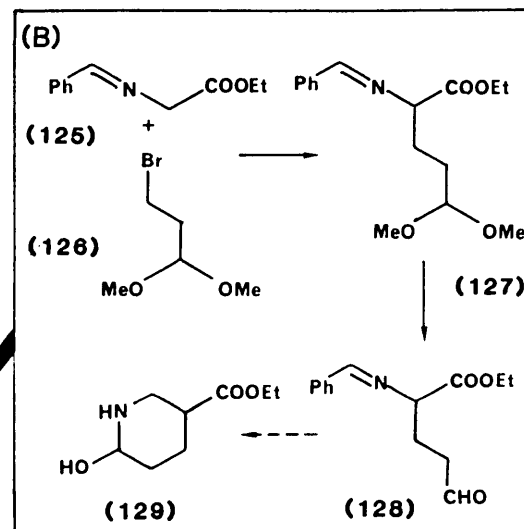
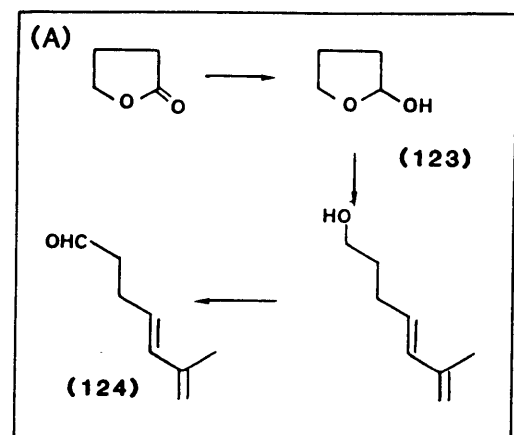
reaction with activated magnesium in the form of ultrasonically generated (anthracene).Mg.3THF⁹⁵ (see 1.7). However, lack of time precluded further investigation into this promising route which should ultimately lead to the highly functionalised substrate required to complete this investigation.

(b) Approaches to the synthesis of a racemic substrate for the preparation of a model carbapenem via a ferrilactam complex

There are a number of literature methods for the preparation of novel α -amino acids. However, with few exceptions, most are not diastereoselective and can only be used to prepare racemic substrates. Of these, the oldest and most routinely used is the Strecker synthesis, and initial attempts at preparation of a racemic model compound centred around preparation of the diene aldehyde (124). This would appear to be readily available from butyrolactone via the route indicated (Route A). However, yields of the volatile lactol (123) could not be made to exceed 25%. Furthermore, reaction with the Wittig reagent could only be carried out using freshly prepared material owing to the pronounced tendency of the lactol to dehydrate. As a result, overall yields of the diene aldehyde (124) were disappointingly low and reaction with sodium cyanide via the bisulphite addition product of the aldehyde failed to produce any of the desired amino acid.

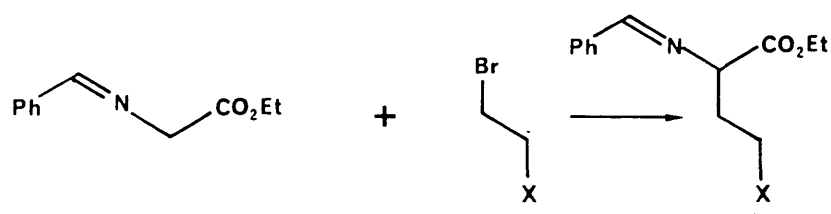
Hence, we turned our attention to the recently developed methods for the preparation of racemic α -amino acids via alkylation of glycine. These generally involve deprotonation of the Schiff's base (125), followed by reaction with an alkyl halide. This suggests that the amino acid aldehyde (128) should be available by alkylation with the dimethylacetal of 3-bromopropanal (126) followed by acidic deprotection of the aldehyde function (Route B). Alternatively, the masked aldehyde can be introduced as the olefin (131) and released when necessary by low temperature ozonolysis (Route C).

The diprotected glycine common to both routes is readily available from the commercially available glycine ethyl ester⁹⁶ by condensation



with benzaldehyde in the presence of triethylamine.

The dimethylacetal of acrolein was then treated with anhydrous hydrogen bromide to give the alkyl bromide (126)⁹⁷. The conditions originally described for the alkylation of the glycine derivative (124) advocated deprotonation by treatment with LDA in the presence of HMPA⁹⁶. However, reaction under these conditions gave a mixture of products, none of which was identifiable as the amino acid (127). Conversely, deprotonation with potassium carbonate in DMF gave a 30% yield of the alkylated product which could be increased to 70% if potassium t-butoxide was employed in its place. Similarly, the amino acid (130) could be generated by coupling the glycine moiety (125) to 1-bromobut-4-ene, although reaction under the phase transfer conditions described by M.J. O'Donnell¹⁰² failed to effect any reaction.

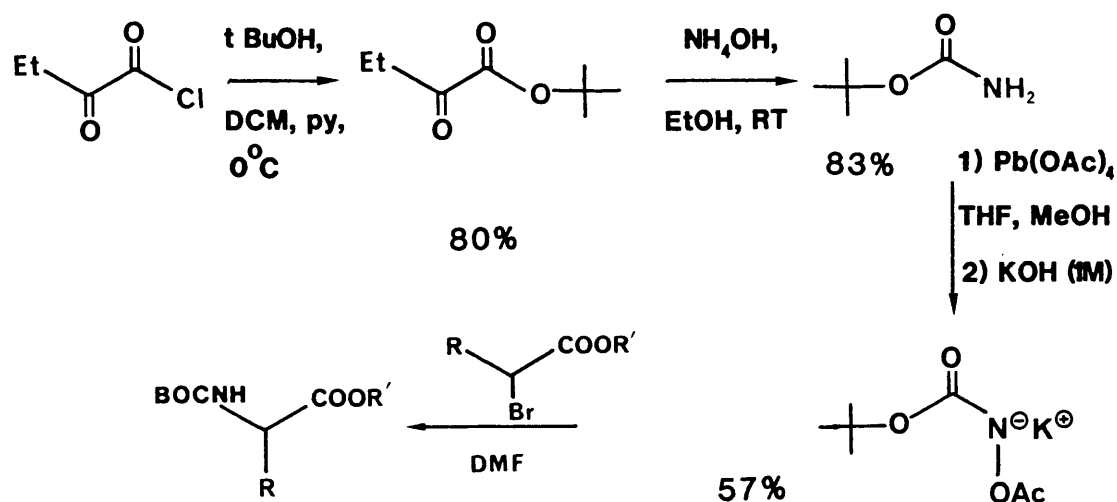


Conditions used	% Yield	
	X=(MeO) ₂ C	X= CH=CH ₂
1. LDA, HMPA, -78°C	0	-
2. K ₂ CO ₃ , DMF, 0°C to RT	30	20
3. KO <u>t</u> Bu, -78°C	70	70
4. 10% NaOH (aq), DCM, <u>t</u> -Bu ₄ NH ₄ I	-	0

Having developed a route to the tri-protected amino acid aldehyde,

removal of the dimethylacetal was attempted by treatment with a catalytic amount of camphor sulphonic acid (CSA). Unfortunately, treatment under these mild conditions resulted in preferential removal of the benzylidene group and spontaneous cyclisation of the unstable amino aldehyde gave the undesired δ -aminal (129). On the other hand, the *N*-benzylidene protected amino acid (130) was readily deprotected by treatment with 1M hydrochloric acid at 0°C. However, lack of time precluded thorough investigation of the type of nitrogen protecting group necessary to withstand the proposed ozonolysis reaction.

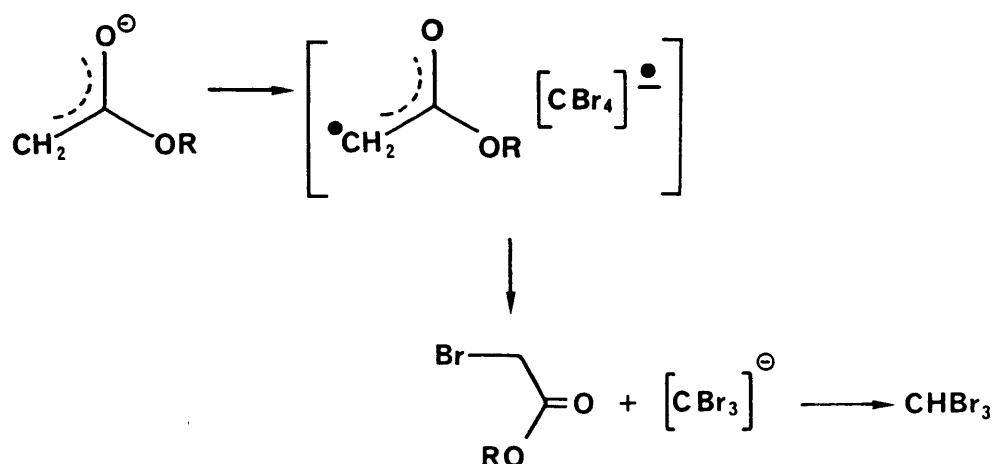
A more concise route was suggested by a short communication published in 1977¹⁰⁰. The required reagent was readily available from ethyloxalyl chloride by way of standard literature procedures^{100,101}.



A suitable strategy for the formation of the required α -bromoester from cyclopentene was then devised. Low temperature ozonolysis in the presence of sodium bicarbonate, followed by treatment with tosic acid and acetic anhydride/triethylamine had been reported to give a 70% yield of the ester/dimethylacetal¹⁰⁰. In our hands the reaction produced an 80% combined yield of the ester/aldehyde (132) and its dimethylacetal (133) in a ratio of 2:1. This is of interest in that the procedure was reported to be unsatisfactory for preparation of the unmasked aldehyde. The mixture obtained was converted to the aldehyde by treatment with Amberlyst-15 resin and isoprenylation proceeded

smoothly to give a 63% overall yield of the required diene ester (134).

A number of methods are available for bromination α to an ester; however, the presence of the diene functionality forced us to concentrate on those which exploit reaction of the enolate anion with



appropriate sources of bromine, such as carbon tetrabromide⁹⁹ and N-bromosuccinimide, that were least likely to brominate the diene. Disappointingly, reaction under these conditions failed to produce any of the desired α -bromoester and lack of time precluded further investigation of this route.

At this point we were forced to abandon this investigation. Most of the problems encountered are associated with the high degree of functionality present in the target molecule. For reasons previously discussed, the most promising route investigated would appear to be that derived from D-serine. This can also be counted amongst the most concise and will hopefully provide a source of material with which to test our original hypothesis.

CHAPTER 3 EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983G grating infrared spectrometer as a thin film, a chloroform solution or a KBr disc. ^1H nmr spectra were recorded at 60MHz on an EM-360, at 90MHz on a Jeol FX 90Q, and at 250MHz on a Bruker WM-250 instrument, and are quoted for solutions in deuteriochloroform with tetramethylsilane as an internal standard, except when stated otherwise. Mass spectra were measured on a VG micromass 7070B instrument. Elemental microanalyses were performed by the staff of the Imperial College Chemistry Department microanalytical laboratory, and optical rotations measured using an Optical Activity Ltd. AA-1000 polarimeter.

Analytical thin-layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F₂₅₄) and preparative chromatography was conducted under low pressure using MN Kieselgel 60 (230-400 mesh); silica gel refers to this grade of Kieselgel. Gas chromatography was carried out using a Perkin-Elmer, Sigma 3 machine.

Petrol refers to redistilled, 40/60° petroleum ether, and ether to diethyl ether. Ether and tetrahydrofuran were distilled from sodium-benzophenone under an argon atmosphere immediately prior to use. Anhydrous dimethylformamide was purchased from Aldrich Chemical Co. Ltd. and was used without further purification. Dimethylsulphoxide was dried by prolonged storage over 4 Å molecular sieves. Benzene and toluene were dried over sodium wire and toluene was distilled under an argon atmosphere before use. Dichloromethane was distilled from phosphorus pentoxide under an argon atmosphere immediately prior to

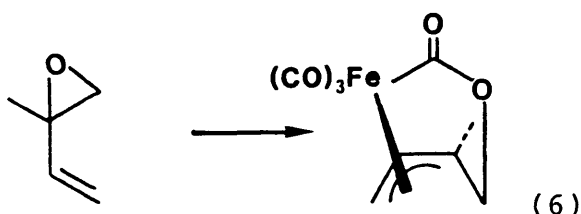
use and triethylamine was distilled from, and stored over, potassium hydroxide pellets, under argon. Ceric ammonium nitrate and chromium trioxide were dried in vacuo overnight. All other solvents and reagents were purified by standard methods. Solutions were dried over magnesium sulphate unless stated otherwise, concentrated with a rotary evaporator followed by static evaporation with an oil pump.

Ultrasound experiments were carried out in a Semat ultrasound cleaning bath (80W, 55kHz), and vinyl epoxides were prepared using previously described procedures^{11, 65}.

General procedure for the preparation of π -allyltricarbonyliron (lactone) complexes using $\text{Fe}_2(\text{CO})_9/\text{THF}$

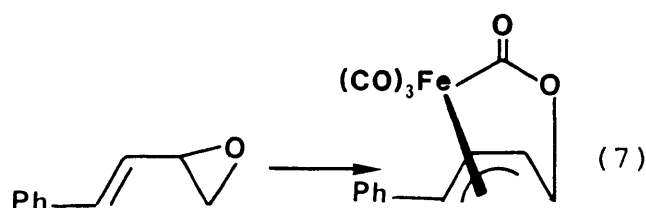
Solid diiron nonacarbonyl (1.1 equivalents) was added to a stirred solution of the vinyl epoxide in THF. The reaction mixture was stirred at room temperature until all the solid carbonyl had disappeared, or until a dark green colouration appeared. The solvent was removed under reduced pressure and the residue taken up in benzene and transferred to the top a silica gel column. The column was eluted with petrol to remove any non-polar iron carbonyl species and further elution with a petrol/ether gradient gave the pure ferrilactone complex.

Preparation of 2-4- η^3 -(1-formyloxy-2-methylbut-3-en-2-ylato) tricarbonyliron (6)



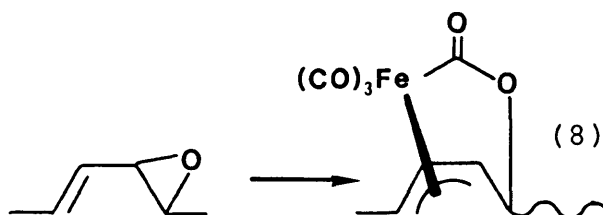
A solution of 2-methyl-1,2-epoxybut-3-ene (3.1g, 39.5mmol) in THF (35ml) was treated with $\text{Fe}_2(\text{CO})_9$ (15.8g, 43.4mmol). After 1h the reaction mixture was worked up as described to give the ferrilactone complex (6) as a pale yellow crystalline solid (6.7g, 75%); ν_{max} (nujol mull) 2950, 2860, 2080, 2040, 2010, 1660, 1380, 1080 cm^{-1} ; δ (250 MHz) 2.01 (3H, s, 2- CH_3), 2.73 (1H, dd, $J_{12.0}$ and 2.0Hz, 4- CH_{endo}), 3.48 (1H, dd, $J_{8.0}$ and 2.0Hz, 4- CH_{exo}), 3.92 (1H, d, $J_{12.5\text{Hz}}$, 1- CH), 4.12 (1H, d, $J_{12.5\text{Hz}}$, 1- CH), 4.88 (1H, dd, $J_{13.0}$ and 8.0Hz, 3- CH).

Preparation of 2-4- η^3 -(1-formyloxy-4-phenylbut-3-en-2-ylato)tricarbonyliron (7)



A solution of 1,2-epoxy-4-phenylbut-3-ene (580mg, 4.0mmol) in THF (60ml) was treated with $\text{Fe}_2(\text{CO})_9$ (1.6g, 4.4mmol). The reaction mixture was worked up after 0.5h in the manner described and column chromatography of the residue gave the ferrilactone complex (7) (1.26g, 100%); mp $>120^\circ\text{C}$ (decomposed). ν_{max} (CHCl_3) 2080, 2030, 1665, 984 cm^{-1} ; δ (250 MHz) 4.05 (1H, dd, $J_{12.5}$ and 5.5Hz, 1-CH), 4.17 (1H, dd, $J_{12.5}$ and 1.5Hz, 1-CH), 4.78 (1H, ddd, $J_{7.5}$, 5.5, and 1.5Hz, 2-CH), 4.82 (1H, d, $J_{12.5}$ Hz, 4-CH), 5.62 (1H, dd, $J_{12.5}$ and 7.5Hz, 3-CH), 7.28 to 7.42 (5H, m, phenyl).

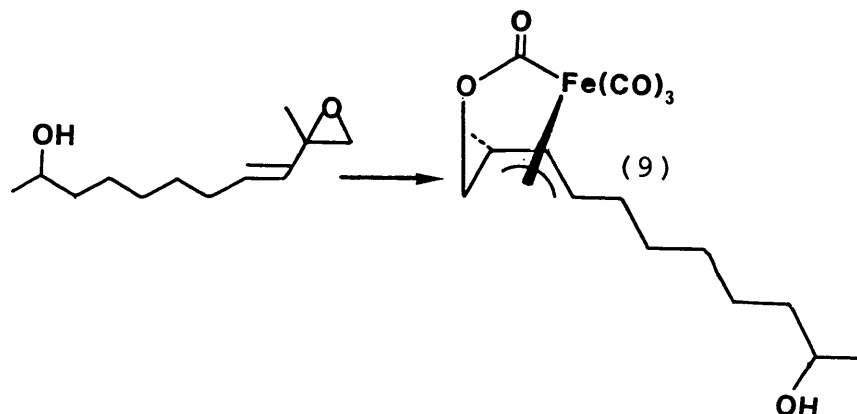
Preparation of 3-5- η^3 -(2-formyloxy-hex-4-en-3-ylato)tricarbonyliron (8)



Treatment of 2,3-epoxyhex-4-ene (2.0g, 21mmol) with $\text{Fe}_2(\text{CO})_9$ (8.4g, 23mmol) in THF (60ml) for 0.8h gave the ferrilactone complex as a crystalline yellow solid (3.6g, 64%); ν_{max} (CHCl_3) 2972, 2894, 2082, 2025, 1653, 1041 cm^{-1} ; δ (250 MHz, d^6 -benzene) 0.98 (3H, d, 7.0Hz, 1-CH₃), 1.14 (3H, d, $J_{5.8}$ Hz, 6-CH₃), 3.40 (1H, d, $J_{6.8}$ Hz, 5-CH), 3.70 (3H, m, 2 to 4-CH) for the *exo* isomer (8a) and 0.92 (3H, d, $J_{5.8}$ Hz, 1-CH₃), 1.09 (3H, d, $J_{5.8}$ Hz, 6-CH₃), 3.46 (2H, m, 2 and 5-CH), 3.78 (2H,

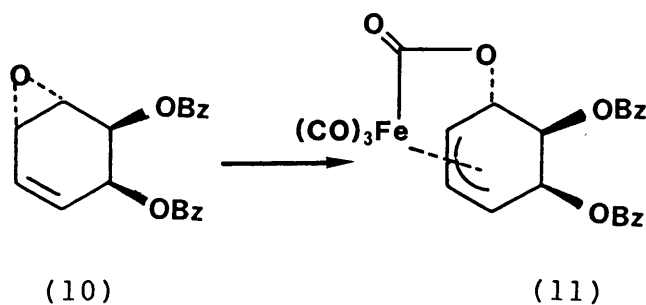
m, 3 and 4-CH) for the exo isomer (8b).

Preparation of 2-4-n³-(1-formyloxy-3-methyl-10-hydroxyundec-3-en-2-ylato)tricarbonyliron (9)



Treatment of a solution of 2-methyl-1,2-epoxy-10-hydroxyundec-3-ene (60mg, 0.38mmol) in THF with $\text{Fe}_2(\text{CO})_9$ (200mg, 0.5mmol) for 1.5h gave the ferrilactone (9) (114mg, 85%) as a syrup which crystallised slowly on standing at -20°C ; ν_{max} 3422, 2073, 2003, 1670 cm^{-1} ; δ (250 MHz) 1.20 (3H, d, J 6.4Hz, 10-CH₃), 1.42 to 1.80 (9H, m, 5 to 8-CH₂ and OH), 1.99 (3H, s, 3-CH₃), 2.20 to 2.30 (1H, m, CHOH), 3.70 to 3.80 (1H, m, 4-CH), 3.87 (1H, dd, J 16.3 and 1.6Hz, 1-CH), 4.09 (1H, d, J 11.8Hz, 1-CH), 4.72 (1H, d, J 11.8Hz, 3-CH); m/z 354

Preparation of 4-6-n³-(cis-2,3-dibenzoyl-5-en-2-ylato)-1-oxycarbonyltricarbonyliron (11)

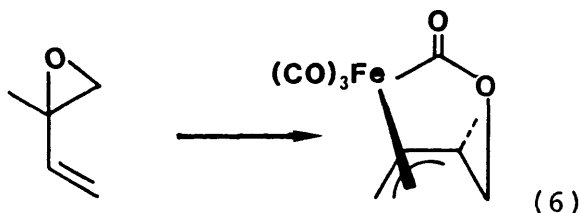


$\text{Fe}_2(\text{CO})_9$ (119mg, 0.33mmol) was added to a solution of cis-1,2-dibenzoyl-3,4-epoxycyclohex-5-ene (100mg, 0.30mmol) in THF (5ml). Work up after 1h gave the ferrilactone complex (11) as a white crystalline solid (21mg, 14%). ν_{max} (nujol mull) 2922, 2853, 2086, 2019, 1721, 1670, 1450, 1270, 1094, 709 cm^{-1} ; δ (250 MHz) 4.30 (1H, bd, J5.2Hz, 1-CH), 4.62 (1H, m, 4-CH), 5.50 to 5.70 (2H, m, 2 and 3-CH), 5.86 to 6.20 (2H, m, 5 and 6-CH₂), 7.20 to 7.70 (6H, m, phenyl), 7.80 to 8.22 (4H, m, phenyl); m/z 476 ($M^+ - \text{CO}$).

General procedure for the preparation of π -allyltricarboxyliron (lactone) complexes by reaction with $\text{Fe}_2(\text{CO})_9$ under sonolytic conditions

Diiron nonacarbonyl was added to a solution of the vinyl epoxide in benzene. The round bottomed flask was then sealed with a rubber septum and the flask carefully positioned in a Semat (80W, 55kHz) ultrasonic cleaning bath at the position where maximum agitation of the flask contents was observed. Sonication of the reaction mixture was continued until all the solid carbonyl had disappeared. Filtration through a celite pad, concentration of the filtrate, and silica gel chromatography of the brown residue (petrol/ether gradient) gave the ferrilactone complexes as previously described.

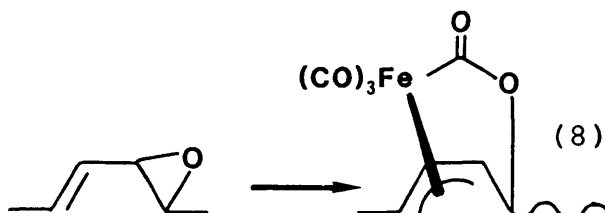
Preparation of 2-4- η^3 -(1-formyloxy-2-methylbut-3-en-2-ylato) tricarbonyliron (6)



Sonolysis of a mixture of 2-methyl-1,2-epoxybut-3-ene (850mg, 10.1mmol) and $\text{Fe}_2(\text{CO})_9$ (1.85g, 51mmol) in benzene (20ml) for 1h gave the

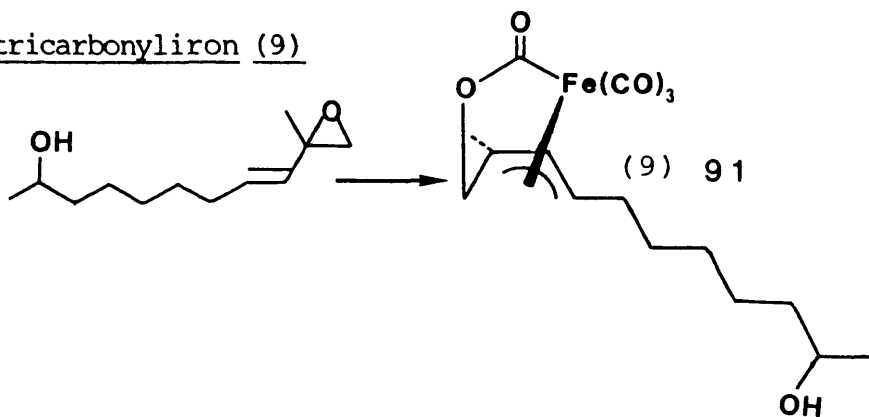
desired ferrilactone complex (6) (1.16g, 90% based on vinyl epoxide) identical to previously prepared material.

Preparation of 3-5- η^3 -(2-formyloxy-hex-4-en-3-ylato)tricarbonyliron (8)



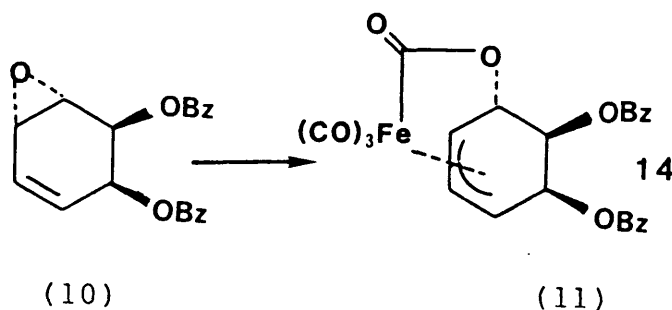
Sonolysis of a mixture of 2,3-epoxyhex-4-ene (250mg, 2.6mmol) and $\text{Fe}_2(\text{CO})_9$ (945mg, 2.6mmol) in benzene (10ml) for 1h gave the desired ferrilactone complex (8) (373mg, 55%) identical to previously prepared material.

Preparation of 2-4- η^3 -(1-formyloxy-2-methyl-9-hydroxydec-3-en-2-ylato)tricarbonyliron (9)



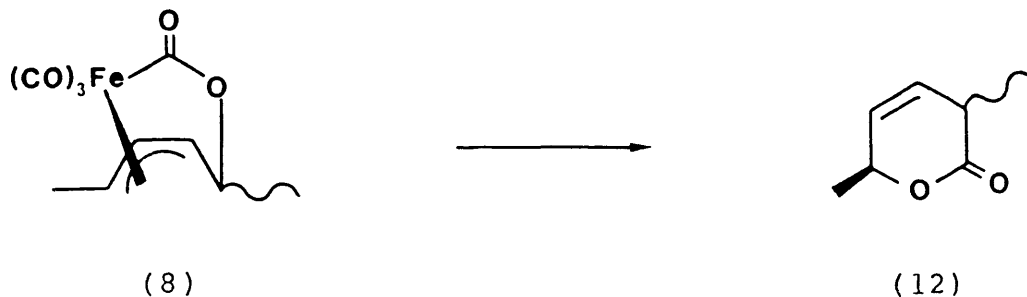
Sonolysis of a mixture of 2-methyl-1,2-epoxy-10-hydroxyundec-3-ene (19mg, 0.11mmol) and $\text{Fe}_2(\text{CO})_9$ (55mg, 0.15mmol) in benzene (10ml) for 0.75h gave the desired ferrilactone complex (9) (34mg, 91%) as a colourless syrup which slowly crystallised on storage at -20°C , identical to previously prepared material.

