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NEW SYNTHETIC METHODS IN ORGANIC CHEMISTRY

by

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Thesis presented in part fulfillment for the
degree of Ph.D.

The Chemistry Department,
The University of Glasgow,

GLASGOW. G12 8QQ

January, 1982

IN MEMORY OF MY MOTHER

"They are ill discoverers that think there is no land,
when they can see nothing but sea."

Francis Bacon.

ACKNOWLEDGEMENTS

I should like to take this opportunity to pay sincere thanks to those without whom this work would have been made more difficult.

I thank the members of the Chemistry Department of Glasgow University, in particular Dr A. Baker and Dr E. Colvin, for fostering in me a deep interest in Organic Chemistry.

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My thanks are due to members of the technical staff whose expertise led to the solution of many problems.

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Finally, I express my gratitude to the University of Glasgow and to Professor G.W. Kirby for financial support, and to Keir and my family for moral support.

SUMMARY

In Part 1, some aspects of the synthetic utility of silyl nitronates (trialkylsilyl esters of aci-nitroalkanes) were investigated. In particular, the decomposition of these species has been studied and it has been shown that trialkylsilyl nitronates derived from primary nitroalkanes decompose to the corresponding aldehyde and oxadiazole. Trialkylsilyl nitronates derived from secondary nitroalkanes, however, decompose to the corresponding ketone and oxime O-silyl ethers. A mechanistic rationale is forwarded to account for these new Nef type reactions.

Electrophilic C-alkylation of silyl nitronates with alkyl halides was attempted with unsatisfactory results. However, formal nucleophilic C-alkylation was successfully achieved with alkyl lithium reagents leading to α -substitution for silyl nitronates derived from primary nitroalkanes, and β -substitution for those derived from secondary nitroalkanes. The generality of this new reaction has been demonstrated and a mechanism is proposed. Other explorations into the chemistry of silyl nitronates have also been discussed.

In Part 2, synthetic approaches to the macrolide antibiotic methymycin have been discussed. A highly efficient stereospecific synthesis of Bergel'son's aldehyde has been achieved, and this was coupled, by a Wadsworth-Emmons olefination, with the 'left hand' fragment of methynolide, derived from α,γ dimethylglutaric anhydride. The synthesis was carried forward to a key

aldehyde, which requires one enantioselective aldol condensation to furnish the hydroxyl protected seco acid of methynolide.

Some comments on acetonide formation via BF_3 -mediated epoxide ring opening are made.

ABBREVIATIONS

Unless otherwise indicated in the text, all compounds are racemic but are drawn as single enantiomers in the interests of clarity.

Ac	Acetyl, CH_3CO
Am	Amyl, C_5H_{11}
Ar	Aromatic Nucleus
9-BBN	9-Borabicyclo(3,3,1)nonane
mCPBA	<u>m</u> -Chloroperbenzoic Acid
DMF	Dimethylformamide
HMPA	Hexamethylphosphoramide
LDA	Lithium diisopropylamide
Nu	Nucleophile
Ph	Phenyl
Pyr	Pyridine
THF	Tetrahydrofuran
Tf	Trifluoromethanesulphonate (triflate)
Ts	<u>p</u> -Toluenesulphonyl

PART 1: NITROALKANES

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INTRODUCTION

Aliphatic nitrocompounds have been known for over one hundred years. In that time a host of multifarious reactions has been discovered, transforming the nitro group into most other functionalities. Somewhat paradoxically, the nitro group has only been little used in synthetic strategies, although ostensibly it would appear to be ideal as a synthetic intermediate. There are, in fact, relatively few naturally occurring aliphatic nitrocompounds and of these only a limited number exhibit significant biological activity. Therefore, it would seem not unreasonable to conclude that the future of nitroalkanes lies, not in their use as synthetic targets, but as intermediates to complex nitro free structures.

In 1856, when Perkin, in an attempt to make quinine, performed experiments which were to initiate the coal-tar dye industry, aromatic nitrocompounds were already well known and of considerable importance. However, it was 16 years later before Victor Meyer¹ prepared nitropentane from amyl iodide and silver nitrite, the first mononitroalkane. Within a year Kolbe² synthesised nitromethane from sodium nitrite and sodium chloroacetate. Shortly before the turn of the nineteenth century, Louis Henry discovered the aldehyde-nitroparaffin reaction now associated with his name³. Many attempts were made subsequently to nitrate saturated hydrocarbons directly. Partial successes were achieved, but it was not until the early nineteen thirties that the reaction was carried out successfully in the vapour phase⁴, opening up the availability and potential utility of

nitroalkanes. Indeed, by 1965, the polymerisation of caprolactam had become important in the commercial preparation of nylon. The Du Pont Company obtained caprolactam by nitrating cyclohexane in the vapour phase and reducing the so produced nitrocyclohexane to the oxime. A simple Beckmann rearrangement then afforded caprolactam cleanly and cheaply.

From the initial simple experiments of Victor Meyer a whole area of organic chemistry has arisen. Many avenues are now open to the organic chemist for the preparation of nitroalkanes and many subsequent manipulations are now possible and indeed are well documented.^{5,6,7} In this introduction particular emphasis is placed on the synthetic utility of aliphatic nitrocompounds, outlining some of the more useful transformations and reviewing a selection of the more interesting applications of the nitro moiety in synthesis.

1. Preparation of Nitroalkanes

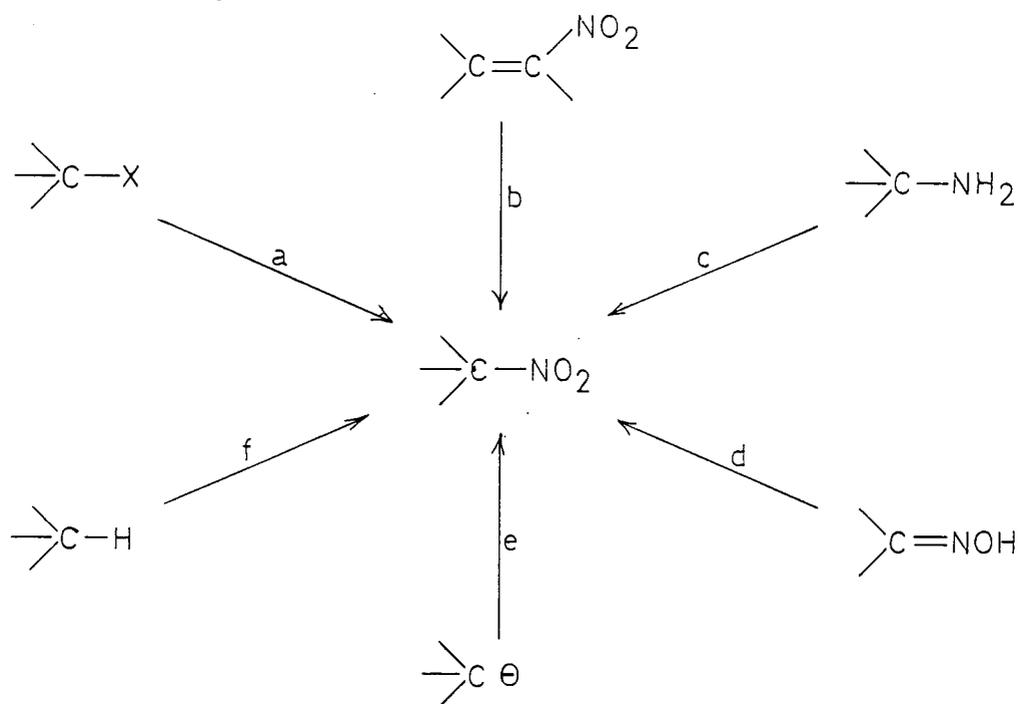
Many methods are now available for the synthesis of nitroalkanes, the most important comprising:-

- i) Treatment of alkyl halides with silver nitrite, a reaction useful only for synthesising primary nitroalkanes.
- ii) The reaction of alkyl bromides and iodides with sodium nitrite, a useful method for the preparation of primary and secondary nitroalkanes and of a wide variety of α -nitro esters.
- iii) The oxidation of oximes, for the preparation of primary and secondary nitroalkanes.

- iv) The oxidation of amines, a general and useful means for the preparation of secondary and tertiary nitrocompounds.
- v) The nitration of active methylene compounds using nitrate esters under basic conditions.
- vi) The nitration of active methylene compounds with nitric acid.

Scheme 1 illustrates these transformations and some of the experimental conditions. Over the years improvements have been made on the original procedures, and some of these improvements have been collated and published⁵.

Scheme 1: Preparation of Nitroalkanes



Experimental Conditions for Reactions of Scheme 1

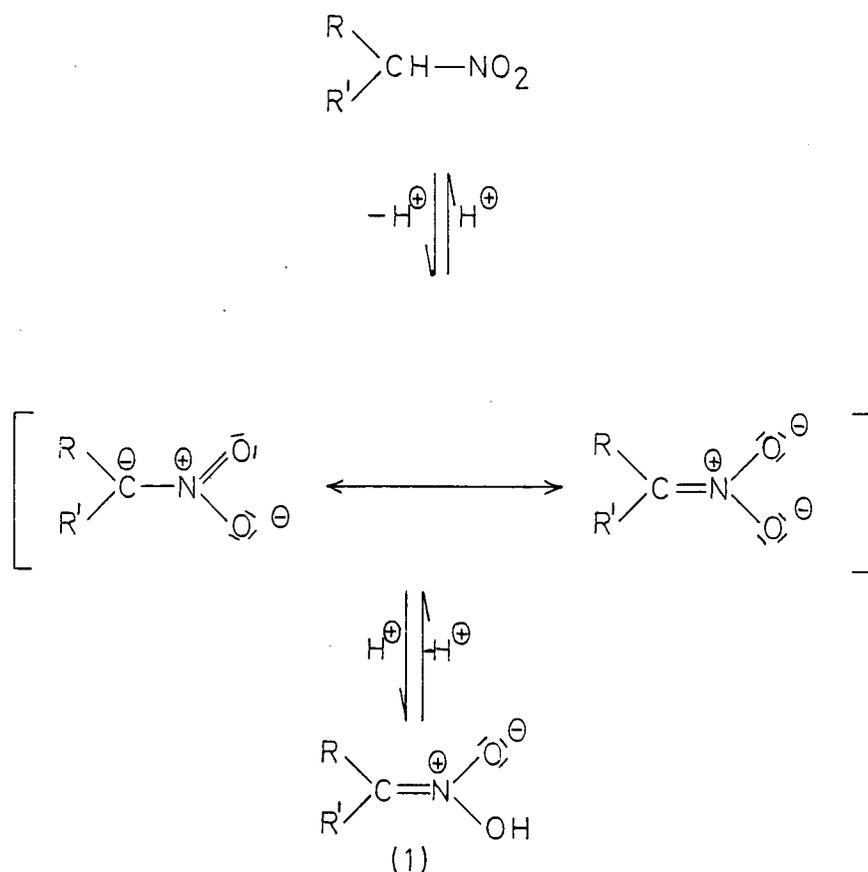
<u>Reaction Type</u>	<u>Reagent</u>	<u>Yield %</u>
a	NaNO ₂	40-70%
	AgNO ₂	40-70%
b	NaBH ₄ -ROH	70-95%
c	3-ClC ₆ H ₄ CO ₃ H	60-90%
d	CF ₃ CO ₃ H	30-50%
e	C ₂ H ₅ ONa-CH ₃ ONO ₂	50-90%
f	HNO ₃	40-60%

2. Properties of Nitro Compounds

Tautomerism and aci-nitro compounds.

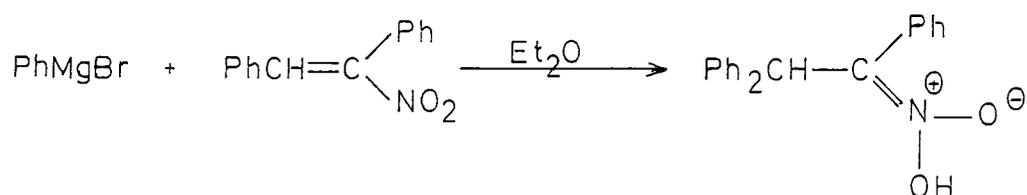
Primary and secondary nitroalkanes take part in tautomeric equilibrium in neutral or basic medium which consists principally of equilibria involving nitronic acid, nitroalkane, with a linking mesomeric nitronate anion (Scheme 2)

The species (1) has been described as an isonitro or as an aci-nitro compound or, more widely, as a nitronic acid. The last name is particularly appropriate for the description of the derived alkyl and silyl esters and will therefore be adopted here.



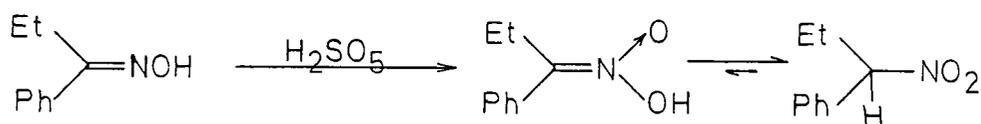
Scheme 2

The tautomerism is generally slow, but can be catalysed by acid or base, in a manner analogous with acid or base catalysed enolisation of aldehydes and ketones. The nitronic acid tautomers can, indeed, be isolated, not by separation of an equilibrium mixture, but by direct preparation. This can be accomplished by careful protonation of a nitronate salt⁸. Michael addition of carbanions or carbanionoids to α -nitroalkenes provides yet another route to nitronic acids⁹ (Scheme 2a).



Scheme 2a

Another method of formation of the nitronic acid is by oxidation of oximes. Here, isolation of the nitronic acid can be difficult, with tautomerisation to the nitro compound often being observed¹⁰ (Scheme 3).



Scheme 3

Nitronic acids are more soluble in water, have higher melting points and are more acidic than the corresponding nitro compounds. Most nitronic acids are, however, metastable, with a half-life of a few minutes being typical for conversion into the more stable nitroalkane tautomer.

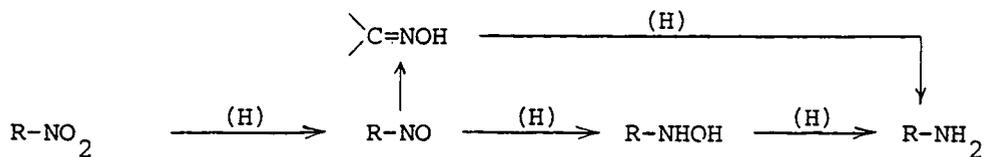
3. Reactions of Nitro Compounds

The chemistry of primary and secondary nitroalkanes and that of the corresponding nitronic acids are often inextricably intertwined; this can cause confusion and uncertainty in elucidating a particular reaction mechanism, a fact of relevance in some of the discussion which follows. Indeed, the Nef reaction¹¹, first reported in 1894¹², was causing no little controversy as to its

mechanistic detail as late as 1956, and, in fact, at present no unambiguous mechanism has been presented.

(a) Reduction

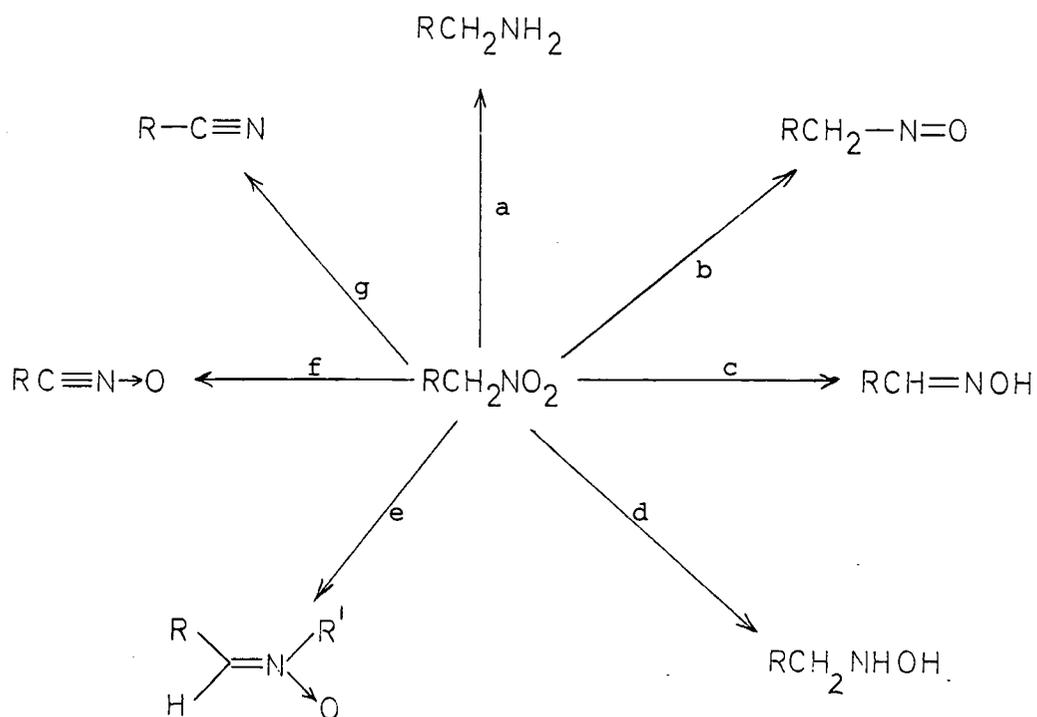
One of the most fundamentally useful transformations of the nitro group is the ease with which it can be reduced to an amine. This is possibly more pertinent to aromatic nitro-compounds, but is becoming increasingly useful in aliphatic systems. In general, reduction of nitroalkanes may give a range of possible products¹³, in varying oxidation states. The flow diagram shown in Scheme 4 was formulated at the end of the 19th century and is customarily referred to as the Haber mechanism¹⁴.



Scheme 4

Inspection of the scheme makes it apparent that formation of a given intermediate in preparatively significant amounts is a delicate balance of competing reaction rates. Reagents have been developed⁵ to effect certain specific transformations, as shown in Scheme 5.

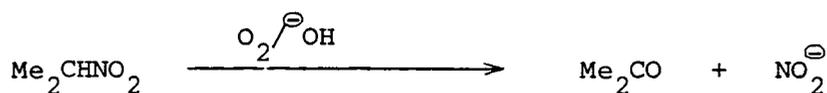
Scheme 5: Reaction of Nitroalkanes



<u>Reaction Type</u>	<u>Conditions</u>	<u>Yields %</u>
(a)	H_2 /catalyst $LiAlH_4$	50-100 %
(b)	$SnO-NaOMe$	30-50 %
(c)	$Zn-AcOH$ HCl	80-90 %
(d)	$Al(Hg)-H_2O$ $H^+ : Ac_2O$	
(e)	$RMgBr$	30-50 %
(f)	$ArNCO-R_3N$	
(g)	PCl_3-Pyr	30-80 %

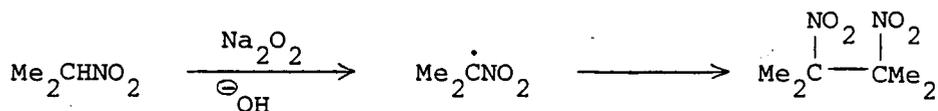
(b) Oxidation

Nitroalkanes are particularly susceptible to aerobic oxidation in alkaline solution, giving products formed by an autocatalytic free radical chain reaction. 2-Nitropropane, for example, is converted to acetone and nitrite ion¹⁵ (Scheme 6).



Scheme 6

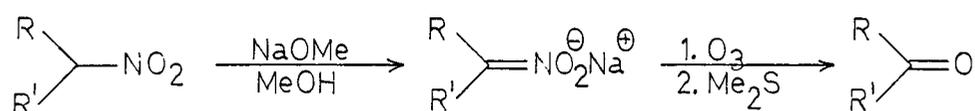
Free radicals can also be formed using other oxidising agents¹⁵, for example, iron(III) chloride, potassium peroxydisulphate and sodium peroxide, but here the radicals, once formed, dimerise to form vic-dinitro compounds (Scheme 7).



Scheme 7

Nitronate salts can be oxidised to aldehydes or ketones by potassium permanganate in neutral solution^{16,17}, or by sodium persulphate¹⁸. The ozonolysis of nitronate salts proceeds

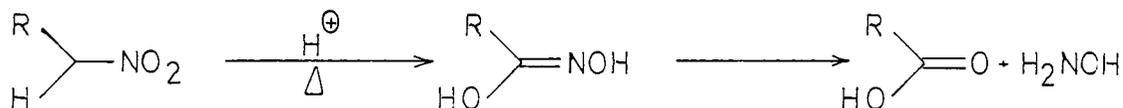
rapidly and, in most cases, cleanly to give the carbonyl compound (Scheme 8). This is the same overall transformation as that brought about by the Nef reaction, which is discussed later.



Scheme 8

(c) Reactions with Acids and Bases

Nitro alkanes bearing a hydrogen atom on the α -carbon are hydrolysed at varying rates by hot concentrated mineral acid²⁰ to give the carbonyl compound or carboxylic acid and hydroxylamine (Scheme 9).



Scheme 9

In the latter case, intermediate hydroxamic acid can be isolated if the amount of water is restricted²¹. The yields are usually excellent in this reaction, which is often referred to as the Victor Meyer reaction²², after its discoverer.

(Confusingly, the preparation of nitroalkanes from silver nitrite and alkyl halide has also been called the Meyer reaction.²³)

A proposed mechanism of this and the related Nef reaction is shown in Scheme 12. The conversion of primary nitrocompounds into carboxylic acids can be achieved in a somewhat milder fashion using a nitrite ester and sodium nitrite²⁴.

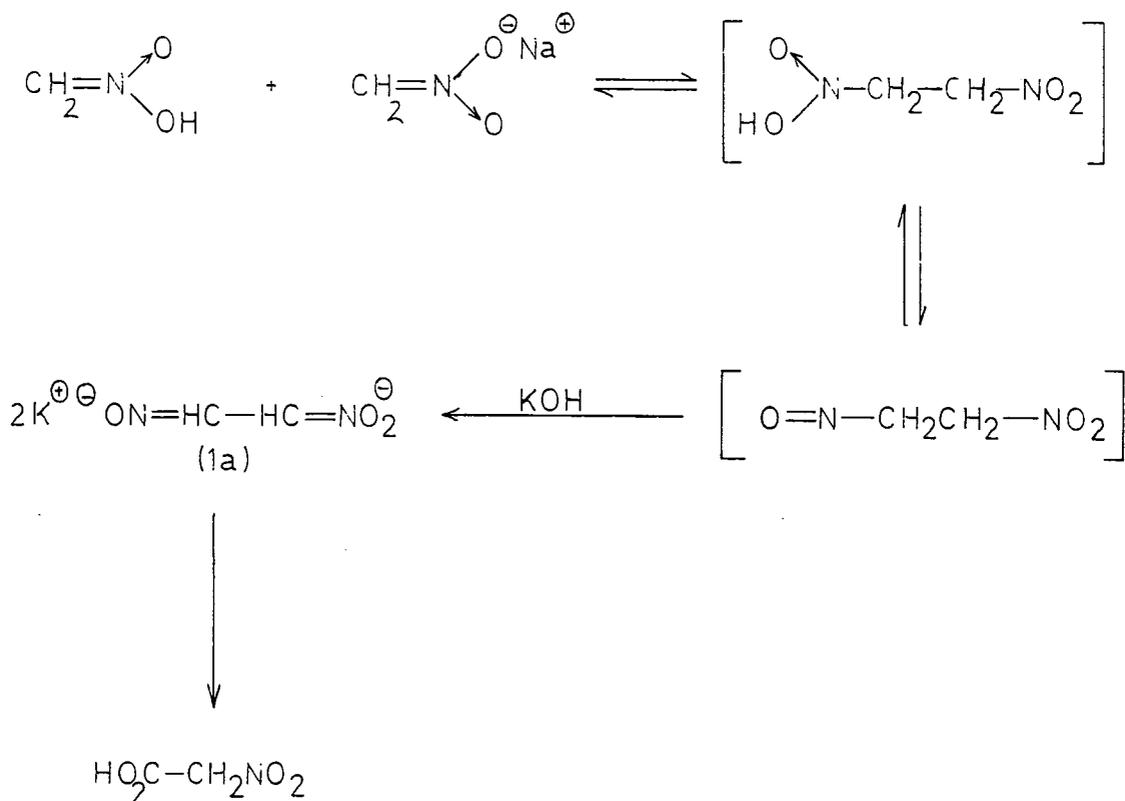
Primary and secondary nitroalkanes react with bases, initially to give salts, which may react further on standing or heating; for example, the potassium salt of nitromethane is converted, on heating,²⁵ into the salt of nitroacetic acid (Scheme 10)



Scheme 10

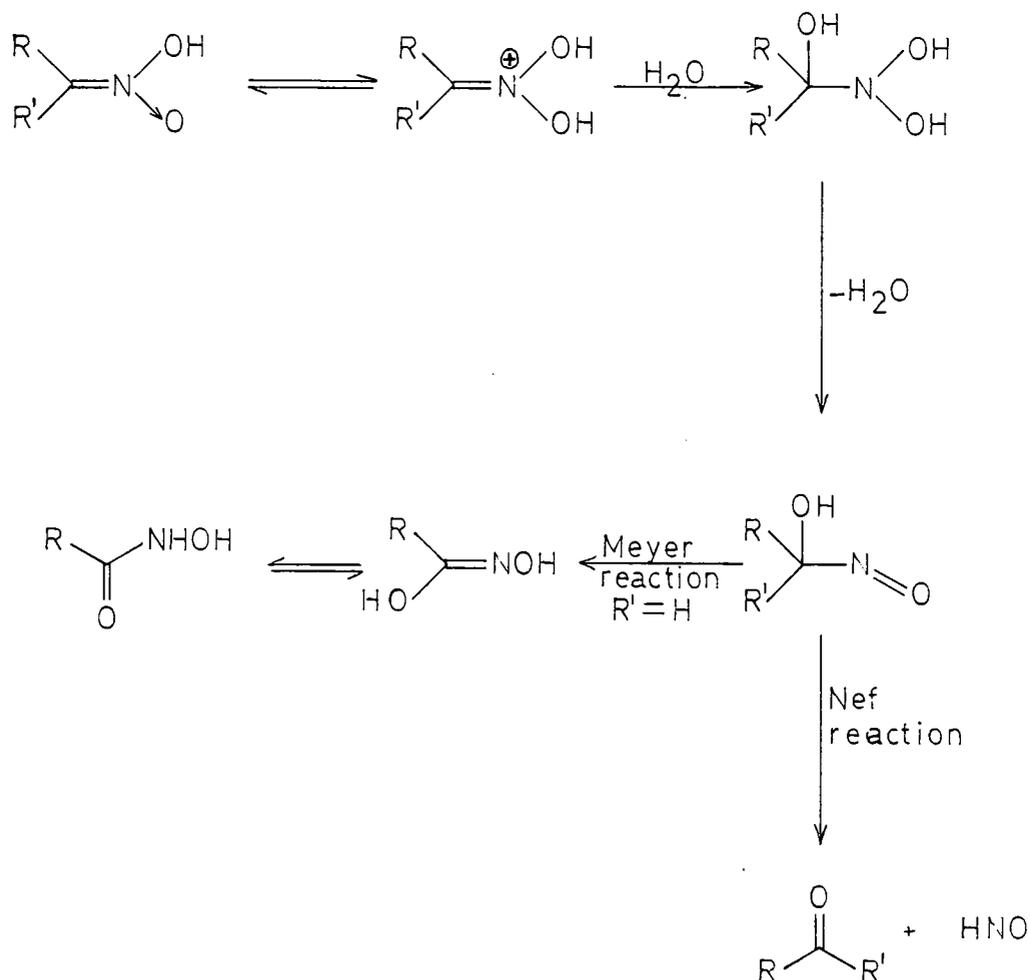
The mechanistic rationale for this preparative route to nitroacetic acid is somewhat cloudy although methazonate dianion (1a) has been isolated. A subsequent Nef reaction will generate the nitroacetic acid (Scheme 11); however, a chain reaction involving nitromethyl radicals cannot be excluded.

Careful acidification of solutions of nitronate salts by dilute acid simply generates the free nitro compound or nitronic acid.



Scheme 11

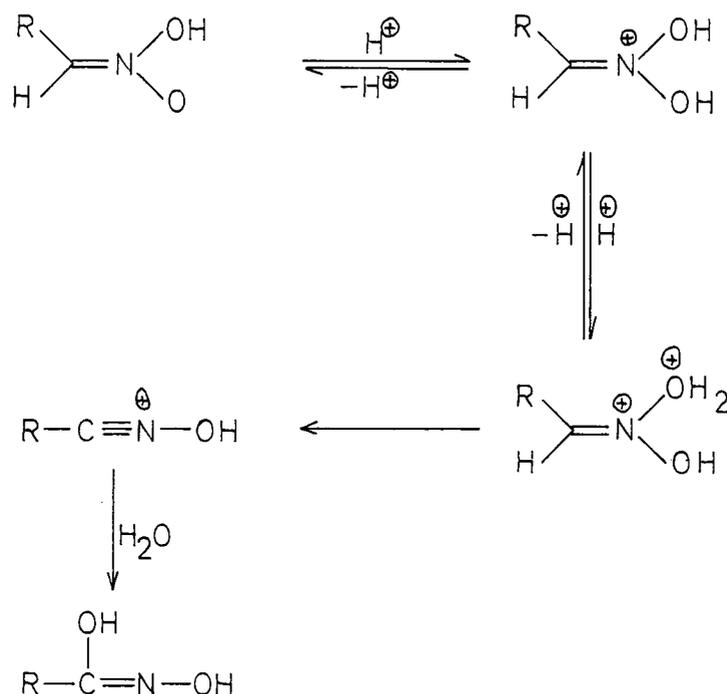
If, however, an excess of strong mineral acid is employed, formation of an aldehyde or ketone accompanied by nitrous oxide usually results. This overall conversion of nitro into carbonyl is the well-known Nef¹¹ reaction, which, since its discovery in 1894, has attracted much attention, both from a practical and a mechanistic basis. The Nef reaction is presumed to begin in the same way as direct acid catalysed hydrolysis, by attack of water at the α -carbon of the nitronic acid, or of its protonated derivative¹¹ (Scheme 12). In hot concentrated mineral acid the product isolated from the primary, but not secondary, nitroalkanes is a hydroxamic acid (the Victor Meyer reaction).



Scheme 12

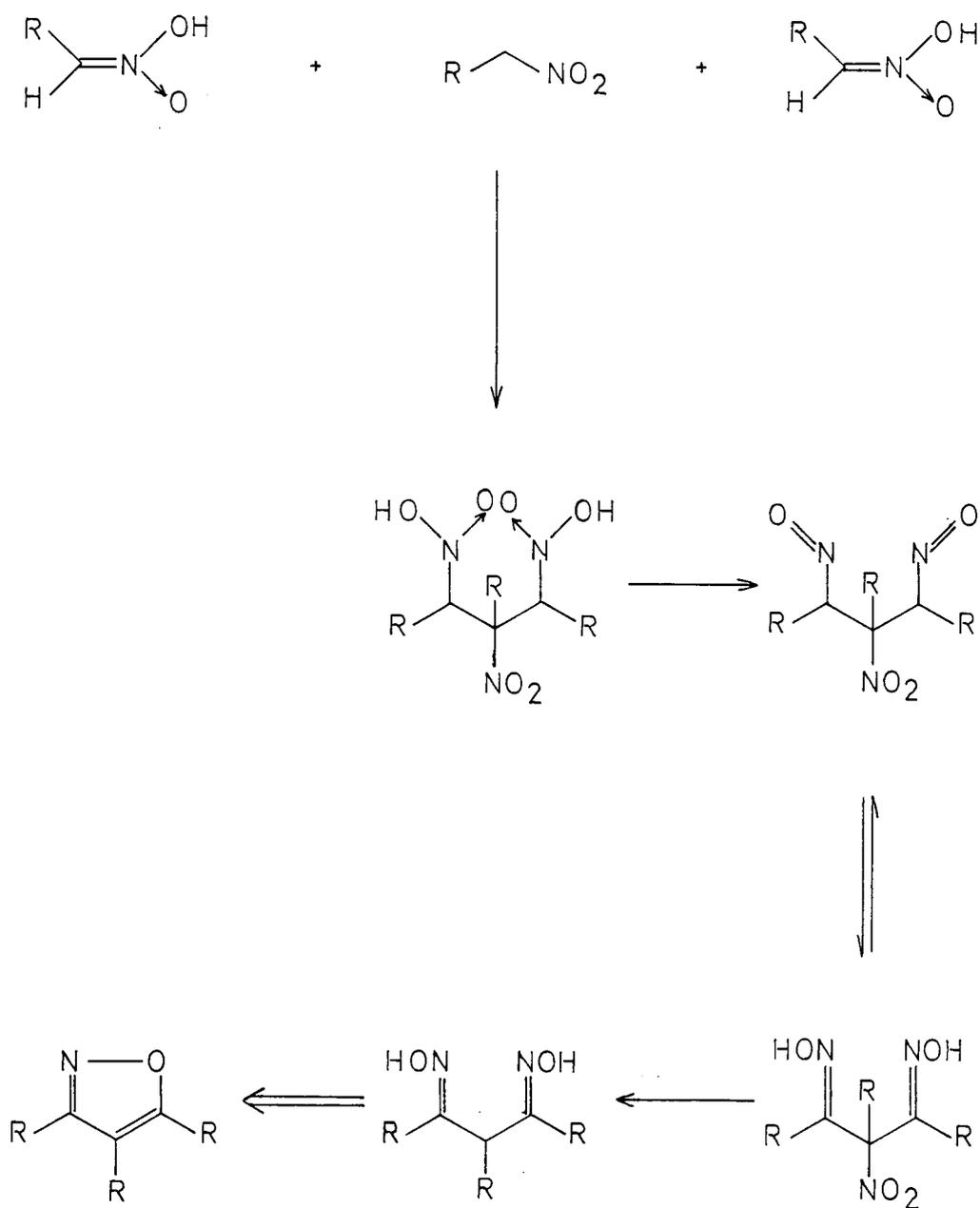
The subsequent difference in behaviour of primary nitroalkanes may be attributed to the relative stabilities of the proposed intermediate α -hydroxy nitroso compound. In hot concentrated acid, tautomerisation to a 1-hydroxy aldoxime would be facile; in cold dilute acid, the nitroso structure would have a much longer lifetime, allowing the reaction pathway to be diverted towards formation of an aldehyde by elimination of nitroxyl. This mechanism can only be regarded as speculative, rather than

definitive; indeed, Dewar²⁶ has proposed a different sequence to the hydroxamic acid (Scheme 13), invoking a protonated nitrile oxide as an intermediate.



Scheme 13

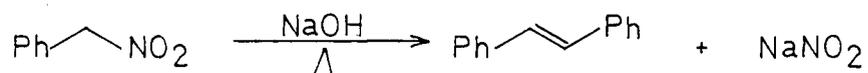
Primary nitroalkanes also undergo condensation in the presence of base;²⁷ the product normally isolated is an isoxazole arising from three molecules of nitroalkane. The way this curious reaction proceeds is partially illuminated by the fact that condensation with a mild amine base allows the isolation of an intermediate 1,3-dioxime. The path of this reaction is similar to that of methazonate formation discussed earlier, with the difference that the anion of the dimeric adduct attacks a third molecule of nitronic acid, giving a 2-nitro-1,3-dioxime (Scheme 14).



Scheme 14

Hydrolysis of one of the oxime groups to the ketone followed by enolisation and cyclisation with loss of water affords the isoxazole.

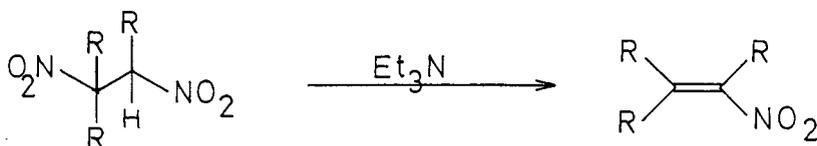
A different type of condensation involving formal elimination of nitrous acid is displayed by phenylnitromethane, which gives rise to stilbene and sodium nitrite when heated with sodium hydroxide¹¹ (Scheme 15)



Scheme 15

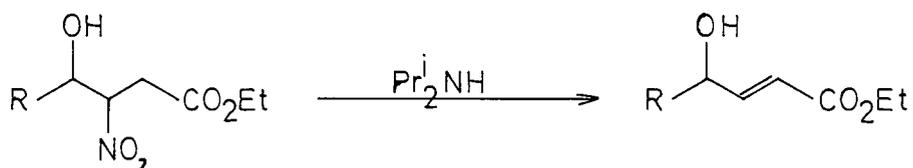
4. Nitrite as a Leaving Group

Nitroalkanes can undergo ready 1,2-elimination of nitrous acid provided the β -hydrogen is activated by an electron withdrawing substituent²⁸ (Scheme 16)

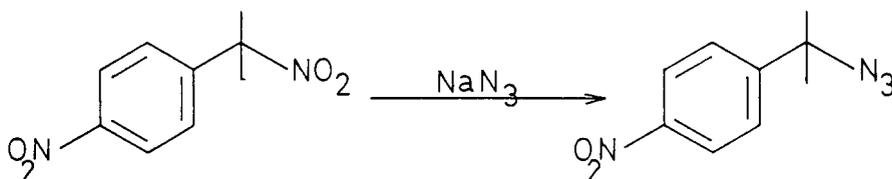


Scheme 16

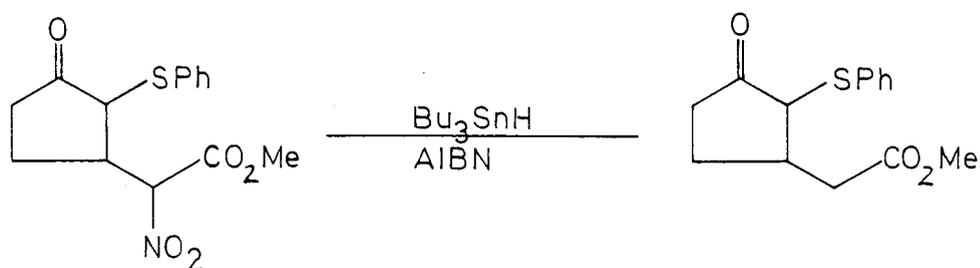
Many mild methods are now available to achieve this 1,2-elimination. For example, in a synthesis of pyrenophorin, aqueous di-isopropylamine was used²⁹ to produce the desired α, β -unsaturated γ -hydroxyester (Scheme 17).

Scheme 17

It has recently been discovered that a nitro group attached to an sp^3 -hybridised carbon atom can act as a leaving group in nucleophilic substitution reaction³⁰. One example of the many substitution reactions discovered by Kornblum²⁹ on the p-nitrocumyl system is shown in Scheme 18.

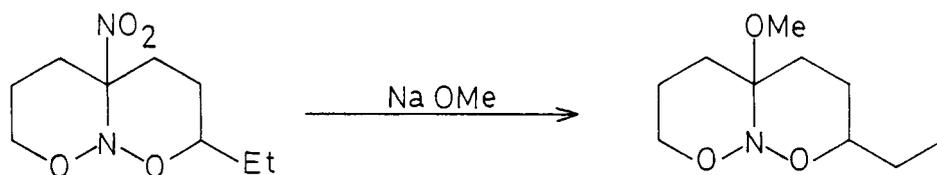
Scheme 18

This reaction requires appropriate phenyl substitution and proceeds by a radical-radical anion mechanism, as does displacement of nitrite with the mercaptide anion³¹. Recently it has proved feasible to replace the nitro group by hydrogen or deuterium³². Tributyltin hydride or deuteride are excellent reagents for this purpose, and in the presence of azobisisobutyronitrile, reduction of nitroalkanes proceeds selectively in near quantitative yields (Scheme 19).



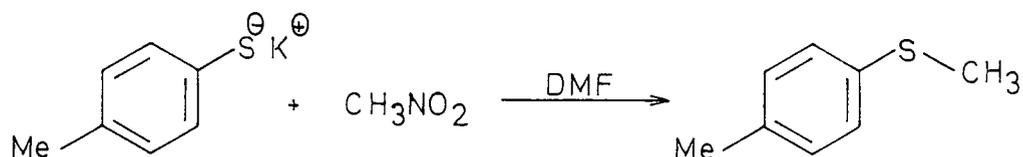
Scheme 19

An example of an S_N1 type of displacement is outlined in Scheme 20. This is a rather unique reaction and relies heavily on the nitrogen atom to stabilise the developing intermediate α -carbonium ion²³.



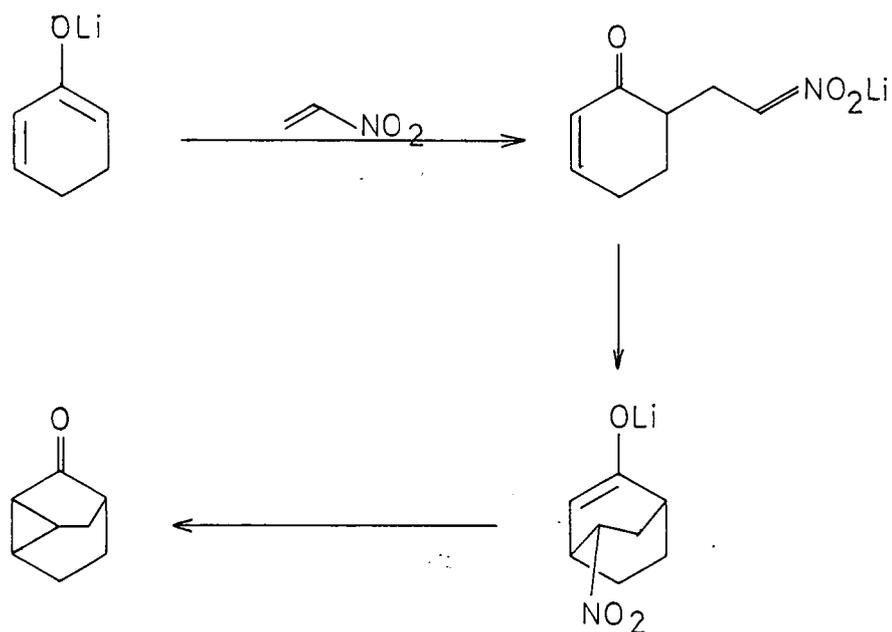
Scheme 20

Genuine S_N2 type displacements are very rare and, to date, only one case has been claimed³⁴ (Scheme 21), but unambiguous mechanistic proof has not been forthcoming, as yet.



Scheme 21

A related example of nitro group displacement is involved in a potentially useful bicycloannulation^{34a} (Scheme 21a).

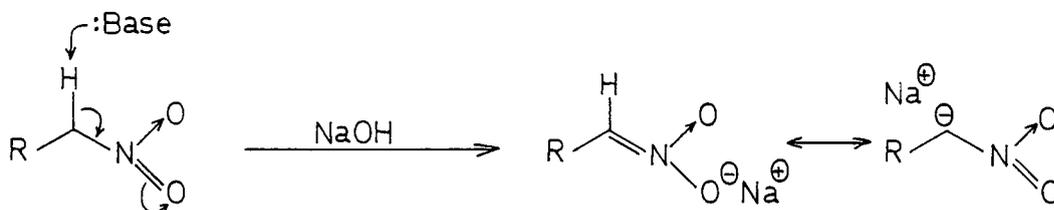


Scheme 21a

The reaction is viewed as a three stage process in which nitroethane first acts as an acceptor in a conjugate addition by a cyclic cross conjugated dienolate. The resulting stabilised carbanionic carbon undergoes intramolecular Michael addition to the α,β -unsaturated ketone, giving a bicyclic enolate intermediate which then loses the nitro group by intramolecular displacement.

5. Reactions at the α -Carbon

Treatment of nitroalkanes possessing an α -hydrogen with base will result in deprotonation and formation of the previously discussed nitronate salt. The nitronate salts are generally considered to be either oxygen or carbon nucleophiles in analogy with enolate anions (Scheme 22).



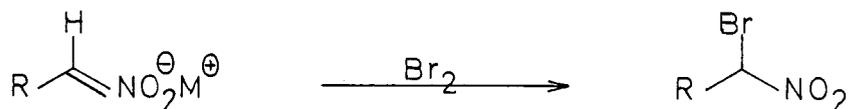
Scheme 22

It is the ambident nature of the nitronate anion which allows the many and varied transformations which will now be discussed.

The nitronate ion also has the potential to be an electrophilic carbonyl analogue, but apart from the Nef reaction few examples of this behaviour are known.

(a) Halogenation

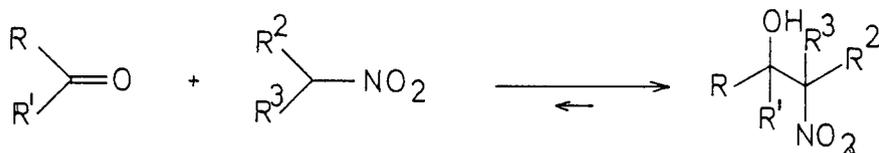
Nitroalkanes are readily halogenated at the α -carbon by treatment of the corresponding nitronate anion with elemental halogen. By controlling the rate of addition, exclusive mono-substituted products can be obtained (Scheme 23). Photochemical chlorination is unpredictable and gives substitution at carbon atoms other than the α -carbon.⁶²



Scheme 23

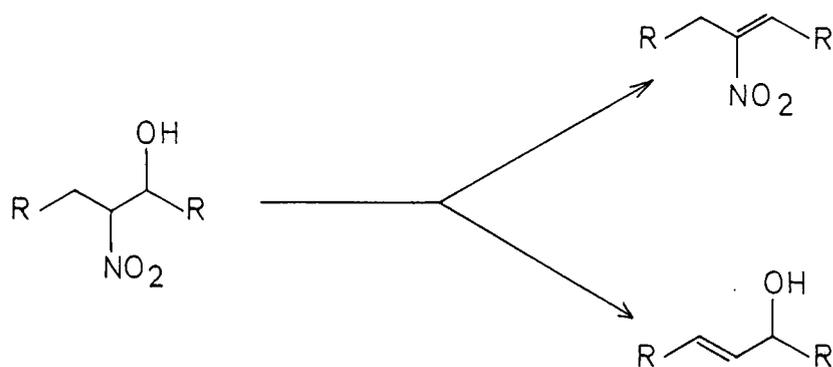
(b) Hydroxyalkylation

The Henry reaction³ is the base-catalysed addition of primary and secondary nitroalkanes to aliphatic aldehydes and ketones and aromatic aldehydes (Scheme 24).

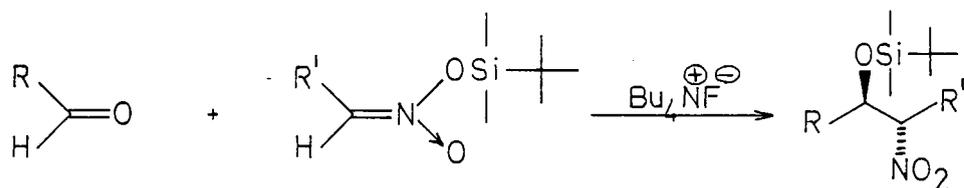


Scheme 24

Due to the ease of reversibility and the possibility of competing aldol or Cannizzaro reactions, normally only catalytic quantities of base are employed. Success can be unpredictable, high yields of nitroalcohols only being obtained reliably in intramolecularly favoured cases, or with nitromethane and/or aldehydes as reaction partners. The product 1,2-nitro-alcohols can be dehydrated to produce nitro-olefins, or base-induced elimination of nitrous acid can be encouraged to yield allylic alcohols (Scheme 25).

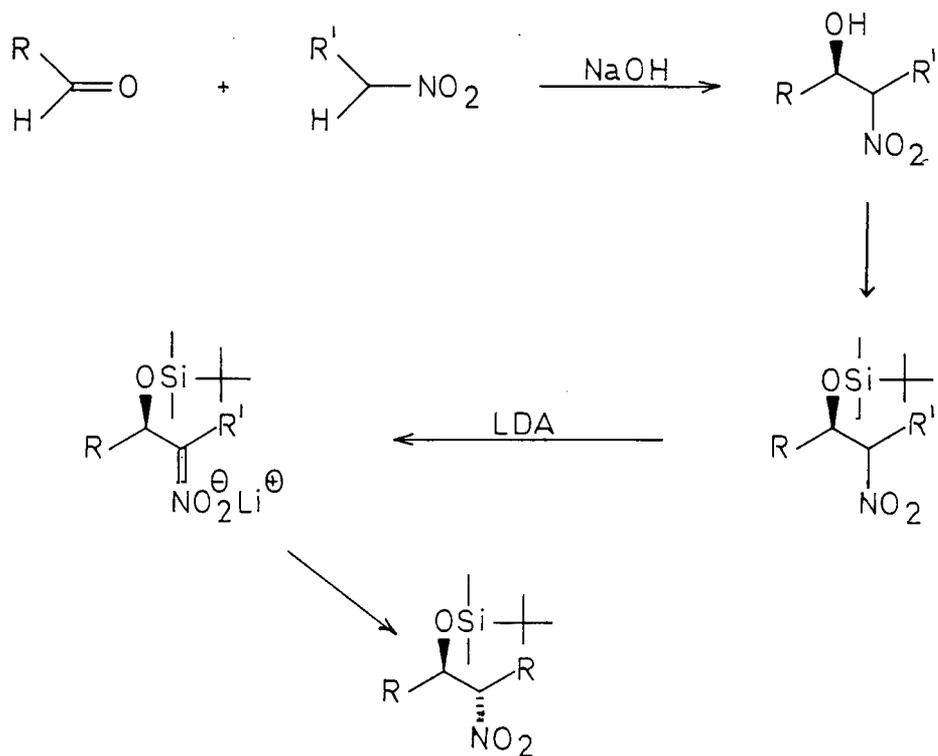
Scheme 25

In an improvement to this nitro-aldol reaction, control of diastereoselectivity of nitro-aldol formation can be attained using a novel fluoride ion catalysed addition of silyl nitronates to aldehydes³⁵. The nitro-alcohols prepared by this variation are obtained as practically pure diastereoisomers (Scheme 26), believed to be in the thermodynamically more stable erythro form.

Scheme 26

A high degree of diastereoselectivity can also be achieved by o-silylation of the classically formed nitroalcohol, deprotonation with lithium diisopropylamide at 78°C and subsequent kinetic

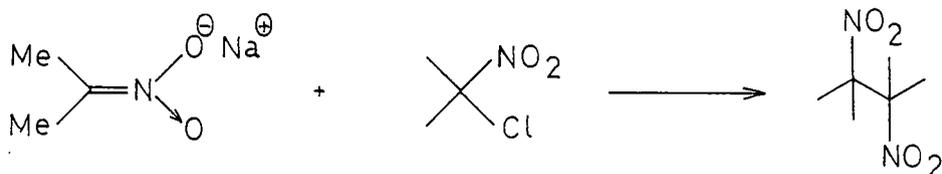
reprotonation at -90°C . This apparently simple procedure can enrich an initial equimolar mixture of diastereoisomers to a new ratio of greater than 20:1 in favour of the erythro form (Scheme 27)



Scheme 27

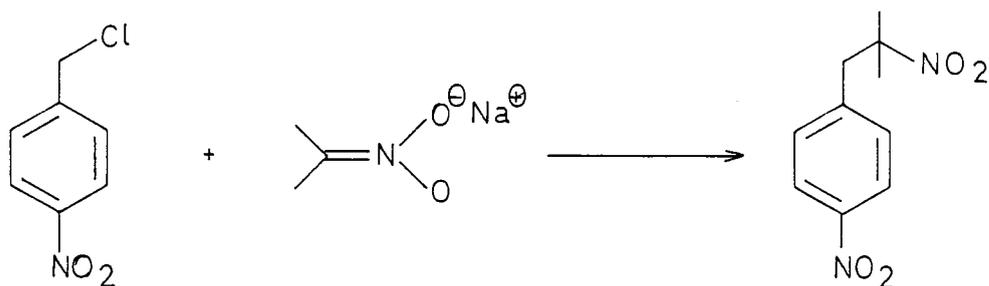
(c) Carbon Alkylation

Alkylation of salts of simple nitroalkanes generally takes place exclusively on oxygen, and this will be discussed in a later section. There are, in fact, very few reported examples of carbon alkylation. Tertiary dinitroalkanes can be prepared by the addition of the sodium salt of a secondary nitroalkane to a α -halonitroalkane³⁶ (Scheme 28), but, at best, the yields are very low.



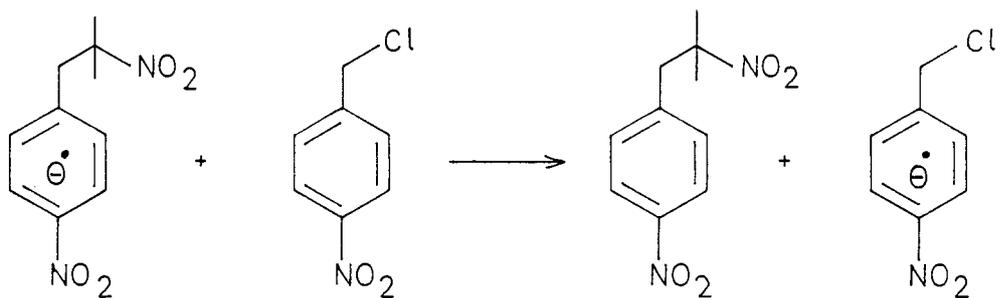
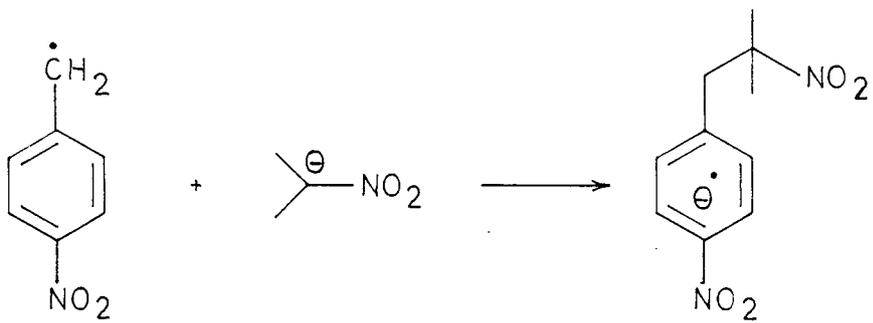
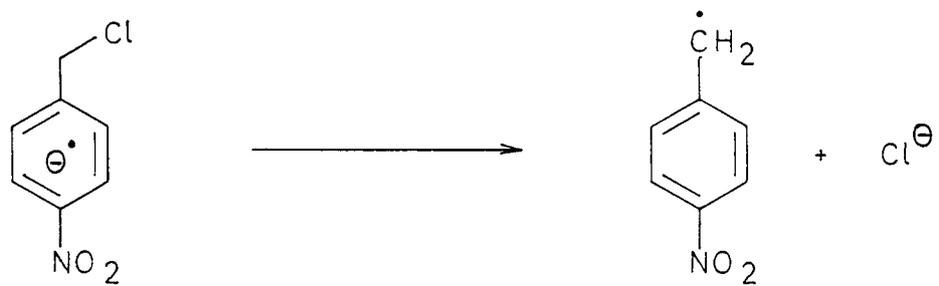
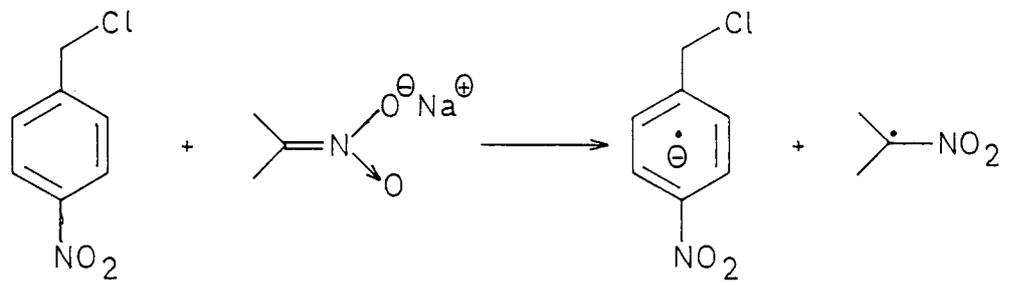
Scheme 28

There have been several reports of C-alkylation by radical chain processes, with the earliest example being reported by Kornblum³⁰ (Scheme 29). The reaction, however, suffered from a lack of generality and the requirement for judicious choice of substrates. After a very thorough investigation, a radical anion chain mechanism was proposed for this transformation, as depicted in Scheme 30.



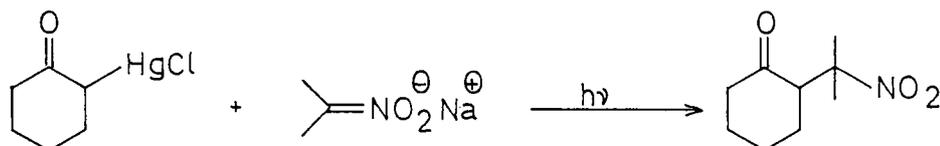
Scheme 29

The success of this reaction (Scheme 30) depends upon the presence of an electron withdrawing p-substituent, specifically nitro or cyano, and of chloride ion as leaving group. More recently, Russell reported that primary or secondary alkyl mercury chlorides



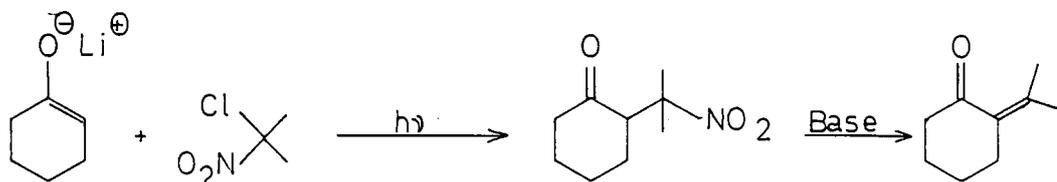
Scheme 30

or bromides will participate in the aforementioned type of free radical chain reaction with nitronate anions³⁷. This reaction requires photo-initiation (Scheme 31).



Scheme 31

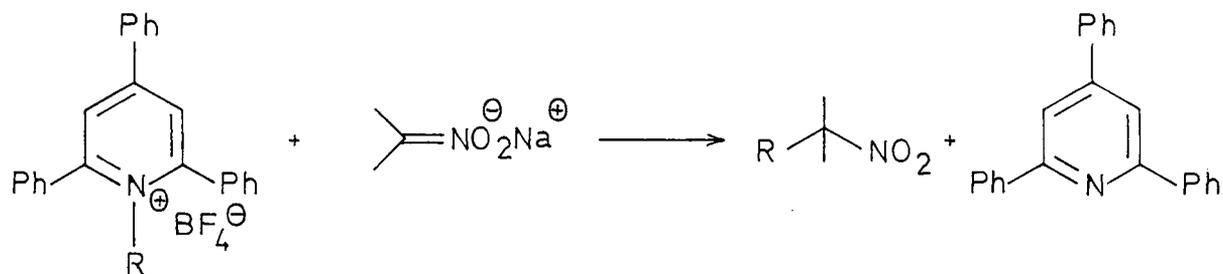
A synthetically more attractive route to the same type of compound can be achieved by controlled crossed aldol condensation using an α -halonitroalkane as a ketone equivalent (Scheme 32). This radical anion chain reaction, SRN1, is similar to that described by Kornblum (page 24).



Scheme 32

Perhaps the most flexible method of radical C-alkylation is achieved by treatment of the nitronate anion with 1-substituted-2,4,6-triphenylpyridinium salts (Scheme 33). Although mechanistic detail of this reaction has still to be elucidated, radical

anions are almost certainly involved.

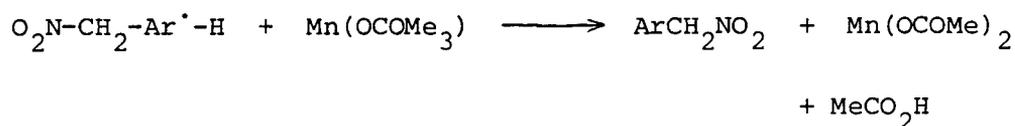
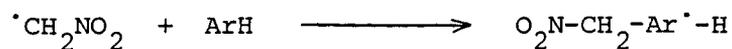
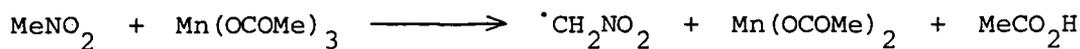


Scheme 33

An unusual type of reactivity is observed in the manganese (III) induced coupling of nitromethane with arenes⁴⁰ (Scheme 34), where the reactive species may be a radical cation (Scheme 35).

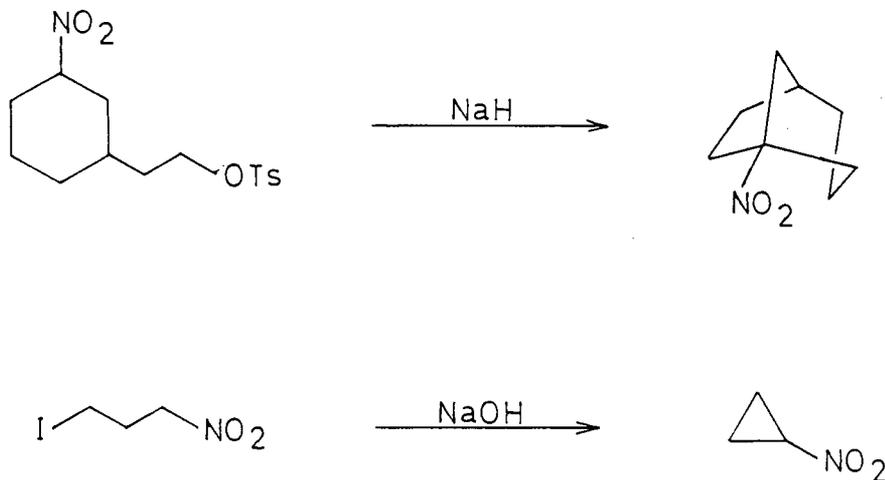


Scheme 34



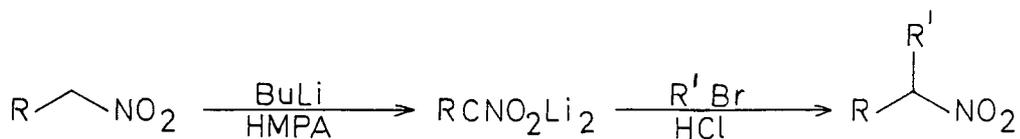
Scheme 35

Apart from the foregoing radical anion chain reactions, there are only two reported cases of \underline{C} -alkylation of a simple nitronate anion; both of these^{41,42} are intramolecular cyclizations (Scheme 36).



Scheme 36

The difficulties in obtaining simple \underline{C} -alkylation have prevented the full exploration of the use of the anions of nitroalkanes in synthetic schemes. However, α, α - doubly deprotonated nitroalkanes, available by treatment with n - butyl lithium at -90°C , are nucleophiles reactive towards carboxylic esters, anhydrides and acyl chlorides as well as alkyl halides (Scheme 37), aldehydes and ketones, giving products of acylation or alkylation at carbon⁴³.

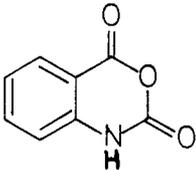
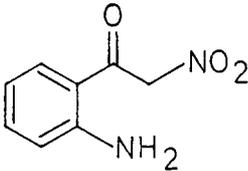
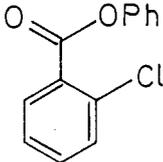
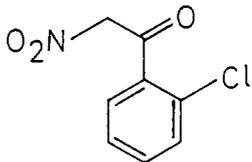


Scheme 37

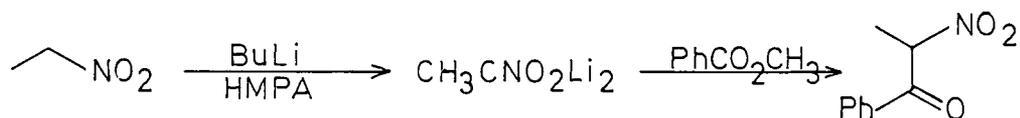
(c) Carbon Acylation

Historically, C-acylation of nitromethane has been achieved with only limited success. In 1903, Gabriel reported that a poor yield of the α -nitroketone could be obtained from the reaction of phthalic anhydride with sodium methane-nitronate⁴². Due to the ambident nature of the nitronate anion, and as with alkylation, O-acylation is generally favoured over C-acylation. Exceptions to this rather broad generalisation do exist, and include methoxymethylmagnesium carbonate, aroyl cyanides and acyl imidazoles as acylating species (Table 1).