Preparation of 4-6- η^3 -(cis-2,3-dibenzoyl-5-en-2-ylato)-1-oxycarbonyltricarboxyliron (11)



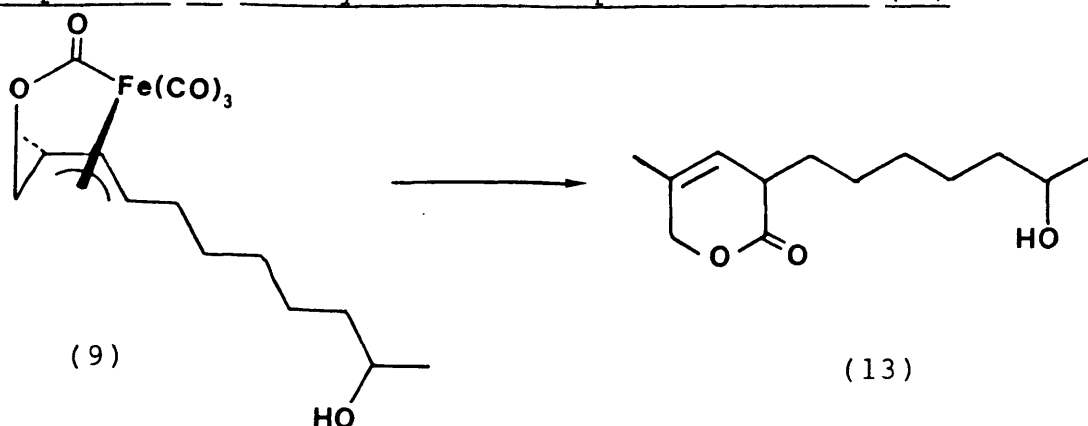
Sonolysis of a mixture of vinyl epoxide (10) (80 mg, 0.24mmol) and $\text{Fe}_2(\text{CO})_9$ (350mg, 0.96mmol) in benzene (10ml) for 3.75h gave the desired ferrilactone complex (11) (121 mg, 100%) identical to previously prepared material.

Preparation of 2,5-dimethylpent-3-en-5-olide (12)

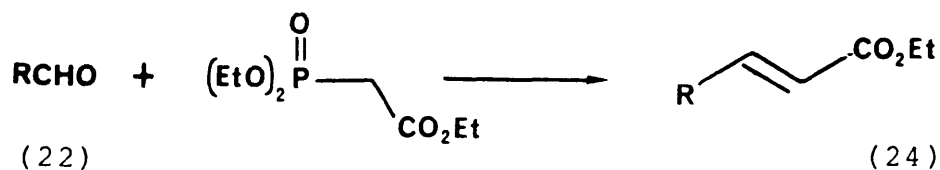


A solution of the ferrilactone complex (8) (200mg, 0.79mmol) in dry, degassed benzene (50ml) was heated to 90°C for 18h under 250 atmospheres of carbon monoxide. The reaction mixture was then cooled and filtered through a silica pad. Removal of solvent and column chromatography (silica; 50% petrol/ether) gave the volatile δ -lactone (12) (19mg, 19%), b.p.¹¹ 61-67°C, 42mm Hg; $\nu_{\text{max}}(\text{CHCl}_3)$ 2974, 2934, 1724, 1662, 1514, 1134, 1104, 1088 cm^{-1} ; δ (250 MHz) 1.37 (3H, d, J 7.0Hz, 2- CH_3), 1.45 (3H, d, J 7.5Hz, 5- CH_3), 3.08 (1H, m, 2- CH), 5.09 (1H, m, 5- CH), 5.80 (2H, m, 3 and 4- CH).

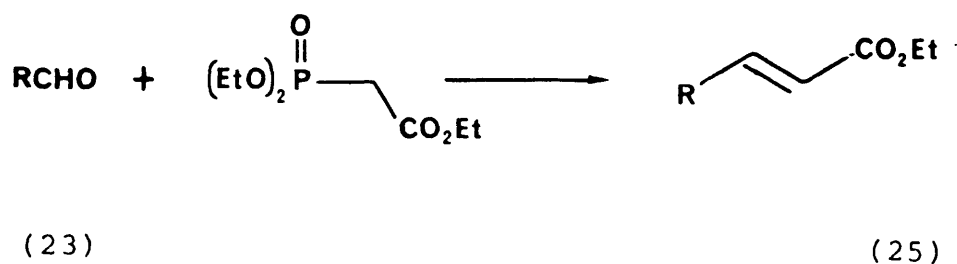
Preparation of 3-methyl-2-hexan-5'-olpent-3-en-5-olide (13)



A solution of the ferrilactone complex (9) (162mg, 0.43mmol) in dry, degassed benzene (20ml) was heated to 90°C for 12h under 250 atmospheres of carbon monoxide. The reaction mixture was then cooled and filtered through a silica pad. Removal of solvent and column chromatography (silica; ethyl acetate) gave the δ -lactone (13) as a colourless oil (47mg, 53%); ν_{max} (CHCl_3) 3429, 2975, 2829, 2871, 1735, 1600, 1110, 736 cm^{-1} ; δ (250 MHz) 1.20 (3H, d, J 4.5Hz, 6'- CH_3), 1.28 to 1.55 (10H, m, 1' to 5'- CH_2), 1.70 (3H, s, 4- CH_3), 2.58 (2H, m, 2- CH_2 and 6'- CHOH), 3.80 (2H, m, 5- CH_2), 6.28 (1H, d, J 2.0Hz, 3- CH); m/z 226 (M^+), 208 ($M^+ - \text{H}_2\text{O}$).

Preparation of ethyl oct-2-enoate (24)

Triethylphosphonacetate (37g, 165mmol) was added dropwise to a stirred suspension of sodium hydride (7.3g of a 60% dispersion, 182mmol) in THF (500ml) at 0°C. Hexanal (15g, 150mmol) was then added as a solution in THF (20ml). After 15min the reaction mixture was warmed to RT and stirring continued overnight. The reaction mixture was then partitioned between saturated ammonium chloride solution (200ml) and ether (500ml). The aqueous phase was then extracted with two further portions of ether and the combined ethereal extracts dried, concentrated, and distilled by Kugelrohr (70°C, 0.25mm Hg) to give ethyl oct-2-enoate (24) as a colourless oil (680mg, 99%). ν_{max} 2930, 2860, 1723, 1653, 1466, 1265, 1204, 1175, 1048 cm^{-1} ; δ (60MHz) 0.86 (3H, t, 6Hz, 8-CH₃), 1.0 to 1.5 (9H, m, 5 to 7-CH₂ and CO₂CH₂CH₃), 2.1 (2H, m, 4-CH₂), 4.1 (2H, q, J8Hz, CO₂CH₂), 5.7 (1H, dd, J2 and 19Hz, 2-CH), 7.0 (1H, dt, J16 and 7Hz, 3-CH); m/z 170 (M+).

Preparation of ethyl tetradec-2-enoate (25)

Triethylphosphonacetate (6.5g, 29.2mmol) was added dropwise to a stirred suspension of sodium hydride (1.06g of a 60% dispersion, 26.5mmol) in THF (100ml) at 0°C. Dodecanal (4.43g, 24.1mmol) was

added as a solution in THF (5ml). After 15min the reaction mixture was warmed to RT and stirring continued overnight. The reaction mixture was then partitioned between saturated ammonium chloride solution (30ml) and ether (70ml). The aqueous phase was then extracted with two further portions of ether and the combined ethereal extracts dried, concentrated, and distilled by Kugelrohr (135°C, 0.1mm Hg) to give ethyl tetradec-2-enoate (25) as a colourless oil (6.0g, 98%). $\nu_{\max}$ 2926, 2855, 1723, 1653, 1466, 1367, 1266, 1181, 1128, 1046, 979, 734 cm^{-1} ; δ (60MHz) 0.9 (3H, t, J6Hz, 14- CH_3), 1.0 to 1.8 (21H, m, 5 to 13- CH_2 and $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.1 (2H, m, 4- CH_2), 4.1 (2H, q, J7Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.7 (1H, m, 2- CH), 6.8 (1H, m, 3- CH); m/z 254 (M^+).

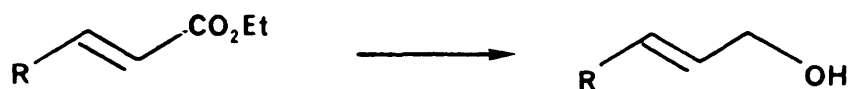
Preparation of oct-2-en-1-ol (26)



A 1.4M solution of DIBAL-H in toluene (118ml, 160mmol) was added dropwise to a cooled (-78°C) solution of ethyl oct-2-enoate (24) (11.1g, 70mmol) in DCM (500ml) whilst maintaining the temperature of the reaction mixture below -60°C . After stirring for a further 0.5h, the reaction was quenched by addition of dry methanol and allowed to warm to 0°C . Saturated sodium sulphate solution (5ml) and dry ether (150ml) were then added and the mixture stirred vigorously for a few minutes. The resulting slurry was then filtered through silica and the solid residue washed repeatedly with ether. Concentration of the filtrate and distillation of the resulting oil gave oct-2-en-1-ol (26) (6.79g, 75%). $\nu_{\max}$ 3324, 2926, 2857, 1670, 1465, 1377 1229, 1090, 1002, 970 cm^{-1} ; δ (250 MHz) 0.88 (3H, t, J6.3Hz, 8- CH_3), 1.20 to 1.45 (8H, m, 4 to 7-

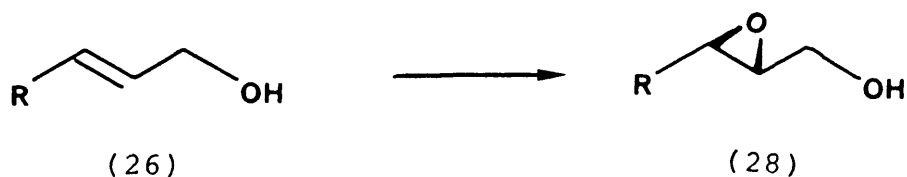
CH_2), 2.03 (1H, bs, OH), 4.07 (2H, d, $J_{5.4\text{Hz}}$, 1- CH_2), 5.55 (2H, m, 2 and 3- CH); m/z 128 (M^+).

Preparation of tetradec-2-en-1-ol (27)



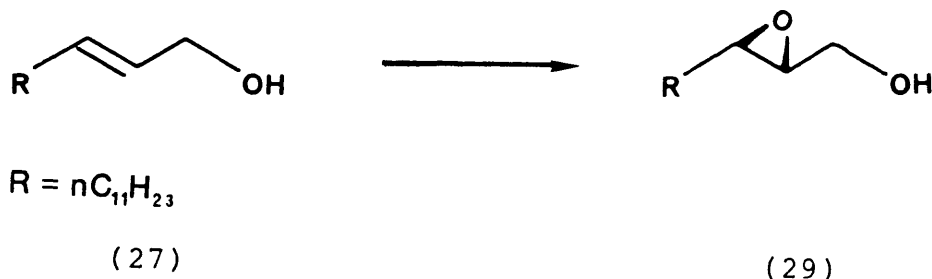
A 1.3M solution of DIBAL-H in toluene (65ml, 85mmol) was added dropwise to a cooled (-78°C) solution of ethyl tetradec-2-enoate (25) (6.0g, 23.6mmol) in DCM (100ml) whilst maintaining the temperature of the reaction mixture below -60°C . After stirring for a further 0.5h, the reaction was quenched by addition of dry methanol and allowed to warm to 0°C . Saturated sodium sulphate solution (5ml) and dry ether (100ml) were then added and the mixture stirred vigorously for a few minutes. The resulting slurry was then filtered through silica and the solid residue washed repeatedly with ether. Concentration of the filtrate and distillation by Kugelrohr (110°C , 0.1mm Hg) of the resulting oil gave tetradec-2-en-1-ol (27) (4.0g, 80%); ν_{max} 3310, 2940, 2880, 1665, 1460, 1450, 905 cm^{-1} ; δ (60MHz) 0.90 (3H, t, $J_{6\text{Hz}}$, 14- CH_3), 1.0 to 1.7 (18H, m, 5 to 13- CH_2), 1.9 (1H, bs, OH), 2.2 (2H, m, 4- CH_2), 3.9 (2H, m, 1- CH_2), 5.3 to 5.6 (2H, m, 2 and 3- CH); m/z 212 (M^+), 210, 194.

Preparation of (2R),(3R)-epoxyoctan-1-ol (28)



A solution of titanium tetraisopropoxide (1.6ml, 5.2mmol) in dry DCM (80ml) was cooled to -80°C under argon. (-)-Diethyl tartrate (1.15ml, 6.73mmol) and the alkenol (26) (1.34g, 10.45mmol) were then added sequentially followed by a 2.2M solution of anhydrous *t*-butylhydroperoxide in toluene (9.5ml, 20.9mmol) that had been pre-cooled to -20°C . At this stage, care was taken to maintain the temperature of the reaction mixture below -60°C ; however, once addition of the peroxide was complete, the reaction mixture was allowed to warm to 0°C over 3h. The reaction mixture was then poured onto a cooled (10°C) solution of ferrous sulphate (5.2g) and tartaric acid (2.1g) in water (20ml). Stirring was continued at ambient temperature for a further 0.5h, after which the two phases were separated and the aqueous phase back extracted with ether (2x20ml). The combined organic phases were dried over sodium sulphate, filtered through a small pad of celite, and concentrated. The residue was then taken up in ether (50ml) and treated with a pre-cooled (3°C) suspension of sodium hydroxide (200mg) in brine (23ml). The mixture was then stirred vigorously for 1h and the two phases separated. The aqueous phase was then back extracted with ether (2x25ml) and the combined organic extracts dried (sodium sulphate). Removal of the solvent and column chromatography (silica, petrol/ethyl acetate 2:1) of the residue gave the epoxyalcohol (28) as a white crystalline solid (1.1g, 73%); mp $28-29^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25} +24.6^{\circ}$ (c, 1.03 in CHCl_3); ν_{max} (CHCl_3) 3585, 2932, 2860, 1460, 1378, 1259, 1080, 1014, 884, 637 cm^{-1} ; δ (250 MHz) 0.91 (3H, t, J 5.4Hz, 8- CH_3), 1.25 to 1.60 (8H, m, 4 to 7- CH_2), 1.82 (1H, bs, OH), 2.94 (2H, m, 1- CH_2), 3.64 (1H, m, 3- CH), 3.92 (1H, m, 2- CH); m/z 144 (M^+), 101, 83.

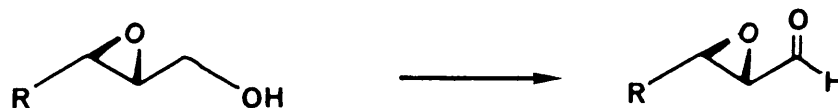
Preparation of (2R),(3R)-epoxytetradecan-1-ol (29)



A solution of titanium tetraisopropoxide (1.4ml, 4.7mmol) in dry DCM (70ml) was cooled to -80°C under argon. (-)-Diethyl tartrate (1.03ml, 6.0mmol) and the alkenol (27) (2.0g, 9.4mmol) were then added sequentially followed by a 1.5M solution of anhydrous *t*-butylhydroperoxide in toluene (12.4ml, 18.8mmol) that had been pre-cooled to -20°C . At this stage the reaction mixture was slowly warmed to 0°C and maintained at this temperature for the next 2h. The reaction mixture was then poured onto a cooled (10°C) solution of ferrous sulphate (4.7g) and tartaric acid (1.9g) in water (20ml). Stirring was continued at ambient temperature for a further 0.5h, after which the two phases were separated and the aqueous phase back extracted with ether (2x50ml). The combined organic phases were dried over sodium sulphate, filtered through a small pad of celite, and concentrated. The residue was then taken up in ether (50ml) and treated with a pre-cooled (3°C) suspension of sodium hydroxide (180mg) in brine (20ml). The mixture was then stirred vigorously for 1h and the two phases separated. The aqueous phase was then back extracted with ether (2x25ml) and the combined organic extracts dried (sodium sulphate). Removal of the solvent and column chromatography (silica, petrol/ethyl acetate 2:1) of the residue gave the epoxyalcohol (29) as a white crystalline solid (1.7g, 85%); m.p. $68-69^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25} +26.8^{\circ}$ (c, 1.0 in CHCl_3), ν_{max} (nujol) 3600, 2934, 2860, 1460, 1375, 1259, 1080, 884, 641 cm^{-1} ; δ (250 MHz) 0.88 (3H, t, J5.1Hz, 14- CH_3), 1.24 to 1.50 (18H, m, 5 to 13- CH_2), 1.57 (2H, m, 4- CH_2), 1.91 (1H, bs OH), 2.93 (2H, m, 1- CH_2), 3.64 (1H, m, 3- CH), 3.91 (1H, m, 2- CH); m/z 212

(M⁺). (Found C, 73.56; H, 12.51%. C₁₄H₂₈O requires C, 73.63; H, 12.36%).

Preparation of (2R),(3R)-epoxyoctanal (30)

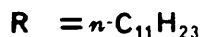


(28)

R = *n*-C₅H₁₁

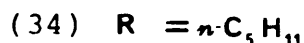
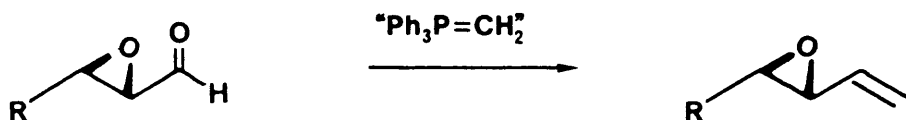
Dry chromium trioxide (11.88g, 119mmol) was added to a stirred solution of dry pyridine (19.5ml) in DCM (220ml) under argon. After 15min, celite (30g) was added and stirring continued for a further 5min. The reaction mixture was then cooled to 10°C before addition of the epoxyalcohol (28) (2.0g, 13.9mmol) in DCM (10ml). The slurry was then warmed to RT and stirring continued until tlc indicated that reaction was complete (0.5h). Potassium bisulphate (20g) and ether (250ml) were then added. After 5min, the reaction mixture was filtered through a pad of silica sandwiched between layers of magnesium sulphate. The filtrate was then concentrated and purified by column chromatography (silica, 50% petrol/ether) to give the epoxyaldehyde (30) (1.56g, 79%) as a colourless oil which crystallised slowly on storage at -20°C; $[\alpha]_D^{25}$ -70.7° (c, 1.22 in CHCl₃); $\nu_{\max}$ (CHCl₃) 2937, 2857, 1710, 1437, 1366, 1346, 1317, 1288, 1097, 1059 cm⁻¹; δ (250 MHz) 0.88 (3H t, J6.6Hz, 8-CH₃), 1.21 to 1.70 (8H, m, 4 to 7-CH₂), 3.14 (1H, dd, J5.95 and 2.1Hz, 2-CH), 3.23 (1H, ddd, J5.5, 5.5 and 2.1Hz, 3-CH), 9.01 (1H, d, J3.4Hz, CHO); m/z 141(M⁺), 127, 123, 113. (Found C, 67.37; H, 9.92%. C₈H₁₄O requires C, 67.57; H, 9.89%).

Preparation of (2R),(3R)-epoxytetradecanal (31)



A solution of the epoxyalcohol (29) (100mg, 0.44mmol) in DCM (10ml) was added to a vigorously stirred suspension of pyridinium dichromate (230mg, 0.61mmol) and powdered 3A molecular sieves (0.9g, 2g/mmol of alcohol) in DCM (15ml). The reaction was stirred at room temperature for 12h, after which tlc indicated that reaction was complete. The mixture was then diluted with ether (25ml) and filtered through a sandwich of MgSO_4 / silica/ MgSO_4 . Concentration of the filtrate and column chromatography of the residue (silica; 50% petrol/ether) gave the epoxyaldehyde (31) as a white powder (100mg, 100%), $[\alpha]_D^{25} -33.6^\circ$ (c, 1.08 in CHCl_3); ν_{max} 2922, 2738, 1725, 1494, 1465, 1364, 1311, 1221, 1185, 868, 826 cm^{-1} ; δ (250 MHz) 0.86 (3H, t, J8.0Hz, 14- CH_3), 1.03 to 1.76 (20H, m, 4 to 13- CH_2), 2.80 to 3.37 (2H, m, 2 and 3- CH), 9.03 (1H, d, J6.0Hz, CHO); m/z 226 (M⁺). (Found C, 74.18; H, 11.80%. $\text{C}_{14}\text{H}_{26}\text{O}_2$ requires C, 74.29; H, 11.58%).

Preparation of (2R),(3R)-epoxynon-1-ene (34)

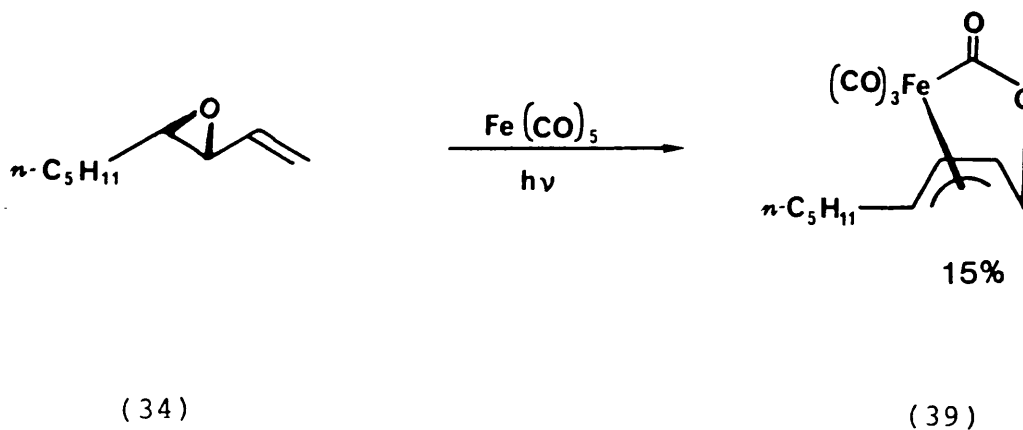


A suspension of methyltriphenylphosphonium iodide (1.6g, 3.9mmol) in THF (40ml) was cooled under argon and treated with *n*-butyllithium (3.1ml of a 1.39M solution in hexane, 4.2mmol). The yellow solution was then warmed to 0°C and maintained at this temperature for the

following hour, after which a solution of the epoxyaldehyde (30) (287mg, 2.0mmol) in THF (5ml) was added. Stirring was then continued at ambient temperature for a further 2h.

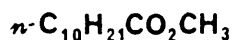
The reaction mixture was then filtered through a pad of silica that had been pre-washed with petrol/ether (6:1 + 1% triethylamine). Concentration of the filtrate and column chromatography of the residue (silica; petrol/ether 6:1 + 1% triethylamine) gave the vinyl epoxide (34) as a colourless oil (182mg, 65%); $[\alpha]_D^{25} +111.3^{\circ}$ (c, 2.40 in CHCl_3); ν_{max} 3053, 3001, 2925, 2854, 1584, 1478, 1433, 1089, 909 cm^{-1} ; δ (60 MHz) 0.87 (3H, t, J6Hz, 9- CH_3), 1.1 to 2.2 (8H, m, 5 to 8- CH_2), 3.0 (1H, m, 4- CH), 3.5 (1H, m, 3- CH), 4.9 to 5.7 (3H, m, 1- CH_2 and 2- CH).

Preparation of 1-3- n^3 -(4-formyloxynon-2-en-3-ylato)tricarbonyliron (39)



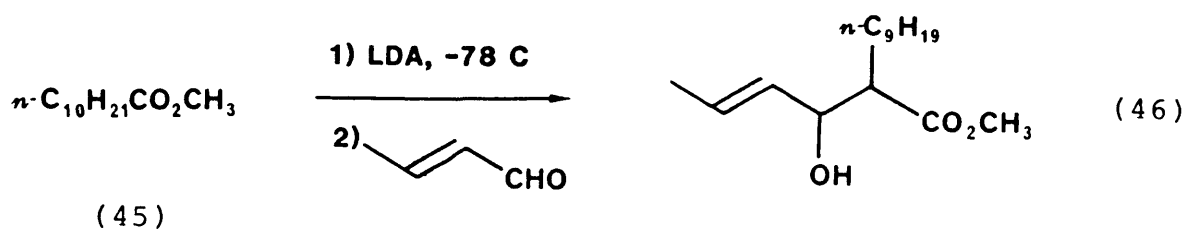
A solution of the vinyl epoxide (34) (26mg, 0.18mmol) and $\text{Fe}(\text{CO})_5$ (115 μl , 0.90mmol) in sodium dried benzene (300ml) were photolysed in an internal well system under a constant stream of argon (450W Applied Photophysics lamp). A circulating sodium bromide filter (2.90M aqueous solution) whose temperature was maintained below 10°C , was employed to cut off transmission below 300nm¹⁰³. After 10min formation of green $\text{Fe}_3(\text{CO})_{12}$ was clearly visible and photolysis was ceased.

The reaction mixture was then freeze dried and column chromatography of the residue gave the ferrilactone (39) as a white crystalline solid (8.2mg, 15%), $[\alpha]_D^{25} +31.7^\circ$ (c, 0.82 in CHCl_3); ν_{max} (CHCl_3) 2929, 2859, 2085, 2029, 1662, 1014, 729, 655 cm^{-1} ; δ (250 MHz) 0.81 (3H, t, J6.3Hz, 9- CH_3), 1.20 to 1.53 (8H, m, 5 to 8- CH_2), 3.07 (1H, dd, J2.0 and 6.0Hz, 3- CH), 3.70 (1H, dt, J3.5 and 8.5Hz, 2- CH), 4.22 (1H, m, 4- CH), 4.69 (1H, ddd, J1.0, 4.5 and 8.0 Hz, 1- CH), 4.77 (1H, ddd, J2.0, 4.5, and 8.0Hz, 1- CH); m/z 309 (M+), 280 (M+ -CO), 252 (M+ -2CO), 224 (M+ - 3CO); (Found 280.0396000, $\text{FeC}_{12}\text{H}_{16}\text{O}_4$ requires 280.0397984; M+ -CO).

Preparation of methyl undecanoate (45)

(45)

98% Sulphuric acid (11.6ml) was added dropwise to a stirred solution of undecanoic acid (13.1g, 6.55mmols) in dry methanol (80ml). After stirring for 1.5h the reaction mixture was cooled (ice/water bath) and excess acid neutralised by addition of 5M sodium hydroxide solution. The reaction mixture was then concentrated under reduced pressure and the residue extracted with ether (3x100ml). The combined ethereal extracts were dried (MgSO_4), concentrated and distilled by Kugelrohr (100°C, 0.4mmHg) to give methyl undecanoate (45) (13.0g, 93%) as a colourless oil. ν_{max} 2926, 2885, 1742, 1461, 1435, 1242, 1198, 1170 cm^{-1} ; δ (60MHz) 0.88(3H, t, J8Hz, 11- CH_3), 1.25 (16H, br s, 3 to 10 CH_2), 2.25(2H, t, J6Hz, 2- CH_2), 3.60(3H, s, CO_2Me); m/z 201 (MH⁺).

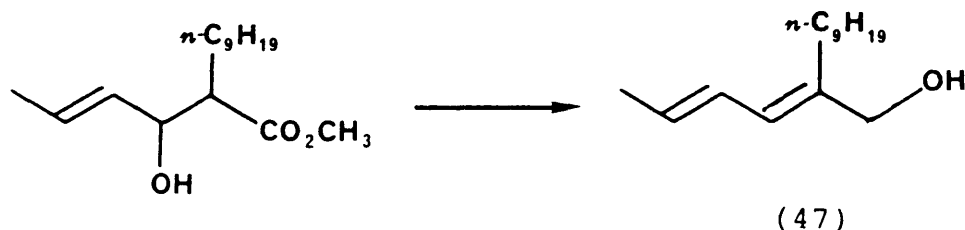
Preparation of 5-carbomethoxytetradec-2-en-4-ol (46)

Lithium diisopropylamide was prepared from diisopropylamine (2.6g, 26mmol) and 1.5M *n*-butyllithium (16.6ml, 27mmol) in THF (10ml). The solution was cooled to -78°C and treated with methyl undecanoate (45) (5.0g, 25mmol). After 0.5h the anion was quenched by addition of crotonaldehyde (2.4g, 34mmol) and the reaction mixture warmed to room

temperature over 1h.

The mixture was then partitioned between saturated ammonium chloride solution (30ml) and ether (90ml). The combined ethereal extracts were then washed sequentially with water (2x20ml) and brine (20ml), dried (MgSO_4) and concentrated to give a yellow oil. Distillation by Kugelrohr (170°C, 0.05mmHg) gave 5-carbomethoxytetradec-2-en-4-ol (46) as a colourless oil (6.2g, 88%). ν_{max} 3446, 2925, 2854, 1735, 1166 cm^{-1} ; δ (250MHz) 0.88 (3H, t, J6.5Hz, 13- CH_3), 1.25 (15H, bs, 7 to 13- CH_2 and OH), 1.52 (2H, m, 6- CH_2), 1.70 (3H, d, J5.1Hz, 1- CH_3), 2.45 (1H, m, 5- CH), 3.60 and 3.65 (3H, s, CO_2Me), 4.16 (1H, m, 4- CHOH), 5.43 (1H, m, 3- CH), 5.70 (1H, m, 2- CH); m/z 270 (M^+), 253 (M^+-OH) (Found; C 71.38%, H 11.37%, (M^+-OH) 253.2157, $\text{C}_{16}\text{H}_{30}\text{O}_3$ requires C 71.07%, H 11.20%, (M^+-OH) 253.2167).

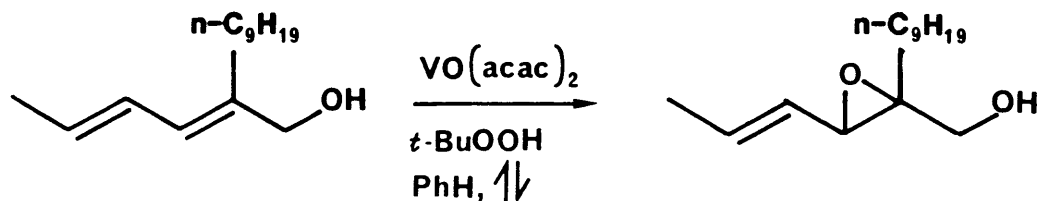
Preparation of 5-hydroxymethyltetradeca-2,4-diene (47)



A mixture of the alcohol (46) (18g, 56mmol) and potassium hydrogensulphate (76g, 56mmol) were azeotroped in toluene for 48h. The reaction mixture was then cooled to room temperature and treated with 1,8-diazobicyclo-[5.4.0]-undecane (8.8ml, 56mmol). After a further 24h the potassium hydrogensulphate was removed and the filtrate diluted with a further portion of dry toluene (giving a total volume of 150ml). The solution was then cooled to -78°C, under argon, and treated with a 1.5M solution of diisobutylaluminium hydride in the same solvent (95ml, 143mmol). After 0.5h, excess diisobutylaluminium

hydride was quenched by addition of excess methanol and the reaction mixture warmed to 0°C. Saturated sodium sulphate solution (5ml) and dry ether (100ml) were then added and the reaction mixture stirred vigorously until a white precipitate appeared. The resulting slurry was then filtered through silica and the filtrate concentrated and distilled by Kugelrohr (165°C, 0.1mm Hg) to give 5-hydroxymethyl tetradeca-2,4-diene (47) as a colourless oil (11.4g, 91%); $\nu_{\max}$ 3446, 2924, 2853, 1637, 1236 cm^{-1} ; δ (250 MHz) 0.80 (3H, t, J7.8Hz, 14-CH₃), 1.34 (14H, m, 13 to 7-CH₂), 1.62 (1H, bs, OH), 1.80 (3H, dd, J6.8 and 1.7Hz, 1-CH₃), 2.18 (2H, m, 6-CH₂), 4.07 (2H, s, CH₂OH), 5.70 (1H, m, 2-CH), 6.00 (1H, d, J10.6Hz, 4-CH), 6.27 (1H, m, 3-CH); m/z 224 (M+), 207 (M+-OH), 155; (Found C, 80.25; H, 12.82%. C₁₅H₂₈O requires C, 80.29; H, 12.58%).

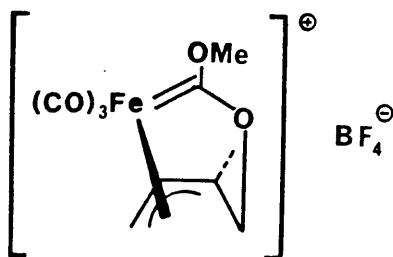
Preparation of 5-hydroxymethyl-4,5-epoxy-tetradec-2-ene (50)



t-Butyl hydroperoxide (83ul of 3.84M solution in toluene, 0.32mmol) was added dropwise to a blue/green solution of the dieneol (36mg, 0.16mmol) and vanadyl bisacetoacetate (3.7mg) in refluxing benzene. This resulted in an immediate colour change from green to yellow. After 12 min, gc showed complete disappearance of the starting material. The solution was then cooled and filtered through a pad of fluorisil (200-300 mesh). Removal of solvent and column chromatography (silica; petrol/ether 1:1 + 1% triethylamine) gave the vinyl epoxide (50) as a colourless oil which darkened rapidly on standing (37mg, 88%).

ν_{max} 3421, 3020, 2950, 2920, 2850, 1660, 1450, 1435, 1370 cm^{-1} ;
 δ (250 MHz) 0.88 (3H, t, J6.3Hz, 14- CH_3), 1.27 (16H, bs, 9 to 13- CH_2), 1.77 (3H, dd, J6.0 and 1.5Hz, 1- CH_3), 2.00 (1H, bs, OH), 3.51 (1H, d, J9.4Hz), 3.72 (2H, m, CH_2OH), 5.39 (1H, dq, J7.8 and 1.5Hz, 2- CH), 5.95 (1H, m, 3- CH); m/z 240 (M^+), 209 ($\text{M}^+ - \text{CH}_2\text{OH}$) (Found 240.2088, $\text{C}_{15}\text{H}_{28}\text{O}_2$ requires 240.2089 (M^+)).

Preparation of carbene complex (52)



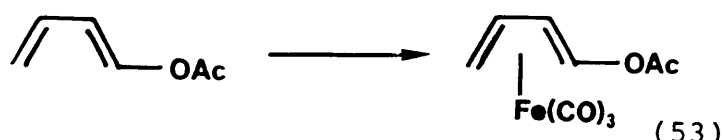
(52)

A stirred solution of ferrilactone complex (6) (100mg, 0.40mmol) in DCM (5ml) under argon was treated with trimethyloxonium tetrafluoroborate (Meerwein's salt) (340mg, 1.79mmol) at RT. After 3h tlc (silica; ether) showed complete disappearance of starting material. Filtration and removal of solvent gave the diastereoisomeric carbene complexes as a yellow crystalline solid in a ratio of 1:1; $\nu_{\max}$ (nujol) 2925, 2112, 2065, 2030, 1493, 1463, 1377, 1345, 1277, 1050, 722, 680 cm^{-1} ; δ (250 MHz, d_6 -acetone) 2.24 (3H, s, 2-CH₃), 3.46 (1H, d, J14.6Hz, 1-CH_{endo}), 4.15 (1H, m, 4-CH_{endo}), 4.24 (3H, s, OCH₃), 4.80 (1H, m, 1-CH_{exo}), 5.13 (2H, bdd, J27.0 and 12.5Hz, 3-CH), 5.78 (1H, dd, J10.4 and 8.3Hz, 4-CH_{exo}) for the minor isomer and δ (250 MHz, d_6 -acetone) 2.35 (3H, s, 2-CH₃), 2.95 (1H, dd, J14.6 and 2.1Hz, 1-CH_{endo}), 4.15 (1H, m, 4-CH_{endo}), 4.24 (3H, s, OCH₃), 4.80 (1H, m, 1-CH_{exo}), 5.13 (1H, bdd, J27.0 and 12.5Hz, 3-CH), 5.59 (1H, m, 4-CH_{exo}) for the major diastereoisomer; m/z (FAB spectrum in acetone/glycerol) 267 ($\text{M}^+ - \text{BF}_4$) 239 ($\text{M}^+ - \text{CO}$), 211 ($\text{M}^+ - 2\text{CO}$), 183 ($\text{M}^+ - 3\text{CO}$).

General procedure for the preparation of η^4 -(diene)tricarbonyliron complexes

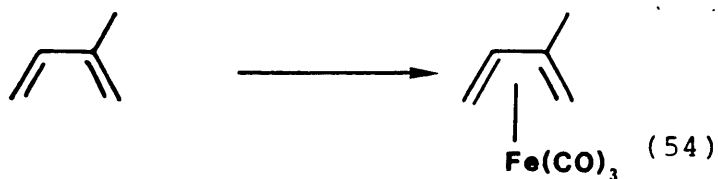
Diiron nonacarbonyl (1.1eq) was added to a solution of the relevant diene in benzene. The mixture was then sonolysed for 1h, or until all the solid carbonyl had disappeared. Concentration of the reaction mixture and column chromatography of the residue on silica (petrol/ether gradient) separated the required complex from any inorganic species.

Preparation of η^4 -(1-acetoxybuta-1,3-diene)tricarbonyliron (53)



Treatment of 1-acetoxybuta-1,3-diene (85mg, 0.76mmol) with $\text{Fe}_2(\text{CO})_9$ (304mg, 0.84mmol) gave the complex (53) as a yellow oil (191mg, 100%).
 ν_{max} 2082, 1995, 1952, 1760, 1460, 1212, 1174, 1102, 1051 cm^{-1} ;
 δ (250MHz, C_6D_6) -0.34 (1H, m, 4-CH endo), 0.45 (1H, m, 1-CH), 1.60 (1H, m, 4-CH exo), 2.12 (3H, s, OCOCH_3), 4.98 (1H, m, 2-CH), 5.30 (1H, m, 3-CH).

Preparation of η^4 -(2-methylbuta-1,3-diene)tricarbonyliron (54)



Treatment of 2-methylbuta-1,3-diene (17mg, 0.25mmol) with $\text{Fe}_2(\text{CO})_9$ (100mg, 0.28mmol) gave the complex (54) as a yellow oil (38mg, 70%).
 ν_{max} 3084, 2922, 2085, 2000, 1968, 1443, 1246, 881 cm^{-1} ; δ (250 MHz

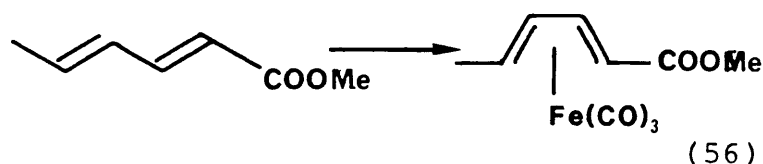
C_6D_6) -0.34 (1H, dd, $J_{7.7}$ and 3.8Hz , 4-CH endo), -0.01 (1H, d, $J_{1.9\text{Hz}}$, 1-CH endo), 1.42 (1H, m, 1-CH exo), 1.50 (1H, m, 4-CH exo), 1.64 (3H, s, 2-CH₃), 4.96 (1H, m, 3-CH).

Preparation of η^4 -(hexa-2,4-diene)tricarbonyliron (55)



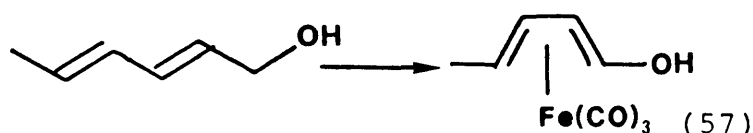
Treatment of hexa-2,4-diene (21mg, 0.25 mmol) with $\text{Fe}_2(\text{CO})_9$ (100mg, 0.28mmol) gave the complex (55) as a yellow oil (20mg, 50%). ν_{max} 2916, 2075, 1982, 1962, 1439, 1379, 1032 cm^{-1} ; δ 0.90 (2H, m, 2 and 5-CH), 1.87 (6H, d, $J_{18\text{Hz}}$, 1 and 6-CH₃), 4.85 to 5.08 (2H, m, 3 and 4-CH).

Preparation of η^4 -(methyloxycarbonylhexa-2,4-diene)tricarbonyliron (56)



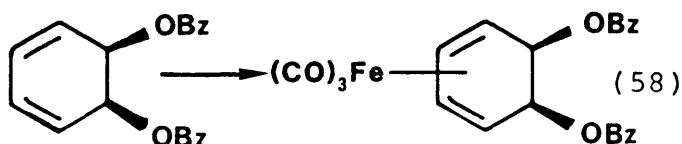
Treatment of methyloxycarbonylhexa-2,4-diene (110mg, 1.0mmol) with $\text{Fe}_2(\text{CO})_9$ (400mg, 1.1mmol) gave the complex (56) as yellow crystals (250mg, 100%). ν_{max} 2953, 2092, 2075, 1979, 1708, 1477, 1330, 1240, 1177, 1140 cm^{-1} ; δ (250 MHz C_6D_6) 0.88 (1H, m, 5-CH), 1.17 (1H, m, 2-CH), 1.36 (3H, d, $J_{6.0\text{Hz}}$, 6-CH₃), 3.37 (3H, s, CO_2CH_3), 5.14 (1H, m, 4-CH), 5.45 (1H, m, 3-CH).

Preparation of η^4 -(1-hydroxyhexa-2,4-diene)-tricarbonyliron (57)



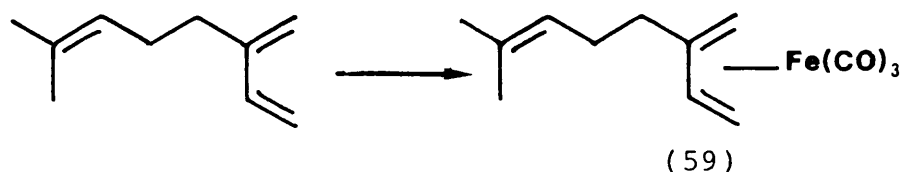
Treatment of 1-hydroxyhexa-2,4-diene (100mg, 1.0mmol) with $\text{Fe}_2(\text{CO})_9$ (400mg, 1.12mmol) gave the complex (57) as a yellow oil (108mg, 51%); ν_{max} 3400, 2090, 2065, 2030, 1448, 1245 cm^{-1} ; δ (250 MHz, C_6D_6) 0.65 to 0.77 (2H, m, 2 and 5-CH), 1.04 (3H, d, $J_{6.7\text{Hz}}$, 6-CH₃), 3.19 (1H, dd, $J_{7.4}$ and 11.5Hz , CHOH), 3.32 (1H, dd, $J_{12.0}$ and 5.1Hz , CHOH), 4.32 (1H, dd, $J_{8.6}$ and 4.8Hz , 3 or 4-CH), 4.72 (1H, dd, $J_{8.6}$ and 4.8Hz , 3 or 4-CH).

Preparation of η^4 -(cis-1,2-dibenzoylcyclohexa-3,5-diene)tricarbonyl iron (58)



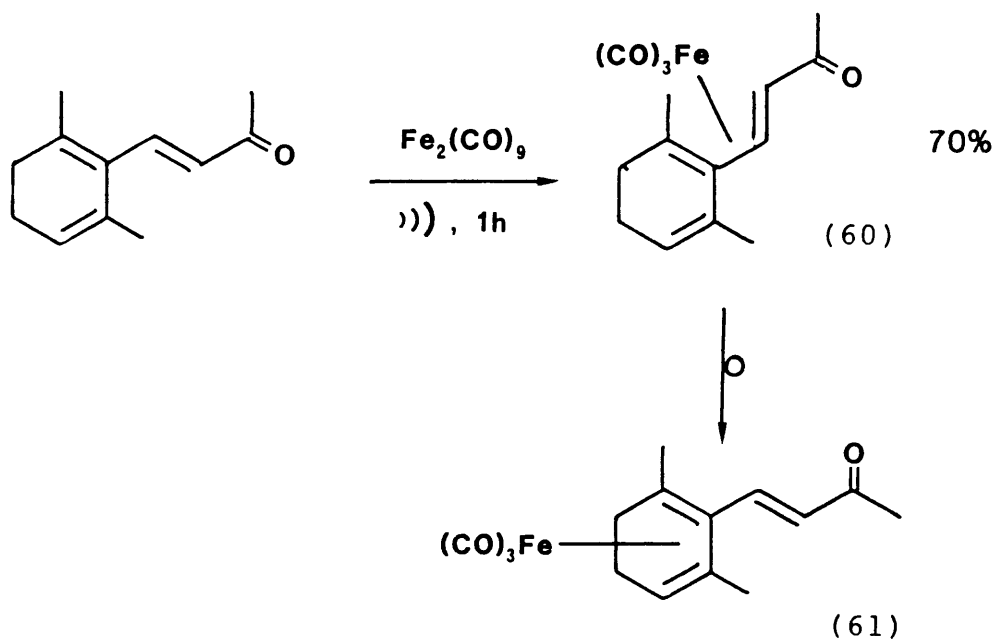
Treatment of cis-1,2-dibenzoylcyclohexa-3,5-diene (55mg, 0.17mmol) with $\text{Fe}_2(\text{CO})_9$ (63mg, 0.17mmol) gave the diene complex (58) as a pale yellow crystalline solid (55mg, 70%); ν_{max} (CHCl_3) 3059, 2087, 2059, 2009, 1717, 1583, 1314, 1270, 112, 708 cm^{-1} ; δ (250 MHz, C_6D_6) 4.78 (4H, m, 2 to 4-CH), 4.98 (2H, bs, 1 and 2-CH), 5.81 to 6.19 (6H, m, phenyl), 7.08 (4H, m, phenyl).

Preparation of η^4 -(β -myrcene)-tricarbonyliron (59)



Treatment of freshly distilled (95°C, 12mm Hg) β -myrcene (150mg, 1.1mmol) with $\text{Fe}_2(\text{CO})_9$ (440mg, 1.2mmol) gave the diene complex (59) as a yellow oil (290mg, 95%) which could be distilled by Kugelrohr (120°C, 0.2mm Hg); ν_{max} 2968, 2925, 2858, 2048, 1968, 1476 cm^{-1} ; δ (250 MHz, C_6D_6) -0.25 (1H, dd, J8.9 and 2.5Hz, 1-CH endo), -0.05 (1H, d, J1.6Hz, 4-CH endo), 1.30 (1H, dd, J8.9 and 2.5Hz, 1-CH exo), 1.46 (4H, m, 4-CH exo and 4'-CH₃), 1.65 (3H, s, 4'-CH₃), 1.97 to 2.13 (4H, m, 1' and 2'-CH₂), 4.73 (1H, t, J7.5Hz, 3'-CH), 5.10 (1H, m, 2-CH).

Preparation of η^4 -(pseudionone)tricarbonyliron complexes (60) and (61)

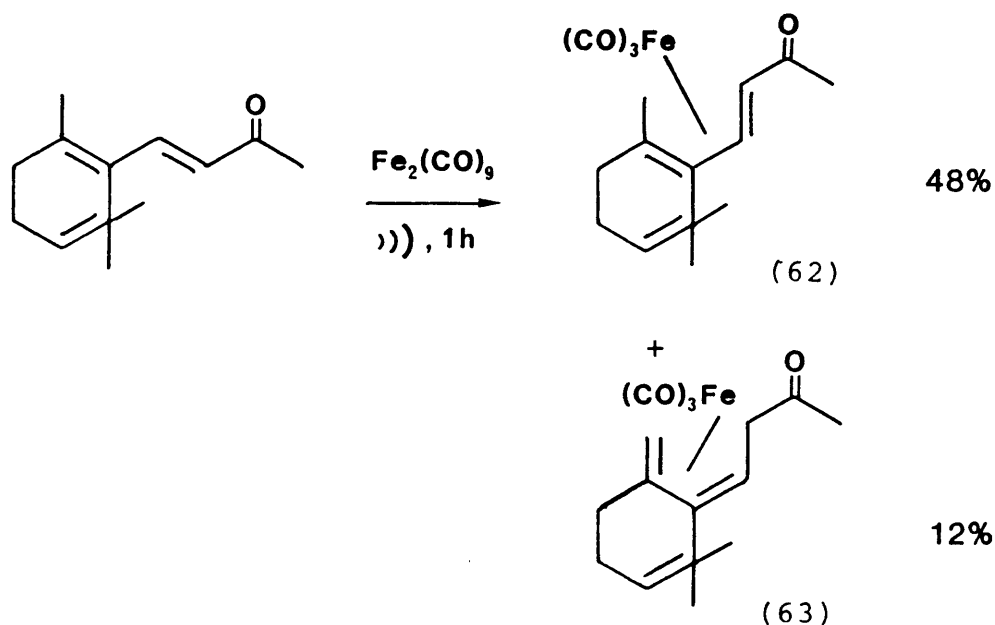


Sonolysis of a slurry of pseudionone (256mg, 1.3mmol) and $\text{Fe}_2(\text{CO})_9$ (533mg, 1.5mmol) in benzene (5ml) for 1h gave the exocyclic diene complex (60) (308mg, 75%) as a yellow oil. ν_{max} 2926, 2088, 2010, 1978,

1672, 1588, 1465, 1357, 1275, 1225 cm^{-1} ; δ (60 MHz C_6D_6) 0.97 (1H, s, 3-CH), 1.30 to 1.70 (4H, m, 7 and 8-CH), 1.65 (3H, s, CH₃), 1.70 (3H, s, CH₃), 2.00 (3H, s, 1-CH₃), 2.30 (1H, m, 4-CH), 5.17 (1H, m, 9-CH).

Allowing the diene complex to stand overnight at -20°C resulted in 95% isomerisation of the complex to give the endocyclic complex (61) as the major product. ν_{max} 2967, 2920, 2089, 2010, 1976, 1671, 1635, 1465, 1376, 1357, 1171 cm^{-1} ; δ (250 MHz C_6D_6) 1.43 to 1.82 (4H, m, 7 and 8-CH), 1.58 (3H, s, CH₃), 1.66 (3H, s, CH₃), 1.90 (3H, s, 1-CH₃), 3.30 (1H, m, 9-CH), 4.92 to 5.23 (2H, m, 3 and 4-CH).

Preparation of η^4 -(β -ionone)-tricarbonyliron complexes (62) and (63)



Treatment of freshly distilled ($130^\circ\text{C}/12\text{mmHg}$) β -ionone (150mg, 0.78mmol) with $\text{Fe}_2(\text{CO})_9$ (312mg, 0.86mmol) gave the 3,5-diene complex (62) and the 4,6-diene complex (63), by analogy with literature⁴⁷.

General procedure for the preparation of sodium phenylselenide

A 50% dispersion of sodium in paraffin (433mg, 9.4mmol), a small portion of benzophenone, and a minimal volume of THF (2ml) were placed in a 25ml flask which was then sealed under argon with a rubber septum. The flask was then suspended in an ultrasound bath at the position where maximum agitation of the flask contents was observed. After a few seconds the characteristic deep blue colour of sodium benzophenoneketyl was observed. A solution of diphenyldiselenide (1.4g, 4.7mmol) in the minimum volume of THF was added dropwise to the reaction mixture whereupon the orange solution was instantaneously transformed into a cream coloured precipitate. After 15min the reaction mixture had developed a pale mauve tinge and sonication was continued for a further 45min, or until all traces of colour had disappeared.

General procedure for the preparation of phenylselenols

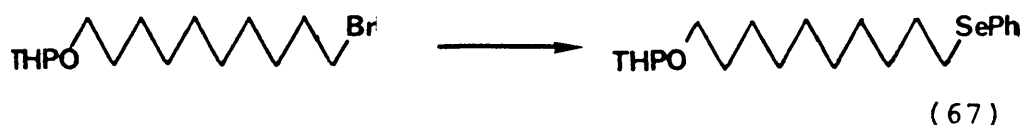
A homogeneous suspension of sodium phenylselenide (1.2 equivalents) was added to a stirred solution of the substrate in dry THF. When the reaction had reached completion, as determined by tlc, the mixture was partitioned between water (20ml) and ether (20ml). The aqueous phase was then extracted with two further portions of ether, and the combined organic phases dried over sodium sulphate. Removal of the solvent gave a yellow oil which was purified by column chromatography (silica gel; petrol/ether gradient).

Preparation of 1-Selenophenyloctane (66)



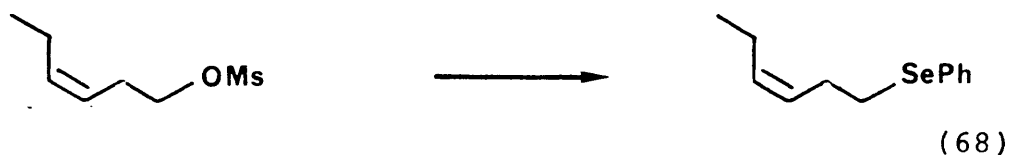
Treatment of octyl iodide (0.24g, 1.00mmol) with sodium phenylselenide (1.2mmol) gave 1-selenophenyloctane (66) (0.247g, 92%) as a pale yellow oil, ν_{max} (film) 3017, 2922, 2857, 1576, 1454, 1377, 1219, 119, 1041, 1022, 795, 735 cm^{-1} ; δ (60MHz; CDCl_3) 0.80 (3H, t, J 8Hz, 8- CH_3), 1.1 to 2.0 (12H, m, 2 to 7- CH_2), 2.8 to 3.3 (2H, m, 1- CH_2), 7.2 to 7.7 (5H, m, phenyl); m/z 270 (MH^+).