Table 1 - C-Acylation of Nitroalkanes

Nitroalkane	Acylating Agent	Product	Reference
RCH_2NO_2	$\text{CH}_3\text{OCO}_2\text{MgOCH}_3$	$\begin{array}{c} \text{R-CH-NO}_2 \\ \\ \text{CO}_2\text{CH}_3 \end{array}$	44
$\text{RCH}=\text{NO}_2^{\ominus}\text{M}^{\oplus}$	$\text{R}^1-\text{C} \begin{array}{l} \text{=O} \\ \text{CN} \end{array}$	$\text{R}^1-\overset{\text{O}}{\parallel}{\text{C}}-\underset{\text{R}}{\text{CH}}-\text{NO}_2$	45
$\text{CH}_2=\text{NO}_2^{\ominus}\text{M}^{\oplus}$	$\text{R}-\text{C}(=\text{O})-\text{N} \begin{array}{c} \diagup \\ \text{Imidazole} \\ \diagdown \end{array}$	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_2-\text{NO}_2$	46
$\text{CH}_2=\text{NO}_2^{\ominus}\text{M}^{\oplus}$			47,48
$\text{CH}_2=\text{NO}_2^{\ominus}\text{M}^{\oplus}$			49

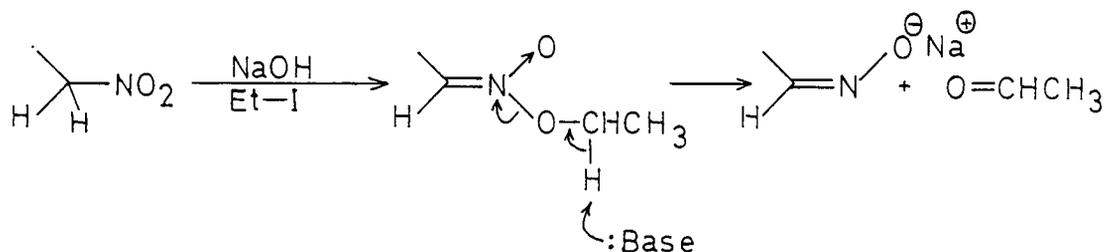
However, doubly deprotonated nitroalkanes provide a much more general method for α -acylation. A wide range of acylating agents react⁵⁰ smoothly and in high yield with the doubly deprotonated species, as exemplified in Scheme 38.



Scheme 38

6(a) Oxygen Alkylation

α -Alkylation of nitro compounds is restricted to primary or secondary nitroalkanes, the product formed being a nitronate ester. This is the normal regiochemistry of addition of alkylating agents, with examples far exceeding the isolated cases of C-alkylation. Normally a base is required to allow nucleophilic displacement by the nitronate ion. Diazomethane, however reacts slowly with α -aryl nitroalkanes to form methyl nitronates⁵¹. The conditions for alkylation are such as to cause decomposition of the labile nitronate esters, the products isolated being an oxime and a carbonyl compound derived from the alkylating agent⁵². This disproportionation most likely results from base catalysed decomposition (Scheme 39).



Scheme 39

Indeed, this reaction constitutes a useful route to carbonyl compounds, as exemplified⁵³ in Scheme 40.

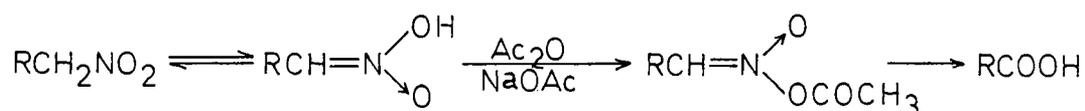


Scheme 40

Nitronate anions react with oxonium salts, which are exceptionally active alkylating agents. Here, alkylation proceeds under conditions mild enough to allow the isolation of aliphatic alkyl nitronates⁵². The nitronic esters thus formed are highly unstable and decompose to a variety of products, including oxime and carbonyl compounds. Hydrolysis with weak acid can lead to Nef products whereas under strongly acidic conditions hydroxamic acids are formed.

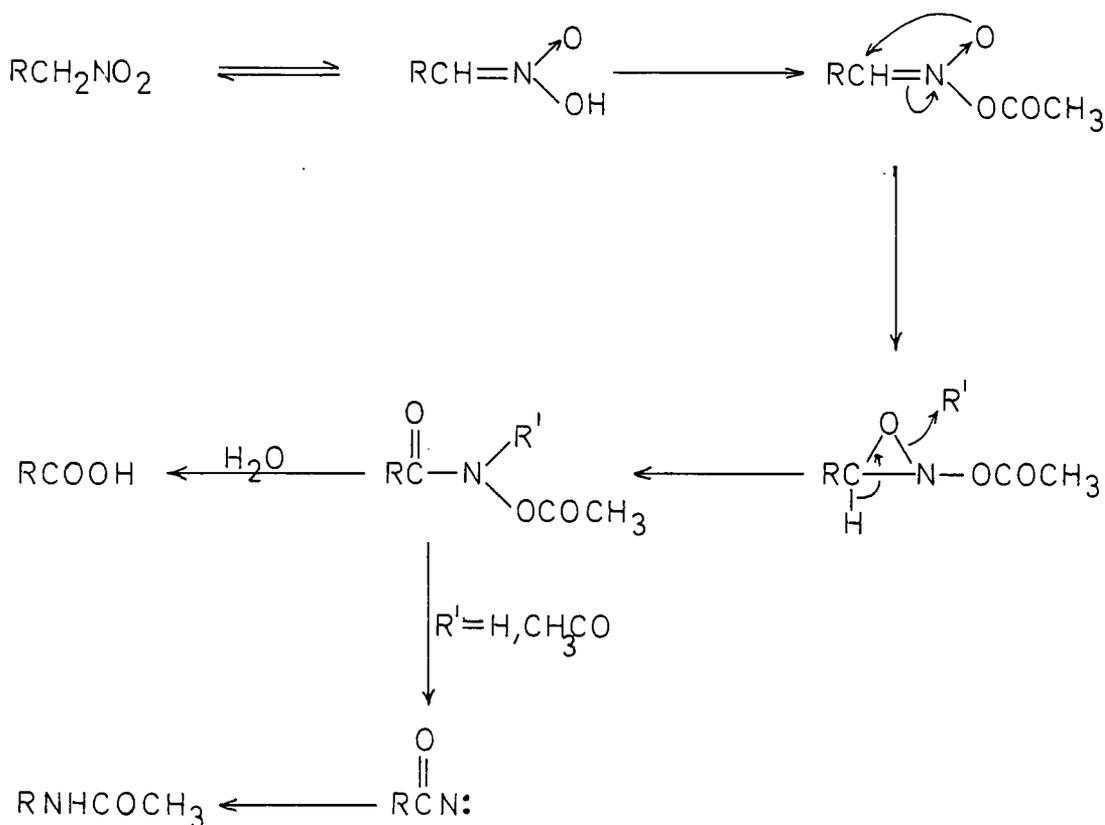
(b) Oxygen Acylation - Nitronic Mixed Anhydrides

In common with alkylation, most conventional acylating agents are attacked by the oxygen of the ambident nitronate anion. The product is a nitronic mixed anhydride, an unstable species prone to re-arrangement to carboxylic acids or hydroxamic acids⁵⁴ (Scheme 41)



Scheme 41

The mechanism of this transformation is poorly understood; it has been suggested that oxidation occurs via a mechanism similar to that involved in the Nef reaction.¹¹ Dewar²⁶ has proposed an alternative mechanism in which a protonated nitrile oxide is formed (c.f. Scheme 13). Urbanski⁵⁵ and Nenitzescu⁵⁶ have formulated less attractive alternatives and McKillop⁵⁴ has suggested the intermediacy of an oxazirane (Scheme 42), though little evidence exists to support this last pathway.

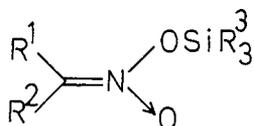


Scheme 42

(c) O-Metallated Nitronates

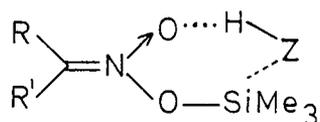
Silyl Nitronates

Silyl nitronates (2) were first prepared unambiguously by Tartakovskii in 1974⁵⁷. A more expeditious synthesis was reported later involving low temperature deprotonation of the nitroalkane and trapping of the resulting anion with a chlorotrialkylsilane⁵⁸.

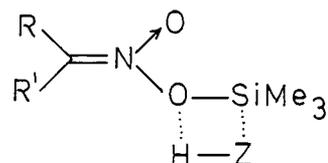


(2)

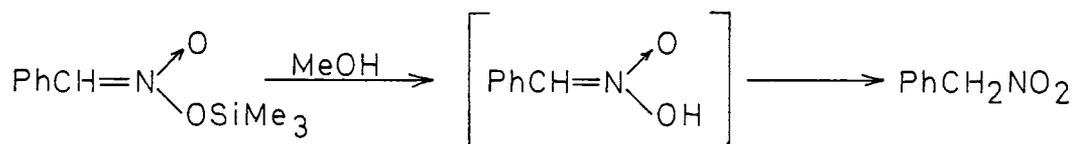
This class of compound is very sensitive to hydrolysis and solvolysis, reacting readily with water, alcohols, acids and primary and secondary amines.⁵⁹ Such reactions may involve a multicentre transition state such as (3) or (4). Indeed, it has been shown that the immediate product of methanolysis of trimethylsilyl phenylmethanenitronate is aci-phenylnitromethane⁵⁹ (Scheme 43).



(3)



(4)

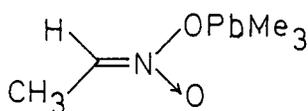


Scheme 43

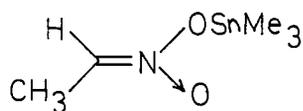
Silyl nitronates take part in 1,3-dipolar cycloaddition reactions with olefins⁵⁷; due to greater thermal stability they have found wider application than the corresponding alkyl nitronates. As previously discussed, they have been used in a fluoride ion catalysed Henry reaction³⁵.

Several highly unstable O-metallated nitronates (5)-(8)⁶⁰ have been prepared, but their chemistry is not well documented. Within

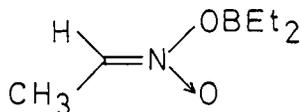
this class of compound the silyl nitronates seem to be unique in their relative thermal stability, their ease of preparation and the number of synthetic transformations they can undergo.



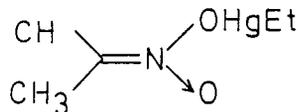
(5)



(6)



(7)

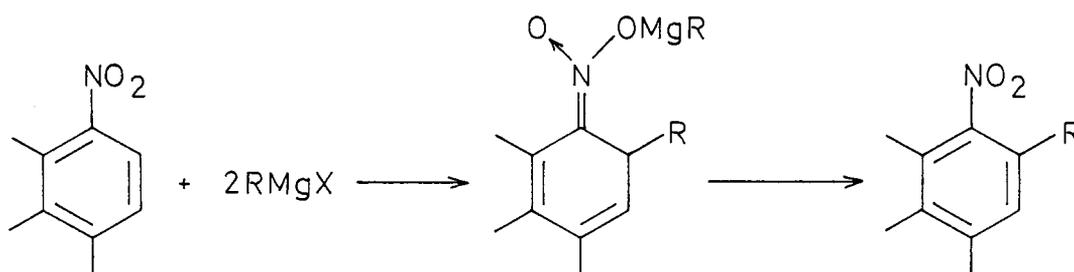


(8)

7. Michael Additions

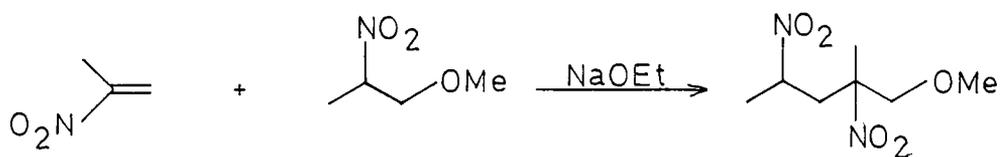
Primary and secondary nitroalkanes can react, in the presence of a basic catalyst, with α , β unsaturated esters, carbonyl compounds and nitriles, as well as with vinyl sulphones and nitroolefins. The basic catalyst is usually sodium ethoxide or diethylamine in an alcohol solvent; in some cases tertiary phosphines have been shown to be of utility⁶¹. Nitroalkenes can act as weak Michael acceptors, and a large number of reactions with active methylene compounds are known⁶².

The reaction is most successful with well stabilised anions, becoming unpredictable with increasing reactivity of the nucleophile, although lowering the temperature allows successful addition of dialkyl cuprates, cadmium alkyls and alkyl lithium reagents⁵. Grignard reagents can be added conjugatively to nitroarenes, giving initial products of 1,4-addition in a useful synthesis⁶³ of ring alkylated aromatic nitrocompounds (Scheme 44).



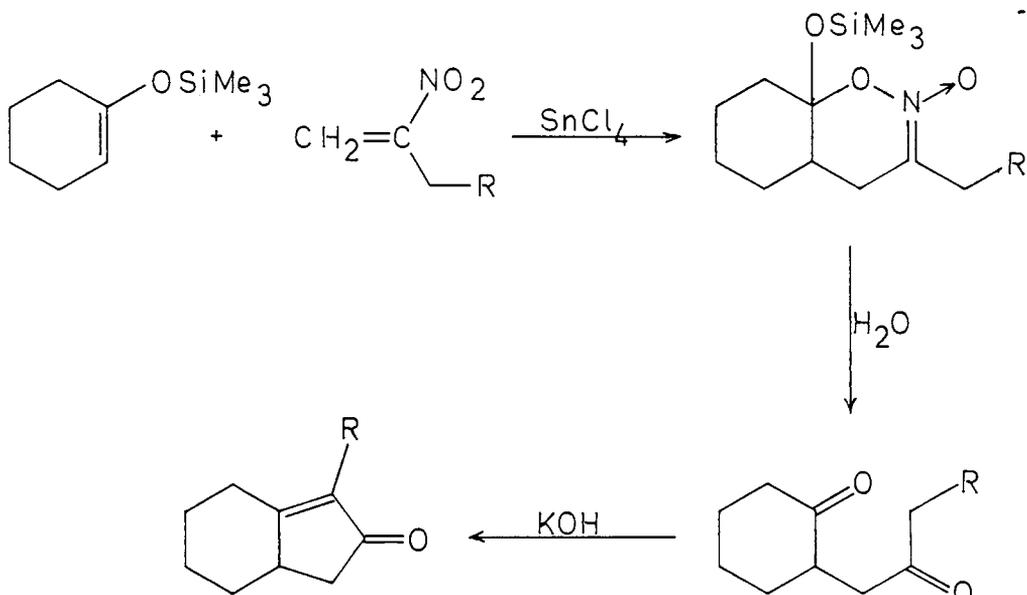
Scheme 44

One of the most convenient routes to aliphatic dinitro- and polynitro compounds combines the above two types of reactivity⁶⁴, viz., the addition of activated nitroalkanes to α, β -unsaturated nitroalkenes (Scheme 45).



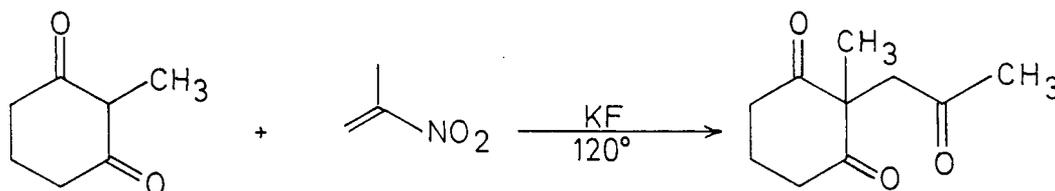
Scheme 45

An elegant synthesis of 1,4-diketones proceeds by Lewis acid promoted addition of silyl enol ethers to nitro olefins. The 1,4-diketones are obtained directly by in situ hydrolysis of the intermediate nitronic ester (Scheme 46). Subsequent intramolecular aldol condensation forms variously substituted cyclopentenones⁶⁵.



Scheme 46

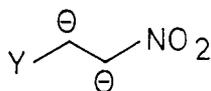
Fluoride ion has been found to be an effective catalyst in these conjugate addition processes, with the diketone being the isolated product⁶⁶; the overall reaction constituting consecutive Michael addition and Nef reactions, as illustrated in Scheme 47.



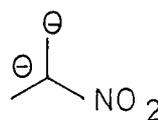
Scheme 47

8. Reactions at the β -Carbon

Dianions of primary nitroaliphatic compounds, discussed earlier, have been thoroughly investigated by Seebach and his co-workers, (page 28). With secondary nitroalkanes and nitroalkanes possessing an electron withdrawing group at the β -position, then α, β doubly deprotonated species (9) and (10) are formed⁴³.



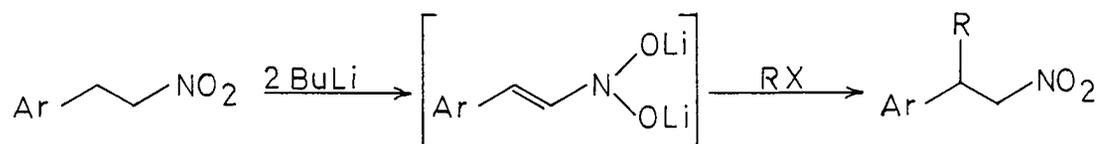
(9)



(10)

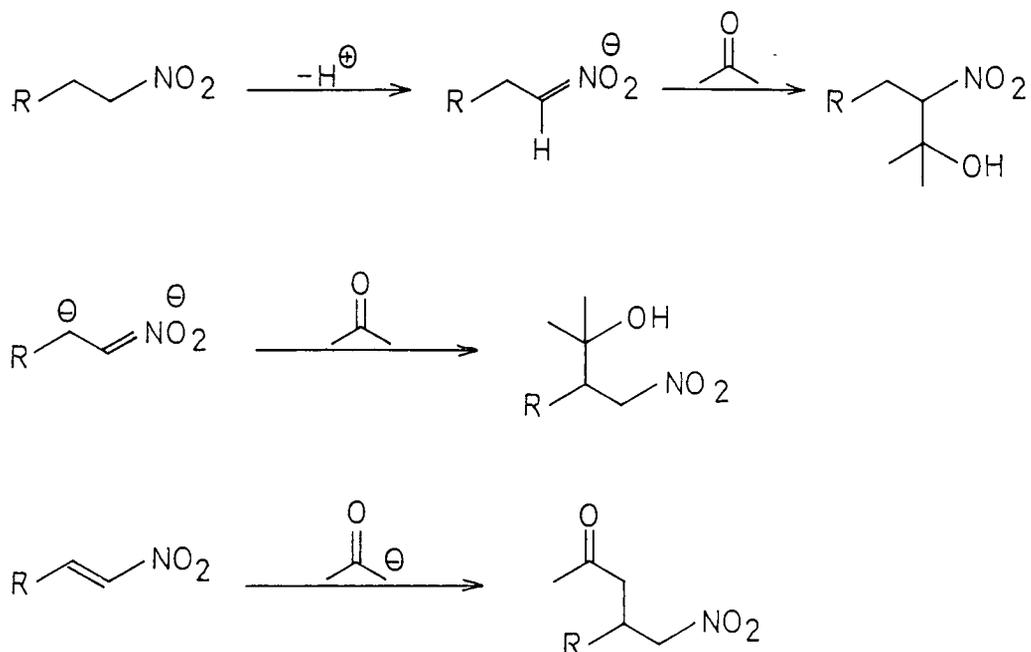
Y = Ar; CH₂ = CH; CO₂CH₃

These dianions react with alkyl halides, carbonyl compounds and enones, at the more reactive β -position (Scheme 48).



Scheme 48

It can thus be demonstrated clearly that three entirely different structural types are available from precursors with the same carbon skeletons and functionality patterns, but at different oxidation levels. By way of example, acetone combines as an electrophile with a nitronate anion to give a 1, 2 nitro alcohol, and with the α, β doubly deprotonated derivative to give an isomeric 1, 3- nitroalcohol, whereas as its nucleophilic enolate it adds to a nitro-olefin to give a 4-nitro ketone (Scheme 49).



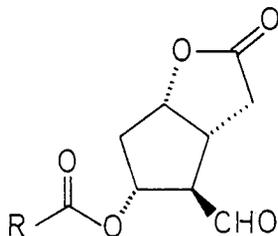
Scheme 49

9. Synthesis Involving the Nitro Moiety

Several of the aforementioned special attributes of the nitro group have been cleverly used in synthetic strategies. A selection of some recent applications will be discussed here.

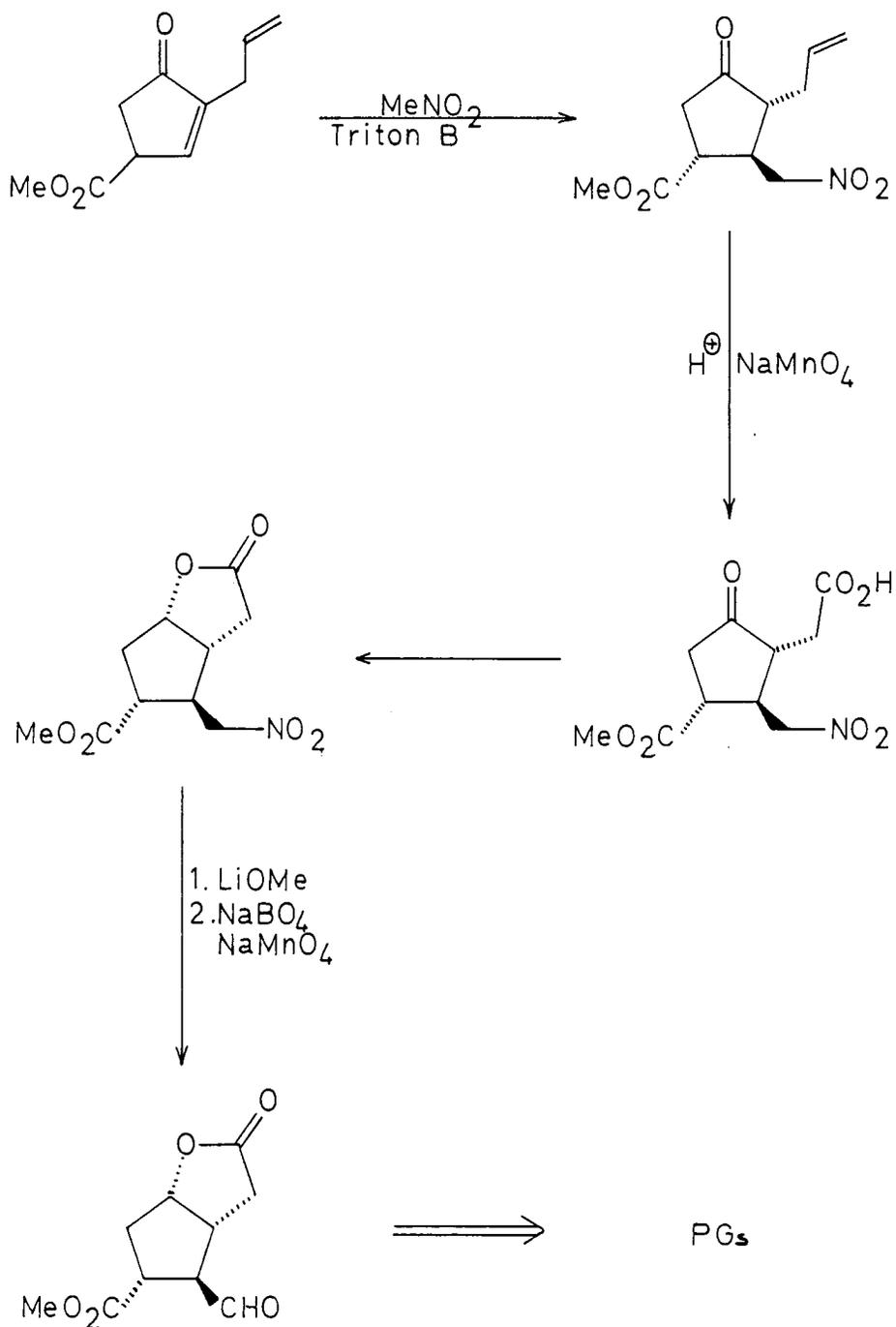
(a) The Prostaglandins

The prostaglandins have fired the imagination of organic chemists since Samuelsson first elucidated their structure in 1960. It is not surprising, therefore, to find embodied in the rich and complex chemistry of the prostaglandins examples of the nitro group being applied in the preparation of key intermediates. Corey was first in the arena of prostaglandin synthesis and many formal syntheses now proceed only as far as the "Corey Lactone" (11).



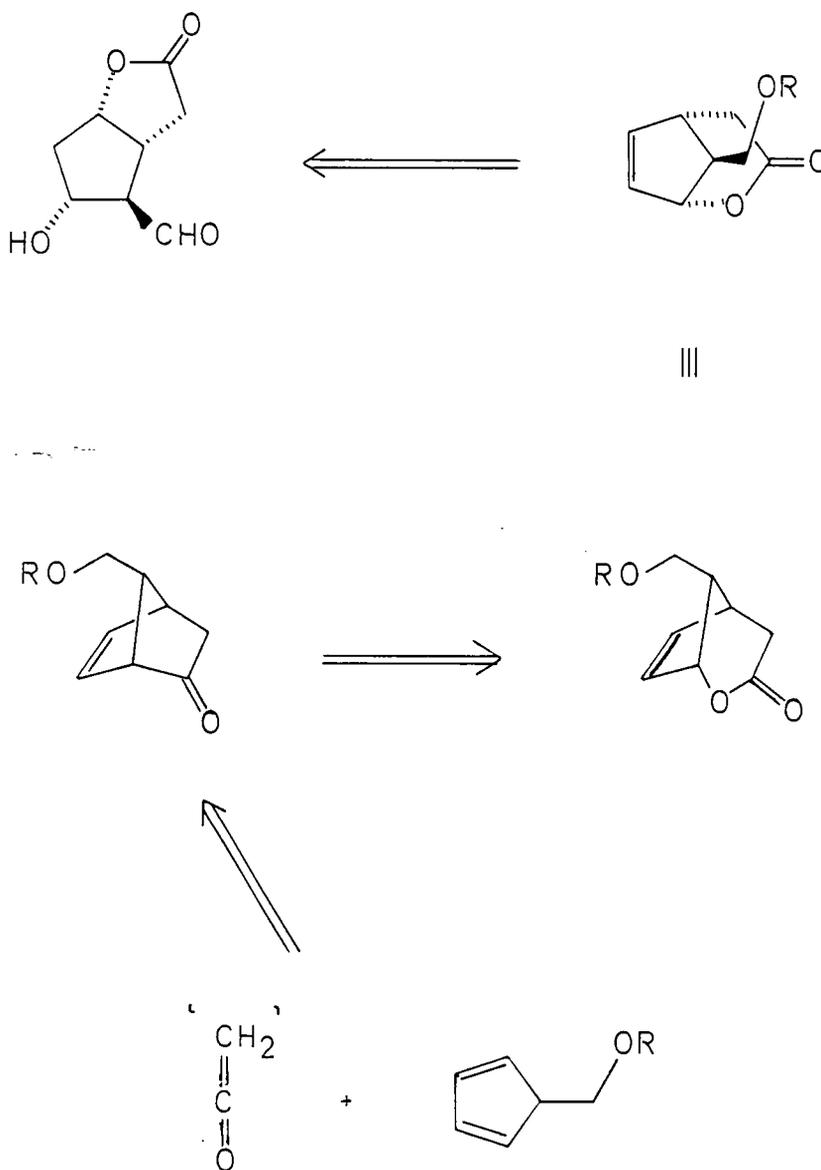
(11)

An elegant example of the synthesis of this aldehyde involves 1,4-addition of nitromethane to an enone⁶⁷, ultimately followed by a Nef reaction to obtain the aldehyde (Scheme 50)



Scheme 50

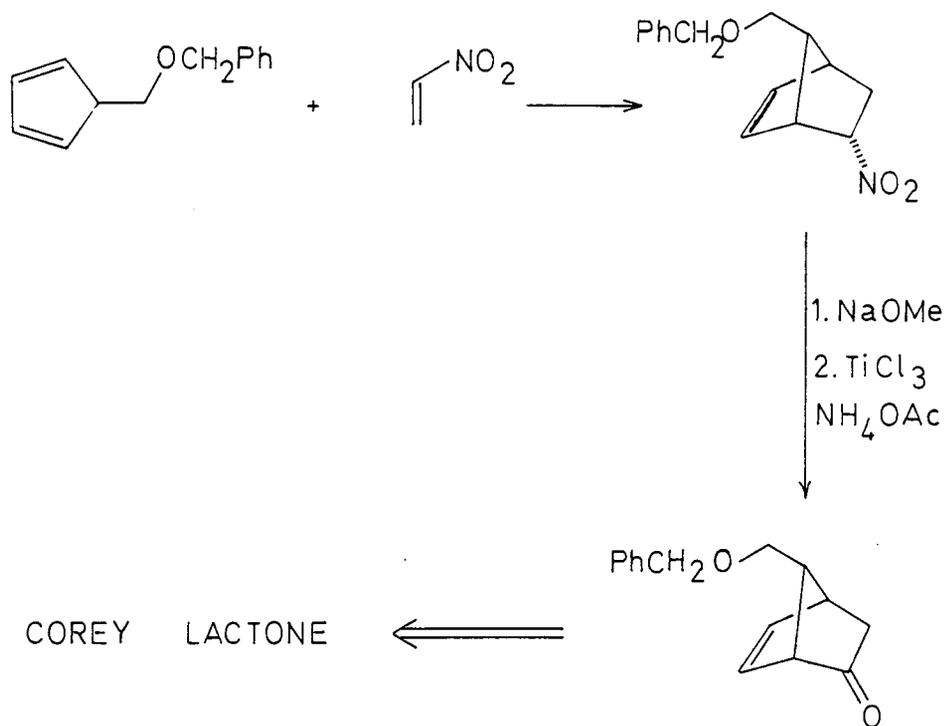
The bicyclo (2,2,1) heptane approach to prostaglandins is a well established path to the Corey aldehyde. Starting with a cyclopentane derivative, sequential introduction of the appropriate substituents around the ring leads to the Corey lactone. For example, Diels-Alder reaction of a 5-substituted cyclopentadiene with a ketene equivalent provides the C₆ and C₇ carbons; selective formation of the anti adduct ensures the required trans orientation of the α and β chain precursors at C₈ and C₁₂ respectively (Scheme 51).



Scheme 51

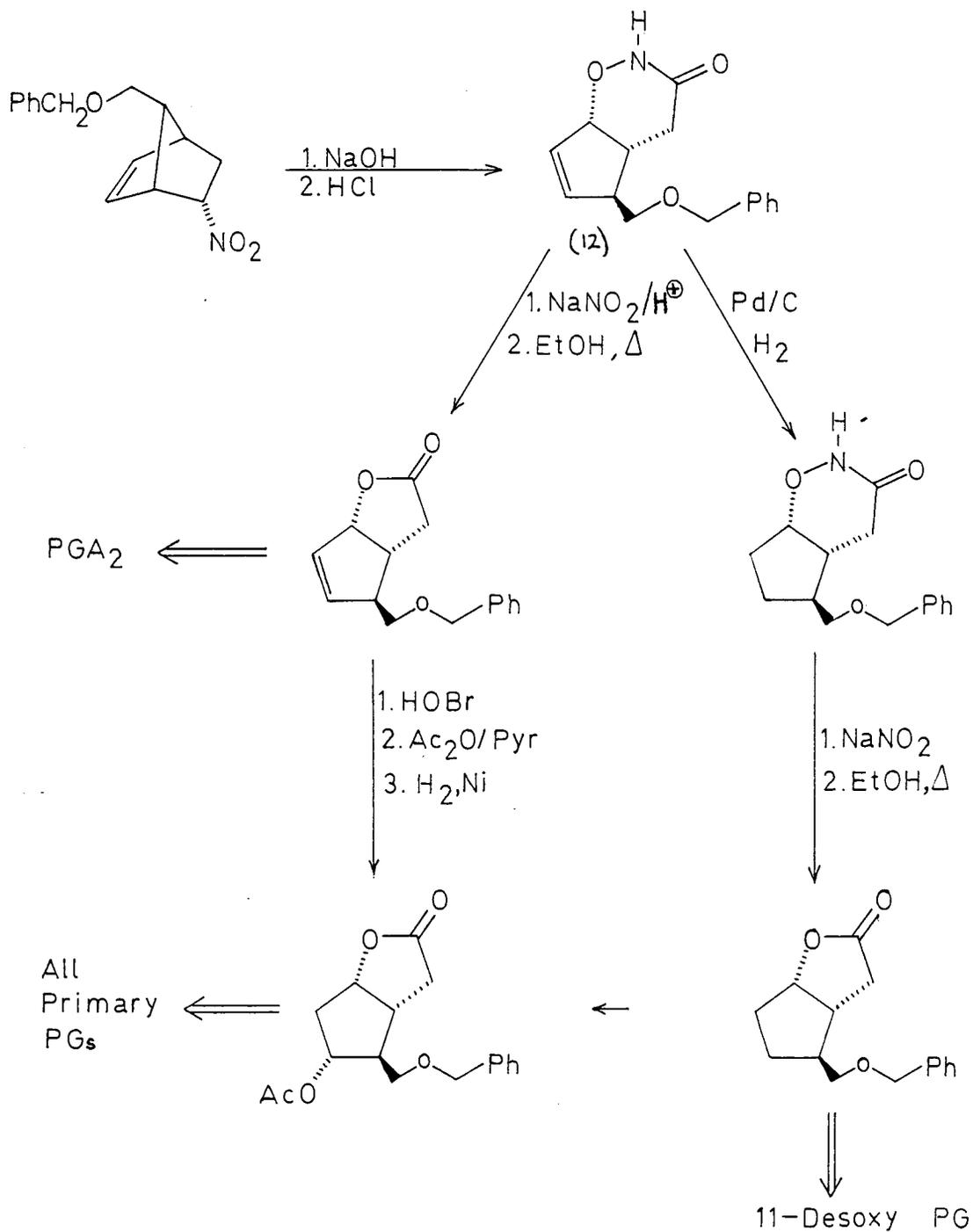
Baeyer-Villiger oxidation gives the δ -lactone, which is transformed into the γ -lactone via iodolactonisation. Subsequent elaborations lead to PGF_{2 α} .

Such a strategy was followed by Ranganathan⁶⁸ using nitroethylene as a ketene equivalent and has proved one of the most expeditious routes to the Corey aldehyde. The Diels-Alder reaction between 5-benzyloxymethylcyclopentadiene and nitroethylene yielded the desired bicycloheptene (Scheme 52). This versatile intermediate can be converted to most of the prostaglandins by varying routes.



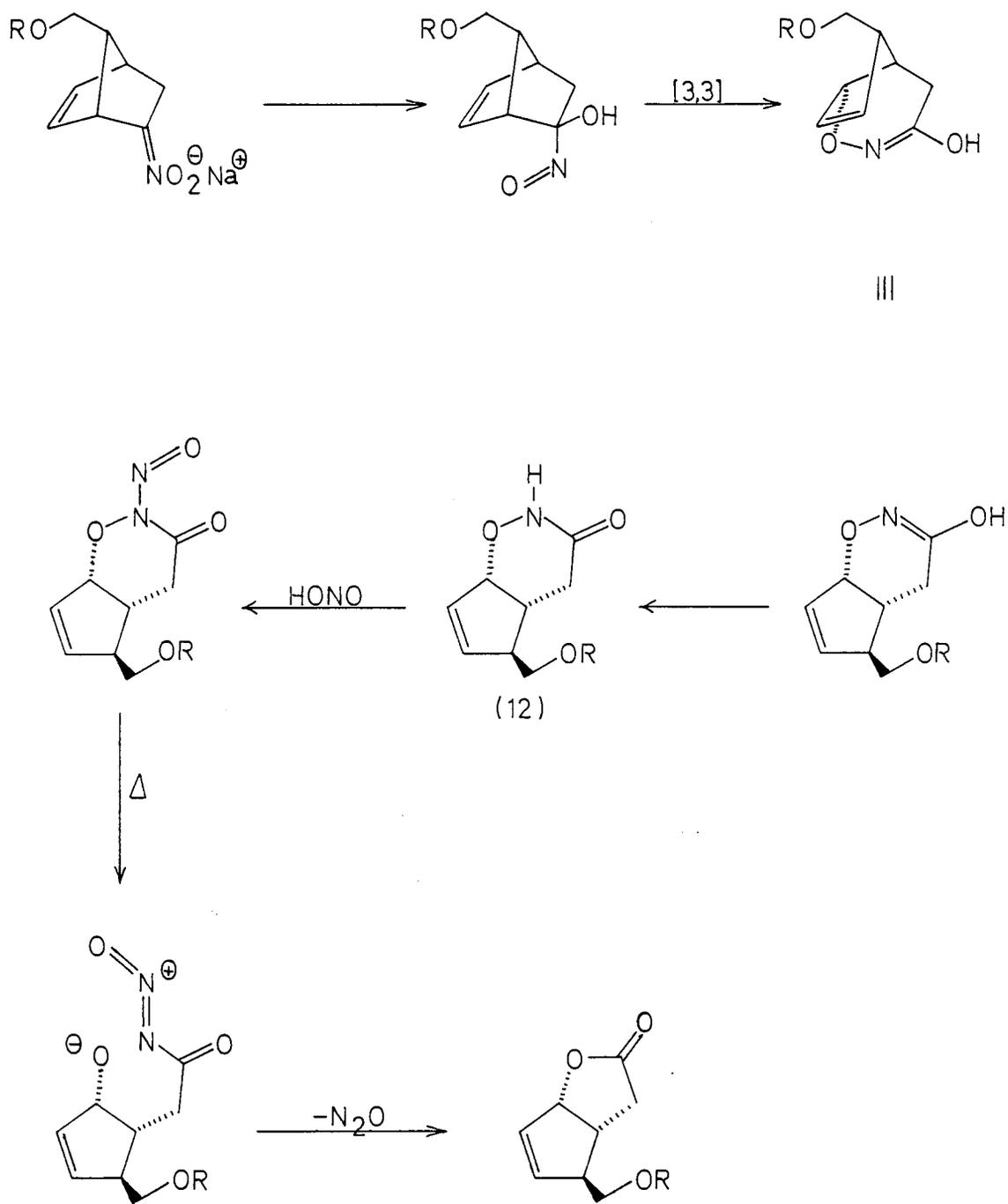
Scheme 52

Attempted generation of the ketone under standard Nef conditions resulted in a serendipitous re-arrangement to the cyclic hydroxamic ester (12), (Scheme 53), a key precursor of diverse types of prostaglandins.



Scheme 53

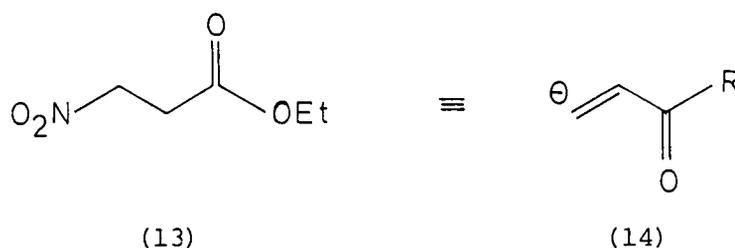
Treating the hydroxamic ester (12) with sodium nitrite in hydrochloric acid illustrates an interesting N_2O extrusion⁶⁸ from the N-nitroso derivative of (12) (Scheme 54).



Scheme 54

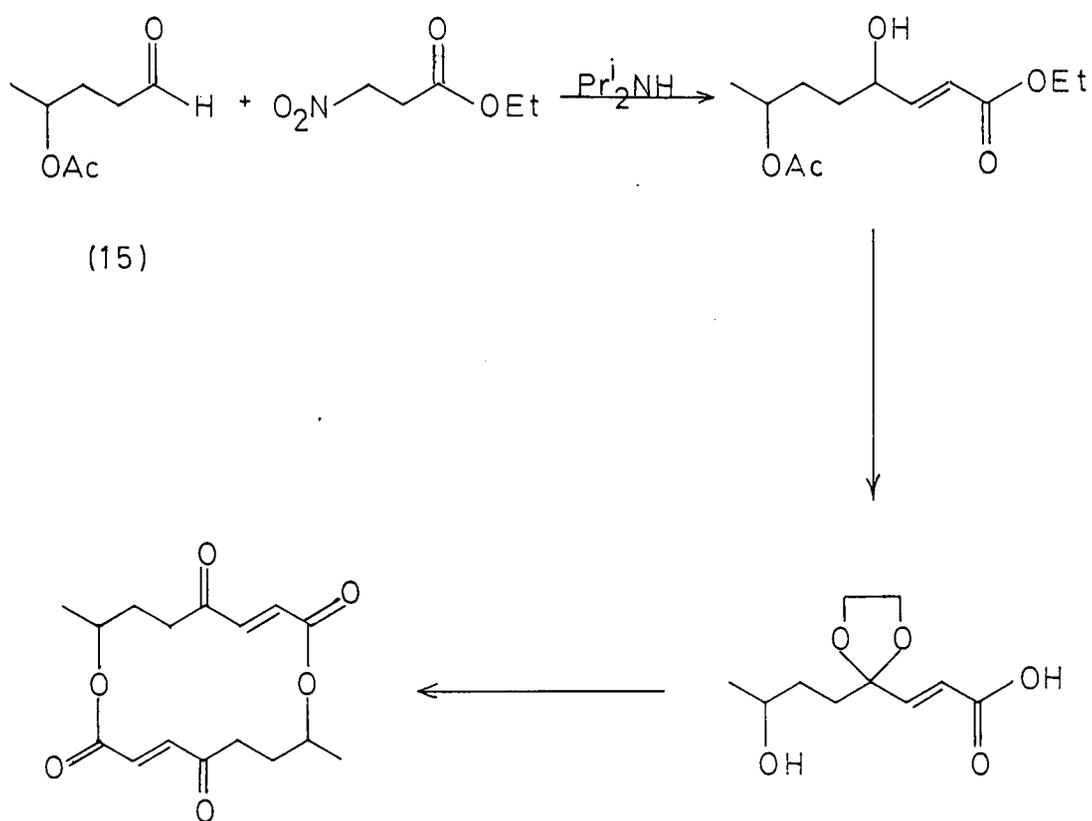
(b)

A recently reported synthesis of the macrocyclic antibiotic pyrenophorin²⁹ utilised ethyl β -nitropropionate (13) as a β -acyl anion equivalent (14).



Clearly, Michael addition of the nitro compound to α,β unsaturated ketones followed by elimination of nitrous acid would correspond to a d^3 synthon of type (14), demonstrating again the particular utility of nitro compounds in umpolung reactions. Thus, treatment of the readily prepared aldehyde (15) with ethyl β -nitropropionate and diisopropylamine ... produced the hydroxy acrylate (Scheme 55).

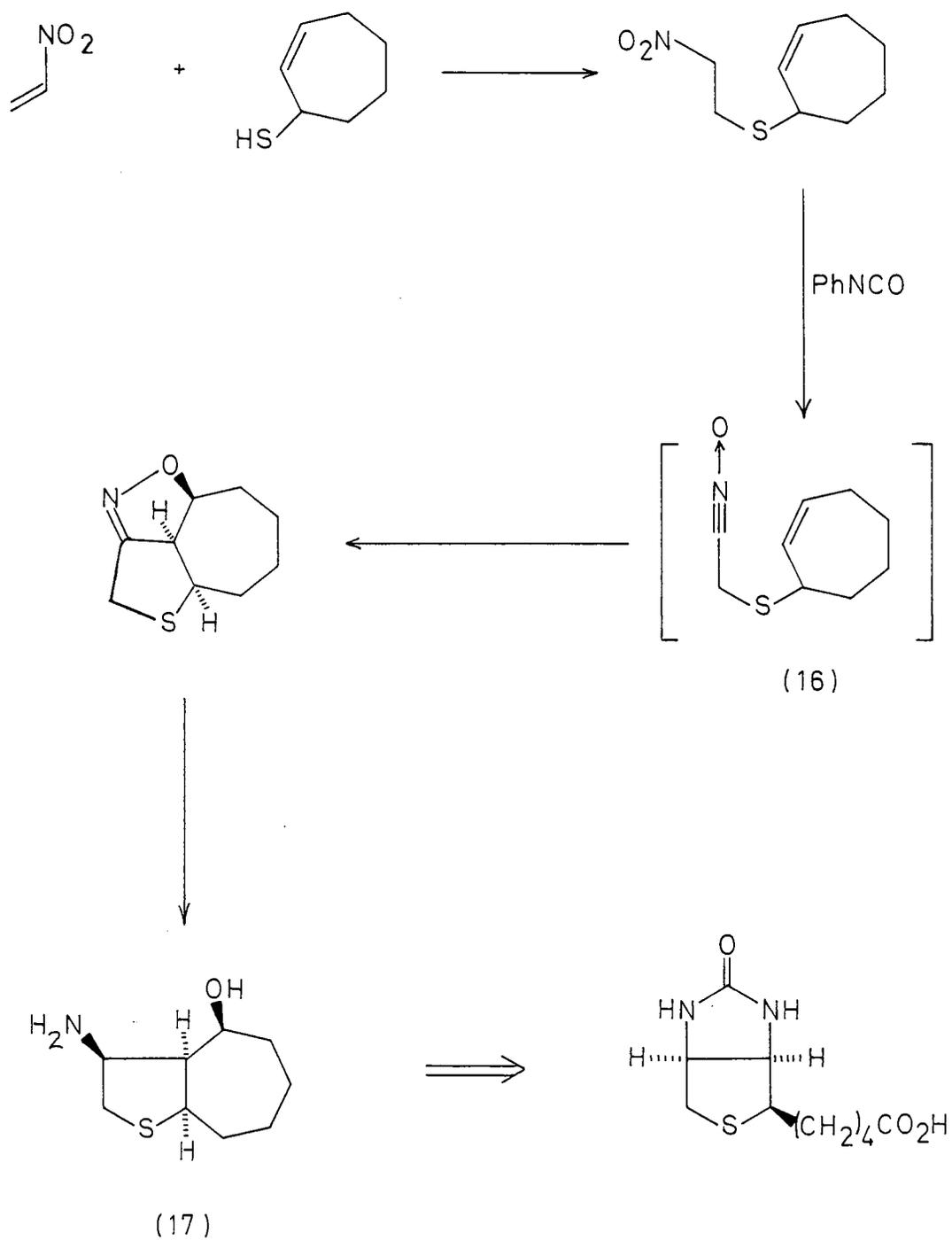
Oxidation of the alcohol, followed by protection of the carbonyl group and hydrolysis gave the hydroxy acid. Lactonisation with dimethyl azodicarboxylate and triphenylphosphine in toluene and finally deprotection afforded racemic pyrenophorin.



Scheme 55

(c)

The special properties of the nitro group were demonstrated in a most elegant synthesis of (+)-biotin⁶⁹. The key amino alcohol (17) was generated by an intramolecular 1,3-dipolar cycloaddition reaction of the olefinic nitrile oxide (16). Lithium aluminium hydride reduction of the tricyclic adduct provided the amino alcohol (17), and further elaborations gave a short synthesis of racemic biotin (Scheme 56).



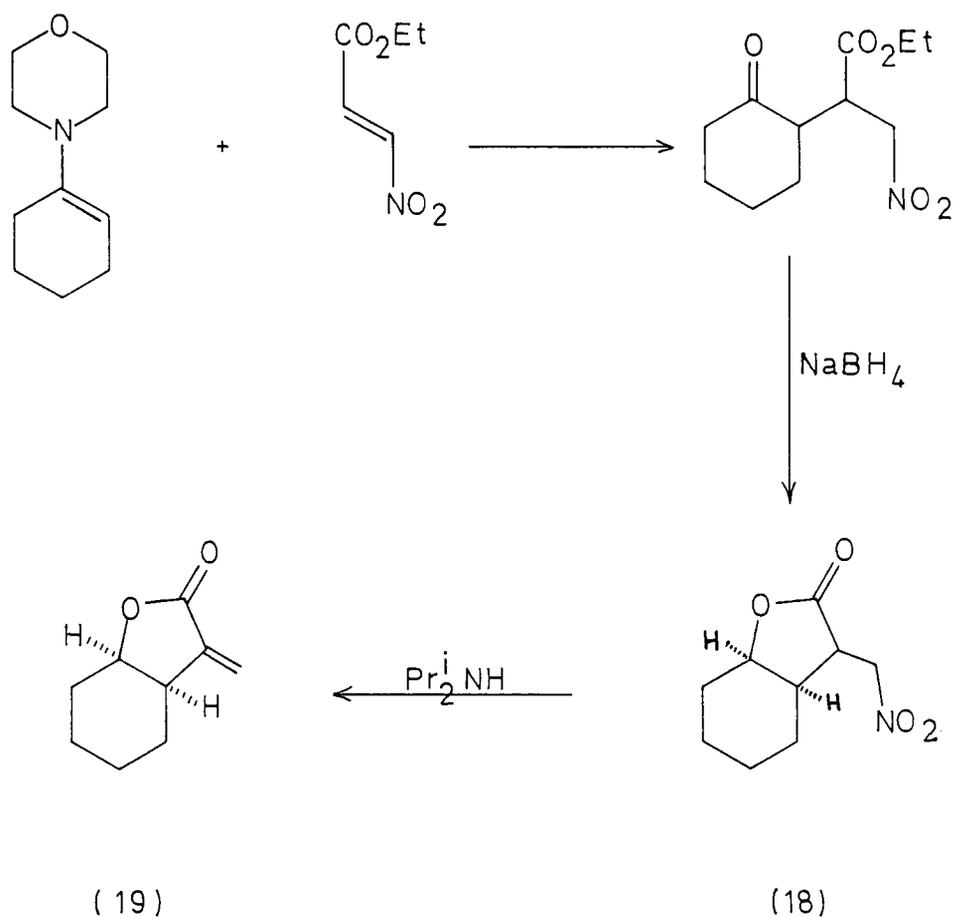
Scheme 56

(d)

Finally, in this section, a short synthesis of α -methylene- γ -butyrolactones is described⁷⁰. These are important intermediates in the synthesis of perhydroazulene sesquiterpene lactones.

Michael addition of the morpholine enamine of cyclohexanone to an α -nitroalkene provided the β -nitroester (18) (Scheme 57).

Elimination of nitrous acid afforded the lactone (19).



Scheme 57

This short review has attempted to demonstrate that nitroalkanes can occupy a crucial position in the interconversion of organic functional groups. In the interests of clarity and cohesion, it is neither a full nor comprehensive account of nitroalkane chemistry. Several excellent reviews are available on this topic⁷¹. Superficially, nitroalkanes appear ideal as intermediates in organic synthesis, but due to inherent problems of, for example, the possibility of O-alkylation rather than C-alkylation, the potential which undoubtedly exists has not been fully realised. However, as this review describes, many of the problems have now been overcome. With the ready availability of α , α - and α , β -doubly deprotonated anions, a greater use of nitroalkanes is envisaged. Recalling the functional group equivalence of the nitro group with most common functional groups, nitroalkanes should adopt a more prominent position in the art of synthesis in the foreseeable future.

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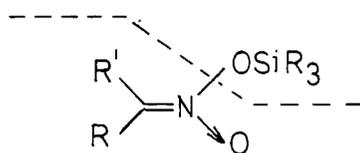
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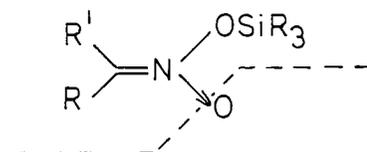
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RESULTS AND DISCUSSION

The research described herein was initiated to delineate the utility of silyl nitronates in synthetic transformations. In the extensive chemistry of nitroalkanes there are areas where improvement would be advantageous. From the representations (1a) and (1b) of the structure of a silyl nitronate, one might expect two diverse modes of reaction.



(1a)

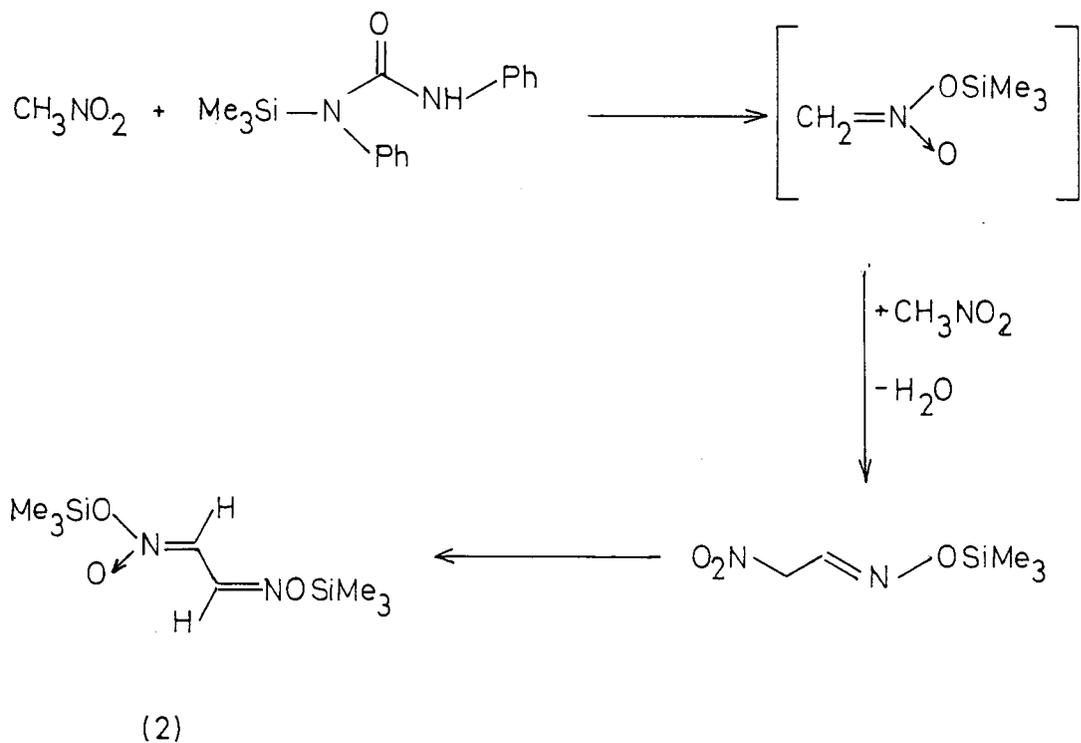


(1b)

From (1a), the silyl nitronate may have some of the properties of a nitron, whereas, from (1b) the silyl nitronate may conceivably show facets of the behaviour of oxime O-silyl ethers. More interestingly and more usefully, some parallels with silyl enol ethers may become apparent. The chemistry of silyl enol ethers is extremely diverse¹ and has found many applications. The possibility that silyl nitronates could show some facets of this chemistry instigated the work to be described.

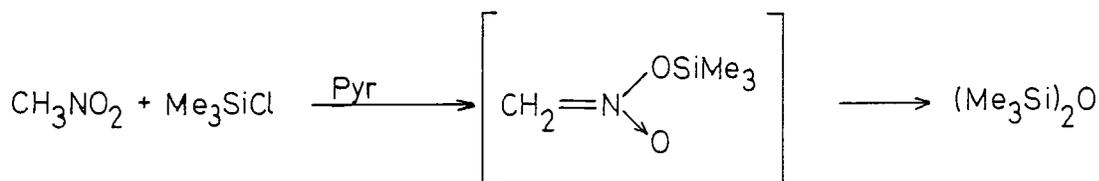
The first attempted silylation of a nitroalkane was reported in 1964. Reaction of nitromethane with trimethylsilyldiphenylurea produced bis(trimethylsilyl)methazonic acid (2). This was

rationalised by proposing the formation of trimethylsilyl methane-nitronate, followed by its condensation with excess nitromethane, and finally silylation of the product² (Scheme 1).



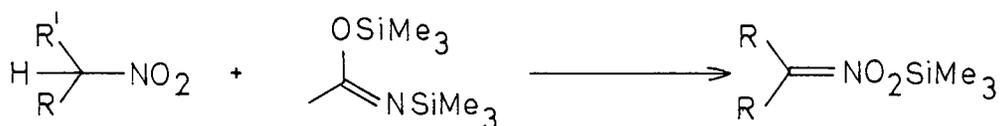
Scheme 1

Notwithstanding this partial success, it was not until 1972 that a further attempted silylation of nitromethane was reported³. Again, no silyl nitronate was isolated, but its intermediacy was inferred, somewhat tenuously, to account for the formation of hexamethyldisiloxane (Scheme 2).



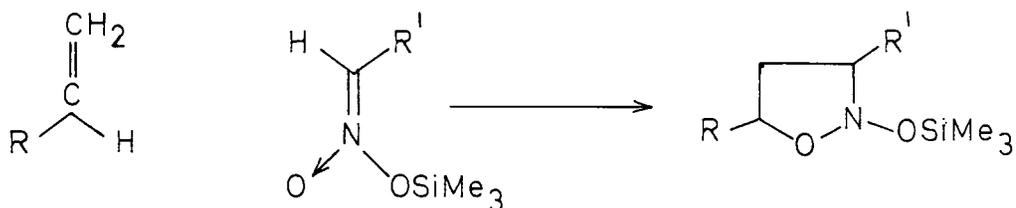
Scheme 2

In 1974, Ioffe and his co-workers prepared a limited number of silyl nitronates⁴. The method of synthesis employed was to heat the appropriate nitroalkane in N,O-bis(trimethylsilyl)acetamide (Scheme 3); good yields were claimed, but product purification was difficult.



Scheme 3

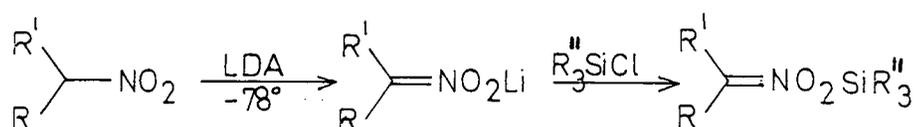
Ioffe demonstrated the utility of these silyl nitronates as 1,3-dipolar species in the preparation of 2-trimethylsiloxyisoxazolidines (Scheme 4). The cyclo adducts thus formed are versatile intermediates in organic synthesis and a full account of their chemistry has been given by Takeuchi and Furasaki⁵.



Scheme 4

Preparation of silyl nitronates can also be achieved using trimethylsilylchloride and triethylamine in benzene⁶; however, yields are generally low and the synthesis is restricted to short chain primary nitroalkanes. The trimethylsilyl nitronate of nitrocyclohexane has been obtained by silylation with trimethylsilylchloride in the presence of lithium sulphide^{6a}. This method is only successful with secondary nitroalkanes.

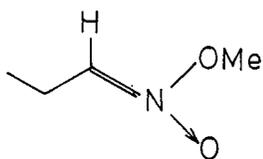
In 1979 a more flexible procedure was described which allowed the silylation of numerous primary and secondary nitroalkanes⁷. This method of synthesis involves deprotonation of the nitroalkane at -78°C with lithium diisopropylamide, and subsequent silylation with a trialkylsilyl chloride at -78°C . Non-aqueous isolation procedures afford almost quantitative conversion to the silyl nitronate (Scheme 5).



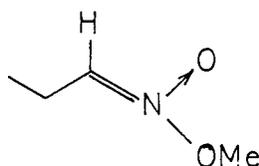
Scheme 5

The ready availability of a variety of silyl nitronates enabled a detailed investigation of their physical properties to be carried out, including X-ray structure analysis. In marked contrast to alkyl nitronates⁸(2), the ^1H n.m.r. spectrum of (3) showed no evidence of the non-equivalence of the α and α' -positions.

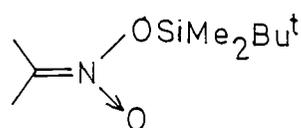
Similarly, in the ^{13}C n.m.r. spectrum of (3), a singlet was observed for the two isopropylidene methyl groups.



E-(2)



Z-(2)



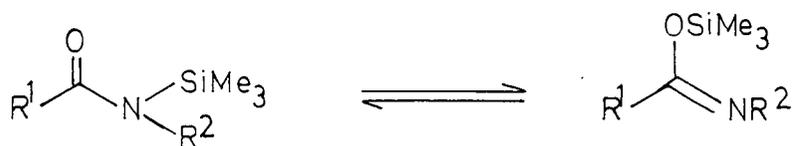
(3)

The undetectable nature of non-equivalence was attributed to rapid exchange of the silyl group between the two oxygen atoms (Scheme 6). Indeed, low temperature ^{13}C n.m.r. analysis established the activation energy for this 1,3-migration to be approximately 10 kcal/mol.



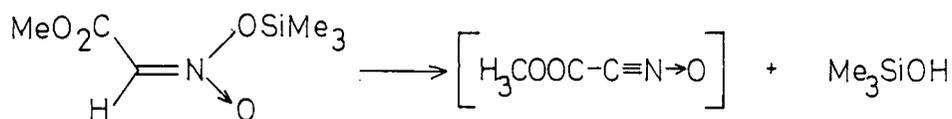
Scheme 6

Such silyl migration has precedent; for example, an activation energy of ca 11 kcal/mol. was estimated⁹ from the ^{13}C n.m.r. coalescence temperatures for the equilibria between N-silyl amides and their imidate tautomers (Scheme 7).



Scheme 7

The silyl nitronates thus far prepared, and in particular those derived from primary nitroalkanes, are relatively stable and, in most cases, can be distilled. This again is in contrast to alkyl nitronates, which decompose on heating to oximes and carbonyl compounds. The product of thermal decomposition of (4) was reported¹⁰ to be nitroalkane and hexamethyldisiloxane. The intermediacy of a nitrile oxide was suggested (Scheme 8), but no evidence for such a species was obtained.



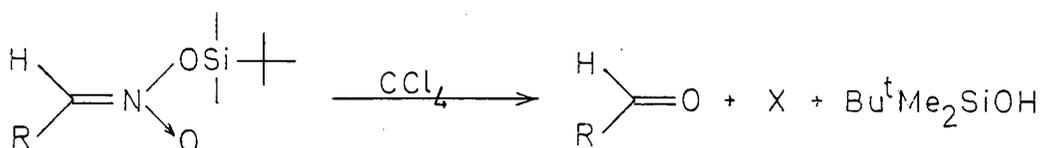
(4)

Scheme 8

Decomposition of Silyl Nitronates

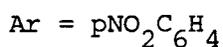
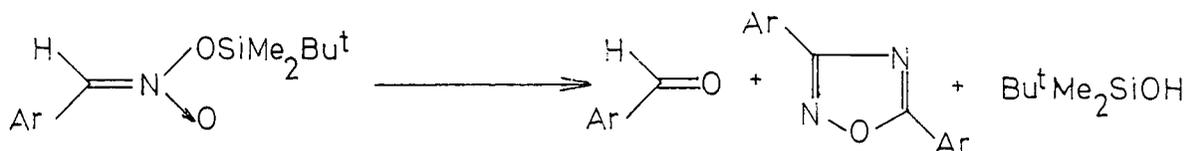
Shortly after the initial preparation of silyl nitronates, it was noticed¹¹ that primary silyl nitronates decompose in CCl_4 solution to aldehydes (Scheme 9). Conversion was only 50% effective, with

50% of an unknown by-product being formed. If yields could be improved, this mild Nef process could have considerable use in synthesis. Also, in view of the uncertainty concerning the pathway of the Nef and related reactions, a study of the mechanism of this transformation might help clarify this situation.



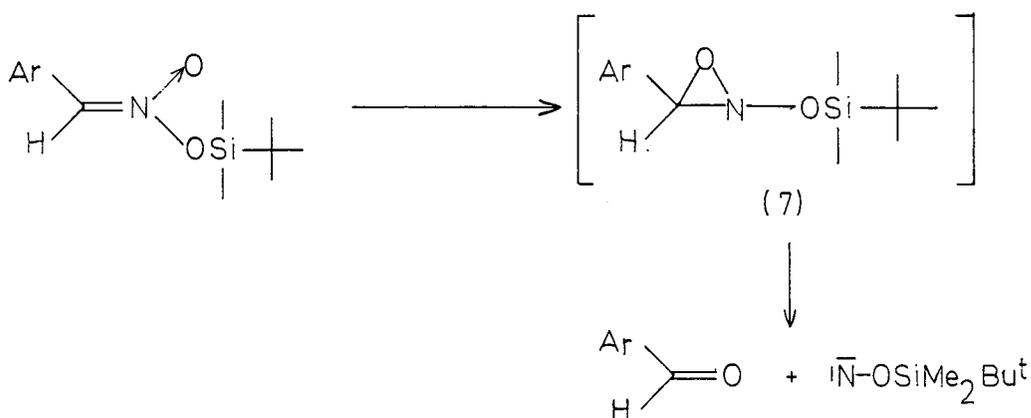
Scheme 9

Thus, the silyl nitronates were prepared according to the literature procedure⁷. Initially, t-butyldimethylsilyl phenylmethane nitronate was chosen for study. Conversion into benzaldehyde in CCl₄ was slow at room temperature; at reflux temperature the reaction was rapid but with no attendant change in yield. Attempted separation of the by-product on the phenylnitromethane system proved extremely difficult, with the intractable nature of t-butyldimethylsilanol being particularly troublesome. However, p-nitrophenylmethanenitronate was smoothly converted into p-nitrobenzaldehyde; careful fractional crystallisation then allowed isolation of the by-product. From spectral data, including accurate mass measurement, this was determined to be the oxadiazole (6) (Scheme 10), identical in all respects with an authentic sample¹².



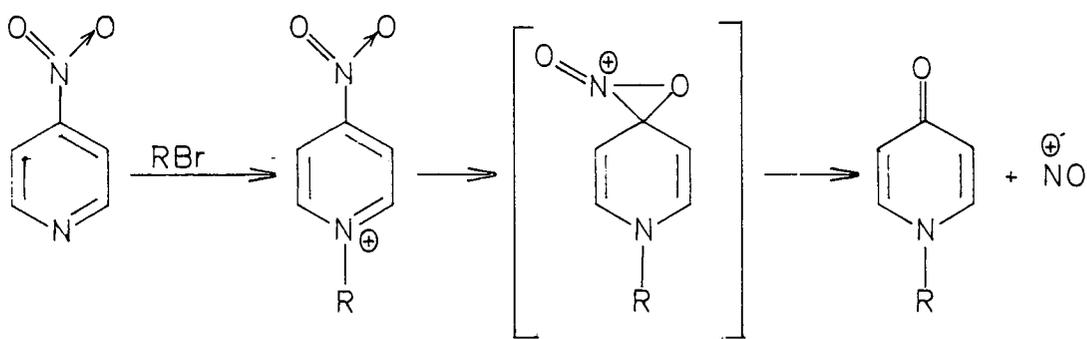
Scheme 10

At this point, an appraisal of the literature suggested the possible intermediacy of an oxazirane (7) (Scheme 11).

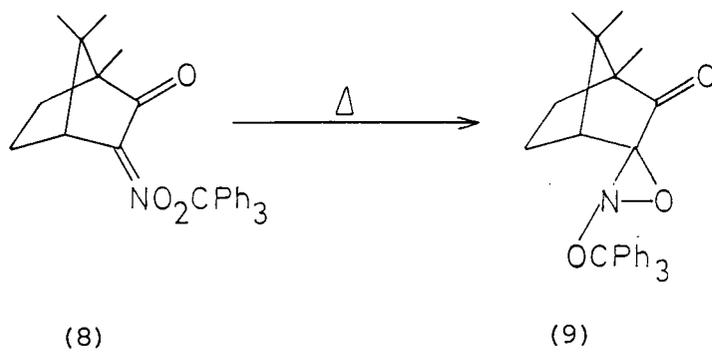


Scheme 11

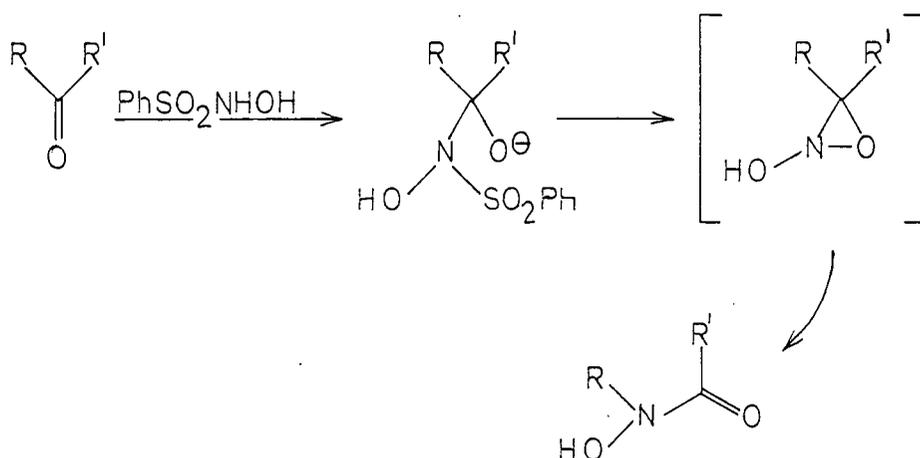
Oxaziranes have been invoked to explain a number of transformations of nitroalkanes. Although some of these mechanisms have subsequently proved to be erroneous¹³, significant effort has been devoted to the detection of oxaziranes as intermediates. An oxazirane was believed to be involved in the overall alkylation-Nef transformation of 4-nitropyridine¹⁴ (Scheme 12), although no direct evidence was presented. More convincing¹⁵ was the thermal isomerisation of trityl camphor-3-nitronate (8) to the stable oxazirane (9).



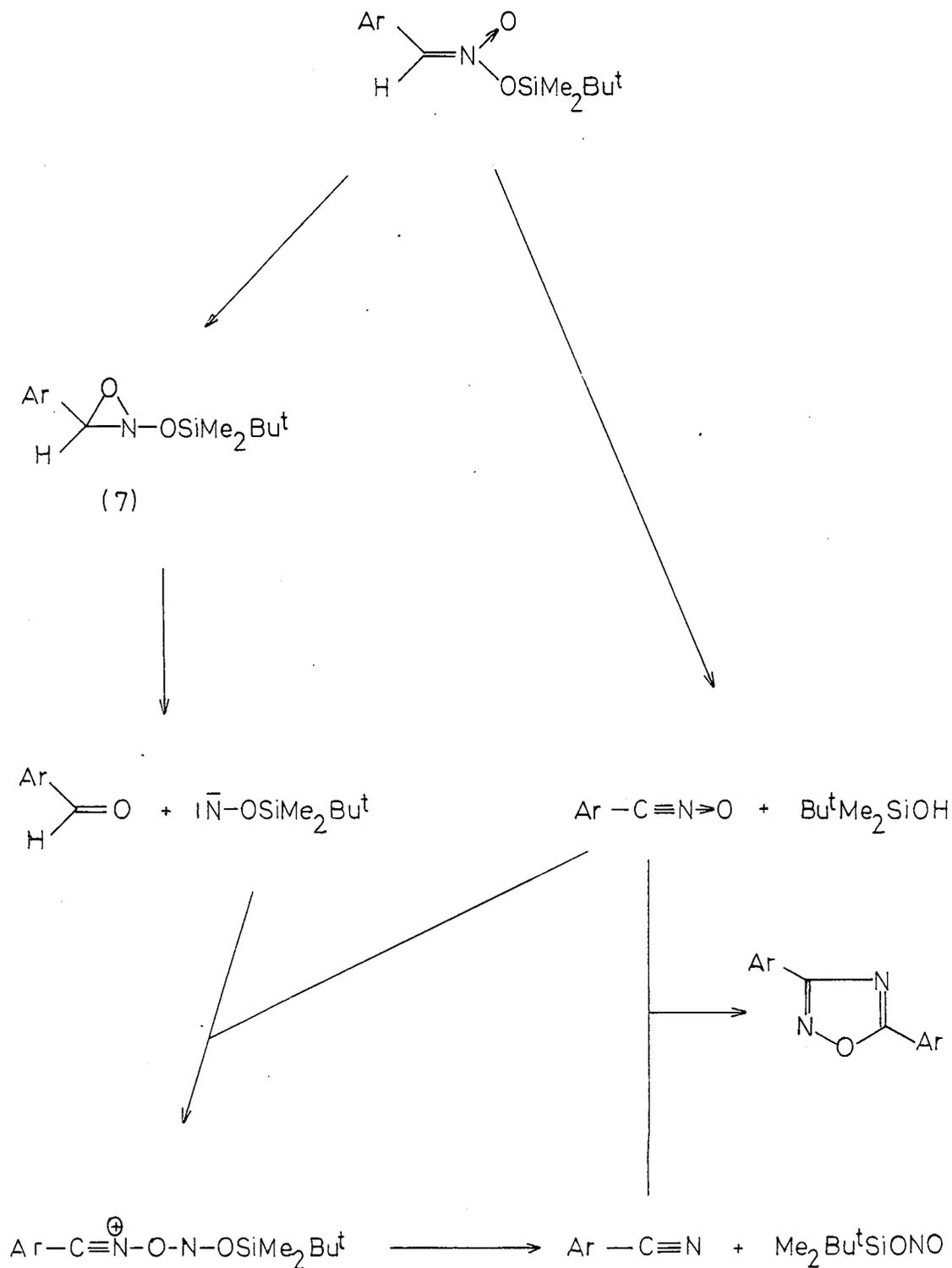
Scheme 12



Similar intermediates have been proposed to account for the photochemistry of nitrones¹⁶, oximes¹⁷, and nitronic acids¹⁸, and the reactions of carbonyl compounds with benzenesulphonyl hydroxamic acid in base¹⁹ (Scheme 13).



Scheme 13



Scheme 14

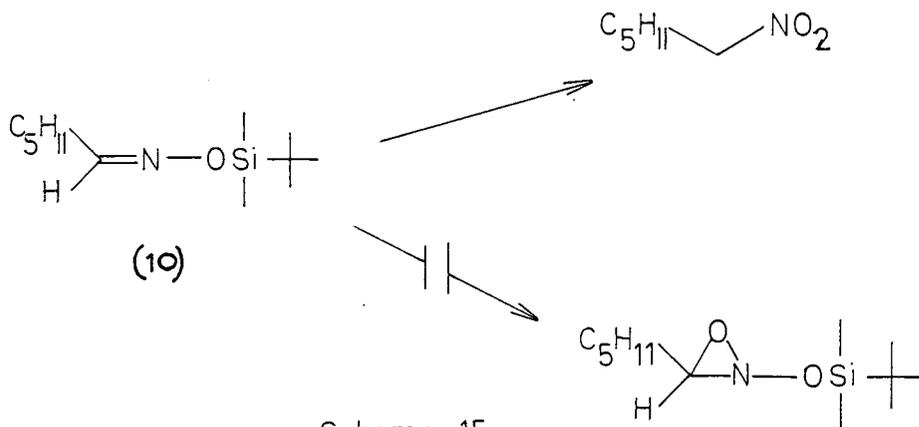
Perhaps more pertinently, oxaziranes have been invoked in the decomposition of nitronic anhydrides²⁰ (page 32) in a transformation analogous to the Victor Meyer reaction. The suggested intermediacy of an oxazirane is, therefore, not

unreasonable. The simultaneous formation of an oxadiazole is, however, somewhat more difficult to envisage. Oxadiazoles can be prepared by 1,3-dipolar cycloaddition of a nitrile oxide with a nitrile. By invoking a branched pathway, as depicted in Scheme 14, the three observed products, aldehyde, oxadiazole and t-butyldimethylsilanol can be accounted for.

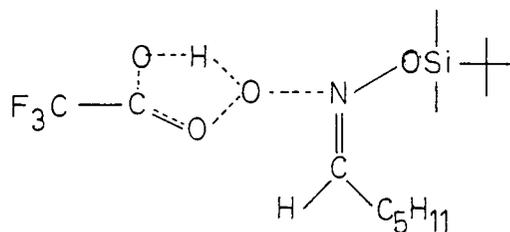
This idea, though sketched on somewhat tenuous lines, seemed worthy of closer inspection, and an attempt was made to synthesise the oxazirane (7).

The oxidation of imines with peroxytrifluoroacetic acid has proven useful for the preparation of oxaziranes²¹.

Unfortunately, and rather discouragingly, treatment of the oxime O-silyl ether (10) with peroxytrifluoroacetic acid (Scheme 15), under a variety of conditions, failed to produce any oxazirane. Furthermore, no trace of aldehyde was observed, the sole product from the reaction being the nitro compound.



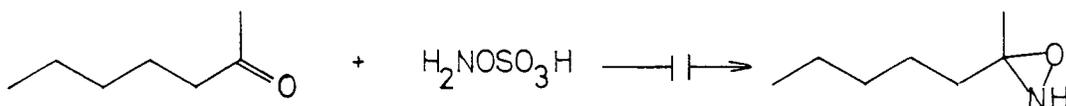
Scheme 15



(11)

On the assumption that the per-acid reacts through a cyclic hydrogen bonded form, a possible transition state for this oxidation could be (11). Thus, the immediate product from the reaction is probably the silyl nitronate, which undergoes hydrolysis.

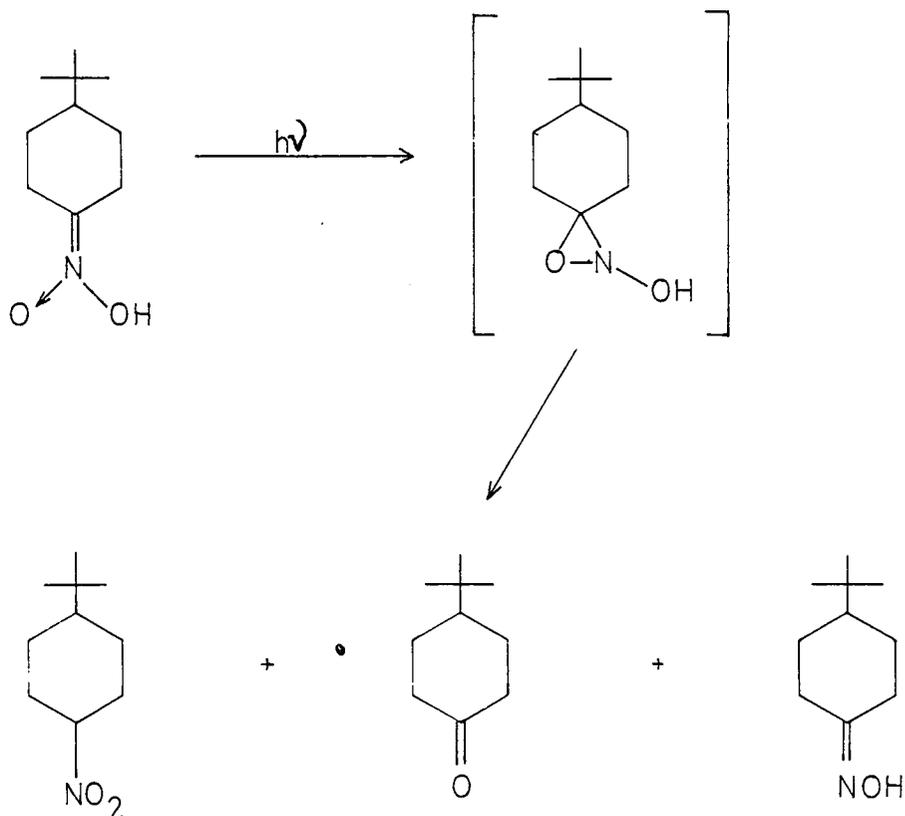
Further attempts to generate oxaziranes were also unsuccessful. Modest yields of oxaziranes have been obtained from a limited number of ketones²² by treating the ketone with hydroxylamine O-sulphonic acid. However, attempted generation of the oxazirane derived from heptan-2-one by this method failed, yielding only unreacted ketone and approximately 10% of the corresponding oxime (Scheme 16).



Scheme 16

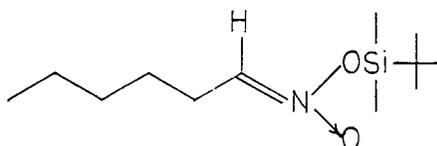
As previously discussed (page 57), Ioffe has shown⁴ that analogy can be drawn between nitrones and silyl nitronates in 1,3-dipolar cycloaddition reactions. The photolysis of nitrones can produce oxaziranes¹⁶. If the ground state analogy can be extended to the excited state, then irradiation of a silyl nitronate may yield an N-oxygenated oxazirane or a derived break-down product. Indeed, a much closer analogy is available: the irradiation of nitronic acids gives products presumed¹⁸ to arise from the

decomposition of an intermediate N-hydroxy oxazirane
(Scheme 17).



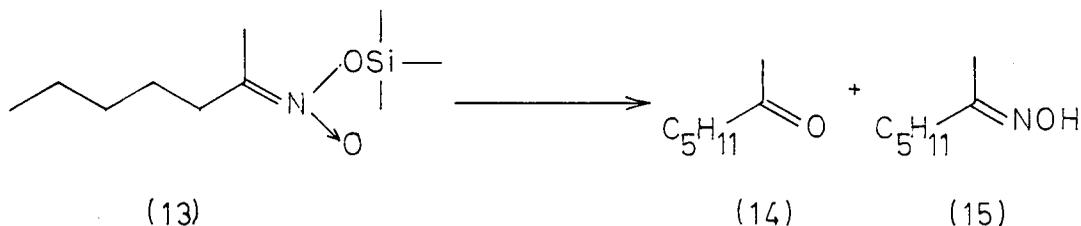
Scheme 17

However, irradiation of a 0.25% solution of (12) in degassed anhydrous benzene, using a 125-w medium pressure mercury lamp and under an inert atmosphere, produced only 1-nitrohexane as a discrete product. In spite of variations in parameters, no convincing evidence for an intermediate oxazirane was forthcoming.



(12)

As will be discussed later, reaction of the methyl lithium: lithium bromide complex with the trimethylsilyl ester (13) of 2-aci-nitroheptane resulted in a rapid decomposition of the silyl nitronate. This decomposition was attributed to the presence of LiBr. Indeed, stirring the nitronate (13) with LiBr in THF produced the ketone (14), and oxime (15) in a matter of minutes at -78°C (Scheme 18).



Scheme 18

^1H n.m.r. spectral analysis of the crude product indicated that (14) and (15) were formed in equal amounts, and heptan-2-one was isolated in 40% yield. Lithium bromide was found to be the most effective catalyst, with tetrabutylammonium bromide being ineffective and lithium perchlorate proving only moderately effective.

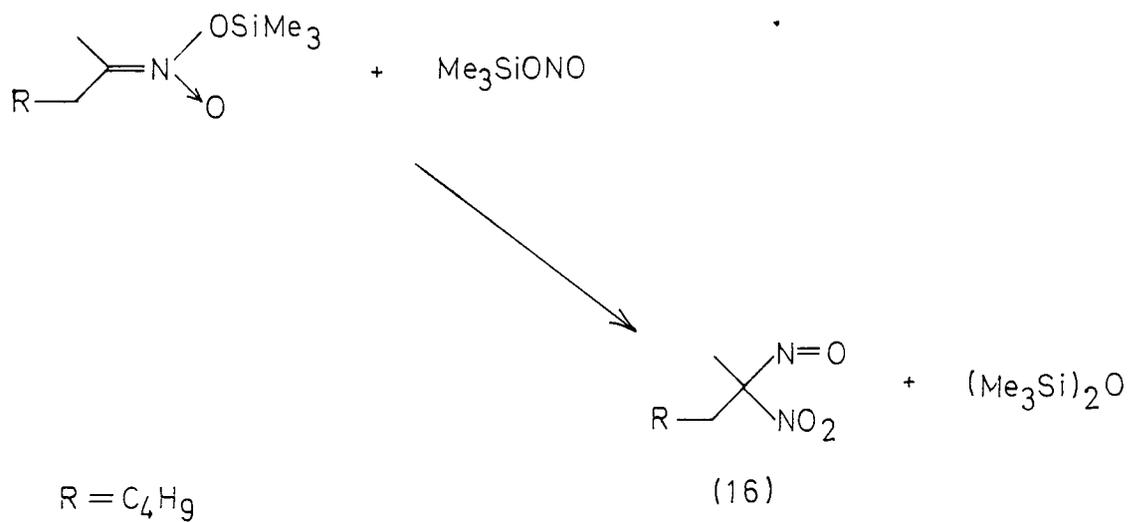
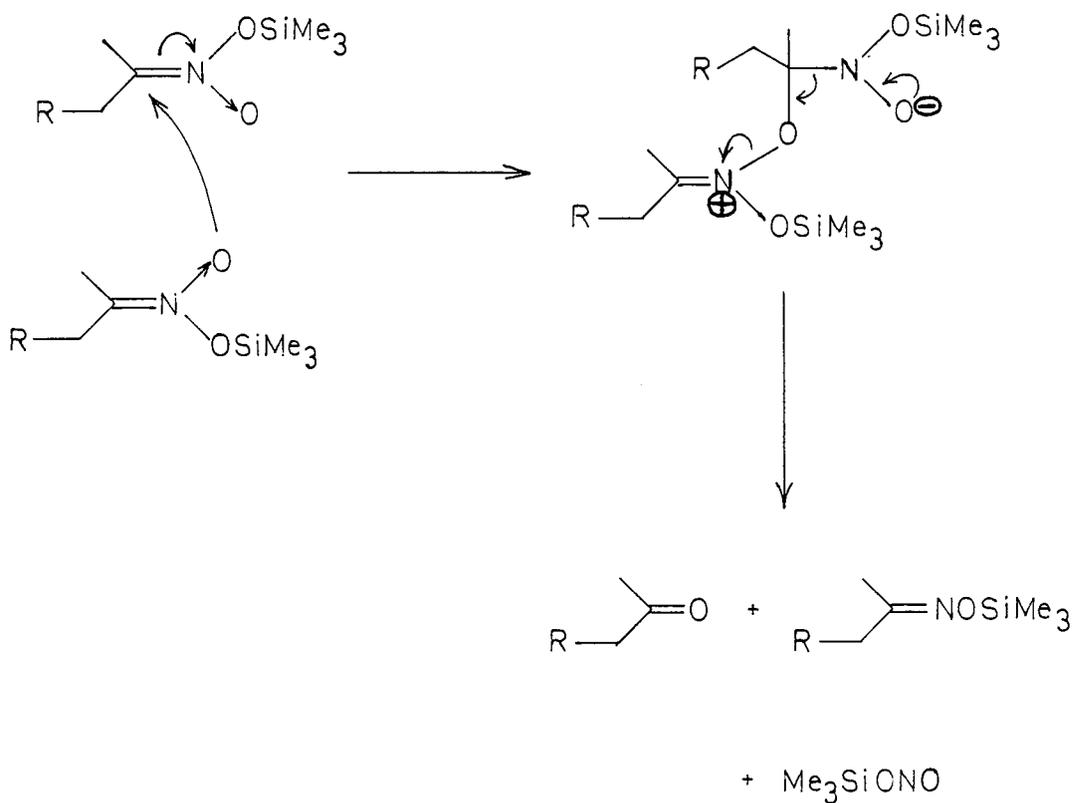
This decomposition could not be extended under similar conditions to silyl nitronates derived from 1-nitrohexane. Secondary silyl nitronates are, however, inherently less stable than their primary counterparts; indeed, the above decomposition can be achieved, albeit more slowly, in THF without added catalyst. Since the reaction is carried out

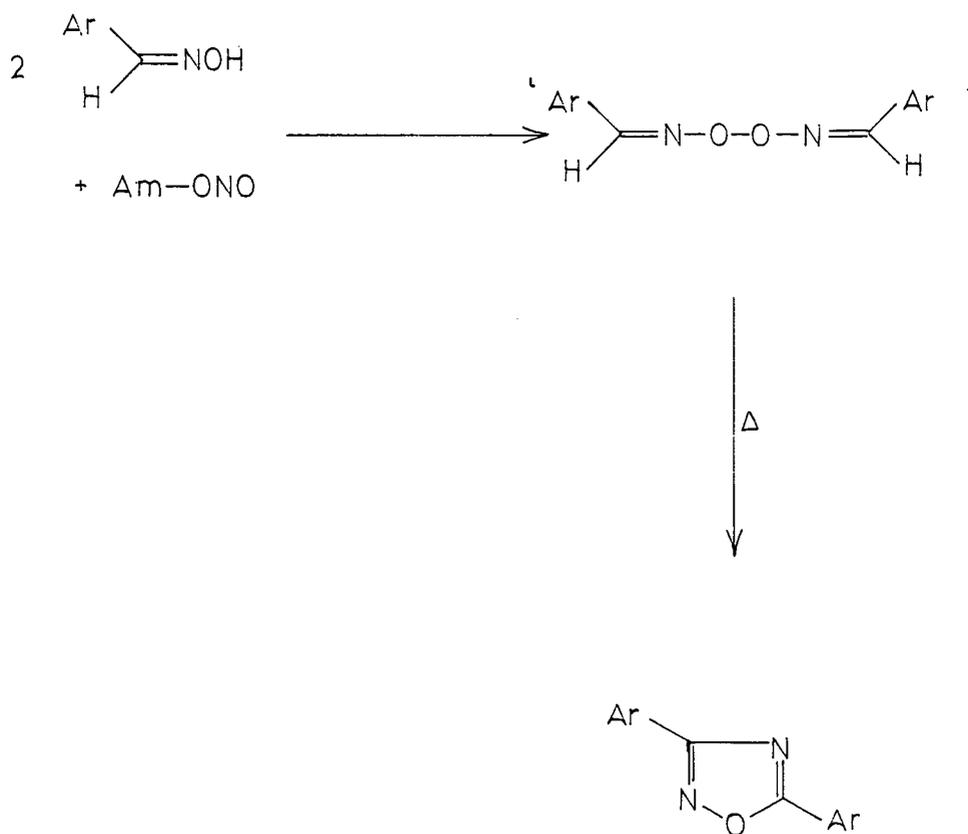
Consequently, the following rationalisation (Scheme 20) is favoured to explain the self-reduction of secondary silyl nitronates. The observation that the reaction mixture develops a green colour suggested the presence of tertiary nitroso compounds. Pseudonitroles such as (16) are known to be formed from secondary nitronic acids in the presence of nitrous acid²⁵. This mechanistic explanation can only be suggestive as no definitive evidence is available.

It should be noted, at this point, that the O-trimethylsilyl oxime of heptan-2-one is very sensitive to hydrolysis, explaining the isolation of the free oxime. By employing a careful, non-aqueous work up, the oxime O-silyl ethers can be obtained.

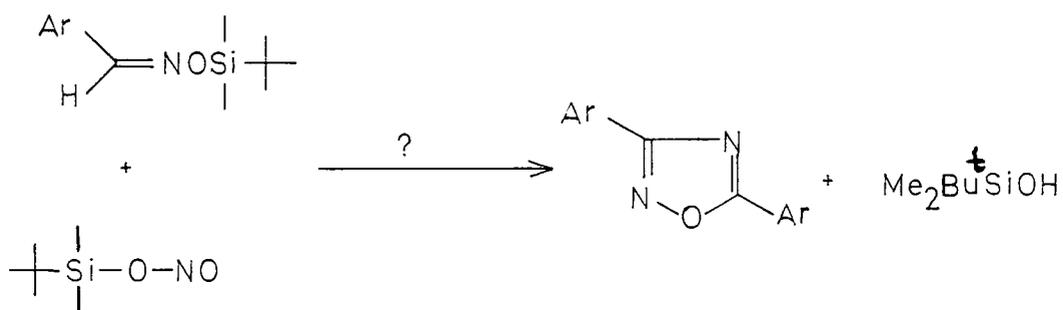
Re-appraising the decomposition of primary silyl nitronates in CCl_4 , it may be recalled that no oxime was detected in the product. It is interesting to note, however, that 1,2,4-oxadiazoles are formed from the reaction of an alkyl nitrite with an araldoxime²⁶, via an intermediate 'araldoxime peroxide' (Scheme 21). Heating the 'aldoxime peroxide' in an inert solvent produces the oxadiazole by an unknown mechanism.

Inspection of the pathway depicted in Scheme 20 reveals an oxime O-silyl ether and a silyl nitrite as two proposed products. By analogy with Scheme 21, Scheme 22 can therefore be conceived; no definitive proof exists, as yet, to substantiate the feasibility of this transformation.



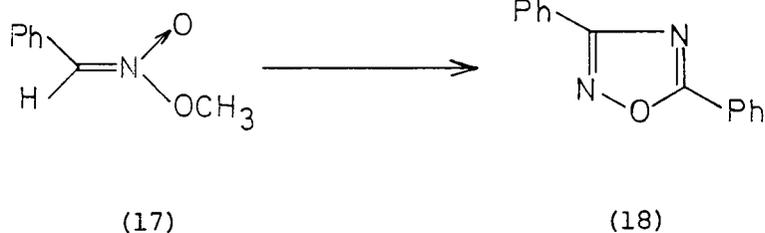


Scheme 21



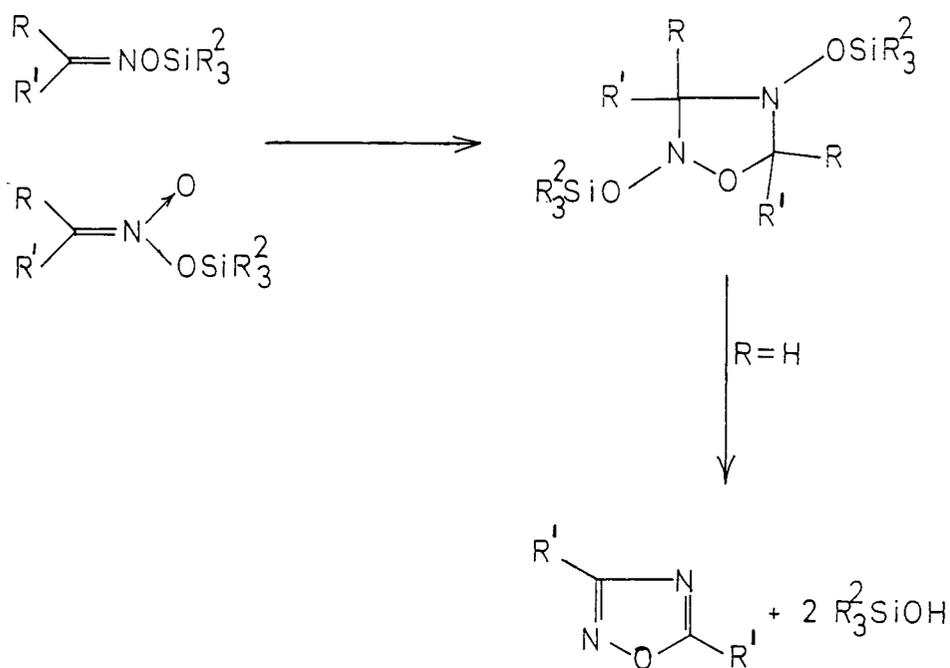
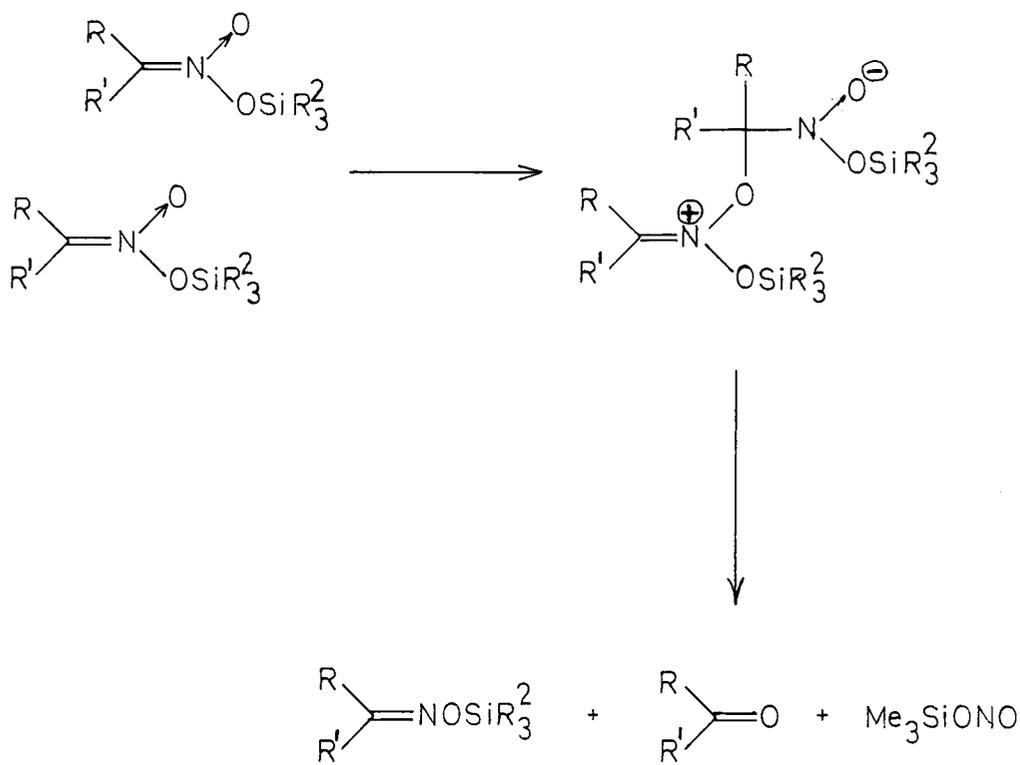
Scheme 22

Perhaps a more plausible explanation for the oxadiazole formation comes from studies on the methyl ester of aci-phenylnitromethane (17). If nitronate (17) is allowed to stand at room temperature, the oxadiazole (18) is ultimately formed²⁸ (Scheme 23).



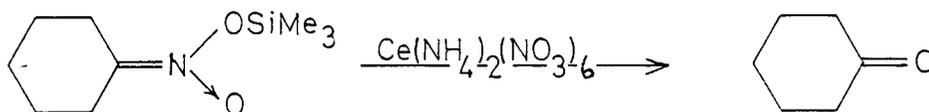
Scheme 23

The oxadiazole (18) is presumed to arise by a 1,3-dipolar cycloaddition with benzaldoxime - a decomposition product of nitronate (17). This ability of nitronic esters to act as 1,3-dipoles is well documented; they react readily with oximes as well as olefinic double bonds²⁸. A perusal of these facts, recalling the 1,3-dipolar character of silyl nitronates, suggests that the oxadiazole, isolated in the decomposition of the silyl ester of aci-p-nitrophenylnitromethane, may arise from addition of the initially formed oxime and excess silyl nitronate. Accordingly, the LiBr promoted decomposition of secondary silyl nitronates and the CCl₄ promoted decomposition of primary silyl nitronates may have a common rationale. This is shown in complete summary in Scheme 24.



Scheme 24

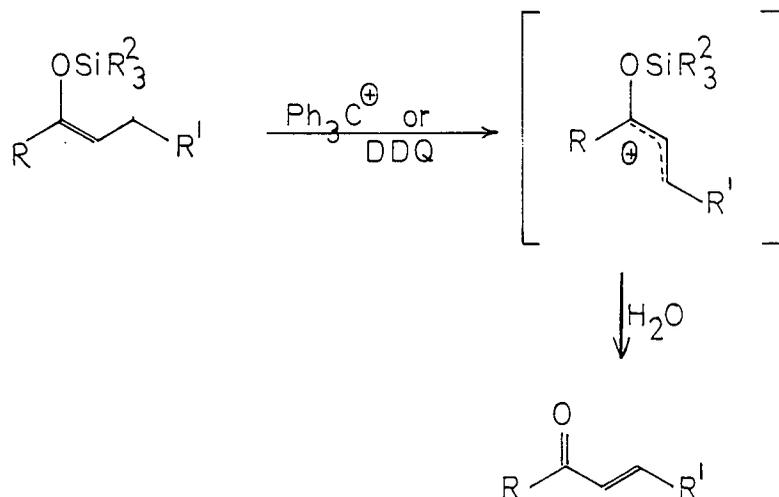
If, as the available evidence suggests, this bimolecular mechanism of breakdown is correct, then the Nef reaction of silyl nitronates, though chemically interesting, can not be considered synthetically useful. It should be mentioned that in one system at least, these problems can be overcome²⁹, although under severe oxidising conditions. When cyclohexyl trimethylsilyl nitronate is heated with ceric ammonium nitrate, cyclohexanone is formed in greater than 90% yield (Scheme 25). The scope and generality of this reaction await definition.



Scheme 25

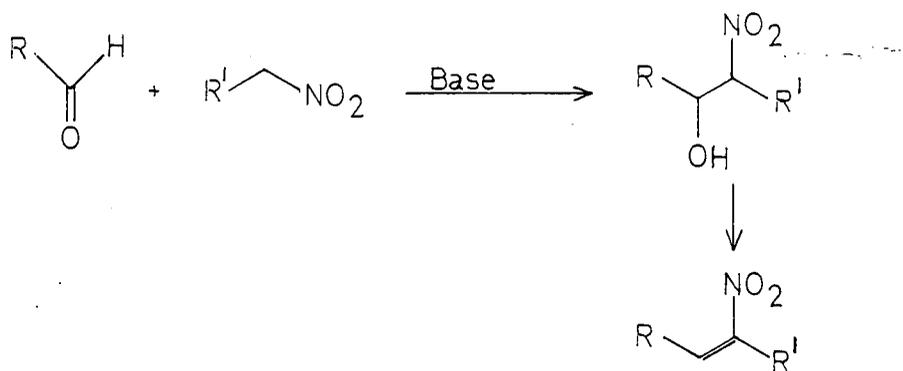
Approaches to Nitroalkenes

In pursuit of some analogy between silyl nitronates and silyl enol ethers, attention was turned to the possibility of a hydride acceptor removing the β -hydrogen atom from a silyl nitronate. This procedure has proven effective in the oxidation of trialkylsilyl enol ethers, with trityl tetrafluoroborate³⁰ or with 2,3-dichloro-5,6-dicyanoquinone (DDQ)³¹ (Scheme 26), giving good yields of enones.



Scheme 26

If a parallel can be drawn, then this procedure could allow facile entry into α,β -unsaturated nitrocompounds, and thence, a range of unsaturated systems. α,β -Unsaturated nitroalkanes can be generated by dehydration of the product from the Henry reaction (Scheme 27).

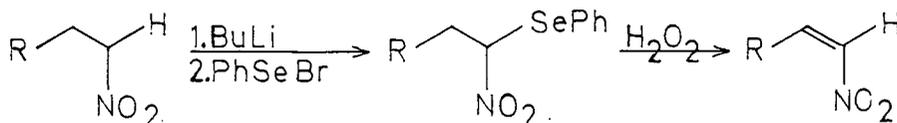


Scheme 27

This method of synthesis has considerable limitations. The dehydration step is normally carried out by first acetylating the hydroxyl group and then effecting elimination with sodium

acetate³². Yields obtained by this method are often low and variable, perhaps because of the rather severe reaction conditions. Improved methods have been devised, the most versatile being mesylation of the hydroxyl group followed by elimination with triethylamine³³.

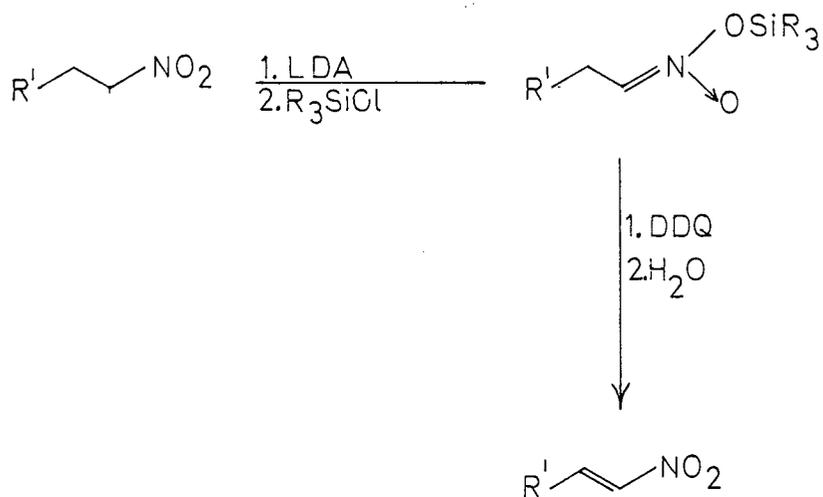
Recently, an oxidation procedure has been described^{33a} for the conversion of nitroalkanes into the corresponding nitroalkenes (Scheme 27a). α -Selenylation followed by selenoxide elimination affords the nitroalkene both efficiently and regioselectively.



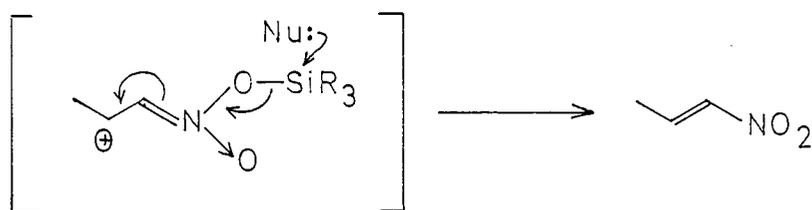
Scheme 27a

It was felt that β -hydride abstraction from a silyl nitronate could give a preparatively useful entry to these compounds (Scheme 28).

Hydride abstraction could be accompanied by loss of the trialkylsilyl group by exposure of an intermediate, such as cation (19), to a nucleophile, thus generating the free nitroalkene directly.



Scheme 28



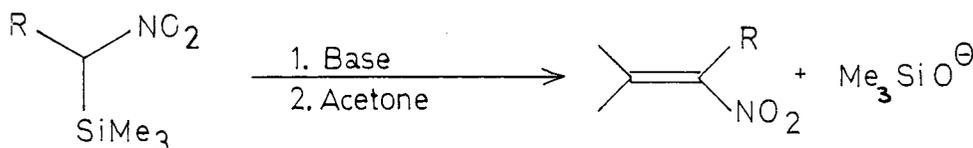
(19)

All attempts at effecting this transformation with trityl tetrafluoroborate or DDQ were accompanied by a marked lack of success on the 1-nitrohexane system. The inclusion of collidine, tetrabutylammonium fluoride, or hexamethyldisilazane³¹ in the reaction was unhelpful, and in all cases an intractible oil was produced. While no nitroalkene was

formed, it is interesting to note that no nitroalkane was isolated either, implying gross decomposition. Such lack of promise did not encourage further interest in this series of reactions.

Another potentially attractive route to nitroolefins was explored.

Taking advantage of the ability of silicon to encourage α -carbanion development, it was anticipated that an α -silylnitroalkane, on treatment with base, may react through carbon with electrophilic reagents. Reaction with aldehydes or ketones should result in thermodynamically favourable loss of trimethylsilanoxide ion³⁴ affording a nitroolefin as outlined in Scheme 29. Aside from the obvious utility of this proposed olefination, the chemistry of the hitherto unknown α -silylnitroalkanes could be investigated.



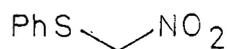
Scheme 29

Many attempts were made to prepare these species, but the problems associated with their synthesis ultimately proved insurmountable. In projecting routes to (20) it was

envisaged that some parallels could be drawn from the chemistry of nitro(phenylthio)methane (21).

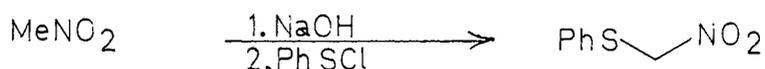
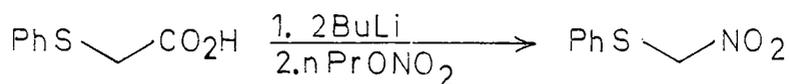


(20)

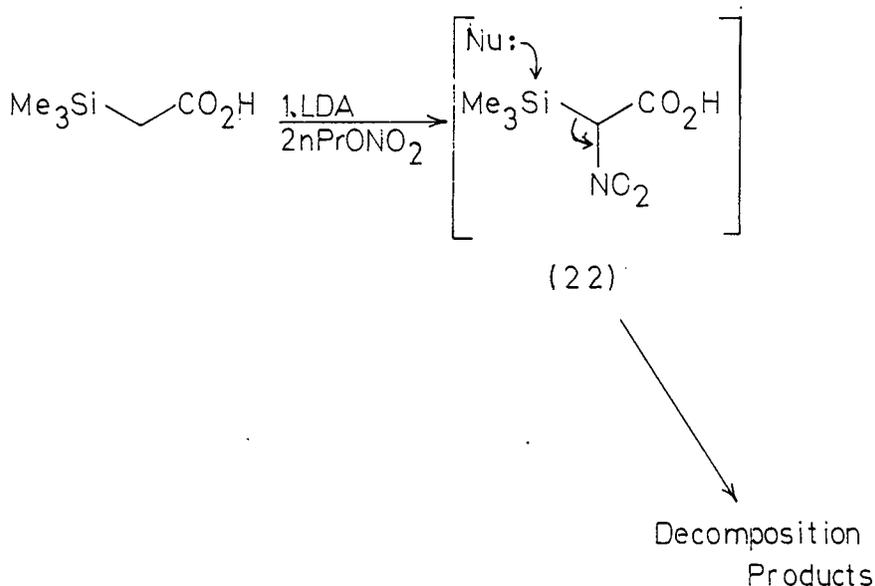


(21)

Two methods^{35,36} for the preparation of (21) exist and are outlined below. It is immediately apparent that only the first method can be considered, as the second, from past experience, would lead to exclusive O-silylation of nitromethane.

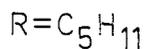
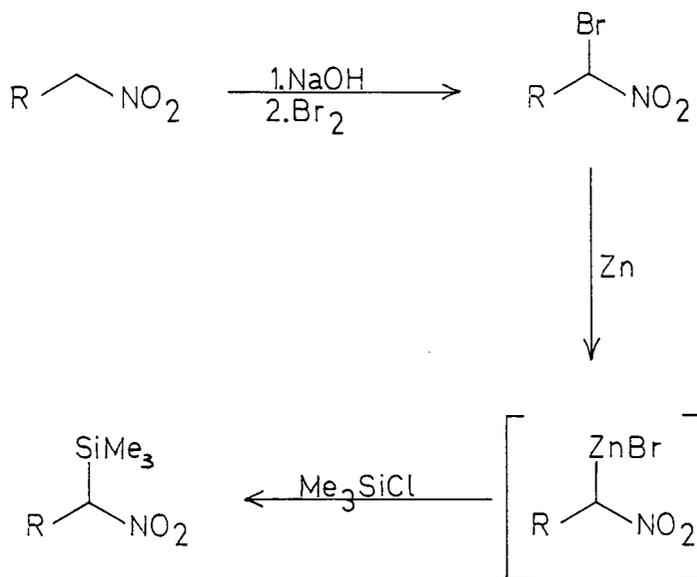


Thus, the dianion of trimethylsilylacetic acid was prepared³⁷ and treated with various electrophilic nitrating reagents - methyl nitrate, propyl nitrate, isopropyl nitrate and tetranitromethane - but without success. In hindsight, a problem may be the possible decomposition of the presumed intermediate (22) in the presence of nucleophiles (Scheme 30).



Scheme 30

The carboxylate dianion derived from the trimethylsilylacetic acid is an obvious source of trouble, and, in an attempt to alleviate the problem, ethyl trimethylsilylacetate was prepared. However, nitration of this species was equally unsuccessful. Further attempts, outlined in Scheme 31, proved fruitless, providing a plethora of products.

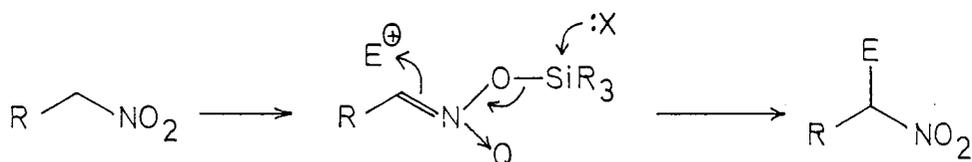


Scheme 31

Attempted electrophilic alkylation of a silyl nitronate

The ambident nature of the nitronate anion has been discussed at some length (pages 20 - 35), most electrophilic agents attacking nitronate anions at oxygen. This situation has been greatly altered with the generation of nitroalkane dianions³⁸ (page 28) which afford C-alkylated products. Further improvement would be desirable because of some practical difficulties in generating the dianions and also to increase the utility of the reaction. By seeking analogy from silyl enol ether chemistry it may be possible

to C-alkylate silyl nitronates. Hydroxyalkylation using aldehydes as electrophiles has been demonstrated in an improvement to the Henry reaction³⁹ (page 22). In a parallel manner, C- alkylation might be encouraged to occur as shown in Scheme 32.



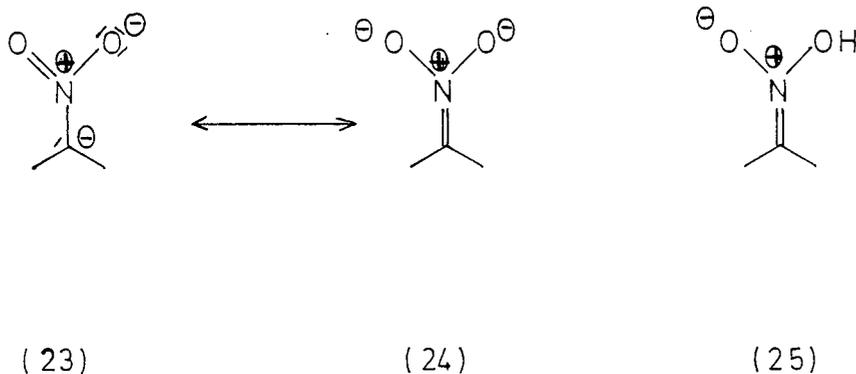
Scheme 32

Alkylation of t-butyldimethylsilyl phenylmethanenitronate was attempted with allyl bromide and with iodomethane, using catalytic quantities of tetra-butylammonium fluoride. A diverse range of reaction conditions and reagents failed to produce the desired reaction. O-Alkylation was observed with iodomethane, whereas use of allyl bromide simply regenerated the starting nitroalkane.

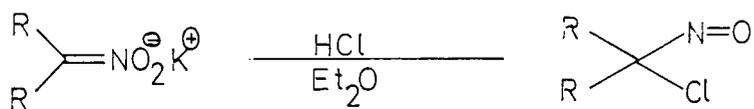
Further attempts at C-alkylation using Lewis acid catalysis⁴⁰, e.g. $ZnBr_2$, furnished the free nitroalkane as the sole product. One is forced to conclude that the nucleophilicity of the α -carbon is not enhanced in silyl nitronates beyond that already available from simple nitronate anions.

Formal Nucleophilic Alkylation of Primary Silyl Nitronates

Nitroalkanes, as the corresponding nitronate anions, are generally considered to be carbon (23) or oxygen (24) nucleophiles and have been used to good effect in this context. However, in their nitronic acid tautomeric forms (25), nitroalkanes can also be considered to be potentially electrophilic at carbon.

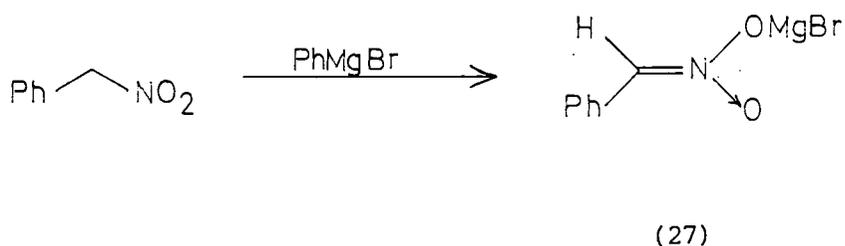
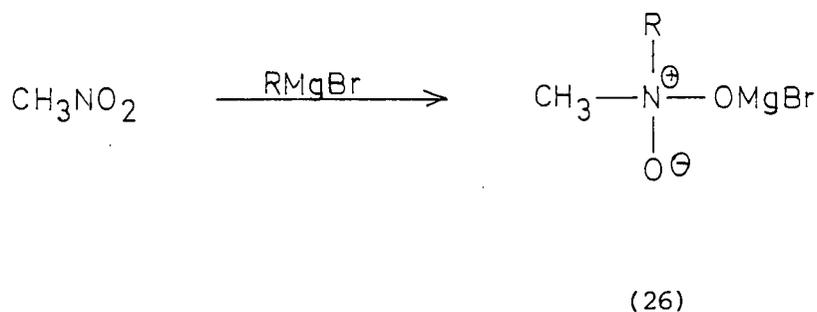


Apart from the Nef reaction, few examples of this type of behaviour are known. α -Chloro nitroso compounds can be obtained by the 1,3-addition of HCl to nitronate anions⁴¹ (Scheme 33).

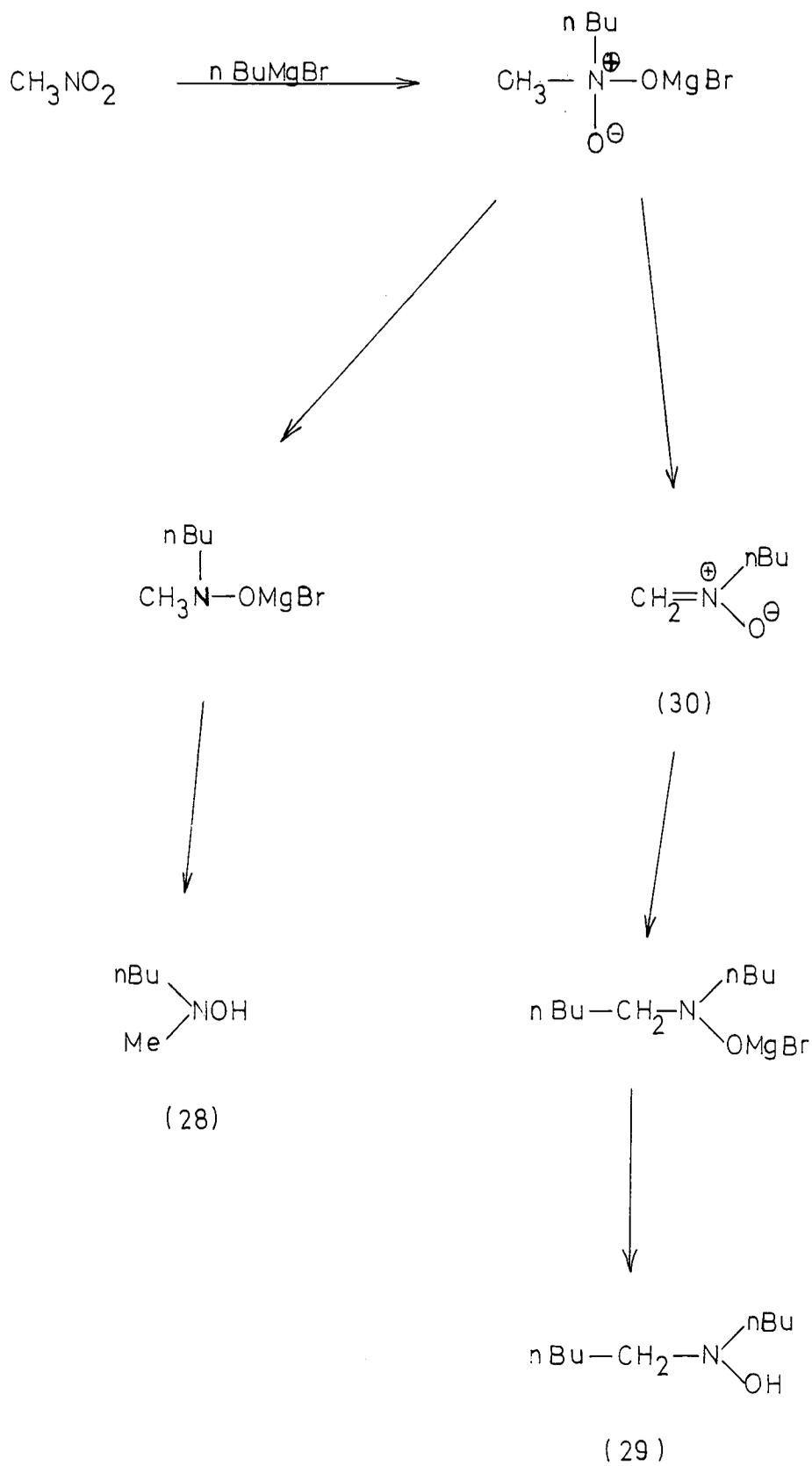


Scheme 33

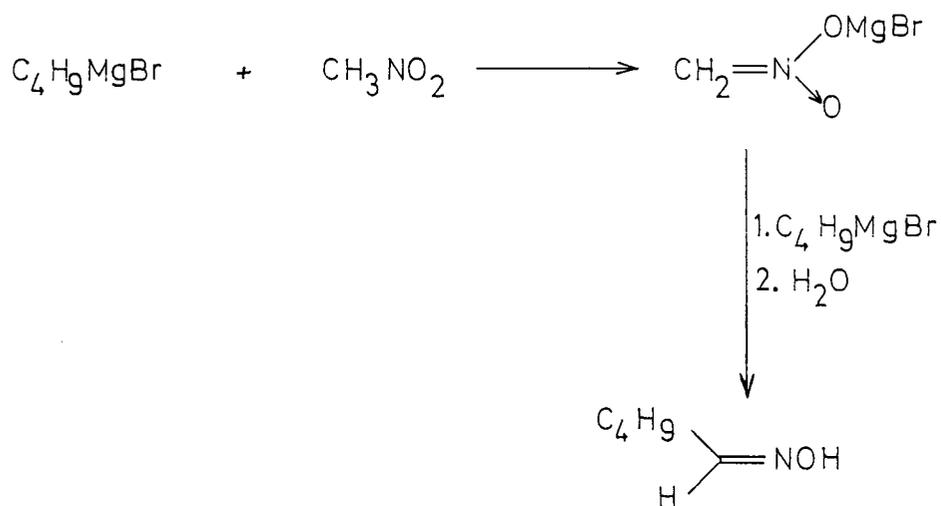
Nitroalkanes react with carbon nucleophiles to give a plethora of products⁴². With a primary nitroalkane⁴³ and a Grignard reagent, the major initial product is probably the adduct (26); some doubt exists as to the mechanistic sequence thereafter⁴⁴. On the other hand, the magnesium nitronate (27) has been proposed as the initial product of the reaction between phenyl-nitromethane and phenylmagnesium bromide⁴⁵.



The main product of addition of n-butylmagnesium bromide to nitromethane are the hydroxylamines (28) and (29). A divergent pathway was proposed⁴⁴ to account for these products (Scheme 34).



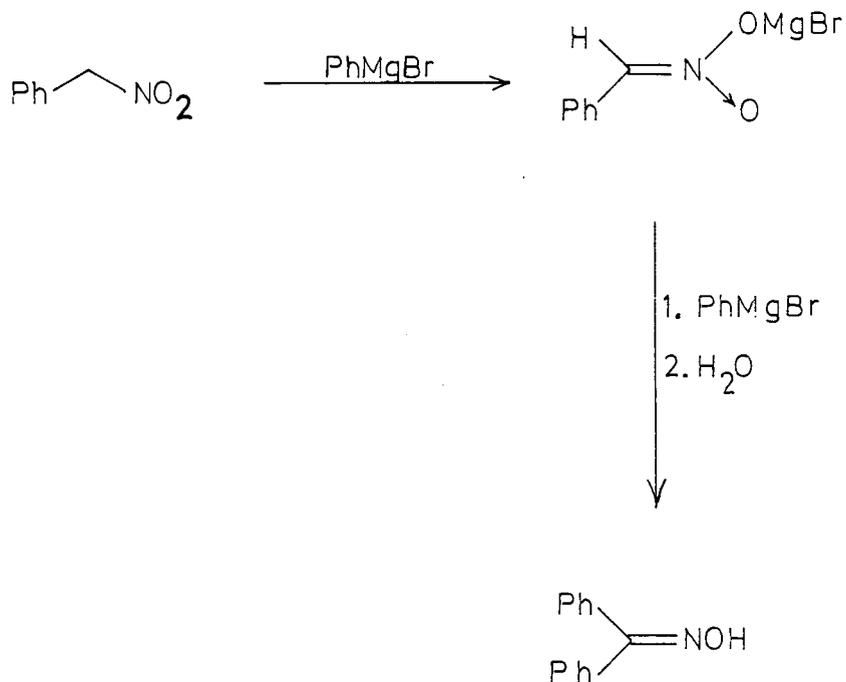
The addition of Grignard reagents to nitrones has ample precedent, and lends encouragement to the possibility of organometallic addition to silyl nitronates. More interestingly, pentanal oxime was isolated as a by-product in 10% yield; this oxime was postulated to have been formed by addition of Grignard reagent to the magnesium salt of nitromethane (Scheme 35).



Scheme 35

Similarly, treatment of phenylnitromethane with two molar equivalents of phenylmagnesium bromide provided a small amount of benzophenone oxime (Scheme 36) amongst other products⁴⁵.

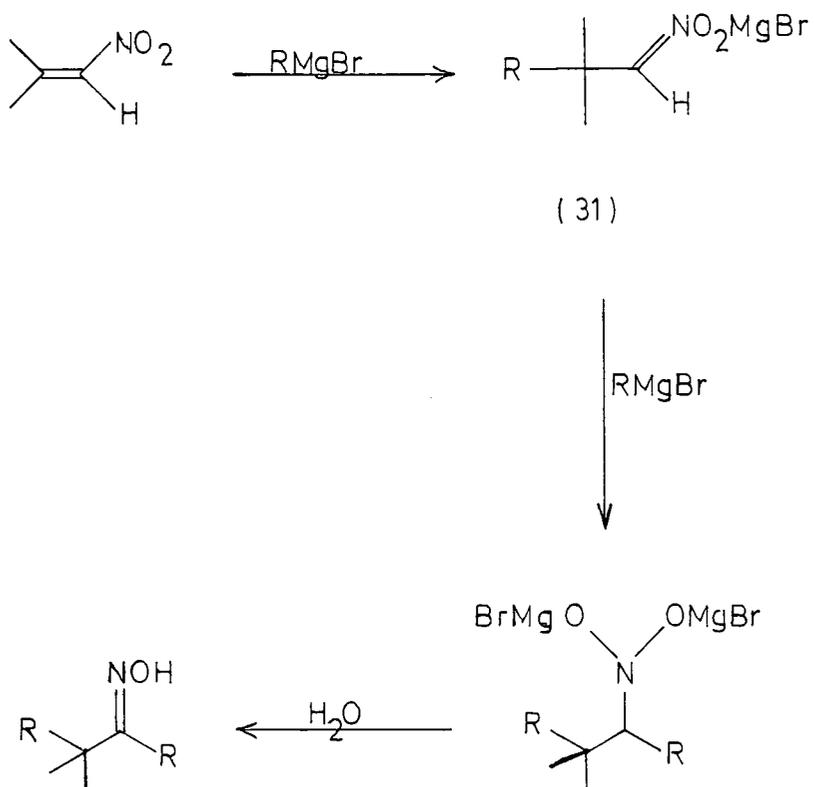
Buckley⁴⁶, on treating α, β -unsaturated nitroalkanes with excess Grignard reagent, observed the addition of two moles of Grignard reagent to produce modest yields of chain



Scheme 36

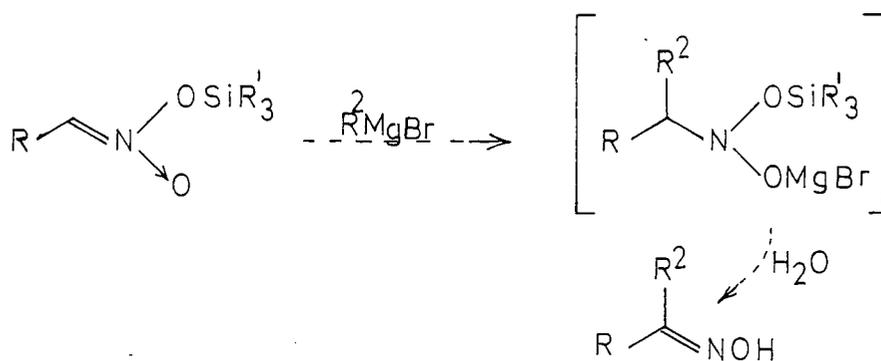
extended oximes (Scheme 37). This result was rationalised by proposing 1,4-addition of one mole of the Grignard reagent to produce the magnesium nitronate (31). Thereafter addition of the Grignard to this nitronate gives the postulated intermediate (32), which, on hydrolysis, would yield the observed oxime.

This situation seemed to be open to improvement; the use of silyl nitronates might enhance the yields and broaden the scope of these reactions. It was hoped that treatment of the silyl nitronates with organometallic reagents would lead to addition at the α -carbon; the final product, once



Scheme 37

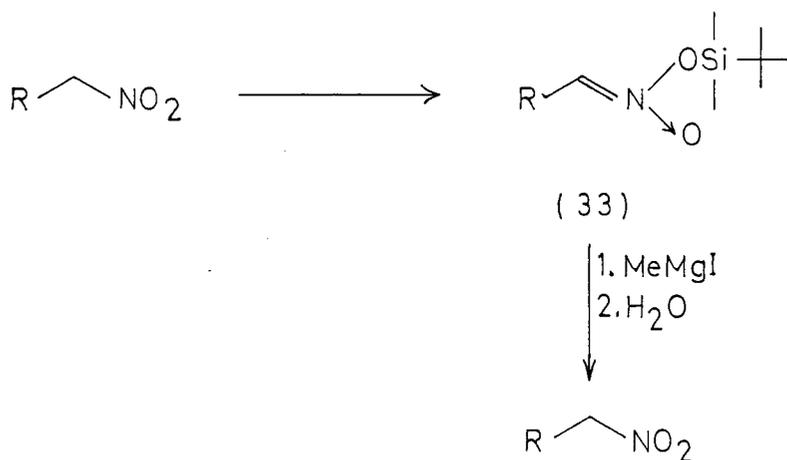
again being the oxime (Scheme 38).



Scheme 38

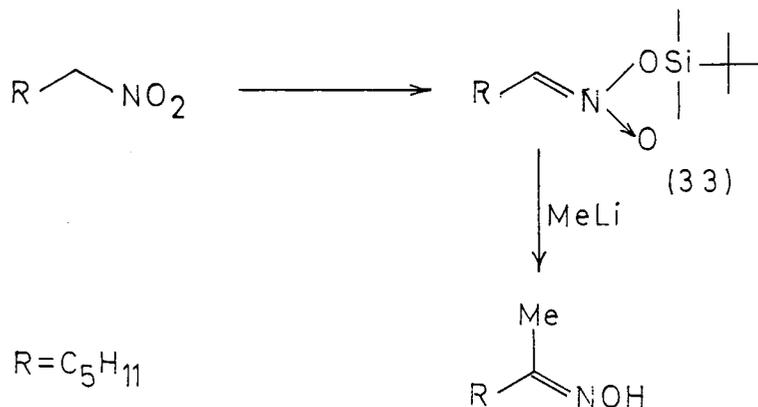
While postulating this sequence of events, one problem becomes immediately apparent on a consideration of silyl enol ether chemistry. It has been shown⁴⁷ that trialkylsilyl enol ethers are transformed into the metal enolates via reaction with organometallic reagents. The metal enolate generation is approximately 3,000 times more rapid with methyl lithium than with methylmagnesium bromide. In order to obviate the possibility of generating the metal nitronate from the silyl nitronate, careful selection of reaction conditions would be required.

The silyl nitronate derived from 1-nitrohexane (33) was treated with 1 equivalent of methylmagnesium iodide at -78°C . As feared, the outcome of the reaction was isolation of 1-nitrohexane (Scheme 39), with C-Si bond fission by the Grignard reagent having occurred.