Preparation of 10-(Selenophenyl)-1-((tetrahydro-2H-pyran-2'-yl)oxy)decane (67)



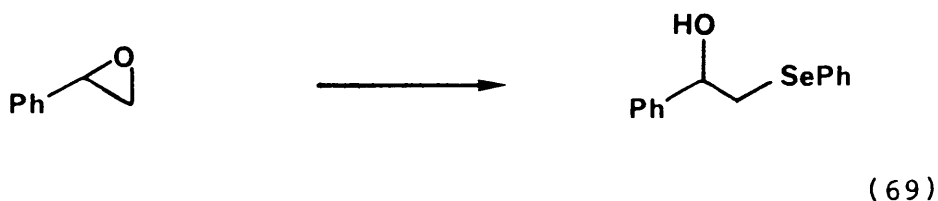
Treatment of 1-bromo-10-tetrahydropyranyldecane (67) (100mg, 0.33mmol) with sodium phenylselenide (0.39mmol) overnight gave 10-(Selenophenyl)-1-((tetrahydro-2H-pyran-2'-yl)oxy)decane (67) (0.33mmol, 100%) as a pale yellow oil, ν_{max} (film) 2926, 2852, 1659, 1576, 1475, 1276, 1119, 1076, 1033, 904, 869, 735 cm^{-1} ; δ 1.28 to 1.86 (24H, m, 3', 4' and 5'- CH_2 and 3 to 9- CH_2), 2.91 (1H, m, 1- CH), 3.73 (1H, m, 2- CH), 3.87 (1H, m, 2- CH), 4.57 (1H, t, J 3.8Hz, 6'- CH), 7.20 to 7.50 (5H, m, phenyl); m/z 398 (M^+).

Preparation of 1-Selenophenylhex-3-ene (68)



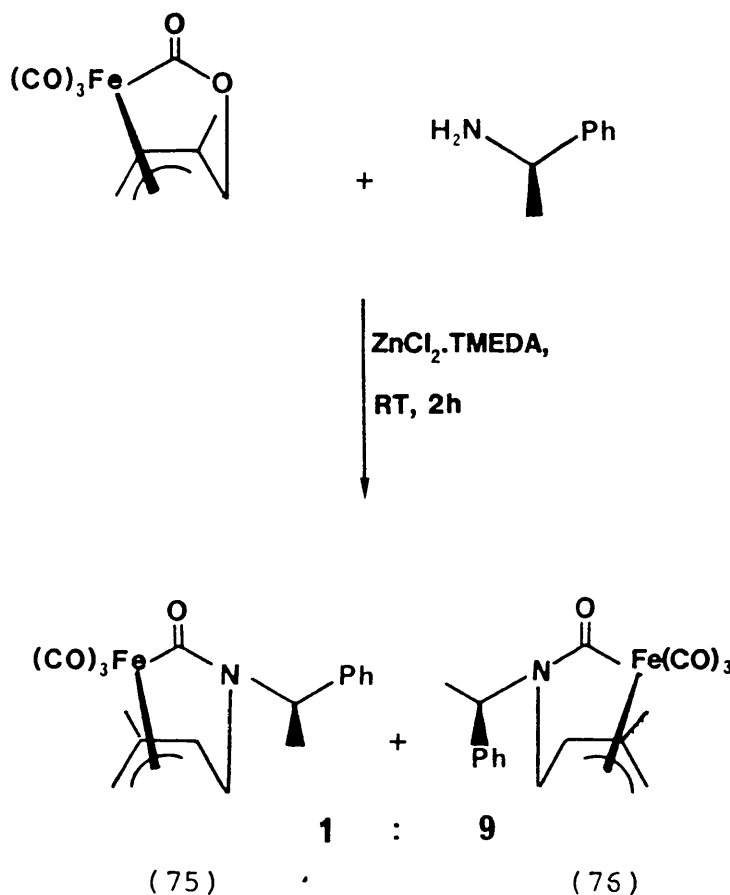
Treatment of methanesulphonyloxyhex-3-en-1-ol (68) (178mg, 1.00mmol) with sodium phenylselenide (1.20mmol) for 10min gave 1-Selenophenylhex-3-ene (68) as a pale yellow oil, ν_{max} (film) 3004, 2961, 2927, 1576, 1474, 1434, 1298, 1258, 1190, 1072, 1022, 733, 689 cm^{-1} ; δ_{nmr} 0.98 (3H, t, J8.0Hz, 6- CH_3), 2.00 (2H, dt, J16.0 and 8.0Hz, 5- CH_2), 2.43 (2H, dd, J15.0 and 8.0Hz, 2- CH_2), 2.93 (2H, t, J8.0Hz, 1- CH_2), 5.41 (2H, m, 3 and 4- CH_2), 7.26 (3H, m, phenyl), 7.50 (2H, m, phenyl); m/z 240 (MH⁺); (Found C, 60.54; H, 6.77%. $\text{C}_{12}\text{H}_{16}\text{Se}$ requires C, 60.25; H, 6.74%).

Preparation of 1-phenyl-2-(selenophenyl)ethan-1-ol



Treatment of styrene oxide (120mg, 1.0mmol) with sodium phenylselenide, overnight, gave 1-phenyl-2-(selenophenyl)ethan-1-ol (69) as a yellow oil (216mg, 78%); ν_{max} 3403, 3058, 2929, 1576, 1475, 1435, 1300, 1054, 1022, 973, 737 cm^{-1} ; δ (250 MHz) 3.00 (1H, brs, OH), 3.12 (1H, dd, J15.5 and 9.0 Hz, 2- CH), 3.30 (1H, dd, J12.5 and 3.7Hz, 2- CH), 4.73 (1H, dd, J9.0 and 3.7Hz, 1- CH), 7.20 to 7.35 (8H, m, phenyl), 7.50 to 7.60 (2H, m, phenyl); m/z 278 (MH⁺).

Preparation of 2-4- η^3 -{1-[formyl-(1'R)-phenylethylamino]-3-methyl-3-buten-2-yl}tricarbonyliron (75) and (76)

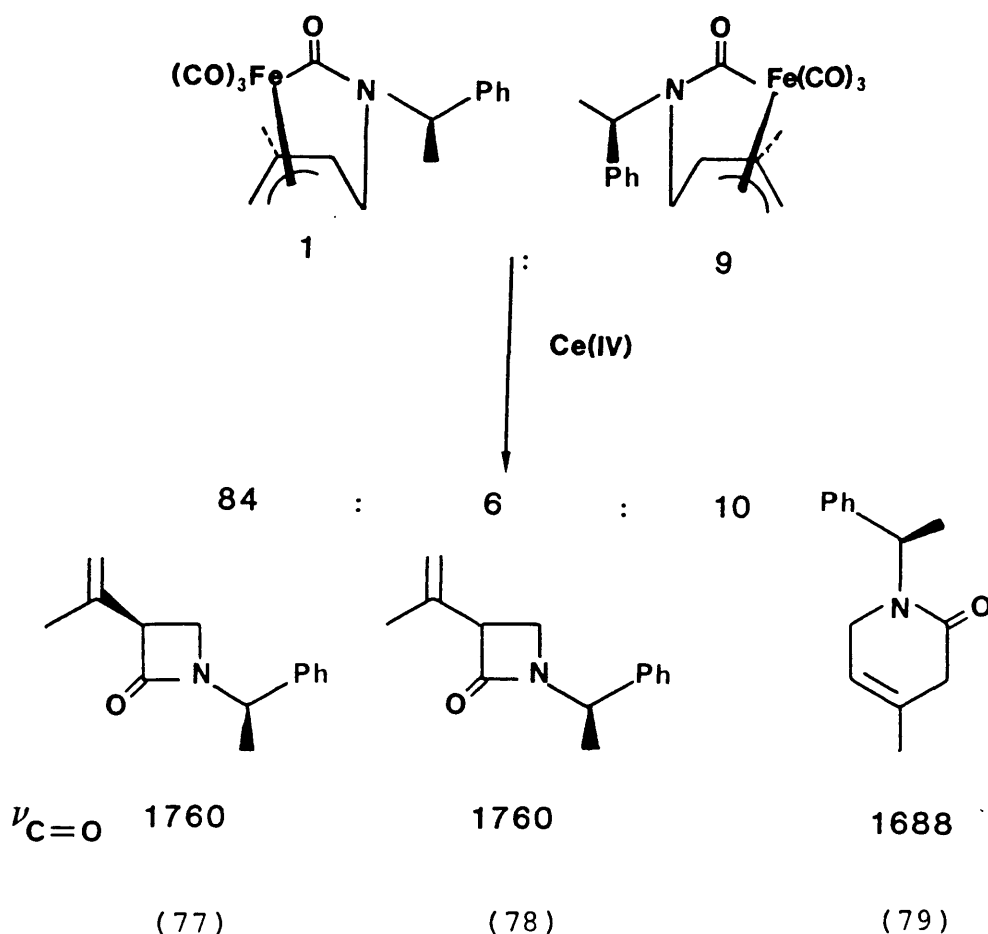


A solution of $\text{ZnCl}_2 \cdot \text{TMEDA}$ (5.42g, 21.4mmol) in dry THF (150ml) was added via a syringe to a stirred solution of the ferrilactone complex (6) (4.5g, 17.9mmol) in ether, under argon. (R)-(+)- α -methylbenzylamine (8.7g, 71.6mmol) was then added and the mixture stirred at RT for 2h, and 0°C for a further 12h.

The reaction mixture was then diluted with ether (200ml), washed with 10% aqueous citric acid (280ml), water (2x140ml), and brine (140ml), and dried. Filtration through celite and concentration of the filtrate gave a mixture of the two diastereoisomeric ferrilactams (75) and (76) as a yellow oil (5.8g, 92%) which could not be separated by silica gel flash chromatography. ν_{max} (CCl_4) 3040, 2990, 2940, 2865, 2080, 2000, 1595, 1555, 1410, 1160, 702, 665 cm^{-1} ; δ (250 MHz) 1.41 (3H, d, J 7.0Hz, CH_3), 1.92 (3H, s, CH_3), 2.63 (1H, d, J 1.0Hz, 4'- CH), 2.84 (1H, dd, J 12.5 and 1.0Hz, 1'- CH), 3.41 (1H, dd, J 12.5 and 7.0Hz,

1-CH), 3.48 (1H, dd, $J_{1.0}$ and 1.0Hz, 4-CH), 4.22 (1H, d, $J_{7.0}$ Hz, 2-CH), 4.40 (1H, q, $J_{7.0}$ Hz, PhCH), 7.13 to 7.19 (2H, m, phenyl), 7.20 to 7.36 (3H, m, phenyl); (Found C, 57.32; H, 4.76; N, 3.91%. $\text{FeC}_{17}\text{H}_{17}\text{NO}_4$ requires C, 57.49; H, 4.82; N, 3.94%).

Preparation of 3(R) and 3(S)-(2'-propenyl)-1-[(1'R)-phenylethyl]-azetidin-2-one (77) and (78)



A solution of cerium (IV) ammonium nitrate (1.28g, 2.34mmol) in cold ethanol (-78°C) (20ml) was added dropwise to a stirred solution of the ferrilactam complexes (75) and (76) (184mg, 0.52mmol) in the same solvent (7ml) over a period of 0.3h.

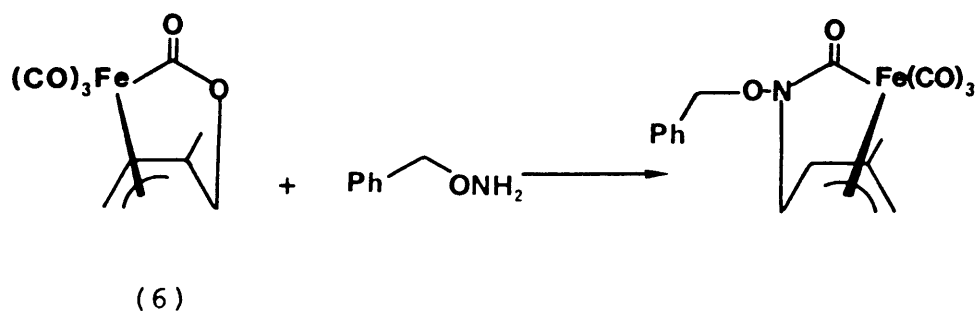
The reaction mixture was then allowed to warm to RT over a period of 4h, during which the solution changed from orange/yellow to red.

Excess solvent was then removed under reduced pressure and the residue

partitioned between water (20ml) and ether (45ml). The ethereal layer was then washed with a further portion of water (10ml), dried and concentrated. Column chromatography of the resulting oil (silica; petrol/ether 7:3) gave the 3(R)-(2'-propenyl)-1-[(1'R)-phenylethyl]-azetidin-2-one (77) (93mg, 84%) as a colourless gum; $[\alpha]_D^{25} 22.45^\circ$ (c, 15.7 in ether); $\nu_{\max}$ (CHCl₃) 3063, 1760, 1648, 1606, 1237, 897, 760, 700 cm⁻¹; δ (250 MHz) 1.60 (3H, d, J7.0Hz, CH₃), 1.70 (3H, s, CH₃), 2.92 (1H, dd, J7.0 and 4.0 Hz, 4-CH trans), 3.36 (1H, t, J5.0Hz, 4-CH cis), 3.73 to 3.78 (1H, m, 3-CH), 4.89 (2H, m, =CH₂), 5.00 (1H, q, J7.0Hz, NCH), 7.28 to 7.40 (5H, m, phenyl); m/z 215 (M⁺), (Found C, 78.09; H, 8.04; N, 6.57%. C₁₄H₁₇NO requires C, 78.10; H, 7.95; N, 6.51%).

Further elution gave 3(S)-(2'-propenyl)-1-[(1'R)-phenylethyl]-azetidin-2-one (78) (7mg, 6%) as a colourless gum; $\nu_{\max}$ (CHCl₃) 3063, 1760, 1648, 1606, 1237, 897, 760, 700 cm⁻¹; δ (250 MHz) 1.60 (3H, d, J7.0Hz, CH₃), 1.80 (3H, s, CH₃), 3.05 (1H, m, 4-CH trans), 3.17 (1H, t, J7.0Hz, 4-CH cis), 3.81 and 3.90 (1H, m, 3-CH), 4.89 (2H, m, =CH₂), 5.00 (1H, q, J7.0Hz, NCH), 7.28 to 7.41 (5H, m, phenyl).

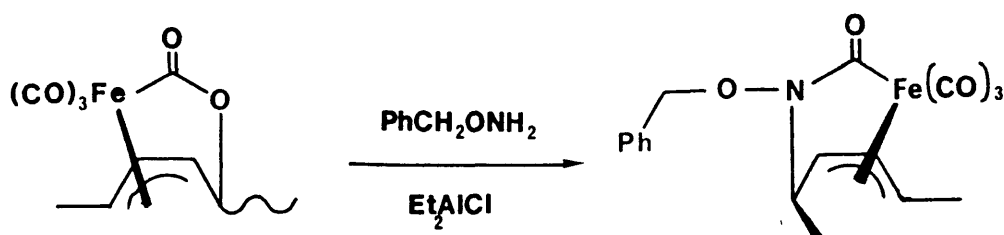
Preparation of 2-4- η^3 -{1-[formyl-O-benzylhydroxylamino]-3-methyl-3-buten-2-yl}tricarbonyliron



A stirred solution of the ferrilactone complex (6) (40mg, 0.16mmol) in

ether/THF (5ml, 1:1) was treated with a 25% solution of diethylaluminium chloride in hexane (188 μ l, 0.32mmol) followed by O-benzylhydroxylamine (78mg, 0.64mmol). The reaction mixture was stirred under argon for 0.75h, after which the reaction mixture was diluted with ether and poured onto 10% citric acid (10ml). The aqueous phase was then extracted with two further portions of ether (2x20ml) and the combined organic phases washed sequentially with water, saturated sodium bicarbonate solution and brine (3x10ml), and dried. Removal of the solvent gave the ferrilactam complex as pale yellow crystals (31mg, 56%); $\nu_{\max}$ (CHCl₃) 3000, 2939, 2042, 2017, 1600, 1460, 1015, 700, 678 cm⁻¹; δ (250 MHz) 2.00 (3H, s, 3-CH₃), 2.72 (1H, d, J1.0Hz, 4-CH_{endo}), 3.12 (1H, dd, J13.2 and 4.4Hz, 1-CH_{endo}), 3.32 (1H, dd, J8.8 and 13.2 Hz, 1-CH_{exo}), 3.44 (1H, bs, 4-CH_{exo}), 4.06 (1H, d, J8.8Hz), 4.70 (2H, bs, PhCH₂), 7.25 to 7.37 (5H, m, phenyl).

Preparation of 3-5- η^3 -[2-[formyl-O-benzylhydroxylamino]-hex-4-en-3-yl]tricarbonyliron

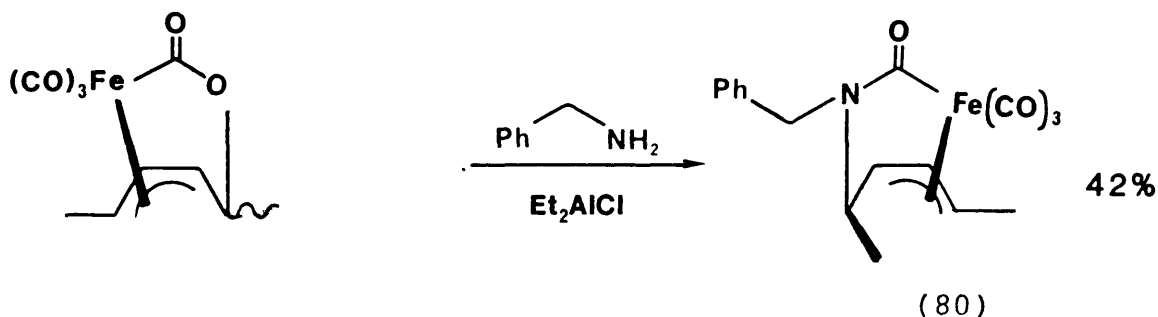


(8)

A stirred solution of the ferrilactone complex (8) (43mg, 0.16mmol) in ether/THF (5ml, 1:1) was treated with a 25% solution of diethylaluminium chloride in hexane (188 μ l, 0.32mmol) followed by O-benzylhydroxylamine (78mg, 0.64mmol). The reaction mixture was stirred under argon for 0.75h, after which the reaction mixture was

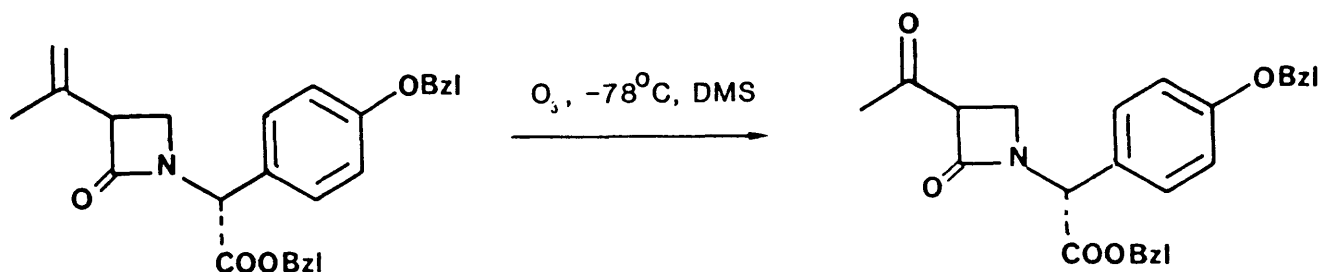
diluted with ether and poured onto 10% citric acid (10ml). The aqueous phase was then extracted with two further portions of ether (2x20ml) and the combined organic phases washed sequentially with water, saturated sodium bicarbonate solution and brine (3x10ml), and dried. Removal of the solvent and column chromatography of the residue (silica; petrol/ether gradient) gave the ferrilactone complex as pale yellow crystals (34mg, 58%); $\nu_{\max}$ (CHCl_3) 3035, 2978, 2920, 2078, 2000, 1600, 1582, 1445, 1350, 1190 cm^{-1} ; δ (250 MHz) C_6D_6 0.92 (3H, d, J4.6Hz, 1- CH_3), 1.12 (3H, d, J4.6Hz, 6- CH_3), 1.35 (1H, m, 4- CH), 3.50 (1H, m, 3- CH), 3.78 (1H, m, 2- CH), 4.72 (2H, bs, PhCH_2), 7.08 to 7.40 (5H, m, phenyl); m/z 303.

Preparation of 3-5 ^{3} -{2-[formylbenzylamino]-hex-4-en-3-yl}tricarbonyl
iron (80)



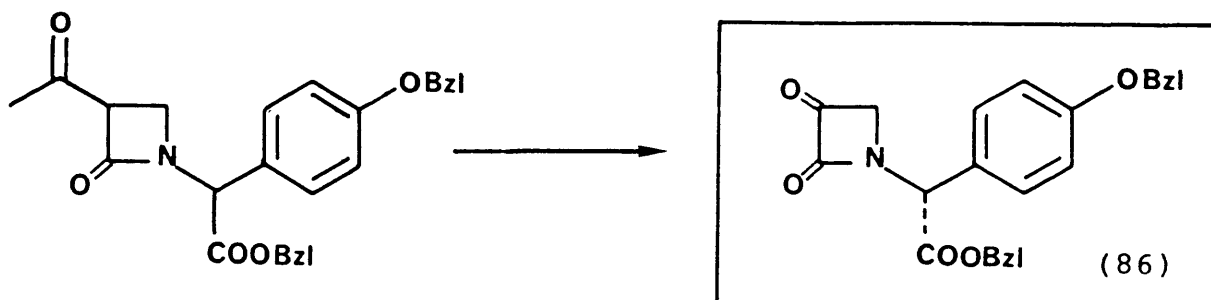
A stirred solution of the ferrilactone complex (8a) and (8b) (200mg, 0.75mmol) in ether/THF (15ml, 1:1) was treated with a 25% solution of diethylaluminium chloride in hexane (880ul, 1.50mmol) followed by benzylamine (321mg, 3.00mmol). The reaction mixture was stirred under argon for 2h, after which the reaction mixture was diluted with ether (50ml) and poured onto 10% citric acid (10ml). The aqueous phase was then extracted with two further portions of ether (2x20ml) and the combined organic phases washed sequentially with water, saturated sodium bicarbonate solution and brine (3x10ml), and dried. Removal of the solvent and column chromatography of the residue (silica; petrol/ether gradient) gave the ferrilactone complex as pale yellow crystals (226mg, 85%); $\nu_{\max}$ (CHCl₃) 2235, 2072, 2012, 1562, 1218, 1183 cm⁻¹; δ (250 MHz) 1.18 (3H, d, J3.5Hz, 1-CH₃), 1.82 (3H, d, J2.5Hz, 6-CH₃), 3.40 (1H, m, 2-CH), 3.94 (1H, dq, J3.5 and 3.0Hz, 5-CH), 4.34 (1H, dd, J3.5Hz, 3-CH), 4.51 (1H, dd, J2.3 and 4.6Hz, 4-CH), 5.06 (2H, d, J8.0Hz, PhCH₂), 7.1 to 7.3Hz (5H, m, phenyl).

Preparation of (3R)- and (3S)-3-Acetyl-1-[(1'R)-(p-benzyloxyphenyl)benzyloxycarbonylmethyl]azetidin-2-one (92) and (93)



A solution of the isopropenylazetidinones (91) and (92) (120mg, 0.27mmol) in DCM (10ml) was treated with ozone at $-78^\circ C$ until no starting material was present, as indicated by tlc (60% ether/petrol). Dimethylsulphide was added and the reaction mixture warmed to room temperature. Stirring was continued for 1h after which the reaction mixture was concentrated to give the diastereoisomeric ketones (92) and (93) (120mg, 100%) (3R)-3-acetyl-1-[(1'R)-(p-benzyloxyphenyl)benzyloxycarbonylmethyl]azetidin-2-one (92) as a colourless gum. ν_{max} (film) 3080, 3060, 3030, 1750, 1740, 1722, 1610, 1510 and 1240 cm^{-1} ; δ (250 MHz) 2.30 (3H, s, $COCH_3$), 3.09 (1H, dd, $J_{5.4}$ and 5.4Hz, cis-4-CH), 3.94 (1H, dd, $J_{5.4}$ and 2.9Hz, trans-4-CH), 4.01 (1H, dd, $J_{5.4}$ and 2.9Hz, 3-CH), 5.06 (2H, s, $PhCH_2$), 5.19 (2H, s, $PhCH_2$), 5.56 (1H, s, NCH), 6.96 (2H, d, J_{AB} 8.8Hz, Ar), 7.10 (2H, d, J_{AB} 8.8Hz, Ar), 7.21-7.45 (10H, m, phenyl); m/z 443 (M^+), 353, 308, 212, 91 (Found: M^+ , 443.1722. $C_{27}H_{25}NO_5$ requires M , 443.1733); and (3R)-3-acetyl-1-[(1'R)-(p-benzyloxyphenyl)benzyloxycarbonylmethyl]azetidin-2-one (93); δ (250 MHz) 2.26 (3H, s, $COCH_3$), 3.47 (1H, dd, $J_{5.4}$ and 2.9Hz, trans-4-CH), 3.56 (1H, dd, $J_{5.4}$ and 5.4Hz, cis-4-CH), 4.20 (1H, dd, $J_{5.4}$ and 2.9Hz, 3-CH), 5.04 (2H, s, $PhCH_2$), 5.19 (2H, s, $PhCH_2$), 5.56 (1H, s, NCH), 6.96 (2H, d, J_{AB} 8.8Hz, Ar), 7.10 (2H, d, J_{AB} 8.8Hz, Ar), 7.21-7.45 (10H, m, phenyl).

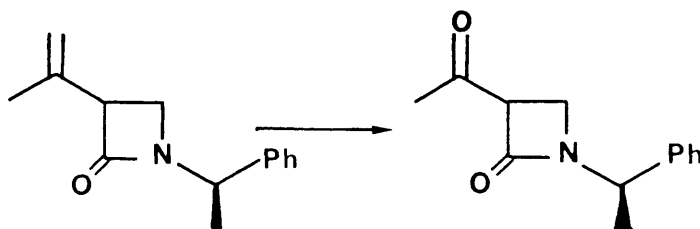
Preparation of (-)-1-[(p-Benzyloxyphenyl)benzyloxycarbonylmethyl]-azetidin-2,3-dione (86)



A stirred solution of the diastereoisomeric mixture of 3-actyl- β -lactams (92) and (93) (63mg, 0.14mmol) in 1,2-dichloroethane (1ml) was cooled to 0°C under argon and treated sequentially with triethylamine (26 μ l, 0.19mmol) and *t*-butyldimethylsilyltrifluoromethane sulphonate (34 μ l, 0.15mmol). After 10min the reaction mixture was diluted with DCM (60ml) and methanol (6ml) and cooled to -78°C. Ozone was then bubbled through the solution until tlc (50% petrol/ether) showed complete disappearance of the starting material (approximately 5min). Powdered zinc (373mg, 5.7mmol) and glacial acetic acid (1ml) were then added and the reaction mixture warmed to RT.

The reaction mixture was then filtered through a celite pad and the solvent removed under reduced pressure. The residue was then taken up in water (10ml) and washed with ether (2x20ml). The combined ethereal fractions were then dried over sodium sulphate. Removal of the solvent and column chromatography (silica gel, petrol/ether 1:5) gave (-)-1-[(p-Benzyloxyphenyl)benzyloxycarbonylmethyl]azetidin-2,3-dione (86) as a syrup (49mg, 84%) whose spectral data was identical with published data⁷⁴; $[\alpha]_D^{29}$ -33.2° (c, 0.46 in chloroform).