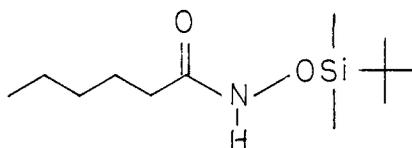
Scheme 39

In spite of this setback, the same reaction was attempted with methyl lithium. Remarkably, the product formed was heptan-2-one oxime in good, ca 50%, yield (Scheme 40).

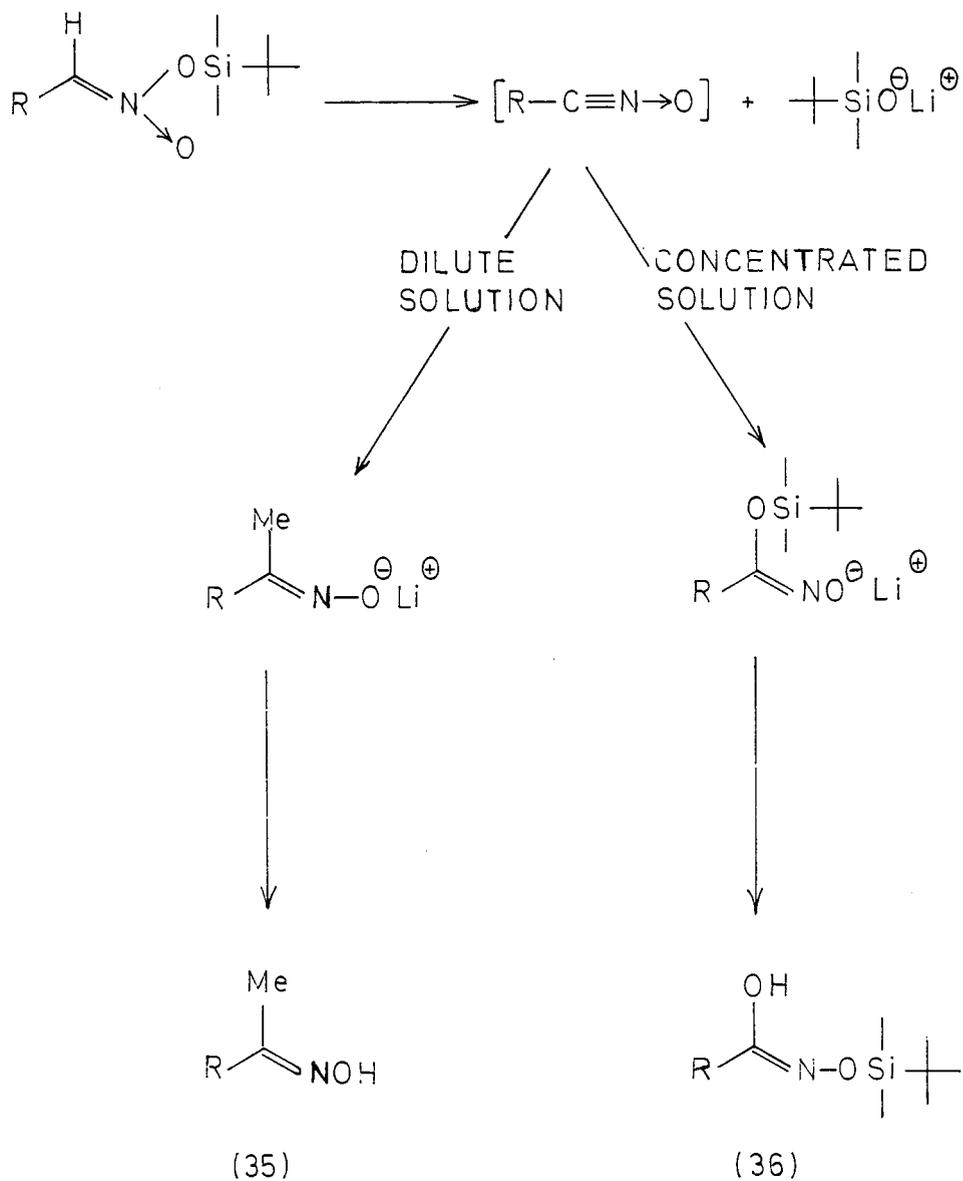


Scheme 40

This result was surprising in light of the exclusive attack at silicon witnessed by methylmagnesium iodide. This, and the fact that two equivalents of methyl lithium are required for complete reaction, suggested that the naive picture presented in Scheme 38 required adjustment. The general experimental procedure utilises 10 ml of THF per mmole of silyl nitronate and addition of methyl lithium at $-78^{\circ}C$. If more concentrated solutions are employed, for example 2 ml of THF per mmole of silyl nitronate, then the silyl ether of a hydroxamic acid (34) is the major product.



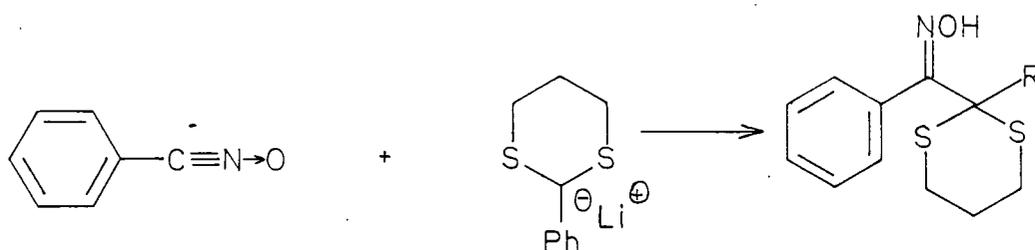
(34)



R=C₅H₁₁

Scheme 41

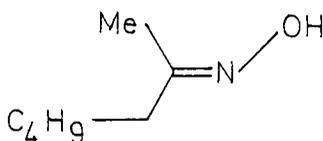
This observation suggests the common intermediacy of a nitrile oxide, which could be formed by elimination of the elements of trialkylsilanol from the silyl nitronate (Scheme 41). Thereafter, addition of either the second equivalent of methyl lithium or trialkylsilanoxide would lead to the observed products (35) and (36). The relatively high acidity of the α -proton of a nitronate anion has been demonstrated by its removal with organolithium reagents in formation of the nitronate dianions³⁸. Nitrile oxides typically thought of as 1,3-dipoles, also react with nucleophiles, including carbanions⁴⁸, to form substituted oximes (Scheme 42).



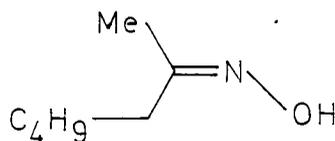
Scheme 42

Further supportive evidence for the intermediacy of a nitrile oxide comes from an analysis of the oxime isomers produced. The normal purification procedure, distillation of the crude reaction product, affords various ratios of the (E) and (Z) oximes (37) and (38) respectively, depending on the distillation temperature. If, however, flash chromatography⁴⁹ is used to effect purification, then only one isomer is isolated, indicating that the kinetic product

of the reaction is a single oxime isomer. Heating this single isomer then produces approximately equal amounts of (E) and (Z) isomers.



(37)

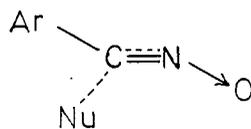


(38)

¹H n.m.r. Spectroscopy was used to determine the ratios, with two signals being observed for the 'vinylic' methyl of (37) and (38) at δ 1.85 p.p.m. and at δ 1.81 p.p.m.

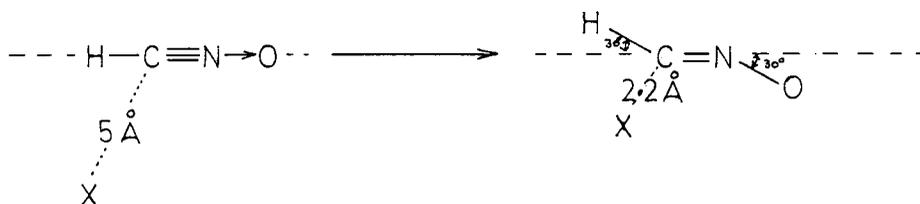
It has been shown^{50,51} that the protons on the α -carbon syn to the oxime hydroxyl resonate at lower field than do those on the α -carbon anti, due to through-space deshielding by the hydroxyl oxygen. By this criterion, the lower field signal at δ 1.85 can be assigned to the (E) isomer (37) and that at δ 1.81 p.p.m. to the (Z) isomer (38) with some confidence. Thus, from ¹H n.m.r. spectral data, the kinetic product from reaction of primary silyl nitronates with methyl lithium is the (E) oxime isomer. The kinetic product of nucleophilic addition⁵² to a nitrile oxide is that oxime isomer with the incoming nucleophile and the

oxygen atom on the same side, giving the transition state (39).



(39)

The interaction of the initially linear nitrile oxide with the nucleophile is sufficient to bend the dipole so that in the product the oxygen is adjacent to the nucleophile. Recent ab initio molecular orbital calculations⁵³ have verified this experimental observation. These calculations show that the formation of one oxime isomer is favoured by the preferential trans bending in the transition state (40). This type of bending is preferred, because of the much higher energy required to bend the nitrile oxide in the opposite sense.

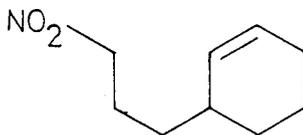


(40)

Formation of the kinetic product, i.e. the (E) isomer (37), from the reaction of methyl lithium and trimethylsilyl

hexylnitronate concurs with the above findings. Thus, the intermediacy of a nitrile oxide may very well account for the dichotomous product formation and also for the stereochemical consequence of the reaction.

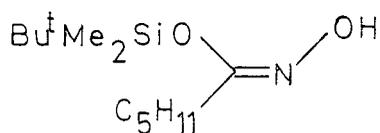
Nitrile oxide intermediates have been proposed⁵⁴ in one mechanism for the Victor Meyer reaction⁵⁵, although some evidence has been amassed²⁰ indicating doubt as to their involvement. Due to the reactivity of silyl nitronates as 1,3-dipoles⁴, attempted trapping of the postulated nitrile oxide intermediate would be of little value, as the ultimate product from nitrile oxide or silyl nitronate addition to an olefin would be identical. It is possible, however, that systems such as the nitroalkene (41) may provide some clue.



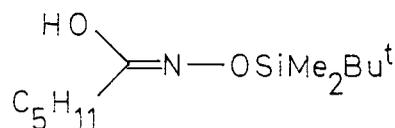
(41)

If the derived silyl nitronate can be prepared without undergoing a 1,3-cycloaddition, then treatment with alkyl lithium would form the postulated nitrile oxide, which, being a more reactive 1,3-dipole, could cyclise^{56a}. A similar approach, using a sulphur analogue of nitroalkene (41), was used in a synthesis of biotin^{56b} where the nitro group was converted into a nitrile oxide, which then cyclised.

If the postulate of an intermediate nitrile oxide is correct the product from reaction in concentrated solution (page 92) of an organolithium reagent and a primary silyl nitronate should be the silylated hydroxamic acid (42). The rationale behind this may lie in the close proximity of the trialkylsilanoxide and the nitrile oxide in concentrated solution. Thus attack of the organo lithium reagent is hindered, while the potential of trialkylsilanoxide addition is enhanced. Comparison (^{13}C n.m.r., ^1H n.m.r., I.R., and mixed melting point) with an independently prepared sample suggests that the isolated product is the isomeric hydroxamate (43), indicating that a 1,4-silyl migration had occurred. This type of migration has considerable precedent⁷.



(42)



(43)

The generality of this novel conversion of nitroalkanes into substituted oximes was investigated with respect to the organolithium reagent. The results are summarised in Table 1. All yields refer to pure distilled oximes and are based on the silyl nitronate. Isolation was achieved by short path distillation, with distillation temperatures referring to the air bath temperature.

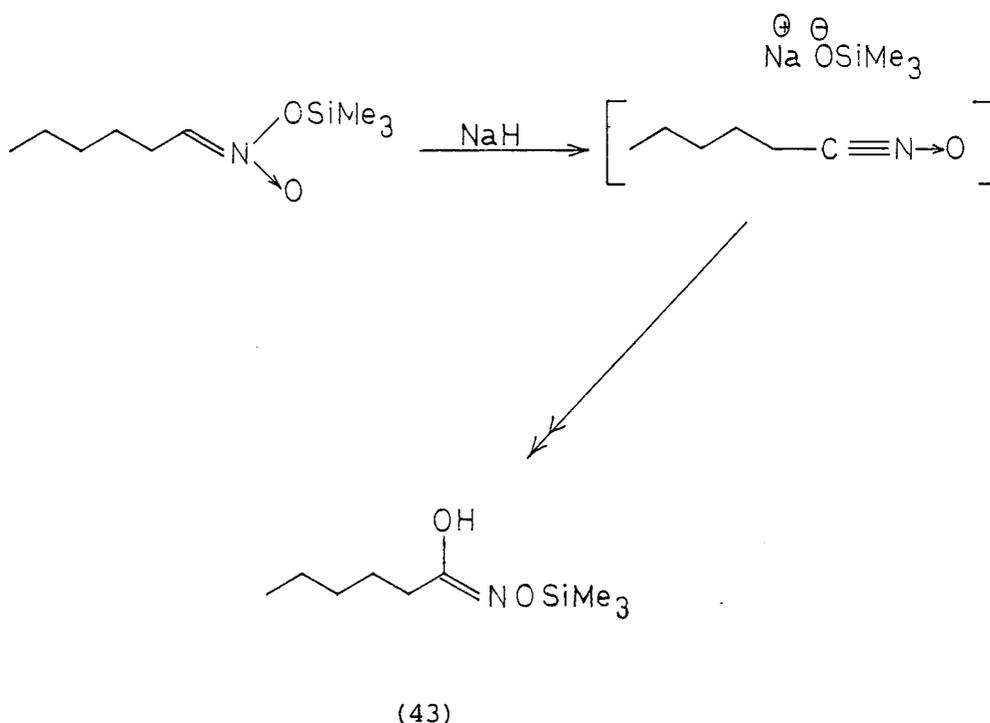
TABLE 1

R-Li	Yield of Oxime	Distillation Temperature
MeLi : LiBr	58%	85-90°C / 0.3 mm Hg
BuLi	51%	105-110°C / 0.7 mm Hg
Bu ^t Li	30%	110°C / 15 mm Hg
PhLi	40%	155-160°C / 0.3 mm Hg

The t-butyl substituted oxime clearly shows the same kinetic preference for one isomer (> 100:1), which isomerises on distillation to a mixture of oxime isomers. The t-butyl group appears as a singlet at δ 1.26 p.p.m. in the chromatographically isolated material. This signal is assigned to the (Z) isomer from literature data⁵⁰, and is as expected on the grounds of the previous argument. The single oxime isomerises to an approximate equal mixture of (Z) and (E) isomers on distillation, the t-butyl group then appearing as two separate signals at δ 1.26 p.p.m. and at δ 1.1 p.p.m for (Z) and (E) oximes isomers respectively.

The n-butyl and phenyl substituted oximes show similar behaviour, but the complexity of their ¹H n.m.r. spectra prevented any direct analysis of the isomeric ratios.

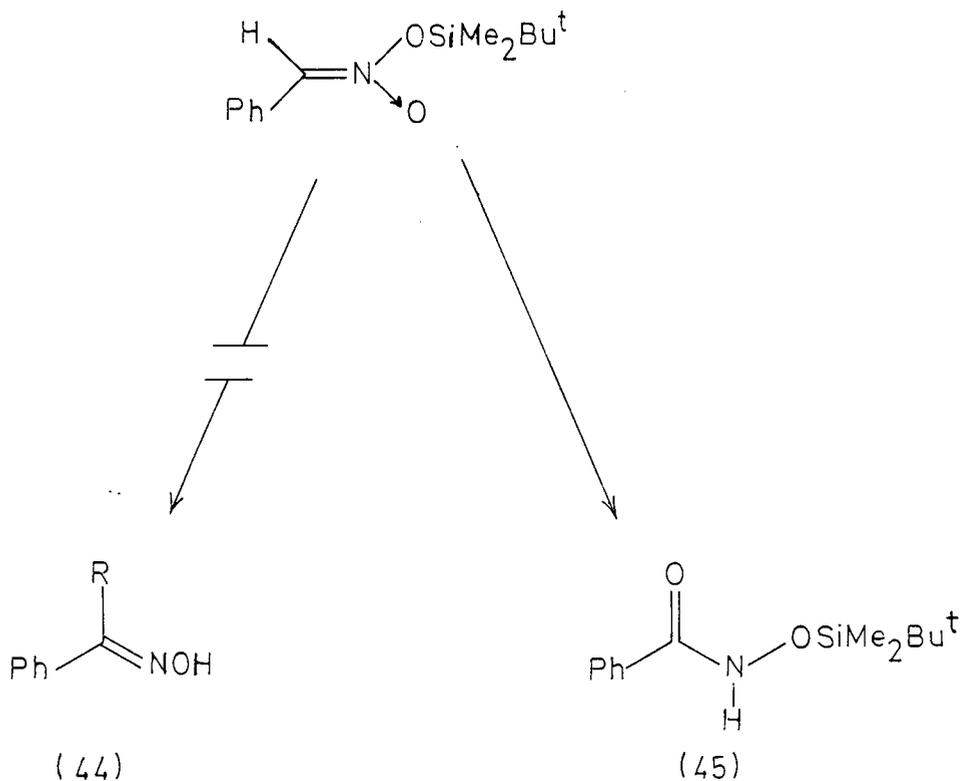
Work is in progress⁵⁷ to enhance the yields of this potentially useful process. An obvious problem is the propensity for nitrile oxides to undergo rapid dimerisation to furoxans. Further evidence is being sought to confirm or negate the postulated nitrile oxide intermediate. It has since been shown^{57a} that sodium hydride is a sufficiently strong base to remove the α -proton from a silyl nitronate, providing silylated hydroxamic acid (43), presumably by way of a nitrile oxide intermediate (Scheme 43).



Scheme 43

A recently reported conversion of primary nitroalkanes into hydroxamic acids^{57b} is suggestive of a similar mechanism.

of benzohydroxamic acid was observed to occur (Scheme 45).



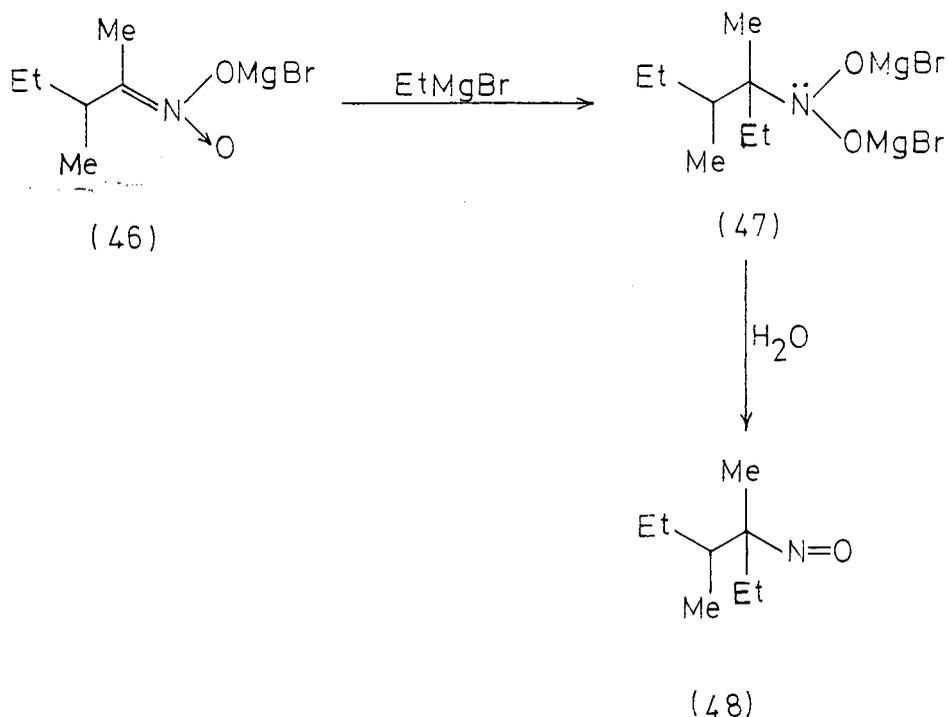
Scheme 45

The hydroxamate (45), isolated as a crystalline solid, m.pt. 139-140°C, was identical in all respects to an independently prepared sample. The failure to undergo alkylation was unexpected, and on previous arguments puzzling considering the implication of a nitrile oxide as intermediate. It would, therefore, seem that benzo-nitrile oxide reacts with trialkylsilanoxide ion in preference to organolithium reagents. Subsequent results showed that the silyl nitronate derived from phenyl-nitromethane to be unique in this series of reactions.

Successful alkylation reactions have now been performed⁵⁷ on a range of primary silyl nitronates demonstrating the potential utility of this new reaction.

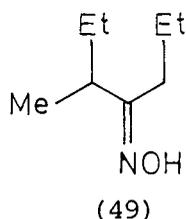
Formal Nucleophilic Alkylation of Secondary Silyl Nitronates

In 1947, while studying the reaction of ethylmagnesium bromide with the in situ generated magnesium nitronate (46), Buckley⁴⁶ isolated a small amount of a colourless oil (Scheme 46). From analytical data this was presumed to be (48), although Buckley states that "it appeared to be an oxime, which may result from a rearrangement of (48) or its complex (47)".



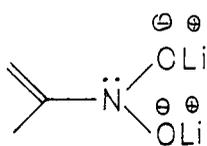
Scheme 46

Evidence is presented below, which suggests the product actually isolated was the oxime (49), arising from a pathway involving deprotonation of nitronate (46), followed by addition of ethylmagnesium bromide.

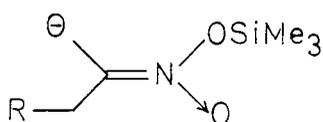


In addition, a new and potentially useful series of reactions is revealed.

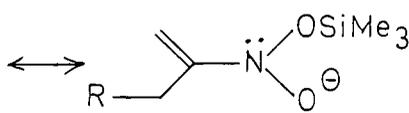
In order to delineate the scope of the reaction of silyl nitronates with organolithium reagents, secondary silyl nitronates were treated with two equivalents of organolithium reagents. In a possible parallel to the double deprotonation of 2-nitropropane¹¹ to give the dianion (50) (page 38), it was anticipated that the alkyl lithium reagent could remove a β -hydrogen to form the β -anion (51). The species actually formed, if a parallel can be drawn, would be the N,N-dioxyenamine (52).



(50)

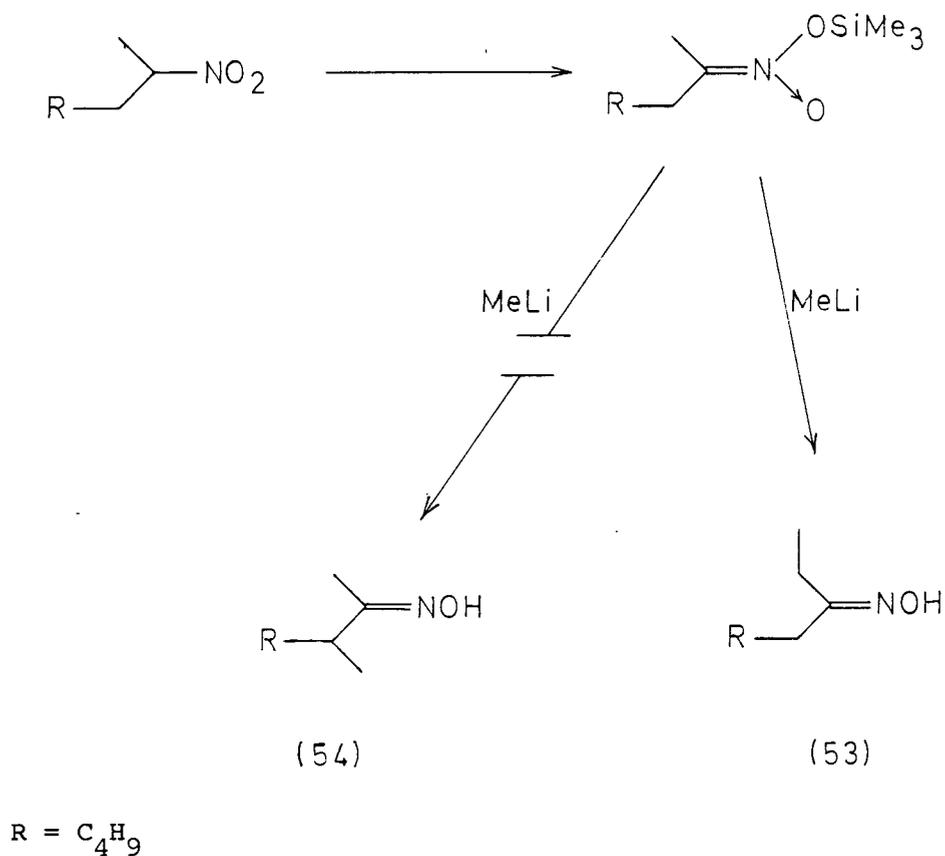


(51)



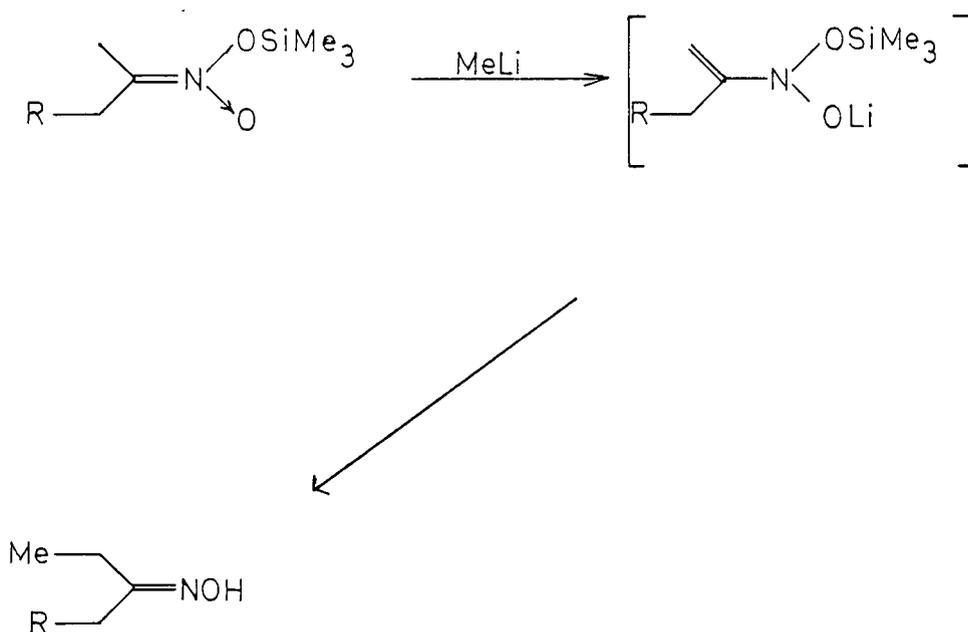
(52)

The dilithio derivative (50) of an N,N-dihydroxyenamine has shown to be highly nucleophilic. Therefore, it was not anticipated that the species (52) would react to any extent with nucleophilic reagents. Despite this uncertainty, treatment of the silyl nitronate derived from 2-nitroheptane with methyl lithium at -78°C afforded the chain extended oxime (53) (Scheme 47). None of the isomeric (54) was observed, suggesting that the first step in the reaction is kinetic deprotonation.



Scheme 47

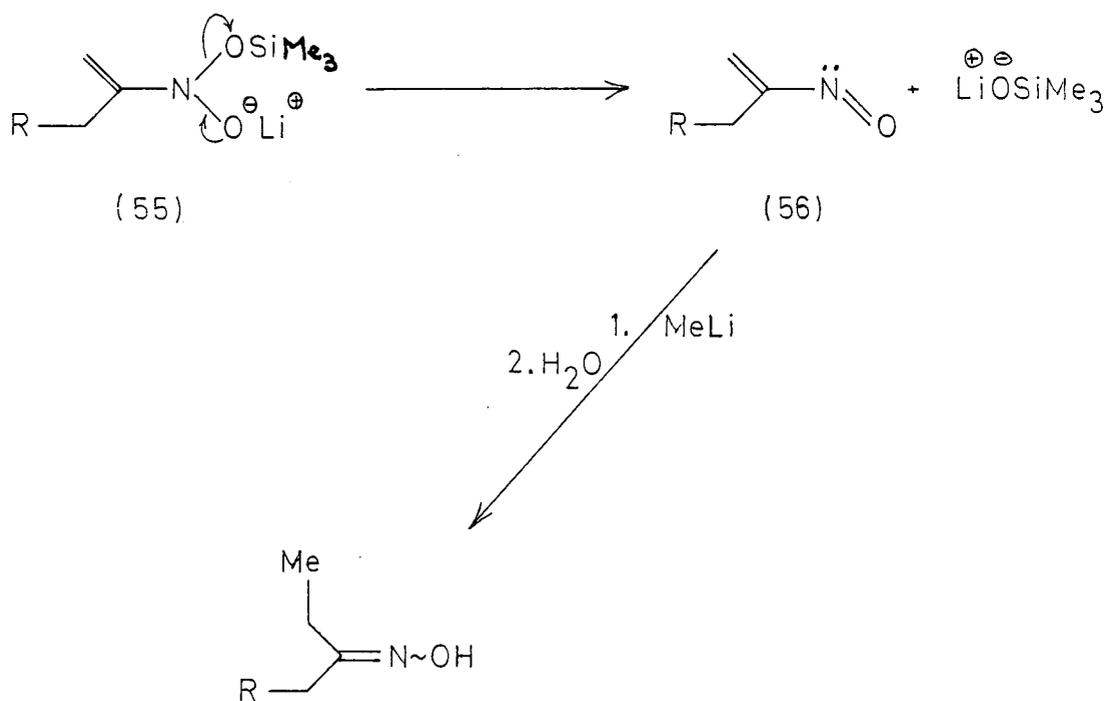
The structures of the oximes (53) were established by accurate mass measurement and ^1H n.m.r. and I.R. spectroscopy. In light of the previously described work on these systems, it would seem unlikely that a pathway such as that depicted in Scheme 48 is operating, considering the nucleophilic character of the species (50).



Scheme 48

Conjugated nitrosoalkenes are well established⁵⁸ as Michael acceptors in reactions with nucleophiles. By elimination of lithium trimethylsilanoxide from enamine (55) (Scheme 49), the nitrosoalkene (56) would result. Subsequent conjugate

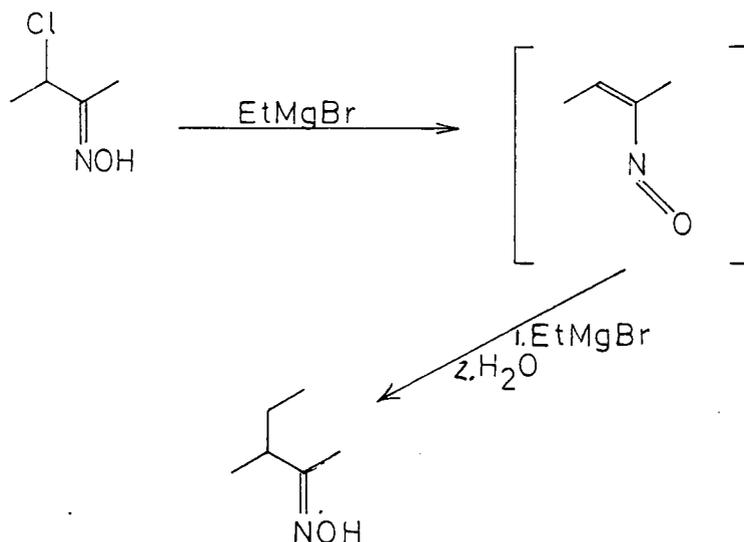
addition would afford the observed oxime after aqueous isolation procedures.



R = C₄H₉

Scheme 49

A similar addition has been observed in the reaction of α -chlorooximes with Grignard reagents⁵⁹. Elimination of the elements of HCl generates the intermediate nitrosoalkene which acts as a Michael acceptor for the second equivalent of Grignard reagent, forming the β -alkylated oxime (Scheme 50).

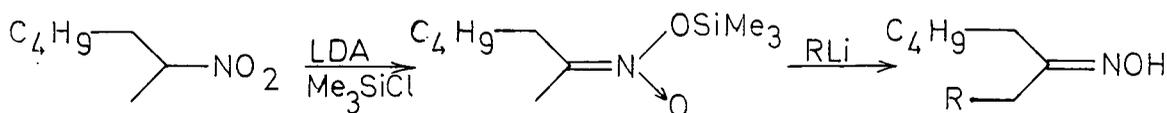


Scheme 50

In contrast to the reactions of primary silyl nitronates with organolithium reagents, ¹H n.m.r. spectral analysis of the crude reaction product revealed an equilibrium mixture of the (Z) and (E) oxime isomers. This may well be a consequence of a nitrosoalkene intermediate. The potential utility of this reaction was investigated by treating the silyl nitronate derived from 2-nitroheptane with various commercially available alkyl or aryl lithium reagents. The findings are summarised in Table 2.

Yields are based on 2-nitroheptane and refer to analytically pure products. If MeLi:LiBr was used, then a LiBr catalysed Nef process (see also page 68) resulted, ultimately forming 2-methylheptan-2-ol. The yields of these reactions have not been optimised, and if improvement can be achieved, then the above described reactions of primary and secondary silyl nitronates should prove synthetically useful.

TABLE 2



R-Li	Yield of oxime	Distillation Temperature
MeLi	35%	95-100°C / 0.5 mm Hg
Bu ⁿ Li	30%	135-140°C / 1.0 mm Hg
Bu ^s Li	50%	135°C / 1.5 mm Hg
PhLi	25%	120°C / 0.9 mm Hg

Silyl nitronates have found some use as 1,3 dipoles and have been implicated in a useful diastereoselective nitro-aldol condensation³⁹. It is hoped that the latter two reactions⁶⁰, formal α -alkylation and reduction of primary nitroalkanes, and formal β -alkylation and reduction of secondary nitroalkanes, will prove generally useful. In summary, the utility of silyl nitronates as intermediates in the transformations of nitroalkanes is at present somewhat limited. The chemistry of this class of compound is, to some extent, unpredictable and few parallels with silyl enol ethers can be drawn. The chemistry described herein is not exhaustive, and all avenues have not been explored. One may feel disappointed with a certain lack

of success, but the potential of silyl nitronates has been demonstrated. It is often unwise to dismiss an area of chemistry solely because initial results have not lived up to expectation⁶¹ :-

"Most, if not all, of the known types of organic derivatives of silicon have now been considered and it may be seen how few they are in comparison with those which are entirely organic; as, moreover, the few which are known are very limited in their reactions, the prospect of any immediate and important advance in this section of organic chemistry does not seem to be very hopeful."

F.S. Kipping, 1936.

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GENERAL EXPERIMENTAL DETAILS AND ABBREVIATIONS

Melting points are uncorrected and were determined on a Kofler hot stage apparatus. Microanalyses were performed by Mrs Harkness and her staff. Mass spectra were recorded by Mr A. Ritchie on A.E.I.-G.E.C./MS12 and A.E.I.-G.E.C./MS902 mass spectrometers. Routine i.r. spectra were recorded on a Perkin Elmer 197 grating spectrophotometer as liquid films. Solution and KBr disc i.r. spectra were obtained using a Perkin Elmer 580 grating spectrophotometer. Routine ^1H n.m.r. spectra were recorded on a Varian T60 and high resolution ^1H n.m.r. spectra were recorded on a Perkin Elmer R32 90 MHz spectrometer, with either tetramethylsilane or methylene chloride as internal standard. ^{13}C n.m.r. spectra were recorded by Dr D.S. Rycroft on a Varian XL100 spectrometer.

Merck Kieselgel G.F.₂₅₄ was used for preparative t.l.c. and, unless otherwise stated, Silica I.C.N. (Woelm, Grade III) was used for column chromatography. Analytical t.l.c. plates were stained with iodine, or with acidic ceric ammonium nitrate solution followed by heating to approximately 150°C.

All dilute mineral acids were 6N aqueous unless otherwise stated. Light petroleum refers to that fraction boiling in the range 40-60°C, and was redistilled prior to use. THF was heated under reflux with lithium aluminium hydride and distilled immediately prior to use. Diethyl ether, benzene, and toluene

were dried over sodium wire. DMF and acetonitrile were distilled from calcium hydride. Methylene chloride was dried by standing over phosphorus pentoxide followed by percolation through a column of alumina (Woelm, Grade I basic). All organic extracts were dried, unless otherwise stated, over anhydrous magnesium sulphate. Short-path distillations were performed on a Büchi GKR-50.

The following abbreviations and symbols have been used throughout this section:-

t.l.c.	thin layer chromatography
i.r.	infrared
n.m.r.	nuclear magnetic resonance
s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
br	broad
M ⁺	molecular ion
m.p.	melting point
b.p.	boiling point

Preparation of Nitroalkanes

1-Nitrohexane, phenylnitromethane and p-nitrophenylnitromethane were prepared from the corresponding bromides and sodium nitrite in DMF, according to the published procedure¹.

1-Nitrohexane

This was obtained as a colourless oil, b.p. 86°C at 16 mm Hg (lit¹: b.p. 82°C at 15 mm Hg).

ν_{\max}	2920 2860 1540 1430 1375
δ (CDCl ₃)	0.9 (3H, t, J=5Hz, CH ₃), 1.42 (6H, m), 1.8-2.3 [2H, m, 2H-C(2)], 4.45 [2H, t, J=5Hz, 2H-C(1)].

Phenylnitromethane

This was obtained as a colourless oil, b.p. 108-110°C at 20 mm Hg, (lit¹: b.p. 104°C at 20 mm Hg).

ν_{\max}	3025 1560 1365
δ (CDCl ₃)	5.39 (2H, s, CH ₂), 7.39 (5H, s, Ph) .

p-Nitrophenylnitromethane

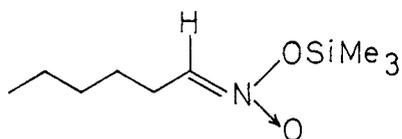
This was obtained from ethanol as pale yellow needles,
m.p. 87-88°C (lit¹: m.p. 89-90°C).

ν_{max}	3030 1565 1365
δ (CDCl ₃)	5.6 (2H, s, CH ₂), 7.7-8.5 (4H, 2 x ABq, J=9Hz, ArH).

2-Nitroheptane

A mixture of 2-bromoheptane (71.64g, 0.4 mol), sodium nitrite (48.3g, 0.7 mol) urea (42g, 0.7 mol) and 1,3,5-benzenetriol (40g, 0.31 mol) in DMF (700 ml) was stirred at room temperature for 3.5 days. The dark brown solution was poured into 1.5 litres of ice/water. The aqueous solution was extracted with pentane (6 x 100 ml) and the combined organic extracts were washed with water (6 x 100 ml), dried and concentrated in vacuo. Distillation of the residue afforded 2-nitroheptane as a colourless oil (28g, 48%), b.p. 85-87°C at 25 mm Hg, (lit²: b.p. 74°C at 10 mm Hg).

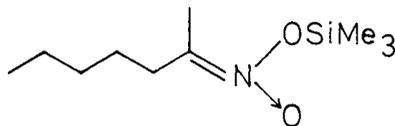
ν_{max}	2920 1540 1450 1350
δ (CDCl ₃)	0.95 (3H, m, CH ₃), 1.2-2.2 (8H, m, -CH ₂ - ₄) 1.5 (3H, d, J=7Hz, CH ₃ -CHNO ₂) 4.5 (1H, m, CHNO ₂)

Trimethylsilyl ester of 1-aci-Nitrohexane

To a stirred solution of diisopropylamine (1.6g, 2.24 ml, 16 mmol) in THF (50 ml) was added, at -78°C , n-butyl lithium in hexane (10.4 ml, 15.6 mmol). The cooling bath was removed, and stirring continued for 30 minutes, after which time the cooling bath was restored. To this solution of lithium diisopropylamide was added, at -78°C , 1-nitrohexane (1.99g, 15 mmol) within 1 minute. The resulting unstorrrable jelly was kept at -78°C for 30 minutes, then trimethylsilyl chloride (2.39g, 2.8 ml, 22 mmol) was added. Stirring was recommenced, and the mixture kept at -78°C for 30 minutes. The cooling bath was then removed, and stirring continued for 1 hour. The THF was removed in vacuo and under nitrogen $< 35^{\circ}\text{C}$. The residual semi-solid was suspended in pentane (50 ml), the suspension filtered through a Celite pad and the pad was washed with pentane (4 x 10 ml). The pentane filtrates were combined and evaporated $< 35^{\circ}\text{C}$. Short path distillation afforded 2.0g (68%) of the trimethylsilyl ester of 1-aci-nitrohexane as a moisture sensitive colourless oil, b.p. $75^{\circ}\text{C}/0.9$ mm Hg (lit²: b.p. 65°C at 0.01 mm Hg).

δ (CDCl_3) 0.3 (9H, s, Me_3Si), 0.95 (3H, brt, CH_3),
 1.45 (6H, m), 2.35 [2H, brq, 2H-C(2)],
 6.05 [1H, t, $J=4\text{Hz}$, H-C(1)].

Trimethylsilyl ester of 2-aci-Nitroheptane



From lithium diisopropylamide (11 mmol), 2-nitroheptane (1.45g, 10 mmol), and trimethylsilyl chloride (1.30g, 12 mmol) in THF (40 ml) was obtained the silyl nitronate (2.50g, 96%) following the general procedure. This material was very moisture sensitive and decomposed on attempted distillation, but its purity (>95% according to the ¹H n.m.r. spectrum) was sufficient for subsequent reactions.

δ (CDCl₃) 0.25 (9H, s, Me₃Si), 0.8-1.65 (9H, m),
1.9 (3H, s, CH₃-C=), 2.25 (2H, m, CH₂-C=) .

Thermal decomposition of t-Butyldimethylsilyl Phenylmethane-nitronate (Scheme 9)

The silyl ester of phenylnitromethane (2.0g, 8 mmol) was dissolved in CCl₄ (50 ml) and heated under reflux for 18 hours. Direct ¹H n.m.r. spectral analysis of the reaction mixture indicated the presence of benzaldehyde, an unidentified substance, and t-butyldimethylsilanol. The solvent was removed in vacuo affording a red viscous oil. Column chromatography on neutral alumina yielded benzaldehyde contaminated with t-butyldimethylsilanol. Repeated chromatography failed to yield a sufficiently pure sample of the third component for characterisation and identification.

Thermal decomposition of *t*-Butyldimethylsilyl *p*-Nitrophenyl-methanenitronate (Scheme 10)

The silyl ester of *aci-p*-nitrophenylnitromethane (2.0g, 6.75 mmol) was dissolved in CCl₄ (50 ml) and heated under reflux for 18 hours. The reaction mixture was concentrated in vacuo and the dark yellow viscous oil diluted with water. The aqueous layer was separated and allowed to crystallise, giving pale yellow needles of *p*-nitrobenzaldehyde (450mg), m.p. 104-105°C (lit⁶: m.p. 105-107°C).

δ (CDCl₃) 8.3-8.7 (4H, 2 x ABq, J=9Hz, ArH),
 10.45 (1H, s, CHO).

The water insoluble oil was triturated with ether to afford a pale yellow solid, which on crystallisation from ether gave pale yellow needles (145mg) of 2,4-bis(*p*-nitrophenyl)oxadiazole (6), m.p. 243-245°C (lit⁴: m.p. 247-248°C), identified by comparison with an authentic sample (page 127).

ν_{max} 3100 1580 1530 1345 868 852 730

δ (CDCl₃) 8.36 (8H, ABq, J=3Hz, ArH).

(Found: m/z 312.0489. C₁₄H₈N₄O₅ requires 312.0495).

Preparation of Trifluoroperacetic Acid

This was prepared from trifluoroacetic anhydride and 90% H₂O₂ in acetonitrile according to the published procedure³. It was used immediately after preparation and without purification.

Preparation of 1-Nitrohexane

To a stirred solution of hexanal oxime (1.15g, 10 mmol), sodium hydrogen carbonate (4.54g, 54 mmol) and urea (0.2g, 3 mmol) in dry acetonitrile (25 ml), was added dropwise at 0°C, trifluoroperacetic acid (20 mmol) in acetonitrile (6ml). The solution was then heated under reflux for 1 hour. The reaction mixture was concentrated in vacuo, and the residue diluted with water and extracted with pentane. The organic extracts were washed with saturated sodium hydrogen carbonate, brine and dried. Removal of solvent under reduced pressure afforded 1.2g of crude 1-nitrohexane as a pale yellow mobile oil, identified by comparison with an authentic sample.

Preparation of Hexanal Oxime O-t-Butyldimethylsilyl ether (10)

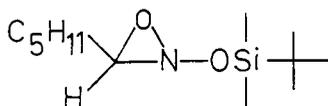
To a stirred solution of hexanal oxime (1.15g, 10 mmol) in dry DMF (1 ml) was added t-butyldimethylsilyl chloride (1.81g, 12 mmol) and imidazole (1.7g, 25 mmol) in dry DMF (2 ml). The reaction mixture was stirred for 19 hours at 20°C, then poured

on to ice/water (25 ml). The aqueous mixture was extracted thoroughly with pentane, and the organic extracts washed with brine, dried, and concentrated in vacuo to afford 2.3g of crude product (10) as a pale yellow oil. Distillation yielded 1.85g (80%) of oxime ether (10) as a colourless mobile oil, b.p. 50-53°C at 20 mm Hg.

δ (CDCl₃) 0.05 (6H, s, Me₂Si), 0.1 (6H, s, Me₂Si-),
 0.8 (9H, s, Bu^tSi), 0.9 (9H, s, Bu^tSi),
 1.05-1.65 [12H, m, 2 x (CH₂)₃],
 2.0-2.5 (4H, m, 2 x CH₂-C=N), 6.82 [1H, t,
 J=5Hz, C-1(H)], 7.5 [1H, t, J=5Hz, C-1(H)].

An approximate equimolar ratio of (Z) and (E) oxime isomers was estimated from the ¹H n.m.r. spectrum of the mixture.

Attempted preparation of 3-Pentyloxazirane O-t-Butyldimethylsilyl ether (Scheme 15)

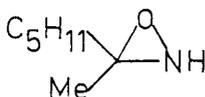


To a vigorously stirred solution of hexanal oxime O-t-butyl-dimethylsilyl ether (1.15g, 5 mmol), disodium hydrogen orthophosphate (3.9g, 27 mmol) and urea (0.1g, 1.5 mmol) in dry acetonitrile (10 ml), was added trifluoroacetic acid (10 mmol) in acetonitrile (3 ml) over 5 minutes at 20°C. The reaction mixture was heated under gentle reflux for 2 hours after which

time the acetonitrile was removed in vacuo, and the residue taken up in water. The aqueous solution was extracted thoroughly with pentane. The combined organic extracts were washed (aqueous sodium hydrogen carbonate and brine), dried, and concentrated under reduced pressure. The resultant pale yellow oil was identified as 1-nitrohexane by comparison with an authentic sample.

The use of methylene chloride, and variation in reaction time and/or temperature failed to produce tangible evidence for the production of the oxazirane.

Attempted preparation of 3-Methyl-3-pentyloxazirane (Scheme 16)

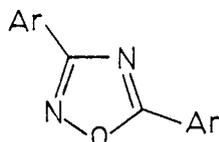


To a stirred solution of heptan-2-one (0.57g, 5 mmol) aqueous sodium hydroxide (2.5 ml, 2M) and ether (9 ml) was added, at 0°C, hydroxylamine O-sulphonic acid, water (5 ml) and aqueous sodium hydroxide (2.5 ml, 2M) in one portion. The reaction mixture was stirred for 15 minutes at 0°C, after which time the organic layer was separated and the aqueous layer extracted repeatedly with ether. The combined organic extracts were washed with brine, dried (sodium sulphate) and concentrated in vacuo to afford a pale yellow mobile oil. The ¹H n.m.r. spectrum indicated the presence of heptan-2-one, δ (CDCl₃), 2.2 [3H, s, 3H-C(1)] and

a small quantity of oxime, δ (CDCl_3), 1.84 [3H, s, 3H-C(1)], both of which were coincident with authentic samples on analytical t.l.c.. The addition of tetrabutylammonium bromide and/or change in solvent (methylene chloride) did not affect the isolated product mixture.

Photolysis of the t-Butyldimethylsilyl ester of 1-aci-Nitrohexane (12)

Freshly distilled silyl nitronate (12) (850mg, 3.3 mmol) was dissolved in degassed benzene (250 ml) and placed in a water cooled photolysis apparatus. After irradiation for 3 hours using a 125-W medium pressure mercury lamp, the solution was concentrated in vacuo to afford a dark yellow viscous oil. The ^1H n.m.r. spectrum indicated this to be mainly 1-nitrohexane. T.l.c. analysis verified this and also showed the presence of a number of intractible polar products.

Preparation of 2,4-Bis(p-nitrophenyl)oxadiazole (6) (Scheme 21)

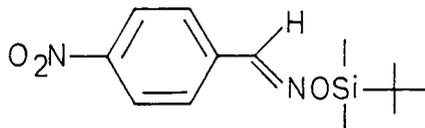
(6)

p-Nitrobenzaloxime (1.66g, 10 mmol) and amyl nitrite (2.46g, 21 mmol) in dry benzene (10 ml) was heated under reflux for 24 hours in accord with the published procedure⁴. On cooling, the reaction mixture deposited pale yellow crystals, which, on filtration and recrystallisation from toluene, afforded oxadiazole (6) as pale yellow needles (0.9g, 30%), m.p. 245-247°C, (lit⁴: m.p. 247-248°C).

ν_{max} 3100 1570 1530 1345 868 852 730

δ (CDCl₃) 8.36 (8H, ABq, J=3Hz, ArH).

(Found: m/z 312.0492, C₁₄H₈O₅N₄ requires 321.0495).

Preparation of p-Nitrobenzaloxime O-t-Butyldimethylsilyl ether

This was prepared by standard methods⁵ previously described for hexanal oxime. Thus, from p-nitrobenzaloxime (1.66g, 10 mmol) was obtained the oxime O-t-butyl dimethylsilyl ether (1.9g, 68%) as very pale yellow needles, m.p. 66-67°C, after crystallisation

from light petroleum.

ν_{\max} (CCl ₄)	2930	2860	1585	1525	1350	970	850
δ (CDCl ₃)	0.1 (6H, s, Me ₂ Si), 0.82 (9H, s, Bu ^t Si)						
	7.55-8.15 (4H, 2 x ABq, ArH),						
	8.11 (1H, s, CH=N).						

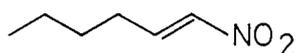
(Found: m/z 280.1240, C₁₃H₂₀N₂O₃Si requires 280.1243).

Attempted preparation of 2,4-Bis(p-nitrophenyl)oxadiazole (6)

(Scheme 22)

A solution of p-nitrobenzaldoxime O-t-butyldimethylsilyl ether (1.4g, 5 mmol) and amyl nitrite (1.23g, 10.5 mmol) in dry benzene (10 ml) was heated under reflux for 24 hours. Direct analytical t.l.c. analysis indicated no conversion of the oxime O-silyl ether to the oxadiazole. Prolonged heating and/or a change of solvent (CCl₄) had no effect on the reaction, from which the oxime O-silyl ether could be quantitatively recovered.

Attempted preparation of 1-Nitrohexene (Scheme 28)



To a stirred solution of the t-butyldimethylsilyl ester of 1-aci-nitrohexane (490mg, 2 mmol) in dry acetonitrile (5 ml) was added dropwise, under an atmosphere of argon and at 0°C, 2,3-dichloro-5,6-dicyanoquinone (680mg, 3 mmol) and tetrabutylammonium fluoride (55.6mg, 0.2 mmol) in acetonitrile (10 ml). The resulting mixture was allowed to warm to room temperature and then stirred for a further 2 hours. Removal of the solvent in vacuo produced a semi-solid which was suspended in pentane and filtered through a Celite pad. After thorough washing of the Celite pad with pentane, the combined pentane washings were concentrated in vacuo to furnish a viscous yellow oil. The ¹H n.m.r. spectrum and analytical t.l.c. analysis of this oil indicated gross decomposition of the silyl nitronate, with no evidence for formation of the desired olefin or of 1-nitrohexane.

Attempted preparation of 1-Nitrohexene (Scheme 28)

To a vigorously stirred solution of the t-butyldimethylsilyl ester of 1-aci-nitrohexane (490mg, 2 mmol) in dry acetonitrile (5 ml) was added dropwise, under an atmosphere of argon and at 0°C, trityl tetrafluoroborate (660 mg, 2 mmol) and tetrabutylammonium fluoride (60mg, 0.2 mmol) in acetonitrile (15 ml). The reaction mixture was allowed to warm to 20°C, and stirred

for a further 2 hours at this temperature. Evaporation of solvent in vacuo produced a semi-solid which was suspended in pentane and filtered through a Celite pad. After thorough washing of the Celite pad with pentane, the combined pentane washings were concentrated in vacuo to furnish an intractible viscous oil.

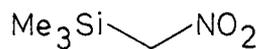
The above two reactions are representative; the reactions were also attempted in benzene and with the addition of collidine or of hexamethyldisiloxane. The reactions were also attempted with no added catalysis, but no deviation from production of an intractible oil was achieved.

Preparation of Trimethylsilylacetic Acid

This was prepared by the literature procedure⁷. From trimethylsilylmethyl chloride (12.2g, 10 mmol) was obtained trimethylsilylacetic acid (9.9g, 75%), m.p. 38-39°C (lit^{6,7}: m.p. 40°C) after crystallisation from pentane.

δ (CDCl₃) 0.05 (9H, s, (CH₃)₃Si), 1.8 (2H, s, -CH₂-), 9.5 (1H, bs, exchanges with D₂O, CO₂H)

Attempted preparation of Trimethylsilylnitromethane (20) (Scheme 30)



(20)

To a stirred solution of diisopropylamine (3.27mg, 32.7 mmol) and THF (40 ml) was added at -20°C and under an atmosphere of argon, n-butyl lithium in hexane (28 ml, 32.7 mmol). The solution was stirred for 30 minutes at -10°C after which time trimethylsilylacetic acid (1.9g, 14.7 mmol) in THF (5 ml) was added dropwise such that the internal temperature was maintained below -5°C . Initially a white suspension formed; after 15 minutes the solution was homogeneous. This solution of the dianion was stirred for a further 45 minutes, then isopropyl nitrate (4.63g, 44 mmol) was added rapidly at 0°C . The reaction mixture was stirred for 4 hours at room temperature, then cooled to -78°C . Trifluoroacetic acid (4.56g, 40 mmol) was added and stirring continued for 30 minutes. The solution was poured onto water and the aqueous layer separated, saturated with NaCl, and thoroughly extracted with pentane. The combined pentane extracts were washed with brine, dried and concentrated in vacuo to afford a pale yellow viscous oil which partially solidified on standing. Analytical t.l.c. and ^1H . n.m.r. spectral analysis indicated that the crude reaction product was comprised of trimethylsilylacetic acid and isopropanol.

A variety of reaction temperatures and times failed to alter this result, as did the employment of propyl or methyl nitrate.

Preparation of Ethyl Trimethylsilylacetate

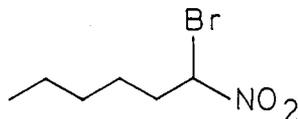
This was prepared by the literature procedure⁸. From ethyl bromoacetate (83.5g, 0.5 mol) was obtained 30g (40%) of pure ethyl trimethylsilylacetate, b.p. 105-110°C at 20 mm Hg (lit⁸: b.p. 76-77°C at 4 mm Hg).

δ (CDCl₃) 0.15 (9H, s, Me₃Si), 1.24 (3H, t, J=7Hz, H₃C), 1.87 (2H, s, -CH₂-), 4.02 (2H, q, J=7Hz, H₃C-CH₂).

Attempted preparation of Ethyl Trimethylsilylnitroacetate

An identical procedure was used to that previously described for the attempted preparation of trimethylsilylnitromethane. Thus, ethyl trimethylsilylacetate (1.6g, 10 mmol), lithium diisopropylamide (30 mmol) and isopropyl nitrate (3.15g, 30 mmol) failed to produce the desired product, with starting material invariably being recovered. The use of lithium isopropylcyclohexylamide or tetranitromethane (as nitrating agent) also furnished starting material as the sole product.

Preparation of 1-Bromo-1-nitrohexane (Scheme 31)



To a vigorously stirred solution of NaOH (1g, 25 mmol) and H₂O (4 ml) was added dropwise, at 0°C, 1-nitrohexane (2.0g, 15 mmol). The resulting solution of the nitronate anion was stirred for 15 minutes at 0°C. Bromine (2.45g, 15 mmol) was added dropwise over 1 hour at 0°C. After stirring for 30 minutes, solid sodium sulphite was added until the solution became colourless. The aqueous solution was then extracted well with ether, and the combined ether extracts washed with water, brine and dried over sodium sulphate. The solution was concentrated in vacuo to furnish a pale yellow mobile oil. Short path distillation afforded 2.88g (80%) of 1-bromo-1-nitrohexane as a colourless oil, b.p. 65-68°C at 0.3 mm Hg.

δ (CDCl₃) 0.92 (3H, m, H₃C), 1.4 [6H, m, -(CH₂)₃-],
2.1-2.6 [2H, m, 2H-C(2)], 5.97 [1H, t,
J=7Hz, H-C(1)].

(Found: m/z 238. C₆H₁₂BrNO₂ requires M 238).

Attempted preparation of 1-Trimethylsilyl-1-nitrohexane (Scheme 31)

A solution of zinc powder (1.16g, 17.7 mmol), copper(II) chloride (0.2g, 1.77 mmol), dry benzene (10 ml) and dry ether (2 ml) was heated under reflux in an atmosphere of argon for 30 minutes.

A solution of 1-bromo-1-nitrohexane (2.73g, 13 mmol), trimethylsilyl chloride (1.3g, 12 mmol), dry benzene (5 ml) and dry ether (1 ml) was then added at reflux temperature over one hour. The resulting solution was heated at reflux temperature for a further 1½ hours then cooled to 0°C. Aqueous HCl (4 ml, 1M) was added slowly over 10 minutes. The aqueous layer was separated and extracted well with ether. The combined organic extracts were washed with brine, dried and concentrated in vacuo to furnish a pale yellow oil. Analytical t.l.c. analysis and ¹H n.m.r. spectral analysis indicated the major product to be hexanoic acid. Other products including nitrohexane were also present.

An alternative aqueous work up was also employed. Concentration of the reaction mixture in vacuo afforded a semi-solid which was suspended in ether and filtered through a pad of Celite. The Celite pad was washed thoroughly with ether and the combined ethereal filtrates concentrated in vacuo. Short path distillation yielded 1-nitrohexane, 1-bromo-nitrohexane and hexanal oxime as identifiable products. The ratio of the products was variable but no 1-trimethylsilyl-1-nitrohexane was detected.

Attempted Lewis Acid catalysed Alkylation of the t-Butyldimethylsilyl ester of 1-aci-Nitrohexane (Scheme 32)

To a stirred solution of the t-butyldimethylsilyl ester of 1-aci-nitrohexane (490mg, 2 mmol) in dry methylene chloride (10 ml) at 20°C and under an atmosphere of argon was added allyl bromide (290mg, 2.4 mmol) followed by zinc bromide (10mg, 0.04 mmol). The resulting solution was stirred at 20°C for 4 hours after which time the solvent was removed in vacuo to furnish a pale green oil. Short path distillation (50°C at 0.2 mm Hg) afforded 1-nitrohexane and residual polymeric materials.

Attempted Alkylation of the t-Butyldimethylsilyl ester of aci-Phenylnitromethane

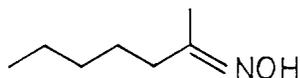
To a stirred solution of tetrabutylammonium fluoride (1.35g, 4 mmol) in THF (25 ml) was added, at -78°C under an atmosphere of argon, methyl iodide (0.25 ml, 4 mmol) followed by the t-butyldimethylsilyl ester of aci-phenylnitromethane (1g, 4 mmol) over 1 minute. The resulting pale yellow mixture was stirred for 30 minutes at -78°C then for 2 hours at room temperature. The solvent was removed in vacuo and the residue taken up in water (20 ml) and extracted with pentane (3 x 50 ml). The combined pentane extracts were washed with brine, dried and concentrated in vacuo. Careful short path distillation afforded a colourless oil (400mg) b.p. 60°C at 0.5 mm Hg. ¹H n.m.r. analysis of this oil indicated a 9:1 mixture of phenylnitromethane and the methyl

ester of aci-phenylnitromethane.

Preparation of Oximes from Primary Silyl Nitronates -

General Procedure

Heptan-2-one oxime (Scheme 40)



To a stirred solution of the trimethylsilyl ester of 1-aci-nitrohexane (509mg, 2.5 mmol) in THF (22 ml) was added, dropwise at -78°C and under an atmosphere of argon, methyl lithium: lithium bromide in ether (3.3 ml, 5 mmol). The resultant straw coloured solution was maintained at -78°C for 1 hour, then allowed to warm to 20°C . The mixture was poured on to saturated ammonium chloride solution. The aqueous layer was saturated with sodium chloride and extracted with ether. The combined ethereal extracts were washed with brine, dried and concentrated in vacuo $< 35^{\circ}\text{C}$. Bulb-to-bulb distillation afforded heptan-2-one oxime (187mg, 58%) as a colourless oil, b.p. $85-90^{\circ}\text{C}$ at 0.3 mm Hg (lit⁹: b.p. 99°C at 12 mm Hg).

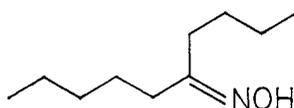
ν max	3290 2960 2930 1460 940
δ (CDCl ₃)	0.87 [6H, t, J=7Hz, 2 x 3H-C(7)], 1.25-1.4 (12H, m), 1.81 [3H, s, 3H-C(1)], 1.85 [3H, s, 3H-C(1)], 2.2 [4H, t, J=8Hz, 2 x 3H-C(3)].

This was found to be identical in all respects with heptan-2-one oxime prepared from heptan-2-one by a published procedure⁹. An approximate equimolar ratio of (E) and (Z) oxime isomers was estimated from the ¹H n.m.r. spectral integrals of the singlet methyl signals at δ 1.85 and δ 1.81 p.p.m. respectively.

Following the above procedure, but subjecting the crude product to rapid column chromatography on silica (eluting solvent ethyl acetate:light petroleum) afforded (E)-heptan-2-one oxime (123mg, 50%) as a colourless oil.

ν_{\max}	3290 2960 2930 1460 940
δ (CDCl ₃)	0.87 [3H, t, J=7Hz, 3H-C(7)], 1.25-1.4 (6H, m), 1.85 [3H, s, 3H-C(1)], 2.2 [2H, t, J=8Hz, 3H-C(3)].

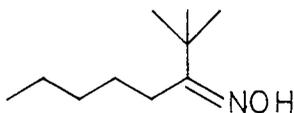
Short path distillation of this oil provided heptan-2-one oxime as an approximately equimolar ratio of (Z) and (E) oxime isomers, identical in all respects with an authentic sample.

Decan-5-one oxime (Table 1)

From the trimethylsilyl ester of 1-aci-nitrohexane (509mg, 2.5 mmol) and a solution of n-butyl lithium in hexane (3.2 ml, 5 mmol) following the general procedure, was obtained decan-5-one oxime (220mg, 50%) as a colourless mobile oil, b.p. 100-110°C at 0.7 mm Hg.

ν max	3225 2970 2940 1465
δ (CDCl ₃)	0.88 [6H, m, 3H-C(1) and 3H-C(10)], 1.33 (1OH, m), 2.15 [4H, t, J=8Hz, 2H-C(4) and 2H-C(6)], 8.8 (1H, br, exchanges with D ₂ O, OH).

(Found: m/z, 171.1620, C₁₀H₂₁NO requires 171.1623).

2,2-Dimethyloctan-3-one oxime (Table 1)

From the trimethylsilyl ester of 1-aci-nitrohexane (1.2g, 6 mmol), t-butyl lithium in pentane (8 ml, 12 mmol) and THF (40 ml), was obtained 2,2-dimethyloctan-3-one oxime (306mg, 30%) as a colourless mobile oil, b.p. 110°C at 25 mm Hg.

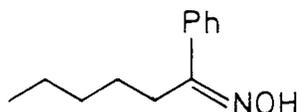
ν max	3300 2960 1470 940
(<u>Z</u>) isomer δ (CDCl ₃)	0.87 [3H, bt, 3H-C(8)], 1.28 (9H, s, Bu ^t) 1.25-1.4 (6H, m), 2.19 [2H, t, J=8Hz,

2H-C(4)], 9.1 (1H, br, exchanges with D₂O, OH).

(E)-isomer δ (CDCl₃) 0.87 [3H, bt, 3H-C(8)], 1.1 (9H, s, Bu^t)
1.25-1.4 (6H, m), 2.19 [2H, t, J=8Hz,
2H-C(4)], 9.2 (1H, br, exchanges with D₂O, OH).

(Found: m/z, 171.1620. C₁₀H₂₁NO requires 171.1623).

The ratio of the (Z) and (E) oxime isomers was dependent upon the distillation temperature and on the time required for distillation. An equilibrium ratio was not established, although in most cases approximately equal quantities of (Z) and (E) isomers were obtained as calculated from the ¹H n.m.r. spectral integrations for the t-butyl groups. Purification of the crude reaction product by means of rapid column chromatography on silica (eluting solvent ethyl acetate:light petroleum) furnished (Z)-2,2-dimethyloctan-3-one oxime (300mg, 29%) as a colourless oil. Short path distillation of this single oxime isomer provided approximately equal amounts of (Z)- and (E)-2,2-dimethyl-octan-3-one oxime.

1-Phenylhexan-1-one oxime (Table 1)

From the trimethylsilyl ester of 1-aci-nitrohexane (675mg, 3.33 mmol) and phenyl lithium in cyclohexane-ether (3.55 ml, 6.6 mmol) in THF (30 ml), was obtained, following the general procedure, 1-phenylhexan-1-one oxime (252mg, 40%) as a colourless oil which solidified on standing, b.p. 155-160°C at 0.3 mm Hg; m.p. 31-33°C, (lit¹⁰: m.p. 52°C).

ν max	3600 3300 2960 2930 1460 690
δ (CDCl ₃)	0.85 [3H, bt, 3H-C(6)], 1.18-1.6 (6H, m) 7.25-7.4 (3H, m, Ph), 7.48-7.6 (2H, m, Ph), 8.6 (1H, b, exchanges with D ₂ O, OH).

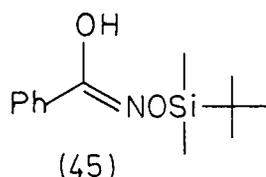
(Found: m/z, 191.1307, C₁₂H₁₇NO requires 191.1310).

Attempted preparation of Heptan-2-one oxime (Scheme 39)

To a stirred solution of the trimethylsilyl ester of 1-aci-nitrohexane (926mg, 4.56 mmol) in THF (20 ml) was added, at -78°C, methyl magnesium iodide in ether (4 ml, 9 mmol) (prepared from magnesium and methyl iodide) dropwise and under an atmosphere of argon. Stirring was continued for 30 minutes at -78°C, then for 12 hours at room temperature. The mixture was poured onto saturated ammonium chloride and the aqueous layer was separated and extracted with ether. The combined ether extracts were

washed with brine, dried and concentrated in vacuo to afford a pale yellow oil (531 mg) identified as 1-nitrohexane by comparison with an authentic sample.

Preparation of t-Butyldimethylsilyl Benzohydroxamate (45)



To a stirred solution of the t-butyldimethylsilyl ester of aci-phenylnitromethane (1.24g, 5 mmol) in THF (20 ml) was added, at -78°C , a solution of methyl lithium:lithium bromide in ether (7 ml, 10 mmol). The resultant dark red solution was stirred for 30 minutes at -78°C , and then for 3 hours at 20°C . The solvent was removed in vacuo and the residual solid dissolved in ether (50 ml). The solution was then poured on to aqueous ammonium chloride and the aqueous layer separated and extracted with ether. The combined ethereal extracts were washed with brine, dried and concentrated in vacuo to furnish a pale yellow solid. Crystallisation from ethyl acetate/petroleum ether afforded the hydroxamate (45) as white needles (670mg, 61%) m.p. $138-140^{\circ}\text{C}$.

ν max	3450 3160 2960 1650 790
δ (CDCl ₃)	0.13 (s, 6H, Me ₂ Si), 0.88 (s, 9H, Bu ^t Si), 7.18-7.68 (m, 5H, Ph).

(Found: C, 62.1; H, 8.4; N, 5.77. C₁₃H₂₁NO₂Si requires
C, 62.3; H, 8.06; N, 5.60%).

The aforementioned reaction was also accomplished in an identical manner using n-butyl lithium or methyl magnesium iodide in place of methyl lithium:lithium bromide. In each case the conversion was approximately 60% effective, and no evidence for the formation of a substituted oxime was obtained.

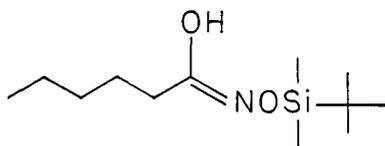
Preparation of Benzohydroxamic acid

This was prepared from ethyl benzoate and hydroxylamine according to the published procedure¹¹.

Preparation of authentic t-Butyldimethylsilyl Benzohydroxamate (45)

This was prepared by standard procedures⁵ previously described for hexanal oxime O-t-butyldimethylsilyl ether (10). Thus, from benzohydroxamic acid (132mg, 1 mmol), imidazole (168mg, 2.5 mmol) and t-butyldimethylsilyl chloride (181mg, 1.2 mmol) in DMF (5 ml) was obtained the hydroxamate (45), (200mg, 80%) as white needles from ethanol, m.p. 139-140°C. This material was identical in all respects to that derived from the reaction of t-butyldimethylsilyl ester of aci-phenylnitromethane with a range of organometallic reagents (mixed m.p. 139-140°C).

Preparation of *t*-Butyldimethylsilyl Hexylhydroxamate (34)



(34)

This was prepared by A. Beck, Laboratorium für Organische Chemie, ETH-Zürich.

To a stirred solution of the *t*-butyldimethylsilyl ester of *l*-aci-nitrohexane (2.45g, 10 mmol) in THF (20 ml) was added, at -78°C , under an atmosphere of argon, butyl lithium in hexane (6.5 ml, 10 mmol) in THF (6.5 ml). The mixture was stirred for 2 hours at -78°C and thereafter until the internal temperature had reached 20°C (1 hour). The resultant solution was poured on to saturated ammonium chloride, and the aqueous layer was separated and extracted with ether. The combined ether extracts were washed with brine, dried and concentrated in vacuo to furnish a viscous oil. Short path distillation afforded a white solid (1.1g), b.p. $100-115^{\circ}\text{C}$ at 0.01 mm Hg, which on crystallisation from ethanol yielded *t*-butyldimethylsilyl hexylhydroxamate (34) (0.64g, 25%) as white needles, m.p. $59.6-61^{\circ}\text{C}$.

ν max	3400 3180 2940 2860 1700 1460 1250
δ (CCl ₄)	0.15 (6H, s, Me ₂ Si), 0.9-1.1 (3H, m, CH ₃), 0.95 (9H, s, Bu ^t Si), 1.15-1.75 (6H, m), 2.15-2.25 [2H, bt, J=5Hz, 2H-C(2)].

(Found: C, 58.46; H, 11.06; N, 6.82% C₁₂H₂₇NO₂Si requires
C, 58.73; H, 11.01; N, 6.64%).

Preparation of Hexylhydroxamic acid

This was prepared from ethyl hexanoate and hydroxylamine according to the published procedure¹¹.

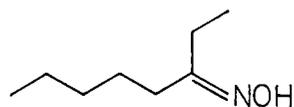
Preparation of authentic t-Butyldimethylsilyl Hexylhydroxamate

This was prepared by standard procedures⁵ previously described for hexanal oxime O-t-butyldimethylsilyl ether (10). Thus, from hexylhydroxamic acid (131mg, 1 mmol), imidazole (168mg, 2.5 mmol) and t-butyldimethylsilyl chloride (181mg, 1.2 mmol) in DMF (5 ml) was obtained the hydroxamate (34), (200mg, 80%) as white needles from ethanol, m.p. 60-61°C (mixed melt with product from silyl nitronate, m.p. 60-61°C).

Preparation of oximes from Secondary Silyl Nitronates -

General Procedure

Octan-3-one oxime (53) (Scheme 47)



(53)

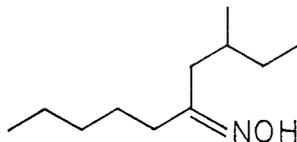
To a stirred solution of the crude trimethylsilyl ester of 2-aci-nitroheptane (~3.8 mmol) prepared from 2-nitroheptane (540mg, 3.8 mmol) in THF (20 ml) was added, at -78°C, and under an atmosphere of argon, methyl lithium in ether (4.75 ml, 7.6 mmol) over 1 minute. The resulting solution was stirred for 2 hours at -78°C, and then for 2 hours at 20°C. The reaction mixture was

poured on to saturated ammonium chloride, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with brine, dried and concentrated in vacuo to afford a pale yellow mobile oil. Bulb-to-bulb distillation yielded octan-3-one oxime as a colourless oil (188mg, 36%), b.p. 90-100°C at 0.5 mm Hg. The yield calculated is from 2-nitroheptane.

ν max	3290 2960 2930 1460 940
δ (CDCl ₃)	0.9 [3H, bt, 3H-C(8)], 1.8 [3H, t, J=5Hz, 3H-C(1)], 1.2-1.6 (6H, m), 2.2 [2H, q, J=5Hz, 2H-C(2)], 2.25 [2H, bt, 2H-C(4)].

(Found: m/z, 143.1313. C₈H₁₇NO requires 143.1310).

3-Methyldecan-5-one oxime (Table 2)

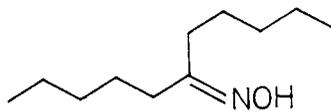


From the trimethylsilyl ester of 2-aci-nitroheptane (~ 3.8 mmol) in THF (20 ml), and s-butyl lithium in cyclohexane (5.43 ml, 7.6 mmol) was obtained, following the general procedure, 3-methyldecan-5-one oxime (350mg, 50%) as a colourless oil, b.p. 135°C at 1.2 mm Hg.

ν max	3220 2910 1445 950
δ (CDCl ₃)	0.88 (9H, bt, H ₃ C-), 1.32 (9H, m) 1.95-2.30 (4H, m).

(Found: m/z 185.1777. C₁₁H₂₃NO requires 185.1779).

Undecan-5-one oxime (Table 2)

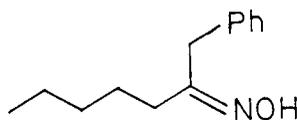


From the trimethylsilyl ester of 2-aci-nitroheptane (~3.8 mmol) in THF (20 ml) and n-butyl lithium in hexane (4.75 ml, 7.6 mmol) was obtained, following the general procedure, undecan-5-one oxime (197mg, 30%) as a colourless oil, b.p. 140°C at 1 mm Hg.

ν max	3240 2940 1460 950
δ (CDCl ₃)	0.85 (6H, bt, H ₃ C-), 1.32 (12H, m), 2.19 [4H, q, J=5Hz, 2H-C(5) and 2H-C(7)].

(Found: m/z 185.1777, C₁₁H₂₃NO requires 185.1779).

1-Phenylheptan-2-one oxime (Table 2)



From the trimethylsilyl ester of 2-aci-nitroheptane (~3.8 mmol) in THF (20 ml) and phenyl lithium in cyclohexane-ether (4.25 ml, 8 mmol) was obtained, following the general procedure, 1-phenylheptan-2-one oxime (170mg, 25%) as a colourless viscous oil, b.p. 115-120°C at 0.9 mm Hg.

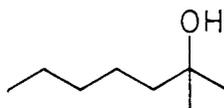
ν max	3220 2920 1450 970 700
δ (CDCl ₃)	1.6 (3H, bt, CH ₃), 1.49 (6H, m), 2.35 [2H, q, J=5Hz, 2H-C(3)], 3.68 [2H, s, 2H-C(1), (<u>E</u>) oxime isomer], 3.92 [2H, s, 2H-C(1), (<u>Z</u>) oxime

isomer], 7.38 (5H, s, Ph).

The ratio of (Z):(E) isomers was 1:3.

(Found: m/z 205.1467. $C_{13}H_{19}NO$ requires 205.1466).

Preparation of 2-Methylheptan-2-ol



To a stirred solution of the trimethylsilyl ester of 2-aci-nitroheptane (7.4 mmol) in THF (20 ml) was added, at $-78^{\circ}C$ and under an atmosphere of argon, a solution of methyl lithium: lithium bromide in ether (8 ml, 12 mmol). The reaction mixture was stirred for 45 minutes at $-78^{\circ}C$, after which time saturated ammonium chloride (20 ml) was added and the temperature was raised to $20^{\circ}C$. The aqueous layer was separated and extracted with ether. The combined ethereal extracts were washed with brine, dried and concentrated in vacuo to furnish a yellow oil (675mg). Column chromatography (eluting solvent ethyl acetate: light petroleum) afforded 2-methylheptan-2-ol as a colourless oil (180mg, 19%) and heptan-2-one oxime as a colourless oil (175mg, 18%).

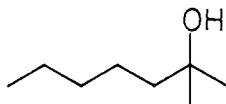
2-methylheptan-2-ol

ν_{max}	3400 2950 1460 1370
δ (CDCl ₃)	0.86 [3H, m, 3H-C(7)], 1.17 (6H, s, 2 x CH ₃) 1.2-1.45 (8H, m) .

^{13}C ; δ (CDCl_3) 13.97, C(7); 22.67, C(6); 32.42, C(5);
 (^1H decoupled) 24.05, C(4); 43.98, C(3); 71.14, C(2);
 29.22, C(1) and $\text{H}_3\text{C}-\text{C}(1)$.

(Found: m/z, 115.1127. $\text{C}_7\text{H}_{15}\text{O}(\text{M}-\text{CH}_3)$ requires 115.1124).

Preparation of authentic 2-Methylheptan-2-ol



To a vigorously stirred solution of methyl magnesium iodide in ether (12 mmol, 12 ml) was added dropwise, at 0°C and under an atmosphere of argon, heptan-2-one (1.14g, 10 mmol) in ether (5 ml). The solution was then heated under reflux for 45 minutes after which time it was cooled to 0°C . The mixture was poured on to saturated ammonium chloride (30 ml) and the aqueous layer was separated and extracted with ether. The combined ethereal extracts were washed with brine, dried and concentrated in vacuo to furnish a pale yellow oil (1.25g). Distillation of this oil afforded 2-methylheptan-2-ol (1.05g, 68%) as a colourless mobile oil, b.p. 70°C at 0.5 mm Hg (lit⁶: b.p. 115°C at 15 mm Hg).

δ max 3400 2950 1460 1370
 δ (CDCl_3) 0.86 [3H, m, 3H-C(7)], 1.17 (6H, s, CH_3),
 1.2-1.45 (8H, m).
 ^{13}C ; δ (CDCl_3) 14.12, C(7); 22.82, C(6); 32.65, C(5);
 24.25, C(4); 44.20, C(3); 70.87, C(2);
 29.26, C(1) and $\text{H}_3\text{C}-\text{C}(1)$.

(Found: m/z, 115.1125. $\text{C}_7\text{H}_{15}\text{O}(\text{M}-\text{CH}_3)$ requires 115.1124).

tetrabutylammonium bromide and following the above procedure did not significantly alter this product ratio.

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MACROLIDE SYNTHESIS

PART 2: MACROLIDE ANTIBIOTICS

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INTRODUCTION

The macrolide antibiotics are currently undergoing sustained attack in terms of isolation, structural determination and synthesis. The macrolides so far identified now number in the hundreds, and new members are revealed with bewildering rapidity. The term 'macrolide' was first coined by R.B. Woodward to describe a group of antibiotics derived from *Streptomyces* species which have as characteristic features, a large lactone ring containing few double bonds and devoid of nitrogen, and one or more sugars which may be amino-sugars, non-nitrogenous sugars or both. Today the term is applied more widely to natural products with large lactone rings. Indeed some of the macrocyclic lactams, such as the ansamycin antibiotics, have also been described as macrolides.

The chemistry of the macrolide antibiotics originated in 1950 with the isolation of pikromycin by Brockmann and Henkel². The original structure for pikromycin³ was wrongly formulated, and this was corrected in 1968⁴. It was at this time that the gross structures of methymycin⁵, erythromycin⁶ and magnamycin (carbomycin A)⁷ were also revealed, necessitating the classification for these new antibiotics. A minor structure modification was made for magnamycin in 1965^{8,9}.

In contrast to the vast number of structural studies that have appeared, it is only since 1972 that major synthetic

accomplishments have been achieved in the macrolide field. The reasons for this were manifold and it is a measure of the advances made in recent years that have allowed these molecules to be synthesised. We have come a long way since 1956:

"Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centres".

R.B. Woodward¹⁰.

Other authors have expressed similar sentiments :

"The presence of a large number of contiguous asymmetric centres in an aliphatic chain presents almost unsurpassable problems to the chemist bent on stereoselective synthesis".

F. Johnson¹¹.

Many of the problems, which will be discussed briefly below, are finding solution, and several syntheses of macrolides have now been reported. It would be reasonable to expect many more to be completed in the near future.

This introduction will highlight some of the synthetic achievements since 1977. This is not an arbitrary choice of date, since several excellent review articles appeared in that year¹²⁻¹⁵, describing earlier successes and failures. Due to limitations of space and in the interest of clarity, only those macrolides subclassified as "polyoxo" (p 159) will be

considered in any great depth, though passing reference, where relevant, will be made to other groups of macrolides. It is also intended to place heavy emphasis on synthesis, with strategies rather than practicalities being emphasised. Little discussion of the biosynthesis of these antibiotics will be found; for this the reader is directed to a review by J.W. Corcoran¹².

MODE OF ACTION

The macrolides are antibiotic in that they interfere with protein synthesis in bacteria. Gram positive bacteria are most susceptible, but when the intracellular concentration of the antibiotic is sufficiently high (ca. 10^{-4} M), intact cells of both Gram positive and negative bacteria are affected.

In protein synthesis in intact cells, the peptidyl-transfer-RNA molecule occupies a site on the ribosomal complex which is often termed the 'donor' site, because the growing peptide chain resides here at the time the peptidyl chain is donated to the incoming amino-acyl-transfer-RNA species. Culmination of this step finds the new elongated peptide chain attached to the 'acceptor' site of the ribosomal complex, via the transfer-RNA of the latest amino-acid. The ensuing migration of the new peptidyl-transfer-RNA molecule back to the 'donor' site, to allow the synthetic cycle to be repeated with further amino acids, is called the 'translocation' process and is distinct from the first half of the cycle which is catalysed

by peptidyl synthase¹⁶.

Macrolide antibiotics inhibit this complex machinery. In particular, erythromycin A inhibits bacterial growth, the mechanism of action involving high affinity binding to a highly specific site on the 50S ribosomal subunit. This occurs most efficiently when the 50S unit is in a free state, and the erythromycin/50S ribosomal adduct is able to form ribosomal assemblies. These change the activity of peptidyl transferase, most likely through an allosteric effect, to stimulate the first peptide bond formation and inhibit the second and subsequent peptide bond formation¹⁷.

In principle, therefore, the 'polyoxo' macrolides should be capable of inhibiting mammalian mitochondrial protein synthesis, as this process is similar to that in bacteria. Fortunately, erythromycin is unable to penetrate the mitochondrial membrane.

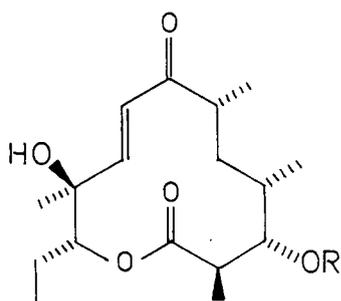
Biochemical and chemical studies of the macrolides were accelerated by the discovery of a high incidence of macrolide resistant strains in various bacteria. After wide scale use of erythromycin, more than 30% of staphylococci species became resistant to the antibiotic. Other macrolides were effective against most of them, stimulating the search for new and more powerful macrolides.

STRUCTURE AND CLASSIFICATION

A number of macrolide antibiotics are introduced below to represent the wide range of structural types known. Although only selected examples from each class are highlighted, an idea of the diverse and complex nature of the macrolides can be obtained from even this brief structural perusal. More comprehensive listings can be found in the reviews by Masamune¹² and his coworkers, and by Nicolaou¹³.

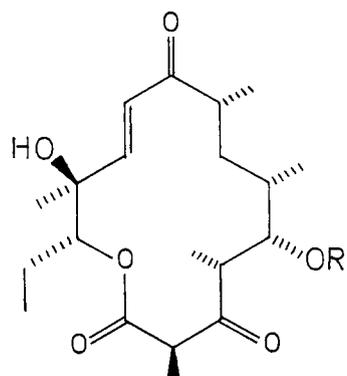
1. 'Polyoxo' Macrolides

These may be regarded as the prototypes of the macrolides, it being for this group that Woodward originally proposed the name. The lactones are normally 12-, 14-, or 16- membered, have no more than two olefinic bonds, and have one or more sugars linked to the ring. Methymycin (1) is the sole member with a 12- membered lactone; other typical 'polyoxo' macrolides are pikromycin (2), erythromycin A (3), oleandomycin (4), tylosin (5) and carbomycin A (6). In his determination of the conformations of macrocyclic hydrocarbons by the use of space filling models, Dale¹⁸ has found that no hydrocarbon ring system from cycloheptane through cyclotridecane can exist in a strain-free conformation.



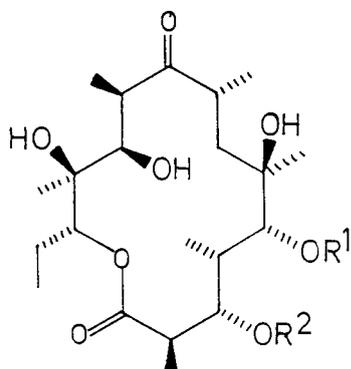
Methymycin (1)

R = Desosaminyl



Pikromycin (2)

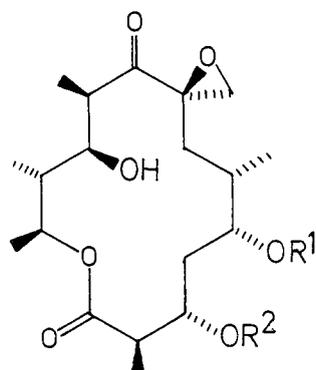
R = Desosaminyl



Erythromycin A (3)

R¹ = Desosaminyl

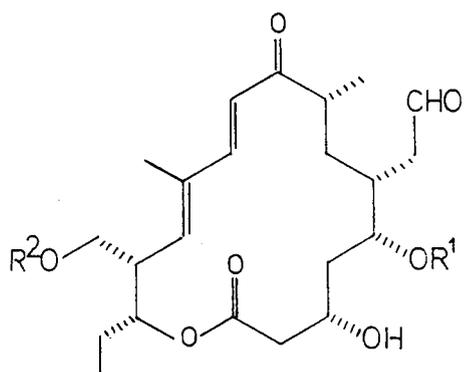
R² = Cladinosyl



Oleandomycin (4)

R¹ = Desosaminyl

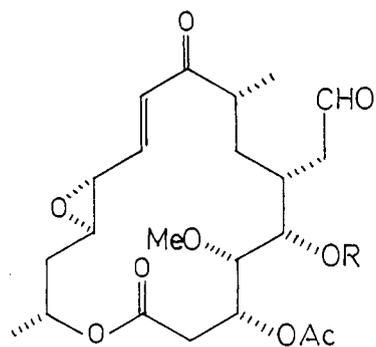
R² = Oleandrose



Tylosin (5)

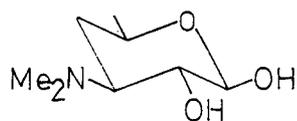
R¹ = Mycarosyl-mycaminosyl

R² = Mycinosyl

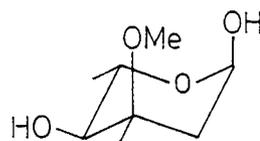


Carbomycin A (6)

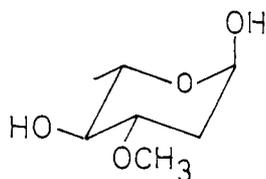
R = (Isovaleryl)-mycarosyl-mycaminosyl



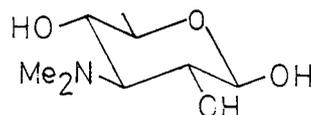
D-Desosamine



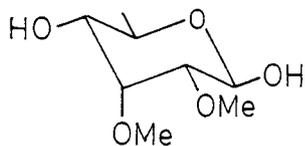
L-Cladinose



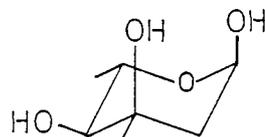
L-Oleandrose



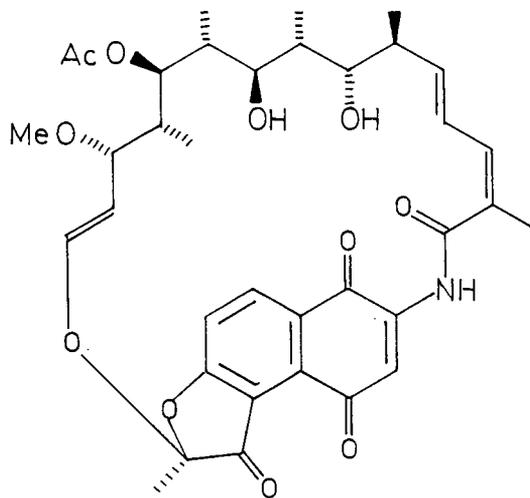
D-Mycaminose



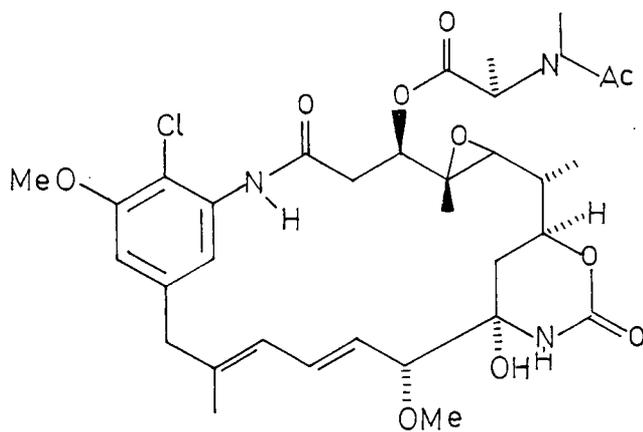
D-Mycinose



L-Mycarose



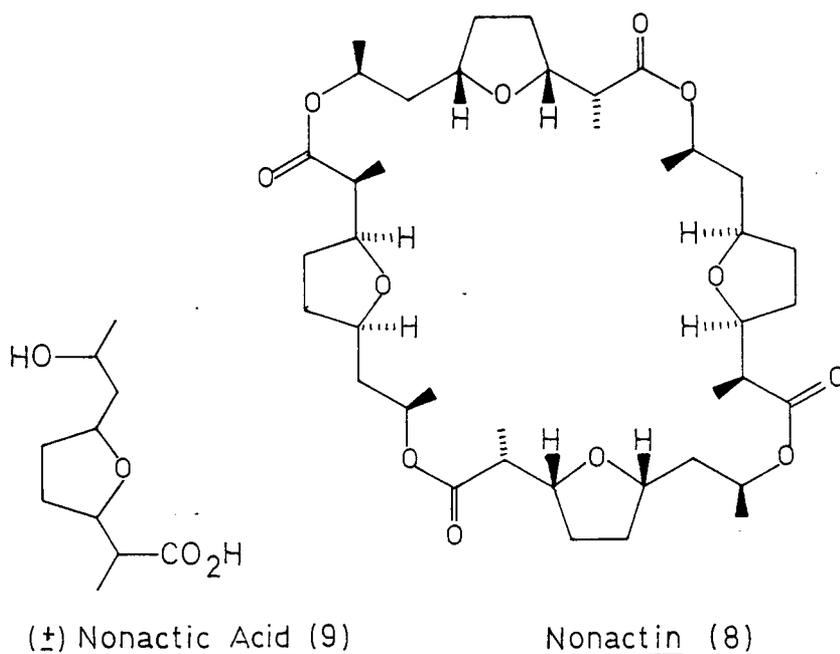
Rifamycin S (11)



Maytansine (12)

3. Ionophore Macrolides

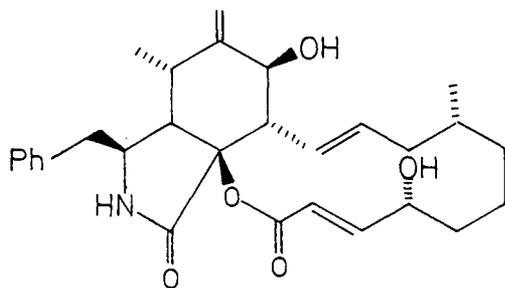
Macrolides in this class contain two or more lactone groups in a large ring system. Nonactin²⁰ (8) is typical and contains four nonactic acid (9) subunits arranged in alternating enantiomeric order. The antibiotics in this group have large hydrophobic centres, which bind alkali metal cations, usually potassium, and transport these ions across biological membranes.



4. Cytochalasin Macrolides

The cytochalasin antibiotics are uniquely different from other macrolides in that the lactone is derived from a type of Baeyer-Villiger oxidation of the carbocyclic ketone at a late stage in the biosynthesis²¹ and for this reason possess 13 and 14 membered rings. Cytochalasin B (10), is a 14 membered lactone of this group which

show antibiotic, antitumour and cytostatic properties, and which induce ejection of the cell nucleus, production of polynuclear cells and platelet aggregation²².



Cytochalasin B (10)

5. Ansamycin Macrolides

The ansamycins²³ are a class of antibiotics sometimes referred to as macrolides, because of the similarity of the aliphatic segment in structure and stereochemistry to that of the "polyoxo" macrolides. They are characterised by possessing an aliphatic bridge linking two non-adjacent positions of an aromatic nucleus through an amide bond. The great number of antibiotics belonging to this class can be divided into two subclasses: those whose ansa bridge is attached to a naphthoquinone or naphthalene nucleus, represented by rifamycin S (11), and those whose ansa bridge is attached to a benzoquinone or benzene nucleus, represented by maytansine (12). Most of the ansamycins are noted for their broad spectrum antibacterial activity.

Synthesis.

1. General Strategy

There are three approaches to macrolide synthesis which

have been actively pursued over the years. These will be discussed briefly below, with emphasis on the advances made since 1977. When considering synthesis of a macrolide, three major problems have to be overcome: (a) construction of a medium- or large- sized lactone; (b) stereochemical control of several contiguous chiral centres; and (c) attachment of sugar residues.

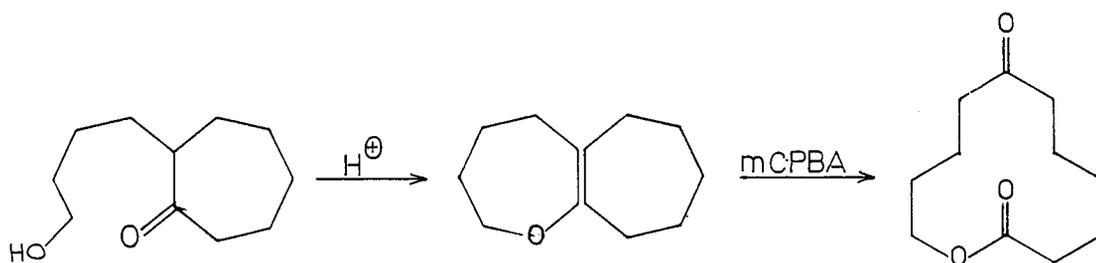
1a. Construction of the lactone ring.

Much effort has been expended in attempting to solve this most fundamental problem. Three uniquely different approaches have been adopted with varying success.

I. The Fragmentation approach.

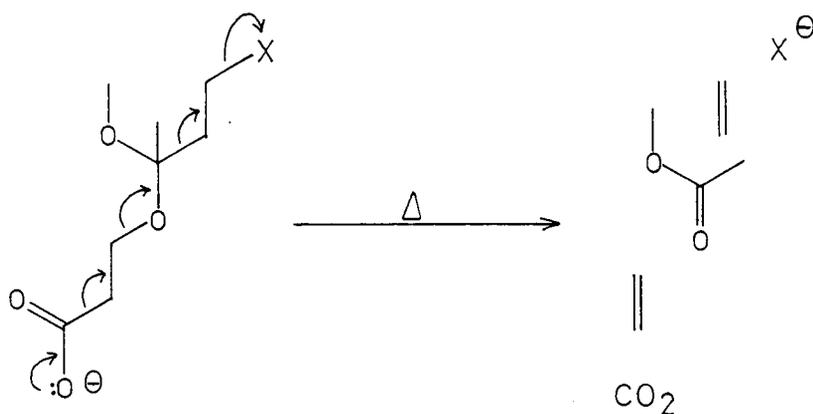
Creation of the lactone ring by oxidative cleavage of appropriate ring junctions of polycyclic precursors was considered at one time to be an extremely promising method of constructing large ring lactones. This principle, though successful on model compounds, was found to be impractical for substituted bicyclic compounds and has largely fallen into disfavour.

Borowitz²⁴ has demonstrated the efficacy of this approach on model systems, creating two of the functional groups of methynolide (Scheme 1). Although the fragmentation proceeds cleanly on the unsubstituted bicycle, the reaction becomes unpredictable with increasing substitution.



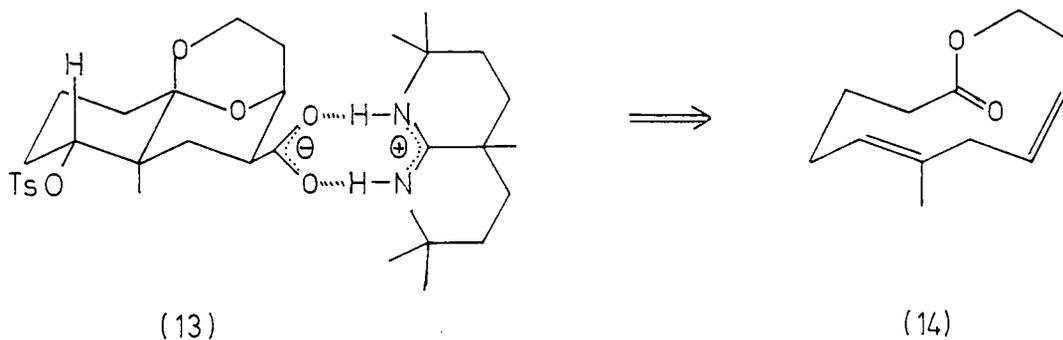
Scheme 1.

Eschenmoser has refined the approach into an elegant non-oxidative decarboxylative double fragmentation^{25,26}, summarised in Scheme 2.

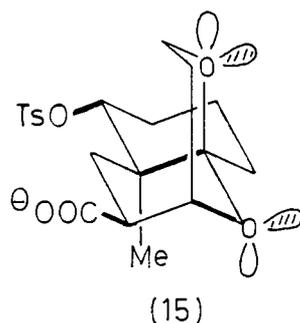


Scheme 2.

Heating an amidinium salt of the readily prepared acid (13) induced quantitative conversion into the twelve membered lactone (14).



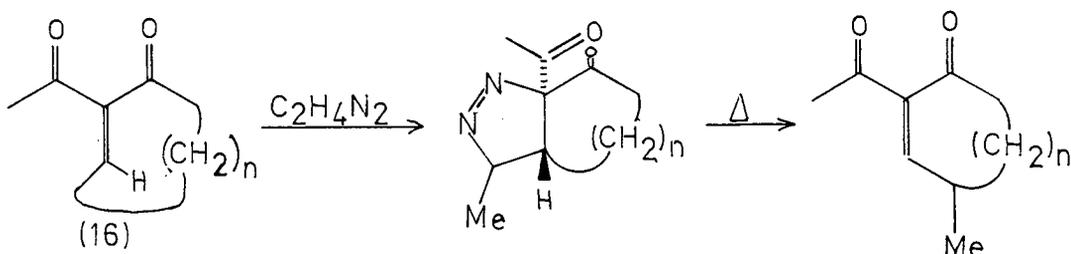
The representation (15) illustrates how the tricyclic acetal (13) is programmed to undergo this double fragmentation. The central c-c bridge is antiperiplanar to the equatorial tosylate group as well as to the two "equatorial" electron pair sp^3 lobes of the acetal function. In addition, the equatorial carboxylate group is antiperiplanar to one of the two acetal linkages. The conformations required for this type of fragmentation have been extensively studied by Deslongchamps²⁷ and his theories based on antiperiplanar relationships predict the feasibility of such a fragmentation. The effect of substitution on this double fragmentation have not thus far been reported.



II. Ring Growing Reactions

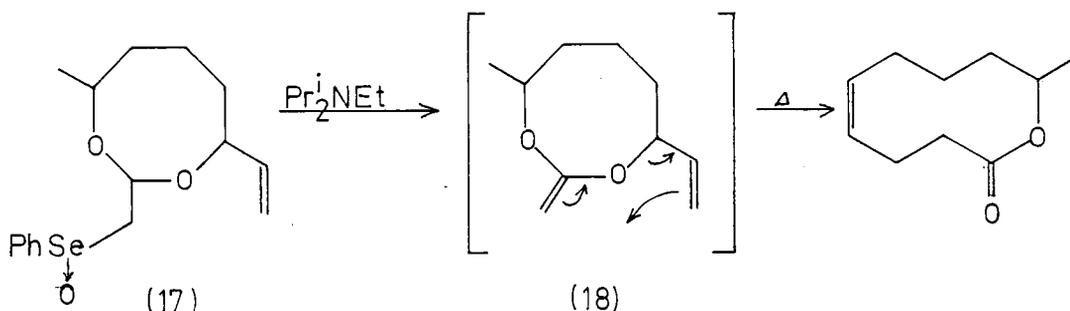
A 'ring growing' process can be visualised as the insertion of a small carbon unit into a functionalised ring system. For example one carbon atom can be inserted by Tiffeneau-Demjanov ring expansion. However, the process would have to be repeated many times to reach a ring of any significant proportion. Similarly, addition of diazoethane²⁸ to the enedione (16) enlarges the ring by one carbon after thermal elimination of nitrogen. This type of expansion (Scheme 2a)

runs into serious stereochemical problems if the sequence is repeated a number of times.



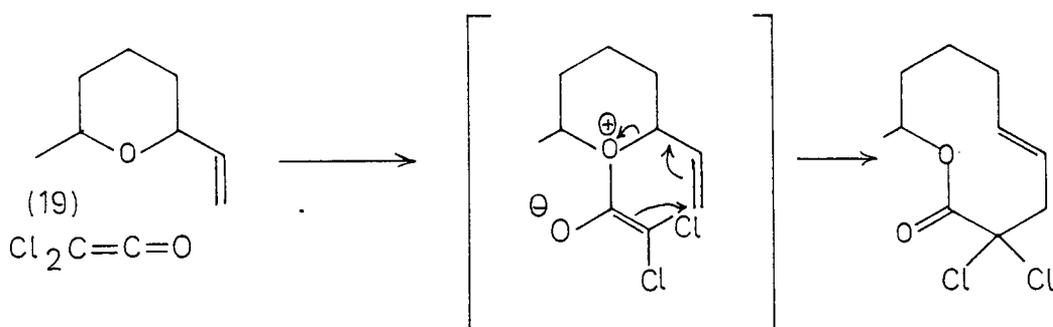
Scheme 2a

A more efficient method²⁹ in that two carbon atoms are introduced in one sequence involves Claisen rearrangement of a cyclic ketene acetal intermediate (18) which is formed by elimination of benzeneseleninic acid from acetal (17) (Scheme 3).



Scheme 3

A potentially useful sequence has been independently developed along similar lines³⁰. Claisen rearrangement is used to introduce four carbon atoms by a simple procedure (Scheme 4). The nucleophilic oxygen of (19) successfully competes with the double bond for the electrophilic dichloroketene. Thus, the 1,3 dipolar intermediate is well positioned for (3,3) sigmatropic rearrangement to a ten-membered lactone, which can be manipulated further.

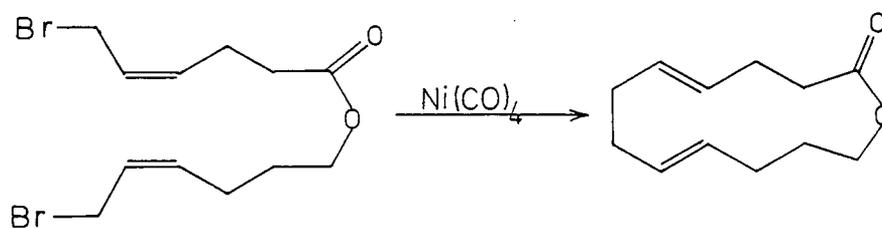


Scheme 4

The clearly defined cis and trans relationships of substituents about a six-membered ring spawned this approach. For larger than twelve-membered lactones, however, seven- and/or eight-membered ring precursors would have to be constructed. The conformational uncertainty of such ring sizes will very likely lead to considerable stereochemical problems, making this approach less widely applicable to macrolide synthesis.

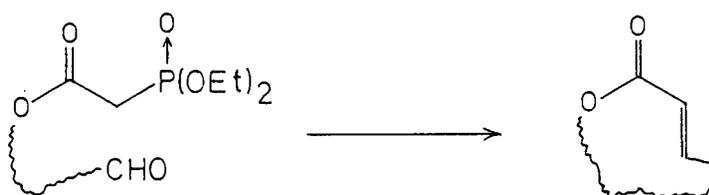
III. Cyclisation of an Acyclic Precursor.

This has been the method of choice in the synthesis of the macrolide antibiotics to date, although both entropy and polymerisation factors can tend to disfavour it. In recent years, numerous methods have been employed to effect cyclisation. Historically the first example of this approach utilised nickel tetracarbonyl to link the two allyl termini of an ester³¹ (Scheme 5). The necessity of creating asymmetric centres from the newly formed double bonds makes this method unattractive.



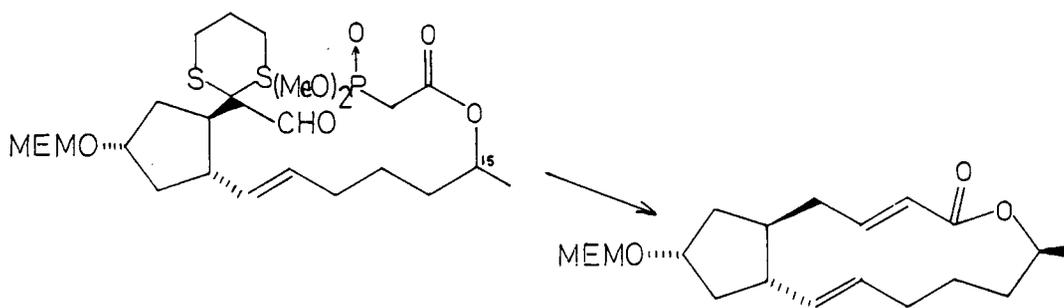
Scheme 5

Intramolecular ketophosphonate cyclisations^{32,33} have been used with success for the formation of α,β - unsaturated lactones. This approach is appealing in that it results in formation of the trans-olefin, normally the desired isomer (Scheme 6).



Scheme 6

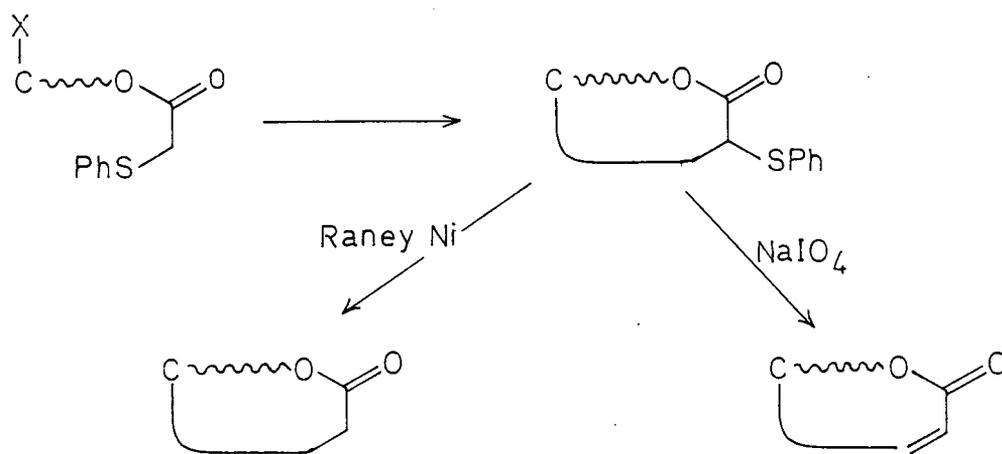
The utility of this cyclisation can be seen in a total synthesis of brefeldin A³⁴. The unnatural isomer at C-15 cyclised more rapidly than the natural isomer (Scheme 7) allowing easy separation of the C-15 epimers. Syntheses of carbomycin B^{72,73} and leucomycin A₃^{72,73} have also employed this cyclisation methodology.



Scheme 7

Another method of ring closure involving carbon-carbon bond formation³⁵ is based on intramolecular alkylation of a carbanion

generated from an ω -halogenoalkyl phenylthioacetate. Subsequent oxidative or reductive removal of the phenylthio group leads to unsaturated or saturated lactones respectively (Scheme 8). This rapid irreversible alkylation has been used to good effect in a recent synthesis of lasiodiplodin³⁶.



Scheme 8

Most efforts to cyclise acyclic precursors now centre on direct lactonisation of the macrolide seco-acid. The biosynthesis of macrolides often proceeds through this final lactonisation step. Apart from being more appealing aesthetically, the entire synthesis is simplified if the stereochemical problems associated with medium- and large- ring systems do not have to be confronted.

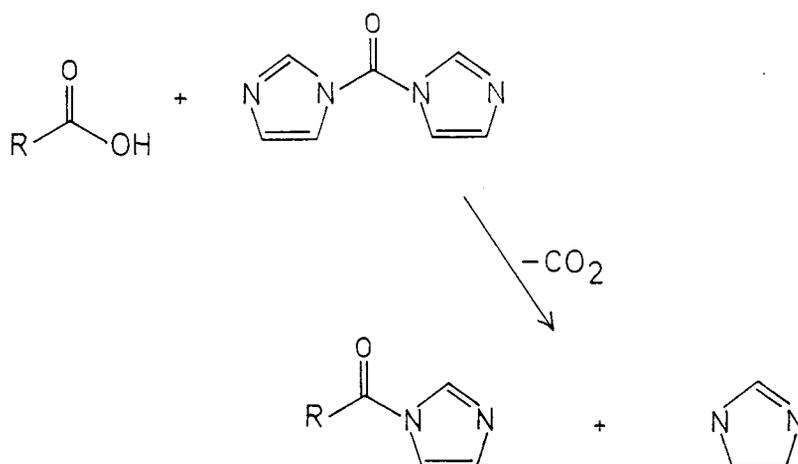
It was due, in large part, to Stoll's³⁷ very detailed investigations into intra versus intermolecular formation of esters from straight chain aliphatic ω -hydroxyacids that the direct lactonisation approach was viewed with such trepidation. The most common way to promote intra over intermolecular reaction is by use of high dilution techniques.

In cases where the reaction proceeds efficiently, slow addition of the hydroxyacid to the reaction medium can effectively simulate high dilution conditions.

One other important aspect should be considered at this point. Fewer available degrees of freedom will tend to favour intra over intermolecular reaction. Thus, cyclisation will be facilitated by increasing substitution on the backbone of the aliphatic chain. Macrolides are conformationally very rigid molecules and it is reasonable to expect that the corresponding seco-acid will retain, to a large extent, this same rigidity. As a consequence, lactonisation may be a more favourable process than initial experiments on unsubstituted systems indicated.

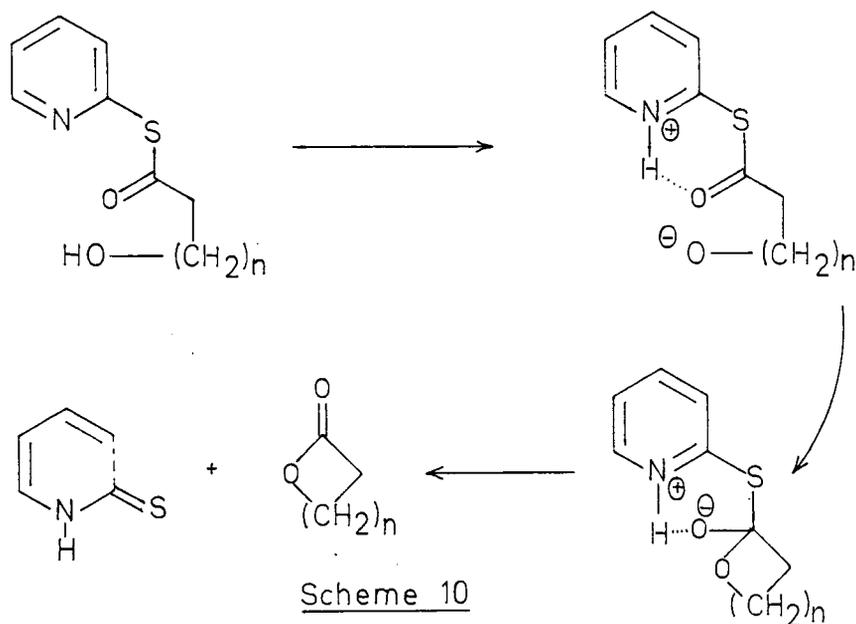
Intensive studies in this sector have led to many methods of effecting lactonisation. All these new methods rely to some degree on activation of the carboxylic acid moiety.

In 1962, Staab and Mannschreck³⁸ introduced a method of activating carboxylic acids towards ester formation with alcohols. The method involved reaction of the carboxylic acid with N, N'-carbonyldimidazole to furnish the imidazolide (Scheme 9). Reaction with an appropriate alcohol and a catalytic amount of base gave excellent conversion into the corresponding ester. This method was successfully applied in a synthesis of the macrolide pyrenophorin,^{38a} demonstrating for the first time the viability of the acyclic approach.



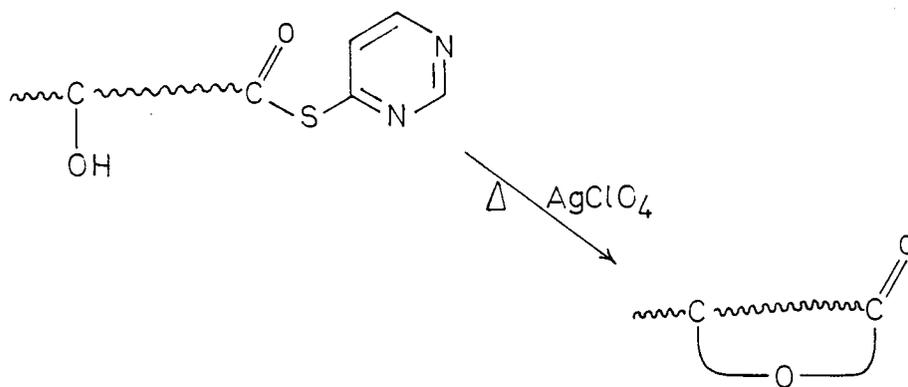
Scheme 9

Corey's 'double activation' method³⁹ uses a 2-pyridinethiol ester of a hydroxyacid to activate simultaneously the carboxyl and hydroxyl groups for mutual reaction. This is achieved (Scheme 10) by proton transfer from hydroxyl to carbonyl oxygen.



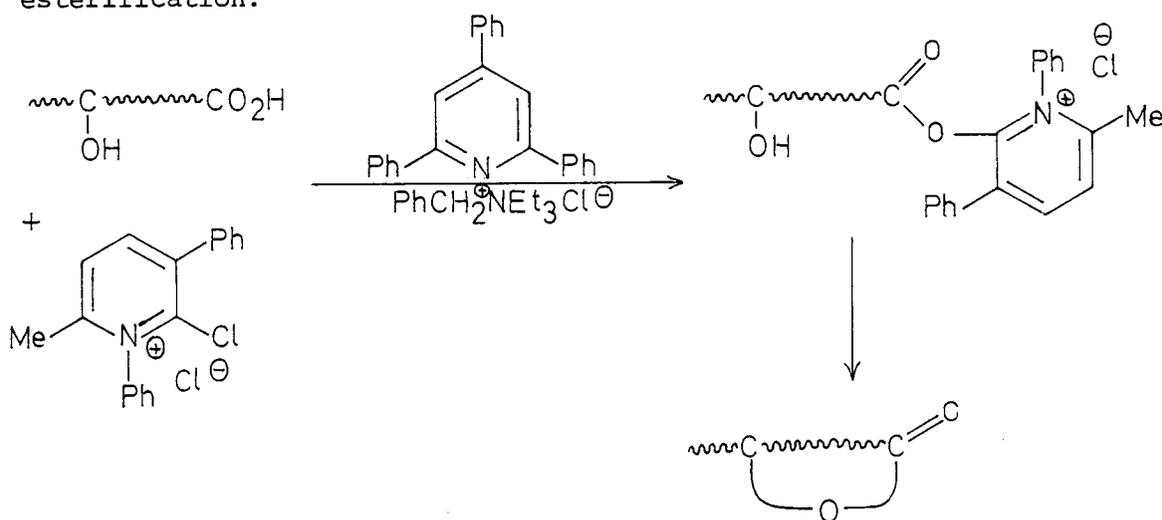
Scheme 10

Refinements to Corey's original procedure have led to milder conditions for the reaction; silver perchlorate allows lactonisation to proceed at room temperature⁴⁰. Likewise, silver ion promoted lactonisation of pyrimidinethiol esters of ω -hydroxyacids proceeds in good yield⁴¹ (Scheme 11).



Scheme 11

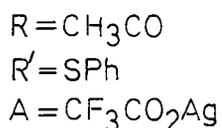
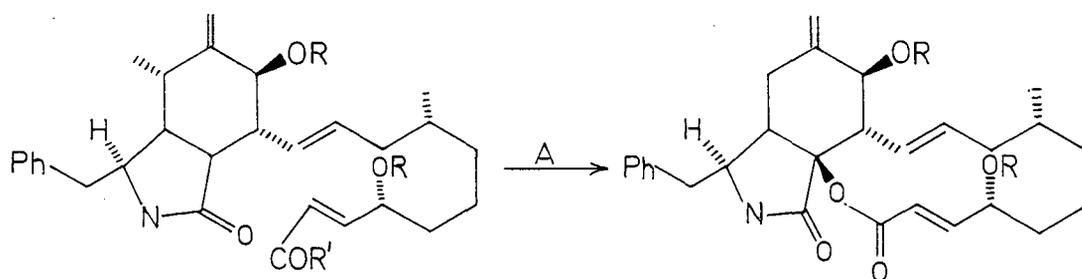
Mukaiyama has developed⁴² an efficient macrocyclic lactone synthesis, converting w-hydroxyacids into triphenylpyridinium esters; on treatment with base and in the presence of benzyltriethylammonium chloride, these esters afford exceptionally high yields of lactones (Scheme 12). This method is similar to the 'double activation' method, though here the greater steric protection to the carbonyl group of the acid reduces to some extent any competing intermolecular esterification.



Scheme 12

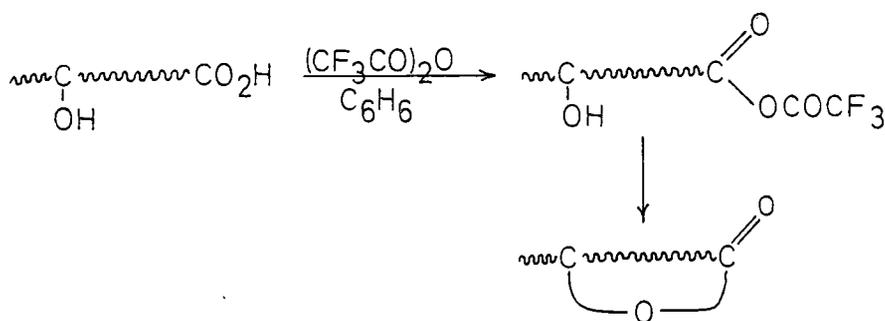
Masamune's method⁴³ for constructing macrocyclic lactones employs s-t-butyl thiol esters of w-hydroxyacids. Originally

mercuric trifluoroacetate was used as an activating agent, but the nondiscriminating reactivity of Hg(II) towards electron rich centres was disadvantageous. Other thiophilic cations [Ag(I), Cu(I), and Cu(II)] have proven to be effective catalysts for lactonisation^{43a}, and are considerably less prone to destroy the seco-acid. For example, attempted lactonisation of the seco-acid derived from cytochalasin with Hg(II) resulted in destruction of the hydroxyacid. However, by employing silver trifluoroacetate, the required lactone can be obtained in 40% yield (Scheme 13).



Scheme 13

Yamaguchi has improved the mixed anhydride method of carboxyl activation⁴⁴, first introduced⁴⁵ for construction of the macrocyclic ring of zearalenone. The Merck group used the mixed trifluoroacetic acid anhydride of the hydroxyacid, ring closure proceeding at room temperature (Scheme 14). The yields obtained by this procedure are generally only modest and the strongly acidic conditions employed make the method somewhat unattractive.

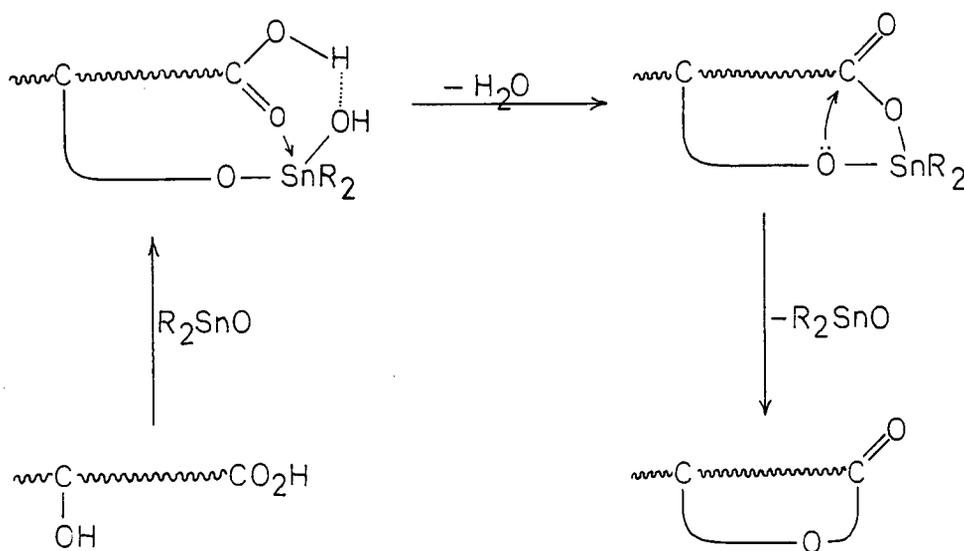


Scheme 14

In an improvement, the mixed 2,4,6 - trichlorobenzoic acid anhydride of the ω -hydroxyacid can be prepared from the acid chloride and triethylamine. After removal of the triethylamine hydrochloride, a solution of the mixed anhydride is added slowly to a refluxing solution of dimethylaminopyridine in toluene. This procedure has also been used for lactonisation of the seco-acid of methynolide⁶⁷, to be discussed later.

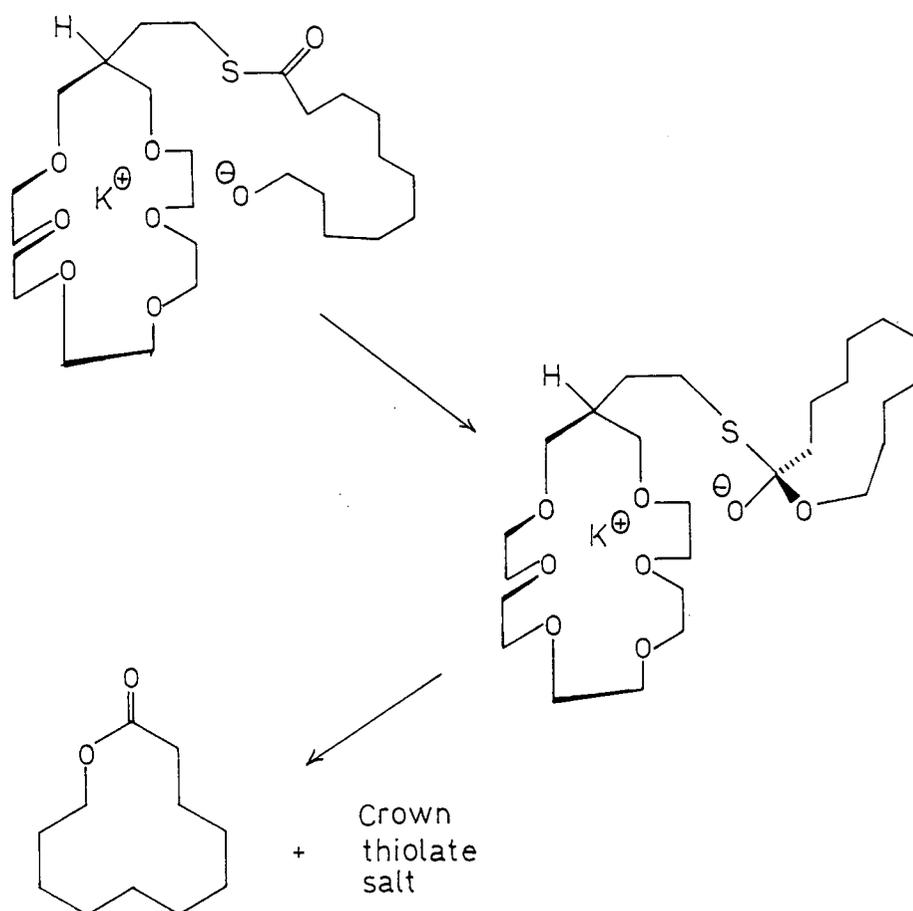
Other miscellaneous reports are available on lactonisation, but none have been tested on complex macrolides, so their general applicability is unclear.

Organostannyl oxides have been used as neutral esterification agents in the preparation of macrocyclic lactones and lactams⁴⁶. This method, depicted in Scheme 15, takes advantage of the ability of tin to enhance the nucleophilicity of heteroatoms bound to it, and of its capacity to expand its valency from four to five and six through coordination. The benefits of this method lie in the catalytic amounts of organotin oxides needed, the neutral conditions, and the lack of necessity for high dilution.



Scheme 15

Among other promising solutions to the problem of large ring lactonisation is the use of thiol-functionalised crown ethers⁴⁷. The thioesters derived from these crown ethers and ω -hydroxy carboxylic acids yield macrolides when treated with potassium *t*-butoxide (Scheme 16). The reaction proceeds via a templated conformation in which the ω -alkoxide is held proximate to the thioester through ionic bonding to the crown-bound potassium cation. By the very nature of this transition state, severe problems may occur on attempted cyclisation of 'polyoxo' macrolide seco-acids.



Scheme 16

With the problems of lactonisation of ω -hydroxy acids largely solved, efforts intensified to overcome the second problem; that of creation of numerous adjacent chiral centres.

CHIRALITY CONTROL

The most practical method for the creation of the seco-acid stereochemistry is to dissect the acid into two or more fragments. The synthesis then becomes much less foreboding, though the problem of combining the proper set of each enantiomeric isomer still exists. This can be overcome in at least three different ways: (a) both segments are resolved or asymmetrically synthesised and combined;

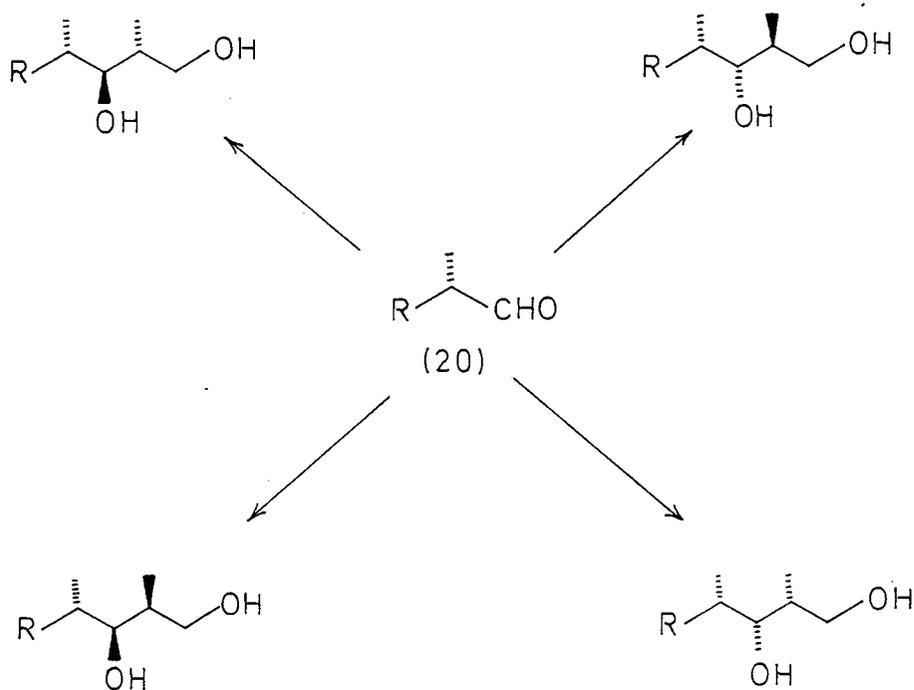
(b) one segment is resolved and used as a resolving agent for the other and; (c) the stereochemical information in one fragment is directly transmitted to the other via chemical reaction.

The effectiveness of the first two methods has been ably demonstrated by making use of the clearly defined cis - and trans - relationships of substituents on a cyclic system, but the third method shows most promise in that it would be closer to the enzymatic reaction and the number of sequences required to generate the contiguous chiral centres would be small. It is this concept which has stimulated tremendous activity in the last few years. With relevance to macrolide synthesis, the most efficacious approach is via enantioselective aldol condensations. The advanced state of the art is demonstrated in Masamune's synthesis of 6-deoxyerythronolide, to be discussed later.