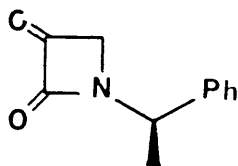
Preparation of (3R) and (3S)-[(1')-oximinoethyl]-1-[(1'R)-phenylethyl] azetidin-2-one



A stream of dry ozone was bubbled through a stirred solution of the isopropenyl β -lactams (77) and (78) (1.0g, 4.64mmol) in dry DCM (55ml) at -78°C , until tlc (ether) showed complete consumption of starting material. Excess dimethylsulphide (1.7ml), and a catalytic amount of methanol were then added and the reaction mixture warmed to RT and stirred overnight.

Removal of solvent and column chromatography of the residue (silica; petrol/ether 1:2) failed to separate the diastereoisomeric acetyl β -lactams which were isolated as a colourless oil (582mg, 60%); ν_{max} (CHCl_3) 2981, 2904, 2256, 1751, 1603, 1470, 1382, 1235, 1015, 915, 750 cm^{-1} ; (3S)-[(1')-oximinoethyl]-1-[(1'R)-phenylethyl] azetidin-2-one; δ (250 MHz) 1.72 (3H, s, COCH_3), 2.34 (3H, d, J 7.0Hz, NCH), 3.00 (1H, dd, J 5.2 and 1.3Hz, 4-CH cis), 3.19 (1H, dd, J 5.2 and 1.3Hz, 4-CH trans), 3.66 (1H, dd, J 5.6 and 2.5Hz, 3-CH), 4.90 (1H, q, J 7.0Hz, PhCH), 7.25 to 7.43 (5H, m, phenyl); (3R)-[(1')-oximinoethyl]-1-[(1'R)-phenylethyl] azetidin-2-one; δ (250 MHz) 1.59 (3H, s, COCH_3), 2.34 (3H, d, J 7.0Hz, NCH), 3.00 (1H, dd, J 5.2 and 1.3Hz, 4-CH cis), 3.19 (1H, dd, J 5.2 and 1.3Hz, 4-CH trans), 3.51 (1H, dd, J 5.6 and 2.5Hz, 3-CH), 4.85 (1H, q, J 7.0Hz, PhCH), 7.25 to 7.43 (5H, m, phenyl) assigned by analogy to (3R) and (3S)-[(1')-oximinoethyl]-1-[(1'S)-phenylethyl] azetidin-2-one as prepared by D.M. Hollinshead⁶⁵.

Preparation of 3-oxo-1-[(1'R)-phenylethyl]azetidin-2-one (100)



(100)

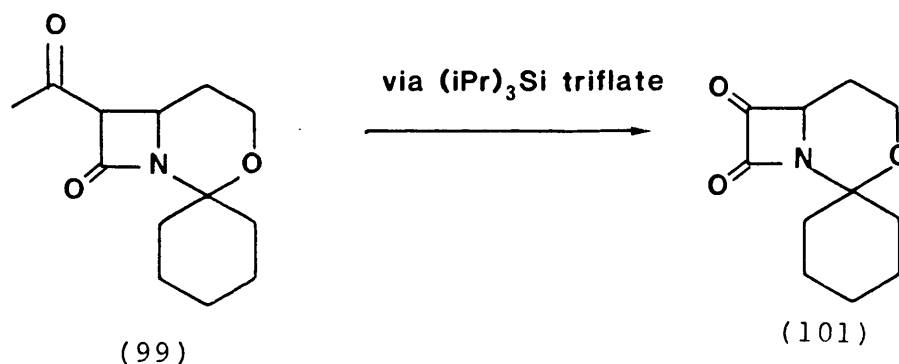
A solution of the (3R) and (3S)-[(1')-oximinoethyl]-1-[(1'R)-phenylethyl] azetidin-2-one (147mg, 0.68mmol) in 1,2-dichloroethane (3ml) was cooled to 0°C under argon and treated with triethylamine (124 μ l, 0.88mmol). After 2 min the solution was treated with tributyltrimethylsilyl trifluoromethanesulphonate (156 μ l, 0.68mol) and the reaction mixture maintained at this temperature until tlc (50% petrol/ether) showed complete consumption of starting material (ca. 10min). The reaction mixture was then concentrated and the residue partitioned between ether (10ml) and saturated sodium bicarbonate solution (5ml). The aqueous phase was then extracted with a further portion of ether and the combined organic phases washed quickly with 0.5M hydrochloric acid, saturated sodium bicarbonate solution and brine. Drying over sodium sulphate and removal of solvent under reduced pressure gave the corresponding silyl enol ether as a colourless gum (85%); ν_{max} 2975, 2931, 2859, 1719, 1604, 1519, 1046, 929, 876 cm^{-1} ; δ (250 MHz) 0.02 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.87 to 0.90 (9H, s, $\text{Si}t\text{Bu}$), 1.59 (3H, d, J.1Hz, NCHMe), 2.10 (3H, s, COCH_3), 3.43 (1H, m, 4-CH), 3.61 (1H, m, 4-CH), 4.96 (1H, m, N-CH), 7.25 to 7.38 (5H, m, phenyl).

The intermediate silyl enol ether was then taken up in DCM (20ml) and methanol (2.5ml) and cooled to -78°C under argon. A stream of ozone was then bubbled through the reaction mixture until the solution

turned bright blue and tlc (50% petrol/ether) indicated complete consumption of the starting material (ca. 5min). Excess ozone was then blown off under a stream of oxygen and the reaction mixture treated with powdered zinc (450mg) and acetic acid (1.1ml) and allowed to warm to room temperature.

The reaction mixture was then filtered through celite and the solvent removed under reduced pressure. The residue was then partitioned between water (5ml) and ether (20ml) and the ethereal phase dried over sodium sulphate. Removal of the solvent gave the 3-ketoazetidin-2-one (100) as a colourless gum (26mg, 82%); $\nu_{\max}$ (CHCl_3) 2930, 2851, 1818, 1763, 1711, 1603, 839, 756 cm^{-1} ; δ (60 MHz) 1.25 (3H, t, J 7.0 Hz, Me), 2.56 (1H, m, NCH), 3.40 (2H, m, 4-CH₂), 7.32 (5H, m, phenyl).

Preparation of the tricyclic 3-keto-azetidin-2-one (101)



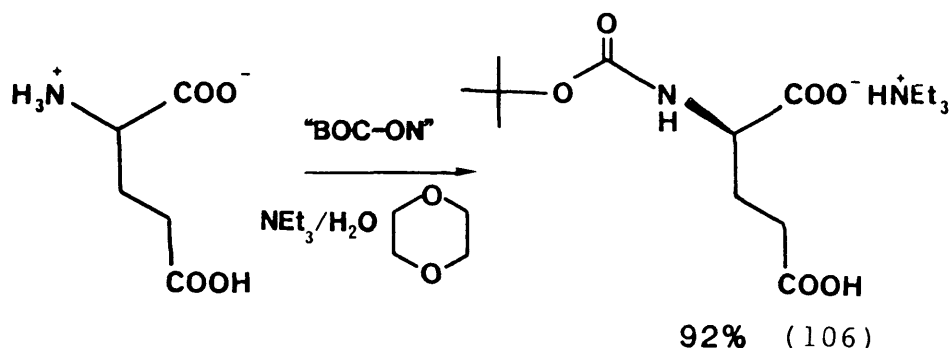
A solution of the 3-acetyl β -lactam (99) (836mg, 1.18mmol) in 1,2-dichloroethane (3ml) was cooled to 0°C under argon and treated with triethylamine (226 μl , 1.65mmol). After 2 min the solution was treated with triisopropylsilyl trifluoromethanesulphonate (350 μl , 1.3mmol) and the reaction mixture maintained at this temperature until tlc (50% petrol/ether) showed complete consumption of starting

material (ca. 10min). The reaction mixture was then concentrated and the residue partitioned between ether (10ml) and saturated sodium bicarbonate solution (5ml). The aqueous phase was then extracted with a further portion of ether and the combined organic phases washed quickly with 0.5M hydrochloric acid, saturated sodium bicarbonate solution and brine. Drying over sodium sulphate and removal of solvent under reduced pressure gave the corresponding silyl enol ether as a colourless gum (85%); $\nu_{\max}$ 2939, 2859, 1751, 1346, 1256, 1198, 1172, 1059 cm^{-1} ; δ (250 MHz) 0.84 (18H, s, (iPr)₃Si), 1.30 to 1.97 (12H, m, 9 to 13-CH₂ and 5-CH₂), 2.29 (3H, s, COCH₃), 3.81 (2H, m, 6-CH₂), 3.95 (1H, m, 4-CH); m/z 393 (M⁺) (Found 393.2704000, calculated 393.2699228 for C₁₉H₂₃SiNO₃ (M⁺)).

The intermediate silyl enol ether was then taken up in DCM (100ml) and methanol (10ml) and cooled to -78°C under argon. A stream of ozone was then bubbled through the reaction mixture until the solution turned bright blue and tlc (50% petrol/ether) indicated complete consumption of the starting material (ca. 5min). Excess ozone was then blown off under a stream of oxygen, the reaction mixture treated with powdered zinc (780mg) and acetic acid (1.9ml) and allowed to warm to room temperature.

The reaction mixture was then filtered through celite and the solvent removed under reduced pressure. The residue was then partitioned between water (5ml) and ether (20ml) and the ethereal phase dried over sodium sulphate. Removal of the solvent gave the 3-ketoazetidin-2-one (101) as a colourless gum (200mg, 95%); $\nu_{\max}$ 3130, 2935, 1849, 1765, 1711, 1287, 1057, 954 cm^{-1} ; δ (250 MHz) 1.21 to 1.93 (12H, m, 9 to 13-CH₂ and 5-CH₂), 3.78 (2H, m, 6-CH₂), 3.92 (1H, m, 4-CH).

Preparation of L-t-butyloxycarbonyl-2-aminopentan-1,5-dioic acid (106)

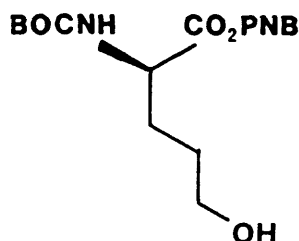


Triethylamine (1.5ml, 10.7mmol) was added to a stirred suspension of L-glutamic acid (500mg 3.4mmol) in 50% aqueous dioxane (10ml).

The mixture was stirred until all the solid had disappeared. Solid "BOC-ON" (837mg, 3.4mmol) was then added and stirring continued for a further 3h.

The dioxane was then removed under reduced pressure and the residue partitioned between water (10ml) and ethyl acetate (10ml). The aqueous phase was then washed with a further portion of ethyl acetate (10ml) and freeze dried to give the N-BOC-derivative (106) as a hygroscopic solid (1.07g, 92%); $\nu_{\max}$ (KBr disc) 3420, 2975, 2932, 2737, 2676, 2491, 2299, 1700, 1591, 1523, 1394, 1365, 1249, 1169, 1053 cm^{-1} ; δ (250 MHz) 1.29 (9H, t, J 7.3Hz, $\text{N}(\text{CH}_2\text{CH}_3)_3$), 1.43 (9H, s, t-Bu), 2.00 to 2.12 (2H, m, 3-CH₂), 2.47 (2H, t, J 6.6Hz, 4-CH₂), 3.08 (6H, q, J 7.4Hz, $\text{N}(\text{CH}_2\text{CH}_3)_3$), 4.22 (1H, m, 2-CH), 5.62 (1H, bd, J 6.1Hz, NH); m/z (FAB spectrum in glycerol) 349 (MH⁺), 248 (MH⁺ for free acid).

Preparation of N-t-butyloxycarbonyl-2-amino-p-nitrobenzyloxy-5-hydroxypentanoic acid (108)

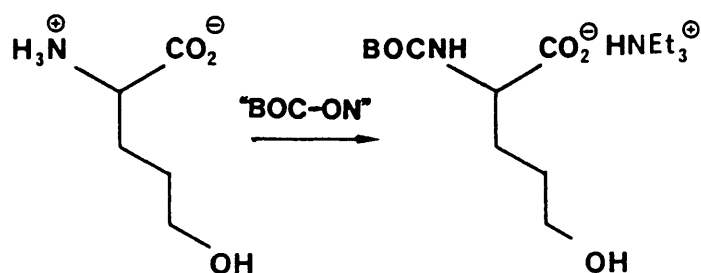


BOC-protected L-glutamic acid (106) (1.48g, 4.3mmol) was treated with acetic anhydride (1.03ml, 4.3mmol) at RT. After 3h, residual acetic anhydride was removed by azeotroping with dry toluene (2x10ml). The residue was then taken up in dry THF (10ml) and treated with solutions of p-nitrobenzylalcohol (1.32g, 8.6mmol) and dicyclohexylamine (857ul, 4.3mmol) in THF. The reaction mixture was then stirred at ambient temperature overnight. Removal of the solvent gave the dicyclohexylamine salt of the diprotected amino acid (107). The residue was then partitioned between ethyl acetate (20ml) and 1M hydrochloric acid (10ml). The aqueous phase was then washed with a further portion of ethyl acetate (10ml), dried and concentrated to give the free acid as a yellow oil.

A solution of the amino acid (1.49g, 3.9mmol) in THF (10ml) was then added dropwise over a period of 0.5h to a cooled solution of $\text{BH}_3\cdot\text{THF}$ (7.8ml of a 1M solution in THF, 7.8mmol) under nitrogen. The reaction mixture was stirred at this temperature for a further 2h, after which the reaction was quenched by addition of 10% glacial acetic acid in methanol. The solvent was then removed and the residue taken up in ethyl acetate and washed sequentially with 1M hydrochloric acid (10ml), water (10ml), and 1M sodium bicarbonate solution (10ml), dried, and concentrated to give N-t-butyloxycarbonyl-2-amino-p-nitrobenzyloxy-5-hydroxypentanoic acid (108) as an orange crystalline solid (807mg, 50%), m.p. 61–63°C; ν_{max} 3513, 3363, 1750, 1684, 1601,

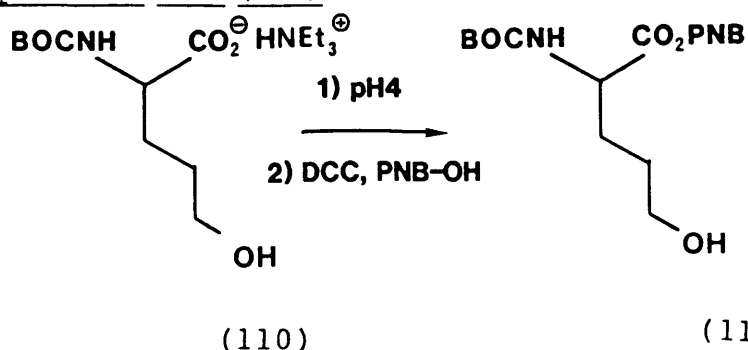
1521, 1343, 829 cm^{-1} ; δ (250 MHz) 1.42 (9H, s, t-Bu), 1.60 (2H, m, 4-CH₂), 2.00 (2H, ddd, J1.7, 4.5, and 9.8Hz, 3-CH₂), 2.12 (1H, bt, J5.5Hz, OH), 3.67 (1H, m, 2-CH), 4.36 (2H, t, J5.5Hz, CH₂OH), 4.84 (2H, d, J5.0Hz, CH₂PNB), 7.55 (2H, dd, J2.9 and 10.6Hz, o-phenyl), 8.22 (2H, dd, J1.8 and 9.1Hz, m-phenyl).

Preparation of N-t-butyloxycarbonyl-2-amino-5-hydroxypentanoic acid (110)



A suspension of the amino acid alcohol (109) (200mg, 1.52mmol) in 50% aqueous dioxane (5ml) was treated with triethylamine (530ul, 3.8mmol) followed by solid "BOC-ON" (374mg, 1.52mmol). The reaction mixture was stirred at RT for a further 2.5h, after which the dioxane was removed under reduced pressure. The residue was then partitioned between water (7ml) and ethyl acetate (10ml). The aqueous phase was then washed with a further portion of ethyl acetate (10ml) and freeze dried to give N-t-butyloxycarbonyl-2-amino-p-nitrobenzyloxy-5-hydroxypentanoic acid (110) as a colourless gum (502mg, 99%); ν_{max} (KBr disc) 3411, 2925, 2935, 1699, 1594, 1497, 1450, 1393, 1248, 1170, 1051 cm^{-1} ; δ (250 MHz) 1.28 (9H, t, J7.3Hz, N(CH₂CH₃)₃), 1.43 (9H, s, t-Bu), 1.69 (2H, m, 4-CH₂), 1.73 to 1.93 (2H, m, 3-CH₂), 3.07 (6H, q, J7.3Hz, N(CH₂CH₃)₃), 3.67 (2H, t, J6.1Hz, 5-CH₂OH), 4.19 (1H, m, 2-CH), 5.52 (1H, m, NH); m/z (FAB spectrum in glycerol) 234 (MH⁺).

Preparation of N-t-butyloxycarbonyl-2-amino-p-nitrobenzyloxy-5-hydroxypentanoic acid (111)



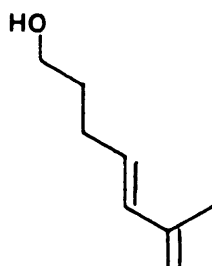
A solution of the N-BOC amino acid alcohol (38mmol) in dry THF (50ml) was treated with p-nitrobenzylalcohol (6.4g, 41.8mmol) and dicyclohexylcarbodiimide (8.6g, 41.8mmol) at 0°C. The reaction mixture was then acidified by dropwise addition of concentrated hydrochloric acid (1.4g) as a solution in THF. The reaction mixture was then allowed to warm to RT overnight.

The resulting suspension was then filtered and the filtrate concentrated. Column chromatography of the residue (silica; ethyl acetate) gave the diprotected amino acid alcohol (111) as an orange crystalline solid (11.0g, 87%) identical to previously prepared material.

Preparation of 1-hydroxybutenolide (123)

(123)

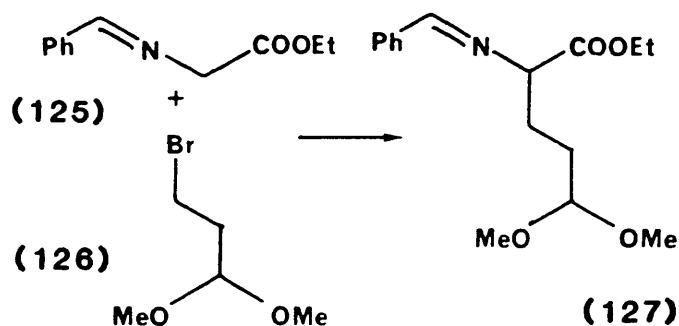
A solution of γ -butyrolactone (17.2g, 15.4ml, 0.2mol) in hexane (220ml) and DCM (100ml), was cooled to -78°C under nitrogen. DIBAL-H (167ml of a 1.5M solution in toluene, 0.25mol) was then added dropwise, whilst maintaining the temperature of the reaction mixture below -60°C . The reaction mixture was stirred at -78°C for a further 0.5h, after which excess DIBAL-H was quenched by addition of methanol (100ml) and the reaction mixture warmed to 0°C . Addition of saturated sodium sulphate solution (20ml) and ether (100ml) precipitated the aluminium salts which were removed by filtration through a silica pad. The filtrate was then distilled through a 15cm Vigreux column to give the lactol (123) as a colourless oil (4.44g, 25%); ν_{max} 3400, 1720, 1460, 1360, 1270, 1060, 1040, 990, 920 cm^{-1} ; δ (250 MHz) 1.58 to 2.25 (4H, m, 2 and 3- CH_2), 3.40 (1H, bs, OH), 3.42 to 4.13 (2H, m, 4- CH_2), 5.53 (1H, bs, 1- CH) identical to previously prepared material¹⁰⁴.

Preparation of 1-hydroxy-6-methylhepta-4,6-diene (124)

A suspension of methylallyltriphenylphosphonium chloride (1.78g, 4.99mmol) in benzene (10ml) was treated with *n*-butyllithium (3.65 ml

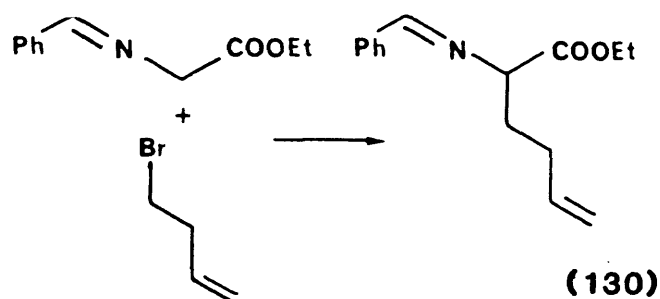
of a 1.5M solution, 5.49mmol). The sealed flask was then placed in an ultrasound cleaning bath at the position where maximum agitation of the flask contents was observed. Sonolysis was continued for an hour, after which a solution of the lactol (123) (400mg, 4.54mmol) in benzene (3ml) was added to the blood red reaction mixture. The reaction was then stirred overnight at RT, and the resulting yellow suspension filtered through a silica pad which was washed thoroughly with ether. Removal of the solvent and repeated trituration with 50% hexane/ethyl acetate gave the dieneol (124) (315mg, 55%) as a pale yellow oil, identical to previously prepared material ¹⁰⁴.

Preparation of N-benzylidene-2-aminocarbethoxy-5,5-dimethoxypentanoic acid (127)



Solid potassium carbonate (4.15g, 30mmol) was added to a solution of the protected glycine (125) in DMF (10ml) at 0°C. The bromide (126) (4.53g, 30mmol) was then added, the reaction mixture warmed to RT and stirred at ambient temperature overnight. The yellow suspension was then partitioned between water (30ml) and ethyl acetate (100ml). The organic phase was then washed with water (2x30ml) and saturated brine (30ml), dried over sodium sulphate, and concentrated to give a yellow oil which was unstable to column chromatography (silica, fluorisil, and basic alumina) (1.91g, 23%); ν_{max} 2934, 2830, 2735, 1701, 1596, 1583, 1122, 1054 cm^{-1} ; δ (250 MHz) 1.30 (3H, t, J 8.2Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.17 (2H, m, 4- CH_2), 3.33 (6H, s, OCH_3), 4.47 to 5.03 (6H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$, 2- CH and 3- CH_2), 7.30 to 8.10 (5H, m, phenyl), 8.30 (1H, s, PhCH).

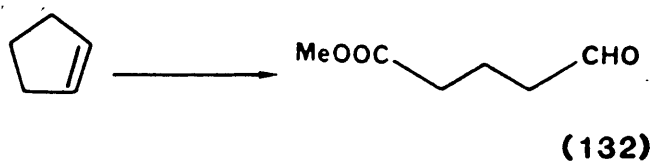
Preparation of N-benzylidene-2-aminocarboethoxy-5-enoic acid (130)



A stirred solution of the diprotected glycine (125) (150mg, 0.79mmol) in THF (10ml) was cooled to -78°C under argon and treated with potassium *t*-butoxide (88mg, 0.79mmol). 1-Bromobut-3-ene (116mg, 0.86mmol) was then added to the deep red solution after 5min and the reaction mixture warmed to RT overnight.

The reaction mixture was then partitioned between saturated ammonium chloride solution (10ml) and ether (20ml). The aqueous phase was then extracted with two further portions of ether (2x10ml) and the combined organic extracts dried and concentrated to give a yellow oil which was unstable to silica gel chromatography and distillation (123mg, 71%); ν_{max} 2925, 2852, 1700, 1596, 1203, 1167 cm^{-1} ; δ (250 MHz) 1.20 to 1.50 (7H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$, 3 and 4- CH_2), 4.20 (1H, m, 2- CH), 4.24 (2H, q, 7.1Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.40 (2H, d, J1.5Hz, 6- CH_2), 5.02 (1H, m, 5- CH), 7.40 to 7.90 (5H, m, phenyl), 8.29 (1H, s, PhCH); m/z 245 (M^+); (Found 244.1337000, $\text{C}_{15}\text{H}_{18}\text{NO}_2$ requires 244.1337540 (M^+)).

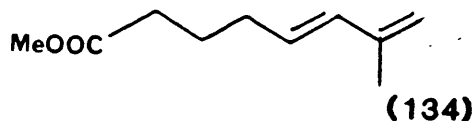
Preparation of methoxycarbonyl-5-oxo-pentanoic acid (132)



A solution of cyclopentene (1.0ml, 11.3mmol) in DCM (50ml)/methanol (10ml) was cooled to -78°C with stirring. A stream of dry ozone was then bubbled through the solution for 0.5h, after which the reaction was judged to be complete by tlc (ether). Excess ozone was then blown off under a stream of oxygen and the reaction mixture treated with tosic acid (77mg, 1.13mmol), and warmed to room temperature. After a further 1.5h the reaction mixture was filtered and azeotroped with benzene. The white residue was then diluted with DCM (10ml) and treated sequentially with triethylamine (1.57ml, 11.3mmol) and acetic anhydride (1.07ml, 11.3mmol). The reaction mixture was then stirred at room temperature for 1.5h, filtered, washed with brine (5ml) and water (5ml), and dried over sodium sulphate. Removal of the solvent and column chromatography (silica; ether) gave a colourless oil which was shown to be a 2:1 mixture of the required methoxycarbonyl-5-oxo-pentanoic acid (132) (793mg, 54%) and its dimethylacetal (133) (517mg, 26%).

A solution of the dimethyl acetal (133) (100mg, 0.57mmol) in acetone (10ml) was treated with a drop of water and stirred over Amberlyst-15 resin for 0.5h. The reaction mixture was then filtered through celite and removal of solvent gave methoxycarbonyl-5-oxo-pentanoic acid (132) as a colourless oil (74 mg, 100%). ν_{max} 2953. 2730. 1733. 1477. 1213. 1167 cm^{-1} ; δ (60 MHz) 6.0 2.17 to 3.10 (6H, m, 1 to 3- CH_2), 3.66 (3H, s, CO_2CH_3), 9.80 (1H, s, CHO) identical to previously prepared material⁹⁸.

Preparation of methoxycarbonyl-7-methyl-octa-5,7-dieneic acid (134)



Methylallyltriphenylphosphonium chloride (428mg, 1.2mmol) was azeotroped with dry toluene (3x10ml), taken up in benzene (5ml) and treated with *n*-butyllithium (846 μ l of a 1.56M solution in hexane, 1.3mmol). The flask was then sealed with a rubber septum and placed in an ultrasound bath and sonicated for 1h, after which the solid had dispersed to give a blood red solution of the Wittig reagent. A solution of the aldehyde (132) (156mg, 1.2mmol) in benzene (1.5ml) was then added dropwise and the reaction mixture stirred overnight at RT.

The pale yellow suspension was then filtered through celite, concentrated and triturated with petrol and filtered to remove excess triphenylphosphine oxide. Removal of the solvent and Kugelrohr distillation (160°C, 14mmHg) gave methoxycarbonyl-7-methyl-octa-5,7-dieneic acid (134) (126mg, 63%) as a colourless oil; $\nu_{\max}$ 2956, 2923, 2851, 1743, 1168, 986, 720 cm^{-1} ; δ (60 MHz) 0.88 (2H, m, 3-CH₂), 1.26 (2H, m, 4-CH₂), 1.67 and 1.76 (3H, s, 7-CH₃), 1.90 to 2.43 (2H, m, 2-CH₂), 3.66 (3H, s, CO₂CH₃), 5.10 to 6.20 (4H, m, 5,6,and 8-CH₂).