THE ALDOL REACTION

In the ensuing section it is intended to contain discussion exclusively to the progress made in enantioselective aldol reactions. It is beyond the scope of this treatise to give a full account of stereocontrol in the synthesis of acyclic systems. An informative and extensive review exists on this subject⁴⁸, and an earlier review on asymmetric synthesis is also available⁴⁹. This enforced restriction precludes any detailed discussion on Kishi's solution to contiguous chiral control⁵⁰, which culminated in syntheses of monensin⁵¹ and

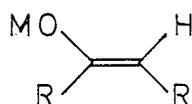
of rifamycin S⁵². Suffice it to say that by judicious choice of reaction conditions any one of the four stereoisomers depicted in Scheme 17 can be stereoselectively synthesised from the aldehyde (20).



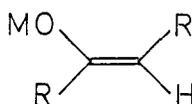
Scheme 17

At the outset one must define the nomenclature to be used. A modified⁵⁵ erythro/threo nomenclature will be adopted. The convention employed is as follows : if the main chain is written in an extended (zig-zag) conformation, the diastereomer which has two adjacent substituents on the same side of the plane defined by the main chain is designated erythro. When considering a given enolate geometry, the descriptors cis and trans rather than (Z) and (E) will be

used. While this may not be strictly accurate, in this limited area it does avoid the confusion which may result from the use of (Z) / (E) nomenclature. For example, and for the same enolate geometry, the sodium enolate may be (Z), whereas the corresponding lithium enolate would be (E).



trans

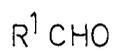


cis

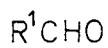
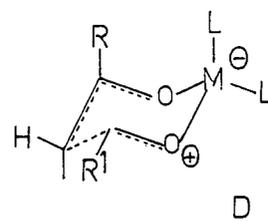
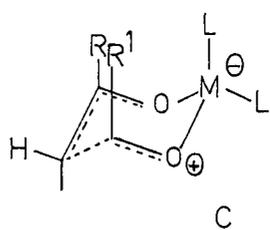
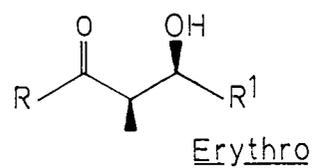
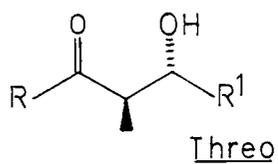
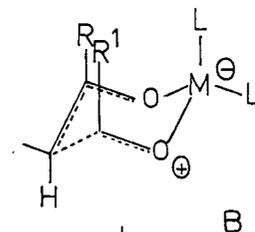
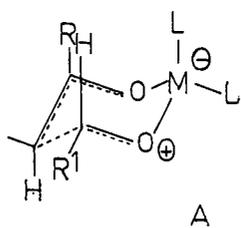
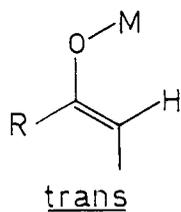
2,3-Stereochemical Control.

Early investigation by Dubois⁵³, House⁵⁴, and Heathcock⁵⁵ established that when an aldehyde is reacted with a ketone-derived enolate under equilibrating conditions, the thermodynamically more stable 2,3 - threo product predominates, regardless of the enolate geometry. If, however, the reaction is kinetically controlled, the cis and trans enolate isomers preferentially provide 2,3 - erythro and 2,3 - threo aldol products, respectively. An examination of these observations in terms of the commonly proposed 6 - electron pericyclic chair transition state⁵⁶ illustrated in Scheme 18 reveals that both trans and cis lithium enolates exhibit excellent kinetic threo and erythro product selection respectively, when the enolate substituent, R, is sterically demanding.

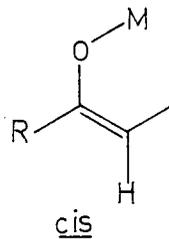
As R becomes less bulky, the stereoselectivity decreases, emphasizing the importance of the $R^1 \leftrightarrow R$ steric interaction.



+



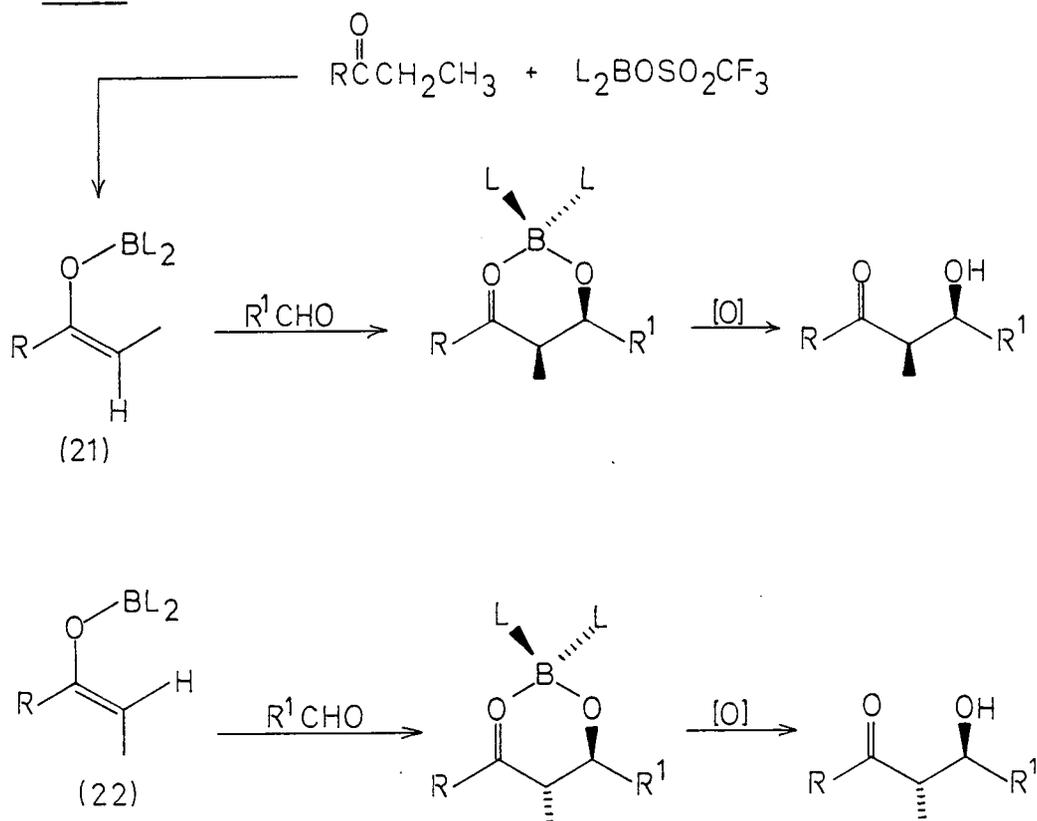
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Scheme 18

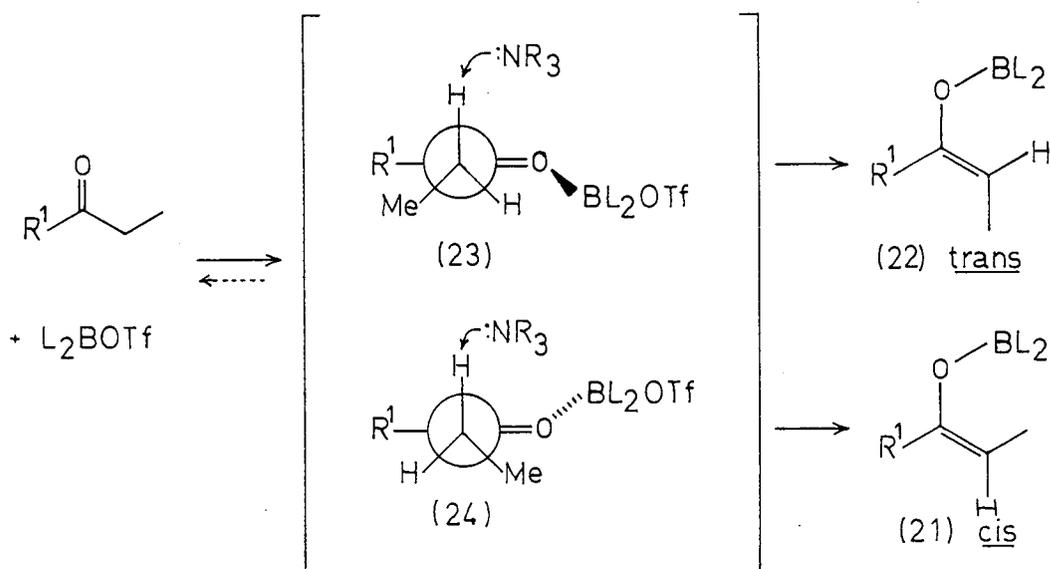
Thus, for example, for trans enolates transition state B is destabilised relative to A.

The necessity for R to be large for successful stereoselectivity was inconvenient. The situation was improved by Evans⁵⁷ and by Masamune⁵⁸ simultaneously. Enhancement of the stereoselectivity was attained by compressing the transition state, and by attaching bulky ligands to the metal. This was achieved using dialkyl boron enolates, maximising both the $R \leftrightarrow R^1$ and $R^1 \leftrightarrow L$ steric parameters. As has been stated, the stereochemical outcome of the aldol reaction is a consequence of enolate geometry. Thus (Scheme 19) cis boron enolates (21) give rise to erythro products, whilst trans boron enolates (22) lead to the threo isomers.



Scheme 19

What are not so clear, however, are the factors governing cis : trans enolate ratios. Evans^{57a} has forwarded the following rationalisation to account for kinetic deprotonation (Scheme 20).

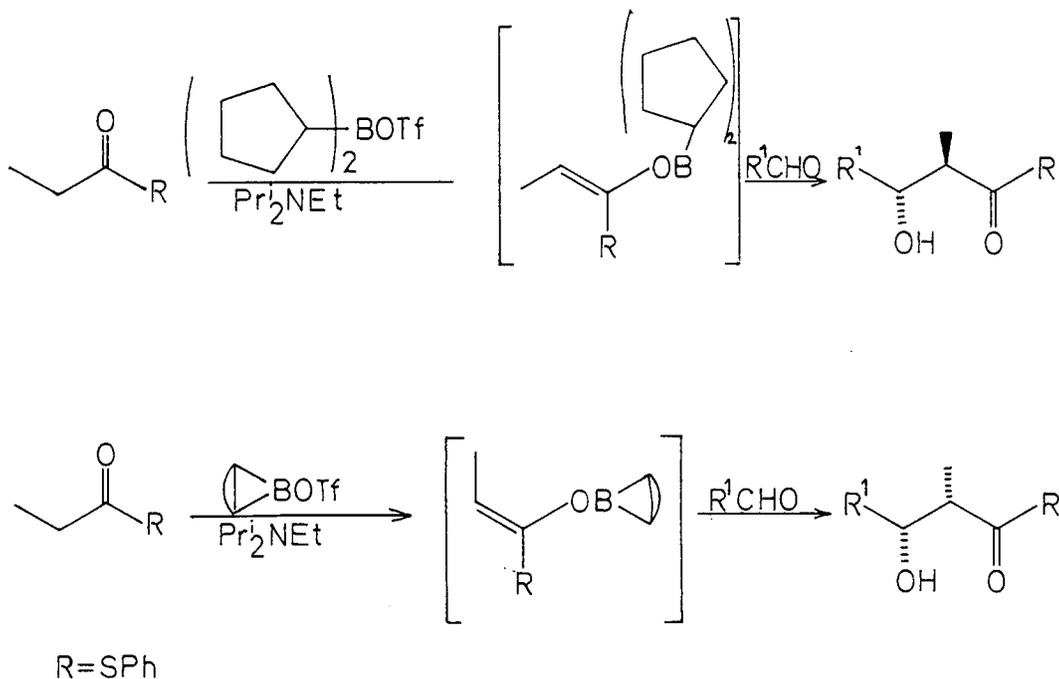


Scheme 20

1. Trans and cis enolates (22) and (21) are derived from deprotonation of syn and anti complexes (23) and (24) respectively.
2. Deprotonation, rather than complexation, is the rate determining step.
3. Anti deprotonation, (24) \rightarrow (21), is preferred on steric grounds over syn deprotonation, (23) \rightarrow (22), with hindered bases.

The observation that t-butyl thiopropionate ($\text{R}^1=\text{S}-\underline{\text{t}}\text{-Bu}$) forms predominantly the trans enolate is consistent with the expectation that complex (23) ($\text{R}^1=\text{S}-\underline{\text{t}}\text{-Bu}$) would be of lower energy than the alternative complex (24) ($\text{R}^1=\text{S}-\underline{\text{t}}\text{-Bu}$).

Interestingly Masamune has shown^{58d} that for phenyl thiopropionate ($R^1 = \text{SPh}$) and 9-BBN triflate selective cis - enolate formation must be inferred from the stereochemical outcome of the resultant aldol condensation. However, for the same thioester ($R^1 = \text{SPh}$) and dicyclopentylboron triflate the geometry of the enolates is reversed (ie, trans). This may well be due to the smaller steric demand of the 9-BBN complex and thus anti deprotonation (24) \rightarrow (21) is favoured. The dicyclopentylboron substituent, having a larger steric demand, will favour syn deprotonation (23) \rightarrow (22). Therefore the relative 2,3 - stereochemistry is easily manipulated by altering the co-ordinating ligand (Scheme 21).

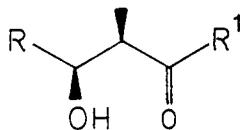


Scheme 21

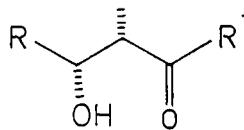
Enantioselective Aldol Condensation.

The scope of the aldol reaction in the synthesis of macrolide antibiotics would be greatly enhanced if the absolute configurations of the aldol products (25) and (26) could be

synthesised independently.

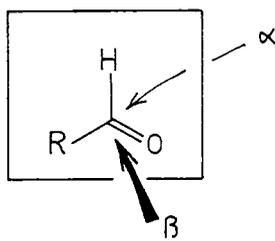


(25)



(26)

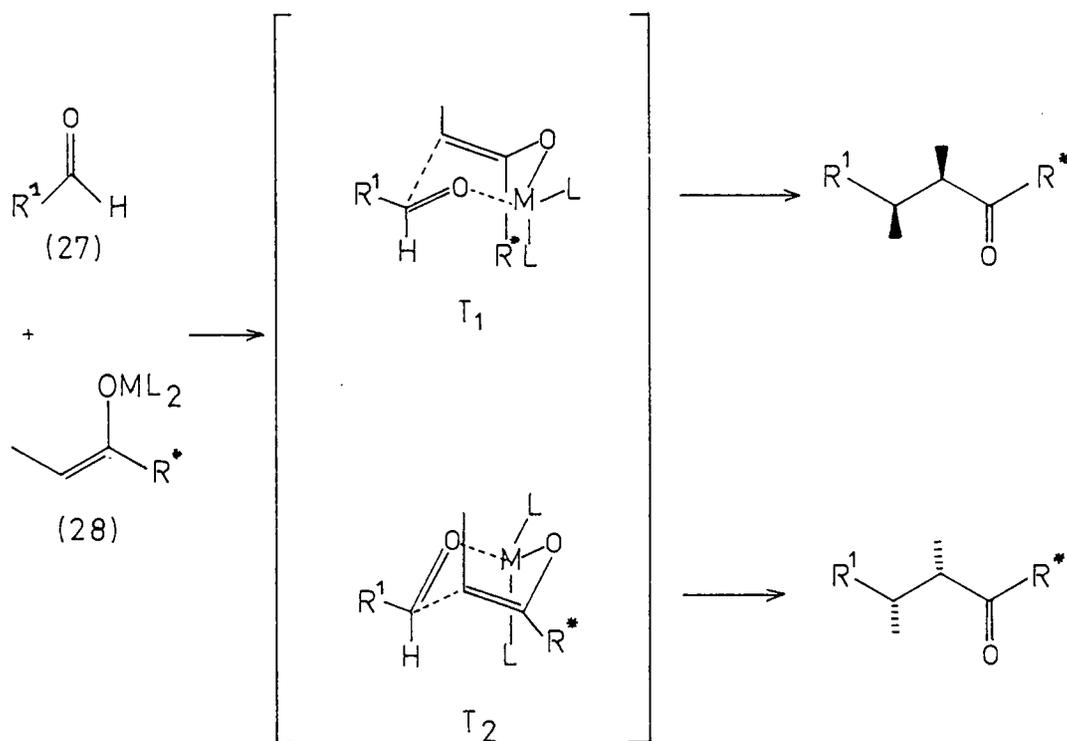
This has been achieved by Heathcock⁵⁹, by Masamune⁶⁰ and by Evans⁶¹. Utilisation of bulky chiral enolate ligands allows the absolute stereochemistry depicted in aldols (25) and (26) to be generated without contamination by other isomers. The stereochemical course of this reaction is very complicated. Assuming the commonly proposed 6-electron pericyclic transition state, then the absolute configuration of the product is determined by the preference of the chiral enolate to approach only one enantioface of the reacting aldehyde. If the aldehydic group is placed in the plane of the paper then the α -face is behind the plane and the β -face in front of the plane (27).



(27)

The absolute stereochemical outcome of the aldol is determined

by the preference for α - or β - face attack by a particular chiral enolate, whereas the relative stereochemical outcome is determined by the cis or trans geometry of the reacting enolate. This is illustrated in Scheme 22 for reaction with a cis enolate.



Scheme 22

Several factors influence the relative stability of transition state T₁ as compared to T₂. A combination of these will make the approach of the enolate more favourable to one enantioface than another. These factors include :

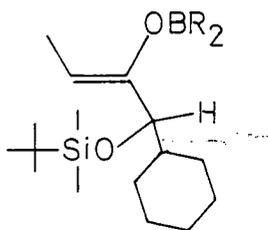
1. Steric or stereoelectronic effects exerted by substituents R¹ attached to the reacting aldehyde (27).
2. Intramolecular chelation of a hetero-substituent present in aldehyde (27) with the metal cation.

3. Chirality of the enolate (28).
4. Chiral ligands attached to the metal.

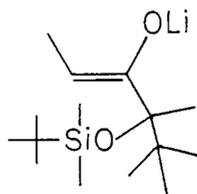
Reagents for achieving high 2,3- enantioselection have been independently developed, i.e. (29)⁶⁰, (30)⁵⁹ and (31)⁶¹.

These reagents should possess several properties :

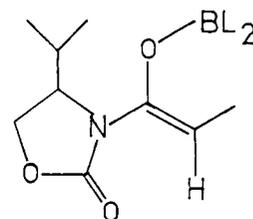
the parent ketone must be readily available; the group R* (28) must be large, so that the resulting enolate will show high erythro selectivity; R* must be easily convertible into OH or H; R* must be chiral.



(29),(R) and (S)

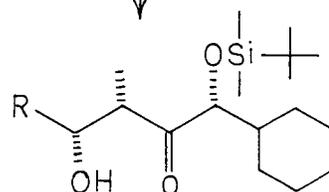
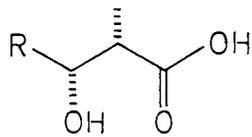
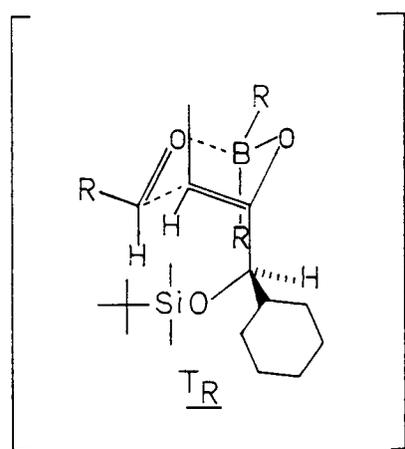
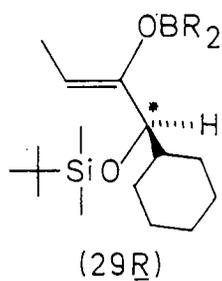
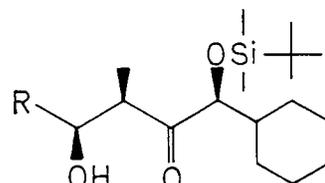
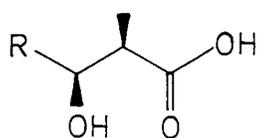
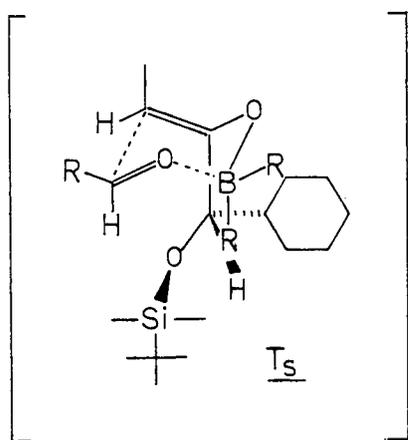
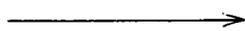
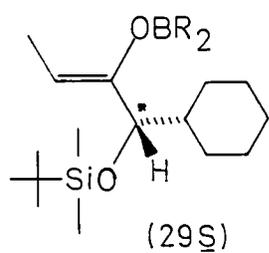


(30),(R) and (S)



(31),(R) and (S)

In general the enolates (29) and (31) give the most favourable results for the reasons advanced earlier. Enolates (29_S) and (29_R) are derived from (S) and (R)- mandelic acids respectively. Advantages of these reagents are facile preparation and ready convertibility into the carboxylic acids.



Scheme 23

In the transition states T_S and T_R (Scheme 23) proposed for the reaction of enolates (29 \underline{S}) and (29 \underline{R}) with an aldehyde, the substituents attached to the chiral centre (*) of the enolate reagent are so orientated as to minimise steric congestion. Interactions between the cyclohexyl moiety and the vinylic hydrogen and the ligands attached to boron are avoided as shown in T_S and T_R . Therefore the stereochemistry of the chiral centre dictates the approach of the enolate with respect to the aldehyde (approach to the α -face of the aldehyde as depicted in T_S , to the β -face as shown in T_R) which is translated into the absolute configuration of the final aldol product.

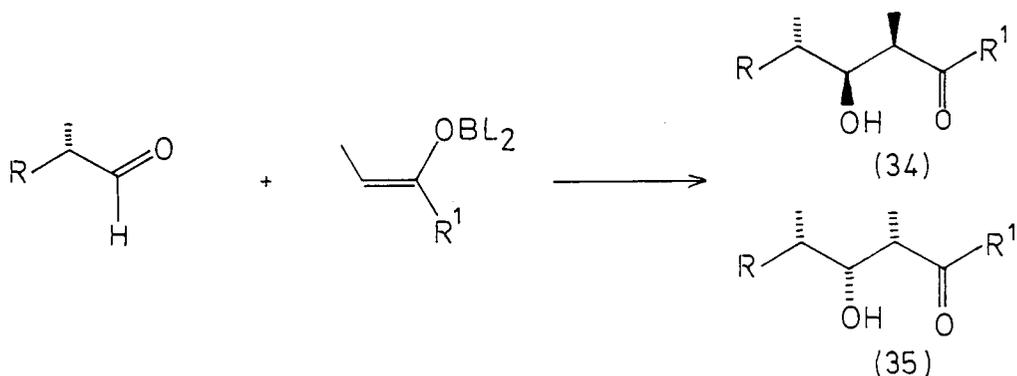
Identical arguments have been advanced by Evans²¹ to account for the aldol products obtained with the chiral oxazolidone imide enolate (31). However the stereochemical course of the aldol condensation is extremely complicated and the above rationalisations are at present only suggestive. Indeed of the aldol reaction Evans has written⁶¹:

" it will be a difficult task at best to sort out all the important control elements in these chirality transfer processes".

Nonetheless a working model has been established and the desired absolute stereochemistry (32) or (33) can now be prepared routinely.

3,4 - Stereochemical Control.

Reaction of an enolate with an α -chiral aldehyde involves further stereochemical problems, in that the 3,4 - stereochemistry can be either erythro or threo. Approach of a cis enolate to the α -face (Scheme 22) will give 2,3-erythro; 3,4-threo product (34) and approach of the same enolate from the opposite side (β -approach) will lead to the formation of 2,3-erythro; 3,4-erythro product (35) (Scheme 24).



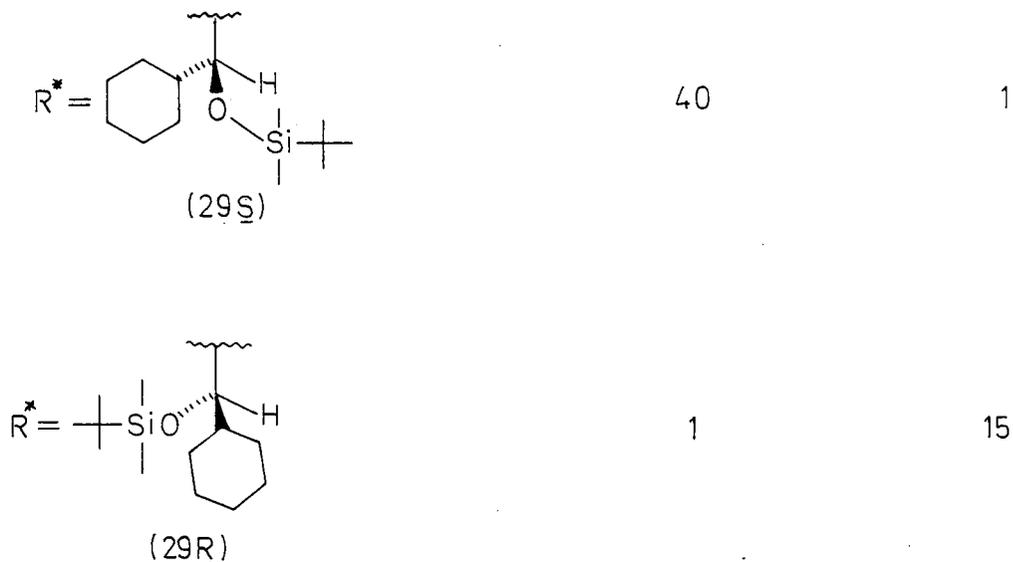
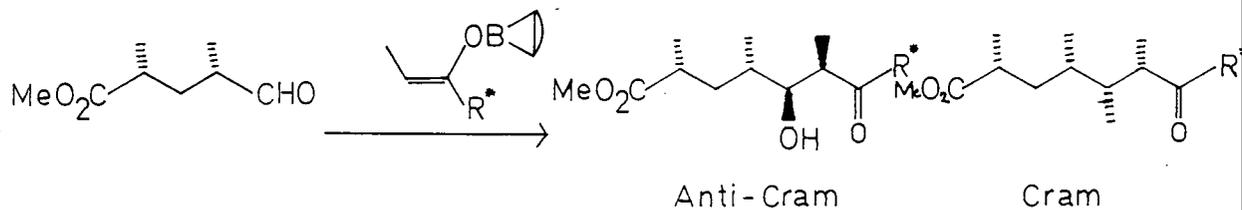
Scheme 24

If a 3,4-erythro product is formed the reaction is said to follow Cram's rule, with the product being termed the Cram product, and the aldehyde being called Cram-selective.

Attempted rationalisation of the 3,4-stereochemistry becomes inordinately complex, and for some results no rationalisation is available at present. The two most important considerations when predicting 3,4-stereochemistry are :

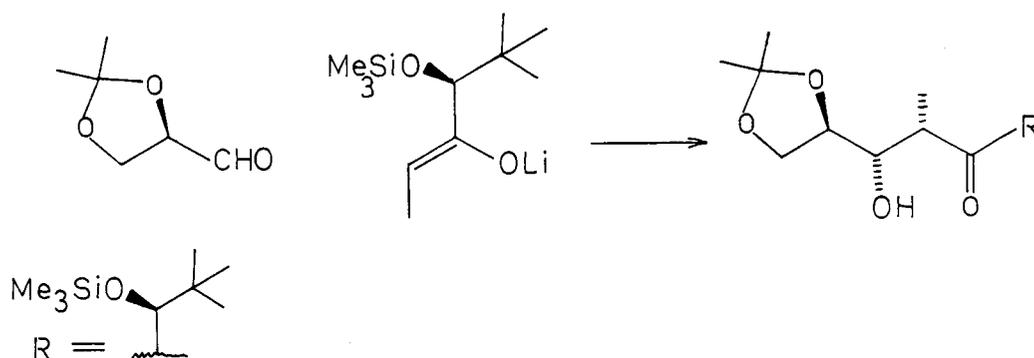
1. The preference of the aldehyde to be approached from its α -or β -face.
2. The preference of the enolate to approach the α -or β -face.

The factors governing these considerations are unclear, and though Cram's acyclic model can account for some results, the features causing an aldehyde to be anti-Cram selective are not known. However if these two propensities can be encouraged to act in consort then excellent 3,4-erythro (Cram) or 3,4-threo (anti-Cram) stereoselectivity can be achieved. The aldol condensations illustrated below (Scheme 25) are given by way of example; different aldehydes will afford different ratios.



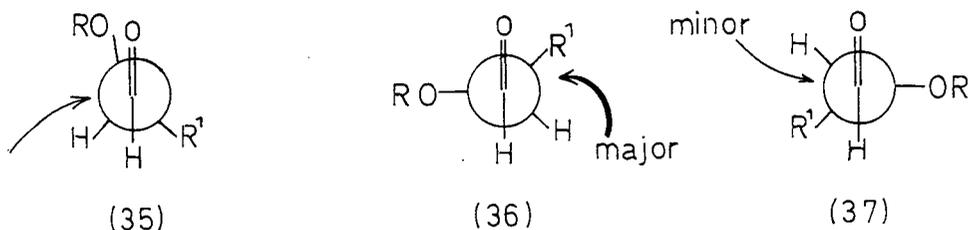
Scheme 25

The addition of lithium enolates to α -alkoxy aldehydes has been thoroughly investigated by Heathcock⁶². It has been demonstrated that Cram's 'cyclic model'⁶³ is not followed (35); instead, Felkin's model⁶⁴ for asymmetric induction (36) can be successfully applied to account for the predominance of anti-Cram product (Scheme 26).



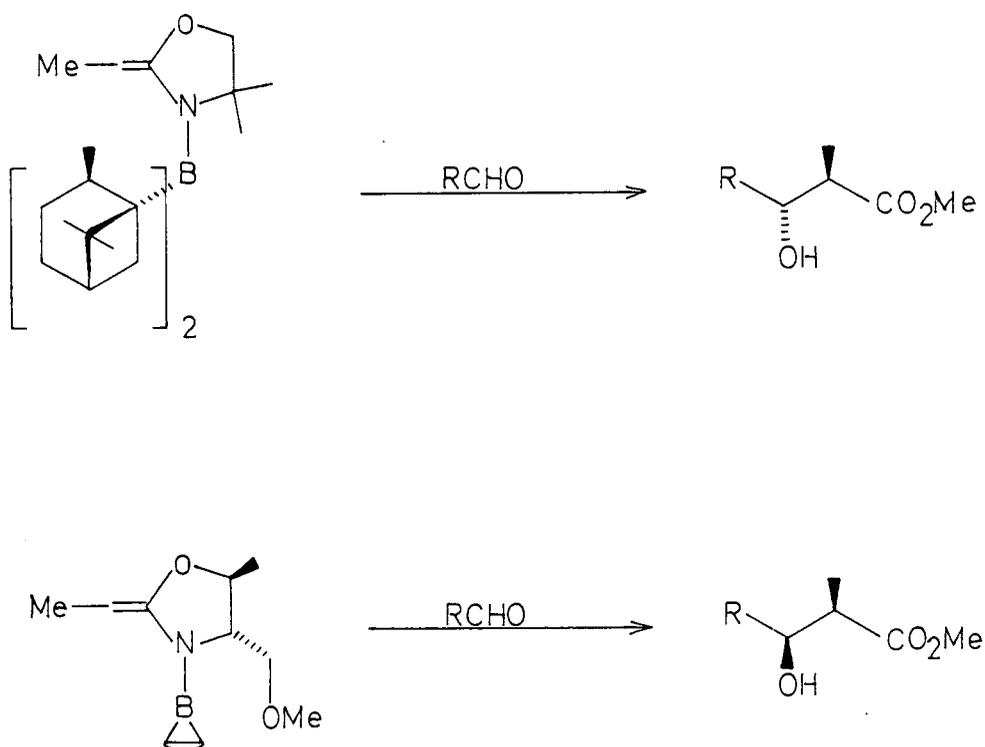
Scheme 26

Felkin's model predicts a strong preference for transition states in which the entering nucleophile is antiperiplanar with the larger substituent bond to the asymmetric carbon (36) and (37). Anh and Eisenstein have advanced⁶⁵ theoretical support for Felkin's model, arguing that the 'larger' substituent is the one with the lower energy $\sigma_{C_2X}^*$ orbital. By this criterion, OR will always be 'larger' than alkyl or aryl.



In summary, most of the practicalities involved in enantioselective aldol condensation have been worked out, although all the relevant control elements are still unclear. A practical model is now available in that the absolute 2,3- and 3,4-stereochemistry can be predicted with some confidence.

Meyers⁶⁶ has recently reported enantioselective aldol reactions with high threo or erythro selectivity using boron azaenolate addition to aldehydes (Scheme 27). The overall yields in this system are only moderate, but the aldol transition states previously discussed do not seem to give a clear indication of the process. It is suggested that boatlike rather than chairlike transition states should also be considered.

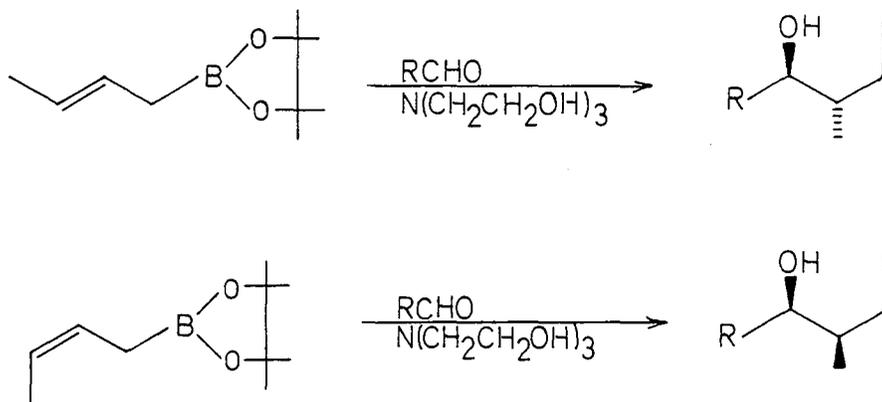


Scheme 27

Aldol diastereoselection has also been achieved via zirconium enolates^{67,68}, where both cis and trans zirconium enolates give rise to erythro products. Clearly the 'chairlike' transition state is insufficient to rationalise these findings, and it is speculated that a trans zirconium enolate reacts preferentially via a 'boat' transition state while the corresponding cis enolate proceeds through a 'chair' transition state.

For aldol reactions with acid⁶⁹ or ester⁷⁰ enolates HOMO-LUMO interactions have been applied to account for the erythro:threo ratios, and it is suggested that these interactions may have some relevance for ketone derived enolates.

Reaction of crotylboronates with aldehydes⁷¹ (Scheme 28) is another promising method for the synthesis of these systems with (E)-crotylboronates forming threo homoallylic alcohols and (Z)-crotylboronates the erythro counterpart.



Scheme 28

Total Synthesis.

In this section a few selected syntheses of the 'polyoxo' macrolide antibiotics will be discussed briefly. Flow diagrams outlining some of the achievements are provided; in the interests of clarity, much practical detail is omitted. Since the first synthesis of methymycin⁷² in 1975, there have been a further two successful syntheses of methynolide^{73,74}. In addition, syntheses of erythronolide A⁷⁵, and B⁷⁶, 6-deoxyerythronolide⁷⁷, carbomycin B^{78,79}, leucomycin A₃^{78,79} and erythromycin⁸⁰, have all been brought to a satisfactory conclusion. In addition, Kishi's synthesis of rifamycin S has been reported⁵²; this will not be discussed here, nor will the approaches to rifamycin S described by Corey⁸¹.

Methymycin, synthesised by Masamune and his team⁷², was the first total synthesis of an 'authentic' macrolide antibiotic¹. The synthetic strategy is outlined in Chart I, with little regard for the practical difficulties involved. Attention should be focussed on a few details which, unique at the time, have now been adopted routinely for the synthesis of these molecules. The intermediacy of the Prelog-Djerassi lactonic acid (38) is highly desirable, in that it possesses four of the chiral centres of methymycin, while allowing differentiation of the two carboxylic acid groups (one is masked as the δ -lactone). The other key feature is the process of lactonisation, achieved by Hg (II) activation of the hydroxycarboxylic thiol ester (39). It was this lactonisation method which made the synthesis a landmark in

Methymycin — Masamune 1975.

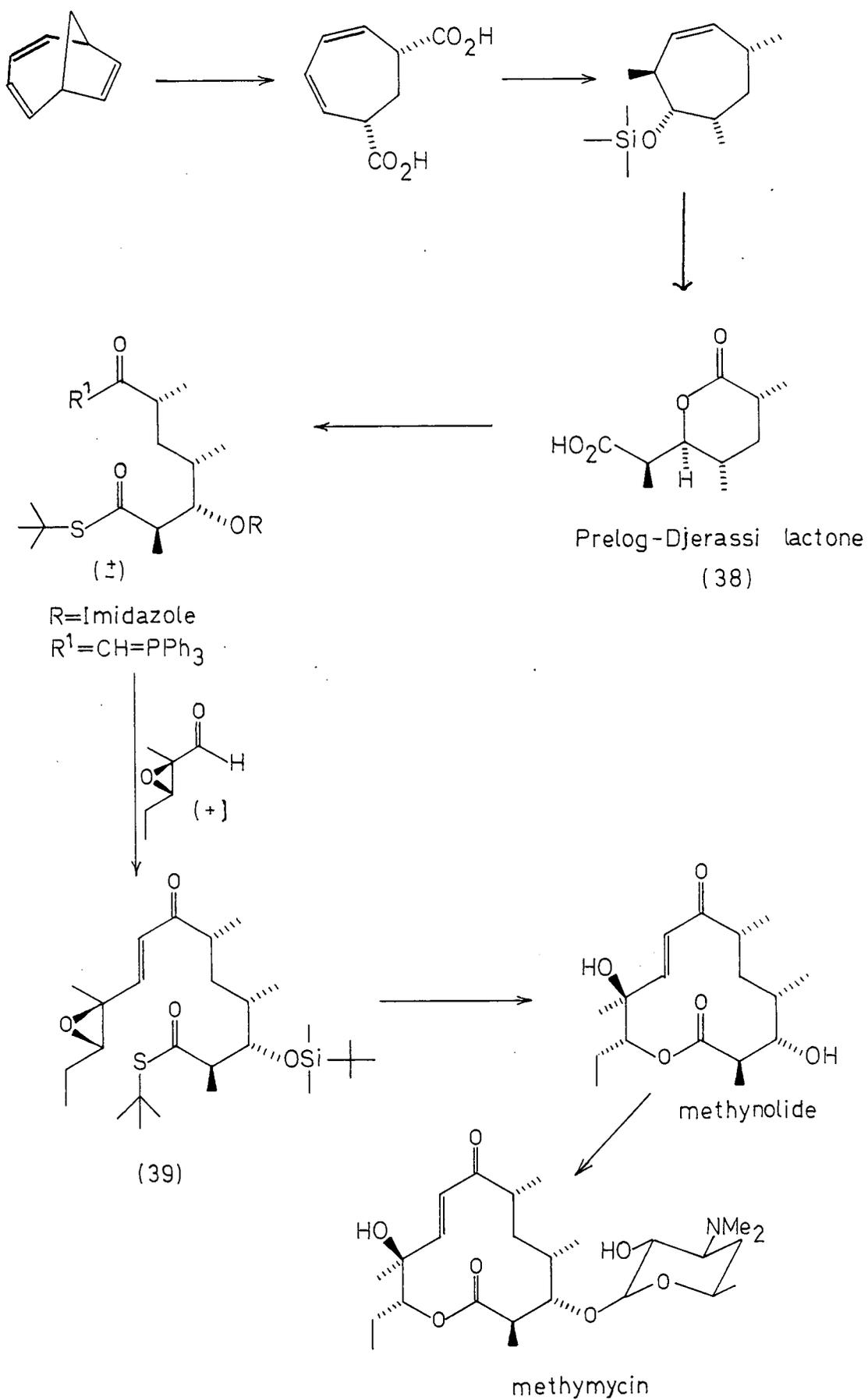


Chart 1

its field. At that time, methods had been developed to permit lactonisation of long chain hydroxy acids, but apart from pyrenophorin^{38a} limited information was available on the lactonisation of functionalised w-hydroxy acids. Adversely affecting this approach was the fact that the seco acid could only be obtained by total synthesis, and not through a conversion of the natural product, as world supply in 1974 was about 500 mg.

The Prelog-Djerassi lactone, intermediate in the above synthesis, is a key degradation product of methymycin, having been isolated independently by Prelog⁸² and by Djerassi⁸³ in 1956. Its stereochemistry was established in 1970 by Rickards and Smith⁸⁴. This lactone has become a stereochemical touchstone in the synthesis of these antibiotics. There are now eleven syntheses of this important lactone⁸⁵, but most of these will not be discussed here.

Methynolide has also been synthesised by Yamaguchi⁷³ and his co-workers. Their approach is outlined in Chart II. This synthesis also involved the key Prelog-Djerassi lactone, prepared in rather poor yield from meso-dimethylglutaric anhydride (40). Lactonisation was achieved by the mixed anhydride method.

In the same year Grieco and his group completed a synthesis of methynolide⁷⁴ seco-acid. The synthetic approach proceeded through a cleverly conceived route to the Prelog-Djerassi lactone (Chart III) and thereafter to the seco-acid (41).

Methymycin — Yamaguchi 1979

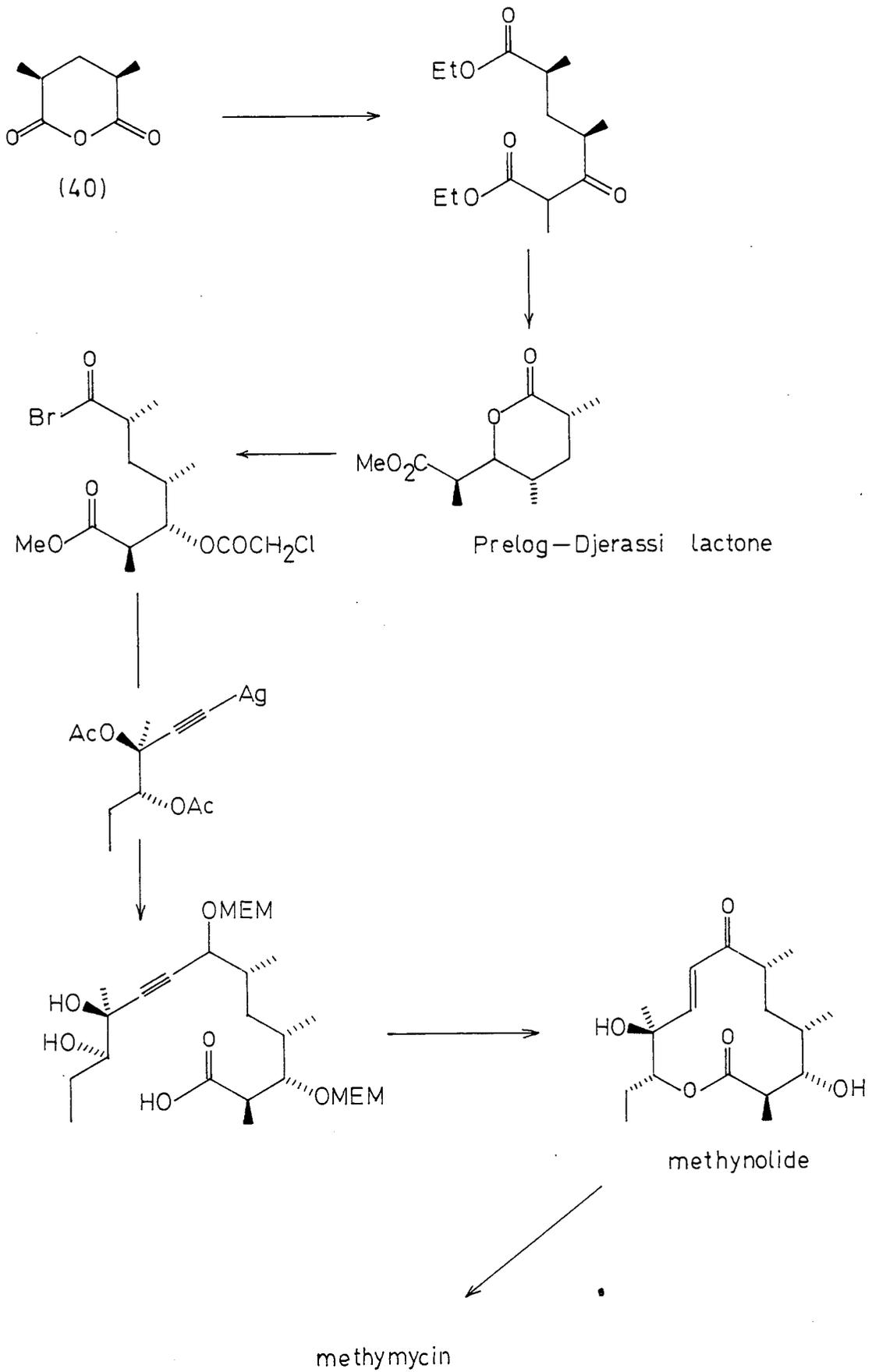


Chart II

Methymycin — Grieco 1979

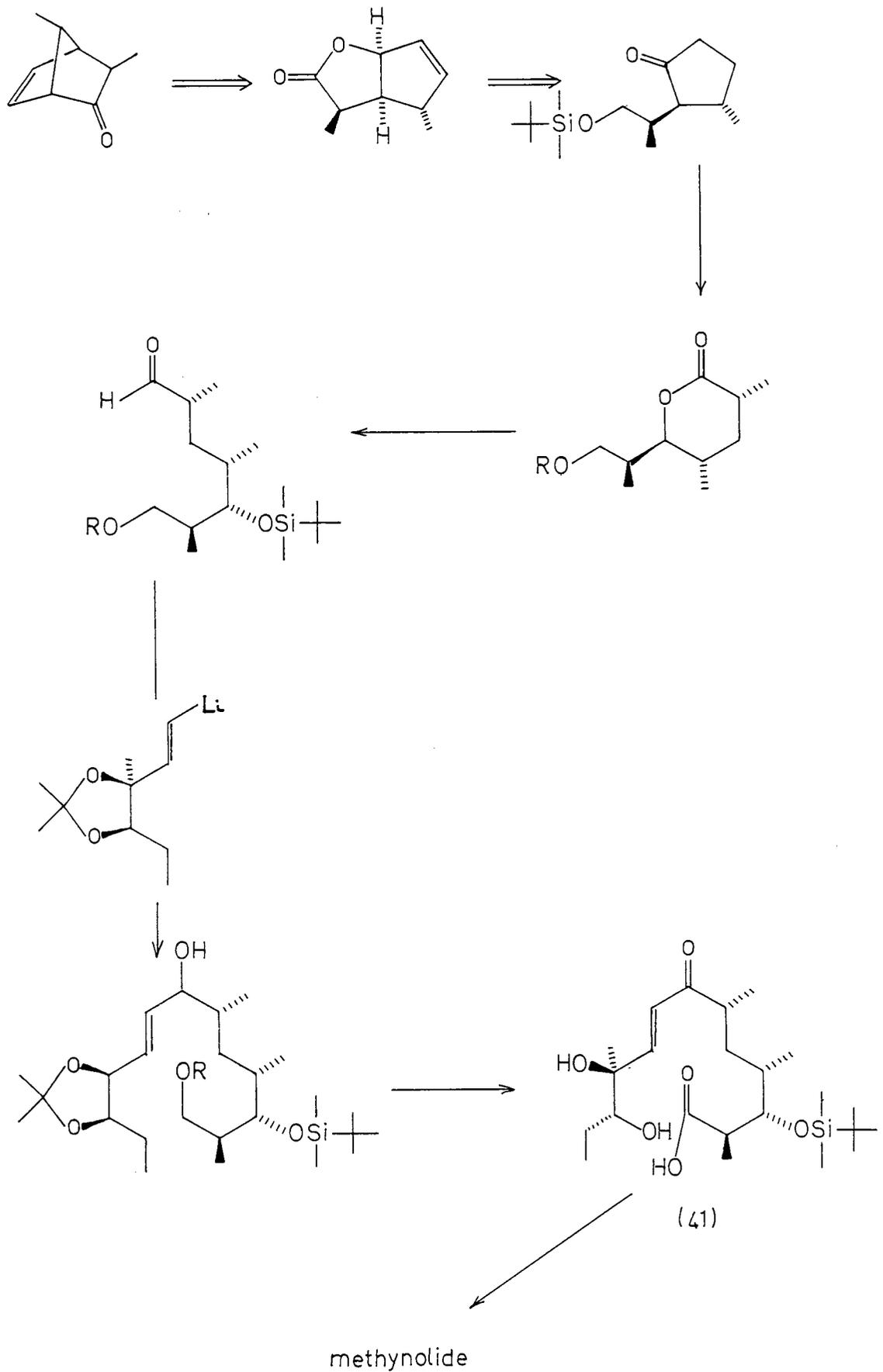


Chart III

Erythronolide A and B

The first total syntheses of the 14-membered macrolide aglycones erythronolide B⁷⁶ and A⁷⁵ were reported by Corey and his team at Harvard (Chart IV). These syntheses are patterned on the same basic plan and for this reason, only that of erythronolide B is discussed. Stereocontrol was exercised primarily with cyclic intermediates, prior to cleavage to the acyclic lactonisation substrate (Chart IV). Stereocontrol at C-2 through C-8 was established by the construction of a bicyclic lactone (41) from the dienone (42). After suitable deprotection/protection steps, the thiol ester (43) was cyclised to the 14-membered lactone. The remaining chiral centres were then introduced, taking advantage of the conformational rigidity of the ketal-bridged ring system. The conformations in Chart IV are chosen purely for convenience and clarity of presentation.

Erythronolide A, differing only in a single hydroxyl function from erythronolide B, proved much more difficult to synthesise due to its instability in protic media; extensive experimentation was required to overcome these problems.

Erythronolide B Corey 1978

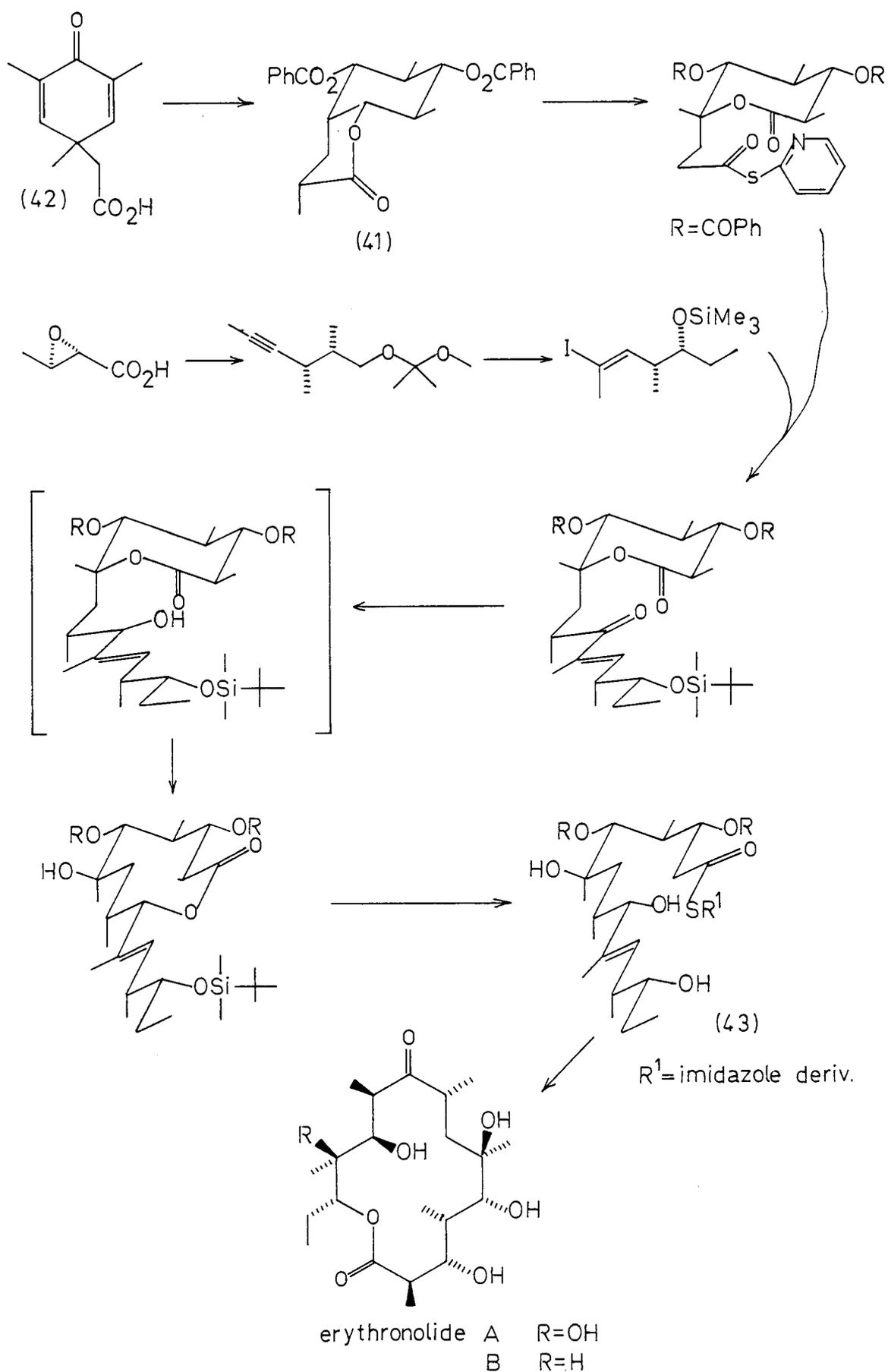
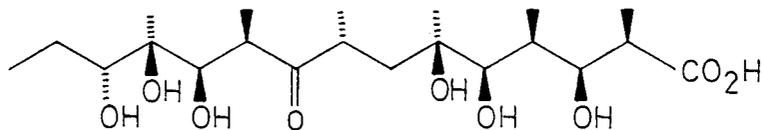


Chart IV

Erythromycin.

The first completed synthesis of erythromycin itself is due to Woodward⁸⁰ and represents a magnificent feat of tenacity, epitomising the problems inherent in macrolide synthesis and their successful solution.

Assuming that a macrolactonisation was feasible, and that the sugars, (L)-cladinose and (D)-desosamine, could be attached later, the problem was reduced (as in Corey's synthesis) to the construction of an appropriate derivative of erythronolide. A seco-acid (44).



(44)

A common intermediate, the cis-fused dithiadecalin (45), (Chart V) was used ingeniously for the construction of both the C-3 through C-8 and C-9 through C-13 portions of the seco-acid. The bridging sulphur atoms introduce sufficient structural rigidity to permit the stereospecific operations required, yet desulphurisation provides the desired acyclic system possessing methyl groups at the required locations. The aldol reaction of (46) with the enolate of t-butyl thiopropionate provided the Cram product exclusively, with

Erythromycin Woodward 1981

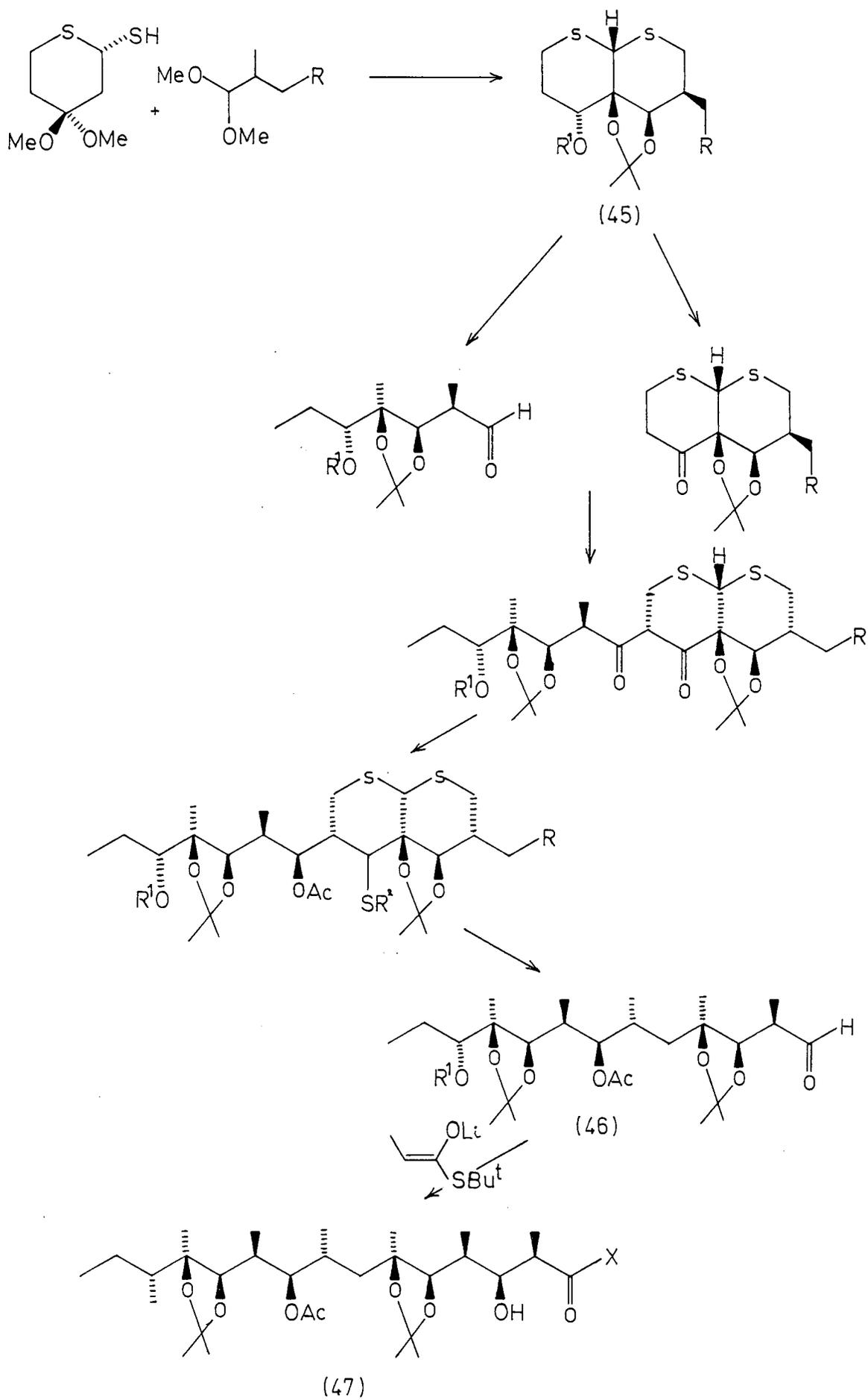
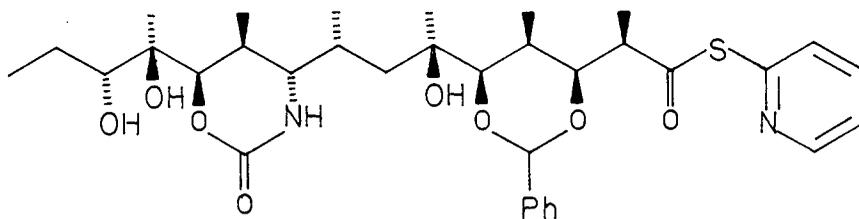
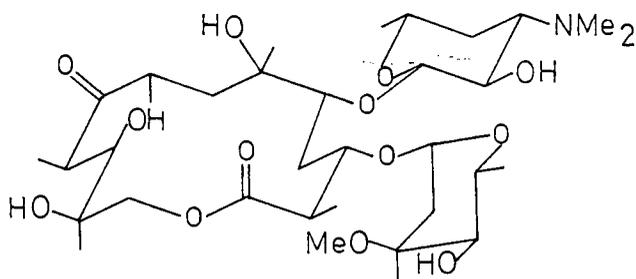


Chart V



(48)

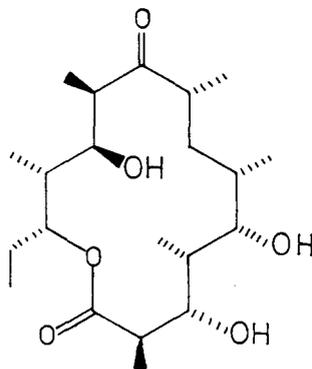


Erythromycin (49)

the wrong stereochemistry at C-2. This was inverted by deprotonation/kinetic protonation. The optically active intermediate (47) proved to be a poor lactonisation substrate; after extensive investigation (17 different analogues were tried) analogue (48) was found to lactonise in good yield. This thorough study seems to indicate that certain structural features are mandatory for efficient lactonisation. These structural essentials probably arise from conformational requirements for lactonisation, allowing the seco-acid to adopt a conformation similar to that of the corresponding lactone. Thus lactonisation, subsequent modification and finally attachment of the sugar residues completed the synthesis of erythromycin (49).

6-Deoxyerythronolide B.

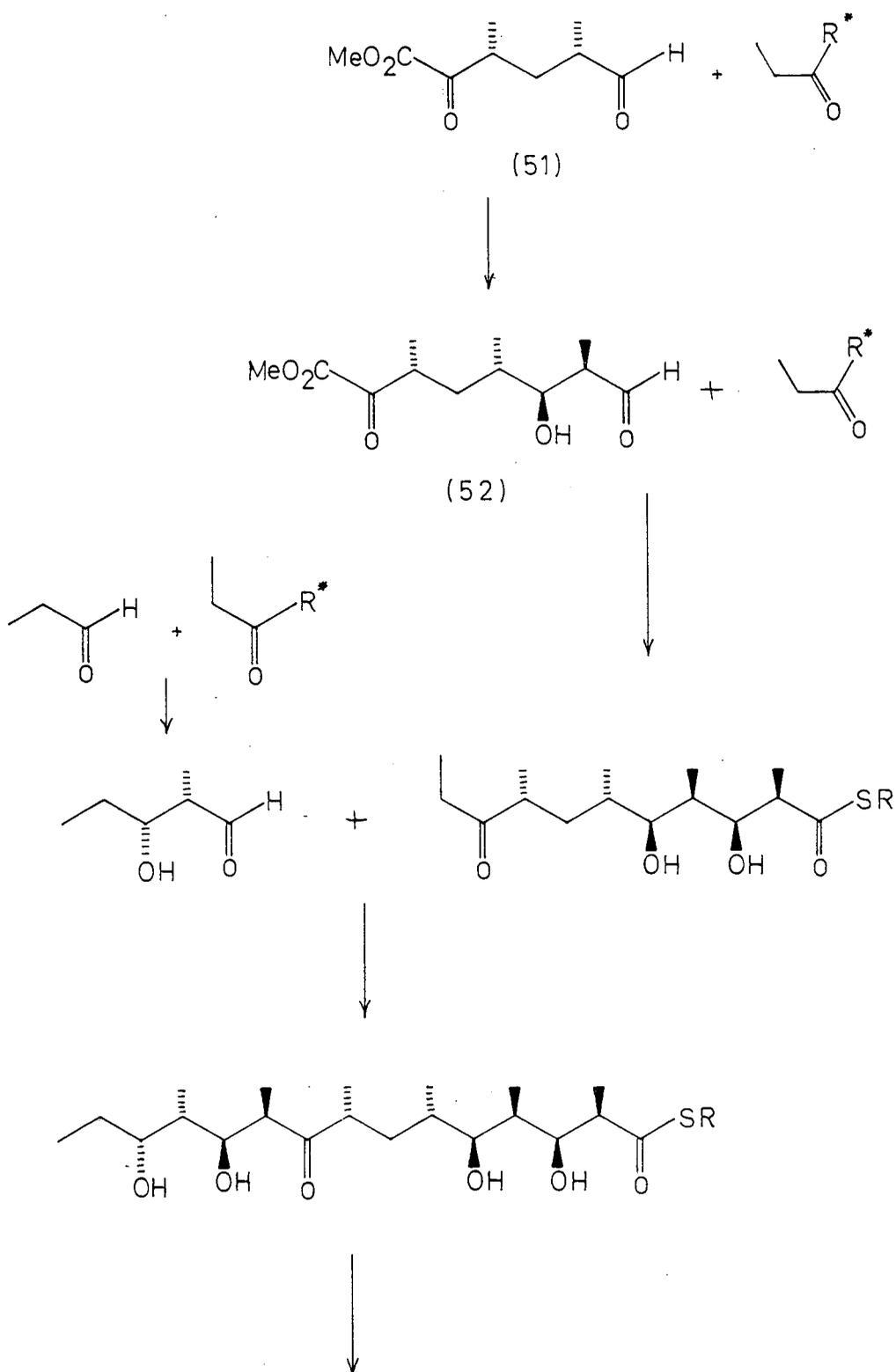
6-Deoxyerythronolide B (50), the biogenetic precursor of all the known erythromycins, is a tempting synthetic target⁷⁷.



(50)

Masamune's approach employed the construction of chiral chain segments from acyclic precursors. Assuming once again that

6-Deoxyerythronolide B - Masamune 1981



6 Deoxyerythronolide B

macrolactonisation is feasible, the problem is reduced to the synthesis of the seco-acid (53), (Chart VI). This synthesis demonstrates the level to which control of the aldol reaction can be exercised; the total number of steps used to create ten chiral centres is relatively small.