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PUBLICATIONS

Use of π -Allyltricarbonyliron Lactam Complexes in the Preparation of Nocardicin Derivatives: Synthesis of (–)-3-Oxo-1-[(*p*-benzyloxyphenyl)-benzyloxycarbonylmethyl]azetidin-2-one

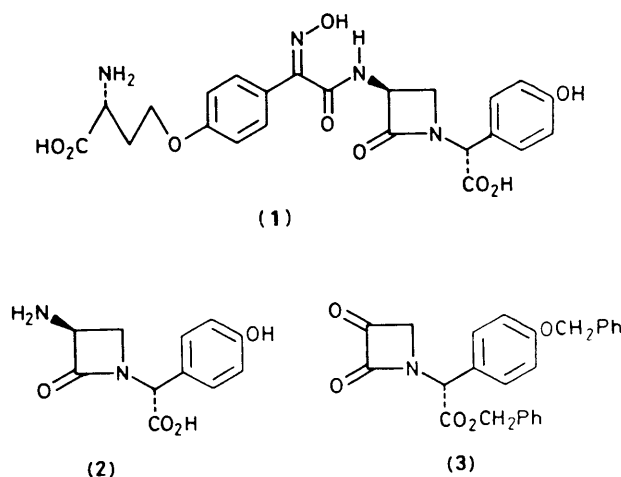
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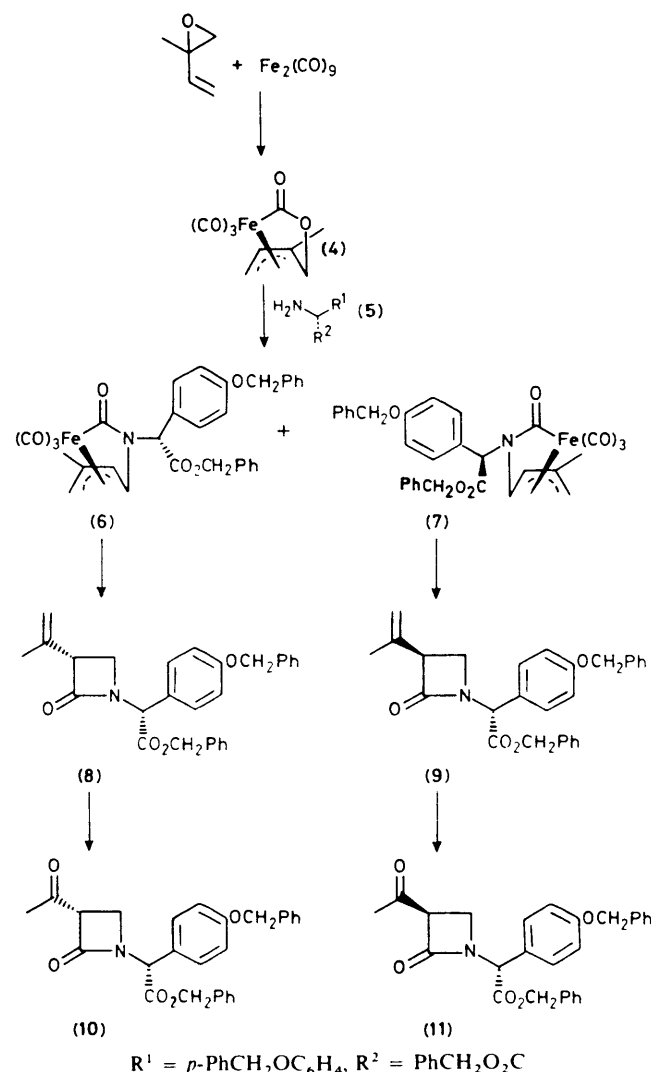
A short five-step synthesis, in 79% overall yield, of (–)-3-oxo-1-[(*p*-benzyloxyphenyl)benzyloxycarbonylmethyl]azetidin-2-one (**3**), a precursor for nocardicin synthesis has been developed from isoprene monoepoxide. The key steps of the procedure rely on the efficient transformation of 2-4- η^3 -(1-formyloxy-2-methylbut-3-en-2-ylato)tricarbonyliron into the corresponding diastereoisomeric lactam complexes (**6**) and (**7**) using D-(–)-benzyl-(*p*-benzyloxyphenyl)glycinate (**5**) and ZnCl_2 -TMEDA (TMEDA = tetramethylethylenediamine), and their oxidation with ceric ammonium nitrate to 3-isopropenylazetidinone derivatives.

The nocardicin antibiotics, typified by nocardicin A (**1**) were first isolated from *Nocardia* species in 1976.¹ Interest in the synthesis of these novel monocyclic β -lactams has been prompted by the wide spectrum of activity they have exhibited against Gram-negative bacteria. Examination of the various published syntheses^{2–7} showed that a general precursor for the nocardicins was 3-aminonocardinic acid (**2**). This had been prepared previously by Ban⁵ in racemic form using a reductive amination sequence from the azetidine-2,3-dione (**3**).

D-(–)-*p*-hydroxyphenylglycine (**5**) in the presence of ZnCl_2 -TMEDA without epimerisation at the chiral centre. The diastereoisomeric lactam complexes (**6**) and (**7**) obtained in 94.5% combined yield, could be readily separated by silica



Here we describe a novel route using iron carbonyl complexes for the preparation of compound (**3**) in its optically pure form. The chemistry is based upon earlier observations, where it was shown that π -allyltricarbonyliron lactone complexes could be converted into the corresponding lactam derivatives which upon oxidation with ceric ammonium nitrate, afford azetidinones.^{8–10} The tricarbonyliron lactone complex precursor (**4**) was prepared from the quantitative reaction of isoprene monoepoxide with nonacarbonyldi-iron in tetrahydrofuran (THF) at room temperature according to our previously published procedure.¹¹ The requisite, suitably protected N-substituent could then be introduced in its entirety by reaction of the lactone complex (**4**) with the dibenzylated derivative of



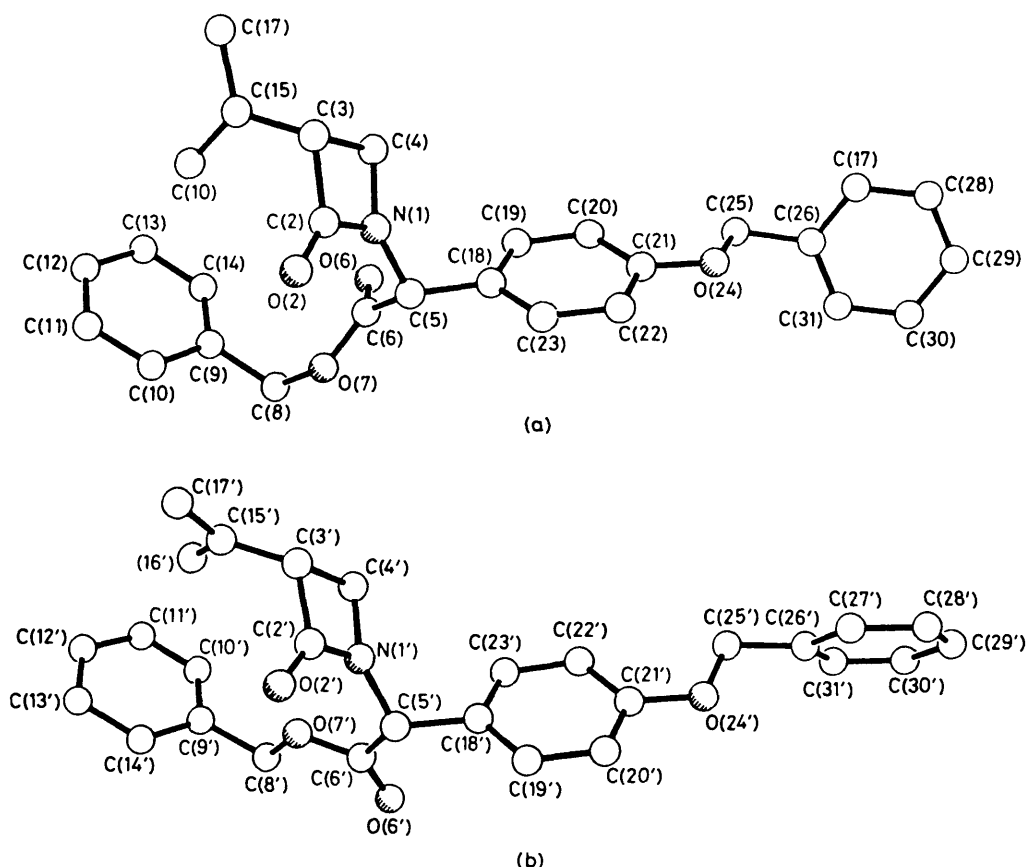
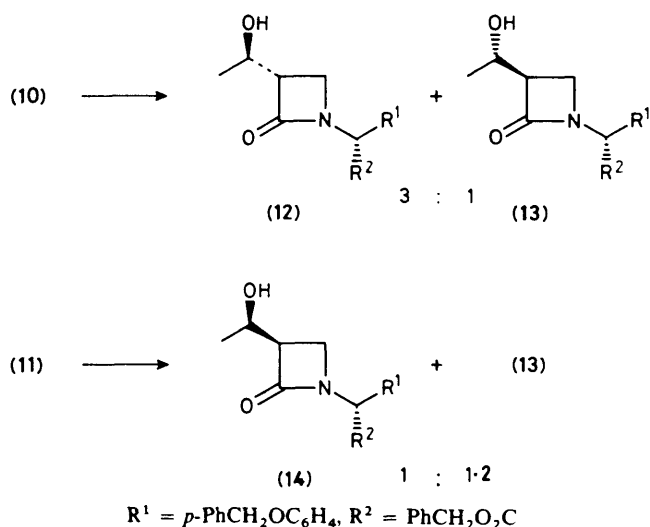
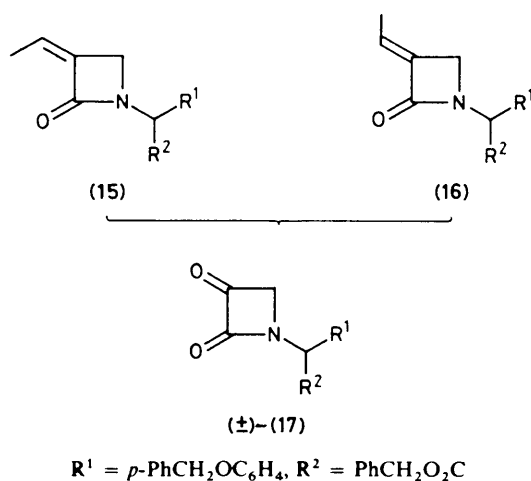


Figure. The molecular structure of 1-(3*R*)-[(1'*R*)-(p-benzyloxyphenyl)benzyloxycarbonylmethyl]-3-isopropenylazetidin-2-one (**8**) showing (a) and (b) the two conformations of the molecule in the crystal and giving the crystallographic numbering scheme.

gel chromatography. The structural assignment for these two diastereoisomers follows from highfield ^1H n.m.r. studies and from an X-ray crystallographic structure determination of a subsequent derivative. Oxidation of the lactam complex (**6**) with cerium(IV) at -30°C afforded the azetidinone (**8**) in an excellent 99% yield. The relative stereochemistry of the appending isopropenyl substituent at C-3 in this compound follows from comparison with similar molecules and was confirmed by X-ray crystallographic analysis (see Figure). This determination also provides evidence for the structure assigned to the original complex (**6**). Similar oxidation of the diastereoisomer (**7**) gave the azetidinone (**9**) in 87% yield. Efforts were then made to convert the isopropenyl substituted azetidinones (**8**) and (**9**) into nocardicin precursors. Low temperature (-78°C) ozonolysis of (**8**) gave the 3 α -acetyl- β -lactam (**10**) while similar treatment of (**9**) afforded (**11**). Although each acetyl derivative was characterised spectroscopically using freshly prepared materials, as a result of the acidity of the 3-H proton, rapid epimerisation occurred upon storage at 0°C over 16 h to give a 1:1 mixture. Reduction of the freshly prepared 3 α -acetyl derivative (**10**) with K-Selectride at -78°C furnished a 3:1 mixture of the diastereoisomeric alcohols (**12**) and (**13**) in 64% yield, which were inseparable by chromatography. Treatment of the 3 β -acetyl derivative (**11**) with the weakly basic zinc borohydride reagent gave a 1.2:1 ratio of separable diastereoisomeric alcohols in 80% yield which we believe to be (**13**) and (**14**) formed by non-selective reduction of the carbonyl function. This lack of selectivity is in contrast to other reports on 3-acetylazetidinones.^{1,2} The major isomer in this last reaction was found to have an ^1H n.m.r. spectrum identical with the minor isomer



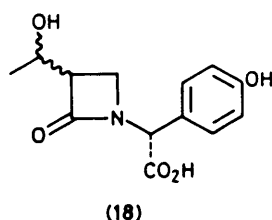
obtained from the K-Selectride reaction of (**10**). From these and later results, it appears that the Selectride reagent is sufficiently basic to cause some epimerisation prior to reduction, but that reduction of the carbonyl group is selective. Indeed, separate treatment of a 1:1 mixture of (**10**) and (**11**) with K-Selectride gave the same alcohols, albeit in a different ratio. Evidence to support the stereochemical assignment for the alcohols (**12**), (**13**), and (**14**) is provided by their subsequent elimination products. Treatment of the diastereoisomeric mixture (**13**) and



(14) with methanesulphonyl chloride gave the corresponding mesylates. Regiospecific elimination with diazabicycloundecene (DBU), proceeded slowly to give an isomeric mixture of the olefins (15) and (16) which are chromatographically separable. Similar exposure of the mesylates derived from (12) and (13) with DBU gave predominantly the *E*-ene lactam (16). The stereochemical assignments of (15) and (16) are made on the basis of the known anisotropy effects due to the carbonyl group,¹³ which profoundly influences the chemical shifts of the methyl and vinyl protons, *e.g.* δ 2.02 and 5.62 for the methyl and vinyl protons respectively in compound (15) and 1.68 and 6.17 for similar protons in (16). In view of the predominant *anti*-elimination of alcohol mesylates,^{12b} the *Z,E*-mixture of ene lactams must have arisen from a *threo*-, *erythro*-mixture of alcohols as in (13) and (14). Conversely, the *E*-ene lactam (16) could only have been derived from an *erythro*-mixture in accord with the assigned structures for (12) and (13).

Although the elimination sequence appeared to be successful, a polarimetry measurement of the isomeric mixture of ene lactams showed that racemisation had apparently occurred at the chiral centre. The base lability at this activated benzylic position has been commented on previously.^{3,4,14} Alternative conditions for effecting elimination of the mesylates *without* epimerisation at the activated centre were investigated but without success. Ozonolysis of the ene lactams (15) and (16) at -25°C gave the racemic 3-oxoazetidinone (17) in 84% yield, characterised by its high carbonyl stretching frequency of ν_{max} . 1855 cm^{-1} .

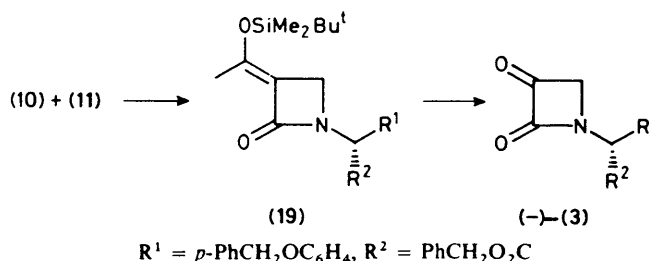
In an effort to prepare potentially interesting pharmaceutical compounds related to the nocardicins in which the C-3 position contained a hydroxyethyl substituent, a group common to many β -lactam antibiotics,¹⁵ the 3-acetylazetidinones (10) and (11) were reduced with K-Selectride to give a diastereoisomeric mixture of alcohols [mainly (12) and (13)] in 64% yield. These were deprotected using Pd-C in a hydrogen atmosphere to afford the free carboxylic acid (18) (82%). However, on



biological evaluation, this mixture of compounds (18) only showed very low levels of antibiotic activity.

Owing to the epimerisation problem noted earlier, an alternative route was sought whereby the configuration at the

chiral centre adjacent to the lactam nitrogen would not be lost and hence permit preparation of the 3-oxoazetidinone (3) in its optically pure form. To this end we found that treatment of a 1:1 mixture of the 3-acetyl derivatives (10) and (11) obtained by quantitative ozonolysis of a crude mixture of (8) and (9), with dimethyl-*t*-butylsilyl triflate at 0°C in the presence of triethylamine gave the enol ether (19) also in essentially



quantitative yield. Isolation of this compound was unnecessary since ozonolysis of the crude reaction mixture, followed by reductive work-up, gave optically pure (-)-3-oxoazetidinone (3) in 84% yield. The whole sequence described above leading to (3) in five steps from isoprene epoxide proceeds in a remarkably high 79% overall yield.

Since 3-oxoazetidinone (17) has been converted into 3-aminonocardicinic acid⁵ (2) and hence the nocardicins, this new route should be considered as a potential enantioselective synthesis of these systems. All attempts to use the existing chirality of the 3 β -acetylazetidinone (11) in a direct synthesis of (-)-3-aminonocardicinic acid by way of a Beckmann-type reaction were unsuccessful. This was attributed to the reluctance of the β -lactam nucleus to stabilise a partial positive charge at C-3 in the transition state for migration.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^1H N.m.r. spectra were obtained on Bruker WH-250, Jeol FX90Q, or Varian EM360A instruments for solutions in CDCl_3 with tetramethylsilane as an internal standard. I.r. spectra were recorded in chloroform solution on either a Perkin-Elmer 298 or 983 G spectrophotometer. Mass spectra were determined with a VG 7070 B instrument. Optical rotations were measured using a Perkin-Elmer 141 polarimeter at ambient temperature. Chromatography was performed on MN-silica gel 60 (230–400 mesh) under pressure. Petroleum refers to a light petroleum fraction of b.p. $40\text{--}60^\circ\text{C}$ which was distilled before use; ether refers to diethyl ether. All solvents were dried and purified by standard techniques.

Preparation of 2-4- η^3 -(1-[(1'R)-(p-Benzyloxyphenyl)-(benzyloxycarbonyl)methyl]formylamino}-3-methylbut-3-en-2-ylato)tricarbonyliron (6) and (7).—To a stirred solution of the lactone complex (4) (838 mg, 2.9 mmol) and $\text{ZnCl}_2\cdot\text{TMEDA}$ (1.46 g, 5.8 mmol) in ether-THF (1:1; 30 ml), D-(-)-benzyl-(p-benzyloxyphenyl)glycinate (5) (4.03 g, 11.6 mmol) (prepared from its hydrochloride salt by shaking an ethereal suspension with anhydrous NaHCO_3) in ether-THF (1:1; 7 ml) was added under argon. After 5 h, a further quantity of the lactone complex (4) (227 mg, 0.8 mmol) was added to the reaction mixture. After a further 3.5 h, the reaction mixture was diluted with ether (120 ml) and washed with 6% aqueous HCl (2×30 ml). The aqueous layers were re-extracted with ether (60 ml) and the combined organic extracts washed with water and then brine and, finally dried. Removal of solvent gave a foam which was carefully

chromatographed using a solvent gradient (25–45% ether–petroleum) to give the complex (6) (1.276 g, 60.5%) as a form, $\nu_{\max}$ 3 050, 2 980, 2 930, 2 070, 2 010, 1 995, 1 735, 1 610, 1 580, 1 505, 1 395, 1 380, 1 280, 1 250, 1 160, and 1 005 cm^{-1} ; δ (250 MHz) 1.97 (3 H, s, 3-Me), 2.85 (1 H, dd, J 12 and 7 Hz, 1-H), 3.07 (1 H, d, J 1.5 Hz, 4'-H), 3.33 (1 H, br d, J 12 Hz, 1'-H), 3.59 (1 H, dd, J 1.5 and 1.5 Hz, 4-H), 4.15 (1 H, br d, J 7 Hz, 2-H), 5.02 (2 H, s, PhCH_2), 5.07 (1 H, d, J_{AB} 16 Hz, PhCH_2), 5.19 (1 H, d, J_{AB} 16 Hz, PhCH_2), 6.00 (1 H, s, NCH), 6.87 (2 H, d, J_{AB} 8 Hz, Ar), 6.97 (2 H, d, J_{AB} 8 Hz, Ar), and 7.22–7.46 (10 H, m, Ph); m/z 441 [$M^+ - \text{Fe}(\text{CO})_3 < 1\%$], 375, and 242 [Found: C, 63.35; H, 4.6; N, 2.3%; $M^+ - \text{Fe}(\text{CO})_3$, 441.1935. $\text{C}_{30}\text{H}_{27}\text{NFeO}_7$ requires C, 63.28; H, 4.78; N, 2.40%; $M^+ - \text{Fe}(\text{CO})_3$, 441.1940] and the complex (7) (0.708 g, 34%) as a foam, $\nu_{\max}$ 3 040, 2 950, 2 920, 2 870, 2 070, 2 010, 1 995, 1 735, 1 605, 1 585, 1 450, 1 400, 1 375, 1 260, 1 160, and 1 000 cm^{-1} ; δ (250 MHz) 1.92 (3 H, s, 3-Me), 2.64 (1 H, d, J 1.5 Hz, 4-H), 2.82 (1 H, br d, J 12 Hz, 1'-H), 3.50 (1 H, dd, J 1.5 and 1.5 Hz, 4'-H), 3.66 (1 H, dd, J 12 and 7 Hz, 1-H), 4.22 (1 H, br d, J 7 Hz, 2-H), 5.02 (2 H, s, PhCH_2), 5.18 (2 H, s, PhCH_2), 5.72 (1 H, s, NCH), 6.87 (2 H, d, J_{AB} 8 Hz, Ar), 6.97 (2 H, d, J_{AB} 8 Hz, Ar), and 7.20–7.46 (10 H, m, Ph) [Found: C, 63.5; H, 4.55; N, 2.35%; $M^+ - \text{Fe}(\text{CO})_3$, 441.1937. $\text{C}_{30}\text{H}_{27}\text{FeNO}_7$ requires C, 63.28; H, 4.78; N, 2.40%; $M^+ - \text{Fe}(\text{CO})_3$, 441.1940].

Preparation of (3R)-1-[(1R')-(p-Benzoyloxyphenyl)benzyloxy-carbonylmethyl]-3-isopropenylazetidin-2-one (8).—A solution of the lactam (6) (1.126 g, 1.98 mmol) in ethanol (70 ml) was cooled to -30°C and a solution of ceric ammonium nitrate (5.42 g, 9.9 mmol) in ethanol (70 ml) was added with stirring over a period of 10 min. The reaction was allowed to warm to room temperature over 2 h, whereupon the solvent was removed and the residue partitioned between water (60 ml) and CH_2Cl_2 (220 ml). The organic layer was further washed with water (60 ml) and brine (60 ml) to give, after drying and chromatography (45% ether–petroleum), the azetidinone (8) (0.865 g, 99%) as an oil which slowly crystallised as white rosettes, m.p. 68°C ; $[\alpha]_{\text{D}}^{22} - 52.1^\circ$ (c, 2.0 in CHCl_3); δ (250 MHz) 1.79 (3 H, s, Me), 3.18 (1 H, dd, J 5.5 and 5.5 Hz, *cis*-4-H), 3.51 (1 H, dd, J 5.5 and 3.0 Hz, *trans*-4-H), 3.70 (1 H, dd, J 5.5 and 3.0 Hz, 3-H), 4.92 (2 H, m, CH_2), 5.06 (2 H, s, PhCH_2), 5.19 (2 H, s, PhCH_2), 5.62 (1 H, s, NCH), 6.94 (2 H, d, J_{AB} 8.5 Hz, Ar), 7.16 (2 H, d, J_{AB} 8.5 Hz, Ar), and 7.21–7.46 (10 H, m, Ph); $\nu_{\max}$ 3 080, 3 060, 3 020, 2 980, 1 750, 1 735, 1 645, 1 610, 1 585, 1 500, 1 455, 1 380, 1 260, 1 225, 1 165, 1 010, and 910 cm^{-1} ; m/z 441 (M^+ , 1%), 373, 306, 238, and 91 (100) (Found: C, 76.4; H, 6.2; N, 3.15%; M^+ , 441.1944. $\text{C}_{28}\text{H}_{27}\text{NO}_4$ requires C, 76.17; H, 6.16; N, 3.17%; M^+ , 441.1940).

Preparation of (3S)-1-[(1R')-(p-Benzoyloxyphenyl)benzyloxy-carbonylmethyl]-3-isopropenylazetidin-2-one (9).—Ceric ammonium nitrate (2.75 g, 5.0 mmol) in ethanol (40 ml) was added dropwise to a cooled (-30°C) solution of the lactam complex (7) (558 mg, 0.98 mmol) in ethanol (25 ml) with stirring. The reaction mixture was allowed to warm to room temperature over 2 h, when solvent was removed and the gummy residue partitioned between CH_2Cl_2 (180 ml) and 3% aqueous NaHCO_3 . The organic phase was washed sequentially with water and brine, and evaporated and the residue chromatographed (45% ether–petroleum) to give the azetidinone (9) (378 mg, 87%) as a colourless oil, $[\alpha]_{\text{D}}^{22} - 140.0^\circ$ (c, 1.5 in CHCl_3); $\nu_{\max}$ 3 070, 3 040, 2 980, 1 750, 1 735, 1 645, and 1 260 cm^{-1} ; δ (250 MHz) 1.65 (3 H, s, Me), 2.96 (1 H, dd, J 5.0 and 2.1 Hz, *trans*-4-H), 3.75 (1 H, dd, J 5.3 and 5.0 Hz, *cis*-4-H), 3.83 (1 H, m, 3-H), 4.86 (2 H, m, $=\text{CH}_2$), 5.06 (2 H, s, PhCH_2), 5.20 (2 H, s, PhCH_2), 5.64 (1 H, s, NCH), 6.94 (2 H, d, J_{AB} 8.9 Hz, Ar), 7.17 (2 H, d, J_{AB} 8.9 Hz, Ar), and 7.20–7.46 (10 H, m, Ph); m/z 441

(M^+ , 1%), 373, 306, 238, and 91 (100) (Found: C, 76.25; H, 6.3; N, 3.10%; M^+ , 441.1931. $\text{C}_{28}\text{H}_{27}\text{NO}_4$ requires C, 76.17; H, 6.16; N, 3.17%; M^+ , 441.1940).