The synthesis proceeded via the Prelog-Djerassi lactone (52), prepared from the aldehyde (51) by one enantioselective aldol reaction. By this method, this important intermediate was prepared in optically pure form, simplifying existing syntheses which required approximately twelve steps. The appropriately protected and activated seco-acid was cyclised using copper (I) trifluoromethanesulphonate to afford 6-deoxyerythronolide (50) after deprotection steps.

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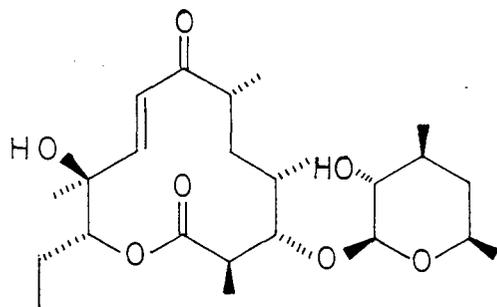
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e. S. Masamune, Sk.A.Ali, D.L. Snitman, and D.S. Garvey, *Angew. Chem. Int. Ed. Engl.*, 1980, 19, 557.
f. R.E. Ireland, and J.P. Daub, *J. Org. Chem.*, 1981 46, 479.
g. S. Jarosz, and B.F. Reid, *Tetrahedron Letters*, 1981, 2533.
h. In addition refs 71, 72, 73 and 77.

RESULTS AND DISCUSSION 2

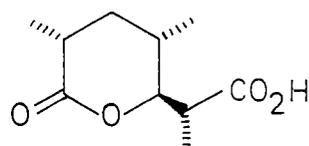
Background

The macrolide antibiotic methymycin (1) was first isolated¹ from a cultured broth of a *Streptomyces* species, later identified² as *Streptomyces venezuelae*. It was the first of the macrolides to have its structure determined³, with stereochemical studies not being completed⁴ until 1970.

Oxidative degradation of methymycin yields the lactonic acid (2) isolated independently by both Prelog⁵ and Djerassi⁶ in 1956. The stereochemistry of this acid (2), and hence of methynolide, was incorrectly assigned⁷ in 1963, apparently^{4a} due to mistaken identification of synthetic with authentic material. In 1970 its full stereochemistry was correctly formulated by Rickards and Smith⁴.



(1)



(2)

The defences of the macrolides against total synthesis are robust indeed, as has been discussed; nonetheless, there are now three reports describing the total synthesis of methymycin^{8,9,10}.

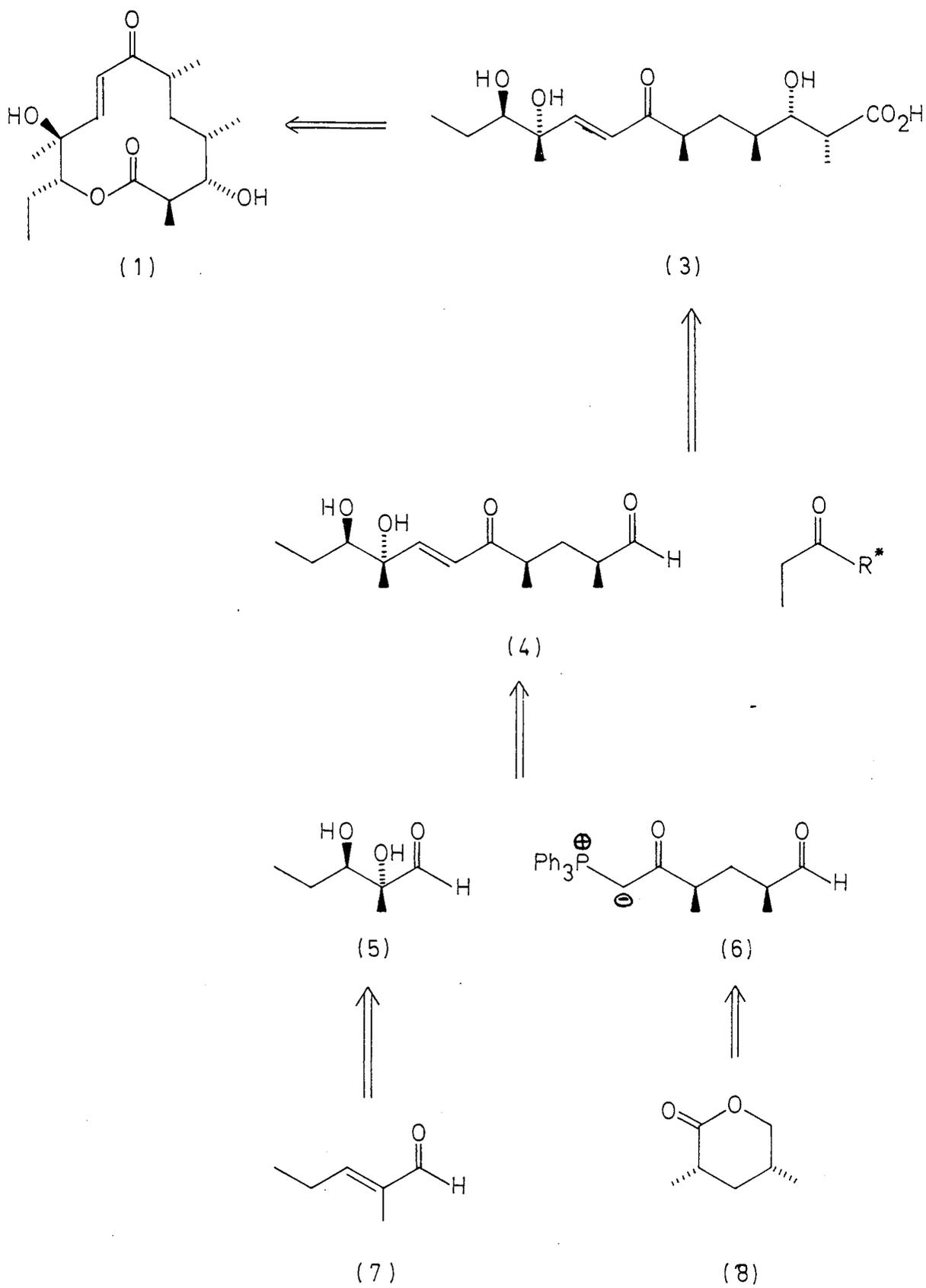
An examination of the complexity of methymycin indicates that a total synthesis would clearly be challenging. As such, it should result in increased knowledge of existing synthetic processes and could lead to new methodology. At the time these investigations were initiated¹¹, no total synthesis of the 'polyoxo' macrolides had been described. Since then, Masamune's landmark achievements⁸ have brought these complex molecules within reach.

The first total synthesis of the aglycone of methymycin, methynolide, proceeded through the Prelog-Djerassi lactonic acid(2) culminating in a macrolactonisation process (page 197). Studies by others have led to syntheses of methynolide⁹ and of methynolide seco-acid¹⁰ (page 199), again with the Prelog-Djerassi lactone as a synthetic cornerstone.

Below is described a strategy conceptionally quite different from those previously reported, in as much as the Prelog-Djerassi lactone (2) is not involved as a crucial building block.

Synthetic Planning

The proposed synthetic route to methynolide was formulated by now standard retrosynthetic analysis. Assuming that a macrolactonisation was feasible, the problem is reduced to the synthesis of the seco-acid (3). It was anticipated (Scheme 1) that this could be generated by a stereoselective aldol reaction on the aldehyde (4), thereby creating two asymmetric centres. Disconnection of aldehyde (4) at the olefinic linkage reveals



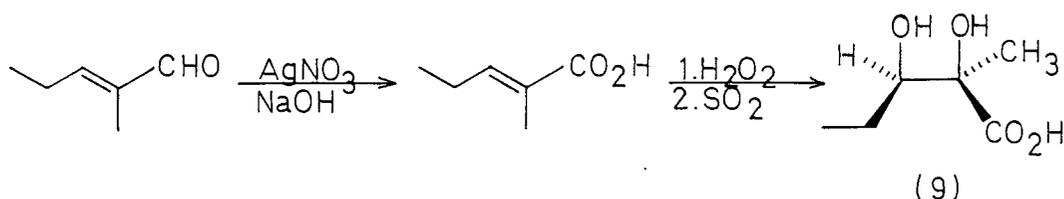
Scheme 1

aldehydes (5) and (6) as the major subgoals. Routes to these aldehydes were conceived from the α, β -unsaturated aldehyde (7) and α, γ -dimethyl- δ -valerolactone (8) respectively.

Aspects of the chemistry of the aldehydes (5) and (6) will be discussed separately and in the final section the crucial intermediate (4) will be discussed. Initially, aldehydes (5) and (6) are used in racemic form. Optically pure aldehyde (5) should be obtainable from the corresponding resolved acid¹². Thus aldehyde (5) can then itself be used to resolve the intermediate (4), leading finally to the correct enantiomer of methynolide. Rather than waste material on tedious resolution procedures, the synthesis proceeded with racemic compounds secure in the knowledge that optically active material was obtainable.

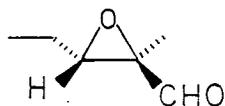
Synthon (5)

The acid (9) has proved to be an important intermediate in the synthesis of macrolide antibiotics, having been used in three total syntheses^{8,9,10}. The first synthesis of the acid (9) was described by Bergel'son¹² in 1962, and is outlined in Scheme 2.



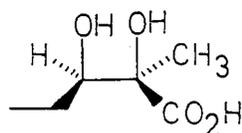
Scheme 2

Masamune^{8a} followed this procedure in preparing the 'left-hand' fragment of methymycin. The acid (9) was resolved as its salt with L-(+)-threo-2-amino-1-(4-nitrophenyl)-1,3-propane diol. A series of transformations then produced the optically pure epoxide (10) which when combined with the 'right-hand' fragment (derived from synthetic Prelog-Djerassi lactone) led ultimately to methymycin.

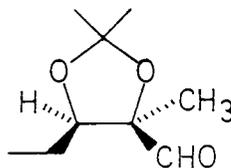


(10)

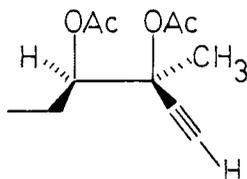
Yamaguchi^{9a} also prepared the acid (9) by the method of Bergel'son, converting it further into the isopropylidenedioxy aldehyde (11). Subsequent elaboration furnished the acetylene (12) which was combined with the Prelog-Djerassi lactone and so to methynolide.



(9)

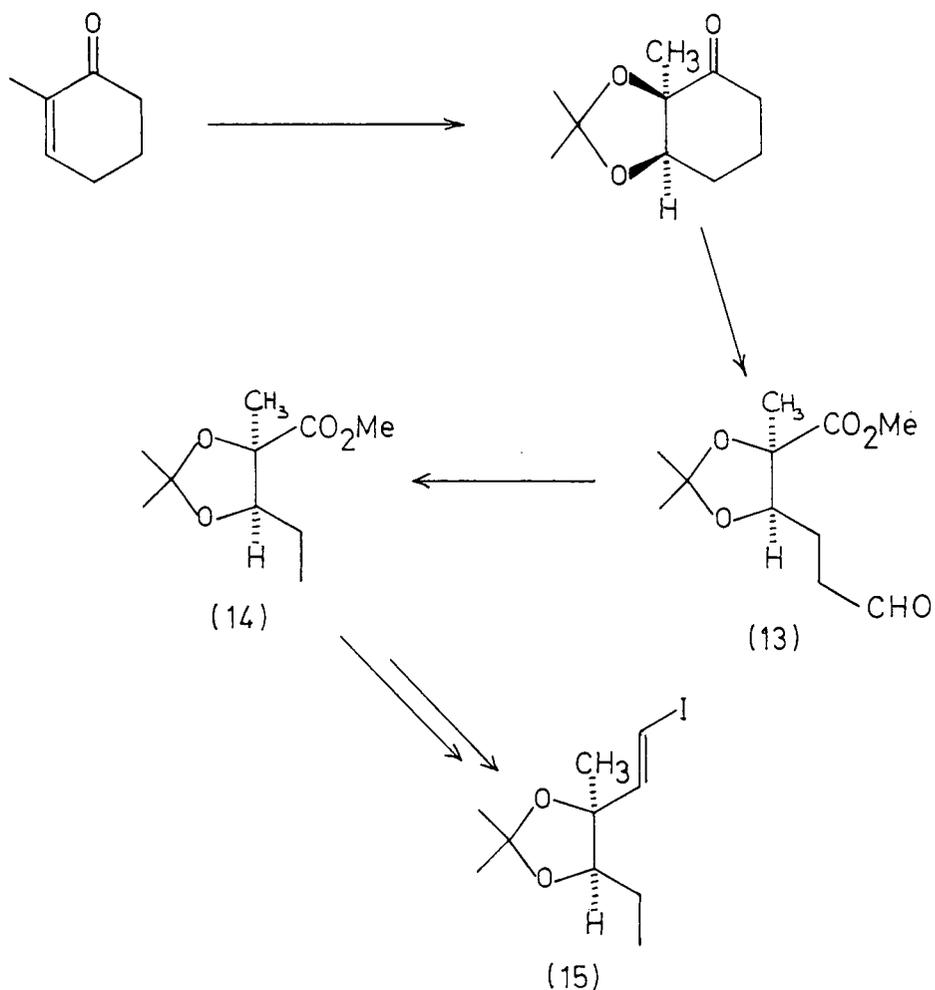


(11)



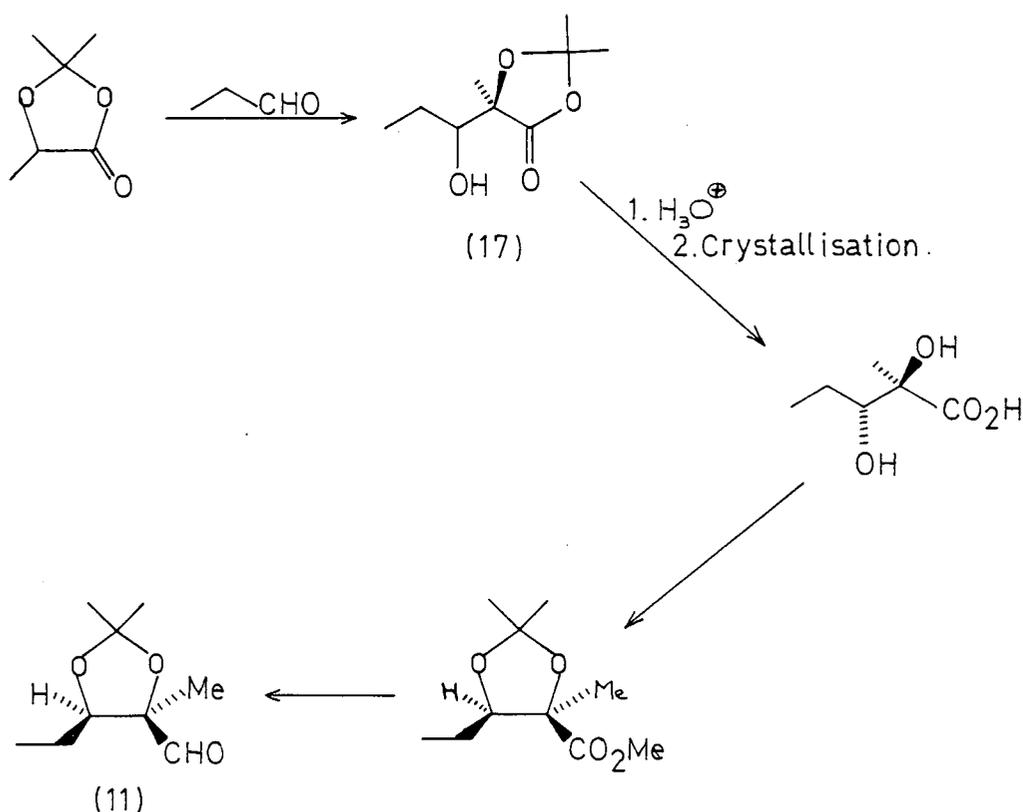
(12)

In the same year Grieco¹⁰ adopted a different approach in preparing the methyl ester (13). cis-Hydroxylation of 2-methylcyclohex-2-enone (Scheme 3) provided the corresponding diol, which was converted into the acetonide with acetone and copper sulphate. Enol acetate formation followed by ozonolysis and esterification generated the aldehyde (13), which on deformylation gave the racemic acetonide (14). Further manipulation produced the (E) vinyl iodide (15) which when combined with the Prelog-Djerassi lactone led to methynolide seco-acid.



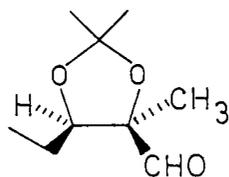
Scheme 3

Heathcock¹³ prepared aldehyde (11) in order to study stereoselective aldol condensations using bulky lithium enolates. A non-stereospecific approach was employed thereby requiring ultimate resolution with attendant lowering of yield; the route adopted is outlined in Scheme 4.



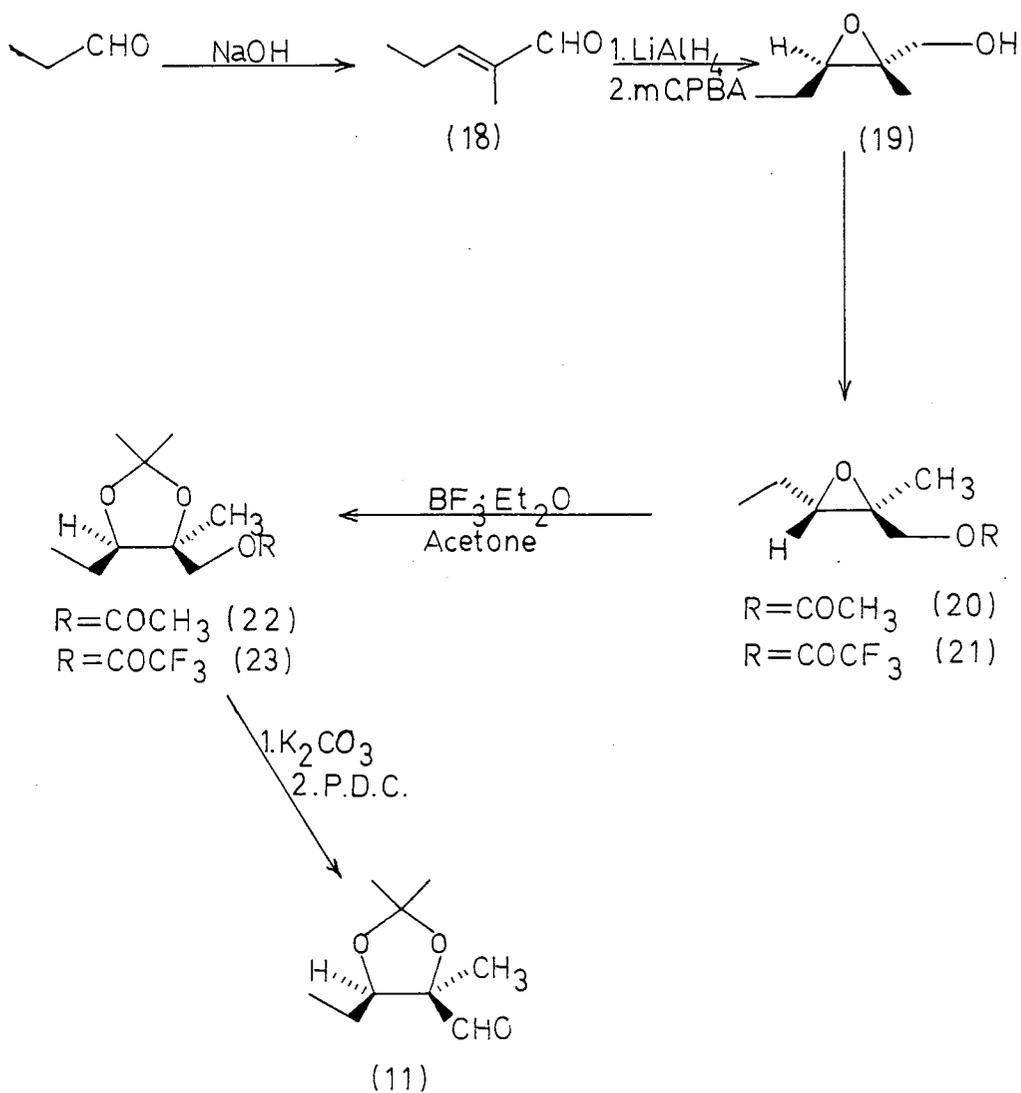
Scheme 4

Returning to the synthon (5), (Scheme 1), protection of the hydroxy groups as the corresponding acetonide seemed a most attractive strategy at this stage in the planning. Synthon (5) now becomes the primary target molecule (11), which should fulfil the necessary requirements in terms of ease of preparation and ease of cleavage, yet should be of sufficient stability to survive the ensuing reaction conditions.



(11)

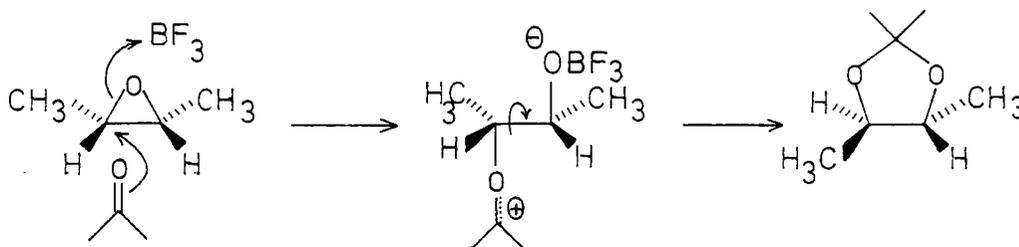
Our approach to aldehyde (11) in racemic form differs from those described above and is summarised in Scheme 5.



Scheme 5

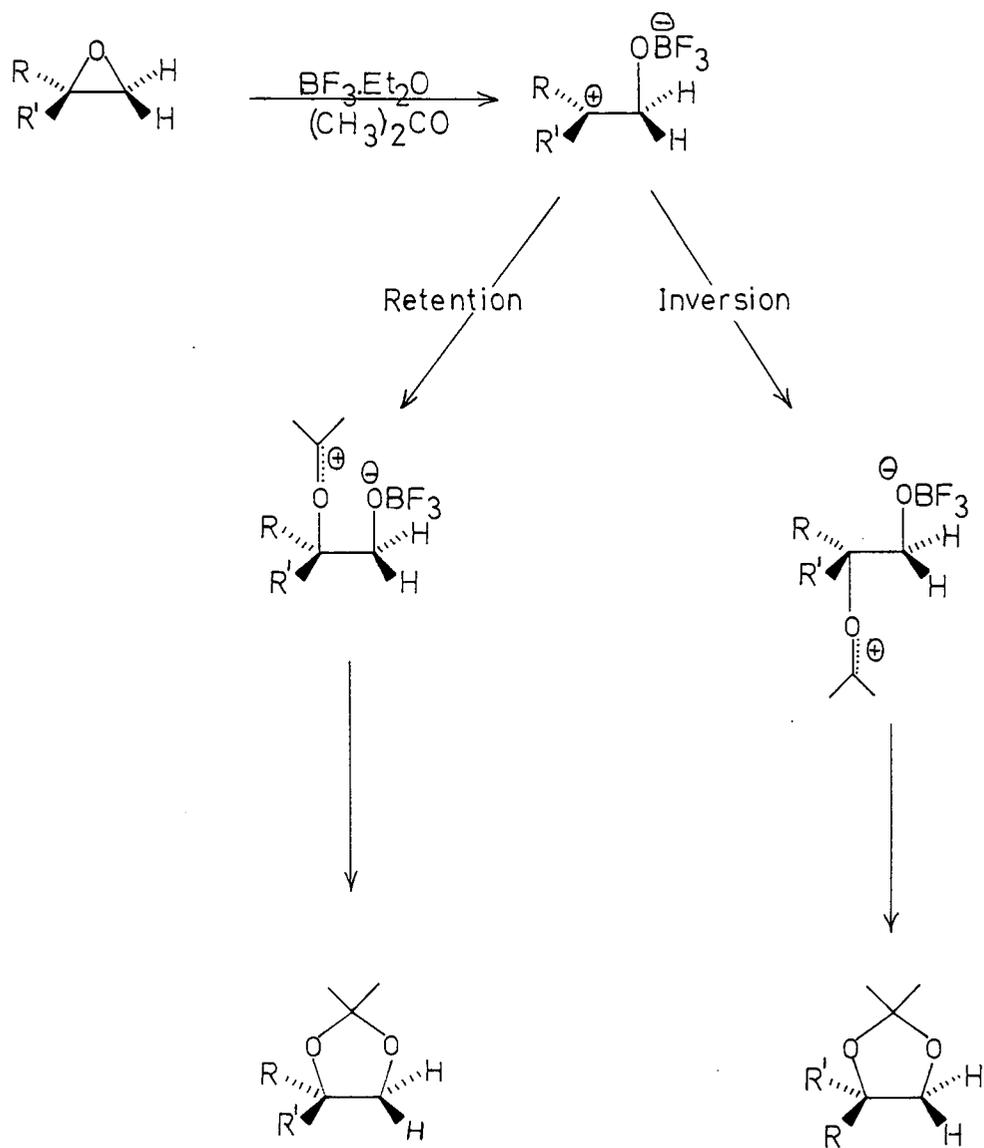
Thus, sodium hydroxide mediated aldol condensation of propionaldehyde afforded the (E)- α, β -unsaturated aldehyde (18). Reduction with lithium aluminium hydride and then epoxidation using m-chloroperbenzoic acid gave the epoxide (19) as a colourless oil in 90% isolated yield from the aldehyde (18).

The Lewis acid catalysed formation of acetonides from oxiranes has been studied extensively by Coxon¹⁴ and his co-workers, who concluded that for the reaction of but-2-ene epoxides with acetone in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, inversion of configuration occurs at the reacting carbon (Scheme 6).



Scheme 6

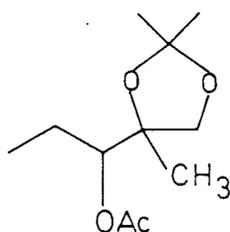
This acetonide formation would, therefore, appear to be an effective method of generating directly the desired acetonide (22) from the protected epoxide (21), with the correct relative stereochemistry. The reaction becomes less attractive when the epoxide ring carbons are primary and tertiary¹⁵; an $\text{S}_{\text{N}}1$ mechanism has been invoked to explain the loss of stereochemical integrity observed in such cases (Scheme 7).



Scheme 7

Notwithstanding this possible complication the epoxy alcohol was protected as its acetate (20) which reacted cleanly (by analytical t.l.c.) and smoothly to afford an acetonide. The ^1H n.m.r. spectrum of the product clearly showed an

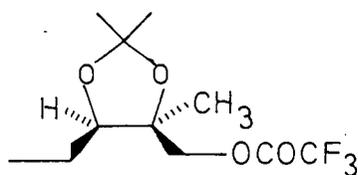
isopropylidene group, and the rest of the spectrum was consistent with the acetonide (22). However, hydrolysis of this product, followed by oxidation¹¹ furnished a compound which, from spectral analysis, was not the expected aldehyde, but was a ketone. Evidently events had gone awry in the acetonide formation, with intramolecular acetate participation the most likely source of problems. Indeed, a more detailed inspection of the ¹H n.m.r. spectrum suggested that the product from this reaction was not the acetonide (22), but the re-arranged acetonide (25).



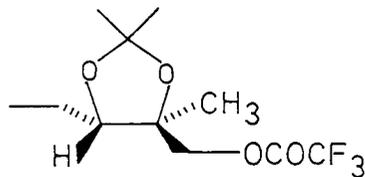
(25)

A modification of the alcohol protecting group of epoxide (19) to its trifluoroacetate (21) reduced the nucleophilicity of the acetate and allowed clean conversion to the acetonide (23) on treatment with acetone and $\text{BF}_3 \cdot \text{Et}_2\text{O}$. The ¹H n.m.r. spectrum of acetonide (23) indicated the presence of only one stereoisomer, suggesting the mechanism shown in Scheme 6, rather than Scheme 7, had operated. An upfield shift is observed by ¹³C-n.m.r. spectroscopy for any carbon which exists in a gauche orientation with respect to another carbon, relative to its anti counterpart. It can safely be anticipated that this so called ' γ -gauche' effect¹⁶ should

manifest itself for the quaternary methyl group and the methylene carbon of the ethyl group if the unwanted diastereoisomer (24) had been formed.



(23)



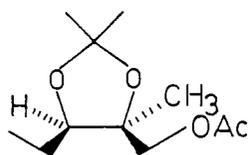
(24)

This relative effect was not observed, indicating that either the acetonide (23) or the acetonide (24) had been formed exclusively. In order to ascertain which diastereoisomer was present, irradiation of the quaternary methyl group in the ¹H n.m.r. spectrum resulted in a Nuclear Overhauser Effect (NOE) on the ring methine proton of approximately 14%. This is in excellent agreement with values reported¹⁷ for similar systems (10-16%). Had the alternative isomer (24) been formed, then a NOE would not have been observed; instead, long range W-coupling would have been detected between these groups.

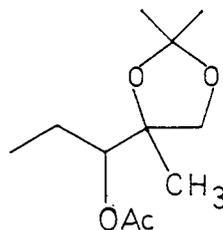
On the basis of this evidence, it can be concluded that this crucial reaction has proceeded with inversion of stereochemistry at C-3, generating acetonide (23) with the desired relative stereochemistry. This short synthesis of the racemic aldehyde (11) is completed by hydrolysis of the acetate (23) with sodium carbonate, followed by oxidation

(pyridinium chlorochromate - sodium acetate) in an overall yield of 65% from the unsaturated aldehyde (18); (Bergel'son¹², 19%; Grieco¹⁰, 21%; Heathcock¹³, 20%).

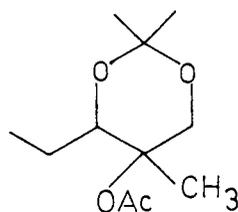
A closer examination of the epoxyacetate (20) revealed that the product on reaction with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and acetone was both concentration and time dependent. Under conditions of high dilution and/or short reaction times, the re-arranged acetates (25) and (26) are formed, whereas concentrated solution and/or long reaction times favour the formation of the acetonide (22) as the major product.



(22)



(25)

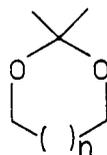


(26)

^{13}C N.m.r. and ^1H n.m.r. spectroscopy were used to identify these acetonides. A diagnostic difference exists¹⁸ in the ^{13}C n.m.r. spectroscopic chemical shifts of cyclic quaternary acetals. This chemical shift difference has been used to assign the ring sizes of various carbohydrate acetonides¹⁹.

Six atom cyclic acetonides have the lowest value for the quaternary methyl, while five-membered acetonides have higher values. For the re-arranged acetates (25) and (26), the ^{13}C n.m.r. spectra exhibited signals at 109.7 p.p.m. and 99.1 p.p.m., which are in excellent agreement with the reported values¹⁹ for monocyclic five- and six-membered acetonides respectively (Table 1).

Table 1: ^{13}C n.m.r. Spectroscopic Values for Cyclic Acetals

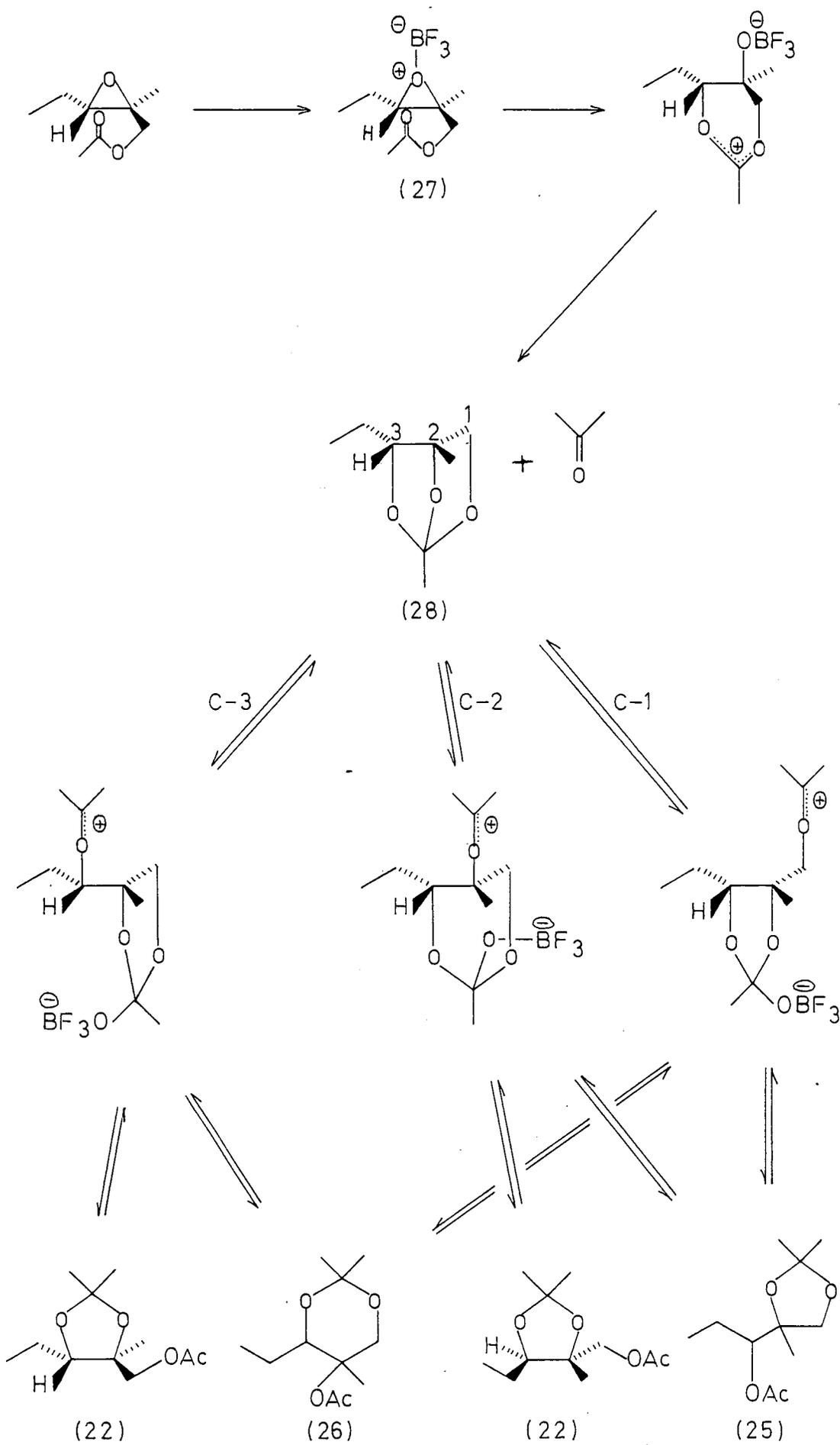


Ring Size	Literature Value	(25)	(26)	Intensity
n = 0	108.5-111.4	109.7	-	5
n = 1	97.1- 99.5	-	99.1	1
n = 2	100.8-103.4			

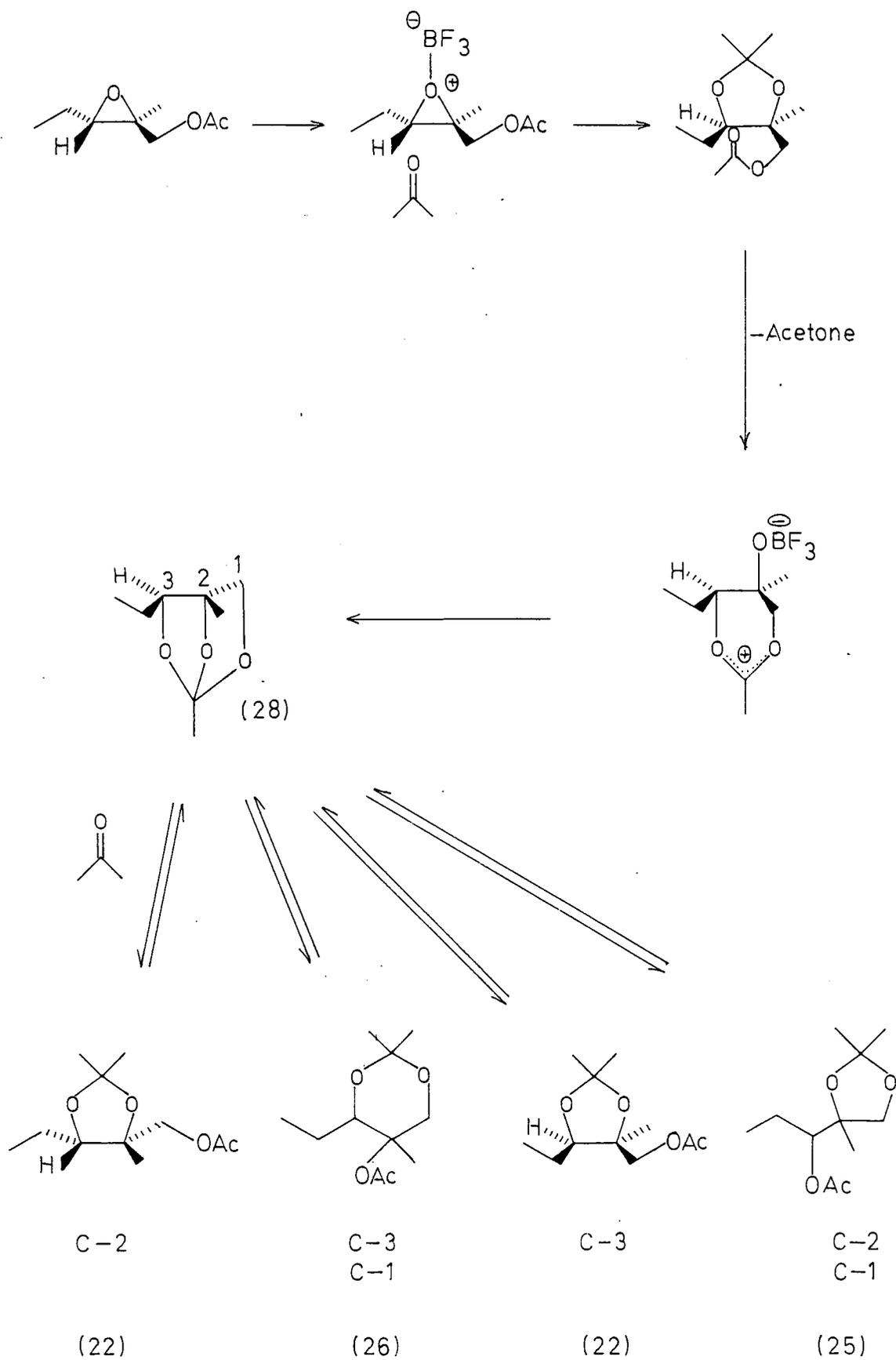
The relative intensities of the quaternary acetal carbon signals indicated that the ratio of acetates (25) and (26) was approximately 5:1. If the reaction of epoxyacetate (20) is not stopped after a short time, but is allowed to continue for 48 hours, the re-arranged acetates (25) and (26) are converted into the 'unre-arranged' acetonide (22). The relative stereochemistry shown for acetate (22) was confirmed by direct comparison with an authentic sample obtained from trifluoro-

acetate (23) by hydrolysis and reacetylation, again exhibiting a NOE of 14%. In summary, under conditions of thermodynamic control, the product acetonide has the relative stereochemistry shown in structure (23), whereas under kinetic control acetonides (25) and (26) are the major products. A mechanistic pathway which could account for the various products is shown in Scheme 10.

Acetate participation at C-3 of the complexed epoxyacetate (27) leads to the orthoester (28) (Scheme 10). This intermediate has three possible sites for BF_3 complexation and three possible sites open to attack. Under kinetically controlled conditions attack by acetone at the primary carbon (C-1) leads to formation of the kinetic products (25) and (26). Conversion into the product of thermodynamic control (22) must involve the reverse reaction to the key intermediate (28) with concomitant loss of acetone. This loss of acetone is a critical step in the conversion of kinetic products (25) and (26) into intermediate (28) and will be disfavoured if the reaction is carried out in a large excess of acetone. Under these conditions, conversion of acetates (25) and (26) into the thermodynamically stable acetonide (22) does not occur. Thus, under equilibrating conditions acetone can attack the C-3 rather than C-1 position to form acetonide (22). This proposal may also explain why acetonide (22) was never formed cleanly, but was invariably contaminated with approximately 10% of the acetonides (25) and/or (26).



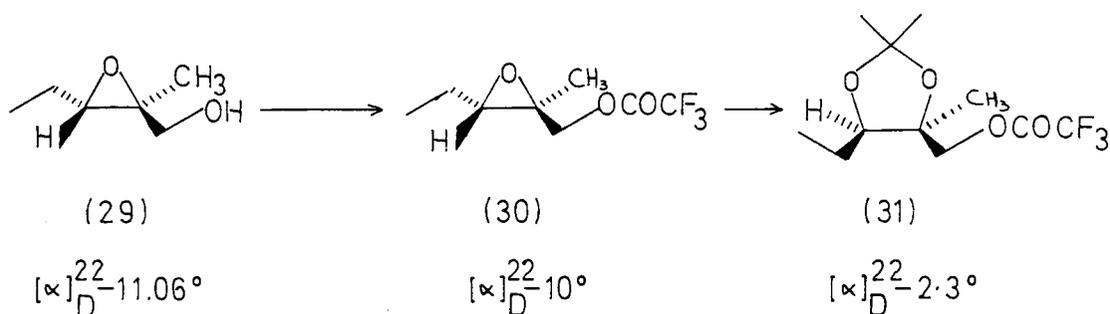
Scheme 10



Scheme 11

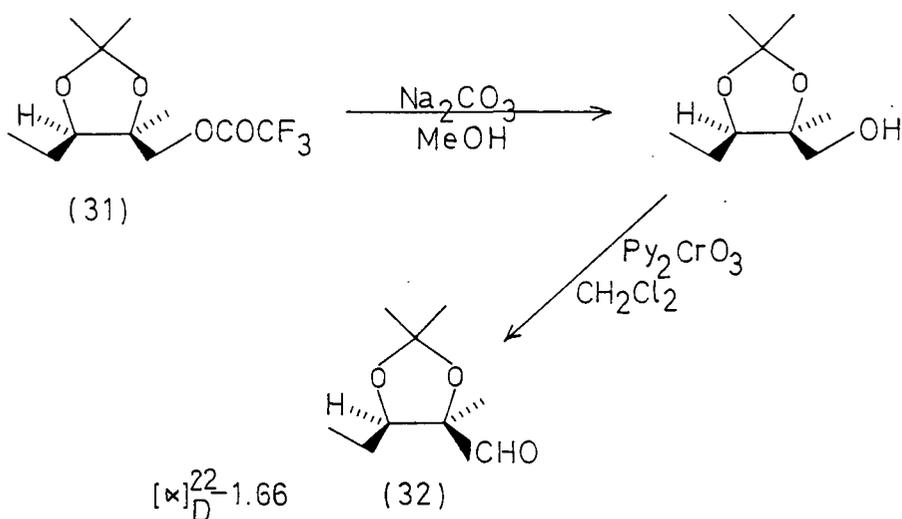
This sequence of events is attractive in principle. However, the thermodynamically formed acetonides (22) have the wrong relative stereochemistry, and would not be expected to show an NOE. The relative C-3 stereochemistry of the orthoester (28) is inverted if intramolecular acetate participation occurs not on the complexed epoxide, but on an initially formed acetonide (Scheme 11). Thus, by an extension of the original pathway, the observed products (22), (25) and (26) are obtained with the correct relative stereochemistry.

One further unfortunate piece of evidence is supportive of a tetrahedral intermediate such as (28). It was assumed that intramolecular acetate participation was only relevant for the 'normal' acetate (20) and that the strong electronegativity of the fluorine atoms in the trifluoroacetate prevented acetate participation, such that the reaction proceeded via the pathway shown in Scheme 6. Therefore, a sequence to the optically active acetonide (31) was envisaged to be possible from the optically active epoxide (29) (Scheme 12).



Scheme 12

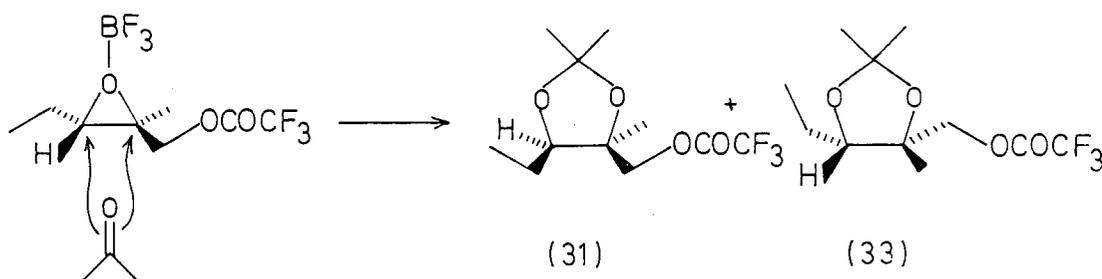
Sharpless *et al*²⁰ have described a method of enantioselective epoxidation of allylic alcohols, using (+)-diethyl tartrate and *t*-butyl hydroperoxide to deliver oxygen to one enantio face of the olefin. By this method Sharpless prepared the epoxide (29) in greater than 95% enantiomeric excess²¹. Following this procedure, the epoxide (29) was obtained and converted to the presumed optically pure trifluoroacetate (30) ($[\alpha]_D^{22} = -9.04$, $c = 0.84$, CHCl_3). Subjection of this compound (30) to the previously described conditions afforded the acetonide (31). This acetonide did show optical activity but the enantiomeric purity was uncertain. However, hydrolysis (sodium carbonate) and oxidation (Collins Reagent) afforded the aldehyde (32), which exhibited some optical activity (Scheme 13)



Scheme 13

The optical purity of the aldehyde was determined using tris 3-(heptafluoropropylhydroxymethylene)-*d*-camphorato europium (III). An examination of the signal for the

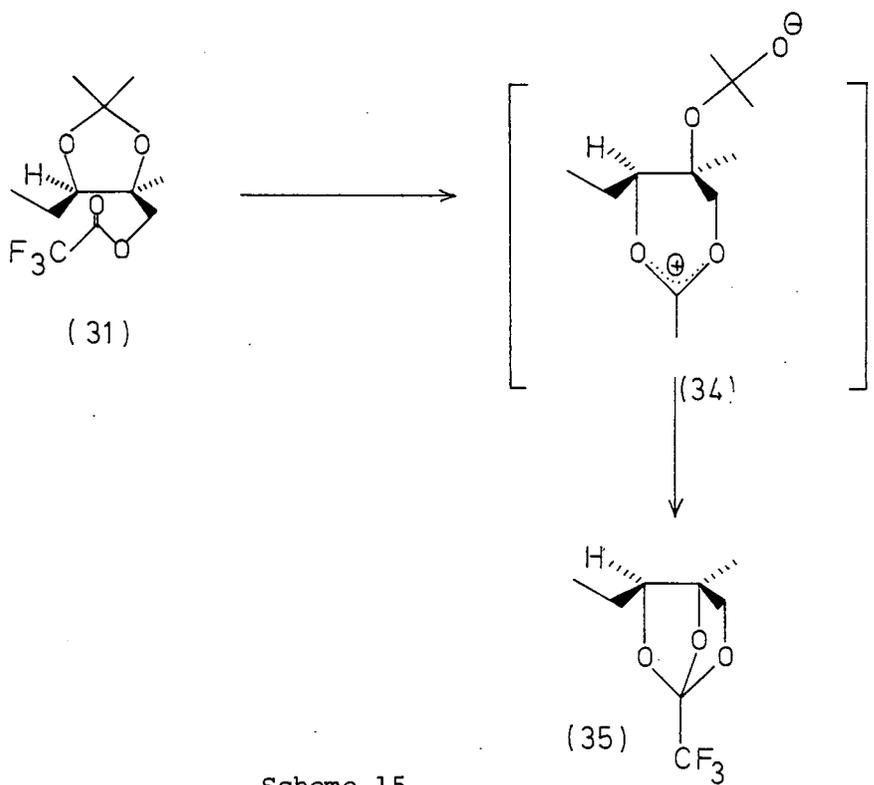
aldehyde proton revealed that racemisation had occurred. The ratio of enantiomers was 3:1, but this ratio was not reproducible, providing further evidence that thermodynamic factors were operating. By reducing the quantities of acetone in the BF_3 -mediated acetonide formation, the ratio could be altered from 3:1 in favour of the desired enantiomer to a 1:1 racemic mixture. Although the acid derived from aldehyde (32) could be resolved, this result had clear implications for the pathway adopted in the acetonide formation reaction. It is possible (Scheme 14) that acetone is attacking the C-2 and C-3 positions of the epoxide, but a rather larger differentiation would be expected for secondary versus tertiary nucleophilic attack under conditions of kinetic control.



Scheme 14

One other possibility must now be considered: acetone attacks the C-3 position of the epoxide and forms (31) as the immediate product. Thereafter the trifluoroacetate group

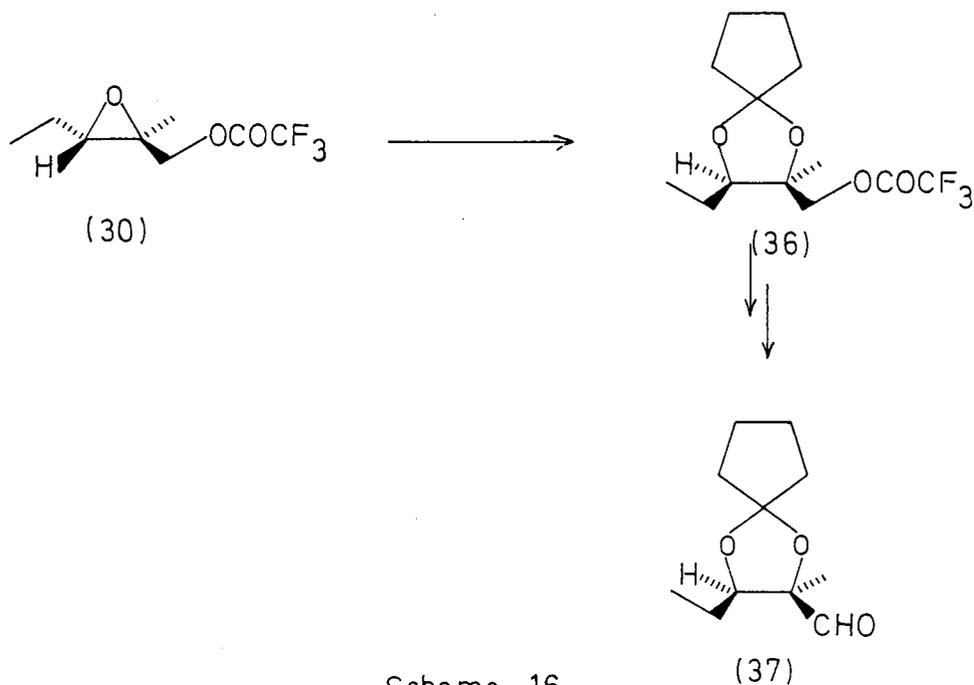
participates, attacking the C-3 position (Scheme 15) to form an intermediate (34) which on losing acetone collapses to the orthoester (35). The proposed species (35) is similar to the previously described orthoester (28) (Scheme 11). Therefore, attack of acetone at C-3 (cf: Scheme 11) leads to acetonide (33) while attack at C-2 leads to the enantiomer (31).



Scheme 15

The reason why the re-arranged acetonides are not formed is presumably due to rapid equilibration to the thermodynamic product. This speculative rationale accounts for all the experimental facts, assuming that acetonides (31) and (33) lie at the bottom of a thermodynamic well. It did not prove possible to obtain direct evidence for the formation of acetonide (31) as kinetic product.

In an attempt to alter this situation, the chiral epoxide (30) was reacted with cyclopentanone and $\text{BF}_3\text{Et}_2\text{O}$ as catalyst (Scheme 16).



Scheme 16

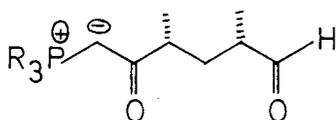
The acetonide (36) was hydrolysed and oxidised, and the enantiomeric ratio of the aldehyde (37) was determined using $\text{Eu}(\text{fod})\text{III}$. An approximate 20% enantiomeric excess, in favour of the described enantiomer, was obtained, indicating no improvement with respect to the isopropylidene series.

In conclusion, the chiral synthesis of (32) by this method is unfortunately impractical. Nonetheless, an efficient synthesis of racemic (10) has been achieved in good overall yield.

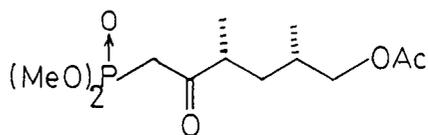
With synthon (5) in hand, attention was then turned to synthon (6), the 'right hand' fragment of methynolide.

Synthon (6)

Some modification to the second major subgoal, synthon (6), is required before a target molecule can be seen clearly. Firstly and most obviously, the aldehyde functionality requires protection. Many methods are available for this, but protection as the reduced acetate is conceptually the most simple at this stage.



(6)



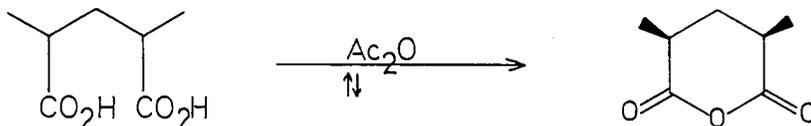
(38)

Phosphonate carbanions are known to be more nucleophilic than are phosphonium ylides²², due to decreased stabilisation of the negative charge in the phosphonate. As a consequence, phosphonate carbanions react with a greater variety of aldehydes and ketones, and under significantly milder conditions. For this reason, and also because of easier separation of the phosphate ion formed on alkene formation, the target molecule became the acetoxyphosphonate (38).

In projecting approaches to this synthon, it was decided to construct the two asymmetric centres on a cyclic framework which could be easily cleaved to the open-chain compound.

α, γ -Dimethylglutaric acid cyclises to the corresponding anhydride in the presence of refluxing acetic anhydride²³;

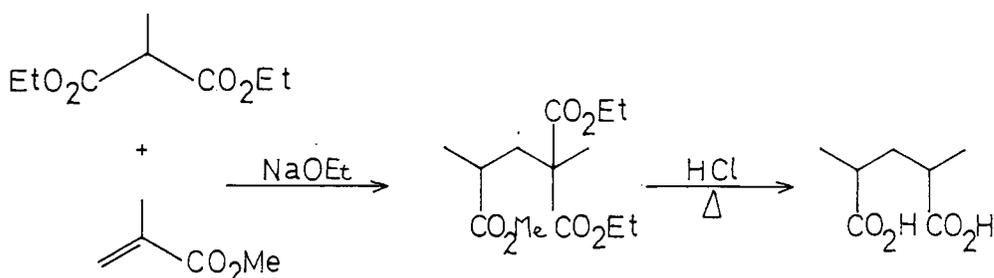
under these equilibrating conditions, only the meso isomer is isolated (Scheme 17), due to the thermodynamically favoured diequatorial configuration of the two methyl groups.



Scheme 17

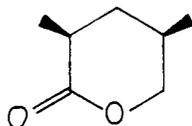
This would appear a facile method of generating the desired asymmetric centres of synthon (38), and was thus chosen for the commencement of the synthesis.

Michael addition of diethyl methylmalonate and methyl methacrylate, then hydrolysis and decarboxylation of the resulting triester, provided α, γ -dimethylglutaric acid²³ (Scheme 18).

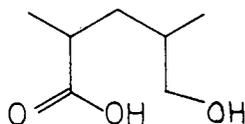


Scheme 18

From this diacid, the meso- anhydride (39) was obtained as a colourless crystalline solid. Careful reduction with sodium borohydride in dioxan²⁴ produced the racemic 2,4-dimethyl valerolactone (40). The choice of dioxan as solvent is critical to the success of this reaction; if, for example, THF is used, then the hydroxy acid (41) is the sole product. This is in contrast to reports of lactone formation from unsubstituted anhydrides using sodium borohydride in THF²⁵.



(40)

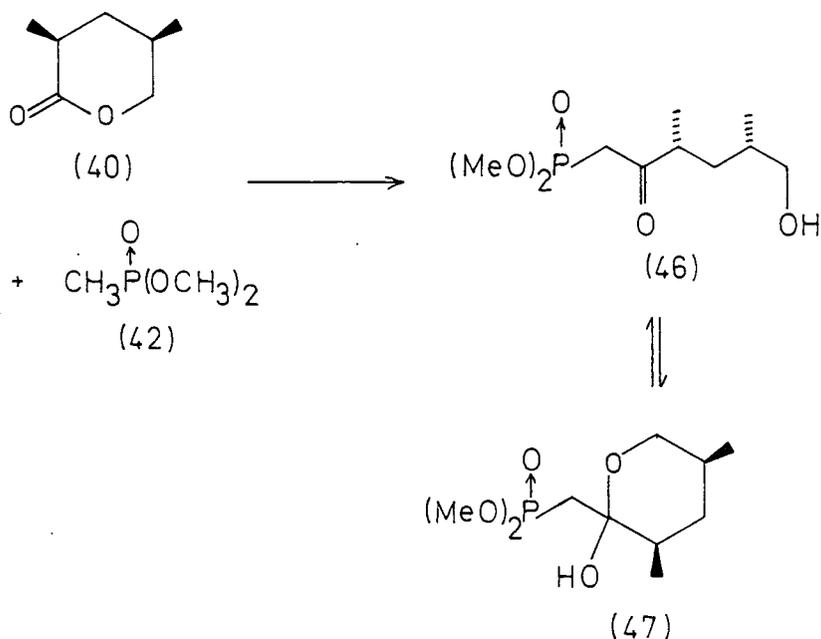


(41)

Corey²⁶ has shown that methyl dimethylphosphonate (42) can be deprotonated with *n*-butyl lithium at -78°C . Prior to this it had not been possible to deprotonate this species by conventional means^{27,28}. Corey also demonstrated that whereas this lithio derivative was not of utility in alkene synthesis, it was of value in the preparation of ketophosphonates from esters. Such ketophosphonates, useful in olefin synthesis²⁹, often prove impractical to prepare by conventional Michaelis-Arbusov procedures.

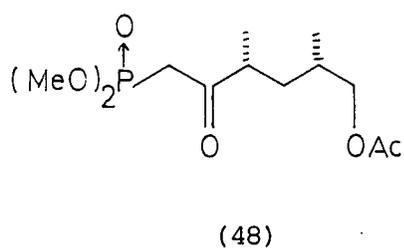
In exploiting this situation it was predicted with some confidence that the lithio derivative of dimethyl methylphosphonate would react with the lactone (40) to form the

ketophosphonate. Thus the phosphonate (42) was deprotonated with one equivalent of n-butyl lithium at -78°C and treated with the lactone (40) (Scheme 20). On aqueous isolation, a compound with spectral characteristics consistent with ketophosphonate (46) was obtained. Inexplicably, this reaction was fraught with practical difficulties and could only be reliably reproduced on a 4 mmolar scale.



Scheme 20

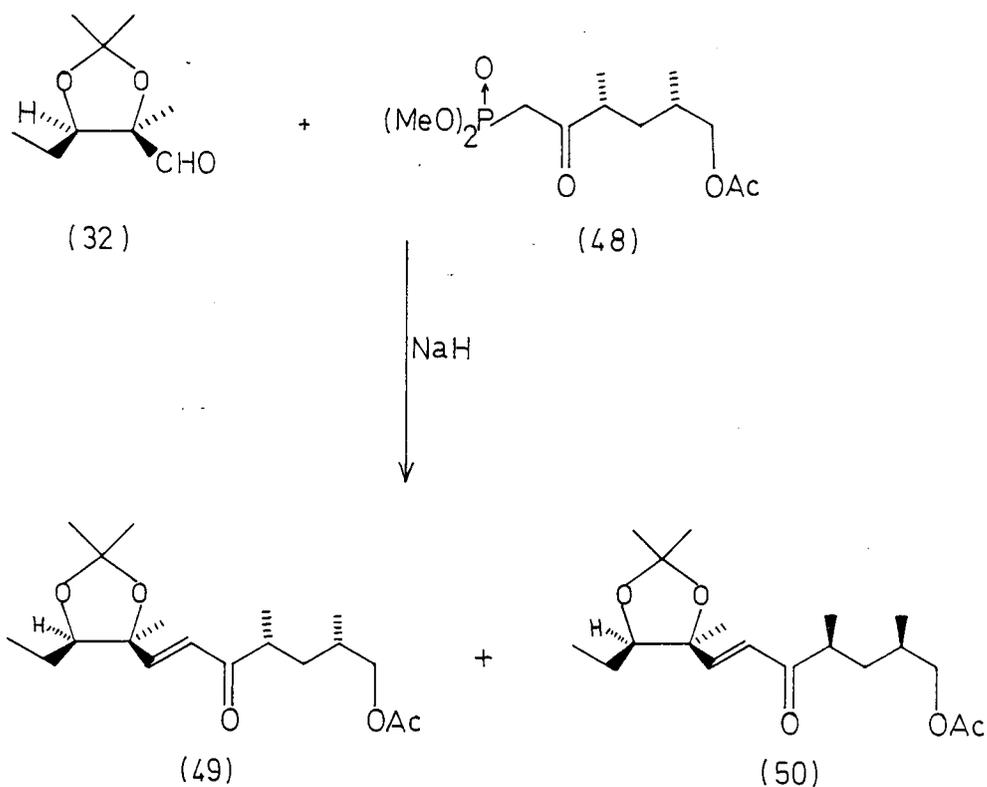
Acetylation of the ketophosphonate (46) provided an acetate (48) that was more polar than the starting alcohol, suggesting that the ketophosphonate (46) exists as the hemiacetal (47).



With the key racemic compounds (32) and (48) readily obtainable in reasonable quantity, their adjoinment could now be considered.

Synthon (4)

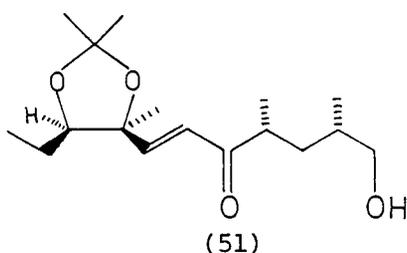
Deprotonation of ketophosphonate (48) with 1 equivalent of sodium hydride occurred rapidly in THF at room temperature. Addition of aldehyde (32), followed by heating at 65°C resulted in the production of a diastereoisomeric mixture of enones (49) and (50) (Scheme 21).



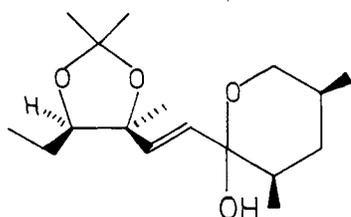
Scheme 21

The stereochemistry of the enone was assigned on the basis of ^1H n.m.r. spectroscopy; the olefinic protons showing coupling constants of $J = 16 \text{ Hz}$, consistent with (E) 1,2-disubstitution. In common with the majority of Wadsworth-Emmons olefinations²⁸, none of the (Z) isomer was present²².

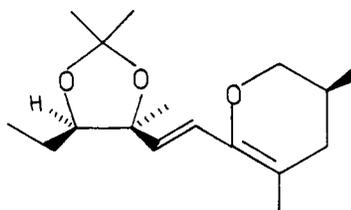
The mixture of diastereoisomers (49) and (50), though detectable by ^1H n.m.r. spectroscopy, was unresolvable by chromatography. This mixture was hydrolysed with potassium carbonate to the primary alcohol (51) and its diastereoisomer.



These alcohols proved to be very labile in aqueous acidic or basic media; thus, efficient acetate hydrolysis required carefully controlled two-phase conditions. This unexpected lability can be attributed to tautomeric hemiacetals such as (52) being the major isomers of the equilibrium mixture. Hemiacetal (52) could readily dehydrate in a basic or protic environment to the conjugated diene (53). This diene should, in principle, be capable of rehydration to the hemiacetal (52), but did so only sluggishly with aqueous hydrochloric acid in methanol, and was accompanied by cleavage of the acetonide to the parent 1,2-diol.

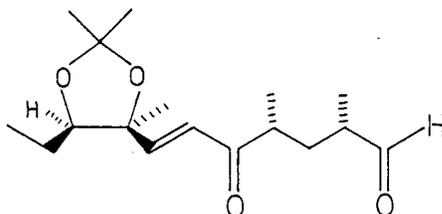


(52)



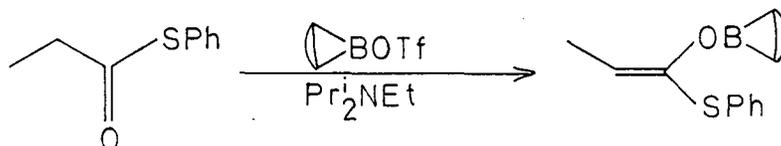
(53)

Flash chromatography³⁰ allowed separation of the diastereoisomeric acetonidoalcohols (51). At this juncture it was not possible to assign relative configurations to the separated stereoisomers, formed as a 2:1 mixture, but it was hoped that comparison with an authentic sample later in the synthetic sequence would allow such assignments; therefore, only the major stereoisomer was manipulated further. The facile dehydration of hemiacetal (52) inevitably proved troublesome in the final oxidation to synthon (4). Oxidation with buffered pyridinium chlorochromate³¹, pyridinium dichromate³² and Celite-supported silver carbonate³³ produced significant amounts of the diene (53) and only about 20% of the desired aldehyde (54). However, oxidation with preformed Collins Reagent³⁴ in dry methylene chloride allowed isolation of aldehyde (54) in 75% yield; this possibly reflects the much shorter reaction time required.