Preparation of (3R)-3-Acetyl-1-[(1R')-(p-benzyloxyphenyl)-benzyloxycarbonylmethyl]azetidin-2-one (10).—A solution of the isopropenylazetidinone (8) (120 mg, 0.27 mmol) in CH_2Cl_2 (10 ml) was treated with ozone at -78°C until no starting material was present by t.l.c. (60% ether–petroleum). Dimethyl sulphide was added and the reaction warmed to room temperature and stirred for 1 h. Removal of solvent gave a single diastereoisomeric ketone (10) (120 mg, 100%) as a syrup, $\nu_{\max}$ (film) 3 080, 3 060, 3 030, 1 750, 1 740, 1 722, 1 610, 1 510, and 1 240 cm^{-1} ; δ (250 MHz) 2.30 (3 H, s, COCH_3), 3.09 (1 H, dd, J 5.4 and 5.4 Hz, *cis*-4-H), 3.94 (1 H, dd, J 5.4 and 2.9 Hz, *trans*-4-H), 4.01 (1 H, dd, J 5.4 and 2.9 Hz, 3-H), 5.06 (2 H, s, PhCH_2), 5.19 (2 H, s, PhCH_2), 5.56 (1 H, s, NCH), 6.96 (2 H, d, J_{AB} 8.8 Hz, Ar), 7.10 (2 H, d, J_{AB} 8.8 Hz, Ar), and 7.21–7.45 (10 H, m, Ph); m/z 443 (M^+ , <1%), 353, 308 (100), 212, and 91 (Found: M^+ , 443.1722. $\text{C}_{27}\text{H}_{25}\text{NO}_5$ requires M , 443.1733).

Preparation of (3S)-3-Acetyl-1-[(1R')-(p-benzyloxyphenyl)-benzyloxycarbonylmethyl]azetidin-2-one (11).—A solution of the alkenylazetidinone (9) (164 mg, 0.37 mmol) in CH_2Cl_2 (10 ml) was treated with ozone at -78°C , until t.l.c. (60% ether–petroleum) indicated the disappearance of all starting material. The mixture was then stirred with dimethyl sulphide for 1 h at room temperature after which the solvent was removed to afford a single diastereoisomeric ketone (11) (164 mg, 100%) which showed an i.r. spectrum similar to that of (10) above, δ (250 MHz) 2.26 (3 H, s, COCH_3), 3.47 (1 H, dd, J 5.4 and 2.9 Hz, *trans*-4-H), 3.56 (1 H, dd, J 5.4 and 5.4 Hz, *cis*-4-H), 4.20 (1 H, dd, J 5.4 and 2.9 Hz, 3-H), 5.04 (2 H, s, PhCH_2), 5.18 (2 H, s, PhCH_2), 5.55 (1 H, s, NCH), 6.96 (2 H, d, J_{AB} 8.5 Hz, Ar), 7.10 (2 H, d, J_{AB} 8.5 Hz, Ar), and 7.21–7.45 (10 H, m, Ph).

Reduction of (3R)-3-Acetyl-1-[(1R')-(p-benzyloxyphenyl)-benzyloxycarbonylmethyl]azetidin-2-one (10).—To a cooled (0°C) solution of the freshly prepared crude ketone (10) in THF (2 ml), K-Selectride (0.5M-solution in THF; 1.1 ml) was added and the reaction stirred for a further 0.25 h. The mixture was quenched with water, warmed to room temperature, and extracted with ethyl acetate to give the hydroxyethylazetidinones (12) and (13) (77 mg, 64%) in a 3:1 ratio as a syrup, $[\alpha]_{\text{D}}^{22} - 30.3^\circ$ (c, 0.65 in CH_2Cl_2); $\nu_{\max}$ (film) 3 400, 3 080, 3 060, 3 030, 2 920, 1 740, 1 610, 1 570, 1 510, and 1 240 cm^{-1} ; (13) δ (250 MHz) 1.18 (3 H, d, J 6 Hz, Me), 2.91 (1 H, dd, J 5.5 and 2.5 Hz, *trans*-4-H), 3.21 (1 H, dd, J 6.5, 5.5, and 2.5 Hz, 3-H), 3.48 (1 H, dd, J 5.5 and 5.5 Hz, *cis*-4-H), 3.91 (1 H, dd, J 6.5 and 6 Hz, CHOH), 5.02 (2 H, s, PhCH_2), 5.17 (2 H, s, PhCH_2), 5.60 (1 H, s, NCH), 6.92 (2 H, d, J_{AB} 8.5 Hz, Ar), 7.16 (2 H, d, J_{AB} 8.5 Hz, Ar), and 7.22–7.44 (10 H, m, Ph); (12) δ (250 MHz), 1.25 (3 H, d, J 6 Hz, Me), 3.10 (1 H, m, 3-H), 3.40 (1 H, dd, J 6 and 5.5 Hz, *cis*-4-H), 4.08 (1 H, dq, J 6 and 5.5 Hz, CHOH), 5.04 (2 H, s, PhCH_2), 5.17 (2 H, s, PhCH_2), 5.57 (1 H, s, NCH), 6.92 (2 H, d, J_{AB} 8.5 Hz, Ar), 7.15 (2 H, d, J_{AB} 8.5 Hz, Ar), and 7.22–7.44 (10 H, m, Ph); m/z 445 (M^+ , <1%), 310 (100), 266, and 91 (Found: M^+ , 445.1890. $\text{C}_{27}\text{H}_{27}\text{NO}_5$ requires M , 445.1889).

Reduction of (3S)-3-Acetyl-1-[(1R')-(p-benzyloxyphenyl)-benzyloxycarbonylmethyl]azetidin-2-one (11) with Zinc Borohydride.—The freshly prepared 3-acetylazetidinone (11) was stirred in ether (8 ml) at 0°C and $\text{Zn}(\text{BH}_4)_2$ (0.13M solution in ether; 1.0 ml) was added. After 0.5 h, the reaction was quenched with water at 0°C and the mixture extracted with ethyl acetate. Chromatography (ether) provided a 1:1.2 diastereoisomeric mixture of the hydroxyethylazetidinones (14) and (13) (132 mg, 80%); $[\alpha]_{\text{D}}^{22} - 139.3^\circ$ (c, 0.9 in CHCl_3); $\nu_{\max}$ 3 400, 3 080, 3 060, 3 030, 1 920, 1 740, 1 610, 1 570, 1 510, and 1 240 cm^{-1} ; (14) δ

(250 MHz) 1.21 (3 H, d, J 7.5 Hz, Me), 3.08 (1 H, dd, J 5.5 and 2.5 Hz, *trans*-4-H), 3.22 (1 H, m, 3-H), 3.58 (1 H, dd, J 5.5 and 5.5 Hz, *cis*-4-H), 4.02 (1 H, dq, J 7.5 and 5.5 Hz, CHOH), 5.01 (2 H, s, PhCH₂), 5.17 (2 H, s, PhCH₂), 6.00 (1 H, s, NCH), 6.91 (2 H, J_{AB} 8.5 Hz, Ar), 7.16 (2 H, d, J_{AB} 8.5 Hz, Ar), and 7.22–7.44 (10 H, m, Ph).

Preparation of (Z)- and (E)-3-Ethylidene-1-[(p-benzyloxyphenyl)benzyloxycarbonylmethyl]azetidin-2-ones (15) and (16).—The diastereoisomeric mixture of β -lactams (13) and (14) (108 mg, 0.24 mmol) in CH₂Cl₂ (3 ml) was stirred with triethylamine (67 μ l, 0.48 mmol) and methanesulphonyl chloride (27 μ l, 0.35 mmol) at 0 °C, for 0.5 h. The reaction mixture was diluted with CH₂Cl₂ (25 ml) and washed with 0.1M-HCl (3 ml), water (2 $\times$ 3 ml), and brine (5 ml), and then dried and evaporated to provide the corresponding mesylates, as a syrup, $\nu_{\max}$ 3 030, 2 920, 1 755, 1 740, 1 610, 1 350, 1 240, 1 175, and 910 cm⁻¹; m/z 522 (M^+ , < 1%), 418, 387, 290, and 91 (100). To a stirred solution of the crude mesylates in CH₂Cl₂ (0.75 ml) at 0 °C, DBU (40 μ l, 0.26 mmol) was added and the reaction followed by t.l.c. (ether). After 5 h, the reaction mixture was diluted with CH₂Cl₂ (20 ml) and washed with 10% aqueous citric acid, water, and brine. Removal of the solvent furnished an isomeric mixture of enelactams (85 mg, 67%) which were chromatographically separated (50% ether–petroleum) to give the (Z)-azetidin-2-one (15), $\nu_{\max}$ 3 040, 2 890, 1 740, 1 610, 1 510, 1 380, 1 250, and 1 195 cm⁻¹; δ (90 MHz) 2.02 (3 H, d, J 7.0 Hz, Me), 3.46 (1 H, d, J_{AB} 7.0 Hz, 4-H), 3.98 (1 H, d, J_{AB} 7.0 Hz, 4-H), 5.04 (2 H, s, PhCH₂), 5.18 (2 H, s, PhCH₂), 5.62 (1 H, q, J 7.0 Hz, vinyl H), 5.68 (1 H, s, NCH), 6.91 (2 H, d, J_{AB} 8.9 Hz, Ar), 7.13 (2 H, d, J_{AB} 8.9 Hz, Ar), and 7.15–7.44 (10 H, m, Ph) and the (E)-azetidin-2-one (16), $\nu_{\max}$ 2 960, 2 870, 1 735, 1 610, 1 305, and 1 180 cm⁻¹; δ (90 MHz) 1.68 (3 H, d, J 7.0 Hz, Me), 3.54 (1 H, d, J_{AB} 7.1 Hz, 4-H), 4.07 (1 H, d, J_{AB} 7.1 Hz, 4-H), 5.05 (2 H, s, PhCH₂), 5.19 (2 H, s, PhCH₂), 5.68 (1 H, s, NCH), 6.17 (1 H, q, J 7.0 Hz, vinyl H), 6.92 (2 H, d, J_{AB} 8.8 Hz, Ar), 7.17 (2 H, d, J_{AB} 8.8 Hz, Ar), and 7.18–7.46 (10 H, m, Ph); m/z 427 (M^+ , < 1%), 292, and 91 (100) (Found: C, 75.65; H, 6.0; N, 3.15%. C₂₇H₂₅NO₄ requires C, 75.85; H, 5.89; N, 3.28%).

Preparation of (E)-3-Ethylidene-1-[(p-benzyloxyphenyl)benzyloxycarbonylmethyl]azetidin-2-one (16).—A solution of methanesulphonyl chloride (23 mg, 0.20 mmol) in CH₂Cl₂ (0.5 ml) was added to a solution of the hydroxyethylazetidinones (12) and (13) (58 mg, 0.13 mmol) and triethylamine (36 μ l, 0.26 mmol) in CH₂Cl₂ (3.5 ml) at 0 °C. After 1 h, the reaction was diluted with CH₂Cl₂ (10 ml), washed with 0.1M-aqueous HCl (2 ml), water, 5% aqueous NaHCO₃, and brine, dried, and evaporated to furnish the crude mesylates which were dissolved in CH₂Cl₂ (300 μ l) and treated with DBU (22 mg, 0.22 mmol) at 0 °C. The reaction mixture was stirred for 3.5 h and then diluted with CH₂Cl₂ (10 ml) and washed with 10% aqueous citric acid, water, and brine. It was then dried (MgSO₄) and evaporated to give the *E*-enelactam (16) (54 mg, 97%), identical with previously prepared material above.

Preparation of 1-[(p-Benzyloxyphenyl)benzyloxycarbonylmethyl]azetidine-2,3-dione (17).—The enelactams (15) and (16) (60 mg, 0.14 mmol) in CH₂Cl₂ (8 ml) were treated with ozone at –25 °C until no starting material remained (by t.l.c.). Dimethyl sulphide was added, and the reaction stirred for 2 h. Solvent was removed and the residue chromatographed (80% ether–petroleum) to give the keto-lactam (17) (47 mg, 84%) as a syrup, $\nu_{\max}$ 2 920, 1 855, 1 780, 1 740, 1 610, 1 510, and 1 195 cm⁻¹; δ (250 MHz) 3.68 (1 H, d, J 10.2 Hz, 4-H), 4.31 (1 H, d, J 10.2 Hz, 4-H), 5.08 (2 H, s, PhCH₂), 5.22 (2 H, d, J 2.5 Hz, PhCH₂), 5.94 (1 H, s, NCH), 6.96 (2 H, dd, J 7.1 and 2.3 Hz, Ar), 7.16 (2 H, dd, J 7.1 and 2.3 Hz, Ar), and 7.21–7.48 (10 H, m, Ph).

Preparation of 3-(1'-Hydroxyethyl)-1-[(1'R)-(p-hydroxyphenyl)carboxymethyl]azetidin-2-ones (18) and (19).—A mixture of azetidin-2-ones (10) and (11) (70 mg, 0.16 mmol) in

Table 1. Atomic co-ordinates ($\times 10^4$) and temperature factors ($\text{\AA}^2 \times 10^3$)

Atom	x	y	z
N(1)	2 438(5)	7 361(5)	8 803(1)
C(2)	1 605(6)	6 114(6)	8 948(1)
O(2)	–303(5)	5 603(4)	8 965(1)
C(3)	3 898(7)	5 737(5)	9 077(1)
C(4)	4 751(7)	7 158(7)	8 903(1)
C(5)	1 311(7)	8 575(5)	8 632(1)
C(6)	1 003(6)	10 155(6)	8 790(1)
O(6)	2 484(5)	11 142(5)	8 845(1)
O(7)	–1 091(4)	10 272(4)	8 872(1)
C(8)	–1 646(8)	11 663(6)	9 048(1)
C(9)	–1 093(7)	12 240(6)	9 330(1)
C(10)	–2 604(8)	10 337(8)	9 474(1)
C(11)	–2 130(11)	9 949(9)	9 736(1)
C(12)	–171(12)	10 472(10)	9 852(1)
C(13)	1 343(10)	11 400(9)	9 711(1)
C(14)	834(8)	11 779(8)	9 451(1)
C(15)	4 052(7)	6 015(6)	9 370(1)
C(16)	2 544(9)	6 977(9)	9 495(1)
C(17)	5 950(9)	5 229(9)	9 502(1)
C(18)	2 494(6)	8 806(5)	8 372(1)
C(19)	4 429(7)	9 687(6)	8 342(1)
C(20)	5 478(7)	9 824(6)	8 102(1)
C(21)	4 514(7)	9 037(6)	7 884(1)
C(22)	2 590(7)	8 109(6)	7 909(1)
C(23)	1 572(7)	8 001(6)	8 152(1)
C(24)	5 384(5)	9 069(4)	7 635(1)
C(25)	7 170(8)	10 165(7)	7 585(1)
C(26)	7 592(7)	10 171(7)	7 293(1)
C(27)	9 456(8)	9 442(7)	7 197(1)
C(28)	9 887(9)	9 459(8)	6 928(1)
C(29)	8 429(10)	10 227(9)	6 760(1)
C(30)	6 543(10)	10 959(9)	6 854(1)
C(31)	6 112(8)	10 942(8)	7 121(1)
N(1')	4 825(6)	4 080(6)	6 285(1)
C(2')	6 606(8)	3 514(10)	6 166(1)
O(2')	8 415(6)	4 166(9)	6 125(1)
C(3')	5 495(9)	1 903(7)	6 085(1)
C(4')	3 414(9)	2 647(8)	6 217(1)
C(5')	4 378(8)	5 703(8)	6 401(1)
C(6')	2 896(13)	6 770(9)	6 227(1)
O(6')	1 863(11)	7 963(8)	6 302(1)
O(7')	2 831(6)	6 299(5)	5 979(1)
C(8')	1 342(12)	7 224(11)	5 801(1)
C(9')	1 391(11)	6 394(10)	5 537(1)
C(10')	–302(12)	5 443(13)	5 457(1)
C(11')	–353(15)	4 661(15)	5 225(1)
C(12')	1 340(16)	4 772(17)	5 065(2)
C(13')	3 160(16)	5 738(18)	5 130(1)
C(14')	3 180(13)	6 607(12)	5 376(1)
C(15')	5 431(11)	1 462(9)	5 803(1)
C(16')	3 993(15)	2 080(13)	5 631(1)
C(17')	7 206(16)	473(18)	5 723(1)
C(18')	3 524(7)	5 566(7)	6 680(1)
C(19')	4 768(7)	6 223(7)	6 890(1)
C(20')	4 010(7)	6 057(7)	7 146(1)
C(21')	2 052(7)	5 233(7)	7 193(1)
C(22')	753(7)	4 561(8)	6 986(1)
C(23')	1 549(7)	4 780(8)	6 730(1)
O(24')	1 447(5)	5 125(4)	7 453(1)
C(25')	–484(8)	4 188(8)	7 510(1)
C(26')	–848(7)	4 174(6)	7 804(1)
C(27')	718(8)	3 468(7)	7 974(1)
C(28')	313(8)	3 422(7)	8 243(1)
C(29')	–1 647(8)	4 080(8)	8 338(1)
C(30')	–3 189(8)	4 760(7)	8 169(1)
C(31')	–2 780(7)	4 818(7)	7 903(1)

Table 2. Bond lengths (Å)

N(1)—C(2)	1.341(5)	N(1)—C(4)	1.460(5)
N(1)—C(5)	1.453(5)	C(2)—O(2)	1.207(5)
C(2)—C(3)	1.525(6)	C(3)—C(4)	1.533(6)
C(3)—C(15)	1.503(6)	C(5)—C(6)	1.510(6)
C(5)—C(18)	1.516(5)	C(6)—O(6)	1.207(5)
C(6)—O(7)	1.321(5)	O(7)—C(8)	1.468(6)
C(8)—C(9)	1.497(6)	C(9)—C(10)	1.374(7)
C(9)—C(14)	1.357(6)	C(10)—C(11)	1.385(7)
C(11)—C(12)	1.356(9)	C(12)—C(13)	1.376(10)
C(13)—C(14)	1.377(7)	C(15)—C(16)	1.347(7)
C(15)—C(17)	1.440(7)	C(18)—C(19)	1.358(6)
C(18)—C(23)	1.388(5)	C(19)—C(20)	1.385(5)
C(20)—C(21)	1.382(6)	C(21)—C(22)	1.369(6)
C(21)—O(24)	1.374(5)	C(22)—C(23)	1.389(6)
O(24)—C(25)	1.401(6)	C(25)—C(26)	1.506(6)
C(26)—C(27)	1.352(7)	C(26)—C(31)	1.370(7)
C(27)—C(28)	1.393(6)	C(28)—C(29)	1.346(8)
C(29)—C(30)	1.359(9)	C(30)—C(31)	1.384(7)
N(1')—C(2')	1.309(7)	N(1')—C(4')	1.454(7)
N(1')—C(5')	1.450(7)	C(2')—O(2')	1.214(7)
C(2')—C(3')	1.499(9)	C(3')—C(4')	1.538(8)
C(3')—C(15')	1.470(8)	C(5')—C(6')	1.494(8)
C(5')—C(18')	1.522(6)	C(6')—O(6')	1.199(9)
C(6')—O(7')	1.314(6)	O(7')—C(8')	1.450(8)
C(8')—C(9')	1.496(8)	C(9')—C(10')	1.316(11)
C(9')—C(14')	1.363(9)	C(10')—C(11')	1.332(11)
C(11')—C(12')	1.308(12)	C(12')—C(13')	1.361(15)
C(13')—C(14')	1.428(12)	C(15')—C(16')	1.303(10)
C(15')—C(17')	1.384(13)	C(18')—C(19')	1.382(6)
C(18')—C(23')	1.357(7)	C(19')—C(20')	1.392(6)
C(20')—C(21')	1.361(6)	C(21')—C(22')	1.397(6)
C(21')—O(24')	1.376(5)	C(22')—C(23')	1.401(6)
O(24')—C(25')	1.404(6)	C(25')—C(26')	1.511(6)
C(26')—C(27')	1.374(6)	C(26')—C(31')	1.362(6)
C(27')—C(28')	1.392(7)	C(28')—C(29')	1.371(7)
C(29')—C(30')	1.352(7)	C(30')—C(31')	1.376(6)

ethanol (10 ml) with 10% palladium on charcoal (10 mg) was stirred in a pressure bottle under 2 atm of hydrogen for 2 h. The suspension was filtered through a pad of Celite and the filtrate concentrated to give the debenzylated azetidin-2-ones (**18**) (35 mg, 82%), $\nu_{\max}$ 3 400, 3 050, 2 960, 2 930, 2 900, 2 600, 1 740, 1 610, 1 510, 1 380, 1 240, and 1 015 cm^{-1} ; δ (250 MHz; D_2O) 1.03 (3 H, d, J 7.0 Hz, Me), 2.85 (1 H, m, *trans*-4-H), 3.15 (1 H, m, 3-H), 3.42 (1 H, m, *cis*-4-H), 3.90 (1 H, m, CH_3CHOH), 5.30 (1 H, s, NCH), 6.79 (4 H, d, J 8.3 Hz, Ar); (**19**) δ (250 MHz, D_2O), 1.13 (3 H, d, J 7.0 Hz, CH_3), 3.08, 3.15, and 3.28 (3 H, m, 3-H, *trans*-4-H and *cis*-4-H), 4.02 (1 H, m, CH_3CHOH), 5.26 (1 H, s, NCHAr), and 6.79 and 7.12 (3 H, d, J 8.3 Hz, Ar).

Preparation of (–)-1-[(p-Benzoyloxyphenyl)benzyloxycarbonylmethyl]azetidine-2,3-dione (3).—Dimethyl *t*-butylsilyltri-fluoromethane sulphonate (34 μl , 0.15 mmol) was added dropwise to a stirred solution of the diastereoisomeric mixture of acetylazetidinones (**10**) and (**11**) (63 mg, 0.14 mmol) and triethylamine (26 μl , 0.19 mmol) in 1,2-dichloroethane (1 ml) under argon at 0 °C. After 10 min the reaction mixture was diluted with CH_2Cl_2 (80 ml) and methanol (8 ml) and treated with ozone at –78 °C until no starting material was present by t.l.c. (60% ether–petroleum). Powdered zinc (373 mg, 5.7 mmol) and glacial acetic acid (1 ml) were then added and the solution warmed to room temperature. It was then passed through a pad of Celite and the solvent removed to leave a residue which was partitioned between water (5 ml) and diethyl ether (10 ml). The organic phase was then washed with water (5 ml) and dried. Solvent was removed and the residue chromatographed [80% ether–petroleum (b.p. 40–60 °C)] to give the azetidine-2, 3-di-

Table 3. Bond angles (°)

C(2)—N(1)—C(4)	94.6(3)	C(2)—N(1)—C(5)	130.9(3)
C(4)—N(1)—C(5)	134.1(4)	N(1)—C(2)—O(2)	130.2(4)
N(1)—C(2)—C(3)	92.7(3)	O(2)—C(2)—C(3)	137.0(4)
C(2)—C(3)—C(4)	84.7(3)	C(2)—C(3)—C(15)	115.4(3)
C(4)—C(3)—C(15)	116.7(4)	N(1)—C(4)—C(3)	87.9(3)
N(1)—C(5)—C(6)	107.4(3)	N(1)—C(5)—C(18)	112.5(3)
C(6)—C(5)—C(18)	115.2(3)	C(5)—C(6)—O(6)	124.8(4)
C(5)—C(6)—O(7)	110.6(3)	O(6)—C(6)—O(7)	124.5(4)
C(6)—O(7)—C(8)	117.9(3)	O(7)—C(8)—C(9)	111.3(4)
C(8)—C(9)—C(10)	119.7(4)	C(8)—C(9)—C(14)	121.7(4)
C(10)—C(9)—C(14)	118.5(4)	C(9)—C(10)—C(11)	120.5(5)
C(10)—C(11)—C(12)	120.0(6)	C(11)—C(12)—C(13)	120.2(5)
C(12)—C(13)—C(14)	118.9(5)	C(9)—C(14)—C(13)	121.9(5)
C(3)—C(15)—C(16)	121.4(4)	C(3)—C(15)—C(17)	115.1(4)
C(16)—C(15)—C(17)	123.4(4)	C(5)—C(18)—C(19)	124.8(3)
C(5)—C(18)—C(23)	117.3(3)	C(19)—C(18)—C(23)	117.8(3)
C(18)—C(19)—C(20)	122.5(4)	C(19)—C(20)—C(21)	118.8(4)
C(20)—C(21)—C(22)	120.2(4)	C(20)—C(21)—O(24)	124.6(4)
C(22)—C(21)—O(24)	115.2(4)	C(21)—C(22)—C(23)	119.7(4)
C(18)—C(23)—C(22)	120.9(4)	C(21)—O(24)—C(25)	118.6(3)
O(24)—C(25)—C(26)	108.9(4)	C(25)—C(26)—C(27)	120.8(4)
C(25)—C(26)—C(31)	120.6(4)	C(27)—C(26)—C(31)	118.6(4)
C(26)—C(27)—C(28)	121.5(4)	C(27)—C(28)—C(29)	119.5(5)
C(28)—C(29)—C(30)	119.7(5)	C(29)—C(30)—C(31)	120.8(5)
C(26)—C(31)—C(30)	119.9(5)	C(2')—N(1')—C(4')	94.9(5)
C(2')—N(1')—C(5')	130.7(5)	C(4')—N(1')—C(5')	133.6(4)
N(1')—C(2')—O(2')	131.0(7)	N(1')—C(2')—C(3')	94.0(4)
O(2')—C(2')—C(3')	134.9(6)	C(2')—C(3')—C(4')	84.3(4)
C(2')—C(3')—C(15')	118.3(5)	C(4')—C(3')—C(15')	120.9(5)
N(1')—C(4')—C(3')	86.8(4)	N(1')—C(5')—C(6')	112.5(4)
N(1')—C(5')—C(18')	112.4(4)	C(6')—C(5')—C(18')	112.7(4)
C(5')—C(6')—O(6')	124.4(5)	C(5')—C(6')—O(7')	113.9(6)
O(6')—C(6')—O(7')	121.7(6)	C(6')—O(7')—C(8')	117.0(5)
O(7')—C(8')—C(9')	107.9(6)	C(8')—C(9')—C(10')	120.2(6)
C(8')—C(9')—C(14')	120.8(6)	C(10')—C(9')—C(14')	119.0(6)
C(9')—C(10')—C(11')	123.1(7)	C(10')—C(11')—C(12')	120.9(9)
C(11')—C(12')—C(13')	120.2(9)	C(12')—C(13')—C(14')	118.6(8)
C(9')—C(14')—C(13')	118.1(8)	C(3')—C(15')—C(16')	124.1(6)
C(3')—C(15')—C(17')	114.8(6)	C(16')—C(15')—C(17')	120.7(7)
C(5')—C(18')—C(19')	120.4(4)	C(5')—C(18')—C(23')	120.9(4)
C(19')—C(18')—C(23')	118.7(4)	C(18')—C(19')—C(20')	120.2(4)
C(19')—C(20')—C(21')	120.4(4)	C(20')—C(21')—C(22')	120.8(4)
C(20')—C(21')—O(24')	116.2(4)	C(22')—C(21')—O(24')	123.1(4)
C(21')—C(22')—C(23')	117.2(4)	C(18')—C(23')—C(22')	122.7(4)
C(21')—O(24')—C(25')	117.6(3)	O(24')—C(25')—C(26')	110.0(4)
C(25')—C(26')—C(27')	120.9(4)	C(25')—C(26')—C(31')	120.1(4)
C(27')—C(26')—C(31')	119.0(4)	C(26')—C(27')—C(28')	119.8(4)
C(27')—C(28')—C(29')	119.9(5)	C(28')—C(29')—C(30')	120.0(4)
C(29')—C(30')—C(31')	120.1(5)	C(26')—C(31')—C(30')	121.1(4)

one (**3**) as a syrup (49 mg, 84%) the spectral data for which were identical with those of compound (**17**): $[\alpha]_{\text{D}}^{29} - 33.2^\circ$ (c , 0.46 in CHCl_3).