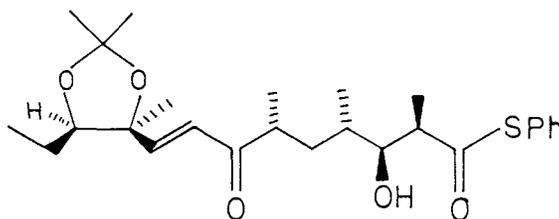
(54)

With the racemic aldehyde (53) or its diastereoisomer synthesised, attempts were then made to add stereoselectively the elements of propionic acid. Initial experimentation centred around the 9-BBN enolate of S-phenyl propanethioate. Masamune³⁵ has shown that S-phenyl propanethioate (readily prepared from propionic acid and benzenethiol) forms the cis vinyloxyborane predominantly using 9-BBN triflate and diisopropylethylamine (Scheme 22).



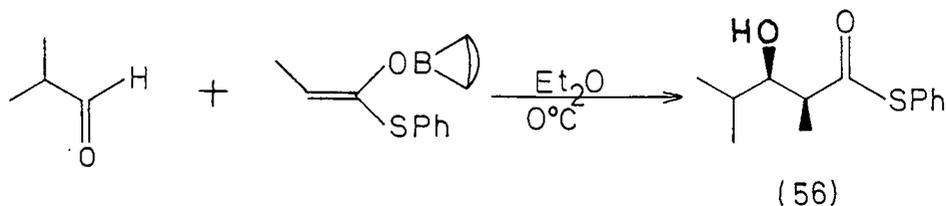
Scheme 22

Reaction of this enolate with certain aldehydes can form selectively the anti-Cram product. It was anticipated, therefore, that this enolate would react with the aldehyde (54) to generate the desired 2,3-erythro-3,4-threo product (55).



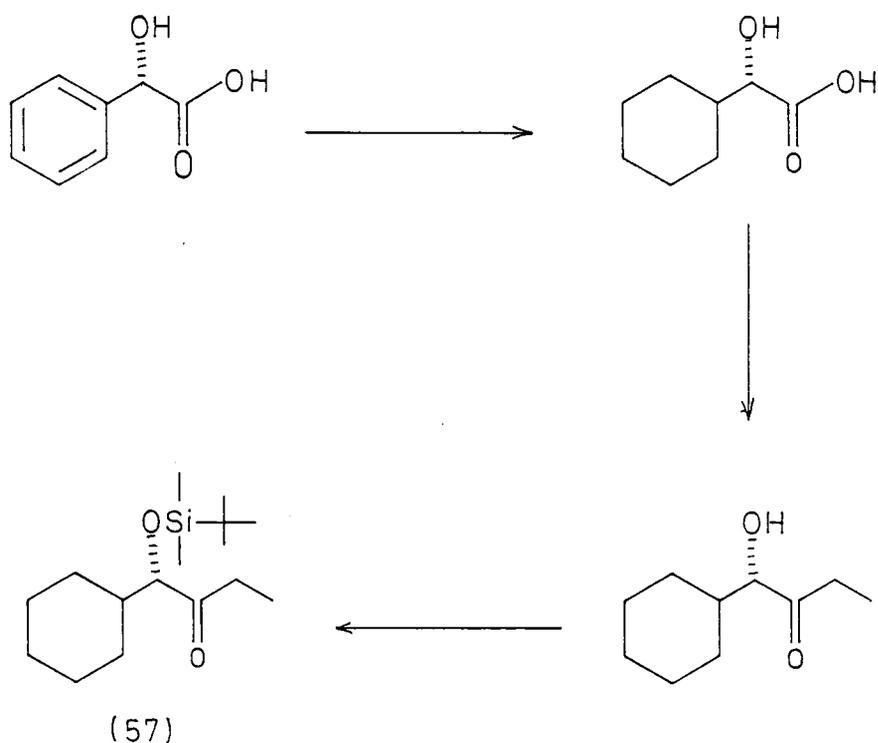
(55)

Model studies on isobutyraldehyde were encouraging and afforded a product having ¹H n.m.r. and I.R. spectral data consistent with the structure (55) (Scheme 23).

Scheme 23

In spite of the inability to obtain an accurate mass analysis for model compound (56), the same 9-BBN enolate was reacted with the racemic aldehyde (54), or its diastereoisomer. Unfortunately, analytical t.l.c. indicated severe decomposition, with ¹H n.m.r. spectroscopy indicating absence of olefinic protons. This negative result suggested that a lengthy synthetic detour would be required to protect the α, β -unsaturated ketone against attack from the boron enolate. However, before the practicalities of this had been put into effect, a milder reagent, exhibiting greater anti-Cram enantioselectivity was introduced³⁶. This chiral reagent (57), derived from (S)-mandelic acid (Scheme 24) offered several advantages, including the possibility that its reduced nucleophilicity might allow selective attack at the aldehyde terminus.

The protected ethyl ketone (57) was prepared by catalytic hydrogenation of (S)-mandelic acid with 10% rhodium on alumina to provide (S)-hexahydromandelic acid (Scheme 24). Treatment of the acid with four equivalents of ethyl lithium

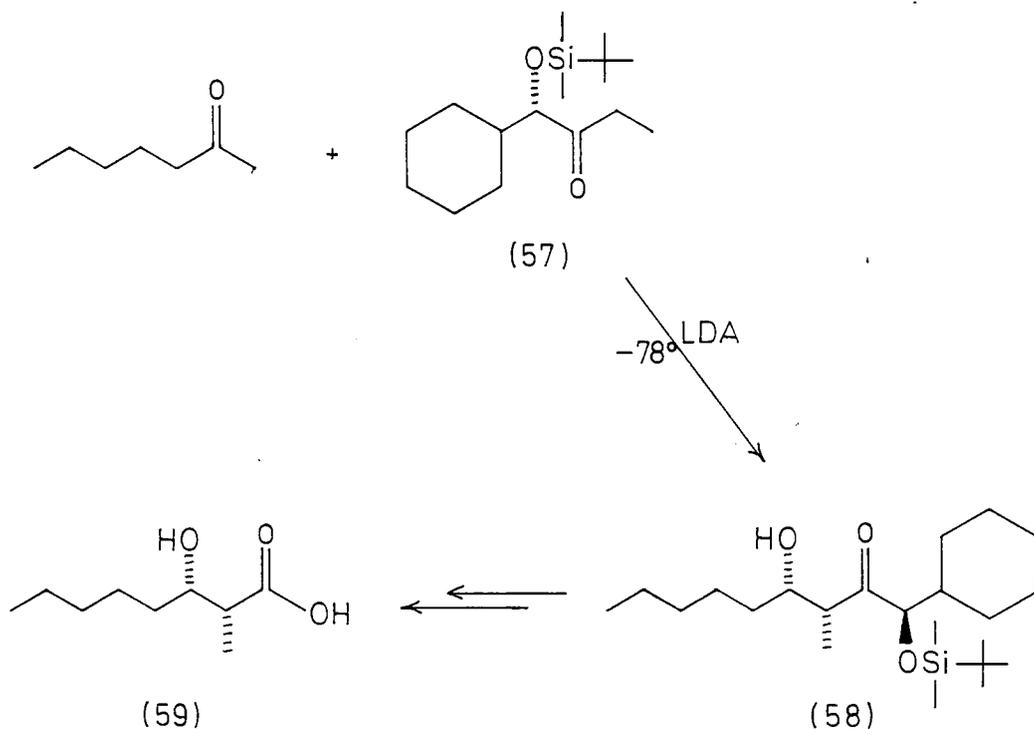


Scheme 24

provided a poor yield of the ethyl ketone, which was in turn silylated with t-butyldimethylsilyl chloride.

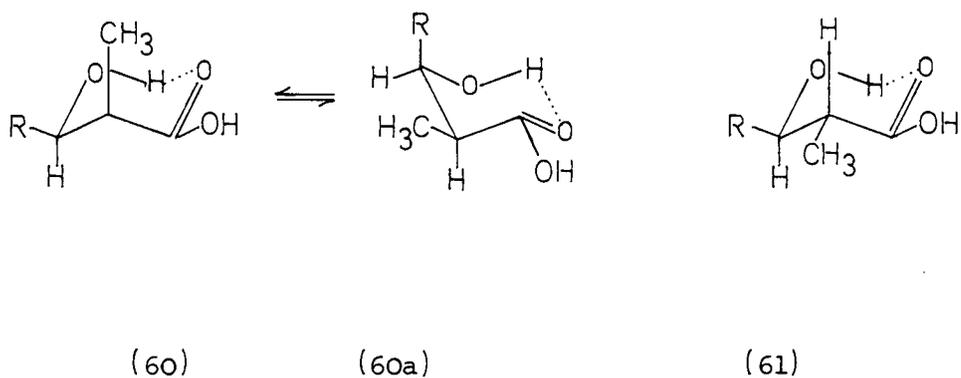
Preliminary experiments on the reaction of the lithium enolate derived from ketone (57) with hexanal (Scheme 25) provided an erythro:threo ratio of 95:5. The ratio was determined by ^{13}C n.m.r. spectral analysis³⁷ of the carboxylic acid (59) derived from adduct (58) by desilylation with aqueous HF, and periodic acid oxidative cleavage.

β -Hydroxycarbonyl compounds exist in intramolecularly hydrogen-bonded forms. Two possible chair-like conformers for the erythro and threo aldol products are illustrated by



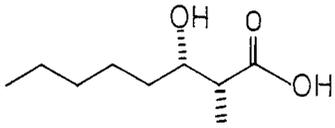
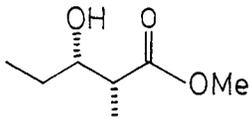
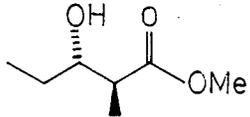
Scheme 25

structures (60) and (61) respectively. Comparison of the number of gauche interactions in these conformers leads to the prediction of an upfield shift of the methyl groups of the erythro isomer (60). This is due to the additional gauche interaction between the methyl and the C-O bond in (60) and between R and the $\text{C}_\alpha-\text{C}=\text{O}$ bond in (60a).



The other conformation of (61) is not considered since ^1H n.m.r. spectroscopic evidence indicates it to be highly disfavoured. The ^{13}C n.m.r. spectroscopic values for the relevant carbon atoms are shown in Table 2; these are in agreement with values reported for similar erythro systems³⁷.

Table 2

	Carbinol	Methyl	Methine
	72.04	10.38	44.21
	72.20	10.60	44.1
	74.40	13.70	44.90

The enantiomeric purity of the erythro hydroxy acid (59) was not determined, but an optical rotation of 56.1° probably indicates a preponderance of one enantiomer. It is very

possible that a dialkyl boron enolate of ketone (57) will allow a more favourable erythro : threo ratio to be attained.

The stage has now been set for the final chapter in this synthesis. Unfortunately time has not permitted further pursuance of these ideas, and it remains to be seen whether an enolate from ketone (57) will react selectively with the aldehyde functionality or whether further protection steps will be necessary. However, significant progress towards the ultimate goal of synthesising methynolide has been made, and it is to be hoped that success will be achieved in the not too distant future.

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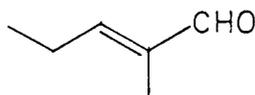
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GENERAL EXPERIMENTAL AND ABBREVIATIONS

The general experimental and abbreviations employed in the previous section (page 14) will also be used here.

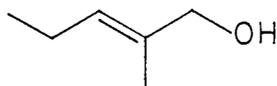
2-Methylpent-2-enal (18)

(18)

This was prepared by the published procedure¹.

From propionaldehyde (174 g) was obtained the aldehyde (18) as a colourless oil (97g, 66%) b.p. 50-53°C at 30 mm Hg (lit.¹ b.p. 31-32°C at 11 mm Hg).

ν_{\max} (CCl ₄)	2980 2720 1680 1390 1000
δ (CDCl ₃)	1.15 (3H, t, J = 7Hz, <u>CH</u> ₃ -CH ₂), 1.75 (3H, s, CH ₃), 2.45 (2H, 8 lines, q, J = 7Hz, further coupled d, J = 1Hz, CH ₂), 6.6 (1H, 6 lines, t, J = 8Hz, further coupled d, J = 1Hz, <u>HC</u> =C-), 9.3 (1H, s, <u>CHO</u>).

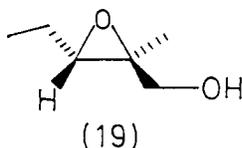
(E)-2-methylpent-2-en-1-ol (Scheme 5)

To a stirred solution of lithium aluminium hydride (4g, 0.1 mol) in ether (100 ml) was added dropwise over 30 minutes, 2-methylpent-2-enal (18) (10g, 0.1 mol) in ether (100 ml). The solution was heated under reflux for 1.5 hours after which time saturated sodium sulphate solution was added carefully. The resulting heterogeneous mixture was filtered, and the inorganic salts

were washed thoroughly with ether. The combined ethereal filtrates were concentrated in vacuo to furnish a colourless oil. Distillation afforded the alcohol as a colourless liquid (9.7g, 95%), b.p. 80-82°C at 30 mm Hg.

$\bar{\nu}$ max	3620 2970 1470 1380 1000
δ (CDCl ₃)	1.05 (3H, t, J=7Hz, H ₃ C-CH ₂), 1.73 (3H, s, CH ₃) 1.7 (1H, bs, exchanges D ₂ O, OH), 2.18 (2H, bq, J=7Hz, CH ₃ -CH ₂), 4.12 (2H, ABq, J=13Hz, CH ₂ OH), 5.6 (1H, 6 lines, t, J=8Hz, further coupled d, J=1Hz, HC=C-).

2-Methyl-2,3-epoxypentan-1-ol (19)



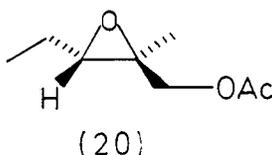
To a stirred solution of 2-methylpent-2-en-1-ol (9.6g, 0.096 mol), and disodium hydrogen orthophosphate (32.7g, 0.23 mol) in methylene chloride (100 ml) was added, at 0°C, 85% m-chloro-perbenzoic acid (21g, 0.115 mol) in methylene chloride (100 ml). The resultant heterogeneous mixture was allowed to warm to 20°C and then stirred for 5 hours. To the vigorously stirred solution was added 10% aqueous sodium sulphite (30 ml) followed by saturated sodium hydrogen carbonate (50 ml). The aqueous layer was separated and extracted with methylene chloride. The combined organic extracts were washed with brine, dried and

concentrated in vacuo. Distillation of the residue afforded the epoxide (19) as a colourless oil (10.0g, 90%), b.p. 85-86°C at 30 mm Hg.

$\gamma_{\max}(\text{CCl}_4)$ 3580 2980 1390 1060

$\delta(\text{CDCl}_3)$ 1.05 (3H, t, J=7Hz, $\text{H}_3\text{C}-\text{CH}_2$), 1.26 (3H, s, CH_3), 1.3-1.8 (2H, m, $\text{H}_3\text{C}-\text{CH}_2-$), 2.6 (1H, bs, exchanged D_2O , OH), 3.05 (1H, t, J=7Hz, $\text{HC}-\text{CH}_2$), 3.65 (2H, ABq, J=13Hz, CH_2OH).

1-Acetoxy-2-methyl-2,3-epoxypentane (20)



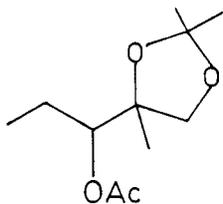
The epoxyalcohol (19) (1.0g, 8.6 mmol) was added fairly rapidly to a stirred solution of pyridine (5 ml) and acetic anhydride (4 ml). Stirring was continued for 15 hours after which time the mixture was poured on to ice-water. The aqueous solution was extracted with ether and the combined organic extracts were washed (saturated copper sulphate and brine) dried and concentrated under reduced pressure. Distillation furnished the epoxyacetate (20) as a colourless oil (1.2g, 88%), b.p. 97-99°C at 30 mm Hg.

γ_{\max} 2980 1745 1380 1235 1040

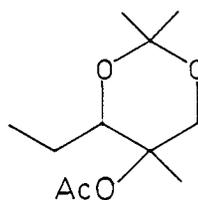
^1H n.m.r. δ (CDCl_3) 1.01 (3H, t, $J=7\text{Hz}$, $\text{H}_3\text{C}-\text{CH}_2$), 1.3 (3H, s, CH_3), 1.52 (2H, 8 lines, q, $J=7\text{Hz}$, further coupled d, $J=1\text{Hz}$, CH_2CH_3), 2.1 (3H, s, $\text{H}_3\text{CCO}-$), 2.87 (1H, t, $J=6\text{Hz}$, $\text{HC}-\text{CH}_2$), 4.1 (2H, ABq, $J=12\text{Hz}$, CH_2OAc).

^{13}C n.m.r. δ (CDCl_3) 170.23 (s), 68.58 (t), 62.37 (d), 58.31 (s), 21.61 (q), 20.62 (t), 14.23 (q), 10.46 (q).

Preparation of the Re-arranged Acetonides (25) and (26)



(25)



(26)

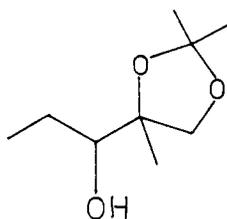
A stirred solution of the epoxyacetate (20) (250mg, 1.6 mmol) in acetone (0.15 ml, 2.0 mmol) was cooled to 0°C in an ice/water bath. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.02 ml, 0.16 mmol) was added by syringe and the solution allowed to warm to 20°C . Stirring was continued for 30 minutes at this temperature, whereupon the reaction mixture was partitioned between saturated sodium hydrogen carbonate and ether. The layers were separated and the aqueous layer extracted with ether. The combined organic extracts were washed with brine and dried. Solvent was removed under reduced pressure to yield the acetonides (25) and (26) (311mg, 90%), as a pale yellow oil.

δ (CDCl₃) 0.85 (3H, t, J=7Hz, CH₂CH₃), 1.16 (3H, s, CCH₃), 1.29 (6H, s, C(CH₃)₂), 1.97 (3H, s, COCH₃), 3.8 (m), 4.75 (1H, dd, J=9Hz and 3Hz, CHCH₂CH₃).

Found: m/z, 201. C₁₀H₁₇O₄ (M-15) requires 201).

The two acetonides (25) and (26) proved to be inseparable by a range of chromatographic techniques, but the ¹³C n.m.r. spectrum of the mixture did show singlet signals at 109.73 and 99.11 ppm. These signals were assigned to the quaternary acetal carbons of (25) and (26) respectively; the relative intensities of these signals suggested that the ratio of (25) to (26) was approximately 5:1.

Hydroxy Acetonide



This experiment was performed by Mr R. McKenzie (B.Sc. thesis project, Glasgow, 1981).

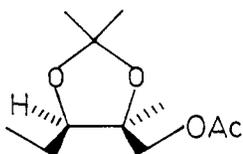
To a mixture of the acetonides (25) and (26) 250mg, 1.16 mmol) was added, with stirring, sodium hydroxide solution (2.5 ml, 1 Molar); to the resulting heterogeneous mixture was added methanol (3 ml) until the mixture became homogeneous. Stirring was continued overnight at 20°C. Water (15 ml) was added to the reaction mixture, the layers were separated, and the aqueous layer was extracted with ether. The combined ethereal extracts were washed with brine

and dried, prior to concentration under reduced pressure. The mixture of alcohols so produced was subjected to chromatography on a 'Chromatotron' using chloroform as eluting solvent, from which the secondary alcohol corresponding to acetate (25) was obtained as a colourless oil, b.p. 85°C at 0.7 mm Hg.

ν_{\max}	3450 2990 1460 1375 1255 1210 1100
^1H n.m.r. δ (CCl_4)	0.95 (3H, t, $J=7\text{Hz}$, CH_2CH_3), 1.2 (3H, s, CCH_3), 1.34 (3H, s, isopropylidene CH_3), 1.4 (3H, s, isopropylidene CH_3), 2.6 (1H, brs, exchanges D_2O , OH), 3.44 (1H, dd, $J=9\text{Hz}$ and 3Hz , CHCH_2CH_3), 3.8 (2H, ABq, $J=9\text{Hz}$, $\text{CH}_2\text{OC}(\text{CH}_3)_2$).
^{13}C n.m.r. δ (CHCl_3)	109.35 (s), 83.82 (s), 76.38 (d), 70.88 (t), 27.43 (q), 26.77 (q), 24.30 (t), 22.22 (q), 11.25 (q).

It did not prove possible to isolate a pure sample of the 1,3-dioxane alcohol corresponding to acetate (26).

1-Acetoxy-2-methyl-2,3-(isopropylidenedioxy)pentane (22)



(22)

To a stirred solution of the epoxyacetate (20) (250mg, 1.6 mmol) in acetone (0.15 ml, 2.0 mmol) at 0°C was added $\text{BF}_3\text{Et}_2\text{O}$ (0.02ml, 0.16 mmol) and the solution allowed to warm to 20°C. Stirring was continued at room temperature for 3 days. The reaction mixture was partitioned between saturated sodium hydrogen carbonate and ether. The layers were separated and the aqueous layer extracted with ether. The combined ethereal extracts were washed with brine and dried. Removal of the solvent in vacuo gave a pale yellow oil. Short path distillation afforded the acetonide (22) as a colourless mobile oil (315mg, 91%), b.p. 80°C at 0.7 mm Hg.

ν max	2990 1745 1460 1375 1230 1040 1010
^1H n.m.r. δ (CCl_4)	1.0 (3H, t, $J=7\text{Hz}$, CH_2CH_3), 1.23 (3H, s, CCH_3), 1.30 (3H, s, isopropylidene CH_3), 1.35 (3H, s, isopropylidene CH_3), 1.47 (2H, q, $J=7\text{Hz}$, CH_2CH_3), 2.0 (3H, s, CH_3COO), 3.7 (1H, t, $J=7\text{Hz}$, CHCH_2CH_3), 3.92 (2H, s, CH_2OAc).
^{13}C n.m.r. δ (CDCl_3)	170.16 (s), 107.26 (s), 84.79 (d), 80.05 (s), 66.04 (t), 28.30 (q), 26.52 (q), 21.69 (q), 20.76 (t), 11.62 (q).

(Found: m/z 201. $\text{C}_{10}\text{H}_{17}\text{O}_4$ (M-15) requires 201).

1-Trifluoroacetoxy-2-methyl-2,3-epoxypentane (21)

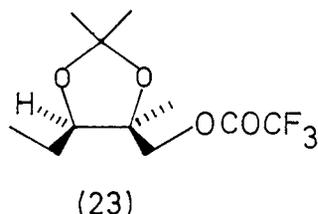


(21)

To a stirred solution of the epoxyalcohol (19) (9.0g, 0.0425 mol) and pyridine (17g, 0.2 mol) in ether (10 ml) was added, at 0°C and under an atmosphere of argon, trifluoroacetic anhydride (23.3g, 15 ml, 0.1mol) in ether (10 ml) over 15 minutes. The resultant pale yellow heterogeneous mixture was stirred for 12 hours at 20°C, after which time it was poured carefully on to ice-water. The aqueous phase was separated and extracted with ether. The combined organic extracts were washed (saturated copper sulphate, and brine), dried and concentrated in vacuo to yield a pale yellow oil (14.5g). Distillation provided the trifluoroacetate (21) as a colourless mobile oil (13.5g, 82%), b.p. 78-80°C at 35 mm Hg.

ν max	2980 1790 1355 1225 1165
δ (CDCl ₃)	1.01 (3H, t, J=7Hz, <u>H</u> ₃ C-CH ₂), 1.38 (3H, s, CH ₃), 1.6 (2H, 8 lines, q, J=7Hz, further coupled d, J=1Hz, <u>CH</u> ₂ -CH ₃), 2.92 (3H, t, J=6Hz, <u>HC</u> -CH ₂), 4.39 (2H, ABq, J=12Hz, <u>CH</u> ₂ O-).

1-Trifluoroacetoxy-2-methyl-2,3-(isopropylidenedioxy)pentane (23)



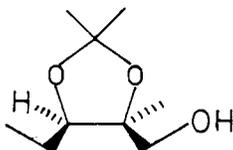
To a stirred solution of the epoxytrifluoroacetate (21) (4g, 18.9 mmol) in acetone (20 ml) was added, at 0°C, a catalytic quantity of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (3 drops). The mixture was allowed to warm to 20°C and thereafter stirred for 24 hours. The solution was poured onto saturated sodium hydrogen carbonate (20 ml) and the aqueous solution extracted thoroughly with ether. The combined ether extracts were dried and concentrated in vacuo to furnish a pale yellow oil (4.7g). Distillation afforded the pure acetonide (23) as a colourless oil (4.3g, 85%), b.p. 85-88°C at 50 mm Hg.

ν max	2980	1790	1465	1380	1220	1160	1010
δ (CDCl ₃)	1.02 (3H, t, J=6Hz, $\text{H}_3\text{C}-\text{CH}_2$), 1.28 (3H, s, CH ₃), 1.34 (3H, s, CH ₃), 1.39 (3H, s, CH ₃), 1.35-1.7 (2H, m, CH_2CH_3), 3.72 (1H, t, J=6Hz, $\text{HC}-\text{CH}_2$), 3.95 (2H, ABq, J=12Hz, $\text{CH}_2-\text{OCOCF}_3$).						

(Found: m/z, 255. $\text{C}_{11}\text{H}_{17}\text{F}_3\text{O}_4$ (M-15) requires 255).

Irradiation of the signal at δ 1.280 p.p.m. produced a change in the integral for the triplet at δ 3.715 p.p.m. corresponding to an enhancement of 15%.

1-Hydroxy-2-methyl-2,3-(isopropylidenedioxy)pentane (Scheme 5)



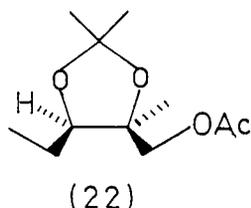
To a stirred solution of the trifluoroacetate (23) (4g, 16 mmol) in methanol (5 ml) was added, at 20°C, sodium carbonate (5g, 48 mmol) in water (5 ml). The reaction mixture was stirred for one hour at this temperature after which time it was heterogeneous. The combined filtrates were extracted thoroughly with ethyl acetate and the combined organic extracts washed with brine, dried and concentrated in vacuo. Distillation of the residue (2.6g) furnished the alcohol as a colourless oil (2.2g, 86%), b.p. 98-100°C at 15 mm Hg.

ν max	3460	2980	2880	1460	1370	1380	1210
	1060	1010					
δ (CDCl ₃)	1.0 (3H, t, J=7Hz, H ₃ C-CH ₂),	1.25 (3H, s, CH ₃)					
	1.35 (3H, s, isopropylidene CH ₃),	1.4 (3H, s, isopropylidene CH ₃),	1.3-1.7 (2H, m, CH ₂),				
	2.2 (1H, brs, exchanges with D ₂ O, OH),						
	3.42 (2H, ABq, J=11Hz, CH ₂ OH),	3.7 (1H, double d, J=5Hz and J=5Hz, CH ₂ CH)					

(Found: m/z, 159.1020. C₈H₁₅O₃(M-CH₃) requires 159.1021).

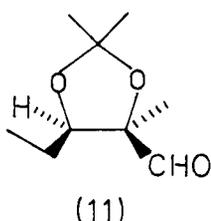
Irradiation of the signal at δ 1.3-1.7 p.p.m. decoupled the signal at δ 3.7 p.p.m., which then became a singlet.

1-Acetoxy-2-methyl-2,3-(isopropylidenedioxy)pentane (22)



To a stirred solution of 1-hydroxy-2-methyl-2,3-(isopropylidenedioxy)pentane (250mg, 1.16 mmol) was added at 20°C, pyridine (6 ml) and acetic anhydride (5 ml). Stirring was continued at room temperature for 18 hours, after which time the mixture was poured on to ice-water. The aqueous solution was extracted well with ether and the combined organic extracts were washed (saturated copper sulphate and brine) dried and concentrated under reduced pressure. Short path distillation of the residue afforded the acetate (22) as a colourless mobile oil (216mg, 86%), b.p. 103-107°C at 30 mm Hg. This was found to be identical in all respects with the acetonide (22) derived directly from the epoxyacetate (20).

2-Methyl-2,3-(isopropylidenedioxy)pentanal (11)



To a stirred suspension of pyridinium dichromate (6g, 14 mmol) in dry methylene chloride (15 ml) were added, at 20°C, 1-hydroxy-2-methyl-2,3-(isopropylidenedioxy)pentane (4g, 11.5 mmol) in dry methylene chloride (5 ml). The resultant black suspension was stirred for 72 hours at 20°C, then diluted with ether (100 ml). The heterogeneous solution was filtered through a pad of Celite and the Celite pad was washed with ether. The combined organic filtrates were concentrated under reduced pressure. Distillation of the residue (3.8g) furnished the aldehyde (11) as a colourless mobile oil (3.5g, 87%), b.p. 98-100°C at 18 mm Hg.

ν max	2990	2700	1735	1460	1370	1380	1220
	1110	1010					

δ (CDCl ₃)	0.97 (3H, t, J=7Hz, <u>CH</u> ₃ CH ₂),	1.28 (3H, s, CH ₃)
	1.43 (3H, s, isopropylidene CH ₃),	1.54 (3H, s, isopropylidene CH ₃),
	1.3-1.7 (2H, m, CH ₂),	
	3.82 (1H, t, J=7Hz, <u>HC</u> CH ₂),	9.60 (1H, s, <u>CHO</u>).

(Found: m/z, 157.0869. C₈H₁₃O₃ (M-15) requires 157.0865).

Preparation of (-)-2-Methyl-2,3-epoxypentan-1-ol (29)

This was prepared by the published procedure². Thus, from (E)-2-methylpent-2-en-1-ol (2g, 20 mmol) and t-butyl hydroperoxide (10 ml, 45 mmol) in methylene chloride in the presence of titanium tetraisopropoxide (5.68g, 20 ml) and (+)-diethyl tartrate (4.12g, 20 mmol) was obtained the chiral epoxide (29) (1.97g, 85%), b.p. 80-85°C at 25 mm Hg, $[\alpha]_D^{22} = -13.5$ (CHCl₃, C=0.842), $\text{lit}^2 [\alpha]_D = -5.8^\circ$ (CHCl₃, C=0.36). This material was identical in all respects (except for optical rotation) with the previously described racemic material (11).

Preparation of (-)-1-Trifluoroacetoxy-2-methyl-2,3-epoxypentane (30)

This was prepared in an analogous manner to that already described for racemic trifluoroacetate (21). Thus from the chiral epoxy-alcohol (29) (1.16g, 10 mmol), pyridine (1.9g, 24 mmol) and trifluoroacetic anhydride (2.6g, 12 mmol) in ether (50 ml) was obtained the chiral trifluoroacetate (30) (1.58g, 75%), b.p. 80-85°C at 35 mm Hg, $[\alpha]_D^{22} = -9.04$ (CHCl₃, C=0.84). This material was identical in all respects (except for optical rotation) with the previously described racemic trifluoroacetate (21).

Attempted Preparation of (-)-Trifluoroacetoxy-2-methyl-2,3-
(isopropylidenedioxy)pentane (31)

To a stirred solution of the (-)-epoxytrifluoroacetate (30) (1.5g, 7 mmol) in acetone (16g, 276 mmol) was added, at 0°C, BF₃.Et₂O (4 drops). The mixture was allowed to warm to room temperature, and the reaction vessel was fitted with a cotton wool stopper. After 17 hours at this temperature, additional BF₃.Et₂O (4 drops) was added. The reaction was incomplete after a further 7 hours and more BF₃.Et₂O (4 drops) was added. After stirring for a total time of 36 hours, the solution was poured onto saturated sodium hydrogen carbonate (40 ml) and the aqueous solution extracted thoroughly with ether. The combined organic extracts were dried and concentrated in vacuo to furnish the acetonide (31) (1.37g, 73%) as a very pale yellow oil. This material was identical (n.m.r. and t.l.c.) with the racemic acetonide (23) and was used without further purification.

Attempted Preparation of (-)-1-Hydroxy-2-methyl-2,3-(isopropyl-
idenedioxy)pentane

To a vigorously stirred solution of the acetonidotrifluoroacetate (31) (1.37g, 5 mmol) in methanol (20 ml) and water (20 ml) was added sodium carbonate (2g, 16 mmol). After stirring for 1 hour, the resultant heterogeneous mixture was filtered through Celite, and the Celite pad was washed with ethyl acetate. The combined filtrates were separated and the aqueous phase was extracted with

ethyl acetate. The organic extracts were combined, washed with brine, dried and concentrated under reduced pressure. Short path distillation of the residue afforded the acetonido alcohol (690mg, 79%) as a colourless oil, b.p. 130-135°C at 35 mm Hg, $[\alpha]_D^{22} = -2.3^\circ$ (CHCl₃, C=0.484). This material was identical in all respects (except for optical rotation) with the previously described racemic acetonido alcohol.

Attempted preparation of (-)-2-Methyl-2,3-(isopropylidenedioxy)pentanal (32)

To a vigorously stirred solution of dipyridine chromium (VI) oxide (5.16g, 20 mmol) in dry methylene chloride (75 ml) was added, at 0°C, and under an atmosphere of argon, optically active 1-hydroxy-2-methyl-2,3-(isopropylidenedioxy)pentane (581 mg, 3.3 mmol) in dry methylene chloride (5 ml) over two minutes. The resultant black suspension was stirred at 20°C for 2 hours and then ether (100 ml) was added. The heterogeneous solution was filtered through a pad of Celite and the Celite pad was washed with ether. The combined organic filtrates were concentrated in vacuo and the residue was diluted with ether (50 ml). The ethereal solution was washed with saturated copper sulphate, brine and dried with sodium sulphate. Removal of the solvent under reduced pressure and short path distillation of the residue furnished the aldehyde (32) as a colourless oil (453 mg, 80%), b.p. 125-130°C at 30 mm Hg, $[\alpha]_D^{22} = -1.6$ (EtOH, C=0.854), $lit^3 : [\alpha]_D^{22} = -9.8$ (EtOH, C=0.82). This material was identical in all respects

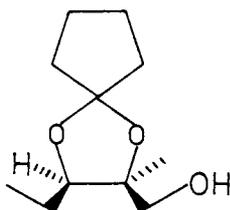
(except for optical rotation) with the previously described racemic acetonido aldehyde (11).

An examination of the optical purity of this aldehyde, using tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]-europium (III), resolved the signal at δ 9.72 p.p.m. for the aldehydic proton into two singlets. The ratio of the (-)- and (+)-enantiomers, as calculated from the ^1H n.m.r. spectral integration, was 2:1.

Attempted Preparation of (-)-1-Trifluoroacetoxy-2-methyl-2,3-(isopropylidenedioxy)pentane (31)

To a stirred solution of optically pure (-)-epoxytrifluoroacetate (30) (210mg, 1 mmol) in acetone (290mg, 5 mmol) was added, at 0°C , $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (4 drops). The flask was stoppered and the reaction stirred at 0°C for 90 minutes after which time the solution was poured onto saturated sodium hydrogen carbonate (10 ml) and the aqueous solution extracted with ether. The combined organic extracts were dried and concentrated in vacuo. Short path distillation of the residue afforded the acetonide (23) as a colourless oil (230mg, 85%), b.p. 135°C at 35 mm Hg, $[\alpha]_D^{22} = 0.0^\circ$ (CHCl_3 , $C=0.932$). This material was found to be identical in all respects with the acetonide (23) derived from the racemic epoxytrifluoroacetate (21).

Preparation of (+)-1-Hydroxy-2-methyl-2,3-(cyclopentylidene dioxo)pentane (Scheme 16)



To a stirred solution of optically pure (-)-epoxy trifluoroacetate (212mg, 1 mmol) and cyclopentanone (420mg, 5 mmol) in ether (1 ml) was added, at 0°C, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (4 drops). The solution was allowed to warm to 20°C and stirred at this temperature for 14 hours. The reaction mixture was poured onto saturated sodium hydrogen carbonate and extracted with ether. The combined ethereal extracts were washed with brine, dried and concentrated in vacuo. After hydrolysis of the trifluoroacetate as previously described, the resulting pale yellow oil (250mg) was subjected to column chromatography on neutral alumina (eluting solvent ethyl acetate: light petroleum) from which the acetono alcohol was obtained as a colourless oil (143mg, 72%), b.p. 160-170°C at 35 mm Hg, $[\alpha]_D^{21} = +1.2^\circ$ (CHCl_3 , $C=0.494$).

ν_{max}

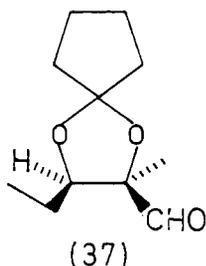
3490 2970 2880 1340 1120

δ (CDCl_3)

0.975 (3H, t, $J=7\text{Hz}$, CH_2CH_3), 1.15 (3H, s, CCH_3), 1.4-1.7 (2H, m, CH_2CH_3), 1.65 8H, brs, $(\text{CH}_2)_4$, 2.15 (1H, brs, exchanges D_2O , OH), 3.30 (2H, ABq, $J=7\text{Hz}$, CH_2OH), 3.49 (1H, double d, $J=8\text{Hz}$, CH)

(Found: m/z, 200.1409. $\text{C}_{11}\text{H}_{20}\text{O}_3$ requires 200.1412)

Preparation of (+)-2-Methyl-2,3-(cyclopentylidenedioxy)pentanal (37)



To a vigorously stirred solution of pyridinium chlorochromate (276mg, 1.28 mmol) and sodium acetate (210mg, 2.55 mmol) in dry methylene chloride (10 ml) was added, at 20°C and under an atmosphere of argon, optically active 1-hydroxy-2-methyl-2,3-(cyclopentylidenedioxy)pentane (116mg, 0.58 mmol) in methylene chloride (5 ml). The resultant black suspension was stirred for 15 hours at this temperature, whereupon the reaction mixture was diluted with ether (100 ml) and filtered through a pad of Celite. The Celite pad was thoroughly washed with ether and the combined filtrates were concentrated under reduced pressure. Distillation of the residue (190mg) afforded the aldehyde (37) as a colourless oil (92mg, 80%), b.p. 100-105°C at 0.4 mm Hg, $[\alpha]_D^{22} = +1.6^\circ$ (CHCl₃, C=0.092).

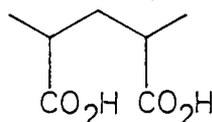
ν_{\max}	2980 1730 1340 1120 975
δ (CDCl ₃)	0.95 (3H, t, J=7Hz, CH ₂ CH ₃), 1.18 (3H, s, CCH ₃), 1.5-2.0 (1OH, m), 3.58 (1H, t, J=8Hz, CH), 9.5 (1H, s, CHO)

(Found: m/z, 118. C₁₁H₁₈O₃ requires M⁺118)

An examination of the optical purity of this aldehyde, using tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]-europium (III), resolved the signal at δ 9.5 p.p.m. for the aldehydic

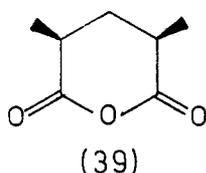
proton into two singlets. The ratio of (+)- and (-)- enantiomers, as calculated from the ^1H n.m.r. spectral integration, is 3.3:1.

α, γ -Dimethylglutaric Acid (Scheme 18)



This was prepared by the published procedure⁴. From diethyl methylmalonate (286g, 1.64mol) and methyl methacrylate (330g, 3.28mol) was obtained α, γ -dimethylglutaric acid (85g, 35%) after crystallisation from ether light petroleum, m.p. 103-105°C (lit⁴: m.p. 101-109°C).

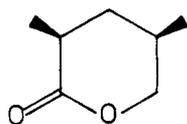
Meso- α, γ -Dimethylglutaric Anhydride (39)



This was obtained by the published procedure⁴. From α, γ -dimethylglutaric acid (15g, 0.09mol) was obtained the anhydride (39) (7.0g, 50%) after one recrystallisation from acetic anhydride, m.p. 92-93°C (lit⁴: m.p. 93.5°C) b.p. 160°C at 30 mm Hg.

(CDCl_3) 1.40 (6H, d, $J=7\text{Hz}$, 2 x CH_3), 2.0 (2H, t, $J=7\text{Hz}$, CH_2), 2.68 (2H, sextet, $J=6\text{Hz}$, 2 x CH).

(Found: C, 59.23; H, 6.94% $\text{C}_7\text{H}_{10}\text{O}_3$ requires C, 59.15; H, 7.09%).

α, γ -Dimethyl- δ -valerolactone (40)

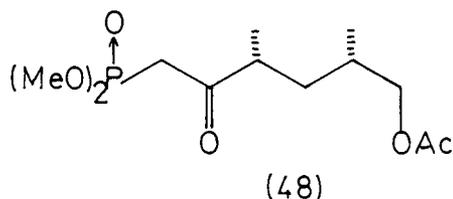
(40)

This was prepared by an extension of a published procedure⁵. To a vigorously stirred solution of sodium borohydride (12g, 0.32 mol) in dioxane (75 ml) was added, at 10°C, α, γ -dimethylglutaric anhydride (39) (25g, 0.17 mol) in dioxane (112 ml). The mixture was stirred for 44 hours at 20°C after which time was added, at 0°C, ice (100g) followed by a solution of concentrated HCl (100 ml) in ice (100g). The resultant solution was then stirred at 20°C for 1 hour followed by heating at 70°C for 30 minutes. After cooling, the solution was extracted with toluene and the combined toluene extracts were washed with brine and dried. Concentration under reduced pressure furnished a pale yellow oil, which on distillation afforded the lactone (40) as a colourless oil (12.2g, 54%), b.p. 120-122°C at 30 mm Hg (lit⁵: b.p. 108-109°C at 15 mm Hg) which solidified on standing at 3°C.

$\gamma_{\max}(\text{CCl}_4)$ 2960 1740 1150

$\delta(\text{CDCl}_3)$ 1.0 (3H, d, J=6Hz, CH₃), 1.25 (3H, d, J=6Hz, CH₃), 1.6-2.3 (4H, m), 4.0 (2H, dd, J=9Hz and 3Hz, OCH₂).

1-Acetoxy-2,4-dimethyl-6-(dimethylphosphonato)hexan-5-one (48)

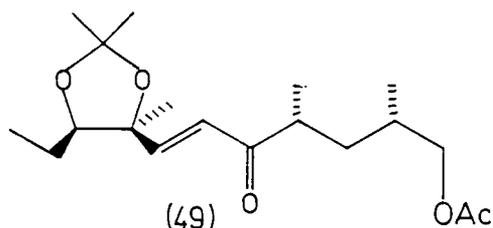


To a stirred solution of acetic anhydride (1.0g, 12.5 mmol) in pyridine (1.2g, 15 mmol) was added, at 20°C, the hydroxyphosphonate (46) (540mg, 2.2 mmol). The solution was stirred for 18 hours, after which time the mixture was poured onto ice-water. The aqueous solution was extracted with ether and the combined organic extracts were washed (saturated copper sulphate and brine) dried and concentrated under reduced pressure. The residual oil was subjected to column chromatography on silica (eluting solvent ethyl acetate:light petroleum) to furnish the acetoxy phosphonate (48) as a colourless viscous oil (517mg, 79%), b.p. 200°C at 0.25 mm Hg.

ν_{\max} (CCl ₄)	2960 1740 1720 1450 1360 1225 1030
δ (CDCl ₃)	0.98 (3H, d, J=6Hz, CH ₃), 1.0-1.9 (4H, m) 1.18 (3H, d, J=6Hz, CH ₃), 2.10 (3H, s, H ₃ CCO), 2.95 and 3.39 (2H, d, coupled to P, J=22Hz, PCH ₂), 3.81 (6H, d, J=11Hz, MeO), 3.90 (2H, t, obscured by MeO, CH ₂ OAc).

(Found: m/z, 234.1018. C₁₀H₁₉O₄P(M-AcOH) requires 234.1021).

Preparation of Acetoxy acetonide (49)



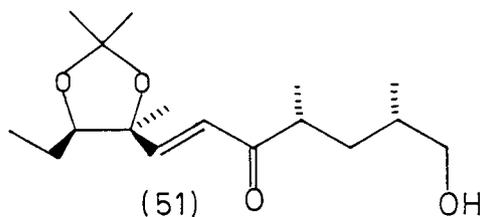
To a stirred suspension of sodium hydride (90mg, 1.9 mmol) in THF (5 ml) was added at 20°C the acetoxy phosphonate (48) (588mg, 2 mmol) in THF (2ml). The mixture was stirred at 20°C for 90 minutes after which time a further 3 ml of THF was added, followed by 2-methyl-2,3-(isopropylidenedioxy)pentanal (11) (350mg, 2.05 mmol) in THF (5 ml). The solution was then heated under reflux for 2 hours, cooled and the THF was removed in vacuo. The residue was partitioned between water and ether, the aqueous layer was removed and extracted with ether. The combined organic extracts were washed with brine, dried and concentrated under reduced pressure. Column chromatography on silica (eluting solvent ethyl acetate:light petroleum) furnished the acetoxy acetonide (49) as a viscous colourless oil, (460mg, 69%).

ν_{\max} (CCl₄) 2980 1740 1700 1630 1460 1580 1570 1240

δ (CDCl₃) 0.9-1.25 (9H, 7 lines, 2 x CHCH₃),
 1.45 (3H, s, isopropylidene CH₃), 1.46 (3H, s, isopropylidene CH₃), 1.58 (3H, s, CCH₃),
 2.10 (3H, s, OCOCH₃), 0.9-1.8 (6H, m)
 2.85 (1H, t, J=6Hz, CH₂CH), 3.99 (2H, d, J=5Hz, CH₂OAc), 6.68 (2H, ABq, J=16Hz, Olefinic CH).

(Found: m/z, 325.2015. C₁₈H₂₉O₅ (M-CH₃) requires 325.2015).

Preparation of Hydroxy acetone (51)



To a stirred solution of the acetoxy acetone (49) (400 mg, 1.23 mmol) in methanol (17 ml) was added potassium carbonate (357mg, 2.6 mmol). The mixture was stirred for 45 minutes, then filtered through a pad of Celite. After washing the Celite pad with ether, the combined organic extracts were concentrated in vacuo, and the residue was triturated with ether. The solution was again filtered through Celite and the Celite pad was washed with ether. The combined organic filtrates were concentrated in vacuo to furnish a pale yellow oil. Column chromatography on silica (eluting solvent ethyl acetate:light petroleum) allowed separation of the diastereoisomeric mixture of alcohols (51) (294mg, 85%, comprising 193mg of isomer A and 101mg of isomer B).

ν max	3400	2980	1720	1630	1460	1370	1380
	1220	1110	1010				

Isomer A

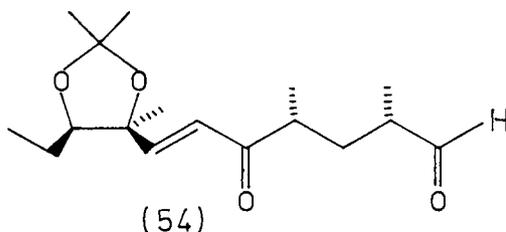
δ (CDCl ₃)	0.85 (3H, t, J=7Hz, CH ₃ CH ₂), 0.99 (3H, d, J= 5Hz, CHCH ₃), 1.07 (3H, d, J=5Hz, CHCH ₃), 1.34 (3H, s, isopropylidene CH ₃), 1.36 (3H, s, isopropylidene, CH ₃), 1.47 (3H, s, CCH ₃), 0.8-1.5 (6H, m), 1.6 (1H, bs, exchanges D ₂ O, OH), 3.42 (2H, bd, J=4Hz, CH ₂ OH), 3.80 (1H, t, J=7Hz, CH ₂ CH), 6.59 (2H, ABq, J=15Hz, olefinic CH).
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Isomer B

δ (CDCl₃) 0.88 (3H, t, J=7Hz, CH₃CH₂), 1.0 (3H, d, J=5Hz, CHCH₃), 1.09 (3H, d, J=5Hz, CHCH₃), 1.34 (3H, s, isopropylidene CH₃), 1.36 (3H, s, isopropylidene CH₃), 1.47 (3H, s, CCH₃), 0.8-1.5 (6H, m), 2.8 (1H, bs, exchanges D₂O, OH), 3.40 (2H, bd, J=4Hz, CH₂OH), 3.80 (1H, t, J=7Hz, CH₂CH), 6.61 (2H, ABq, J=15Hz, olefinic CH).

(Found: m/z, 265. C₁₆H₂₅O₃ [M⁺-(CH₃+H₂O)] requires 265).

Preparation of Acetonido aldehyde (54)



To a stirred solution of dipyridine chromium (VI) oxide (774mg, 3 mmol) in dry methylene chloride (20 ml) was added, at 20°C, the hydroxy acetonide (51) (175mg, 0.58 mmol) in dry methylene chloride (2 ml). The mixture was stirred at this temperature for 90 minutes when ether (150 ml) was added. The resultant suspension was filtered through Celite, and the Celite pad was well washed with ether. The combined organic extracts were concentrated in vacuo followed by 15 minutes at 1.0 mm Hg. Preparative t.l.c. on silica (developing solvent ethyl acetate: light petroleum) furnished the aldehyde (54) as a colourless

oil (148mg, 82%).

ν max 2980 2720 1720 1690 1630 1460 1370
 1380 1210 1110 1010

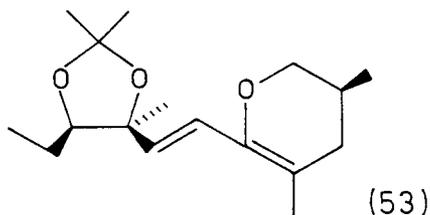
δ (CDCl₃) 0.88 (3H, t, J=7Hz, $\underline{\text{C}}\text{H}_3\text{CH}_2$), 1.08 (3H, d, J=4Hz, $\text{CH}\underline{\text{C}}\text{H}_3$), 1.18 (3H, d, J=4Hz, $\text{CH}\underline{\text{C}}\text{H}_3$), 1.40 (3H, s, isopropylidene CH_3), 1.42 (3H, s, isopropylidene CH_3), 1.0-2.0 (5H, m) 2.70 (1H, m, $\underline{\text{C}}\text{HCHO}$), 3.85 (1H, t, J=6Hz, $\text{CH}_2\underline{\text{C}}\text{H}$), 6.66 (2H, ABq, J=15Hz, olefinic CH) 9.75 (1H, d, J=1Hz, $\underline{\text{C}}\text{HO}$).

δ (CDCl₃) identical except: 6.71 (2H, ABq, J=15Hz, olefinic CH).

For other stereo-
isomer

(Found: m/z, 281.1821. $\text{C}_{16}\text{H}_{25}\text{O}_4$ ($\text{M}^+ - \text{CH}_3$) requires 281.1822).

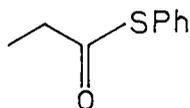
Preparation of the acetonidodiene (53)



To a stirred solution of the acetonido alcohol (51) (235mg, 0.79 mmol) in dry methylene chloride (15 ml) was added, at 20°C, pyridinium dichromate (308mg, 0.82 mmol). The mixture was stirred for 28 hours at this temperature whereupon ether (100 ml) was added and the resultant suspension was filtered through a Celite pad. The Celite pad was washed with ether and the combined organic filtrates were concentrated in vacuo. Column chromatography of the residue (eluting solvent ethyl acetate: light petroleum) furnished the aldehyde (54) (100mg, 42%) identical with an authentic sample, and the diene (53) as a colourless oil (125mg, 56%).

ν_{\max}	2980 1720 1650 1450 1360 1160
δ (CDCl ₃)	0.96 (3H, t, J=7Hz, CH ₂ CH ₃), 1.01 (3H, d, J=3Hz, CHCH ₃), 1.2-1.8 (5H, m), 1.31 (3H, s, isopropylidene, CH ₃), 1.33 (3H, s, isopropylidene, CH ₃), 1.42 (3H, s, CCH ₃), 2.12 (3H, s, vinylic CH ₃), 2.25 (2H, t, J=4Hz, allylic CH ₂), 3.75 (1H, t, J=6Hz, CH ₂ CH), 3.87 (2H, d, J=5Hz, OCH ₂ CH), 5.98 (1H, A part of ABq, J=15Hz, olefinic CH), 6.80 (1H, B part of ABq, J=15Hz, olefinic CH).

(Found: m/z, 265. C₁₆H₂₅O₃ (M⁺-CH₃) requires 265).

S-Phenyl Propanethioate

To a vigorously stirred solution of benzenethiol (11.02g, 0.1 mole) and dry pyridine (8.7g, 0.11 mole) in dry benzene (50 ml) was added, dropwise, at -5°C , and under an atmosphere of argon, propionyl chloride (9.25g, 0.1 mole). Precipitation of pyridinium hydrochloride resulted almost immediately. Upon completion of addition, the mixture was warmed to 20°C and benzene (200ml) was added and stirring continued for 18 hours. The solution was then filtered through a sintered glass filter funnel and washed with pentane. The solvents were then removed in vacuo to give a pale yellow liquid. Distillation furnished S-phenyl propanethioate (14.3g, 88%) as a colourless oil, b.p. $138-140^{\circ}\text{C}$ at 20 mm Hg.

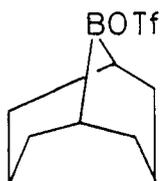
$\bar{\nu}_{\text{max}}$ 3050 2980 1705 1475 1440 925 750 690

$\bar{J}(\text{CDCl}_3)$ 1.23 (3H, t, $J=8\text{Hz}$, CH_3), 2.75 (2H, q, $J=8\text{Hz}$, CH_2), 7.48 (5H, s, Ar)

(Found: m/z , 162. $\text{C}_9\text{H}_{10}\text{OS}$ requires 162) .

Preparation of 9-Borabicyclo[3,3,1]non-9-yl trifluoromethane

Sulphonate

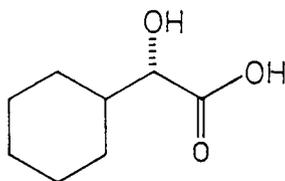


To a stirred solution of 9-borabicyclo[3,3,1]nonane (17.35g, 0.142 mole) in hexane (55 ml) was added, at 20°C, and under an atmosphere of argon, freshly distilled trifluoromethanesulphonic acid (21.3g, 12.6 ml, 0.142 mole) over 30 minutes. The pale yellow mixture was allowed to stir for 18 hours, after which time a homogeneous reaction mixture was obtained. The slightly yellow homogeneous solution was transferred to a 1-neck flask via a flex needle and positive nitrogen pressure. The solvent was removed under reduced pressure (30 mm Hg) and under nitrogen. The resulting yellow liquid was distilled to yield 9-BBNOTf (ca. 25 ml) as an extremely moisture sensitive, and heat sensitive colourless oil, b.p. 53-55°C at 0.5 mm Hg. (lit.⁶ : b.p. 38°C at 0.03 mm Hg.)

ν(CCl₄) 2930 1410 1220 1150 1085

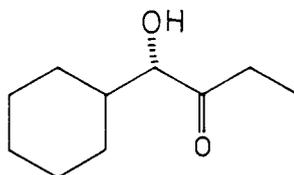
Attempted Aldol Reaction between the Acetonido aldehyde (54)
and S-Phenyl Propanethioate⁷

To a stirred solution of 9-BBNOTf (403.5mg, 1.5 mmol) in dry ether (3 ml) were added, at 0°C, and under an atmosphere of argon, S-phenyl propanethioate (250mg, 1.5 mmol) and diisopropylethyl amine (194.0mg, 1.5 mmol) in dry ether (3 ml) over 5 minutes. The resultant pale yellow solution was warmed to 25°C and stirred at this temperature for 15 minutes, by which time a white precipitate of amine triflate had formed. The mixture was cooled to -50°C and the acetonido aldehyde (54) (450mg, 1.6 mmol) was added. The solution was allowed to warm to 25°C and stirred for 30 minutes. The reaction mixture was hydrolysed by stirring with phosphate buffer (10.5 ml, pH7), methanol and 30% hydrogen peroxide (1.8 ml) for 30 minutes at 25°C. The solvent was removed in vacuo and the aqueous solution was extracted with ether. The combined ether extracts were washed with brine, dried and concentrated under reduced pressure to furnish a pale yellow viscous oil (460mg). Analytical t.l.c. analysis indicated two major products amongst a variety of products. Purification of these products (preparative t.l.c.) proved exceptionally difficult, and indeed, a sufficiently pure sample for unambiguous identification could not be obtained. However, ¹H n.m.r. analysis indicated that the conjugated enone system was not present.

(+)-Hexahydromandelic Acid

This was prepared by the published procedure⁸. Thus, from (+)-mandelic acid (5g, 0.033 mole) and 5% rhodium on alumina (1g) in methanol (10 ml) was obtained hexahydromandelic acid after crystallisation from methanol (3.5g, 70%), m.p. 128-129°C (lit⁸: m.p. 128-129°C), $[\alpha]_{\text{D}}^{22} = +10.6^{\circ}$ (ethanol, C=2.0), (lit⁸: $[\alpha]_{\text{D}}^{22} = +12.0^{\circ}$) (ethanol, C=2.0).

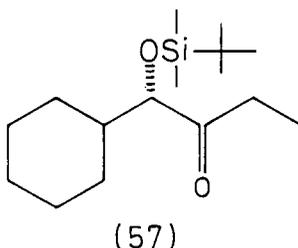
δ (CDCl₃) 1.2-1.9 (11H, m), 4.15 (1H, d, J=2Hz, CHOH), 4.15 (1H, b, exchanges D₂O, OH), 6.80 (1H, b, exchanges D₂O, COOH).

(+)-1-Cyclohexyl-1-hydroxybutan-2-one

This was prepared by the published procedure⁹. Thus, from ethyl lithium (23 ml, 11.9 mmol) in pentane and (+)-hexahydromandelic acid (316mg, 2 mmol) in ether (10 ml) at -78°C was obtained the ethyl ketone (238mg, 70%) as a colourless oil after column chromatography on silica (eluting solvent ethyl acetate:light petroleum), $[\alpha]_{\text{D}}^{22} = +126.3^{\circ}$ (CHCl₃, C=1.22); [lit⁹: $[\alpha]_{\text{D}}^{22} = +128.5^{\circ}$ (CHCl₃, C=1.22)].

ν_{\max}	3480 2920 1710 1450 1100
δ (CDCl ₃)	1.05 (3H, t, J=7Hz, CH ₃), 1.15-1.80 (11H, m), 2.40 (2H, q, J=7Hz, CH ₂ CH ₃), 3.20 (1H, bs, exchanges D ₂ O, OH), 3.90 (1H, d, J=2Hz, CHOH).

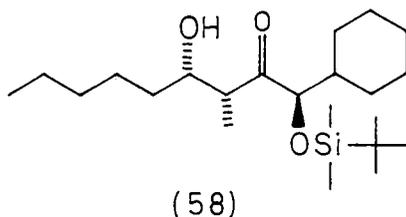
(-)-1-t-Butyldimethylsilyloxy-1-cyclohexylbutan-2-one (57)



This was prepared by standard procedures . Thus, from the alcohol (1.64g, 9.62 mmol), imidazole (1.6g, 23.2 mmol) and t-butyldimethylsilyl chloride (1.8g, 11.6 mmol) in DMF (5 ml) was obtained the t-butyldimethylsilyl ether (57) (2.45g, 99%) after short path distillation, b.p. 150-155°C at 30 mm Hg, $[\alpha]_{\text{D}}^{22} = -50.6^{\circ}$ (CHCl₃, C=1.18), [lit⁹ : $[\alpha]_{\text{D}}^{25} = -60.3^{\circ}$ (CHCl₃, C = 1.15)].

ν_{\max}	2925 2860 1710 1450 1100
δ (CDCl ₃)	0.1 (6H, d, J=4Hz, Me ₂ Si), 1.0 (9H, d, J=4Hz, Bu ^t Si), 1.10 (3H, t, J=7Hz, partially obscured, CH ₃), 1.25 (11H, m), 2.55 (2H, dq, J=7Hz and 2Hz, CH ₂ CH ₃) 3.85 (1H, d, J=6Hz, OCH).

Several signals showed diastereotopic multiplicity.

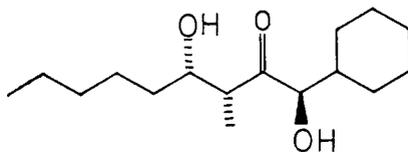
Preparation of the Aldol product (58)

To a stirred solution of diisopropylamine (182mg, 1.8 mmol) in THF (5 ml) was added, at -78°C , butyl lithium (0.7 ml, 1.8 mmol) in hexane. The solution of lithium diisopropylamide was stirred for 30 minutes at -78°C when the ethyl ketone (57) (455mg, 1.6 mmol) was added dropwise over 5 minutes. The mixture was stirred for 1 hour at -78°C , after which time hexanal (170mg, 1.7 mmol) was added rapidly. After 10 minutes, saturated ammonium chloride (10 ml) was added and the solution was allowed to warm to 20°C . The aqueous layer was separated and extracted with ether. The combined organic extracts were washed with brine, dried and concentrated in vacuo. Column chromatography on silica of the residue (eluting solvent ethyl acetate: light petroleum) afforded the hydroxy ketone (58) (280mg, 43%) as a colourless oil.

ν max	2820 1720 1700 1450 1010
δ (CDCl_3)	0.01 (6H, d, $J=2\text{Hz}$, Me_2Si), 1.00 (9H, d, $J=2\text{Hz}$, Bu^tSi), 1.12 (3H, dd, $J=7\text{Hz}$, and 2Hz , CHCH_3), 1.13-1.9 (22H, m), 3.38 (1H, dq, $J=7\text{Hz}$ and 2Hz , CHCO), 3.48 (1H, bs, exchanges D_2O , OH), 4.16 (1H, dt, $J=7\text{Hz}$ and 3Hz , CHOH), 4.19 (1H, d, $J=5\text{Hz}$, CHOSi).

Several signals showed diastereotopic multiplicity.

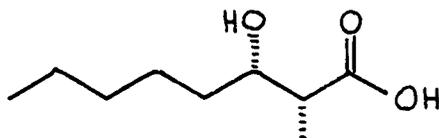
Preparation of the dihydroxy ketone (Scheme 25)



This was prepared by an extension of the literature method⁹. Thus, the silyl ether (58) (280mg, 0.73 mmol) in acetonitrile (5 ml) was added to a stirred solution of aqueous hydrofluoric acid (5.5 ml, 15%) in acetonitrile (15 ml) at 20°C. The mixture was stirred for 1 hour at this temperature, then poured onto water. The aqueous solution was extracted with chloroform and the combined organic extracts were washed with brine, dried and concentrated in vacuo. Column chromatography on silica (eluting solvent ethyl acetate:light petroleum) furnished the dihydroxy ketone as a colourless oil (182mg, 98%).

$\bar{\nu}$ max	3320 2920 2830 1720 1700 1450 1010
δ (CDCl ₃)	0.9 (3H, m, CH ₂ CH ₃), 1.1 (3H, d, J=7Hz, CHCH ₃), 1.15-1.90 (22H, m), 2.83 (1H, dq, J=7Hz and 3Hz, CH ₃ CHCO), 3.76 (1H, m, CH ₂ CHOH), 3.98 (1H, d, J=2Hz, CHOH), 3.05-3.90 (2H, b, exchanges D ₂ O, 2 x OH).

Preparation of erythro 2-Methyl-3-hydroxyoctanoic acid (59)



(59)

To a stirred solution of the dihydroxy ketone (182mg, 0.72 mmol) in methanol (14 ml) was added dropwise aqueous periodic acid (7.4 ml of a 0.54 M solution) at 20°C. The mixture was stirred at this temperature for 3 hours; the methanol was removed in vacuo and the aqueous residue extracted with methylene chloride. The combined organic extracts were washed with saturated sodium hydrogen carbonate and the basic washings were acidified carefully with hydrochloric acid (4 molar). The resultant neutral solution was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried and concentrated under reduced pressure to furnish the acid as a colourless oil (85mg, 71%).

ν_{max} 3600 2920 1700 1450 1000

δ (CDCl₃) 0.89 (3H, m, $\underline{\text{CH}}_3\text{CH}_2$), 1.14 (3H, d, J=7Hz, $\text{CH}\underline{\text{CH}}_3$), 1.2-1.6 (8H, m), 2.45 (1H, m, J=4Hz, $\underline{\text{CH}}\text{CO}_2\text{H}$), 3.65 (1H, dd, J=6Hz and 1Hz, $\underline{\text{CHOH}}$), 6.91 (1H, bs, exchanges D₂O, $\underline{\text{OH}}$), 9.6 (1H, b, exchanges D₂O, CO₂H).

¹³C n.m.r. δ (CDCl₃)

erythro 180.65 (s), 72.04 (d), 44.21 (d), 33.68 (t), 31.74 (t), 25.68 (t), 22.61 (t), 14.02 (q), 10.38 (q).

^{13}C n.m.r. δ (CDCl_3)

<u>threo</u>	180.65 (s), 72.27 (d), 45.35 (d),
	34.38 (t), 31.74 (t), 25.68 (t),
	22.61 (t), 14.02 (q), 14.02 (q).

Inspection of the ^{13}C n.m.r. spectral signal integrals revealed an erythro:threo ratio of 95:5.



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