Crystallographic Analyses of (3R)-1-[(1'R)-(p-Benzoyloxyphenyl)benzyloxycarbonylmethyl]-3-isopropenylazetidin-2-one (8).— $\text{C}_{28}\text{H}_{22}\text{O}_4\text{N}$, $M = 441.5$, monoclinic, $a = 5.929(1)$ $b = 7.985(1)$, $c = 50.712(13)$ Å, $\beta = 91.31(2)^\circ$, $U = 2\,400$ Å³, space group $P2_1$, $Z = 4$ (two crystallographically independent molecules in the asymmetric unit), $D_c = 1.23$ g cm^{–3}. Refined unit-cell parameters were obtained by centring 25 reflections on a Nicolet R3m diffractometer. 3 534 Independent reflections were measured ($\theta \leq 58^\circ$) with $\text{Cu-K}\alpha$ radiation (graphite monochromator) and using ω scans. 2 797 Had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied.

Despite the presence of 66 non-hydrogen atoms in the asymmetric unit, the structure was solved straightforwardly by

direct methods and ΔE -map recycling. The non-hydrogen atoms were refined anisotropically. The positions of the β -lactam (C-3 and C-3') hydrogen atoms, also those of the methyl groups were found in a ΔF -map. The former were refined isotropically and the methyl groups were refined as rigid bodies. All the other hydrogen atom positions were idealised (C-H = 0.96 Å), assigned isotropic thermal parameters, $U(H) = 1.2 U_{eq}(C)$ and allowed to ride on their parent carbons. Refinement was by block-cascade full-matrix least-squares to $R = 0.051$, $R_w = 0.052$, [$w^{-1} = \sigma^2(F) + 0.00055F^2$]. Computations were carried out on an Eclipse S140 Computer using the SHELXTL program system.¹⁶ The fractional atomic co-ordinates are given in Table 1. Tables 2 and 3 give the bond lengths and valence angles. The fractional co-ordinates of the hydrogen atoms and their isotropic thermal parameters and the thermal parameters of the non-hydrogen atoms, have been deposited as Supplementary Data, Sup. No. 56307 (6 pp.).* The observed and calculated structure factors are available on request from the Editorial office.

The two crystallographically independent molecules have markedly different conformations [Figures 1 (a), (b)]; whereas in both molecules the lactam and phenyl rings are similarly orientated with respect to each other, notably both the propenyl group and the benzyl ester carbonyl adapt very different orientations to the lactam ring in the two molecules. The N(1),C(5),C(6),O(6) torsion angle is 76° cf. 161° for N(1'),C(5'),C(6'),O(6') and the C(4),C(3),C(15),C(16) torsion angle is 78° cf. 21° for C(4'),C(3'),C(15'),C(16'). The terminal benzyl ring [C(26)—C(31)] is also differently orientated.

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Preliminary communication

APPLICATION OF ULTRASOUND TO THE PREPARATION OF TRICARBONYLIRON DIENE COMPLEXES

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Summary

The reaction of nonacarbonyldiiron with 1,3-conjugated dienes is promoted by ultrasound and has been shown to give high yields of the corresponding η^4 -(diene)tricarbonyliron complexes. In addition, 3-chloro-2-chloromethyl-prop-1-ene reacts with nonacarbonyldiiron in the presence of ultrasound to give a quantitative yield of the trimethylenemethanetricarbonyliron complex.

Recent investigations into the properties of η^4 -(diene)tricarbonyliron complexes have begun to demonstrate their potential for use as synthetic intermediates [1]. Their interesting chemistry and the number of methods available for ready removal of the tricarbonyliron moiety [2, 3] has led to their exploitation as both protecting and stabilising groups for conjugated dienes. However, the major stumbling block to their general acceptance lies in the problems encountered in their preparation.

The sensitivity of both products and starting materials to aerial oxidation dictates that reactions must be carried out under inert atmospheres. Many examples of the reaction of dienes with carbonyliron species under the influence of heat or ultraviolet radiation have been published [2, 4]. The most commonly employed procedure involves heating the diene with pentacarbonyliron in a high boiling inert solvent, such as di-n-butyl ether, for long periods of time. Sensitivity of the product to peroxides present in these solvents often requires that the solvent be filtered through basic alumina immediately prior to use. However, despite all these precautions, yields of the diene complexes are seldom better than low to moderate [5] which therefore constitutes a major barrier to their general acceptance as synthetic intermediates. This is especially true where the demands of modern organic synthesis impose extremely high competitive standards. Similarly, the chemistry of trimethylenemethanetricar-

bonyliron complexes remains unexplored despite the elegant use that Trost et al. [6] have made of the analogous palladium complexes.

Here we report a convenient high yielding method for the synthesis of both trimethylenemethanetricarbonyliron and a variety of η^4 -(diene)tricarbonyliron complexes as a result of the exposure of a mixture of the substrate and nona-

SCHEME 1

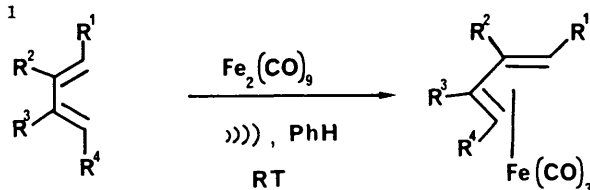


TABLE 1

Diene	Complex	Yield
		100 %
		70 %
		50 %
		62 %
		100 %
		51 %
		95 %

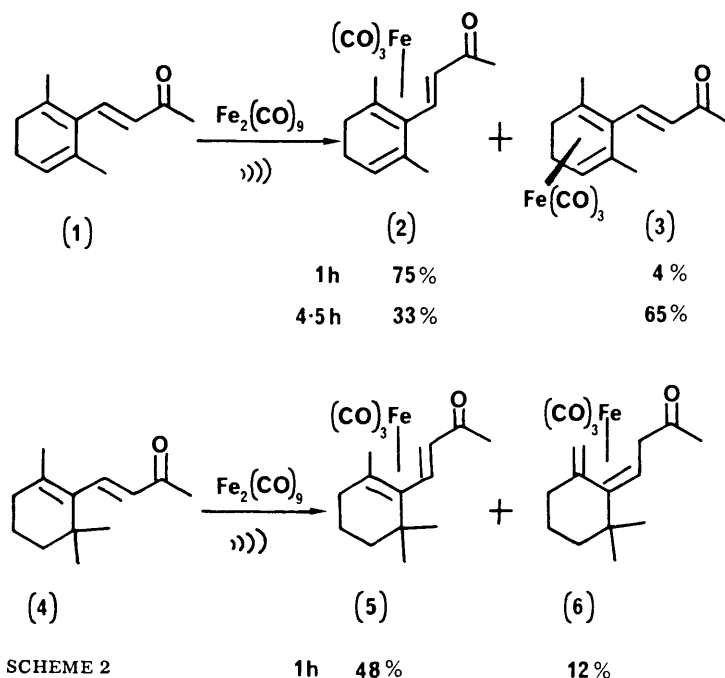
carbonyldiiron to ultrasound (Scheme 1)*. This method has also previously found application in the preparation of ferrilactone complexes from vinyl epoxides [7].

Preparation of η^4 -(diene)tricarbonyliron complexes

Nonacarbonyldiiron (1.1 eq) was added to a solution of the relevant diene (see Table 1) in benzene and the mixture sonolysed for 1 h, or until all the solid carbonyl had disappeared. Concentration of the reaction mixture and column chromatography of the residue on silica (40/60° petroleum ether/diethyl ether gradient) separated the required complex from any inorganic species. Yields in these reactions were essentially quantitative and limited solely by the volatility of the product.

The method was applied to a variety of dienes and the yields were consistently higher than previous literature preparations despite the fact that no attempt was made at optimisation.

The reaction with pseudionone (1) is of interest in that after 1 h it was possible to isolate a 75% yield of the kinetic product 2 which, on further exposure to ultrasound, isomerised to give a 1/2 ratio of the kinetic 2 and thermodynamic products 3, Scheme 2. Storing the 3,5-diene complex 2 overnight at -20°C resulted in almost complete conversion to the 5,9-diene complex 3. Hence, variation of the reaction time allows access to good yields of both isomers selectively. This was not possible by other conventional methods. The reaction of β -ionone (4) with $\text{Fe}_2(\text{CO})_9$ gave a 4/1 mixture of the *endo* to



SCHEME 2

* In our previous paper ref. 7a we incorrectly reported that dienes failed to react with $\text{Fe}_2(\text{CO})_9$ under ultrasonic conditions.

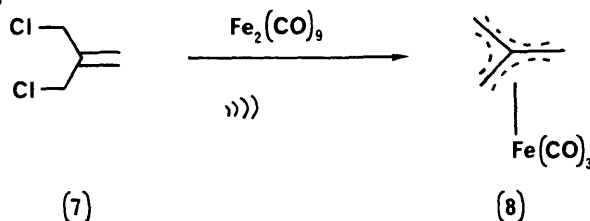
All sonolysis reactions were carried out in a Semat 80W 50KHz ultrasonic bath.

exo diene complexes 5 and 6 (Scheme 3) in contrast to Cais and Maoz [8] who obtained a 3/1 ratio in favour of the *exo* isomer 6 via the thermal reaction of β -ionone with $\text{Fe}(\text{CO})_5$. However, it should also be noted that the combined overall yield of this reaction was only 21%.

Preparation of trimethylenemethanetricarbonyliron

Equimolar amounts of nonacarbonyldiiron and 3-chloro-2-chloromethyl-prop-1-ene (7) were sonolysed together in 30/40° petroleum ether for 1 h. Careful concentration of the solution and Kugelrohr distillation of the residue gave a remarkable 90% yield of the desired product 8 (Scheme 3). The previous best recorded yield was a meagre 30% described by Emerson et al. [9].

SCHEME 3



In conclusion, having demonstrated the ease with which high yields of these complexes can now be obtained, we hope that this will promote increased use of such species as synthetic intermediates.

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ULTRASONIC FORMATION AND REACTIONS OF SODIUM PHENYLSELENIDE

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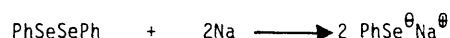
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Abstract: Treatment of diphenyldiselenide with sodium metal in tetrahydrofuran under ultrasonic conditions conveniently gave a suspension of sodium phenylselenide which could be transferred by syringe or cannula and reacted with sulphonates, halides and epoxides.

The impact that organoselenium chemistry has had on modern organic synthesis is undisputed. While there are many methods for the introduction of the seleno-substituent, the use of phenylselenide anions is especially common. Several methods for the preparations of the requisite selenide anions have been recommended, the more important of which include the use of diphenyldiselenide with sodium borohydride in THF/EtOH¹ or using resin bound borohydride,² reduction of the diselenide with sodium in ammonia³ or in boiling THF followed by solvation in HMPA.⁴ Alternatively sodium phenylselenide may be obtained from the selenol using sodium hydride in THF⁴ or even by treatment with aqueous sodium hydroxide under certain conditions.⁵ The use of diphenyldiselenide and lithium aluminium hydride has also recently been reported⁶ to give the selenide anion. Grignard reagents react with selenium to give selenide anions,⁷ although aggregates formed in these reactions can react with variable results.

Despite these extensive studies the clean and efficient generation of selenide salts continues to cause practical problems owing to the odiferous nature of certain reagents, the use of toxic or incompatible solvents and the lack of reactivity of some of these salts. Here we report a method which solves these problems and provides an extremely mild and convenient process for the preparation of sodium phenylselenide.[†]

The method is based upon the observation that low intensity ultrasonication⁸ dramatically improves the rate of reaction between diphenyldiselenide and metallic sodium in tetrahydrofuran.



The role of ultrasound in systems such as these has not been fully established but its rate enhancing effects would appear to stem from a combination of cavitation effects and increased mass transport from the bulk of the liquid to the surface of the metal as a result of acoustic streaming. Collapse of the cavitation bubbles at the interface momentarily produces huge increases in local pressures and temperatures. It also causes erosion of the surface which can be construed to augment the number of initiation sites available for reaction. Furthermore it generates high intensity shock waves, thought to be of the magnitude of 10^4 atmosphere, that is strong enough to produce plastic deformation in malleable metals.⁸

In our system the dependence of the rate of reaction on the total surface area of metal available is illustrated by the 3-fold decrease in reaction time observed when a commercial dispersion was used in place of the solid metal (Table 1).

In common with Luche *et al*⁹ we have noted the tendency of sodium to aggregate in THF and found that the reaction time could be halved by using xylene in its place. However, from a practical point of view, the high boiling point of xylene makes its removal difficult and its use would limit the method to preparation of involatile and thermally stable selenides.

Experimental

^1H NMR spectra were obtained on Bruker WH-250 and Varian EM-360A spectrometers in deuteriochloroform solutions with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 983 G spectrophotometer as liquid films or chloroform solutions. Mass spectra were obtained on a VG Micromass 7070B instrument. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on MN-silica gel 60 230-400 mesh, under pressure. Light petroleum refers to the fraction boiling in the range 40°-60°C and ether to diethyl ether. Solutions were dried over anhydrous sodium sulphate, and solvents by standard methods.

General procedure for the preparation of sodium phenylselenide

A 50% dispersion of sodium in paraffin (433 mg, 9.4 mmols) in THF (2 ml) was sonicated with a small portion of benzophenone in a sealed flask under argon for a few seconds until a deep blue colour had developed. Diphenyldiselenide (1.4 g, 4.7 mmols) was dissolved in the minimum volume of THF and the orange solution added dropwise to the reaction mixture. After 15 mins the reaction mixture had turned pale mauve and sonication was continued until all traces of colour had disappeared.

General procedure for the preparation of phenylselenenols

Sodium phenylselenide (1.2 equivalents) was added to a stirred solution of the substrate in dry THF (10 ml) and the reaction followed by tlc. When the reaction had reached completion, the mixture was partitioned between water (20 ml) and diethylether (20 ml). The aqueous phase was then extracted with two further portions of ether and the combined organic phases dried over sodium sulphate. Removal of the solvent gave a yellow oil which was purified by column chromatography (silica gel; 40/60° petrol/diethyl ether gradient)

Preparation of Diethylphenylselenomethylphosphonate (2).— Treatment of iodide (1) (0.280g, 1.00mmol) with sodium phenylselenide (1.20 mmol) gave diethylphenylselenomethylphosphate (2) (0.283g, 92%) as a pale yellow oil, ν_{max} (film) 3467, 2982, 2938, 1635, 1477, 1440, 1389, 1249, 1163, 1097, 1024 and 968 cm^{-1} ; δ_{H} (60MHz; CDCl_3) 1.26 (6H, t, $J = 7.0$ Hz, Me), 2.90 (2H, d, $J = 13.0$ Hz, CH_2), 4.03 (4H, dq, $J = 8.0, 7.0$ Hz, CH_2CH_2), 7.10-7.30 (3H, m, aromatic), 7.40-7.70 (2H, m, aromatic); $m/z = 308$ (M^+).

Preparation of (+) 3-(Selenophenyl)-1-((tetrahydro-2H-pyran-2'-yl)oxy) propane (4).— Treatment of iodide (3) (0.270g, 1.00mmol) with sodium phenylselenide (1.20mmol) gave 3-(selenophenyl)-1-((tetrahydro-2H-pyran-2-yl)oxy) propane (4) (0.258g, 86%) as a pale yellow oil, ν_{max} (film) 3055, 2939, 2867, 1576, 1476, 1352, 1259, 1200, 1134, 1075 and 870 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.45-1.90 (6H, m, H-3', H-4', H-5'), 1.98 (2H quintet $J = 7.9$ Hz, H-2), 3.00 (2H, t, $J = 7.9$ Hz, H-3), 3.49 (2H, m, H-1), 3.82 (2H, m, H-6'), 4.54 (1H, t, $J = 3.6$ Hz, H-2') 7.20-7.50 (5H, m, aromatic); $m/z = 300$ (M^+) (Found: C, 55.98; H, 6.76%. $\text{C}_{14}\text{H}_{20}\text{O}_2\text{Se}$ requires C, 56.19; H, 6.74%).

Preparation of Methyl-3-(selenophenyl) propanoate (6).— Treatment of iodide (5) (0.214g, 1.00mmol) with sodium phenylselenide (1.20mmol) gave methyl-3-(selenophenyl) propanoate (6) (0.214g, 88%) as a pale yellow oil, ν_{max} (film) 2949, 1736, 1476, 1434, 1347, 1223, 1165, 1022 and 738 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 2.72 (2H, max , $J = 7.9$ Hz, H2), 3.10 (2H, t, $J = 7.9$ Hz, H-3), 3.68 (3H, s, CO_2Me), 7.27 (3H, m, aromatic), 7.52 (2H, m, aromatic); $m/z = 243$ (M^+).

Preparation of (+) 4-(Selenophenylmethyl)-2-phenyl-1,3-dioxane (8).— Treatment of iodide (7) (0.304g, 1.00mmol) with sodium phenylselenide (1.20mmol) gave 4-(selenophenylmethyl)-2-phenyl-1,3-dioxane (8) (0.280g, 84%) as a pale yellow oil, ν_{max} (film) 3062, 2954, 2925, 2853, 1576, 1476, 1450, 1395, 1359, 1248, 1175, 1127, 1022, 983 and 738 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.80 (2H, m, H-5), 3.00 (1H, dd, $J = 14.3, 7.2$ Hz, PhSeCH_2), 3.23 (1H, dd, $J = 14.3, 7.2$ Hz PhSeCH_2), 3.86-4.10 (2H, m, H-6), 4.38 (1H, ddd, $J = 14.6, 7.2, 2.7$ Hz, H-4), 5.49 (1H, s, H-2), 7.20-7.58 (10H, m, aromatic); $m/z = 334$ (M^+) (Found: C, 61.14; H, 5.60%. $\text{C}_{17}\text{H}_{18}\text{O}_2\text{Se}$ requires C, 61.26; H, 5.44%).

Preparation of z-4-(Selenophenyl)-1-((tetrahydro-2H-pyran-2-yl)oxy)but-2-ene (10).— Treatment of allylic bromide (9) (0.234g, 1.00mmol) with sodium phenylselenide (1.20mmol) gave z-4-(selenophenyl)-1-((tetrahydro-2H-pyran-2-yl)oxy)but-2-ene (10) (0.292g, 94%) as a pale yellow oil, ν_{max} (film) 3022, 2940, 2868, 1576, 1474, 1436, 1321, 1201, 1118, 1075, 1024 and 739 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.40-1.92 (6H, m, H-3', H-4', H-5'), 3.40-3.55 (2H, m, H-6'), 3.58 (1H, dd, $J = 8.2, 1.8$ Hz, H-4), 3.73-3.93 (2H, m, H-1, H-4), 4.04 (1H, ddd, $J = 16.1, 5.4, 1.0$ Hz, H-1), 4.62 (1H, dd, $J = 3.6$ and 4.3 Hz, H-1'), 5.57 (1H, m, H-3), 5.78 (1H, m, H-2), 7.24 (3H, m, aromatic), 7.51 (2H, m, aromatic); $m/z = 312$ (M^+) (Found: C, 58.07; H, 6.58%. $\text{C}_{15}\text{H}_{20}\text{O}_2\text{Se}$ requires C, 57.88; H, 6.48%).

Preparation of 1-(Selenophenyl)propan-2-one (12).— Treatment of tosylate (11) (0.23g, 1.00mmol) with sodium phenylselenide (1.20mmol) gave 1-(selenophenyl)propan-2-one (12) (0.198g, 93%) as a pale yellow oil, ν_{max} (film) 3055, 2998, 2923, 1699, 1576, 1477, 1436, 1356, 1229, 1139, 1022 and 738 cm^{-1} ; δ_{H} (60MHz; CDCl_3) 2.30 (3H, s, COMe), 3.65 (2H, s, CH_2), 7.20-7.75 (5H, m, aromatic); $m/z = 214$ (M^+) (Found: C, 50.67; H, 4.94%. $\text{C}_9\text{H}_{10}\text{OSe}$ requires C, 50.72; H, 4.73%).

Preparation of (+) 3 α -Methyl-4 β -(selenophenylmethyl)- γ -butyrolactone (14).— Treatment of tosylate (13) (0.256g, 1.00mmol) with sodium phenylselenide (1.20mmol) gave (+) 3 α -Methyl-4 β -(selenophenylmethyl)- γ -butyrolactone (14) (0.223g, 83%) as a pale yellow oil, $v_{\max}$ (film) 3055, 2871, 2961, 1930, 2871, 1774, 1476, 1418, 1293, 1192, 1150, 1022, 939 and 739cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.15 (3H, d, J = 7.1 Hz, Me), 2.19 (1H, dd, J = 17.8, 8.5 Hz, H-2 α), 2.42 (1H, m, H-3), 2.74 (1H, dd, J = 17.8, 8.2 Hz, H-2 β), 3.10 (1H, dd, J = 12.8, 5.7 Hz, CH₂SePh), 3.28 (1H, dd, J = 12.8, 5.7 Hz, CH₂SePh), 4.23 (1H, dd, J = 12.8, 5.7 Hz, H-4), 7.24–7.31 (5H, m, aromatic), 7.50–7.60 (2H, m, aromatic); m/z = 270 (MH⁺) (Found: C, 53.65; H, 5.44%. C₁₂H₁₄O₂Se requires C, 53.54; H, 5.34%).

Preparation of 1-Phenyl-2-(selenophenyl)ethan-1-ol (16).— Treatment of styrene oxide (15) (0.120g, 1.00mmol) with sodium phenylselenide (1.20mmol) gave 1-phenyl-2-(selenophenyl)ethan-1-ol (16) (0.216g, 78%) as a pale yellow oil, $v_{\max}$ (film) 3403, 3058, 2929, 1576, 1475, 1435, 1300, 1054, 1022, 973 and 737cm⁻¹; δ_{H} (250 MHz; CDCl₃) 2.83 (1H, br, OH), 3.12 (1H, dd, J = 12.5, 9.0 Hz, H-2), 3.30 (1H, dd, J = 12.5, 3.7 Hz, H-2'), 4.73 (1H, dd, J = 9.0, 3.7 Hz, H-1), 7.20–7.35 (8H, m, aromatic), 7.50–7.60 (2H, m, aromatic); m/z = 278 (MH⁺) (Found: C, 60.39; H, 5.12%. C₁₄H₁₄Se requires C, 60.65; H, 5.09%).

Preparation of 1-(Prop-2'-eneoxy)-3-(selenophenyl)propan-2-ol (18).— Treatment of epoxide (17) (0.113g, 1.00mmol) with sodium phenylselenide gave 1-(prop-2'-eneoxy)-3-(selenophenyl)propan-2-ol (18) (0.233g, 86%) as a pale yellow oil, $v_{\max}$ (film) 3429, 3068, 2857, 1642, 1475, 1266, 1108, 1020, 929 and 737cm⁻¹; δ_{H} (250 MHz; CDCl₃) 2.79 (1H, d, J = 4.6 Hz, OH), 3.03 (1H, dd, J = 14.3, 6.4 Hz, H-3), 3.12 (1H, dd, J = 14.3, 6.4 Hz, H-3'), 3.52 (2H, m, H-1), 3.86–4.01 (3H, m, H-2, H-1'), 5.20 (1H, dd, J = 11.4, 2.0 Hz, H-3' anti), 5.27 (1H, dd, J = 17.8, 2.0 Hz, H-3' syn), 5.88 (1H, m, H-1'), 7.20–7.32 (3H, m, aromatic), 7.50–7.61 (2H, m, aromatic); m/z = 272 (MH⁺) (Found: C, 53.34; H, 6.03%. C₁₂H₁₆O₂Se requires C, 53.14; H, 5.95%).

Preparation of 1-Selenophenyl-octane (20).— Treatment of octyl iodide (19) (0.240 g, 1.00 mmol) with sodium phenylselenide (1.2 mmol) gave 1-selenophenyl-octane (20) (0.247 g, 92%) as a pale yellow oil, $v_{\max}$ (film) 3017, 2922, 2857, 1576, 1454, 1377, 1219, 1119, 1041, 1022, 795, 735 cm⁻¹; δ_{H} (60 MHz; CDCl₃) 0.80 (3H, t, J = 8 Hz, H-8), 1.1–2.0 (12H, m, H-2 to H-7), 2.8–3.3 (2H, m, H-1), 7.2–7.7 (5H, m, aromatic); m/z = 270 (MH⁺).

Preparation of 10-(selenophenyl)-1-((tetrahydro-2H-pyran-2'-yl)oxy)decane (22).— Treatment of 1-bromo-10-tetrahydropyranyl decane (21) (0.100 g, 0.33 mmol) with sodium phenylselenide (0.39 mmols) gave 10-(selenophenyl)-1-((tetrahydro-2H-pyran-2'-yl)oxy)decane (0.33 mmol, 100%) as a pale yellow oil, $v_{\max}$ (film) 2926, 2852, 1559, 1576, 1475, 1276, 1119, 1076, 1033, 904, 869, 735 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 1.28–1.86 (24H, m, H-3', H-4', H-5', H-3 to H-9), 2.91 (2H, t, J 7.6 Hz, H-10), 3.37 (1H, m, H-1), 3.49 (1H, m, H-1), 3.73 (1H, m, H-2), 3.87 (1H, m, H-2), 4.57 (1H, t, J 3.8 Hz, H-6'), 7.20–7.50 (5H, m, aromatic); m/z = 398 (M⁺).

Preparation of 1-Selenophenylhex-3-ene (24).— Treatment of methanesulphonyloxyhex-3-en-1-ol (23) (0.178 g, 1.00 mmol) with sodium phenylselenide (1.20 mmols) gave 1-selenophenylhex-3-ene (24) as a pale yellow oil $v_{\max}$ (film) 3004, 2961, 2927, 1576, 1474, 1434, 1298, 1258, 1190, 1072, 1022, 733, 689 cm⁻¹; δ_{H} (250 MHz; CDCl₃) 0.98 (3H, t, J = 8 Hz, H-6), 2.00 (2H, dt, J 16, 8 Hz, H-5), 2.43 (2H, dd, J 15, 8 Hz, H-2), 2.93 (2H, t, J 8 Hz, H-1), 5.41 (2H, m, H-3, H-4), 7.26 (3H, m, aromatic), 7.50 (2H, m, aromatic); m/z = 240 (MH⁺) (Found: C, 60.54; H, 6.77%. C₁₂H₁₆Se requires C, 60.25; H, 6.74%).

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Footnotes

+ The anions Se²⁻₂ and Se²⁻ have also been prepared by the ultrasonically promoted electrochemical reduction of selenium. Reaction with alkyl halides gave the dialkyl mono- and diselenides.
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++ Other literature routes to introduce the phenylseleno group in this example or to directly reduce the mesylate group rather than proceed through the selenide failed.

Δ Dimethyldisulphide may be converted to sodium methane thiolate using this method E.M. Naylor and W.B. Motherwell personal communication.

§ All reactions were carried out using a Semat 80W, 50 kHz ultrasonic cleaning bath.

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